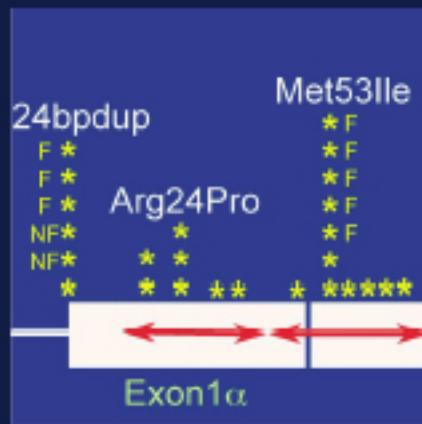
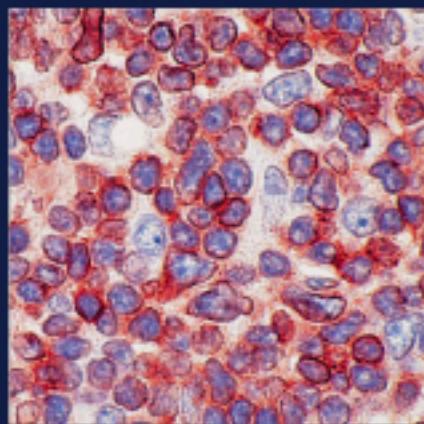
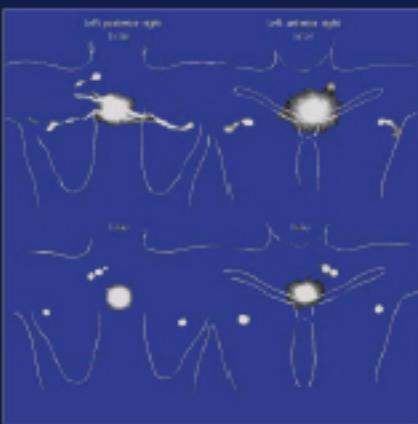
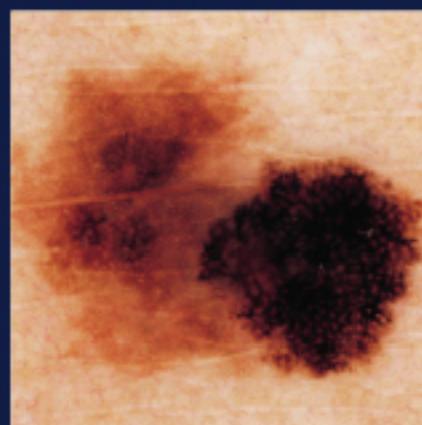
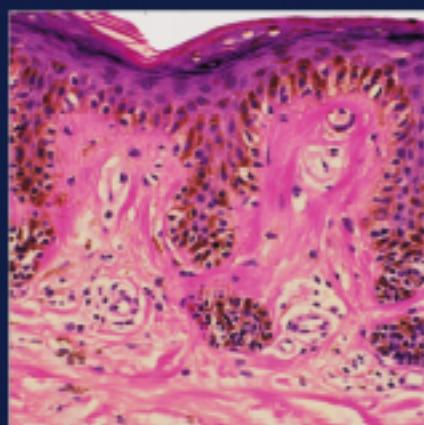




Pathology & Genetics

Skin Tumours

Edited by Philip E. LeBoit, Günter Burg, David Weedon, Alain Sarasin



World Health Organization Classification of Tumours

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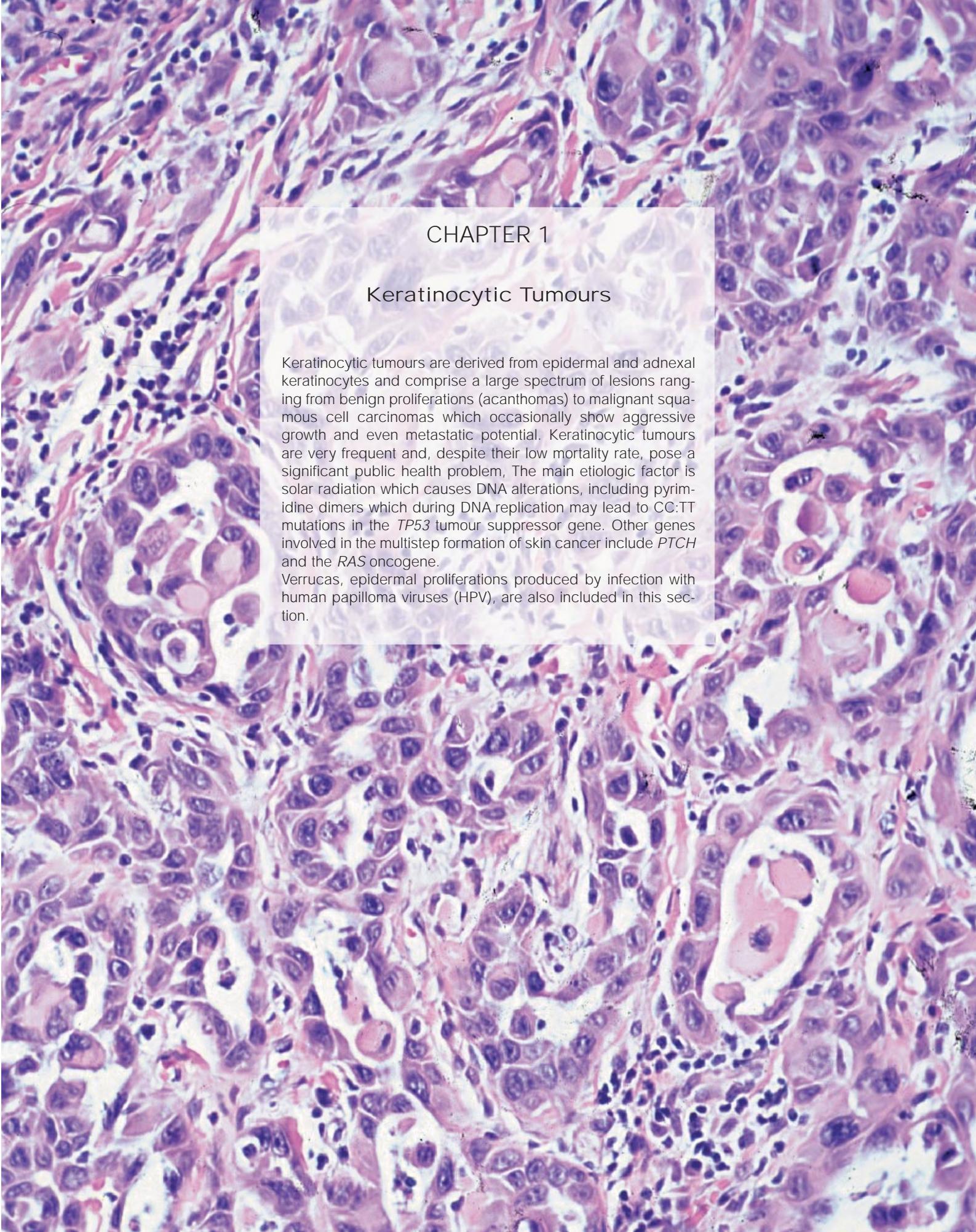
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Contents

1 Keratinocytic tumours	9	
WHO and TNM classification	10	
Introduction	11	
Basal cell carcinoma	13	
Superficial basal cell carcinoma	15	
Nodular basal cell carcinoma	16	
Micronodular basal cell carcinoma	16	
Infiltrating basal cell carcinoma	17	
Fibroepithelial basal cell carcinoma	17	
Basal cell carcinoma with adnexal differentiation	18	
Basosquamous carcinoma	18	
Keratotic basal cell carcinoma	19	
Other variants	19	
Squamous cell carcinoma	20	
Acantholytic squamous cell carcinoma	21	
Spindle-cell squamous cell carcinoma	22	
Verrucous squamous cell carcinoma	22	
Pseudovascular squamous cell carcinoma	23	
Adenosquamous carcinoma	24	
Bowen disease	26	
Bowenoid papulosis	28	
Actinic keratosis	30	
Arsenical keratosis	32	
PUVA keratosis	33	
Verrucas	34	
Verruca vulgaris	36	
Verruca plantaris	37	
Verruca plana	38	
Acanthomas	39	
Epidermolytic acanthoma	39	
Warty dyskeratoma	39	
Acantholytic acanthoma	40	
Lentigo simplex	40	
Seborrhoeic keratosis	41	
Melanoacanthoma	43	
Clear cell acanthoma	43	
Large cell acanthoma	44	
Keratoacanthoma	44	
Lichen planus-like keratosis	47	
2 Melanocytic tumours	49	
WHO classification	50	
TNM classification	51	
Malignant melanoma: Introduction	52	
Superficial spreading melanoma	66	
Nodular melanoma	68	
Lentigo maligna	70	
Acral-lentiginous melanoma	73	
Desmoplastic melanoma and desmoplastic neurotropic melanoma	76	
Melanoma arising from blue naevus	79	
Melanoma arising in giant congenital naevi	83	
Childhood melanoma	84	
Naevoid melanoma	86	
Persistent melanoma and local metastasis of melanoma	90	
Congenital melanocytic naevus	93	
Superficial type	93	
Proliferative nodules in congenital melanocytic naevi	93	
Blue naevi	95	
Common blue naevus	95	
Mongolian spot	96	
Naevus of Ito and naevus of Ota	96	
Cellular blue naevus	96	
Deep penetrating naevus	98	
Combined naevus	100	
Melanotic macules	103	
Simple lentigo – lentiginous melanocytic naevus	104	
Dysplastic naevus	105	
Site specific and Meyerson naevi	110	
Acral naevus	110	
Genital naevus	110	
Meyerson naevus	111	
Persistent (recurrent) melanocytic naevus	113	
Spitz naevus	114	
Pigmented spindle cell naevus (Reed)	117	
Halo naevus	118	
3 Appendageal tumours	121	
WHO and TNM classification	122	
Introduction	123	
Malignant tumours with apocrine and eccrine differentiation	125	
Tubular carcinoma	125	
Microcystic adnexal carcinoma	125	
Malignant mixed tumour	127	
Porocarcinoma	128	
Spiradenocarcinoma	130	
Hidradenocarcinoma	131	
Mucinous carcinoma	131	
Digital papillary carcinoma	133	
Adenoid cystic carcinoma	134	
Apocrine carcinoma	135	
Paget disease and extramammary Paget disease	136	
Benign tumours with apocrine and eccrine differentiation	139	
Hidrocystoma	139	
Syringoma	140	
Poroma	141	
Syringofibroadenoma	142	
Hidradenoma	143	
Spiradenoma	143	
Cylindroma	145	
Tubular and tubular papillary adenoma	145	
Syringocystadenoma papilliferum	146	
Hidradenoma papilliferum	147	

Mixed tumour (chondroid syringoma)	147	B-cell lymphoma	199
Malignant tumours with follicular differentiation	149	Intravascular large B-cell lymphoma	200
Pilomatrical carcinoma	149	Lymphomatoid granulomatosis	202
Proliferating tricholemmal tumour	150	Cutaneous involvement in primary extracutaneous	
Benign tumours with follicular differentiation	152	B-cell lymphoma	204
Trichoblastoma	152	Mantle cell lymphoma	204
Pilomatricoma	153	Burkitt lymphoma	205
Tricholemmoma	155	Chronic lymphocytic leukaemia / small	
Trichofolliculoma	156	lymphocytic lymphoma	205
Pilar sheath acanthoma	157	Hodgkin lymphoma	207
Tumour of the follicular infundibulum	158	Blastic NK-cell lymphoma	208
Fibrofolliculoma / trichodiscoma	158	Precursor T-lymphoblastic leukaemia / lymphoma	
Tumours with sebaceous differentiation	160	and precursor B-lymphoblastic	
Sebaceous carcinoma	160	leukaemia / lymphoma	210
Sebaceous adenoma	161	Cutaneous involvement by myeloid leukaemia	211
Sebaceoma	162	Lymphoid infiltrates of the skin mimicking	
Cystic sebaceous tumour	163	lymphoma	212
4 Haematolymphoid tumours	165	Parapsoriasis	215
WHO / EORTC classification	166	Small plaque parapsoriasis	215
TNM classification	167	Parapsoriasis – Large patch type,	
Introduction	168	with or without poikiloderma	215
Mycosis fungoides (MF)	169	Langerhans cell histiocytosis	217
Pagetoid reticulosis	173	Indeterminate cell histiocytosis	220
Syringotropic MF	173	Sinus histiocytosis with massive lymphadenopathy	
Folliculotropic MF	173	(Rosai-Dorfman)	221
Granulomatous MF	174	Juvenile xanthogranuloma	222
Sézary syndrome	175	Reticulohistiocytosis	224
Granulomatous slack skin	178	Mastocytosis	226
CD30+ T-cell lymphoproliferative disorders	179	5 Soft tissue tumours	229
Lymphomatoid papulosis (LyP)	179	WHO and TNM classification	230
Primary cutaneous anaplastic large-cell		Introduction	231
lymphoma	180	Vascular tumours	233
Subcutaneous panniculitis-like T-cell lymphoma	182	Haemangioma of infancy	233
Primary cutaneous peripheral T-cell lymphoma,		Cherry haemangioma	233
unspecified	184	Sinusoidal haemangioma	234
Cutaneous $\gamma\delta$ T-cell lymphoma	184	Hobnail haemangioma	234
Primary cutaneous aggressive epidermotropic		Glomeruloid haemangioma	235
CD8+ cytotoxic T-cell lymphoma	185	Microvenular haemangioma	236
Primary cutaneous small-medium CD4+ T-cell		Angiolymphoid hyperplasia with eosinophilia	237
lymphoma	186	Spindle cell haemangioma	239
Primary cutaneous PTL, unspecified	186	Tufted angioma	239
Cutaneous adult T-cell leukaemia / lymphoma	189	Bacillary angiomatosis	240
Extranodal NK/T-cell lymphoma, nasal-type	191	Reactive angioendotheliomatosis	241
Hydroa vacciniforme-like cutaneous T-cell		Verrucous haemangioma	242
lymphoma	192	Pyogenic granuloma	243
Cutaneous involvement in primary extracutaneous		Cavernous haemangioma	243
T-cell lymphoma	193	Angiokeratomas	244
Systemic anaplastic large cell lymphoma (ALCL)	193	Arteriovenous haemangioma	245
Angioimmunoblastic T-cell lymphoma (AITL)	193	Cutaneous angiosarcoma	246
Cutaneous marginal zone B-cell lymphoma	194	Lymphatic tumours	247
Cutaneous follicle centre lymphoma	196	Lymphangioma circumspectum	247
Cutaneous diffuse large B-cell lymphoma	198	Progressive lymphangioma	248
Diffuse large B-cell lymphoma, leg-type	198	Lymphangiomatosis	249
Diffuse large B-cell lymphoma, other	198	Smooth and skeletal muscle tumours	250
T-cell / histiocyte-rich large B-cell lymphoma	199	Smooth muscle hamartoma	250
Plasmablastic lymphoma	199	Pilar leiomyoma	251
Secondary skin involvement by diffuse large		Cutaneous leiomyosarcoma	251

Rhabdomyomatous mesenchymal hamartoma	252
Fibrous, fibrohistiocytic and histiocytic tumours	254
Keloid scar	254
Hypertrophic scar	254
Dermatomyofibroma	255
Infantile myofibromatosis	256
Sclerotic fibroma	256
Digital mucous cyst	257
Digital fibrokeratoma	257
Pleomorphic fibroma	258
Giant cell fibroblastoma	258
Dermatofibrosarcoma protuberans	259
Dermatofibroma (fibrous histiocytoma)	261
6 Neural tumours	263
WHO and TNM classification	264
Palisaded, encapsulated neuroma and traumatic	
neuroma	265
Palisaded encapsulated neuroma	265
Traumatic neuroma	266
Primary malignant peripheral primitive	
neuroectodermal tumour (PNET) /	
Extraskeletal Ewing sarcoma (ES)	268
Nerve sheath myxoma / neurothekeoma	270
Merkel cell carcinoma	272
Granular cell tumour	274
7 Inherited tumour syndromes	277
Familial cutaneous melanoma	279
Xeroderma pigmentosum	282
Naevoid basal cell carcinoma (Gorlin) syndrome	285
Cowden syndrome	288
Carney complex	291
Contributors	295
Source of charts and photographs	300
References	301
Subject index	341



CHAPTER 1

Keratinocytic Tumours

Keratinocytic tumours are derived from epidermal and adnexal keratinocytes and comprise a large spectrum of lesions ranging from benign proliferations (acanthomas) to malignant squamous cell carcinomas which occasionally show aggressive growth and even metastatic potential. Keratinocytic tumours are very frequent and, despite their low mortality rate, pose a significant public health problem. The main etiologic factor is solar radiation which causes DNA alterations, including pyrimidine dimers which during DNA replication may lead to CC.TT mutations in the *TP53* tumour suppressor gene. Other genes involved in the multistep formation of skin cancer include *PTCH* and the *RAS* oncogene.

Verrucas, epidermal proliferations produced by infection with human papilloma viruses (HPV), are also included in this section.

WHO histological classification of keratinocytic skin tumours

Keratinocytic tumours			
Basal cell carcinoma	8090/3	Actinic keratosis	
Superficial basal cell carcinoma	8091/3	Arsenical keratosis	
Nodular (solid) basal cell carcinoma	8097/3	PUVA keratosis	
Micronodular basal cell carcinoma	8090/3	Verrucas	
Infiltrating basal cell carcinoma	8092/3	Verruca vulgaris	
Fibroepithelial basal cell carcinoma	8093/3	Verruca plantaris	
Basal cell carcinoma with adnexal differentiation	8098/3	Verruca plana	
Basosquamous carcinoma	8094/3	Acanthomas	
Keratotic basal cell carcinoma	8090/3	Epidermolytic acanthoma	
Squamous cell carcinoma	8070/3	Warty dyskeratoma	
Acantholytic squamous cell carcinoma	8075/3	Acantholytic acanthoma	
Spindle-cell squamous cell carcinoma	8074/3	Lentigo simplex	
Verrucous squamous cell carcinoma	8051/3	Seborrhoeic keratosis	
Pseudovascular squamous cell carcinoma	8075/3	Melanoacanthoma	
Adenosquamous carcinoma	8560/3	Clear cell acanthoma	
Bowen disease	8081/2	Large cell acanthoma	
Bowenoid papulosis		Keratoacanthoma	8071/1
		Lichen planus-like keratosis	

¹ Morphology code of the International Classification of Diseases for Oncology (ICD-O) {786} and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, /2 for in situ carcinoma and /1 for borderline or uncertain behaviour.

TNM classification of skin carcinomas

TNM classification^{1,2}

T – Primary tumour

- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Tis Carcinoma in situ

- T1 Tumour 2 cm or less in greatest dimension
- T2 Tumour more than 2 cm but no more than 5 cm in greatest dimension
- T3 Tumour more than 5 cm in greatest dimension
- T4 Tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle, or bone

Note: In the case of multiple simultaneous tumours, the tumour with the highest T category is classified and the number of separate tumours is indicated in parentheses, e.g., T2(5).

N – Regional lymph nodes

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

M – Distant metastasis

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

¹ {894,2219}.

² A help desk for specific questions about the TNM classification is available at www.uicc.org/index.php?id=508.

Keratinocytic tumours: Introduction

D. Weedon
R. Marks
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The keratinocytic tumours are a clinically and histopathologically diverse group of lesions derived from the proliferation of epidermal and adnexal keratinocytes. At one end of the spectrum the proliferations are benign (acanthomas) and usually of cosmetic importance only, while at the other there are malignant tumours, which uncommonly may be aggressive with metastatic potential, as seen with some squamous cell carcinomas. Included in the spectrum are the epidermal dysplasias (actinic keratosis, arsenical keratosis and PUVA keratosis) and intraepidermal carcinomas (Bowen disease and bowenoid papulosis). Ackerman and others have proposed that solar keratoses should be regarded as squamous cell carcinoma *de novo* and not as pre-malignancies or pre-cancers that evolve into squamous cell carcinoma {994,1443,1701}.

Epidemiology

Keratinocytic tumours are an important public health problem, despite their comparatively low mortality rate {2484}. The lifetime risk for the development of skin cancer in the USA is now 1 in 5 {1937}. It is much higher in subtropical Australia. There is an increasing incidence of squamous cell carcinoma of the skin in some countries {2462}. Keratinocytic tumours account for approximately 90% or more of all skin malignancies, of which approximately 70% are basal cell carcinomas. The latter exceed squamous cell carcinomas in frequency by a factor of approximately 5:1 although in lower latitudes the incidence of squamous cell carcinoma increases and this ratio becomes 3:1. If solar keratoses are regarded as squamous cell carcinomas (see above), then squamous cell carcinoma becomes the more common tumour {300}.

Precursor lesions

There are no known precursor lesions to basal cell carcinoma. On the other hand, there are a number of intra-epidermal proliferative disorders (dysplasias) that

may be precursors of squamous cell carcinoma. These include actinic keratosis and Bowen disease (intraepidermal carcinoma/squamous cell carcinoma *in situ*).

Actinic keratoses are erythematous, scaling lesions occurring on heavily sun-light exposed areas that increase in prevalence with increasing age in fair-skinned people. Histologically, they demonstrate confluent keratinocytic atypia involving predominantly the keratinocytes in the basal layer of the epidermis {2475}.

It is difficult to determine the incidence of actinic keratoses as they come and go over time {788}. Longitudinal studies suggest that they are likely to be a precursor of squamous cell carcinoma, although the malignant transformation rate is small, certainly less than one in a hundred per year {1517}. Data suggest, also, that remission of these lesions will occur if sunlight exposure can be reduced. Thus the majority of lesions do not progress to squamous cell carcinoma {1516,2349}.

Bowen disease demonstrates keratinocyte atypia involving the full thickness of the epidermis. There is also involvement of the hair follicle and rarely the sweat duct. Although Bowen disease has been classified as a full thickness *in situ* squamous cell carcinoma, there are no longitudinal studies published on the frequency of malignant transformation. Even if invasive squamous cell carcinoma does occur within one of these lesions, it is believed that the *in-situ* phase may be very prolonged, lasting many years {1203}.

Etiology

Findings regarding the genetic basis of non-melanoma skin cancer (NMSC) have confirmed that UV radiation, especially UVB (290-320 nm in the solar spectrum), contributes to the formation of squamous {1336} and basal cell carcinomas {602}. Squamous cell carcinomas (SCCs) of the skin develop through a multistep process that involves activation of proto-onco-

genes and/or inactivation of tumour suppressor genes in the human skin keratinocytes. NMSCs are caused by genetic abnormalities, most often induced by UVB exposure. Actinic keratoses, which lead to SCCs, have gene mutations in K-ras {2235}. H-rasV12 and cyclin dependent kinase 4 (CDK4) produce human epidermal neoplasia. Therefore, a combination of these genetic abnormalities might be crucial to the carcinogenesis at least in a subset of SCCs {1336}.

High doses of ultraviolet light can also lead to skin cancers by inducing reactive oxygen species (ROS) that play an important role in tissue injury. Increased production of ROS and/or decreased efficiency of antioxidant defence system contribute to a number of degenerative processes including cancer {1161}. UV induces pyrimidine dimers and loss of heterozygosity (LOH). TP53 and PTCH, two tumour suppressor genes, have LOH which lead to basal cell carcinoma (BCC) {1265}. LOH in TP53 is related to elevated microsatellite instability at selected tetranucleotide repeats {587}. LOH at 9q22 loci in PTCH genes causes non-melanoma skin cancer tumours {1265}. The type of mutations for TP53 and PTCH are predominantly UV-signature transitions, C->T and CC->TT at dipyrimidine sites {1265}. SCCs have mutations of H-Ras gene and the INK4a locus whereas BCC has missense mutations leading to rasGTPase activating protein {168}. Further, mutations have been found in both TP53 tumour suppressor gene and ras in patients with xeroderma pigmentosum (XP), a disease of DNA repair deficiencies {1717}.

Common exogenous carcinogenic agents in addition to UV radiation include 1) tobacco use {2457}, 2) human papilloma viruses {1703}, 3) arsenic {2184}, 4) industrial chemicals such as vinyl chloride {1362}, polycyclic aromatic hydrocarbons {1086}, 5) MNNG (N-methyl-N-nitro-N-nitrosoguanidine), an alkylating agent {335}, and 6) exposure to gasoline or gasoline vapours {1567}.

Clinical features

Keratinocytic tumours vary in their clinical appearance depending on the type of lesion and stage of development.

Histopathology

The histopathologic changes noted in keratinocytic proliferative lesions involve disturbance of normal surface maturation. The degree and extent of keratinocytic atypia vary in these lesions. The atypical keratinocytes show enlarged nuclei with hyperchromasia, dyskeratosis and mitoses in any layer of the epidermis. In lesions of epidermal dysplasias (AK, arsenical, and PUVA keratoses), surface keratinocytic maturation is present, i.e. a granular cell layer is usually noted.

In intraepidermal carcinomas (Bowen disease, bowenoid papulosis), there is full-thickness involvement of the epidermis by the atypical keratinocytes.

Molecular markers

A number of potentially useful molecular markers or tests have been proposed. These include the demonstration of a different pattern of basic fibroblast growth factor expression in neoplastic keratinocytes by *in situ* hybridization and the persistence of integrated HPV sequences in the host cell genome of HPV asso-

ciated keratinocytic lesions detected by ligation mediated PCR assay. The lower level of TIG-3 mRNA expression in SCC is visualized by immunohistochemistry or by *in situ* mRNA hybridization. Upregulation of S100 protein subtypes in specific keratinocyte disorders is confirmed by immunohistochemistry.

Prognosis and predictive factors

Most patients with primary cutaneous non-melanoma skin cancer (NMSC) have an excellent prognosis. The overall mortality rates are generally low, on average approximately 0.1% of the incidence rates, but significantly higher for SCCs than BCCs {2483}. Invasive SCC has the potential to recur and metastasize with an overall 5-year rate of recurrence for primary tumours of 8%. With the exception of lip tumours, squamous cell carcinomas arising in actinic keratoses have a frequency of metastatic spread of 0.5-3% {1459,1630}. For those with metastatic disease the long-term prognosis is poor; 10-year survival rates are <20% for patients with regional lymph node involvement and <10% for patients with distant metastases {50}. More than 70% of SCC recurrences and metastases develop within 2 years of treatment of the primary tumour {635}, and 95% within 5 years {1985}. The 3-year cumulative risk

of non-melanoma skin cancer developing in an individual diagnosed with SCC is 35-60% and the risk of melanoma is also increased {1507}. Five-year cure rates for BCC of up to 99% are obtainable with surgical techniques {1617, 1984}, and metastasis is extremely rare, occurring in approximately 0.05% of cases {1440}. As with SCC, patients with BCC are at high risk of further primary BCCs; in patients with one lesion the 5-year risk is 27%, and in those with 10 lesions the risk is 90% {1208}, and the risk of SCC and malignant melanoma is also increased {1208,1430}.

Basal cell carcinoma

S. Kossard
E.H. Epstein, Jr.
R. Cerio
L.L. Yu
D. Weedon

Definition

A group of malignant cutaneous tumours characterised by the presence of lobules, columns, bands or cords of basaloïd cells ("germinative cells").

ICD-O code 8090/3

Synonyms

Basal cell epithelioma, trichoblastic carcinoma.

Epidemiology

Basal cell carcinomas (BCC) develop predominantly in sun-damaged skin in individuals who are fair skinned and prone to sunburn {330,888,889}. Migration of such individuals particularly as children, to countries with high UV radiance is associated with increased rates of skin cancer. Although basal cell carcinomas typically occur in adults, the tumours also develop in children {1873}. Arsenic exposure {924} and ionizing radiation may also induce basal cell carcinomas.

Nodular basal cell carcinomas occur at a later age than superficial basal cell carcinomas and are more frequently on the head whereas the trunk is the most frequent site for superficial tumours {1550, 2121}.

Basal cell carcinomas are very frequent tumours particularly in light-skinned individuals living in countries at low latitudes. Incidences of 2000 per 100,000 population have been recorded in Queensland,

Australia. The rate of basal cell carcinomas has increased in the older age groups. Older men have a higher incidence of basal cell carcinoma than women, but women have been found to outnumber men in younger age groups. The latter may be due to increased sun exposure in younger women in association with tanning bed use as well as smoking {293}.

Clinical features

Basal cell carcinomas typically have a pearly appearance with telangiectasia that may appear as a papule or nodule that can be eroded or ulcerated. These features may be more subtle in the superficial forms that appear as erythematous patches resembling an area of dermatitis. Pale scar-like lesions may also be a presentation of basal cell carcinoma and these slowly grow over years. Pigmented basal cell carcinomas may masquerade as melanomas but usually can be distinguished by the presence of a pearly component. Dermatoscopy is also helpful in analysing pigmented basal cell carcinoma and distinguishing these from melanocytic tumours {1587}. Erosive lesions on the lower limbs may be mistaken for slowly healing traumatic wounds. Delays in clinical diagnosis may occur for basal cell carcinomas that are localized within non-sun exposed sites {225} such as the perianal area {1312} or between the toes, young age of onset, tumours with very slow

growth, or superficial erythematous patches that appear as a dermatitis or tumours complicating vaccination scars, rhinophyma or a venous ulcer. The clinical capacity to differentiate some basal cell carcinomas from squamous cell carcinoma or even melanoma may be impossible without skin biopsy. In countries with a high incidence of basal cell carcinomas it is not unusual to have individuals with multiple basal cell carcinomas, and regular review is required to deal with new skin tumours. Incomplete removal of basal cell carcinoma may result in delayed recurrences that may not be recognized for years, particularly if the tumour recurrence is deep or masked by skin grafts.

Genetics

Genetic analysis of sporadic basal cell carcinoma {2024} has been propelled by the identification of mutations in PTCH1 (chromosome 9q22.3) as the cause of the basal cell nevus syndrome (BCNS), a rare autosomal dominant disorder {110, 1146,2395}. These patients develop multiple basal cell carcinomas which may appear in childhood (see Chapter 2). PTCH1 encodes a protein that functions as an inhibitor of the hedgehog signalling pathway, and BCCs, whether sporadic or occurring in BCNS patients, all have abnormalities of this signalling pathway {110,1146,2272,2395}. In most sporadic BCCs this is due to somatically-acquired mutations in PTCH1 {802}, and in many

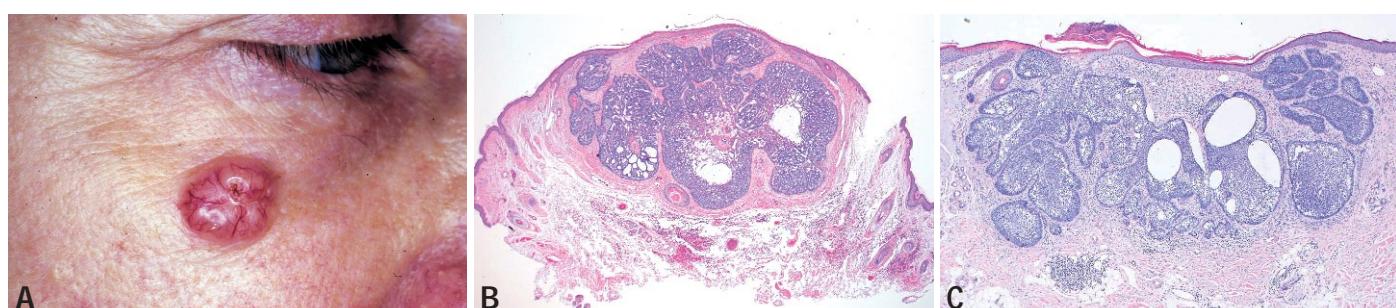


Fig. 1.1 Basal cell carcinoma, nodular type. **A** and **B** The epidermis is raised with flattening of the rete ridges overlying solid and cystic groups of atypical basaloid cells with peripheral palisading showing invasion of the deep dermis in a nodular pattern. **C** High power view of nodular basal cell carcinoma showing focal cystic change, peripheral palisading and cleft between tumour nests and stroma.

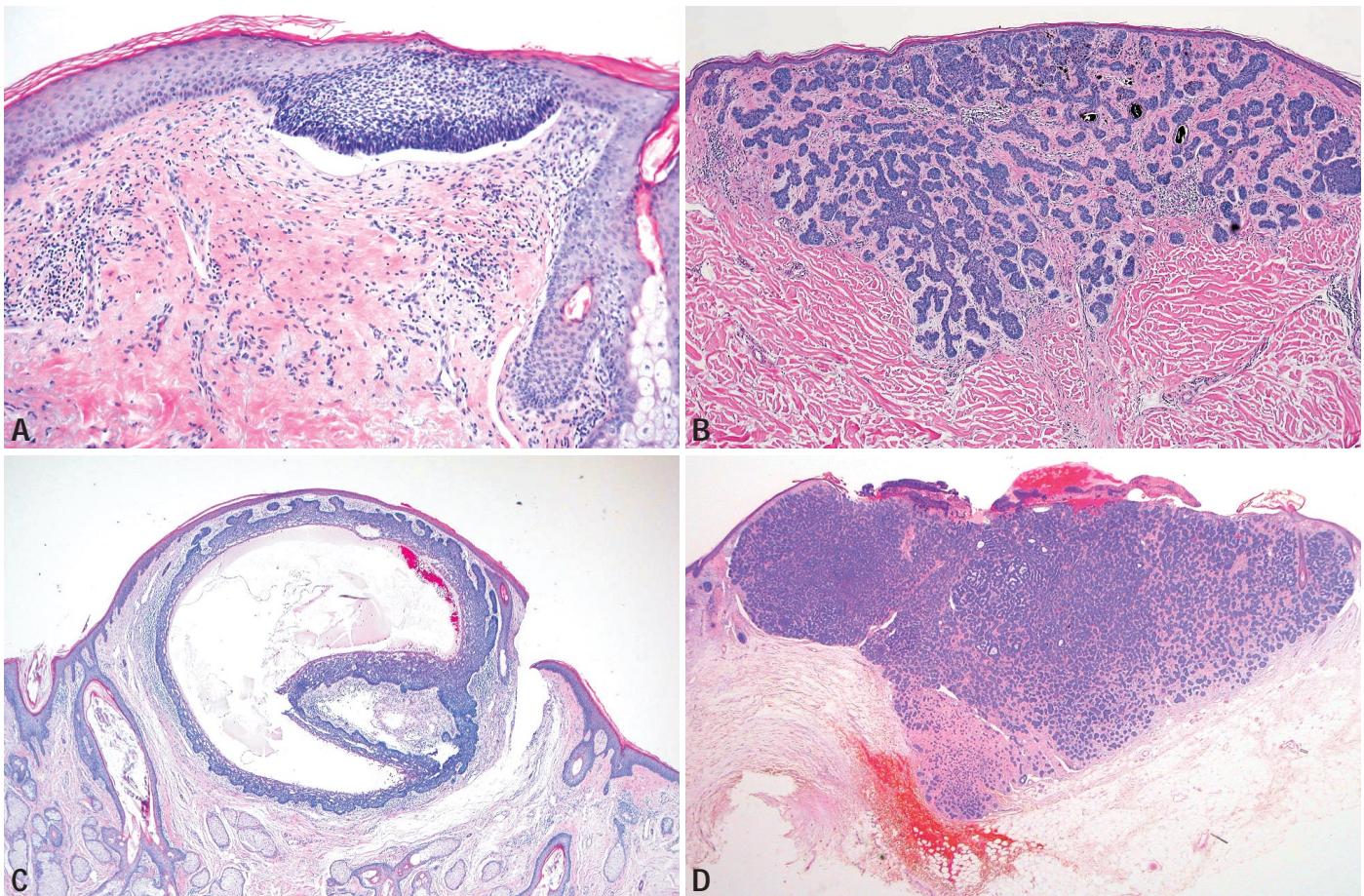


Fig. 1.2 **A** Basal cell carcinoma, superficial type. A solid group of atypical basaloid cells is present at the dermo-epidermal junction showing peripheral palisading and cleft formation between tumour nest and dermis. The dermis shows fibrosis and a patchy lymphocytic infiltrate which frequently accompany basal cell carcinoma of the superficial type. **B** Basal cell carcinoma, nodular type, pigmented. The appearances are those of typical nodular basal cell carcinoma with the additional feature of melanin pigmentation of the tumour nests. **C** Basal cell carcinoma, cystic type. There is extensive cystic change in an otherwise nodular basal cell carcinoma. The cystic space contains connective tissue type mucin. In the purely cystic variant, tumour cells may be compressed to only 1 to 2 cell layers thick. **D** Basal cell carcinoma, micronodular type. The tumour cell nests are tightly packed, with a diameter of 3 to 10 cells across with deep dermal invasion. In this example, there is also tumour-associated amyloid in the stroma.

tumours the type of PTCH1 mutations are those expected from UV-mutagenesis {108,1265}. Approximately 10% of sporadic BCCs have mutations in SMOOTHENED which encodes the protein whose function is inhibited by the PATCHED1 protein {2553}. Thus it appears that the relevant dysfunction driving BCCs is abnormal hedgehog signaling, irrespective of which gene controlling that signaling is mutated. The identification of hedgehog signaling abnormalities as crucial to BCC formation has stimulated the development of genetically-engineered mice with hedgehog signaling abnormalities {109,708, 1716,2163}. Unlike previously studied mouse carcinogenesis models, which uniformly produce tumours of the squamous cell lineage, these mice develop

BCCs and either spontaneously or in response to environmental mutagens (i.e. UV or ionizing radiation) develop BCCs and adnexal basaloid tumours.

Histopathology

The multiple variants of basal cell carcinoma are connected by the common histological feature of lobules, columns, bands and cords of basaloid cells ("germinative cells") associated with scant cytoplasm and a characteristic outer palisade of cells associated with a surrounding loose fibromucinous stroma {2147,2282}. Artefactual retraction spaces between the tumour and stroma are often present. The tumour-stromal interaction is weakened by the characteristic lack of the hemidesmosomes that anchor the normal epidermis to the der-

mis {475}. Apoptosis is usually apparent. The release of keratin into the stroma as a result of apoptosis may lead to the formation of amyloid deposits {2067}. Mucinous cystic degeneration, focal vacuolation with lipid or ductular differentiation, and in rare cases, sebocytes or follicular differentiation with squamous eddies, trichohyaline granules and blue-grey corneocytes may be seen. Melanocytes may proliferate within some tumours and produce pigmentation by melanin production that can be stored in tumour cells or in surrounding melanophages {1365}.

Problematic lesions include tumours that merge with squamous cell carcinoma (basaloid squamous cell carcinoma) or those that share adnexal differentiation demonstrating trichilemmal or seba-

ceous areas. Some examples of morpheeic or sclerotic basal cell carcinoma may resemble desmoplastic trichoepithelioma or microcystic adnexal carcinoma particularly when a small sample is obtained for analysis. The growth pattern of the basal cell carcinoma should be included in the pathology report as well as the presence of perineural involvement and excision margins particularly if less than 1 mm. Although the majority of basal cell carcinomas can be classified into the nodular, micronodular, superficial, sclerosing/morpheeic or infiltrative subtypes, it is not unusual to have a mixed pattern.

Immunoprofile

Occasionally in curette specimens, differentiation from small cell melanoma may require the use of a combination of light-weight keratin markers and S100 acidic protein to differentiate the tumours. BerEP4, a keratin marker, has been used to differentiate basal cell carcinoma from squamous cell carcinomas {2334}. CK20, a marker for Merkel cells, has been used to differentiate some forms of trichoblastoma, trichoepithelioma or fibroepitheliomas as these have scattered CK20 positive Merkel cells compared to basal cell carcinoma where they are rare or absent {13,2104}.

Prognosis and predictive factors

Basal cell carcinomas are locally invasive tumours and metastases occur in

less than 1 in 10,000 tumours {1440, 1950,2443}. Morbidity is increased with deeply invasive tumours which may extend into the deep tissue to bone and follow fusion planes particularly on the face where they follow nerves through bony channels. Morbidity also increases with neglected tumours that may measure more than 10 cm in diameter and have been described as giant basal cell carcinomas {1502,2009}. Multiple recurrences with deep residual tumour on the head may be associated with particular morbidity as basal cell carcinomas can ultimately penetrate the cranium. Increased recurrences are associated with infiltrative, morpheeic and micronodular basal cell carcinomas as surgical margins may be underestimated {639, 1940}. The possibility of the BCNS should be considered in children who develop BCCs. Families can be screened for mutations of the PTCH1 gene. Low bcl-2 protein expression has been found to correlate with clinically aggressive basal cell carcinomas with infiltrative, sclerosing/morpheeic patterns as compared to superficial and nodular tumours {296,1883}.

BCC recurrences are more common in lesions on the nose and nasolabial fold, but this may be in part due to the difficulty in achieving adequate margins in these sites {638,651}. Tumours recurring after radiotherapy are usually aggressive and infiltrative {2209}. Lesions which metastasize are usually large, ulcerated,

deeply infiltrating and recurrent {70}. The risk of further primary BCCs is increased by male gender, age over 60 years and truncal site {1208,1378}.

Rarely, extensive perineural invasion is seen in infiltrative primary BCCs of the face, presenting life-threatening complications of CNS extension {317,946}. Distance to the closest resection margin is an important predictor of BCC recurrence {639}.

Superficial basal cell carcinoma

ICD-O code

8091/3

Clinical features

This variant appears as erythematous patches that are often multiple and may vary from a few millimetres to over 10 cm in diameter. A fine pearly border or central superficial erosions with a history of contact bleeding may be present. Areas of regression may appear as pale patches or fibrosis. This variant makes up 10-30% of basal cell carcinomas and occurs most frequently on the trunk.

Histopathology

The histopathology consists of superficial lobules of basaloid cells which project from the epidermis or from the sides of follicles or eccrine ducts into the dermis and are surrounded by loose myxoid stroma. The lobules are usually confined

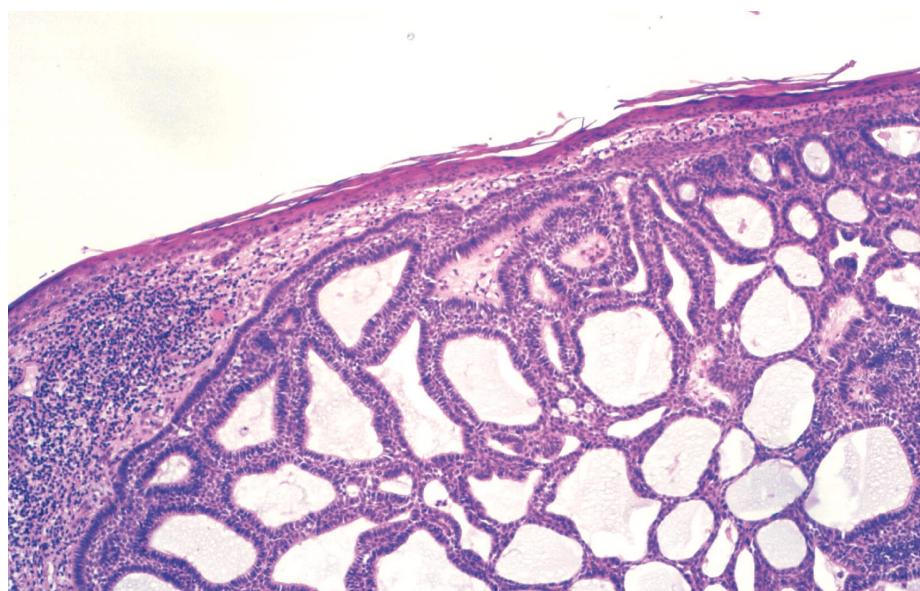


Fig. 1.3 Nodular BCC. Cribriform nodular basal cell carcinoma.

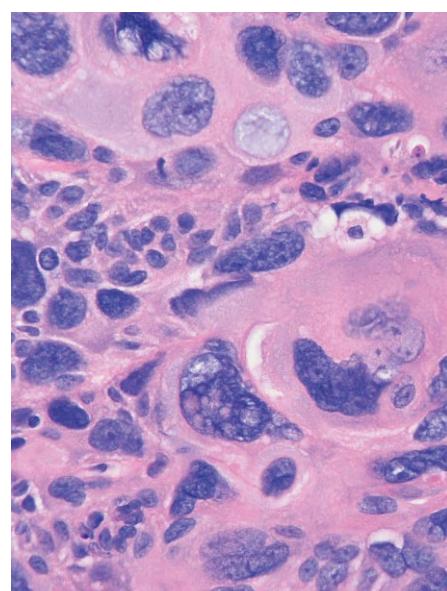


Fig. 1.4 Nodular BCC with monster giant cells.

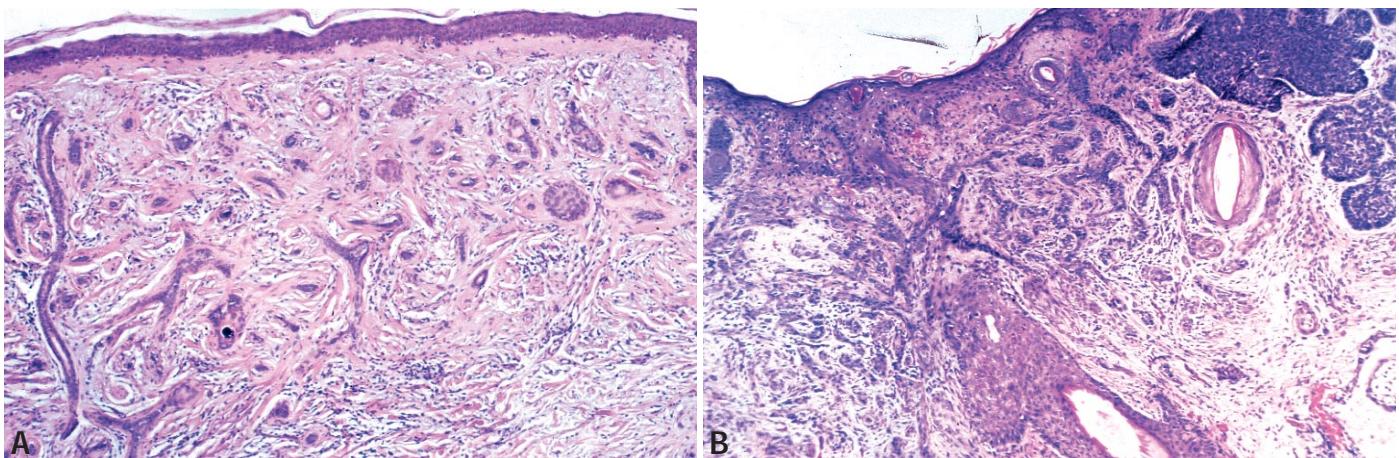


Fig. 1.5 A Infiltrative basal cell carcinoma. B 0172.Mixed nodular and infiltrative basal cell carcinoma.

to the papillary dermis. Some examples of superficial basal cell carcinoma appear multifocal on vertical sections but may be connected by a stroma when reconstructed by three-dimensional techniques using digital image analysis. There are, however, examples of multi-focal superficial basal cell carcinoma where the lobules are separated by large distances and represent discrete tumours that are truly multifocal and may measure only a few millimetres in diameter. Mixed patterns with a nodular, micronodular or infiltrative component may be seen in some tumours.

Nodular basal cell carcinoma

ICD-O code 8097/3

Clinical features

Nodular (solid) basal cell carcinomas often appear as elevated pearly nodules

associated with telangiectasia but may become ulcerated or cystic. Endophytic nodules may present as flat indurated lesions. Haemorrhagic lesions may resemble haemangiomas or melanoma when pigmented. Nodular basal cell carcinomas make up 60-80% of tumours and occur most frequently on the head.

Histopathology

Histopathology shows large lobules of basaloid cells ("germinative cells") with peripheral palisading nuclei that project into the reticular dermis or deeper. The lobules may have associated mucinous degeneration with cysts or have an adenoid (cribriform) pattern. Some nodules may have an organoid appearance with smaller basaloid lobules that are connected by loose fibromucinous stroma. The periphery of such nodules should be scanned to ensure that an outlying micronodular pattern has not developed.

Micronodular basal cell carcinoma

ICD-O code 8090/3

Clinical features

Micronodular basal cell carcinoma presents as elevated or flat infiltrative tumours. The most common site is the back.

Histopathology

This variant has small nodules that permeate the dermis {1010}. Individual nodules may appear to be separated by normal collagen. The tumour nodules may approximate the size of follicular bulbs and form subtle extensions into deep tissue. In contrast to nodular basal cell carcinoma the surgical margins of micronodular basal cell carcinoma may be underestimated. Perineural extension may be seen.

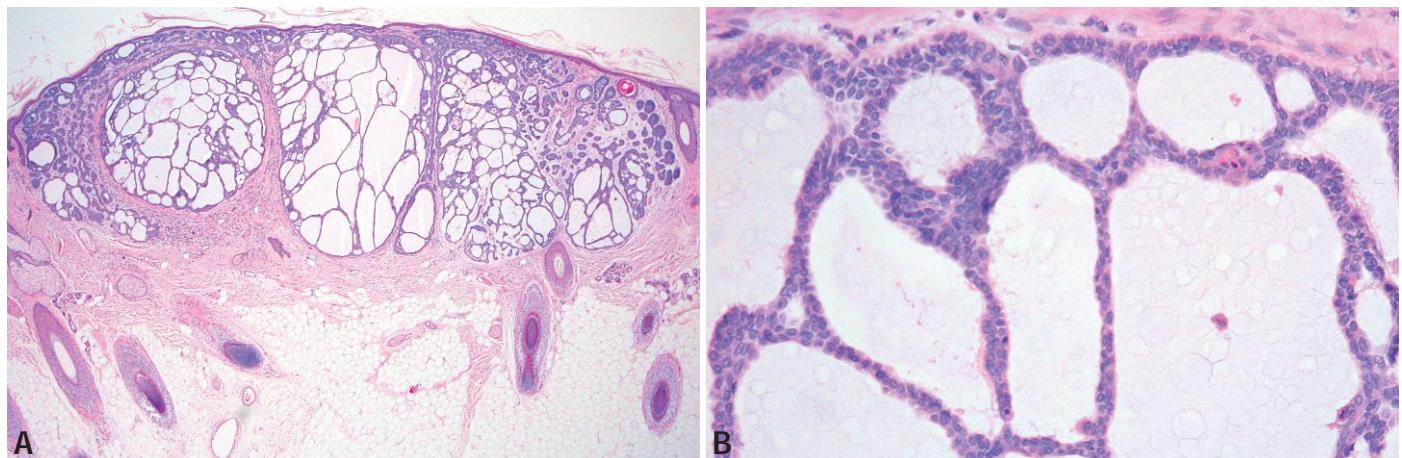


Fig. 1.6 Nodular cystic BCC A There are well circumscribed cystic nodules of atypical basaloid cells pushing into the deep dermis in a nodular pattern. B High power view of nodulocystic basal cell carcinoma showing cribriform cystic spaces filled with stromal mucin.



Fig. 1.7 Fibroepithelial basal cell carcinoma (fibroepithelioma of Pinkus).

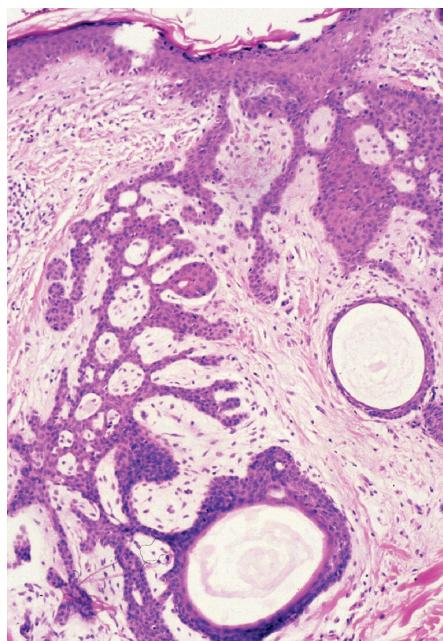


Fig. 1.8 BCC with adnexal differentiation; basaloid follicular hamartoma.

Infiltrating basal cell carcinoma

Definition

This variant of BCC is composed of thin strands, cords and columns of basaloid cells that infiltrate between the collagen bundles of the dermis and may extend into deeper tissues.

ICD-O code 8092/3

Clinical features

The infiltrative basal cell carcinoma presents as a pale, indurated poorly-defined plaque. These tumours are usually found on the upper trunk or face. Paraesthesia or loss of sensation may develop rarely as a manifestation of perineural extension, particularly in lesions on the face. This variant is important in that the margins at the time of surgery may be frequently underestimated.

Histopathology

Infiltrative patterns of basal cell carcinoma appear as strands, cords and columns of basaloid cells with scant cytoplasm. Peripheral palisading and retraction spaces are usually not seen. There is no fibrosis/sclerosis as seen in the sclerosing/morphoeic variant. The infiltrative pattern is particularly associated with perineural invasion. Low molecular-weight keratin markers are useful in

highlighting subtle groups of tumour cells (that may consist of 1-2 keratinocytes on cross section), in assessing clearance of the tumour and in confirming perineural involvement.

Differential diagnosis

Due to the cord-like arrangement of this variant there is a morphological overlap with the tumour pattern seen in microcystic adnexal carcinoma (sclerosing sweat duct carcinoma), desmoplastic squamous cell carcinoma and desmoplastic trichoepithelioma.

Fibroepithelial basal cell carcinoma

Definition

This variant of BCC is characterised by a unique clinicopathological presentation and an indolent behaviour.

ICD-O code 8093/3

Synonyms

Fibroepithelioma of Pinkus, Pinkus tumour

Clinical features

These tumours usually appear as an elevated flesh coloured or erythematous nodule that may resemble a seborrhoeic keratosis or acrochordon. The lesions are

most often found on the back and are rarely multiple {1834}. Prior radiotherapy may predispose to these tumours.

Histopathology

The histopathology is characterised by an arborising network of cords of basaloid cells that extend downwards from the epidermis and create a fenestrating pattern. There are strands of basaloid cells that surround fibrovascular stroma. Ductules may be present in some of the cords which may represent extension of the tumour down pre-existing eccrine ducts {2263}. The cords also are associated with small follicle-like bulbs which project into the surrounding connective tissue.

Histogenesis

Fibroepitheliomas, like BCCs, may be best classified as a form of appendageal tumour. These tumours have mutations of the PTCH1 gene. In some fibroepitheliomas transition to classical basal cell carcinomas may be seen, and this conversion may reflect a further mutation. A variant of fibroepithelioma with extra-mammary Paget's cells has been described in the perianal area {2461}.

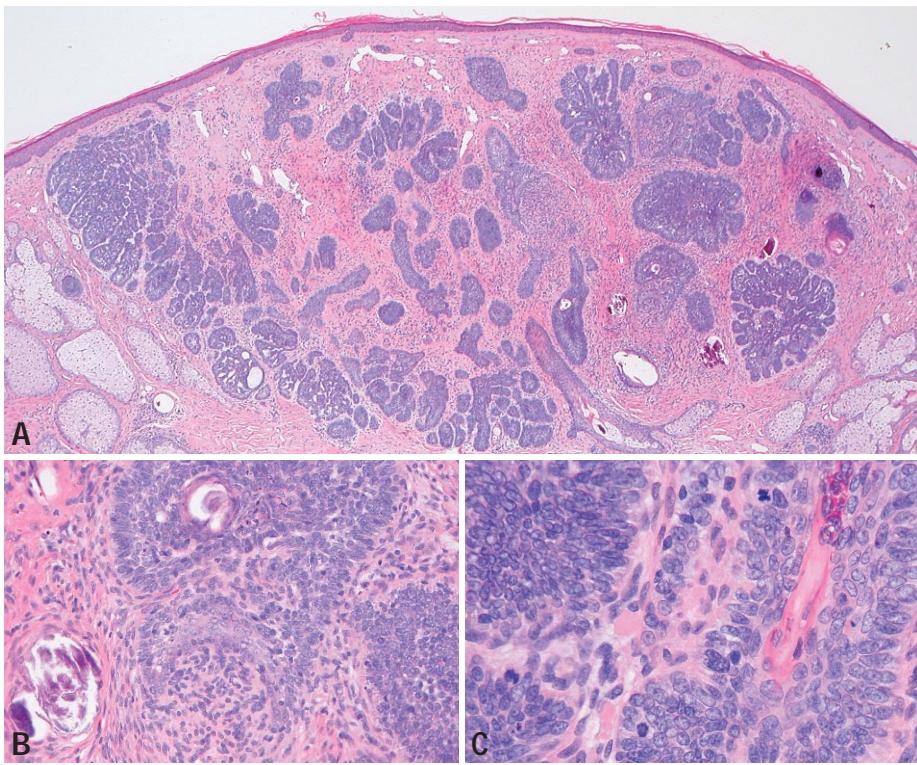


Fig. 1.9 Basal cell carcinoma, nodular type, with follicular differentiation. **A** The overall view shows a resemblance to typical nodular basal cell carcinoma, with the addition of a cellular fibrous stroma. **B** There is follicular bulbar differentiation in parts of the tumour, with formation of hair bulb accompanied by mesenchymal bodies. Focal dystrophic calcification. **C** 1603 High power view showing groups of atypical basaloid cells with peripheral palisading with trichohyaline granules and abrupt trichilemmal keratinization.

Basal cell carcinoma with adnexal differentiation

Definition

This variant is characterized histologically by adnexal differentiation in a BCC.

ICD-O code

8098/3

Clinical features

This variant has no distinguishing clinical features.

Histopathology

This variant is characterized by the presence of adnexal differentiation including basaloid buds, ductal, sebaceous and trichilemmal elements. Follicular differentiation may be prominent in more superficial BCCs. Eccrine or apocrine differentiation has also been observed in some basal cell carcinomas [997,2022]. It is important to distinguish such tumours from sweat gland carcinomas which have an increased risk for metastases. Some forms of adnexal basal cell carcinomas show overlap and may be better

classified as benign adnexal tumour such as a basaloid follicular hamartoma, trichoepithelioma, trichoblastoma or trichilemmoma.

Histogenesis

The cytokeratin profile of basal cell carcinoma is essentially identical to that of trichoblastomas (immature trichoepithelioma) and developing fetal hair follicles linking all basal cell carcinomas to the pilosebaceous pathway of differentiation [2086]. It has been proposed that basal cell carcinoma be renamed trichoblastic carcinoma [1623].

Prognosis and predictive factors

These patterns of adnexal differentiation do not appear to have any prognostic implications.

Basosquamous carcinoma

Definition

Basosquamous carcinoma is a term used to describe basal cell carcinomas that are associated with squamous differentiation [285,2102].

ICD-O code

8094/3

Synonyms

Metatypical carcinoma, basosquamous cell carcinoma

Clinical features

This variant has no distinguishing clinical features.

Histopathology

The tumour cells have more abundant cytoplasm with more marked keratinization than typical basal cell carcinomas. The nuclei have vesicular chromatin with pleomorphism and palisading may be focally lost. Some examples of this variant may merge with sebaceous carcinoma as lipid vacuoles or ducts may be focally apparent. This tumour may also have central fibrosis and a radiating peripheral rim of infiltrative cells extending into the deep dermis or subcutis.

Prognosis and predictive factors

This variant has a more aggressive behaviour and has been associated with regional or widespread metastases [1525].

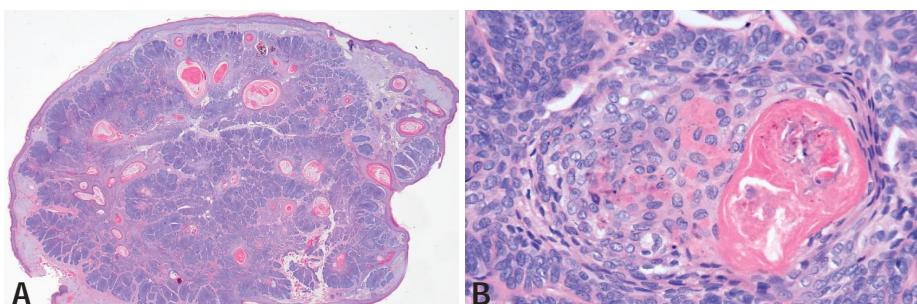


Fig. 1.10 Basal cell carcinoma, keratotic type. **A** Prominent keratin horn cysts in the center of the tumour nests. **B** Detail of trichilemmal keratinization.

Keratotic basal cell carcinoma

Definition

This variant is characterized by the presence of prominent keratin formation (horn cysts) in the centre of tumour islands.

ICD-O code

8090/3

Clinical features

This variant characteristically appears pearly and may be studded with small keratin cysts (milia).

Histopathology

These tumours share the overall architectural features of a nodular BCC. Keratinization may be laminated and infundibular in type or hyaline and trichilemmal in type or consist of keratinised shadow cells representing pilomatrixomal differentiation {66}. Dysrophic calcification is frequently present. Trichilemmal keratin may be associated with accentuated apoptosis in surrounding tumour cells and the presence of pale keratinocytes.

Differential diagnosis

This variant is distinguished from basosquamous carcinoma by the presence of numerous, superficial small keratin cysts. Basosquamous carcinoma is usually larger and less well circumscribed.

Other variants

Other variants account for less than 10% of all basal cell carcinomas. Many of them do not have distinctive clinical features.

Cystic

One or more cystic spaces, of variable size, are present near the centre of the tumour nests. There is sometimes increased mucin between the cells bordering the central space {2112}.

Adenoid

There are thin strands of basaloid cells in a reticulate pattern. Stromal mucin is often present. The adenoid type may occur in association with the nodular (solid) type.

Sclerosing / morpheiform

Strands and nests of tumour cells are

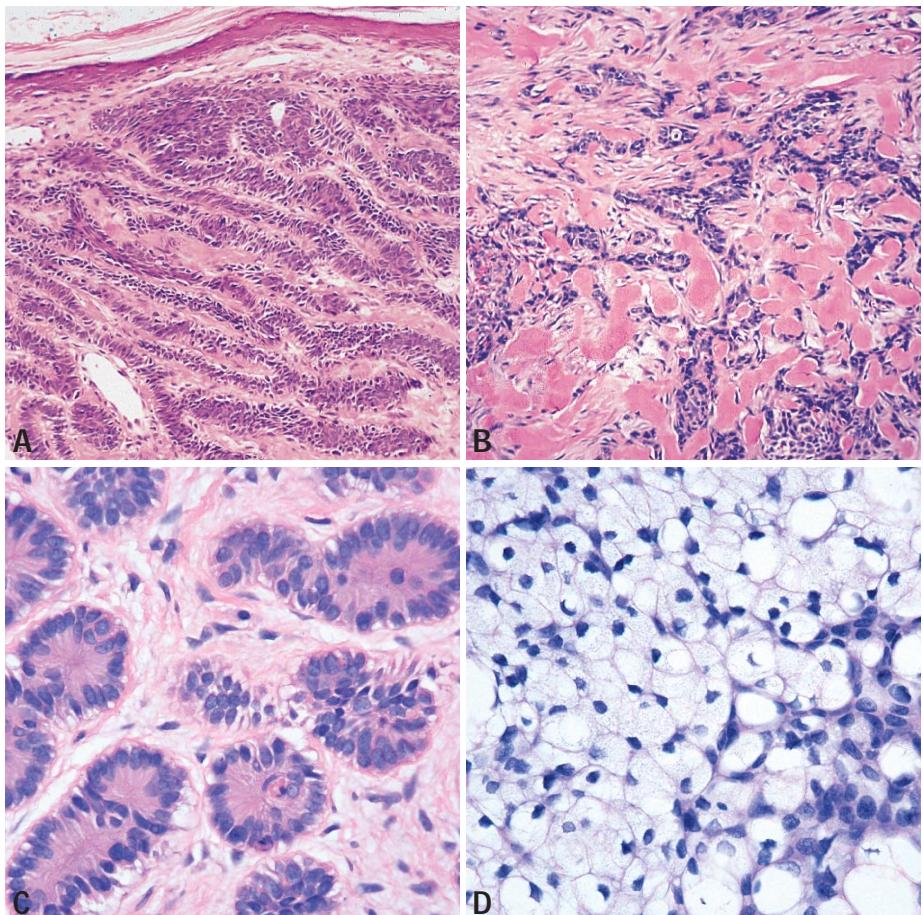


Fig. 1.11 Basal cell carcinoma (BCC). **A** Adenoid BCC. **B** Morpheiform BCC. **C** BCC with rosettes. **D** BCC with sebaceous differentiation.

embedded in a dense fibrous stroma {1932}. Some authors use the term morpheaic for any BCC with a fibrous stroma, while others restrict it to those BCC's with keloidal collagen bundles in the stroma {1923}. Enhanced procollagen gene expression has been found in this variant {1657}. Furthermore, smooth muscle α -actin is often present in the stroma. This variant usually presents as an indurated, pale plaque with a slightly shiny surface and indistinct margins.

Infundibulocystic

Often confused with the keratotic type, this variant is composed of small infundibular-like structures with a central keratinous plug and a peripheral component of basaloid cells {1218}. The nests are arranged in an anastomosing pattern. Multiple lesions are sometimes present {1178}.

Pigmented

Pigmentation may occur in several of the

variants including the nodular, micronodular, multifocal superficial and keratotic types. Melanocytes are scattered through the tumour nests, while melanophages are present in the stroma {1495}. This variant can be misdiagnosed clinically as malignant melanoma.

Miscellaneous

Other rare variants, subject to isolated case reports, include the clear-cell {165}, "signet-ring"-cell {1269,2503}, granular-cell {1659} and giant ("monster")-cell {680} types. Adamantoid {1403}, neuroendocrine {817} and schwannoid {2032} variants have also been described.

Squamous cell carcinoma

D. Weedon
M.B. Morgan
C. Gross
E. Nagore
L.L. Yu

Definition

Squamous cell carcinoma is a malignant neoplasm of epidermal (and mucous membrane) keratinocytes in which the component cells show variable squamous differentiation.

ICD-O code

8070/3

Epidemiology

Most cases arise on the sun-exposed skin of elderly people. They can occur on all cutaneous surfaces and mucous membranes, and in younger patients, especially those with a fair complexion who tan poorly. Its incidence in an Australian study was 166 cases per 100,000 of the population, the highest in the world [828]. It is relatively uncommon in Black people.

Etiology

Ultraviolet-B radiation is the most important etiological factor. Less important factors include radiation therapy, previous burns, arsenic, coal tar [1759]; industrial carcinogens, immunosuppression, HPV infection, and inflammatory lesions and ulcers of long standing (see Introduction). Organ transplant recipients are particularly prone to develop these tumours. Most of the fatal cases have been reported from Australia, suggesting that sunlight, which also has a profound effect on the cutaneous immune system plays a role in the formation of these aggressive tumours [1974]. HPV infection is commonly found in these immunosuppressed patients [264].

Localization

Most SCCs arise in areas of direct exposure to the sun, such as the forehead, face, ears, scalp, neck and dorsum of the hands. The vermillion part of the lower lip is another common site.

Clinical features

Squamous cell carcinomas present as shallow ulcers, often with a keratinous crust and elevated, indurated surrounds, or as plaques or nodules. The surround-

ing skin usually shows changes of actinic damage.

Histopathology

Squamous cell carcinoma consists of nests, sheets and strands of squamous epithelial cells which arise from the epidermis and extend into the dermis for a variable distance. The cells have abundant eosinophilic cytoplasm and a large, often vesicular, nucleus. There are prominent intercellular bridges. There is variable central keratinization and horn pearl formation, depending on the differentiation of the tumour.

The degree of anaplasia in the tumour nests is used to grade the tumours. A rather subjective assessment is usually made using the categories of 'well,' 'moderately' and 'poorly' differentiated. Most squamous cell carcinomas arise in solar keratoses and evidence of this lesion is usually present at the periphery of the invasive tumour.

Squamous cell carcinomas occasionally infiltrate along nerve sheaths, the adventitia of blood vessels, lymphatics, fascial planes and embryological fusion plates [218]. The presence of perineural lymphocytes is a clue to the likely presence of perineural invasion in deeper sections [2289].

There may be a mild to moderate chronic inflammatory cell infiltrate at the periphery of the tumours. This infiltrate sometimes includes eosinophils [1455].

Rare histological variants of SCC include clear-cell [1344], signet-ring [1557], pigmented [451], basaloid [573], inflammatory, infiltrative [1395], desmoplastic [1546] and rhabdoid [1534] types.

The cells in SCC are positive for epithelial membrane antigen and cytokeratin. The keratins are of higher molecular weight than those found in basal cell carcinoma [1672].

Prognosis and predictive factors

The majority of squamous cell carcinomas are only locally aggressive and are cured by several different modalities [1656]. SCC developing in patients who

are immunocompromised (including those infected with the human immunodeficiency virus [1704]), are usually more aggressive. Tumours with deep invasion, poor differentiation, perineural invasion and acantholytic features are more likely to recur or metastasize. Narrow surgical margins are another risk factor for recurrence [2389].

The clinical setting in which the SCC arises also influences the risk of metastasis. Tumours arising in sun-damaged skin have the lowest risk, in the order of 0.5% or less, while for those arising in skin not exposed to the sun, the risk is 2-3%. The risk is further increased for tumours arising in Bowen disease [1203], on the lip, vulvar, perineal and penile skin and in a Marjolin ulcer, radiation scar or thermal burn. Tumour thickness is a prognostic variable, just as it is for melanoma. SCCs less than 2 mm in thickness rarely metastasize, while those between 2 and 5 mm thick are of intermediate risk (about 5%). Tumours greater than 5 mm in thickness have a risk of metastasis of about 20% [1254]. Tumours greater than 2 cm in diameter are more likely to recur and metastasize than smaller lesions [1985].



Fig. 1.12 Squamous cell carcinoma in an elderly male with delayed medical treatment. This is an unusually large neoplasm which spread to the regional lymph nodes.

Acantholytic squamous cell carcinoma

Definition

Acantholytic squamous cell carcinoma (ASCC) is a histologic variant of cutaneous squamous cell carcinoma (SCC) that is histologically defined by loosening of the intercellular bridges resulting in acantholysis. These tumours may present as intraepidermal (*in-situ*) or invasive SCC.

ICD-O code 8075/3

Synonyms

Adenoid squamous cell carcinoma, pseudoglandular squamous cell carcinoma

Epidemiology

The acantholytic variant accounts for 2-4% of all cutaneous SCC {1149,1687, 1819,2549}. The age range is wide but it usually affects aged individuals with a male predominance.

Etiology

As in conventional SCC, ultraviolet light constitutes the most important etiologic risk factor.

Localization

The tumour involves predominantly the skin of the head and neck region, particularly on and around the ears {1149, 1687,1819,2549}.

Clinical features

ASCC presents similarly to conventional SCC, as a slowly growing scaly and occasionally ulcerated papule/plaque on the sun-exposed skin.

Histopathology

Invasive lesions typically show a thickened, and/or ulcerated epithelium. Scanning magnification reveals a flattened thinned, normal or hyperplastic epidermis with or without asymmetric and infiltrating dermal tumour islands. At intermediate power, prominent suprabasilar or intratumoural acantholysis is seen. Zones of acantholysis are capable of producing large intra-epidermal cavities. Acantholytic areas may extend down adjacent follicular structures involving the follicular epithelium and rarely, circumscribe the follicle simulating a glandular arrangement. Acantholytic foci may also produce a pseudovascular pattern mimicking angiosarcoma (pseudovascular SCC) {139,1675,1688}. At high power typical features of squamous malignancy are identified including dyskeratosis, keratinocytic atypia, consisting of an increased nuclear-to-cytoplasmic ratio and nuclear hyperchromasia, altered maturation within the epithelium, and increased typical and atypical mitotic figures.

Immunoprofile

The lesional cells in ASCC stain for cuta-

neous epithelial markers that include high molecular weight keratins such as AE-2/3. Involucrin, vimentin and EMA immunostains may also be positive {1808,2011}. Low-molecular weight keratins such as AE-1, CAM 5.2 are typically negative. Various intercellular peptides have been invoked in the pathogenesis of acantholysis including the intercellular adhesion molecule syndecan, E-cadherin and the anhidrotic ectodermal dysplasia gene product {183,1635}. It has also been recently shown that decreased TP53 and PCNA expression correlated with a decrement in desmosomes seen ultrastructurally {1889}.

Differential diagnosis

The changes described above constitute an important histologic means of separating this entity from acantholytic disorders. The differential also includes true adenosquamous cell carcinoma of the skin that exhibits squamous and glandular differentiation on ultrastructural examination and histochemical staining {2482}.

Prognosis and predictive factors

The behaviour of ASCC like other SCCs is depth-dependent and may be more aggressive than conventional SCC {461, 1097,1149,1687,1819,1985}. *In-situ* lesions are capable of recurrence and in up to 10% of cases, may show micro-invasion. The overall rate of metastases with lesions greater than 2.0 cm of invasion ranges from 5-19%.

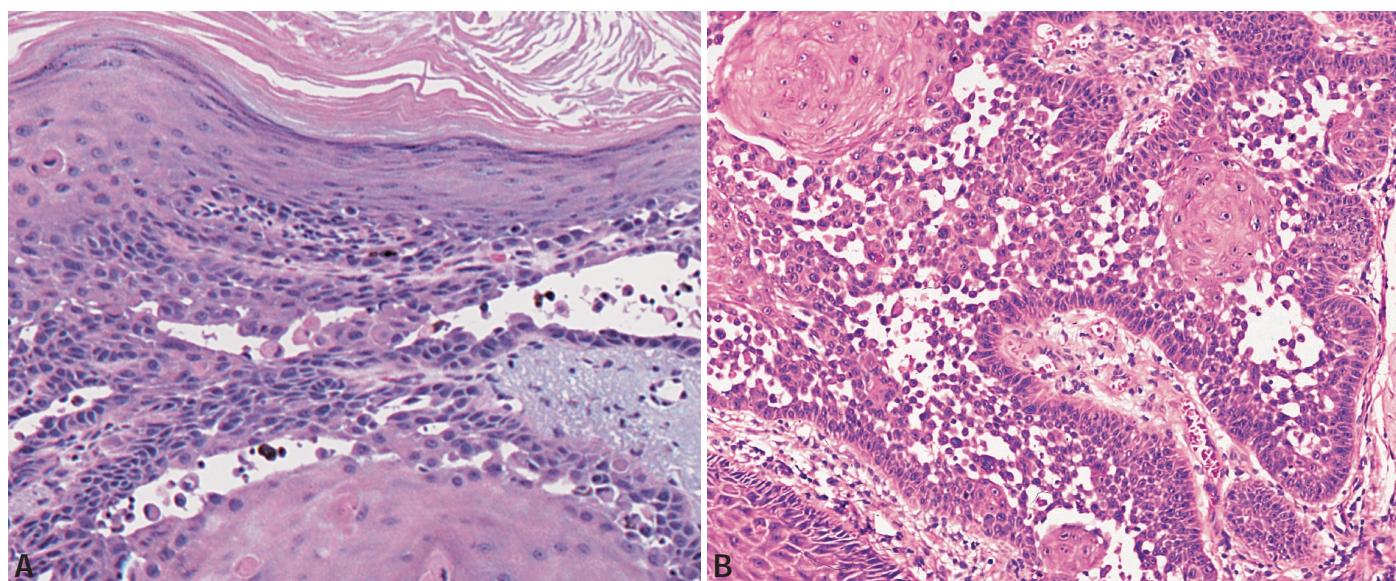


Fig. 1.13 A Acantholytic SCC, Intermediate-power photomicrograph depicting acantholysis extending down adjacent follicle epithelium. B Squamous cell carcinoma (acantholytic)

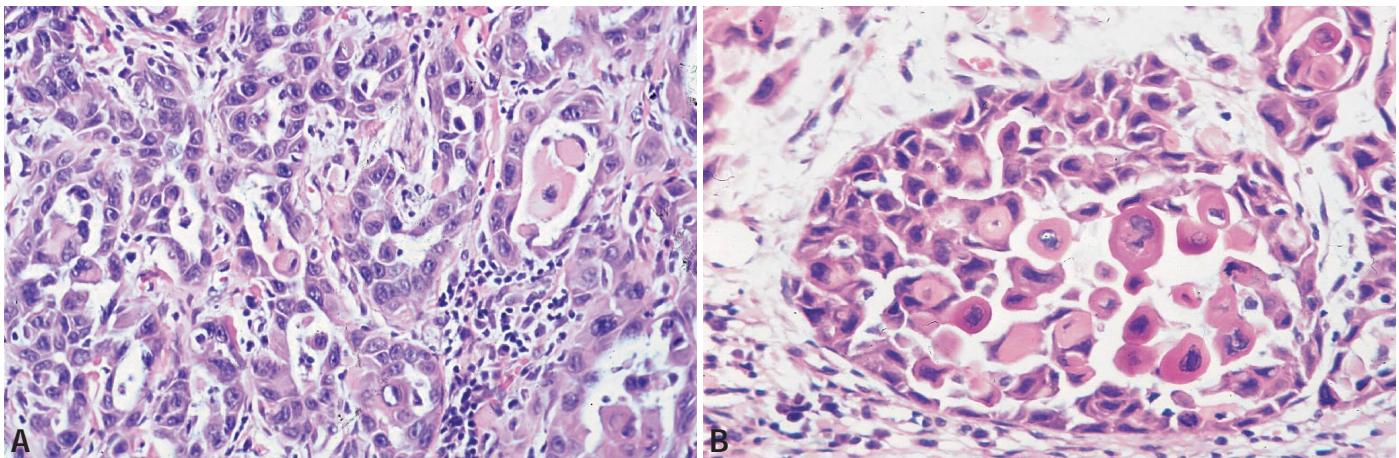


Fig. 1.14 Squamous cell carcinoma (acantholytic) A, B Note the pseudoglandular pattern and the loss of cohesion between tumour cells.

Spindle-cell squamous cell carcinoma

Definition

This is an uncommon variant of squamous cell carcinoma that exhibits a prominent spindle cell morphology.

ICD-O code 8074/3

Etiology

Lesions usually arise in sun-damaged or irradiated skin. A case has been reported in association with lichen sclerosus of the vulva {2057}. The incidence of this variant may be higher in immuno-suppressed patients.

Clinical features

Spindle-cell squamous cell carcinoma presents as a plaque or nodule on the skin. It may be clinically indistinguishable from the more usual type of squamous

cell carcinoma. Sometimes there is a history of rapid growth.

Histopathology

It may be composed entirely of spindle cells, or have a variable component of more conventional squamous cell carcinoma. The spindle cells have a large vesicular nucleus and scanty eosinophilic cytoplasm, often with indistinct cell borders. There is variable pleomorphism, usually with many mitoses.

Differential diagnosis

It may be difficult to separate from other cutaneous spindle cell neoplasms including spindle cell melanoma, atypical fibroxanthoma and, less often, leiomyosarcoma. Some cases can only be confirmed ultrastructurally, as all keratin markers are negative {2180}. CK5/6 is positive in two-thirds of all cases, a higher figure than obtained with AE1/3,

CAM5.2 or MNF116. Some tumours may coexpress cytokeratin and vimentin, suggesting metaplastic change to a neoplasm with mesenchymal characteristics {1116}.

Prognosis and predictive factors

Spindle-cell squamous cell carcinoma is a poorly differentiated variant of squamous cell carcinoma that may be associated with an aggressive clinical course {2180}. These tumours account for slightly over one-third of cutaneous squamous cell carcinomas which metastasize {1985}. Metastases usually occur to the regional lymph nodes in the first instance.

Verrucous squamous cell carcinoma

Definition

Verrucous squamous cell carcinoma is a rare variant of well-differentiated squamous cell carcinoma with low malignant potential.

ICD-O code 8051/3

Synonyms

Oral florid papillomatosis, Ackerman's tumour {32,348}, epithelioma cuniculatum {41,2096,2108}, giant condyloma acuminatum, Buschke-Löwenstein tumour {359,1347,1947,2124,2570}, papillomatosis cutis carcinoides {218,870, 2108}.

Epidemiology

Verrucous carcinoma comprises 2-12%



Fig. 1.15 Verrucous squamous cell carcinoma



Fig. 1.16 Verrucous squamous cell carcinoma

of all oral carcinomas, and is found predominantly in men (age peak in 5th decade, range 34-85) {348}. Verrucous carcinoma of the extremities (epithelioma cuniculatum) most often affects men in the 6th decade {2108}. The incidence of the genital type (Buschke-Löwenstein tumour) varies between 5- and 24% of all penile cancers; the tumour tends to occur in men younger than 50 years (range 18-86) {218}.

Etiology

Leading theories of the pathogenesis include chronic irritation, inflammation and impaired immune response {2096, 2108}. Important factors for the development of oral verrucous carcinomas are poor oral hygiene with ill-fitting dentures or decaying teeth, chewing of tobacco or betel nuts, and use of snuff. In genital lesions poor hygiene and phimosis play a major role. Other theories include HPV infection (mostly HPV 6, 11) {898} and chemical carcinogens {2096,2108}.

Localization

Common sites include buccal and retro-molar mucosa, gingiva, floor of mouth, tongue and hard palate. They also arise on the soles, rarely the palms and distal fingers, and on amputation stumps. Genital lesions occur primarily on the glans and prepuce of the penis {778, 2108,2570}. It is uncommon in the vagina and the perianal region {1347,1947, 2124}. Rare cases have been described on the scalp, face, back and extremities, sometimes associated with long-standing ulcerations or scars, especially in the pretibial area (papillomatosis cutis carcinoides) {218,870,2096,2108}.

Clinical features

These lesions show cauliflower-like appearance with exophytic and endophytic growth, and a papillomatous surface. They are pale in colour and sometimes have draining sinuses. Some are tender and painful, particularly on the sole of the foot. There is slow but relentless growth over the course of a long time {2570}.

Histopathology

In all cases a well-differentiated proliferative epithelial process is visible, the malignant nature of which may easily be overlooked, particularly if the biopsy is small and superficial. The squamous

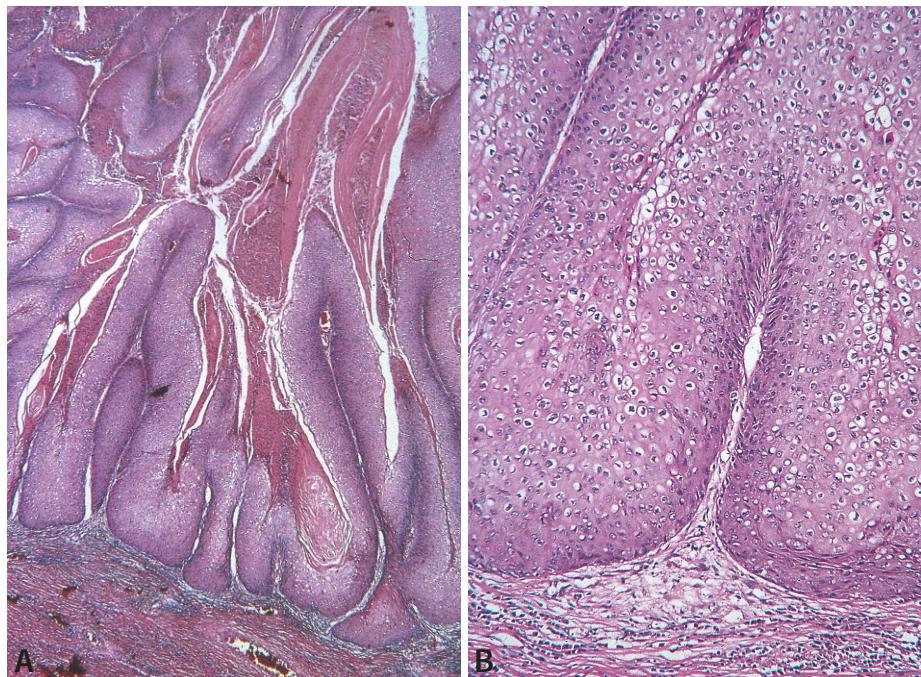


Fig. 1.17 Verrucous squamous cell carcinoma **A, B** Note the well-differentiated proliferative process and the bulbous nature of the squamous downgrowths.

epithelium shows an asymmetric exo- and endophytic growth pattern with pushing rather than destructive or infiltrative margins. Usually, there is deep penetration below the level of the surrounding epidermis / mucosa. Tumour cells exhibit only minimal atypia and very low mitotic activity. The presence of neutrophils is an important diagnostic clue; they may form small intraepidermal abscesses. Draining sinuses containing inflammatory cells and keratin debris may also be present. No foci of the usual squamous cell carcinoma should be found {1833}.

Differential diagnosis

The separation from benign reactive processes and SCC of the more usual type can be difficult. The presence of blunted projections of squamous epithelium in the mid and/or deep dermis is suspicious for verrucous carcinoma. The squamous downgrowths are bulbous. Small collections of neutrophils may extend into the tips. Clinicopathological correlation and adequate sampling are often helpful.

Precursor lesions

Oral lesions may develop in areas of previous leukoplakia, lichen planus, lupus erythematosus or candidiasis {218}.

Prognosis and predictive factors

If the tumour is completely excised, prognosis is excellent; after inadequate excision, the recurrence rate is high and the survival decreases. In long-standing cases or after irradiation and / or chemotherapy the biologic character of the disease may change into a metastasizing squamous cell carcinoma {1216}.

Pseudovascular squamous cell carcinoma

Definition

Pseudovascular SCC is an aggressive variant of SCC with marked acantholysis resulting in angiosarcoma-like areas {139,1688}.

ICD-O code

8075/3

Synonyms

Pseudoangiosarcomatous SCC, pseudoangiomatous SCC

Epidemiology

The tumour is exceedingly rare.

Clinical features

It usually presents as a circumscribed white-grey ulcer or a nodular tan-red/pink tumour, most often located on sun-

exposed areas of middle-aged or elderly patients.

Histopathology

It is characterized by areas of anastomosing cord-like arrays of polygonal or flattened tumour cells, with internal pseudolumina that contain detached tumour cells and amorphous basophilic material {550,1675,2558}. Erythrocytes may also be seen in pseudovascular spaces. Immunohistochemical examination is essential to differentiate it from angiosarcoma. Pseudovascular SCC is positive for one or more monoclonal antibodies to cytokeratin and consistently negative for CD31 and factor VIII-related antigen.

Differential diagnosis

In classical angiosarcoma vascular markers are positive, keratin staining is negative; in epithelioid angiosarcoma in addition to vascular markers epithelial markers are frequently expressed.

Prognosis and predictive factors

The prognosis is worse than it is for other variants of SCC, with a mortality up to 50%. Large size may confer a worse prognosis {1675}.

Adenosquamous carcinoma

Definition

Adenosquamous carcinoma is a rare variant of squamous cell carcinoma arising

from pluripotential cells related to acrosyringia, characterized by the formation of mucin secreting glands.

ICD-code

8560/3

Epidemiology

Most reported cases occurred on the head and neck of elderly patients, with male predominance {120,140,572, 1933,2482}. The penis can also be involved {120}.

Clinical features

It can present as an asymptomatic smooth surfaced dermal nodule or a large ulcerated deeply invasive tumour indistinguishable from squamous cell carcinoma or basal cell carcinoma.

Histopathology

The tumour consists of invasive tongues, sheets, columns and strands of atypical dyskeratotic squamous cells, merging with glandular structures with epithelial mucin secretion, which can be demonstrated by a PAS, mucicarmine or alcian blue stain at pH 2.5. The mucin is hyaluronidase resistant and sialidase sensitive. Intracytoplasmic neolumina containing targetoid mucin secretions can also be seen. The tumour cells are positive for cytokeratin and epithelial membrane antigen, whereas those cells forming glands stain with carcinoembryonic antigen. There may be connection between tumour cells and acrosyringia, as well as perineural invasion.



Fig. 1.18 Adenosquamous carcinoma of the ear. There are deeply invasive tongues, columns and strands of atypical dyskeratotic squamous cells abutting the cartilage.

Differential diagnosis

Adenosquamous carcinoma should be distinguished from mucoepidermoid carcinoma, which had been reported as adenosquamous carcinoma in early reports. Adenosquamous carcinoma has well formed glands with mucin secretion and no goblet cells. Mucoepidermoid carcinoma consists of polygonal squamous cells and goblet cells without glands. Signet ring squamous

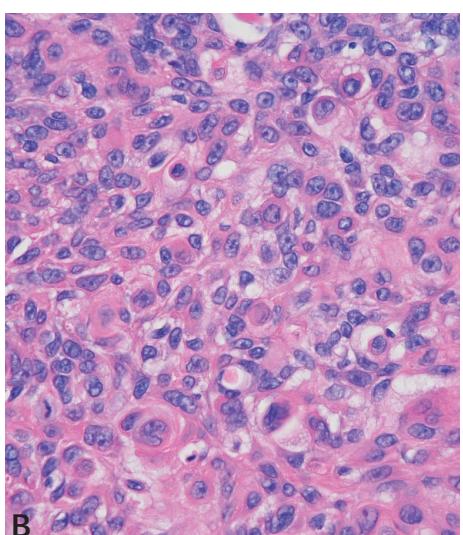
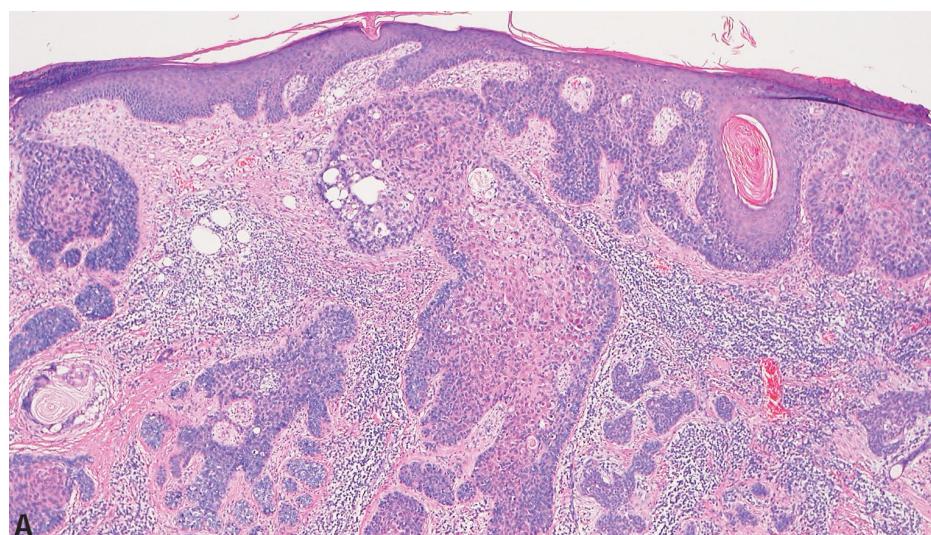


Fig. 1.19 Adenosquamous carcinoma. **A** Overt squamous differentiation in parts of the tumour. **B** Sheets of atypical dyskeratotic squamous cells from the squamous area of the tumour.

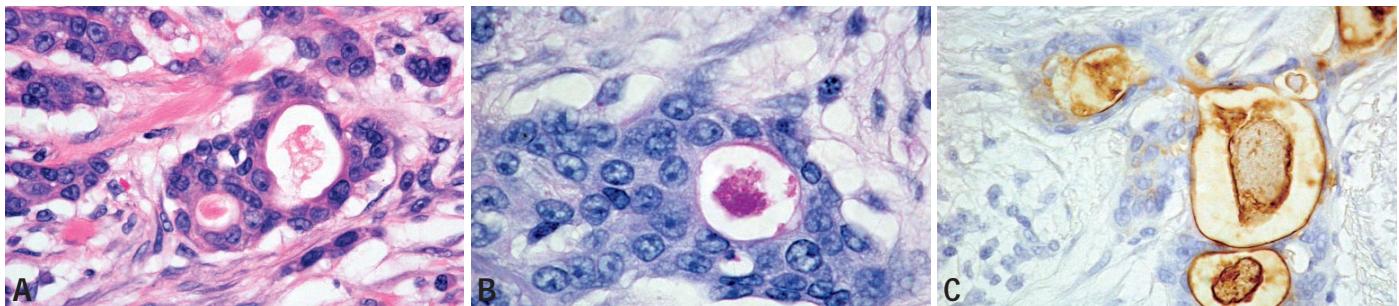


Fig. 1.20 Adenosquamous carcinoma. **A** Well formed glandular structures containing mucinous secretion in the glandular area of the tumour. **B** PAS stain. Intracytoplasmic targetoid PAS positive and diastase sensitive globules in the glandular areas of the tumour. **C** CEA immunohistochemical stain. Positive luminal staining in glandular structures.

cell carcinoma has foamy cytoplasmic mucin globules with displacement of the cell nucleus but no glands. Microcystic adnexal carcinoma (syringomatous carcinoma, sclerosing sweat duct carcinoma) shows a more ductal appearance with prominent tubular structures but no mucin secretion. Metastatic adenosquamous carcinoma from other primary sites such as the lung, salivary gland, female genital tract should also be excluded.

Prognosis and predictive factors

The tumours usually follow an aggressive course with the capacity for metastasis and local recurrence. Early superficially located tumours tend to have a better prognosis.

Bowen disease

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Definition

Bowen disease (BD) is a form of squamous cell carcinoma *in situ*. It is a distinct clinicopathologic entity of the skin and mucocutaneous junction.

ICD-O code 8081/2

Synonyms

Squamous cell carcinoma *in situ* (SCCIS), intraepidermal carcinoma, bowenoid dysplasia, bowenoid squamous carcinoma *in situ* (BSCIS), vulvar intraepithelial neoplasia (VIN III).

The terms bowenoid dysplasia and BSCIS are customarily applied to cutaneous and mucocutaneous lesions of the male and female external genitalia. BD is no longer used in gynaecological pathology. It has been replaced by the concept of vulvar intraepithelial neoplasia (VIN). The degree of epithelial atypia seen in BD corresponds to VIN, grade III (VIN III) {362,1580}.

Epidemiology

Bowen disease occurs predominantly in fair-complexioned Caucasian men, but both sexes are affected. One in five patients (20%) is a woman. The disease commonly affects patients in the 6-8th decades of life. However, the average age at onset of the disease is 48 years,

and the average age at first biopsy is 55 years. Both exposed and non-exposed skin sites are equally affected. The disease uncommonly affects black skin, in which it is found more commonly on non-sun-exposed areas.

Etiology

The exact underlying cause of BD remains unclear, although multiple factors are likely to be responsible for it. Many lesions arise without an apparent cause. However, it is known that chronic sun damage disrupts normal keratinocytic maturation, causes mutation of the tumour suppressor gene protein (TP53) {375,1075}, and results in the development of keratinocytic atypia as seen in lesions of BD. The predilection for anatomic sites affected by BD on sun-exposed glabrous skin and lesions being reported more commonly in patients with a history of PUVA or UVB therapy {1410}, attest to the critical role of causal relationship between UV damage and BD. Ingestion of inorganic arsenic may play a role, as lesions of arsenical keratosis (As-K) may display identical histopathologic features to BD. A large number of cases of As-K with associated invasive carcinoma have been reported in a rural population using well water containing a high concentration of inorganic arsenic {2070}.

{2567,2572}. Human papillomavirus (HPV) genomes have been demonstrated by *in situ* hybridization in the nuclei of keratinocytes in the stratum malpighii and stratum corneum of the BD lesions. HPV types 16 and 18 have been linked to lesions of genital BD and non-condylomatous genital warts, i.e., bowenoid papulosis {1098}. HPV is less commonly associated with nongenital BD. HPV types 15 and 16 have been identified in some cases of BD of the distal extremities. Evidence of other papillomavirus types, including HPV31, 54, 58, 61, 62 and 73, have also been identified in some cases of BD. Aberrations in local and systemic immunity, trauma, chronic irritation, mutagenic factors, and tobacco exposure are other possible etiologies of BD.

Localization

Based upon a large series of 1001 biopsy-proven BD in Australia, most lesions occurred on a sun-exposed glabrous area {1315}. About one-third (33%) of the lesions occurred in the head and neck areas, especially the face. Men had predominance of lesions on the scalp and ears, whereas women had a predominant involvement of the legs and cheeks. BD rarely affects the nail bed and perungual area {2070}.

Clinical features

The classic appearance of cutaneous BD is a single or multiple erythematous, rounded to irregular, lenticular, scaly, keratotic, fissured, crusty, nodular, eroded, pigmented patches or plaques. The plaques are devoid of hair, and usually appear sharply demarcated from the surrounding unaffected skin. Areas of normal-appearing skin may occur within the boundaries of larger lesions of BD. The plaques vary from 1-5 cm in overall dimensions. In intertriginous areas, BD may appear as moist patches without scale. In anogenital locations, the lesions appear polypoid or verrucoid, frequently pigmented. Erythroplasia of Queyrat (EPQ) presents as an asymptomatic,



Fig. 1.21 A Bowen disease. Sharply circumscribed, bright red plaque of erythroplasia of Queyrat (EPQ). B Bowen disease. Erythematous, scaly, fissuring plaques of BD on lower leg of a middle-aged woman.

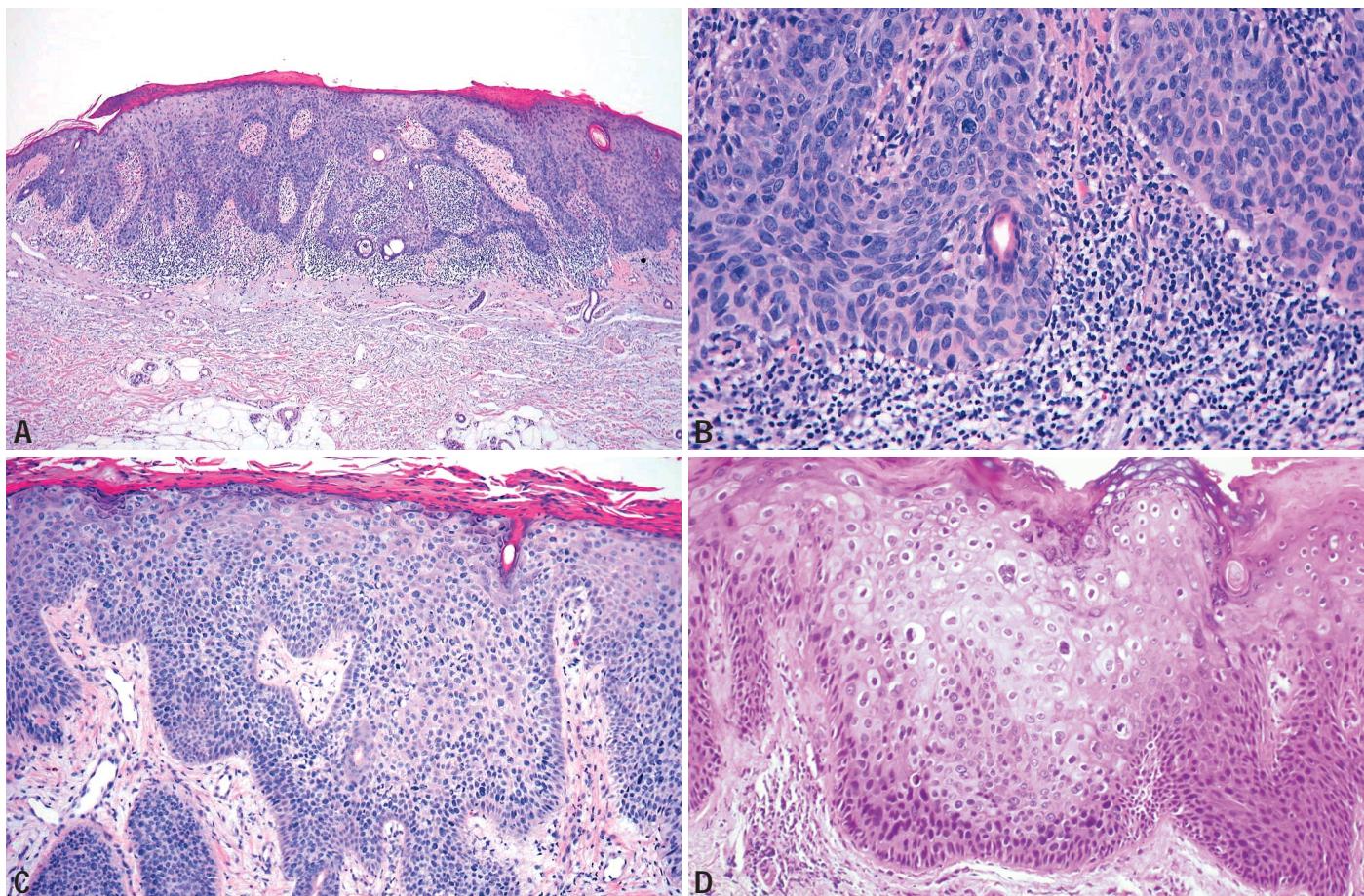


Fig. 1.22 Bowen disease (BD). **A** Low-power photomicrograph of BD. Note hyperkeratosis, full-thickness of epidermal atypia, extensive pilar epithelial involvement, and a lichenoid upper dermal mixed chronic inflammatory infiltrate. **B** Atypical keratinocytes encircle an acrosyringium. **C** Atypical squamous cells extend along acrosyringia. **D** Prominent vacuolated atypical cells, focally mimicking koilocytotic change and pagetoid appearance seen in BD.

bright red, velvety to shiny, sharply circumscribed plaque. The mucocutaneous junction of the glans penis, coronal sulcus, or undersurface of the foreskin is involved, and lesions are usually found in older, uncircumcised men.

There are two clinical variants of BD: those involving glabrous skin, and those of the anogenital area. On the glabrous skin, BD manifests as asymptomatic, slowly enlarging, scaly patches or plaques. The average duration of the lesion is 6.4 years. Plaques of BD enlarge slowly, and expand centrifugally, sometimes for decades. Anogenital BD involves the mucocutaneous junction and adjacent mucosa. If untreated, 5–8% of patients may develop invasive carcinoma. The invasive carcinomas are larger (up to 15 cm), rapidly growing tumours that occur in pre-existing scaly plaques [1203].

The clinical entity of erythroplasia of Queyrat (EPQ) is regarded as BD of the

glans penis. Such lesions have a greater potential for developing into invasive carcinoma than does BD involving glabrous skin [875]. Although evidence for the association of BD and internal malignancies is reported in earlier studies, more recent population-based cohort studies do not confirm the link [484].

Histopathology

The typical low-power microscopic features of BD are hyperkeratosis, parakeratosis, hypo- or hypergranulosis, plaque-like acanthosis with increased cellularity, and a chronic inflammatory infiltrate in the upper corium. The epidermis exhibits loss of normal polarity and progression of normal surface keratinocytic maturation. A “windblown” appearance of crowding of atypical keratinocytes, with hyperchromatism, pale-staining to vacuolated cells, occasional multinucleated cells, individual cell keratinization (dyskeratosis), and abnormal mitoses are noted.

These changes are confined by an intact dermoepidermal basement membrane. Lesions of BD from hair-bearing areas invariably demonstrate involvement of the pilar acrotrichium, infundibulum, and sebaceous gland. In some lesions, prominent vacuolated atypical cells focally mimic koilocytotic viral cytopathic change and exhibit a pagetoid appearance. The acrosyringium is occasionally involved. An inflammatory infiltrate of lymphocytes, macrophages, and plasma cells is seen in the upper dermis. Capillary ectasia is commonly noted. Prominent solar elastosis is also present in lesions on sun-exposed skin. An invasive carcinoma arising in BD shows variable histologic differentiation, with squamous, basosquamous, pilar, sebaceous [1120], pilosebaceous, poorly-differentiated, and occasionally ductal features [1203,2016]. The atypical vacuolated keratinocytes are negative for cytoplasmic mucin; some, however, contain

glycogen. Melanin pigment may be present in the atypical cells, and in the pigmented genital lesions, melanophages are numerous. The abnormal keratinizing cells are intensely reactive with glucose-6-phosphate dehydrogenase. Ultrastructural changes of BD include decrease in tonofilament-desmosomal attachments, aggregated tonofilaments and nuclear substance, and absence of keratohyaline granules {1204}.

Differential diagnosis

Bowenoid solar keratosis differs from BD by its clinically smaller size, exclusive location on sun-exposed skin, and presence of superficial keratinocytic maturation. Bowenoid papulosis is distinguished from BD by its clinical appearance of multiple papular to coalescing lesions on the anogenital areas, and the typical microscopic salt and pepper distribution of atypical keratinocytes and mitoses in the affected cutaneous and mucocutaneous lesions, as well as frequent HPV positive koilocyotic cells {1790}. The pagetoid variant of BD is sometimes difficult to distinguish from extramammary Paget disease. In the latter, mucicarmine, Cam 5.2 and CEA positive tumour cells are present in the epidermis, individually or in small nests, forming glandular structures at the dermoepidermal junction. These features are absent in BD. The vacuolated cells in BD contain glycogen and not mucin. In malignant melanoma *in situ*, the basilar keratinocytes are replaced by neoplastic melanocytes. The presence of intercellular bridges and prominent dyskeratotic keratinocytes are features favouring the diagnosis of BD. Melanoma cells do not contain cytokeratins of 54 and 66 kilodaltons (kd); the reverse applies with the cells in BD.

Histogenesis

It has been suggested that BD most likely originates from germinal cells of the pilar outer root sheath and the pluripotential epidermal cells of the acrotrichium. This concept is substantiated by the findings of various types of histologic differentiation in carcinoma arising in BD {1120,1203,2016}. Using immunohistochemical localization of keratins and involucrin, the atypical cells of BD exhibit a diversity of differentiation {1093}.

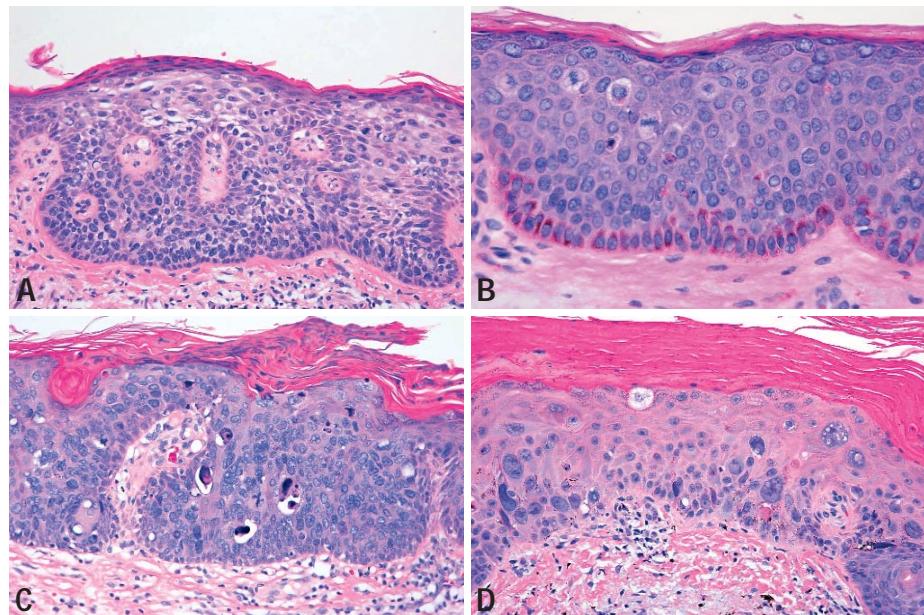


Fig. 1.23 Bowen disease. **A** Full thickness squamous cell atypia. **B** There is full thickness squamous cell atypia with apparent sparing of the basal keratinocytes and hyperpigmentation of the basal keratinocytes. **C** Full thickness squamous cell atypia with scattered bizarre keratinocytes. **D** Full thickness squamous cell atypia with marked nuclear pleomorphism.

Genetics

The atypical keratinocytes of BD contain large numbers of aneuploid cells {241}. Increased expression and mutation of TP53 observed in lesions of BD suggest that loss of normal TP53 tumour suppressor activity may be an important mechanism of oncogenesis in BD {375,1075,1946}. Allelic deletion of one or more 9q chromosome markers has been detected in occasional lesions of BD. However, no deletion of 9p markers was seen {1866}. There have been no clonal chromosomal abnormalities by cytogenetic analysis of cell cultures from BD {1003}.

Prognosis and predictive factors

Surgical excision with complete removal may cure BD. The origin of BD from pilar outer root sheath cells at the sebaceous gland level explains in part the high recurrence rate, following treatment with superficial curettage and desiccation, topical fluorouracil, and X-ray. Invasive adnexal carcinoma may develop in untreated plaques of BD of prolonged duration following expansive growth. The metastatic rate in these uncommon tumours was 18% and fatality was observed in 10% of cases in a large case series {1203}.

Bowenoid papulosis

Definition

Bowenoid papulosis is a clinicopathological entity characterised by the presence on the genitalia of solitary or multiple veruca-like papules or plaques with histology resembling full thickness epidermal dysplasia as seen in Bowen disease.

Synonyms

Multicentric pigmented Bowen disease, multifocal indolent pigmented penile papules

Epidemiology

Bowenoid papulosis occurs mainly in young individuals and although uncommon the incidence is increasing. There is a male predominance.

Etiology

The etiopathogenesis of this condition almost certainly favours linkage to human papillomavirus infection particularly oncogenic types 16, 18, 33,35 and 39. DNA sequences have been identified by various workers {908,1737,2113}. Consequently in females there is a higher incidence of abnormal cervical/vaginal smears both in affected patients and in partners of men with penile lesions. Whilst controversies regarding the bio-

logical potential of bowenoid papulosis exist, with the possibility of invasive malignancy, in most cases the clinical course is benign and some lesions regress.

Localization

Bowenoid papulosis was first described as a condition affecting the groin {1438}. It was later defined {1305,2447} as an entity involving the genitalia or perigenital areas. Isolated cases of extragenital bowenoid papulosis have been described {902,1147}.

Clinical features

The lesions are usually asymptomatic with variable clinical presentation: multiple generally small, round fleshy papules, isolated or confluent (2.0-20 mm), with a smooth papillomatous surface, sometimes with desquamation resembling lichenoid or psoriasiform dermatoses. The colour of lesions can vary from pink to reddish-purple to brown / black.

Histopathology

The histological features demonstrate epidermal atypia ranging from partial to full thickness atypia similar to *in situ* squamous cell carcinoma i.e. Bowen disease. On the genitalia changes may be termed vulvar intraepithelial neoplasia

(VIN) III or penile intraepithelial neoplasia (PIN) III by some pathologists {570}. There is loss of architecture. The basement membrane is intact. Mitoses are frequent, sometimes with abnormal forms often in metaphase. Dyskeratotic cells are also seen. Typical koilocytes are uncommon {908}. The stratum corneum and granular cell layer often contain small inclusion - like bodies which are deeply basophilic, rounded and surrounded by a halo.

Differential diagnosis

The basophilic bodies, together with the numerous metaphase mitoses, are the features which suggest a diagnosis of bowenoid papulosis rather than Bowen disease itself.

Histogenesis

A study based on histomorphology and DNA ploidy analysis has suggested that bowenoid papulosis is a form of low-grade squamous cell carcinoma *in situ* {269}. Electron microscopy has shown structures resembling viral particles {1274,1790} within the granular layer.

Somatic genetics

Many of the atypical keratinocytes of bowenoid papulosis not unlike Bowen disease, contain large numbers of aneuploid cells. Increased expression and

mutation of TP53 observed in lesions suggest that loss of normal TP53 tumour suppressor activity is likely to be an important mechanism of oncogenesis in bowenoid papulosis. To date, there have been no clonal chromosomal abnormalities by cytogenetic analysis of cell cultures from bowenoid papulosis.

Prognosis and predictive factors

Bowenoid papulosis appears in many cases to remain benign {1790} and spontaneous regression has occasionally occurred; however, close follow up is essential.

Actinic keratosis

C. James
R.I. Crawford
M. Martinka
R. Marks

Definition

A common intraepidermal neoplasm of sun-damaged skin characterized by variable atypia of keratinocytes.

Synonyms

Solar keratosis

Epidemiology

Actinic keratoses (AK's) usually present in older individuals. The fair-skinned, the freckled and those who do not tan easily are at increased risk. Lesions have developed in areas of vitiligo {2023, 2564}. The rate is higher in men because of greater sun exposure {1049}. In the Australian Caucasian population, AK's are discovered in 40-60% of individuals over 40 {789,1515}, rising to 80% in the seventh decade {1049}. Patients with Rothmund-Thompson, Cockayne and Bloom syndromes and xeroderma pigmentosum are at increased risk {791}.

Etiology

Both cumulative and intermittent sunlight exposure is implicated {790}. Ultraviolet B (UVB) is the most harmful, but a supplemental effect of ultraviolet A (UVA) is demonstrated {694}. AK's are increased after PUVA therapy {11}. UVB induces DNA thymidine dimer formation, which can target TP53, with impaired apoptosis



Fig. 1.24 Actinic keratosis on the face, presenting as a group of irregularly shaped small papules.

of damaged keratinocytes in cells with two TP53 mutations {1150,1396,1696, 2602}. Clonal proliferations of these cells form actinic keratoses and after further genetic damage, invasive SCC may develop. Ultraviolet light can act as an initiator and promoter of carcinogenesis {2602}. Epidermodysplasia verruciformis-associated HPV types have been discovered in AK's after renal transplantation {2354}.

Localization

Sun-exposed areas are involved: face, ears, balding scalp, dorsal hands, forearms and lateral neck {2218}.

Clinical features

Patients commonly present with multiple

persistent, asymptomatic erythematous lesions. Most measure less than 1 cm and are hyperkeratotic. Atrophic lesions predominate on the face. Thickening and tenderness may indicate the development of invasive carcinoma.

Macroscopy

Most lesions are circumscribed <1cm scaly macules or slightly elevated papules or plaques, ranging from erythematous to grey-brown with adherent yellow-brown scale. Some are larger, more irregularly shaped and pigmented {1128}, whilst others, particularly on the dorsal hands and forearms, are hyperkeratotic or verrucous {244}. A keratin horn may be produced.

Histopathology

Six types of AK are described: hypertrophic, atrophic, bowenoid, acantholytic, pigmented and lichenoid {233,1446}. Most lesions reveal parakeratosis and hypogranulosis. Disordered keratinocyte maturation with cytologic atypia is present, including nuclear enlargement, hyperchromasia, pleomorphism, nucleolar prominence, mitotic activity, dyskeratosis and cytoplasmic pallor. Grading as Keratinocyte Intraepidermal Neoplasia (KIN I, II and III) in a manner similar to that used for the uterine cervix {506} has

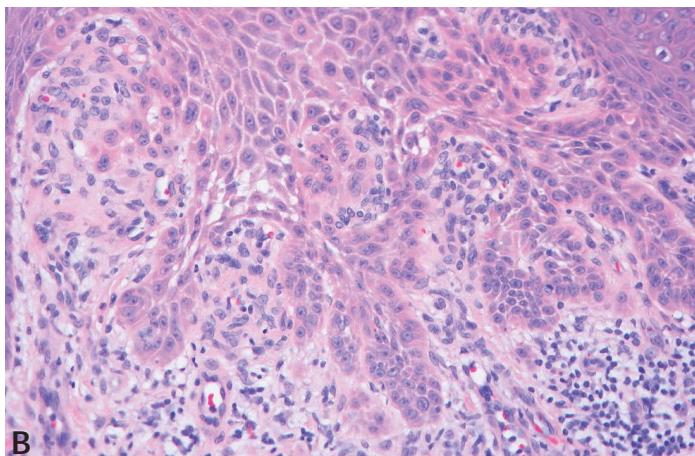
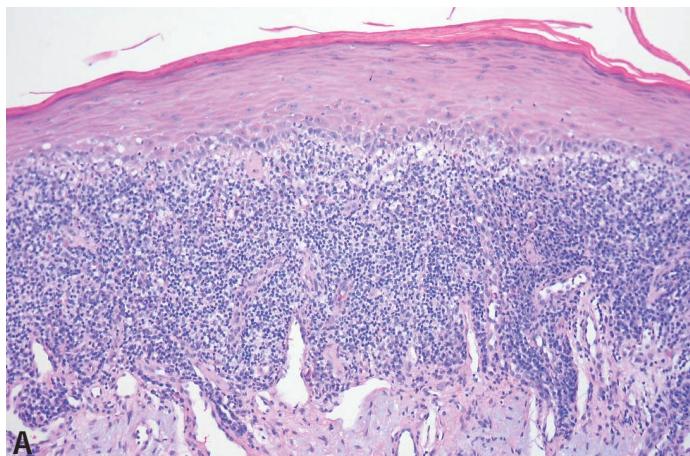


Fig. 1.25 Actinic keratosis. **A** There is focal parakeratosis, acanthosis and basal squamous atypia overlying a dense lichenoid infiltrate. **B** Actinic keratosis. There are elongated rete ridges with squamous cell atypia and focal acantholysis.

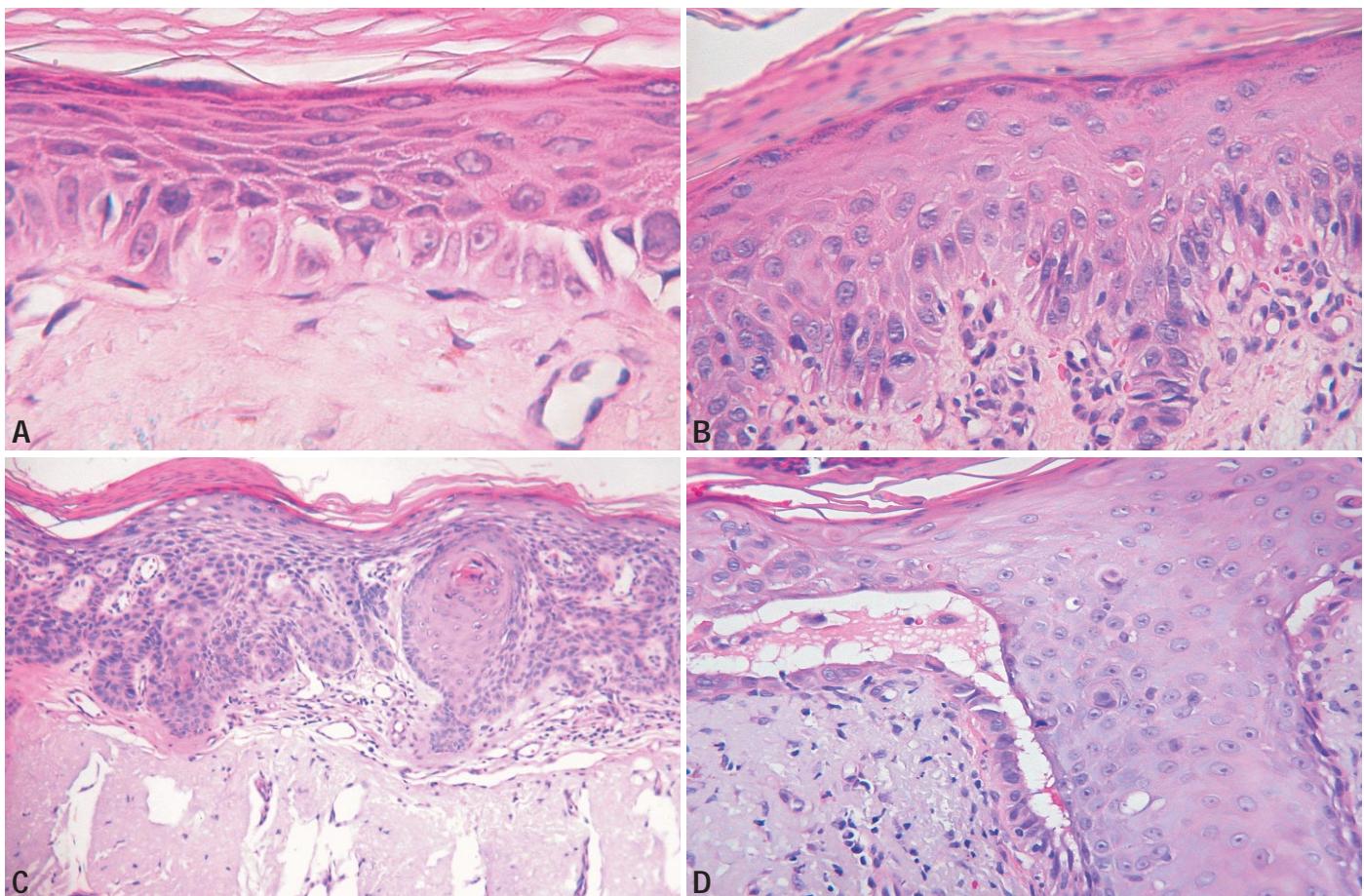


Fig.1.26 Actinic keratosis. **A** Atrophic variant with atypical basal keratinocytes and focal parakeratosis. **B** Medium power magnification shows keratinocyte atypia in the stratum malpighii with a loss of polarity, nuclear enlargement, hyperchromasia, dyskeratosis, increased mitotic activity and parakeratosis. **C** Downward prolongations and buds of atypical squamous cells does not indicate true stromal invasion. Note severe dermal solar elastosis and telangiectasia. **D** Acantholytic variant with suprabasal acantholysis, squamous atypia, dyskeratosis and superficial follicular involvement.

been proposed, however, invasive SCC commonly arises from KIN I or II.

Lesions in which impaired maturation and atypia appear to involve the full epidermal thickness have been labelled "bowenoid actinic keratoses" (BAK) {1128}. Multinucleate keratinocytes and a verrucous architecture, can be seen in AKs in the setting of immunosuppression {294,1856}.

The abnormal keratinization often involves the epidermis between spared acrotrichia and acrosyringia, which in contrast retain columns of normal keratinization. Some lesions show spread into the infundibular and isthmic segments of follicles or less commonly along eccrine ducts {1835}. Dermal changes include solar elastosis, an infiltrate of lymphocytes and plasma cells and increased vascularity. Inflammation is most frequent in lesions of the head and neck, particularly the lips.

The *hypertrophic* variant shows acanthosis, papillomatosis and conspicuous hyperkeratosis with alternating parakeratosis {244}. Elongation of rete ridges, dilated vessels and vertically oriented collagen bundles in the papillary dermis suggest superimposed lichenification.

The *atrophic* AK variant is easily misdiagnosed if the basal keratinocytic atypia in a parakeratotic epidermis devoid of rete ridges is missed. Budding of the basal epidermis and extension of atypia into adnexae are common.

The *bowenoid* variant is difficult to differentiate from Bowen disease. Whilst some claim they are identical, others emphasize the lack of full thickness atypia, less defined edge, follicular sparing and acrosyringeal involvement in BAK {1128,2476}.

The *acantholytic* variant reveals clefting, usually suprabasal, with varying acantholysis and dyskeratosis {1409}.

Keratinocyte atypia aids distinction from acantholytic dermatoses. Downward extensions of the basal epidermis can induce pseudoducts, and acantholysis may spread along appendages.

The *pigmented* variant shows increased melanization of atypical keratinocytes and dermal macrophages {1128}.

The *lichenoid* variant has keratinocyte apoptosis and vacuolation, exocytotic lymphocytes and a band-like superficial dermal lymphocytic infiltrate including colloid bodies {2318}. The epidermis in early lesions is acanthotic, but more advanced regressing lesions are atrophic with pigment incontinence. Keratinocyte atypia exceeding that expected in a reactive process differentiates this lesion from benign lichenoid keratosis.

The confident identification of early SCC in an AK can be difficult {1158}. Detachment of individual irregular aggre-

gates of keratinocytes from the epidermis, keratin pearl formation and extension of atypical squamous cells into the reticular dermis are helpful {1158,2476}

Immunoprofile

Keratin and involucrin distribution is similar to normal epidermis {1093} whilst CD95 (Fas) is lost in two thirds of AK {741} and retinoid receptors are reduced {2554}. Expression of E-cadherin/catenin and TP53 increases in the progression to invasive SCC {1770,2170}.

Genetics

There is a 2-fold risk of AK in an Australian Caucasian population carrying the glutathione-S-transferase null genotype {386}, further increased by fair skin and an inability to tan.

Around 50% of AK's show TP53 mutations {1696,2602} and over-expression of Cyclin D1 {2235} whilst independent activation of HRAS is identified in 16% {2235,2307}.

The majority of TP53 mutations involve single cytosine to thymine substitution {1396,1696,2307}. Progression of AK into invasive SCC may involve deletion of the 9p21 region of the p16 (CDKN2A) tumour suppressor gene {1653}.

Loss of heterozygosity (LOH) at four or more loci has been demonstrated in >50% of AK's in a UK Caucasian population {1913} and in just under 20% of lesions in a Japanese group {1350}. PCR microsatellite analysis has exposed loss on 17p(64%), 13q(52%), 17q(46%), 9p(39%), 3p(31%) and 9q(22%) {1914}.

The higher rate of LOH in AK than invasive SCC could reflect the low progres-

sion rate of the former {1350}.

69% of AK were aneuploid in one image analysis DNA-cytometry study {241}. Recurrent chromosomal changes are numerical (+7,+20) and structural, involving the distal long arm of chromosome 4, 1p31,3p13 and the centromeric region of chromosome 3 {1143}.

Prognosis and predictive factors

Untreated AK have been reported to develop into invasive SCC in 8-20% of patients {838}. AK's are also risk markers for basal cell carcinoma and melanoma {2023}. Individual AK's can however be stable for many years, and may regress after sun protection. One estimate has suggested a rate of malignant transformation less than 0.1% yearly {1516, 1517}. Older patients with multiple lesions followed over 10 years demonstrate a lifetime risk of progression between 6-10% {641} whilst 14% of patients with >10 AK's develop invasive SCC within 5 years {1639}. Sixty percent of invasive SCC's have been proposed to develop from AK's and, more recently, contiguous AK has been identified in 82.4-97% of SCC {1085,1517,1627}. Clinically hypertrophic lesions reveal invasive SCC in 36% {2290}.

Some classify AK as a type of SCC {791,994,1442} rather than a precursor. It cannot however be proven that AK inescapably progresses to invasive SCC. The hypothesis that AK requires further genetic aberrations before the expression of clinical malignancy, is plausible {1810}.

Immune responses and adjacent normal keratinocytes modulate the behaviour of

AK {791}. Metastases from invasive carcinomas arising in AK are infrequent if the lip is excluded, occurring in 0.5-3% of such carcinomas {1459,1630}.

Arsenical keratoses

Definition

Arsenical keratoses is a precancerous lesion occurring in patients exposed (therapeutic, environmental or occupational) to arsenic {2109}. This is a clinicopathological diagnosis. Arsenic is concentrated in a variety of tissues, including skin, hair, and nails {49,421,2007, 2109}.

Epidemiology

Lesions may occur after a latent period of 2 years, but usually take 20-30 years to manifest {2568}. A study of 262 exposed individuals revealed characteristic keratoses of the palms and soles in over 40% {49}. Other skin lesions include melanosis, Bowen disease, squamous cell and basal cell carcinoma {421,2007, 2109}. Visceral cancers, particularly involving the lung, and genitourinary tract can also occur {49,421,2007,2109}. There is a high arsenic content in some drinking waters and naturopathic medicines {1823,2007,2109}.

Clinical features

Arsenical keratoses begin as yellowish verrucous papules, 4-10 mm in diameter. These typically occur on thenar eminences, lateral borders of palms, base or lateral surfaces of fingers, soles, heels and toes {49}. A combination of mela-

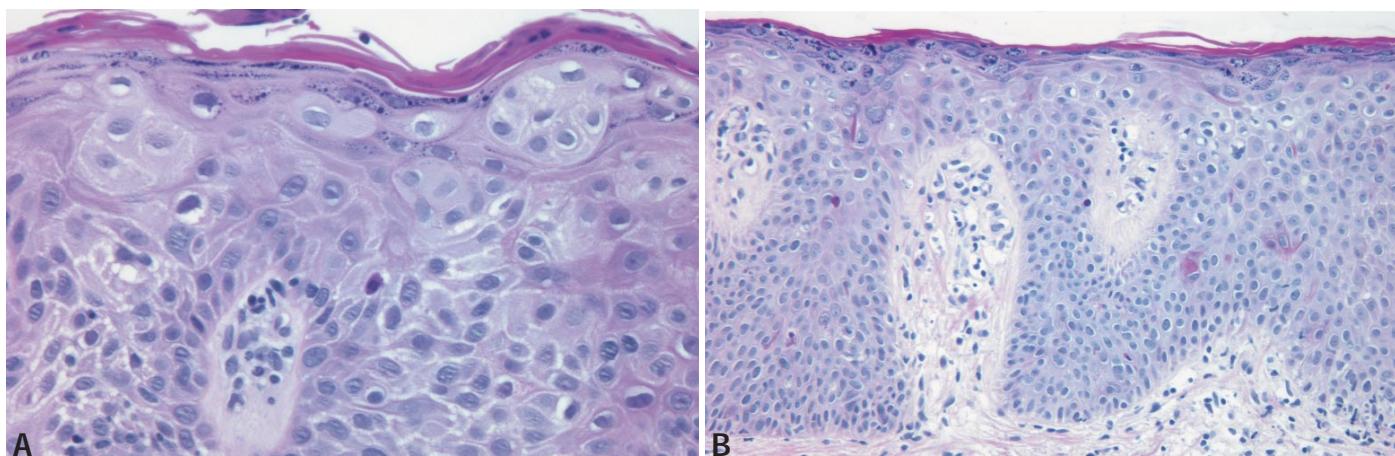


Fig. 1.27 Arsenical keratoses. **A** Arsenical keratoses with vacuolation of the keratinocytes. **B** Arsenical keratoses showing acanthotic epidermis, some vacuolation of the keratinocytes and dysplasia.

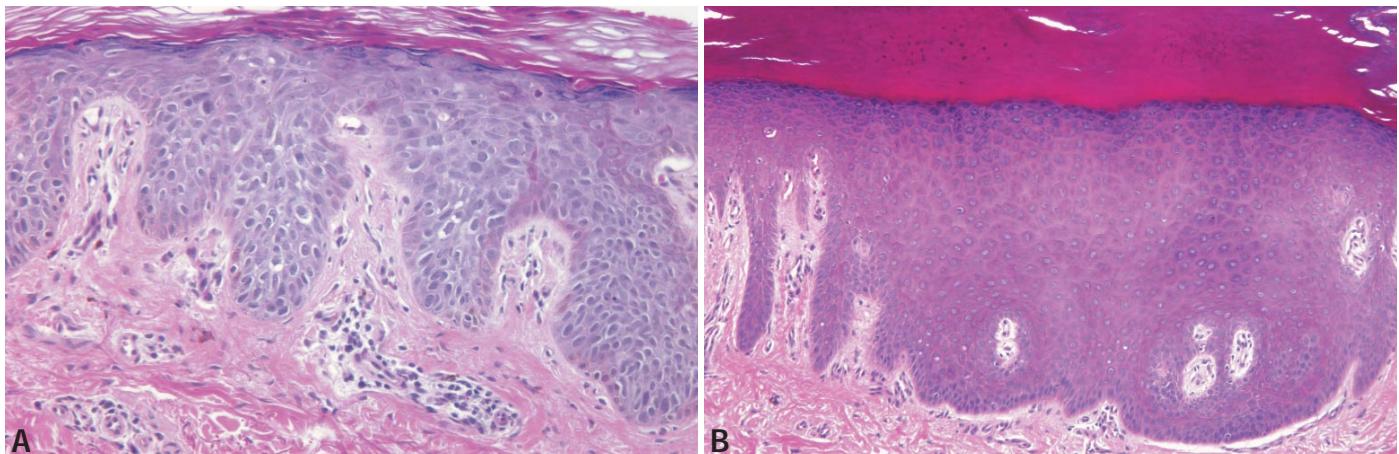


Fig. 1.28 Arsenical keratosis. **A** Arsenical keratosis with full thickness dysplasia, resembling Bowen disease. **B** Hyperkeratotic type.

nosis and multiple keratoses in non-sun-exposed areas in adults is highly suggestive of chronic arsenic exposure {2007}.

Histopathology

A spectrum of histological appearances exists {49,421,2007,2109}. Lesions may show compact hyperkeratosis, acanthosis, papillomatosis, hypertrophic actinic keratosis-like lesions and a pattern resembling seborrhoeic keratosis {2007, 2109,2568}. Vacuolated cells in the Malpighian layer suggest arsenical keratosis, but this is not a reliable criterion. Arsenical keratoses may spare adnexae, similar to solar-related keratoses {2109}. Bowenoid arsenical keratoses may display vacuolated, dyskeratotic cells with abnormal mitoses and multinucleated giant cells {1823}. Arsenical-induced pigmentation comprises melanosis and dermal arsenic deposition {49}.

Histogenesis

The exact nature of arsenical carcinogenesis is unclear.

Arsenic and its metabolites are shown to cause chromosomal abnormalities and gene amplification {421,1823,2109}. Human papillomavirus may be a co-factor in the pathogenesis {820}.

PUVA keratosis

Definition

PUVA keratosis is a form of keratosis that arises in response to PUVA therapy.

Epidemiology

There are no detailed studies on the true frequency of actinic keratoses attributable solely to PUVA, but estimates have varied from 2-5% {11,1057}. There are long term epidemiological data indicating increased risk of squamous cell carcinoma in patients on high dose PUVA, recorded as 300 treatments or more {2265}. More recently, phototherapy using a narrow band of ultra-violet radiation in the UVB range has been used with increasing frequency, substituting for PUVA therapy in a substantial proportion of patients {2264}. There are no long-term data published as yet on the risk of actinic keratoses and squamous cell carcinoma in patients receiving narrow band UVB phototherapy.

Etiology

PUVA is a photochemotherapy using either an oral or topical psoralen product in association with long-wave ultraviolet radiation (UVA) {374}. This treatment is locally immunosuppressive, and delivers

high doses of UVA to epidermal keratinocytes. PUVA is used in the treatment of patients with psoriasis and other disorders.

Patients treated with long-term PUVA therapy are at increased risk for development of actinic keratoses and squamous cell carcinoma.

Clinical features

PUVA keratoses resemble actinic keratoses. They occur on PUVA-treated skin.

Histopathology

PUVA keratoses are said to have less keratinocytic atypia than sunlight-induced actinic keratoses {2417}.

Verrucas

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M. Martinka
C. Gross

Definition

Verrucas or condyloma are common, contagious, epithelial tumours caused by human papillomaviruses (HPV).

Synonyms

Verrucae vulgares (common warts); verrucae palmares (deep palmar or hand warts); verrucae plantares (deep foot warts, myrmecia); superficial plantar warts (mosaic warts); verrucae planae (plane warts, flat warts); condylomata acuminata (genital warts); condylomata plana (flat cervical condylomas, plane condylomas).

Epidemiology

HPVs are widespread in nature and the

prevalence of cutaneous warts is up to 10% in children 2-12 years old, occurring with equal frequency in both sexes and regressing spontaneously in 1-2 years {1282}. HPV infection of the lower genital tract is one of the most common sexually transmitted diseases among adolescents and adults. Most benign genital warts resolve spontaneously and are usually caused by HPV types 6 and 11, which are considered low-risk types as they are rarely found in high-grade genital dysplasias and almost never in invasive cancer. However, persistent infection with high-risk types, predominantly HPV-16 and 18, represents the most important risk factor for development of anogenital malignancies and their precursors, squa-

mous intraepithelial lesions {288}. HPV infection occurs by direct contact with individuals who harbour clinical or sub-clinical HPV-associated lesions, or indirectly via contaminated surfaces and objects. Autoinnoculation from the lesion to surrounding skin is frequently observed {1282,1641}. Impaired cell-mediated immunity is associated with markedly increased incidence of viral warts, for example after organ transplantation, HIV infection, chronic lymphocytic leukaemia and lymphoma {1641}.

Etiology

Verrucas are caused human papillomaviruses (HPV), a large family of DNA viruses which are epitheliotropic and induce benign and malignant epithelial tumours in skin and mucosa. The definition of an HPV type is based upon nucleotide sequence homology; more than 95 HPV types have been fully characterized to date, and additional partial DNA sequences have been obtained indicating the existence of at least 130 HPV genotypes {188,605,1738}.

HPV structure and lifecycle {2283, 2608,2609}: HPVs are 55 nm diameter, non-enveloped, double-stranded DNA viruses. The icosohedral capsid surrounds the viral genome which is approximately 8kb in length and is composed of the upstream regulatory region containing the origin of replication and control elements for transcription and replication, the early region containing the open reading frames for viral genes that are principally expressed early in the papillomavirus lifecycle (E1, E2, E4, E5, E6, E7), and the late region encoding the viral capsid proteins (L1, L2). Productive infection and induction of hyperproliferation are initiated when the virus enters proliferating basal epithelial cells, and this requires abrasion or other minor trauma to the epithelium. The HPV lifecycle is only completed in fully differentiated squamous epithelia since the programme of viral gene expression is intimately linked to the differentiation state of keratinocytes. HPV does not encode

Table 1.01

Clinical manifestations and associated HPV types

Skin lesions	Frequently detected HPV	Less frequently detected
Common, palmar, plantar, mosaic	1,2,4	26,27,29,41,57,60,63,65
Flat warts	3,10	28,29
Butcher's warts	2,7	1,3,4,10,28
Epidermodysplasia verruciformis	3,5,8,10	9,12,14,15,17,19-25,36-38, 46,47,49,50
EV-squamous cell carcinoma	5,8	14,17,20,47
Periungual SCC	16	34,35
Other SCCs	EV HPV types	Other cutaneous types
Mucosal lesions		
Condyloma acuminata	6,11	42-44,54,55,70,2,27,57
High grade intraepithelial neoplasia (including cervical tumours, Bowenoid papulosis)	16,18	31,33-35,39,40,51-59,61,62
Buschke-Lowenstein tumours	6,11	
Recurrent respiratory papillomatosis, conjunctival papillomas	6,11	
Focal epithelial hyperplasia (Heck's disease)	13,32	

the enzymes required for transcription or replication of viral DNA and therefore is entirely dependent on subverting cellular proteins for these functions. In particular, in HPV types 16 and 18, proteins E6 and E7 promote continued cell cycling of suprabasal epidermal cells by abrogation of the functions of TP53 and pRb respectively. HPV genomes are thereby amplified to high levels during vegetative viral replication for assembly into infectious virions after encapsulation by L1 and L2 proteins in the granular layer and above. Virus assembly does not lyse keratinocytes, but rather the infectious virus is shed with desquamating cornified cells, and viral release is facilitated by disruption of the keratinocyte intracellular

filamentous network by viral E4 proteins. *Host immune response* {2246,2608}: Persistent papillomavirus infections are common, indicating that HPVs have evolved mechanisms to evade immune surveillance. There is no viraemic phase, low levels of viral proteins are expressed in the basal cell layer, and extensive virion production only occurs in the more immunologically privileged terminally differentiated layers. However, a successful immune response is eventually generated in most cases, since two thirds of cutaneous warts regress spontaneously within 2 years and multifocal lesions often regress concomitantly. Cell mediated immune responses appear to be primarily responsible.

Localization

Warts can occur on any skin or mucosal surface. Certain HPV subtypes cause specific kinds of warts and show special affinity for particular body locations. Subtypes causing common warts are found on the hands, fingers, and palms. Periungual subtypes are often seen in nail biters. Verruca plantaris is seen on the sole of the feet. Condylomata acuminata lesions (genital HPV infection) appear on the vulva, cervix, perineum, anus, or penis. Scrotal condylomata are very rare and only seen in 1% of HIV positive males.

Table 1.02

Correlation between cytopathological changes of verrucas and causal HPV types

Clinical manifestation	HPV types ^a	Epidermal changes ^b	Cytopathic effect (location)
Verruca vulgaris	2	Prominent	Eccentric nucleus; condensed heterogeneous keratohyaline granules (granular)
	4	Prominent; endophytic	Large, vacuolated keratinocytes with no keratohyaline granules and small, peripherally located, 'signet ring' nuclei (granular)
	7 (Butcher's wart)	Prominent	Central, small, shrunken nuclei within proliferating rete ridges (granular)
Palmo-planter	1 (Myrmecia)	Prominent, endophytic	Vacuolated cells with large, eosinophilic keratohyaline granules forming ring-like and sickle-like figures. Basophilic nuclear inclusions (spinous, granular)
	60 (Ridged wart)	Acanthosis and mild papillomatosis; endophytic	Eosinophilic, homogeneous and solitary inclusions
	65 (Pigmented plantar wart)	Prominent; endophytic	Eosinophilic, homogeneous and solitary inclusions
	63	Prominent; endophytic	Intracytoplasmic, heavily stained keratohyaline material with filamentous inclusions that encase the vacuolated nucleus
Verruca Plana	3	Subtle; no parakeratosis and basket-weave like appearance of stratum corneum	Central, pyknotic, strongly basophilic 'bird's eyes' nuclei (upper spinous and granular)
Epidermodysplasia verruciformis	5	Nests of large, clear cells; stratum corneum loose with basket-weave like appearance	Basophilic cytoplasm containing keratohyaline granules of various shapes and sizes; clear nucleoplasm (upper spinous and granular)
Condyloma acuminata	6,11	Marked acanthosis, some papillomatosis and hyperkeratosis	Less prominent vacuolisation of granular cells

^a Most common associated HPV genotype

^b Epidermal changes comprise papillomatosis, compact hyperkeratosis, focal parakeratosis, hypergranulosis, acanthosis.

Clinical features and correlation with viral genotyping

Cutaneous and mucosal HPV types form two distinct groups that infect skin or mucosa, although viral tropism is not absolute [605]. Clinical manifestations depend on the HPV type involved, the anatomical location and the immune status of the host [1282].

Cutaneous infections: In general, classification of warts is based on morphology and anatomic localization and cutaneous warts have traditionally been classified as verruca vulgaris or common warts, palmoplantar warts, including superficial and deep types, verruca plana or plane warts and epidermodysplasia verruciformis (EV). Recent studies suggest that histological and clinical characteristics of warts are mainly determined by viral genotype, indicating that HPV typing may allow a more accurate classification. However, the use of highly sensitive PCR techniques for HPV detection and genotyping has highlighted the presence of a greater diversity of HPV types than was previously appreciated [975]. These individuals often harbour multiple HPV types, particularly epidermodysplasia-verruciformis (EV)-HPV types. These HPVs were previously thought to occur only in the context of the rare genodermatosis EV, characterised by infection with unusual, widespread, cutaneous warts and associated with increased risk of non-melanoma skin cancers harbouring EV-HPV types on ultraviolet radiation exposed sites [1492]. There is also mounting evidence that EV-HPV types play a cofactor role with UVR in NMSCs arising in immunosuppressed individuals [974].

Mucosal infections: Over 25 HPV types are recognized to infect anogenital and aerodigestive mucosa [605], and sub-

clinical infections are more common than visible warts [1282]. Genital warts are generally caused by low-risk mucosal HPV types rather than the high-risk types associated with anogenital neoplasia [605]. Bowenoid papulosis (section 1.5.01) may clinically resemble genital warts, but histologically resembles squamous cell carcinoma in situ and contains high-risk HPV types. Giant condyloma acuminata (Buschke-Lowenstein tumour) may also resemble genital warts but is an anogenital verrucous carcinoma harbouring low-risk HPV types [2476]. Oral warts are also associated with HPV types 6 and 11 and focal epithelial hyperplasia (Heck's disease) resembling gingival, buccal and labial flat warts or condylomata usually harbours HPV 13 or 32 [2476].

HPV-4 and HPV-7. In children, HPV-6 and/or HPV-11 are rarely found. Other HPV types have rarely been implicated, usually in immunosuppressed individuals [106].

Localization

Common warts may be solitary or multiple, and they are usually found on exposed parts, particularly the fingers and on the dorsum of the hands.

Clinical features

They are hard, rough-surfaced papules that range in diameter from about 0.2:1.5-2.0 cm. New warts may sometimes form at sites of trauma (Koebner phenomenon).

Histopathology

Common warts show marked hyperkeratosis and acanthosis. There are outgrowths of epidermis presenting as slender spires in filiform warts or blunter digitate processes in other variants. Columns of parakeratosis overlie the papillomatous projections. There may be haemorrhage into these columns. Hypergranulosis is present where the cells contain coarse clumps of keratohyaline granules. Koiocytes (large vacuolated cells with small pyknotic nuclei) are present in the upper malpighian layer and the granular layer. Small amounts of keratohyalin may be present in the cytoplasm of these cells. There is often some inward turning of the elongated rete ridges at the edges of the lesion. Tricholemmal differentiation and squamous eddies may be seen in old warts. Dilated vessels are often found in the core of the papillomatous projections. A variable lymphocytic infiltrate is sometimes seen, and this may be lichenoid in presumptive regressing lesions.

Prognosis and predictive factors

Most warts are only a cosmetic problem. Rarely, Bowen disease or squamous cell carcinoma may develop in a common wart, usually in immunocompromised patients [1611]. Thrombosis of superficial vessels, haemorrhage and necrosis of the epidermis are rarely seen in regressing common warts.



Fig. 1.29 Verruca vulgaris showing the Koebner phenomenon. Note the linear arrangement of the lesions as a consequence of scratching.

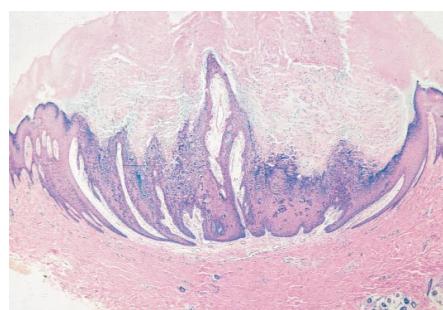


Fig. 1.30 Verruca vulgaris. There is hyperkeratosis, papillomatosis and interning of the elongated rete ridges.

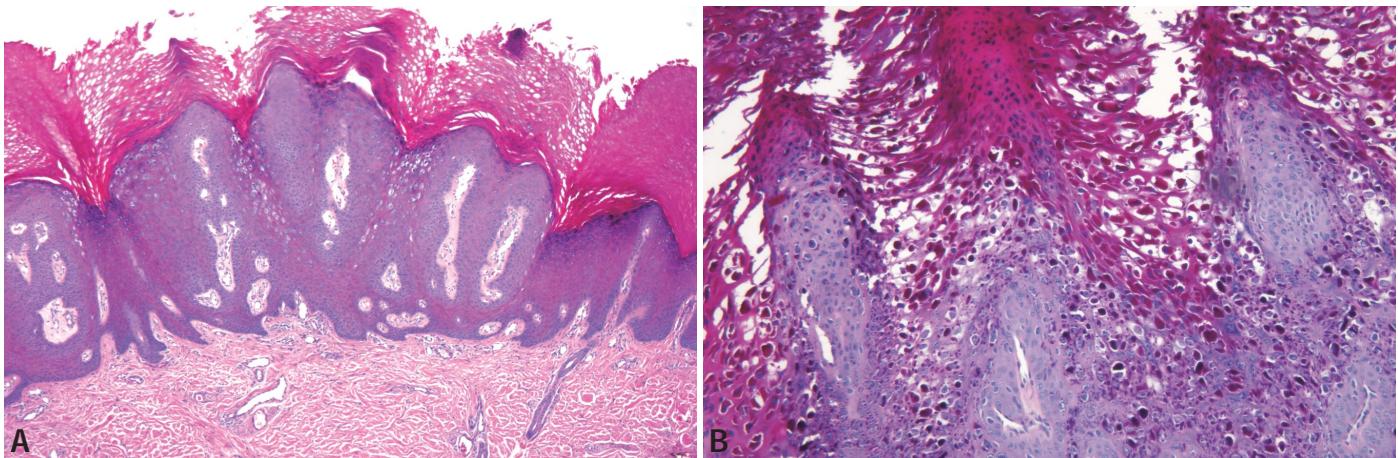


Fig. 1.31 Verruca plantaris. **A, B** Plantar wart. Note papillomatosis, acanthosis, hyperkeratosis, viral cytopathic changes.

Verruca plantaris

Definition

Verruca plantaris is a benign, human papillomavirus (HPV)-induced epithelial proliferation occurring on the sole of the foot. It is characterized by the formation of thick, hyperkeratotic lesions {505,648,1214}.

Synonyms

Plantar wart, deep foot warts, myrmecia

Epidemiology

Plantar warts are most common in children and young adults; possibly because of immaturity of the immune system or sport-related repetitive micro-trauma. They are most frequent over pressure points {505,648}. Particularly in children they may spontaneously regress within a few months, but in adults and immunocompromised patients they can persist for years. Rarely chronic lesions are associated with the development of verrucous carcinoma {594}.

Clinical features

Plantar warts are sharply defined, rounded lesions, with a rough keratotic surface, surrounded by a thickened horn. They tend to grow into the foot and are covered by black dots representing thrombosed capillaries {505,648,1214}. They do not retain the normal fingerprint lines of the feet, as calluses (corns) do. They often occur in multiples, and can be painful {1055,2390}. They are traditionally divided into the superficial warts (mosaic), which are ordinary verrucae, and deep warts (myrmecia). Several other variants have been recently described {1055,1214,1556}.

Histopathology

The mosaic-type shows acanthosis, papillomatosis, hyperkeratosis, vacuolated cells (koilocytes) in the upper Malpighian layer, vertical tiers of parakeratotic cells and clumped keratohyaline granules. Myrmecia are characterized by an endophytic proliferation of rete ridges covered by thickened keratin and prominent eosinophilic intracytoplasmic inclusions. The nuclei are retained in the stratum corneum and appear as basophilic round bodies surrounded by a clear halo {505,1055,1214}.

Regression of palmo-plantar warts is often associated with thrombosis of superficial vessels, haemorrhage and necrosis of the epidermis and a mixed inflammatory cell infiltrate.

Pathogenesis

HPV is the established cause. Correlations between the variety of wart and the HPV type are as follows:

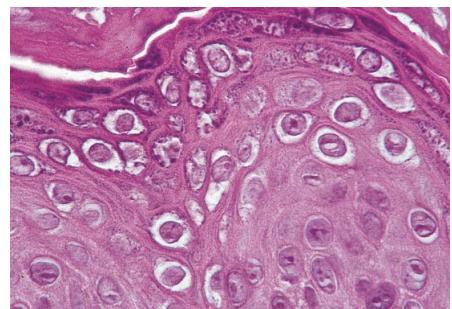


Fig. 1.34 Flat wart.



Fig. 1.32 Verruca plantaris on the volar surface of the toe. Clinically, the lesion was painful.

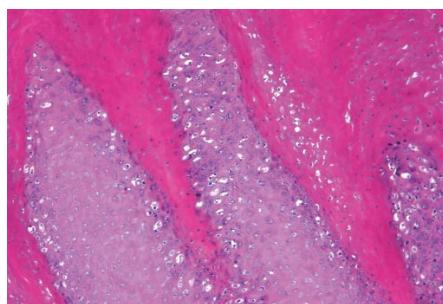


Fig. 1.33 Plantar wart (myrmecia type). Nuclei are retained in the stratum corneum as basophilic round bodies surrounded by a clear halo.



Fig. 1.35 Multiple flat warts on the chin of a young female.

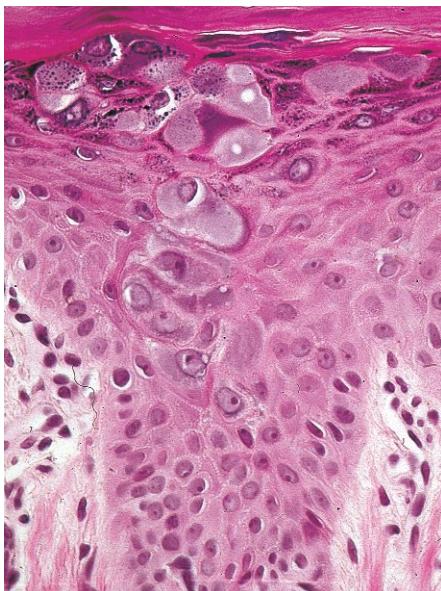


Fig. 1.36 Flat wart in a patient with epidermolytic hyperplasia.

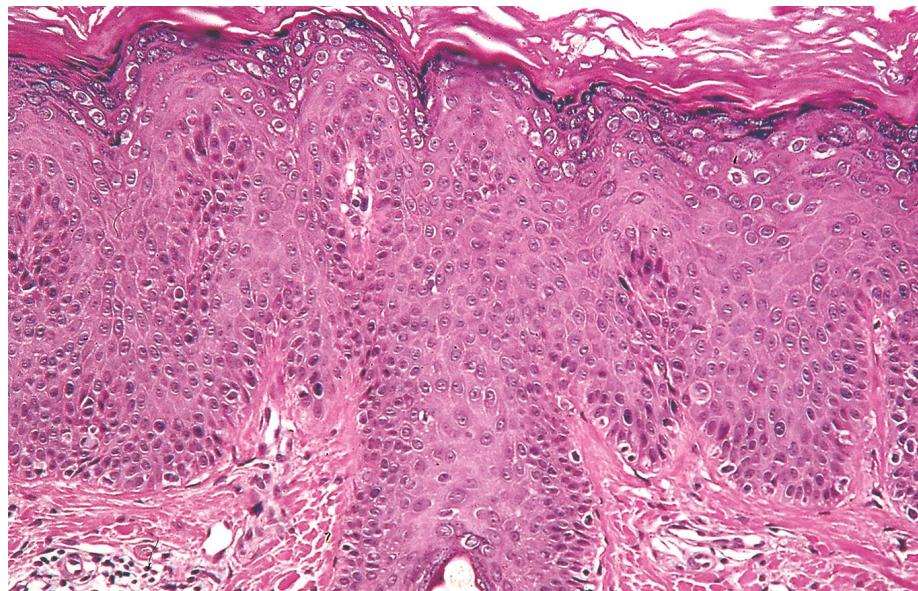


Fig. 1.37 Flat wart. There are superficial vacuolated keratinocytes with perinuclear clearing.

Deep plantar wart (myrmecia) - HPV1, HPV63 {505,2390}.

Common and mosaic wart - HPV2, HPV4 {1055}

Endophytic common wart - HPV4 {1055}

Ridged and flat warts (associated with or without cyst, respectively) - HPV60 {505, 1055, 1214, 2390}

Large plantar wart - HPV66 {1556}

Verruca plana

Definition

Verruca plana are benign, HPV-induced, slightly elevated, flat-topped, smooth papules.

Synonyms

Flat wart, verruca plana juvenilis.

Epidemiology

Verruca plana are relatively common. Children, adolescents and young adults are most frequently affected.

Etiology

HPV types 3 and 10 are most commonly associated with verruca plana. Minor trauma, atopic dermatitis and immuno-

suppression are possible predisposing factors {778,909,2262}.

Localization

Most lesions are located on the back of the hands and fingers, distal forearm, lower leg and face.

Clinical features

Flat warts generally are smaller than common warts and typically develop as small round to oval epidermal papules measuring 1-4 mm in diameter. Lesions are mostly skin-coloured with a smooth and flat surface, but may be hyperpigmented. The number ranges from one to several hundred and the distribution is asymmetric, sometimes linear (Koebner phenomenon).

Histopathology

Histology reveals a loose hyperkeratosis with basket-weave-pattern but little or no papillomatosis as in verruca vulgaris. There is plate-like epidermal hyperplasia of about twice the thickness of the surrounding normal epidermis with compressed papillae but dilatation and tortuosity of capillaries in the papillary dermis. Superficial epidermal layers show koilo-

cytosis, vacuolated keratinocytes with perinuclear clearing around centrally located nuclei (so-called "birds-eye cells") and hypergranulosis.

Flat wart-like lesions can be encountered in patients with epidermolytic hyperplasia verruciformis. These lesions may show typical blue-grey cytoplasm {907,909,1491}.

Regression of plane warts is accompanied by superficial lymphocytic infiltrate in the dermis with exocytosis and single epidermal cell apoptosis {2476}.

Prognosis and predictive factors

Flat warts commonly persist for several years. Due to immunologic rejection in some long-standing cases, lesions have disappeared almost from one day to the next showing some local inflammation without leaving a scar. There are no reports regarding recurrences in such cases. In other cases warts lose evidence of viral cytopathic change and persist as localized verrucous epidermal hyperplasia {909}.

Acanthomas

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Definition

Acanthomas are benign tumours of epidermal keratinocytes. The proliferating keratinocytes may show normal epidermoid keratinization or a wide range of aberrant keratinization, which includes epidermolytic hyperkeratosis (epidermolytic acanthoma), dyskeratosis with acantholysis (warty dyskeratoma) or acantholysis alone (acantholytic acanthoma). Seborrhoeic keratosis, melanocanthoma, clear cell acanthoma, large cell acanthoma and keratoacanthoma all fulfil the criteria for an acanthoma.

Epidermolytic acanthoma

Definition

A benign tumour presenting as solitary or multiple discrete lesions and demonstrating the characteristic histologic features of epidermolytic hyperkeratosis {1628, 2151}.

Epidemiology

The reported age range is 3-72 years with a slight male predominance and various racial groups affected {515}.

Etiology

The etiology remains unknown but trauma {2033}, sun exposure {2298} and PUVA {1677} have been proposed as causes of disseminated epidermolytic acanthoma.

Localization

They can occur at any skin site and may involve oral or vaginal mucosa {515, 601, 1869, 2151}.

Clinical and macroscopic features

Epidermolytic acanthomas are generally asymptomatic, flat or elevated keratotic papules 2-12 mm in diameter {515, 601, 1291, 1628, 1677, 1712, 1869, 2033, 2151, 2298}. Lesions may be solitary, multiple (localized to a region), or disseminated {515}.

Histopathology

Epidermolytic acanthoma is characterised by compact hyperkeratosis, perinuclear vacuolisation of the cells of the stratum Malpighii sparing only the basal layer, indistinct reticulate cell boundaries and hypergranulosis with larger basophilic keratohyaline granules than

normal and intracytoplasmic amorphous eosinophilic bodies i.e. epidermolytic hyperkeratosis {14}.

Genetics

Based on patterns of keratin expression determined by immunohistochemical techniques, a somatic mutation involving K1 and K10 genes has been postulated {515}.

Patients with disseminated disease may also have germline mutations, with offspring at risk for congenital ichthyosiform erythroderma/generalized epidermolytic hyperkeratosis.

Warty dyskeratoma

Definition

Warty dyskeratoma is a benign papulonodular lesion characterized by an endophytic proliferation of squamous epithelium typically occurring in relation to a folliculosebaceous unit and showing prominent acantholytic dyskeratosis.

Synonyms

Isolated dyskeratosis follicularis
Follicular dyskeratoma

Epidemiology

Warty dyskeratoma occurs mostly in middle aged to elderly adults {1166}.

Etiology

There are no known etiological factors. A recent study showed no evidence of HPV in 13 cases using PCR {1166}.

Localization

The head and neck region is most commonly involved {873, 1166, 2306, 2321}. Cases arising in oral {869} and laryngeal {1185} mucosa and in a subungual {147} location have been reported. It has been suggested that lesions arising in sites devoid of hair follicles maybe a separate entity {1166}.

Clinical features

Most lesions are solitary flesh coloured to

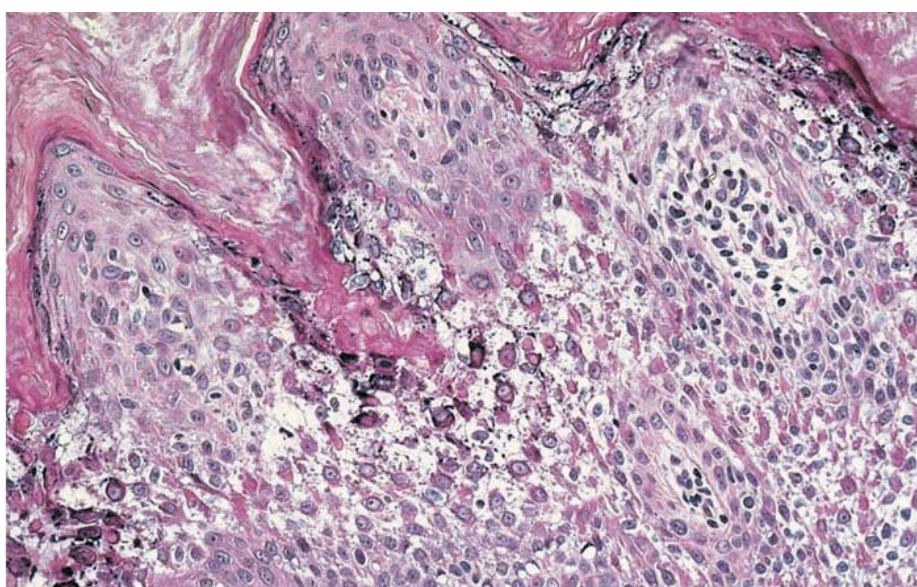


Fig. 1.38 Epidermolytic acanthoma. This lesion shows hypergranulosis and marked cytoplasmic vacuolization with clumps of eosinophilic material, sparing the basal layer.

brown papules, nodules or cysts with an umbilicated or pore-like centre or central keratin plug {873,1166}. Most are 1-10mm in size {873}. Occasionally the lesions are multiple {121,2306}.

Histopathology

Warty dyskeratoma is a well-demarcated endophytic lesion characterized by prominent acantholytic dyskeratosis. This results in suprabasal clefting with formation of villi which protrude into a lacuna. There is typically abundant keratin present within the centre of the proliferation forming a plug {829,873,1166, 2306}. Keratin pearls are commonly seen as are small cysts lined by infundibular type epithelium {1166}. Mitotic figures are commonly identified and may exceed 5 per HPF {1166}.

Three architectural variants have been described namely cup-shaped, cystic and nodular and combinations of these may occur {1166}. There may be an epidermal collarette present and the surrounding epidermis may show papillomatosis, hypergranulosis and hyperplasia {1166}. A connection to folliculosebaceous structures is commonly demonstrable {873,1166}.

The stroma often shows a characteristic appearance with dense collagen or fibroblasts and focal intrastromal clefts. There may be an associated mixed inflammatory cell infiltrate {873,1166, 2321}.

Differential diagnosis

Comedonal Darier disease shows identical histological features and is differentiated on clinical grounds {623}.

Familial dyskeratotic comedones is a rare condition which tends to spare the scalp and face and shows less marked acantholysis and dyskeratosis than warty dyskeratoma {941}.

Histogenesis

It has been recently suggested that this lesion is a follicular adnexal neoplasm {1166}.

Acantholytic acanthoma

Definition

Acantholytic acanthoma is a rare benign epidermal tumour. The lesion displays a striking characteristic microscopic feature of acantholysis that bears resem-

blance to that seen in several vesiculobullous disorders {320,1566,1885,2476}.

Epidemiology

In the 31 cases reported by Brownstein {320}, the patients ranged in age from 32-87 years. The median age was 60 years; the male to female ratio was 2:1.

Etiology

Although it is known that immunosuppression increases the incidence of cutaneous neoplasms, the role of impaired immune surveillance resulting in acantholytic acanthoma is speculative {1885}.

Localization

Truncal skin, i.e., back, chest, or flank, is most commonly involved, followed by extremities, neck, groin, axilla, ear, scrotum and shoulder.

Clinical features

Acantholytic acanthoma is a solitary, keratotic, asymptomatic to occasionally pruritic papule or nodule. Multiple lesions have been recorded in a renal transplant patient {1885}.

Macroscopy

The scaly, flesh-coloured, hyperkeratotic growths range in size from 0.5-1.2 cm.

Histopathology

The tumour shows a well-defined area of papillomatous epidermal hyperplasia. There is hyperkeratosis with prominent acantholysis involving multiple levels of the epidermis. Suprabasal or subcorneal clefts with some dyskeratotic cells (corps ronds and grains) and occasional villi are noted. The upper dermis contains a variable perivascular lymphohistiocytic and occasional eosinophilic infiltrate.

Differential diagnosis

Acantholytic acanthoma must be distinguished from other acantholytic disorders and from various acanthomas. Pemphigus, Grover disease, and Hailey-Hailey disease are disorders with more extensive clinical papulovesicular eruptions.

Epidermolytic acanthoma shows epidermolytic hyperkeratosis, and no acantholysis is present. Clear cell acanthoma contains numerous pale cells, with abundant intracytoplasmic glycogen, which is absent in acantholytic acanthoma.

Lentigo simplex

Definition

Lentigo simplex is characterized by a clinically flat epidermis with microscopic acanthosis and highly localized well-circumscribed pigment on sun exposed skin.

Synonyms

Solar lentigo, actinic lentigo, "ink spot" lentigo and lichen planus like keratosis.

Epidemiology

Lentigines are common pigmented lesions most frequently seen on the sun-exposed skin of light skinned individuals.

Localization

These lesions occur essentially only on skin or mucosa and spare the palms and soles. There is relative sparing of sun-protected areas, but some lesions may occur in these sites.

Clinical features

Lentigines are well-circumscribed mainly flat (macular) localized collections of pigment. The lesions are common and are ubiquitous in light skinned individuals. Most are somewhat randomly distributed on sun-exposed skin. The presence of many lesions may raise the consideration of a syndrome, particularly when there is extensive involvement of the lips. Peutz-Jeghers syndrome is the presence of numerous lentigines associated with multiple hamartomatous gastrointestinal polyps {893}.

Macroscopy

Individual lesions may be smooth-edged, but many have an irregular outline. Most appear entirely uniform in colour and range from light tan to brown to black. While lesions may approach 1 cm in greatest dimension, nearly all clinical lesions are 1-5 mm.

In the large cell acanthoma variant, the tumours are macroscopically very deeply pigmented and may simulate malignant melanoma *in situ*.

Lichen planus like keratoses have a highly variable appearance and may show pink, orange, or rust coloured hues. Most are minimally raised from the skin surface and have a paving stone outline that is frequently polygonal rather than rounded {677}.

Histopathology

All lentigines demonstrate a sharply circumscribed focus of epidermal hyperplasia. The tumours are strikingly melanized, and many retain residual melanin in the overlying stratum corneum. This pigment occasionally simulates parakeratotic nuclei seen in dermatitis, a feature referred to as "pigmented parakeratosis".

While clinically macular, the typical lesion of lentigo simplex demonstrates a specific form of epidermal hyperplasia characterized by elongate rete ridges with somewhat club shaped or bulbous ends. This appearance is characteristic of other settings of epidermal hypermelanization, such as in melanocytic nevi. However, it is so typical of lentigines that in every circumstance where found, this form of epidermal hyperplasia is referred to as lentiginous epidermal hyperplasia. In most circumstances where it is seen, the underlying papillary dermis demonstrates a variable amount of eosinophilic collagen deposition (or fibrosis). This may imply that the epidermal proliferation requires a scar like response in the underlying dermis. However, inflammation is an inconstant feature in these lesions {277,1634}.

Because of the histologic similarity to the epidermis of melanocytic nevi, lentigines are defined partially by what is absent in the tumours: namely nevomelanocytic nests. The presence of even rare nests is sufficient to separate the diagnosis as lentiginous junctional nevus (or "jengigo").

Thus, to make a diagnosis of lentigo the requisite features are: localized lentiginous epidermal hyperplasia, marked epidermal hypermelanosis, and the lack of nevomelanocytic nests. In fact, despite the remarkable melanization of the tumour, increased numbers of melanocytes are not found in lentigines.

Two clinical variants are known: large cell acanthoma and lichen planus like keratosis. In large cell acanthoma, the presence of a localized proliferation of larger-than-normal keratinocytes with marked melanization is seen. These lesions are strikingly dark and are often clinically highly suspicious for malignant melanoma.

The other characteristic histologic feature of this variant is the larger than normal appearance of the keratinocytes. The reason for this feature is unknown,

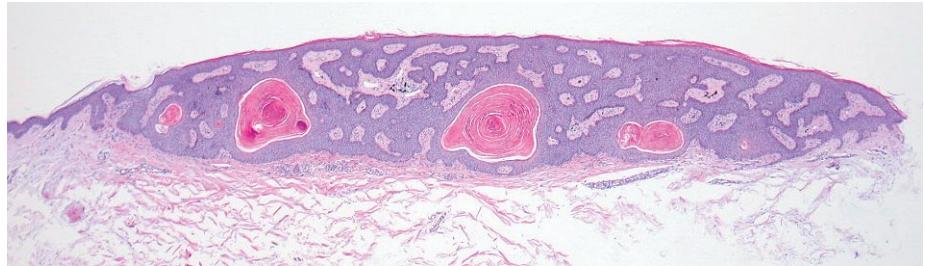


Fig. 1.39 Pigmented seborrheic keratosis. There are elongated interlocking rete consisting of a proliferation of bland and pigmented basaloid and squamous cells with formation of pseudo horn cysts

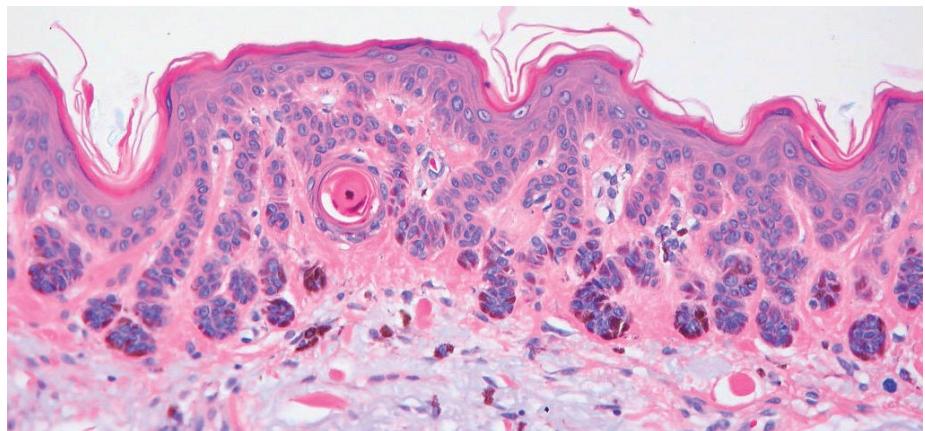


Fig. 1.40 Pigmented reticulated seborrheic keratosis. There are slender elongated rete ridges with hyperpigmentation and no squamous cell atypia, accompanied by focal pseudo cyst.

but may relate to the marked accumulation of melanin pigment {277,1033,1959}. A final variant is the lichen planus like keratosis. While some authors maintain that a variety of lesions may develop into these lichenoid proliferations, most concur that a large proportion begin as lentigines. Several lines of evidence point to this origin and have been reviewed. Histologically, these lesions often suggest a solitary lesion of lichen planus as they were initially described. Most demonstrate hypergranulosis and a band like superficial infiltrate but unlike routine lichen planus they may show overlying parakeratosis or an inflammatory infiltrate which contains a mixture of inflammatory cell types with some neutrophils or eosinophils. Careful evaluation of most lesions demonstrates some residual lentigo simplex and pigment within dermal melanophages {1373}.

Differential diagnosis

The separation between seborrheic keratosis and lentigo is somewhat arbitrary, but most authors describe the epidermis as flat in lentigo simplex while the skin surface is clearly raised in seborrheic keratosis.

Seborrheic keratosis

Definition

Seborrheic keratoses are benign hyperplastic tumours of epidermis which are more common in older individuals.

Synonyms

Seborrheic wart, senile wart, stucco keratosis, melanoacanthoma.

Epidemiology

Seborrheic keratoses are the most common of the cutaneous neoplasms and occur in the majority of elderly Caucasian patients. These lesions are by no means limited to Caucasians, but are present in numerous older individuals of any race. The lesions are unusual in children and even young adults are rarely affected. Identical histological features are seen in certain epidermal naevi.

There is no appreciable sex predilection. In part due to the very widespread incidence of the lesion, most cases are sporadic although several syndromes are associated with seborrheic keratosis. Recent studies support the long held belief that seborrheic keratosis is a clonal process in the skin {1679}.

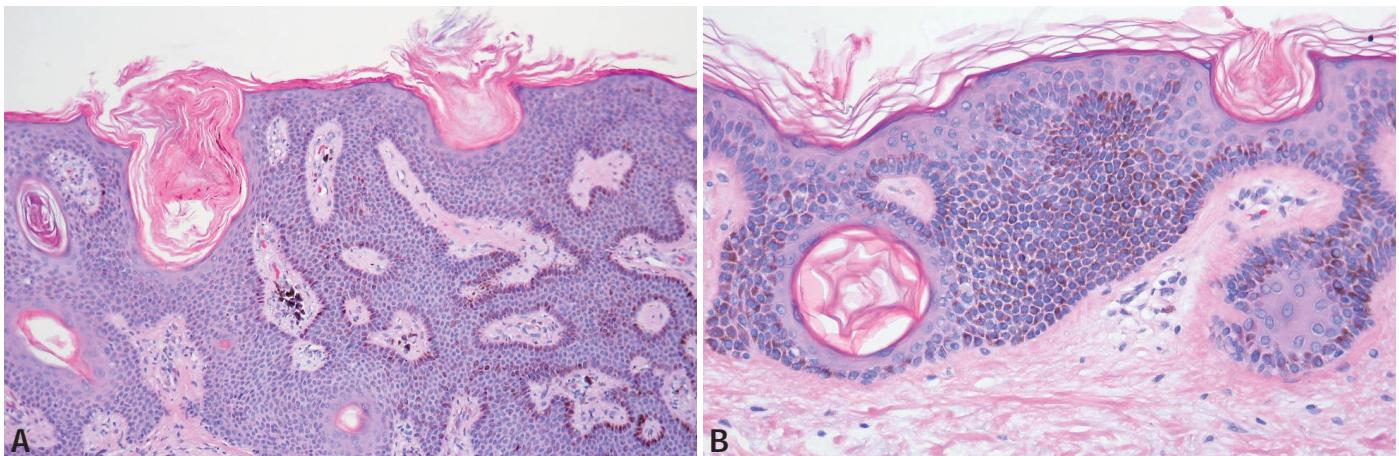


Fig. 1.41 Pigmented seborrheic keratosis. **A** and **B** There are elongated interlocking retes consisting of a proliferation of bland and pigmented basaloid and squamous cells with formation of pseudo horn cysts

Clinical features

Seborrheic keratoses are slightly raised, tan to brown or black papules. Sun exposed skin is especially affected, but lesions may be present on any site of the skin except for palms or soles. They often have a "stuck on" appearance and may be easily removed. Irritated lesions often demonstrate a crust and prominent hyperkeratosis which diminishes the visibility of the epidermal pigment. Thus, many of these irritated seborrheic keratoses are pink to red and quite scaly. Many of these lesions appear more smooth-surfaced and are mistaken for basal cell carcinoma clinically.

While most seborrheic keratoses are uniform in colour, speckled examples are common. Pigmented seborrheic keratoses may be mistaken clinically for malignant melanoma. There is some correlation between the many described histological variants of seborrheic keratosis and the clinical appearance of the tumour.

Keratoses are generally very well circumscribed clinically. Usual lesions are oval in configuration, but linear or unusually shaped lesions are common.

Dermatosis papulosa nigra appears to be a form of multiple seborrheic keratoses of the face seen primarily in patients of African descent. This condition is not known to be associated with any type of internal malady {658}.

Leser-Trélat syndrome

This syndrome is the rapid onset of multiple pruritic seborrheic keratoses associated with malignancy. The tumours associated have primarily been of gas-

trointestinal origin, but lymphomas and leukaemias have also been reported. It should be emphasized that some authors dispute the syndrome entirely and favour a coincidental association due to the high frequency of seborrheic keratoses in the elderly patients {955, 2110}.

Histopathology

Seborrheic keratoses are well-defined proliferations of epidermal keratinocytes which may be endophytic, exophytic or flat. There are seven major types of seborrheic keratosis:

Acanthotic (common) seborrheic keratosis

The acanthotic type is composed of broad columns or sheets of basaloid or squamoid cells with intervening horn cysts. There may be varying degrees of hyperkeratosis, papillomatosis and acanthosis.

Reticulated seborrheic keratosis

This common variant is often sampled histologically because clinical examples are frequently deeply pigmented. They form a net like or retiform pattern of acanthosis.

Pigmented seborrheic keratosis

Pigmented seborrheic keratoses are in every way similar to usual seborrheic keratoses, but in addition demonstrate pronounced epidermal melanin pigment.

Clonal seborrheic keratosis

Clonal seborrheic keratosis is an unusual variant, which demonstrates whorled

collections or nests of keratinocytes within the thickened epidermis. These foci of enlarged keratinocytes arranged in circular collections are suggestive of the epidermal collections seen in some cases of *in situ* squamous carcinoma, but lack the cytological atypia inherent in malignant neoplasms.

Irritated seborrheic keratosis

There is a heavy lichenoid inflammatory cell infiltrate in the upper dermis. Apoptotic keratinocytes are usually quite numerous. Features of the hyperkeratotic type (see below) may also be present. Sometimes there is a heavy inflammatory cell infiltrate, including neutrophils, which may not have lichenoid features. Squamous eddies are often present in the epidermis.

Hyperkeratotic seborrheic keratosis

This variant shows varying degrees of hyperkeratosis, papillomatosis and acanthosis. Some cases show inflammatory features similar to the irritated variant.

Flat seborrheic keratosis

There is mild hyperkeratosis, often mild basal pigmentation ('dirty feet') and only minimal acanthosis. There are no horn cysts. The cells contrast with those of the adjacent normal epidermis by being more compact.

Immunoprofile

All studies confirm the presence of keratins throughout the tumour. Some studies have also demonstrated the presence of carcinoembryonic antigen (CEA) {314,319,665}.

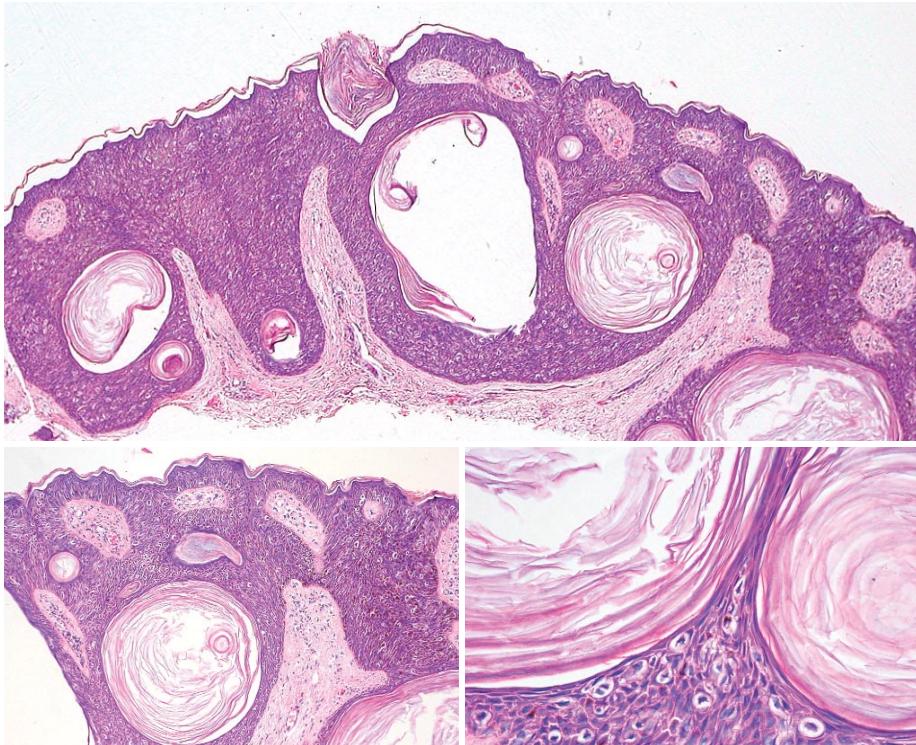


Fig. 1.42 Melanoacanthoma. There are elongated interlocking rete ridges consisting of a proliferation of bland basaloid and squamous cells with formation of pseudo horn cysts, intimately mixed with numerous melanocytes throughout the lesion.

Differential diagnosis

Dowling Degos disease has lesions indistinguishable from seborrhoeic keratosis except for their small size and the presence of a reticulated network of adjacent lesions.

The hyperkeratotic form may resemble a verruca vulgaris. Seborrhoeic keratoses lack parakeratotic columns overlying the digitate hyperkeratosis and there is no haemorrhage, dilated capillaries, koilicytosis or inward turning of the acanthotic downgrowths.

Precursor lesions

Some believe that the solar lentigo (lentigo senilis) is a precursor lesion of reticulated seborrhoeic keratosis. Others regard it as an early form of this lesion.

Prognosis and predictive factors

In a small number of cases Bowen disease coexists with seborrhoeic keratosis.

Melanoacanthoma

Definition

Melanoacanthoma of the skin is a benign mixed proliferation of keratinocytes and

melanocytes. It is considered to be a variant of seborrhoeic keratosis.

Melanoacanthoma of the oral mucosa is an unrelated disorder.

Synonyms

Melanoacanthosis, deeply pigmented seborrhoeic keratosis.

Epidemiology

Most patients are adults beyond 40 years of age. Sex predominance is not known. There are no reliable frequency data.

Localization

Most melanoacanthomas are located on the trunk.

Clinical features

Clinically, the lesion resembles a darkly pigmented seborrhoeic keratosis. There are no characteristic symptoms. It may resemble a melanoma with dermatoscopy.

Histopathology

Melanoacanthoma has the same architecture as common seborrhoeic keratoses. However, they stand out by their abundant dendritic melanocytes in virtu-

ally all layers of the lesion. The keratinocytes are rich in melanin granules.

Clear cell acanthoma

Definition

Clear cell acanthoma (CCA), is a benign epidermal neoplasm characterized by the presence of glycogen-rich clear/pale cells.

Synonyms

Degos acanthoma, pale cell acanthoma.

Localization

It is usually located on the lower extremities of middle-aged or elderly individuals. Other sites are the upper extremities, head and neck, trunk, buttocks and genital area.

Clinical features

It usually occurs as a solitary, slowly growing, dome-shaped papule, nodule or plaque. The lesion has sharp margins, sometimes with a keratotic scale, and a red or pink colour, giving the tumour a vascular appearance. Clinical variants include multiple, pigmented, giant, atypical, cystic and polypoid CCA [345].

The clinical differential diagnosis may include pyogenic granuloma, irritated seborrhoeic keratosis, squamous and basal cell carcinoma, melanocytic naevus and nodular amelanotic melanoma.

Histopathology

There is a circumscribed, sharply demarcated epidermal proliferation with psoriasiform elongation of plump and interconnected rete ridges. The keratinocytes differ from those of the adjacent normal epidermis by their pale/clear cytoplasm containing a large amount of glycogen, best demonstrated with a periodic acid-Schiff reaction. The keratinocytes of the basal layer and the intraepidermal portion of the adnexae are not involved. Parakeratosis, infiltration of neutrophils, which may form microabscess in the stratum corneum, and the absence of the granular layer are additional characteristic findings. Dilated capillaries and a scattered inflammatory infiltrate can be observed in the papillary dermis. The presence of melanophages in the papillary dermis and an increased number of melanocytes provide clues to the diagnosis of a pigmented CCA.

Histogenesis

The histogenesis of CCA is not yet completely clear. Initially considered a tumour of sweat gland or hair follicle origin, these sites were later excluded because of the different cytokeratin expression compared to CCA {1743}. Some investigators hypothesized that CCA is a benign epidermal tumour of unknown etiology, probably caused by a specific disturbance of keratinocyte differentiation. The expression of involucrin and epithelial membrane antigen further suggest that CCA is derived from surface epithelium. However, since CCA shows histopathologic findings and cytokeratin expression similar to those observed in psoriasis, others believe that it might represent an inflammatory disease rather than a neoplastic process {742}.

Large cell acanthoma

Definition

Large cell acanthoma, a benign lesion, is now considered to be a stage in the evolution of a solar lentigo to a reticulated seborrhoeic keratosis {1576,1959}. It was thought to represent a particular type of actinic keratosis {1875,2095}, Bowen disease {2038}, or a distinct entity {69,1871,2039}.

Epidemiology

Most patients are middle-aged to elderly persons. Sanchez Yus et al (1988) estimated that approximately 1-2.5 LCAs are diagnosed per 1000 skin biopsies whereas Scholl (1982) saw only 4 cases among > 1000 actinic keratoses and > 3200 seborrhoeic keratoses.

Etiology

Chronic sun exposure is the probable cause of LCA.

Localization

Most lesions tend to occur on the trunk and extremities.

Clinical features

The lesion resembles a solar lentigo, flat seborrhoeic keratosis or stucco keratosis. Most cases are lightly pigmented flat plaques or patches, usually less than 10 mm in diameter. Hyperkeratosis or even verrucous appearance has been described. In Black patients, LCA may present as darkly pigmented lesions

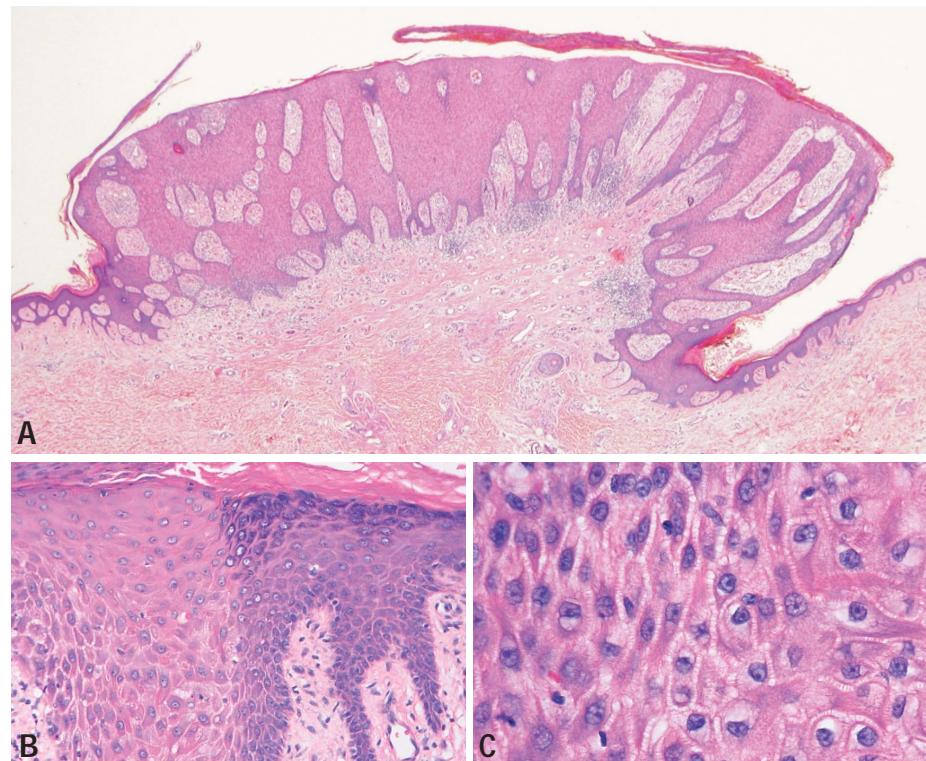


Fig. 1.43 Clear cell acanthoma. **A** There are well circumscribed interlocking columns of pale to clear keratinocytes with absent granular layer and no squamous cell atypia. **B** Note sharp demarcation between normal epidermis (right) and tumour (left). **C** High power view of tumour cells showing pale cytoplasm due to glycogen accumulation.

{2165}. Hypopigmentation is also seen {69}. Dermatoscopy may rule out melanoma.

Histopathology

Large cell acanthoma is a sharply delimited lesion standing out by its unique large keratinocytes that have about double the size both of their cytoplasm and nuclei compared to normal keratinocytes. Often, considerable numbers of melanocytes are present. Three variants have been described: a basic pattern with mild to moderate acanthosis, a verrucous pattern with papillomatosis and hyperkeratosis, and a flat-hyperkeratotic pattern {2039}. The granular layer is thick, there is usually orthohyperkeratosis and the rete ridges may be slightly bulbous.

The growth fraction is low {86,1576} although there is a considerable proportion of both aneuploid and hyperdiploid cells {86}.

Differential diagnosis

Flat seborrhoeic keratoses differ by the smaller size of the constituent cells. Solar

keratoses show parakeratosis and greater nuclear pleomorphism.

Keratoacanthoma

Definition

Keratoacanthoma is a squamoproliferative tumour, mainly of hair-bearing skin. Although it has distinctive clinical and histological features, some regard it as a variant of squamous cell carcinoma {190,1701}.

ICD-O code

8071/1

Synonym

Well-differentiated squamous cell carcinoma (keratoacanthoma type).

Epidemiology

Most cases develop in older persons, particularly in the sixth and seventh decades. There is a male preponderance. Keratoacanthomas are more frequent in subtropical areas.

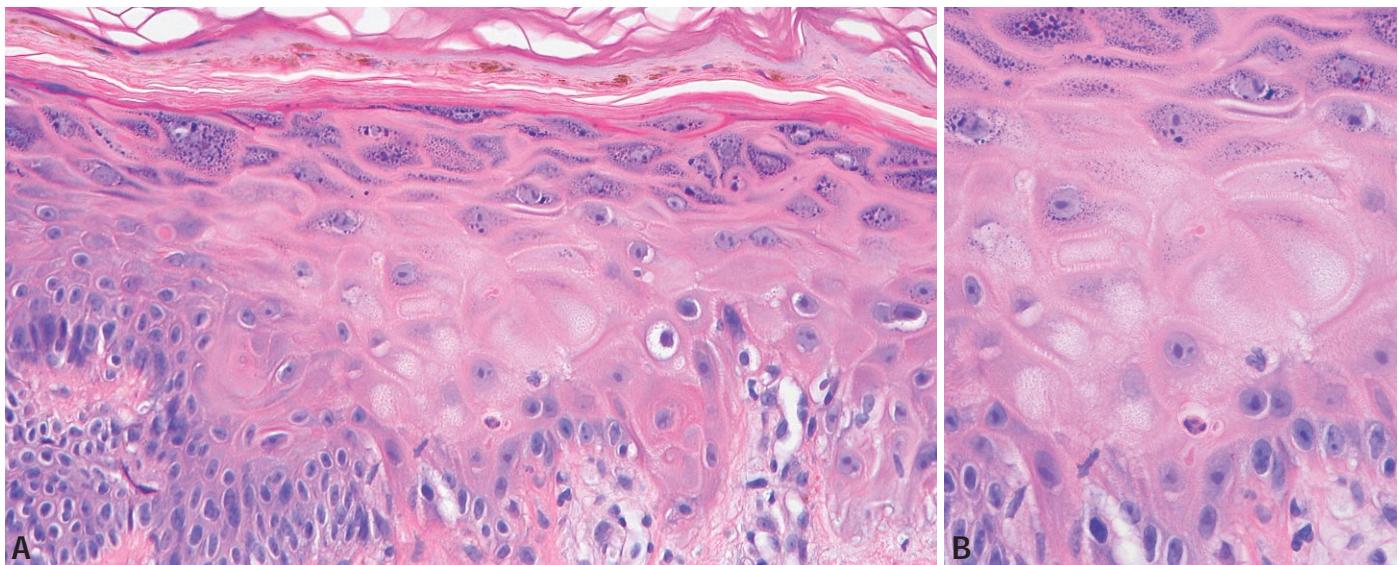


Fig. 1.44 Large cell acanthoma. **A** There is abrupt transition between normal epidermis (left) and large cell acanthoma (right). There is hyperkeratosis, hypergranulosis and markedly enlarged keratinocytes. **B** The tumour cells have enlarged nuclei without hyperchromasia and a low nuclear to cytoplasmic ratio.

Etiology

Exposure to excessive sunlight is the most frequently incriminated factor in their etiology. Viruses have also been implicated, particularly in immunosuppressed patients in whom DNA sequences of HPV have been detected in 20% of cases [2270]. Chemical carcinogens produce similar tumours in some animals, but their role in humans is speculative.

Localization

In temperate climates, up to 70% of lesions develop on the face. In subtropical areas, there is a much greater tendency for lesions to arise on the arms, dorsum of the hands and the lower extremities.

Clinical features

Keratoacanthomas are usually solitary



Fig. 1.45 Keratoacanthoma. Typical clinical appearance of exophytic tumour with central crateriform ulceration filled with keratin plug.

pink or flesh-coloured, dome-shaped nodules with a central keratin plug. They measure 1-2 cm in diameter. They tend to grow rapidly over 1-2 months with spontaneous involution after 3-6 months. Uncommonly, lesions persist for more than 12 months. Because local tissue destruction can occur during growth and involution, active treatment is usually advocated.

Several clinical variants occur:

Giant keratoacanthoma, a lesion greater than 2-3 cm in diameter

Keratoacanthoma centrifugum marginatum, which undergoes progressive peripheral growth with coincident central healing [1740]

Subungual keratoacanthoma, a destructive form that may produce pressure erosion of the distal phalanx. They usually fail to regress spontaneously [146]

Multiple keratoacanthomas, which may be eruptive (Grzybowski type), self-healing (the Ferguson Smith type, which is autosomal dominant in inheritance and caused by an abnormality on chromosome 9q22-q31), and a mixed eruptive and self-healing type (Witten and Zak type).

Multiple lesions can also occur in immunosuppressed patients [625], in the Muir-Torre syndrome (see below) and at sites of trauma [1789].

Macroscopy

They are usually pale nodules with a central keratin plug.

Histopathology

Keratoacanthomas are exoendophytic, squamoproliferative nodules with a central, keratin plug. Fully developed lesions show lipping (buttressing) of the edges of the lesion which overlap the central keratin-filled crater, giving it a symmetrical appearance. Blunt downgrowths of squamous epithelium extend into the dermis with an irregular lower border to the tumour. The cells at the periphery of the squamous islands are basaloid in type. As they mature, they become large squamous cells with a distinctive pale eosinophilic cytoplasm. Mitoses may be seen, but atypical mitoses and stromal infiltration suggest a squamous cell carcinoma. SCCs are acknowledged to occur in less than 1% of keratoacanthomas found in subtropical regions. In one series, the reported incidence of a supervening squamous cell carcinoma was approximately one-quarter of all keratoacanthomas [2040].

A mixed inflammatory cell infiltrate, often including eosinophils and neutrophils may be present in the stroma. Neutrophils may extend into the epithelial nests, producing small microabscesses. Hyperplasia of sweat duct epithelium may be present in some cases.

Perineural invasion is an incidental and infrequent finding, often in facial lesions. It does not usually affect the prognosis or behaviour of the lesions, although local recurrence has been reported in such cases. Several cases with intravenous

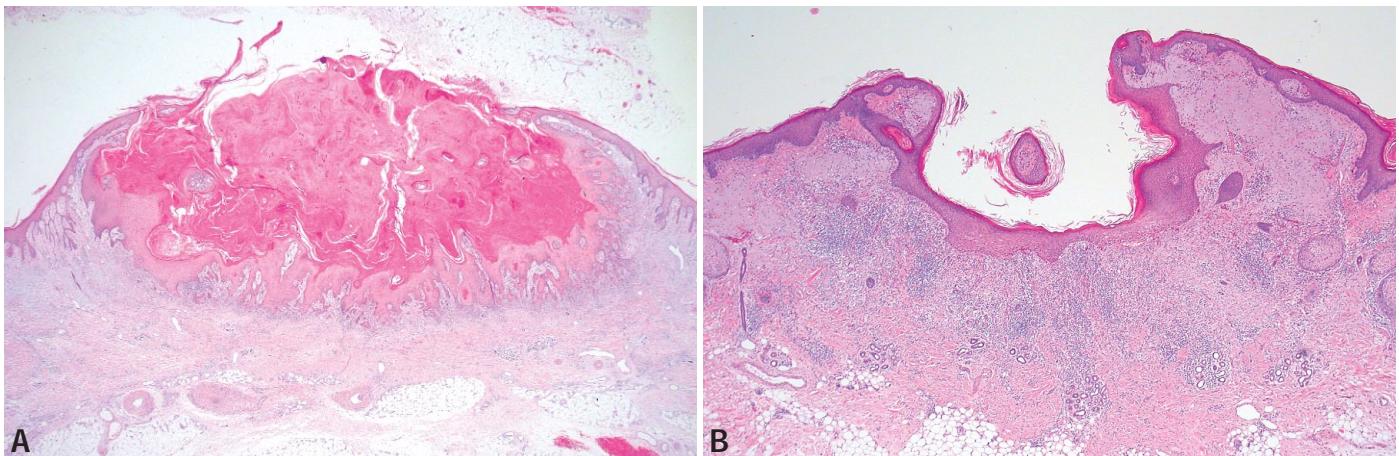


Fig. 1.46 **A** A low power view of keratoacanthoma demonstrating a central crateriform lesion filled with a keratotic plug and flanked by epidermal buttresses and consisting of tongues and lobules of squamous cells pushing into the deep dermis. **B** Regressed keratoacanthoma. The crateriform architecture remains but the tumour cells are replaced by flattened epidermal keratinocytes, accompanied by dermal fibrous scarring, a lichenoid inflammatory infiltrate and focal foreign body giant cell reaction to keratin in the dermis.

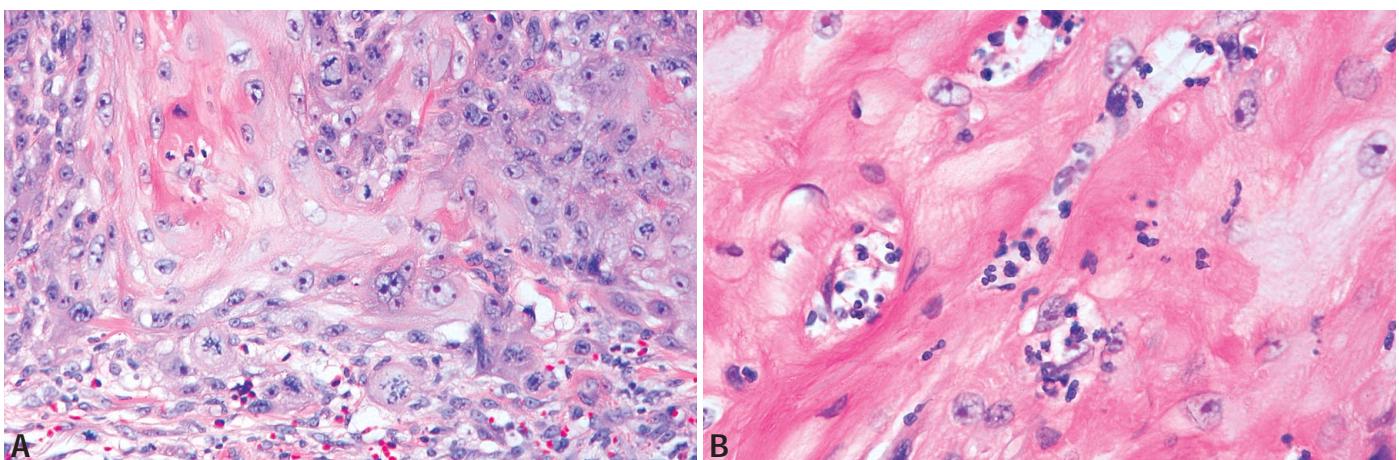


Fig. 1.47 Keratoacanthoma. **A** The tumour cells have abundant pale eosinophilic cytoplasm and pleomorphic nuclei, accompanied by a dermal lymphocytic and eosinophilic infiltrate. **B** Focal neutrophilic aggregates in tumour nests are characteristic of keratoacanthoma.

growth and a favourable outcome have been recorded {842}.

Regressing keratoacanthomas are shallower lesions with a large keratin plug and buttressing at the margins. There is progressive dermal fibrosis and disappearance of tumour nests in the dermis. Foreign body giant cells may be present around residual keratin fragments.

(PCNA / MIB-1 labelled proliferating cells are found in the periphery of the squamous nests in keratoacanthoma, in contrast to a more diffuse pattern in squamous cell carcinoma. Expression of TP53 is found in both tumours. Subungual keratoacanthomas have characteristic dyskeratotic cells, some showing dystrophic calcification, towards the centre of the tumour nests. This variant has fewer neutrophils and eosinophils.

The differential diagnosis from squamous cell carcinoma may be difficult or impossible in superficial shave and punch biopsies. Features favouring keratoacanthoma include the flask-like configuration with a central keratin plug, the pattern of keratinization, the large central squamous cells, the lack of anaplasia and a sharp outline between tumour nests and the stroma {555,2477}.

Histogenesis

The great majority of keratoacanthomas develop on hair-bearing skin {474} and are presumed to be derived from follicular keratinocytes, perhaps with a programmed life span. Those rare tumours that arise on glabrous skin and mucous membranes presumably derive from epithelial keratinocytes.

Genetics

A genetic defect has been reported in patients with the Ferguson Smith type of "multiple self-healing epitheliomas" (keratoacanthomas). The Muir Torre syndrome, in which sebaceous tumours develop in association with visceral tumours, usually gastrointestinal cancers, and often with keratoacanthomas, epidermal cysts and colonic polyps, is inherited as an autosomal dominant trait. Mutations have been found in some cases in one of the DNA mismatch repair genes MLH1 and MSH2.

Prognosis and predictive factors

Most lesions regress spontaneously over several months {260}. This regression may, in part, be immunologically mediated {1782}. Even lesions with perineural and intravenous invasion have a

favourable outcome. Keratoacanthomas can recur in up to 8% of cases. This is more likely with lesions on the fingers, hands, lips and ears. Trauma may be responsible for recurrent lesions in some cases. Rare cases that have developed metastasis have been reported {1038}. Possible explanations include misdiagnosis of the original lesion, the development of a supervening squamous cell carcinoma not recognized in the original material, genuine 'rogue' variants or transformation of the initial lesion into a squamous cell carcinoma in immunosuppressed patients {2476}.

Lichen planus-like keratosis

Definition

Lichen planus-like keratosis (LPLK) is a benign lesion of the skin that represents the attempted immunologic regression of a solar lentigo, seborrhoeic keratosis, large cell acanthoma or other epidermal proliferative lesion {1569,2150}.

Synonyms

Benign lichenoid keratosis.

Epidemiology

LPLK is a relatively common lesion. Most patients are middle-aged to elderly. There is a female predominance.

Etiology

The cause of the lesion is not exactly known. However, chronic sunlight exposure appears to be an important factor.

Localization

Most LPLKs are located on the upper trunk and upper extremities.

Clinical features

Clinically, LPLK presents as a flat, irregularly hyperkeratotic plaque with often irregular borders. It may be irregularly pigmented or pale in colour. The lesion resembles a basal cell carcinoma, Bowen disease, actinic keratosis or flat seborrhoeic keratosis. Itching and some pain may occur {1373}. Dermatoscopy can rule out melanocytic lesions.

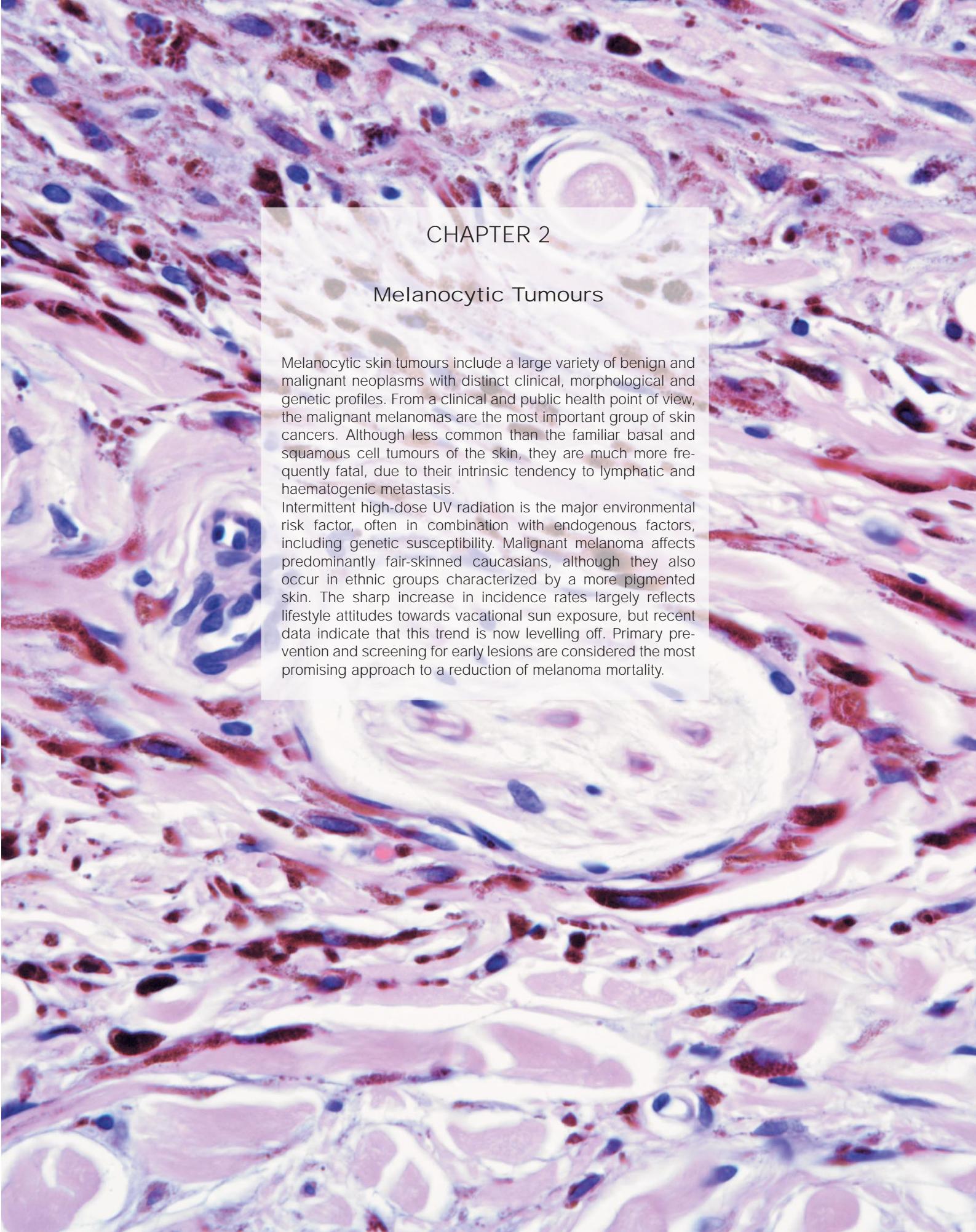
Histopathology

LPLK is characterized by a lichenoid lymphocytic infiltrate leading to basal vacuolar change and numerous apoptotic cells. There is hypergranulosis and

hyperkeratosis, frequently with parakeratotic foci. Actinic elastosis is often present {785}. Features of solar lentigo, large cell acanthoma or early seborrhoeic keratosis may be present at the margins. The inflammatory infiltrate often extends around the superficial vascular plexus.

Differential diagnosis

Lichenoid solar keratosis shows atypia of epidermal keratinocytes. In lichen planus, the inflammatory cells do not usually extend around the superficial vascular plexus. Furthermore parakeratosis, plasma cells and/or eosinophils may be present in LPLK. Similar changes may be seen in lichenoid drug eruptions. Clinical information may be required to separate these entities.



CHAPTER 2

Melanocytic Tumours

Melanocytic skin tumours include a large variety of benign and malignant neoplasms with distinct clinical, morphological and genetic profiles. From a clinical and public health point of view, the malignant melanomas are the most important group of skin cancers. Although less common than the familiar basal and squamous cell tumours of the skin, they are much more frequently fatal, due to their intrinsic tendency to lymphatic and haematogenous metastasis.

Intermittent high-dose UV radiation is the major environmental risk factor, often in combination with endogenous factors, including genetic susceptibility. Malignant melanoma affects predominantly fair-skinned caucasians, although they also occur in ethnic groups characterized by a more pigmented skin. The sharp increase in incidence rates largely reflects lifestyle attitudes towards vacational sun exposure, but recent data indicate that this trend is now levelling off. Primary prevention and screening for early lesions are considered the most promising approach to a reduction of melanoma mortality.

WHO histological classification of melanocytic tumours

Malignant melanoma		
Superficial spreading melanoma	8743/3	Dermal melanocytic lesions
Nodular melanoma	8721/3	Mongolian spot
Lentigo maligna	8742/2	Naevus of Ito and Ota
Acral-lentiginous melanoma	8744/3	Blue naevus
Desmoplastic melanoma	8745/3	Cellular blue naevus
Melanoma arising from blue naevus	8780/3	Combined naevus
Melanoma arising in a giant congenital naevus	8761/3	Melanotic macules, simple lentigo and lentiginous naevus
Melanoma of childhood		Dysplastic naevus
Naevoid melanoma	8720/3	Site-specific naevi
Persistent melanoma	8720/3	Acral
		Genital
		Meyerson naevus
Benign melanocytic tumours		Persistent (recurrent) melanocytic naevus
Congenital melanocytic naevi		Spitz naevus
Superficial type	8761/0	Pigmented spindle cell naevus (Reed)
Proliferative nodules in congenital melanocytic naevi	8762/1	Halo naevus

¹ Morphology code of the International Classification of Diseases for Oncology (ICD-O) [786] and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, /2 for non-invasive tumours, and /1 for borderline or uncertain behaviour.

TNM classification of malignant melanoma

TNM classification^{1,2}

T – Primary tumour

The extent of the tumour is classified after excision, see pT.

N – Regional lymph nodes

- NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1: Metastasis in one regional lymph node
 N1a: only microscopic metastasis (clinically occult)
 N1b: macroscopic metastasis (clinically apparent)
N2: Metastasis in two or three regional lymph nodes or intralymphatic regional metastasis
 N2a: only microscopic nodal metastasis
 N2b: macroscopic nodal metastasis
 N2c: satellite or in-transit metastasis *without* regional nodal metastasis
N3: Metastasis in four or more regional lymph nodes, or matted metastatic regional lymph nodes, or satellite or in-transit metastasis *with* metastasis in regional lymph node(s)

Note: Satellites are tumour nests or nodules (macro- or microscopic) within 2cm of the primary tumour. In-transit metastasis involves skin or subcutaneous tissue more than 2 cm from the primary tumour but not beyond the regional lymph nodes.

M – Distant metastasis

- MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
 M1a: Skin, subcutaneous tissue or lymph node(s) beyond the regional lymph nodes
 M1b: Lung
 M1c: Other sites, or any site with elevated serum lactic dehydrogenase (LDH)

pT – Primary tumour (pathological classification)

- pTX Primary tumour cannot be assessed*
pT0 No evidence of primary tumour
pTis Melanoma in situ (Clark level I) (atypical melanocytic hyperplasia, severe melanocytic dysplasia, not an invasive malignant lesion)
- pT1: Tumour 1mm or less in thickness
 pT1a: Clark level II or III, without ulceration
 pT1b: Clark level IV or V, or with ulceration
pT2: Tumour more than 1mm but not more than 2mm in thickness
 pT2a: without ulceration
 pT2b: with ulceration
pT3: Tumour more than 2mm but not more than 4mm in thickness
 pT3a: without ulceration
 pT3b: with ulceration
pT4: Tumour more than 4mm in thickness
 pT4a: without ulceration
 pT4b: with ulceration

Note: *pTX includes shave biopsies and regressed melanomas.

Stage grouping³

Stage 0	pTis	N0	M0
Stage I	pT1	N0	M0
Stage IA	pT1a	N0	M0
Stage IB	pT1b	N0	M0
	pT2a	N0	M0
Stage IIA	pT2b	N0	M0
	pT3a	N0	M0
Stage IIB	pT3b	N0	M0
	pT4a	N0	M0
Stage IIC	pT4b	N0	M0
Stage III	Any pT	N1, N2, N3	M0
Stage IIIA	pT1a-4a	N1a, 2a	M0
Stage IIIB	pT1a-4a	N1b, 2b, 2c	M0
	pT1b-4b	N1a, 2a, 2c	M0
Stage IIIC	pT1b-4b	N1b, 2b	M0
	Any pT	N3	M0
Stage IV	Any T	Any N	M1

¹ UICC (2002). TNM classification of malignant tumours. Sixth edition. Wiley, New York

² AJCC (2002). Cancer staging manual. Sixth edition. Springer, New York

A help desk for specific questions about the TNM classification is available at <http://www.uicc.org> (activities, TNM)

³ Clinical staging includes complete excision of the primary melanoma [pT] with clinical/radiological assessment for regional and distant metastases.

Pathologic staging includes complete excision of the primary melanoma [pT] and pathologic assessment of the regional lymph nodes [pN] after partial or complete lymphadenectomy. Stage 0 or stage IA patients do not require pathological evaluation of their lymph nodes.

Malignant melanoma: Introduction

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Incidence and mortality

Approximately 79,000 males and 81,000 females were diagnosed with melanoma world-wide in 2002, of which about 80% occurred in the predominantly white populations of Northern America, Australia, New Zealand and Europe. On a global scale, malignant melanoma was the 16th and 15th most commonly diagnosed cancer in males and females respectively and occurred most frequently in Australia and New Zealand (4th most common males, 3rd in females), North-America (6th in males, 5th in females), and Europe (16th in males, 8th in females) {724}.

In 2002, around 22,000 males and 19,000 females died of the disease worldwide {724}. Melanoma is one of the most important cancers when considered as a cause of loss of life as it is commonly diagnosed in relatively young people {54,310,350,1761}, and can be fatal if untreated. It has been calculated that, in the United States, a person dying of melanoma would die, on average, some 17 years before the age of 65, whereas in Denmark, the mean figure is put at 14-15 years, and in Belgium 6-8 years {54, 310,1761}.

Melanoma had a poor prognosis in the 1950's and 1960's, but from the mid 1970s, mortality rates have been stabilising in many high-risk populations, although incidence rates are still increas-

ing. Survival has improved substantially, mainly in countries with high incidence rates. This is mainly due to early detection of melanomas as a result of an increasing awareness of the disease, probably partly owing to the success of primary and secondary prevention campaigns.

Geographical differences

The levels of both melanoma incidence and mortality vary considerably worldwide. Rates are high in populations where Caucasians predominate, and correspondingly low in countries where inhabitants are of mainly Asian or African origin.

Melanoma in Caucasians

As the most important environmental risk factor in Caucasians is exposure to ultraviolet radiation, incidence within white populations generally increases with increasing proximity to the equator. The highest rates are observed in Australia, where many inhabitants are of Northern European descent and live in a climate with substantially more sunshine than the norm in Northern Europe.

In Western Europe, a diverging pattern is observed: incidence rates are higher in Northern Europe (more distant from the equator) than in the South, reflecting a combination of lighter skin type and higher wealth in the North of Europe. In wealthy populations, a high incidence of

melanoma is observed with relatively low mortality rates, due to the fact that melanomas are diagnosed in early stages {609}.

Migrant studies

Groups of migrants from regions of low melanoma incidence to high incidence regions acquire higher rates of melanoma than in their home country, but lower than those in the host country, in both sexes {96,689}. Incidence and mortality rates of native Australians and New Zealanders, who are largely of British origin, are estimated to be roughly twice those of recent British immigrants to these countries {96,1255}. Likewise, native Israelis experience a twofold increased risk of incidence compared to immigrants to Israel from Europe, a risk that remains at least three decades following immigration {2260}. The risk of immigrants has been shown to approach that of the native populations in both Australia and Israel with increasing duration of residence in the host country {96, 533,689,1255,2260}.

Amongst Northern European migrants to Australia, the incidence rates of melanoma have been observed to increase with duration of residence, but decrease with later age of arrival, suggesting that exposure at young ages is important in determining risk {1255}. The lowest risk in immigrants to Australia has been found to be for Southern European and Eastern Asian migrants, reflecting the protective effect of a higher degree of skin pigmentation {1255}. Differences in skin colour are also assumed to be the reason underlying the higher incidence of melanoma in white immigrants to Hawaii from the United States mainland {1031}.

Melanoma in non-Caucasians

U.S. Whites have rates 15 times higher than U.S. Blacks, and a similar contrast in risk is observed in the White and Black populations of South Africa and Zimbabwe {1780}. Melanoma is also relatively uncommon among Asians {1295},

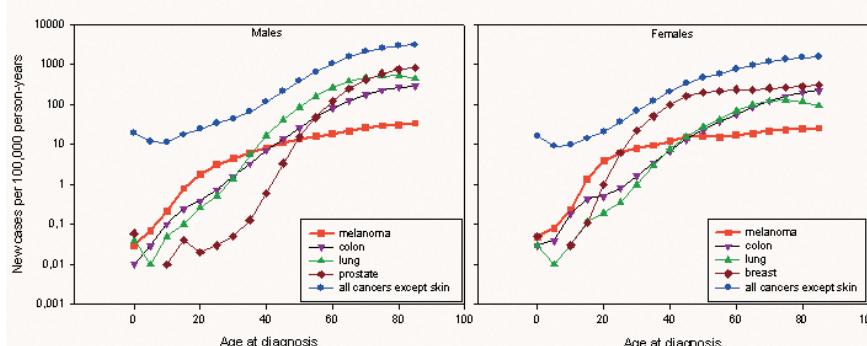


Fig. 2.1 Age-specific incidence of cancer. All data are based on data from Europe 1990-1997.
Source: European Network of Cancer Registries, EUROCIM 4.0, Lyon 2001.

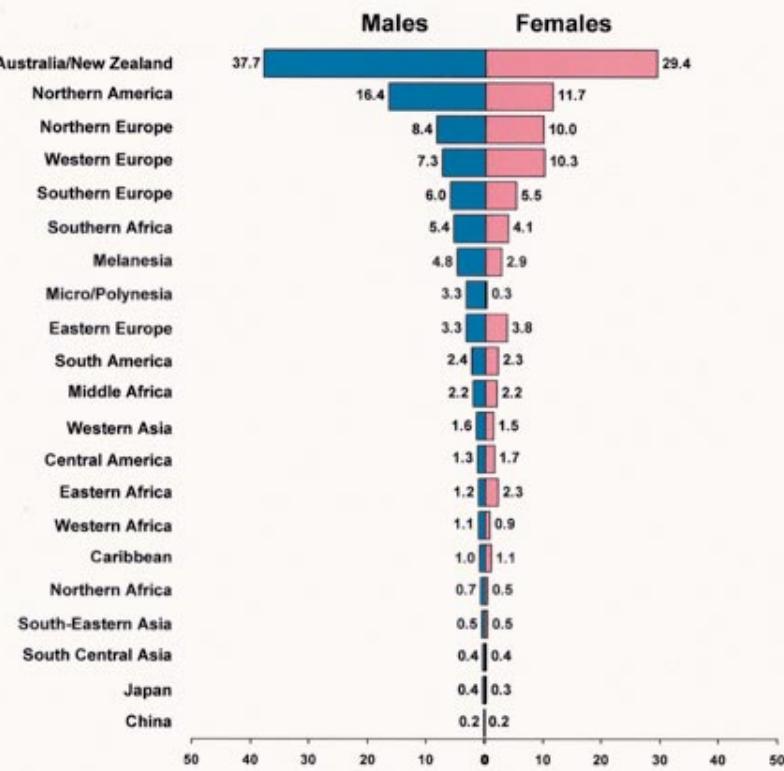


Fig. 2.2 Age-standardized incidence rates for malignant melanoma of skin, per 100 000 population and year, adjusted to the world standard population. From D.M. Parkin et al. (1779).

1746} and Middle- and South-American populations {891}, probably due to a better protection afforded by a larger amount of pigment in the skin and possibly different ('wiser') sun-exposure patterns. Melanomas appear more often on the non-pigmented areas of the skin in non-Caucasians {940}, are often of the acral lentiginous melanoma type and appear on the palms of hands, soles of the feet and under the nails {200,554}. A common problem in these populations is that pigmented lesions in the skin are often more difficult to notice, and are therefore often detected at relatively late stages, which, at least in part, explain the high case-fatality rates {200,554}. In many African and Asian societies it is

considered beautiful to have a light skin. The avoidance of sun-exposure and even more extreme measures, such as bleaching of the skin, have been reported {952,2081}.

Time trends

Since the 1970's there have been reports of alarming increases in melanoma, initially in terms of mortality {1393} and then in incidence {1481}. These reports observed a doubling in rates every one or two decades (mean annual increments of between 3% and 7%) per annum in populations of European origin for both genders {1761}. The incidence rates increased markedly for intermittently exposed body sites (trunk, legs, etc.) whereas increases in the face and neck were moderate. In males, the largest increases were found on the trunk, and in females on the legs and arms {332,459, 1007,1472,1482,1699,2120,2245,2350}. In an analysis of the SEER data, it was found that melanomas of all stages increased from 1988-1997, but that localized and *in situ* lesions increased the most {1137}.

In the United States, Australia and Northern Europe, where incidence rates were very high during the 1980s, the rates have been rising less sharply or levelling off since the mid-1990's, especially in younger age groups {516,609, 1137,1353,1472,2144,2244,2245}. In contrast, in Southern and Eastern Europe and in Latin America, rates are increasing {7,609,1353,1579,2144}. Incidence rates in Asia have been rather stable {1142,1295}. There is insufficient data at present to report on time trends in melanoma incidence among African populations. Over the last decades, increases in incidence have mainly been observed for thin melanomas, whereas the rate of thick melanomas seems to be relatively stable {618,1433}. This increase in the number of thin melanomas is mainly observed in countries with high incidence rates, where increases in rates are mainly seen in the superficial spreading melanomas {414, 560,1052,1137,1472,1501}. In countries with lower incidence rates, increases are generally more evenly spread across thickness categories.

Although trends in incidence rates of melanoma vary greatly, mortality rates show less variation. Mortality rates have been levelling off in many populations with high melanoma incidence rates, such as Australia, the United States, and North-western Europe {516,609,827, 1353,1411,1412}. In some countries, a levelling off of incidence rates is now also observed, starting in younger age groups {609}.

Stabilisation of melanoma incidence rates

Age-period-cohort analyses indicate that in Western populations (USA, Australia, New Zealand, Sweden, the Netherlands, Germany) the increasing mortality rates have started to level off, starting in cohorts born in the 1930s and 1940s {534,827,1050,1136,1692,1983,2244, 2352}. In Southern Europe, generally those with lower incidence rates (e.g. Italy and Spain) there has been no sign, as yet, of a downwards trend {1480, 1849,2144}.

A recent plateau in melanoma mortality rates (in some cases followed by incidence rates) is reported in high-incidence countries, such as Australia, USA, Sweden, Norway and Germany {609, 1353,1761,2120,2245}. Only the mortalit-

Table 2.01

Age-standardized incidence rates per 100 000 person / year in the SEER registry (USA) {1781A}.

Population	Males	Females
Blacks	1.00	0.5
Whites	15.4	11.6

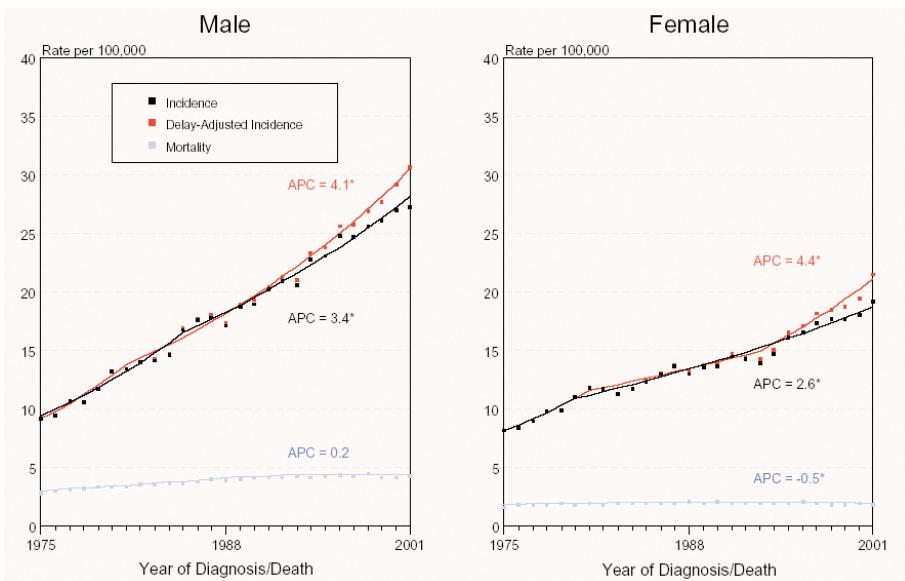


Fig. 2.3 Melanoma of the skin in Whites. SEER Incidence, delay adjusted incidence and US death rates. Despite rising incidence rates, mortality is now stable in men and shows a recent decrease in women. From: L.A.G. Ries et al. (1936). http://seer.cancer.gov/csr/1975_2001/

ty rates levelled off initially, starting in the late 1970s, with increasing incidence rates. This was most likely because of improving survival {1472, 2245,2351} due to earlier detection, as there were no major advances in systemic treatment. Melanoma incidence rates have been reported to be levelling off, or even decreasing in younger age groups, starting in the 1980s {609}. Furthermore, the mean and median stage or thickness at diagnosis is decreasing {560,618,1433, 1472,2351}, with an increasing registration of thin, superficial spreading melanomas.

Changes in the biology of melanoma, characterized by a tendency towards less aggressive lesions being observed {353} could also be consistent with a continuing rise in melanoma incidence, and a corresponding moderation or stabilisation in the mortality rates.

Etiology

There has been much discussion and debate as to the reasons underlying the dramatic increases in melanoma incidence and mortality, and in particular, whether they are real or due to artefacts, via, for example, increased efforts at screening and diagnosing the disease, changes in diagnostic criteria, or the existence of a non-metastasizing biolog-

ically benign form of melanoma. Although some artefacts may have contributed to the increases, a substantial part of the increases is assumed to be genuine {610}.

Both familial and environmental factors play a role in the etiology of melanoma. The familial/genetic components include skin type, number of naevi, having clinical atypical naevi, and having a family history of skin cancer. They are the most important predictors of melanoma risk. As it is not likely that there has been a substantial change over time in familial/genetic risk factors in most populations, these cannot have contributed substantially to the observed increases in melanoma incidence over the past 50 years.

Exposure to UV radiation

Intermittent exposure to UVR is the major environmental risk factor for melanoma, especially in combination with endogenous factors (skin types I and II, immune deficient status, genetic predisposition) {95}. The association between UVR and melanoma is ambiguous, with differences in risks associated with the dose, the way it is delivered (intermittent vs. chronic exposures) and critical time periods (childhood vs. cumulative exposure during life). Intermittent exposure to UVR in white people, especially during childhood, has been postulated to be the

main risk factor for the development of melanoma, although exposure in adulthood also plays a part. The relative risk of UV exposure for the development of melanoma is around 2, but when skin characteristics are taken into account, the relative risks increase markedly for those with a sun-sensitive skin. As sunbeds also emit UV-radiation, they most likely also confer a risk for the development of melanoma, as was recently confirmed in a large prospective study {2426}.

Although high sun exposure in childhood is a major determinant {2509}, multiple sunburns {683} and high exposure throughout life {117} raise risk of disease significantly. Cutaneous melanomas appear to arise by different pathways. Those on the head and neck relate mainly to chronic sun exposure while those on the trunk occur in people with many melanocytic naevi {2508}. High numbers of naevi reflect an innate propensity to melanocytic proliferation {2196,2197} and stimulation by sun exposure {591}. The risk of acral melanoma is also increased by exposure to high cumulative UVR and to agricultural chemicals {890}. Occupational sun exposure, especially farming, is associated with risk of ocular melanoma {2401}. Inherited mutations of tumour-suppressor genes (eg CDKN2A) are strongly associated with familial melanoma but probably underlie less than 1% of all cutaneous melanoma {42}.

Occupational vs. recreational exposure

Before the Industrial Revolution, many wealthy people had a pale skin: they worked or stayed indoors, whereas the lower classes tended to work mainly outdoors. During the industrialisation of society (1750-1800), working class people started working indoors and only the rich had the time and money to afford recreational outdoor life. By the early 1920s, daily exposure to sunlight was also advised as a cure for many diseases (acne, rickets, tuberculosis), especially for children. By the 1930s a suntan had become a symbol for wealth and health and since the 1950s, holidays to sunny destinations became popular and affordable to many.

The rising melanoma incidence is most commonly attributed to changes in lifestyle with increasing intermittent exposure to ultraviolet radiation (UVR), due to

the popularity of sunbathing and tanning. Given an induction time of some 20-40 years between exposure and melanoma occurrence, these factors are in accordance with the continuing increases - mainly on the trunk in men and on the legs in women {331,332,619,620,682,772,2409}.

Ozone layer

Another explanation for the increases is the depletion of the ozone layer, which protects the earth's surface against UVR by filtering out a large part of the UVR from the sunlight before it reaches the earth's surface. Chemical substances released in the earth's atmosphere are slowly breaking down the ozone layer {2199}, increasing the amount of UVR that reaches the earth's surface and likely increasing the risk of skin cancer. Estimates indicate that skin cancer incidence rates could increase dramatically by the end of this century compared to the situation around 2000 {1240}.

Socio-economic status

Melanoma is more common among people with a higher socio-economic status, probably due to a higher excessive intermittent exposure to UVR (outdoor sports, winter sports, sunbathing, getting a tan) in this group. Increasing wealth over the past 6 decades in large parts of the Western (i.e. predominantly Caucasian) populations may indirectly have contributed to the increases in incidence rates of melanoma and other skin cancers.

Melanoma prevention

Sunscreens

An international group of experts convening at the International Agency for Research on Cancer investigated the preventive effects of sunscreen use on the development of skin cancer: They concluded that the use of protective cream could indeed prevent erythema and squamous cell carcinoma after non-intentional sun-exposure (i.e., exposure to the sun without the objective of getting exposed, for example, work-related exposure). Its protective effect for basal cell carcinoma and melanoma, however, is not yet determined, as it is difficult to study due to a long latency period. Paradoxically, there is inconsistent evidence that the use of sunscreens may

increase the risk of melanoma development by increasing sunbathing-time. Of fifteen case-control studies examined by an expert panel, only 3 showed a significantly reduced risk of melanoma, with relative risks between 0.2 and 0.6, the others observing no significant effect (4 studies) or an increased risk (8 studies, RR between 1.7 and 3.5) {2400A}. The increasing use of sunscreens may therefore have contributed to the increases in melanoma incidence.

Vaccination

Vaccination during childhood against tuberculosis with the Bacille Calmette-Guérin (BCG) vaccine or against smallpox with the vaccinia vaccine, or having experienced one or more infectious diseases may decrease the risk of developing melanomas (odds ratios between 0.29 and 0.44) {1303,1330,1331,1821,1822}. Part of the increases in melanoma incidence could be due to the abolishment of this type of vaccination in Europe.

Clinical features

Sites of involvement

Most commonly affected site per unit surface area of skin in both sexes is the face and male ear head and neck {772,890}, with back and shoulders in men and the lower limbs in females also having high rates per unit area.

Major subtypes

Most classification schemes of melanoma categorize them clinically into four major types, but such classification has little prognostic value and diagnostic relevance, thus being of very limited usefulness in clinical practice.

Lentigo maligna melanoma.

This type of melanoma develops when an invasive tumour arises in a lentigo maligna. It is most common in the head and neck region and in elderly people, and has a relatively favourable prognosis.

Superficial spreading melanoma.

This type of melanoma grows laterally before vertical invasion develops. Increasingly, this is the most common type of melanoma in Caucasians, and has a relatively favourable prognosis

being frequently observed in young patients, and on body sites that are intermittently exposed to sunlight.

Nodular melanoma

It usually presents as a rapidly growing pigmented nodule (amelanotic nodular melanomas are rarely observed), which bleeds or ulcerates. This is the most aggressive type of melanoma. It often presents on body sites that are intermittently exposed to sunlight.

Acral lentiginous melanoma

These lesions are pigmented, arising on the palm of the hand, sole of the foot or under the nails. They often present late and represent the most common type of melanoma in heavily pigmented people.

Age distribution

Malignant melanoma (hence referred to as melanoma) is a tumour affecting predominantly adults and elderly patients, with a peak of incidence around the sixth decade of life. In recent years, however, it has been increasingly recognized in middle-aged and young adults, and can be observed in children and adolescents as well. Thus, no age group is spared, and a high level of suspicion should be exerted in examination of any dubious pigmented lesion regardless of the age of the patient.

Origin

The clinical features of melanoma are variable and depend on type and stage of evolution of the tumour, and on location of it. Melanoma may occur de novo, that is, without a precursor lesion, or may develop within a pre-existing benign melanocytic naevus {1168,1750}. It has been estimated that 20-30% of melanomas arise within a pre-existing melanocytic naevus, but this figure in truth may be higher, as in many instances it is very difficult to distinguish histopathologically residual complexes of a benign naevus from those of the melanoma. All types of melanocytic naevi can give rise to a melanoma, but some are more frequently involved, such as congenital melanocytic naevi. Melanoma has only rarely been observed in association with Spitz naevi {1380}, but this may be due also to the difficulty in discerning histopathologically melanocytes of a melanoma from the atypical melanocytes frequently found in

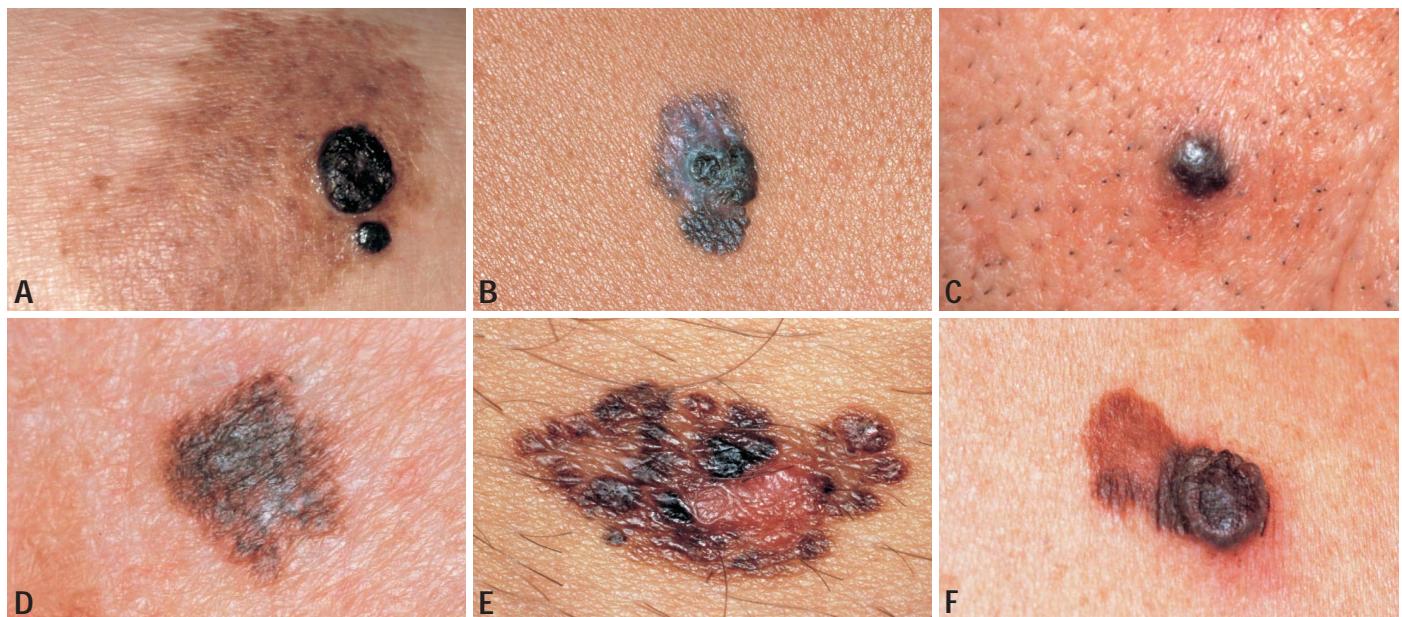


Fig. 2.4 Clinical presentation of melanomas. **A** Malignant melanoma arising in a congenital naevus. **B** Stereotypical cutaneous melanoma characterized by asymmetry, uneven pigmentation, and irregular margins. **C** "Small" melanoma (< 3 mm) characterized by a relatively symmetrical, evenly pigmented small papule. **D** Melanoma in situ. Note flat pigmented lesion with different hues of brown and slightly irregular margins. **E** Early "invasive" melanoma characterized by marked asymmetry and variegations in colour. **F** A nodule of melanoma arising within an in situ component. Note the irregular pigmentation and asymmetry of the flat part of the lesion.

Spitz naevi. Melanoma arising within a pre-existing blue naevus is commonly referred to as malignant blue naevus, an imprecise term that should be avoided. Melanoma may arise at the site of pre-existing scars (e.g., burn scar) {1758}. Recurrence at the site of a scar from previous biopsy or narrow excision is a sign of incomplete excision of the primary tumour. Recurrence at the site of a complete excision (with negative margins verified histologically) represents locally metastatic disease rather than persistence {1000}.

ABCD rule

The most useful criteria for clinical diagnosis of melanoma are asymmetry and uneven pigmentation of the lesion, and have been integrated in the acronym "ABCD" (Asymmetry, irregular Border, uneven Colour, Diameter > 6 mm) {1552}. Although the "ABCD" mnemonic is considered the standard approach for the clinical diagnosis of melanoma, it has severe limitations when applied to early lesions of it, that may have a relatively homogenous pigmentation, sharp margins, and small diameter. Melanomas less than 5 mm in diameter have been referred to as "small melanomas" in the literature, and may be the source of diagnostic pitfalls both clinically and histo-

pathologically {282}. In addition, when assessed with the ABCD rule many benign melanocytic naevi have atypical features, thus decreasing specificity of this diagnostic criteria, too.

Pigmentation and growth

Most (practically all) de novo melanomas are pigmented lesions that begin as a flat macule, representing the neoplastic growth of malignant melanocytes confined to the epidermis (melanoma in situ). Lesions in this stage are characterized by a relatively homogenous brown pigmentation with slightly irregular borders. Over time (in most instances probably several years) lesions spread horizontally showing more irregular contours and variegations of the pigmentation, and revealing histopathologically involvement of the superficial (papillary) dermis. When the papillary dermis is filled by neoplastic melanocytes the lesions appear as irregular, unevenly pigmented plaques. In later stages the neoplasms exhibit vertical growth resulting in the formation of papules or nodules, usually confined to one area of the lesion. The papules and nodules represent areas where the tumour grows vertically through the dermis, eventually involving the subcutaneous tissues. In a minority of cases, melanoma exhibits a rapid nodu-

lar growth from the outset without horizontal spread, usually within a few months (so-called nodular melanoma). Finally, exceptional cases of dermal melanomas without any intraepidermal component have been recorded {2305}.

Regression

Partial regression of part of the lesion takes place commonly during the entire process of growth of melanoma, resulting in the presence of whitish-grey areas that accentuate the asymmetry and uneven pigmentation of the lesion. In rare cases, complete regression can be observed, leading to the disappearance of all neoplastic melanocytes. Usually, these lesions show uneven pigmentation with whitish, grey and black areas corresponding to the presence of variable fibrosis and infiltrates of melanophages in the dermis. With time, the pigmentation may disappear almost completely. Although regression is an immune-mediated phenomenon corresponding to the elimination of malignant melanocytes by cytotoxic lymphocytes, complete regression of a melanoma can be associated with metastatic spread, thus being a bad rather than a good prognostic sign. The prognostic role (if any) of partial or focal regression has not yet been elucidated, but it seems negligible {764}.

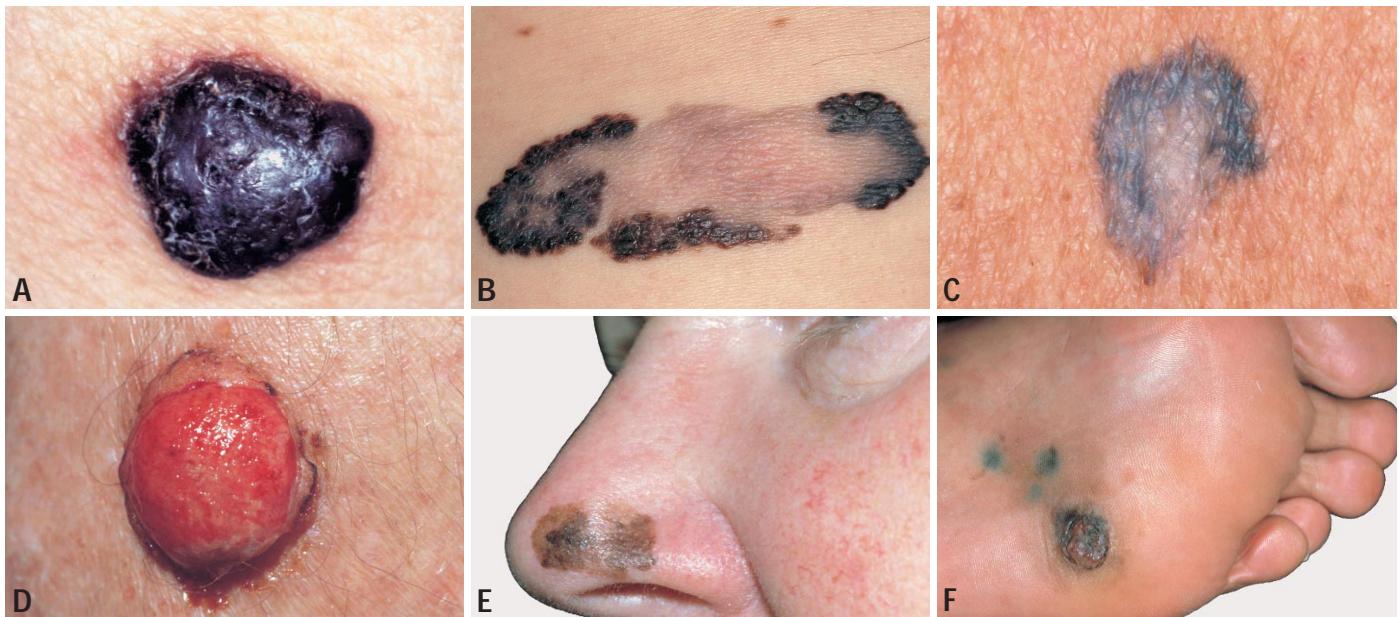


Fig. 2.5 Clinical presentation of melanomas. **A** Nodular melanoma. Large, darkly pigmented tumour practically devoid of a flat component. **B** Melanoma with prominent regression resulting in almost complete disappearance of large part of the lesion. **C** Complete regression of melanoma. The grey pigmentation is due to the presence of heavy infiltrates of melanophages within a fibrotic papillary dermis. The patient had regional lymph node metastases at presentation. **D** Ulcerated nodular melanoma resembling a granuloma pyogenicum. Note focally small areas of slight pigmentation at the margins. **E** So-called "lentigo maligna" (melanoma in situ on sun-damaged skin) arising on the nose. **F** Acral melanoma. Note the marked irregularity of the margins, conferring a "multifocal" appearance to the lesion.

Melanoma is more frequent in particular settings (so-called "markers") including a familial history of melanoma, a previous melanoma in the same patient, presence of many melanocytic naevi, presence of giant congenital naevi, skin type 1 or 2, as well as in rare conditions such as xeroderma pigmentosum among others {53,901,1196,1202,2231,2481}. Patients presenting with one or more of these features should be monitored closely, and suspicious lesions should be biopsied. It is important to remember that multiple primary melanomas may be observed rarely in some patients {1196}.

Clinical variants

Amelanotic melanoma

Although melanoma is a tumour characterized by variable degrees of pigmentation, in rare instances the pigment may be missing altogether (so-called amelanotic melanoma). Amelanotic melanomas are more frequent on the face, where they often display the histopathologic features of desmoplasia (desmoplastic melanoma), but can be observed also on other parts of the body {77,2285}.

Mucosal melanoma

Melanomas arising within a mucosa (oral mucosa, genital mucosa) are often multifocal, and are characterized by dark,

uneven pigmentation {670,1963}. Differentiation of early lesions of mucosal melanoma from so-called melanosis (a benign condition characterized by prominent hyperpigmentation of the mucosa without or with only slight increase of melanocytes at the dermo-epidermal junction) may be very difficult or even impossible clinically as well as histopathologically.

Subungual melanomas

In early stages these are sometimes characterized by the presence of a well demarcated, pigmented longitudinal streak (longitudinal melanonychia) {263}. The so-called Hutchinson sign (periumgual spread of the pigmentation on the proximal or lateral nail fold) may be absent in early lesions, thus representing a pitfall in the clinical diagnosis.

Ulceration

Rapidly growing, ulcerated melanomas may be misdiagnosed clinically as granuloma pyogenicum. Pigmentation in these cases may be scant and confined only to small areas of the tumour.

Verrucous phenotype

In rare cases, melanoma may present with a verrucous surface similar to what can be observed in seborrhoeic ker-

atoses or common warts (verrucous melanoma) {101}. These cases may be misinterpreted clinically as pigmented seborrhoeic keratoses or other verrucous tumours.

Dermatoscopy

Besides clinical examination, dermatoscopy (dermoscopy, skin surface microscopy, epiluminescence microscopy) has been increasingly regarded as a valuable aid in diagnosis of early melanoma clinically. Dermatoscopic instruments enlarge the lesion 6-100-fold, thus allowing detection of structures and signs not visible to the naked eye. In addition, connection of the dermatoscopic devices to a computer allows one to take standardized digital pictures that can be compared over time, thus being much more sensitive for detection of minimal structural changes of the examined lesion {719}. Finally, computer-assisted diagnostic systems based on dermatoscopic images are available as aids for the evaluation of suspicious pigmented lesions {91}.

Several dermatoscopic diagnostic approaches have been proposed, all of them relying on the examination of distinct patterns and structures. Of particular value in the diagnosis of melanoma are the presence of an irregular pigment

network (uneven thickness of the lines, presence of broad lines at the periphery of the lesion), of black or brown dots irregularly distributed within the lesion, of irregular lines at the periphery of the lesion that are not clearly combined with the pigment network (streaks), of a bluish-whitish veil corresponding to infiltrates of melanophages below a thick epidermis with hypergranulosis, of an atypical vascular pattern, and of regression structures. A 7-point checklist for dermatoscopic scoring of atypical melanocytic lesions using the aforementioned criteria has been proposed, and it has been suggested that this approach allows diagnosis of melanoma with a sensitivity of 95% and a specificity of 75% [91,1671]. Other proposed approaches include the Menzies method and the ABCD rule [91]. Besides dermatoscopy, the use of several other devices has been proposed for the early *in vivo* diagnosis of melanoma, including confocal laser microscopy [1509].

Staging

Staging investigations depend on stage and extent of the disease and should always include a complete clinical examination [2218A]. Sonography of the superficial lymph nodes and of the abdomen, radiography of the thorax and evaluation of serum markers such as lactate dehydrogenase (LDH), S-100-beta or melanoma-inhibiting activity (MIA) seem to be of little value in asymptomatic patients. Computer tomography (CT) scan, magnetic resonance imaging (MRI), bone scintigraphy and positron emission tomography (PET) are useful methods for evaluation of patients with metastatic disease.

Histopathology

Architectural criteria in the epidermis

Lesional breadth

A proliferation of melanocytes wholly within the epidermis can range in size from >1 mm to a patch many cm in width. Both melanocytic naevi (conventional and Spitz) and melanoma begin as proliferations in which single melanocytes predominate.

By the time most melanomas can be recognized as such clinically they are over 4 mm in diameter, and often far broader [730]. While a large lesional diameter is a

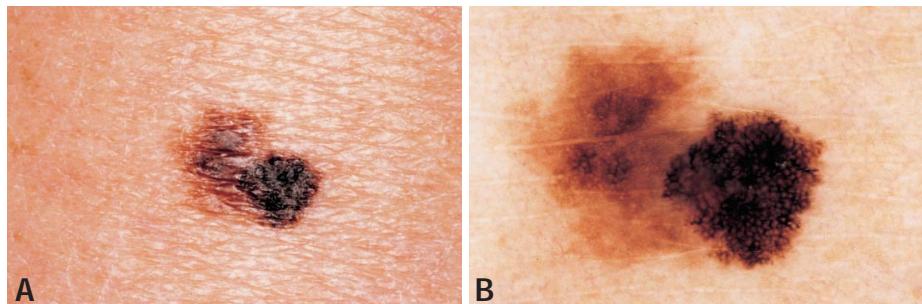


Fig. 2.6 Clinical presentation. **A** and dermatoscopic picture **B** of an early melanoma developing within a "dysplastic" naevus. Note the marked asymmetry of the lesion and the presence of an area with irregular pigment network and broad lines at the periphery, representing melanoma *in situ*.

finding favouring melanoma, there are many exceptions.

Symmetry of changes in the epidermis

The most important attribute of symmetry is in reference to that of melanocytes themselves. The symmetry or lack thereof in terms of the distribution of melanocytes in the epidermis is more difficult to judge than is the overall silhouette of the lesion. It is evaluated by comparing the density of melanocytes on one side of the lesion with the other; pattern of distribution of melanocytes (are they at the junction or above it) on one side of the lesion with the other; disposal as nests or as single cells on one side of the lesion with the other; cytological findings (are melanocytes on one side of the lesion different cytologically with those on the other side). Asymmetry in any of these attributes favours melanoma. Secondary forms of asymmetry, less important than that of the distribution of melanocytes include asymmetry in pigmentation, epidermal thickness and inflammatory infiltrates. Most of these attributes are not decisive [2506].

Pigmentation in the epidermis in melanocytic neoplasms is usually in the basal layer (exceptions are particularly dark lesions, such as so-called hypermelanotic naevi) [513]. In such naevi, and in very dark foci of some melanomas, there may be copious melanin in keratinocytes not only in the basal layer but also in the spinous and cornified layers. Either an asymmetrical distribution of melanoma in the basal layer of the epidermis, or melanin above the basal layer on one side of the lesion but not on the other raises the possibility of melanoma. An irregular distribution of epidermal pigment is the cause of one of the "ABCD" rules (variegated colour) of clinical diag-

nosis of melanoma [8]. The distribution of melanophages also affects pigmentation.

Circumscription

Most melanocytic naevi have sharp borders, and melanomas indistinct ones. A melanocytic neoplasm is easiest to judge as well circumscribed if the edge of the lesion is defined by a nest, rather than by single melanocytes. In such cases, care must be taken that the distances between nests do not exceed or even approximate those between the most peripheral nest and the edge of the section (in other words, one must be sure that the "last" nest is truly the last one). One should also assess whether the nests at the periphery of the lesion are at irregular intervals. A lesion can have an entirely nested junctional component, with small nests at increasingly long intervals at its edges. This is often the cause of a "fuzzy" border in a dysplastic (Clark) naevus.

Predominance of single cells vs. nests

At an early stage in the intraepidermal development of a melanocytic proliferation, benign or malignant, single melanocytes in increased number will be present. Therefore, a 1 or 2 mm lesion, as noted above in which single melanocytes predominate is not necessarily aberrant. In the evolution of most acquired melanocytic naevi, the single melanocytes aggregate into nests by the time the lesion is 2 or 3 mm. in diameter.

The distribution of single melanocytes is also noteworthy. One can imagine a dotted line connecting the tops of dermal papillae with one another. Very few melanocytes should reside in the epidermis above that line.

Confluence of melanocytes is another

clue to the diagnosis of melanoma. Confluent single melanocytes replace the basal layer in a manner such that, at least focally, keratinocytes do not seem to intervene between them. Confluence of nests of melanocytes is a more subjective determination.

Scatter of melanocytes above the junction

If any criterion expounded herein emblemizes intraepidermal melanoma in the minds of pathologists, it is suprabasal scatter of melanocytes. Pagetoid, buckshot and birdshot scatter also describe this distribution of neoplastic cells. It can be difficult to tell if "slight" suprabasal scatter of melanocytes is present.

Physical trauma, such as excoriation or abrasion or by ultraviolet light exposure provokes scatter of melanocytes above the epidermis {2374}. Signs of physical trauma include erosion, necrosis of superficial keratinocytes, parakeratosis, subepidermal fibrin deposits and extravasation of erythrocytes in the papillary dermis. Suprabasal scatter of melanocytes is typical of naevi on acral skin {292}.

Configuration of the epidermis

An uneven epidermal contour is more apt to be present in melanoma than in a naevus. The most typical diagnostic alteration is a thinned epidermis in the area of the melanoma (or melanoma in situ) and elongated rete ridges in an area in which a pre-existent naevus is present. In the case of melanomas in which a large mass of neoplastic cells is present in the dermis, a finding known as "consumption of the epidermis" can occur. The epidermis is thinned, and instead of small cuboidal keratinocytes in the basal layer, one sees large, flat squamous ones, often with vacuolar change. This finding is much more common in melanoma than in naevi {947}.

Kamino bodies

The finding of many large, well formed Kamino bodies favours a Spitz naevus over melanoma. There are few convincing reports of melanomas with Kamino bodies, and these describe few, and smaller bodies. In some such reports, the bodies are not PAS-D positive, suggesting that dyskeratotic cells were mistaken for them. In addition to Spitz naevi, small

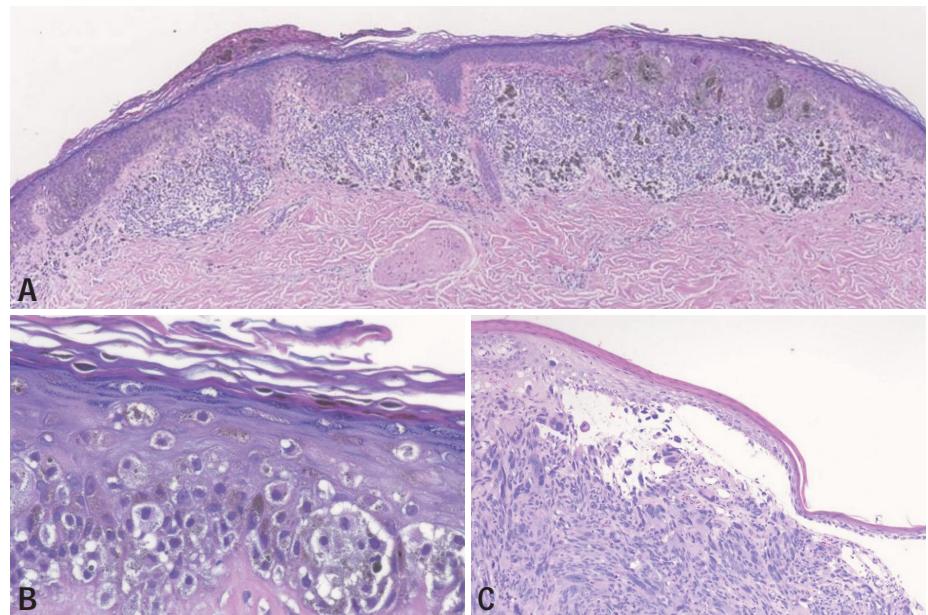


Fig. 2.7 **A** Melanoma with asymmetry. Asymmetry in the distribution of nests and of pigment- which can be within keratinocytes, melanocytes or melanophages is typical of intraepidermal melanoma. **B** Pagetoid scatter of melanocytes is practically emblematic of intraepidermal melanoma. **C** Consumption of the epidermis in melanoma. The epidermis is thinned, with squamous rather than cuboidal cells in the basal layer.

Kamino bodies occur in some dysplastic (Clark) naevi, and in some halo naevi

Cytological features of melanoma in the epidermis

Cytologic findings are less of a link to the correct diagnosis in the realm of melanocytic neoplasia than in other tumours. Melanocytes can be large or small, deeply pigmented or amelanotic, and vary from appearing to be round to oval to spindled to thin and dendritic. Most acquired naevi feature small round, oval or small spindled melanocytes within junctional nests. There may be no visible pigment, or some may be intracytoplasmic. In general, the amount of cytoplasm is scant in most "common" and even in most dysplastic naevi. The nuclei of such cells are usually monomorphic, allowing for different shapes due to various planes of sectioning if the cells are elongated. Melanomas with similar cytologically bland cells do occur, and the diagnosis in such cases must be made via the architectural features of the lesion.

Small melanocytes with scant cytoplasm and angulated, darkly stained nuclei are particularly apt to be found in melanomas in severely sun-damaged skin (lentigo maligna and lentigo maligna melanoma). A similar appearance can be induced by processing artefact, and

by the use of some alcohol-based fixatives instead of formalin.

Large round or oval, or epithelioid melanocytes occur in both benign proliferations and in melanoma. Such cells often have abundant pale cytoplasm, with "dusty" (fine and evenly dispersed) melanin. These cells are typically seen in the intraepidermal components of melanomas of all types. Large, pale melanocytes are also present in naevi of the scalp (especially in children and teens), breast and genitalia, and in some dysplastic naevi {1532}.

Spindled melanocytes occur within the epidermis in the junctional nests of dysplastic naevi and in Spitz naevi, as well as in melanoma, where their orientation is haphazard (some nests may be vertical and some horizontal). The nuclei of spindled melanoma cells are more often pleomorphic, and there is heterochromasia, i.e. some may be vesicular and some stain darkly.

Dendritic melanocytes are present in melanomas in dark skin patients in diverse settings, and light skinned ones in so-called lentigo maligna and the lentigo maligna pattern of melanoma, and in melanomas of acral-volar skin, the nail bed and of mucous membranes. The nuclei of dendritic melanocytes may be inconspicuous. The findings of dendrites that ascent to the mid-spinous zone, and

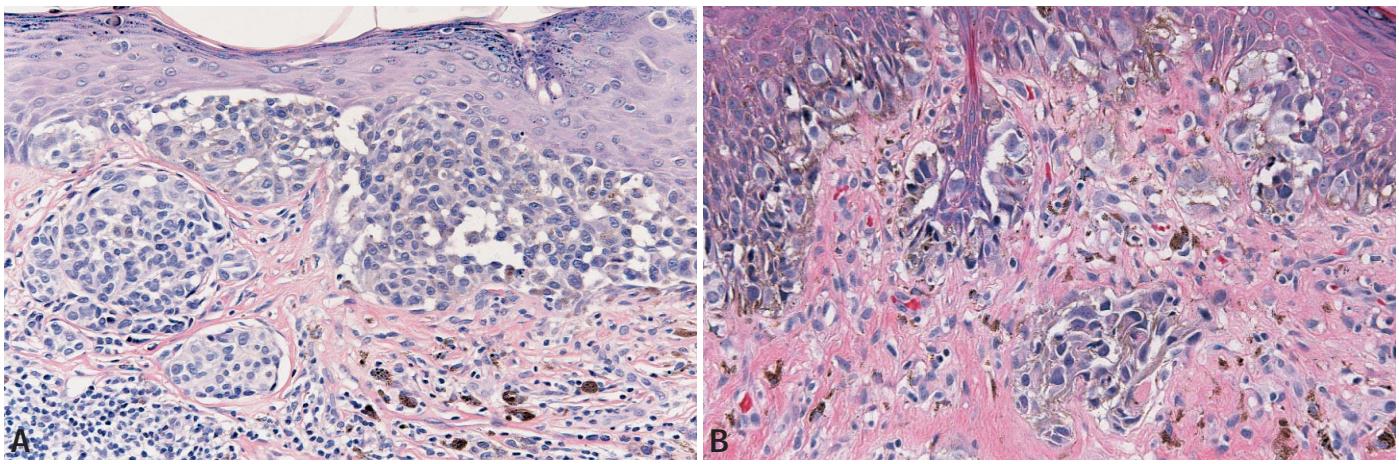


Fig. 2.8 **A** Melanoma, invasive radial growth phase (invasive but non-tumorigenic melanoma). Clusters of cells are present in the dermis (see bottom left) that are not larger than the largest intraepidermal clusters. **B** A thin invasive and tumorigenic melanoma. The cluster of cells in the dermis is slightly larger than the largest cluster in the epidermis, constituting a pattern consistent with a very early tumorigenic melanoma.

especially variability in the widths of dendrites at the same level of the epidermis (anisodendrocytosis) are useful clues to melanoma in these settings.

The extreme cytologic atypia typically seen in thick melanomas in the dermis and in metastases of melanoma, with very large, irregularly shaped and brightly eosinophilic nucleoli is not usually to be found in the intraepidermal component of a melanoma.

Architectural criteria in the dermis

The presence of the intraepidermal changes of melanoma is of course a clue that the dermal component of a melanocytic neoplasm might represent melanoma as well. Again, architectural criteria are more important than cytologic ones, although the balance is more even than in assessing the intraepidermal portion of a melanoma.

Symmetry

The most important aspect of symmetry of the dermal component of a melanocytic neoplasm pertains to its outline, or silhouette.

Other forms of symmetry pertain to what lies within the silhouette- the composition of the neoplasm. The sizes and shapes of nests, the pigmentation and cytologic features of the melanocytes and infiltrates of lymphocytes and melanophages ideally are the same on both sides of the lesion, at the same level of the dermis. A disproportionately large nest of cells with cytologic features that contrast with those on the other side of the lesion may be a clue to melanoma.

Contour

Dysplastic naevi have a flat base at the interface between the papillary and reticular dermis, Spitz naevi have flat or wedge shaped bases, superficial blue naevi are wedge shaped, congenital and congenital-like naevi have an uneven base, with melanocytes clustered around adnexa and sometimes around vessels, and deep (often cellular) blue naevi have a lobulated base, with blunt masses of cells that protrude into the subcutis.

Melanomas that involve the dermis typically have uneven, sometimes jagged bases.

Maturation

Maturation of melanocytes is in some ways a misnomer- a mature melanocyte is dendritic, and synthesizes pigment within an epithelium. The process commonly referred to as maturation is really senescence; it reflects a loss of metabolic activity, reproductive capacity and in some cases a tendency to become fat- just as mammalian senescence does. Maturation of melanocytes occurs in most naevi, with the exception of blue naevi (including deep penetrating naevi). The best-known form of maturation is the progressive diminution in the size of the nuclei of melanocytes at increasing depth within a lesion. Nucleoli also diminish in size, and if they are eosinophilic in the upper part of a lesion they tend to become basophilic at its base. Nuclear maturation in melanocytic lesions can be quantified by morphometric studies {211,1398}.

In addition to nuclear maturation, the

amount of cytoplasm is less at the base of a benign melanocytic neoplasm than in its upper nests. If the cytoplasm of the upper cells of a naevus is pigmented, its lower cells tend to be less pigmented or achromatic. The sizes of aggregations of melanocytes also should be smaller toward the bottom of a benign neoplasm of melanocytes.

The scientific basis of maturation rests on changes in metabolism (less tyrosinase activity and more acetylcholinesterase activity) and telomeric exhaustion {865,1620}.

Maturation occurs to a limited extent in some melanomas, but in most there are cells at the base of the lesion nearly as large as those at the top, and dispersion from large nests to small ones and single cells is often absent {1989}. Pigmentation near the base of a melanocytic neoplasm can also be a clue to melanoma, but it commonly occurs in blue naevus.

Mitotic activity

Mitoses in the dermal portion of a lesion do not mandate a diagnosis of melanoma. As a rule, the mitotic figures in benign naevi are found in melanocytes within the papillary or superficial reticular dermis. If the lesion in question only extends to this depth, the number of mitoses becomes important, as does the question of whether the mitoses are in clusters (reflecting "hot spots") or are atypical. Atypical (asymmetric, tripolar or ring) mitotic figures can occur in Spitz naevi, but are rare in other forms of naevus. Ki67 / MIB-1 marks cells that are actively cycling, and the number of such

cells should diminish toward the bottom of a benign melanocytic neoplasm. The finding of a low proliferation rate is no guarantee of benignancy. A high rate in a lesion thought to be benign should trigger reassessment.

Cytologic features of melanoma in the dermis

The cells of a melanoma may be large or small melanocytes, round or spindled, amelanotic or deeply pigmented.

Large spindled melanocytes comprise the dermal component in some melanomas. They often are not reliably demarcated from each other by clefts, as is the case in Spitz naevi. They can form elongated, sometimes sinuous fascicles, especially in melanomas with neuroid differentiation and in desmoplastic melanomas. The spindled melanocytes of desmoplastic melanoma can also be found singly between thickened collagen bundles. They tend to be hyperchromatic, and have irregular nuclear membranes and small nucleoli.

Melanocytes with abundant pale cytoplasm and dusty melanin (large, pale melanocytes) are typically present in the dermis in some dysplastic naevi, naevi at special sites (scalp, breast and genitalia) and in deep penetrating naevi. They are a common cytologic type in melanoma, especially in the superficial spreading and nodular patterns.

Small round melanocytes with scant cytoplasm, resembling those of the mature portion of a naevus can predominate in naevoid melanomas

Radial and vertical growth

Radial growth phase

Most melanomas evolve through an initial stage of tumor progression, as a flat or plaque-like lesion which expands along the radii of an imperfect circle. Because of this clinical analogy, this phase has been termed the "radial growth phase" {494}.

The radial growth phase may be *in situ* (confined to the epidermis), or *in situ* and invasive, but in the latter case the cells do not have capacity for proliferation in the dermis {674,832}. Proliferation in the epidermis may give rise to a pattern of single cells, or of clusters or nests of atypical neoplastic melanocytes. Like the cells of junctional naevi, which may migrate into the dermis to form compound naevi, the cells of *in situ*

melanomas may migrate into the papillary dermis. In the dermis, these cells may either undergo apoptosis and disappear {1070}, or may survive without proliferating. In the latter case, the lesional cells may persist in the dermis, but they do not expand to form a tumorigenic nodule.

Vertical growth phase (tumorigenic)

In the next phase of progression, a tumor nodule appears either within the confines of a pre-existing plaque, or, sometimes, *de novo* in a lesion which is then termed "nodular melanoma" {675} cells.

The key biological feature of vertical growth phase is the ability of the lesional cells to survive and proliferate in the dermis. This ability may be manifested by growth to form a true "tumour" or swelling, or by the presence of mitotic activity. Tumorigenic vertical growth is easily recognized when there is a bulky nodule present. In thin lesions, such as AJCC stage I melanomas, either of two criteria suffices for the diagnosis of vertical growth phase, namely the presence of either "tumorigenicity" or "mitogenicity". The term "mitogenic" refers to the presence of any mitotic figures in lesional cells in the dermis. The term "tumorigenic" is here defined as the presence of a cluster of cells in the dermis larger than the largest intraepidermal cluster.

Metastatic spread

Most distant metastases from melanoma become evident clinically or are detected during follow-up visits within a few years from excision of the primary tumour. However, it is important to remember that late metastases (> 10 years, sometimes even over 25 years after excision of the primary tumour) are not uncommon in this neoplasm {566},

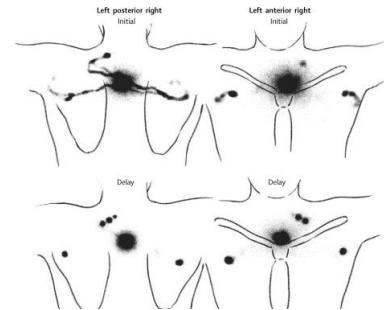


Fig. 2.9 Lymphoscintigraphy in a patient with a melanoma on the central upper back.

Top: summed 10-min dynamic images in posterior and anterior projections after injection of technetium-99m antimony sulphide colloid intradermally at melanoma site. Dominant lymphatic channels pass laterally to both axillae and upwards to interval nodes on back. Delayed scans 2 h later show a single sentinel node in each axilla and three interval nodes (also sentinel nodes in this patient) on upper back. From J.F. Thompson et al. (2348A), with kind permission of The Lancet.

2088}. The reason why "dormant" metastases begin to grow after such a long time is yet unknown.

In most patients with metastatic disease, the regional lymph nodes are affected first, but distant metastases may be observed in patients who do not have obvious lymph node involvement. Besides lymph nodes, the most common site of metastatic spread is the skin. Visceral metastases are more frequently located in the lungs, liver, central nervous system, and bones, but any organ may be affected.

In 1992, sentinel node (SN) biopsy was proposed as a minimally invasive procedure that provided accurate assessment of regional node status in melanoma patients {1655}, allowing full regional node dissection to be avoided in the 80% of patients who had negative SNs. The SN concept is simple: lymph draining from a tumour site passes first to a so-called sentinel node before onward

Table 2.02
Melanoma antigens

Type of antigen	Antigen
Differentiation antigens	Tyrosinase, gp100, Melan-A/MART-1, TRP-1, TRP-2, MC1R, AIM-1
Gangliosides	GM3, GD3, GD2, GM2, 0-acetyl GD3
Mutated proteins	CDK4, β -catenin, CDC27, MUM-2, triosephosphate isomerase
Products of unusual DNA transcripts	TRP-2, N-acetylglucosaminyl transferase
Cancer / testis antigens (CTAs)	MAGE, BAGE, GAGE, RAGE, NY-ESO-1

Table 2.03
Melanoma markers

Type of marker	Marker ¹			
Differentiation	Tyrosinase, gp100, Melan-A/MART-1	TRP-1, TRP-2, MC1R	AIM-1 S-100	Mitf, HMW-MAA
Progression	Cyclin A ↑ Cyclin B1 ↑ Cyclin D1/D3 ↑ Cyclin E ↑	Cdk2 ↑ p15 ↓ p16 ↓	p21 ↑ p27 ↓ Ki67 ↑	PCNA ↑ mdm-2 ↑ telomerase ↑
Proliferation	c-Kit ↓ c-Myc ↑	N-ras ↑ α-catenin ↓ receptor ↑	EGFR ↑ Transferrin	PTEN ↓
Signaling	ATF-1 ↑	AP-2 ↓		
Transcription	E-Cadherin ↓ N-Cadherin ↑ VCAM-1 ↓	ICAM-1 ↑ MCAM ↑	ALCAM ↑ αvβ3 ↑	α4β1 ↑ CD44 v6 ↑
Adhesion	MMP-1 ↑ MMP-2 ↑ MMP-9 ↑	MMP-13 ↑ MT1-MMP ↑ TIMP-1 ↑	TIMP-3 ↑ EMMPRIN ↑	PA-system ↑ Cathepsin B, D, H, L ↑
Proteases	ME491/CD63 ↓ HLA Class II ↑	HLA class I ↓ CTAs ↑	Osteonectin ↑	Fas/Fas ligand ↑
Other				

¹ ↑ Upregulation with tumour progression; ↓ downregulation with tumour progression

passage to other nodes in the regional node field. Thus the SN is most likely to contain tumour cells, and if none are present in this node, tumour cells are unlikely to be present in other nodes in the node field. Within 3 years of the landmark publication by Morton et al {1915}, confirmation of the accuracy of such assessment was provided by studies in

the USA {1915} and Australia {2347}. It soon became clear that identification of this node was most accurate if three methods were used: a preoperative lymphoscintigram, injection of blue dye around the primary melanoma site immediately preoperatively, and the use of a hand-held gamma probe intraoperatively. Preoperative lymphoscintigraphy for

many melanoma patients before SN biopsy provided important new insights into cutaneous lymphatic drainage pathways {2348,2396} and this new information highlighted the importance of preoperative lymphoscintigraphy before undertaking a SN biopsy procedure.

The prognostic value of determining SN status has now been shown in several large studies. All show a large difference in probability of 5-year survival between patients who are SN positive and those who are SN negative, independently of other prognostic variables. Results from the Sydney Melanoma Unit {2565} are typical, with a 5-year survival rate of 56% for SN positive patients (n=145) and 90% for SN negative patients (n=846). Prognostic information from SN biopsies may be further refined by PCR to detect melanoma-specific mRNA in lymph nodes that are negative by standard histopathological techniques {1916}.

SN assessment not only provides important prognostic information; recent clinical trials suggest that as an removal, with complete regional node field dissection if micrometastatic melanoma is found, improves the survival of patients {1655A}.

Stage distribution

Survival from melanoma is related to stage at diagnosis. The stage distribution is generally more favourable in high-resource settings, and thus countries with high incidence rates tend to also have better survival than lower incidence (and lower resource) countries {608, 1472,2245,2351}.

Most melanomas are localized in high incidence countries and the proportion that are localized continues to increase with time. Of the cases reported in the U.S. SEER program 1992-1998, 82% had localized disease, 9% regional disease, 4% distant metastases, and 6% were unstaged {186}.

Young patients and women are often diagnosed with melanomas that have a thinner Breslow thickness than older patients and men. Because of the shift in the stage distribution of melanomas towards thinner lesions, together with a disproportionate increase in incidence relative to mortality, some have questioned whether some of these thin lesions that were removed would have ever progressed to metastatic disease {353}.

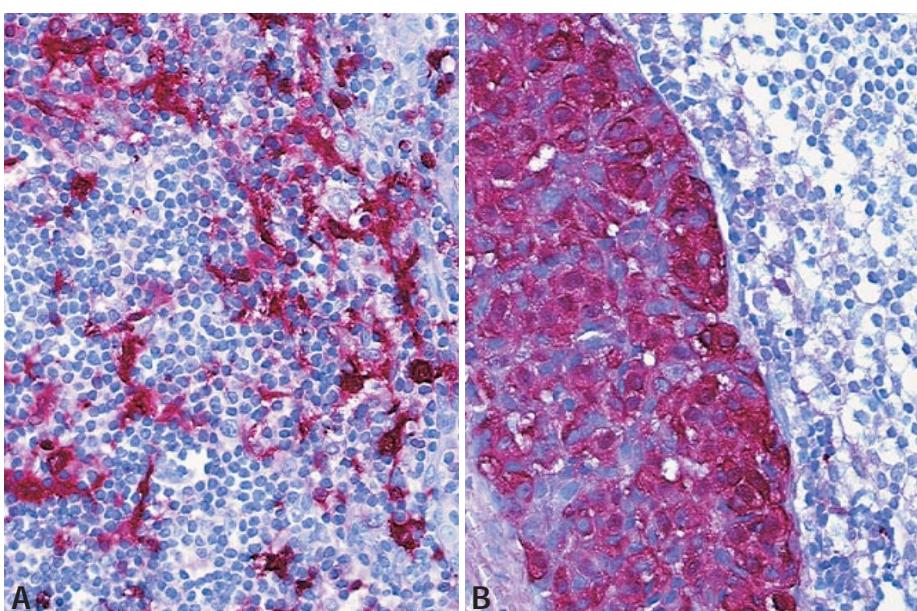


Fig. 2.10 Immunoreactivity of melanoma. **A** Immunohistochemical staining for S-100 of dendritic cells in reactive lymphadenopathy and **B** Melanoma micrometastasis in a sentinel lymph node.

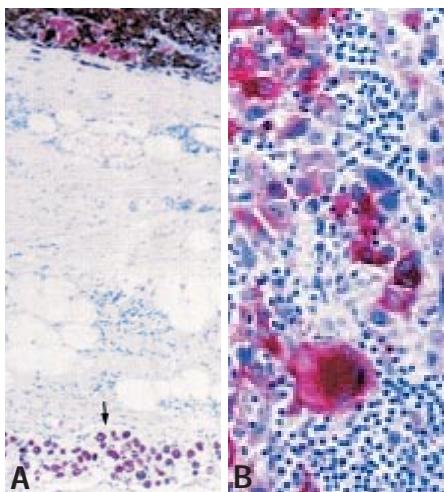


Fig. 2.11 Immunoreactivity for **A** gp100 and **B** MART-1 of metastatic melanoma cells. Note the extranodal tumour embolus in **A** (arrow).

Immunoprofile

Melanoma antigens

The term "melanoma antigen" is used two-fold. Firstly, it refers to a large variety of molecules recognized by (monoclonal) antibodies, that were generated to explore their potential as biological and/or clinical markers. Secondly, melanoma antigen in a strict sense implies a tumour molecule that evokes an immune response in the autologous host [1944]. Some overlap exists between genuine melanoma antigens and melanoma markers. Melanoma antigens currently are used in vaccination trials.

Melanoma markers

Three groups of markers can be distinguished:

Differentiation markers

These markers indicate melanocytic differentiation which is manifested by signs of melanin synthesis. Hereby cells of the melanocytic lineage are identified, but

also ectopic melanin synthesis in cells of other lineages. Differentiation markers show a broad expression in many benign melanocytic lesions and (most) primary melanomas. However, in melanoma metastases expression decreases which is accompanied by heterogeneity.

Progression markers

These markers are preferentially expressed in one or few stages in melanocytic tumour progression. Based on their tissue distribution, early, intermediate and late progression markers are discerned. Progression markers include molecules that are involved in key processes in the pathogenesis of metastasis, i.e. proliferation, migration and matrix degradation. They may be derived from the neoplastic cells and/or the stromal cells, and serve as targets for various clinical interventions.

Other markers

These represent molecules that cannot be incorporated into either of the above groups.

Clinical applications

The markers mentioned can be used for several clinical applications [392]. For this purpose currently immunohistochemistry on paraplast embedded tissue sections is applied, preferentially employing a red chromagen in order to contrast with the brown colour of melanin. For some applications RT-PCR is used.

Differential diagnosis of poorly differentiated malignant tumours

In case of a differential diagnosis between poorly differentiated carcinoma, sarcoma, lymphoma and melanoma a panel of various differentiation markers is applied. Melanoma is likely if the tumour is diffusely staining for S-100 and the

markers for the other diagnostic options are negative. Given the low specificity of S-100 for melanocytic differentiation the diagnosis has to be substantiated. For this purpose MART-1 (syn. Melan-A) is a powerful marker both having a high sensitivity and specificity. Its sensitivity is higher than gp100 (recognized by HMB45) in cutaneous melanoma and metastasis, although in non-cutaneous melanoma it may be the reverse.

Immunotherapy

Vaccination trials have been started using gp100 and tyrosinase presented by dendritic cells, and MAGE3. Patients are selected on the basis of an appropriate HLA haplotype and extent of antigen expressed [611]. Expression of gp100 and tyrosinase is estimated on immunohistochemically stained melanoma slides; for MAGE3 RT-PCR is used.

Genetic susceptibility

If melanoma runs in the family (i.e. if a parent or sibling was diagnosed with a malignant cutaneous melanoma), the relative risk of developing a melanoma compared to persons without a family history of melanoma is 2-3 [1006] and some melanoma pedigrees have been discovered. Clustering of melanoma in families is however not frequent and the genes implicated in large melanoma families probably only play a small role in population-based melanomas. Two genes have been discovered in melanoma families: CDKN2A (p16) on chromosome 9p21, and CDK4 on chromosome 12. Mutations in the CDKN2A gene have been found in up to 25% of melanoma families worldwide, whereas CDK4 has only been observed in a few rare families. The CDKN2A/p16 gene acts as a tumour suppressor gene and plays a crucial role in cell cycle regulation and senescence. The p16 protein is a cyclin-dependent kinase inhibitor which works by binding to CDK4. The p16 gene tends to be transmitted in an autosomal dominant fashion. Its penetrance varies with population incidence rates, indicating that the same factors that affect population incidence of melanoma may also mediate CDKN2A penetrance. The frequency of mutated p16 in the general population is estimated to be 0.01% [176].

Table 2.04

Prognostic indicators for melanoma.

Prognostic factor	Most favourable when:
Breslow thickness	Thin (<1.51 mm)
Histology	Superficial spreading melanoma
Age	Young
Sex	Female
Body site	Not on the trunk, hands, feet
Ulceration	Absent
Mitotic index	Low

Other genes, such as *MC1R* (Melanocortin 1 Receptor) and DNA repair genes, are likely to be more important in determining susceptibility for melanoma in the general population. The *MC1R* gene is involved in skin and hair pigmentation and in senescence and immunity {176,251,2385}. Patients with inherited abnormalities in the DNA repair system, like xeroderma pigmentosum patients, are at a 1000-fold increased risk {891}.

Prognosis and predictive factors

Melanoma thickness, body site, histological type of the melanoma, gender of the patient and ulceration are important indicators of patient prognosis {130}. Generally, older patients do less well than younger patients for the same tumour thickness, while females do better than males. Superficial spreading melanomas generally have a better prognosis compared with other histological subtypes, because they usually have a thin Breslow thickness {1471}. One report suggests that sun exposure is associated with increased survival from melanoma {224}.

Reports on prognosis from specialized centres {130}, may contain survival rates lower than reported by population based cancer registries {2051}, possibly because patients with less favourable prognosis are being referred to specialized centres.

Morphological prognostic factors

Several clinical and histologic attributes are useful in predicting the probability of survival for patients with melanoma, and, as targeted therapies begin to be developed, no doubt these or similar attributes may be useful in predicting therapeutic responsiveness. Staging of melanoma has been discussed above, and in the 2002 AJCC classification, this staging includes clinical as well as histologic attributes {130}. The basic purpose of staging is to describe the clinical extent of disease. This may be done by physical exam, by clinical investigations, and by gross and microscopic pathologic examination. The process of predicting prognosis using pathological attributes may be referred to as "microstaging". Some of these attributes useful in prognostication are discussed below.

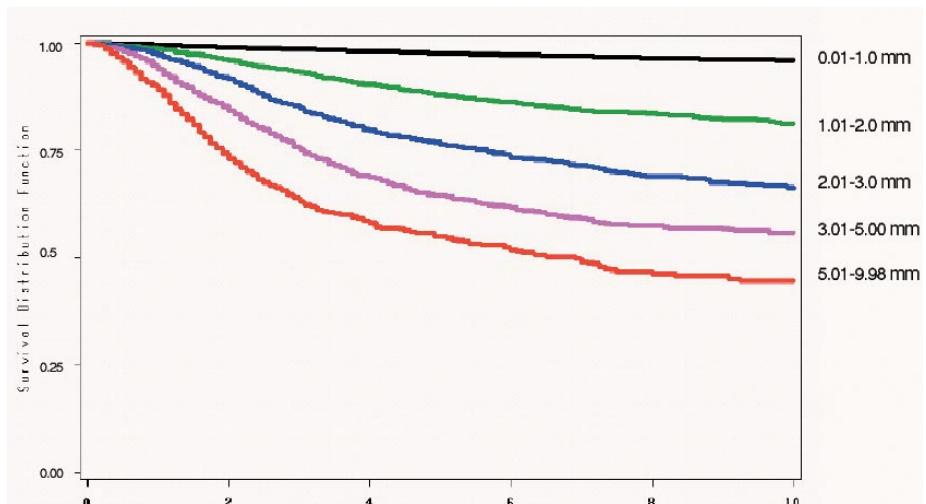


Fig. 2.12 Thickness and prognosis. Kaplan-Meier ten year survival curves by thickness, SEER cohort. Thickness groups presented in various colours are from top to bottom <1.00mm, 1.01-2mm, 2.01-3.0 mm, 3.0-5.0 and >5mm, respectively. Adapted from Gimotty et al, 2005 {830}.

Clark's levels of invasion

First described in 1967, these attributes along with Breslow's thickness measurements are the best known prognostic attributes for melanoma {492}. In Clark's level I, the melanoma is confined to the epidermis (melanoma in situ). In level II, melanoma cells are present in the papillary dermis, which may be expanded but has not filled by tumour. Most level II melanomas are non-tumourigenic, but a few meet criteria for tumourigenicity discussed above. In level III, there is a tumour that fills and expands the papillary dermis. In level IV, tumour cells infiltrate to the collagen fibres of the reticular dermis which unlike the papillary dermis are not specialized maintain epithelium. In level V, the subcutaneous tissue is infiltrated.

Breslow's thickness

According to Breslow's definition, published in 1969, thickness is measured from the top of the granular layer to the deepest invasive tumour cell. This can occasionally be misleading, for example when there is marked epithelial hyperplasia but only a few tumour cells are present in the dermis. In the 2002 AJCC staging system, thickness is grouped in 1 mm intervals {130}. If only one attribute is known, thickness is the single strongest prognostic attribute for melanoma.

Ulceration

Ulceration is a significant stage modifying factor in the 2002 AJCC classifica-

tion. For any given thickness level, the prognosis is significantly worse when ulceration is present. In "thin" melanomas (Breslow thickness less than 1 mm) this remains true however only a few melanomas are ulcerated. Ulceration loses its significance when mitotic rate is included in a population based multivariable prognostic model {160}.

Mitotic rate

Mitotic rate was the single strongest attribute in the 1989 Clark prognostic model, which was developed in a cohort of patients all of whom had vertical growth phase. Patients with a mitotic rate of six or greater were at approximate twelve-fold greater risk of metastasis than patients whose tumours had no mitoses {491}. In addition, the presence of any mitoses at all in the dermis ("mitogenicity") is predictive not only of survival {831} but also of sentinel lymph node positivity {1251}.

Tumour infiltrating lymphocytes

First demonstrated in the 1989 Clark model {491} and later confirmed by others {502,1609}, the presence of "brisk" tumour infiltrating lymphocytes (lymphocytes present among and in contiguity with tumour cells) is almost as powerful an attribute as mitotic rate.

Lymphovascular invasion

Although not commonly observed, and therefore not found to be an independent factor in most prognostic models, vascu-

lar invasion when present appears to be associated with a worse prognosis [1213].

Radial growth phase regression

Several studies have demonstrated worse prognosis when radial growth phase regression is present [491]. Possibly in these cases, a small area of tumourigenic vertical growth phase was present before the regression obliterated it.

Microscopic satellites

Like clinical satellites, microscopic satellites are indicative of a lesion with competence for metastasis and are associated with a worse prognosis [962].

Patient gender and lesional cell location

In most series, even when other prognostic factors are controlled, female patients have better survivals, and the survival is better for patients whose lesions are on the limbs compared to the trunk or extremities [491].

Immunoprofiling for the assessment of prognosis

Two strategies are followed:

1. Identification of markers suggestive of aggressive subpopulations in primary melanoma [1990]. For this purpose late progression markers are used. Only a limited number of progression markers have prognostic implication independent of the conventional dominant factors, i.e.

tumour thickness and ulceration. A list of prognostic markers is presented in Table 2.5. It should be noted here that the clinical relevance of these markers is increasing as the primary melanomas currently diagnosed are relatively thin (1.0-1.5 mm) and rarely show ulceration. It is expected that a set of prognostic markers may help to select melanoma patients for adjuvant therapy. Such a set may be designed on the basis of the outcome of ongoing expression array studies.

2. Microstaging. The presence of melanoma deposits in various stages of the disease is assessed by the demonstration of differentiation markers. However, they may decrease during tumour progression and do not reveal the aggressiveness of the tumour cells. Nevertheless, the extension of the primary tumour that includes thickness measurement and identification of microsatellites, can be facilitated by S-100 or MART-1 immunohistochemistry. This also is applicable for the detection of melanoma cells in sentinel nodes. Immunohistochemistry on serial sections is preferred to molecular staging of sentinel nodes as it has a similar sensitivity, a higher specificity and it preserves morphology.

Table 2.05

Prognostic markers in malignant melanoma

Marker	Expression	Prognosis ¹
Ki67	↑	—
PCNA	↑	—
Cyclin A	↑	—
p16	↓	—
αvβ3	↑	—
ICAM-1	↑	—
CD44	↑	+
MMP-2	↑	—
t-PA	↑	+
gp100	↓	—
Mitf	↑	+
c-kit	↓	—
c-myc	↑	—
p53	↑	+
Osteonectin	↑	—

¹-: Unfavourable; +: favourable

Superficial spreading melanoma

E. Haneke
B.C. Bastian

Definition

Superficial spreading melanoma (SSM) is a subtype of melanoma which tends to occur on usually covered skin and is characterized by a radial growth phase comprised of large neoplastic melanocytes that extend among keratinocytes in a "buckshot" or pagetoid pattern [493,494]. It is controversial whether SSM is truly different from other melanoma forms of the skin or whether the differences are only due to differences in the skin architecture [22].

ICD-O

8743/3

Synonym

Pagetoid melanoma.

Epidemiology

SSM makes up almost two thirds of all melanomas in light-skinned people (Fitzpatrick skin types 1–3) and is thus the most frequent subtype of all melanomas. The sex incidence is identical in most areas.

Etiology

Its etiology is not exactly clarified, however, repeated severe sunburns in childhood appear to play an important role. Intermittent sun exposure in adult life is also important.

Localization

SSM may appear on almost the entire body, particularly on sites with acute-intermittent sun exposure. SSM in women is most frequently observed on the legs, in men more commonly on the trunk.

Clinical features

Signs and symptoms

SSM in situ begins as an irregularly pigmented and outlined macule. With the onset of invasion, it develops into a slightly raised plaque. Its borders are usually sharply delimited, often irregular indicating progressive peripheral extension, but they may also be ill-defined. The pigmentation within an individual lesion varies from light to dark brown to even jet-black. Grey or white areas indicate regression. White vitiliginous areas, sometimes even poliosis (white hair) may be observed. Red areas are due to inflammation or increased vascularity. Some SSMs are amelanotic, resembling Bowen or Paget disease. The tumour may reach a considerable diameter until it develops a papule representing the transition from the radial growth to vertical growth phase of SSM. These papules tend to become erosive, ulcerated and crusted with a tendency to easy bleeding. In rare instances satellite nodules are present. Most lesions are asymptomatic, but can present with bleeding once the lesion ulcerates.

Histopathology

SSM in situ or the intraepidermal part of an invasive lesion stands out by pagetoid spread throughout the epidermis of atypical melanocytes that often have large nuclei and nucleoli and abundant pale cytoplasm. Mitoses are frequently absent. The melanocytes may be distributed singly or in nests. The distribution is often irregular and the nests may have irregular shapes or show confluence. Poor lateral circumscription is often present, with single enlarged melanocytes found lateral to the last nest. Hair follicles and eccrine duct epithelium can be involved in a similar pattern. To one side or in the subjacent dermis there may be a residuum of a naevus. In MIS the stromal and inflammatory reaction tends to be inconspicuous and can be absent. An irregular distribution of lymphocytes and/or melanophages may be a diagnostic clue that the lesion is a melanoma. Actinic elastosis may or may not be present.

With development of invasive melanoma, an asymmetric outline becomes a major characteristic. Extensive and highly irregular junctional tumour nests are found at a variable distance to each

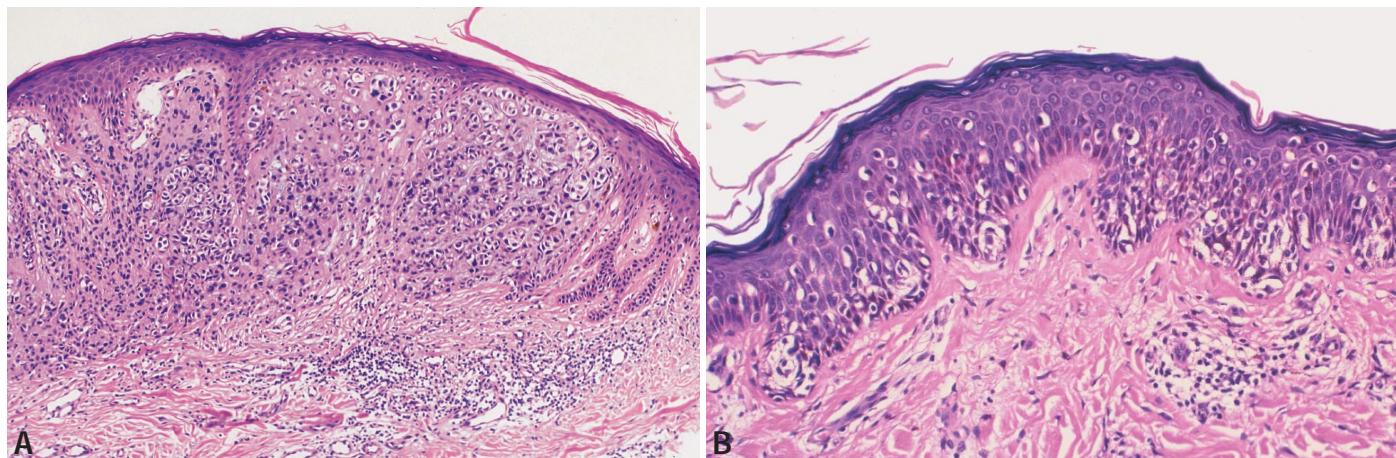


Fig. 2.13 Superficial spreading melanoma. **A** Low power magnification of the papular component. **B** Pagetoid spread of single melanocytes as is typically found in many examples.

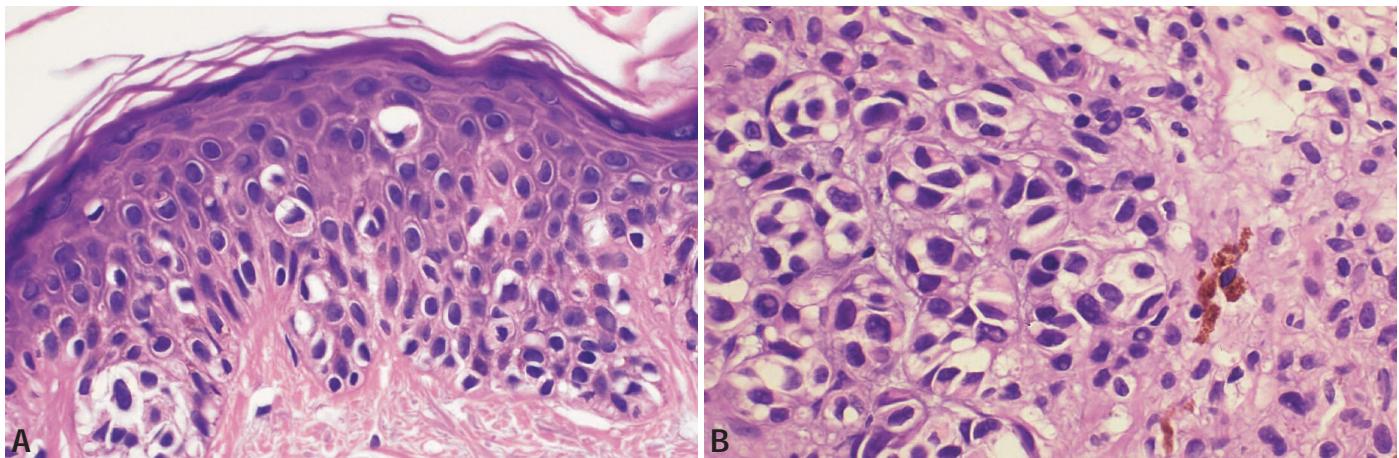


Fig. 2.14 Superficial spreading melanoma. **A** Single cells and small nests are irregularly arranged along the junction. Toward the centre a large melanocyte is present in mid-spinous layer. A Langerhans cell is in nearly the same position toward the edge but is much smaller. **B** The invasive portion of the melanoma, showing nuclear pleomorphism. At the base there is a lymphocytic infiltrate.

other and may merge. There is often a lack of maturation, manifested by a failure of nests, cells, nuclei or nucleoli to become smaller towards the base of the lesion. Pigment is often irregularly distributed. Mitoses, sometimes atypical, are often seen whereas necrotic melanocytes are rarely identified. A lymphocytic infiltrate may be present at the base of the neoplasm or may infiltrate among its cells (so called tumour infiltrating lymphocytes or TILS). Melanoma may undergo regression, which clinically and grossly most often involves a portion of the lesion, or occasionally its entirety. Histologically this regression may be complete or partial within a given area. Complete regression of a portion of a melanoma ("segmental regression") is manifested by absence of melanocytes in the affected area. In partial regression, there is a strikingly diminished number of melanocytes compared to the remainder

of the lesion. In both forms there is fibrosis of the papillary dermis, vascular proliferation and ectasia, and variably dense infiltrates of lymphocytes and melanophages. The epidermis may show loss of rete ridges. The type of regression described above affects the radial growth phase. Occasionally, a vertical growth phase may undergo regression, and sometimes the regressed portion may be replaced by a large mass of melanophages, representing a phenomenon called "tumoural melanosis".

Immunoprofile

There are no specific differences in the immunophenotype of SSM and other forms of melanoma.

Somatic genetics

SSM has a high incidence of mutations in the BRAF oncogene on chromosome 7q34 {1493}. The most common chromo-

somal aberrations in SSM are losses of chromosomes 9, 10, 6q, 8p and gains of chromosomes 1q, 6p, 7, 8q and 20 {173}. Melanomas with increased copies of chromosome 7 that show mutations of BRAF selectively increase the copy number of the mutated allele suggesting that the mutation precedes the chromosomal aberration {1493}. The minimal deleted region on chromosome 9 includes the CDKN2A locus on 9p21 as can be seen by high-resolution comparative genomic hybridization (CGH) {876}.

Prognosis and predictive factors

The prognosis of SSM does not differ significantly from other forms of melanoma (see Introduction).

Nodular melanoma

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Definition

Nodular melanoma (NM) is a subtype of malignant melanoma (MM) exclusively in vertical growth phase.

ICD-O code 8721/3

Epidemiology

In most parts of the world, NM is the second most common subtype of MM, and accounts for 10 to 15% of all melanomas in Caucasian people {163,436}. NM appears on the average, in older individuals than the common superficial spreading MM (SSM) {436,493}.

Etiology

Most of the skin characteristics and risk factors associated with the development of NM are similar to those of SSM {1364}, including fair or red hair, blue eyes, fair skin, tendency to develop freckles and sunburns, excessive exposure to ultraviolet radiation, numerous common naevi, giant congenital naevi, atypical (dysplastic) naevi, melanoma in a first degree relative, familial atypical mole-melanoma syndrome, immunosuppression, xeroderma pigmentosum and prior melanoma {624,2304}.

Localization

NM may occur in any location, but as for SSM, it is more common on the trunk, head and neck, and lower legs {163}.

Clinical features

NMs typically present as a rapidly expanding papule, nodule or plaque. They are occasionally polypoidal and even pedunculated. They are usually well circumscribed and symmetric and frequently reach a size of approximately 1 cm before diagnosis. The skin markings are often obliterated with frequent ulceration and crust. The colour is often black or blue, although a subset of NM is amelanotic. The amelanotic variety frequently has a subtle blush or peripheral rim of pigment {163,436}.

Macroscopy

As in the clinical features

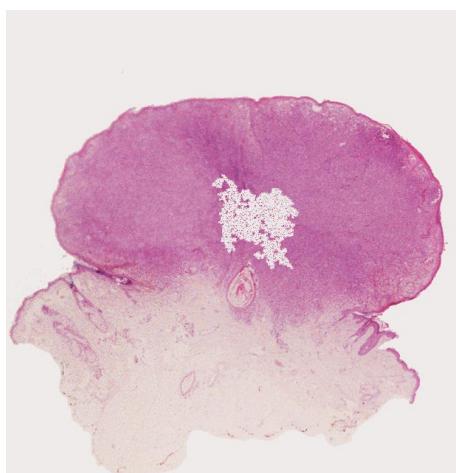
Tumour spread and staging

The tumour spreads first to the local lymph nodes and then to internal organs. The staging system devised by the American Joint Committee on Cancer includes aspects of the primary tumour, the status of lymph nodes, and the pres-

ence and location of any metastases (TNM staging) {130}.

Histopathology

Scanning magnification discloses a raised, dome-shaped, or polypoid tumour, often, but not always, exhibiting some asymmetry. The overlying epidermis may be thin, effaced or ulcerated. Melanoma cells may be present in the overlying epidermis but not beyond the margins of the dermal component (some allow an extension up to 3 adjacent epidermal rete ridges beyond the dermal component). The dermal component is typified by a cohesive nodule or small nests of tumour cells that have a "pushing" or "expansile" pattern of growth. The tumour cells most frequently are epithelioid, but other cell types, including spindle cells, small epithelioid cells resembling naevus cells, and giant mononuclear or multinucleate forms, may predominate or be admixed with other cell types. The cell population usually appears monomorphic but closer examination reveals frequent cellular enlargement, nuclear enlargement, variation in nuclear size and shape, hyperchromatism, and prominent nucleoli.



A

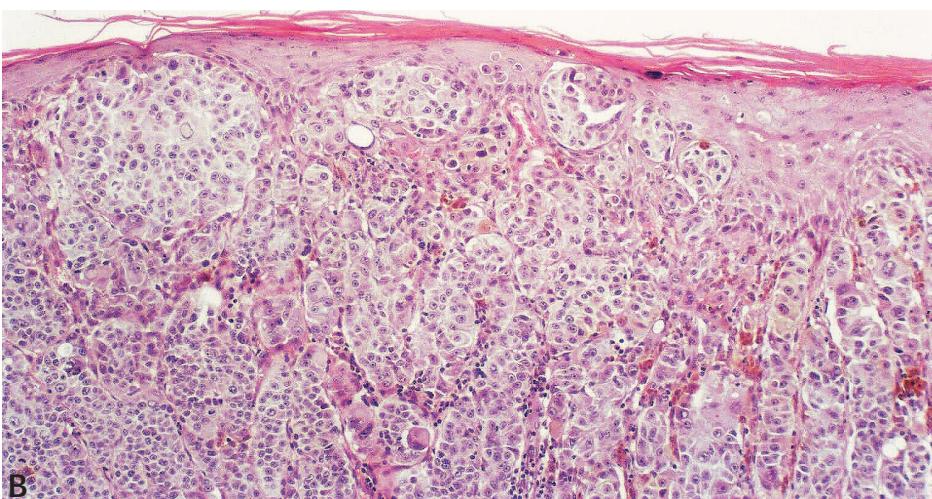


Fig. 2.15 Nodular melanoma. **A** On scanning magnification the tumour has a polypoid configuration with slight asymmetry. Cohesive nodules of tumour cells fill the dermis. **B** Superficial portion of the tumour. Epithelioid melanoma cells are present as single units and in nests that vary in size and shape along the dermoepidermal junction and above it. Similar nests are present in the upper dermis along with numerous melanophages and lymphocytic infiltrates. Some of the epithelioid melanoma cells contain fine melanin granules.

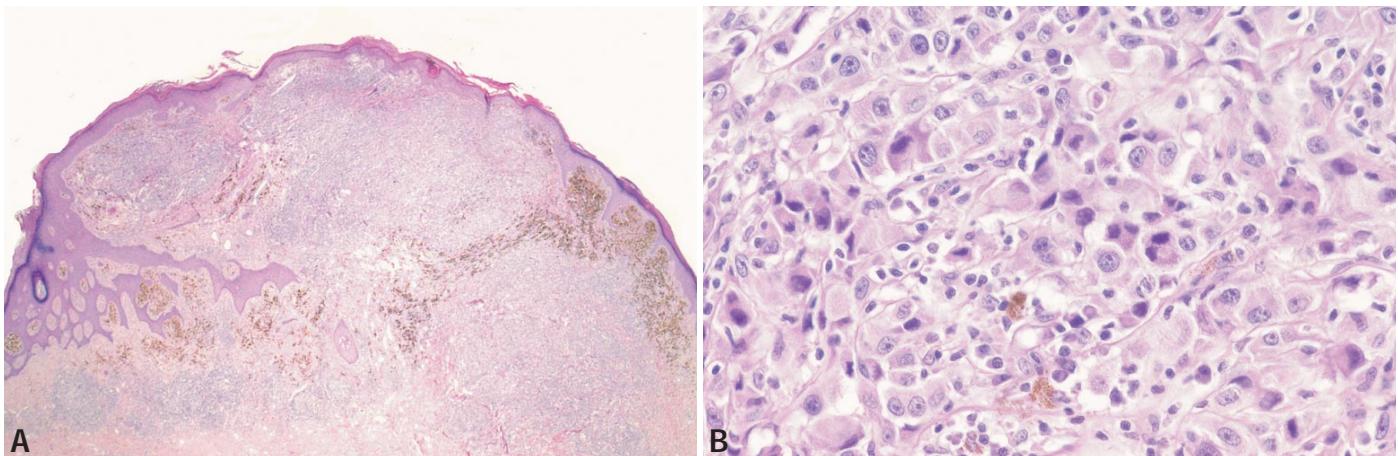


Fig. 2.16 **A** Nodular melanoma with asymmetrical distribution of lesional cells, lymphocytic infiltrates and melanophages. **B** The tumour is composed of melanocytes with large, pleomorphic, vesicular nuclei, some in mitosis.

High nuclear-to-cytoplasmic ratios are often noted. The tumour cells fail to "mature" with progressive descent into the dermis. The cytoplasm of the epithelioid cells often has eosinophilic granular qualities. It may contain melanin granules that vary in size, or appear fine and "dusty". There is absence of melanin in the amelanotic tumours. The surrounding stroma may demonstrate variable mononuclear cell infiltrates, fibroplasia, telangiectasia, and melanophages {154,163}.

Immunoprofile

S-100 protein, HMB-45, Melan A (MART-1), MAGE-1, NKI/C-3, tyrosinase, melanoma cell adhesion molecule (Mel-CAM) MUC18 and microphthalmia transcription factor (MITF), are expressed by most melanomas {732,1500,1855}. Melanoma cells also express bcl-2 protein, neuron specific enolase and vimentin {626,1861,2131}. Antigens which may demonstrate higher rates of expression in melanoma cells than in naevus cells include Ki-67 (MIB-1), proliferating nuclear antigen (PCNA), p53, cyclin D1, and p21 WAF1(9). The loss of expression of CDKN2A (cyclin dependent kinase inhibitor), and the increased expression of β 3 integrin, have been associated with vertical growth phase and more invasive forms of melanomas {1029,1500,1904,2277,2278,2406}.

Electron microscopy

The demonstration of stage II melanosomes is the hallmark of melanoma diagnosis. They are rarely

found in other tumours. Other frequent findings are nuclear pseudoinclusions, prominent nucleoli and cytoplasmic intermediate filaments corresponding morphologically to vimentin filaments. In a minority of melanomas poorly developed intercellular junctions may be present {1016}.

Precursor lesions and histogenesis

It is more common for NM to begin de novo than to arise in a pre-existing naevus {163}. One hypothesis holds that NM represents a final common pathway of very rapid tumour progression from a brief intraepidermal proliferative phase of SSM, lentigo maligna, or acral lentiginous MM {154,163}.

Somatic genetics

Comparative genomic hybridization and mutation analyses have revealed marked differences between melanomas depending on the anatomic site and sun-exposure patterns {173,1493}. These studies did not find unique genetic features in nodular melanomas that justify regarding them as a unique type, supporting the 'common pathway hypothesis' {154,163}.

Genetic susceptibility

The proportion of melanomas that have a familial basis ranges from 6% to 14%. Approximately 20% of all individuals with a family history of melanoma have mutations in CDKN2A which maps to chromosome 9p21. In a very few families CDK4 mapping to chromosome 12q14 has been found to be mutated {1851}.

Prognosis and predictive factors

In the T (tumour) category, tumour thickness increased mitotic rate and ulceration are the most powerful predictors of survival, and the level of invasion has a significant impact only within the subgroup of thin (≤ 1 mm) melanomas {131}. Other adverse prognostic factors include increased tumour vascularity, vascular invasion, microscopic satellites, male gender, increased age, and anatomic location on the head, neck and trunk {122,1528,2597}. In the N (nodes) category the following three independent factors have been identified: the number of metastatic nodes, whether nodal metastases were clinically occult or clinically apparent, and the presence or absence of primary tumour ulceration. In the M (metastases) category, nonvisceral metastases are associated with a better survival compared with visceral metastases {131}.

Lentigo maligna

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Definition

Lentigo maligna (LM) is a form of melanoma in situ that occurs on the sun exposed skin of elderly people, mainly on the face but also, less often, at extrafacial sites including the neck, upper back and forearm. It is characterized histologically by linear and nested proliferation of atypical melanocytes along the dermo-epidermal junction and down the walls of hair follicles and sweat ducts. The melanocytic lesion is associated with severe actinic damage, manifested by epidermal atrophy and solar elastosis. When dermal invasion by atypical melanocytes occurs in association with (LM), the term lentigo maligna melanoma (LMM) is used.

ICD-O code

8742/2

Synonyms and historical annotation

LM has also been known as Hutchinson melanotic freckle, after Hutchinson first

described it as "senile freckle" in 1892 {1090} and subsequently as "lentigo-melanosis" {1089}. Dubreuilh {652} described these lesions as "mélanoïse circonscrite précancéreuse" which subsequently came into common use as melanosis circumscripta precancerosa until the classification of Clark {492} in 1967 introduced the category of melanoma commencing in lentigo maligna (Hutchinson's melanotic freckle). That classification was widely but not universally accepted; the World Health Organisation (WHO) classification of 1974 classified superficial spreading melanoma and melanoma arising in Hutchinson melanotic freckle (lentigo maligna melanoma) in one category {2337}. The World Health Organization (WHO) classification of 1996 separated melanoma in-situ into superficial spreading or pagetoid type and lentigo maligna melanoma, whilst acknowledging that there may be no essential biological difference between some or perhaps all categories of melanoma {999}.

Etiology

The strong association between LM and its occurrence in the severely sun damaged skin of elderly people has been widely accepted as evidence that LM and LMM represent a distinctive form of melanoma, resembling etiologically the non-melanocytic skin cancers, and suggesting that LM arises in response to accumulated sun exposure, in contrast with the more common forms of melanoma that appear to be related to intermittent sun exposure {1048}. It has also been suggested, however, that differences in body site distribution between the commonly accepted different types of melanoma, through their interaction with amount and pattern of sun exposure, can explain virtually all the observed pathological and epidemiological differences between LM and the more common types of melanoma that occur in widespread anatomical distribution {16,996}. Recent studies have found that LM remains the main histologic type

of melanoma in situ on the head and neck and that patients with LM are less likely than patients with melanomas of the trunk to have more than 60 naevi whereas they had a stronger association with the number of solar keratoses {2508}.

Pathogenesis

According to some authorities, the term LM encompasses a phase regarded as a melanoma precursor in which there is proliferation of melanocytes in severely sun damaged skin in intermittent pattern without the confluent growth, pagetoid spread and nesting of atypical melanocytes that, according to this concept, represent malignant melanoma in-situ of LM type, whereas the lesions with less severe, intermittent junctional proliferation are termed atypical melanocytic hyperplasia {759} or, preferably, atypical lentiginous melanocytic proliferation.

Localization

Head and neck are by far the most common sites in both sexes. Extrafacial LMM differs in its site distribution between women and men {549}. A study in Scotland showed that extrafacial LMM in men occurred mainly on the trunk whereas in women 80% occurred on the limbs, mainly the lower leg. The mean age of patients with extrafacial LMM was significantly lower than that of patients with head and neck LM, suggesting that the association between LMM and sunlight may not be related only to the cumulative effects of solar exposure.

Clinical features

LM may be recognized as a small lesion, usually as a mottled light brown macule with irregular margins on the face of a fair skinned elderly patient with evidence of severe solar skin damage, only a few millimetres in diameter, but usually greater than 10 mm. The classical lesions are broad, flat zones of varied pigmentation with an irregular border. With increasing size of the lesion, variation in pigment and irregularity of the border also

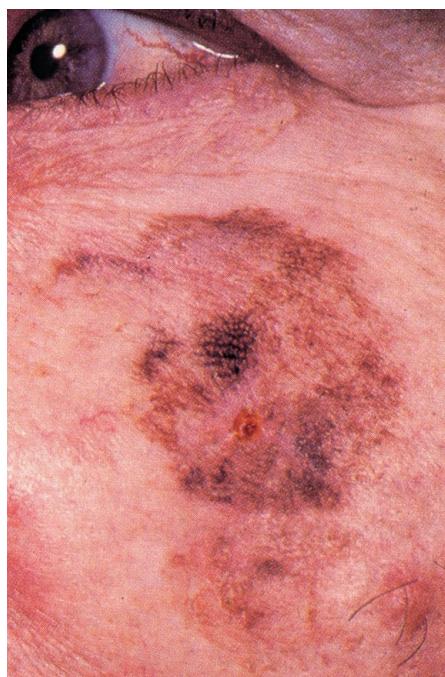


Fig. 2.17 Lentigo maligna. Broad, flat, variably pigmented lesion with a very irregular, ill-defined border on the cheek of a 78-year-old patient.

become more pronounced, nodules may develop within the lesion and the borders may become difficult or impossible to define where zones of pallor or mottled pigmentation merge imperceptibly with the surrounding skin.

Histopathology

LM is characterized by a predominantly junctional proliferation of atypical melanocytes, frequently extending down the walls of hair follicles and sweat ducts, in association with epidermal atrophy and severe solar elastosis. Although the junctional proliferation may form confluent linear pattern in some areas, elsewhere the atypical melanocytes may be distributed as single units separated by basal cells. Irregular junctional nests of atypical melanocytes are frequently present, as are multinucleate giant cells including those of starburst type {512}. Marked pleomorphism is a feature of the atypical melanocytes which show cytoplasmic retraction artefact and nuclei of stellate, ovoid and crescentic forms, some of them pressed against the cell wall, with a variable chromatin pattern and clear or variably pigmented cytoplasm. Pagetoid foci of atypical epithelioid melanocytes present an appearance indistinguishable from melanoma *in situ* of so-called superficial spreading type.

A lymphocytic infiltrate and focal fibroplasia are frequently present in the papillary dermis underlying LM, with severe solar elastosis and telangiectasia. Regression, shown by fibrosis, hypervascularity, melanophages and a patchy lymphocytic infiltrate, is a common feature and should prompt a careful search for invasion by atypical melanocytes. The presence of regression at a lateral margin of excision should be emphasized in the report as an indication for re-excision, even when the margins appear clear of atypical melanocytes.

In LMM, dermal invasion occurs in association with LM. The invasive component may consist of atypical melanocytic spindle cells more frequently than is seen in the other common forms of cutaneous melanoma, but epithelioid, small naevoid and tumour giant cells may also be present in varied proportions. The cells of these various types may occur in cohesive groups, strands or as single cells in a diffuse pattern, often associated with lymphocytes and melanophages. The

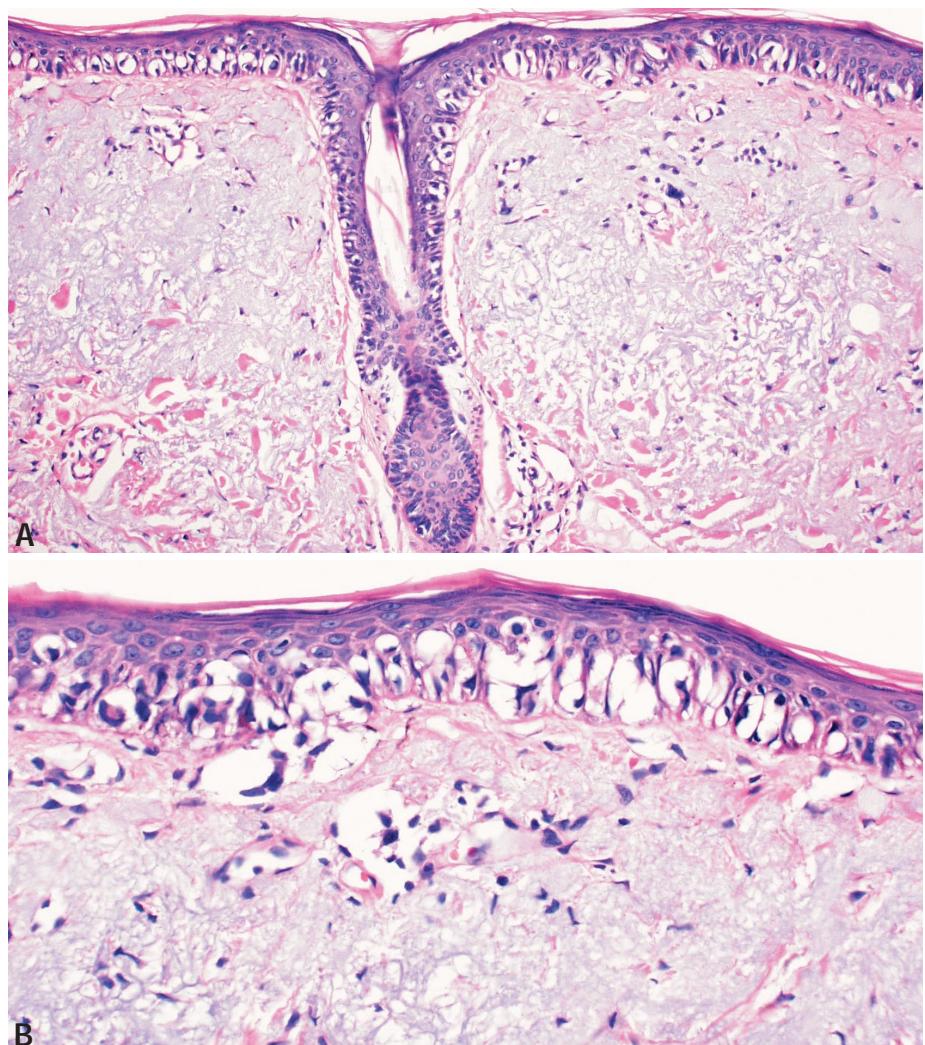


Fig. 2.18 Lentigo maligna. **A** Atypical melanocytes, mainly epithelioid cells with clear cytoplasm, are arranged in confluent pattern along the dermo-epidermal junction and extending down the wall of a central hair follicle. A few single atypical melanocytes are also present above the basal layer. The epidermis is atrophic overlying severe elastosis. **B** Severe nuclear pleomorphism and scattered multinucleate giant cells are present in the junctional proliferation and down the walls of adnexal structures including a sweat duct.

degree of pigmentation varies, including cells with abundant clear cytoplasm adjacent to cells in which the morphologic detail may be obscured by coarse melanin granules.

The invasive component in LMM may be desmoplastic and/or neurotropic with very subtle, diffuse invasion that predisposes to incomplete excision and true local recurrence. Dermal invasion may also originate from atypical melanocytes in the walls of hair follicles and sweat ducts, thus creating a problem in measurement of tumour thickness because it is inappropriate to measure tumour thickness from the granular layer of the epidermis in this instance.

The degree of pigmentation in LM may vary markedly between different examples of the tumour and within one tumour. Zones of amelanosis at the periphery of the lesion may lead to failure by the pathologist to detect atypical cells at the margin of excision, thus leading to persistent growth and "local recurrence" of the tumour.

Differential diagnosis

In cases of extensive amelanosis (amelanotic LM) {60}, the distinction between *in-situ* squamous cell carcinoma or extra-mammary Paget disease may be difficult in routine sections, necessitating the use of special stains to demonstrate epithe-

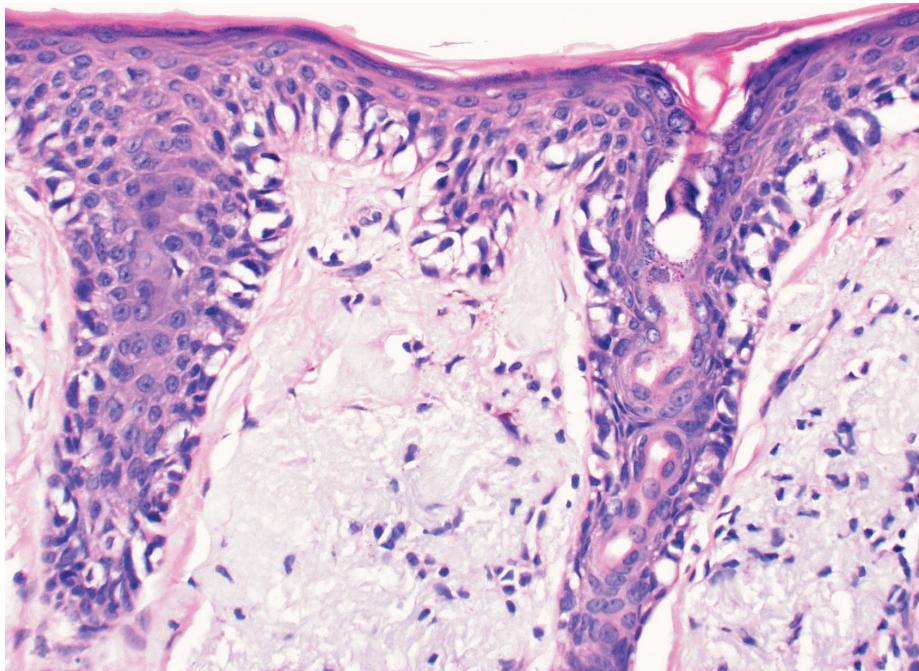


Fig. 2.19 Lentigo maligna. Focal pagetoid growth is present in addition to junctional proliferation including small nests of atypical melanocytes.

lial mucin in extra-mammary Paget disease, and immunostaining, including the use of antibodies to cytokeratins, melan-A and S-100 protein and, as further aids to the diagnosis of Paget disease, carcinoembryonic antigen, and BerEP4. The distinction between LM and benign forms of junctional melanocytic proliferation is made on the basis of the characteristic cytologic atypia, confluent growth of atypical cells along the junction with frequent extension down the walls of adnexal structures and, commonly, extension of growth above the basal layer in pagetoid pattern.

Histogenesis

LM develops from epidermal melanocytes, most likely due to the cumulative DNA damage resulting from long-term sun exposure {1048}. A recent study of the differential expression of proliferation- and apoptosis-related markers in lentigo maligna and the keratinocytes in solar keratosis has found that the epidermis in LM shows overall low proliferation and a low apoptotic tendency, perhaps aiding aberrant melanocyte proliferation in the early stages of melanoma development {718}.

Somatic genetics

A recent study has shown an association between DNA repair-deficiency and a high level of *TP53* mutations in melanomas of xeroderma pigmentosum patients {2231}. The LMM found in xeroderma pigmentosum patients of the XP complementation group, group XP-C, were associated with an accumulation of unrepaired DNA lesions. Lentigo maligna melanomas have been found to rarely show mutations in *BRAF* {1493}. Comparative genomic hybridization shows more common losses involving chromosome 13 and less common losses of chromosome 10, when compared to other melanoma types {173}.

Prognosis and predictive factors

Complete excision of lentigo maligna, as a form of melanoma in situ and, therefore, incapable of metastasis, is curative. Prognosis for LMM has been a contentious issue. For many years, it was commonly believed that the prognosis for melanomas of LMM type is better than for other types of melanoma. Most evidence, however, suggests that for melanomas classified as different types according to their histological features, their differences in survival correspond to differences in tumour thickness rather than to their differences in histologic type {20,1296}.

Acral-lentiginous melanoma

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Definition

Acral lentiginous melanoma (ALM) is a distinct variant of cutaneous melanoma, which occurs on the palms, soles, and subungual sites, and has a characteristic histologic picture. Following the three other major clinicopathological subtypes of melanoma, i.e. superficial spreading melanoma, lentigo maligna melanoma, and nodular melanoma, ALM was proposed as the fourth subtype by Reed in 1976 [1905]. In this article, we also use the term acral melanoma and define it as a melanoma located on the non-hair bearing skin of the palms and soles or under the nails. The reason for this usage is described below.

ICD-O code

8744/3

Synonyms

Historically, this type of melanoma has been designated as ALM [1905], acral melanoma [494], palmar-plantar-subun-

gal-mucosal melanoma (P-S-M melanoma) [2129], or unclassified plantar melanoma [100]. Although often considered to be interchangeable, ALM and acral melanoma embody distinct concepts that must be distinguished from each other. ALM is a histologic designation that shows similarities to lentigo maligna melanoma, while acral melanoma is an anatomic designation that refers to melanoma located on the acral sites. Acral melanoma, thus, encompasses both ALM and such subtypes as superficial spreading melanoma and nodular melanoma that may develop in acral locations. Occasionally, the terms acral melanoma and acral lentiginous melanoma are used interchangeably, since the majority of cases of acral melanoma are ALM [1071,1592,1905] and the histological distinction between ALM and superficial spreading melanoma is not always possible [2220]. Even if acral melanoma is

an anatomic nomenclature, its use is different among articles. We define it as a melanoma located on the non-hair bearing skin of the palms and soles or under the nails because of presentation of the genetic data. Although P-S-M melanoma was described on the basis of clinical and histologic similarities between the tumours on these sites, the acral melanomas and mucosal ones are recommended to be treated separately, because of their different clinical behaviours [494].

Epidemiology

Racial differences are quite pronounced in the incidence and predilection sites of melanomas. This is particularly true for acral melanoma wherein acral melanoma comprises 2% and 80% of cutaneous melanomas in Caucasian and dark-skinned patients respectively. In a German study approximately 7% of patients with cutaneous melanoma had

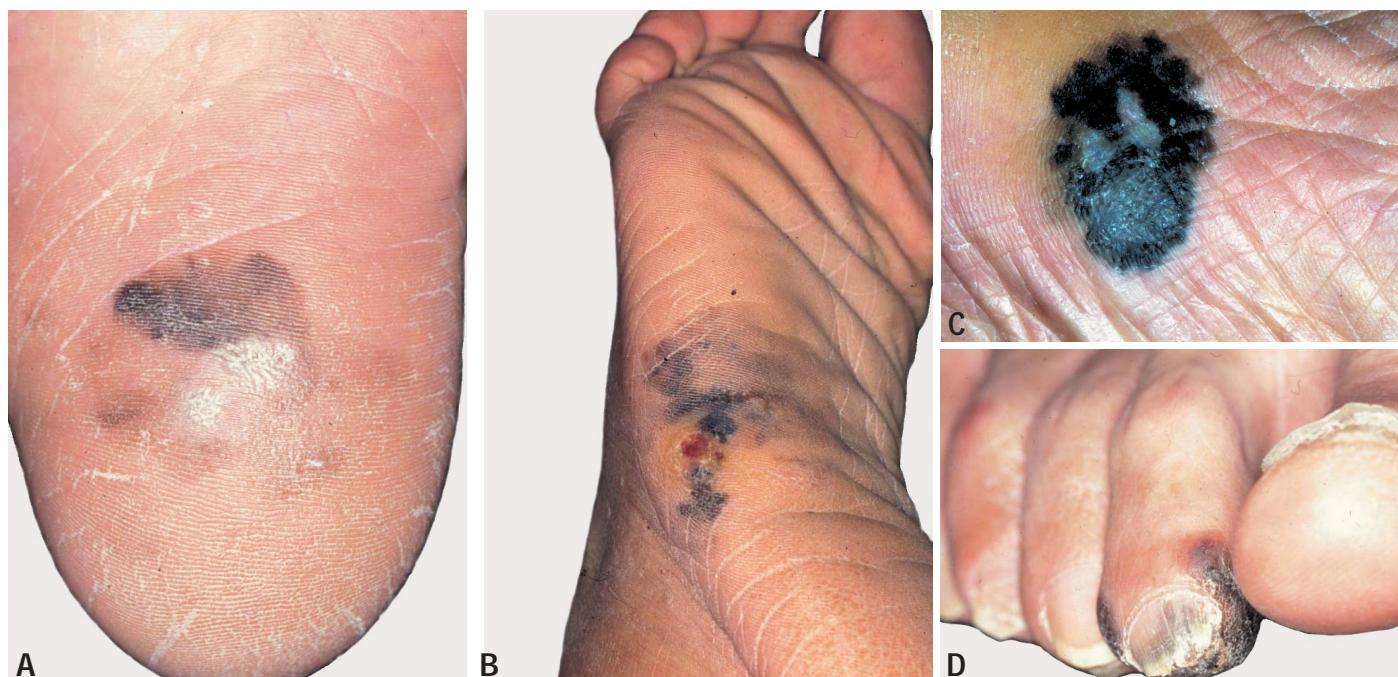


Fig. 2.20 Acral-lentiginous melanoma (ALM). **A** ALM on the heel, showing varying shades of tan to brown pigmentation. **B** ALM on the lateral aspect of the foot, showing irregularly bordered pigmentation with a slightly ulcerated lesion. **C** ALM on the sole, showing an irregularly pigmented macule with notched borders. **D** ALM on the second toe, showing subungual pigmented lesion extending to adjacent skin.

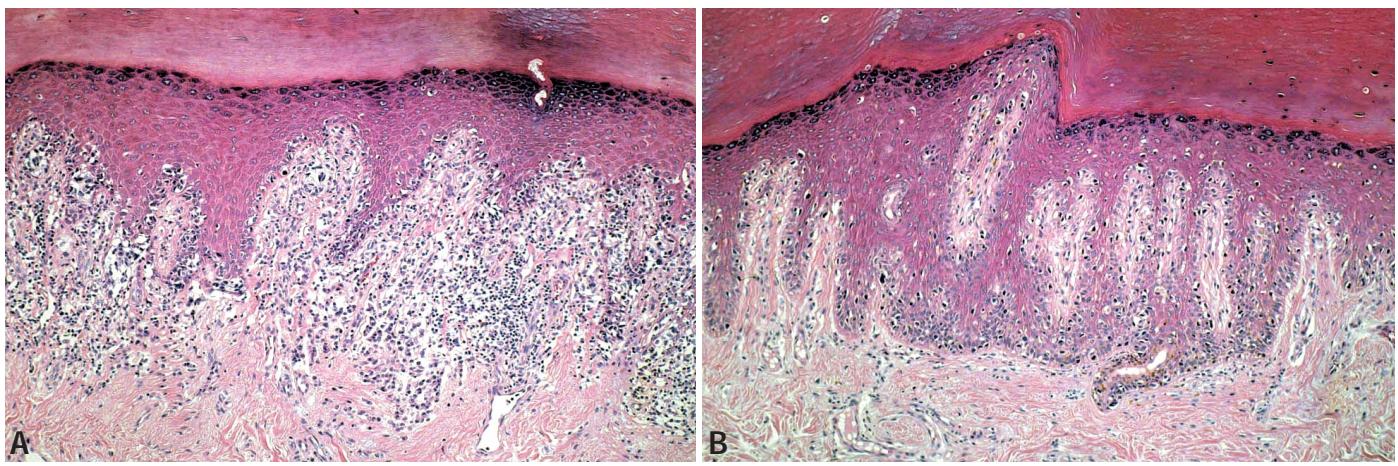


Fig. 2.21 Acral-lentiginous melanoma. **A** ALM, showing marked acanthosis, elongation of the rete ridges, broadened horny layer, and large, atypical melanocytes with large, often bizarre nuclei and nucleoli, and cytoplasm filled with melanin granules. **B** ALM, showing lentiginous proliferation of atypical melanocytes at the border of the tumour.

tumours located on acral sites [1337]. Whereas 77% of cutaneous melanoma in Japanese patients occurs on acral sites [2130]. In African and African-Americans, the highest incidence of cutaneous melanoma has been reported on relatively non-pigmented areas, such as the soles, nail plates, and mucous membranes [1417]. Thus, ALM is the most common type of melanoma in dark-skinned peoples and Asians [1268, 2129]. Nevertheless the absolute incidence of acral melanoma in dark-skinned African and light-skinned Caucasian populations in North America is similar, suggesting that the observed racial difference may relate to a decreased incidence of non-acral melanoma in African American populations [2268]. Compared with the escalating incidence that typifies other melanoma subtypes, the incidence of ALM has remained static [661]. Overall, ALM occurs in an older patient population than does superficial spreading or nodular melanoma, and, in populations where ALM is common, this tumour more often afflicts men than women. Overall, the age distribution of ALM is similar to that of lentigo maligna melanoma, peaking in the seventh decade of life, whereas superficial spreading melanoma and nodular melanoma peak in the sixth decade [1337]. The mean age of ALM ranges from 55 to 68 years in European countries [767,1337,2123]. In Japanese patients, there is a peak in the sixth decade in both males and females. In Japan, Korea, and Taiwan, men are

affected twice as often as women [1220, 1268,1428,2130]. On the other hand in western countries, there is less of a male predominance in patients with ALM [1337,2220].

Localization

The term acral has been used differently throughout the literature. Most publications use acral for the non-hair bearing, i.e. glabrous skin of the palms and soles, and the nail bed, whereas others also include the dorsal aspect of the hands and feet under this term. In a German study, using the latter definition, acral melanoma occurred on the feet in 87% cases (plantar sites, 57%; subungual, 5%; and dorsum, 9%) and on the hands in 23% (palm, 1%; subungual, 14%; and dorsum, 9%) [1337]. Thus, the plantar sites were greatly more often affected than the palmar sites [1337,2130,2201, 2220,2296]. In contrast to ALM, superficial spreading melanoma occurs more commonly on the sun-exposed dorsal aspects of the hands and feet, whereas nodular melanoma occurs on all acral sites with relatively equal frequency [1337]. In addition to the sole, nail plate is an especially frequent site with a frequency of 16-19% in ALM [1337,2130]. In contrast to the palmar/plantar melanomas, subungual melanomas occur more often on the hands than on the feet [745,1221,2130,2315]. In the Japanese series, the number of subungual melanomas on the fingers is 62-72% and on the toes 28-38%, with an 82% incidence on the thumbs and great toes [1221,2130]. The high percentage of

occurrence on the thumbs and great toes may suggest a role for trauma in the etiology of subungual melanoma [2130]. Since sun exposure obviously plays little role in palmoplantar sites, the causative role of ultraviolet light is presumed to be negligible in ALM.

Clinical features

Acral melanomas in the early stages appear as a pigmented macule similar to lentigo maligna. Acral melanomas commonly exhibit clinical evidence of a biphasic growth pattern, with a more rapid evolution from an entirely flat clinical lesion to a lesion containing an elevated focus than is observed in the other types of melanoma. The radial growth phase of ALM is characterized by a macular pigmented lesion with highly irregular, notched borders and varying shades of pigmentation. Within a background pigmented macule, acral melanomas often develop a clinically apparent vertical growth phase. This is manifest as an elevated papule or nodule, sometimes with a verrucous surface, and corresponds to the histological vertical growth phase of malignant melanocytes. Ulceration is more often seen in ALM than in other types of melanoma. Subungual melanomas often begin as brown to black discolouration of the nail that frequently become bands or streaks of pigmentation. Thickening, splitting, or destruction of the nail plate may occur. The irregular macular hyperpigmentation, coloured tan to dark brown, is also recognized around the nail plate [2130]. In one study, 17% of the patients noticed

the pre-existence of some pigmented skin lesions, and 21% related a history of trauma [2130]. Pigmented streaks are not uncommon in patients with deeply pigmented skin, nevertheless, a history of a new or recently changing pigmented lesion should prompt the consideration of a biopsy for histological evaluation of the lesion. In this case, reflection of the proximal nail fold to enable biopsy of the nail bed may be necessary for definitive diagnosis.

Unfortunately, clinical misdiagnosis is not uncommon in patients with ALM [409, 767, 1327, 1592, 2222]. Therefore, awareness of atypical presentations of ALM that may contribute to misdiagnosis or diagnostic delay assumes particular importance. ALM lesions are frequently treated or followed for considerable time under the clinical diagnosis of wart, callosus, fungal disorder, subungual haematoma, keratoacanthoma, nonhealing ulcer, foreign body, naevus, ingrown toenail, etc [2222].

Histopathology

The histology of ALM is characteristic but not distinct. In the radial growth phase, the lesions are characterized by marked acanthosis, expanded cornified layer, elongation of the rete ridges, and lentiginous proliferation of atypical melanocytes along the basal epidermis at the border of the tumour [1337, 1767]. The intraepidermal component of acral melanoma includes large, atypical melanocytes with large, often bizarre nuclei and nucleoli, and cytoplasm filled with melanin granules [2130]. These melanocytes in the basal layer often exhibit long, elaborate dendritic processes [2130].

Atypical melanocytes can extend along the sweat ducts into the deep dermis. In the vertical growth phase, tumour nodules often contain predominantly spindle-shaped cells and are associated with a desmoplastic reaction [2130]. The junctional component of thicker tumours often shows nesting of tumour cells and upward migration to the cornified layer [1337].

Immunoprofile

As in the other types of melanomas, immunohistochemical stainings for S-100 protein, HMB-45, and MART-1 (also known as Melan-A) are of great diagnostic value in ALM. S-100 protein (positive

cases, 95%) is a more sensitive marker than either HMB-45 (80%) or MART-1 (70%) [1268]. However, S-100 protein-negative ALM has been reported [83]. The intensity of HMB-45 but not of S-100 protein is correlated well with the melanin content. HMB-45-negative cases are all amelanotic, but amelanotic cases are not all negative for HMB-45 [1268]. The melanoma cells also express vimentin [1268]. Focal staining for CAM5.2 or epithelial membrane protein may occasionally be found [1268].

Somatic genetics

Comparative genomic hybridization (CGH) of melanomas on acral non-hair bearing skin showed distinct differences to melanomas on non-acral skin [171]. A study of 15 acral melanomas and 15 superficial spreading melanomas from non-acral sites showed that all (100%) acral cases had gene amplifications, whereas amplifications were found in two of the superficial spreading melanomas (13%). The most common amplified region is chromosome 11q13 which occurred in 50% of these types of melanoma. A recent study has shown that cyclin D1 is one of several candidate genes in this region. This conclusion was based on the observation that amplification of the cyclin D1 gene was always accompanied with overexpression of the cyclin D1 protein, and that inhibition of cyclin D1 expression in vitro and in xenograft models led to apoptosis or tumour shrinkage [2072].

FISH studies on primary lesions of acral melanoma showed that the amplifications arise early in acral melanoma and can already be detected at the *in situ* stage [171]. The *in situ* portion of acral melanoma may extend beyond what is recognizable histopathologically. FISH detected gene amplifications were identified in single basal melanocytes immediately adjacent to the *in situ* component of acral melanoma; they were equidistantly spaced and looked histopathologically inconspicuous [171]. Based on the observation that these "field cells" were found at the histopathologically uninvolved excision margins of an acral melanoma that recurred multiple times the authors propose that field cells may be a form of minimal residual melanoma that leads to persistence if not removed. More recent studies using array CGH have confirmed the frequent gene ampli-

fications in acral melanoma preferentially involving chromosome 11q13. In addition, the studies revealed that all melanomas showed these features, independent of their histological growth pattern, as long as they were located on glabrous, i.e. non-hair bearing skin of the palms and soles or subungual sites (Bastian et al, to be published). In addition, melanomas involving these anatomic sites also had a significantly lower mutation rate of the BRAF oncogene (6/39, 15%) than melanomas on the trunk (23/43, 53%) [1493]. The molecular genetic analyses therefore suggest melanomas of the palms of soles and subungual sites represent a genetically distinct form of melanoma, independent of their histological growth pattern.

Prognosis and predictive factors

In general, the prognosis of invasive acral melanoma is poor. This can partly be explained by the above described diagnostic delay and increased tumour thickness at the time of diagnosis. However, there are some studies suggesting that acral melanomas may undergo a more aggressive course independent of tumour thickness [151, 308, 661, 1337]. In a study from Germany, 63 out of 64 patients (98.5%) with melanoma of the sole subsequently developed metastases [775]; a corresponding figure from Japan in 1983 was 35% [2130]. The same hospital recorded that the 5-year survival rate of subungual melanoma increased from 53% in 1969-82 to 83% in 1983-93 [1221], presumably because of early awareness of lesions and development of treatment [2012]. However, others have reported that ALM is not a significant prognostic indicator [661, 2201], and adjustment for histologic and clinical stage renders the prognostic importance of anatomic location insignificant [151, 308]. These conflicting results can in part be explained by the different definitions used for acral melanomas in the studies. Future studies using refined criteria including genetic information are necessary to assess the prognosis of this melanoma type.

Desmoplastic melanoma and desmoplastic neurotropic melanoma

S.W. McCarthy
K.A. Crotty
R.A. Scolyer

Definition

Desmoplastic melanoma (DM) is a spindle cell melanoma in which the malignant cells are separated by collagen fibres or fibrous stroma. It displays variable cytological atypia, cellularity and stromal fibrosis and more often than not has an accompanying junctional component. Neurotropism is a common associated feature (in at least 30% of cases) and when it occurs such tumours are termed desmoplastic neurotropic melanomas (DNM). The neurotropism may be pe-

rineural or intraneuronal and often extends beyond the desmoplastic component. DM may also present as a recurrence or occasionally as a metastasis from other types of melanoma.

ICD-O code

8745/3

Historical annotations

DM was first described by Conley et al. in 1971 [526] as a clinically inconspicuous superficial melanocytic lesion, mainly on the head and neck, with an atypical

junctional component, preceding the development of a bulky dermal and subcutaneous tumour. The latter was composed of atypical melanocytes and spindle cells often with elongated nuclei and a dense collagenous ground substance. Many others subsequently highlighted the frequent neurotropism of DMs.

Epidemiology

Desmoplastic melanomas represent between 1-4% of melanomas. In a large series from the Sydney Melanoma Unit

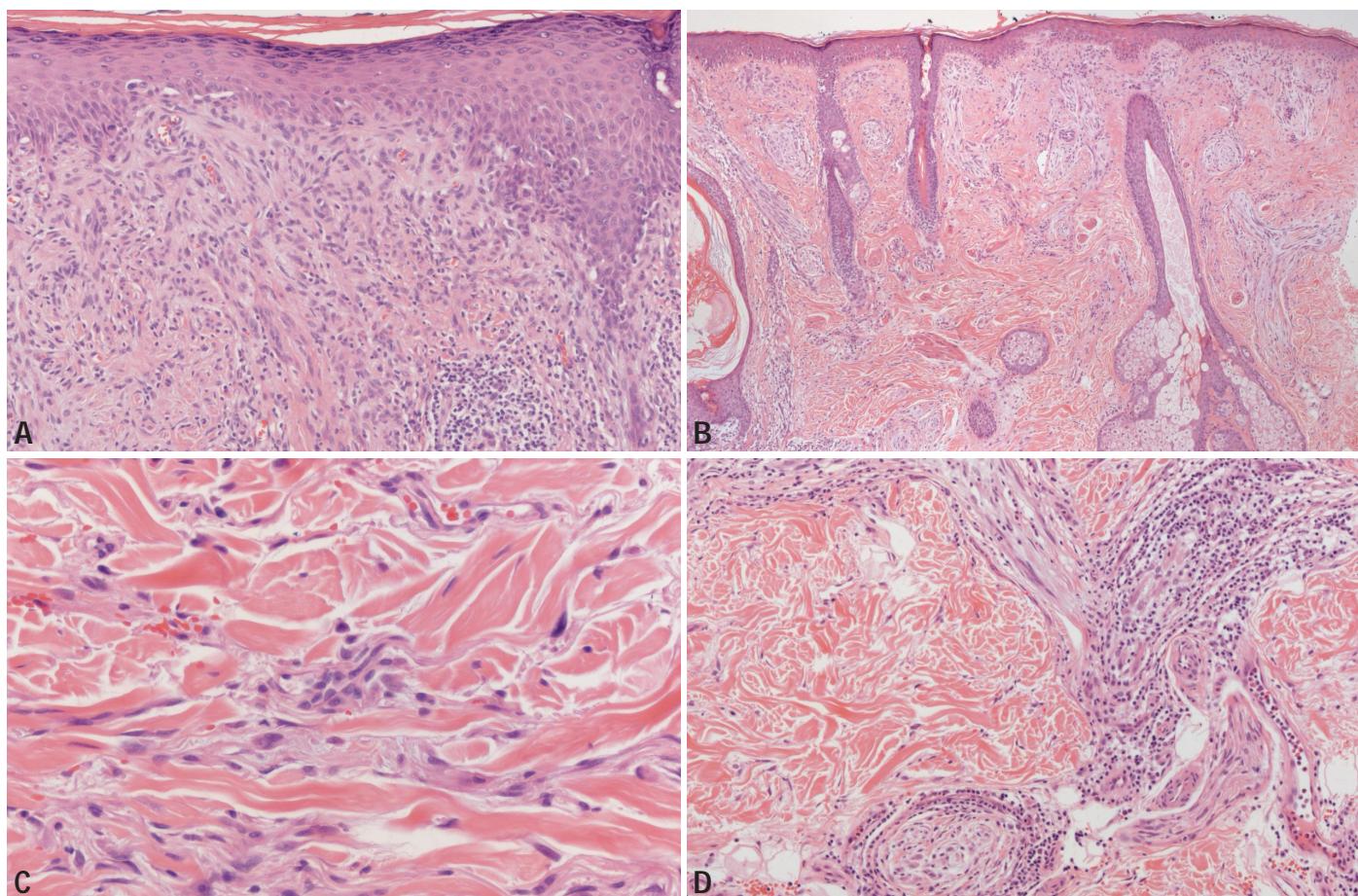


Fig. 2.22 Desmoplastic neurotropic melanoma. **A** Male, 73 yrs, cheek. A few atypical enlarged melanocytes are present in the junctional zone. The fibrohistiocytic pattern is accompanied by scattered lymphocytes, some in clusters. Mitoses are hard to find. **B** Female, 24 yrs, lip. There are "neural transforming" areas with thick neuroid bundles in the upper dermis. Note occasional atypical junctional melanocytes, a few subepidermal spindle cells and scattered lymphocytes. **C** Male, 73 yrs, cheek. Malignant spindle cells with elongated nuclei appear to be within and between collagen bundles. **D** Female, 24 yrs, lip. "Neural transforming" areas with neuroid bundle (top of picture) containing atypical elongated spindle nuclei. Intraneuronal and perineurial involvement of a small nerve is also present. There is a prominent infiltrate of lymphocytes.

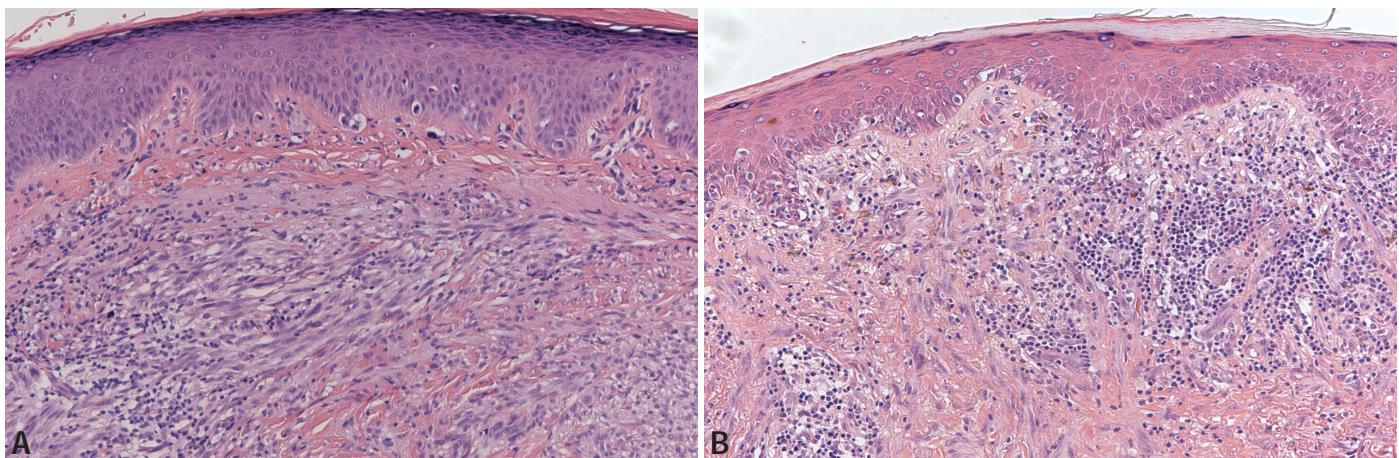


Fig. 2.23 Desmoplastic melanoma. **A** Male, 57 yrs, upper lip. Abnormal junctional melanocytes, spindling dermal melanocytes and a patchy lymphocytic infiltrate. **B** Female, 76 yrs, forearm. Abnormal junctional melanocytes and dermal spindle cells with patchy lymphocytes.

(SMU) the median age at diagnosis was 61.5 years (range 24-91) {1867,1868}. As in other histogenetic types of melanoma, males are more often affected (M:F = 1.75:1) {358A,1867,1868}.

Etiology

The etiology is unknown, but the majority occurs in sun-exposed skin. Some have occurred in irradiated areas {1125}.

Localization

DM may be found in many sites but most commonly involves the head and neck region (37%), including ear, nose and lip {1077}. Males predominate except on the lower limbs. The vulva is a rare site for DM {1664}.

Clinical features

Most present as a painless indurated plaque but some begin as a small papule or nodule {2501}. Almost half lack pigmentation {1867}. Pale lesions are often mistaken for basal cell carcinoma, dermatofibroma or a scar. Pigment is usually due to an associated lentigo maligna

(LM)/Hutchinson melanotic freckle (HMF) or superficial spreading melanoma. Unusual presentations include a young age {439,1077}, an erythematous nodule {1326} and alopecia {563}.

Macroscopy

Ulceration is uncommon although it was found in 17% of the SMU cases {1868}.

Tumour spread and staging

The tumours usually infiltrate deeply into the reticular dermis but local spread may involve subcutaneous tissue, deep fascia including periosteum and pericranium, bone and salivary gland. Neurotropic foci may be found well beyond the main tumour. In the SMU series, neurotropism was found only in tumours exceeding 1.5 mm in thickness and Clark level 4 or 5 {1867,1868}. Initial metastases from DM may involve regional lymph nodes or distant sites.

Histopathology

In DM the spindle-shaped melanocytes, which often resemble fibroblasts and are

usually non-pigmented, are found in and between mature collagen bundles. The latter may be thickened and/or associated with a mild to marked stromal fibrosis. The distribution of spindle cells is usually haphazard but occasionally they form parallel bundles or storiform areas. The spindle cells often extend into the subcutis diffusely or in fibrous bands and may involve deep fascia, especially pericranium. The overlying epidermis may be thinned or thickened. Characteristically there are accompanying small islands of lymphocytes and plasma cells within and/or at the edge of the tumour. The cytological atypia of the spindle cells usually varies from mild to moderate. However, even in cases with mild atypia, there are usually a few larger or more elongated hyperchromatic nuclei. The cytoplasm of the spindle cells is often poorly defined. In examples where the spindle cells are small, well scattered and associated with solar elastosis, the lymphoid islands may be the main clue to the diagnosis. Paucicellular variants are easily missed on punch and shave biopsies.

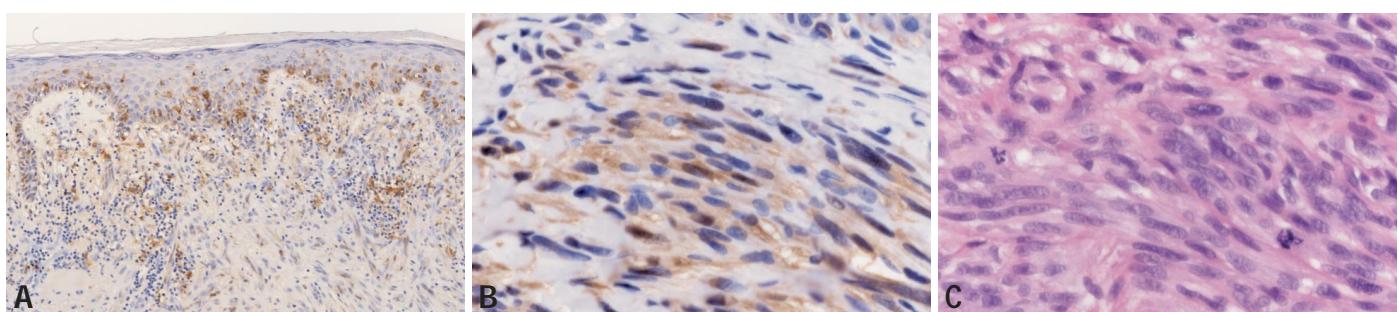


Fig. 2.24 Desmoplastic melanoma. **A** The spindle cells stain poorly with S100 unlike the Langerhans cells and interdigitating cells. **B** Variable S-100 positive nuclear and cytoplasmic staining. **C** Crowded abnormal spindle cells and atypical mitoses.

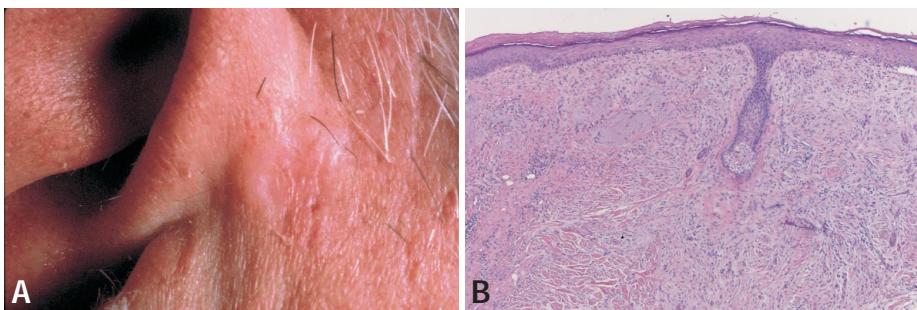


Fig. 2.25 Desmoplastic melanoma. **A** Firm, skin-coloured plaque. **B** Male, 68 yrs, scalp. This punch biopsy was initially diagnosed as a scar. Only an occasional spindle cell was S-100 positive and no abnormal junctional melanocytes were found. A larger desmoplastic melanoma was removed from the same site 6 months later. Clues to the diagnosis are the small foci of lymphocytes and permeation of the band of dermal elastosis by spindle cells.

sies. Junctional change is sometimes minimal or absent {1125}. Occasionally there is an associated banal naevus. Vascular invasion is rare. Even rarer cases show heterotopic bone and cartilage {1644}.

The median Breslow thickness in the SMU series was 2.5 mm (0.2-18 mm) {1867,1868}. The thickness and extent of invasion is usually best determined in S-100 stains. The mitotic rate is variable but is often low. Abnormal mitoses are common in the more cellular tumours.

The neurotropism is characterized by the presence of one or more foci in which the spindle cells extend in a circumferential fashion around nerves in the dermis or deeper and/or thickened nerves containing abnormal cells within their nerve sheath. Spindle cells may also form structures resembling nerves ("neural transforming"). Neurotropism may be present in melanomas without desmoplasia.

Melanomas of any histogenetic type may have desmoplastic areas. The proportion of desmoplasia in a melanoma necessary for the diagnosis of DM has been ill defined in several studies, but proposals for diagnostic criteria have been made {358A,985A,1546A}.

Metastases in lymph nodes may be epithelioid cells, or spindle cells with or without desmoplasia.

Immunoprofile

The spindle cells are positive with S-100 although only a few nuclei are positive in some otherwise typical cases. HMB45 is usually negative except for any foci of epithelioid cells {2476}. NSE, NKI/C-3 and smooth muscle actin {1929} may be positive. Melan A (MART-1) is usually negative. Microphthalmia transcription

factor (MTF) is not a sensitive or specific marker {356,885,1294}. Type IV collagen and laminin are frequently expressed in DM {1857}. Vimentin is usually positive although positive staining does not usually assist in diagnosis.

Differential diagnosis

The differential diagnosis includes desmoplastic naevus {958}, which like DM may have perineural extension but lacks asymmetry, mitotic activity, marked nuclear atypia and lymphoid infiltrates. Well established desmoplastic Spitz naevi may have many HMB45 negative spindle cells but these naevi are usually symmetrical with epidermal thickening, include at least a few plump cells and have rare or absent mitoses. Sclerosing cellular blue naevi, which are most frequent on the scalp, also lack mitoses and are more or less diffusely HMB45 positive. Immature scars, especially in re-excision specimens, may focally resemble DM as they may have some S-100 positive spindle cells {476,1951}, foci of lymphocytes and mitoses.

Other differential diagnoses include dermatofibroma/fibrous histiocytoma, fibrosarcoma, "malignant fibrous histiocytoma", malignant peripheral nerve sheath tumour and leiomyosarcoma. These tumours can usually be separated by morphology and appropriate immunohistochemistry.

Histogenesis

It is most likely that the desmoplastic cells are derived from melanocytes that have undergone adaptive fibroplasia. Some authors have suggested that the desmoplasia occurs because of a fibroblastic stromal response and neurofibrosarcomatous differentiation of the

tumour cells {2476}. Ultrastructurally, premelanosomes and melanosomes are rare and the spindle cells have the features of fibroblasts. There is abundant rough endoplasmic reticulum and sometimes intracytoplasmic collagen and macular desmosomes {2476}.

Somatic genetics

Chromosomal aberrations and gene mutations have been found in sporadic and familial melanoma {799}. Allelic loss at the neurofibromatosis type 1 (NF1) gene locus is frequent in DM {931}. Basic fibroblast growth factor (bFGF) and other fibrocytokines are often present in the nuclei of DMs {1335}. Loss of heterozygosity of matrix interacting protein 1 (MX1) is frequent {1893}. No BRAF mutations were found in 12 desmoplastic melanomas {596}, consistent with the finding that melanomas on chronically sun-exposed skin only rarely have BRAF mutations {358B,596,1493}.

Prognosis and predictive factors

Recurrences are common especially after incomplete excision {526}, marginal excision <10 mm or if neurotropism is present {1867,1868}. The conflicting results regarding the risk of regional node field metastases and prognosis of DM patients may be due to a heterogeneity of tumours classified as DM and failure to account for tumour thickness {2115A}. Regional nodal metastases appear to very uncommon in paucicellular DMs with prominent fibrosis and are associated with longer survival {358A, 932A, 985A}. Otherwise, disease free survival rates are similar to other melanomas of comparable thickness {126}. Neurotropism, HMB45 positivity, high mitotic rate, male gender, thickness, ulceration and site all appear to affect survival which overall is 79% at 5 years {1868}. Of patients with a recurrence, 78.2% experienced it within 2 years. Wide local excision is the treatment of choice {99A}. Radiation therapy has been effective in some cases {71,1125}.

Melanoma arising from blue naevus

L. Requena
J. A. Carlson

Definition

A melanoma that arises in association with dermal melanocytosis, most frequently cellular blue naevus.

Synonyms

"Malignant blue naevus" or "blue naevus-like melanoma" are terms used to describe melanomas arising in association with a cellular blue naevus or those primary melanomas that resemble blue naevi and lack an *in situ* component.

ICD-O 8780/3

Epidemiology

Melanoma associated with blue naevus is an exceedingly rare tumour with over 165 reported cases. It affects predominantly Caucasians and all age groups with the majority of cases occurring between 20 and 60 years, with a mean age at diagnosis of 44 years {2066, 2332}. Slightly more females than males have been reported (82 females; 76 males). Occasionally, dark-skinned patients develop melanoma in association with a blue naevus {548, 1352, 1629}.

Localization

In decreasing order, the sites most frequently affected are the scalp (33%), orbit and face (32%), trunk- mostly back and buttocks (19%), extremities (7%) and hands or feet (7%). Involvement of the vulva and vagina have also been reported {422, 2233}.



Fig. 2.26 Melanoma arising from blue naevus. Note the presence of satellitosis (Courtesy of Dr. H. Kerl).

Clinical features

Most melanomas associated with blue naevus (93%) develop in a pre-existing dermal melanocytosis that was congenital (35%), acquired during infancy or childhood (15%) or identified during their adult years (43%). These associated lesions were cellular blue naevi (52%), common blue naevus (16%), naevus of Ota (14%), naevus of Ito (1%) {2066, 2414}, or ocular melanocytosis {542, 1127, 2332, 2431}. On average, these melanocytoses were present for 24 years before melanoma developed, with a range of 3 months (infant with congenital facial blue naevus {2066}) to 78 years (naevus of Ito {2414}). For congenital and childhood onset melanocytoses, melanoma developed after a mean duration of 34 years (range 3 months to 78 years) whereas for adult onset common or cellular blue naevi, melanoma developed on average after 14 years (range 1 – 56 years). The majority (83%) of affected patients described recent, often rapid, growth or presented with proptosis in the case of orbital melanomas within a year of diagnosis. Other symptoms include colour change or ulceration, and in the case of orbital melanomas, diplopia and blurred vision. The melanoma is typically a large black nodule with mean diameter of 2.1 cm (range 0.5–8.0 cm). In some cases, satellitosis due to cutaneous metastatic deposits appear around the primary nodule {64, 276, 364, 856, 1018, 1588, 1981, 2066}. However, this feature

can also represent the well-known phenomenon of satellitosis associated with the common and cellular blue naevus (agminated blue naevus) {616, 1059, 1195, 2008}. Similarly, cellular blue naevus can also present with regional lymph node deposits {143, 1357, 2261}. In the former cases, histopathologic examination of the satellite lesions reveals features of benign blue naevus and the lesions present benign biological behaviour with no development of distant lesions.

Etiology

The etiology of melanoma associated with blue naevus is unknown, but the presence of longstanding dermal melanocytosis is likely a risk factor. Ocular and oculodermal melanocytosis (naevus of Ota) is strongly associated with uveal melanoma {2192, 2193} and has been reported with meningeal melanocytoma (blue naevus) of the brain {1877} and primary melanomas of the central nervous system {253, 569, 1104, 1713, 1930, 2046}. Based on this association and numerous reports of melanoma of the face, orbit or brain associated with oculodermal melanocytosis patients presenting with naevus of Ota should be considered at lifetime risk for melanoma of the skin, orbit or central nervous system, a risk that maybe similar in nature to that identified for large congenital melanocytic naevi with melanoma and neurocutaneous melanocytosis {254}.

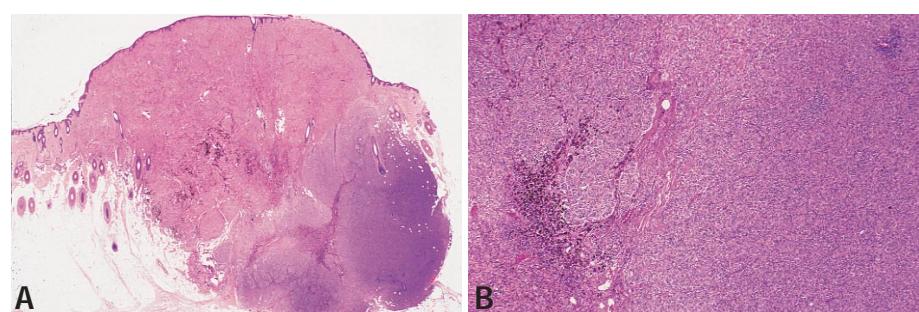


Fig. 2.27 Melanoma arising from blue naevus. **A** Scanning magnification showing a blue naevus with a nodule of malignant melanoma in deeper areas. **B** In deeper areas the nodule of malignant melanoma was composed of sheets of cells destroying pre-existing structures of the dermis.

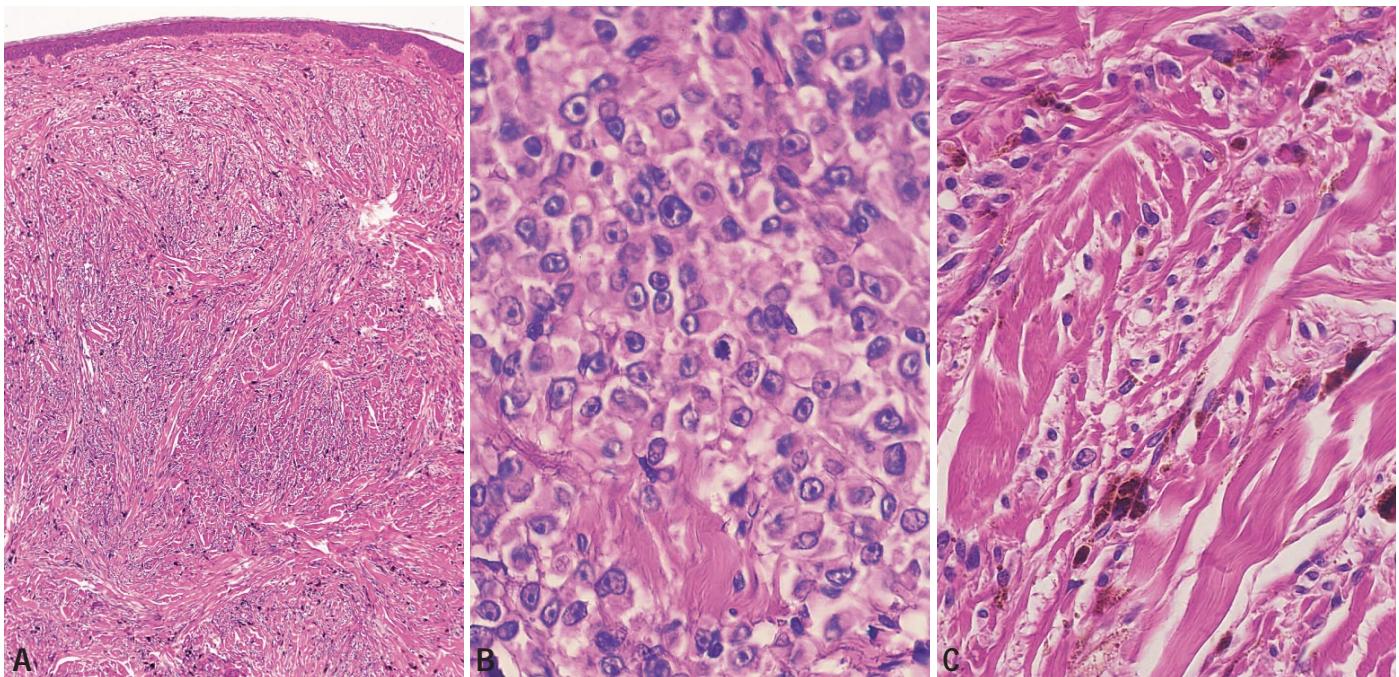


Fig. 2.28 **A** Superficial areas showing stereotypical histopathologic features of a common blue naevus. **B** Higher magnification demonstrated that neoplastic melanocytes of the melanoma showed epithelioid appearance and marked atypia, with large eosinophilic cytoplasm, pleomorphic nuclei and prominent nucleoli. **C** Neoplastic melanocytes of the blue naevus showed small monomorphous nuclei. Note the striking collagenization of the dermis and the abundant number of melanophages.

Additional associations of unknown influence include subacute cutaneous lupus erythematosus, leukoderma, Becker's naevus and prostate adenocarcinoma in one patient {1629}, papillary thyroid carcinoma {94}, acute lymphocytic leukaemia {2119}, psoriasis {238}, and oral contraceptives {1404}. Phototherapy has been associated with cellular blue naevus development {810}.

Histopathology

By definition, a melanoma that develops in a pre-existing blue naevus is a dermal melanoma without the features of melanoma *in situ* involving the dermo-epidermal junction or adnexal epithelium. In fact, 82% of all reported cases described an adjacent common and/or cellular blue naevus. The absence of an identifiable benign naevus component in some reports may be the result of replacement of it by the melanoma or incomplete sampling of the benign element. Although these cases could represent *de novo* melanomas, a subtle, hypocellular dermal melanocytosis as seen in naevi of Ota and Ito, and Mongolian spots may not have been observed. Reports of orbital, facial and shoulder melanomas associated with

naevi of Ota and Ito, and ocular melanocytoses attest to this latter possibility of under-reporting {542,660,1783, 2332,2414}.

At scanning magnification, two histopathologic patterns are evident. One is represented by the benign component of the blue naevus, which may range from very focal to comprising the main bulk of the neoplasm. Often this benign component is represented by a cellular blue naevus and less frequently the lesion contains a common blue naevus. Most cases, however, show a combination of the so-called cellular and common blue naevi, making this distinction useless. The areas of cellular blue naevus consist of solid aggregations of closely arranged monomorphous ovoid cells with abundant pale cytoplasm containing little or no melanin and round vesicular nuclei with inconspicuous nucleoli. In contrast, the areas of common blue naevus are made up of elongated spindled bipolar melanocytes, with long branching dendritic processes most of them filled with abundant granules of melanin. Melanophages and sclerotic bundles of collagen are also frequently observed between the fascicles of dendritic melanocytes.

Although the malignant component may involve the superficial dermis and ulcerate the epidermis, more often it appears as a deep-seated expansive asymmetric nodule involving the reticular dermis and subcutaneous fat. Usually, there is an abrupt transition from the benign blue naevus component to the nodule of melanoma. The nodule or nodules of melanoma show both architectural and cytological features of malignancy. The melanomatous component consists of sheets of cells that involve diffusely the deep dermis destroying the pre-existing structures with pushing margins and sharp demarcation between the neoplasm and adjacent dermis or subcutaneous tissue. Neoplastic melanocytes appear as large spindled to epithelioid cells with abundant cytoplasm and pleomorphic and hyperchromatic nuclei, with prominent nucleoli and frequent mitotic figures. Usually they contain little or no melanin. Without the associated benign component, these dermal nodules would be histopathologically indistinguishable from typical nodular or metastatic melanoma. Necrosis of individual cells as well as necrosis *en masse* may be also seen in the melanoma component, although this finding seems to be less

frequent than in melanomas arising de novo ("malignant blue naevus") {973}. A perivascular inflammatory infiltrate, mostly composed of lymphocytes, which is usually lacking in blue naevus, is often seen around the melanoma arising in blue naevus.

Melanoma arising in the setting of blue naevus should be differentiated from the so-called atypical cellular blue naevus {118,2371}. These lesions show clinicopathologic features intermediate between typical cellular blue naevus and malignant melanoma associated with blue naevus. The lesions show architectural atypia, characterized by asymmetry and infiltrative margins, as well as cytologic atypia, which consist of hypercellularity, nuclear pleomorphism, hyperchromasia, mitotic figures and necrosis. However, follow-up data of patients with atypical cellular blue naevus demonstrated that no patient experienced either a local recurrence or lymph node or visceral metastasis.

Melanoma associated with blue naevus should be also distinguished from *large plaque-type or giant cellular blue naevus* with subcutaneous cellular nodules {358, 1059}. Large pigmented plaques of childhood onset that show slow enlargement during adolescence and subsequent nodule formation clinically characterize this rare plaque variant of cellular blue naevus. Histopathologically, they exhibit multifocal dermal and subcutaneous proliferations of fusiform and dendritic pigmented melanocytes, with highly cellular nodules located in deeper areas of the plaque. The follow-up of patients with large plaque-type blue naevus with subcutaneous cellular nodules indicates that these lesions behave in a benign fashion.

Metastatic melanoma mimicking blue naevus can also be confused with melanoma associated with a blue naevus {354,2517}. These blue-naevus like metastases occurred in the same anatomic region as the primary tumour or near the skin scar of a dissected lymph node metastasis and were histopathologically characterized by atypical epithelioid melanocytes, mitotic figures, and an associated inflammatory cell infiltrate at the periphery of the lesions. In contrast with melanoma arising in a pre-existing blue naevus, metastatic melanoma to the skin simulating blue naevus lacks the benign blue naevus component.

Animal type melanoma (epithelioid melanocytoma) is a rare variant of primary cutaneous melanoma that may also mimic melanoma associated with blue naevus {567,1917}. Sheets and nodules of heavily pigmented epithelioid melanocytes that tend to aggregate along hair follicles and involve the entire thickness of the dermis with extension into the subcutaneous tissue histopathologically characterize animal-type melanoma. Epithelioid melanocytes in deeper areas show abundant, heavily pigmented cytoplasm and pleomorphic nuclei with prominent eosinophilic nucleoli and mitotic figures. Histopathologic features of melanoma in situ at the dermo-epidermal junction are few or absent, and neoplastic cells do not show evidence of maturation from superficial to deeper dermal areas. The overall architectural and cytologic features of animal-type melanoma closely resemble those of melanoma associated with blue naevus, but animal-type melanoma lacks the benign component of blue naevus or history of a pre-existing melanocytosis.

Metastatic spread

Melanoma associated with blue naevus is an aggressive tumour with frequent metastatic disease to regional lymph nodes (31% of reported cases) and distant sites (42%). Sites of metastasis, in decreasing order of frequency, include liver (36%), lung (22%), brain (16%), skin (13%), bone (9%), and in less than 6% of reported cases, spleen, heart, kidney, pancreas, adrenal, thyroid and parotid glands, ovary, and gastrointestinal tract. Melanuria and generalized melanosis have also been described in its terminal stage {2185}. Metastases can appear as late as 20 years after diagnosis {813}, but the median and mean time of discovery is 1.75 and 3.6 years after diagnosis. Metastasis to lymph nodes should be differentiated from the presence of blue naevus cells in the capsule of the node {181,392,405,1357,1358}. This well-known pseudo-metastasizing phenomenon seems to be the result of migration arrest during embryogenesis and is characterized by monomorphic melanocytes of blue naevus involving only the capsule and the marginal sinuses of the lymph node. In authentic metastases, nests of atypical melanocytes replace most of the parenchyma of the node, effacing its architecture.

Immunoprofile

Immunohistochemical studies in lesions of melanoma associated with blue naevus have demonstrated a strongly positive reaction of the neoplastic cells, both of the benign and malignant components, for vimentin, S-100 protein, HMB-45 and NKI/C-3 {280,1708,1996}. However, the number of silver positive nucleolar organizer regions (AgNOR score) {813,1826} and growth fraction as measured by proliferating cell nuclear antigen (PCNA) and Ki-67 (MIB-1) are significantly lower in the benign component of blue naevus than in the nodule of melanoma {1708,1826}.

Electron microscopy

Although some authors have interpreted the neoplastic cells of melanoma associated with blue naevus as being related with Schwann cells {1588}, electron microscopic studies have demonstrated the presence of melanosomes in the cells, as well as the lack of cytoplasmic enclosures of unmyelinated axons, which rule out the possibility of Schwann cell differentiation. Although the melanosomes in many cells of the malignant component are devoid of melanin {1014}, incubation with dopa demonstrates that they are strongly dopa-positive {1625}, thus confirming their melanocytic nature.

Somatic genetics

Results of DNA flow cytometry studies in melanoma associated with a blue naevus are variable revealing diploid cell populations in 4 cases {1574,1826} and aneuploid populations in 2 cases {1826}. A molecular analysis failed to demonstrate loss of heterozygosity on microdissected samples in one case of melanoma associated with blue naevus, using a panel of eight genes (MTS1, MXI1, CMM1, p53, NF1, L-myc, hOGG1, and MCC), many of which are commonly associated with conventional melanomas {94}. These findings suggest that melanoma associated with blue naevus may represent a distinct entity with a different molecular pathway to tumourigenesis than that of conventional melanomas. However, in a comparative genomic hybridization study comparing common blue naevi, cellular blue naevi, and atypical cellular blue naevi with melanoma associated with a blue naevus, melanomas associated with blue naevus showed chromosomal abnormalities similar to that of con-

ventional melanoma whereas cellular and atypical cellular blue naevi exhibit infrequent numerical chromosome aberrations similar in character to that identified in proliferative nodules found in congenital melanocytic naevi {1490}.

Prognosis and predictive factors

Some authors have proposed that melanoma associated with blue naevus is a low-grade malignancy {1574}. However, the literature review does not support this opinion. For instance, in a series of 12 cases, metastases developed in 10, and 8 died of metastatic disease {527}, and in another series of 10 cases, 4 patients developed metastases and 3 of them died of disease {883}. Of the 160 cases reported with follow up data, 34% of patients have died due to locally invasive or metastatic melanoma 20 months median, 41 months mean time from diagnosis (range 2–240 months). Therefore, melanoma arising in blue naevus is a highly aggressive tumour with poor prognosis similar to that of thick (>4.00 mm), AJCC stage IIB conventional melanomas {392}. Indeed, the Breslow thickness for this melanoma variant typically is much greater than 4 mm with a mean tumour thickness of 10 mm (range 2.8–45 mm){64,640,813,883,1844}. Possible prognostic factors indicative of a poor outcome include the presence of congenital melanocytosis, mixed melanoma cell type (both spindle and epithe-

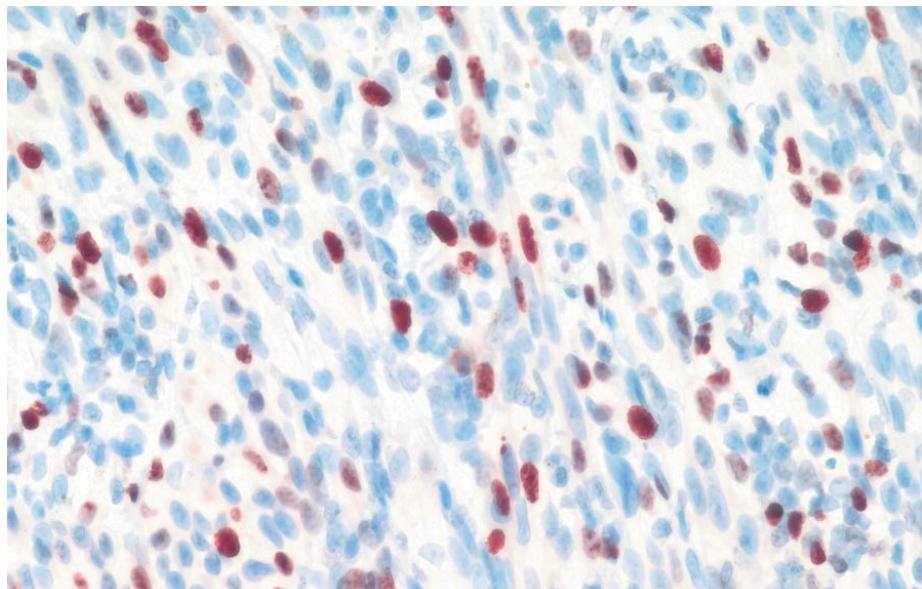


Fig. 2.29 High Ki-67 labelling index in hyperchromatic spindle nuclei of the melanoma arising from blue naevus. The benign portion of the lesion (not shown) had a very low labelling index.

lioid melanocytes), older age, high mean mitotic count ($>4/40$ high power field), and lymphocyte count (>100 per 20 high power field) {2332}. These prognostic factors were identified in a study of primary orbital melanoma where 90% of the patients had an associated blue naevus and 47.5% had congenital melanocytosis (naevus of Ota or ocular melanocytosis). The role of sentinel lymph node dissection and postoperative adjuvant therapy remains to be determined. Sentinel

lymph node dissection in the staging of melanoma associated with a blue naevus is advocated by some authors {2173} and one patient with metastatic disease to the lymph nodes was alive and without evidence of disease two years after surgery followed by therapy with interferon {640}.

Melanoma arising in giant congenital naevi

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P.E. North

I Sanchez-Carpintero
M.C. Mihm
B.C. Bastian

Definition

A proliferation of malignant melanocytes arising either in the epidermal component or the dermal component of a giant congenital naevus associated with risk of metastasis and death.

ICD-O code

8761/3

Synonyms

Malignant melanoma arising in a garment naevus;
malignant melanoma arising in a bathing trunk naevus;
malignant melanoma arising in a giant hairy naevus.

Epidemiology

About 1% of all infants have some kind of a congenital pigmented skin lesion {568}. The giant congenital naevus (GCN) is estimated to occur in around 1 per 20,000 infants {67,411,1306}. The risk of malignant transformation of a GCN has been estimated at from 5-20% but more recent studies based on statistical analyses suggest a figure of 6%. The GCN is a direct precursor of melanoma {1197, 1207,1927,2218}. There is a bimodal distribution to the occurrence of melanoma in GCN. Most develop in childhood before the age of 10 {1508} with a second peak of incidence in adult life.



Fig. 2.30 Malignant melanoma presenting as a reddish brown nodule in the midst of the congenital naevus.

Sites of involvement

Malignant melanoma can occur anywhere in a giant congenital naevus. The lesion most commonly arises in lesions on the trunk but can appear in any area even in congenital naevi of the meninges {568,1306,1927}.

Clinical features

The definition of GCN varies and includes a naevus with a diameter larger than 20 cm. Frequently large areas of the body (more than 2% of the body surface) are covered in a garment-like fashion {1306,1927}. The trunk and head and neck are the most common sites for these naevic lesions. The melanoma, very rarely present at birth, usually

appears as a rather rapidly growing asymmetrical nodule or plaque of blue-black, reddish or even rarely flesh colouration {568,1009}. Melanoma can occasionally present as a cystic lesion. Therefore, any GCN that develops an apparent subcutaneous cyst must be biopsied. Melanoma is only one of many benign and malignant tumours that may occur in GCN {1009,1928}.

Macroscopy

The lesion usually appears either as a firm nodule, or as a boggy discoloured area, usually dark brown or black in the midst of the naevus. If the lesion arises in the dermis, the tumour can sometimes only be seen on cut surface as a separate nonencapsulated nodule amidst the otherwise tan or pale tan coloured naevus in the dermis or subcutis.

Histopathology

Histologically, the tumours are often asymmetrical and sharply demarcated from the adjacent congenital naevus. If superficial, there is effacement of the rete ridges of the epidermis and often ulceration. The intraepidermal component usually is composed of epithelioid cells with pigmentation. Pagetoid spread is commonly noted. The tumour cells of the dermal component usually form expansile

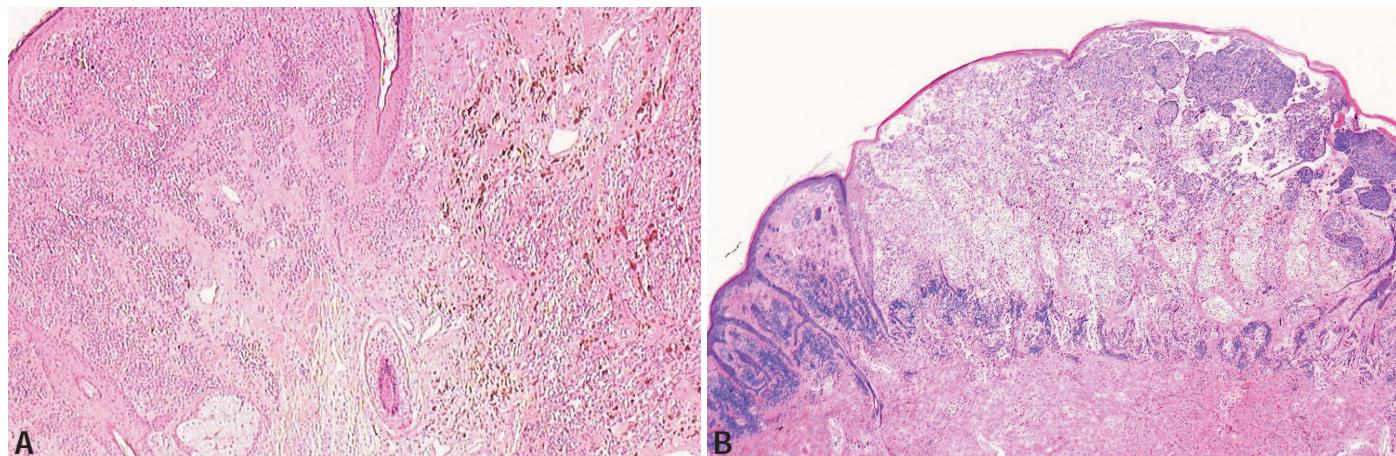


Fig. 2.31 Melanoma arising from large congenital naevus. **A** The melanoma is clearly separate from the naevus cells that are on the left. **B** A protuberant nodule shows the small dark naevus cells to the left and at the base of the melanoma that is composed of nests with dyscohesion.

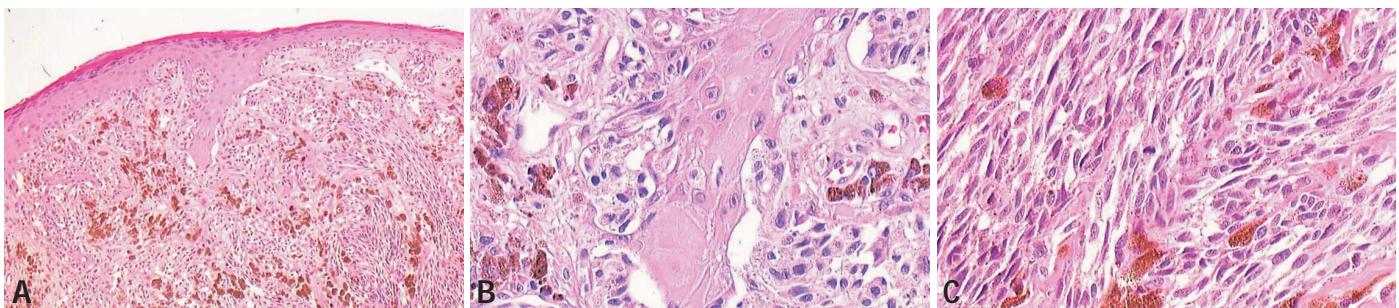


Fig. 2.32 Melanoma arising from large congenital naevus. **A** There is a distinctive proliferation of malignant melanocytes invading the dermis. Note thinning of the rete ridges with a proliferation of malignant melanocytes invading the dermis as spindle cells with an admixed population of melanophages. **B** Reveals epithelioid cells in nests invading the epidermis giving rise to spindle cells in the dermis. **C** The malignant spindle cells show nuclear hyperchromasia and mitoses.

nodules. They exhibit fully transformed malignant characteristics with very irregular chromatin patterns and prominent nucleoli. There is variable pigmentation. Both single cell and zonal necrosis may be observed. The melanoma cells as they abut or infiltrate as cords into the adjacent naevus show no evidence of maturation but maintain their fully malignant characteristics. Mitoses are common and atypical forms are usually present. A lymphocytic host response is often noted. Occasionally, a desmoplastic host

response may be observed as well as focal mucinosis. In our experience, the vertical growth phase dermal nodules may exhibit prominent areas of different cell types with different degrees of pigmentation {568,703,1197,1928}. Histologically, the presence of a residual dermal naevic component with congenital features may be quite difficult to find, particularly, if present in the wall of a vessel. The differential diagnosis includes the proliferative nodules that also arise in large congenital naevi.

Somatic genetics

Comparative genomic hybridization shows that melanomas arising in congenital naevi show similar chromosomal aberrations as melanoma arising independently {175}. By contrast, the proliferative nodules arising in early life do not show chromosomal aberration supporting the view that they are benign {175}.

Childhood melanoma

R.L. Barnhill

Definition

Melanomas developing in individuals prior to the onset of puberty are childhood melanomas and thereafter they are designated as melanomas in adolescents with the age limitation of 18 to 20 years. Childhood melanomas can be further subcategorized as 1) congenital melanoma (onset in utero to birth), 2) infantile melanoma (birth to one-year of age), and 3) childhood melanoma (one year to onset of puberty).

Epidemiology

The incidence of melanoma is exceptionally rare in prepubertal individuals (estimated incidence approximately 0.4% among all melanomas) {269A, 1487A} and uncommon under the age of 20 years (incidence approximately 2%) {123A}. The incidence of melanoma has

doubled in patients aged 15 to 19 years over the past decade but has remained unchanged in younger individuals {204A,1037A}. Less than 80 well documented cases of melanoma in children younger than 10 years have been recorded in the literature over a period of 30 years. As in adults, childhood melanomas have a predilection for Caucasians. Individuals with congenital naevi especially large varieties, atypical naevi, family history of melanoma, xeroderma pigmentosum, and immunosuppression are at increased risk for childhood melanoma.

Localization

Melanomas developing in patients up to 16 years of age most commonly involve the trunk (50%), followed by the lower extremities (20%), head and neck

(15%), and upper limbs (15%).

Clinical features

Melanomas in individuals under the age of 20, particularly in adolescents, show fairly similar clinical features as compared to melanomas in adults {123A,1916A}. However melanomas in prepubertal individuals are so rare that they are usually unsuspected. Features suggesting melanoma in a pigmented lesion such as a congenital naevus are rapid increase in size, bleeding, development of a palpable nodule (e.g., in a giant congenital naevus), colour change of a nodular lesion, surface changes such as ulceration, and loss of clearly defined margins. Recognition of melanoma appearing de novo requires a high index of clinical suspicion, especially for amelanotic lesions. Utilizing the

conventional ABCDE criteria (Asymmetry, ill-defined Borders, irregular Colour, and large Diameter, Elevation) the clinical detection of melanoma in adults, all such suspicious lesions in children should be evaluated for biopsy and histopathological examination. Melanoma in children also may be associated with pain or pruritus {155,417A,530A, 1037A,1619A,1859A,1930A,1990A, 2003A,2089,2232}.

Histopathology

The same histopathological criteria should be utilized for diagnosis as have been developed for adult melanomas {155,159A,417A,1990A,2232}. However, clinical information must be strongly considered, particularly age, since cutaneous melanoma is almost nonexistent under the age of two years and especially in the neonatal period.

The important stimulants of melanoma must be excluded: 1) atypical nodular proliferations developing in congenital naevi in infants and young children and 2) Spitz naevi.

Great attention should be given to avoiding over diagnosis melanoma and at the same time to the under recognition of atypical and borderline lesions that require adequate surgery and follow-up for disease recrudescence. Lesions not clearly meeting sufficient criteria for melanoma should be designated as biologically indeterminate. Features appearing to be most useful for the distinction of melanomas from naevi are large size (i.e., >7 mm), ulceration, high mitotic rate (>4 mitoses/mm²), mitoses in the lower third of the lesion, asymmetry, poorly demarcated lateral borders, lack of maturation, finely-divided melanin, and marked nuclear pleomorphism {155, 159A,2232}. Melanomas in children can be (somewhat artificially) categorized into three principal groups {155, 159A,2232}.

Conventional melanomas

About 40 to 50% of melanomas in children are similar histologically to those in adults {159A,2232}. The intraepidermal components of such melanomas consequently may be pagetoid, lentiginous, or nested. Melanomas of glabrous skin are exceedingly rare in childhood {159A, 2232}. Solar (so-called lentigo maligna) melanomas do not occur in childhood. However, melanomas diagnosed in

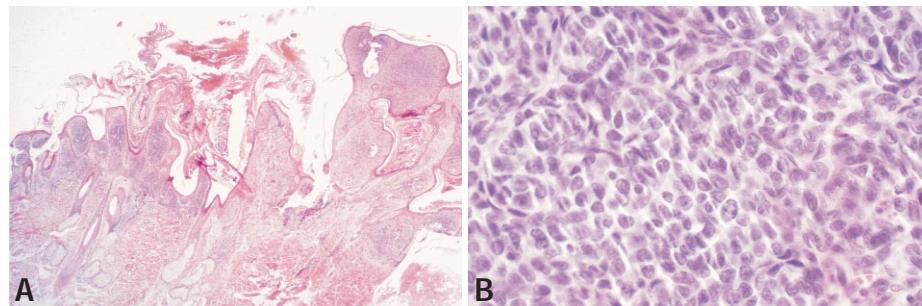


Fig. 2.33 Small-cell melanoma from the scalp of a prepubertal individual. **A** The lesion resembles a conventional melanocytic naevus at scanning magnification. **B** High magnification shows a highly cellular dermal component without maturation. There is a monomorphic population of small round melanocytes with scant cytoplasms resembling the neoplastic cells in lymphoma or neuroendocrine carcinoma. The nuclei are pleiomorphic.

patients with XP are histologically often similar to solar melanomas except that the actinic damage characteristic of adult tumors is absent {159A,2232}.

Small-cell melanomas

Small-cell melanomas are comprised of monomorphic small cells, reminiscent of small round cell malignancies such as lymphoma, or a melanocytic naevus {155,159A,2232}. These cells are often arranged in sheets or in organoid configurations. The melanocytes contain basophilic round nuclei and condensed chromatin. The high cellular density, lack of maturation, and often prominent mitotic rate are features suggesting melanoma. In children, small cell melanomas may appear de novo or may develop in a congenital naevus. Such melanomas with small-cell phenotypes have often been localized to the scalp, shown striking Breslow thicknesses, and fatal outcome in most patients {159A}.

Melanomas simulating Spitz naevus

On occasion melanomas in both children and adults may exhibit features strongly suggesting a Spitz naevus. These features include both architectural and cytological attributes such as epidermal hyperplasia, wedge-shaped configuration, epidermal clefting about intraepidermal nests, large epithelioid cells and spindle cells arranged in fascicles, etc. {155,159A,2232}.

In addition to conventional melanomas and typical Spitz naevi, there is also an intermediate group of Spitz-like lesions that demonstrate not only some features of Spitz naevi but also varying degrees of atypicity.

Differential diagnosis

Childhood melanomas must be distinguished from congenital and other naevi exhibiting pagetoid melanocytosis, lentiginous melanocytic proliferation, atypical nodular melanocytic proliferation, and from Spitz naevi. Conventional criteria such as age, clinical presentation, size, asymmetry, circumscription, degree of cellular density, maturation, degree of cytological atypia, and mitotic rate should facilitate this discrimination in most cases.

Pagetoid melanocytosis and lentiginous melanocytic proliferation are features commonly observed in naevi developing in children, particularly in glabrous skin. These changes must not be overinterpreted unless architectural disorder is prominent and cytological abnormalities are present throughout the breadth of the lesion.

Virtually all atypical nodular melanocytic proliferations developing in congenital naevi are biologically benign. Examination of these atypical tumors with reference to karyotype, expression of cell-surface antigens, growth in soft agar, chromosomal aberrations, and other parameters has shown that they have the properties of an immature proliferative but benign tumor {71A,175,1496A}.

Various authors have proposed criteria for distinguishing Spitz naevi from melanomas. Criteria favoring melanoma include asymmetry, ulceration, deep extension (particularly subcutaneous fat), large size (>1 cm), prominent cellular density, lack of maturation, deep mitoses (i.e., more than 3 mitoses in the lower third), high mitotic rate (i.e., >4 to 6/mm²), abnormal mitoses, and marked nuclear atypia.

Naevoid melanoma

N.S. McNutt
S. Kossard

Definition

Naevoid melanoma is a subtype of malignant melanoma of the skin that is distinctive in that the primary lesion mimics many of the architectural features of a common compound or intradermal naevus when composed of small melanoma cells, or with Spitz naevus when composed of medium-sized to large melanoma cells. These lesions are defined not as atypical naevi but as melanomas because they involve the dermis and have the potential for metastasis.

ICD-O code

8720/3

Synonym

The term minimal deviation melanoma has been used for some examples.

Epidemiology

Naevoid melanoma is uncommon, being estimated to be approximately 1–2% or less of melanomas {2096,2255}. Due to the low incidence, the small size of series of studies of these tumours, and the slightly different definitions of the lesion, the demographic profiles are not well-established. Naevoid melanomas can occur at any age but often are in young to middle-aged adults. Both men and women are affected, but there is a slight female predominance, perhaps due to early detection in women. In combining data from three similar studies with a total of 65 patients, the distribution of lesions

Table 2.06
Sex and ages in series of patients with naevoid melanomas.

Reference	Number of subjects	M/F Ratio	Mean Age
	Females	Males	
McNutt {1563}	5/16	11/16	2.2
Schmoekel {2092}	25/33	8/33	0.32
Zembowicz {2596}	10/20	10/20	1
Blessing 2000 {262}	10/14	4/14	0.4
Blessing 1993 {261}		M>F	57 (verrucous MM)

was mostly on the trunk and proximal extremities, specifically on the leg (38.5%), trunk (26.1%), arm (18.5%), head (12.3%), and neck (4.6%) {261, 262,1563,2092,2596}.

Clinical features

The lesions are generally small papular, nodular, or verrucous, with tan to dark brown colour. The colour may be uniform or irregular. The borders of the lesion are sharp and not very irregular. The lesions often are approximately 5–10 mm in diameter {568}. Clinically apparent inflammation is uncommon. The patient may report that there was a pre-existing macular pigmentation, which became a papule. The lesions are soft and non-tender. They are usually solitary lesions that often are removed because of recent growth or for cosmetic purposes.

Etiology

Unknown. The tumour may arise in clinically normal skin, or in a pre-existing naevus that maintains a naevus pattern of differentiation, or in a lentigo.

Histopathology

The microscopic features of naevoid melanoma are at present restricted by an arbitrary definition to lesions that do not have much intraepidermal spread of tumour cells (pagetoid upward migration) and have a relatively symmetrical profile at low magnification.

There is sharp lateral demarcation of the lesion. Usually there are areas of sheet-like confluent melanocytic proliferation in the dermis. Some lesions have only large nests of cells in the dermis, often larger in the deep portion of the lesion when compared to the upper portion. Mitotic

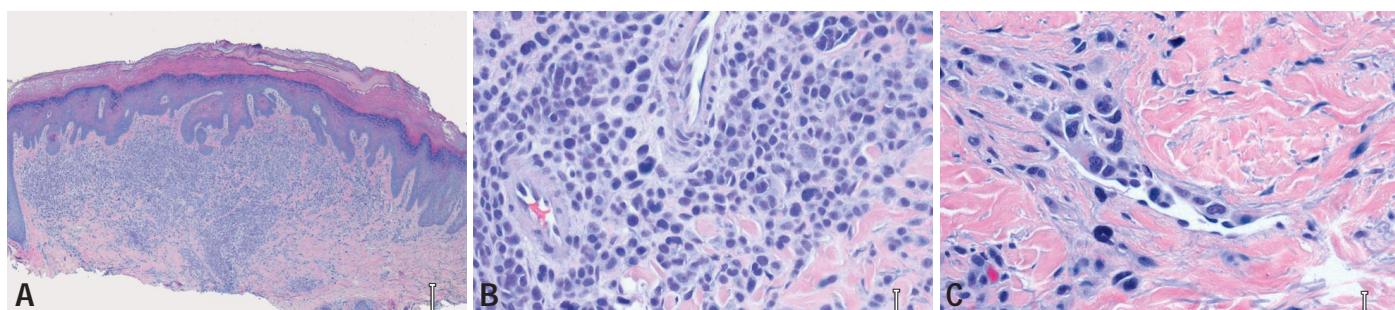


Fig. 2.34 Naevoid melanoma. **A** Naevoid melanoma, papular lesion. (A) At low magnification, note the lack of maturation and the lack of good naevus nest formation in the dermis. **B** Naevoid melanoma, papular lesion. (B) At intermediate magnification, many of the cells are hyperchromatic and atypical. **C** Naevoid melanoma, papular lesion. Perivascular infiltration is at the base of the lesion.

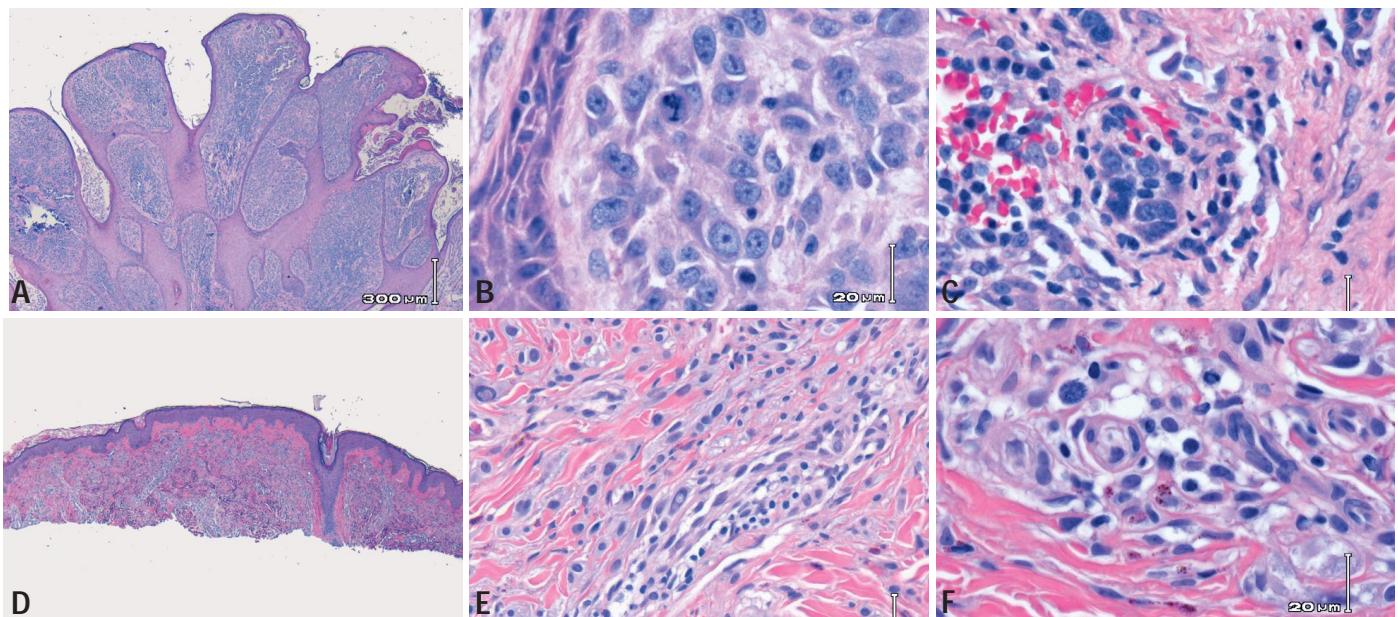


Fig. 2.35 Naevoid melanoma. **A** Verrucous type. Note the crowding of the cells in the dermal papillae. **B** Naevoid melanoma, verrucous type. Note the atypical mitosis in the dermis. **C** Naevoid melanoma, verrucous type. There is vascular invasion at the base of the lesion. **D** Naevoid melanoma with spindle and epithelioid cells. The diffuse dermal pattern with scattered atypical cells, without dermal maturation, shares some features with early desmoplastic melanomas. **E** Naevoid melanoma with spindle and epithelioid cells. Note the nuclear atypia. **F** Naevoid melanoma with spindle and epithelioid cells. Note the lack of maturation of cells in the base of the lesion.

figures can be found in the dermis in most lesions and often multiple mitoses are noted. However, small lesions may have very few mitoses. Naevoid melanomas can occupy a portion of a pre-existing intradermal or compound naevus. The melanomas have a relatively uniform population of small cells with hyperchromatic angulated nuclei or a population of medium-sized to large melanoma cells with more open nuclear chromatin and pale cytoplasm. Inflammatory reaction usually is slight and may be absent. The lesions often are dome-shaped, polypoid, or verrucous in profile {261,568,1562,1563,2092,2543, 2596}.

Immunoprofile and other special stains

HMB-45 reactivity is variable and may be negative or positive {265,1562,1563}. When positive, aberrant patterns of reactivity are common. HMB-45 reactivity may be uniform throughout the dermal portion of the lesion even though there is no junctional component. This reactivity pattern can also be found in blue naevi, some Spitz naevi, and in so-called deep penetrating naevi, and combined naevi {1563,2198}. HMB-45 antibody reacts with the premelanosomal glycoprotein, gp100, and indicates an immature status of the cell with regard to melanin produc-

tion. A103 antibody, which binds to the antigen Melan-A, reacts with the melanocytic cells throughout the lesion {265}.

The reactivity of the tumour cells with the antibody MIB-1 to detect the protein Ki-67 in cycling cells is positive in both the upper and lower portions of the tumour. In some lesions, the reactivity is slight but greater in the deep portion than in the superficial portion of the lesion. Under controlled conditions, antibodies to detect proliferating cell nuclear antigen (PCNA) have been used to grade melanomas {1160,1934}. In specimens with varied fixation conditions, PCNA has not been found to be reliable because it is sensitive to underfixation and to overfixation in formalin {1563}. Silver staining of nucleolar organizing regions (AgNORs) in 10 small cell melanomas

showed an average number of 5.83 (SD +/- 1.69) AgNORs per nucleus. This provided some separation from benign small dermal naevus cells, which had an average of 2.71 (SD +/- 0.50) AgNORs per nucleus. The comparison mean number in 10 superficial spreading melanomas was 8.49 (SD +/- 1.58) AgNORs per nucleus {1316}.

Histogenesis

Naevoid melanomas may arise from the dermal component of small compound or intradermal naevi or from the junctional component of melanocytes in normal skin, or a pre-existing small naevus or lentigo. It is possible that some naevoid melanomas represent early nodular melanomas lacking an evident junctional component.

Prognosis and predictive factors

Predictive features of naevoid melanoma prognosis are tumour thickness, mitotic rate, and large cell type. From 3,500 melanomas, Schmoekel et al. {2092} selected naevoid melanomas with at least 5 years of follow-up unless there was earlier metastasis. Thirty-three cases were selected: 18 were disease free for at least 5 years. Fifteen had developed metastases. Eight had died of disseminated melanoma. The "most

Table 2.07 Histological criteria for metastatic spread of naevoid melanoma.

Metastases	Mean thickness	Mean mitotic index
Without (n=18)	2.24 mm	0.99/mm ²
With (n=15)	1.82 mm	2.96/mm ²

important criterion was tumour thickness" (but mitoses also seem important {1160}):

McNutt et al. {1562} studied 16 naevoid melanomas and observed that 2 died of melanoma (both large cell type), and one was alive with metastases (10 years, small cell type). Thirteen had wide excisions with no evidence of residual disease or were lost to follow-up.

Zembowicz et al. {2596} selected 20 cases of naevoid melanomas from their files. Three had died and 6 had metastases. There was a three-year follow-up on 8 cases, with a mean follow-up period of 2 years. They conclude: "Naevoid melanoma, as currently defined in the literature and in the present study, seems to have a prognosis similar to that of classical melanoma."

Wong et al. {2543} studied 7 cases of naevoid melanoma (two dome-shaped and five verrucous types) and found local recurrences in 3 and regional metastasis in one patient after 2 years, with a follow-up of 5 months to 5 years.

Lohmann et al. {1444} studied 10 patients with diagnostically controversial lesions who underwent sentinel node biopsy. The differential diagnosis was between Spitz naevus and melanoma. In 5 of the 10 patients, there were sentinel node deposits of tumour in the parenchyma. All patients were alive and free of disease on follow-up of 10 to 54 months.

Variants and differential diagnosis

Minimal deviation melanoma

In the writings of Dr Richard Reed et al. {1911}, this category was analogous to the minimal deviation hepatomas of experimental liver carcinogenesis, which

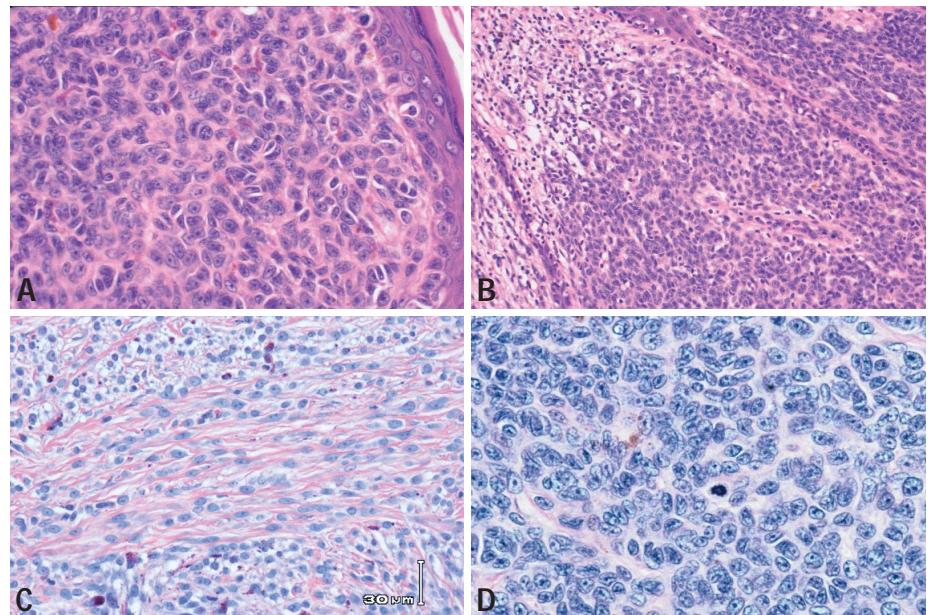


Fig. 2.37 Naevoid melanoma. **A** The melanocytes are arranged as a sheet rather than as discrete nests. **B** The aggregates of melanocytes do not disperse very much at the base of the lesion, where there is a dense lymphocytic infiltrate. **C** Naevoid melanoma and its recurrence. Atypical spindle and epithelioid cells are at the base of the lesion. **D** Mitotic figure among small and monotonous melanocytes.

were thought to deviate from the normal cells by only a single enzyme defect, and greatly resembled normal hepatocytes. Initially the minimal-deviation melanomas were characterized as having small cells, without much cytologic atypia, but they all had the architectural patterns of other melanomas. As this concept evolved, minimal deviation melanomas were divided into the following types: blue naevus type, Spitz naevus type, halo naevus type, borderline melanoma, as well as the ordinary minimal deviation melanomas. This created considerable confusion, particularly since the name "minimal deviation" implies a better prognosis, which has not been a consistent finding {2255}. Naevoid melanoma as defined here was mixed into the various types of minimal deviation melanoma and was not recognized as a separate category {1911}. The concept of minimal deviation melanoma has become so vague that the recommendation has been made to stop use of that term. However, there are attempts to clarify the definition of minimal deviation melanoma as distinct from naevoid melanoma {568}.

Small cell melanoma

Melanomas composed of small cells have been studied separately by Kossard and Wilkinson in 1997 {1317}.

While some of them are naevoid melanomas, many have the architectural patterns of ordinary superficial spreading melanomas, lentigo maligna melanomas, and acral-lentiginous melanomas. In contrast, naevoid melanomas closely resemble a benign compound or intradermal naevus in architecture. They are all included in the original concept of minimal deviation melanoma. Confusion in terminology arises between small cell melanoma and what we define as naevoid melanoma. This confusion is due to the use of the terms "small naevoid cell type" in small cell melanomas, just on the basis of cell size and without restrictions on the architecture of the lesion. As defined above, a diagnosis of naevoid melanoma requires both architectural and cytological mimicry of a naevus.

Recently a subtype of small-cell naevoid melanoma has been described that develops predominantly in elderly individuals with sun-damaged skin {1313}. This variant has an atypical lentiginous junctional melanocytic proliferation with a nested pattern that may be mistaken for a junctional naevus. This variant has a male predominance and the melanomas occur predominantly on the trunk. The epidemiology suggests that these junctional lesions may be precursors of lentigo maligna or superficial spreading

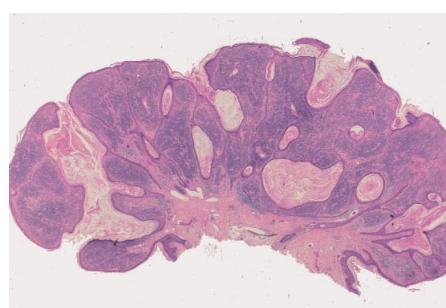


Fig. 2.36 Naevoid melanoma. The lesion has a verrucous profile, easily mistaken for papillomatous naevus.

melanoma *in situ*. This type of lesion needs further studies as to whether it represents a melanoma *sui generis* or a lesion with a high propensity to develop further mutations leading to melanoma. It does not fit into the current restricted definition of naevoid melanoma since it has a prominent junctional component and does not involve the dermis in the early stages.

Deep penetrating naevus

This type of naevus has a plexiform growth pattern in the dermis, and despite its name "deep penetrating" most of the lesions are restricted to the upper and middle reticular dermis, giving rise to the concept of the "superficial form of deep penetrating naevus" {2127}. The naevus cells form cords in the dermis composed of large spindled and epithelioid cells resembling a combination of the cells in a blue naevus with cells in a Spitz naevus. Mitotic figures are very rare and are not atypical. They do not have much of an epidermal component unless the deep penetrating naevus component is part of a combined naevus. They must be distinguished from naevoid melanoma, large cell type, which has mitoses in the dermis. However, some lesions given a diagnosis of deep penetrating naevus (with mitoses) have metastasized and may represent examples of naevoid melanomas.

Spitzoid melanoma

This designation is used primarily for melanomas that mimic a Spitz naevus. The presence of a significant junctional component and prominent pagetoid upward migration of large atypical melanocytes distinguish this tumour from a naevoid melanoma. If the Spitzoid melanoma is almost entirely intradermal, it is a variant that would fit into the definition of naevoid melanoma, large cell type.

Metastasizing Spitz naevus

A small number of lesions given the initial diagnosis of Spitz naevi have led to metastases and even the death of patients. Some cases have had only a single lymph node metastasis removed without further evidence of disease on

short-term follow-up. The cases with only a single nodal metastasis have been called metastasizing Spitz naevi. Some of these lesions fit the restricted definition of naevoid melanomas if they do not have a significant junctional component. Anecdotal reports indicate that some cases classified as metastasizing Spitz naevus by one institution go to another institution years later with widespread metastases leading to death. The criteria to distinguish between Spitzoid melanoma, melanoma arising in a Spitz naevus, Spitzoid variant of naevoid melanoma, and metastasizing Spitz naevus are controversial and require further investigation. Examination of sentinel lymph nodes in controversial cases of Spitzoid tumours has found a significant number of nodal implants of tumour {1444}.

Proliferative nodules in a congenital naevus

Benign proliferative nodules may arise in the dermis in congenital naevi in some very young patients and may be multiple. Distinction from naevoid melanoma may be difficult since mitotic figures are present in the dermal nodules of naevus cells. Features of benign proliferative nodules that have been emphasized are multiplicity of nodules of similar sizes and appearances, and a gradual blending of the cells of the nodule with the surrounding background congenital naevus cells at the periphery of the nodules. Sharp demarcation of the proliferative nodules is more common in naevoid melanomas arising in the dermal component of a congenital naevus {568}.

Melanoma arising in the dermal component of a large or "giant" congenital naevus

In studies of melanomas arising in giant congenital naevi, many arose from the dermal component {254,1912,1928}. A significant proportion of such melanomas are composed of small, hyperchromatic atypical cells and were interpreted to be similar to melanoblasts, leading to diagnosis of melanoblastoma. These lesions were highly malignant. They are a variant that fits the current definition of naevoid melanoma since

they lack an epidermal component and are composed of small epithelioid cells.

Early nodular melanoma

It is most likely that some naevoid melanomas are an early stage in the evolution of nodular melanomas.

Desmoplastic/neurotropic melanoma

Although some of these lesions could fit into the definition of naevoid melanoma, it is conventional to separate them as a distinct entity. Desmoplastic melanomas generally have spindle-shaped cells and naevoid melanomas, as defined here, generally have more epithelioid cells. Both tumours can present as predominantly dermal lesions. Desmoplastic melanomas can resemble desmoplastic naevi, especially hypopigmented blue naevi. Desmoplastic and neurotropic melanomas are best separated from naevoid melanomas since they can be recognized as a distinct group of tumours that has been characterized sufficiently for diagnosis.

Metastatic melanoma

The histologic features of naevoid melanoma can be exactly reproduced in satellite metastatic papules and nodules of melanoma in the skin. The lack of an intraepidermal component, confluent growth patterns, sharp circumscription, symmetry, and dermal mitotic figures can all be found in metastatic melanoma. A diagnosis of naevoid melanoma should be made with great caution in an individual with a known history of melanoma. Misdiagnosis of primary naevoid melanoma as metastatic melanoma can lead to the clinical impression of a metastatic melanoma for which a primary lesion is never found. On the other hand, individuals given a diagnosis of naevoid melanoma, who subsequently rapidly develop extensive metastases, may actually represent patients with a metastatic lesion that resembled a primary naevoid melanoma. Multiplicity of lesions resembling naevoid melanomas simultaneously in the same patient points toward metastatic disease. However multiple naevoid melanomas have been reported in an immunodeficient patient {1804}.

Persistent melanoma and local metastasis of melanoma

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J.C. Maize
M.G. Cook
P.E. LeBoit

Definition

Persistent melanoma is defined as the persistent growth of residual, incompletely excised primary malignant melanoma, of either the epidermal or the invasive component, or both. It represents one form of "local recurrence" of melanoma, the other being local metastasis {30,1001}.

Synonym

Local recurrence of melanoma.

Epidemiology

The epidemiological characteristics are those of the original primary melanoma.

Etiology

The etiological factors are those of the primary melanoma.

Localization

Persistent melanoma may follow removal of melanoma from any site of the body although it seems more common on the

head and neck, probably due to the higher incidence of poorly defined variants of melanoma in this site. These include lentigo maligna, in particular the amelanotic variant, and desmoplastic melanoma which is particularly susceptible to incomplete excision because of its poorly defined borders.

Clinical features

The most common clinical presentation is the persistence or recurrence of a flat,

Table 2.08

Histological features of persistent melanoma and local metastases of melanoma.

	Persistent melanoma	Metastatic melanoma
Epidermal component	Usually present, with or without a dermal component	A. Absent in most cases. B. Epidermotropism uncommonly. The dermal component usually extends beyond a zone of epidermotropism when present. Sometimes the epidermotropic component is more extensive, simulating primary melanoma {998}.
Dermal growth pattern	The full range of patterns associated with primary melanoma.	A. Single or multiple symmetrical dermal and/or subcutaneous nodules. B. Diffuse small groups and strands of neoplastic melanocytes (this pattern occurs in the smallest and presumably earliest metastases).
Inflammation	Lymphocytic inflammation usually present.	Absent or sparse.
Vascular invasion	Sometimes present.	Present in many cases.
Mitotic rate	Variable	High (usually > than 6/mm ²)
Cell type	The full range of cell types seen in primary melanoma, frequently including a mixture of cell types.	Usually monomorphic atypical melanocytic population of epithelioid, spindle or small (naevoid) cells.
Associated naevus	Commonly present.	Rare (coincidental).
Necrosis	Uncommon	Often present in the centres of the nodules.
Epidermal collarette	Uncommon	Usually present, when nodules of metastatic melanoma are in the superficial dermis.
Fibrosis	Frequently present in zones of regression and in desmoplasia.	Little or no reactive fibrosis in the stroma of the tumour.
Scarring	Present in the dermis and often also in the subcutis.	Present when the metastasis occurs at the primary excision site.

- NOTE: 1. In cases of persistent melanoma, histological review of the primary excision confirms the presence of in-situ or invasive melanoma (or both) at a margin of excision.
2. The microscopic features of metastatic melanoma involving the scar of the primary excision are the same as those of metastatic melanoma at a site distant from the scar, with the additional feature of the scar at the site of the completely excised primary melanoma {2573}.

variably pigmented patch adjacent to or surrounding the scar of the primary excision site. In some cases there may also be nodule formation when there is persistent dermal invasion, especially of desmoplastic melanoma.

Macroscopy

The lesion frequently is a variably pigmented, often pale macule with poorly defined borders. In many cases of persistent desmoplastic melanoma there is no abnormal pigmentation in the epidermis overlying a firm nodule.

Histopathology

In the uncommon event of incomplete excision of both the epidermal and invasive components of one of the common forms of cutaneous melanoma, the histologic appearances are those of the original tumour, frequently with pagetoid infiltration of the epidermis overlying invasive atypical epithelioid melanocytes, usually with little or no pigmentation, forming an expansile growth pattern adjacent to a zone of scarring. More commonly, the persistent lesion consists of in-situ melanoma with or without focal dermal invasion. Persistence of incompletely excised desmoplastic melanoma may present only sparse, subtle infiltration of a sclerotic nodule in the dermis and/or subcutis, containing atypical spindle cells with hyperchromatic, variably pleomorphic nuclei and sometimes only sparse mitoses, distributed singly and in strands between the collagen bundles. As in the primary tumour, a patchy lymphocytic infiltrate may provide a clue to perineural invasion. Desmoplastic melanoma may very closely simulate a surgical scar in the primary lesion and can be very poorly circumscribed {1194}. However it can be distinguished by its infiltrative pattern beyond the zone usually expected to be involved with



Fig. 2.38 Local melanoma metastasis. So-called "local recurrence" of melanoma in the scar at the excision site of a primary melanoma completely excised with a margin of 25mm.

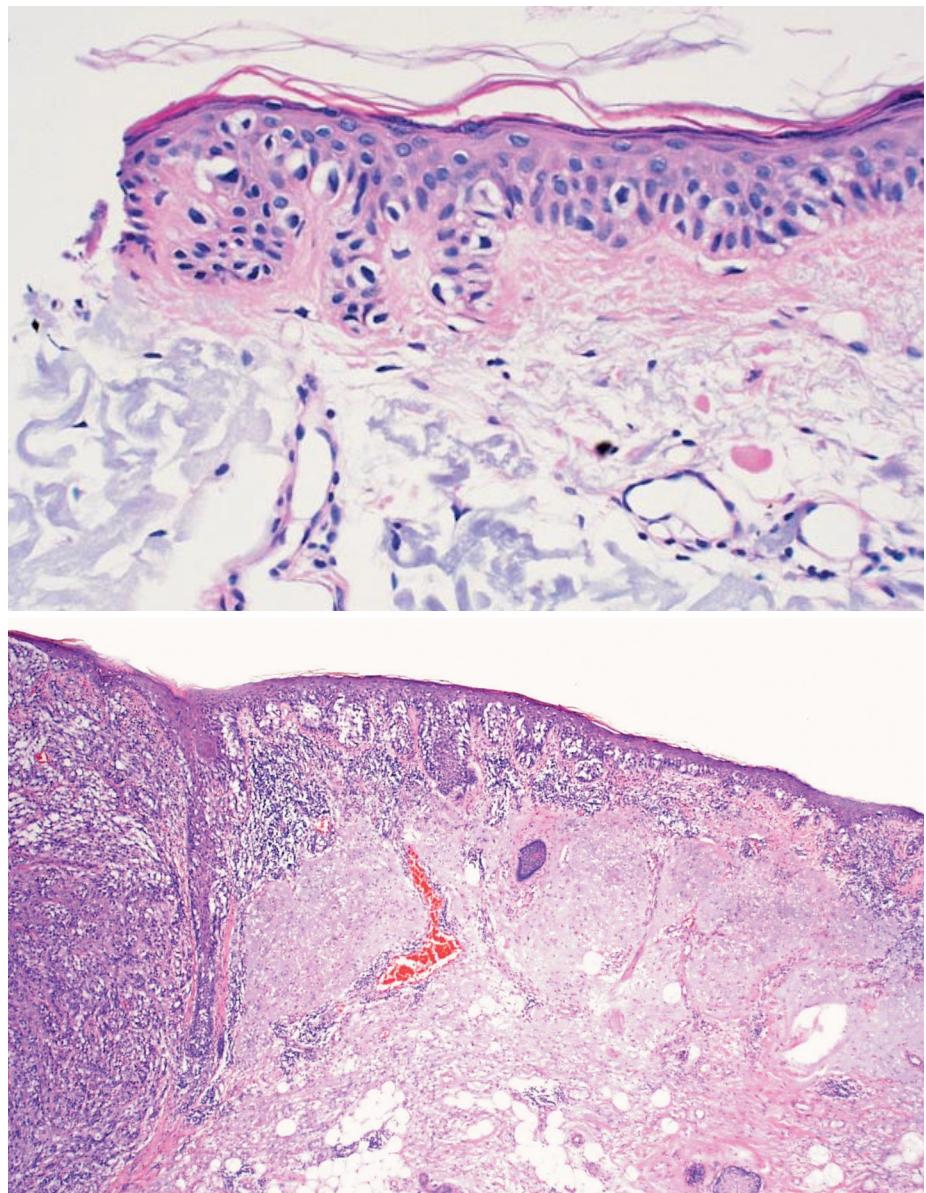


Fig. 2.39 Persistent melanoma. **A** Melanoma in-situ at the lateral margin of the excision of a primary melanoma. **B** "Local recurrence", at the excision site two years later, showing invasive melanoma, extensive adjacent melanoma in-situ and dermal scarring.

scarring following surgery. The features of persistent desmoplastic/neurotropic melanoma may be seen proximal or distal to the scar at the primary excision site, along the line of nerves.

In assessing locally recurrent melanoma it should always be remembered that melanoma metastases may be epidermotropic and simulate primary melanoma {998}.

Differential diagnosis

Rarely, pigmentation of the epidermis or growth of a nodule at the site of previous

excision of melanoma may be due to the coincidental growth of an entirely new and distinct tumour such as dermatofibroma or pigmented basal cell carcinoma. The most important differential diagnosis, however, lies between true persistence of incompletely excised primary melanoma and the other form of "local recurrence" due to metastatic melanoma. Metastatic melanoma in or adjacent to the primary excision scar usually presents as a rapidly growing papule or nodule without pigmentation of the overlying dermis, sometimes associated with

multiple similar, rapidly growing lesions separate from the primary excision site. Histologically, metastases involving the scar present exactly the same features as cutaneous metastases at a distance from the scar {2573}

Histogenesis

Persistent melanoma occurs because a primary melanoma was incompletely excised. The histogenesis, therefore, is essentially that of the original melanoma.

Somatic genetics

The genetic factors are those that apply to the original melanoma.

Prognosis and predictive factors

The prognosis for persistent melanoma is assessed in the same manner as for the original tumour, tumour thickness still being the most important single factor, unlike local recurrence due to metastasis which is a manifestation of systemic metastasis and portends a poor prognosis.

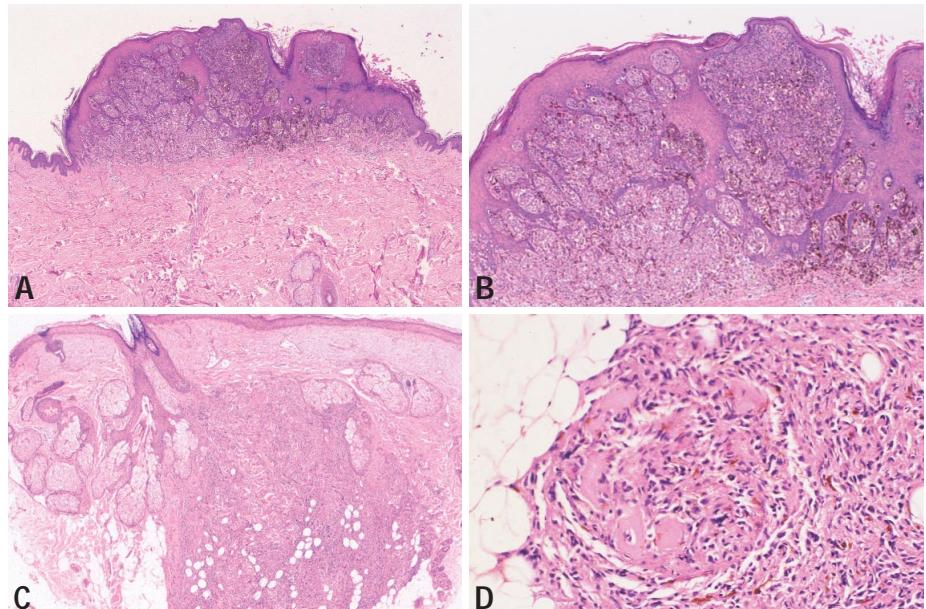


Fig. 2.40 Metastatic melanoma. **A** In this epidermotropic metastatic melanoma, a papule has formed largely due to the irregular epidermal hyperplasia. **B** On the left side of the lesion, one can see sharp circumscriptive borders, contributing to resemblance to a Spitz naevus. **C** Metastatic melanoma simulating blue naevus. **D** Irregular nests of melanoma cells are visible at the base of the lesion in the subcutis.

Congenital melanocytic naevus

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Superficial type

Definition

Congenital melanocytic naevi (CMN) of the superficial type are melanocytic proliferations present at birth. The term congenital has been also applied to lesions displaying clinical and histopathological features of congenital melanocytic naevi which may not be apparent at birth. These lesions are designated as tardive congenital melanocytic naevi.

ICD-O code 8761/0

Synonyms

Congenital pattern-like naevus; tardive congenital naevus; congenital naevus-like naevus.

Clinical features

Congenital melanocytic naevi - superficial type are frequently observed. They can be found on any anatomic site and belong to the group of small congenital naevi with a diameter smaller than 1,5 cm.

On gross examination they vary from macules and papules to plaques and reveal different colours from light brown to black. The lesions are usually round or oval with a smooth or papillated surface. They may be hairy or hairless.

Histopathology

In the superficial type of CMN, dense dif-

fuse infiltrates of small monomorphous melanocytes are found in the upper part of the dermis and the mid-portion of the reticular dermis. The melanocytes are frequently arranged in a band-like pattern and are disposed in single files between collagen bundles ("splaying of melanocytes").

An important criterion for diagnosis is the presence of melanocytes along epithelial structures of adnexa and their angiocentric distribution. They may be found within sebaceous glands, vessels, nerves and in smooth muscles {1168,1531}. In the compound type of a congenital naevus – superficial type, nests of melanocytes are present in the epidermis, mostly at the dermo-epidermal junction.

Melanomas are very rare in newborn and young infants (see chapter on childhood melanoma). Congenital melanocytic naevi, biopsied shortly after birth or in the first years of life can display atypical intraepidermal changes (pagetoid melanocytes arranged as solitary units and nests; single cells present in the upper layers of the epidermis) similar to those of melanoma in situ {1514}. This finding is more commonly found in giant congenital naevi than in small ones.

The clues for diagnosis of this unusual change in a benign naevus are found in the dermis where the large, pale melanocytes merge with smaller ones that have the characteristic features of a congenital melanocytic naevus.

Somatic genetics

Like the majority of melanocytic naevi except Spitz and blue naevi, congenital melanocytic naevi have frequent BRAF mutations and show no chromosomal aberrations {173,1850}.

Prognosis and predictive factors

Recent studies revealed in a significant number of malignant melanomas an association with melanocytic naevi with a congenital histopathologic pattern {159,1245}. However, the pathogenetic role of small congenital melanocytic naevi as precursor lesions of melanoma is controversial {1508, 2323}. Clinical follow-up of 3922 patients with small CMN found no significant risk of melanoma development {205}.

Proliferative nodules in congenital melanocytic naevi

Definition

Proliferative nodules in congenital melanocytic naevi are defined as atypical melanocytic proliferations which manifest predominantly in the neonatal period within a pre-existing large (deep) congenital melanocytic naevus.

ICD-O code 8762/1

Synonyms

Atypical proliferative nodules in giant

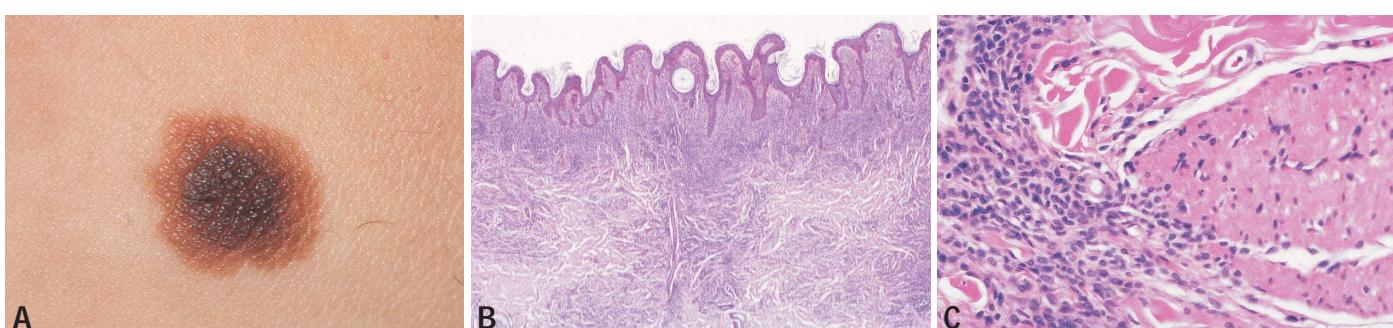


Fig. 2.41 Congenital melanocytic naevus, superficial type. **A** Papule with brown to black colors and a mamillated surface. **B** Band-like infiltrate of melanocytes in the upper dermis. Adnexocentric arrangement and "splaying" of melanocytes between bundles of collagen in the upper and mid-portion of the reticular dermis. **C** Monomorphic melanocytes around and focally within an arrector pili muscle.



Fig. 2.42 Proliferative nodule in a large congenital melanocytic naevus (garment type). A black plaque above the sacrum representing the proliferative nodule is recognizable.

congenital naevi; dermal variant of minimal deviation melanoma in a giant congenital naevus {1907}, dermal melanocytic tumour of uncertain potential in a giant congenital naevus.

Clinical features

There is usually a dark brown to black plaque or nodule above a giant congenital melanocytic naevus. The lesions may become lighter and show regression after years. Occasionally a palpable mass can be found deeply in the skin. These nodular proliferations in congenital melanocytic naevi behave in a benign fashion.

Histopathology

The background congenital melanocytic naevus reveals the characteristic features of a congenital melanocytic naevus of the deep type. A dense diffuse infiltrate of small melanocytes involving the

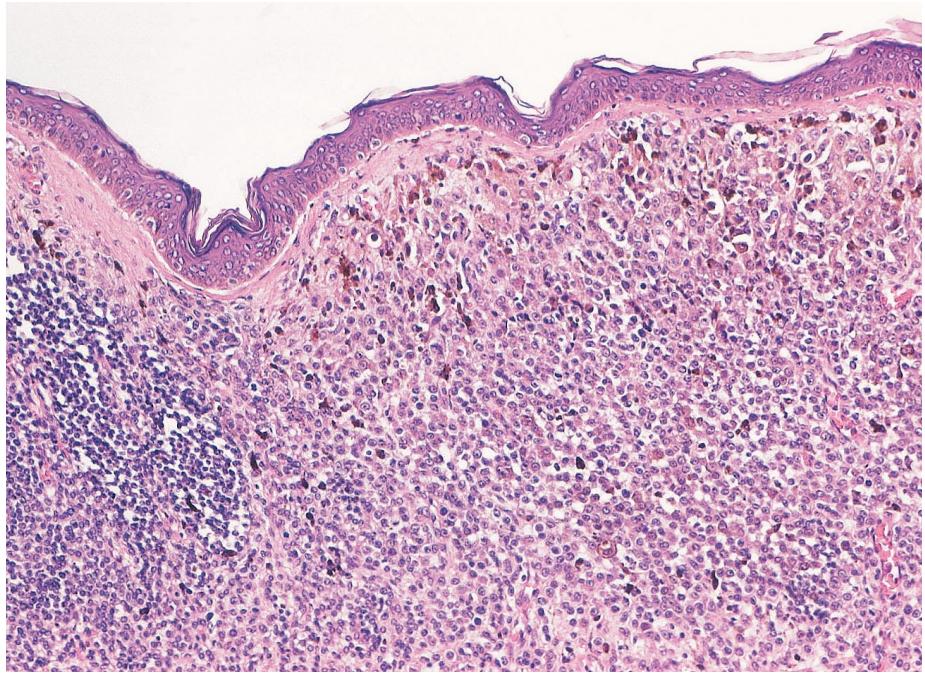


Fig. 2.43 Proliferative nodule in a congenital melanocytic naevus. The congenital melanocytic naevus, with small naevoid cells can be recognized on the left side of the picture. Melanophages are distributed in a uniform fashion in the upper dermis. The proliferative nodule reveals cellularity with relatively monomorphic large cells with prominent nucleoli.

entire dermis and often extending into the septa of the subcutaneous fat can be observed.

The "proliferative" nodule, which is usually found in the upper and mid dermis consists of roundish epithelioid or spindled melanocytes. The cells are large and appear to blend with the surrounding smaller melanocytes (naevus cells). Atypical nuclei and mitotic figures can be observed.

Differential diagnosis

Proliferative nodules in congenital melanocytic naevi can be misinterpreted as a melanoma that developed in the intradermal component of a congenital naevus (see Melanoma arising in giant congenital naevi) {1009}.

Somatic genetics

In a study of proliferative nodules using comparative genomic hybridization

seven out of nine cases showed chromosomal aberrations {175}. Six of the seven cases with aberrations (86%) showed numerical aberrations of whole chromosomes exclusively. This pattern differs significantly from the findings in melanomas arising in congenital naevi or melanoma in general in which the majority (96%) have aberrations involving only partial chromosomes {173}. Loss of chromosome 7 was seen in three of the nine proliferative nodules. Loss of chromosome 7 was not observed in 132 melanomas that were not associated with giant congenital naevi {173}. However, one melanoma arising in a congenital naevus in an eight-year-old boy showed a similar loss of chromosome 7.

Blue naevi

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Common blue naevus

Definition

Common blue naevus (BN) is a benign, usually intradermal melanocytic lesion characterized by pigmented dendritic spindle-shaped melanocytes and, more rarely, epithelioid melanocytes. The melanocytes are usually separated by thickened collagen bundles.

ICD-O code 8780/0

Epidemiology

BN is relatively frequent, has predilection for females and presents mainly in young adults between the second and fourth decades. Although most tumours are acquired, congenital examples have been documented {1872}. Familial cases may be seen and usually present with multiple lesions {258,1292}.

Localization

The anatomical distribution is wide but most lesions occur on the distal upper limbs (particularly the dorsum of the hand), followed by the lower limbs, scalp, face and buttocks. Lesions have also been documented in the vagina {1002,2356}, cervix {2393}, prostate {1414}, oral cavity (mainly the hard palate) {327,328} and the capsule of lymph nodes without a primary cutaneous lesion {695,858,1497}.

Clinical features

The most common presentation consists of a single asymptomatic, relatively well-circumscribed, dome-shaped blue or blue-black papule less than 1 cm in diameter. The characteristic blue colour is produced by the Tyndall effect. Tumours may rarely present as a plaque {1025,2494}. Eruptive lesions have rarely been documented. Exceptional clinical presentations include a speckled variant {1044}, hypopigmented lesions {278}, an example with satellite lesions {1195} and a case with widespread lesions. Localized hypertrichosis has been described in a single case {57}.

Histopathology

BN and cellular blue naevus show a wide histological spectrum, frequently overlapping with other melanocytic lesions including deep penetrating naevus and pigmented Spitz naevus {1637}. BN is typically located in the reticular dermis and only exceptionally extends into the papillary dermis or subcutis. The epidermis appears unremarkable, except in the rare so-called compound blue naevus, in which dendritic junctional melanocytes are identified {733, 1190}. Low power examination reveals a generally symmetric but often ill-defined tumour of variable cellularity. Concentration around adnexa without adnexal destruction is typical. Poorly cellular

lesions often display prominent sclerotic stroma making the diagnosis difficult. Lesions with very poor pigmentation are rarely encountered {234,402}. Tumour cells are bland and spindle-shaped or dendritic and usually contain abundant cytoplasmic coarse melanin pigment. Nuclei are small, and an inconspicuous basophilic nucleolus is sometimes present. Numerous melanophages are a relatively constant feature in the vicinity of tumour cells. Extension of tumour cells into nerves and, less frequently, blood vessel walls, may be found. Mitotic figures are exceptional. Rarely, a blue naevus may coexist with a trichoepithelioma {48}.

In some instances, metastatic melanoma may mimic common blue naevus {354}. Blue naevus may co-exists with other types of naevus (see combined naevus).

Immunoprofile

Tumour cells are usually diffusely positive for melanocytic markers including S-100, HMB45, melan A and microphthalmia transcription factor (MITF-1). Unlike the case in most other benign melanocytic naevi and in melanomas, HMB45 strongly stains the entire lesion in blue naevi.

Somatic genetics

Mutations in the BRAF gene appear to be rare in BN. Chromosomal aberrations are uncommon {1490}.

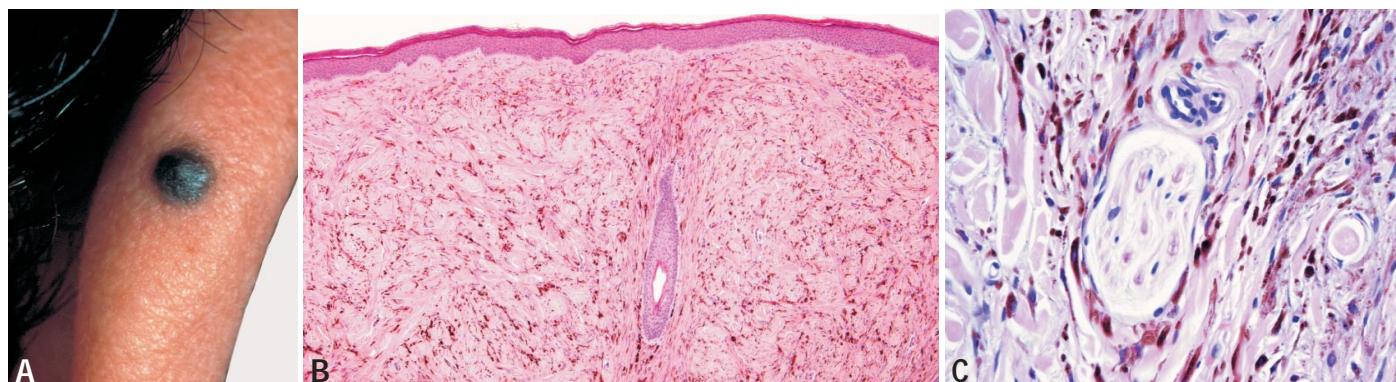


Fig. 2.44 Common blue naevus. **A** Typical clinical appearance of a common blue naevus. **B** A more cellular example with hyalinization of dermal collagen. **C** Melanocytes often extend into the perineurium of dermal nerves.



Fig. 2.45 **A** Mongolian spot. Typical prominent macular blue/grey discolouration on lower back and buttocks. **B** Naevus of Ota with involvement of the periorbital skin and conjunctiva. The blue cast is typical. **C** Naevus of Ota. Bipolar, deeply pigmented melanocytes in the reticular dermis.

Prognosis and predictive factors

BN is benign, and malignant transformation is exceptional {883} (see chapter Melanoma arising from blue naevus). Simple excision is curative and local recurrence is very rare {973}.

Mongolian spot

Definition

Mongolian spot (MS) is a form of dermal melanocytosis presenting on the lower back and characterized by scattered pigmented dendritic melanocytes in the reticular dermis.

Epidemiology

MS presents at birth and has marked predilection for Black and Oriental patients with the same sex incidence {1260,1261}. The incidence in Caucasian children is approximately 9.5% {543}.

Localization

Most lesions occur on the lower posterior trunk with predilection for the sacrogluteal region. Lesions identical to MS and naevus of Ito or naevus of Ota may present rarely in other anatomical sites.

Clinical features

MS is characterized by a macular area of blue-green or blue-grey discolouration varying in size from a few to 10 or more cm. Lesions fade gradually, usually disappearing completely when patients reach adolescence.

Association with cleft lip {1096} and the mucopolysaccharidoses, including Hurler and Hunter syndromes) {880, 2063} has been documented. Lesions with the clinical and histological features of MS may rarely present at other body sites.

Histopathology

The epidermis and superficial dermis

appear unremarkable. Low power examination reveals a mild increase in cellularity in the deep reticular dermis, consisting of few variably pigmented dendritic melanocytes, which are usually, oriented parallel to the epidermis. Melanophages are occasionally seen.

Naevus of Ito and Naevus of Ota

Definition

Naevus of Ito (NI) and naevus of Ota (NO) are dermal melanocytoses with identical histological features, which differ in their characteristic clinical presentation. NI typically presents in the shoulder region, following the distribution of the lateral brachial and posterior supraclavicular nerves. NO involves the skin and mucosal surfaces (including the conjunctiva), following the distribution of the ophthalmic and maxillary branches of the trigeminal nerve.

Synonyms

Naevus Ota: Oculodermal melanocytosis, Naevus fuscoceruleus ophthalmomaxillaris.

Epidemiology

Both NI and NO are relatively rare, affect mainly patients of Oriental or African origin and have some predilection for females {1027,1307,1626,2243}. Presentation is mainly at birth (up to 50%) or during childhood and adolescence. Adult onset is very rare {447}.

Localization

NI typically involves the supraclavicular, deltoid and less commonly, the scapular area. NO usually involves the sclera, conjunctiva, and skin around the eye and zygomatic and temporal areas. Rarely

the nasal and oral mucosa, optic tract and the leptomeninges are involved. Lesions identical to naevus of Ito or naevus of Ota may present rarely in other anatomical sites. A limited form resembling naevus of Ota presenting in the zygomatic area is called naevus of Sun.

Clinical features

Lesions are usually large, macular, ill defined and have a blue or blue-grey colour. A speckled appearance is seen rarely. There is no tendency for spontaneous regression. Bilateral involvement has been documented rarely {1026}. Co-existence between NI and NO is a rare occurrence {615,1026}. Glaucoma is a rare complication of NO {1434}.

Histopathology

The histology of NI and NO is indistinguishable. The epidermis appears unremarkable but may show increased melanin in basal cells and a mild increase in the number of basal melanocytes. In the superficial and mid-dermis there are scattered dendritic or spindle-shaped, often bipolar deeply pigmented melanocytes. Melanophages are rare.

Prognosis and predictive factors

Malignant transformation is exceptional and more common in NO {1783,2194, 2345,2414}. In the latter setting it may occur in the skin, eye or meninges.

Cellular blue naevus

Definition

Cellular blue naevus (CBN) is an acquired dermal/subcutaneous pigmented tumour with prominent cellularity and an expansile growth pattern.

ICD-O code

8790/0

Epidemiology

CBN tends to present between the second and fourth decades of life with female predilection, and it is more common in Caucasians. Congenital cases are exceptional {1095}.

Localization

The anatomical distribution is wide, but CBN have predilection for the buttocks and sacral region (50% of cases), followed by the scalp, face, distal limbs and other sites on the trunk {1957,2336}. Lesions may also rarely occur on the eyes, cervix, vagina, breast and spermatic cord {266,1957,2336}. Aggregates of tumour cells have been reported in the capsules of regional lymph nodes draining an area where an otherwise typical benign cellular blue naevus is present {287,1957,2261,2336}. This phenomenon is regarded as a benign occurrence rather than an ominous finding.

Clinical features

Tumours are usually large, varying from 1 to several centimetres, and the colour varies from light blue-brown to dark blue. Lesions are asymptomatic and grow very slowly, presenting as a non-ulcerated firm nodule {1957,2336}. Exceptional cases present as a large plaque {358}. Rare tumours arising in the scalp have been described with invasion of the underlying bone {1596} and even the brain {854}.

The epithelioid variant of blue naevus is very rare and has mainly been described in patients with Carney complex who



Fig. 2.46 Cellular blue naevi on the upper back.

usually present with multiple lesions {396,399}. Sporadic lesions are usually solitary and may occur in genital skin {1117,1646,1736}.

Macroscopy

The cut surface of a CBN characteristically shows a dark brown to black, well-defined dermal and subcutaneous tumour. In some cases there are areas of haemorrhage and cystic degeneration.

Histopathology

Low-power examination reveals a fairly characteristic picture with a dumbbell-shaped multinodular tumour occupying the reticular dermis and often extending into subcutaneous tissue. A junctional component is not usually found. Areas of pigmentation alternate with poorly pigmented areas and, in a minority of cases, pigment is very scanty {2595}. Cellular areas tend to be more prominent towards the centre of the tumour, and the cellularity may be most marked where the neoplasm protrudes into the subcutis. The

cellular areas may alternate with sclerotic or hypocellular areas. In most cases there are focal areas representing or simulating a common blue naevus. High power examination reveals bundles of oval or spindle-shaped cells with pale cytoplasm, alternating with bundles of deeply pigmented spindle-shaped cells. In addition, dendritic melanocytes and/or round, somewhat epithelioid melanocytes may be seen. Cytoplasmic melanin is coarse and granular, and nuclei are regular and vesicular, with a single small inconspicuous basophilic nucleolus. Maturation with depth is not a feature. A frequent finding however, is the focal presence of elongated slender melanocytes resembling Schwann cells, indicative of neurotization as seen in ordinary naevi. Some tumours exhibit a focal alveolar growth pattern {1597} and desmoplasia is occasionally prominent {1599}. Degenerative changes including haemorrhage, cystic change and fibrosis, are seen in some cases. Focal mild or prominent myxoid oedematous change may also be a feature {1598}, and balloon cell change has been documented {1806}. Occasional cases display a number of unusual features including mitotic figures (1/10 HPFs), focal necrosis, and/or nuclear pleomorphism or hyperchromatism. Such cases show some overlap with the malignant variant of CBN and have been described as atypical CBN {118,2371}.

The epithelioid blue naevus is composed of large round epithelioid and short spindle-shaped deeply pigmented melano-

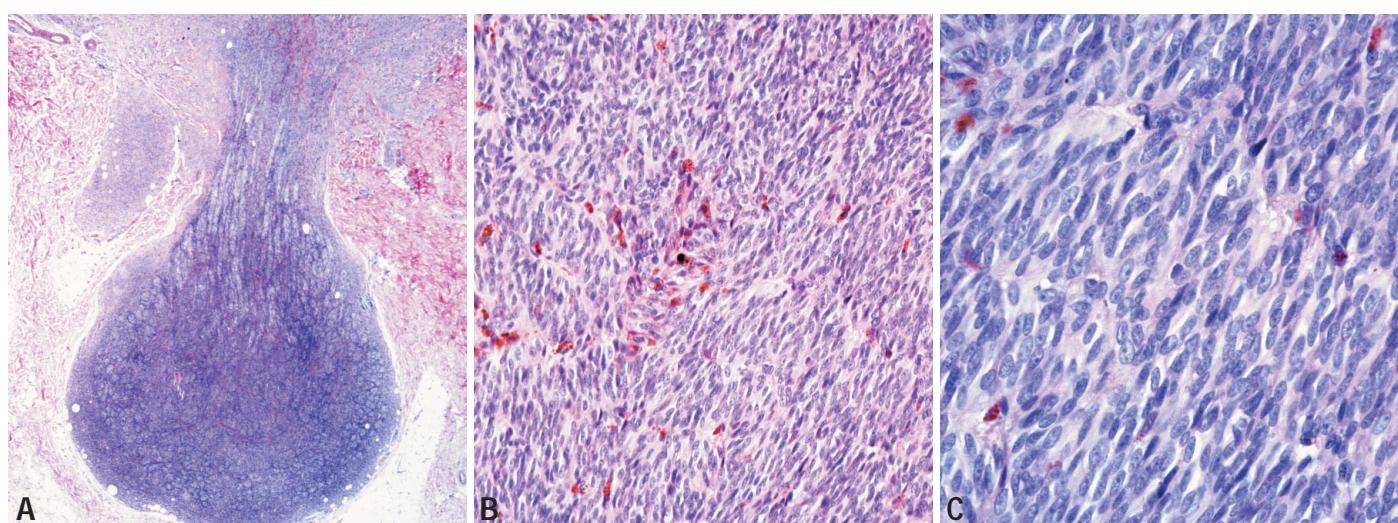


Fig. 2.47 Cellular blue naevus. **A** Typical low-power appearance with a dumb-bell architecture. **B** Bundles of bland spindle-shaped melanocytes alternating with focally pigmented cells. Scattered melanophages are also seen. **C** Typical small vesicular nuclei with a small basophilic nucleolus.

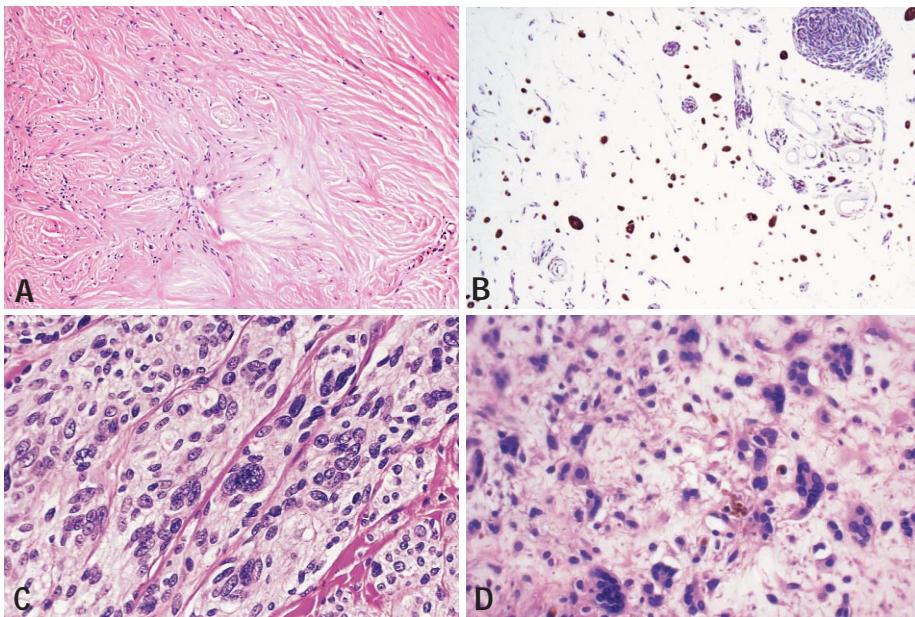


Fig. 2.48 Hypopigmented cellular blue naevus. **A** In some cases, melanin is almost completely absent. **B** Myxoid change may be prominent in some cases. **C** One of the melanocytes is much larger than the others. Some refer to such cases as 'atypical cellular blue naevus'. **D** Large melanocytes are present, some are multinucleated.

cytes. Some examples of this variant of BN probably represent combined naevi {903}.

Immunoprofile

Tumour cells in CBN are positive for S-100, melan-A and HMB45. In tumours with prominent desmoplasia, and in those with neurotization, staining for melan-A and HMB45 tends to be patchy. CD34 has been reported to be positive in tumour cells in a group of congenital CBN {2204}.

Genetics

Similar to other naevi, cellular blue naevi do not show chromosomal aberrations when analysed by CGH. In a small series of atypical cellular blue naevi, three out of eight cases showed single chromosomal losses with chromosome 3p being affected in two of these cases {1490}.

Prognosis and predictive factors

Although limited case series have characterized these lesions as benign, some cases with atypical features have resulted in recurrences or death from systemic metastasis. They may therefore be regarded as having uncertain malignant potential and treated with complete excision if possible and perhaps long term follow-up. Malignant transformation in CBN is very rare {64,883}.

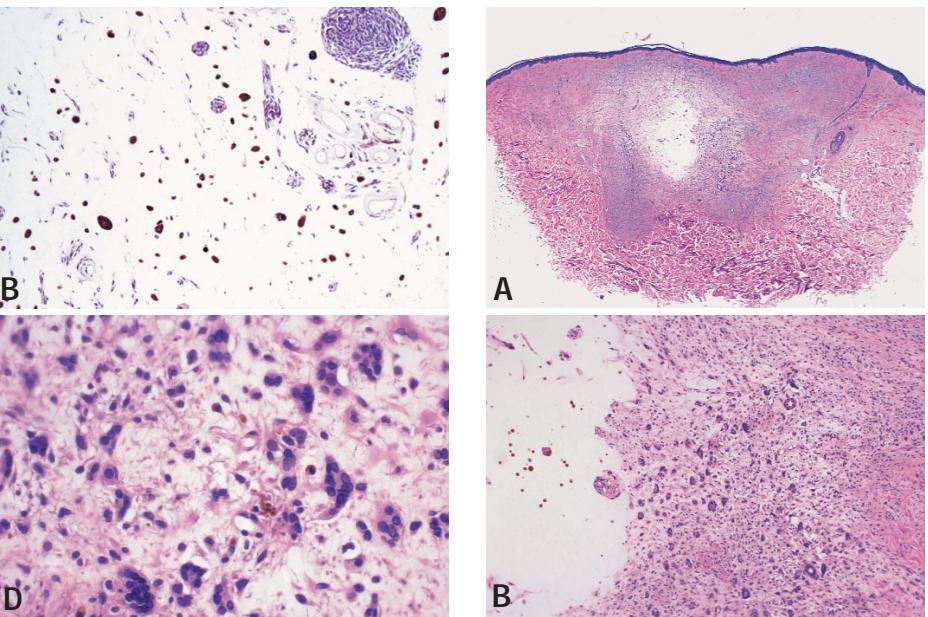


Fig. 2.49 Cellular blue naevus. **A** This lesion has a central focus of cystic change. **B** The edge of the cystic area.

Deep penetrating naevus

Definition

Deep penetrating naevus (DPN) is a distinctive deeply pigmented lesion showing overlapping features with blue naevus and Spitz naevus.

Synonym

Some cases have been described under the heading of plexiform spindle cell naevus {164}.

Epidemiology

DPN is an acquired lesion presenting mainly between the second and third decades of life with no sex predilection {1953,2127}.

Localization

DPN has a wide anatomical distribution with predilection for the face, upper trunk and proximal limbs {164,537,1575,1953,2127}.

Clinical features

The tumour presents as a solitary, well-circumscribed blue or dark brown/black dome-shaped papule or nodule usually less than 1 cm in diameter.

Histopathology

Low power examination typically reveals a compound wedge-shaped deeply pig-

mented dermal and, very rarely, superficial subcutaneous tumour. The base of the lesion parallels the epidermis. The junctional component, which is usually present and may be subtle, consists of small round nests of ordinary naevus cells. In fact, in most cases, a superficial dermal component, representing an ordinary naevus, may be found and therefore these lesions may be regarded as combined naevi {1953}. Much less commonly, focal changes mimicking a Spitz naevus or a blue naevus are found {1953,2127}. Tumour cells are arranged in nests or bundles and have a short spindle-shaped or, less commonly, round morphology. The cytoplasm contains

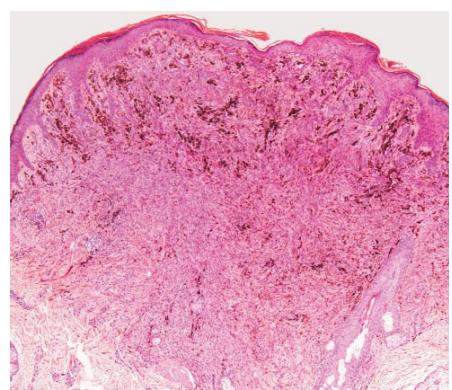


Fig. 2.50 Deep penetrating naevus with a typical wedge-shaped architecture.

abundant melanin and nuclei are vesicular with frequent intranuclear inclusions and a single small basophilic nucleolus. Hyperchromatism and variation in nuclear size may be seen, but as a rule mitotic activity is low or absent (usually not more than 1 per section). The melanocytes follow the path of adnexal structures and blood vessels and there is frequent perineural extension. Maturation is not seen. Some tumours have the cytomorphology of DPN but are superficial and lack the deep penetrating component. Similar changes are seen in a common form of combined naevus.

Prognosis and predictive factors

Local recurrence is exceptional, and only a single case has been reported spreading to a regional lymph node {874}.

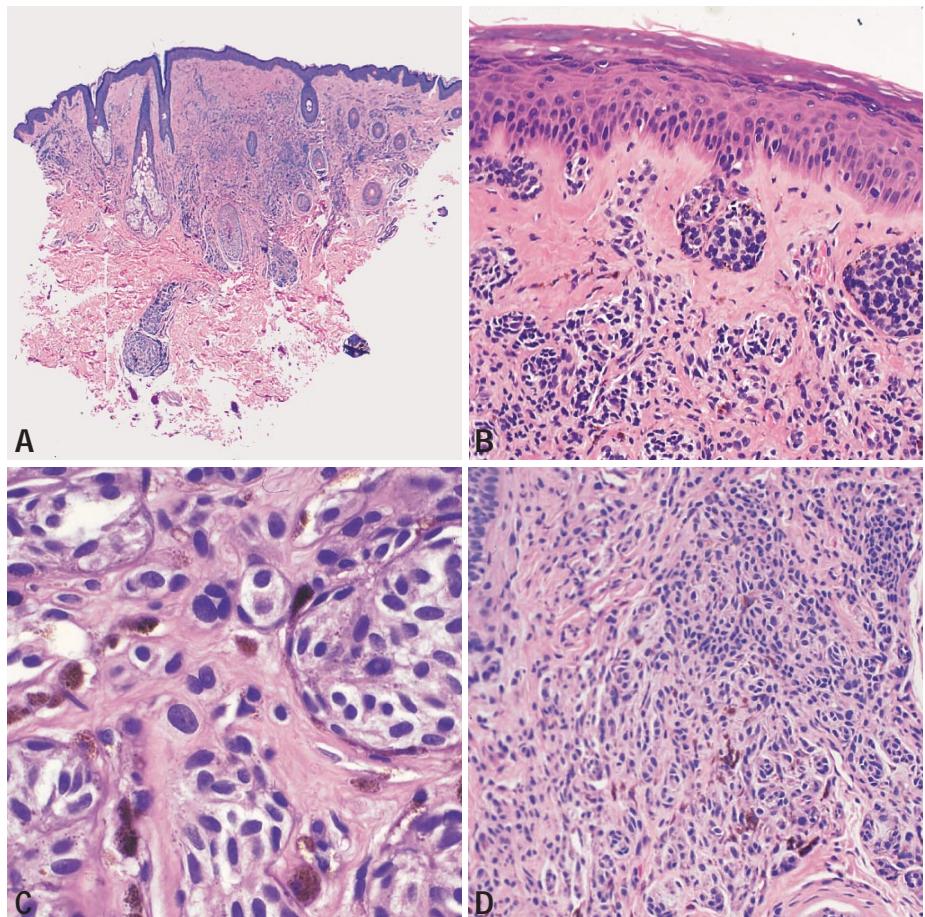


Fig. 2.51 Deep penetrating naevus. **A** A wedge shape and nests of cells around adnexal structures are characteristic findings. **B** The large pale cells in a deep penetrating naevus are arranged as discrete nests. **C** A thin rim of sustentacular cells is present around the edges of many nests. **D** Toward the base of the lesion nests of pale large cells are present near adnexal structures.

Definition

A combined naevus or "melanocytic naevus with phenotypic heterogeneity" is a melanocytic naevus either congenital or acquired, containing two or more distinct melanocytic naevus components.

Synonyms and historical annotation

Melanocytic naevus with phenotypic heterogeneity; inverted type A naevus; naevus with focal dermal epithelioid component, and naevi with dermal nodules.

The term combined naevus was used initially to describe the combination of a conventional naevus and blue naevus {61,653,702,1402,2331}. However, the spectrum of combined naevus has been subsequently extended to include components of any type of naevus (Table 2.09){135,156,520,1610}. There may be poor concordance in the interpretation of some cases, because of overlapping features and the difficulty of defining the morphological limits of blue naevi, Spitz naevi, deep penetrating naevi, plexiform pigmented spindle cell naevi, and naevi with dermal epithelioid cell components.

Epidemiology

There are no population-based data available as to the prevalence of combined naevi. However they appear to constitute less than 1% of melanocytic naevi sampled for histopathological examination {2116}. These naevi occur in all age groups (3 to 83 years in a recent study) with a mean age of 30 years {2116}. A slight predominance of women has been consistently reported in several studies {757,1864,1961,2116}.

The developmental biology of combined naevi has not been delineated. Their genesis may be related to more than one pathway of melanocytic differentiation occurring in a single naevus. It cannot be excluded that there is focal neoplastic progression in some proportion of these lesions.

Localization

Scolyer et al. found a predilection for the trunk (chest, back, abdomen) in 35.2% of

cases, the head and neck in 23.6%, upper extremities in 22.0%, lower extremities in 9.9%, and perineum and buttocks in 4.4% {2116}. Naevi with a significant blue naevus component commonly involve the face, back, and shoulder {757}. Naevi with prominent components of Spitz naevus often occur on the head and neck (face) or extremities as do conventional Spitz naevi {1961}.

Clinical features

The gross morphological features of combined naevi are probably related to the types of and predominant cellular populations present, e.g., focal dermal pigmented components, blue naevus, Spitz naevus, etc. Most of these naevi measure less than 5 to 6 mm in greatest diameter {156,757,1864,2116}, are reasonably symmetrical, are well-circumscribed papular or dome-shaped lesions, and exhibit dark brown, blue to black colouration. Thus many such naevi are often diagnosed clinically as blue naevi or melanoma because of the predominant dark colour. Some of these naevi may also demonstrate a small well-circumscribed blue or blue-black focus, e.g., often 1–3 mm in diameter, within an otherwise ordinary flesh-coloured, tan, or brown naevus (melanocytic naevi with focal dermal pigmented components) {135,156,520,757,2116}. Some naevi may show irregular borders and pigment patterns also raising concern for melanoma.

Naevi with prominent Spitz components are often diagnosed as an unusual naevus, Spitz naevus, dermatofibroma, or possibly melanoma.

Histopathology

Combined naevi may potentially encompass the entire phenotypic repertoire of melanocytic naevi. By definition two or more distinct naevus components are present. Any combination of naevus components and percentage of the naevus components may occur. However 99% of combined naevi have only two components {2116}. The two compo-

Table 2.09 The naevus components potentially occurring in combined naevus

Common acquired naevi
– junctional
– compound
– dermal
Congenital naevi
– junctional
– compound
– dermal
Dysplastic naevi (naevi with architectural disorder and cytological atypia)
– junctional
– compound
Blue naevi
– ordinary or common
– hypercellular
– cellular
– plaque
– epithelioid
Spitz naevi
– junctional
– compound
– dermal
– desmoplastic
Deep penetrating naevi
Plexiform pigmented spindle cell naevi
Naevi with dermal epithelioid cell components (clonal naevus)
– inverted type A naevus
– naevus with dermal nodules
Other

nents are intimately admixed in 82% of cases whereas they are adjacent in the remainder. The most common pattern of combined naevus is that of a common acquired or congenital naevus in combination with discreet foci of pigmented epithelioid and/or spindle cells (which probably includes inverted type A naevus and melanocytic naevus with dermal epithelioid cell components, dermal nodules, or a component of "deep penetrating" or plexiform pigmented spindle cell naevus) {158,164,537,2126}. The latter cells are often enlarged, contain abundant granular melanin, and are disposed in nests or fascicles in the superficial, superficial and deep, or deep portions of or beneath the ordinary naevus, sometimes or commonly in plexiform arrangements. The sizes of the nests or fascicles

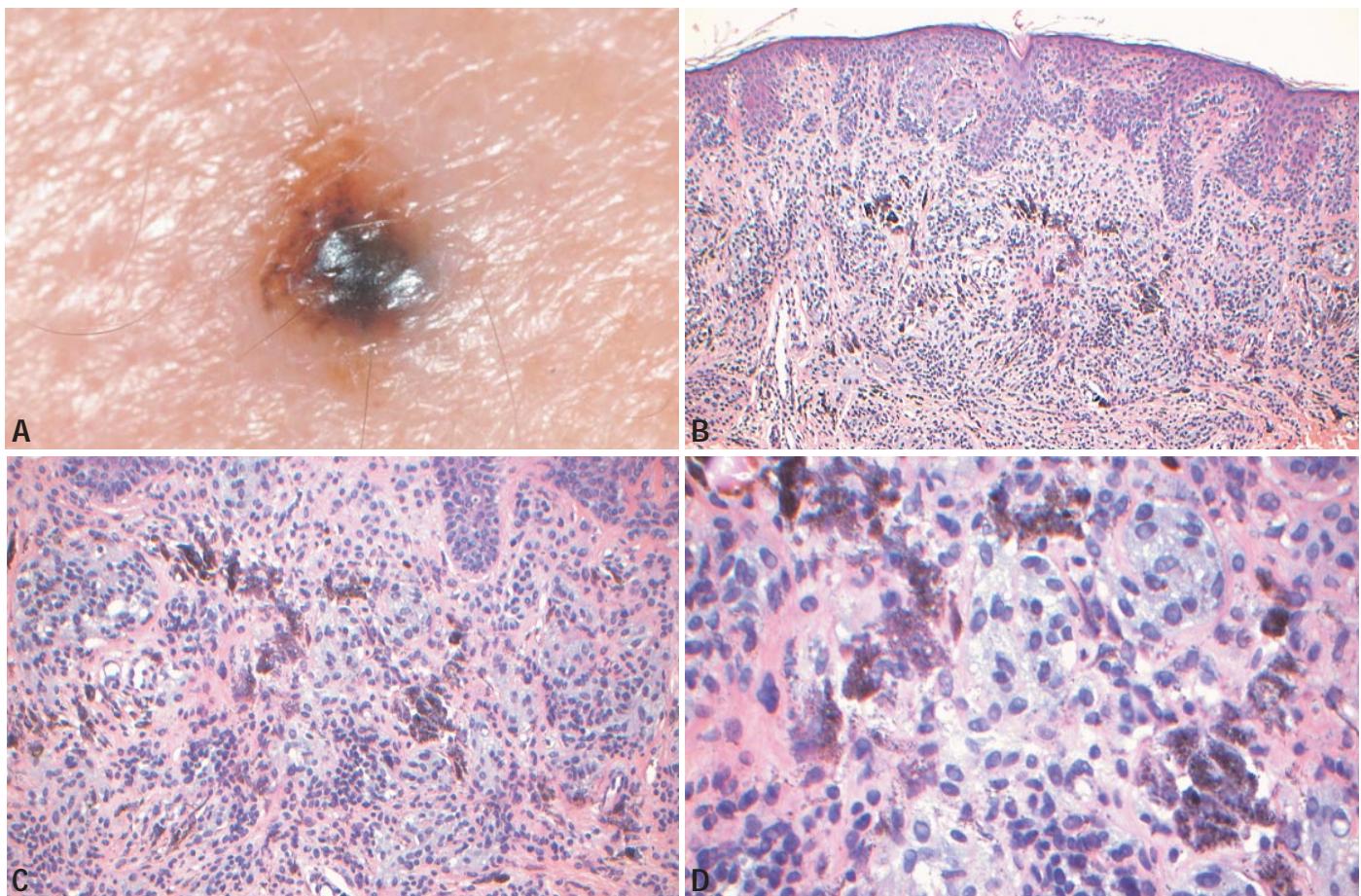


Fig 2.52 Combined naevus. **A** Combined naevus (melanocytic naevus with phenotypic heterogeneity). The lesion is well-defined with central dark brown papule and lighter brown annulus (Courtesy of Harold Rabinovitz, M.D.). **B** There is a conventional compound naevus with small fairly discrete aggregates of heavily pigmented cells in the dermis. **C** This field shows small nests of pigmented polygonal melanocytes and melanophages admixed with the background conventional naevus. **D** The pigmented polygonal melanocytes have abundant cytoplasms and contain nuclei that resemble those in the surrounding small naevus cells. The polygonal cells show transition to the surrounding conventional cells.

may vary from being minuscule to large lobular or digitate aggregates. The nuclei are usually comparable in size to the surrounding conventional naevus cells, or may be slightly enlarged round, oval, or elongate and uniform. On occasion the nuclei may show variable often slight to moderate atypia. Melanophages are also frequently associated with these pigmented foci. This pattern of combined naevus is also probably morphologically identical to that of deep-penetrating naevus and plexiform pigmented spindle cell naevus {158,164,537,2126}.

Another common pattern is that of an ordinary naevus and blue naevus. The ordinary naevus component may be compound or dermal, often overlies or is adjacent to the blue naevus component, and commonly has a congenital pattern. The blue naevus elements most often consist of heavily-pigmented dendritic

melanocytes, melanophages, and variable fibrosis. Less commonly, the spindle cells typical of cellular blue naevus may also be present with or without dendritic cells. The component of blue naevus may extend deeply into the reticular dermis as nests or fascicles, often in a plexiform configuration. Despite the two or more components, such naevi are usually symmetric, well-circumscribed, orderly, and display little or no cellular atypia. Spitz naevi uncommonly are observed in association with ordinary naevus elements {1961}. The topographic relationships of these two components include the Spitz naevus component being adjacent to, beneath, or admixed with the common naevus elements. Such naevi also may have a desmoplastic stroma as in desmoplastic Spitz naevi. After the above relatively well-recognized forms of combined naevus, almost any

combination of cell types is possible {156,2116}. Thus, one may encounter naevi containing various admixtures of ordinary naevus cells, dendritic melanocytes, Spitz naevus cells, and perhaps other transitional cell types. Atypical features may also be observed such as disordered patterns of melanocytes and cytological atypia of both the intraepidermal and dermal components.

Somatic genetics

The conventional naevus component will demonstrate frequent BRAF mutations in contrast to their absence in blue or Spitz naevus components.

Differential diagnosis

The differential diagnosis of combined naevus is dependent on the particular cellular populations present. The histological feature often of most concern is

Table 2.10

Comparison of combined naevus and melanoma

	Combined naevus	Melanoma
Symmetry	Frequent	Uncommon
Size	< 6mm often	> 1cm often
Lateral border	Sharply defined	Poorly-defined
Focus, foci of altered cells*	Present, transition (maturation) to surrounding ordinary naevus	Variable
Cytologic atypia	Usually absent or low-grade	High-grade
Mitotic activity	Absent or minimal (usually < 2/mm ²)	Frequent
Mononuclear cell infiltrates	Uncommon	Frequent

*Focus of epithelioid/spindle cells in ordinary naevus (as also observed in inverted type A and clonal naevi)

ly is of ordinary type is generally unremarkable with reference to atypicality. An occasional mitosis may be observed in such a focus without undue concern; however, the presence of 2 or more mitoses per high power field should prompt careful inspection for melanoma {156}.

Prognosis and predictive factors

Combined naevi are by definition benign. However it must be acknowledged that as with cellular blue naevi and Spitz naevi, there are unusual variants often characterized by a number of abnormal features. Such atypical lesions rarely may result in metastases and require further study as to more definitive criteria for malignancy. Thus such atypical variants prospectively are best designated as biologically indeterminate and require complete excision and close clinical monitoring.

an aberrant focus of cytologically altered/atypical cells in an otherwise ordinary naevus. Such a finding is of concern for early transformation to melanoma or, even fully-evolved melanoma. The latter histologic alteration is present most commonly in the dermis. However, the development of melanoma in the dermal component of a naevus is highly unusual. Therefore, such a diagnosis must be carefully considered and based on sufficient criteria of atypicality, mitotic activity, nodular (confluent) proliferation, and usually the lack of transition

(maturation) to the surrounding naevus. Although combined naevi are heterogeneous, they are usually present in young individuals (< 30 to 40 years), measure less than 5 or 6 mm, and exhibit an overall symmetry and regular appearance. A focal aggregate of pigment-laden epithelioid/spindle cells is usually the feature of concern. Although occasional aggregates of epithelioid cells are large, many are small and well-circumscribed. Cytologic atypia is usually low-grade or insignificant compared to melanoma. The surrounding naevus which common-

Melanotic macules, simple lentigo and lentiginous melanocytic naevus

H. Kerl
D. Massi

Melanotic macules

Definition

Melanotic macules are pigmented lesions that occur on skin, mucous membranes, and in nail units [2035]. The lesions are characterized by hyperpigmentation of the epidermal/epithelial basal layer accompanied by a slight increase in number of melanocytes.

There are several syndromes, which are associated with multiple melanotic macules/lentigines (Peutz-Jeghers, NAME, LAMB, LEOPARD, Carney complex (See Chapter 7).

Synonyms

Genital: Genital melanosis/lentiginosis; Vulvar melanotic macule; penile melanotic macule; penile lentigo.

Labial/oral: Labial/oral melanosis; labial melanotic macule; labial lentigo.

Volar: Volar melanosis.

Nail apparatus: Melanosis of the nail bed and matrix; ungual melanosis.

Skin: Reticulated black solar lentigo; "ink spot" lentigo.

Clinical features

Melanotic macule of vulvar and other female genital sites

The condition occurs usually on the vulva as a flat asymmetric macule with a diameter from less than 1–5 cm. Multiple lesions are present in >50% of the cases. The tan-brown to blue-black macules mostly involve the labia minora. But they can also occur on the labia majora, per-

ineum, the introitus, vagina and cervix. They may be difficult to distinguish from melanoma [1400].

Penile melanotic macule

This lesion usually presents in adult life as a pigmented patch, uniform or variegated in colour with irregular borders, on the glans penis or on the penile shaft. Multiple macules can be observed.

Labial melanotic macule

The lesion occurs in about 3% of persons, mostly in women on the vermillion border of the lower lip. The lesions can be also present on the oral mucosa and on the tongue. A single or multiple (oral melanosis), brownish-black or black macules with irregular sharply demarcated borders can be observed [925].

Variants

Volar melanotic macule

Clinically a brown, tan, or grey macule (less than 5 mm in diameter) is located on palms and soles usually in Black patients.

Ungual melanotic macule

Pigmented bands (not thicker than 3 mm) are observed in the fingernails of young individuals (longitudinal melanonychia). The lesions are common in dark-skinned races and in the Japanese population. In Laugier-Hunziker syndrome, longitudinal melanonychia is accompanied with labial/oral melanotic macules.

Reticulated melanotic macule

These lesions appear on sun-exposed areas of the trunk or shoulders as a dark-brown or black reticulated macule with irregular borders.

Although the lesion has been named "reticulated black solar lentigo" [277], it is different from the conventional solar lentigo [1171].

PUVA-lentigines

PUVA-lentigines are pigmented macules, which develop as a direct response to the effects of long-term therapy with PUVA (psoralens + UVA).

Histopathology

Similar histopathologic changes can be demonstrated in all types of melanotic macules. There is usually no perceptible or a slight increase in the number of melanocytes, which are situated at the dermo-epidermal junction in solitary units. The melanocytes exhibit small and monomorphous nuclei and delicate dendrites. Using Fontana-Masson silver stain, the dendrites are better visible. Atypia is not observed. The basal layer reveals prominent hyperpigmentation. Occasionally hyperplasia of the epidermis can be seen. Melanophages and a mild inflammatory infiltrate are often present in the superficial dermis.

Reticulated melanotic macules show marked hyperpigmentation of the epidermis especially at the tips of the rete ridges whereas the suprapapillary plates are spared and nearly devoid of melanin. A slightly increased number of finely dendritic melanocytes can be observed in the lower layers of the epidermis. In contrast, solar lentigo represents an evolving seborrhoeic keratosis revealing small buds or nubbins of hyperpigmented keratinocytes.

PUVA-lentigines are characterized by an increased number of melanocytes, which are concentrated mostly in pigmented rete ridges as solitary units. Some melanocytes may show atypical nuclei.

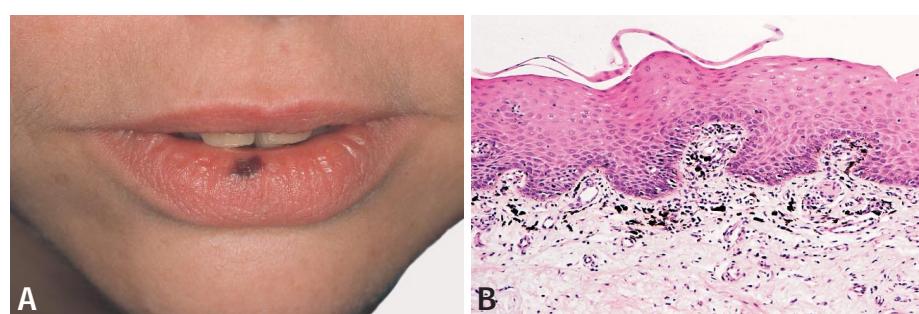


Fig. 2.53 Melanotic macule on the lip. A Brown-black macule with irregular margins on the lower lip. B Pigmentation of the epithelial basal layer and melanophages in the papillary dermis.

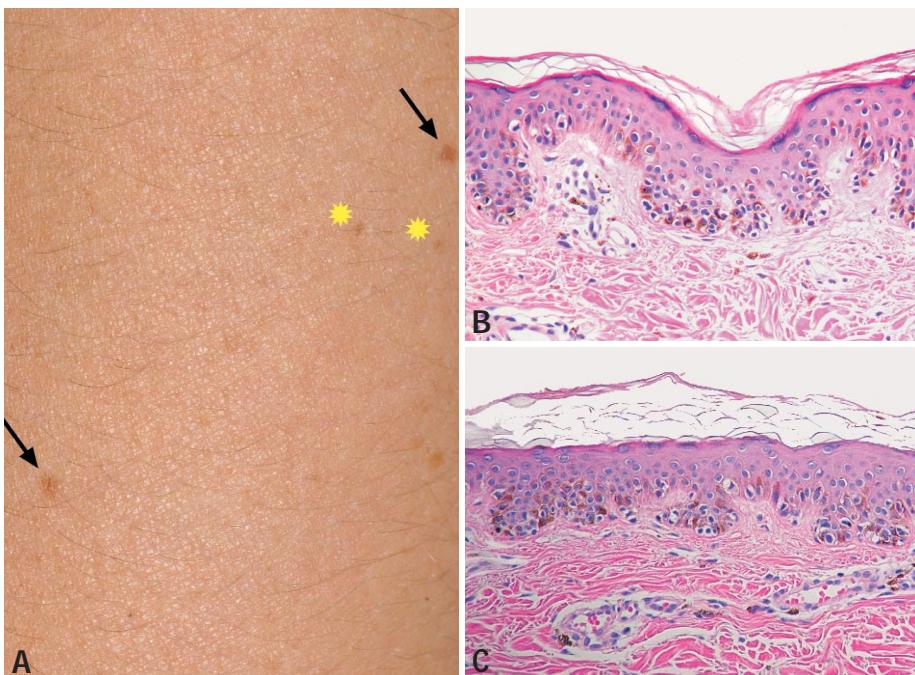


Fig. 2.54 Simple lentigo - Lentiginous melanocytic naevus. **A** Small uniform brown macules; (stars) simple lentigo. (arrows) lentiginous melanocytic naevus. **B** Simple lentigo. Increase in the number of melanocytes in single units along the basal layer - especially around elongated hyperpigmented rete ridges. Distinct nests are absent. **C** Lentiginous melanocytic naevus. Features of lentigo simplex can be recognized. The aggregation of melanocytes in tiny nests indicates the transformation of this lentigo simplex into a lentiginous melanocytic naevus.

Differential diagnosis

Early stages of melanoma in situ must be differentiated from melanotic macules. Melanoma in situ (genital / labial areas) can manifest as a sparsely cellular proliferation of melanocytes. Sometimes in a partial biopsy the only clues are nuclear hyperchromasia or irregularly shaped dendrites. In more fully developed cases, melanocytes are more regularly distributed, can become confluent and may also be situated above the junction. Lesions with more than a slight increase in melanocytes, even without atypia should be carefully evaluated, with additional sampling, over time if indicated. If the problem cannot be resolved complete excision may be appropriate.

layer; lentiginous junctional melanocytic naevus shows in addition formation of small junctional nests. In compound lentiginous melanocytic naevi, small round melanocytes are also present in the papillary dermis.

Synonyms

Lentigo simplex, naevus incipiens.

Clinical features

Small flat roundish uniform brown or black sharply circumscribed macules usually less than 6 mm in diameter, which are most frequently found on the trunk and extremities of children and adults, are observed.

Histopathology

Simple lentigo consists of an increased number of melanocytes disposed as solitary units in the basal layer of variably elongated and hyperpigmented rete ridges. The melanocytes have small round to oval and monomorphous nuclei. They are positioned equidistant from one another and are seen more pronounced at the tips of the rete ridges. Pigment is abundant and found throughout the epidermis including the stratum corneum. Melanophages are usually present in the papillary dermis. Giant melanosomes can be present.

When one or more small nests of melanocytes (i.e. three or more melanocytes per congregation) in such a lesion is observed, it is then called lentiginous naevus (evolving junctional naevus).

The histology of naevus spilus (congenital speckled lentiginous naevus) is indistinguishable from simple lentigo-lentiginous melanocytic junctional naevus.

Prognosis and predictive factors

Melanotic macules have been incorrectly interpreted as premalignant lesions and possible precursors of melanoma {1757A,2394A}. Current evidence supports the notion that melanotic macules, irrespective of their location, should be considered benign in their clinical behaviour, since they tend to remain stable and unchanged when followed over a long period of time.

Simple lentigo and lentiginous melanocytic naevus are wholly benign melanocytic proliferations which have no potential for malignant transformation.

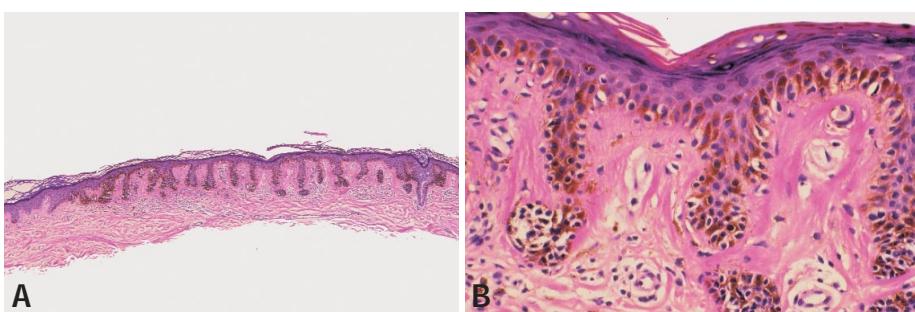


Fig. 2.55 Lentiginous junctional melanocytic naevus. **A** There are elongated rete ridges with increased numbers of single melanocytes at their sides and bases, with some tiny junctional nests. **B** In this example, there are lymphocytic infiltrates and fibroplasia of the papillary dermis.

Dysplastic naevus

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Definition

Solitary or multiple naevi, variable in colour, border, and size, with preferential location on the upper trunk and extremities. Dysplastic naevi (DN) occur as sporadic lesions and in a familial setting. They may progress to malignant melanoma.

ICD-O code 8727/0

Synonyms

Atypical naevus {896} has been proposed as a synonym for clinically dysplastic naevus. Other past designations include naevus with architectural disorder {1}, and melanocytic naevus with architectural disorder and cytologic atypia {1,2158}. The concept of Clark naevus includes a large number of junctional and superficial compound naevi of which the dysplastic naevus is a subset.

Historical annotation

Originally, Wallace H. Clark and coworkers described patients with multiple atypical naevi for which they proposed the term "B-K mole syndrome", using the first initial of the surname of two probands {496}. The authors photographically documented two lesions that progressed over time to malignant melanoma. Therefore, the authors considered the "B-K mole" a precursor of melanoma. Soon thereafter, in 1980, Elder et al found lesions similar to those in "B-K mole" patients with non-familial cutaneous malignant melanoma {673}. Subse-

quently, the "B-K Mole Syndrome" was renamed to 'Dysplastic Naevus Syndrome', with further sub-classification into sporadic or familial types.

In 1992, a U.S. National Institutes of Health Consensus Conference recommended "naevus with architectural disorder" in order to avoid the negative connotation associated with the word "dysplasia" {1}. However, this term has failed to gain wide acceptance {2153}.

In a recent survey by the American Academy of Dermatology, 98% of respondents recognized the dysplastic naevus as a distinct entity {2373}.

Epidemiology

The estimated total number of individuals affected by the familial form is approximately 32 000 in the United States {1320}.

Sporadic, *histologically* dysplastic naevi are seen in up to 50% of White adults, depending on how the lesion is defined. {535,571,1828}. The estimated prevalences of dysplasia in a population based series of naevi ranged from 7-32% {1829}. The prevalence of *clinically* defined dysplastic naevi also varies according to the criteria used, ranging from 5-20%.

Etiology

Ultraviolet radiation has been implicated in the genesis of dysplastic naevi and melanoma. Noz et al found higher in vitro sensitivity to DNA damage by ultraviolet B radiation in melanocytic naevus cells compared to foreskin melanocytes {1732}. One recent study found an increased relative risk for melanoma in a dysplastic naevus group with poor in vitro DNA repair capacity {1360}.

Localization

Dysplastic naevi can occur anywhere on the body but are most commonly found on the trunk {496}. In females, there may be a considerable number on the legs {5559}. A "quadrant" form of dysplastic naevus distribution has been reported where a 59-year-old man had numerous

aggregated pigmented lesions (common acquired naevi and dysplastic naevi) confined to the left upper quadrant of his body. Within this quadrant, two malignant melanomas at different stages of progression developed from dysplastic naevi {2266}. Hidden areas such as the scalp and genitalia need thorough evaluation as dysplastic naevi may be seen in these areas {731,2029}. In Greene's original description, it was noted that unlike ordinary moles, dysplastic naevi are often found on the scalp, buttocks and female breast {897}. Lesions on the scalp, genitalia and upper back should be considered for excision due to the difficulty with patient self-examination of these locations {749}, although careful follow-up is a reasonable alternative.

Clinical features

Patients may have one, several or up to hundreds of lesions. In one study, patients who had DN outside the familial melanoma setting had an average of 10 per person {157}. The clinical features originally ascribed to DN included ill-defined or irregular border, irregularly distributed pigmentation, background erythema, and size greater than 5 mm {496,2029}. Lesions often differ from one another in the same individual and in addition, they are often different between individuals {778}. Some lesions may have a central papular component with a macular flare that blends into surrounding tissue resulting in an ill-defined, fuzzy periphery. The surface texture has been described as "pebbly" {2476}. Other lesions are macular or plaque-like without a central papule or nodule. Irregularities in pigment range from tan to dark brown to black. There are often areas of pink and some lesions are amelanotic. Characteristically, lesions first appear around the time of puberty and if they are not apparent by age 20, it is unlikely that an individual has the familial melanoma/dysplastic naevi trait {897}.

Diagnostic criteria

The Dutch Working Group produced five



Fig. 2.56 Dysplastic naevus. A solitary lesion on the abdomen. Note the variegated appearance.

criteria for the clinical diagnosis of dysplastic naevi: 1) size greater than or equal to 5mm in diameter, 2) vague border, 3) asymmetric shape, 4) irregular pigmentation, and 5) red hue {212}. Additional diagnostic criteria have been advocated by Newton et al. and consist of a scoring system. One point was awarded for the presence of one of five parameters: 1) 100 or more naevi > 2mm, 2) > two atypical naevi, 3) > one naevus on the scalp, 4) one naevus on buttock or > 2 on dorsa of the feet, 5) > one iris naevus. Individuals who have three or more points are considered to have the dysplastic naevus syndrome phenotype {1700}.

Dermoscopy and imaging

Dermoscopy can be used to assist in differentiating a DN from other benign or malignant lesions. A lesion that does not demonstrate features of the predominant type of naevus seen in that individual should be considered atypical and receive special attention {1043}. This is analogous to the "ugly duckling" lesion that refers to one that is distinct from others in a given patient. It has been recommended that such lesions be biopsied as they are more likely to be the ones that demonstrate features suggestive of melanoma {900}.

Several studies have demonstrated the usefulness of regular whole body photographs {1474} and computerized imaging for melanoma surveillance {387, 1286, 2440}.

Progression to malignant melanoma

Although melanomas in patients with dysplastic naevi may arise within preexisting dysplastic naevi, the vast majority

Table 2.12
Dermoscopy findings. From Steiner et al. {2259A}

Dermoscopy finding	Dysplastic naevi	Melanoma
Pigment network	Irregular discrete pigment network 55%	Irregular, prominent (darkly pigmented) in 81%
Overall pigment	Irregular 82%	Irregular (85%)
Brown globules	Irregularly arranged and of variable size (45%)	Irregular arrangement and size (35%)
Margin of pigment network	Irregular margin ends gradually (68%)	Abrupt ending of an irregular margin (63%)
Black dots		Present in 34% with irregular arrangement at periphery in 26%
Radial streaming	1.7%	25%
Pseudopods	1.7%	31%
Depigmentation		Periphery (56%)

arise de novo. Histologic changes indistinguishable from those of dysplastic naevi are often observed at the peripheries of primary melanomas not associated with naevi and such findings have been interpreted as representing "precursor" dysplastic naevi {672}. Dysplastic naevi may have chromosomal instability and poor repair mechanisms after sunlight induced injury {1067, 2128}. Landi et al demonstrated an increased relative risk for melanoma in a dysplastic naevus group with poor in vitro DNA repair capacity {1360}. Elder classified 6 stages of tumour progression via monoclonal antibodies to melanoma cells or their extracts on frozen tissue sections {675A}.

recommend evaluating both cytology and architecture in the diagnosis of DN {2158}. More recent descriptions of features common in DN histology included a central dermal naevocytic component with a peripheral extension of a junctional component, elongated epidermal rete ridges, bridging of nests of melanocytes at the dermo-epidermal junction, nests of melanocytes at the sides of rete ridges as well as at their bases, and concentric eosinophilic papillary dermal lamellar fibrosis {1943}. Ackerman and others have placed emphasis on the "shoulder phenomenon" which describes peripheral extension of the junctional component beyond the dermal component in dysplastic naevi {18, 1828}.

In general, histologic criteria involving architecture used to describe dysplastic naevi include: circumscription, symmetry, cohesion, suprabasilar melanocytes, confluence and single cell proliferation. Cytologic features include: nuclear shape and staining, nuclear size, nucleolar prominence, and cell size {2158}. One of the problems in the definition of these lesions is that the histologic changes are non-specific and may be seen in a number of other naevi without clinical features of "dysplastic" naevi such as growing naevi in children and naevi located on certain anatomic sites such as the scalp and flexural areas. Furthermore, the definitions used to describe cytologic atypia are subjective

Table 2.11.
Clinical characteristics of dysplastic naevi

- >Variable size (<5mm-over 1 cm): great intralesional variation with respect to size
- >Irregular colour: irregular browns, red papule with brown halos, speckled
- >Irregular contour: macular or macular with central papular component
- >Ill-defined border, often "fuzzy"
- >Preferential location on the trunk

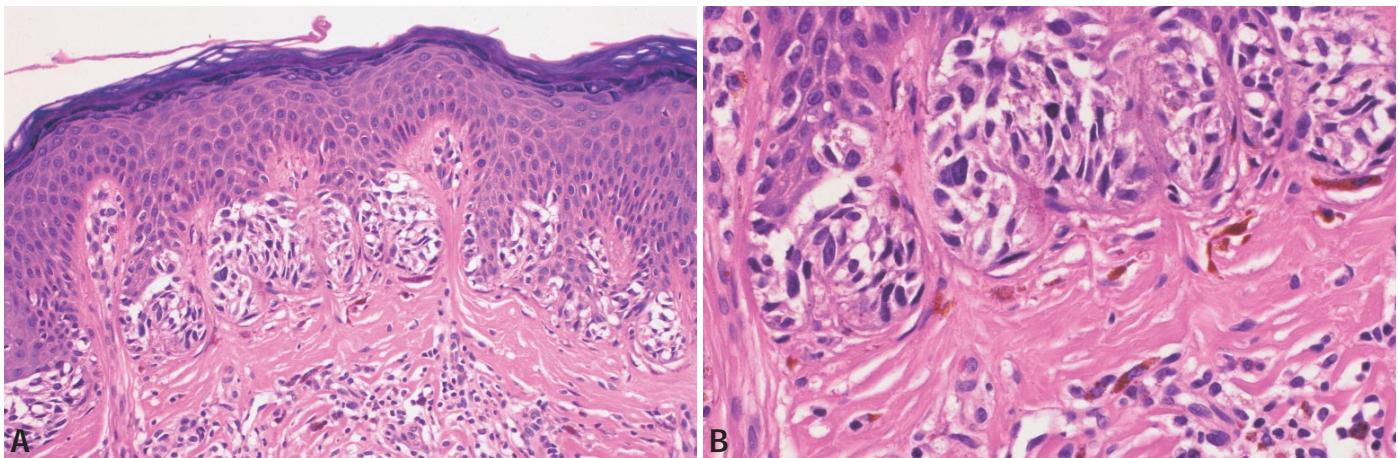


Fig. 2.57 Dysplastic naevus. **A** The naevus cell nests are confined predominantly to the tips of the rete pegs. **B** Note the cytological atypia with nuclear hyperchromasia.

as in no case are the atypical cytologic features as frankly atypical as seen in fully developed melanoma.

Immunoprofile

Mild to moderate staining of dysplastic naevi is observed using antibody to HMB45 antigen. This antibody also often stains intradermal melanocytes within melanomas but not as strongly in common melanocytic naevi [2214]. S-100 is a protein found in the central nervous system that is also present in melanocytes, including melanoma. S-100 protein is found at the dermo-epidermal junction and at all levels of the dermis in dysplastic naevi [1792]. However, S-100 staining is non-specific as it is seen in common naevi, dysplastic naevi as well as malignant melanoma.

Growth fraction / MIB-1 index

Some authors assert that the presence of the proliferation marker Ki-67 in dysplastic naevi indicates that these lesions are precursors to melanoma [760]. The percentage of cells that expressed Ki-67 was an independent prognostic factor [1308]. Kanter et al found that percentages of MIB-1 immunoreactivity in the intradermal portion of the lesions was negligible for benign congenital and acquired naevi, as well as in dysplastic naevi compared to melanomas which exhibited a markedly increased proliferative activity, especially vertical phase melanomas [1201]. At the current time, it is not recommended that proliferation markers be used as a reliable method for distinguishing between naevi and melanoma.

Electron microscopy

The melanosomes in epidermal melanocytes in dysplastic naevi are abnormal, with incompletely developed lamellae and uneven melanization [2476]. Abnormal spherical and partially melanized melanosomes similar to those observed in superficial spreading melanoma have been observed by electron microscopy [672,1363]. Based on these transmission electron microscopy findings, one group suggested that dysplastic naevi lie on a continuum between naevi and superficial spreading melanoma. No correlation has been shown prospectively between ultrastructural findings and progression or predilection to the development of MM.

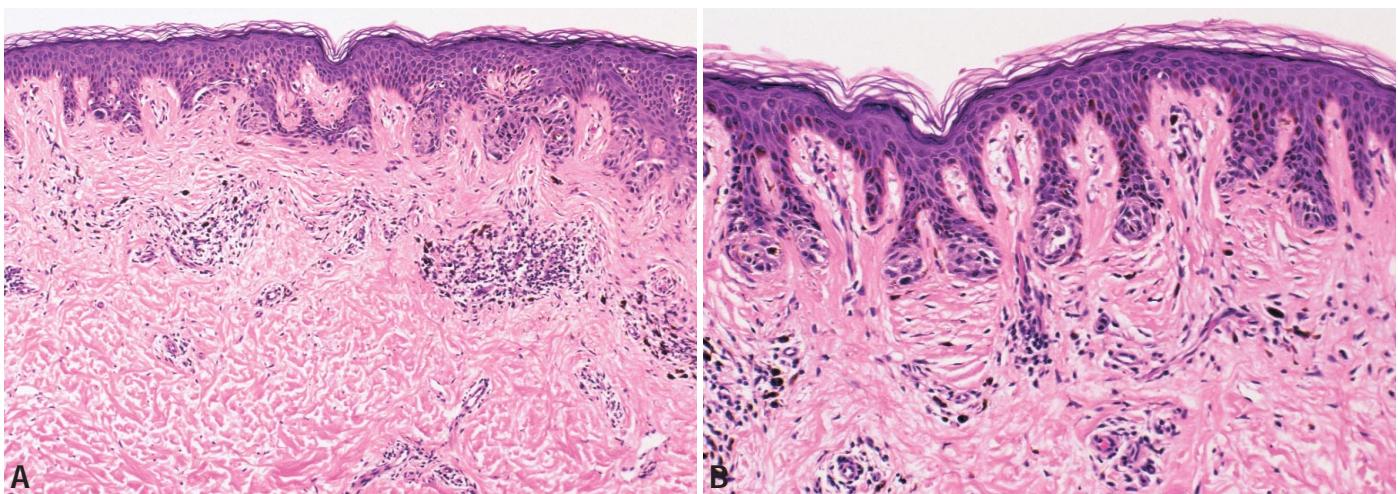


Fig. 2.58 Dysplastic naevus. **A** The junctional component shows both architectural and cytological atypia. There is a mild, superficial perivascular lymphocytic infiltrate. **B** Mild atypia of the junctional nests and dermal papillary fibroplasia. There is some melanin incontinence.

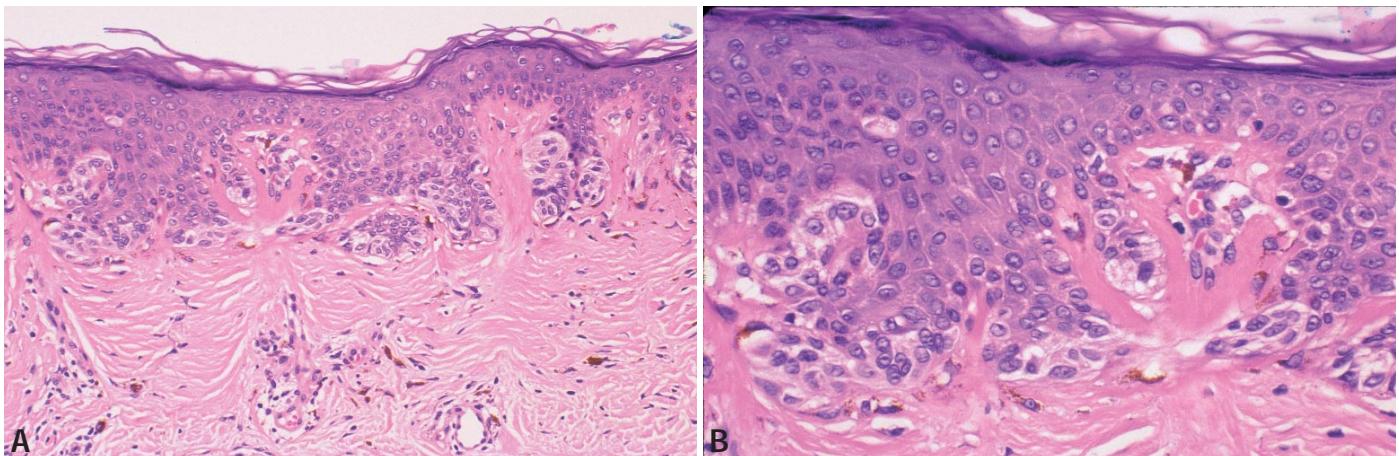


Fig. 2.59 Dysplastic naevus. **A** Some naevus cell nests extend above the tips of the rete pegs. **B** Mild cytological atypia of the junctional nests.

Variants

Toussaint and Kamino observed histopathologic changes of "dysplastic" naevi in other types of naevi. They also noted that some dysplastic naevi demonstrated features of other varieties of naevi. 2,164 cases of compound melanocytic naevi that fulfilled the histopathologic criteria for the diagnosis of compound dysplastic naevus were reviewed. 87.6% had the histopathologic characteristics of dysplastic naevus, 8.3% showed a dermal component with a congenital pattern, 3.1% demonstrated epidermal and dermal characteristics of Spitz naevus, 0.3% had features of a combined blue naevus, 0.6% had a halo phenomenon and 0.1% showed intradermal naevus. The authors advocate describing dysplastic melanocytic naevi by categorizing them into six groups: 1) dysplastic naevus; 2) dysplastic naevus with a congenital pattern; 3) dysplastic Spitz naevus; 4) dysplastic combined blue naevus; 5) dysplastic halo naevus; and 6) dysplastic nevus of Goltz.

Differential diagnosis

The clinical differential diagnosis of dysplastic naevi includes congenital melanocytic naevi, pigmented basal cell carcinoma, Spitz naevus, common acquired melanocytic naevi, melanoma in situ, and superficial spreading malignant melanoma. The histologic differential diagnosis includes melanoma, recurrent naevus, halo naevus, congenital naevus, a growing naevus in a child and Spitz naevus.

Grading

Some authors emphasize cytologic crite-

ria for grading dysplastic naevi [1925]. In 1993, Duncan et al advocated grading dysplastic naevi into groups based on cytology. Dysplastic naevi with slight, moderate and severe cytologic atypia were differentiated. However, concordance between experienced dermatopathologists ranged from 35% to 58%. Because of lack of reproducibility, DeWit et al. did not recommend grading atypia in dysplastic naevi [612]. An analysis of 12 histologic parameters in 123 dysplastic naevi failed to identify parameters useful in differentiating mild from moderate dysplasia [1854]. Despite these considerations, melanoma risk has been associated with the degree of atypia in dysplastic naevi [102].

Somatic genetics

Cytogenetics and CGH

Jaspers et al performed cytogenetic investigations on lymphocytes and fibroblasts from 25 individuals with dysplastic naevus syndrome and compared the results with a control population of clinically normal relatives and unrelated individuals. In five DNS patients, increased frequencies of cells with random chromosomal rearrangements including translocations and inversions were observed. These abnormalities were absent in the control population [1134].

Caporaso analyzed the karyotypes of 163 family members from 13 melanoma-prone families to investigate whether chromosomal instability contributes to familial melanoma. Cutaneous malignant melanoma and dysplastic naevi syndrome patients each had increased structural and numerical abnormalities

compared with pooled controls [377]. However, the criteria used to define lesions as "dysplastic" naevi were subjective from the outset so the validity of such studies remains in question.

Park and Vortmeyer examined the frequency of p16 and p53 deletion in nine dysplastic naevi and 13 benign intradermal naevi with five microsatellite markers. Hemizygous deletion was detected in seven of nine dysplastic naevi at one or more loci for p16. No loss of heterozygosity was detected in any of the benign intradermal naevi [1775].

Molecular genetic alterations

Greene performed an extensive review of the genetics of malignant melanoma and dysplastic naevi in 1998. Many studies demonstrate an autosomal dominant mode of inheritance and speculate pleiotropic manifestations of a proposed melanoma gene on chromosome 1 (1p36). CDKN2A, a tumour suppressor gene localized on chromosome 9, is also reported to be a melanoma gene. The relationship of melanoma to mutation of CDKN2A has been confirmed [895]. Hussein evaluated skin tissue samples of melanoma, dysplastic naevi and benign melanocytic naevi for microsatellite instability. Microsatellites are short single sequence motifs repetitively scattered throughout the human genome. The variation in microsatellite pattern length between tumourous and matching non-tumourous tissues is referred to as microsatellite instability. Microsatellite instability has been associated with other familial and sporadic tumours. Hussein's results demonstrated MSI at 1p and 9p chromosomal regions in dysplastic naevi.

and malignant melanoma but not in benign naevi lending further support to others that have speculated on the presence of "melanoma genes" involving the short arm of chromosomes 1 (1p36) and 9 (9p21) {1087}. In 2002, Tucker provided 25-year prospective data regarding 33 families with familial melanoma and dysplastic naevi. Seventeen members were found to have mutations in CDKN2A. Tucker found that the majority of clinically diagnosed dysplastic naevi remained stable or regressed over time. The majority of melanomas detected over the course of the study arose from naevi although some arose de novo {2384}.

Genetic susceptibility

As discussed above, Clark originally described dysplastic naevi in relation to a familial syndrome called the B-K mole syndrome {496}. Most dermatologists agree that family members of patients with dysplastic naevi need evaluation {2373}. Familial dysplastic naevi and melanomas have rarely been reported with other systemic malignancies involving the central nervous and digestive system {129,213}.

Prognosis and predictive factors

The incidence of melanoma developing in a given dysplastic naevus has been estimated at 1:3000 per year. Therefore, dysplastic naevi should not be consid-

ered as high risk precursors of melanoma, but rather as markers that allow identification of individuals at increased risk for melanoma.

Number of dysplastic naevi and family history

Patients with greater numbers of naevi, dysplastic or otherwise, are at greater risk for melanoma {2386}. Dermatologists acknowledge patients with multiple dysplastic naevi, especially if there is a personal or family history, are at greater risk for developing melanoma {2373}. If patients are from "melanoma-prone families" and have clinically dysplastic naevi, as defined by criteria that include lesional diameter, their individual risk for developing a melanoma is several hundred times that of the general population, with a risk for lifetime incidence of melanoma approaching 100% {744,846}. The significance of a single histologically dysplastic naevus in this context has not been determined. One study evaluated patients with an established diagnosis of melanoma (n=716) compared with normal controls (n=1014) and found that one clinically dysplastic naevus was associated with a 2-fold risk, while 10 or more conferred a 12-fold risk of melanoma {2386}. In the same study, patients who bore 100 or more clinically non-dysplastic naevi had a relative risk of 3.4. Approximately 50% of dysplastic naevi patients with a family history of MM

may have multiple primary melanomas {1320}.

Histopathological criteria

There is evidence that histological atypia does correlate with melanoma risk. A recent study of more than 20,000 naevi divided them microscopically into mild, moderate, or severe categories of dysplasia. A personal history of melanoma was present in 5.7 of the patients with mild, 8.1 with moderate and 19.7 with severe atypia. It was concluded that the risk of melanoma was greater for persons who tend to make naevi with high-grade histological atypia {102}.

Genetic predictive factors

Currently, there are no commercially available genetic tests that would be predictive of dysplastic naevi progression to melanoma.

Site specific and Meyerson naevi

H. Kamino
D. Weedon

In some anatomic sites, naevi may have atypical histological features. This chapter discusses three clinicopathologic entities: acral, genital and Meyerson naevi, but other site specific features have been described, including naevi occurring in flexures, umbilicus, ear and scalp.

Acral naevus

Definition

Acral naevi (AN) are benign melanocytic proliferations from the palms and soles.

Synonyms

AN or "naevi on volar skin" include histologic subtypes termed "Melanocytic Acral Naevus with Intraepidermal Ascent of Cells (MANIAC)" {1545} and "atypical or acral lentiginous naevus" {501,1511}.

Epidemiology

Clinical studies which are unable to distinguish lentigines from true naevi, record discrete pigmented volar lesions in less than 1{1763} to 92% {1416} of subjects, with most studies suggesting a range of 3 – 41% of the population {63,519,574, 1338,2223,2418}. In a histologically confirmed study, 3.9% of Caucasians had AN {1473}. Darker patients tend to have a greater percentage {519,1763} and higher total of naevi on acral surfaces {63,519,1553,2418}, though this is not always found {574,1416}. Pigmented acral lesions are generally more common in the second and third decades {63,1338,1415,2418}.

Localization

Plantar naevi are probably more common than palmar naevi {63,574,1473,2418}. AN may occur on both pressure-bearing and pressure-spared surfaces {45,63, 1415}.

Clinical features

AN are usually less than 8 mm with a light to dark brown striated macular component. Congenital AN can be particularly

difficult to clinically distinguish from melanoma {289,1511,2013,2017,2018}. On epiluminescence microscopy (ELM) dermatoscopy, the pigmentation of AN is accentuated in dermal glyptic furrows and occasionally around eccrine ostia, thereby creating reproducible patterns {45,1232,2014,2015}. In acral melanomas the pigment is distributed along the dermatoglyphic ridges {45}.

Etiology

The origin of AN is hypothesized to involve repeated trauma {701,2181, 2182}, foci of "unstable" melanocytes {1416} and racially-correlated variations in melanosome aggregation {1612}.

Histopathology

Distinction of acral naevi from melanoma can be difficult because both may be asymmetric, poorly circumscribed and have intraepidermal ascent of cells {292, 701,984,1545,2181,2182}. Suprabasal melanocytes in AN are relatively more columnar, circumscribed and less voluminous than in melanomas {1246}. Signoretti et-al. have shown that symmetry, circumscription, the columnar organization of ascending melanocytes and organization of the junctional component are all influenced by the histologic plane of section; to wit, naevi sectioned perpendicular to dermal glyptic furrows are more likely to have benign attributes {2017, 2018}. Subsequently, severe melanocytic atypia and a dense lymphocytic infiltrate

have been found the most reliable features indicative of melanoma {493,707}.

Genital naevus

Definition

Melanocytic naevi on the perineum and genitalia, hereafter "genital naevi (GN)", include different naevic types distinguished and united by unusual, variably present junctional features.

Synonyms

A subgroup of GN with "unusual histologic features" {480,782} or "atypism" {1608} have been dubbed "atypical melanocytic naevus of the genital type (AMNGT) {495}".

Epidemiology

About 10% of men and women have pigmented genital lesions {574,784,1955}, but many are lentigines {784,1955}. Histologically confirmed GN occur in 2% of women {267,480,1955}.

AMNGT comprise a minority of all GN {267,480,1955}. They typically present by the twenties {1608} and, in contrast to vulvar melanoma, are seen exclusively in premenopausal women {1608,2015}. Dysplastic naevi may also occur on the genitalia but they are usually observed in people with dysplastic naevi elsewhere on their bodies {267,1608}. Vulvar naevi were said to have increased premalignant potential {1763}, though recent data

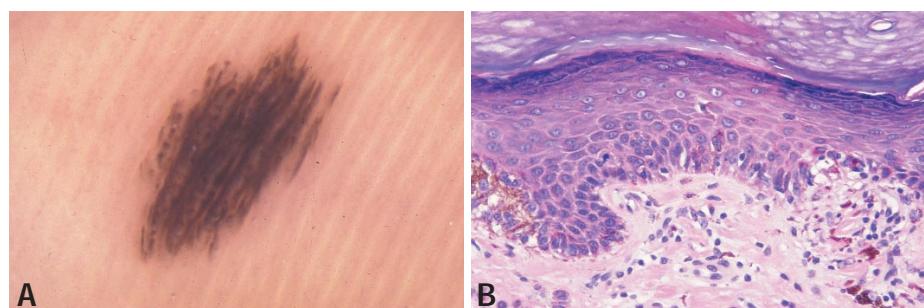


Fig. 2.60 Acral naevus. **A** Epiluminescence microscopy of an acral naevus demonstrating linear hyperpigmentation within the furrows of dermal glyptic furrows. **B** Intraepidermal melanocytes with short dendrites are seen along and above the basal layer.

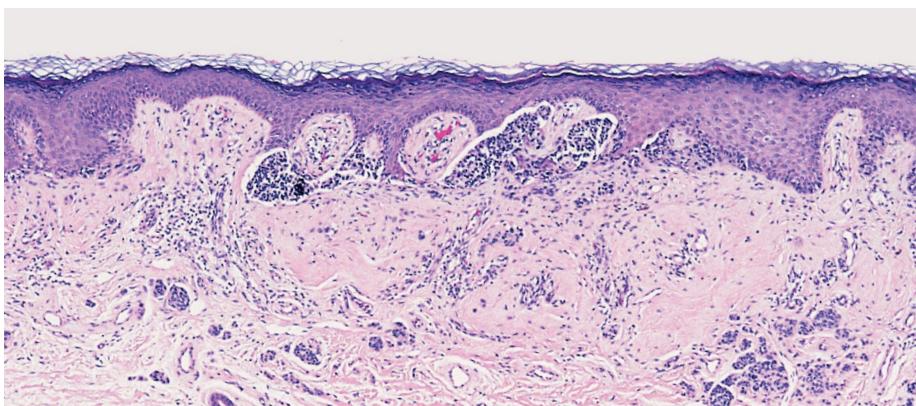


Fig. 2.61 Genital naevus. This example contains features of a dysplastic naevus. Junctional melanocytes are arranged as both nests and single units. There is bridging of rete ridges and lamellar fibroplasia. Dermal melanocytes mature and melanocytes do not ascend above the basal layer.

refutes this {1954}. Histological studies suggest that from 1% {391} to 12% {495} of vulvar melanomas are associated with a naevus.

Localization

AMNGT are more commonly seen on the labia minora and clitoris {495}. Although infrequent, AMNGT may occur on male genitalia {495}. Naevi with histologic features similar to AMNGT may be observed on flexural sites and along the vestigial "milk-line" from the axilla to the upper thighs {1964}. Dysplastic naevi more commonly occur on the labia majora and perineum {495}

Clinical features

Common type GN are dome shaped, evenly pigmented, tan to dark brown papules less than 1 cm {1955}. Both AMNGT and dysplastic GN can be polypoid or flat {495}. They are usually tan-brown, often with some black areas {495}. Clark et-al report a size range from 2 to 24 mm {495}. Despite a long history of advice to the contrary, prophylactic removal of all genital naevi is not recommended {480,784,1955}. AMNGT observed from 1 to 16 years have not recurred or metastasized; yet, their conservative reexcision has been advised {495}.

Etiology

The genesis of GN is poorly understood. Possible influences include repeated superficial trauma, sex hormones, genetic determination and stroma type {391, 495, 1964}.

Histopathology

AMNGT are typically "mushroom

shaped" with a base composed of maturing melanocytes similar to a common naevus. Melanocytes at the dermal-epidermal junction are arranged in one of three patterns: nests; dyshesive nests; and crowded, ill-defined nests and single melanocytes. In about half of AMNGT there are "skip areas" at the dermo-epidermal junction which lack melanocytes. Thus, it is the junctional component in AMNGT which is worrisome for melanoma. Unlike dysplastic naevi, AMNGT usually lack a lymphocytic infiltrate. The "ill-defined" stroma of AMNGT is different from that typically seen in melanomas or dysplastic naevi {495}. The histopathologic features of dysplastic GN are similar to dysplastic naevi elsewhere {267,495,1955}. Rarely, genital naevi may be distorted by coexistent lichen sclerosus et atrophicus, producing histologic changes similar to those seen in recurrent naevi {17,352,390}. Unlike melanomas, vulvar naevi are said to lack intraepidermal ascent of melanocytes {17,24,391,782}, though this has been disputed {984,1608}. Regardless of subtype, GN differ from



Fig. 2.62 Meyerson naevus. Note the eczematous halo around a pigmented naevus.

melanoma by circumscription, maturation, and symmetry {17,24,391,782}.

Meyerson naevus

Definition

Meyerson naevus is a benign naevus of junctional, compound or intradermal type surrounded by an eczematous halo {2478}.

Synonyms and historical annotation

"Spongiotic change in melanocytic naevi" {2478}, halo dermatitis {352,2330}, halo eczema {1329} and perinaevic eczema {1816}.

The eponym "Meyerson naevus" (MN) was suggested {1706} to honour the 1971 description of a spongiotic dermatitis involving melanocytic naevi {1595}.

Epidemiology

MN typically occur in young adults {1706} and children {2167}. Affected men have been reported about three times more frequently than women {1706}.

Localization

Eczema may involve one or several naevi {1329,1706} and may spread beyond naevi to previously normal skin {306, 729}. There are no clinical features to suggest which naevi become dermatitic {1329,1706}.

Clinical features

The change may involve one or more naevi simultaneously. The naevus does not usually undergo regression as a result of this change although the transformation of a Meyerson naevus into a halo naevus has been recorded once {1884}. MN are characterized by a pruritic, raised erythematous, scaling and crusted plaque which extends symmetrically 1–2 cm from the central naevus {306, 1329,1595}. Upon resolution the naevus persists unchanged {1595,2330}, though post-inflammatory hypopigmentation may occur {1595,2330}.

Etiology

The inflammation of MN has been likened to pityriasis rosea {564,1595} and allergic contact dermatitis {2478}. One case was triggered by interferon alpha {1328}.

Histopathology

MN are characterized by spongiosis,

microvesication, irregular acanthosis, parakeratosis, focal crust and a superficial perivascular infiltrate of lymphocytes and eosinophils {306,676,1595,2478}. There is no histologic regression nor depigmentation {2478}.

There is a naevocellular naevus of junctional, compound or intradermal type with an associated subacute spongiotic dermatitis {1706}. There is variable epidermal acanthosis and a mild to moderate superficial perivascular and interstitial infiltrate of lymphocytes. Usually there are a few eosinophils. There is often mild exocytosis of lymphocytes into the epidermis. There is no regression, although one exception has been recorded (see above). Rarely, dysplastic naevi have been involved {676,1328}.

Immunoprofile

Lymphocytes in MN are predominately CD4 positive {729,1816}. ICAM-1 has been reported to be increased on keratinocytes and endothelium within MN {717}.

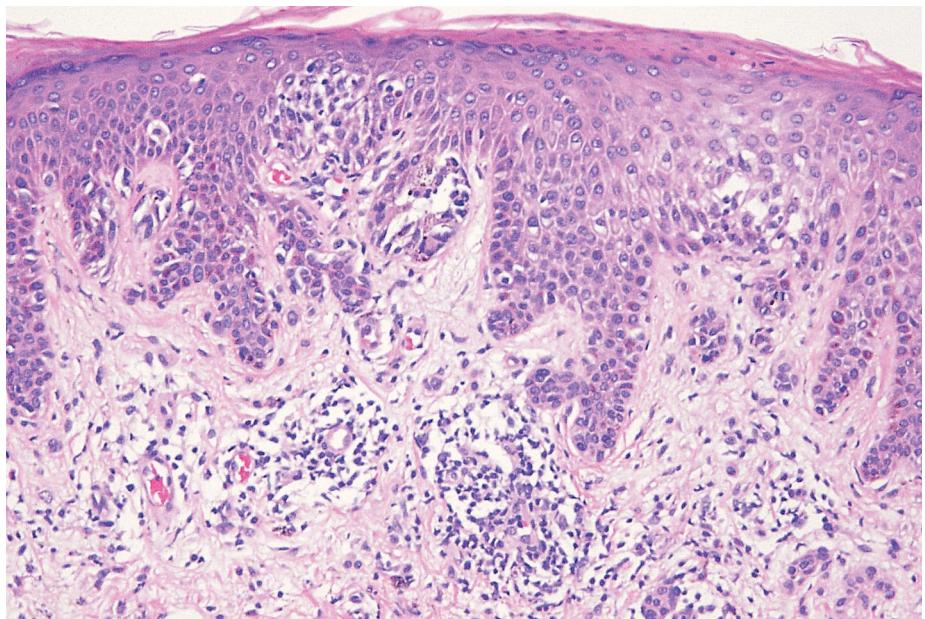


Fig. 2.63 Meyerson naevus. Spongiosis, parakeratosis and irregular acanthosis characterize the epidermis.

Persistent (recurrent) melanocytic naevus

H. Kerl

Definition

Persistent melanocytic naevi are benign compound or intradermal melanocytic naevi that persist (recur) after incomplete excision.

Synonym

Pseudomelanoma {1310}

Clinical features

Persistent melanocytic naevi are the result of incomplete removal after superficial shave technics, dermabrasion or laser treatment {271}. The lesions 'recur' usually after weeks or months after therapy. They are characterized by variably pigmented macules, papules or plaques with irregular borders. A scar from previous surgery can be usually recognized.

Histopathology

Scanning magnification shows commonly above a dermal melanocytic naevus a scar with fibrosis. The intraepidermal changes are characterized by sharp circumscription and confluent nests of melanocytes, that are not equidistant and vary in sizes and shapes. The nests are mostly situated at the dermo-epidermal junction. Melanocytes are also arranged as solitary units at the dermo-epidermal junction and sometimes above it in upper layers of the epidermis {1037}.

Assessment of the original specimen is very important for an accurate diagnosis to ensure that the lesion is really a persistent melanocytic naevus and not a persistent melanoma.

Differential diagnosis

The features within the epidermis and in epithelial structures of adnexa may simulate a melanoma *in situ*.

However, the sharp circumscription of the intraepidermal component, the presence of melanocytes in nests and as single units mostly at the junction and the typical naevoid cells of the preexisting dermal melanocytic naevus beneath a scar are helpful clues to the diagnosis of persistence (recurrence). Furthermore in persistent melanocytic naevi the melanocytic proliferation within the epidermis is confined to the area above the scar.

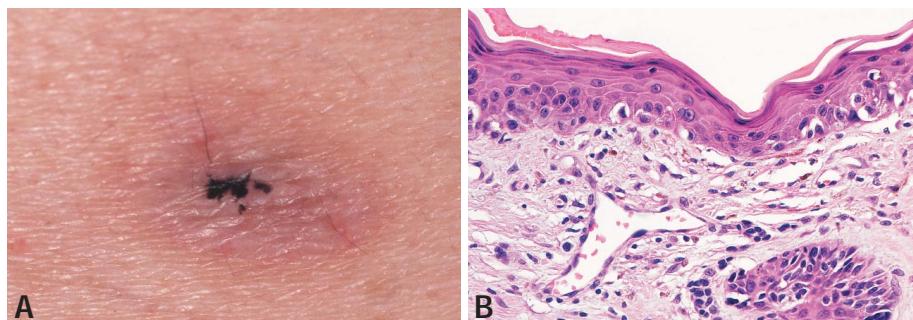


Fig. 2.64 Persistent (recurrent) melanocytic naevus. **A** Small irregular black macule. A scar surrounds the lesion. **B** Persistent (recurrent) melanocytic naevus. Melanocytes are arranged as solitary units along the dermo-epidermal junction and also above it. Atypical nuclei can be observed. Note involvement of the follicle.

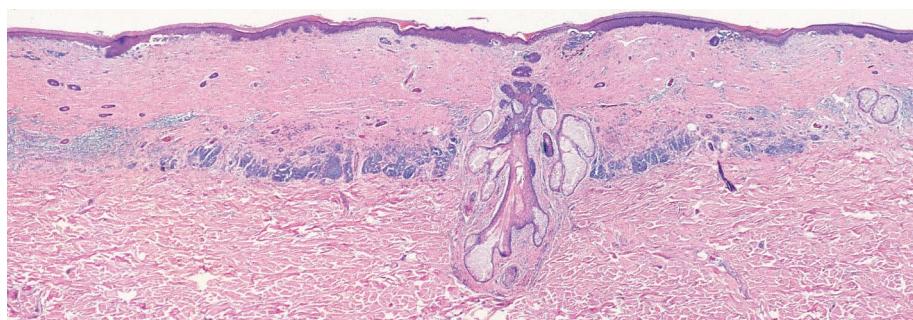


Fig. 2.65 Persistent (recurrent) melanocytic naevus. Trizonal arrangement: 1) Dermal melanocytic naevus. 2) Above the melanocytic naevus a scar revealing fibrosis. 3) Intraepidermal changes with nests of melanocytes with irregular shapes and a tendency to confluence at the dermo-epidermal junction.

Spitz naevus

P.E. LeBoit
B.C. Bastian
W.J. Mooi

Definition

Spitz naevus is a benign proliferation of large spindled, oval or large round (epithelioid) melanocytes that begins in the epidermis, and evolves into compound or intradermal stages. This distinguishes it from some forms of blue naevus, in which the lesion is wholly intra-dermal from the outset.

ICD code

8770/0

Synonyms

Spindle and epithelioid cell naevus, naevus of spindled and/or epithelioid cells, benign juvenile melanoma {2239}. Pigmented spindle cell naevus (Reed) is probably a distinctive variant of Spitz naevus {158,162,2005}.

Epidemiology

Spitz naevus is most common in the first two decades of life {1015,2155}. Accurate population based studies on its prevalence are not available, and are coloured by the caution shown by pathologists in making an outright diagnosis of Spitz naevus in middle aged or older adults, and in making a diagnosis of Spitz naevus in young adults if there are any unusual microscopic features. Spitz naevi are mostly recorded in Caucasian patients. However, they occur in all racial groups, and their occurrence in Asians and Africans may be underestimated.

Localization

Spitz naevi can occur on any areas of the body, although the face of children and thighs of young women are stereotypical associations.

Clinical findings

The earliest recognizable Spitz naevi are about a mm. or so in diameter, and the largest recorded are over 2 cm. While the criterion of size has been popularized in the differential diagnosis between Spitz naevus and melanoma, many Spitz naevi are over 1 cm. in diameter. There appears to be an initial period of rapid growth, followed by stabilization. This is in contrast to melanoma, in which the diameter of the lesion is seldom stable. Most Spitz naevi are lightly pigmented. The classic lesion is a pink to red papule, with an even round border and a domed shape. There is slight scale. The degree of erythema is often such that the clinician considers the diagnosis of haemangioma. However, if one looks at the initial description by Spitz, it is clear that there is considerable heterogeneity, with tan and medium or even dark brown lesions, and verrucous ones also possible {2239}. In dark skinned people, Spitz naevi are usually darker than their normal skin colour. There is usually a uniformity of pigmentation, with the notable exceptions of combined Spitz naevi and Spitz naevi with a halo reaction. Ulceration is practically never present in

Spitz naevi, except in children who traumatize them in play or excoriate them. The presence of an ulcer outside of these settings merits reconsideration as melanoma.

Most Spitz naevi are single lesions. However, groups of Spitz naevi can occur in a single area in agminated Spitz naevus {44,2002}. In such cases, the epidermis in between the papules of Spitz naevus can be normal in appearance, or more commonly is lightly pigmented, resembling a café au lait spot (when it occurs in Caucasian patients). In eruptive Spitz naevus, a patient may have many papules of Spitz naevus appear on a limb or even over the entire integument within a few weeks or months. This obviously distressing situation can be confused with metastasis of melanoma.

Etiology

The cause of Spitz naevus is unknown. Sunburn and biopsy of a single Spitz naevus have been linked to eruptive lesions {597}.

Histopathology

Because the findings of Spitz naevus differ significantly at various stages, we will describe those in detail. Spitz naevus begins as a proliferation of large oval melanocytes at the dermal-epidermal junction. This can occur along a front of only a few mm., and is first recognizable by single, large melanocytes with abundant eosinophilic cytoplasm and large vesicular nuclei. There are often a large number of cells with several nuclei, even in small lesions. Cytoplasm is abundant, and even though the nuclei may be large, they are usually monomorphic. Clefts demarcate the melanocytes from adjacent keratinocytes. Even if single cells are present in number above the junction, they are evenly distributed {355}. As these lesions enlarge, the epidermis above the proliferation thickens, and nests begin to form. The epidermal thickening is largely via hyperplasia of the spinous layer, with squamatization of the basal layer and pointed rete ridges.



Fig. 2.66 Spitz naevus. **A** A sharply circumscribed, dome-shaped lesion, which may be mistaken for haemangioma. **B** Small brown papules form an agminated lesion. This configuration is often alarming.

There is corresponding hypergranulosis and compact hyperkeratosis.

Within the junctional nests of a Spitz naevus are clefts, separating the melanocytes from one another, and from the epidermis. The clefts tend to be prominent over the apices of junctional nests. The nests may appear to be embedded in the epidermis, rather than lying at the bases of rete ridges. The epidermal hyperplasia of a well developed junctional Spitz naevus, and the nests of the naevus itself are both well circumscribed {19,1636, 1638,1769,2479}. By the time that nests are of substantial size, one may encounter Kamino bodies in the epidermis. Kamino bodies are dull pink staining globules, up to the size of several keratinocytes, often with a scalloped border and a periphery in which there are crescent shaped, compressed appearing keratinocytes {1186}. Unlike dyskeratotic cells, which are more brightly eosinophilic, their major ingredient is basement membrane material. They stain with PAS-D and with immunoperoxidase stains for basement membrane components, such as laminin and type IV collagen {2499}. Compound Spitz naevus forms when junctional nests become incorporated into the dermis. In early compound lesions, one may see a dense lymphocytic infiltrate, rather than the sparse perivascular one that most authors describe. The dermal nests tend to be smaller than the junctional ones, and as melanocytes descend into the reticular dermis, one can discern a gradient from large nests to smaller ones, and single cells may predominate at the base. Mitotic figures can be present in the upper part of a compound Spitz naevus, but tend to decrease in number toward the base of the lesion. Maturation of melanocytes is also a correlate, with smaller cells that have less cytoplasm, smaller nuclei, and smaller and less eosinophilic nucleoli all findings that reassure the pathologist. If a Spitz naevus is pigmented, the pigmentation lessens in the lower half of the lesion. Fully formed compound lesions often have a domed surface and a wedge shape. Unlike the case in early compound, or even junctional lesions, lymphocytic infiltrates are usually sparse and perivascular.

Intradermal Spitz naevi preserve the domed/wedge shape noted above. The epidermis is often slightly hyperplastic.

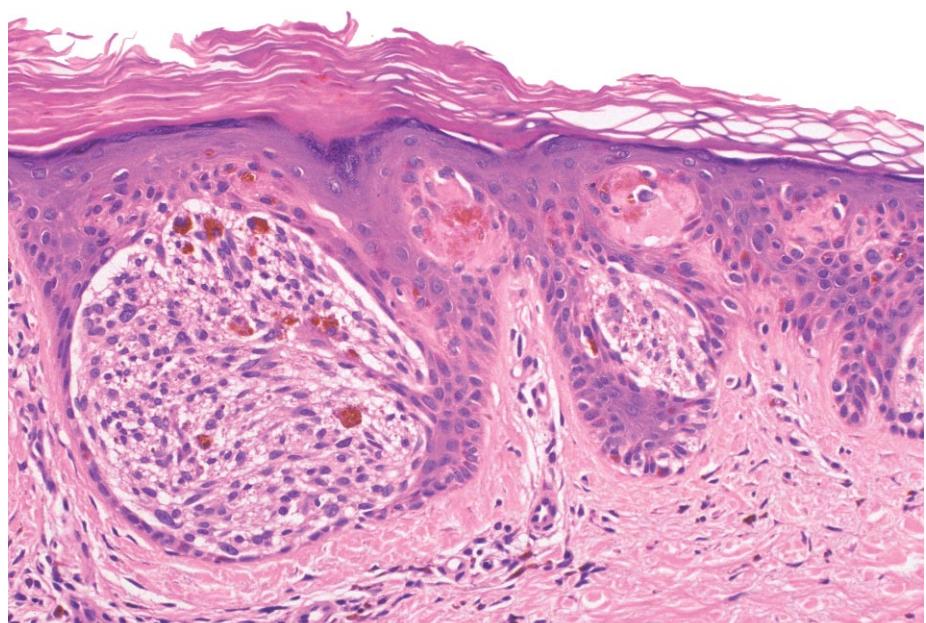


Fig. 2.67 Spitz naevus, junctional type. Clefts separate melanocytes from one another. Several large Kamino bodies are present.

The nests of melanocytes are often present between thickened collagen bundles in the lower part of the lesion. When this is prominent, some apply the term desmoplastic Spitz naevus. Unlike the case in desmoplastic melanoma, there are no markedly elongated fascicles of cells. If the proliferation abuts the subcutis, one may see lymphoid nodules. For both compound and intradermal lesions, an important finding is that the nests at each level of the lesion should be similar in size, with the cells similar in overall and nuclear size and in pigmentation.

There are many important variants of Spitz naevus. On acral skin, one may see many single melanocytes scattered above the junction. A halo reaction may be present, sometimes accompanied by a clinical halo. The lymphocytes are evenly dispersed throughout the lesion, and some may be apposed to pyknotic melanocytes. The stroma may be sclerotic (hyalinizing Spitz naevus) or highly vascular {2293}. Some nests may have an empty appearing centre (tubular Spitz naevus) {2228}. In combined Spitz naevus, other populations of melanocytes (e.g. small round, bipolar-dendritic, balloon, etc.) may be present {1961}. This is one of the most difficult variants to deal with, as the large cells may not mature and dense lymphocytic infiltrates (up to a halo reaction) may be present {972}.

Another difficult variant is persistent Spitz naevus. The great majority of Spitz naevi do not recur at the biopsy site if the lesion seems to be removed clinically, but goes to a margin. Those that do can show suprabasal scatter of melanocytes (as in other recurrent naevi), a compound Spitz naevus over a scar, a nodule next to a scar, or a picture resembling desmoplastic Spitz naevus {969}.

Lastly, there is a "grey zone" of lesions in which there are many findings of Spitz naevus, but the diagnosis is less certain. For lesions in which the diagnosis is Spitz naevus, but there are a few findings that are unusual, many use the term "atypical Spitz naevus", although this may be attacked on semantic and functional grounds. If one is not sure of the diagnosis, a descriptive term, such as "proliferation of large melanocytes involving the epidermis and dermis" is preferable. This should be accompanied by a note or comment explaining the difficulties, differential diagnosis, including if appropriate, microstaging parameters that would be appropriate if the lesion were regarded as melanoma, and advising reasonable management. The role, if any for sentinel lymph node biopsy in difficult cases is currently considered controversial {1444,2286}.

Among these "grey-zone" lesions is an emerging, relatively homogeneous group of lesions with a distinctive pattern, often

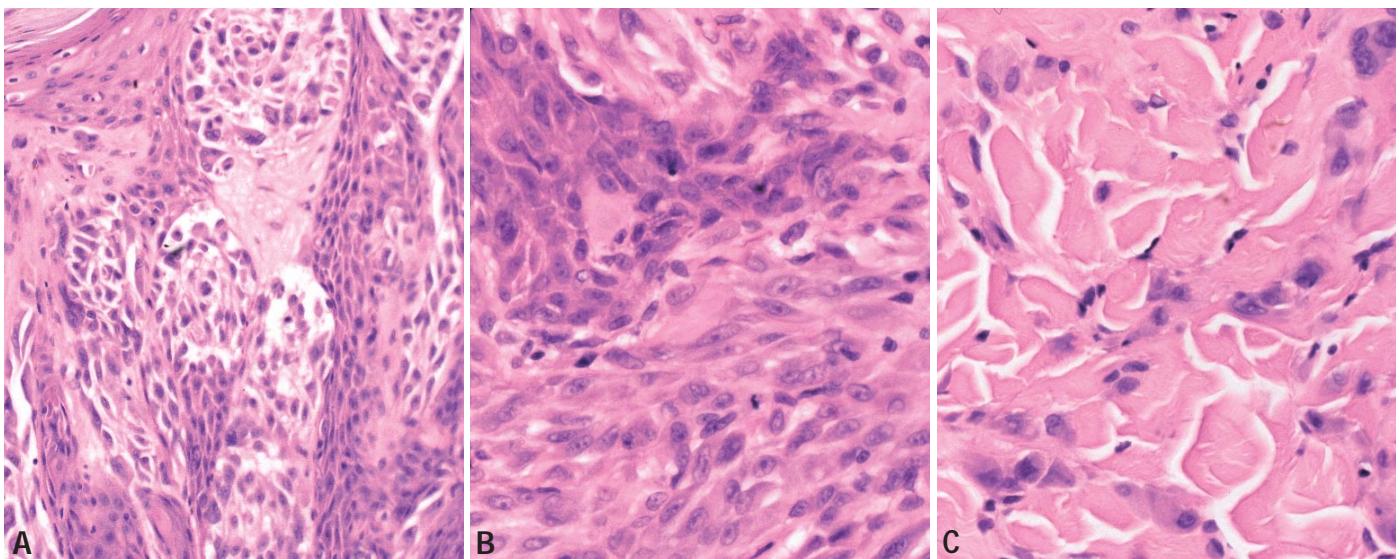


Fig. 2.68 Spitz naevus, compound type. **A** Junctional portion of Spitz naevus with epidermal hyperplasia. **B** The upper part of the lesion is highly cellular. **C** Toward the base single large oval melanocytes are interspersed between thick collagen bundles.

found from early childhood to young adulthood in which there are some features of Spitz naevus and others of melanoma. Common denominators include a vertical orientation, extension into the subcutis with no diminution in cellularity and a blunt, multinodular interface, ulceration, a plasmacytic infiltrate and deep mitotic figures. Such cases have been described as "malignant Spitz naevus" and also simply regarded as melanomas [2205]. In the initial study of "malignant Spitz naevus" there were 3/32 lesions in which palpable lymph node enlargement had occurred, and another 3 in which lymph node involvement was detected on elective dissection. Very similar lesions have been described as melanomas in children [1632]. Follow up

data has been presented to the effect that systemic metastasis may not occur, or may be much less frequent than in adults with conventional melanomas matched for thickness. Clearly, further studies are needed to determine if these lesions are fundamentally Spitz naevus, melanoma, or neither.

Somatic genetics

While most cells in most Spitz naevi seem to be diploid, there are a proportion of polyploid cells, at least in the upper part of lesions as judged by image analysis cytometry [1386]. True aneuploidy may be uncommon, as evaluated by flow cytometry [2439]. In an analysis using comparative genomic hybridization the majority of Spitz naevi did not

show chromosomal aberrations, whereas 25% showed an isolated gain of chromosome 11p [174]. Preliminary studies indicate that the increased copy number of chromosome 11p is due to the formation of an isochromosome 11p [1494]. About 70% of the Spitz naevi with increased copies of chromosome 11p have mutations in the HRAS gene which maps to this location [172]. HRAS mutations have been found only in a minority of cases (< 10%) with normal copy number of chromosome 11p. Preliminary studies indicate that mutations in BRAF occur infrequently in Spitz naevi.

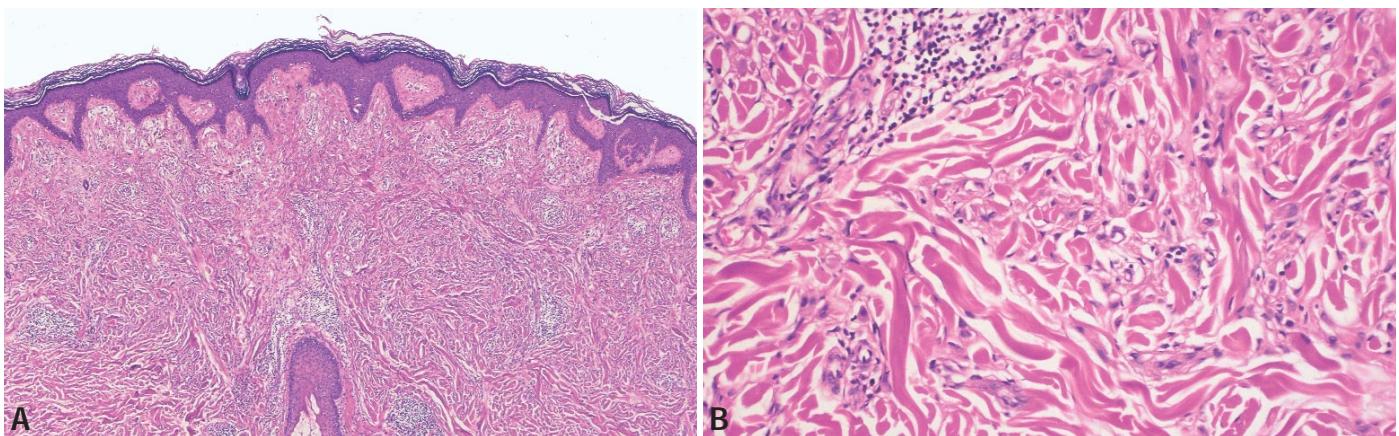


Fig. 2.69 Spitz naevus, desmoplastic type. **A** Rete ridges are uniformly elongated but jagged above the upper part of the lesion. **B** Thin spindle cells are present between collagen bundles.

Pigmented spindle cell naevus (Reed)

L. Cerroni

Definition

Pigmented spindle cell naevus (Reed) is a benign melanocytic naevus showing dark pigmentation clinically, and a proliferation of spindled melanocytes histopathologically.

ICD-O code 8770/0

Synonyms and annotation

This melanocytic naevus has been named eponymously after Richard Reed, who described it in 1975 (1909). It has also been referred to as Reed naevus or Reed tumour. While some authors regard it as a subtype of the Spitz naevus, pigmented spindle cell naevus (Reed) presents with peculiar clinical and histopathologic features, allowing a reproducible diagnosis and classification to be made.

Epidemiology

Pigmented spindle cell naevus (Reed) is a melanocytic tumour found in children, adults, and, rarely, older patients, with a peak in the third decade. There is a predominance for females.

Clinical features

The patients present with a darkly, homogenously pigmented, flat or slightly dome-shaped, sharply circumscribed papule or plaque located usually on the limbs, especially the thigh (158,2005, 2068). Less common locations are the trunk and the head and neck region. The lesions are usually of recent onset and smaller than 1 cm. Surface skin microscopy (dermatoscopy, dermoscopy) reveals typically a "starburst" pattern (characterized by the presence of pigmented streaks disposed in a radial arrangement at the edge of the lesion). A clinical misdiagnosis of malignant melanoma is not infrequent, due to the dark pigmentation and recent onset of the lesions.

Histopathology

Histologically, the tumours are symmetrical and show a sharp lateral circum-

scription. Spindled, pigmented melanocytes arranged in vertical nests at the dermo-epidermal junction predominate (158,2005,2068). A few, and in some instances many, melanocytes may be seen above the dermal/epidermal junction, as well as confluence of the nests. The proliferation of melanocytes may be confined to the epidermis, or may extend into the papillary dermis. Occasional mitoses may be found. Cytomorphologically there is a uniform proliferation of elongated, fusiform melanocytes, usually without atypical features. The nuclei are relatively small, with uniform, delicate chromatin. Epithelioid melanocytes are admixed in a minority of cases. Commonly, the epidermis is slightly hyperplastic and shows marked hyperpigmentation of the basal keratinocytes. Intraepidermal eosinophilic globules (so-called "Kamino bodies") can be observed in about half of the cases. An inflammatory infiltrate composed of lymphocytes and histiocytes with many

melanophages is found within the papillary dermis. A subset of cases shows a considerable overlap with Spitz naevi. Cases with some cytological atypia have been termed "atypical pigmented spindle cell naevus - pigmented spindle cell naevus with architectural and/or cytologic atypia", and may represent a source of problem in differential diagnosis from malignant melanoma (158). A variant described as "plexiform pigmented spindle cell naevus" probably represents a pigmented spindle cells naevus involving the reticular dermis (158).

Prognosis and predictive factors

Pigmented spindle cell naevus (Reed) is a benign melanocytic proliferation with no potential for distant metastases. Local recurrences may be observed in tumours that were incompletely excised.

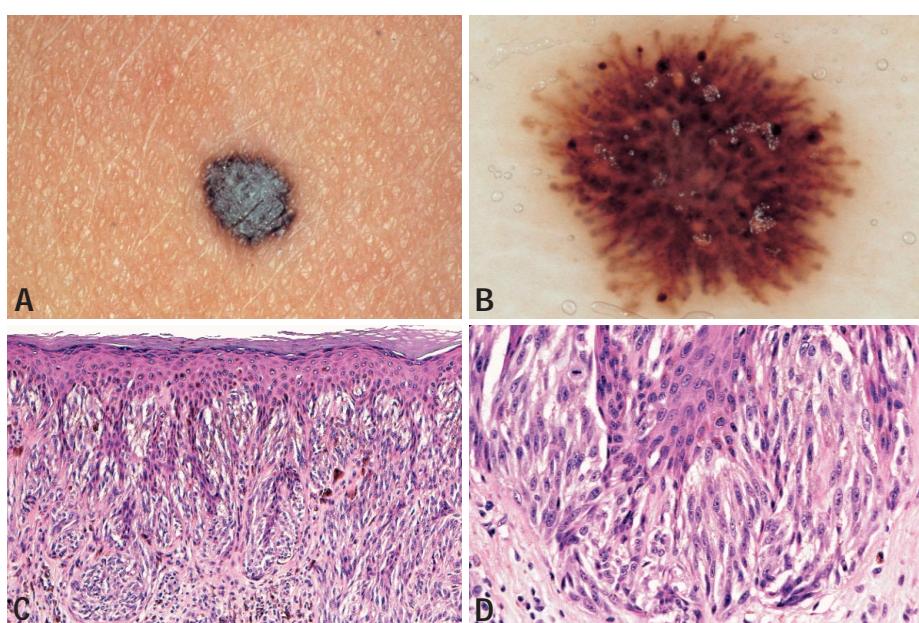


Fig. 2.70 Pigmented spindle cell naevus (Reed). **A** Small, flat, dark papule. **B** Dermoscopy shows the characteristic "starburst" pattern. **C** Elongated nests at the dermoepidermal junction and in the papillary dermis; note pigmentation of the basal keratinocytes and melanocytes, and the presence of numerous melanophages in the papillary dermis. **D** Fusiform melanocytes predominate. Note the mitosis in the upper left corner.

Halo naevus

D. E Elder
X. Xu

Definition

A halo naevus presents as a small circumscribed symmetrical, usually papular pigmented lesion with the appearance of a common benign compound naevus, surrounded by a symmetrical area of depigmentation, representing the "halo" [2469]. The lesion is defined histologically by the presence of a brisk lymphocytic infiltrate among dermal naevus cells, and by loss of pigment in the epidermis adjacent to the naevus. Some naevi with a lymphocytic response of the type seen in halo naevi do not have an obvious clinical or histologic depigmented halo [948].

ICD-O code 8723/0

Synonyms

Sutton naevus; leukoderma acquisitum centrifugum [2297].

Clinical features

Halo naevi often present during the summer, perhaps because the halo contrasts better with tanned skin. They are most common in teenagers and young adults. In these cases, they are sometimes associated with dysplastic naevi, and are sometimes multiple. Less often, a solitary halo lesion develops in an older adult, and in this circumstance the possibility of melanoma should be ruled out histologically, especially if the central pigmented lesion is clinically atypical or if the halo is eccentric or asymmetrical in contour. Serial follow-up of halo naevi demonstrates a characteristic time sequence, beginning with the appearance of the

halo around a compound naevus, followed by fading and disappearance of the naevus. The halo then gradually repigments over a year or two, returning to the appearance of normal skin. During this period, especially in teenagers, other similar lesions may develop.

Studies in patients with halo naevi have demonstrated circulating antibodies that are reactive with neoplastic melanocytes including melanoma cells, and the infiltrating cells have been shown to be mainly T lymphocytes [2090]. Antigen-presenting cells and CD8+ T cells have been identified in the inflammatory infiltrates of halo naevi, implicating cytotoxic mechanisms in destruction of naevus cells [2581]. Affected individuals also show activated lymphocytes in their peripheral blood [148] as well as T cell clonal expansion [1670] and anti-naevic IgM antibody production [2359]. These findings are consistent with the idea that halo naevi represent immunologically mediated rejection of a naevus. The halo develops outside the naevus proper, suggesting that there may be a cross-reaction with a "field" of melanocytes that surrounded the naevus prior to the onset of the intense inflammation in the dermal component.

Histopathology

An early halo naevus presents as a small circumscribed lesion, less than 4 mm in diameter as a rule, composed of naevus cells located in the papillary dermis and usually also in the epidermis. The lesion is symmetrical, and is composed of cells that are uniform from side to side and

tend to become smaller (i.e., more "mature") from the top to the bottom of the lesion. The epidermis may be hyperkeratotic with follicular plugging [2469]. The feature that distinguishes a halo naevus from a banal naevus is the presence of a striking dense lymphocytic infiltrate, an appearance that may arouse a suspicion of melanoma in some cases. The lymphocytes extend among the lesional naevus cells, tending to obscure their underlying nested pattern in some cases. Melanin-laden histiocytes and mast cells can be present as well as lymphocytes [2090]. Occasional halo naevi contain a few giant cells or there may be a frankly granulomatous response. Over the ensuing weeks or months, the dermal naevus cells disappear and then the histologic differential diagnosis may include lichenoid inflammatory dermatoses. Over a period of a year or two, the inflammatory cells disappear and histologic examination of the site of a completely resolved halo naevus may disclose essentially normal skin, with little or no evidence of scarring or residual pigment [2469]. In most halo naevi, there is little or no readily observable melanocytic abnormality in the epidermis at the "shoulder" of the lesion beyond the lateral border of the dermal component, even though it is in this region that the striking clinical halo is located. However, DOPA stains for tyrosinase and immunohistochemical (e.g. Melan-A) or argentaffin stains for melanocytes reveal greatly reduced numbers of them in the area of the halo compared to the surrounding skin [2469].



Fig. 2.71 Halo naevus. There are two small naevi surrounded by rims of depigmentation.

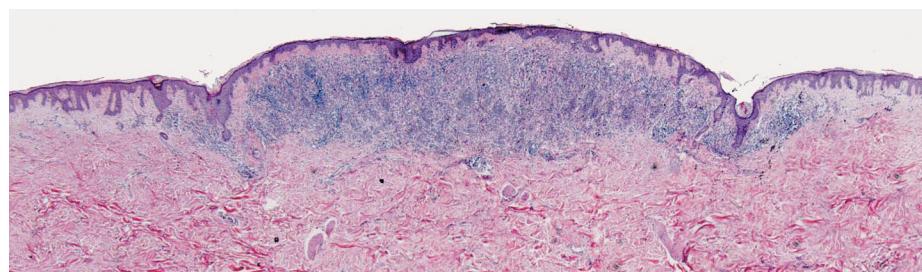


Fig. 2.72 Halo naevus. There is an apparently well circumscribed lesion which at first glance may be mistaken for a lymphocytic infiltrate.

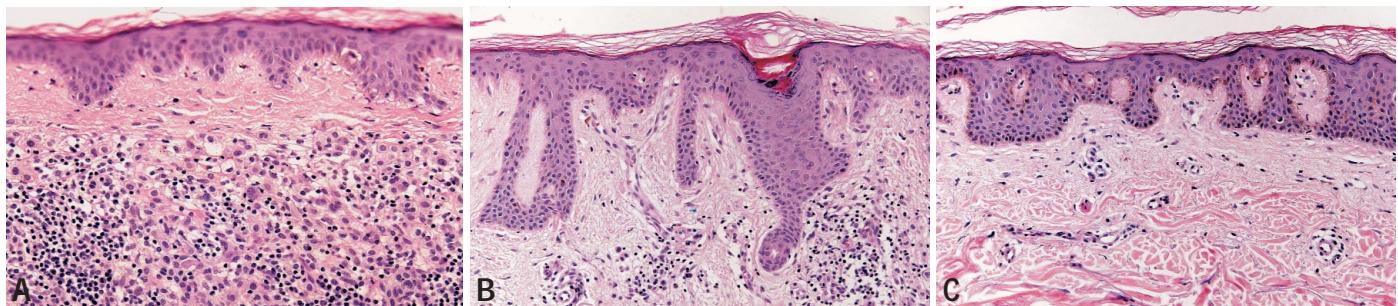


Fig. 2.73 Halo naevus. **A** Infiltrating lymphocytes are intimately admixed with naevus cells, which will lead to apoptosis and ultimate disappearance of the naevus cells. In later examples, naevus cells are more inconspicuous than they are in this field. **B** Extending 1 to 2 mm beyond the lateral border of the dermal naevus component, the papillary dermis is widened with slight fibroplasia, there is a patchy lymphocytic infiltrate, and there is absence of pigment and of melanocytes in the overlying epidermis. This region constitutes the clinical halo. **C** Normal skin adjacent to the halo shows a normal papillary dermis, normal melanin pigment in basal keratinocytes, and the presence of melanocytes, which can be demonstrated if desired with a Melan-A stain.

The lesional cells in most halo naevi are unremarkable dermal naevus cells of the large pigmented (type A) or small non-pigmented (type B) cytology. Pigment is located in naevus cells and in melanophages superficially, and is usually coarse in texture. In some lesions, the dermal cells have nuclei that are larger than is usual in common naevi, and sometimes there is hyperchromatism and a degree of pleomorphism, with or without nucleoli, representing cytologic atypia which is present in about 50% of halo naevi and is usually mild or at worst moderate in degree {1640}. This cytologic atypia may represent a form of "inflammatory" or reactive atypia. Mitotic figures are completely absent in most lesions. However, a few lesions judged to be benign halo naevi have shown one or two mitotic figures {1909}. Such a finding should provoke careful examination of the lesion to rule out melanoma, with deeper sections and embedding of any residual gross tissue. Findings suggestive of melanoma in a lesion simulating a halo naevus include the presence of a separate population of cells with an expansile pattern of growth, severe uniform cytologic atypia, and/or the presence of frequent mitoses, ulceration or necrosis. The halo phenomenon may occasionally involve other types of naevi, including dysplastic naevi {2370}, Spitz naevi {972} and congenital naevi {2359}, as well as melanomas {2090}, and therefore careful inspection of the underlying lesional architecture and cytology in multiple sections may be required for definitive classification.

The halo region at the periphery of the dermal component of the lesion may contain a few lymphocytes at the dermal-epidermal interface, with a reduction or

an absence of identifiable melanocytes. In comparison with adjacent normal epidermis, pigment may be visibly reduced, and this contrast can be enhanced with a melanin stain. In most lesions, there is no intra-epidermal melanocytic proliferation adjacent to the dermal component, but in a few lesions an adjacent component of melanocytic dysplasia may be observed. If an *in situ* or microinvasive ("radial growth phase") component diagnostic of melanoma is present adjacent to a dermal lesion simulating halo naevus, the entire lesion is most likely to represent melanoma.

Differential diagnosis

The distinction from common acquired or most other types of naevi is usually easy because of the dense lymphocytic infiltrate. The most important differential diagnosis is with melanoma. Compared to nodular melanoma or to the tumourigenic (vertical growth phase) component of superficial spreading melanoma, a halo naevus is usually smaller (the central naevus is usually less than 4 mm in diameter, while most melanomas are larger than 6 mm, though these values are by no means absolute). However, we have rarely observed small melanomas with naevoid characteristics but with diffuse cellular atypia combined with mitotic activity in which diffuse lymphoid infiltration was a prominent pattern. When pigment is present in a halo naevus, it is usually in the form of coarsely divided granules as is the case in most benign naevi, and if there is a junctional component, its character is that of a naevus rather than a melanoma. Thus, there is usually a discontinuous rather than continuous proliferation of predominantly nested rather than predominantly single

naevus cells, and there is little or no tendency to single-cell upward ("pagetoid") intraepidermal spread of the junctional cells.

Some halo naevi may be difficult to distinguish from dysplastic naevi that have an unusually brisk lymphocytic infiltrate. Indeed, not only do halo naevi appear to be common in patients with dysplastic naevi but also a halo response may be seen, clinically and histologically, in dysplastic naevi themselves. If the characteristic patterns of dysplasia are seen at the "shoulder" of the compound portion of a lesion whose other features are consistent with a halo naevus, the diagnosis of dysplastic naevus with halo reaction can be made. Especially if there is a history of other atypical naevi and/or a personal or family history of melanoma, surveillance may be warranted for such individuals.

When naevus cells are inconspicuous among a dense infiltrate of lymphocytes, inflammatory dermatoses such as lichenoid keratoses may be simulated {844}. In these circumstances, an S-100, Melan-A or HMB45 stain may reveal the hidden naevus cells. Care must be taken in interpretation, since histiocytes may weakly express S-100, whereas activated melanocytes and melanoma cells may express HMB45. Finally, there are lesions that have an infiltrative lymphocytic response similar to that of a halo naevus but there is no clinical halo. These lesions may be signed out descriptively as "compound (or dermal) naevi with halo reaction" {1909}. Conversely, some naevi with a clinical halo may lack a lymphocytic infiltrate of the type seen in halo naevi {812}. These may be termed "non-inflammatory halo naevi".



CHAPTER 3

Appendageal Tumours

Appendageal tumours are neoplasms whose differentiation is toward one or more of the adnexal structures of the skin. While mesenchymal tumours of various kinds are technically in this category, conventionally, the term refers to those with origin from, or differentiation toward epithelial adnexal neoplasms. Depending on their presumed origin, adnexal tumours are categorized into those with apocrine and eccrine, follicular and sebaceous differentiation. For most of these tumour types there are benign and malignant counterparts. The histopathological criteria for prognosis of biological behaviour are well established.

The WHO Working Group was aware of recent evidence indicating that basal cell carcinoma (BCC) should be included under the adnexal neoplasms under the term trichoblastic carcinoma. The inclusion of BCC in the chapter on keratinocytic tumours reflects the traditional categorization but does not indicate that the Working Group denies their adnexal origin.

WHO histological classification of appendageal tumours

Tumours with apocrine and eccrine differentiation			
Malignant tumours			
Tubular carcinoma	8211/3	Tubular adenoma	8211/0
Microcystic adnexal carcinoma	8407/3	Tubular papillary adenoma	8263/0
Porocarcinoma	8409/3	Syringocystadenoma papilliferum	8406/0
Spiradenocarcinoma	8403/3	Hidradenoma papilliferum	8405/0
Malignant mixed tumour	8940/3	Mixed tumour (chondroid syringoma)	8940/0
Hidradenocarcinoma	8400/3		
Mucinous carcinoma	8480/3	Tumours with follicular differentiation	
Digital papillary carcinoma	8408/3	Malignant tumours	
Adenoid cystic carcinoma	8200/3	Pilomatrical carcinoma	8110/3
Apocrine carcinoma	8401/3	Proliferating tricholemmal tumour	8103/1
Paget disease of breast	8540/3	Benign tumours	
Extramammary Paget disease	8542/3	Trichoblastoma	8100/0
Benign tumours		Pilomatricoma	8110/0
Hidrocystoma	8404/0	Tricholemmoma	8102/0
Syringoma	8407/0	Multiple tricholemmomas	8102/0
Poroma	8409/0	Trichofolliculoma	8101/0
Syringofibroadenoma	8392/0	Fibrofolliculoma / trichodiscoma	8391/0
Hidradenoma	8402/0		
Spiradenoma	8403/0	Tumours with sebaceous differentiation	
Cylindroma	8200/0	Sebaceous carcinoma	8410/3
		Sebaceous adenoma	8410/0
		Sebaceoma	8410/0
		Cystic sebaceous tumour	8410/0

¹ Morphology code of the International Classification of Diseases for Oncology (ICD-O) {786} and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

TNM classification of skin appendageal carcinomas

TNM classification^{1,2}

T – Primary tumour

- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Tis Carcinoma in situ

- T1 Tumour 2 cm or less in greatest dimension
- T2 Tumour more than 2 cm but no more than 5 cm in greatest dimension
- T3 Tumour more than 5 cm in greatest dimension
- T4 Tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle, or bone

Note: In the case of multiple simultaneous tumours, the tumour with the highest T category is classified and the number of separate tumours is indicated in parentheses, e.g., T2(5).

N – Regional lymph nodes

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

M – Distant metastasis

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

¹ (894,2219).

² A help desk for specific questions about the TNM classification is available at www.uicc.org/index.php?id=508.

Appendageal skin tumours: Introduction

P.E. LeBoit

Epidemiology

Most studies on adnexal neoplasms have taken place in western countries with Caucasian populations. Benign adnexal neoplasms tend to occur in younger patients than carcinomas do. Adnexal carcinomas vary from those in which actinic damage is the norm, such as the common basal cell carcinoma (which differentiates toward follicular germ) to those that seem to have little relationship to sun exposure (such as spiradenocarcinoma).

Etiology

No known triggering event is evident in the vast majority of adnexal neoplasms. There are some cases in which the cause is an autosomal dominant mutation in a tumour suppressor gene.

Clinical signs and symptoms

Most benign adnexal neoplasms are smooth surfaced, symmetrical papules or nodules the same colour as the patient's skin or darker. Some, such as sebaceous adenoma and syringocystadenoma papilliferum, have eroded surfaces, but in general, ulceration is a sign of malignancy. Most adnexal carcinomas are irregularly shaped plaques, sometimes ulcerated.

Tumour spread and staging

In general, low-grade carcinomas seldom metastasize; for some, e.g. microcystic adnexal carcinoma, metastasis has not yet been recorded.

A haematogenous pattern seems the rule for a few carcinomas, such as adenoid cystic carcinoma, but most can spread via either lymphatic or haematogenous dissemination. Carcinomas with eccrine differentiation have a propensity to metastasize to the skin.

Sentinel node biopsy

While a few sentinel node biopsies have been performed for adnexal carcinomas, not enough data have been collected to validate this procedure {274}.

Pathology

Diagnostic criteria of adnexal carcinomas

- > Irregular borders, asymmetry at scanning magnification
- > Horizontal orientation
- > Markedly irregular aggregates of epithelial cells
- > Necrosis en masse
- > Infiltration of the dermis or subcutis without the interposition of densely fibrotic stroma
- > Mitoses frequent, can be atypical
- > Stroma irregular, often scant, sometimes myxoid
- > Nuclei pleomorphic. Some neoplasms with monomorphic nuclei, e.g. microcystic adnexal carcinoma, are exceptions.

Diagnostic criteria of benign epithelial adnexal neoplasms {28}:

- > Symmetric and smooth bordered at scanning magnification
- > Vertically oriented with respect to the surface of the skin
- > Aggregates of epithelial cells uniform
- > No necrosis en masse (with the exception of poroma)
- > Mitoses variable, but typical
- > Densely fibrotic stroma, rich in fibrocytes in the case of trichogenic
- > Neoplasms forming a blunt, rounded interface with the native dermis. An exception is poroma, which has vascular, myxoid stroma.
- > Nuclei monomorphic; rare exceptions include atypical squamous nuclei in poromas.

Immunoprofile

Most adnexal neoplasms are accompanied by variably dense infiltrates of T-cells. These are intimately admixed with the neoplasm (spiradenoma, cutaneous lymphadenoma, adamantinoid trichoblastoma) and lymphoepithelioma-like carcinoma among malignancies are examples. Syringocystadenoma papilliferum has a complement of plasma cells, many of which secrete IgA.

A complex array of keratins are expressed in adnexal neoplasms. Those with follicular germinative differentiation express cytokeratins seen in follicular germs in embryonic and neonatal life. Those with ductular differentiation have lumens that stain for carcinoembryonic antigen (CEA), and express simple epithelial keratins. Sebaceous differentiation is characterized by expression of epithelial membrane antigen in a microvacuolar pattern.

Precursor lesions

Benign adnexal neoplasms of various sorts can arise in naevus sebaceous, a malformation involving the epidermis, dermis and adnexae. Otherwise, most benign adnexal neoplasms arise de novo. This is also the case for malignant adnexal neoplasms. Rare apocrine carcinomas arise in naevus sebaceous. Rarely, porocarcinoma, spiradenocarcinoma or hidradenocarcinoma may arise in a pre-existent poroma, spiradenoma, or hidradenoma, respectively. The vast majority of basal cell carcinomas arises de novo. Rarely, basal cell carcinomas occur in pre-existent trichoblastomas.

Histogenesis

The origin of most adnexal neoplasms is unknown. It is better to speak of their differentiation. The most clear-cut evidence of differentiation is in follicular neoplasms, where such signs as follicular papillae and germs (as in the trichoblastomas) or trichohyaline granules (as are focally found in pilomatricoma and in matrical carcinomas) can occur. Clear-cut apocrine differentiation, in which decapitation secretion of columnar cells that have brightly eosinophilic cytoplasmic granules is also specific. However, there is a marked similarity between eccrine and apocrine ducts. Also, the columnar cells of eccrine secretory coils can resemble poorly differentiated apocrine secretory cells. Hence, neoplasms with ductular differentiation often have debatable histogenesis {1543}. To some

extent, the differentiation of neoplasms probably reflects their distribution {1544}.

Genetics

Approximately one third of sweat gland carcinomas contain TP53 mutations {239A}. Otherwise, little is known about the genetics of most epithelial neoplasms, with the exception of those that occur in multiplicity as part of autosomal dominant syndromes (see Chapter 7). The mutations found in the germlines of patients with syndromes and multiple tumour suppressor genes tend to be the same as occur as somatic mutations in sporadic adnexal neoplasms. Some trichoblastomas have mutations in the PTCH gene, as found in naevoid basal cell carcinoma syndrome (Gorlin-Goltz

syndrome). Trichilemmomas have mutations in PTEN, the same gene as involved in Cowden syndrome. Mutations in DNA repair genes occur in the sebaceous neoplasms of the Muir-Torre syndrome and, to a lesser degree, in sporadic sebaceous neoplasms.

Prognosis and predictive factors

In general, adnexal carcinomas of low cytologic grade have a good prognosis, especially if the lesion is relatively small and completely excised. Those of high cytologic grade may metastasize widely. For many adnexal carcinomas, there are simply insufficient numbers of reported cases to develop much of an idea regarding their prognosis.

Malignant tumours with apocrine and eccrine differentiation

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H. Kutzner
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D. J. Santa Cruz
A.H. Mehregan

Y. M. Mengesha
S. Kohler
Z B. Argenyi
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Tubular carcinoma

Definition

Tubular carcinoma is the malignant counterpart of tubular adenoma, featuring apocrine differentiation with prominent tubular structures.

ICD-O code

8211/3

Historical annotation

Probably the first reported examples of tubular carcinoma were included in the series of carcinomas of sweat glands published by Stout and Cooley in 1951 {2274}.

Epidemiology

Tubular carcinoma seems to be slightly more frequent in women. Most patients are middle-aged adults.

Localization

The axilla is the most common location, with rare bilateral involvement. Other sites rich in apocrine glands may also be involved {114,127,1705,1785,2274,2397, 2460,2569}.

Clinical features

Tubular carcinoma usually presents as a firm erythematous nodule, which may be ulcerated or adherent to deeper tissues. Tubular carcinomas may arise in naevus sebaceous {644}.

Histopathology

At scanning magnification, the neoplasm is asymmetric, poorly circumscribed, and infiltrative with prominent and crowded tubular and ductal structures. The lesion often involves the full-thickness of the dermis and it may extend to the subcutaneous tissue. Neoplastic structures show marked variation in size and shape, but, in general, the size of the tubules tends to decrease from superficial to deeper areas. The more superficial larger tubules may show luminal papillations. At higher magnification, epithelial cells lining the tubules show abundant eosinophilic or granular cytoplasm and pleomorphic nuclei, some of them in mitosis. Often the cytoplasm of these cells exhibits signs of decapitation secretion. Lumina are often filled with homogenous eosinophilic material, foamy histiocytes and necrotic debris.

Examples of tubular carcinoma may also exhibit focally solid areas with a combination of cribriform or adenoid cystic patterns as additional morphologic expressions. Areas of necrosis en masse are also frequent, but in contrast with adenoid cystic carcinoma, tubular carcinoma shows no deposits of basement membrane material within the aggregations of neoplastic cells and perineural involvement is usually absent. The stroma is sparse.

Before a diagnosis of primary tubular

carcinoma of the skin is established, the possibility of cutaneous metastasis from a visceral tubular carcinoma should be ruled out.

Immunoprofile

Tubular carcinoma shows immunoreactivity with low molecular weight cytokeratins and the luminal cells express EMA and GCDGP-15. Expression of CEA is variable {1785,2569}.

Histogenesis

The presence of decapitation secretion and continuity between neoplastic tubules and follicular infundibula are signs of apocrine differentiation. This is further supported by enzyme histochemistry.

Prognosis and predictive factors

Tubular carcinoma of the skin behaves in a highly malignant fashion. Of the 44 examples reported in the literature, neoplasms from 21 patients metastasized and at least 9 patients died as a result of widespread metastatic disease {1705, 1785,2397,2569}.

Microcystic adnexal carcinoma

Definition

Microcystic adnexal carcinoma {861} is a locally infiltrative and destructive low-



Fig. 3.01 Tubular carcinoma on the retroauricular left region.

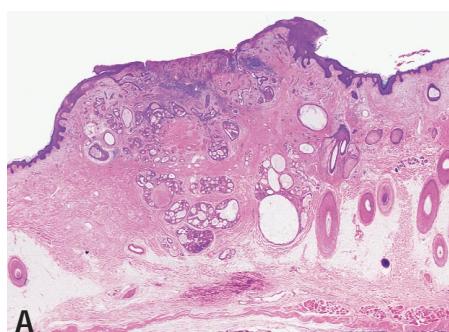
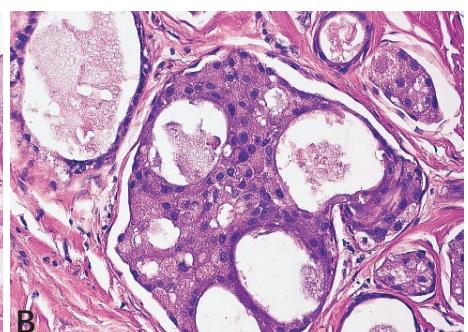


Fig. 3.02 Tubular carcinoma. **A** The neoplasm involves the full-thickness of the dermis and extends into subcutaneous tissue. The stroma is sparse and the epithelium predominates over the stroma. **B** Some neoplastic aggregations of this tubular carcinoma exhibit focally an adenoid cystic pattern.



grade adenocarcinoma differentiated toward ducts. It has little capacity to metastasize.

ICD-O code

8407/3

Synonyms

Sclerosing sweat duct carcinoma {541}, eccrine epithelioma, syringomatous carcinoma.

Clinical features

The carcinoma occurs on the face of adults, more commonly in women. It affects commonly the face {469} and lip, uncommonly other locations, and grows slowly over a period of months to years. It is similar usually to a depressed scar and rarely causes ulceration.

Histopathology

The classical pattern is that of small, superficial, solid to cystic structures that are similar to small infundibular cysts and ducts. In the middle depth, the lesion is composed completely of small ducts, often in very subtle patterns, frequently with involvement of nerves and perineurial spaces. In the deepest areas, "Indian" filing and sclerosis are common findings. Thus, there is a sense that the lesion is stratified from superficial (tubules and

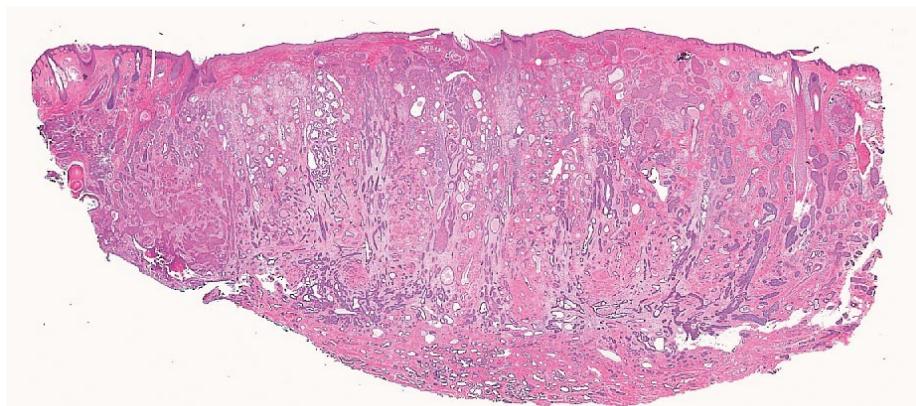


Fig. 3.03 Microcystic adnexal carcinoma. Scanning magnification of microcystic adnexal carcinoma illustrates the zonal effect with solid nests and cysts superficially with complex glands deep.

cysts) to deep (epithelial cords and sclerosis).

Unusual examples contain sebocytic zones {1862}, and others contain areas similar to follicular sheath, thus suggesting differentiation toward the folliculo-sebaceous-apocrine unit. In other cases, the lesions are exclusively ductal, causing some authors to designate them as "syringomatous carcinoma" or "sclerosing sweat duct carcinoma" and suggesting that these examples could be derived from eccrine ducts. Some MACs have solid poromatous or clear cell cytol-

ogy. Cytologically, the lesions are well differentiated, lacking nuclear pleomorphism or mitotic figures. In fact, the finding of nuclear pleomorphism should cause one to reconsider whether the diagnosis of microcystic adnexal carcinoma is correct.

Immunoprofile

There is cytoplasmic staining with AE1/AE3, CK7, and bcl-2. EMA and Ber-EP4 stain in a membranous pattern around ductal cells near the lumen. Alpha SMA and S100 protein stain the

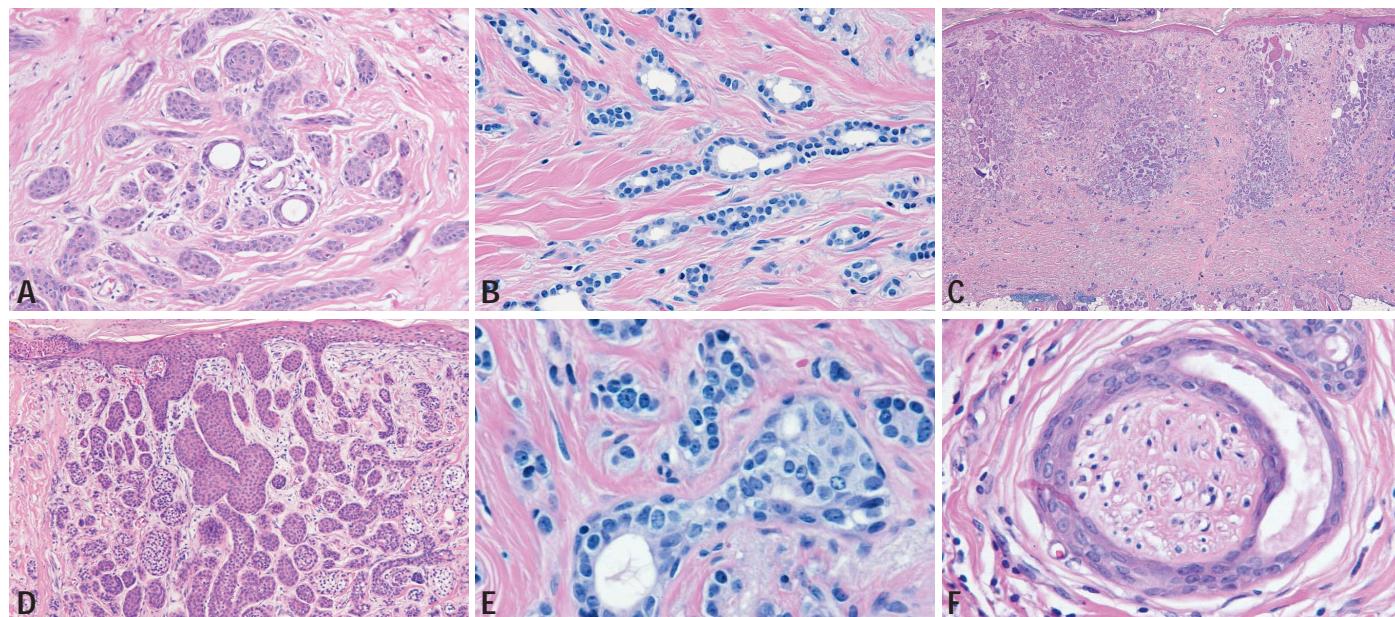


Fig. 3.04 Microcystic adnexal carcinoma. **A** There are a few cysts and solid nests, but no nuclear pleomorphism. The pattern of the lesion helps to recognize it as carcinoma. **B** Not only are there ducts; there are also strands and small nests of neoplastic cells. **C** This example of microcystic adnexal carcinoma again illustrates the zonation pattern, in this case with a few cysts superficially. Note the deep nests that are present in and around the sweat ducts; not every case will contain compressed ducts exclusively in the deep zones. **D** This example is similar to some poromas. There are solid nests of monomorphic cells as wells as nests of cells with clear cytoplasm. Some authors have designated these lesions "syringomatous" carcinoma. **E** Despite the striking structural patterns of these lesions, most do not contain nuclear pleomorphism. **F** Peripheral nerve, completely encircled by the neoplasm. Note the ductal space.

tubules peripherally. P53 is positive in less than 25% of the neoplastic cells. There is a low proliferative index, as Ki-67 is positive in less than 5% of the neoplastic cells. CK20, c-erb-2, and CD34 are negative {2207}.

Differential diagnosis

The principal differential diagnoses are with superficial biopsies of columnar trichoblastoma (desmoplastic trichoepithelioma) or morpheiform basal cell carcinoma (trichoblastic carcinoma), all of which are CK7 negative. Syringoma is a possible consideration in some cases. Rare examples of metastatic carcinoma to the skin can also mimic it.

Genetics

There is a single report of a 6q deletion {2538}. There is also a report of 2 microcystic adnexal carcinomas, one of which was diploid, and the other, aneuploid, when examined with DNA image cytometry {2437}.

Prognosis

Treatment is surgical, with microscopic control of margins if possible {9}. Radiotherapy has proven successful rarely, but some reported cases have taken on an even more virulent biology after such treatment.

Malignant mixed tumour

Definition

Malignant mixed tumour (MMT) is an exceedingly rare cutaneous adnexal carcinoma with a significant risk for aggressive behaviour and a propensity for metastasis. MMT is regarded as the malignant counterpart of benign mixed tumour {1919} albeit histological diagnosis is foremost based on the biphasic nature of the neoplasm rather than an admixture of benign mixed tumour remnants with carcinomatous tissue {2515}.

ICD-O code 8940/3

Synonyms

Malignant apocrine mixed tumour.
Malignant chondroid syringoma.

Epidemiology

MMT represents an exceedingly rare cutaneous adnexal neoplasm which occurs in a wide age range (15 months

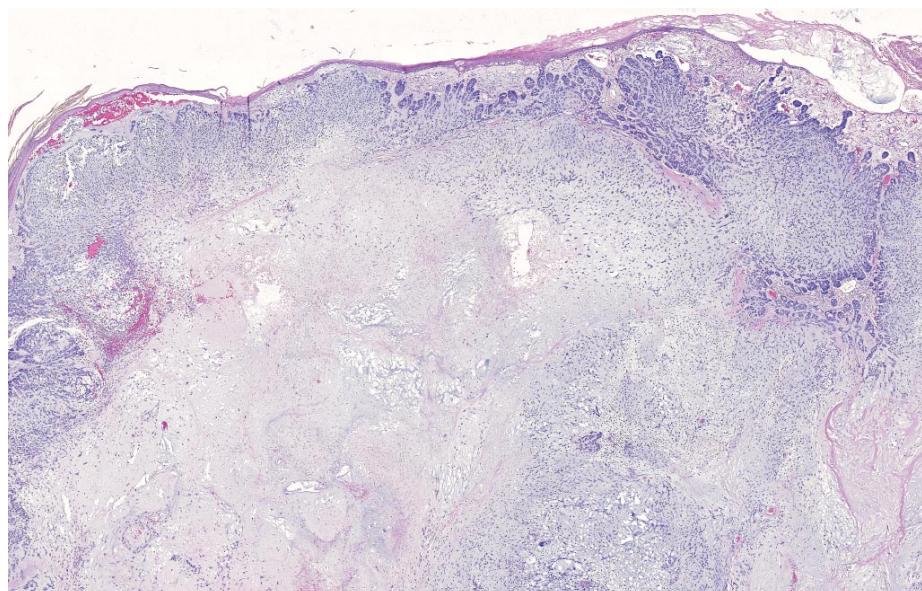


Fig. 3.05 Malignant mixed tumour. Lobulated biphasic tumour consisting of epithelial and mucinous-mesenchymal components. The former predominate at the periphery, while the latter predominate at the center.

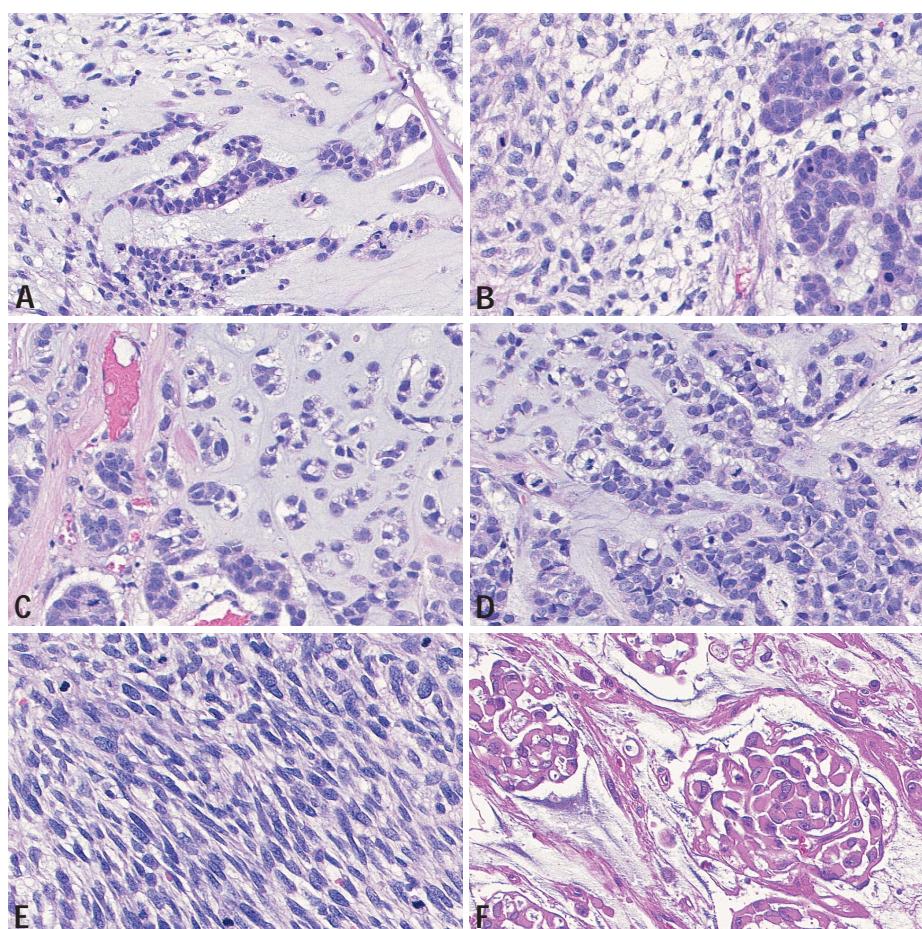


Fig. 3.06 Malignant mixed tumour. **A** Hyperchromatic tumour cells with mitoses. **B** Note variations of cytological differentiation and pleomorphism. **C** Focal zone of tubule formation. **D** Highly pleomorphic tumour lobules with mitoses at the periphery of the tumour. **E** Note the pseudo-sarcomatous pattern with hyperchromatic spindle cells and many mitoses. **F** Nests of plasmacytoid tumour cells amidst a myxoid stroma. Plasmacytoid epithelial differentiation is a hallmark of myoepithelial differentiation.

to 89 years; average 50 years) and is twice more common in women than in men {177,1919}.

Localization

In marked contrast to its benign counterpart MMT shows a predilection for the trunk and the extremities, foremost the hands and feet {177,961,1593,1903, 1919,2177,2377}.

Clinical features

MMT shares most clinical characteristics with its benign counterpart, albeit tumours of the former are much larger at the time of presentation (2-15 cm in diameter). Rarely, rapid growth, ulceration, or pain in a previously indolent skin tumour indicate carcinomatous growth. Most MMT, however, present in a rather bland way with a long history prior to excision. These tumours are well circumscribed and may appear cystic. They are not painful, not ulcerated, and show no distinctive clinical appearance.

Macroscopy

Grossly, most MMT are firm, circumscribed, asymmetrical cutaneous or subcutaneous tumours with a diameter of up to 15 cm. The tumour cut surface may reveal gelatinous material in variable amount {1919}. Because of the infiltrative tumour growth enucleation is not possible.

Histopathology

MMT originates within the dermis or superficial subcutis, and presents as a large, asymmetrical, poorly circumscribed, lobulated biphasic tumour with infiltrative tumour margins and adjacent satellite tumour nodules. Juxtaposed areas of benign and malignant mixed tumour may rarely occur, but are not a prerequisite for the diagnosis of MMT. MMT is composed of both epithelial and mesenchymal components, with epithelial components predominating at the periphery and mesenchymal chondromyxoid elements being more abundant toward the centre {2100}. The chondromyxoid tumour stroma is PAS-negative and consists of hyaluronic acid and sulphated acid mucopolysaccharides {1112}. Stroma ossification is rare {961, 2177}. Epithelial tumour aggregations present as confluent cords and nests of variable size and shape, with interspersed zones of tubule formation.

Tubular structures may be either of the elongated apocrine type lined by at least two layers of epithelial cells, with luminal cells exhibiting signs of apocrine secretion and abluminal cells showing plasmacytoid / myoepithelial differentiation, or – more rarely – of the eccrine type showing small round structures lined by a single layer of atypical epithelial cells {961, 1919}. Often, however, MMT consists only of solid aggregations devoid of tubules {928, 1919, 2471}. Epithelial tumour cells may either have a deceptively bland appearance {1112,2100} or show distinctive atypia and pleomorphism of nuclei with a high nuclear-cytoplasmic ratio and numerous mitotic figures {1919}. Zones of necrosis are common. Characteristic epithelial tumour cells are cuboidal with distinctive polygonal or plasmacytoid features {961, 1919}. The latter is considered an indicator of the myoepithelial/apocrine origin of the neoplasm and may be seen as a clue to the diagnosis of MMT {1919}.

Immunoprofile

Tumour cells may show a myoepithelial immunophenotype with coexpression of S100 and cytokeratin {177,976,1839, 2471} and actin expression in a minority of cells {1488}. Spindle cells within the myxoid stroma are vimentin-positive {2117}.

Electron microscopy

Tumour cells exhibit ultrastructural features of myoepithelia with desmosomes and abundant intracytoplasmic filaments {177,1839,2471}. However, ultrastructural studies so far have not presented convincing evidence of either apocrine or eccrine differentiation of MMT {1919}.

Variants

MMT may exhibit deceptively bland cytological features {1112,2100} albeit associated with distinctive architectural criteria of malignancy, e.g. asymmetry, poor circumscription, infiltrative tumour margins, and satellite nodules.

The recently described malignant mixed tumour of soft tissue {1062} shows overlapping histologic criteria with MMT of the skin. The former is considered to be part of the morphological spectrum of myoepithelial tumours of soft tissue.

Differential diagnosis

Extraskeletal myxoid chondrosarcoma

consists of non-cohesive elongated tumour nests without ductal or tubular structures. Tumour cells are cytokeratin negative. Mucinous carcinoma and myxopapillary ependymoma show distinct PAS positivity of the extracellular myxoid stroma. Cutaneous myoepithelial carcinoma favours monophasic differentiation with a very discrete myxoid stroma {1585}. MMT and cutaneous myoepithelial carcinoma may fall along a spectrum of tumours with overlapping histologic appearances {1585}.

Histogenesis

MMT probably does not originate in association with its benign counterpart, but develops *de novo* {1919}. A myoepithelial origin of MMT appears to be most plausible {177,1585,2100}, and MMT may be included in the spectrum of cutaneous myoepithelial neoplasms {1585}.

Prognosis and predictive factors

MMT proliferates in an invasive and destructive fashion, with a high rate of local recurrences and metastases (>50%) into regional lymph nodes, lung, and bone {177,1593}. Death ensues in >25% {177}. However, in >30% MMT neither recurred nor metastasized ("atypical mixed tumour of the skin") {177}. In general, MMT is characterized by its prolonged course {2467}. It is remarkable that non-metastasizing MMTs showed the same histological spectrum as those of proven malignancy {1919}, ranging from bland cytological appearance {961} to marked nuclear pleomorphism and a high mitotic count {2377}. Complete excision before metastasis results in tumour free survival {1919}.

Porocarcinoma

Definition

Eccrine porocarcinoma is a malignant tumour related to the sweat gland duct, showing both intraepidermal and dermal components.

ICD-O code

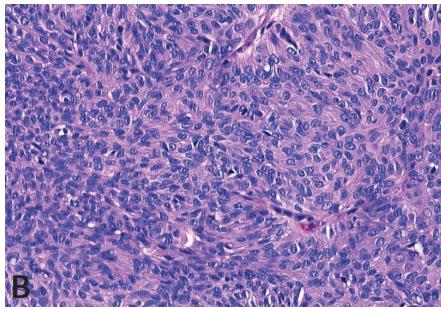
8409/3

Synonyms and historical annotation

Epidermotropic eccrine carcinoma, malignant eccrine poroma, malignant hidroacanthoma simplex, malignant intraepidermal eccrine poroma, poroepithelioma. The tumour was first described



A



B

Fig. 3.07 Porocarcinoma. **A** Multinodular ulcerated plaque. **B** Closely arranged polygonal cells with hyperchromasia.

by Pinkus and Mehregan in 1963 as epidermotropic eccrine carcinoma {1837}.

Epidemiology

Eccrine porocarcinoma is a rare tumour, predominantly observed in elderly patients with an average age of 67 years {1072}. Women and men are equally affected. The incidence in one large series was 18 per 450,000 cases (0.004%) {1571}.

Etiology

Eccrine porocarcinomas may arise de novo or as a malignant transformation in a pre-existing poroma, hidroacanthoma simplex, or in association with naevus sebaceous {1571,2216,2604}. 18 to 50% of eccrine porocarcinomas are associated with pre-existing eccrine poromas.

Localization

Forty-four to 50% of eccrine porocarcinomas arise on the legs, buttocks, or feet {2216}. The trunk accounts for 24% of the lesions and the head 18% of the lesions with less frequent lesions located on the upper extremities {1072}.

Clinical features

Eccrine porocarcinoma presents as a verrucous nodulo-ulcerative plaque. Clinically the lesions may resemble an eccrine poroma, verruca vulgaris, seborrhoeic keratosis, melanocytic naevus,

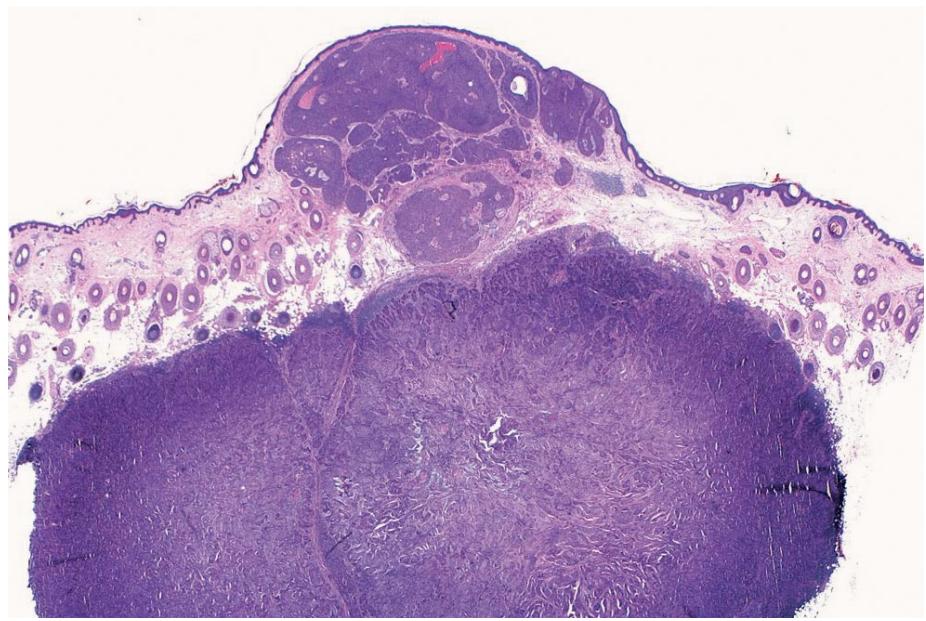


Fig. 3.08 Porocarcinoma. There is a dermal component, partly in apposition with the epidermis, and a large tumour nodule extending into the deep subcutaneous tissues. The lesion is remarkably well demarcated.

fibroma, basal cell carcinoma, squamous cell carcinoma, or pyogenic granuloma. Diagnosis is made by skin biopsy.

Histopathology

Eccrine porocarcinoma forms intraepidermal and dermal nests and cords of epithelial cells with pale cytoplasm. The tumour masses form clearly demarcated and frequently rounded nests of polygonal cells with pleomorphic and irregularly-shaped nuclei, prominent nucleoli, and numerous mitotic figures. There is sharp demarcation of the epithelial nests of cells from the adjacent epidermal keratinocytes {1837}. The overlying epidermis may be acanthotic. Both single tumour cells and nests of cells may involve the epidermis in a pagetoid fashion {1359}. Keratinization is usually absent. Intercellular bridging between the tumour cells is inconspicuous. The tumour cells may contain glycogen {2000}. Connection to the intradermal eccrine ducts may be observed. Deep dermal intralymphatic invasion may be observed in up to 15% of the lesions {1952}.

The differential diagnosis includes eccrine poroma, hidroacanthoma simplex, and Paget disease {913}. Eccrine poroma and hidroacanthoma simplex may show focal atypia, but the lesions are symmetrical and well circumscribed. Eccrine porocarcinoma may be differen-

tiated from Paget disease by its relatively sparse epidermal involvement and greater dermal invasion, and the presence of glycogen rather than mucin in tumour cells {913}. In the absence of residual eccrine poroma, it is very difficult to differentiate eccrine porocarcinoma from squamous cell carcinoma {1571}.

Immunoprofile

The tumour nodules stain with antibodies to pan-cytokeratin; tumour cells may stain paler than adjacent epidermal keratinocytes {499,1072}. Ductal structures within the tumour stain strongly positive with CEA and EMA {1359,2216}.

Genetics

Mutation of the p53 gene with loss of its suppressor function has been widely noted with malignant transformation. P53 protein expression has been observed in both eccrine poromas and eccrine porocarcinoma {43,2327}. P16 staining is uniformly negative {914}.

Prognosis and predictive factors

Approximately 20% of eccrine porocarcinomas recur after excision {2216}. Regional lymph node metastasis occurs in 20% of patients, while 12% develop distant metastases {2216}. Patients with metastatic disease have a high mortality rate {170}. Increased number of mitoses,

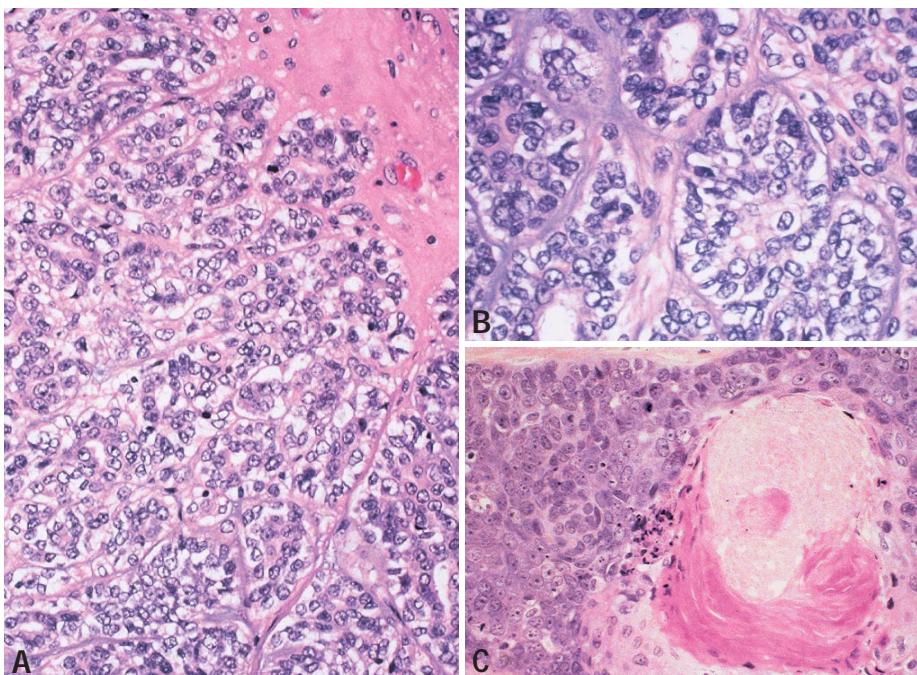


Fig. 3.09 Spiradenocarcinoma. **A** Transitional changes from benign to malignant. Note transitional area with hypercellularity, hyperchromasia and diminished preservation of the usual histologic pattern of a spiradenoma. **B** Spiradenocarcinoma with transitional changes from benign to malignant. Malignant area with occasional residual duct-like structures with clear cell changes and prominent cytologic atypia. **C** Spiradenocarcinoma with unusual cytodifferentiation, squamous "bowenoid" dysplasia.

lymphovascular invasion and tumour depth greater than 7 mm have all been associated with a relatively poor prognosis {1952}.

Spiradenocarcinoma

Definition

Spiradenocarcinoma is a malignant adnexal neoplasm resulting from malignant transformation of a benign spiradenoma.

ICD-O code

8403/3



Fig. 3.10 Spiradenocarcinoma. Well-defined, encapsulated mass with areas of solid and cystic changes and haemorrhage.

Histopathology

In all cases there are recognizable areas of a benign spiradenoma with the usual well-defined dermal nodules composed of two cell types. Spiradenocarcinoma arising from benign spiradenoma presents two major histologic patterns {89, 725, 884}. In one type, there are areas showing gradual transition from benign to a malignant neoplasm. In these lesions the dual cell population of the benign neoplasm imperceptibly merges with the monomorphic cell population of the carcinoma. The usual structural pattern of spiradenoma disappears and is replaced by poorly defined cell nests and cords. Glandular and duct-like structures, as well as hyaline globules, are diminished or may be missing. These changes can be very focal in early lesions and can easily be missed without adequate tissue sampling. In the second type, the malignant changes are adjacent to the spiradenoma without structural or cytological transition. These neoplasms can present a wide spectrum of histologic features including squamous, bowenoid, adenomatous, ductal carcinoma-like, and even histiocyte-like and carcinosarcomatous changes with rhabdomyoblastic or osteosarcomatous differentiation {1391, 1548, 1958}. In advanced stages of both subtypes, necrosis, haemorrhage, and infiltrative growth can be observed.

Immunoprofile

Spiradenocarcinoma is positive for the majority of cytokeratins, CEA, EMA, and shows a spotty reaction for S-100 protein. Over-expression of P53 has also been reported {89, 726, 1555, 2516}.



Fig. 3.11 Hidradenocarcinoma involving the left preauricular skin of an elderly male. Note the presence of a retroauricular lymphadenopathy.

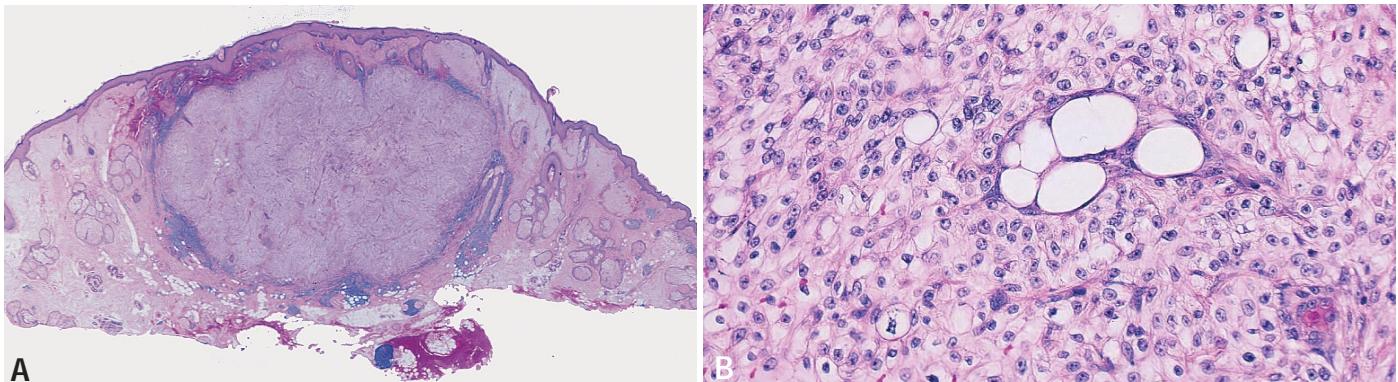


Fig. 3.12 Hidradenocarcinoma. **A** At scanning power the neoplasm appears as a well-circumscribed round nodule involving the full thickness of the dermis. **B** Although the neoplasm is mostly a solid tumour, in some areas there is evidence of ductal differentiation in the form of cytoplasmic vacuoles and small round ducts.

Histogenesis

Theoretically, spiradenocarcinoma can develop de novo. However, the tumour lacks distinctive microscopic features, therefore its histopathologic diagnosis requires recognition of a spiradenoma in association with the malignant changes.

Somatic genetics

TP53 mutations have been identified in carcinomatous portion of spiradenocarcinoma, whereas the spiradenoma part lacked mutations [239A].

Prognosis and predictive factors

Spiradenocarcinoma is an aggressive neoplasm with multiple local recurrences and eventual widespread metastases, resulting in death. The metastases most often involve lymph nodes, bones, and lungs. Management is primarily surgical; the role of radiation and chemotherapy is still to be defined [1110,1594].

Hidradenocarcinoma

Definition

Hidradenocarcinoma is the malignant counterpart of hidradenoma.

ICD-O code

8400/3

Synonyms

Clear-cell papillary carcinoma {1436}, clear-cell hidradenocarcinoma {1249, 1470}, malignant clear-cell hidradenoma {578,1237}, malignant clear-cell acrospiroma {992}, malignant eccrine acrospiroma {1741}, primary mucoepidermoid carcinoma of the skin {803, 2497}, nodular hidradenocarcinoma, clear-cell eccrine carcinoma {2300}, mucoepider-

moid hidradenocarcinoma {637}, and malignant nodular clear-cell hidradenoma {204}.

Epidemiology

Hidradenocarcinoma seems to be slightly more frequent in women than in men, with the mean age of 50 years, but cases have been also recorded in children {237,477}.

Etiology

Most cases of this carcinoma arise de novo, but some cases are associated with a hidradenoma {237,1013,1237, 1249,1427}.

Localization

This carcinoma may appear in any area.

Clinical features

The neoplasm does not have any distinctive clinical features and usually presents as a slow growing solitary dermal or subcutaneous nodule.

Histopathology

Hidradenocarcinoma is composed of one or several tumour nodules, which vary in size and shape. Focal tubular and ductal structures may be present. Areas of necrosis en masse are common. Usually there is no connection between the epidermis and the tumour, but the surface epithelium may be ulcerated. The same cell types as seen in hidradenoma are found in hidradenocarcinoma. Atypical cells with pleomorphic nuclei and mitotic figures may be focally prominent, but some tumours lack nuclear atypia. Therefore, the diagnosis can be established only on the basis of architectural characteristics.

Immunoprofile

Neoplastic cells express low molecular weight cytokeratin CAM 5.2 and cytokeratin 19. CEA and EMA decorate the luminal border of ductal structures.

Histogenesis

Most neoplasms have apocrine differentiation, but some show eccrine features.

Prognosis and predictive factors

This carcinoma may metastasize widely and cause death. Of the 76 patients with this carcinoma described in the literature, 22 developed metastases {204,485, 992,1013,1162, 2468}.

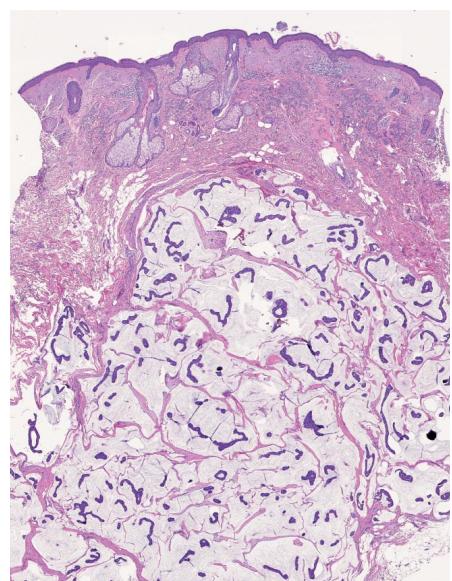


Fig. 3.13 Mucinous carcinoma. Note typical "honeycomb pattern" with small epithelial strands floating in lakes of mucin.

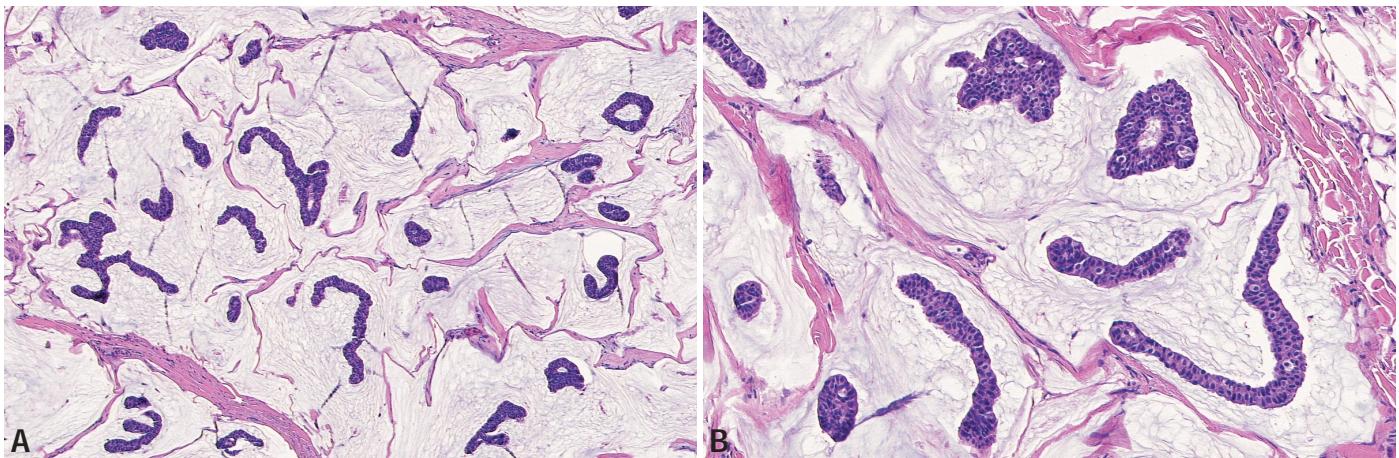


Fig. 3.14 Mucinous carcinoma. **A** Large mucin deposits clearly predominate over epithelial tumour components - in sharp contrast to cutaneous metastasis of mucinous breast carcinoma where epithelial tumour cells predominate and delicate fibrous septa are scarce. **B** Thin strands of epithelial tumour cells with little atypia and very scarce mitoses. Note delicate fibrous septa and incipient tubule formation.

Mucinous carcinoma

Definition

Primary cutaneous mucinous carcinoma (MC) is a rare epithelial neoplasm occurring mostly, but not exclusively, in middle-aged and older patients. Although MC is characterized by destructive local growth and the potential of metastasizing to regional lymph nodes and even beyond them, it generally follows an indolent course with frequent local recurrences. Mucinous carcinoma metastatic to skin from another organ, particularly the breast and gastrointestinal tract, may be histologically indistinguishable from MC.

ICD-O code

8480/3

Synonyms

Primary cutaneous mucinous carcinoma. Colloid, gelatinous and adenocystic carcinoma.

Epidemiology

MC is very rare and occurs mostly between the fifth and seventh decades of life, with an age range between 8 and 84 years. MC is slightly more common in men than in women {1919}.

Localization

Most MC arise on the head, favouring scalp and face with preference of the eyelids {199,305,1212,2217,2319}. Rare sites are axillae, trunk, lower extremities, perianal area and vulva {1919}.

Clinical features

MC presents as a solitary, slowly grow-

ing, painless nodular neoplasm. The tumour has a tan, grey, or reddish colour, a smooth surface, and a consistency ranging from soft to firm. Positive transillumination may be a helpful diagnostic tool.

Macroscopy

Grossly, most MC are well-circumscribed, un-encapsulated tumours in the dermis and the subcutaneous fat. Tumour diameters range between 1 and 8 centimetres, albeit larger variants have been reported {1231}. On excision, the tumour appears fixed to the adjacent dermis and does not "shell out" {1919}. The cut surface of excised specimens is gelatinous.

Histopathology

MC presents as an un-encapsulated asymmetric dermal tumour that may extend into the subcutis and even deeper tissue planes {1919}. Tumour satellites may occur at some distance from the main tumour. MC is characterized by large pools of basophilic mucin, which are compartmentalized by delicate fibrous septa, thereby creating a honeycomb pattern. Within the lakes of mucin are small "floating" islands and bizarre clusters of neoplastic epithelial cells, sometimes exhibiting a cribriform arrangement. The epithelial component is denser at the periphery of the tumour. Small glandular or tubular structures containing mucin or showing signs of apocrine secretion occur only rarely. The small neoplastic cells are cuboidal, round, or oval with abundant cytoplasm

that may be vacuolated. Nuclei are small with very little atypia. Mitoses are rare. The epithelial mucin is PAS-positive, hyaluronidase and sialinase labile, and consists of non-sulphated acid mucopolysaccharides with sialic acid.

Immunoprofile

Neoplastic cells express low molecular weight cytokeratins, CEA, EMA, GCDFP-15, alpha-lactalbumin, salivary amylase, beta-2-microglobulin. S100 expression is inconstant {199,404,664}. Nuclear expression of oestrogen receptors may be strong, but the pattern of progesterone receptors is more variable {945}. Cytokeratin 20 expression allows differentiation of mucinous gastrointestinal carcinoma metastatic to the skin from primary cytokeratin 20-negative cutaneous MC {664}.

Variants

MC very rarely presents with focal neuroendocrine differentiation {1876}, or with a growth pattern imitating infiltrating carcinoma of the breast {2557}. Epidermotropism of neoplastic cells is unusual.

Electron microscopy

There are less well-differentiated inner pale cells and mucin-containing peripheral dark cells {990}.

Differential diagnosis

Before a diagnosis of MC is established, a primary carcinoma in a breast or another organ (salivary and lacrimal glands, gastrointestinal tract, nose and

paranasal sinuses, bronchi, ovary and renal pelvis) should be specifically sought and excluded as most cases of mucinous carcinoma in the skin are metastatic to it. Histological differentiation between primary cutaneous MC and metastatic mucinous carcinoma to the skin may be impossible, albeit the latter exhibits subtle histological variations {1919}: e.g. larger clusters of cohesive neoplastic cells, less quantities of mucin, a striking predominance of epithelium over mucin, and the absence of delicate fibrous septa that intersect the lakes of mucin.

Malignant mixed tumour of the skin exhibits tubular structures embedded in a myxoid, chondroid, or osteoid stroma, and distinctive polygonal and plasmacytoid neoplastic epithelia. The characteristic honeycomb pattern of MC is not present {1919}.

Histogenesis

Histogenesis of MC has not yet been elucidated, but there is strong morphological evidence that MC may be apocrine in nature {1919}.

Prognosis and predictive factors

In contrast to most other sweat gland carcinomas, MC is a low-grade malignant neoplasm with a tendency to persist at the original site but with a low metastatic potential. 10% of the MC so far reported metastasized to regional lymph nodes, but only 3% metastasized in a more widespread fashion {1830}. While multiple recurrences, due to the existence of tumour satellites, are not unusual, death from MC is exceptional {1919}.

Digital papillary carcinoma

Definition

Digital papillary carcinoma is regarded as an uncommon malignant adnexal neoplasm with potential for both recurrence and metastasis.

ICD-O code 8408/3

Synonyms

Aggressive digital papillary adenoma, digital papillary adenocarcinoma

Historically, this group of lesions was divided histologically into aggressive digital papillary adenomas and digital adenocarcinomas {1205}. However,

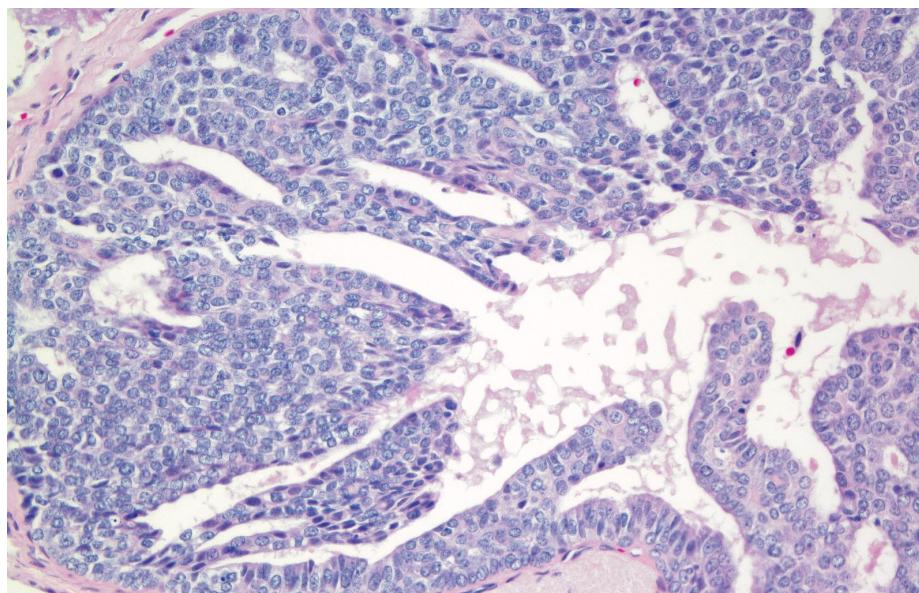


Fig. 3.15 Digital papillary carcinoma. Within the tumour nodules, papillae are formed by heaped up epithelium without stromal cores.

cases originally classified histologically as adenoma developed metastases, demonstrating that histologic parameters do not accurately predict behaviour or allow distinction between adenoma and adenocarcinoma {655}. Therefore, the term aggressive digital papillary adenoma has been abandoned in favour of classification of all such lesions as digital papillary carcinoma.

Epidemiology

Digital papillary carcinomas present almost exclusively on the fingers, toes, palms, and soles. Hands are involved more frequently than feet. There is a male predilection, and most affected individuals are adults in the fifth and sixth decades of life.

Clinical features

Most cases present as a slowly growing deeply seated nodule on a digit. Lesions may be several centimetres in diameter. Pain is occasionally a presenting complaint, and may be related to tumour extension into underlying bone, joint, or nerve. Rarely, metastasis is the first manifestation of disease. Unless underlying bone has been invaded, routine roentgenographic examination may be essentially unremarkable.

Histopathology

Typically, tumours are composed of multi-nodular epithelial aggregates with cystic spaces in the dermis. A cribriform

pattern of glands often fills the solid areas of tumour, while papillary epithelial projections are common within cystic spaces. The papillary projections are associated with fibrovascular cores in some areas, while in other areas papillae are formed by heaped up epithelium without stromal support. The epithelium is composed of low columnar or cuboidal cells. Cytologic atypia is usually not marked. Mitoses and necrosis are frequent findings. Cysts contain either necrotic debris or eosinophilic secretory material. Some tumours are well-circumscribed, while others have an infiltrative growth pattern.

Differential diagnosis

The differential diagnosis includes papillary eccrine adenoma, which is usually well-circumscribed, and composed of dilated ducts with a distinct two cell layer and delicate papillae. Malignant adnexal neoplasms such as malignant acrospiroma and malignant spiradenoma are also in the differential, but typically lack the pattern of papillary growth and/or back-to-back glands that characterize digital papillary carcinoma. In addition, malignant spiradenoma usually retains its characteristic two cell population (small basaloid cells and large pale peripheral cells) in at least some foci.

Histogenesis

The occurrence of digital papillary carcinoma on acral sites where eccrine

glands are abundant suggests an eccrine origin of this tumour. Although some cases show decapitation secretion, as is common in apocrine lesions, this phenomenon has also been observed in eccrine tumours. In addition, immunoreactivity for ferritin had led investigators to favour that digital papillary carcinomas derive from eccrine glands [417].

Prognosis and predictive factors

Complete surgical excision with negative margins is indicated, and sometimes requires amputation. Tumour recurrence is seen in up to 50% of patients, especially in cases without adequate primary excision [1205]. Metastatic disease has been observed in 14% of cases [655]. Metastases may accompany recurrent disease or occur without evidence of local recurrence. Lungs seem a favoured site for metastases, suggesting the probability of haematogenous spread of tumour. Tumour recurrence and metastasis does not seem to correlate with patient age, tumour size, or duration of tumour. Similarly, histologic features such as tumour differentiation, circumscription, or nuclear grade are not predictive of behaviour [655].

Adenoid cystic carcinoma

Definition

Primary cutaneous adenoid cystic carcinoma is a neoplasm of disputed histogenesis characterized by a cribriform pattern and frequent perineural involvement.

ICD-O code

8200/3

Epidemiology

Over 40 cases have been reported in the literature. Adenoid cystic carcinoma (ACC) affects middle-aged and older individuals (mean age: 58.1) and has a predilection for women [1219].

Localization

This neoplasm is most common on the scalp (35%) and chest and abdomen (24%) [446,1219].

Clinical features

Primary cutaneous adenoid cystic carcinoma has an indolent and progressive course. The average duration of the tumour prior to diagnosis is approximate-

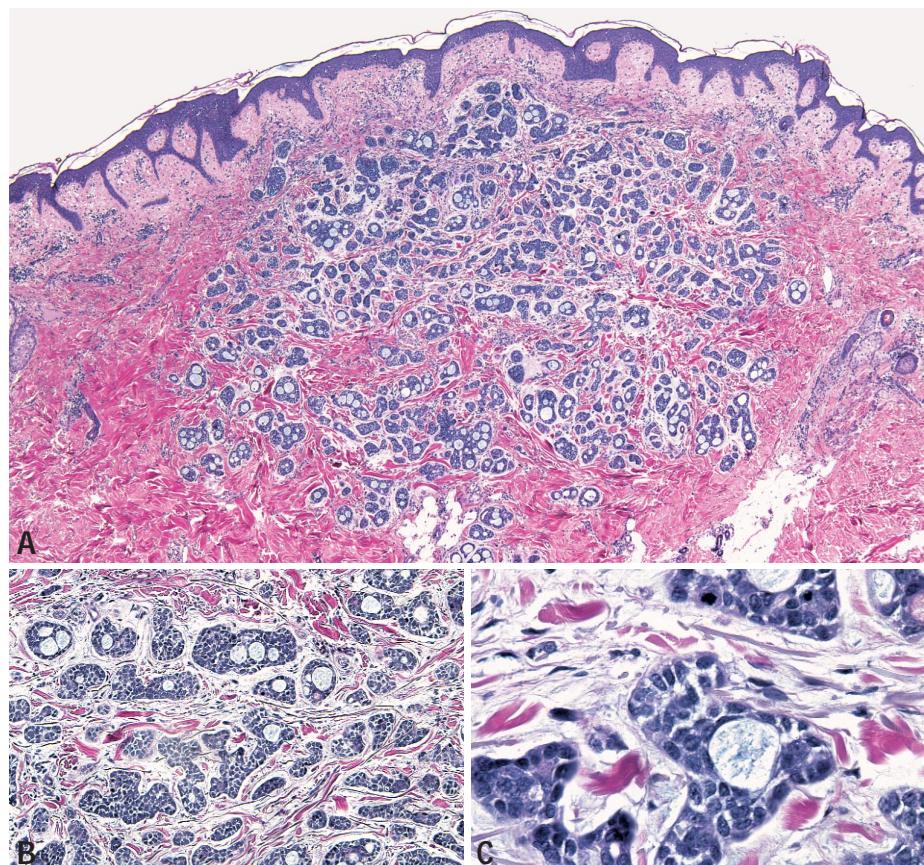


Fig. 3.16 Adenoid cystic carcinoma. **A** Low power view of an adenoid cystic carcinoma demonstrating a poorly circumscribed neoplasm which is composed of collections of basophilic cells arranged in a sieve-like pattern. **B** This photograph highlights the sieve-like pattern with prominent mucin within the glandular spaces. Note also the irregularity of the size and shape of the cellular collections. **C** Mild degree of pleomorphism is seen within the neoplastic cells.

ly 9.8 years [1219]. The size of the tumour ranges from 0.5-8 cm, with an average size of 3.2 cm. Patients typically present with slowly expanding, firm, skin coloured nodules. Tenderness, ulceration and bleeding are variable and depend on the site of involvement. In the scalp region, alopecia may be an associated finding.

Histopathology

Primary cutaneous ACC is usually poorly circumscribed and is composed of islands, cords and strands of basaloid cells with a glandular, cystic, cribriform and tubular arrangement embedded in a loose fibrous and sometimes mucinous stroma. It typically occupies the mid and deep dermis and may extend into the subcutaneous fat [793]. The epithelial cords have an infiltrative pattern and are not connected to the overlying epidermis. The tumour has a characteristic basophilic appearance on low power

due to nuclear hyperchromatism and crowding. Nuclear palisading is absent. The tumour nests are surrounded by a prominent eosinophilic hyaline basement membrane-like material which is periodic acid-Schiff-positive, and diastase-resistant. The cystic spaces often contain abundant mucin [1812]. The mucin is characteristically alcian blue (pH 2.5) positive. The epithelium consists of fairly uniform cells with darkly staining nuclei, which sometimes contain conspicuous, small, solitary nucleoli. Individual tumour cells have a scant amphophilic cytoplasm and an increased nuclear-cytoplasmic ratio. Mitotic activity is usually sparse with 1-2 division figures per high power field (x40) [2514]. Perineural extension, a characteristic feature of salivary gland adenoid cystic carcinoma may be seen, however, not with the frequency seen in other organs. Before the diagnosis of a primary cutaneous ACC is made, the possibility of a

metastasis from other organs needs to be ruled out on clinico-pathological grounds. The adenoid cystic type of basal cell carcinoma is differentiated by the presence of palisading of the nuclei and stromal retraction.

Immunoprofile

Primary cutaneous adenoid cystic carcinoma stain positively for epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), broad-spectrum keratins, and low-molecular-weight keratins (CAM 5.2). Focal staining with S-100 and vimentin may be seen {210}. Epithelial cells at the periphery of the tumour islands may express actin.

Histogenesis

The eccrine or apocrine origin of this tumour remains disputed. In the past, it has been regarded as an eccrine tumour, although some have been shown to arise from modified apocrine glands {2407}.

Prognosis and predictive factors

An indolent but progressive course is the major characteristic of this tumour. The recurrence rate is high, ranging from 57–70% and therefore wide surgical excision extending well beyond the clinical confines of the tumour is recommended. Recurrences have been reported even with 2 cm margins and may occur many years after excision. For this reason some people favour Mohs micrographic surgery {462}. Only 4 cases have metastasized to the lymph nodes and lungs.

Apocrine carcinoma

Definition

Apocrine carcinoma (AC) is a malignant sweat gland neoplasm with apocrine differentiation. Although an apocrine origin has also been postulated for adenoid cystic carcinoma, hidradenocarcinoma, spiradenocarcinoma, malignant cylindroma, and microcystic adnexal carcinoma, this remains unproven. These entities shall, therefore, be presented separately.

ICD-O code

8401/3

Synonyms

Apocrine adenocarcinoma, apocrine gland carcinoma

Epidemiology

AC is a rare tumour. Both genders are almost equally affected, and there appears to be no racial predilection. {1785,2460}

Etiology

The etiology of AC is unknown. The fact that all patients were over 25 years {824} suggests that full maturity of the apocrine glands is a prerequisite.

Localization

Most AC arise in the axilla and, to a lesser extent, in the anogenital region. Rare locations include the scalp, face, chest, and distal upper extremities. {536,988, 1785,2055,2460} Peculiar variants have been described on the ear (ceruminous

gland carcinoma) and the eyelid (Moll gland carcinoma) {2139,2172}.

Clinical features

Because reports are sporadic and may have included a proportion of benign lesions it is difficult to establish a precise clinical profile for AC. Apparently, there are no distinctive features that might enable a confident clinical diagnosis of AC. Most tumours are solitary, but a patient with bilateral axillary AC has been reported. AC presents as single or multiple, firm or cystic nodules with a reddish or purplish hue of the overlying skin, sizing between 1.5 and 8 cm {2460}. Ulceration and haemorrhage may be present. The patients' age at presentation ranges from 25 to 91 years, with an average age of 57.9 years {2460}. In many cases, the lesions had been standing for more than 10 years, and even up to 30 years before diagnosis {1650}. Some tumours have arisen within a naevus sebaceous {644}.

Histopathology

AC is typically centred on the deeper dermis and tends to spread into the subcutaneous fatty tissue {1785,2460}. Extension into the epidermis also occurs, occasionally in the form of extramammary Paget disease {1647}. The tumours are usually poorly circumscribed with infiltrating borders. Neighbouring apocrine glands occasionally show *in situ* carcinoma. {988,2460}. The growth patterns of AC are highly variable, including tubular,

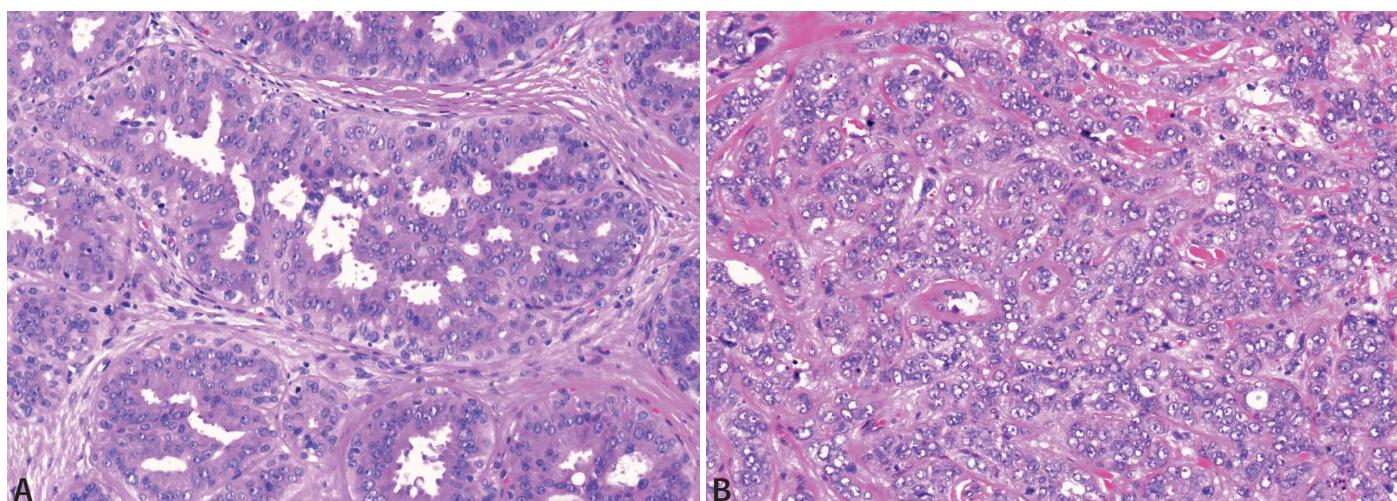


Fig. 3.17 Apocrine carcinoma. **A** Well differentiated cutaneous apocrine carcinoma. Glandular structures with tubulopapillary growth pattern and apical decapsulation secretion. **B** Poorly differentiated cutaneous apocrine carcinoma. Micronodular and trabecular growth pattern with hardly any gland formation, hyaline stroma. The cells have scanty amphophilic cytoplasm and contain vesicular nuclei with prominent nucleoli and occasional mitotic figures.

papillary, cystic, cribriform, micronodular, and solid formations {1785,2460}. The cells have abundant eosinophilic cytoplasm and large, round to oval, mostly vesicular nuclei that often contain a single prominent eosinophilic nucleolus {1785}. Intracytoplasmic PAS-positive diastase-resistant granules are characteristic, and intracytoplasmic iron is sometimes demonstrable {988,1785,2139}. A key diagnostic criterion, decapitation secretion in the form of apical snouts {2460} is usually recognizable but may be lacking in poorly differentiated tumours. There is variable mitotic activity, ranging from single mitotic figures in well differentiated tumours and up to 4 mitotic figures per high power field in poorly differentiated carcinomas {2460}. Long standing tumours tend to show increasing anaplasia. The tumour stroma is usually densely fibroblastic or hyaline and may contain prominent lymphoplasmacytic infiltrates.

AC may exhibit focal mucinous carcinoma-like features {2556} or may be composed of signet ring cells {1126}. The latter tumours are mostly located on the eyelid but may occur in the axilla {1343}. Signet ring cell AC show a striking predominance (10:1) in elderly males {1343}.

Immunoprofile

The cells of AC express low molecular weight cytokeratin (CAM5.2), epithelial membrane antigen, carcinoembryonic antigen, cytokeratin15, gross cystic disease fluid protein (GCDFP)-15 {1785} and occasionally S-100 protein {1343, 1785}. Myoepithelial cells, detectable by SMA or CK 5/6 immunostaining, are typically absent {988,2460}.

Differential diagnosis

The main differential diagnosis is with (tubular) apocrine adenoma, and the histologic features that distinguish these two conditions are often subtle. Whilst vascular and neural invasion are diagnostic of carcinoma, stromal invasion is less so and may be difficult to ascertain. Tumour silhouette, cellular pleomorphism and mitotic activity may provide clues to malignancy. As focal squamous differentiation may occur in AC {1785} acantholytic squamous cell carcinoma may have to be considered in the diagnostic differential.

AC is otherwise indistinguishable from apocrine mammary carcinoma metastat-



Fig. 3.18 Mammary Paget disease (MPD). Sharply circumscribed erythematous and scaly plaque affecting the nipple and areola.

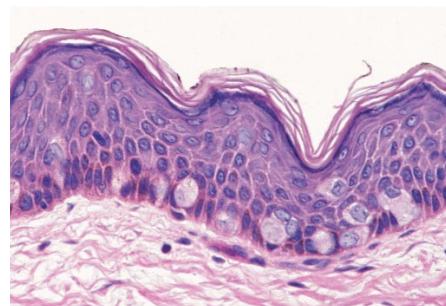


Fig. 3.19 MPD. Cytoplasmic melanin can accumulate in Paget cells and does not indicate melanocytic differentiation.

ic to the skin or apocrine carcinomas arising in ectopic breast tissue in the axilla. Therefore, the diagnosis of primary cutaneous AC rests on a meticulous clinico-pathologic correlation.

Histogenesis

AC is thought to arise from preexisting apocrine (sweat) glands {988,1785,2139, 2459}. An interesting alternative origin are the newly described mammary-like sweat glands of the anogenital region, which may also give rise to eccrine tumours {2408}.

Prognosis and predictive factors

The majority of AC are slow growing tumours with a tendency toward a prolonged course. The overall mortality is low, despite frequent recurrences (30%) and metastases to regional lymph nodes (50%) {536,1785,2460}. Wide dissemination and tumour-related deaths have nevertheless been described {437,1785, 2172,2460}. As distant metastases may be a late event in the course of AC a prolonged follow-up is advisable. Reliable predictive factors have not been established.

Page 3.19 Paget disease and extramammary Paget disease

Definition

Paget disease of the breast and extramammary Paget disease are intraepidermal adenocarcinomas characterized by large atypical and pale staining cells scattered throughout the epidermis either as single cells or in small clusters. *Mammary Paget disease (MPD)* resembles an eczematous eruption of the nipple and areola, and in almost all cases constitutes skin involvement by an

underlying in situ or invasive ductal carcinoma of the breast.

Extramammary Paget disease (EMP) is a scaly erythematous eruption affecting apocrine gland bearing areas of the skin, mainly the female and male genital areas. The majority of cases represent an apocrine adenocarcinoma in situ that has a high recurrence rate and may invade the dermis and then possesses metastatic potential. In a subset of cases EMP is the skin manifestation of an underlying internal malignancy. The skin manifestations of these cases are clinically and histologically indistinguishable from cases not associated with internal malignancy.

ICD-O codes

Page disease of breast	8540/3
Extramammary Paget disease	8542/3

Historical annotation

In 1874 Sir James Paget first described "about fifteen cases" of a chronic eczematous eruption of the nipple and areola and noted that mammary cancer developed in all patients within two years {1766}. George Thin described the histopathologic features of this condition in 1881. The term Paget disease was coined in 1889 by Radcliffe Crocker when he described a morphologically and histologically similar eruption affecting the penis and scrotum {561}.

Epidemiology

MPD occurs almost exclusively in women. Exceptional cases of men with MPD have been reported {927}. One to two percent of female patients with breast carcinoma develop Paget disease {1971}. Ten to 28% of cases of Paget dis-

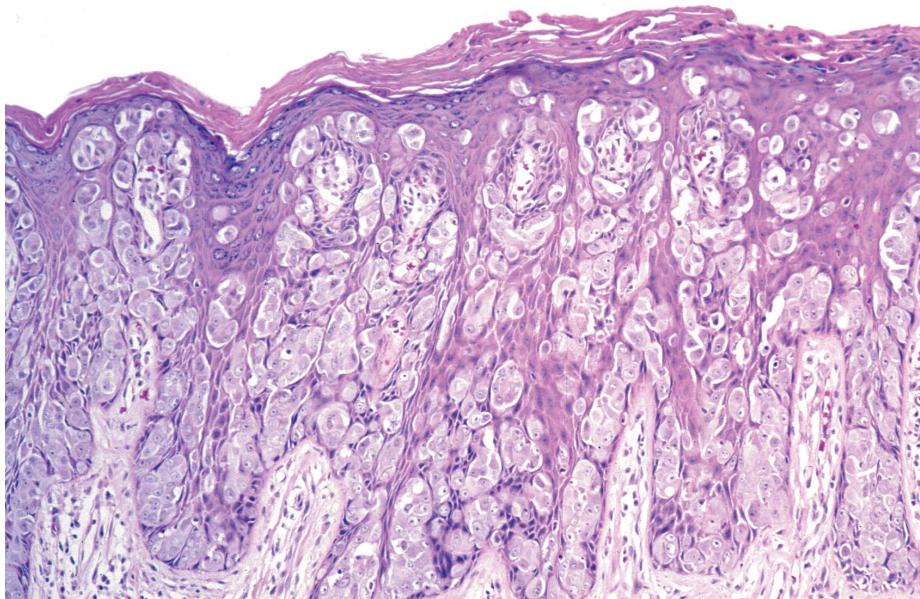


Fig. 3.20 Mammary Paget disease (MPD). Paget cells with large nuclei, prominent nucleoli and abundant pale cytoplasm permeate the entire epidermal thickness.

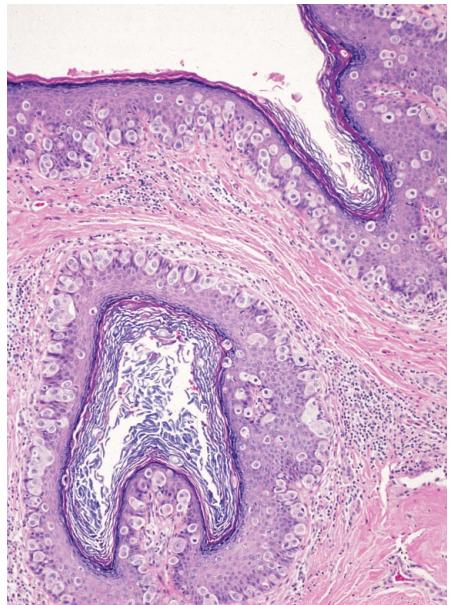


Fig. 3.21 Extramammary Paget disease (EMP). Paget cells often have a propensity for tracking along skin appendages.

ease are detected only on histologic examination of the nipple in a mastectomy specimen, without a clinically apparent lesion {1971}.

No accurate epidemiologic data is available for EMP. It is a rare condition that comprises less than 2% of primary neoplasms of the vulva. EMP occurring in sites other than the vulva is even less common. In genital EMP, women are more commonly affected than men. Most patients are above the age of 60.

Etiology

MPD is almost always associated with an underlying carcinoma of the breast, and the etiology is the same as for breast carcinoma. The inciting factors for primary EMP are unknown. Secondary EMP is an expression of an underlying internal malignancy and the etiology parallels that of the underlying tumour.

Localization

MPD involves the nipple and areola and in advanced cases may extend to the adjacent skin.

EMP involves apocrine gland bearing areas and is most common in the genital area, groin, perineum or perianal region. Axillae, eyelids and external auditory canals rarely may be involved.

Clinical features

Patients who present with MPD initially

develop erythema of the nipple and areola. The lesion then progresses to scaly, crusted thick plaques and ultimately to areas of erosion and ulceration. Patches and plaques are almost always unilateral and sharply circumscribed, and sometimes pruritic or painful. In approximately half of the cases a breast mass is palpable. Nipple retraction and serosanguinous discharge may be features of advanced cases with a large underlying carcinoma. Not all patients with MPD have clinical symptoms; 10-28% of cases are detected only on histologic examination in a mastectomy specimen {1971}. The differential diagnosis includes squamous cell carcinoma in situ and eczema. Once a diagnosis of MPD is established the patient needs to be evaluated with imaging studies and other procedures for breast carcinoma. If MPD is associated with a palpable tumour mass, the underlying carcinoma will be invasive in more than 90% of cases. If no tumour mass can be detected clinically, less than 40% of women will have invasive carcinoma.

Patients with EMP most commonly present with pruritus or burning. The skin shows well-demarcated erythematous scaly patches and plaques, which may be ulcerated. Following a diagnosis of EMP the patient needs to undergo thorough examination to rule out an associated internal malignancy.

Tumour spread and staging

MPD without invasive carcinoma on histologic examination is classified as carcinoma in situ (Tis). MPD with a contiguous or non-contiguous invasive component on histology is staged according to the invasive component using the guidelines for staging of breast carcinoma.

Primary EMP is staged either according to the FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) or the TNM system of the AJCC (American Joint Committee on Cancer) for vulvar tumours. After a long period of in situ growth EMP can eventually invade the dermis and acquire metastatic potential. Typically, invasive carcinoma associated with EMP first spreads to locoregional lymph nodes and ultimately may develop distant metastases. Secondary EMP is staged according to the criteria for the associated internal malignancy.

Histopathology

On histologic examination MPD and EMP are characterized by neoplastic cells with large nuclei, prominent nucleoli and abundant pale to amphophilic cytoplasm that are scattered throughout the entire epidermal thickness. These cells occur singly and in clusters and often are more numerous in the basal layers of the epidermis. Acinus formation may be present. Paget cells can contain cytoplasmic melanin pigment, a feature that should

not imply melanocytic differentiation. The epidermis is often hyperkeratotic and acanthotic, especially if the disease has been chronic. Particularly in EMP, the tumour cells have a propensity to track along skin appendages. A dermal perivascular lymphohistiocytic infiltrate accompanies the epidermal changes. Paget cells are positive with conventional mucin histochemistry in 40-70% of cases [1297]. In MPD the associated *in situ* or invasive breast carcinoma is of ductal differentiation in the majority of cases. Lobular carcinoma only rarely gives rise to MPD. Histologically, EMP without an internal malignancy cannot be differentiated from those cases with associated neoplasm.

The histopathologic differential diagnosis includes pagetoid squamous cell carcinoma *in situ*, superficial spreading malignant melanoma, pagetoid Spitz naevus, clear cells of Toker, pagetoid dyskeratosis, clear cell papulosis, sebaceous carcinoma, intraepidermal Merkel cell carcinoma, eccrine porocarcinoma, cutaneous T-cell lymphoma, Langerhans cell histiocytosis and epidermotropic metastasis.

Immunoprofile

The immunophenotype of MPD closely matches that of the underlying breast carcinoma [511]. Paget cells are practically always positive for low molecular weight cytokeratins (detectable by specific or broad spectrum cytokeratins such as CK7, CAM5.2 and AE1/AE3) and epithelial membrane antigen (EMA), variably positive for polyclonal carcinoembryonic antigen (pCEA) and lack lymphoid markers such as leukocyte common antigen (LCA) and CD3 [1036,1461]. Gross cystic disease fluid protein-15 (GCDFP-15) has been reported in approximately 50% of cases, similar to that of breast carcinoma in general [511]. As in breast carcinoma, reports of S100 reactivity are quite variable, ranging from 0-26% [1757,2548]. Approximately 5% of Paget cases are oestrogen receptor (ER) and/or progesterone receptor (PR) positive [511].

The tumour cells in primary and secondary EMP are positive for simple cytokeratins (CAM5.2, AE1/AE3), EMA and CEA {1004,1539,1757,2548}. Immunohistochemistry can also suggest the presence of an associated internal malignancy, because primary EMP has the staining characteristics of an apocrine carcinoma and is almost always CK7 positive and gross-cystic disease fluid protein (GCDFP) positive, while CK20 is commonly negative whereas the opposite is true for EMP with associated internal malignancy. The cells in these latter cases are also mostly CK7 positive, but more often express CK20 and do not stain for GCDFP {851,852,1298,1461}. In EMP positive staining with CK20 and lack of staining with GCDFP should prompt an even more thorough evaluation for underlying malignancy.

The most useful keratin markers for MPD and EMP are CAM5.2 and CK7 because they stain >90% of Paget cells but do not react with epidermal or mucosal keratinocytes, a characteristic that makes both antibodies very useful in the evaluation of surgical margins and invasion.

Histogenesis

MPD is almost always associated with an underlying carcinoma of the breast either *in situ* or invasive. MPD represents the retrograde extension of an underlying carcinoma into the epidermis, either in a contiguous fashion, through spread along the lactiferous ducts or through intraepidermal metastasis. Cases without underlying carcinoma exist but are exceptional [1159]. The etiology of these cases is speculative, but probably they are analogous to primary EMP, representing apocrine adenocarcinomas *in situ*, derived from Toker cells. Toker cells are cells with bland cytologic features and clear cytoplasm that have been identified by standard light microscopic means in ~10% of normal nipples [1461]. They are derived from lactiferous duct lining cells and preferentially cluster in the epidermis near lactiferous duct ostia. Primary EMP is an apocrine adenocarcinoma *in situ* that most likely arises from

intraepidermal cells of apocrine gland ducts. These cells, analogous to Toker cells of the nipple, have been recently demonstrated in the epidermis of vulvectomy specimens in association with mammary-like glands [2531]. In secondary EMP the disease represents migration of an underlying internal malignancy to the epidermis. Tumours associated with EMP include rectal adenocarcinoma, transitional cell carcinoma of the urethra and bladder, carcinoma of the Bartholins glands, prostate carcinoma, cutaneous adnexal carcinoma and carcinoma of the vagina and cervix.

Prognosis and predictive factors

The prognosis of MPD depends on the size and characteristics of the underlying breast carcinoma. Patients with MPD but without a clinically detectable breast mass have a much better prognosis. In a recent study, 61 patients with MPD and without palpable mass were treated with a cone excision of the nipple-areola complex and radiation therapy. Histologic examination revealed underlying DCIS in 93.3% of patients and Paget disease, only, in 7%. The recurrence rate at a median follow up of 6.4 years was 5.2% (1 patient with DCIS and 3 patients with invasive carcinoma) [242].

The majority of cases of EMP are not associated with another neoplasm and show a recurrence rate of approximately 30% after surgery, but do not metastasize. Around 10% of patients will develop invasive adenocarcinoma that may progress to metastatic disease [710]. The rate of an associated internal malignancy varies from 15% to 33% and is more common in perianal EMP than vulvar EMP [1024]. In these cases the associated tumour drives the clinical behaviour, treatment and prognosis.

Benign tumours with apocrine and eccrine differentiation

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Hidrocystoma

Definition

Hidrocystomas are cystic proliferations of the sweat glands. They have either apocrine or eccrine differentiation, with the majority being of apocrine nature. Apocrine hidrocystomas are cystic adenomas that arise from the apocrine secretory coil, while eccrine hidrocystomas represent retention cysts of the eccrine cyst duct {607,1919,2047,2188}.

ICD-O code

8404/0

Synonyms

Several and sometimes confusing terms have been used to designate hidrocystomas, to wit: apocrine gland cyst, papillary apocrine gland cyst {1919}, apocrine cystadenoma {1568}.

Epidemiology

Hidrocystomas are relatively rare and account for approximately one per thousand of submitted cutaneous biopsies {607}. They normally present as solitary lesions, however patients with multiple lesions have been observed. Hidrocystomas usually affect middle-aged or older individuals although rare examples have been described in children and adolescents; both sexes are equally affected.

Localization

Hidrocystomas have a predilection for the face and neck, mainly the periorbital area, but may also affect other parts of the body such as the perineum.

Clinical features

Hidrocystomas present as dome-shaped, cystic firm papules or nodules, with a slightly blue colouration. In some cases the content of the cyst is brown or black.

Etiology

The exact cause of hidrocystomas is not known. They have been reported to be exacerbated with high temperatures and



Fig. 3.22 Hidrocystoma presenting as small, dome-shaped lesion on the right side of the face, containing a clear fluid.

to completely disappear with cold weather and atropine therapy {2236}. There is an increased incidence of hidrocystomas in hyperthyroid patients, perhaps related to hyperhidrosis {1270,1673}.

Macroscopy

The lesions are of variable size ranging from 0.5-1.0 cm, although lesions of up to 7.0 cm have been reported. Hidrocystomas are usually located in the dermis,

but in some cases they may be present in the subcutaneous fat. The cut surface reveals a well-circumscribed, unilocular or multilocular cyst.

Histopathology

Hidrocystomas can be uni or multilocular and are usually lined by a double layer of epithelium. The inner layer contains large columnar cells with eosinophilic cytoplasm which has luminal decapitation secretion, while the outer layer is flat and composed of myoepithelial cells. The term "papillary apocrine gland cyst" has been applied for hidrocystomas with papillary projections of epithelium into the lumen {1919}. Occasionally, hidrocystomas may show a single cystic cavity lined by one or two layers of flattened epithelium as a consequence of the pressure exerted by the contents of the cyst. In this circumstance, distinction from eccrine hidrocystomas, which have a similar lining, becomes impossible {671}.

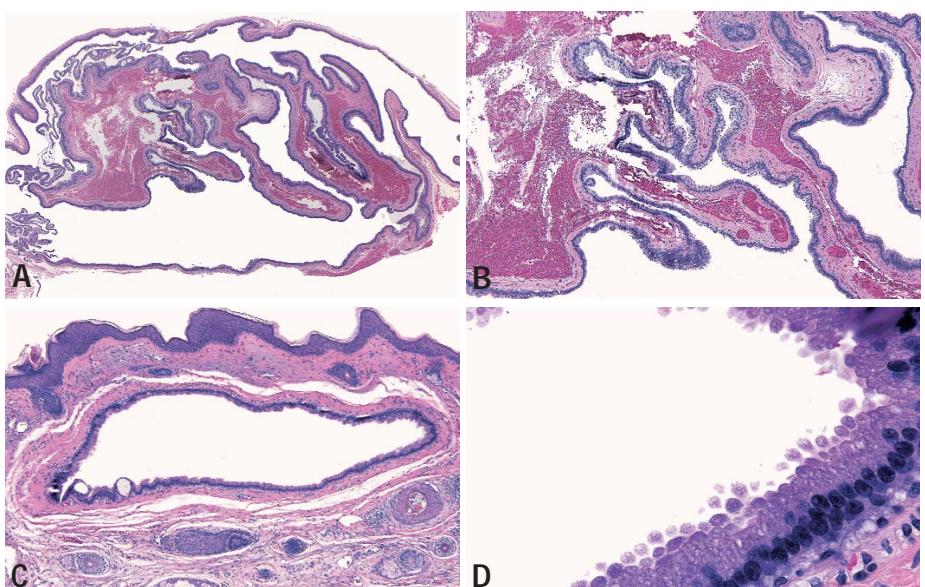


Fig. 3.23 Hidrocystoma, papillary cystadenoma. **A** Example of the so-called "papillary apocrine gland cyst". These lesions are characterized by the presence of papillary projections of epithelium into the lumen. **B** The papillary projections contain a core of connective tissue and are lined by cuboidal epithelium. **C** This picture depicts a typical example of an apocrine hidrocystoma. The lesion is cystic and lined by a cuboidal epithelium. **D** At higher magnification the cyst is lined by a double layer of cuboidal cells with evidence of decapitation and secretion.

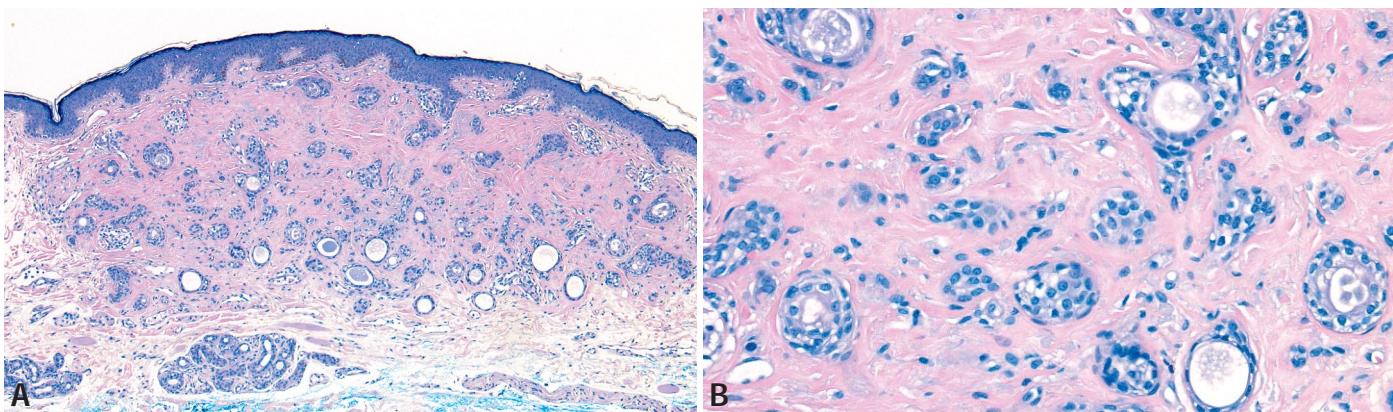


Fig. 3.24 Syringoma. **A** Well circumscribed nodule within the upper dermis. **B** Tubules and cords of uniform epithelial cells in sclerotic stroma.

Immunoprofile

Hidrocystomas express epithelial membrane antigen (EMA) and lysozyme in the cells of the cyst wall; carcinoembryonic antigen (CEA) decorates the luminal cells {1217}. The pattern of cytokeratin expression is variable {607,17444}; there is expression of cytokeratins 7,8,18,19 in the luminal cell layer and cytokeratins 1,5,10,14 in the basal and luminal cell layers.

Smooth muscle actin (SMA) is present in the basal layer {607}. Human milk fat globulin 1 (HMFG) is expressed by the apocrine sweat gland only {607}. S-100 protein is positive in the secretory portion of normal eccrine glands and in the myoepithelial cells of apocrine glands {1678,2358}.

Prognosis and predictive factors

Complete excision is usually curative. Topical atropine or scopolamine has also been used {56,503,2236}. Avoidance of a hot environment or other factors that increase perspiration lessens the severity of these lesions {1668}.

Syringoma

Definition

Syringomas are small benign adnexal neoplasms that are almost always multiple. They are composed of sweat gland epithelium (presumably eccrine) within densely sclerotic stroma.

ICD-O code

8407/0

Synonyms

Eccrine syringoma, lymphangioma tuberosum multiplex.

Epidemiology

Syringomas are common lesions, found more often in women than men. They appear more commonly in Asians than in other races. Syringomas usually arise in adolescence or early adulthood, but are most often biopsied in the 4th decade. Most are sporadic, though some eruptive and disseminated forms may be familial. Syringomas appear to be more common in Down syndrome. A clear cell variant has been associated with diabetes mellitus in many instances {800,2474}.

Localization

By far, the most common sites of involvement are the lower eyelids. Involvement of the upper cheeks is not uncommon. Unusual sites of involvement include the neck, chest, axillae, pubic area, perumbilical region, penis, vulva, hands and forehead. Unilateral linear lesions have been described {552}. Eruptive syringomas are typically numerous, widespread and may appear in crops {1388}.

Clinical features

The lesions are numerous, firm, smooth, dome-shaped, skin coloured or slightly yellowish papules, 1-3 mm in diameter, usually situated in skin of the lower eyelids. Syringomas are rarely solitary.

Histopathology

Syringomas are small lesions, restricted to the upper reticular dermis. They are composed of numerous small solid nests, cords and tubules of epithelial cells within a dense stroma of compactly arranged bundles of collagen, accompanied by relatively few fibrocytes. The epithelial aggregates are usually evenly distributed throughout the lesion. The

epithelial cells of syringoma show small nuclei, inconspicuous nucleoli and absent mitotic figures. Cytoplasm ranges from eosinophilic to clear.

The epithelial cells within tubular structures show an inner layer of luminal cells and one or two rows of more peripheral cells. Tubular lumina may be distended, causing flattening of the inner most lining cells. Larger aggregates of cords and nests of cells may exhibit a "comma-like" or "tadpole-like" configuration. The cords, nests and tubules of syringomas branch and anastomose. Milia may be present, and these may rupture producing granulomatous inflammation and subsequent calcification. Syringomas may become confluent. Eruptive syringomas are similar to standard syringomas; however, the stromal component is sometimes less prominent.

In most conventional syringomas some epithelial cells have pale cytoplasm. In some lesions, these cells predominate, and this pattern has been termed "clear-cell syringoma"; it has frequently been associated with diabetes mellitus, but it may be seen sporadically.

Differential diagnosis

Desmoplastic trichoepitheliomas differ from syringomas by being larger, deeper, and composed of epithelial elements that show follicular differentiation. Superficial biopsies of microcystic adnexal carcinoma may greatly resemble syringoma. Microcystic adnexal carcinomas are larger, asymmetric and less circumscribed than syringoma. Virtually all microcystic adnexal carcinomas extend into subcutaneous fat or skeletal muscle, whereas syringomas are restricted to the upper two thirds of the reticular dermis.

Prognosis

Syringomas are benign. Association with or progression towards carcinoma has not been described.

Poroma

Definition

Poromas are benign adnexal neoplasms with terminal ductal differentiation. Although historically considered a neoplasm of eccrine differentiation, poromas can show either eccrine or apocrine lineage.

ICD-O code

8409/0

Synonyms

Eccrine poroma, hidroacanthoma simplex, dermal duct tumour, syringoacanthoma

Epidemiology

Poromas usually present as solitary tumours on acral sites, although they can be seen in virtually any cutaneous location. Most poromas arise in middle age with no sex predilection. Uncommonly, multiple poromas are seen, either limited to palms and soles or in a widespread distribution, for which the term poromatosis has been applied.

Clinical features

Poromas typically manifest as dome-shaped cutaneous papules, nodules or plaques, generally measuring less than 1 cm in diameter. Some lesions are highly vascular and may show a tendency to bleed, particularly on acral sites. Uncommonly, poromas are pigmented. Rapid growth has been reported during pregnancy {920}. Multiple poromas have developed after electron beam therapy for mycosis fungoides {1348} and occur-

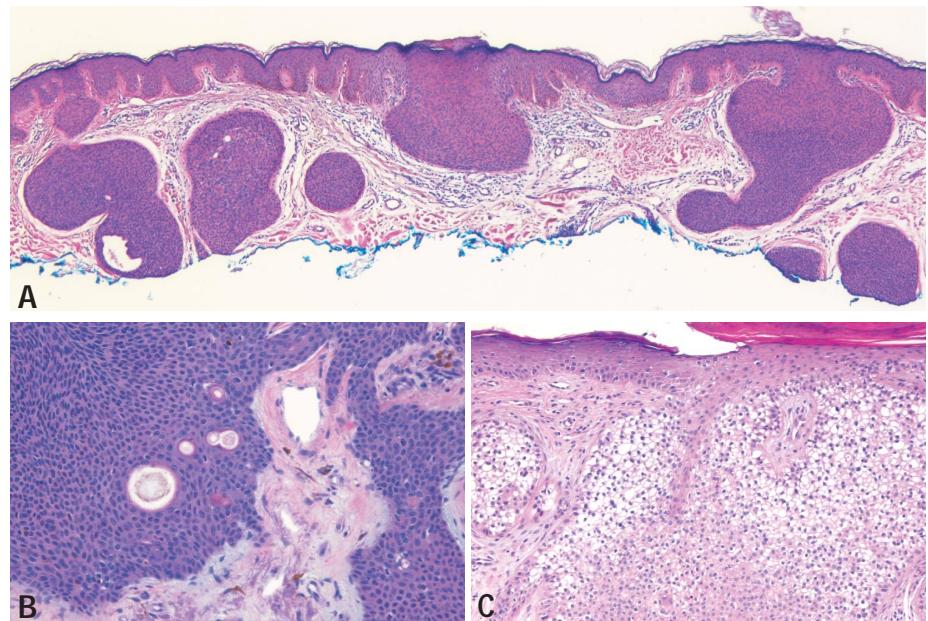


Fig. 3.25 Poroma. **A** Broad tongues of uniform epithelium extend into the dermis from the undersurface of the epidermis. **B** Pigmented poroma illustrating ductal structures and fibrovascular stroma. **C** Clear cell change may be prominent in some poromas.

rence in areas of chronic radiation dermatitis has been reported {1802}. Occurrence of poroma within a naevus sebaceous has been documented {1133}.

Histopathology

Poromas are well-circumscribed tumours composed of a proliferation of uniform basaloid, cuboidal cells punctuated by focal ducts and occasional cysts. The epithelial cells of poromas typically extend from the lower epidermis into the dermis in broad columns. The epithelium of poromas is sharply demarcated from adjacent keratinocytes. Nuclei are small and regular, and cytoplasm is modest in amount. The cytoplasm often contains glycogen. Most poromas contain ductal structures lined by PAS positive diastase-resistant cuticles. Small areas of necrosis as well as mitoses are seen in otherwise banal poromas, and are of no prognostic significance. Foci of sebaceous differentiation may be observed. The stroma surrounding poromas is often richly vascular, and may contain granulation tissue. Architecturally, poromas show a spectrum of change from predominantly intraepidermal lesions (hidroacanthoma simplex) to primarily dermal-based neoplasms (dermal duct tumour). Another rare variant has been termed syringoacanthoma, representing a clonal pattern

of poroma within an acanthotic epidermis with prominent surface keratinization.

Differential diagnosis

Histologically the differential diagnosis includes seborrheic keratosis, which typically shows keratinization with horn cysts, a more sharply demarcated lower border, and absence of ductal structures. Basal cell carcinoma may sometimes be considered histologically, but shows more obvious peripheral palisading, nuclear variability, and little or no glycogen.

Histogenesis

Poromas may show evidence of either eccrine or apocrine differentiation {970}. Immunohistochemical studies reveal that poroma cells express a cytokeratin phenotype similar to basal cells of the eccrine ducts in some cases {2466}. The absence of myoepithelial cells also suggests differentiation toward the excretory (ductal) component of sweat glands. Occurrence of poromas within folliculosebaceous lesions such as naevus sebaceous, and presence of sebocytes within poroma, implicates origin from apocrine glands in some cases {662, 970}.

Genetics

Some cases of poromatosis have been

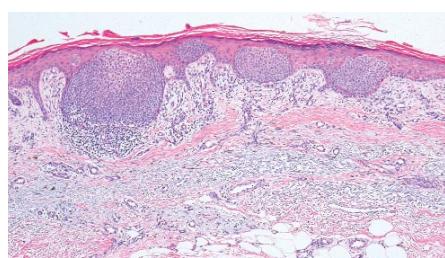


Fig. 3.26 Intraepidermal variant of poroma. There are discrete nests of bland basaloid and cuboidal cells within the epidermis, associated with acrosyringium.



Fig. 3.27 Syringofibroadenoma. **A** Clinical features of the verrucous, solitary type of syringofibroadenoma; a nodule localized on left sole of a 75-years old female, lasting for three years. **B** Eccrine syringofibroadenoma (Mascaro). Presents in many cases as a verrucous plaque. **C** Eccrine syringofibroadenoma (Mascaro). There are branching cords of small keratinocytes attached in multiple foci to the undersurface of the epidermis

associated with hidrotic ectodermal dysplasia {2519}. Rare cases of poroma have occurred in the setting of naevus basal cell carcinoma syndrome {904}. Studies of p53 protein have shown high expression in some poromas as well as in some porocarcinomas, but staining is not correlated with duration of tumours {43}. Therefore, while p53 mutation may be involved in progression of some poromas to porocarcinoma, other oncogenes or factors are also likely play a role in malignant transformation of poromas.

Prognosis

Poromas are benign and simple excision is curative.

Syringofibroadenoma

Definition

Syringofibroadenoma is a rare benign eccrine tumour with anastomosing strands and fibrovascular stroma, first described by Mascaro {1529}. Multiple lesions of syringofibroadenoma are referred to as eccrine syringofibroadenomatosis {456,2189}.

ICD-O code

8392/0

Synonyms

Eccrine syringofibroadenoma {663}, eccrine syringofibroadenomatous hyperplasia {1721}, eccrine syringofibroadenomatosis {456,2189}, acrosyringeal adenomatosis {950}.

Epidemiology

Syringofibroadenoma is rare, with about 75 reported cases. It occurs primarily in older adults.

Localization

Most of syringofibroadenomas arise on acral areas {498,685,769,2248,2313, 2344,2399}.

Clinical features

The most common clinical presentation is solitary, often verrucous papules or nodules {1529,2248,2313}. Unusual presentations include large plaques, linear lesions, and disseminated tumours {1259,2189,2248}.

Etiology

Occasionally, syringofibroadenoma can be associated with other entities, both inflammatory and neoplastic, including bullous pemphigoid {1720,1721}, lichen planus {780}, ulcers {1092,2399}, squamous cell carcinoma {1399}, sebaceous naevus {1719}, and chronic lymphoedema {806}. Based on the latter association and the presence of fibrous stroma, some authors consider syringofibroadenoma as a hyperplasia rather than a neoplasia {779,780,806,1092,1399,1719, 1720}. It may be associated with Schöpf-Schultz-Passarge syndrome {2189}, an autosomal dominant syndrome with palmarplantar keratoderma, hypodontia, and

eyelid hidrocystomas, whose genetic aberration has been localized to chromosome 13q {1259}.

Histopathology

Syringofibroadenoma is characterized by multiple anastomosing cords and strands of monomorphic cuboidal cells {26,1529}. The epithelial cords extend usually into the mid-dermis, and are embedded in a loose fibrovascular stroma. Rarely, a clear cell variant has been observed {781,2415}.

Immunoprofile

Light microscopy usually leads to a specific diagnosis. The tumour cells are usually positive for both keratin 6 and 19 as well as filaggrin {1108,1304,1742,1745, 2314}.

Prognosis and predictive factors

Syringofibroadenoma is a benign condition, and solitary lesions are cured by complete excision, while the treatment of multiple lesions is dependent on the size and location. Cases of syringofibroadenoma with foci of atypical squamous cells have also been described {255, 1215}.

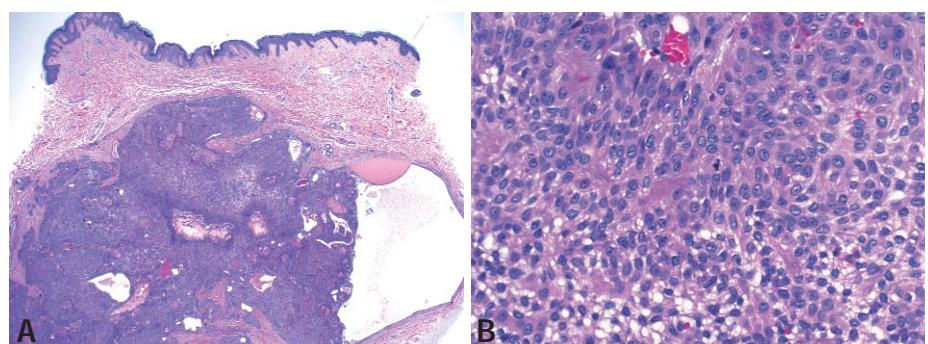


Fig. 3.28 Hidradenoma. **A** There is a multinodular solid and cystic proliferation of monomorphous adnexal keratinocytes. **B** Areas with cytoplasmic pallor are common ('clear cell hidradenoma').

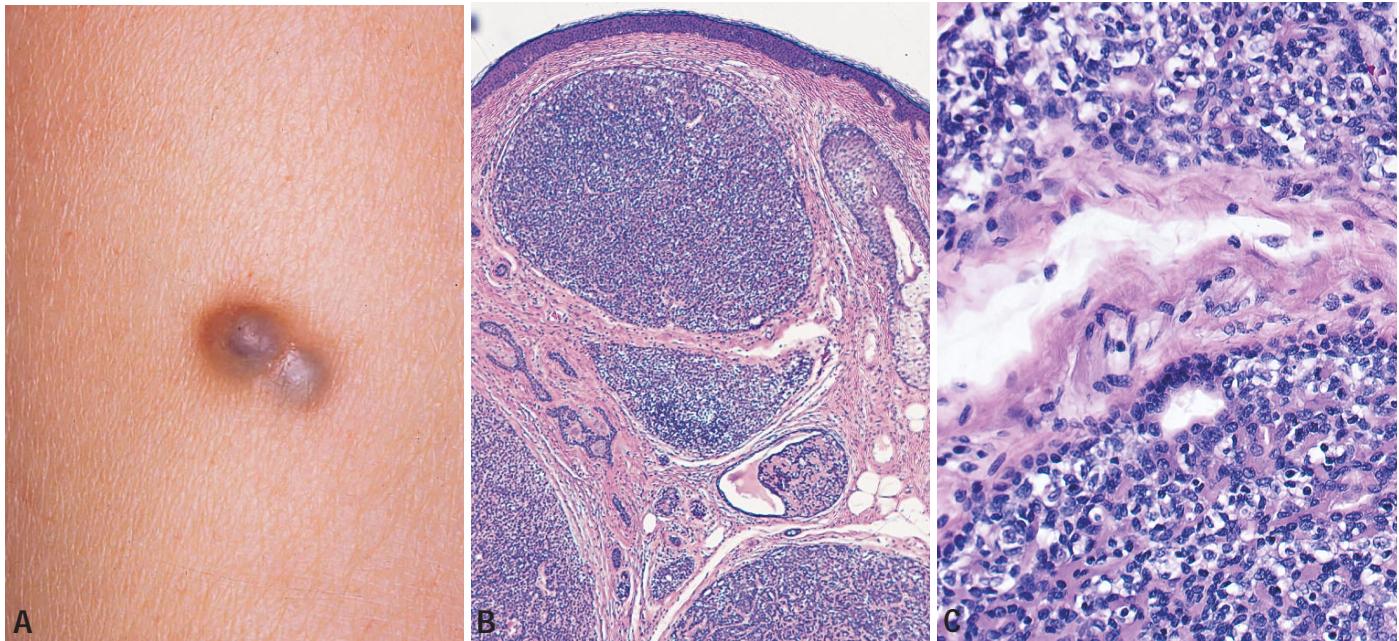


Fig. 3.29 Spiradenoma. **A** A pigmented and painful nodule on the posterior aspect of the arm. **B** These aggregations of neoplastic cells show round shape and smooth borders. **C** At higher magnification, numerous lymphocytes are seen scattered within the nodules of neoplastic epithelial cells. There are two distinct populations of neoplastic epithelial cells, dark and pale. Dark cells are small, basaloid cells with hyperchromatic nuclei and pale cells are larger with vesicular nuclei and ample pale cytoplasm.

Hidradenoma

Definition

Hidradenoma is a benign adnexal neoplasm, closely related to poroma, that displays a limited degree of ductal differentiation. While historically considered eccrine, recent evidence suggests that hidradenoma can be either apocrine or eccrine {825,1543}.

ICD-O code

8402/0

Synonyms

Clear cell hidradenoma, nodular hidradenoma, poroid hidradenoma, acrospiroma, solid-cystic hidradenoma {825,980,1374}.

Epidemiology

Hidradenomas are sporadic with no sex predilection. Most develop in adults, but childhood onset has been documented {715,1652}. Hidradenoma can also arise as a secondary neoplasm with naevus sebaceous.

Localization

Hidradenomas commonly develop on the scalp, trunk, and proximal extremities, and rarely on the hands and feet. Eyelid lesions have also been noted {911}.

Clinical features

Hidradenomas lack any distinctive clinical features, presenting as skin-coloured to red-brown nodules.

Histopathology

Hidradenoma is a mostly dermal neoplasm with a nodular, circumscribed pattern at scanning magnification. Sometimes an epidermal attachment can be identified. The intervening stroma is often sclerotic and may be highly vascularized, with ectatic vascular channels. Hidradenoma is composed of several types of cells:

Clear or pale cells, which contain abundant glycogen, and show distinct cell membranes {578}. The number of clear cells varies from lesion to lesion. When these cells predominate, the name clear-cell hidradenoma is appropriate {2544}. Squamoid cells are polygonal with a central vesicular nucleus and eosinophilic cytoplasm, and often are arranged in whorls {1774}.

Mucinous cells are the least common component. They are large cells with fine basophilic granular cytoplasm. Cuboidal or columnar cells line the tubules and show evidence of apocrine differentiation {1427}.

Transition between different types of cells is frequent. The cells are arranged in

sheets, punctuated by ducts and glandular areas which may show apocrine differentiation. Hybrid lesions including compact poroid cells with prominent ductal differentiation have been referred to as poroid hidradenomas.

Prognosis

Complete excision is curative.

Spiradenoma

Definition

Spiradenoma is a benign dermal neoplasm that can show either eccrine or apocrine differentiation, and significant morphologic overlap with cylindroma.

Historical annotation

Chadeluz, in 1882, probably first described this tumour {765}. Unna first coined the term spiradenoma. In 1956 Kersting and Helwig published the classic paper on spiradenoma in 136 patients {1250}. Additional series of spiradenoma have since been published {12,1496}.

ICD-O code

8403/0

Localization

Most spiradenomas appear on the face

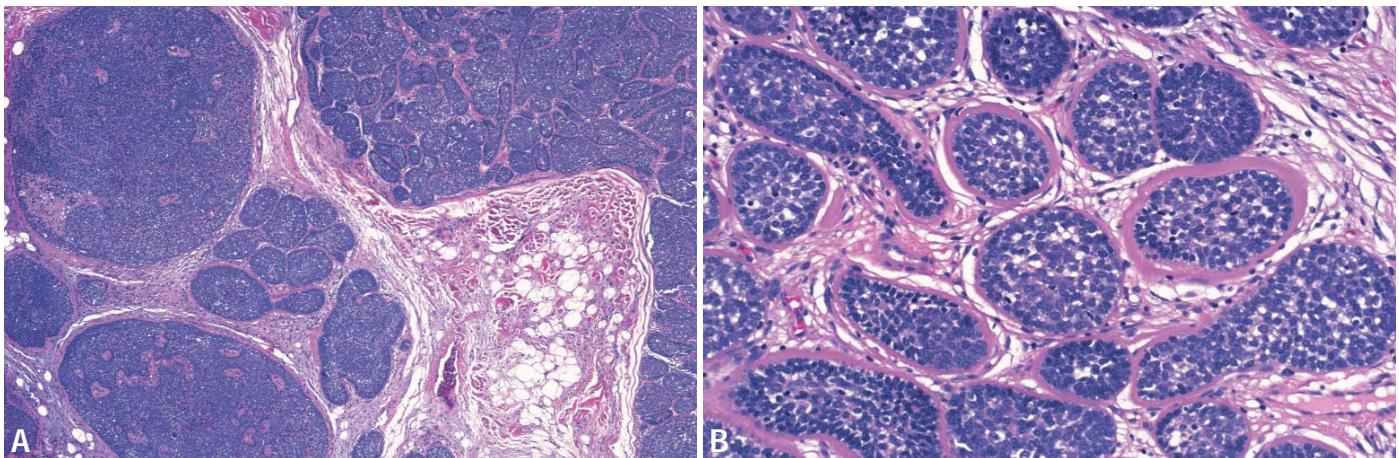


Fig. 3.30 Cylindroma. **A** There is a puzzle-like array of basaloid cells with relatively sharp circumscription of individual nodules. The larger nodules on the left show trabecular internal structure, suggesting overlap with spiradenoma. **B** The nests are outlined by a thick rim of PAS-positive and diastase-resistant basement membrane material.

and upper trunk, but they can also affect other sites.

Clinical features

Usually, spiradenoma appears as a solitary, well-circumscribed, firm nodule, measuring usually less than 1 cm, but giant variants {546} and multiple lesions have also been described {1725}. Unusual cases show multiple spiradenomas arranged in a zosteriform linear pattern {926,2162}. Spiradenoma appears in adult life, although there are also reports of congenital cases {2091}, and in one patient spiradenoma developed within a naevus sebaceous of Jadassohn {2154}. Pain is one of the main clinical characteristics of spiradenoma {926, 2091,2154}. The mechanism of pain or tenderness in spiradenoma is not clear.

Histopathology

At low power magnification, spiradenoma appears as a solid neoplasm composed of a single or few nodules of basaloid cells. These aggregations are round with smooth borders and involve the full thickness of the dermis, sometimes extending into the subcutaneous fat. Often, the intervening stroma is oedematous with ectatic vessels {546}. Dilated vessels rimmed by sclerosis have been interpreted as "ancient" changes due to long-standing lesions {2229}.

Another characteristic finding is the presence of abundant lymphocytes scattered within the tumour nodules. At higher magnification, two distinct populations of neoplastic epithelial cells can be seen, dark and pale. Dark cells are small,

basaloid cells with hyperchromatic nuclei located at the periphery, whereas pale cells, which are larger with vesicular nuclei and ample pale cytoplasm, tend to be near the centre of the clusters. Tubules lined by two rows of epithelial cells may be found within the tumour nodules. A characteristic feature is the presence of eosinophilic PAS positive globules throughout the entire neoplasm, sometimes surrounded by neoplastic cells in pseudorosette fashion. These globules are composed of basement membrane material. Sometimes the stroma shows striking oedema. Spiradenoma in children may show a different histopathologic pattern. The neoplastic cells appear more immature, making the distinction between clear and dark neoplastic epithelial cells difficult, and the neoplasm may be misinterpreted as a mesenchymal neoplasm {1206}.

Spiradenoma and cylindroma show significant morphological overlap. In some patients with multiple lesions, some tumours show features of spiradenoma, and others features of cylindroma. This supports the notion that spiradenoma and cylindroma are closely related, probably representing two morphologic expressions of the same basic neoplastic process {846,2280}.

Immunoprofile

The tumour cells express cytokeratins, and the tubular structures are CEA positive {1801,2465}. Inflammatory cells scattered within the neoplastic aggregations have been identified as abundant T lymphocytes and Langerhans cells.

Histogenesis

The histochemical and immunohistochemical studies have not clarified the histogenesis of spiradenoma. The frequent association of spiradenoma and cylindroma, a likely apocrine neoplasm, and the sporadic association of spiradenoma with neoplasms with follicular differentiation such as trichoepithelioma {2500}, support an apocrine line of differentiation for spiradenoma on the basis of the common embryologic origin for the three elements of the folliculo-sebaceous-apocrine unit. This is furthermore supported by some examples of spiradenoma that show decapitation secretion in the cells lining the luminal border of the tubular structures. Therefore, the qualifying term of "eccrine" that almost invariably is applied to spiradenoma is inaccurate.

Prognosis and predictive factors

Spiradenoma is a benign neoplasm. Because of the sharp demarcation of the tumour from the surrounding stroma, excision is easily accomplished. Several examples of carcinomas arising in long-standing spiradenomas have been described. In those instances, enlargement of a nodule that had been stable for many years seems to be the sign of malignant transformation {89,240,539, 699,884,2602}. It appears to be accompanied by increased expression of p53 protein {239}.

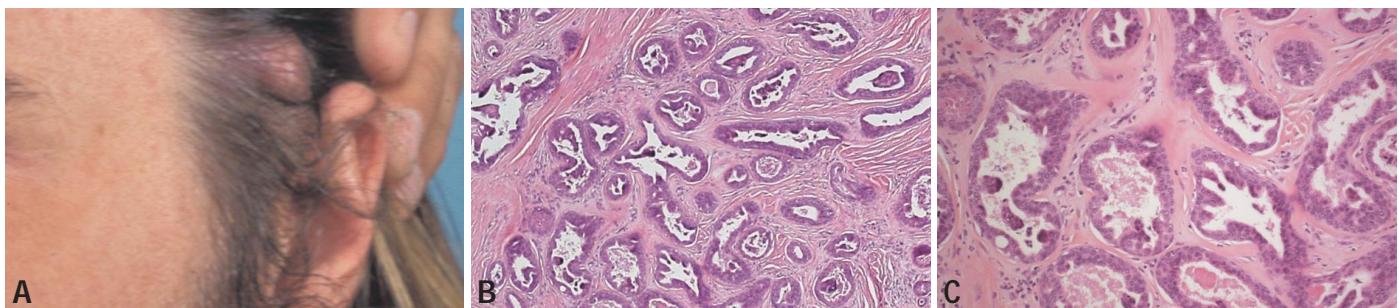


Fig. 3.31 Tubular adenoma. **A** A skin-coloured smooth surfaced nodule on the left parietal scalp. **B** Multiple irregularly shaped tubular glandular structures within a partly sclerosed stroma. **C** Banal appearing tubular glandular elements lined by a double layer of epithelial cells within a sclerosed stroma. The peripheral layer is cuboidal in appearance and the luminal layer demonstrates decapitation secretion. The lumina are filled with cellular debris and granular eosinophilic material.

Cylindroma

Definition

Cylindroma is a relatively undifferentiated benign adnexal neoplasm with a mosaic microscopical pattern. Cylindroma commonly occurs as a hybrid with spiradenoma, an event that has been referred to as cylindrospiradenoma or spiradenocylindroma {301,846,1543,1600}.

ICD-O code 8200/0

Synonyms

Cylindrospiradenoma {301}, spiradenocylindroma {1600}

Epidemiology

Cylindromas may be solitary or multiple, arising on a sporadic basis or as part of Brooke-Spiegler syndrome. There is no sex predilection.

Etiology

The etiology is unknown. A link to chromosome 9 seems likely for multiple spiradenomas and cylindromas in the context of the Brooke-Spiegler syndrome, as the gene has been mapped to 9p21 {951,1538}.

Localization

The vast majority of cylindromas occur on the scalp or face, especially in the vicinity of the ear. Uncommonly, cylindromas develop on the trunk or proximal extremity.

Clinical features

Cylindromas are typically smooth, dome-shaped hairless red-brown papules and nodules. Extensive scalp involvement can create clinical morphology resembling a headpiece ("turban tumour").

Cylindroma can rarely be found as a secondary neoplasm within naevus sebaceous.

ICD-O code

Tubular adenoma	8211/0
Tubular papillary adenoma	8263/0

Histopathology

Cylindroma is a mostly dermal and sometimes subcutaneous neoplasm with a multinodular, circumscribed pattern at scanning magnification. Individual nodules are composed of mosaic nests of undifferentiated basaloid cells with small darkly-staining nuclei and scant cytoplasm; individual nests fit tightly and neatly within larger nodules in a pattern that has been likened to that of a jigsaw puzzle. The nests of cylindroma are commonly surrounded by a rim of densely eosinophilic PAS-positive basement membrane material, and the nests are also punctuated by small round "droplets" with similar staining qualities. Hybrid lesions with areas of cylindroma and spiradenoma in juxtaposition are not uncommon {301,846,1543,1600}.

Immunoprofile and histogenesis

Refer to the previous chapter on spiradenoma.

Prognosis and predictive factors

Simple excision is usually curative. Malignant transformation is extremely uncommon.

Tubular and tubular papillary adenoma

Definition

Tubular apocrine adenoma is a benign dermal adnexal neoplasm demonstrating apocrine differentiation that typically occurs in a broad age group of women on the scalp region.

Synonyms

Apocrine adenoma, tubular adenoma, tubulopapillary hidradenoma, papillary tubular adenoma

Epidemiology

Tubular apocrine adenomas occur sporadically with a female predilection {1361}. A broad age group may be affected {1361}. Some neoplasms may occur in association with a syringocystadenoma papilliferum {76,489,1111, 2364} and can also arise within an organoid naevus {1111,1361,2394}.

Localization

Tubular apocrine adenomas commonly occur on the scalp and less often at other sites including the leg, trunk, axillary and anogenital areas {1361}.

Clinical features

Tubular apocrine adenomas present as asymptomatic solitary nodules that are skin-coloured to pink-red in appearance with either a smooth or irregular appearance {1361}. Most tumours range in overall dimension between 1 to 2 cm but rarely may be as large as 7 cm {1361}.

Histopathology

Tubular apocrine adenomas are well-circumscribed dermal neoplasms that may extend into the subcutis. They have an overall lobular architecture and are typically encased by a fibrous stroma. The lobules consist of multiple irregularly shaped tubular structures that have a double to several layered epithelial lin-

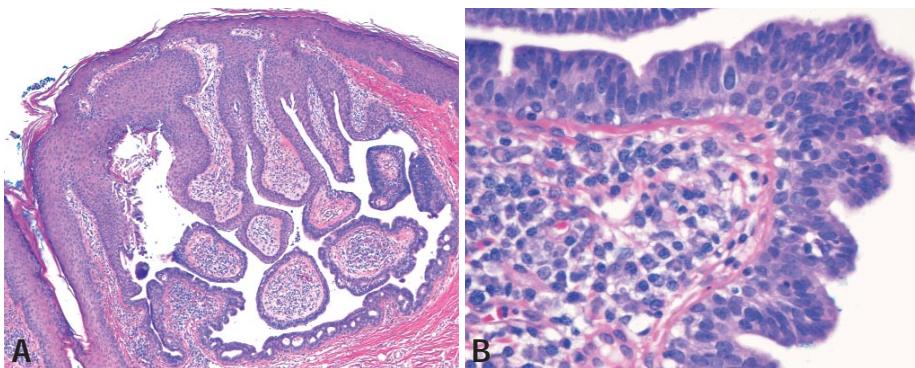


Fig. 3.32 Syringocystadenoma papilliferum. **A** Keratinizing squamous epithelium at the surface merges with columnar epithelium in the deeper portions of the tumour. **B** Papillary projections are lined by pseudosтратified columnar epithelium, and plasma cells are typically noted in the stroma.

ing. The peripheral epithelial layer consists of cuboidal to flattened cells (myoepithelial) and the luminal layer of columnar cells that demonstrate decapitation secretion. In some tubules papillary cellular extensions that are devoid of stroma project into the lumina. Additionally, cellular debris and eosinophilic granular material are identified within some lumina {1361}. The neoplasm lacks cytologic atypia and mitotic activity. Overlying epidermal hyperplasia may be present. In those neoplasms that occur in conjunction with syringocystadenoma papilliferum {76,489,2364}, the tubular adenoma component is typically present underlying the syringocystadenoma component. The differential diagnosis includes apocrine adenocarcinoma and papillary eccrine adenoma. In contrast to apocrine adenocarcinoma tubular apocrine adenomas lack cytologic atypia, are well circumscribed and possess a peripheral myoepithelial layer {1751}. Tubular apocrine adenomas resemble papillary eccrine adenomas in many respects and previously these were believed to be related neoplasms {489}. However on the basis of morphologic criteria (papillary eccrine adenomas lack decapitation secretion) and enzyme histochemistry and ultrastructural analysis demonstrating differences in differentiation (apocrine versus eccrine) they are now believed to represent distinct neoplasms. In some instances both eccrine and apocrine differentiation may be observed making a distinction between these neoplasms impossible {771}. The terms tubulopapillary hidradenoma {705} and papillary tubular adenoma {2335} have been suggested for cases with apocrine and eccrine differentiation.

Histogenesis

Enzyme histochemistry {1361} and ultrastructural analysis {1361,2394} have demonstrated tubular apocrine adenomas to be of apocrine differentiation.

Prognosis

Tubular apocrine adenomas are benign slow-growing neoplasms. Simple excision is curative.

Syringocystadenoma papilliferum

Definition

Syringocystadenoma papilliferum is a benign adnexal neoplasm that occurs in association with an organoid naevus such as naevus sebaceous in at least one-third of cases.

ICD-O code

8406/0

Synonyms

Syringoadenoma

Epidemiology

Syringocystadenoma papilliferum occurs with equal frequency in both sexes. It is a tumour of childhood or adolescence, with many examples noted at birth. These lesions tend to increase in size at puberty, and sometimes multiply in number as well as becoming more papillomatous over time.

Clinical features

The majority of syringocystadenomas affect the head and neck area, typically as one or more warty papules, sometimes in a linear array, or as a solitary grey or red plaque. Scalp and neck are

favoured sites; those on the scalp are typically alopecic. Syringocystadenomas may develop during puberty in a pre-existing naevus sebaceous, and at least one-third are associated with an underlying organoid naevus.

Histopathology

Histologically, endophytic invaginations of epithelium extend from the epithelial surface into the dermis. Typically squamous epithelium is present at the surface of the invaginations, and is contiguous with a double layer of cuboidal and columnar epithelium in the deeper portions of the lesion. Within the dermis, broad villous projections protrude into cystic spaces. Columnar epithelium is present toward the lumen of the spaces, and simple cuboidal epithelium can be seen at the periphery. Decapitation secretion of luminal cells is a frequent finding. Plasma cells are consistently numerous within the stroma, and are a highly reproducible finding in the stroma of syringocystadenomas.

The differential diagnosis includes hidradenoma papilliferum, which differs clinically by location in the perineal region, and histologically by dermal nodules showing a more complex papillary growth pattern, and absence of plasma cells in the stroma. The epithelial lining of the two lesions shows histologic overlap, however.

Precursor lesions

Approximately one-third of cases arise in organoid naevi.

Histogenesis

Syringocystadenomas show differentiation that is predominantly apocrine in pattern, but eccrine origin has been suggested in some cases, as exemplified by immunohistochemical labelling with eccrine marker IKH-4 {1109}. An intriguing finding is the presence of IgA and secretory component within the epithelial cells in syringocystadenomas, and IgA and well as IgG within the plasma cells {2420}. This observation suggests that plasma cells are attracted to tumour epithelium via a mechanism similar to that used by glands of the normal secretory immune system.

Somatic genetics

Allelic deletions of the patched gene 9q22 and loss of heterozygosity at 9p21

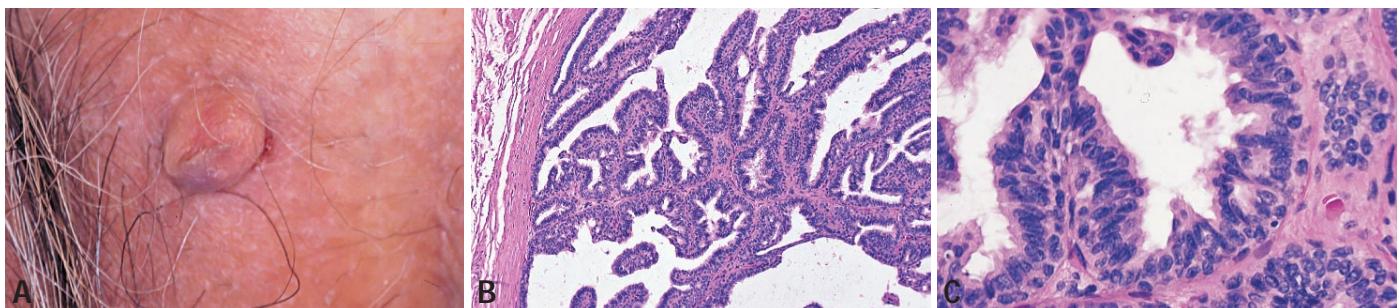


Fig. 3.33 Hidradenoma papilliferum. **A** Hidradenoma papilliferum of the vulva. A polypoid exophytic lesion involving the left labium majus of an elderly woman. **B** The neoplasm shows a prominent papillary pattern. **C** Columnar cells shows evidence of decapitation secretion in their luminal border.

(p16) have been reported in syringocystadenoma papilliferum {281}.

Prognosis and predictive factors

Syringocystadenomas are benign and simple excision is curative.

Hidradenoma papilliferum

Definition

Hidradenoma papilliferum is a benign cystic and papillary neoplasm that almost always develops in the vulval and perianal regions of middle-aged women.

ICD-O code 8405/0

Epidemiology

Most cases appear in women, although there are also reports in males {588, 1441, 1697, 2421}. The neoplasm is rare in Black patients. The age of presentation ranges from 20-90 years {2428, 2435}.

Localization

The skin of the vulva and perianal regions are the most frequently involved areas {588, 1106, 1441, 1565, 1568, 1697, 2324, 2421}, although rare examples of extra-genital or ectopic hidradenoma papilliferum have been reported on postauricular skin {247}, eyelids {1106, 1697, 2056, 2421}, external auditory canal {1718}, face {1106, 1697} scalp {845}, axilla {1106, 2421}, upper limb {2421}, back {727, 1106} and thigh {2421}.

Clinical features

The lesion appears as a slow-growing cystic dermal nodule, usually asymptomatic, although it sometimes ulcerates and bleeds. The neoplasm is a unilateral skin-coloured nodule, papule or polypoid exophytic lesion, most commonly located on the labium majus.

Histopathology

At scanning magnification, hidradenoma papilliferum consists of a cystic neoplasm composed of elongated tubules and large papillary structures with a frond-like pattern. The papillae are composed of a central axis of connective tissue lined by two layers of epithelial cells. The basal layer is composed of pale-staining cuboidal myoepithelial cells and the luminal layer is made up by columnar cells with decapitation secretion. The cystic cavity and the lumina of the tubular structures contain apocrine secretions in the form of eosinophilic homogeneous material.

The epithelial cells at the periphery are flattened, and decapitation secretion is less evident, as a consequence of the pressure exerted by the cyst contents. The stroma surrounding the cystic cavity is composed of compressed fibrous tissue that is separated from the normal adjacent dermis by clefts. These clefts are responsible for the tendency of the neoplasm to shell out easily after incision of the epidermis.

In contrast with syringocystadenoma papilliferum, hidradenoma papilliferum is not connected with follicular infundibula and there are no plasma cells in the axis of connective tissue of the papillations. Sometimes, neutrophils are scattered within the connective tissue framework.

Immunoprofile

Immunohistochemical studies demonstrated that epithelial cells lining the papillations express low-molecular weight cytokeratins. The luminal border of the cells lining tubular structures is also decorated by carcinoembryonic antigen, epithelial membrane antigen and gross cystic disease fluid protein-15. Immunostains for S-100 protein and high-molecular-weight keratins are negative {2257}. Neoplastic epithelial cells lining tubules and papillations also express strong immunoreactivity for androgen and oestrogen receptors {1739}.

Histogenesis

Both the histopathologic and ultrastructural characteristics of hidradenoma papilliferum support an apocrine line of differentiation, although some authors have postulated the possibility of origin from Wolffian ducts or accessory mammary glands {576, 1633}.

Prognosis and predictive features

Hidradenoma papilliferum is a benign neoplasm cured by simple excision. Malignant transformation is a very uncommon event {588, 1730, 2274, 2460}. A case of adenosquamous carcinoma of the vulva developing from a pre-existing hidradenoma papilliferum has also been reported {142}.

Mixed tumour (chondroid syringoma)

Definition

Cutaneous mixed tumours are benign adnexal tumours of skin composed of epithelial and stromal elements with a wide spectrum of patterns. These tumours are histologically analogous to mixed tumours of the salivary gland, but lack the tendency for local recurrence seen in the latter lesions.

ICD-O code 8940/0

Synonyms

Chondroid syringoma, mixed tumour of skin.

Epidemiology

Mixed tumours most often occur as solitary slowly growing nodules on the head

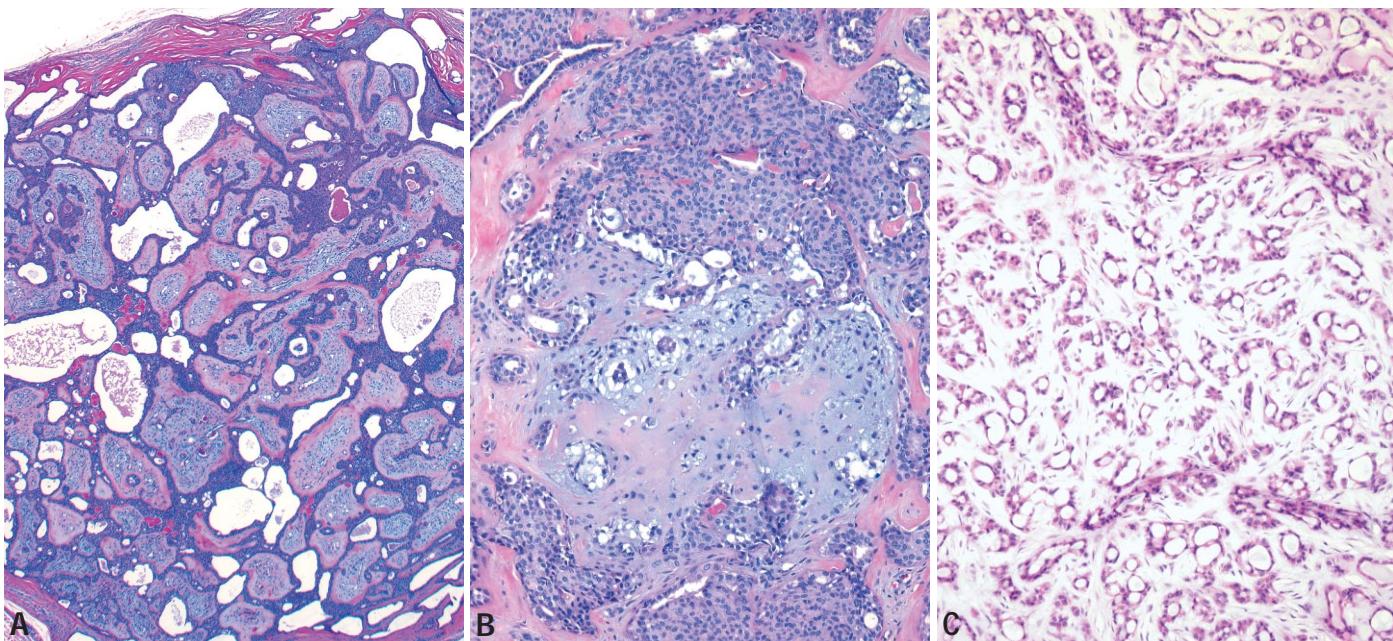


Fig. 3.34 Mixed tumour (chondroid syringoma). **A** Well-circumscribed mixed tumour with branching tubules and myxochondroid stroma. **B** Mixed tumour with epithelial tubules embedded in a myxoid and hyaline stroma. **C** Predominately ductal epithelial pattern of mixed tumour.

and neck of adults, although other sites may be affected. There is a male predilection. Most lesions are between 1–3 cm in diameter, although examples as large as 6 cm have been reported {1182}.

Clinical features

Cutaneous mixed tumours present as asymptomatic dermal nodules, with no specific distinguishing clinical characteristics.

Histopathology

At low power, cutaneous mixed tumours are well-circumscribed lesions located in the dermis and/or subcutis. A biphasic growth pattern can be readily detected, with epithelial elements embedded within a myxoid, chondroid, or fibrous stroma. The epithelium often shows a pattern of branching tubules, sometimes with decapitation secretion suggesting apocrine differentiation. Solid cords and islands of epithelium as well as single cells may also be present. In some cases, the epithelial elements are composed of small non-branching tubules that may contain eosinophilic cuticles. Follicular differentiation occurs in some mixed tumours, in the form of follicular germinative cells, shadow cells, or seocytes. Mixed tumours may exhibit clear cell change within the epithelial cells. In an estimated 40% of cases, mixed

tumours contain hyaline cells characterized by an ovoid shape, dense ground-glass or hyaline-like cytoplasm, and an eccentric nucleus {85}. The cells resemble plasma cells, and have been called plasmacytoid cells. In some cases, hyaline cells are the predominant cell type, leading to the term hyaline-cell rich chondroid syringoma {735}. The presence of hyaline cells appears to be of no prognostic significance, although such cells may present a diagnostic challenge to the unsuspecting pathologist {735}.

Immunoprofile

Immunohistochemical studies reveal staining of the inner layer of epithelial cells with cytokeratin, CEA, and EMA, and staining of the outer cellular layer with S100 and vimentin {2559}. The stroma of mixed tumours usually comprises at least half of the lesion, and may show variable patterns of differentiation, including myxoid, fibroblastic, fibrocartilagenous, chondroid, and even osteoid components. Combinations of matrix components are the rule. Despite the name chondroid syringoma, chondroid areas may be absent in the stroma. The stroma stains strongly for alcian blue with hyaluronidase resistance.

Differential diagnosis

In mixed tumours where stroma predominates, the differential diagnosis includes

entities such as myxoma. In other lesions with abundant epithelial elements, the differential diagnosis includes benign adnexal tumours such as hidradenoma and syringoma, depending on the pattern of epithelial growth.

Histogenesis

It is generally accepted that there are both apocrine and eccrine variants of mixed tumours. Ultrastructural studies confirm that myoepithelial cells surround the epithelial cells, and appear to produce the stromal components of the lesions {2423}. The stroma of mixed tumours contains matrix components such as types II and IV collagen, tenascin, fibronectin, and laminin {773}. Ultrastructural and immunohistochemical studies of hyaline cells in mixed tumours suggest these cells derive from both the epithelial and stromal components of the lesions, possibly representing a regressive process {85}.

Prognosis

Cutaneous mixed tumours are benign lesions cured by simple excision.

Malignant tumours with follicular differentiation

S. Kaddu
L. Requena

Pilomatrical carcinoma

Definition

Pilomatrical carcinoma is the malignant counterpart of pilomatrixoma.

ICD-O code 8110/3

Synonyms

Pilomatrix carcinoma, matrical carcinoma, invasive pilomatrixoma, malignant pilomatrixoma, matrix carcinoma.

Epidemiology

Pilomatrical carcinoma is an extremely rare tumour. Most cases present in adults with a broad age range [28,804,954, 2064]. The mean age at the time of diagnosis is about 48 years. The male to female ratio is 2:1.

Etiology

The majority of pilomatrical carcinomas develop de novo, although malignant transformation from a pre-existing pilomatrixoma has been reported [2064]. It is conceivable that proliferating pilomatrixoma, a variant of pilomatrixoma that

occurs mainly in middle aged and elderly individuals, may represent an intermediate precursor lesion.

Localization

Pilomatrical carcinomas mostly occur in the head and neck, upper extremities and buttocks. Rare tumours have been reported in the axilla and inguinal regions.

Clinical features

The clinical appearance of pilomatrical carcinoma is generally not distinctive. Patients show solitary, occasionally ulcerated or fungating nodules ranging in size from 1-10 cm in diameter. Skin nodules are often of long duration ranging from several months to years before diagnosis, although occasional cases of recent onset and a history of rapid growth have been reported.

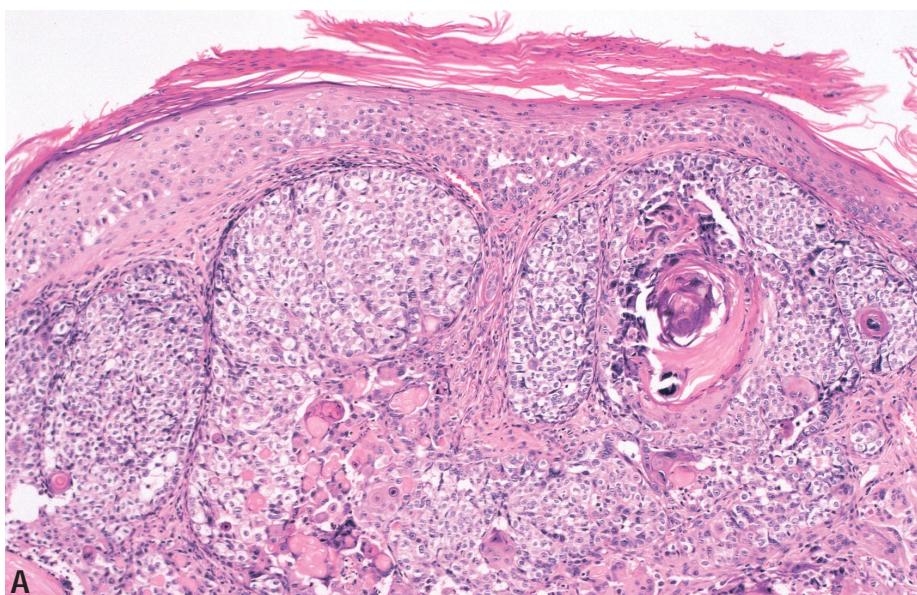
Histopathology

The tumour is a large, asymmetrical, poorly circumscribed dermal or dermal-subcutaneous mass composed of several, irregularly shaped and variously sized

aggregations of basaloid cells (matrical and supramatrical cells) [28,804,954, 2064]. Foci of cornified material containing shadow cells are characteristically observed within the basaloid cell aggregations. Some neoplasms show a variable desmoplastic stroma surrounding the basaloid cell aggregations. Focal connections of basaloid cell aggregations to the overlying epidermis and/or ulceration are often noted. Basaloid cells exhibit hyperchromatic nuclei, with one or more prominent nucleoli and ill-defined cytoplasmic margins as well as variable numbers of occasionally atypical mitotic figures (up to 10 mitoses per high-power field). Foci of geographical necrosis, calcification and ossification are observed. Mitotic activity is not a reliable indicator of malignancy, because mitoses are common in pilomatrixoma. Other parameters, such as an infiltrative growth pattern, as well as angiolymphatic, perineural, and bone invasion, are more reliable features [804,2064].

Immunoprofile

Immunohistological studies have previ-



A

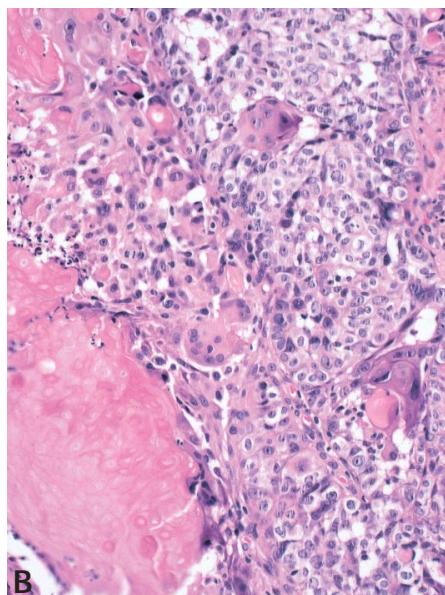


Fig. 3.35 Pilomatrical carcinoma. A The neoplastic cells are present in apposition to the epidermis. B A large mass of shadow (ghost) cells is present. The clear cells have more nuclear pleomorphism than in the pilomatrixoma.



Fig. 3.36 Proliferating tricholemmal tumour. A large tumour on the scalp of an elderly woman.

ously revealed keratin staining in both basaloid and shadow cells {556}.

Prognosis and predictive factors

Treatment of choice is by surgical excision with adequate margins. Mohs micrographic surgery technique may be useful in treating some patients. Pilomatrical carcinoma is a mainly locally aggressive tumour which often recurs if not completely removed but very rarely shows distant metastases. Metastatic spread is

evidenced by involvement of regional lymph nodes, lungs and/or bone.

Proliferating tricholemmal tumour

Definition

Proliferating tricholemmal tumour is a solid-cystic neoplasm that shows tricholemmal differentiation similar to that of the isthmus of the hair follicle.

ICD-O code

8103/1

Synonyms and historical annotation

Epidermoid carcinoma in sebaceous cyst {252,416} subepidermal acanthoma {1458}, proliferating epidermoid cyst {1152}, invasive hair matrix tumour of the scalp {1910}, trichochlamydocarcinoma {1053}, giant hair matrix tumour {583}, proliferating tricholemmal cyst {321}, proliferating pilar cyst {68,92}, proliferating follicular cystic neoplasm {23}, proliferating tricholemmal cystic squamous cell carcinoma {1631}, proliferating isthmic cystic carcinoma. These different names reflect the distinct histogenetic and biologic interpretations for this neoplasm among different authors.

Epidemiology

The neoplasm is more frequent in women than in men and most patients are elderly {2069}.

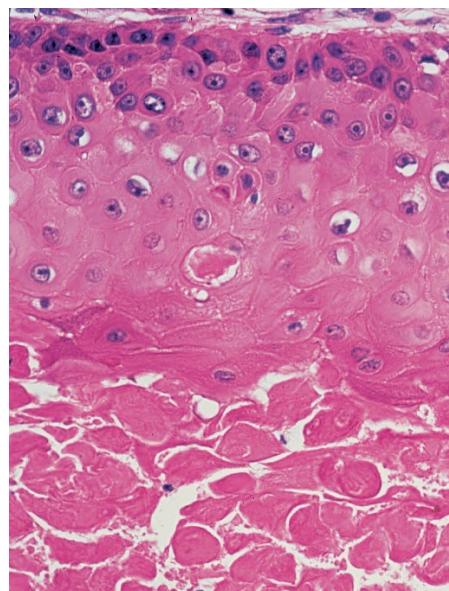


Fig. 3.37 Proliferating tricholemmal tumour. The lobules of the neoplastic epithelium show tricholemmal keratinization, characterized by peripheral palisading of small basaloid cells and large keratinocytes with ample eosinophilic cytoplasm that develop abrupt keratinization without previous granular layer, resulting in compact orthokeratotic eosinophilic keratin. This type of keratinization is similar to that of the outer sheath at the level of the isthmus of the hair follicle.

Localization

More than 90% of the lesions are situated on the scalp. Other described locations, in decreasing order of frequency, include face, trunk, back and forehead {2069}.

Clinical features

The tumour is a solitary, multilobular, large, exophytic mass, which may develop within a naevus sebaceous {866, 1874}. Multiple lesions are very rare. The size ranges from 2-10 cm in diameter, although lesions up to 25 cm in diameter have been described {407}. Alopecia and ulceration can be found.

Macroscopy

The lesions often show a multilobular appearance. The cystic structures often contain compact keratin and calcified material.

Histopathology

Proliferating tricholemmal tumour occurs on a morphologic continuum. On one end of the spectrum, it consists of a well-circumscribed solid and cystic neoplasm which involves the dermis and sometimes extends to the subcutaneous tis-

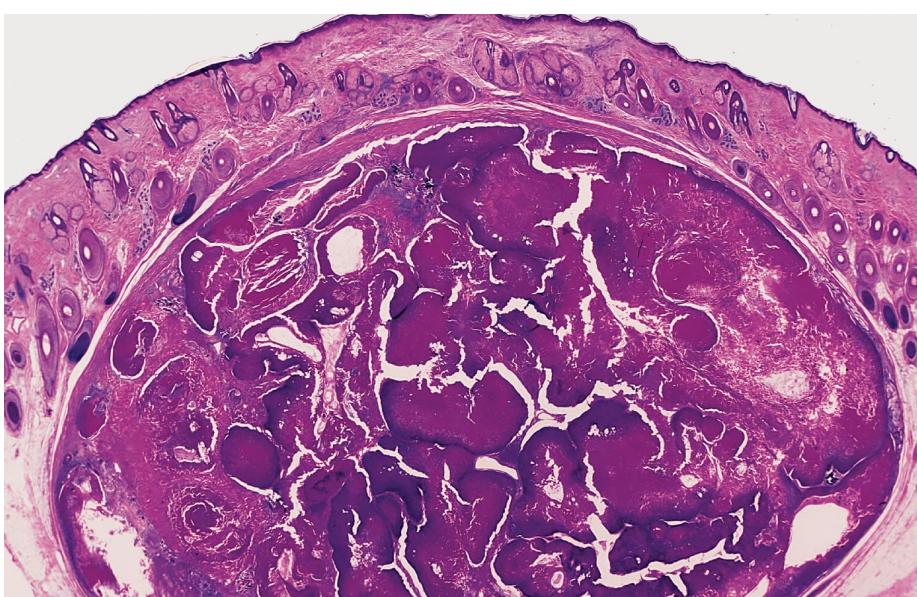


Fig. 3.38 Proliferating tricholemmal tumour. At scanning power the neoplasm appears as a well-circumscribed cystic neoplasm involving deeper dermis and subcutaneous tissue of the scalp.

sue. In addition to the typical features of a tricholemmal (pilar) cyst, this tumour shows prominent epithelial infoldings into the cyst lumen. The epithelium shows peripheral palisading of small basaloid cells arranged along a thick vitreous membrane, differentiating towards large keratinocytes with ample eosinophilic cytoplasm and abrupt keratinization without a granular layer. Often, areas of calcification and abundant cholesterol crystals are seen within the compact eosinophilic keratin. The neoplastic cells are monomorphic without significant cytologic atypia and with only rare mitoses {1135,1724}.

On the other end of the morphologic spectrum are neoplasms with malignant features such as invasive growth extending beyond the confines of the cyst wall coupled with nuclear pleomorphism and high mitotic activity. These areas may be indistinguishable from squamous cell carcinoma. Additional findings include shadow cells as an expression of focal matrical differentiation similar to that of pilomatricoma {1726}, areas of sebaceous and apocrine differentiation {2021}, and spindle cells {1649}.

Differential diagnosis includes tricholemmal cyst, which lacks the multilobular architecture, as well as proliferating epidermoid (infundibular) cyst {2069}. The latter occurs most commonly in the anogenital region of male patients and shows a cystic cavity lined by stratified squamous epithelium with infundibular keratinization. Up to 20% of the lesions may undergo malignant transformation into squamous cell carcinoma {2069}. Differentiation between proliferating tricholemmal tumour and proliferating infundibular cyst is straightforward, because the former shows tricholemmal keratinization, whereas the latter has mainly infundibular keratinization. Tricholemmal carcinoma should also be considered.

Immunoprofile

Proliferating tricholemmal tumour expresses fetal hair root cytokeratin, as well as cytokeratin 7 {933}.

Histogenesis

The pathogenesis remains unknown. In some cases, human papillomavirus has been implicated in the etiology {23}. It is

unclear if proliferating tricholemmal tumours arise de novo or from pre-existing tricholemmal cysts {1631,1847}.

Prognosis and predictive factors

Proliferating tricholemmal tumours without atypical features generally behave in a benign fashion {762}. Yet, complete excision is recommended to avoid recurrences, and to allow for complete histopathological evaluation. Tumours with an invasive growth pattern or cytologic atypia have an unpredictable course. They may be locally aggressive, recur, or metastasize {68,178,982,1017,1537,1572,1727,1728,1773,2311,2486}. For this reason, it has been suggested that even the classical benign lesions are squamous cell carcinoma {1631}.

Benign tumours with follicular differentiation

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H. Kutzner

B. Cribier
T. Schulz
W. Hartschuh

Trichoblastoma

Definition

Trichoblastoma is a benign neoplasm differentiated toward the trichoblast, i.e., the folliculo-sebaceous-apocrine germ, or follicular germ, for short. In many cases, advanced follicular differentiation can be present also {28,989,1083}.

ICD-O code 8100/0

Synonyms

Trichoepithelioma, trichoblastic fibroma, trichogenic trichoblastoma, lymphadenoma (adamantinoid trichoblastoma), trichogerminoma, sclerosing epithelial hamartoma, Brooke-Fordyce disease, Brooke-Spiegler disease.

Clinical features

Trichoblastomas, as a rule, are solitary, small papules that occur on any hair follicle-bearing location (usually head and neck), at any age, and can affect either sex. They can also present as multiple centrofacial papules or nodules, particularly in the diseases of Brooke-Fordyce and Brooke-Spiegler. The size of an individual neoplasm can vary from a few millimetres to several centimetres, but most are less than 1 cm in diameter. Most are skin-coloured and ulcerated only rarely.

The differential diagnosis is non-specific for solitary lesions, but includes the "angiofibroma" of tuberous sclerosis when multiple.

Histopathology

Trichoblastic epithelial components associated with stereotyped stroma, chiefly the follicular papilla, must be present to establish the diagnosis with certainty. There are five patterns; these can be mixed in any given neoplasm.

Large and small nodular trichoblastomas are usually circumscribed, sometimes subcutaneous, and contain a uniform distribution of solid trichoblasts with follicular papillae. In some cases, the follicular "papillae" are not papillary in that they fail to invaginate into the epithelial components of the germ. The epithelial cells are deeply basophilic, uniform, and overlap each other usually. Melanocytes can be prominent within the epithelial areas in some cases. Some cases have nodules that are lymphocyte-rich, a pattern termed originally lymphadenoma {1561,2053}.

It should be noted that, rarely, lesions with a pattern similar to nodular trichoblastoma are really trichoblastic (basal cell) carcinomas that mimic trichoblastoma. While it is not completely understood what are all the factors that

differentiate these lesion from trichoblastoma, one seems to be that the carcinomas infiltrate through skeletal muscle or other deep structures while there is a conspicuous absence of the usual stroma present in a classic nodular trichoblastoma. Rare examples with this pattern have metastasized {1960}.

Retiform trichoblastomas are reticulated, with large fenestrations containing follicular stroma.

Cribriform trichoblastoma is the most common pattern when the neoplasms are multiple, characteristic of Brooke-Fordyce disease. The trichoblasts are usually fenestrated, but with small fenestrations compared to the retiform pattern. Racemiform trichoblastoma contains epithelial nests that simulate "clusters of grapes". This results in stromal components that connect with the surrounding stroma rather than being isolated from it in fenestrations.

Columnar trichoblastoma (desmoplastic "trichoepithelioma") occurs most commonly as a solitary depression on the face of a young woman. As a rule, these neoplasms are confined to the superficial dermis. They contain stereotyped, thin strands of epithelium compressed by dense stroma. Small trichoblasts can be seen in some cases, but are less common compared to conventional forms of

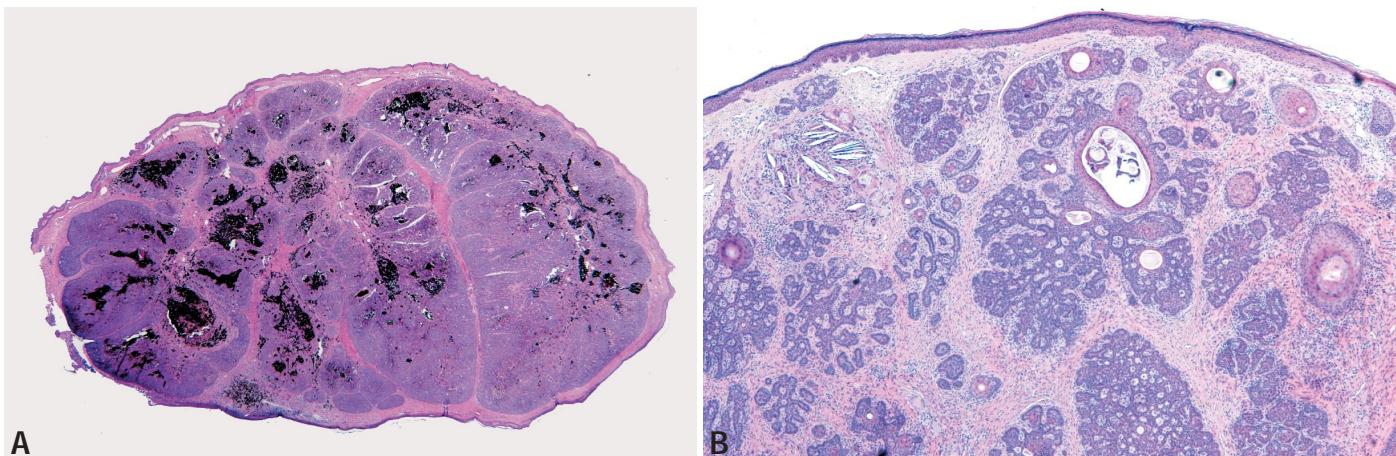


Fig. 3.39 Trichoblastoma. **A** Large nodular trichoblastoma. Note the circumscription. Melanin pigmentation is present in this lesion. **B** Cribriform trichoblastoma. At scanning magnification, there are small groupings of basophilic cells containing small fenestrations of stroma.

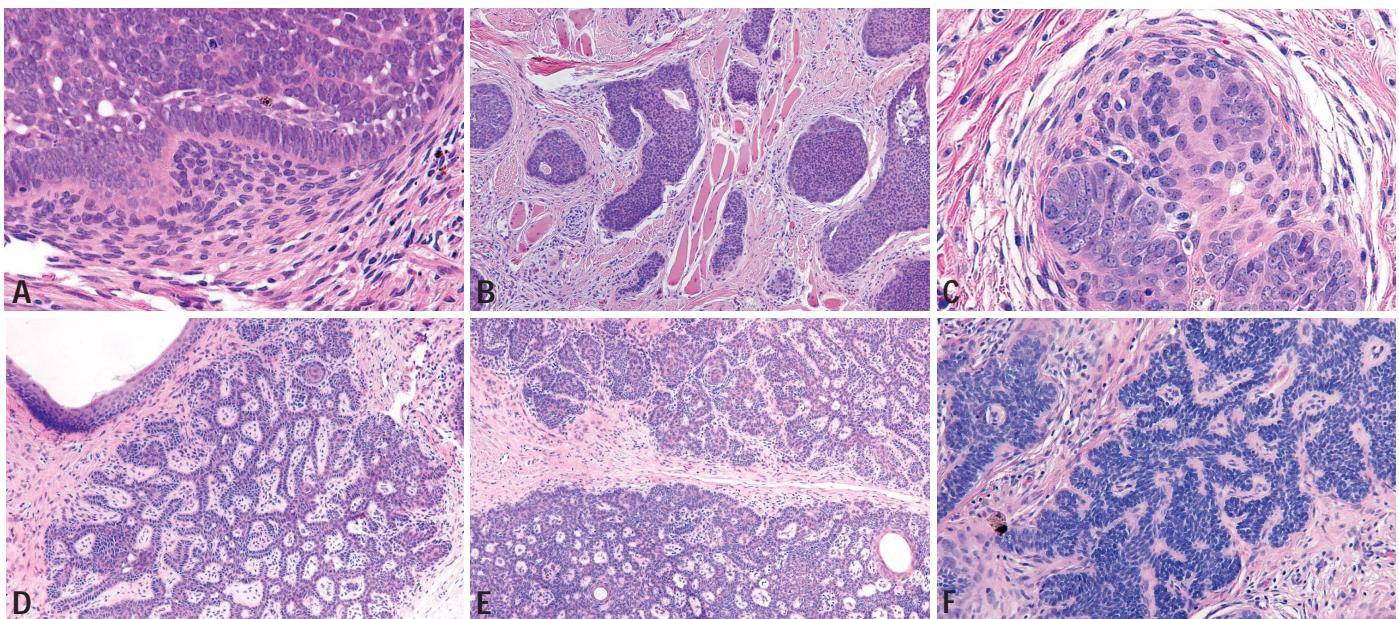


Fig. 3.40 Trichoblastoma. **A** This trichoblast has a typical follicular "papilla" that does not extend cleanly into an invaginated epithelial component of the follicular germ. **B** Compared to the usual types of trichoblasts seen in nodular trichoblastoma, this trichoblastic carcinoma has diminished mesenchymal stroma, specifically diminished mesenchyme of the follicular papilla. **C** Trichoblast containing a superficial follicular papilla that protrudes into an invaginated follicular germ. This is a fundamental finding in trichoblastomas of any pattern. **D** Retiform trichoblastoma. This reticulated pattern is seen often in large, solitary lesions. **E** This sieve-like pattern is commonly present in the small centrofacial lesions of Brooke-Fordyce disease and is the pattern known classically "trichoepitheliom". **F** Groupings of follicular germinative cells that branch out, mimicking a "cluster of grapes". Absence of sieve-like areas seen in the cribriform pattern.

trichoblastoma. The differential diagnosis includes morpheiform basal cell carcinoma, microcystic adnexal carcinoma, and, rarely, metastatic carcinoma from breast. Thus, superficial biopsies of such lesions should be investigated thoroughly, and additional biopsy or excision should be requested for cases in which the diagnosis is uncertain.

Immunoprofile

Trichoblastomas, as a rule, cannot be differentiated from basal cell (trichoblastic) carcinoma based solely on specific expression of cytokeratins. The presence of presumed Merkel cells within a neoplasm, however, does seem to favour trichoblastoma over basal cell carcinoma [1349]. Some trichoblastomas can contain zones of ductal differentiation; when this occurs, markers, such as CEA will highlight those areas [2398] but they will not aid in establishing the diagnosis. Uncommonly, excessive pigmentation is seen in nodular trichoblastoma, and these lesions contain markers for melanocytes [1199], but they are non-specific for the diagnosis, as basal cell (trichoblastic) carcinoma can have similar findings.

Desmoplastic trichoepithelioma contains AE14, EMA, and Leu-M1 (CD15) focally,

but is negative for CEA and S100 [2511]. CK 5, 8, 14 and 15 have been identified in some cases [2555]. It can be differentiated from morpheiform basal cell carcinoma and microcystic adnexal carcinoma, in most cases, by applying CK20, which marks neuroendocrine cells in desmoplastic trichoepithelioma, but not in basal cell carcinoma or microcystic adnexal carcinoma [13]. Furthermore, CK7 is usually positive in breast carcinoma metastatic to skin and in microcystic adnexal carcinoma, but not in desmoplastic trichoepithelioma. Stromelysin 3 has also been identified in the stroma of morpheiform basal cell carcinoma, but not in the stoma of desmoplastic trichoepithelioma [2346].

Somatic genetics

Multiple trichoblastomas (Brooke-Fordyce disease) are transmitted as an autosomal dominant trait linked to chromosome 9p21 [6,951]. Solitary (sporadic) trichoblastomas have been linked, in some cases, to 9q22.3 [1538], the same locus for the naevoid basal cell carcinoma syndrome [4]. Familial multiple trichoblastomas and cylindromas (Brooke-Spiegler disease) have been linked to chromosome 16q12-q13 [5,722].

Prognosis and predictive factors

Because these are benign neoplasms, no treatment is required, in most cases, if the diagnosis is established with certainty. Because some trichoblastomas may occur, rarely, in association with basal cell (trichoblastic) carcinoma, and because of the difficulty in establishing the diagnosis in superficial biopsies, in some cases, additional biopsy or excision should be considered if there is uncertainty about the diagnosis.

Pilomatricoma

Definition

Pilomatricoma is a relatively common benign cutaneous adnexal neoplasm with differentiation towards the matrix and inner sheath of a normal hair follicle as well as hair cortex [28,1169].

ICD-O code

8110/0

Synonyms

Pilomatixoma, calcifying epithelioma of Malherbe, benign calcifying epithelioma

Epidemiology

Pilomatricoma accounts for up to 0.2% of all routine dermatopathologic specimens

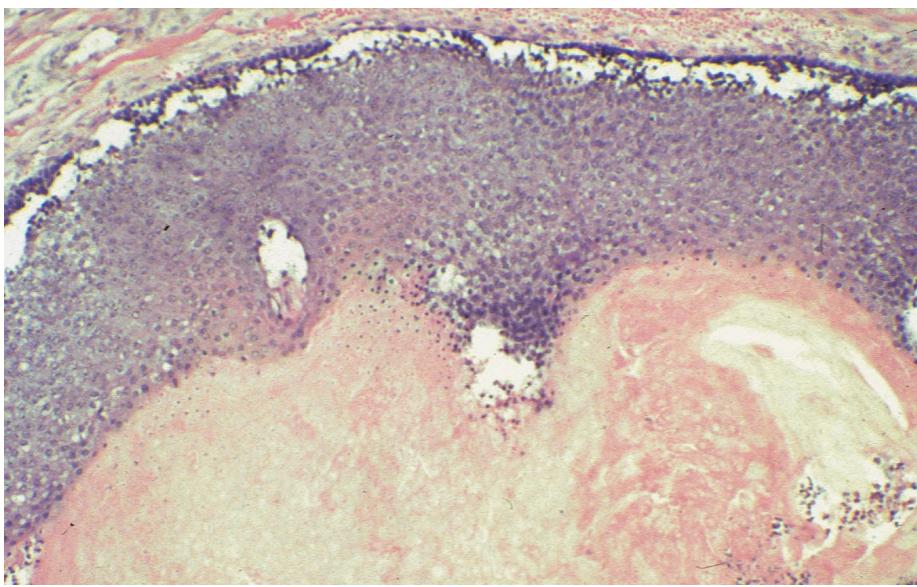


Fig. 3.41 Pilomatrixoma. There is a growth component of basoid cells with transition to pilar 'shadow cells'.

in certain centres. The tumour occurs in all age groups [1169]. About 30-50% of cases present in young individuals less than 30 years of age. Previous studies have shown a female predominance.

Localization

Pilomatrixomas favour hair-bearing areas, with the majority of cases arising in the head and neck region as well as upper extremities.

Clinical features

Patients present with solitary, asymptomatic, slowly growing, cystic or firm nodules measuring 0.5-3 cm in diameter [28,1169,1170]. Lesions are commonly

skin-coloured, but may show a bluish-purple to reddish hue or pigmentation. Unusual presentations include rapidly growing or giant tumours (measuring up to 15 cm in diameter), lesions with overlying striae or anetodermic changes, and multiple tumours. Multiple pilomatrixomas are quite rare. They are a marker for myotonic dystrophy, and may rarely be associated with a number of different conditions including Rubinstein-Taybi syndrome, Turner syndrome, Goldenhar syndrome, sternal cleft defects, coagulative defects, and sarcoidosis. Pilomatricoma-like features are an occasional finding in cutaneous cysts removed from patients with Gardner syndrome.

Macroscopy

Grossly, pilomatrixomas occur mostly as lobulated masses with variable amounts of chalky white or yellow keratinous material on their cut surfaces. Foci with bone may be observed.

Histopathology

There is usually a relatively well-circumscribed, deep dermal or dermal-subcutaneous, cystic neoplasm surrounded by a variable connective tissue stroma [28, 1169]. A spectrum of histopathologic features reflecting mainly different stages of development is observed in individual lesions. Early and well-developed pilomatrixomas are characterized by small to large-sized, cystic lesions lined focally by aggregations of basaloid cells (matrical and supramatrical cells) and few squamoid cells and filled centrally with large masses of eosinophilic cornified material (faulty hair matrix) containing shadow (ghost) cells as well as a few keratin filaments. A transition zone of retained nuclei from basaloid cells to eosinophilic cornified material containing shadow cells is focally observed. Basaloid cells exhibit deeply basophilic oval or round nuclei and a variable number of mitotic figures. Inflamed or regressing pilomatrixomas are relatively large cystic tumours with prominent areas of shadow cells and foci of basaloid and/or squamoid cells surrounded by a variable, often dense inflammatory infiltrate with histiocytic giant cells, and occasionally siderophages and/or melanophages. Areas of granulation tissue may be present. Occasional lesions dis-

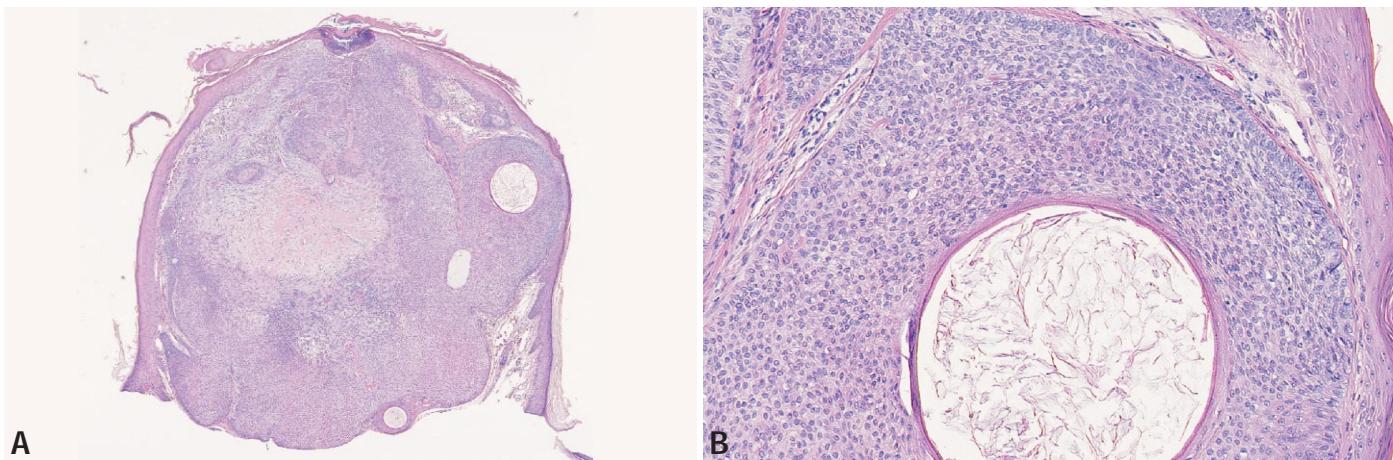


Fig. 3.42 Tricholemmoma. **A** Exo-endophytic tumour with wart-like silhouette and focal desmoplastic stroma. **B** Peripheral epithelia are arranged in a palisade. Small central follicular microcyst.

play features of transepidermal elimination of shadow cells (perforating pilomatricoma) or a keratoacanthoma-like pattern. Old pilomatricoma lesions reveal no epithelial components but show irregularly shaped, partially confluent, focally calcified or metaplastically ossified shadow cell areas embedded in a desmoplastic stroma, with little or no inflammatory infiltrate. Extramedullary haematopoiesis has been observed in some regressing and old pilomatricoma lesions.

A subset of pilomatricomas, also termed "proliferating pilomatricoma", is characterized by the presence of relatively large, solid or solid-cystic basaloid cell areas with small foci of shadow cells {1170}. This variant presents mainly in middle aged and elderly individuals. "Matricoma" represents another unusual pilomatricoma variant characterized by discrete, small, solid aggregations of basaloid cells with several connections to pre-existing infundibula at different points {28}.

Molecular and cytogenetics

Derivation of pilomatricomas from the hair matrix has been underlined by recent biochemical studies demonstrating prominent staining of tumour cells with antibodies directed against LEF-1, a marker for hair matrix cells. Mutations in the gene CTNNB1 have been detected in up to 75% of pilomatricomas studied implicating beta-catenin/LEF misregulation as a possible cause of hair matrix cell tumourigenesis {438}. In another study, all 10 pilomatricomas examined were found to display strong bcl-2 immunostaining, a proto-oncogene well known to help in suppressing apoptosis in benign and malignant tumours {712}. This finding supports a role for faulty suppression of apoptosis in the pathogenesis of pilomatricomas.

Prognosis and predictive factors

Treatment is recommended mainly to avoid a foreign body reaction and inflammation with eventual scarring. Surgical excision is usually curative, but occasional recurrences may be observed. Spontaneous regression has been reported in a few cases. Malignant transformation has only been suspected in a single case of pilomatrical carcinoma {2064}.

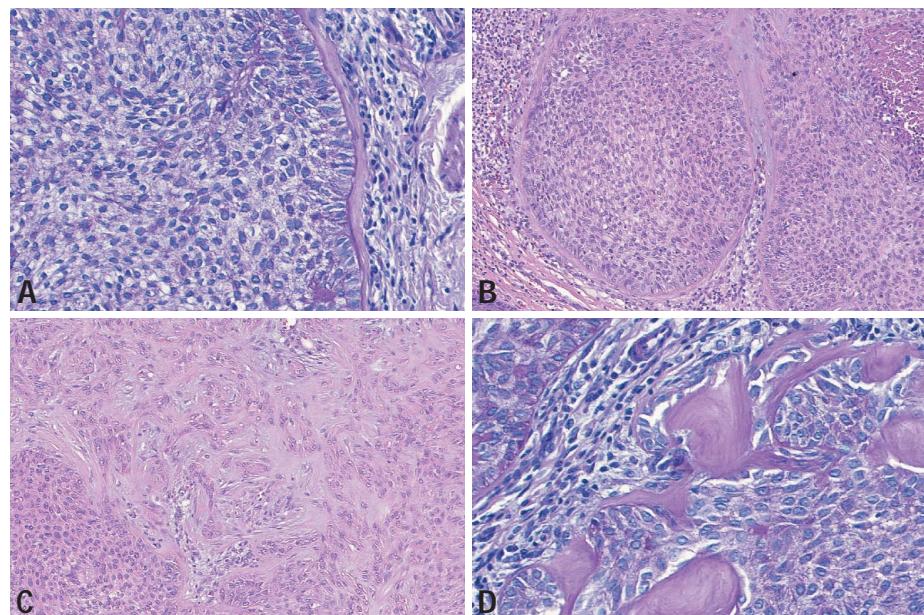


Fig. 3.43 Tricholemmoma. **A** Thick PAS-positive basement membrane. **B** Focal necrosis within bulbous follicular hyperplasia. Thickened basement membrane. **C** Desmoplastic stroma with entrapped bizarre epithelial strands ("pseudo-invasive interface"). **D** PAS-positive desmoplastic stroma and basement membrane.

Tricholemmoma

Definition

Tricholemmoma (TL) is a benign folliculo-infundibular proliferation occurring frequently but not exclusively on the face of adults. Multiple tricholemmomas may be associated with Cowden disease.

ICD-O code

Tricholemmoma	8102/0
Multiple tricholemmomas	8102/0

Synonyms

Trichilemmoma

Epidemiology

TL is a relatively common cutaneous proliferation that occurs mostly in adults and affects both sexes equally {323}. Multiple TLs, often in conjunction with acral keratoses, palmar pits, and oral fibromas, are a cutaneous marker of Cowden disease (multiple hamartoma and neoplasia syndrome) {322,325,681,2025,2247, 2249-2251}.

Localization

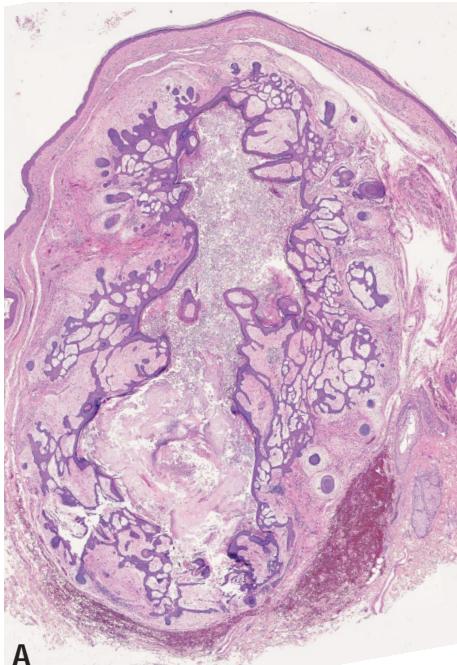
TL arises on the head and neck, almost exclusively on the face, favouring the centrofacial area. Rarely, TL may occur in naevus sebaceous {410,1979}.

Clinical features

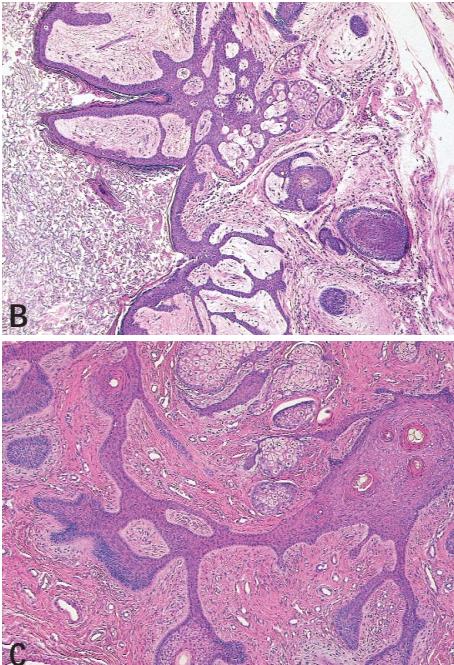
Patients usually present with a solitary asymptomatic exophytic centrofacial lesion which is either wart-like with verrucous and keratotic features or dome shaped with a smooth surface. Individual lesions are small, varying in diameter between 3 and 8 mm {28}. Multiple facial TLs are almost invariably associated with Cowden disease {2247,2249-2251}.

Histopathology

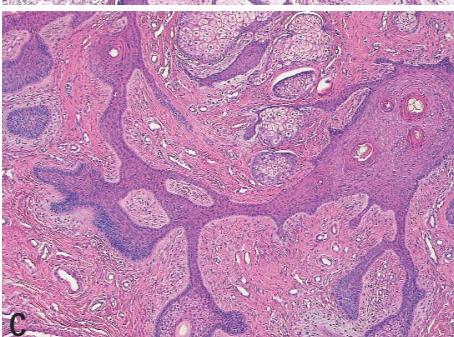
Most cases of TL present as a sharply circumscribed superficial exo-endophytic proliferation with a papillated surface. There is marked parakeratosis, hyperkeratosis, and wedge-shaped hypergranulosis of the infundibula, in conjunction with a collarette of embracing adnexal epithelium {28,323}. TL does not involve the interfollicular epidermis. The dominating histological pattern of TL is that of a bulbous infundibular hyperplasia with tricholemmal differentiation, akin to the outer root sheath of the hair follicle {28}. There are one or more bulbous lobules, always in continuity with the epidermis. These lobules consist of numerous pale and clear isomorphic epithelia, most of which are PAS positive. At the periphery, pale columnar cells are arranged in a palisade, bordered by a prominent PAS-



A



B



C

Fig. 3.44 Trichofolliculoma. **A** Note reticulate pattern of vellus follicles in devolution. **B** Detail. Reticulate epithelial strands, sebaceous lobules and few vellus follicles. **C** Note sebaceous lobules and dense fibrotic stroma. Vellus follicles in different stages of devolution.

and type IV collagen-positive basement membrane. Central foci of epidermal / infundibular keratinization, occasional small and inconspicuous squamous eddies, and keratinous microcysts in larger lesions are occasional findings [28]. There are no mitoses.

Desmoplastic tricholemmoma is a variant of TL characterized by a highly desmoplastic stroma with broad zones of sclerosis and distinctive artifactual clefts. Instead of "pushing" smooth lobular contours there may be a pseudoinvasive interface akin to pseudocarcinomatous epithelial hyperplasia, simulating carcinomatous growth [1079,2333].

Differential diagnosis

Warts, basal cell carcinomas, squamous cell carcinomas, trichoblastomas, seborrhoeic keratoses, and keratosis follicularis inversa may contain areas of tricholemmal differentiation [31,1931]. The tumour of the follicular infundibulum exhibits a plate-like pattern with interconnecting horizontally oriented epithelial strands. Inverted follicular keratosis consists of basaloid and squamous epithelia, associated with large numbers of squamous eddies (i.e. concentric layers of squamous cells in a whorled pattern, sometimes keratinized).

ICD-O code

8101/0

Epidemiology

TF represents a rare hamartoma mostly occurring during adulthood (with a wide range of ages between 11 and 77 years [28]) without sex predilection [887].

Localization

TF favours the head and neck region, foremost the face. Most lesions are situated around the nose [887].

Clinical features

TF presents as a solitary asymptomatic dome-shaped lesion with a smooth surface and a widely dilated central ostium from which a small tuft of delicate white hairs emerges. Lesions are small, ranging between 0.5 and 1.0 cm in diameter [28].

Histopathology

The main histological features of TF are reflected by its "Caput Medusae" pattern [28]: embedded in a highly fibrocytic stroma, large numbers of vellus follicles with upper and lower segments like those of normal follicles radiate from the perimeter of a dilated infundibulum.

TF is a symmetrical, well-circumscribed, vertically oriented lesion composed of three components: infundibulo-cystic, follicular, and stromal [28]. The centre of the lesion is occupied by one or more widely dilated infundibulo-cystic structures that are continuous with the epidermis and open to the surface of the skin through an ostium. The cystic lumina may be filled with innumerable corneocytes and vellus hairs. From the epithelial walls of the infundibular cystic spaces smaller infundibula radiate, to which are attached vellus follicles in various numbers. These vellus follicles are not associated with muscles of hair erection or with sebaceous ducts, albeit sebaceous cells arranged as solitary units or in lobules may occur within the lining epithelium of the central infundibulo-cystic structure.

The morphology of the individual vellus follicles may vary from normal to strikingly aberrant [28]. Normal vellus follicles may exhibit all stages of the follicular cycle [2106]. The whole lesion is embedded in a cellular connective tissue sheath, which is separated from the adjacent normal dermis by prominent shrinkage clefts. The highly fibrocytic stroma

Histogenesis

According to strict topographical anatomical criteria, TL arises from the follicular infundibulum and differentiates toward the outer [tricholemmal] root sheath [28]. Its superficial folliculo-infundibular location militates against the classification of TL as a neoplasm of the lower portion of the hair follicle (i.e. the [outer] tricholemmal sheath).

However, it is still a matter of debate whether TL is of hamartomatous/neoplastic [318,991,1906,1931] or of viral origin [15,28,31]. The detection of HPV DNA in tricholemmomas by PCR [2688] favours the latter view of TL as a resolving verruca vulgaris with tricholemmal differentiation [15,28, 31].

Prognosis and predictive factors

TL is an entirely benign cutaneous neoplasm. Multiple TLs are a hallmark of Cowden disease and should prompt a search for internal malignancy.

Trichofolliculoma

Definition

Trichofolliculoma (TF) is a follicularly differentiated hamartoma generally appearing during adult life.

which surrounds the individual vellus follicle resembles perifollicular sheath [28]. The existence of considerable numbers of Merkel cells in all trichofolliculomas underlines their classification as hamartomas with follicular differentiation [967].

Variants

TF is a complex lesion with protean features [28]. Some of these are caused by the evolutionary and devolutionary alteration of the vellus hair follicles in their regular biological cycles [2106]. In this context, folliculo-sebaceous cystic hamartoma [1275,2187] may be interpreted as a TF at its very late stage with nearly complete regression of the transient follicular epithelium, but with concurrent growth and maturation of sebaceous elements [2105]. Sebaceous trichofolliculoma [1846] exhibits distinct sebaceous lobules at its outer circumference, but lacks vellus follicles that radiate from the epithelial lining of the dilated infundibulum. The latter criterion militates against the classification of sebaceous trichofolliculoma as a true TF [28]. Hair follicle naevus is regarded as a TF that was histologically sampled at its periphery [28]. There is a striking predominance of mature vellus follicles and the central infundibular lumen may be quite inconspicuous.

Prognosis and predictive factors

TF represents an entirely benign cutaneous hamartoma with no reports of tumour progression or aggressive clinical course.

Pilar sheath acanthoma

Definition

Pilar sheath acanthoma is a follicular neoplasm differentiated toward the permanent part of the hair follicle, to wit, the infundibulum and the isthmus. [The infundibulum is an extension of epidermis to meet the isthmus, but both function as part of the follicular sheath].

Synonyms

Infundibuloisthmicoma

Clinical features

Pilar sheath acanthomas affect adults of either sex, and are identified usually on the face. They are small, solitary papules up to 5 mm in diameter, with a central 1-

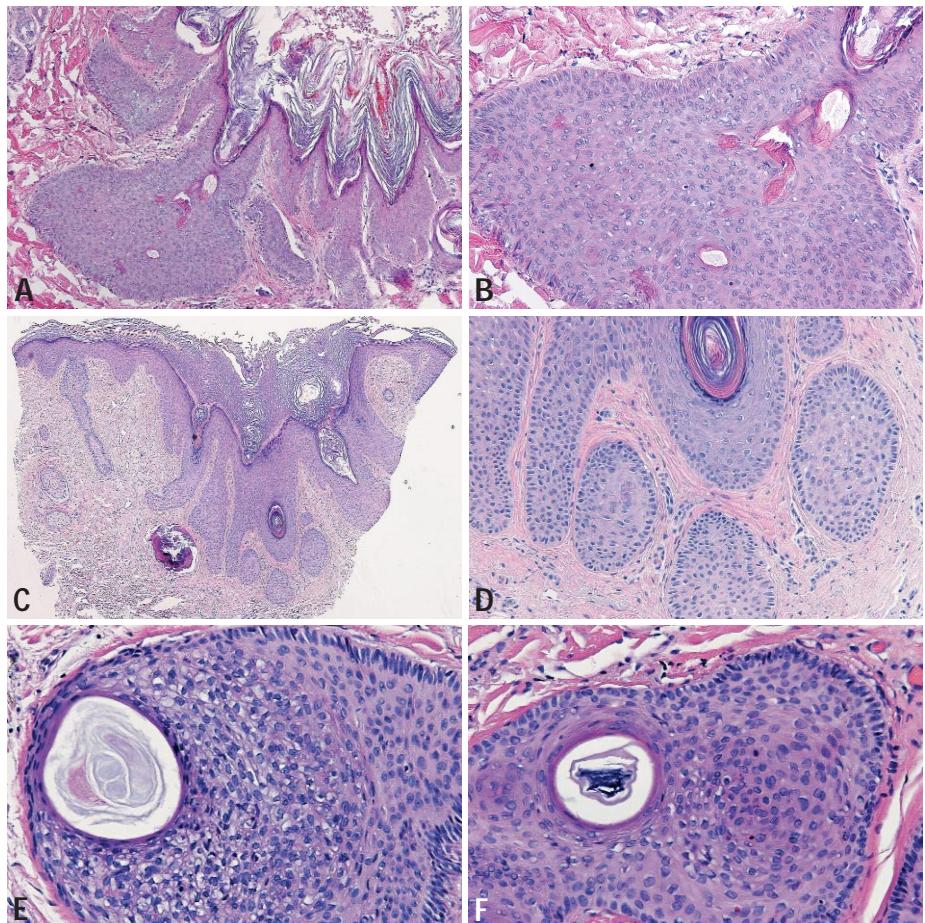


Fig. 3.45 Pilar sheath acanthoma. **A** The characteristic infundibular and isthmic differentiation is stereotyped. Note the lack of a hair filament or inner root sheath. **B** The lobule contains red-pink corneocytes, characteristic of the isthmus. **C** This pilar sheath acanthoma does not have the obvious widened ostium, but it does contain the lobules of isthmic epithelium. **D** The lobules have a nearly syncytial pattern. **E** This lobule has clear-cell changes and syncytial, pink cell changes. Note the lack of inner sheath or hair filament. **F** The small, partly cornified cyst seen here contains no hair filament. Parts of the transient portion of the follicle are rarely seen in pilar sheath acanthoma.

2 mm punctum, lacking hair filaments, and will express corneocytes if squeezed. There are no known associated syndromes and no known genetic abnormalities within the neoplasms [29, 232,473,1570,2212,2402].

Histopathology

The classical example consists of a patent infundibulum that connects with lobules of epithelium differentiated toward both the infundibulum and the isthmus. This differentiation results in blue-gray (infundibular) and pink (isthmic) corneocytes that fill the follicular canal. There can be a minor component of stem or bulb (or both) differentiation in some examples. Consequently there is, as a rule, no evidence of hair filaments in these neoplasms.

Differential diagnosis

Pilar sheath acanthoma should be differentiated from dilated pore (Winer), trichofolliculoma, and fibrofolliculoma/trichodiscoma. Dilated pore is an infundibular cyst that has proliferated minimally, but lacks isthmic differentiation.

Trichofolliculoma is a hamartoma and contains fully formed vellus hair follicles that radiate around a centrally positioned cyst. Fibrofolliculoma/trichodiscoma is also a hamartoma found characteristically in the Birt-Hogg-Dubé syndrome and that contains thin strands of infundibular epithelium connected so that fenestrations of delicate fibrous stroma are found within. Additionally, considerable stroma, lacking epithelium, is often identified (trichodiscoma).

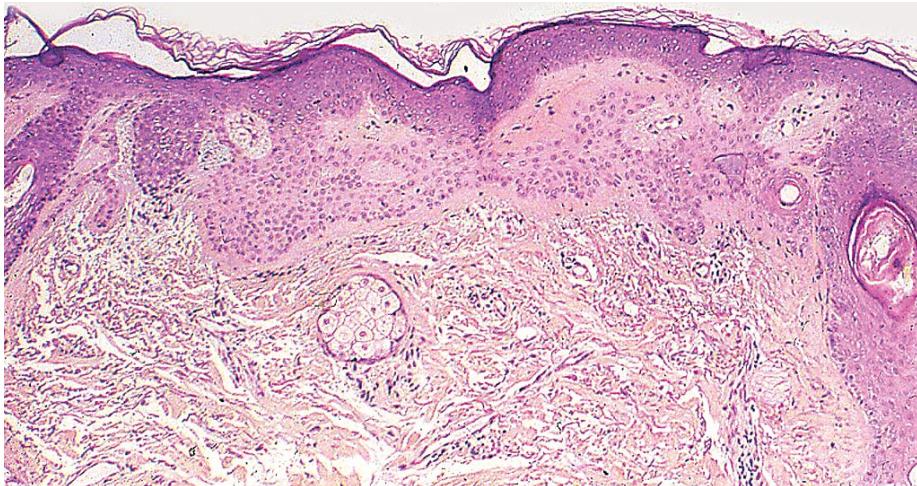


Fig. 3.46 Histopathology of a typical tumour of the follicular infundibulum, with horizontal proliferation of pale keratinocytes in the papillary dermis. Note the connection with the overlying epidermis.

Prognosis and predictive factors

The neoplasm is benign; no treatment is necessary.

Tumour of the follicular infundibulum

Definition

Tumour of the follicular infundibulum (TFI) is a benign epithelial neoplasm of follicular origin.

Synonym

Infundibular tumour.

Epidemiology

TFI is an uncommon tumour occurring in adults, mainly after the age of 50. In two studies, TFI accounted for less than 10 per 100,000 skin samples. They can be observed on the face of patients with Cowden syndrome or on the surface of naevus sebaceous.

Localization and clinical features

Solitary TFI is mainly localized on the face and presents as a small flesh-coloured nodule, resembling basal cell carcinoma. Multiple or eruptive TFI present as hundreds of symmetrically distributed hypopigmented geometric macules localized on the face, neck, trunk, or on the periocular area. Sun exposure increases the contrast between normal skin and the tumours.

Histopathology

TFI is a plate-like horizontal proliferation

of pale keratinocytes, which is localized in the papillary dermis and shows multiple connections with the overlying epidermis or with the infundibulum. The cells are paler and larger than normal keratinocytes and their cytoplasm stains with PAS. The tumour is sharply circumscribed and limited by a dense network of elastic fibres easily demonstrated by orcein staining. Desmoplastic and sebaceous variants have been described {557,1485}.

Histogenesis

TFI derives from the normal follicular infundibulum. The occurrence of multiple TFI suggests a possible genetic basis, which remains to be established.

Prognosis and predictive factors

The prognosis is good, except in rare patients with multiple TFI who may develop basal cell carcinomas.

Fibrofolliculoma / trichodiscoma

Definition

Fibrofolliculoma and trichodiscoma are different developmental stages in the life of one single benign appendageal hamartomatous tumour, which differentiates towards the mantle of the hair follicle {27}. Fibrofolliculoma represents the early and trichodiscoma the late stage in the development of this lesion {27}.

ICD-O code

8391/0

Synonyms

Trichodiscoma first was erroneously thought to arise from or to differentiate toward the hair disk (Haarscheibe) and therefore bears this name {1836}. Fibrofolliculoma was often used for perifollicular fibroma in the past. Neurofollicular hamartoma and trichodiscoma are the same {2048}. "Mantleoma" was used as the overall term for both fibrofolliculoma and trichodiscoma {27}.

Epidemiology

Fibrofolliculomas/trichodiscomas are rare appendageal tumours, occurring equally in males and females, usually not before the third decade of life.

Etiology

The etiology of the solitary lesions is unknown. The BHD gene was mapped to 17p11.2 {1256}.

Localization

The preferred sites of location are the face, neck and chest.

Clinical features

Fibrofolliculomas and trichodiscomas cannot be distinguished clinically {248}. The onset of the lesions is mostly in the third to fourth decade of life. They are skin coloured, smooth, dome-shaped papules, measuring 2-4 mm in diameter {248}. The lesions are asymptomatic.

Histopathology

There is a histomorphological continuum between fibrofolliculoma and trichodiscoma. However, most of these presented cases were actually fibrofolliculomas which were merely prepared histologically in an unusual sectioning technique, resulting in misinterpretation as perifollicular fibroma {2107}.

Fibrofolliculoma

The fibrofolliculoma is composed of similar amounts of epithelial as well as mesenchymal elements. At scanning magnification there are one or several adjacent small, vertically oriented infundibulocystic structures, surrounded by a prominent stroma, which is well demarcated from the surrounding normal reticular dermis by clefts. Anastomosing cords and strands of epithelium arise from the dilated infundibulum. Often, cells with sebaceous differentiation are apparent in these epithelial cords. The surrounding

prominent stroma is made up of fine, fibillary ribbon-like bundles of collagen, often arranged parallel to one another and perpendicular to the epithelial cords. The stroma contains numerous spindled fibrocytes and many venules and capillaries. Elastic fibres are markedly reduced. The stroma is often mucinous, comparable to the stroma of the follicular mantle-region.

Trichodiscoma

Trichodiscoma is a horizontally oriented dome-shaped tumour composed of more mesenchymal tissue than epithelial elements. A prominent tumour stroma of elliptical shape is seen, possessing the same cellular characteristics as in fibrofolliculoma. In peripheral zones of this prominent stroma, small groups of sebaceous lobules may be found. Mantle-like epithelial structures are uncommon. Plaque-like variants of fibrofolliculomas/trichodiscomas with confluence of single lesions and a resulting extension up to several cm in diameter have been described {2103}.

The differential diagnosis of fibrofolliculoma includes trichofolliculoma at a late stage {2105}. Fatty tissue is a typical finding in late stages of trichofolliculoma but not in fibrofolliculoma. Perifollicular fibroma/fibrous papule is also similar to fibrofolliculoma. However, it is usually devoid of mucin and shows no mantle-like epithelial proliferations {27}. Trichodiscomas have to be differentiated from neurofibromas and cutaneous myxomas {521}. However, the latter tumours lack the sebaceous epithelial component, typical of trichodiscoma.

Immunoprofile

The epithelial and mesenchymal parts of the lesions show the common reactivities to cytokeratins and vimentin. The tumour stroma is strongly reactive with antibodies to CD34, reflecting its differentiation towards the follicular mantle region.

Histogenesis

Histologic and immunohistologic data suggest that fibrofolliculoma/trichodiscoma is derived from/differentiated to the mantle region of the hair follicle {27,521}. The mantle region is a specialized epithelial-mesenchymal structure, located at the lower end of the follicular infundibulum {606} and is the source and starting point for the development of the

sebaceous glands {27}. Fibrofolliculoma/trichodiscoma is considered to be a hamartomatous lesion. Its mesenchymal part may be responsible for the origin and growth of the whole lesion, leading to the distinctive mesenchymal-epithelial proliferation, reminiscent of a deformed mantle region {2103}. The postulated cell of origin therefore might be a specialized dermal dendritic spindle cell, normally situated in the mantle region {521,2103}.

Genetic susceptibility

Multiple fibrofolliculomas/trichodiscomas are part of the Birt-Hogg-Dubé syndrome (BHD), an autosomal inherited syndrome, also affecting the lung and kidney {248,2579}. The BHD gene is located at 17p11.2 {806} and encodes folliculin whose function is unknown. The patients may have multiple, often bilateral renal carcinomas, frequently representing unusual histological subtypes. They also have an increased frequency of spontaneous pneumothoraces.

Prognosis and predictive factors

Fibrofolliculoma/trichodiscoma is a benign lesion, excised primarily for cosmetic reasons. However, it is an important marker for Birt-Hogg-Dubé syndrome and its associated complications.

Tumours with sebaceous differentiation

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M.R. Wick
O. P. Sangüeza
C. Wallace

Sebaceous carcinoma

Definition

Sebaceous carcinoma (SC) is a cytologically- and/or architecturally- malignant neoplasm demonstrating exclusive sebaceous differentiation.

ICD-O code

8410/3

Historical annotation

Historically, SCs have been subcategorized into ocular and extraocular subtypes {1510A, 1696A, 1827A, 1856A, 2511A, 2609A}, although there is no inherent biological difference between such lesions.

Epidemiology

SC usually arises in adults, with an average patient age of 62 yrs. and a female predominance, by a factor of roughly 2:1. Tumours of the eyelids are preferentially seen in Asian patients, and also may represent a complication of prior radiotherapy {1067A}.

Clinical features

All SCs present as painless masses, which can be multifocal. In the ocular adnexae, they may be mistaken clinically for chalazions, blepharitis, cicatricial pemphigoid, or conjunctivitis {642,839, 2542}. In extraocular sites, sebaceous malignancies are commonly confused with basal cell carcinomas and squamous cell carcinomas.

Most extraocular SCs are encountered in the skin of the head and neck, followed by the trunk, genitals, and extremities. Rare cases may also be seen in the mouth, salivary glands, lungs, and breasts.

Macroscopy

SCs are nodules that typically enlarge slowly but may occasionally grow rapidly; some become ulcerated. A minority of individuals with this tumour have the Muir-Torre syndrome {2227}.

Histopathology

Sebocytic differentiation, typified by multivesicular and vacuolated clear cytoplasm, is the sine qua non for sebaceous neoplasms including SC. It must be separated from simple cytoplasmic clarity, a microscopic change that is relatively common in cutaneous neoplasms of many other lineages {2294}. SCs are organoid proliferations comprising dermal lobules of variably-atypical polygo-

nal cells, with a fibrovascular stroma that typically lacks desmoplasia. Central portions of the tumour cell nests may be necrotic, yielding a "comedo" growth pattern. The cells of well-differentiated neoplasms show abundant cytoplasm and oval vesicular nuclei with distinct nucleoli; mitotic figures are variable in number. On the other hand, more poorly-differentiated SCs show high nuclear-to-cytoplasmic ratios, nuclear pleomor-

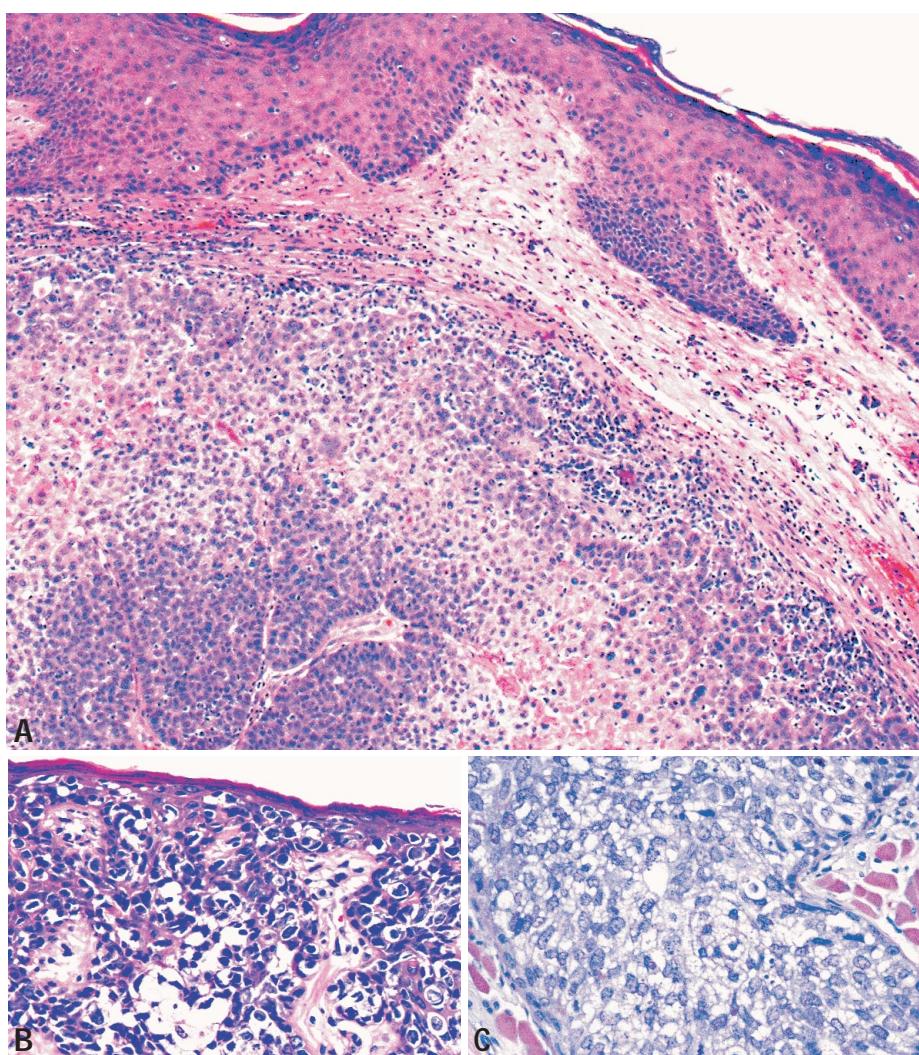


Fig. 3.47 Sebaceous carcinoma. **A** Sebaceous carcinoma, represented by a lobular proliferation of atypical epithelioid cells in the dermis. Multivesicular cytoplasmic vesication is present. **B** Extensive in-situ involvement of the surface epithelium is present in this example of sebaceous carcinoma. **C** "Bubbly" cytoplasmic vacuolization is apparent in sebaceous carcinoma.

phism, prominent nucleoli, brisk mitotic activity - sometimes with pathologically-shaped forms - and amphophilic or basophilic cytoplasm. Intracellular vacuoles are sometimes not seen easily in those lesions, and may require the use of special histochemical stains, such as the oil-red-O or Sudan IV methods, to detect them {2540}.

The grading of SCs - into grades I through III - is based on growth patterns rather than on their cytological features {1892}. Tumours that are constituted by well-demarcated, roughly equally-sized cellular lobules are graded as I; those with an admixture of well-defined nests with infiltrative profiles or confluent cell groups are grade II lesions; and grade III SCs exhibit highly-invasive growth or a medullary sheet-like pattern.

All SCs have the potential for an association with overlying carcinoma in-situ (CIS), or extramammary Paget disease (EPD) of the sebaceous type, or both, in the surface epithelium and in other epidermal appendages (especially pilosebaceous units) {448,1702}. The latter lesions are probably marker lesions that represent a cutaneous "field" defect, rather than being direct precursors of, or extensions from, underlying SC. This premise has support from occasional cases in which only intraepithelial sebaceous carcinoma is present, in the absence of an invasive component in the dermis {1510}. In pragmatic terms, however, one should always consider the possibility of infiltrative SC whenever EPD or carcinoma in-situ is seen in a superficial biopsy.

Variants

Selected microscopic variants of SC deserve special comment because they may engender interpretative confusion with other cutaneous tumours {2540, 2542}.

Basaloid SC comprises small cells with scant cytoplasm, and may often show nuclear palisading at the periphery of cellular nests. It commonly manifests a grade III growth pattern, and overtly-sebocytic elements are sparse and difficult to identify as such.

Squamoid SC shows prominent squamous metaplasia, often with keratin pearl formation; some examples may also demonstrate spindle-cell areas, equating with a sarcomatoid image.

Still other examples of SC may demonstrate pseudo-neuroendocrine organoid growth, focally resembling the pattern of "carcinoid" tumours {1235}. Based on these brief descriptions, one could easily predict that basal cell carcinoma, squamous cell carcinoma, neuroendocrine tumours, epithelial malignancies with potential spindle-cell differentiation, and a variety of clear-cell neoplasms in the skin may enter differential diagnostic consideration in selected cases of SC.

Immunoprofile

SC shows immunoreactivity for several generic epithelial markers such as pankeratin, epithelial membrane antigen (EMA), CD15, CU18, CA15.3, and Thomsen-Friedenreich antigen {75}. EMA labeling may enhance the cytoplasmic "bubbliness" of the tumour cells in this neoplasm. That pattern is distinctive, but

it is not observed in all examples of SC. Reactivity for androgen receptor protein and human milk fat globule protein-2 also has been reported in SC {182,2191}. However, it is not yet known whether the latter markers are diagnostically helpful in excluding other clear-cell tumours.

Genetic susceptibility

Immunoreactivity in SC for various DNA-mismatch repair gene products, especially for MSH-2, has been correlated with a relationship to the Muir-Torre complex {1468,1536}. However, virtually no systematic data are available on the detailed genetic profiles of either sporadic or syndromic SC.

Prognosis and predictive factors

Both ocular and extraocular SCs have a 30-40% risk for local tumour recurrence, 20-25% for distant metastases, and 10-20% for tumour-related mortality {1645}. Some reports appear to support the premise that immunoreactivity for mutant p53 protein at a level of >10%, and for proliferating cell nuclear antigen at a level of >25% may be linked to an adverse outcome {977}. A similar comment may apply to those lesions that overexpress the c-erbB-2/HER-2/neu protein {472,977}.

Sebaceous adenoma

Definition

Sebaceous adenoma is a small tumour composed of basaloid cells and fully differentiated sebocytes.

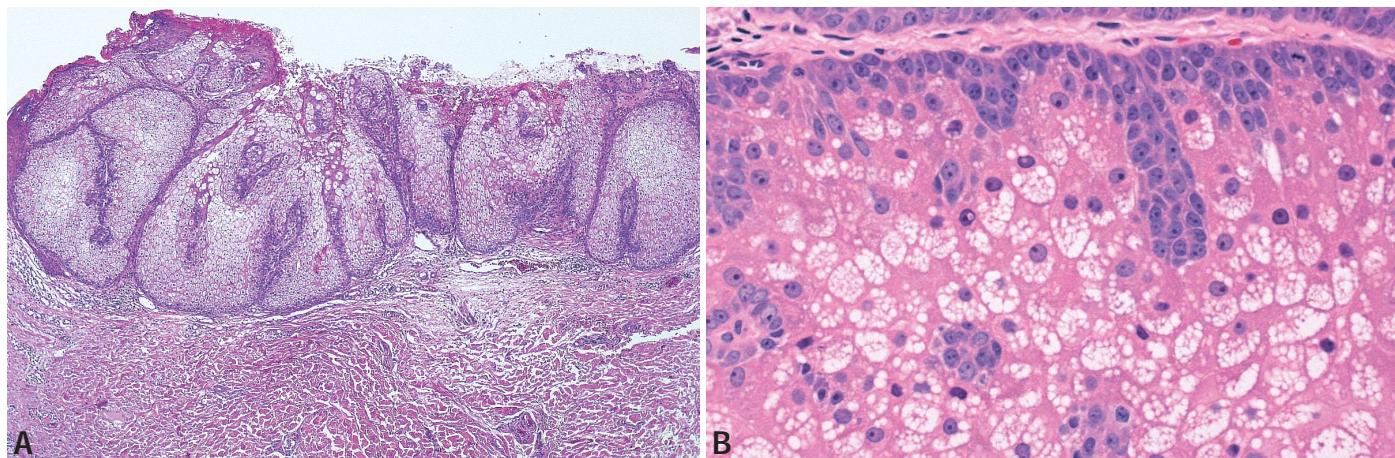


Fig. 3.48 Sebaceous adenoma. **A** Well circumscribed lobulated sebaceous tumour. Fully differentiated sebocytes predominate and epidermis is replaced by the tumour. **B** High magnification of the periphery of the lobule.

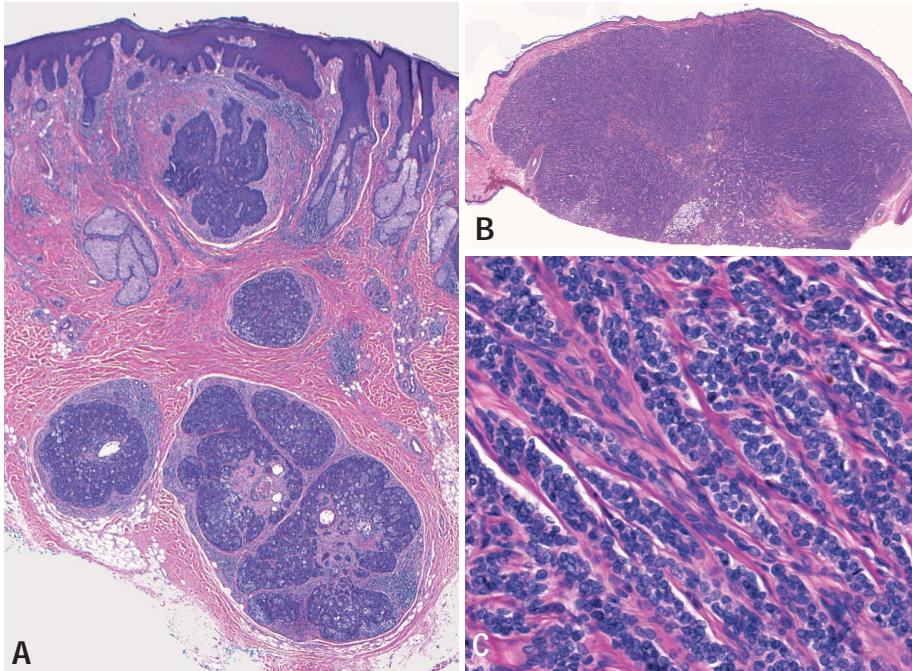


Fig. 3.49 Sebaceoma. **A** Low power view demonstrating a neoplasm with multiple well-circumscribed nodules of different sizes. **B** Example of a reticulated sebaceoma. The neoplasm is composed predominantly of uniform basaloid cells distributed in a reticulated pattern. Please note the presence of cells with sebaceous differentiation at the base of the lesion. **C** Cytologically the basaloid cells are uniform and present between collagen bundles.

ICD-O code 8410/0

Epidemiology

Sebaceous adenomas occur mostly as solitary lesions in persons older than forty years {1993}. Lesions are located usually on sun-damaged skin of the head and neck area. Rarely patients have multiple lesions {2258}, then the possibility of Muir-Torre syndrome should be considered.

Clinical features

Sebaceous adenomas are relatively small yellowish tumours often covered by a scale or crust {2353}.

Histopathology

This well-circumscribed tumour is made up of small lobular aggregations of sebocytes with a rim of basaloid cells at the periphery, recapitulating the maturation of sebocytes from the periphery to the centre comparable to normal sebaceous glands {1542}. Lobules are composed of vacuolated fully differentiated sebocytes and these cells predominate markedly over the basaloid sebocytes. Sebaceous adenoma is often connected to the overlying epidermis, and may be covered by a thick plug of keratin and disintegrated

sebocytes. Ductal structures are rare, as are mitotic figures.

Sebaceous adenoma has to be differentiated from sebaceous hyperplasia, where the sebaceous lobules are arranged around a central placed follicular infundibulum that is connected to the epidermis. In sebaceous hyperplasia the epidermis may show changes mimicking seborrhoeic keratosis.

Sebaceomas are nodular lesions of basaloid undifferentiated sebocytes and only a few small groups of vacuolated sebocytes. There may be morphological overlaps between sebaceous adenoma and sebaceoma. The term sebomatricoma was introduced as an attempt to simplify the nomenclature of the different benign sebaceous adnexal tumours and to summarize them under one name {2003}.

Genetics

Little is known about the genetics of sebaceous adenoma. Most of the tumours occur as solitary lesions but a few examples of SA are part of the spectrum of different sebaceous tumours in MTS. By immunohistochemistry it is possible to look for a loss of MSH-2, MLH-1 repair proteins. Tumours related to a mis-

match repair gene defect show a microsatellite instability in a high percentage {1334}.

Prognosis and predictive factors

Sebaceous adenomas are benign tumours. If the patient has Muir-Torre syndrome, the prognosis depends on the associated internal malignancies.

Sebaceoma

Definition

Sebaceoma is a benign, adnexal neoplasm with sebaceous differentiation. It is characterized by multiple, smooth-bordered lobules and cystic spaces composed primarily of immature sebaceous cells admixed with randomly scattered mature sebocytes.

ICD-O code

8410/0

Synonyms

Sebaceous epithelioma, basal cell epithelioma with sebaceous differentiation, and sebomatricoma.

Epidemiology

Sebaceomas are rare sebaceous neoplasms that may be associated with the Muir-Torre syndrome {1624,2114}. They typically arise in late adulthood with the mean age of diagnosis being at approximately 70 years of age, but may be seen in early adulthood {2378}. The tumours have a predilection for females.

Localization

Sebaceomas occur mainly on the face and scalp, with rare cases reported on the trunk {226,636,1710,1749,1922, 2258,2378}.

Clinical features

Clinically, sebaceomas present as yellow to orange solitary papules on the head and neck {636,2258,2378}. Those lesions associated with the Muir-Torre syndrome may be multiple {347,1624, 2114}. They are slow-growing neoplasms and do not recur after excision {636, 2258,2378}.

Histopathology

Architecturally sebaceoma is composed of multiple well-circumscribed lobules of various size centred on the dermis. The lobules often contain ducts and cystic

areas containing holocrine secretion and only rarely do they connect with the overlying epidermis. A brightly eosinophilic cuticular material lines both the ducts and cysts, similar to what is seen in the normal sebaceous ducts.

Cytologically the neoplasm is comprised predominantly of small, uniform basaloid cells with bland nuclear features admixed with haphazardly distributed mature-appearing sebaceous cells. The mature sebaceous cells have abundant vacuolated cytoplasm and ovoid nuclei, which often have a scalloped nuclear membrane. Rare typical mitoses may be seen, however, atypical mitosis and necrosis are not features of sebaceoma. The surrounding stroma is dense, eosinophilic connective tissue. There is no cleft seen between the neoplasm and the stroma, as is the case with basal cell carcinoma.

A wide variety of patterns have been described for sebaceoma, sometimes even within the same neoplasm. These include reticulated, cribriform and glandular {634,1710}. There have been reports of a variant with eccrine differentiation, a pigmented variant and a sebaceoma that arose in a seborrhoeic keratosis {226,1749,1922}. Those lesions that arise in Muir-Torre syndrome may have a keratoacanthoma-like architecture {347}.

Immunoprofile

Immunohistochemistry demonstrates positivity with high-molecular weight keratin. EMA stains most mature sebocytes, and thus will only show positivity of the mature vacuolated sebaceous cells scattered amongst the tumour, while the basaloid cell compartment will be negative {1710}. Several reports have demonstrated loss of heterozygosity as well as microsatellite instability in a marker gene located near hMSH2 in patients with sebaceoma and Muir-Torre syndrome {1332,1536}. By immunohistochemistry it is possible to look for a loss of MSH-2, MLH-1 repair proteins {1334}.

Prognosis and predictive factors

Sebaceoma is a benign neoplasm that does not recur after treatment or metastasize. It may be a marker of Muir-Torre syndrome, in which case the patient has a high risk of internal malignancies.

Cystic sebaceous tumour

Definition

Cystic sebaceous tumour is a large distinctive tumour with is almost always associated with Muir-Torre syndrome (MTS) {1999}.

ICD-O code 8410/0

Epidemiology

Cystic sebaceous tumours occur nearly exclusively in MTS, which is a phenotypic variant of the hereditary non polyposis colon cancer syndrome (HNPCC). MTS is inherited in an autosomal-dominant fashion and is caused by genetic alterations within the DNA mismatch repair system. Patients often have a family history of malignancies and most are affected with a variety of internal malignancies such as colon cancer, urothelial cancer, endometrial cancer and others. MTS patients develop a broad spectrum of different sebaceous skin tumours, which may be difficult to classify {347, 1624}, and keratoacanthomas. Among the sebaceous tumours, CSTs are unique because they serve as diagnostic markers for the syndrome. MTS has a male preponderance and is clinically diagnosed mostly in adults older than 40 years.

Localization

The upper trunk is the most common location.

Clinical features

CSTs are usually solitary, but rarely can be multiple. They resemble hair follicle cysts and present as dermal nodules. In patients diagnosed with internal malignancies CST is often excised in order to rule out a metastatic skin lesion.

Histopathology

CST are large, well circumscribed dermal tumours which may connect to the upper dermis, and usually extend into the subcutis. The outer surface of the neoplasm may be obscured in cases with an accompanying granulomatous inflammation due to the ruptured cyst wall. Well-differentiated CST show a cystic growth pattern with a small line of basaloid undifferentiated sebaceous matrix cells at the periphery and a broad

zone of fully differentiated vacuolated sebocytes towards the centre of the cystic tumour. Well-differentiated CST do not show cytological atypia, and have only few mitoses. Ductal structures may be seen in the cyst wall. Proliferation of tumour cells produces infoldings of the cyst wall in some CST. The more solid variants are predominantly composed of undifferentiated sebaceous cells with mitotic figures and variable cytologic atypia.

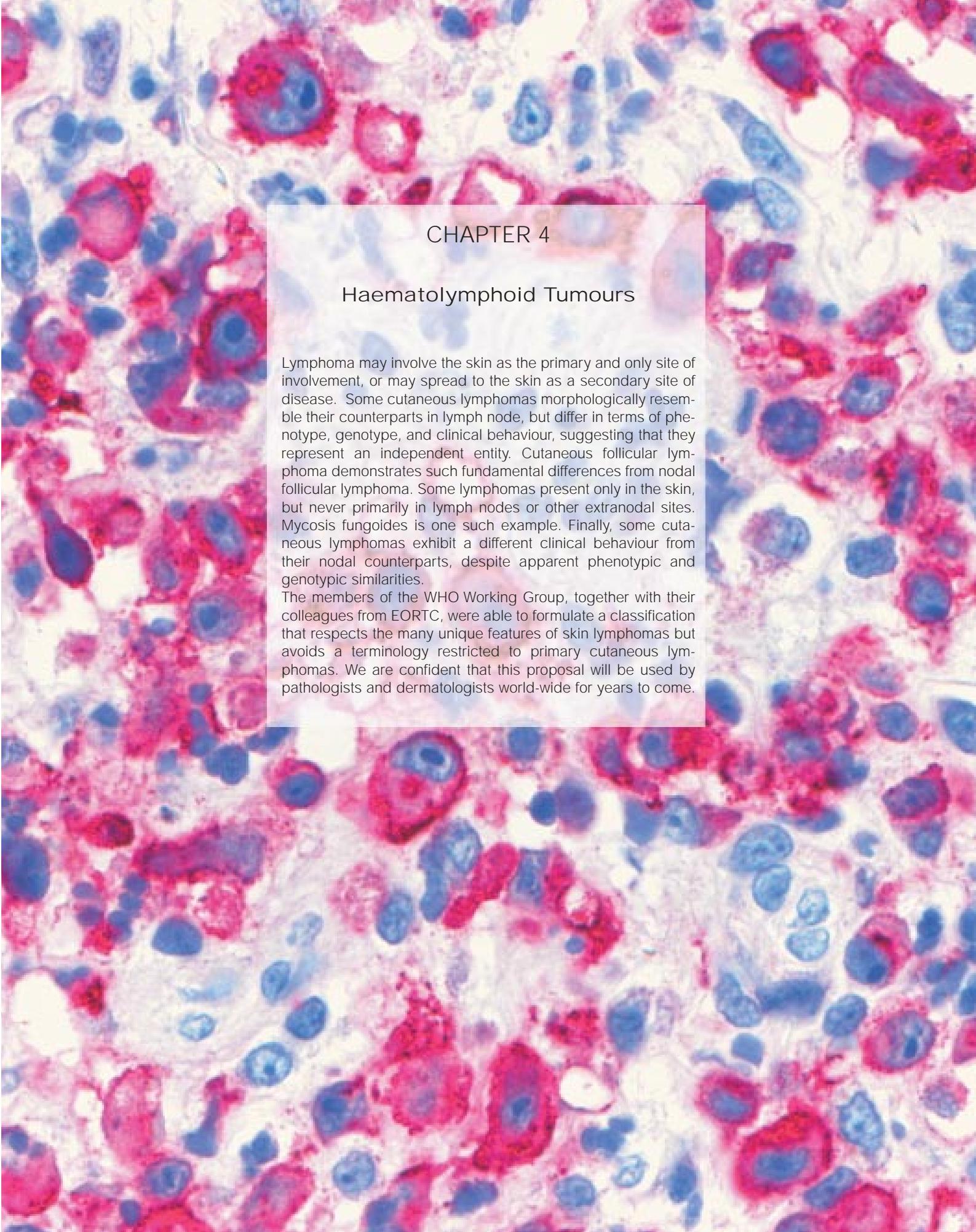
Genetics

Germline mutations of the DNA mismatch repair genes are responsible for MTS. In the vast majority of cases the associated tumours show a complete loss of the corresponding mismatch repair protein (MSH2 or MLH1). This can be demonstrated immunohistochemically by antibodies directed against MSH2 and MLH1 protein {1469,1536,2227}. A loss of the nuclear staining for one of these antibodies within the tumour cells accompanied by a positive staining of nuclei in the surrounding tissue strongly suggests loss of the corresponding DNA mismatch repair protein. Typically, these tumours show high microsatellite instability {1332, 1469, 1999}.

Prognosis and predictive factors

Some authors interpret cystic sebaceous adenoma as a variant of sebaceous carcinoma {1733}. So far there is no clinical evidence that these tumours in any case represent malignant sebaceous tumours {872,1624,1999}. Because of these conflicting views, complete excision is recommended.

The prognosis in MTS is determined by the nature of the associated internal malignancies. In most cases CST develops after the first internal malignancy, but in up to 25% of cases they represent the first clinical sign of MTS. Even in a patient with a solitary CST who does not fulfil the clinical criteria for MTS, a molecular genetic analysis may show a germline mutation in a mismatch repair gene {1333}. Because of the specific marker function of CST it is possible to detect patients and families with an inherited DNA mismatch repair defect predisposing to various types of internal cancer.



CHAPTER 4

Haematolymphoid Tumours

Lymphoma may involve the skin as the primary and only site of involvement, or may spread to the skin as a secondary site of disease. Some cutaneous lymphomas morphologically resemble their counterparts in lymph node, but differ in terms of phenotype, genotype, and clinical behaviour, suggesting that they represent an independent entity. Cutaneous follicular lymphoma demonstrates such fundamental differences from nodal follicular lymphoma. Some lymphomas present only in the skin, but never primarily in lymph nodes or other extranodal sites. Mycosis fungoides is one such example. Finally, some cutaneous lymphomas exhibit a different clinical behaviour from their nodal counterparts, despite apparent phenotypic and genotypic similarities.

The members of the WHO Working Group, together with their colleagues from EORTC, were able to formulate a classification that respects the many unique features of skin lymphomas but avoids a terminology restricted to primary cutaneous lymphomas. We are confident that this proposal will be used by pathologists and dermatologists world-wide for years to come.

WHO / EORTC classification of cutaneous lymphomas¹

Mature T-cell and NK-cell neoplasms			
Mycosis fungoides	9700/3	Mature B-Cell neoplasms	
Pagetoid reticulosis (localized disease)		Cutaneous marginal zone B-cell lymphoma (MALT-type)	9699/3
Follicular, syringotropic, granulomatous variants		Cutaneous follicle centre lymphoma	9690/3
Granulomatous slack skin		Cutaneous diffuse large B-cell lymphoma	9680/3
Sezary syndrome	9701/3	<i>Intravascular large B-cell lymphoma*</i>	9680/3
CD30+ T-cell lymphoproliferative disorders of the skin		<i>Lymphomatoid granulomatosis*</i>	9766/1
Lymphomatoid papulosis	9718/1	<i>Chronic lymphocytic leukaemia*</i>	9823/3
Primary cutaneous anaplastic large cell lymphoma	9718/3	<i>Mantle cell lymphoma*</i>	9673/3
Subcutaneous panniculitis-like T-cell lymphoma**	9708/3	<i>Burkitt lymphoma*</i>	9687/3
Primary cutaneous peripheral T-cell lymphoma (PTL), unspecified	9709/3	Immature haematopoietic malignancies	
Subtypes of PTL (provisional)		Blastic NK-cell lymphoma *** /	9727/3
Primary cutaneous aggressive epidermotropic		CD4+/CD56+ haematodermic neoplasm	
CD8-positive cytotoxic T-cell lymphoma		Precursor lymphoblastic leukaemia/lymphoma	
Cutaneous gamma/delta-positive T-cell lymphoma		<i>T-lymphoblastic leukaemia*</i>	9837/3
Primary cutaneous small/medium CD4+ T-cell lymphoma		<i>T-lymphoblastic lymphoma*</i>	9729/3
Extranodal NK/T-cell lymphoma, nasal type	9719/3	<i>B-lymphoblastic leukaemia*</i>	9836/3
Hydroa vacciniforme-like lymphoma (variant)		<i>B-lymphoblastic lymphoma*</i>	9728/3
Adult T-cell leukaemia/lymphoma*		<i>Myeloid and monocytic leukaemias*</i>	
9827/3		<i>Hodgkin lymphoma*</i>	
Angioimmunoblastic T-cell lymphoma*	9705/3		

¹ Morphology code of the International Classification of Diseases for Oncology (ICD-O) {786} and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

* Extracutaneous lymphomas frequently involving the skin as a secondary site are printed in *italics*.

** Definition is restricted to lymphomas of alpha/beta T-cell origin

*** Recent evidence suggests an origin from a dendritic cell precursor. In recognition of uncertain histogenesis, the term "CD4+/CD56+ haematodermic neoplasm" is preferred.

TNM classification of cutaneous T-cell lymphomas (CTCL)

Stage	T	N	M
Ia	T1 Limited lesions covering <10% of the skin surface	N0 no palpable lymph nodes, pathology negative for CTCL	M0 no involvement of visceral organs
Ib	T2 generalized lesions covering 10% and more of the skin surface	N0 no palpable lymph nodes, pathology negative for CTCL	N0 no involvement of visceral organs
IIa	T1 Limited lesions covering <10% of the skin surface, or T2 generalized lesions covering 10% and more of the skin surface	N1 palpable peripheral lymph nodes, pathology negative for CTCL	M0 no involvement of visceral organs
IIb	T3 tumours, one or more	N0: no palpable lymph nodes, pathology negative for CTCL or, N1 palpable peripheral lymph nodes, pathology negative for CTCL	M0 no involvement of visceral organs
III	T4 generalized erythroderma	N0: no palpable lymph nodes, pathology negative for CTCL or N1 palpable peripheral lymph nodes, pathology negative for CTCL	M0 no involvement of visceral organs
IVa	T1-4	N2: no palpable peripheral lymph nodes, pathology positive for CTCL or N3: palpable peripheral lymph nodes, pathology positive for CTCL	M0 no involvement of visceral organs
IVb	T1-4	N0-3	M1 involvement of visceral organs

Modified, from Refs. [333,344,2537].

WHO / EORTC Classification of cutaneous lymphomas

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The skin is the second most common site of extranodal lymphoma, following the gastrointestinal tract [340]. Lymphoma may involve the skin as the primary and only site of involvement, or may spread to the skin as a secondary site of disease. Because the clinical implications of primary and secondary cutaneous lymphoma are different, the dermatologist and pathologist should be familiar with both types of neoplasms. For this reason it also is problematic to use a classification system restricted to primary cutaneous lymphomas [2523]. It is important for dermatologists, haematooncologists, and pathologists to use a unified system for the diagnosis and treatment of cutaneous lymphoma [1858].

Nevertheless, cutaneous lymphomas present some unique clinical aspects. There are some diseases that present only in the skin, and are never primary in lymph nodes or other extranodal sites. Mycosis fungoides is one such example. Some cutaneous lymphomas morphologically resemble their counterparts in lymph node, but differ in terms of phenotype, genotype, and clinical behaviour, suggesting that they represent an independent entity. Cutaneous follicular lymphoma demonstrates such fundamental differences from nodal follicular lymphoma. Finally, some cutaneous lymphomas exhibit a different clinical behaviour from their nodal counterparts, despite apparent phenotypic and genotypic similarities. These differences may be related to stage or tumour burden, or more fundamental biological differences. For example, some lymphomas composed of large centrocytes and centroblasts have an indolent clinical course when presenting as a localized cutaneous tumour, but a similar cytological process in lymph node would be considered aggressive, i.e. diffuse large B-cell lymphoma.

Dermatologists, haematooncologists, and pathologists must use a common language. In this spirit we utilize the WHO classification of lymphoid neo-

plasms [1121], but we expand upon the unique features of many cutaneous lymphomas to emphasize their distinctive clinical and biological characteristics [336A,2522]. Additional clinical and morphological variants have been added, where appropriate, in order to comprehensively cover the many manifestations of cutaneous lymphoma. Atypical reactive lesions that may represent precursors of cutaneous lymphoma are discussed where relevant [336A,2522].

Cutaneous lymphoproliferative disorders (CLD)

These include reactive lymphoid hyperplasias (so called cutaneous "pseudolymphomas"), prelymphomatous conditions and definite malignant lymphoma of low grade or of high grade malignancy. According to their biologic behaviour, CLD can be subgrouped into prognostic categories which are not reflected in the classifications, which however are of special interest for the patient and for the treating physician.

When diagnosing a cutaneous lymphoproliferative disorder, both the clinicopathologic classification and the biologic category should be considered. The advantage of such an approach is to provide the diagnosis according to the current WHO-classification of lymphomas, and in addition, to include essential information about the biologic behaviour, which may be significantly different than that of the nodal counterpart. These data are crucial for the clinician involved in counseling and treatment of the patient.

Reactive lymphoid hyperplasias (RLH) (pseudolymphomas)

These are reactive benign lymphoproliferative processes, localized or disseminated, which heal either spontaneously after elimination of the causative factor (e.g. drugs) or after treatment with non-aggressive (no severe side effects to be expected after long term application) modalities, and which do not recur after removal of the causative agent.

Prelymphomatous ("abortive") disorders (PLD)

PLD show a chronic long-standing course, no spontaneous regression in most cases, and no extracutaneous spread with involvement of visceral organs. In some cases, clonality of the infiltrate can be demonstrated. However, in most cases the neoplastic cell clone never overcomes host control mechanisms and cannot expand and therefore does not convert into definite malignant lymphoma. Survival time is not affected. Definite malignant lymphoma of low-grade malignancy (LLM). This category includes cutaneous lymphomas that show a slowly progressive course with systemic spread in later stages and have the potential for transformation into more aggressive high-grade malignant lymphomas. Survival time usually is greater than 5 years.

Definite malignant lymphoma of high-grade malignancy (LHM)

These diseases are characterized by a more rapid course than the low-grade lymphomas and usually exhibit a bad prognosis with survival times less than 5 years.

Mycosis fungoides

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Definition

Mycosis fungoides (MF) is the prototype of cutaneous T-cell lymphomas (CTCL) and can be defined as a peripheral, epidermotropic non-Hodgkin T-cell lymphoma of low grade malignancy initially presenting in the skin and showing step-wise clinical progression from patches to plaques and tumours, and distinct histological (except in early stages), phenotypic and genotypic features.

ICD-O code 9700/3

Synonyms and historical annotation

In 1806 Jean-Louis Alibert (1768-1837) [58] presented an extraordinary skin disease which he described in detail under the name of "Pian fungoides" in 1814 and as "Mycosis fungoides" in 1832 [58]. At his time the etiology of the disease was completely unclear. It is worth noting that Alibert in 1832 copied part of the text from Bontius [283]. Ernest Bazin (1807-1878) published three different stages [184]:

Période érythémateuse (erythematous stage: red colored patches)

Période lichénoïde (the lichenoid stage: itching and different plaques with small papules).

Période fongoïdique, mycositique (fungal stage:mushroom-like tumours of different size).

Epidemiology

The incidence of MF from 1973 through

1992 in the USA was 0.36/ 100'000 persons per year [2445].

Most frequently MF affects adults, usually in their 5th-6th decade, with a male to female ratio of approximately 2:1 and a preponderance of black (1.7) vs white populations.

The increase of frequency paralleled by a decrease of mortality rates between 1979 and 1991 [2485] most probably is due to changing criteria resulting in over-diagnosing MF by including non-neoplastic conditions into this group.

Data collected by the Surveillance, Epidemiology and End Results Program (SEER) of the US National Cancer Institute indicate that the relative survival changed little after 11 years, at which point it was 66% [2485].

Etiology

The etiology of MF is unknown. The role of environmental antigens, viruses or bacteria is controversial [2605].

Localization

All parts of the skin may be involved without any predilection site.

Clinical features

Clinically MF is characterised by a step-wise evolution with sequential appearance of patches, plaques and tumours. Patches are circumscribed lesions with discolouration and sometimes little scaling, without palpable infiltration of the skin. Plaques usually evolve out of

patches and present with palpable infiltration of various degree (thin and thick plaques). Tumours exhibit an exophytic growth in most of the cases and tend to ulcerate. In advanced stages of the disease there may be spread into the peripheral blood, involvement of lymph nodes, bone marrow and internal organs. Besides physical examination, including mapping of skin lesions and photodocumentation, a skin biopsy for paraffin embedding and for cryo-preservation should be taken, preferentially at multiple sites. Additional investigations include blood cell counts with PAS staining for Sézary cells, chest x-ray and CT-scan of abdomen and of peripheral lymph nodes. There is no need for taking a bone marrow biopsy in early patch and plaque stages of MF without atypical cells in the peripheral blood. Biopsy of enlarged lymph nodes is mandatory.

The current TNM-staging System for CTCL takes into account body surface involved less (T1) or more (T2) than 10%, quality of skin manifestation, i.e. patches/plaques or tumours (T3) or erythroderma (T4) in conjunction with presence or absence of lymph node (N0-N3) or visceral organ involvement (M0-M1) [334].

Tumour spread and staging

MF, like other cutaneous lymphomas, is a systemic disease with preferential homing and proliferation of neoplastic lymphocytes into the skin. Therefore skin lesions may spread all over the body sur-



Fig. 4.1 Mycosis fungoides. **A** Large patches involving hip and abdomen. **B** Plaque-stage MF affecting the left arm. **C** Medium-sized hyperconvoluted cerebriform cells with prominent cytoplasmic halos in the epidermis, aligned within the basal layer.

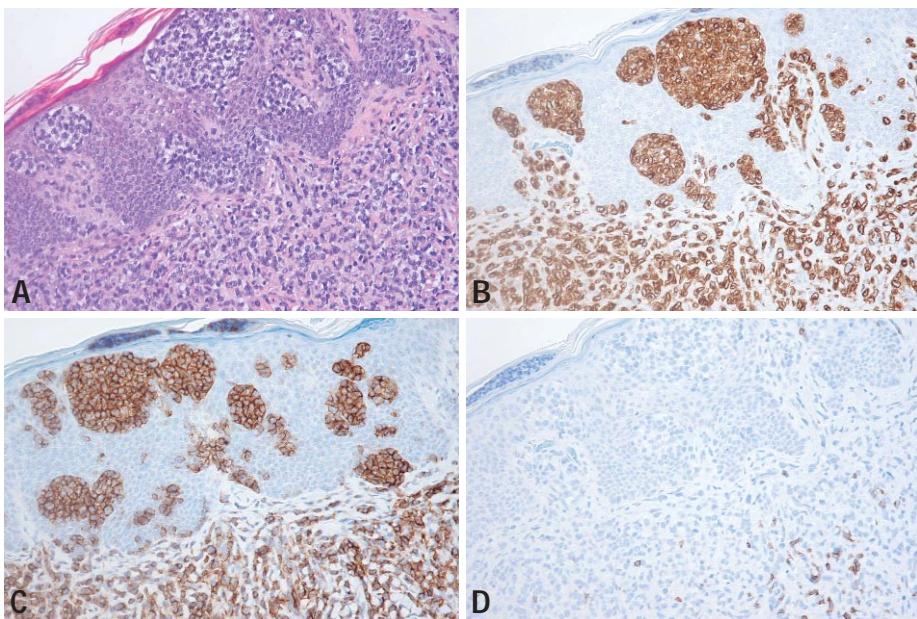


Fig. 4.2 Mycosis fungoides (MF). **A** Typical Pautrier abscesses. The neoplastic cells are strongly positive for **B** CD3 and **C** CD4, while **D** CD8 is negative.

face. Spread to extracutaneous compartments occurs in advanced stages of the disease, due to change or loss of homing receptors. These changes are usually accompanied by a change of cytomorphology of the tumour cells from small cerebriform to medium-sized pleomorphic or large blast-like cells.

Histopathology

The histologic diagnosis of MF is based on numerous subtle changes, most of which may be present to some degree in many inflammatory and neoplastic cutaneous conditions. The most significant criteria, which however in early lesions often are missing or are only present in part, are Pautrier microabscesses, exocytosis of lymphocytes, disproportionate epidermotropism. The presence of cells with hyperconvoluted cerebriform nuclei in the epidermis larger than dermal lym-

phocytes, or lymphocytes in clusters in the dermis, and lymphocytes aligned within the basal layer without or with only little spongiosis and without prominent vacuolisation in the dermo-epidermal junction are typical but not specific features. Haloed lymphocytes have proved to be the most robust discriminator of MF from non-MF.

Patch stage

The diagnosis is usually based on a combination of specific histologic criteria, without the necessity of confirmatory immunophenotyping {2058,2059,2213}. Whereas in very early "prelymphomatous" patch stages the histological picture often is non-specific, the histological findings become diagnostic in the thin plaque stage, when a denser infiltrate with lymphocytes lining up in the basal layer, especially at the tips of the rete

ridges with epidermotropism of single cells is present. The majority of cells are small, differentiated lymphocytes with round or only slightly cerebriform nuclei. Haloed cells may predominate in the epidermis in early patch lesions of patients with otherwise advanced disease. In addition, there can be mild acanthosis, hyperkeratosis, signs of basal layer damage (pigment incontinence), edema or fibrosis of the papillary dermis. There is proliferation of postcapillary venules with prominent endothelial cells, simulating giant cells. The infiltrate may contain an admixture of eosinophils, plasma cells, macrophages, and dermal dendritic cells {922,2156}.

Thick plaque stage

This is typified by a dense, subepidermal, usually band-like infiltrate containing a high number of cerebriform cells. Epidermotropism is more prominent with small intraepidermal clusters (2-3 cells) of lymphocytes. Typical Pautrier microabscesses are seen only in approximately one-third of cases. Subcorneal, intraepidermal and subepidermal bullous formation may result from confluence of Pautrier microabscesses {1460}.

Progression to tumour stage

With progression from plaque stage to tumour stage the dermal infiltrates become more diffuse, and epidermotropism may be lost. The proportion of tumour cells increase both in number and size, and may include cells with small, medium-sized and large cerebriform nuclei, blast cells with prominent nuclei and intermediate forms. There is a concomitant decrease in the numbers of reactive T-cells and dendritic cells. In approximately 25% of advanced cases, transformation to a CD30 positive or negative large T-cell lymphoma defined by



Fig. 4.3 **A** Plaque-stage mycosis fungoides (MF). **B** Thick plaque with haemorrhage in MF. **C** Histopathology of plaque-stage MF. Intra-epidermal and dermal infiltrate.

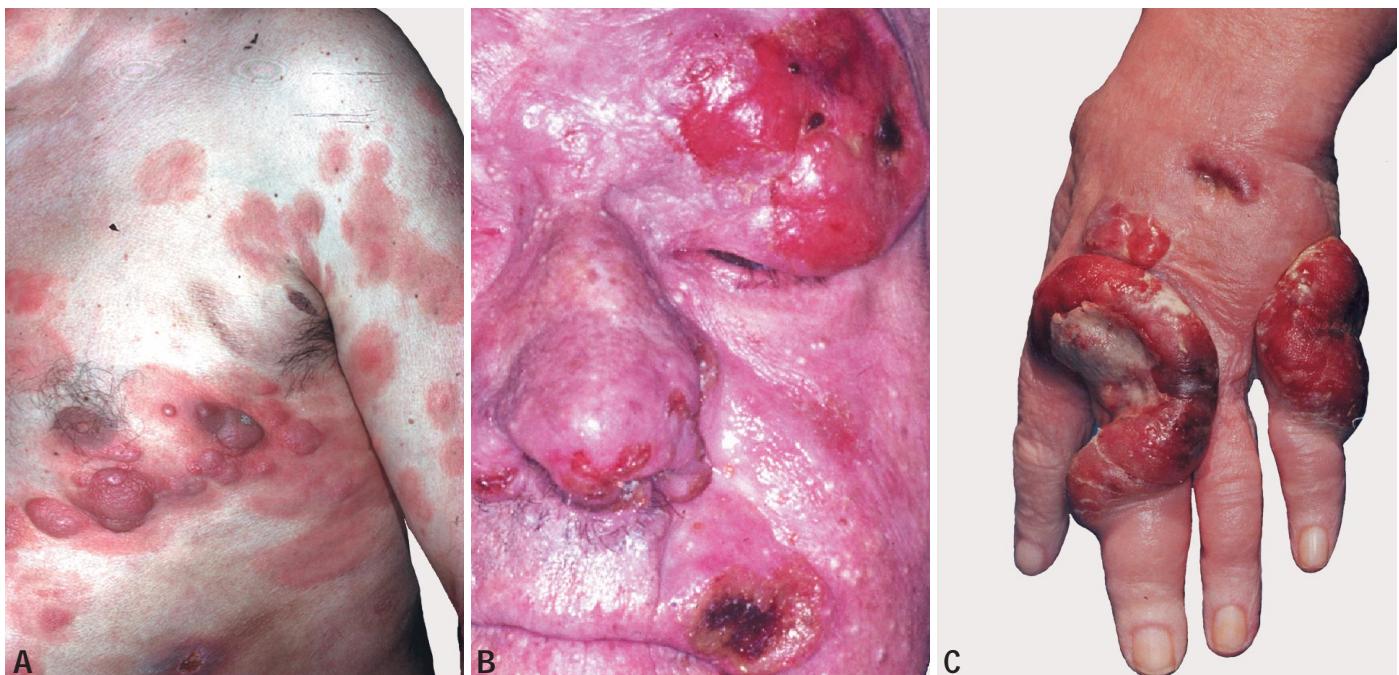


Fig. 4.4 Tumour-stage mycosis fungoides (MF). **A** Patches, plaques and tumours. **B** Ulcerating tumours in the face. **C** 'Fungoid' tumours on the hands.

the presence of more than 25% blast cells may be observed.

Immunoprofile

The immunophenotypical prototype of MF is CD2+, CD3+, CD4+, CD5+, CD45RO+, CD8, TCR-beta +, CD30-. During progression of the disease loss of CD7, 2 and 5 can occur. Helpful in the diagnosis is the loss of CD7, CD2, CD5, or CD4 in the epidermotropic cerebriform cells. During progression of the disease especially when transformation is present CD4 positive epidermotropic cells can have a cytotoxic phenotype (TIA-1, Granzyme B). In the transformed stage the blast cells can express CD30. Besides the CD4 prototype, a small number of MF cases have a CD8 positive cytotoxic phenotype (TIA-1 and gran-

zyme B). These cases have the same clinical behaviour as the CD4 positive cases.

Prelymphomatous precursor lesions

The term "parapsoriasis" is confusing and requires explanation. It encompasses a number of different pathologic states clinically manifested by chronic recalcitrant erythematous scaling lesions {311,312,1375}.

Two groups of parapsoriasis can be differentiated {337}. The benign form 'parapsoriasis en plaques' (Brocq disease), never evolve into malignant lymphoma. The large plaque forms (LPP) with poikiloderma (prereticulotic poikiloderma, parapsoriasis en grandes plaques poikilodermiques, poikiloderma vasculare atrophicans, parapsoriasis lichenoides,

parakeratosis variegata) or without poikiloderma (parapsoriasis en plaques, premalignant type, parapsoriasis en grandes plaques simples), may after several decades evolve into mycosis fungoides or CTCL in up to 10-50% of cases. Few large (more than 5 cm in diameter) patches show pityriasisiform scaling with (poikilodermatous variant) or without telangiectasia and netlike pigmentation. There is no palpable infiltration.

Histologically lesions in large plaque parapsoriasis (LPP) are different from MF or other CTCL. Under patchy parakeratosis there is slight atrophy of the epidermis, due to loss of rete ridges. The subepidermal zone is free of lymphocytes, which accumulate in a band-like arrangement in the upper dermis, spar-

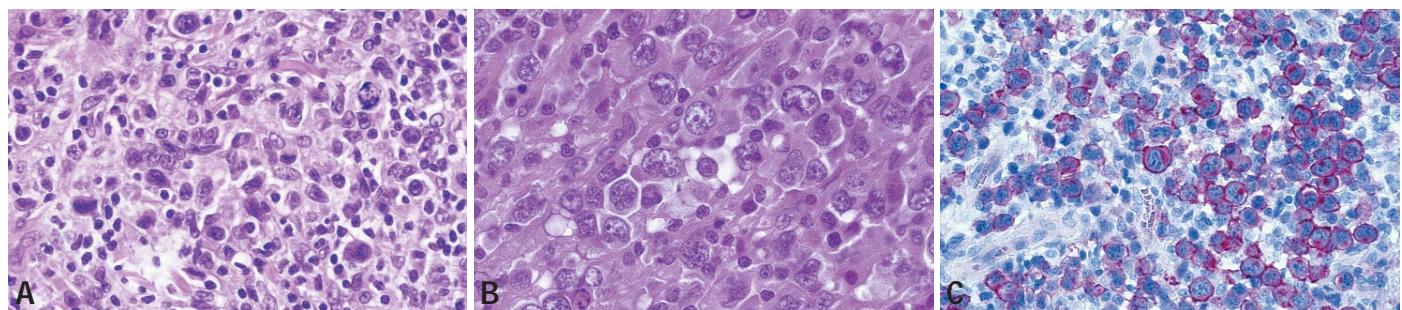


Fig. 4.5 Histopathology of transformed mycosis fungoides(MF). **A** Large-cell pleomorphic transformation. **B** Large cell anaplastic transformation. **C** Immunohistochemistry reveals CD30 positive tumour-cells.



Fig. 4.6 **A** Plaque in mono-lesional mycosis fungoides (MF). **B** Symptomatic mucinosis follicularis in MF. **C** Hypo-pigmented lesions in MF.

ing the papillary region. There is no significant epidermotropism as usually seen in early stages of mycosis fungoides. The poikilodermatous variant of the disease in addition shows dilated blood vessels in the upper dermis. T-cell receptor gamma gene rearrangement, which is clonal in about half of the patients with LPP, is without any prognostic significance [2186]. There is no significant difference between the observed and expected survivals in patients with LPP.

Histogenesis

Mature skin homing T cells that express the cutaneous lymphocyte antigen (CLA) enable them to specifically home into the skin. Functionally, the neoplastic cells in MF express TH2 phenotype, which accounts for many systemic changes associated with MF due to the production of a TH2-specific cytokine pattern (IL-4, IL-5, IL-10) leading to fever, oedema, eosinophilia, increase of IgE or IgA, and impaired delayed type reactivity [656,2445].

Somatic genetics

There have been a few reports on familial occurrence of MF or CTCL [2160] and on a possible association of HLA-DR5 with MF [2004]. HLA class II susceptibility alleles, i.e. HLA-DRB1*11, HLA-DQB1*03 and HLA-DRB1*1104 are more prevalent among patients with MF and are likely to be important in the pathogenesis of MF [1039,1118]. T-cell receptor beta and gamma chain genes are clonally rearranged. In advanced cases with extracutaneous involvement, the same clone is usually detected in the skin and in the extracutaneous lesions. In transformed cases the same clone is present in the pre-existing lesions and the high-grade lymphoma [207]. In advanced stage, the rate of chromosomal aberrations, especially of chromosomes 1, 6 and 11, increase with the activity of the disease and has prognostic significance in patients with MF. Aberrations of chromosomes 8 and 17 are especially associated with active or progressive disease.

Chromosomal abnormality possibly results in increased genetic instability as a basic prerequisite for the development of CTCL. In G-banding studies, numerical aberrations of chromosomes 6, 13, 15, and 17, marker chromosomes, and structural aberrations of chromosomes 3, 9, and 13 were increased in MF [1209]. In contrast to nodal lymphomas, the large cell transformation in cutaneous T-cell lymphoma (CTCL) is not associated with t(2;5)(p23;q35) chromosomal translocation [613,1420].

Increased expression of C-myc, p62, TP53 and proliferation markers (PCNA) has been found in advanced stages of MF as compared to early stages of MF suggesting a relationship between levels of these proteins and aggressiveness of CTCL [1192].

Prognosis and predictive factors

The majority of MF patients show an indolent clinical course over years or decades. The prognosis of the disease is defined by its stage. Patients with early

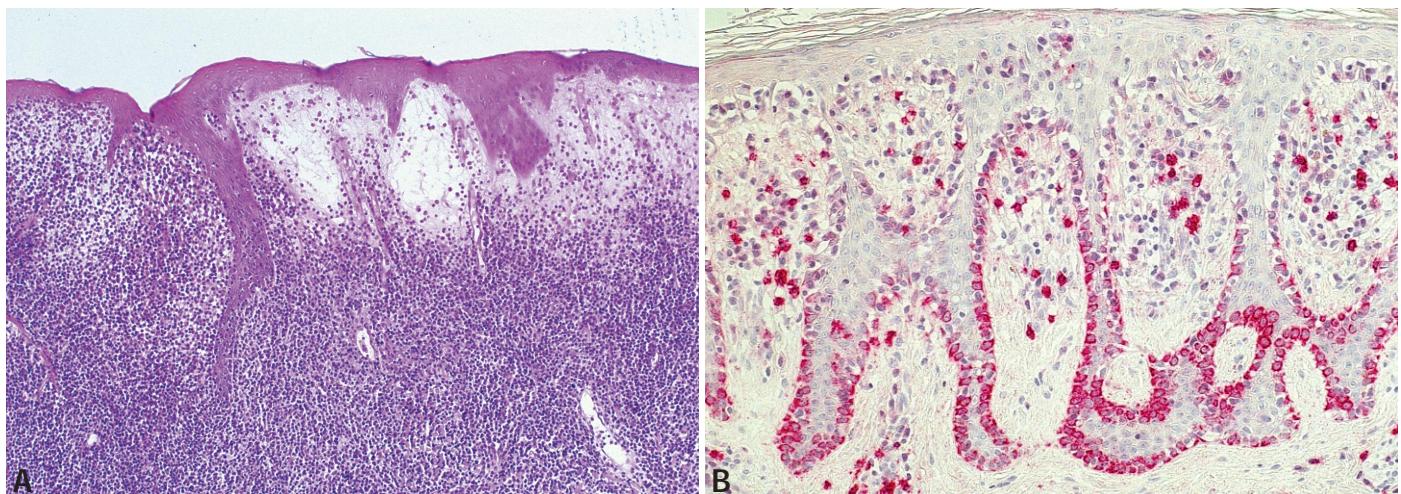


Fig. 4.7 Mycosis fungoides (MF). **A** Bullous variant of MF. **B** Immunohistochemistry shows CD8 positive tumour-cells lining up in the basal layer.

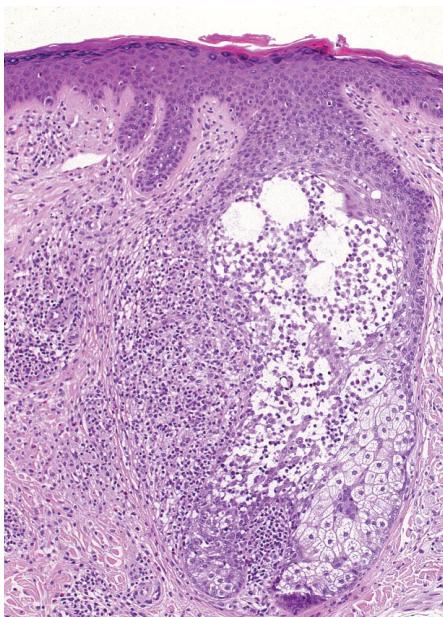


Fig. 4.8 Mucinous follicular variant of MF.

stages, i.e. with patches or thin plaques, without involvement of lymph nodes, peripheral blood or other extracutaneous compartment have an excellent prognosis with survival similar to that of an age, sex, and race-matched population {2575}.

Advanced stage and age above 60 years of age indicate a poor prognosis. When extracutaneous involvement or transformation into high-grade lymphoma occurs, expected survival is usually less than one year {2367,2412}.

Variants

Apart from the classical form of MF, there are several variants of this disease with unusual or atypical clinical and/or histopathological features. These comprise follicular, bullous, dyshidrotic, granulomatous, hypopigmented, poikilodermic, hyperpigmented, pigmented purpu-

ra-like, unilesional, palmoplantar, hyperkeratotic/verrucous, vegetating/papillomatous, ichthyosiform, pustular and other forms {1234}.

Pagetoid reticulosis, syringotropic MF, folliculotrophic (pilotropic) and granulomatous MF also are variants and deserve special emphasis.

Pagetoid reticulosis

Pagetoid reticulosis, in its localized form also referred to as Woringer-Kolopp disease (WKD) {302,2550} clinically presents as a solitary, slowly growing psoriasisiform crusty or hyperkeratotic patch or plaque, typically on a distal limb.

The histological hallmark is the sponge-like disaggregation of the epidermis by small to medium-sized lymphoid cells (pagetoid) which immunophenotypically correspond to those found in MF in most of the cases {336}. However, the neoplastic cells in WKD often demonstrate a higher proliferation rate (>30%) in comparison to lymphocytes in patch or plaque stage MF (<10%), and in some cases infiltrates in WKD may contain high numbers of CD30+ cells {937}. CD8+ {792} variants have also been reported. There exists a disseminated form featuring the same distinct pagetoid pattern of the infiltrate {1252}, which is now regarded as a separate disease, primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma.

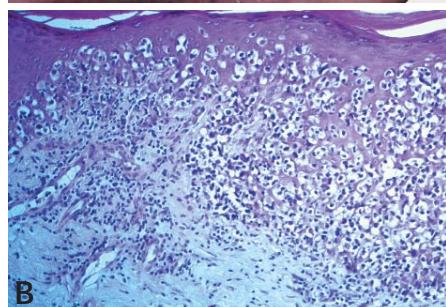


Fig. 4.9 Pagetoid reticulosis. **A** Solitary psoriasisiform lesion on the foot. **B** Pagetoid reticulosis showing sponge-like disaggregation of the epidermis by invading haloed lymphoid cells.

irregularly proliferating eccrine sweat glands by small cerebriform lymphocytes {343,2586}.

Folliculotrophic MF

Follicular MF, also referred to as pilotropic MF {776} is a rare variant, histopathologically characterized by infiltrates of atypical T lymphocytes around and within the epithelium of the hair follicles with sparing of interfollicular skin. The follicles may show cystic dilatation and/or cornified plugging. There may or may not be mucinosis. When present, mucinous degeneration of the follicular epithelium varies from focal spots of mucin deposition to complete destruction of follicles with mucin lakes. The folliculotropism is

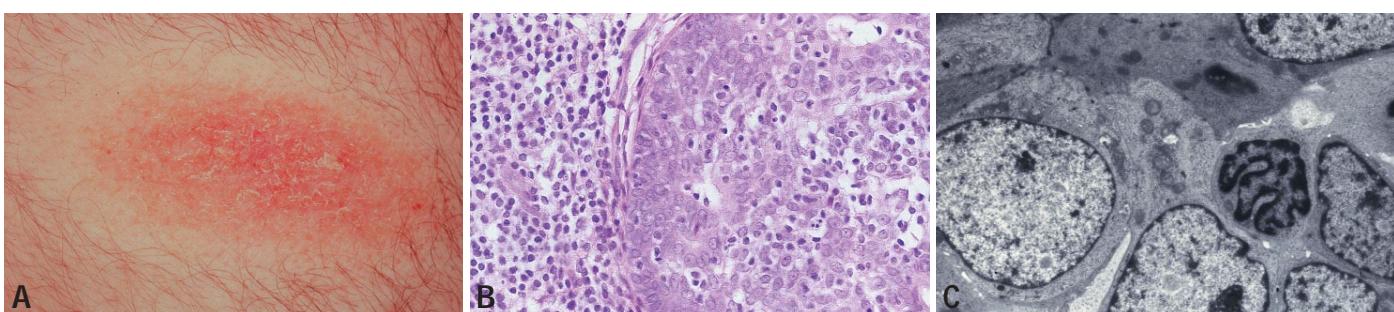


Fig. 4.10 Syringotropic cutaneous T-cell lymphoma (CTCL). **A** Cutaneous patch with hair-loss. **B** Infiltration of a sweat gland. **C** EM showing the convoluted nucleus of a neoplastic cell between acinar cells.



Fig. 4.11 Pilotropic lymphoid infiltrate in follicular mycosis fungoides (MF).



Fig. 4.12 Granulomatous MF. Granulomatous plaques with ulceration on the leg.

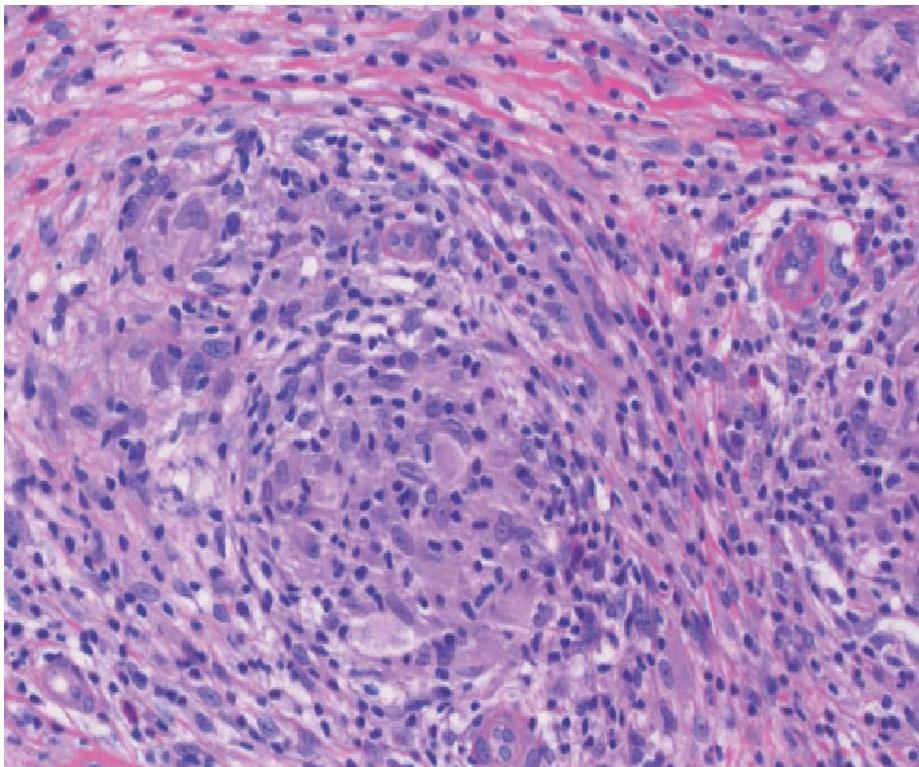


Fig. 4.13 Granulomatous mycosis fungoides (MF) with sarcoidal infiltrate pattern.

possibly due to an increased expression of skin-selective homing receptors and adhesion molecules in the follicular epithelium {1805}. A recent study has demonstrated that follicular MF shows a more aggressive behaviour and a worse prognosis than classical MF {829,2411}.

Granulomatous MF

Granulomatous MF is characterized by the histological presence of a granulomatous reaction {584}, sometimes featuring a sarcoidal or granuloma annulare-like pattern. Multinucleated giant cells may be present {1387}.

The prognostic and clinical significance of a granulomatous reaction in MF remains uncertain {454}.

Sézary syndrome

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E. Vonderheide
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Definition

Sézary syndrome (SS) is a rare variant of cutaneous T-cell lymphoma (CTCL), characterized by erythroderma, blood involvement and a poor prognosis. Neoplastic lymphocytes are typically mature T-helper cells with cerebriform nuclei. Criteria for the diagnosis of SS include the demonstration of a peripheral blood T-cell clone by molecular or cytogenetic methods; an expanded CD4+ population resulting in a CD4:CD8 ratio > 10, and immunophenotypic abnormalities such as absent expression of T-cell antigens (CD2, CD3, CD4 and/or CD5). Sézary syndrome (SS) is part of a broader disease spectrum, erythrodermic CTCL. The presence of a clonal T-cell population in the peripheral blood distinguishes SS from reactive disorders that exhibit erythroderma and circulating cells with cerebriform nuclei (pseudo-SS) {777}.

ICD-O code

9701 / 3

Epidemiology

Sézary syndrome accounts for less than

5% of all cutaneous T-cell lymphomas {2523}. It occurs almost exclusively in adults, characteristically presents over the age of 60 and has a male predominance {2523}.

Etiology

SS is of unknown etiology. However, a syndrome clinically indistinguishable from SS is occasionally seen in HTLV-1 associated lymphoma/leukaemia.

Clinical features

SS comprises a clinical triad of pruritus, erythroderma and lymphadenopathy. The pruritus is commonly intractable and sufficiently severe to prevent the patient sleeping or pursuing a normal life. Additional clinical features include alopecia, ectropion, nail dystrophy, palmo-plantar keratoderma and leonine facies. Bacterial skin infection is common in Sézary patients and may lead to a marked deterioration in their cutaneous disease. An increased prevalence of secondary malignancies, both cutaneous and systemic, has been reported in SS and attributed to the immunopare-

sis associated with loss of normal circulating CD4 cells {2075}.

Tumour spread and staging

Haematological involvement was defined in the TNM classification of MF as more than 5% atypical circulating lymphocytes (B1), but was not included as part of the Bunn-Lamberg staging system {1356}. Sézary patients are all T4/B1 (erythroderma with blood involvement) but staging will vary from stage III if there is no lymph node involvement to IVB if there is bone marrow involvement. In practice, most cases of SS are staged as IVA. In 1988, the definition of B1 was increased from 5 to 20%, by the NCI, but was still not included as part of the staging system {2071}.

The problem is that erythrodermic CTCL represents a spectrum and that any attempt to distinguish SS from cases that show a lesser degree of haematological involvement is necessarily arbitrary. An alternative approach is to develop a staging system that incorporates both lymph node status and haematological stage. A haematological staging system

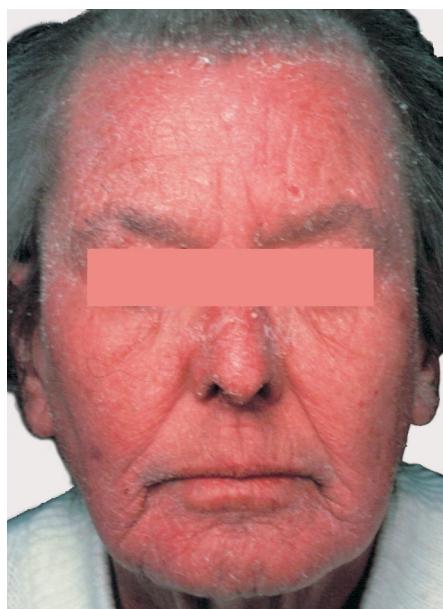


Fig. 4.14 Erythroderma and scaling of the face in Sézary syndrome.



Fig. 4.15 Palmar hyperkeratosis and onychodystrophy in Sézary syndrome.



Fig. 4.16 Sézary syndrome. Note erythroderma, oedema of the skin, and swelling of lymph nodes.

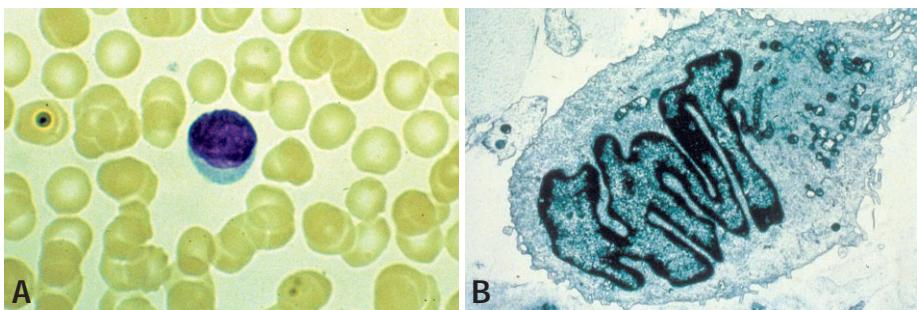


Fig. 4.17 Morphology of Sézary cells. **A** Blood film and **B** Ultrastructure showing a typical convoluted nucleus.

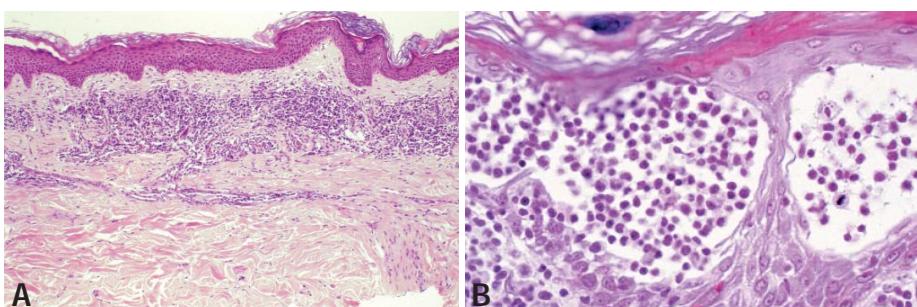


Fig. 4.18 Sézary syndrome. **A** Band-like infiltrate in the epidermis without epidermotropism. **B** Intraepidermal Pautrier microabscesses.

comprising five categories (H0-H4) was proposed by Russell-Jones and Whittaker {1998}, and subsequent data showed an increase in disease-specific death rates for each category with the most significant change occurring at H2,

defined by 5% Sézary cells with a T cell clone demonstrated by PCR, or a T cell clone demonstrated by Southern blot analysis only {2077}. The need for a haematological staging system has also been recognised by the International

Society for Cutaneous Lymphoma ISCL {2444}. Currently this is being tested in a larger, multi-centre study under the auspices of the ISCL.

Histopathology

Despite minor differences {1099}, the range of histological changes in SS are not dissimilar to those seen in patients with mycosis fungoides {2135}. Epidermotropism is a variable feature, and the size of Sézary cells varies in the skin as it does in blood. Only 2/3 of the skin biopsies and 73% of patients had diagnostic changes in the skin biopsies. Other causes of erythroderma need to be differentiated from SS, particularly drug induced erythroderma and chronic actinic reticuloid, both of which may show a high proportion of activated lymphocytes with cerebriform nuclei {2135}. In cases with a non-specific histology, the differential diagnosis would include other causes of erythroderma such as eczema or psoriasis.

Immunoprofile

A typical Sézary cell is a mature helper T cell with a memory phenotype. A classic immunoprofile is CD2, CD3, CD4, CD5, CD45RO positive and CD8 negative {1368,2526}. The majority of Sézary cells are also CLA positive {1827} and CD7 negative, and this latter feature has been proposed as a method of distinguishing Sézary cells from normal lymphocytes {957}. However, further studies have shown that the neoplastic cell population is present in both the CD7 positive and CD7 negative subset in the same patient {657}. More recently, Bernengo et al have demonstrated that CD4 positive Sézary cells typically lose the CD26 marker and that a diagnosis of SS or MF with haematological involvement can be made if the CD26 negative subset exceeds 30% of the CD4 positive cells {215}.

Complete loss of T cell antigens such as CD2, CD3, CD4, or CD5 is present in approximately 2/3 of patients with SS {957}. An alternative approach would be the identification of a tumour-specific antigen {669}. Recently two differentiation antigens P140 and SCS have been reported in circulating Sézary cells and P140 was also found in skin-infiltrating cells of patients with SS {1715}.



Fig. 4.19 Sézary syndrome transforming into blast-stage. **A** Multiple nodules and tumours. **B** Large atypical cells in blastic transformation of Sézary syndrome.

Histogenesis

The postulated cell of origin is a mature peripheral T cell which has skin-homing properties and exhibits a helper-cell phenotype.

Somatic genetics

Recurrent chromosomal translocations have not been detected in Sézary syndrome, but complex clonal numerical and structural chromosomal abnormalities are common and associated with a poor prognosis [1505,2343]. M-FISH techniques have shown a high rate of unbalanced translocations and associated deletions often involving chromosomes 1p, 10q, 14 and 15 [1505]. CGH studies have identified a consistent pattern of chromosomal gains/deletions (1p, 10q, 13q, 19, 17p losses and 4/4q, 17q and 18 gains) which, with the exception of 17q gains in Sézary syndrome, are identical to mycosis fungoides suggesting a similar pathogenesis [1210,1504]. Allelic losses on 1p, 9p, 10q and 17p have been confirmed by LOH studies and a high rate of microsatellite instability (MSI) has also been detected [2079, 2080]. These findings suggest that dysregulated genes at these chromosomal loci are involved in the pathogenesis [1554,2078]. There is a high rate of genomic instability as indicated by the presence of chromosomal instability [1505]. Constitutive activation of Stat 3 and chromosomal amplification of JUNB, a member of the AP-1 transcription factor complex, have been identified in Sézary syndrome [1089,1506]. A recent cDNA array study in Sézary syndrome has confirmed the presence of JunB overexpression and has also revealed overexpression of other genes associated with a TH2 phenotype such as Gata-3 and RhoB [1211]. These array findings appear to allow the identification of a poor prognostic group [1211].

Prognosis and predictive factors

Sézary syndrome has a poor prognosis with a median survival of 2 to 4 years depending on the exact definition used [777,1271,2044,2523]. Absolute Sézary cell count and lymph node involvement are independent prognostic factors. In addition, large cell transformation and the development of skin tumours on a background of erythroderma are poor prognostic signs.

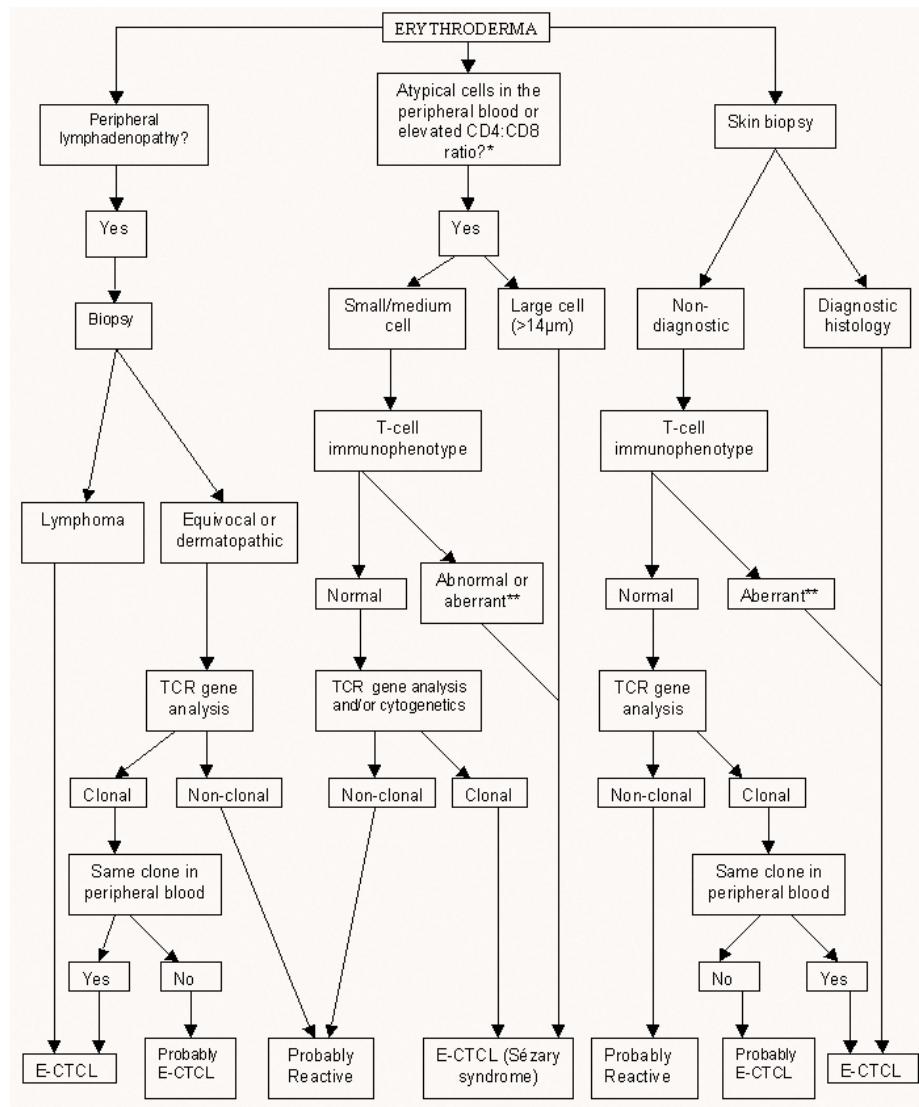


Fig. 4.20 Diagnostic pathways for the differential diagnosis of erythroderma. Algorithm for the evaluation and diagnosis of erythroderma due to cutaneous T-cell lymphoma (E-CTCL) vs. 'reactive' causes of erythroderma. TCR, T-cell receptor. *A CD4/CD8 ratio > 10 or an absolute Sézary cell count of $1 \times 10^9 \text{ L}^{-1}$ have been proposed as diagnostic criteria for Sézary syndrome (SS), but this algorithm requires additional immunophenotypic or genotypic data. Even so, a Sézary cell count > $1 \times 10^9 \text{ L}^{-1}$ or a CD4/CD8 ratio > 10 increases the probability of neoplasia, and separates SS from E-CTCL with a lesser degree of blood involvement. **Abnormal T-cell immunophenotype = an increased population of CD4+ cells that are CD26 (> 30%) or p140+. CD7 is less reliable. Aberrant T-cell immunophenotype = loss of pan T-cell markers such as CD2, CD3 or CD5, and/or double-negative T cells (CD4⁻ and CD8⁻). In skin, the loss of CD7 from epidermal lymphocytes is CTCL specific.

From: R. Russell-Jones (1997).

Granulomatous slack skin

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Definition

Granulomatous slack skin (GSS) is clinically characterized by the development of bulky skin lesions in the major skin folds and histologically by a granulomatous infiltrate composed of small lymphocytes and scattered multinucleated giant cells containing nuclei arranged in a wreath-like fashion.

Synonyms

Progressive atrophying chronic granulomatous dermohypodermatitis

Epidemiology

GSS is a rare form of primary cutaneous T-cell lymphoma. GSS usually appears in the third or fourth decade, but can also affect children [373]. GSS occurs almost exclusively in Whites. The male to female ratio is 2:1 to 3:1 [490].

Clinical features

GSS begins with slightly infiltrated, poikilodermatos sharply demarcated patches and plaques. Predilection sites are the intertriginous areas, especially the axillary and inguinal folds. After years,

pathognomonic bulky pendulous skin folds develop as a result of progressive destruction of elastic fibres. The lesions then resemble cutis laxa. Occasionally ulceration occurs. Regional lymphadenopathy may be present. In contrast to granulomatous MF, GSS is in almost all cases confined to intertriginous areas, and runs a more benign course than classic MF [1387].

Histopathology

Early lesions of GSS display a bandlike infiltrate of small lymphocytes without significant nuclear atypia [1379]. More advanced lesions show a dense lymphocytic infiltrate throughout the entire dermis. Nuclear atypia of lymphocytes is less pronounced than in granulomatous MF. The diagnostic hallmark is numerous multinucleated histiocytic giant cells, which are scattered throughout the background of the dense lymphocytic infiltrate. These giant cells contain 20-30 nuclei located at the periphery of the cytoplasm. Elastophagocytosis and emperipoleisis (phagocytosis of lymphoid cells by giant cells) are present. Elastic

stains demonstrate the loss of elastic fibres at the sites of the infiltrates in all dermal layers. On occasion, involvement of large vessels occurs. Ultrastructurally, the lymphocytes show hyperchromatic cerebriform nuclei similar to those seen in mycosis fungoides and Sézary syndrome [490]. Specific infiltration of regional lymph nodes or internal organs exhibiting similar features as in the skin has been observed in rare cases.

Immunoprofile

The lymphoid tumour cells display a T helper phenotype with expression of CD3, CD4 and CD45RO. There may be loss of other T-cell markers like CD5 or CD7. In rare cases, the tumour cells express CD30.

Genetics

Clonal rearrangement of TCR genes can be found in most cases and is a useful diagnostic tool in early stages of the disease [1382]. Trisomy 8 has been reported in two cases [136,2442].

Histogenesis

The tumour cells represent skin-homing T-helper cells.

Prognosis and predictive factors

The disease has a long natural history with a slowly progressive course over decades. Occasionally involvement of regional lymph nodes is found, but does not seem to affect survival. Although life expectancy is not reduced by GSS *per se*, other cutaneous and nodal lymphomas such as mycosis fungoides, Hodgkin lymphoma and peripheral T-cell lymphomas occur in approximately 20 – 50% of the patients, often years or even decades after the manifestation of GSS [202,490,1729,2413].



Fig. 4.21 Granulomatous slack skin (GSS). Large slightly infiltrated plaque in the groin.

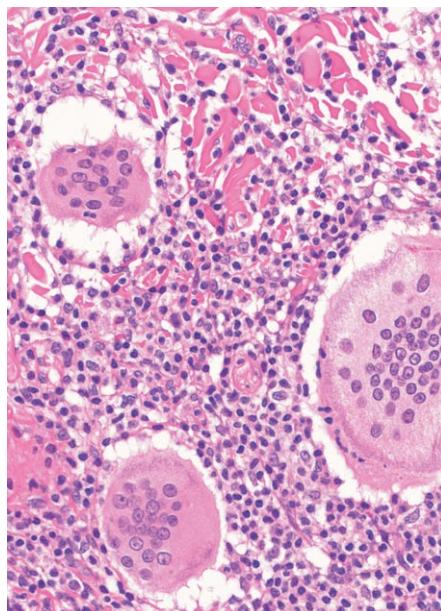


Fig. 4.22 GSS showing characteristic multinucleated giant cells with emperipoleisis of lymphocytes.

CD30+ T-cell lymphoproliferative disorders

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E.S. Jaffe
G. Burg
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CD30-positive T-cell lymphoproliferative disorders (LPD) of the skin (CD30+LPD) represent a distinctive group of primary cutaneous T-cell lymphoma. The spectrum of CD30+ LPD includes lymphomatoid papulosis (LyP), primary cutaneous anaplastic lymphoma (C-ALCL) and borderline cases which differ in their clinical and histological presentations {191, 1174, 1225, 1795, 2520}.

A feature common to all is the expression of CD30, a cytokine receptor belonging to the tumour necrosis factor receptor superfamily.

The term 'borderline lesions' has been applied to lesions that show clinical presentation of one entity (e.g. C-ALCL) but histological features of another one (e.g. LyP). This discrepancy may result in difficulties to assign such lesions to a distinct entity. Clinical presentation plays a crucial role in such discordant cases.

Lymphomatoid papulosis (LyP)

Definition

LyP is a chronic recurrent lymphoproliferative skin disease with self-regressing

papulo-nodular skin lesions and atypical lymphoid cells in a polymorphous inflammatory background {1466}.

ICD-O code 9718/1

Epidemiology

LyP is a rare disease with an estimated prevalence of 0.1 to 0.2 cases per 100 000 and a male to female ratio of 1.5:1 {2456}. Mostly people in the third and fifth decades are affected, but children can also be involved.

Localization

Although no definite predilection site has been identified, LyP lesions more often arise on the trunk, especially the buttocks, and extremities.

Etiology

The cause of the disease is unknown. Endogenous retroviral elements have been identified in LyP lesions {1242}. Interaction of CD30 and CD30L as well as TGF-beta and its receptor play an important role in growth regulation, including regression of tumoural lesions {1177, 1648}.

Clinical features

LyP is characterized by grouped or disseminated asymptomatic papules and/or nodules, which regress spontaneously after a few weeks sometimes leaving behind varioliform scars {1174}. Often new lesions develop concurrently in the same or another body region. Larger nodules up to 2 cm can develop and persist for months {2524}. Clinicopathologic variants of LyP include regional follicular and pustular forms {2076}.

Histopathology

The histological features of LyP are variable and depend on the stage of the lesions and disease. Three histologic subtypes (types A, B and C) have been delineated {2524} which represent a spectrum with overlapping features {2148}. In fully developed LyP lesions, there is a wedge-shaped diffuse dermal infiltrate which contains medium-sized to large pleomorphic or anaplastic lymphoid cells with irregular nuclei, sparse chromatin and mitotic activity. Some of the large atypical lymphoid cells resemble Reed-Sternberg cells. Ulceration may be present. In type A lesions, scat-



Fig. 4.23 Lymphomatoid papulosis with papules and ulcerating nodules.

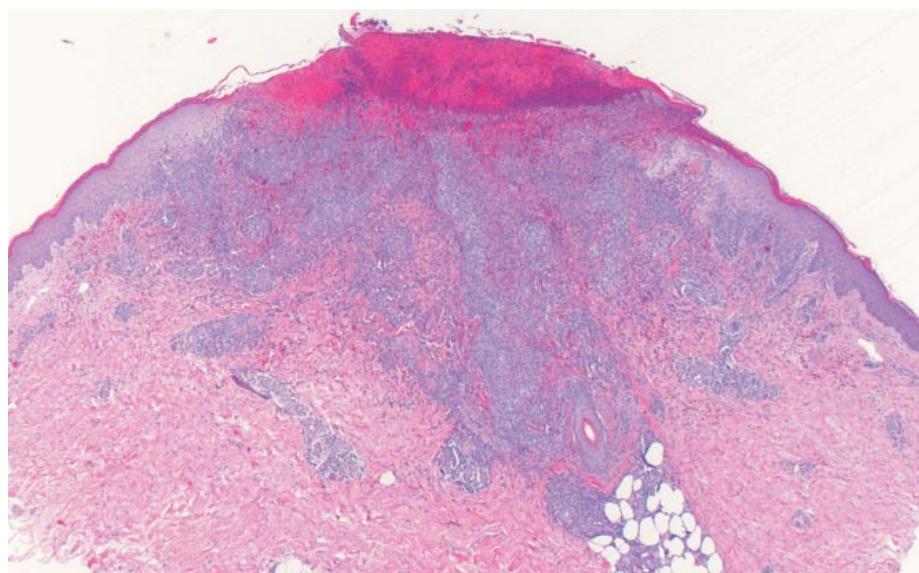


Fig. 4.24 Lymphomatoid papulosis. Wedge-shaped infiltrate with superficial ulceration and crust formation.

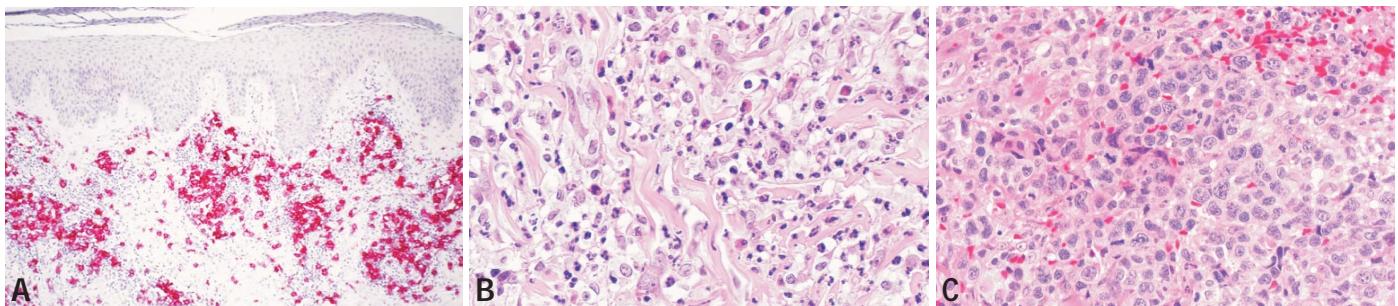


Fig. 4.25 Lymphomatoid papulosis. **A** Grouped and scattered CD3+ lymphocytes of various sizes. **B** Mixed infiltrate consisting of large atypical lymphocytes, eosinophils and neutrophils (LyP, type A). **C** Cohesive sheets of large atypical lymphocytes with only a few neutrophils (LyP, type C).

tered tumour cells are intermingled with numerous inflammatory cells such as neutrophils, eosinophils and histiocytes. Type C lesions show cohesive sheets of large atypical lymphoid cells with only a few intermingled reactive inflammatory cells. The rare type B is characterized by an epidermotropic infiltrate of small atypical lymphoid cells with cerebriform nuclei and histologically resembles mycosis fungoides. Various histologic types may be present in individual patients at the same time. Due to an overlap of histologic features between LyP and primary as well as secondary cutaneous ALCL, final diagnosis depends on correlation of clinical presentation and histologic findings.

Immunohistochemistry

A hallmark of the large atypical lymphoid cells is their positivity for CD30 {1173, 1227}. The large atypical lymphoid cells

in LyP are of T-cell origin with a CD3+, CD4+, CD8-. In 10% of the cases tumour cells express CD56+ {193}. Usually CD2 and CD5 are expressed, whereas often CD7 and sometimes CD3 are absent. In addition, expression of activation markers such as HLA-DR and CD25 (interleukin 2-receptor) is found. Cytotoxic molecules such as TIA-1 and granzyme B are expressed in 70% of the cases {1342}. CD56 is generally negative {968}. CD15, a marker for Reed-Sternberg cells in Hodgkin lymphoma, is usually not expressed in LyP. In contrast to the tumour cells expressing CD30 as in LyP type A and type C, the small atypical lymphocytes present in LyP type B are usually negative for CD30.

20% of patients with LyP {191,1174}. Long-term follow-up is therefore recommended. These lymphomas are usually referred to as LyP-associated malignant lymphomas. They can develop prior to, concurrent with, or after the manifestation of LyP {1175} and result in a fatal outcome in 2% of patients {191}. No risk factors have been identified which definitely indicate likely progression to associated lymphomas in LyP patients. So far, only fascin expression is found at a significantly higher rate in LyP cases associated with systemic lymphomas {1243}.

Primary cutaneous anaplastic large-cell lymphoma

Definition

Primary cutaneous anaplastic lymphoma (C-ALCL) is a neoplasm composed of large atypical lymphocytes of either pleomorphic, anaplastic or immunoblastic cytomorphology and expression of the CD30 antigen by the majority, i.e. more than 75% of tumour cells. Primary cutaneous and primary nodal CD30+ ALCL are distinct clinical entities that can have similar morphologic features and some overlap in immunophenotype, but differ in age of onset, genetic features, etiology and prognosis {600,2259,2493}.

ICD-O-code 9718/3

Synonyms

Regressing atypical histiocytosis , EORTC: Primary cutaneous large cell T cell lymphoma CD30+

Epidemiology

C-ALCL is the second most common form of cutaneous T-cell lymphoma with an incidence of 0.1-0.2 patients per 100'000. This form of lymphoma affects



Fig. 4.26 Primary cutaneous anaplastic CD30+ large-cell lymphoma. Solitary large ulcerated nodule on the leg.

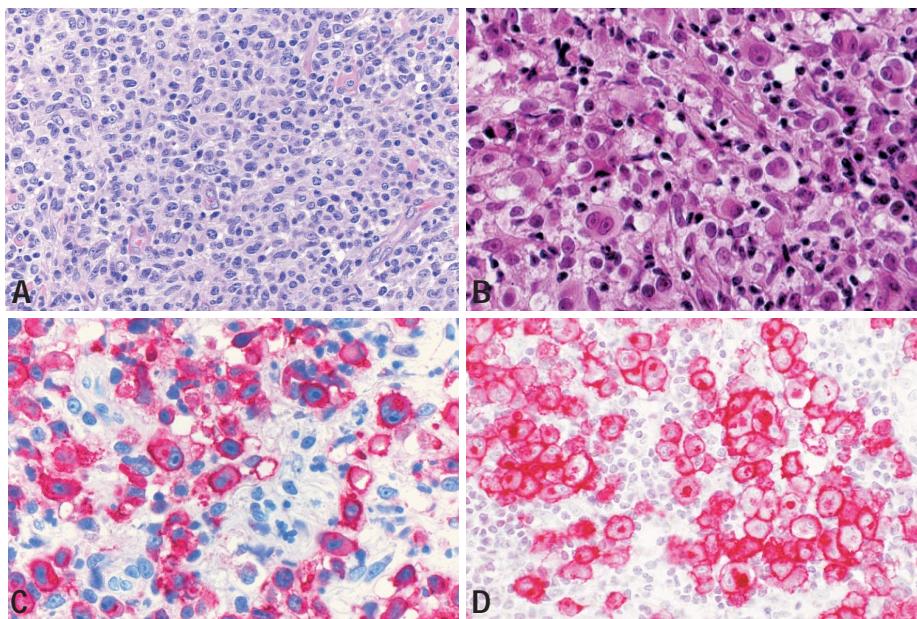


Fig. 4.27 CD30+ Primary cutaneous anaplastic large-cell lymphoma. **A** Large cells in a background of histiocytes, plasma cells and small lymphocytes. **B** Large atypical cells in CD30+ anaplastic large-cell lymphoma. **C** Scattered tumour cells expressing CD30. **D** Expression of CD30 by almost all tumour cells.

mainly people in their sixth decade with a male to female ratio of 2-3:1 {191,1226}, but it can also occur in childhood. C-ALCL is a common form of cutaneous T-cell lymphoma in HIV-infected individuals {1248}.

Localization

The extremities and head are predilection sites {196,1228}.

Clinical features

ALCL usually presents as an asymptomatic, solitary firm nodule which rapidly grows and often ulcerates {1174}. Approximately 20% of the patients have multifocal disease, i.e. two or more lesions at multiple anatomic sites {191}. Involvement of regional lymph nodes can occur. Other extra-cutaneous spread is rare. If there is no therapeutic intervention, spontaneous regression occurs in 10-40% of the tumour lesions {191,1226}.

Histopathology

There is a dense nodular infiltrate extending through all levels of the dermis into the subcutis. Epidermotropism may be found. The infiltrate consists of cohe-

sive sheets of large, cells with irregularly shaped nuclei and one or multiple nucleoli and an abundant, clear or eosinophilic cytoplasm. Mitoses are frequent. Clusters of small reactive lymphocytes are found within and around the tumour. Eosinophils, plasma cells, and accessory dendritic cells usually are not prominent in C-ALCL. Variants of C-ALCL include neutrophil-rich or pyogenic CD30+ ALCL presenting histologically with small aggregations or scattered CD30+ medium to large pleomorphic lymphoid cells within an extensive infiltrate of neutrophils {341,1549}.

Immunohistochemistry

C-ALCL displays an activated T-cell phenotype with expression of T-cell associated antigens CD2, CD3, CD4 and CD45RO, activation markers such as CD25 (IL-2R), CD30, CD71 and HLA-DR, and frequent expression of cytotoxic molecules such as TIA-1, granzyme B and perforin {290,1342}. CD30 must be expressed by at least 75% of the large pleomorphic or anaplastic lymphoid cells. Variable loss of T cell antigens (CD2, CD3, CD5 and CD7) can be found

{1228}. In contrast to systemic (nodal) ALCL, C-ALCL does not express EMA, but may express the cutaneous lymphocyte antigen (CLA, HECA-452) and homeobox gene HOXC5 {243}. C-ALCL is consistently negative for the anaplastic lymphoma related tyrosine kinase (ALK).

Genetics

Clonal rearrangement of T cell receptor genes is detected by Southern blot and PCR in most cases (over 90%) of C-ALCL {1467}. The translocation t(2;5) (p23;q35) resulting in expression of npm-alk protein (p80), which is a characteristic feature of systemic anaplastic large cell lymphomas, is rarely if ever found in C-ALCL {228,613}. Systemic ALCL may present with cutaneous disease, and the identification of ALK-expression is helpful in this distinction.

Histogenesis

Activated skin-homing T-cell.

Prognosis and predictive factors

C-ALCL has a favourable prognosis with 5 year-survival rates of 90% {191,1795}. Up to 40% of C-ALCL show spontaneous regression {198}. Regional lymph nodes may be involved, but the survival rate is similar to patients with skin lesions only {191}. Other extracutaneous spread occurs in 10% of the patients, especially in those with multiple grouped or multifocal tumour lesions with a fatal outcome in only a minority of the patients {191}. Spontaneous regression and age less than 60 years are associated with a better prognosis, while extracutaneous disease and higher age tend to have a worse outcome. Cytomorphology (anaplastic or pleomorphic and immunoblastic) seems not to be a prognostic factor {191,1795}.

Subcutaneous panniculitis-like T-cell lymphoma

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Definition

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a T-cell lymphoma with preferential infiltration of subcutaneous tissue by atypical lymphoid cells of varying size, often with marked tumour necrosis and karyorrhexis.

ICD-O code 9708/3

Historical annotation

In the historical literature, most cases of SPTCL were probably diagnosed as histiocytic cytophagic panniculitis {562, 1527}.

Epidemiology

Subcutaneous panniculitis-like T-cell lymphoma is a rare form of lymphoma, representing less than 1% of all non-Hodgkin lymphomas. It occurs in males and females equally, and has a broad age range. Cases have been reported in children under the age of two years. Most cases occur in adults {1060,1341,2026, 2480}.

Etiology

Unknown. In most patients the disease presents sporadically.

Localization

Patients present with multiple subcuta-

neous nodules, usually in the absence of other sites of disease. The most common sites of localization are the extremities and trunk.

Clinical features

Clinical symptoms are primarily related to the subcutaneous nodules. The nodules range in size from 0.5 cm to several cm. in diameter. Larger nodules may become necrotic, but ulceration of cutaneous lesions is rare. Systemic symptoms, most commonly fever, are variable but usually present. Some patients may present with a haemophagocytic syndrome with pancytopenias, fever, and hepatosplenomegaly {338,863,2480}. Lymphadenopathy is usually absent.

Histopathology

The infiltrate extends diffusely through the subcutaneous tissue, usually without sparing of septae. The overlying dermis and epidermis are typically uninvolved. The neoplastic cells range in size from small cells with round nuclei and inconspicuous nucleoli to larger transformed cells with hyperchromatic nuclei. The lymphoid cells have a moderate amount of pale-staining cytoplasm. A helpful diagnostic feature is the rimming of the neoplastic cells surrounding individual fat cells {1341}. Admixed reactive histio-

cytes are frequently present, particularly in areas of fat infiltration and destruction. The histiocytes are frequently vacuolated, due to ingested lipid material. Vascular invasion may be seen in some cases, and necrosis and karyorrhexis are common. However, the infiltrates usually are confined to the subcutaneous tissue, with sparing of the dermis. This feature is helpful in the differential diagnosis from other lymphomas involving skin and subcutaneous tissue. The necrosis is primarily apoptotic in nature, possibly related to the release of cytotoxic molecules {1341,2133}. Cutaneous $\gamma\delta$ T-cell lymphomas can have a panniculitis-like component, but commonly show both dermal and epidermal involvement in addition to subcutaneous disease {1060, 1341,2026,2366}. Plasma cells and reactive lymphoid follicles are generally absent, in contrast to lupus profundus panniculitis, and other forms of lobular panniculitis.

In some cases of SPTCL the infiltrates in initial phases may appear deceptively benign, and the differential diagnosis with benign panniculitis may be difficult {338,863}.

Immunoprofile

SPTCL is derived from $\alpha\beta$ cells, T-cells with a cytotoxic profile. The cells are usu-

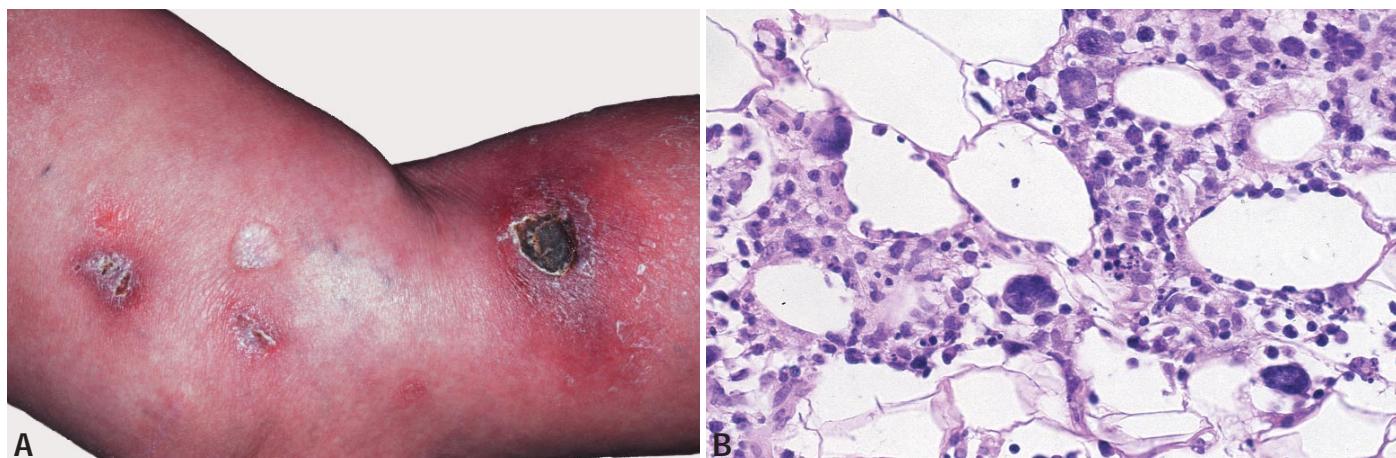


Fig. 4.28 Subcutaneous panniculitis-like T-cell lymphoma (SPTCL). **A** Erythematous plaques and nodules on the leg with ulceration. **B** Diffuse infiltration of subcutaneous tissue simulating lobular panniculitis. Large atypical cells rimming around fat lobules.



Fig. 4.29 Subcutaneous panniculitis-like T-cell lymphoma (SPTCL). Subcutaneous erythematous plaques and nodules on the legs.

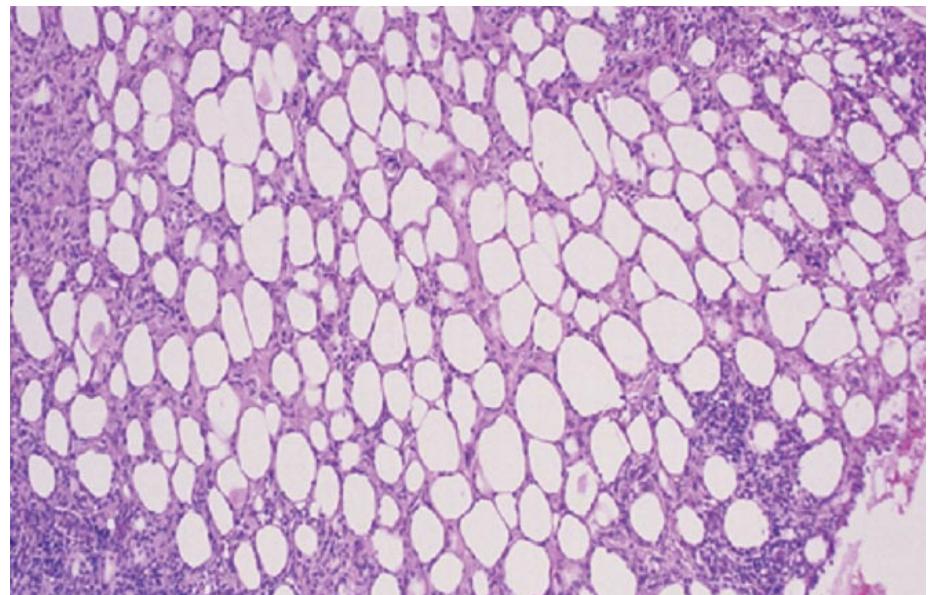


Fig. 4.30 Subcutaneous panniculitis-like T-cell lymphoma (SPLTCL) Lobular panniculitis-like infiltrate of neoplastic lymphoid cells.

ally CD8-positive, with expression of cytotoxic molecules including granzyme B, perforin, and T-cell intracellular antigen (TIA-1) {1341,2026}. However, in contrast to other cytotoxic TCLs related to the innate immune system (enteropathy-type T-cell lymphoma, extranodal NK/T-cell lymphoma), the cells are negative for granzyme M (metase) {694, 1122,1325,2564}. The neoplastic cells are capable of producing a number of cytokines and chemokines, a feature that is related to development of systemic symptoms and the haemophagocytic syndrome {338,2340}. Cutaneous $\gamma\delta$ T-cell lymphomas {119,338,1341,2026} are distinguished from SPTCL, even if a pan-

neculitis-like component is present.

Histogenesis

Mature cytotoxic T-cell of the adaptive immune system.

Precursor lesions

Oligoclonal T-cell populations may be found in some cases of lobular panniculitis, suggesting the potential for clonal evolution in rare cases {1484}. However, progression from cytophagic panniculitis without monoclonality to SPTCL rarely if ever occurs {1527}.

Somatic genetics

The neoplastic cells show rearrangement

of T-cell receptor genes, and are negative for Epstein Barr sequences.

Prognosis and predictive factors

Dissemination to lymph nodes and other organs is uncommon and usually occurs late in the clinical course. The natural history is often aggressive {694,863,917, 1300,2026}. A haemophagocytic syndrome is a frequent complication in $\alpha\beta$ cases and usually precipitates a fulminant downhill clinical course. However, if therapy for the underlying lymphoma is instituted and is successful, the haemophagocytic syndrome may remit.

Primary cutaneous peripheral T-cell lymphoma, unspecified

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Definition

A heterogeneous group of cutaneous T-cell lymphomas that do not fit into one of the well-defined subtypes of T-cell lymphoma/leukaemia. Three provisional entities have been separated: Cutaneous $\gamma\delta$ T-cell lymphoma, primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma and primary cutaneous small-medium CD4+ T-cell lymphoma.

ICD-O code 9709/3

Synonyms and historical annotation

The category of the peripheral T-cell lymphomas, unspecified (PTL) was introduced in the REAL classification {960} and was maintained in the WHO classification {1369}. It encompasses per definition all T-cell neoplasms that do not fit into any of the better defined subtypes of T-cell lymphoma/leukaemia. As such it constitutes a heterogeneous group of diseases. These conditions are most frequently systemic {1121}. Primary cutaneous PTL are rare and constitute less than 10% of all cutaneous T-cell lymphomas (CTCL) in large series {195}. They correspond to the CD30-negative CTCL in the EORTC classification and show an aggressive behaviour in most cases {195,2523}. Therefore, distinction between "primary" and "secondary" cutaneous involvement seems less important for this category.

Although it is still controversial how these tumours can be grouped into separate diseases, recent investigations have suggested that some disorders within this broad group of neoplasms can now be separated out as provisional entities. For the remaining diseases that do not fit into either of these provisional entities (Table 4.1), the designation PTL, unspecified, is maintained.

Cutaneous $\gamma\delta$ T-cell lymphoma

Definition

Cutaneous $\gamma\delta$ T-cell lymphoma (CGD-

Table 4.1

Characteristic features of three provisional cutaneous T-cell lymphomas.

	Skin lesion	Pattern of infiltration	Cytology	Phenotype	EBV	Behaviour
$\gamma\delta$ -TCL	Patches, plaques, tumours, disseminated	E, D, S	Medium-large, pleomorphic	TCRd1+, CD3+, CD4-, CD8-, CyAg+, CD56 +/-	-	A
AECD8+	Eruptive nodules, hyperkeratotic patches/ plaques, disseminated ,	E	Medium-large pleomorphic	bF1+, CD3+, CD4-, CD8+, CyAg+	-	A
PTL, CD4+	Solitary nodules, tumours	D, S	Small-medium pleomorphic	bF1+, CD3+, CD4+, CD8-	-	I

Abbreviations: $\gamma\delta$ -TCL= gamma delta-T-cell lymphoma; AECD8+= aggressive, epidermotopic, CD8+ cytotoxic T-cell lymphoma; E=epidermal; D=dermal; S=subcutaneous; CyAg= cytotoxic antigens (TIA-1, granzyme B, perforin); EBV= Epstein-Barr Virus; A =aggressive; I=indolent.

TCL) is a lymphoma composed of a clonal proliferation of mature, activated gd T-cells expressing a cytotoxic phenotype. This group includes cases of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) with a gamma/delta phenotype. In the WHO classification 2001, these were grouped together with SPTCL of $\alpha\beta$ origin {1121}, but they show distinctive features and seem to be more closely related to other CGD-TCL {192,1060, 1533,2026,2366}. A similar and possibly related condition may present primarily in

mucosal sites {98}. Whether cutaneous and mucosal $\gamma\delta$ TCLs are all part of a single disease, i.e. muco-cutaneous $\gamma\delta$ TCL, is not yet clear {1122,2539}.

Epidemiology

CGD-TCLs are rare, with approximately 50 cases reported {1533,1665,2366}. In one series they represented <5% of cutaneous T-cell lymphomas {1879}. Most cases occur in adults. There is no reported sex predilection.



Fig. 4.31 Cutaneous $\gamma\delta$ T-cell lymphoma presenting with skin tumours.

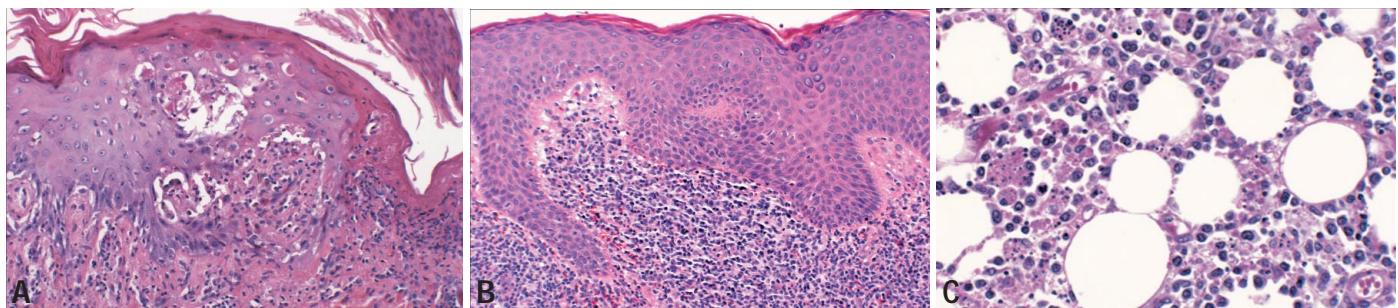


Fig. 4.32 Cutaneous $\gamma\delta$ T-cell lymphoma. **A** The infiltrates may be epidermotropic, **B** dermal **C** subcutaneous or combined.

Etiology

The distribution of disease reflects the localization of normal $\gamma\delta$ T cells, which are believed to play a role in host mucosal and epithelial immune responses [268]. Impaired immune function associated with chronic antigen stimulation may predispose to the development of mucosal and CGD-TCLs [98,2539]. Epstein-Barr virus (EBV) is generally negative in CGD-TCLs, but may be positive in primary $\gamma\delta$ TCL in mucosal sites [98,1191,2366,2539].

Clinical features

The clinical presentation is variable. The disease may be predominantly epidermotropic and present with patches/plaques, or it may be predominantly deep dermal/subcutaneous with necrotic tumours or nodules, resembling subcutaneous panniculitis-like T-cell lymphoma (SPTCL) of $\alpha\beta$ type [192,221,1060,1533, 1665,1879,2026,2366]. The lesions are often mainly present on the extremities [2366], but other sites may be affected as well [1533,2365]. Patients with CGD-TCL usually lack involvement of lymph nodes, spleen, and bone marrow, but the disease may disseminate to extranodal/mucosal sites. A haemophagocytic syndrome may occur in patients with panniculitis-like tumours [119,2365].

Histopathology

The neoplastic cells are generally medium to large in size with coarsely clumped chromatin [2366]. Large blastic cells with vesicular nuclei and prominent nucleoli are infrequent. Apoptosis and necrosis are common, often with angioinvasion [1533]. Three major histologic patterns of involvement are present: epidermotropic, dermal, and subcutaneous. However, usually more than one histologic pattern is present in the same patient in different biopsy specimens or within a single

biopsy specimen [2366]. Epidermal infiltration may occur as mild epidermotropism to marked pagetoid reticulosis-like infiltrates [221,1665,1879]. Subcutaneous nodules may be panniculitis-like or more solid in appearance and may show rimming of fat cells, similar to SPTCL of alpha/beta origin [1533]. Dermal and epidermal involvement often coexists with subcutaneous disease, in contrast to SPTCL of $\alpha\beta$ origin, which is mainly or exclusively subcutaneous in distribution [192,1060,2026].

radiation [1665,2366]. In a recent series of 33 patients, 22 (66%) died within 5 years of diagnosis, and in the same study TCR $\delta 1$ expression was an independent predictor of survival [2366]. Among 33 patients with CGD-TCL, there was a trend for decreased survival for patients who had subcutaneous fat involvement in comparison with patients who had epidermotropic or dermal disease only. Age, sex, and lymphadenopathy did not have any discernible prognostic impact [2366].

Immunoprofile

The cells are CD3+, CD2+, CD7 +/-, but usually negative for CD5 [2539]. Most CGD-TCLs lack both CD4 and CD8, but some are CD8+ [2366]. The cells are positive for TCR- δ , but lack $\beta F 1$ of the $\alpha\beta$ T-cell receptor. The absence of $\beta F 1$ may be used to infer a $\gamma\delta$ origin under appropriate circumstances [1151,2026,2365]. The cells are positive for TIA-1 and the cytotoxic proteins granzyme B, granzyme M, and perforin. [1325,1341, 1533]. CD56 is frequently expressed [1533].

Histogenesis

Functionally mature and activated cytotoxic $\gamma\delta$ T-cells of the innate immune system.

Somatic genetics

The cells show clonal rearrangement of the TCR gamma gene. TCR beta may be rearranged or deleted, but is not expressed. Cases with predominant subcutaneous involvement express V $\delta 2$, but this has not been studied in other CGD-TCL [1860,2026]. EBV is generally negative in primary CGD-TCL [98,119].

Prognosis and predictive factors

Patients have aggressive disease resistant to multiagent chemotherapy and/or

Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma

Definition

A cutaneous T-cell lymphoma characterized by epidermotropic infiltrates of CD8-positive, cytotoxic T-cells of $\alpha\beta$ origin. The behaviour is aggressive in most cases [223].

Epidemiology

This disease occurs mainly in adults and is rare with approximately 30 cases published worldwide [36,192,223,1533, 2062].

Clinical features

The clinical presentation is characterized by sudden eruptions of localized or disseminated papules, nodules and tumours, often with central ulceration and necrosis. Superficial, hyperkeratotic patches and plaques may also be present [36,223]. The disease may resemble epidermotropic variants of other cutaneous T-cell lymphomas and is similar, if not identical to cases described as generalized pagetoid reticulosis of the Kertes-Goodman type [1252,1533]. Classical MF, which may express CD8 in rare cases [1456,1880, 2062,2510], usu-

ally does not show overt destruction and necrosis and has a more protracted behaviour with progression over years from patches to plaques and tumours. The disease may disseminate to other visceral sites (lung, testis, central nervous system, oral mucosa), but lymph nodes are often spared {223}.

Histopathology

The histological and cytological appearance is very variable ranging from a lichenoid pattern with marked, pagetoid epidermotropism and subepidermal edema to deeper, more nodular infiltrates. The epidermis may be acanthotic or atrophic, often with necrosis, ulceration and blister formation {36,223}. Invasion and destruction of adnexal skin structures are commonly seen {1533}. Angiocentricity and angioinvasion may be present {1533}. Tumour cells are small-medium or medium-large with pleomorphic or blastic nuclei {223}.

Immunoprofile

The tumour cell have a β F1+, CD3+, CD8+, Granzyme B+, perforin+, TIA-1+, CD2-, CD4-, CD5-, CD7-/+ phenotype {36,223,2062}. EBV is generally negative {192,1533}.

Histogenesis

Skin homing, CD8-positive, cytotoxic T-cells of $\alpha\beta$ type.

Somatic genetics

The neoplastic T-cells show clonal TCR gene rearrangements. Specific genetic abnormalities have not been described.

Prognosis

These lymphomas have an aggressive clinical course with a median survival of 32 months {36,223,1533,2062}.



Fig. 4.33 Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma presenting with an ulcerated skin tumour

Primary cutaneous small-medium CD4+ T-cell lymphoma

Definition

A cutaneous T-cell lymphoma characterized by a predominance of small to medium-sized CD4-positive pleomorphic T-cells with clinical features different from MF. Most cases have a favourable clinical course {195,878}.

Epidemiology

A rare disease, accounting for 5-10% of cutaneous lymphomas in large series {195,878}.

Clinical features

Characteristically, these lymphomas present with a solitary plaque or tumour, generally on the face, the neck or the upper trunk {195}. Less commonly, they present with one or several papules, nodules or tumours, but always without patches typical of mycosis fungoides {195,783,2267}.

Histopathology

These lymphomas show dense, diffuse or nodular infiltrates within the dermis with tendency to infiltrate the subcutis.

Epidermotropism may be present focally. There is a predominance of small/medium-sized pleomorphic T cells {195,783,2267}. A small proportion (<30%) of large pleomorphic cells may be present {195}. A considerable admixture with small reactive lymphocytes and histiocytes may sometimes be observed {2074}.

Immunoprofile

By definition these lymphomas have a CD3+, CD4+, CD8-, CD30- phenotype sometimes with loss of pan T-cell markers {195,783}. Cytotoxic proteins are generally not expressed {195}.

Histogenesis

Skin homing, CD4-positive T-cell.

Somatic genetics

The TCR genes are clonally rearranged {783,878}. Demonstration of clonality is a useful criterion for distinction from pseudo-T-cell lymphomas, which may also present with a solitary plaque or nodule. No consistent cytogenetic abnormalities have yet been identified.

Prognosis and predictive factors

These lymphomas have a rather favourable prognosis with an estimated 5-year survival of 60-80% {195,783,878,2267}. Cases presenting with solitary or localized skin lesions seem to have an especially favourable prognosis {195,878}.

Primary cutaneous PTL, unspecified

Definition

The designation PTL, unspecified is maintained for cutaneous T-cell lym-

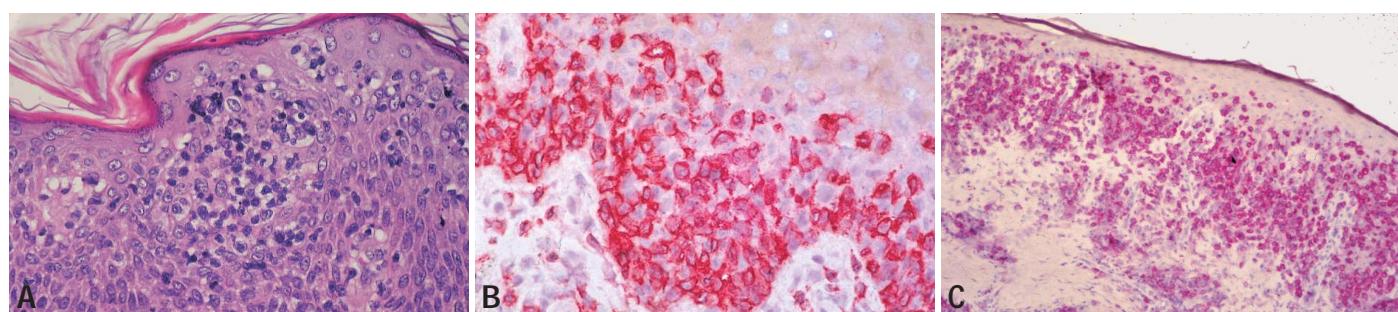


Fig. 4.34 Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. **A** The neoplastic infiltrate is markedly epidermotropic and pleomorphic and is **B** positive for CD3 and **C** for CD8.

phomas that originate from mature, transformed T-lymphocytes and that do not fit into any of the better defined subtypes of mature cutaneous T-cell neoplasms. Hence, other categories of T-cell lymphoma must be excluded. These include the 3 provisional entities described above. Furthermore, given the wide variety of histologic appearances of tumour stage mycosis fungoides (MF), a diagnosis of MF should always be ruled out by complete clinical examination and an accurate clinical history.

Epidemiology

These tumours account for 5 to 10% of all primary cutaneous T cell or NK cell lymphomas {195}. All ages may be affected, but the disease is most common in adults.

Clinical features

Most lymphomas in this category present with rapidly growing tumours or nodules that may be multiple or (more rarely) solitary or localized {195,197,878,2523}. No sites of predilection have been recorded.

Histopathology

Skin infiltrates are most often diffuse, but nodular or band-like patterns can be seen. Epidermotropism is mild or absent in most cases. The tumour cells are medium to large, usually with markedly pleomorphic nuclei. Rare cases may show a predominance of cells that are more immunoblastic in appearance {197,2523}. Small reactive lymphocytes, eosinophils and plasma cells may be present {195}, but the inflammatory background is usually not as pronounced as it can be in nodal malignancies.

Immunoprofile

The tumour cells express T-cell associated antigens (CD2, CD3, CD5), but usually lack CD7; most cases are CD4+, but rare tumours may be CD8+ or positive (or negative) for both CD4 and CD8 {195}. Cytotoxic antigens (TIA-1+, granzyme B) are usually not expressed {195}. Occasional tumour cells may be CD30-positive.

Histogenesis

Skin homing T-cells.

Precursor lesion

There are no known precursor lesions. As

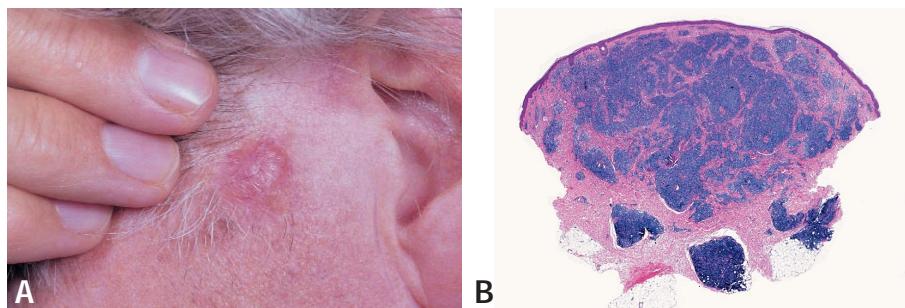


Fig. 4.35 Primary cutaneous small-medium T-cell lymphoma. **A** Small-medium CD4+ T-cell lymphoma with a solitary skin nodule on the face. **B** Nodular infiltrates of lymphocytes involving the entire dermis and superficial part of subcutaneous tissues.

mentioned, cases of transformed MF may closely resemble peripheral T cell lymphoma unspecified and can only be distinguished on clinical grounds.

Somatic genetics

The TCR genes are clonally rearranged. No consistent cytogenetic abnormalities have yet been identified.

Prognosis and predictive factors

The prognosis is poor with 5-year survival rates of less than 20% {195,878}. Cases with immunoblastic morphology may have an even more aggressive behaviour {197,2523}. Cases with solitary/localized lesions seem to behave just as aggressively as those with multiple lesions {195}.

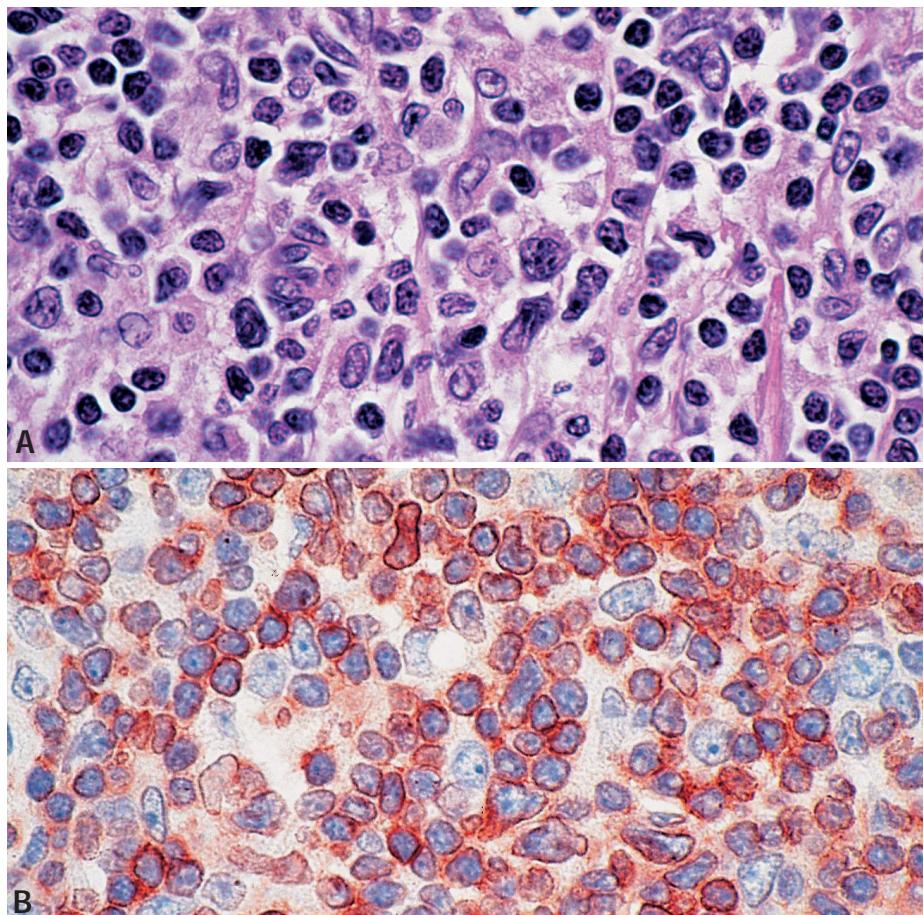


Fig. 4.36 Cutaneous small-medium pleomorphic T-cell lymphoma. **A** Small-medium lymphocytes with pleomorphic nuclei predominating. **B** Staining for CD3 confirms the T-cell lineage of the lymphocytes.

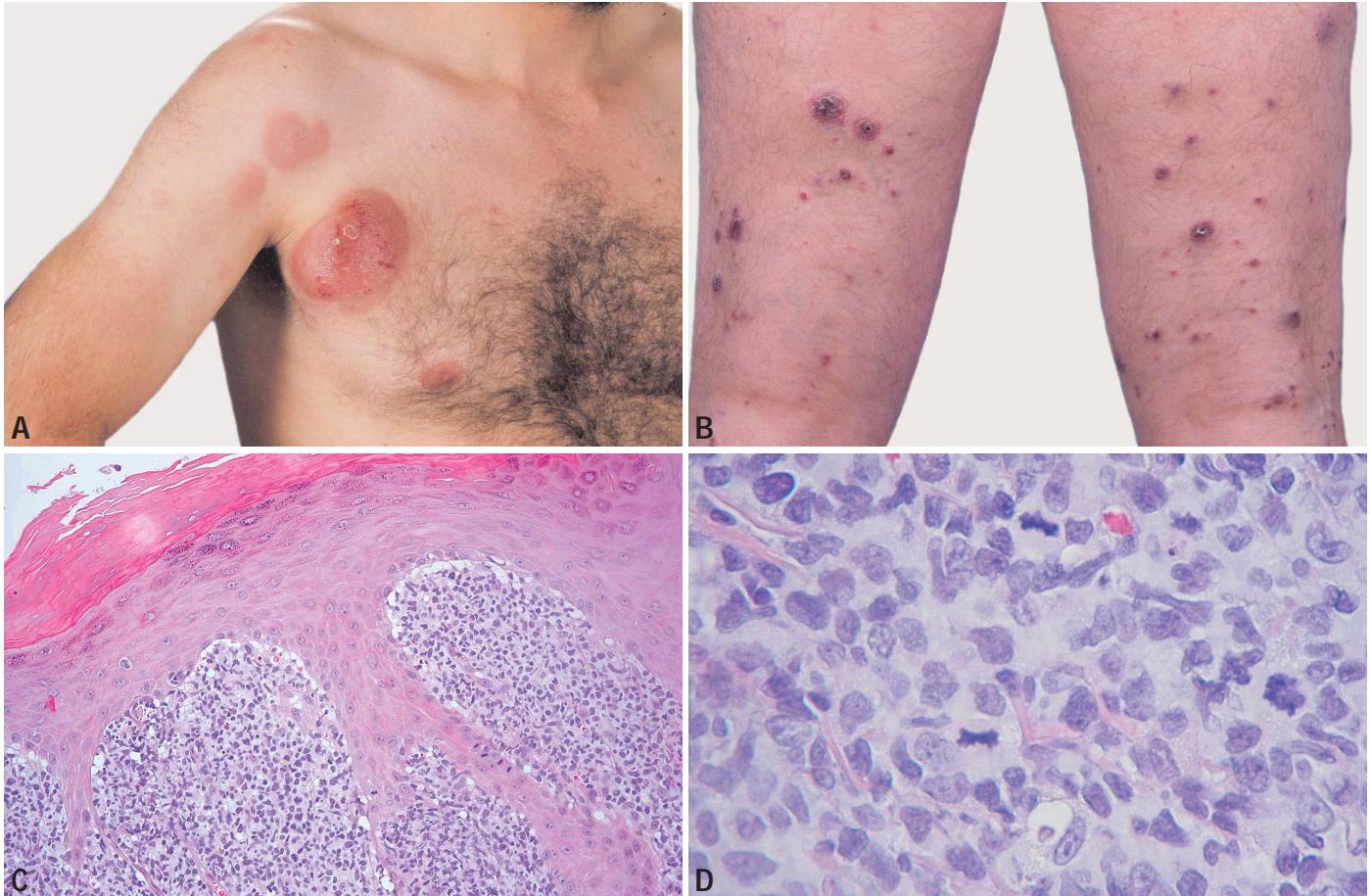


Fig. 4.37 Primary cutaneous peripheral T-cell lymphoma, unspecified. **A** Grouped and **B** disseminated skin lesions. **C** The dermal neoplastic infiltrate is dense and **D** consists of large, pleomorphic cells with irregular nuclei and numerous mitoses.

Cutaneous adult T-cell leukaemia / lymphoma

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Definition

Adult T cell leukaemia / lymphoma (ATLL) is a malignancy of mature CD4+ T cells caused by the human T-cell leukaemia virus type I (HTLV-1).

ICD-O code 9827/3

Synonyms

Adult T-cell leukaemia (ATL)

Epidemiology

ATLL is endemic in some regions of the world, especially in southwest Japan, the Caribbean islands, South America, and parts of Central Africa {1848,2392}.

Etiology

ATLL develops in 1% to 5% of individuals infected with HTLV-1 after more than 2 decades of viral persistence. In most patients viral exposure occurs early in life, and incidence figures are related to the place of birth, not residence.

HTLV-1 proviral DNA is monoclonally

integrated in the malignant T cell. HTLV-1 encodes the transcriptional activator Tax, which can transform T cells by increasing the expression of a unique set of cellular genes involved in T cell proliferation {1589}.

Localization

Based on organ involvement and severity, ATLL is divided into four clinical categories: acute, chronic, lymphoma, and smoldering types {2171}. Cutaneous involvement is seen in up to 50% of patients. Lymph nodes, liver and spleen are frequently involved.

Clinical features

Patients with ATLL exhibit various cutaneous manifestations. The most frequent manifestation is nodules/tumours (33.9%), followed by red papules (22.6%), erythematous plaques (19.4%) and macules (6.5%) {2142}. Nodules/tumours usually occur as solitary or several lesions on limited sites, whereas

multiple papules tend to be distributed over large areas of the body. Subcutaneous tumours (4.8%), erythroderma (3.5%), and purpura (1.6%) are less frequent, and alopecia, folliculitis, erythema multiforme, and prurigo are rarely seen. In addition to the four clinical types, the cutaneous type of ATLL has been proposed to indicate skin-limited lesions without lymph node involvement or leukaemic involvement {1144}. ATLL limited to the skin may be considered part of the smouldering type. Two patterns of skin involvement are seen; i.e., tumoural and erythematopapular. The tumoural subtype has been reported to have a worse prognosis than the erythematopapular one.

Histopathology

Individual skin lesions of ATLL exhibit varying degrees of tumour cell infiltration from the epidermis to subcutaneous tissue. Epidermotropism of the malignant T-cells is present in the majority of cases,



Fig. 4.38 Adult T-cell leukaemia/lymphoma (ATLL) **A** A large tumour on the right cheek. **B** Multiple erythematous plaques on the trunk. **C** Multiple papules on the hand and forearm.

and even Pautrier microabscesses, indistinguishable from those of mycosis fungoides and Sézary syndrome, are often seen. The cells have medium- to large-sized pleomorphic nuclei, and occasionally show mitoses. Nuclear irregularity may be marked, with polylobated flower cells often seen in the blood and tissues. Eosinophils may be intermingled with lymphocytes. In some cases, the tumour cells infiltrate mainly in the subcutaneous tissue {2142,2171}.

Immunohistochemistry

In general, the malignant T cells are positive for CD3, CD4, CD25, and CD45RO but negative for CD7, CD8, CD19, and CD20 {2171}. CD30 expression may be seen in larger transformed cells.

Prognosis and prognostic factors

The prognosis of ATLL patients with skin lesions is dependent on clinical and histological factors, and relates to the four main clinical subtypes. It has been suggested that cases of the smoldering type of ATLL have a poorer prognosis if there are deep dermal cutaneous infiltrates, as compared to cases in which skin manifestations are absent, or only present as superficial infiltration {2142}.

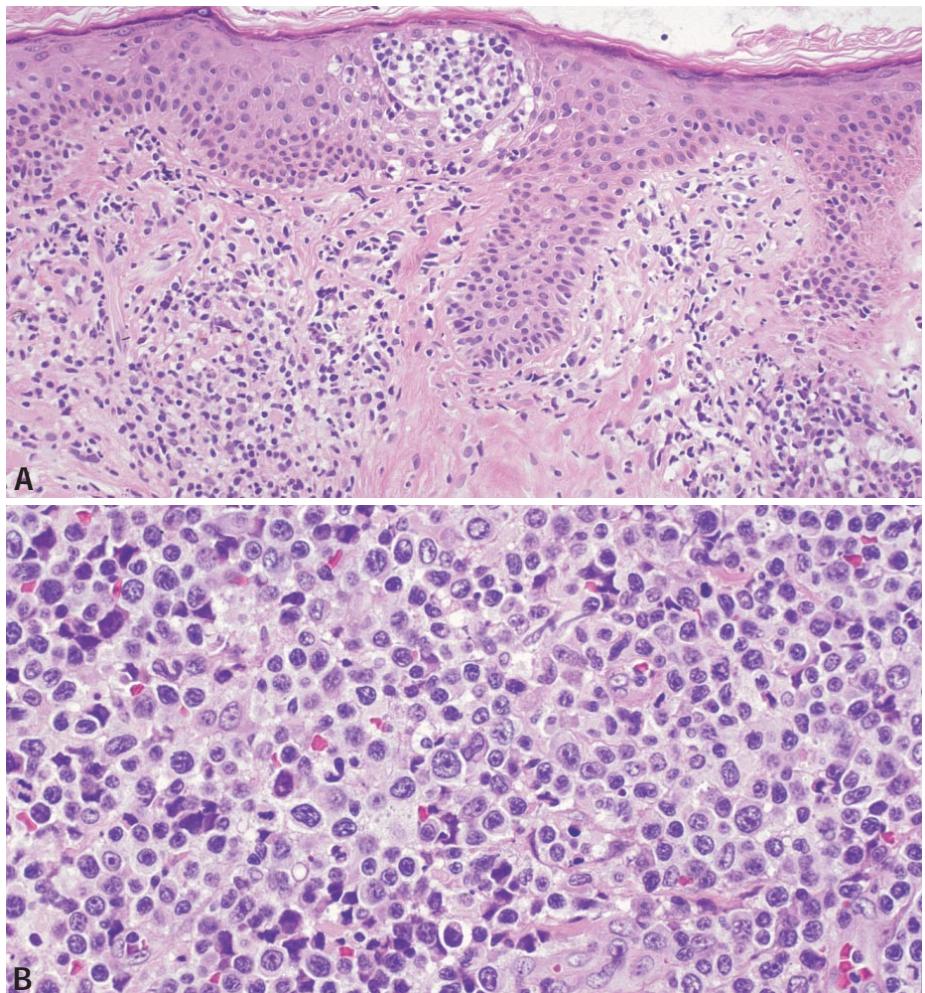


Fig. 4.39 Adult T-cell leukaemia/lymphoma (ATLL). **A** Erythematous macule, showing infiltration of atypical lymphocytes in the upper dermis with Pautrier microabscess. **B** Tumour, massive infiltration of pleomorphic lymphocytes in the dermis.

Extranodal NK/T-cell lymphoma, nasal-type

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Definition

Extranodal NK/T-cell lymphoma, nasal-type, is an EBV+, nearly always extranodal lymphoma of small, medium or large cells usually with an NK-cell, or more rarely cytotoxic T-cell phenotype. The skin is the second most common site of involvement after the nasal cavity/nasopharynx, and skin involvement may be a primary or secondary manifestation of the disease.

ICD-O code: 9719/3

Synonyms

REAL: angiocentric T-cell lymphoma; EORTC used to include in CTCL, large cell, CD30- and CTCL, pleomorphic, small/medium-sized

Epidemiology

Extranodal NK/T-cell lymphoma is a rare disease occurring in adults, with a male predominance. This lymphoma is more prevalent in Asia, Central America and South America.

Etiology

It is universally associated with EBV, and genetic factors play a role in susceptibility to the disease {443,1689}.

Localization

The majority of patients present with skin lesions affecting more than one anatomic region, most commonly the trunk and extremities {443,1660}.



Fig. 4.40 Extranodal NK/T-cell lymphoma, nasal-type. Clinical appearance with violaceous tumour nodules.

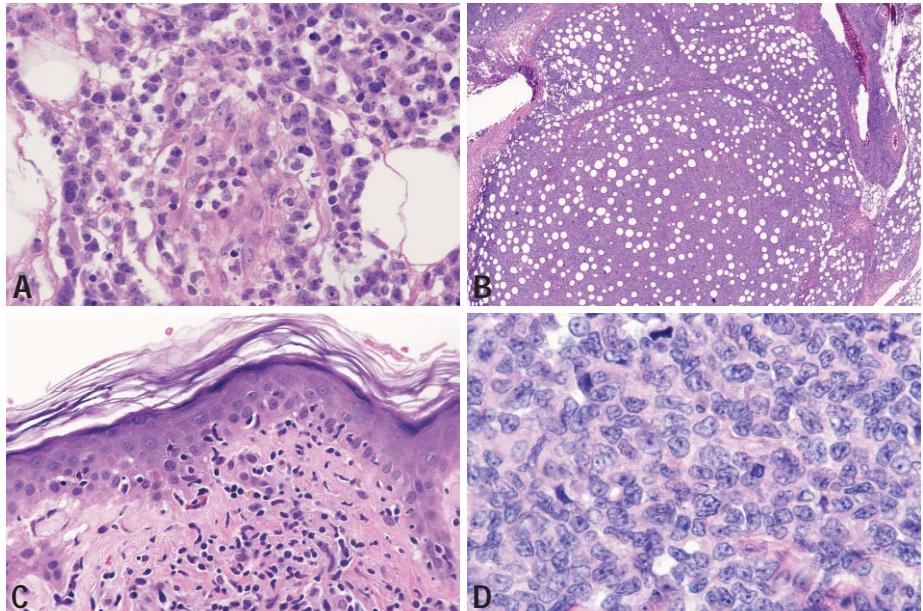


Fig. 4.41 Extranodal NK/T-cell lymphoma, nasal-type. **A** Angiocentricity and angiodesctruction. **B** Involvement of the subcutis. **C** Focal epidermotropism, present in approx. 30% of cases. **D** Cytologic detail showing medium sized cells with irregular nuclear foldings.

Clinical features

Cutaneous involvement consists of tumour nodules and plaques. Systemic symptoms such as fever, malaise and weight loss are common. Some cases are accompanied by a haemophagocytic syndrome. The disease is closely related to aggressive NK-cell leukaemia, which also may have cutaneous manifestations, and is also EBV-associated.

Histopathology

A dense dermal infiltrate is often centred on the skin appendages and blood vessels resulting in a column-like low power appearance {1689}. Prominent angiocentricity and angiodesctruction are often accompanied by extensive necrosis {443,1689}. Extension into the subcutis is common. Approximately 30% of cases show at least focal epidermotropism {1689}. The mitotic rate is high and apoptotic bodies are numerous. NK/T-cell lymphoma has a broad cytologic spectrum ranging from small to large cells, with most cases consisting of medium sized

cells. The cells often exhibit irregular nuclear foldings, moderately dense chromatin, and pale cytoplasm.

Immunoprofile

The most common immunophenotype is: CD2+, CD56+, surface CD3-, cytoplasmic CD3ε+, CD43+ and cytotoxic granules + (TIA-1, granzyme B, perforin) {1325}. Occasional cases are CD56-, but then require EBV positivity or presence of cytotoxic granules for diagnosis; otherwise they should be classified as peripheral T-cell lymphoma, unspecified. LMP-1 is inconsistently expressed, with EBER in situ hybridization preferred for diagnosis.

Genetics

The T-cell receptor is usually in germline configuration.

Prognosis and predictive factors

Extranodal NK/T-cell lymphoma presenting in the skin is a highly aggressive tumour with a median survival of less than 15 months {443,1660}. The most

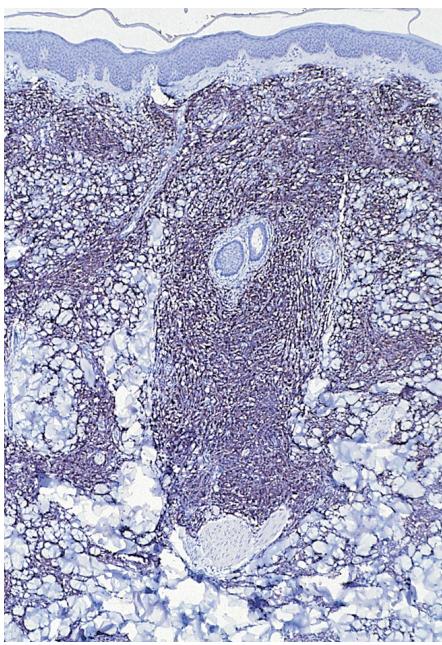


Fig. 4.42 Nasal type NK/T-cell lymphoma (EBV+), immunostained for CD56. Almost all cells are CD56 positive.

important factor predicting poor outcome is the presence of extracutaneous involvement at presentation {1660}. Preliminary data indicate that co-expression of CD56 and CD30 may be associated with a better prognosis {1660,1690}.

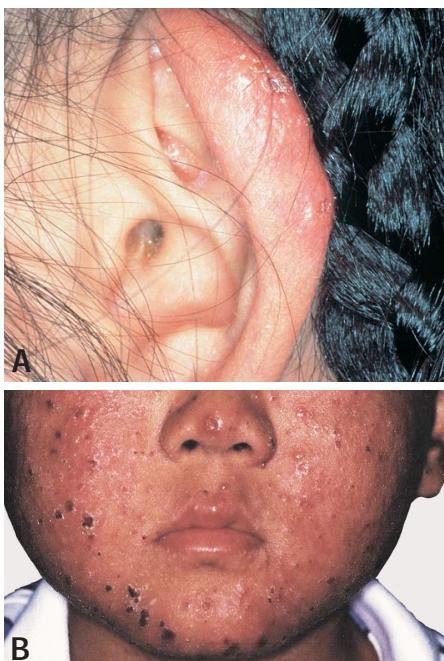


Fig. 4.43 Hydroa vacciniforme-like cutaneous T-cell lymphoma. **A** Infiltrate on the sun-exposed earlobe. **B** Papules, vesicles and crusted erosions on face of young boy.

Hydroa vacciniforme-like cutaneous T-cell lymphoma

Definition

Hydroa-vacciniforme-like cutaneous T-cell lymphoma is a rare EBV-associated lymphoma of cytotoxic T-cell or NK-cell origin that affects children, characterized by a vesiculopapular skin eruption that clinically resembles hydroa vacciniforme.

Synonym

Angiocentric cutaneous T-cell lymphoma of childhood

Epidemiology

Hydroa vacciniforme-like CTCL affects children and teenagers, with almost all reported cases being from Latin America (such as Peru, Bolivia, Mexico) {166, 1479,1991} and Asia (such as Korea and Japan). Boys and girls are affected in an equal ratio {471,765}.

Etiology

The strong association with EBV suggests a pathogenetic role of the virus and genetic predisposition, as in extranodal NK/T-cell lymphoma. The anatomic distribution of the skin lesions suggests sun exposure as a risk factor although tests for minimal erythema doses are usually within normal limits.

Localization

The lesions occur predominantly in sun-exposed areas, particularly the face and limbs.

Clinical features

Patients present with facial and hand oedema and a papulovesicular eruption that affects sun-exposed and to a lesser extent sun-protected areas. Individual lesions start with oedema and erythema and then progress to vesicles, necrosis, ulceration, crusts, and heal as varicelliform scars. Fever, wasting, hepatosplenomegaly, lymphadenopathy and hypersensitivity to insect bites are common. Some cases are accompanied by a haemophagocytic syndrome. The disease may progress to lymph node and visceral involvement.

Histopathology

The infiltrate consists of medium-sized atypical lymphoid cells set in an inflammatory background. The depth of the

infiltrate seems related to the age of the lesion {166}. A fully developed lesion shows a dense dermal infiltrate with epidermotropism and extension into the fat in a lobular fashion. Ulceration is common. The infiltrate is often angiotropic/angioinvasive and in addition may display a periadnexal and perineural growth pattern.

Immunoprofile

The tumour cells are cytotoxic T-cells, that have often lost expression of some pan T-cell markers. The most common phenotype is: CD2+, CD3+, CD8+, CD43+, CD45RO+, TIA-1+, Granzyme B+; CD4-, CD5-, CD7-. CD56 is variably positive, but CD57 is negative. CD30 reactivity can be seen in a subset of cells (<30%).

Somatic genetics

The T-cell receptor gene is clonally rearranged {166,1479}, although in cases of NK-cell derivation, T-cell receptor genes are germline.

Prognosis

The prognosis is poor, with a 2-year survival rate of 36% {166}.

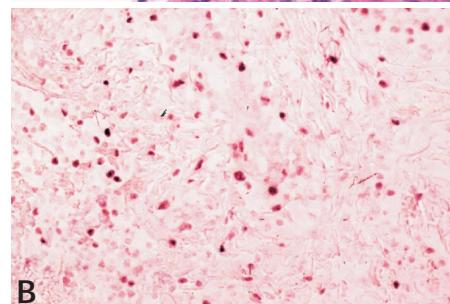
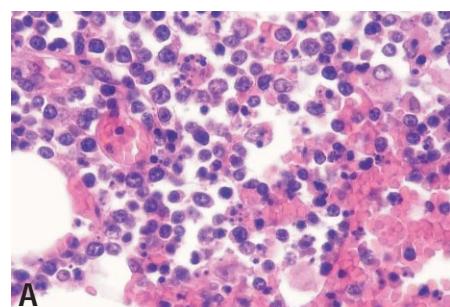


Fig. 4.44 **A** Subcutaneous infiltrate of tumour cells with prominent cytophagocytosis. **B** In situ hybridisation showing EBER+ tumour cells

Cutaneous involvement in primary extracutaneous T-cell lymphoma

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Systemic peripheral T-cell lymphoma (PTL), unspecified, involves the skin in approximately 20-30% of the cases [836, 1453]. Skin lesions may be present at diagnosis or can develop during disease progression. Lesions are most often tumours or nodules that may be solitary or multiple. No sites of predilection have been recorded. The histological and phenotypic features are identical to the systemic disease. The prognosis is very poor [104,690,836,1453].

Systemic anaplastic large cell lymphoma (ALCL)

Primary systemic anaplastic large cell lymphoma affects lymph nodes and extranodal sites, including in 20% of the cases the skin. The skin lesions may be present at diagnosis or can develop at relapse or during disease progression. The skin lesions are usually tumours or nodules that can be solitary or multiple. No sites of predilection have been recorded. The histological, phenotypic and genotypic features are identical in lymph nodes and the skin. The tumour cells are most often large with abundant cytoplasm and characteristic so-called hallmark cells with eccentric, horseshoe- or kidney-shaped nuclei often with an eosinophilic region near the nucleus. The principal morphological variants are the small cell variant and the histiocyte rich variant [809]. It is important to distinguish these lesions from primary cutaneous ALCL. The histological appearance of systemic cases is usually more monomorphic with infrequent tumour

giant cells. The tumour cells in systemic ALCL express a cytotoxic phenotype and are positive for CD30 and EMA. CD3 is negative in more than 75% of cases [191, 1121]. CD5 and CD7 are often negative. CD2, CD4 and CD43 are more useful and are expressed in a significant proportion of cases. ALK expression and t(2;5) or variant translocations involving ALK and fusion partners other than NPM are present in the majority of cases [706, 809]. The natural history is aggressive but long term complete remissions can be obtained in most patients with ALK-positive disease [191].

Angioimmunoblastic T-cell lymphoma (AITL)

ICD-O code 9705/3

Skin lesions in angioimmunoblastic T-cell lymphoma (AITL) occur in half of the cases, usually as a generalized maculopapular eruption simulating viral exanthem or drug eruption, or as urticaria, purpura, erythematous-squamous plaques, prurigo-like lesions, erythroderma, erosions and necrotic lesions. The disease occurs mostly in middle-aged or elderly people without gender preponderance [787]. Other findings are fever, weight loss, night sweats, lymphadenopathy, hepatomegaly and splenomegaly, anaemia, an elevated sedimentation rate, leukocytosis, neutropaenia or thrombocytopaenia, as well as polyclonal hypergammaglobulinemia. AITL exhibits an aggressive course with a median survival ranging from 11 to 30 months and a fatal outcome

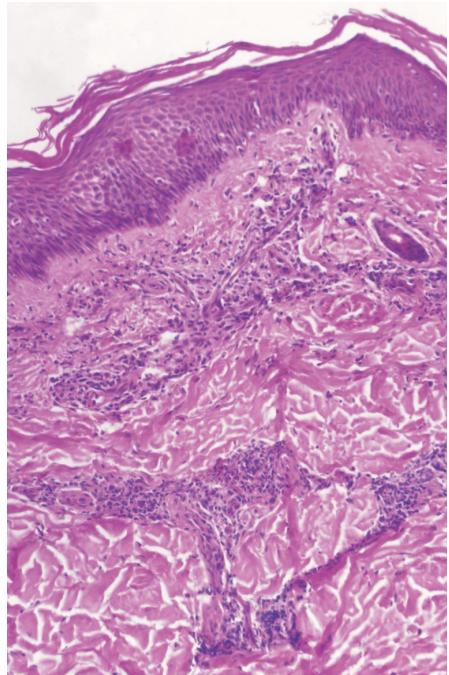


Fig. 4.45 Cutaneous involvement in AITL. A polymorphous perivascular infiltrate is present in the superficial dermis

in 50 to 70% of patients. Histologically, the skin lesions are characterized by nonspecific subtle superficial perivascular infiltrates composed of eosinophils and lymphocytes without atypia accompanied by hyperplasia of capillaries. Admixed plasma cells and histiocytes can be found [2087]. Clonal T cell receptor rearrangement has been reported in some cases [1522]. However, it is not clear whether the cutaneous manifestations are generally due to tumour cell involvement or a secondary phenomenon related to cytokine production.

Cutaneous marginal zone B-cell lymphoma

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E.S. Jaffe

Definition

Primary cutaneous marginal zone B-cell lymphoma (MZL) is an indolent lymphoma composed of small B cells including marginal zone (centrocyte-like) or monocyteid cells, lymphoplasmacytoid cells and plasma cells. It is considered part of the broad group of extranodal marginal zone B-cell lymphomas commonly involving mucosal sites (mucosa associated lymphoid tissue, MALT). Primary cutaneous immunocytoma, primary cutaneous plasmacytoma and cutaneous follicular lymphoid hyperplasia with monotypic plasma cells are considered variants of MZL.

ICD-O code

9699/3

Synonyms

EORTC (1997): Primary cutaneous immunocytoma / marginal zone B-cell lymphoma

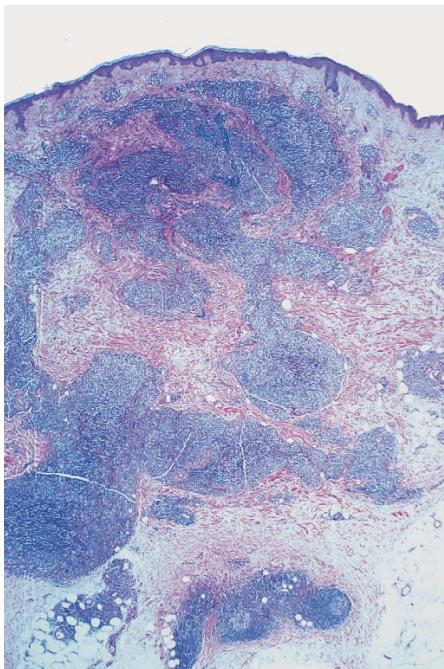


Fig. 4.46 Cutaneous marginal zone B-cell lymphoma. Infiltrate extends through dermis to subcutaneous tissue.

Epidemiology

MZL most commonly affects adults aged over 40 years. There is no clear gender preponderance {132,2141}.

Etiology

In Europe, *Borrelia burgdorferi* DNA has been identified in some cases of MZL suggesting that it may play an etiological role. {433}. However, no association of *Borrelia* with CBCL has been found in the United States and Asia {2547}.

Localization

MZL is predominantly localized on the upper extremities, and less often head and trunk.

Clinical features

In most cases, cutaneous MZL presents with red to violaceous plaques or nodules with an erythematous border {2141}. Ulceration and visceral dissemination are



Fig. 4.48 Marginal-zone lymphoma. Firm nodules on the forehead.

uncommon. MZL with secondary spread to the skin is often multifocal {1418}.

Histopathology

The infiltrate is characterized by residual reactive lymphoid follicles surrounded by pale staining cuffs of tumour cells. Reactive germinal centres with distinct mantle zones are commonly found in early lesions but may become colonized by tumour cells as the disease progresses. The interfollicular infiltrate is composed of small to medium-sized, centrocyte-like or monocyteid cells with slightly irregular nuclei, moderately dispersed chromatin, inconspicuous nucleoli and a rim of pale cytoplasm {2234,2362}. Variable numbers of lymphoplasmacytoid cells and plasma cells are typically present at the periphery of the infiltrates or in the subepidermal area. Intranuclear PAS positive pseudoinclusions (Dutcher bodies), are commonly found, particularly in plasma cell rich forms of MZL. Diffuse infiltrates almost completely consisting of monocyteid cells, lymphoepithelial lesions with infiltration of sweat glands and the presence of very immature plasma cells should raise suspicion of secondary cutaneous involvement.

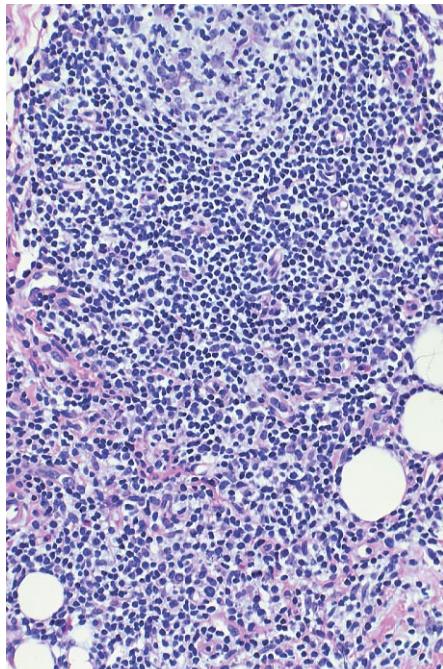


Fig. 4.47 Cutaneous marginal zone B-cell lymphoma. Neoplastic cells surround a residual germinal centre.

Immunoprofile

The neoplastic cells express CD19+, CD20+, CD22+, CD79a+, but are negative for CD5-, CD10-, bcl-6, CD23-. CD43 may be positive {132}. In contrast to FL, the tumour cells are bcl-2+, but negative for bcl-6 and CD10 {603,1418}. Reactive

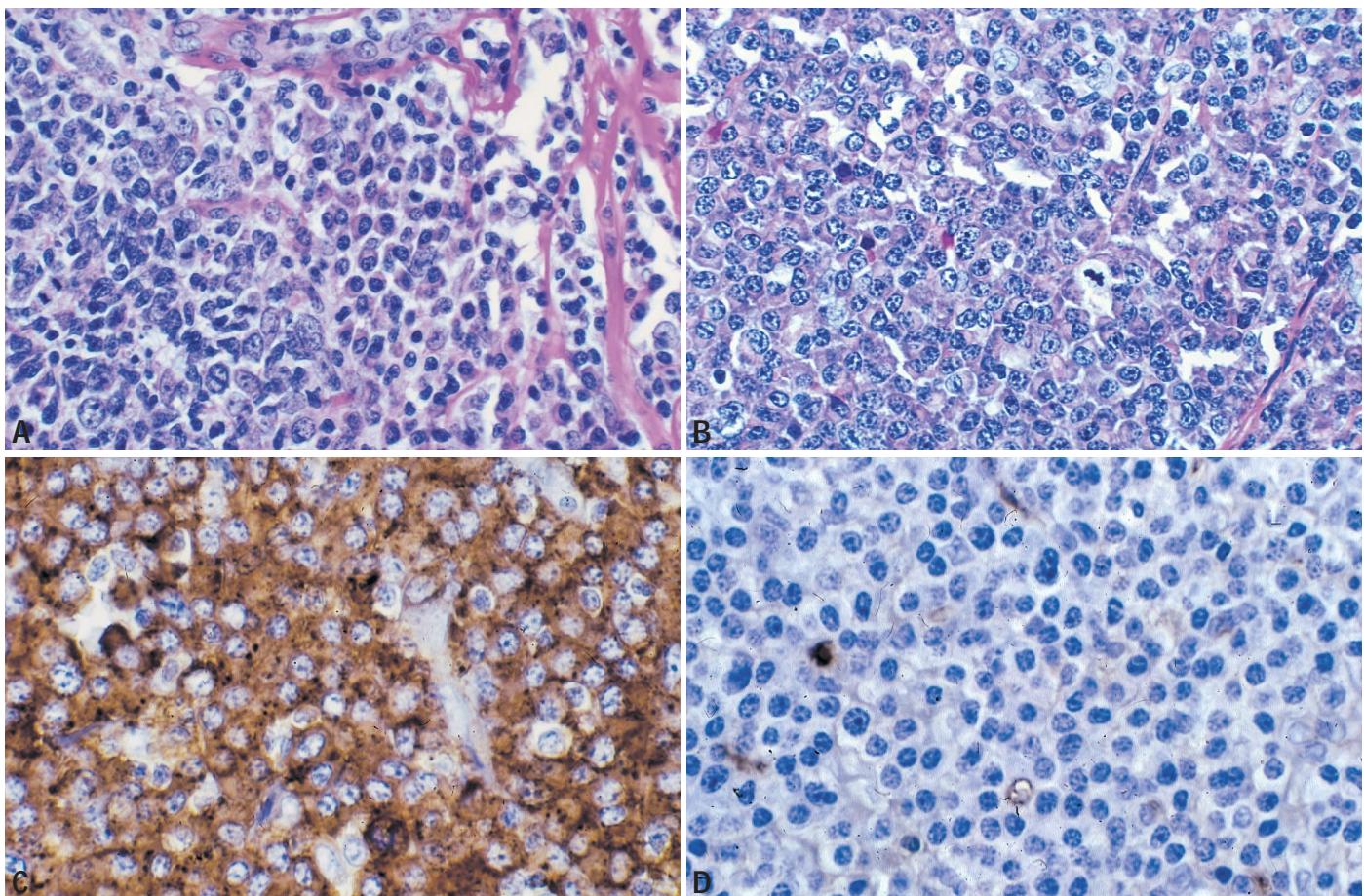


Fig. 4.49 Plasmacytoid cells in cutaneous marginal zone B-cell lymphoma. **A** Monoclonal plasma cells are admixed with cells with monocyteid features. **B** In a subsequent biopsy from the same patient, all of the cells have a plasmacytic morphology and express monoclonal Ig light chains. **C** Kappa. **D** Lambda.

germinal centres are bcl-6+ and bcl-2-. Anti-CD21 staining often reveals regular and irregular networks of follicular dendritic cells (FDC) in reactive follicles, but not associated with tumour cells. The lymphoplasmacytoid cells and the plasma cells show monotypic expression of immunoglobulin light chains. There are numerous admixed reactive T-cells.

Precursor lesion

Cutaneous lymphoid hyperplasia due to Borrelia infection may mimic MZL and has been postulated to represent a precursor lesion in some circumstances.

Histogenesis

Post germinal centre B-lymphocyte with plasmacytic differentiation and gene expression pattern {2273}.

Somatic genetics

IgH genes are clonally rearranged. The most common translocation in gastric MZL, the t(11;18) involving the API2/MLT genes, has not been demonstrated in primary cutaneous MZL {1418,2141,2279}. However, the t(14;18)(q32;q21) involving IGH and MALT1 was reported in approximately one third of cases in a small series. Fas gene mutations are present in

a minority of cases, similar to MZL of other extranodal sites. Abnormalities of BCL10 are absent {906}.

Prognosis

MZL shows a protracted clinical course with a tendency for recurrences. However, the prognosis is favourable with 5-year-survival rates between 90 and 100%. Transformation into diffuse large B cell lymphoma occurs infrequently {2141}.

Cutaneous follicle centre lymphoma

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Definition

Primary cutaneous follicle centre lymphoma (PCFCL) is defined as a tumour of neoplastic follicle centre cells (FCC), usually a mixture of small and large cleaved cells (centrocytes) and, to a lesser extent, large noncleaved cells (centroblasts) with prominent nucleoli. The growth pattern varies from follicular to follicular and diffuse to diffuse.

ICD-O Code

9690/3

Synonyms

Kiel: centroblastic-centrocytic (follicular, follicular and diffuse), centroblastic.
Working formulation: follicular, follicular and diffuse (predominantly small cleaved, mixed small cleaved and large cell, predominantly large cell).
WHO: follicular lymphoma, diffuse follicle centre lymphoma, diffuse large B-cell lymphoma.
EORTC (1997): follicular centre cell lymphoma.
Reticuloschistocytoma of the dorsum (Crosti disease): {220, 2061,2523}.

Epidemiology

Primary cutaneous B cell lymphoma (CBCL) in Europe account for up to 25% of cutaneous lymphomas, manifesting predominantly in middle aged adults, with no gender predominance {2523}, and having an incidence rate of 0.1-0.2 per 100,000 persons per year {1831}. Among primary CBCL, marginal zone B cell lymphoma and FCL are by far the most common subtypes {744,1281, 2576}.

Etiology

The etiology of primary cutaneous FCL is unknown.

Localization

Most patients have local or regional disease. Trunk and head and neck regions are by far the most frequent localizations {429,744,2061,2523}. Presentation with multifocal skin lesions is observed in a small minority of patients.



Fig. 4.50 Cutaneous follicle centre lymphoma. Firm nodules on the trunk.

Clinical features

The clinical presentation consists of firm erythematous to violaceous plaques, nodules or tumours of variable size. Larger nodules may be surrounded by small papules and slightly infiltrated, sometimes figurate plaques. The skin surface is smooth. Lesions may be present for months to many years {220, 2061,2523}.

Histopathology

The infiltrates show a spectrum of growth patterns, with a morphologic continuum

from follicular to follicular and diffuse to diffuse. The lesions are by definition composed of a mixture of centrocytes (which may be small and/or large) and centroblasts in varying proportion. Small centrocytes and a predominantly follicular growth pattern are more frequently found in small, early lesions. A predominance of large neoplastic cells, particularly large centrocytes or multilobated cells and less frequently centroblasts (not in confluent sheets), are generally found in more advanced lesions (large nodules or tumours) {2523}. When morphologically identifiable, follicles are often ill-defined and show a monotonous population of FCC, lack starry sky histiocytes, and generally have an attenuated or absent mantle zone, different from cutaneous follicular hyperplasias {425, 429,603,864,1397}. The infiltrates are found primarily in the dermis, with extension into subcutaneous tissue seen in larger nodules. The overlying epidermis is generally unaffected.

Immunoprofile

The cells express B-cell markers including CD19, CD20, and CD22, and may show (more often in cryostat sections)

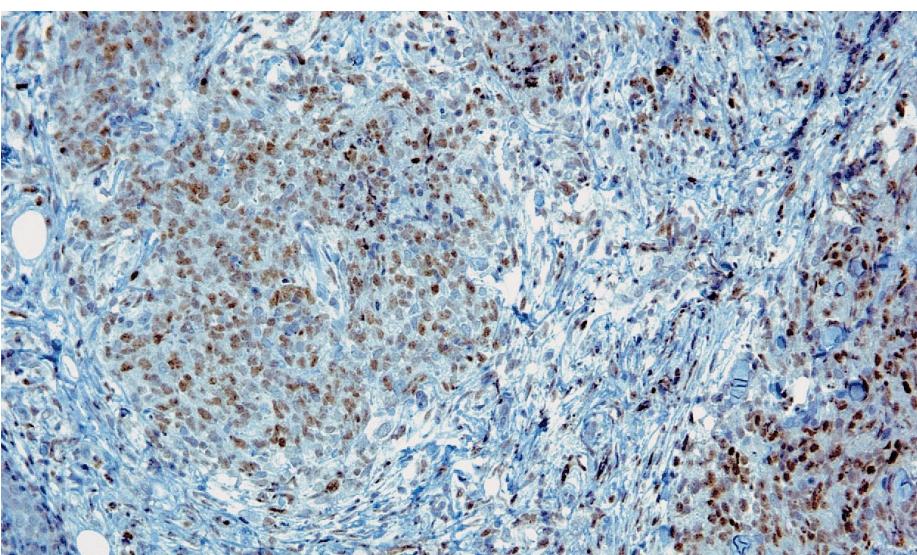


Fig. 4.51 Primary cutaneous follicle centre lymphoma. Neoplastic bcl6+ cells surround and infiltrate a reactive follicle with bcl6+ germinal center.

monotypic staining for surface immunoglobulins (slg). However, absence of detectable slg staining is common in tumours showing a diffuse population of large FCC. In PCFCL, neoplastic cells consistently express Bcl-6 protein, while CD10 is variably expressed (often positive in follicular cases and more frequently negative in lesions with diffuse pattern of growth) {425,429,823,1042,1832, 2061}. Bcl-2 protein is usually not expressed but may be faintly positive, less than reactive T-cells {38, 209, 425, 603, 774, 1042, 1622}. The follicles are associated with follicular dendritic cells, positive for CD21, CD23, and CD35. Residual, scattered FDC may be sometimes found in diffuse large cell infiltrates. Neoplastic cells are constantly CD5- and CD43-negative. Admixed T-cells may be abundant and sometimes predominant, particularly in small, early lesions.

Histogenesis

Mature germinal centre derived B-lymphocyte {2273,2523}.

Somatic genetics

Clonally rearranged immunoglobulin genes are present. Bcl-2 gene rearrangement and t(14;18) chromosomal translocation are absent in most cases {209,430,467,1622,1820,2523}. Inactivation of p15 and p16 tumour suppressor genes by promotor hypermethylation has been reported in about 10% and 30% of PCFCL, respectively {468}. Chromosomal imbalances have been identified by comparative genomic hybridization (CGH) analysis in a minority of PCFCL, but a consistent pattern has not been emerged {942,1503}.

Prognosis and predictive factors

Primary cutaneous FCL have an excellent prognosis (>95% 5-year survival). Local recurrences, most often near the initial site of cutaneous presentation, may develop but will not influence clinical outcome. Cytologic grade or growth pattern (follicular or diffuse) do not appear to have an impact on prognosis in patients with primary cutaneous disease. Locally

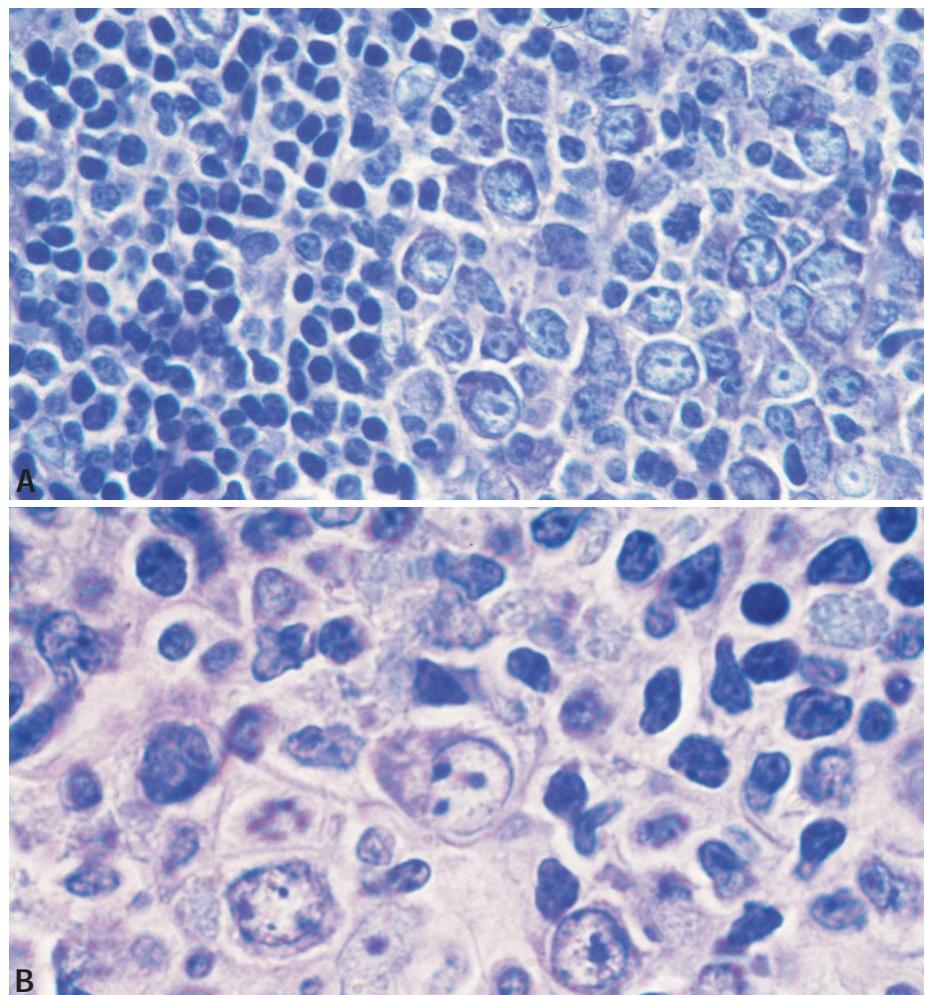


Fig. 4.52 Cutaneous follicle centre lymphoma, follicular growth pattern. **A** Small and large follicle centre cells. **B** Detail of large follicle centre cells

directed forms of therapy, most commonly radiation or surgical excision (small, isolated lesions), are generally effective {194, 429, 1283, 1824, 1825, 1938, 2060, 2061, 2202, 2523}.

cases. These secondary cutaneous forms are managed like a systemic lymphoma. Whether cutaneous involvement by FCL has an impact on prognosis is presently unknown.

Secondary cutaneous follicular lymphoma (FL)

Patients more often present with multiple lesions in non-contiguous skin sites {429,2060}. Unlike PCFCL, neoplastic cells strongly express CD10 and Bcl2, and show t(14;18) translocation in most

Cutaneous diffuse large B-cell lymphoma

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Definition

Primary cutaneous diffuse large B-cell lymphomas (DLBCLs) are neoplastic proliferations showing a completely diffuse growth pattern consisting of large transformed B-cells without significant admixture of centrocytes.

The most common variant, DLBCL, leg-type, usually occurs on the leg and less frequently at other sites. Other variants are referred to as DLBCL, other and comprise T-cell/histiocyte-rich LBCL, plasmablastic lymphoma and lesions that do not fulfill the criteria for a DLBCL, leg type.

ICD-O code

9680/3

Diffuse large B-cell lymphoma (DLBCL), leg-type

Epidemiology

Approximately 5-10% of cutaneous B-cell lymphomas are classified as DLBCL, leg type. The median age is around 70 years, and the tumours are more common in females than males {2432}. DLBCL of the skin is rare in children {1005}.

Clinical features

DLBCL, leg type occurs primarily in elderly females who present with rapidly developing multiple tumours, most commonly on the leg but sometimes at other localizations. Therefore analogous to the "nasal-type" designation for a distinct

extranodal variant of NK/T-cell lymphomas, the term "DLBCL, leg-type" is chosen for all cutaneous diffuse large B-cell lymphomas with the designated cytological and immunophenotypic features. Clinically multiple disseminated or aggregated dome shaped red tumours with a firm consistency and a shiny surface without scaling are seen. Ulceration may occur in advanced stages.

Histopathology

The tumour cells diffusely infiltrate the dermis with a destructive growth pattern, often obliterating adnexal structures. The infiltrate may extend into subcutaneous tissue. The epidermis is often spared, with a Grenz zone. The infiltrate is composed of medium to large sized B cells, which are usually monomorphic in appearance. Cells may resemble immunoblasts, and less commonly centroblasts. There is usually a minimal inflammatory component and little stromal reaction.

Immunohistochemistry

The tumour cells are positive for CD20 and CD79a, negative for CD10 and CD138, have variable BCL-6 expression and are usually strongly positive for BCL-2 protein and MUM-1/IRF-4 {1797}. These features have been shown in nodal DLBCL to correlate with an activated B-cell gene expression profile, which is usually predictive of a more aggressive clinical course {1041, 1977}.

Histogenesis

Transformed peripheral B cell of probable post germinal centre origin {816}.

Somatic genetics

The immunoglobulin genes are clonally rearranged. The BCL-2/JH translocation is absent {814,905,2472}. Recent studies using gene expression profiling have identified increased expression of genes associated with cellular proliferation. The gene expression profile of the leg-type of tumour resembles that of activated B-cell type of nodal or systemic DLBCL {1041} Significant differences have not been identified among tumours of the leg-type arising in different sites {814,1797}. The primary cutaneous large B-cell lymphoma of the leg-type can be seen in a variety of anatomic locations and is not restricted to the leg {1797}.

Prognosis and Predictive factors

In multivariate analysis, BCL-2 expression, multiple skin lesions, and age remained independent prognostic factors. The 5-year disease-specific survival rates in BCL-2-positive and BCL-2-negative patients were 41% and 89%, respectively ($P < .0001$). 11,12 13 Thus, these studies support the identification of DLBCL leg type, as a clinically and biologically distinctive group.

Diffuse large B-cell lymphoma, other



Fig. 4.53 Diffuse large B-cell lymphoma. **A** Dome-shaped nodules and tumours without ulceration on the trunk and in the face. **B** Soft tumour surrounded by an erythematous infiltrate on the back. **C** Aggregation of non-ulcerated nodules and tumours confined to a limited area of the lower leg.

Definition

The term DLBCL, other, refers to diffuse lymphomas composed of large transformed B-cells that lack the typical features of DLBCL, leg-type, and do not conform to the definition of primary cutaneous follicle centre lymphoma. These tumours may be comprised of a monomorphic population of centroblast-like cells, but with a mixed inflammatory background.

BCL-2 protein may be negative, whereas BCL-6 will usually be expressed. The presence of multiple lesions is a poor prognostic indicator; such cases must be distinguished from secondary involvement by DLBCL.

There are some primary cutaneous follicle centre lymphomas in which the majority of tumour cells are centroblasts. Previously these lesions have been categorized as DLBCL by most observers {864,877,879,1263}. These lymphomas invariably contain a population of centrocytes as well as some reactive cells. A focal follicular growth pattern may be seen. Despite the predominance of centroblasts, clinical studies have suggested that these lymphomas have an benign clinical course, and may usually be treated in a conservative manner. Based on the clinical behaviour and the spectrum of cytological composition, these tumours are classified under the single heading of cutaneous follicle centre lymphoma.

T-cell / histiocyte-rich large B-cell lymphoma

T-cell / histiocyte-rich large B-cell lymphoma is an unusual morphological variant of "diffuse" LBCL {1886} that rarely occurs primarily in the skin {645,1423}. It is characterized by a small number of large neoplastic B-cells (<10%), scattered within an abundant background of small reactive T-lymphocytes with or without histiocytes. Some T-cell/histiocyte-rich large B-cell lymphomas may represent progression from a more indolent B-cell lymphoma {645,2042}.

Plasmablastic lymphoma

Plasmablastic lymphomas rarely may present as a primary cutaneous lymphoma. The tumour cells can be positive

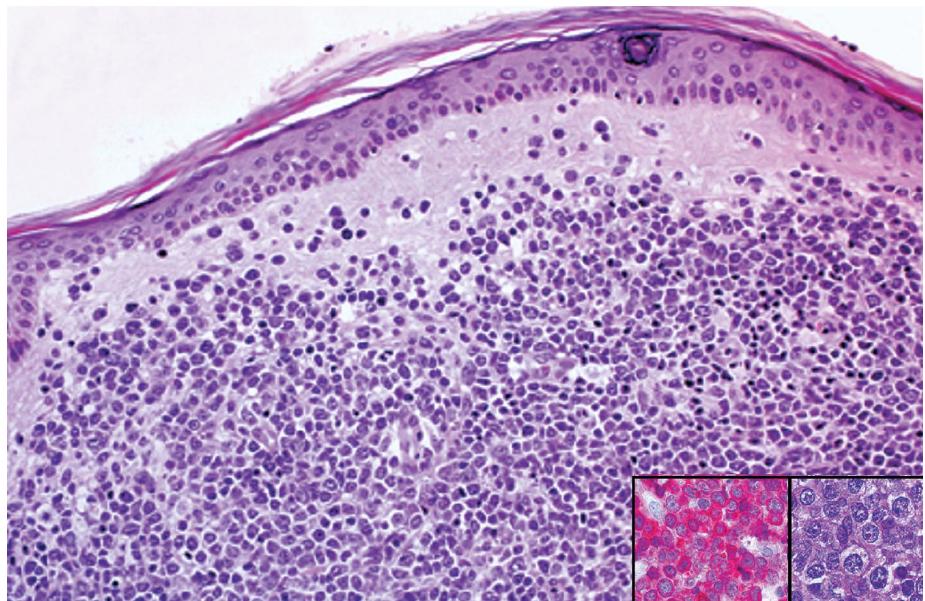


Fig. 4.54 Diffuse large B-cell lymphoma (DLBCL) leg type. Lymphoid cells in the dermis; no infiltration of the epidermis. Left insert: lymphoid cells with strong immunoreactivity for BCL-2. Right insert: large, densely packed lymphoid cells.

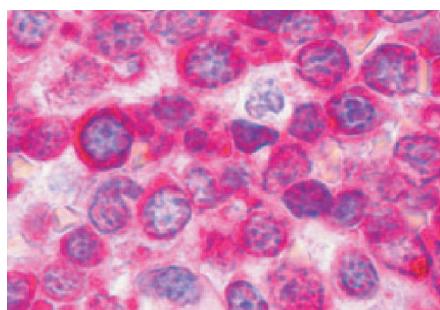


Fig. 4.55 Diffuse large B-cell lymphoma (DLBCL), leg type. BCL-2 staining of atypical lymphoid cells.

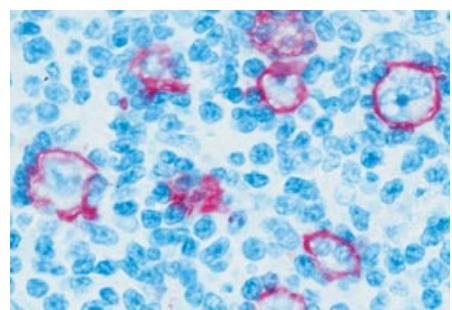


Fig. 4.56 T-cell/histiocyte-rich large B-cell lymphoma. CD20 staining highlights the few neoplastic B-cells intermingled in a dense infiltrate of reactive T-cells.

for Epstein Barr virus (EBV), and have a phenotype that reflects terminal stages of B-cell differentiation (CD20-, MUM-1+, CD138+, EMA+). Plasmablastic lymphomas are usually a heterogenous group of disease entities {524} and can be encountered in settings of immunodeficiency, HIV-associated, or iatrogenic {617,985}.

Secondary skin involvement by diffuse large B-cell lymphoma

Secondary skin involvement most commonly shows localisation of the disease on the trunk and the extremities {1263}. The prognosis is worse than in primary DLBCL, which can be controlled by local treatment modalities, particularly if one is dealing with a single lesion.

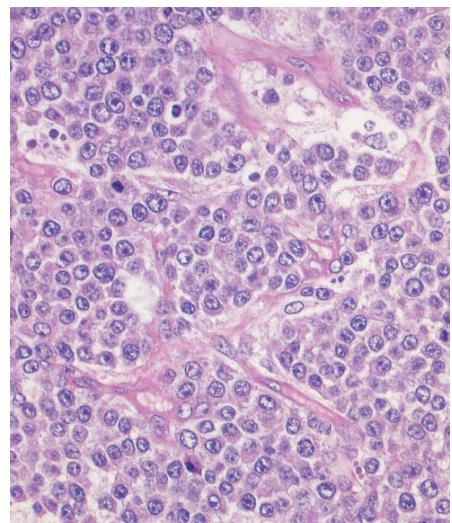


Fig. 4.57 Plasmablastic lymphoma. Tumour displays a spectrum of immunoblasts, plasmablasts, and plasma cells between collagen bundles.

Intravascular large B-cell lymphoma

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Definition

Intravascular large B-cell lymphoma (IL) is a rare disease with multiorgan involvement, which also affects the skin. This extranodal subtype of diffuse large B-cell lymphoma (DLBCL) is characterized by the presence of large lymphoid cells within the lumina of small to medium-sized blood vessels, particularly capillaries and postcapillary venules. Skin is a common site of presentation, but most patients have systemic disease at time of diagnosis {696,2523}.

ICD-O code

9680/3

Synonyms

Intravascular lymphomatosis; intravascular lymphoma; angioendotheliomatosis proliferans systematisata; malignant angioendotheliomatosis; angiotropic large cell lymphoma (Lukes-Collins), diffuse large B-cell lymphoma (REAL) intravascular large B-cell lymphoma (WHO).

Epidemiology

IL is rare and can occur at any age, but most patients are in their 6th – 9th decade of life. Male to female ratio is 0.8 (range 0.7 – 5.0) {2566}.

Localization

Dermatological manifestations are present in up to one third of patients. Sites of predilection are the lower extremities, but lesions may involve all parts of the integument. A wide range of organ involvement has been described: central nervous system, skin, adrenal glands, thyroid, gastrointestinal system, kidneys, lungs, genitourinary tract, and eye {275}. At autopsy, involvement of the majority of organs is seen despite the absence of prior clinical manifestations or mass lesions {1257}.

Clinical features

The clinical manifestations are predominantly neurologic (85%) {214} and dermatologic {633} and are attributed to vascular occlusion. There is a notable absence of lymphadenopathy, splenomegaly or circulating lymphoma cells in the majority of cases {631,684, 837, 1257,2387}.

There is a plethora of different skin lesions including tender, indurated nodules, livedo-like reticulate erythema, linear erythematous streaks, and painful indurated telangiectasias. Lesions may imitate phlebitis, panniculitis, or vasculitis {1809}.

Histopathology

The angiotropic lymphoid infiltrate often spares the dermis, requiring deep biopsies including parts of the subcutaneous fat. The large neoplastic lymphoid cells are usually confined to the lumina of capillaries and postcapillary venules {1809, 2513}, albeit extravascular involvement may occur {1257}. Tumour cells are large with vesicular nuclei, prominent nucleoli, and frequent mitoses. Fibrin thrombi in the upper and deep dermal plexus, with partial occlusion of the vascular lumina, and few entrapped hyperchromatic lymphocytes are typical of IL presenting with reticulate and livedoid erythema.

Immunoprofile

Tumour cells usually express B-cell associated antigens and may coexpress CD10 or CD5. {406,697,953,1193,1253, 2566}. Although most IL present with overexpression of the BCL-2 protein {1257} they lack BCL-2 gene rearrangement {1193,2566}. These cases have to be distinguished from other intravascular lymphomas of different lineages {112, 113,633,697,736,1355,2138,2143}. The precise mechanisms of lymphoid-endothelial interaction leading to vascular occlusion and thrombotic events are

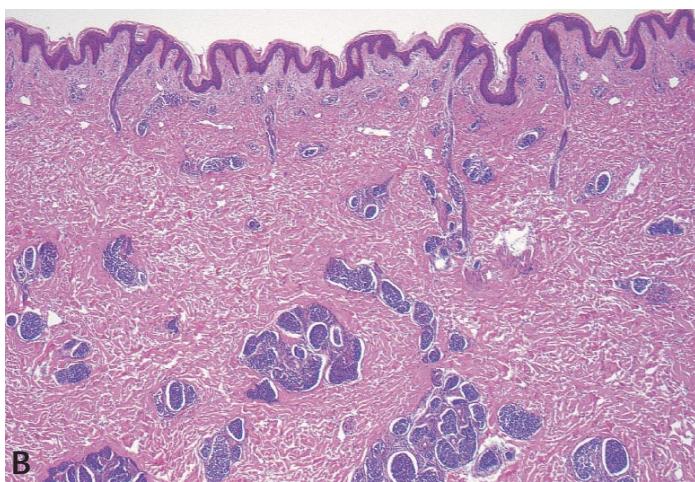


Fig. 4.58 Intravascular large B-cell lymphoma. **A** Involvement of the cutis with livedoid palpable erythema. **B** Dilated dermal vessels filled with densely packed neoplastic lymphoid cells.

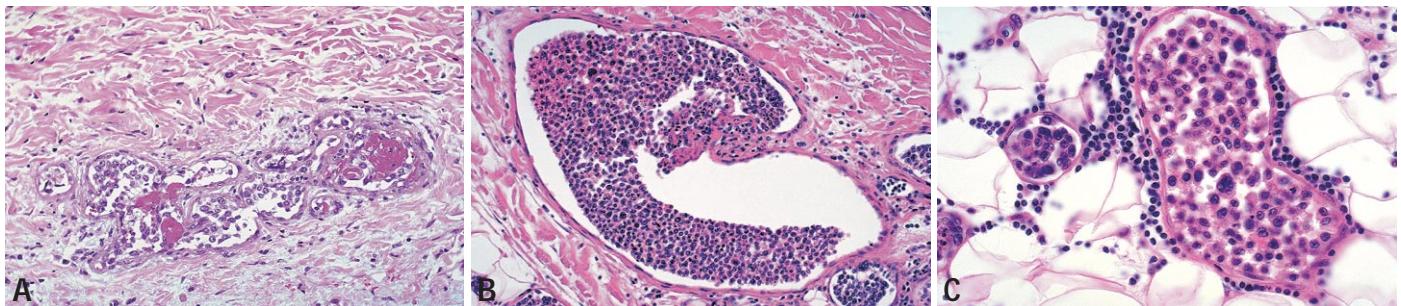


Fig. 4.59 Intravascular large B-cell lymphoma. **A** Tortuous dermal venules with fibrin thrombi and entrapped neoplastic lymphoid cells. **B** Dilated postcapillary venules with intraluminal pleomorphic lymphoid cells. **C** Neoplastic lymphoid cells within lumina of subcutaneous postcapillary venules. Extravascular lymphocytes are distinctly smaller, lacking pleomorphism and mitoses.

not clear. The intravascular trapping of lymphoid tumour cells might be the result of a defect in homing receptors and adhesion molecules on the neoplastic cells and the endothelial cells {737, 1852}.

Histogenesis

The postulated cell of origin is a post follicle centre transformed peripheral B-cell.

Lymphomatoid granulomatosis

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Definition

Lymphomatoid granulomatosis (LYG) is an angiocentric and angiolytic lymphoproliferative disease involving extranodal sites, composed of Epstein Barr virus (EBV)-positive B-cells, admixed with numerically predominant T-cells. The skin is the most common extrapulmonary site of involvement.

ICD-0 code 9766/1

Synonyms

Angiocentric immunoproliferative lesion {1432}, angiocentric lymphoma.

Epidemiology

LYG is rare, usually presenting in adult life. It affects males more often than females (at least 2:1) {1223}.

Etiology

Patients with underlying congenital or acquired immunodeficiency are at increased risk for LYG {921,949}. Predisposing conditions include allogeneic organ transplantation, Wiskott Aldrich syndrome, human immunodeficiency virus infection, and X-linked lymphoproliferative syndrome.

In patients without evidence of underlying immunodeficiency, reduced immune function can usually be demonstrated upon careful clinical or laboratory analysis {2534}.

Localization

Skin is the most common site of involvement outside the lung (25-50%), but cutaneous involvement is rarely seen without pulmonary disease. Extremities and trunk are the most frequent localizations {185,393,1047,1124,1223,1560}.

Clinical features

Patients usually present with signs and symptoms related to the respiratory tract {1124,1223,1426}. Skin lesions consist of multiple erythematous dermal papules and/or subcutaneous nodules {185}. Necrosis and ulceration are generally associated with larger nodules. Indurated plaques, lichen sclerosus et atrophicus-like lesions, and alopecia are less commonly seen {185,1129}. Cutaneous lesions rarely precede pulmonary disease, and are seen either at diagnosis (30%) or later in the course {185}. Other sites of involvement include brain (26%), kidney (32%), liver (29%) {1124}. Lymph nodes and spleen are spared.

Histopathology

LYG is characterized by an angiocentric and angiolytic lymphohistiocytic infiltrate. Most cutaneous lesions show infiltration of subcutaneous fat, with or without dermal involvement. Lymphocytic vasculitis is frequent, and fibrinoid necrosis may be present {2339}. Well-formed granulomas are usually absent,

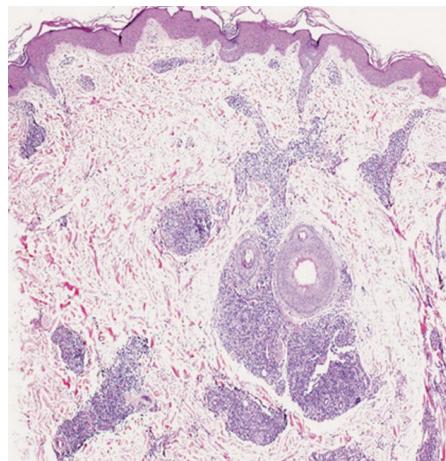


Fig. 4.62 Lymphomatoid granulomatosis. Histological features include perivascular dermal infiltrate.

but a granulomatous reaction may be seen secondary to fat necrosis.

Immunohistochemistry

While EBV-positive B-cells are readily found in the lung, they are generally rare in skin, with the predominant cell being a CD3+, CD4+ lymphocyte {185}.

Histogenesis

Mature B lymphocyte, transformed by EBV.

Somatic genetics

The ability to detect clonal immunoglob-



Fig. 4.60 Lymphomatoid granulomatosis. **A** The most common manifestations of LYG in the skin are papules which may grow into nodules. **B** Larger nodules may ulcerate superficially. From M.W. Beaty et al. {185}.

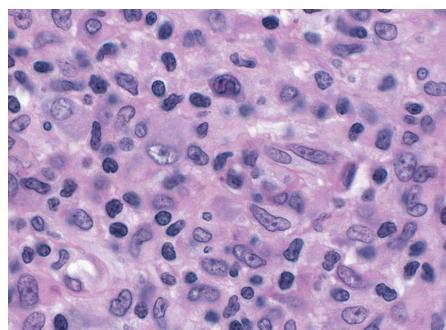


Fig. 4.61 Cutaneous lymphomatoid granulomatosis. Atypical EBV-positive large B-cells represent a minority of infiltrating cells.

ulin heavy chain gene rearrangement is related to grade, with clonal B-cell populations usually found only in grade 2-3 lesions. Southern blot, polymerase chain reaction (PCR), and in situ hybridization techniques can be used to detect EBV sequences {921,1224,1560}.

Prognosis and predictive factors

The natural history of LYG is variable {714,1223}. In some patients it may follow a waxing and waning clinical course, with spontaneous remissions without therapy. However, in most patients the disease is more aggressive, with a median survival of less than two years. Histological grade and clinical aggressiveness relate to the proportion of EBV+ B-cells, but even grade 3 lesions may show spontaneous regression {2534}. The most common cause of death is progressive pulmonary involvement. Skin lesions may appear, without evidence of relapse at other sites {185,2534}.

Cutaneous involvement in primary extracutaneous B-cell lymphoma

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M. Bernengo
S. Büchner

Mantle cell lymphoma

Definition

Mantle cell lymphoma is a B-cell lymphoma that almost always overexpresses cyclin D1 and is composed either of small lymphocytes bearing some resemblance to centrocytes or, in the blastoid variant, by cells resembling lymphoblasts or large B-cells. Neither classic centroblasts nor paraimmunoblasts are present.

ICD-O code 9673/3

Epidemiology

MCL occurs in middle aged to older individuals with a male predominance and accounts for up to 10% of all non-Hodgkin lymphomas {2301}.

Clinical features

Most patients present with adenopathy and stage III/IV disease. Hepatosplenomegaly and bone marrow involvement are common and peripheral blood involvement is seen in about 25% of patients. Gastrointestinal disease is also common but often subtle {2254}.

Cutaneous MCL

Skin involvement is rare (2-6% of cases) {2030} but when it occurs, is usually, but

not always, seen at initial presentation and associated with extracutaneous disease {654,2132}. Rare cases that appear to be primary are described. Lesions are most common on the thorax and extremities and usually occur as multiple erythematous macules, papules, plaques or nodules {654,2132}.

Histopathology

MCL are usually composed of relatively small lymphocytes with slightly irregular to very clefted nuclei and somewhat dispersed chromatin. In the blastoid variant, which may be relatively more common in cutaneous lesions, the cells either have very dispersed chromatin with inconspicuous nucleoli resembling lymphoblasts, or are larger and more pleomorphic, sometimes with very prominent nucleoli, resembling cells of a diffuse large B-cell lymphoma.

MCL infiltrates in the skin occur in the dermis sometimes with extension to the subcutaneous tissue. A grenz-zone should be present. The infiltrate may be relatively scanty and perivascular/periappendageal, form nodules or be very dense and diffuse. A mantle zone growth pattern with MCL growing around reactive germinal centres may occur {219,654}. Admixed inflammatory cells may be present {654}.

Immunohistochemistry

MCL are distinguished in most cases from other non-Hodgkin lymphomas by their frequent but not invariable CD5+, CD10-, CD23-, cyclin D1+, BCL-6-, CD20+ light chain class restricted phenotype {376,2301,2303}. Cyclin D1 staining can be problematic and CD5 not always positive. With one interesting exception, the cases are negative for the cutaneous lymphocyte-associated antigen {2132}.

Histogenesis

Mature B-cell, probably of the inner mantle zone, usually but not always with unmutated immunoglobulin heavy chain genes.

Somatic genetics

Immunoglobulin genes show clonal rearrangement in all cases and in many, but not all, cases they lack somatic hypermutation {1756,2451}. The vast majority of MCL have a t(11;14)(q13;q32) translocation involving the CCND1 (cyclin D1) and immunoglobulin heavy chain genes with subsequent CCND1/cyclin D1 overexpression {376, 2303}. The most sensitive technique to document the translocation in diagnostic specimens is cytogenetic fluorescence in situ hybridization (FISH) analysis

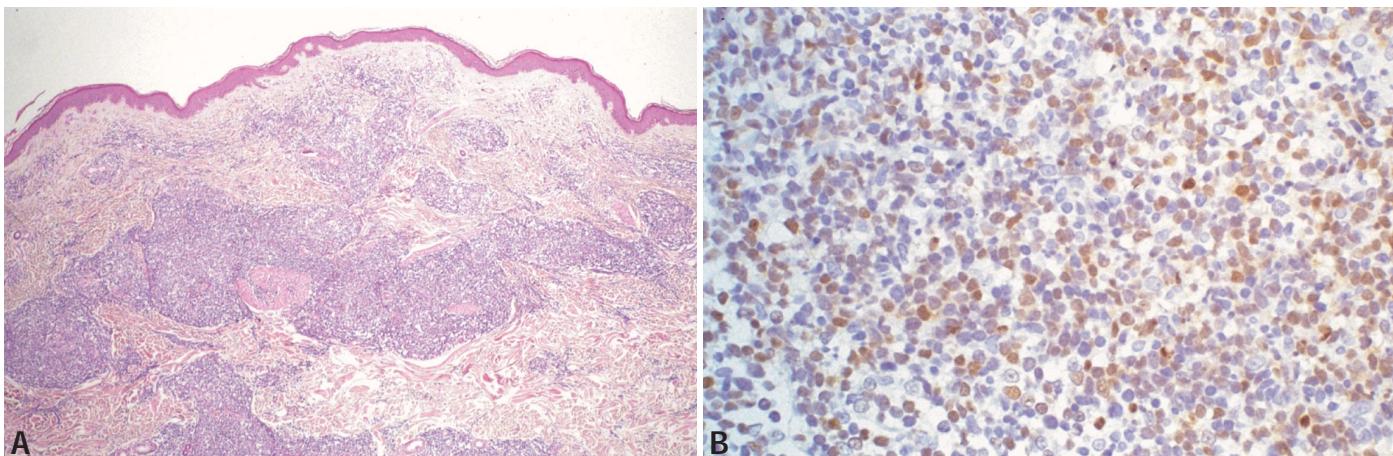


Fig. 4.63 Mantle cell lymphoma. **A** Nodular perivascular and periappendageal infiltrates in all layers of the dermis. A subepidermal grenz-zone is present. **B** Tumour cells show nuclear immunoreactivity for cyclin D1.

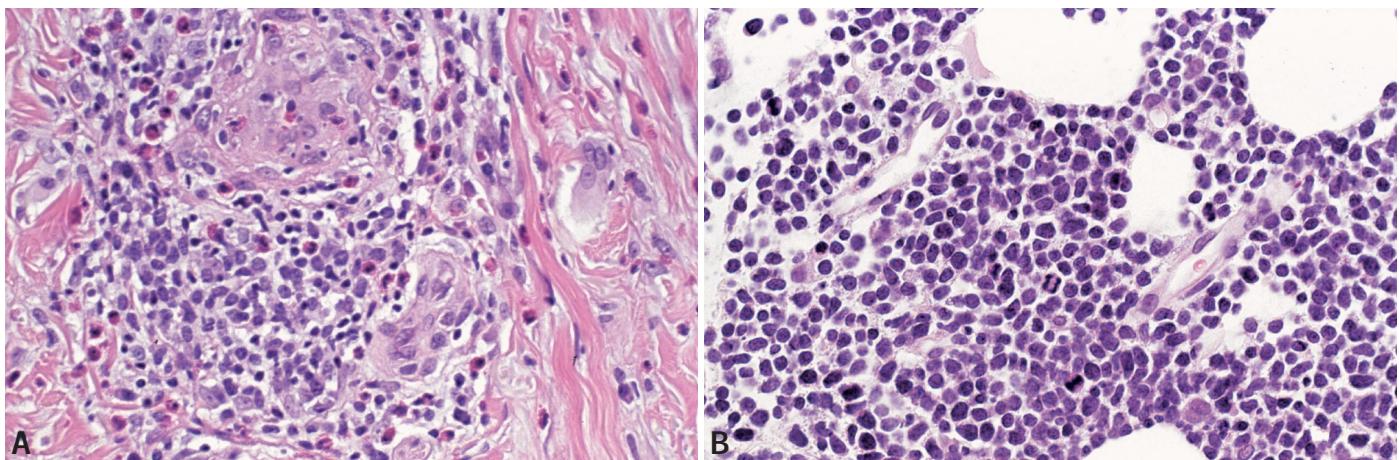


Fig. 4.64 Mantle cell lymphoma. **A** Perivascular infiltrate of small atypical lymphoid cells. **B** Densely packed small atypical lymphoid cells showing polygonal or indented nuclei and homogeneous chromatin staining.

{654,1422}. Gene profiling has suggested the presence of a small subset of cases that lack cyclin D1 abnormalities {1978}. Other primary and mostly secondary abnormalities are also described {376,1045,2303}.

Prognosis and predictive factors

MCL has a median survival of 3-5 years with those having "non-nodal" disease doing better {376,1756,2301,2303}. Adverse prognostic indicators include a high proliferative fraction, probably blastoid morphology, secondary genotypic abnormalities and blood involvement (at least in patients with nodal disease). Whether skin involvement in particular is an independent prognostic indicator is uncertain.

Burkitt lymphoma

Definition

Burkitt lymphoma is a mature B-cell neoplasm composed of relatively uniform medium sized transformed B-cells with a C-MYC translocation {630}.

ICD-O code

9687/3

Epidemiology

BL occurs in children in equatorial Africa (endemic), primarily in children and young adults elsewhere (sporadic) and in immunodeficient patients. There is a male predominance.

Etiology

Endemic BL and a minority of sporadic BL are Epstein-Barr virus positive.

Clinical features

BL usually presents as an extranodal mass often in the abdomen or, in endemic cases, in jaw or other facial bones. Other patients have a leukaemic presentation. Cutaneous involvement in BL appears to be extremely rare and at least usually is associated with disease at other sites {123,141,349,700}. It has rarely been described as occurring with ulceration from direct invasion from underlying bony lesions {349}, as distinct cutaneous lesions at relapse {123} and in 12% of autopsied cases of American BL (2 cases) {141}.

Histopathology

Histologic sections show a diffuse proliferation of medium sized transformed lymphocytes with relatively round nuclei with several nucleoli and a narrow rim of very amphophilic/basophilic cytoplasm. There are many apoptotic bodies and tingible body macrophages creating a starry sky appearance. Skin involvement demonstrates a diffuse but sometimes patchy dermal and subcutaneous infiltrate with a Grenz zone {123,700}.

Immunohistochemistry

Immunophenotypic studies demonstrate CD5-, CD10+, BCL-2-, CD20+ mature B-cells with surface immunoglobulin expression.

Histogenesis

Germinal centre/post germinal centre B-cell

Somatic genetics

All cases have clonal immunoglobulin

gene rearrangements and a C-MYC translocation, most often with a t(8;14)(q24;q32) {1483}. Many, if not all, cases also have C-MYC mutations {230, 1483}.

Prognosis and predictive factors

BL is an aggressive but curable neoplasm with a 5 year overall survival of 44% {3}.

Chronic lymphocytic leukaemia / small lymphocytic lymphoma

Definition

Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) is a mature B-cell neoplasm composed of small, usually CD5+, CD23+, cyclin D1+ B-cells with relatively round nuclei having clumped chromatin {1662}. Especially in lymph nodes, there is often an associated minor population of prolymphocytes and paraimmunoblasts that form proliferation centres.

ICD-O code

Chronic lymphocytic leukaemia
9823/3

Small lymphocytic lymphoma
9670/3

Epidemiology

CLL is the most common type of leukaemia in the West and SLL are reported to account for 6.7% of non-Hodgkin lymphomas {3,1064}.

Clinical features

CLL/SLL is seen most commonly in middle aged and older adults with a male predominance. It usually presents with blood and marrow involvement, frequent adenopathy and sometimes hepatosplenomegaly. Skin involvement is reported in 2% of patients without a marked predilection for any region of the body and occurs in patients who also have blood involvement {273,1167}. The face and scalp are frequent sites of involvement. It may be present either at the time of diagnosis or, much more frequently, develops subsequently {431}. Lesions may be single or multiple erythematous macules, papules, violaceous plaques, nodules or tumours either occurring in a limited or less frequently more generalized area {431,1167}. Atypical presentations include chronic paronychia, papulovesicular eruption and finger clubbing. Skin involvement may occur at sites of previous viral (eg, herpes zoster, herpes simplex) or Borrelia burgdorferi infection {427} and at sites of epithelial neoplasms {2215}. Spontaneous regression of CLL infiltrates at least at sites of prior herpetic infection may occur {2449}. In contrast to the absence of virus in at least most of the lesions in viral scars, B. burgdorferi DNA is found in at least some cutaneous CLL lesions {427}.

Histopathology

Histologic sections demonstrate a diffuse proliferation of small relatively round lymphocytes with condensed chromatin with lymph node biopsies typically demonstrating paler (pseudofollicular) proliferation centres where the cells have more abundant pale cytoplasm, more dispersed chromatin and sometimes prominent central nucleoli. The latter cells represent paraimmunoblasts and some of the former cells prolymphocytes.

Cutaneous lesions show a patchy perivascular, nodular, more diffuse or rarely band-like dermal infiltrate of small, usually but not always round, lymphocytes with occasional single lymphocytes in the epidermis and frequent extension into the subcutaneous tissue {431}. Patients with more than one biopsy can demonstrate more than one growth pattern. There may be overlying epidermal changes infrequently including ulceration. Proliferation centres are seen only in a minority of cases although there may be scattered larger cells in other cases {427}. A minority of cases have admixed eosinophils, neutrophils, and/or histiocytes. A granulomatous reaction may be present especially in some of the lesions arising in scars following prior viral infection {432}. Cutaneous CLL associated with granuloma annulare-like changes has also been reported {797}.

Immunoprofile

Immunophenotypic studies demonstrate a characteristic CD5+, CD43+, CD10-, CD23+, FMC7-, cyclin D1-, weakly CD20+ monoclonal B-cell population with weak surface immunoglobulin expression {1662}. In the cutaneous lesions, the admixed T-cells present are mostly of CD4+ type {431}.

Histogenesis

Mature B-cell most likely of memory type (including cases with either mutated or unmutated immunoglobulin heavy chain genes) {586,1288,1976}.

Somatic genetics

All cases have clonal immunoglobulin gene rearrangement although oligoclonal bands suggesting admixed reactive B-cells may also be present in the cutaneous lesions {431}. In some cases the immunoglobulin genes show somatic

hypermutation and in others they do not {586,943,1288,1976}. There are no chromosomal abnormalities specific for CLL/SLL; however, the most commonly described abnormalities include 13q and 11q deletions, trisomy 12 and 17q deletion {643}.

Genetic susceptibility

There is an inherited susceptibility to CLL; however, the critical genes remain to be determined {1064}.

Prognosis and predictive factors

CLL/SLL is one of the indolent lymphoid neoplasms. Clinically advanced stage, 17q deletions, unmutated immunoglobulin genes, CD38 and ZAP-70 expression include some of the more important adverse prognostic indicators {553,643, 943,1662,1760,2518}. Most do not believe that skin involvement portends an adverse outcome; however, it has been reported that cases with >5% medium and large-sized B-cells, admixed reactive cells and epidermal changes did worse than those without these features and there are reports in the literature suggesting a poor outcome following any cutaneous involvement {427,432,1167}. Transformation to a large cell lymphoma (Richter syndrome), Hodgkin lymphoma or prolymphocytic leukaemia is also associated with an aggressive course {826}. Richter syndrome can present as cutaneous lesions {427,2578}.

Hodgkin lymphoma

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H. Kerl

Definition

Hodgkin lymphoma (HL) is a neoplasm characterized by large tumour cells of B-cell lineage in a characteristic inflammatory background. It encompasses two entities distinguishable by their morphology and phenotype, namely nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL). Cutaneous involvement by NLPHL has not been reported, and is rare in cHL. For details see the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues {1121}.

ICD-O code

Nodular lymphocyte predominant Hodgkin lymphoma	9659/3
Classical Hodgkin lymphoma	9650/3

Synonym

Hodgkin disease

Epidemiology

Cutaneous involvement by cHL is rare and is seen in <5 % of cases, and <1% of cases at presentation {1076,1457, 2326,2505}. The incidence appears slightly increased in patients infected with

the human immunodeficiency virus (HIV) {2094,2157}. cHL has also been reported to occur with increased frequency in patients with mycosis fungoides and cutaneous CD30+ T-cell lymphoproliferative disease (CD30+ LPD), but is usually nodal in localization without cutaneous spread {1123,1176,1324, 2190}.

Etiology

The etiology of cHL is not established. However, an association with the Epstein Barr virus has been suggested, especially in cutaneous cases {1340}.

Localization and Clinical features

Three mechanisms of cutaneous involvement have been implicated: 1) retrograde lymphatic spread from regional lymph nodes; 2) direct extension, usually from a mass lesion; and 3) haematogenous dissemination {2326,2505}. The distribution of cHL lesions relates to the manner of spread. Direct extension is most common in patients with massive mediastinal disease, with involvement of the skin of the chest wall. The lesions are manifested as erythematous papules or nodules. Rare cases of HL presenting as primary disease in the skin have been reported 12 {2195}.

Histopathology, immunoprofile and genotype

The histological features resemble those of cHL in other sites. Classical Reed-Sternberg (RS) cells and variants are seen in an inflammatory background. The immunophenotype also is characteristic of cHL, with the neoplastic cells expressing CD30 and CD15 {426,1340}. However, while most cases of cHL are of B-cell lineage {1340}, cases of cHL with cutaneous involvement may express a T-cell phenotype {595,1176,2527}. Such cases are usually associated with concomitant CD30+ LPD. Common clonal T-cell gene rearrangement has been identified in the atypical cells of CD30+ LPD and cHL involving lymph nodes. Because RS-like cells may be seen in CD30+ LPD, the differential diagnosis between these disorders is often difficult.

Prognostic factors

In patients with cutaneous involvement secondary to haematogenous spread, the prognosis is poor. However, other patterns of cutaneous involvement are not necessarily associated with a poor prognosis {415,1023,1457,1651,1987, 2326,2505}.



Fig. 4.65 Hodgkin lymphoma. **A** Secondary involvement of the skin often occurs by direct extension, as in this large cutaneous nodule with ulceration. **B** cHL, skin. Classical Reed Sternberg cells are present in a background of reactive lymphocytes.

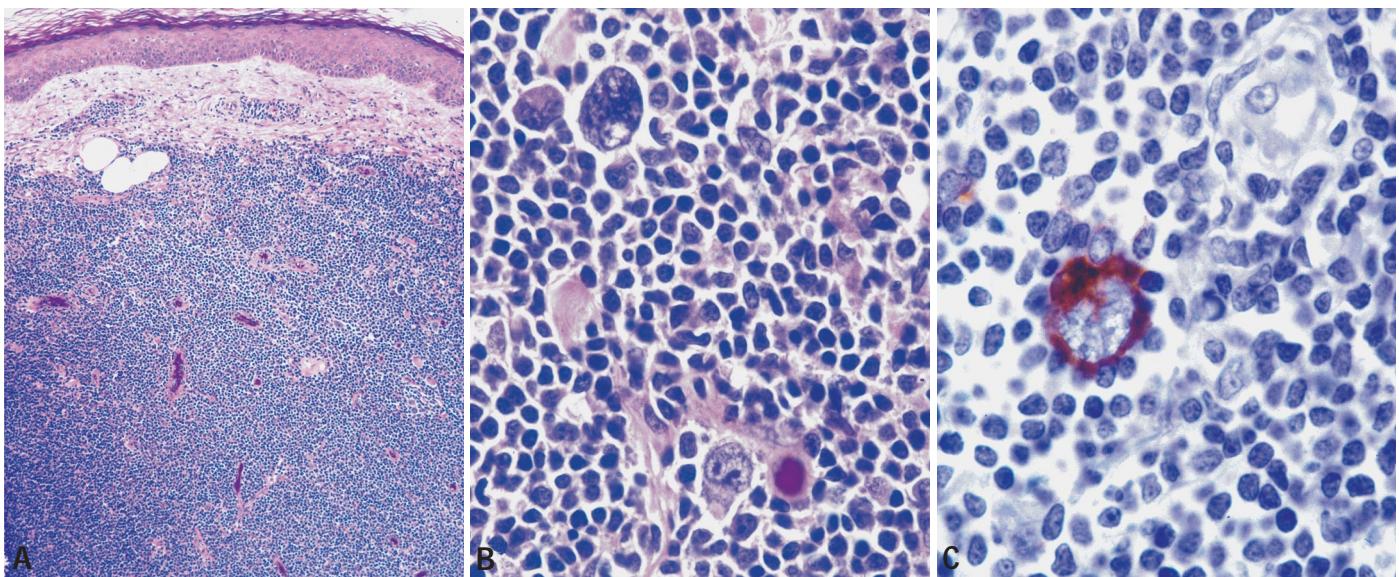


Fig. 4.66 Hodgkin lymphoma. **A** Subcutaneous nodule from primary cutaneous cHL. This patient presented with multiple nodules on the right and left arms. Two years later, she developed a mixed cellularity cHL subtype involving lymph nodes and bone marrow. **B** Reed-Sternberg cells in a background of reactive lymphocytes. **C** Reed-Sternberg cells were strongly CD30-positive, and were positive for CD15 and EBV by *in situ* hybridization (not shown).

Blastic NK-cell lymphoma

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M.J. Flraig
R. Dummer

D.V. Kazakov
W. Kempf
G. Burg

Definition

Blastic NK-cell lymphoma is a clinically aggressive lymphoma, with a high incidence of cutaneous involvement and risk of leukaemic dissemination. The blastic appearance and CD56 expression initially suggested an NK-precursor origin [632]. More recent studies suggest derivation from a dendritic cell precursor, as reflected in the designation CD4+, CD56+ haematodermic neoplasm.

ICD-O code 9727/3

Synonyms

CD4+, CD56+ agranular haematodermic neoplasm, blastoid NK-cell lymphoma, monomorphic NK-cell lymphoma

Epidemiology

Blastic NK-cell lymphoma is a rare lymphoma. Currently, there are no reports showing any racial or ethnic predilection. Most patients are middle-aged or elderly [632,739,1817]. However, every age can be affected.

Localization

Blastic NK-cell lymphoma has a

predilection for skin. At presentation there may be a single tumour, nodule or plaque [632,1817]. Lymph node, soft tissue, peripheral blood or bone marrow can be simultaneously involved. Central nervous system involvement can develop during the course of the disease.

Clinical features

Blastic NK-cell lymphoma frequently involves the skin at presentation with a single tumour, or tumours and plaques. Additionally, lymph nodes, soft tissue, peripheral blood or bone marrow can be simultaneously involved. Most cases of blastic NK-cell lymphoma presenting in the skin progress quickly to develop lymph node, bone marrow, and central nervous system involvement [450,739]. The clinical course is aggressive. There may be initial responses to multiagent chemotherapy, but a high risk of relapse. Regimens for both aggressive lymphomas and acute myeloid or lymphoid leukaemias have been utilized.

Histopathology

The dermis contains a dense, monotonous infiltrate of medium-sized cells with

finely clumped chromatin, and absent or indistinct nucleoli resembling lymphoblasts or myeloblasts [632,1121, 1817]. The cells have sparse cytoplasm. Mitotic figures are frequent. The overlying epidermis is spared, with a distinct grenz zone. Inflammatory cells are absent. There is generally no necrosis or angioinvasion.

Immunoprofile

The tumour cells usually express CD4, CD56, and CD43. Expression of CD7, CD2 is variable, whereas surface and cytoplasmic CD3 are negative [632, 1817,2391]. Cytotoxic molecules are generally absent. In some cases TdT and/or CD34 can be positive [313,1681, 2159]. CD68 can be weakly positive, showing focal staining in the Golgi region. Since lymphoblastic and myeloblastic neoplasms can also be positive for CD56, stains for myeloperoxidase, and CD3 should always be performed in order to exclude these entities [2118,2299]. The cells express CD123 and TCL1, both of which support a relationship to dendritic cells [450,1012]. Blastic malignancies of precursor NK-



Fig. 4.67 Blastic CD4+ CD56+. NK-cell lymphoma. Brownish haemorrhagic plaques and infiltrates. From D.V. Kazakov et al {1236}.

cell origin also exist, and may be difficult to distinguish in the absence of specialized techniques {1012,1681,2302}. There has been one report showing expression of KIR receptors {1293}.

Histogenesis

Based on the expression of CD56, an NK-cell derivation was initially proposed. However, the tumour was considered to be of uncertain lineage in the WHO classification. Recently studies have suggested a derivation from plasmacytoid dendritic cells based on gene expression studies and cytokine production. The cells express high levels of interleukin-3 receptor alpha chain (IL-3R-alpha).

Genetics

T-cell receptor genes are in germline configuration. Tumour cells are negative for EBV.

Prognosis and predictive factors

Blastic NK-cell lymphoma is an aggressive disease with a poor prognosis {311,739}. While close to 80% of patients obtained an initial complete remission, the majority of patients relapsed within two years. Patients with single isolated skin lesions appear to have a better prognosis {525}.



Fig. 4.68 Blastic CD4+ CD56+. NK-cell lymphoma. Diffuse infiltration of the trunk and upper extremities.

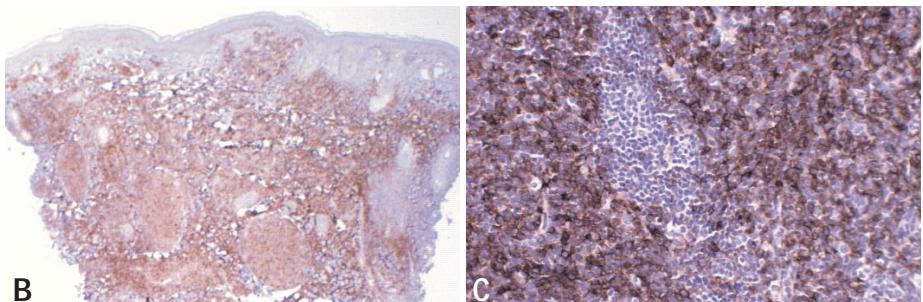
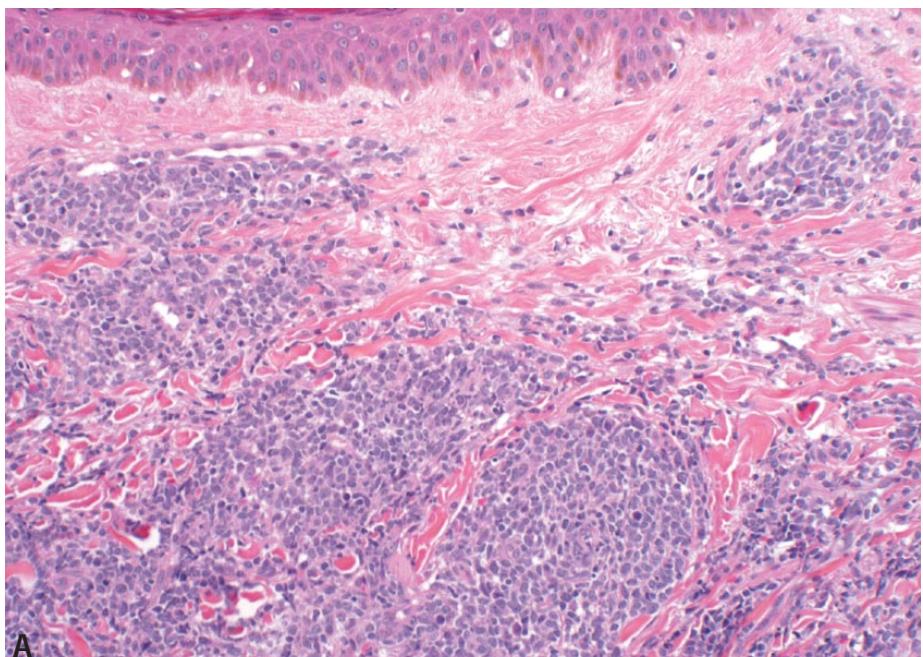


Fig. 4.69 Blastic CD4+ CD56+ NK-cell lymphoma. **A** Tumour cells diffusely infiltrate the dermis, but not epidermis. Note the finely distributed chromatin and inconspicuous nucleoli. **B** Tumour cells are positive for CD4 and **C** CD56.

Precursor T-lymphoblastic leukaemia/lymphoma and precursor B-lymphoblastic leukaemia / lymphoma

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G. Burg

Definition

Precursor lymphoblastic leukaemia/lymphoma is a malignancy derived from precursor cells of either T-cell or B-cell lineage. There is overlap in the clinical presentation, and patients may present with disease primarily in the bone marrow and peripheral blood (leukaemia) or in solid tissues (lymphoma). Because of similarities in stage of differentiation, and manner of presentation, precursor T-cell and B-cell malignancies will be discussed together.

ICD-O code

Precursor T-lymphoblastic leukaemia	9837/3
Precursor T-lymphoblastic lymphoma	9729/3
Precursor B-lymphoblastic leukaemia	9836/3
Precursor B-lymphoblastic lymphoma	9728/3

Synonyms

Acute lymphoblastic leukaemia
Lymphoblastic lymphoma

Epidemiology

Lymphoblastic leukaemia/lymphoma is rare. Approximately 3.5% to 7% of all malignant lymphomas of the skin are of the lymphoblastic type {339,2041}. Most cases are diagnosed in children and young adults. However, every age can be affected. Precursor B-cell malignan-

cies are more common in skin than those of precursor T-cell origin {470,1431,1489,2043}.

Clinical features

Lymphoblastic lymphoma/leukaemia may initially present in cutaneous or other extranodal sites as a single nodule or tumour {1429,2041}. Frequent sites are the head and neck region, especially for patients with precursor B-cell disease {2043}. However, there is a high likelihood of occult disease in the bone marrow, and patients should be regarded as having systemic disease for therapeutic purposes.

Morphology

The dermis contains a monotonous infiltrate composed of small to medium sized cells with fine chromatin and scant cytoplasm, characteristic of lymphoblasts. Nuclear irregularities are variable, and do not correlate with lineage. The epidermis is uninvolved, with a distinct Grenz zone. The cells are interspersed among dermal collagen fibres, without a stromal or inflammatory response.

Immunoprofile

T-cell lymphoblastic leukaemia/lymphoma. The tumour cells are positive for terminal transferase (TdT), CD43, CD99 {1489,1949,2043}. They variably express CD1a, CD2, CD3, CD4, CD5, and CD8. CD10 may be positive in some cases.

Cytoplasmic CD3 appears before surface CD3. CD7 is nearly always positive {1843}. The phenotype reflects stages in the maturation of a thymic T-cell.

B-cell lymphoblastic leukaemia/lymphoma. The tumour cells are positive for TdT, CD43, and CD99 {1489,2043}. The cells are usually positive for CD19 and CD79a {326}. CD10 is expressed in most cases. CD20, CD22, and CD24 are variably expressed. LCA may be negative. The cells may contain cytoplasmic μ heavy chain, usually in the absence of light chains.

Histogenesis

Precursor T- or B- lymphoblast.

Somatic genetics

Rearrangement of immunoglobulin heavy chain genes, and T-cell receptor genes usually correlates with B-cell or T-cell lineage, respectively {544,1311}. However, lineage infidelity is common in precursor lymphoid malignancies. Light chain gene rearrangement is a relatively late event in B-cell differentiation.

The classification of lymphoblastic malignancies is closely related to a complex series of genetic abnormalities that correlate with pathogenesis and clinical outcome {1121}.

Prognosis and predictive factors

Precursor lymphoblastic leukaemia/lymphoma is an aggressive disease. However, cutaneous involvement is not a poor prognostic factor, and response to systemic multiagent chemotherapy may be excellent {2043}.

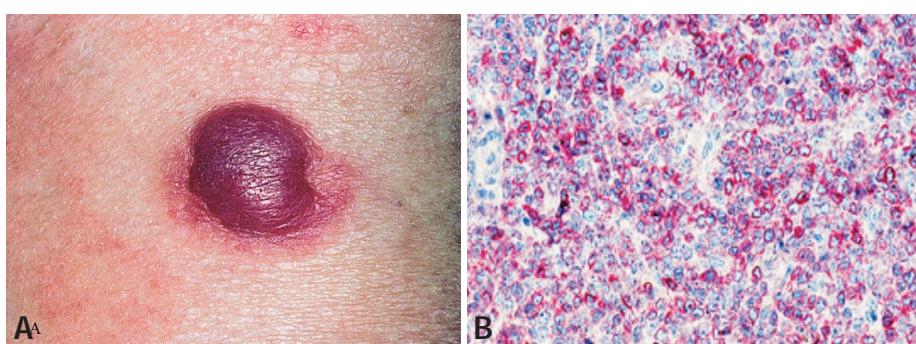


Fig. 4.70 Precursor B lymphoblastic leukaemia/lymphoma. **A** Soft non-ulcerated tumour on an erythematous plaque without scaling. **B** Tumour cells expressing CD79a.

Cutaneous involvement by myeloid leukaemia

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J. Vardiman

Definition

Myeloid leukaemia is a heterogeneous malignant disorder of myeloid precursor cells characterized by an increase in blast forms in the peripheral blood and bone marrow. Specific skin involvement results from direct infiltration of the skin by neoplastic cells.

Synonyms

Extramedullary myeloid sarcoma, granulocytic sarcoma, chloroma.

Epidemiology

Acute myeloid leukaemia (AML) accounts for 10–15% of childhood leukaemia but the incidence increases steadily with age. More than 50% of patients are older than 60 years [1838]. Chronic myelogenous leukaemia (CML) is generally a disease of older adults, with a median age between 50 and 60 years at presentation [1183].

Skin involvement is reported to occur in 2% to 30% of patients with AML [35,125, 649]. Specific skin lesions are equally common among males and females. It is found more frequently in patients with acute myelomonocytic (AMML) and monoblastic/monocytic leukaemias (AMOL). Specific cutaneous lesions are less common in chronic myelomonocytic leukaemia (CMML) and CML.

Clinical features

Specific skin lesions present as solitary or multiple violaceous to red-brown

papules, nodules and plaques. The most common sites of involvement are the scalp, face, trunk, and extremities [2288]. Haemorrhagic lesions are common. Leukaemic gingival hyperplasia is a striking feature of AMML and AMOL [649]. In the majority of cases, specific skin lesions develop in the setting of established leukaemia. In rare instances, leukaemic skin infiltrates may precede peripheral blood and bone marrow involvement [445,589,2368].

Histopathology

There is a moderate or dense, diffuse or nodular infiltrate in the dermis that extends into the subcutaneous fat [329, 1172]. The epidermis usually is spared. The infiltrates typically show perivascular and periadnexal accentuation. A characteristic feature is the presence of rows of atypical cells between collagen bundles [2137]. The infiltrate is composed of medium-sized or large neoplastic cells with round, oval or folded basophilic nuclei. Mitotic figures are usually present. In CML, the infiltrate is more pleomorphic and dominated by mature and immature cells of the granulocytic series. Cutaneous infiltrates of plasmacytoid monocytes may occur in CMML [297].

Immunoprofile

The majority of the tumour cells shows reactivity for lysozyme, myeloperoxidase, CD45, CD43, and CD74. Staining for chloroacetate esterase and CD68 is vari-

able [1172,1899]. Staining for CD34 is variable, and often negative in monoblastic leukaemias. The neoplastic cells are negative for CD3, CD20, CD30 and S-100 protein. The presence of CD56 expression in specific skin infiltrates of AML has been reported [1163,1258].

Histogenesis

Haematopoietic stem cells.

Somatic genetics

Genetic studies of specific cutaneous lesions in AML are scant and limited to isolated cases. An increased incidence of trisomy 8 in AML with skin infiltration has been reported [35]. Rarely, cases of congenital AML may be present with skin lesions.

Genetic susceptibility

Patients with Down syndrome, Fanconi anaemia, ataxia telangiectasia, Bloom syndrome, and Kostmann syndrome are predisposed to AML.

Prognosis and predictive factors

The prognosis of patients with specific skin lesions of AML is generally poor [125,805]. In one series, all patients died within 24 months after onset of skin lesions [1172].



Fig. 4.71 Acute myeloid leukaemia presenting as generalized erythematous papules and plaques.

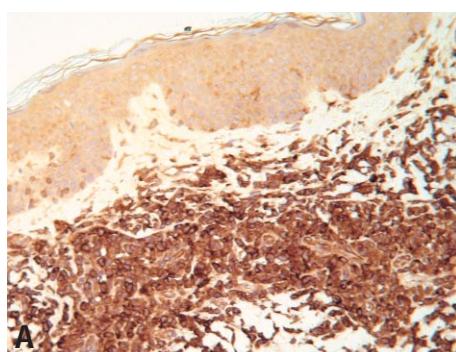
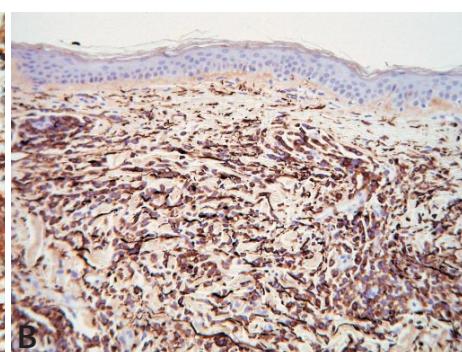


Fig. 4.72 Myeloid and monocytic leukaemias. A Acute monocytic leukaemia. Immunohistochemical expression of CD68. B Acute myeloid leukaemia. Positive lysozyme stain.



Lymphoid infiltrates of the skin mimicking lymphoma (cutaneous pseudolymphoma)

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G Wood
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S Cagliatti

Definition

The term pseudolymphoma (PSL) is defined as a reactive polyclonal benign lymphoproliferative process predominantly composed of either B-cells or T-cells, localized or disseminated. It heals spontaneously after cessation of the causative factor (e.g. drugs) or after non-aggressive treatment.

Synonyms and historical annotation

In 1923, Biberstein coined the term lymphocytoma cutis. Since then, a variety of designations have been proposed: lymphadenosis benigna cutis {124}, pseudolymphoma of Spiegler {2237} and Fendt. {721}, cutaneous lymphoid hyperplasia and lymphocytoma cutis {401}. In retrospect, most of these terms were describing cutaneous B-cell pseudolymphomas (B-PSL). The concept of cutaneous T-cell pseudolymphomas (T-PSL) was not widely accepted until the early 1980's.

Epidemiology

Cutaneous pseudolymphomas affect all age groups with a predilection of Borrelia-induced B-pseudolymphomas in children and young adults, whereas drug induced T-pseudolymphomas more frequently are seen in adults. Even though Borrelia-induced pseudolymphomas may be precursors for B-cell lymphomas of the skin, in general cutaneous pseudolymphomas are selfregressing and do not affect survival.

Etiology

Pseudolymphomatous proliferations in the skin may be induced by microbial, physical or chemical agents including Borrelia burgdorferi infection, tattoos and drugs.

Localization

In most cases, skin lesions are confined to the site of external irritation, i.e. tick bite. Due to the preferential "docking" of ticks to body areas where the skin is relatively soft, e.g., scrotum of young boys, the mamilla, ear lobes, large skin folds are preferentially involved.

Clinical features

Several variants of cutaneous PSL exist, presenting with different clinical symptoms.

Pseudolymphoma (PSL) with predominant T-cell infiltrates (T-PSL)

Lymphocytic infiltration (idiopathic or drug induced)

Palpable migratory arciform erythema

Lymphomatoid contact dermatitis

Actinic reticuloid

Persistent nodular arthropod-bite reactions

Inflammatory molluscum contagiosum

The original description of lymphocytic infiltration (idiopathic or drug induced cutaneous T-cell pseudolymphoma) given by Jessner and Kanof in 1953 {1141} is still valid today.

The lesions are flat, discoid, more or less elevated, pinkish to reddish brown, starting as small papules, expanding peripher-

ally, sometimes clearing in the centre, sometimes showing a circinate arrangement. The surface is smooth, occasionally uneven. There is no follicular hyperkeratosis as seen in discoid lupus erythematosus, which may be simulated. There may be only one, a few, or numerous lesions

Histopathology

Characteristic is a sleeve-like, predominantly lymphocytic infiltrate around the vessels of the upper and mid dermis. In addition, some macrophages and eosinophils may be found.

Phenotyping has shown the infiltrate to consist of both B and T cells {423} even though T cells seem to predominate in most cases {2521}.

Palpable migratory arciform erythema clinically shows a circinate or annular slightly elevated erythematous lesion.

Table 4.02 Differentiation between B-pseudolymphoma (B-PSL) and cutaneous B-cell lymphoma (CBCL)
Taken from Burg et al. {340}.

	CBCL	PSL
Clinical features		
Number of lesions	solitary or multiple	usually solitary
Extracutaneous involvement	possible	absent
Recurrences	likely	usually no recurrences
Survival time	affected	not affected
Histological features		
Pattern of infiltrate	diffuse or nodular,	nodular (> 90%)
Structure of infiltrate	"bottom-heavy"	"top-heavy"
Border of the infiltrate	convex, sharply demarcated "infiltrating" between collagen bundles	concave, poorly demarcated
Additional cells	usually absent	eosinophils, plasma cells
Transformation	may occur	never occurs
Immunophenotype		
Immunoglobulin light chains	monotypic (kappa or lambda)	polytypic expression
B-cell marker expressing cells	>50% cells	≤50% cells
T-cell marker expressing cells	usually few	>50% cells
CD21-positive dendritic cells	mostly absent irregular pattern	mostly present regular pattern
Genotype		
Ig heavy chain gene rearrangement	present in most cases	absent in most cases

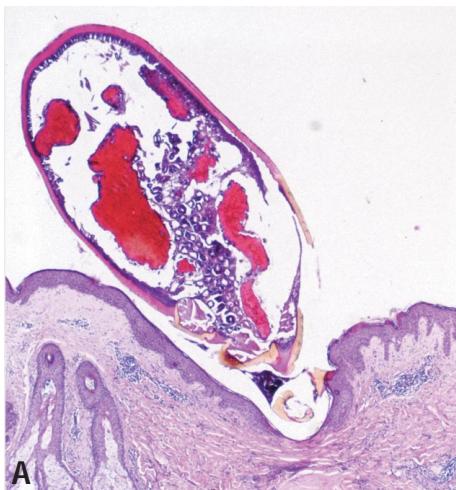
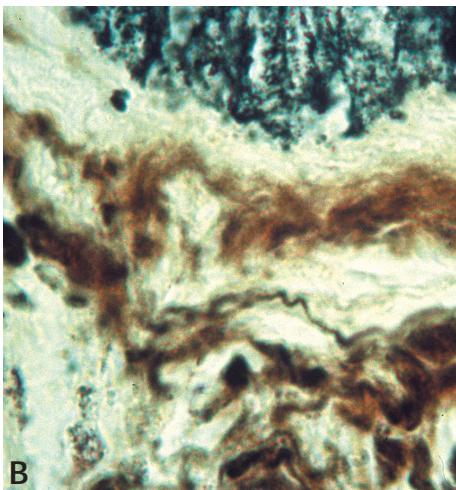


Fig. 4.73 A Head of *Ixodes ricinus* fixed to the skin. **B** 1384. *Borrelia burgdorferi* in the dermis, silver stain.



Histologically there is a scant sleeve-like perivascular lymphocytic infiltrate in the mid or deep dermis.

Lymphomatoid contact dermatitis has been reported as a reaction to various allergens (i.e. nickel, Peru balsam) or drugs (diphenylhydantoin) inducing mycosis fungoides-like features [1975]. Genotyping has shown clonal rearrangement in some cases. Such cases may be closely related to "clonal dermatitis" some of which develop into overt CTCL [2545,2546]. Histologically, eczematous features with epidermotropism of lymphocytes and accumulations of CD1a-positive Langerhans cells may be found. Actinic reticuloid is a chronic photoallergic infiltrative dermatitis of light exposed areas associated bearing a clinical and histological resemblance to malignant lymphoma, especially to Sézary syndrome. Histologically there is a dense infiltrate of lymphocytes mixed with many polyclonal plasma cells, eosinophils and macrophages.

There is a considerable overlap between T- and B-PSL in persistent nodular arthropod-bite reaction, nodular scabies and inflammatory molluscum contagiosum which show a dense polymorphous infiltrate consisting of a mixture of T-cells, B-cells, macrophages and predominantly eosinophilic granulocytes.

Lymphomatoid papulosis even though showing biologic features of pseudolymphoma is considered to belong to the group of lymphomas since despite spontaneous regression of single lesions, the

disease is not curable and may show transitions to other lymphomas.

PSL with predominant B-cell infiltrates

Lymphadenosis benigna cutis (LABC) [124] -the prototype of this group of B-PSL- is synonymous with lymphocytoma cutis. In Europe it is most commonly caused by infection with *Borrelia burgdorferi* after a tick bite (*Ixodes ricinus*). However other microbiological (medicinal leeches, *Hirudo medicinalis*) [2211], physical or chemical agents as well may induce lymphocytoma-like reactions.

Two thirds of all lesions are situated on the head, tending to occur on the ear lobes. Other predilections are the nose as well as the nipples, the inguinal area and scrotum. Usually the lesion is a solitary papule or nodule, but several disseminated lesions may occur as well [1068].

Microscopic examination shows a nodular dermal infiltrate with reactive follicles. In addition, there is a rather diffuse infiltrate containing T cells, histiocytes, eosinophils and polyclonal plasma cells. The presence of macrophages containing ingested nuclear material (tingible body macrophages) within the follicles producing a "starry sky" pattern is a common feature in B-PSL and a hallmark of all reactive germinal centres. The infiltrate is predominantly located in the upper and mid dermis, but may extend into the deep dermis. Small groups of lymphoid cells between collagen bundles may be observed at the periphery of

the lesions. This is a helpful histological criterion in the differentiation from cutaneous B-cell lymphoma, in which the nodular infiltrate shows convex rather than concave sharply demarcated borders.

Phenotypically [428] a polyclonal B-lymphocytic infiltrate without light chain restriction of the infiltrate is found in most cases. The cells express the phenotype of mature B-cells (CD 20, CD 79a). In B-PSL, regular and sharply demarcated networks of CD21+ follicular dendritic cells are present, whereas in CBCL these networks are irregularly shaped [342].

Acral pseudolymphomatous angiokeratoma of children (APACHE) is a rare benign pseudolymphomatous disorder occurring mainly in children [1888].

The typical clinical presentation is multiple (up to 40), asymptomatic, small papules located unilaterally on the fingers, toes and hands. Their colour is usually red-violet, accounting for their angiokeratous appearance [1887].

Histologically the dermis contains a moderately to very dense, non-epidermotropic infiltrate composed of small well-differentiated lymphocytes admixed with a few plasma cells, histiocytes, and giant cells. Blood vessels show prominent plump endothelial cells [1165,1887].

Immunohistochemically the cellular infiltrate represents a mixture of polyclonal mature T- and B-lymphocytes [936].

Inflammatory pseudotumour (IPT) (plasma cell granuloma, inflammatory myofibroblastic pseudotumour) refers to a spectrum of idiopathic benign conditions with unknown etiology that can develop in various organs and deep tissues, particularly in the lung. Cutaneous IPT occurs as a solitary, slowly growing, tender nodule measuring 1-3 cm in diameter. Irrespective the anatomic location, the lesions share common histological features, showing well circumscribed proliferation of myofibroblasts/fibroblasts expressing smooth muscle actin (SMA) and vimentin, a mixed cell infiltrate containing high numbers of plasma cells with prominent germinal centres dispersed throughout the lesion. The plasma cells are polyclonal and are seen in the interfollicular areas (plasma cell granuloma) 21, [508,509]. Later stages show marked fibrosis/sclerosis with thick collagen bundles arranged in concentric whorls.



Fig. 4.74 Lymphadenosis benigna cutis (LABC, B-pseudolymphoma) following tick bite in the earlobe.

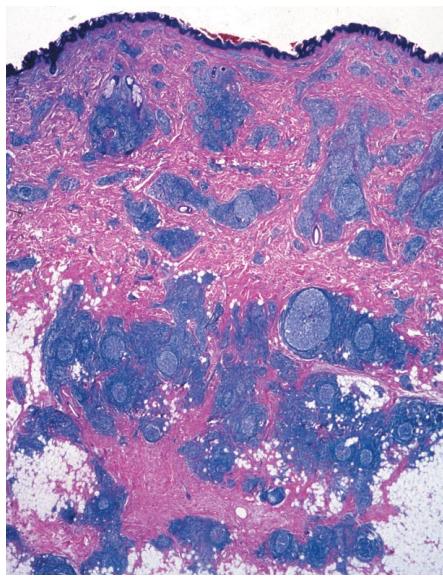


Fig. 4.75 B-PSL. Reactive follicles in lymphadenosis benigna cutis (B-pseudolymphoma).

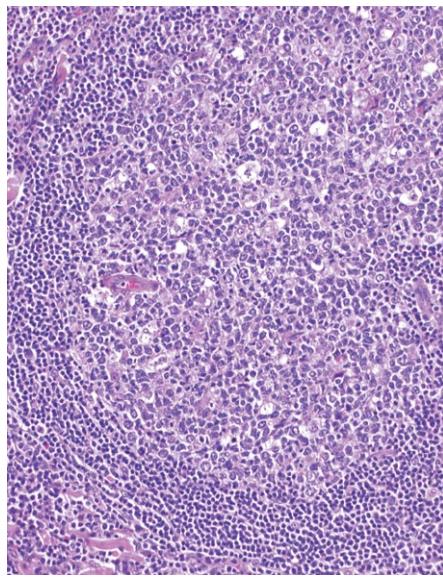


Fig. 4.76 Close up view showing follicular centre with tingible-body macrophages featuring a starry sky pattern.

Histological variations include presence of high endothelial venules, admixture of eosinophils, calcification, psammoma bodies, and presence of large polygonal myofibroblasts (vimentin+, CD15-, CD30-) {1476} with single, double or multiple nuclei and prominent eosinophilic nucleoli resembling Reed-Sternberg cells {388,1084,1476,1881,2561}.

Differential diagnosis of cutaneous IPT includes lymphoma, angiolympoid hyperplasia with eosinophilia and Kimura and infectious dermatoses (mycobacteria, deep fungal infections). The later stages of cutaneous IPT should be distinguished from erythema elevatum diutinum, granuloma faciale and dermatofibroma with lymphoid infiltrate.

PSL with mixed and unclassified infiltrates

There are reactive lymphocytic infiltrates in the context of other skin disorders that can be referred to as pseudolymphomatous reactions in an even broader sense. Neoplasms, especially squamous cell carcinoma, basal cell carcinoma, and malignant melanoma, or naevi (halo [Sutton] naevi) may show a dense mononuclear infiltrate, composed of T cells or of B cells, sometimes with follicle formation, with polyclonal plasma cells being numerous especially in head and neck localizations.

Histogenesis

Polyclonality is the hallmark of cutaneous pseudolymphomas. Besides T-cells and B-cells, mononuclear phagocytes represent a considerable proportion of the infiltrate. Eosinophils and polytypic plasma cells as well are present in most cases of either B-cell or T-cell pseudolymphomas of the skin {342}.

Somatic genetics

No clonal rearrangement of T-cell receptor genes or of immunoglobulin heavy chain genes or light chain restriction of plasma cells is found.

Prognosis and predictive factors

The prognosis of cutaneous pseudolymphomas by definition is excellent, showing spontaneous regression of the lesions after cessation of the causative factor or due to treatment with non-aggressive treatment modalities. However there is a potential for some cutaneous pseudolymphomas to progress to cutaneous B-cell lymphoma (CBCL) {433,807,1339}, or to cutaneous T-cell lymphoma (CTCL) {2545,2546}.

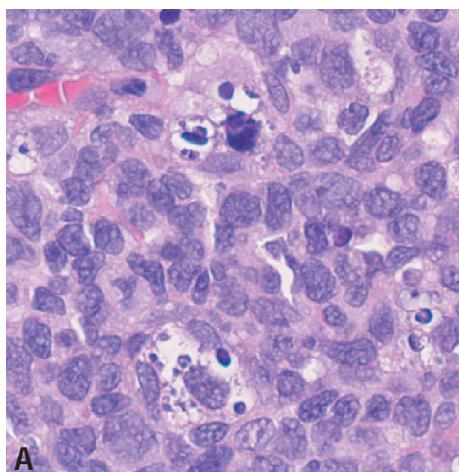
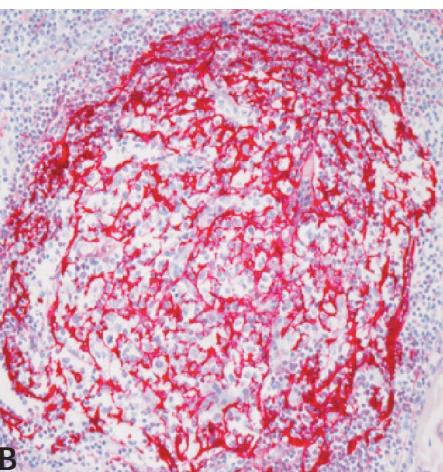


Fig. 4.77 A Tingible body macrophages containing ingested nuclear fragments. **B** Regular network of CD21+ dendritic cells.



Parapsoriasis

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Definition

The term "parapsoriasis" is confusing. It encompasses a number of different pathologic states clinically manifested by chronic recalcitrant erythematous scaling skin lesions.

Those diseases which have distinct clinical and histological changes do not fulfill criteria of malignancy, deserve to be labeled with a term which reflects this intermediate situation and labels them as distinct nosologic entities. This term since the days of Brocq has been "parapsoriasis" and there is no reason for changing it {311,312}. Otherwise there will be a bias in epidemiologic data on frequencies, mortality rates and other parameters.

Two groups of parapsoriasis can be differentiated. The benign form ("parapsoriasis en plaques" [Brocq's disease]), which never evolves into malignant lymphoma and large plaque forms with or without poikiloderma which after several decades may evolve into mycosis fungoides or CTCL in up to 50% of the cases. Table 4.3 summarizes criteria for differentiation of benign and premalignant forms of parapsoriasis en plaques.

Small plaque parapsoriasis

Synonyms

Parapsoriasis, small patch (digitiform) type (Brocq's disease); Parapsoriasis en plaques, benign type; digitate dermatosis, xanthoerythrodermia perstans; chronic superficial dermatitis

Epidemiology

This form preferentially occurs in young adults and affects males more frequently than females. There are no statistically reliable data on the incidence, which is estimated less than 0.1 per 100.000 per year. There is little tendency to progress. Survival is not affected since SPP never evolves into malignant lymphoma

Clinical Features

Trunk and upper extremities are preferentially involved. Small (2-5cm in diameter), mostly oval or finger-like patches, slightly erythematous, following skin lines. The color is brown red, and fine and powdery (pityriasisiform) scaling may be present. The surface is slightly wrinkled resulting in a pseudoatrophic appearance.

Histopathology

The epidermis is normal or slightly spongiotic with patchy parakeratosis. Patchy loose perivascular and disseminated lymphocytic infiltrate, but no edema, are present in the dermis. Significant epidermotropism of lymphoid cells is lacking.

Immunohistochemistry

Lymphoid cells exhibit mostly CD4+ and some CD8+ {935}.

Somatic genetics

Clonal rearrangement for the T-cell receptor genes is not detectable. However clonal rearrangement of lymphoid cells in the peripheral blood of patients has been reported {1661}.

Prognosis and predictive factors

The skin lesions are extraordinarily stable in shape and size over years and decades without spreading to extracutaneous localizations. Lymph nodes, peripheral blood, bone marrow or internal organs are not affected. Life-expectancy is normal. Progression into mycosis fungoides or other CTCL does not occur.

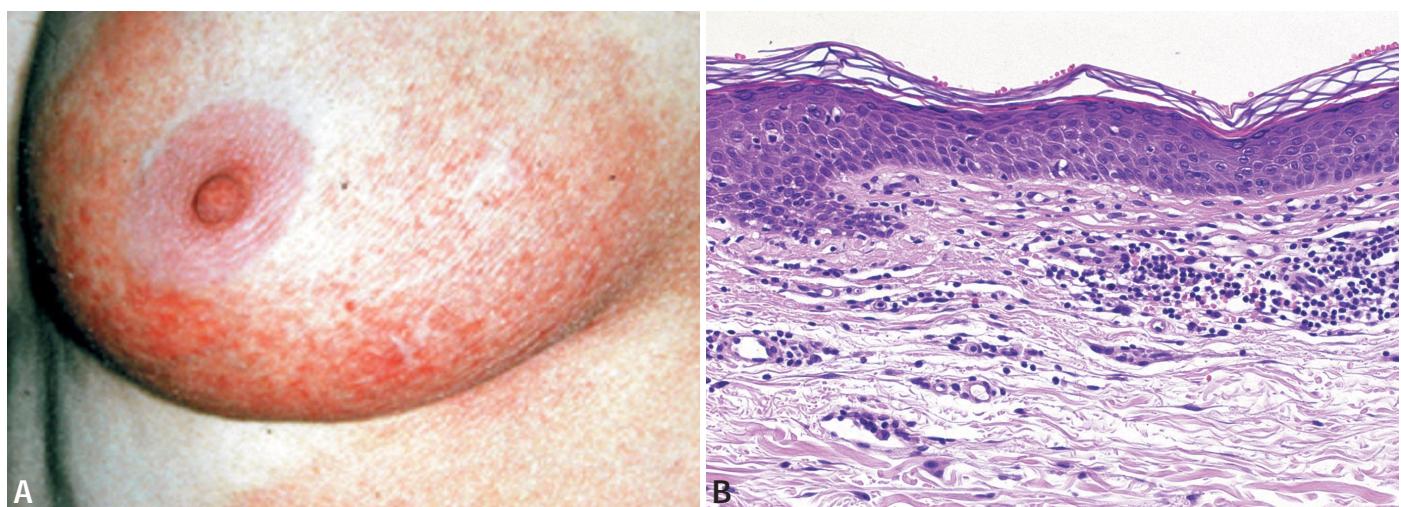


Fig. 4.78 Parapsoriasis. **A** Large plaque parapsoriasis with poikiloderma, showing large teleangiectatic patches and a netlike pigmentation. **B** Flattening of the epidermal rete ridges. Band like lichenoid infiltrate. Dilated small blood vessels in the upper dermis.

Parapsoriasis - Large patch type, with or without poikiloderma

Definition

Pre-malignant inflammatory disorder with tendency to evolve into mycosis fungoides. Some authors consider this lesion a manifestation of early cutaneous T-cell lymphoma (CTCL).

Synonyms

Non-poikilodermatosus variant. Parapsoriasis en plaques, premalignant type, parapsoriasis en grandes plaques simples.

Poikilodermatosus variant : Prereticulotic poikiloderma, parapsoriasis en grandes plaques poikilodermiques; poikiloderma vasculare atrophicans; parapsoriasis lichenoides; parakeratosis variegata

Epidemiology

All age groups may be affected with a slight male preponderance.

Localization

Breast and buttocks are most commonly involved.

Clinical Features

Few large (more than 5 cm in diameter) patches showing pityriasisiform scaling with (poikilodermatosus variant), telangiectasia and netlike pigmentation are present. There is no palpable infiltration.

Tumour spread and staging

Lesions may stay unchanged over years and decades, or slowly show enlargement in a few cases. No plaques or tumours occur, except when the disease evolves into CTCL in some of the cases.

Histopathology

Under patchy parakeratosis there is slight atrophy of the epidermis, due to

Table 4.03

Criteria for distinguishing benign and premalignant forms of parapsoriasis en plaques.

	Benign form (small patch type)	Premalignant form (large patch type) with or without poikiloderma
Age distribution	Adults	All ages
Sex incidence (m:f)	5:1	2:1
Clinical features	Small (2-5cm in diameter), mostly oval, or finger-like patches, slightly erythematous and wrinkled surface (pseudoatrophy) uniformly pinkish or yellowish with pityriasisiform scaling	Few large patches (>5cm in diameter) pityriasisiform scaling with or without telangiectases and netlike pigmentation, sometimes slightly hyperkeratotic (parakeratosis variegata)
Preferential localizations	Trunk and upper extremities	Breast and buttocks
Histological features	Patchy parakeratosis, slight perivascular patchy infiltrate, no oedema, no significant epidermotropism	Slight epidermal atrophy with loss of rete ridges, significant band-like dermal lymphocytic infiltrate sparing the subepidermal zone, no significant epidermotropism, no oedema; telangiectases may be prominent in the poikilodermatosus variant
Prognosis	Life expectancy normal; no progression to mycosis fungoides	Life expectancy normal in most cases; progression to mycosis fungoides occurs

loss of rete ridges, in the poikilodermatosus form. The subepidermal zone is free of lymphocytes, which accumulate in a band-like arrangement in the upper dermis, sparing the papillary region. There is no significant epidermotropism as usually seen in early stages of mycosis fungoides. The poikilodermatosus variant of the disease in addition shows dilated blood vessels in the upper dermis.

Somatic genetics

T-cell receptor gamma gene rearrangement, which is clonal in about half of the patients with LPP, is probably without any prognostic significance {2186}.

Increased telomerase activity and short-

ened telomere length was also detected in CD4+ T cells from patients with parapsoriasis {2552}.

Prognosis and predictive factors

There is no significant difference between the observed and expected survivals in patients with less than 10% skin involved. {2575}. However when skin involvement exceeds 10%, as seen in LPP, sporadic cases have an increased risk of transforming into mycosis fungoides after years or decades {2031}.

Langerhans cell histiocytosis

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Definition

Langerhans cell histiocytosis (LCH) is a clonal disorder with systemic spread, characterized by proliferation of dendritic cells which bear morphologic and phenotypic markers of Langerhans cells, characterized by Birbeck granules and expression of CD1a and S-100.

ICD-O code 9751/1

Synonyms

Histiocytosis-X, Langerhans cell granulomatosis, Langerhans cell disease

Epidemiology

LCH predominantly occurs in infants. Median age at diagnosis is 3-5 years {2,299}. It has also been reported in patients up to the ninth decade of life {1551,1578,1941}, and occurs equally in men and women. The incidence has been estimated as 0.1–0.5 per 100.000 population per year. There have been reports on familiar cases with autosomal recessive inheritance.

Etiology

The etiology is unknown. Different groups have studied female patients with cutaneous LCH using a variety of x-linked polymorphisms to demonstrate clonality {2530,2574}. In some cases, association with lymphomas, leukaemias and lung tumours {666} has been observed; in others, infections and environmental factors, including El Nino, have been related to childhood LCH {455}. Many view LCH as reactive process {716,2583} because of its tendency toward spontaneous remission and response to mild, non-toxic therapy.

Localization

Two thirds of the sites of involvement diagnosed throughout the course of the disease are present at diagnosis {2}. Initial bone involvement is found in almost all patients. Other organs involved skin (25-100%, depending on subtype), ear, liver, lung, and lymph nodes {299}.

Clinical Features

The clinical presentation of LCH is very diverse and depends on the subtype. Skin lesions may be seen either as single organ involvement or as part of a multorgan systemic disease in 25-100% of cases. Any anatomic site can be involved including scalp, nails, palms and soles as well as mucous membranes.

Letterer-Siwe Disease

This is the most severe, disseminated form of Langerhans cell histiocytosis. It affects children in their first year of life but occurrence in adults has been reported {1731}. Tiny (0.5 mm in diameter) rose-yellow or brownish-red, translucent papules and patches are found on the scalp, diaper and seborrhoeic sites like nasolabial folds, perioral region, and on the upper trunk. In time, the papules become scaly and crusted and may coalesce into plaques. Petechial and purpuric lesions, pustules and vesicles as

Table 4.04

Langerhans cell histiocytoses and their characteristics. This classification has limitations because of the highly variable manifestations of the disease with many overlapping features {340}.

Disease	Age	Skin involvement	Clinical Features	Course	Prognosis
Letterer Siwe	First years of life	~90-100%	Fever, weight loss, lymphadenopathy, hepatosplenomegaly, pancytopenia, bone lesions	Acute	Mortality rate: 50-66%
Hand-Schüller Christian	Children adults	~30%	Osteolytic bone lesions, diabetes insipidus exophthalmos, otitis	Subacute to chronic	Mortality rate: < 50%
Eosinophilic granuloma	Mainly adults	<10%	Solitary bone or skin lesions	Chronic	Favorable
Congenital self-healing reticulohistiocytosis (CSHR)	Congenital	100%	Skin lesions only	Self healing	Excellent*

*Both relapses and conversion to systemic disease can occur, so long-term follow-up is needed {1369}.



Fig. 4.79 Multiple nodules in a patient with Congenital self-healing reticulohistiocytosis (CSHR).

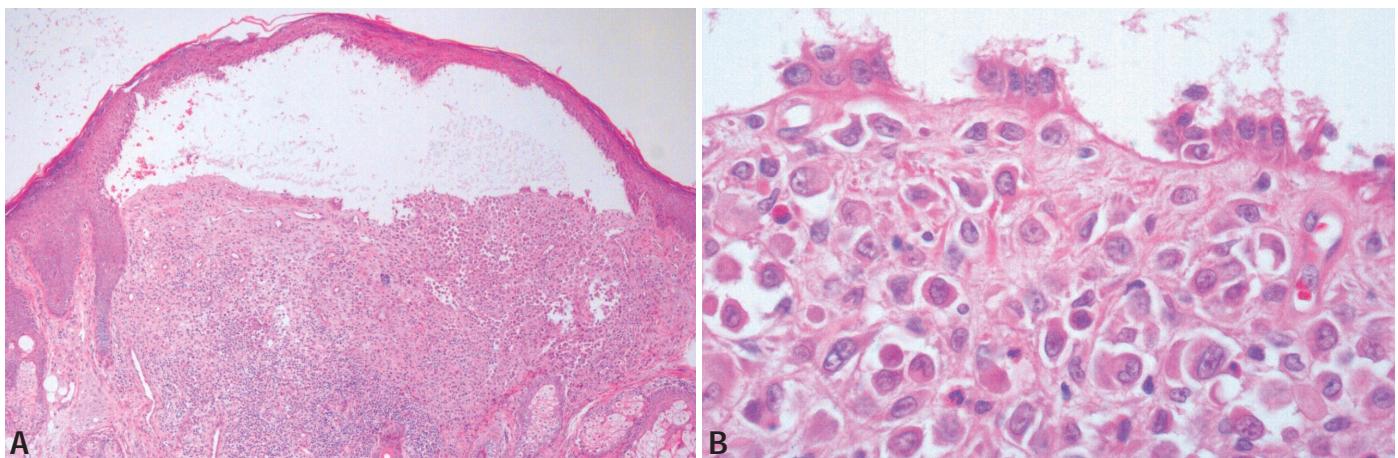


Fig. 4.80 Congenital self-healing reticulohistiocytosis (CSHRH). **A** Papule of CSHRH with **B** Characteristic kidney-shaped nuclei.

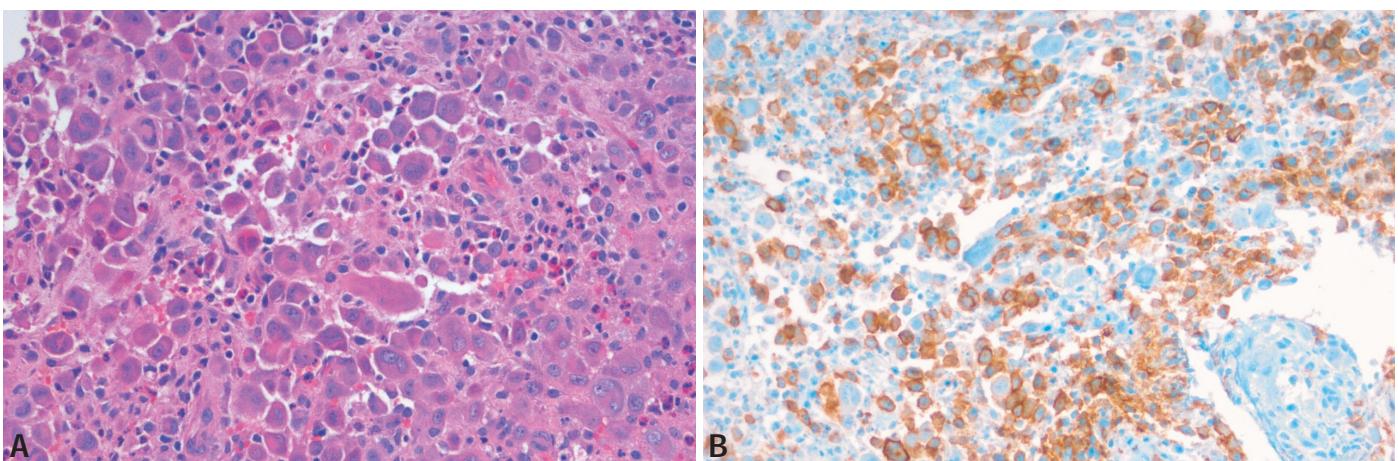


Fig. 4.81 Langerhans cell histiocytosis. **A** Typical ground glass ("reticulocytic") appearance of Langerhans cells. **B** Langerhans cells with membranous staining for CD1a.

well as small erosions can also be seen. Nodules are uncommon, but may be found on the trunk and tend to ulcerate. Additional symptoms include fever, weight loss, rash, lymphadenopathy, hepatosplenomegaly, pancytopenia and purpura.

Hand – Schüller - Christian disease

The typical triad includes osteolytic skull lesions (100%), hypopituitarism induced diabetes insipidus (50%), and exophthalmos (10%). Otitis media, generalized lymphadenopathy, hepatosplenomegaly, and pulmonary disease may be additional findings.

Skin lesions occur in about 30% of cases, usually in the intertriginous areas, most often as papules and nodules which may be ulcerated, erosive and superinfected.

Eosinophilic granuloma

The most common site of involvement is bone. The uncommon cutaneous lesions are deep dermal or subcutaneous nodules which are not clinically distinct {818,1956}. Lesions have to be differentiated from granuloma eosinophilicum faciei, a chronic variant of leukocytoclastic vasculitis with variable presence of eosinophils, but usually no extracutaneous manifestation {452}.

Congenital self-healing reticulohistiocytosis (CSHRH)

CSRH (synonyms: Hashimoto-Pritzker disease; congenital reticulohistiocytosis; congenital self-healing Langerhans cell histiocytosis) {981,2082} is a rare condition (5% of all LCH), initially seen at birth or in the neonatal period, with solitary, localized to generalized papules, vesicles, or nodules on the trunk, head,

palms and soles, sometimes showing central ulceration {217}. The skin lesions tend to involute spontaneously within weeks to months leaving behind hypo- or hyperpigmented macules or patches {979,1372}. Affected infants are otherwise well {1369}. Patients should be carefully followed since relapses may occur, including bone involvement, and the occasional case may progress to Letterer-Siwe disease {1445}. Some cases of CSHRH may be clinically confused with the blueberry muffin syndrome, congenital leukaemic infiltrates, xanthogranulomas or mast cell disease, but the microscopic picture brings clarity {360}.

Histopathology

The hallmark and unifying feature of all variants of LCH is a cell with large, pale, folded or lobulated, often reniform, vesic-

ular nucleus and abundant, slightly eosinophilic or amphophilic cytoplasm. Nucleoli are not prominent. Histological variations correlate with the clinical appearance of the lesions. Features may be predominantly proliferative in Letterer-Siwe disease, xanthomatous in Hand-Schüller-Christian-disease, granulomatous as in eosinophilic granuloma, or "reticulocytic" with abundant eosinophilic cytoplasm (ground glass appearance of giant cells) in Hashimoto-Pritzker disease. Fully developed papules and plaques show a dense band-like infiltrate obscuring the dermo-epidermal junction. Epidermotropism of LCs with intraepidermal microabscess formation can be found. In addition to LCs and eosinophils, the infiltrate may contain variable numbers of lymphocytes, epithelioid macrophages including foam cells and giant cells, neutrophils, plasma cells, and extravasated erythrocytes.

Immunohistochemistry

The phenotypic hallmarks in LCH are expression of CD1a, CD4 and S-100 protein, while macrophage markers, including CD68 and lysozyme, are usually negative.

Electron microscopy

Rod- or rocket-shaped granules measuring 200-400 nm (Birbeck granules, Langerhans cell granules) are the ultra-

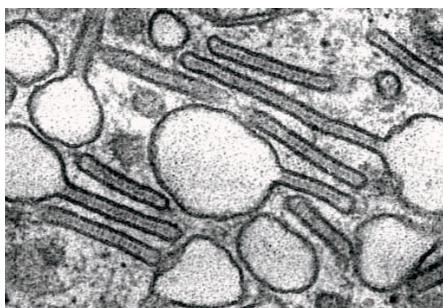


Fig. 4.82 Electron microscopy with numerous Birbeck or Langerhans cell granules. Courtesy Dr. N. Romani, University of Innsbruck, Austria

structural hallmark of LCs. The number of Birbeck granules varies, with usually greater prominence in early lesions. Co-existence of myelinoid laminated inclusions or "vermiform" bodies {1372} and Birbeck granules is common in CSHRH.

Genetics

A variety of inconsistent cytogenetic abnormalities have been found in several patients with LCH studied so far using comparative genomic hybridization, loss of heterozygosity (LOH) and other techniques {107,227,848,1666}. Heterogeneous overexpression of TGF β receptor I and II, MDM2, p53, p21, p16, Rb, and BCL2 has been detected in lesional LCH cells {2097}. Familial clustering of two different manifestations of LCH support a role for genetic factor(s) in LCH

and raise the possibility of inherited mutations that promote emergence of clonal Langerhans cells {93,134,1200}. LCH may follow precursor T-cell acute lymphoblastic leukaemia, and in such cases a clonal relationship has been shown for T-cell receptor gene rearrangements {720}.

Prognosis and predictive factors

The biologic behaviour of LCH ranges from spontaneous remission to lethal dissemination, and such behaviour cannot be predicted on the basis of histologic features {1941}. The presence and degree of organ dysfunction, age less than 1 year at diagnosis (except the Hashimoto-Pritzker type), male sex, progressive episodes, and the absence of response to therapy are the most reliable indicators of prognosis {2,1019}. In general, about 10% of patients with multifocal disease die, 30% undergo complete remission, and the remaining 60% embark upon a chronic course {1065, 1425}.

Indeterminate cell histiocytosis

R. Caputo
E. Berti

Definition

Indeterminate cell histiocytosis (ICH) is a proliferative cutaneous disorder of the so-called "indeterminate cells" (IC), i.e. distinct dendritic cells of the skin that display histological, ultrastructural and antigenic features similar to those of Langerhans cells, but do not contain Birbeck granules.

Epidemiology

The disease is very rare (about 15 cases described up to 2003), usually occurs during adulthood, although two cases were in teenagers {1621,2019} and two cases in children {1413,1524}. Both sexes have been affected.

Etiology

The origin of indeterminate cells is still debated. Indeterminate cells may derive from an arrest of Langerhans cell migration and maturation {1302}, may represent precursors of Langerhans cells which acquire Birbeck granules as they transit from dermal to epidermal sites {1499}. Furthermore it has been suggested {222} that indeterminate cells represent members of the epidermal/dermal dendritic cell system which migrate from skin to regional lymph nodes. According to this concept, indeterminate cell histiocytosis can be considered a disorder due to locally arrested dermal indeterminate cells proliferating prior to their departure for lymph nodes.

Localization

Lesions are usually restricted to the skin. Solitary lesions have been described on the trunk and arms, while multiple lesions are widespread.

Clinical features

The eruption consists of a solitary nodular lesion {222,279,1413,1621} or of multiple papulonodules {279,531,1499,2019, 2179}.

Solitary nodules are soft, red in colour and about 1 cm in diameter, and may be ulcerated. Multiple lesions are firm, asymptomatic papulonodules ranging in size from a few millimetres to 1 cm, varying in colour from dark-red to brownish, and covered by intact skin. These lesions appear in successive crops. Mucous membranes are always spared. Visceral involvement has been observed only in a child. Patients are in good general health.

Histopathology

Light-microscopic evaluation reveals an infiltration of histiocytic cells in the whole dermis and sometimes within the epidermis. The proliferating cells show an abundant pale eosinophilic cytoplasm and large irregular folded or twisted nuclei. A few mitotic figures and multinucleated giant cells may be observed. Clusters of lymphocytes are admixed.

Immunohistochemistry

Proliferating cells are weakly positive for CD1a, CD68 (KP1), CD11c (Leu M5), CD14 (OKM1), factor XIIIa, lysozyme, $\alpha 1$ -antitrypsin, HLA-DR, but negative for CD207 (langerin) {1302,1499,1524,1621, 2179}.

Electron microscopy

The proliferating cells reveal an indented nucleus and an abundant cytoplasm with lysosomes, phagosomes and a well-developed endoplasmic reticulum. Birbeck granules are absent {222,531, 1413}.

Prognosis and predictive factors

Most cases have exhibited complete or partial spontaneous regression of lesions without recurrences. Two cases displayed malignant behaviour {279,1524}. The prognosis is reasonably good, but leukaemia may be associated with this disease {279,1302}.



Fig. 4.83 Indeterminate cell histiocytosis. Multiple firm, asymptomatic papulonodules on the trunk, ranging in size from few millimetres to 1 cm, varying in colour from dark red to brownish.

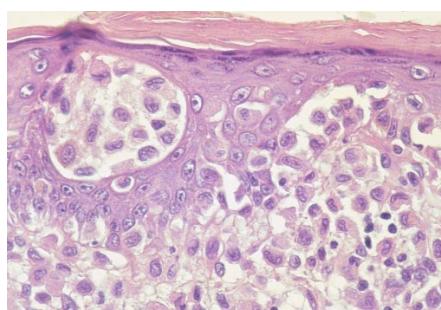


Fig. 4.84 Indeterminate cell histiocytosis. The proliferating cells show an irregular, often reniform, vesicular nucleus, surrounded by abundant pale cytoplasm. From: R. Caputo {378}.

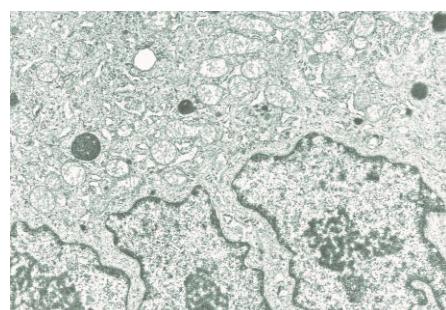


Fig. 4.85 The proliferating cells reveal an indented nucleus and an abundant cytoplasm with lysosomes, phagosomes and a well developed endoplasmic reticulum. Birbeck granules are absent.

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)

B. Zelger
S. Kohler
W. Burgdorf

Definition

Sinus histiocytosis with massive lymphadenopathy is a reactive condition of unknown etiology, characterized by a proliferation of histiocytes which usually exhibit emperipoleisis of lymphocytes. The disease can mimic lymphoma. Extranodal involvement is frequent.

Synonyms

Sinus histiocytosis with massive lymphadenopathy, Rosai-Dorfman disease

Epidemiology

Sinus histiocytosis is a rare non-neoplastic disease. Lymph nodes are predominantly affected in children and young male adults; the cutaneous form is particularly seen during the third and fourth decades in female patients {74,307,483}.

Etiology

The etiology is unknown. Lesions are polyclonal, probably the consequence of a cytokine dysregulation {1603}.

Localization

Cervical lymph node involvement is most characteristic. Cutaneous lesions frequently occur on the head and neck, mucous lesions {1105,2498} in the nose

and paranasal sinus. Extranodal disease may also affect any other organ {2455}.

Clinical features

Children with massive cervical lymph node swellings frequently suffer from fever and malaise. Laboratory tests show leukocytosis, anemia, polyclonal hypergammaglobulinaemia and an accelerated erythrocyte sedimentation rate. Extranodal involvement is common, up to 40%. Pure cutaneous forms are rare; solitary, clustered or wide-spread, red to brownish papules, rarely plaques and nodules are seen. Regression leaves atrophic, brown macules.

Histopathology

Lymph node architecture is replaced by sheets of faintly stained ("clear") to slightly eosinophilic macrophages. In extranodal location infiltrates frequently simulate lymph node sinuses ("sinusoidal pattern").

Emperipoleisis of lymphocytes, erythrocytes or other nuclear debris is prominent, but not specific; it can also be seen in, e.g., subcutaneous T-cell lymphomas. Lymphocytes, plasma cells, neutrophils and fibrosclerosis are found to a variable degree.

Immunohistochemistry

Macrophages are positive for CD68 (PGM1, KP1) and S100 protein; CD1a, factor XIIIa and CD34 are negative {1796}.

Electron microscopy

Macrophages ingest intact lymphocytes. Phagolysosomal structures, but no Birbeck granules are found.

Prognosis and predictive factors

Manifestation in children and lymph node involvement are more readily and rapidly associated with regression than in adults and spread to extranodal sites. The vast majority of lesions is self-limited and benign. Rare fatalities have been associated with immunologic disorders, lymphomas of Hodgkin and non-Hodgkin type, leukaemias {62}, and exceptional cases with solid tumours {1900}.

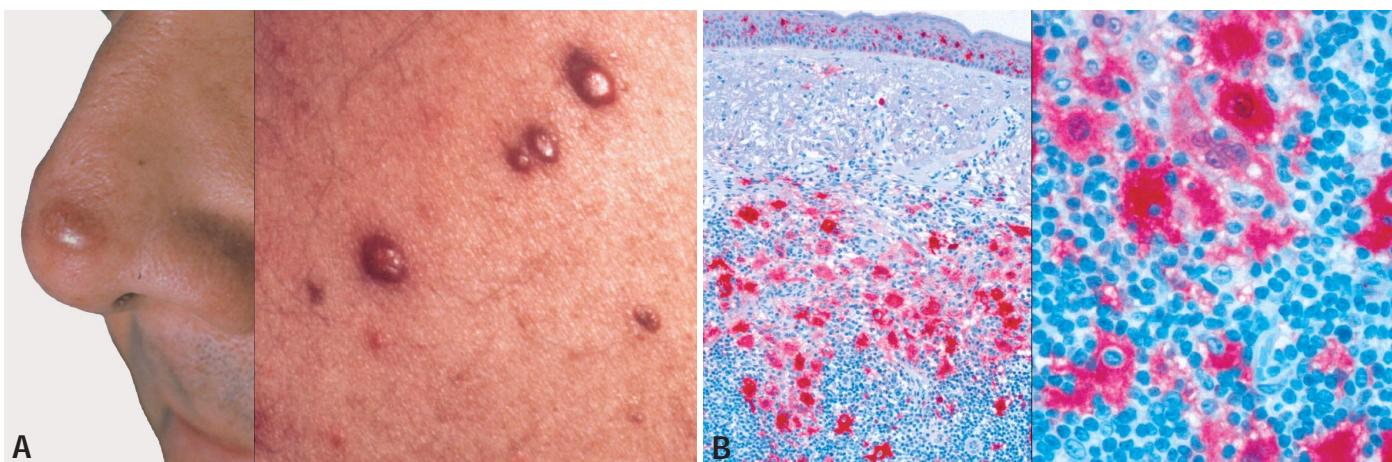


Fig. 4.86 Sinus histiocytosis with massive lymphadenopathy. **A** Left: Brownish nodule of sinus histiocytosis on the nose. 1595 Right: Clustered brownish papules of sinus histiocytosis on the trunk. **B** Left: Sheets of macrophages in sinus histiocytosis positive for S100 protein. Right: Lymphocytes within cytoplasm of histiocytes, i.e., emperipoleisis.

Juvenile xanthogranuloma

R. Caputo
B. Zelger

Definition

Juvenile xanthogranuloma (JXG) is a benign, self-healing, non-Langerhans-cell (LC) histiocytosis most frequently seen in infants and children, characterized by yellowish asymptomatic papules and/or nodules located in the skin and other organs and consisting of an infiltrate of macrophages with a variable degree of lipidization in the absence of a metabolic disorder.

Synonyms

Xanthoma multiplex {33}; Nevoxanthoendothelioma {1551}.

Epidemiology

JXG is the most common form of non LC histiocytosis {378,824}. JXG appears within the first year of life in about 75% of cases; in 15-30% it is present at birth.

Etiology

The etiology is unknown. Foamy cells constitute the main part of the mature lesions of JXG and accumulate lipids, despite normal levels of plasma lipids. It has been suggested {208} that the uptake of low-density lipoprotein cholesterol and the biosynthesis of intracellular cholesterol are both enhanced; such enhancement might play a role in the process of accumulation of cholesterol esters in the macrophage.

Localization

Cutaneous lesions are irregularly scattered throughout the skin without a tendency to cluster, and are mainly located on the upper part of the body {378,824}. Mucous membranes may rarely be involved.

The most common extracutaneous mani-

festation of JXG (occurring mainly in the papular and subcutaneous {256} forms) is ocular involvement {256,614,2045, 2603}. Ocular lesions may occur in about 1-10% of affected children and are almost always unilateral and may lead to haemorrhage and glaucoma. Such lesions may precede or follow the cutaneous lesions. The nodular variant of JXG may occasionally be related to systemic lesions of lungs, bones, kidneys, pericardium, colon, ovaries, testes and central nervous system {378,824,2536}.

Clinical features

Two main clinical variants can be distinguished: a papular form and a nodular form {824}

The *papular form* is the most frequent and is characterized by numerous (up to 100), firm hemispheric lesions, 2-5 mm in diameter, that are red-brown at first and then quickly turn yellowish. These lesions are associated in perhaps 20% of patients with café-au-lait spots of neurofibromatosis {1140} and may be related to juvenile chronic myeloid leukaemia {538,1650}.

The *nodular form* is less frequent, and is marked by one or a few lesions. The nodules are round to oval, 1-2 cm in diameter, high-domed, shiny, translucent, yellowish or red brown and sometimes show telangiectasias on their surface. The term giant JXG has been used to indicate lesions larger than 2 cm. Unusual clinical variants {378,383} are the mixed form (simultaneous presence of both papules and nodules) and the form en plaque, a group of JXG lesions with a tendency to coalesce into a plaque as the only expression of the disease.

Histopathology

Early lesions are characterized by a dense infiltrate of monomorphous, non-lipid containing, macrophages with abundant, slightly eosinophilic, cytoplasm {378,824}. With time the cytoplasm of macrophages becomes laden with lipid and appears foamy.

Mature lesions contain foamy cells, for-



Fig. 4.87 Juvenile xanthogranuloma. **A** Mixed form: this form is characterized by the simultaneous presence of both red brown papules and nodules, irregularly scattered throughout the skin. Previously published by R. Caputo in "Text Atlas of Histiocytic Syndromes. A Dermatological Perspective", Martin Dunitz, London 1998 {378}. **B** Plaqueform: this cluster of yellow nodules on the back of the neck is the only expression of the disease. **C** Nodular form: a round, high-domed, yellow brown nodule on the right shoulder.

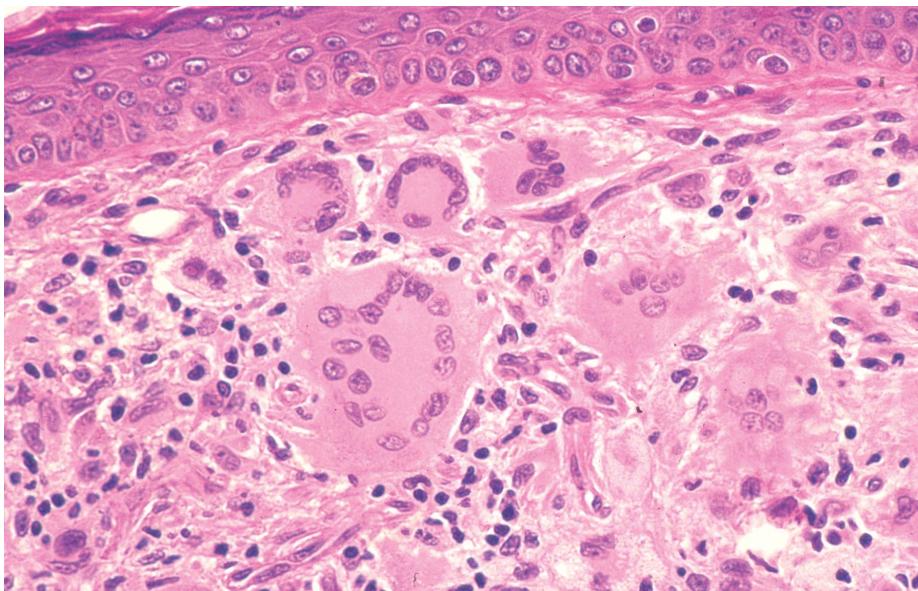


Fig. 4.88 Juvenile xanthogranuloma. Conventional microscopy. In mature lesions, giant cells are mainly distributed in the superficial dermis and on the border of the infiltrate. From: R. Caputo (378).

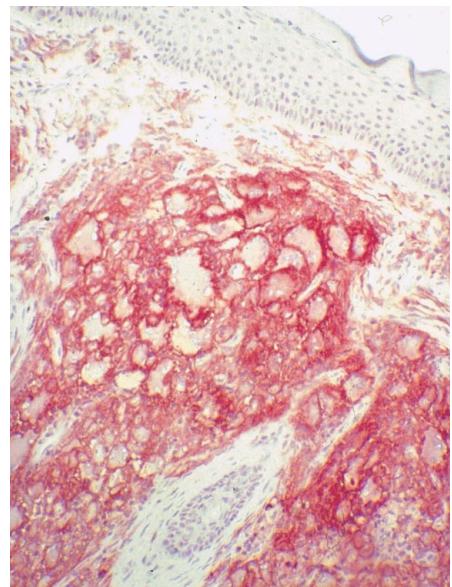


Fig. 4.89 Juvenile xanthogranuloma. Frozen section showing large macrophages stained by CD14.

eign body giant cells and Touton giant cells, mainly distributed in the superficial dermis and on the border of the infiltrate. In addition to macrophages and foamy cells, there may be lymphocytes, eosinophils, neutrophils and plasma cells scattered throughout the lesion. In older lesions fibrosis replaces the cellular infiltrate, and lipids are not present extracellularly.

Immunohistochemistry

Immunohistochemically {824,2049} macrophages and Touton cells show a uniform positive staining with CD14, CD68, HAM56 (markers with specificity for macrophages) and vimentin, frequent positive staining for factor XIII (markers of dermal dendrocytes) and for cathepsin B and occasional staining for MAC387 (a marker for monocytes and macrophages).

S100 protein, CD1a (OKT6), CD15 (Leu M1) and peanut agglutinin (PNA) are not usually expressed on the macrophages of JXG.

Electron microscopy

Under the electron microscope {378, 824}, the macrophages that characterize the early stage of the disease exhibit pleomorphic nuclei, are rich in pseudopods, and contain many elongated and irregular dense bodies.

Clusters of comma-shaped bodies, but

no Langerhans granules (LG) can occasionally be observed. In older lesions there is a predominance of foamy cells, the cytoplasm of which is completely filled with lipid vacuoles, cholesterol clefts, and myeloid bodies. The cells corresponding to Touton giant cells are large (150-250 µm) and sometimes contain more than 10 nuclei. At their periphery, such cells are rich in lipid material, whereas in their centre, mitochondria and lysosomes predominate.

Genetics

JXG is not linked to any genetic locus, but the association with café-au-lait spots of neurofibromatosis (NF1) {2536} and the occasional association with neurilemmomatosis (NF2) {1115} suggests that a JXG locus could reside on

chromosome 17q11.2 or 22q12. Clinical {1115} and genetic analyses {1056} indicate that neurilemmomatosis and neurofibromatosis type 2 (NF2) genes are identical.

Prognosis and predictive factors

The papules and nodules of the skin tend to flatten with time and both the skin and most of the visceral lesions disappear spontaneously within 3-6 years. A few cases of JXG with fatal evolution, probably due to central nervous system involvement {378} or fatal liver disease {614}, have been reported. In JXG periodic complete blood count and peripheral smears would be judicious during a patient's first two years of life, which is the time of the peak incidence for juvenile chronic myeloid leukaemia.

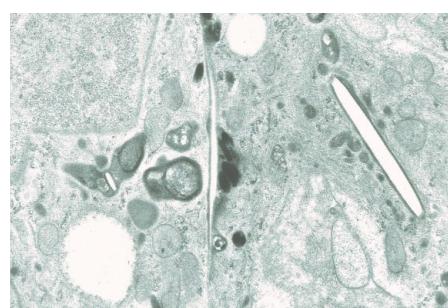


Fig. 4.90 Juvenile xanthogranuloma. Electron microscopy. This large macrophage exhibits lipid droplets, myeloid bodies and cholesterol clefts.

Reticulohistiocytosis

E. Berti
B. Zelger
R. Caputo

Definition

Reticulohistiocytosis of the skin represents a spectrum of rare clinical entities, ranging from the solitary cutaneous form (SCR) through the generalized cutaneous form without systemic involvement (GCR), to multicentric reticulohistiocytosis with systemic involvement (MR). The skin lesions in all these conditions demonstrate an identical histological pattern, characterized by numerous mononucleated or multinucleated macrophages with abundant, eosinophilic, homogeneous to finely granular cytoplasm with a characteristic ground-glass appearance.

Synonyms

Giant cell reticulohistiocytosis, giant cell histiocytosis; cutaneous reticulohistiocytoma, reticulomatosis with giant cell histiocytes; normocholesterolemic xanthomatosis; lipoid dermatitis; lipoid rheumatism; multicentric reticulohistiocytosis; non-diabetic cutaneous xanthomatosis; reticulohistiocytic granuloma; reticulohistiocytosis of the skin and synovia.

Epidemiology

Reticulohistiocytosis mostly occurs in adults over 40 years of age, but the disease may appear during adolescence: SCR and GCR have been also observed in children. In adults, the most frequent variant is MR, with about 50 and GCR with 10 patients reported in the literature.

There is no preference for either sex {167,465,1405,1462}.

Etiology

The etiopathogenesis is unknown. Reticulohistiocytosis may represent an abnormal macrophage response to different stimuli. In solitary forms, local trauma such as insect bites, folliculitis or ruptured infundibular cysts may play a role {379}, while in systemic forms the association with autoimmune disorders and internal malignancies suggests an immunological basis for the initiation of this reaction {1752}.

Localization

SCR involves mainly the head and the neck, but may be found in any cutaneous site {382,1082}. In GCR the lesions are widely scattered on the skin {381,547,847,2363}. In MR {167,413,465,1405,1752} skin lesions preferentially affect the fingers, the palms and the back of the hands, the juxta-articular regions of the limbs and the face. Oral, nasal and pharyngeal mucosa are involved in 50% of cases. Osteoarticular lesions involve mainly the hands (80%), knee (70%) and wrists (65%).

Clinical features

The solitary cutaneous reticulohistiocytosis (SCR) or reticulohistiocytoma cutis {382,1082} is characterized by a single, firm, rapidly growing nodule varying in colour from yellow-brown to dark-red.

The lesion is often clinically misdiagnosed, it occurs without evidence of systemic involvement, and its onset may be preceded by trauma.

Generalized cutaneous histiocytosis (GCR) {381,547,847,2363} is a purely cutaneous form characterized by the eruption of firm, smooth, asymptomatic papulonodular lesions, 3-10 mm in diameter. The colour of the recent lesions is pink-yellow, while the older lesions show a red-brown colour. Joint and visceral lesions are absent. Possibly, this purely cutaneous form could represent an early stage of multicentric reticulohistiocytosis, before the appearance of joint or visceral lesions.

The term multicentric reticulohistiocytosis {167,413,465,1405,1752} is used to indicate a form of reticulohistiocytosis characterized by the association of a cutaneous and mucous membrane papulonodular eruption with severe arthropathy and other visceral symptoms. The papulonodular lesions range in diameter from a few mm to 2 cm, and are round, translucent and yellow-rose or yellow-brown in colour. Grouping of lesions into plaques can give a cobblestone appearance, but lesions are mostly scattered and isolated. They do not tend to ulcerate, and are pruritic in about one-third of cases. Osteoarticular manifestations cause severe chronic polyarthritis with arthralgias, and are the initial sign of the disease in about 5-65% of cases {167,465,1405}. The osteoarticular lesions



Fig. 4.91 Multicentric reticulohistiocytosis. **A** Purplish-brown, firm nodules characteristically affect the fingers. Periungual papules are arranged about the nail folds. **B** Papulonodular lesions are spread on the face, lips and oral mucosa. Mucous membranes are involved in about 50% of cases. **C** Symmetrical involvement of the knees. In this patient, osteoarticular manifestations were the initial sign of the disease. From: R. Caputo {378}

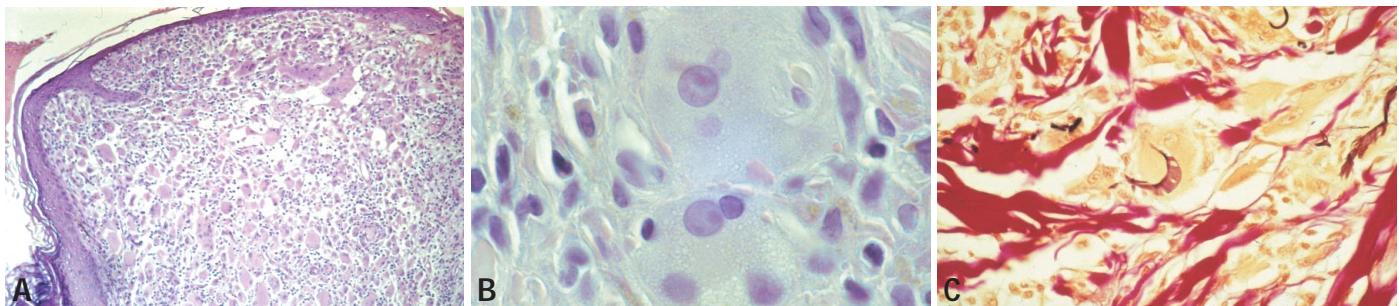


Fig. 4.92 Reticulohistiocytosis. **A** Conventional microscopy: the histological pattern of the lesions is characterized by the presence of numerous, large, mononucleated histiocytes with an abundant eosinophilic, finely granular cytoplasm. **B** Conventional microscopy: in these giant cells showing leukocyte phagocytosis, the typical ground-glass appearance of the cytoplasm is evident. **C** Conventional microscopy: Weigert-Van Gieson staining. Collagen phagocytosis is an occasional finding.

show a progressive destructive course of 6-8 years, and then become stable. Other systemic localizations, histopathologically documented are very rare. Muscular {667} (myositis, myotonia and myoatrophy), cardiopulmonary {532} (pericarditis, cardiac insufficiency, pleuritis, pulmonary infiltration), ocular {667} (exophthalmos, conjunctival infiltration), gastric (gastric ulcer), thyroid (thyroid nodules) and submandibular salivary gland involvements have occasionally been reported. Fever, weight loss and weakness can be present. In MR there is an association with a variety of autoimmune disorders such as dermatomyositis, lupus erythematosus, or Hashimoto thyroiditis as well as internal malignancies in 15-27% of cases {167,413,1405, 1752}. Solid tumours such as bronchial, breast, stomach and cervical carcinomas are most common. Lymphomas and myelodysplastic syndromes have been found less frequently.

Histopathology

The histological findings in the three types of reticulohistiocytosis and in the different tissues are identical {167,465, 1405,1462}. Early lesions are composed of macrophages and lymphocytes, and therefore may be confused with other histiocytoses of the skin. Older lesions show the characteristic histological pattern: the presence of numerous large, mononuclear or multinucleated macrophages with an abundance of eosinophilic, homogeneous to finely granular cytoplasm having a ground glass appearance. At times, phagocytosis of connective tissue and/or cellular components may be seen {379,532}. Histochemically, the granular material in macrophages and giant cells stains with periodic acid-Schiff, Sudan black and

scarlet red, indicating the presence of glycolipids and/or glycoproteins and neutral fat {167}.

Immunohistochemistry

Macrophages stain with macrophage markers KP1/PGM1 (CD68), Ki-M1p, and for the mesenchymal epitope of vimentin, and show variable reactivity with HAM56 and for factor XIIIa, lysozyme and $\alpha 1$ -antitrypsin {381,382,424,2027,2585}. In contrast, these cells are usually negative for CD1 α , S100 protein, Leu-M1 (CD15) and MAC387. Rare exceptions have been reported. According to Zelger et al. {2585}, SCR differs histopathologically and immunohistochemically from MR as lesions are better circumscribed, multinucleated giant cells more prominent, gigantic and bizarre, and macrophages regularly negative for factor XIIIa in the former entity.

Electron microscopy

The infiltrate is formed by large mononuclear to multinucleated cells exhibiting numerous peripheral villi {532,667}. Nuclei are irregular and often polylobated, with nucleoplasm of medium electron density and one or two nucleoli. The

cytoplasm contains one or more Golgi apparatus, and is rich in mitochondria, lysosomes, dense bodies, phagosomes and myelin figures. The cytoplasm of about 5-40% of the cells of the infiltrate in many cases contains the so-called pleomorphic cytoplasmic inclusions {380-382,532}, varying in number from cell to cell. The pleomorphic cytoplasmic inclusions are unique and highly complex structures consisting mainly of unit membranes, occasionally surrounding electron-dense areas containing vesicles. Birbeck granules are absent. About 20% of all macrophages show collagenophagic activity {379,766}, but not pleomorphic cytoplasmic inclusions.

Prognosis and predictive factors

The purely cutaneous forms of reticulohistiocytosis (solitary and generalized) may involute spontaneously {382,847}. It is possible that the generalized purely cutaneous form is an early stage of MR, before the appearance of joint and visceral lesions {381,847}. In MR, there is no parallelism between the mucocutaneous and articular manifestations. The mucocutaneous lesions have an unpredictable course, and may remit spontaneously. In half of the patients, the osteoarticular manifestations become stable, while in the other half, they show a progressive destructive course {1405}. The prognosis is favourable for the cutaneous forms. The prognosis of MR is related to the importance of the osteoarticular manifestations and of the underlying immunological disorders and neoplasms.

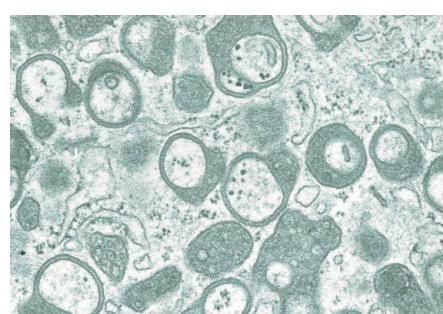


Fig. 4.93 Reticulohistiocytosis. Electron microscopy: the polymorphism of the granules is evident at higher magnification.

Mastocytosis

B.J. Longley
B.M. Henz

Definition

Mastocytosis is a heterogeneous group of disorders characterized by the abnormal growth and accumulation of a clone of mast cells in one or more organ system {1448}. Most patients have cutaneous mastocytosis (CM) with indolent disease that is confined to the skin and that may regress spontaneously. A minority of patients, usually adults, have systemic mastocytosis (SM) that may rarely be highly aggressive and associated with multi-system involvement and short survival time, or that may be associated with non-mast-cell haematopoietic malignancies {1450, 2372,2405}.

ICD-O Codes

Cutaneous mastocytosis (CM); maculopapular or plaque type mastocytosis, formerly urticaria pigmentosa (UP); telangiectatic mastocytosis, formerly

telangiectasia macularis eruptiva perstans (TMEP); diffuse cutaneous mastocytosis (DCM); solitary mastocytoma {965,2405}	9740/1
Indolent systemic mastocytosis	9741/1
Aggressive systemic mastocytosis	9741/3
Mastocytosis with associated haematopoietic disorder	9741/3
Mast cell leukaemia	9742/3

Synonyms

Mast cell disease; mast cell proliferative disease

Epidemiology

Cutaneous mastocytosis may be present at birth and usually first appears before six months of age. A second peak incidence is found in young adults in their 3rd and 4th decades. Paediatric mastocytosis usually regresses by adolescence. Adult mastocytosis is more likely to be persistent and may be associated with SM, rarely also with aggressive systemic mastocytosis. There is no clear gender or ethnic predominance of cases {964,1450}.

Etiology

The KIT protein is a receptor tyrosine kinase that is also known as the mast cell growth factor receptor. Adult mastocytosis and rare pediatric cases are associated with somatic mutations in the c-KIT proto-oncogene that alter the enzymatic site of the KIT protein {361,1449}. Rare kindreds with familial mastocytosis have germ line c-KIT mutations that affect regulatory portions of the KIT protein, also causing constitutive kinase activation. These patients may also have gastrointestinal stromal tumours (GISTs) which are known to be caused by regulatory type c-KIT activating mutations {189, 2372, 2405}.

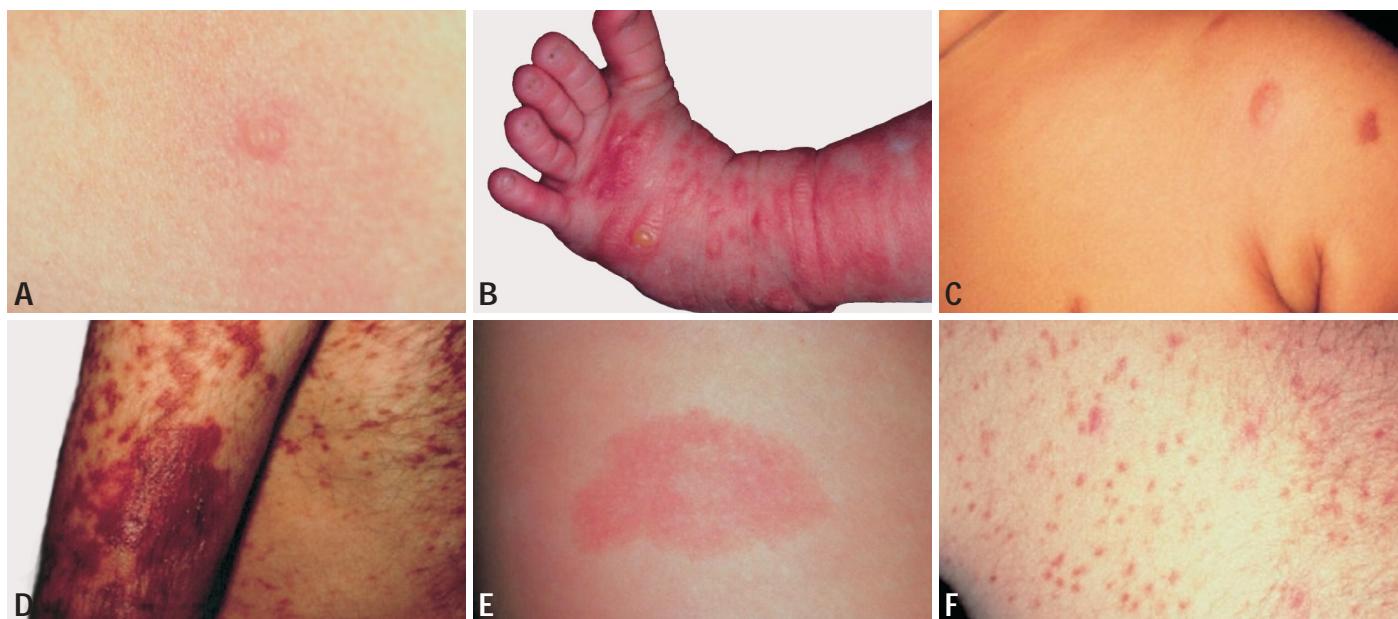


Fig. 4.94 Cutaneous mastocytosis. **A** Wheal and flare of Darier sign. The skin lesions of all forms of cutaneous mastocytosis may urticate when stroked. A palpable wheal appears a few moments after physical stimulation, due to histamine from the mast cells. **B** Tense blister containing clear fluid on skin of infant with diffuse cutaneous mastocytosis. The skin may appear thickened and reddish brown with diffuse involvement. Note the blister caused by mast cell degranulation and histamine release. Blisters may form in infants because the dermal-epidermal junction is not yet well developed. **C** Large pigmented papules of paediatric urticaria pigmentosa. **D** Reddish brown macules, patches and plaques on abdomen and arm of an adult with cutaneous and systemic mastocytosis. **E** Telangiectasia macularis eruptiva perstans form of cutaneous mastocytosis in an adult. **F** Pigmented macules of adult type urticaria pigmentosa. The number of lesions may range from a few to thousands.

1447}. In skin and bone marrow mast cells, there is also an increased expression of anti-apoptotic molecules in both paediatric and adult mastocytosis {963, 966}.

Localization

Eighty percent of patients with mastocytosis have disease confined to the skin. Conversely, of the 20% of patients with systemic mastocytosis, about half have cutaneous involvement. Essentially all patients with SM are adults and have involvement of the bone marrow, but any other organ may also be involved, most commonly the spleen, lymph nodes, or gastrointestinal tract {116,580,2224, 2372}.

Clinical features

Cutaneous mastocytosis includes several distinct clinico-pathologic entities whose morphologies include solitary tumours (Mastocytoma), maculo-papular or plaque-type lesions that are mostly symmetrically distributed (UP/TMEP), and diffuse cutaneous involvement (DCM).

stroking of any lesion of CM may cause mast cell degranulation with localized swelling or urtication (Darier sign). Clinically normal skin may also urticate when stroked, (so-called dermographism). Moderate itching is present in about half of the patients {579}. Most cutaneous lesions show an increase in epidermal melanin pigment which, combined with the tendency of these lesions to urticate, has led to the term "urticaria pigmentosa", a historic designation that has recently been proposed to be abandoned {2405}. Blistering or bullous mastocytosis is not a distinct entity but represents an exaggeration of Darier sign seen in infants whose dermo-epidermal junction is not well developed so that accumulation of edema fluid results in the formation of localized blisters {964}. Other symptoms of mastocytosis may be due to mast cell infiltration of specific organs or due to release of mast cell mediators into the circulation. Organs affected include: the gastrointestinal tract (peptic ulcer disease, diarrhoea and cramping) or the cardio-pulmonary and cardio-vascular systems (flushing, syncope, headache, seizures, hypertension, hypotension including anaphylaxis, tachycardia, and respiratory symptoms). Patients with extensive involvement may

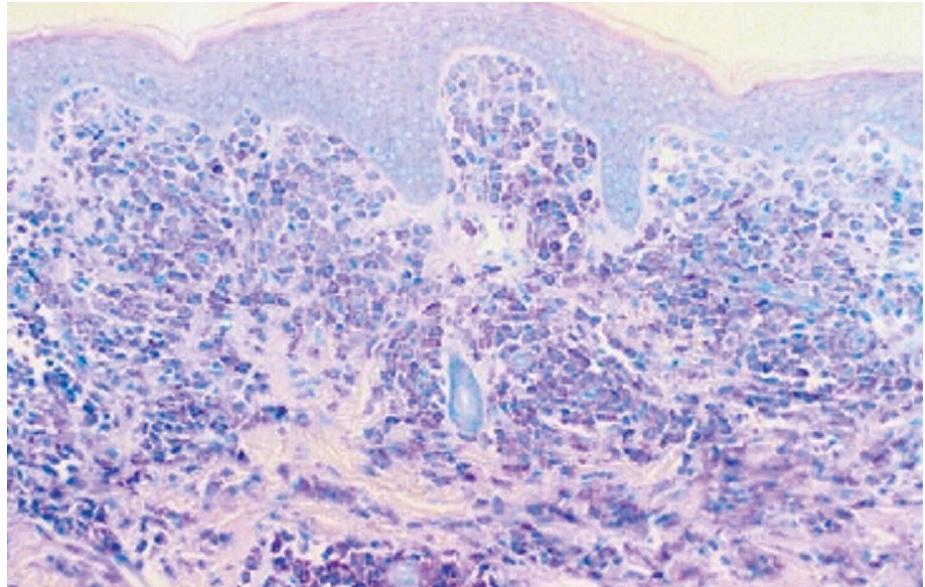


Fig. 4.95 Mastocytoma of the skin. Stains containing toluidine blue stain the mast cell cytoplasmic granules metachromatically purple.

have relatively vague constitutional symptoms including fatigue, weight loss, fever, sweats, and non-specific psychiatric symptoms {964,1450}.

Patients with SM may have also bone-related complaints such as pain, fractures, or arthralgias, secondary to direct mass effects or generalized osteoporosis.

The diagnosis of cutaneous mastocytosis is established by skin biopsy that demonstrates increased numbers of mast cells in the dermis. Imaging studies or biopsy of bone marrow or other internal organs are usually not indicated in the absence of abnormality of the peripheral blood counts or specific signs or symptoms pointing to internal organ involvement.

The clinical presentation of CM may range from subtle diffuse erythema to grossly evident, widespread doughy dermal thickening with accentuation of cutaneous surface markings, giving a so-called "grain leather", (peau chagrine) or orange skin (peau d'orange) appearance {964,1449,1450,2430,2525}. Tense blisters filled with clear fluid, occasionally slightly-tinged with blood, may be seen overlying lesions of any form of cutaneous mastocytosis in infants.

Individual lesions in young children tend to be lightly pigmented and occur as solitary nodules or multiple papules, or rarely as large heavily pigmented macules, large plaques, or diffuse infiltration of the skin {964}. Large lesions or diffuse

involvement in children may point to the presence of c-KIT activating mutations {2405}. In adolescents and adults, the individual lesions tend to be more heavily pigmented and macular, rather than papular, like those of young children. The term TMEP has been used for these macular lesions and for larger, lightly pigmented patches with telangiectasias that may rarely occur in adults {964}. Cutaneous involvement in SM usually appears morphologically identical to CM in adults, but may also show larger plaque like lesions.

Histopathology

In haematoxylin and eosin (H&E) stained sections, normal mast cells have moderately abundant, oval or polygonal shaped cytoplasms with round to oval nuclei, sometimes giving the appearance of a "fried egg". The nuclei have clumped chromatin and indistinct or inapparent nucleoli. The cytoplasms are filled with small, faintly visible, eosinophilic or amphiphilic granules which stain metachromatically with the Giemsa or toluidine blue stains. Occasionally, mast cells may be spindle shaped or show bi- or multi-lobated nuclei {1401,1450,1607, 2405}.

In normal skin, individual mast cells are found perivascularly and scattered throughout the dermis, without formation of clusters. Mast cells in mastocytosis also tend to accumulate perivascularly, and are most often evident in the super-

ficial dermis, within the dermal papillae {1401,1607}. In solitary mastocytomas and papular, nodular, or diffuse CM, the papillary and/or reticular dermis may show either scanty increases in mast cell numbers or heavy mast cell infiltrates, and there may be extension into the subcutaneous fat. In CM, individual mast cells may rarely be found in the lower epidermis. Unequivocal diagnosis of cutaneous mastocytosis requires the demonstration of aggregates of mast cells within the dermis, and this may be difficult and require multiple biopsies in the TMEP form of adult mastocytosis. Lesions of mastocytosis are usually composed of an infiltrate of monomorphous mast cells, and rarely observed infiltrating eosinophils should raise the possibility of dermal hypersensitivity reaction, parasitosis or an arthropod bite.

Immunohistochemistry

Mast cells are bone-marrow derived cells and therefore express CD45 (CLA). They also express CD117 (the KIT protein) and HLA-DR. Relatively specific mast cell markers include highly sulfated glycosaminoglycans like heparin (toluidine blue stain), tryptase and chymase. CD-2 and/or CD25 may be aberrantly expressed in mast cells of SM {934, 2404, 2405}.

Histogenesis

Mast cells are derived from CD34+ haematopoietic precursor cells {1982}.

Somatic genetics

Mastocytosis is a clonal disease in both adults and children {1448,1449}. The tumour cells of almost all cases of adult onset sporadic disease carry somatic point mutations of c-KIT that change the enzymatic site of the KIT protein, causing constitutive activation {361,1449}. Paediatric sporadic mastocytosis has also been shown to be clonal, but c-KIT activating mutations are rare {361,1449}. Very rare cases of familial mastocytosis, usually associated with GISTs tumours, are associated with germ line c-KIT mutations that activate KIT by affecting regulatory portions of the molecule, rather than the enzymatic site {189, 1447}.

ing mutations may indicate persistent disease in this population, and classification of mastocytosis based on both clinical and molecular genetic features may eventually prove to be both prognostically and therapeutically useful {1446, 1465}. In adults, although CM may be symptomatic and persist, overall survival is usually not adversely affected, even in the face of concomitant systemic involvement. Patients having aggressive variants of SM, however, may have a rapidly progressive downhill course with survival measured in months. In patients with associated haematologic malignancies, the prognosis is determined by the course of the related haematologic disease {964}.

Prognosis and predictive factors

Patients with mastocytosis confined to the skin generally have a good prognosis, and cutaneous involvement is usually an indicator of a relatively better prognosis in SM. CM in paediatric patients with solitary mastocytomas or typical papular and macular rashes usually regresses by adolescence. The presence of enzymatic site type KIT activat-



CHAPTER 5

Soft Tissue Tumours

Most soft tissue tumours are benign, outnumbering malignant ones by about 100 to 1. Soft tissue sarcomas comprise over 50 histological types, many of which have more than one subtype. Their behaviour varies from indolent to very aggressive, with consequent variation in survival, according to histological type, grade, and sometimes genetic constitution, but the overall 5 year survival is about 65-75%. In general, sarcomas in skin or subcutis have a more favourable outcome than those located beneath deep fascia. Only those tumours with a predilection for the skin, and not already covered in the WHO Classification of Tumours of Soft Tissue and Bone are described in this chapter.

WHO histological classification of soft tissue tumours

Vascular tumour		Smooth and skeletal muscle tumours	
Haemangioma of infancy	9131/0	Pilar leiomyoma	8890/0
Cherry haemangioma	9120/0	Cutaneous leiomyosarcoma	8890/3
Sinusoidal haemangioma	9120/0		
Hobnail haemangioma	9120/0	Fibrous, fibrohistiocytic and histiocytic tumours	
Glomeruloid haemangioma	9120/0	Dermatomyofibroma	8824/0
Microvenular haemangioma	9120/0	Infantile myofibromatosis	8824/1
Angiolymphoid hyperplasia with eosinophilia		Sclerotic fibroma	8823/0
Spindle cell haemangioma	9136/0	Pleomorphic fibroma	8832/0
Tufted angioma	9161/0	Giant cell fibroblastoma	8834/1
Arteriovenous haemangioma	9123/0	Dermatofibrosarcoma protuberans	8832/3
Cutaneous angiosarcoma	9120/3	Dermatofibroma (fibrous histiocytoma)	8832/0
Lymphatic tumours			
Lymphangioma circumscripum	9170/0		
Progressive lymphangioma	9170/0		

¹ Morphology code of the International Classification of Diseases for Oncology (ICD-O) {786} and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

TNM classification of soft tissue sarcomas

Primary Tumour (T)		G Histopathological Grading <i>Translation table for three and four grade to two grade (low vs. high grade) system</i>			
TX:	Primary tumour cannot be assessed	TNM two grade system	Three grade systems	Four grade systems	
T0:	No evidence of primary tumour	Low Grade	Grade 1	Grade 1	
T1:	Tumour ≤ 5cm in greatest dimension			Grade 2	
	T1a: superficial tumour*				
	T1b: deep tumour			Grade 3	
T2:	Tumour > 5cm in greatest dimension	High Grade	Grade 2		
	T2a: superficial tumour		Grade 3	Grade 4	
	T2b: deep tumour				
Regional lymph nodes (N)		Stage grouping			
NX:	regional lymph nodes cannot be assessed	Stage IA	T1a	NO,NX	MO
N0:	no regional lymph node metastasis		T1b	NO,NX	MO
N1:	regional lymph node metastasis	Stage IB	T2a	NO,NX	MO
			T2b	NO,NX	MO
Notes: Regional node involvement is rare and cases in which nodal status is not assessed either clinically or pathologically could be considered N0 instead of NX or pNX.		Stage IIA	T1a	NO,NX	MO
			T1b	NO,NX	MO
		Stage IIB	T2a	NO,NX	MO
		Stage III	T2b	NO,NX	MO
Distant metastasis (M)		Stage IV	Any T	N1	MO
M0:	no distant metastasis		Any T	Any T	M1
M1:	distant metastasis				Any grade
<hr/>					
From references {892,2219}. Superficial tumour is located exclusively above the superficial fascia without invasion of the fascia; deep tumour is located either exclusively beneath the superficial fascia, or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal and pelvic sarcomas are classified as deep tumours.					

Soft tissue tumours: Introduction

C. Fisher

Epidemiology

Age-standardized incidence rates of soft tissue sarcomas, which are fairly constant in most areas covered by cancer registration, range from 1-3 per hundred thousand population {1781}. Sarcomas of cutaneous origin are relatively rare, and are far outnumbered by carcinomas, melanoma and benign mesenchymal neoplasms of skin and subcutis (superficial soft tissue). The most common benign tumours are lipomas, fibrous histiocytomas, vascular or smooth muscle lesions including angioleiomyomas, and nerve sheath tumours (schwannoma, neurofibroma). Some of these tumours are covered elsewhere {756}. The vast majority are located superficially and do not exceed 5 cm in diameter.

Sarcomas are mostly found in older adults. They arise mainly in the extremities, especially the thigh, followed by trunk, head and neck and retroperitoneum.

Etiology

Most soft tissue sarcomas arise spontaneously and are of unknown etiology. A small number arise in rare familial cancer syndromes with germline mutations. A number of other congenital and inherited syndromes are associated with benign and malignant soft tissue tumours; type examples include Mafucci syndrome (chondroid and vascular tumours) and Cowden disease (lipomas, haemangiomas). Further details can be found in the WHO Classification of Tumours of Soft Tissue and Bone {756}.

Non-hereditary genetic factors are also presumed to be pathogenetic in various tumour types which have consistent chromosomal translocations, although it is not known how or in what cell these rearrangements arise. Viruses associated with sarcomas include human herpes virus 8 (HHV8) in Kaposi sarcoma {434,2487}, and EBV in some smooth muscle tumours in children and adults with immunosuppression, including transplant recipients and patients with HIV infection {1390,1547}. Angiosarcoma

complicating longstanding lymphoedema, especially after radical mastectomy (Stewart-Treves) might also be due to local immunosuppression {1995}.

An association between exposure to herbicides, including dioxin, and sarcomagenesis is controversial and remains unproven. Sarcomas can arise in the field of prior therapeutic irradiation. This is a dose- and time-related phenomenon, resulting mostly in subfascial, high-grade pleomorphic sarcomas after an interval of 5 or more years. Following irradiation for carcinoma of breast, low-grade cutaneous angiosarcomas have been described after an interval as short as 18 months {1772}.

Clinical features

Benign and malignant tumours present as usually painless masses, with varying growth rate. Cutaneous lesions form a plaque or elevated nodule that can ulcerate when malignant. Large (>5 cm) superficial lesions, and all subfascial or deep-seated tumours, should be referred to a specialist multidisciplinary centre before surgery and preferably before biopsy {180}.

Pathology

In general, malignant soft tissue neoplasms are characterized by nuclear pleomorphism, mitotic activity including abnormal forms, necrosis and vascular invasion. Some benign tumours, however, can show one or more of these features. Examples include nuclear atypia in cutaneous pleomorphic fibroma and atypical benign fibrous histiocytoma (which can also display necrosis), and frequent mitoses in nodular fasciitis. Detailed diagnostic criteria are provided for each subtype.

Diagnostic procedures

Investigation includes clinical assessment of size and depth of tumour, the use of imaging modalities, and biopsy.

Imaging

Imaging is of value for assessing the

extent of a primary tumour and its relationship to normal structures, and for revealing metastases. Both computerized tomography (CT) and magnetic resonance imaging (MRI) are used. CT is particularly useful for tumours in body cavities, and for detecting pulmonary metastases. MRI can demonstrate intratumoural heterogeneity, including presence of solid, fatty, fibrous, haemorrhagic or necrotic tissue, and the interface between neoplastic and normal tissue including involvement of neurovascular bundles.

Biopsy

Superficial lesions smaller than 2-5 cm in diameter can be excised in their entirety. Larger ones, and all subfascial and deep-seated tumours need diagnostic sampling. For this, some practitioners prefer open incisional biopsy with an appropriately placed incision that is subsequently excised in continuity with the formal resection. Needle core biopsy, preferably using a Trucut or larger needle can provide diagnostic information for malignancy, subtype and grade, with high sensitivity and specificity in experienced hands {1021,1040}. Fine-needle aspiration cytology is used in a few centres where a large volume of cases allows accrual of sufficient experience {46}; it is not particularly sensitive for diagnosing malignancy in differentiated adipose or in sub-typing low-grade myxoid lesions, partly because the sample might not be representative.

Tumour spread and staging

The recent WHO classification of Tumours of Soft Tissue and Bone {756} recognizes three behavioural categories:

1. Benign tumours. These rarely recur locally, and those that recur do so in a non-destructive fashion and are usually cured by local excision. Exceptionally rarely, an otherwise (and histologically typical) benign tumour, such as cutaneous fibrous histiocytoma, can metastasize.
2. Intermediate tumours are those that

are locally aggressive and/or very occasionally metastasizing. Locally aggressive tumours, such as fibromatosis, recur locally and infiltrate surrounding tissues. Rarely-metastasizing tumours are generally dermal or subcutaneous tumours which have a low (1-2%) but definite risk of metastasis, most often to regional lymph nodes but occasionally to lung. Examples are recorded for plexiform fibrohistiocytic tumour {2028} and angiomyxoid fibrous histiocytoma {693}. 3. Malignant tumours infiltrate and recur locally and have an appreciable risk of metastasis (exceeding 20%).

Grading

This is an attempt to predict clinical behaviour based on histological variables. Grading of a tumour should be done on material from a primary untreated neoplasm, though change (increase) of grade can be noted in recurrent or metastatic tumour. It is not applicable to all sarcomas; for example, angiosarcoma, clear cell sarcoma and epithelioid sarcoma are always considered to be of high-grade malignancy. Several grading systems have been proposed, but that of the French Cancer Centres is gaining wide usage {917}. Briefly, tumours are given a score of 1,2 or 3 depending on degree of differentiation; 1, 2 or 3 for number of mitoses per 10 hpf (<10, 11-20, or >20); and 0-2 for amount of necro-

sis (0, <50%, >50%). A total score count of 2 or 3 is classified as grade 1, a score count of 4 or 5 as 2, and a score of 6, 7 or 8 as grade 3.

Staging

A widely used staging system for soft tissue sarcomas is that of the International Union against Cancer (UICC) (TNM system) and American Joint Commission on Cancer (AJCC) {892,2219}. Unlike for many other tumours, staging of sarcomas includes histological grading as well as tumour size and depth from surface, regional lymph node involvement and distant metastasis.

Prognosis and predictive factors

Completeness of excision (assessed by clear surgical margins in the excision specimen) is the most important factor in prevention of local recurrence {2376}. Some sarcomas, notably epithelioid sarcoma, are relentlessly recurrent, even though they might not metastasize until late in the course of the disease {2238}. For metastasis, general adverse factors are large tumour size and increasing depth from surface. Thus, cutaneous sarcomas have a lower risk of metastasis than those located more deeply {2001}; indeed, histologically malignant leiomyosarcomas confined to skin are essentially non-metastasizing tumours {1164}. In some instances, histological

subtype is predictive, but one of the principal factors in assessing prognosis and determining management is the histological grade. Low-grade sarcomas, however, when located in sites where complete surgical excision is difficult, such as retroperitoneum or head and neck, have a worse outcome than similar tumours in the extremities. Molecular genetic findings, especially fusion gene types, might relate to prognosis.

Vascular tumours

Haemangioma of infancy

Definition

Haemangioma of infancy (HOI) is a proliferation of benign capillaries characterized by perinatal or congenital onset, rapid proliferation in the first year, followed by spontaneous regression. Strong expression of GLUT1 is distinctive.

ICD-O code 9131/0

Synonyms

Infantile haemangioma, juvenile haemangioma.

Epidemiology

HOI is the most common tumour of infancy, affecting up to 10-12% of children {1051,1119}. There is a predilection for females (at least 3:1) {1663}, Caucasians and premature infants {1051,1853}. Presentation is exclusively in infants, although involuting lesions persist into childhood.

Etiology

The unique immunophenotypic resemblance of HOI and placental vessels suggests shared regulatory mechanisms, or possibly a common cellular origin {1723}. Two recent studies have demonstrated endothelial cell clonality in HOI {295,2452}, suggesting a possible role for somatic mutation {2452}.

Localization

It most commonly affects the skin and subcutis of the head and neck, followed by the trunk and extremities. Visceral involvement, although rare, is most common in the liver, followed by the lung, brain, and intestine {746}.

Clinical features

Nascent lesions appear as blanched macules or erythematous patches, often with central telangiectasias, typically around 2 weeks of age. Approximately 30% are congenital. Following a rapid growth phase of 3-18 months, involution occurs over several years, often leaving

a fibrofatty residuum. Most develop as focal masses, although some show a diffuse, segmentally distributed pattern {2453}. Although usually solitary, many affected infants have several lesions. Rare cases of "diffuse neonatal haemangiomatosis" have multiple small skin lesions accompanied by visceral lesions {1454}. Large facial haemangiomas may be associated with posterior fossa malformations, aortic coarctation, cardiac defects, arterial abnormalities, eye abnormalities, and sternal clefting (PHACES syndrome) {1591}. Lumbo-sacral haemangiomas may be associated with spinal dysraphism, tethered cord syndrome, and other caudal abnormalities {850}. MRI in the proliferative phase shows a tumoural mass with flow voids.

Macroscopy

Proliferative phase lesions show solid tan lobules, are well-defined but not encapsulated.

Histopathology

Proliferative phase lesions are cellular masses of plump endothelial cells and pericytes with abundant cytoplasm and enlarged nuclei that together form capillaries with tiny rounded lumina. Investing basement membranes are multilaminated; mast cells are numerous. The capillaries are arranged in delicately defined lobules, separated by thin fibrous septi or normal intervening tissue. Mitotic figures may be numerous; supportive arteries and veins are prominent.

During involution, endothelial cells and pericytes flatten, lumina enlarge, and mitotic figures diminish. Capillaries progressively drop out and are replaced by loose connective tissue. End-stage lesions often show isolated groups of "ghost" vessels composed of thick, acellular basement membrane rings containing apoptotic debris.

Immunohistochemistry

All stages are distinguished from other vascular tumours by their strong endothelial positivity for several antigens,

O. P. Sangueza
R.C. Kasper
P. LeBoit
E. Calonje
K.C. Lee
J. K.C. Chan
I. Sanchez-Carpintero

M.C. Mihm, Jr.
K.J. Smith
H.G. Skelton
E.J. Glusac
G.F. Kao
P.E. North
D. Weedon

including GLUT1, Lewis Y antigen, FcgRII, and IGF-II {1722,1723,1942}. Basement membranes strongly express merosin {1723}.

Differential diagnosis

Proliferative phase HOI must be distinguished from other cellular vascular proliferations including congenital non-progressive haemangioma, kaposiform haemangioendothelioma, tufted angioma, pyogenic granuloma, and intramuscular haemangioma. Involuting HOI may mimic vascular malformations. The characteristic GLUT1 immunoreactivity of HOI is helpful in routinely fixed specimens {1722}.

Somatic genetics

HOI are generally sporadic, although autosomal dominant inheritance has been suggested in several kindreds {259}. Monozygotic and dizygotic twins show no significant difference in concordance for haemangioma development {464}. No cytogenetic abnormalities have been reported.

Cherry haemangioma

Definition

Cherry haemangioma (CH) is a benign, acquired, well-circumscribed aggregate of dilated capillaries and venules in the superficial dermis.

ICD-O code 9120/0

Synonyms

Campbell de Morgan spots, de Morgan spots, senile haemangioma.

Epidemiology

CH is rare before puberty, with a few lesions developing in early adulthood. Number and incidence increase through adulthood, becoming almost universally present with large numbers in some patients. Sex predilection is not a feature, with the exception of lesions that can occur in pregnancy {169}.

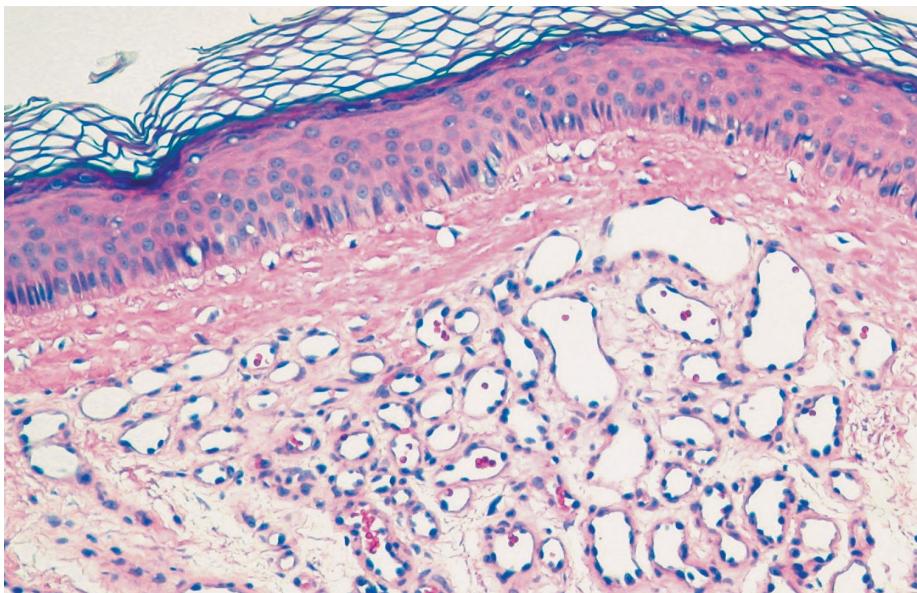


Fig. 5.1 Cherry haemangioma. Thickened basement membrane material around some vessels and protuberant endothelial cells.

Etiology

Age is the most common factor in the development of the majority of lesions. Eruptive cases have been reported after exposure to sulphur, mustard gas, bromide compounds and 2-butoxyethanol solvent {510,747,1901}. There are two reports of outbreaks in populations, without definite causes {1058,2145}. CH lesions that develop in pregnancy can involute in the puerperium and eruptive lesions have been reported in two patients with elevated prolactin levels suggesting a hormonal factor in some lesions {169,1924}.

Localization

The majority of lesions are located on the trunk and upper limbs with relative sparing of the head and neck. There is no predilection for exposed skin.

Clinical features

CH begins as a barely discernible red macule that enlarges to become a slightly elevated erythematous papule 1–5 mm in diameter. It may resist blanching with pressure.

Histopathology

CH is a tightly grouped, well-circumscribed collection of capillary vessels and venules in the superficial dermis with minimal dilatation of some lumina. Elevated lesions show epidermal atrophy with loss of rete ridges and sometimes an epithelial collar.

Endothelial cell nuclei may be protuberant. Sheaths of hyaline multilayered basement membrane material composed of laminin, collagen IV and collagen VI surround most vessels {2317}. Stromal mast cells may be increased compared to normal skin {938}. The endothelial cells are fenestrated and show high levels of carbonic anhydrase {668}. Ki-67 proliferating cell marker is not positive in endothelial cells of CH {2388}.

Histogenesis

Ultrastructural three-dimensional studies show that CH is composed of interconnected spherical and tubular dilatations of venous capillaries and postcapillary venules in the dermal papillae {303}.

Somatic genetics

A genetic or angiogenic factor has not yet been implicated in the development of CH.

Sinusoidal haemangioma

Definition

Sinusoidal haemangioma is a benign vascular neoplasm in which cavernous appearing vascular spaces occur in a well circumscribed, generally small papule or nodule. Most clinicians use the term cavernous haemangioma to refer to much larger and more poorly circumscribed lesions in infants.

ICD-O code

9120/0

Synonym

Cavernous haemangioma (erroneous, in part).

Epidemiology

Most reported cases are in adult women.

Localization

The arms and torso are the most common sites {366}.

Clinical features

Most sinusoidal haemangiomas are freely movable deep dermal or subcutaneous papules or small nodules. When deep, they may be colourless or bluish, but when superficial, they may be red.

Histopathology

Sinusoidal haemangiomas are round or oval and very well circumscribed dermal or subcutaneous neoplasms {366,1680}. They are composed of thin walled vessels with capacious round lumina. The vessels are very closely apposed to one another ("back to back appearance"). Occasional lesions have smooth muscle in their walls. Thrombosis of vascular channels occurs in a proportion of cases. This can lead to intravascular papillary endothelial hyperplasia (a potential stimulant of angiosarcoma in a partial biopsy) and calcification may result {1680}.

Hobnail haemangioma

Definition

Hobnail haemangioma (HH) {389,916, 1584,1896,2052} is a benign vascular proliferation characterized by a wedge-shaped dermal proliferation of irregular vascular channels lined in its superficial portion by endothelial cells with hobnail morphology.

ICD-O code

9120/0

Synonym

Targetoid haemosiderotic haemangioma

Epidemiology

HH is relatively rare and presents mainly in young to middle-aged adults with predilection for males.

Etiology

Trauma may play a role in the formation

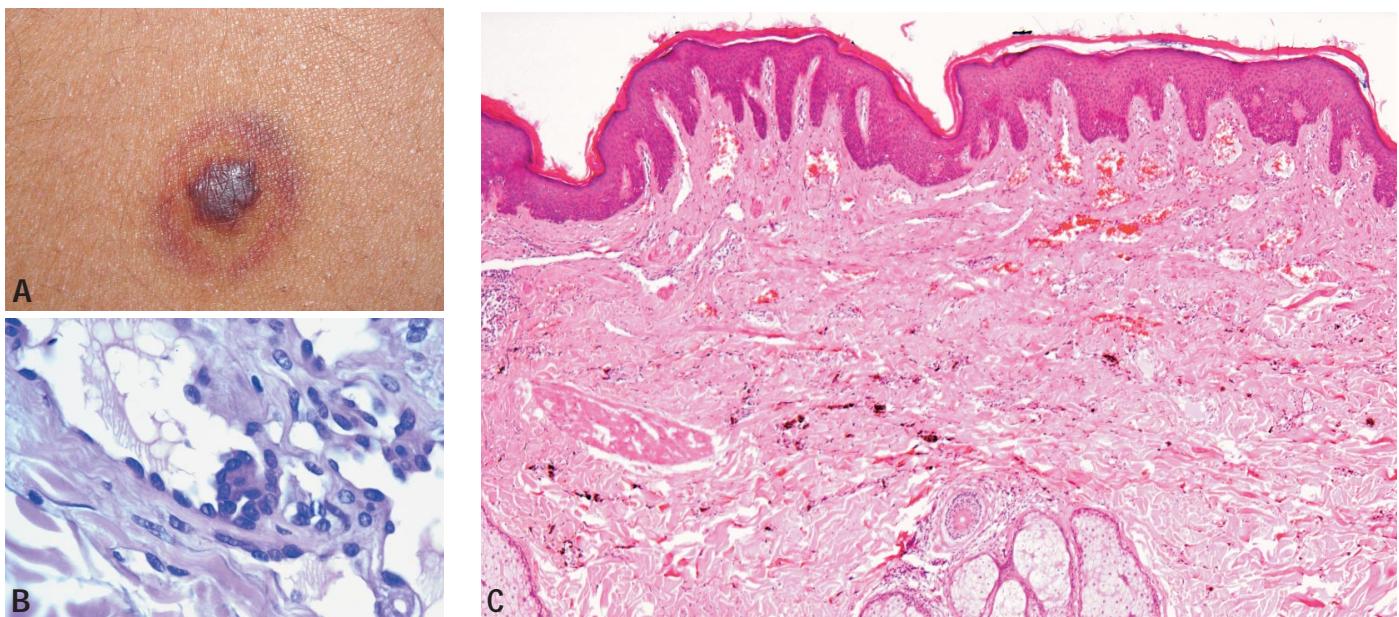


Fig. 5.2 Hobnail haemangioma. **A** Typical targetoid clinical appearance, only seen in a minority of cases. **B** Intravascular papillae lined by hobnail endothelial cells are sometimes seen. **C** Dilated irregular superficial vascular spaces and prominent haemosiderin deposition.

of these lesions {2052}. One possible origin is via trauma to lymphangiomas or angiokeratomas, resulting in dispersion of endothelial cells and erythrocytes into the surrounding dermis.

Localization

Most cases occur on the lower limbs with predilection for the thigh followed by the upper extremities and the trunk. Rare lesions have been reported in the oral cavity including the tongue and gingivae.

Clinical features

Some lesions show a characteristic targetoid clinical appearance with variably pigmented ecchymotic haloes secondary to bleeding and haemosiderin deposition within the tumour {2052}. Most often however, the clinical presentation is non-distinctive and the clinical differential diagnosis includes haemangioma, naevus or fibrous histiocytoma. HH is asymptomatic, usually less than 2 cm in diameter and increases in size very slowly. Patients usually describe cyclic changes {389}. Multiple lesions are exceptional. Similar histological changes may occur after trauma {481}.

Histopathology

The most striking low-power feature is the presence of a wedge-shaped vascular proliferation consisting of superficial, dilated and thin-walled vascular chan-

nels lined by bland endothelial cells that appear flat or have hobnail morphology. Some of the vascular channels resemble lymphatics. Focally, intraluminal small papillary projections with collagenous cores are occasionally seen. As the vascular channels descend further into the reticular dermis they gradually become smaller and disappear. Inflammation is not usually a feature. Haemorrhage and haemosiderin deposition are prominent but vary according to the stage of evolution. A Perls stain may be useful in highlighting the haemosiderin.

Immunohistochemistry

The endothelial cells in HH stain diffusely for vascular markers including CD31 and VWF (von Willebrand factor). CD34 is usually negative or very focal. A layer of alpha-smooth muscle actin pericytes surrounds some of the vascular channels. The positive staining for vascular endothelial growth factor receptor-3 (VEGFR-3) in some cases has led to the suggestion that HH displays lymphatic differentiation {1584}. VEGFR-3 is however, not entirely specific for lymphatic endothelium. Staining for human herpes virus 8 is consistently negative {932}.

Differential diagnosis

Kaposi sarcoma differs by the absence of dilated blood vessels lined by hobnail cells.

Prognosis

The lesion is entirely benign and there is no tendency for local recurrence.

Glomeruloid haemangioma

Definition

Glomeruloid haemangioma is a benign vascular proliferation that occurs inside ectatic blood vessels, producing a pattern reminiscent of renal glomeruli.

ICD-O code

9120/0

Epidemiology

This is a very rare vascular proliferation that occurs exclusively in patients with POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal paraproteinaemia and Skin lesions), which is associated with multicentric Castleman disease {440,2562}. Multiple haemangiomas occur in 24-44% of all patients with POEMS syndrome, with most being cherry-type haemangiomas, and only some being glomeruloid haemangiomas {1301,2312,2580}. The reported cases of glomeruloid haemangiomas show female predominance, with patients ranging in age from 40-68 years {440,1278,1285,1965,2083,2380, 2562}.

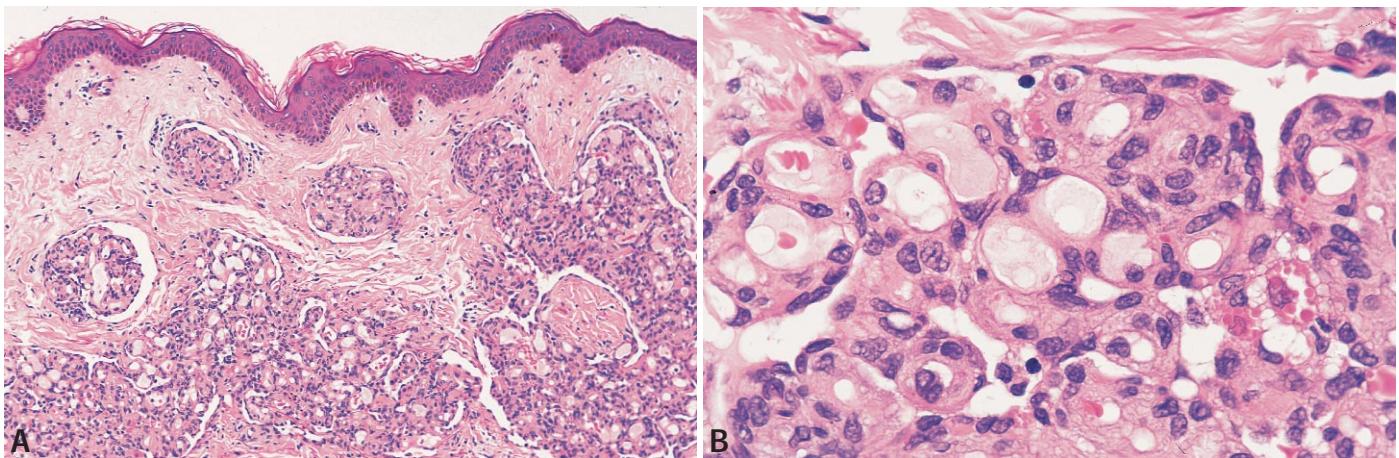


Fig. 5.3 Glomeruloid haemangioma. **A** The dermis shows a vascular proliferation occurring exclusively within thin-walled ectatic vascular spaces, producing a glomerulus-like appearance. **B** The vascular proliferation consists of aggregates of capillaries projecting as a broad tuft into a vascular space. The endothelial cells that line the vascular space and surface of the tuft have dark-staining nuclei ("sinusoidal endothelium"), while those that line the capillaries have plumper and paler nuclei. "Interstitial" cells containing eosinophilic hyaline globules are also seen.

Etiology

Glomeruloid haemangioma has so far only been found in patients with POEMS syndrome. Its development may be mediated by circulating vascular endothelial factor, which is present at high titres in the blood of most patients with POEMS syndrome {2225,2464}.

Localization

The lesions are mainly found on the trunk, face and proximal limb, and exceptionally also in the fingers and deep soft tissues {440,1278,1285,1965,2380,2562}.

Clinical features

The lesions manifest as multiple purplish-red papules or nodules, ranging in size from a few to 15 mm {1278,1285,1965,2380,2562}. They occur in patients already known to have POEMS syndrome, or as an early phenomenon before the full-blown syndrome develops {1278,1285,1965,2083,2380,2562}.

Histopathology

Glomeruloid haemangioma is mainly centred in the upper and mid dermis. It is characterized by tufts of proliferated, coiled capillaries projecting inside thin-walled ectatic blood vessels, mimicking renal glomeruli. The "sinusoidal" endothelial cells that line the ectatic vascular spaces and the surface the vascular tufts possess dark round nuclei. These cells also show cleft-like extensions into the cores of the vascular tufts. The capillary loops within the tufts are lined by plump

endothelium with slightly larger and paler nuclei, and supported by pericytes. Scattered "interstitial" cells that contain PAS-positive eosinophilic globules are found between the capillary loops, but similar cytoplasmic globules can also be seen in some endothelial cells.

Immunohistochemistry

On immunohistochemical staining, the endothelial cells of the capillary loops stain for CD31 and CD34, and they are well supported by actin-positive pericytes. The sinusoidal endothelial cells covering the tufts are positive for CD31 but not CD34, while those lining the ectatic vascular spaces are strongly CD31 positive but weakly CD34 positive. The eosinophilic globules probably represent immunoglobulin. The cells that contain these globules represent a mixture of histiocytes (CD68+) and endothelial cells (CD31+).

Precursor lesions

Progression from cellular immature, non-specific, vascular proliferation with slit-like canals reminiscent of tufted angioma to classical glomeruloid haemangioma has been reported {2562}. In addition, cherry-type haemangiomas with miniature glomeruloid structures formation can coexist with glomeruloid haemangiomas in patients with POEMS syndrome {440}. Thus these might represent precursor lesions of glomeruloid haemangioma.

Histogenesis

The currently favoured view is that glo-

meruloid haemangioma is a reactive vascular proliferation, perhaps representing a distinctive form of reactive angioendotheliomatosis.

Prognosis and predictive factors

Glomeruloid haemangioma per se is a totally innocuous lesion. The outcome of the patients depends on the underlying POEMS syndrome.

Micovenular haemangioma

Definition

Micovenular haemangioma is an acquired, slowly growing asymptomatic lesion with an angiomatous appearance {1080}.

ICD-O code

9120/0

Etiology

A histogenetic relationship between micovenular haemangioma and hormonal factors such as pregnancy and hormonal contraceptives has been postulated {144,2065}, but this feature has not been corroborated by other authors. An example of micovenular haemangioma has developed in a patient with Wiskott-Aldrich syndrome {1939}. Haemangiomas identical to micovenular haemangioma can be seen in patients with POEMS syndrome {25}.

Localization

It most commonly affects the upper limbs, particularly the forearms.

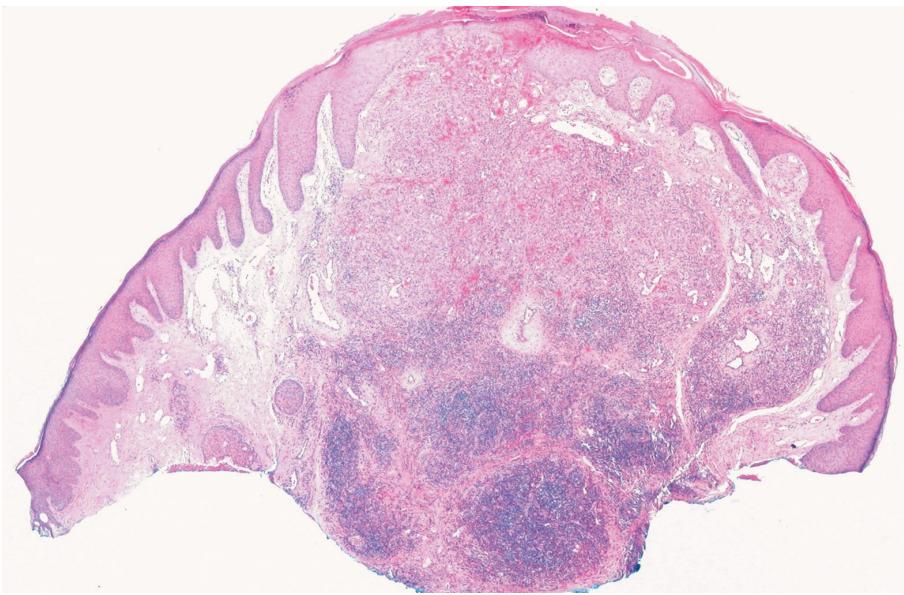


Fig. 5.4 Angiolymphoid hyperplasia with eosinophilia. Lobulated proliferation of small to medium size blood vessels with admixed inflammation and a central prominent vessel.

However, lesions on the trunk, face and lower limbs have also been recorded {65,1061}.

Clinical features

Microvenular haemangiomas appear as sharply circumscribed, bright red, solitary lesions varying in size from 0.5-2 cm.

Histopathology

Microvenular haemangioma appears as a poorly circumscribed proliferation of irregularly branched, round to oval, thin-walled blood vessels lined by a single layer of endothelial cells. They involve the entire reticular dermis and a variable degree of dermal sclerosis is present in the stroma. The lumina of the neoplastic blood vessels are inconspicuous and often collapsed with only a few erythrocytes within them.

The main differential diagnosis is with Kaposi sarcoma in the patch stage. Kaposi sarcoma shows irregular anastomosing vascular spaces, newly formed ectatic vascular channels surrounding pre-existing normal blood vessels and adnexa (promontory sign), plasma cells, hyaline (eosinophilic) globules, and small interstitial fascicles of spindle cells. All of these features are absent in microvenular haemangioma.

Immunohistochemistry

Immunohistochemically, the cells lining the lumina show positivity for factor VIII-related antigen and Ulex europaeus I lectin {144,1080,2065} which qualifies them as endothelial cells. Some smooth muscle actin positive perithelial cells have been also described surrounding this vascular space {65,1061}.

Prognosis

Microvenular haemangioma is a benign neoplasm and it is cured by simple excision.

Angiolymphoid hyperplasia with eosinophilia

Definition

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a benign skin or subcutaneous tumour that is a circumscribed combined proliferation of immature blood vessels and chronic inflammatory infiltrate usually containing eosinophils. Endothelial cells have a distinctive epithelioid or histiocytoid appearance with ample eosinophilic cytoplasm.

Synonyms

Epithelioid haemangioma, cutaneous histiocytoid angioma, pseudo- or atypical pyogenic granuloma, inflammatory angiomatous nodule, intravenous atypical vascular proliferation, nodular angioblastic hyperplasia with eosinophilia and lymphofolliculosis {201,1154, 1967,1968,2381}.

Epidemiology

ALHE was originally described as a lesion commonly found in young women on the head and neck {1011}. Recent reviews show a wide age range peaking at 20-50 years without female predominance {738,1753}. There is no predilection for Asian populations.

Etiology

Reactive vascular proliferation and inflammation {2441} in a traumatized vascular structure is a postulated cause of some ALHE lesions. History of antecedent trauma, histologic evidence of

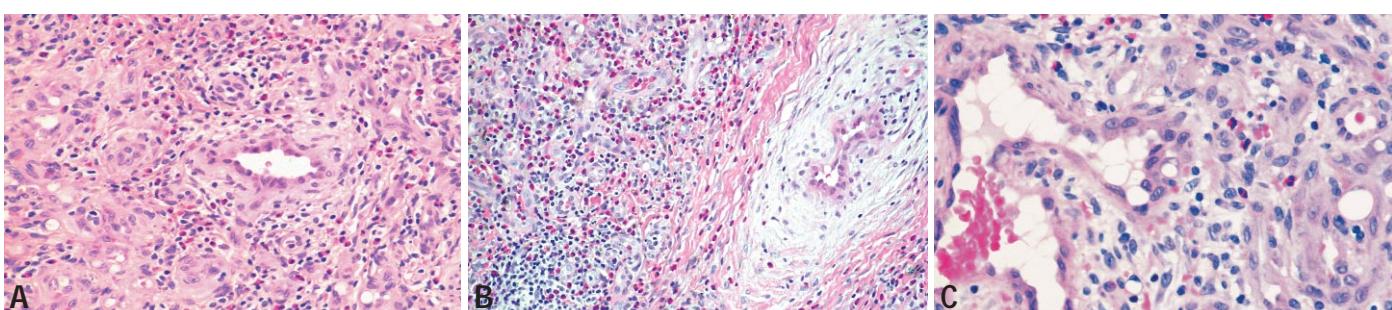


Fig. 5.5 Angiolymphoid hyperplasia with eosinophilia. **A** Epithelioid endothelial cells with abundant cytoplasms, some of which are vacuolated. **B** Proliferating immature vessels with protuberant endothelial nuclei associated with lymphoid and eosinophilic inflammation. **C** Epithelioid endothelial cells with abundant cytoplasms, some of which are vacuolated.

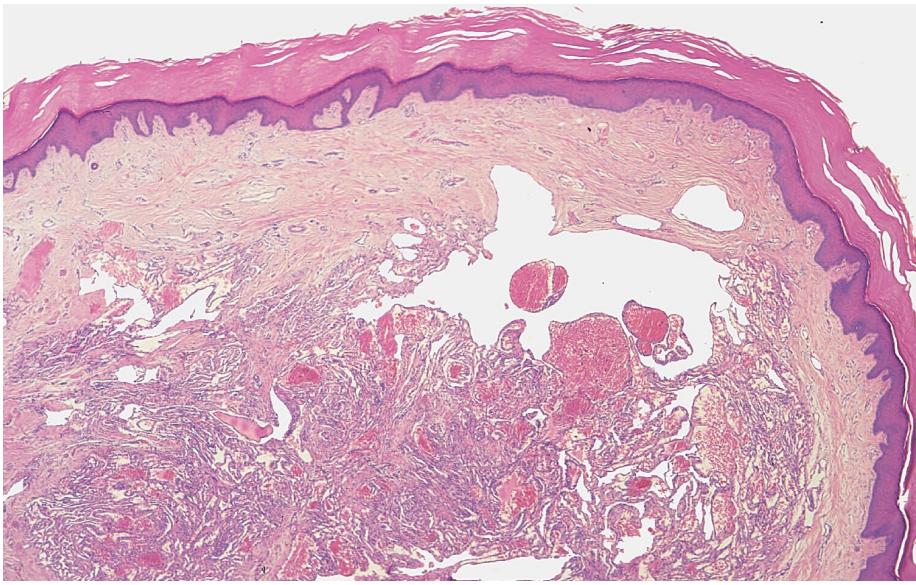


Fig. 5.6 Spindle cell haemangioma. This tumour involving the dermis shows pushing borders, and comprises cavernous vessels intimately intermingled with spindle cells.

adjacent vascular damage {738,2400} and pre-existing arteriovenous malformation {1754} are found in some cases. Although earlier reported, HHV-8 has not been consistently found in ALHE {1130,1241}.

Localization

ALHE most commonly occurs on the head and neck with a predilection for the forehead, scalp and skin around the ear {738,1011,1753}. Occurrence on distal extremities and digits is not uncommon {97}. Multiple other reported sites include trunk, breast {1676}, oral mucosa {1512, 1530,1776}, orbital tissues {145,1513}, vulva {37,2125} and penis {2240}.

Clinical features

ALHE lesions are small red or violaceous papules or plaques with an average size of 1 cm, measuring up to 10 cm. When symptomatic they can be pulsatile, painful and pruritic with scale crust {1011,1753}. When multiple they are usually grouped or zosteriform {647} and may coalesce. In contrast to Kimura disease, lymphadenopathy, eosinophilia, asthma and proteinuria are uncommon and serum IgE is usually normal {97, 441}.

Histopathology

The lobulated, circumscribed dermal or subcutaneous proliferation has a combined vascular and inflammatory compo-

nent. Sometimes an origin from a medium-sized vessel, usually a vein, is seen. There are arborizing small blood vessels that may surround a larger vascular structure. The vessel walls have smooth muscle cells or pericytes and contain mucin. The endothelial cells have distinct abundant eosinophilic (epithelioid) cytoplasms that can be vacuolated. They protrude into and can occlude vascular lumina or form solid sheets that may mimic angiosarcoma {2582}. Their nuclei have open chromatin, often with a central nucleolus and may protrude into lumina with occasional mitoses.

Multinucleate cells that are endothelial sprouts or histiocyte-like cells can be present {2020}. The density of the inflammatory component between vessels is variable with a prominence of lymphocytes and eosinophils.

Plasma cells, mast cells and lymphoid follicles with reactive germinal centres can be present. Older lesions typically become more fibrotic, less inflammatory and their vascular nature becomes less conspicuous.

Immunoprofile

The endothelial cells are positive for CD31, CD34, VWF (VIIIrAg) and are keratin negative. The proliferative index of the endothelial cells has been reported as 5% using Ki-67 with negative staining for Cyclin D1 and bcl-2. This may support a reactive rather than neoplastic

endothelial proliferation {97}. Lymphocytes are a mixture of T- and B-cells. There is no light chain restriction {97, 1753}. One series has shown T-cell clonality in ALHE that may define a subgroup of lesions with a higher incidence of recurrences {1241}.

Differential diagnosis

Kimura disease is a distinct clinicopathological entity, characterized by a more prominent lymphoid proliferation and less prominent vascular component with almost complete absence of epithelioid endothelial cells.

Prognosis and predictive factors

The lesions tend to persist if not completely excised and only rarely will they spontaneously regress. Local recurrence can occur and may be related to persistence of an underlying arteriovenous fistula that is not completely excised {97, 1753,1754}.

Spindle cell haemangioma

Definition

Spindle cell haemangioma is a benign

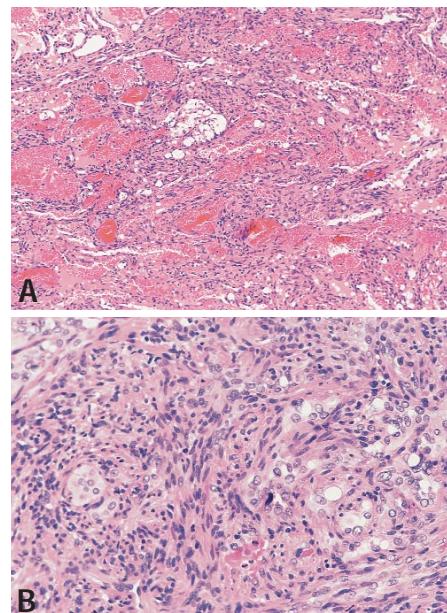


Fig. 5.7 Spindle cell haemangioma. **A** There is intricate mixing of cavernous vessels and spindly cells, with irregular branching narrow vascular spaces coursing through the latter component. **B** Short fascicles of uniform spindly cells are evident. There are interspersed small groups of epithelioid cells with lightly eosinophilic cytoplasm, sometimes with vacuolation.

vascular tumour composed of an intimate admixture of cavernous blood vessels and Kaposi sarcoma-like spindle cell vascular zones.

ICD-O code 9136/0

Synonym

Spindle cell haemangioendothelioma {1807,2488}

Epidemiology

The tumour is uncommon, and mainly affects children and young adults. Those who present late in adulthood usually have long-standing tumours {270,1807}. There is no sex predilection.

Etiology

In a small proportion of cases, spindle cell haemangioma develops in the setting of multiple enchondromas (Maffucci syndrome), Klippel-Trenaunay syndrome, venous malformation, early onset varicose veins, or congenital lymphoedema {709,754,1807}. The onset in young patients and frequent finding of abnormal vessels around the lesion suggest that an underlying vascular malformation may predispose to the development of spindle cell haemangioma {754}.

Localization

They occur on the distal extremities and less commonly on the proximal limb, trunk, head and neck {1807}. Exceptionally, it has been reported in the spleen {709}.

Clinical features

The tumour usually presents as a superficial, slow-growing, painless, solitary purplish mass, or multiple nodules within an anatomical region {1807}. Rare examples may be painful {1784}. The lesion is a discrete red-brown nodule that ranges in size from a few mm to over 10 cm, but most are smaller than 2 cm.

Histopathology

Spindle cell haemangiomas are mostly found in the dermis and subcutis, and occasionally in the deep soft tissues. The tumour is often well-circumscribed but non-encapsulated. It is characterized by intricate blending of cavernous and solid spindle cell zones. The cavernous blood vessels are empty or filled with blood, and may contain organizing thrombi or phleboliths. In the spindle cell regions,

short fascicles of spindle cells are interspersed with ramifying narrow vascular spaces. The spindle cells possess uniform, elongated, dark nuclei and eosinophilic cytoplasm. There are scattered single or groups of vacuolated cells or epithelioid cells with lightly eosinophilic cytoplasm.

In about half of the cases, residual vessel walls can be found in the periphery of the lesion, indicating that the lesion is partly or entirely intravascular {754,1807}. Intravascular extension of the lesion can sometimes be seen around the main lesion.

Immunohistochemistry

The cells that line the vascular spaces stain for VWF (VIIIrAg), CD31 and variably for CD34. The spindle cells are negative for the various endothelial markers including CD34, and may show patchy and variable staining for actin {754,796,1667}.

Differential diagnosis

Spindle cell haemangioma can be distinguished from Kaposi sarcoma by the following features: irregular-shaped, dilated and ramifying vascular spaces rather than short narrow vascular slits among the spindle cells, presence of vacuolated endothelial cells, frequent partial or complete localization within muscular blood vessels, absence of eosinophilic hyaline globules, lack of CD34 immunoreactivity in the spindle cells, and lack of association with HHV-8 {1034}.

Histogenesis

There are controversies on the nature of spindle cell haemangioma, with theories ranging from neoplastic, malformative to hamartomatous {754,1100,1807}. The lesion itself comprises heterogeneous cellular populations, including endothelial cells, pericyte-like cells, fibroblasts, smooth muscle cells and primitive mesenchymal cells.

Somatic genetics

There are no molecular data on spindle cell haemangioma; one studied case shows a normal karyotype {754}. The lesions are diploid on flow cytometric analysis {796,1035}.

Prognosis and predictive factors

Recurrence after local excision occurs in 50-60% of cases, and often results from

new lesions developing within the same anatomical region due to intravascular extension. However, there is no metastatic potential.

Tufted angioma

Definition

Tufted angioma is an unusual, acquired, benign vascular neoplasm characterized by slow, indolent growth {1153,1475}.

ICD-O code 9161/0

Synonyms

Tufted haemangioma, progressive capillary haemangioma, angioblastoma of Nakagawa.

Epidemiology

Tufted angioma most commonly affects children and young adults, but both congenital and very late onset cases have been described {995,1264}.

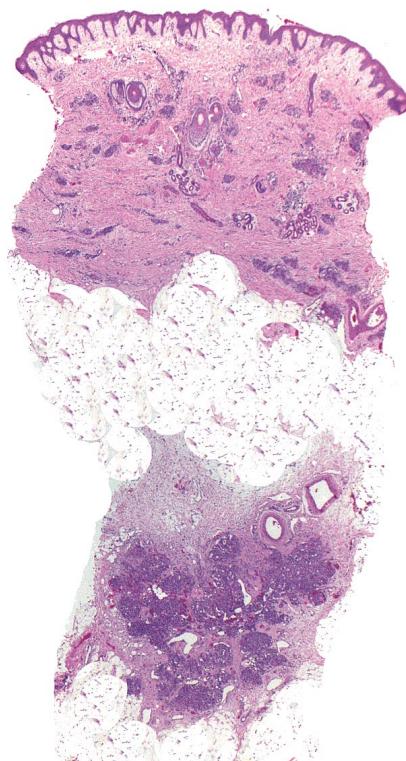


Fig. 5.8 Tufted haemangioma. Another example of a tufted angioma present in the dermis and subcutaneous tissue.

Localization

Tufted angioma favours the shoulders, upper chest, back, and neck {1747}, although examples of these lesions have also been reported on the oral mucosa, extremities and head {1289,2458}.

Clinical features

The most common forms of presentation are enlarging erythematous, brown macules or plaques with an angiomatic appearance. In other instances the lesions resemble granulomas or a connective tissue naevus. Pain and hyperhidrosis have been described {216, 2291}. Raised papules or nodules resembling pyogenic granulomas are sometimes seen within the lesion and occasionally they adopt a linear arrangement {1765}. In some cases the patients present with sclerosing plaques {412}. Tufted angiomas have been associated with vascular malformations including naevus flammeus {1267,1601}, pregnancy {1272}, non-regressing lipodystrophy centrifugalis abdominalis {1032}, and liver transplant {482}. In some cases of Kasabach-Merritt syndrome the underlying lesion is a tufted angioma {691,692, 2136}. In most cases the growth is halted after some years, and in some cases there is a slight tendency towards spontaneous regression {1131}. Tufted angioma grows slowly and insidiously, and may eventually come to cover large areas of the body.

Histopathology

There are multiple individual vascular lobules within the dermis and subcutaneous fat. These aggregations are more prominent in the middle and lower part of the dermis. Each lobule is composed of aggregates of endothelial cells that whorl concentrically around a pre-existing vascular plexus.

Some lobules bulge into the walls of dilated thin-walled vascular structures, creating a slit-like or semi-lunar appearance of vessels. This peculiar shape in addition to the angiocentricity of the vascular structures prompted the name "tufted angioma." Small capillary lumina are identified within the aggregations of endothelial cells. Unusual histopathologic findings in tufted angioma include a mucinous stroma, abundant sweat glands {137}, an intravenous location {795} of the lesion and a proliferation of lymphatic-like channels.

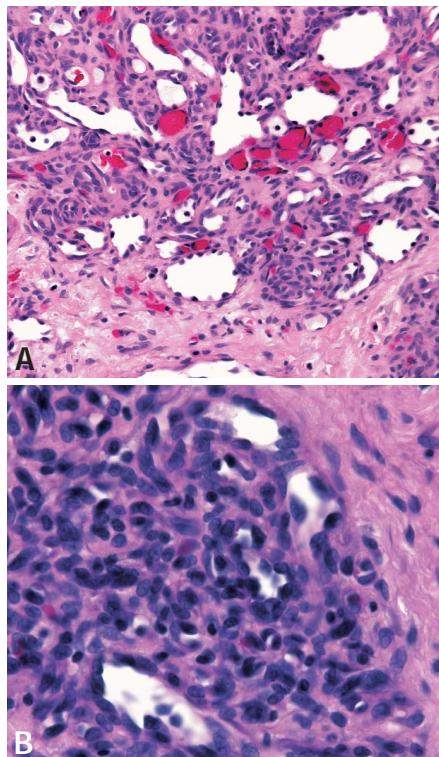


Fig. 5.9 Tufted haemangioma. **A** The vascular lobules in the subcutaneous tissue are composed of irregular vascular spaces, some of them lined with prominent endothelial cells. **B** The neoplastic cells are uniform, in some areas with a slit-like or semi-lunar appearance.

Immunohistochemistry

Cells in the capillary tufts are weakly positive or negative for VWF (VIIrAg). They exhibit strong positivity for CD31, CD34 and alpha-smooth muscle actin {1156, 1709}. The cells that show reactivity for smooth muscle actin, most likely represent pericytes.

Electron microscopy

Ultrastructural studies have shown characteristic crystalloid inclusions within endothelial cells in addition to Weibel-Palade bodies {1709}.

Genetics

Most cases are sporadic, although a family with several members affected by tufted angioma has been reported {993}. In this particular family the mode of transmission was autosomal dominant.

Prognosis

Tufted angioma showing spontaneous regression is a rare event. Although benign, symptomatic lesions need to be treated {1131,1709,1948}.

Bacillary angiomatosis

Definition

Bacillary angiomatosis is a reactive vascular proliferation caused by infection with bacteria of the genus *Bartonella*, most commonly *B. henselae* and *B. quintana* {507,855,1383,1845,2492}.

Synonyms

Disseminated pyogenic granulomas (not generally accepted), epithelioid angiomas.

Epidemiology

Bacillary angiomatosis most commonly occurs in immunosuppressed patients although there have been a few reports in apparently immunocompetent patients, both adults and children {504,507, 1233,1383,1613,1793,1845,2111,2206, 2325}. Bacillary angiomatosis has most frequently been seen in HIV/AIDS patients.

Localization

Cutaneous involvement may occur at any site and less commonly lesions may involve mucosal surfaces and deeper soft tissue such as muscle, bone, lymph node and liver (peliosis hepatis) {442,507,1383,1845,2085}.

Clinical features

The lesions present as multiple reddish to red-brown cutaneous nodules and occasionally as subcutaneous nodules. In immunocompetent patients there may be fewer nodules {507,1383,1845}.

Histopathology

Sections show a lobular proliferation of well-formed vessels with plump occasionally epithelioid endothelial cells. There is an oedematous to fibrous stroma with a variable infiltrate of neutrophils with nuclear dust, macrophages and ill-defined pale basophilic granular material (representing the bacteria). Diagnosis is made by identifying the characteristic cocco-bacillary organisms with a Warthin -Starry or Giemsa stain {507, 1383,1845}.

Differential diagnosis

Pyogenic granuloma lacks the characteristic basophilic granular material and the dispersed pattern of neutrophils seen in bacillary angiomatosis. Histologically identical lesions can be seen in verruga peruana (verruca peruana).

Prognosis and predictive factors

The infection may be cleared by antibiotics with resolution of the lesions. The overall prognosis depends upon the immune status of the patient and sites of involvement {507,1383,1845}.

Reactive angioendotheliomatosis

Definition

Reactive angioendotheliomatosis (RA) is a relatively rare condition associated with diverse systemic diseases, usually confined to the skin and characterized by a multifocal dermal proliferation of capillaries {1559,2513}.

Synonym

Diffuse dermal angiomyomatosis. The so-called malignant angioendotheliomatosis represents a form of intravascular lymphoma not related to reactive angioendotheliomatosis {2512}.

Epidemiology

Presentation is mainly in adults with no sex predilection. Occurrence in children is exceptional {304}.

Localization

There is a predilection for the trunk and limbs.

Clinical features

Clinical presentation is variable and consists of fairly widespread erythematous macules, papules, nodules and plaques {1559,2513}. Purpura is a frequent finding. Ulceration is very rare. Many systemic illnesses are related to the development of RA and it can be said that this condition often represents a marker of systemic disease.

Patients affected with RA not uncommonly are immunosuppressed as a result of transplantation. Many conditions have been associated with reactive angioendotheliomatosis including valvular cardiac disease, alcoholic cirrhosis, rheumatoid arthritis, polymyalgia rheumatica, cryoglobulinaemia, the antiphospholipid syndrome, and sarcoidosis {551,1385,1559,2178, 2341,2361}. A more localized variant may be seen in some patients and it is usually associated with peripheral vascular atherosclerosis or iatrogenic arteriovenous fistulas {1266,1276,1918}.

Histopathology

Histologically, the dermis and rarely the superficial subcutaneous tissue show numerous clusters of closely packed capillaries. Many of these capillaries proliferate within pre-existing blood vessels. Cytological atypia is mild or absent but endothelial cells are often prominent and may show focal epithelioid cell change. A layer of pericytes surrounds the newly formed small vascular channels. Extravasation of red blood cells tends to be prominent. PAS positive microthrombi are numerous in cases associated with cryoglobulinaemia. Dermal changes resembling fasciitis have also been described.

Differential diagnosis

Distinction from Kaposi sarcoma is easy as in RA there is no proliferation of individual irregular lymphatic-like channels around pre-existing normal blood vessels, proliferating vascular channels are

surrounded by a layer of pericytes and inflammatory cells are very rare or absent. Tufted angioma may be distinguished from RA by the typical cannonball appearance at scanning magnification and the presence of slit-like crescent shaped lymphatics around individual tufts in the former. An unusual entity characterized by the presence of aggregates of histiocytes within vascular lumina and described as intravascular histiocytosis has been recently described and may closely mimic reactive angioendotheliomatosis {1935}. Distinction from the latter may be difficult and in difficult cases immunohistochemistry is useful in demonstrating the histiocytic nature of the intravascular cells.

Prognosis and predictive factors

RA tends to be self-limiting in the majority of cases with complete spontaneous resolution over weeks or months.

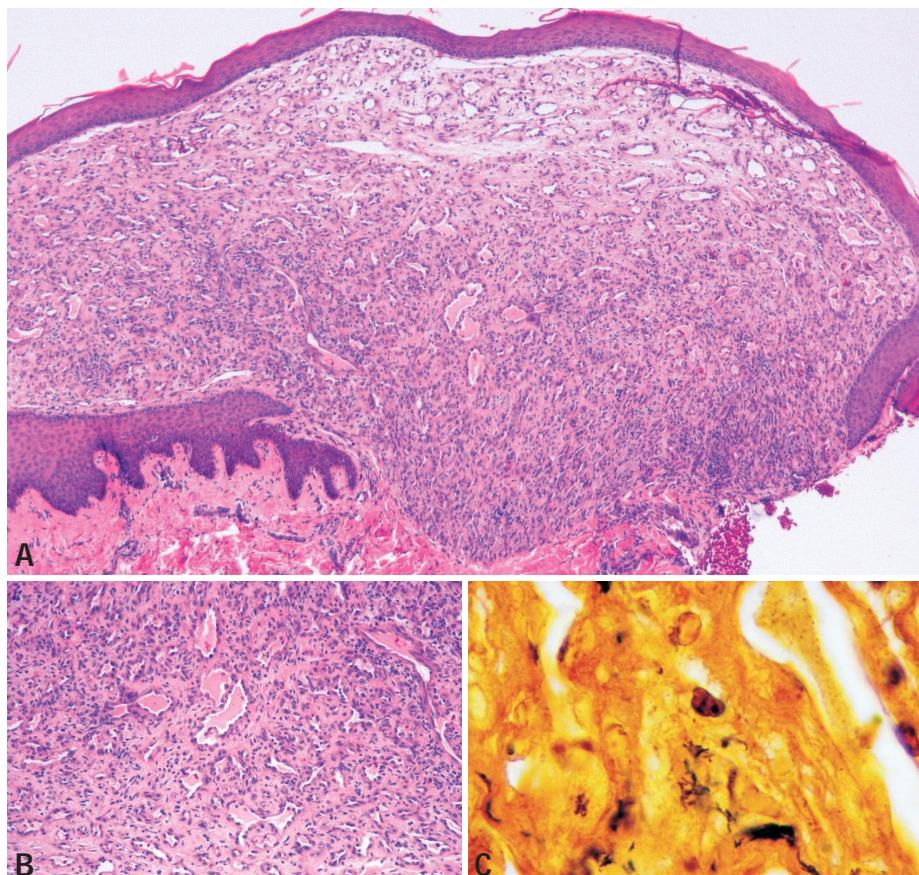
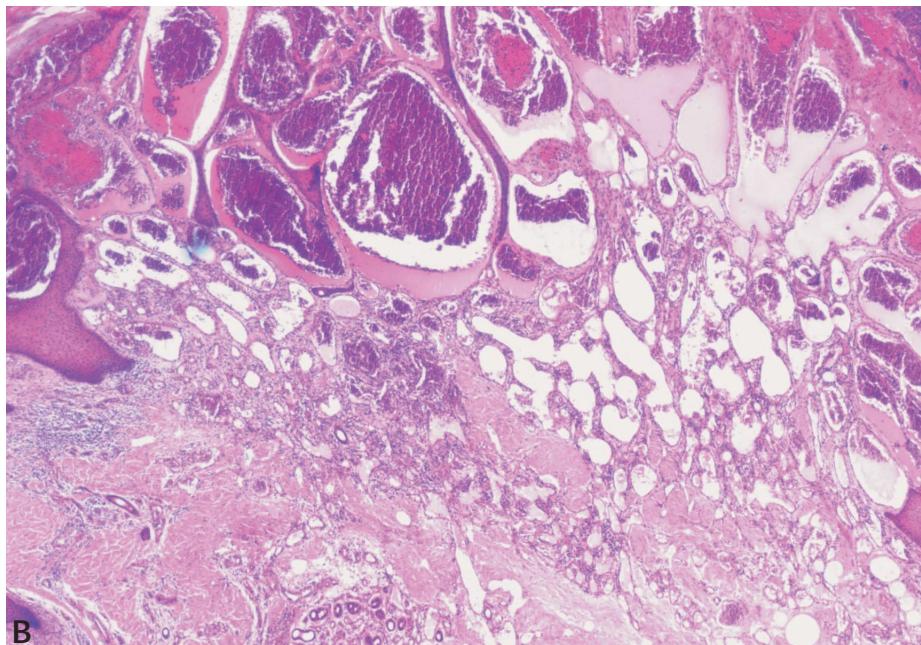


Fig. 5.10 Bacillary angiomatosis. **A** Low power view of a skin lesion of bacillary angiomatosis shows dome shaped expansion of the upper dermis due to a proliferation of small well formed vessels. **B** High power view showing the plump endothelial cells lining the vessels. **C** A Warthin-Starry stain shows the small cocco-bacillary organisms.



A



B

Fig. 5.11 Verrucous haemangioma. **A** A large, irregularly outlined, hyperkeratotic lesion is typical of verrucous haemangioma. **B** This low magnification view of verrucous haemangioma exhibits a superficial and deep proliferation of variously sized blood vessels.

Verrucous haemangioma

Definition

Verrucous haemangioma (VH) is an uncommon variant of haemangioma with capillary or cavernous features {444, 2489}. It is evident at birth or in early childhood and enlarges and becomes hyperkeratotic in later life.

Synonyms

Haemangioma unilateralis naeviforme, unilateral verrucous haemangioma, angiokeratoma circumspectum naeviforme, naevus vascularis unius lateralis, keratotic haemangioma, naevus angiokeratoticus, naevus keratoangiomaticus {363}.

Epidemiology

VH is usually apparent at birth or in the first few years of life {1102}. The condition is rare, and there is no known gender predilection.

Localization

VH is almost always a unilateral isolated condition, with most cases affecting the leg. Less commonly, it presents on the arm. It is not common on the trunk, but when present on the back in association with underlying spinal malformation, it is a component of Cobb syndrome.

Clinical features

The condition usually presents with lesions that are clustered, discrete to nearly confluent, bluish-red, well demarcated, soft and compressible {363,444, 1102}. The lesions that comprise these clusters may coalesce to form large lesions that cover broad areas over time. Satellite lesions are typical. The condition may show linear or serpiginous distribution. Lesions become hyperkeratotic over time and show a brown to bluish-black appearance. Hyperkeratosis may be so pronounced as to appear verrucous; consequently, the lesion may be mistaken clinically for a wart or keratosis {2560}. Size usually allows distinction from the later two, as verrucous haemangioma tends to be large.

Histopathology

Within the superficial and deep dermis and sometimes the subcutis there are dilated capillaries and venules. Vessels tend to be cavernous in the upper dermis, few in numbers in the deep dermis, and capillary-like in the subcutis. A pseudo-infiltrating pattern may be seen in the subcutis, but close inspection reveals an overall lobulated pattern {444}. There may be thrombosis with secondary papillary endothelial hyperplasia. The vessels are lined by a single layer of

endothelial cells without evidence of endothelial proliferation. Inflammatory cells, haemosiderin and fibrosis may be associated. Older lesions show prominent acanthosis, hyperkeratosis with crust and papillomatosis. Ulceration is sometimes present.

Differential diagnosis

Angiokeratoma may also show verrucous epidermal hyperplasia. Verrucous haemangioma differs from angiokeratoma by its large size, involvement of deep vasculature and the presence of vessels that usually vary significantly in size. Angiokeratomas also show a hereditary basis in some cases, are often multiple and show a predilection for the lower trunk, thigh and external genitalia {444}.

Prognosis and predictive factors

VH has a propensity to recur locally {2489}. The condition progresses over time, and superficial therapy has been reported to exacerbate spread {2560}. This may be due, in large part, to the fact that size of the lesion is usually underestimated clinically {444}. Recurrence may also be seen in skin grafts.

Pyogenic granuloma

Definition

Pyogenic granuloma (PG) are rapidly growing, mostly exophytic lesions which may ulcerate.

Synonym

Lobular capillary haemangioma

Epidemiology

An epidemiologic study of 325 cases, {1959} showed that 86% of the lesions were cutaneous, while only 12% of the cases affected mucosa. Overall, male patients outnumbered female patients. Pyogenic granuloma is especially common in children and young adults and the peak incidence is around the second decade of life.

Etiology

Most authors consider PG to be a hyperplastic rather than a neoplastic process {598,1615}. Most lesions develop at sites of superficial trauma; in some cases lesions of PG are associated with endocrine alterations or medication and usually regress upon cessation of the stimuli.

Localization

PG preferentially affects the gingiva, lips, mucosa of the nose, fingers, and face {1247,1619}, but examples of pyogenic granuloma have been described in all parts of the skin and mucous membranes including vulva, scrotum, penis, and glans penis {10,929,1477,2360}.

Clinical features

PG presents typically as a papule or polyp with a glistening surface, which bleeds easily. Pyogenic granuloma usually develops at the site of a pre-existing injury. The lesions evolve rapidly over a period of weeks to a maximum size, then shrink and become replaced by fibrous tissue, which disappears within a few months. Epulis gravidarum a gingival lesion that develops during pregnancy, is identical to pyogenic granuloma {1669}. Occasionally, pyogenic granuloma develop within a pre-existing lesion such as a naevus flammeus {1394} or in a spider angioma {1748}. Multiple lesions tend to be localized {1787,2309} but they can also extend in an eruptive and disseminated fashion {2533}. With few exceptions, multiple recurrent lesions are more common in adolescents and young

adults, and they usually occur after attempts of electrodesiccation or surgical removal of the primary single lesion. Multiple lesions may also occur after removal of other lesions such as melanocytic neoplasms {621} or in burns {435}. Multiple lesions most commonly affect the trunk, especially the interscapular region. In some cases, eruptive widespread lesions of pyogenic granuloma are a paraneoplastic manifestation {1800}. Rare variants of pyogenic granuloma include the subcutaneous {1777} and intravenous {540} forms.

Histopathology

Early lesions of pyogenic granuloma are identical to granulation tissue, containing, numerous capillaries and venules disposed radially to the skin surface, which is often eroded and covered with scabs. The stroma is oedematous and contains mixed inflammatory infiltrates with lymphocytes, histiocytes, plasma cells, neutrophils and an increased number of mast cells. Fully developed lesions of pyogenic granuloma are polypoid and show a lobular pattern with fibrous septa intersecting the lesion; hence the name lobular capillary haemangioma used by some authors for lesions at this stage. Each lobule is composed of aggregations of capillaries and venules lined by plump endothelial cells. At this stage most lesions have entirely re-epithelialized, and the epidermis forms collarettes of hyperplastic adnexal epithelium at the periphery, partially embracing the lesion; inflammatory infiltrates are sparse and the oedema of the stroma has disappeared. In the late stages of pyogenic granuloma there is a steady increase in the amount of fibrous tissue, so as the fibrotic struts widen, the lobules of capillaries become smaller and, with time, pyogenic granuloma evolves into a fibroma. When the specimen is deep enough, a small feeding artery and one or more veins may be seen ascending from the subcutaneous fat throughout the reticular dermis to directly enter the base of a pyogenic granuloma. The histopathological findings are the same in all variants of pyogenic granuloma.

Uncommon histopathological features in lesions of pyogenic granuloma include intravascular papillary endothelial hyperplasia {1103} and extramedullary haematopoiesis {1986}. When the lesions of PG recur they may show some atypical

features which in some cases resemble an angiosarcoma especially in the deeper areas of the lesion. When lesions of PG develop within a vein, they are usually attached to the wall of the vein by a stalk and the lobular pattern is less prominent than in their extravascular counterparts.

Immunohistochemistry

PG lesions express factor VIII related antigen positivity in the endothelial cells lining large vessels, but are negative in the cellular areas {346}, whereas Ulex europaeus I lectin binds to the endothelial cells in both large vessels and cellular aggregates {1606}. There is also expression of inducible nitric oxide synthase {2169}, increased expression of vascular endothelial growth factor {298}, low apoptotic rate expression of Bax/Bcl-2 proteins {1682}, and strong expression of phosphorylated mitogen activated protein kinase {79} in lesions of pyogenic granuloma.

PCR investigations for human papillomavirus {1615} and human herpes virus type 8 (HHV8) {598} have yielded negative results.

Prognosis and predictive factors.

Lesions of PG are benign and easily removed by electrodesiccation and curettage; however lesions may recur, especially in those cases in which the proliferating vessels extend deep within the reticular dermis.

Cavernous haemangioma

Until a few years ago, the term "cavernous haemangiomas" was used to designate venous malformations. These lesions were also erroneously considered to be neoplasms, when in reality they are vascular malformations. They consist of slow-flowing, haemodynamically inactive vascular malformations, which are present at birth and slowly but progressively worsen throughout the lifetime of the patient. In some cases the lesions form a continuum of localized venous malformations, which include blue capillary spongy blebs, "cavernous" lesions (in which the venous lacunae are connected to the venous circulation by capillaries), localized saccular anomalies (connected by veins to the venous circulation) and diffuse venous ectasias. Many of the apparently localized and

superficial venous lesions tend to coexist with venous ectasias and deep vein anomalies.

Angiokeratomas

Definition

Angiokeratomas are acquired vascular lesions that result from the ectatic dilatation of pre-existing vessels in the papillary dermis, accompanied by hyperkeratotic epidermis [1101]. Four clinical variants of angiokeratomas have been recognized, these are: solitary, angiokeratoma corporis diffusum, Mibelli and Fordyce.

Epidemiology

Solitary angiokeratomas affect mainly young adults. Angiokeratoma of Fordyce affects elderly people [34], however, there are examples of congenital cases [768]. Mibelli angiokeratomas usually appear in childhood or adolescence and they are more common in females [986]. Angiokeratomas of Fabry disease usually appear shortly before puberty and as an X-linked disease, they exclusively affect males; females may be asymptomatic carriers. Fabry disease is a rare error of the metabolism that results in a deficiency of the lysosomal enzyme hydrolase alpha-galactosidase A. It is transmitted as an X-linked recessive trait, the gene responsible for the coding of alpha-galactosidase A has been localized to the middle of the long arm of the X chromosome [250,770].

Etiology

Solitary angiokeratomas are thought to be the result of injury, trauma, or chronic irritation to the wall of a venule in the papillary dermis.

Fordyce angiokeratomas are usually associated with varicocoele, inguinal hernia and thrombophlebitis [1788]. The lesions may develop after surgical injuries to the genital veins [857], and there have been cases of angiokeratomas involving the glans penis mucosa of young patients developing after circumcisional surgery [249]. Similar lesions have been described in the vulva of young females [403,857]. These lesions are thought to be the result of increased venous pressure that occurs during pregnancy or develops secondarily to the use of contraceptive pills.

Mibelli angiokeratoma is a condition that is inherited in an autosomal dominant fashion. Angiokeratoma corporis diffusum is the most unusual variant of all the angiokeratomas. It represents a cutaneous manifestation of a group of hereditary enzymatic disorders, but there is also an idiopathic form that presents with no other associated anomalies. Fabry disease is the disease most commonly associated with angiokeratoma corporis diffusum.

Localization

Solitary angiokeratomas may affect any anatomic site, including the oral cavity, although the lower limbs are the most frequent location [1101]. Fordyce angiokeratomas are most common in the scrotum and vulva. Mibelli angiokeratomas usually affect the dorsum of the fingers, toes and interdigital spaces. Lesions of angiokeratoma corporis diffusum in Fabry disease affect the lower part of abdomen, genitalia, buttocks, and thighs in a bathing-trunk distribution.

Clinical features

Although their biologic significance varies greatly, angiokeratomas range from lesions that have very little clinical repercussion to widespread eruptions that are a manifestation of potentially fatal, systemic, metabolic diseases. Solitary angiokeratomas consist of small, warty, black, well-circumscribed papules. Sometimes solitary angiokeratomas develop thrombosis and recanalization with the development of secondary intravascular papillary clinically endothelial hyperplasia. Due to their colour, these lesions may be clinically confused with malignant melanoma [857]. Fordyce angiokeratoma is characterized by the presence of multiple purple to dark papules, measuring 2-4 mm in diameter. In Mibelli angiokeratoma, the lesions consist of several dark papules with a slightly hyperkeratotic surface, and may be associated with acrocyanosis and chilblains. In rare instances, ulceration of the fingertips may appear as a complication of Mibelli angiokeratoma [592]. Lesions of angiokeratoma corporis diffusum are small punctate dark red papules, some of them less than 1 mm in diameter. A frequent and asymptomatic finding is the so-called cornea verticillata, which is a superficial corneal dystrophy. This finding is of diagnostic importance.

tance for the detection of mild cases and female carriers. Other cutaneous manifestations include dry skin, anhidrosis, hyperthermic crises [1198], and acroparaesthesiae secondary to capillary changes in the nail matrix [1132]. In rare instances patients with Fabry disease may also present with concurrent Klippel-Trenaunay-Weber syndrome [821]. Patients with Fabry disease who are devoid of cutaneous lesions have been reported [497]. Angiokeratoma corporis diffusum is not exclusive to Fabry disease and has also been described in association with other rare inherited lysosomal storage diseases. By the same token, rare cases of angiokeratoma corporis diffusum have been described in patients without metabolic anomalies [565,1518]. In some of these patients the angiokeratomas were multiple and presented in a zosteriform distribution.

Histopathology

All variants of angiokeratomas are identical under a conventional microscope. Common features of all angiokeratomas include the presence of dilated thin-walled blood vessels, lined by a layer of endothelial cells, in the papillary dermis and a variable degree of hyperkeratosis [1101]. Occasionally, angiokeratomas may be seen overlying deep vascular malformations [1323]. Hyperkeratosis is usually absent in Fordyce angiokeratomas and in angiokeratoma corporis diffusum (Fabry disease). In patients with Fabry disease there is vacuolization of the cytoplasm of the endothelial cells of the arterioles and smooth muscle cells of the arrector pili. The presence of these vacuoles may be a clue to the specific diagnosis in sections stained with haematoxylin and eosin. However, in most cases the amount of glycolipid in the skin is small making it extremely difficult, if not impossible to identify them, in routinely prepared sections. Special stains such as Sudan black B and PAS highlight the presence of glycolipid deposits within the vacuoles in patients with Fabry disease and related disorders. The lipid material is double refractive, which can be demonstrated by means of polaroscopic examination of unfixed, or formalin fixed frozen sections. Deposits of glycolipids in Fabry disease are not restricted to the lesions of angiokeratoma, but may also be seen in skin that appears to be normal.

Electron microscopy

Ultrastructural studies in angiokeratomas have demonstrated quantitative alterations of cytoplasmic organelles within the endothelial cells {833}. Electron microscopy examination of the skin in Fabry disease show large electron dense lipid deposits in endothelial cells, pericytes, fibroblasts, arrector pili muscles and in secretory, ductal, and myoepithelial cells of the eccrine glands {1683}. These deposits show a characteristic lamellar structure {1366,2438}, not seen in other types of angiokeratomas or in lesions of angiokeratoma corporis diffusum with no enzymatic anomalies. Other ultrastructural findings in patients with Fabry disease consist of intersecting short crescent shaped, tightly packed membranes in the endothelial cells of the small cutaneous blood vessels {679} and cytoplasmic vacuoles in the epithelial cells of the eccrine glands {1094}.

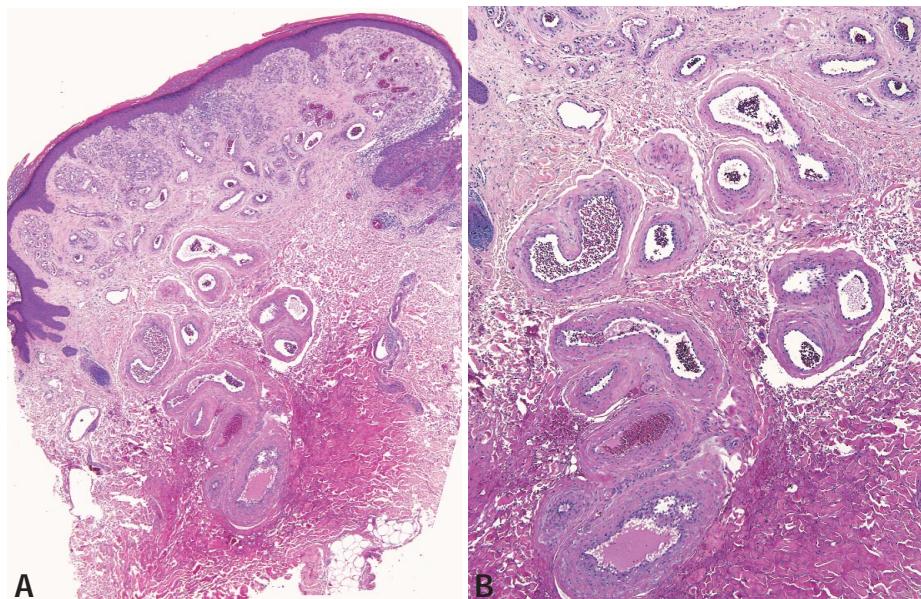


Fig. 5.12 Superficial arteriovenous haemangioma (cirsoid aneurysm). **A** Low power magnification that shows a neoplasm characterized by vessels with thick walls at the base of the lesion and a proliferation of small vessels on the surface. **B** Irregular vessels with thick walls and lined by a single layer of epithelium.

Arteriovenous haemangioma

Definition

Arteriovenous haemangiomas are benign, asymptomatic vascular proliferations. They are not associated with significant arterio-venous shunting.

ICD-O code 9123/0

Synonyms

Cirsoid aneurysm, acral arteriovenous tumour {384,385,528,1811}.

Epidemiology

It occurs mainly in middle-aged adults, with no sex predilection.

Localization

Arteriovenous haemangioma is a neoplasm mainly affecting facial skin. Intraoral and vulvar examples have been also described {1318,1376,1698,1972}.

Clinical features

Arteriovenous haemangioma presents as a red, purple, or skin coloured asymptomatic papule measuring 0.5-1.0 cm. Usually the lesions are solitary, although multiple examples have been cited. When the lesions are multiple they tend to cluster. Occasionally, they are associated with other abnormalities including epidermal naevus syndrome, vascular hamartomas and malformations {372}.

Several examples of multiple arteriovenous haemangiomas have been described in patients with chronic liver disease {47}.

Macroscopy

Grossly, lesions of arteriovenous haemangioma present as raised papules and on sectioning there is an admixture of white and red to brown areas, which represent the walls of the thick blood vessels containing blood.

Histopathology

Arteriovenous haemangioma is a well-circumscribed vascular proliferation that involves the upper and mid reticular dermis. The neoplasm is composed mainly of thick-walled muscle-containing blood vessels, lined by a single layer of endothelial cells. Intermingled with the thick-walled blood vessels are thin-walled dilated blood vessels and variable amounts of mucin. Although the thick-walled blood vessels resemble arteries, they lack a well-formed elastic internal membrane, and most likely represent ectatic veins {1318}. In about one-fourth of the studied cases it is possible to identify both the arteriovenous shunts and the spiralled ascending small muscular artery ("feeder" vessel) with serial sections {834}. The lesions recently described as symplastic haemangioma

probably represent ancient arteriovenous haemangiomas with atypical cells due to degenerative changes that occur in long-standing lesions {1351}.

Histogenesis

The precise nature of arteriovenous haemangioma is uncertain. Initially it was considered to be a multicentric hamartoma of the sub-papillary vascular plexus with one or more arteriovenous anastomoses {834}. Other authors have suggested that a hamartoma of the Sucquet-Hoyer canal of the glomus body is the cause of this lesion. The latter interpretation, however, is unlikely because glomus cells are usually absent in arteriovenous haemangioma, and to date, they have been identified in only one example of all the reported cases {1318}.

Prognosis

Arteriovenous haemangioma is a benign lesion and local excision suffices.

Cutaneous angiosarcoma

Definition

Angiosarcoma is a malignant neoplasm of endothelial cells. Differentiation between lymphangiosarcoma and sarcomas with blood vascular differentiation appears problematic at the current time.

Synonyms

Lymphangiosarcoma, haemangiosarcoma.

Epidemiology

There are low-grade forms of angiosarcoma that can occur outside the circumscribed clinical settings detailed herein. Almost all high-grade angiosarcomas are in one of the following settings: the head and neck of predominantly male elderly patients (the most common setting) {1046}, the chest of patients who have undergone mastectomy for breast cancer (Stewart-Treves syndrome) {2269}, lymphoedema (congenital or acquired), or post-irradiation {2271}.

Localization

Most of the epidemiologic settings also define the sites of disease.

Clinical features

Angiosarcoma, regardless of its genesis usually begins as a very poorly defined red plaque resembling a bruise {1046}. Lesions can become quite large before metastasis occurs. When it does, the spread is usually haematogenous. Its borders may extend for several centimetres beyond what is visible {1969}. Areas of nodularity arise after a time, but not in all patients. Unless a lesion is detected very early, multiple relapses and death are frequent occurrences.

Histopathology

Angiosarcoma begins as a plaque, with small, jagged thin walled vessels that insinuate themselves between collagen bundles of the reticular dermis. Unlike in Kaposi sarcoma, there is no tendency of

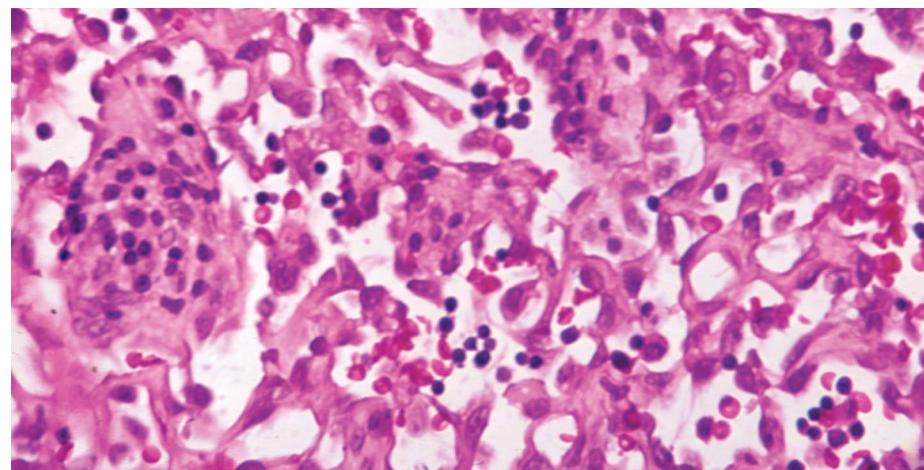


Fig. 5.14 Cutaneous angiosarcoma. The blood vessels have swollen endothelial cells with hyperchromatic nuclei.

spindled cells to first appear in increased number around pre-existent vessels and/or adnexa. The endothelial cells become progressively more protuberant, with enlarged, hyperchromatic nuclei. Lymphoid nodules are sometimes seen. The edges of plaques of angiosarcomas can be very poorly demarcated, making it practically impossible to provide accurate information about the resection margins. Plaques of spindled endothelial cells in the post-mastectomy setting are not necessarily those of angiosarcoma, as Kaposi sarcoma can also occur {59}. The plaque stage of angiosarcoma can give rise to nodules, composed of compact masses of spindled or epithelioid cells, or both. Vascular lumina may be hard to detect in such nodules, and careful inspection may be needed to differentiate these from melanoma and spindle cell squamous carcinoma if only a partial biopsy is submitted. Cytoplasmic vacuoles may be a clue to endothelial differentiation in poorly differentiated cases.

Immunohistochemistry

The cells of angiosarcoma are usually positive for CD31, CD34 or VWF(VIIIrAg). Poorly differentiated tumours can lose one or more of these antigens, necessitating a panel in difficult cases {1755}. Recently FLI-1 has been described as a useful marker with the additional advantage of nuclear staining {761}. Angiosarcoma in the post-mastectomy setting may show blood vascular differentiation, despite a pathogenesis related to lymphoedema {1277}. Angiosarcomas are consistently negative for HHV-8 {1371}.



Fig. 5.13 Angiosarcoma of the upper arm in a patient with a previous carcinoma of the breast (Stewart-Treves syndrome).

Differential diagnosis

It includes the atypical vascular proliferation after radiation therapy, Kaposi sarcoma and pseudovascular squamous cell carcinoma.

Genetics

Cytogenetic changes include gains of 5pter-p11, 8p12-qter, and 20pter-q12, losses of 7pter-p15 and 22q13-qter, and -Y {2101}. Insufficient numbers of cases have been analyzed to determine if there are reproducible differences between different types of angiosarcoma.

Prognosis and predictive factors

Metastases to regional lymph nodes and to the lungs occur, often after repeated local recurrences and surgical excisions. The prognosis is poor, and in one series, only 15% of patients survived for 5 years or more after diagnosis {1046}. This, in part, reflects the delayed diagnosis of these lesions. This limited survival is despite the use of various treatment modalities, sometimes involving surgery, radiotherapy, and chemotherapy.

Lymphatic tumours

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Lymphangioma circumscripum

Definition

Lymphangioma circumscripum refers to a vascular malformation involving the lymphatic vessels of the superficial dermis. A denomination as superficial lymphatic malformation would be more appropriate to describe this lesion.

ICD-O code 9170/0

Epidemiology

Usually, lymphangioma circumscripum is present at birth or appears early in life.

Localization

Lymphangioma circumscripum may be located in any anatomic site, but has predilection for the axillary folds, shoulders, neck, proximal parts of the extremities and tongue {750,1798,2502}. Lesions involving eyelids and conjunctiva {841} and genital skin of males and females {149,419,2006,2436} have also been described.

Clinical features

Clinically, the lesion consists of numerous small vesicle-like lesions, often with a verrucous surface, grouped in a plaque.

Sometimes purplish areas within the lesion are seen due to haemorrhage and thrombus formation within the blood vessel component. Probably, the superficial vesicles are the result of saccular dilatations of superficial lymphatics secondary to raised pressure transmitted from the underlying pulsating cisterns {2502}. Magnetic resonance imaging accurately demonstrates the true extent of involvement {1541}. In rare instances, superficial lymphatic malformations are associated with visceral lymphatic malformations involving the mediastinum {1643} or the bladder wall {1107}. Additional associations include Becker naevus {1762}, and superficial lymphatic malformations have been described in patients with Maffucci syndrome {2292} and Cobb syndrome {2168}.

Macroscopy

The excised specimens of lymphangioma circumscripum show dilated vascular spaces involving both the superficial dermis and deeper subcutaneous tissue, which correspond to the malformed lymphatic vessels.

Histopathology

The stereotypical superficial lymphatic malformation is accompanied by deep

lymphatic dilated cisterns with muscular walls situated in the subcutaneous fat, resulting in swelling of the tissue beneath the superficial vesicles {1768}. The superficial component consists of dilated lymph vessels, lined by flat endothelial cells in a discontinuous layer, and situated in the papillary dermis, and the superficial reticular dermis {179,750}.

Sometimes, the lymphatic vessels are arranged in clusters in the papillary dermis, resulting in a papillated or verrucous skin surface. The vessels may contain homogeneous eosinophilic proteinaceous lymph or blood, and occasionally foamy macrophages. Scattered lymphocytes may be seen in the connective tissue stroma between dilated lymphatic vessels. In extensive lesions, large irregular lymphatic channels are usually seen beneath the superficial vessels in deep reticular dermis and subcutaneous fat.

Immunohistochemistry

The usual immunohistochemical markers for endothelial cells, such as factor VIII-related antigen, Ulex europaeus, and CD31 do not differentiate between blood and lymphatic vessels {1799}. In these cases, new endothelial cell markers such as vascular endothelial growth factor receptor-3 (VEGFR-3) {763,1463}, D2-40

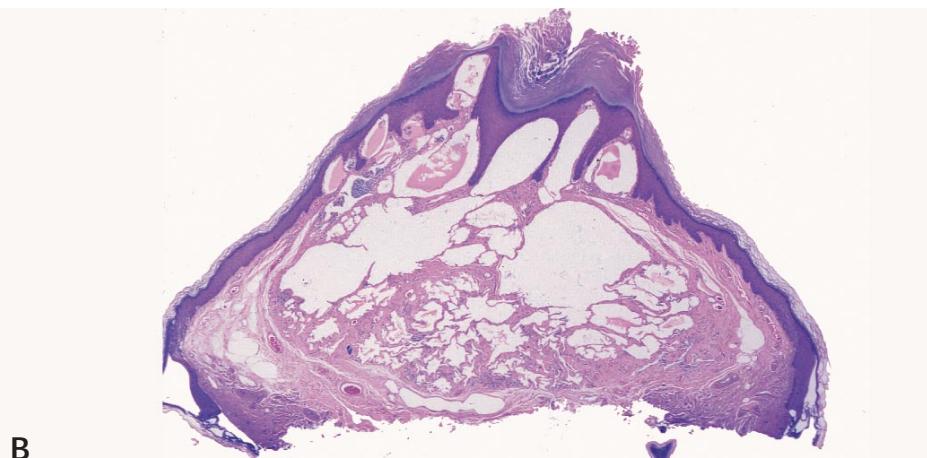
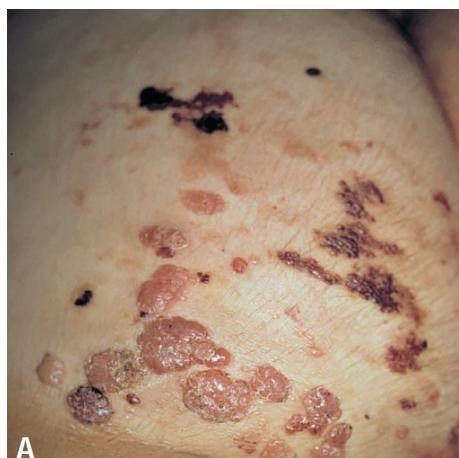


Fig. 5.15 Lymphangioma circumscripum. **A** Close-up view of the lesions showed that it consisted of numerous vesicle-like lesions, some of them with a verrucous surface, grouped in a plaque. Purplish areas are seen due to haemorrhage and thrombus formation within a blood vessel component. **B** Histopathologically, the lesion consisted of dilated lymph vessels involving the superficial dermis and covered by hyperplastic epidermis with compact hyperkeratosis.

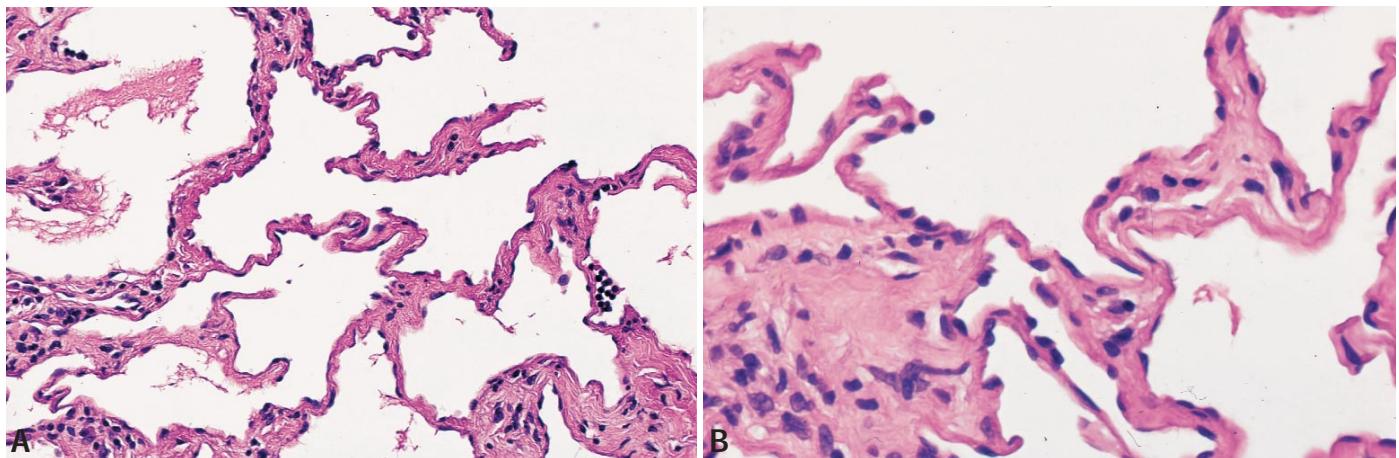


Fig. 5.16 Lymphangioma circumscripum. **A** The lymphatic channels were lined by a discontinuous layer of flat endothelial cells. **B** The stroma between the lymphatic vessels was scant.

{1179} and Prox1 {2535} may be helpful, since these markers are expressed by lymphatic endothelium {763,1463}.

Histogenesis

Lymphangioma circumscripum results from abnormalities in the embryologic development of lymphatic vessels of the skin. Lymphangioma circumscripum probably represents sequestered dermal lymphatic vessels that failed to link up with the rest of the lymphatic system {2502}. However, an ultrastructural study suggested that lymphangioma circumscripum was induced by long-standing lymphatic stasis {103}. In some patients, lymphangioma circumscripum has developed after surgery or radiotherapy on the involved area {1406,1859}.

Prognosis and predictive factors

Usually, lymphangioma circumscripum is a localized and superficial lymphatic malformation that only causes cosmetic problems and does not require treatment. The presence of a deep component may explain the tendency of the lesions to persist after superficial excision.

Progressive lymphangioma

Definition

Progressive lymphangioma is a benign, localized, slow-growing neoplasm composed of thin-walled, interconnecting vascular channels in the dermis and subcutis.

ICD-O code

9170/0

Synonyms

Acquired progressive lymphangioma, benign lymphangioendothelioma.

Epidemiology

Progressive lymphangioma is rare. It occurs chiefly in middle-aged or older adults and does not show a sex predilection {918}.

Etiology

Progressive lymphangioma has been reported after trauma, such as surgical procedures and tick bites. Inflammation secondary to trauma has been claimed to play a role {2463,2532}.

Localization

Lesions have been reported most com-

monly on the lower extremities, but any region of the skin may be affected {918}.

Clinical features

Lesions usually present themselves as solitary, well-circumscribed, red or violaceous patches or plaques. Although usually asymptomatic, patients may complain of tenderness, pain, or itching. Because of slow growth over years, lesions may measure several centimetres in diameter {918,1157}.

Histopathology

Progressive lymphangioma is characterized by delicate, often widely dilated vascular spaces lined by a monolayer of monomorphic endothelial cells. In some foci, endothelium-lined papillary stromal projections extend into those spaces. With progressive extension into the deep dermis, vascular spaces become narrower. They tend to dissect between collagen bundles and to surround pre-existing vessels and adnexal structures. Endothelial cells are more numerous than in normal lymphatic vessels and may be closely crowded together. Nuclei may be hyperchromatic, but there is no prominent nuclear atypia.

Immunohistochemistry

Endothelial cells are usually stained by antibodies against CD31 and CD34, whereas other endothelial markers give more inconsistent results. Actin-positive pericytes around vascular lumina are present focally {918,1157}.

Differential diagnosis

Lymphangioma-like Kaposi sarcoma dif-



Fig. 5.17 Progressive lymphangioma. Solitary, rather well-circumscribed red patch on the thigh.

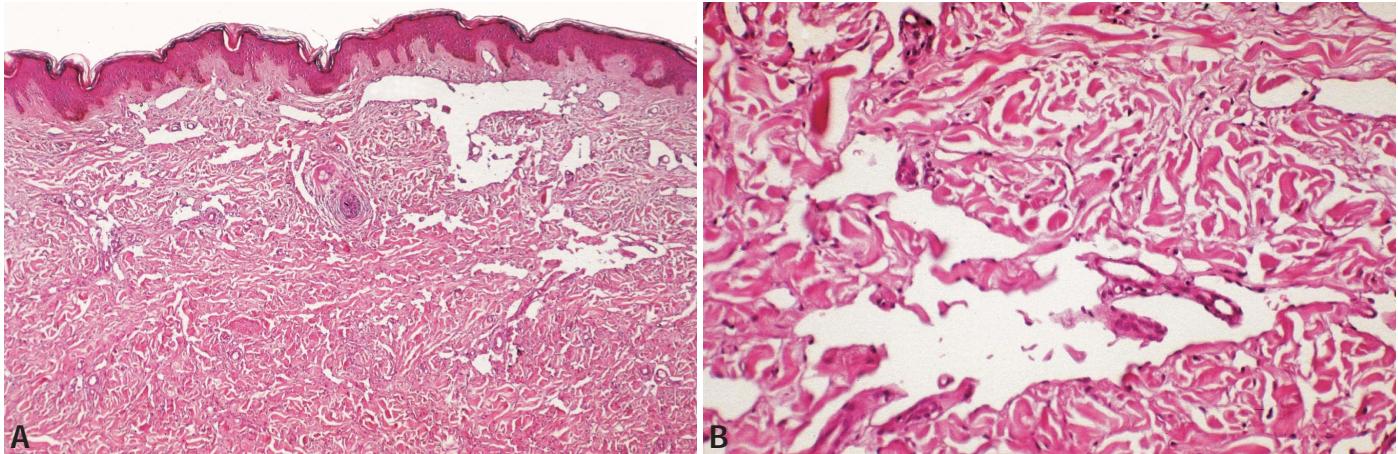


Fig. 5.18 Progressive lymphangioma. **A** Widely dilated, bizarre-shaped vascular spaces dissecting between collagen bundles and surrounding preexisting vessels. Papillary stromal projections extend into vascular lumina. **B** Vascular spaces are lined by a monolayer of monomorphic endothelial cells.

fers from progressive lymphangioma by the presence of plasma cells, the invariable presence of HHV-8 and more classic areas of Kaposi sarcoma elsewhere in the lesion. The so-called atypical vascular proliferation following radiotherapy (benign lymphangiomatous papules) differs from progressive lymphangioma clinically and histopathologically by presenting as tiny vesicles and histopathologically by being associated with much wider spaces in the upper dermis. Moreover, these lesions are thought to represent lymphangiectasias, rather than a neoplastic process (628,1921).

Histogenesis

Progressive lymphangioma is considered to be a neoplastic proliferation of lymphatic vessels. A neoplastic nature is suggested by its slowly progressive course. Derivation from lymphatic endothelia has been suggested on the basis of rare erythrocytes within and around vascular lumina and absence of a peripheral ring of actin-positive pericytes in most vessels.

Prognosis and predictive factors

Following surgical excision, local recurrences are exceptional. Metastases do not occur. Regression of lesions after systemic therapy with corticosteroids and in the absence of any treatment has been reported (918,1577,2463).

Lymphangiomatosis

Definition

Lymphangiomatosis is characterized by

a diffuse proliferation of lymphatic vessels that may involve bones, parenchymal organs, soft tissue, and skin.

Synonyms

Generalized lymphangioma, systemic cystic angiomas, multiple lymphangiectasias.

Epidemiology

Lymphangiomatosis is a rare disease occurring mainly in the first two decades of life. There seems to be no sex predilection (862,1882).

Localization

Lesions occur in the skin and the superficial soft tissues of the neck, trunk, and extremities. Most cases of lymphangiomatosis affect bones and parenchymal organs, especially the lung, pleura, spleen, and liver. Soft tissue involvement occurs in the mediastinum and retroperitoneum.

Clinical features

Cutaneous and subcutaneous lesions present themselves as soft, fluctuant swellings that can be squeezed from one area to another and that may be associated with tiny vesicles. In patients with involvement of bones and visceral organs, the presenting signs range from pathologic fractures to chylothorax, chylous ascites, and other symptoms related to particular organs affected by the process. The interconnected lymphatic channels can be visualized by lymphangiography or direct injection of contrast media into cystic vascular spaces. Plain x-rays often reveal osteolytic areas as a

consequence of involvement of bones (862,1882).

Histopathology

Cutaneous lesions of lymphangiomatosis are characterized by markedly dilated lymphatic channels throughout the skin and subcutis that are lined by a single attenuated layer of flattened endothelial cells and usually appear empty. Those channels tend to dissect between collagen bundles and to surround pre-existing structures in a manner reminiscent of well-differentiated angiosarcoma. Unlike angiosarcoma, cytologic atypia, endothelial multilayering, and mitotic figures are absent. The stroma often contains numerous siderophages and focal aggregates of lymphocytes. Exceptionally extramedullary haematopoiesis may be seen.

Histogenesis

Lymphangiomatosis probably represents a vascular malformation, rather than a neoplastic process.

Prognosis and predictive factors

When present on the neck and trunk, lymphangiomatosis of soft tissues is usually associated with extensive osseous or visceral involvement and carries a grave prognosis with a high rate of mortality (1882). In lymphangiomatosis of the limbs, involvement of bones and visceral organs is usually insignificant and prognosis, therefore, favourable (1021).

Smooth and skeletal muscle tumours

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Smooth muscle is found in the skin in the arrector pili muscles, the walls of blood vessels and in 'genital' skin, which includes the scrotum (dartos muscle), vulva and nipple (areolar smooth muscle). Each of these sites of smooth muscle can give rise to a tumour. Tumours of striated muscle are exceedingly rare in the skin. Only the rhabdomyomatous mesenchymal hamartoma (striated muscle hamartoma) will be considered below.

Smooth muscle hamartoma

Definition

Smooth muscle hamartoma is a proliferation of dermal smooth muscle bundles that is usually congenital.

Synonyms

Arrector pili hamartoma, congenital pilar and smooth muscle naevus, congenital smooth muscle naevus

Epidemiology

Smooth muscle hamartoma is usually congenital with only occasional reports of lesions with onset in adolescence or adulthood {590,1069}. There is a slight male predominance. The lesion is uncommon {1028}.

Localization

The lesions are most often located on the trunk and extremities, particularly proximally {1145}. Cases have been reported involving the head and neck region {1290}, scrotum {1870} and conjunctiva {1966}.

Clinical features

The typical presentation is as a solitary patch or plaque of varying size, usually between 1 and 10 cm, which may show hyperpigmentation and/or hypertrichosis {1145} and which may increase in size with the growth of the patient {2610}. A positive pseudo-Darier sign is seen in most cases {2610}. Occasional cases have an atrophic appearance {886}. Less

common presentations may include papular follicular lesions {659}, multiple lesions {915,2200} and the so-called "Michelin tyre baby", the latter typically in boys. Patients with Michelin tyre syndrome may have various other associated abnormalities {2093}. A clinical classification has been proposed in which type 1 refers to the usual localized form, type 2 the follicular variant, type 3 to multiple lesions and type 4 to the diffuse variant {819}.

Histopathology

There are increased numbers of variably orientated discrete smooth muscle bundles within the dermis and sometimes the subcutis and these may connect to hair follicles {1145,2093}. The overlying epidermis may show acanthosis and basal hyperpigmentation and there may be prominent folliculosebaceous units present, although these do not appear to be increased in number {206,1145}.

Immunohistochemistry

Lesions have been positive for smooth muscle actin and desmin as expected {886,1299,2093}. CD34 positive dendrocytes have been reported to be an integral part of the proliferation {1299}.

Differential diagnosis

Becker naevus may show dermal changes identical to smooth muscle hamartoma. It has been suggested that these lesions may form a spectrum {1145}.

Pilar leiomyoma differs from smooth muscle hamartoma in being acquired, frequently multiple, often painful and comprising less discrete smooth muscle bundles with intervening collagen.

Genetic susceptibility

Rare cases of smooth muscle hamartoma have been described in siblings and in a mother and her children {915}. Xp microdeletion syndrome is characterized by an unbalanced translocation between the X and Y chromosomes leading to deletion of the distal short arm of the X chromosome. Affected infants show microphthalmia, linear skin defects and sclerocornea. The linear skin defects have been reported to show histological features similar to smooth muscle hamartoma {1794} although this was not described in another case {686}.

A child with a familial paracentric inversion of chromosome 7q and Michelin tyre syndrome with smooth muscle hamar-



Fig. 5.19 Pilar leiomyoma. Multiple pilar leiomyomas of the upper back. The lesions were painful in response to cold.

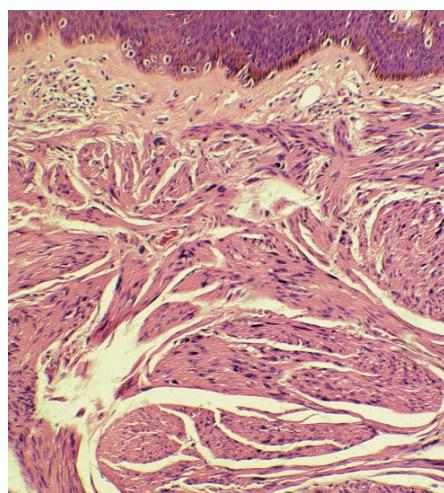


Fig. 5.20 Pilar leiomyoma. There are interlacing bundles of smooth muscle fibres forming a nodule.

toma has been described. The relevance, if any, of the genetic abnormality is unknown {2093}.

Pilar leiomyoma

Definition

Pilar leiomyoma is a benign tumour derived from the arrector pili muscle {1054,1878}.

ICD-O code

8890/0

Synonym

Piloleiomyoma

Epidemiology

Solitary lesions have a female preponderance. They usually develop in adult life. Rarely, they are present at birth. Multiple lesions usually have their onset in the late second or third decades of life.

Localization

Solitary lesions may develop anywhere on hair-bearing skin, particularly the trunk and limbs. Multiple lesions have a predilection for the face, back and extensor surfaces of the extremities.

Clinical features

Pilar leiomyomas may be solitary or multiple, with up to several hundred lesions. Multiple lesions may be grouped, linear, or zosteriform. Solitary lesions may measure up to 2 cm or more in diameter, but multiple lesions are much smaller. Leiomyomas are firm reddish-brown papulonodules. Multiple lesions are usually painful; solitary lesions are infrequently so.

Histopathology

Pilar leiomyomas are circumscribed (but not sharply so), non-encapsulated tumours of the dermis, composed of bundles of smooth muscle arranged in an interlacing or haphazard pattern. The cells have abundant cytoplasm and elongated nuclei with blunt ends. Mitoses are infrequent or absent {1878}. Atypical cells, similar to those seen in the symplastic leiomyoma of the uterus, are uncommon {1486}. Granular cell variants are extremely rare {1586}.

Small amounts of fibrous stroma are present between the muscle bundles in older lesions, but there is usually less stromal collagen than in the smooth mus-

cle hamartoma. Overlying epidermal hyperplasia is sometimes present {1878}. The tumour cells stain for desmin and smooth muscle actin.

Genetics

Some of the multiple cases are familial, with an autosomal dominant inheritance {728}. The syndrome of multiple cutaneous and uterine leiomyomas is also autosomal dominant with the locus on chromosome 1q42.3-q43 {51,1526}.

Cutaneous leiomyosarcoma

Definition

Cutaneous (dermal) leiomyosarcoma is a malignant neoplasm of smooth muscle cells arising in the dermis. Subcutaneous and soft tissue leiomyosarcomas are discussed in the soft tissue monograph.

ICD-O code

8890/3

Epidemiology

Over 100 cases of dermal leiomyosarcoma have now been reported {1164}. Most cases develop in adults, with a peak incidence in the sixth decade. Childhood cases are extremely rare {2563}. There is a male predominance.

Localization

These tumours have a predilection for the extensor surfaces of the extremities

and to a lesser extent the scalp and trunk {593}.

Clinical features

Dermal leiomyosarcomas are solitary, firm nodules measuring 0.5-3 cm in diameter. They are usually asymptomatic, but pain and tenderness have been recorded.

Histopathology

By definition, the major portion of the tumour is in the dermis, although subcutaneous extension is present in some cases. They have an irregular outline with tumour cells infiltrating into, or blending with the collagen fibres at the periphery. The tumour is composed of interlacing bundles of elongated spindle-shaped cells with eosinophilic cytoplasm and blunt-ended nuclei. Sometimes there is a suggestion of nuclear palisading. There is at least one mitosis per 10 high-power fields in cellular areas. Pockets of greater mitotic activity (mitotic 'hot spots') are found, usually in areas showing nuclear pleomorphism. Granular cell, epithelioid, inflammatory and desmoplastic variants have all been described {2476}. Two different growth patterns have been described: A nodular pattern which is quite cellular with nuclear atypia and many mitoses; and a diffuse pattern which is less cellular with well-differentiated smooth muscle cells and inconspicuous mitoses {1164}.

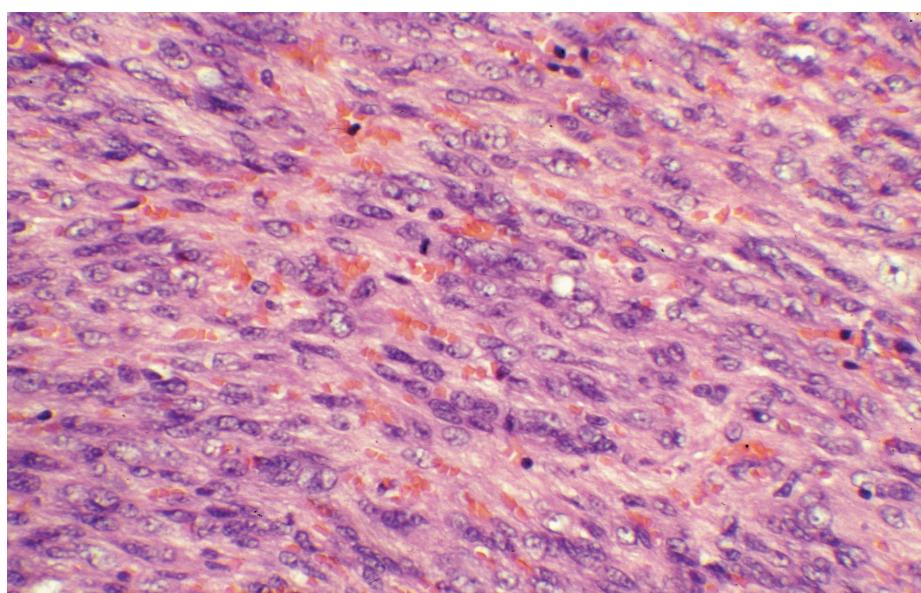


Fig. 5.21 Leiomyosarcoma, confined to the dermis. There are bundles of spindle shaped cells and scattered mitotic figures. Not the nuclear pleomorphism.

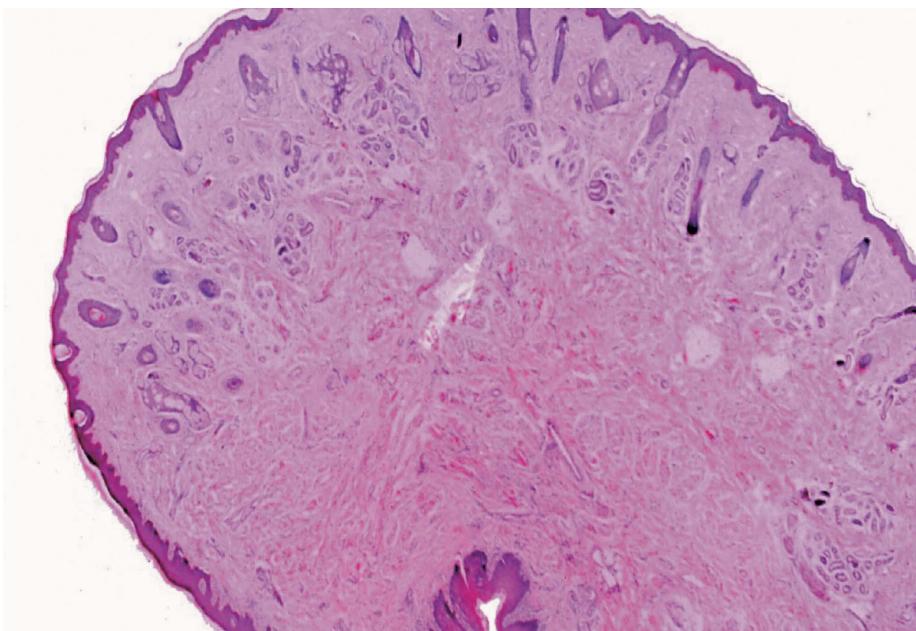


Fig. 5.22 Rhabdomyomatous mesenchymal hamartoma. Low power view of rhabdomyomatous mesenchymal hamartoma, showing polypoid configuration, intact epidermis, numerous small vellus follicles, and a central core containing skeletal muscle.

Immunohistochemistry

The cells express smooth muscle actin. Desmin is present in the majority of cases. Pan-muscle actin (HHF-35) is sometimes present focally.

Histogenesis

The majority of tumours are derived from the arrector pili muscles. Rare cases derived from areolar smooth muscle in the nipple {1452} and dartos muscle in the scrotum {758} have been reported.

Genetics

An unequivocal genetic fingerprint for these tumours is currently lacking {2175}. Various genes have been identified that are expressed differentially in tumour and normal tissue. Soft tissue leiomyosarcomas most often show genomic alterations in the 13q4-q21 region {622}.

Prognosis and predictive factors

Dermal leiomyosarcomas may recur locally, but the reported incidence (5-30%) varies widely {2476}, but metastases of confirmed cases are unknown {1139}.

Rhabdomyomatous mesenchymal hamartoma

Definition

Rhabdomyomatous mesenchymal ha-

martoma (RMH) refers to single or multiple, congenital, frequently polypoid lesions that typically arise near the midline of the head and neck. They contain skeletal muscle fibres within the dermis {1618}.

Synonyms

Striated muscle hamartoma {1008}, congenital midline hamartoma.

Epidemiology

About 25 examples of this lesion have been reported {1973,2320}. Typically, the lesions have been present since birth or early childhood, and most patients are children. Rare cases have been reported in adults {2037}. Thus far, the male: female ratio is 2:1.

Etiology

These lesions may be derived from striated muscle of the branchial arch {105, 899,1008,1973}.

Localization

RMH typically arises in the midline of the head and neck, with a particular predilection for the nose and chin. There have also been cases involving the preauricular region {1902,2010,2122}, lateral forehead {1973}, and cheek {2320}.

Clinical features

The majority of lesions are described as papules or polyps, but a few have presented as nodules {105,1973,2320} or "sessile masses" {1685}. RMH lesions are generally asymptomatic, but they can demonstrate the interesting property of contractile motion, spontaneously or during crying or feeding {1973,2010}. Most patients lack other congenital anomalies, but there have been associations with cleft lip and palate, ocular abnormalities (coloboma, microphthalmia, limbal dermoid), low-set ears, craniofacial clefts, thyroglossal duct sinus, lipoma of the brain, and upper extremity and syndactyly {1008,1902, 1973,2010,2037}. Histologic features of RMH have been found in the cutaneous polyps {2037} of a case of Delleman syndrome, which consists of orbital cysts, cerebral malformations, and focal dermal hypoplasia as well as cutaneous appendages {723}. In addition, a patient {1902} with RMH in association with ipsilateral limbal dermoid and coloboma (Goldenhar syndrome), has been reported.

Initially, it was believed that RMH might be an X-linked disorder, as the first few cases were reported in males, but this

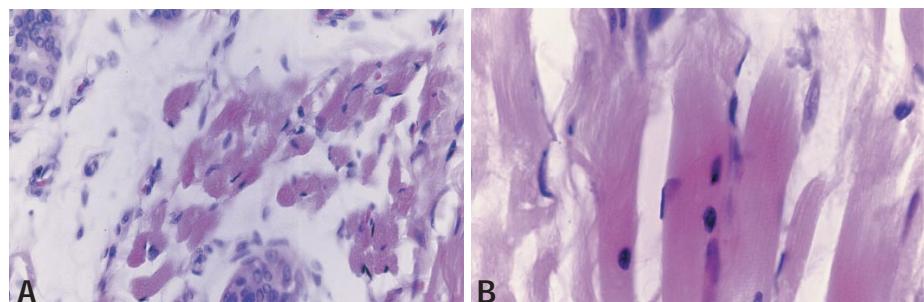


Fig. 5.24 Rhabdomyomatous mesenchymal hamartoma. **A** In the superficial dermis, small skeletal muscle fibers surround eccrine sweat ducts. **B** This high power view shows mature intradermal skeletal muscle fibers with cross-striations.

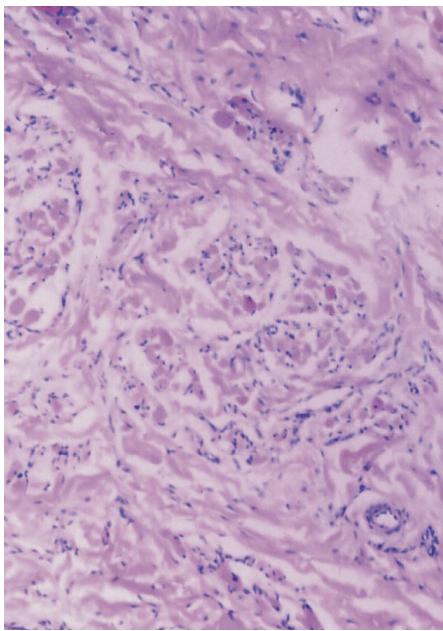


Fig. 5.23 Rhabdomyomatous mesenchymal hamartoma. In the lower part, skeletal muscle fibers among thick collagen bundles of the reticular dermis. In the upper part there are eccrine sweat coils and aggregates of smooth muscle.

was not substantiated when a number of examples were described in girls. Thus far, familial occurrence of this lesion has not been documented.

Histopathology

The most striking feature is the presence of intersecting bundles of mature skeletal muscle fibres, with demonstrable cross striations, and with a general orientation perpendicular to the surface epidermis.

Varying amounts of collagen and mature fat surround these muscle fibres {2037}. They extend through the reticular dermis and become attenuated in the papillary dermis {1618}, where they appear to surround adnexal structures, particularly vellus follicles and sebaceous glands {678,713,1618}. Sebaceous and eccrine sweat glands are usually observed, and in one case there were ectopic apocrine glands {2320}. Nerve elements in these lesions vary considerably; in some cases they are not prominent {2010}, but in others there may be numerous small nerve twigs {987} or a large nerve bundle in the central core of the lesion {2037}. One example contained elastic cartilage {2037}, and calcification or ossification have also been reported {2010}. In some cases, elastic fibre distribution has been reported to be normal {1618}, while in others these fibres are markedly decreased {2037}.

Immunoprofile

Skeletal muscle fibres in RMH stain positively for actin, desmin and myoglobin {678,899}.

Differential diagnosis

Although RMH bears a resemblance to fibroepithelial polyp, naevus lipomatous, and accessory tragus, the combination of midline location and a microscopic skeletal muscle component should permit distinction from those lesions (though small amounts of skeletal muscle have been reported in accessory tragic) {324}). Deeper or more primitive tumours

such as fetal rhabdomyoma, fibrous hamartoma of infancy, or neuromuscular hamartoma (benign Triton tumour) should not be difficult to distinguish from RMH {678,2010}.

Somatic genetics

There has been speculation about a human homolog of the mouse disorganization gene (Ds), which is responsible, directly or indirectly, for the development of hamartomas and other defects {1973,2242}.

Fibrous, fibrohistiocytic and histiocytic tumours

W. Weyers
T. Mentzel
R.C. Kasper
A. Tosti
M. Iorizzo
B. Zelger
R. Caputo

H. Kamino
J. D. Harvell
P. Galinier
G.F. Kao
E.J. Glusac
E. Berti
D. Weedon
C. Rose

Keloid scar

Definition

Keloid scars are raised scars that extend beyond the confines of the original wound.

Epidemiology

Keloid scars occur with equal frequency in men and women. They affect all races, but are more common in dark-skinned individuals. In Black, Hispanic, and Asian populations, the incidence ranges between 4.5 and 16%. Keloids occur chiefly in persons under 30 years of age {1711,2149}.

Etiology

There is a genetic predisposition to the formation of keloid scars. Moreover, hormonal and immunological factors may play a role. Keloids often appear in puberty and tend to enlarge during pregnancy; they have been claimed to be more common in patients with signs of allergy and increased serum levels of IgE. Wounds subjected to great tension or become infected are more likely to heal with a keloid scar {1711,2149}.



Fig. 5.25 Keloid. Raised erythematous plaques are present.

Localization

Keloids are most common on the earlobes, cheeks, upper arms, upper part of the back, and deltoid and presternal areas. They are seen only rarely on the genitalia, eyelids, and on palms and soles {1711,2149}.

Clinical features

Keloids are well-circumscribed, firm, smooth-surfaced erythematous papules or plaques that occur at the site of an injury. The preceding injury may be only minor and, therefore, not always apparent (e.g., rupture of an inflamed hair follicle). Older lesions may be pale or hyperpigmented. Especially in early stages, keloids are often itchy, tender, or painful {1711,2149}.

Histopathology

After a prolonged period of wound healing thick, homogeneous, strongly eosinophilic bundles of collagen, in haphazard array, develop {1498}. Those "keloidal" collagen bundles are the histopathologic hallmark of keloid scars, but are not seen in many cases fulfilling the clinical definition of keloids. The border of keloids is often irregular, with tongue-like extensions of bands of thickened collagen underneath normal appearing epidermis and superficial dermis.

Histogenesis

Keloid scars are characterized by an enhanced proliferation and metabolic activity of fibrocytes that seems to result, in part, from the excess of various cytokines produced by inflammatory cells, including transforming growth factor- β 1 and platelet-derived growth factor. Moreover, a deficiency of cytokines that down-regulate collagen synthesis and inhibit proliferation of fibrocytes, such as interferon- α , has been noted. There is also evidence of reduced degradation of collagen caused, in part, by inhibition of collagenase activity through acid mucopolysaccharides, proteoglycans, and

specific protease inhibitors {1686,1711, 2149,2551}.

Genetic susceptibility

Keloidal scar formation may run in families. It is also more common in Black individuals. A relationship with various human leukocyte antigens has been reported {1711}.

Prognosis and predictive factors

The clinical and histopathologic features of keloid scars indicate a high probability of recurrence following surgical excision alone. Recurrence rates of 45-100% have been described {1711}.

Hypertrophic scar

Definition

Hypertrophic scars are raised scars that do not extend beyond the confines of the original wound. As such, they are closely related to keloids, both being examples of a disturbance of wound healing leading to the formation of exuberant fibrous tissue. Whether hypertrophic scars are simply a less severe variant of keloid scars or represent a different pathologic process is controversial.

Epidemiology

Hypertrophic scars are common. The incidence of hypertrophic scarring (including keloid scars) ranges between 39 and 68% after surgery and between 33 and 91% after burns, depending on the depth of the wound {1711}.

Localization

Hypertrophic scars are most common above the flexor aspects of joints and on the abdomen {2149}.

Clinical features

By definition, hypertrophic scars differ from keloid scars by remaining confined to the original wound. Other distinguishing features are earlier manifestation of

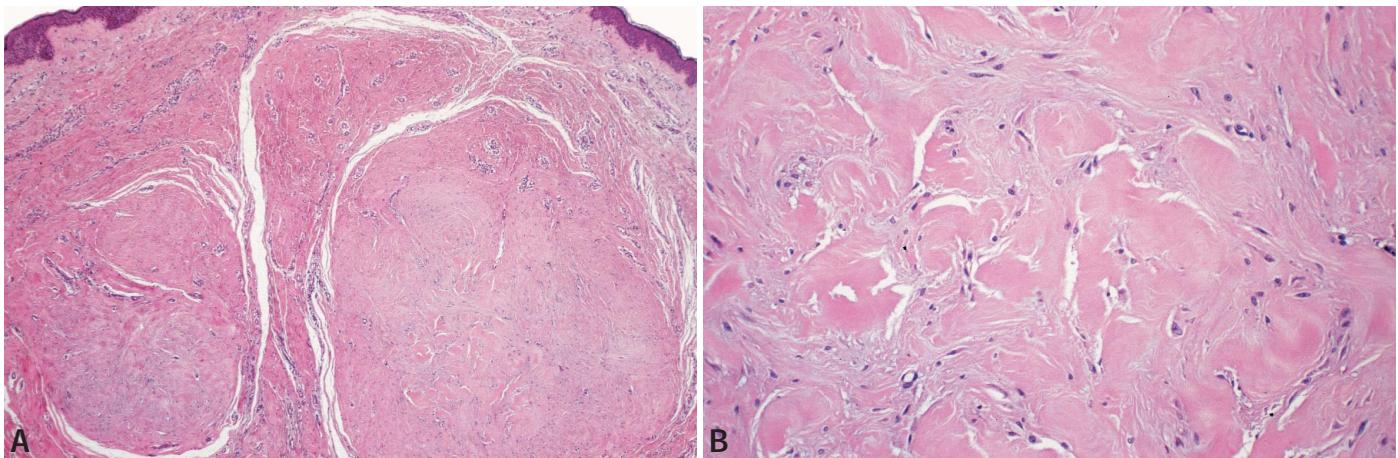


Fig. 5.26 Keloid. **A** Nodular masses of collagen and fibrocytes separated from one another by elongated bands of collagen and containing foci of thick homogeneous, strongly eosinophilic collagen bundles. **B** Thickened homogeneous, strongly eosinophilic bundles of collagen ("keloidal collagen") are the histopathologic hallmark of keloid scars.

hypertrophic scars (usually within 4 weeks after injury, whereas keloids may manifest themselves several months later), a tendency to regression and to contractures not seen in keloid scars, a lower tendency to recur after surgery, and different sites of predilection. In other respects, the clinical features of hypertrophic and keloid scars are essentially the same [2149].

Histopathology

Hypertrophic scars differ from normal scars chiefly by presence of nodular aggregates of collagen with many fibrocytes. The main distinguishing feature from keloid scars is the absence of keloidal (i.e., thick, strongly eosinophilic) bundles of collagen. Moreover, unlike keloid scars, hypertrophic scars show prominent blood vessels arranged perpendicularly to the skin surface. Borders of hypertrophic scars tend to be more regular, and nodules of collagen tend to be distributed more evenly.

Differential diagnosis

Keloids show thick hyaline collagen bundles. Cases with overlap features between keloids and hypertrophic scars are seen.

Histogenesis

No principal differences have been noted in the histogenesis of hypertrophic scars and keloid scars [1711].

Prognosis and predictive factors

Although hypertrophic and keloid scars are closely related, the distinguishing features, clinically and histopathologically, allow a judgment to be made about the probability of recurrence following surgical excision. In one series, the recurrence rate of hypertrophic scars was 10%, as opposed to 63% in keloid scars [257].

Dermatomyofibroma

Definition

Dermatomyofibroma is a distinct biologically benign fibroblastic/myofibroblastic cutaneous proliferation occurring frequently, but not exclusively in young female patients.

ICO-O code

8824/0

Synonym

Plaque-like dermal fibromatosis

Epidemiology

Dermatomyofibroma represents a relatively rare cutaneous mesenchymal neoplasm and usually occurs in young women. Infrequently, dermatomyofibroma is seen in male patients [1073,1189, 1581] and children [1654,1970].

Localization

Most cases of dermatomyofibroma arise in the shoulder and axilla regions, fol-

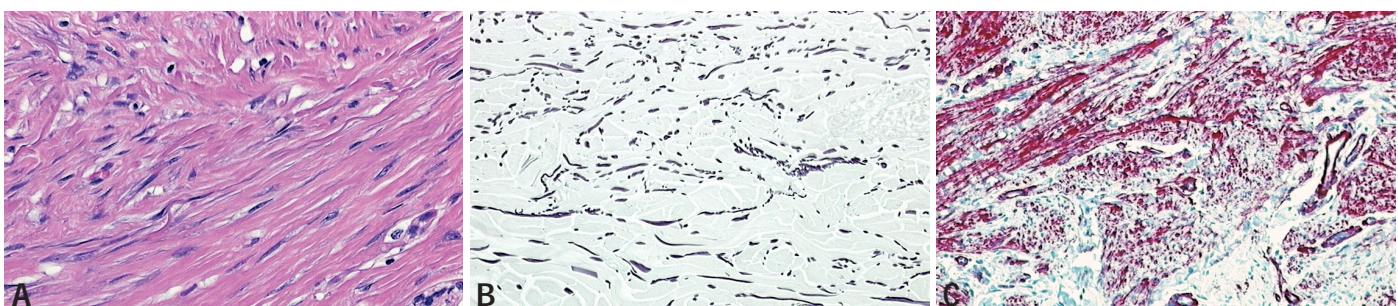


Fig. 5.27 Dermatomyofibroma. **A** Neoplastic cells in dermatomyofibroma have typical cytological features of myofibroblasts with an ill-defined, pale eosinophilic cytoplasm and elongated, tapering nuclei. **B** Characteristically, elastic fibres are slightly increased and fragmented in dermatomyofibroma in comparison to non-neoplastic tissue (bottom). **C** Neoplastic cells in dermatomyofibroma stain variably positive for alpha-smooth muscle actin.

loured by the trunk, the neck, and the upper arm {523,1073,1189,1581,2322, 2375}; more rarely these lesions are seen on the thigh {1073,1189}.

Clinical features

The patients usually present with a slowly increasing, plaque-like, indurated, often red-brown lesion; rarely these neoplasms may reach a considerable size {1073,2375} or may occur as multiple lesions. Grossly, most neoplasms are circumscribed, oval or annular and present as firm plaques or flat nodules measuring usually 1-2 cm, however, larger lesions have been reported {2375}.

Histopathology

Dermatomyofibroma is characterized by an ill-defined proliferation of cytologically bland spindle-shaped tumour cells arranged mainly in bundles and fascicles oriented parallel to the overlying epidermis.

Adnexal structures are typically spared. In most cases the lesions are confined to the dermis, however, a focal extension into superficial subcutaneous tissue is sometimes noted {1581}. The tumour cells contain an ill-defined pale eosinophilic cytoplasm and uniform fusiform nuclei that are either elongated with tapering edges containing an evenly distributed chromatin or vesicular with small nucleoli.

Tumour cells are set in a collagenous matrix with slightly increased and fragmented elastic fibres, a helpful clue in the distinction of dermatofibroma and scarring processes. The overlying epidermis may show mild acanthosis and focal hyperpigmentation.

Immunoprofile

Tumour cells in dermatomyofibroma stain variably for actin and alpha-smooth muscle actin {1189,1581}. As in other myofibroblastic conditions, the expression of actin seems to be dependent on the age and activity of neoplastic cells, and only approximately 50% of cases are positive for this marker {1582}. Lesional cells are negative for S-100 protein, CD34, desmin, and h-caldesmon {581,1074, 1189,1581}.

Prognosis and predictive factors

Complete excision is advised since these neoplasms may reach a considerable size.

Infantile myofibromatosis

Definition

Infantile myofibromatosis (IM) is a tumour of the skin and soft tissues of disputed histogenesis, which is solitary in two thirds of cases. Multicentric lesions (myofibromatosis) occur {634A}.

ICD-O code

8824/1

Synonyms

Solitary cutaneous myofibroma.

Historical annotation

IM was described by Chung and Enzinger in 1981 as a proliferative disorder of myofibroblasts {486}. Cases had been described earlier as congenital fibrosarcoma {2529}, congenital generalized fibromatosis {1229} and congenital mesenchymal hamartoma {203}.

Epidemiology

Most lesions are present at birth, or appear in the first 2 years of life; onset in adults also occurs {2541}. There is a male predominance.

Clinical features

About a third of lesions are situated in the deep soft tissues and the remainder are located in the skin and/or the subcutaneous tissues {1778}. The head, neck and trunk are the usual sites.

They measure 0.5 to 7 cm or more in diameter; they are greyish-white in colour, and fibrous in consistency.

Histopathology

The nodules are reasonably well circumscribed, although there be an infiltrative border in the subcutis. There are plump to elongated spindle cells, grouped in short fascicles. Delicate bundles of collagen separate or enclose the cellular aggregates. Mitoses are variable in number, but not atypical {486,753}.

Vascular spaces resembling those seen in haemangiopericytoma are often found in the centre of the tumour, giving a biphasic appearance. Necrosis, hyalinization, calcification, and focal haemorrhage may be present centrally {753}. For details, see WHO Classification of Tumours of Soft Tissue and Bone {756}.

Immunoprofile

The tumour cells are positive for vimentin and alpha-smooth muscle actin, but neg-

ative for S-100, myoglobin, and cytokeratins {2425}. Reports on immunoreactivity for desmin vary {923}.

Histogenesis

Fletcher and colleagues have suggested that the spindle cell component shows smooth muscle differentiation {753}. Requena et al have suggested an origin from myopericytes. {1920}. Recently, the lesion has been included in a spectrum of tumours showing perivascular myoid differentiation {882}.

Genetics

Familial occurrence is too rare to allow any conclusions regarding genetic susceptibility {2427}

Prognosis

The prognosis is excellent, with recurrence unlikely after excision; aggressive variants are rare {849}. There are no features predictive of recurrence.

Sclerotic fibroma

Definition

Sclerotic fibroma is a benign soft tissue tumour composed of eosinophilic collagen bundles arranged in a storiform pattern {1895}.

ICD-O code

8823/0

Synonym

Storiform collagenoma

Epidemiology

Solitary sclerotic fibroma is rare and occurs in both sexes at any age, from infancy to adulthood. Multiple tumours are typical of Cowden disease, a rare genodermatosis.

Localization

Most frequent sites of involvement are the face, upper and lower extremities and trunk.

Clinical features

Sclerotic fibroma presents as a translucent, white, flesh-coloured or waxy nodule. It is usually unique and measures less than 1 cm. It has a slowly progressive growth, over months or years. The lesion is asymptomatic {1590,1895, 2369}.

Histopathology

The tumour is usually situated in the reticular dermis. It is sharply demarcated and it is composed of hyalinized bands of collagen with a decreased number of fibroblasts. The collagen fibres are thick, glassy and aligned in parallel bundles with a storiform pattern. Elastic fibres are absent. The proliferation tends to expand, pushing aside the normal dermal collagen without engulfing the adnexae {1590,1895,2369}. Alcian Blue staining reveals an increased amount of mucopolysaccharide.

Immunoprofile

Staining for S100 protein, myelin basic protein and neuron specific enolase and desmin are negative {1590,1895}.

Prognosis and predictive factors

Although the lesion is benign, it should be removed due to its tendency to expand.

Digital mucous cyst

Definition

Two types of lesions both with a pseudo-cystic circumscribed dermal mucin deposition exist. In the more common type a connection with the underlying joint cavity can be demonstrated (ganglion type). The second type represents a focal mucinosis produced by fibroblasts (myxomatous type).

Synonyms

Myxoid pseudocysts of the digits, ganglion of the distal interphalangeal joint, digital focal mucinosis.

Epidemiology

Women are more often affected and patients are middle aged or elderly.

Localization

They typically occur on the dorsum of the fingers near the distal interphalangeal joint or near the proximal nail fold. The index fingers and thumb are primarily affected. The toes are rarely involved {1148,2221}.

Clinical features

The lesions are solitary, soft, smooth surfaced and usually not greater than 1.5 cm. A connection of the pseudocyst to the underlying joint can be demonstrated



Fig. 5.28 A Digital mucous cyst on the dorsum of a finger. B Digital fibrokeratoma on a toe.

in the majority of cases by magnetic resonance imaging or injection studies with dye {599,1034}. Osteoarthritis is sometimes evident.

Histopathology

Myxomatous type: this variant has a large pseudocystic area with a myxomatous stroma with scattered spindle-shaped or stellate fibroblasts analogous to focal mucinosis in other areas of the body. The overlying epidermis is often attenuated. The mucin contains mucopolysaccharides which stain positively with alcian blue and colloidal iron. Ganglion type: cystic spaces containing mucin with a collagenous fibrous wall characterize these lesions. Occasionally in some areas of the wall a synovial lining can be demonstrated.

Digital fibrokeratoma

Definition

Digital fibrokeratoma is a benign fibrous tumour often accompanied by a hyperplastic epidermis that arises mostly in the periungual area.

Synonyms

Acquired ungual fibrokeratoma, periungual fibromas of tuberous sclerosis (Koenen tumours), subungual and periungual fibromas, acral fibrokeratoma.

Epidemiology

Most patients are adults. Males are affected more frequently than females {2429}. More than half the patients with tuberous sclerosis develop about puberty multiple fibrokeratomas {2470}.

Localization

The majority of lesions occur on a finger or a toe. Occasionally, lesions present on the palms or soles.

Clinical features

The patients usually present with a solitary lesion. Normally, tumours are small and measure 3-5 mm in diameter. A case of a huge lesion measuring up to 5 cm has been described {1181}.

Histopathology

Digital fibrokeratoma is composed of dense collagen fibres, often with vertical orientation, with a variable number of mature fibroblasts and small blood vessels. A few inflammatory cells can be observed. There is often epidermal hyperplasia. In the stroma thin elastic fibres are present and hair follicles are absent. In a rare variant an oedematous and less dense stroma is found {1279,1280}.

Genetics

In patients with tuberous sclerosis mutations in two different genes, TSC1 on

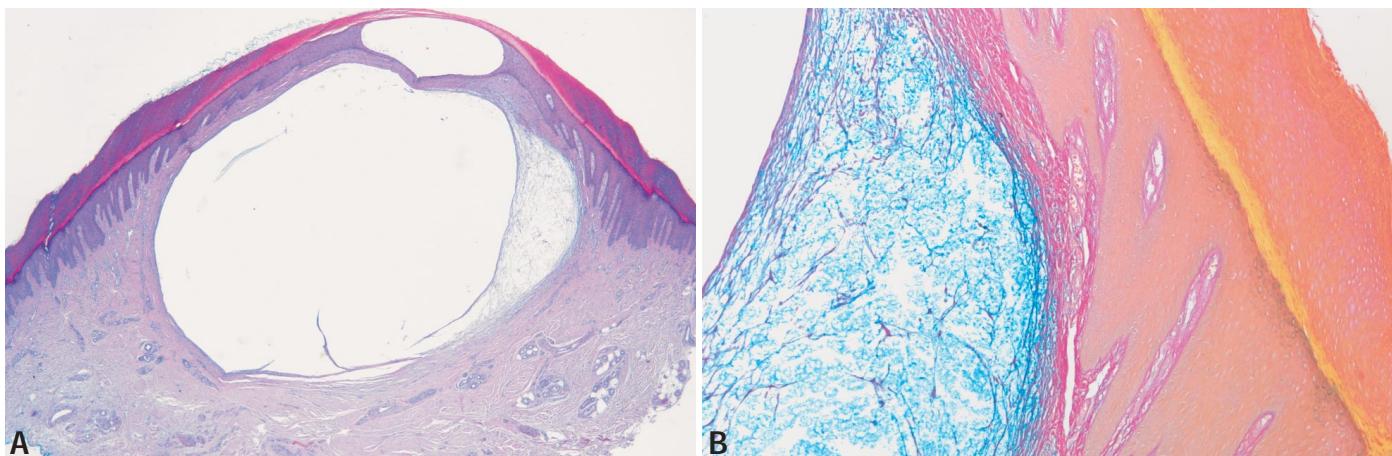


Fig. 5.29 Digital mucous cyst. **A** Low-power view of digital mucous cyst (myxomatous type) shows a cystic lesion with an attenuated epidermis. **B** Colloidal iron stain from this lesion demonstrates the myxomatous stroma.

chromosome 9 and TSC2 on chromosome 16 have been identified {582}.

Pleomorphic fibroma

Definition

Pleomorphic fibroma (PF) is a benign, polypoid or dome-shaped cutaneous neoplasm with cytologically atypical fibrohistiocytic cells {1188}.

ICD-O code 8832/0

Epidemiology

PF occurs mostly in adults {39,1188}.

Localization

They are located on the trunk, extremities, head {39,1188} and rarely the subungual region {983}.

Clinical features

PF are asymptomatic, solitary, slowly growing, flesh coloured and non-ulcerated dome-shaped to polypoid papules from 4-16 mm. The clinical differential diagnosis includes acrochordon, neurofibroma, intradermal naevus and haemangioma. Although clinical behaviour is benign, lesions may locally recur when incompletely removed {1188}.

Etiology

Degeneration, ischemia {808} or the paracrine influence of mast cells {1842} may create the cytologic atypia of PF {1188}.

Histopathology

PF are circumscribed, dome-shaped to

polypoid, hypocellular dermal proliferations of spindle and irregularly shaped stellate or multinucleate cells. Lesional cells have scant cytoplasm and large, pleomorphic, hyperchromatic nuclei with small nucleoli and rare mitotic figures. Foam cells are rarely present. Haphazardly arranged, hyalinized dermal collagen is admixed with moderate mucin. The collagenous bundles in pleomorphic sclerotic fibromas are more storiform and clefted {458,808,1523}. Myxoid {1614} and sclerotic variants have been described {808,1523}.

Immunoprofile

Lesional cells are positive for muscle

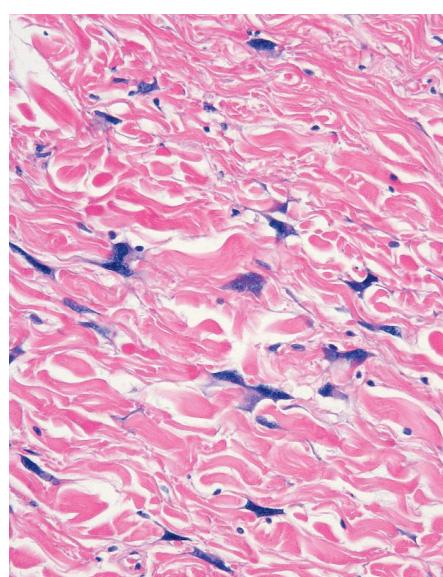


Fig. 5.30 Pleomorphic fibroma. Amid coarse collagen bundles are mesenchymal cells with coarse chromatin and scalloped nuclear borders.

specific actin, CD34 and rarely alpha-1 antichymotrypsin {1188,1988}.

Differential diagnosis

The histologic differential diagnosis includes: atypical fibroxanthoma, variants of dermatofibroma, fibrosarcoma, fibrous papule of the face, angiofibroma, giant cell fibroblastoma, desmoplastic Spitz naevus and fibroepithelial polyp with monster cells {1188}.

Giant cell fibroblastoma

Definition

Giant cell fibroblastoma (GCF) is a histologic variant of DFSP, which primarily affects children.

ICD-O code 8834/1

Epidemiology

GCF is a rare tumour that primarily affects children in the first decade of life, with a strong male predilection. Occasional cases have also been reported in adults {751}.

Localization

GCF most commonly affects the trunk, shoulder region and groin (similar to DFSP), but other reported sites include the extremities and head and neck {971,2174,2338}.

Clinical features

Giant cell fibroblastoma is described as a slow growing, firm, dermal or subcutaneous mass which is painless and asymptomatic.

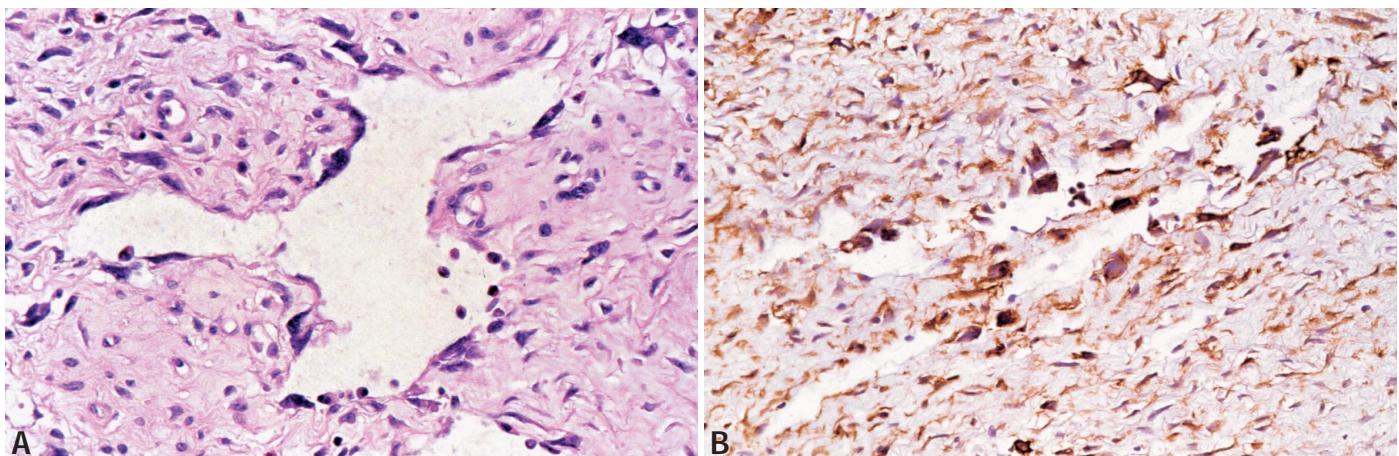


Fig. 5.31 Giant cell fibroblastoma. **A** Angiectoid space lined by hyperchromatic spindle and multinucleate giant cells. **B** CD34 highlights both the giant cells and the surrounding spindle cells.

Macroscopy

Grossly, GCF is a firm yellow or grey tumour with gelatinous or rubbery consistency and without haemorrhage or necrosis {751,2174}.

Histopathology

GCF is usually a subcutaneous tumour, but it often extends into the overlying dermis. Cellularity is variable, but for the most part, GCF is a hypocellular neoplasm composed of wavy spindle shaped cells and scattered giant cells set within a stroma that varies from myxoid to collagenous to sclerotic and contains scattered mast cells. Scattered giant cells with hyperchromatic and angulated nuclei are characteristic. Most giant cells are multinucleated, but some are mononucleated. The nuclei of multinucleate cells are either conglomerated towards the centre of the cell or arranged peripherally, in a characteristic floret pattern. Irregularly branching "angioid" spaces which resemble the vascular spaces of lymphangioma are characteristic but are not seen in all cases. These are lined by spindle and multinucleate cells with morphology identical to those seen in the surrounding stroma. Cellular areas representing DFSP or less often pigmented DFSP (Bednar tumour) may be present. Recurrent lesions are uncommon, but when they occur, the lesions may show a pattern of DFSP. Fibrosarcomatous transformation of GCF has been reported in a recurrent lesion originally diagnosed as DFSP {1841}.

Immunoprofile

The stromal and lining cells are CD34

positive, but negative for VWF (VIIIrAg), CD31, S100, actin, desmin, and EMA {971,2338}.

Differential diagnosis

Since CD34 can be focally positive in other soft tissue lesions, finding the characteristic giant cells is important in diagnosing GCF.

Histogenesis

GCF and DFSP are currently classified as neoplasms derived from fibroblasts, but CD34 positivity suggests possible derivation from interstitial dendritic cells {971}.

Somatic genetics

Both GCF and DFSP exhibit an identical t(17;22) (q22;q13) translocation, which in some cases results in a ring chromosome. The t(17;22) translocation fuses the collagen type I alpha 1 gene from chromosome 17q22 to the platelet-derived growth factor β chain gene from chromosome 22q13, resulting in a chimeric COL1A1-PDGFB gene that encodes for a transforming protein with biologic effects similar to normal PDGFB. The neoplastic cells not only harbour the mutation, but also have PDGFB receptors on their cell surface, resulting in an autocrine loop whereby the tumour cells stimulate their own growth {1735}.

Prognosis and predictive factors

Like DFSP, GCF is a locally aggressive tumour of intermediate malignancy, with up to 50% local recurrence in the original series. Metastases from GCF have not been reported.

Dermatofibrosarcoma protuberans

Definition

Dermatofibrosarcoma protuberans (DFSP) is a mesenchymal neoplasm of the dermis and subcutis, generally regarded as a superficial low-grade sarcoma {1605,2491}.

ICD-O code

8832/3

Synonym

Progressive and recurring dermatofibroma.

Epidemiology

DFSP typically presents during early or middle adult life, with male predominance. However, there is evidence that many tumours may have begun during childhood and become apparent during young adulthood.

Localization

The tumour occurs most commonly on the trunk, including chest, back, and abdominal wall. Less commonly, the neoplasm is located on the proximal extremities; it rarely involves the distal extremities. The head and neck, especially the scalp, are also commonly involved. The vulva {1377} and parotid gland are unusual sites of involvement.

Clinical features

DFSP typically presents as a nodular cutaneous mass, with a history of slow but persistent growth, often of several years duration. Early lesions may be sharply demarcated, and may some-

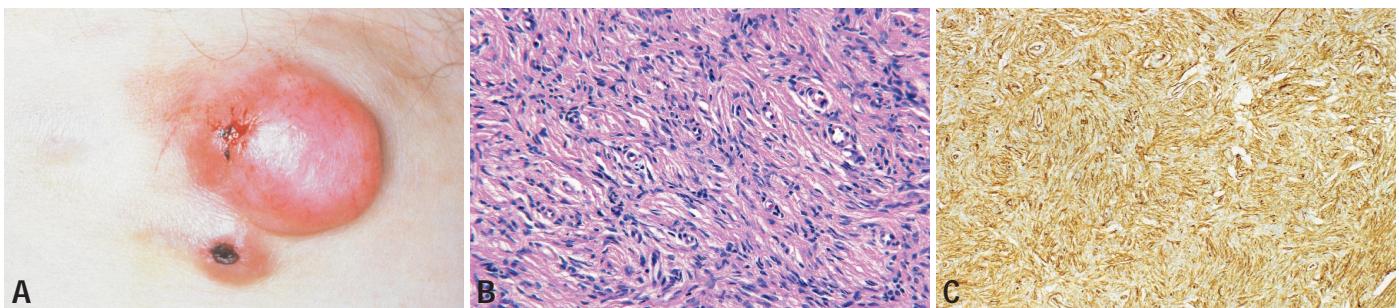


Fig. 5.32 Dermatofibrosarcoma protuberans. **A** DFSP presenting as two reddish nodules with focal ulceration. **B** Compact, uniform, spindle-shaped tumour cells arranged in a storiform pattern. **C** Tumour cells show a strong immunoreactivity for CD34.

times be observed as plaque-like areas of induration, often with peripheral red or blue discolouration. These tumours may resemble morphoea (localized scleroderma) or a morphoeic basal cell carcinoma. The lesion expands slowly, and eventuates in the typical, fully developed protuberant appearance with single or multiple nodules on a plaque-like base. Fungating ulcerated lesions with satellite nodules characterize an advanced neoplasm.

Patients with advanced DFSPs do not exhibit signs and symptoms of chronic wasting, as seen in patients with aggressive, high-grade soft tissue sarcomas. Previous burns, surgical scars, and antecedent trauma have been reported in association with this tumour. There are reports of DFSP occurring at Bacille-Calmette-Guérin (BCG) vaccination sites {1558}, and in association with chronic arsenism {2176}, acanthosis nigricans, and acrodermatitis enteropathica {2161}. The tumour may show rapid enlargement during pregnancy {2329}.

Macroscopy

Most excised primary DFSPs are indurated plaques with one or more associated nodules. Multiple discrete, protuberant skin and subcutaneous tumours are more characteristic of recurrent neoplasms. Often, there is evidence of a surgical scar on the skin surface of the

tumorous tissue. Ulceration may be present. The cut surface of the tumour is grey-white and firm, with occasional areas showing a gelatinous or translucent appearance, corresponding to microscopic areas of myxoid change. Haemorrhage and cystic change are sometimes seen. However, necrosis, a common feature of malignant fibrous histiocytoma, is rarely observed in DFSP. It is unusual to encounter DFSP confined solely to subcutaneous tissue without involvement of the dermis {629}.

Histopathology

DFSP diffusely infiltrates the dermis, and invades into subcutaneous tissue, especially along the fibrous septa of fat. The epidermis is usually uninvolved. A grenz zone may be present. In a well-sampled specimen, the tumour shows some variation in histologic features. The centre of the tumour is typically composed of compact, uniform, slender, mildly atypical, spindle-shaped cells, arranged in a whorled, storiform, or cartwheel pattern. The tumour cells tightly encase skin appendages without destroying them. Nuclear pleomorphism is inconspicuous, and mitotic activity is low-to-moderate (<less than 5/10 HPF). Some tumours have a prominent myxoid matrix, and microscopic myxoid changes have been observed in both primary and recurrent tumours {368}. Superficial areas of the neoplasm are less cellular, and spindle cells are separated by dermal collagen. The deep portion of the tumour shows a proliferation of spindle cells which expand fibrous septa and interdigitate with fat lobules, resulting in a honeycomb appearance. In some tumours, giant cells similar to those of giant cell fibroblastoma are seen. At times, peculiar myxoid nodules may be present, which represent a nonneoplastic myointimal or

myofibroblastic proliferation. Occasional foci may resemble a low-grade fibrosarcoma, with longitudinal fascicles of spindle cells demonstrating more prominent nuclear atypia and mitotic activity (but not greater than 5/10 HPF). Such areas have been seen in a minority of primary or recurrent lesions {853}.

Immunoprofile

DFSP cells label diffusely and strongly with antibodies to CD34 and vimentin. CD34 positivity may be lost in nodular regions. P75 (low-affinity nerve growth factor receptor) has been reported positive in DFSP cells {853}. Tumour cells are negative for S-100 protein, smooth muscle actin, desmin, keratins, and epithelial membrane antigen. Scattered Factor XIIIa positive cells may be present. Tenascin is negative at the dermoepidermal zone (DEZ) in DFSP {1180}. Stromelysin 3 is not expressed in the cells of a DFSP in contrast to dermatofibroma in which it is invariably expressed {558}.

Differential diagnosis

Benign and cellular fibrous histiocytoma or dermatofibroma (DF) can be differentiated from DFSP by the presence of epidermal (sometimes basal cell) hyperplasia, more prominent collagenous stroma, collagen trapping, and infiltration of the fibrous septa, but minimal extension into fat lobules. Immunostains are also helpful. DF contains a focally but not diffusely positive CD34 spindle cell component. P75 and stromelysin 3 are negative, and tenascin is positive at the DEZ in DF. Diffuse positivity for S-100 protein and the presence of Meissner-like corpuscles separate lesions of diffuse neurofibroma from DFSP.

Malignant fibrous histiocytoma (MFH) exhibits a higher degree of cellular atypia, pleomorphism, and mitotic activity



Fig. 5.33 Dermatofibroma (fibrous histiocytoma). Cut surface with distinctive yellow colour.

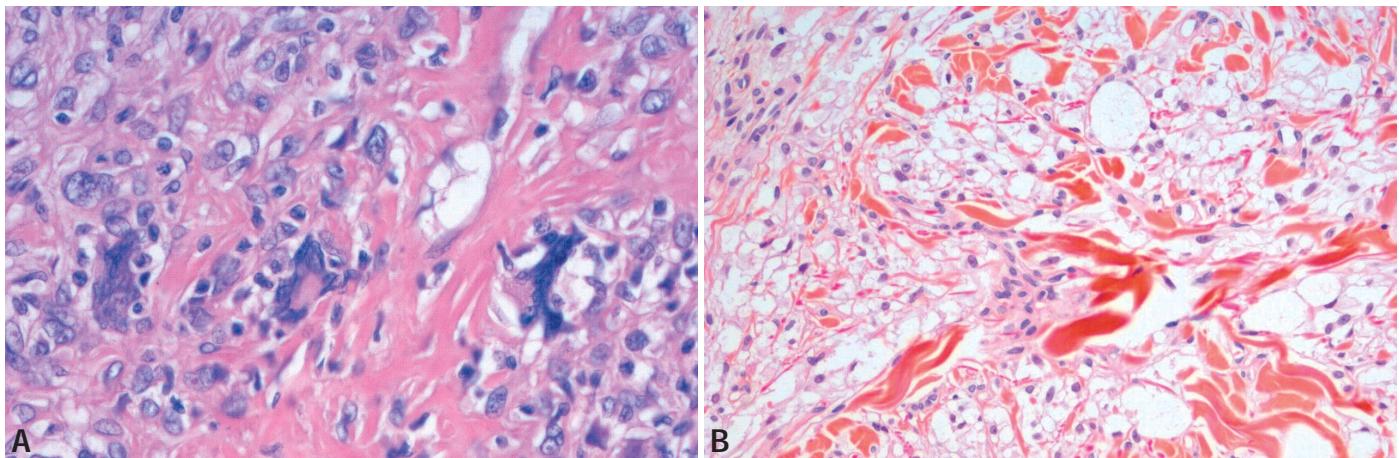


Fig. 5.34 Dermatofibroma (fibrous histiocytoma). **A** Dermatofibroma with monster cells. **B** Clear cell dermatofibroma. Typical cytology with prominent collagen bundles.

than DFSP. Necrosis is usually not a feature of DFSP, but is generally seen in MFH. Myxoid liposarcoma is distinguished from myxoid forms of DFSP by the presence of lipoblasts, negative CD34 staining, and deep soft tissue involvement.

Histogenesis

DFSP and its variant, giant cell fibroblastoma (GCF) are currently classified as neoplasms derived from fibroblasts. CD34 labelling suggests a close linkage to dermal dendrocytes.

Somatic genetics

DFSP and GCF exhibit an identical chromosomal translocation. See page 259.

Prognosis and predictive factors

As with GCF, DFSP has a significant risk of local recurrence. The average recurrence rate in reported cases treated by wide local excision (2-3 cm.) is 18%. A much higher recurrence rate (43%) is reported in tumours treated by superficial or incomplete excisions only {853}. Local recurrence usually develops within three years after initial surgery. Metastasis occurs rarely.

Dermatofibroma (fibrous histiocytoma)

Definition

Dermatofibroma (fibrous histiocytoma) {21} is an ill-defined, predominantly dermal lesion characterized by a variable number of spindle and/or rounded cells. A variable admixture of inflammatory

cells, coarse collagen bundles in haphazard array, and variable epidermal, melanocytic and folliculosebaceous hyperplasia are present.

ICD-O code 8832/0

Synonyms

Histiocytoma (cutis) {2134}, fibroma durum, subepidermal nodular fibrosis or sclerosis {1602}, sclerotic or sclerosing fibroma {1895}, sclerosing haemangioma {910}.

Epidemiology

Dermatofibroma is a very common lesion and may develop at any age, but particularly during the third and fourth decades. The gender distribution varies among different populations.

Etiology

The etiology has not been established unequivocally. It is controversial whether it is an inflammatory {21,2590,2591} or neoplastic process {365,518,522,919}. Dermatofibroma has been reported following local injuries such as trauma, insect bites or folliculitis, suggesting an inflammatory etiology. By contrast some examples have been reported to be clonal, supportive of a neoplastic etiology {457,1078,2422}.

Localization

Most lesions, including various clinicopathological variants, occur on the extremities {840,1081,1114,1155,1187,1346,1786,1895,2115,2587,2592-2594} and trunk {187,370,2403}. Rare cases occur on the face {1583}.

Clinical features

Most lesions are single, round, oval to targetoid papules. Early lesions are reddish, but older ones are brown to skin coloured, frequently with a brown rim at the periphery. They usually evolve rapidly. Dermatofibromas are moderately well circumscribed; the consistency usually is hard, but may be cystic, eroded or crusted when secondary changes such as prominent haemorrhage, lipidization or trauma alter the lesions. Most lesions are flat, slightly elevated or show a shallow dell. The "dimpling" sign, when lesions are squeezed between the thumb and index finger, is characteristic.

Occasionally, there may be a few, up to several dozen, sometimes grouped ("agminated") papules. Multiple dermatofibromas are regarded as a marker of immune suppression; they have been observed in Black females with systemic lupus erythematosus; various other autoimmune disease such as Sjögren syndrome, pemphigus vulgaris, myasthenia gravis and ulcerative colitis treated with immunosuppressive drugs; occasionally in renal graft recipients or AIDS patients. Still other lesions form plaques or nodules to tumours. Dermatofibromas usually are long standing lesions which cause no symptoms.

Macroscopy

Gross examination reveals a moderately well-circumscribed, hard papule, nodule or tumour. The cut surface reveals a skin-coloured to distinctive yellow colour, which may show areas of haemorrhage and lipidization and then become cystic.

Histopathology

Dermatofibromas show a dense infiltrate of spindle-shaped and/or round cells, some of which may be fibrocytes and/or macrophages, centred in the reticular dermis and sometimes, the upper part of the subcutis. Early lesions are rich in macrophages, some of which may be siderophages, and/or lipophages, others multinucleate, e.g. Touton or foreign body giant cells. Established lesions show prominent cellularity and coarse haphazardly arranged collagen bundles. They are frequently arranged in short fascicles that interweave ("storiform"), sometimes with a sclerotic centre. Lesions are ill-defined and at the periphery there can be collagen trapping by lesional cells ("collagen ball formation"). Epidermal, melanocytic and folliculosebaceous hyperplasia is characteristically found above the lesions, and this can be so prominent that buds of hair follicles mimic superficial basal cell carcinoma. Rare cases show smooth muscle proliferation {1381}. Lymphocytes are often spread throughout the lesion with frequent prominence at the periphery, but may be lacking in later stages. At times foam cells may be prominent in deeper areas adjacent to subcutaneous fat. A wide number of variants of dermatofibromas have been proposed {369}. Early lesions may show prominent proliferation of blood vessels, previously called sclerosing haemangioma {910}, more recently haemangiopericytoma-like fibrous histiocytoma {2594}. Prominent lipophages and siderophages are seen in the xanthomatous/histiocytic variant {1081,1114} and haemosiderotic variant {2036}, respectively. Older lesions become progressively fibrotic, with shrinkage of the lesion, particularly seen in atrophic dermatofibroma. Other variants show a heavy eosinophilic infiltrate {40} or pseudolymphomatous features {150}, respectively. Lichenoid, erosive and ulcerated variants {2034} have also been reported. Deep penetrating variants extend into the subcutis and may be easily confused with dermatofibrosarcoma protuberans {1187,2587}. Other rare variants include dermatofibroma with monster cells {2316}; ossifying dermatofibroma with osteoclast-like giant cells {1345}; granular {2403} and clear cell dermatofibromas {1786,2592}; myofibroblastic dermatofibroma with slender cytoplasmic cell extensions {2593}; myxoid der-

matofibromas {2183,2588}; or combined dermatofibromas {2589}, which show a combination of several unusual histopathologic features in one lesion.

Immunoprofile

Dermatofibromas reveal a variable immunohistochemical profile: early lesions are rich in reactivity for macrophage markers such as PGM1 or KP1 (CD68), but also exhibit strong reactivity for factor XIIIa in both macrophages and fibroblasts {2590}. This reactivity is mostly seen at the periphery and continuously diminishes with the ageing of the lesion to be completely absent in atrophic variants. Actin expression is variably seen in dermatofibromas particularly in the myofibroblastic variant {2593}. Occasionally dermatofibromas are focally positive for CD34 {1840,2584}. Recently, stromelysin 3 expression has been reported. It is not expressed in DFSP {558}.

Differential diagnosis

The most important histologic differential diagnoses are dermatofibrosarcoma protuberans (particularly with the cellular variant of dermatofibroma) and Kaposi sarcoma. Dermatofibrosarcoma protuberans is poorly circumscribed, usually much broader and deeper with irregular dissection of subcutis, and shows cells with wavy nuclei in association with delicate fibrillary bundles of collagen frequently arranged in a storiform pattern. In contrast to dermatofibroma it is regularly positive for CD34. Kaposi sarcoma in nodular and tumour stage is characterized by erythrocytes extravasated into slits between interweaving fascicles of spindle-shaped cells; often, tiny pink hyaline globules that represent degenerated erythrocytes are found in these spindle-shaped endothelial cells. Lesions are positive for CD34 and vascular markers such as CD31.

Variants

Aneurysmal fibrous histiocytoma

This is not uncommon {367,2054}. It may rapidly enlarge because of spontaneous or traumatic haemorrhage into a previously unspectacular lesion or rarely de novo development, and frequently is painful. Clinically, it may mimic nodular melanoma or nodular Kaposi sarcoma. Histology reveals extravasation of erythrocytes, pseudovascular spaces and iron deposits. This histology may occa-

sionally also be confused with melanoma or nodular Kaposi sarcoma, yet the absence of melanocytic as well as vascular markers in the spindle cells easily excludes these simulants.

Epithelioid cell histiocytoma

This lesion {840,1155}, including a cellular variant {794} is rare. It occurs on the upper extremities and trunk as a skin-coloured to reddish-brown, hard, exophytic papule, frequently thought to be a Spitz naevus. Histology reveals a lesion mostly restricted to the papillary dermis, prominent epidermal hyperplasia ("collarette") and a sheet-like infiltrate of epithelioid to scalloped fibroblasts. These features may also closely simulate Spitz naevus, yet lesions are negative for melanocytic markers, but positive for factor XIIIa.

Cellular fibrous histiocytoma

This variant is rare {370}. It occurs on the trunk or distal extremities and has a tendency to recur when incompletely excised. Histology reveals a dense, frequently deeply infiltrating lesion of spindle cells in an otherwise typical dermatofibroma. There may be moderate nuclear atypia, occasional mitoses and bizarre giant cells and these lesions have therefore also been called pseudosarcomatous or atypical fibrous histiocytomas {794}. Exceptional cases of this variant have been reported to metastasize and, accordingly, they should always be completely excised.

Prognosis and predictive factors

The vast majority of lesions are benign. Occasionally incomplete excision may result in recurrence. The cellular and aneurysmal variants and lesions of the face may recur in a significant percentage of cases {1583}. Exceedingly rare cases of local aggressive growth or metastases to local or regional lymph nodes or even with wide spread metastases to lung have been recorded in the cellular variant.



CHAPTER 6

Neural Tumours

Cutaneous neural tumours represent a small but important part of the cutaneous soft tissue neoplasms. Their histogenesis is conceptually analogous to their deep soft tissue or visceral counterpart, i.e., they recapitulate to variable extent the architectural and cytologic constituents of normal peripheral or autonomic nerves. Likewise, their classification is identical to their soft tissue counterparts. In this chapter, only those tumours are discussed which are particularly relevant for the dermatopathologist by their distinct morphology, predominant cutaneous manifestation, or their recent recognition and significance in the cutaneous pathology. These include the neuroendocrine carcinomas, rare but problematic peripheral variants of primitive neuroectodermal tumours, the non-neoplastic neurofibroma group with its spontaneous and reactive types and the recently defined, but still histogenetically controversial, nerve sheath myxoma-neurothekeoma spectrum.

WHO histological classification of neural tumours

Primitive neuroectodermal tumour (PNET)	9364/3
Ewing sarcoma	9260/3
Nerve sheath myxoma	9562/0
Merkel cell carcinoma	8247/3
Granular cell tumour	9580/0

¹ Morphology code of the International Classification of Diseases for Oncology (ICD-O) {786} and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

TNM classification of skin (Merkel cell) carcinomas¹

TNM classification^{2,3}

T – Primary tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ

T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but no more than 5 cm in greatest dimension
T3	Tumour more than 5 cm in greatest dimension
T4	Tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle, or bone

Note: In the case of multiple simultaneous tumours, the tumour with the highest T category is classified and the number of separate tumours is indicated in parentheses, e.g., T2(5).

N – Regional lymph nodes

Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M – Distant metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

¹ For PNET and Ewing sarcoma see TNM table of soft tissue tumours

² {894.2219}.

³ A help desk for specific questions about the TNM classification is available at www.uicc.org/index.php?id=508.

Palisaded, encapsulated neuroma and traumatic neuroma

Z.B. Argenyi

Palisaded, encapsulated neuroma

Definition

Palisaded, encapsulated neuroma (PEN) is considered a spontaneous proliferation of nerve fibres without evidence of previous trauma.

Synonyms

Solitary circumscribed neuroma, spontaneous neuroma, true neuroma

Historical annotation

The tumour was described by Reed et al. in 1972, who pointed out that despite the occasional nuclear palisading and encapsulation, the tumour is different from Schwannoma {1908}.

Epidemiology

PEN is most common in the 5th and 7th decades and occurs in an approximately equal ratio in both genders. The majority of the lesions, about 90%, are located on the face, but they can occur anywhere on the body. Mucosal involvement has also been recorded {453,752,1908}.

Clinical features

PEN usually manifests as a solitary, small (2-6 cm), skin-coloured or pink, firm or rubbery, dome-shaped, asymptomatic

papule or nodule. There is no established association with neurofibromatosis {453,752,1908}.

Macroscopy

On cut sections, the tumour is a yellow-pink, firm ovoid mass in the dermis.

Histopathology

On low magnification, PEN is a well-circumscribed, round or oblong nodule located in the dermis. It is surrounded by a thin fibrous capsule, which is poorly discernible or incomplete near to the epidermal aspect of the tumour. The tumour is composed of tightly woven fascicles which are separated by cleft-like spaces. The proliferating cells are slender spindle cells with ovoid, evenly chromatic nuclei and eosinophilic cytoplasm.

A parallel arrangement of nuclei resembling a palisading pattern or rudimentary Verocay bodies is occasionally present. Mitotic figures are rare or absent. PEN lacks distinct fibrosis, inflammation or granulomatous reaction. A connection with the originating nerve usually requires serial sectioning of the tissue. Silver impregnation reveals numerous nerve fibres (axons), usually in parallel arrangement with the longitudinal axes of the fascicles {55,80,90,453,585,646,752,1314,1908}.

Immunophenotype

The cells in the capsule stain for epithelial membrane antigen, whereas the spindle cells of the fascicles are positive for S-100 protein and collagen type IV. The axons are labeled with antibodies to neural filaments. Variable myelinization is detected by CD57 (Leu-7) and myelin basic protein {55,80,90}.

Variants

Plexiform and multinodular types.

These rare variants represent unusual growth pattern, but otherwise they retain the usual internal structures and composition of PEN {81,84}.

Spontaneous, non-encapsulated neuromas

These tumours are part of the Multiple Mucosal Neuroma (MMN) syndrome, which is often part of the Multiple Endocrine Neoplasia syndrome (MEN2b), which is associated with pheochromocytoma and medullary carcinoma of the thyroid {815}. The neuromas in MMN manifest as numerous, soft-rubbery, skin-coloured or pink papules and nodules around mucosal orifices, lip, eyelids, and tongue, but scattered cutaneous involvement can also occur {835,1658,1994}. Musculoskeletal abnormalities and intestinal ganglioneuromato-

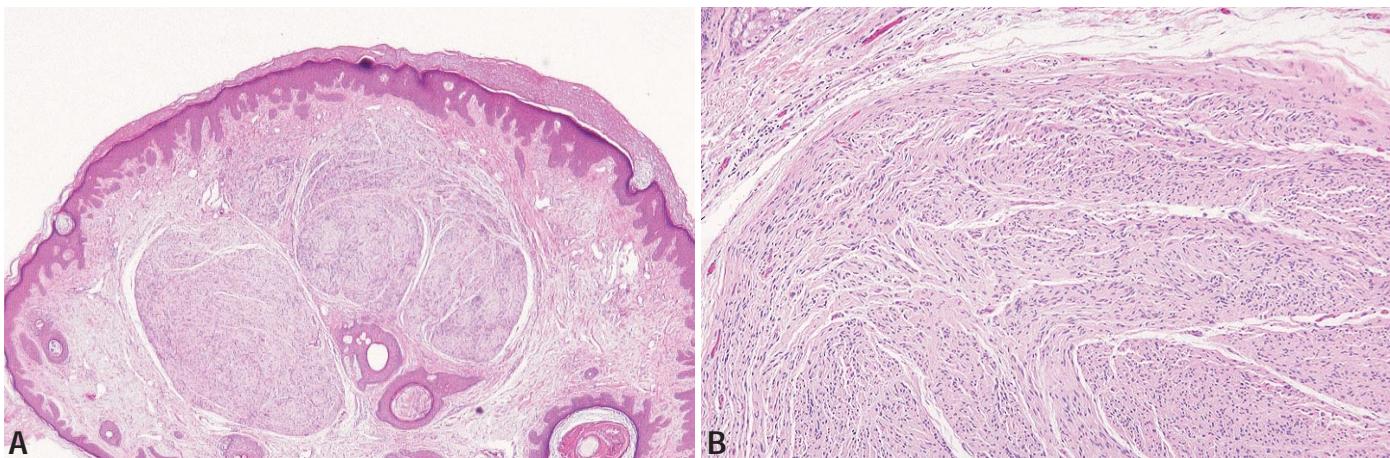


Fig. 6.1 Palisaded, encapsulated neuroma. **A** Multinodular variant of palisaded encapsulated neuroma. **B** The tumour is formed by compactly arranged fascicles separated by artificial clefts.

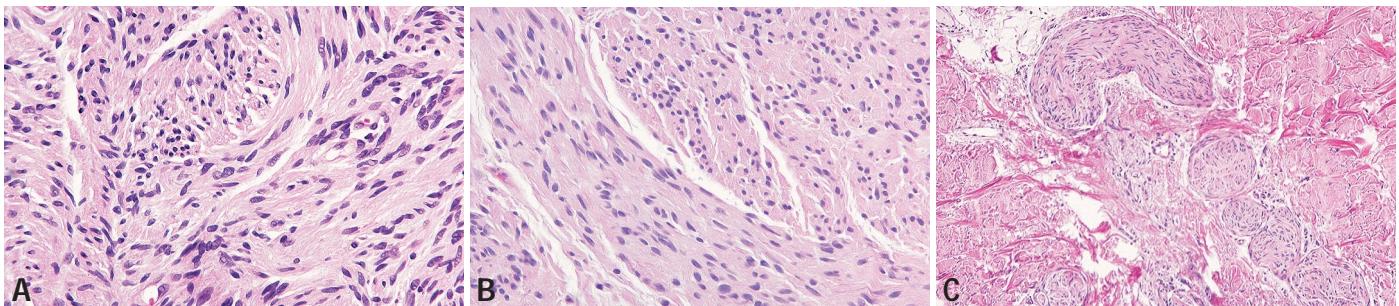


Fig. 6.2 Palisaded, encapsulated neuroma (PEN). **A** Internal structure and cytology correspond to the classical type of PEN. **B** The fascicles are composed of uniform spindle cells without cytologic atypia. Despite the term, no distinct nuclear palisading is present. **C** Spontaneous, non-encapsulated neuromas of Multiple Mucosal Neuroma Syndrome. The tumour is composed of linearly arranged hyperplastic nerve bundles infiltrating the dermis.

sis are also part of the syndrome {236,2504}. Histologically, the tumour is composed of numerous tortuous or fascicular arrangements of hyperplastic nerve bundles infiltrating the submucosa or the dermis, hence the term "non-encapsulated neuroma" has also been applied. The individual fascicles have a linear, elongated appearance instead of the round or oblong structure of PEN; however, the constituent cells are identical to those seen in PEN. Occasionally perineurial and endoneurial increase of mucin can be noted. The immunohistochemical profile of this variant is similar to PEN {815, 835,1658,1994}.

Genetics

Activated mutations of the RET proto-oncogene, involving the somatic or the germinal cell-lineage are found in both the inherited and acquired forms {466, 545,2310}. However, MMN without genetic abnormalities have also been reported {1863,2379}.

Prognostic factors

PEN and its variants are benign, and simple excision is a sufficient treatment. The mucosal neuromas of MEN2b often precede the manifestation of the other endocrine tumours. Therefore their correct recognition is important {1020}.

Traumatic neuroma

Definition

Traumatic neuromas represent reactive or regenerative proliferation of the nerve sheath components as an attempt to reestablish lost nerve integrity after sharp or blunt physical trauma.

Synonyms

Amputation neuroma, supernumerary digit

Epidemiology

Traumatic neuromas can occur at any age or gender. The amputation type is more common on the extremities {1535}. A special variant sometimes referred to incorrectly as "supernumerary digit" occurs on the lateral aspects of hands or feet of newborns. They represent amputation neuromas at the site of the in-utero separated extranumerary digit {487,2152}.

Clinical features

Traumatic neuromas develop at the sites of previous trauma usually as solitary, skin-coloured, broad-based, firm papules and nodules. They are often sensitive or painful on pressure. Lancinating pain is characteristic of amputation neuromas {351,530,2342}.

Macroscopy

Traumatic neuromas are firm, white-yellow, ill-defined dermal or subcutaneous masses often in a discernible association with the proximal nerve stump.

Histopathology

The tumour is composed of an irregular, haphazardly arranged proliferation of regenerating nerve fascicles of various sizes and shapes embedded in a fibrous stroma. Earlier lesions show acute and chronic inflammation, occasional granulomatous inflammation, whereas more established lesions are markedly fibrotic. Although the tumour is encased in the sclerotic stroma, there is no true encapsulation, and the distal end of the regenerating nerve fascicles often infiltrates the stroma {90,2084}. The individual nerve fascicles appear to recapitulate the architecture of the normal nerve fascicles, but there is considerable variation in their diameter. The constituent cells

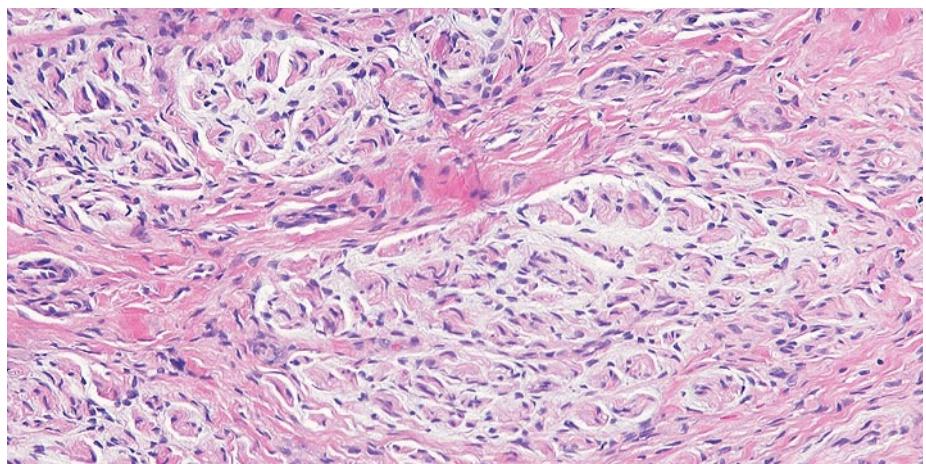


Fig. 6.3 Traumatic neuroma. There is an ill-defined dermal nodule composed of irregularly arranged proliferation of nerve fascicles embedded in a fibrotic (scarred) stroma.

are slender spindle cells (Schwann cells, perineurial cells, and endoneurial fibroblasts). Silver impregnation reveals numerous nerve fibres (axons) in the tumour in a pattern approximating the normal 1:1 ratio of Schwann cells and axons. The "supernumerary digit" is a polypoid lesion covered by thick hyperorthokeratosis with a fibrous stalk containing regenerating nerve fascicles. The morphology of the regenerating nerve fibres is identical to the ones seen in other amputation neuromas.

Immunohistochemistry

The constituent spindle cells of the nerve fascicles are positive for S-100 protein, collagen type IV, whereas the surrounding perineurial cells, when present, stain for epithelial membrane antigen. Antibodies to neural filaments highlight the axons, and myelinization can be demonstrated by antibodies to myelin basic protein and CD57 (Leu-7).

Pronostic factors

Traumatic neuroma is a reactive lesion, however it can cause local interference with adjacent organs and is often symptomatic. The usual treatment is simple excision.

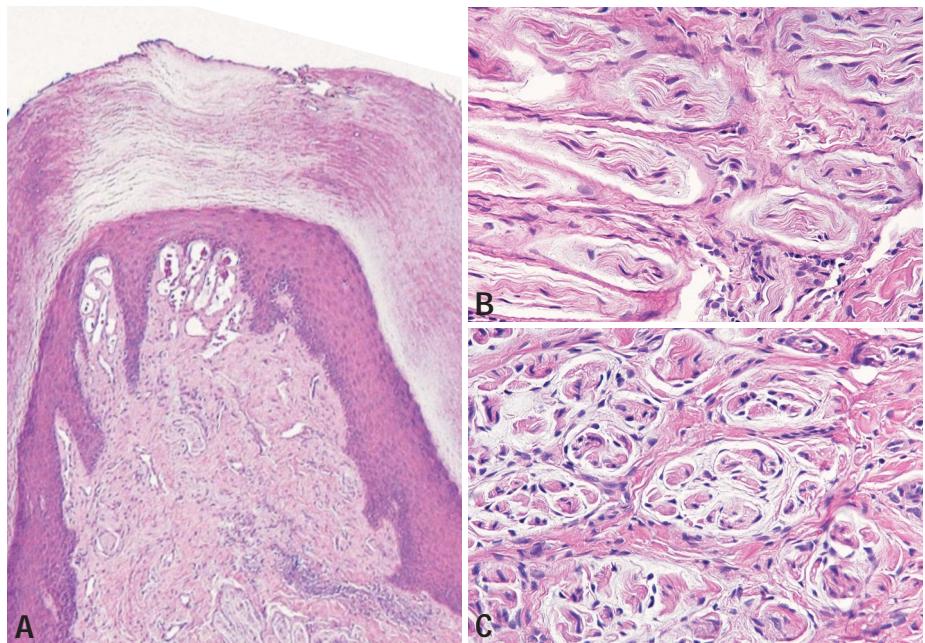


Fig. 6.4 Traumatic neuroma. **A** Supernumerary digit (amputation neuroma). Acral polypoid lesion with proliferation of nerve fascicles at the base of stalk. **B** Higher magnification of the regenerating nerve fascicles in the fibrous stroma. **C** The regenerating nerve fascicles show variation of diameter and orientation. The clear spaces correspond to increased perineurial mucin.

Primary malignant peripheral primitive neuroectodermal tumour (PNET) / Extraskeletal Ewing sarcoma (ES)

S.S. Banerjee

Definition

PNET/ES are malignant small blue round cell tumours, which exhibit varying degrees of neuroectodermal differentiation. In the past, they were regarded as separate entities, but recent cytogenetic and molecular genetic studies have proven that they represent two ends of a phenotypic spectrum of the same tumour type – Ewing sarcoma being relatively undifferentiated and PNET showing morphological (light microscopic/ultrastructural) and/or immunohistochemical features of neuroectodermal differentiation.

ICD-O codes

PNET	9364/3
Ewing sarcoma	9260/3

Synonyms

Peripheral neuroepithelioma, peripheral neuroblastoma

Epidemiology

Primary PNET/ES of skin and subcutaneous tissue are rare neoplasms. These tumours are mainly seen in children and young adults (median age 18 yrs), but they occasionally afflict elderly individuals. There is no significant sex predilection {72,82,138,449,978,1389,1791, 1815,2050,2146,2210,2295,2328,2416}.

Etiology

The etiology of this tumour is unknown.

Localization

These neoplasms have been described

on the scalp, face, neck, shoulder, trunk and extremities.

Clinical features

The tumours usually present as ulcerated or non-ulcerated, often painless, but rarely tender, nodules. Occasionally, they appear polypoid {138,978}. Not infrequently, they are clinically misdiagnosed as benign tumours or cysts. A case of cutaneous PNET with numerous tumour nodules that were present for several years has been documented {2050}.

Macroscopic features

The tumours are greyish white and fleshy. Foci of haemorrhage are sometimes noted. Their sizes usually vary from 5 cm to 10 cm.

Histopathology

The tumours usually occupy the dermis with focal extension into subcutis. Some tumours are entirely subcutaneous in location. The overlying epidermis may become ulcerated. The margins may be pushing or infiltrative. The neoplastic cells are small, round to oval and contain hyperchromatic or vesicular nuclei and scanty pale eosinophilic or vacuolated cytoplasm with ill-defined borders. The nucleoli are indistinct or absent. The cells are arranged in sheets, lobules, nests and trabeculae. The mitotic activity and necrosis vary from case to case. Many dark apoptotic cells may be seen. Prominent fibrovascular septa are present in most lesions and some exhibit

peritheliomatous or pseudopapillary arrangement of cells. Occasionally, the stromal blood vessels form glomeruloid tufts with prominent endothelial and myointimal cells. Microcystic, pseudoglandular and pseudovascular spaces are observed in many neoplasms. Homer Wright rosettes and neuropil are only rarely present. In atypical examples of this tumour, larger cells with prominent nucleoli, pleomorphic cells with irregular nuclei or groups of mononuclear or binucleate rhabdoid or plasmacytoid cells are seen. Prominent epidermal inclusion cysts within the tumour have been described in one case. Intracytoplasmic glycogen can be demonstrated in most cases. The reticulin stain reveals fibrils around groups of tumour cells. The differential diagnosis of this neoplasm includes deposits of lymphoma/ leukaemia, Merkel cell carcinoma, metastatic small cell neuroendocrine carcinoma, metastatic neuroblastoma, primary or metastatic rhabdomyosarcoma, glomus tumour, small cell melanoma and rare types of sweat gland tumour such as eccrine spiradenoma and non-neuroendocrine small cell carcinoma. Attention to histological detail, immuno- histochemistry, EM studies and genetic analysis help to reach the right diagnosis.

Immunohistochemistry

Characteristically, the neoplastic cells exhibit positivity for CD99 (MIC2 gene product), β 2 microglobulin, FLI-1 gene product, vimentin and one or more puta-

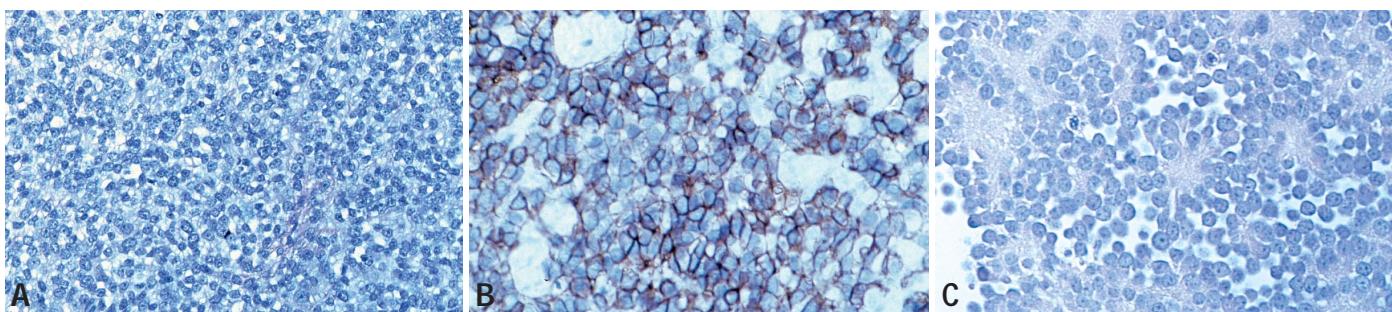


Fig. 6.5 Primary PNET/EES of skin. A Tumour composed of sheets of monomorphic small round cells containing hyperchromatic nuclei and scanty cytoplasm. B Strong membranous CD99 positivity in the neoplastic cells. C Homer-Wright rosettes. They are only rarely seen in these neoplasms.

tive neural/neuroendocrine markers such as NSE, PGP 9.5, neurofilament proteins, synaptophysin and Leu-7. Usually the stain for chromogranin is negative. The CD99 positivity is usually strong, diffuse and membranous. The FLI-1 stains the nuclei of the neoplastic cells. Aberrant cytokeratin, desmin, GFAP, S100 protein and NKIC3 expression may be noted in scattered cells in some cases. The tumour cells are negative for LCA, B&T cell markers, myeloperoxidase, muscle specific actin, MYO-D1, myogenin, EMA and HMB 45 {138}.

Electron microscopy

At the Ewing end of the spectrum, the cells appear rather non-descript with round nuclei and scanty organelles. There is usually abundant glycogen. The PNETs show elongated interdigitating cytoplasmic processes with a few rudimentary junctions, intermediate filaments, microtubules and sparse membrane bound dense core neurosecretory granules (100-250 nm in diameter). No myofilaments, desmosomes or melanosomes are seen {138}.

Genetics

Around 90% of skeletal and extraskeletal PNET/ES exhibit a characteristic chromosomal translocation, t(11;22)(q24;q12). This results in the fusion of EWS gene on chromosome 22q12 with FLI-1 gene on chromosome 11q24. A small number of cutaneous cases have been subjected to cytogenetic/genetic studies and these have also demonstrated the typical genetic defects {978,1389}. An additional copy of chromosome 22 was detected in one case. Conventional cytogenetic study, FISH and RT-PCR techniques have been used to detect these abnormalities.

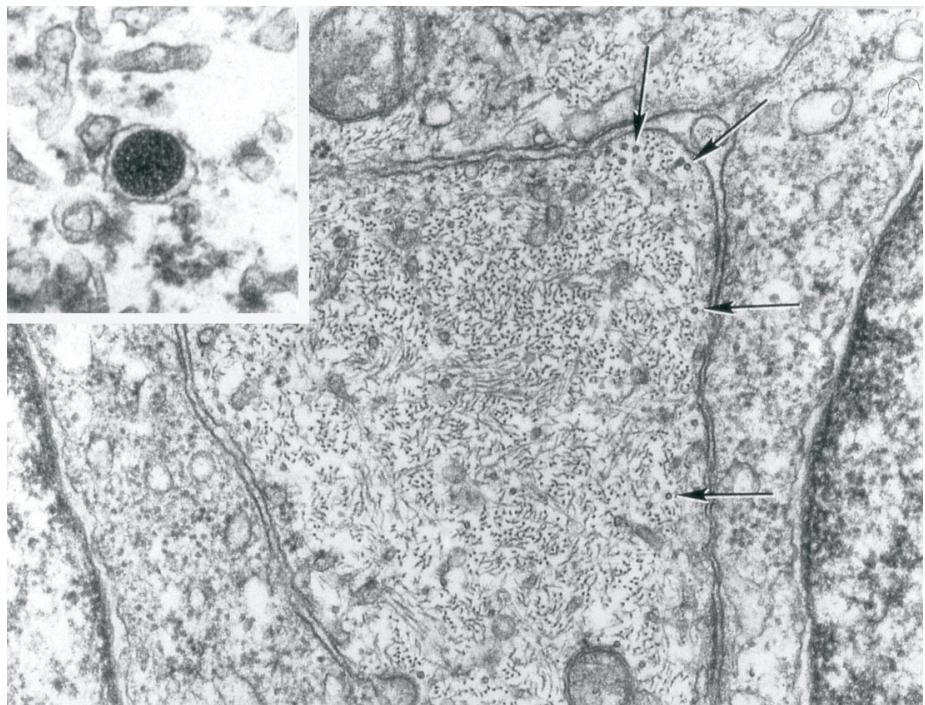


Fig. 6.6 Primary PNET of skin. Electron microscopy of a cutaneous PNET: the cytoplasmic processes of the neoplastic cells contain intermediate filaments and microtubules (arrow). The inset shows a neurosecretory granule.

Prognosis and predictive factors

These neoplasms are aggressive with metastatic potential. The usual sites of metastasis are regional lymph nodes, lung, liver and bones. However, the cutaneous PNET/ES appear to have a better prognosis than their soft tissue counterparts, probably because they are detected early and can be resected adequately. Long term survival has been recorded in a few cases with or without radiotherapy and adjuvant combination chemotherapy {138,478,978,2328}. A prognostically relevant grading or staging system is not yet available for these neoplasms.

Nerve sheath myxoma / neurothekeoma

Z.B. Argenyi

Definition

These tumours encompass a spectrum of neuromesenchymal neoplasms characterized by proliferation of nerve sheath cells in a variable myxomatous stroma. They can be further classified into "classic" and "cellular" types.

ICD-O code 9562/0

Synonyms

Cellular neurothekeoma (used exclusively for the cellular variant), cutaneous lobular neuromyxoma, myxomatous perineuroma

Epidemiology

These tumours are rare. The "classic type" has been reported in middle-aged adults (mean 48.4), with predominance in females, of the head and neck areas and upper extremities {73,1865}. The "cellular type" has been observed in younger adults (mean 24 yrs), more common in females, predominantly on the head and neck areas {88,99,161,371}. However, both types can occur at any age and at any location {229,418,479, 1222,1674,1684,2355}.

Clinical features

The "classic types" manifest as skin-coloured, pink, soft, rubbery papules

and nodules, whereas the "cellular types" have a firmer, rather red-tan-brown appearance. Their size ranges between 0.5–2.0 cm. Both types are commonly asymptomatic, but may become sensitive or tender {73,88,99, 161,371,1865}.

Histopathology

The "classic type" is usually a well-defined, multilobular or fascicular tumour located in the dermis with or without extension to the subcutis. The lobules contain abundant myxomatous stroma, which appear to be confined by a thin fibrous encapsulation. The mucin is connective tissue type acidic mucopolysaccharide and stains strongly with colloidal iron, which clears after hyaluronidase treatment. Within the mucinous stroma, there are sparsely distributed spindle, stellate, and polygonal cells without appreciable cytologic atypia. Mitotic figures are rare or absent {73,88,755,1865}. The "cellular variant" shows an ill-defined, often infiltrative growth pattern involving the dermis and subcutis. The proliferating cells form fascicles and nests and are arranged in a plexiform or multilobular pattern. The constituent cells are mainly epithelioid type with ample eosinophilic cytoplasm and indistinct cytoplasmic membranes. The cells have

large "bubbly nuclei" with prominent nucleoli. In a smaller percentage of the cases, the tumour is composed of spindle cells with plump or ovoid nuclei forming nests and whorls. In the "cellular type", cytologic and nuclear atypia are more common and mitotic figures can be conspicuous. Myxoid material is usually scant or present only around the individual nests {88,99,161,371}. In both the "classic" and "cellular types", associated stromal changes, such as fibrosis, hyalinization of the collagen, patchy chronic inflammation, and angioplasia can occur. Changes showing transition between the "classic" and "cellular types" within the same lesion have been documented. A direct connection with nerve twigs can be demonstrated only rarely.

Immunohistochemistry

The stromal cells in the "classic" type stains strongly for S-100 protein, collagen type IV and weakly for neuron-specific enolase and CD57 (Leu-7). The capsule, when present, may label for epithelial membrane antigen. The "cellular" type does not have a specific or consistent phenotype. The cells show variable expression of PGP9.5, collagen type IV, NK1/C3, CD34, and occasionally smooth muscle specific actin and CD57 (Leu-7). Staining for S-100 protein is rare, and

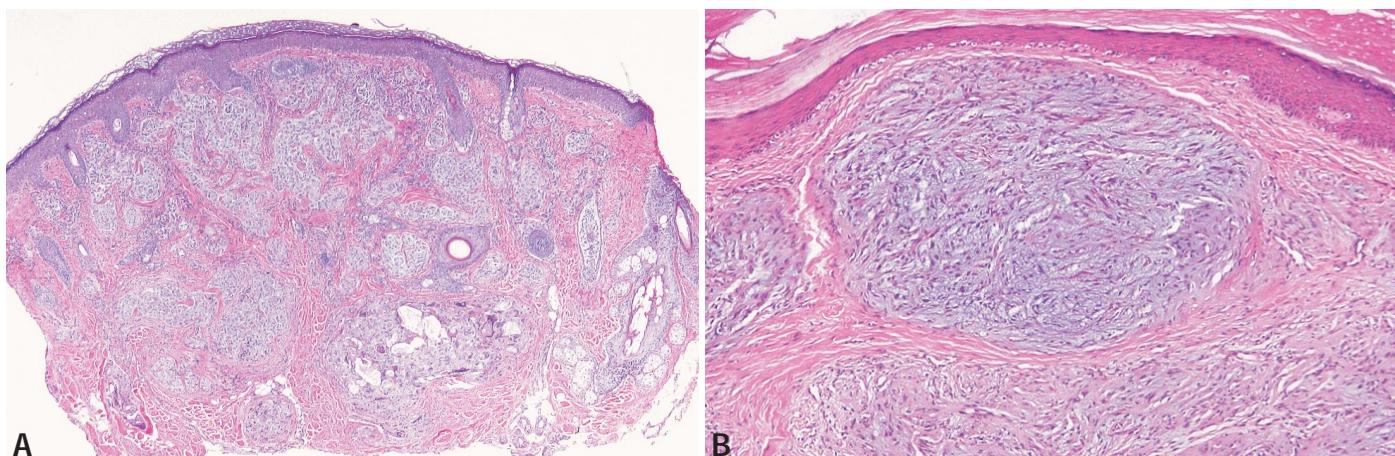


Fig. 6.7 Nerve sheath myxoma (neurothekeoma). **A** Cellular neurothekeoma (cellular variant of nerve sheath myxoma). The tumour cells form nests and strands infiltrating the dermis. **B** Nerve sheath myxoma "classical type". Lobular and fascicular dermal proliferation with myxomatous stroma.

when present it is usually in lesions where there are elements of the "classical" type {87,88,99,161,371,798,1370, 2281,2454}

Prognosis

Both variants are considered benign tumours, although rare cases of the "cellular" type with concerning cytologic atypia and mitotic activity have been reported {231,357}. Both tumours can recur after incomplete removal; therefore, a complete excision is recommended for treatment.

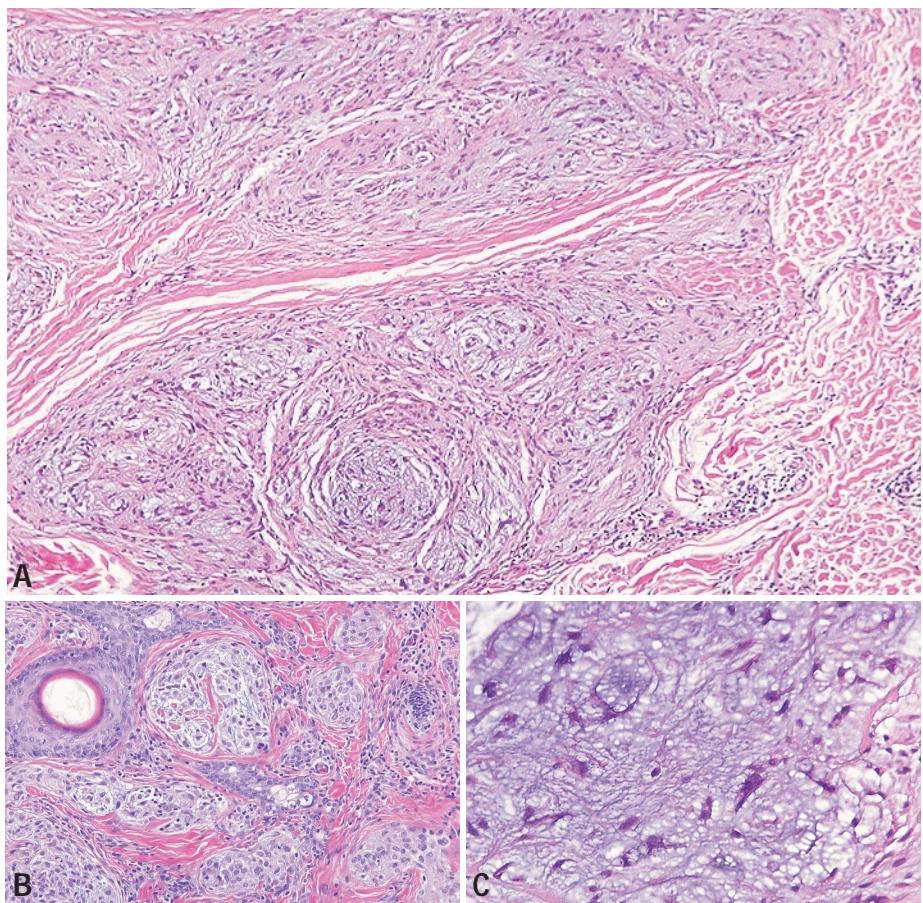


Fig. 6.8 Nerve sheath myxoma (neurothekeoma). **A** Higher magnification of the lobules shows the mixture of variable cellularity and myxomatous changes. **B** The tumour nests are well defined, but not encapsulated and contain minimal or no mucin. The adjacent stroma is hyalinized. **C** Stellate, polygonal, and spindled cells are embedded in a markedly mucinous matrix.

Merkel cell carcinoma

S. Kohler
H. Kerl

Definition

Merkel cell carcinoma is a rare malignant primary cutaneous neoplasm with epithelial and neuroendocrine differentiation. Tumour cells share morphologic, immunohistochemical and ultrastructural features with Merkel cells, but a direct histogenetic link is unproven.

ICD-O code 8247/3

Synonyms

First described in 1972 by Cyril Toker as trabecular carcinoma [2357]. Other synonyms include neuroendocrine carcinoma of the skin, primary small-cell carcinoma of the skin, and cutaneous APUDoma.

Epidemiology

The estimated incidence of Merkel cell carcinoma is about 470 new cases per year in the United States. The tumour most commonly affects Caucasians (0.23 annual age adjusted incidence per

100,000) and is exceptionally rare in black individuals (0.01 annual age adjusted incidence per 100,000) [1616]. Merkel cell carcinoma is more common in men than in women with a ratio of 2.3:1. This tumour typically occurs on the sun-exposed skin of older adults with a median age at presentation of 69 years.

Etiology

Anatomic and geographic distribution of Merkel cell carcinoma imply sun exposure as a major risk factor. A relatively high incidence of this neoplasm in solid organ transplant recipients and in patients with human immunodeficiency virus infection point towards an etiologic role of chronic immunosuppression.

Localization

The majority of Merkel cell carcinomas arise on sun-exposed skin. The most frequently affected sites are the head and neck (50%) and extremities (40%) [843]. The trunk and genitalia are involved in

less than 10% of cases. Exceptional cases on mucosal surfaces have been recorded.

Clinical features

Most tumours are solitary and present as a painless dome shaped nodule or indurated plaque that is red, violaceous or skin-coloured and, at times, ulcerated. Growth is typically rapid over a period of weeks to months. Most lesions measure less than 2 cm in diameter.

Tumour spread and staging

Merkel cell carcinoma has a high incidence of local recurrence, regional lymph node metastasis and, ultimately, haematogenous and/or distant lymphatic spread [517]. Clinical staging after histopathologic diagnosis should include at the minimum a chest x-ray and CT of the chest and abdomen to exclude other possible primary sites and to evaluate for the presence of metastatic disease. Merkel cell carcinoma in locations other

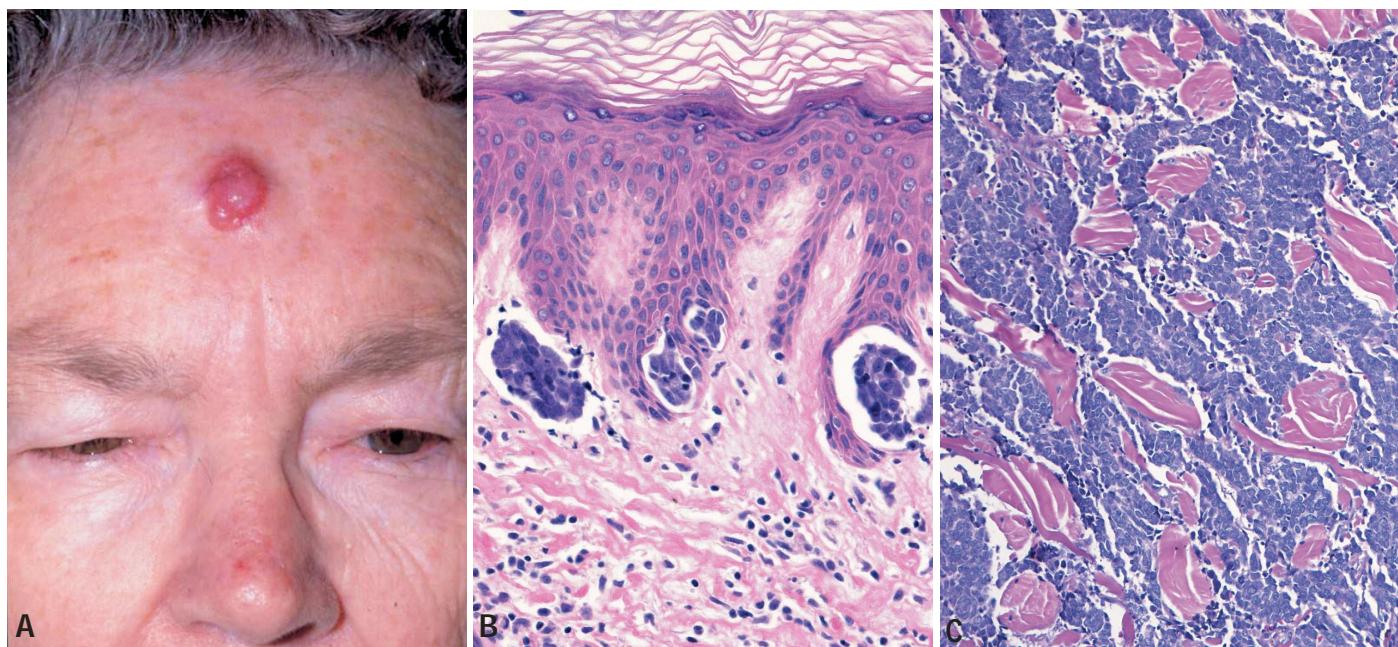


Fig. 6.9 Merkel cell carcinoma. **A** Rapidly growing, violaceous nodule on the forehead (courtesy Dr. Scott Dinehart). **B** Pagetoid involvement of the epidermis. **C** Trabecular growth is one of the architectural patterns of Merkel cell carcinoma.

than the eyelid, vulva and penis is staged according to the TNM system for non-melanoma skin cancers.

Histopathology

Merkel cell carcinoma is a small blue cell neoplasm, composed of cells of uniform size with a round to oval nucleus and scant cytoplasm. Nuclear membranes are distinct, the chromatin is finely dispersed and nucleoli are usually inconspicuous. Mitotic figures and nuclear fragments are numerous. Focal spindle cell differentiation may be present.

The tumour is centred on the dermis and frequently extends into the subcutaneous fat. The epidermis may be involved in a pagetoid fashion {1384} and in exceptional cases the tumour cells are entirely limited to the epidermis. Ulceration of the epidermis occurs in a subset of cases. This neoplasm forms diffuse sheets and solid nests in the dermis. A trabecular growth pattern, ribbons or festoons can be seen mainly in the periphery. Pseudorosette formation is rare. The dermis occasionally shows a desmoplastic response. Larger lesions may show zonal tumour necrosis and angiolymphatic involvement is commonly present around the primary neoplasm. Not infrequently, Merkel cell carcinoma occurs in intimate association with an in situ or

invasive squamous cell carcinoma {2450}. Biphenotypic differentiation with squamoid or eccrine foci or even tripartite differentiation with squamoid, glandular and melanocytic foci are described. Areas of partial or complete regression can be found {529}.

The histopathologic differential diagnosis includes basal cell carcinoma, melanoma, lymphoma, eccrine carcinoma, poorly differentiated squamous cell carcinoma, metastatic neuroblastoma, primary peripheral primitive neuroectodermal tumour and metastatic neuroendocrine carcinoma.

Immunohistochemistry

Merkel cell carcinoma shows epithelial and neuroendocrine differentiation. Tumour cells express low molecular weight cytokeratins (detectable by specific or broad spectrum cytokeratins such as AE1/AE3, CAM5.2, pan-cytokeratin), epithelial membrane antigen and the epithelial marker BER-EP4. Cytokeratin 20 is a sensitive and quite specific marker for Merkel cell carcinoma {1604}. The staining pattern for low molecular weight cytokeratins and CK20 typically is as paranuclear dots, but may also show cap-like paranuclear or diffuse cytoplasmic staining {1138}. CK20 is useful in combination with thyroid-trans-

cription factor-1 to differentiate between Merkel cell carcinoma (CK20 positive, TTF-1 negative) and small cell carcinoma of the lung (<10% CK20 positive, TTF-1 positive) {463}. CK20 and broad spectrum cytokeratin are also useful for the detection of occult micrometastases in sentinel lymph nodes {2287}. Markers of neuroendocrine differentiation include chromogranin, synaptophysin, neuron-specific enolase, bombesin, somatostatin, calcitonin, gastrin and others. Merkel cell carcinoma also expresses CD117, the KIT receptor tyrosine kinase {2284}, and in approximately a third of cases CD99 {1707}. The tumour cells are negative for leukocyte common antigen and S-100.

Histogenesis

The histogenesis of Merkel cell carcinoma is controversial. A direct histogenetic link between tumour cells and Merkel cells is unproven despite overlap in the morphologic, immunologic and ultrastructural features. Another theory postulates that Merkel cell carcinoma arises from a primitive epidermal stem cell with a capacity to differentiate towards neuroendocrine cells and keratinocytes.

Somatic genetics

A deletion on the short arm of chromosome 1 (1p36) is commonly observed and is shared with other neoplasms of neural crest derivation including neuroblastoma and melanoma {2208}.

Numerous other chromosomal abnormalities are described in Merkel cell carcinoma, the most common being trisomy 6, affecting nearly 50% of tumours. As of yet, no candidate oncogenes or tumour suppressor genes have been identified.

Prognostic factors

Diverse clinical prognostic factors include older age, location on head and neck, size greater than 2 cm, immunosuppression and advanced disease stage {517,843,2208}.

Adverse histopathologic and immunologic features include more than 10 mitotic figures per single high power field, small cell size, angiolymphatic invasion, and immunoreactivity for CD44 {1803}.

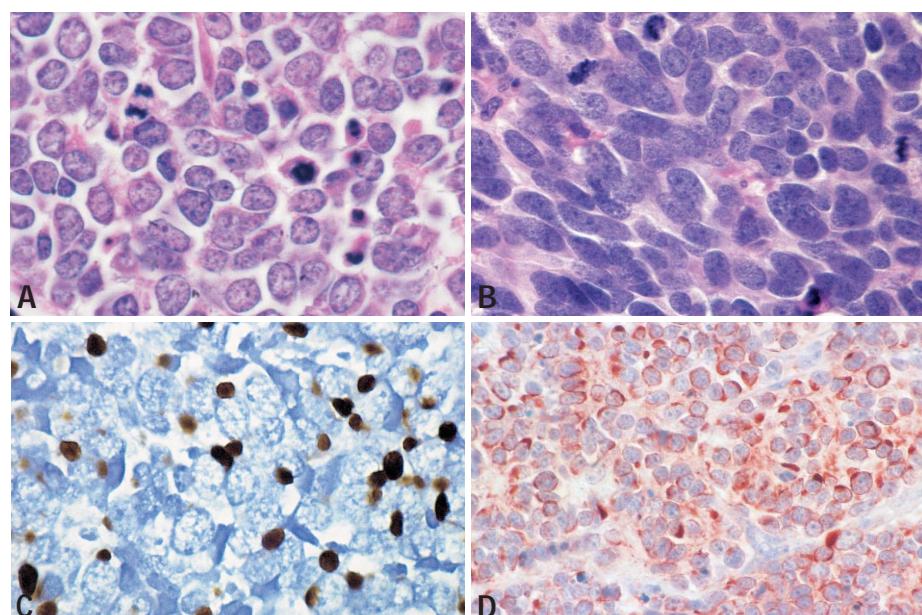


Fig. 6.10 Cutaneous neuroendocrine carcinoma. **A** Cytomorphological details. Note pyknotic nuclei and mitoses. **B** Cytologic detail of Merkel cell carcinoma: Nuclear membranes are distinct, the chromatin is finely dispersed and nucleoli are inconspicuous. Mitotic figures and nuclear fragments are numerous. **C** Punctate perinuclear staining with CK20. **D** Staining with anti-cytokeratin 20 reveals a ring-like and paranuclear dot-like pattern.

Granular cell tumour

Z. B. Argenyi

Definition

Granular cell tumours (GCT) encompass a cytologically similar, but etiologically and clinically diverse group of entities that are characterized by proliferation of large cells with granular-appearing eosinophilic cytoplasm. Herein, only the variant with direct or indirect evidence of peripheral nerve sheath association and common cutaneous manifestation is considered.

ICD-O code

9580/0

Synonyms

Granular cell Schwannoma, granular cell nerve sheath tumour, granular cell myoblastoma, Abrikossoff tumour

Historical annotation

The tumour was thought to be derived from skeletal muscle cells by Abrikossoff (1927). The association with nerve sheath differentiation was proposed by Feyrter (1935).

Epidemiology

GCT affects mainly adults (age 30-50), but can occur at any age. The male to

female ratio is about 1:3; it is more common in African Americans than in Whites {78,245,1354}. The tumour is characteristically solitary, and about 70% are located in the head and neck area, including 30% of these in the tongue. Other common locations are the breast and the proximal extremities. GCT usually involves the skin and subcutis; however, visceral involvement can also occur, primarily in the respiratory tract (larynx and trachea) and the gastrointestinal tract (oesophagus, large bowel, and anal area) {245}. In about 10% of the cases GCT is multifocal, simultaneously involv-

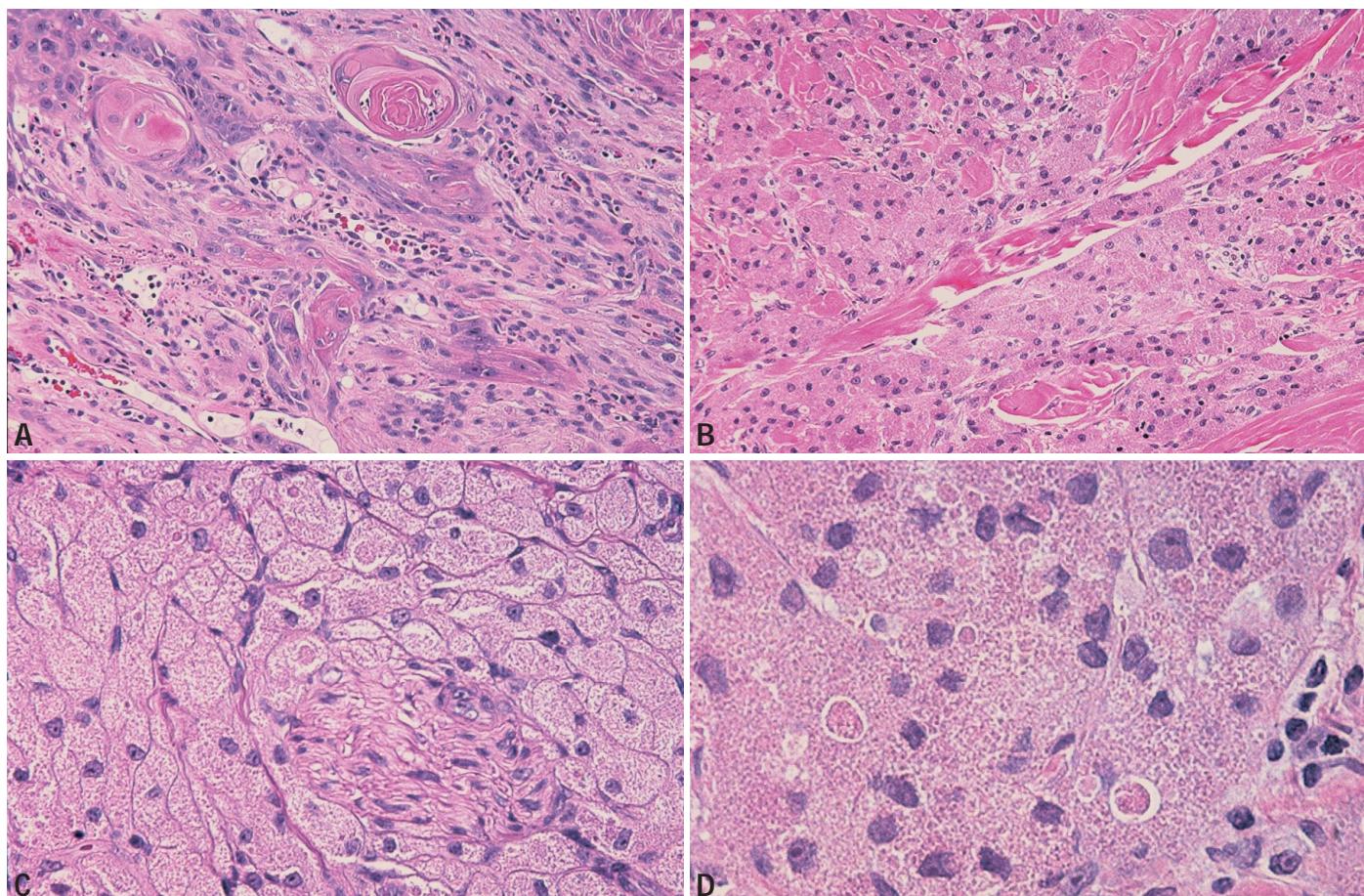


Fig. 6.11 Granular cell tumour. **A** Reactive squamous pseudoepitheliomatous hyperplasia with prominent cytologic atypia mimicking squamous cell carcinoma. The granular cells are intermingled with squamous epithelial cells. **B** Granular cell tumour. The brightly eosinophilic granular cells form solid nests and strands infiltrating the dermis. **C** Granular cell tumour associated with a peripheral nerve. The granular cells have polygonal shape, distinct cytoplasm and eosinophilic granular cytoplasm with round, fairly uniform nuclei. **D** The large, ovoid, brightly eosinophilic globules surrounded by clear halo represent giant lysosomes.

ing the skin, submucosa, and viscera {577}. Congenital presentation has also been reported. No definite association with neurofibromatosis type 1 has been established {1642,2577}.

Clinical features

GCT usually presents as an asymptomatic or occasionally tender or pruritic, skin-coloured or brown-red, firm dermal or subcutaneous papulo-nodule, ranging in size from 0.5-3.0 cm in diameter. Verrucous changes of the surface epithelium are common, whereas ulceration is uncommon. The cutaneous tumours grow slowly; most symptoms are related to visceral locations.

Macroscopy

GCTs are nodular, but not encapsulated, and present as firm dermal or subcutaneous masses with a thickened or verrucous epidermal surface. On cut-surface the tumour has a pink-yellow, finely granular appearance {2084,2490}.

Histopathology

The tumour forms poorly cohesive nests, strands, fascicles, and sheets of polygonal, pale eosinophilic cells in the dermis and subcutis. Commonly, the cells form indistinct delicate fascicles that infiltrate the dermal collagen and extend to the subcutaneous septa. A variant of GCT with a distinctly plexiform growth pattern has been documented {1392}. Perineural spread is a common feature. The cells have an abundant granular, faintly eosinophilic cytoplasm with round, small, hyperchromatic nuclei. The fine, eosinophilic, intracytoplasmic granules correspond to lysosomes, which are PAS positive and diastase resistant.

Occasional larger, brightly eosinophilic ovoid bodies surrounded by a clear halo can be identified within the granules representing residual "giant" lysosomes. Interspersed between the granular cells, there are spindle cells with fibroblast-like features and histiocyte-like cells often with triangular, coarsely granular eosinophilic lysosomes designated as "angulate bodies". Nuclear pleomorphism, prominent nucleoli, and mitotic figures are uncommon. A characteristic feature of most cutaneous GCTs is the overlying pseudoepitheliomatous hyperplasia, which can be so extensive that it can mimic a verruca or a well-differentiated squamous cell carcinoma.

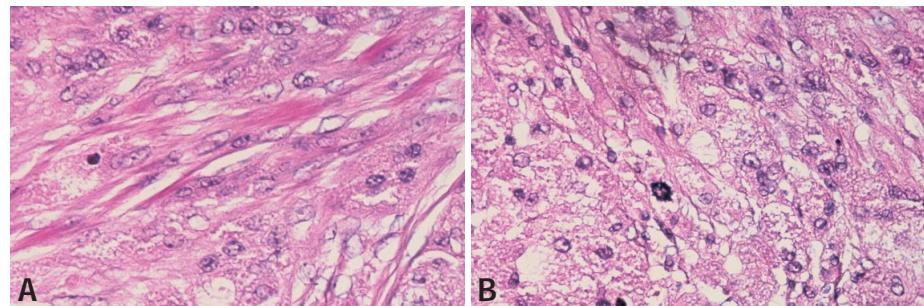


Fig. 6.12 Malignant granular cell tumour. **A** Malignant granular cell tumour shows cells with polygonal and spindled morphology and coarse eosinophilic granularity. **B** Malignant granular cell tumour with pleiomorphic cells, single cell necrosis and atypical mitotic figure.

Immunohistochemistry

GCT expresses markers associated with both neural (S-100 protein, PGP 9.5, neuron specific enolase, laminin, NGFR, calretinin, peripheral myelin proteins, P2-P0, myelin basic protein, CD57) and histiocytic (CD68, α-1-antitrypsin) differentiation. The tumour cells are positive for vimentin. Most studies report a negative reaction for neural filaments and GFAP {246,743,1063,1487,1540,1714}.

Variants

Granular cell epulis of infancy

This is a rare, polypoid tumour of the alveolar ridge of the gingiva of the newborn with a predilection for girls. The tumour has cytologic features similar to GCT, but lacks globular cytoplasmic inclusions, angulate body histiocytes, and contains a distinct plexiform capillary pattern. The immunohistochemical profile is also different; the lesions are negative for S-100 protein, NSE, laminin, MBP, CD57, and α-1-ACT {740,1367, 1764,2528}.

Malignant granular cell tumour

These are extremely rare and comprise less than 2% of all granular cell tumours. The age and sex distribution is similar to that of their benign counterparts, but they are more common on the extremities (particularly on the thighs) rather than the head and neck areas, or the oral mucosa. Malignant GCTs grow rapidly, often ulcerate, invade locally and tend to spread via extensive metastases.

Histologically and cytologically two forms can be distinguished: the more common type of malignant GCT is essentially identical to the benign tumour. Since cytologic atypia or mitotic activity are not reliable biologic indicators, correlation of clinical data (large size, rapid growth,

ulceration) with the histologic features (necrosis, spindling, and lymphocapillary invasion) should guide in the diagnosis of malignancy. Additional features cited as useful for predicting malignancy are vesicular nuclei with large nucleoli and a mitotic rate greater than 2 mitoses/10 HPF.

The second type of malignant GCT is quite rare; both the primary tumour and its metastases display histologic and cytologic characteristics of malignancy. The immunophenotype of malignant GCT is also similar to that of the benign tumour, however the proliferation markers (Ki-67) show increased labelling indices, and p53 expression is prominent {2084}.

Genetics

Only limited genetic studies have been performed on malignant GCT of the soft tissue. This showed two clonal karyotypes. One atypical tumour was aneuploid and all 11 benign tumours were either diploid (9 cases) or hyperdiploid (2 cases) {627}.

Prognosis and predictive factors

GCT is benign, however local recurrence is common due to incomplete removal complicated by the typical perineural spread. The malignant variants are aggressive tumours and usually have numerous local recurrences before distant spread. Their overall prognosis is poor, with metastases developing within two years in the majority of cases and there is close to 60% mortality within three years {2084,2490}. Because of the potential for recurrence and the morphologic overlap between benign and malignant GCT, complete excision is recommended.

CHAPTER 7

Inherited Tumour Syndromes

The study of familial cancer syndromes has led to the discovery of key genes that are important not only for the understanding of the mechanisms of genetic susceptibility but also for giving new insights into genetic and signaling pathways involved in sporadic cancers. Investigations into the rare skin disease xeroderma pigmentosum has led to the discovery of 7 DNA repair genes involved in the nucleotide excision repair pathway. Studies of these patients allowed us to understand the mechanism of DNA repair in the general population. Eventually, the in-depth analysis of the activity of these repair genes may allow us to define a subpopulation of individuals at higher risk of developing cancers in different organ sites.

This chapter contains a detailed description of clinical, pathological and genetic data of some major, well characterized inherited syndromes associated with skin cancer or other skin disorders.

Table 7.1

Inherited disorders associated with skin abnormalities

OMIM	Disease	Inheritance	Tumour types	Locus	Gene	Protein	Function
	Xeroderma Pigmentosum	AR	BCC SCC MM				
278700	Complementation group A			9q22.3	XPA	XPA	Damaged DNA-binding interaction with TFIH and XPF/XPG endonucleases
133510	Complementation group B			2q21	XPB/ERCC3	XPB	3'Δ5' helicase in TFHII
278720	Complementation group C			3p25.1	XPC	XPC	Damaged DNA-binding only involved in global genomic repair. Heterodimer with HHR23B
126340	Complementation group D			19q13.2-3	XPD/ERCC2	XPD	5'Δ3' helicase in TFHII
600045	Complementation group E			11q12-13	DDB1	XPE P127	Damaged DNA-binding only involved in global genomic repair. Heterodimer with DDB2
600811	Complementation group E			11p11-12	DDB2	XPE P48	Damaged DNA-binding only involved in global genomic repair. Heterodimer with DDB1
278760	Complementation group F			16p13.3-13.13	XPF/ERCC4	XPF	5' structure-specific endonuclease heterodimer with ERCC1
133530	Complementation group G			13q32-33	XPG/ERCC5	XPG	3' structure-specific endonuclease. Stabilization of the open complex
603968	Xeroderma pigmentosum variant			6p21.1	POLh	POL h	Translesion DNA polymerase
600160	Familial melanoma		MM	9p21	CDKN2A	P16/INK4	Inhibits CDKs from phosphorylating Rb, thereby freezing cell cycle
						P14ARF	Stabilizes p53 by inhibiting MDM2, thereby promoting apoptosis
123829	Familial melanoma		MM	12q14	CDK4	CDK4	Activated protein kinase resistant to p16 inhibition ; overphosphorylates Rb, thereby driving cell cycle
155600	Familial atypical mole-malignant melanoma syndrome (FAMMM)/ Dysplastic naevus syndrome (DNS)	AD	MM	1p36(?)	unknown	unknown	CDKN2A and CDK4 genes have been excluded
109400	Naevoid basal cell carcinoma syndrome	AD	BCC	9q22.3	PTCH1	PTCH1	Development gene ; regulates the Sonic Hedgehog signaling pathway
158350	Cowden disease b	AD	MH	10q23	PTEN/MMAC1	PTEN/TEP1/MMAC1	Lipid/protein phosphatase
158320	Muir-Torre syndrome	AD	CSN	2p22	hMSH2	hMSH2	Involved in DNA mismatch repair
175100	Gardner syndrome a	AD	EC	5q21	APC	APC	Negatively regulates β-catenin, a cytoskeletal and growth-promoting protein, and the WNT signaling pathway
131100	Multiple endocrine neoplasia 1	AD	MFA	11q13	MEN1	menin	Inhibitor of Jun D-activated transcription
171400	Multiple endocrine neoplasia 2	AD	CLA	10q11.2	RET	RET	Tyrosine kinase receptor involved in signal transduction
605284	Tuberous sclerosis 1	AD	MSL	9q34	TSC1	hamartin	Interacts with tuberin and exhibits growth-inhibitory activity
191092	Tuberous sclerosis 2	AD	MSL	16p13.3	TSC2	tuberin	GTPase-activating protein for RAP1 and RAB5 ; interacts with hamartin
162200	Neurofibromatosis 1 b (von Recklinghausen disease)	AD	FTK	17q11.2	NF1	neurofibromin	Negatively regulates ras-family of signal molecules through GAP function : Tumour suppressor activity
101000	Neurofibromatosis 2 b	AD	ST	22q12.2	NF2	merlin	Integrates cytoskeletal signaling
210900	Bloom syndrome b	AR	ST	15q26.1	BLM/RECQL3	BLM	DNA helicase ; unwinds DNA at blocked replication forks
175200	Peutz-Jeghers syndrome	AD	MML	19p13.3	STK11	STK11	Serine/threonine protein kinase : Tumour suppressor activity
268400	Rothmund-Thomson syndrome ^b	AR	D	8q24.3	RECQL4	RECQL4	DNA helicase ; unwinds DNA at blocked replication forks/recombination sites
277700	Werner syndrome b	AR	SSC	8p12	WRN/RECQL2	WRN	DNA helicase ; unwinds DNA at blocked replication forks/recombination sites
135150	Birt-Hogg Dubé Syndrome	AD	HFH	17p11.2	BHD	folliculin	Unknown
132700	Cylindromatosis familial	AD	C	16q12-13	CYLD1	CYLD1	Tumour suppressor gene. Protein with 3 cytoskeletal-associated-protein-glycine-conserved domains implicated in the attachment of organelles to microtubules

Familial cutaneous melanoma

B. Bressac-de Paillerets
F. Demenais

Definition

Familial melanoma is defined as the occurrence in at least two affected blood-relatives up to the third degree on one side of the family. This genetic susceptibility is caused germline mutations in the CDKN2A/p14ARF or CDK4 gene.

OMIM numbers

600160: Cyclin-dependant kinase inhibitor 2A; CDKN2A

Synonyms: CDK4 Inhibitor; multiple tumour suppressor 1, MTS1; TP16; p16(INK4); p16(INK4A); p19(ARF); p14(ARF).

123829: Cyclin-dependant kinase 4; CDK4

Synonyms: Cell Division Kinase 4; Cutaneous malignant melanoma 3, CMM3.

155600: Melanoma, cutaneous malignant; CMM

Synonyms: Melanoma, malignant; Familial atypical mole-malignant melanoma syndrome, FAMMM; Melanoma familial, MLM; Dysplastic naevus syndrome, hereditary, DNS; Melanoma, cutaneous malignant 1, CMM1; B-K Mole syndrome.

155755: Melanoma-astrocytoma syndrome

Synonyms: Melanoma and neural system tumour syndrome

606719: Melanoma-pancreatic cancer syndrome

Synonyms: Familial atypical multiple mole melanoma pancreatic carcinoma syndrome (FAMMMPC)

Epidemiology

Cutaneous melanoma is a typical example of a multifactorial disease, where both genetic and environmental factors are involved and interact. Genetic factors were first suspected through the existence of familial aggregations of CM. The proportion of familial cases varies from 4-15% across different studies. Within large families, familial aggregation of melanoma was consistent with autosomal, dominant inheritance. In addition to CM family history, numerous epidemiological studies have demonstrated that cutaneous and pigmentary characteristics (the presence of numerous naevi, naevi atypia, skin colour, red hair and freckles), sun exposure (particularly during childhood) and reactions to sun exposure (inability to tan and propensity to develop sunburns) are major CM risk factors. Some melanoma risk factors also show familial aggregations independently of melanoma, suggesting the existence of genetic factors specific to these phenotypes [309]. The various patterns of associations of these different phenotypes (phototype, naevus phenotypes and CM) across families are likely to result from complex interactions of genetic and environmental factors underlying these traits.

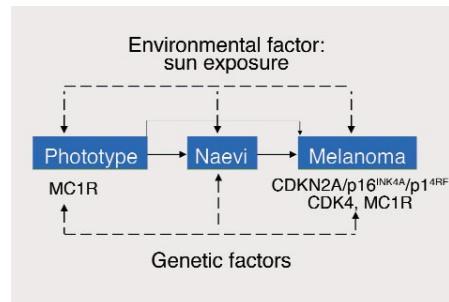


Fig. 7.1 Interaction of environmental (sun exposure) and genetic factors in the evolution of cutaneous melanoma (CM).

Clinical features and neoplastic disease spectrum

Cutaneous melanoma (CM)

Characteristics of familial melanoma include multiple cases of CM among blood-relatives on the same side of the family. Potential genetic predisposition may be suspected also in sporadic cases such as multiple primary CM in the same individual or early age of onset [1239].

Pancreatic cancer

The existence of an increased risk of pancreatic cancer in a subset of CDKN2A families has been reported [286,859].

Breast cancer

An excess of breast cancer has been described in two sets of families, Italian and Swedish [286,822].

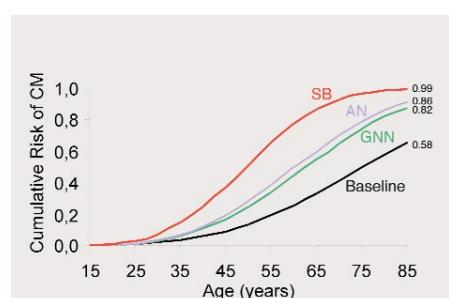


Fig. 7.2 Effect of great number of naevi (GNN), atypical naevi (AN) and sunburns (SB) on cutaneous melanoma (CM) risk in CDKN2A mutation carriers.

Table 7.2:
Inherited tumour syndromes
Abbreviations

AR*	Autosomal Recessive
AD	Autosomal Dominant
BCC**	Basal Cell Carcinoma
SCC	Squamous Cell Carcinoma
MM	Malignant Melanoma
MH	Multiple Hamartomatous
CSN	Cutaneous Sebaceous Neoplasms
EC	Epidermoid Cysts
MFA	Multiple Facial Angiofibromas
CLA	Cutaneous Lichen Amyloidosis
MSL	Multiple Skin Lesions
FTK	Fibromatous Tumours of the Skin
ST	Skin Tumours
MML	Melanocytic Macules of the Lip
D	Dermatoses
SSL	Scleroderma-like Skin Changes
HFH	Hair Follicle Hamartomas
C	Cyclindroma

* Already described in the WHO Classification of Tumours of the Digestive System [944]

** Already described in the WHO Classification of Tumours of Soft Tissue and Bone [756]

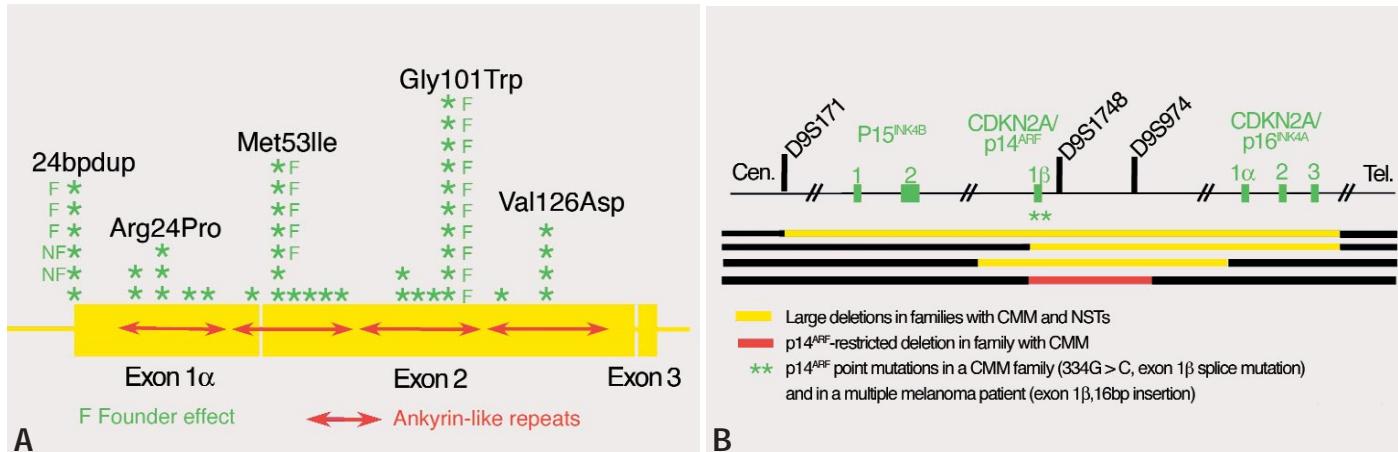


Fig. 7.3 A. *CDKN2A/p16^{INK4A}* germ-like mutations. B *CDKN2A/p14^{ARF}* gene mutations.

Nervous system tumours

Rare families have been described displaying melanoma and neural system tumours (NSTs) over several generations [129,1230]. This has been termed melanoma-astrocytoma syndrome due to the presence of cerebral astrocytomas in the first family described.

Uveal melanoma (UM)

Certain melanoma-prone kindred have members affected by either uveal and/or cutaneous melanoma. The first *CDKN2A* germline mutation was detected recently in a melanoma-prone family, where one carrier was affected by UM and the other by a CM (Kannengiesser C. et al., *Gene Chromosome and Cancer*, pending). Naevus: total number (TN), clinically atypical (AN), histologically dysplastic (DN)

These naevus phenotypes are major risk factors for CM but whether they represent precursor lesions in the course of tumour development is still unclear. There are several lines of evidence suggesting that distinct genetic factors may be involved in CM and number of naevi [309]. *CDKN2A* does not appear to be a "naevus" predisposing gene; this phenotype was found in only half of the subjects with a *CDKN2A* gene mutation and who had developed melanoma [2226] and a study of Australian twins has reported that a *CDKN2A*-linked gene may influence flat moles but has no effect on raised or atypical moles [2601]. Naevus phenotypes (TN, AN and/or DN) have been shown to influence the penetrance of *CDKN2A* in melanoma-prone North-American and French families

{860,452A} with a greater effect of DN in non-carriers than in carriers of *CDKN2A* mutations in the American sample.

Genetics

Gene structure and mutations

Two genes (encoding three proteins) conferring a high risk of developing melanoma have been identified to date, *CDKN2A/p14^{ARF}* and *CDKN2A*. In addition, a low-risk melanoma susceptibility gene has also been identified, the melanocortin-1 receptor gene (MC1R).

CDKN2A/p16^{INK4A} gene

Linkage analyses, cytogenetic studies and loss of heterozygosity (LOH) studies in tumour cells have led researchers to suspect the existence of a CM susceptibility gene at 9p21 locus. The gene, *p16^{INK4A}/CDKN2A*, was cloned in 1993 [2140] and formally identified as a melanoma susceptibility gene in 1994 [1088,1184].

The *CDKN2A* transcript includes exons 1a, 2 and 3. It encodes the 156 amino-acid *p16^{INK4A}* protein composed of four ankyrin repeats which are motifs involved in protein-protein interactions. *P16^{INK4A}* binds to cyclin-dependent kinase 4 (CDK4) and 6 (CDK6), therefore preventing binding of cyclin D1 to the CDKs. Cyclin D1/CDK4/6 complexes participate in the phosphorylation of the retinoblastoma protein (RB), allowing the cell to progress beyond the G1 phase of the cell division cycle [2166]. The *p16^{INK4A}* protein inhibits RB-dependant cell cycle and therefore acts as a tumour suppressor.

The search for mutations of the *CDKN2A*

gene in numerous familial studies around the world shows that the frequency of *CDKN2A* mutations is about 20% on average but varies from 5-50% depending on the criteria for family selection. Homozygotes for *CDKN2A* germline mutation have been described in relation to a Dutch founder effect; they display similar phenotypes than heterozygous individuals [912]. Mutations of the *CDKN2A* gene are detected in approximately 10% of sporadic multiple melanoma cases, without any evidence of de novo mutations up to date but in relation to the existence of a founder effect for some of them [115]. To date, no germline mutations have been found in cases of childhood melanoma (<18-20 years of age) lacking a family CM context [2507]. Most *CDKN2A* mutations are missense mutations scattered throughout the coding sequences of exons 1a and 2. Functional studies of mutant *p16^{INK4A}* proteins have been carried out using several assays displaying various sensitivity: CDK-binding, kinase activity inhibition, growth arrest and protein cellular localisation assays. Two more complex mutations have been also described: a mutation located within *CDKN2A* 5'UTR, creating an aberrant initiation codon {1435} and a deep intronic mutation (IVS2-105A/G) of *CDKN2A*, leading to aberrant mRNA splicing [956]. Recurrent mutations described in melanoma-prone families from different continents have been shown to be founder mutations [115,488].

Within the International Melanoma Consortium, *CDKN2A* mutation penetrance was estimated to be, in a set of 80

families, 0.58 in Europe, 0.76 in the United States and 0.91 in Australia, by age 80 years [251]. This variation of penetrance by geographical location was found to be similar to the variation of overall population incidence rates among these countries. This suggests that the same risk factors mediate CM risk to the same extent in CDKN2A mutation carriers as in non-carriers. Moreover, CM risk does not change according to whether or not the mutation can simultaneously alter the p16INK4A and p14ARF proteins.

Three MC1R variant alleles also act as modifiers of melanoma risk in families segregating CDKN2A mutations: MC1Rvar/var genotypes increased the melanoma penetrance in CDKN2A carriers from 50-84% in Australia (sunny country) and from 18-55% in the Netherlands (less sunny country) [291,2410].

CDKN2A/p14ARF gene

In 1995, it was discovered that part of CDKN2A gene was common to another transcript. This second transcript (exons 1b, 2 and 3) encodes the human p14ARF protein (ARF meaning "alternative reading frame") composed of 132 amino-acid, encoded by exons 1b and 2. According to the current state of knowledge, p14ARF is involved in regulation of the cell cycle and apoptosis via the p53 and RB pathways, by interacting with MDM2 (leading to p53 protein accumulation and to RB inactivation) and E2F1 proteins [1437].

Mutations in exon 2 potentially affect p16INK4A and p14ARF proteins at the same time. Despite this dual coding capacity of the INK4A/ARF locus, recent description of three p14ARF germ-line alterations involving only exon 1b suggests a direct role for p14ARF haploinsufficiency in melanoma predisposition : (1) a deletion restricted to exon 1b and segregating with melanoma and neural cell tumours within a family [1890], (2) a 16bp insertion in exon 1b in a sporadic multiple melanoma case [1945], (3) a splice mutation in exon 1b in a two melanoma-cases family [1022].

A role for both p14ARF and p16INK4A/CDKN2A genes?

Germ-line alterations presumably alter-

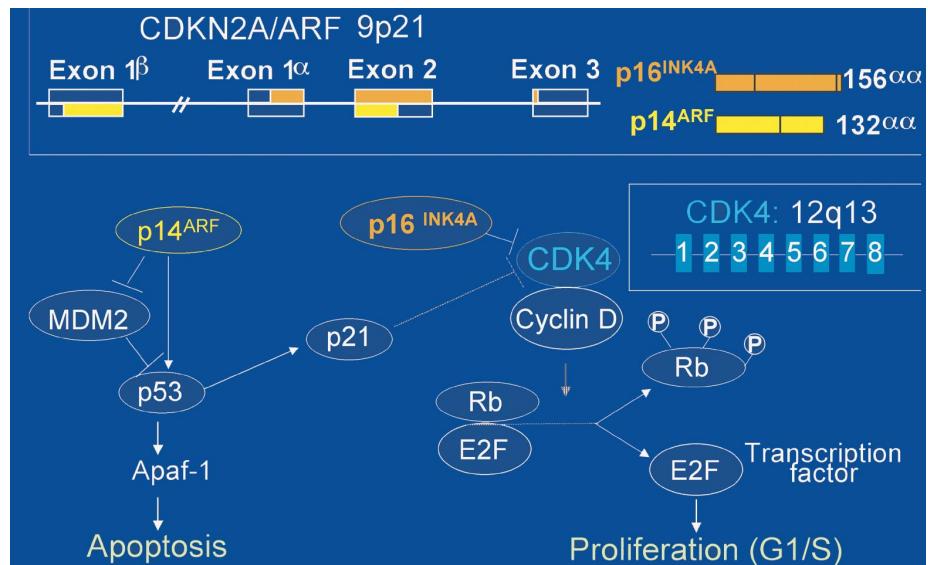


Fig. 7.4 p14ARF and p16INK4A signaling pathways and their role in apoptosis and proliferation of melanocytes.

ing both p16INK4A and p14ARF functions, have been described in three CM and NSTs families: two large deletions involving the INK4A locus [128] and a CDKN2A splice point mutation, leading to p16INK4A and p14ARF transcripts lacking exon2 [1818]. However, it cannot be concluded that both p16INK4A and p14ARF inactivation are necessary for melanoma-astrocytoma syndrome as a fourth such family has been also described with a germ line deletion apparently restricted to the p14ARF - specific exon 1b [1890].

CDK4 gene

The CDK4 gene on chromosome 12q13 is composed of 8 exons within a 5-kilobases (kb) segment. The initiation codon is located in exon 2, the stop codon in exon 8. This gene encodes the cyclin-dependant kinase 4 (CDK4), a 304 amino-acid protein. It has been identified as a melanoma predisposing gene in three families world-wide [2226,2607]. Germline mutations affect Arg-24 residue in exon 2, which plays a key role in p16INK4A binding. The mutation induces the loss of the cell cycle down-regulation signal that p16INK4A exerts through RB phosphorylation. In a "knock-in" Cdk4R24C/R24C mouse model, constitutive Cdk4 activation is oncogenic [1891].

Application of genetic testing in the clinical testing

There is some evidence that non-carrier of CDKN2A mutations in melanoma-prone families may have a higher incidence of melanoma than the general population, presumably due to co-inheritance of other low-risk susceptibility genes and common environmental risk amongst family members. Therefore, genetic testing for melanoma is of limited clinical utility to date, mainly because a negative genetic test may give dangerously false security. Testing should be done in research protocols and first-degree relatives of high-risk individuals should be engaged in the same programs of melanoma prevention and surveillance, irrespective of the results of any gene testing. However, in countries of low melanoma incidence such as most European countries, DNA testing may improve compliance with sun protection and surveillance in identified mutation carriers. In such situations, CDKN2A testing could be proposed after careful genetic counselling [1238].

Xeroderma pigmentosum

K.H. Kraemer
A. Sarasin

Definition

Xeroderma pigmentosum (XP) is an autosomal recessive disease with sun sensitivity, photophobia, early onset of freckling, and subsequent neoplastic changes on sun-exposed surfaces [284, 778]. There is cellular hypersensitivity to UV radiation and to certain chemicals in association with abnormal DNA repair [2419]. Some of the patients have progressive neurologic degeneration. The XP syndrome is genetically heterogeneous. Patients with defective DNA nucleotide excision repair (NER) have defects in one of 7 NER genes, while XP variant patients have normal NER and a defect in a polymerase gene [316,500].

OMIM Numbers

278700 - XPA
133510 - XPB
278720 - XPC
278730 - XPD
278740 - XPE
278760 - XPF
278780 - XPG
278750 - XP variant

Synonyms

De-Sanctis Cacchione syndrome, pigmented xerodermod, xeroderma pigmentosum variant

Epidemiology

Incidence

Xeroderma pigmentosum occurs with an estimated frequency of 1:1,000,000 in the United States [1322]. It is more common in Japan, the Middle East and North-Africa. Patients have been reported worldwide in all races including Whites, Asians, Blacks, and Native Americans. Consanguinity is common. There is no significant difference between the sexes.

Clinical features

Abnormalities may be present in the skin, eyes, or nervous system. There is a greatly increased frequency of cancer on sun-exposed sites.

Skin

Approximately half of the patients with XP have a history of acute sunburn reaction on minimal UV exposure [1322]. The other patients give a history of normal tanning without excessive burning. In all patients, numerous freckle-like hyperpigmented macules appear on sun-exposed skin.

The median age of onset of the cutaneous symptoms is between 1 and 2 years [1321]. Repeated sun exposure results in dry and parchment-like skin with increased pigmentation, hence the name xeroderma pigmentosum ("dry pigmented skin"). Pre-malignant actinic keratoses may develop at an early age.

Eyes

Ocular abnormalities are almost as common as the cutaneous abnormalities [801,871,2424]. Clinical findings are strikingly limited to the anterior, UV-exposed structures. Photophobia is often present and may be associated with prominent conjunctival injection. Continued UV exposure of the eye may result in severe keratitis leading to corneal opacification and vascularization. The lids may develop loss of lashes and atrophy of the skin of the lids results in the lids turning out (ectropion), or in (entropion), or complete loss of the lids in severe cases. Benign conjunctival inflammatory masses or papillomas of

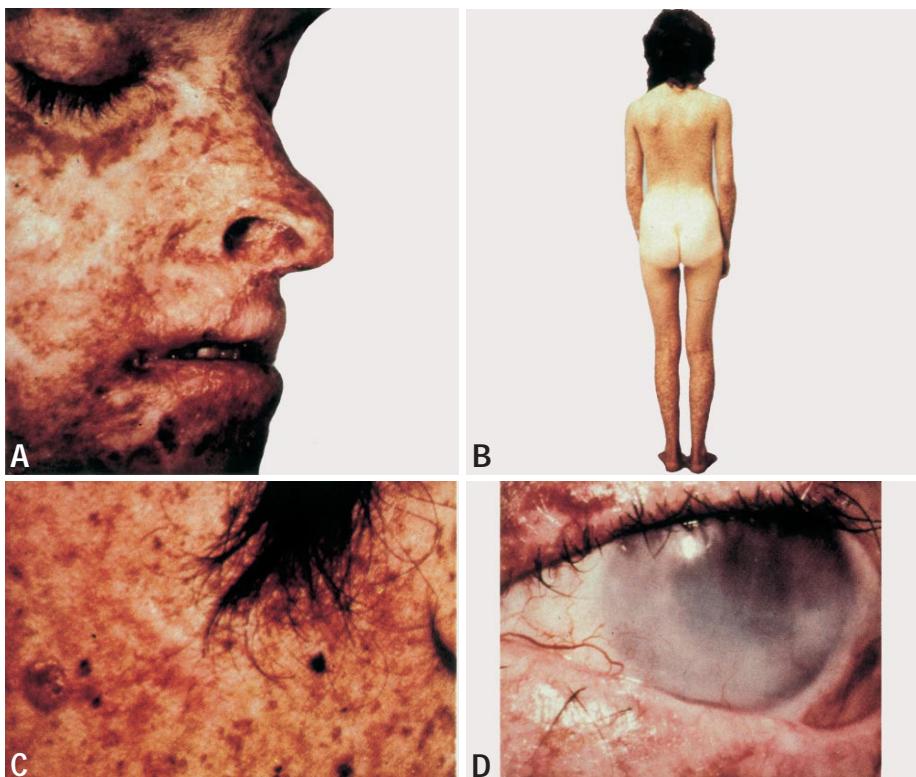


Fig. 7.5 Xeroderma pigmentosum. **A** Face of a 16 year old patient showing dry skin with hyperpigmentation, atrophy and cheilitis. **B** Posterior view of the same patient showing absence of pigmentary changes on areas protected from sunlight. **C** Face of a 14 year old patient showing freckle-like lesions with different amounts of pigmentation, an actinic keratosis, a basal cell carcinoma and a scar with telangiectasia at the site of removal of another neoplasm. **D** Xeroderma pigmentosum. Eye of the 22 year old patient showing secondary telangiectasia invading the cloudy cornea, and atrophy and loss of lashes of the lower lid. Figures from K.H. Kraemer [1319].

the lids may be present. Basal and squamous cell carcinoma, and melanoma of UV-exposed portions of the eye are common.

Nervous system

Neurologic abnormalities have been reported in approximately 30 percent of the patients. The onset may be early in infancy (the De-Sanctis Cacchione syndrome) or delayed until the second decade. The neurologic abnormalities may be mild (e.g., isolated hyporeflexia) or severe, with progressive mental retardation, sensorineural deafness (beginning with high-frequency hearing loss), spasticity, or seizures. In clinical practice, deep tendon reflex testing and routine audiometry can usually serve as a screen for the presence of XP-associated neurologic abnormalities. The predominant neuropathologic abnormality found at autopsy in patients with neurologic symptoms was loss (or absence) of neurons, particularly in the cerebrum and cerebellum {1894}.

Cancer

Patients with XP under 20 years of age have a greater than 1000-fold increased risk of skin cancer (basal cell or squamous cell carcinoma or melanoma) {1321}. Multiple primary skin cancers are common. The median age of onset of non-melanoma skin cancer reported in patients with XP was 8 years. This 50-

year reduction in comparison to the general population is an indication of the importance of DNA repair in protection from skin cancer in normal individuals. There is a greatly increased frequency of cancer of the anterior portion of the eye and of the oral cavity, particularly squamous cell carcinoma of the tip of the tongue. These are presumed sun-exposed sites. Brain (sarcoma and medulloblastoma), central nervous system (astrocytoma of the spinal cord), lung, uterine, breast, pancreatic, gastric, renal, and testicular tumours and leukaemias have been reported in a small number of XP patients. Overall, these reports suggest an approximate ten to twenty-fold increase in internal neoplasms {1321}.

Diagnosis

There have been no consistent routine clinical laboratory abnormalities in patients with XP. Diagnosis is based on clinical features and confirmed by tests of cellular hypersensitivity to UV damage along with a defect in nucleotide excision repair for classical XP {778}.

Cellular hypersensitivity

Cultured cells from patients with XP generally grow normally when not exposed to damaging agents. The population growth rate or single-cell colony-forming ability is reduced to a greater extent than normal, however, following exposure to

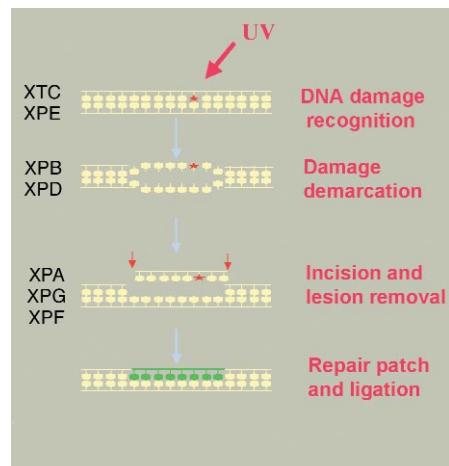


Fig. 7.6 General scheme for nucleotide excision repair (NER). The "classical" XP patients carry mutations in one of the seven XP genes indicated. Adapted from A. Stary and A. Sarasin {2253}.

UV radiation. A range of post-UV colony-forming abilities has been found with fibroblasts from patients, some having extremely low post-UV colony-forming ability and others having nearly normal survival. XP fibroblasts are also deficient in their ability to repair some UV-damaged viruses or plasmids to a functionally active state. XP variant cells are specifically sensitive killing by UV-irradiation in the presence of caffeine.

DNA repair

Cells from most XP patients have a defect in one of 7 genes (XPA through XPG) involved in the nucleotide excision repair (NER) system {500}. The NER pathway is described in Figure 7.6 {2253}. The DNA repair defect can be measured by post-UV unscheduled DNA synthesis. Host cell reactivation assays can be used to determine the complementation group by use of a panel of cloned DNA repair genes. Cells from XP variant patients have normal NER but have a defect in an error-prone polymerase (pol eta) {316}.

Prenatal diagnosis can be performed by use of unscheduled DNA synthesis assays on cultured amniotic fluid cells and by molecular analysis of trophoblast biopsies {52,1309}.

Most XP cells have a normal response to treatment with x-rays, indicating the specificity of the DNA repair defect.

Genetics

The seven complementation groups found for the classical XP correspond to

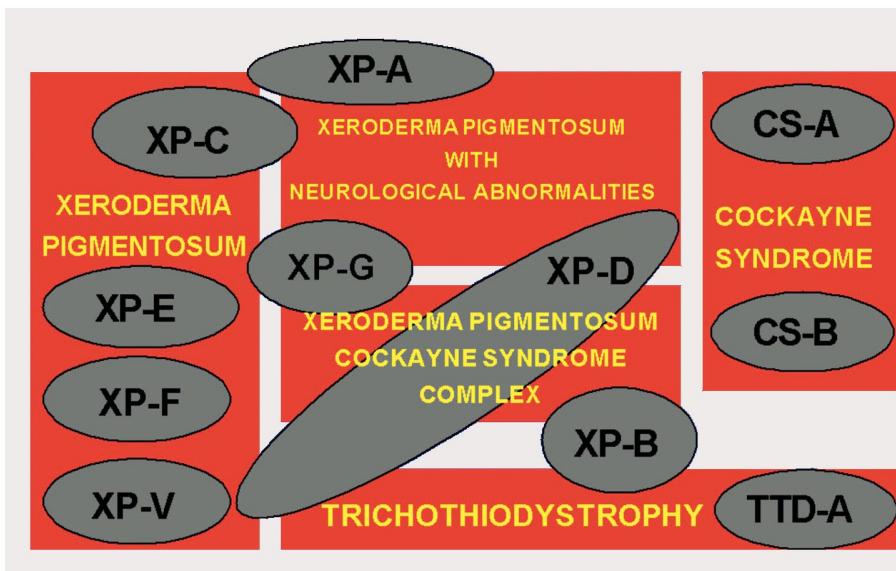


Fig. 7.7 DNA repair diseases. Correlation between clinical disorder (yellow letters) and molecular defects (black letters).

seven genes involved in NER {2253, 2419}; XPC, XPE and XPA code for proteins able to recognize DNA lesions produced by various DNA damaging agents, including UV-radiation. XPB and XPD are two helicases necessary to open the double helix at the site of the lesion. XPF and XPG are two endonucleases able to cut the damaged strand at the 5' and 3' sites, respectively.

Numerous other enzymes are necessary to complete the error-free repair but defects have not yet been identified in these genes in association with human diseases.

There is marked clinical and molecular heterogeneity in XP. Patients in XP complementation groups A, B, D, and G may have neurological abnormalities in addition to skin involvement. Patients with defects in XP complementation group D may have one of at least 5 different clinical phenotypes: XP with skin disease, XP with neurological disease, the XP/Cockayne syndrome complex {1894}, trichothiodystrophy (TTD - a disorder with sulphur deficient brittle hair) {1113} or XP/TTD {315}.

Treatment

Management of patients with XP is based on early diagnosis, life-long protection from UV radiation exposure, and early detection and treatment of neoplasms {778}.

Naevoid basal cell carcinoma (Gorlin) syndrome

R.J. Gorlin
J.C. Ehrhart

Definition

The naevoid basal cell carcinoma syndrome (NBCCS) is a genodermatosis caused by germline mutations of the PTCH gene. It is characterized by numerous basal cell cancers and epidermal cysts of skin, odontogenic keratocysts of jaws, palmar and plantar pits, calcified dural folds, various neoplasms or hamartomas (ovarian fibromas, medulloblastoma, lymphomesenteric cysts, fetal rhabdomyomas, etc.) and various stigmata of maldevelopment (rib and vertebral abnormalities, Sprengel anomaly, enlarged head circumference, cleft lip and/or palate, cortical defects of bones and other lesions.

OMIM number 109400

Synonyms

Naevoid basal cell carcinoma syndrome, Gorlin syndrome, Gorlin-Goltz syndrome, basal cell naevus syndrome.

Epidemiology

The frequency of NBCCS has been vari-

ously estimated. It constitutes about 0.4% of all cases of basal cell carcinomas. Evans et al {698} suggested that the minimal prevalence was 1 per 57,000.

Clinical features

Although the syndrome is remarkably variable in sites of involvement, the most persistent problems are the odontogenic keratocysts and the inordinate number of basal cell carcinomas, only a fraction of which become aggressive {867,868, 1273}.

Skull

The head appears large (>60 cm in adults). Relative macrocephaly (occipitofrontal circumference greater than 95th centile for height) is found in 50%. Mild mandibular prognathism, noted as "pouting lower lip", is seen in 35%.

Basal cell carcinomas

These may appear as early as 2 years of age, especially on the nape, most often proliferate between puberty and 35

years. There appears to be a relationship to increased sun exposure. The basal cell cancers, which vary in number from a few to literally thousands, range in size from 1-10 mm in diameter. They are pearly to flesh coloured to pale brown and may be mistaken for skin tags or naevi. The basal cell carcinomas which most often involve the face and upper chest may become aggressive and invade locally. Increase in size, ulceration, bleeding and crusting indicate invasion. Radiation therapy causes proliferation of basal cell carcinomas and invasion several years later.

Milia

Small keratin-filled cysts (milia) are found intermixed with basal cell carcinomas in 30-50%. Larger, often multiple, epidermal cysts arise on the limbs and trunk in about 35-50% of whites. Multiple cysts are located on the palpebral conjunctiva in about 40%.

Pits

Palmar and, somewhat less often, plantar

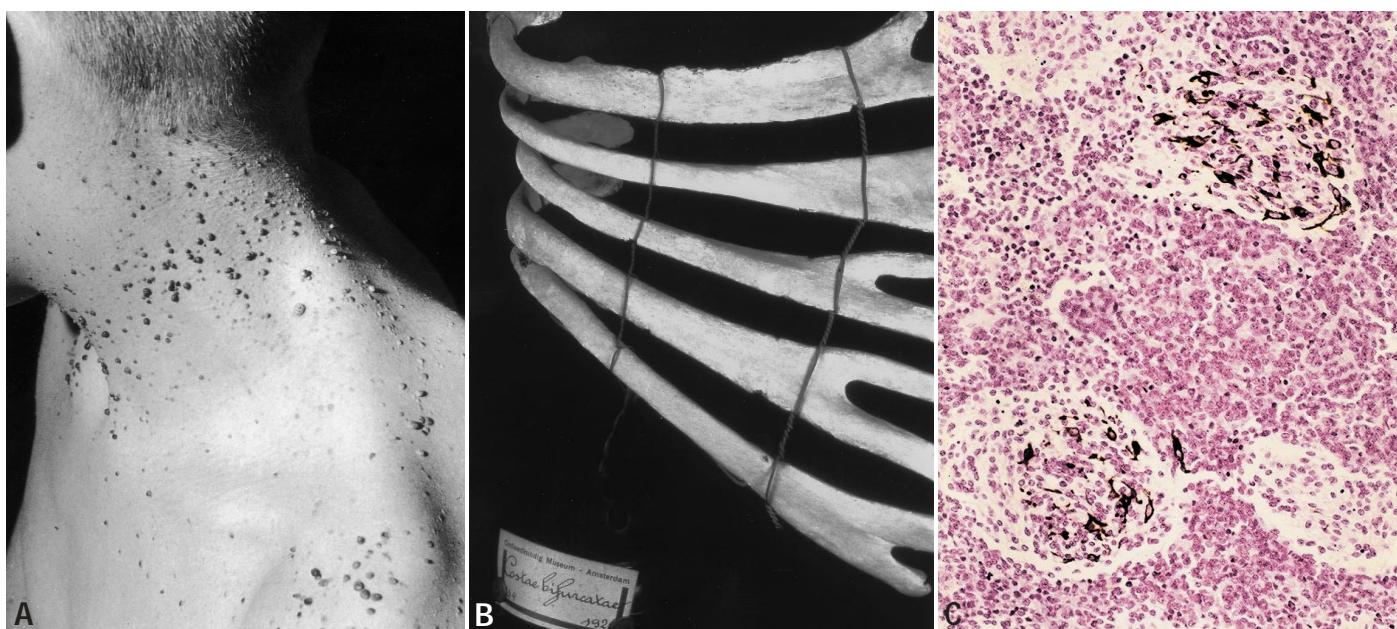


Fig. 7.8 A Multiple naevoid basal cell carcinomas scattered over neck and shoulder. B Multiple bifid ribs. C Desmoplastic medulloblastoma. The pale, reticulin-free nodules often show focal astrocytic differentiation. GFAP immunohistochemistry. From {1287}. NBCCS is typically associated with this variant.

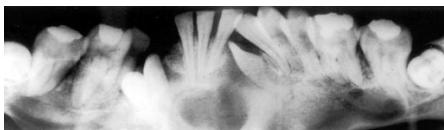


Fig. 7.9 Panoramic radiograph (panorex) showing multiple keratocystic odontogenic tumours / odontogenic keratocysts.

pits (1-2 mm) are asymmetrically present in 65-80%.

Keratocystic odontogenic tumours

Characteristically, multiple (average-6; range 1-30) odontogenic keratocysts, now termed keratocystic odontogenic tumours {153}, of both the upper and more often lower jaws appear after the seventh year of life with an overall frequency of 65%. They effect marked tooth displacement but only rarely cause fracture. There is marked tendency (over 60%) for these cysts to recur following surgery.

Medulloblastoma

This embryonal neoplasm is present in 3-5% of NBCCS patients and characteristically presents during the first 2 years of life as opposed to 7-8 years in the general population {698}. Because medulloblastoma presents early (mean 2.5 years) in patients with NBCCS, children who present with the tumour, especially those less than 5 years, should be care-

fully examined for signs of the syndrome. Radiation therapy of medulloblastoma results in profuse numbers of invasive basal cell carcinomas appearing in the radiation field (from nape to base of spine).

Fibromas

Cardiac fibromas occur in 3% {698}. Conversely, about 5% of patients with cardiac fibromas have NBCCS. Presentation time has varied from birth to 60 years. Most have been found incidentally. Ovarian fibromas are noted in 25% {698}. The ovarian fibromas associated with NBCCS are most often bilateral (75%). Minor kidney anomalies and hypogonadotropic hypogonadism are found in roughly 5%. Gorlin {868} reviewed examples of fetal rhabdomyoma.

Imaging

Lamellar calcification of the falx cerebri is found in 55-95% (normal-5%). Calcification of the tentorium cerebelli has been noted in 20-40%, the petroclival ligament in 20%, and the diaphragma sellae in 60-80%. Radiographically, this appears as if the sella turcica is bridged, i.e., as if there were fusion of the anterior and posterior clinoid processes {1897,1898}.

Odontogenic keratocysts first appear at about 7-8 years of age and increase in number from puberty onward. They peak during the second and third decades. The cysts cause marked tooth displacement. They may invade the paranasal sinuses and, in the mandible, may extend from the molar-ramus area to the coronoid processes.

Fused, splayed, hypoplastic or bifid ribs have been documented in 45-60%. Kyphoscoliosis with or without pectus is found in 25-40% with spina bifida occulta of the cervical or thoracic vertebrae in 60%. Sprengel deformity and/or unusual narrow sloping shoulders have been described in 10-40%. Other anomalies seen in about 40% include cervical or upper thoracic vertebral fusion, hemivertebra, and lumbarization of the sacrum. Pectus occurs in about 15-25% {1897,1898}.

Small pseudocystic bone lesions (flame-shaped lucencies) have been identified in the phalanges, metapodial bones, carpal and tarsal bones, long bones, pelvis and calvaria in 30%. Calvarial

Table 7.3

Diagnostic findings in adults with naevus basal cell carcinoma syndrome.
Modified, from R.J. Gorlin {868}.

50% or greater frequency

- Enlarged occipitofrontal circumference (macrocephaly, frontal-parietal bossing)
- Multiple basal cell carcinomas
- Odontogenic keratocysts of jaws
- Epidermal cysts of skin
- High-arched palate
- Palmar and/or plantar pits
- Rib anomalies (splayed, fused, partially missing, bifid, etc.)
- Spina bifida occulta of cervical or thoracic vertebrae
- Calcified falx cerebri
- Calcified diaphragma sellae (bridged sella, fused clinoids)
- Hyperpneumatization of paranasal sinuses

49-15% frequency

- Brain ventricle asymmetry
- Calcification of tentorium cerebelli and petroclival ligament
- Calcified ovarian fibromas
- Short fourth metacarpals
- Kyphoscoliosis or other vertebral anomalies
- Lumbarization of sacrum
- Narrow sloping shoulders
- Prognathism
- Pectus excavatum or carinatum
- Pseudocystic lytic lesion of bones (hamartomas)
- Strabismus (exotropia)
- Syndactyly
- Synophrys

14% or less but not random

- Medulloblastoma
- True ocular hypertelorism
- Meningioma
- Lymphomesenteric cysts
- Cardiac fibromas
- Fetal rhabdomyoma
- Ovarian fibrosarcoma
- Marfanoid build
- Anosmia
- Agenesis of corpus callosum
- Cyst of septum pellucidum
- Cleft lip and/or palate
- Low-pitched female voice
- Polydactyly, postaxial - hands or feet
- Sprengel deformity of scapula
- Vertebral body fusion
- Congenital cataract, glaucoma, coloboma of iris, retina, optic nerve, medullated retinal nerve fibers
- Subcutaneous calcifications of skin (possibly underestimated frequency)
- Minor kidney malformations
- Hypogonadism in males
- Mental retardation

Table 7.4

Diagnostic criteria for NBCCS

Diagnosis based on two major or one major and two minor criteria.

Major criteria

1. More than 2 BCCs or one under age of 20 yrs
2. Odontogenic keratocyst
3. Three or more palmar pits
4. Bilamellar calcification of falx cerebri
5. Bifid, fused or splayed ribs
6. First degree relative with NBCCS

Minor criteria

1. Macrocephaly adjusted for height
2. Frontal bossing, cleft lip/palate, hypertelorism
3. Sprengel deformity, pectus, syndactyly of digits
4. Bridging of sella turcica, hemivertebrae, flame-shaped radiolucencies
5. Ovarian fibroma
6. Medulloblastoma

Based on V.E. Kimonis et al {1273}.

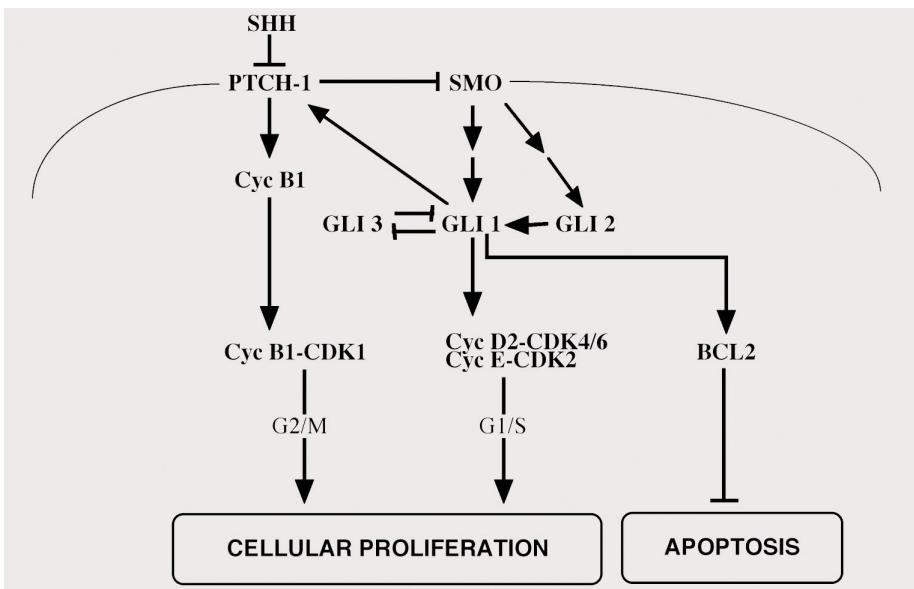


Fig. 7.10 Model of Sonic Hedgehog (SHH) signalling pathway. The function of the pathway is to stimulate cellular proliferation and inhibit apoptosis. The *PTCH-1* gene is predicted to encode a 12-transmembrane receptor with high affinity for the SHH secreted 19 kDa protein ligand. In presence of SHH, the pathway releases the 7-transmembrane protein Smoothened (SMO) from its inhibition by *PTCH-1*, thus activating target genes through the glioma (GLI) family of zinc-finger transcription factors (GLI1 is the most studied of the three GLI factors). GLI1 may control the G1/S transition checkpoint through activation of the transcription of *Cyclin D2* and *E* genes, and apoptosis through activation of *BCL2* expression. *PTCH-1* may also be involved in a G2/M transition checkpoint via Cyclin B1 which localizes to the nucleus upon SHH binding {152}. *PTCH-1* transcription is induced by GLI1, thus generating a negative feedback loop.

Abbreviations : Cyc, cyclin ; CDK, cyclin-dependent kinase.

involvement may give the impression that medulloblastoma has spread to bone. Histologically, the flame-like lesions are hamartomas consisting of fibrous connective tissue, nerves and blood vessels. Subcutaneous calcification of fingers and scalp has been rare. Sclerotic bone lesions have been reported occasionally. Ovarian fibromas are found in about 25% of females. They are bilateral and often calcified, at times overlapping medially. Prenatal diagnosis by sonography has been accomplished {235}.

Genetics

The first link between the SONIC HEDGEHOG (SHH) signalling pathway and tumour formation in humans was in

familial cancers, as 30-40% of NBCCS patients harbour loss-of-function mutations in the PATCHED1 (*PTCH1*) gene {514,939,1992}. That disruption of the SHH signalling pathway is a major determinant of tumour formation, particularly for BCCs, was established from the discovery that *PTCH1* is mutated in 10-38% of sporadic BCCs {514,1992}.

Inactivation of both *PTCH1* alleles also results in the formation of cysts {1408}. Consistent with its pivotal role in embryonic development, aberrant SHH signalling is associated with a range of human developmental anomalies {2434}. In NBCCS, tumours (BCCs, keratocysts, meningiomas, ovarian fibromas, odontogenic keratocysts) exhibit loss of het-

erozygosity (LOH) in the *PTCH1* locus (9q22.3) {514}. Various physical anomalies (bifid rib, macrocephaly, cleft lip, etc.) apparently need but one-hit {1407}. LOH in the *PTCH1* locus was observed in 89% of hereditary BCCs. The majority (61-71%) of germline *PTCH1* mutations are rearrangements. Most mutations (>80%) are likely to represent null mutations since they are predicted to result in truncation of the *PTCH1* protein {133, 514,1408,1992}.

The *PTCH1* tumour suppressor gene comprises 23 exons which encode 12 putative transmembrane domains and two large extracellular loops. The function of *PTCH1* is to silence the SHH signalling pathway in absence of active SHH ligand {2308}. In presence of SHH, the pathway acts in at least two ways to regulate target genes. One is to activate GLI 1/2 transcription factors and the other is to inhibit the formation of GLI repressors, mostly from GLI3, to derepress target genes {1992}.

Prognosis and predictive factors

New keratocystic odontogenic tumours (odontogenic keratocysts) and basal cell carcinomas continue for life. Limitation of sun exposure reduces the appearance of the skin cancers. The medulloblastoma appears before the age of 4 years, the ovarian fibromas after puberty.

Therapeutic radiation should be avoided whenever possible due to the high occurrence of basal cell carcinomas in the radiation field.

Cowden syndrome

D. V. Kazakov
G. Burg
C. Eng

Definition

Cowden syndrome (CS) is an autosomal-dominant disorder with age-related penetrance and variable expression, characterized by multiple hamartomas arising in tissues derived from all three embryonic germ cell layers and with a high risk of developing benign and malignant neoplasms in many organ systems, especially in the skin, breast, and thyroid gland. The condition was described in 1963 by Lloyd and Dennis {1439}. It is caused by germline mutations in the tumour suppressor gene *PTEN* located on chromosome 10q23 {1424}.

OMIM number 158350

Synonyms

Multiple hamartoma syndrome, Cowden disease

Epidemiology

Incidence

The incidence of CS, after *PTEN* was identified as the gene, was found to be 1 in 200 000 {1693}. The latter may be an underestimate, since CS has variable expression and often manifests itself only with subtle skin changes, so that this condition may be difficult to recognize {688}. Although the exact proportion of isolated and familial cases is not known, previous and on-going observations suggest that 40-60% are familial {1521, 2448, 688A}.

Clinical features

CS is classically characterized as a multiple hamartoma syndrome with a high risk of breast and thyroid cancers. Although the reported age at onset varies from 4–75 years {1451}, CS usually manifests in the second or third decade. More than 90% of individuals affected with CS are likely to manifest a phenotype by the age of 20 years, and 99% develop at least mucocutaneous lesions by the age of 30 years {1694, 2448}. CS is characterized by the development of hamartomas, benign and malignant tumours in multiple organ systems including the skin, soft tissues, breast, thyroid gland, gastrointestinal tract, genitourinary tract, and central nervous system. The most common lesions are trichilemmomas (90-100%), breast fibroadenomas (70%), thyroid adenomas (40-60%), multinodular goiter (40-60%), and multiple gastrointestinal polyps (35-40%) {688, 1451}. Macrocephaly is seen in 35-40% of cases. Malignant neoplasms develop in the breast in 25–50% of CS females, in the thyroid gland in 3–10% (usually follicular adenocarcinoma) and in the uterus in 3–6%. The most common malignant neoplasm in the breast is ductal adenocarcinoma, which is bilateral in one third of cases {2098}. The average age of CS patients at diagnosis of breast cancer is 10 years younger than in those with sporadic disease {2252}. Male breast cancers also occur, but with unknown frequency {704, 1519}. A feature that distinguishes CS from other breast cancer susceptibility syndromes is the occurrence of benign breast disease prior to the development of breast cancer {2098, 2099}.

Many other internal malignancies have been reported to occur in individuals affected with CS. There are no data to state whether they are true components of this syndrome or merely coincidental.

Bannayan–Riley–Ruvalcaba syndrome (BRRS)

This pediatric disorder characterized by congenital macrocephaly, multiple lipomatosis and angiomyomatosis involving the skin and visceral tissues, intestinal hamartomatous polyposis, and pigmented penile lesions, shows a partial clinical overlap with CS {711, 1519}.

Diagnostic criteria

The International Cowden Consortium originally proposed a set of operational diagnostic criteria in 1996 {1694}. Because of new data, the Consortium revised the criteria in 2000 {688}, which



Fig. 7.11 Acral hyperkeratotic papules.

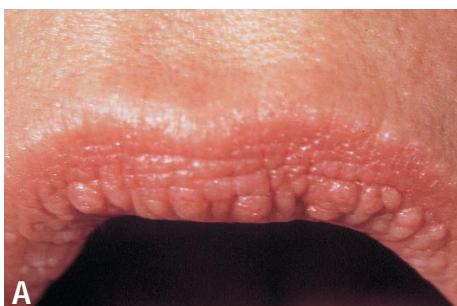


Fig. 7.12 Cowden disease (*PTEN*). **A** Multiple confluent papules on the upper lip. **B** Multiple wart-like lesions on the gingivae.

have also been adopted by the United States' National Comprehensive Cancer Center (NCCN) Practice Guidelines Panel.

Cutaneous and mucosal lesions

Cutaneous lesions are the most important hallmarks for CS, since they are present in almost every patient and frequently appear prior to the development of any internal disease [1030]. Facial papules are the most frequent lesions (85-90%). They are mainly located in periorificial regions, sometimes extending into the nostrils. Histopathologically, the papules frequently show non-specific verrucous acanthomas, trichilemmomas, perifollicular fibromas or may reveal lesions with features intermediate between trichilemmomas, inverted follicular keratosis, and tumour of follicular

infundibulum [322,2249-2251]. Although human papilloma virus has not been consistently found in these lesions, some experts believe that trichilemmomas in CS represent verrucae vulgaris with trichilemmal differentiation [28]. Acral verrucous hyperkeratosis on the extensor sides of the extremities and palmo-plantar translucent keratoses are seen in approximately 20-30% of cases. Histopathologically, they show wart-like changes, with prominent compact orthokeratosis, hypergranulosis, and acanthosis, in some cases with trichilemmal differentiation. Involvement of the oral mucosa is present in over 80% of cases. Coalescent lesions produce the characteristic cobblestone-like pattern in 40% of patients. Histopathologically, these lesions are composed of acellular collagen fibres, with a predominantly whorl-

like arrangement [2251]. Mucosal papules and nodules with trichilemmoma-like histopathological features are also common. A scrotal tongue is another common finding. Usually mucocutaneous lesions are present in multiple locations, and extension to the oropharynx, larynx, tongue, and nasal mucosa may occur.

Other cutaneous lesions reported to occur in individuals affected with CS include lipoma, angiolioma, multiple sclerotic fibromas, squamous cell carcinoma, melanoma, basal cell carcinoma, Merkel cell carcinoma, haemangiomas, xanthoma, vitiligo, neuroma, apocrine hidrocystoma, café au lait spots, periorificial and acral lentigines and acanthosis nigricans (reviewed in [748,1030])

Genetics

PTEN/MMAC1/TEP1 on 10q23.3, is the susceptibility gene for CS [1424,1694].

Gene structure and function

PTEN comprises 9 exons spanning 120-150 kb of genomic distance. It encodes a 1.2 kb transcript and a 403 amino acid lipid dual-specificity phosphatase (it dephosphorylates both protein and lipid substrates) [1419,1421,2256,2448]. A classic phosphatase core motif is encoded within exon 5, which is the largest exon, constituting 20% of the coding region [1419,1421,1519,2256].

PTEN is the major 3-phosphatase acting in the phosphatidylinositol-3-kinase (PI3K)/Akt pathway [1478,2241]. To date, virtually all naturally occurring missense mutations tested abrogate both lipid and protein phosphatase activity, and one mutant, G129E, affects only lipid phosphatase activity. Overexpression of *PTEN* results, for the most part, in phosphatase-dependent cell cycle arrest at G1 and/or apoptosis, depending on cell type (reviewed in [687,2448]). There is also growing evidence that *PTEN* can mediate growth arrest independent of the PI3K/Akt pathway and perhaps independent of the lipid phosphatase activity [460,1564,2448,2495,2496].

Mutation spectrum

Approximately 70-85% of CS cases, as strictly defined by the Consortium Criteria, have a germline *PTEN* mutation [1424,1519,2599]. If the diagnostic criteria are relaxed, then mutation frequencies drop to 10-50% [1464,1695,2382]. A

Table 7.5

International Cowden Consortium operational criteria for the diagnosis of Cowden syndrome 2000 [688].

Pathognomonic criteria
Mucocutaneous lesions
Trichilemmomas, facial
Acral keratoses
Papillomatous papules
Mucosal lesions
Major criteria
Breast carcinoma
Thyroid carcinoma (nonmedullary), especially follicular thyroid carcinoma
Macrocephaly (megalencephaly) (~95th percentile or more)
Lhermitte-Duclos disease
Endometrial carcinoma
Minor criteria
Other thyroid lesions (eg, adenoma or multinodular goitre)
Mental retardation (IQ<75 or less)
Gastrointestinal hamartomas
Fibrocystic disease of the breast
Lipomas
Fibromas
Genitourinary tumours (eg, renal cell carcinoma, uterine fibroids) or malformation
Operational diagnosis in an individual
1. Mucocutaneous lesions alone if there are:
(a) 6 or more facial papules, of which 3 or more are trichilemmoma, or
(b) cutaneous facial papules and oral mucosal papillomatosis, or
(c) oral mucosal papillomatosis and acral keratoses, or
(d) 6 or more palmo-plantar keratoses,
2. Two major criteria, one of which is macrocephaly or Lhermitte-Duclos disease
3. One major and three minor criteria
4. Four minor criteria
Operational diagnosis in a family where one individual is diagnosed with Cowden syndrome
1. The pathognomonic criterion or criteria
2. Any one major criterion with or without minor criteria
3. Two minor criteria

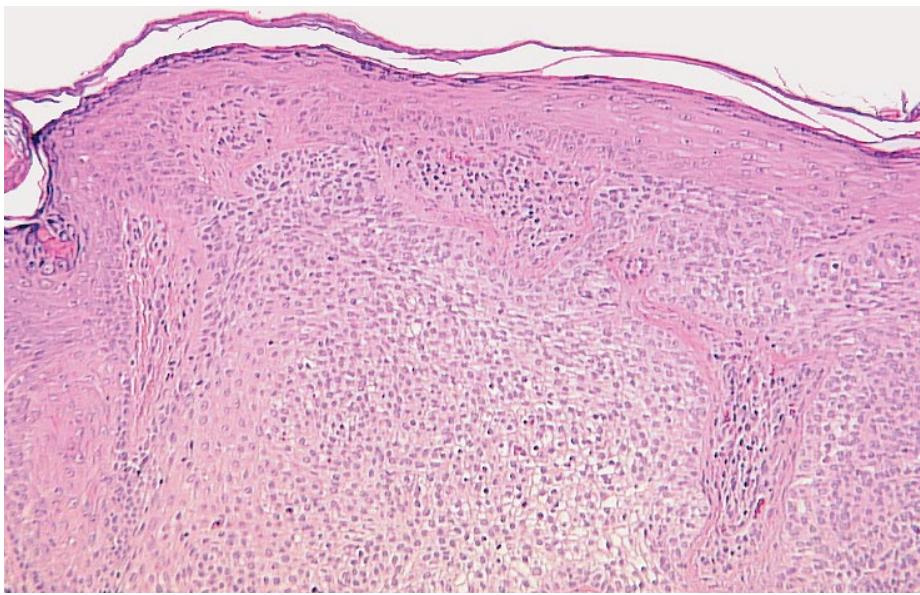


Fig. 7.13 Histopathological appearance of trichilemmoma in a patient with Cowden syndrome (Courtesy of Carl D. Morrison, MD, Ohio State University, USA).

formal study which ascertained 64 unrelated CS-like cases revealed a mutation frequency of 2% if the criteria are not met, even if the diagnosis is made short of one criterion {1519}. A single research centre study involving 37 unrelated CS families, ascertained according to the strict diagnostic criteria of the Consortium, revealed a mutation frequency of 80% {1519}.

As with most other tumour suppressor genes, the mutations found in *PTEN* are scattered throughout all 9 exons. They comprise loss-of-function mutations including missense, nonsense, frame-shift and splice-site mutations {1519, 1521,2448}. Approximately 30-40% of germline *PTEN* mutations are found in exon 5. Further, approximately 65% of all mutations can be found in one of exons 5, 7 or 8 {1519,1521}.

Although *PTEN* is the major susceptibility gene for CS, one CS family, without *PTEN* mutations, was found to have a germline mutation in the bone morphogenic protein receptor type 1A gene (*BMPR1A*, MIM 601299), which is one of the susceptibility genes for juvenile polyposis syndrome {1066,2600}.

Whether *BMPR1A* is a minor CS susceptibility gene or whether this family with CS features actually has occult juvenile polyposis is yet unknown.

Genotype-phenotype associations

Clinically useful genotype-phenotype correlations are being intensively investigated. Exploratory genotype-phenotype analyses revealed that the presence of a germline mutation was associated with a familial risk of developing a malignant breast disease. Further, missense muta-

tions and/or mutations 5' of the phosphatase core motif seem to be associated with a surrogate for disease severity (multiorgan involvement) {1519}.

Previously thought to be clinically distinct, BRRS is likely allelic to CS {1519}. Approximately 65% of BRRS families and isolated cases combined carry a germline *PTEN* mutation {420,1520,1521, 2599}. Interestingly, there were 11 cases classified as true CS-BRR overlap families in this cohort, and 10 of the 11 had a *PTEN* mutation. The overlapping mutation spectrum, the existence of true overlap families and the genotype-phenotype associations which suggest that the presence of germline *PTEN* mutation is associated with cancer, strongly indicate that CS and BRR are allelic and are along a single spectrum at the molecular level. The aggregate term "*PTEN* hamartoma tumour syndrome" (PHTS) has therefore been proposed {688,1521}. The clinical spectrum of PHTS has recently been expanded to include also subsets of Proteus syndrome and Proteus-like (non-CS, non-BRR) syndromes {2203,2598}. Genetics of Cowden syndrome is also reviewed in detail in the WHO Classification of the Tumours of the Nervous System, Tumours of the Digestive System, as well as in the WHO Classification of Tumours of the Breast and Female Genital Organs.

Carney complex

W.H.C. Burgdorf
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Definition

Carney complex (CNC) is a lentiginosis-multiple endocrine neoplasia syndrome caused by at least two distinct mutations and characterized by multiple often unique tumours including myxomas and schwannomas, endocrine abnormalities, and cutaneous pigmentary lesions {397}.

OMIM numbers

CNC1 160980; CNC2 605244

Synonyms

NAME syndrome {111}, LAMB syndrome {1926}.

Epidemiology

Carney complex is an uncommon disorder, inherited in an autosomal dominant fashion. More than 350 cases are known involving more than 65 families.

The penetrance is high but the expressivity is highly variable. Patients may present with cutaneous, cardiac, or endocrine lesions; often the diagnosis is delayed until multiple manifestations are present.

Localization

The most commonly involved organs are the skin (75%), heart (50%) and adrenal glands (25%).

Clinical features

The cutaneous findings in CNC are often most dramatic. Patients may have multiple flat pigmented lesions that have been described both as ephelides (freckles) with an increased amount of melanin {111} and as lentigines with an increased number of melanocytes {1926}. Blue naevi are another marker of the syndrome; many exhibit epithelioid features on microscopic examination {396}. Pigmented lesions are also common on mucosal surfaces, such as the lips, mouth, conjunctiva and genital mucosa {1244}. Some patients have no pigmentary changes. Another highly specific cutaneous finding is myxomas, especially when they affect the eyelids and the external ear canal {734}. Histologically, these benign tumours often feature strands of lacy epithelium {398}.

The most dramatic systemic finding is cardiac myxoma(s). The CNC-associated myxomas have important differences from sporadic cardiac myxomas; they are more likely to be familial, multiple, occur at a younger age, involve the ventricles and recur {2433}. Recurrent cardiac myxoma(s) may require multiple surgical resections that may result in postoperative arrhythmias and increased mortality.

The most common endocrine finding is primary pigmented nodular adrenal disease, a very rare ACTH-independent cause of Cushing syndrome (25%) {2164}. The adrenal glands show bilateral small, pigmented nodules with internodular cortical atrophy {881,2571}. One of Cushing's first patients, Minnie G., may well have had CNC {395}. Acromegaly and thyroid tumours {2275} are each seen in around 10% of patients. About one-third of male patients have large-cell calcifying Sertoli cell tumours of the testes, often bilateral and sometimes leading to precocious puberty {1734}. Two other uncommon tumours which should suggest the presence of CNC are psammomatous melanotic schwannomas (20%) of the GI tract, sympathetic chain and skin {394}, and myxoid mammary fibroadenomas (25% of women) {400}.

Diagnostic procedures

Both epithelioid blue naevi and myxomas (the latter sometimes with a characteristic epithelial component) may be identified on skin biopsies and suggest the diagnosis of CNC. When investigation for Cushing syndrome reveals low or undetectable ACTH levels and no adrenal tumour, a diagnosis of primary pigment-

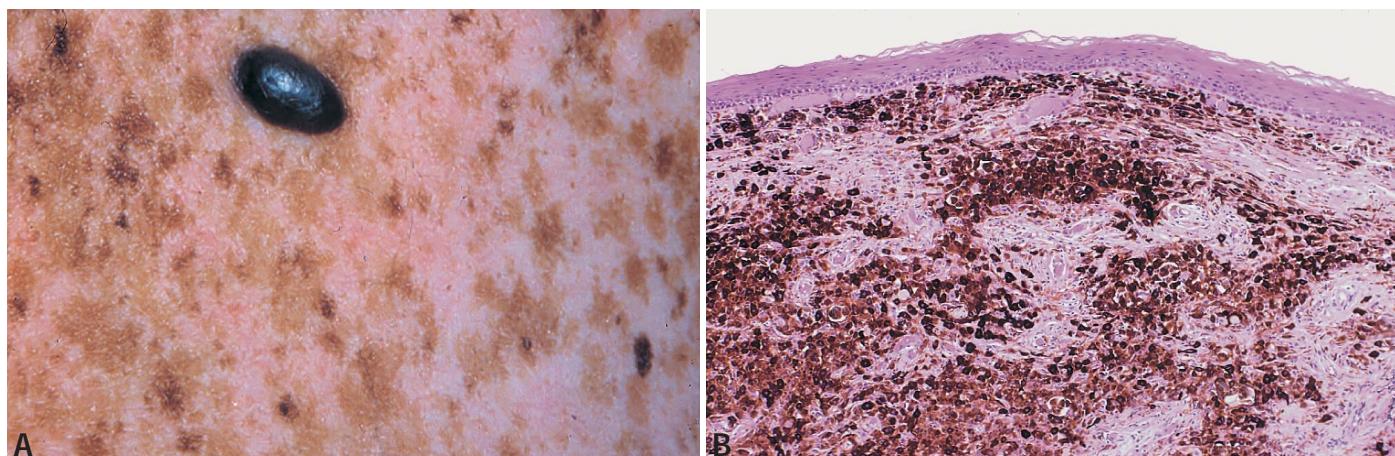


Fig. 7.14 **A** Spotty pigmentation and blue naevus in CNC. Courtesy of Dr. David J. Atherton, London, UK, and reference {111}. **B** Histological specimen of blue naevus showing large epithelioid melanocytes. Courtesy of Dr. Luis Requena, Madrid, Spain.

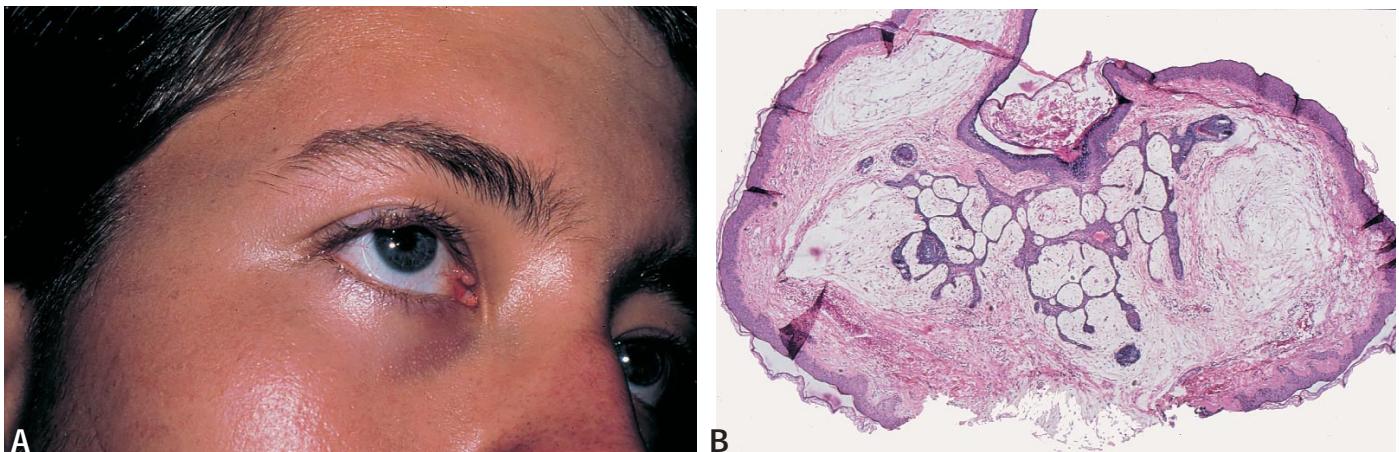


Fig. 7.15 **A** Eyelid myxoma in a young man with CNC and no cutaneous pigmentary changes. **B** Microscopic view of the same lesion, showing lacy epithelial strands amidst deposits of mucin.

ed nodular adrenal disease should be considered and the patient evaluated for CNC, particularly if the patient is young or has multiple pigmented skin spots or lumps. Echocardiography is particularly important {2276}.

Differential diagnosis

When multiple pigmented lesions are present, LEPARD syndrome should be considered but myxomas are absent in this condition and the systemic manifestations more protean. Mucosal pigmentation strongly resembles that of Peutz-Jeghers syndrome, but intestinal polyps are not part of the usual spectrum of Carney complex.

Genetics

Carney complex is inherited in an autosomal dominant fashion. The gene for CNC1, known as *PRKAR1A*, normally encodes the protein kinase A regulatory subunit R1a {408,1284}. When the mutat-

ed gene is present, the regulatory subunit is no longer produced. The patients are heterozygous for the mutation: the tumours tend to have LOH of the wild type allele for this regulatory gene. The *CNC2* gene is less well characterized but appears to be involved in regulating genomic stability, perhaps via the telomeres.

Prognosis and predictive factors

The prognosis depends on detecting cardiac myxoma, the most serious complex of CNC. The average age of 22 patients who died as the result of cardiac causes (cardiac failure from myxoma, cardiac myxoma emboli or cardiac arrhythmia) was 31 years. Timely diagnosis of the neoplasms requires an awareness of the possible significance of the pigmented skin spots, skin tumours, primary pigmented nodular adrenal disease and psammomatous melanotic schwannoma. Patients with lesions sug-

gestive of CNC should be advised to have a general medical evaluation and an echocardiogram. Primary relatives of CNC patients should be similarly advised.



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 2.45B Dr. P.E. LeBoit
 2.45C Dr. E. Calonje
 2.46 Dr. P.E. LeBoit
 2.47A-2.48B Dr. E. Calonje
 2.48C-2.49B Dr. P.E. LeBoit
 2.50 Dr. E. Calonje
 2.51A-D Dr. P.E. LeBoit
 2.52A-D Dr. R.L. Barnhill
 2.53A-2.54C Dr. H. Kerl
 2.55A,B Dr. P.E. LeBoit
 2.56 Dr. D. Weedon
 2.57A-2.59B Dr. P.E. LeBoit
 2.60A-2.61 Dr. B. Putnam
 2.62 Dr. D. Weedon
 2.63 Dr. B. Putnam
 2.64A-2.65 Dr. H. Kerl
 2.66A-2.69B Dr. P.E. LeBoit
 2.70A-D Dr. L. Cerroni
 2.71 Dr. P.E. LeBoit
 2.72-2.73C Dr. D.E. Elder

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3.01-3.02B Dr. L. Requena
 3.03A Dr. M. A. Hurt
 3.03B Dr. L.L. Yu
 3.04A-F Dr. M. A. Hurt
 3.05-3.06F Dr. H. Kutzner
 3.07A Dr. D.R. Mehregan
 3.07B-3.08 Dr. O.P. Sangüeza
 3.09A-3.10 Dr. Z.B. Argenyi
 3.11-3.12B Dr. L. Requena
 3.13-3.14B Dr. H. Kutzner
 3.15A Dr. L. Requena
 3.15B Dr. J. McNiff
 3.16A-C Dr. O.P. Sangüeza
 3.17A,B Dr. P. Rudolph
 3.18-3.21 Dr. S. Kohler
 3.22-3.23 Dr. O.P. Sangüeza
 3.24A,B Dr. E.J. Glusac
 3.25A,B Dr. J. McNiff
 3.26 Dr. L.L. Yu
 3.27A Dr. G. Borroni
 3.27B,C Dr. P.E. LeBoit
 3.28A,B Dr. T.H. McCalmont
 3.29A-C Dr. L. Requena
 3.30A,B Dr. T.H. McCalmont
 3.31A-C Dr. I. Ahmed
 3.32A,B Dr. J. McNiff
 3.33A-C Dr. L. Requena
 3.34A-C Dr. J. McNiff
 3.35A,B Dr. P.E. LeBoit
 3.36-3.38 Dr. L. Requena

3.39A-3.40F

3.41 Dr. R.L. Barnhill
 3.42A-3.44C Dr. N.S. McNutt
 3.45A-F Dr. P.E. LeBoit
 3.46 Dr. P.J. Heenan
 3.47A-C Dr. H. Kerl
 3.48A Dr. E. Calonje
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3.49A-C Dr. M. A. Hurt
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 3.49A-C Dr. H. Kutzner
 3.49A-C Dr. M. A. Hurt
 3.49A-C Dr. B. Cribier
 3.49A-C Dr. T. Schulz
 3.49A-C Dr. T. Schulz
 3.49A-C Dr. M.R. Wick
 3.49A-C Dr. A. Rütten
 3.49A-C Dr. P.E. LeBoit
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4.01A-C Dr. P.E. LeBoit
 4.02A-D Dr. E. Calonje
 4.03A-4.13 Dr. R.L. Barnhill
 4.14-4.15 Dr. H. Kerl
 4.16 Dr. E. Calonje
 4.17A-4.18A Dr. P.E. LeBoit
 4.18B-4.19B Dr. R. Russell-Jones
 4.20 Dr. R. Russell-Jones
 4.21-4.27A Dr. D. Weedon
 4.27B Dr. E. Calonje
 4.27C,D Dr. R. Russell-Jones
 4.28A,B Dr. G. Burg
 4.29-4.30 Dr. E. Calonje
 4.31-4.35A Dr. H. Kutzner
 4.35B-4.36B Dr. L. Cerroni
 4.37A-D Dr. P.E. LeBoit
 4.38A-4.39B Dr. Y.Tokura
 4.40-4.42 Dr. S. Kohler

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4.43A Dr. G. Burg
 4.43B-4.44A Dr. E. Calonje
 4.44B Dr. R. Russell-Jones
 4.45-4.47 Dr. H. Kutzner
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 4.51 Dr. D. Weedon
 4.52A-4.56A Dr. L. Cerroni
 4.56B Dr. E. Calonje
 4.57 Dr. H. Kutzner
 4.58A-4.59C Dr. R. Russell-Jones
 4.60A-4.62 Dr. H. Kutzner
 4.63A-4.64B Dr. E. Calonje
 4.65A-4.66C Dr. L. Cerroni
 4.67-4.68 Dr. R. Russell-Jones
 4.69A-C Dr. E. Calonje
 4.70A,B Dr. H. Kutzner
 4.71-4.72B Dr. E. Calonje
 4.73A-4.77B Dr. R. Russell-Jones
 4.78A,B Dr. H. Kutzner
 4.79 Dr. E. Calonje
 4.80A-4.81B Dr. R. Russell-Jones
 4.82 Dr. H. Kutzner

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4.83-4.93 Dr. H. Kutzner
 4.94A-4.95 Dr. R. Russell-Jones
 4.94A-4.95 Dr. R. Russell-Jones
 4.94A-4.95 Dr. R. Russell-Jones

5.

5.01 Dr. R.C. Kasper
 5.02A-C Dr. E. Calonje
 5.03A,B Dr. J.K.C. Chan
 5.04-5.05C Dr. R.C. Kasper
 5.06-5.07B Dr. J.K.C. Chan
 5.08-5.09B Dr. O.P. Sangüeza
 5.10A-C Dr. H.G. Skelton
 5.11A,B Dr. E.J. Glusac
 5.12A,B Dr. O.P. Sangüeza
 5.13-5.14 Dr. D. Weedon
 5.15B-5.16B Dr. L. Requena
 5.17-5.18B Dr. W. Weyers
 5.19-5.21 Dr. D. Weedon
 5.22-5.24B Dr. J.W. Patterson
 5.25 Dr. J. McNiff
 5.26A,B Dr. W. Weyers
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 5.30 Dr. B. Putnam
 5.31A,B Dr. J.D. Harvell
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6.

6.01A-6.04C Dr. Z.B. Argenyi
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 6.07A-6.08C Dr. Z.B. Argenyi
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 7.05A-7.08B Dr. A. Sarasin
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Subject index

A

ABCD 56, 58
ABCDE criteria 85
Abrikossoff tumour 274
Acantholytic acanthoma 39, 40
Acantholytic squamous cell carcinoma 21
Acanthoma 39
Acanthosis nigricans 260, 289
Accessory tragus 253
Acetylcholinesterase 60
Acid mucopolysaccharides 132, 254
Ackerman tumour 22
Acquired progressive lymphangioma 248
Acquired ungual fibrokeratoma 257
Acral arteriovenous tumour 245
Acral fibrokeratoma 257
Acral lentiginous melanoma 55, 73
Acral melanoma 73-75
Acral naevus 110
Acral pseudolymphomatous angiokeratoma of children (APACHE) 213
Acral verrucous hyperkeratosis 289
Acrochordon 17, 258
Acrodermatitis enteropathica 260
Acromegaly 291
Acrospiroma 131, 133, 143
Acrosyringeal adenomatosis 142
Acrosyringia 24, 31
Acrotrichium 27, 28
Actinic elastosis 47, 66
Actinic keratoses 11, 12, 30-33, 44, 47, 282
Actinic lentigo 40
Actinic reticuloid 212, 213
Activated skin-homing T-cell 181
Acute lymphoblastic leukaemia 210
Acute lymphocytic leukaemia 80
Acute monoblastic/monocytic leukaemia (AMOL) 211
Acute myeloid leukaemia (AML) 211
Acute myelomonocytic leukemia (AMML) 211
Adamantinoid trichoblastoma 123
Adenoid basal cell carcinoma 19

Adenoid cystic carcinoma 123, 125, 134, 135
Adenopathy 204, 206
Adenosquamous carcinoma 24
Adnexal basaloid tumours 14
Adnexal carcinoma 123
Adult T cell leukaemia / lymphoma (ATLL) 189, 190
AE1 21, 22, 126, 138, 273
AE1/3 22
AE2/3 21
AE3 126, 138, 273
AE14 153
Aggressive digital papillary adenoma 133
Aggressive systemic mastocytosis 226
Agminated blue naevus 79
AIDS 261
AJCC classification 61, 64, 82
ALCL 180, 181, 193
Alcoholic cirrhosis 241
ALHE 237, 238
ALK 181, 193
Alkylating agent 11
Allergic contact dermatitis 111
ALM 73, 74, 75
Alopecia 77, 134, 175, 189, 202
Alpha SMA 126
Alpha-1 antichymotrypsin 258
Alpha-1-ACT 275
Alpha-1-antitrypsin 220, 225
Alpha-smooth muscle actin 256
Amelanotic melanoma 57
Amelanotic nodular melanoma 55
American Joint Commission on Cancer (AJCC) 232
American Joint Committee on Cancer 68, 137
AML See Acute myeloid leukaemia
AMML See Acute myelomonocytic leukemia
AMNGT See Atypical melanocytic naevus of the genital type
AMOL See Acute monoblastic/monocytic leukaemia
Amputation neuroma 266, 267
Anaphylaxis 227
Anaplastic large cell lymphoma 181
Anaplastic lymphoma 179

Anaplastic lymphoma related tyrosine kinase (ALK) 181
ANEURYSMAL fibrous histiocytoma 262
Angioblastoma of Nakagawa 240
Angiocentric cutaneous T-cell lymphoma of childhood 192
Angiocentric immunoproliferative lesion 202
Angiocentric lymphoma 202
Angiocentric T-cell lymphoma 191
Angioendotheliomatosis 236, 241
Angioendotheliomatosis proliferans systematisata 200
Angiofibroma 152, 258
Angioimmunoblastic T-cell lymphoma (AITL) 193
Angiokeratoma 242, 244, 245
Angiokeratoma circumscripum naeviforme 242
Angiokeratoma corporis diffusum 244
Angiokeratoma corporis diffusum in Fabry disease 244
Angiokeratoma corporis diffusum, Mibelli and Fordyce 244
Angiokeratoma of Fordyce 244
Angiokeratoma 242, 244
Angiokeratoma of Fabry disease 244
Angioleiomyoma 231
Angiolymphoid hyperplasia with eosinophilia (ALHE) 214, 237
Angiomatoid fibrous histiocytoma 232
Angiosarcoma 21, 23, 24, 231, 232, 234, 238, 243, 246, 249
Angiotropic large cell lymphoma 200
Anhidrosis 244
Anhidrotic ectodermal dysplasia gene product 21
Animal type melanoma (epithelial melanocytoma) 81
Anisodendrocytosis 60
Anogenital verrucous carcinoma 36
Antiphospholipid syndrome 241
AP-1 transcription factor complex 177
APC 278
Apical snouts 135

- Apocrine adenocarcinoma 135
 Apocrine adenocarcinoma in situ 136, 138
 Apocrine adenoma 136, 145
 Apocrine carcinoma 135
 Apocrine cystadenoma 139
 Apocrine gland carcinoma 135
 Apocrine gland cyst 139
 Apocrine hidrocystoma 139, 289
 Apocrine mammary carcinoma 136
 Apoptosis 14, 185
 Apoptotic bodies 191, 205
 Appendageal tumours 122
 A pudoma 272
 Array CGH 75
 Arrector pili hamartoma 250
 Arrector pili muscles 245, 250, 252
 Arsenic 11, 20, 26, 32, 33
 Arsenic exposure 13
 Arsenical keratosis (As-K) 26, 32
 Arteriovenous anastomoses 245
 Arteriovenous haemangioma 245
 Arteriovenous malformation 238
 Arthropod bite 228
 Asthma 238
 Astrocytoma of the spinal cord 283
 Ataxia telangiectasia 211
 ATLL See Adult T cell leukaemia / lymphoma
 Atrophic dermatofibroma 262
 Atypical fibrous histiocytoma 262
 Atypical lentiginous melanocytic proliferation (ALMP) 70
 Atypical melanocytic naevus of the genital type (AMNGT) 110
 Atypical mixed tumour of the skin 128
 Atypical naevus 105
 Atypical nodular melanocytic proliferation 85
 Atypical pigmented spindle cell naevus 117
 Atypical proliferative nodules in giant congenital naevi 93
- B**
- Bacillary angiomatosis 240
 Bacille Calmette-Guérin (BCG) vaccine 55, 260
 Back to back appearance 234
 Bannayan-Riley-Ruvalcaba syndrome (BRRS) 288
 Bartonella bacteria 240
 Basal cell carcinoma 13-19, 285
 Basal cell carcinoma with adnexal differentiation 18
 Basal cell epithelioma 13
 Basal cell epithelioma with sebaceous differentiation 162
 Basal cell naevus syndrome (BCNS) 13, 15, 285
 Basaloid squamous cell carcinoma 14, 20
 Basaloid follicular hamartoma 18
 Basaloid sebaceous carcinoma 161
 Basic fibroblast growth factor (bFGF) 78
 Basosquamous carcinoma 18, 19
 Basosquamous cell carcinoma 18
 BCC See Basal cell carcinoma
 B-cell lymphoblastic leukaemia/lymphoma 210
 B-cell lymphoma 168, 198, 199, 200, 204
 BCL10 195
 Bcl-2 15, 69, 126, 155, 194, 197-200, 205, 219, 238,
 Bcl-6 194, 197-199, 204
 BCNS See Basal cell naevus syndrome
 Becker naevus 80, 250
 Bednar tumour 259
 Benign calcifying epithelioma 153
 Benign juvenile melanoma 114
 Benign lichenoid keratosis 47
 Benign lymphangioendothelioma 248
 Benign lymphangiomatous papules 249
 Ber-EP4 15, 72, 126, 273
 Beta 2 microglobulin 268
 BF1 185, 186
 BFGF 78
 BHD gene 158
 Birbeck granules 217, 219-221, 225
 Birds-eye cells 38
 Birt-Hogg-Dubé syndrome (BHD) 157, 158, 278
 B-K mole syndrome 105, 109, 279
 Blastic NK-cell lymphoma 208
 Blastoid NK-cell lymphoma 208
 Bloom syndrome 30, 211, 278
 Blue naevi 95-99
 Blue naevus-like melanoma 79
 Blueberry muffin syndrome 218
 BMPR1A 290
 Bombesin 273
 Bone morphogenic protein receptor type 1A gene (BMPR1A) 290
 Borrelia 195, 206, 212, 213
 Borrelia burgdorferi 194, 206, 212, 213
 Borrelia infection 195
 Borrelia-induced pseudolymphoma 212
 Bourneville disease See Tuberous sclerosis
 Bowen disease 11, 12, 20, 26, 28, 29, 31, 32, 36, 43, 44, 47
 Bowen or Paget disease 66
 Bowenoid actinic keratoses (BAK) 31
 Bowenoid dysplasia 26
 Bowenoid papulosis 11, 12, 26, 28, 29, 36
 Bowenoid solar keratosis 28
 Bowenoid squamous carcinoma in situ (BSCIS) 26
 BRAF 67, 72, 75, 78, 95, 101, 116
 BRAF mutations 78, 93
 Breast cancer 279
 Breast carcinoma 136-138, 153
 Breast fibroadenoma 288
 Breslow thickness 62, 64, 78, 82, 85
 Brocq disease 171, 215
 Bromide compounds 234
 Brooke-Fordyce disease 152, 153
 Brooke-Spiegler disease 145, 152, 153
 Brooke-Spiegler syndrome 145
 Brook-Fordyce disease 152
 Bullous pemphigoid 142
 Bunn-Lamberg staging system 175
 Burkitt lymphoma 205
 Burn scar 56
 Buschke-Löwenstein tumour 22, 23
 2-Butoxyethanol solvent 234
- C**
- C to T mutation 11
 CA15.3 161
 Café-au-lait spots 222, 223, 289
 Calcification 19, 46, 140, 149, 151, 214, 234, 253, 256, 286, 287
 Calcifying epithelioma of Malherbe 153
 Calcitonin 273
 C-ALCL 179, 180, 181
 Callus 75
 Calretinin 275
 CAM 5.2 21, 22, 28, 75, 131, 135, 136, 138, 273
 Campbell de Morgan spots 233
 Candidiasis 23
 Caput Medusae pattern 156

- Carbonic anhydrase 234
 Carcinoembryonic antigen 24, 43, 72, 123, 135, 136, 138, 140, 147
 Carcinoma in-situ (CIS) 161
 Carcinoma of the Bartholins glands 138
 Cardiac arrhythmia 292
 Cardiac insufficiency 225
 Cardiac myxoma 292
 Cardiac myxoma emboli 292
 Cardiopulmonary 225
 Carney complex 97, 103, 291, 292
 Cathepsin B 223
 Cavernous haemangioma 234, 243
 CC to TT mutation 11
 CCND1/cyclin D1 204
 CD1a 210, 213, 217, 219-221, 223, 225
 CD2 171, 175, 176, 180, 181, 185-187, 191-193, 208, 210
 CD3 138, 171, 175, 176, 178, 180, 181, 185-187, 190-193, 202, 208, 210, 211
 CD3e 191
 CD4 112, 171-76, 178, 180, 181, 185-187, 190, 192, 193, 202, 206, 208, 210, 215, 216, 219
 CD4+, CD56+ agranular haematodermic neoplasm 208
 CD5 171, 175, 176, 178, 180, 181, 185-187, 192-194, 197, 200, 204-206, 210
 CD7 171, 176, 178, 180, 181, 185-187, 190, 192, 193, 208, 210
 CD8 118, 171, 173, 175, 176, 180, 183, 185-187, 190, 192, 210, 215
 CD8+ cytotoxic T cell lymphoma 118, 185
 CD10 194, 197, 198, 200, 204-206, 210
 CD11c 220
 CD14 220, 223
 CD15 153, 161, 180, 207, 214, 223, 225
 CD19 190, 194, 196, 210
 CD20 190, 194, 196, 198, 199, 204-206, 210, 211, 213
 CD21 195, 197, 213
 CD22 194, 196, 210
 CD23 194, 197, 204-206
 CD24 210
 CD25 (interleukin 2-receptor) 180, 181, 190, 228
 CD26 176
 CD30 170, 171, 173, 178-181, 184, 186, 187, 190, 192, 193, 207, 211, 214
 CD30+ T-cell lymphoproliferative disorders 179
 CD30L 179
 CD30-positive T-cell lymphoproliferative disorders (LPD) of the skin (CD30+LPD) 179
 CD31 24, 235, 236, 238-240, 246-259, 262
 CD34 98, 127, 159, 208, 211, 221, 235, 236, 238-240, 246, 248, 250, 256, 258-262, 270
 CD34+ haematopoietic precursor cells 228
 CD35 197
 CD38 206
 CD43 191, 192-194, 197, 206, 208, 210, 211
 CD44 273
 CD45 211, 228
 CD45RO 171, 176, 178, 181, 190, 192
 CD56 180, 185, 191, 192, 208, 209, 211
 CD57 (Leu-7) 192, 265, 267, 270, 275
 CD68 208, 211, 219-221, 223, 225, 236, 262, 275
 CD71 181
 CD74 211
 CD79a 194, 198, 210, 213
 CD95 (Fas) 32
 CD99 210, 268, 273
 CD117 228, 273
 CD123 209
 CD138 198, 199
 CD207 (langerin) 220
 CDK 280
 CDKN2A (p16) 32, 54, 63, 67, 69, 108, 109, 278-281
 CDKN2A germline mutation 280
 CEA 28, 43, 123, 125, 129-132, 135, 138, 140, 144, 148, 153
 Cell adhesion molecule 69
 Cell division kinase 4 279
 Cellular blue naevus 9 6
 Cellular fibrous histiocytoma 262
 Cellular neurothekeoma 270
 C-erbB-2/HER-2/neu 127, 161
 Cerebriform nuclei 170, 175, 176, 178, 180
 Ceruminous gland carcinoma 135
 CGD-TCL 184, 185
 CGH See Comparative genomic hybridization
 Chemotherapy 23, 131, 185, 208, 210, 246, 269
 Cherry haemangioma 233
 Cherry-type haemangioma 235, 236
 Childhood melanoma 8 4
 Chimeric COL1A1-PDGFB gene 259
 CHL See Classical Hodgkin lymphoma
 Chloroma 211
 Chondroid syringoma 147, 148
 Chromogranin 269, 273
 Chromosomal translocation 172, 197, 261
 Chromosome 1 (1p36) 108, 109, 273
 Chromosome 11q24 269
 Chromosome 13q 142
 Chromosome 16q12-q13 153
 Chromosome 17p11.2 158
 Chromosome 6q deletion 127
 Chromosome 9p21 63, 69, 109, 145, 153
 Chromosome 9q22-q31 45
 Chronic actinic reticuloid 176
 Chronic arsenism 260
 Chronic lymphatic leukaemia 34
 Chronic lymphocytic leukaemia 205
 Chronic lymphocytic leukaemia/small lymphocytic lymphoma 205
 Chronic myelogenous leukaemia (CML) 211
 Chronic myelomonocytic leukaemia (CMMI) 211
 Chronic superficial dermatitis 215
 Chylothorax 249
 Chylous ascites 249
 Cirsoid aneurysm 245
 CK 5, 8, 14 and 15 153
 CK5/6 22
 CK7 126, 127, 138, 153
 CK20 15, 127, 138, 153, 273
 C-KIT 226, 228
 C-KIT mutations 226, 228
 CLA 172, 176, 228, 278, 279
 Clark model 64
 Clark naevus 105
 Clark's levels of invasion 64
 Classical Hodgkin lymphoma (CHL) 207
 Clear basal cell carcinoma 19
 Clear cell acanthoma 39, 40, 43
 Clear cell hidradenoma 143
 Clear cell papulosis 138
 Clear cell sarcoma 232
 Clear cells of Toker 138
 Clear-cell eccrine carcinoma 131
 Clear-cell hidradenocarcinoma 131
 Clear-cell papillary carcinoma 131

- Clear-cell squamous cell carcinoma 20
 Clear-cell syringoma 140
 Cleft lip 96
 Clonal dermatitis 213
 Clonal rearrangement of T cell receptor genes 180, 181, 183
 Clonal seborrhoeic keratosis 42
 Clonally rearranged IgH genes 195
 Clonally rearranged immunoglobulin genes 197
 Clonally rearranged T-cell receptor gene 186, 192
 CML See Chronic myelogenous leukaemia 211
 CMM1 81, 279
 CMML See Chronic myelomonocytic leukaemia
 C-MYC 172, 205
 C-MYC mutations 205
 C-MYC translocation 205
 CNC1 gene 291, 292
 CNC2 gene 292
 Coagulative defects 154
 Cobb syndrome 242, 247
 Cocco-bacillary organisms 240
 Cockayne syndrome 30
 Collagen ball formation 262
 Collagen type IV 234, 265, 267, 270
 Colloid, gelatinous and adenocystic carcinoma 132
 Coloboma 253
 Colonic polyps 46
 Columnar trichoblastoma 152
 Combined dermatofibroma 262
 Combined naevus 89, 95, 99, 100, 101
 Comedonal Darier disease 40
 Common acquired melanocytic naevi 108
 Common basal cell carcinoma 123
 Common blue naevus (BN) 95
 Common wart 36
 Comparative genomic hybridization (CGH) 67, 69, 72, 75, 81, 84, 94, 98, 108, 116, 177, 197
 Condylomata acuminata (genital warts) 34, 35
 Condylomata plana (flat cervical condylomas, plane condylomas) 34
 Congenital fibrosarcoma 256
 Congenital generalized fibromatosis 256
 Congenital ichthyosiform erythroderma 39
 Congenital leukaemic infiltrates 218
 Congenital lymphoedema 239
 Congenital melanocytic naevi (CMN) 55, 79, 82, 93, 94, 108
 Congenital melanoma 84
 Congenital mesenchymal hamartoma 256
 Congenital midline hamartoma 252
 Congenital naevi of the meninges 83
 Congenital naevus 84, 85, 89, 94, 108
 Congenital naevus-like naevus 93
 Congenital non-progressive haemangioma 233
 Congenital pattern-like naevus 93
 Congenital pilar and smooth muscle naevus 250
 Congenital reticulohistiocytosis 218
 Congenital self-healing Langerhans cell histiocytosis 218
 Congenital self-healing reticulohistiocytosis (CSHRH) 218
 Congenital smooth muscle naevus 250
 Consumption of the epidermis 59
 Contraceptive pills 244
 Cornea verticillata 244
 Corneocytes 14, 156, 157
 Cowden disease 155, 156, 231, 253, 256, 278, 288
 Cowden syndrome (CS) 124, 158, 288, 290
 Craniofacial clefts 253
 Cribriform trichoblastoma 152
 Crusts 192
 Cryoglobulinaemia 241
 CSHRH 218, 219
 CT 58, 169, 231, 272
 CTNNB1 155
 CU18 161
 Cushing syndrome 291
 Cutaneous (dermal) leiomyosarcoma 251
 Cutaneous adnexal carcinoma 127, 138
 Cutaneous adult T-cell leukaemia / lymphoma 189
 Cutaneous angiosarcoma 246
 Cutaneous B-cell lymphoma (CBCL) 198, 213, 214
 Cutaneous B-cell pseudolymphoma (B-PSL) 212
 Cutaneous diffuse large B-cell lymphoma 198
 Cutaneous follicle centre lymphoma (FCL) 196, 199
 Cutaneous follicular lymphoid hyperplasia with monotypic plasma cells 194
 Cutaneous gd T-cell lymphoma (CGD-TCL) 184
 Cutaneous histiocytoid angioma 237
 Cutaneous involvement by myeloid leukaemia 211
 Cutaneous involvement in primary extracutaneous B-cell lymphoma 204
 Cutaneous involvement in primary extracutaneous T-cell lymphoma 193
 Cutaneous leiomyosarcoma 251
 Cutaneous lichen amyloidosis 279
 Cutaneous lobular neuromyxoma 270
 Cutaneous lymphocyte antigen (CLA) 172
 Cutaneous lymphoid hyperplasia 212
 Cutaneous lymphoproliferative disorders (CLD) 168
 Cutaneous malignant melanoma 279
 Cutaneous marginal zone B-cell lymphoma 194
 Cutaneous mastocytosis (CM) 226-228
 Cutaneous melanoma 54, 63, 73, 81, 279, 280
 Cutaneous pseudolymphoma 212, 214
 Cutaneous reticulohistiocytoma 224
 Cutaneous sebaceous neoplasms 279
 Cutaneous T-cell lymphoma (CTCL) 138, 169, 172, 175, 180, 184-186, 214, 216
 Cutaneous T-cell pseudolymphoma (T-PSL) 212
 Cyclin D1 32, 69, 75, 238, 204-206, 280
 Cyclin-dependent kinase inhibitor 69
 Cyclin-dependent kinase inhibitor 2A 279
 Cyclin-dependent kinase 63, 280
 Cyclindroma 279
 CYLD1 278
 Cylindroma 130, 143-145
 Cylindrospiradenoma 145
 Cystic BCC 19
 Cystic sebaceous tumour 163
 Cytophagic panniculitis 182
 Cytoplasmic CD3 210

Cytoplasmic intermediate filaments 69
 Cytotoxic gd T-cells 185
 Cytotoxic T-cell lymphoma 173
 Cytotoxic T-cells 185, 186, 192

D

D2-40 247
 Darier sign 227
 DDB2 278
 DDBI 278
 De Morgan spots 233
 Deep foot warts 34, 37
 Deep penetrating naevi 60, 61, 87, 89, 98, 100
 Deeply pigmented seborrhoeic keratosis 43
 Definite malignant lymphoma of high-grade malignancy (LHM) 168
 Definite malignant lymphoma of low-grade malignancy (LLM) 168
 Degos acanthoma 43
 Delleman syndrome 253
 Dendritic cells 63, 101, 170, 181, 195, 197, 209, 213, 217, 220, 259
 Dermal duct tumour 141
 Dermal leiomyosarcoma 251
 Dermal melanocytic tumour of uncertain potential in a giant congenital naevus 94
 Dermal variant of minimal deviation melanoma in a giant congenital naevus 94
 Dermatofibroma 77, 78, 91, 100, 214, 256, 258, 260-262
 Dermatofibroma (fibrous histiocytoma) 261
 Dermatofibroma with monster cells 262
 Dermatofibrosarcoma protuberans 259, 262
 Dermatomyofibroma 255, 256
 Dermatomyositis 225
 Dermatoscopy 13, 43, 44, 47, 57, 58, 110, 117
 Dermatosis 42, 279
 Dermatosis papulosa nigra 42
 Dermographism 227
 Dermoscopy 57, 117
 De-Sanctis Cacchione syndrome 282, 283
 Desmin 250, 251, 253, 256, 257, 259, 260, 269

Desmoplasia 57, 78, 97, 98, 160
 Desmoplastic melanoma 57, 61, 76, 89-91, 115
 Desmoplastic naevus 78, 89
 Desmoplastic neurotropic melanoma (DNM) 76
 Desmoplastic squamous cell carcinoma 20
 Desmoplastic Spitz naevus 101, 115, 258
 Desmoplastic trichoepithelioma 15, 17, 127, 140, 153
 Desmoplastic/neurotropic melanoma 89
 Diabetes insipidus 218
 Diabetes mellitus 140
 Diffuse cutaneous mastocytosis 226
 Diffuse dermal angiogenesis 241
 Diffuse large B-cell lymphoma (DLBCL) 195, 199, 200
 Diffuse large B-cell lymphoma (DLBCL), leg-type 198
 Diffuse large B-cell lymphoma, other 198, 199
 Diffuse neonatal haemangiomatosis 233
 Digital fibrokeratoma 257
 Digital focal mucinosis 257
 Digital mucous cyst 257
 Digital papillary adenocarcinoma 133
 Digital papillary carcinoma 133, 134
 Digitate dermatosis 215
 Dilated pore (Winer) 157
 Dioxin 231
 Diphenylhydantoin 213
 Diplopia 79
 Disseminated pyogenic granuloma 240
 DLBCL 198, 199
 DNA mismatch repair 46, 163, 278
 DNA repair 11, 64, 72, 105, 106, 282, 283
 DNA repair genes 124, 283
 Dowling-Degos disease 43
 Down syndrome 140, 211
 Ductal adenocarcinoma of the breast 288
 Ductal carcinoma in situ (DCIS) 138
 Dutcher bodies 194
 Dyskeratosis 12, 21, 27, 30, 31, 39, 40
 Dyskeratosis with acantholysis (warty dyskeratoma) 39
 Dysplastic (Clark) naevus 58, 59

Dysplastic combined blue naevus 108
 Dysplastic halo naevus 108
 Dysplastic naevus (DN) 59-61, 105-112, 118, 119
 Dysplastic naevus syndrome 105, 279
 Dysplastic naevus with a congenital pattern 108
 Dysplastic nevus 108
 Dysplastic Spitz naevus 108

E

E4 proteins 35
 Early nodular melanoma 89
 EBER 191
 EBV 185, 186, 191, 192, 202, 203, 209, 231
 E-cadherin 21, 32
 Eccrine epithelioma 126
 Eccrine hidrocystoma 139
 Eccrine porocarcinoma 128
 Eccrine poroma 129, 141
 Eccrine syringofibroadenoma 142
 Eccrine syringofibroadenomatous hyperplasia 142
 Eccrine syringoma 140
 Ectropion 175, 282
 Eczema 111, 137, 176
 Eczematous halo 111
 Elevatum diutinum 214
 EMA 21, 125, 126, 129-132, 135, 138, 140, 148, 153, 161, 163, 181, 193, 199, 259, 269
 Endocrine tumour 266
 Endoneurial fibroblast 267
 Endophytic common wart 38
 Enteropathy-type T-cell lymphoma 183
 Entropion 282
 EORTC 184
 Eosinophilia 172, 238
 Eosinophilic bodies 39
 Eosinophilic granuloma 218, 219
 Epidermal cyst 46, 285
 Epidermal dysplasia 11, 12
 Epidermodysplasia verruciformis 30, 36, 38
 Epidermodysplasia-verruciformis (EV)-HPV types 36
 Epidermoid carcinoma in sebaceous cyst 150
 Epidermoid cysts 279
 Epidermolytic acanthoma 39, 40
 Epidermolytic hyperkeratosis 39, 40

Epidermotropic eccrine carcinoma 128
Epidermotropic metastasis 138
Epidermotropism 132, 170, 172, 176, 181, 185-187, 189, 191, 192, 213, 215, 216, 219
Epiluminescence microscopy 57
Epiluminescence microscopy 110
Epithelial melanocytoma 81
Epithelioid angiomytosis 240
Epithelioid angiosarcoma 24
Epithelioid cell histiocytoma 262
Epithelioid haemangioma 237
Epithelioid sarcoma 232
Epithelioma cuniculatum 22, 23
Epstein Barr 207
Epstein Barr virus (EBV) 183, 185, 199, 202
ERCC1 278
ERCC2 278
ERCC4 278
ERCC5 278
Eruptive syringoma 140
Erythema 55, 105, 114, 137, 189, 192, 200, 212, 214, 227
Erythematous nodule 17, 77, 125
Erythematous scaly patches 137
Erythroderma 169, 175-177, 189, 193
Erythrodermic CTCL 175
Erythroplasia of Queyrat (EPQ) 27
Ewing sarcoma 264, 268
EWS gene 269
Exophthalmos 218, 225
Expansile pattern of growth 68
Extramammary Paget disease 71, 136
Extramammary Paget's cells 17
Extramedullary myeloid sarcoma 211
Extranodal marginal zone B-cell lymphoma 194
Extranodal NK/T-cell lymphoma 183, 191, 192
Extranodal NK/T-cell lymphoma, nasal-type 191
Extraskeletal Ewing sarcoma 268
Eyelid hidrocystoma 142

F

Fabry disease 244, 245
Factor VIII 24, 237, 243, 247
Factor VIII-related antigen 24, 237, 247
Factor XIII 223
Factor XIIIa 220, 221, 225, 262

Familial atypical mole-malignant melanoma syndrome, FAMMM 279
Familial atypical mole-melanoma syndrome 68
Familial atypical multiple mole melanoma pancreatic carcinoma syndrome (FAMMMPC) 279
Familial cancer syndromes 231
Familial cutaneous melanoma 279
Familial dyskeratotic comedones 40
Familial melanoma 54, 105, 108, 109, 278, 279
Familial multiple trichoblastoma and cylindroma (Brooke-Spiegler disease) 153
Fanconi anaemia 211
Faulty hair matrix 154
FCC 196, 197
FcgrII 233
FCL 196, 197
Ferguson Smith type keratoacanthoma 45
Ferguson Smith type of "multiple self-healing epitheliomas" 46
Fetal rhabdomyoma 253, 285, 286
Fibrocytokines 78
Fibroepithelial polyp 253
Fibroepithelioma of Pinkus 17
Fibroepithelioma 15, 17
Fibroepithelial basal cell carcinoma 17
Fibroepithelial polyp 258
Fibrofolliculoma 157, 158, 159
Fibroma durum 261
Fibroma 286
Fibromatous Tumours of the Skin 279
Fibromin 278
Fibroplasia 69, 71, 78
Fibrosarcoma 78, 258, 260
Fibrosclerosis 221
Fibrous hamartoma of infancy 253
Fibrous histiocytoma 78, 231, 232, 235, 260, 261
Fibrous papule of the face 258
FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) 137
Fine-needle aspiration cytology 231
FISH 75, 177, 204, 269
Fitzpatrick skin types 66
Flat macule 56
Flat seborrhoeic keratosis 42, 44
Flat wart 38
FLI-1 246, 268, 269
Fluorouracil 28

Focal epithelial hyperplasia (Heck's disease) 36
Follicular adenocarcinoma 288
Follicular centre cell lymphoma 196
Follicular dyskeratoma 39
Follicular hyperkeratosis 212
Follicular infundibulum 156
Follicular MF 173
Follicular stroma 152
Folliculo-sebaceous cystic hamartoma 157
Folliculotrophic MF 173
Fordyce angiokeratoma 244
Foreign body 75, 155, 222, 262
Fungal disorder 75

G

Ganglion of the distal interphalangeal joint 257
Gardner syndrome 154, 278
Gasoline 11
Gastrin 273
Gastrointestinal stromal tumours (GISTs) 226
Gata-3 177
GCDFP-15 125, 132, 138
Gene rearrangement of immunoglobulin heavy chain genes, and T-cell receptor genes 210
Generalized cutaneous histiocytosis (GCR) 224
Generalized lymphangioma 249
Genital melanosis/lentiginosis 103
Genital naevus 110, 111
Genital naevus with unusual histologic features 110
Genodermatoses 36, 256, 285
Germinative cells 13, 14, 16, 148
Germline 39, 163, 191, 192, 209, 280, 287-290
Germline mutations 231
GFAP 269, 275
Ghost vessels 233
Giant cell fibroblastoma 258, 260, 261
Giant cell histiocytosis 224
Giant cell reticulohistiocytosis 224
Giant condyloma acuminata (Buschke-Lowenstein tumour) 36
Giant condyloma acuminatum 22
Giant congenital naevus (GCN) 83
Giant hair matrix tumour 150
Giant keratoacanthoma 45
Glabrous skin 26, 27, 46, 74

- Glans penis 27, 103, 243, 244
 GLI 287
 Glomeruloid haemangioma 235, 236
 Glomus tumour 268
 Glucose-6-phosphate dehydrogenase 28
 GLUT1 233
 Glutathione-S-transferase null genotype 32
 Goldenhar syndrome 154, 253
 Gorlin syndrome 285
 Gorlin-Goltz syndrome 124, 285
 Gp100 63, 87
 Gp100 (recognized by HMB45) 63
 Grain leather 227
 Granular cell dermatofibroma 262
 Granular cell epulis of infancy 275
 Granular cell myoblastoma 274
 Granular cell nerve sheath tumour 274
 Granular cell Schwannoma 274
 Granular cell tumours (GCT) 274
 Granular-cell 19
 Granulocytic sarcoma 211
 Granuloma faciale 214
 Granulomatous inflammation 140, 163, 266
 Granulomatous MF 174
 Granulomatous slack skin 178
 Granzyme B 171, 180, 181, 183, 185-187, 191
 Granzyme M (metase) 183
 Grenz zone 198, 205, 210
 Gross cystic disease fluid protein (GCDFP) 136, 138
 Grover disease 40
 Grzybowski type keratoacanthoma 45
 GTPase-activating protein 278
- H**
- Haemangioma 16, 114, 233-237, 239, 242, 243, 245, 258, 289, 262
 Haemangioma of infancy 233
 Haemangioma unilateralis naeviforme 242
 Haemangiopericytoma-like fibrous histiocytoma 262
 Haemangiosarcoma 246
 Haematopoietic stem cells 211
 Haemophagocytic syndrome 182, 183, 185, 191, 192
 Hailey-Hailey disease 40
 Hair disk (Haarscheibe) 158
 Hair follicle hamartoma 279
 Hair follicle naevus 157
 Halo dermatitis 111
 Halo eczema 111
 Halo naevus 59, 108, 111, 118, 119
 HAM56 223, 225
 Hamartin 278
 Hamartoma 156, 157, 245, 250, 251, 288
 Hand-Schüller-Christian-disease 218, 219
 Hashimoto thyroiditis 225
 Hashimoto-Pritzker disease 218, 219
 Hashimoto-Pritzker type 219
 H-caldesmon 256
 Heck's disease 36
 Hedgehog signaling pathway 13
 Hepatosplenomegaly 182, 192, 206, 218
 Hereditary non polyposis colon cancer syndrome (HNPCC) 163
 Herpes simplex 206
 Heterochromasia 59
 HHV-8 238, 239, 246, 249
 Hidradenocarcinoma 123, 131, 135
 Hidradenoma 123, 131, 143, 146, 147, 148
 Hidradenoma papilliferum 147
 Hidroacanthoma simplex 129, 141
 Hidrocystoma 139, 140
 High-frequency hearing loss 283
 Hirudo medicinalis 213
 Histiocytoma (cutis) 261
 Histiocytosis-X 217
 HIV 34, 35, 181, 199, 207, 231
 HIV infection 34, 231
 HIV/AIDS 240
 HLA haplotype 63
 HLA-DQB1*03 172
 HLA-DR 180, 181, 220, 228
 HLA-DR5 172
 HLA-DRB1*11 172
 HLA-DRB1*1104 172
 HMB-45 63, 69, 75, 78, 81, 87, 95, 98, 107, 119, 269
 HMSH2 163, 278
 Hobnail haemangioma 234
 Hodgkin disease 207
 Hodgkin lymphoma (HL) 178, 206, 207
 HOOG1 81
 HOI 233
 Homer Wright rosettes 268
 Hormonal contraceptives 236
 Horn cysts 19, 42, 141
 HOXC5 181
 HPV 12, 20, 23, 26, 28, 30, 34-39, 45, 156
 HPV-1 36, 37
 HPV-2 38
 HPV-4 36, 38
 HPV-6 34, 36
 HPV-7 36
 HPV-11 34, 36
 HPV-13 36
 HPV-16 26, 34, 35
 HPV-18 26, 34, 35
 HPV-31 26
 HPV-32 36
 HPV-54, 26
 HPV-58 26
 HPV-61, 26
 HPV-62, 26
 HPV-63 37
 HPV-66 38
 HPV-73, 26
 HRAS 11, 32, 116
 HRAS mutations 116
 HTLV-1 175, 189
 Human herpes virus type 8 (HHV8) 231, 235, 243
 Human immunodeficiency virus 20, 202, 207, 272
 Human milk fat globule protein-2 161
 Human milk fat globulin 1 (HMFG) 140
 Human papilloma virus (HPV) 11, 28, 34, 37, 151, 243
 Human T-cell leukaemia virus type I (HTLV-1). 189
 Hutchinson melanotic freckle 70, 77
 Hutchinson sign 57
 Hutchinson's melanotic freckle 70
 Hyaline collagen bundles 255
 Hyaline-cell rich chondroid syringoma 148
 Hyalinization 256, 270
 Hyalinizing Spitz naevus 115
 Hyaluronidase resistance 148
 Hydroa vacciniforme-like cutaneous T-cell lymphoma 192
 Hydrolase alpha-galactosidase A. 244
 Hyperchromasia 12, 21, 30, 81, 104
 Hypergammaglobulinemia 193
 Hyperkeratotic seborrhoeic keratosis 42
 Hypermelanotic naevi 58
 Hypersensitivity to insect bites 192
 Hypertension 227
 Hypertrophic scar 254, 255

Hypodontia 142
Hypogonatrophic hypogonadism 286
Hypopigmentation 44
Hypopituitarism 218
Hyporeflexia 283
Hypotension 227

I

Iatrogenic arteriovenous fistulas 241
ICAM-1 112
IgA 123, 146, 172
IgE 172, 254
IGF-II 233
IgG 146
IKH-4 146
IL-4 172
IL-5 172
IL-10 172
Immature trichoepithelioma 18
Immunoglobulin 195, 198, 202, 204, 205, 206, 214, 236
Immunosuppression 20, 31, 36-38, 40, 45, 47, 68, 231, 240, 272, 273
In situ hybridization 12, 26, 191, 203, 204
Indeterminate cell histiocytosis (ICH) 220
Indolent systemic mastocytosis 226
Industrial carcinogens 20
Infantile haemangioma 233
Infantile melanoma (birth to one-year of age) 84
Infantile myofibromatosis 256
Infiltrating basal cell carcinoma 17
Inflammatory angiomatic nodule 237
Inflammatory molluscum contagiosum 212
Inflammatory myofibroblastic pseudotumour 213
Inflammatory pseudotumour (IPT) 213
Infundibular tumour 158
Infundibulocystic basal cell carcinoma 19
Infundibuloisthmoma 157
Ingrown toenail 75
Inguinal hernia 244
Inherited tumour syndromes 277
Ink spot 40
Ink spot lentigo 103
INK4a 11

Interferon 82, 111, 254
Interleukin-3 receptor alpha chain (IL-3R-alpha). 209
International Society for Cutaneous Lymphoma ISCL 176
Intestinal ganglioneuromatosis 266
Intradermal Spitz naevi 115
Intraepidermal carcinoma 11, 12, 26
Intraepidermal Merkel cell carcinoma 138
Intra-epidermal proliferative disorders (dysplasias) 11
Intramuscular haemangioma 233
Intravascular large B-cell lymphoma (IL) 200
Intravascular lymphoma 200, 241
Intravascular lymphomatosis 200
Intravenous atypical vascular proliferation 237
Invasive hair matrix tumour of the scalp 150
Invasive pilomatrixoma 149
Inverted type A naevus 100
Involucrin 21, 28, 32, 44
Ionizing radiation 13, 14, 23, 231, 246, 283
Irregular acanthosis 112
Irritated seborrhoeic keratosis 42
Isochromosome 11p 116
Isolated dyskeratosis follicularis 39
Ixodes ricinus 213

J

JH translocation 198
Jun D 278
Juvenile chronic myeloid leukaemia 222, 223
Juvenile haemangioma 233
Juvenile polyposis syndrome 290
Juvenile xanthogranuloma (JXG) 222, 223
JXG See Juvenile xanthogranuloma

K

K1 and K10 genes 39
Kamino bodies 59, 115, 117
Kaposi sarcoma 231, 235, 237, 239, 241, 246, 249, 262
Kaposiform haemangioendothelioma 233
Kasabach-Merritt syndrome 240
Keloid scar 254, 255
Keratin cysts 19

Keratinocyte intraepidermal neoplasia (KIN I, II and III) 30
Keratinocytic tumours 9-48
Keratinous microcysts 156
Keratoacanthoma 39, 44-47, 75, 155, 163
Keratoacanthoma centrifugum marginatum 45
Keratocystic odontogenic tumours 286
Keratoses 12, 32, 33, 40-43, 57, 119, 155, 289
Keratosis follicularis inversa 156
Keratotic basal cell carcinoma 19
Keratotic haemangioma 242
Ketron-Goodman type 185
Ki-67 60, 69, 81, 87, 107, 127, 234, 238, 275
Kimura disease 238
KIN See Keratinocyte intraepidermal neoplasia 30
KIR receptors 209
KIT 226-228, 273
Klippel-Trenaunay syndrome 239
Klippel-Trenaunay-Weber syndrome 244
Koebner phenomenon 36, 38
Koilocytes 29, 36, 37
Koilocytosis 38, 43
Kostmann syndrome 211
KP1 220, 221, 225, 262
K-ras 11
Kyphoscoliosis 286

L

Labial lentigo 103
Labial melanotic macule 103
Labial/oral melanosis 103
Lactate dehydrogenase (LDH) 58
LAMB syndrome 103, 291
Laminin 78, 115, 148, 234, 275
Langerhans cell disease 217
Langerhans cell granules 219
Langerhans cell granulomatosis 217
Langerhans cell histiocytosis (LCH) 138, 217
Langerhans cells 144, 213, 217, 219, 220
Large cell acanthoma 39-41, 44, 47
Large cell lymphoma (Richter syndrome) 206
Large plantar wart 38
Latitudes 11, 13
Laugier-Hunziker syndrome 103
LDH 58

- LEF-1 155
 Leiomyosarcoma 22, 78
 Lentigines 40, 41, 103, 110, 289, 291
 Lentiginosis-multiple endocrine neoplasia syndrome 291
 Lentiginous melanocytic naevus 103
 Lentiginous melanocytic proliferation 70, 85
 Lentigo maligna melanoma (LMM) 55, 59, 69, 70, 72-74, 77, 88, 90
 Lentigo simplex 104
 Lentigo-melanosis 70
 Leonine facies 175
 LEOPARD syndrome 103, 292
 Leser-Trélat syndrome 41
 Letterer-Siwe disease 218, 219
 Leu M5 220
 Leu-7 265, 267, 269, 270
 Leukaemia 175, 184, 191, 205, 211, 219, 220
 Leukocyte common antigen (LCA) 138
 Leukocytosis 193, 221
 Leukoderma 80
 Leukoderma acquisitum centrifugum 118
 Leukoplakia 23
 Leu-M1 (CD15) 153, 225
 Lewis Y antigen 233
 Lichen planus 23, 40, 41, 47, 142
 Lichen planus-like keratosis (LPLK) 41, 47
 Lichen sclerosus of the vulva 22
 Lichenoid solar keratosis 47
 Limbal dermoid 253
 Linear skin defects 250
 Lipoid dermatoarthritis 224
 Lipoid rheumatism 224
 Lipoma of the brain 253
 Lipoma 231
 Liver transplant 240
 LMP-1 191
 L-myc 81
 Lobular capillary haemangioma 243
 Lobular panniculitis 182
 Local recurrence of melanoma 90
 LOH at 9q22 11
 Longitudinal melanonychia 57, 103
 Long-wave ultraviolet radiation (UVA) 33
 Loss of chromosome 7 94
 Loss of heterozygosity (LOH) 11, 219, 280, 287
 Loss of heterozygosity at 9p21 (p16) 147
 Loss of heterozygosity at 9q22 11
 Low-grade squamous cell carcinoma *in situ* 29
 Low-molecular-weight keratins 135
 Low-set ears 253
 LPLK 47
 Lumbosacral haemangioma 233
 Lupus erythematosus 23, 80, 212, 225, 261
 Lupus profundus panniculitis 182
 Lymphadenoma (adamantoid trichoblastoma) 152
 Lymphadenopathy 175, 178, 185, 192, 193, 200, 218, 221, 238
 Lymphadenosis benigna cutis (LABC) 212, 213
 Lymphangiectasias 249
 Lymphangiography 249
 Lymphangioma 247-249, 259
 Lymphangioma circumscripum 247, 248
 Lymphangioma tuberosum multiplex 140
 Lymphangioma-like Kaposi sarcoma 248
 Lymphangiomatosis 249
 Lymphangiosarcoma 246
 Lymphatic tumours 247
 Lymphoadenopathy 218
 Lymphoblastic leukaemia/lymphoma 210
 Lymphoblastic lymphoma 210
 Lymphocytic infiltration (idiopathic or drug induced) 212
 Lymphocytoma cutis 212, 213
 Lymphoedema 142, 231, 246
 Lymphoid infiltrates of the skin mimicking lymphoma (cutaneous pseudolymphoma) 212
 Lymphomatoid contact dermatitis 212
 Lymphomatoid granulomatosis (LYG) 202
 Lymphomatoid papulosis (LyP) 179, 213
 Lymphomesenteric cysts 285
 Lymphoplasmacytoid cells 194, 195
 Lymphoscintigraphy 62
 LyP See lymphomatoid papulosis
 Lysozyme 140, 211, 219, 220, 225
- M**
- MAC387 223, 225
 Macrocephaly 288
 Maculopapular or plaque type mastocytosis 226
 Maffucci syndrome 231, 239, 247
 MAGE3 63
 Malignant acrospiroma 133
 Malignant angioendotheliomatosis 200, 241
 Malignant apocrine mixed tumour 127
 Malignant blue naevus 56, 81
 Malignant chondroid syringoma 127
 Malignant clear-cell acrospiroma 131
 Malignant clear-cell hidradenoma 131
 Malignant cutaneous melanoma 63
 Malignant cylindroma 135
 Malignant eccrine acrospiroma 131
 Malignant eccrine poroma 128
 Malignant fibrous histiocytoma (MFH) 78, 260
 Malignant hidroacanthoma simplex 128
 Malignant intraepidermal eccrine poroma 128
 Malignant lymphoma 168
 Malignant melanoma 12, 52-92, 107, 108, 279
 Malignant melanoma arising in a garment naevus 83
 Malignant melanoma arising in a giant hairy naevus 83
 Malignant mixed tumour 127, 133
 Malignant nodular clear-cell hidradenoma 131
 Malignant peripheral nerve sheath tumour 78
 Malignant pilomatrixoma 149
 Malignant spiradenoma 130, 133
 Mantle cell lymphoma 204
 Mantleoma 158
 Marginal zone B cell lymphoma 196
 MART-1 63, 65, 69, 75, 78
 Mast cell disease 218, 226
 Mast cell leukaemia 226
 Mast cell proliferative disease 226
 Mastocytoma 227
 Mastocytosis 226, 228
 Mastocytosis with associated haematopoietic disorder 226
 Matrical carcinoma 149
 Matricoma 155
 Matrix carcinoma 149
 Matrix interacting protein 1 (MXI1) 78
 Mature B lymphocyte 202
 Mature skin homing T cells 172

- MC1R (Melanocortin 1 Receptor)
 See
 MCC 81
 MDM2 219, 278, 281
 Medicinal leeches 213
 Medullary carcinoma of the thyroid 265
 Medulloblastoma 283, 285-287
 Melan-A 63, 72, 75, 87, 98, 118, 119
 Melanoacanthoma 39, 41, 43
 Melanoacanthosis 43
 Melanocortin-1 receptor gene (MC1R) 64, 280
 Melanocytic acral naevus with intraepidermal ascent of cells (MANIAC) 110
 Melanocytic macules of the lip 279
 Melanocytic naevi 54-58, 93, 93-95, 100, 104, 195, 107, 108, 113, 117, 129
 Melanocytic naevus with architectural disorder and cytologic atypia 105
 Melanocytic naevus with phenotypic heterogeneity 100
 Melanocytosis 79, 80, 81, 82, 96
 Melanoma 52-92
 Melanoma and neural system tumour syndrome 279
 Melanoma arising in a bathing trunk naevus 83
 Melanoma arising in giant congenital naevi 83
 Melanoma arising in the dermal component of a large or "giant" congenital naevus 83, 89
 Melanoma arising from blue naevus 79
 Melanoma familial, MLM 279
 Melanoma in situ 59, 64, 70, 80, 81, 108
 Melanoma prevention 55
 Melanoma-astrocytoma syndrome 279, 280
 Melanoma-inhibiting activity (MIA) 58
 Melanoma-pancreatic cancer syndrome 279
 Melanoma simulating Spitz naevus 85
 Mélanose circonscrite précancéreuse 70
 Melanosis 32, 33, 57, 70, 81, 103
 Melanosis circumscripta precancerosa 70
 Melanosis of the nail bed and matrix 103
 Melanotic macules 103
 MEN2b 265, 266
 Meningeal melanocytoma (blue naevus) of the brain 79
 Meningioma 287
 Menzies method 58
 Merkel cell carcinoma 268, 272, 273, 289
 Merkel cells 15, 153, 157, 272, 273
 Merosin 233
 Metastasizing Spitz naevus 89
 Metastasizing squamous cell carcinoma 23
 Metastatic adenosquamous carcinoma 25
 Metastatic melanoma 81, 89, 91
 Metastatic melanoma mimicking blue naevus 81
 Metastatic neuroblastoma 268, 273
 Metastatic small cell neuroendocrine carcinoma 268
 Metatypical carcinoma 18
 Meyerson naevus 110, 111
 MIB-1 labeling index 46, 60, 69, 70, 81, 87, 107
 Mibelli angiokeratoma 244
 MIC2 gene product 268
 Michelin tyre baby 250
 Michelin tyre syndrome 250, 251
 Microcystic adnexal carcinoma 15, 17, 25, 123-125, 126, 135, 140, 153
 Micronodular basal cell carcinoma 16
 Microphthalmia 69, 250, 253
 Microphthalmia transcription factor (MITF) 69, 78
 Microphthalmia transcription factor (MITF-1) 95
 Microsatellite instability 11, 108, 162, 163, 177
 Microvenular haemangioma 236, 237
 Microvesication 112
 Milia 140, 285
 Minimal deviation melanoma 88
 Mismatch repair genes 46, 162, 163
 Mitogenicity 61, 64
 Mixed tumour of skin 147, 148
 MLH1 46, 162, 163
 MMAC1 278, 289
 MNF116 22
 N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) 11
 Moll gland carcinoma 135
 Mongolian spot 80, 96
 Monomorphic NK-cell lymphoma 208
 Morpheiiform basal cell carcinoma 19, 127, 153
 MSH-2 46, 161-163
 MTS 162, 163
 MTS1 81, 279
 Mucicarmine 24, 28
 Mucinous carcinoma 128, 131, 132
 Mucoepidermoid carcinoma 24, 131
 Mucoepidermoid hidradenocarcinoma 131
 Mucopolysaccharide 257, 270
 Mucopolysaccharidoses (including Hurler and Hunter syndromes) 96
 Mucosa associated lymphoid tissue, MALT 194
 Mucosal melanoma 57
 Muir-Torre syndrome (MTS) 45, 46, 124, 160-163, 278
 Multicentric Castleman disease 235
 Multicentric pigmented Bowen disease 28
 Multicentric reticulohistiocytosis 224
 Multifocal indolent pigmented penile papules 28
 Multinodular goiter 288
 Multiple cutaneous and uterine leiomyoma syndrome 251
 Multiple enchondroma (Maffucci syndrome) 239
 Multiple endocrine neoplasia 1 278
 Multiple endocrine neoplasia syndrome (MEN2b) 265
 Multiple facial angiofibroma 279
 Multiple gastrointestinal polyps 288
 Multiple Hama small blue round cell tumours 279
 Multiple hamartoma and neoplasia syndrome 155
 Multiple hamartoma syndrome 288
 Multiple hamartomatous gastrointestinal polyps 40
 Multiple lymphangiectasias 249
 Multiple mucosal neuroma (MMN) syndrome 265
 Multiple pilomatrixoma 154
 Multiple tricholemmomas 155
 MUM-1/IRF-4 198, 199
 Musculoskeletal abnormalities 265
 Mustard gas 234
 MXI1 78, 81

Mycosis fungoides 141, 168, 169-174, 177, 178, 180, 186, 187, 190, 207, 213, 215, 216
Myelin basic protein 257, 265, 267, 275
Myeloid leukaemia 211
Myoatrophy 225
MYO-D1 269
Myoepithelial carcinoma 128
Myofibroblastic dermatofibroma 262
Myofibromatosis 256
Myogenin 269
Myoglobin 253, 256
Myositis 225
Myotonia 225
Myotonic dystrophy 154
Myrmecia 34, 37
Myxoid dermatofibroma 262
Myxoid liposarcoma 261
Myxoid mammary fibroadenoma 291
Myxoid pseudocysts of the digits 257
Myxoma 148, 159, 270, 291, 192
Myxomatous perineuroma 270
Myxopapillary ependymoma 128

N

Naevi on volar skin 110
Naevi with dermal epithelioid cell components 100
Naevi with dermal nodules. 100
Naevoid basal cell carcinoma (Gorlin) syndrome See next line.
Naevoid basal cell carcinoma syndrome (NBCCS) 124, 142, 153, 285
Naevoid melanoma 61, 86-89
Naevi 93-120 ,
Naevus angiokeratoticus 242
Naevus flammeus 240
Naevus fuscoeruleus ophthalmomaxillaris 96
Naevus incipiens 104
Naevus keratoangiomatosus 242
Naevus lipomatous 253
Naevus of Ito 79, 96
Naevus of Ota 79, 82, 96
Naevus of spindled and/or epithelioid cells 114
Naevus of Sun 96
Naevus sebaceous 125, 141
Naevus sebaceous of Jadassohn 144
Naevus spilus (congenital speckled lentiginous naevus) 104

Naevus vascularis unius lateralis 242
Naevus with architectural disorder 105
Naevus with focal dermal epithelioid component 100
Nail dystrophy 175
NAME syndrome 103, 291
Naturopathic medicines 32
Necrosis en masse 123
NER See Nucleotide excision repair
Nerve sheath myxoma/neurothekeoma 270
Nerve sheath tumours 231
Neurilemmomatosis 223
Neurocutaneous melanocytosis 79
Neuroendocrine carcinoma of the skin 272
Neurofibroma 231, 258, 260
Neurofibromatosis 78, 222, 223, 265
Neurofibromatosis type 1 (NF1) 78, 81, 223, 275, 278
Neurofibromatosis type 1 b (NF1b) 223, 278
Neurofibromatosis type 2 (NF2) 223
Neurofibromatosis type 2 b (NF2b) 278
Neurofilament 269
Neurofollicular hamartoma 158
Neuroma 265, 266
Neuromuscular hamartoma 253
Neurotization 98
Neurotropism 76, 77, 78
Neutropaenia 193
Nevoxanthoendothelioma 222
NF1 See neurofibromatosis type 1 (NF1)
NF2 See Neurofibromatosis type 2 (NF2)
NGFR 275
Nickel 213
NK/T-cell lymphoma 191
NKI/C-3 69, 78, 81, 269, 270
Nodular amelanotic melanoma 43
Nodular angioblastic hyperplasia with eosinophilia and lymphofolliculosis 237
Nodular basal cell carcinoma 16, 19
Nodular hidradenocarcinoma 131
Nodular hidradenoma 143
Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) 207
Nodular melanoma 55, 56, 68, 73, 74, 119, 262
Non-cutaneous melanoma 63

Non-diabetic cutaneous xanthomatosis 224
Non-encapsulated neuroma 265
Non-Hodgkin lymphoma 204, 205
Non-inflammatory halo naevi 119
Non-Langerhans-cell (LC) histiocytosis 222
Non-melanoma skin cancer (NMSC) 11, 12
Non-neuroendocrine small cell carcinoma 268
Non-regressing lipodystrophy centrifugalis abdominalis 240
Normocholesterolemic xanthomatosis 224
Npm-alk protein (p80) 181
Nuclear pseudoinclusions 69
Nucleolar organizing regions (AgNORs) 87
Nucleotide excision repair (NER) 282-284

O

Ocular melanocytosis 79, 82
Oculodermal melanocytosis 79, 96
Odontogenic keratocysts 287
OKM1 220
OKT6 223
Oral contraceptives 80
Oral florid papillomatosis 22
Orange skin 227
Orbital melanoma 79
Organ transplantation 20, 34, 202
Ossification 128, 149, 253
Ossifying dermatofibroma with osteoclast-like giant cells 262
Osteoarthritis 257
Osteolytic skull lesions 218
Osteoporosis 227
Otitis media 218
Ovarian fibroma 285, 286, 287
Ozone layer 55

P

p14ARF 278, 280, 281
p15 197, 246
p16 32, 63, 108, 197, 219, 278, 279
P16/INK4 278
p16INK4A 280, 281
p19 (ARF) 279
p21 69, 219
p21 WAF1 69
p62 172
P75 260

- P75 (low-affinity nerve growth factor receptor) 260
- Paget disease 28, 72, 129, 135, 136, 138
- Paget disease of breast 136
- Paget disease (extramammary, EPD) 136, 161
- Pagetoid dyskeratosis 138
- Pagetoid melanocytosis 85
- Pagetoid melanoma 66
- Pagetoid reticulosis 173
- Pagetoid reticulosis of the Ketron-Goodman type 185
- Pagetoid Spitz naevus 138
- Pagetoid upward migration 86, 89
- Pagetoid variant of Bowen disease 28
- Pale cell acanthoma 43
- Pale scar-like lesions 13
- Palisaded, encapsulated neuroma (PEN) 265
- Palisading pattern 265
- Palmar pits 155
- Palmar-plantar-subungual-mucosal melanoma (P-S-M melanoma) 73
- Palmo-plantar keratoderma 142, 175
- Palpable migratory arciform erythema 212
- Pan T-cell markers 192
- Pancreatic cancer 279
- Pan-cytokeratin 273
- Pancytopenias 182, 218
- Pan-muscle actin (HHF-35) 252
- Panniculitis 182, 183, 184, 185, 200
- Papillary apocrine gland cyst 139
- Papillary thyroid carcinoma 80
- Papillary tubular adenoma 145, 146
- Papillomatosis 22, 23, 31, 33, 37, 38, 40, 42, 44, 242
- Papillomatosis cutis carcinoides 22, 23
- Parakeratosis 27, 30, 31, 36, 41, 44, 47, 59, 112, 155, 171, 215, 216
- Parakeratosis variegata 171, 216
- Parapsoriasis 171, 215, 216
- Parapsoriasis - Large patch type, with or without poikiloderma 215
- Parapsoriasis en grandes plaques poikilodermiques 171, 216
- Parapsoriasis en plaques (Brocq disease) 215, 216, 171
- Parapsoriasis lichenoides 171, 216
- Parasitosis 228
- PATCHED1 14, 287
- Pautrier microabscesses 170, 190
- PCFCL 196, 197
- PCNA 21, 46, 69, 81, 87, 172
- Peanut agglutinin (PNA) 223
- Peliosis hepatis 240
- Pemphigus 40
- PEN 265, 266
- Penile intraepithelial neoplasia 29
- Penile lentigo 103
- Penile melanotic macule 103
- Peptic ulcer disease 227
- Perforin 181, 183, 185, 186, 191
- Pericarditis 225
- Perifollicular fibroma 158
- Perifollicular fibroma/fibrous papule 159
- Perifollicular fibroma 289
- Perinaevic eczema 111
- Perineural invasion 15, 17, 20, 24, 91
- Perineural lymphocytes 20
- Perineurial cells 267
- Période érythémateuse 169
- Période fongoïdique 169
- Période lichénoïde 169
- Peripheral myelin proteins 275
- Peripheral neuroblastoma 268
- Peripheral neuroepithelioma 268
- Peripheral T-cell lymphoma 178, 184, 191
- Peripheral vascular atherosclerosis 241
- Periungual fibroma of tuberous sclerosis (Koennen tumours) 257
- Perls stain 235
- Persistent (recurrent) melanocytic naevus 113
- Persistent and metastatic melanoma 90
- Persistent melanocytic naevi 113
- Persistent melanoma 92
- Persistent nodular arthropod-bite reactions 212
- Peutz-Jeghers syndrome 40, 103, 278, 292
- PGM1 221, 225, 262
- PGP 9.5 269, 275
- PHACES syndrome 233
- Pheochromocytoma 265
- Phlebitis 200
- Phosphatidylinositol-3-kinase (PI3K)/Akt pathway 289
- Phosphorylated mitogen-activated protein kinase 243
- Photochemotherapy 33
- PI3K/Akt pathway See phosphatidylinositol-3-kinase (PI3K)/Akt pathway
- Pian fungoides 169
- Pigment incontinence 31, 170
- Pigmented basal cell carcinoma 13, 19
- Pigmented seborrhoeic keratosis 42
- Pigmented spindle cell naevus 117
- Pigmented spindle cell naevus (Reed) 114, 117
- Pigmented spindle cell naevus with architectural and/or cytologic atypia 117
- Pigmented xerodermod 282
- Pilar leiomyoma 250, 251
- Pilar sheath acanthoma 157
- Piloleiomyoma 251
- Pilomatrical carcinoma 149, 150
- Pilomatricoma 123, 149, 151, 153-155
- Pilomatrix carcinoma 149
- Pilomatrixoma 153
- Pilosebaceous pathway of differentiation 18
- Pilotropic mycosis fungoides (MF) 173
- Pinkus tumour 17
- Pits 285
- Pityriasis rosea 111
- Plantar wart 37
- Plaque-like dermal fibromatosis 255
- Plasma cell granuloma 213
- Plasmablastic lymphoma 199
- Pleomorphic fibroma 258
- Pleuritis 225
- Plexiform pigmented spindle cell naevus 100, 117
- Plexiform spindle cell naevus 98
- PNET/ES 264, 268, 269
- POEMS syndrome 235, 236, 237
- Poikiloderma 171, 215
- Poikiloderma vasculare atrophicans 171, 216
- POLh 278
- Poliosis (white hair) 66
- Polycyclic aromatic hydrocarbons 11
- Polymyalgia rheumatica 241
- Porocarcinoma 123, 128, 129, 138, 142
- Poroepithelioma 128
- Poroid hidradenoma 143
- Poroma 123, 129, 141-143
- pRb 35
- Precursor B-lymphoblastic leukaemia/ lymphoma 210

Precursor lymphoblastic leukaemia/
lymphoma 210
Precursor T-lymphoblastic leukaemia 210
Precursor T-lymphoblastic leukaemia/ lymphoma 210
Precursor T-lymphoblastic lymphoma 210
Pregnancy 141, 234, 236, 240, 243, 244, 254, 260
Prelymphomatous ("abortive") disorders (PLD) 168
Prereticulotic poikiloderma 271, 216
Primary cutaneous adenoid cystic carcinoma 134, 135
Primary cutaneous aggressive epitheliotrophic CD8+ cytotoxic T-cell lymphoma 184, 185
Primary cutaneous anaplastic large-cell lymphoma 180
Primary cutaneous anaplastic lymphoma (C-ALCL) 179, 189
Primary cutaneous B cell lymphoma (CBCL) 196
Primary cutaneous diffuse large B-cell lymphoma (DLBCLs) 198
Primary cutaneous follicle centre lymphoma (PCFCL) 196, 197
Primary cutaneous immunocytoma/marginal zone B-cell lymphoma 194
Primary cutaneous large B-cell lymphoma 198
Primary cutaneous large cell T cell lymphoma CD30+ 180
Primary cutaneous marginal zone B-cell lymphoma (MZL) 194
Primary cutaneous mucinous carcinoma 131, 132
Primary cutaneous T-cell lymphoma 178
Primary cutaneous peripheral T-cell lymphoma, unspecified 184
primary cutaneous plasmacytoma 194
primary cutaneous small-medium CD4+ T-cell lymphoma 184, 186
Primary malignant peripheral primitive neuroectodermal tumour (PNET) / Extraskeletal Ewing sarcoma (ES) 268
Primary mucoepidermoid carcinoma of the skin 131

Primary small-cell carcinoma of the skin 272
Primary systemic anaplastic large cell lymphoma 193
PRKAR1A 292
Progesterone receptor 138
Progressive and recurring dermatofibroma 259
Progressive atrophying chronic granulomatous dermohypodermatitis 178
Progressive capillary haemangioma 239
Progressive lymphangioma 248, 249
Proliferating epidermoid cyst 150
Proliferating follicular cystic neoplasm 150
Proliferating isthmic cystic carcinoma 150
Proliferating pilar cyst 150
Proliferating tricholemmal cyst 150
Proliferating tricholemmal cystic squamous cell carcinoma 150
Proliferating tricholemmal tumour 150, 151
Proliferative nodules in a congenital naevus 89, 93
Proliferative nodules in congenital melanocytic naevi 93, 94
Prolymphocytic leukaemia 206
Prostate carcinoma 138
Proteinuria 238
Proteoglycans 254
Proteus syndrome 290
Proteus-like (non-CS, non-BRR) syndromes 290
Pruritus 137, 175
Psammoma bodies 214
Psammomatous melanotic schwannoma 291
Pseudoangiomatous squamous cell carcinoma (SCC) 23
Pseudoangiosarcomatous squamous cell carcinoma (SCC) 23
Pseudo-Darier sign 250
Pseudoglandular squamous cell carcinoma 21
Pseudoinclusions 194
Pseudolymphoma (PSL) 168, 212-214
Pseudolymphoma (PSL) with predominant T-cell infiltrates (T-PSL) 212
Pseudolymphoma of Spiegler and Fendt 212
Pseudomelanoma 113
Pseudo-T-cell lymphoma 186

Pseudovascular squamous cell carcinoma (SCC) 21, 23
P-S-M melanoma 73
Psoralen 33
Psoriasis 33, 44, 80, 176
PTCH gene 9q22 11, 13-15, 17, 124, 146, 278, 287
PTEN hamartoma tumour syndrome (PHTS) 290
PTEN gene 124, 278, 288, 289, 290
Purpura 218, 241
Pushing pattern of growth 68
PUVA (psoralens + UVA). 11, 12, 26, 30, 33, 39, 103
PUVA keratosis 11, 33
PUVA-lentigines 103
Pyogenic granuloma 43, 129, 233, 237, 241, 243
Pyrimidine dimers 11

R

RAB5 278
Racemiform trichoblastoma 152
Radiation therapy 15, 17, 20, 78, 138, 160, 246, 248, 269, 285, 286
Radical mastectomy (Stewart-Treves) 231
RAP1 278
RAS 11
RasGTPase activating protein 11
Rb 219, 278, 280, 281
Reactive angioendotheliomatosis 241
Reactive lymphoid hyperplasias (RLH) 168
Reactive oxygen species (ROS) 11
REAL classification 184
Receptor tyrosine kinase 226
RECQL2 278
RECQL3 278
Recurrent naevus 108
Reed naevus 117
Reed tumour 117
Reed-Sternberg (RS) cells 179, 180 207, 214
Regressing atypical histiocytosis 180
Regression 37, 38, 56, 71, 221, 249
Renal carcinoma 158
RET proto-oncogene 266, 278
Reticulated black solar lentigo 103
Reticulated melanotic macule 103
Reticulated seborrhoeic keratosis 42, 44

- Reticulohistiocytic granuloma 224
 Reticulohistiocytoma cutis 224
 Reticulohistiocytoma of the dorsum (Crosti disease) 196
 Reticulohistiocytosis 218, 224, 225
 Reticulohistiocytosis of the skin and synovia 224
 Reticulomatosis with giant cell histiocytes 224
 Rhabdoid squamous cell carcinoma (SCC) 20
 Rhabdomyomatous mesenchymal hamartoma (RMH) 252
 Rhabdomyomatous mesenchymal hamartoma (striated muscle hamartoma) 250
 Rhabdomyosarcoma 268
 Rheumatoid arthritis 241
 Rhinophyma 13
 RhoB 177
 Richter syndrome 206
 Rosai-Dorfman disease 221
 Rothmund-Thomson syndrome 30, 278
 Rubinstein-Taybi syndrome 154
 Rudimentary Verocay bodies 265
- S**
- S-100-beta 58
 Sarcoidosis 154, 241
 Sarcoma 63, 268, 283
 Scattered Factor XIIIa 260
 SCC See Squamous cell carcinoma
 Schöpf-Schultz-Passarge syndrome 142
 Schwann cells 81, 97, 266
 Schwannoid basal cell carcinoma (BCC) 19
 Schwannoma 231, 265, 292
 Sclerocornea 250
 Scleroderma-like Skin Changes 279
 Sclerosing basal cell carcinoma (BCC) 19
 Sclerosing cellular blue naevi 78
 Sclerosing epithelial hamartoma 152
 Sclerosing haemangioma 261
 Sclerosing sweat duct carcinoma 17, 25, 126
 Sclerotic fibroma 256
 Sclerotic or sclerosing fibroma 261
 Scrotal condylomata 35
 Sebaceousoma 162, 163
 Sebaceous adenoma 161, 162
 Sebaceous carcinoma 18, 138, 160, 161, 163
 Sebaceous epithelioma 162
 Sebaceous trichofolliculoma 157
 Sebocytes 14, 141, 148, 161-163
 Sebomatrixoma 162
 Seborrhoeic keratosis 17, 33, 39, 41-44, 47, 57, 103, 129, 156, 162, 163
 Seborrhoeic wart 41
 Secondary cutaneous follicular lymphoma (FL) 197
 Secondary skin involvement by diffuse large B-cell lymphoma 199
 Segmental regression 67
 Seizures 227, 283
 Senile haemangioma 233
 Senile wart 41
 Sentinel node (SN) biopsy 123
 Sertoli cell tumours of the testes, 291
 Sessile masses 253
 Sézary cells 169, 176
 Sézary syndrome 175, 177, 178, 190, 213
 Shadow cells 19, 148-151, 154, 155
 SHH signalling pathway See Sonic Hedgehog 287
 Shortened telomere length 216
 Shoulder phenomenon 106
 Signet ring cell apocrine carcinoma AC 136
 Signet-ring squamous cell carcinoma (SCC) 20, 25
 Simple lentigo 103, 104
 Simple lentigo and lentiginous melanocytic naevus 104
 Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) 221
 Sinusoidal haemangioma 234
 Sinusoidal pattern 221
 Site specific and Meyerson naevi 110
 Sjögren syndrome 261
 Skin homing T-cells 180, 187
 Skin homing T-helper cells 178
 Skin surface microscopy 57
 Skin types I and II 54
 Small cell melanoma 85, 88, 268
 Small cell naevoid melanoma 88
 Small keratin-filled cysts (milia) 19, 285
 Small lymphocytic lymphoma 205
 Small plaque parapsoriasis 215
 Smallpox 55
 Smooth and skeletal muscle tumours 250
- Smooth muscle hamartoma 250
 SMOOTHENED 14
 Socio-economic status 55
 Solar keratoses 11, 20, 30, 44, 70
 Solar lentigo 40, 43, 44, 47, 103
 Solar lentigo (lentigo senilis) 43
 Solid-cystic hidradenoma 143
 Solitary angiokeratoma 244
 Solitary circumscribed neuroma 265
 Solitary cutaneous myofibroma. 256
 Solitary cutaneous reticulohistiocytosis (SCR) 224
 Solitary mastocytoma 226
 Solitary sclerotic fibroma 256
 Somatostatin 273
 Sonic Hedgehog (SHH) 278, 287
 Spinal dysraphism 233
 Spinal malformation 242
 Spindle and epithelioid cell naevus 114
 Spindle cell haemangioendothelioma 239
 Spindle cell haemangioma 239
 Spindle cell melanoma 76
 Spindle-cell squamous cell carcinoma 22
 Spiradenocarcinoma 123, 130, 131, 135
 Spiradenocylindroma 145
 Spiradenoma 123, 130, 143, 144, 145, 268
 Spitz naevi 114-116,
 Spitzoid melanoma 89
 Spitzoid variant of naevoid melanoma 89
 Splaying of melanocytes 93
 Splenomegaly 193, 200
 Spongiotic change in melanocytic naevi 111
 Spongiotic dermatitis involving melanocytic naevi 111, 112
 Spontaneous neuroma 265
 Sprengel anomaly 285
 Sprengel deformity 286
 Squamoid sebaceous carcinoma 161
 Squamous cell carcinoma 20-25
 Squamous cell carcinoma de novo 11
 Squamous cell carcinoma in situ (SCCIS) 11, 26, 138
 Squamous eddies 42
 Sternal cleft defects 154
 Stewart-Treves syndrome 246
 Storiform collagenoma 256
 Striated muscle hamartoma 252

Stromelysin 3 153, 260, 262
 Stucco keratosis 41, 44
 Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) 182, 184, 185
 Subcutaneous T-cell lymphoma 221
 Subepidermal acanthoma 150
 Subepidermal fibrin deposits 59
 Subepidermal nodular fibrosis 261
 Sub-papillary vascular plexus 245
 Subungual and periungual fibroma 257
 Subungual haematoma 75
 Subungual keratoacanthoma 45, 46
 Subungual melanoma 57, 74
 Sulphur 234, 284
 Sun exposure 70
 Sunburns 54, 66, 68, 279
 Sunscreens 55
 Superficial basal cell carcinoma 15
 Superficial plantar warts (mosaic warts) 34
 Superficial spreading malignant melanoma (SSMM) 55, 66, 68, 70, 73, 74, 89, 107, 108, 119, 138
 Superficial warts (mosaic) 37
 Supernumerary digit 266, 267
 Surface immunoglobulins (sIg) 197
 Sutton naevus 118
 Sweat gland carcinoma 18, 133
 Sweat gland tumour 268
 Synaptophysin 269, 273
 Syringoacanthoma 141
 Syringoadenoma 146
 Syringocystadenoma papilliferum 123, 145, 146, 147
 Syringocystadenoma 146
 Syringofibroadenoma 142
 Syringofibroadenomatosis 142
 Syringoma 127, 140, 141, 148
 Syringomatous carcinoma 25, 126
 Syringotropic mucosis fungoides (MF) 173
 Systemic anaplastic large cell lymphoma (ALCL) 193
 Systemic cystic angiomyomatosis 249

T

T(11;14) (q13;q32) translocation 204
 T(11;18) involving the API2/MLT genes 195
 Tachycardia 227
 Tardive congenital naevus 93

Targetoid haemosiderotic haemangioma 234
 Tax 189
 T-cell / histiocyte-rich large B-cell lymphoma 199
 T-cell associated antigens 181, 187
 T-cell clonality in angiolymphoid hyperplasia with eosinophilia (ALHE) 238
 T-cell intracellular antigen (TIA-1) 183
 T-cell lymphoblastic leukaemia/lymphoma 210
 T-cell lymphoma 170, 184
 T-cell receptor 172, 185, 191, 209, 214, 215, 219
 T-cell receptor gamma gene rearrangement 172, 216
 T-cell/histiocyte-rich large B-cell lymphoma 199
 TCL1 209
 TCR gene 178, 185, 186, 187
 TCR-beta 171
 TCR-d 185
 TCRd1 185
 TdT 208, 210
 Telangiectasia 13, 16, 69, 71, 216, 226
 Telangiectasia macularis eruptiva perstans 226-228
 Telangiectatic mastocytosis 226
 Telomeric exhaustion 60
 Tenascin 148, 260
 Tethered cord syndrome 233
 TGF-beta 179
 TGF-beta receptor I and II 219
 TH2 172, 177
 The cutaneous lymphocyte antigen (CLA, HECA-452) 181
 Thomsen-Friedenreich antigen 161
 Thrombocytopaenia 193
 Thrombophlebitis 244
 Thrombosis 36, 234
 Thymidine dimer formation 30
 Thyroglossal duct sinus 253
 Thyroid adenoma 288
 Thyroid tumours 291
 Thyroid-transcription factor-1 273
 TIA-1 171, 180, 181, 185, 186, 187, 191, 192
 TIG-3 12
 Tingible body macrophages 213
 TMEP See Telangiectasia macularis eruptiva perstans 226-228
 Tobacco use 11, 13, 26
 Touton giant cells 222, 223
 Trabecular carcinoma 272
 Transforming growth factor-b1 254
 Translocation 195, 197, 205, 259
 Translocation between the X and Y chromosomes 250
 Translocation t(2;5) (p23;q35) 181
 Translocation t(11;22) (q24;q12) 269
 Transplant patient 40
 Traumatic neuroma 266, 267
 Trichilemmoma 155, 288, 289
 Trichoblastic (basal cell) carcinoma 152
 Trichoblastic carcinoma 13, 18, 127
 Trichoblastic fibroma 152
 Trichoblastoma 15, 18, 123, 124, 152, 153, 156
 Trichochlamydocarcinoma 150
 Trichodiscoma 157-159
 Trichoepithelioma 15, 18, 95, 144, 152
 Trichofolliculoma 156, 157
 Trichogeronimoma 152
 Trichohyaline granules 14, 123
 Tricholemmoma 155, 156
 Trichothiodystrophy (TTD) 284
 Trisomy 8 178
 Trisomy 21 140
 Triton tumour 253
 TSC1 (tuberous sclerosis gene 1) 257, 278
 TSC2 (tuberous sclerosis gene 2) 257, 278
 TTF-1 (thyroid-transcription factor-1) 273
 Tuberin 278
 Tuberous sclerosis 257, 278
 Tubular adenoma 125, 145, 146
 Tubular apocrine adenoma 145, 146
 Tubular carcinoma 125
 Tubular papillary adenoma 145
 Tubulopapillary hidradenoma 145
 Tufted angioma 233, 236, 239-241
 Tufted haemangioma 239
 Tumour of the follicular infundibulum 158
 Tumoural melanosis 67
 Turban tumour 145
 Turner syndrome 154
 Tyndall effect 95
 Type IV collagen 78, 115, 155
 Types II and IV collagen 148
 Tyrosinase activity 60
 Tyrosine kinase 273

U

Ulex europaeus I lectin 237, 243, 247
Ultraviolet A (UVA) 30
Ultraviolet B radiation 11, 20, 26, 30, 33, 105
Ultraviolet radiation 36, 54, 55
Unclassified plantar melanoma 73
Ungual melanosis 103
Ungual melanotic macule 103
Unilateral verrucous haemangioma 242
Unscheduled DNA synthesis 283
Upper extremity and syndactyly 253
Urticaria pigmentosa 226, 227
UV radiation (UVR) 11, 13, 14, 26, 54, 55, 282, 283, 284
Uveal melanoma (UM) 79, 280
UVR See Ultraviolet radiation

V

Vaccination 55, 63
Vaccination scars 13
Vaccinia vaccine 55
Valvular cardiac disease 241
Varicelliform scars 192
Varicocoele 244
Vascular endothelial growth factor receptor-3 (VEGFR-3) 235, 247
Vascular malformations 233, 240, 243, 244
Vascular tumours 233
Vasculitis 200, 202, 218
Vd2 185
VEGFR-3 See Vascular endothelial growth factor receptor-3
Venous malformation 239
Venous ulcer 13
Verruca peruviana 241
Verruca plana 38
Verruca plana juvenilis 38
Verruca plantaris 35, 37
Verruca vulgaris 36
Verrucae palmares (deep palmar or hand warts) 34
Verrucae planae (plane warts, flat warts) 34
Verrucae plantares (deep foot warts, myrmecia) 34
Verrucae vulgares (common warts) 34
Verrucas 34
Verrucous carcinoma 22, 23, 37
Verrucous haemangioma 242

Verrucous melanoma 57
Verrucous phenotype 57
Verrucous squamous cell carcinoma 22
Verruga peruviana 241
Vinyl chloride 11
Vitiligo 30, 289
Volar melanosis 103
Volar melanotic macule 103
Von Recklinghausen disease 278
Vulvar intraepithelial neoplasia (VIN III) 26
Vulvar melanoma 111
Vulvar melanotic macule 103
Vulvar naevi 110
VWF (von Willebrand factor, VIIIrAg) 235, 238-240, 246, 259

W

Wart 36-38, 75, 155, 242, 289
Warty dyskeratoma 39, 40
Weibel-Palade bodies 240
Werner syndrome b 278
Wiskott-Aldrich syndrome 202, 237
Witten and Zak type 45
Wolffian ducts 147
Woringer-Kolopp disease (WKD) 173

X

Xanthoerythrodermia perstans 215
Xanthogranuloma 218
Xanthoma multiplex 222
Xanthomatous 219
Xeroderma pigmentosum (XP) 11, 30, 57, 64, 68, 72, 278, 282-284
Xeroderma pigmentosum variant 282
X-linked lymphoproliferative syndrome 202
XP See Xeroderma pigmentosum
XP Complementation groups 283
XP Microdeletion syndrome 250
XPA 278, 282-284
XPB 278, 282, 284
XPC 278, 282, 284
XPD 278, 282, 284
XPE 278, 282, 284
XPF 278, 282, 284
XPG 278, 282-284

Z

ZAP-70 206