



World Health Organization Classification of Tumours



International Agency for Research on Cancer (IARC)

4th Edition

WHO Classification of Tumours of the Central Nervous System

Edited by

David N. Louis

Hiroko Ohgaki

Otmar D. Wiestler

Webster K. Cavenee

International Agency for Research on Cancer

Lyon, 2007

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Series Editors Fred T. Bosman, M.D.
 Elaine S. Jaffe, M.D.
 Sunil R. Lakhani, M.D.
 Hiroko Ohgaki, Ph.D.

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Editors David N. Louis, M.D.
 Hiroko Ohgaki, Ph.D.
 Otmar D. Wiestler, M.D.
 Webster K. Cavenee, Ph.D.

Layout Sébastien Antoni
 Marlen Grassinger

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WHO Classification of Tumours of the Nervous System

TUMOURS OF NEUROEPITHELIAL TISSUE		Neuronal and mixed neuronal-glial tumours	
Astrocytic tumours		Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	9493/0
Pilocytic astrocytoma	9421/1 ¹	Desmoplastic infantile astrocytoma/ ganglioglioma	9412/1
Pilomyxoid astrocytoma	9425/3*	Dysembryoplastic neuroepithelial tumour	9413/0
Subependymal giant cell astrocytoma	9384/1	Gangliocytoma	9492/0
Pleomorphic xanthoastrocytoma	9424/3	Ganglioglioma	9505/1
Diffuse astrocytoma	9400/3	Anaplastic ganglioglioma	9505/3
Fibrillary astrocytoma	9420/3	Central neurocytoma	9506/1
Gemistocytic astrocytoma	9411/3	Extraventricular neurocytoma	9506/1*
Protoplasmic astrocytoma	9410/3	Cerebellar liponeurocytoma	9506/1*
Anaplastic astrocytoma	9401/3	Papillary glioneuronal tumour	9509/1*
Glioblastoma	9440/3	Rosette-forming glioneuronal tumour of the fourth ventricle	9509/1*
Giant cell glioblastoma	9441/3	Paraganglioma	8680/1
Gliosarcoma	9442/3		
Gliomatosis cerebri	9381/3		
Oligodendroglial tumours		Tumours of the pineal region	
Oligodendrogioma	9450/3	Pineocytoma	9361/1
Anaplastic oligodendrogioma	9451/3	Pineal parenchymal tumour of intermediate differentiation	9362/3
Oligoastrocytic tumours		Pineoblastoma	9362/3
Oligoastrocytoma	9382/3	Papillary tumour of the pineal region	9395/3*
Anaplastic oligoastrocytoma	9382/3		
Ependymal tumours		Embryonal tumours	
Subependymoma	9383/1	Medulloblastoma	9470/3
Myxopapillary ependymoma	9394/1	Desmoplastic/nodular medulloblastoma	9471/3
Ependymoma	9391/3	Medulloblastoma with extensive nodularity	9471/3*
Cellular	9391/3	Anaplastic medulloblastoma	9474/3*
Papillary	9393/3	Large cell medulloblastoma	9474/3
Clear cell	9391/3	CNS primitive neuroectodermal tumour	9473/3
Tanycytic	9391/3	CNS Neuroblastoma	9500/3
Anaplastic ependymoma	9392/3	CNS Ganglioneuroblastoma	9490/3
Choroid plexus tumours		Medulloepithelioma	9501/3
Choroid plexus papilloma	9390/0	Ependymoblastoma	9392/3
Atypical choroid plexus papilloma	9390/1*	Atypical teratoid / rhabdoid tumour	9508/3
Choroid plexus carcinoma	9390/3		
Other neuroepithelial tumours		TUMOURS OF CRANIAL AND PARASPINAL NERVES	
Astroblastoma	9430/3	Schwannoma (neurilemoma, neurinoma)	9560/0
Chordoid glioma of the third ventricle	9444/1	Cellular	9560/0
Angiocentric glioma	9431/1*	Plexiform	9560/0
		Melanotic	9560/0
		Neurofibroma	9540/0
		Plexiform	9550/0

¹ Morphology code of the International Classification of Diseases for Oncology (ICD-O) (614A) 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.

* The italicised numbers are provisional codes proposed for the 4th edition of ICD-O. While they are expected to be incorporated into the next ICD-O edition, they currently remain subject to change.

Perineurioma		Haemangiopericytoma	9150/1
Perineurioma, NOS	9571/0	Anaplastic haemangiopericytoma	9150/3
Malignant perineurioma	9571/3	Angiosarcoma	9120/3
		Kaposi sarcoma	9140/3
Malignant peripheral		Ewing sarcoma - PNET	9364/3
nerve sheath tumour (MPNST)			
Epithelioid MPNST	9540/3	Primary melanocytic lesions	
MPNST with mesenchymal differentiation	9540/3	Diffuse melanocytosis	8728/0
Melanotic MPNST	9540/3	Melanocytoma	8728/1
MPNST with glandular differentiation	9540/3	Malignant melanoma	8720/3
		Meningeal melanomatosis	8728/3
TUMOURS OF THE MENINGES			
Tumours of meningotheelial cells		Other neoplasms related to the meninges	
Meningioma	9530/0	Haemangioblastoma	9161/1
Meningothelial	9531/0		
Fibrous (fibroblastic)	9532/0		
Transitional (mixed)	9537/0		
Psammomatous	9533/0	LYMPHOMAS AND HAEMATOPOIETIC NEOPLASMS	
Angiomatous	9534/0	Malignant lymphomas	9590/3
Microcystic	9530/0	Plasmacytoma	9731/3
Secretory	9530/0	Granulocytic sarcoma	9930/3
Lymphoplasmacyte-rich	9530/0		
Metaplastic	9530/0		
Chordoid	9538/1	GERM CELL TUMOURS	
Clear cell	9538/1	Germinoma	9064/3
Atypical	9539/1	Embryonal carcinoma	9070/3
Papillary	9538/3	Yolk sac tumour	9071/3
Rhabdoid	9538/3	Choriocarcinoma	9100/3
Anaplastic (malignant)	9530/3	Teratoma	9080/1
		Mature	9080/0
Mesenchymal tumours		Immature	9080/3
Lipoma	8850/0	Teratoma with malignant transformation	9084/3
Angiolipoma	8861/0	Mixed germ cell tumour	9085/3
Hibernoma	8880/0		
Liposarcoma	8850/3	TUMOURS OF THE SELLAR REGION	
Solitary fibrous tumour	8815/0	Craniopharyngioma	9350/1
Fibrosarcoma	8810/3	Adamantinomatous	9351/1
Malignant fibrous histiocytoma	8830/3	Papillary	9352/1
Leiomyoma	8890/0	Granular cell tumour	9582/0
Leiomyosarcoma	8890/3	Pituicytoma	9432/1*
Rhabdomyoma	8900/0	Spindle cell oncocytoma	
Rhabdomyosarcoma	8900/3	of the adenohypophysis	8291/0*
Chondroma	9220/0		
Chondrosarcoma	9220/3		
Osteoma	9180/0		
Osteosarcoma	9180/3		
Osteochondroma	9210/0	METASTATIC TUMOURS	
Haemangioma	9120/0		
Epithelioid haemangioendothelioma	9133/1		

WHO grading of tumours of the central nervous system

P. Kleihues
D.N. Louis
O.D. Wiestler
P.C. Burger
B.W. Scheithauer

Histological grading is a means of predicting the biological behaviour of a neoplasm. In the clinical setting, tumour grade is a key factor influencing the choice of therapies, particularly determining the use of adjuvant radiation and specific chemotherapy protocols. Since its first publication in 1979, the WHO Classification of Tumours of the Nervous System has included a grading scheme that is a "malignancy scale" ranging across a wide variety of neoplasms rather than a strict histological grading system [1121, 1122, 2513]. WHO grading is widely used, having incorporated or largely replaced other previously published grading systems. Although it is not a requirement for application of the WHO classification for some tumours, including gliomas and meningiomas, numerical WHO grades are useful additions to the diagnosis. The WHO Working Group responsible for the 4th Edition has expanded its application to include additional entities; however, since the number of cases of some newly defined entities is limited, the assignment of grades is preliminary, pending publication of additional data and long-term follow-up.

Grading across tumour entities

Grade I lesions generally include tumours with low proliferative potential and the possibility of cure following surgical resection alone. Lesions designated grade II are generally infiltrative in nature and, despite low level proliferative activity, often recur. Some type II tumours tend to progress to higher grades of malignancy, for example, low-grade diffuse astrocytomas that transform to anaplastic astrocytoma and glioblastoma. Similar transformation occurs in oligodendrogloma and mixed gliomas. The designation grade III is generally reserved for lesions with histological evidence of malignancy, including nuclear atypia and brisk mitotic activity. In most settings, patients with grade III tumours receive adjuvant radiation and/or chemotherapy. The designation grade IV is

assigned to cytologically malignant, mitotically active, necrosis-prone neoplasms often associated with rapid pre- and postoperative disease evolution and a fatal outcome. Examples of grade IV neoplasms include glioblastoma, most embryonal neoplasms and many sarcomas as well. Although not an essential feature, widespread infiltration of surrounding tissue and a propensity for craniospinal dissemination characterize some grade IV neoplasms.

Grading of astrocytic tumours

Grading has been systematically evaluated and successfully applied to a spectrum of diffusely infiltrative astrocytic tumours. These neoplasms are graded in a three-tiered system similar to that of the Ringertz [1891], St. Anne-Mayo [421] and the previously published WHO schemes [2513]. As currently defined by the WHO, tumours with cytological atypia alone are considered grade II (diffuse astrocytoma), those also showing anaplasia and mitotic activity are considered grade III (anaplastic astrocytoma), and tumours additionally showing microvascular proliferation and/or necrosis are WHO grade IV. This system is similar to the St. Anne/Mayo classification [421], with the only major difference being grade I; in the WHO system, grade I is assigned to the more circumscribed pilocytic astrocytoma, whereas the St. Anne/Mayo classification assigns grade 1 to an exceedingly rare diffuse astrocytic tumour without atypia. St. Anne/Mayo grades 2 to 4 closely correspond to WHO II to IV. In the St. Anne/Mayo system [421], the definition of histopathological features is important. Atypia is defined as variation in nuclear shape or size with accompanying hyperchromasia. Mitoses must be unequivocal, but no special recognition is given to their number or morphology. Since the finding of a solitary mitosis in an ample specimen does not confer grade III behaviour, separation of grade II from grade III tumours may be more reliably achieved by determination of MIB-1 labelling

indices {676, 876, 1574}. Endothelial proliferation is defined as apparent multilayering of endothelium, rather than simple hypervascularity, or glomeruloid vasculature. Necrosis may be of any type; perinecrotic palisading need not be present. Simple apposition of cellular zones with intervening pallor suggestive of incipient necrosis is insufficient. The aforementioned criteria make their appearance in a predictable sequence, i.e., atypia followed in turn by mitotic activity and increased cellularity and finally microvascular proliferation and/or necrosis.

Tumour grade as a prognostic factor

WHO grade is one component of a combination of criteria used to predict a response to therapy and outcome. Other criteria include clinical findings, such as age of the patient, performance status and tumour location; radiological features such as contrast enhancement; extent of surgical resection; proliferation indices; and genetic alterations. For each tumour entity, combinations of these parameters contribute to an overall estimate of prognosis. Despite these variables, patients with WHO grade II tumours typically survive more than 5 years, and those with grade III tumours survive 2-3 years. The prognosis of patients with WHO grade IV tumours depends largely upon whether effective treatment regimens are available. The majority of glioblastoma patients, particularly the elderly, succumb to the disease within a year. For those with other grade IV neoplasms, the outlook may be considerably better. For example, cerebellar medulloblastomas and germ cell tumours such as germinomas, both WHO grade IV, are rapidly fatal if untreated, while state-of-the-art radiation and chemotherapy result in 5-year survival rates exceeding 60% and 80%, respectively.

WHO grades of CNS tumours

	I	II	III	IV		I	II	III	IV
Astrocytic tumours									
Subependymal giant cell astrocytoma	•						•		
Pilocytic astrocytoma	•						•		
Pilomyxoid astrocytoma		•					•		
Diffuse astrocytoma		•							
Pleomorphic xanthoastrocytoma		•							
Anaplastic astrocytoma			•						
Glioblastoma					•				
Giant cell glioblastoma					•				
Gliosarcoma					•				
Oligodendroglial tumours									
Oligodendrogioma		•							
Anaplastic oligodendrogioma				•					
Oligoastrocytic tumours									
Oligoastrocytoma			•						
Anaplastic oligoastrocytoma				•					
Ependymal tumours									
Subependymoma	•								
Myxopapillary ependymoma	•								
Ependymoma		•							
Anaplastic ependymoma				•					
Choroid plexus tumours									
Choroid plexus papilloma	•								
Atypical choroid plexus papilloma		•							
Choroid plexus carcinoma				•					
Other neuroepithelial tumours									
Angiocentric glioma	•								
Chordoid glioma of the third ventricle			•						
Neuronal and mixed neuronal-glial tumours									
Gangliocytoma	•								
Ganglioglioma	•								
Anaplastic ganglioglioma				•					
Desmoplastic infantile astrocytoma and ganglioglioma	•								
Dysembryoplastic neuroepithelial tumour	•								
Pineal tumours									
Pineocytoma		•							
Pineal parenchymal tumour of intermediate differentiation			•			•			
Pineoblastoma									•
Papillary tumour of the pineal region				•		•			
Embryonal tumours									
Medulloblastoma									•
CNS primitive neuroectodermal tumour (PNET)									•
Atypical teratoid / rhabdoid tumour									•
Tumours of the cranial and paraspinal nerves									
Schwannoma		•							
Neurofibroma		•							
Perineurioma		•	•			•			
Malignant peripheral nerve sheath tumour (MPNST)			•			•			•
Meningeal tumours									
Meningioma		•							
Atypical meningioma						•			
Anaplastic / malignant meningioma									•
Haemangiopericytoma						•			
Anaplastic haemangiopericytoma									•
Haemangioblastoma		•							
Tumours of the sellar region									
Craniopharyngioma		•							
Granular cell tumour of the neurohypophysis		•							
Pituicytoma		•							
Spindle cell oncocyrtoma of the adenohypophysis		•							

CHAPTER 1

Astrocytic Tumours

Pilocytic astrocytoma (WHO grade I)

A relatively circumscribed, slowly growing, often cystic astrocytoma occurring in children and young adults, histologically characterized by a biphasic pattern with varying proportions of compacted bipolar cells associated with Rosenthal fibers and loose-textured multipolar cells associated with microcysts and eosinophilic granular bodies/hyaline droplets.

Subependymal giant cell astrocytoma (WHO grade I)

A benign, slowly growing tumour typically arising in the wall of the lateral ventricles and composed of large ganglioid astrocytes (See Chapter 13, Tuberous sclerosis complex and subependymal giant cell astrocytoma).

Pleomorphic xanthoastrocytoma (WHO grade II)

An astrocytic neoplasm with a relatively favourable prognosis, typically encountered in children and young adults, with superficial location in the cerebral hemispheres and involvement of the meninges; characteristic histological features include pleomorphic and lipidized cells expressing GFAP and often surrounded by a reticulin network as well as eosinophilic granular bodies.

Diffuse astrocytoma (WHO grade II)

A diffusely infiltrating astrocytoma that typically affects young adults and is characterized by a high degree of cellular differentiation and slow growth; the tumour occurs throughout the CNS but is preferentially located supratentorially and has an intrinsic tendency for malignant progression to anaplastic astrocytoma and, ultimately, glioblastoma.

Anaplastic astrocytoma (WHO grade III)

A diffusely infiltrating malignant astrocytoma that primarily affects adults, is preferentially located in the cerebral hemispheres, and is histologically characterized by nuclear atypia, increased cellularity and significant proliferative activity. The tumour may arise from diffuse astrocytoma WHO grade II or *de novo*, i.e. without evidence of a less malignant precursor lesion, and has an inherent tendency to undergo progression to glioblastoma.

Glioblastoma (WHO grade IV)

The most frequent primary brain tumour and the most malignant neoplasm with predominant astrocytic differentiation; histopathological features include nuclear atypia, cellular pleomorphism, mitotic activity, vascular thrombosis, microvascular proliferation and necrosis. It typically affects adults and is preferentially located in the cerebral hemispheres. Most glioblastomas manifest rapidly *de novo*, without recognizable precursor lesions (primary glioblastoma). Secondary glioblastomas develop slowly from diffuse astrocytoma WHO grade II or anaplastic astrocytoma (WHO grade III). Due to their invasive nature, glioblastomas cannot be completely resected, and despite progress in radio/chemotherapy, less than half of patients survive more than a year, with older age as the most significant adverse prognostic factor.

Gliomatosis cerebri

A diffuse glioma (usually astrocytic) growth pattern consisting of exceptionally extensive infiltration of a large region of the central nervous system, with involvement of at least three cerebral lobes, usually with bilateral involvement of the cerebral hemispheres and/or deep gray matter, and frequent extension to the brain stem, cerebellum, and even the spinal cord. Gliomatosis cerebri most commonly displays an astrocytic phenotype, although oligodendroglomas and mixed oligoastrocytomas can also present with the gliomatosis cerebri growth pattern.

Pilocytic astrocytoma

B.W. Scheithauer
C. Hawkins
T. Tihan
S.R. Vandenberg
P.C. Burger

Definition

A relatively circumscribed, slowly growing, often cystic astrocytoma occurring in children and young adults, histologically characterized by a biphasic pattern with varying proportions of compacted bipolar cells associated with Rosenthal fibers and loose-textured multipolar cells associated with microcysts and eosinophilic granular bodies/hyaline droplets.

ICD-O code 9421/1

Grading

Pilocytic astrocytomas correspond to WHO grade I.

Incidence

Pilocytic astrocytomas comprise approximately 5–6% of all gliomas [305] with an overall incidence of 0.37 per 100 000 persons per year. Pilocytic astrocytoma is the most common glioma in children, in whom the majority (67%) arise in the cerebellum [1625].

Age and sex distribution

Pilocytic astrocytoma most commonly develops, without a clear gender predilection, during the first two decades of life with an age-adjusted incidence rate of 0.8 per 100 000 persons per year. From 0–14 years and 15–19 years, it comprises about 21% and 16% of CNS tumours, respectively [305]. In a study of 1195 paediatric tumours from a single institution, pilocytic astrocytoma was the single most common tumour (18%) in the cerebral compartment [1925]. In adults, these astrocytomas tend to appear one decade earlier (mean age 22 years) than low-grade diffusely infiltrating cerebral astrocytomas [648] but relatively few arise in patients older than 50 years.

Localization

Pilocytic astrocytomas arise throughout the neuraxis; however in the paediatric population more tumours arise in the infratentorial region. Preferred sites include the optic nerve (optic nerve glioma) [873], optic chiasm/hypothalamus [1905],

thalamus and basal ganglia [1432], cerebral hemispheres [592, 1061, 1766], cerebellum (cerebellar astrocytoma) [405, 798], and brain stem (dorsal exophytic brain stem glioma) [247, 249, 1769]. In the paediatric population, the most common supratentorial site is the hypothalamus/optic pathways followed by the thalamic/basal ganglia region [1925]. Pilocytic astrocytomas of the spinal cord are less frequent, but not uncommon [1482, 1835, 1939], and in children represent about 11% of spinal tumours [1925]. Large hypothalamic, thalamic, and brain stem lesions may largely occupy the ventricle, their site of origin being difficult to define. In the spinal cord, these tumours tend to occur in older patients than at other sites and comprise a significant proportion (58%) of spinal astrocytic tumours [1482].

Clinical features

Signs and symptoms

Pilocytic astrocytomas produce focal neurological deficits or non-localizing signs, e.g. macrocephaly, headache, endocrinopathy, or increased intracranial pressure due to mass effect or ventricular obstruction. Seizures are uncommon since the lesions infrequently involve the cerebral cortex [356, 592]. Given their slow rate of growth, the clinical presentation of pilocytic tumours is generally that of a slowly evolving lesion. Pilocytic astrocytomas of the optic pathways often

produce visual loss. Proptosis may be seen with intraorbital examples. Early, radiologically detected lesions may be unassociated with visual symptoms or ophthalmologic deficits [873, 1333]. Hypothalamic/pituitary dysfunction, including obesity and diabetes insipidus, is often but not invariably apparent in large hypothalamic examples [1905]. Some hypothalamic-chiasmatic lesions of young children have been associated with leptomeningeal seeding and a poor outcome [1717]. It is unclear whether such tumours represent a distinct entity [388, 2245].

Pilocytic astrocytomas of the thalamus generally present with signs of CSF obstruction or neurological deficits, such as hemiparesis, due to internal capsule compression.

Cerebellar pilocytic astrocytomas usually present in the first two decades with clumsiness, worsening headache, nausea and vomiting. Brain stem examples usually cause hydrocephalus or signs of brain stem dysfunction. In contrast to diffuse astrocytoma of the pons, which produces symmetric “pontine hypertrophy”, pilocytic tumours of the brain stem are usually dorsal and exophytic or just into the cerebellopontine angle. Spinal cord examples produce non-specific signs of an expanding mass [1482, 1835, 1939].

Neuroimaging

By either CT or MRI, pilocytic astrocytomas are well-circumscribed and contrast-enhancing [626, 1283]. Only a minority are calcified. Tumours of the optic nerve, being somewhat restrained in their outward expansion by the optic sheath, grow along the course of the nerve to produce a fusiform mass. Optic pathway lesions have only a limited capacity to spread posteriorly, for example from optic nerve to chiasm or from chiasm to optic tracts. Although sensitive neuroimaging may suggest extensive infiltration, the relative contributions of tumour tissue, edema and Wallerian degeneration to the observed T2 hyperintensity is unclear.

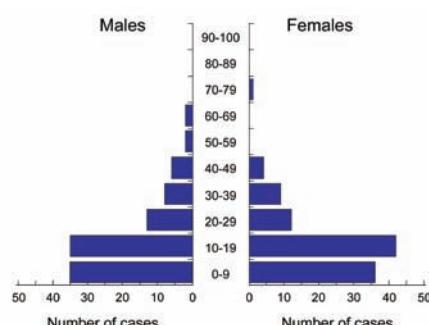


Fig. 1.01 Age and sex distribution of pilocytic astrocytoma, based on biopsies from 205 patients treated at the University Hospital, Zurich.

Pilocytic astrocytomas are found at all levels of the brain stem, are relatively discrete, often exophytic, and variably contrast enhancing [249, 1769]. Cyst formation is common. These characteristics distinguish them from diffuse astrocytomas (WHO grade II) of the basal pons which only show contrast enhancement after progression to anaplastic astrocytoma or glioblastoma. A diagnostically important feature suggesting pilocytic astrocytoma or some other WHO grade I lesion is cyst formation [1671A], a common feature of cerebellar, spinal cord and cerebral hemispheric examples. Cysts may be either solitary and massive, the tumour being a mural nodule, or multiple, smaller and intratumoural.

Macroscopy

Most pilocytic astrocytomas are soft, grey and rather discrete. Intra- or paratumoural cyst formation is common. In spinal cord examples, syrinx formation may be conspicuous and can extend over many segments [1482, 1835]. Chronic lesions may contain calcium or haemosiderin deposits. Optic nerve tumours also often show collar-like involvement of the subarachnoid space [2153]. Primary diffuse leptomeningeal pilocytic astrocytoma is a rarity [194].

Histopathology

This astrocytic tumour of low to moderate cellularity exhibits an often biphasic pattern with varying proportions of compacted bipolar cells with Rosenthal fibers and loose-textured multipolar cells with microcysts and granular bodies/hyaline droplets. Rare mitosis, hyperchromatic and pleomorphic nuclei, glomeruloid vascular proliferation, infarct-like necrosis and infiltration of leptomeninges are compatible with the diagnosis of pilocytic astrocytoma and are not signs of malignancy.

Due to heterogeneity of histologic features, smear preparations of pilocytic astrocytomas show considerable cytological variation. Basic cytologies are seen, often in combination. Compact portions of the tumour yield bipolar piloid cells, long, hair-like processes that often extend across a full microscopic field, and Rosenthal fibers. Their nuclei are typically elongate and cytologically bland. Due to their high content of refractile, eosinophilic fibrils, these cells are strongly glial fibrillary acidic protein (GFAP) immunopositive.

Cells derived from microcystic areas are often termed "protoplasmic astrocytes" and possess round to oval, cytologically bland nuclei, a small cell body and relatively short, cobweb-like processes which are fibril-poor and only weakly GFAP-positive. This growth pattern is typically associated with eosinophilic granular bodies and/or hyaline droplets. Less frequently seen are cells closely resembling oligodendrocytes. Cells indistinguishable from those of diffuse astrocytoma, WHO grade II, are often seen within peripheral, more infiltrative parts of the tumour. While many pilocytic astrocytomas are benign, some show considerable hyperchromasia and pleomorphism. Rare mitoses are seen in up to 30%. In occasional, often cerebellar tumours, a diffuse growth pattern overshadows more typical compact and

microcystic features. In such cases, finding hyperchromatic nuclei or the occasional mitotic figure can cause confusion with high-grade diffuse astrocytoma. Less worrisome are obvious degenerative atypia with pleomorphism, smudgy chromatin, and nuclear-cytoplasmic pseudo-inclusions, frequently seen in long-standing lesions. The designation 'pennies on a plate' describes the circumferential localization of multiple nuclei within large or giant cells [798]. Hyalinized and glomeruloid vessels are prominent features of pilocytic astrocytoma. Necrosis, when seen, is often infarct-like and non-palisading. Perivascular lymphocytes may also be seen. Since pilocytic astrocytomas to some extent overrun normal tissue, pre-existing neurons are sometimes trapped. Such lesions should be distinguished from ganglion cell tumours.

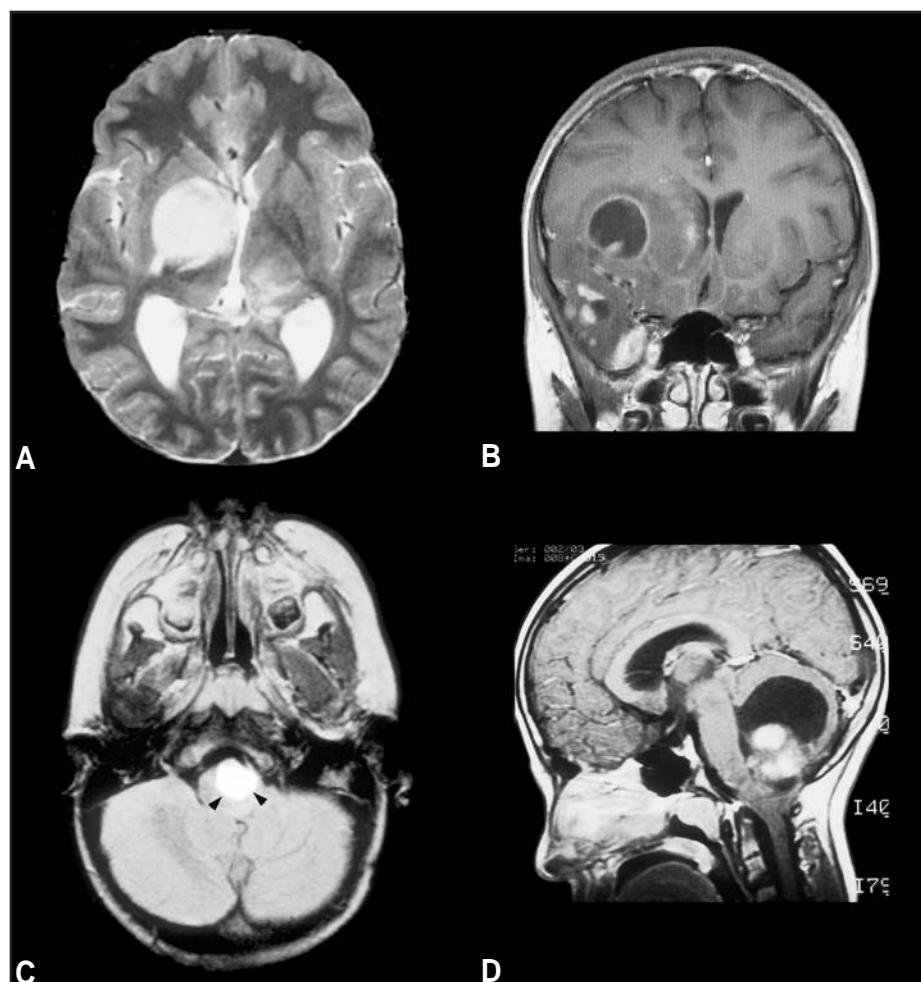


Fig. 1.02 Neuroimaging of pilocytic astrocytoma. A Solid, well-circumscribed hyperintense hemispheric lesion in a T2-weighted image. B Pilocytic astrocytoma of the frontal lobe presenting on T1 MRI as a hyperintense mural nodule with a large cyst. C Discrete pilocytic astrocytoma in the medulla (T1 MRI). D Cystic cerebellar lesion with a contrast-enhancing mural nodule.

Rosenthal fibers

These tapered corkscrew-shaped, brightly eosinophilic, hyaline masses are intracytoplasmic in location, a fact best seen on smear. Rosenthal fibers are most common in compact, piloid tissue. They appear bright blue on a Luxol fast blue (LFB) stain. Although helpful in diagnosis, their presence is not required. Lastly, Rosenthal fibers are neither specific to pilocytic astrocytoma nor indicative of neoplasia. They are often seen in ganglioglioma and are a common finding in chronic reactive gliosis. Densely fibrillar, paucicellular lesions containing Rosenthal fibers are as likely to be reactive gliosis as pilocytic astrocytoma. Ultrastructurally, Rosenthal fibers lie within astrocytic processes and consist of amorphous, electron-dense elements surrounded by intermediate (glial) filaments {475, 1246}. Being composed of α -B crystallin {704}, they lack GFAP immunoreactivity at all but their fibral rich periphery.

Eosinophilic granular bodies (EGB)

EGBs form globular aggregates within astrocytic processes. Brightly eosinophilic in H&E sections and PAS-positive, they show α -1-antichymotrypsin and α -1-antitrypsin immunoreactivity {1062}. EGBs are best seen in smear preparations. Their intracellular localization is usually not discernible in tissue sections. EGBs are an important diagnostic feature of several neoplasms, including ganglion cell tumours and pleomorphic xanthoas-

trocytoma, but again are not indicative of neoplasia. Occasional examples occur in diffusely infiltrating astrocytomas, usually after radiotherapy.

Vascularity

Pilocytic astrocytomas are highly vascular, as is evidenced by their contrast enhancement {626, 1283}. Although generally obvious in H&E sections, it is accentuated in *Ulex europeus* preparations or on immunostains for basement membrane (collagen IV, laminin) or endothelial cells (CD31, CD34). Also seen lining tumoural cyst walls and occasionally at a distance from the lesion, such glomeruloid vasculature should not prompt tumour misclassification or over-grading. Ultrastructural studies have shown fenestration of endothelium and a variety of abnormalities {2205}. Endothelial proliferation, a feature of high-grade diffuse astrocytic tumours, is generally not seen in conventional pilocytic tumours.

Regressive changes

Given the indolent nature and often slow clinical evolution of pilocytic astrocytomas, it is not surprising that regressive changes are seen. Markedly hyalinized, sometimes ectatic vessels are one such feature. When neoplastic cells are scant, it can even be difficult to distinguish the tumour from cavernous angioma with accompanying piloid gliosis. Evidence of previous haemorrhage (haemosiderin) further augments the likeness. Presentation

with acute haemorrhage is infrequent. Calcification, infarct-like necrosis, and lymphocytic infiltrates are additional examples of regressive changes {908}. On balance, calcification is an infrequent finding, only rarely seen in optic nerve or hypothalamic/thalamic tumours, or in superficially situated cerebral examples. Cysts are a common feature of pilocytic astrocytoma, especially in the locations specified above. Single or multiple, their fluid content is apparently rich in factors capable of stimulating vascular proliferation. Such neovascularity often lines cyst walls, thus explaining the narrow band of intense contrast enhancement seen at the circumference of some cysts. One frequently sees dense piloid tissue with accompanying Rosenthal fibers external to this vascular layer. When this layer is narrow and well defined from surrounding normal tissue, it may be considered reactive in nature. In other instances, the glial zone is more prominent, less well demarcated, and resembles tumour. Surgeons generally assume that the walls of large cysts are non-neoplastic and do not attempt resection of the cyst walls.

Tissue patterns

Although most pilocytic astrocytomas appear as a clearly defined clinical, radiologic, and pathologic entity, they exhibit a wide range of tissue patterns, sometimes several within the same lesion {257}. This is further complicated by a lack of tumour-specific immunohistochemical, cytogenetic and molecular markers. Some pathologists accept a wide range of patterns, whereas others are less accepting of what to them are unproven variants. The classic lesion consists of often alternating compact tissue composed of piloid cells and microcystic tissue rich in so-called protoplasmic astrocytes. This biphasic pattern is best seen in cerebellar tumours. Microcysts often contain peripherally vacuolated colloid. EGBs occur mainly in microcystic tissue, whereas Rosenthal fibers populate compact regions. A variant of the compact, piloid pattern occurs when the elongate cells are less compact but separated by mucin. In such cases, individual cell processes can be visualized and cell shape varies to include more full-bodied and pleomorphic, less obviously piloid cells. A distinctive lobular pattern results when leptomeningeal involvement engenders a

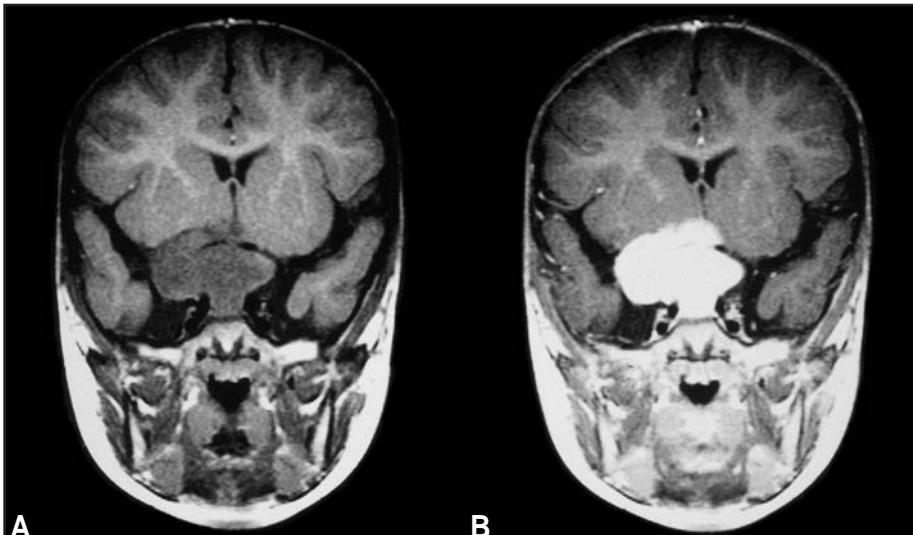


Fig. 1.03 Pilocytic astrocytoma of the optic nerve and chiasm. A Coronal T1-weighted MRI shows a well-demarcated lesion with (B) intense gadolinium (Gd)-enhancement. The tumour causes a compression and shift of the adjacent fronto-basal brain structures.

desmoplastic reaction. At this site, tissue texture varies but Rosenthal fibers are usually abundant.

Oligodendrogloma-like cells may be seen in pilocytic astrocytomas, especially in cerebellar examples. Arranged in sheets or dispersed within parenchyma, the overall appearance is that of an oligodendrogloma, particularly in a limited sample. It is the finding of foci of classic pilocytic astrocytoma that usually permits the correct classification of these lesions. A striking feature in some pilocytic astrocytomas is alignment of cells in prominent, regimented palisades. Such enfilades resemble those of what was termed the "primitive polar spongioblastoma," which is thought to be more a tissue pattern than a defined tumour entity and is therefore no longer included in the WHO classification. Tumours with distinctive palisades, clusters, or organoid cell aggregates are examples of contentious lesions. The same is true of mucin-rich spindle cell neoplasms. Although astrocytomas in children are usually assigned to either the pilocytic or fibrillary type, in reality there are many which do not fit clearly into either category. In some instances, small biopsy size contributes to difficulties in classification.

Growth pattern

As a rule, pilocytic astrocytomas are macroscopically somewhat discrete. Thus, when anatomy permits, e.g. cerebellum or cerebral hemispheres, many can be removed *in toto* [592, 798, 1766]. Microscopically, however, many lesions are not well defined with respect to surrounding brain. Typical lesions permeate parenchyma for a distance of millimetres to several centimetres. As a result, neurons may be entrapped within the tumour. Nevertheless, as compared to diffuse gliomas, pilocytic tumours are relatively solid and do not aggressively overrun surrounding tissue. This property, evidenced by at least partial lack of axons on Bodian/Bielschowsky and NF protein immunostains, is of diagnostic value.

Pilocytic astrocytomas of the optic nerve and chiasm differ somewhat in their macroscopic and microscopic pattern of growth, often being less well-circumscribed and therefore difficult to stage, both macro- and microscopically. They share the same propensity for leptomeningeal involvement as seen in pilocytic tumours at other sites, but are somewhat more



Fig. 1.04 Large pilocytic astrocytoma extending into the basal cisterns.

diffuse, especially within the optic nerve. This is evident when pathologists stage a lesion by analysis of sequential nerve margins. Microscopically, the lesion can be followed to a point beyond which it becomes less cellular but has no clearly defined termination.

There has been considerable discussion regarding a "diffuse" variant of pilocytic astrocytoma [692, 798, 1672]. Although some are simply classic pilocytic tumours in which the infiltrative edge is somewhat broader than expected or an artifact of plane of section, there are occasional, distinctly infiltrative lesions that mimic diffuse fibrillary astrocytoma. In two large studies, outcomes for children with "diffuse" pilocytic astrocytoma of the cerebellum were favourable, thus confirming the notion that such tumours belong to the spectrum of pilocytic astrocytoma [798, 1672]. Regarding cerebellar astrocytic tumours in neurofibromatosis type 1 (NF1), the relative incidence of diffuse vs. pilocytic examples and their natural history and prognosis, see Chapter 13. Bona fide infiltrating, diffuse astrocytomas represent up to 15% of astrocytic tumours of the cerebellum. Of these, most are high-grade tumours (WHO grade III and IV) [798].

Infiltration of the meninges

Involvement of the subarachnoid space is a common finding in pilocytic astrocytoma. It is not indicative of aggressive or

malignant behaviour, nor does it portend subarachnoid dissemination. In contrast, it is a characteristic, even diagnostically helpful feature. Leptomeningeal invasion occurs at any tumour site, but is particularly common in the cerebellum and optic nerve. In optic nerve, more so than in the cerebellum, the leptomeningeal component may be reticulin-rich. Another typical pattern of extraparenchymal spread is extension into perivascular spaces.

Distant spread and metastasis

Surprisingly, otherwise typical pilocytic astrocytomas very occasionally seed the neuraxis, rarely even before the primary tumour is detected [640, 1717, 1770]. The proliferation index in such cases varies but is usually low [1488]. Thus, this atypical behaviour of pilocytic astrocytoma cannot be predicted [388]. The hypothalamus is the usual primary site. Even this finding is not necessarily an indicator of future aggressive growth, since both the primary lesion and the implants may grow only slowly [640, 1770]. Indeed, the implants may be asymptomatic and long-term survival is possible, even without adjuvant treatment [1770]. A related, less favourable lesion, the pilomyxoid astrocytoma [2245] typically occurring in the hypothalamic region, more often undergoes craniospinal spread. This lesion is discussed below.

Malignant transformation

As a group, pilocytic astrocytomas are remarkable in maintaining their WHO grade I [263A] status over years and even decades. As a rule, alterations over time are in the direction of regressive change rather than of anaplasia. One large study found the acquisition of atypia, particularly of increased cellularity, nuclear abnormalities and occasional mitoses, to be of no prognostic significance [2256]. There have, however, been rare examples of pilocytic astrocytoma undergoing malignant transformation [476, 2256]. They often feature multiple mitoses per single high power field, endothelial proliferation and palisading necrosis. Such tumours should not be designated glioblastoma, since their prognosis is not uniformly grim. The designation anaplastic (malignant) pilocytic astrocytoma is preferred. Since most such tumours had previously been irradiated, radiation may be a factor promoting malignant change [476, 2256].

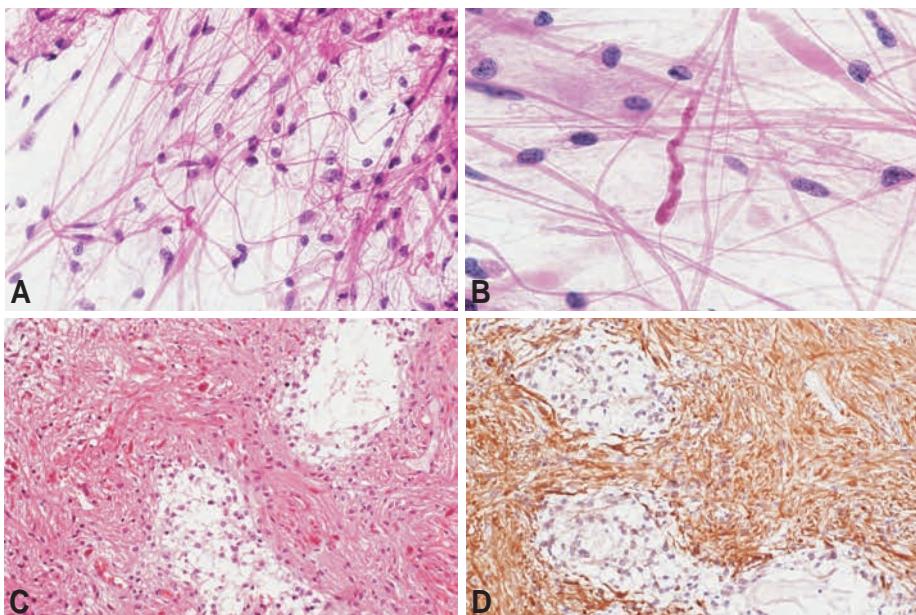


Fig. 1.05 Intraoperative squash preparations of pilocytic astrocytoma showing (A) long, bipolar tumour cells and (B) a Rosenthal fiber. C,D Typical biphasic pattern of compact, fiber-rich, GFAP-expressing areas and hypocellular areas with microcysts, lacking GFAP immunoreactivity.

Proliferation

Studies using the DNA S-phase marker bromodeoxyuridine have documented a generally low labelling index, typically less than 1% and only occasionally higher. Although in one study this index was of little prognostic value [930], higher labelling was generally noted in young patients as was a tendency toward reduced labelling in subsequently obtained specimens. Indeed, tumour growth appeared to slow by about age 20. A more recent study of proliferative activity in both pilocytic and diffuse astrocytomas showed mitoses to vary from 0 to an exceptional 4 per 10 high-power fields and MIB-1 labelling indices to range from 0 to 3.9% (mean 1.1%) in pilocytic tumours [676]. The latter values overlapped with those of diffuse astrocytoma WHO grade II (mean 2.3%). Thus, MIB-1 labelling was of little use in differential diagnosis. These observations are in keeping with the facts that growth of the solid component of pilocytic astrocytomas is an infrequent cause of death and that such tumours show little tendency to progression and almost none to malignant transformation [2256].

Genetic susceptibility

Pilocytic astrocytomas are the principal central nervous system neoplasm associ-

ated with NF1. Optic nerve involvement, especially when bilateral, is the classic finding, but other anatomic sites, sometimes multiple, may also be affected. Approximately 15% of patients with NF1 develop pilocytic astrocytomas [1306], particularly of the optic nerve. Conversely, up to one third of patients with a pilocytic astrocytoma at this location have NF1 [649].

Genetics

Cytogenetic analyses of paediatric and adult pilocytic astrocytomas have been performed on approximately 132 tumours; the majority showed a normal karyotype [1007, 1985, 2092]. However, the possibility that these tumours harbour very small copy number changes, balanced translocations, and/or epigenetic alterations awaits future studies [1007]. To date, there has been no association between cytogenetic abnormalities and the location of the tumour. In some studies the majority of paediatric tumours with detectable abnormalities were from females [1985] and adults. A genome-wide study of 44 tumours with array-based comparative genomic hybridization (0.97Mb resolution) showed a non-random pattern of genetic alterations with whole chromosomal gains detected in 32% of tumours. Consistent with earlier studies demonstrating chromosomal gains, the most frequently affected chromosomes

were 5 and 7 followed by chromosomes 6, 11, 12, 15, 17, 19, 20 and 22. In tumours of patients under 15 years with chromosomal gains, 50% had only one chromosome affected, whereas in tumours of patients over 15 years, all chromosomal gains were multiple. Smaller regions of chromosomal gain have involved a variety of loci on 1p, 2p, 4, 5q, 6q, 7q, 9q or 13q, and loss on 1p, 9q, 12q, 19, 20 or 22.

There appears to be no role for either *TP53* mutations or aberrant PDGF signalling in the development of pilocytic astrocytomas when compared to the role of *TP53* mutations and increased expression of PDGF-A and PDGF-R α as common, early events in the formation of diffuse-type astrocytomas [1311, 1621, 2194]. Gene expression analyses in sporadic pilocytic astrocytomas have demonstrated that these tumours are uniquely distinct from non-neoplastic white matter and other low-grade gliomas, and that they share similarities with fetal astrocytes [742] and oligodendroglial lineages [95, 369, 742, 1311]. Consistent with the presence of oligodendroglial progenitors, pilocytic astrocytomas, especially optic nerve tumours, contain significant numbers of O4 immunoreactive cells, and posterior fossa examples contain the highest number of A2B5+ glial progenitor cells [369]. Additional evidence for the relationship of pilocytic astrocytomas to gene expression associated with developmental processes is an expression analysis of 21 juvenile pilocytic astrocytomas by oligonucleotide microarray [2437]. Two potential subgroups differing in biologic behaviour were identified based on significant differences in the expression of genes involved in cell adhesion, cell growth regulation, motility, nerve ensheathment and angiogenesis. Neurogenesis seems to be one of the major biological processes affected, with detection of 18 deregulated genes including the up-regulation of four neurogenesis-related genes (SEMA5A, SCRG1, DPYSL3, and ASCL1), one central nervous system development-related gene (PTPRZ1), and achaete-escute homologue-1 (ACSL1), a transcription factor involved in neurogenesis.

Pilocytic astrocytomas arising in NF1 patients are molecular genetically distinct from sporadic tumours [418, 740, 1136, 1619, 2070, 2194]. The archetypic change is loss of normal NF1 expression, allelic loss and genetic mutations resulting in

constitutive RAS activation and downstream hyperactivation of the mTOR pathway [417]. Pilocytic astrocytomas appear not to show aberrant promoter methylation of the *NF1* gene [505]. In addition, microsatellite analysis has shown a loss of heterozygosity on chromosome 10, including loss of *PTEN* and a homozygous deletion of *p16^{INK4a}* in a small number of *NF1* tumours [2194]. Sporadic pilocytic astrocytomas do not demonstrate loss of *NF1* gene expression and may even show its overexpression [1136, 1761, 2417]. Despite the apparently normal expression of *NF1*, sporadic tumours may activate RAS by other mechanisms [2071]. The paired overexpression of ErbB3 with SOX3 in sporadic pilocytic astrocytomas suggests that SOX10 may drive the over-expression of ErbB3 in the development of these tumours [15]. Pilocytic astrocytomas in *NF1* also manifest dysregulation of methionine aminopeptidase-2 expression [418] as compared to over-expression of the matrilin-2 and EF-1 α 2 genes in the sporadic pilocytic astrocytomas [742, 2070].

Pilocytic astrocytomas differ from the diffuse astrocytomas in their altered and increased expression of immune response genes [880] in addition to demonstrating their high content of proliferating microglia [1126]. Apolipoprotein D (apoD) is also expressed at 8.5 fold higher levels in pilocytic astrocytomas compared to diffuse gliomas [891, 892]. Compared to low grade diffuse gliomas, pilocytic astrocytomas express increased levels of galectin-3 transcripts, a feature shared with glioblastomas [1575]. Pilocytic astrocytomas differ from glioblastoma by the expression of apoD, protease-serine-11 receptor, PLEKHB1, EF-1 α 1 and SPOCK1, whereas glioblastomas differ from pilocytic astrocytomas by expression of 5 genes involved in invasion and angiogenesis (fibronectin, osteopontin, YKL-40, keratoepithelin, fibromodulin) [368].

Histogenesis

Having the capacity to form Rosenthal fibers, the hair-like, piloid cells of pilocytic astrocytomas are remarkably similar to reactive astrocytes surrounding various chronic lesions of the hypothalamus, cerebellum and spinal cord. Similar cells are also found in the glial stroma of the normal pineal gland. Their histologic and cytologic resemblance

makes such astrocytes prime candidates as precursors. Obviously, this simple notion does not take into consideration protoplasmic astrocytes and microcystic forms of pilocytic astrocytoma rich in EGBs.

Prognostic and predictive factors

As a group, pilocytic astrocytomas are slowly growing masses which may stabilize at any point in their evolution. Rare examples even spontaneously regress [735]. Stability in tumour grade and differentiation is typically maintained for decades [118, 263A, 1666]. Long survival is the rule [565, 1625]. Although the lesion may eventually prove fatal, there are few long-term studies documenting the ultimate outcome of patients with pilocytic astrocytoma. As a rule, supratentorial examples and delay in radiotherapy, when needed, are associated with less-favourable progression-free survival [1102]. Recurrent

hypothalamic and brain stem lesions can result in death, but usually only after a prolonged course with multiple local recurrences [592, 798, 1482, 1770, 1905]. Clinical "recurrence" in the short term is more often a reflection of cyst reformation than of enlargement of the solid tumour component. Generally, *NF1*-associated pilocytic astrocytomas remain stable or grow only slowly, especially those of the optic nerve [873, 1333, 1905]. One large series of paediatric pilocytic astrocytomas in *NF1* found them to be less aggressive than non-syndromic lesions [1935]. One series suggesting that cerebellar examples in *NF1* are more aggressive [908] should be viewed in light of the fact that a clear distinction between pilocytic and diffuse astrocytomas is not always achievable in this setting. Again, occasional *NF1*-associated pilocytic tumours spontaneously regress [1287].

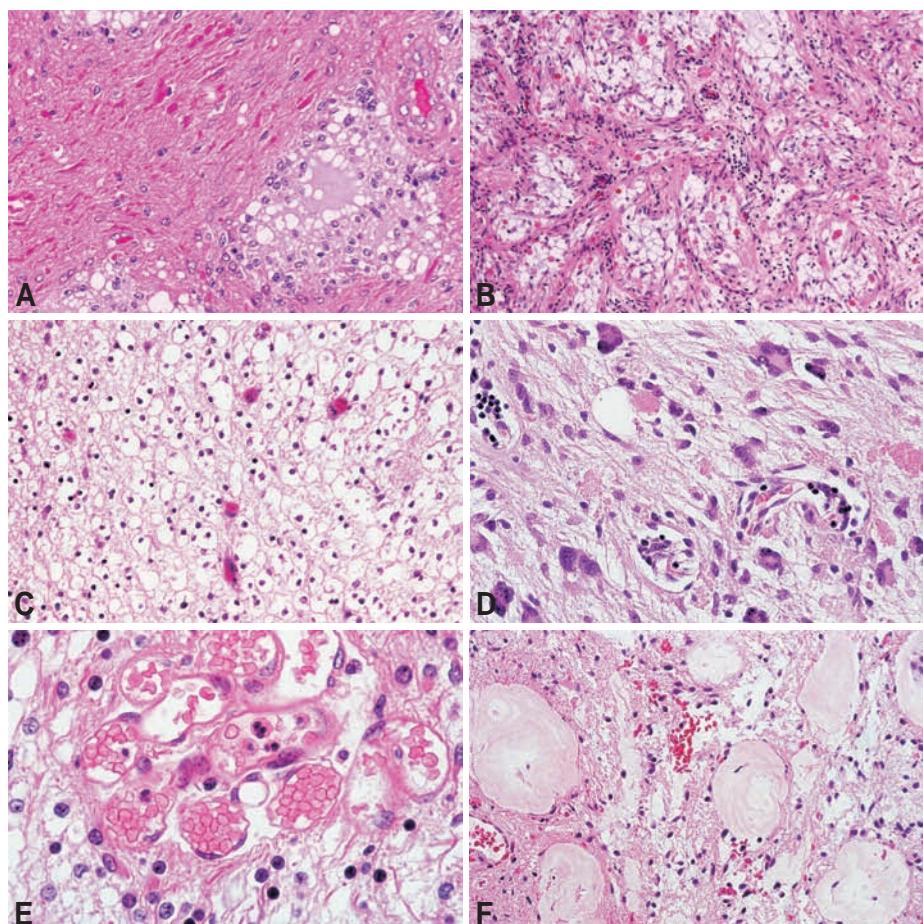


Fig. 1.06 Histological features of pilocytic astrocytoma. A Compacted piloid cells with Rosenthal fibers and loose-textured multipolar cells with microcysts. B A biphasic, compact and spongy pattern. C Tumour area with honeycomb cells resembling oligodendrogloma. D Marked nuclear atypia is not a sign of malignancy. Note the numerous eosinophilic granular bodies. E Vascular wickerwork pattern typically encountered in cerebellar lesions. F Tumour vessels with extensive hyalinization.

The definition and prognostic significance of lesions sometimes designated as “atypical” or “malignant” have been addressed [2256]. Such tumours often occur in the cerebellum and are more often solid than cystic [1909]. It is the varied presence of increased cellularity, mitotic activity, MIB-1 labelling, microvascular proliferation (glomeruloid and endothelial), and necrosis that generates concern. The rare mitosis (1-2/50 HPF) occurs in approximately 30% of pilocytic astrocytomas [676]. When seen in conjunction with significant nuclear atypia and increased cellularity, the designation atypical pilocytic astrocytoma has been applied but, in one large series [2256], was not found to be of clinical significance. At present, there are no reliable, prognostically meaningful criteria of atypical pilocytic astrocytoma; this includes combined MIB-1 and p53 immunolabelling [2246]. Only when mitotic activity is expressed in terms of mitoses per single HPF and is associated with endothelial proliferation and/or palisading necrosis can the designation anaplastic (malignant) pilocytic astrocytoma be applied [2256]. Most such tumours are associated with aggressive behaviour, yet others are cured by resection with or without adjuvant radio- and/or chemotherapy. Classic pilocytic astrocytoma must be

distinguished from pilomyxoid astrocytoma, a tumour which with rare exception [1158], affects the hypothalamic/third ventricular region [354, 2245]. Prone to undergo craniospinal seeding, they are associated with a less favourable prognosis.

Pilomyxoid astrocytoma

Definition

A piloid neoplasm, closely related to pilocytic astrocytoma, that has a prominent mucoid matrix and angiocentric arrangement of monomorphic, bipolar tumour cells, typically without Rosenthal fibers or eosinophilic granular bodies/hyaline droplets.

ICD-O code

The provisional code proposed for the fourth edition is 9425/3.

Grading

Pilomyxoid astrocytoma corresponds to a WHO grade II neoplasm.

Synonyms and historical annotation

Earlier reports refer to tumours with similar features as “infantile” pilocytic astrocytoma [968]. The term “pilomyxoid” was introduced in 1999 to describe its two distinct histological features [2247].

The occasional phenotypical conversion of a pilomyxoid astrocytoma to a typical pilocytic astrocytoma supports a common origin for these two tumours [306].

Incidence

The incidence of pilomyxoid astrocytoma is not known, but it comprises a small percentage of tumours historically classified as pilocytic astrocytoma.

Age and sex distribution

Pilomyxoid astrocytoma typically presents in the very young (median 10 months), but can occur in older children. They are rare in adults. Male:female distribution is roughly equal.

Localization

The hypothalamic/chiasmatic region is the most common location, although the tumour can occur in the thalamus [565, 2247], cerebellum [565], brain stem [565], temporal lobe [2247] and spinal cord [1159].

Clinical features

Pilomyxoid astrocytoma presents with non-specific signs and symptoms referable to its anatomic site. Radiological examination highlights a circumscribed mass with relatively distinct borders. On MRI scan, the tumour is typically hypointense on T1-, and hyperintense on T2-weighted images, and shows homogeneous contrast enhancement [68]. Evidence of CSF dissemination may be evident at presentation.

Macroscopy

Intraoperative reports often describe a solid, gelatinous mass [2247]. In at least some parts, the tumours may infiltrate parenchyma. Thus, a clear surgical plane may not be identified.

Histopathology

Pilomyxoid astrocytoma is dominated by a markedly mucoid matrix, monomorphic bipolar cells, and a predominantly angiocentric cell arrangement. The tumour typically has a compact, rather solid architecture, but some are infiltrative. The lesion is composed of relatively monomorphic, intermediate size, bipolar cells the processes of which may radiate from vessels in a pseudorosette fashion. Cells may be also aligned along the long axis of vessels. When strictly defined, the lesion does not contain Rosenthal fibers

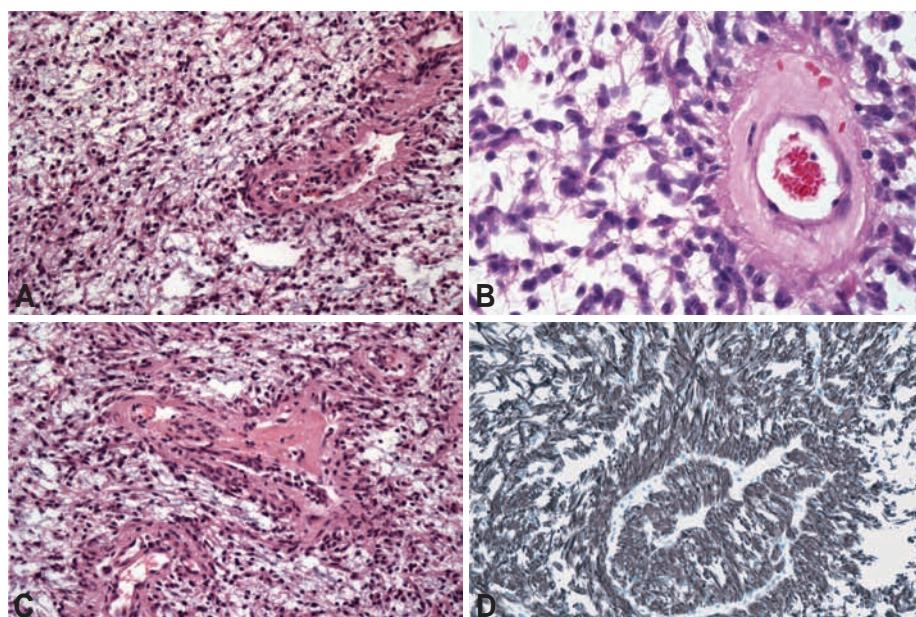


Fig. 1.07 Pilomyxoid astrocytoma. A Tumours typically show a monomorphic population of cells in a homogeneously myxoid background. B The prominent feature of pilomyxoid astrocytoma is the angiocentric arrangement of tumour cells. C The vascularity is often prominent with the above-mentioned angiocentric arrangement of tumour cells, but florid vascular proliferation is rare. D Tumours are typically diffusely and strongly positive for GFAP.



Fig. 1.08 Axial T1-weighted, gadolinium-enhanced image of pilomyxoid astrocytoma in a typical location.

or eosinophilic granular bodies/hyaline droplets. Mitotic figures can be present. Vascular proliferation, present in some cases, often takes the form of linear glomeruloid tufts associated with cystic degeneration. Rare examples may be focally necrotic. Limited pilomyxoid

changes in an otherwise typical pilocytic astrocytoma do not warrant a diagnosis of pilomyxoid astrocytoma. Immunohistochemical staining demonstrates strong, diffuse reactivity for GFAP, S-100 protein and vimentin. Some tumours are positive for synaptophysin, but staining for neurofilament protein or chromogranin is typically negative.

Proliferation

In limited studies of pilomyxoid astrocytomas, Ki-67 labelling indices were found to vary substantially, ranging from 2–20% {565, 1157, 2247}. There is considerable overlap of Ki-67 labelling indices in such tumours and pilocytic astrocytomas.

Genetic susceptibility

No genetic susceptibility has thus far been established, although two patients with NF1 and pilomyxoid astrocytoma have been reported {1097}.

Genetics

One report found no genetic abnormalities using conventional comparative genomic hybridization {1157}.

Histogenesis

The cell of origin for pilomyxoid astrocytoma is unclear. Some reports of pilomyxoid astrocytoma underscore the close relationship to pilocytic astrocytoma, thus implying a common astrocytic origin. An alternative suggestion that the tumour arises from radial glia in proximity to the optic tract remains to be substantiated {335}.

Prognostic and predictive factors

Pilomyxoid astrocytomas are more aggressive than pilocytic astrocytomas {565, 1157, 2247}. Local recurrence as well as cerebrospinal spread occur more often in pure pilomyxoid tumours than in pilocytic astrocytomas {2247}.

Pleomorphic xanthoastrocytoma

C. Giannini
W. Paulus
D.N. Louis
P. Liberski

Definition

An astrocytic neoplasm with a relatively favourable prognosis, typically encountered in children and young adults, with superficial location in the cerebral hemispheres and involvement of the meninges; characteristic histological features include pleomorphic and lipidized cells expressing GFAP and often surrounded by a reticulin network as well as eosinophilic granular bodies.

ICD-O code

9424/3

Grading

Pleomorphic xanthoastrocytoma corresponds histologically to WHO grade II. For lesions with significant mitotic activity (5 or more mitoses per 10 HPF) and/or with areas of necrosis, the designation "pleomorphic xanthoastrocytoma with anaplastic features" may be used {675}; when not completely excised, such tumours have an increased risk of early recurrence.

Synonyms and historical annotation

Before the introduction of immunostaining, pleomorphic xanthoastrocytomas were thought to represent mesenchymal neoplasms of the meninges and brain, partly because the lipidized neoplastic glial cells resemble "xanthoma" cells, and partly because many tumour cells produce a basement membrane. However, immunohistochemical and ultrastructural studies have clearly shown that the tumour cells

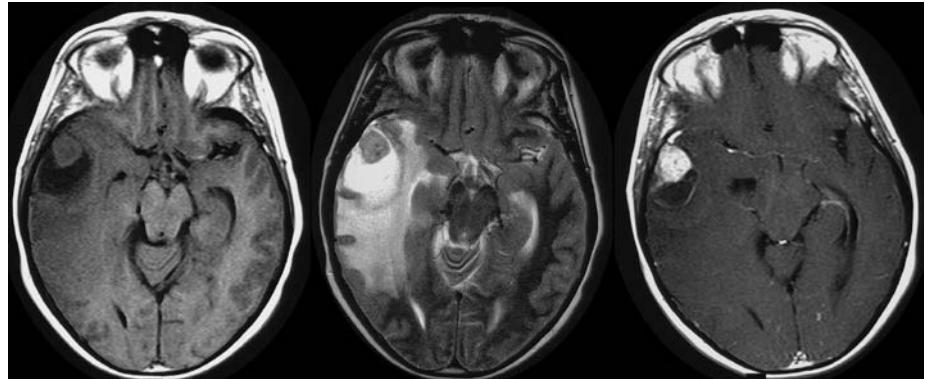


Fig. 1.10 T1, T2 and T1 with contrast of a typical PXA of the temporal lobe, presenting as a cystic tumour with a superficial enhancing mural nodule.

are neoplastic astrocytes, often with evidence of neuronal differentiation {678, 827, 1090}.

Incidence

Pleomorphic xanthoastrocytoma accounts for less than 1% of all astrocytic neoplasms. Since the initial description of 12 cases in 1979 {1090}, well over 200 additional cases have been reported {675}.

Age and sex distribution

This neoplasm typically develops in children and young adults. Two thirds of patients are less than 18 years old {674}, but manifestation in older patients, e.g. 62 and 82 years old {675, 1374} has also been reported. There is no documented gender bias, although one study reports these tumours appear more commonly in females {597}.

Etiology

No specific aetiologies have been implicated in the evolution of pleomorphic xanthoastrocytoma. The rare *TP53* mutations encountered do not suggest particular carcinogenic insults {673, 1067, 1702}. The occasional association with cortical dysplasia or with ganglionic lesions has suggested that their formation may be facilitated in malformative states {1243}. Given reports in patients with neurofibromatosis type 1 (NF1) {769, 1550}, a relation to defective NF1 function is possible.

Localization

A superficial location, involving the meninges and cerebrum ("meningocerebral") is typical of this neoplasm. Ninety-eight percent occur supratentorially, in particular the temporal lobe {675, 1090}. Cases involving the cerebellum and spinal cord are also on record {683, 1557}, and two children with primary pleomorphic xanthoastrocytoma of the retina were reported {2484}.

Clinical features

Symptoms and signs

Because of the superficial cerebral location of the lesion, many patients present with a fairly long history of seizures. Cerebellar and spinal cord cases have symptoms that reflect the sites of involvement.

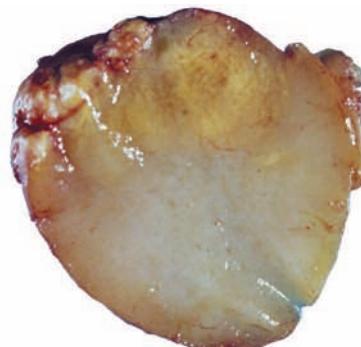


Fig. 1.11 Typical macroscopic appearance of a pleomorphic xanthoastrocytoma. The yellow areas correspond to xanthomatous parts of the tumour.

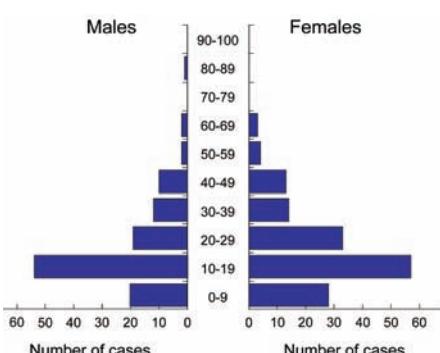


Fig. 1.09 Age distribution of patients with pleomorphic xanthoastrocytoma.

Neuroimaging

CT and MRI scans usually outline the tumour mass and/or its cyst. Perifocal edema is usually not pronounced, owing to the slow growth of the tumour.

Macroscopy

Pleomorphic xanthoastrocytomas are mainly superficial tumours attached to the meninges. They are frequently accompanied by a cyst, sometimes forming a mural nodule within the cyst wall. Invasion of the dura {436}, predominantly exophytic growth {1494}, multicentricity {1437} and leptomeningeal dissemination {1691} are exceptional.

Histopathology

The key histopathological features of the pleomorphic xanthoastrocytoma are well established {1205}. The adjective 'pleomorphic' refers to the variable histological appearance of the tumour, in which spindly elements are intermingled with mono- or multinucleated giant astrocytes, the nuclei of which show great variation in size and staining. Intranuclear inclusions are frequent {675}. In some cases, the neoplastic astrocytes are closely packed and assume an 'epithelioid' pattern {936}. The term 'xanthoastrocytoma' refers to the presence of large xanthomatous cells showing intracellular accumulation of lipids. This is usually in the form of droplets, which quite often occupy much of the cell body, pushing to the periphery cytoplasmic organelles and glial filaments that by conventional or GFAP stains generally make the astrocytic character easy to recognize. Granular bodies, intensely eosinophilic or pale, are almost a constant finding {675}. Focal collections of small lymphocytes, occasionally with plasma cells, are also frequent {675}. The third histological hallmark of pleomorphic xanthoastrocytoma is the presence of reticulin fibers best seen using silver impregnation. Not only reactive changes in the meninges result in the presence of reticulin fibers; the individual tumour cells may be surrounded by basement membranes that stain positively for reticulin, and these can be recognized ultrastructurally as pericellular basal laminae. Histological features of anaplasia, including significant mitotic activity (5 or more mitoses per 10 HPF) and necrosis are uncommon at initial presentation, respectively seen in 18% and 11% of cases in one series {675}. At recurrence,

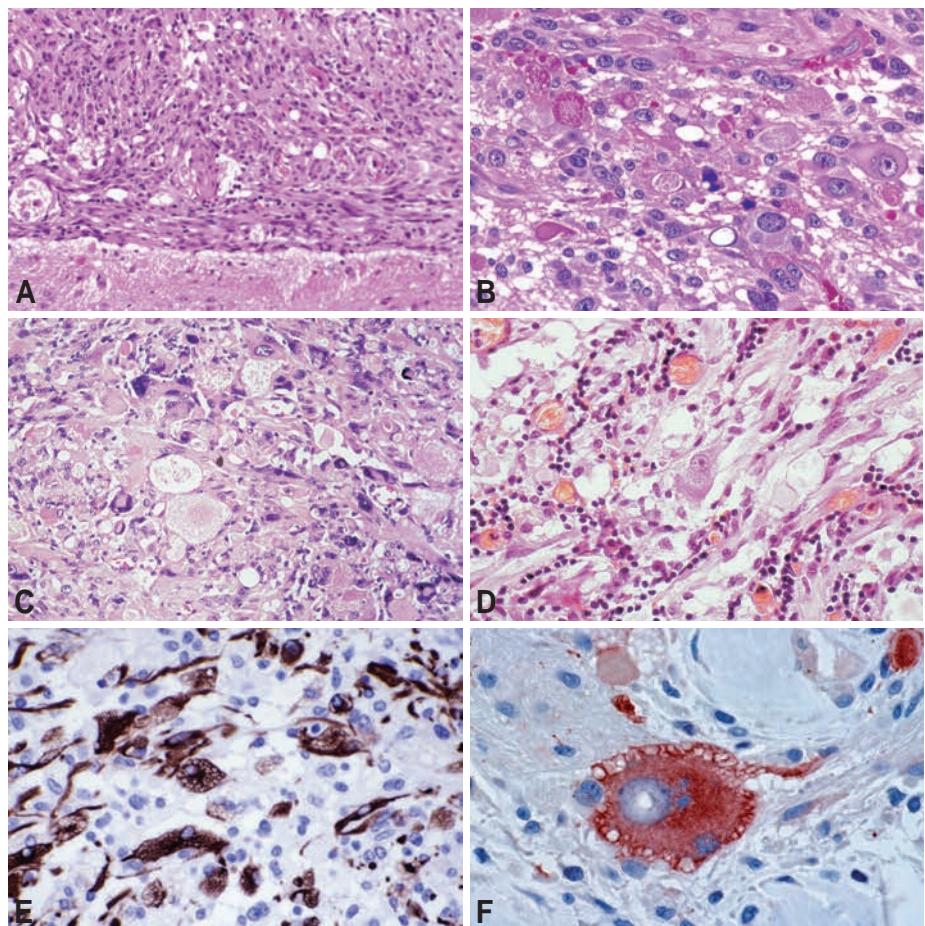


Fig. 1.12 Histological features of pleomorphic xanthoastrocytoma (PXA). A Leptomeningeal PXA, sharply delineated from the underlying cerebral cortex. B Granular bodies, intensely eosinophilic or pale, are almost a constant finding. C Tumour cells showing nuclear and cytoplasmic pleomorphism and xanthomatous change. D Mature ganglion cell and lymphocytic infiltrates in a PXA. From Kros *et al.* {1205}. E GFAP expression in large pleomorphic and xanthomatous cells. F Synaptophysin immunostaining in PXA cells. From Giannini *et al.* {678}.

tumours may show histological patterns similar to the original, or increasing anaplasia, in some cases being histologically indistinguishable from glioblastoma and featuring both necrosis and endothelial hyperplasia. Pleomorphism may cease to be a feature, and closely packed smaller cells may come to dominate the tumour. In addition, with increasing malignancy, the rich reticulin network may become fragmented or disappear completely {1088}. Rarely, pleomorphic xanthoastrocytoma is part of a combination tumour in which it forms the glioma portion of a ganglioglioma {1725}. Exceptional is the occurrence of a combined pleomorphic xanthoastrocytoma/oligodendrogloma {1735}. Some highly vascularized forms have been denoted as 'angiomatous' {2170}.

Immunohistochemistry

Although the essential nature of pleomorphic xanthoastrocytoma is clearly and uniformly glial with nearly constant immunoreactivity for GFAP and S-100 protein {675, 678}, the tumour shows a significant tendency to exhibit neuronal differentiation. Expression of neuronal markers including synaptophysin, neurofilament, class III β-tubulin and MAP2 has been reported with variable frequency {678, 1780}. This biphenotypic glioneuronal appearance in some cases has been confirmed ultrastructurally {827}. The haematopoietic progenitor cell and vascular endothelial cell associated antigen CD34 is frequently expressed in pleomorphic xanthoastrocytoma cells {1843}.

Proliferation

In most cases, mitotic figures are rare or

absent {675}. MIB-1/Ki-67 and PCNA labelling indices are generally lower than 1% {675, 1365, 2368}. S-phase fractions, as determined by flow cytometry, are also low {872, 2368}.

Genetic susceptibility

There are no distinct associations with hereditary tumour syndromes, with the exception of rare reports of pleomorphic xanthoastrocytoma in NF1 patients {1213, 1658}. Given the well-known association of NF1 with many different forms of astrocytomas, these occasional cases are not surprising. Familial clustering of pleomorphic xanthoastrocytoma has not been reported.

Genetics

Complex karyotypes have been documented, with gains of chromosomes 3 and 7, as well as alterations of the long arm of chromosome 1 {1314, 2002, 2003}. These cytogenetic changes, however, have also been reported in other types of astrocytoma. The tumours appear to be predominantly diploid {872, 2368}, occasionally with polyploid populations {872}, possibly due to subgroups of particularly bizarre, multinucleated tumour cells. A CGH analysis of 50 cases revealed -9 as the chromosomal hallmark alteration (50% of cases), while less common recurrent chromosomal imbalances included +X (16%), -17 (10%), +7, +9q, +20 (8% each) and -8, -18, -22, +4, +5 and +19 (4% each) {2379}. Analysis of 10 tumours by array-based CGH indicated homozygous 9p21.3 deletions involving the *CDKN2A/p14^{ARF}/CDKN2B* loci in six cases (60%) {2379}. In four series with a total of 123 tumours, mutations in the *TP53* gene were found in only 7 cases (6%) {673, 1067, 1536, 1702}, being

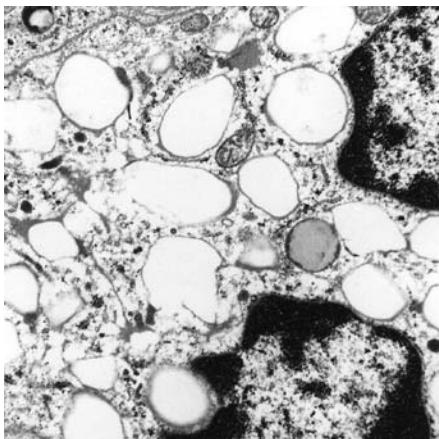


Fig. 1.13 Vacuolated cytoplasm in pleomorphic xanthoastrocytoma.

unrelated to absence or presence of histological features of anaplasia. Amplification of the *EGFR*, *CDK4* and *MDM2* genes were absent in a series of 62 tumours {1067}. These findings distinguish pleomorphic xanthoastrocytoma from diffusely infiltrating cerebral astrocytoma.

Histogenesis

The most popular hypothesis, originally proposed by Kepes *et al.* {1090}, postulates that pleomorphic xanthoastrocytoma originates from subpial astrocytes. This hypothesis would explain the superficial location of most pleomorphic xanthoastrocytomas, and is supported by ultrastructural features shared between subpial astrocytes and the neoplastic cells in pleomorphic xanthoastrocytomas, in particular the presence of a basal lamina surrounding individual cells. On the other hand, expression of neuronal markers {678} and the haematopoietic progenitor cell associated antigen CD34 {1843} in many

pleomorphic xanthoastrocytomas as well as the occasional association with cortical dysplasia suggests a more complex histogenesis and a possible origin from multipotential neuroectodermal precursor cells or from a pre-existing hamartomatous lesion {911, 1243}.

Prognostic and predictive factors

With some notable exceptions {1088, 2392, 2405}, pleomorphic xanthoastrocytoma behaves in a less malignant fashion than might be suggested by its highly pleomorphic histology {1090}. Cases with survival as long as 40 years after surgery have been published soon after the original description of this tumour {1671}. A series of 71 patients reported recurrence-free survival of 72% at 5 years and 61% at 10 years {675}. Recurrence-free survival curves, based on a review of previously published cases (n=121), are similar. The extent of the resection of the original tumour mass appears to be the most significant predictive factor, followed by a low mitotic index {675}. Both factors are independently predictive of recurrence-free survival.

Overall survival has been estimated as 81% at 5 years and 70% at 10 years {675}. Mitotic activity (more than 5 per 10 HPF) is the only independent predictor of survival. Necrosis, although significantly associated with survival, was not an independent predictor. A review of the previously published cases has also shown a significant association of necrosis with survival {675, 1667}.

No reliable correlation between *TP53* mutation and malignant progression or recurrence has been established in the few cases analysed to date {1536, 1702}.

Diffuse astrocytoma

A. von Deimling
P.C. Burger
Y. Nakazato
H. Ohgaki
P. Kleihues

Definition

A diffusely infiltrating astrocytoma that typically affects young adults and is characterized by a high degree of cellular differentiation and slow growth; the tumour occurs throughout the CNS but is preferentially located supratentorially and has an intrinsic tendency for malignant progression to anaplastic astrocytoma and, ultimately, glioblastoma.

ICD-O codes

Diffuse astrocytoma	9400/3
- Fibrillary astrocytoma	9420/3
- Gemistocytic astrocytoma	9411/3
- Protoplasmic astrocytoma	9410/3

Grading

Diffuse astrocytoma corresponds to WHO grade II. Although the gemistocytic variant appears to be particularly prone to progress to anaplastic astrocytoma and glioblastoma {1208, 1959, 2023}, the WHO Working Groups did not recommend assigning it a WHO grade III as for anaplastic astrocytoma {257, 2023}.

Synonyms and historical annotation

The term diffuse astrocytoma (WHO grade II) was proposed in the previous edition of the WHO Classification {1122}. The synonymous term 'low-grade diffuse astrocytoma (WHO grade II)' may be preferred. The designation 'well-differentiated astrocytoma' is not recommended since it could be confused with the pilocytic astrocytoma, which is usually more circumscribed and has a different age distribution, location and biology. 'Fibrillary astrocytoma' is commonly used for the most typical histological subtype of diffuse astrocytoma WHO grade II.

Incidence

Diffuse astrocytoma represents 10–15% of all astrocytic brain tumours, with an incidence rate of approximately 1.4 new cases / 1 million population a year {432}. Epidemiological data suggest that the incidence of astrocytoma in children has slightly increased during the past three decades in several Scandinavian countries and in North America {432, 807, 839, 2189}.

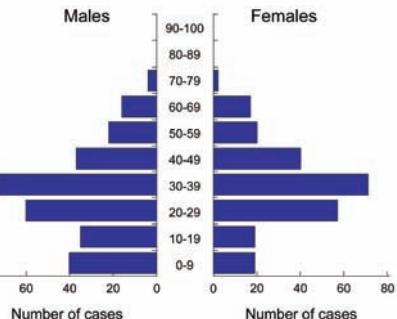


Fig. 1.14 Age distribution of diffuse astrocytoma WHO grade II, based on biopsies of 529 patients from the Tumour Registry of the University of California, San Francisco (courtesy of Ms Nancy Drungilas) and the Institute of Neuropathology, University Hospital Zurich.

Age and sex distribution

The age distribution of diffuse astrocytoma shows a peak incidence in young adults between ages 30 and 40. Approximately 10% occur below the age of 20, 60% between 20–45 years of age, and about 30% over 45 years of age with a mean of 34 years. There is a predominance of affected males (M:F ratio, 1.18:1).

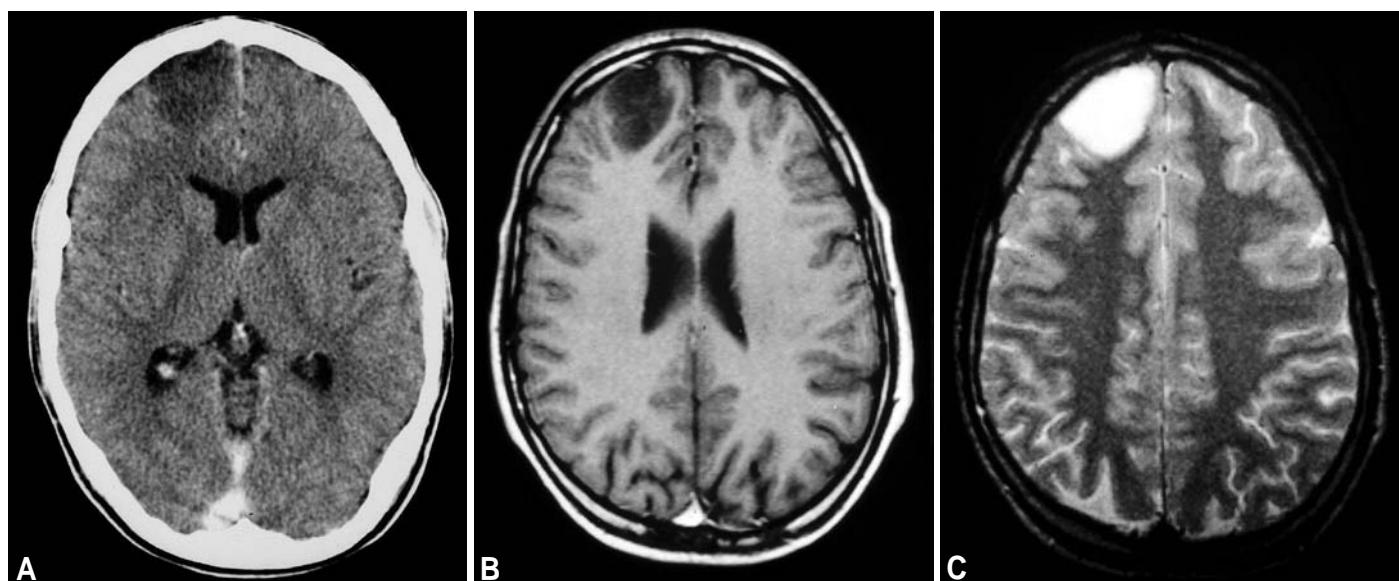


Fig. 1.15 Diffuse astrocytoma WHO grade II, presenting as (A) hypodense frontal lesion on contrast-enhanced CT, as (B) hypointense focus on gadolinium-enhanced MRI and (C) as well-delineated hyperintense lesion on T2-weighted MRI.



Fig. 1.16 T2-weighted MRI of a diffuse astrocytoma involving the fronto-temporal region with considerable mass effect. In the affected brain region, the cortex is enlarged but still recognizable.

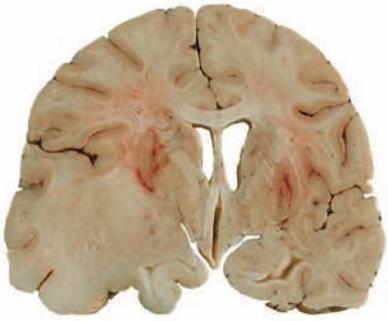


Fig. 1.17 Large fibrillary astrocytoma occupying the left temporal lobe, with extension to the Sylvian fissure. Note the homogeneous surface and the enlargement of local anatomical structures.

Localization

Diffuse astrocytoma may be located in any region of the CNS, but it most commonly develops supratentorially in the frontal and temporal cerebral lobes of both children and adults (one third of cases each). The brain stem and spinal cord are the next most frequently affected sites, while diffuse astrocytoma is distinctly uncommon in the cerebellum.

Clinical features

Symptoms and signs

Seizures are a common presenting symptom, although in retrospect subtle abnormalities such as speech difficulties, changes in sensation, vision, or some motor change may have been present earlier. With frontal lobe tumours, changes in behaviour or personality may be the

presenting feature. Any such change may have been present for months before diagnosis, but symptoms may also be abrupt in onset.

Neuroimaging

On CT scans, diffuse astrocytoma most often presents as ill-defined, homogeneous masses of low density without contrast enhancement. However, calcification, cystic changes and even lower degrees of enhancement may be present early. MRI studies usually show hypodensity on T1-weighted and hyperintensity on T2-weighted images, with enlargement of the areas involved early in the evolution of the tumour. Gadolinium enhancement is uncommon in low-grade diffuse astrocytoma, but tends to appear during progression to anaplastic astrocytoma (WHO grade III).

Macroscopy

Because of their infiltrative nature, these tumours usually show blurring of the gross anatomical boundaries. There is enlargement and distortion, but not destruction, of the invaded anatomical structures, e.g. cortex and compact myelinated pathways. Local mass lesions may be present in either grey or yellow-white matter, but they have indistinct boundaries, and changes such as smaller or larger cysts, granular areas and zones of firmness or softening may be seen. Cystic change most commonly appears as a focal spongy area, with multiple cysts of varying size. Extensive microcyst formation may cause a gelatinous appearance. Occasionally, a single large cyst filled with clear fluid may be present. Tumours with prominent gemistocytes sometimes have single, large smooth-walled cysts. Focal calcification may also be present, and a more diffuse grittiness may be observed. Extension into contralateral structures, particularly in the frontal lobes, is also observed.

Histopathology

Diffuse astrocytoma is composed of well differentiated fibrillary or gemistocytic neoplastic astrocytes on the background of a loosely structured, often microcystic tumour matrix. In comparison to normal brain, cellularity is moderately increased and occasional nuclear atypia is a typical feature. Mitotic activity is generally absent, and a single mitosis does not yet allow the diagnosis of anaplastic astrocytoma.

The presence of necrosis or microvascular proliferation is incompatible with the diagnosis of diffuse astrocytoma.

Phenotypically, neoplastic astrocytes may vary considerably with respect to their size, the prominence and disposition of cell processes, and the abundance of cytoplasmic glial filaments. The pattern may vary markedly in different regions of the neoplasm.

Histological recognition of neoplastic astrocytes using H&E staining on sectioned material depends mainly on nuclear characteristics. The normal astrocytic nucleus is oval-to-elongate, but on sectioning, occasional round cross-sections are seen. It is typically vesicular, with intermediate-sized masses of chromatin and often with a distinct nucleolus. Normal human astrocytes show no H&E stainable cytoplasm that is distinct from the background neuropil. Reactive astrocytes are defined by enlarged nuclei and the presence of stainable, defined cytoplasm, culminating in the gemistocyte, which has a mass of eosinophilic cytoplasm, often an eccentric nucleus, and a cytoplasm that extends into fine processes.

Differential diagnosis. The diffuse astrocytoma contains astrocytes that are increased in number and also usually in size, but are otherwise difficult to distinguish on an individual basis from the normal or reactive cells. In minor degrees of anaplasia, it is their number and, most commonly, the monotony of their morphology that is most helpful in recognising their neoplastic nature. Reactive astrocytes are rarely all in the same stage of reactivity at one time, so reactions reveal mixtures of astrocytes; some with enlarged nuclei, others with varying amounts of cytoplasm, most often on a somewhat rarefied background. With diffuse astrocytoma, almost all of the nuclei appear identical, and the background is at least of normal density, or shows increased numbers of cellular processes. Microcystic change may be present, but again most cells look like one another, without the admixture of gemistocytes more often seen as reactions to injury. Pre-existing cell types, e.g. neurons, are often entrapped.

Intraoperative diagnosis. The smear or 'squash' technique is often used during stereotaxic biopsies and yields similar findings, although estimating cellularity with this method is highly unreliable.

Many histological features are exaggerated and amplified, e.g. nuclear folds, abnormal chromatin pattern and astrocytic processes. On reducing the light by removing the top lens of the condenser, astrocytic processes are often emphasized. The presence of many round-to-oval nuclei with smooth chromatin can herald the presence of a mixed oligodendroglial component or, if the nuclei are less prominent, the background white matter. Histologically, there may be significant variation between tumours, and within the same lesion. According to the prevailing cell type, three major variants can be distinguished, but often a clear subclassification is not feasible.

Fibrillary astrocytoma

This most frequent histological variant of astrocytoma is predominantly composed of fibrillary neoplastic astrocytes. Nuclear atypia is a diagnostic criterion but mitotic activity, necrosis and microvascular proliferation are absent. A single mitosis does not allow the diagnosis of anaplastic astrocytoma. The occasional or regional occurrence of gemistocytic neoplastic cells is compatible with the diagnosis of fibrillary astrocytoma. Cell density is low to moderate. The cytoplasm is often scant and barely discernible, creating the appearance of naked nuclei. Nuclear atypia (i.e. enlarged, cigar-shaped, or irregular hyperchromatic nuclei) is a histological hallmark distinguishing tumour cells from normal and reactive astrocytes. Even prominent nuclear atypia is compatible with the diagnosis of diffuse astrocytoma WHO grade II so long as mitoses are very rare or absent. In more cellular lesions, neoplastic cell processes form a loose fibrillary matrix. Microcysts containing mucinous fluid are a characteristic feature and often dominate the histological picture. Cartilage formation is very rare {1089, 1412}.

Immunohistochemistry. Glial fibrillary acidic protein (GFAP) is consistently expressed, although to a variable degree and not by all tumour cells. In particular, small round cells with scanty cytoplasm and processes tend not to express GFAP. Often, GFAP immunoreactivity is restricted to a small perinuclear rim. The fibrillary matrix, which consists of a network of neoplastic cell processes (and entrapped reactive astrocytes), forms a diffuse GFAP-positive background {1123}. Vimentin, a 57 kDa intermediate filament protein,

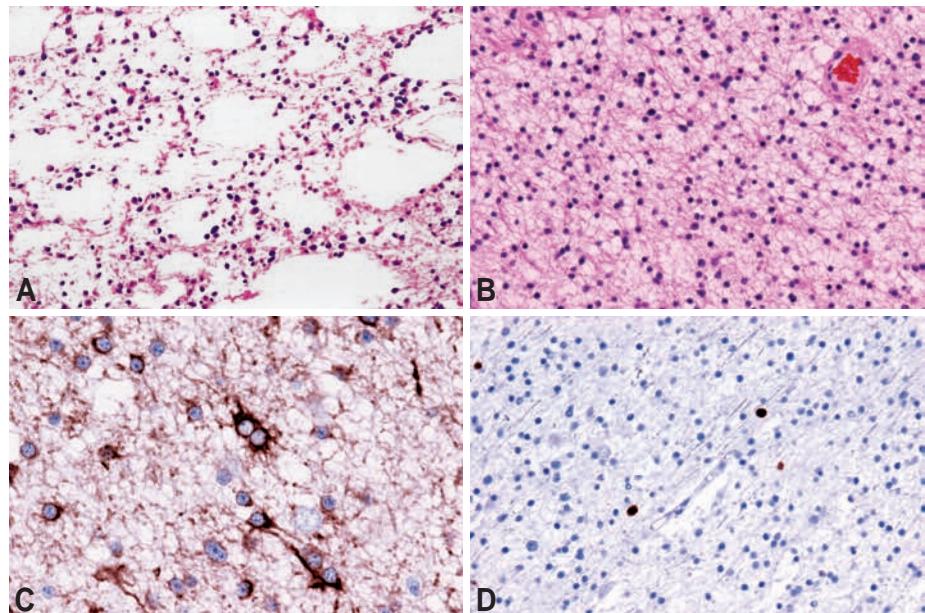


Fig. 1.18 Fibrillary astrocytoma. A Extensive microcyst formation. B A moderately cellular tumour composed of uniform fibrillary astrocytic cells with microcystic stroma. C Cytoplasm and processes showing GFAP immunoreactivity. D Low MIB-1 labelling index.

shows a pattern of immunoreactivity similar to that of GFAP, although vimentin immunoreactivity has a tendency to be seen mainly in the perinuclear region while GFAP is also expressed intensively in the cellular processes {815}. Vimentin-positive cells may lack GFAP expression. As vimentin is expressed early in astrogliogenesis, its presence in astrocytomas could indicate a lower degree of differentiation and there is a tendency for vimentin to be expressed more consistently in high-grade astrocytomas {1524}. Tumour cells usually show immunoreactivity to S-100 protein in the nucleus and in cell processes, but this feature has no diagnostic relevance {1114, 1123}. This is also true of the expression of B-crystallin {1055}.

Electron microscopy. Fibrillary neoplastic astrocytes are characterized by the presence of intermediate filaments ranging in diameter from 7 to 11 nm in the perikaryon and cell processes. However, these and other ultrastructural features are of limited diagnostic significance. In particular, they do not allow a distinction between tumour cells and reactive astrocytes.

Proliferation. Mitotic activity is typically absent in diffuse astrocytoma. Accordingly, the growth fraction, as determined by the Ki-67/MIB-1 labelling index, is usually less than 4%, with a mean of 2.5% {2369}.

Gemistocytic astrocytoma

This variant of astrocytoma is characterized by the presence of a conspicuous, though variable, fraction of gemistocytic neoplastic astrocytes. Gemistocytes should amount to more than approximately 20% of all tumour cells; the occasional occurrence of gemistocytes in a diffuse astrocytoma does not justify the diagnosis of gemistocytic astrocytoma. The mean size of the fraction of gemistocytes is approximately 35% {2370}. The cut-off value of 20% is somewhat arbitrary, but a useful criterion in borderline cases {1208, 2249}. The histopathological picture of gemistocytes is dominated by plump, glassy, eosinophilic cell bodies of angular shape. Stout, randomly oriented processes, forming a coarse fibrillary network, characterize the tumour cells, and are often useful to discriminate them from the minigemistocytes found in oligodendrogloma. The gemistocytic neoplastic astrocytes consistently express GFAP in their perikarya and cell processes. Expression of p53 protein and bcl-2 is frequently seen in gemistocytes {1586, 2373}. Nuclei are usually eccentric, with distinct nucleoli and densely clumped chromatin. Perivascular lymphocyte cuffing is frequent {261}. Electron microscopy confirms the presence of abundant, compact glial filaments in the cytoplasm and in cell processes.

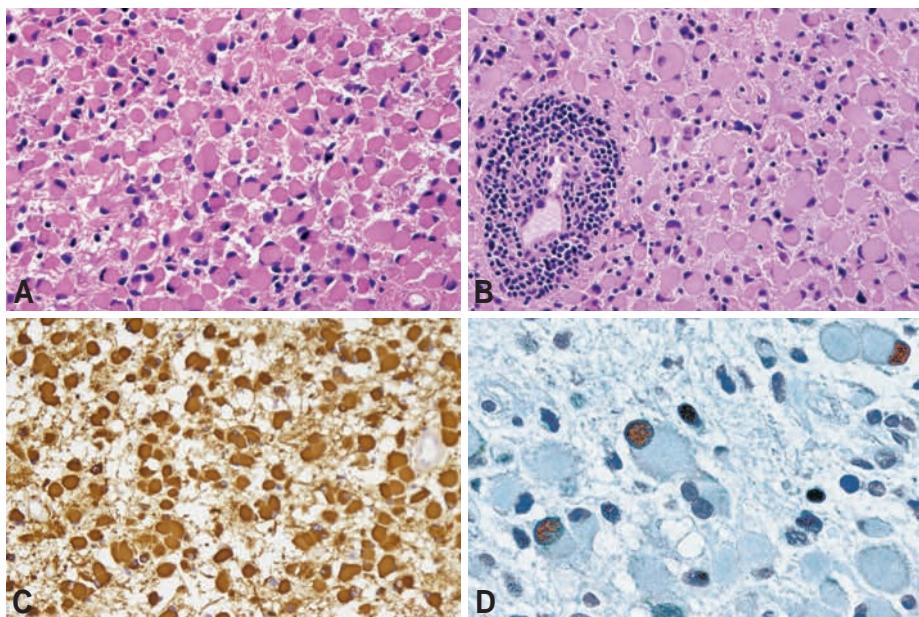


Fig. 1.19 Gemistocytic astrocytoma. A Tumour cells have a large eosinophilic cytoplasm with nuclei displaced to the periphery. B Characteristic feature of perivascular lymphocytic infiltrate. C Strong, consistent GFAP expression. D p53 accumulation is marked in nuclei of small and gemistocytic tumour cells.

Proliferation. The growth fraction, as determined by the Ki-67/MIB-1 labelling index, is usually less than 4%. The gemistocytic neoplastic astrocytes show a significantly lower rate of proliferation than the intermingled small-cell component {871, 1200, 1208, 1645, 2373, 2459}. However, microdissection discloses identical *TP53* mutations in both gemistocytes and non-gemistocytic tumour cells {1855}. Although the gemistocytic variant appears to be particularly prone to progress to anaplastic astrocytoma and glioblastoma {1208, 1959, 2023}, this does not justify a general classification as anaplastic astrocytoma {257, 2023}.

Protoplasmic astrocytoma

This rare variant is predominantly composed of neoplastic astrocytes showing a small cell body with a few flaccid processes with a low content of glial filaments and scant GFAP expression. Cellularity is low and mitotic activity absent. Mucoid degeneration and microcyst formation are common and characteristic features.

Nuclei are uniformly round to oval. GFAP immunostaining is variable and generally low. A clinico-pathological study indicates that protoplasmic astrocytoma is preferentially located in the frontotemporal region {1796}. The mean size of the growth fraction as determined by the

MIB-1 labelling index was <1% {1797}. Immunohistochemical expression of p53, cyclooxygenase-2 and bcl-2 is limited to only a minority of tumours {1791, 1797}. A FISH analysis indicated no allelic loss on chromosome 1p {1791}. This lesion is not well defined and is considered by some authors as an occasional histopathological feature rather than a reproducibly identifiable variant. When occurring in children, this neoplasm may be difficult to distinguish from pilocytic and pilomyxoid astrocytoma {1796, 1959}.

Genetic susceptibility

Diffuse astrocytoma may occur in patients with inherited *TP53* germline mutations/Li-Fraumeni syndrome (see Chapter 13) although affected family members more frequently develop anaplastic astrocytoma and glioblastoma. More recently, low-grade astrocytoma has been diagnosed in patients with inherited multiple enchondromatosis type 1 (Ollier disease; MIM No. 225795) which also predisposes to chondrosarcoma {605, 854}.

Genetics

TP53. A genetic hallmark of low-grade diffuse astrocytomas is frequent *TP53* mutation (>60%) {1634, 1851, 2371}. The frequency of *TP53* mutations does not significantly increase during malignant progression of low-grade astrocytomas

to secondary glioblastomas, indicating that this genetic change is an early event {2098, 2333, 2371, 2372}. In particular, in the gemistocytic variant, >80% of cases contain a *TP53* mutation {1634, 2370}.

PDGFR. Increased mRNA expression of the platelet-derived growth factor receptor α has been observed in astrocytic tumours of all stages, but gene amplification was only detected in a small subset of glioblastomas {814}.

Other genetic changes. Comparative genomic hybridization (CGH) analyses showed a gain of chromosome 7q and amplification of 8q as the most frequent genomic imbalance {1600, 2037}. The presence of LOH on 22q has been reported at a frequency of 17% {884} and chromosome 6 deletions in 14% of cases {1495}. LOH on 22q was found at one or more loci in 27–33% of grade II diffuse astrocytomas {776, 1558}. CGH after microdissecting small regions of tumours from paraffin sections and amplifying extracted DNA using degenerate oligonucleotide-primed polymerase chain reaction (DOP-PCR) in 30 grade II astrocytomas revealed that the most frequent copy number aberrations were gains on 7q, 5p, 9 and 19p, and losses on 19q, 1p and Xp {836}.

Promoter methylation. Approximately one third of low-grade astrocytomas show *p14^{ARF}* promoter methylation {1562}. *MGMT* promoter methylation was detected in approximately 50% of low-grade diffuse astrocytomas, and this was significantly associated with *TP53* mutations, in particular G:C->A:T transitions at CpG sites {1563}.

Gene expression profile. Gene expression patterns of low-grade diffuse astrocytoma are significantly different from those of normal brain tissues {879, 880}, pilocytic astrocytoma {880}, oligodendrogloma {882} and glioblastoma {702}.

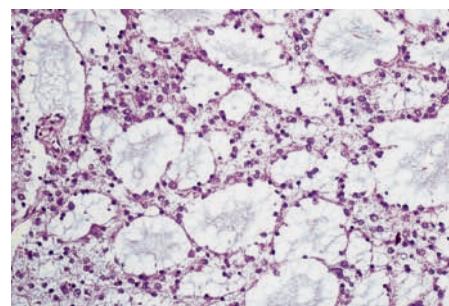


Fig. 1.20 Protoplasmic astrocytoma showing extensive mucoid degeneration.

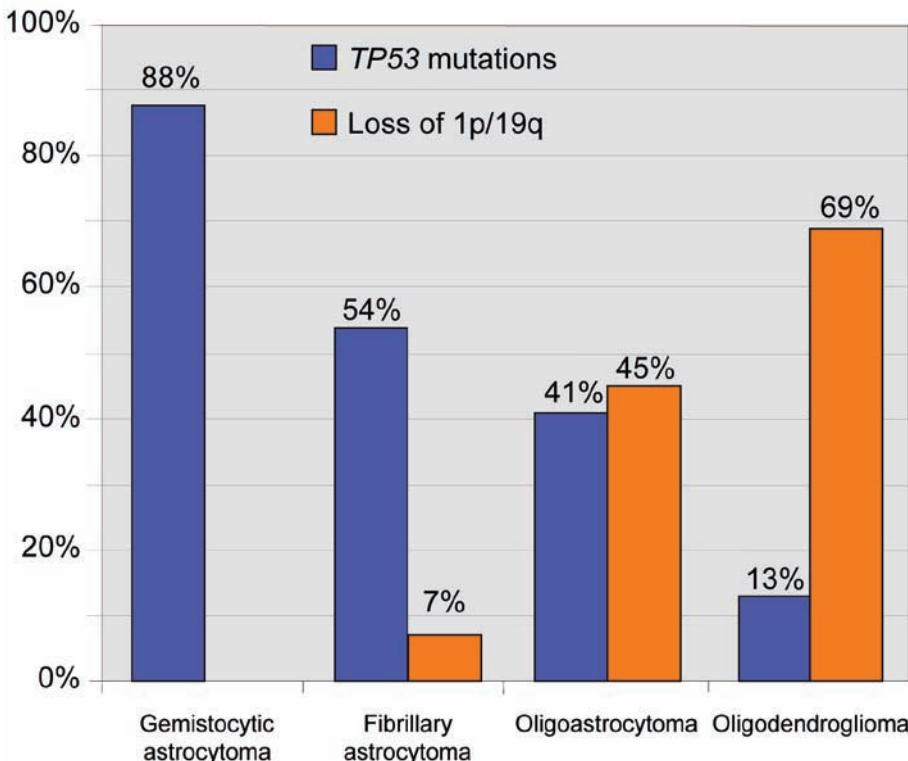


Fig. 1.21 *TP53* mutations are the genetic hallmark of low-grade astrocytomas in particular gemistocytic astrocytomas, whereas loss of 1p and 19q are frequent in oligodendroglomas. Oligoastrocytomas commonly show either *TP53* mutations or loss of 1p/19q, with these changes being largely mutually exclusive. Modified from Okamoto *et al.* {1634}.

Prognostic and predictive factors

The mean survival time after surgical intervention is in the range of 6–8 years, with marked individual variation. The total length of disease is mainly influenced by the dynamics of malignant progression to glioblastoma, which tends to occur after a mean time interval of 4–5 years {1625, 2324, 2371}. Even in the presence of a *TP53* mutation in the first biopsy, long-term survival is possible in the absence of additional genetic alterations, e.g. LOH on 10 and 19q {1627}. Despite numerous correlative studies, there is

currently no validated factor that unambiguously predicts in individual patients whether and how soon malignant progression to anaplastic astrocytoma and glioblastoma is likely to occur.

Clinical prognostic factors. Young age at diagnosis has been consistently predictive of a more favourable clinical course of patients with low-grade astrocytoma {1634, 2060}, while large tumour size appears to be a negative predictor {1046}. Gross total resection is significantly associated with longer survival

{934, 1712, 2310}. Patients with low-grade astrocytoma who present with epilepsy as the single symptom appear to have a more favourable prognosis {2310}. Conversely, presentation with a neurological deficit is associated with worse prognosis than presentation with seizures or pressure symptoms alone {413}.

Proliferation. Analysis of a wide range of astrocytic tumours showed a gross correlation of proliferation with clinical outcome {870, 1783}. A MIB-1/Ki-67 labelling index of >5% was found to constitute a threshold value for predicting shorter survival {974}.

Histopathological factors. Diffuse astrocytoma WHO grade II with a significant fraction of gemistocytes tend to undergo malignant progression more rapidly than the ordinary fibrillary astrocytoma {1208, 1634, 1712, 1713}, despite the fact that the majority of neoplastic gemistocytes are in a non-proliferative state (G0 phase of the cell cycle), suggestive of terminal differentiation {2373}. Some studies indicate that perivascular lymphocyte cuffing carries a somewhat more favourable prognosis {228, 1670}, while others failed to note a correlation with patient survival {262, 928}. The presence of numerous microcysts appears to be associated with a somewhat better prognosis {2023}.

Genetic alterations. The presence of *TP53* mutations in low-grade astrocytoma has not been shown to be a predictor of clinical outcome {1634, 1713}, although some studies have found a shorter time interval before progression in patients with low-grade astrocytoma carrying a *TP53* mutation {2139, 2371}.

Anaplastic astrocytoma

P. Kleihues
P.C. Burger
M.K. Rosenblum
W. Paulus
B.W. Scheithauer

Definition

A diffusely infiltrating, malignant astrocytoma that primarily affects adults, preferentially located in the cerebral hemispheres, and that is histologically characterized by nuclear atypia, increased cellularity and significant proliferative activity. The tumour may arise from diffuse astrocytoma WHO grade II or *de novo*, i.e. without evidence of a less malignant precursor lesion, and has an inherent tendency to undergo progression to glioblastoma.

ICD-O code

9401/3

Grading

Anaplastic astrocytoma corresponds to WHO grade III {1120, 1121}.

Synonyms

These neoplasms are also referred to as 'malignant astrocytoma' and 'high-grade astrocytoma', but these terms are ambiguous as they are occasionally also applied to glioblastoma.

Age and sex distribution

Hospital-based data from the University of Zurich show a mean age of anaplastic astrocytoma at diagnosis of approximately 45 years, with a male/female ratio of 1.6:1. In a population-based study, the mean age at biopsy was 46 years, with male/female ratio of 1.1:1 {1625}, while population-based registry data from the USA {305} show a mean age at manifesta-

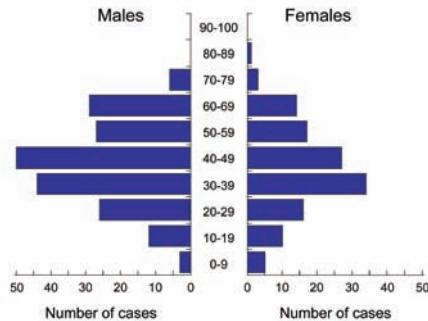


Fig. 1.22 Age distribution of anaplastic astrocytoma, based on biopsies of 319 patients treated at the University Hospital, Zurich.

tion of 51 years, with a male/female ratio of 1.31:1 {305}.

Localization

The localization of anaplastic astrocytoma corresponds to that of other diffuse infiltrating astrocytomas, with a preference for the cerebral hemispheres.

Clinical features

Symptoms and signs

Symptoms are similar to those of patients with diffuse astrocytoma WHO grade II. In some cases with a prior history of a diffuse grade II astrocytoma there are increasing neurological deficits, seizures and signs of intracranial pressure. Some patients have a shorter course, present without clinical evidence of a preceding astrocytoma WHO grade II.

Macroscopy

As diffuse astrocytoma WHO grade II, there is a tendency to infiltrate the surrounding brain without frank tissue destruction. This often leads to a marked enlargement of invaded structures, such as adjacent gyri and basal ganglia. Macroscopic cysts are uncommon, but frequently there are areas of granularity, opacity and soft consistency.

It is often difficult to grossly distinguish between anaplastic astrocytoma WHO grade III and a diffuse astrocytoma WHO grade II. On cut surface, the higher cellularity of the anaplastic astrocytoma produces a discernible tumour mass with a more clear distinction from surrounding structures than is the case in diffuse astrocytomas WHO grade II.

Histopathology

The principal histopathological features are those of a diffusely infiltrating astrocytoma with increased cellularity as compared to the grade II equivalent, distinct nuclear atypia and mitotic activity. Evaluation of the latter should be done in the context of sample size. In small specimens, such as are obtained at stereotactic biopsy, a single mitosis suggests significant proliferative activity. In such cases, Ki-67/MIB-1 immunohistochemistry may be helpful. In larger resection specimens, a single mitosis is not sufficient for WHO grade III designation {676}. Regional or diffuse hypercellularity is an important diagnostic criterion, but



Fig. 1.23 Macroscopic appearance of anaplastic astrocytomas (A) in the right fronto-temporal region. Note the ill-defined borders with the adjacent brain structures. B Another lesion in a similar location contains a large cyst but no macroscopically discernible necrosis. C Anaplastic astrocytoma of the medulla with gross enlargement of local structures.

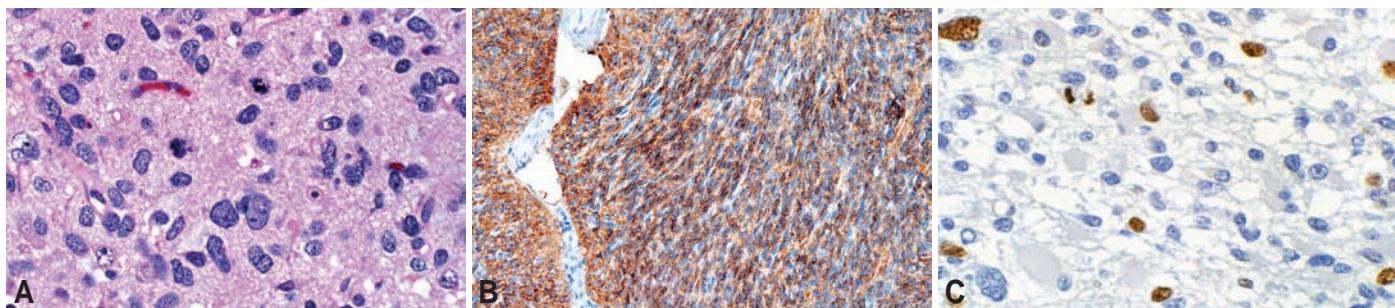


Fig. 1.24 Histological features of anaplastic astrocytoma. A Hypercellularity and hyperchromatic, irregular "naked nuclei" appearing within a fibrillary background. Several mitotic figures are evident. B GFAP immunoreactivity. C Several tumour cells show immunoreactivity for the proliferation marker MIB-1, including a cell in mitosis.

the diagnosis is still appropriate, even in the face of low cellularity if there is sufficient mitotic activity. With progressive anaplasia, nuclear morphology becomes more atypical, with increasing variations in nuclear size, shape, coarsening and dispersion of chromatin and increasing nucleolar prominence and number. Additional signs of anaplasia include multinucleated tumour cells and abnormal mitoses, but these are not required for grade III. By definition, microvascular proliferation (multilayered vessels) and necrosis are absent.

Proliferation

In contrast to diffuse astrocytoma WHO grade II, anaplastic astrocytoma displays mitotic activity. Growth fraction, as determined by the antibodies Ki-67/MIB-1, is usually in the range 5–10%, but may overlap with values for low-grade diffuse astrocytoma on one side and with glioblastoma on the other [376, 974, 1044, 1820]. Indices may vary considerably, even within a given tumour.

Genetics

From a clinical, morphologic and genetic point of view, anaplastic astrocytoma represents an intermediate stage on the route of progression to glioblastoma. It has a high frequency of *TP53* mutations and LOH 17p (50–60%), similar to that of diffuse astrocytoma (WHO grade II) [1620, 1634, 2332]. LOH 10q has been reported in 35–60% of anaplastic astrocytomas [89, 904], and *PTEN* mutations in 18–23% of anaplastic astrocytomas [430, 2370]. LOH 22q occurs at a frequency similar to that of low-grade astrocytoma (20–30%) [776, 2332], while LOH 19q is significantly more frequent (46%) than in low-grade diffuse astrocytoma [2332]. LOH 6q occurs in approximately one third of cases [1495]. *EGFR*

amplification is very uncommon in anaplastic astrocytoma (<10% of cases).

Histogenesis

Anaplastic astrocytomas are presumably derived from precursor cells committed to astrocytic differentiation. Their evolution from diffuse astrocytoma WHO grade II and their progression to glioblastoma is morphologically well defined and is supported by molecular genetic findings. Less clear is whether all anaplastic astrocytomas develop from diffuse astrocytoma WHO grade II, since some cases present clinically *de novo*, without an identifiable precursor lesion. The pattern of genetic changes, in particular the high frequency (>70%) of *TP53* mutations [2371] would be compatible with the assumption that such tumours progressed rapidly from diffuse astrocytoma WHO grade II.

Prognostic and predictive factors

Anaplastic astrocytoma has a strong tendency to progress to glioblastoma. The pace of progression is variable, but population-based studies suggest a mean time interval of approximately 2 years [1620]. As in low-grade diffuse

astrocytoma and glioblastoma, increasing age is a negative prognostic factor. One study suggests that the survival of patients with *EGFR*-amplified anaplastic astrocytoma is significantly shorter [975].

Glioneuronal tumour with neuropil-like islands

Rare infiltrating astrocytomas, usually WHO grade II or III, have focal, sharply delimited, round oval islands composed of a delicate, neuropil-like matrix with granular immunolabelling for synaptophysin. Save for one example situated in the cervico-thoracic spinal cord [770], cases have arisen in the cerebrum (8 frontal, 1 bifrontal/callosal, 2 frontotemporal, 1 temporal, 3 parietal). The islands are rimmed in rosetted fashion, inhabited at highly variable density or traversed in streaming array by oligodendrocyte-like cells as well as larger, atypical forms showing at least focal nuclear reactivity for the neuron-associated NeuN or Hu antigens. Mature-appearing neurons of intermediate or large size only exceptionally adjoin these loci, which are randomly distributed among the glial cells freely permeating the neuroparenchyma. The latter, often showing a high level of

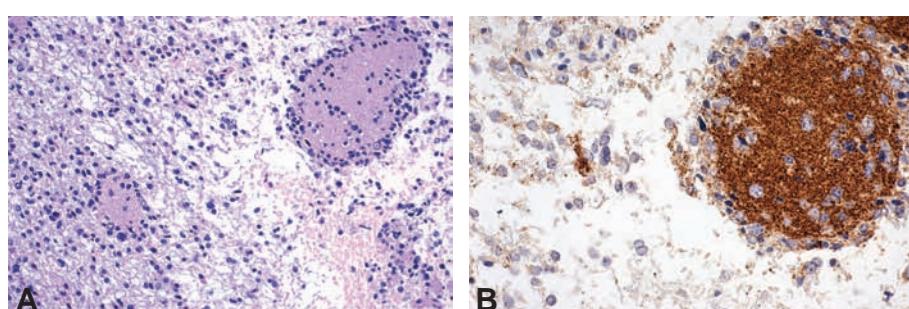


Fig. 1.25 Histological features of glioneuronal tumour with neuropil-like islands. A Neuropil-like islands appear as micronodules bordered or inhabited by oligodendrocyte-like cells and larger, more atypical cellular elements. These structures are surrounded by predominantly astroglial components of fibrillary or gemistocytic types. B Neuropil-like islands exhibit granular matrix immunoreactivity for synaptophysin.

atypia, consist mainly of GFAP-positive, fibrillary and gemistocytic elements identical to those populating conventional astrocytomas, but can include small numbers of GFAP/NeuN/ Hu-negative cells resembling oligodendrocytes. When present, mitotic activity is typically associated with the infiltrating glial components and may be conspicuous. The same can be said of complex microvascular proliferation and rarely necrosis. These anaplastic features may emerge on tumour recurrence. Aberrant nuclear immunoexpression of p53 is not uncommon and tends to be especially widespread among glial elements.

MIB-1/Ki-67 labelling activity, with occasional exceptions {1094}, is highest in regions of glial differentiation, generally modest (<4-5%) in examples of low histologic grade, and may be conspicuously elevated in tumours exhibiting features of anaplasia. Dramatically increased MIB-1/Ki-67 indices may also be encountered in recurrences {1792}. CGH assessment of one example {1094} revealed 7q21.1-qter gain and 9p21-pter loss, non-specific abnormalities observed in some diffuse astrocytomas. PCR-based loss of heterozygosity assessment of 8 cases for chromosome 1p/19q deletions revealed intact 1p/19q status in 7,

with 1 example exhibiting small interstitial deletions at 1p36 and 19q13 {99}, findings that distance these tumours from oligodendrogiomas (including variants with neurocytic rosettes). Losses of 1p and 22q have been observed in a rosette-forming glioneuronal tumour of the paediatric spinal cord {1874}; the relationship of this lesion to glioneuronal tumour with neuropil-like islands is unclear. Glioneuronal tumours with neuropil-like islands seem to behave in a manner comparable to neoplasms of diffuse astrocytic type when matched for WHO grade of their glial components.

Glioblastoma

P. Kleihues
P.C. Burger
K.D. Aldape
D.J. Brat
W. Biernat
D.D. Bigner

Y. Nakazato
K.H. Plate
F. Giangaspero
A. von Deimling
H. Ohgaki
W.K. Cavenee

Definition

The most frequent primary brain tumour and the most malignant neoplasm with predominant astrocytic differentiation; histopathological features include nuclear atypia, cellular pleomorphism, mitotic activity, vascular thrombosis, microvascular proliferation and necrosis. It typically affects adults and is preferentially located in the cerebral hemispheres. Most glioblastomas manifest rapidly *de novo*, without recognizable precursor lesions (primary glioblastoma). Secondary glioblastomas develop slowly from diffuse astrocytoma WHO grade II or anaplastic astrocytoma (WHO grade III). Due to their invasive nature, glioblastomas cannot be completely resected and despite progress in radio/chemotherapy, less than half of patients survive more than a year, with older age as the most significant adverse prognostic factor.

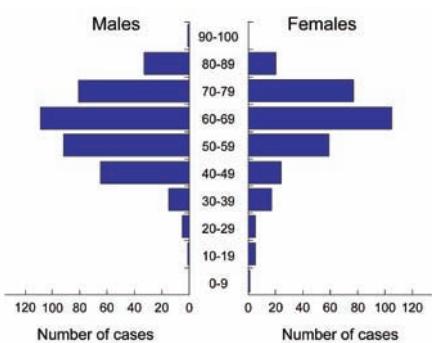
ICD-O code 9440/3

Grading

Glioblastoma and its variants correspond to WHO grade IV.

Synonyms and historical annotation

The term glioblastoma is used synonymously with "glioblastoma multiforme". Scherer {2013} and Kernohan {1093} were instrumental in developing the concept that glioblastoma is a malignant astrocytoma that sometimes develops by progression from a lower grade lesion.



Incidence

Glioblastoma is the most frequent brain tumour, accounting for approximately 12–15% of all intracranial neoplasms and 60–75% of astrocytic tumours {1260, 1625}. In most European and North American countries, the incidence is in the range of 3–4 new cases per 100 000 population per year {1260}. The incidence rate of glioblastoma in the USA, adjusted to the US Standard Population, is 2.96 new cases per 100 000 population per year {305}. The corresponding rate in a population-based study in Switzerland was 3.55 new cases, adjusted to the European Standard Population {1625}.

Age and sex distribution

Glioblastoma may manifest at any age, but preferentially affects adults, with a peak incidence at between 45 and 75 years of age. In a population-based study in the Canton of Zurich, Switzerland, the mean age of patients with glioblastoma was 61.3 years: more than 80% of patients were older than 50 years {1620}, whereas only 7 out of 715 cases (1%) were diagnosed in patients younger than 20 years old. The male:female ratio of glioblastoma patients is 1.26 in USA and 1.28 in Switzerland {1624}.

Localization

Glioblastoma occurs most often in the subcortical white matter of the cerebral hemispheres. In a series of 987 glioblastomas from the University Hospital

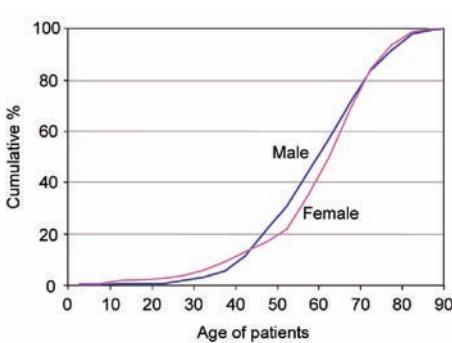


Fig. 1.26 Age and sex distribution of glioblastoma, based on 715 cases from a population-based study, Canton of Zurich, Switzerland.

Zurich, the most frequently affected sites were the temporal (31%), parietal (24%), frontal (23%) and occipital lobes (16%). Combined fronto-temporal location is particularly typical. Tumour infiltration often extends into the adjacent cortex and through the corpus callosum into the contralateral hemisphere. Glioblastoma of the basal ganglia and thalamus is not uncommon, especially in children. Intraventricular glioblastoma is exceptional {1281}. Glioblastoma of the brain stem ('malignant brain stem glioma') is infrequent and often affects children {478}. Cerebellum and spinal cord are rare sites for this neoplasm.

Clinical features

The clinical history of the disease is usually short (less than 3 months in more than 50% of cases), unless the neoplasm has developed from a lower grade astrocytoma (secondary glioblastoma). Symptoms and signs of raised intracranial pressure (for example headache, nausea/vomiting with papilledema) are common. Up to one third of patients will experience an epileptic seizure. Non-specific neurological symptoms such as headache and personality changes can also occur.

Macroscopy

Despite the short duration of symptoms in many cases of glioblastoma, the tumours are often surprisingly large at the time of presentation, and may occupy much of a lobe. The lesion is usually unilateral, but those in the brain stem and corpus callosum can be bilaterally symmetrical. Supratentorial bilateral extension is due to rapid growth along myelinated structures, in particular across the corpus callosum and along the fornices toward the temporal lobes.

Glioblastomas are poorly delineated, the cut surface showing a variable colour with peripheral greyish tumour masses and central areas of yellowish necrosis from myelin breakdown. The peripheral hypercellular zone appears macroscopically as a soft, grey rim or a grey band of tumour tissue. However, necrotic tissue

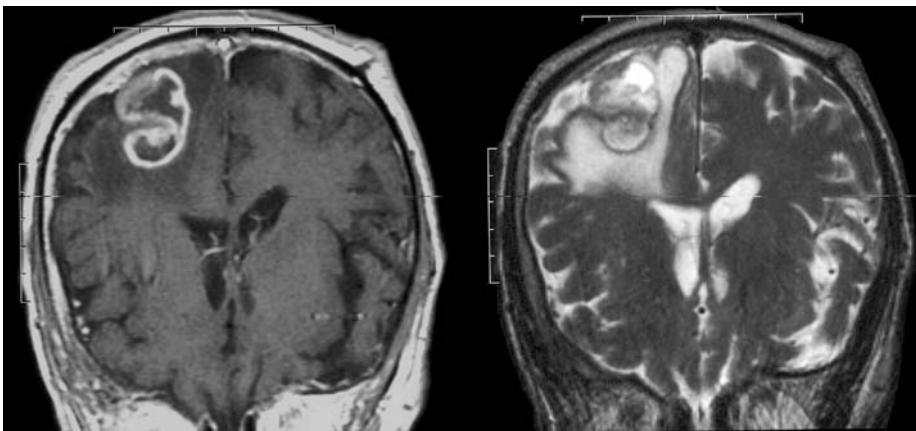


Fig. 1.27 Glioblastoma. A T1-weighted MRI with marked gadolinium-enhancement, indicating neovascularization and vascular permeability. B T2-weighted MRI reveals extensive perifocal edema.

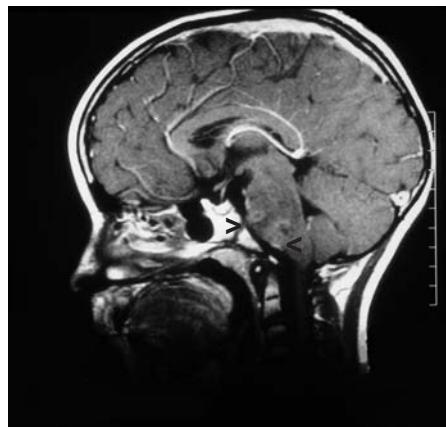


Fig. 1.28 MRI of a malignant brain stem glioblastoma in a 6 year-old child. Arrows indicate foci of necrosis.

may also border adjacent brain structures without an intermediate zone of macroscopically detectable tumour tissue. The central necrosis may occupy as much as 80% of the total tumour mass. Glioblastomas are typically stippled with red and brown foci of recent and remote haemorrhages. Extensive haemorrhages may occur and evoke stroke-like symptoms, which are sometimes the first clinical sign of the tumour.

Macroscopic cysts, when present, contain a turbid fluid and represent liquefied necrotic tumour tissue, quite in contrast to the well-delineated retention cysts in diffuse astrocytomas WHO grade II.

Most glioblastomas of the cerebral hemispheres are clearly intraparenchymal with an epicentre in the white matter. Infrequently, they are largely superficial and in contact with the leptomeninges and dura and may be interpreted by the neuroradiologist or surgeon as metastatic carcinoma, or as an extra-axial lesion such as meningioma. Cortical infiltration may produce a preserved gyriform rim of thickened grey cortex overlying a necrotic zone in the white matter.

Spread and metastasis

Although infiltrative spread is a common feature of all diffuse astrocytic tumours, glioblastoma is particularly notorious for its rapid invasion of neighbouring brain structures {253}. A very common feature is extension of the tumour through the corpus callosum into the contralateral hemisphere, creating the image of a bilateral, symmetrical lesion ('butterfly glioma'). Similarly, rapid spread is observed in the internal capsule, fornix, anterior commissure and optic radiation.

These structures may become enlarged and distorted but continue to serve as a 'highway', allowing the formation of new tumour masses at their opposite projection site, thus leading to the neuro-radiological image of a multifocal glioblastoma. Invading cells reside outside the contrast-enhancing rim of the tumour, thereby escaping surgical resection and evading high doses of radiation during radiotherapy. This likely represents the source for local recurrence usually seen after such therapy.

Despite its rapid, infiltrative growth, glioblastoma tends not to invade the subarachnoidal space, and consequently rarely metastasizes via the cerebrospinal fluid {688}. Extension within and along perivascular spaces is another typical mode of infiltration, but invasion of the vessel lumen seems to occur infrequently {142, 242}. Haematogenous spread to extraneuronal tissues is very rare in patients without previous surgical intervention {1687, 1688}. Peritoneal metastasis via ventriculoperitoneal shunt has been observed {558}. Penetration of the dura, venous sinus and bone is exceptional {1708, 1776, 2095}.

Mechanisms of invasion

A number of molecular mediators of invasion in glioblastoma have been described, including activation of the TGF- β and AKT pathways {1177, 2406}. Tumour hypoxia may also promote invasion through the activation of HIF-1 α {1068}. An important aspect of glioblastoma invasion is the elaboration of a migration-enhancing extracellular matrix by tumour cells {1142}, as well as secretion of proteolytic enzymes which

permit invasion through this matrix. Consistent with this notion are recent gene expression profiling studies that identify a subset of tumours with elevated expression of extracellular matrix components as well as intracellular proteins associated with cell motility {608, 1742}. The interplay between the variety of matrix and growth factor receptors as well as activation of signalling pathways which facilitate tumour cell invasion is being recognized as a composite, dynamic consequence of altered cell-cell adhesion, proteolytic remodelling and synthesis of ECM, as well as selective expression and activation of integrins {136}. Activation of migration (seen at the leading edge of the neoplasm) appears to be associated with a decrease in proliferation rate {681}, which may have therapeutic consequences {2136}.

Multifocal glioblastomas

Although multifocality is not unusual when defined radiologically, the incidence of truly multiple, independent gliomas occurring outside the setting of inherited neoplastic syndromes is unclear. Even careful post-mortem studies on whole brain sections may not always reveal a connection between apparently multifocal gliomas, as the cells infiltrating along myelinated pathways are often small, polar and largely undifferentiated. In a careful histological analysis, Batzdorf & Malamud {114} concluded that 2.4% of glioblastomas are truly multiple independent tumours, a value similar to that reported by Russell & Rubinstein (2.3%) {1959}. In a post-mortem study, Barnard & Geddes {102} found that 7.5% of gliomas (including oligodendrogiomas) are multiple independent tumours and

that in approximately 3% of these, tumour foci vary in their histological appearance. True multifocal glioblastomas are most likely polyclonal if they occur infra- and supratentorially, i.e. outside easily accessible routes like the cerebrospinal fluid pathways or the median commissures [1977]. Multiple independently arising gliomas would, by definition, be of polyclonal origin and their existence can only be proven by application of molecular

markers which, in informative cases, allow a distinction between tumours of common or independent origin [141, 157, 1184].

Primary and secondary glioblastoma

The terms primary and secondary glioblastoma were first used by Scherer in 1940 who noted: "From a biological and clinical point of view, the secondary glioblastomas developing in astrocy-

tomas must be distinguished from 'primary' glioblastomas; they are probably responsible for most of the glioblastomas of long clinical duration" [2013]. The majority of glioblastomas (>90%) develop very rapidly with a short clinical history (usually <3 months), without clinical or histopathological evidence of a pre-existing, less malignant precursor lesion (primary or *de novo* glioblastoma). They typically develop in older patients (mean,

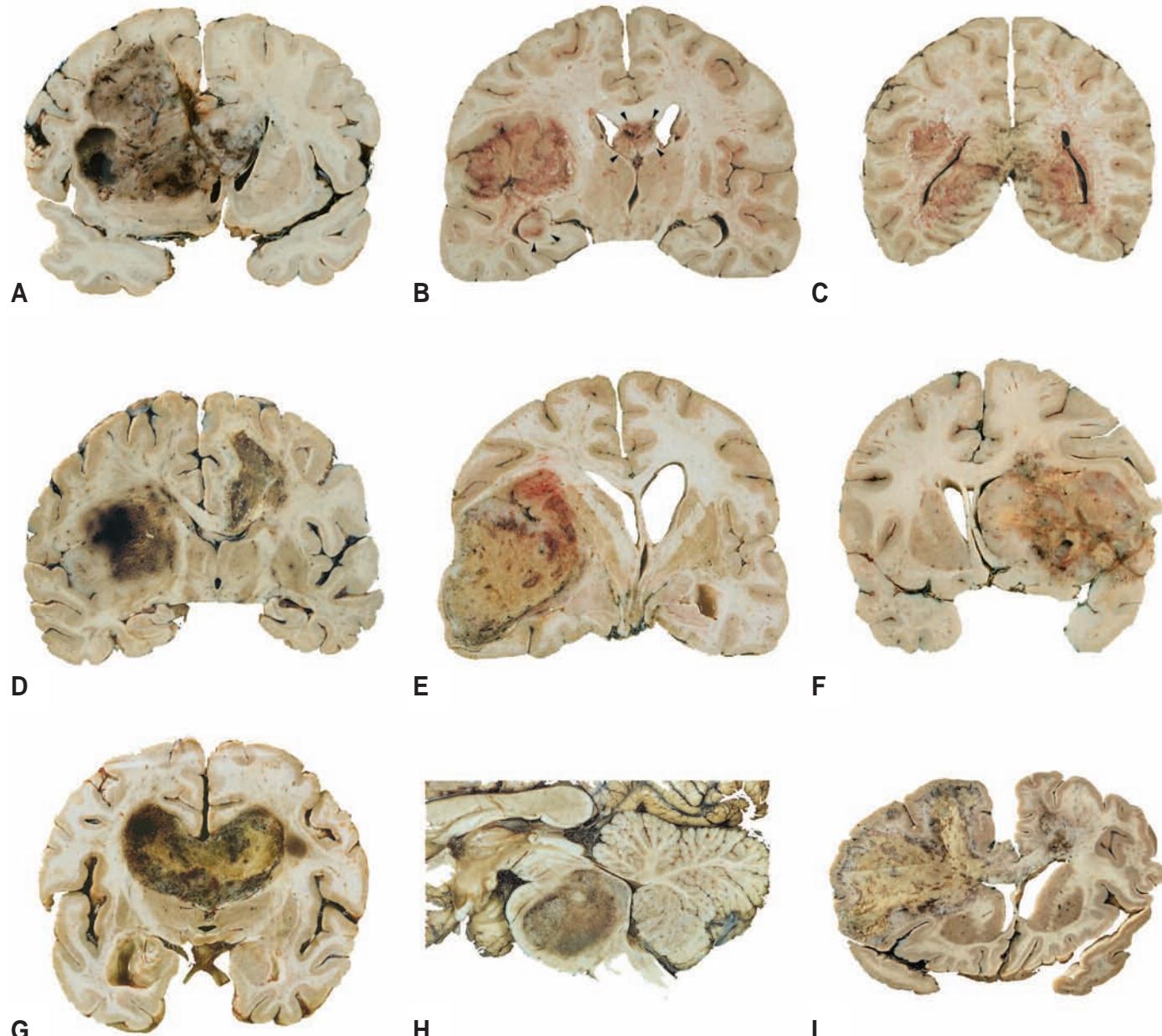


Fig. 1.29 Macroscopic features of glioblastoma (GBM). A Large GBM in the left frontal lobe extending into the corpus callosum and the contralateral white matter. B,C GBM of the left fronto-temporal region with invasion of the fornices, spread to the lower horn of the left ventricle and (C) extension to the corpus callosum and adjacent parieto-occipital structures. D GBM of the left basal ganglia and spread into the right hemisphere with formation of a cystic necrosis. E GBM of the left hemisphere with extensive necrosis occupying most of the tumour mass. F Right fronto-temporal GBM with mass shifting and subfalcial herniation. G GBM with unusual intraventricular location. H Malignant brain stem GBM in a child. I GBM of the left hemisphere with extensive necrosis and spread to the right frontal lobe via the corpus callosum.

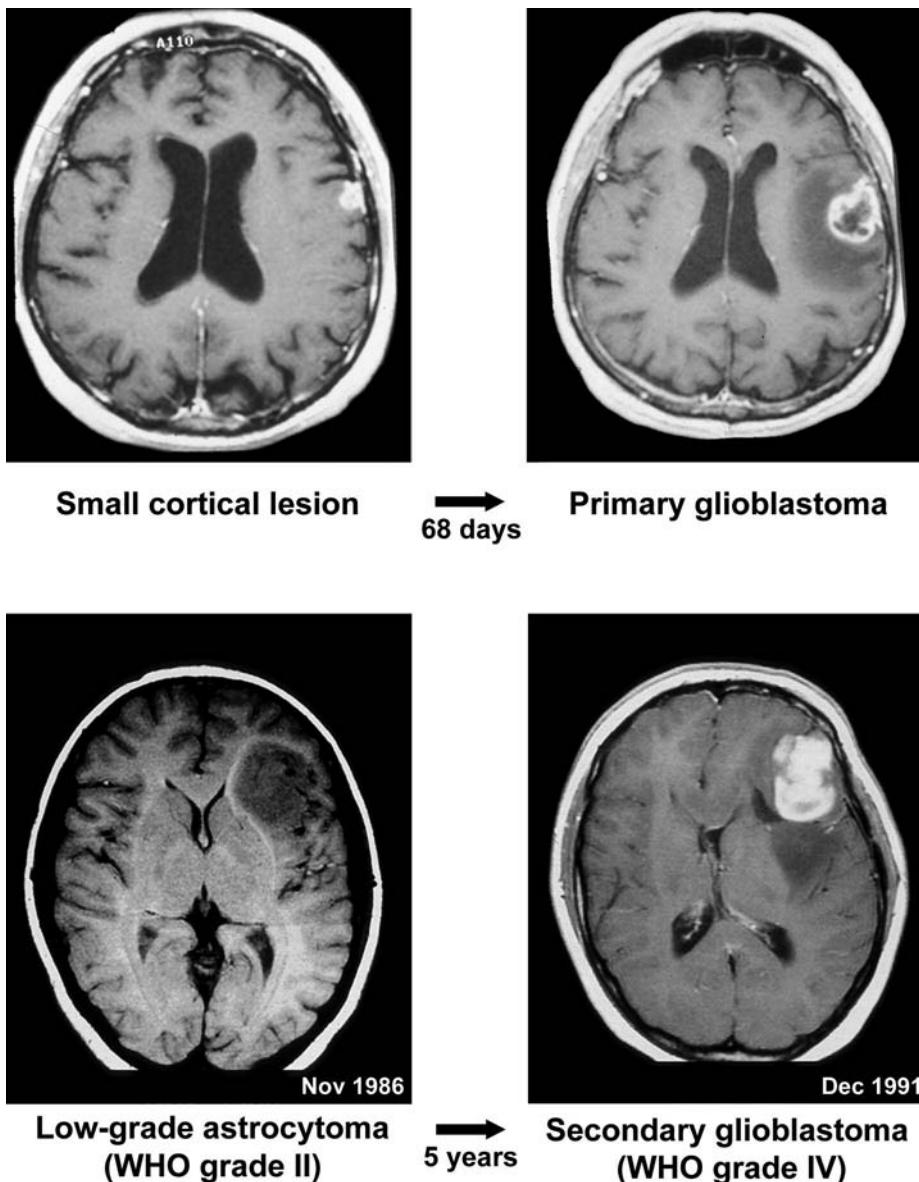


Fig. 1.30 Rapid evolution of a primary glioblastoma in a 79 year-old patient (upper). MRI shows a small cortical lesion that within 68 days developed into a full-blown glioblastoma with perifocal edema and central necrosis. This is in contrast to the development of secondary glioblastoma through progression from low-grade astrocytoma (lower).

62 years) {1620, 1625A}. Neuroimages of the dynamic growth of a primary glioblastoma and a secondary glioblastoma are shown in Fig. 1.30. Glioblastoma may also develop through progression from diffuse astrocytoma (WHO grade II) or anaplastic astrocytoma (WHO grade III); and these are termed "secondary glioblastomas". They are much less frequent than primary glioblastomas (<10% of all glioblastomas) {486, 1620, 1625A}, and typically develop in younger patients (mean, 45 years). The time to progression from diffuse astrocytoma WHO grade II to gli-

blastoma varies considerably, with time intervals ranging from less than 1 year to >10 years {1627}, the mean interval being 4–5 years {1625, 2371}. Survival of patients with secondary glioblastoma is significantly longer (median survival time, 7.8 months) than for those with primary glioblastoma (4.7 months), but this is likely to be the reflection of younger age of secondary glioblastoma patients {1620, 1625}. Primary and secondary glioblastoma constitute relatively distinct disease entities that evolve primarily through different genetic pathways, show different expression

profiles {1625}, and are likely to differ in response to therapy, but share a high frequency of LOH 10q, which is likely to be associated with the overall glioblastoma phenotype {620, 622, 1620, 1625A}.

Histopathology

Glioblastoma is an anaplastic, cellular glioma composed of poorly differentiated, often pleomorphic astrocytic tumour cells with marked nuclear atypia and brisk mitotic activity. Prominent microvascular proliferation and/or necrosis are essential diagnostic features.

As the term glioblastoma "multiforme" suggests, the histopathology of this tumour is extremely variable. While some lesions show a high degree of cellular and nuclear polymorphism with numerous multinucleated giant cells, others are highly cellular, but rather monotonous. The astrocytic nature of the neoplasms may be easily identifiable, at least focally, in some tumours, but difficult to recognize in others owing to the high degree of anaplasia. The regional heterogeneity of glioblastoma is remarkable and poses challenges to histopathological diagnosis on specimens obtained by stereotactic needle biopsies {254}.

Tissue patterns

The diagnosis of glioblastoma is typically based on the tissue pattern rather than on the identification of certain cell types. The presence of highly anaplastic glial cells, mitotic activity and vascular proliferation and/or necrosis is required. The distribution of these key elements within the tumour is variable, but large necrotic areas usually occupy the tumour centre, while viable tumour cells tend to accumulate in the periphery. The circumferential region of high cellularity and abnormal vessels corresponds to the contrast-enhancing ring seen radiologically. Vascular proliferation is seen throughout the lesion, often around necrotic foci and in the peripheral zone of infiltration.

Secondary structures

The migratory capacity of glioblastoma cells within the CNS becomes readily apparent when they reach borders that constitute a barrier: tumour cells line up and accumulate in the subpial zone of the cortex, in the subependymal region, around neurons ("satellitosis"), and about

vessels. Such patterns, known as “secondary structures” {2014}, result from the interaction of glioma cells with host brain structures, and are highly diagnostic. Secondary structures may be noted in other highly infiltrative gliomas such as gliomatosis cerebri and oligodendrogloma {2012, 2014}. This concept also extends to the adaptation of tumour cells to myelinated pathways, where the former often acquire a fusiform, polar shape. Identifying neoplastic astrocytes in the perifocal zone of edema and at more distant sites poses a challenge for the pathologist, in particular when dealing with stereotaxic biopsies {423}. A feature of many glioblastomas, especially the small cell variants, is the extensive involvement of the cerebral cortex. Secondary structures and most of the apparently multifocal glioblastomas reflect the pathways of migration of glioma cells in the CNS {1268}. The subependymal region may also be diffusely infiltrated, especially in the terminal stages of disease.

Epithelial structures

Occasionally, glioblastoma contains foci with glandular and ribbon-like epithelial structures {1932}. These elements have a large oval nucleus, prominent nucleolus and round, well-defined cytoplasms. They are also referred to as “adenoid” glioblastoma. Expression of GFAP in these areas may be reduced, but the astrocytic nature of these structures can usually be established unequivocally. Small cells with even more epithelial features and cohesiveness are less

common {1084}. A mucinous background and a ‘mesenchymal’ component (gliosarcoma) are not uncommon in such neoplasms.

Cellular composition

Few human neoplasms are as heterogeneous in composition as is glioblastoma. While poorly differentiated, fusiform, round or pleomorphic cells may prevail, more differentiated neoplastic astrocytes are usually discernible, at least focally {254}. This is particularly true of glioblastoma resulting from the progression of diffuse astrocytoma WHO grade II. The transition between areas that still have recognizable astrocytic differentiation and highly anaplastic cells may be either continuous or abrupt. A sudden change in morphology may reflect the emergence of a new tumour through the acquisition of one or more additional genetic alterations {620}. Cellular pleomorphism includes the formation of small, undifferentiated, lipidized, granular and giant cells. In addition, there are often areas where bipolar, fusiform cells form intersecting bundles and fascicles prevail. The accumulation of highly polymorphic tumour cells with well-delineated plasma membranes and a lack of cell processes may mimic metastatic carcinoma or melanoma.

Small cell glioblastoma. Although small cells are common in glioblastoma, they are predominant or exclusive in a subset known as “small cell glioblastoma” {1720}. These tumours feature a highly mono-

morphic cell population characterized by small, round to slightly elongated, densely packed cells with mildly hyperchromatic nuclei, high nuclear: cytoplasmic ratio and modest atypia. GFAP immunoreactivity may be minimal. The tumours must be distinguished from poorly differentiated anaplastic oligodendroglomas. Small cell glioblastoma has high proliferative activity.

Glioblastoma with oligodendrogloma component.

Occasional glioblastomas contain foci that resemble oligodendrogloma. These areas are variable in size and frequency. Two large studies of malignant gliomas suggest that necrosis is associated with significantly worse prognosis in the setting of anaplastic gliomas with both oligodendroglial and astrocytic components {1474, 2301}: patients whose tumours had necrosis had a substantially shorter median overall survival compared to patients whose tumours did not (see Anaplastic oligoastrocytoma in Chapter 2). Such tumours should be classified as “glioblastoma with oligodendroglial component”, although they may have a better prognosis than standard glioblastoma {799, 857, 1185}.

Multinucleated giant cells

Large, multinucleated tumour cells are often considered a hallmark of glioblastomas and occur with a spectrum of increasing size and pleomorphism. While typical, the presence of multinucleated giant cells is neither an obligatory feature nor associated with a more malignant

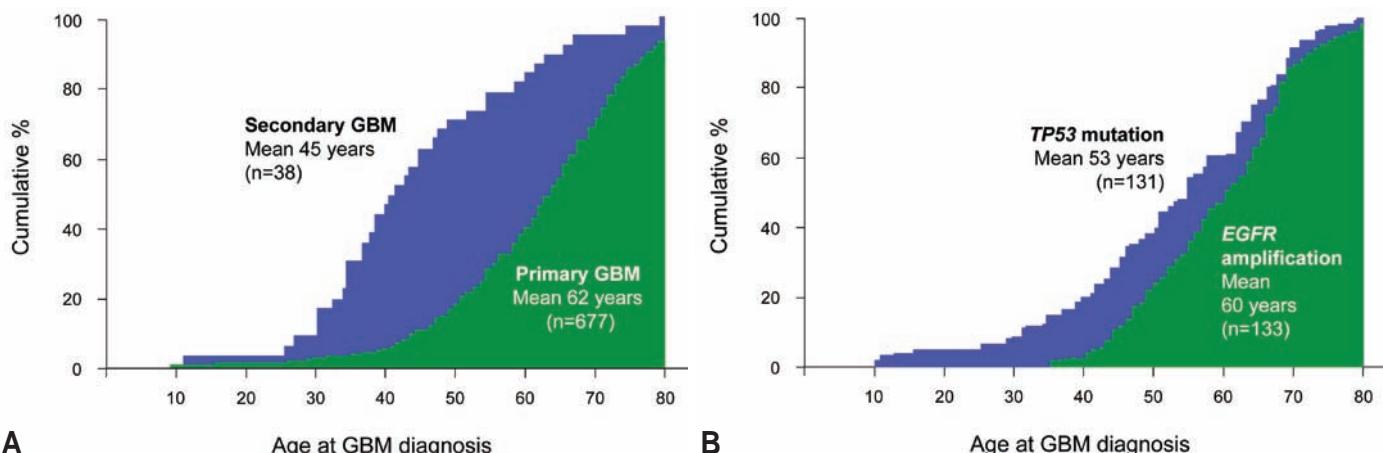


Fig. 1.31 A Cumulative age distribution of patients with primary and secondary glioblastomas. Secondary glioblastomas develop in younger patients than primary glioblastomas. B Cumulative age distribution of patients with TP53 mutations and those with EGFR amplification. TP53 mutations are present in glioblastoma in all of the age groups of patients, whereas no glioblastoma in patients less than 35 years shows EGFR amplification. Modified from Ohgaki *et al.* {1620}.

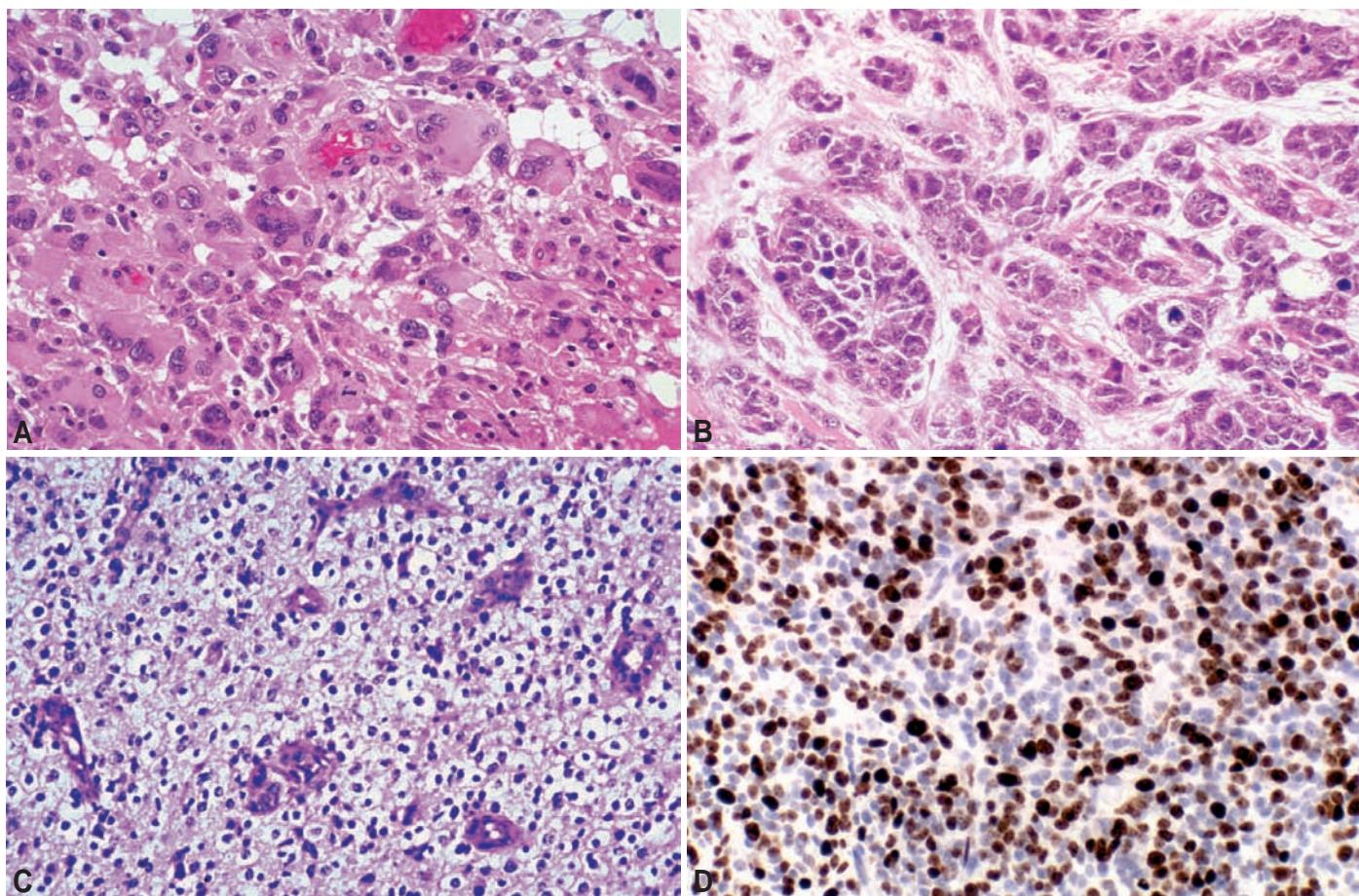


Fig. 1.32 Glioblastoma. A Glioblastoma with high degree of anaplasia. B Adenoid GBM with formation of glandular structures. C Oligodendroglial component in a GBM. D Small cell glioblastoma with very high MIB-1 labelling index.

clinical course [252]. Despite their malignant appearance, these cells are regarded as a type of regressive change. If multinucleated giant cells dominate the histopathological picture, the designation ‘giant cell glioblastoma’ is justified.

Gemistocytes

At the other extreme of glioblastoma differentiation are “gemistocytes” and the related “fibrillary astrocyte”, recognizing that transition forms connect these two types. Gemistocytes have copious, glassy, non-fibrillary cytoplasm that appears to displace the dark, angulated nucleus to the periphery of the cell. Processes radiate from the cytoplasm, but are stubby and not long-reaching. GFAP staining is largely confined to the periphery of the cell, with the central hyaline organelle-rich zone remaining largely unstained. Perivascular lymphocytes frequently populate gemistocytic regions while often avoiding other

regions in the same neoplasm. When present in large numbers, particularly in a patient known to have a pre-existing glioma, these cells may represent a lower-grade precursor lesion within a secondary glioblastoma. Better-differentiated areas can sometimes be identified radiologically as a non-contrast-enhancing peripheral region and, in whole brain sections, as grade II to III astrocytomas clearly distinct from foci of glioblastoma [254, 2012]. Immunohistochemical studies have emphasized the low proliferation index of the neoplastic gemistocyte itself, despite the tendency of gemistocytic astrocytoma WHO grade II or III lesions to rapidly progress to glioblastoma [2373]. The proliferating component appears to be a population of cells with larger hyperchromatic nuclei and scant cytoplasm [2373].

Granular cells

Large cells with a granular, periodic acid-Schiff (PAS) positive cytoplasm may

occur scattered within glioblastoma. In rare cases, they may dominate and create the impression of a granular cell tumour similar to that of the pituitary stalk or other tissues [457, 771], where they are thought to be myogenic or Schwann-cell-derived (see Chapter 14). In the cerebral hemispheres transitional forms between granular cells and neoplastic astrocytes can be identified in some cases, but in others it is difficult to identify any conventional astrocytoma component. Although larger and more coarsely granular, the tumour cells also resemble macrophages. Given their lysosomal content the tumour cells may be immunoreactive for macrophage markers such as CD68. Occasional cells may have peripheral immunopositivity for GFAP, but most cells are negative [219, 655]. On the basis of both these findings it is most likely that the granular cells represent glioma cells with a distinct degenerative pathway.

Lipidized cells

Cells with a foamy cytoplasm are another feature occasionally observed in glioblastoma. In rare cases, they predominate, and the respective lesion has been designated 'malignant glioma with heavily lipidized (foamy) tumour cells' {1080, 1087, 1932, 2208}. The lipidized cells may be grossly enlarged {664}. If such lesions are superficially located in young people, the diagnosis of pleomorphic xanthoastrocytoma should be considered, particularly if the xanthomatous cells are surrounded by basement membranes positive on reticulin staining {1081}. Other lipid-rich lesions have epithelioid cytological features {1932}.

Perivascular lymphocytes

Perivascular lymphocyte cuffing occurs in a minority of glioblastomas, most typically in areas with a homogeneous gemistocytic component. The inflammatory cells have been phenotypically characterized on the basis of their immunoreactivity. CD8+ T-lymphocytes, which are MHC-class-I-restricted, prevail and occur in approximately 75% of tumours. CD4+ lymphocytes appear to be present in smaller numbers {185, 1937} while B-lymphocytes are detectable in less than 10% of cases {1937}. Expression of CD44 and ICAM-1 is observed in glioma cells, but not in tumour-infiltrating lymphocytes {1229}. Whether perivascular lymphocyte infiltration influences tumour growth is still a matter of dispute: while some studies indicate a beneficial effect {228, 1670}, others failed to note a correlation with patient survival. The presence or absence of lymphocytes is not

used in prognostication {262, 928}. In addition to haemotogenous lymphocytes, there are perivascular cells that are supposedly resident in the CNS; they express MHC class II antigens and immunoreactivity to PGM1 antibody, and may have a scavenger role {1101}.

Metaplasia

In general, this term refers to the reversible acquisition by a differentiated cell of morphological features typical of another differentiated cell type, and is most frequently observed as a preneoplastic lesion of epithelial tissues. However, the term is also used to designate aberrant differentiation in neoplasms. In glioblastoma, this reflects a high degree of genomic instability and is exemplified by foci displaying features of squamous epithelial cells, i.e. epithelial whorls with keratin pearls and cytokeratin expression {257, 1526}. Adenoid and squamous epithelial metaplasia are more common in gliosarcoma than in the ordinary glioblastoma {1084, 1526}. This is similarly true for the formation of bone and cartilage, which prevails in gliosarcoma and in a variety of childhood CNS neoplasms {1412}.

Microvascular proliferation

In addition to necrosis, the presence of microvascular proliferation (previously called endothelial cell proliferation) is a histopathological hallmark of glioblastoma. On light microscopy, classic microvascular proliferations typically appear as 'glomeruloid tufts', which are most commonly located in the vicinity of necrosis and

appear directionally oriented to it. Histologically, microvascular proliferation in glioblastoma typically consists of multilayered, mitotically active endothelial cells together with smooth muscle cells/pericytes {751, 1547, 2396}.

Morphologically inconspicuous vessels have a MIB-1 labelling index of 2–4%, while proliferated tumour vessels have an index of >10% {2369}. A less common form of vascular malformation with a claim to the term endothelial proliferation is an intraluminal proliferation of cells in small and medium-sized vessels. Vascular thrombosis often occurs, and this may play a role in the pathogenesis of ischaemic tumour necrosis {1917}.

Proliferation

Proliferative activity is usually prominent, with detectable mitoses in nearly every case. Atypical mitoses are frequently present. Mitotic activity, however, can vary widely between tumours and also shows regional heterogeneity within a tumour. The growth fraction, as determined by the antibodies Ki-67/MIB-1, shows great regional variation. Mean values of 15–20% have been reported {260, 448, 974, 1044, 2038}. Tumours with small, undifferentiated, fusiform cells often show marked proliferative activity, in contrast to tumours composed of neoplastic gemistocytes, which typically have a lesser degree of proliferation {2373}. Despite the wide range of proliferation indices observed in glioblastoma, an association between proliferation index and clinical outcome has not been demonstrated {1527}.

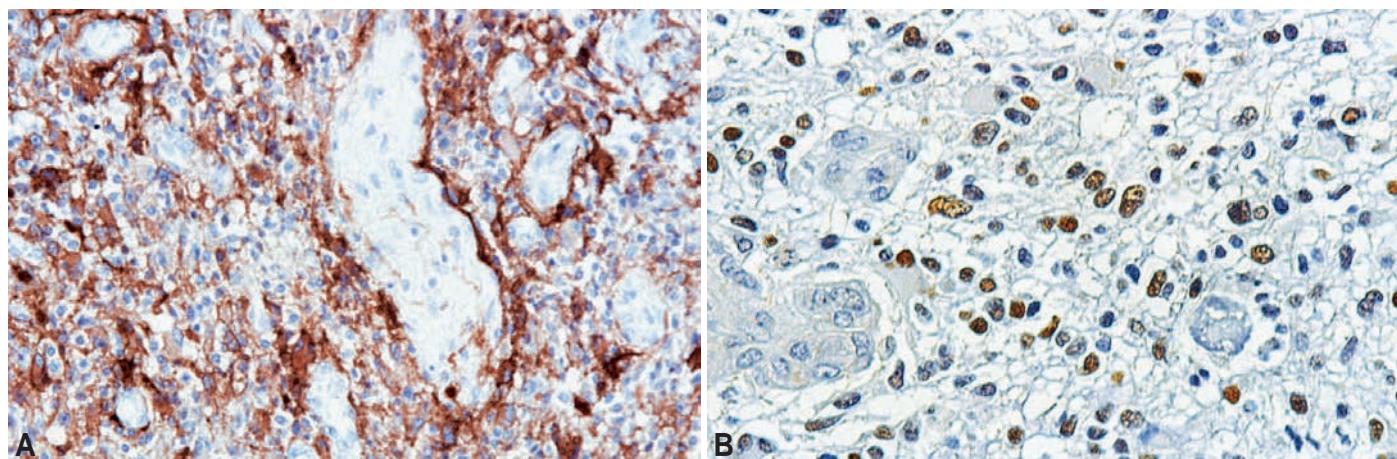


Fig. 1.33 Glioblastoma with (A) overexpression of EGFR in the plasma membrane of tumour cells and (B) nuclear accumulation of p53 protein in tumour cells but not endothelial cells.

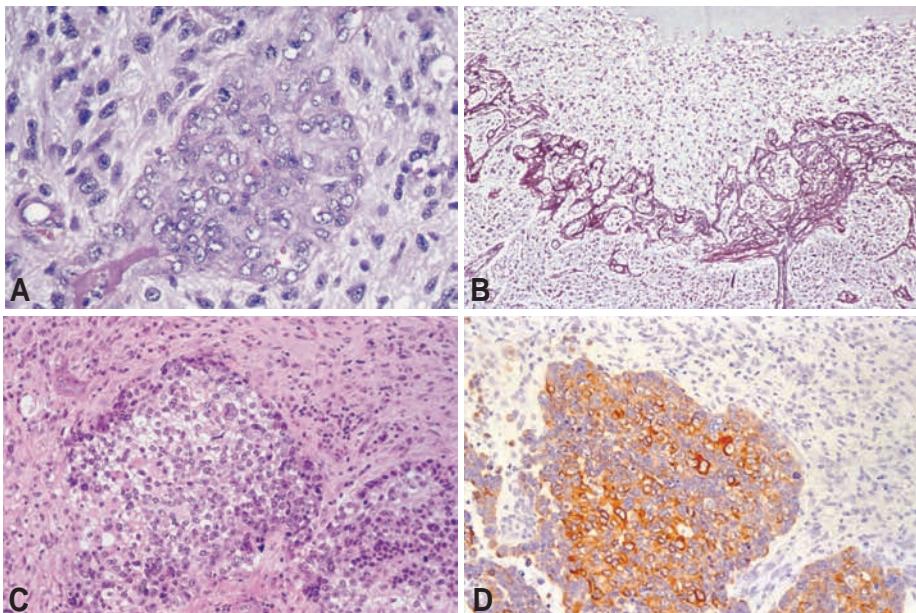


Fig. 1.34 A Microvascular proliferation in a glioblastoma with formation of a multilayered 'glomeruloid tuft'. B Reticulin stain showing a 'garland' of proliferated glioma vessels. C Focal squamous cell metaplasia in a glioblastoma characterized by (D) marked cytokeratin expression.

Angiogenesis

Glioblastomas are among the most vascularized tumours in humans. Glioblastoma vascularization occurs through several mechanisms including {583A} vessel co-option, e.g. adoption of pre-existing vessels by migrating tumour cells, {1371A} classical angiogenesis, e.g. sprouting of capillaries from pre-existing vessels by endothelial cell proliferation and migration and {10A} vasculogenesis, e.g. homing of bone marrow-derived cells that support vessel growth from the peripheral blood into the perivascular space {583A, 1371A}. Hypoxia is considered a major driving force of glioblastoma angiogenesis {10A} and leads to intracellular stabilization of the hypoxia master-regulator hypoxia-inducible factor 1- α (HIF-1 α). HIF-1 α accumulation leads to transcriptional activation of more than 100 hypoxia-regulated genes that control angiogenesis (VEGF, angiopoietin), cellular metabolism (carbonic anhydrase, lactate dehydrogenase), survival/apoptosis (BNIP) and migration (c-met, CXCR4). Vascular endothelial growth factor (VEGF) appears to be the most important mediator of glioma-associated vascular dysfunctions. VEGF is primarily produced by perinecrotic palisading cells as a consequence of cellular hypoxia. VEGF induces tumour angiogenesis, increases vascular permeability (edema) and regulates homing of

bone marrow derived cells {10A}. In addition to endothelial cells, pericytes/smooth muscle cells and perivascular bone marrow derived cells participate in the vascular remodelling processes typically observed in glioblastoma. These remodelling processes lead to microvascular proliferations that are a histopathological hallmark of glioblastoma.

Necrosis

Tumour necrosis is a fundamental feature of glioblastoma, and its presence is one of the strongest predictors of aggressive clinical behaviour in diffuse astrocytomas {252, 857, 1840}. Necrosis can be seen by neuroimaging as a non-enhancing core, which represents large areas of non-viable tumour tissue and may comprise more than 80% of the total tumour mass. These regions appear grossly as a yellow or white granular coagulum {250}. Microscopically, necrotic glioma cells can vaguely be identified, as well as the faded images of large, dilated necrotic tumour vessels. Areas of necrosis do not generally attract a large number of phagocytes. Occasionally, preserved tumour vessels with a corona of viable tumour cells are seen within extensive areas of necrosis. It is assumed that these large necroses are due to insufficient blood supply and are therefore ischaemic in nature.

A second form of necrosis that can be

noted microscopically consists of multiple, small, irregularly-shaped band-like {2514} or serpiginous {257} foci, surrounded by radially oriented, densely packed, small, fusiform glioma cells in a 'pseudopalisading' pattern, a histological hallmark of the glioblastoma {1261}. These pseudopalisading necroses are equally frequent in primary and secondary glioblastoma {2253}. The relationship of pseudopalisading necrosis to the larger regions of confluent necrosis has not been clearly defined, yet some have suggested that there is a temporal evolution. The central area of smaller pseudopalisading structures often consists of a fine fibrillary network without viable or necrotic glioma cells, whereas larger pseudopalisading structures always contain necrotic centres. Compared to adjacent tumour cells, pseudopalisading cells have higher rates of apoptosis and lower rates of proliferation {214}. They also are hypoxic and strongly express HIF-1 α and its transcriptional target VEGF {2498}. Hypoxic upregulation of VEGF and other pro-angiogenic factors is considered to be responsible for the microvascular proliferation noted in glioblastoma {1760}. Many aspects of necrogenesis remain to be elucidated. It has been suggested that a sequence starting from small clusters of apoptotic cells leads to pseudopalisading necrosis and, eventually, large areas of ischaemic necrosis. Others have speculated that microscopic vaso-occlusion and thrombosis leads to hypoxia and hypoxia-induced cell migration to form pseudopalisading structures with central necrosis {1917}.

Apoptosis

Apoptosis, the programmed death of individual cells, is initiated through mechanisms that include death receptor (DR) ligation by members of the tumour necrosis factor (TNF) family, including TRAIL (TNF-related apoptosis-inducing ligand)/DR5 and FasL (CD95L)/Fas (CD95) {1660}. The higher levels of apoptosis seen in pseudopalisading cells may be due to increased expression or ligation of death receptors {214}. TRAIL induces apoptosis in glioblastoma by binding to DR5 and ultimately activating caspase-8 {767}. Both Fas and FasL levels are higher in astrocytomas than normal brain and correlate with tumour grade {2192, 2253}. Most Fas

expression in glioblastoma is within pseudopalisading cells around necrosis and physical interactions between tumour cells expressing Fas and FasL may promote apoptosis. Compared to coagulative necrosis, the overall levels of cell death due to apoptosis are low in malignant gliomas, and apoptotic rates do not correlate with prognosis {1471, 2020}.

Histogenesis

The cellular origin of glioblastoma is a topic of considerable contemporary investigation and controversy. It has been thought for many years that the expression of markers of differentiated astrocytes by glioblastoma cells arose because of the de-differentiation of the cells after transformation. More recently, the cellular, biochemical and genetic heterogeneity that typify glioblastoma, together with the different clinical responses of histologically similar tumours has led to the notion that the tumours arise from the malignant transformation of either a bipotential precursor cell {2448} or an even more primordial cell, the neural stem cell {1422}. This idea has received considerable support because of the coincident anatomical position in the subventricular zone of the brain of dividing cells with stem-like properties and the development of glioblastoma. Moreover, cells with stem cell-like properties have been isolated from glioblastoma tumours and cell lines. These cells, termed brain tumour stem cells (BTSC), represent a small subpopulation but have the capacity of self-renewal as well as tumourigenic behaviour in animals. Thus, these BTSC may represent the descendants of a neural stem cell that was the target of a carcinogenic insult and that is seeding the tumour through its unlimited growth potential. While the accumulating data {1161, 1979, 2104, 2325} are consistent with this interpretation, direct proof remains to be found {1008A}.

Genetics

Malignant transformation of neuroepithelial cells is a multistep process driven by the sequential acquisition of genetic alterations. One would therefore expect that of all astrocytic neoplasms, glioblastoma should contain the greatest number of genetic changes, and this is indeed the case. On the basis of the different combinations of *TP53* mutations, loss of heterozygosity (LOH) on chromo-

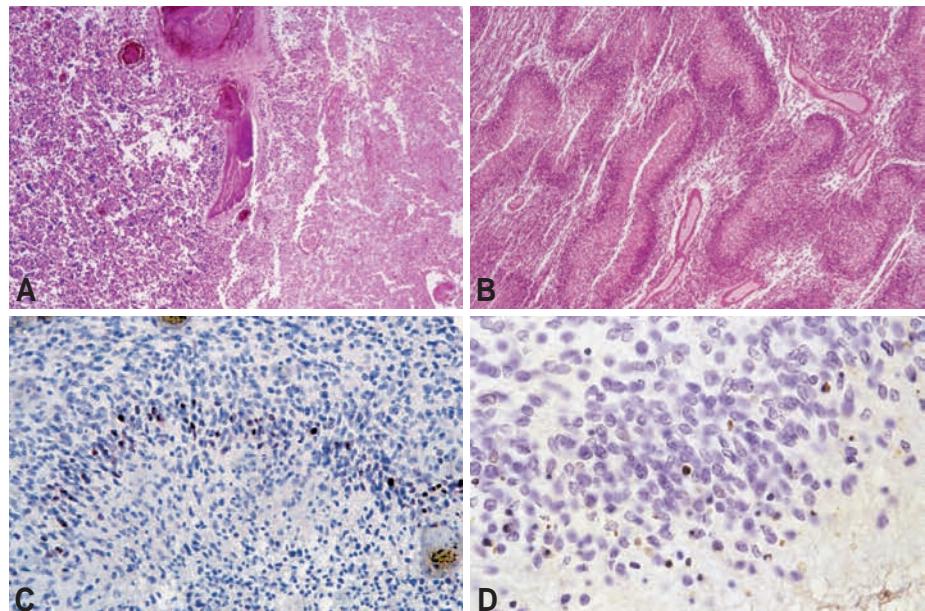


Fig. 1.35 Necrosis and apoptosis in glioblastoma. A Large ischaemic necrosis (right). Also note several large, thrombosed tumour vessels. B Multiple serpentine pseudopalisading necroses. C HIF-1 α expression in perinecrotic palisading cells. D Apoptosis accumulating in pseudopalisading tumour cells (TUNEL).

somes 10 and 17p and *EGFR* amplification, the presence of subsets of glioblastomas with distinct genetic alterations {1257, 2341} has been correlated with clinical pathways to glioblastoma (see primary and secondary glioblastoma).

Epidermal growth factor receptor (*EGFR*)

The gene encoding *EGFR*, a cellular homologue of v-erbB {2284}, is located on chromosome 7. *EGFR* encodes a 170 kDa protein, which is a transmembrane receptor responsible for sensing its extracellular ligands, such as EGF and TGF- α , and for transducing this proliferation signal. *EGFR* is the most frequently amplified gene in glioblastoma {629}, and the amplified *EGFR* genes are typically present as double-minute extrachromosomal elements. *EGFR* amplification is associated with overexpression: all glioblastomas with *EGFR* amplification showed EGFR overexpression and 70–90% of those with EGFR overexpression showed *EGFR* amplification {158, 2252}. *EGFR* amplification occurs in approximately 40% of primary glioblastoma {513, 1620, 2435}, but rarely in secondary glioblastoma {1620, 2372}. In a population-based study, *EGFR* amplification was not detected in any glioblastoma from patients younger than 35 years {1620}. Amplification of the *EGFR* gene is often associated with structural alterations, and several major

truncated variants have been identified {1833}, the most common being variant III (*EGFR*VIII), also called de2-7*EGFR* or delta *EGFR* {2411}, which is present in 20–50% of glioblastomas with *EGFR* amplification {158, 2042, 2169}. *EGFR*VIII results from a non-random 801-bp in-frame deletion of exons 2–7 of the *EGFR* gene {607,2169}; it is structurally and functionally similar to v-erbB, and constitutively activated in a ligand-independent manner, leading to cell proliferation via the PI3-kinase, RAS and mitogen-activated protein kinase signalling pathways {351}. *EGFR*VIII is a promising target for therapy, since it is tumour-specific and occurs on the surface of glioblastoma cells with *EGFR* amplification {513, 1019, 2042}. *EGFR* point mutations are infrequent (3–5%) in glioblastomas of both European and Asian patients {624}.

PI3K/PTEN/AKT pathway

The *EGFR*, or other growth factor receptors, becomes activated upon binding of growth factors (EGF, TGF- α) and recruits PI3K (phosphatidylinositol 3-kinase) to the cell membrane. PI3K converts phosphatidylserine-4,5-bisphosphate (PIP2) to PIP3. PIP3 activates downstream effector molecules such as AKT and the mammalian target of rapamycin (mTOR), which results in cell proliferation and cell survival. The *PTEN*

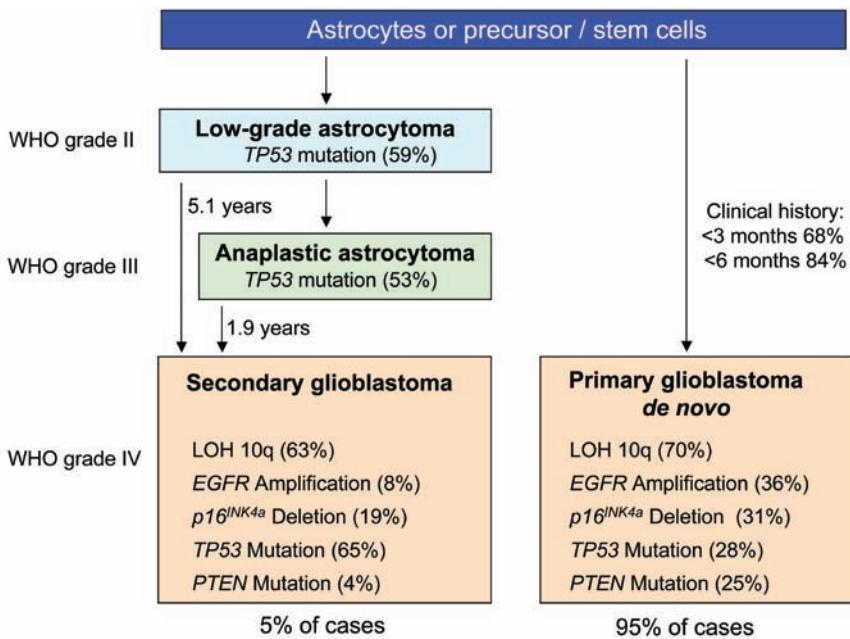


Fig. 1.36 Timing and frequency of genetic alterations in the evolution of glioblastoma. Note that LOH 10q is frequent in both primary and secondary glioblastomas, and TP53 mutations are early and frequent genetic alterations in the pathway leading to secondary glioblastoma. Modified from Ohgaki *et al.* {1620}.

(phosphatase and tensin homology) gene, located at 10q23.3 {1312, 2145}, encodes a protein with a central domain homologous to the catalytic region of protein tyrosine phosphatases, which is important in the function of protein phosphatase {1544, 2207} and 3'-phosphoinositol phosphatase activities {1377}. PTEN inhibits the PIP3 signal {1446}, thereby inhibiting cell proliferation. The amino terminal domain of PTEN is homologous to tensin and auxilin, which is important in regulating cell migration and invasion by directly dephosphorylating focal adhesion kinase (FAK) {2207}.

PTEN is mutated in 15-40% of cases {491, 1139, 2252}, and almost exclusively in primary glioblastoma {1620, 2252}. PTEN homozygous deletion may occur, but is rare in glioblastoma (<2%) {1140}. Of 78 PTEN mutations detected in glioblastoma, nonsense mutations (13%) and deletions or insertions leading to stop codons (32%) were equally distributed throughout the exons, whereas 33% were missense mutations leading to amino acid changes, preferentially located in exons 1-6, i.e. in the region homologous to tensin, auxilin and dual-specificity phosphatases {1620}. This suggests that cells with PTEN truncation at any site or PTEN missense mutations

in the region homologous to tensin/auxilin and dual-specificity phosphatases acquire a transformed phenotype.

The PIK3CA p110 α catalytic subunit of PI3K is a 34kb gene located at 3q26.3 that consists of 20 exons coding for a protein of 124 kDa. PIK3CA mutations appear to be infrequent (<10%) in glioblastoma {225, 775, 1117A, 1141} except for one study which reported a 27% frequency {1978}. PIK3CA amplification also occurs in glioblastoma but studies vary significantly, with reported frequencies ranging from 0% to 64% {887, 1140, 1500}.

TP53/MDM2/p14^{ARF} pathway

The TP53 gene (at 17p13.1) encodes a protein which plays a role in several cellular processes including the cell cycle, response of cells to DNA damage, cell death, cell differentiation, and neovascularization {188}. Following DNA damage, p53 is activated and induces transcription of genes such as p21Waf1/Cip1 {2079, 2159}. The MDM2 gene (at 12q14.3-q15) encodes a 54 kDa protein, that binds to mutant and wild-type p53 proteins, thereby inhibiting the ability of wild-type p53 to activate transcription from minimal promoter sequences {1510, 1635}. Conversely, the transcription of the MDM2 gene is induced by wild-type

p53 {97, 2486}. In normal cells, this autoregulatory feedback loop regulates both the activity of the p53 protein and the expression of MDM2 {1743}. In addition, MDM2 promotes the degradation of p53 {792, 1212}. The p14^{ARF} (a part of the complex CDKN2A locus on chromosome 9p21) gene {1394, 2157, 2159, 2495} encodes a protein that directly binds to MDM2 and inhibits MDM2-mediated p53 degradation and transactivational silencing {1033, 1772, 2159, 2495}. Conversely, expression of p14^{ARF} is negatively regulated by p53 {2159}. Thus, loss of normal p53 function may result from altered expression of any of the TP53, MDM2 or p14^{ARF} genes.

TP53 mutations are a genetic hallmark of secondary glioblastoma (>65%), and in almost all cases they are already present in precursor low-grade lesions or anaplastic astrocytoma {2371, 2372}. TP53 mutations are significantly less frequent (approx. 25%) in primary glioblastoma {1620, 2372}. The distribution and type of TP53 mutations also differs between primary and secondary glioblastoma: in the latter, 57% of mutations were located in the two hotspot codons 248 and 273; in the former, mutations were more equally distributed among the exons, with only 17% occurring in codons 248 and 273. G:C->A:T transitions at CpG sites were significantly more frequent in secondary than in primary glioblastoma {1620}, suggesting different molecular mechanisms underlying the acquisition of TP53 mutations in these subtypes.

Amplification or overexpression of MDM2 is an alternative mechanism for escaping p53-regulated control of cell growth. Amplification is observed in about 10% of those glioblastomas without TP53 mutations {1844}, i.e. the primary glioblastoma {159}. Overexpression of MDM2 was observed immunohistochemically in more than 50% of primary glioblastomas {159}.

Loss of p14^{ARF} expression is frequent in glioblastoma (76%), and this correlated with homozygous deletion or promoter methylation of the p14^{ARF} gene {1562}. There was no significant difference in the overall frequency of p14^{ARF} alterations between primary and secondary glioblastomas (50% vs. 75%) {1562}. The analysis of multiple biopsies from the same patients revealed that p14^{ARF} methylation was already present in one third of low-grade astrocytoma {1562}.

p16^{INK4a}/CDK4/RB1 pathway

This signalling pathway is important for the control of progression through G1 into the S phase of the cell cycle [2054]. The *RB1* gene (at 13q14) encodes the 107 kDa retinoblastoma (RB1) protein. The CDK4/cyclin D1 complex phosphorylates the RB1 protein, thereby inducing release of the E2F transcription factor that activates genes involved in the G1->S transition [2079]. The *p16^{INK4a}* gene (at the *CDKN2A* locus, 9p21) encodes a protein that binds to CDK4 and inhibits the CDK4/cyclin D1 complex, thereby negatively regulating G1->S transition [2079]. Loss of cell cycle control may therefore result from altered expression of any of these genes, i.e. loss of *p16^{INK4a}* expression, overexpression/amplification of CDKs or loss of RB function. In glioblastoma, *p16^{INK4a}* deletion and *RB1* alterations appear to be mutually exclusive [160, 265, 2282]. Inactivation of genes in this pathway is common in both primary and secondary glioblastoma [160] at an overall frequency of 40-50% [160, 1562].

The *CDK4* gene (at 12q13-14) is amplified in about 15% of high-grade gliomas [1596, 1846], particularly in those without *p16^{INK4a}* deletion. A few tumours without *p16^{INK4a}* deletion or *CDK4* amplification had *CDK6* amplification, suggesting that the two proteins can functionally compensate for each other [386].

LOH on 13q including the *RB1* locus was detected in 12% of primary and 38% of secondary glioblastoma [1564]. Promoter methylation of the *RB1* gene was significantly correlated with loss of RB1 expression and was found significantly more frequently in secondary (43%) than in primary glioblastoma (14%) [1565]. *RB1* promoter methylation was not detected in low-grade and anaplastic astrocytoma, indicating that it is a late event during astrocytoma progression [1565].

Loss of chromosome 10

LOH 10 is the most frequent genetic alteration in glioblastoma, occurring in 60-80% of cases [904, 1048, 1620, 1626, 1832]. Many glioblastomas show loss of one entire copy of chromosome 10, but LOH studies identified at least 3 commonly deleted regions, i.e. 10p14-p15, 10q23-24, and 10q25-pter, suggesting the potential of several tumour-suppressor genes [632, 634, 904, 1048,

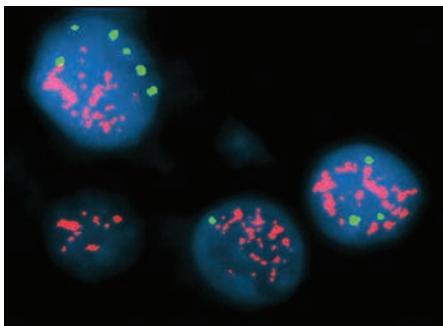


Fig. 1.37 *EGFR* amplification (many more red *EGFR* versus green centromere 7 signals) by FISH analysis in a small cell glioblastoma.

1832]. LOH 10q occurs at similar frequencies in primary and secondary glioblastoma [622, 1620], with common deletions at 10q25-qter. LOH 10q25-qter is also directly associated with histologically recognized transition from low-grade or anaplastic astrocytoma to glioblastoma phenotypes [622]. In contrast, LOH 10p occurs almost exclusively in primary glioblastoma, leading to loss of entire chromosome 10, but very rarely in secondary glioblastoma [622]. LOH 10 is rare in lower grades of astrocytic tumours [167, 966]. There is a discrepancy between LOH for the chromosomal region containing the *PTEN* gene (75-95% of glioblastoma) and the frequency of *PTEN* mutations (30-44%) [2234], suggesting the involvement of another not yet identified tumour suppressor gene(s) on 10q. The Deleted in Malignant Brain Tumours 1 (*DMBT1*) gene (at 10q25.3-26.1) is considered one of the candidate tumour suppressor genes on 10q [1508]. It is homozygously deleted in 13-38% of glioblastomas [1508, 2123]. The genomic structure of *DMBT1* has recently been elucidated and points to a possible role in the evolution of chromosomal instability [1507]. Screening for genome wide chromosomal imbalances using array CGH revealed that loss of chromosome 10 was associated not only with changes in the expression of genes located on chromosome 10, but also with genome-wide differences in gene expression [1593].

Loss of other chromosomal loci

LOH 1p was detected at a similar frequency in primary and secondary glioblastoma (12-15%). LOH 19q occurs in 20-25% of unselected glioblastomas

[2332, 2339, 2340], and is significantly more frequent in secondary glioblastoma (54%) than in primary glioblastoma (6%) [1564]. Deletion mapping has narrowed the candidate region to the 19q13.3 region between the D19S412 and STD loci [1929]. LOH 22q occurs in 20-30% of gliomas of all grades [633, 966], suggesting the presence of a tumour suppressor gene that plays a role in the early stages of astrocytoma progression. LOH 22q was significantly more frequent in secondary glioblastoma (82%) than in primary glioblastoma (41%) [1558].

Characterization of 22q deletions in primary glioblastoma identified two minimally deleted regions at 22q12.3-13.2 and 22q13.31, while 22 of 23 secondary glioblastomas affected shared a deletion in the same small (957 kb) region of 22q12.3, a region in which the human tissue inhibitor of metalloproteinases-3 (*TIMP-3*) is located. *TIMP-3* promoter methylation was observed at a significantly higher frequency in secondary than in primary glioblastoma and correlated with loss of *TIMP-3* expression [1558]. Array CGH has revealed two small common and overlapping regions at 6q26 in glioblastoma and anaplastic astrocytoma [903].

Co-presence of genetic alterations in glioblastomas

LOH 10q is not only the most frequent genetic alteration, but also typically co-presents with any of the other genetic alterations, consistent with it occurring late in disease progression [1620]. *EGFR* amplification is typically associated with *p16^{INK4a}* deletions [797, 802, 1620], while *TP53* mutations, *EGFR* amplification and *PTEN* mutations show inverse associations [1620, 2114]. Analyses using array CGH in 50 primary glioblastomas revealed 3 major genetic subgroups, i.e. tumours with chromosome 10 loss and chromosome 7 gain, tumours with only chromosome 10 loss in the absence of chromosome 7 gain, and tumours without copy number change in chromosomes 7 or 10 [1489].

Correlation between genetic alterations and histologic features

The small cell glioblastoma phenotype frequently shows *EGFR* amplification [255, 857, 1720], *p16^{INK4a}* homozygous deletion [857], *PTEN* mutations [857] and LOH 10q [1720]. Glioblastomas containing

>5% multinucleated giant cells were found to be associated with frequent TP53 mutations but infrequent EGFR amplification [857].

Promoter methylation

O⁶-Methylguanine-DNA methyltransferase (MGMT) is a repair protein that specifically removes promutagenic alkyl groups from the *O⁶* position of guanine in DNA, thereby protecting cells against alkylating agents [713, 1399]. Loss of MGMT expression may be caused by methylation of promoter CpG islands [537, 1811]. *MGMT* promoter methylation is frequently present in glioblastoma (45–75%) [129, 801, 1034, 1563], and was associated with longer survival of glioblastoma patients treated with temozolomide [801]. Secondary glioblastoma showed a higher frequency of *MGMT* promoter methylation than primary glioblastoma [129, 1563]. The presence of *MGMT* promoter methylation in low-grade astrocytomas is significantly associated with frequent G:C->A:T transitions. Promoter methylation of the *TP53*, *p14^{ARF}*, *RB1* and *TIMP-3* genes are also common in glioblastoma and were reported to be more frequent in secondary than primary glioblastoma [1562, 1563, 1565, 1886].

Expression profiles

Based on gene expression patterns, glioblastoma can be distinguished from pilocytic astrocytoma [1886], low-grade astrocytoma [999], anaplastic astrocytoma [630] and oligodendrogloma [630]. However, expression patterns also vary significantly among glioblastoma cases [702, 1317]. This is particularly true for primary glioblastoma [702], possibly due to a higher degree of genomic instability. Several studies using expression arrays revealed that glioblastoma typically shows overexpression of growth factor-related genes, and genes involved in cell migration [1870] and angiogenesis [702, 1317]. EGFR-overexpressing glioblastoma has a distinct global gene transcriptional profile, and the expression of 90 genes could distinguish EGFR-overexpressing from EGFR-nonexpressing glioblastoma [1487]. Primary and secondary glioblastoma also show different expression profiles [2122, 2271].

Adult vs. paediatric glioblastomas

Glioblastoma in children has a genetic

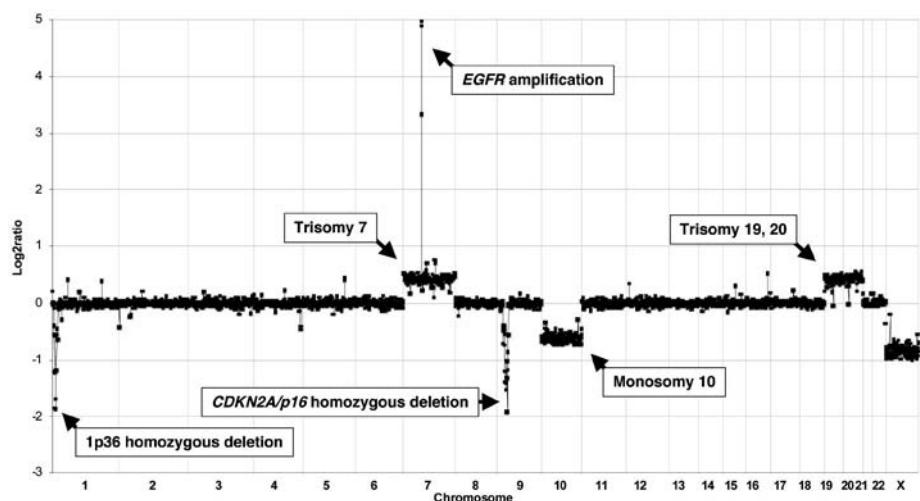


Fig. 1.38 1 Mb array-CGH profile of a male glioblastoma against female reference. Unpublished data from K. Ichimura and V.P. Collins.

profile distinct from that of glioblastoma of adult patients. Although paediatric glioblastoma usually develops *de novo*, the genetic pathway leading to primary glioblastoma in adults appears to be rarely involved in children, as reflected by high frequency of *TP53* mutations (approx 40%), and the low frequency of *EGFR* amplification (6%), *p16^{INK4a}* deletion (19%), and the absence of *MDM2* amplification [1585, 2180]. *TP53* mutations appear to be less frequent in high-grade gliomas (glioblastoma and anaplastic astrocytoma) in children <3 years old (12%) than older children (40%) [1767]. Microsatellite instability (MSI) due to DNA mismatch repair deficiency is rare in adult glioblastoma, but occurs in 27% of anaplastic astrocytoma and glioblastoma manifesting in children, and this phenomenon is associated with shorter survival. The frequency of *TP53* mutations was significantly lower in cases with MSI [49]. Comparative genomic hybridization revealed that chromosomal alterations significantly differ between paediatric and adult high-grade astrocytoma, and those characteristic for paediatric glioblastoma are +1q, +3q, +16p, -8q and -17p [1884].

Genetic susceptibility

The occurrence of glioblastoma in more than one member of a family is sometimes seen. This is most often the case within the inherited tumour syndromes (see Chapter 13) that include the Turcot and Li-Fraumeni

syndromes, neurofibromatosis type 1 and multiple enchondromatosis [605, 1447, 2306].

Prognostic and predictive factors

Despite progress in surgery, radiotherapy and chemotherapy of brain tumours, the overall survival of patients with glioblastoma remains extremely poor. In retrospective population-based studies from Switzerland and Canada, less than 20% of patients survived more than one year and less than 3% lived longer than 3 years [1620, 1625]. Clinical trials show a better outcome, with median survival rates of approximately 12 months, as they have a strong bias toward the recruitment of younger patients and those with higher preoperative Karnofsky performance scores, which are strong predictors of a more favourable clinical outcome.

Age

Virtually all therapy trials have shown that younger glioblastoma patients (<50 years at diagnosis) have a significantly better prognosis [252, 712]. In a large population-based study, age was the most significant prognostic factor; this persisted through all of the age groups in a linear manner [1620]. Patients with secondary glioblastoma survived significantly longer than those with primary glioblastoma [1620], but this is likely due to their age rather than a reflection of different biological behaviour.

Histopathology

The presence and extent of necrosis are associated with shorter survival {252, 764, 857, 1744}.

Genetic alterations

Data on the prognostic value of *TP53* mutations in glioblastomas are contradictory, showing either no association or that the presence of *TP53* mutations was a favourable prognostic factor. In a large population-based study, the presence of *TP53* mutations was predictive of longer survival but this was not significant when adjusted for their usually younger age {1620}. There is no consistent correlation of *EGFR* amplification with survival, largely irrespective of the age at clinical manifestation {1620}. LOH 10 is the most frequent genetic alteration in glioblastoma and is associated with reduced survival {1620}. The presence of *PTEN* mutations is not associated with prognosis of glioblastoma patients {78, 1620, 2032, 2114}.

Biomarkers

YKL-40 (chitinase-3-like-1), a secreted protein of unknown function, is over-expressed in glioblastoma {2271}, and its expression is associated with LOH 10q, poorer radiation response, shorter time to progression and reduced overall survival {1708A}. It is typically co-expressed with matrix metalloproteinase-9 (MMP-9), and its detection in serum has been used to monitor patients for recurrent tumour growth {864}. One report showed that increased expression of GD3 synthase mRNA in combination with decreased GalNAcT message correlated with increased survival in glioblastoma patients {1613}. Insulin-like growth factor-binding protein-2 (IGFBP-2) and IGFBP-5 accumulate in glioma cells and the extent of expression correlated with histological grade {518, 2362}. IGFBP-2 enhances invasion {2361}, but there is currently no evidence that it is predictive of poorer outcome.

Mechanisms of treatment response

Glioblastoma is highly resistant to therapy, with only marginal survival increases in a small fraction of patients, even after aggressive surgical resection, external beam radiation therapy (both conformal and whole brain), and maximum tolerated doses for chemotherapy with agents such as temozolomide or nitrosourea. Over the

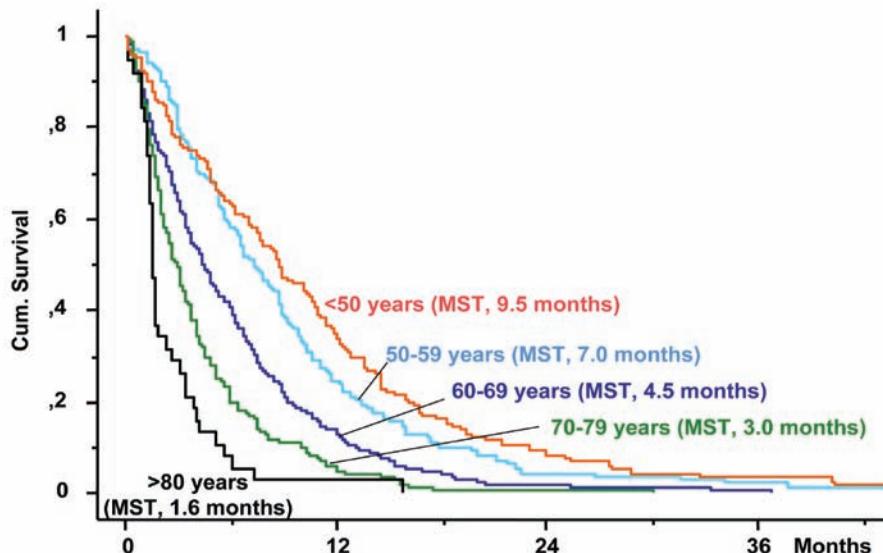


Fig. 1.39 Age of patient is a significant prognostic factor of survival of glioblastoma patients at the population level. Modified from Ohgaki et al. {1620}.

last 30–40 years, hundreds of clinical trials have had only marginal therapeutic success, although most brain tumour centres are observing a few long-term survivors among patients treated aggressively with multimodality therapy. Therapeutic resistance is due to: 1) poor drug delivery because of partial blood-brain-barrier preservation and high tumour interstitial pressure; 2) genome instability produced by point mutations, loss of heterozygosity, chromosome deletions and rearrangements, gene amplification, and epigenetic gene silencing which leads to broad genotypic and phenotypic heterogeneity resulting in clonal populations of cells resistant to any single therapeutic modality; 3) invasive properties of glioblastoma cells enabling malignant cells to cross the corpus callosum, spread even to the brain stem and spinal cord, and reside behind a completely intact blood-brain barrier; 4) the presence of a population of neural stem cell-like cells that may harbour resistance mechanisms that are distinct from those of the majority of non-stem-like tumour cells and that may contribute to cellular heterogeneity; and 5) retention of abundant DNA repair machinery that abrogates effectiveness of chemotherapy and radiotherapy.

Molecular abnormalities in glioblastoma provide specific mechanisms of resistance and susceptibility to therapy. The *TP53* pathway inactivated by multiple mechanisms leads to a lack of apoptosis and

cell cycle arrest. Mutations of the retinoblastoma pathway in both primary and secondary glioblastoma result in failure to provide appropriate cell cycle arrest. Although point mutations of the *Ras* gene in glioblastoma are rare, the *Ras* pathway is secondarily activated through *IGFR*, *EGFR*, and *PDGFR* signalling.

Downstream events such as silencing of the *NF1* tumour suppressor gene may also activate the *Ras* pathway to cause uncontrolled cellular proliferation. Similarly, the *PI3K* pathway may be activated by abnormal *IGF1*, *EGF*, or *PDGF* signalling or downstream by abnormalities in the *PTEN* gene {1853}. These redundant signalling pathway abnormalities suggest that a single, specific, small-molecule signalling-pathway inhibitor might be expected to be ineffective in treating glioblastoma. This expectation has proven true in the testing of a large number of small-molecule inhibitors of signalling pathways in multiple glioblastoma xenografts. In a clinical trial of gefitinib, an EGF tyrosine kinase inhibitor, minimal responses were observed {1871}. On the other hand, testing individual glioblastoma biopsies for *EGFRvIII* and *PTEN* {1446} was able to identify patients responsive to the erlotinib or gefitinib *EGFR* kinase inhibitors. This may suggest that combinations of mutations common to glioblastoma may need to be targeted in these therapeutic approaches.

Recently, a population of neural stem-like glioma cells (SCLGCs) has been identified in glioblastoma [96, 643, 905, 2105]. These SCLGCs are highly tumourigenic in immunosuppressed mice, inducing intracranial tumours with a much smaller cellular inoculum than non-SCLGC cells from glioblastomas. Intracranial tumours induced by these SCLGCs had morphologic hallmarks of glioblastoma, such as markedly increased vascularity and endothelial cell proliferation, necrosis, and haemorrhage. These intracranial tumours responded to treatment with a neutralizing antibody to VEGF, bevacizumab, and the same humanized VEGF neutralizing antibody has showed a 60–65% response rate in a phase II trial in recurrent glioblastomas [2351]. Bao *et al.* [96] have shown that one of the mechanisms of radiation resistance may reside in the SCLGC population preferentially, and that the mechanism of radiation resistance is activation of the DNA checkpoint response. Bone morphogenic protein BMP4 causes a significant reduction of stem-like precursor cells of human glioblastoma and abolishes their tumour-initiating capacities *in vivo*.

Cellular immunotherapy or tumour vaccine approaches began decades ago, but have had little effect on the survival of glioblastoma patients. One of the mechanisms discovered for the failure of cellular immunotherapy was the production of TGF- β by glioblastoma cells, which caused a relatively profound immunosuppression that was evident at the time of diagnosis and prior to any therapy. Only recently has the cellular mechanism of the immunosuppression in glioblastoma patients been discovered. Fecci *et al.* [556, 557] showed that glioblastoma patients have a diminished population of CD4 cells, which although capable of normal immune function, are hindered in immune function by an increased number of regulatory T (Treg) cells in the CD4 compartment. Moreover, depletion of Treg cells in a syngenic murine animal model bearing intracranial tumours derived from a spontaneous astrocytoma resulted in immune rejection of the intracranial astrocytomas, with statistically significant survival increases. Removing Treg cells and targeting tumour-specific antigens such as EGFRvIII by pulsing autologous dendritic antigen-presenting cells and re-administering them to individual glioblastoma



Fig. 1.40 Well-circumscribed, superficially located giant cell glioblastoma in the left parietal lobe.

patients are avenues that may have promise.

As molecular methods advance for obtaining comprehensive data from glioblastoma biopsies in real time on genetic abnormalities, gene expression, signalling and programmed cell death pathway status, hypoxia, SCLGC composition, and DNA repair protein levels and cellular distribution, subsets of patients that will respond to specific monotherapies should be identified. Examples are clinical tools such as recursive petition analysis (RPA) [1486] which identified patients surviving longest in RPA class III in the Stupp *et al.* [2166] EORTC/NCIC randomized trial of radiation therapy alone versus radiation therapy with temozolomide. Further analysis also showed the benefit of gross total surgical resection versus biopsy or partial resection [2302]. Another subset of patients within the Stupp *et al.* [2166] trial that had significantly better survival were those with methylation silencing of the methyl guanine-methyltransferase gene, whose gene product is known to repair the mono-DNA adduct at the O⁶ position of guanine, a DNA adduct essential for the cytotoxic effect of temozolomide [801].

Because of our knowledge of the molecular abnormalities in subsets of glioblastoma and the identification of patients likely to respond or be resistant

to specific therapies, there is good reason to hope that much more progress in treating glioblastoma should be made in the next decade than has been made in the past 50 years. A multitude of new molecularly targeted therapies, such as monoclonal antibodies reactive with growth factors or their receptors, small-molecule signal transduction inhibitors, improvements in cellular immunotherapies, the use of neural stem cells as therapy or therapeutic carriers, and the targeting of tumour stem cells all bode well for improving glioblastoma therapy. Drug delivery will also be improved with methodologies such as convection-enhanced delivery and nanotechnology.

Giant cell glioblastoma

Definition

A histological variant of glioblastoma with a predominance of bizarre, multinucleated giant cells, an occasionally abundant stromal reticulin network and a high frequency of TP53 mutations.

ICD-O code

9441/3

Grading

Giant cell glioblastoma corresponds histologically to WHO grade IV.

Synonyms and historical annotation

Because of the often prominent stromal reticulin network, giant cell glioblastoma was originally termed monstrocellular sarcoma [2513, 2514] but the consistent expression of GFAP has firmly established its astrocytic nature [972, 1120, 1959].

Incidence

Giant cell glioblastoma is a rare variant that accounts for less than 1% of all brain tumours [1669] and up to 5% of glioblastoma [857, 1669].

Age and sex distribution

In a series of 55 cases, the mean age at clinical manifestation was 41 years, but the age distribution of this tumour covers a wider range than other diffuse astrocytomas and includes children [857, 1464, 1714]. Males and females are equally affected (M/F ratio, 1.1).

Clinical features

Symptoms and signs

Giant cell glioblastomas develop *de novo*

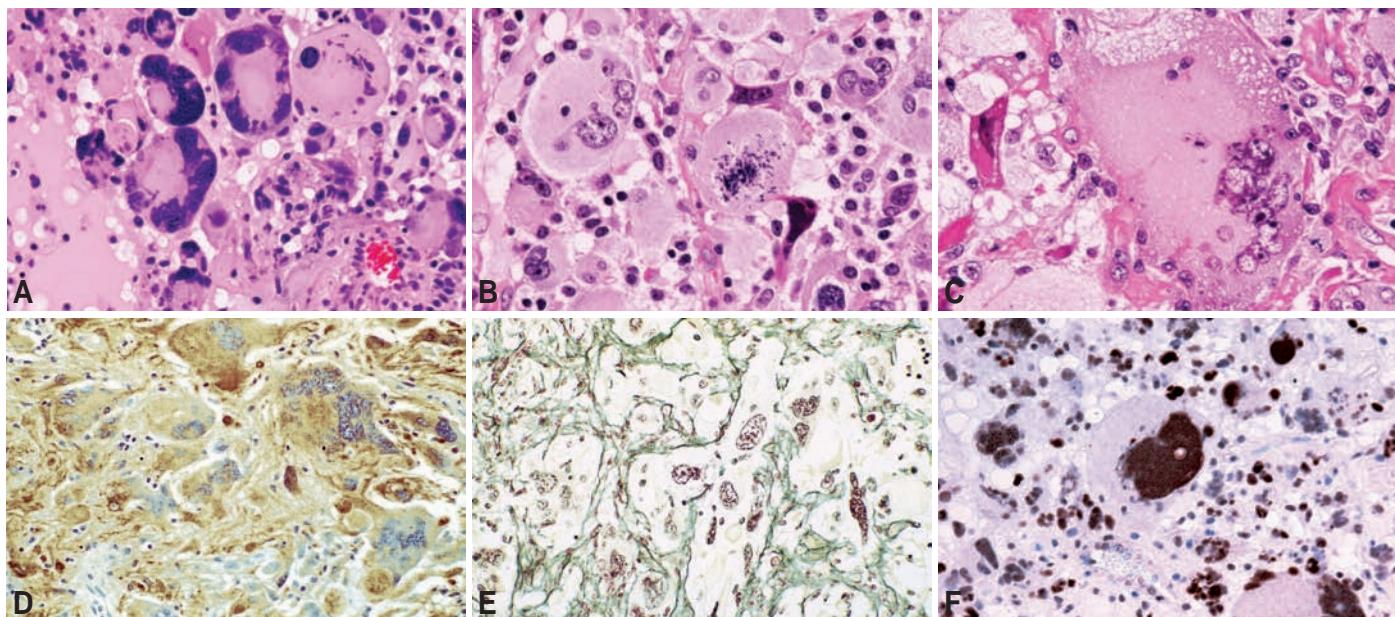


Fig. 1.41 A Giant cell glioblastoma consists of cells with variable size and shape. B An atypical mitotic figure in a giant cell. C A very large multinucleated giant cell. D Most but not all tumour cells express GFAP. E Marked stromal reaction (Bodian silver stain). F Tumour shows a high labelling index with MIB-1 antibody.

after a short preoperative history and without clinical or radiological evidence of a less malignant precursor lesion. Symptoms are similar to those of the ordinary glioblastoma.

Neuroimaging

Giant cell glioblastomas are distinctive because of their circumscription and firmness caused by the marked production of tumour stroma. They are often located subcortically in the temporal and parietal lobes. On CT and MRI, they may mimic a metastasis.

Histopathology

This type of glioblastoma has numerous multinucleated giant cells, smaller fusiform cells and, to a varying extent, a reticulin network [1398, 1959]. The giant cells often have extremely bizarre and grotesque appearances, and may measure more than 500 µm in diameter. They may be heavily lipidized [1812, 1959]. The number of nuclei ranges from a few to more than 20. They are often angulated, may contain prominent nucleoli and, on occasion, have cytoplasmic inclusions. Atypical mitoses are frequent, but the overall proliferation rate is similar to that of ordinary glioblastoma. Necrosis, often of a large geographic type or, more rarely a pseudopalisading one, is observed. Giant cells are immunopositive for S-100 protein, vimentin, class III β-tubulin, p53

and EGFR, but their GFAP expression is highly variable [1057, 1714, 1966]. Neuronal markers are virtually negative, in contrast to pleomorphic xanthoastrocytoma [1408]. Occasionally, perivascular lymphocyte cuffing is noted. Microvascular proliferation is exceptional.

Genetics

Giant cell glioblastoma is characterized by frequent *TP53* mutations (75–90% of cases) and *PTEN* mutations (33%), but typically lacks *EGFR* amplification/overexpression and homozygous *p16* deletion [1464, 1714, 1715]. These results indicate that giant cell glioblastoma occupies a hybrid position, sharing with

primary (*de novo*) glioblastoma a short clinical history, the absence of a less malignant precursor lesion and frequent *PTEN* mutations. In common with secondary glioblastoma that develops through progression from low-grade astrocytomas, they have a younger patient age at manifestation and a high frequency of *TP53* mutations [1715].

Prognostic and predictive factors

Most giant cell glioblastomas carry a poor prognosis [884] but some reports indicate that the clinical outcome is somewhat better than that of ordinary glioblastoma [262, 1398, 2088], possibly because of a less infiltrative behaviour.

Table 1.01 Clinical and genetic profile of the giant cell glioblastoma, in comparison with primary and secondary glioblastoma. Modified from Peraud *et al.* (1714, 1715).

	Primary GBM	Giant cell GBM	Secondary GBM
Clinical onset	<i>de novo</i>	<i>de novo</i>	Secondary
Preoperative history	1.7 months	1.6 months	>25 months
Age at GBM diagnosis	55 years	42 years	39 years
Sex ratio M/F	1.4	1.1	0.8
<i>PTEN</i> mutation	32%	33%	4%
<i>EGFR</i> amplification	39%	5%	0%
<i>TP53</i> mutation	11%	84%	67%
<i>p16^{INK4a}</i> deletion	36%	0%	4%

Gliosarcoma

Definition

A glioblastoma variant characterized by a biphasic tissue pattern with alternating areas displaying glial and mesenchymal differentiation.

ICD-O code

9442/3

Grading

Gliosarcoma corresponds histologically to WHO grade IV.

Synonyms and historical annotation

Gliosarcoma was originally defined as a glioblastoma in which the sarcomatous component was the consequence of malignant transformation of proliferating tumour vessels [560]. There is cytogenetic and molecular evidence for a monoclonal origin of both the glial and mesenchymal components.

Incidence

Gliosarcoma constitutes approximately 2% of all glioblastoma [559, 1444], although a higher frequency (up to 8%) has also been reported [1521, 1991].

Age and sex distribution

The age distribution is similar to that of glioblastoma, with preferential manifestation between ages 40 and 60 (mean, 52.1 years). Rare cases may occur in children, even in the very young [748, 1991]. Males are more frequently affected.

Localization

Gliosarcoma is usually located in the cerebral hemispheres, involving the temporal, frontal, parietal and occipital lobes in decreasing order of frequency. Rarely, gliosarcoma may occur in the posterior fossa and the spinal cord [291, 1587, 1601]. An unusual location of a gliosarcoma developing from an ependymoma has been identified [822]. Multifocal occurrence of gliosarcoma has also been reported [1668].

Clinical features

Symptoms and signs

The clinical profile of the gliosarcoma is that of the primary glioblastoma, with symptoms of short duration which reflect the location of the tumour and increased intracranial pressure. Most tumours arise

in the absence of recognized predisposing factors, but gliosarcoma has been associated with prior irradiation [1320, 1738]. Radiotherapy may also favour sarcomatous growth in a recurrent standard glioblastoma [32].

Neuroimaging

In cases with a predominant sarcomatous component, the tumour appears as a well-demarcated hyperdense mass with homogeneous contrast-enhancement that may mimic a meningioma [794, 1387, 1975]. In cases with a prevalence of the gliomatous component, the radiological features are similar to those of glioblastoma.

Macroscopy

The high content of connective tissue gives the gross appearance of a firm, well-circumscribed mass that can be mistaken for a metastasis or, when attached to the dura, for a meningioma. Lesions less rich in connective tissue may have typical features of glioblastoma.

Histopathology

A mixture of gliomatous and sarcomatous tissues confer to gliosarcoma a striking biphasic tissue pattern. The glial portion is astrocytic in nature and anaplastic, mostly showing the typical features of a glioblastoma. Epithelial differentiation, manifest as carcinomatous features [1659] with gland-like or adenoid formations and squamous metaplasia [1084, 1526] may occur in the glial portions of selected cases. The sarcomatous component by definition shows signs of malignant transformation, e.g. nuclear atypia, mitotic activity and necrosis, and often demonstrates the typical pattern of fibrosarcoma, with densely packed long bundles of

spindle cells. Occasionally, the histology resembles features of a malignant fibrous histiocytoma [1444, 1587]. A subset of cases may show additional lines of mesenchymal differentiation, e.g. the formation of cartilage [93], bone [1412], osteoid-chondral tissue [794, 2195], smooth and striated muscle [101, 750] and even lipomatous features [2329]. The distinction between the two components is facilitated using combined histochemical and immunohistochemical staining. Collagen deposition in the mesenchymal part is well demonstrated by a trichrome stain. Similarly the reticulin staining shows abundant connective tissue fibers. This component does not express GFAP, which, on the contrary, is observed in the glial part. The demonstration of a clearly malignant mesenchymal GFAP-negative component is important to distinguish true gliosarcoma from glioblastoma with a florid fibroblastic proliferation (desmoplasia) elicited by meningeal invasion [1443].

Genetics

Gliosarcoma contains *PTEN* mutations (38–45%), *p16^{INK4a}* deletions (38%), and *TP53* mutations (23–24%), but shows infrequent *EGFR* amplifications (0–8%) [11, 1856], suggesting that they have a distinct profile, similar to that of primary glioblastoma, except for the infrequent *EGFR* amplification. Comparative genomic hybridization (CGH) in 20 gliosarcomas revealed that chromosomal imbalances commonly detected were gains on chromosomes 7 (75%), X (20%), 9q and 20q (15% each); and losses on chromosomes 10 and 9p (35% each) and 13q (15%) [11]. Similar genetic alterations have been found in the gliomatous and sarcomatous components, indicating a monoclonal origin.

Table 1.02 Genetic and clinical profile of the gliosarcoma in comparison with primary GBM. Modified from Reis et al. [1856].

	Primary GBM	Gliosarcoma
Preoperative clinical history	1.7 months	2 months
Sex ratio M/F	1.4	1.65
Age at diagnosis	55 years	56 years
<i>TP53</i> mutation	11%	23%
<i>PTEN</i> mutation	32%	38%
<i>p16^{INK4a}</i> deletion	36%	37%
<i>MDM2</i> amplification	8%	5%
<i>EGFR</i> amplification	39%	0%

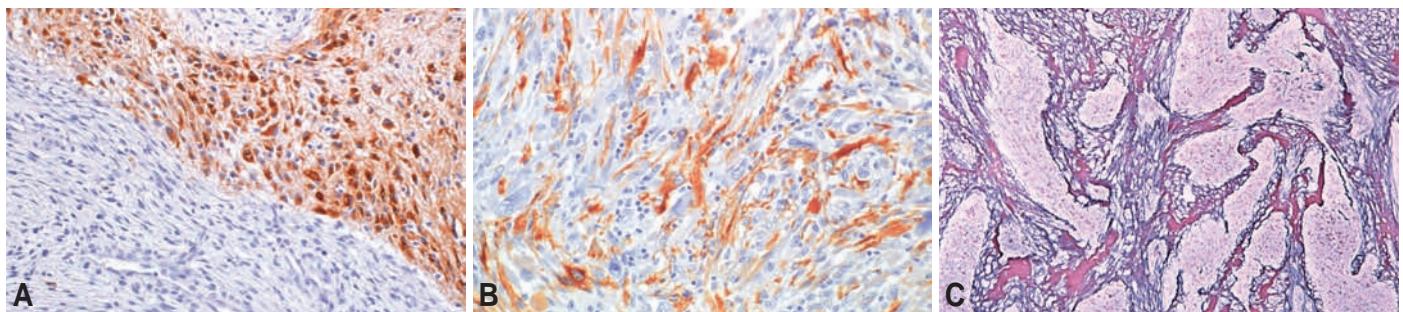


Fig. 1.42 Gliosarcoma. The gliomatous component shows strong GFAP expression and may be (A) geographically separated from or (B) intermingled with the sarcomatous tumour cells. C A biphasic tissue pattern denoting reticulin-rich sarcomatous and reticulin-free gliomatous elements.

Histogenesis

Originally, gliosarcoma was perceived as a collision tumour with a separate astrocytic component and an independent development of the sarcomatous portion from the proliferating vessels. Several immunohistochemical studies seemed to support that concept by demonstrating immunoreactivity to factor-VIII-related antigen {2028}, Ulex europaeus I agglutinin (UEA-I) {2111}, and monohistiocytic markers {718, 719, 1147}. Another hypothesis suggested that the sarcomatous portion results from advanced glioma dedifferentiation with subsequent loss of GFAP expression and acquisition of a sarcomatous phenotype {1008, 1443}. In a study using fluorescent *in situ* hybridization, two of three gliosarcomas showed identical numerical aberrations of chromosomes 10 and 17 in the glial and mesenchymal components, whereas in a third case, trisomy X was restricted to the chondrosarcomatous element {1695}. Similar cytogenetic patterns were also observed in both glial and mesenchymal components in a study using fluorescent *in situ* hybridisation and microsatellite allelic imbalance and cytogenetic analysis {526}. These results suggest that both components were derived from neoplastic glial cells. This view has further been supported by the observation of TP53 immunoreactivity in both tumour components {34}. Biernat et

al. {157} provided proof of a monoclonal origin by demonstrating that in two cases of gliosarcoma the gliomatous and sarcomatous components each contained an identical *TP53* mutation. Identical *PTEN* and *TP53* mutations were also detected in the gliomatous and sarcomatous tumour components of gliosarcoma {1856, 2359}. Monoclonality of both components of the gliosarcoma was also confirmed by identification of *p16* deletion and co-amplification of *MDM2* and *CDK4* in both tumour areas {1856}. These studies strongly support the view that the sarcomatous areas represent an aberrant differentiation of the glioblastoma cells, rather than coincidental development of two separate neoplasms.

Prognostic and predictive factors

It has been suggested that gliosarcoma has a somewhat more favourable prognosis {1387} than ordinary glioblastoma, but large clinical trials have failed to reveal significant differences in outcome {641, 1444, 1738}.

Gliofibroma

This is a very rare tumour that usually affects children. The age range of patients is from 11 days to 54 years (mean 14 years). It is more common in females (M:F=2:3). Gliofibroma frequently occurs in the cerebrum (36%) and the spinal cord (28%). In contrast to desmoplastic infantile astrocytoma, gliofibroma is not

dura-based and does not form large cystic tumours. It is a biphasic tumour composed of a glial component that ranges from a low-grade to high-grade level of differentiation, and a non-sarcomatous fibroblastic component. In contrast to gliosarcoma, the 'marbled' appearance of two tissue components is lacking. In some gliofibromas, collagen seems to be produced by the glioma cells themselves (desmoplastic astrocytoma) {612}, whereas in others it appears to be deposited by mesenchymal cells (mixed glioma/fibroma) {1786}. Necrosis or vascular microproliferation is not a typical feature of gliofibroma {1786}. Cellularity, nuclear pleomorphism and increased mitotic activity are rarely present and may indicate more aggressive clinical behaviour; these tumours have been designated "malignant" or "anaplastic gliofibroma" {307, 1786}. Recently, the morphological variant with psammoma bodies has been described {1603}.

The prognosis of gliofibromas is usually favourable. The majority of the tumours has an indolent clinical course without evidence of recurrence or metastasis, even several years after resection. Occasionally, dissemination {278, 612, 2321} and/or death {612, 2067, 2119, 2321} has been reported, but most of these cases showed signs of cellular anaplasia or increased mitotic activity.

Gliomatosis cerebri

G.N. Fuller
J.M. Kros

Definition

A diffuse glioma (usually astrocytic) growth pattern consisting of exceptionally extensive infiltration of a large region of the central nervous system, with involvement of at least three cerebral lobes, usually with bilateral involvement of the cerebral hemispheres and/or deep gray matter, and frequent extension to the brain stem, cerebellum, and even the spinal cord. Gliomatosis cerebri most commonly displays an astrocytic phenotype, although oligodendrogloma and mixed oligoastrocytoma can also present with the gliomatosis cerebri growth pattern.

ICD-O code 9381/3

Grading

Gliomatosis cerebri (GC) is usually an aggressive neoplasm. The overall biologic behaviour corresponds to WHO grade III in a majority of cases. Several studies have demonstrated that, similar to all diffuse gliomas, substratification of gliomatosis patients by histologic

subtype and grade using WHO criteria correlates with time to progression and overall survival [1718, 2320]. Given the extensive, multilobar nature of GC, diagnosis is typically confirmed through limited tissue biopsy; similar to diffuse gliomas in general, histologic subtyping and grading in this setting are subject to non-representative tissue sampling and undergrading.

Historical annotation

The term gliomatosis cerebri was coined by Nevin in 1938 to describe the extensive involvement of large areas of the brain by glial cells in the absence of a mass lesion [1584]. A number of names, such as glioblastomatosis and central diffuse schwannosis, were used in the early literature. The term gliomatosis cerebri is currently widely accepted. Uncertainty concerning histogenesis and whether GC warrants designation as a separate clinicopathologic entity apart from the other diffuse gliomas is reflected by the varying inclusion of GC under different rubrics in previous editions of the WHO

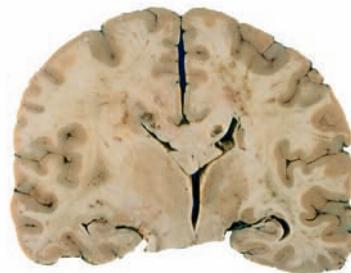


Fig. 1.44 Gliomatosis cerebri infiltrating the left hemisphere with enlargement of anatomic structures, in particular the thalamus.

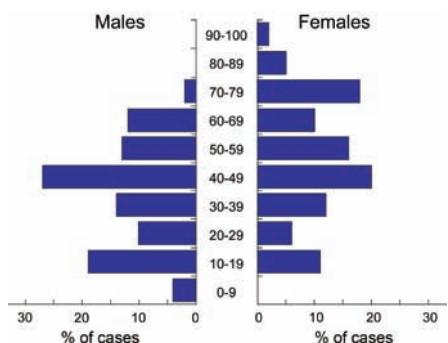


Fig. 1.45 Age distribution of 151 patients with gliomatosis cerebri. Modified from Jennings *et al.* [992].

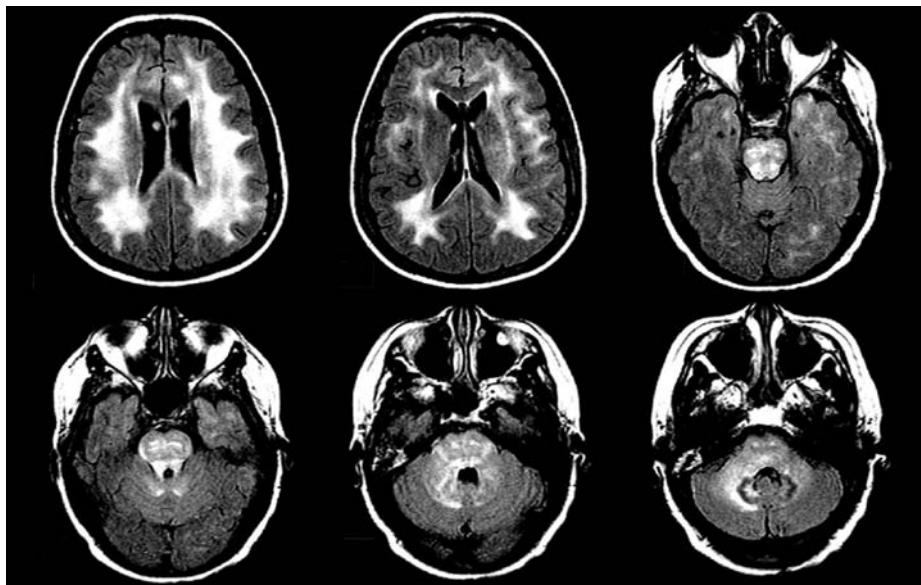


Fig. 1.43 MR imaging of gliomatosis cerebri, as seen on FLAIR sequences, reveals the characteristically extensive involvement of the central nervous system, which, in this case, includes the cerebral hemispheres bilaterally, the brain stem, and the cerebellum.

Classification [1121, 2513]. GC is currently viewed as a pattern of particularly extensive glioma infiltration. Early study of GC predated the advent of modern neuroimaging technologies by decades and consisted exclusively of autopsy examination. Contemporary MR imaging techniques (especially T2-weighted and FLAIR sequences), combined with biopsy, permit diagnosis during life. Gliomatosis cerebri has been divided by some investigators into primary and secondary subtypes, with primary GC exhibiting extensive CNS involvement at the time of initial clinical presentation, and secondary GC consisting of progressive infiltration of the brain by a typical locally infiltrative diffuse glioma observed on clinical follow-up over time. Primary GC has been further divided by some investigators into type 1 (classical form), in which no tumour mass is present at initial clinical presentation, and

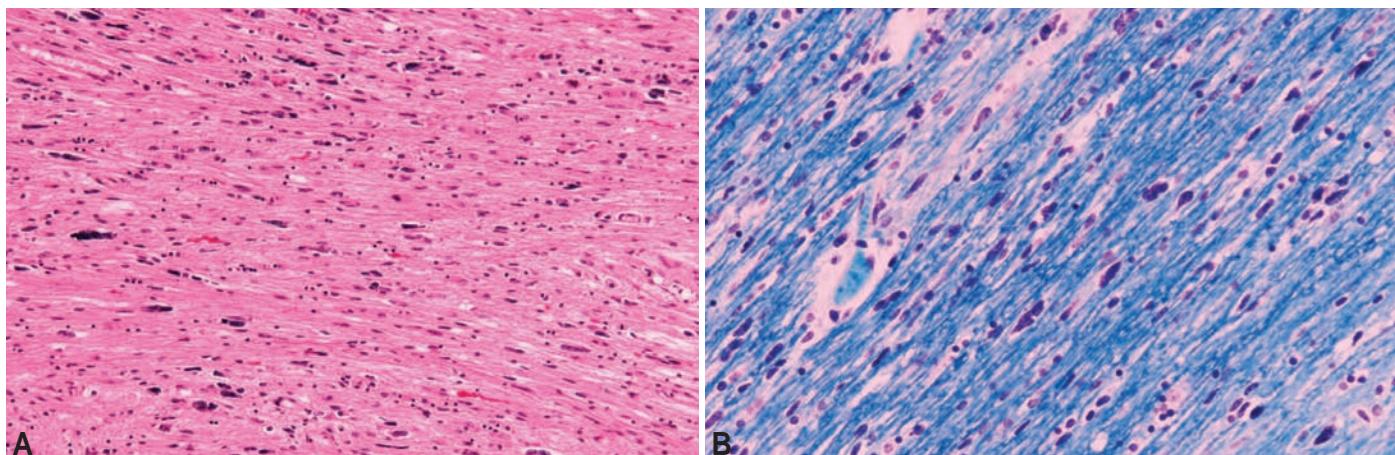


Fig. 1.46 Histological features of gliomatosis cerebri. A Diffuse infiltration of the corpus callosum with elongated tumour cells. B Tumour cell infiltration along the myelinated axons (Kluver-Barrera staining).

type 2, in which, in addition to extensive CNS involvement, a tumour mass is also present. In these schemes, primary, type 1 GC corresponds to classical GC. GC considered in the strict and classical sense would exclude secondary GC and type 2 GC, as defined above, as well as diffuse gliomas that by virtue of their anatomic location (e.g. in the region of junction of the frontal, temporal and parietal lobes) involve three cerebral lobes but are relatively localized in overall extent of CNS involvement.

Gliomatosis cerebri should be distinguished from two other types of gliomatosis, i.e. leptomeningeal gliomatosis and gliomatosis peritonei. Leptomeningeal gliomatosis is the widespread infiltration of the subarachnoid space by a diffuse glioma, most commonly an intra-axial glioma that has invaded the leptomeninges (secondary leptomeningeal gliomatosis), or, rarely, leptomeningeal spread of a glioma originating in an ectopic leptomeningeal glial or glioneuronal rest (primary leptomeningeal gliomatosis). Gliomatosis peritonei is the presence of disseminated miliary foci of mature glial tissue throughout the peritoneal cavity, most commonly arising in association with an ovarian teratoma.

Incidence, age and sex distribution

In a review of 151 patients in which age at diagnosis was available, the age ranged from neonatal to 83 years, with the peak incidence between 40 and 50 years and males presenting somewhat earlier than females [992]. Both sexes were equally affected.

Localization

Virtually no anatomic site of the brain has been excluded from descriptions of GC. The most commonly involved areas, based on post-mortem studies [992], are the cerebral hemispheres (76%), the mesencephalon (52%), the pons (52%), the thalamus (43%), the basal ganglia (34%), the cerebellum (29%), the medulla oblongata (13%), the hypothalamus, the optic nerves and chiasm, and the spinal cord (each at 9%). When GC involves the cerebral hemispheres, the centrum semiovale is always affected, whereas the cerebral cortex is infiltrated only in 19% of such cases, with spread to the leptomeninges in 17%. In 77% of cases of GC, the lesion is located bilaterally, and there is a predilection for the right side of the brain [2320].

Clinical features

Symptoms and signs

The signs and symptoms vary considerably depending on the cerebral areas infiltrated and include changes in mental status such as dementia and lethargy, seizures (generalized and partial complex), headache, pyramidal symptoms (gait disturbances), cranial nerve dysfunction, signs and symptoms of increased intracranial pressure, spinocerebellar deficits, sensory deficits and paraesthesia, and visual disturbances [992, 2320].

Neuroimaging

Diffuse enlargement of the involved cerebral structures, without tissue destruction or focal tumour mass formation, is seen both by CT scan and MR

imaging, [458, 1809, 2086]. MRI gives superior results: on CT scans, GC may appear as only poorly defined, very subtle low density or isodensity, and the extent of involvement is typically smaller compared to T2-weighted or FLAIR MR sequences, on which signal hyperintensity reveals the full extent of the tumour and correlates best with post-mortem investigations [458, 2086]. FLAIR sequences are currently preferred over T2-weighted sequences by virtue of increased sensitivity and suppression of background "noise" from ventricular and subarachnoid space cerebrospinal fluid. Nevertheless, the ante-mortem diagnosis of gliomatosis cerebri can be difficult, especially in the case of limited tissue sampling of low-grade lesions by stereotactic biopsy. Proton MR spectroscopy may be of value in identifying target areas of denser tumour cellularity or higher grade tumour for subsequent sampling by stereotactic biopsy [2320].

Histopathology

On macroscopic examination of autopsy or lobectomy specimens, involved regions of the brain are usually swollen and firm, with blurred distinction between grey and white matter but intact, recognizable gross anatomy. Classical histologic features include a proliferation of small glial cells with elongated, fusiform nuclei. A wide range of glial, predominantly astrocytic cellular morphologies can be seen, including larger tumour cells with irregular pleomorphic nuclei. Histological variation exists not only between different lesions, but also within the same

neoplasm. In some areas, the tumour cells are more obviously astrocytic, and gemistocytic forms may also be seen [1599]. Cases of GC exhibiting classical morphologic features of oligodendrogloma have also been described [90]. When infiltrating white matter, signs of demyelination may be present, but neurons and axons are intact [69]. Mitotic activity is variable and dependent on the extent of tissue sampling, but is typically low. Microvascular proliferation and necrosis are generally absent in classical (primary, type 1) GC at clinical presentation and during much of the disease course, but may appear in longer-surviving patients later in the clinical course through tumour progression. Perivascular cuffs of inflammatory cells are absent. GC should be distinguished from diseases in which prominent microglial cell proliferation is seen. Morphometric analysis has shown that most cellular parameters of cerebral gliomatosis are comparable to those of low grade astrocytoma [642].

Immunohistochemistry

GFAP and S-100 protein immunostaining results are variable; in many cases, tumour cells exhibit strong positivity for both markers, whereas in others a majority of tumour cells are non-reactive [642, 2416].

Proliferation

Proliferation in GC generally correlates with grade, as for other diffuse gliomas. Reported Ki-67 labelling indices range from <1 to 30% [403, 1104, 2187].

Genetics

Molecular genetic characterization has lagged behind that of other types of diffuse gliomas. Secondary to the essential diagnostic criterion of widespread infiltration of extensive regions of the central nervous system, large surgical resections are generally not performed, and the amount of tissue available for scientific investigation is thus usually very small, often limited to stereotactic biopsy cores. Nevertheless, the data collected from surgical specimens and from the study of autopsy specimens suggest that the qualitative genetic abnormalities found in GC, such as *TP53* mutation, are similar to those of diffuse astrocytoma, although occurring with a lower frequency [1419, 1420]. There is no definitive evidence for unique genetic alterations that distinguish gliomatosis from diffuse astrocytoma. As expected, for the limited number of cases studied of oligodendrogloma presenting with a GC pattern, an increased incidence of chromosome 1p deletion has been noted [1986].

Histogenesis

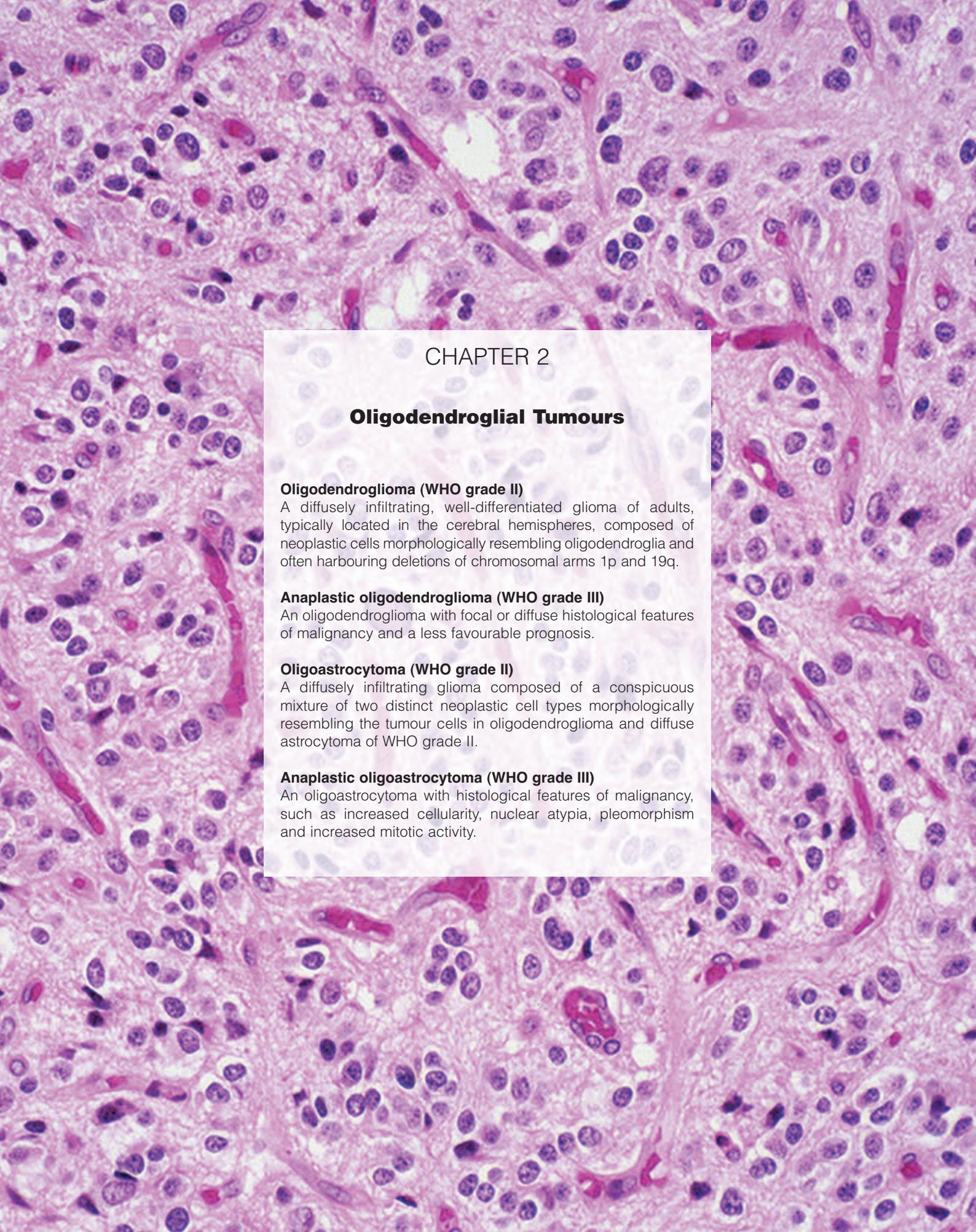
Historically, the two competing hypotheses of gliomatosis origin were that: 1) it represents a subtype or subset of otherwise ordinary diffuse glioma characterized by exceptional infiltrative capacity, or 2) it results from the simultaneous neoplastic transformation of an extensive tissue field within the central nervous system ("field cancerization"). Central to this debate is the issue of clonality. Data from a majority of the limited number of studies available

support a monoclonal origin for GC, with subsequent widespread diffuse glioma infiltration [1206, 1419].

Also integral to the issue of histogenesis is that of differentiation. Classical gliomatosis most commonly exhibits an astrocytic phenotype, as reflected by cellular morphology (elongated and/or pleomorphic nuclei) and immunopositivity for GFAP. Oligodendrogloma and mixed oligoastrocytoma can also present with the GC pattern of extensive brain infiltration, with exceptional cases involving the cerebral hemispheres bilaterally, the brain stem and the cerebellum [2211]. Such cases that exhibit classical morphologic features have been referred to as "oligodendrocytic GC" or "oligodendroglial GC" and, not surprisingly, tend to respond more favourably to treatment compared with astrocytic GC and to exhibit the favourable oligodendroglial genetic signature of chromosome 1p deletion [1299, 1986]. Thus, most investigators favour the interpretation of classical GC as exceptionally extensive involvement of a large contiguous region of the central nervous system by a diffuse, usually astrocytic glioma.

Prognostic and predictive factors

Median survival in gliomatosis patients is associated with younger patient age and higher Karnofsky performance status at clinical presentation, lower WHO grade and histologic subtype [1718, 2196]. The associations, however, are not unique to GC, and apply to diffuse gliomas in general.



CHAPTER 2

Oligodendroglial Tumours

Oligodendroglioma (WHO grade II)

A diffusely infiltrating, well-differentiated glioma of adults, typically located in the cerebral hemispheres, composed of neoplastic cells morphologically resembling oligodendroglia and often harbouring deletions of chromosomal arms 1p and 19q.

Anaplastic oligodendroglioma (WHO grade III)

An oligodendroglioma with focal or diffuse histological features of malignancy and a less favourable prognosis.

Oligoastrocytoma (WHO grade II)

A diffusely infiltrating glioma composed of a conspicuous mixture of two distinct neoplastic cell types morphologically resembling the tumour cells in oligodendroglioma and diffuse astrocytoma of WHO grade II.

Anaplastic oligoastrocytoma (WHO grade III)

An oligoastrocytoma with histological features of malignancy, such as increased cellularity, nuclear atypia, pleomorphism and increased mitotic activity.

Oligodendroglioma

G. Reifenberger

J.M. Kros

D.N. Louis

V.P. Collins

Definition

A diffusely infiltrating, well-differentiated glioma of adults, typically located in the cerebral hemispheres, composed of neoplastic cells morphologically resembling oligodendroglia and often harbouring deletions of chromosomal arms 1p and 19q.

ICD-O code

9450/3

Grading

Oligodendroglioma corresponds histologically to WHO grade II.

Histologically, oligodendroglial tumours comprise a continuous spectrum ranging from well-differentiated neoplasms to frankly malignant tumours. The WHO grading system recognizes two malignancy grades for oligodendroglial tumours: WHO grade II for well-differentiated tumours, and WHO grade III for anaplastic oligodendroglioma. Several recent studies have confirmed the WHO grading of oligodendroglial tumours as a significant predictor of survival {563, 680, 1269, 1625}. Several other systems have been used for grading of oligodendroglial tumours, including the four-tiered Kernohan {1093} and St Anne/Mayo systems {2074}, the Smith grading system {2115}, as well as three-tiered systems such as the Ringertz system {1891} and a three-tiered modification of the Smith scheme {1199, 1202}.

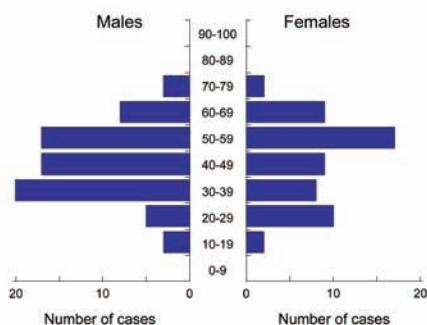


Fig. 2.01 Age and sex distribution of 130 patients with oligodendroglioma and anaplastic oligodendroglioma, based on combined biopsy series from the Universities of Düsseldorf (Germany) and Zürich (Switzerland).

In addition, a two-tiered system based on morphological and imaging criteria has been proposed {424}. Each of these grading systems is capable of distinguishing subsets of oligodendroglial tumours, but most studies suggest that there are basically two groups that differ prognostically, which is in line with the two-tiered WHO system.

Historical annotation

The first description of an oligodendroglioma was published by Bailey & Cushing {86} followed by the classic paper of Bailey & Bucy {83} on oligodendrogliomas of the brain.

Incidence

Adjusted annual incidence rates have been estimated to range from 0.27 to 0.35 per 100 000 persons {305, 1625}. Oligodendroglioma accounts for approximately 2.5% of all primary brain tumours and 5–6% of all gliomas {305, 1625}. The incidence of oligodendroglioma has significantly increased over the past years {305}, but this may primarily be due to the use of less stringent diagnostic criteria in recent years, possibly triggered by a desire not to impede any patient from gaining a benefit of chemotherapy {248}.

Etiology

Individual cases of oligodendroglioma in patients previously irradiated for other reasons have been documented {18, 383, 878}, but these account for an insignificant fraction of all oligodendroglial tumours. Although oligodendroglioma and oligoastrocytoma are among the most frequent types of CNS tumours to be induced experimentally in rats by chemical carcinogens such as ethylnitrosourea and methylnitrosourea, there is no convincing evidence of an etiological role for these substances in human gliomas. Some studies have reported the presence of viral genome sequences and proteins (SV40, BK and JC virus) in oligodendroglioma {460}; however, other authors failed to detect virus sequences {1913} and thus a viral etiology is uncertain at present.

Age and sex distribution

The majority of oligodendrogliomas arise in adults, with a peak incidence between 40 and 45 years of age {305, 1269, 1625}. Oligodendroglioma is rare in children, accounting for only 2% of all brain tumours in patients younger than 14 years {305}. Males appear to be affected slightly more frequently than females, with a ratio of 1.1:1 reported in a population-based series of 1559 patients {305}.

Localization

Oligodendroglioma arises preferentially in the cortex and white matter of the cerebral hemispheres. The frontal lobe is involved in 50–65% of the patients, followed with decreasing frequencies by the temporal, parietal and occipital lobes {1199, 2074}. Involvement of more than one cerebral lobe or bilateral tumour spread is common. Patients have been reported with oligodendroglioma in the posterior fossa {1663}, basal ganglia {1739}, brain stem {50} or spinal cord {599}, as well as primary leptomeningeal oligodendroglioma {1588}, and oligodendroglial gliomatosis cerebri {2196}.

Clinical features

Symptoms and signs

Approximately two thirds of the patients present with seizures. Further common presentations include headache and other signs of increased intracranial pressure, focal neurological deficits, and cognitive or mental changes {1269, 1642}. In older studies, intervals of more than 5 years between onset of symptoms and diagnosis were common, but modern neuroimaging has shortened the time to diagnosis {1642}.

Neuroimaging

On CT, oligodendroglioma usually appears as hypo- or isodense, well-demarcated mass lesions, usually located in the cortex and subcortical white matter. Calcification is common but not diagnostic. MRI studies typically demonstrate a hypointense lesion in T1-weighted images and a hyperintense lesion in T2-weighted



Fig. 2.02 A Well-circumscribed, partly haemorrhagic oligodendrogloma of the left frontal lobe. B Recurrent oligodendrogloma with bilateral, diffuse infiltration of the frontal and temporal lobes.

images which appears well-demarcated and shows little perifocal edema [1282]. Some tumours demonstrate heterogeneous features due to intratumoural haemorrhages and/or areas of cystic degeneration. Gadolinium enhancement has been associated with less favourable prognosis [2074]. Correlation with 1p/19q status revealed that oligodendroglomas without 1p/19q deletions more often demonstrate mixed signal intensity on T1- and T2-weighted images [991, 1442]. One study suggested that 1p/19q deletions are associated with indistinct tumour borders on T1-weighted images, paramagnetic susceptibility and calcification [1442], but these associations have not held true in other studies [991].

Macroscopy

Oligodendrogloma usually appears as well-defined soft masses of greyish-pink colour. Cases with extensive mucoid degeneration may appear gelatinous. The tumour is typically located in the cortex and white matter, and infiltration of the overlying leptomeninges may be seen. Perifocal edema is uncommon.

Calcification is frequent and may impart a gritty texture to the tumour. Zones of cystic degeneration, as well as intratumoural haemorrhages, may be seen.

Histopathology

Oligodendroglomas are diffusely infiltrating gliomas of moderate cellularity that are composed of monomorphic cells with uniform round nuclei and perinuclear halos on paraffin sections ('honeycomb' appearance). Additional features include microcalcifications, mucoid/cystic degeneration and a dense network of branching capillaries. Marked nuclear atypia and an occasional mitosis are compatible with the diagnosis of WHO grade II oligodendrogloma but significant mitotic activity, prominent microvascular proliferation or conspicuous necrosis indicate progression to anaplastic oligodendrogloma (WHO grade III).

Cellular composition

Oligodendrogloma is moderately cellular, although areas of increased cellularity, often in the form of circumscribed nodules, may occur in some otherwise well-

differentiated tumours. On the other hand, small biopsies may sometimes show only scattered oligodendrogloma cells, identifiable by their characteristic nuclei, infiltrating the brain parenchyma. The tumour cells have uniformly round nuclei that are slightly larger than those of normal oligodendrocytes and show an increase in chromatin density. Mitotic activity is either absent or low. In routinely formalin-fixed and paraffin-embedded material, the tendency of the tumour cells to undergo degeneration by acute swelling results in an enlarged rounded cell with a well-defined cell membrane and clear cytoplasm around a central spherical nucleus. This creates the typical honeycomb appearance which, although artifactual, is a helpful diagnostic feature when present. This artifact is seen neither in smear preparations nor in frozen sections, and may also be absent in rapidly fixed tissue and in paraffin sections made from frozen material.

Some oligodendroglomas contain tumour cells with the appearance of small gemistocytes, which have a somewhat larger, often eccentric cytoplasm that is positive for glial fibrillary acidic protein (GFAP). These cells have been referred to as minigemistocytes or microgemistocytes. In rare tumours, GFAP-negative mucocytes or even signet-ring cells may be seen. Rare cases of oligodendrogloma consisting largely of signet-ring cells (signet-ring cell oligodendrogloma) have been described [1203]. Eosinophilic granular cells may also occur in some oligodendroglomas [2202]. Reactive astrocytes are typically scattered throughout oligodendroglomas and may be particularly prominent in the infiltration rim. These should not be confused with the neoplastic astrocytes in diffuse astrocytoma or oligoastrocytoma.

Calcifications

An important histological feature is the presence of microcalcifications, sometimes associated with blood vessels, within the tumour tissue proper as well as in the invaded brain. However, this feature is not specific for oligodendroglial tumours and, due to the generally incomplete tumour sampling, may sometimes not be found in the available tissue sections even if clearly demonstrated neuro-radiologically. Areas characterized by extracellular mucin deposition and/or microcyst formation are frequent.

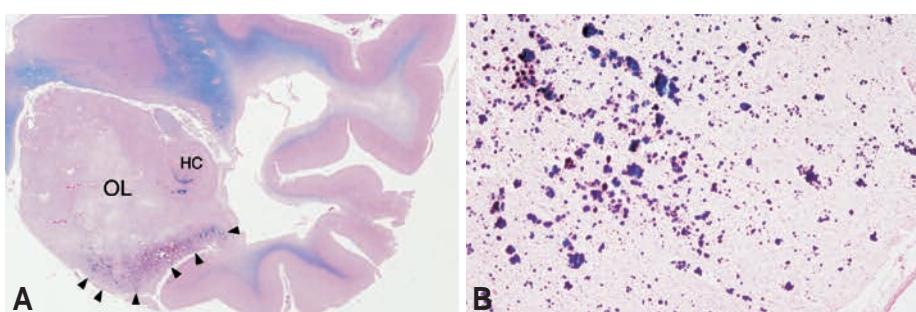


Fig. 2.03 A and B Oligodendrogloma (OL) of the temporal lobe with infiltration of the hippocampus (HC). Note the zone of calcification (arrows) at the periphery of the lesion and at higher magnification (B).

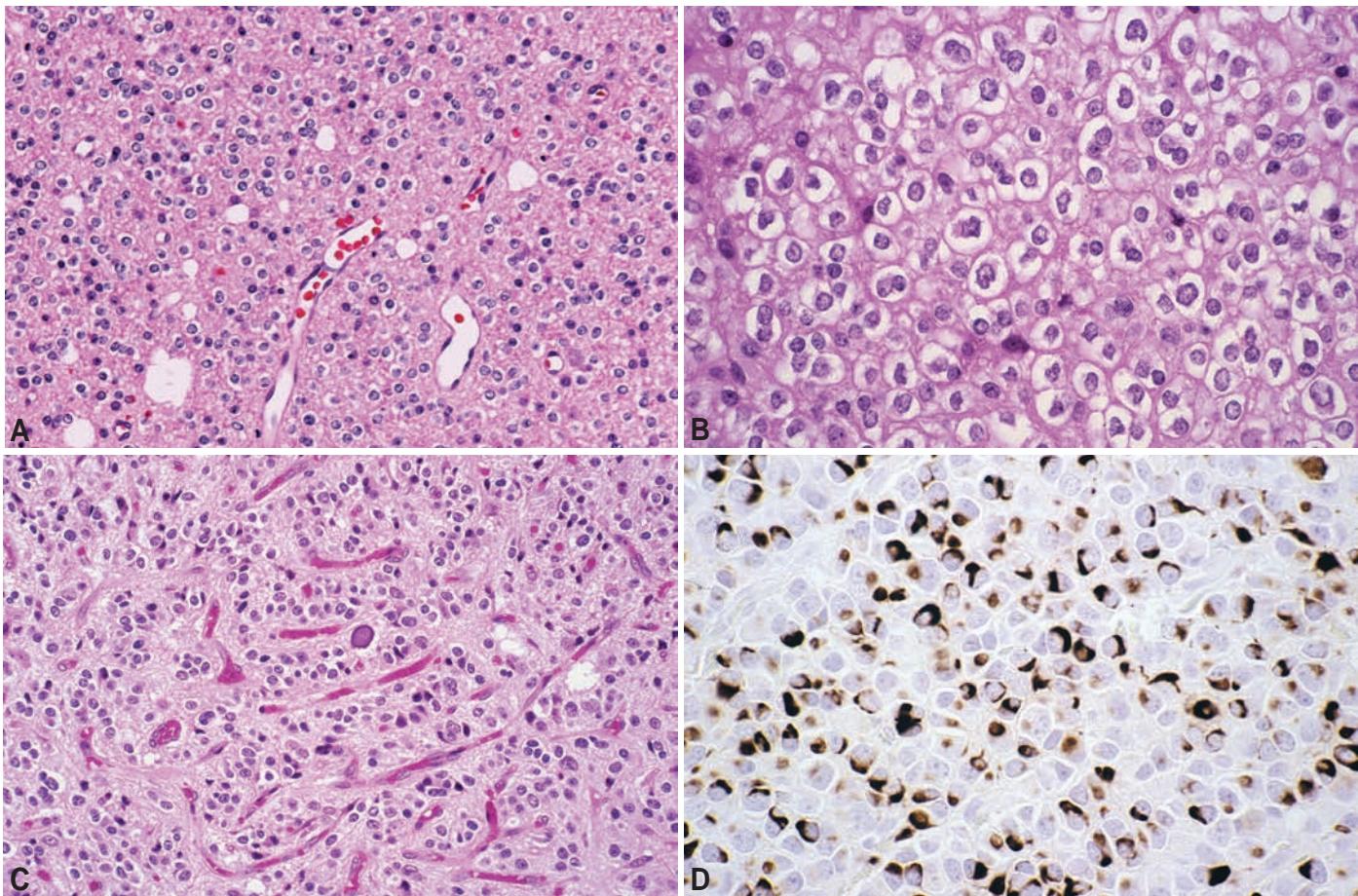


Fig. 2.04 Histological features of oligodendrogloma. A Typical honeycomb pattern. B Tumour cells with clear cytoplasm and well defined plasma membrane. C Typical dense network of branching capillaries. D Minigemistocytes with marked perinuclear immunoreactivity for GFAP.

Vasculature

Oligodendrogloma typically shows a dense network of branching capillaries resembling the pattern of chicken-wire. In some cases, the capillary stroma tends to subdivide the tumour into lobules. The tumours have a tendency for intratumoural haemorrhages.

Growth pattern

Oligodendroglomas grow diffusely in the cortex and white matter. Within the cortex, tumour cells tend to form secondary structures such as perineuronal satellitosis, perivascular aggregates, and subpial accumulations. Circumscribed leptomeningeal infiltration may induce a desmoplastic reaction. A rare growth pattern is the formation of parallel rows of tumour cells with somewhat elongated nuclei forming palisades reminiscent of the so-called polar spongioblastoma. Occasionally, perivascular pseudorosettes may be seen. These patterns are generally present only focally.

Immunohistochemistry

There is no immunohistochemical marker available that allows the specific and sensitive recognition of human oligodendroglial tumour cells. Oligodendrogloma shares with many other neuroectodermal tumours the expression of S-100 protein and the HNK1 (anti-Leu7, CD57) carbohydrate epitope [1529, 1553, 1847]. Immunoreactivity for γ -enolase is also frequent [1842]. GFAP may be present not only in intermingled reactive astrocytes but also in neoplastic oligodendroglial cells such as minigemistocytes and gliofibrillary oligodendrocytes [816, 1204, 1847]. The presence of GFAP in minigemistocytes and gliofibrillary oligodendrocytes has been corroborated by ultrastructural studies [816, 1201, 2434]. Some authors have suggested that these cells represent transitional forms between astrocytes and oligodendrocytes [816, 1201, 1204]. Alternatively, they may recapitulate a phenotype characteristic of a transient stage during oligodendroglial development [340, 957]. Vimentin is

infrequently expressed in low-grade oligodendrogloma but more often found in anaplastic oligodendrogloma [455, 1165]. Cytokeratins are absent [1842], although certain antibodies such as AE1/ AE3 may cross-react with other intermediate filament proteins, including GFAP, and thus give false-positive staining [1188].

Oligodendrogloma is consistently positive for the microtubule-associated protein 2 (MAP2), a protein linked to the neuronal cytoskeleton in the mature central nervous system but also expressed in glial progenitor cells during development [179]. However, MAP2 immunoreactivity is also commonly seen in astrocytic gliomas as well as in neuronal and neurocytic tumours [179]. The oligodendrocyte lineage-specific transcription factors OLIG-1 and OLIG-2 are expressed not only in oligodendrogloma but also in the vast majority of other gliomas [1321, 1887]. Similarly, SOX10, another transcription factor critically involved in oligodendroglial differentiation, is expressed in both oligodendrogloma and astrocytic tumours [95].

A number of differentiation antigens that are specifically expressed by normal oligodendrocytes *in vivo* or *in vitro* have been identified. These include myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated glycoprotein (MAG), galactolipids like galactocerebroside (GC) and galactosulphatide, and a number of gangliosides, as well as several enzymes such as carbonic anhydrase C, 2'-3'-cyclic nucleotide-3'-phosphatase (CNP), glycerol-3-phosphate dehydrogenase and lactate dehydrogenase (LDH). However, so far, none of these antigens has gained significance as a diagnostically useful marker for oligodendrogloma. They either are no longer expressed by neoplastic oligodendrocytes, e.g. MBP {1553, 1842}, or they are expressed only in a minority of cases, e.g. MAG {1553}, GC {1075, 2178}, PLP and CNP {2178}, or their expression is not restricted to oligodendroglial tumour cells, e.g. carbonic anhydrase C {1554}.

Immunohistochemical expression of neuronal markers in oligodendrogloma is a complicated issue. Synaptophysin immunoreactivity due to residual neuropil is frequently seen, in particular at the infiltrating tumour borders. Such staining of tumour-infiltrated neuropil should not be mistaken as evidence for neuronal or neurocytic differentiation. However, some oligodendroglomas, including cases with combined losses of 1p and 19q {1731}, may contain neoplastic cells that express synaptophysin and/or other neuronal markers, such as NeuN, neurofilaments and others {454, 1165, 1731, 2401}. 1p/19q

deletion analysis may be helpful to separate such cases from neurocytomas. Oligodendrogloma usually lacks nuclear p53 staining, a finding corresponding to the rarity of *TP53* gene mutations in these tumours. In fact, *TP53* mutation and p53 immunopositivity are mutually exclusive to 1p/19q deletion in oligodendroglial tumours {1226, 1625, 1634, 2432}.

Proliferation

Mitotic activity is low in WHO grade II oligodendrogloma, and labelling indices for proliferation markers are accordingly low, usually below 5%. Minigemistocytes are reported to be mostly MIB-1 negative and thus non-proliferative, whereas gliofibrillary oligodendrocytes are more commonly positive {1197}. Other proliferation markers, such as proliferating cell nuclear antigen (PCNA) {1854}, topoisomerase II α (Ki-S1) {1170} and mini-chromosome maintenance 2 (MCM2) protein {2400} also correlate with histological grade and survival in oligodendroglial tumours, but do not provide any clear advantages over MIB-1 staining.

Differential diagnosis

The differential diagnosis of oligodendrogloma includes both reactive and neo-plastic lesions. Among the former, oligodendrogloma needs to be distinguished from macrophage-rich processes such as demyelinating diseases or cerebral infarcts. In addition, increased numbers of oligodendrocytes sometimes seen in partial lobectomy specimens performed for intractable seizures should not be mistaken for oligodendrogloma.

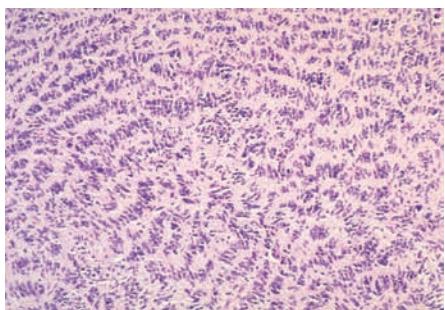


Fig. 2.06 Oligodendrogloma with a striking pattern of nuclear palisading.

Important neoplastic lesions that may mimic oligodendrogloma are clear cell ependymoma, neurocytoma and dysembryoplastic neuroepithelial tumour. These entities share with oligodendrogloma the presence of neoplastic cells with a uniform, round nucleus and clear cytoplasm, collectively referred to as oligodendroglial-like cells (OLC); these cells can readily be differentiated on the basis of their ultrastructural features {300}. In the routine diagnostic setting, immunostaining for neuronal markers, in particular synaptophysin, usually helps to distinguish neurocytoma from oligodendrogloma. However, rare cases of oligodendrogloma with deletion of 1p/19q and evidence of neurocytic differentiation have been reported {1731}. Clear cell ependymoma often shows at least focal perivascular pseudorosettes as well as dot- or ring-like EMA immunoreactivity, which helps to distinguish them from oligodendrogloma. Molecular analysis may be helpful since neurocytomas, clear cell ependymomas and DNTs lack 1p/19q losses. However, absence of 1p/19q deletion does not exclude an oligodendrogloma since a minor fraction of oligodendroglomas in adults and the majority of paediatric oligodendroglomas {1819} lack these deletions despite typical histology.

Pilocytic astrocytoma may occasionally mimic oligodendrogloma, however, at least foci of classic pilocytic features are usually present. A rare differential diagnosis is clear cell meningioma, which can readily be distinguished by abundant diastase-sensitive PAS positivity and immunoreactivity for EMA. Metastatic clear cell carcinoma differs from oligodendrogloma by its sharp tumour borders and immunoreactivity for cytokeratins and EMA.

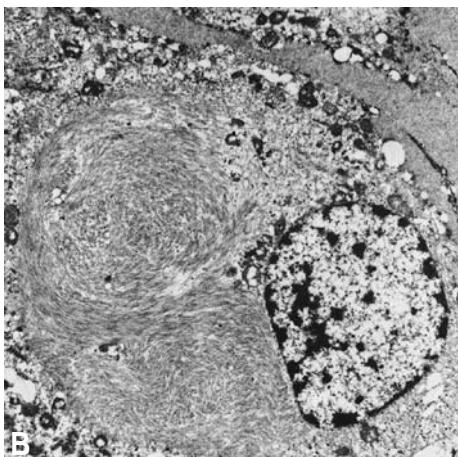
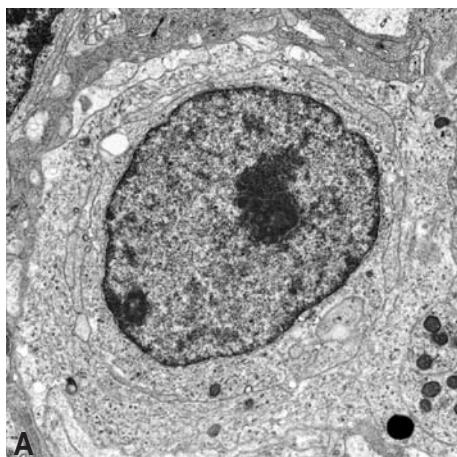


Fig. 2.05 Ultrastructure of a typical oligodendrogloma cell (A) and of a microgemistocytic cell with whorls of intermediate filaments (B).

Genetic susceptibility

Occasional familial clustering of oligodendrogloma has been reported: examples include two brothers [1681], mother and daughter [1920], twin sisters [1906] and a father and son [567]. Polymorphous oligodendrogloma has been reported in a brother and sister [1198]. Only occasional patients with an oligodendroglial tumour have been reported in families with hereditary cancer syndromes. In a survey of 47 families from Southern Sweden with *BRCA1* mutations, one patient with an oligodendrogloma was reported [1001]. One patient with Turcot syndrome, who carried a germline mutation in exon 5 of the *hPMS2* mismatch repair gene, developed two metachronous glioblastomas showing histological features of oligodendroglial differentiation [2228]. In addition, a child with retinoblastoma syndrome [18], another child with oligodendrogloma and hereditary nonpolyposis colorectal cancer syndrome [1455], and identical twins with oligodendrogloma and Ollier's disease have been documented [319]. Oligodendrogloma is rare in patients carrying a *TP53* germline mutation (See Chapter 13). Studies of genetic polymorphisms, in as yet limited numbers of patients, have suggested that some polymorphisms are more frequently seen in patients with gliomas including oligodendrogloma; examples of positively correlated polymorphisms include the *GSTM1* null genotype and polymorphisms in *GLTSCR1* and *ERCC2* [1074, 2460].

Genetics

G-banded karyotypes of more than 60 oligodendroglomas have been published [1379, 1829, 2237]. The vast majority showed normal or non-clonal karyotypes. A minor subset demonstrated simple clonal abnormalities, while occasional tumours had complex clonal karyotypes. Recently discovered is the frequent occurrence of an unbalanced translocation between chromosomes 1 and 19 [*t(1;19)(q10;p10)*] in oligodendrogloma [721, 989], which appears responsible for the characteristic co-deletion of 1p and 19q in these tumours.

1p and 19q deletion. Concurrent deletion of chromosomal arms 1p and 19q constitutes the hallmark alteration in oligodendrogloma being found in up to 80% of cases [997, 1634, 1845]. Most

tumours show losses of one entire copy of 1p and 19q due to an unbalanced *t(1;19)(q10;p10)* translocation [721, 989], while partial deletions are rare in oligodendrogloma. 1p/19q deletions are more common in oligodendrogloma located in the frontal, parietal and occipital lobes as compared to locations in the temporal lobe, insula and diencephalon [1534, 2507]. The relevant tumour suppressor genes on these chromosomal arms are as yet unclear, although various candidates have been proposed. The *CDKN2C* gene at 1p32 showed point mutations or homozygous deletion in a minor fraction of anaplastic oligodendrogloma [1845]. Several other genes on 1p, including the calmodulin-binding transcription activator 1 gene the DNA fragmentation factor subunit β gene, *SHREW1*, *TP73* and *RAD54*, demonstrated reduced expression in 1p-deleted oligodendrogloma, sometimes associated with promoter hypermethylation but never with mutation [98, 480, 1429, 1430]. Reported candidate genes on 19q are *p190RhoGAP* [2429], the myelin-related epithelial membrane protein gene 3 [31], *ZNF342* [860], and the maternally imprinted *PEG3* gene on 19q13.4 [2269]. However, none of these candidate genes has been definitively implicated.

Other genetic alterations. Several chromosomal aberrations other than 1p/19q deletion are found at more than random

frequency in oligodendrogloma, most frequently gains on chromosome 7 and losses on chromosomes 4, 6, 11p, 14 and 22q [997, 1845]. Losses of chromosomes 9 and 10 are more common in anaplastic variants, although they can occasionally be detected in oligodendrogloma, including one case with a circumscribed 10q25-q26 deletion [1383]. In contrast to astrocytic tumours, loss of 17p and *TP53* mutations are rare in oligodendroglial tumours and mutually exclusive to 1p/19q deletion [997, 1845].

Epigenetic changes. Several genes have been demonstrated to be epigenetically silenced by aberrant promoter methylation in variable fractions of oligodendrogloma, including the tumour suppressors *CDKN2A*, *p14^{ARF}* *CDKN2B*, and *RB1*, as well as *DAPK1* (death-associated protein kinase 1), *ESR1* (estrogen receptor 1), *THBS* (thrombospondin 1) and *TIMP3* (tissue inhibitor of metalloproteinase 3) [1845]. *MGMT* promoter hypermethylation and reduced expression is also common, in particular among 1p/19q-deleted tumours [1506].

Growth factors and receptors

About half of both WHO grade II and anaplastic oligodendroglomas show strong expression of *EGFR* mRNA and protein in the absence of *EGFR* gene amplification [1849]. The simultaneous

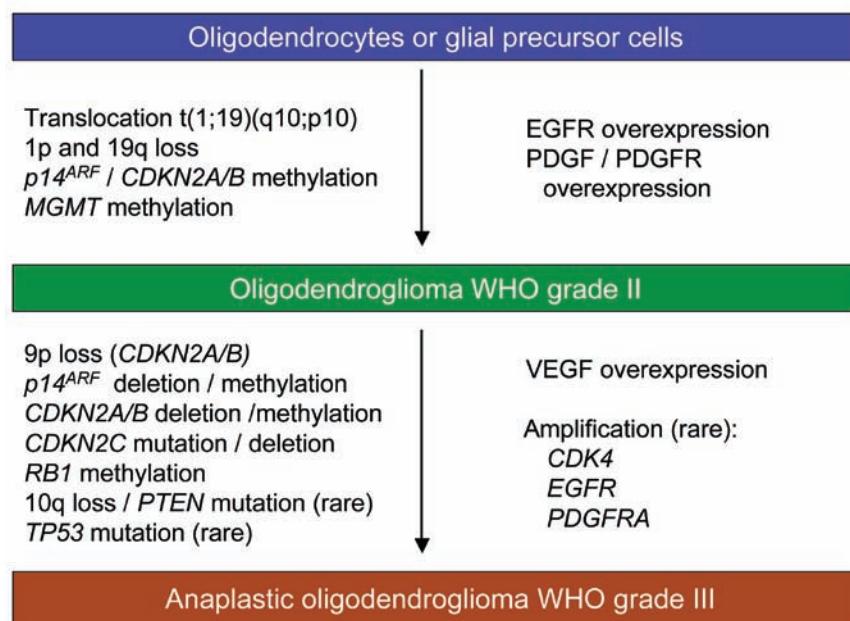


Fig. 2.07 Genetic alterations in oligodendroglial tumours.

expression of the mRNAs for the pre-proforms of EGF and/or TGF α indicates the possibility of auto-, juxta-, or paracrine growth stimulation via the EGFR system [512]. Several other growth factors, including basic FGF, PDGFs, TGF β , IGF1 and NGF, have been reported to be involved in the regulation of proliferation and/or maturation of oligodendroglial cells [1845]. Platelet-derived growth factors A and B, as well as the corresponding receptors (PDGFR- α and PDGFR- β) are co-expressed in virtually all oligodendroglomas [464]. Expression of vascular endothelial growth factor (VEGF) and its receptors play roles as angiogenic factors in oligodendroglial tumours, in particular in anaplastic oligodendrogloma [313, 347].

Histogenesis

Although the designation of CNS neoplasms as oligodendroglial tumours implies a histogenesis from cells of the oligodendroglial lineage, evidence for this assumption is circumstantial and is based mainly on morphological similarities of the neoplastic cells in these tumours to normal oligodendrocytes. It is also not known whether human oligodendrogloma arises from neoplastic transformation of mature oligodendrocytes or immature glial precursors. Experimental data in transgenic mice suggests the likelihood that these tumours arise from progenitor cells [2082], although it is interesting to note that an oligodendrogloma phenotype is commonly found in transgenic brain tumours, despite a variety of targeted cell types and oncogenic events [2391]. One suggested precursor cell has been the human equivalent of the rodent bipotential progenitor cell (designated O2-A progenitor), which may differentiate either into oligodendrocytes or type 2 astrocytes, but this hypothesis is unproven.

Prognostic and predictive factors

WHO grade II oligodendroglomas are typically slowly growing tumours with relatively long survival times. A population-based study from Switzerland demonstrated a median survival time of 11.6 years and a 10-year survival rate of 51% [1625]. The Central Brain Tumour Registry of the United States has documented 5- and 10-year survival rates of 71% and 54%, respectively [305]. Estimates have varied markedly, however, with some studies documenting even longer median

overall survival times (e.g. over 15 years [1642]) and others shorter median survivals (e.g. 3.5 years [455]). Some of this variability may be accounted for by different diagnostic criteria (hence varying proportions of cases with 1p/19q loss) and differing treatment approaches. Malignant progression on recurrence is common, although it takes longer on average than in the setting of diffuse astrocytoma.

Clinical factors. Features associated with more favourable outcome include younger age at operation [2026, 2074], frontal location [1199], post-operative Karnofsky score [2026], lack of contrast enhancement on neuroimaging [2074] and macroscopically complete surgical removal [455, 2074].

Histopathology. Parameters that are associated with worse prognosis include necrosis, high mitotic activity, increased cellularity, nuclear atypia, cellular pleomorphism and microvascular proliferation (see anaplastic oligodendrogloma). The presence of minigemistocytes or gliofibrillary oligodendrocytes is not correlated to patient survival [1204].

Proliferation. A number of studies have evaluated the prognostic significance of the Ki-67 (MIB-1) index [455, 800, 1197]. In general, higher proliferation rates (>3–5%), significantly correlate with worse prognosis. A study of 32 WHO grade II oligodendroglomas [800] found that Ki-67 labelling indices of >3% were indicative of a worse prognosis, and a study of 89 oligodendrogloma patients documented a 5-year survival rate of 83% for patients whose oligodendrogloma had a MIB-1 labelling index of <5% but only 24% for patients with tumours displaying >5% MIB-1 positive cells [455]. Similar data [377] have discriminated two groups of patients with significantly different survival times when using a cut-off value of 5% MIB-1 positive cells. The value of measuring proliferation rates appears independent of patient age, tumour site, and histological grade [1197].

Genetic alterations. Several retrospective studies have reported that 1p loss or combined 1p/19q loss is associated with longer patient survival in WHO grade II oligodendrogloma [563, 1039, 1226, 1994, 2113]. WHO grade II oligodendrogloma with 1p and 19q loss therefore appears to be a particularly slowly growing lesion, with survival times often

exceeding 10 years. In this regard, diagnostic testing for 1p and 19q status provides prognostic information in the setting of grade II oligodendrogloma. It is likely that 1p/19q status provides predictive as well as prognostic information in the setting of grade II oligodendrogloma; however, this has been more difficult to prove than in the setting of anaplastic oligodendrogloma because grade II oligodendrogloma shows less dramatic neuroradiological responses to therapy, requires long follow-up times for evaluation, and has high prevalence of 1p/19q loss. Nonetheless, small studies of low-grade oligodendrogloma patients treated with temozolamide have found that 1p loss is associated with objective radiological treatment response [846, 1300]. Such findings suggest that the longer survivals noted in such patients may reflect a combination of more indolent natural behaviour as well as greater therapeutic sensitivity.

Anaplastic oligodendrogloma

G. Reifenberger
J.M. Kros
D.N. Louis
V.P. Collins

Definition

An oligodendrogloma with focal or diffuse histological features of malignancy and a less favourable prognosis.

ICD-O code 9451/3

Grading

Anaplastic oligodendrogloma corresponds histologically to WHO grade III.

Anaplastic features that have been linked to malignancy in oligodendrogloma are similar to those in astrocytic gliomas, i.e. high cellularity, marked cytological atypia, high mitotic activity, microvascular proliferation and necrosis with or without pseudopalisading. Anaplastic oligodendro-

glioma usually shows several of these features. However, the individual impact of each parameter is not quite clear, although it has been argued that endothelial proliferation and mitotic activity are of particular importance [680]. Thus, the diagnosis of an anaplastic oligodendrogloma should require either the presence of conspicuous microvascular proliferation and/or high mitotic activity. In borderline cases, immunostaining for MIB-1 and attention to clinical and neuroradiological features such as rapid symptomatic growth and contrast enhancement may be helpful in assessing prognosis.

Incidence

Anaplastic oligodendrogloma accounts for approximately 1.2% of all primary brain tumours and adjusted annual incidence rates ranging from 0.07 to 0.18 per 100 000 population have been reported [305, 1625]. In population-based series, approximately 20–35% of oligodendroglial tumours are anaplastic oligodendroglomas [305, 1625].

Age and sex distribution

Anaplastic oligodendrogloma manifests preferentially in adults, with a peak incidence between 45 and 50 years of age [305, 1625, 2301]. Thus, patients with anaplastic oligodendrogloma manifest

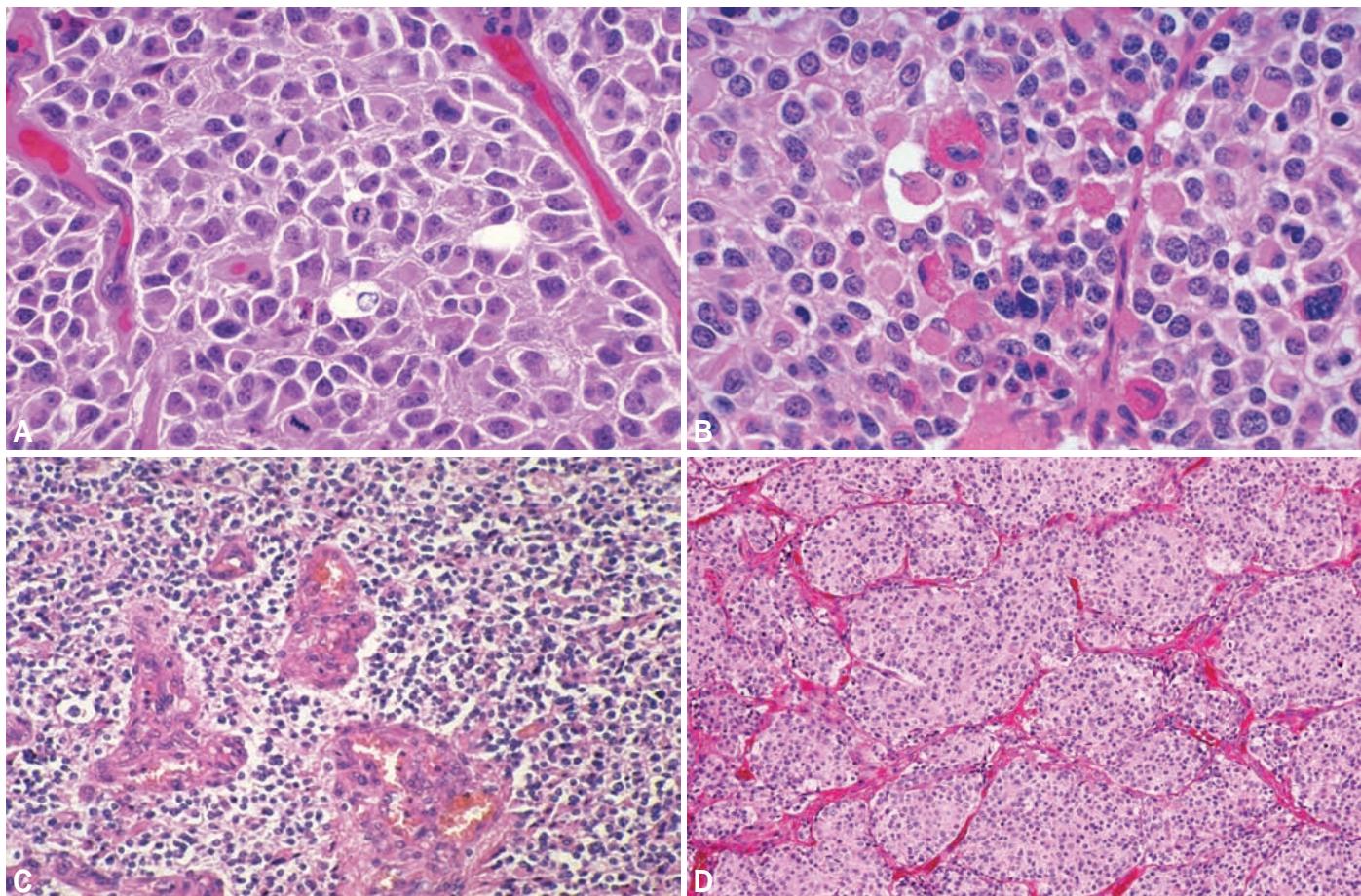


Fig. 2.08 A and B Anaplastic oligodendrogloma showing marked nuclear atypia and brisk mitotic activity. C Marked microvascular proliferation. D Highly cellular anaplastic oligodendrogloma with branching capillary network.

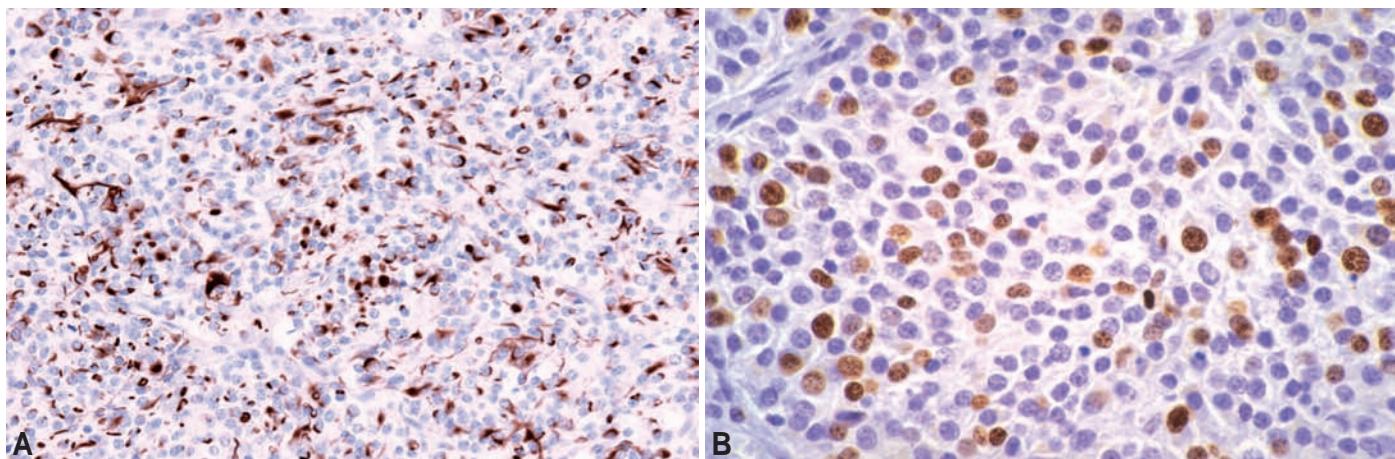


Fig. 2.09 Anaplastic oligodendrogloma. A Variable GFAP immunoreactivity. B High proliferative activity (MIB-1).

approximately 7–8 years later on average than patients with WHO grade II oligodendrogloma [305, 1625]. Anaplastic oligodendrogloma shows a slight male predominance, with a male:female ratio of 1.1:1 reported in a population-based series of 781 patients [305].

Localization

Anaplastic oligodendrogloma shares with WHO grade II oligodendrogloma a preference for the frontal lobe, followed by the temporal lobe.

Clinical features

Symptoms and signs

Anaplastic oligodendrogloma may develop either *de novo* or by progression from a pre-existing WHO grade II oligodendrogloma. The preoperative history of patients with *de novo* tumours is usually short with seizures being the most common presenting symptom [1269]. Some patients may present with long-standing signs, suggesting a pre-existing tumour of lower grade. The mean time to progression from WHO grade II oligodendrogloma to secondary anaplastic oligodendrogloma is approximately 6–7 years [1269, 1625].

Neuroimaging

Anaplastic oligodendrogloma may show heterogeneous patterns, owing to the variable presence of necrosis, cystic degeneration, intratumoural haemorrhages and calcification. Contrast enhancement on CT and MRI is usual and may be patchy or homogeneous. Ring-enhancement is uncommon and, when present, heralds a poor prognosis [276].

Macroscopy

The macroscopic features are similar to those of WHO grade II oligodendrogloma, except that anaplastic oligodendrogloma may demonstrate areas of tumour necrosis.

Histopathology

Anaplastic oligodendrogloma is a cellular, diffusely infiltrating glioma that may show considerable morphological variation. The majority of tumour cells demonstrate features that are reminiscent of oligodendroglial cells, i.e. rounded hyperchromatic nuclei, perinuclear halos, and few cellular processes. Focal microcalcifications are often present. Mitotic activity is usually prominent. Occasional tumours are characterized by marked cellular pleomorphism with multinucleated giant cells (polymorphic variant of Zülch [2514]), or have a conspicuous spindle-cell appearance. Rare cases with sarcoma-like tumour areas have also been observed [561, 1685]. Gliofibrillary oligodendrocytes and minigemistocytes are frequent in anaplastic oligodendrogloma; they do not argue against the diagnosis and are not of prognostic significance [1204]. The characteristic vascular pattern of branching capillaries is typically still recognizable, although pathological microvascular proliferation is often prominent. In addition, anaplastic oligodendroglomas may feature areas of necrosis, including pseudopalisading necroses resembling those of glioblastoma. However, if the tumour shows the typical cytological characteristics and other histological hallmarks of oligodendroglomas, such as the branching capillary network and microcalcifica-

tions, classification as anaplastic oligodendrogloma WHO grade III is appropriate. A study on 1093 adults with newly-diagnosed high-grade gliomas showed that the presence of necrosis, in contrast to anaplastic oligoastrocytoma, is not indicative of shorter survival in patients with anaplastic oligodendrogloma [1474]. Thus, if an anaplastic oligodendroglial tumour shows a significant astrocytic component, classification as anaplastic oligoastrocytoma is more appropriate and the presence of necrosis then is indicative of less favourable prognosis (see Anaplastic oligoastrocytoma). In such cases the presence of necrosis should be considered as a prognostically unfavourable.

Genetics

Chromosomal and array-based comparative genomic hybridization studies have revealed total losses of 1p and 19q in up to two thirds of anaplastic oligodendroglomas, which is slightly less common than in WHO grade II oligodendrogloma. Several studies identified additional chromosomal abnormalities in anaplastic oligodendrogloma; these include gains on 7 and 15q, as well as losses on 4q, 6, 9p, 10q, 11, 13q, 18 and 22q [997, 1845]. Double minute chromosomes, a cytogenetic hallmark of gene amplification, have been reported in occasional cases [2237].

The average number of chromosomes involved in copy number abnormalities and loss of alleles is higher in anaplastic oligodendrogloma than in WHO grade II oligodendrogloma [166, 1850, 1907], a finding in line with the hypothesis that

malignant progression is associated with the acquisition of multiple genetic abnormalities. Although the most frequent genetic alterations encountered in oligodendroglial tumours, i.e., 1p and 19q losses, differ significantly from those in astrocytoma, the current limited data on the genes involved in malignant progression indicate common molecular mechanisms. There is an increased incidence of deletions on the short arm of chromosome 9. The tumour suppressor locus *CDKN2A* at 9p21, which codes for *p16^{INK4A}* and *p14^{ARF}*, is homozygously deleted in up to a third of anaplastic oligodendroglomas, including tumours both with and without 1p/19q loss, albeit being somewhat more common in 1p/19q-deleted tumours {166, 276, 997, 1845}. Homozygous deletion or mutation of the *CDKN2C* gene at 1p32 has been observed in rare anaplastic oligodendroglomas that do not carry *CDKN2A* deletions {896, 1765}. Losses of 10q are infrequent occurring in only approximately 10% of cases {1993}. Mutations of the retained copy of the *PTEN* gene occur in about half of the cases with 10q loss, suggesting that there may be another progression-related gene target in the region {546, 997, 1845, 1993}. Anaplastic oligodendrogloma with loss of chromosome 10 and gain of chromosome 7 often lacks deletions on 1p and 19q. Rare tumours have activating mutations of the *PI3KCA* gene {225}. A small subset (<10%) of anaplastic oligodendroglomas may demonstrate amplification of proto-oncogenes, including *EGFR*, *PDGFRA*, *MYC*, *MYCN*, *CDK4*, *MDM2* and *MDM4* {997, 1845}. In addition, several genes have been shown to be epigenetically silenced in subsets of oligodendroglial tumours including anaplastic oligodendrogloma (see Oligodendrogloma).

Prognostic and predictive factors

Recent therapeutic advances have improved survival times of patients with anaplastic oligodendroglomas. Reports antedating the advent of combined chemotherapy-radiotherapy—particularly those antedating the procarbazine, CCNU and vincristine (PCV) regimens—demonstrated relatively shorter survival times. For example, median survival has been reported to range from less than 1 year {455} to 3.9 years {2074}. A population-based analysis noted a median survival time of 3.5 years {1625}. Combination of

chemotherapy-radiation therapy significantly prolongs progression-free survival (to approximately 2–2.5 years) and yields overall survival times of about 4–5 years {275, 2301}. In individual patients, notably longer survivals have been reported, typically in patients with 1p and 19q loss {276}. Indeed, prognosis is tightly linked to the allelic status of 1p and 19q {276}. In one large prospective trial, patients whose tumours lost 1p and 19q had markedly longer median survival times (>7 years compared to 2.8 years in patients whose tumours did not have 1p and 19q loss), and improvements in progression-free survival were most significant in this group {275}. Another large prospective trial showed that three-fourths of patients whose tumours had 1p and 19q loss were alive 5 years after diagnosis {2301}. Analysis of other genetic parameters, such as *CDKN2A* deletion, *PTEN* mutation or chromosome 10 loss, may also provide prognostic information {546, 1845}, but the results of such analyses are less powerful than 1p/19q status and have not been as extensively validated.

In addition to 1p/19q status, better prognosis has been noted in younger patients, those with better performance status and those receiving more extensive resections {275, 2074, 2301}. On the other hand, ring enhancement on initial neuroimaging has also been reported to correlate with a lack of response to PCV chemotherapy and poor prognosis {276}. Most patients die from local tumour recurrence. Occasionally, patients may develop metastases via the CSF or even systemic metastases {1370, 1461}. A rare complication of both oligodendrogloma and anaplastic oligodendrogloma is leptomeningeal 'oligodendroglomatosis' {594, 1755}. Occasional patients may present with primary leptomeningeal oligodendroglomatosis in the absence of any solid tumour {1588}.

In addition to prognostic importance, molecular genetic analysis of 1p and 19q status appears to have predictive importance, providing information about the likelihood of response to therapy {276}. Although the use of 1p and 19q testing varies in terms of how results affect therapeutic decisions, 1p and 19q analysis is commonly performed {8}. Those anaplastic oligodendroglomas that have allelic loss on the short arm of chromosome 1, or combined allelic losses

on 1p and 19q, are typically sensitive to PCV chemotherapy, with many such tumours showing complete neuro-radiological responses to PCV {276}. Large prospective trials have shown improved responses to both radiation therapy alone and to combined radiation-PCV chemotherapy in patients whose tumours harbour 1p and 19q loss {275, 2301}. Responses to temozolomide as initial chemotherapy also appear related to 1p status {2206}. Overall, however, it remains unclear if improved responses are specific to particular therapies; more likely, tumours with 1p and 19q loss are biologically distinct entities that feature sensitivity to a variety of cytotoxic therapeutic approaches.

Oligoastrocytoma

A. von Deimling
G. Reifenberger
J.M. Kros
D.N. Louis
V.P. Collins

Definition

A diffusely infiltrating glioma composed of a conspicuous mixture of two distinct neoplastic cell types morphologically resembling the tumour cells in oligodendrogloma and diffuse astrocytoma of WHO grade II.

ICD-O code 9382/3

Grading

Oligoastrocytoma corresponds histologically to WHO grade II.

Historical annotation

Mixed oligoastrocytoma was first recognized as an entity by Cooper in 1935 [379].

Incidence

Over the last 10 years the reported incidence of oligoastrocytoma has been increasing; this is probably a result of varying pathological criteria and to some degree increased recognition [248], and must be interpreted with caution. Among 4859 patients with intracranial glioma registered by the Norwegian Cancer Registry between 1956 and 1984, mixed glioma accounted for 9.2% of the tumours [805]. Another study reported an incidence between 10 and 19% of supratentorial low-grade glioma [976]. In contrast, among 5216 gliomas registered from 1990–1992 by the Central Brain Tumour Registry of the United States of America, only 96 tumours were listed under the diagnosis mixed glioma (1.8%) [305]. The annual incidence was estimated as 0.1 per 100 000 individuals.

Age and sex distribution

Oligoastrocytoma usually develops in middle-aged individuals, with a median age at operation between 35 and 45 years [305, 976, 1625]. Males are affected slightly more frequently than females, with ratios of 1.3:1 in the Central Brain Tumour Registry of the United States [305] and 1.7:1 in a smaller series of 20 low-grade and 10 anaplastic oligoastrocytomas [125].

Etiology

DNA sequences similar to those of the JC virus, the etiologic agent of progressive multifocal leukoencephalopathy, have been detected in a human oligoastrocytoma and viral antigen was found to be expressed in the tumour cells [1859]. However, a possible role of the JC virus in the development of glial neoplasms requires further corroboration.

Localization

Oligoastrocytoma arises preferentially in the cerebral hemispheres. The order of site frequency parallels the relative sizes of the cerebral lobes: frontal, temporal, parietal, occipital [125, 1534, 2073]. Occasional oligoastrocytomas are encountered in the brain stem, but cerebellar localization is very uncommon.

Clinical features

Symptoms and signs

Oligoastrocytoma presents with symptoms and signs similar to those described for astrocytomas and oligodendroglomas, most commonly epileptic seizures, paresis, personality changes, and signs of increased intracranial pressure [125, 2073].

Neuroimaging

Neuroradiologically, oligoastrocytoma demonstrates no specific features. In the series of Shaw *et al.* [2073], calcifications were demonstrable in 14% of the tumours; however, the criteria used to define pure oligodendrogloma in this series were not clear.

Macroscopy

The macroscopical appearance of oligoastrocytoma does not usually allow their distinction from other WHO grade II gliomas. Only occasionally are there regional differences in colour and consistency reflecting areas of distinct cellular differentiation.

Histopathology

Oligoastrocytomas are moderately cellular neoplasms with no or low mitotic activity.

Microcalcifications and microcystic degeneration may be present but necrosis and microvascular proliferation are absent.

The diagnosis of oligoastrocytoma requires the recognition of neoplastic glial cells with convincing astrocytic or oligodendroglial phenotypes. Oligoastrocytoma may be divided into biphasic ("compact") and intermingled ("diffuse") variants [773]. In the biphasic variant, which is rare, distinct areas of oligodendroglial and astrocytic differentiation are juxtaposed. This histopathology should not be confused with that of classic oligodendrogloma, in which the margins are often indistinguishable from fibrillary astrocytoma. In the most common variant of mixed oligoastrocytoma, both oligodendroglial and astrocytic tumour cells are intimately mixed. A diffuse admixture in oligodendrogloma of GFAP-positive minigemistocytes and gliofibrillary oligodendrocytes should not prompt the diagnosis of oligoastrocytoma instead of oligodendrogloma. Only tumours in which fibrillary, protoplasmic or classic gemistocytic astrocytic cells are present, in addition to the oligodendroglial tumour cells, qualify for the diagnosis of oligoastrocytoma. In the presence of numerous minigemistocytes, a careful search for an astrocytic component should be performed. A particular nosological problem are tumours composed of cells with phenotypical characteristics somewhere in between those of oligodendroglial and astrocytic tumour cells.

The pronounced phenotypic heterogeneity of the astroglial and oligodendroglial cell lineages and a lack of reliable markers make it difficult to define diagnostic criteria. It has been recommended to assess the fractions of the two components, but opinions diverge, with the proposed minimum astroglial component ranging up to 50% [894, 1108]. In most instances the precise extent of each component is difficult to determine since tumour cells may not always be easily recognized as either oligodendroglial or astrocytic, i.e. they may have features of

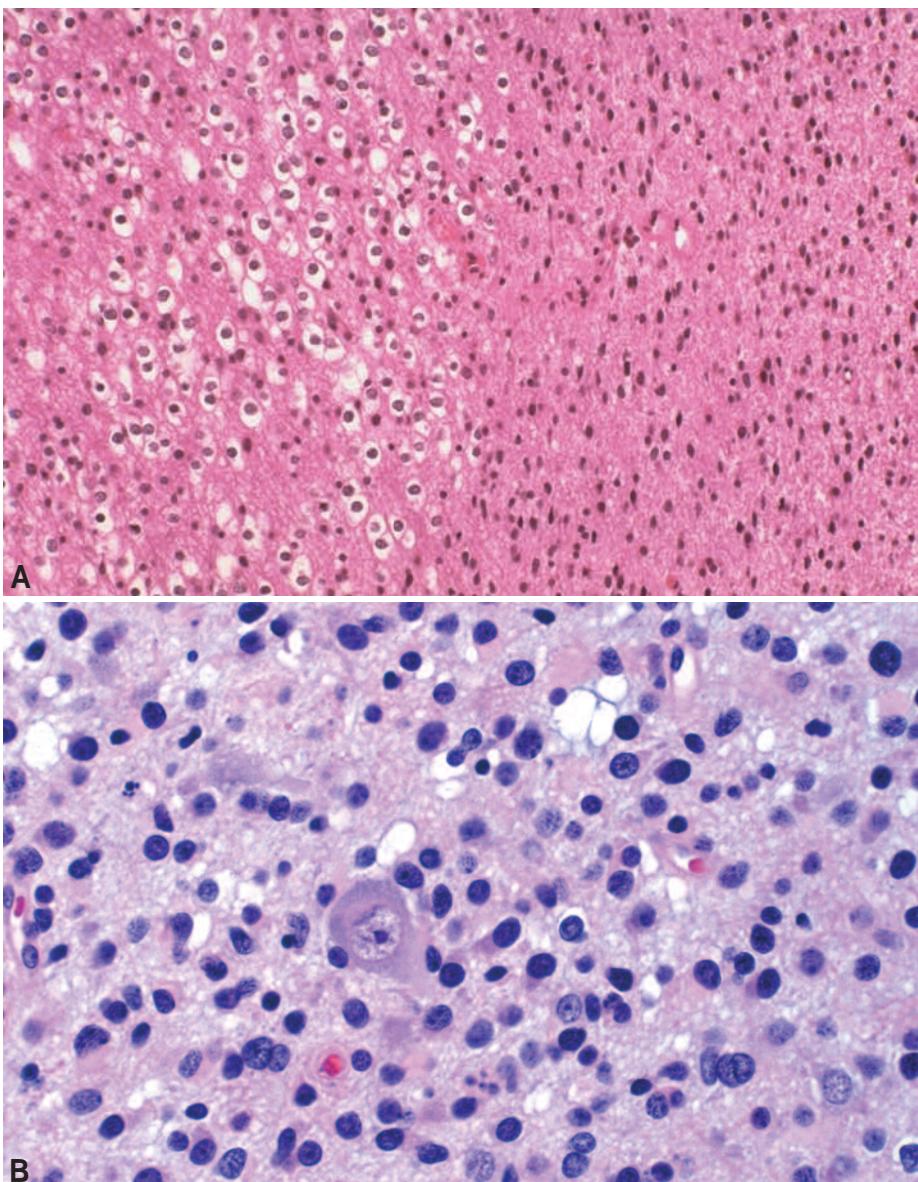


Fig. 2.10 A Oligoastrocytoma with distinct components displaying oligodendroglial (left) and astrocytic (right) differentiation. B Oligoastrocytoma, intermingled ("diffuse") variant. Nuclear cytology ranges from rounded profiles with minimal atypia, crisp nuclear membranes, and small nucleoli to irregular, hyperchromatic forms.

both lineages. Various studies have been undertaken to estimate interobserver concordance in gliomas with an oligodendroglial tumour component [378, 628, 1194]. Because of the poor delineation of the cell lineages causing considerable subjectivity in histological evaluation, interobserver variability for oligoastrocytoma is significantly larger compared to that for pure glioma [628, 1194]. There is no specific grading scheme for oligoastrocytoma. The features that are commonly used for diffuse glioma, i.e., cellularity, mitotic activity, nuclear pleomorphism, microvascular proliferation

and necrosis, are also used for oligoastrocytomas. Necrosis and microvascular proliferation showed highest concordance in pathology panel review [1194], and necrosis is considered a feature with independent prognostic value.

Immunohistochemistry

The oligodendroglial and astroglial components in oligoastrocytoma show the same immunoreactivity patterns as 'pure' oligodendrogloma and astrocytoma, respectively. There is no specific immunocytochemical marker that can be used for the reliable distinction of both

components. GFAP and vimentin expression are more consistently found in the astroglial component, compared with a more variable expression in the oligodendroglial tumour cells. In support of this immunohistochemical data, analysis of GFAP and its fragments by two-dimensional gel electrophoresis and Western blot analysis has allowed a discrimination of astrocytoma from oligodendrogloma [1357]. However, these techniques are not suitable as routine diagnostic methods and cannot be applied to oligoastrocytoma with a diffuse mixture of both cell types. Approximately one third of the oligoastrocytoma demonstrates nuclear p53 accumulation [125].

Proliferation

Immunocytochemistry for the Ki-67 proliferation-associated nuclear antigen generally correlates well with the presence or absence of features of anaplasia in oligoastrocytoma, with an average value of less than 6% reported in a series of 20 tumours [448, 2083]. Expression of p21 correlated with outcome in oligoastrocytoma [796].

Genetic susceptibility

Two family members with cerebral low-grade diffuse astrocytoma and cerebellar oligoastrocytoma have been reported [312]. Further, oligoastrocytoma was observed in identical twins [545]. Another study reported two siblings with glioblastoma and mixed oligoastrocytoma, respectively [2293]. No data are available on germline mutations in cases of familial clustering of oligoastrocytoma.

Genetics

The molecular genetic alterations underlying the oncogenesis and progression of oligoastrocytoma resemble those of oligodendrogloma and astrocytoma. About 30–50% of oligoastrocytomas are characterized by combined loss of genetic information on chromosomes 1p and 19q [1184, 1386, 1634, 1850]. The mechanisms leading to 1p and 19q deletions in oligoastrocytoma are likely to be similar to those in oligodendrogloma. About 30% of oligoastrocytomas carry mutations of the *TP53* gene [1386, 1534, 1634, 1850]. Oligoastrocytoma with *TP53* mutations tends not to have combined LOH on 1p and 19q, and vice versa [1386, 1534, 1850]. This suggests that

oligoastrocytomas are clonal neoplasms originating from a single precursor cell rather than representing composition tumours that had developed concurrently. Oligoastrocytoma of the temporal lobe is more frequently characterized by *TP53* mutations and less frequently by deletions of 1p and 19q than those from other localizations [528, 1534]. Taken together, these data indicate that tumours morphologically classified as oligoastrocytoma are genetically heterogeneous. One subset appears to be genetically related to oligodendroglial tumours, while another is genetically related to diffuse astrocytomas. The biological basis of the presence of two distinct glial phenotypes in each of these tumours remains to be elucidated.

Histogenesis

The histogenesis of oligoastrocytoma is unresolved, but derivation from a multipotent progenitor cell able to undergo astrocytic and oligodendroglial differentiation is a tenable hypothesis supported by transgenic mouse studies.

Prognosis and predictive factors

A median survival time of 6.3 years and 5- and 10-year survival rates of 58% and 32%, respectively, have been reported in a study of 60 patients with low-grade (Kernohan grade 1 and 2) oligoastrocytoma [2073]. A population-based study noted a median survival time of 6.6

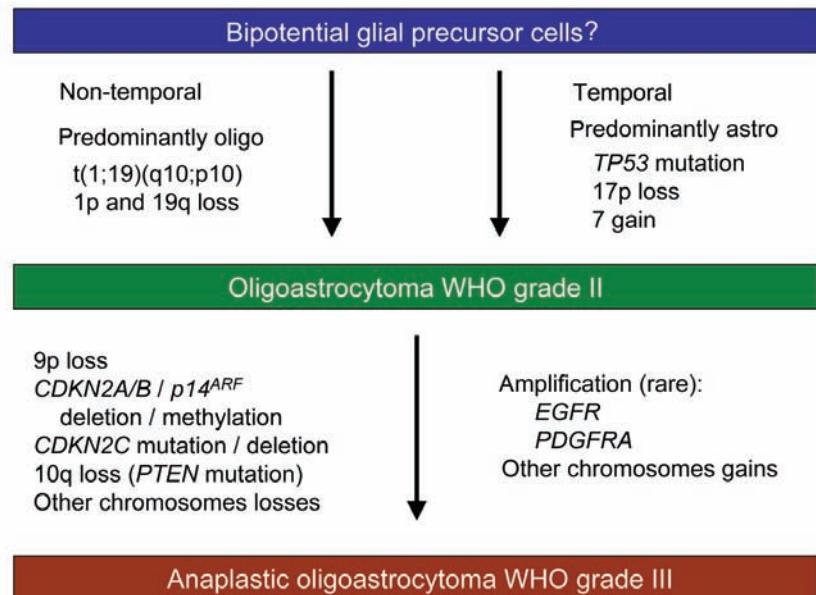


Fig. 2.11 Genetic alterations involved in the development of oligoastrocytoma and anaplastic oligoastrocytoma.

years and a 10-year survival rate of 49% [1634]. Factors associated with longer survival include younger age at operation (less than 37 years), gross total tumour resection, and postoperative radiation therapy [2073] as well as lower Ki-67 indices [2058]. Notably, as for oligodendrogloma, favourable prognosis appears associated with combined loss of 1p and 19q [528, 846]; a progression-

free survival time of 60 months was observed in patients whose tumours had 1p and 19q loss, compared with 30 months in patients whose tumours lacked these changes [528]. In a small series, response to temozolomide was also suggested to be associated with combined loss of 1p and 19q [846].

Anaplastic oligoastrocytoma

A. von Deimling
G. Reifenberger
J.M. Kros
D.N. Louis
V.P. Collins

Definition

An oligoastrocytoma with histological features of malignancy, such as increased cellularity, nuclear atypia, pleomorphism and increased mitotic activity.

ICD-O code 9382/3

Grading

Anaplastic oligoastrocytoma corresponds histologically to WHO grade III.

Incidence

Precise epidemiological data on the incidence of anaplastic oligoastrocytoma are not available. The limited published

data are confounded by the source of patients and the variability in the histological classification of these tumours. In a population-based series from Switzerland, only 11 tumours out of 987 (1%) oligodendroglial and astrocytic gliomas were diagnosed as anaplastic oligoastrocytoma [1625]. In a series of 285 supratentorial anaplastic gliomas in adults, anaplastic oligoastrocytoma accounted for 11 tumours (4%) [2419]. A single-institution review of 1093 patients with newly-diagnosed cerebral malignant gliomas in adults included 215 anaplastic oligoastrocytoma patients (20%); however, this high percentage may be an

overestimate due to a consultation bias [1475]. In prospective trials on patients with anaplastic oligodendrogloma and anaplastic oligoastrocytoma, the latter accounted for 27% [2301] and 49% [275] of the cases.

Age and sex distribution

The incidence peaks in the fifth decade, with mean age at diagnosis of 44 years reported in 215 patients [1475]. The male to female ratio was 1.15:1 [1475].

Localization

Anaplastic oligoastrocytomas are predominantly hemispheric tumours, with more

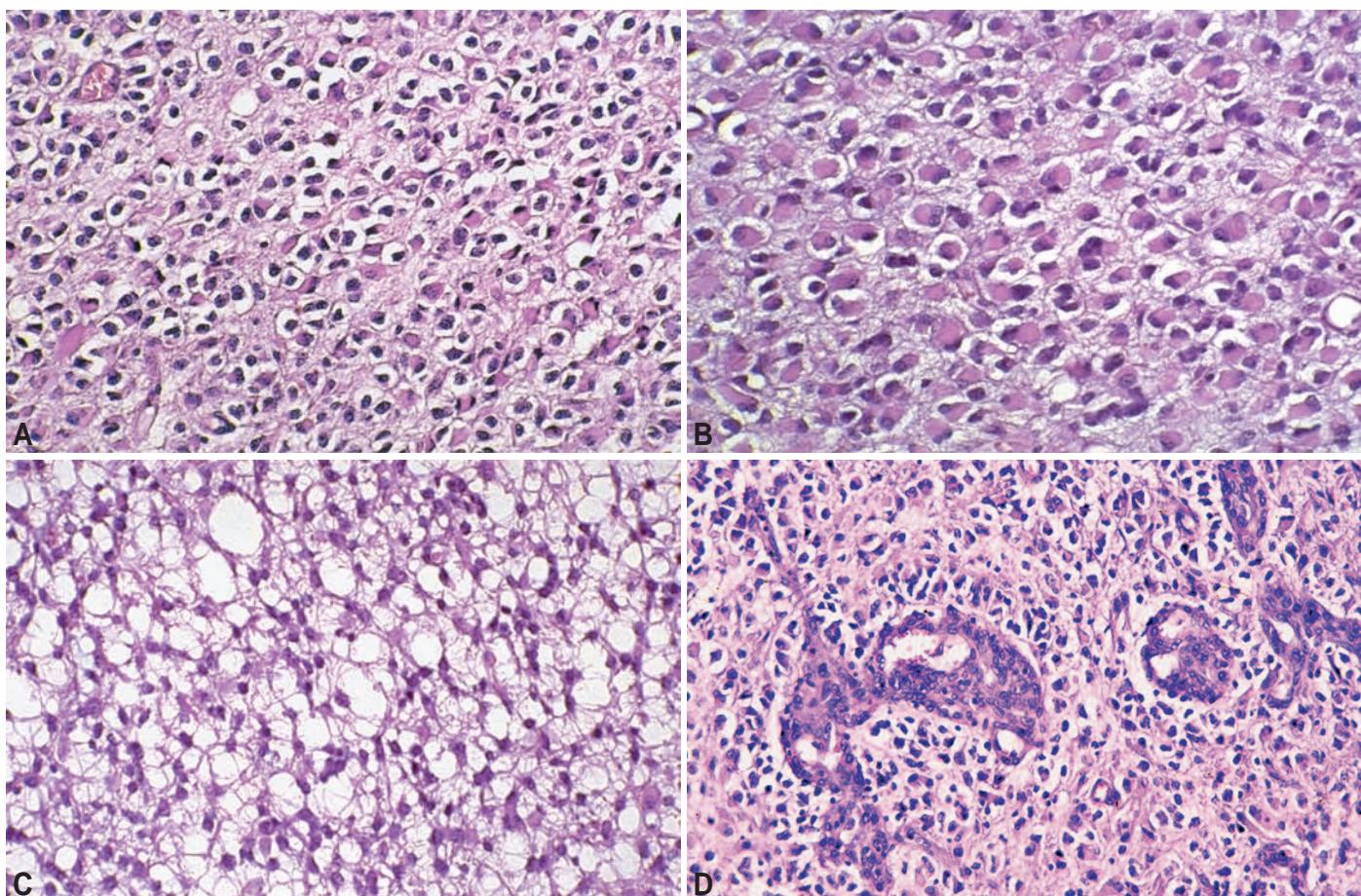


Fig. 2.12 Histological features of anaplastic oligoastrocytoma. A Tumour area showing the typical morphology of an oligodendrogloma with little evidence of anaplasia. B Region with marked nuclear atypia and numerous minigemistocytes. C Another area of the same tumour showing fibrillary astrocytic differentiation. D Marked microvascular proliferation in the same tumour.

than half of the tumours arising in the frontal lobe, followed by the temporal lobe.

Clinical features

Symptoms and signs

The clinical history of patients with anaplastic oligoastrocytoma is usually short. However, a preoperative history of several years may occasionally be encountered, suggesting a pre-existing low-grade glioma.

Neuroimaging

Anaplastic oligoastrocytoma usually shows contrast enhancement on CT and MRI.

Macroscopy

There are no consistent features that would allow the macroscopic distinction of anaplastic oligoastrocytoma from other anaplastic glioma types. Intratumoural haemorrhages may be seen, as well as areas of cystic degeneration and calcifications.

Histopathology

Anaplastic oligoastrocytomas are oligoastrocytomas with histological features of anaplasia, including nuclear atypia, cellular pleomorphism, high cellularity, and high mitotic activity. In addition, microvascular proliferation may be present. The differential diagnosis of

anaplastic oligoastrocytoma primarily includes anaplastic oligodendrogloma, anaplastic astrocytoma and glioblastoma. The identification of an astrocytoma component can be particularly challenging in a high-grade oligodendrogloma with considerable pleomorphism or in the presence of many gemistocytic cells, often in transition from minigemistocytes to classical gemistocytes.

Genetics

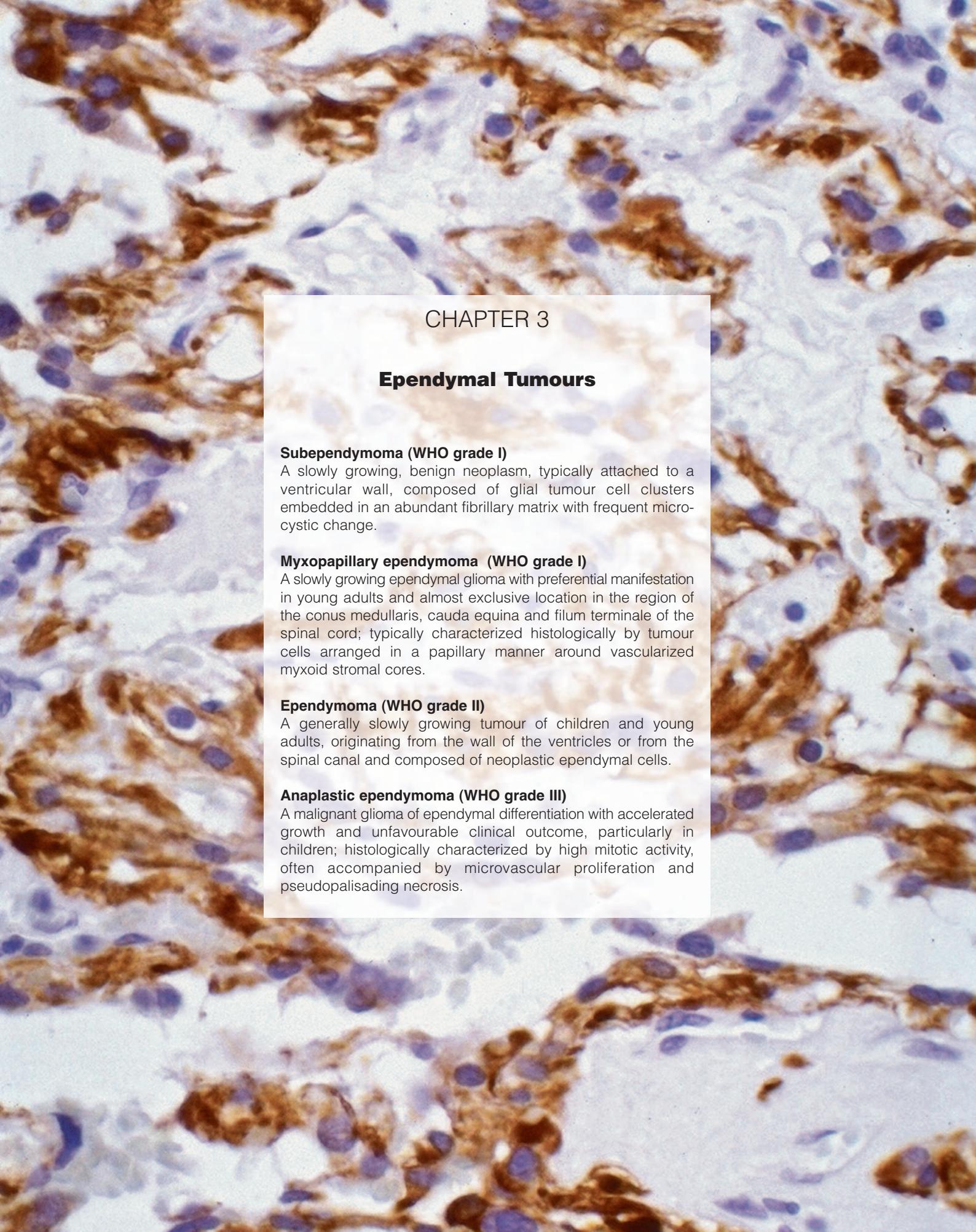
Anaplastic oligoastrocytoma typically exhibits the type and distribution of molecular lesions observed in oligoastrocytoma, i.e. loss of 1p/19q or *TP53* mutations {1534}. With respect to progression-associated genetic abnormalities, anaplastic oligoastrocytoma has been found to share many alterations that are also implicated in the progression of astrocytoma and oligodendrogloma, including allelic loss of 9p and homozygous deletion of *CDKN2A*, as well as allelic loss on chromosomes 10 and 11p {1850}. Individual cases of anaplastic oligoastrocytoma with amplification of the *EGFR* gene have been reported {1850}.

Prognostic and predictive factors

The prognosis of patients with anaplastic oligoastrocytoma is better than for patients with classical glioblastoma. A

median survival time of 2.8 years and 5- and 10-year survival rates of 36% and 9%, respectively, have been reported for anaplastic oligoastrocytoma {2073} in a study of 11 patients treated by operation and postoperative radiation therapy. A study on 19 patients with anaplastic oligoastrocytoma treated by operation, irradiation, and PCV chemotherapy, however, noted a median survival time of 49.8 months {1108}. In this study, seven patients with anaplastic oligodendrogloma treated in the same way showed a considerably longer median survival time of 76 months, most likely reflecting a subset of the cases with favourable genotype.

Important prognostic markers include necrosis and 1p status. One study of 180 patients with anaplastic oligoastrocytoma suggests that necrosis is associated with significantly worse prognosis {1474}. Anaplastic oligoastrocytoma with necrosis should be classified as "glioblastoma with oligodendroglial component" (see Glioblastoma chapter), although it may carry a better prognosis than standard glioblastoma {799,1185}. Some of these differences, however, may be related to 1p loss, since 1p loss was powerfully prognostic of improved progression-free and overall survival in a series of 48 anaplastic oligoastrocytomas {528}.



CHAPTER 3

Ependymal Tumours

Subependymoma (WHO grade I)

A slowly growing, benign neoplasm, typically attached to a ventricular wall, composed of glial tumour cell clusters embedded in an abundant fibrillary matrix with frequent microcystic change.

Myxopapillary ependymoma (WHO grade I)

A slowly growing ependymal glioma with preferential manifestation in young adults and almost exclusive location in the region of the conus medullaris, cauda equina and filum terminale of the spinal cord; typically characterized histologically by tumour cells arranged in a papillary manner around vascularized myxoid stromal cores.

Ependymoma (WHO grade II)

A generally slowly growing tumour of children and young adults, originating from the wall of the ventricles or from the spinal canal and composed of neoplastic ependymal cells.

Anaplastic ependymoma (WHO grade III)

A malignant glioma of ependymal differentiation with accelerated growth and unfavourable clinical outcome, particularly in children; histologically characterized by high mitotic activity, often accompanied by microvascular proliferation and pseudopalisading necrosis.

Subependymoma

R.E. McLendon
D. Schiffer
M.K. Rosenblum
O.D. Wiestler

Definition

A slowly growing, benign neoplasm, typically attached to a ventricular wall, composed of glial tumour cell clusters embedded in an abundant fibrillary matrix with frequent microcystic change.

ICD-O code 9383/1

Grading

Subependymoma corresponds histologically to WHO grade I.

Synonyms and historical annotation

Subependymoma was first described by Scheinker in 1945 [2005]. Alternative designations include subependymal astrocytoma and subependymal glomerate astrocytoma [617], but the use of these terms is discouraged.

Incidence

The true incidence of subependymomas is difficult to determine, because these tumours frequently remain asymptomatic and are often found incidentally at autopsy. In two studies, they accounted for approximately 8% of ependymal tumours [1236, 2024].

Age and sex distribution

Subependymomas develop in both sexes and in all age groups, but occur most frequently in middle-aged and elderly patients. The male:female ratio is approximately 2.3:1.

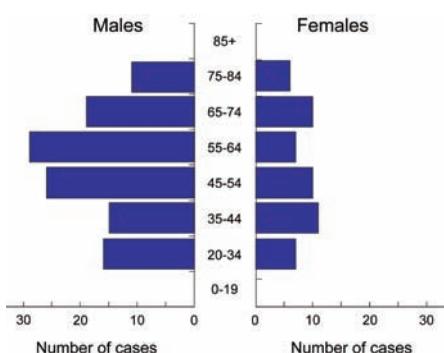


Fig. 3.01 Age and sex distribution of subependymoma, based on 167 cases. Data from CBTRUS 1995-2002.

Localization

The most frequent site is the fourth ventricle (50–60% of cases), followed by the lateral ventricles (30–40%). Less common sites include the third ventricle and septum pellucidum. In the spinal cord, subependymomas manifest as cervical and cervico-thoracic intramedullary or, rarely, extramedullary mass lesions [965].

Clinical features

Symptoms and signs

Subependymomas may become clinically apparent through ventricular obstruction and raised intracranial pressure. Spontaneous intratumoural haemorrhage has been observed. Spinal tumours manifest with motor and sensory deficits according to the affected anatomical segment. Incidental detection of asymptomatic subependymomas at autopsy is not uncommon.

Neuroimaging

Subependymomas are sharply demarcated, nodular masses that are usually non-enhancing. Calcification and foci of haemorrhage may be apparent. Intramedullary examples are typically eccentric in location, rather than centrally positioned as is typical of intraspinal ependymomas. These lesions are hypo- to hyperintense on T1- and T2-weighted MRI, with minimal to moderate enhancement [1818].

Macroscopy

These tumours present as firm nodules of variable size, bulging into the ventricular lumen. In most instances, the diameter does not exceed 1–2 cm. Intraventricular as well as spinal subependymomas are generally well demarcated. Large subependymomas of the fourth ventricle may cause brain stem compression.

Histopathology

Subependymomas are characterized by clusters of isomorphic nuclei embedded in a dense fibrillary matrix of glial cell processes with frequent occurrence of small cysts, particularly in lesions

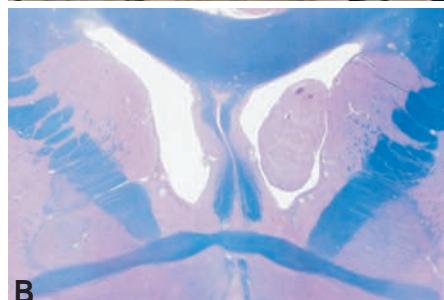


Fig. 3.02 A Subependymoma of the lateral ventricle originating from the roof of the lateral ventricle. B Subependymoma of the lateral ventricle.

originating in the lateral ventricles. Mitoses are rare or absent.

Tumour cell nuclei appear isomorphic and resemble those of subependymal glia. In solid tumours, occasional pleiomorphic nuclei may be encountered, however, nuclear variation, sometimes of a disturbing quality, is the rule in multicystic tumours. Some subependymomas exhibit low-level mitotic activity, but this is exceptional. Calcifications and haemorrhage can occur. Prominent tumour vasculature may be accompanied by microvascular proliferation. Occasionally, cell processes are oriented around vessels, thus forming ependymal pseudorosettes. In some cases, subependymomas represent the most superficial aspects of a cellular ependymoma; such combined tumours are classified as mixed ependymoma/subependymoma and are graded based on the ependymoma component. On record are examples of subependymoma with melanin formation [1931], rhabdomyosarcomatous differentiation [2257], and sarcomatous transformation of

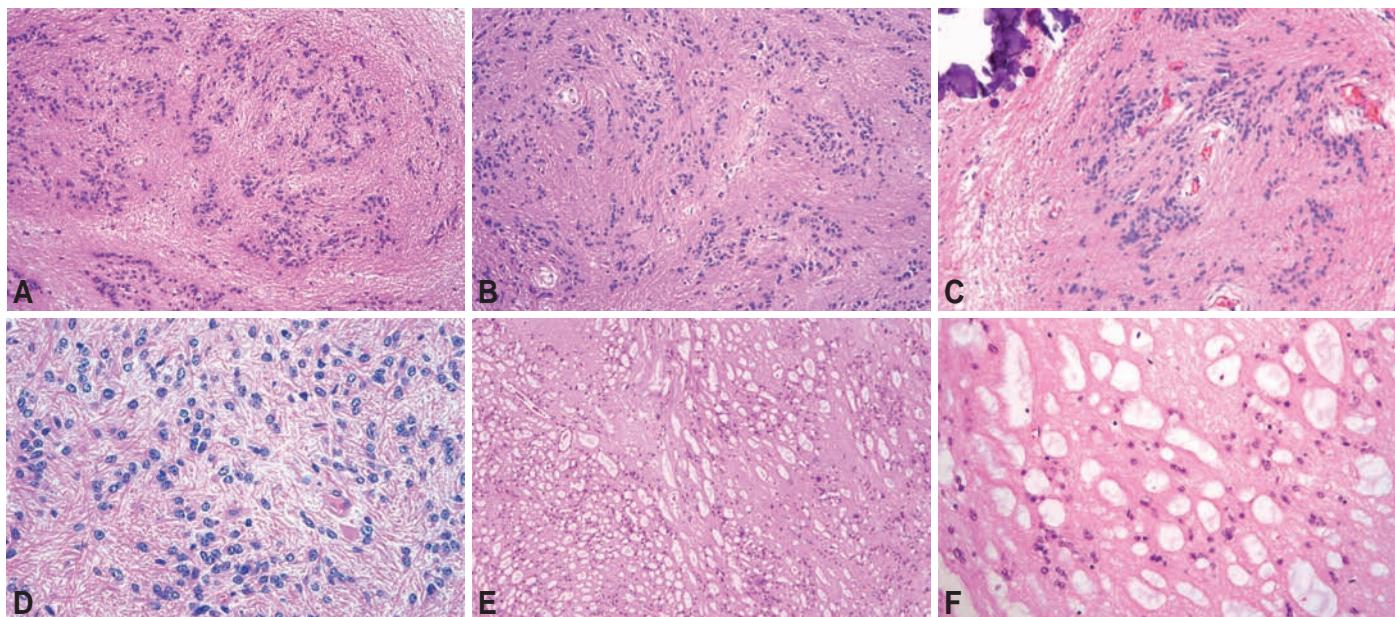


Fig. 3.03 Histological features of fourth ventricle subependymoma. A Lobular architecture and clustered nuclei. B Clustered nuclei and fibrillary stroma. C Clustered nuclei, lobular pattern and calcification. D Bland nuclei and abundant fibrillary stroma. E Microcystic degeneration. F High power of microcystic change.

vascular stromal elements {1351}. Immunoreactivity for GFAP is usually present, although to a variable extent, and positivity can be found for neuronal markers of low specificity (NCAM and neuron specific enolase) {2474}.

Electron microscopy

At the ultrastructural level, subependymomas show cells with typical ependymal characteristics, including cilia formation and microvilli, and sometimes with abundant intermediate filaments {76, 1528, 2018}

Proliferation

Mitotic activity is usually low or absent. Scattered mitoses and cellular pleomorphism are of no clinical significance {1342}. MIB-1 studies revealed labelling indices below 1%, compatible with the slow growth of this entity.

Genetic susceptibility

Rare familial cases have been described {1965}. The simultaneous clinical manifestation of infratentorial subependymomas in identical twins has been reported {355}.

Genetics

Consistent cytogenetic aberrations have not yet been uncovered {411A}. A molecular genetic analysis of 2 subependymomas for allelic deletions on chromosomes 10q and 22q and for point mutations of the *NF2* and *PTEN* tumour suppressor genes did not reveal any changes at these loci {504}.

Histogenesis

Proposed cells of origin include subependymal glia {76, 1528}, astrocytes of the subependymal plate, ependymal cells {1959} and a mixture of astrocytes and ependymal cells {617, 2006}.

Development from subependymal glial precursors appears most likely.

Prognostic and predictive factors

Subependymomas carry a good prognosis. Surgical removal is usually curative in cerebral as well as spinal subependymomas. Recurrences have been reported following incomplete resection {2358}. Neoplasms with a mixed ependymoma and subependymoma morphology appear to follow a clinical course corresponding to the ependymoma component (WHO grades II-III).

Myxopapillary ependymoma

R.E. McLendon
M.K. Rosenblum
D. Schiffer
O.D. Wiestler

Definition

A slowly growing ependymal glioma with preferential manifestation in young adults and almost exclusive location in the region of the conus medullaris, cauda equina and filum terminale of the spinal cord; typically characterized histologically by tumour cells arranged in a papillary manner around vascularized myxoid stromal cores.

ICD-O code

9394/1

Grading

These slowly growing tumours have a favourable prognosis and correspond to WHO grade I. Anaplastic variants are virtually unknown.

Historical annotation

In his original description of 1932, Kernohan {1092} defined the distinct morphological properties and preferential location of this entity.

Incidence

Among all ependymomas, the frequency of myxopapillary variants is 9–13% {1236, 2024}. In the conus medullaris/cauda equina region, myxopapillary ependymomas constitute the most common intramedullary neoplasm having an approximate incidence of 0.08 in males and 0.05 per 100 000 persons per year in females {305}.

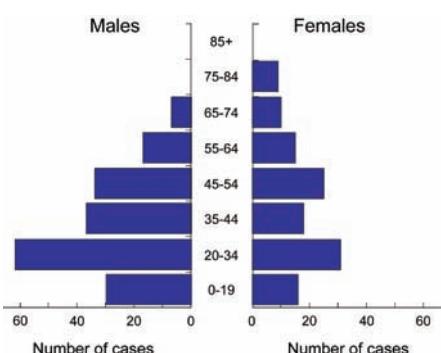


Fig. 3.04 Age and sex distribution of myxopapillary ependymoma, based on 311 patients. Data from CBTRUS 1995–2002.

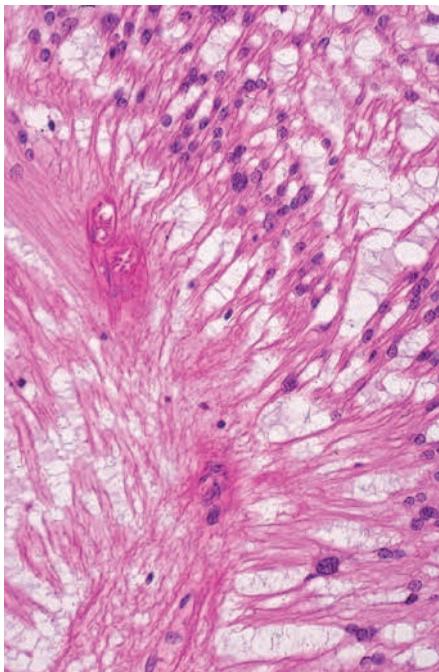


Fig. 3.05 Myxopapillary ependymoma showing radial perivascular arrangement of tumour cell processes.

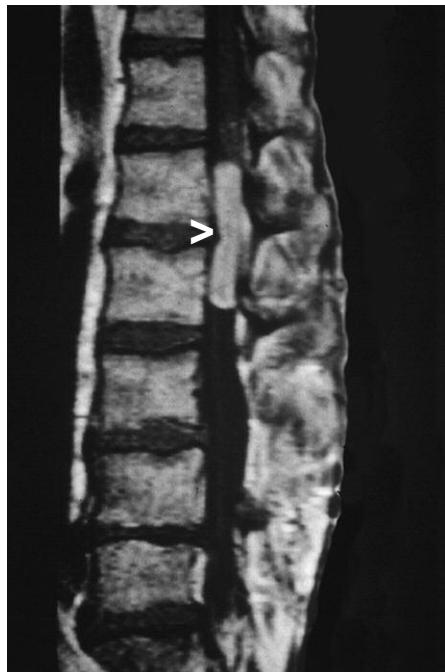


Fig. 3.06 MRI of a myxopapillary ependymoma of the filum terminale (arrow) presenting as a hyperintense spinal mass.

Age and sex distribution

An average age at manifestation of 36 years has been reported, with a broad range between 6 and 82 years. In a study of 320 ependymomas of the filum terminale, 83% were of the myxopapillary type, with a male:female ratio of 2.2:1 {311}.

Localization

Myxopapillary ependymomas occur almost exclusively in the conus medullaris-cauda equina-filum terminale region. They may originate from ependymal glia of the filum terminale, involve the cauda equina, and only rarely invade nerve roots or erode sacral bone. Multifocal tumours have been described {1555}. Myxopapillary ependymomas can occasionally be observed at other locations, such as the cervical-thoracic spinal cord {2125}, the fourth ventricle {1322}, the lateral ventricle {1995}, or the brain parenchyma {2366}. Subcutaneous sacrococcygeal or presacral myxopapillary ependymomas

represent a distinct subgroup. They appear to originate from ectopic ependymal remnants {909}. Intraspinal variants may masquerade clinically as chordoma.

Clinical features

Myxopapillary ependymomas are typically associated with back pain, often of long duration. MRI usually reveals a sharply circumscribed lesion with enhancement that is often bright. Extensive cystic change and haemorrhage may be apparent.

Macroscopy

Myxopapillary ependymomas display a lobulated, soft and greyish appearance. They are often encapsulated and do not usually exhibit grossly infiltrative properties.

Histopathology

Myxopapillary ependymomas are characterized by GFAP-expressing, cuboidal to elongated tumour cells radially arranged in a papillary manner around vascularized stromal cores. Some tumours, however,

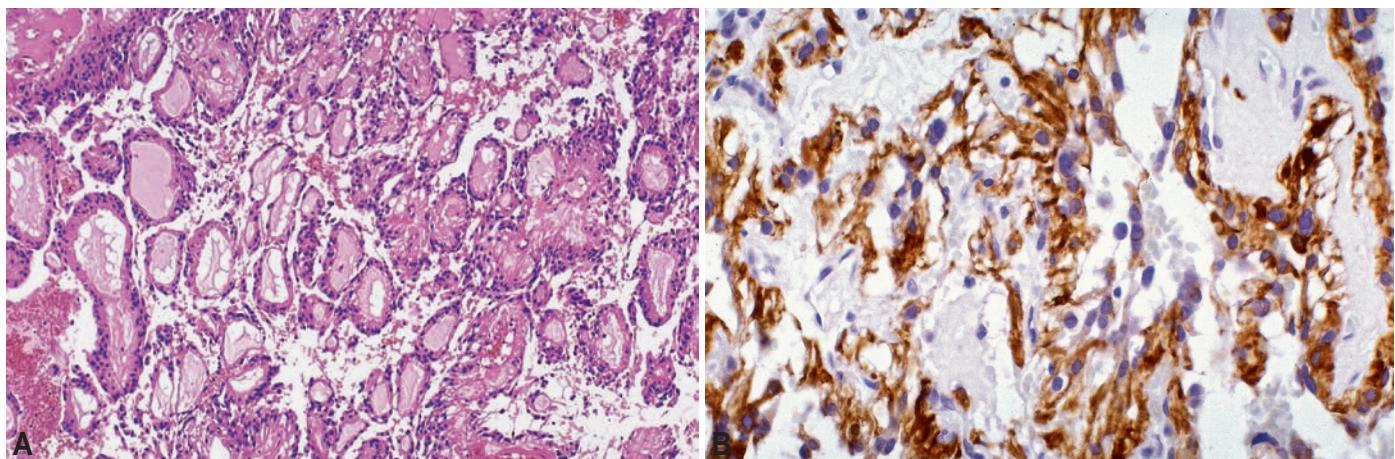


Fig. 3.07 Myxopapillary ependymoma of the cauda equina. A Layers of tumour cells around vessels with mucoid degeneration. B Perivascular tumour cells consistently express GFAP.

show minimal or no papillary areas and instead feature fascicles of more elongated cells. An Alcian-blue positive, myxoid matrix material accumulates between tumour cells and blood vessels, also collecting in microcysts. Alcian-blue positivity in small cystic spaces is particularly characteristic of those lesions lacking prominent papillary features. Mitotic activity is low, which correlates with a low MIB-1 labelling index {1787}.

Immunohistochemistry

Immunohistochemistry for GFAP, S-100 and vimentin are positive, whereas immunoreactivity for cytokeratins is typically absent. Co-occurrence of the tumour with lipoma {13} and paraganglioma {1071} has been described. Tumour entities to be distinguished from myxopapillary ependymomas include chordoma, myxoid chondrosarcoma, paraganglioma, mesothelioma and

papillary adenocarcinoma. In these situations, immunoreactivity for GFAP and lack of cytokeratin expression confirm the diagnosis {366}.

Electron microscopy

The cells do not show polarity, but junctions of zonulae adherens type with cytoplasmic thickening and wide spaces containing amorphous material or loose filaments {1838, 2018, 2131}. Extracellular spaces, delineated by cells with basal membrane, contain projected villi {1838}. Few cilia, complex interdigitations and abundant basement membrane structures have been described, with a distinctive feature of some examples being aggregation of microtubules within endoplasmic reticulum complexes {844}.

Genetics

This entity has not yet been subjected to systematic molecular studies. A molecular

genetic analysis of 6 myxopapillary ependymomas for allelic deletions on chromosomes 10q and 22q and for point mutations of the *NF2* and *PTEN* tumour suppressor genes did not reveal any changes at these loci {504}.

Prognostic and predictive factors

Prognosis is favourable, with more than 10-year survival after total or partial resection {2125}. Late recurrence and distant metastases may occur with incomplete resections in both adults {25} and children {553}. Subarachnoid dissemination has occasionally been observed {2423}. The subcutaneous sacrococcygeal myxopapillary ependymoma appears to be associated with a significant rate of regrowth and occasional distant metastases {909}.

Ependymoma

R.E. McLendon
O.D. Wiestler
J.M. Kros
A. Korshunov
H.-K. Ng

Definition

A generally slowly growing tumour of children and young adults, originating from the wall of the ventricles or from the spinal canal and composed of neoplastic ependymal cells.

ICD-O codes

Ependymoma	9391/3
- Cellular ependymoma	9391/3
- Papillary ependymoma	9393/3
- Clear cell ependymoma	9391/3
- Tanyctic ependymoma	9391/3

Grading

Ependymoma corresponds histologically to WHO grade II.

Incidence

In the United States, WHO grade II-III ependymomas have an approximate incidence of 0.29 in males and 0.22 per 100 000 persons per year in females [305]. There appears to be a racial disparity with an incidence of 0.35 in whites versus 0.14 in African Americans [305]. Ependymomas account for 2–9% of all neuroepithelial tumours, amounting to 6–12% of all intracranial tumours in children, and up to 30% of those in children younger than 3 years [495]. In the spinal cord, ependymomas are the most common neuroepithelial neoplasms, comprising 50–60% of spinal gliomas [2018] in adults, but are rare in children [73].

Age and sex distribution

Ependymomas develop in all age groups, with a range from 1 month to 81 years [305] but incidence is greatly affected by histological type and location. Infratentorial ependymomas predominate in children, with a mean age at clinical manifestation of 6.4 years and a range of 2 months to 16 years [2358]. A second age peak at 30–40 years has been reported for spinal tumours. Supratentorial ependymomas affect paediatric as well as adult patients. Ependymomas appear equally distributed between males and females.

Etiology

The identification of SV40 virus large T antigen-related DNA sequences in a significant proportion of human choroid plexus papillomas and ependymomas received attention since it was thought possible to reflect latent infection following widespread use of SV40-contaminated polio vaccines during 1955–1962 [138, 883]. Natural SV40 strains have been also identified in human ependymomas [1270]. However, other investigators did not confirm these findings [2384].

Localization

These tumours may occur at any site along the ventricular system and in the spinal canal. They most commonly develop in the 4th ventricle and in the spinal cord, followed by the lateral ventricles and the third ventricle [1788, 2024]. In adults, infratentorial and spinal ependymomas arise with almost equal frequency, whereas infratentorial ependymomas clearly predominate in young children [1222]. In the spinal cord, cervical and cervico-thoracic segments appear to represent primary sites. In contrast, the myxopapillary variant of ependymoma predominantly affects the conus-cauda equina region. Supratentorial parenchymal ependymomas may occur outside the ventricular system, particularly in children. Rare extraneuronal ependymomas have been observed in the ovaries [1160], broad ligaments

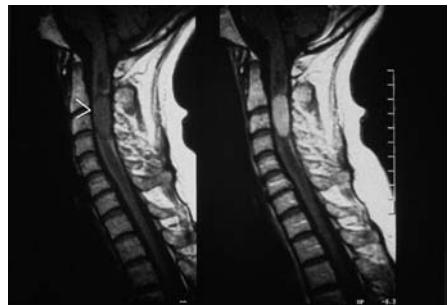


Fig. 3.09 Sagittal MRI showing an ependymoma in the upper cervical spinal cord (left, arrow) with marked gadolinium-enhancement (right), delineated on both sides by a typical cyst.

[127], soft tissues, mediastinum and the sacrococcygeal area.

Clinical features

Symptoms and signs

Clinical manifestations are localization-dependent. Infratentorial ependymomas may present with signs and symptoms of hydrocephalus and increased intracranial pressure, such as headache, nausea, vomiting and dizziness. Involvement of posterior fossa structures may cause cerebellar ataxia, visual disturbance, dizziness and paresis. Patients with supratentorial ependymomas show focal neurological deficits, seizures and features of intracranial hypertension [495]. Head enlargement can be encountered in children below the age of two years. Spinal ependymomas present with motor and sensory deficits.

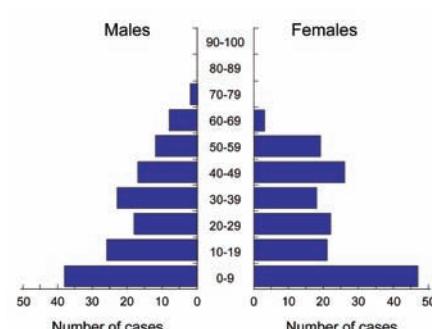


Fig. 3.08 Age and sex distribution of ependymoma, based on 298 cases. Data from Schiffer *et al.* [2024].

Neuroimaging

Gadolinium-enhanced MR scans demonstrate rather well circumscribed lesions with varying degrees of contrast enhancement. Ventricular obstruction or brain stem displacement and hydrocephalus are frequent accompanying features. Supratentorial tumours may exhibit cystic components. Intratumoural haemorrhage and extensive calcification are occasionally observed. Gross infiltration of adjacent brain structures and edema are rare. However, in supratentorial parenchymal ependymomas, the

neuroradiological distinction from other glioma entities constitutes a diagnostic challenge. MRI appears particularly useful for determining the relationship to surrounding structures and invasion along the CSF pathway and syrinx formation [636].

Macroscopy

Ependymomas are typically soft tan masses with well-demarcated borders. Visible foci of haemorrhage or necrosis are uncommon. Macroscopically striking examples are the so-called "plastic ependymomas" which can fill the fourth ventricle, emerge out the foramina of Luschka or Magendie and surround the brain stem via subarachnoid growth [392].

Histopathology

The most common, or classic, pattern of ependymoma is a well-delineated, moderately cellular glioma with a

monomorphic nuclear morphology, characterized by round to oval nuclei with "salt and pepper" speckling of the chromatin. Mitoses are rare or absent. Apart from the nuclear aspects, key histological features are perivascular pseudorosettes and ependymal rosettes. Perivascular pseudorosettes originate from tumour cells arranged radially around blood vessels with perivascular anuclear zones of glial fibrillary protein (GFAP)-rich, fibrillary processes. True ependymal rosettes and ependymal canals are composed of columnar cells arranged around a central lumen. They develop in only a minority of cases. Areas of more extensive fibrillarity are frequently encountered. Regressive changes include regions of myxoid degeneration, intratumoural haemorrhage, calcifications and, occasionally, foci of cartilage and bone. Marked hyalinization of tumour vessels can be common and may precede calcification.

Occasional non-palisading, geographic foci of necrosis are compatible with the diagnosis of ependymoma WHO grade II. The tumour/parenchymal interface is typically sharp [2358] though evidence of infiltration may be encountered. In small samples, distinction from pilocytic astrocytoma can be difficult.

The following histopathological variants of ependymoma can be distinguished.

Cellular ependymoma

This variant is more common in extraventricular locations [2096] and shows conspicuous cellularity without a significant increase in mitotic rate. Pseudorosettes may be inconspicuous, and true ependymal rosettes may be absent. Lacking other properties of anaplasia, this variant is therefore classified as WHO grade II.

Papillary ependymoma

Ependymomas form linear, epithelial-like surfaces along their CSF exposures. Occasionally, exuberant growths arise in which fingerlike projections are lined by a single layer of cuboidal tumour cells with smooth contiguous surfaces and with GFAP-positive tumour cell processes; in contrast, choroid plexus papillomas and metastatic carcinomas form bumpy, hobnail cellular surfaces that do not feature extensive GFAP-positivity.

Clear cell ependymoma

Clear cell ependymomas display an oligodendroglial-like appearance with clear perinuclear halos. This variant appears to be preferentially located in the supratentorial compartment of young patients [596, 1479]. Clear cell ependymomas need to be distinguished from oligodendrogloma, central neurocytoma, clear cell carcinoma and haemangioblastoma. Ependymal and perivascular rosettes, immunoreactivity for GFAP and epithelial membrane antigen (EMA) and ultrastructural studies can be helpful in this differential diagnosis. Recent data suggest that clear cell ependymoma may follow a more aggressive course [596]. The clear cell tumour of the lateral ventricles previously classified as ependymoma of the foramen of Monro [2512] is now recognized as central neurocytoma in most instances (See Chapter 6).

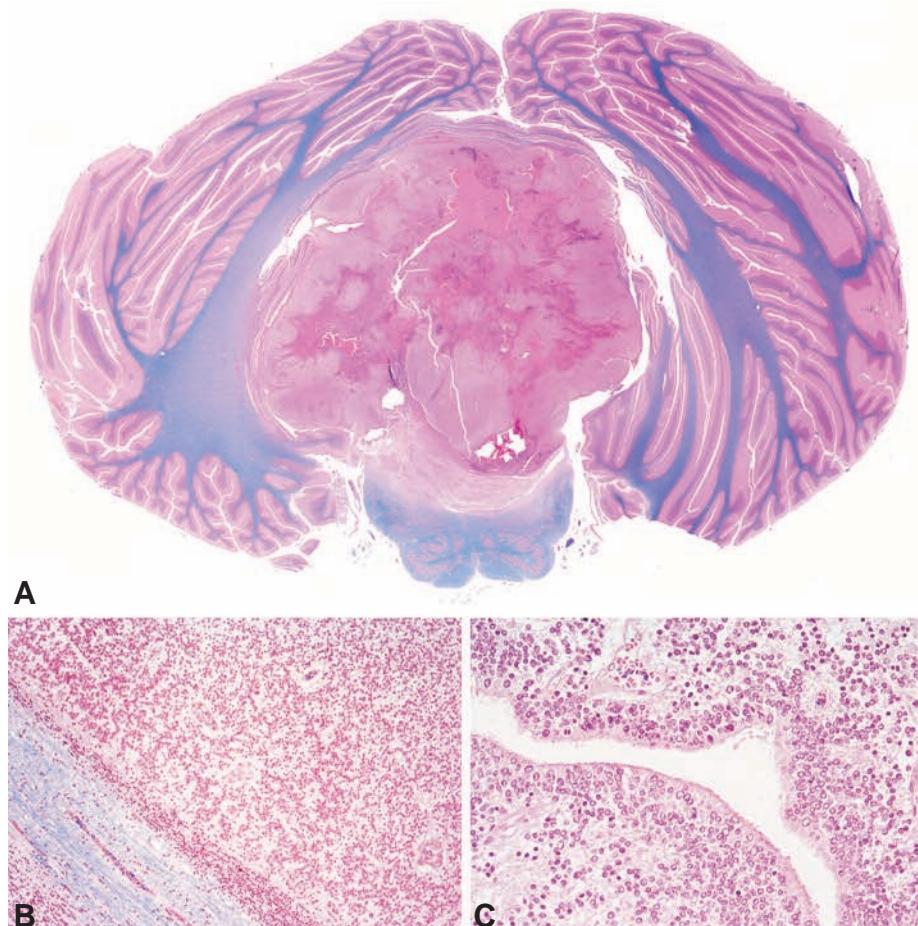


Fig. 3.10 A Ependymoma in a child, filling the entire lumen of the fourth ventricle. Note the displacement of the medulla, (B) the relatively clear demarcation from the cerebellar parenchyma and (C) the involvement of the ependymal lining in the neoplastic process.

Tanycytic ependymoma

Tanycytic tumours are most commonly found in the spinal cord. Their tumour cells are arranged in fascicles of variable width and cell density and only poorly intertwine. Nuclei exhibit the salt-and-pepper speckling of other ependymomas. The term tanycytic ependymoma has been chosen since its spindly, bipolar elements resemble tanycytes, the paraventricular cells with elongated cytoplasmic processes that extend to ependymal surfaces [585]. As ependymal rosettes are typically absent and pseudorosettes only vaguely delineated, the lesion may be misconstrued as an astrocytoma, particularly as pilocytic astrocytoma. Its ultrastructural characteristics, however, are ependymal.

Other patterns

Rare ependymoma variants include ependymoma with lipomatous differentiation [1952], giant cell ependymoma [600], ependymoma with extensive tumour cell vacuolation [826], melanotic ependymoma [1931], signet ring cell ependymoma [2515], ovarian ependymoma [286, 732, 1127], ependymoma with neuropil-like islands [661] and ganglioglioma with a tanycytic glial component [795].

Immunohistochemistry

The great majority of ependymomas display GFAP immunoreactivity with a prominent reaction for GFAP usually observed in pseudorosettes. Immunoreactivity is more variable in the ependymal rosettes, ependymal canals and papillae where positive cells may alternate with unlabeled elements. Ependymomas typically express S-100 protein and vimentin [1114]. EMA immunoreactivity has been reported in a high percentage of ependymomas with a prominent signal along the luminal surface of ependymal rosettes or as dot-like cytoplasmic vacuoles representing microrosettes in scattered cells [1070]. However, dot-like EMA positivity is not specific to ependymomas and has been noted in glioblastomas. Focal immunoreactivity to cytokeratins can be seen in some cases [1393], and thyroid transcription factor 1 (TTF-1) has been seen in ependymomas of the third ventricle [2481]. Expression of nestin, a neuro-developmental intermediate filament protein, may be strong in ependymomas

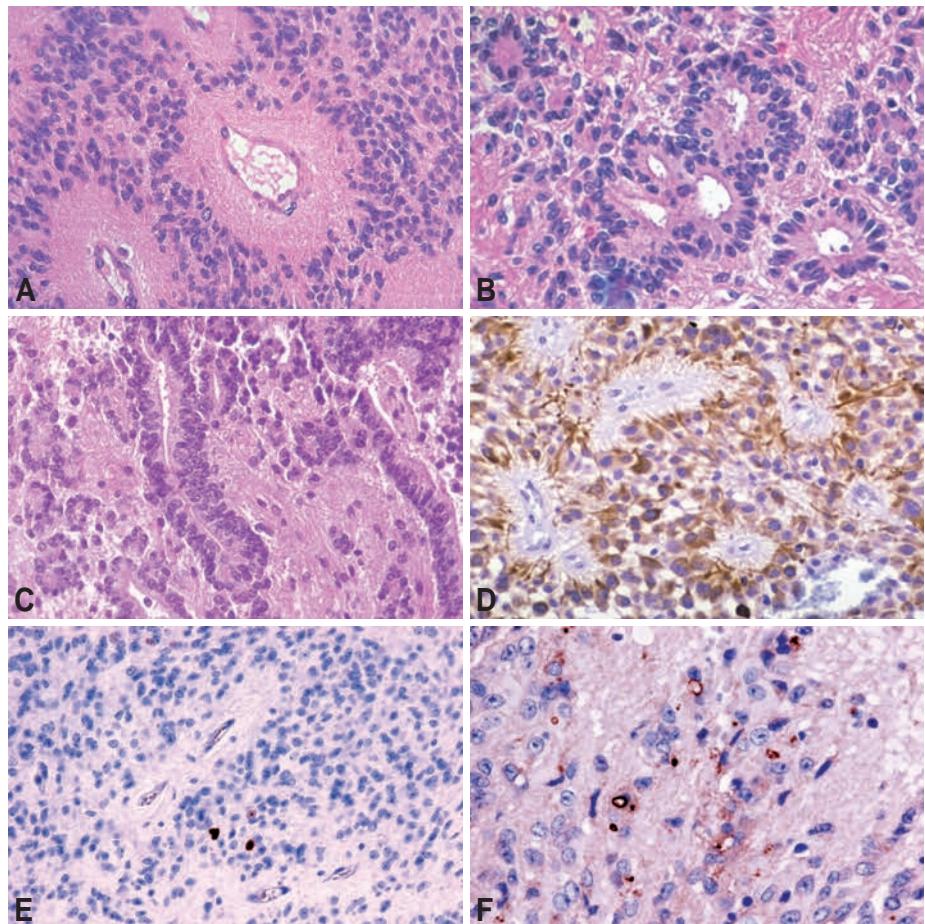


Fig. 3.11 Histological features of ependymoma. A Perivascular pseudorosettes. B Ependymal rosettes. C Ependymal canals. D GFAP immunoreactivity predominantly around tumour vessels. E Low MIB-1 labelling index. F Ring-like and dot-like EMA positivities.

[48]. Ependymomas do not express most neuronal antigens, although reactivity to anti-NeuN has been described [1800].

Electron microscopy

Ependymomas maintain characteristic ultrastructural properties of ependymal cells such as cilia in a 9+2 arrangement, blepharoblasts and microvilli located at the luminal surface, junctional complexes at the lateral surface and lack of a basement membrane at the internal surface. Cells may form microrosettes into which microvilli and cilia project. Junctional complexes (zonulae adherentes), irregularly linked by zonulae occludentes or gap junctions, and cell processes filled with intermediate filaments, may also be encountered [703]. A basal lamina may be present at the interface between tumour cells and vascularized stroma. Neuronal features are absent.

Growth pattern and invasion

Tumour expansion with formation of a clear-cut edge toward the adjacent nervous tissue is characteristic. From the fourth ventricle, ependymomas typically extend into the cerebellopontine angle and protrude into the cisterna magna. Sometimes, isolated tumour cells can be found in the adjacent tissue. Low cellular density may suggest parenchymal invasion. Infrequently, there is spread via the CSF, particularly from infratentorial lesions [1746, 2397] which may occur independent of grade. Several case reports describe extraneuronal metastases, mostly to the lungs.

Proliferation

Proliferation has been correlated with survival in most recent studies. Ki-67 labelling indices of less than 4% have been associated with significantly longer survival times than labelling indices (LIs)

greater than 5% {1236, 1788, 2431}. However, the prognostic significance of the LI, particularly with regard to progression-free survival, has not yet been firmly established. Evaluation of tumour cell apoptosis has not yielded prognostically relevant information {2020}.

Histogenesis

Stem cells isolated from ependymomas indicate a radial glia phenotype. These findings suggest radial glia cells as a candidate cell of origin for ependymoma {2229}.

Genetic susceptibility

Spinal ependymomas are a major manifestation of neurofibromatosis type 2 (NF2), indicating a role for the *NF2* gene in these neoplasms. Other hereditary forms of ependymoma are uncommon. Two patients with Turcot syndrome and ependymomas have been reported {2261} and parental colon cancer is associated with a risk of ependymomas arising in offspring with a standardized incidence ratio of 3.70 {808}. A series of 10 brain tumour families exhibiting ependymomas has been reviewed {474}. Ependymomas have also been described, albeit uncommonly, in neurofibromatosis type 1 (NF1) {1890, 2303}. Very rarely, loss of a 22q11 locus has been found in patient constitutional DNA, raising the possibility of germline susceptibility {52}.

Genetics

Cytogenetic changes have been found in a significant fraction of ependymomas, with a 30% incidence of aberrations involving chromosome 22 as the most frequent change {761}. Monosomy 22 as well as deletions or translocations involving 22q appear to prevail and are more frequently identified in spinal cord tumours than in intracranial ones. Also commonly found are losses of 6q and 9q. Less frequently are losses of 3p14, 10q23 and 11q {877}. Gains of chromosome 7 are noted {1987} but *EGFR* is not amplified. Monosomy 13 was reported in eight cases, half of which occurred in paediatric patients {2162}.

Supratentorial tumours preferentially show loss of chromosome 9 {292, 723, 996, 2497}. Clear cell ependymomas, though mimicking oligodendroglial tumours focally, do not have 1p or 19q deletions but instead exhibit gains of chromosome 1q, and loss of chromosome

9, 3, and 22q {1875}. Childhood tumours tend to show balanced karyotypes, but gains of 1q correlate with anaplastic features in childhood posterior fossa ependymomas. Tumours exhibiting loss of chromosome 13 or 14q/14 show a strong association with spinal cord origin {292}.

At the molecular genetic level, ependymomas exhibit changes distinctive from most other gliomas. The *NF2* gene is clearly involved in ependymoma tumorigenesis, although initial studies yielded conflicting results, largely reflecting the increased incidence of *NF2* mutations in spinal ependymomas. For instance, a study of spinal cord tumours showed mutations of the *NF2* gene {170}, whereas others were unable to identify such mutations in a significant fraction of ependymomas from all locations {1951, 2342}. A subsequent analysis of 62 ependymal tumours revealed 6 cases with mutant *NF2*, all of which were localized in the spinal cord {504}. These data strongly indicate that ependymomas occur as genetically distinct subtypes, a finding that may also extend to clear cell ependymomas {1875}. The rhabdoid tumour suppressor gene *hSNF5/INI1* at 22q11 is not implicated in ependymoma tumorigenesis {1183}.

Disruptions of the *TP53* gene pathway are rare in paediatric ependymomas

{653,1621}, although inactivation of *CDKN2A* gene (deletions or promoter methylation) has been found in intracranial ependymomas {1453, 1942, 2229}. The promoters of the *RASSF1A* (3p21.3) and *HIC-1* (17p13.3) genes have been shown to be methylated in a large percentage of ependymomas, suggesting that down-regulation of these genes may play a role in ependymoma pathogenesis {760, 1468, 2355}.

Amplification of *EGFR* was found in one of 68 ependymomas, although most showed EGFR overexpression on mRNA and protein levels {1453}. Adult ependymomas commonly exhibit *MDM2* amplification and/or overexpression {2186}. A RNA expression profile of 39 ependymomas revealed *CLU*, *IGF2*, *RAF1*, *MMP12*, *PSAP* and *MSX1* to be highly expressed in these tumours. Gene expression levels could be correlated with chromosomal aberrations described including increased expression of *PRELP*, *EPHX1*, *FY* and *HSPA6*, located on chromosome 1q, and decreased expression of *COX7A2*, *COL10A1* and *TCP1* from chromosome 6q; *CNTFR*, *RAGA*, *TXN*, *AMBP* and *HSPA5* from chromosome 9; *TUBA2*, *PRDX2* and *LCP1* from chromosome 13; and *RANBP1*, *MCM5*, *EP300*, *G22P1*, *BZRP* and *MAPK12* from chromosomal arm 22q {1173}. Gene expression patterns also differ between

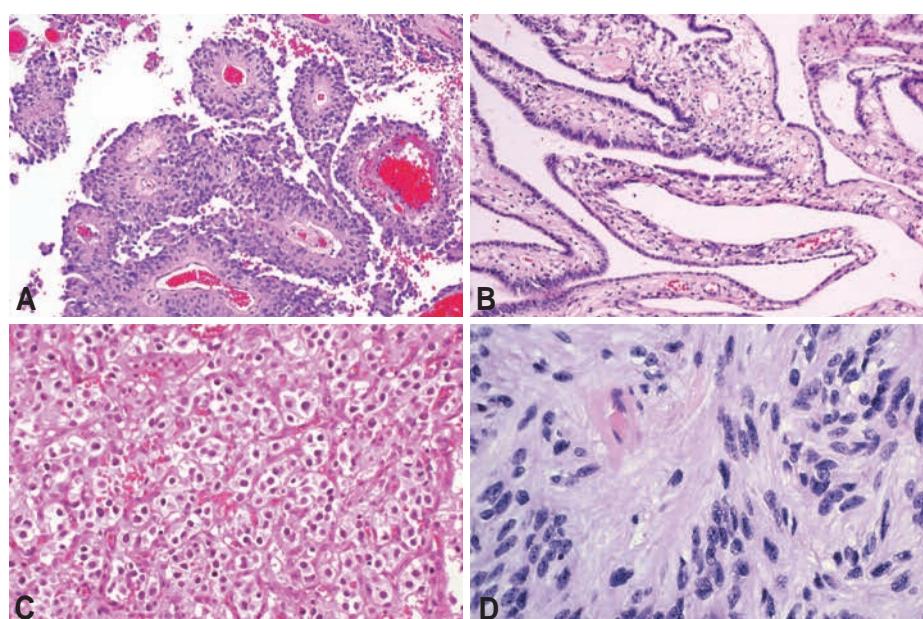


Fig. 3.12 A Papillary ependymoma with dis cohesive growth, pseudopapillae, and perivascular pseudorosettes. B Papillary ependymoma. Finger like projections are lined by single or multiple layers of cuboidal tumour cells with smooth contiguous surfaces. C Clear cell ependymoma. D Tanycytic differentiation.

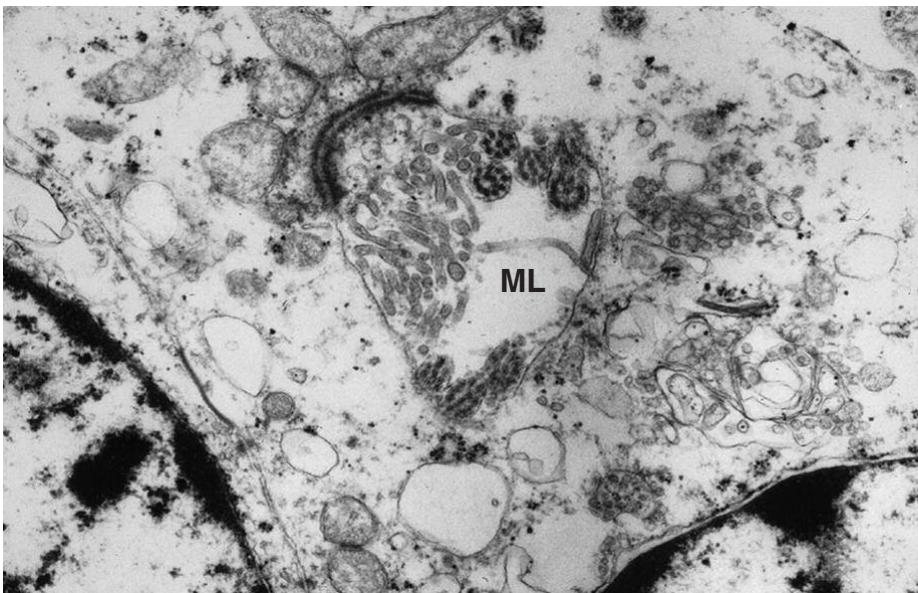


Fig. 3.13 Ultrastructural features of ependymal differentiation: intercellular microlumen (ML) containing microvilli and cilia, bordered by an elongate intercellular junction.

ependymomas from different sites of origin. Supratentorial tumours express high levels of various members of the EPHB, NOTCH, CYCLIN and CDK families, whereas spinal ependymomas show high-expression levels for multiple HOX family members {1173, 2229}.

Prognostic and predictive factors

The identification of parameters with prognostic value in ependymomas remains an important but controversial issue {2027}. The significance of histopathological properties has been confounded in many studies by the

variable inclusion of spinal cord, brain stem and intraparenchymal tumours. The following factors have to be considered in order of importance:

Age and extent of resection. Children tend to fare worse than adults. To some extent, this difference may reflect the more common posterior fossa location in paediatric patients versus spinal location in adults. In addition, tumours with frank histopathological anaplasia may occur at a higher incidence in this age group. A multi-institutional retrospective analysis of 83 paediatric ependymoma patients revealed age below 3 years, anaplastic

histopathological features and incomplete tumour resection as indicators of a poor outcome {865}. The Children's Cancer Group reported a 5-year progression-free survival of 50% in children with intracranial ependymomas {1899}. Children affected during the first two years of life carry a particularly dismal prognosis {1222, 1746}. In one adult series, survival at 5 and 10 years was 57% and 45%, respectively. Complete or near complete resection has emerged as an independent prognostic factor {981, 1768}.

Location. Tumour site is usually identified as the most important prognostic factor. Supratentorial ependymomas are associated with better survival rates compared to posterior fossa neoplasms {534}. Spinal ependymomas show a significantly better outcome compared to cerebral lesions although late recurrences (>5 years) are common. Cerebrospinal dissemination indicates a poor prognosis.

Histopathological grading. A major and not completely resolved problem relates to the definition of reliable histopathological indicators of anaplasia. Of the features usually associated with anaplastic change in gliomas, only mitotic index, proliferation indices and foci of hypercellular, less differentiated tumour cells, appear to correlate with poor outcome in ependymomas {1171, 1236, 2027}. Many other histological parameters have been tested in various studies, with contradictory results {840, 1837}.

Anaplastic ependymoma

R.E. McLendon
O.D. Wiestler
J.M. Kros
A. Korshunov
H.-K. Ng

Definition

A malignant glioma of ependymal differentiation with accelerated growth and unfavourable clinical outcome, particularly in children; histologically characterized by high mitotic activity, often accompanied by microvascular proliferation and pseudopalisading necrosis.

ICD-O code 9392/3

Grading

Anaplastic ependymomas correspond histologically to WHO grade III.

Incidence

Incidence data vary considerably, due to the uncertainty regarding histological criteria of malignancy. Anaplastic changes are far more frequent in childhood intracranial ependymomas, particularly posterior fossa examples, than in those of the spinal cord [305].

Clinical features

Signs and symptoms of anaplastic ependymomas are similar to those of ependymoma WHO grade II, but they usually develop more rapidly and may cause increased intracranial pressure at an early stage of the disease. MR images typically show contrast enhancement.

Histopathology

Anaplastic ependymomas show increased cellularity and brisk mitotic activity, often associated with microvascular proliferation and pseudopalisading necrosis. Perivascular pseudorosettes are a histological hallmark. Anaplastic ependymomas tend to remain well demarcated, but are occasionally frankly invasive. They often appear highly cellular and poorly differentiated, with pseudorosettes of narrow radial width. Geographic tumour necrosis (a particularly common phenomenon in posterior fossa ependymomas) is not a diagnostic feature of malignancy in the absence of vascular proliferation, frequent mitotic activity, or a high proliferation index {1172, 1236, 1837}. Poorly differentiated

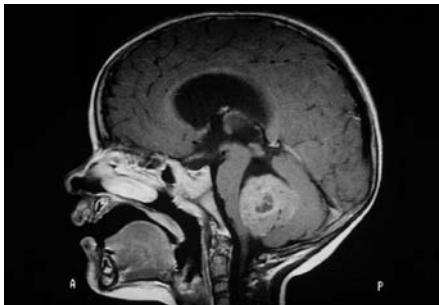


Fig. 3.14 Sagittal, gadolinium-enhanced, T1-weighted MRI of an anaplastic ependymoma of the fourth ventricle.

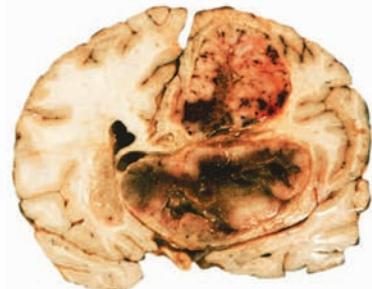


Fig. 3.15 Anaplastic ependymoma of the lateral ventricle in a four-year-old boy with extensive invasion of the right frontal lobe.

examples may be difficult to identify as ependymal in the absence of supporting ultrastructural evidence. By definition, embryonal components and ependymoblastic rosettes are not present (see Chapter 8).

Immunohistochemistry

The phenotypic profiles of anaplastic ependymomas resemble those of

ependymoma, grade II, but GFAP expression may be reduced.

Genetics

Genetic alterations specifically encountered in anaplastic ependymomas are largely unknown. Although some lesions may develop through malignant progression from WHO grade II ependymomas, no underlying sequence of genetic

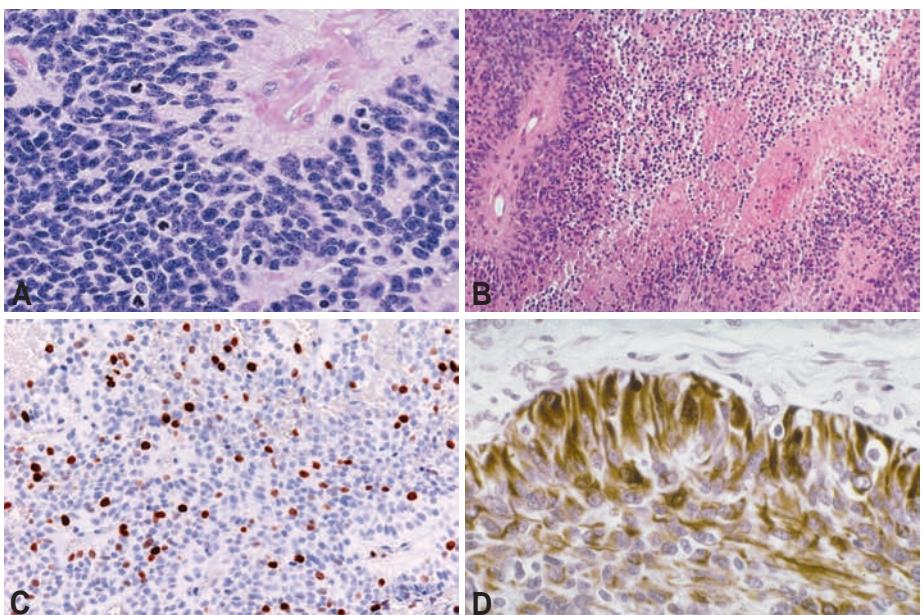


Fig. 3.16 Histological features of anaplastic ependymoma. A Poorly differentiated tumour cells with brisk mitotic activity. B Large foci of necrosis. C High MIB-1 labelling index. D Strong GFAP expression in an anaplastic ependymoma invading adjacent brain structures.

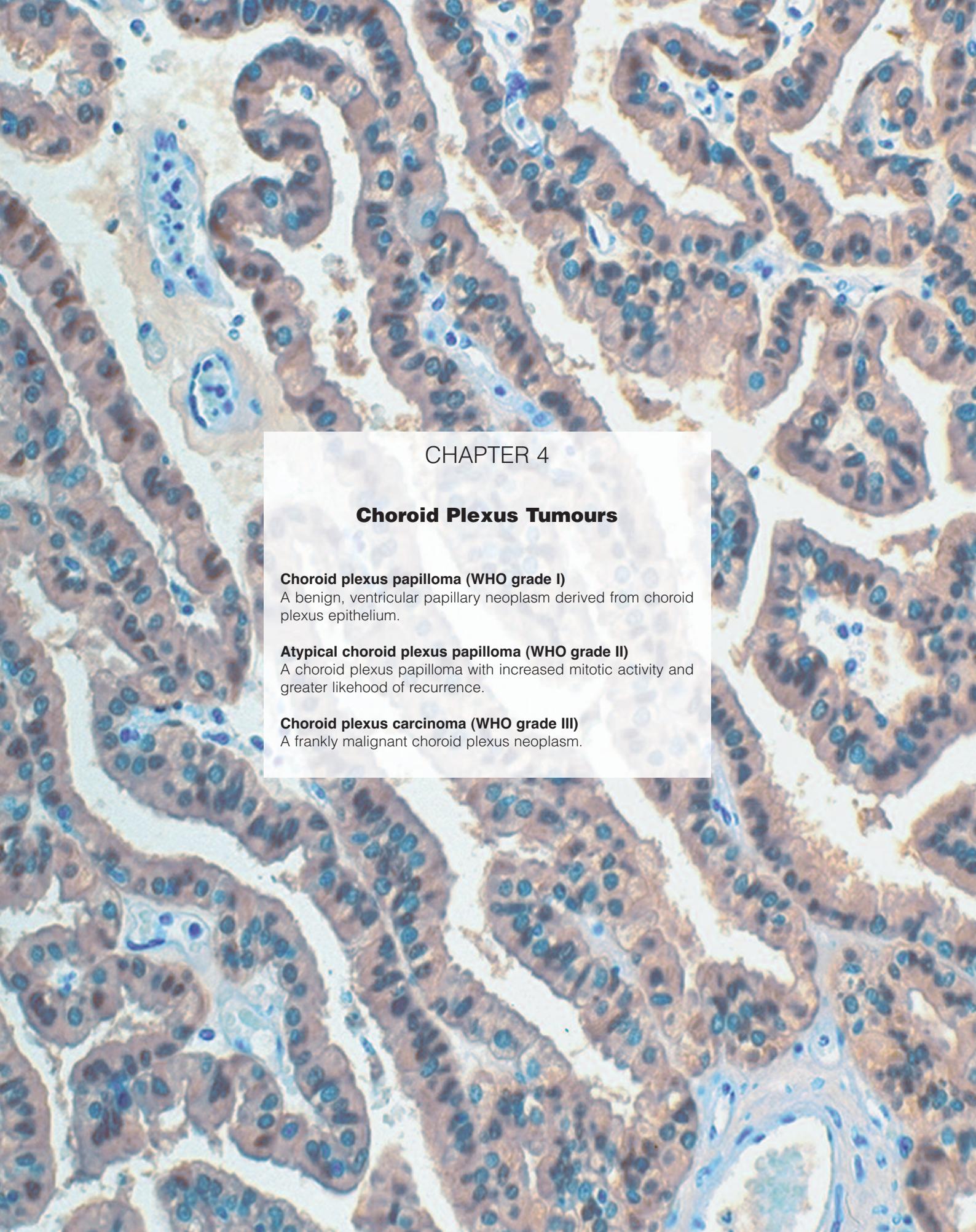
events has been identified. There is evidence for a putative tumour suppressor gene on chromosome 22 in familial anaplastic ependymomas [1595]. An analysis of 23 anaplastic ependymomas revealed loss of 10q in 4 cases [504]. A comparative genomic hybridization (CGH) study of 35 ependymomas showed that gain of 1q and loss of 9 and 13 were associated with WHO grade III tumours [835]. One array CGH study also identified two regions of gain on 1q (1q21.3-23.1 and 1q31.1-31.3); DUSP12 at 1q23 was proposed to be a “driver oncogene” for anaplastic ependymomas [1453]. An RNA expression analysis of ependymomas was able to distinguish supratentorial WHO grade II and III tumours with 100% accuracy. However, infratentorial examples were more difficult to classify,

with 5 of 18 tumour samples misclassified. The similar gene expression patterns of WHO grade II and III infratentorial malignancies may suggest that grade III tumours develop through progression [1173].

Prognostic and predictive factors

An inconstant relationship between histology and outcome has emerged from the clinical studies [535, 577, 1458, 1930, 2431]. In two series with more than 200 cases, no correlation was observed between patient survival and classical histopathological signs of malignancy. However, a relationship with survival was evident when high cell density plus brisk mitotic activity [2022] or high cell density, vascular proliferation and/or cytologic atypia, were considered as independent

variables [1171]. Age below 3 years, anaplastic histopathological features, incomplete tumour resection and evidence for CSF metastases have been proposed as indicators of an adverse outcome in children [865, 960]. Among spinal intramedullary tumours, extent of resection is most predictive of progression-free survival, with 12 of 21 treatment failures occurring after 5 years of follow-up in one study [705]. Paradoxically, a high frequency of imbalanced chromosomal regions, as revealed by CGH in ependymomas, does not indicate a high WHO grade [2004]. Several studies have suggested an association between p53 immunoreactivity and adverse outcome for ependymomas [1172, 2185, 2323].



CHAPTER 4

Choroid Plexus Tumours

Choroid plexus papilloma (WHO grade I)

A benign, ventricular papillary neoplasm derived from choroid plexus epithelium.

Atypical choroid plexus papilloma (WHO grade II)

A choroid plexus papilloma with increased mitotic activity and greater likelihood of recurrence.

Choroid plexus carcinoma (WHO grade III)

A frankly malignant choroid plexus neoplasm.

Choroid plexus tumours

W. Paulus
S. Brandner

Definition

Intraventricular, papillary neoplasms derived from choroid plexus epithelium.

ICD-O codes

Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3

Grading

Choroid plexus papilloma (CPP) corresponds to WHO grade I, atypical CPP to grade II, and choroid plexus carcinoma (CPC) to grade III.

Incidence

Although choroid plexus tumours account for 0.3–0.6% of all brain tumours, they represent 2–4% of those that occur in children under 15 years, and 10–20% of those manifesting in the first year of life. CPP outnumber CPC by a ratio of at least 5:1. Around 80% of CPC arise in children, in whom they constitute 20–40% of choroid plexus tumours. The average annual incidence is approximately 0.3 per 1 000 000 population per year {969, 1877, 2430}.



Fig. 4.01 MRI of a choroid plexus carcinoma in the lateral ventricle of a 5 year-old child with a *TP53* germline mutation.

Age and sex distribution

Around 80% of lateral ventricular tumours present in patients younger than 20 years, whereas fourth ventricle tumours are evenly distributed in all age groups. A meta-analysis found that median age was 1.5 years for the lateral and third ventricle, 22.5 years for the fourth ventricle, and 35.5 years for the cerebellopontine angle {2430}. Congenital tumours and fetal tumours have been observed in utero using ultrasound techniques. The overall male: female ratio is 1.2:1; this ratio is 1:1 for lateral ventricle tumours and 3:2 for fourth ventricle tumours.

Etiology

DNA sequences of the simian virus 40 (SV40) have been found in about 35% of brain tumours, including about 50% of choroid plexus tumours {138}. Since (i) surrounding brain tissue only rarely contains SV40 sequences, (ii) SV40 induces brain tumours in hamsters and in transgenic mice, (iii) SV40 large T antigen inactivates several tumour suppressor proteins including p53 and Rb, and (iv) SV40 large T antigen is capable of transforming human cells *in vitro*, it has been hypothesized that SV40 plays a role in the etiology of brain tumours, including choroid plexus tumours {138}. However, SV40 sequences in CPP were found only in populations that received SV40-contaminated polio vaccine between 1955 and 1963 (e.g. USA and Switzerland), but not in populations that did not use SV40-contaminated vaccine (e.g. Finland) {1623}. Because the incidence of brain tumours is not different among these nations, the data can be interpreted as reflecting a bystander infection caused by an intratumoural microenvironment that favours viral replication in humans with latent SV40 infection, rather than reflecting a causal role of SV40 {1623}.

Localization

CPP and CPC are confined to areas where choroid plexus is normally found, i.e. the lateral (50%), third (5%) and fourth (40%) cerebral ventricles, with two

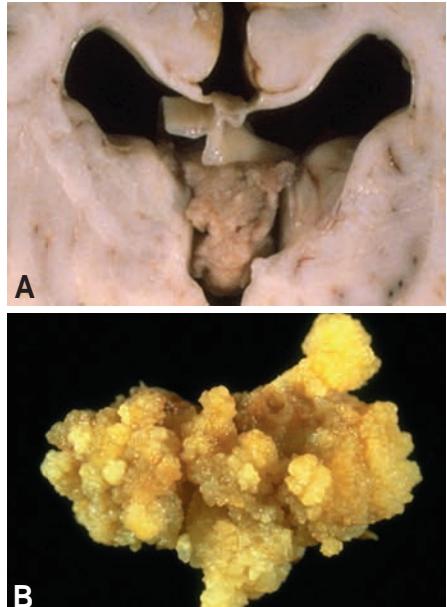


Fig. 4.02 A Choroid plexus papilloma arising in the posterior third ventricle producing partial obstruction with ventricle dilatation. B Villous architecture.

or three ventricles being involved in 5% of cases {969, 2163}. Primary manifestation in the cerebellopontine angle near the openings of the fourth ventricle is uncommon. Exceptional cases of ectopic locations, e.g. intraparenchymal, suprasellar or spinal epidural, are on record {1113, 1238, 1749}.

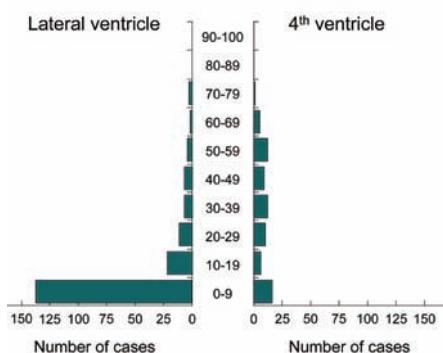


Fig. 4.03 Age vs. localization of choroid plexus tumours, based on a compilation of 264 published cases {2430}.

Clinical features

Symptoms and signs

Choroid plexus tumours tend to block CSF pathways. Accordingly, patients present with signs of hydrocephalus (in infants, increased circumference of the head) and raised intracranial pressure.

Neuroimaging

CT and MRI of CPP usually shows iso- or hyperdense, T1-isointense, T2-hyperintense, irregularly contrast-enhancing, well-delineated masses within the ventricles, but irregular tumour margins and disseminated disease may occur [731]. MRI features typical of CPC include large intraventricular lesions with irregular enhancing margins, heterogeneous signal on long TR/long TE images and short-TR images, edema in adjacent brain, hydrocephalus, and presence of disseminated tumour [1467].

Macroscopy

CPP are circumscribed cauliflower-like masses that may adhere to the ventricular wall, but are usually well-delineated from brain tissue. Cysts and haemorrhages may occur. CPC are invasive tumours that may appear solid, haemorrhagic and necrotic.

Histopathology, immunohistochemistry and electron microscopy

Choroid plexus papilloma

Delicate fibrovascular connective tissue fronds are covered by a single layer of uniform cuboidal to columnar epithelial cells with round or oval, basally situated monomorphic nuclei. Mitotic activity is extremely low. Brain invasion, high cellularity, necrosis, nuclear pleomorphism and focal blurring of the papillary pattern are unusual, but may occur. CPP closely resembles non-neoplastic choroid plexus,



Fig. 4.04 Large choroid plexus carcinoma in the atrium of the right lateral ventricle with extensive invasion of the adjacent brain.

but cells tend to be more crowded, elongated or stratified instead of the normal cobblestone-like surface. Rarely, CPP may acquire unusual histological features, including oncocytic change, mucinous degeneration, melanization and tubular glandular architecture of tumour cells, as well as degeneration of connective tissue, such as xanthomatous change, angioma-like increase of blood vessels, and bone, cartilage or adipose tissue formation [64,236,1990].

Cytokeratins, vimentin and podoplanin are expressed by virtually all CPP. The most common CK7/CK20 combination is CK7-positive and CK20-negative (74%), but the other three combinations are also possible [743]. Prominent staining for epithelial membrane antigen is typically not found. S-100 protein is present in 55–90% of cases. GFAP is absent from normal choroid plexus, but is present focally in 25–55% of CPP. Approximately 70% of CPP are positive for transthyretin (pre-albumin) [782]. Staining for synaptophysin has been reported to be strongly positive in normal and neoplastic choroid plexus epithelial cells [1083], but this finding has not been confirmed by others [285,1696].

Electron microscopy shows interdigitating cell membranes, tight junctions, microvilli, occasional apical cilia and a basement membrane at the abluminal pole.

Atypical choroid plexus papilloma

Atypical CPP is defined as CPP with increased mitotic activity. One study indicates that a mitotic index of two or more mitoses per 10 randomly selected HPF (one HPF corresponding to 0.23 mm²) can be used to establish this diagnosis [983]. The same study showed that up to two of the following four features may also be present: increased cellularity, nuclear pleomorphism, blurring of the papillary pattern (solid growth) and areas of necrosis, but these features are not required for making a diagnosis of atypical CPP. Using these criteria, a series of 124 CPP had 19 cases of atypical CPP (15%).

Choroid plexus carcinoma

This tumour shows frank signs of malignancy. According to one study, frank signs of malignancy included at least four of the following five features: frequent mitoses (usually greater than 5 per 10 HPF), increased cellular density,

nuclear pleomorphism, blurring of the papillary pattern with poorly structured sheets of tumour cells, and necrotic areas. If brain tissue is available, diffuse brain invasion is common.

Immunohistochemically, CPC express cytokeratins, while positivity for S-100 protein and transthyretin is less frequent than in CPP. About 20% of CPC are GFAP-positive. Epithelial membrane antigen is usually not expressed [983].

Differential diagnosis

Various immunostains have been recommended for the distinction between choroid plexus tumours and metastatic carcinomas. A microarray-based expression profiling study revealed inward rectifier potassium channel Kir7.1 and stanniocalcin-1 as markers of normal and neoplastic choroid plexus epithelial cells: immunostaining for Kir7.1 was seen in 17 of 23 (74%) choroid plexus tumours but in none of 100 other tumours, while an

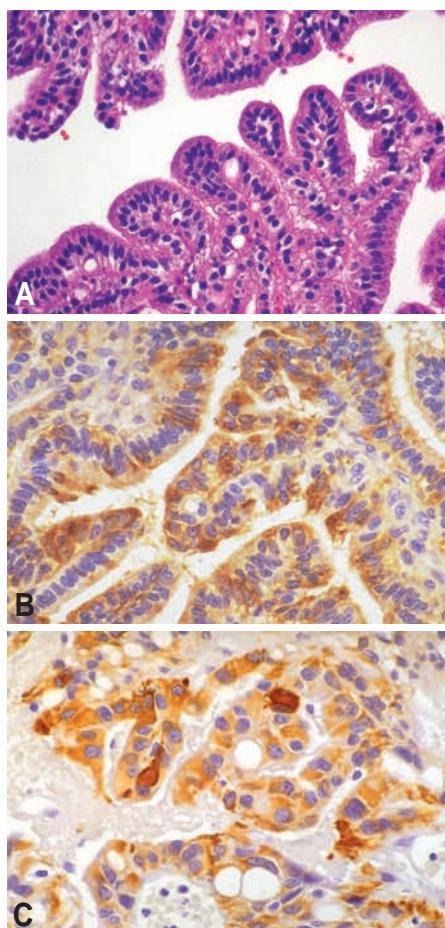


Fig. 4.05 Histological features of choroid plexus papilloma (A). Immunoreactivity for transthyretin (TTR) (B) and GFAP (C) in choroid plexus papillomas.

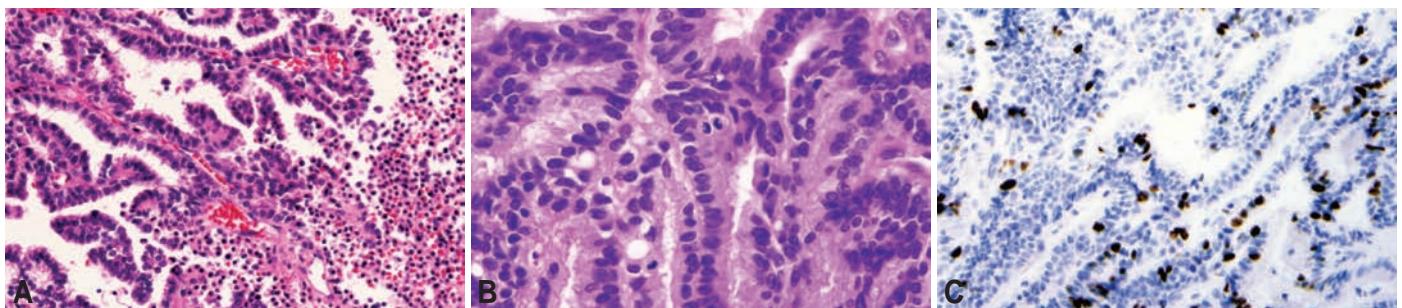


Fig. 4.06 Atypical choroid plexus papilloma. A A well-differentiated choroid plexus papilloma with an area of necrosis (lower right). B Prominent mitotic activity. C High Ki-67 (MIB-1) labelling.

antibody against stanniocalcin-1 stained 19 of 23 (83%) choroid plexus tumours but only 2% of other primary brain tumours and cerebral metastases [782]. Another study described membranous staining for the excitatory amino acid transporter-1 (EAAT1) in 23 of 35 (66%) choroid plexus tumours, but in none of 77 metastatic carcinomas [143]. Antibodies against transthyretin label most normal and neoplastic choroid plexus epithelia. However, up to 30% of CPP are negative, and other brain tumours as well as metastatic carcinomas may be positive [782]. The antibodies HEA125 and BerEP4 may be useful, because they label more than 95% of cerebral metastatic carcinomas, but only 10% of CPP or CPC [715]. Expression of carcinoembryonic antigen (CEA) suggests metastatic carcinoma [1698], although occasional CPC are also positive [1056]. Due to overlapping clinical, histologic, ultrastructural or immunophenotypic features, differentiation between CPC and atypical teratoid/rhabdoid tumour (AT/RT) may be difficult. An immunohistochemical study suggested that staining

for INI1 protein is retained in the majority of CPC and lost in AT/RT [1016]. Villous hypertrophy is a diffuse enlargement of the choroid plexus in both lateral ventricles with normal histological appearance, often associated with hypersecretory hydrocephalus. Ki-67/MIB-1 and neuroimaging may be useful in differentiating these lesions from monomorphic bilateral CPP [408, 533].

Seeding and metastasis

Even benign CPP may seed cells into the CSF; drop metastases in the surroundings of the cauda equina may result. In contrast, CPC commonly produce frank metastases along CSF pathways, while exceptional cases of CPP with CSF-mediated metastases are also on record [1426, 2476]. Shunt-related metastases in the abdomen [482] and extracranial metastases in lung and tibia [793] are extremely rare.

Proliferation

Mean Ki-67/MIB-1 labelling indices for choroid plexus tumours have been reported as 1.9% (range, 0.2–6%) for

CPP, 13.8% (range, 7.3–60%) for CPC, and less than 0.1% for the normal choroid plexus [2296]. Another study described mean Ki-67/MIB-1 indices of 4.5% (range, 0.2–17.4) for CPP, 18.5% (range, 4.1–29.7%) for CPC, and 0% for the normal choroid plexus [285].

Genetic susceptibility

CPC and, more rarely, CPP have been reported in about 20 families with germline *TP53* mutations or in families with unknown *TP53* status but with clustering of cancer suggestive of Li-Fraumeni syndrome [1210]. CPC has also been described in the rhabdoid predisposition syndrome, a familial cancer syndrome caused by germline mutations in the *INI1* (*SMARCB1/SNF5*) gene [2057], but such cases may be difficult to distinguish from atypical teratoid/rhabdoid tumours. CPP represents a major diagnostic feature of Aicardi syndrome, a genetic but sporadic condition presumably linked to the X chromosome and defined by the triad of total or partial agenesis of the corpus callosum, chorioretinal lacunae

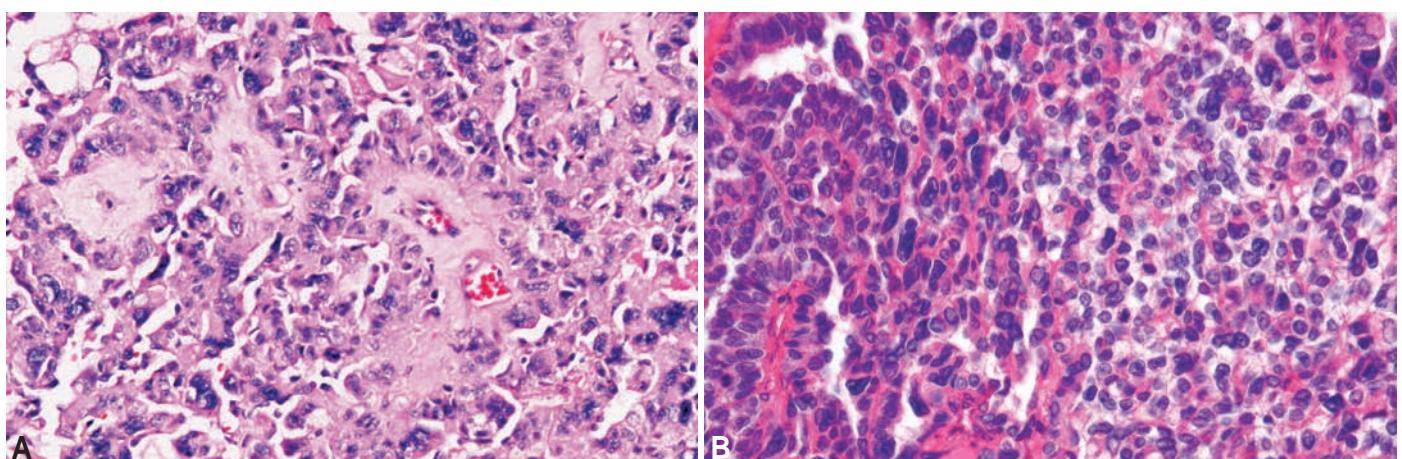


Fig. 4.07 A and B Choroid plexus carcinoma showing mitoses, increased cellular density, nuclear pleomorphism and blurring of the papillary pattern.

and infantile spasms [22]. In the setting of an X;17(q12;p13) translocation, hypomelanosis of Ito has been associated with the development of CPP in a few cases [2478]. Duplication of the short arm of chromosome 9, a rare constitutional abnormality, was associated with pathologically confirmed hyperplasia of the choroid plexus in one of two cases, and a CPP in another [1605].

Genetics

Classical cytogenetics and FISH of CPP typically shows hyperdiploidy with gains particularly on chromosomes 7, 9, 12, 15, 17 and 18 [483]. CPC may exhibit loss of heterozygosity on chromosomes 1p, 1q, 3p, 5q, 9q, 10q, 13q, 18q and 22q [2480]. In a CGH study of 49 tumours, CPP frequently showed +7q (65%), +5q (62%), +7p (59%), +5p (56%), +9p (50%) and -10q (56%); while CPC mainly showed +12p, +12q, +20p (60%), +1, +4q, +20q (53%) and -22q (73%) [1885]. These data suggest that CPP and CPC may develop via different genetic pathways.

Some CPP and almost all CPC show immunohistochemical positivity for p53 [285,2451], while *TP53* mutations are

virtually absent in CPP and rare (< 10% of cases) in sporadic CPC [1621,2480]. Mutations in the *INI1* gene have been described in 6 of 18 apparently sporadic CPC [2056,2377, 2480], but in none of 26 CPP [1533,2056]. However, given the histologic overlap between CPC and atypical teratoid/rhabdoid tumour, the frequency of *INI1* mutations in histologically unequivocal and immunohistochemically scrutinized CPC remains to be determined.

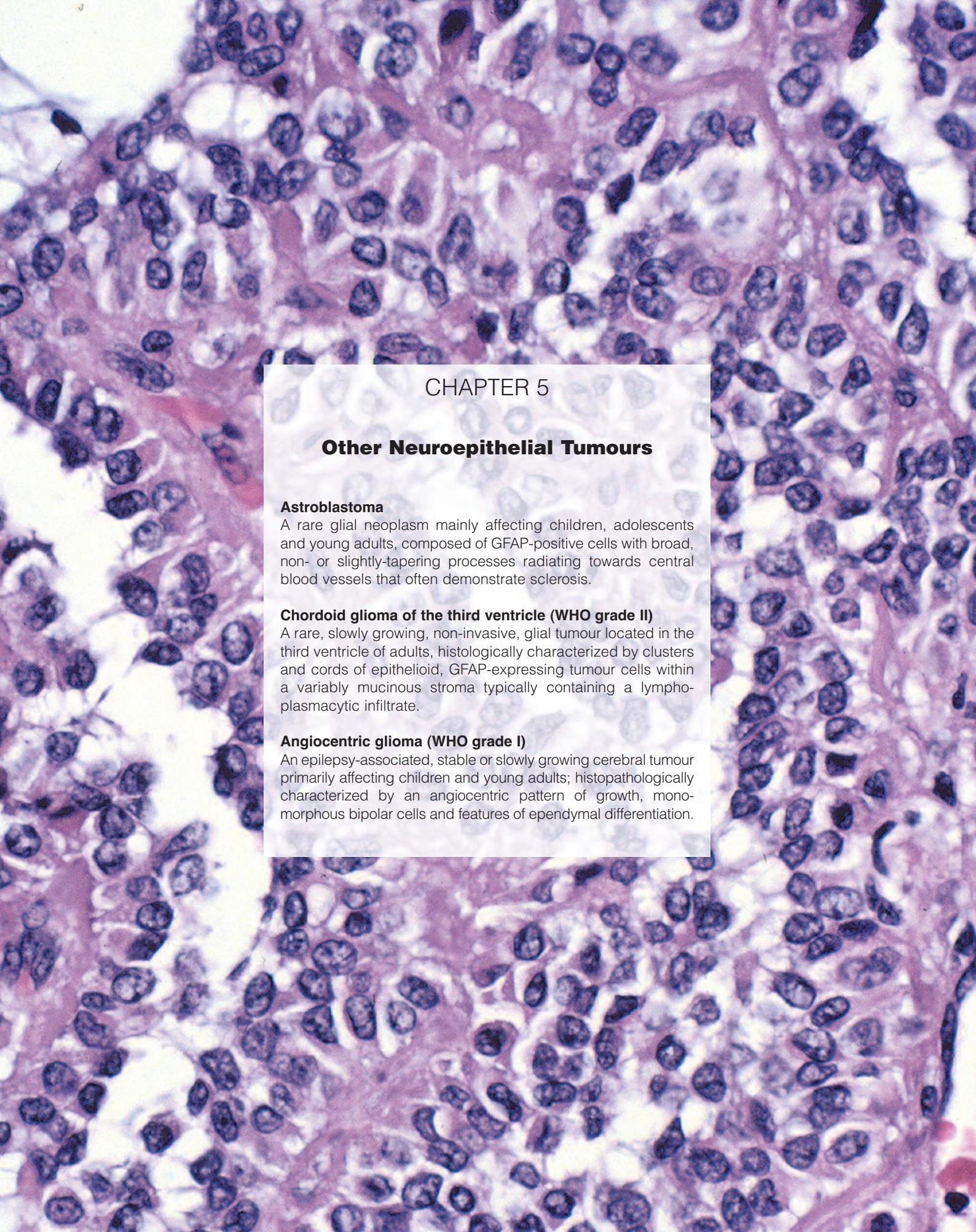
Notch3 signalling may play a role in the pathogenesis of choroid plexus tumours, because introduction of constitutively active Notch3 into periventricular cells of embryonic day 9.5 mice caused the formation of CPP; furthermore, in a small series of 7 human CPP there was nuclear translocation or overexpression of at least one Notch receptor (Notch1, Notch2, Notch3), suggesting Notch pathway activity [412].

Prognostic and predictive factors

CPP can be cured by surgery, with a 5-year survival rate of up to 100%. In a series of 41 cases of CPP, five-year local control, distant brain control and overall survival were 84%, 92%, and 97%,

respectively; local control at 5 years is better after gross total resection than after subtotal resection (100% vs. 68%) [1189]. A meta-analysis of 566 choroid plexus tumours revealed that one-, five-, and 10-year projected survival rates were 90%, 81% and 77% in CPP compared with only 71%, 41% and 35% in CPC [2430]. Malignant progression of CPP is rare, but has been described [344,1698].

In a clinicopathological study of 52 patients, poor prognosis (recurrence and/or fatal outcome) correlated with the following pathological features: mitoses, necrosis, brain invasion, lack of immunoreactivity for transthyretin, and decreased expression of S-100 protein [1698]. Another study did not find evidence for prognostic relevance of brain invasion in otherwise benign CPP [1302]. In a series on 124 CPP, multivariate analysis revealed that increased mitotic activity (2 or more mitoses per 10 HPF), corresponding to atypical CPP, was the sole histological feature independently associated with recurrence, resulting in a 4.9-fold higher probability of recurrence after 5 years of follow-up [983].



CHAPTER 5

Other Neuroepithelial Tumours

Astroblastoma

A rare glial neoplasm mainly affecting children, adolescents and young adults, composed of GFAP-positive cells with broad, non- or slightly-tapering processes radiating towards central blood vessels that often demonstrate sclerosis.

Chordoid glioma of the third ventricle (WHO grade II)

A rare, slowly growing, non-invasive, glial tumour located in the third ventricle of adults, histologically characterized by clusters and cords of epithelioid, GFAP-expressing tumour cells within a variably mucinous stroma typically containing a lymphoplasmacytic infiltrate.

Angiocentric glioma (WHO grade I)

An epilepsy-associated, stable or slowly growing cerebral tumour primarily affecting children and young adults; histopathologically characterized by an angiocentric pattern of growth, monomorphous bipolar cells and features of ependymal differentiation.

Astroblastoma

K.D. Aldape
M.K. Rosenblum

Definition

A rare glial neoplasm mainly affecting children, adolescents and young adults, composed of GFAP-positive cells with broad, non- or slightly-tapering processes radiating towards central blood vessels that often demonstrate sclerosis.

ICD-O code 9430/3

Grading

The biological behaviour of astroblastoma is variable. In the absence of sufficient clinico-pathologic data, it is considered premature to establish a WHO grade at this time.

Historical annotation

Current conceptions of the astroblastoma as a circumscribed, vasocentric glial neoplasm with a predilection for relatively young subjects derive principally from the 1989 study of Bonnin and Rubinstein {195}, the term being originally applied by Bailey and Bucy {84} sixty years earlier to a disparate collection of, for the most part, infiltrating and aggressive gliomas mainly affecting the middle aged. The concept of the astroblastoma as a unified, distinct entity remains controversial.

Incidence

Since these are unusual tumours and uniform criteria have not been applied diagnostically, definitive epidemiological data are not available. However, astroblastomas appear to be most frequent in



Fig. 5.01 MRI of a well-circumscribed cystic astroblastoma with edema and mass effects. The mural tumour component exhibits contrast enhancement.

children, adolescents and young adults {1959}.

Age and sex distribution

Combining three published series totalling 40 cases {195, 726, 2238} the median age was 11 years (range 1–58). Among these, there were 10 males and 30 females, suggesting a female predominance for this entity.

Localization

Astroblastomas typically involve, but are not restricted to, the cerebral hemispheres {895, 1959}.

Clinical features

They are visualized in CT and MR studies as well-demarcated, non-calcified, nodular or lobulated masses with frequent cystic change and conspicuous contrast enhancement {2048}.

Macroscopy

Tumour tissue is grey-pink or tan, its consistency depending on the extent of associated collagen deposition. Foci of necrosis or haemorrhage do not necessarily indicate anaplasia.

Histopathology

Tumours under consideration for a diagnosis of astroblastoma should be circumscribed at the histologic level and cannot contain elements of diffusely infiltrating astrocytoma, gemistocytic astrocytoma or conventional ependymoma. A well-defined or “pushing” margin is characteristic, although a narrow rim of neuroparenchymal permeation can be seen. Areas of perivascular structuring can be solid or loosely textured, the latter imparting regional pseudopapillary appearances. Unipolar cytoplasmic processes anchor neoplastic cells to stromal blood vessels in formations of radial (“cartwheel”), papillary or ribboned profiles. These columnar or subtly tapered processes are shorter and stouter than those of ependymal pseudorosettes and do not collect as a conspicuous fibrillary matrix. Polygonal

or spindled tumour cells surround gliovascular structures, either densely or as a rarefied population. Nuclei are rounded, oval or irregularly indented and can exhibit coarse chromatin clumping. A case manifesting signet-ring or adipocyte-like features has been reported {2171}. Progressive hyalinization of blood vessel walls is regularly seen and may result in large areas of fibrous overgrowth as well as regional tumour infarction.

Astroblastomas can be divided into well-differentiated and anaplastic (high-grade)

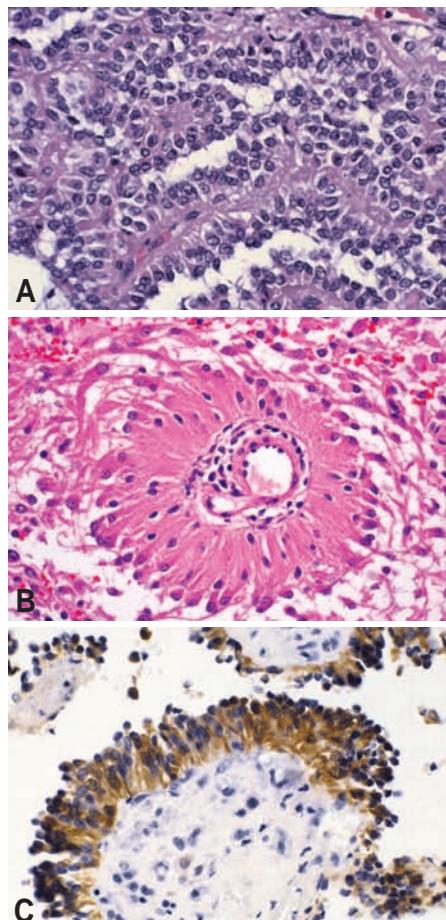


Fig. 5.02 Histological features of astroblastoma. A and B Anchoring of tumour cells to blood vessels by short, stout cytoplasmic processes. C Tumour cell processes radiating towards fibrovascular cores show strong immunoreactivity to GFAP.

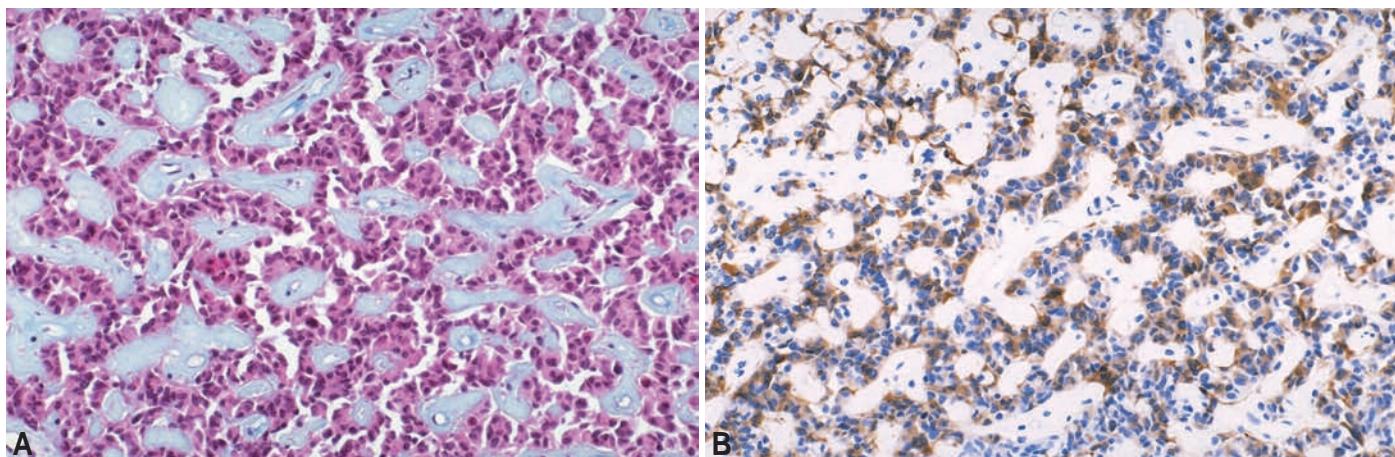


Fig. 5.03 A Astroblastoma with extensive vascular sclerosis (trichrome stain) and B variable GFAP immunoreactivity.

variants. The latter evidence conspicuous mitotic activity, cytologic atypia and architectural disorganization, i.e. a breakdown of the orderly perivascular structuring manifest throughout well-differentiated counterparts. Anaplastic (high-grade) examples may also exhibit complex microvascular hyperplasia and pseudopalisading necrosis. Necrosis without pseudopalisading may be encountered in either setting.

Immunohistochemistry

Cytoplasmic immunoreactivity for vimentin, S-100 and GFAP is characteristic, although the extent of labelling (particularly for GFAP) varies considerably [270, 1757, 1959]. Cell membranes may label for EMA [270, 977], typically as a focal phenomenon. Limited immunoexpression of low molecular weight cytokeratins has been described [977], other studies finding no CAM5.2 [270] or AE1/3 labelling [977]. Reactivity for NSE is inconstant [270, 895] and isolated cases have proven negative for synaptophysin [977].

Electron microscopy

Regularly observed are intermediate filament-laden cell processes that form parallel or radial arrays terminating on perivascular basement membranes [895]. Compelling evidence of neuronal differentiation has not been forwarded, nor have ependymal features been encoun-

tered in most studied cases. Two reports examining ultrastructural features suggest an origin from tanycytes [1215, 1225]. These features included cell body polarization with investing basement membranes, apical cytoplasmic blebs capped by microvilli with "purse-string" pedicular constrictions, and lamellar cytoplasmic interdigitations ("pleatings"). Zonula adherens-type junctions framing occasional microrosettes and rare cilia were also identified in these cases.

Proliferation

Reported Ki-67 labelling indices vary between 1% and 18% [215, 977]. A relationship between proliferation index and outcome has not been established in the literature, although elevated indices tend to be associated with high-grade histology.

Histogenesis

The histogenesis of astroblastomas is controversial, and the entity is not universally accepted. Bailey and Cushing considered these tumours to arise from embryonic cells programmed to become astrocytes. The presence of intermediate filaments on ultrastructural examination, lack of evidence of neuronal or, in most cases, ependymal differentiation, together with positive staining for GFAP and S-100 protein, suggest the possibility that the tumour is derived from a cell most similar to an astrocyte. The tanycyte, a cell with

features intermediate between astrocytes and ependymal cells, has been suggested as a cell of origin for astroblastoma on the basis of ultrastructural observations.

Genetics

DNA copy number aberrations identified by comparative genomic hybridization have been described for 7 cases [217] and the most common identified alterations in this small series (gains of chromosomes 19 and 20q) were not typical of either ependymoma or diffuse glial neoplasms. Conventional cytogenetic studies performed on two cases [215, 977] lead to the same overall conclusion. Although the number of cases studied to date is small, they are consistent with the concept that astroblastoma is distinct from conventional glial neoplasms.

Prognostic and predictive factors

Astroblastomas with low-grade histology have a better prognosis than those with high-grade features [195, 2238]. However, gross total resection of astroblastoma, even when high-grade, may result in a favourable outcome [195]. In general, however, anaplastic histology is associated with recurrence and progression [195, 2238]. In one study, only a single recurrence was noted (histologic features notwithstanding) in 14 informative cases treated by gross total resection at a mean follow-up of 24 months [215].

Chordoid glioma of the third ventricle

D.J. Brat
B.W. Scheithauer

Definition

A rare, slowly growing, non-invasive, glial tumour located in the third ventricle of adults, histologically characterized by clusters and cords of epithelioid, GFAP-expressing tumour cells within a variably mucinous stroma typically containing a lymphoplasmacytic infiltrate.

ICD-O code

9444/1

Grading

This neoplasm corresponds histologically to WHO grade II.

Synonyms and historical annotation

In 1995, Wanschitz *et al.* {2365} described a solid, third ventricular tumour occurring in a 24-year-old woman and having histologic and immunohistochemical features of a chordoid glioma. The authors concluded the tumour was a meningioma with 'peculiar expression of GFAP'. Subsequent immunohistochemical and ultrastructural studies of similar cases have not supported a meningotheelial derivation; rather, evidence indicates that they are glial in nature. Based on a series of eight third ventricular masses with identical histologic features, chordoid glioma was proposed as a distinct entity in 1998 {220}.

Incidence

These tumours are rare, but must enter into the limited differential diagnosis of a solid, contrast-enhancing third ventricular mass in an adult. Approximately 45 cases have been reported.

Age and sex distribution

Chordoid gliomas occur in adults, with the large majority presenting between 35 and 60 years (mean, 46 years) {220, 1690}. There is a 2:1 female predominance. Only one paediatric example, occurring in a 12-year-old male, has been reported {297}.

Localization

Chordoid gliomas occupy the anterior portion of the third ventricle, with larger

tumours filling the middle and posterior aspects {1775}. They generally arise in the midline and displace normal structures in all planes as they enlarge. Neuroimaging descriptions, including reports of small, localized tumours, suggest that chordoid gliomas arise in the region of the lamina terminalis in the ventral wall of the third ventricle {1284, 1690}. In at least some instances, radiologic studies have demonstrated an intraparenchymal hypothalamic component.

Clinical features

Symptoms and signs

Most patients present with symptoms of obstructive hydrocephalus, including headache, nausea, and ataxia. Other tumours cause endocrine hypofunction, particularly hypothyroidism, and/or visual disturbances due to inferior displacement of the optic chiasm. Psychiatric and memory abnormalities have also been noted, presumably due to compression of the medial temporal lobes.

Neuroimaging

MRI typically demonstrates a bulky, well-circumscribed 2–4 cm, third ventricular mass. Aside from the uncommon finding of cystic change, the tumours are uniformly contrast-enhancing and appear contiguous with hypothalamic or suprasellar structures.

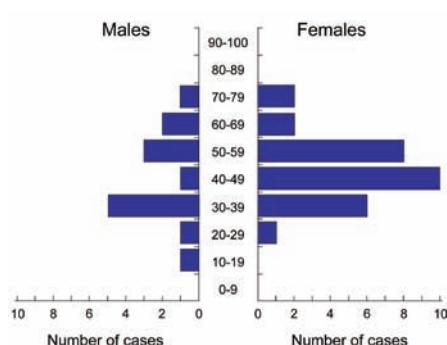


Fig. 5.04 Age and sex distribution of chordoid glioma of the third ventricle, based on 43 cases.

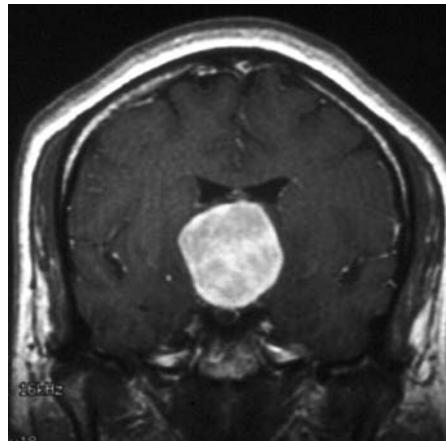


Fig. 5.05 MRI of a chordoid glioma of the third ventricle demonstrating a large contrast-enhancing, sharply delineated mass that fills the anterior third ventricle and compresses adjacent structures.

Histopathology

Chordoid gliomas are solid neoplasms composed of clusters and cords of epithelioid tumour cells within a variably mucinous stroma typically containing a lymphoplasmacytic infiltrate. Immunohistochemical and ultrastructural features indicate a glial derivation. The oval-to-polygonal epithelioid cells with abundant eosinophilic cytoplasm are embedded in a mucinous, often vacuolated stroma. In many instances, obvious but limited glial differentiation in the form of coarsely fibrillar processes can be seen {220}. Neoplastic nuclei are moderate in size, and relatively uniform. The majority of tumours lack mitoses; in the remainder, they are rare (<1 per 10 high-power fields). A stromal lymphoplasmacytic infiltrate, often with numerous Russell bodies, is a consistent finding. Chondroid differentiation has been described in one example {297}. Conforming to radiographic impressions, tumours are architecturally solid, and show little tendency to microscopic infiltration of surrounding brain structures. Reactive astrocytes, Rosenthal fibers and often chronic inflammatory cells including lymphocytes, plasma cells and Russell bodies are seen in adjacent non-neoplastic tissue.

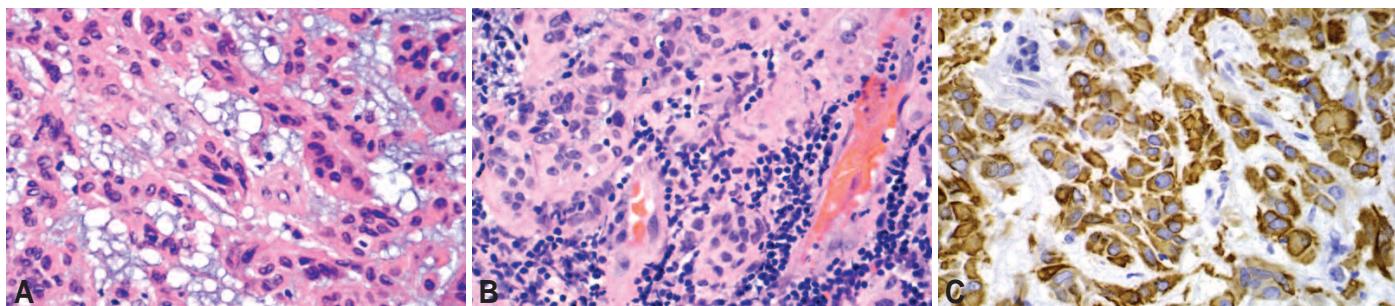


Fig. 5.06 Histological features of chordoid glioma of the third ventricle. A Cords and clusters of epithelioid tumour cells embedded in a mucinous matrix. B Solid arrangements of packed tumour cells and dense lymphoplasmacytic infiltrate. C Tumour cells with diffuse immunoreactivity for GFAP.

Immunohistochemistry

The most distinctive immunohistochemical feature of chordoid gliomas is their strong, diffuse reactivity for GFAP. Staining for vimentin is also strong, while S-100 protein immunoreactivity is variable. EMA staining can be seen focally, but it is usually more prominent in stromal plasma cells. Further, tumours show immunoreactivity for EGFR and the *NF2* gene product merlin, but no nuclear accumulation of the p53, p21 or MDM2 proteins {1848}.

Electron microscopy

On ultrastructural examination, parallels have been drawn with the morphology of ependymoma {1690} or the specialized ependyma of the subcommissural organ {303}. Features include intermediate filaments, intercellular lumina and apical microvilli, hemidesmosomes and basal lamina. In addition, some have been suggested to contain secretory granules {303}.

Proliferation

The proliferative potential of chordoid gliomas corresponds to that of a low-grade glioma. Mitoses are either very rare or absent, and the MIB-1 labelling index is low, with values of 0 to 1.5% in one study {220} and <5% in another {1848}.

Differential diagnosis

The strikingly ‘chordoid’ appearance of these neoplasms, with their eosinophilic clustered tumour cells in a blue mucinous matrix, is distinctive among other regional lesions, including chordoid meningioma, pilocytic astrocytoma, and ependymoma. While there are histological similarities between chordoid gliomas and chordoid meningiomas, the latter are GFAP-negative and EMA-positive {390}. In contrast to chordoid gliomas, chordoid meningiomas are typically dural-based. Histologic similarities include the clustering of epithelioid cells and the presence of a lymphoplasmacytic infiltrate, but the latter is often more prominent in meningiomas and may feature germinal centre formation.

Genetics

Analysis of 4 chordoid gliomas by comparative genomic hybridization revealed no chromosomal imbalances {1848}. None of the neoplasms contained genetic alterations of the *TP53* or *CDKN2A* genes. Similarly, no amplification of *EGFR*, *CDK4* or *MDM2* genes was found.

Histogenesis

The ultrastructural demonstration of microvilli and hemidesmosome-like structures in chordoid glioma has supported an ependymal histogenesis {303}.

Further evidence of ependymal or specialized-ependymal differentiation came from a report of abnormal cilia in a juxtanuclear location {1690}. The presence of a cytologic zonation pattern and secretory vesicles indicated a specialized ependymal differentiation as might be expected of cells derived from a circumventricular organ such as the lamina terminalis. Tanyctic derivation has been suggested based on ultrastructural studies and the occurrence of tanyctyes in the lamina terminalis {1284, 1997}.

Prognostic and predictive factors

Chordoid gliomas are histologically low-grade. However, their location within the third ventricle and their attachment to hypothalamic and suprasellar structures often precludes a complete resection. Postoperative tumour enlargement has been noted in half of the patients undergoing subtotal resections. Among reported cases of chordoid gliomas, approximately 20% of patients died in the perioperative period or from tumour regrowth {1233}. The most frequent morbidity reported following neurosurgical resection is hypothalamic dysfunction.

Angiocentric glioma

P.C. Burger
A. Jouvet
M. Preusser
V.H. Hans
M.K. Rosenblum
A. Lelouch-Tubiana

Definition

An epilepsy-associated, stable or slowly growing cerebral tumour primarily affecting children and young adults; histopathologically characterized by an angiocentric pattern of growth, monomorphous bipolar cells, and features of ependymal differentiation.

ICD-O code

The provisional code proposed for the fourth edition of ICD-O is 9431/1.

Grading

The lesion corresponds to WHO grade I.

Synonyms and historical annotation

Alternatively designated as "monomorphous angiocentric glioma" {2364} or "angiocentric neuroepithelial tumour" {1289}, this is a recently described lesion of uncertain relationship to other neoplasms exhibiting ependymal differentiation.

Incidence

Incidence figures are not yet available for this uncommon lesion.

Age and sex distribution

Three publications from France {1289}, the United States {2364} and Austria/Germany {1799A} have reported a total

of 26 patients. The age at surgery ranged from 2.3 to 70 years (mean, 17 years). Both sexes were equally affected (M/F ratio, 1.0).

Localization

A superficial, cerebrocortical location is typical. Reports to date indicate an excess of lesions involving the frontoparietal lobe (38% of cases) followed by temporal lobe including the hippocampus/parahippocampus (35%) and the parietal lobe (15%).

Clinical features

Symptoms and signs

Angiocentric gliomas are epileptogenic lesions, chronic and intractable partial epilepsy being especially characteristic. Most patients have a history of several years of pre-surgical epilepsy (mean, 7.5 years).

Neuroimaging

On fluid-attenuated inversion recovery (FLAIR) images, angiocentric gliomas are well delineated solid, hyperintense, non-enhancing cortical lesions that usually extend into the subcortical white matter {1799A}. Usually, there is a focal enlargement of the affected cortical gyrus. However, in one case, angiocentric glioma appeared radiologically as hippocampal and parahippocampal atrophy {1799A}. Calcifications are very rare. A stalk-like extension to an adjacent ventricle, hyperintense on T2-weighted MR and FLAIR images, is considered diagnostic {1289}. Sequential imaging indicates that these tumours are stable or very slowly growing {2364}.

Macroscopy

Gross features have not been detailed save for one temporal lobe example described at surgery as producing hippocampal enlargement with darkening and induration of the amygdala.

Histopathology

A unifying feature is the structuring of remarkably monomorphic, bipolar spindled cells oriented about cortical blood

vessels (of all calibers) in mono- or multi-layered sleeves that extend lengthwise along vascular axes and as radial pseudorosettes of ependymomatous appearance. These cells often aggregate beneath the pia-arachnoid in horizontal streams or perpendicular, strikingly palisaded arrays, and can diffusely colonize the neuroparenchyma proper at variable density. Nuclei are slender, with granular chromatin stippling. Some examples exhibit regions of solid growth containing more conspicuously fibrillary elements in compact, miniature schwannoma-like nodules as well as rounded, epithelioid cells in nests and sheets interrupted by irregular clefts or cavities. The latter may contain paranuclear, round or oval eosinophilic densities with an internal granular stippling. These cytoplasmic structures correspond to EMA-immunoreactive microlumens (as seen in conventional ependymomas). Included neurons, interpreted as either entrapped {2364} or possibly intrinsic to the lesion {1289}, do not exhibit significant dysmorphism. Mitoses are unapparent or rare, and neither complex microvascular proliferation nor necrosis is seen, but one example exhibiting recurrence as a mitotically active, anaplastic astrocytoma-like lesion has been described {2364}.

In patients aged 35, 37 and 70 years at surgery, Alzheimer-type features were observed around and within tumours, including neurofibrillary tangles and plaque-like accumulations of hyperphosphorylated tau {1799A}.

Immunohistochemistry

Spindled and epithelioid tumour cells are reactive for GFAP, S-100, and vimentin, but do not label for neuronal antigens (synaptophysin, chromogranin or NeuN). Ependymomatous features are exhibited frequently in a dot-like, microlumen-type cytoplasmic labelling for EMA. Surface EMA expression may also be seen in epithelioid perivascular and subpial formations. Podoplanin immunoreactivity has been reported in some cases.

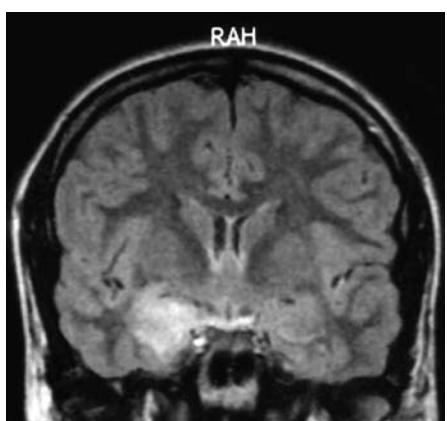


Fig. 5.07 Angiocentric glioma. The bright lesion with little mass effect is based largely in the amygdala of the gray matter.

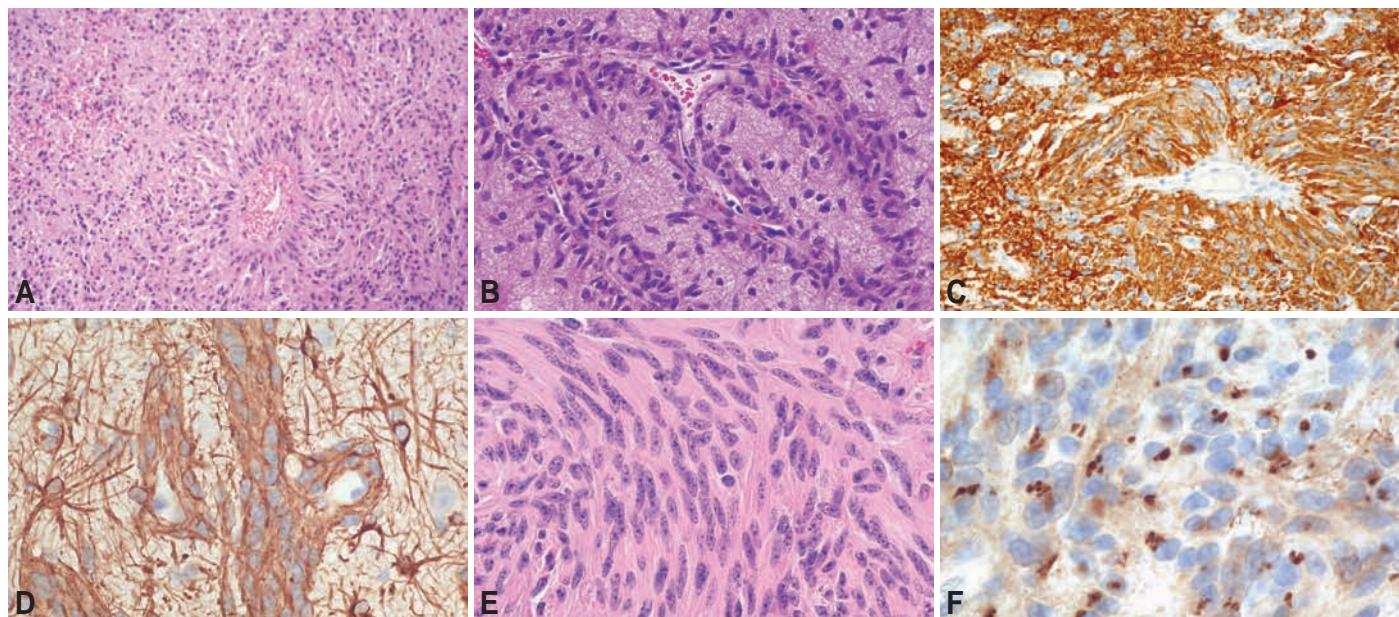


Fig. 5.08 Histological features of angiocentric glioma. A Elongated tumour cells forming occasionally perivascular pseudorosettes. B Perivascular rosettes. C Tumour cells in perivascular pseudorosettes express GFAP. D Longitudinally oriented GFAP-positive cells. E Compact areas that resemble schwannoma. F EMA-positive "dot-like" structures corresponding to microlumens.

Aberrant p53 expression and anomalous labelling patterns of included neurons for synaptophysin, chromogranin and NeuN have not been found.

Electron microscopy

Evidence of ependymal differentiation has been depicted in the form of tumoural microlumens filled with microvilli and cilia, and delimited by elongated intermediate junctions {2364}.

Proliferation

Reported MIB-1/Ki-67 labelling indices in primary neurosurgical material have ranged from 1% or less (most reported cases) to 5%. One anaplastic recurrence exhibited elevation of the labelling index to 10% (from 1% in the primary) {2364}.

Genetic susceptibility

Angiocentric gliomas have not been

recorded in association with dysgenetic syndromes or in familial form.

Genetics

Using chromosomal comparative genomic hybridization (CGH), one in eight cases was found to have a loss at 6q24-q25. High-resolution array CGH revealed in one out of three cases a copy number gain at 11p11.2, containing the PTPRJ (protein-tyrosine phosphatase receptor type J) gene {1799A}.

Histogenesis

Angiocentric gliomas appear to differentiate along ependymal lines, but their cortical localization argues against an origin from native ependymocytes or tanycytes. It has been suggested that these tumours derive, via a maldevelopmental or neoplastic process, from the bipolar radial glia that span the neuroepithelium

during embryogenesis and that may share ependymoglia traits or be capable of generating ependymocytes {1289}.

Prognostic and predictive factors

Angiocentric gliomas are stable tumours for which excision alone is generally curative. A possible antiepileptogenic effect of radiation therapy is described in one case without surgical resection {1799A}. The only angiocentric glioma reported as recurring (in anaplastic form) exhibited typical histologic features at presentation, affected an adult and had been subtotaly resected {2364}.

CHAPTER 6

Neuronal and Mixed Neuronal-Glial Tumours

Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease)

A benign cerebellar mass composed of dysplastic ganglion cells. (See Chapter 13, Cowden disease)

Desmoplastic infantile astrocytoma and ganglioglioma (WHO grade I)

Large cystic tumours of infants that involve superficial cerebral cortex and leptomeninges, often attached to dura, with a generally good prognosis following surgical resection; histologically composed of a prominent desmoplastic stroma with a neuroepithelial population, mainly restricted to neoplastic astrocytes (desmoplastic infantile astrocytoma, DIA) or to astrocytes together with a variable neuronal component (desmoplastic infantile ganglioglioma, DIG), in addition to aggregates of poorly differentiated cells, which are present in both.

Dysembryoplastic neuroepithelial tumour (WHO grade I)

Benign, usually supratentorial glial-neuronal neoplasms, occurring in children or young adults, characterized by a predominantly cortical location and by drug-resistant partial seizures; typically exhibiting a complex columnar and multinodular architecture and often associated with cortical dysplasia.

Gangliocytoma and ganglioglioma (WHO grade I)

Well-differentiated, slowly growing neuroepithelial tumours, composed of neoplastic, mature ganglion cells, alone (gangliocytoma) or in combination with neoplastic glial cells (ganglioglioma); the most frequent entity observed in patients with long-term epilepsy.

Papillary glioneuronal tumour (WHO grade I)

A relatively circumscribed, clinically indolent and histologically biphasic cerebral neoplasm composed of flat to cuboidal, GFAP-positive astrocytes lining hyalinized vascular pseudopapillae and synaptophysin-positive interpapillary collections of sheets of neurocytes, large neurons and intermediate size "ganglioid" cells.

Rosette-forming glioneuronal tumour of the fourth ventricle (WHO grade I)

A rare, slowly growing neoplasm of the fourth ventricular region, preferentially affecting young adults and composed of two distinct histological components, one with uniform neurocytes forming rosettes and/or perivascular pseudorosettes, the other being astrocytic in nature and resembling pilocytic astrocytoma.

Central neurocytoma and extraventricular neurocytoma (WHO grade II)

A neoplasm composed of uniform round cells with neuronal differentiation, typically located in the lateral ventricles in the region of the foramen of Monro (central neurocytoma) or brain parenchyma (extraventricular neurocytoma); affecting mostly young adults, and with a favourable prognosis.

Cerebellar liponeurocytoma (WHO grade II)

A rare cerebellar neoplasm of adults with consistent neuronal, variable astrocytic and focal lipomatous differentiation, and with a low proliferative potential; the tumour usually has a favourable clinical prognosis, although recurrences are frequent.

Spinal paraganglioma (WHO grade I)

A unique neuroendocrine neoplasm, usually encapsulated and benign, arising in specialized neural crest cells associated with segmental or collateral autonomic ganglia (paraganglia); consisting of uniform chief cells exhibiting neuronal differentiation forming compact nests (Zellballen), surrounded by sustentacular cells and a delicate capillary network; within the central nervous system, primarily affecting the cauda equina/filum terminale region.

Desmoplastic infantile astrocytoma and ganglioglioma

D.J. Brat
S.R. Vandenberg
D. Figarella-Branger
A.L. Taratuto

Definition

Large cystic tumours of infants that involve superficial cerebral cortex and leptomeninges, often attached to dura, with a generally good prognosis following surgical resection; histologically composed of a prominent desmoplastic stroma with a neuroepithelial population, mainly restricted to neoplastic astrocytes (desmoplastic infantile astrocytoma, DIA) or to astrocytes together with a variable neuronal component (desmoplastic infantile ganglioglioma, DIG), in addition to aggregates of poorly differentiated cells, which are present in both.

ICD-O code

9412/1

Grading

Histologically, desmoplastic infantile astrocytoma/ganglioglioma corresponds to WHO grade I.

Synonyms and historical annotation

The desmoplastic infantile astrocytoma (DIA) was originally defined in 1982 by Taratuto *et al.* {2216} as meningocerebral astrocytoma attached to dura with desmoplastic reaction. The lesion was further described as a superficial cerebral astrocytoma attached to dura {2217}, thus delineating a previously unrecognized entity. In 1993, it was included in the WHO Classification {1120} under the term 'desmoplastic

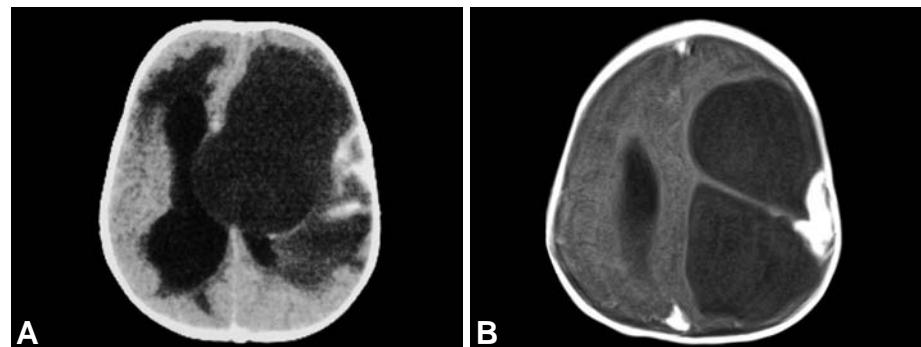


Fig. 6.02 A CT scan of a desmoplastic infantile ganglioglioma with a solid component involving the superficial parietal lobe and large cystic component that extends across the midline. B Post contrast axial MR image demonstrating a superficial enhancing component of a desmoplastic infantile ganglioglioma together with a large septated cystic component that enlarges the skull and displaces the midline.

cerebral astrocytoma of infancy'. In 1987, Vandenberg *et al.* {2314} described desmoplastic supratentorial neuroepithelial tumours of infancy with divergent differentiation ('desmoplastic infantile ganglioglioma', DIG), occurring in the same clinical setting. The histopathology of DIG differed from DIA by the presence of a neuronal component with variable differentiation, and this description also stressed the presence of immature neuroepithelial cell aggregates {2314}. Since both lesions have similar clinical and neuroimaging features, including a favourable prognosis, they have been categorized together as desmoplastic infantile astrocytoma/ganglioglioma in this and previous editions of the WHO classification.

DIA/DIG accounted for 16% of intracranial tumours {2511}.

Age and sex distribution

The age range for 84 reported cases of desmoplastic infantile astrocytoma/ganglioglioma is 1–24 months, with a male: female ratio of 1.5:1. The large majority of infantile cases present within the first year of life. Several non-infantile cases, with ages ranging from 5 to 25 years, have been reported. There is a strong male predominance in the non-infantile cases {645,1774}.

Localization

These tumours invariably arise in the supratentorial region and commonly involve more than one lobe, preferentially the frontal and parietal, followed by the temporal and, least frequently, the occipital.

Incidence

Desmoplastic infantile astrocytoma/gangliogliomas (DIA/DIG) are rare neoplasms of childhood. Their incidence can only be estimated from their frequency in institutional series. One series of 6500 CNS tumours from all ages reported 22 cases of desmoplastic infantile ganglioglioma (0.3%) {2312}. In a series of CNS intracranial tumours limited to the paediatric age group, 6 desmoplastic infantile astrocytomas were found, accounting for 1.25% of all childhood brain tumours {2217}. When studies have been limited to brain tumours of infancy,

Clinical features

Symptoms and signs

These are of short duration and include increasing head circumference, tense and bulging fontanelles, lethargy, and setting-sun sign. Occasionally, patients present with seizures, focal motor signs or skull bossing over the tumour.

Neuroimaging

On CT scans, DIA/DIG are seen as large, hypodense cystic masses with a solid isodense or slightly hyperdense superficial

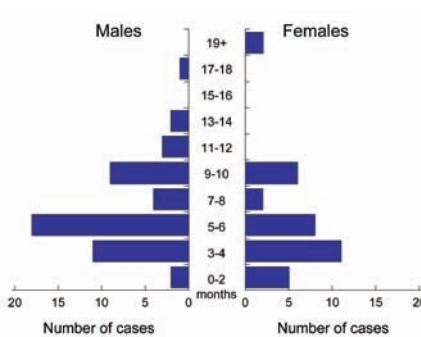


Fig. 6.01 Age (months) and sex distribution of desmoplastic infantile astrocytoma and ganglioglioma, based on 84 published cases.

portion that extends to the overlying meninges and shows contrast enhancement. The cystic portion is usually located deep, whereas the solid portion is peripheral. T1-weighted images on MRI are characterized by a hypointense cystic component with an isointense peripheral solid component that enhances with gadolinium. On T2-weighted images, the cystic component is hyperintense and the solid portion is heterogeneous. Edema is usually absent or moderate {2263}.

Macroscopy

These tumours are large, measuring up to 13 cm in diameter, and have deep uni- or multiloculated cysts filled with clear or xanthochromic fluid. The solid superficial portion is primarily extracerebral, involving leptomeninges and superficial cortex and is commonly attached to the dura, firm or rubbery in consistency, and grey or white in colour. There is no gross evidence of haemorrhage or necrosis.

Histopathology

Diagnostic features are those of a slowly growing superficial neuroepithelial tumour with three distinctive components: the main desmoplastic leptomeningeal component, the poorly differentiated neuroepithelial component and the cortical component. The desmoplastic leptomeningeal compo-

nent consists of a mixture of fibroblast-like spindle-shaped cells and more pleomorphic neoplastic neuroepithelial cells with eosinophilic cytoplasm both arranged in fascicles or in a storiform or whorled pattern. Reticulin impregnations show a prominent reticulin positive network surrounding almost every cell and mimicking a mesenchymal tumour. Astrocytes are the sole tumour cell population in DIA or the predominant neoplastic population, associated with neoplastic neurons, in DIG. Neoplastic neurons range from atypical ganglionic cells to small polygonal cell types {2311, 2314}. In addition to this desmoplastic leptomeningeal component, both DIA and DIG contain a population of poorly differentiated neuroepithelial cells with small, round, deeply basophilic nuclei and minimal surrounding perikarya. Such an immature component, lacking desmoplasia, may predominate in some areas. A cortical component devoid of desmoplasia may also be observed, and this neoplastic component is often multinodular, with some nodules being microcystic {1774}.

There is a sharp demarcation between the cortical surface and the desmoplastic tumour although Virchow-Robin spaces in the underlying cortex are often filled with tumour cells. Calcifications are common but mononuclear inflammatory

cells are not usually seen. Mitotic activity and necrosis are uncommon, but when present are mostly restricted to the population of poorly differentiated neuroepithelial cells {2311, 2312}. Some tumours may contain angiomyoid vessels, but microvascular proliferation is not evident {434, 1354}.

Immunohistochemistry

In the desmoplastic leptomeningeal component, fibroblast-like cells express vimentin. Most often, they also express GFAP, and a few express smooth muscle actin. In addition, most other neuroepithelial tumour cells react with GFAP. Therefore, astrocytes predominate in this component. Antibodies to type IV collagen react in a reticulin-like pattern around tumour cells {75, 405}. Expression of neuronal markers (synaptophysin, NF-H, class III β -tubulin), is observed in the neoplastic neuronal cells but also in cells lacking apparent neuronal differentiation in routine stains {1703}.

In the poorly differentiated neuroepithelial component, cells react with GFAP {1589, 2219, 2312} and vimentin, but also with neuronal markers and MAP2 {1703, 1957, 2312}. Desmin expression may be encountered {1957} but epithelial markers (CAM 5.2, AE1/AE3, EMA) are lacking {1703}.

Electron microscopy

Astrocytic tumour cells are characterized by intermediate filaments typically arranged in bundles as well as scattered cisternae of rough endoplasmic reticulum and mitochondria. An extensive basal lamina surrounds individual tumour cells. Fibroblasts containing granular endoplasmic reticulum and well-developed Golgi complexes are also noted, particularly in collagen-rich areas {434, 1354, 2217}. The neuronal cells of DIG contain dense core secretory granules and may elaborate small processes containing neurofilaments. Immunoelectron microscopy has shown filamentous reactivity to NF-H in these neuronal cell bodies as well as processes lacking a basal lamina. The occurrence of Schwann cell differentiation remains unsettled {1156}.

Proliferation

Mitotic activity is rare and, when present, is mostly restricted to the undifferentiated, small cell population in DIG {2311, 2312}.

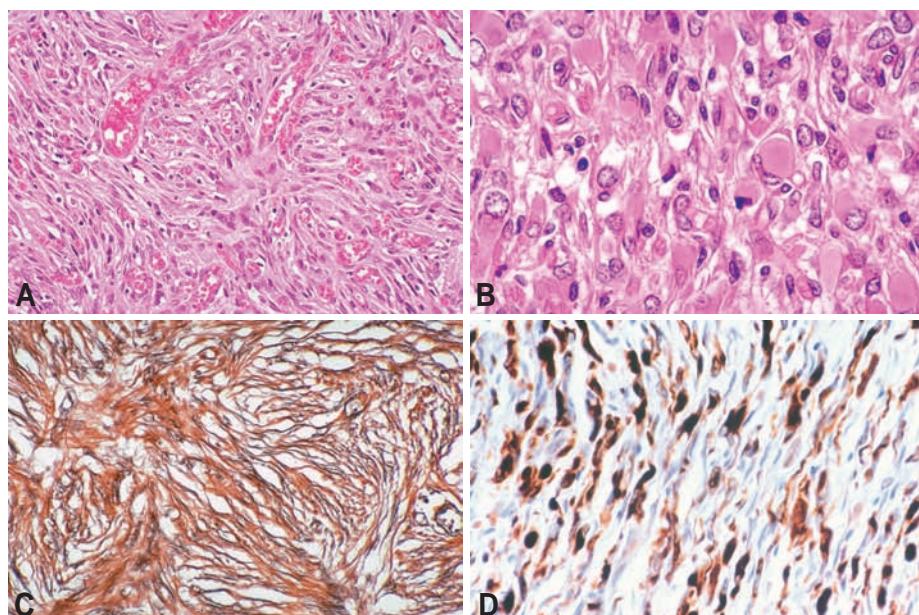


Fig. 6.03 Desmoplastic cerebral astrocytomas of infancy. A Neoplastic astrocytes arranged in streams, with a (C) marked desmoplastic component (reticulin stain). B Field of gemistocytic neoplastic astrocytes. D GFAP-expressing neoplastic astrocytes: the desmoplastic component remains unstained.

Ki-67 labelling indices reported in the literature range from less than 0.5% to 5%. The majority of Ki-67 labelling indices reported are less than 2% [1196]. In those unusual DIA/DIG that show histologic anaplasia, mitotic activity is readily identified, and Ki-67 indices up to 45% have been reported [437]. Proliferation does not appear to be related to clinical behaviour in completely resected tumours but may predict more aggressive behaviour in subtotally resected cases. [437, 2220, 2235]. In three cases analyzed by flow cytometry, the S-phase fraction ranged from 3.7% to 12%, with a mean of 6.6% [2220].

Genetics

Classic cytogenetic analysis has been carried out on only a limited number of cases. In each case, either a normal karyotype or non-clonal abnormalities were described, including alterations involving 1p, 3p, 3q, 5q, 7q, 9p, 11q, 14q, 17p, 21q and 22q [308].

Molecular studies of DIA revealed no loss of heterozygosity on chromosomes 10 and 17 and no TP53 mutations [1354, 2220]. A comparative genomic hybridization study of 3 cases of DIA and DIG did not reveal any consistent chromosomal gains or losses [1196]. One case of DIG showed a loss on 8p22-pter, while one DIA showed gain on 13q21 [308]. Hypermethylation of the p14^{ARF} gene was reported in one tumour [308].

Histogenesis

The cellular origins of desmoplastic infantile astrocytomas and gangliogliomas have not been established. The presence of primitive small cell populations that express both glial and neuronal proteins might suggest that these are progenitor cells to the more differentiated neuroepithelial components and supports the contention that DIA/DIG are embryonal neoplasms programmed to progressive maturation. The basal lamina-associated proteins that are seen in abundance in these neoplasms are known to inhibit cellular proliferation and to induce differ-

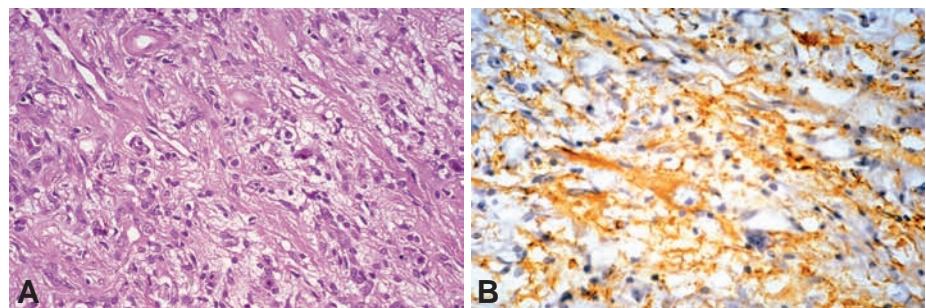


Fig. 6.04 Desmoplastic infantile ganglioglioma with (A) scattered ganglion cells and (B) marked synaptophysin immunoreactivity of ganglion cells and their processes.

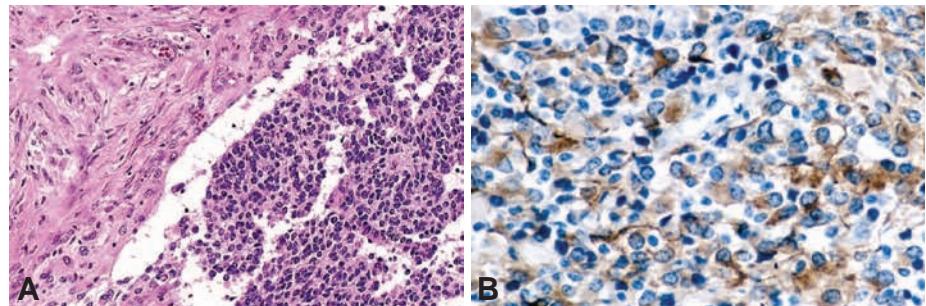


Fig. 6.05 Desmoplastic infantile ganglioglioma demonstrating (A) a component of low grade spindle cells in a collagen-rich matrix and a component of primitive small round blue cells and (B) the primitive, poorly differentiated component immunoreactive for neuronal marker MAP2.

entiation of human glioma cells *in vitro* [1354, 1961]. An origin from the specialized subpial astrocytes that form a continuous, limiting basal lamina investing their terminal processes could account for a comparable phenomenon occurring in desmoplastic infantile tumours and for their superficial localization [75, 1354]. The lack of genetic alterations typical of most diffuse astrocytomas suggests they are not related to these neoplasms.

Prognostic and predictive factors

Follow-up studies indicate that gross total resection results in long term survival in cases of DIA and DIG [2172]. In one study of eight patients with DIA (median follow-up, 15.1 years), six survived to the end of follow-up [2217, 2220]. In another study, no deaths or evidence of tumour recurrence were observed in 14 patients with DIG (median follow-up, 8.7 years) [2312]. Thus, surgery alone with total removal appears to offer local tumour control. In

cases of subtotal resection or biopsy, most tumours are stable or regrow slowly. Two tumours showed radiologic evidence of tumour regression following subtotal resection [2204]. Dissemination of these tumours through the CSF has been reported, but should be considered a rare event [437].

Long-term tumour control can be achieved by total surgical resection in DIA and DIG despite the presence of primitive-appearing cellular aggregates with mitotic activity or foci of necrosis. In two cases of DIG that showed frankly anaplastic features (high mitotic rate, microvascular proliferation and perinecrotic palisading tumour cells), there was no evidence of tumour recurrence following gross total resection [1219, 1220]. Tumour progression has been recorded in DIGs that could not be completely resected, including those with high proliferative indices and anaplastic features [437, 1156].

Dysembryoplastic neuroepithelial tumour

C. Daumas-Duport
T. Pietsch
C. Hawkins
S.K. Shankar

Definition

Benign, usually supratentorial glial-neuronal neoplasms, occurring in children or young adults, characterized by a predominantly cortical location and by drug-resistant partial seizures; typically exhibiting a complex columnar and multinodular architecture and often associated with cortical dysplasia.

ICD-O code 9413/0

Grading

These lesions correspond histologically to WHO grade I.

Synonyms and historical annotation

This tumour entity was originally identified in patients who had undergone epilepsy surgery for the treatment of long-standing drug-resistant partial seizures. They showed unusual morphological features including cortical topography, multinodular architecture, a 'specific glioneuronal element' with a columnar structure, and foci of cortical dysplasia. Long-term follow-up demonstrated no clinical or radiological evidence of recurrence, even in patients with incomplete surgical removal. Moreover, several factors strongly suggested that these tumours might have a dysembryoplastic

origin. Therefore the term "dysembryoplastic neuroepithelial tumour" (DNT) was proposed for these distinctive lesions [422]. In the WHO classification in 1993 [1120], DNTs were included in the category of "neuronal and mixed neuronal-glial tumours". These histological criteria were based on the initial description of DNTs and allow only for the diagnosis of a morphological variant now referred to as the "complex form". A "simple form" of DNT with a unique glioneuronal element was later described [419]. It has been suggested that DNTs include a large spectrum of tumours that cannot be distinguished histologically from ordinary gliomas, and that the diagnosis of such "non-specific histological forms" requires that clinical presentation and imaging features be taken into consideration [419, 426, 858, 1689]. Furthermore, it has been demonstrated that DNTs are not exclusively located within the supratentorial cortex, but may also arise in various other supratentorial or infratentorial locations.

Incidence

Large variations are observed in the reported incidence of DNTs according to the surgical protocol and/or to the criteria used for their diagnosis. In epilepsy surgery, the incidence of "typical" DNTs was 12% in adults [1362] and 13.5% in children, while in series that included "non-specific" histological variants, DNTs were identified in 19–22% of the patients [426, 603, 1689]. Among all neuroepithelial tumours diagnosed in a single institution, DNTs were identified in 1.2% of the patients under 20 years of age and in 0.2% of those aged more than 20 years [1926].

Age and sex distribution

Patient age at the onset of symptoms is an important diagnostic criterion. In about 90% of cases, the first seizure occurs before 20 years of age; however, ages of onset from 3 weeks [1649] to 38 years [1839] have been reported. At diagnosis, the patients are often in the



Fig. 6.07 Surgical specimen of the complex form of DNT showing the cortical topography of the lesion and several pseudo-cysts with the larger being an enlarged sulcus.

second or third decade of life, but detection of DNTs by imaging in children or young adults with recent onset seizures has become more common, and these tumours are increasingly operated on in the setting of paediatric neurosurgery [206, 298, 566, 691, 1602]. Males are more frequently affected.

Localization

DNTs may be located in any part of the supratentorial cortex, but they show a predilection for the temporal lobe, preferentially involving the mesial structures [315, 419, 420, 422, 426, 427, 451, 858, 1689, 1795]. In series based on general practice, the temporal lobe accounts for 50% or fewer of the cases [419, 2218, 2222]. DNTs have also been identified in the area of the caudate nucleus [310, 733] or lateral ventricle [1646], the

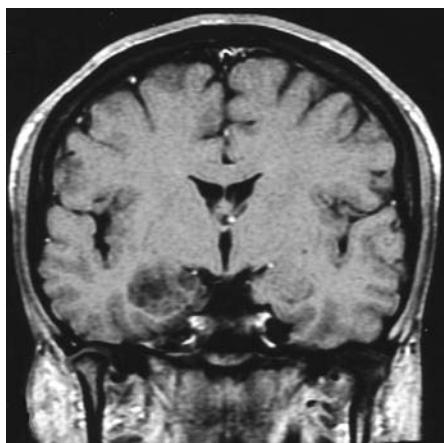


Fig. 6.06 MRI of supratentorial cortical DNT. Complex histological form with a pseudo-polycystic appearance (T1 post-contrast).

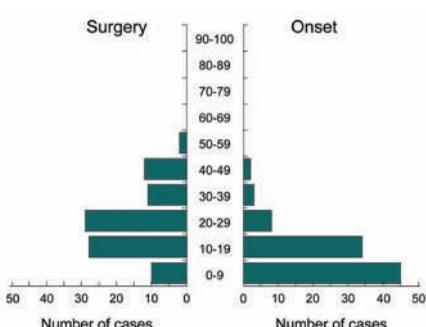


Fig. 6.08 Age distribution of dysembryoplastic neuroepithelial tumours, based on 92 cases from the Ste-Anne Hospital, Paris.

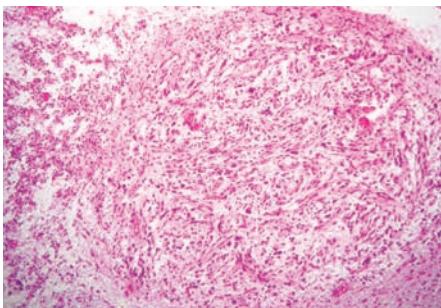


Fig. 6.09 Low-power micrograph of a cortical lesion showing a glial nodule within a specific glioneuronal element.

septum pelucidum {87, 774} the trigono-septal region {733}, the midbrain and tectum {1237}, and the cerebellum {422, 1216, 2464} or cerebellum and brain stem {619}. In total, 25 cases of extra-cortical examples were reported. In addition, four examples of multifocal DNTs have been reported, showing that these tumours may also be found in the region of the third ventricle, the basal ganglia and the pons {1290, 1296, 2404}.

Clinical features

Symptoms and signs

Patients who harbour supratentorial DNTs typically present with drug-resistant partial seizures, with or without secondary generalization and no neurological deficit. A congenital neurological deficit may, however, be observed in a minority of cases {315, 422, 426, 451, 566, 1602, 1689, 1795, 1839, 1928, 2218}. The duration of the seizures prior to surgical intervention can vary from weeks to decades, leading to variability in the age of the patients at pathologic diagnosis.

Neuroimaging

Cortical topography of the lesion, the absence of mass effect and no peritumoural edema are important criteria for differentiating between DNTs and gliomas. The tumours usually encompass the thickness of the normal cortex and, in a minority of the cases, the area of signal abnormality may also extend into the subcortical white matter {419, 426, 427, 566, 1234, 1653, 2140}. The cortical location of the lesion is better seen on MRI than on CT scan. DNTs appear hyperintense on T2-weighted and hypointense or, less often, iso-intense on T1-weighted images. These tumours may look like macrogryi but often have a pseudo-cystic or multi-cystic appearance {419, 426, 427, 1234, 2140}; however,

true cyst formations are uncommon and are usually small {2140}. In tumours that are located at the convexity, deformation of the overlying calvarium is often seen on imaging, and this finding further supports the diagnosis of DNT {419, 426, 427, 1234, 1839, 2140, 2218}. Calcifications are often seen on CT scan and may be voluminous. About one third of DNTs show contrast enhancement on CT scan or MRI, which often appears as multiple rings rather than homogeneous enhancement {1602, 2140}. Ring-shaped contrast enhancement may occur in a previously non-enhancing tumour {2140} and increased lesion size, with or without peritumoural edema, may also be observed on imaging follow-up. However, in DNTs, these changes are not signs of malignant transformation but are usually due to ischaemic and/or haemorrhagic changes {425, 993, 1653}.

Macroscopy

DNTs may vary in size from some millimeters to several centimeters {1689}. In their typical location, they are often easily identified at the cortical surface and may show an exophytic development. However, the leptomeninges are not involved. The appearance of DNTs on cut sections may reflect the complex histoarchitecture of

the lesion. The most typical feature is the viscous consistency of the glioneuronal component. This may be associated with multiple or single firmer nodules. The affected cortex is often expanded.

Histopathology

The histological hallmark of the classical DNT is the 'specific glioneuronal element', characterized by columns oriented perpendicularly to the cortical surface. They are formed by bundles of axons lined by small oligodendroglia-like cells. Between these columns, neurons with normal cytology appear to float in a pale, eosinophilic matrix. Associated with this element are scattered GFAP-positive stellate astrocytes. Depending on the amount of fluid extravasation, subtle variation from a columnar to an alveolar or a more compact structure may be observed {419}. Several histological forms of DNTs have been described but this subclassification has no clinical or therapeutic implication.

Simple form

In this morphological variant, the tumour consists of the unique glioneuronal element. It may show a patchy pattern {419}, owing to the juxtaposition of foci of tumour and of well-recognizable cortex.

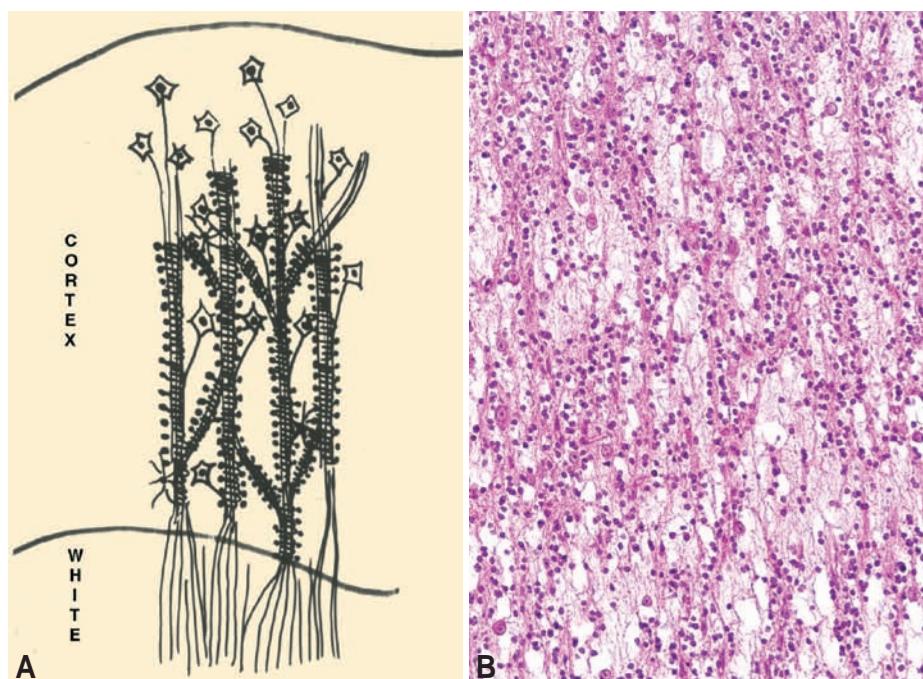


Fig. 6.10 A and B Bundles of axon (black) are attached to oligodendroglia-like cells while neurons float in the interstitial fluid. Histology shows the glioneuronal elements in a columnar orientation.

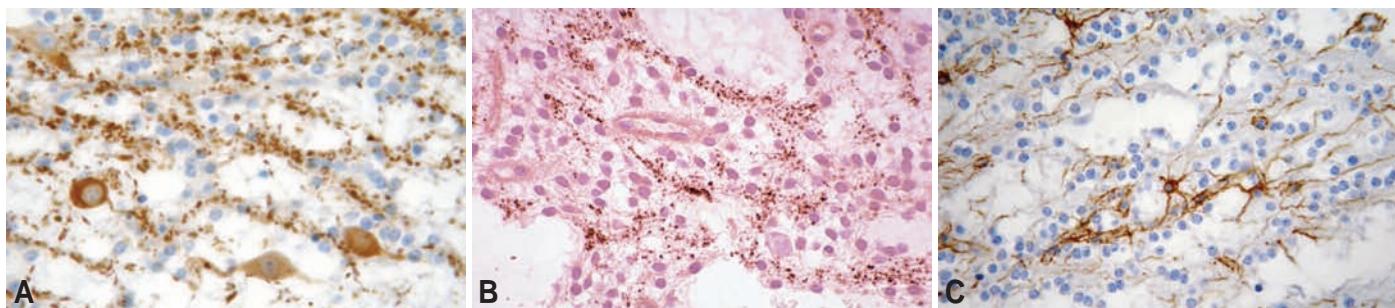


Fig. 6.11 Immunohistochemical features of dysembryoplastic neuroepithelial tumour. A Floating neurons showing immunoreactivity to MAP2. B Synaptophysin immunoreactivity. C Scattered astrocytes evidenced by GFAP immunostaining.

Complex form

In this variant, glial nodules, which lend the tumour a characteristic multinodular architecture, are seen in association with the specific glioneuronal element. The heterogeneous appearance of these tumours is due to the presence of astrocytic, oligodendrocytic and neuronal components. These constituent cell populations may vary from case to case, and from area to area within the same tumour. The glial components seen in the complex forms of DNTs have a highly variable appearance: (i) they may form typical nodules, but may also show a rather diffuse pattern; (ii) they may closely resemble conventional categories of gliomas or may show unusual features; (iii) they often mimic low-grade gliomas, but may show nuclear atypia, rare mitosis, or microvascular-like proliferation and ischaemic necrosis; (iv) their microvascular network may also vary from poor to exuberant, including glomerulus-like formations. In these vessels, the endothelial cells may be hyperplastic and mitotically active. Within the glial components, frankly hamartomatous, usually calcified vessels are not uncommon [419, 426, 1839]. They may behave as vascular malformations

and be responsible for haemorrhage [425, 566, 1653, 2140, 2240].

On the basis of their similar clinical presentation, cortical topography, neuro-radiological features and stability on long-term preoperative imaging follow-up, 'non-specific' histological variants of DNTs have been described [426]. As they lack the specific glioneuronal element and multinodular architecture these variants of DNTs are often histologically indistinguishable from low-grade gliomas, particularly when the cortical topography of the tumour is not apparent on non-representative samples. The diagnosis of these tumours thus requires that the clinical presentation and imaging appearance of the lesion be taken into consideration. Non-specific histological forms accounted for 20–50% of DNTs in three studies [426, 1689, 2299]. Although gliomas identified in patients with long-term epilepsy during epilepsy surgery are usually associated with a distinct benign prognosis [108, 181, 360, 1362], the concept of 'non-specific' histological variants of DNTs remains controversial.

Cortical dysplasia

In association with the tumour, a dysplastic disorganization of the cortex may be observed in up to 80% of the cases with adequate sampling [1689, 1974, 2200, 2299].

Neuronal populations of DNTs

Supratentorial cortical DNTs contain mature neurons. Both in the tumour itself and in the area of cortical dysplasia, the neurons may show various degrees of cytological anomalies. However, DNTs do not contain atypical neurons that resemble dysplastic ganglion cells, such as those found in gangliogliomas. Tumour cells with an oligodendrocytic appearance were found to occasionally

express neuronal markers and to exhibit axo-somatic synapses [831, 859, 2424], suggesting that the so-called oligodendroglial-like cells of DNTs may show an early neuronal differentiation. However, recent results with *in situ* hybridization demonstrated that oligodendroglial-like cells transcribe myelin genes and express myelin oligodendrocyte glycoprotein protein, indicating oligodendroglial differentiation [2436].

Cortical topography

The limits of the tumour most often coincide strikingly with that of the cortex. In other instances, the tumour seems also to involve the adjacent white matter, however, neurons may usually be identified even in the deeper part of the tumour and/or in the adjacent white matter, this likely reflecting disordered neuronal migration [426, 2427].

Diagnostic criteria

The histological diagnosis of DNTs may be difficult, particularly with limited material. The typical columnar architecture of the specific glio-neuronal element may be obscured when the samples are not adequately oriented and, as a result of its semi-liquid consistency, this element may be lost because of inadvertent surgical aspiration and/or fragmentation during fixation. It is thus important that the diagnosis of DNT be taken into consideration whenever all of the following criteria are present: (i) partial seizures with or without secondary generalization, usually beginning before the age 20 years; (ii) no progressive neurological deficit; (iii) predominantly cortical topography of a supratentorial lesion, best demonstrated on MRI; and (iv) no mass effect on CT or MRI, except if related to a cyst, and no peritumoural edema [420, 426, 427].

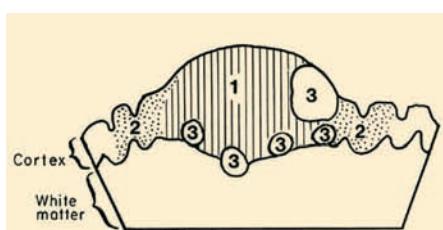


Fig. 6.12 Schematic representation of complex forms of DNTs. 1. Glioneuronal element; 2. cortical dysplasia; 3. glial nodules. Reproduced from Daumas-Dupont *et al.* [422].

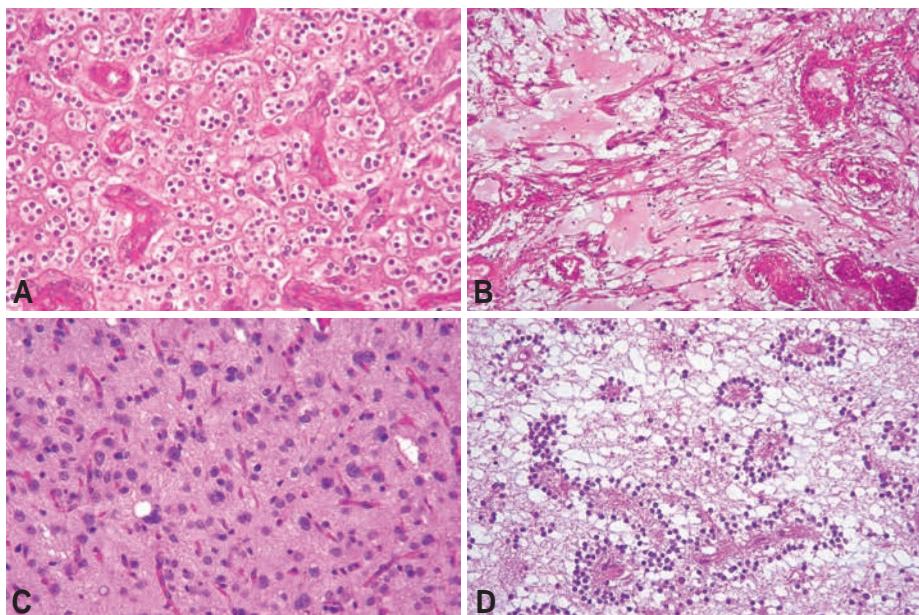


Fig. 6.13 Examples of glial components observed in cortical DNTs: A resembling oligodendrogloma, B resembling pilocytic astrocytoma, C showing marked nuclear atypia, D with small oligodendroglial-like cells forming perivascular pseudorosettes.

DNT versus low-grade diffuse gliomas.

The above clinical and radiological criteria help in distinguishing these benign tumours from diffuse gliomas. It is noteworthy that (i) in low-grade diffuse gliomas, infiltrative microcystic formation may mimic a “specific glioneuronal element”, (ii) these tumours may occasionally exhibit so called “floating” neurons, (iii) oligodendrogloma may exhibit a nodular pattern and (iv) in the cortex, secondary architectural changes caused by the growth of gliomas may be difficult to distinguish from a dysplastic cortical disorganization.

DNT versus ganglioglioma

Gangliogliomas may also pose a difficult problem of differential diagnosis with DNTs because (i) the neoplastic ganglion cells of gangliogliomas may not be present in small or non-representative samples (ii), these tumours may show a multinodular structure, (iii) small gangliogliomas may show a predominant cortical topography and (iv) the clinical presentation of gangliogliomas is often similar to that of DNTs. A ganglioglioma should however be suspected when the tumour shows perivascular lymphocytic infiltration, a network of reticulin fibers and/or a large cystic component. Since gangliogliomas may undergo malignant transformation, their distinction from DNT

is important from a prognostic point of view. Nonetheless, examples of composite ganglioglioma and DNT have been reported and were considered to represent a transitional form between these two tumours {315, 828, 1789, 2084}.

Proliferation

MIB-1 labelling indices of DNTs have been reported to vary from 0% up to 8% focally {419, 426, 427, 1689, 1795, 2218}.

Genetic susceptibility

DNTs may occasionally occur in patients with neurofibromatosis type 1 (NF1) or with XYY syndrome {1041, 1207, 1290}.

Genetics

No deletion on 1p, 17p or 19q {621, 1004, 1793} and no TP53 gene mutations {621} have been detected in DNTs.

Histogenesis

Several factors suggest that DNTs have a malformative origin, including the presence of focal cortical dysplasia and of ectopic neurons in the adjacent white matter, the young age at the onset of symptoms and bone deformity adjacent to the tumours {419, 422, 426, 427}. It was initially proposed that the sites in which these tumours are observed were in accordance with a hypothesis that DNTs may be derived from the secondary germinal

layers {422}. However, the notion of secondary germinal layers and, in particular, the hypothesis that the subpial granular layer may produce neurons and glial cells, is now obsolete. The histogenesis of DNT thus remains unsolved.

Prognostic and predictive factors

DNTs are benign. Their stability has been demonstrated in a study that included 53 patients for whom successive pre-operative CT or MRI was available with a mean duration of follow-up of 4.5 years {2140}. Long-term clinical follow-up usually demonstrates no evidence of recurrence, even in patients with partial surgical removal {419, 422, 426, 427, 566, 1116, 1274, 1362, 1839, 1981, 2140}. However, ischaemic or haemorrhagic changes may occur, with or without an increase in size of the lesion or peritumoural edema {425, 566, 993, 1653, 2140}. Risk factors for the development of recurrent seizures after operation at long-term follow-up were longer pre-operative history of seizures {66, 810}, presence of residual tumour {1602} and presence of cortical dysplasia adjacent to DNT {1974}. Although more than 700 cases of DNT have to-date been reported (http://www.wnfs.org/re4-2/reviews4-2_3.htm), only two cases of malignant transformation, one of which occurred after radiation and chemotherapy, have yet been described {1958}; in addition, in both patients, the initial clinical presentation was atypical.

Ganglioglioma and gangliocytoma

A.J. Becker
O.D. Wiestler
D. Figarella-Branger
I. Blümcke

Definition

Well differentiated, slowly growing neuroepithelial tumours, composed of neoplastic, mature ganglion cells, alone (gangliocytoma) or in combination with neoplastic glial cells (ganglioglioma); the most frequent entity observed in patients with long-term epilepsy.

ICD-O codes

Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3

Grading

Gangliocytomas and most gangliogliomas correspond to WHO grade I. Some gangliogliomas with anaplastic features in their glial component are considered WHO grade III (anaplastic ganglioglioma) {183, 1363}. Criteria for grade II have been suggested, but are not established {1363}.

Incidence

Available data indicate that gangliocytomas and gangliogliomas together represent 0.4% of all CNS tumours and 1.3% of all brain tumours {1030, 1363}. There are no population-based epidemiological data on gangliogliomas.

Age and sex distribution

The age of patients ranges from 2 months to 70 years. Data from five large series

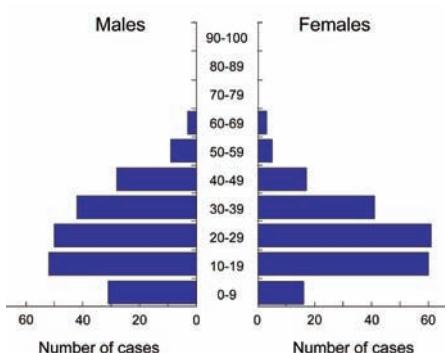


Fig. 6.14 Age and sex distribution of ganglioglioma patients, based on 418 cases from the German Neuropathology Reference Center for Epilepsy Surgery.

with a total of 626 patients indicate a mean/median age at diagnosis from 8.5 to 25 years. The male:female ratio varied from 1.1:1 to 1.9:1 {832, 1256, 1798, 2425}. In 99 cases involving only children, the mean age at diagnosis was 9.5 years, with 52% female patients {1002}. In a survey of the German Neuropathology Reference Centre for Epilepsy Surgery, the mean age of 124 children with gangliogliomas was 10.3 years, with 44% being female patients.

Localization

These tumours occur throughout the CNS, including cerebrum, brain stem, cerebellum, spinal cord, optic nerves, pituitary and pineal glands. The majority of gangliogliomas localize in the temporal lobe (>70%) {183, 832, 1256, 1798, 2425}. A distinct entity, dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos), is discussed in Chapter 13.

Clinical features

Symptoms and signs

Symptoms vary according to tumour size and site. Tumours in the cerebrum are frequently associated with a history of seizures ranging in duration from 1 month to 50 years before diagnosis, with a mean/median interval of 6–25 years {1256, 1798, 2425}. For tumours involving the brain stem or spinal cord, the mean duration of symptoms before diagnosis is 1.25 and 1.4 years, respectively {1256}. Gangliogliomas have been reported in 15–25% of patients undergoing surgery for control of seizures {2425, 2428}. They are the most common tumours associated with chronic temporal lobe epilepsy {1362}.

Neuroimaging

CT shows a circumscribed solid mass or cyst with a mural nodule. The tumour may be calcified. Contrast enhancement is typical but may be faint or absent. Scalloping of the calvarium may be seen adjacent to superficially located cerebral tumours. MRI shows a T1-weighted hypointense, T2-weighted hyperintense circumscribed mass. Enhancement varies

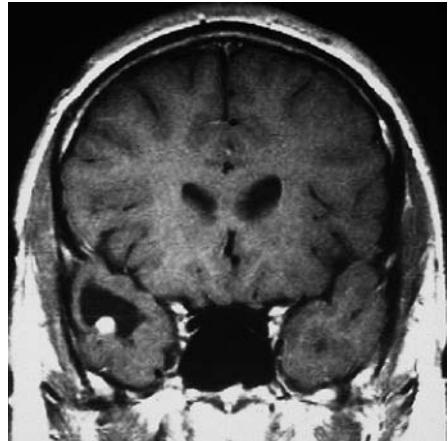


Fig. 6.15 MRI of a cystic ganglioglioma in the left temporal lobe with an intramural nodule.

in intensity from none to marked, and may be solid, rim or nodular {727, 1651}.

Macroscopy

Gangliogliomas are solid or cystic lesions, usually with little mass effect. Calcification may be observed. Haemorrhage and necrosis are rare.

Histopathology

Gangliocytomas are composed of irregular groups of large, multipolar neurons with often dysplastic features. The stroma consists of non-neoplastic glial elements and a network of reticulin fibers, often in perivascular location.

Table 6.01 Regional manifestation of gangliogliomas (GG) and other long-term epilepsy-associated tumours (LEAT). Other localizations include striatum and spinal cord. Data based on 413 GG and 802 LEAT.

Localization	GG	LEAT
Frontal	7%	12%
Parietal	3%	5%
Occipital	3%	3%
Temporal	86%	78%
Other	1%	2%
Multiple lobes	7%	7%

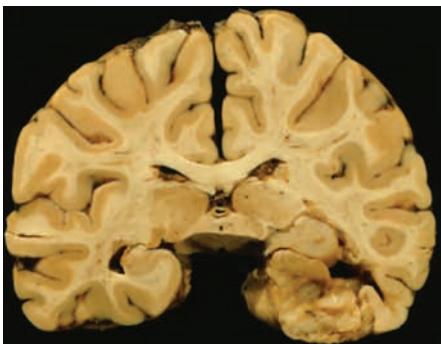


Fig. 6.16 Ganglioglioma of the right temporal lobe also involving the hippocampal formation.

The histopathological hallmark of gangliogliomas is a combination of neuronal and glial cell elements, which may exhibit marked heterogeneity. Dysplastic neurons should be characterized by (i) loss of cytoarchitectural organization, (ii) abnormal (subcortical) localization, (iii) clustered appearance, (iv) cytomegaly, (v) perimembranous aggregated Nissl substance or (vi) presence of bi- or multi-nucleated neurons (in up to 50% of cases). The glial component in gangliogliomas shows substantial variability, but constitutes the proliferative cell population of the tumour. It may include cell types resembling fibrillary astrocytoma, oligodendrogloma or pilocytic astrocytoma.

Table 6.02 Spectrum of long-term epilepsy-associated tumours. Data from the German Reference Center for Epilepsy Surgery, based on 1006 cases.

Entity		
Astrocytoma	Pilocytic	5%
	Diffuse	5%
	Anaplastic	3%
Cysts	Arachnoid	0.5%
	Epidermoid	1%
	Dermoid	0.1%
DNT		17%
Gangliocytoma		0.3%
Ganglioglioma	WHO I	44%
	WHO II	4%
	WHO III	0.6%
Meningioma		1%
NOS		4%
Oligodendrogloma	WHO II	3%
	WHO III	1%
Oligoastrocytoma	WHO II	3%
	WHO III	1%
Pleomorphic		
xanthoastrocytoma		3%
SEGA		1%
Other		1%

Rosenthal fibers and eosinophilic granular bodies are present in many cases. A fibrillary matrix is usually prominent and may contain microcystic cavities and/or mucous substance. Gangliogliomas may develop a reticulin fiber network apart from the vasculature. Occasional mitoses are compatible with the diagnosis of ganglioglioma. Necrosis is absent, unless the glial component is undergoing malignant progression. Additional histopathological features frequently identified in gangliogliomas are: (i) calcifications, either excessive or as neuronal/capillary incrustation; (ii) extensive lymphoid infiltrates along perivascular spaces or within the tumour/brain parenchyma; (iii) a prominent capillary network. In few cases, the latter manifests as malformative angiomatic component.

In anaplastic gangliogliomas, malignant change almost invariably involves the glial component {832, 1363, 1798, 2425}. Few cases have been observed in which a malignant glioma arises from the site of a previously resected ganglioglioma {183}.

The spectrum of gangliogliomas varies from a predominantly neuronal phenotype towards variants with a prominent glial population. Some tumours may also display a clear cell morphology, which raises the differential diagnosis of oligodendrogloma or dysembryoplastic neuroepithelial tumour. Ganglion cells may also be a component of extraventricular neurocytic tumours and papillary glioneuronal tumours.

Immunohistochemistry

Neuronal proteins, such as MAP2, NeuN, neurofilaments and synaptophysin are useful to demonstrate the neuronal component in gangliogliomas. The reactions usually demarcate the dysplastic nature of the neuronal cell types. There is still no specific marker available to differentiate dysplastic/neoplastic neurons from normal counterparts. Immunostains for the oncofetal CD34 antigen can be helpful. CD34 is not present in neural cells of the adult brain, but is consistently expressed in 70–80% of gangliogliomas, especially those variants emerging from the temporal lobe. CD34 immunoreactive neural cells are prominent not only in the solid tumour areas but also in peritumoural satellite lesions {178}. Staining for GFAP demonstrates the astrocytes that usually form the neoplastic glial

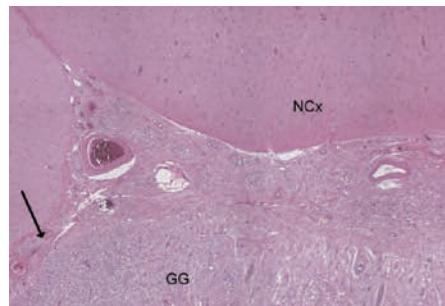


Fig. 6.17 Ganglioglioma (GG) with sharp demarcation towards the adjacent brain parenchyma (NCx) and infiltration into subarachnoid space (arrow).

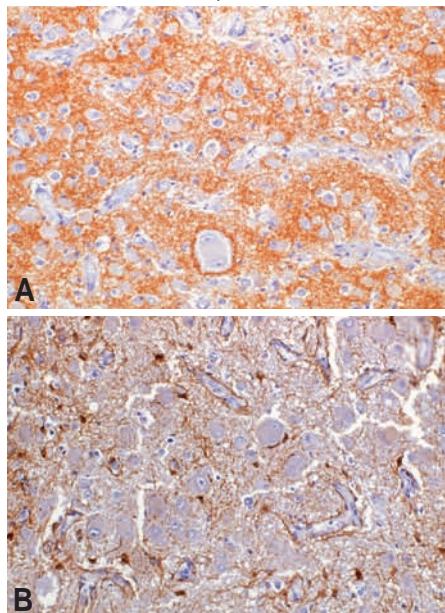


Fig. 6.18 Ganglioglioma. A Strong immunoreactivity to synaptophysin of ganglion cells and their processes. Note the binucleate neuron with synaptophysin staining of perisomatic synapses. B GFAP expression by neoplastic astrocytes.

element of gangliogliomas. In contrast to diffuse gliomas, MAP2 immunoreactivity is faint or absent in the astrocytic component of gangliogliomas {182}.

Electron microscopy

Neurons with dense core granules are characteristic and diagnostically useful ultrastructural features of these tumours. Synaptic junctions may be absent, or present in only small numbers {832, 1477}. Spherical protein bodies have been described in gangliogliomas {926}.

Proliferation

Mitotic figures are rare. Ki-67/MIB-1 labelling involves only the glial component, mean values ranging from 1.1 to 2.7% {832, 1363, 1798, 2425}.

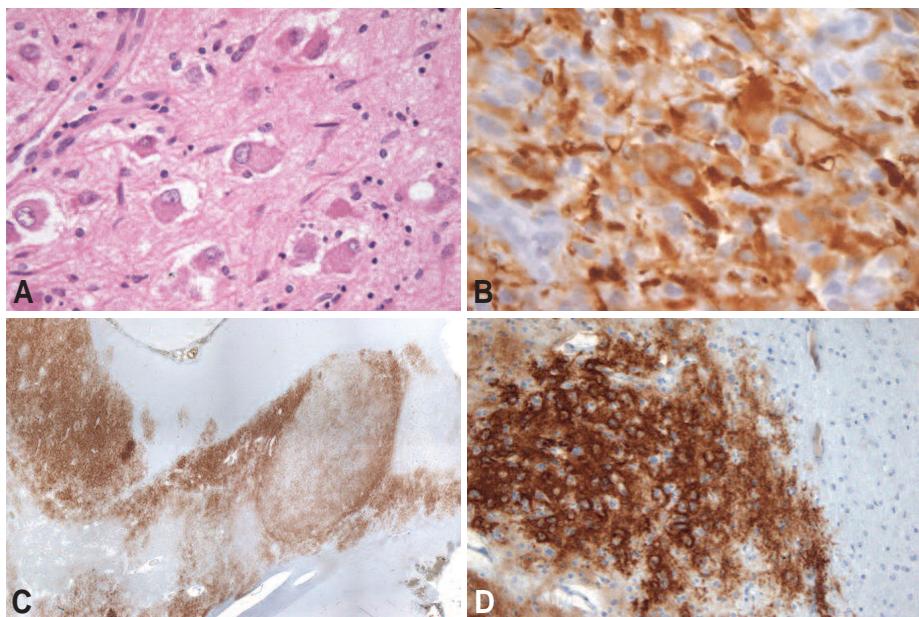


Fig. 6.19 A Ganglioglioma showing a biphasic pattern of dysplastic neurons and neoplastic glial cells. B MAP2 expression in dysplastic, occasionally binuclear neurons. C CD34 demarcates the tumour and demonstrates tumour satellites in adjacent brain parenchyma. D Focal expression of the stem cell epitope CD34 in a ganglioglioma.

Genetic susceptibility

A ganglioglioma of the optic nerve has been noted in a patient with neurofibromatosis type 1 [1465]. One case of spinal cord ganglioglioma was reported in a child with neurofibromatosis type 2 [2001]. A Peutz-Jeghers patient has also been described with a ganglioglioma [1862].

Genetics

About thirty cases of gangliogliomas have been studied cytogenetically [148, 2135, 2353, 2467]. Chromosomal abnormalities were recorded in one third. Although structural and numerical abnormalities differ greatly between cases, gain of chromosome 7 was the most recurrent alteration. Correlation between cytogenetic data, grade and outcome was not fully addressed, but karyotype was abnormal in three cases with adverse outcome [978, 980, 2353]. Chromosomal imbalances were detected

in 5/5 gangliogliomas by comparative genomic hybridization [2467]. Partial loss of chromosome 9p and gain of chromosome 7 were recurrent genetic events. In spite of gain of chromosome 7, abnormal EGFR expression was not recorded in 5/5 gangliogliomas [2467]. In a study of 14 cases (11 grade I and 3 grade III), TP53 mutation, PTEN mutation, CDK4 and EGFR amplification were not detected. CDKN2A deletion was observed in 2/3 anaplastic gangliogliomas [2334]. However, a TP53 mutation was reported in the recurrence of a grade I ganglioglioma [796]. Mutational analysis of the tuberous sclerosis 1 (*TSC1*) and *TSC2* genes revealed sequence alterations in the *TSC2* gene including polymorphisms in intron 4 and exon 41 to be significantly overrepresented in patients with gangliogliomas. A somatic mutation in intron 32 was identified in the glial portion but not in neurons of a ganglioglioma [121].

Mutations in the coding region of the *TSC1* and *TSC2* genes have not been documented [121, 1683]. A study of ezrin and radixin genes, coding for interaction partners of *TSC1* and *TSC2*, was negative [1388]. Analysis of genes involved in the Reelin signalling cascade with a major role in neuronal development failed to uncover mutations of the cyclin dependent kinase *CDK5*, doublecortin *DCX*, *TP53* and disabled-1, *DAB-1* [120, 1031]. Although a Peutz-Jeghers patient with a germline mutation in the serine-threonine kinase *LKB1* gene developed a ganglioglioma, *LKB1* gene mutations were not recorded in the three sporadic gangliogliomas [1862].

Histogenesis

The histogenesis of these intriguing neoplasms remains unresolved. An origin from a dysplastic, malformative glioneuronal precursor lesion with neoplastic transformation of the glial element has been hypothesized. A monoclonal origin was shown for 5 of 7 gangliogliomas by both methylation-based and transcription-based clonal analysis [2503]. Neoplastic transformation of subpial granule cells or of glial cells within hamartomas has also been discussed [1030, 2425].

Prognostic and predictive factors

Gangliogliomas are benign tumours with a 7.5 year recurrence-free survival rate of 94% [1363]. Good prognosis is associated with temporal localization, complete surgical resection and long-standing epilepsy. Anaplastic change in the glial component, i.e. histological similarities to high-grade gliomas such as increased mitotic activity, prominent microvascular proliferation and necrosis, as well as high MIB-1 and TP53 labelling indices, may indicate aggressive behaviour and less favourable outcome [832, 1030, 1798].

Central neurocytoma and extraventricular neurocytoma

D. Figarella-Branger
F. Söylemezoglu
P.C. Burger

Definition

A neoplasm composed of uniform round cells with neuronal differentiation, typically located in the lateral ventricles in the region of the foramen of Monro (central neurocytoma) or brain parenchyma (extraventricular neurocytoma); affecting mostly young adults, and with a favourable prognosis.

ICD-O codes

Central neurocytoma 9506/1

The provisional code for extraventricular neurocytoma proposed for the fourth edition of ICD-O is 9506/1.

Grading

Central neurocytoma corresponds histologically to WHO grade II.

Synonyms and historical annotation

The term central neurocytoma was coined by Hassoun *et al.* {786} to describe a neuronal tumour with pathological features distinct from cerebral neuroblastomas, occurring in young adults, located in the third ventricle, and histologically mimicking oligodendrogloma. These tumours had been previously reported as ependymomas of the foramen of Monro or intraventricular oligodendroglomas. Central neurocytomas were then reported in other intraventricular locations, mainly lateral and third ventricle but also the fourth. The term "central neurocytoma" should be restricted to

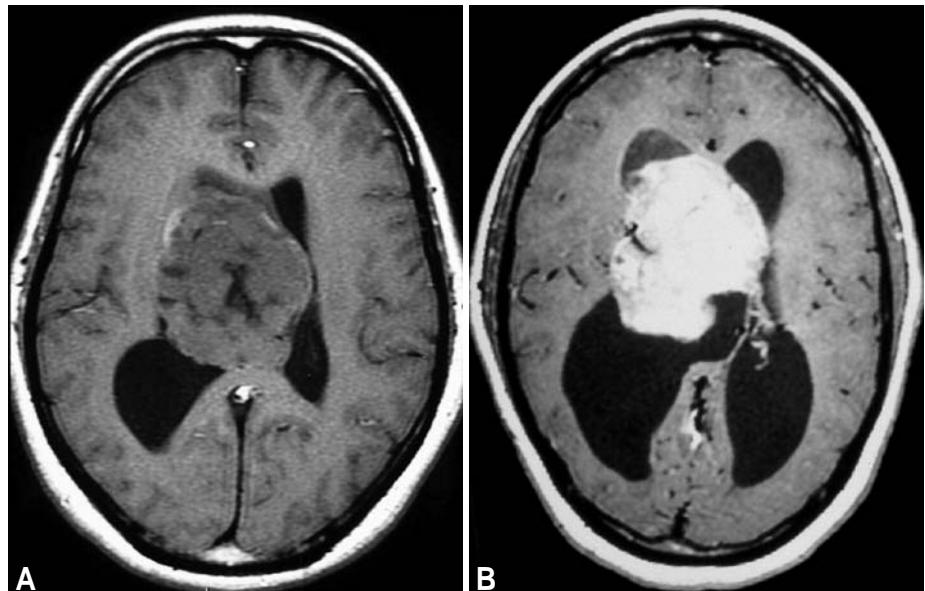


Fig. 6.21 MRI of central neurocytoma. A A large tumour of the lateral ventricle with heterogeneous hypointensity on T1-MRI. B A large contrast-enhancing central neurocytoma in the region of the foramen of Monro (gadolinium injection).

neoplasms located within the intracerebral ventricles. Subsequently, tumours mimicking central neurocytomas but occurring within the cerebral hemispheres ("cerebral neurocytomas") {1598} or the spinal cord {362, 2223} were documented. The term "extraventricular neurocytoma" is now given to neoplasms that arise within the central nervous system parenchyma and share histological features with the more common central neurocytomas but exhibit a wider morphological spectrum {666}. Notably, some tumours have neurocytic tumour cells but are not classified as central or extraventricular neurocytomas; for example, neurocytic differentiation has been reported in an increasing number of tumours with distinctive morphological features, some of them emerging as new entities such as cerebellar liponeurocytoma and papillary glioneuronal tumour {1153} or variants {301}.

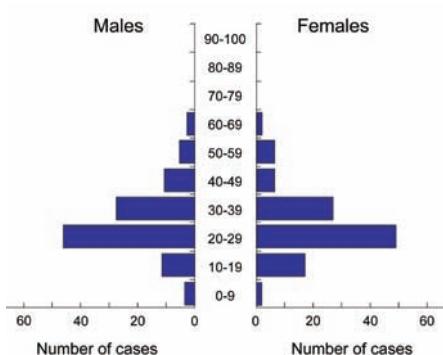


Fig. 6.20 Age and sex distribution of central neurocytoma excluding extraventricular neurocytoma, based on 243 patients.

Age and sex distribution

In analysis of 243 cases, age at clinical manifestation ranged from 8 days to 67 years (mean age, 29 years); 44% were diagnosed in the third decade of life, and

69% between the ages of 20 and 40 years. Both sexes are equally affected.

Incidence

Population-based incidence rates for central neurocytoma are not available. In large surgical series, incidence ranged from 0.25–0.5% {788} of all intracranial tumours.

Localization

Central neurocytomas are typically located supratentorially in the lateral ventricle(s) and/or the third ventricle. The most common site is the anterior portion of one of the lateral ventricles (50%), with a preference for the left, followed by combined extension into the lateral and third ventricles, and by a bilateral intraventricular location. Attachment to the septum pellucidum seems to be a feature of the tumour. Isolated third ventricular occurrence is rare.

Clinical features

Symptoms and signs

The majority of patients present with symptoms of increased intracranial

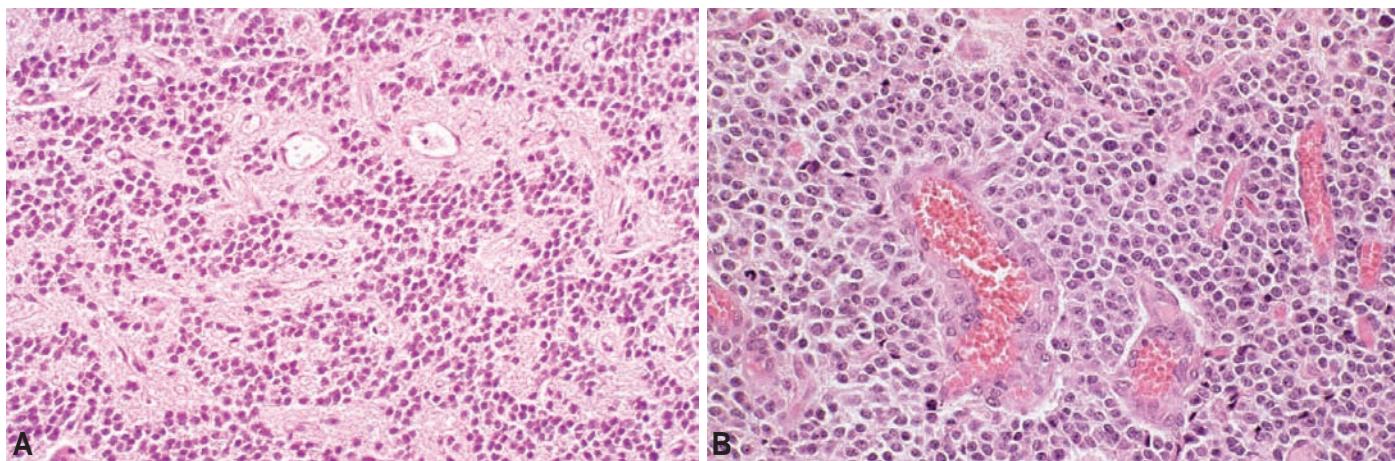


Fig. 6.22 Central neurocytoma. A Round cells and nucleus-free areas of neuropil. B Microvascular proliferation associated with mitotic activity.

pressure, rather than with a distinct neurological deficit. The clinical history is short (mean 3.2 months). Occasionally, visual and mental disturbances and hormonal dysfunction may be observed. Central neurocytomas may present as acute haemorrhage or as an incidental finding on imaging [788].

Neuroimaging

On CT scans, mass are usually isodense or slightly hyperdense. Enhancement is observed after administration of contrast medium. Calcifications and cystic changes may be seen. MRI shows heterogeneous hypointensity on T1 and hyperintensity on T2-weighted images and FLAIR, with a well-defined margin and, in all cases, mild to strong enhancement after gadolinium injection [2491].

Macroscopy

The intraventricular tumours are usually greyish and friable, with varying calcifications and occasional haemorrhage.

Histopathology

Neurocytoma is a neuroepithelial tumour composed of uniform round cells that show immunohistochemical and ultrastructural features of neuronal differentiation. Additional features include fibrillary areas mimicking neuropil, and a low proliferation rate. Central neurocytomas have a benign histological appearance. Various architectural patterns may be observed, even in the same specimen. They include an oligodendrogloma-like honeycomb appearance, large fibrillary areas mimicking the irregular "rosettes"

in pineocytomas, cells arranged in straight lines, or perivascular pseudo-rosettes as observed in ependymomas. Cells are isomorphic, having a round or oval nucleus with a finely speckled chromatin and an occasional nucleolus. Capillary-sized blood vessels, usually arranged in a linear arborizing pattern, give the tumours an endocrine appearance. Calcifications are seen in half the cases, usually distributed throughout the tumour. Rarer findings may include Homer Wright rosettes and ganglioid cells [1896, 2335]. The main differential diagnoses include oligodendrogloma, ependymoma, pineocytoma and dysembryoplastic neuroepithelial tumour. In rare instances, anaplastic histological features, including brisk mitotic activity [788, 2335, 2336] and microvascular proliferation, have been observed [1214, 2335, 2463]. In some cases, necrosis was associated with anaplastic features [1692, 2335, 2463]. Necrosis may also be observed in rare cases that are otherwise devoid of any malignant features, perhaps as a vascular effect [580, 821, 1214].

Immunohistochemistry

Synaptophysin is the most suitable and reliable diagnostic marker, with immunoreactivity diffusely present in neuropil, especially in fibrillary zones and perivascular nuclei-free cuffs [580]. A significant number of nuclei are immunopositive for NeuN in almost all cases [2128]. The mean labelling index was 74% in one series of 11 cases, with a significantly lower Ki-67 staining rate for cells expressing NeuN [525]. Chromogranin A

and neurofilament staining are usually absent except when ganglion cells are present [788]. In extraventricular neoplasms, intracytoplasmic and para-nuclear immunolabelling must be cautiously interpreted whenever other histological, immunohistochemical or ultrastructural evidence of neuronal differentiation is lacking. Of particular interest is the anti-Hu antibody because it labels the nuclei of neurocytes [734]. Although most reports find GFAP expressed only in trapped reactive astrocytes, the antigen has been detected by some authors in tumour cells [2127, 2272, 2335, 2336].

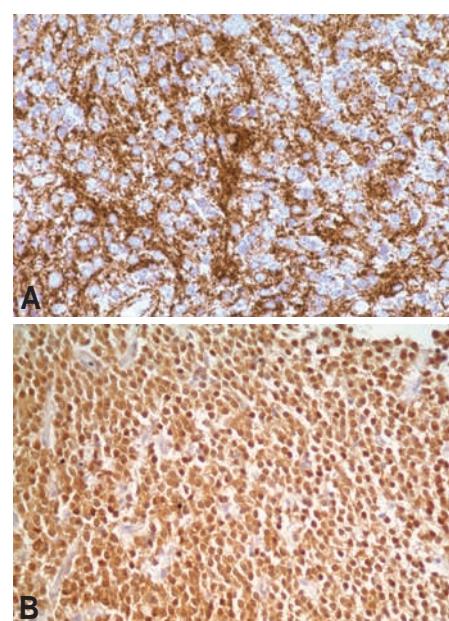


Fig. 6.23 Central neurocytoma. A Diffuse immunoreactivity for synaptophysin. B Nuclear NeuN expression.

Electron microscopy

Electron microscopy is required when expression of specific neuronal markers (synaptophysin, NeuN) is lacking or doubtful and in all extraventricular neoplasms mimicking central neurocytomas. Typically, central neurocytoma cells show regular round nuclei with a finely dispersed chromatin and a small distinct nucleolus in a few cells. The cytoplasm contains mitochondria, a prominent Golgi apparatus and some cisternae of rough endo-plasmic reticulum often arranged in concentric lamellae. Numerous thin and intermingled cell processes containing microtubules, dense core and clear vesicles, are always observed {300, 788}. Furthermore, well-formed or abnormal synapses may be present, but are not required for the diagnosis.

Proliferation

MIB-1 labelling indices are usually low, less than 2%. Tumours with indices greater than 2%, or in one series 3% {1815}, have been referred to as "atypical neurocytomas" and associated with a significantly shorter recurrence-free interval {1373, 2127}. Vascular proliferation may be present in these lesions. DNA flow cytometry performed in ten neurocytomas revealed diploidy in all {1103}.

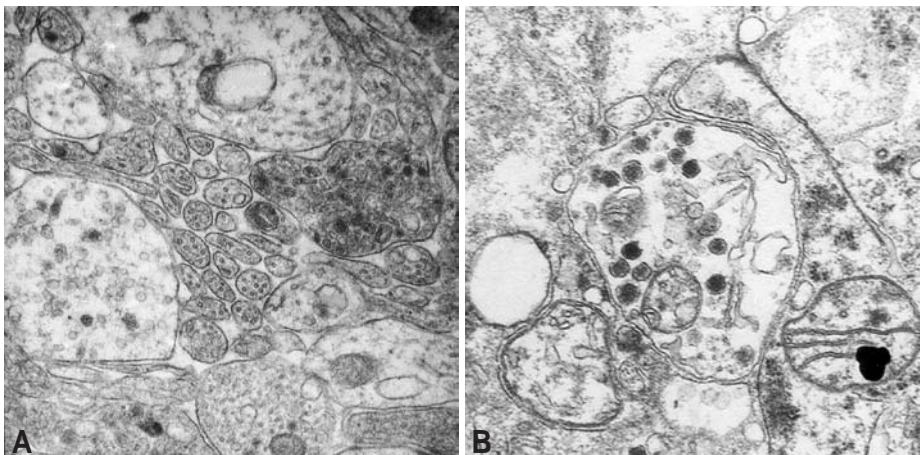


Fig. 6.25 A Ultrastructure of a central neurocytoma showing numerous cell processes filled with neurotubules and synaptic structures containing dense core granules and clear vesicles. B A neoplastic process containing dense-core vesicles in central neurocytoma.

Genetic susceptibility

One case of central neurocytoma, although originally reported as intraventricular cerebral neuroblastoma, was associated with von Hippel-Lindau disease {1707}.

Genetics

Though the molecular pathogenesis of central neurocytomas remains largely unknown, some genetic alterations, mainly chromosomal gains, have been reported. Gain on chromosome 7 was observed in 3 of 9 neurocytomas {2221}. However another study did not find EGFR amplification in central neurocytomas {2260}. Gains on chromosomes 2p, 10q, 18q and 13q were found in over 20% of tumours studied {2468}. In two others, an isochromosome 17 and complex karyotype were reported {309, 979}. TP53 mutations and MYCN amplification are rare or absent {621, 979, 1621, 2260, 2336}. There are two studies on loss of 1p and 19q: in one report, allelic loss on 1p and 19q was not detected {621}; in the other, 6 of 9 tumours showed loss at one or more loci on 1p, and 5 of the cases had 19q loss but the majority of informative markers are reported to be retained {2260}. These data suggest that central neurocytomas are genetically distinct from oligodendroglomas. The expression profiles of cerebellar liponeurocytoma show a closer relationship to the central neurocytoma, however the lack of TP53 mutations in central neurocytomas suggests the involvement of different genetic pathways {867}.

Histogenesis

Given the neuronal nature of the tumour and its location, central neurocytomas were previously thought to derive from the nuclei of the septum pellucidum {786}. However, the demonstration of both astrocytic and neuronal differentiation in some tumour cells by various approaches *in vivo* {2272, 2336} and *in vitro* {922, 2399} has suggested that they derive from neuroglial precursor cells having the potentiality of dual differentiation, although neuronal commitment largely predominate. This precursor cells might originate from the subependymal plate of the lateral ventricle {2336} or from circumventricular organs {1013}.

Prognostic and predictive factors

The clinical course of central neurocytoma is usually benign, with the extent of resection being the most important prognostic factor. Local recurrence is common in the face of incomplete removal, but the pace of residual tumour growth can be retarded by radiotherapy {1813, 1814}. Craniospinal dissemination is exceptional {524, 2258}. It is worth noting that histological findings alone cannot predict adverse outcomes {524, 1103}. Moreover, central neurocytomas showing aggressive histological features have been described in few patients {2335, 2336, 2463}. These features were not generally associated with poor prognosis. Central neurocytomas with a MIB-1 labelling index (LI) >2% {1373, 2127} or >3% {1815} have significantly shorter recurrence-free intervals. In one

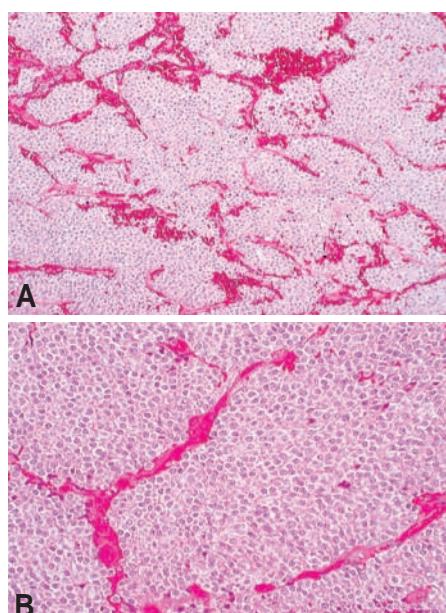


Fig. 6.24 Central neurocytoma, showing sheet-like growth composed of uniform round cells (A), and with endocrine appearance with linear arborizing capillaries (B).

small study, cytological atypia had little relationship to MIB-1 index or length of survival {1373}. Involvement of periventricular parenchyma is associated with poor outcome in some cases {1103, 1896}.

Extraventricular neurocytoma

Extraventricular neurocytomas are well circumscribed, contrast-enhancing, and often have a cyst-mural nodule complex that is useful in distinguishing the tumour from histologically similar neoplasms such as oligodendrogloma. They present throughout the CNS. Histologically extraventricular neurocytomas may be identical to the densely cellular cytologically monomorphic central lesion, but are often more complex, less cellular,

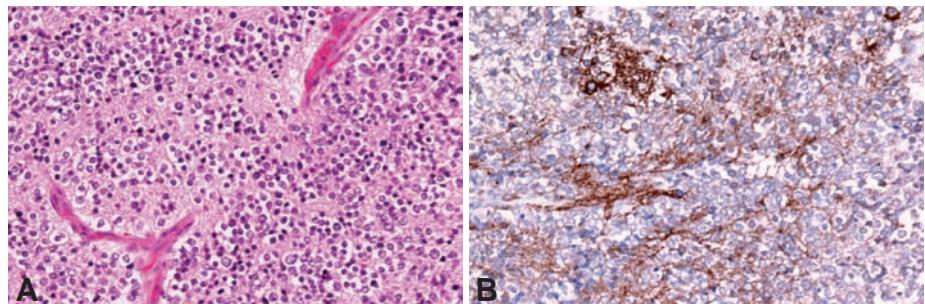


Fig. 6.26 Extraventricular neurocytoma. A Isomorphic tumour cells with perinuclear halos arranged in a fibrillary stroma. B Immunopositivity for synaptophysin in the cytoplasm and fibrillary stroma.

and more likely to contain ganglion cells or smaller ganglioid cells with nuclei that are larger and paler than those of neurocytes {218, 666}. Lower cellularity, in combination with perinuclear haloes, may

create an appearance of oligodendrogloma. GFAP-positive glia are present, but it has been difficult to incriminate these as clearly neoplastic. Hyalinized vessels and dense calcification are common.

Cerebellar liponeurocytoma

P. Kleihues
L. Chimelli
F. Giangaspero
H. Ohgaki

Definition

A rare cerebellar neoplasm of adults with consistent neuronal, variable astrocytic and focal lipomatous differentiation, and with a low proliferative potential; the tumour usually has a favourable clinical prognosis, although recurrences are frequent.

ICD-O code

The provisional code proposed for the fourth edition of ICD-O is 9506/1.

Grading

Histological features and data on postoperative survival available at the time the previous edition of the WHO Classification was published {1122} suggested that this tumour typically corresponded to WHO grade I. However, recurrences have been reported in almost 50% of cases, typically without histological features of malignant progression. Although the time to clinical progression is often long (mean, 6.5 years), relapse may also occur within a few months {990}. The current WHO classification therefore assigns the cerebellar liponeurocytoma to WHO grade II.

Synonyms and historical annotation

In 1978, Bechtel *et al.* {119} reported a case of lipomatous medulloblastoma in a 44-year-old man. Subsequently, 28 more cases were reported. The terms neurolipocytoma {517}, medullocytoma {667}, lipomatous glioneurocytoma {46}, and lipidized mature neuroectodermal tumour of the cerebellum {707} have also been proposed, so as to emphasize the similarity to central neurocytoma and the prognostic difference from the cerebellar medulloblastoma. In accordance with this, the WHO Classification in 2000 {1122} proposed the term 'cerebellar liponeurocytoma' since the label medulloblastoma could lead to unnecessary aggressive adjuvant therapy. This term is now largely accepted and is supported by genetic analyses that indicate that this lesion is not a variant of medulloblastoma

{867}. Clinical, morphological, immunohistochemical, genetic and gene expression data strongly suggest that the cerebellar liponeurocytoma constitutes a rare but distinct clinico-pathological entity {241, 867, 2129}. Tumours with features of liponeurocytoma have also been observed in supratentorial locations; it remains to be shown whether these belong to the same clinico-pathological entity.

Age and sex distribution

In 29 patients with cerebellar liponeurocytoma published to date {23, 237, 867, 1441, 1657, 2300}, the mean age was 50 years (range 24–77 years), with a peak in the third to sixth decade of life. This is in sharp contrast with the age distribution of cerebellar medulloblastomas, more than 70% of which occur in children {885}. There is no significant gender predilection (13 males and 16 females) in patients with cerebellar liponeurocytoma {23, 237, 867, 1441, 1657, 2300}.

Clinical features

Symptoms and signs

Headache and other symptoms and signs of raised intracranial pressure, from either the lesion itself or obstructive hydrocephalus, are the most common presentations. Cerebellar signs referable to the location of the lesion are also frequent {1657}.

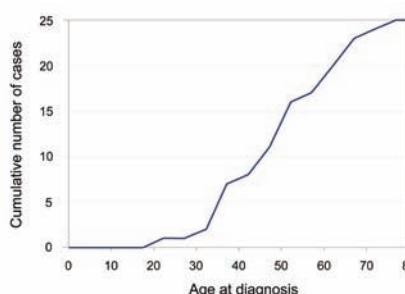


Fig. 6.27 Age distribution of cerebellar liponeurocytoma, based on 25 published cases.

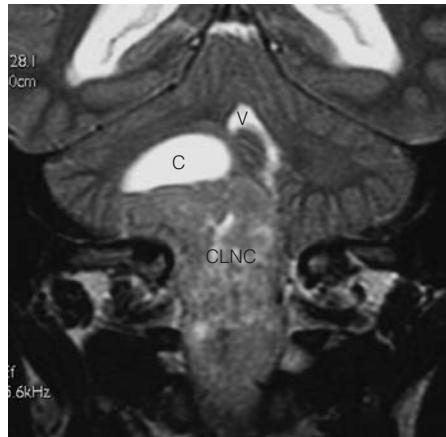


Fig. 6.28 T2-weighted MRI of a cerebellar liponeurocytoma (CLNC) with an adjacent cyst (C) and compression of the fourth ventricle (V).

Neuroimaging

MRI appearance is variable and may be related to the distribution and proportion of lipidized tissue. On T1-weighted MRI, the mass is generally hyperintense but heterogeneous. Hyperintense streaks on T2-weighted images have been associated with the macroscopic appearance of adipose tissue at surgery. Enhancement with gadolinium is usually heterogeneous, with areas of tumour demonstrating variable degrees of enhancement. Associated edema is minimal if present {24}.

Localization

Tumours are predominantly located in the cerebellar hemispheres, followed by a more central location in the vermis. Occasionally, they have been found in the cerebellopontine angle {23, 867}. Several cases resembling liponeurocytomas have been diagnosed in the supratentorial ventricular system, i.e. the typical location of central neurocytomas {1218}. However, these are rare lesions, amounting to approximately 3% of central neurocytomas {1449} while only two cases of cerebellar neurocytomas without adipose component have been reported {211, 520}. In one case, it was shown that the lipid vacuoles progressively accumulate and coalesce within

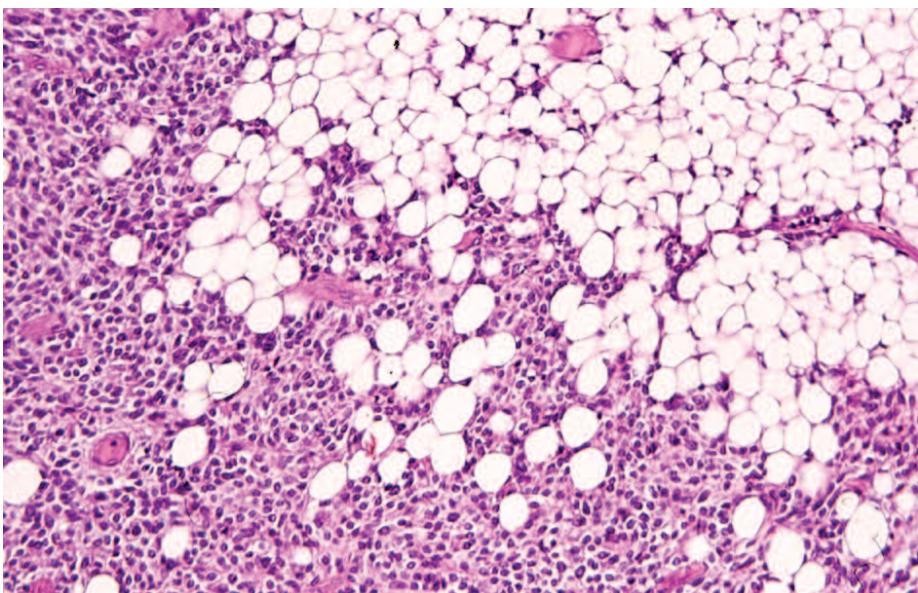


Fig. 6.29 Cerebellar liponeurocytoma with accumulation of adipocytes in a background of small round neoplastic cells.

cells retaining neurocytic features, indicating tumoural lipidization rather than true adipose metaplasia [658]. It remains to be seen whether these observations justify the delineation of central liponeurocytoma as a separate entity [658] and to what degree these lesions share histogenetic and biological characteristics with the cerebellar liponeurocytoma.

Histopathology

Biphasic in appearance, the tumour consists of isomorphic small neuronal cells with the cytology of neurocytes and focal lipomatous differentiation, characterized by lipidized cells resembling mature adipose tissue. Tumour cells have round or oval nuclei and often show a clear cytoplasm resembling neoplastic oligodendrocytes, but also have many morphological similarities to

medulloblastoma and clear cell ependymoma. Despite the cellularity of the lesion, tumour cells have a uniform cytological appearance, with absent or very few mitotic figures.

Immunohistochemistry

Neuronal differentiation is reflected by a consistent, diffuse expression of NSE, synaptophysin and MAP-2. Accordingly, several reported cases were diagnosed as neurocytoma or neuroblastoma rather than medulloblastoma. Focal GFAP expression by tumour cells, indicating astrocytic differentiation, is observed in the majority of cases [2129]. Immunoreactivity for neuronal markers and GFAP is also seen in the adipose cells, indicating an aberrant differentiation of tumour cells rather than an admixture of entrapped adipocytes. It is important to note that xanthomatous histiocytes, as

occasionally observed in ordinary medulloblastomas, are not considered evidence of lipomatous differentiation. Two reports mention additional immunoreactivity to desmin and morphologic features of incipient myogenic differentiation [119, 707].

Differential diagnosis

The most important differential diagnosis is that of medulloblastoma with lipidized cells [689, 1657, 2066]. In these lesions, the adipose tumour cells are usually more diffusely distributed, but may also show the typical clustering seen in the liponeurocytoma [237]. Most importantly, the growth fraction is in the range of 15–40%, which is incompatible with the diagnosis of liponeurocytoma. Cerebellar liponeurocytoma is a neoplasm of adults, while lipidized medulloblastomas also occur in children [689, 1657, 2066]. The distinction between these two lesions is crucial since medulloblastomas with lipidized cells require adjuvant radio/chemotherapy.

The small cell component of liponeurocytomas may also resemble neoplastic oligodendrocytes and clear cell ependymoma [947].

Proliferation

The growth fraction of the small cell component, as determined by the Ki-67/MIB-1 labelling index, is usually in the range of 1–3% but may be as high as 6%, with a mean value of 2.5% [517, 1021, 2129]. In the adipose component, the MIB-1 labelling index is even lower.

Histogenesis

Immunoreactivity to neuronal antigens and GFAP includes cell bodies embracing fat globules. This suggests that the fat-containing cells result from lipomatous differentiation of tumour cells. The cell or

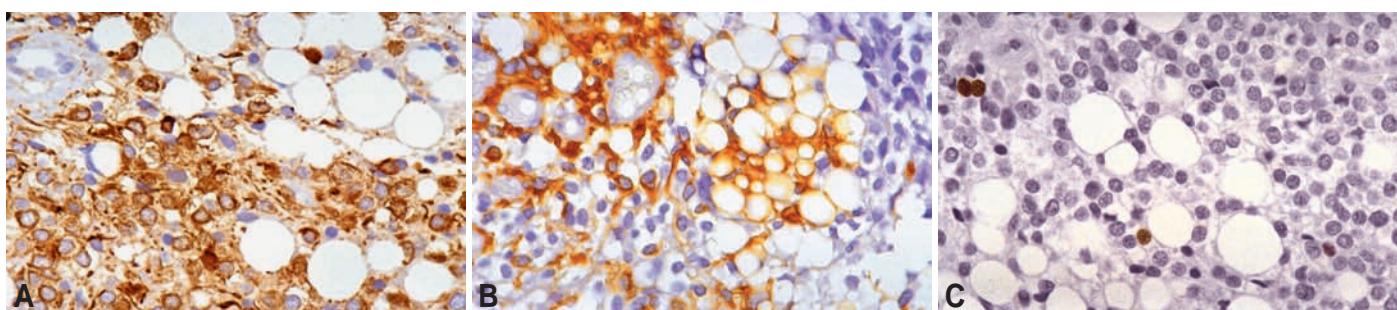


Fig. 6.30 Immunohistochemical features of cerebellar liponeurocytoma. A Small tumour cells and adipocytes focally express the neuronal marker MAP-2 (A) and GFAP (B). C Low MIB-1 labelling index reflecting the slow growth of liponeurocytomas.

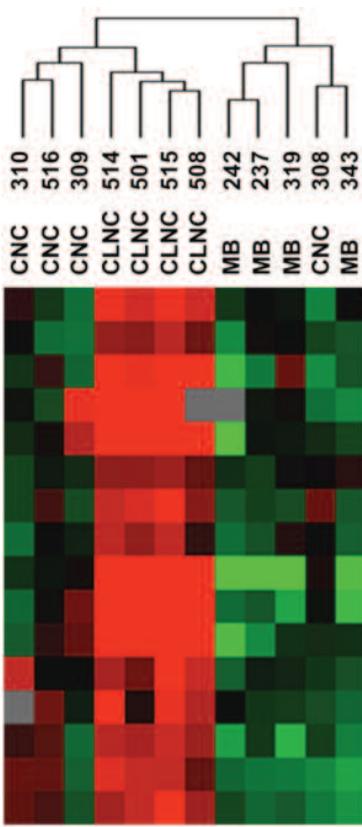


Fig. 6.31 Gene expression pattern of cerebellar liponeurocytomas (CLNCs), central neurocytomas (CNCs), and medulloblastomas (MBs). Cluster analysis suggests a relationship between cerebellar liponeurocytomas and central neurocytomas. Modified from Horstmann *et al.* {867}.

origin is most likely a precursor cell with preferential commitment to neuronal differentiation but a capacity for divergent, i.e. astrocytic and myogenic differentiation. An origin from the external granular layer of the cerebellum cannot be ruled out, although there is no evidence of a relationship to the cerebellar medulloblastoma and the histology as well as age at manifestation would be unusual for an embryonal neoplasm.

Genetics

Genetic analysis of 20 cerebellar liponeurocytomas collected by an international consortium revealed *TP53* missense mutations in 4 cases (20%), a frequency higher than in medulloblastomas (6%) {867}. There was no case with a *PTCH*, *APC*, or β -catenin mutation, each of which can be present in subsets of medulloblastomas. FISH analysis of isochromosome 17q, a genetic hallmark present in 40% of cerebellar medulloblastomas, was not observed in any of the cases investigated. This supports the view that the cerebellar liponeurocytoma is a distinct tumour entity and not a variant of medulloblastoma. cDNA expression profiles showed a relationship to central neurocytoma, but the presence of *TP53* mutations, which are absent in central neurocytomas, suggests they develop through different genetic pathways {867}.

Prognostic and predictive factors

Because of the rarity of this tumour and the lack of systematic follow-up data, survival and recurrence rates must be interpreted with some caution. A review of published cases {23, 867} indicates that this lesion generally carries a favourable prognosis. Of 21 patients with follow-up data, 6 (29%) died within 6 months to 2 years, 5 (24%) died after 2–4 years and 10 (48%) survived 5–16 years after surgical intervention. The 5-year survival rate was 48% and the mean overall survival was 5.8 years.

However, 62% of patients developed a recurrence after periods ranging from 1 to 12 years (mean, 6.5 years) and in 3 patients there was a second relapse 1 to 5 years later (mean, 3 years). Despite being clinically progressive, recurrent liponeurocytomas did not show histological features of malignant progression. Early recurrence may even be associated with a relative increase in the lipomatous component {990}. There was no indication of age or gender affecting clinical outcome. Histopathological features predicting recurrence have not been identified.

Papillary glioneuronal tumour

Y. Nakazato
D. Figarella-Branger
A.J. Becker
B.W. Scheithauer
M.K. Rosenblum

Definition

A relatively circumscribed, clinically indolent and histologically biphasic cerebral neoplasm composed of flat to cuboidal, GFAP-positive astrocytes lining hyalinized vascular pseudopapillae and synaptophysin-positive interpapillary collections of sheets of neurocytes, large neurons and intermediate-sized "ganglionoid" cells.

ICD-O code

The provisional code proposed for the fourth edition of ICD-O is 9509/1.

Grading

Limited experience suggests that papillary glioneuronal tumours behave in a manner corresponding to WHO grade I lesions, but a rare example undergoing late biologic progression has been reported {924}.

Synonyms and historical annotation

The papillary glioneuronal tumour, listed in the 2000 WHO classification as a variant of ganglioglioma, was first established as a distinct clinicopathologic entity by Komori *et al.* in 1998 {1153}. Morphologically similar tumours were previously described under a variety of designations, including pseudopapillary ganglioglioneurocytoma {1154} and pseudopapillary neurocytoma with glial differentiation {1105}.

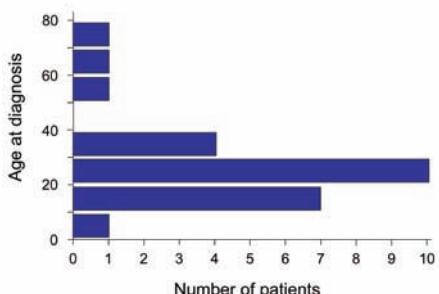


Fig. 6.32 Age distribution of papillary glioneuronal tumour, based on 25 published cases.

Incidence

To date, no population-based epidemiologic data regarding papillary glioneuronal tumour are available. However, they are rare neoplasms; only several dozen have been reported {226, 473}.

Age and sex distribution

These tumours occur over a wide range of ages. No gender predilection has been observed {208, 2273}. The mean age at presentation is 27 years, the oldest being 75 years, and the youngest being 4 years {103, 2273}.

Localization

Papillary glioneuronal tumours generally affect the cerebral hemispheres, with a predilection for the temporal lobe {226, 1153, 1790}. On MR and CT imaging, the tumours appear as demarcated, solid to cystic, contrast-enhancing masses with little mass effect. A cyst-mural nodule architecture may be seen.

Clinical features

Principal manifestations include headache and seizures. Disturbances of vision, gait, sensation, cognition and emotional affect may also be encountered. Haemorrhage as a presentation has been reported {238}.

Macroscopy

These tumours may be solid or often cystic lesions that exert variable, only occasionally considerable mass effect. Calcification may be observed. Haemorrhage and necrosis are rare.

Histopathology

Papillary glioneuronal tumour is characterized by prominent pseudopapillary architecture in which a single or pseudostratified layer of small, cuboidal glial cells with rounded nuclei and scant cytoplasm covers hyalinized blood vessels, as well as interpapillary sheets or focal collections of neurocytes and occasionally ganglion cells and/or medium-sized "ganglionoid cells" {1153}. At the immunohistochemical level,

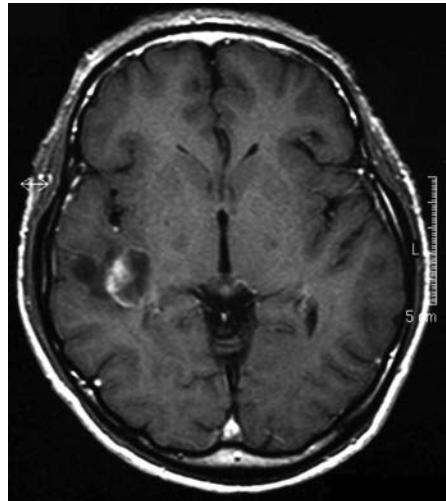


Fig. 6.33 MRI of papillary glioneuronal tumour presenting as a multicystic tumour with a gadolinium-enhanced solid component in the right temporal lobe.

vessels with mural hyalinization are ensheathed by a layer of small uniform, GFAP-positive cells with rounded nuclei and scant cytoplasm. In some cases, Olig2-positive, GFAP-negative glial cells surround this layer {2210}. These glial elements lack both nuclear atypia and mitotic activity. Interpapillary neuronal elements show a considerable variation in size and shape. Any combination of small neurocytes, intermediate-sized ganglionoid cells and large ganglion cells can be found with accompanying neuropil; all are stained with antisera to synaptophysin, NSE and class III β -tubulin {1153, 2210}. The majority of neuronal cells are positive for NeuN, but NFP expression is mostly confined to larger ganglionoid and ganglion cells {1153}. Membranous immunoreactivity for NCAM is also found {2297}, but chromogranin-A expression is lacking. In addition to neuronal elements, mini-gemistocytes with eccentrically placed nuclei and eosinophilic hyaline cytoplasm, showing intense GFAP-immunoreactivity, are occasionally noted in the interpapillary spaces {924, 2210}. Microvascular proliferation or necrosis is exceptional, even in cases with increased

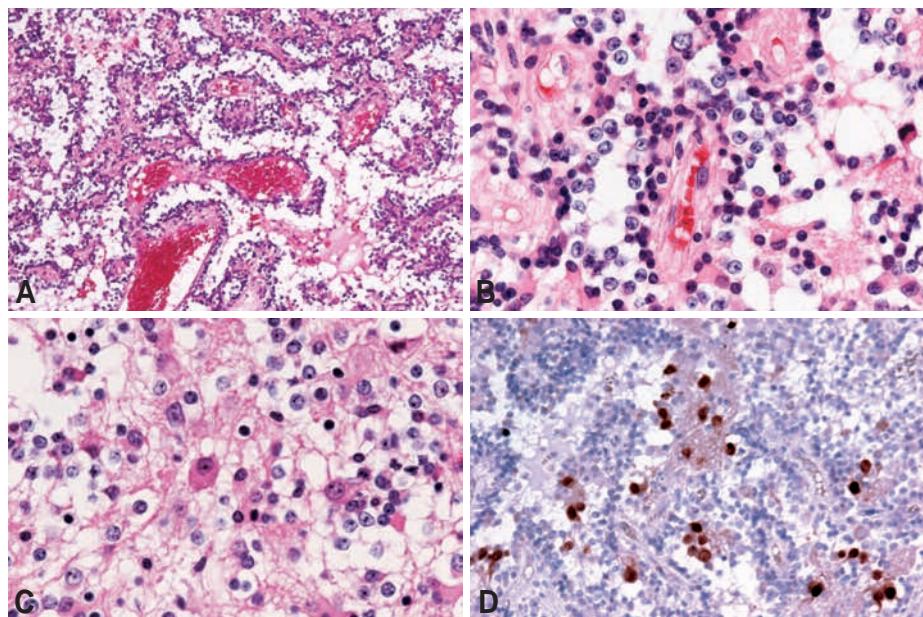


Fig. 6.34 Histological features of papillary glioneuronal tumour. A Layers of tumour cells around vessels, forming pseudopapillary structures. B A pseudopapilla covered by inner cells with hyperchromatic nuclei and outer cells with vesicular nuclei. C Neuronal cells of variable size and oligodendroglia-like cells. D Neuronal cells clearly shown by NeuN immunostaining.

proliferative activity. At the periphery of the lesion, scattered tumour cells are intermingled with gliotic brain tissue containing Rosenthal fibers, eosinophilic granular bodies, hemosiderin pigment, and microcalcifications, the result being a blurred tumour margin.

Electron microscopy

Few papillary glioneuronal tumours have been studied ultrastructurally. Three cell types have been reported, including astrocytic, neuronal and poorly differentiated, possibly glioneuronal progenitor cells [208, 1153]. Astrocytes, some elongate, contain bundles of intermediate filaments and are separated from vessels

exhibiting thick collagen-rich adventitia by a basal lamina. Minigemistocytes and OLIG-2-expressing oligodendrocyte-like cells may also be present [924]. Neurons vary in size; large forms with abundant organelles lie between the papillae, their neuronal processes filled with parallel microtubules, showed terminations containing clear vesicles and occasional synapses. The poorly differentiated cells contain mitochondria, ribosomes, occasional dense bodies, intermediate filaments and microtubules, but no well formed dense core granules. The relative proportion of neuronal and poorly differentiated cells vary from one case to another.

Proliferation

MIB-1 labelling indices are generally low, in the range of 1–2%. Only one tumour featuring minigemistocytes showed an increased (10%) labelling index in that unusual element [924].

Genetic susceptibility

Papillary glioneuronal tumours reported to date have been sporadic in occurrence. No familial or syndrome-associated cases have been reported.

Genetics

In one series of 6 patients, 1p status was studied by FISH but showed no abnormality [2210].

Histogenesis

The histogenesis of papillary glioneuronal tumours is unclear, but an origin from multipotent precursors capable of divergent glioneuronal differentiation is presumed. Paraventricular examples could derive from the subependymal matrix [1153], while more superficially situated papillary glioneuronal tumours might arise from the secondary germinal layer.

Prognostic and predictive factors

The cyst formation, hyalinized vessels, and low proliferative activity are paralleled by a favourable clinical outcome. In most cases, gross total resection without adjuvant therapy results in recurrence-free, long-term survival. Only one example of tumour regrowth has been reported [924].

Rosette-forming glioneuronal tumour of the fourth ventricle

J.A. Hainfellner
B.W. Scheithauer
F. Giangaspero
M.K. Rosenblum

Definition

A rare, slowly growing neoplasm of the fourth ventricular region, preferentially affecting young adults and composed of two distinct histological components, one with uniform neurocytes forming rosettes and/or perivascular pseudorosettes, the other being astrocytic in nature and resembling pilocytic astrocytoma.

ICD-O code

The provisional code proposed for the fourth edition of ICD-O is 9509/1.

Grading

Both the benign histology and favourable postoperative course indicate that rosette-forming glioneuronal tumour (RGNT) corresponds to WHO grade I.

Synonyms and historical annotation

A lesion displaying features of RGNT was the subject of an early report of "dysembryoplastic neuroepithelial tumour (DNT) of the cerebellum" {1216}. Komori *et al.* described RGNT as a distinct entity, a variant of mixed glioneuronal tumour {1155}. Preusser *et al.* confirmed RGNT as a tumour entity {1799}. In 5 independent studies, a total of 17 cases have been reported {33, 952, 1003, 1155, 1799}.

Incidence

RGNT is a rare brain tumour, but population-based incidence rates are not yet available.

Age and sex distribution

The age range at disease manifestation is 12–59 years (mean, 33 years). Current data suggest a slight female predilection.

Localization

RGNTs arise in the midline, occupy the fourth ventricle and/or aqueduct, and may extend to involve adjacent brain stem, cerebellar vermis, pineal gland or thalamus. MR imaging reveals a relatively circumscribed, solid tumour of the fourth ventricular region showing high intensity on T2-weighted images, low intensity on T1, and focal/multifocal gadolinium

enhancement. Secondary hydrocephalus may be seen.

Clinical features

The presentation is most often with headache, a reflection of obstructive hydrocephalus, and/or ataxia. Cervical pain is occasionally experienced. Rare examples are asymptomatic and discovered as incidental imaging findings.

Macroscopy

RGNT involves primarily the cerebellum and wall or floor of the fourth ventricle. An intraventricular component is the rule, occasionally with aqueductal extension.

Histopathology

RGNTs are somewhat demarcated but some infiltration of brain stem and/or cerebellar parenchyma may be seen. They are characterized by a biphasic neurocytic and glial architecture {952, 1155, 1799}. The neurocytic component consists of a uniform population of neurocytes forming neurocytic rosettes and/or perivascular pseudorosettes. Neurocytic rosettes feature ring-like arrays of neurocytic nuclei around delicate eosinophilic neuropil cores. Perivascular

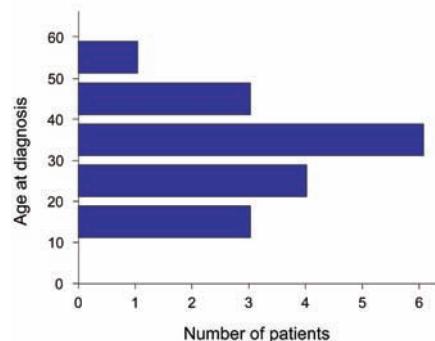


Fig. 6.35 Age distribution of RGNT, based on 17 published cases.

pseudorosettes feature delicate cell processes radiating toward vessels. Both, when viewed longitudinally, may assume columnar arrangement. Neurocytic tumour cells have spherical nuclei with finely granular chromatin and inconspicuous nucleoli, scant cytoplasm and delicate cytoplasmic processes. These neurocytic structures may lie in a partly microcystic, mucinous matrix. The glial component of RGNT typically dominates and in most areas resembles pilocytic astrocytoma. Astrocytic tumour cells are spindle to stellate in shape with elongate to oval nuclei and moderately dense

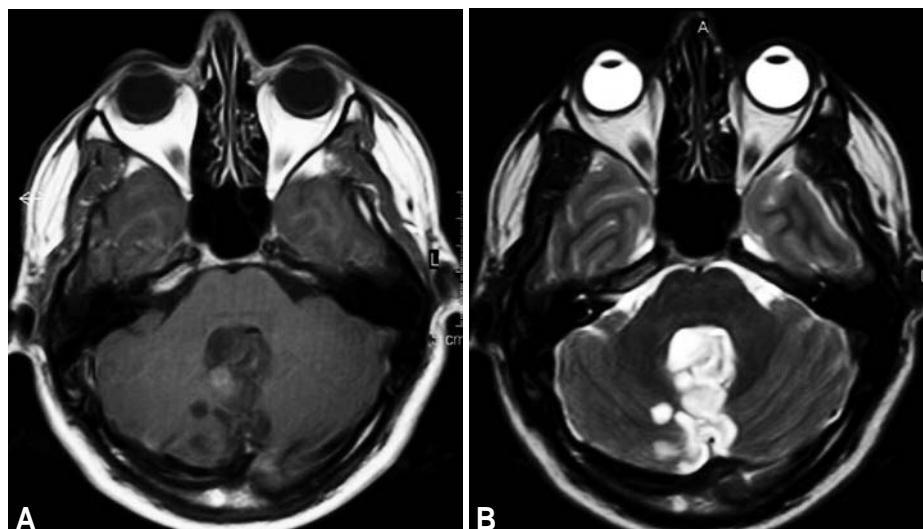


Fig. 6.36 A T1-weighted MR imaging shows low intensity of the tumour mass and focal gadolinium enhancement. B T2-weighted imaging demonstrates a relatively hyperintense, midline tumour, occupying the fourth ventricle and involving cerebellar vermis.

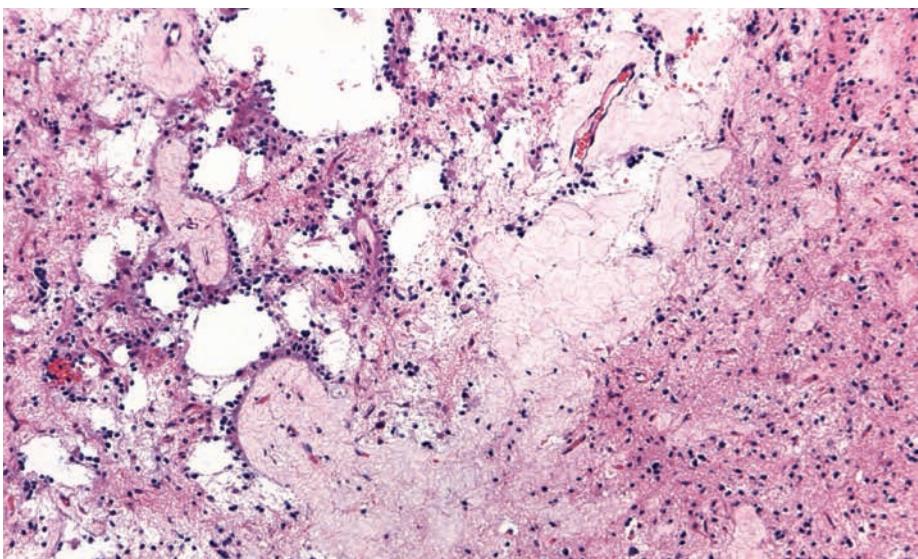


Fig. 6.37 RGNT consists of two components: neurocytic (left) and astrocytic (right).

chromatin. Cytoplasmic processes often form a compact to loosely textured fibrillary background. In areas the glial component may be microcystic, containing round to oval, oligodendroglia-like cells with occasional perinuclear halos. Rosenthal fibers, eosinophilic granular bodies, microcalcifications, and hemosiderin deposits may be encountered. Overall, cellularity is low. Mitoses and necroses are absent. Vessels may be thin-walled and dilated or hyalinized. Thrombosed vessels and glomeruloid

vasculature may also be seen. Ganglion cells are occasionally present, but adjacent, perilesional cerebellar cortex does not show dysplastic changes.

Immunohistochemistry

Immunoreactivity for synaptophysin is present at the centers of neurocytic rosettes and in the neuropil of perivascular pseudorosettes {952, 1155, 1799}. In addition, both cytoplasm and processes of neurocytic tumour cells may express MAP-2 and neuron-specific enolase.

GFAP and S-100 immunoreactivity is present in the glial component, but absent in rosettes and pseudorosettes.

Electron microscopy

Astrocytic cells of the glial component contain dense bundles of glial filaments. Rosette-forming neurocytic cells are intimately apposed and feature spherical nuclei with delicate chromatin, cytoplasm containing free ribosomes, scattered profiles of rough endoplasmic reticulum, prominent Golgi and occasional mitochondria. Cytoplasmic processes, loosely arranged, form the centres of rosettes and contain aligned microtubules as well as occasional dense core granules. Presynaptic specializations may be seen and mature synaptic terminals may form surface contacts with perikarya and other cytoplasmic processes.

Proliferation

Mitoses are absent and Ki-67 labelling indices are low, being less than 3% in reported cases.

Genetic susceptibility

One reported patient with RGNT had a Chiari type I malformation {1155}. No other evidence of an underlying neurologic disorder or association with a familial tumour syndrome has been reported.

Histogenesis

Neuroimaging and histological investigations indicate that RGNTs arise from brain tissue surrounding the infratentorial ventricular system. An origin of RGNT from the subependymal plate, i.e. remnants of the periventricular germinal matrix in the mature mammalian brain, has been suggested {1155}.

Prognostic and predictive factors

The clinical outcome of these essentially benign lesions is favourable in terms of survival, but disabling postoperative deficits have been reported in approximately half of cases.

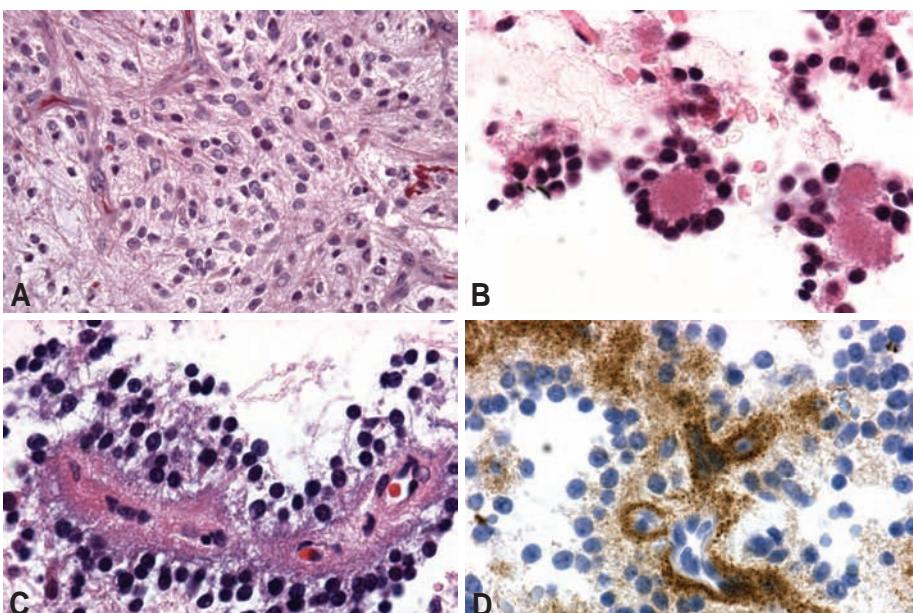


Fig. 6.38 Histological features of RGNT. A Pilocytic astrocytoma component. B Neurocytic rosette: ring-like array of neurocytic tumour cell nuclei around an eosinophilic neuropil core. C Perivascular pseudorosette with delicate cell processes radiating toward a capillary. D Synaptophysin immunoreactivity in the pericapillary area of a perivascular pseudorosette.

Spinal paraganglioma

B.W. Scheithauer
S. Brandner
D. Soffer

Definition

A unique neuroendocrine neoplasm, usually encapsulated and benign, arising in specialized neural crest cells associated with segmental or collateral autonomic ganglia (paraganglia); consisting of uniform chief cells exhibiting neuronal differentiation forming compact nests (Zellballen), surrounded by sustentacular cells and a delicate capillary network; within the central nervous system, primarily affecting the cauda equina/filum terminale region.

ICD-O code 8680/1

Grading

Paragangliomas of the filum terminale correspond histologically to WHO grade I.

Synonyms and historical annotation

The terminology surrounding paragangliomas is confusing. Early authors divided them into chromaffin and non-chromaffin on the basis of their reaction with chromic acid. However, since this reaction does not reliably reflect their functional activity, current terminology is based upon anatomic site, e.g. carotid body paraganglioma (chemodectoma), jugulotympanic paraganglioma (glomus jugulare tumour), etc. Usually, a descriptor of functional status is also appended, i.e. "functional" or "non-functional."

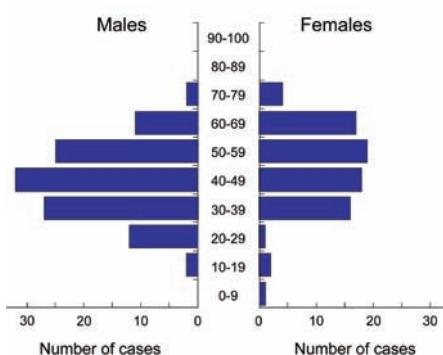


Fig. 6.39 Age and sex distribution of paraganglioma (spinal), based on 71 published cases.

Incidence and location

Paragangliomas of the CNS are uncommon. The vast majority present as spinal intradural tumours in the cauda equina region. Since the first description of cauda equina region paraganglioma in 1970 {1473}, more than 210 cases have been reported. For a complete list of 174 cases reported prior to 2003, see Gelabert-Gonzalez {656}. Altogether, paragangliomas of the cauda equine region comprise 3.4% to 3.8% of all tumours affecting this region {2420, 2461}. Other spinal levels are far less often involved; 14 paragangliomas were reported in the thoracic region, most being extradural with an intravertebral and paraspinal component {374, 2232} and 2 tumours involved the cervical region {174, 2177}. Intracranial paragangliomas are usually extensions of jugulotympanic paragangliomas {946}. However, rare examples of purely intracranial tumours have also been described. These include tumours of the sellar region {1549}, the cerebellopontine angle {443} and examples in cerebellar parenchyma {1794}, the fronto-temporal lobes {1857}, a functional paraganglioma of the temporo-parietal dura occurring 23 years after an adrenal phaeochromocytoma {1459} and one questionable pineal example {2117}.

Age and sex distribution

Cauda equina paragangliomas generally affect adults, their peak incidence being in the fourth through the sixth decades. Patient age ranges from 9 to 74 years (mean, 46 years), with a slight predominance in males (M:F 1.4:1). Jugulotympanic paragangliomas are more common in Caucasians, show a strong female predilection and occur mainly in the fifth and sixth decades {946}.

Clinical features

Symptoms and signs

As with other spinal tumours, cauda equina paragangliomas exhibit no distinctive clinical features. Most common presenting symptoms include a few-year

history of low-back pain and sciatica. Sensory deficit, paraparesis and sphincter disturbances are infrequent, and full-blown cauda equina syndrome is uncommon. An unusual presentation is intracranial hypertension, a feature reported in 8 cases {94, 656, 1983}. Only 3 endocrinologically functional paragangliomas of the cauda equine region have been reported {656}. The few reported paragangliomas of the thoracic spine presented with signs of spinal cord compression, one example being functional {982}. About 36% of glomus jugulare paragangliomas extend into the cranial cavity {946}. These most often present with pulsatile tinnitus and lower cranial nerve dysfunction {946}; signs of catecholamine secretion may be seen.

Neuroimaging

Radiographically, cauda equina paragangliomas lack specific features {1303, 2461}. Most appear as isodense, homogeneously enhancing masses on computed tomography (CT). However,



Fig. 6.40 MRI of a paraganglioma of the cauda equina with a cystic component.

since CT without contrast may miss the lesion, magnetic resonance (MR) imaging is the procedure of choice. MR images typically show a sharply circumscribed, occasionally partly cystic mass that is hypo- or isointense to spinal cord on T1-weighted images, markedly contrast-enhancing and hyperintense on T2-weighted images. The presence of serpentine, congested, ecstatic vessels and of a low signal intensity rim ("cap sign") on T2-weighted images are considered diagnostically helpful clues {1303, 2461}. Plain X-rays are usually non-informative, but rarely show erosion (scalloping) of vertebral laminae due to chronic bone compression.

Macroscopy

Cystic components may be found. An occasional tumour penetrates dura to invade bone. Most paragangliomas of the cauda equina are entirely intradural and are attached either to the filum terminale or less often to a caudal nerve root. As a rule, paragangliomas are oval to sausage-shaped, delicately encapsulated, soft, red-brown and measure 1.5 to 13 cm. Capsular calcification may be encountered.

Histopathology

Tumours are well-differentiated, resembling normal paraganglia, composed of chief (type I) cells disposed in nests or lobules (Zellballen), surrounded by an inconspicuous, single layer of sustentacular (type II) cells. The Zellballen are surrounded by a delicate capillary network that may undergo sclerosis. The uniform round or polygonal chief cells possess central, round-to-oval nuclei with finely stippled chromatin and inconspicuous nucleoli. Degenerative nuclear pleomorphism ("endocrine anaplasia") is generally mild. Cytoplasm varies somewhat in quantity and is usually eosinophilic and finely granular. In some instances, it is amphophilic or clear. Sustentacular cells are spindle-shaped. Encompassing the lobules, their long processes are often so attenuated as to be undetectable by routine light microscopy and visible only on immunostains for S-100 protein. Nearly half of cauda equina paragangliomas contain mature ganglion cells, as well as cells transitional between chief and ganglion cells {256}. Such "gangliocytic paragangliomas" are also found in the duodenum and are

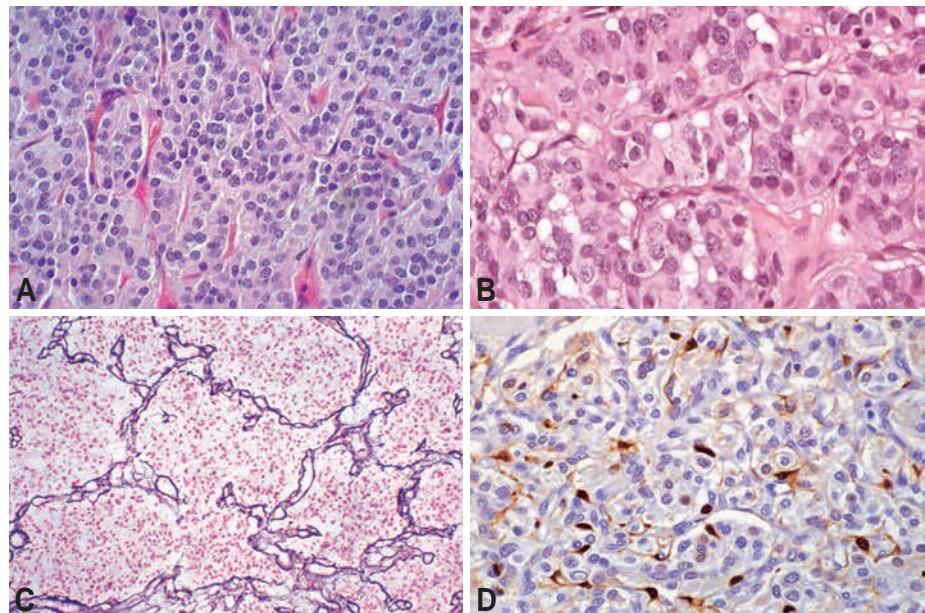


Fig. 6.41 Histological features of paraganglioma. A,B Typical Zellballen architecture. C Reticulin stain showing the septae delineating Zellballen. D Sustentacular cells identified by immunoreactivity to S-100.

analogous to phaeochromocytoma with neuronal differentiation. Some paragangliomas of the cauda equina region show architectural features reminiscent of carcinoid tumours, including angiomatous, adenomatous and pseudorosette patterns {2124}. Tumours composed predominantly of spindle {1520} and melanin-containing cells (melanotic paragangliomas) {638, 1520} have also been described at this site, as has oncocytic paraganglioma {1678}. Foci of haemorrhagic necrosis may occur and scattered mitotic figures can be seen. Neither these features nor nuclear pleomorphism are of prognostic significance {2124}.

Immunohistochemistry

Markers permit the identification of both chief and sustentacular cells. Neuron-specific enolase (NSE), although a sensitive marker of chief cells, lacks specificity, but synaptophysin and chromogranin {1132, 2124} are sensitive and reliable. Chromogranin A reactivity parallels the Grimelius (argyrophil) reaction {256}. Neurofilament proteins are also useful markers of chief cells. Expression of serotonin (5H-T) and of various neuropeptides (somatostatin, leu and metenkephalin) has been demonstrated in paraganglioma of the cauda equina region {1520, 2124}. Paranuclear cytokeratin immunoreactivity is particularly

prominent in cauda equina examples {330}. Sustentacular cells are uniformly reactive for S-100 protein and usually show staining for glial fibrillary acidic protein (GFAP) as well. Chief cells may also show variable S-100 immunoreactivity.

Electron microscopy

The distinctive ultrastructural feature of chief cells is the presence of dense core (neurosecretory) granules measuring 100 to 400 nm (mean, 140 nm) {531}. Depending on their cytoplasmic electron density, "light" and "dark" chief cells are recognized. Both feature interdigititation of cell processes and rudimentary junctions. A layer of basal lamina is present at the interface of Zellballen and surrounding stroma. In addition to well-developed Golgi, extensive smooth endoplasmic reticulum and lysosomes, chief cells may contain numerous atypical mitochondria as well as paranuclear whorls of intermediate filaments {531,2124}. Cytoplasmic crystalloids, hexagonal or quadrilateral in configuration and non-membrane-bound, are rarely seen {2469}. Sustentacular cells are characterized by an elongated nucleus with marginal chromatin, increased cytoplasmic electron density, relative abundance of intermediate filaments, and lack of dense core granules {531, 2124}.

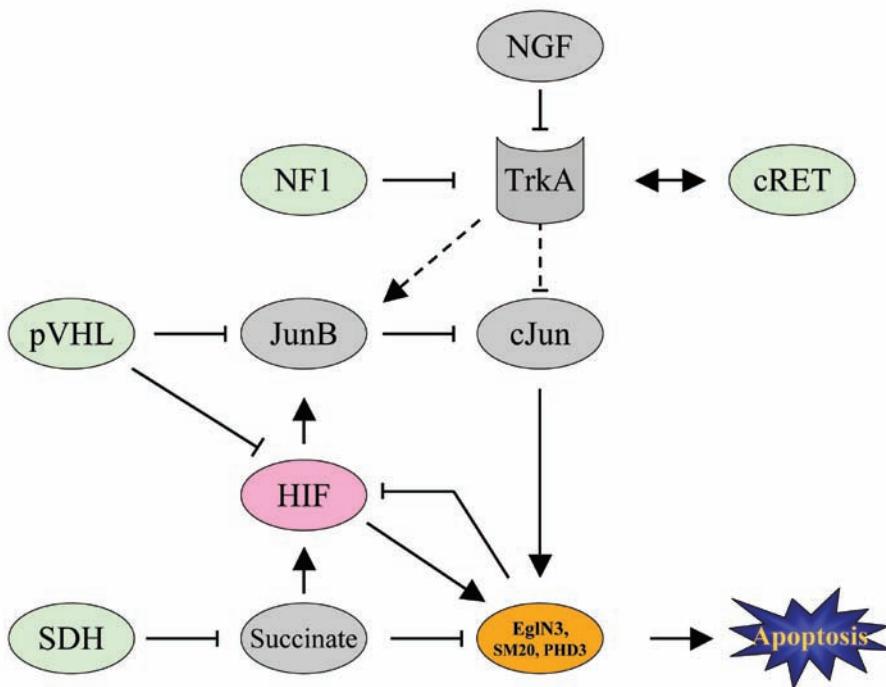


Fig. 6.42 Molecular pathways likely involved in paraganglioma pathogenesis. Mutant VHL fails to inhibit JunB, which would antagonize c-Jun. RET, which is the receptor for glial derived neurotrophic factor (GDNF), and NF1 act on the same pathway by modulating the NGF receptor TRK A, which all interact downstream with PHD, HIF-PH or Egln3 enzymes that hydroxylate HIF1- α . Mutations of *cRET*, *NF1*, *VHL* and *SDH* decrease apoptosis during development, when NGF levels become limiting. Apoptosis is mediated by Egln3, SM20 and PHD3. Adapted from Maxwell P. {1420A}.

Genetics

Systemic paragangliomas may be multifocal but to date there has been no reported association of cauda equina or other spinal paragangliomas. The concurrence of spinal paraganglioma with brain tumours {272, 373}, spinal epidural haemangioma {2398}, syringomyelia {2146} and intramedullary cysts {550} are notable, but these associations may be coincidental.

Several autosomal dominant inherited syndromes predispose to paraganglioma or phaeochromocytoma: von Hippel-Lindau disease (VHL), multiple endocrine neoplasia type 2 (*RET* mutations), neurofibromatosis type 1 (*NF1*) and mutations in subunits B, C, or D of the succinate dehydrogenase genes (*SDHB*, *SDHC*, *SDHD*) which form part of mitochondrial complex II. Multiple,

benign, head and neck paragangliomas are often caused by *SDHD* mutations while *SDHB* mutations are associated with phaeochromocytoma. To date, only four families with *SDHC* mutation have been identified.

Spinal paragangliomas are considered non-familial, but a study of 22 spinal paraganglioma showed an *SDHD* germline mutation in one patient with recurrent spinal paraganglioma and a cerebellar metastasis {1411}.

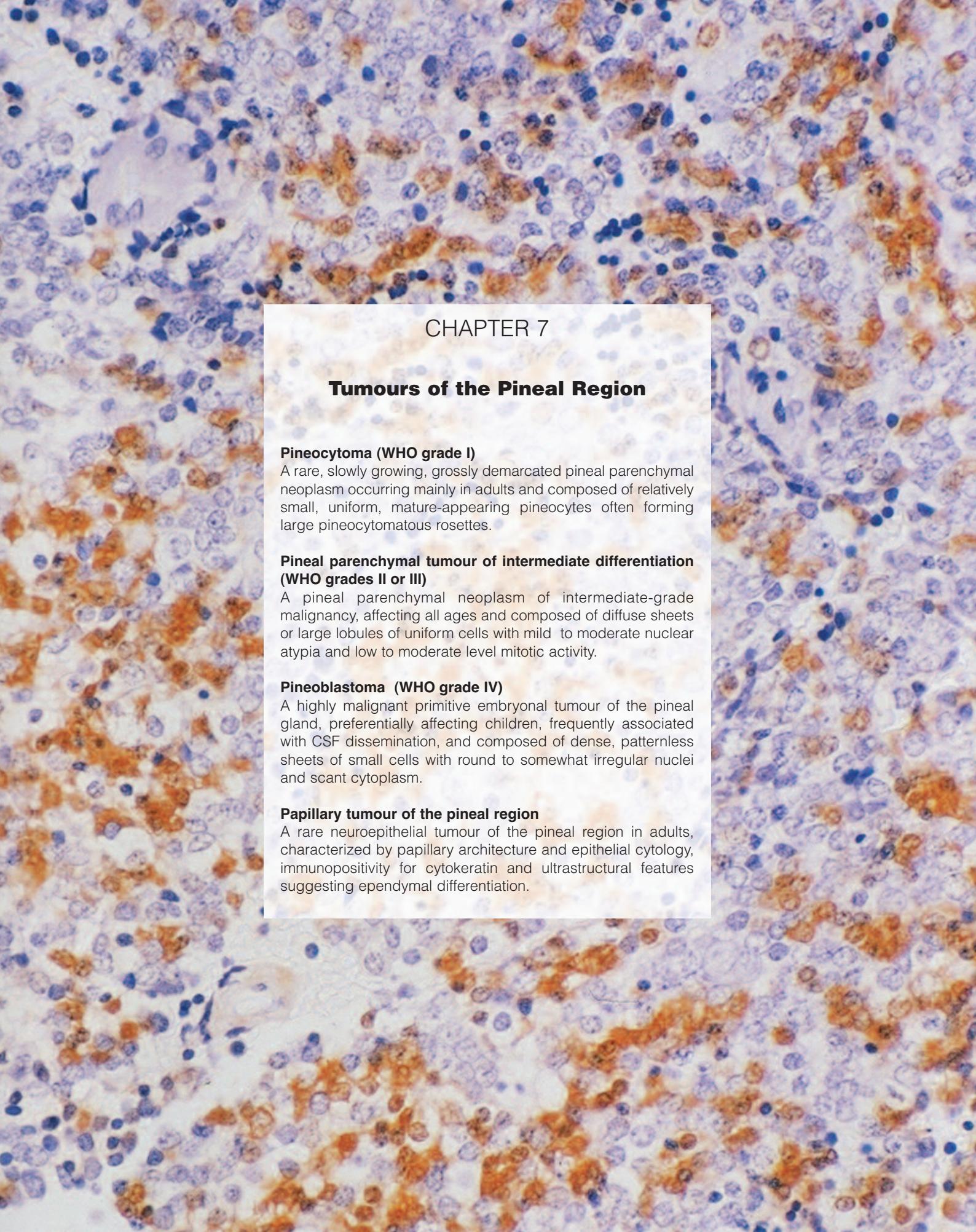
Histogenesis

The histogenesis of cauda equina paraganglioma is a matter of debate. Despite the fact that such cells have not been identified at this site, some authors favour an origin from paraganglion cells associated with regional autonomic nerves and blood vessels {1331}. Others

have suggested that peripheral neuroblasts normally present in the adult filum terminale undergo paraganglionic differentiation {272, 1959}. Jugulotympanic paragangliomas presumably arise from microscopic paraganglia within the temporal bone {1247}. Of interest, although perhaps not relevant to histogenesis, are reports of the coexistence of a paraganglioma and myxopapillary ependymoma in the cauda equina region {1071} and a biphasic tumour consisting primarily of paraganglioma and, to a lesser extent, ependymoma {272}.

Prognostic and predictive factors

Tumour location is often more relevant than histology in determining the prognosis of paragangliomas {1133}. For example, the metastasis rate of para-aortic paraganglioma is high (28 to 42%), whereas that of carotid body tumours is only 2 to 9% {1133}. Nearly half of the glomus jugulare tumours recur locally {1248} but only 5% metastasize {1247}. Several studies have demonstrated a correlation of MIB-1 labelling and malignant behaviour in phaeochromocytoma {231, 358}. In contrast, tumour vascularity is of no significance {1630}. The vast majority of cauda equina paragangliomas are slowly growing and curable by total excision. Based on long-term follow-up, it is estimated that 4% will recur following gross total removal {2164}. CSF seeding of spinal paragangliomas has occasionally been documented {373, 1901, 2164, 2239}. Metastasis outside the CNS (bone) has been reported only once {1520}. Although it is not possible to predict the biological behaviour of cauda equina paraganglioma on the basis of histologic criteria alone, truly anaplastic and metastasizing extraneuronal paragangliomas have been shown to be either devoid or markedly depleted of sustentacular cells {1132, 1133}. One case report of a recurring and metastasising spinal paraganglioma has confirmed this finding {2239}.



CHAPTER 7

Tumours of the Pineal Region

Pineocytoma (WHO grade I)

A rare, slowly growing, grossly demarcated pineal parenchymal neoplasm occurring mainly in adults and composed of relatively small, uniform, mature-appearing pineocytes often forming large pineocytomatous rosettes.

Pineal parenchymal tumour of intermediate differentiation (WHO grades II or III)

A pineal parenchymal neoplasm of intermediate-grade malignancy, affecting all ages and composed of diffuse sheets or large lobules of uniform cells with mild to moderate nuclear atypia and low to moderate level mitotic activity.

Pineoblastoma (WHO grade IV)

A highly malignant primitive embryonal tumour of the pineal gland, preferentially affecting children, frequently associated with CSF dissemination, and composed of dense, patternless sheets of small cells with round to somewhat irregular nuclei and scant cytoplasm.

Papillary tumour of the pineal region

A rare neuroepithelial tumour of the pineal region in adults, characterized by papillary architecture and epithelial cytology, immunopositivity for cytokeratin and ultrastructural features suggesting ependymal differentiation.

Pineocytoma

Y. Nakazato
A. Jouvet
B.W. Scheithauer

Definition

A rare, slowly growing, grossly demarcated pineal parenchymal neoplasm occurring mainly in adults and composed of relatively small, uniform, mature-appearing pineocytes often forming large pineocytomatous rosettes.

ICD-O code 9361/1

Grading

Pineocytomas correspond histologically to WHO grade I {1010, 1014}.

Incidence, age and sex distribution

Pineal region tumours account for less than 1% of all intracranial neoplasms, of which approximately 14–27% are of pineal parenchymal origin {1163, 1841}. Of these, based upon previous criteria, pineocytomas represent 14–60%. Pineocytomas occur throughout life, but most frequently affect adults (mean age: 38 years) {199, 337, 818, 1014, 1452, 1480, 1841, 2031, 2456}. There is no sex predilection.

Localization

Pineocytomas typically remain localized to the pineal area where they compress adjacent structures, including the cerebral aqueduct, brain stem and cerebellum. Protrusion into the posterior third ventricle is often seen.

Clinical features

Symptoms and signs

Clinically, it is not possible to differentiate pineocytoma from other pineal region lesions. Signs and symptoms vary, and relate to increased intracranial pressure, neuro-ophthalmologic dysfunction (Parinaud syndrome), changes in mental status, brain stem dysfunction, or cerebellum as well as hypothalamic-based endocrine abnormalities {199, 337, 851, 1014, 1163, 1841, 2031}. The majority of patients exhibit neuro-ophthalmologic signs, particularly Parinaud syndrome {337, 554, 851, 1163}. In rare cases, the presentation may be with intratumoural haemorrhage ("pineal apoplexy") {851}.

Neuroimaging

On CT scans, pineocytomas are usually globular, demarcated masses, measuring less than 3 cm in diameter. They appear hypodense and homogeneous, but some show peripheral calcification or occasional cystic changes {333, 2031}. Most tumours exhibit homogeneous contrast enhancement. Accompanying hydrocephalus is a common feature {1561}. On MRI, the tumours tend to be low or isointense on T1 and hyperintense on T2-weighted images with strong, homogeneous contrast enhancement {1169, 1561}.

Macroscopy

Pineocytomas are well-circumscribed lesions with a grey-tan, homogeneous or granular cut surface {199, 818}. Degenerative changes, including cyst formation and foci of haemorrhage may be present {1452}.

Histopathology

Pineocytoma is a well-differentiated, moderately cellular neoplasm composed of relatively small, uniform, mature cells resembling pineocytes. It grows primarily in sheets or ill-defined lobules, and often also features large pineocytomatous rosettes composed of abundant, delicate tumour cell processes.

The majority of nuclei are round-to-oval with inconspicuous nucleoli, and finely dispersed chromatin. Cytoplasm is moderate in quantity and homogeneously eosinophilic. Processes are conspicuous



Fig. 7.02 Pineocytoma showing rounded contours and homogeneous enhancement on a T1-weighted MRI.

and short, often ending in club-shaped expansions that are optimally demonstrated on neurofilament, Bodian or Bielschowsky stains. Mitotic figures are lacking in all but occasional large specimens (fewer than 1/10 HPF) {1014}. Pineocytomatous rosettes vary in number and size, their anucleate centres being composed of delicate, enmeshed cytoplasmic processes resembling neuropil {199, 1014, 1608, 2031}. Nuclei surrounding the periphery of the rosette are not regimented. In some pineocytomas, large ganglion cells and/or multinucleated giant cells with bizarre nuclei are seen {199, 818, 1221, 1452, 2031}. Mitotic activity of this pattern is still low in spite of their ominous nuclear appearances. The stroma of pineocytoma consists of a delicate network of vascular channels lined by a single layer of endothelial cells and supported by scant reticulin fibers. Microcalcifications are occasionally seen.

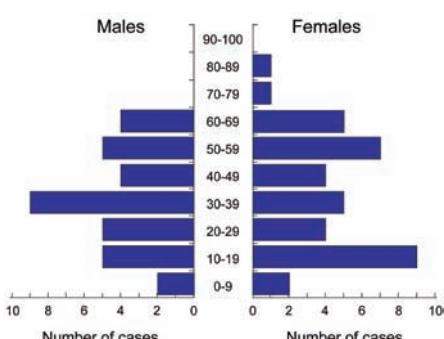


Fig. 7.01 Age and sex distribution of pineocytoma based on 72 cases.

Immunohistochemistry

Pineocytoma cells usually show strong immunoreactivity for synaptophysin, NSE and NFP. Also reported is variable staining for other neuronal markers, including class III β-tubulin, tau protein, PGP 9.5, chromogranin and the neuropeptide serotonin {363, 1012, 1014, 1221, 1608, 2456}. Photosensory differentiation is associated with immunoreactivity for retinal S-antigen and rhodopsin {1452,

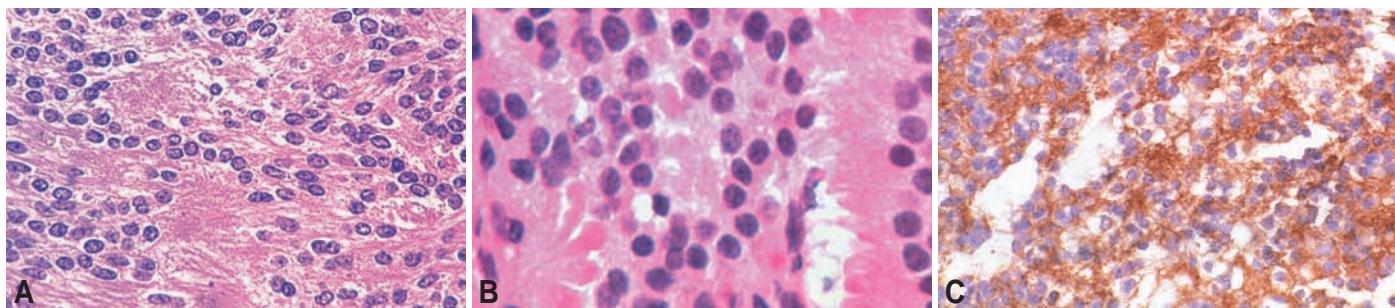


Fig. 7.03 Histological features of pineocytoma. A Pineocytomatous rosettes with nucleus-free spaces filled with a fine meshwork of cell processes. B High magnification shows tumour cells with irregular hyperchromatic nuclei and prominent processes with bulbous extensions. C Diffuse staining for synaptophysin.

1608, 1716}. In tissue culture, pineocytoma cells are also capable of synthesizing serotonin and melatonin {574}.

Electron microscopy

Pineocytomas are composed of clear and varying numbers of dark cells joined with zonulae adherentes {787, 818, 1012, 1480}. Cells extend tapering processes which occasionally terminate in bulbous ends. Their cytoplasm is relatively abundant and contains well-developed organelles, including smooth and rough endoplasmic reticulum, Golgi complex, mitochondria, multivesicular bodies and lysosomes. Pineocytoma cells share numerous ultrastructural features with normal mammalian pineocytes, such as paired twisted filaments {785, 1012}, annulate lamellae {787}, 9+0 cilia {787, 1012, 1480}, microtubular sheaves {787, 1012}, fibrous bodies {787, 1012}, vesicle-crowned rodlets {787, 818, 1012, 1480}, heterogeneous cytoplasmic inclusion {787}, membrane whorls {787, 1012} and mitochondrial as well as centriolar clusters {1012}. Membrane-bound, dense-core granules and clear vesicles are present in both cytoplasm and cellular processes, the latter showing occasional synapse-like junctions {787, 818, 1012, 1480}.

Genetics

Cytogenetic studies have suggested that monosomy or loss of chromosome 22, deletions in the distal 12q region, and

partial deletion or loss of chromosome 11 are related to tumour progression {130, 1821}. A relationship between the *RB1* gene and pineocytoma has not been established. A microarray analysis of pineocytoma has shown high-level expression of genes coding for enzymes related to melatonin synthesis (*TPH1*, *H1OMT*), and also genes involved in retinal phototransduction (*OPN4*, *RGS16*, *CRB3*), such reactivities indicating bi-directional neurosecretory and photosensory differentiation {572}.

Histogenesis

The histogenesis of pineal parenchymal tumours is linked to the pineocyte, a cell with photosensory and neuroendocrine functions. The ontogeny of the human pineal gland recapitulates the phylogeny of the retina and the pineal organ {1481}. During late stages of intrauterine life and

the early post-natal period, the human pineal gland consists primarily of cells arranged in rosettes similar to those of the developing retina. These feature abundant melanin pigment as well as cilia with a 9+0 microtubular pattern. By the age of three months, the number of pigmented cells gradually decreases so that pigment becomes undetectable by histochemical methods {1481}. As differentiation progresses, cells strongly immunoreactive for NSE accumulate. By postnatal age one year, pineocytes predominate. To a variable extent, pineal parenchymal tumours mimic the developmental stages of the human pineal gland.

Prognostic and predictive factors

The clinical course of pineocytomas is characterized by a lengthy interval (4 years in one series) between the onset of symptoms and surgery {199}. In series of strictly classified tumours, no pineocytomas have been shown to metastasize {554, 2030}. The 5-year survival rate of pineocytoma patients has ranged from 86% {2030} to 100% {554}, there being no relapses following gross total resection {554}. The prognosis of patients with pineocytomas with divergent differentiation, including glial, neuronal and retinoblastic elements, appears to be similar to that of conventional pineocytomas {1452}.

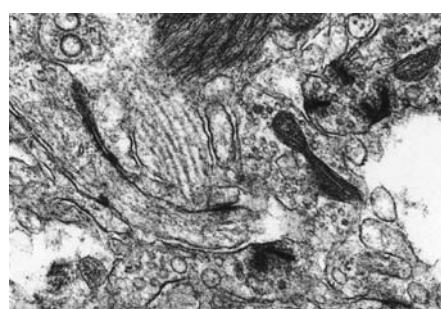


Fig. 7.04 Electron micrograph of pineocytoma. Terminal cell processes show synaptic vesicles and rods.

Pineal parenchymal tumour of intermediate differentiation

Y. Nakazato
A. Jouvet
B.W. Scheithauer

Definition

A pineal parenchymal neoplasm of intermediate-grade malignancy, affecting all ages and composed of diffuse sheets or large lobules of uniform cells with mild to moderate nuclear atypia and low- to moderate-level mitotic activity. Without justification, the few rare tumours showing coexistent patterns of both pineocytoma and pineoblastoma have occasionally been included in this category.

ICD-O code 9362/3

Grading

Pineal parenchymal tumour of intermediate differentiation (PPTID) may correspond to WHO grade II or III, but definite grading criteria have yet to be established.

Synonyms and historical annotation

The category of PPTID {1012, 1480, 2031} first introduced by Schild *et al.* in 1993 has since come to include mixed pineocytoma/pineoblastoma, and tumours such as "malignant pineocytomas" {818} and "pineoblastomas with lobules" {199}. This has obscured the value of the designation, and is not recommended terminology.

Incidence

PPTID comprises at least 20% of all pineal parenchymal tumours. The reported incidence of 0% to 60% reflects the

frequent misdiagnosis of this pineal parenchymal tumour and/or the inclusion of mixed pineocytoma-pineoblastoma and other unusual pineal parenchymal tumours.

Age and sex distribution

PPTID occurs at all ages, including childhood to adult life, with a peak incidence in early adults (mean; 38 years; range, 1–69) {851, 1014, 1452, 2031}. There is a slight female preponderance.

Clinical features

The presentation of PPTID, the largest subgroup of pineal parenchymal tumours {1014}, is like that of pineocytoma, i.e. combinations of increased intracranial pressure, Parinaud's syndrome, ataxia and occasional diplopia. When defined according to histologic pattern {2031}, it is clear that cerebrospinal metastases occur in a minority.

Macroscopy

The gross appearance PPTID is similar to that of pineocytoma. The tumours are circumscribed, soft in texture and lacking gross evidence of necrosis.

Histopathology

PPTID are either diffuse (neurocytoma-like) or somewhat lobulated tumours characterized by moderately high cellularity, mild to moderate nuclear atypia, and low to moderate mitotic activity. Preliminary studies suggest that tumours corresponding to grades II and III can be distinguished on the basis of mitotic activity and neurofilament protein immunoreactivity {554, 1014}. PPTID include transitional cases in which typical pineocytomatous areas are associated with a diffuse pattern. Occasional giant cells, Homer Wright rosettes or ganglion cells may infrequently be seen.

Immunohistochemistry shows synaptophysin and neuron-specific enolase positivity {1012, 1014, 1608}. Variable labelling is also seen with antibodies to neurofilament protein, chromogranin A, retinal S-antigen and S-100 protein {1012, 1014, 1608, 2276, 2456}.

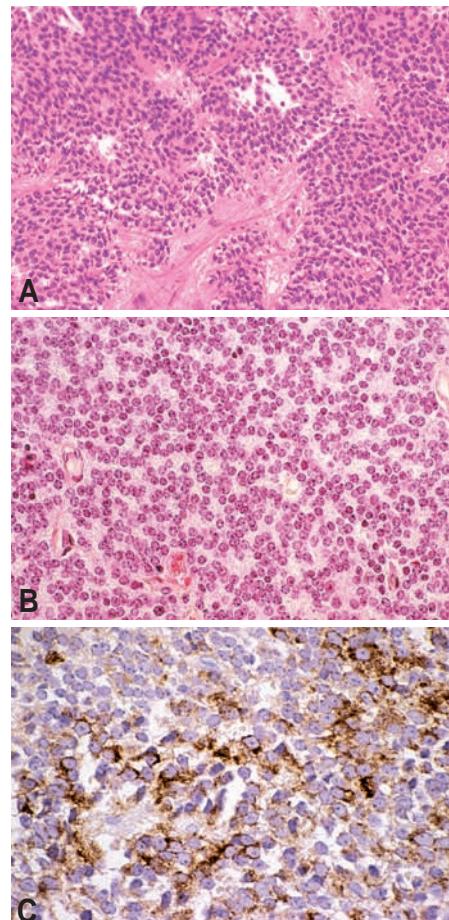


Fig. 7.06 A Highly cellular pineal parenchymal tumour of intermediate differentiation. Note the absence of rosettes and the tendency to form nucleus-free perivascular spaces. B Moderate cellularity, nuclear pleomorphism, and formation of small rosettes. C Focal chromogranin staining of a pineal parenchymal tumour of intermediate differentiation.

Proliferation

PPTID is a potentially aggressive neoplasm. Reflecting the difficulty encountered in making the diagnosis, often in a small biopsy, is the wide range of reported mitotic indices in a large published series, being 0/10 HPF in 58%, 1–2 in 28%, 3–6 in 14%, and rarely higher {1014}. Similarly, the mean MIB-1 labelling index reportedly ranges from 3 to 10% {1608, 1883, 2276}.

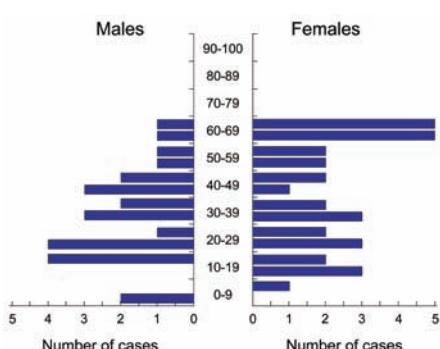


Fig. 7.05 Age and sex distribution of PPTID, based on 58 cases.

Genetics

By comparative genomic hybridization, frequent chromosomal changes have been identified in pineal parenchymal tumours. An average of 3.3 gains and 2 losses has been noted {1883}. The most common chromosomal imbalances in PPTID are +4q, +12q, and -22. In a real-time RT-PCR analysis, the expression of 4 genes (*PRAME*, *CD24*, *POU4F2* and *HOXD13*) in PPTID is distinctly high, almost the same level as in pineoblastoma, and in contrast to the low expression of these genes in pineocytoma {572}.

Histogenesis

Strong evidence indicates that pineal parenchymal tumours arise from pineocytes or their precursor cells. The close kinship among pineocytoma, PPTID and pineoblastoma is supported by a number of shared clinical, morphologic and genetic features {572, 1012, 1014, 1452, 1480, 1608, 2031}. The very occurrence of rare mixed tumours (pineocytoma-pineoblastoma) confirms the existence of a spectrum from pineocytoma through PPTID to pineoblastoma.

Prognostic and predictive factors

The five-year survival of patients with PPTID is 39% to 74% {554}. Only very occasional examples of PPTID are associated with central nervous system or extraneuronal metastases {2031}. One series found the first relapse to be local in 22% and spinal-leptomeningeal in 4% {554}. Factors affecting the survival of pineal parenchymal tumours are morphological subtype as well as histologic grading according to presence or absence of necrosis, mitotic index and NFP immunostaining {1014}.

Pineoblastoma

Y. Nakazato
A. Jouvet
B.W. Scheithauer

Definition

A highly malignant primitive embryonal tumour of the pineal gland, preferentially affecting children, frequently associated with CSF dissemination, and composed of dense, patternless sheets of small cells with round to somewhat irregular nuclei and scant cytoplasm.

ICD-O code 9362/3

Grading

Pineoblastomas correspond histologically to WHO grade IV.

Incidence

Pineoblastomas are rare, comprising approximately 40% of all pineal parenchymal tumours.

Age and sex distribution

They may occur at any age, but most present in the first two decades of life (mean age, 18.5 years) with a distinct predilection for children {818, 851, 1010, 1014, 1452, 2456}. No gender preference is apparent.

Clinical features

Symptoms and signs

The clinical presentation of pineoblastoma is similar to that of other tumours of the pineal region. The interval between initial symptoms and surgery may be shorter than one month {199}. Median post-surgical survivals vary from 24 to 30 months {818, 1452}.

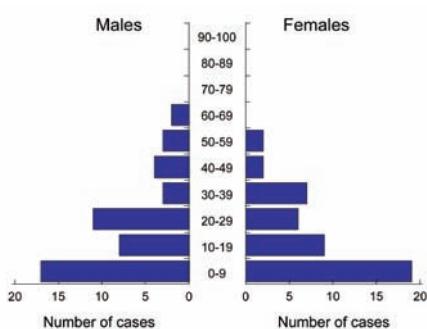


Fig. 7.07 Age and sex distribution of pineoblastoma based on 93 cases.

Neuroimaging

In contrast to pineocytoma, the CT appearance of pineoblastoma is that of a large, lobulated or poorly-demarcated, homogeneous mass, which is hyperdense after contrast enhancement. Calcification is infrequent. On T1-weighted MRI scan, pineoblastomas are hypo-to isointense, but they show heterogeneous contrast enhancement {333, 1561}. Extensive cystic change is rare.

Macroscopy

Pineoblastomas are soft, friable and poorly demarcated {199, 2456}. Haemorrhage and/or necrosis may be present, but calcification is rarely seen. Infiltration of surrounding structures, including leptomeninges, is common, as is craniospinal dissemination {199, 452, 554, 818, 851, 1278, 1452}.

Histopathology

Representing the most primitive of pineal parenchymal tumours, pineoblastomas are composed of highly cellular, patternless sheets of densely packed small cells with round to somewhat irregular nuclei and scant cytoplasm. Pineocytomatous rosettes are lacking, but Homer Wright and Flexner-Wintersteiner rosettes may be seen. Pineoblastomas resemble other small cell, or primitive neuroectodermal tumours of the CNS. The cells feature a high nuclear: cytoplasmic ratio, hyperchromatic nuclei with an occasional, small nucleolus, scant cytoplasm, and indistinct cell borders. The diffuse growth pattern is only interrupted by occasional rosettes. Flexner-Wintersteiner rosettes indicate retinoblastic differentiation, as do highly distinctive but infrequently occurring fleurettes. Mitotic activity varies, but is generally high, and necrosis is common. Only rarely does one encounter mixed tumours showing a biphasic pattern with alternating areas resembling pineocytoma and pineoblastoma. The former must be distinguished from overrun normal parenchyma. Microcalcifications may be seen. Silver impregnations for pineal parenchymal cells demonstrate

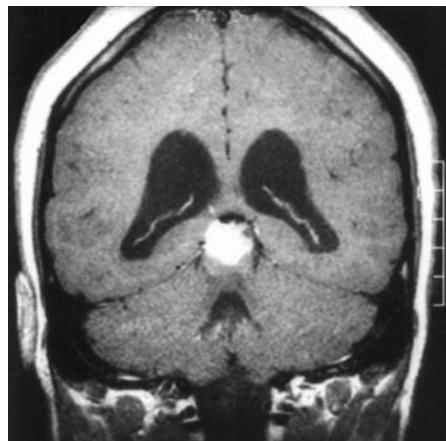


Fig. 7.08 On T1-weighted MRI, pineoblastoma shows homogeneous contrast enhancement.

scant cytoplasm and relatively few processes {453}. Melanin production as well as cartilaginous and rhabdomyoblastic differentiation are encountered in rare pineoblastomas referred to as "pineal anlage tumours" {818, 1608}.

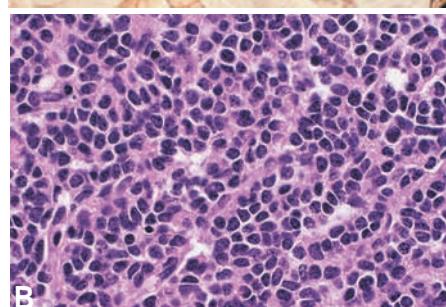
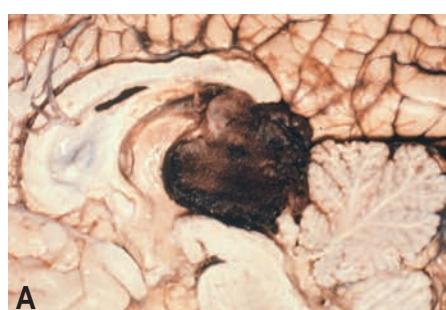


Fig. 7.09 A Large, haemorrhagic pineoblastoma. B Highly cellular pineoblastoma showing undifferentiated small cell histology.

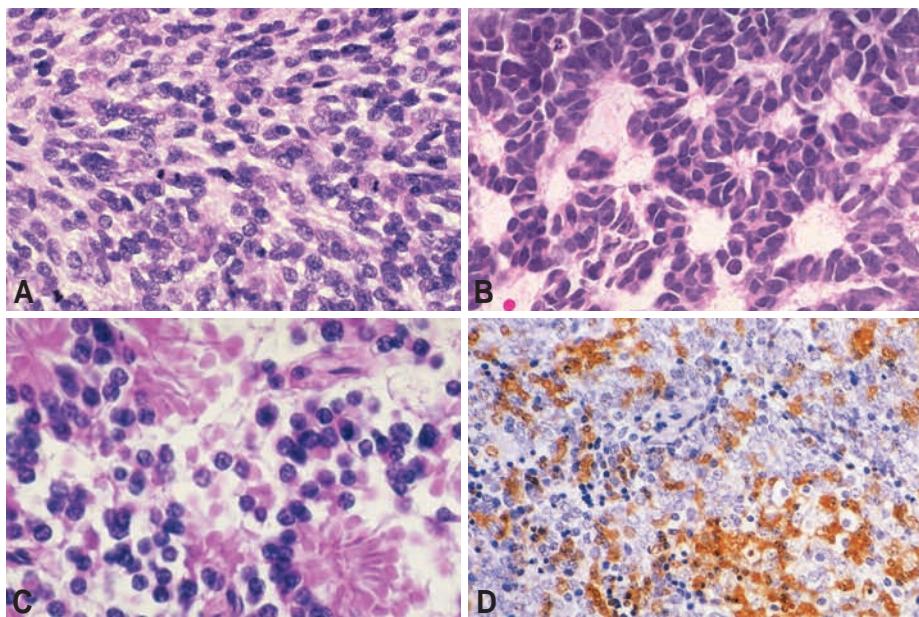


Fig. 7.10 Histopathological features of pineoblastoma. A High cellularity with numerous mitotic figures. B Homer Wright and Flexner-Wintersteiner rosettes. C Fleurettes. D Focal expression of retinal S-antigen.

Immunohistochemistry

The immunophenotype of pineoblastomas is similar to that of pineocytomas and includes reactivity for neuronal, glial and photoreceptor markers. Positivity for synaptophysin, NSE, NFP, class III β -tubulin and chromogranin A may be seen, as can retinal S-antigen staining {1014, 1452, 1608, 1716, 2456}. Reactivity for GFAP and α B crystallin, should prompt the exclusion of entrapped reactive astrocytes. Average MIB-1 indices are high {1608, 1883}.

Electron microscopy

Characterized by a relative lack of significant differentiation, the fine structure of pineoblastoma is similar to that of any poorly differentiated neuroectodermal neoplasm. Cells have round to oval with slightly irregular nuclei and abundant euchromatin as well as heterochromatin. Cytoplasm is scant and contains polyribosomes, few profiles of rough endoplasmic reticulum, small mitochondria, as well as occasional microtubules, intermediate filaments, and lysosomes {1403, 1480, 1608}. Dense core granules are rarely seen in the cell body {1403, 1480}. Cell processes, poorly formed and short, may contain microtubules as well as scant dense core granules {1403}. Bulbous endings are not identified {1480}. Junctional complexes of zonula adherens and zonula occludens type

may be present between cells and processes {1012, 1403, 1480, 1608}. Synapses are absent {1608}. Cilia with a 9+0 microtubular pattern are occasionally seen {1403}. Rarely, cells radially arranged around a small central lumen may be encountered {1608}.

Genetic susceptibility

Pineoblastomas may be seen in patients with familial (bilateral) retinoblastoma, an occurrence termed "trilateral retinoblastoma syndrome" {438, 1118} and have also been reported in patients with familial adenomatous polyposis {637, 907}. The rare association of pineoblastoma with embryonal rhabdomyosarcoma has been reported in an infant {380}.

Genetics

In 7 pineoblastomas studied, no consistent cytogenetic changes have been identified {1313}. In yet another analysis of pineoblastoma, both monosomy 22 and a missense *IN1* mutation were found {154}. No aberrations of the *TP53* and *Waf1/p21* genes have been detected {2274, 2275}. Pineoblastomas are known to occur in patients with *RB1* gene abnormalities; their prognosis is significantly worse than that of sporadic cases {1762}. A comparative genomic hybridization analysis of three pineoblastomas has shown an average of 5.6 chromosomal changes, including 2.3 gains and 3.3

losses {1883}. The most common chromosomal imbalance in pineoblastoma is -22; in addition, high-level gains are identified on 1q12-qter, 5p13.2-14, 5q21-qter, 6p12-pter, and 14q21-qter. In a microarray analysis of pineal parenchymal tumours, 7 genes were expressed in only pineoblastoma: HOXD13, PITX2, POU4F2, Hist1H3D, Hist1H4E, DSG1 and TERT, thus implicating cellular growth, junctional modification and immortalization {572}.

Histogenesis

Pineoblastomas share morphologic and immunohistochemical features with cells of the developing human pineal gland and retina. Evidences for this ontogenic concept include the finding of interphotoreceptor retinoid-binding protein and its mRNA in one mixed pineocytoma/pineoblastoma, and the occasional concurrence of bilateral retinoblastoma and pineoblastoma (trilateral retinoblastoma syndrome) {53, 438}.

Prognostic and predictive factors

With the exception of pineocytomas, all other pineal parenchymal tumours are potentially aggressive, as demonstrated by the occurrence of craniospinal seeding and, rarely, of extracranial metastases {372, 818, 2031}. Extent of disease at the time of diagnosis, as determined by CSF examination and MRI of the spine, directly affects the survival of patients with pineoblastoma. Extent of resection and radiotherapy also affect prognosis {1278}. Metastases of the pineal tumour within the CNS and vertebral column are the most common causes of death {1397}. The prognosis for patients with sporadic and familial trilateral retinoblastoma is dismal, survival being less than one year after diagnosis {438, 1397}. Occasionally, the pineal tumour remains asymptomatic and is discovered on routine imaging studies; in such instances, the outcome is better {438, 1397}. In one series, projected 1-, 3- and 5-year survival rates of pineoblastoma patients treated by various modalities are 88%, 78% and 58%, respectively {2031}.

Papillary tumour of the pineal region

A. Jouvet
Y. Nakazato
B.W. Scheithauer
W. Paulus

Definition

A rare neuroepithelial tumour of the pineal region in adults, characterized by papillary architecture and epithelial cytology, immunopositivity for cytokeratin and ultrastructural features suggesting ependymal differentiation.

ICD-O code

The provisional code proposed for the fourth edition of ICD-O is 9395/3.

Grading

The biological behaviour of papillary tumour of the pineal region (PTPR) is variable and may correspond to grades II or III, but histological grading criteria remain to be defined.

Synonyms and historical annotation

Based on a series of 6 cases of tumours with identical histology features, PTPR was described as a distinct entity in 2003 {1011}. An origin from specialized ependymal cells of the subcommissural organ was suggested. It is highly likely that some PTPRs were previously reported as "papillary pineocytoma" {2267, 2317}, pineal parenchymal tumour {1014}, choroid plexus tumour {1192, 1567}, ependymoma {1679} and even papillary meningioma {28}.

Incidence

Since these tumours are rare, incidence data are not available.

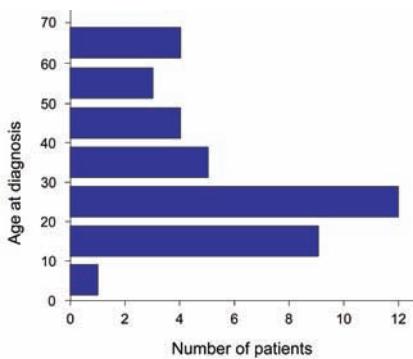


Fig. 7.11 Age distribution of papillary tumour of the pineal region, based on 38 published cases.

Age and sex distribution

Among 38 PTPR reported to date, examples have been identified in both children and adults {572, 573, 781, 1011, 1091, 1217, 2080}. Ages have ranged from 5 to 66 years (mean, 32 years). No sex predilection has been noted.

Localization

Papillary tumours of the pineal region arise exclusively in the pineal region.

Clinical features

Symptoms are non-specific, may be of short duration and include headache due to obstructive hydrocephalus. On neuroimaging, PTPRs appear large, well circumscribed, and occasionally feature a cystic element. CT shows them to be hypodense and variably contrast enhancing. MRI scans show a low T1 signal, increased signal on T2-weighted images, and contrast enhancement.

Macroscopy

PTPR present as relatively large (2.5–4 cm), well-circumscribed tumours indistinguishable grossly from pineocytoma.

Histopathology

PTPR is an epithelial-appearing tumour with papillary features and more densely cellular areas, often exhibiting ependymal-like differentiation (true rosettes and tubes). In papillary areas, the vessels are covered by layers of large, pale to eosinophilic columnar cells. In cellular areas, cells with a somewhat clear or vacuolated cytoplasm, and occasionally an eosinophilic, PAS-positive, cytoplasmic mass, may also be seen. Nuclei are round to oval, with stippled chromatin; pleomorphic nuclei may be present. Mitotic activity ranges from 0–10 per 10 HPF. Necrotic foci are often seen. Microvascular proliferation is usually absent. Instead, vessels are often hyalinized when seen, there is a clear demarcation between the tumour and the adjacent pineal gland.

Immunohistochemistry

The most distinctive immunohistochemical feature of PTPRs is their reactivity for keratins (KL1, AE1/AE3, CAM5.2, CK18), particularly in papillary structures. In contrast to ependymoma, only focal GFAP expression may be seen. PTPRs also stain for vimentin, S-100 protein, NSE, MAP2, N-CAM and transthyretin {781, 2080}. Focal membrane or dot-like EMA staining can sometimes be seen

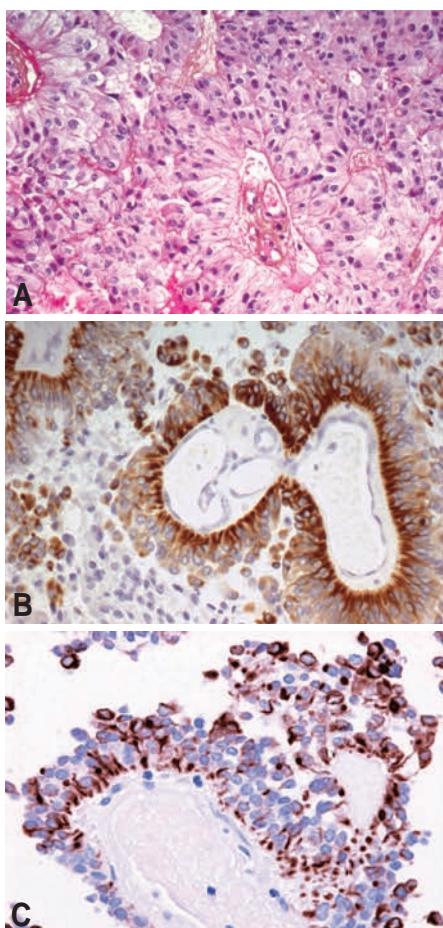


Fig. 7.12 Histological features of papillary tumour of the pineal region. A The tumour is characterized by papillary architecture and epithelial cytology. In papillary areas, the tumoral cells are large and columnar or cuboidal. B Expression of cytokeratin (KL1) in tumoral cells with strong immunoreactivity particularly in papillary structure. C A distinct immunoreactivity for cytokeratin CAM5.2.

{1011, 1217}. NFP immunolabelling is never seen, while the neuroendocrine markers synaptophysin and chromogranin A are sometimes weakly and focally expressed {1011}. The majority of PTPR are characterized by absence of staining for membranous Kir 7.1 or cytoplasmic stanniocalcin-1, both of which are frequently seen in choroid plexus tumours {781}.

Proliferation

Mitotic activity is moderate (range 0–10 per 10 HPF) {573, 781, 1011}. The Ki-67/MIB-1 labelling index is also moderate {573, 1217, 2080}, highest indices being seen in tumours of young patients {573}. The prognostic significance of proliferation indices has yet to be established.

Genetic susceptibility

At present, no syndromic association or

evidence of genetic susceptibility has been documented.

Genetics

In one comparative genomic hybridization study of 5 tumours, chromosomal imbalances were found in 4 cases; the most common changes were loss of chromosomes 10 (4 cases) and 22q (3 cases) as well as gain of chromosomes 4 (4 cases), 8, 9, and 12 (each in 3 cases) {781}.

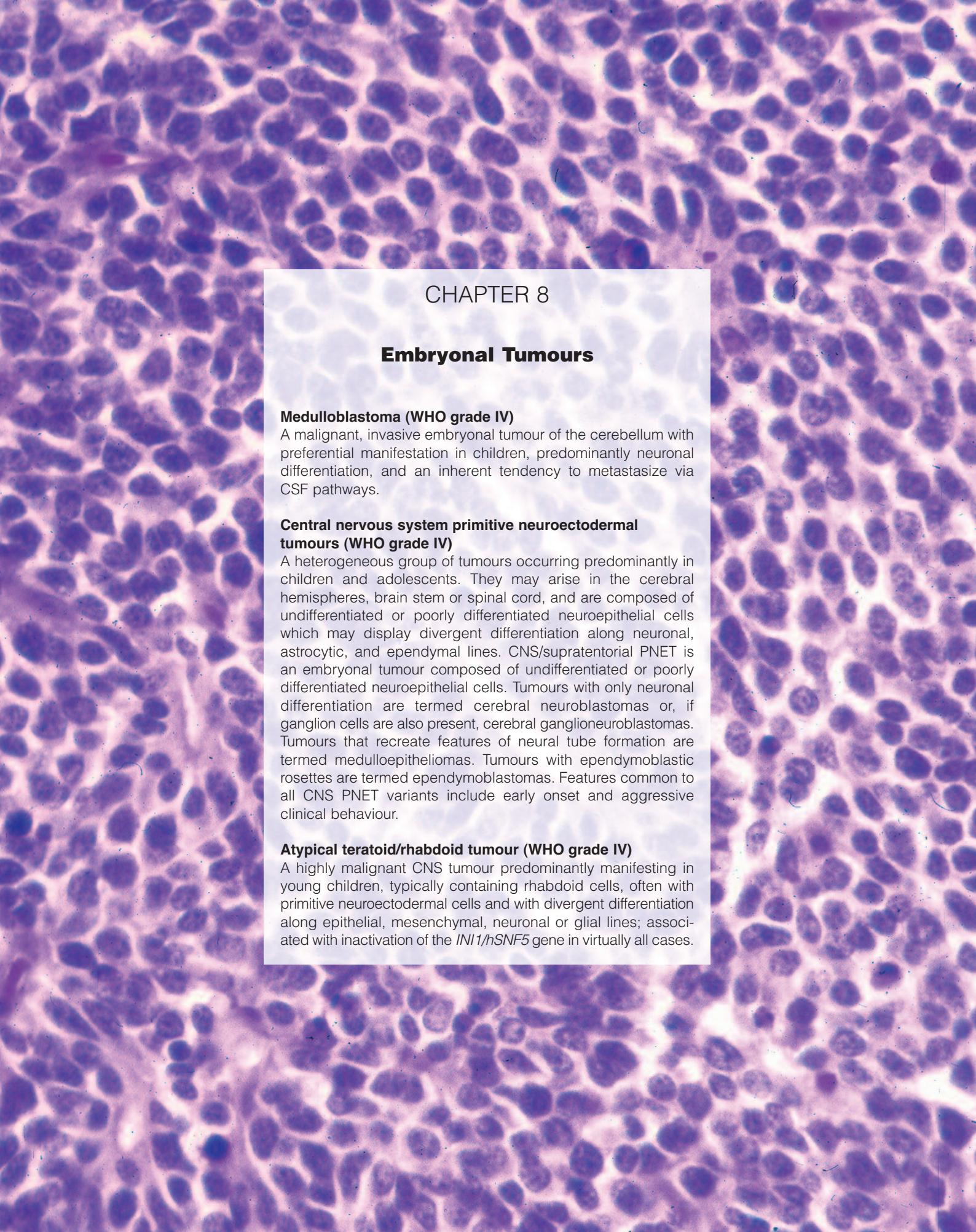
Histogenesis

Immunohistochemical findings (cytokeratin-positivity) and ultrastructural demonstration of ependymal, secretory, and neuroendocrine organelles suggest that PTPR may originate from remnants of the specialized ependymal cells of the subcommissural organ (SCO) {1011}. Further support for a putative origin from specialized ependymocytes of the SCO

comes from a DNA microarray study showing high expression of genes expressed in the SCO, namely ZFH4, RFX3, TTR, and CGRP {572}.

Prognostic and predictive factors

In a retrospective multicentre study of 31 patients, tumour progression occurred in 72% of cases, while the 5-year estimates for overall survival and progression-free survival were 73% and 27%, respectively. Incomplete resection and marked mitotic activity (5 or more mitoses per 10 HPF) tend to be associated with decreased survival and recurrence {573}.



CHAPTER 8

Embryonal Tumours

Medulloblastoma (WHO grade IV)

A malignant, invasive embryonal tumour of the cerebellum with preferential manifestation in children, predominantly neuronal differentiation, and an inherent tendency to metastasize via CSF pathways.

Central nervous system primitive neuroectodermal tumours (WHO grade IV)

A heterogeneous group of tumours occurring predominantly in children and adolescents. They may arise in the cerebral hemispheres, brain stem or spinal cord, and are composed of undifferentiated or poorly differentiated neuroepithelial cells which may display divergent differentiation along neuronal, astrocytic, and ependymal lines. CNS/supratentorial PNET is an embryonal tumour composed of undifferentiated or poorly differentiated neuroepithelial cells. Tumours with only neuronal differentiation are termed cerebral neuroblastomas or, if ganglion cells are also present, cerebral ganglioneuroblastomas. Tumours that recreate features of neural tube formation are termed medulloepitheliomas. Tumours with ependymoblastic rosettes are termed ependymoblastomas. Features common to all CNS PNET variants include early onset and aggressive clinical behaviour.

Atypical teratoid/rhabdoid tumour (WHO grade IV)

A highly malignant CNS tumour predominantly manifesting in young children, typically containing rhabdoid cells, often with primitive neuroectodermal cells and with divergent differentiation along epithelial, mesenchymal, neuronal or glial lines; associated with inactivation of the *INI1/hSNF5* gene in virtually all cases.

Medulloblastoma

F. Giangaspero
C.G. Eberhart
H. Haapasalo
T. Pietsch
O.D. Wiestler
D.W. Ellison

Definition

A malignant, invasive embryonal tumour of the cerebellum with preferential manifestation in children, predominantly neuronal differentiation, and an inherent tendency to metastasize via CSF pathways.

ICD-O codes

Medulloblastoma	9470/3
- Desmoplastic/nodular medulloblastoma	9471/3
- Medulloblastoma with extensive nodularity	9471/3
- Anaplastic medulloblastoma	9474/3
- Large cell medulloblastoma	9474/3

Grading

Medulloblastomas correspond histologically to WHO grade IV.

Incidence

The annual incidence has been estimated at 0.5 per 100 000 children less than 15 years [304, 2154]. In the United States, whites are more frequently affected than African-Americans [1438].

Age and sex distribution

The peak age at presentation is 7 years. Seventy percent of medulloblastomas occur in individuals younger than 16 [67, 1898]. In adulthood, 80% of medulloblastomas arise in the 21–40 years age group [690, 885]. This tumour rarely occurs beyond the fifth decade of life. Approximately 65% of patients are male.

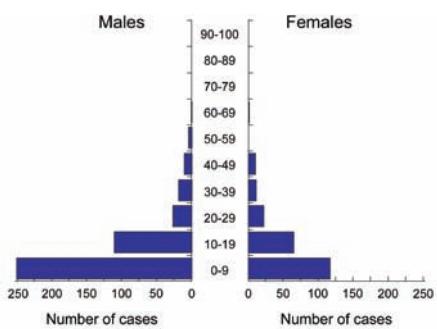


Fig. 8.01 Age and sex distribution of medulloblastoma, based on 651 cases.

Etiology

Different polyomaviruses have been discussed as possible causative agents. In experimental animals, cerebellar neoplasms with a phenotype similar to that of human medulloblastoma have been induced in hamsters by perinatal intra-cerebral injection with JC virus [1413, 2510], and in rats by retrovirus-mediated transfection of fetal rat brain cells with the large T antigen of SV40 [510]. Other models of medulloblastoma-like PNETs have been produced using transgenic mice that express SV40 large T antigen under the influence of different promoters [635]. Some studies have demonstrated a high frequency of detection of JC virus DNA sequences and its viral oncoproteins, T-antigen and agnoprotein, by immunohistochemistry in human medulloblastoma [461, 1095, 1211]. SV40 sequences have also been identified in medulloblastomas [883]. However, these findings have not been confirmed by others in independent larger series [1913, 2384]. Therefore, the role of polyomavirus infections in the development of medulloblastomas remains unclear.

An increased risk for medulloblastoma was found in children born before term (standardized incidence ratio 3.1) [1445]. A protective function of folate substitution in maternal diet against the development of medulloblastoma in children was claimed in an earlier study [244], but was not confirmed in a more recent study [245].

Localization

At least 75% of childhood medulloblastomas arise in the vermis, and project into the fourth ventricle. Involvement of cerebellar hemispheres increases with the age of the patient. Most tumours located in the hemispheres are of the desmoplastic/nodular subtype [243].

Clinical features

The presenting clinical manifestations include truncal ataxia, disturbed gait, intracranial hypertension secondary to

obstruction of CSF-flow and lethargy, headache and morning vomiting. On computerized tomography (CT) or magnetic resonance imaging (MRI), medulloblastomas appear as solid, intensely contrast-enhancing masses.

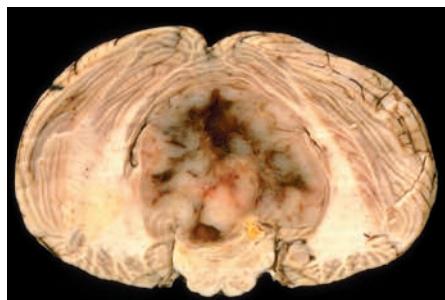


Fig. 8.02 Medulloblastoma of the cerebellar vermis compressing the brain stem.

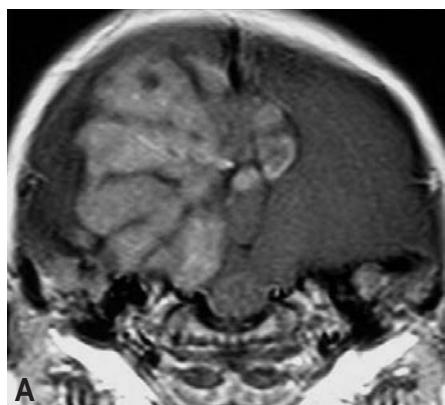


Fig. 8.03 A. Grape-like appearance of medulloblastoma with extensive nodularity in a 18-month-old child.
B. MRI appearance of desmoplastic/nodular medulloblastoma in an adult patient. Note the hemispheric location and the well-circumscribed appearance.

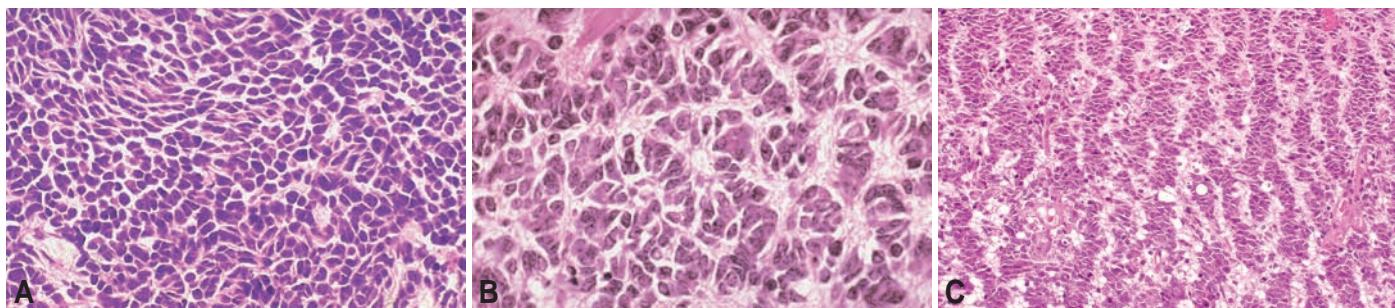


Fig. 8.04 Histopathological features of medulloblastoma. A Typical arrangement of sheets of undifferentiated tumour cells. B Area with Homer Wright (neuroblastic) rosettes. C Arrangement of tumour cells in parallel rows.

Medulloblastomas involving the peripheral cerebellar hemispheres in adults may occasionally appear as extra-axial lesions simulating meningiomas or vestibular nerve schwannomas [124]. A nodular, “grape-like” pattern on MRI characterizes the medulloblastoma with extensive nodularity, because of its distinctive and diffuse nodular architecture [669, 1551]. CSF-borne metastases are seen as foci of nodular or diffuse contrast enhancement in the leptomeninges or on the ventricular surface. They are present in one third of patients at presentation.

Macroscopy

The majority of medulloblastomas arise in the region of the vermis and appear as pink or grey masses that can fill the fourth ventricle. Medulloblastoma occurring in the cerebellar hemispheres tends to be firm and more circumscribed than the classic variant. Small foci of necrosis can be evident but extensive necrosis is rare.

Histopathology

Medulloblastoma is composed of densely packed cells with round-to-oval or carrot-shaped hyperchromatic nuclei surrounded by scanty cytoplasm. Neuroblastic (Homer Wright) rosettes, which are observed in less than 40% of cases, are often associated

with marked nuclear pleomorphism and high mitotic activity. Spongioblastic features, characterized by tumour cell nuclei arranged with their long axes in parallel, can be encountered. Nuclear size and pleomorphism in medulloblastomas may be variable [1435], which has led to the concept of anaplasia. Although usually numerous, mitoses are infrequent in about 25% of the cases [251]. The most common type of differentiation in medulloblastoma is neuronal, most commonly manifesting as immunopositivity for neuronal markers such as synaptophysin. In addition, small groups of frankly neurocytic cells or ganglion cells are found in approximately 5% of medulloblastomas. Glial differentiation is unusual, and takes the form of scattered small groups of cells with an astrocytic phenotype. Vascular hyperplasia as exemplified by the glomeruloid neovascularization of high-grade gliomas is rare. Areas of necrosis are quite uncommon, but when present necrotic zones may show pseudopalisading similar to that observed in glioblastomas. Tumour in the subarachnoid space may elicit a considerable desmoplastic reaction with ribbons or small clusters of neoplastic cells entrapped among collagenous fibers.

Desmoplastic/nodular medulloblastoma

Synonym: Desmoplastic medulloblastoma This variant is characterized by nodular, reticulin-free zones ('pale islands') surrounded by densely packed, highly proliferative cells with hyperchromatic and moderately pleomorphic nuclei which produce a dense intercellular reticulin fiber network [257, 668, 1059]. This characteristic pattern may be present only focally. The nodules, which represent regions of neuronal maturation, exhibit a reduced nuclear cytoplasmic ratio, a fibrillary matrix and uniform cells with a neurocytic appearance. Accompanying this maturation are negligible mitotic activity and increased apoptosis. Medulloblastomas showing only an increased amount of collagenous and reticulin fibers without the nodular pattern are not classified as the desmoplastic/nodular variant.

Medulloblastoma with extensive nodularity

The medulloblastoma with extensive nodularity, which was previously designated “cerebellar neuroblastoma”, occurs in infants and differs from the related desmoplastic/nodular variant by having an expanded lobular architecture, due to the fact that the reticulin-free zones become unusually enlarged and rich in

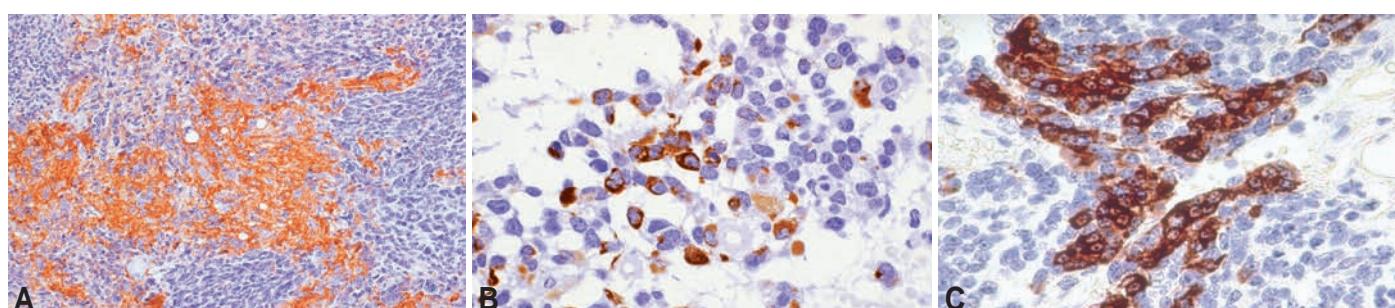


Fig. 8.05 Medulloblastoma. A Focal expression of synaptophysin. B Focal GFAP staining of tumour cells. C Clusters of medulloblastoma cells expressing retinal S-antigen.

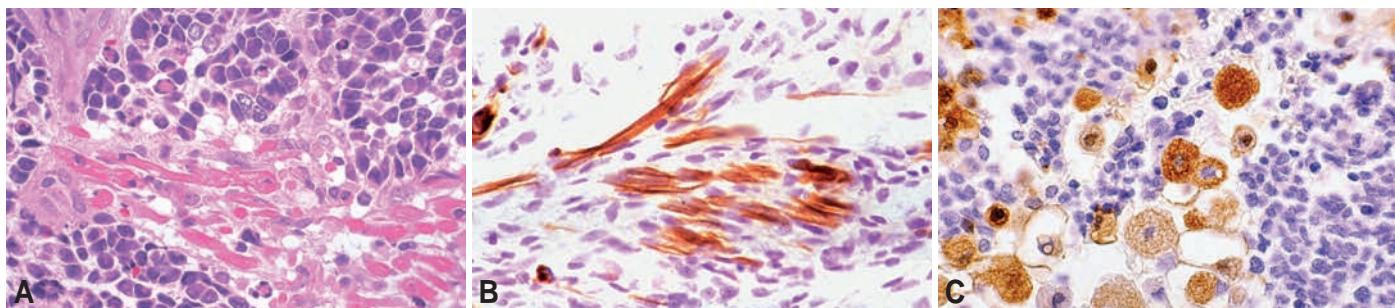


Fig. 8.06 Medulloblastoma with myogenic differentiation, showing (A) striated muscle fibers with brisk mitotic activity, (B) anti-fast-myosin immunostaining of highly differentiated, striated myogenic cells and (C) biphasic pattern of small undifferentiated medulloblastoma cells and large rhabdomyoblasts immunostaining for myoglobin.

neuropil-like tissue. Such zones contain a population of small cells with round nuclei, which resemble the cells of a central neurocytoma and exhibit a streaming pattern. The internodular component is markedly reduced in some areas [669, 2183]. Following radiotherapy and/or chemotherapy, medulloblastomas with extensive nodularity may occasionally undergo further maturation to tumours dominated by ganglion cells [433].

Anaplastic medulloblastoma

Marked nuclear pleomorphism, nuclear moulding, cell-cell wrapping and high mitotic activity, often with atypical forms, are characteristics of this variant. Apoptosis is also prominent. Although all medulloblastomas show some degree of atypia, these changes are particularly pronounced and widespread in anaplastic medulloblastomas. The presence of such features only in focal areas is not sufficient to define the lesion as an anaplastic medulloblastoma.

Histological progression over time, from non-anaplastic to anaplastic medulloblastoma, has been described in several studies, and a transition can be even observed within a single specimen, as inferred from the presence of differing

degrees of cytological atypia or anaplasia in one tumour [230, 498, 670, 671, 1255].

Large cell medulloblastoma

The large cell variant represents approximately 2–4% of medulloblastomas. The term derives from its monomorphic cells with large, round, vesicular nuclei, prominent nucleoli and variable amount of eosinophilic cytoplasm [230, 498, 670, 1255]. The cells lack cohesiveness, and mitotic and apoptotic figures are abundant. Large cell and anaplastic medulloblastomas have considerable cytological overlap. The large cell medulloblastoma frequently contains anaplastic regions, and in several studies, a combined large cell/anaplastic category has been proposed [230, 1292, 1435].

Myogenic differentiation

Synonym: medullomyoblastoma
(ICD-O: 9472/3)

Medulloblastoma with myogenic differentiation was previously termed medullomyoblastoma. However, genetic changes in medulloblastoma with myogenic differentiation are similar to those in other medulloblastomas, suggesting that this is not a distinct entity [806, 1292]. The descriptive term “medullomyoblastoma” therefore describes any variant (classic, desmoplastic/nodular, etc.) of medulloblastoma containing focal rhabdomyoblastic elements [806, 1292]. This population of spindle-shaped cells is admixed with scattered or clumped large oval cells, which have hyaline eosinophilic cytoplasm [2116]. Occasionally, elongated ‘strap cells’ with the cross-striations of skeletal muscle are evident [1830]. The rhabdomyoblastic component is immunoreactive for desmin [855, 2029], myoglobin [471, 855, 2116], and fast myosin [1026], but not smooth muscle α -actin [855, 2029]. Ultrastructural

studies demonstrate thick and thin filaments arranged in sarcomeres and Z-band material characterizes the rhabdoid element [855, 1026, 2029, 2116].

Melanotic differentiation

Synonym: Melanocytic medulloblastoma
(ICD-O: 9470/3)

Medulloblastoma with melanotic differentiation was previously termed melanocytic medulloblastoma. However, groups of melanotic tumour cells can occur in different variants of medulloblastoma and therefore this is not regarded as a separate variant. The phenotype of the melanotic tumour cells varies; they may appear undifferentiated, like the PNET component, or epithelial and form tubules, papillae [117, 479, 647] or cell clusters [187, 755, 1000]. They usually immunolabel with antibodies to S-100 protein [117, 647], but they may also be immunonegative, as described for cells of the ocular pigment layer at very early stages of development [479]. Ultrastructural analysis of some tumours has verified that the pigment is oculocutaneous melanin with distinct melanosomes [187, 479, 647, 1000]. However, neuromelanin may occur in some of these lesions [1047].

Immunohistochemistry

The frequent differentiation of the medulloblastoma along neuronal lineage manifests immunophenotypically as expression of neuronal antigens. Class III β -tubulin, microtubule-associated protein 2, neuron specific enolase (NSE) and synaptophysin, are demonstrated, at least focally, in many medulloblastomas [1063, 1396]. Homer Wright rosettes and the pale islands of the desmoplastic/nodular medulloblastomas are immunoreactive for these markers [251, 364, 1064]. Neurofilament protein expression occurs less commonly. [1396]. Particularly in the large cell variant,

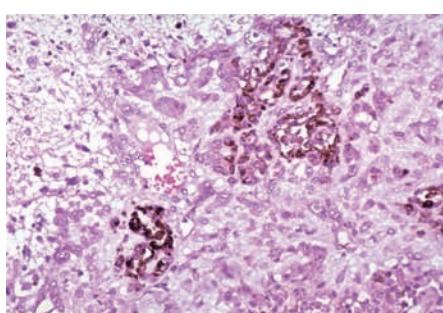


Fig. 8.07 Medulloblastoma with melanotic differentiation. Melanotic cells commonly appear as tubular epithelial structures.

synaptophysin immunoreactivity may have a characteristic dot-like appearance. In this variant, immunoreactivity for neurofilaments and chromogranin may also be demonstrated.

Cells positive for GFAP are often found among the undifferentiated cells of classic medulloblastomas; however, they mostly show the typical spider-like appearance of reactive astrocytes and tend to be more abundant near blood vessels. These cells are usually considered entrapped astrocytes, though the observation of similar cells in extra-cerebral metastatic deposits raises the possibility that at least some represent well-differentiated neoplastic astrocytes. Cells showing GFAP immunoreactivity and the cytological appearance of bona fide neoplastic elements can be observed in approximately 10% of cases of classic medulloblastoma [514]. The pale islands of the desmoplastic/nodular medulloblastoma may show fibrillary, GFAP-positive cells [1064]. However, GFAP-positive tumour cells can also be found in the inter-nodular areas of large cell and anaplastic medulloblastomas. Focal GFAP immunoreactivity has been documented in large cell medulloblastoma, but is rare [514].

The immunophenotype of the medulloblastoma also includes reactivities for vimentin, nestin [2254], neuronal cell adhesion molecules [579, 615, 1505], nerve growth factors [2199] and even photoreceptor-associated proteins, such as rodopsin and retinal S-antigen [407, 956, 1396]. Nuclear INI1 expression is retained in all medulloblastoma variants.

Electron microscopy

In areas of neuroblastic differentiation, such as rosettes and pale islands, the cells elaborate neurite-like cytoplasmic processes joined by specialized adhesion plaques, and are laden with microtubules in parallel array. Dense-core vesicles and synapses may also be observed [1058, 1531]. Abundant intermediate filaments may be noted in areas of glial differentiation. Tissue from histologically and immunohistochemically undifferentiated areas may reveal few, if any, specific ultrastructural features.

Apoptosis

Apoptosis is a major contributor to cell loss in medulloblastomas. Apoptotic indices generally parallel mitotic indices

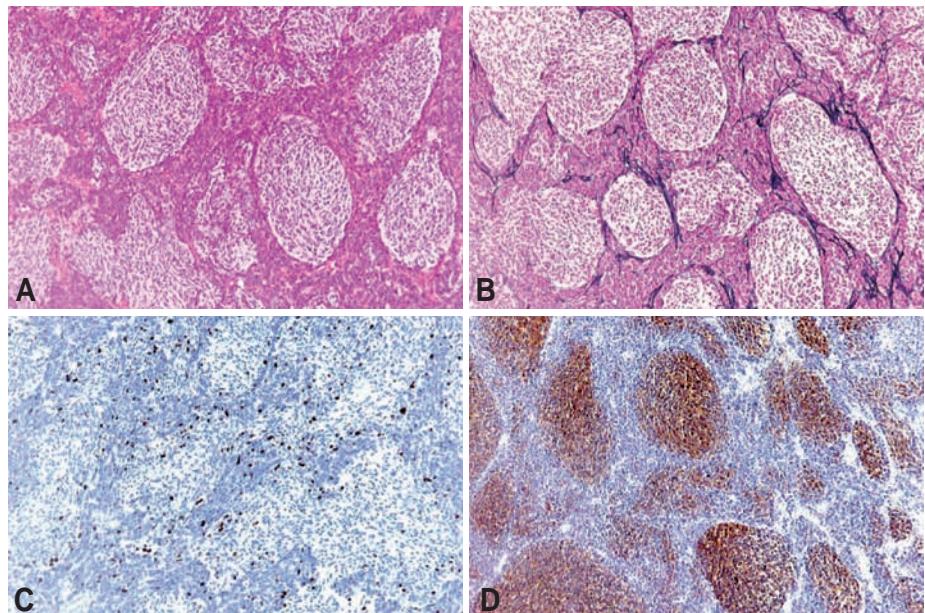


Fig. 8.08 Desmoplastic/nodular medulloblastomas. A Pale nodular areas surrounded by densely packed hyperchromatic cells. B Reticulin stain showing the reticulin-free pale islands. C MIB-1 staining shows that the proliferative activity predominates in the highly cellular, internodular areas, whereas (D) neuronal differentiation, shown by immunoreactivity to NSE, occurs in the pale islands.

in histological preparations [2020], with the notable exception of the apoptosis that characterizes nodules in desmoplastic medulloblastomas, which have a low growth fraction [514]. The proportion of nuclei in apoptosis is in the range of 1–4% [239, 1989, 2019], and does not appear to differ significantly between classic and desmoplastic variants [1784], despite the regional variation seen in desmoplastic/nodular tumours. Various regulators of apoptosis have been studied in medulloblastoma. Bcl-2 inhibits apoptosis in many conditions, and is expressed in approximately 30% of all medulloblastomas, though Bcl-2 immunoreactivity appears to be more frequent (67%) in desmoplastic tumours [2021, 2040]. Bcl-2 expression is found in the internodular regions of desmoplastic

tumours, and thus correlates inversely with markers of neurocytic differentiation [499, 2040]. Caspase-8 is involved in death receptor-mediated apoptosis, and its CpG island is hypermethylated in a significant proportion (62–100%) of medulloblastomas [625]. Survivin is a member of the inhibition of apoptosis gene family, and also regulates the cell cycle. It is expressed in a wide range of neoplasms, including medulloblastoma [186]. REN is a putative tumour suppressor that antagonises the effects of Shh on the proliferation of cerebellar granule cells. In this paradigm, REN promotes growth arrest and apoptosis by enhancing the activity of caspase-3. Loss of REN has been implicated in the development of medulloblastoma [65].

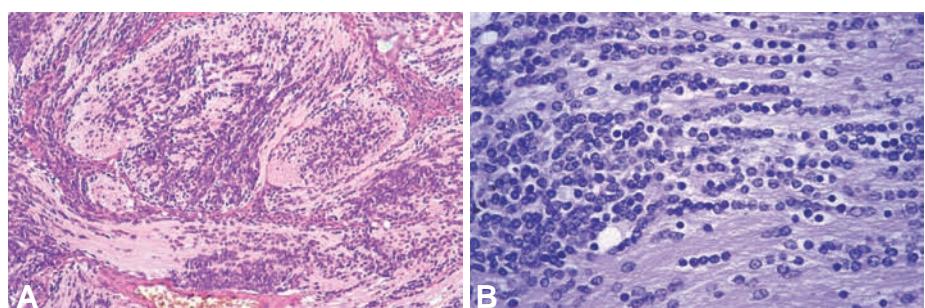


Fig. 8.09 A Medulloblastoma with extensive nodularity has a lobular architecture with large elongated reticulin-free zones. B These zones contain small round neurocytic cells in the fibrillary background.

Proliferation

Cell turnover in most medulloblastomas is high; indices of proliferation and apoptosis can be as high as in any other malignant neuroepithelial tumour [239]. However, for an embryonal tumour, these measures can be unexpectedly low in some classic tumours, and foci of differentiation in medulloblastomas, such as the nodules of the desmoplastic variant or groups of ganglion cells, may contain no mitotic activity and a negligible growth fraction by Ki-67 immunolabelling [514]. In contrast, particularly large numbers of mitotic figures and apoptotic bodies are hallmarks of the large cell and anaplastic medulloblastoma [498, 1435]. The mitotic index for childhood medulloblastomas is usually in the range of 0.5–2% [685, 1435]. The growth fraction, as assessed by Ki-67 immunolabelling, is generally >20% [1435, 2019].

Genetic susceptibility

Several cases of medulloblastoma have been reported in monozygotic twins [331] as well as in dizygotic twins and siblings [150, 890, 2458] or other relatives [2344]. Associations with other brain tumours [552] and extraneuronal malignancies, including Wilms' tumour [1643, 1822], have also been observed. Moreover, medulloblastomas have been diagnosed in several familial cancer predisposition

syndromes (see Chapter 13), including patients with *TP53* germline mutations (Li-Fraumeni syndrome), *PTCH1* mutations (the naevus basal cell carcinoma syndrome or Gorlin syndrome; NBCCS [1249], and *APC* mutations (Turcot syndrome), *CBP* (Rubinstein-Taybi syndrome) [2227] and *SUFU* [2226]. Occasionally, medulloblastomas develop in the setting of complex malformations, e.g. intestinal malrotation, omphalocele, and bladder extrophy [1615], and Coffin-Siris syndrome (mental retardation, deficiency of postnatal growth, joint laxity, brachydactyly of the fifth digit with absence of the nail bed) [1910]. Some studies suggest that relatives of patients with medulloblastomas have an increased risk of developing other childhood tumours, particularly leukaemia and lymphoma [551, 1224].

Genetics

Modern molecular cytogenetic strategies, such as comparative genomic hybridization (CGH), fluorescence *in situ* hybridization (FISH) and spectral karyotyping, have superseded conventional cytogenetic analysis over the last 10 years, though some findings made in the era of chromosomal analysis remain biologically relevant. The most common cytogenetic abnormality in medulloblastomas is isochromosome 17q, which is present in about 30–40% of tumours [164, 722]. In

the majority of cases, the breakpoint is in the proximal portion of the short arm, so that the resultant structure is dicentric. Both loss of 17p and gain of 17q, which result from isochromosome 17q, can also occur independently [1590]. Whether generated as part of an isochromosome 17q, an interstitial deletion or monosomy 17, loss of 17p appears to be an indicator of poor prognosis [1255, 1590]. Other abnormalities detected by early cytogenetic studies were on chromosomes 6, 7, 8 and 11 [151]. It was noted that loss of chromosome 6 occurred independently of isochromosome 17q, a finding reinforced in recent studies that have shown an association between loss of chromosome 6 and Wnt pathway activation [2244]. In contrast, trisomy 7 is common and associated with isochromosome 17q [151]. Double minutes and homogeneously staining regions are demonstrated in medulloblastomas and are particularly linked to amplification of the *MYCC* gene [39, 163]. Amplification of *MYCC*, which is present in 5–10% of tumours, has been associated with the large cell and anaplastic variants and a poor outcome [501, 1255].

Common genetic gains

Chromosomal gains of the *MYCC* locus (8q24) have been identified in primary medulloblastoma using Southern blot, FISH, and CGH. The frequency of amplification varies, ranging from 4% to 17% [39, 79, 502, 1454, 1573, 2015]. The frequency of *MYCN* amplification is also variable, but generally falls into a similar range [39, 502, 1454]. *MYC* amplicons are even more common in medulloblastoma cell lines and xenografts than in primary tumours, suggesting *MYC* might promote growth outside the normal tumour milieu [163]. Consistent with this concept, amplification of *MYCC* or *MYCN* is associated with the aggressive large cell tumour variant and with poor clinical outcomes [39, 79, 502, 2015]. *MYC* gene amplification has been reported in 3 of 6 medulloblastomas using FISH [806, 1292]. Additional chromosomal loci commonly gained in medulloblastoma that include potential oncogenes include 7q21 (*CDK6*) [1454], 5p15 (*hTERT*) [502, 1454] and 14q22 (*OTX2*) [197, 466]. All three of these oncogenes have also been shown to be overexpressed and associated with worse clinical outcomes. The *PIK3CA* gene, a member of the PI3

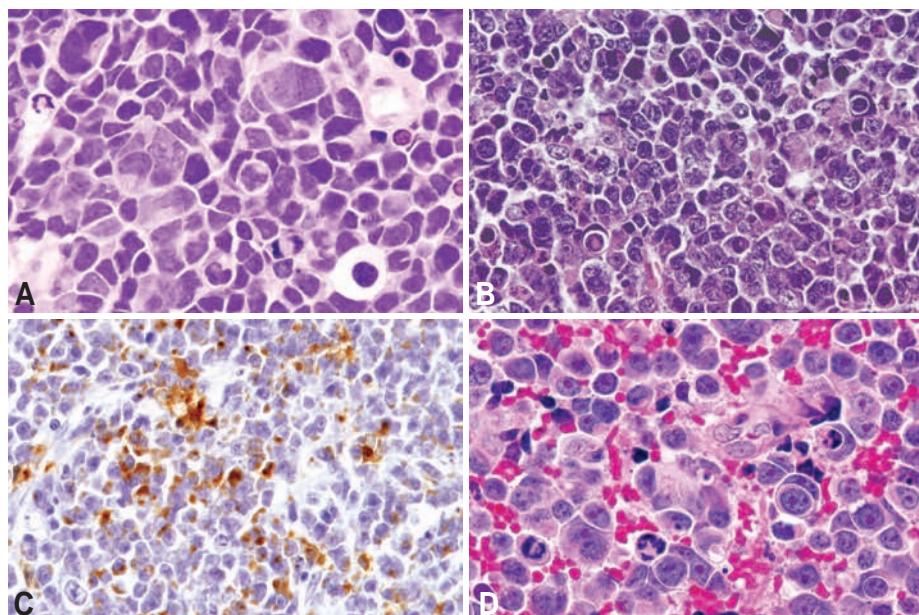


Fig. 8.10 A Anaplastic medulloblastoma characterized by increased nuclear size and pleomorphism. B Large cell medulloblastoma displaying pleomorphic, large nuclei with prominent nucleoli. C Large cell medulloblastoma displaying dot-like immunoreactivity for synaptophysin. D Large cell medulloblastoma showing enlarged vesicular nuclei, prominent nucleoli, and moderate cytoplasm. Tumour "cell wrapping" is also prominent.

kinase pathway, was found to be amplified in one study {2259} and activated by mutation in another {225}.

Common genetic losses

Two compilations of metaphase chromosome CGH data from over 200 medulloblastoma cases found that the chromosomal arms most commonly lost were 17p (23–28%), 16q (16–17%), 8p (15–22%), 10q (21%) and 11q (11–16%) {502,1881}. Array CGH studies have identified similar large regions of loss, and have begun to more precisely localize smaller deletions {888, 1454, 1938}. Studies of loss of heterozygosity (LOH) by both RFLP and microsatellite analysis, as well as FISH analyses, disclose that deletion or recombination of material on chromosome arm 17p is seen in 38–54% of cases {1145, 1255, 1428, 2016}. In the majority of cases, most of the short arm is missing with breakpoints in the 17p11 region {2016}. In occasional cases, partial 17p deletions have been identified, mapping the smallest overlapping region of deletion to 17p13.3 {1145, 1428}. As *TP53* is located on 17p13 and is mutated in a variety of human tumours, this gene was initially considered as a candidate gene. *TP53* mutations have been identified in only a small subset (5–10%) of medulloblastomas {16, 38, 1621}, but the p53 pathway can be altered in up to 21% of cases by other mechanisms such as *INK4A/ARF* deletion {602}. Nonetheless, because of the low incidence of mutations and the localization of the smallest region of deletion to 17p13.3 (distal to *TP53* at 17p13.1), *TP53* is not considered a major target of chromosome 17p loss. One potential tumour suppressor gene in the 17p13.3 region is *HIC1*, which is commonly hypermethylated in medulloblastoma {1919,2356}. While hypermethylation of *HIC1* is not significantly associated with LOH at the locus, it does appear to correlate with decreased transcription. *REN*, a negative regulator of the Hedgehog pathway located at 17p13.2, is also frequently deleted in medulloblastoma and appears to suppress the growth of tumour cells {463}.

Candidate genes on chromosome 10q

Two candidate genes have been studied in detail on 10q: *PTEN* and *DMBT1*. The tumour suppressor gene *PTEN*, located on 10q23, encodes a dual specificity

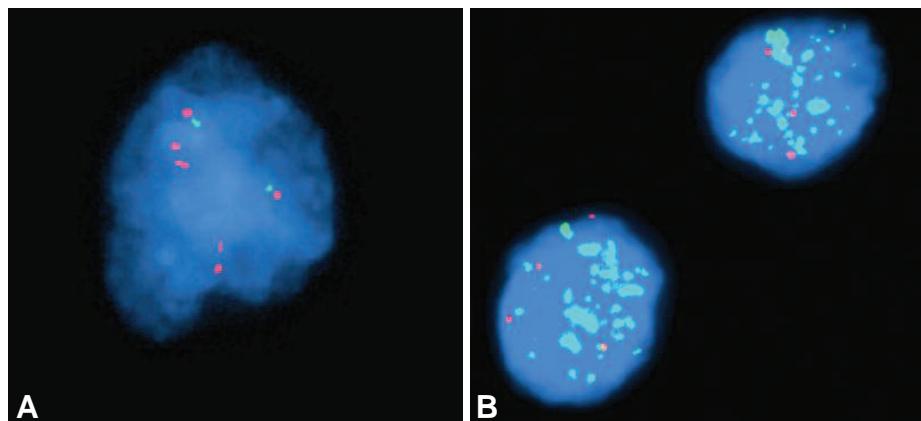


Fig. 8.11 A Isochromosome 17q. This nucleus shows two sets of 3:1 (17q - red:17p - green) signal profiles indicating loss of 17p and gain of 17q. B *MYC* amplification. These nuclei show multiple clumped *MYC* signals (green). The red signals from centromeric probes indicate chromosome 8 copy number.

phosphatase frequently deleted in cancers. Most studies have only identified rare medulloblastoma cases in which *PTEN* is lost {778, 1454}. In one report, however, differential PCR identified homozygous loss of *PTEN* in 30% (7 of 23) of medulloblastomas {915}. *PTEN* promoter methylation may represent a more common mechanism by which this tumour suppressor is down-regulated {778}. *DMBT1* was initially cloned in a medulloblastoma cell line following identification of a homozygous deletion at 10q25.3-26.1 using representational difference analysis {1508}. It contains multiple scavenger receptor cysteine-rich (SRCR) domains, but its role in tumour pathogenesis remains unclear. Intragenic homozygous deletions were detected in 2/20 medulloblastomas in the initial study, while two later reports found such deletions in 7/23 and 5/24 cases {915, 1674}. Mutations, however, were not detected in *DMBT1* {1674}.

The Hedgehog signalling pathway

Another tumour suppressor locus, *PTCH*, is located on the long arm of chromosome 9, where allelic losses have been described in 10–18% of medulloblastoma cases {2015, 2035}. *PTCH* is altered in NBCCS, which predisposes patients to develop basal cell carcinoma and medulloblastomas of the desmoplastic variant {2035}. *PTCH* is an inhibitor of the Hedgehog signalling pathway. It is the human homologue of the Drosophila segment polarity gene *PATCHED*, and it plays an important role in the development of the central nervous system and in tumourigenesis {588, 1401}. Hedgehog

signalling is particularly important in cerebellar development; as a pathway ligand, Sonic Hedgehog (SHH), is secreted by Purkinje cells, and is a major mitogen for cerebellar granule cell progenitors in the external granular cell layer {2382}. Activation of the pathway occurs by binding of Hedgehog ligand to *PTCH*, which stops *PTCH* from inhibiting *SMO*, and thereby activates Gli transcription factors {588}. The Hedgehog pathway can thus be aberrantly activated, at least in theory, by loss of *PTCH* function, or increased activity of SHH, *SMO* or Gli factors. Inactivating mutations of the *PTCH* gene, most of which result in truncated proteins, have been identified in approximately 8% of sporadic medulloblastomas {1747, 1816, 2345, 2433, 2516}. This seems to be the most common genetic mechanism of Hedgehog pathway activation in medulloblastoma, but other genes in the pathway can also be altered. A potentially activating point mutation in exon 2 of the *SHH* gene was identified in 1/14 medulloblastomas in one study {1648}, but not in others {2407, 2516}. An amplicon containing *SHH* has also been reported, suggesting increased gene dosage as another mechanism for increased activity {1454}. Mutation analysis of the *SMO* gene in medulloblastomas uncovered two cases with missense mutations {1252, 1852}, one being an activating mutation at position 1604 in exon 9. Others, however, have failed to identify *SMO* mutations in medulloblastoma {2516}. An inactivating mutation of *PTCH2*, a human homologue of *PTCH* located on chromosome 1p32-34, has been reported in a single case of

medulloblastoma [2118]. *SUFU*, another hedgehog pathway inhibitor, has been found to be mutated in the germline of a small number of medulloblastoma patients [2226]. Array-based expression studies have in general supported the concept that Hedgehog signalling is active in a subset of medulloblastomas, and that this developmentally critical pathway is associated with the desmoplastic/nodular medulloblastoma subtype [1773, 2244]. Hedgehog pathway activity also appears to regulate expression of oncogenic ErbB-4 isoforms [570].

APC and the Wnt signalling pathway

The adenomatous polyposis coli (APC) gene was originally identified as the target of germline mutations causing familial adenomatous polyposis (FAP), a syndrome of inherited predisposition to colon cancer [1751]. Some FAP patients also develop medulloblastoma, a condition known as Turcot syndrome [762]. The APC protein is a negative regulator of the Wnt pathway. It forms a complex with glycogen synthase kinase 3b (GSK-3 β) and Axin, and together they regulate the activity of β -catenin [588, 1751]. In the absence of Wnt ligands, GSK-3 β phosphorylates the N-terminal domain of β -catenin and thereby targets it for degradation. When ligands are present, the APC/GSK-3 β /Axin complex is inactivated, allowing β -catenin to enter the nucleus, where it binds TCF cofactors and positively regulates transcription of pathway targets [588, 1751]. While germline mutations in APC underlie medulloblastoma formation in Turcot syndrome patients, somatic APC mutations in sporadic medulloblastoma are relatively rare, with only 3–4% of tumours containing sequence changes [881, 1146]. Unlike the APC alterations in FAP patients, which result in a truncated, non-functional protein, the sequence changes identified to date in sporadic medulloblastoma are missense mutations of undetermined functional significance.

Clear involvement of the Wnt pathway in the evolution of sporadic medulloblastomas was first indicated by the presence of β -catenin mutations predicted to activate signalling by ablating inhibitory phosphorylation sites in 3/67 (4.5%) cases [2517]. Three other studies detected similar β -catenin mutations in 5 to 10% of sporadic medulloblastoma [503, 881, 1146]. Finally, point mutations have been

reported in the *Axin* gene in sporadic medulloblastoma [81, 411, 2472]. These studies suggest that the Wnt pathway is activated in a significant fraction of medulloblastoma. Indeed, if one uses nuclear immunopositivity for β -catenin as a marker, between 18% and 25% of medulloblastoma show evidence of Wnt activity [503, 516, 2472]. This correlates fairly well with a recent expression array study, in which 6 of 46 medulloblastoma (13%) were classified into a Wnt subgroup [2244].

The Notch signalling pathway

Like Hedgehog and Wnt, Notch is a pathway that plays a critical role in patterning of multiple organs, including the brain, and in the regulation of neural stem cells [1264]. In the cerebellum, Notch2 is known to promote the proliferation of external granular cell layer progenitor cells [2121]. Elevated levels of Notch signalling have been found in human medulloblastoma and medulloblastoma cell lines [548, 757]. *Notch2* gene amplification could account for this in 15% of cases [548]. γ -secretase inhibitors, which block Notch pathway activity, slow medulloblastoma growth, and appear to deplete stem-like medulloblastoma cells [547, 757].

Neural transcription factors

Many transcription factors implicated in the development of the brain appear to be deregulated in medulloblastoma. In general, however, the altered expression of these proteins is not associated with copy number changes or mutations of the loci in question. *PAX5* and *PAX6* mRNA was detected in 70% and 78% of medulloblastomas by *in situ* hybridization [1182]. The lack of expression of the *PAX5* gene in normal neonatal cerebellum and its upregulation in medulloblastoma indicates that it may play a role in development of medulloblastoma. Other neural transcription factors found to be expressed in medulloblastomas include the granule cell marker *ZIC*, and transcription factors of the *NEUROD* family [269, 1773, 1940, 2470]. SOX transcription factors are also expressed in medulloblastoma, with increased levels of *SOX4* most commonly reported [1272, 1573, 2471]. REST, a repressor of neural differentiation, is also overexpressed in medulloblastoma, and seems to cooperate with proliferative oncogenes to promote tumour formation [631, 2167].

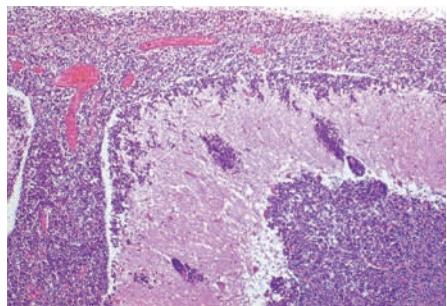


Fig. 8.12 Infiltration by a cerebellar medulloblastoma of the subarachnoid space. Note clusters of tumour cells in the molecular layer, particularly in the subpial region.

Histogenesis

Bailey and Cushing recognized the medulloblastoma as a distinct clinicopathological entity in 1925 [85]. They assumed a derivation from medulloblasts, i.e. undifferentiated, proliferating embryonal cells with the capacity to differentiate into spongioblasts and neuroblasts. The existence of such precursor cells was postulated, but not unequivocally identified, in subsequent neuro-anatomical studies of the developing nervous system [2313]. The histogenesis of medulloblastoma has been controversial for over 75 years. There are two main hypotheses: One view suggests that medulloblastoma originate from the external granular layer (EGL) of the cerebellum, which forms during embryogenesis by migration of undifferentiated cells from the roof of the fourth ventricle to the surface of the fetal cerebellar cortex, where they give rise to cells which later form the internal granular layer neurons [2313]. This view is supported by the observation that the proliferation of precursor neurons in the external granular layer of the cerebellum is controlled by sonic Hedgehog [2382], by analysis of murine medulloblastoma models based on Hedgehog activation [1107, 1637], and by comparison of gene expression patterns in medulloblastoma to those in the cerebellar EGL [1098]. The second hypothesis is the basis of the PNET concept and assumes that medulloblastomas are derived from subependymal matrix cells, which reside throughout the embryonal CNS, including the fourth ventricle, and which give rise to neuronal and glial cells. The PNET concept implies that medulloblastomas and supratentorial PNETs originate from a common precursor cell. However, there is evidence that infratentorial PNETs (medulloblastomas) and supratentorial PNETs show different

genetic alterations. Unlike medulloblastoma, supratentorial PNETs do not show allelic loss of chromosome arm 17p [264]. Similarly, inactivating mutations of the *PTCH* locus seem not to occur in this entity [2433]. Supratentorial PNETs express the human ACHAETE SCUTE homologue (HASH1) which is absent in medulloblastomas [1940]. Indeed, large scale gene expression analysis shows that medulloblastoma and PNET have distinct profiles [1773]. These findings argue against the hypothesis that PNETs of different locations may derive from closely related progenitor cells by similar genetic mechanisms. Perhaps most likely is a combined theory proposing that medulloblastomas can arise from more than one cell type, a concept supported by a range of expression studies. Calbindin-D, a ventricular matrix-associated calcium binding protein not expressed in the EGL or in granule neurons, was detected in 20 of 49 cerebellar medulloblastoma, primarily those of the classic (non-desmoplastic/nodular) subtype [1060]. Based on this, it was suggested that classic medulloblastoma derive from the ventricular zone, while nodular tumours originate from EGL cells. Others have advanced a similar "dual origin" hypothesis based on the elevated percentage of nodular tumours immunoreactive for the neurotrophin receptor p75, which is highly expressed in the cerebellar EGL but not in the ventricular zone [243]. Wnt activity, in contrast, seems to be associated with non-desmoplastic/nodular tumours, and may represent a signature of some ventricular zone-derived lesions [2244]. OTX1 and OTX2 expression also differentiates medulloblastoma subtypes, with the former associated with desmoplastic/nodular lesions, and the latter found in classic tumours [435]. Our understanding of stem and progenitor cells in the brain continues to evolve, and new candidate cells of origin continue to emerge. One such candidate is a class of CD133 positive stem cells found predominantly in the white matter of the postnatal cerebellum [1271].

Prognostic and predictive factors

Significant advances have been made in the treatment of childhood medulloblastoma; the 30% 5-year survival in the 1960s has now risen to 60–70%. This improvement has been attributed to improved surgical

and anaesthetic techniques, better neuroimaging and perioperative care, and more refined adjuvant therapies, which combine radiotherapeutic and chemotherapeutic regimens [428, 515, 687, 1661, 1662, 1898, 1962]. A similar increase in survival has been achieved in adult patients [210]. Current challenges are finding novel therapies for aggressive disease and the accurate identification of disease risk, which would facilitate the targeted use of adjuvant therapies, intensive regimens for high-risk tumours and reduced long-term adverse effects for patients with relatively responsive tumours [962, 1025]. Since the last edition of this classification, many prognostic indicators have been proposed for the medulloblastoma, but few have been proven to be independent in large cohorts of patients treated in the context of therapeutic trials.

Clinical criteria

The clinical stratification of childhood medulloblastoma currently involves distinguishing high-risk and standard-risk patients. The former group is aged less than 3 years, has an incomplete surgical resection of the tumour ($>1.5\text{ cm}^2$ residuum), or has metastatic disease (Chang stages M1–4) at presentation [962, 1661].

Histopathology

For some time, distinguishing the histopathological variants of medulloblastoma was not thought to be of particular clinical utility. However, a dismal prognosis has clearly been established for the large cell medulloblastoma [230, 670, 1255, 1435]. This variant is associated with a high frequency of metastatic disease [230, 498, 670]. In addition, several studies have now demonstrated that this variant and classic tumours with anaplastic cytological features form a continuum, and that large cell medulloblastomas and tumours with marked and widespread anaplasia (anaplastic medulloblastoma variant) have a significantly poorer prognosis than other tumours [230, 500, 671, 1435].

The desmoplastic variant has been associated with a better prognosis than the classic medulloblastoma in some studies, but others report no significant difference in outcome for these two tumour types [82, 322, 1535, 2182]. This discrepancy could relate to the use of different criteria in the diagnosis of desmoplastic medulloblastoma; if diagnosis relies on finding a nodular architecture among reticulin-positive internodular zones, then a better prognosis is often demonstrated for this variant [671, 2182]. A favourable outcome was recognized for

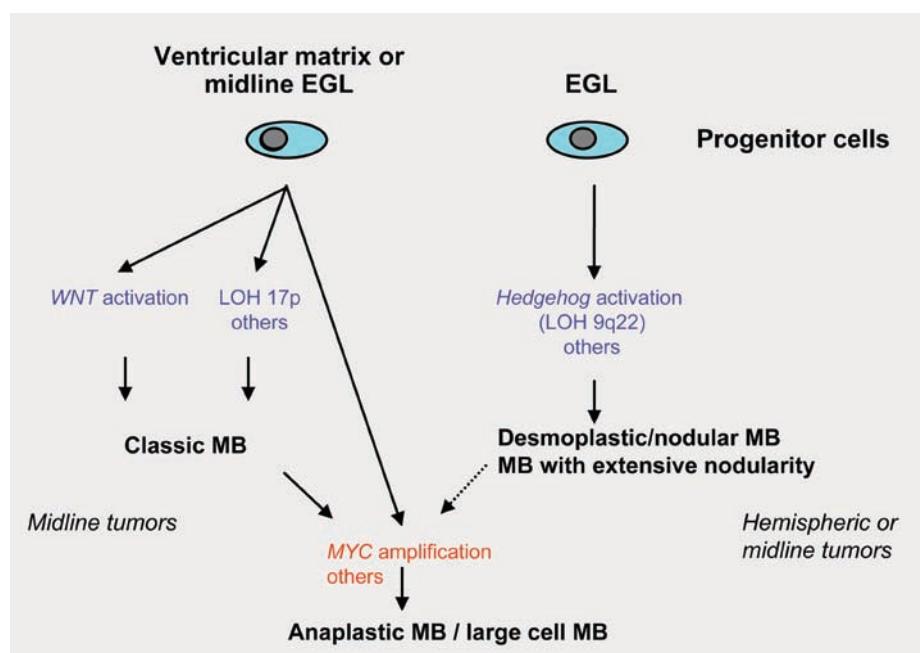


Fig. 8.13 Hypothetical model of the different origin and pathogenetic pathways of medulloblastoma variants. EGL, external granular layer. MB, medulloblastoma.

the desmoplastic/nodular tumours including medulloblastoma with extensive nodularity in a large proportion (47%) of one trial cohort of infants with a medulloblastoma. This tumours were associated with a much better survival than classic medulloblastomas {1963}.

Proliferation and apoptosis

There is no conclusive evidence that measures of proliferation or apoptosis have clinical utility; relevant studies provide conflicting data. However, an association between a simple evaluation of mitotic count or index and survival has been demonstrated for children with medulloblastoma {685, 1435}. Survival analyses do not support the use of PCNA labelling index (LI) or Ki-67/MIB-1 LIs as prognostic indicators {687, 1435, 1484, 1631, 2020}. BrdU LI may be associated with outcome; tumours with a LI of >20% appeared to have a worse prognosis in one study {929}.

Apoptotic indices have not been related

to prognosis in a consistent way {780, 1174, 1631, 1756, 2040}. However, the categorization of apoptosis into 'focal', 'diffuse' and 'extensive' produced an association with survival in medulloblastomas with focal apoptosis showing a better prognosis than tumours in the other two categories. This study also found a link between cytological anaplasia and survival {671}. The overall picture is further confounded by studies of markers that have functional roles in the regulation of apoptosis. Thus, although Bcl-2 prevents programmed cell death induced by irradiation, medulloblastomas with immunoreactivity for Bcl-2 do not recur earlier than those lacking Bcl-2 expression {1568}. This result could be related to a lack of correlation between Bcl-2 expression and apoptotic indices {2040}.

Molecular markers

Molecular genetic markers that have been shown to have independent prognostic significance alongside clinical and

pathological variables in patients from trial cohorts include isochromosome 17q, loss of 17p, and amplification of the MYCC or MYCN genes {113, 1255, 2015}. These are indicators of an adverse prognosis, as is overexpression of ErbB2 {686}. In contrast, nuclear accumulation of β -catenin, a marker of activation in the canonical Wnt/Wg pathway, is an independent marker of a good outcome {516}. Medulloblastomas with this immunophenotype generally lack molecular cytogenetic abnormalities, with the exception of monosomy 6 {2244}. Measuring a combination of TrkC expression, which appears to be associated with prolonged survival, and c-MYC expression may be useful in separating biologically distinct groups of medulloblastoma {728}. Abnormally overexpressed PDGF receptor, p53, STK15 and CDK6 may be validated as indicators of a poor prognosis {684, 973, 1371, 1454, 1573, 2440}.

Central nervous system primitive neuroectodermal tumours

R.E. McLendon
A.R. Judkins
C.G. Eberhart
G.N. Fuller
C. Sarkar
H.-K. Ng

Definition

A heterogeneous group of tumours occurring predominantly in children and adolescents. They may arise in the cerebral hemispheres, brain stem, or spinal cord, and are composed of undifferentiated or poorly differentiated neuroepithelial cells which may display divergent differentiation along neuronal, astrocytic and ependymal lines. CNS supratentorial PNET is an embryonal tumour composed of undifferentiated or poorly differentiated neuroepithelial cells. Tumours with only neuronal differentiation are termed cerebral neuroblastomas or, if ganglion cells are also present, cerebral ganglioneuroblastomas. Tumours that recreate features of neural tube formation are termed medulloepitheliomas. Tumours with ependymoblastic rosettes are termed ependymoblastomas. Features common to all CNS PNET variants include early onset and aggressive clinical behaviour.

ICD-O codes

CNS PNET, NOS	9473/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
Medulloepithelioma	9501/3
Ependymoblastoma	9392/3

Since the designation of some primitive neuroectodermal tumours of the central nervous system (CNS) is also used for similar, but not identical tumours at extra-cerebral sites, the WHO Working Group

proposes to add the prefix CNS to these entities, in order to avoid any confusion. The term CNS PNET, not otherwise specified (NOS) is synonymous with the current ICD-O term supratentorial PNET (9473/3) and used for undifferentiated or poorly differentiated embryonal tumours that occur at any extracerebellar site in the CNS.

Grading

As with other embryonal brain tumours, all CNS PNETs correspond histologically to WHO grade IV.

CNS/supratentorial PNET

Definition

An embryonal tumour composed of undifferentiated or poorly differentiated neuroepithelial cells which have the capacity for, or display, divergent differentiation along neuronal, astrocytic, muscular or melanocytic lines. Tumours with only neuronal differentiation are termed cerebral neuroblastomas or, if ganglion cells are also present, ganglioneuroblastomas.

Incidence

Precise incidence is difficult to determine because of differing viewpoints regarding classification and the rarity of these tumours. One percent of 933 primary paediatric CNS neuroepithelial tumours were found to be located in the cerebrum or suprasellar region; among CNS PNETs, 10 of 178 (5.6%) were located in these regions.

Age and sex distribution

The age range for CNS PNET is 4 weeks to 20 years, with a mean of 5.5 years. The male:female ratio for supratentorial PNETs and cerebral neuroblastomas is 1.2:1.

Localization

These tumours are found most commonly in the cerebrum, but can also be encountered in the spinal cord or suprasellar region.

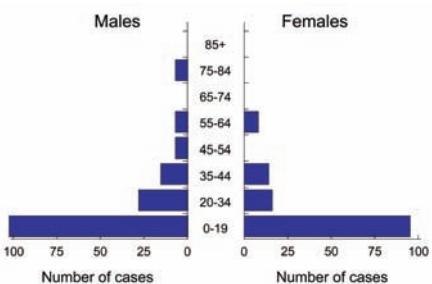


Fig. 8.14 Age and sex distribution of supratentorial PNET and cerebral neuroblastomas, based on 305 cases. Data from CBTRUS 1995-2002 (305).

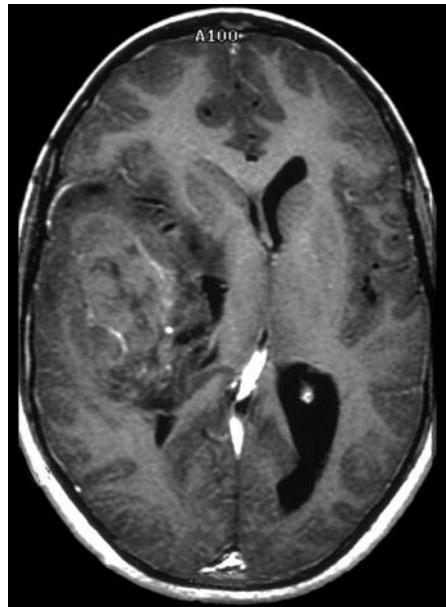


Fig. 8.15 T1-weighted MRI of a large, hemispheric PNET with advanced neuronal differentiation (neuroblastoma).

Clinical features

Signs and symptoms are related to the site of origin of the tumour. Those arising in the cerebrum often present with seizures, disturbances of consciousness, increased intracranial pressure or motor deficit. The suprasellar lesions produce visual and/or endocrine problems. If the patient is an infant, the head circumference may increase more rapidly than normal.

Neuroimaging

Computed tomographic findings in CNS PNET are similar, regardless of the site of origin of the tumour. They are iso-to-hyperdense, but density increases following injection of contrast material. They may appear as solid masses or may contain cystic or necrotic areas. Between 50 and 70% of all CNS PNET contain calcium. Edema surrounding parenchymal masses is not usually extensive. Appearance of PNET on magnetic resonance imaging may vary with the site of origin. On T1-weighted MRI, the tumours are hypointense relative to cortical grey matter. They look

similar on T2-weighted imaging, but cystic or necrotic areas are hyperintense. There is contrast enhancement with gadolinium on T1-weighted imaging. If the tumour has bled, the region of haemorrhage is hypointense on T2-weighted imaging.

Macroscopy

The tumours are of variable size at the time of clinical presentation. Those in the suprasellar region tend to be smaller than those in the cerebrum. The parenchymal tumours may be massive growths, with or without cysts or haemorrhages. Demarcation between tumour and brain may range from indistinct to clear-cut. They have a pink-red to purple colour. They are soft unless they contain a prominent desmoplastic component, in which case they are more firm and have a tan colour.

Histopathology

The typical tumour is very poorly differentiated, being composed of cells with round regular nuclei and high nucleus:cytoplasm ratios. Better differentiated tumours may show more clearly neuronal features, with oval to elongated nuclei that have vesicular chromatin and nucleoli; occasionally, processes and even Nissl substance may be encountered in such tumours when more mature populations are evident (ganglioneuroblastomas). Fibrillar cytoplasm may form the background in these tumours. A fibrous stroma can vary from a delicate lobular framework to dense fibrous cords. Homer Wright rosettes are often found but vary in frequency. Tumour cells

may occasionally be arranged in parallel streams and palisades, resembling the pattern seen in polar spongioblastoma {868, 1259} or in single file patterns akin to the adrenal neuroblastoma. Populations of more mature round regular neurocytic (granule cell) forms may rarely be found {1865}. Calcification is a relatively constant feature within degenerate regions. Vascular endothelial proliferation may also be seen. Cerebrospinal dissemination can be found in up to one third of patients {868}. Extraneuronal metastases to bone, liver and cervical lymph nodes have been reported {134}.

An unusual PNET that occurs in the brain stem, cerebellum and cerebrum has been called "embryonal tumour with abundant neuropil and true rosettes" {497}. These are characterized by focal high cellularity, broad bands of neoplastic neuropil, and true rosettes with slit-like or oval lumens that often arise in the fibrillar areas. Tumours with this pattern of growth are associated with extremely poor clinical outcomes, and may eventually be recognized as a unique variant.

Immunohistochemistry

Neuroblastomas express many of the phenotypic markers of neuronal cells, including synaptophysin, class III β -tubulin, and neurofilament protein {716}. Cerebral neuroblastomas also express S-100, NSE, and Leu-7 (CD-57) {1865}. However, a pure population of phenotypically recognizable neuroblasts is rarely encountered in these neoplasms. Undifferentiated small anaplastic cells, by both light microscopic and ultrastructural

methods, typically constitute the majority of the cellular populations of these tumours. Immunohistochemical techniques occasionally reveal GFAP to be expressed among these undifferentiated cells, indicative of divergent cellular phenotypes. Antigen expression is unique for each tumour, making prediction of patterns of expression for one or a group of tumours unreliable.

Electron microscopy

The typical tumour is very poorly differentiated, revealing only a sparse population of cytoplasmic organelles. While microtubules may be found, dense core vesicles, although not always present, are diagnostic of neuroblastoma. With ganglionic differentiation, some processes may terminate as growth cones containing arrays of microtubules. Demonstration of synapses is exceptional {1865}. Compact arrays of cytoplasmic glial filaments supports glial differentiation, although intervening reactive astrocytes must be ruled out {1959}.

Proliferation

PNET at any site show a variable amount of mitotic activity. Proliferation is most accurately measured by use of the immunohistochemical marker Ki-67. The percentage of cells undergoing proliferation is generally high but may vary from 0–85% in any given high-power field.

Genetics

The i(17)q abnormality found in 30 to 50% of medulloblastomas has been found in only one supratentorial PNET

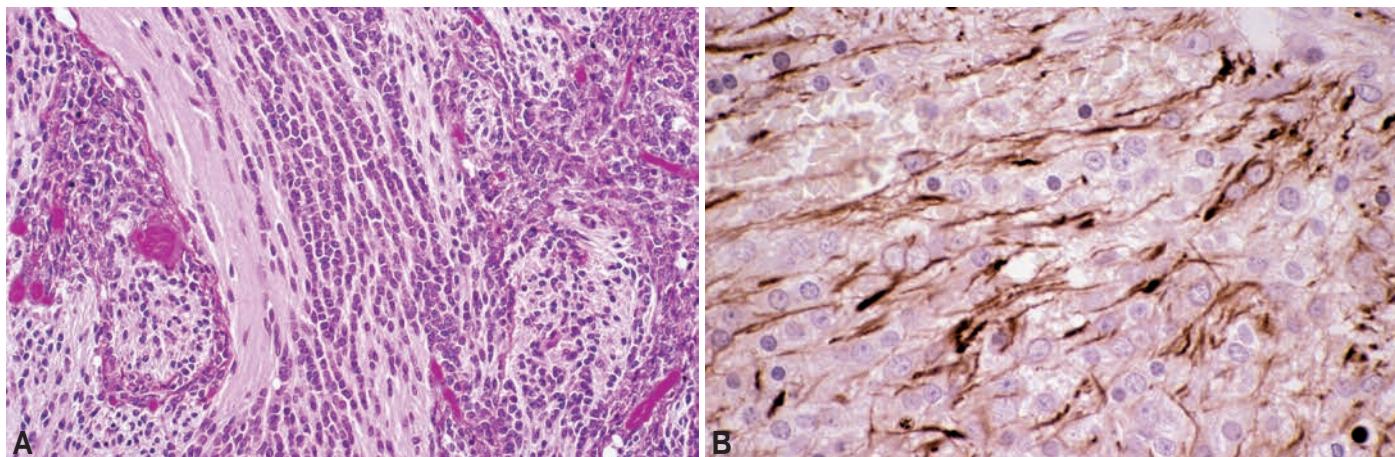


Fig. 8.16 A CNS PNET with advanced neuronal differentiation (cerebral neuroblastoma) exhibiting a nodular architecture with typical streaming of tumour cells. B Neurofilament staining predominantly of tumour cell processes.

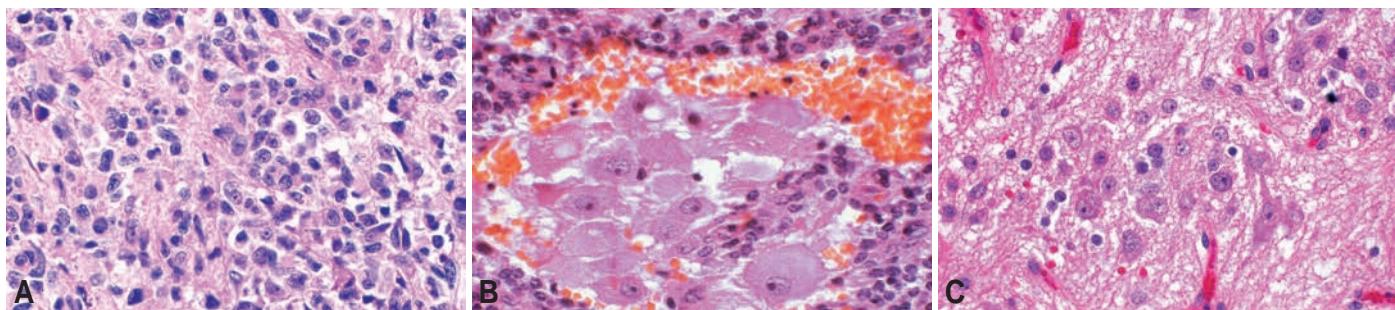


Fig. 8.17 Tumour cells in different stages of neuronal differentiation (A) and cluster of mature ganglion cells next to an area of poorly differentiated elements (B) in cerebral neuroblastoma. C Region of low cellularity in a ganglioneuroblastoma showing some tumour cells with neuronal phenotype.

{1805} and in one neuroblastic tumour with abundant neuropil and true rosettes {627}. Several studies disclosed a variety of non-random cytogenetic gains and losses {264, 152}, but no i(17q) {165}. Scattered reports of other genetic abnormalities in these tumours include identification of *RASSF1A* promoter methylation {318}, expression of the Neuro D family of basic helix-loop-helix transcription factors, and achaete scute, another neurogenic transcription factor with homology to *Neuro D* genes {1940}. This latter gene was actually expressed in 3 of 5 PNET arising outside the cerebellum, but not in medulloblastoma. Thus, although the number of cytogenetic studies is small, it appears that genetic events associated with development of PNET in the supratentorial compartment are different from medulloblastoma {1960, 1425}.

Histogenesis

The histogenesis of PNETs as a group has been a controversial issue for many years, and the only issue upon which consensus has been achieved is that these embryonal tumours arise from primitive neuroepithelial cells {1121, 1921}. The recent identification of neurons derived from haematopoietic stem cells only adds to the controversy {1467A}.

Prognostic and predictive factors

Infants who are less than two years old at the time of diagnosis of a CNS PNET have a bleaker prognosis than older children {663}. Children with CNS PNET have a worse overall 5-year survival rate compared to children with medulloblastoma {662, 2250}. The relationship between survival and various histological features has not been determined in supratentorial PNET.

Medulloepithelioma

Definition

A rare, malignant embryonal brain tumour affecting young children, histologically characterized by papillary, tubular or trabecular arrangements of neoplastic neuroepithelium mimicking the embryonic neural tube.

Age and sex distribution

Medulloepitheliomas are rare tumours that typically affect children between 6 months and 5 years, with half occurring during the first two years {1509}. In 37 published cases the age at presentation ranged from <1 month to 23 years with a mean age of 45 months; cases were equally distributed between males and females (male:female ratio, 1:1) {2068, 1509, 2326, 1606}. Congenital tumours have been described. Rare cases occurring beyond the first decade have also been reported {1509, 2010}.

Localization

Medulloepitheliomas develop in both the supra- and infratentorial compartments {1509, 429, 1606, 1988}. The most common site within the cerebral hemispheres is periventricular, involving in order of frequency: temporal, parietal, occipital and frontal lobes. Occasionally, these tumours may be very large and involve multiple lobes or both cerebral hemispheres {2176}. Medulloepitheliomas may also be intraventricular and have also been described in the sella/parasellar region, cauda equina, and presacral area {578, 1675, 2326}. Outside the central nervous system these tumours may arise along nerve trunks, within the pelvic cavity, and in the eye where they are typically intraorbital {1566, 233, 481}. Intraorbital medulloepitheliomas rarely metastasize, are

effectively treated by enucleation and generally carry a favourable prognosis {1606, 2326}. Medulloepitheliomas may also arise in the optic nerve. Based on a small number of reported cases, these tumours do not appear to carry the favourable prognosis of intraorbital medulloepitheliomas but may be associated with somewhat better long-term survival than intracerebral medulloepitheliomas {720A, 324, 2295, 332}.

Clinical features

The tumour is often large at the time of clinical presentation, with symptoms of increased intracranial pressure such as headaches, nausea and vomiting. All patients have had abnormal neurological examination at clinical presentation. CT and MR imaging characteristics have been variable. At initial presentation, these tumours have been described as well circumscribed and isodense to minimally hypodense on CT and non-enhancing with intravenous contrast; enhancement typically appears with tumour progression {1509}. On T1-weighted MR imaging, medulloepitheliomas have been either hypointense or isointense {431}; however, they are hyperintense on T2-weighted images {1675}. Cysts and calcifications have been reported.

Macroscopy

Medulloepitheliomas are often massive, grayish pink in color and well-circumscribed with areas of haemorrhage and necrosis. Occasionally, there is infiltration of the subarachnoid space at the initial presentation, while diffuse dissemination is frequent at the time of death.

Histopathology

Medulloepitheliomas are malignant neoplasms that mimic the embryonic neural tube and are characterized by papillary,

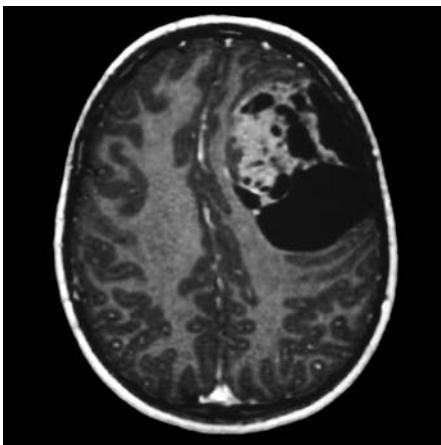


Fig. 8.18 T1-weighted gadolinium-enhanced MRI of a cystic medulloepithelioma in the frontal lobe.

tubular or trabecular arrangements of neoplastic neuroepithelium with an external limiting membrane. These tumours often display multiple lines of differentiation, including neural, glial and mesenchymal elements. The diagnostic feature of medulloepithelioma is the distinctive pseudostratified epithelium arranged in papillary and tubular patterns that resembles the structure of the primitive neural tube [1045]. On the luminal (inner) marginal surface of the tubules there are no cilia or blepharoblasts, but there may be discrete protruding blebs. On the outer surface of the epithelium is an external limiting membrane which stains with PAS and is immunopositive with antiserum to collagen type IV. This basement membrane rests on a delicate network of reticulin. The cells have a columnar to cuboidal shape. The nuclei are oval to piloid, are perpendicular to the inner and outer surfaces, and are characterized by coarse chromatin and multiple nucleoli. Mitotic figures are abundant and tend to be located near the luminal surface similar to the early stages of neural tube development. In areas distinct from the neuroepithelium there are sheets of tumour cells with hyperchromatic nuclei and a high nuclear to cytoplasmic ratio. These cells may show a range of differentiation: neuronal, astrocytic, ependymo-blastic or oligodendroglial [72, 444]. There is also a spectrum in the degree of differentiation from embryonic early differentiated cells to mature neurons and astrocytes. In medulloepitheliomas, ependymoblastomatous rosettes are more common than ependymal rosettes, but both may occur.

Areas of oligodendro-glial differentiation are suggested by round regular nuclei and white halos and negative immunohistochemistry with antiserum for synaptophysin. A primitive neuroectodermal tumour with tubules containing melanin pigment has been described as a pigmented medullo-epithelioma [2068]. Rare tumours may manifest development along mesenchymal lines that range from a prominent vascular and fibrous connective tissue stroma to areas of cartilage, bone and striated muscle [72, 271].

Immunohistochemistry

The neuroepithelial components of medulloepitheliomas show immunoreactivity for nestin and vimentin. Both of these markers demonstrate an expression gradient with basal greater than luminal labelling; indeed, nestin is largely confined to the basal area [1099, 2254]. Less frequently, tumour cells in some cases may also display focal expression of neurofilament protein, cytokeratins, and epithelial membrane antigen [271, 1099, 2268]. Neuroepithelial areas do not exhibit GFAP, neuron specific enolase or S-100 protein expression. Expression of both basic fibroblast growth factor and insulin-like growth factor I (IGF-I) has been reported in medulloepithelioma [2091]. In areas away from the neuro-epithelium, immunoreactivity reflects the pattern and degree of differentiation of the tumour. Neuron-specific enolase, synaptophysin, neurofilament and microtubule associated proteins reveal an increasing degree of expression commensurate with the degree of neuronal differentiation [271]. Astrocytic differentiation spans the spectrum, from densely cellular areas with high mitotic activity and variable GFAP expression to areas of low to moderate cellularity with mature differentiation and consistently strong GFAP expression.

Proliferation

Medulloepitheliomas have a high rate of proliferation. The epithelium is also mitotically active, with mitotic figures located predominantly near the luminal surface. Ki-67 labelling may be extremely variable within these tumours with areas of low (1–3%) labelling adjacent to those with extremely high labelling (>50%).

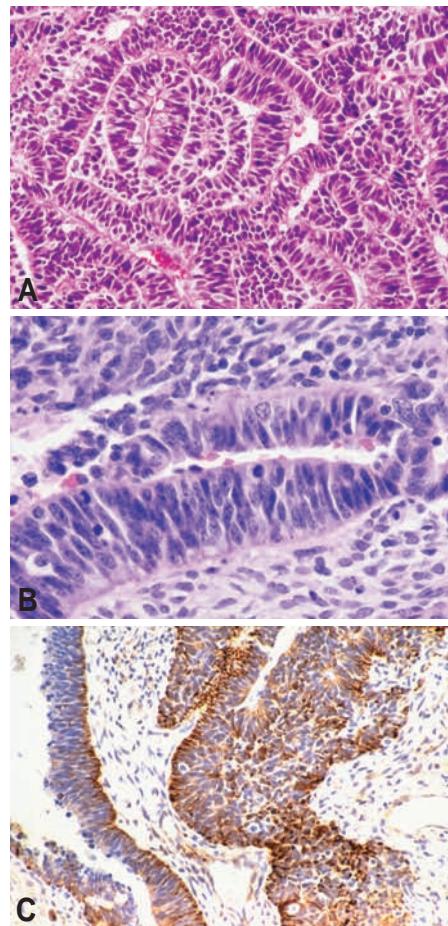


Fig. 8.19 A Typical papillary and trabecular pattern in medulloepithelioma. B Immature neuroepithelial cells resting on a basement membrane. Mitotic cells tend to be located towards the luminal surface. C Nestin expression predominates on the basal side of neoplastic neuroepithelial cells.

Electron microscopy

Ultrastructural examination of the neuroepitheliomatous areas reveals extensive primitive lateral cell junctions (zonulae adherentes) and a basal lamina on the outer surface of the epithelial cells, consisting of a distinct, continuous, often folded, basement membrane [1771, 2268]. On the luminal side, there is an amorphous surface coating but no true membrane. Cells appear poorly differentiated with sparse cytoplasmic organelles and absence of cilia or microvilli.

Histogenesis

Microscopy, immunohistochemistry and electron microscopy of medulloepitheliomas demonstrates features that resemble the primitive neural tube [1099, 2254]. It has therefore been proposed that medulloepitheliomas may derive from a primitive

cell population in the subependymal region.

Differential diagnosis

Medulloepitheliomas may show a variety of histologic patterns that can raise a broad differential diagnosis including medulloblastoma, ependymoblastoma, neuroblastoma and choroid plexus carcinoma. However, careful examination of most medulloepitheliomas will reveal the distinctive tubular or trabecular arrangements of neoplastic neuroepithelium that are unique to this tumour. Where ependymoma and choroid plexus carcinoma may be difficult to eliminate on histologic grounds alone, the distinctive immunohistochemical staining of medulloepitheliomas will resolve these diagnoses. Immature teratomas are included in the differential diagnosis because they frequently contain primitive medullary epithelium, together with neuroectodermal differentiation. The distinction from medulloepithelioma is that immature teratomas contain tissue of foetal appearance from other germ layers.

Genetics

The molecular genetics of medulloepitheliomas of the central nervous system have not been extensively characterized. However, molecular analysis of two cases demonstrated *hTERT* gene amplification similar to and even exceeding that seen in medulloblastomas. CGH analysis of both the primary and recurrent specimens from one of these tumours was also performed. This showed gains in 3p13-22, 6p21.2-21.3, 14q24-qter, 15q15-25 and 20q in the primary medulloepithelioma. Additional gains were identified in the recurrent tumour including high level gains at 5p15 consistent with *hTERT* gene amplification, as well as losses involving 4p14-q28, 4q34-qter, 5q, 13q and 18q12-qter [549]. Analysis of a single intraocular medulloepithelioma demonstrated only non-specific cytogenetic changes [146].

Prognostic and predictive factors

Medulloepitheliomas are rapidly growing tumours that arise at a young age, and their optimal management is unknown. Treatment with gross total resection is a feature of long-term survivors [1509]. Radiation may also provide some benefit. However, most children with medulloepithelioma die within a year of

diagnosis, often with cerebrospinal fluid dissemination but rarely with systemic metastases.

Ependymoblastoma

Definition

A rare, malignant, embryonal brain tumour manifesting in neonates and young children, histologically characterized by distinctive multilayered rosettes.

Age and sex distribution

Consistent with the primitive neuroepithelial nature of the tumour, the ependymoblastoma occurs in young children, including neonates [477, 1393]. Males and females appear to be equally affected.

Localization

These neoplasms are often large and supratentorial and generally relate to the ventricles although they do occur at other sites [1337, 1525]. A sacrococcygeal congenital ependymoblastoma with elevated serum α -fetoprotein [1537] and a primary leptomeningeal ependymoblastoma have been documented [2354].

Clinical features

In the first and second year of life, the most common clinical manifestation is increased intracranial pressure and hydrocephalus. Focal neurological signs are more common in older children. Neuroimaging criteria do not allow a distinction from other primitive neuroectodermal tumours [484]. CT and MR usually show a contrast-enhancing, large tumour mass surrounded by an extensive area of edema.

Macroscopy

Ependymoblastomas tend to be well circumscribed with a distinct tumour margin, although focal microscopic extension and leptomeningeal invasion are common. Widespread leptomeningeal invasion and extraneuronal metastases have been described [281]. The unusual extension of a supratentorial ependymoblastoma through the tentorium into the cerebellum has been documented [1512].

Histopathology

Diagnostic features are those of a central primitive neuroectodermal tumour with distinctive multilayered rosettes, with cells in the outer rim of the rosette merging with

the surrounding undifferentiated neuroectodermal cells. The chief histological characteristic of ependymoblastoma is dense cellularity with prominent numbers of distinctive true "ependymoblastomatous" rosettes. These rosettes are multi-layered and form concentric cellular rings around small round central lumina. The nuclei of these cells tend to be pushed away from the lumen towards the outer cell border, and the chromatin is coarse and nuclei distinct. The cells have high mitotic activity. The cells facing the lumen have a defined apical surface beneath which is a faint stippling that corresponds to blepharoplasts. These apical surfaces may form a prominent internal limiting membrane. The outer layer of cells merges with the background of undifferentiated cells with small round-to-oval nuclei and wispy cytoplasmic processes.

Immunohistochemistry

Expression of S-100, vimentin, cytokeratin, GFAP and carbonic anhydrase isoenzyme II has been demonstrated [509, 1393, 400, 1682]. One report describes immunoreactivity to NF 68, 160 and 200 kDa neurofilaments [1509].

Electron microscopy

Tumour cells are compactly arranged and poorly differentiated, with large nuclei and a high nuclear to cytoplasmic ratio. Cytoplasm is scanty with few organelles. In rosettes the cells are united by long or short junctional complexes featuring thickened and electron dense membranes. Frequent "abortive" cilia [400] and a few basal bodies oriented toward the lumen of the rosette [1258] have been observed,

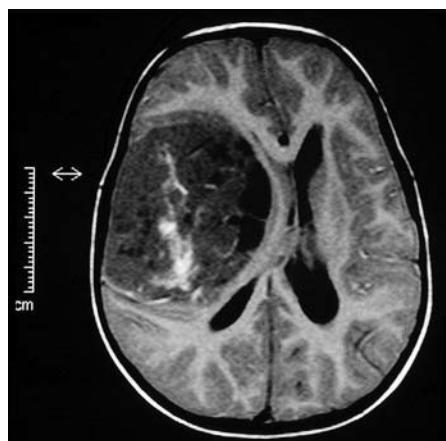


Fig. 8.20 MRI of an ependymoblastoma bordering the lateral ventricle.

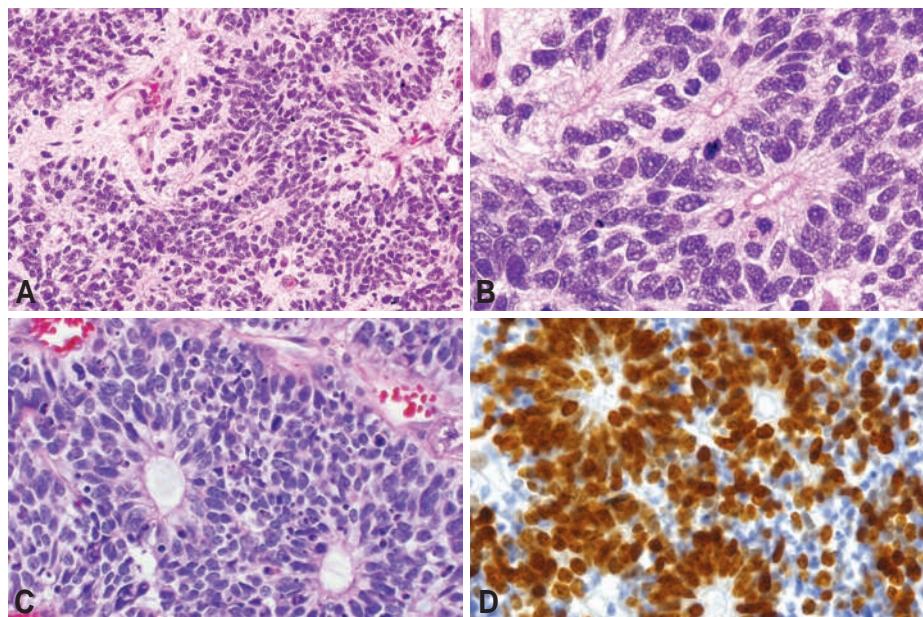


Fig. 8.21 Histological features of ependymoblastoma. A and B Ependymoblastoma with well-formed true rosettes arising within the background of PNET-like cytology. C Ependymoblastoma characterized by ependymal rosette formation. D Very high proliferative activity in ependymoblastic rosettes (MIB-1).

as have short bands of glial-like filaments.

Differential diagnosis

Ependymoblastoma must be distinguished from anaplastic ependymoma, which is characterized by prominent perivascular pseudorosettes in which radially-oriented cell processes form nuclei-free zones around blood vessels (perivascular pseudorosettes) and ependymal rosettes that, in contrast to ependymoblastoma-type rosettes, exhibit only a limited,

often single, circumferential layering of cells. Medulloepitheliomas may contain ependymoblastoma-type rosettes, but are primarily characterized by distinctive diagnostic neuroepithelium that is based on an outer basement membrane and characteristic architectural features that include long linear tubular, canalicular and papillary patterns. The latter tumours also often display a spectrum of neuroectodermal differentiation including ependymal, glial, neuronal and oligodendroglial features. Medulloblastomas

are characterized by a cerebellar location and frequent presence of Homer Wright (neuroblastoma-type) rosettes that, in contrast to ependymoblastoma-type rosettes, lack a central lumen [396, 1923]. Embryonal tumour with abundant neuropil and true rosettes [497], discussed previously, should also be considered in this differential.

Histogenesis

These tumours are presumed to arise from periventricular neuroepithelial precursor cells. The term 'ependymoblast' implies an incompletely differentiated phenotype showing glial and ependymal features together with immature characteristics, such as a high nucleus-to-cytoplasmic ratio, dense chromatin and brisk mitotic activity [400, 1948].

Prognostic and predictive factors

Biological characteristics are similar to other embryonal neuroepithelial tumours [396]. Ependymoblastomas grow rapidly, with craniospinal dissemination and fatal outcome usually within 6 months to one year of diagnosis. Development of effective treatment protocols for ependymoblastomas is limited by the rarity of occurrence, young age of onset and aggressive tumour behaviour. Some studies suggest that gross total resection of ependymoblastoma is a predictor of outcome [1899]. Consistent with the response of other primitive neuroepithelial tumours, post-operative irradiation may prolong survival.

Atypical teratoid/rhabdoid tumour

A.R. Judkins
C.G. Eberhart
P. Wesseling

Definition

A highly malignant CNS tumour predominantly manifesting in young children, typically containing rhabdoid cells, often with primitive neuroectodermal cells and with divergent differentiation along epithelial, mesenchymal, neuronal or glial lines; associated with inactivation of the *INI1/hSNF5* gene in virtually all cases.

ICD-O code 9508/3

Grading

This tumour corresponds to WHO grade IV.

Synonyms and historical annotation

Malignant rhabdoid tumours were initially described in the kidney and subsequently in soft tissues of infants and young children. The first example affecting the CNS was reported in 1985 {1519A} and simply called 'rhabdoid tumour'. These tumours were named 'atypical teratoid/rhabdoid tumours' (AT/RT) when they occurred in the CNS to call attention to the disparate combination of rhabdoid, primitive neuroepithelial, epithelial and mesenchymal components {1924}. The complex histologic pattern resulting from these disparate elements has sometimes resulted in misclassification of these tumours as CNS PNET/medulloblastomas, choroid plexus carcinomas, germ cell tumours and malignant gliomas.

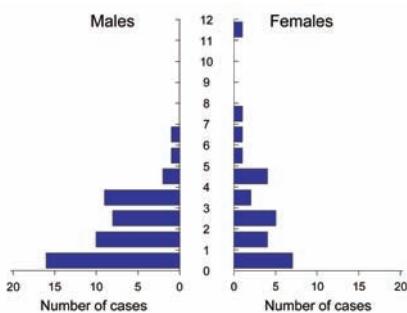


Fig. 8.22 Age and sex distribution of atypical teratoid/rhabdoid tumour, based on 73 patients {823, 2231}.

Incidence

Several large series have established the incidence of AT/RT at 1–2% of paediatric brain tumours {1876, 1922, 2438}. However, due to the preponderance of cases in children under the age of three, AT/RTs are estimated to account for at least 10% of CNS tumours in infants {153}.

Age and sex distribution

AT/RTs are paediatric tumours most often presenting under the age of 3, and rarely in children older than 6 years (mean age, approx 2 years). There is a male predominance ranging from 1.6–2:1 {823, 2231}. AT/RTs occur rarely in adults {1823}.

Localization

In two large series of paediatric cases, the ratio of supratentorial to infratentorial tumours is 1.3:1 {823, 2231}. Supratentorial tumours are often located in the cerebral hemispheres, and less frequently in the ventricular system, suprasellar region or pineal gland. Infratentorial tumours can be located in the cerebellar hemispheres, cerebellopontine angle and brain stem, and are relatively frequent in the first two years of life. Infrequently, AT/RTs arise in the spinal cord. Seeding of AT/RTs via the cerebrospinal fluid pathways is common and may be found in more than 20% of the patients at presentation {823}. Infratentorial localization is relatively rare in adult patients diagnosed with AT/RT {529}.

Clinical features and neuroimaging

Symptoms and signs

Clinical presentation is variable, depending upon the age of the patient, location, and size of the tumour. Infants, in particular, present with non-specific signs of lethargy, vomiting or failure to thrive. More specific problems include head tilt and cranial nerve palsy, most commonly sixth and seventh nerve paresis. Headache and hemiplegia are more commonly reported in children older than three years.



Fig. 8.23 Atypical teratoid/rhabdoid tumour with multiple haemorrhages, arising in the right cerebellopontine angle.

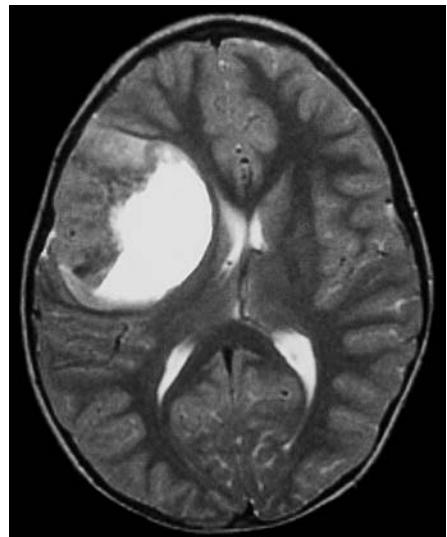


Fig. 8.24 Enhanced, T1-weighted MRI of a large, cystic supratentorial atypical teratoid/rhabdoid tumour.

Neuroimaging

Findings on both CT and MRI are similar to those seen in patients with PNET/medulloblastoma. AT/RTs are iso- to slightly hyperintense by fluid-attenuated inversion-recovery (FLAIR) and show restricted diffusion. Cystic and/or necrotic regions are apparent as zones of heterogeneous signal intensity. Almost all tumours are variably contrast-enhancing, and leptomeningeal dissemination can be seen in up to a quarter of cases at presentation {1466}.

Macroscopy

These tumours (and their deposits along the cerebrospinal fluid pathways) generally have a similar gross appearance to medulloblastoma and other CNS PNET. The tumours tend to be soft, pinkish-red and bulky, and often appear to be demarcated from adjacent parenchyma. They typically contain necrotic foci and may be haemorrhagic. Those with significant amounts of mesenchymal tissue are firm and tan-white in some regions. Tumours arising in the cerebellopontine angle wrap themselves around cranial nerves and vessels and invade the brain stem and cerebellum to a variable extent.

Histopathology

AT/RTs can be heterogeneous lesions that are sometimes difficult to recognize solely using histopathologic criteria [263,1924]. The most striking feature in many cases are cells with classic rhabdoid features: eccentrically placed nuclei containing vesicular chromatin, prominent eosinophilic nucleoli, abundant cytoplasm with an obvious eosinophilic globular cytoplasmic inclusion and well-defined cell borders. In practice, the appearance of these cells typically falls along a spectrum ranging from this classic rhabdoid phenotype to cells with less striking nuclear atypia and large

amounts of pale eosinophilic cytoplasm. The cytoplasm of these cells has a fine granular homogeneous character or may contain a poorly defined dense pink 'body' resembling an inclusion. Ultrastructurally, rhabdoid cells typically contain whorled bundles of intermediate filaments filling much of the perikaryon [162, 745]. A frequently encountered artifact in these cells is extensive cytoplasmic vacuolation. Rhabdoid cells may be arranged in nests or sheets and often have a jumbled appearance. However, it is only the minority of cases in which these cells are the exclusive or predominant histopathologic finding. Most tumours contain variable components with primitive neuroectodermal, mesenchymal and epithelial features. In practice, a small cell embryonal component is the most commonly encountered, in about two thirds of tumours. Mesenchymal differentiation is less common and typically appears as areas with spindle cell features and a basophilic or mucopolysaccharide rich background. Epithelial differentiation is the least common histopathologic feature. When present, however, it can take the form of papillary structures, adenomatous areas or poorly differentiated ribbons and cords. In cases where this is the predominant histopathologic pattern, distinction from choroid

plexus carcinoma can be challenging. Mitotic figures are usually abundant. Broad areas of geographic necrosis and haemorrhage are commonly encountered in these tumours.

Immunohistochemistry

AT/RTs demonstrate a broad spectrum of immunohistochemical reactivity that is consistent with their histologic diversity. However, the rhabdoid cells characteristically demonstrate consistent expression of EMA and vimentin, with only slightly less frequent expression of SMA. Expression of GFAP, NFP, synaptophysin and keratins are also commonly observed. By contrast, germ cell markers are not typically expressed. Regions of the tumour showing other histologic patterns may also show expression of these markers, though the pattern and frequency varies. Immunohistochemical staining for expression of the INI1 protein has been shown to be a sensitive and specific marker for AT/RTs. In normal tissue and most neoplasms, INI1 is a constitutively expressed nuclear protein; in AT/RTs, there is loss of nuclear expression of INI1 in tumour cells. Paediatric primitive neuroectodermal CNS tumours without rhabdoid features but with loss of INI1 expression in the biopsy material may very well represent

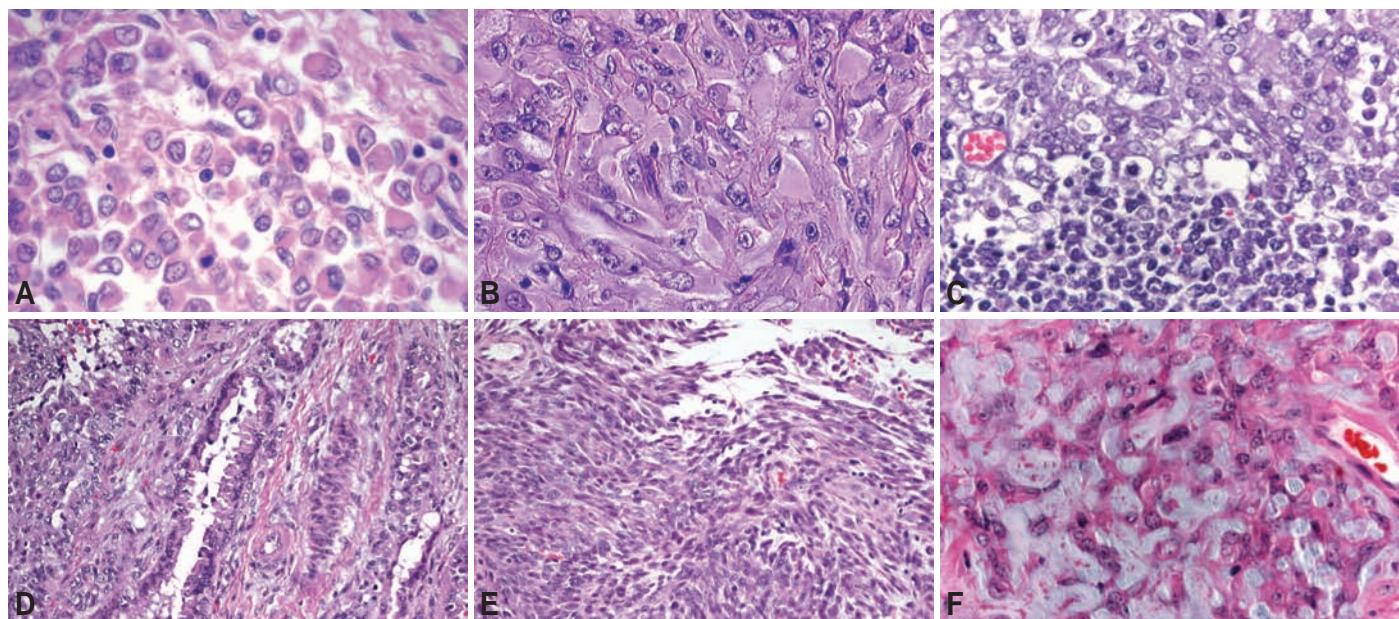


Fig. 8.25 Atypical teratoid/rhabdoid tumours. A Rhabdoid cells with vesicular chromatin, prominent nucleoli and eosinophilic globular cytoplasmic inclusions. B Tumour cells with abundant pale eosinophilic cytoplasm. C Tumour with prominent primitive neuroectodermal component and rhabdoid cells with vacuolar artifact. D Tumour with epithelial differentiation exhibiting a glandular component. E Tumour with mesenchymal differentiation exhibiting a spindle cell component. F Tumour with mesenchymal differentiation exhibiting a mucopolysaccharide-rich background.

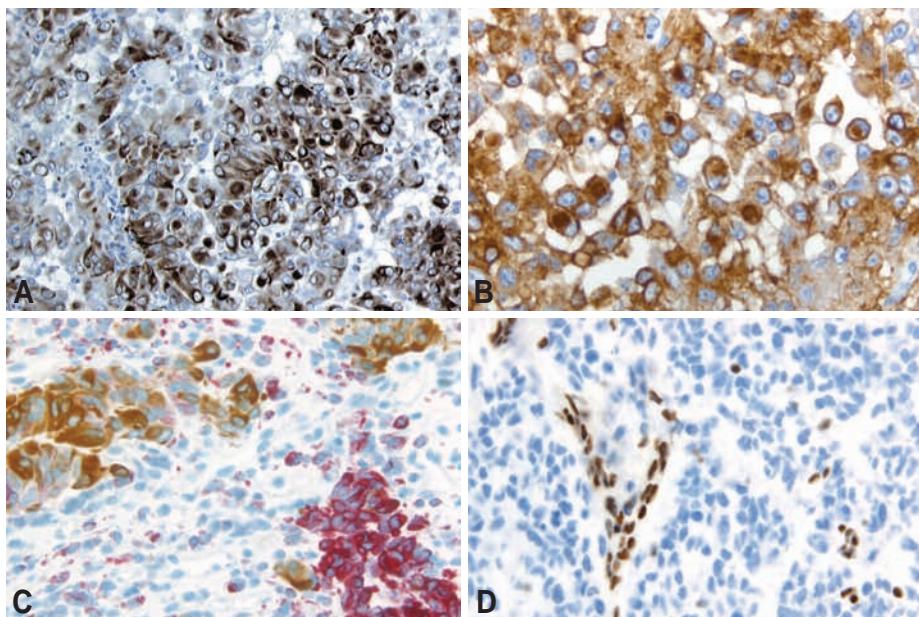


Fig. 8.26 Immunohistochemical features of atypical teratoid/rhabdoid tumours. A Strong expression of vimentin. B Membranous and cytoplasmic expression of EMA. C Expression of GFAP (brown) and NFP (red). D Loss of expression of INI1 in nuclei of tumour cells with retained expression in intratumour blood vessels.

AT/RTs {747}. While some authors have reported inactivation of *INI1* in choroid plexus carcinoma, others believe that such lesions have histopathological features justifying a diagnosis of AT/RT and that classic choroid plexus carcinomas do not lose *INI1* expression {660,1016}.

Proliferation

AT/RTs in children have marked proliferative activity with Ki-67/MIB-1 labelling indices that are often more than 50%, focally up to 100% {841}. Limited data are available on adult patients, but in some cases the labelling index may be significantly lower {1361}.

Histogenesis

The histogenesis of rhabdoid tumours is unknown. Neural, epithelial, and mesen-

chymal markers can all be expressed and, given their association with young children, it has been suggested that AT/RTs derive from pluripotent fetal cells {204, 1654}. Meningeal, neural crest or germ cell origins have also been proposed {343, 1677, 1924}. In one case, an AT/RT was reported to arise from a ganglioglioma, raising the possibility of progression from other tumour types {44}.

Genetics

AT/RT can occur sporadically or as part of a rhabdoid tumour predisposition syndrome (see Chapter 13) {153}. Mutation or loss of the *INI1*(*hSNF5/SMARCB1*) locus at 22q11.2 is the genetic hallmark of AT/RT {156,2322}. The *INI1* protein is a component of the mammalian SWI/SNF complex, which functions in an ATP-dependent manner to alter chromatin structure {1897}. The specific function of *INI1* and its role in malignant transformation are not entirely clear, but it appears to act at least in part via p16-Rb-E2F and p53-dependent pathways {914, 919}. Loss of *INI1* expression at the protein level is seen in almost all AT/RTs, and most (75%) of the tumours have detectable deletions or mutations of *INI1*. Among cases with deletions or mutations, homozygous deletions of the *INI1* locus are detected in 20–24% of tumours {153, 2231}. In

other cases, one *INI1* allele is mutated, and the second allele is lost by deletion or mitotic recombination. Rare tumours demonstrate two coding sequence mutations. Nonsense and frameshift mutations that are predicted to lead to truncations of the protein are identified in the majority of these cases {153}. Localization of mutations within the *INI1* gene appears to vary somewhat between rhabdoid tumours arising at various sites in the body, and exons 5 and 9 are hotspots in CNS AT/RT. No differences in outcome have been identified in patients with mutations in specific *INI1* exons. In familial cases of rhabdoid tumour, both unaffected adult carriers and gonadal mosaicism have been identified {971, 2057}. Because expression of *INI1* is sometimes decreased in AT/RT in the absence of genetic alterations, its promoter was analysed in 24 cases, but no evidence of hypermethylation was detected {2492}.

Prognostic and predictive factors

The overall prognosis of AT/RTs is poor. In one study of 55 patients with AT/RT, the mean survival after surgery was only 11 months {263}. A more recent analysis of 42 patients enrolled in a tumour registry found a median survival of 17 months, while an institutional study of 11 cases reported a mean time to death of 24 months {328, 823}. Age older than 3 years appears to be associated with longer survival, perhaps due to the use of more intensive therapies {2231}.

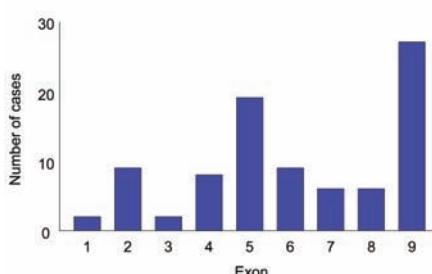
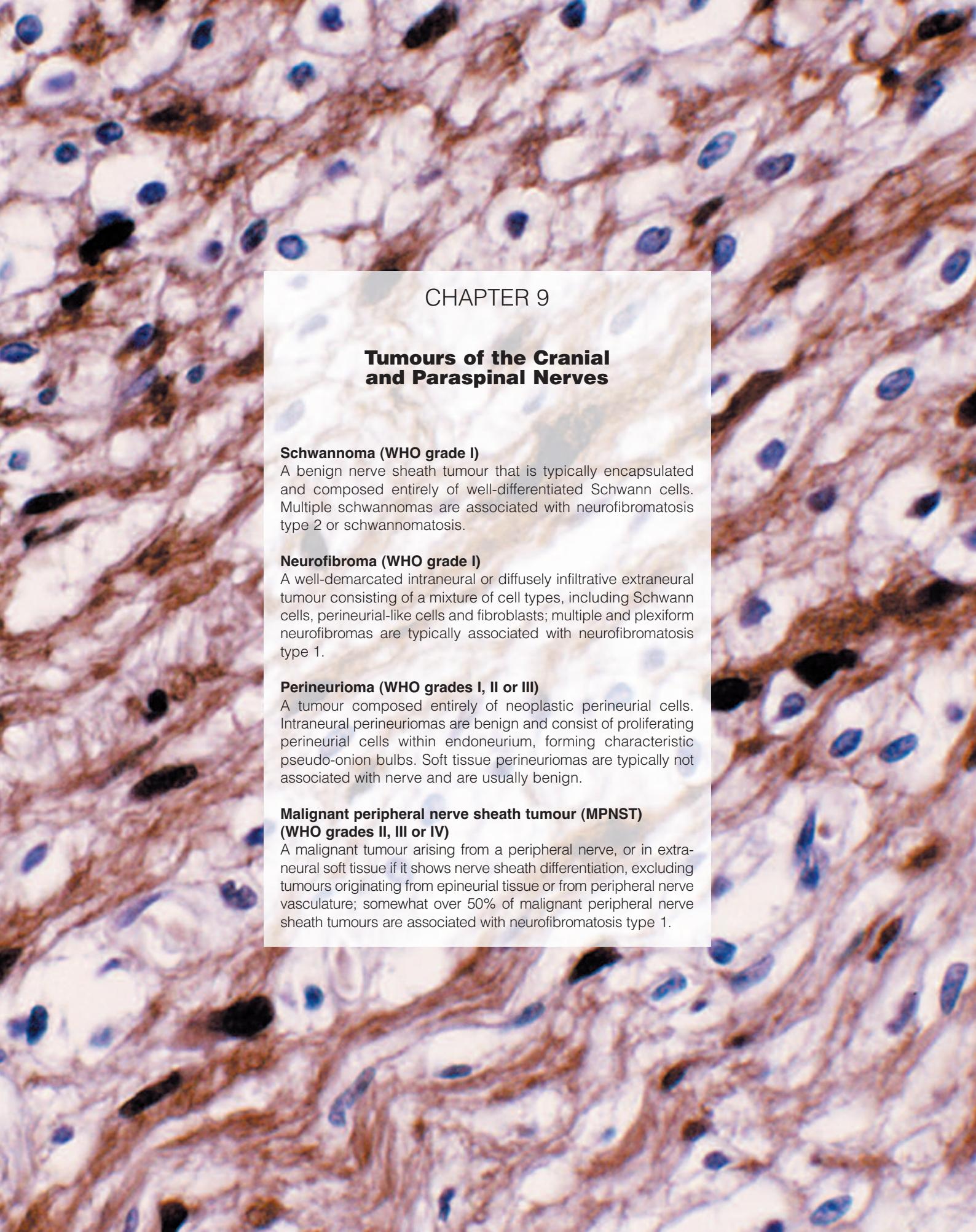


Fig. 8.27 Distribution of mutations in exons 1-9 of the *INI1* gene. Results are representative of 80 patients with brain and spinal cord AT/RTs.



CHAPTER 9

Tumours of the Cranial and Paraspinal Nerves

Schwannoma (WHO grade I)

A benign nerve sheath tumour that is typically encapsulated and composed entirely of well-differentiated Schwann cells. Multiple schwannomas are associated with neurofibromatosis type 2 or schwannomatosis.

Neurofibroma (WHO grade I)

A well-demarcated intraneuronal or diffusely infiltrative extraneuronal tumour consisting of a mixture of cell types, including Schwann cells, perineurial-like cells and fibroblasts; multiple and plexiform neurofibromas are typically associated with neurofibromatosis type 1.

Perineurioma (WHO grades I, II or III)

A tumour composed entirely of neoplastic perineurial cells. Intraneuronal perineuriomas are benign and consist of proliferating perineurial cells within endoneurium, forming characteristic pseudo-onion bulbs. Soft tissue perineuriomas are typically not associated with nerve and are usually benign.

Malignant peripheral nerve sheath tumour (MPNST) (WHO grades II, III or IV)

A malignant tumour arising from a peripheral nerve, or in extraneuronal soft tissue if it shows nerve sheath differentiation, excluding tumours originating from epineurial tissue or from peripheral nerve vasculature; somewhat over 50% of malignant peripheral nerve sheath tumours are associated with neurofibromatosis type 1.

Schwannoma

B.W. Scheithauer
D.N. Louis
S. Hunter
J.M. Woodruff
C.R. Antonescu

Definition

A benign nerve sheath tumour that is typically encapsulated and composed entirely of well-differentiated Schwann cells. Multiple schwannomas are associated with neurofibromatosis type 2 or schwannomatosis.

ICD-O code 9560/0

Grading

Conventional, non-melanotic schwannoma corresponds histologically to WHO grade I.

Synonyms

Neurilemoma and neurinoma.

Incidence

Schwannomas represent 8% of intracranial tumours, 85% of cerebellopontine angle tumours and 29% of spinal nerve root tumours [1959]. Approximately 90% of cases are solitary and sporadic, while 4% arise in the setting of neurofibromatosis type 2 (NF2), and 5% are multiple but unassociated with NF2 [56]. Some of the latter are associated with schwannomatosis [1369].

Age and sex distribution

All ages are affected but paediatric cases are rare. The peak incidence is in the fourth to sixth decade of life. Most studies show no gender predilection, but some series have shown a female

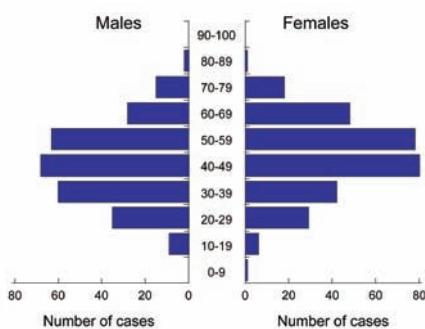


Fig. 9.01 Age and sex distribution of schwannoma based on 582 patients, treated at the University Hospital, Zürich.

predominance among intracranial tumours [415, 1417, 1959]. Cerebral or spinal intra-parenchymal schwannomas are associated with a younger age and a male predominance [293]. Schwannomas of spinal cord parenchyma are too rare to assess their epidemiology [817].

Localization

The vast majority of schwannomas occur outside the central nervous system. Most often affected is skin and subcutaneous tissue [1682A]. Intracranial schwannomas show a strong predilection for the eighth cranial nerve in the cerebellopontine angle. This is particularly the case in NF2. They arise at the transition zone between central and peripheral myelination and affect the vestibular division. The adjacent cochlear division is almost never their site of origin. This characteristic location, which is not shared by neurofibromas or MPNSTs, results in diagnostically helpful enlargement of the internal auditory meatus by neuroimaging. Intralabyrinthine schwannomas are uncommon [1576]. Intradural schwannomas show a strong predilection for sensory nerve roots. Motor and autonomic nerves are far less often affected. Occasional CNS schwannomas are not associated with a recognizable nerve. These include approximately 70 reported cases of spinal intramedullary and 40 of cerebral parenchymal or intraventricular schwannomas [293, 416, 817, 1110, 1750, 2388]. Dural examples are rare [58]. Peripheral schwannomas, in contrast with neurofibromas, tend to be attached to nerve trunks, most often involving the head and neck region or flexor surfaces of the extremities. Visceral schwannomas are rare, as are osseous examples [1469, 1801, 2011, 2288].

Clinical features

Symptoms and signs

Peripherally situated schwannomas may present as asymptomatic paraspinal tumours, as incidental findings on imaging studies, as spinal nerve tumours with radicular pain and signs of nerve root, spinal cord compression, or as eighth



Fig. 9.02 Vestibular schwannoma. MRI showing location in the cerebellopontine angle. Note the tumour protrusion at the upper margin extending into the internal acoustic canal.

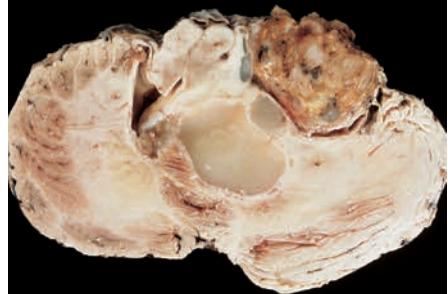


Fig. 9.03 Vestibular schwannoma. Large schwannoma causing compression of and cyst formation in the cerebellum, and displacement of the medulla.

cranial nerve tumours with related symptoms. Motor symptoms are uncommon since schwannomas favour sensory nerve roots. Bilateral vestibular tumours are the sine qua non of NF2. Pain is the most common presentation for schwannomas in patients with schwannomatosis.

Neuroimaging

MRI reveals a well-circumscribed, sometimes cystic and often heterogeneously enhancing mass. Those in paraspinal and head and neck sites may be associated with bone erosion that is sometimes evident on plain x-rays [293].

Macroscopy

The majority of schwannomas are globoid masses measuring from a few centimeters to 10 cm in size. With the exception of rare examples arising at intraparenchymal CNS sites, viscera, skin and bone, they usually are encapsulated. In peripheral tumours, a nerve of origin is identified in less than half of cases. The cut surface of the tumour typically reveals light tan glistening tissue interrupted by bright yellow patches with or without cysts and haemorrhage. Infarct-like necrosis related to degenerative vascular changes may be evident in sizable tumours.

Histopathology

Conventional schwannoma is a tumour composed entirely of neoplastic Schwann cells and forming two basic patterns in varying proportion: areas of compact, elongated cells with occasional nuclear palisading (Antoni A pattern) and less cellular, loosely textured cells with indistinct processes and variable lipidization (Antoni B). A retiform pattern is very uncommonly seen. The Schwann cells comprising the tumour have moderate quantities of eosinophilic cytoplasm without discernible cell borders. Antoni A tissue features normochromic spindle-shaped or round nuclei approximately the size of those of smooth muscle cells, but tapered instead of blunt-ended. In Antoni B tissue, tumour cells have smaller, often round to ovoid nuclei. Nuclear pleomorphism, including bizarre forms with cytoplasmic-nuclear inclusions ("ancient schwannoma") and the occasional mitotic figure may be seen, but should not be misinterpreted as indicating malignancy. The Antoni A growth pattern consists of closely apposed tumour cells, forming nuclear palisades (Verocay bodies) consisting of alternating, parallel rows of tumour cell nuclei and their

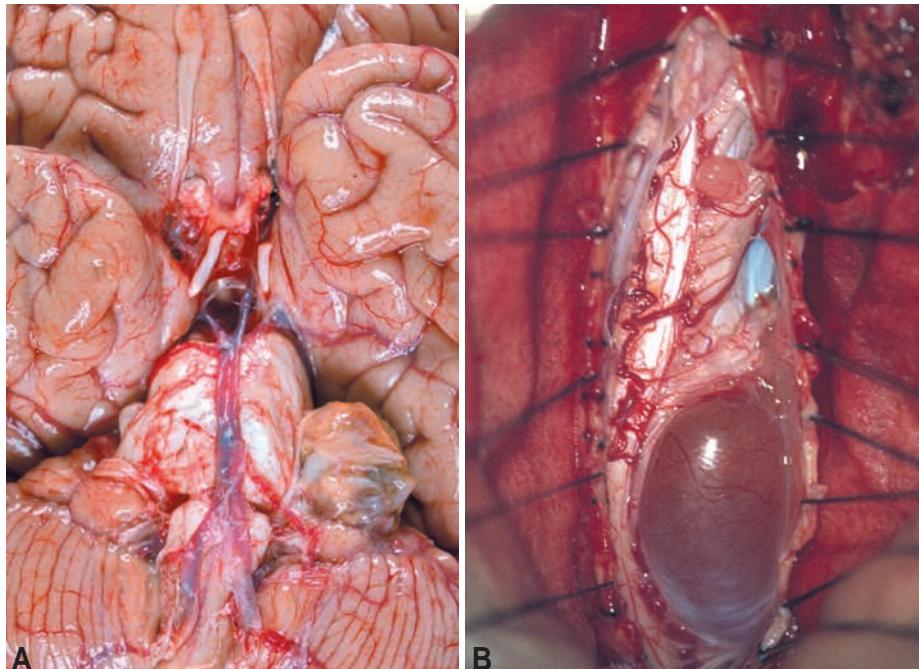


Fig. 9.04 A Macroscopic appearance of a vestibular schwannoma in the left cerebellopontine angle and B a spinal schwannoma (intraoperative view).

densely packed, aligned cell processes. All schwannoma cells show a pericellular reticulin pattern corresponding to surface basement membranes. In Antoni B areas, tumour cells are loosely arranged. Collections of lipid-laden cells may be present within either Antoni A or B tissue. Schwannoma vasculature is typically thick-walled and hyalinized. In addition, dilated blood vessels surrounded by haemorrhage are common. Eighth cranial nerve schwannomas are known for their infrequent presence of Verocay bodies, predominance of Antoni B tissue, and often clusters of lipid-laden cells. Schwannomas with meningothelial islands are a curiosity and are virtually limited to NF2 {1355}. Malignant transformation, less often microscopic {1436} than exten-

sive and transcapsular, {1436, 2447} rarely occurs in conventional schwannomas. Rhabdomyoblastic differentiation has been reported {1239}.

Cellular schwannoma

This variant is defined as a hypercellular schwannoma composed exclusively or predominantly of Antoni A tissue and devoid of well-formed Verocay bodies {2444}. The most common location of cellular schwannoma is at paravertebral sites in the pelvis, retroperitoneum and mediastinum {2444}. Cranial nerves, especially the fifth and eighth, may be affected {294}. Clinical presentation of cellular schwannoma is similar to that of conventional schwannoma, but the histological features of hypercellularity,

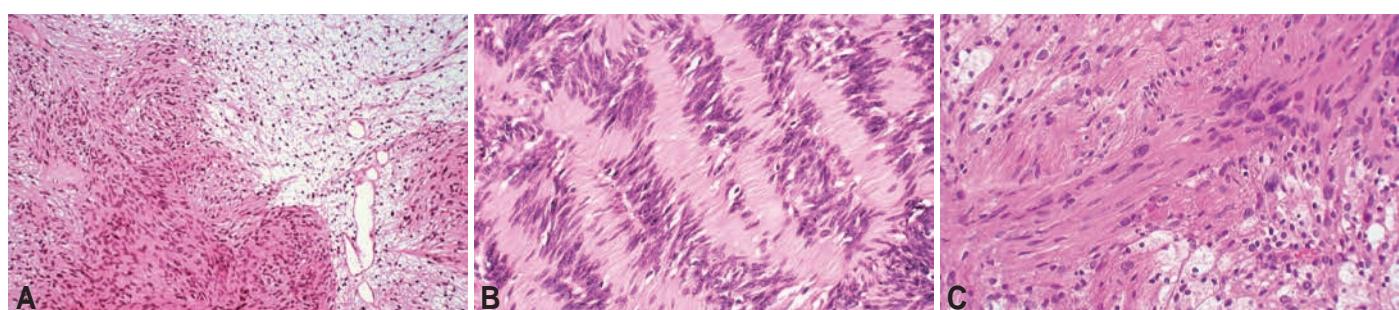


Fig. 9.05 Histological features of schwannoma. A Biphasic pattern with cellular Antoni A and hypocellular Antoni B areas. B Schwannoma cell nuclei forming palisades. C Schwannoma, showing compact fascicles of elongated tumour cells with slight nuclear polymorphism. Note scattered lipid-laden macrophages.

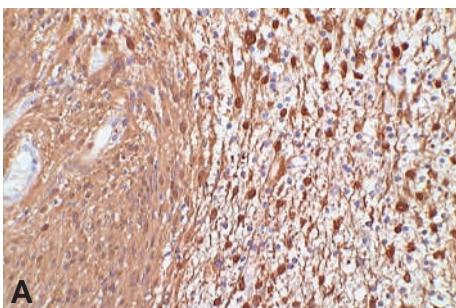
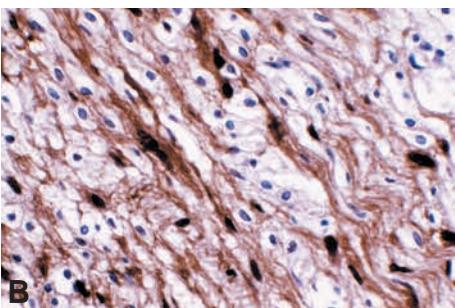
**A****B**

Fig. 9.06 Schwannoma with diffuse S-100 immunoreactivity (A). B S-100 immunostaining of elongated tumour cells in a predominantly immunonegative Antoni B area.

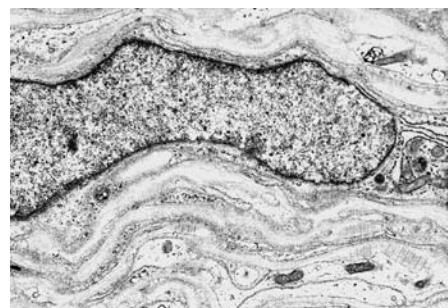


Fig. 9.07 Ultrastructural features of a schwannoma showing a continuous lining of tumour cells by basal lamina.

fascicular growth of cells, occasional nuclear hyperchromasia and atypia, as well as low-level mitotic activity (usually <4/10 HPF) may lead to a mistaken diagnosis of malignancy (MPNST). Again, the reticulin pattern is pericellular. In one series [294], reported labelling indices for the proliferation markers PCNA and MIB-1 were 5.6% and 6%, respectively, in non-recurring tumours [294]. On flow cytometry, two thirds were diploid, and the rest either tetraploid or aneuploid [294]. p53 immunostaining has been reported in roughly half of cellular schwannomas, but immunolabeled cells are relatively few [294]. Cellular schwannomas are benign. Although recurrences are seen, notably in intracranial, spinal and sacral examples [294], no cellular schwannoma is known to have metastasized or reportedly followed a clinically malignant, fatal course. Only two examples of cellular schwannoma, one associated with NF2, have been reported to undergo malignant transformation [60].

Plexiform schwannoma

This variant is defined as schwannoma growing in a plexiform or multinodular manner and can be of either conventional or cellular type [2445]. Presumably involving a nerve plexus, the vast majority

arise in skin or subcutaneous tissue of an extremity, head and neck, or trunk. The tumour has a low association with NF2, but not NF1, and has also been noted in non-NF2 patients with multiple schwannomas (schwannomatosis) [937]. Cranial and spinal nerves are usually spared.

Melanotic schwannoma

This rare, circumscribed but unencapsulated, grossly pigmented tumour is composed of cells having the ultrastructure and immunophenotype of Schwann cells but containing melanosomes and being reactive for melanoma markers. Cytologic atypia is not uncommon, including hyperchromasia and macronucleoli. The reticulin pattern is often poor in this subtype. Its peak incidence is a decade earlier than that of conventional schwannoma. Melanotic schwannomas occur in non-psammomatous [591] and psammomatous [289, 508] varieties. The vast majority of non-psammomatous tumours affect spinal nerves and paraspinal ganglia, whereas the psammomatous lesions also involve autonomic nerves of viscera, such as the intestinal tract and heart. Cranial nerves may also be affected. Distinguishing between these two varieties of melanotic schwannoma is of importance, since about 50% of

patients with psammomatous tumours have Carney complex, an autosomal-dominant disorder [288] characterized by lentiginous facial pigmentation, cardiac myxoma and endocrine over-activity. The latter includes Cushing syndrome associated with multinodular adrenal hyperplasia and acromegaly due to pituitary adenoma [289]. Slightly over 10% of melanotic schwannomas follow a malignant course [2011].

Immunohistochemistry

Tumour cells strongly and diffusely express S-100 protein [2390], often express Leu-7 and calretinin [582], and may focally express GFAP [1448]. All schwannoma cells possess surface basal lamina, so membrane staining for collagen IV and laminin is a regular feature of the tumour. The pattern is rich and most commonly pericellular in all but melanotic schwannomas, where envelopment of cell nests is more frequently seen. Low-level p53 protein immunoreactivity may be seen, particularly in cellular schwannomas [294]. Neurofilament protein-positive axons are generally lacking but small numbers may be encountered within the substance of schwannomas, particularly in NF2 or schwannomatosis-associated tumours [2383].

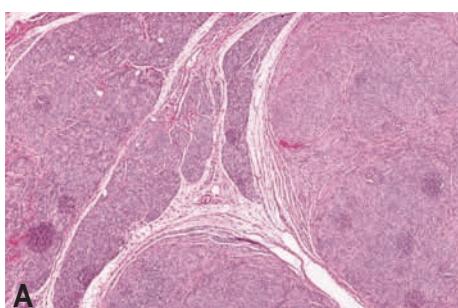
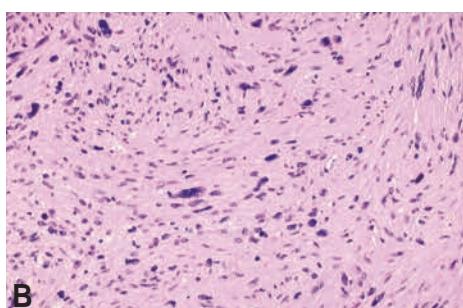
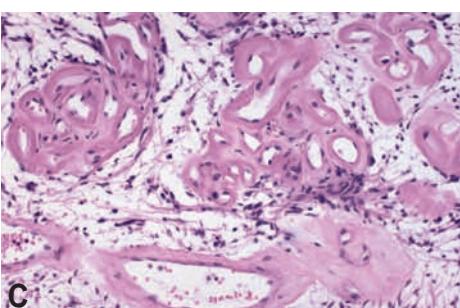
**A****B****C**

Fig. 9.08 A Plexiform schwannoma involving multiple small nerves. B Nuclear polymorphism seen in many cellular schwannomas from any site, not to be interpreted as a sign of malignancy. C Hyalinized vessels in an Antoni B area of a conventional schwannoma.

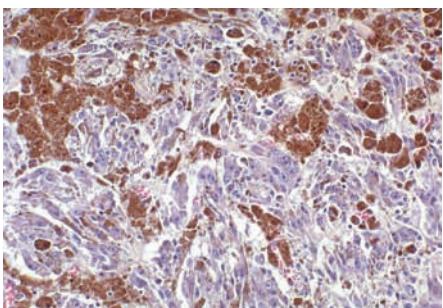


Fig. 9.09 Melanotic schwannoma with clusters of plump, spindled, heavily pigmented tumour cells.

Electron microscopy

Ultrastructural features are diagnostic and consist of cells with convoluted, moderately thin cytoplasmic processes that are nearly devoid of pinocytotic vesicles but are lined by a continuous basal lamina [531]. Stromal long-spacing collagen (Luse body) is a common finding in conventional schwannoma but less so in the cellular variant. Melanotic schwannomas feature true melanosomes and less uniform envelopment of individual cells by basal lamina.

Genetic susceptibility

Although most schwannomas are sporadic in occurrence, multiple schwannomas may occur in the setting of two tumour syndromes. Bilateral vestibular (eighth cranial nerve) schwannomas are pathognomonic of NF2 (see Chapter 13), while multiple peripheral schwannomas in the

absence of other NF2 features is characteristic of schwannomatosis (see Chapter 13). Schwannomatosis patients present with multiple, often painful schwannomas, which in some cases are segmental in distribution [613, 644, 1176]. NF2 inactivation has been shown in tumours, but not in non-tumour tissue, suggesting that another gene may be the underlying cause of schwannomatosis [644, 948, 1368]. In addition, psammomatous melanotic schwannoma is a component of Carney complex, in which patients have mutations of the *PRKAR1A* gene on chromosome 17q, encoding the type 1A regulatory subunit of protein kinase A [2161].

Genetics

Extensive analyses have implicated the *NF2* gene as a tumour suppressor integral to the formation of sporadic schwannomas [950, 2045]. The *NF2* gene and the merlin (schwannomin) protein which it encodes are discussed in detail in the chapter on NF2. Inactivating mutations of the *NF2* gene have been detected in approximately 60% of schwannomas [168, 949, 950, 1941, 2266]. These genetic events are predominantly small frameshift mutations that result in truncated protein products [1352]. Although not been described for exons 16 and 17, mutations occur throughout the coding sequence of the gene and at intronic sites. In most cases,

such mutations are accompanied by loss of the remaining wild-type allele on chromosome 22q. Still other cases demonstrate loss of chromosome 22q in the absence of detectable *NF2* gene mutations. Nonetheless, loss of merlin expression, demonstrated by Western blotting or immunohistochemistry, appears to be a universal finding in schwannomas, regardless of their mutation or allelic status [838, 901, 1971]. This suggests that abrogation of merlin function is an essential step in schwannoma tumourigenesis. Loss of chromosome 22 has also been noted in cellular schwannoma [1341]. Other genetic changes are rare in schwannomas, although small numbers of cases with chromosome 1p loss, gain of 9q34 and gain of 17q have been reported [1293, 2367]. Allelic loss of the *PRKAR1A* region on 17q has been noted in tumours from patients with Carney complex, but has not been documented in non-psammomatous melanotic schwannomas [2161].

Prognostic and predictive factors

Schwannomas are benign, slowly growing tumours that infrequently recur and only very rarely undergo malignant change [2447]. Recurrences are more common (30–40%) for cellular schwannomas of the intracranial, spinal and sacral regions [294].

Neurofibroma

B.W. Scheithauer
D.N. Louis
S. Hunter
J.M. Woodruff
C.R. Antonescu

Definition

A well-demarcated intraneuronal or diffusely infiltrative extraneuronal tumour consisting of a mixture of cell types, including Schwann cells, perineurial-like cells, and fibroblasts; multiple and plexiform neurofibromas are typically associated with neurofibromatosis type 1.

ICD-O codes

Neurofibroma	9540/0
Plexiform neurofibroma	9550/0

Grading

Neurofibroma corresponds histologically to WHO grade I.

Incidence

Neurofibromas are common and occur either as sporadic solitary nodules unrelated to any apparent syndrome or, far less frequently, as solitary, multiple or numerous lesions in individuals with neurofibromatosis type 1 (NF1).

Age and sex distribution

All ages and both sexes are affected.

Localization

Neurofibroma presents most commonly as a cutaneous nodule (localized cutaneous neurofibroma) and less often as a circumscribed mass in a peripheral nerve (localized intraneuronal neurofibroma) or as a plexiform enlargement of a plexus or major nerve trunk. Less frequent is diffuse but localized involvement of skin

and subcutaneous tissue (diffuse cutaneous neurofibroma), or extensive to massive involvement of soft tissue (localized gigantism and "elephantiasis neuromatosa"). Neurofibromas occasionally involve spinal roots [2049] but are almost unknown on cranial nerves.

Clinical features

Rarely painful, the tumours present as a mass. The presence of multiple neurofibromas is the hallmark of NF1, in which they are associated with pigmented cutaneous macules (café-au-lait spots) as well as 'freckling', often axillary in location (see Chapter 13).

Macroscopy

Cutaneous neurofibromas are either nodular to polypoid and rather circumscribed, or are diffuse and involve skin and subcutaneous tissue. On cut surface, both are firm, glistening and grey-tan. Neurofibromas confined to nerves are fusiform and, in all but their proximal and distal margins, well-circumscribed. Plexiform neurofibromas consist of either multinodular tangles ("bag of worms") when tumour involves multiple trunks of a plexus or rope-like lesions when multiple fascicles of a large, non-branching nerve such as the sciatic are affected [2011, 2441].

Histopathology

Neurofibromas are composed in large part of Schwann cells with ovoid to thin, curved to elongate nuclei and scant cytoplasm as well as fibroblasts in a matrix of collagen fibers and Alcian blue-positive, myxoid material. The Schwann cells are considerably smaller than those of schwannomas. Cell processes are thin and often not visible on routine light microscopy. Neurofibromas may also exhibit numerous atypical nuclei (atypical neurofibroma) or significantly increased cellularity (cellular neurofibroma). Even in the latter, mitotic figures are rare. Stromal collagen formation varies greatly in abundance and sometimes takes the form of dense, refractile bundles resembling

"shredded carrots." Growth of neurofibroma cells is initially along the course of nerve fibers, which become enmeshed by tumour. When arising from a medium-size or large nerve, neurofibromas often remain confined to the nerve, being encompassed by its thickened epineurium. In contrast, tumours arising in small nerves often spread diffusely into the surrounding dermis and soft tissues. Large diffuse neurofibromas often contain highly characteristic tactile-like structures, specifically pseudo-Meissnerian corpuscles, and may also contain melanotic cells. The multiple fascicles constituting plexiform neurofibromas, although expanded by tumour cells and collagen, commonly demonstrate residual, bundled nerve fibers at their centres. A very small proportion of neurofibromas are thought to exhibit limited perineurial differentiation [2482]. Unlike schwannomas, blood vessels in neurofibromas generally lack hyalinization.

Immunohistochemistry

Staining for S-100 protein is invariably seen, but the proportion of reactive cells is less than in schwannomas. Expression for basement membrane markers is less consistent and more variable than in schwannoma. In contrast to perineurioma, neurofibromas contain only limited numbers of EMA-positive cells [2011, 2482]. In most neurofibromas, EMA reactivity is simply limited to residual perineurium [2011]. Scattered neoplastic cells, presumably the perineurial-like cells seen ultrastructurally (see below) also show glut-1 [834] or claudin positivity [1807]. Axons in varying number, as shown by positivity for neurofilament proteins, are present in neurofibromas, particularly plexiform tumours, within which they are often centrally grouped.

Electron microscopy

Electron microscopy shows a mixture of cell types, the two most diagnostically important being the Schwann cell, either associated or unassociated with axons, and the perineurial-like cell [532, 2011,



Fig. 9.10 Neurofibroma of a spinal root, with a firm consistency and homogeneous cut surface.

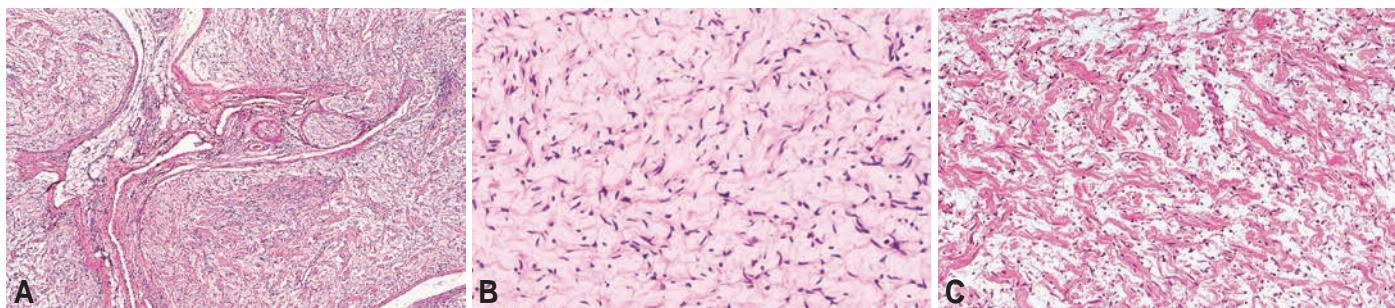


Fig. 9.11 A Plexiform neurofibroma involving small skin nerves. B Neurofibroma with small ovoid nuclei lacking obvious cell processes. The eosinophilic curved strands are collagen fibers produced by tumour cells. C Extensive collagen formation may cause a 'shredded carrots' appearance.

2441). The latter features long, very thin cell processes, numerous pinocytotic vesicles, and interrupted basement membrane. Fibroblasts are the least frequent.

Genetic susceptibility

The occurrence of multiple and plexiform neurofibromas is a hallmark of NF1 (see Chapter 13). Neurofibromas are rare in NF2 and schwannomatosis.

Genetics

Given their mixed cellular composition, it has been difficult to determine whether neurofibromas are monoclonal. NF1-associated neurofibromas contain monoclonal neoplastic cells {2110}. As sporadic neurofibromas are histologically identical to those occurring in NF1, it seems likely that they too are monoclonal. Notably, allelic loss of the *NF1* gene region of 17q appears confined to the S-100 protein-immunoreactive Schwann or perhaps

perineurial-like cells in neurofibromas {1730}, suggesting that they are the clonal neoplastic element.

In view of the association of neurofibromas with NF1, investigations of the genetic basis of sporadic tumours have focused on the *NF1* gene. In NF1 patients harbouring germline *NF1* mutations, loss of the remaining wild-type *NF1* allele within their neurofibromas {2052, 2109} confirms the two-hit hypothesis for the genesis of these lesions {370, 1998}. Point mutations affecting *NF1* gene splicing are common {2051}. The situation in sporadic tumours has yet to be elucidated, but the morphologic similarity between sporadic and inherited neurofibromas, as well as the clear involvement of the *NF1* gene in sporadic MPNSTs, suggests that *NF1* alterations are also involved in the genesis of sporadic neurofibromas. This has been documented in rare cases {2158}. Moreover, mitotic recombination events may underlie

biallelic inactivation of *NF1* in neurofibromas {2053}, which would complicate assessment of chromosomal loss in such cases.

Additional chromosomal losses are not common in neurofibromas, but have been noted on 19p, 19q and 22q in NF1-associated neurofibromas and on 19q and 22q in sporadic neurofibromas {1149}.

Prognostic and predictive factors

Plexiform neurofibromas and neurofibromas of major nerves are considered a precursor lesion to the majority of malignant peripheral nerve sheath tumours. Malignant transformation occurs in 5% of sizable plexiform tumours, but is a rare event in diffuse cutaneous and massive soft tissue neurofibromas. Patients with a sizable plexiform neurofibroma are highly likely to have NF1 and must be investigated for other evidence of the disorder.

Perineurioma

B.W. Scheithauer
J.M. Woodruff
C.R. Antonescu

Definition

A tumour composed entirely of neoplastic perineurial cells. Intraneural perineuriomas are benign and consist of proliferating perineurial cells within endoneurium, forming characteristic pseudo-onion bulbs. Soft tissue perineuriomas are typically not associated with nerve and are usually benign.

ICD-O codes

Intraneural and benign soft tissue

perineurioma 9571/0

Malignant soft tissue perineurioma

9571/3

Grading

Intraneural perineuriomas correspond histologically to WHO grade I. In keeping with the FNCLCC approach to grading of soft tissue tumours, soft tissue perineuriomas range from benign (WHO grade I) to variably malignant and corresponding to WHO grades II-III.

Synonyms and historical annotation

Intraneural perineurioma, long mistakenly considered a form of hypertrophic neuropathy, is now recognized as a neoplasm [519]. Soft tissue perineurioma is a morphologically distinct tumour.

Incidence

Both the intraneural and soft tissue variants of perineurioma are rare and represent approximately 1% of nerve sheath and soft tissue neoplasms, respectively. Over 50 cases of intraneural perineurioma have been reported to date, including cranial nerve examples. Well over 100 cases of soft tissue perineurioma have been described [571, 677, 717, 866, 1828], including a cranial nerve example [107].

Clinical features

Intraneural perineuriomas typically present in adolescence or early adulthood and show no sex predilection. Progressive muscle weakness with or without obvious atrophy is more frequent than are sensory disturbances. Peripheral nerves

of the extremities are primarily affected; cranial nerve lesions are rare [47, 398, 1308]. One example was reportedly associated with Beckwith-Wiedemann syndrome [327].

Soft tissue perineuriomas occur in adults, predominantly females (2:1), and present with non-specific mass effects. They are deep soft tissue and are, with the rare exception of a cranial nerve example [107], grossly unassociated with nerve. Visceral involvement is rare [866A, 2298A]. One example involving the central nervous system arose within a lateral ventricle [679]. Malignant examples prone to recurrence and occasional metastasis have been reported [623, 833, 1043, 1927, 2184], and are apparently unassociated with NF1 [833].

Macroscopy

Intraneural perineuriomas produce segmental, tubular, several-fold enlargement of the affected nerve. Individual nerve fascicles appear coarse and pale. Most lesions are less than 10 cm in length but one 40 cm long sciatic nerve example has been reported [519]. Although multiple fascicles are often involved, a "bag of worms" plexiform growth is not seen. Involvement of two neighbouring spinal nerves has been reported [519]. Soft tissue perineuriomas are solitary, generally small (1.5–7 cm) and well-circumscribed but not encapsulated. Rarely, the tumour may be multinodular [60]. Larger examples are exceptional [829, 866]. On cut surface they are firm and grey-white to infrequently focally myxoid. Malignant soft tissue perineuriomas are usually not associated with a nerve and may feature invasive growth as well as variable necrosis.

Histopathology

Intraneural perineurioma consists of neoplastic perineurial cells proliferating throughout the endoneurium, forming concentric layers around nerve fibers, enlargement of fascicles and characteristic pseudo-onion bulbs. This distinctive architectural feature is best seen on cross

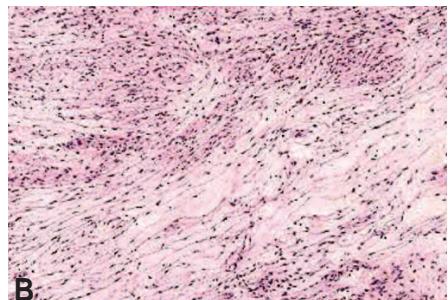
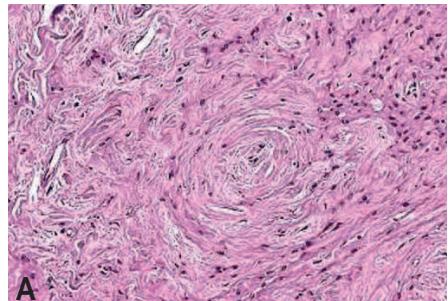


Fig. 9.12 A The sclerotic variant of perineurioma features abundant collagen deposition and crude whorls. The latter occasionally center upon nerve fibers. B Reticular variant of perineurioma. Tumour cells surround collagen aggregates resulting in a loose-textured tissue pattern.

section, wherein fascicles vary in cellularity. Proliferation of perineurial cells largely takes place within endoneurium but perineurium is often affected as well. Numerous perineurial cells, most of which appear cytologically normal, are concentrically disposed in multiple layers around nerve fibers. Particularly large whorls may envelop numerous nerve fibers. Occasionally, perineurial cells enclosing one or several axons will contribute to an adjacent onion bulb as well. Thus, pseudo-onion bulbs anastomose one with the other, forming a complex endoneurial network. Bielschowsky or Bodian stains often show one or multiple axons at the centre of pseudo-onion bulbs. Luxol-fast blue preparations typically show myelin to be scant or absent. Even within a single fascicle, cell density and the complexity of the lesion may vary. Mitotic activity is rare. In early lesions, axonal density and myelination may be almost normal, whereas in fully

developed lesions, when most fibers are surrounded by perineurial cells and therefore widely separated, myelin is often scant or absent on Luxol-fast blue stain. At late stages, only Schwann cells without accompanying axons may remain at the centre of the perineurial whorls. Hyalinization may also be an impressive finding.

Soft tissue perineuriomas are composed of spindled, wavy cells with remarkably thin cytoplasmic processes arranged in lamellae and embedded in collagen fibers. Crude whorls or storiform arrangements are commonly seen. Aggregates of collagen fibers are often encircled by long, remarkably narrow tumour cell processes. Nuclei are elongate with tapered ends and are often curved or wrinkled. Nucleoli are inconspicuous. Granular cells are a very uncommon feature of perineurioma [467]. Mitoses vary in number; in the largest published series [866], they varied from 0-13/30 high-power (40x) fields (mean, 1), 65% of tumours having none. Degenerative atypia (nuclear pleomorphism, hyperchromasia, cytoplasmic-nuclear inclusions) is seen primarily in long-standing tumours [866]. As a rule, necrosis is lacking. The sclerotic variant of soft tissue perineurioma is characterized by an abundant collagenous stroma has been described occurring mainly in the fingers of young males [571]. This tumour features only crude whorl formation occasionally centred upon a minute nerve. A reticular variant occurring at a variety of anatomic sites and affecting primarily adults, features a lace-like or reticular growth pattern composed of anastomosing cords of fusiform cells [717]. Malignant soft tissue perineuriomas (perineurial MPNSTs) are uncommon and characterized by hypercellularity, hyperchromasia, and variable, often brisk mitotic activity (WHO grade II), necrosis usually being a feature of WHO grade III tumours. Progressive malignant change of WHO grade II to grade III lesions may be seen,

but transformation of benign soft tissue perineuriomas to malignant examples has yet to be documented.

Immunohistochemistry

All intraneuronal perineuriomas, like normal perineurial cells, are vimentin and epithelial membrane antigen (EMA)-immunoreactive. The pattern of EMA staining is membranous, as is that for collagen IV and laminin. Axons at the centre of pseudononion bulbs and residual Schwann cells stain for neurofilament protein and S-100 protein, respectively. Staining for p53 protein has also been reported [519]. Soft tissue perineurioma features the same basic immunophenotype as the intraneuronal variant. Recently, claudin-1 [590,1828] and glut-1 [834] immunostaining have been applied to perineuriomas. Both have been shown to be diagnostically useful markers of normal and neoplastic perineurial cells. Unlike various other soft tissue tumours, perineuriomas generally lack reactivity for CD34 and particularly S-100 protein. Malignant soft tissue perineuriomas usually show at least some EMA staining and lack S-100 protein reactivity.

Proliferation

Intraneuronal perineuriomas, despite a paucity of mitoses, may show MIB-1 labelling indices ranging from 5 to 15% [519]. In contrast to the often low mitotic index of benign soft tissue perineuriomas, malignant soft tissue perineuriomas are more proliferative, indices ranging from 1-85/10 high-power fields (median, 16) in the largest reported series [833].

Electron microscopy

Intraneuronal perineuriomas feature myelinated nerve fibers circumferentially surrounded by ultrastructurally normal appearing perineurial cells. The cells have long, thin cytoplasmic processes bearing numerous pinocytotic vesicles and are lined by patchy surface basement membrane. Stromal collagen

may be abundant.

Soft tissue perineuriomas typically consist of spindle-shaped cells with long, exceedingly thin cytoplasmic processes embedded in an abundant collagenous stroma. Cytoplasm is scant and contains sparse profiles of rough endoplasmic reticulum, occasional mitochondria and a few randomly distributed intermediate filaments. The processes exhibit numerous pinocytotic vesicles and a patchy lining of basement membrane. Intercellular tight junctions are relatively frequent. One example featuring ribosome-lamella complexes has been reported [462]. Malignant soft tissue perineuriomas show similar ultrastructural features [833, 1927, 2184], only some being poorly differentiated [833].

Genetics

Both intraneuronal and soft tissue perineuriomas feature the same cytogenetic abnormality, monosomy of chromosome 22 [519, 677]. Loss of chromosome 13, an abnormality found in a number of soft tissue tumours, has also been described in soft tissue perineurioma [1530]. Loss of chromosome 10 and a small chromosome 22q deletion involving *NF2* have also been reported [224,2044]. No genetic studies of malignant soft tissue perineuriomas have been reported.

Prognosis

Intraneuronal perineuriomas are benign. Long-term follow-up indicates that they show neither a tendency to recurrence nor metastasis. Biopsy alone is sufficient for diagnosis. Conventional soft tissue perineuriomas are usually amenable to gross total removal; recurrences are very infrequent, even in the face of histologic atypia; none have been reported to metastasize. Neither sclerotic nor reticular tumours are prone to recurrence [571, 717]. Malignant perineuriomas are far less prone to metastasize [623, 833, 1043] than are conventional malignant peripheral nerve sheath tumours [833].

Malignant peripheral nerve sheath tumour (MPNST)

B.W. Scheithauer
D.N. Louis
S. Hunter
J.M. Woodruff
C.R. Antonescu

Definition

A malignant tumour arising from a peripheral nerve, or in extraneuronal soft tissue if it shows nerve sheath differentiation, excluding tumours originating from epineurial tissue or from peripheral nerve vasculature; somewhat over 50% of malignant peripheral nerve sheath tumours are associated with neurofibromatosis type 1.

ICD-O code 9540/3

Grading

Histologically, malignant peripheral nerve sheath tumour (MPNST) corresponds to WHO grades II, III or IV, an approach similar to that applied to sarcoma grading {587}.

Synonyms

Once considered equivalent, but misleading and to be avoided, are the terms neurogenic sarcoma, neurofibrosarcoma, and malignant schwannoma.

Incidence

MPNSTs are uncommon, accounting for nearly 5% of malignant tumours of soft tissue {1305}. Approximately one half to two thirds arise from neurofibromas {490, 874, 1178}, often of the plexiform type and in the setting of neurofibromatosis type 1 (NF1). Second in frequency are MPNSTs arising *de novo* from peripheral nerves {2011, 2441}. The remainder are unassociated with a nerve or NF2 and simply resemble invasive soft tissue sarcomas. Only very rare examples develop from conventional schwannoma {2447}, ganglioneuroblastoma/ganglio-neuroma {1869, 2011} or phaeochromocytoma {1972}.

Age and sex distribution

MPNSTs primarily affect adults in the third to the sixth decades of life. The mean age of patients with NF1-associated MPNSTs is approximately a decade younger (28–36 years) than that of sporadic cases (40–44 years) {490, 874}. Childhood and adolescent cases are

uncommon {489}, children less than six years of age rarely being affected. MPNSTs do not show a strong gender predilection; however, NF1-associated cases are somewhat more common in males, while non-NF1-associated cases may be slightly more common in females, with a M:F ratio of 1.16:1.

Localization

Large and medium-size nerves are distinctly more prone to involvement than are small nerves. Most commonly involved sites include the buttock and thigh, brachial plexus and upper arm, and the paraspinal region. The sciatic nerve is most frequently affected. Cranial nerve MPNSTs are rare {145, 765, 1223, 1434, 1532, 2457}, the vestibular and vagal nerves being most often involved. Cranial nerve examples arise either *de novo* or from schwannoma or neurofibroma {603, 2447}. Primary intraparenchymal MPNST is rare {2072, 2147}.

Clinical features

Symptoms and signs

About half of MPNSTs occur in the clinical setting of NF1. An additional approximately 10% of MPNSTs develop at a site of prior irradiation {487, 589}. The most common presentation of tumours of the extremities is a progressively enlarging mass with or without neurological symptoms {874}. Spinal tumours often present with radicular pain {1178}.

Neuroimaging

Findings correspond to those of a soft tissue sarcoma. Inhomogeneous contrast enhancement and irregularity of contour, a reflection of invasion, are commonly seen. However, some MPNSTs are indistinguishable from benign nerve sheath tumours {2011}.

Macroscopy

The gross appearance of MPNST varies widely. Since a significant proportion arises in neurofibroma, some as focal transformations, the process may be minimally apparent on gross examination.

In contrast, larger, typically high-grade tumours originating in or unassociated with a nerve produce either fusiform, expansile masses or globular soft tissue tumours entirely lacking encapsulation. Both infiltrate surrounding structures. The vast majority of tumours are larger than 5 cm, and examples over 10 cm are common. What appears to be a pseudo-capsule is in actuality infiltrated peritumoural soft tissue. Their consistency varies from firm to hard, and the cut surface is typically cream coloured or grey. Foci of necrosis and haemorrhage are common and may be extensive. Both cranial and spinal intradural MPNSTs may show parenchymal invasion {456}. Primary brain or spinal cord examples are rare {2147} as are primary MPNSTs of bone. Metastatic MPNST to the CNS is also very uncommon.

Histopathology

MPNSTs vary greatly in appearance. Many often exhibit a herringbone (fibrosarcoma-like) or interwoven-fasciculated pattern of cell growth. Both feature tightly packed spindle cells with variable quantities of eosinophilic cytoplasm. Nuclei are typically elongate, wavy, and in contrast to those of smooth muscle, have tapered ends. Tumours show either alternating loose and densely cellular areas or a diffuse growth pattern. MPNSTs grow within nerve fascicles but commonly

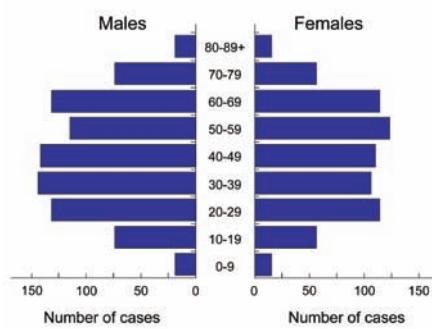


Fig. 9.13 Age and sex distribution of MPNST, based on 1711 histologically confirmed cases. Data from Surveillance Epidemiology and End Result (SEER), National Cancer Institute, Washington DC.

invade through perineurium and epineurium into the adjacent soft tissues. A pseudo-capsule of variable thickness consisting of tumour-invaded soft tissue and reactive fibrous tissue is often present. Three quarters of tumours have geographic necrosis and mitotic activity, often showing more than 4 mitotic figures per high-power field. A distinction is made between WHO grades III and IV based on the presence of necrosis. At the low end of the grading spectrum (WHO grade II), MPNSTs merge with cellular neurofibromas, from which they are distinguished on the basis of increased cellularity, nuclear size ($>3x$ that of neurofibroma cells) and hyperchromasia. An increased mitotic rate is often seen but is not requisite for the diagnosis. Unusual growth patterns may be seen, including haemangiopericytoma-like areas or, rarely, nuclear palisading. Rare MPNST show histologic and ultra-structural features of perineurial differentiation [833]. Standardized routine histologic criteria for distinguishing MPNSTs from high-grade sarcomas are not available; consequently, diagnosis may ultimately rely on demonstration of tumour origin from either a neurofibroma or a peripheral nerve or upon immunohistochemical or ultrastructural features. About 15% of cases exhibit unusual histological

features such as epithelioid morphology or divergent differentiation [488, 2011]. MPNST arising in schwannoma is rare; examples feature either anaplastic small or large, epithelioid cells [1436, 2447].

Epithelioid MPNST

Fewer than 5% of MPNSTs are either partially or purely epithelioid [469, 1263, 1340]. This variant shows no association with NF1 and can occur in a background of a benign schwannoma. Both superficial (above the fascia) and deep-seated examples are recognized. Superficial tumours carry a better prognosis.

MPNST with mesenchymal differentiation

A variety of mesenchymal tissues may be represented in MPNST. The term "malignant Triton tumour" refers to MPNSTs showing rhabdomyosarcomatous differentiation. Their incidence is nearly four times that of glandular MPNSTs. There are now at least 100 reported cases of this example of divergent mesenchymal differentiation [2446]. Sometimes accompanying the myoid element are areas of chondro- and/or osteosarcoma. Coexistent neoplastic epithelium (pluridirectional differentiation) is less common. Nearly 60% of the patients with malignant Triton tumour have NF1. Few cranial nerve examples have been reported [145, 765].



Fig. 9.14 Fusiform MPNST of the sciatic nerve with a partially trimmed pseudocapsule. The cut surface is firm, cream-tan and focally necrotic.

The prognosis of malignant Triton tumours is poor, with 2- and 5-year survival rates of approximately 33 and 12%, respectively [227]. Only one example of MPNST with smooth muscle differentiation has been reported [1903]. Schwannoma with associated angiosarcoma [1953, 2262] or rhabdomyosarcoma [1239] are both exceedingly rare.

Glandular MPNST

This variant is defined as an MPNST containing glandular epithelium that is often histologically benign. The epithelium resembles that of intestine. Neuroendocrine differentiation is frequently seen, whereas squamous epithelium is far less often encountered. Three quarters of the patients have NF1, and mortality is high (79%) [2443].

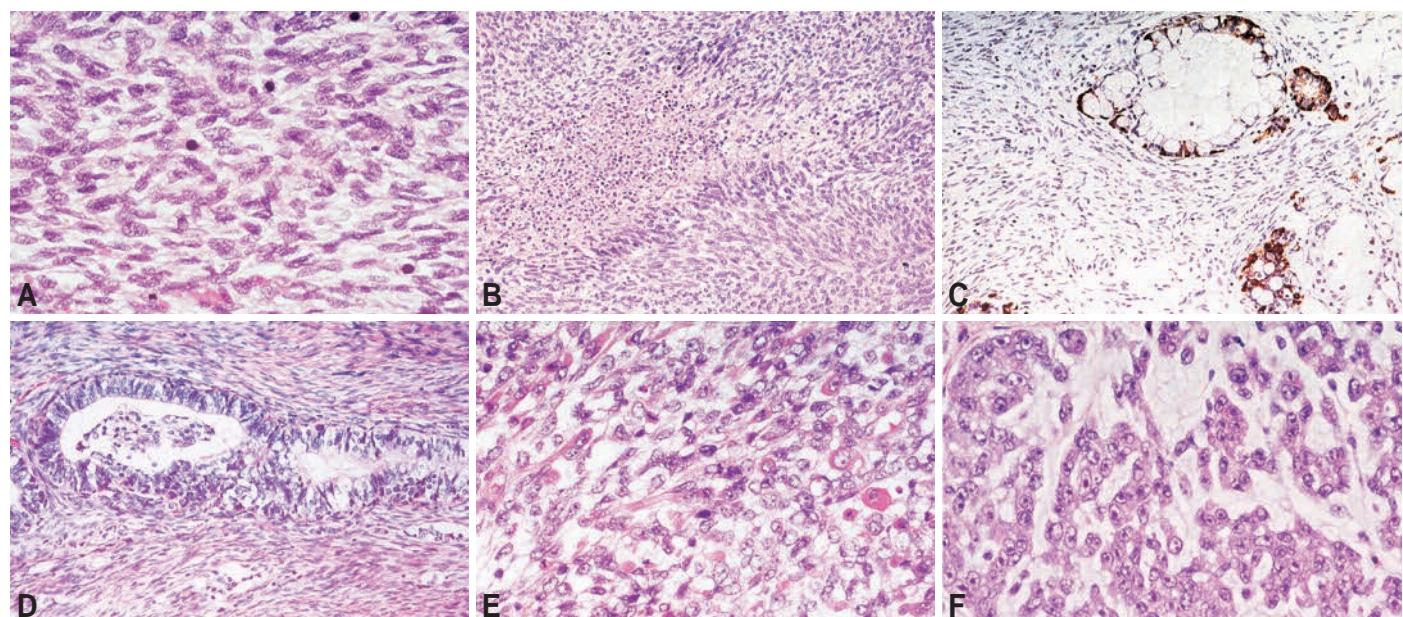


Fig. 9.15 Histological features of MPNST. A Brisk mitotic activity. B Well-delineated geographic necrosis. C Benign glandular MPNST containing neuroendocrine cells immunoreactive to chromogranin. D Formation of glands in an MPNST is interpreted as aberrant differentiation and considered as a sign of malignancy. E Malignant Triton tumour arising in a plexiform neurofibroma. Note strap-shaped and round rhabdomyoblasts on the background of anaplastic MPNST cells. F Epithelioid MPNST. Tumour cells are embedded in a mucinous matrix and show abundant cytoplasm and prominent nucleoli.

Immunohistochemistry

Only 50–70% of MPNSTs exhibit S-100 protein staining. Reactivity is grade-related. In high-grade tumours it is either patchy or found in individual cells, whereas in low-grade examples it may be extensive [2390]. Diffuse S-100 protein expression is more common in the epithelioid variant of MPNST [1263, 1340]. Immunostaining for p53 is present in a majority of tumours, in contrast to the infrequent staining in neurofibromas [758]. Conversely, immunostaining for other selected cell cycle regulatory proteins is common in neurofibromas but uncommon in MPNSTs; these include p27 [1179] and p16 [1591]. Glandular MPNSTs show keratin- and CEA-positive glands and neuroendocrine cells immunoreactive for chromogranin, somatostatin or serotonin.

Electron microscopy

Given the poor differentiation of most MPNSTs, electron microscopy is usually of little diagnostic aid short of excluding histologically similar sarcomas, such as leiomyosarcoma, synovial sarcoma and fibrosarcoma. Glandular MPNSTs show true gland formation with terminal bars and luminal microvilli. Individual cells or cell aggregates featuring dense core granules [346, 2443] may also be seen. Squamous differentiation is less common.

Proliferation

In the majority of MPNSTs, the growth fraction, as determined by Ki-67/MIB-1 immunoreactivity, ranges from 5 to 65%, in contrast to values often below 1% in conventional schwannomas and neurofibromas [1115].

Genetic susceptibility

Approximately one half of MPNSTs manifest in patients with NF1 (see Chapter 13). This association is particularly strong for the malignant Triton tumour and glandular variants of MPNST. NF1 patients with plexiform neurofibromas have the highest likelihood of developing MPNST [2278].

Genetics

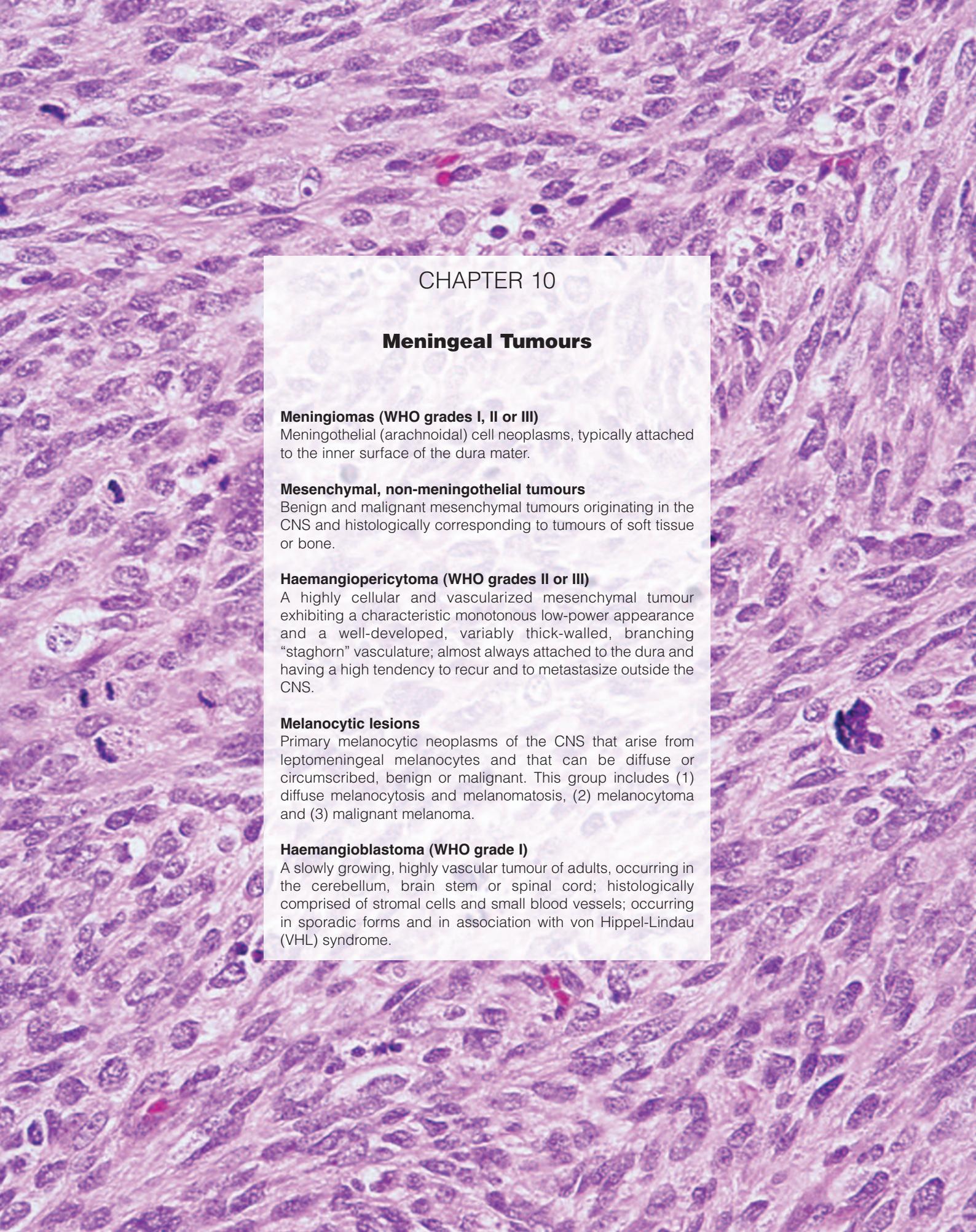
Sporadic and NF1-associated MPNSTs typically have complex karyotypic abnormalities that are both numerical and structural. Observed abnormalities include near-triploid or hypodiploid chromosome numbers [1462], chromosomal losses, loss of genetic material related to structural aberrations [998] and recombinations that involve almost all chromosomes [1462]. In one study of 10 tumours, structural abnormalities of chromosome 17 involving the *NF1* and *TP53* loci were common [998]. Chromosome 22 loss has also been noted [998, 1831], as have gains of chromosomes 2 and 14 and losses of chromosomes 13, 17 and 18 [1144]. No cytogenetic differences have been noted between sporadic and NF1-associated tumours.

In MPNSTs of NF1 patients, inactivation of both *NF1* alleles has occurred [1286], implicating this gene in MPNST formation (see Chapter 13). Sporadic MPNSTs also show alterations at the *NF1* locus, ones which are more likely to be involved in early stages of nerve sheath tumorigenesis, i.e. in neurofibroma-genesis rather than in malignant progression to MPNST. Instead, the latter is associated with alterations of genes controlling cell cycle regulation. One clearly implicated

gene is *TP53* [1285, 1349, 1456]. Both *TP53* mutations and altered protein expression have been found in MPNSTs. In addition, homozygous deletions of the *CDKN2A* gene on 9p21, which encodes the p16^{INK4a} and p14^{ARF} cell cycle inhibitory molecules, occur in the progression of neurofibromas to MPNSTs, being found in over 50% of MPNSTs but not in neurofibromas [1180, 1591, 1719]. These homozygous deletions also inactivate the neighbouring *CDKN2B* gene that encodes the p15 inhibitory molecule [1719]. In combination, these genetic events suggest inactivation of the p53 and pRb regulatory pathways in approximately 75% of MPNSTs [1719].

Prognostic and predictive factors

Except those with perineurial cell differentiation [833], MPNSTs are highly aggressive tumours with a poor prognosis. About 60% of patients die of the disease [490], with an even higher mortality (80%) in individuals with paraspinal lesions [1178] and those (100%) with divergent angiosarcoma [2011]. Overall 5- and 10-year survival rates are 34% and 23% respectively [490]. MPNSTs vary from low-grade lesions to a vast majority of high-grade tumours featuring high cellularity, brisk mitotic activity and necrosis. No firm association has been established between histologic grade and survival, but high (>25%) MIB-1 labelling indices are associated with reduced survival [490, 2375]. The effect of NF1 upon survival is unsettled, in that some report an association with poor survival [490], whereas others do not [874, 1178].



CHAPTER 10

Meningeal Tumours

Meningiomas (WHO grades I, II or III)

Meningothelial (arachnoidal) cell neoplasms, typically attached to the inner surface of the dura mater.

Mesenchymal, non-meningothelial tumours

Benign and malignant mesenchymal tumours originating in the CNS and histologically corresponding to tumours of soft tissue or bone.

Haemangiopericytoma (WHO grades II or III)

A highly cellular and vascularized mesenchymal tumour exhibiting a characteristic monotonous low-power appearance and a well-developed, variably thick-walled, branching "staghorn" vasculature; almost always attached to the dura and having a high tendency to recur and to metastasize outside the CNS.

Melanocytic lesions

Primary melanocytic neoplasms of the CNS that arise from leptomeningeal melanocytes and that can be diffuse or circumscribed, benign or malignant. This group includes (1) diffuse melanocytosis and melanomatosis, (2) melanocytoma and (3) malignant melanoma.

Haemangioblastoma (WHO grade I)

A slowly growing, highly vascular tumour of adults, occurring in the cerebellum, brain stem or spinal cord; histologically comprised of stromal cells and small blood vessels; occurring in sporadic forms and in association with von Hippel-Lindau (VHL) syndrome.

Meningiomas

A. Perry
D.N. Louis
B.W. Scheithauer
H. Budka
A. von Deimling

Definition

Meningothelial (arachnoidal) cell neoplasms, typically attached to the inner surface of the dura mater.

ICD-O code

Meningioma 9530/0

Grading

Most meningiomas are benign and correspond to WHO grade I. Certain histological subtypes or meningiomas with specific combinations of morphologic parameters are associated with less favourable clinical outcomes and correspond to WHO grades II (atypical) and III (anaplastic or malignant).

Incidence

Meningiomas account for about 24–30% of primary intracranial tumours occurring in the USA {305, 359}, with an annual incidence rate of up to 13 per 100 000 population in Italy {381}. Many small meningiomas are asymptomatic incidental neuroimaging findings. In Scandinavia,

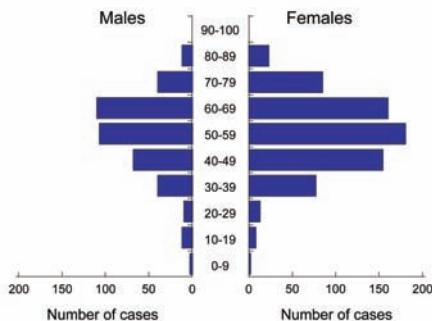


Fig. 10.01 Age and sex distribution of meningioma, based on 1078 cases treated at the University Hospital Zurich.

the incidence has increased between 1968 and 1997 from 2.6 to 4.5 per 100 000 in women, and from 1.4 to 1.9 in men {1119}. In one Italian study, the numbers have remained stable for decades {381}. At autopsy, meningiomas are found incidentally in 1.4% of cases {1836}. Meningiomas are often multiple in patients with neurofibromatosis type 2 (NF2) and in

other, non-NF2 families with a hereditary predisposition to meningioma {1352}. Sporadic meningiomas are multiple in somewhat less than 10% of cases. Atypical meningiomas comprise between 4.7% and 7.2% of meningiomas, although using more current definitions, it has been reported in up to 20%; anaplastic (malignant) meningiomas account for between 1.0% and 2.8% {941, 1384, 1734, 1736, 2413}. An annual incidence of anaplastic (malignant) meningiomas of 0.17 per 100 000 persons has been reported {1911}.

Age and sex distribution

Meningiomas occur most commonly in middle-aged and elderly patients, with a peak during the sixth and seventh decades. Nonetheless, they also occur in children and the elderly. Childhood examples tend to include more aggressive forms of meningioma. Among middle-aged patients, there is a marked female bias, the female:male ratio being approximately 1.7:1 {381}; the ratio peaks at 3.5:1 in the patients 40–44 years of age {1119}. Spinal meningiomas show a marked predominance in women, the frequency approaching 90% in some series. The female:male ratio has increased over time, suggesting the possibility that increasing use of hormonal medications affects meningioma incidence {1119}; however, this hypothesis has not been proven to date. Meningiomas associated with hereditary tumour syndromes generally occur in younger patients, and more equally in men and women. On the other hand, atypical and particularly anaplastic meningiomas show a male predominance {941}. These observations may be related to higher proliferation indices in meningiomas occurring in male patients {1414}.

Etiology

Meningiomas are known to be induced by low-, moderate-, and high-dose radiation, with an average time interval to tumour appearance of 35, 26 and 19–24 years, respectively {1130}. The majority of patients

Table 10.01 Meningiomas grouped by likelihood of recurrence and grade.

Meningiomas with low risk of recurrence and aggressive growth:		
Meningothelial meningioma	WHO grade I	9531/0
Fibrous (fibroblastic) meningioma	WHO grade I	9532/0
Transitional (mixed) meningioma	WHO grade I	9537/0
Psammomatous meningioma	WHO grade I	9533/0
Angiomatous meningioma	WHO grade I	9534/0
Microcystic meningioma	WHO grade I	9530/0
Secretory meningioma	WHO grade I	9530/0
Lymphoplasmacyte-rich meningioma	WHO grade I	9530/0
Metaplastic meningioma	WHO grade I	9530/0
Meningiomas with greater likelihood of recurrence and/or aggressive behaviour:		
Chordoid meningioma	WHO grade II	9538/1
Clear cell meningioma (intracranial)	WHO grade II	9538/1
Atypical meningioma	WHO grade II	9539/1
Papillary meningioma	WHO grade III	9538/3
Rhabdoid meningioma	WHO grade III	9538/3
Anaplastic (malignant) meningioma	WHO grade III	9530/3
Meningiomas of any subtype or grade with high proliferation index and/or brain invasion		

with radiation-induced meningiomas have a history of low-dose irradiation (800 rad) to the scalp for tinea capitis. The second largest group of patients with radiation-induced meningiomas received high-dose irradiation (>2000 rad) for primary brain tumours [772]. Radiation-induced meningiomas are more commonly atypical or aggressive, multifocal, highly proliferative, and generally occur in younger age groups [772, 1372, 1540].

The role of sex hormones in the genesis of meningiomas is less clear. The over-representation of women among meningioma patients suggests an aetiological role for sex hormones. At first operation, 88% of meningiomas have progesterone, 40% have estrogen and 39% have androgen receptors [1168]. In any case, the higher incidence of meningiomas in women cannot be explained by differences of sex hormone expression alone [1168].

Localization

The vast majority of meningiomas arise in intracranial, intraspinal or orbital locations. Intraventricular and epidural examples are uncommon. Rare meningiomas have been reported in almost all organs. Within the cranial cavity, most meningiomas occur over the cerebral convexities, often parasagittal in association with the falx and venous sinus. Other common sites include the olfactory grooves, sphenoid ridges,

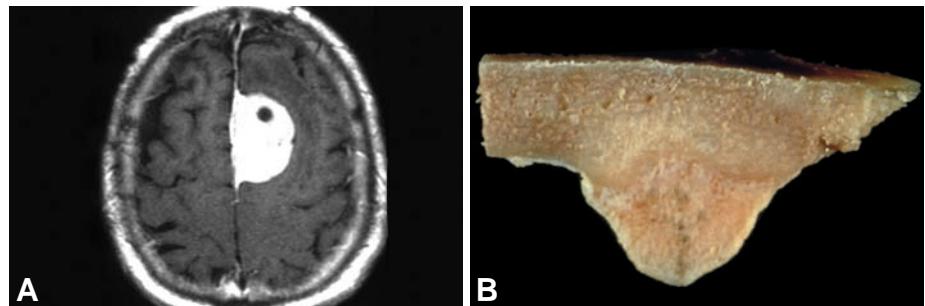


Fig. 10.03 A Large meningioma of the falx, presenting as a contrast-enhanced mass with a central cyst. Note the dural tail at either side of the neoplasm. B Ossifying meningioma including hyperostosis in the overlying skull.

para/suprasellar regions, optic nerve sheath, petrous ridges, tentorium and posterior fossa. Most spinal meningiomas occur in the thoracic region. Atypical and anaplastic meningiomas most commonly affect the falx and the lateral convexities [1384]. Among other sites, metastases of malignant meningiomas most often involve lung, pleura, bone and liver.

Neuroimaging

On MRI, meningiomas are typically iso-dense, contrast-enhancing dural masses. Some, like microcystic meningiomas, may show little enhancement on CT and MRI [2085]. Calcification is best seen on CT scan. A characteristic feature of meningiomas is the so-called 'dural tail' surrounding the dural perimeter of the mass. This familiar imaging sign may or may not indicate dural extension of the tumour or correspond to a rim of reactive fibrovascular tissue. Peritumoural cerebral edema is occasionally prominent, particularly around atypical or anaplastic examples. It has also been described in association with the secretory variant [42] and in meningothelial tumours with so-called pericyte accumulation about vessels [1900]. Cyst formation may occur within or at the periphery of a meningioma. Findings on neuroimaging have not always been reliable in identifying meningiomas, predicting tumour behaviour or excluding differential diagnostic possibilities.

Clinical features

Symptoms and signs

Meningiomas are generally slowly growing and produce neurological signs and symptoms by compression of adjacent structures; specific deficits depend upon the location of the tumour. Headache and seizures often herald the presence of a meningioma.

Macroscopy

Most meningiomas are rubbery or firm, well-demarcated, sometimes lobulated, rounded masses that feature broad dural attachment [257, 259, 1261, 1959]. Invasion of underlying dura or of dural sinuses is quite common. Occasional meningiomas invade through dura to involve the skull, where they may induce characteristic hyperostosis: such bony changes are highly indicative of skull invasion. Meningiomas may attach to or encase cerebral arteries, but only rarely do they infiltrate arterial walls. They may also infiltrate the skin and extend to extracranial compartments, such as the orbit. Adjacent brain is often compressed but rarely shows frank parenchymal invasion. In certain sites, particularly along the sphenoid

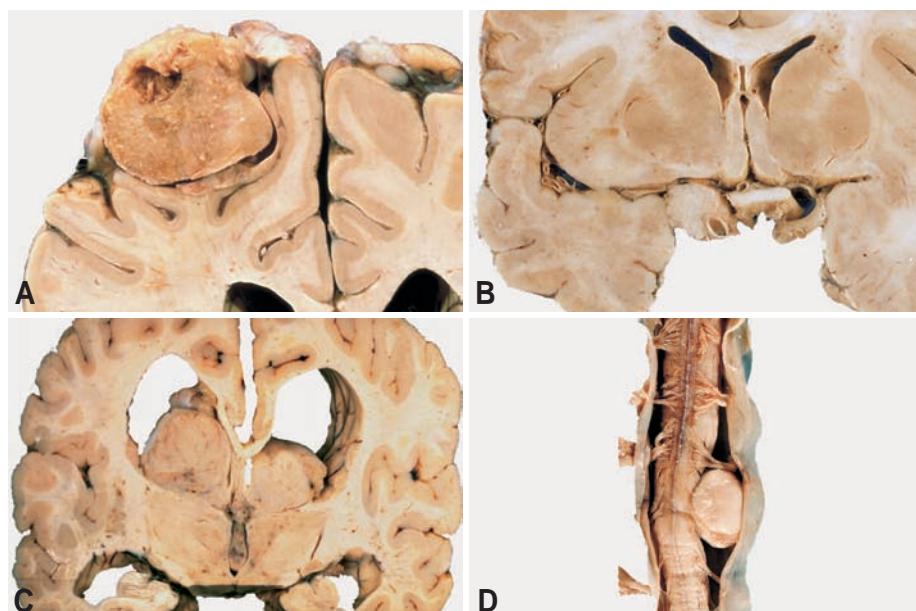


Fig. 10.02 Macroscopic features of meningioma. A Large parasagittal meningioma compressing the adjacent parietal lobe. B Meningioma of the medial sphenoid wing encasing the carotid artery. C Large meningioma of the lateral ventricles and the third ventricle. D Spinal meningioma compressing the spinal cord.

wing, meningiomas may grow as a flat, carpet-like mass, a pattern termed "en plaque meningioma." Some meningiomas may appear gritty on gross inspection, implying the presence of numerous psammoma bodies. Bone formation is far less common. Atypical and anaplastic meningiomas tend to be larger than benign examples {1384} and may feature necrosis.

Histopathology

Meningiomas exhibit a wide range of histologic appearances {259, 1079, 1261, 1959}. Of the subtypes in the WHO classification, meningothelial, fibrous and transitional meningiomas are the most common. The majority of subtypes behave in a common clinical manner, but four histologic variants, falling into the grade II and III categories, are far more likely to recur and follow a more aggressive clinical course including metastasis. Pleomorphic nuclei and occasional mitoses may be noted in any of the meningioma variants, without necessarily connoting more aggressive behaviour. Furthermore, the criteria used to diagnose atypical meningiomas are applied independent of specific meningioma subtype.

Meningothelial meningioma

In this classic and common variant, tumour cells form lobules, some partly demarcated by thin collagenous septae. Like normal arachnoidal cap cells, the tumour cells are largely uniform, with oval nuclei with delicate chromatin that on occasion show central clearing, or the

formulation of cytoplasmic-nuclear inclusions. Whorls and psammoma bodies are not common in meningothelial meningioma, but when present tend to be less-well formed than in transitional, fibrous or psammomatous tumour subtypes. Larger lobules should not be confused with the 'sheeting', or loss of architectural pattern seen in atypical meningioma. Within the lobules, tumour cells appear to form a syncytium, as the delicate, intricately interwoven tumour cell processes cannot be discerned at the light microscopic level. Since the tumour cells closely resemble those of the normal arachnoid cap cells, reactive meningothelial hyperplasia may simulate meningioma in small biopsy specimens. The most florid examples are associated with optic nerve gliomas, or adjacent to other tumour types, haemorrhage in the setting of chronic renal disease, advanced patient age, arachnoiditis ossificans, spontaneous intracranial haemorrhage and occasionally in other patients with diffuse dural thickening and contrast enhancement on neuroimaging {1729}.

Fibrous (fibroblastic) meningioma

Uncommon in pure form, this meningioma variant consists of spindle cells forming parallel, storiform and interlacing bundles in a collagen-rich matrix. Whorl formation and psammoma bodies are infrequent. Nuclear features characteristic of meningothelial meningioma are often found focally as well. The tumour cells of fibrous meningioma form wide fascicles, with varying amounts of intercellular collagen. In some cases, collagen deposition may be striking.

Transitional (mixed) meningioma

These common tumours feature the coexistence of meningothelial and fibrous patterns as well as transitions between these patterns. Vaguely lobular and fascicular arrangements often appear side by side in association with conspicuous tight whorls and psammoma bodies.

Psammomatous meningioma

This designation is applied to meningiomas containing a predominance of psammoma bodies over that of the tumour cells which give rise to them. They often become confluent, forming irregular calcified masses and occasionally bone.

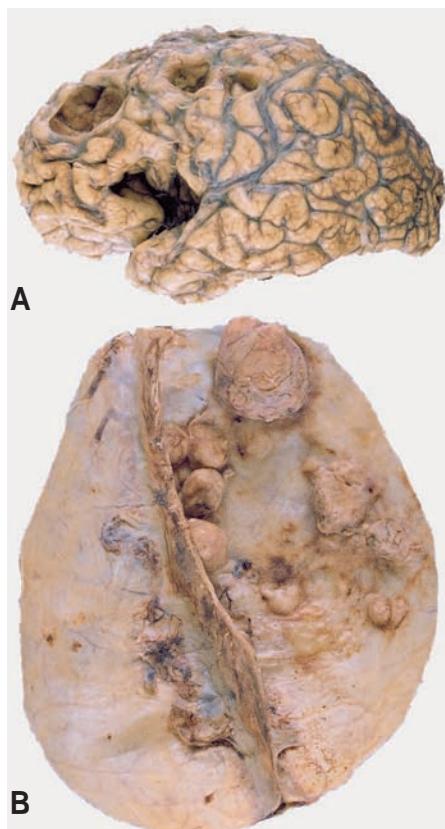


Fig. 10.05 Multiple meningiomas (B) of the hemispheric convexity and (A) the impressions caused in the left cerebral hemisphere.

The neoplastic cells of this variant usually have a transitional appearance with whorl formation. Some tumours are almost completely replaced by psammoma bodies, intervening meningothelial cells being hard to find. Psammomatous meningiomas characteristically occur in the thoracic spinal region and usually in middle-aged women.

Angiomatous meningioma

This meningioma variant features a predominance of blood vessels over that of the tumour cells. The vascular channels may be small- or medium-sized, thin-walled or thick. Most are small with markedly hyalinized walls. Moderate to marked degenerative nuclear atypia is common, but the vast majority of such tumours are histologically and clinically benign {783}. The differential diagnosis includes vascular malformations and capillary haemangioblastoma, depending on the prominence of vessels and the occasionally non-meningothelial appearance of the tumour cells. The designation angiomatous should not be equated with the obsolete term 'angioblastic'

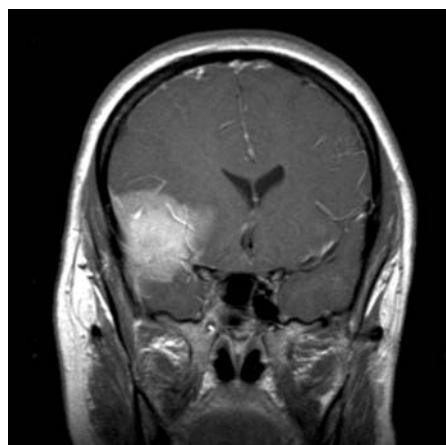


Fig. 10.04 T1-weighted MRI with gadolinium showing large, irregular meningeal mass displaying an indistinct interface with adjacent brain and marked mass effect.

meningoma' (see Haemangiopericytoma). Angiomatous meningiomas do not exhibit aggressive behaviour. Adjacent cerebral edema may be out of proportion to tumour size.

Microcystic meningioma

This variant is characterized by cells with thin, elongate processes encompassing microcysts containing pale, eosinophilic mucinous fluid. Pleomorphic cells may be numerous, but microcystic meningiomas are typically benign. Like the angiomatous variant, accompanying cerebral edema may be seen {1665}.

Secretory meningioma

The hallmark of this tumour variant is the presence of focal epithelial differentiation in the form of intracellular lumina containing PAS-positive, eosinophilic secretion. These structures, known as pseudopsammoma bodies {1076}, show immunoreactivity for carcinoembryonic antigen (CEA) and a variety of other epithelial and secretory markers, while the surrounding tumour cells are both CEA and cytokeratin-positive. Secretory meningiomas may be associated with blood levels of CEA that drop with resection and rise with recurrence {1350}. Mast cells may be numerous. Peritumoural edema may be significant {2251}.

Lymphoplasmacyte-rich meningioma

This meningioma variant features extensive chronic inflammatory infiltrates often over-shadowing the inconspicuous meningotheelial component. Lymphoplasmacyte-rich meningioma is among the rarest of variants. Its very existence as a distinct clinicopathologic entity remains controversial, since its behaviour often resembles that of an inflammatory process {235}. Systemic haematologic abnormalities, including hyperglobulinemia and iron refractory anemia have been documented in some cases {665}.

Metaplastic meningioma

A meningioma with striking focal or widespread mesenchymal components including osseous, cartilaginous, lipomatous, myxoid or xanthomatous tissue, singly or in combinations. The clinical significance of these alterations, if any, is unclear. Correlation with intra-operative findings is occasionally needed to distinguish ossified meningiomas from ones exhibiting bone invasion.

Chordoid meningioma

A meningioma variant consisting predominantly of tissue histologically similar to chordoma, featuring cords or trabeculae of eosinophilic, often vacuolated cells in an abundant mucoid matrix background.

Such chordoid areas are often interspersed with more typical meningioma tissue; pure examples are uncommon. Chronic inflammatory infiltrates, often patchy, may be prominent. Chordoid meningiomas are typically large, supratentorial tumours that exhibit a very high rate of recurrence following subtotal resection (WHO grade II) {389}. Infrequently, patients have associated haematological conditions, such as Castleman's disease {1082}.

Clear cell meningioma

An often patternless meningioma composed of polygonal cells with clear, glycogen-rich cytoplasm and prominent blocky perivascular and interstitial collagen. A rare meningioma variant, it shows prominent PAS-positive, diastase-sensitive cytoplasmic clearing due to glycogen accumulation. Classic features of meningioma are few; whorl formation is vague at best and no psammoma bodies are seen. The tumour shows a proclivity for the cerebellopontine angle and cauda equina region. It also tends to affect younger patients, both children and young adults. Clear cell meningiomas are associated with a more aggressive behaviour including frequent recurrence and occasional CSF seeding (WHO grade II) {1655, 2509}.

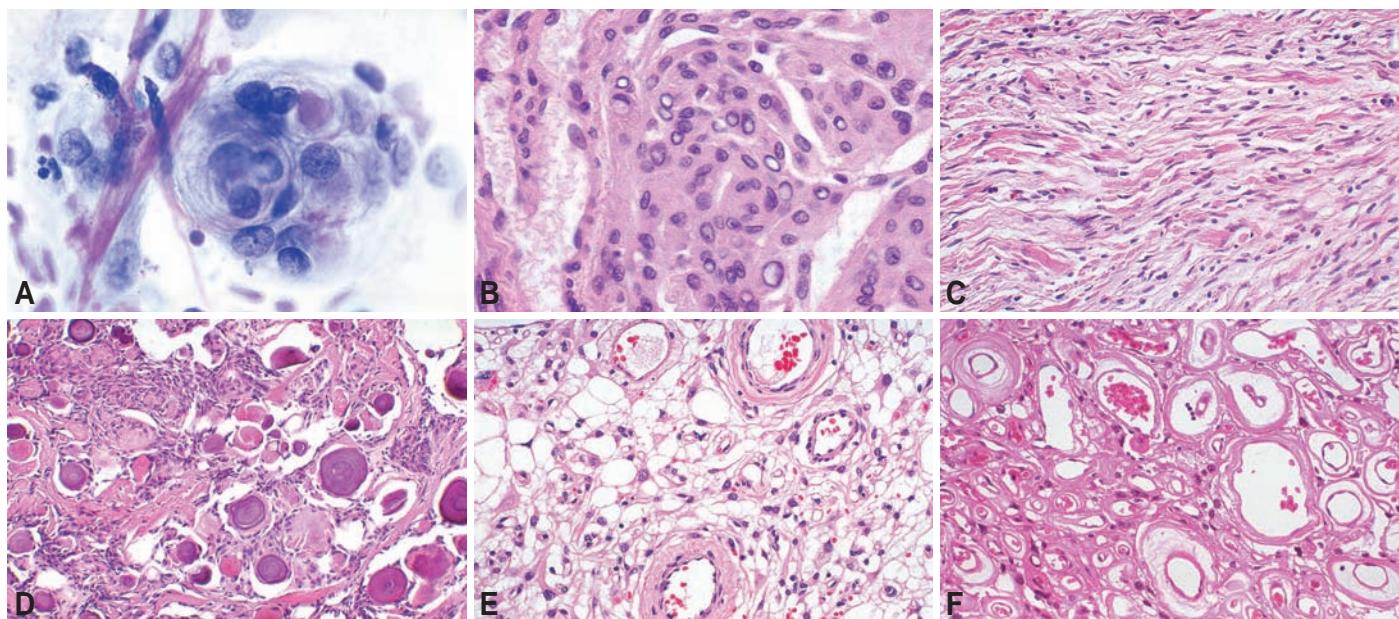


Fig. 10.06 Histological features of meningioma. A Squash preparation of a meningotheelial meningioma showing the typical whorl formation. B Meningothelial meningioma with typical intranuclear inclusions. C Fibrous meningioma characterized by parallel fascicles of fibroblastic cells. D Psammomatous meningioma with numerous calcified psammoma bodies and inconspicuous meningotheelial component. E Microcystic meningioma characterized by intercellular microcystic spaces. F Angiomatous meningioma dominated by excessive vascularization interspersed with small meningotheelial tumour cells.

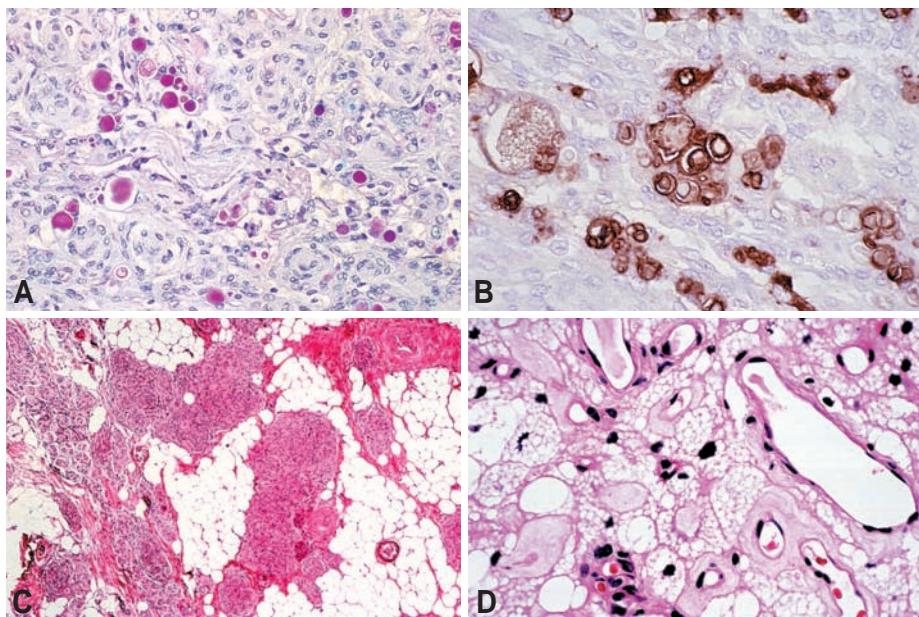


Fig. 10.07 Secretory meningioma with numerous PAS-positive pseudopasmoma bodies rich in glycogen (A) and marked immunoreactivity for (B) epithelial membrane antigen (EMA). C Metaplastic/lipomatous meningioma. D Metaplastic/xanthomatous meningioma.

Atypical meningioma

A meningioma with increased mitotic activity or three or more of the following histologic features: increased cellularity, small cells with a high nuclear: cytoplasmic ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, and foci of 'spontaneous' or 'geographic' necrosis. Increased mitotic activity is defined as 4 or more mitoses per 10 high-power (40x) fields (defined as 0.16 mm^2) {1736}. The above criteria have been shown to correlate with 8-fold higher recurrence rates {1736}. Alternative grading approaches a) identify individually scored parameters to arrive at a sum {941}, or b) simply combine hypercellularity with 5 or more mitoses per 10 high power fields {1384}. Atypical meningiomas often have moderately high MIB-1 labelling indices and correspond histologically to WHO grade II.

Papillary meningioma

A rare meningioma variant defined by the presence of a perivascular pseudopapillary pattern comprising the majority of the tumour. The pattern frequently increases in extent with recurrences. Papillary meningiomas tend to occur in young patients, including children {1356}. Local invasion and invasion of the brain have been noted in 75% of cases, recurrence in 55%, metastasis in 20% (mostly to lung) and death of disease in roughly half

{1195,1686}. Given their aggressive clinical behaviour {1356}, these tumours have been graded as WHO grade III.

Rhabdoid meningioma

An uncommon tumour predominantly containing sheets of rhabdoid cells, i.e. plump cells with eccentric nuclei, often open chromatin, a prominent nucleolus, and prominent inclusion-like eosinophilic cytoplasm appearing either as discernible whorled fibrils or compact and waxy. Such rhabdoid cells resemble those described in tumours in other sites, particularly kidney and the atypical teratoid/rhabdoid tumour of the brain. Rhabdoid cells may become increasingly evident with tumour recurrences. Most rhabdoid meningiomas have high proliferative indices and other histological features of malignancy. Some even combine a papillary architecture with rhabdoid cytology. Rhabdoid meningiomas often undergo an aggressive clinical course and correspond to WHO grade III {1085,1733}. A minority of meningiomas with rhabdoid features shows this only focally and lacks other histological features of malignancy; the behaviour of these tumours remains to be determined.

Anaplastic (malignant) meningioma

A meningioma exhibiting histological features of frank malignancy far in excess of the abnormalities present in atypical

meningioma. These include either obviously malignant cytology resembling that of carcinoma, melanoma or high-grade sarcoma, or a markedly elevated mitotic index (20 or more mitoses per ten high-power fields) (defined as 0.16 mm^2) {1734}. Tumours that meet the above criteria correspond to WHO grade III and are often fatal, median survival being less than 2 years {1734}. Invasion of the brain alone is not sufficient for a diagnosis of anaplastic meningioma {1734}. Since malignant progression in meningiomas, like that of gliomas, is a continuum of increasing atypia and anaplasia, tumours with features intermediate between atypical and anaplastic meningioma are occasionally encountered.

Other morphologic variations

As a reflection of the wide morphologic spectrum that may be encountered in meningiomas, rare examples are difficult to classify as any of the accepted variants. These include meningiomas with oncocytic, mucinous, sclerosing, whorling-sclerosing, GFAP-expressing and granulofilamentous inclusion-bearing features {41, 139, 277, 746, 861, 863, 1109, 1778, 1914}. There is currently insufficient data to indicate that these tumours represent unique variants. Skepticism is justified in that the majority of tumours once termed "pigmented meningiomas" are now known to be melanocytomas instead. However, recruitment of melanocytes from the adjacent meninges into the substance of a true meningioma accounts for dark pigmentation in rare cases {1580}.

Brain invasion and metastasis

Invasion of the brain by meningioma is characterized by irregular, tongue-like protrusions of tumour cells infiltrating underlying parenchyma, without an intervening layer of leptomeninges. This causes reactive astrocytosis with entrapped islands of GFAP-positive parenchyma at the periphery of the tumour. Brain invasion may occur in histologically benign, atypical or anaplastic (malignant) meningiomas. The presence of brain invasion connotes a greater likelihood of recurrence. Brain-invasive, histologically benign and histologically atypical meningiomas both have recurrence and mortality rates similar to those of atypical meningiomas in general {1736}. As such, they should prognostically be considered

WHO grade II. Whereas the genetic changes that characterize higher-grade meningiomas have generally not been found in brain-invasive, histologically benign meningiomas {1858, 2101, 2378}, one study showed chromosome 1p and 14q deletions in this group, changes similar to those in atypical meningiomas {273}. Anaplastic (malignant) meningiomas are considered WHO grade III whether or not they display brain invasion.

Extracranial metastases are extremely rare, being estimated to occur in roughly 1 in 1000 meningiomas and most often in association with anaplastic tumours. The rare metastases of histologically benign meningiomas typically occur following surgery, but can arise *de novo* as well.

Immunohistochemistry

The vast majority of meningiomas stain for epithelial membrane antigen (EMA), although EMA immunoreactivity is less consistent in atypical and malignant lesions. Vimentin positivity is found in all meningiomas. Immunohistochemical studies of S-100 protein have found varying positivity in meningiomas, but such staining is not usually prominent. Secretory meningiomas characteristically show strong positive staining for CEA in the pseudopasmoma bodies and in the surrounding cytokeratin-positive cells immediately surrounding the lumina containing them. Claudin-1 has also been found useful in some studies {754, 1825}. Other potentially useful immunohistochemical markers in selected cases include Ki-67 and progesterone receptor.

Electron microscopy

Diagnostic ultrastructural features of meningiomas include abundance of intermediate filaments (vimentin), complex interdigitating cellular processes (particularly in meningotheelial variants), and desmosomal intercellular junctions. These cell surface specializations as well as intermediate filaments are few in fibrous meningiomas, the cells being separated by collagen. Secretory meningiomas feature single or multiple epithelial-like lumina within single meningotheelial cells. These cell surfaces show short apical microvilli and surround electron-dense secretions of variable morphology {1230}. Microcystic meningiomas feature long cytoplasmic processes enclosing intercellular electron-lucent matrix and joined by desmosomes. Large cytoplasmic

lysosomes may be seen in this tumour variant.

Proliferation

In general, cellular proliferation of tumour cells increases from benign through atypical to anaplastic (malignant) meningioma. Mitotic indices correlate roughly with volume growth rate. There are significant differences in mitotic indices (total counts per ten high-power fields) between tumour grades: 0.08 ± 0.05 in benign, 4.8 ± 0.9 in atypical and 19 ± 4.1 in malignant variants. Similarly, MIB-1/Ki-67 indices show a highly significant increase from benign (mean, 3.8%), through atypical (mean 7.2%), to anaplastic meningiomas (mean 14.7%) {1385}. Other studies have suggested that meningiomas with indices >4% have increased risk of recurrence similar to atypical meningioma, whereas those with indices >20% are associated with death rates analogous to those associated with anaplastic meningioma {1734, 1737}. However, significant differences in technique and interpretation make it difficult to apply specific cutoffs that would translate accurately from one laboratory to another.

Flow cytometric studies have demonstrated approximately equal numbers of diploid and aneuploid meningiomas, and have shown significant correlations

between aneuploid tumours and features such as recurrence, pleomorphism, high cellular density, mitotic activity and infiltration of brain and soft tissue {401}.

Genetic susceptibility

Meningiomas are a key feature of neurofibromatosis type 2 (see NF2 in Chapter 13). However, a number of families with an increased susceptibility to meningiomas, but without NF2, have also been reported {1352}. In at least one of these families the disease did not show linkage to the *NF2* locus on chromosome 22q {1806}, thus suggesting that there may be a second meningioma predisposition locus. The possible relationship of meningioma to other rare, inherited tumour syndromes, such as Gorlin, Werner or Cowden syndromes, is less well-defined {714, 1353}. A familial history of benign brain tumours (meningioma, schwannoma, neurofibroma or neuroma), melanoma and possibly breast cancer may be associated with an increased risk of meningioma development {825}.

Genetics

Meningiomas were among the first solid tumours recognized as having cytogenetic alterations, the most consistent change being deletion of chromosome 22 {2483}. In general, karyotypic abnormalities are

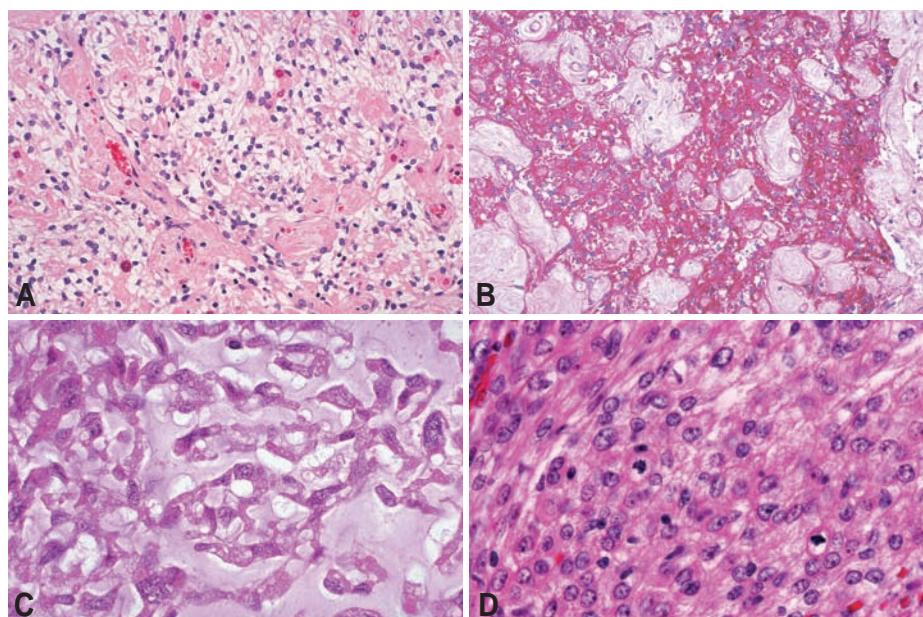


Fig. 10.08 Clear cell meningioma showing (A) a patternless neoplasm dominated by clear and (B) glycogen-rich cytoplasm (PAS staining). C Chordoid meningioma with eosinophilic tumour cells in a mucous-rich matrix. D Atypical meningioma with frequent mitoses despite bland cytologic features.

more extensive in atypical and anaplastic (malignant) meningiomas [26, 1727]. Among the other cytogenetic changes associated with meningioma, deletion of the short arm of chromosome 1 [1151] and loss of chromosomes 6, 10, 14, 18 and 19 are the most frequently seen [2483]. Molecular genetic findings indicate that approximately half of meningiomas have allelic losses that involve band q12 on chromosome 22 [494, 1326, 1964]. In addition, atypical meningiomas often show allelic losses of chromosomal arms 1p, 6q, 9q, 10q, 14q, 17p and 18q, suggesting that progression-associated genes may lie at these loci [26, 1457, 1726, 1858, 2101, 2378]. These alterations, with more frequent losses of chromosomes 6q, 9p, 10 and 14q, also occur in anaplastic meningiomas.

Chromosomal gains noted in higher-grade meningiomas include primarily chromosomes 20q, 12q, 15q, 1q, 9q and 17q.

NF2 gene

Mutations in the *NF2* gene are detected in the majority of NF2 associated and in up to 60% of sporadic meningiomas [1288, 2266, 2393]. Most are either small insertions or deletions, or are nonsense mutations that affect splice sites, create stop codons or result in frameshifts occurring mainly in the most 5' two thirds of the gene [1352]. The common predictable effect of these mutations is a truncated and presumably non-functional merlin (schwannomin) protein. The frequency of *NF2* mutations varies among meningioma variants. Fibroblastic, transi-

tional and psammomatous meningiomas often carry *NF2* mutations. In contrast, meningothelial, secretory and microcystic meningiomas only rarely harbour *NF2* mutations, suggesting that their genetic origin is largely independent of *NF2* [777, 1193, 2393]. The observation of a close association between allelic loss on 22q and the fibroblastic meningiomas supports this hypothesis [1964], as does the observation that most non-NF2 meningioma families develop meningothelial tumours [1352]. Furthermore, reduced expression of merlin (schwannomin) has been observed in different histopathological variants of meningiomas, but appears to be rare in meningothelial tumours [1276]. In atypical and anaplastic meningiomas, *NF2* mutations occur in approximately 70% of cases, matching the frequency of *NF2* mutations in benign fibroblastic and transitional meningiomas. In radiation-induced meningiomas, the frequencies of *NF2* mutations and loss of chromosome 22 are lower, whereas structural abnormalities of chromosome 1p are more common than in sporadic tumours. This finding suggests a different molecular pathogenesis for radiation-associated meningiomas [1826, 2094, 2485].

Other genes

The close association of *NF2* mutations in meningiomas with allelic loss on chromosome 22 suggests that *NF2* is the major meningioma tumour suppressor gene on that chromosome [2393]. Nonetheless, deletion studies of chromosome 22 have detected losses and translocations of genetic material outside the *NF2* region, thus raising the possibility that a second meningioma gene resides on chromosome 22. Candidate genes include *LARGE*, *MN1*, *BAM22*, and *INI1*, although these show only rare alterations [1817, 1889, 2033]. *DAL1* of the protein 4.1 family has also been shown to be deleted in meningiomas, its expression being suppressed in meningiomas [741, 1609]. Although allelic losses of chromosome 17p have been reported to occur in higher-grade meningiomas, studies of the *TP53* gene residing on that chromosome segment have not shown significant gene alterations. Nonetheless, immunohistochemical positivity for p53 protein occurs in subsets of both benign and atypical meningiomas. Furthermore, rare

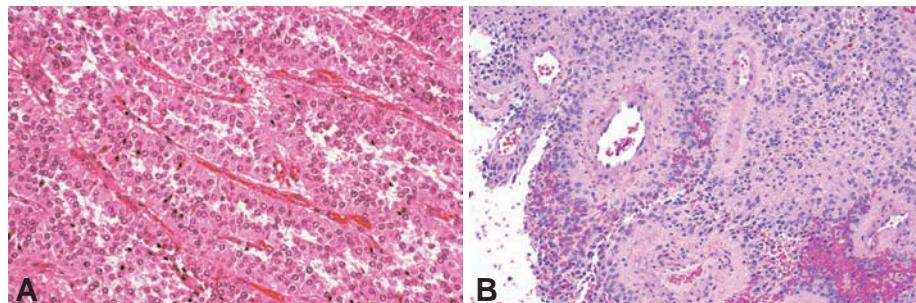


Fig. 10.09 A Papillary meningioma with papillary pattern on a collagenous stroma. B Papillary meningioma characterized by dis cohesive growth with pseudopapillae and perivascular pseudorosettes.

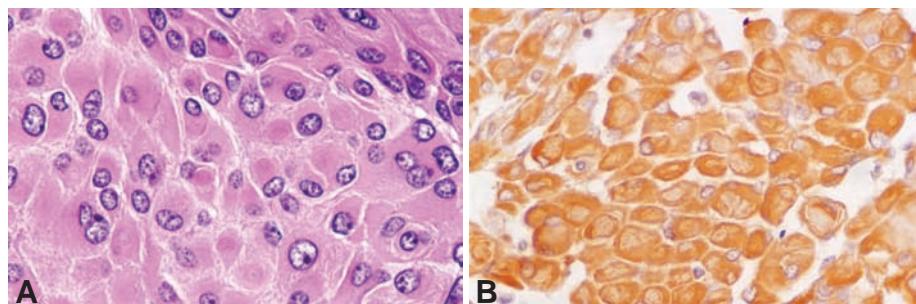


Fig. 10.10 A Rhabdoid meningioma with eccentrically placed vesicular nuclei, prominent nucleoli, and eosinophilic globular/fibrillar paranuclear inclusions (A) and cytoplasmic immunoreactivity for vimentin (B).

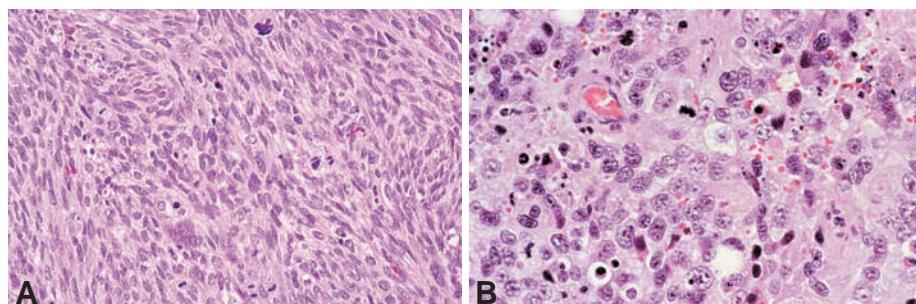


Fig. 10.11 Anaplastic meningioma with sarcoma-like cytology and markedly elevated mitotic index (A) and loss of meningiomatous tissue pattern and numerous typical and atypical mitoses (B).

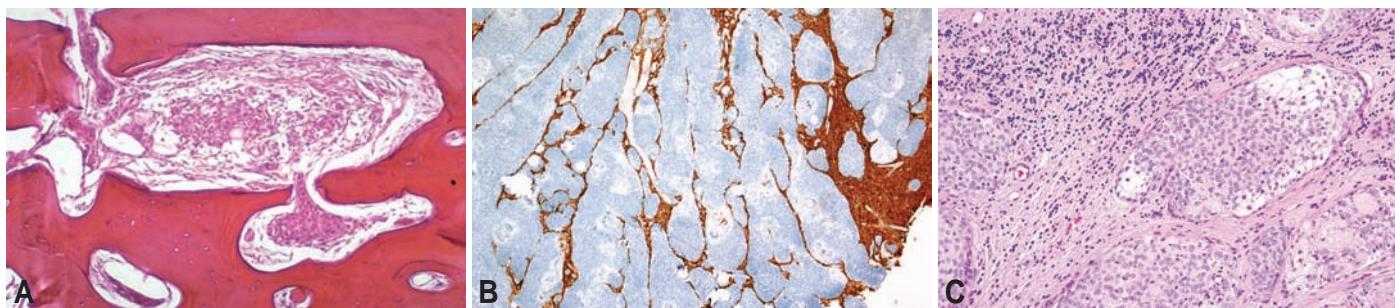


Fig. 10.12 A Invasion of bones by meningiomas through osseous canaliculari is not a sign of malignancy. B The brain invasion in this meningioma is highlighted by the presence of entrapped GFAP-positive brain parenchyma between tongues of GFAP-negative tumour. C Despite otherwise benign histology, this meningioma has breached the pia and has invaded the cerebellum. Brain invasion corresponds to WHO grade II.

anaplastic meningiomas contain *TP53* mutations [2363]. Mutations and deletions of the *CDKN2A* gene are rare in meningiomas, as are alterations of the *PTEN* and *PTCH* genes [1726]. However, deletions of the 9p21 region, which includes the *CDKN2A* gene, are particularly common in the anaplastic meningiomas and are associated with shortened survival [203, 1721]. Other molecular alterations associated with high tumour grade and aggressive clinical behaviour include loss of the *NDRG2* gene on 14q11.2, gains of the *S6K* gene and other loci on the 17q23 amplicon, loss of various *NF2* homologues within the protein 4.1 family, e.g. the *4.1B* gene on chromosome 18p11.3, and loss of the protein 4.1B binding partner *TSCLC-1* [266, 274, 1359, 1609, 1726, 2181]. In summary, in most of the chromosomal loci commonly gained or lost during meningioma tumour progression, the relevant genes affected have yet to be identified.

Microsatellite instability

This finding is thought to result from mutations in DNA mismatch repair genes. One study reported microsatellite instability in 4 of 16 meningiomas [1810].

However, other studies have reported low frequencies or absence of microsatellite instability altogether [2100, 2120, 2309].

Clonality of solitary, recurrent and multiple meningiomas

Studies of X-chromosome inactivation using Southern blot analysis indicate that meningiomas are monoclonal tumours [951], while PCR-based assays have hinted that a small fraction could be polyclonal [2502]. Nevertheless, both the Southern blot data [951] and the observation that the overwhelming majority of meningiomas with *NF2* mutations only have a single mutation [2393] argue that the origin of this group of lesions is clonal. Similarly, all recurrent meningiomas have been found to be clonal with respect to the primary tumour [2338]. The clonality of multiple meningiomas has also been analysed using studies of X-chromosome inactivation and by mutational analysis of the *NF2* gene in multiple tumours from the same patient [1262, 2141, 2337]. In these, lesions from patients with three or more meningiomas have been shown to have either the same copy of the X-chromosome inactivated, or to carry the same *NF2* mutation. These

data provide strong evidence for a clonal origin of multiple meningiomas in patients with more than two lesions. Furthermore, they suggest that multiple lesions arise through dural spread, a notion also supported by the common finding of peritumoural implants in 10% of meningiomas [201] and of small meningotheelial nests in grossly unremarkable dural strips from the convexities of patients with meningiomas [201]. Nevertheless, it remains possible that some cases with multiple meningiomas represent genetic mosaics, with segmental, dural constitutional *NF2* mutations.

Histogenesis

Meningiomas are considered to be derived from meningotheelial (arachnoidal) cells.

Prognostic and predictive factors

The major prognostic questions regarding atypical meningiomas involve prediction of recurrence. For malignant variants, the issue is prediction of survival.

Clinical factors. In most cases, meningiomas can be removed entirely according to operative or neuro-radiologic criteria. In one series, 20% of gross-

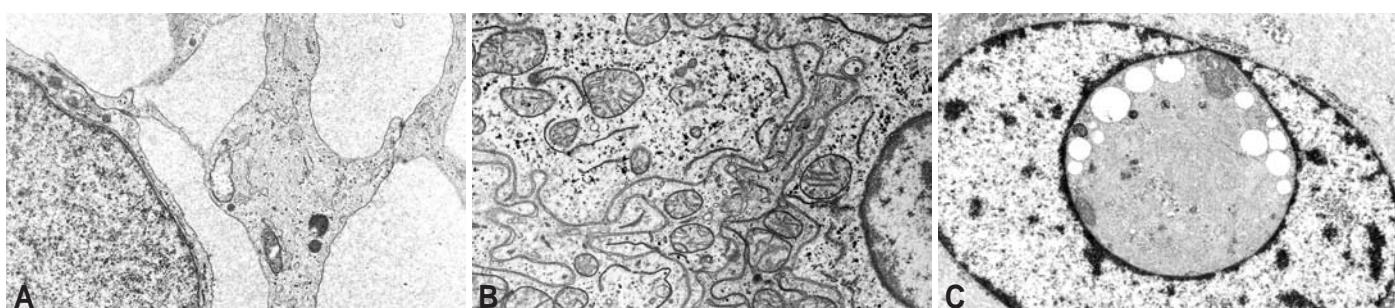


Fig. 10.13 Electron micrographs of meningiomas. A Microcystic meningioma characterized by intercellular microcystic spaces. B Numerous interdigitated cellular processes and occasional desmosomal junctions. C Nucleus containing a pseudoinclusion.

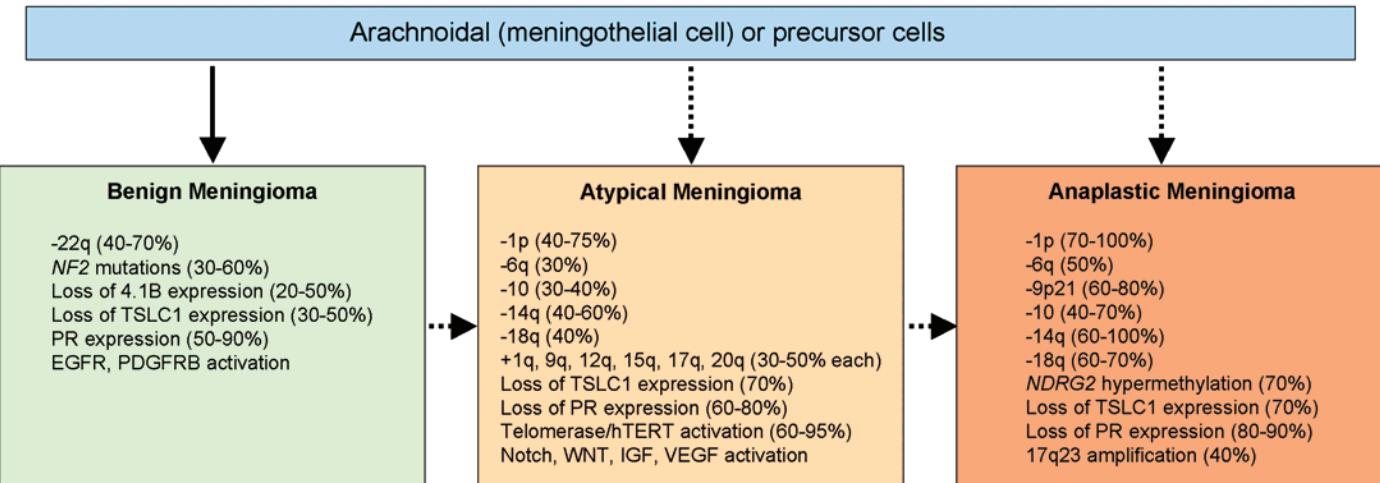


Fig. 10.14 Genetic model of meningioma tumourigenesis and malignant progression.

totally resected, benign meningiomas recurred within 20 years [940]. The major clinical factor in recurrence is extent of resection, which is influenced by tumour site, extent of invasion, attachment to vital intracranial structures, and the skill and experience of the surgeon. Other clinical factors, such as young age and male gender, are less powerful predictors of recurrence. Both are partially explained by the increased frequency of high-grade meningiomas in such patients.

Histopathology and grading. Some histological variants of meningioma are more likely to recur [1726]. Overall, however, histologic grade (WHO I or benign; WHO II or atypical; WHO III or anaplastic) is the most useful morphologic predictor of recurrence. While benign meningiomas have recurrence rates of about 7–25%, atypical meningiomas recur in 29–52% of cases and anaplastic meningiomas at rates of 50–94% [1175, 1384, 1734, 1736]. Malignant histological

features are associated with shorter survival times [1027], one series reporting a median survival of under 2 years [1734]. Similarly, high proliferation indices correlate with aggressive behaviour.

Progesterone receptor status. The absence of progesterone receptors, and a high mitotic index as well as tumour grade are significant factors in assessing disease-free intervals [1722, 1933]. Multivariate analysis has shown that a three-factor interaction model incorporating a progesterone receptor score of 0, a mitotic index greater than 6, and malignant (WHO III) tumour grade, was a highly significant predictor of poor outcome [212, 875]. Atypical and anaplastic tumours frequently lack progesterone receptors [1722], thus progesterone-receptor-negative meningiomas tend to be larger than receptor-positive tumours [212]. Since a significant subset of histologically and clinically benign meningiomas also lacks progesterone

receptor expression, the significance of this single immunohistochemical parameter should not be overestimated in the absence of the other features mentioned above.

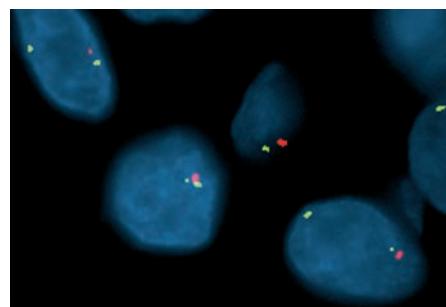


Fig. 10.15 FISH analysis showed hemizygous deletion of the 9p21 (p16^{INK4a}) region (only one red signal in most nuclei) in this anaplastic meningioma, whereas the centromere for chromosome 9 is retained (two green signals in most nuclei). This genetic pattern is associated with decreased survival.

Mesenchymal, non-meningothelial tumours

W. Paulus
B.W. Scheithauer
A. Perry

Definition

Benign and malignant mesenchymal tumours originating in the CNS and histologically corresponding to tumours of soft tissue or bone.

ICD-O codes

Lipoma	8850/0
Liposarcoma	8850/3
Angiolipoma	8861/0
Hibernoma	8880/0
Solitary fibrous tumour	8815/0
Fibrosarcoma	8810/3
Malignant fibrous histiocytoma (MFH)	8830/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Osteoma	9180/0
Osteochondroma	9210/0
Chondrosarcoma	9220/3
Osteosarcoma	9180/3
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/1
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma-peripheral primitive neuroectodermal tumour	9364/3

Grading

According to their histological features and clinical behaviour, they range from benign neoplasms (WHO grade I) to highly malignant sarcomas (WHO grade IV).

Terminology and historical annotation

The histological features of mesenchymal tumours affecting the CNS are the same as those of corresponding extracranial soft tissue and bone tumours [258, 527]. Haemangiopericytoma, by far the most common mesenchymal, non-meningothelial neoplasm, is described separately. Antiquated nosologic terms, such as spindle-cell sarcoma, polymorphic cell sarcoma and myxosarcoma have been replaced by designations indicating specific differentiation [527]. The non-specific diagnostic term 'meningeal

sarcoma' is also to be avoided since it has been used to denote both malignant meningioma and various types of sarcoma. Some non-mesenchymal tumours were previously classified as sarcomas; examples include CNS lymphoma ('reticulum cell sarcoma'), desmoplastic medulloblastoma ('cerebellar arachnoidal sarcoma') and giant cell glioblastoma ('monstrocellular sarcoma').

Incidence

Whereas the various forms of lipoma represent 0.4% of intracranial tumours, the other benign mesenchymal tumours are rare. Based on two series of 19 and 17 cases, sarcomas represent less than 0.1% to 0.2% of intracranial tumours [1636, 1704]. Reported higher values are a reflection of over-diagnosis related to historical classification schemes. The most common tumour types include fibrosarcoma, malignant fibrous histiocytoma (MFH), and undifferentiated sarcoma [1636, 1704].

Age and sex distribution

Mesenchymal tumours may occur at any age. Rhabdomyosarcoma occurs preferentially in children, while malignant fibrous histiocytoma and chondrosarcoma usually manifest in adults. As a whole, sarcomas show no obvious gender predilection.

Etiology

Intracranial fibrosarcoma, MFH, chondrosarcoma and osteosarcoma may occur several years after cranial irradiation, most commonly for sellar region tumours [257, 1597]. Single cases of intracranial and spinal fibrosarcoma, pleomorphic sarcoma and angiosarcoma have also been related to previous trauma or surgery [845], an etiology that may be more common to fibromatoses [1490]. The Epstein-Barr virus probably plays a role in the development of intracranial smooth muscle tumours of immunocompromised patients [229].

Localization

Tumours arising in meninges are more

common than ones originating within CNS parenchyma or in choroid plexus. Whereas most mesenchymal tumours are supra- rather than infratentorial or spinal in location, rhabdomyosarcomas are more often infratentorial. Chondrosarcomas involving the CNS arise most often in the skull base. Intracranial lipomas typically occur at midline sites, such as the anterior corpus callosum, quadrigeminal plate, cerebellopontine angle, suprasellar and hypothalamic region as well as the auditory canal. Spinal cord examples involve the conus medullaris-filum terminale as well as occurring at the thoracic level. Intra-ventricular and tuber cinereum [189] lipomas are rare. Occasional CNS lipomas have a fibrous connection to extend into surrounding soft or subcutaneous tissue. Osteolipomas prefer the suprasellar/interpeduncular regions [189, 2106]. Most spinal lipomas and particularly angioliopomas arise in the epidural space.

Clinical features

Clinical symptoms and signs are variable and non-specific, and depend largely upon tumour location. Spontaneous regression is rare [1228].

While the neuroradiologic appearance of most mesenchymal tumours is non-specific, the neuroimaging characteristics of lipoma are virtually diagnostic, as T1-weighted MRI images show fat having a high-signal intensity. Speckled calcifications are typical of chondroid and osseous tumours.

Macroscopy

The macroscopic appearance of mesenchymal tumours depends entirely upon their differentiation and is similar to that of the corresponding extracraniospinal soft tissue tumours. Lipomas are bright yellow, lobulated lesions. Whereas epidural lipomas are delicately encapsulated and discrete, intradural examples are often intimately attached to leptomeninges and CNS parenchyma. Lumbosacral lipomas (leptomylolipomas) are comprised of subcutaneous and intradural

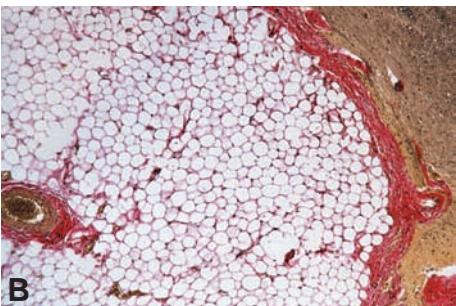


Fig. 10.16 A Lipoma beneath the mammillary bodies. B Histology of a cerebral lipoma composed of uniform fat cells sharply delineated from brain tissue.

components, the two being linked by a fibrolipomatous stalk that may attach to the dorsum of the cord, to the filum terminale, or to both. A "tethered cord" commonly results. Chondromas are demarcated, bosselated grey-white, translucent, and typically form large, dural-based masses indenting brain parenchyma. Meningeal sarcomas are firm in texture and tend to invade adjacent brain. Although intracerebral sarcomas appear well delineated, parenchymal invasion is a feature. As a rule, the cut surface of sarcomas is firm and fleshy; high-grade lesions often show necrosis and haemorrhage.

Tumours of adipose tissue

Lipoma

This benign lesion microscopically resembles normal adipose tissue {240}. Most lipomas show lobulation at low magnification. The ample capillary vasculature of even typical encapsulated lipomas is inconspicuous. Patchy hyalinization is a common feature, but calcification and myxoid change are occasionally seen. Osteolipomas are exceedingly rare and may show zonation with central adipose tissue and peripheral bone {2106}.

Angiolipoma

The proportion of adipose cells and vasculature varies in this lipoma variant {1752, 2106}. By definition, vessels are of capillary dimension and generally most prominent beneath the tumour capsule. Fibrin thrombi are a diagnostic finding. With time, interstitial fibrosis may ensue. Angiolipomas may be over-diagnosed since by their nature, ordinary haemangiomas are often accompanied by fat.

Hibernoma

This lipoma variant is rare in the CNS. It

resembles brown fat and is composed of uniform granular or multivacuolated cells with small, centrally placed nuclei {336}.

Complex lipomatous lesions

These vary considerably in terms of their histological composition. For example, lumbosacral lipomas (leptomylolipomas) {837} consist of lobulated adipose tissue, often in association with fibrous tissue, vascular proliferation, smooth muscle elements, and neuroglial tissue, particularly ependyma ('fibrolipomatous hamartoma'). Lipomas of the cerebellopontine angle {161}, an uncommonly affected off-midline site, may incorporate intradural portions of cranial nerve roots and their ganglia. Many also feature striated muscle or other mesenchymal tissues. It has even been suggested that intracranial lipomas containing various other tissue types represent a transition between lipoma and teratoma {2264}. Whether these various lesions are neoplasms or neomafomative overgrowths remains to be determined.

Epidural lipomatosis

This rare lesion consists of diffuse hypertrophy of spinal epidural adipose tissue. As such, it is not a neoplasm but

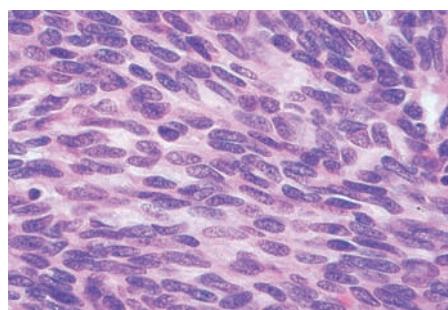


Fig. 10.17 Primary CNS leiomyosarcoma, fascicles of spindle cells showing characteristic cigar-shaped nuclei.

a metabolic response, often to chronic administration of steroids {749}.

Intracranial liposarcoma

This neoplasm is extremely rare. An example associated with subdural haematoma has been described {352}. An example of gliosarcoma with a liposarcomatous element has also been reported {200}.

Fibrous tumours

Fibromatosis

This locally infiltrative but cytologically benign, generally hypocellular lesion is composed of elongate fibroblasts in an abundant collagenous stroma {1490}. The process must be differentiated from pseudotumoural cranial fasciitis of childhood, a process histologically related to nodular fasciitis, featuring rapid growth within the deep scalp, lacking an intradural component and having no malignant potential {1267}. Cranial infantile myofibromatosis also enters into the differential diagnosis {2130}. Another pseudotumoural lesion, hypertrophic intracranial pachymeningitis, entails progressive dural thickening owing to pachymeningeal fibrosis and chronic inflammation often associated with autoimmune disorders {2209}. Myofibroblastomas of the CNS are akin to mammary type myofibroblastoma. They are closely related to benign fibrous proliferation, differing only in their strong smooth muscle actin and desmin immunoreactivity and their myofibroblastic ultrastructure {2089}.

Solitary fibrous tumour

This lesion affects both cranial and spinal meninges, rarely arises in spinal nerve roots, affects mainly adults and may show invasion of CNS parenchyma or nerve roots {287, 964} as well as the skull base {295}. Spinal seeding is rare {1499}. Its spindle cells are disposed in fascicles between prominent, eosinophilic bands of collagen. There is strong immunoreactivity for vimentin, CD34, and Bcl-2, but not EMA or S-100 protein. The relation of solitary fibrous tumour to rare cases of intracranial fibroma {1864} and myxoma {717A} is unclear.

Inflammatory myofibroblastic tumour

Inflammatory myofibroblastic tumour (IMT) is a distinctive neoplastic proliferation once considered synonymous with

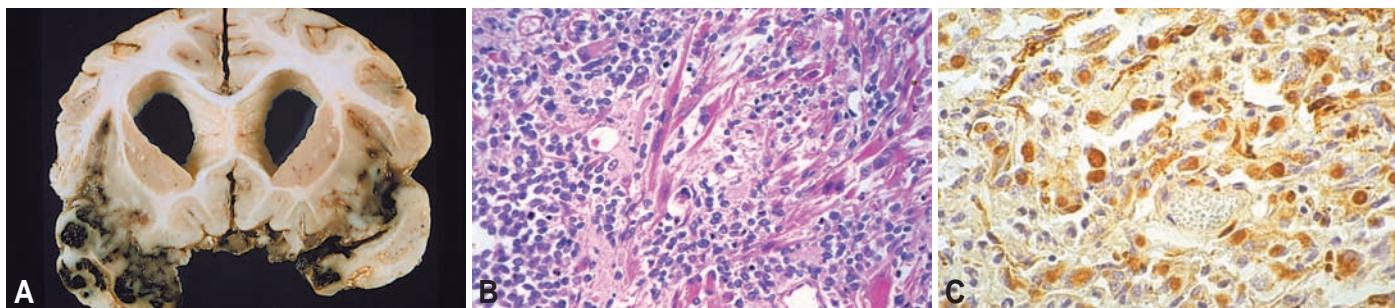


Fig. 10.18 Rhabdomyosarcoma. A Bilateral fronto-temporal lesion. B Small, undifferentiated cells intermingled with rhabdomyoblasts and strap-like cells. C Embryonal rhabdomyosarcoma showing strong desmin immunoreactivity.

inflammatory pseudotumour or plasma cell granuloma and a variant of inflammatory fibrosarcoma [365]. Initially reported to involve the mediastinum and pulmonary parenchyma, IMTs were subsequently found in various other organs. Recent studies demonstrated their neoplastic nature, the demonstration of ALK fusion genes separating IMT from non-neoplastic inflammatory lesions in the “inflammatory pseudotumour” and “plasma cell granuloma” categories.

IMTs of the CNS are rare and can occur at any age. Their radiological characteristics are often similar to meningiomas. Unlike pseudoneoplastic, inflammatory pseudotumours, IMTs appear to be unassociated with immune deficiency or other systemic diseases.

Histologically, IMTs are composed of myofibroblasts in association with stromal lymphoplasmacyte and eosinophil infiltrates. The three different patterns reported in IMTs of soft tissue, including the myxoid-nodular fasciitis-like, fibromatosis-like and scar-like, have all been observed in the CNS. The myofibroblast, the cell comprising the majority component, typically shows significant cytological atypia and mitotic figures. The immunohistochemical stains demonstrate uniform vimentin, smooth muscle actin, and often, but invariably strong, focal or diffuse ALK staining, especially in young patients. Most IMTs have favourable outcomes following gross total resection.

Fibrosarcoma

This rare, malignant tumour shows interlacing bundles of spindle cells disposed in a “herringbone” pattern. Fibrosarcomas are markedly cellular, exhibit brisk mitotic activity, and often feature necrosis [652]. Sclerosing epithelioid fibrosarcoma has also been reported to affect the CNS [169].

Fibrohistiocytic tumours

Benign fibrous histiocytoma

This lesion, also termed fibrous xanthoma or fibroxanthoma, may involve dura or cranial bone [2292], is composed of a mixture of spindled (fibroblast-like) and plump (histiocyte-like) cells arranged in a storiform pattern. Scattered giant cells and/or inflammatory cells are commonly seen. Many tumours initially published as fibrous xanthoma were subsequently shown to be GFAP-positive [1078], and reclassified as pleomorphic xanthoastrocytoma.

Malignant fibrous histiocytoma (MFH)

This neoplasm consists of spindled, plump and pleomorphic giant cells that can be arranged in a storiform or fascicular pattern. Most MFH are obviously malignant, featuring numerous mitoses as well as necrosis. Only isolated cases of the inflammatory variant of MFH have been reported to involve brain [1409].

Myogenic tumours

Leiomyoma

Most benign smooth muscle tumours are readily recognized by their pattern of intersecting fascicles composed of eosinophilic spindle cells with blunt-ended nuclei [1323]. As a rule, they lack mitotic activity. Occasional examples feature nuclear palisading and should not be mistaken for schwannoma. Diffuse leptomeningeal leiomyomas [967] as well as an angioleiomyomatous variant [1244] have been described. EB virus and AIDS-associated cases have also been reported [1050].

Leiomyosarcoma

Intracranial leiomyosarcomas [442] correspond histologically to their soft-tissue counterparts, expressing desmin and smooth muscle actin. Most arise in the dura, but the parasellar region and

epidural space may also be affected [1406, 2490]. Parenchymal examples are rare [507]. An association with EB virus and AIDS is established [2490]. One unique example originating in a pineal teratoma has been reported [2108].

Rhabdomyoma

This lesion consists entirely of mature striated muscle, but one reported example associated with a cranial nerve featured a minor adipose tissue component [2315]. CNS rhabdomyoma must be distinguished from skeletal muscle heterotopias, most of which occur within prepontine leptomeninges [584].

Rhabdomyosarcoma

Whether meningeal or parenchymal, nearly all CNS rhabdomyosarcomas are of the embryonal type [1827, 2215], while alveolar rhabdomyosarcoma has not been reported. Strap cells with cross striations may be observed. However, most tumours consist primarily of small cells that show little or no specific differentiation at the H&E level. Thus, immunohistochemistry and/or electron microscopy may be necessary for diagnosis. Immunostains for desmin and myogenin usually confirm the diagnosis. The ultrastructural findings of thick (myosin) and thin (actin) filaments arrayed in sarcomeres is also diagnostic. Rhabdomyosarcoma must be differentiated from other brain tumours that occasionally show skeletal muscle elements, such as medullomyoblastoma, gliosarcoma, germ cell tumours and even a rare meningioma [953]. Malignant ectomesenchymoma, a mixed tumour composed of ganglion cells or neuroblasts and one or more mesenchymal elements, usually rhabdomyosarcoma, may also occur in the brain [1704].

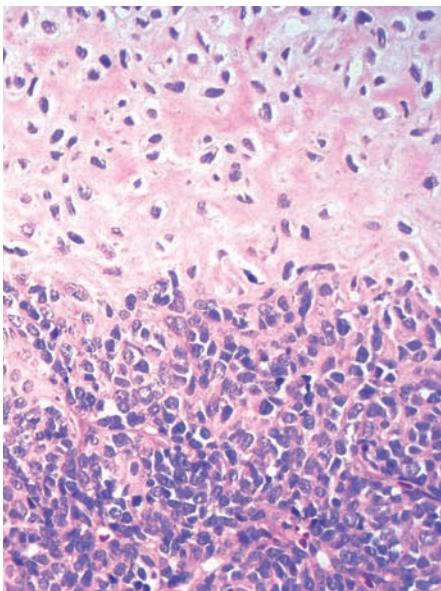


Fig. 10.19 Mesenchymal chondrosarcoma with cellular portion resembling a haemangiopericytoma.

Osteocartilaginous tumours

These benign osteocartilaginous tumours are usually dural-based; outside the CNS, they often develop in the skull and only secondarily displace dura and brain {385, 1235}. Histologically, they correspond to similar tumours arising in bone, but are to be separated from asymptomatic dural calcification, ossification related to metabolic disease or trauma, and neuroectodermal tumours such as astrocytoma and gliosarcoma that occasionally show osseous or chondroid differentiation. Transition of CNS chondroma to chondrosarcoma has rarely been documented {1497}.

Mesenchymal chondrosarcoma

This neoplasm more often arises in bones of the skull or spine than within dura or brain parenchyma {1956, 2009, 2465}. Nonetheless, the CNS is the most common site of extraosseous examples. Some tumours consist primarily of the small-cell component punctuated by scant islands of atypical hyaline cartilage, whereas the cartilage predominates in others. The histological pattern of the small-cell element closely resembles haemangiopericytoma, replete with staghorn vascular spaces and an intercellular pattern of reticulin staining. Although the diagnosis of mesenchymal chondrosarcoma generally poses no problem, in the absence of cartilage, immunohistochemistry is of no particular

benefit in distinguishing this lesion from haemangiopericytoma or other small-cell sarcomas {2188}. Even less frequent in the CNS are differentiated chondrosarcoma and myxoid chondrosarcoma {1176, 1704}. Chondrosarcomas arising in the skull base, particularly in the midline, should be distinguished from chondroid chordoma. Unlike chondroid chordoma, chondrosarcomas are non-reactive for keratin and epithelial membrane antigen {1491}. Intracranial, extraosseous chondrosarcomas of the classic type are rare {317, 1650}. The same is true of myxoid chondrosarcoma, which has been reported to arise within brain {321} as well as in the leptomeninges of the brain.

Osteosarcoma

Preferred sites are the skull or spine and, more rarely, the meninges or the brain {115, 283, 1969, 1976, 2055}. Direct formation of bone or osteoid by the proliferating tumour cells is requisite to the diagnosis. Osteosarcomatous elements may exceptionally be encountered as components of germ cell tumour and gliosarcoma {106}.

Vascular tumours

Most vascular lesions of the central nervous system are malformative in nature and include arteriovenous malformation, cavernous angioma, venous angioma and capillary telangiectasis {984}. Blood vessel tumours are to be differentiated from intravascular papillary endothelial hyperplasia, a tumour-like, reactive papillary proliferation of endothelium associated with thrombosis, which may occur in brain or meninges {1190}. This discussion is limited to vascular neoplasms: benign (haemangioma), intermediate grade (haemangioendothelioma), and malignant (angiosarcoma, Kaposi sarcoma).

Haemangioma

These lesions vary in size from microscopic to massive. Depending upon their histological appearance, haemangiomas are classified as capillary or cavernous. Of those affecting the CNS, most are primary lesions of bone that impinge secondarily upon the CNS. Dural {1, 1072} and parenchymal {2102} haemangiomas are less common.

Epithelioid haemangioendothelioma

Skull base, dura or brain parenchyma are rare locations for this neoplasm {1522, 1604}. Its cells possess relatively abundant eosinophilic cytoplasm and may be vacuolated. In general, nuclei are round or occasionally indented, vesicular, and show only minor atypia. Mitoses and limited necrosis may be seen. Vascular lumens are often small and intracytoplasmic. Their somewhat nodular architecture often features chondroid or myxoid stromal change. Immunohistochemical (factor VIII-related antigen, Ulex europeus lectin, CD31) and ultrastructural studies (Weibel-Palade bodies) confirm the endothelial nature. Conventional haemangioendothelioma {849} and the related epithelioid {80} and polymorphous {1916} variants have all been reported to occur in the central nervous system.

Angiosarcoma

The rare examples originating in brain or meninges {1450} vary in differentiation from patently vascular tumours with anastomosing vascular channels lined by mitotically active, cytologically atypical endothelial cells, to poorly differentiated, often epithelioid lesions in which immunohistochemical and ultrastructural studies are required for a definitive diagnosis. Occasional cytokeratin reactivity complicates distinguishing poorly differentiated

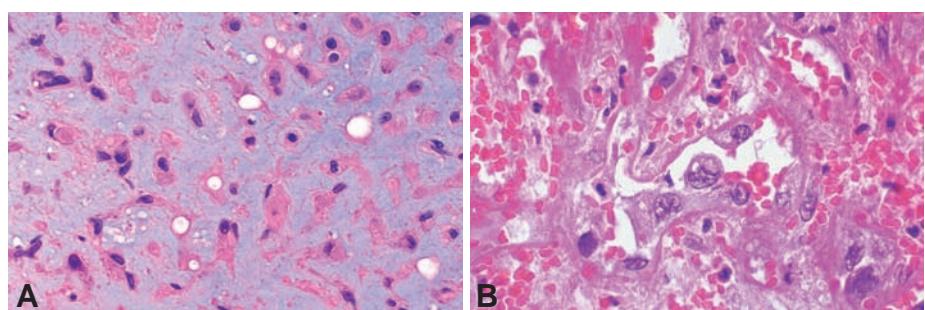


Fig. 10.20 A Epithelioid haemangioendothelioma with intracellular lumina and basophilic extracellular matrix. B Angiosarcoma showing abnormal vascular channels lined by atypical plump endothelial cells.

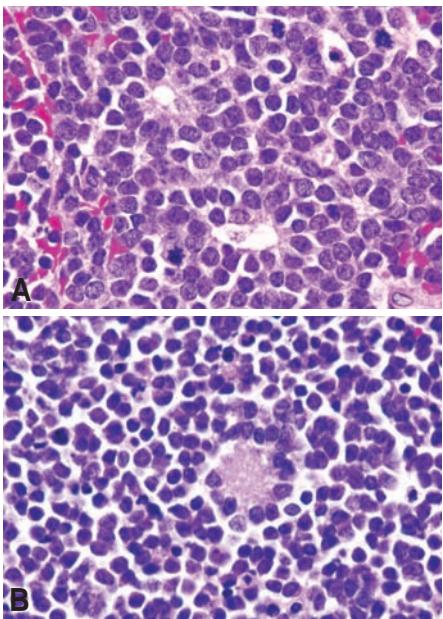


Fig. 10.21 Histological features of EWS-pPNET, showing rare rosettes (A) and a rare Homer Wright rosette (B).

angiosarcoma from metastatic carcinoma {1893}.

Kaposi sarcoma

This malignant neoplasm is characterized by spindle-shaped cells lining or forming slit-like blood vessels and is only exceptionally encountered as a parenchymal or meningeal tumour in the setting of AIDS {268}. In such instances, it is often difficult to determine whether the lesion is primary or secondary. The tumour is almost always immunopositive for herpesvirus 8 (HHV-8) {1899A}

Meningeal sarcomatosis

Meningeal sarcomatosis is a diffuse leptomeningeal sarcoma lacking circumscribed masses {2287}. Strictly defined as a non-meningothelial mesenchymal tumour, most are poorly differentiated "spindle cell" sarcomas. Re-examination of published cases using immunohistochemistry has revealed that most actually represented carcinoma, lymphoma, glioma or primitive neuroectodermal tumours.

Ewing sarcoma-peripheral primitive neuroectodermal tumour (EWS-pPNET)

EWS-pPNET is a rare small round cell tumour that involves the CNS as either a primary dural neoplasm {450, 1424, 1502, 2097} or by direct extension from contiguous bone or soft tissue (e.g. skull, vertebra, paraspinal soft tissue). Both

spinal and intracranial examples have been encountered and may mimic meningioma radiologically. A wide age range has been reported, although peak incidence is in the second decade. The histology, immunophenotype, and biology is essentially identical to that encountered in bone or soft tissue {587}. The tumour is composed of sheets of small, round, primitive appearing cells with thin rims of PAS-positive, diastase sensitive, glycogen-rich cytoplasm. The latter imparts a variable degree of cytoplasmic clearing. Homer Wright rosettes are occasionally seen, but are usually not prominent. The majority of tumours stain at least focally with neuronal markers, such as synaptophysin and neuron specific enolase, whereas cytokeratin stains are typically negative or only focally reactive. CD99, the so-called "Ewing sarcoma antigen", shows strong and diffuse membrane immunoreactivity, but can also be expressed by a variety of other tumour types, including haemangiopericytoma and less commonly medulloblastoma/CNS PNET, two potential differential diagnostic considerations. Therefore, it is advisable to confirm the diagnosis of EWS-pPNET genetically via the t(11;22) (q24;q12) either karyotypically or by the presence of an EWS-FLI1 (or other EWS variant) fusion transcript. In paraffin-embedded tissue, FISH may be superior to RT-PCR for demonstrating the latter {223}.

Genetic susceptibility

Several associations with inherited disease are worth noting; intracranial cartilaginous tumours may be associated with Maffucci syndrome and Ollier disease, lipomas with encephalocraniocutaneous lipomatosis, and osteosarcoma with Paget disease.

Genetics

Although the molecular genetic alterations of intracranial sarcomas may be similar to those of corresponding soft tissue lesions {59}, few data are available to date. Nevertheless, examples of meningeal-based EWS-pPNET have shown the typical EWS type rearrangements found in the bone and soft tissue counterparts {450, 1424}. One case of MFH showed a complex karyotype, similar to those reported for soft tissue MFH {155}.

Histogenesis

Mesenchymal tumours affecting the CNS are thought to arise from craniospinal

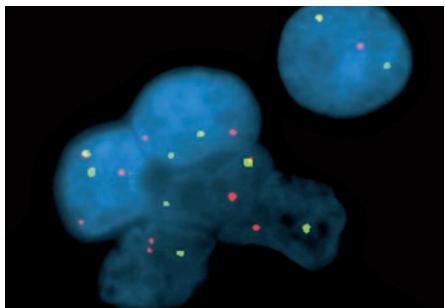


Fig. 10.22 EWS-pPNET with yellow or red-green EWS-FLI1 fusion signals by FISH analysis.

meninges, vasculature and surrounding osseous structures. Osteocartilaginous and myoid tumours may arise: (i) from rarely occurring meningeal heterotopias, (ii) from multipotential mesenchymal cells, (iii) by acquisition of additional lines of mesenchymal differentiation in fibrous or fibrohistiocytic tumours, or (iv) within a teratoma {283}. Since cranial and intracranial mesenchymal structures, such as bone, cartilage and muscle, are in part derived from the neuroectoderm (ectomesenchyme), the development of the corresponding sarcoma types could also represent reversion to a more primitive stage of differentiation. Lipomas arising within the CNS are often associated with developmental anomalies, particularly partial or complete agenesis of the corpus callosum and spinal dysraphism with tethered cord {177, 2466}. Intracranial rhabdomyosarcoma may also be associated with malformations of the CNS {820}.

Prognostic and predictive factors

Whereas most benign mesenchymal tumours can be completely resected and carry a favourable prognosis, primary intracranial sarcomas are aggressive and associated with a poor outcome. Local recurrence and/or distant leptomeningeal seeding are typical. For example, despite aggressive radiation and chemotherapy, CNS rhabdomyosarcomas have been almost uniformly fatal within two years. Systemic metastases of intracranial sarcomas are relatively common. Nevertheless, primary CNS sarcomas are less aggressive than glioblastomas with 5-year survivals in a series of 18 cases estimated at 28% for high-grade and 83% for low-grade examples {1636}.

Haemangiopericytoma

C. Giannini
E.J. Rushing
J.A. Hainfellner

Definition

A highly cellular and vascularized mesenchymal tumour exhibiting a characteristic monotonous low-power appearance and a well-developed, variably thick-walled, branching "staghorn" vasculature; almost always attached to the dura and having a high tendency to recur and to metastasize outside the CNS.

ICD-O codes

Haemangiopericytoma 9150/1
Anaplastic haemangiopericytoma 9150/3

Grading

Haemangiopericytomas correspond histologically to WHO grade II, with anaplastic haemangiopericytomas corresponding to WHO grade III.

Synonyms and historical annotation

Haemangiopericytoma was described as a distinctive soft tissue tumour in 1942 by Stout and Murray [2160], who postulated its pericytic origin. In 1938, Cushing and Eisenhardt [406] described three variants of 'angioblastic meningiomas'; in retrospect, variant 1 represented haemangiopericytoma [1959]. The 1979 WHO classification [2513] still contained the 'haemangiopericytic' variant of meningioma, but it has now been long accepted that haemangiopericytoma and meningioma are different entities. In soft tissue tumours, the term haemangiopericytoma has evolved to describe a heterogeneous group of tumours, which simply shared a common "haemangiopericytic growth" pattern [586]. The nosological position of CNS haemangiopericytoma remains uncertain, but at present meningeal haemangiopericytoma is still recognized as a clinicopathologically well-characterized malignancy distinct from meningioma. Whereas in most cases it is distinct from solitary fibrous tumour, a spectrum between the two has been suggested [2248].

Incidence

Meningeal haemangiopericytoma consti-

tutes approximately 0.4% of all primary CNS tumours. In three large series of meningeal tumours, the ratios of meningeal haemangiopericytoma to meningioma were about 1:40 [738], 1:50 [943] and 1:60 [987].

Age and sex distribution

Meningeal haemangiopericytomas tend to occur at a younger age than meningiomas, and slightly more often in men than in women. In three large clinical series of 66 men and 47 women (M/F ratio, 1.4:1), the mean age at diagnosis was 43 years [738, 943, 986].

Localization

Primary haemangiopericytomas of the CNS are almost invariably solitary [2039] and attached to the cranial or spinal dura. In four large series of 153 meningeal haemangiopericytomas, 8% were spinal and two were intraparenchymal [738, 869, 986, 1754]. Rare intraventricular examples have been reported [5, 790, 1543]. Haemangiopericytoma occurs slightly more often in the occipital region, around the confluence of sinuses, and attached to venous sinuses [406, 944, 1754].

Clinical features

As suggested by their location, the symptoms of meningeal haemangiopericytoma are indistinguishable from those of meningioma.

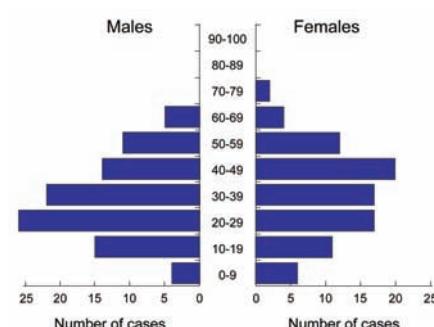


Fig. 10.23 Age and sex distribution of haemangiopericytoma, based on 186 cases.



Fig. 10.24 Liver metastasis of a primary intracranial haemangiopericytoma seven and one half years after surgical resection. From Jaaskelainen et al. [943].

Neuroimaging

On plain films, a well-demarcated, lytic lesion of adjacent bone supports haemangiopericytoma, whereas hyperostosis, a typical feature of meningioma, is absent [598, 738, 944]. The hypervascularity seen on angiography explains the tendency to bleed; it typically shows a dual blood supply from meningeal and cortical arteries and corkscrew-like vessels in a densely stained tumour [598, 944]. CT and MRI show a sharply demarcated tumour with dural attachment, smooth or nodular margin and intense contrast enhancement. Significant edema in underlying brain parenchyma is frequently present [598]. Unlike meningiomas, haemangiopericytomas typically lack calcification [40, 598].

Macroscopy

At surgery, meningeal haemangiopericytoma is a solid, well-demarcated tumour. It has a tendency to bleed during removal, sometimes profusely [943]. The resected tumour specimen is usually globoid, slightly lobulated and rather firm. Cut surfaces are fleshy, greyish to red-brown or frankly hemorrhagic in appearance, often with a number of visible vascular spaces.

Histopathology

Haemangiopericytomas are monomorphic tumours composed of closely

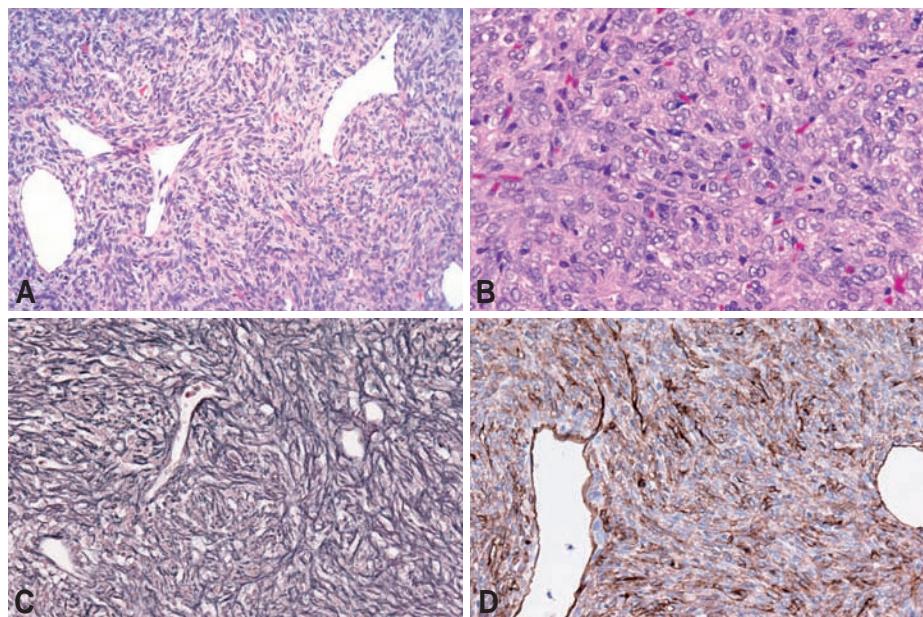


Fig. 10.25 Histological features of haemangiopericytoma. A Highly cellular tumour with dilated, staghorn-type vessels. B Higher power demonstrates jumbled arrangement of spindle cells. C Well developed reticulin fibers. D CD34 immunoreactivity in tumour cells and endothelial cells.

packed, randomly oriented tumour cells with little intervening fibrosis. Cytoplasm is scant and cell borders are indistinct. Nuclei are round to oval, occasionally elongated, with moderately dense chromatin and inconspicuous nucleoli, lacking the pseudo-inclusions characteristic of meningiomas {986, 1451}. Nuclear atypia and mitotic activity vary. Anaplastic (grade III) tumours show a high degree of mitotic activity (at least 5 mitoses per 10 HPF) and/or necrosis, plus at least two of the following: haemorrhage, moderate to high nuclear atypia and cellularity {1451}. A rich network of reticulin fibers, typically investing individual cells, is one of the most characteristic but not invariable features of this neoplasm. Haemangiopericytoma is highly vascular, with numerous slit-like vascular channels lined by flattened endothelial cells and frequent gaping, thin-walled and branching vascular spaces, so-called "staghorn sinusoids". The uniform cellularity of the tumour may be interrupted by "geographic" areas of reduced cell density with a corresponding increase in tumour matrix and/or perivascular fibrosis. Necrosis is uncommon. Calcification, including psammoma bodies, are not seen. Despite their gross appearance of forming discrete masses, haemangiopericytomas may invade and destroy adjacent bone, without the

hyperostotic reaction characteristic of meningiomas. Infiltration of adjacent brain parenchyma may be observed.

Immunohistochemistry

Haemangiopericytoma cells are diffusely immunoreactive for vimentin (85%), factor XIIIa (80–100 %) in individual scattered cells, Leu-7 (70%), and, in 33–100% of cases, for CD34 {1732, 1861}. The latter is usually patchy, in contrast to the diffuse pattern typical of solitary fibrous tumour. Focal positivity for desmin, smooth muscle actin, and cytokeratin may be occasionally encountered {986, 1732, 1825, 2418}. Although strong and diffuse immunoreactivity for epithelial membrane antigen and claudin-1 are typical of meningioma {754, 1861}, focal, generally weak immunoreactivity has been reported in haemangiopericytoma {1732, 1825}. Tumour cells are negative for S-100 protein, classical endothelial antigens such as CD31 {1732}, as well as progesterone receptor {492}. Although the immunoreactivity pattern of haemangiopericytoma is diverse and no single antibody is either 100% sensitive or specific, its immunoprofile is generally sufficiently distinctive to permit the exclusion of meningioma and solitary fibrous tumour {1732, 1825, 2248}.

Vascular endothelial growth factor VEGF-A is up-regulated in tumour cells and the

receptors VEGFR-1 and VEGFR-2 (but not VEGFR-3) in endothelial cells, suggesting a paracrine mode of interaction {791}. Endothelial cells also express Tie-1 {791}, a tyrosine kinase receptor associated with enhanced neovascularization.

Electron microscopy

Closely spaced elongated cells with short processes may contain small bundles of intracytoplasmic intermediate filaments and are surrounded by electron-dense, extracellular basement membrane-like material, the ultrastructural equivalent of the reticulin network visible on light microscopy. True desmosomes and gap junctions are absent {414, 986}.

Proliferation

The time to recurrence after complete removal, a rough indicator of the volume growth rate, varies remarkably, but the median time intervals of 40 {738} and 70 months {943} suggest that meningeal haemangiopericytomas grow more rapidly than meningiomas {2039}. In most cases, mitotic activity is prominent. The median Ki-67 (MIB-1) labelling index was 10% (0.6–36%) in a series of 31 tumours {2352} and 5% (1.2–39 %) in another study of 62 tumours {1802}, i.e. values at the level of anaplastic (WHO grade III) meningiomas. The median S-phase fraction was 4% (1.6–15%) in 31 tumours {2352}.

Genetic susceptibility

There is no evidence of familial clustering of meningeal haemangiopericytoma. One report notes the occurrence of peripheral haemangiopericytoma in three members of one family {1763}.

Genetics

Karyotypes of meningeal haemangiopericytomas show abnormalities of chromosome 12, particularly in the region 12q13-15. The second most frequent alterations are abnormalities of chromosome 3 {1407}. Rearrangements of chromosome 12q13, a region that includes a number of oncogenes, are less consistent; alterations on 6p21, 7p15 and 19q13 have been reported in meningeal and/or peripheral haemangiopericytomas {809, 813, 1392}. However, no consistent chromosomal losses or gains were found in 11 peripheral haemangiopericytomas by comparative genomic hybridization (CGH) {1470}. No allelic losses have

been reported on 22q, the region harbouring the *NF2* gene. Neither meningeal nor peripheral haemangiopericytomas contain *NF2* mutations (0/38), whereas 32% of meningiomas have such alterations [1009]. Heterozygous deletions of the *CDKN2A* gene on 9p were found in about 25% (7/28) of meningeal haemangiopericytomas, but infrequently (1/26) in meningiomas [1647]. No point mutations in *CDKN2A* or *TP53* genes are found [1647].

Histogenesis

The histogenesis of meningeal haemangiopericytoma is uncertain. The Working Group of the new WHO Classification of Tumours of Soft Tissue and Bone stated that most lesions formerly known as haemangiopericytoma show no evidence of pericytic differentiation and, instead, are fibroblastic in nature and form a morphological continuum with solitary fibrous tumour [586]. This concept may pertain to meningeal haemangiopericytomas as well [657].

Prognostic and predictive factors

The majority of tumours can be removed in a seemingly complete manner but, unlike meningiomas, local recurrences are almost inevitable. In two series, they occurred in 91% [2352] and 85% of cases [738] after 15 years. In one series, 9 of 17 irradiated haemangiopericytomas recurred with a median of 58 months, but 13 of the 15 non-irradiated tumours

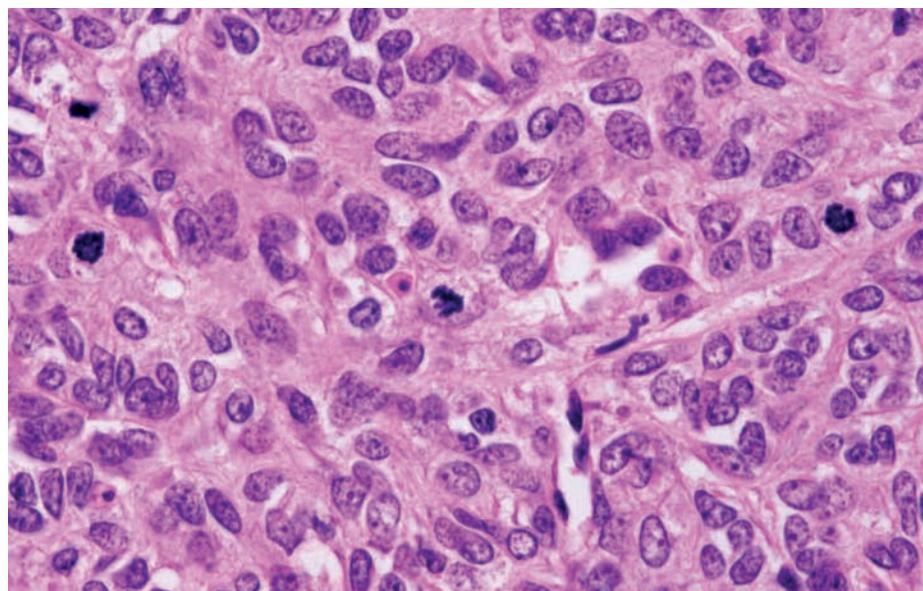


Fig. 10.26 Anaplastic haemangiopericytoma (WHO grade III) with brisk mitotic activity.

recurred with a median of only 29 months [738]. The majority of meningeal haemangiopericytomas eventually metastasize to the bones, lungs and liver. Mean survival time after diagnosis of metastasis was 2 years [738, 2352]. In a series of 28 patients who had survived the primary removal, the probability of tumour-related death was 61% at 15 years [2352]. One study found that the 5-year survival of patients with haemangiopericytoma has improved during the past 10 years and suggested that improved treatment of patients with cancer, a low

intraoperative mortality rate and the use of radiosurgery in the treatment of recurrent disease may all contribute [506]. The prognostic significance of proliferation is discussed above. Using the criteria noted above [1451] in distinguishing "low" from "high" grade tumours, one study found that high-grade tumours recurred 6.7 years earlier than low-grade [506]. Despite the increased recurrence rate for anaplastic examples, no significant survival effect was associated with tumour grade [506].

Melanocytic lesions

D.J. Brat
A. Perry

Definition

Primary melanocytic neoplasms of the CNS that arise from leptomeningeal melanocytes and that can be diffuse or circumscribed, benign or malignant. This group includes (1) diffuse melanocytosis and melanomatosis, (2) melanocytoma and (3) malignant melanoma.

Incidence

Melanocytomas account for 0.06–0.1% of brain tumours. The annual incidence is approximately 1 per 10 million population [954]. Primary CNS melanomas are also infrequent, with an incidence of 0.005 cases per 100 000 population [804]. The diffuse leptomeningeal melanocytic lesions are rare and population-based incidence is not available [1022].

Age and sex distribution

Diffuse leptomeningeal melanocytosis and melanomatosis are strongly linked with neurocutaneous melanosis, a rare phakomatosis of childhood that typically presents before age two. Among one series of 39 such cases, ages at presentation ranged from stillbirth to the second decade with an equal gender distribution and no racial predisposition [1022]. Melanocytomas occur in all ages (range 9–73 years), but are most frequent in the fifth decade (45–50 years), with a slight female predominance (female: male 1.5:1) [216, 357]. Primary nodular melanomas arise in patients ranging from 15–71 years old (mean, 43 years).

Localization

Diffuse melanocytosis and melanomatosis involve the supra- and infratentorial leptomeninges and the superficial brain parenchyma. They involve large expanses of the subarachnoid space, with focal or multifocal intensity. Sites of highest frequency include the cerebellum, pons, medulla and temporal lobes. Most melanocytomas arise in the extramedullary, intradural compartment at the cervical and thoracic spinal levels. They can be dural-based or associated with nerve roots or spinal foramina [216, 701]. Less

frequently, they arise from the leptomeninges in the posterior fossa and supratentorial compartments. Meckel's cave is a site with a peculiar predilection for primary melanocytic neoplasms and tumours of this site are associated with ipsilateral Ota's nevus [91, 1745]. Nodular melanomas are dura-based and occur throughout the neuroaxis, showing a slight predilection for the spinal cord and posterior fossa.

Clinical features

Symptoms and signs

Melanocytosis and melanomatosis are associated with neurocutaneous melanosis, a rare phakomatosis characterized by large or numerous congenital cutaneous nevi together with benign or malignant diffuse leptomeningeal melanosis [1389]. Neurologic symptoms arise secondary to either hydrocephalus or local effects on the CNS parenchyma. Neuropsychiatric symptoms, bowel and bladder dysfunction, and sensory and motor disturbances are common. Once malignant transformation occurs, symptoms progress rapidly, with increasing intracranial pressure resulting in irritability, vomiting, lethargy and seizures. Melanocytomas and malignant melanomas present with symptoms related to compression of the spinal cord, cerebellum or cerebrum by an extra-axial mass, with focal neurological signs depending on the location [1614].

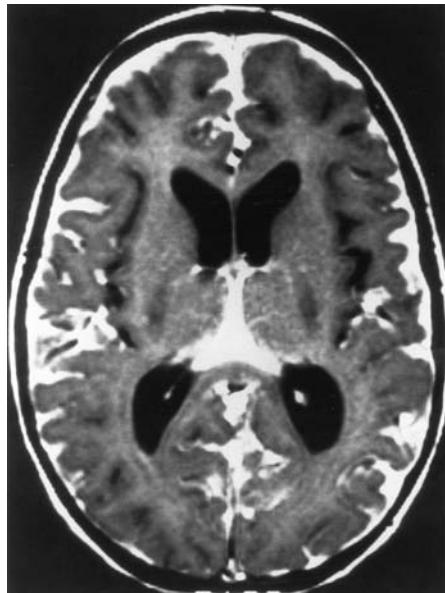


Fig. 10.28 Post-contrast T1-weighted MRI of diffuse melanocytosis, showing contrast enhancement of the infiltrated meninges.

Neuroimaging

CT and MRI of melanocytosis and melanomatosis shows diffuse thickening and enhancement of the leptomeninges, often with focal nodularity. Melanocytomas have characteristic MRI appearance due to the paramagnetic properties of melanin; they are isodense or hyperintense on T1-weighted images and hypointense on T2-weighted images. They also show homogeneous enhancement on post-contrast images [1614]. Primary CNS melanomas show the same general pattern on MRI, depending on the content of melanin. CNS structures adjacent to melanoma are often T2-hyperintense, reflecting vasogenic edema generated in response to rapid tumour growth.



Fig. 10.27 Diffuse melanocytosis involving the subarachnoid space of the cerebral hemisphere and invading the cerebral cortex.

Macroscopy

Diffuse melanocytic lesions appear as a dense black replacement of the subarachnoid space or as dusky clouding of the meninges. Melanocytoma and malignant melanoma are solitary mass lesions, generally extra-axial, that may appear black, red-brown, blue or macroscopically non-pigmented.

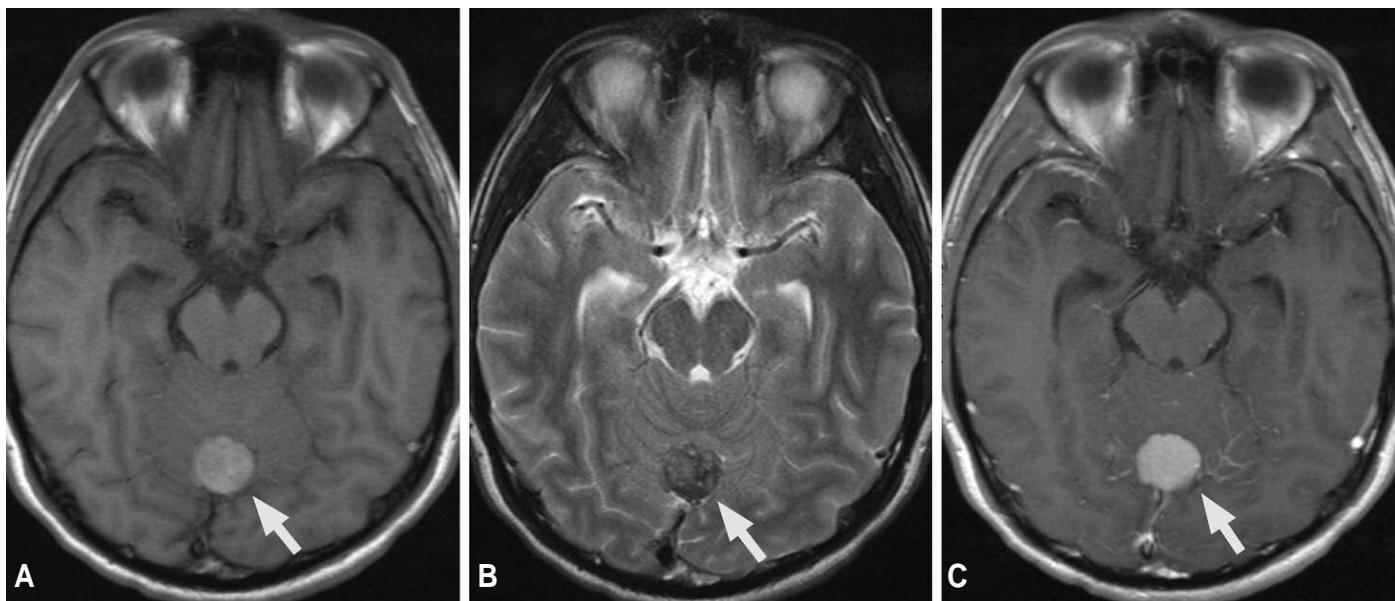


Fig. 10.29 MRI features of melanocytoma. A T1-weighted axial images (pre-contrast) reveal a hyperintense, well-circumscribed mass in the midline of the cerebellum arising from the dura. B On T2-weighted images, the mass is hypointense. C Following the administration of contrast agent, the melanocytoma shows homogeneous enhancement.

Histopathology

Diagnosis hinges on the recognition of tumour cells that have melanocytic differentiation. Most benign and malignant melanocytic lesions display melanin pigment finely distributed within tumour cells and coarsely distributed within the tumour stroma and the cytoplasm of tumoural macrophages (melanophages). Rare melanocytomas and occasional primary melanomas will not demonstrate melanin pigment; diagnosis then relies more heavily on electron microscopy and immunohistochemistry. Identification of melanocytic lesions usually requires histopathological examination, yet the diagnosis of diffuse melanosis and melanomatosis has occasionally been made by CSF cytology {307, 468, 1863}.

Diffuse melanocytosis

The pathologic proliferation of leptomeningeal melanocytes and their production of melanin is the source of melanosis {465, 1022}. Tumour cells diffusely involving the leptomeninges assume a variety of shapes, including spindled, round, oval or cuboidal. In melanocytosis, individual cells are cytologically bland. Melanocytic cells can accumulate within Virchow-Robin spaces without demonstrating overt CNS invasion. In distinction, unequivocal CNS parenchymal invasion should not be seen in melanocytosis, and when identified, must be considered evidence of malignant change to melanomatosis.

Melanocytoma

Melanocytomas are solitary, low-grade tumours that do not invade surrounding

structures {216, 1781, 2280}. Slightly spindled or oval tumour cells containing variable melanin often form tight nests with a superficial resemblance to whorls of meningioma. Heavily pigmented tumour cells and tumoural macrophages are seen at the periphery of nests. Other melanocytoma variants demonstrate storiform, vasocentric and sheetlike arrangements. Only rare amelanotic melanocytomas have been described. Nuclei are oval or bean-shaped with small eosinophilic nucleoli. Cytologic atypia and mitoses are generally absent (on average, less 1/10 HPF). It has been suggested that melanocytic tumours with bland cytologic features, such as those of melanocytoma, but showing CNS invasion or elevated mitotic activity, should be classified as intermediate grade melanocytic neoplasms {216}.

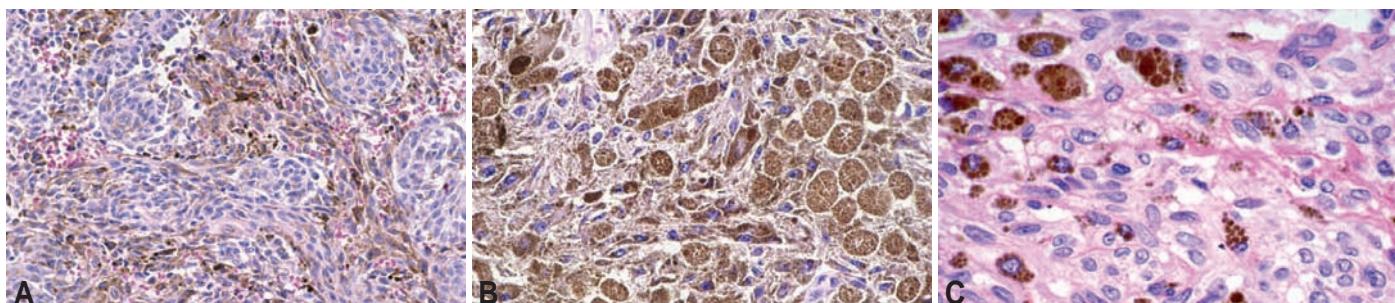


Fig. 10.30 Histological features of melanocytoma. A Loose or tight nests of low-grade, pigmented spindle cells with intervening stroma containing higher levels of melanin pigment. B Melanin containing macrophages (melanophages). C Melanocytoma cells showing clear to eosinophilic cytoplasm with variable fine pigment. Nuclei are bean-shaped and have micronucleoli. Melanin within the cytoplasm of melanophages is typically in larger aggregates.

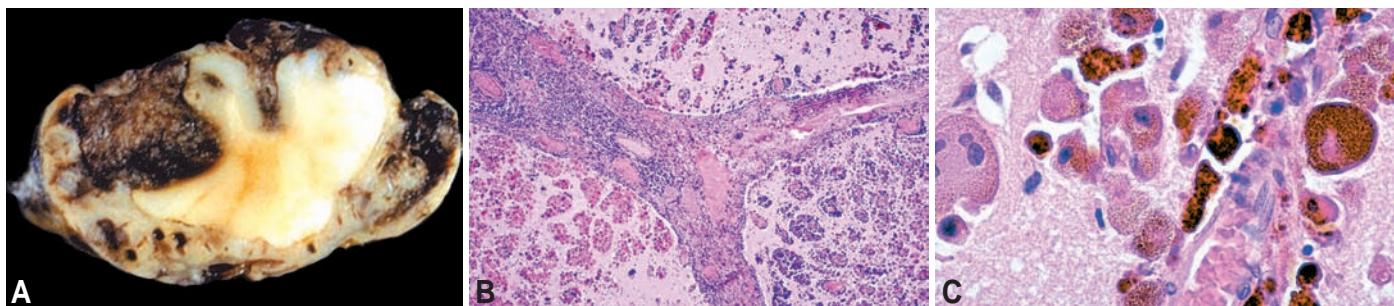


Fig. 10.31 A Primary spinal melanoma originating from the spinal cord and invading the subarachnoid space. B Primary malignant CNS melanoma showing extensive invasion of the cerebral cortex and subarachnoid space. C Highly polymorphic melanin-laden cells of a malignant melanoma invading the cerebral cortex.

Malignant melanoma

Malignant leptomeningeal melanoma is histologically similar to melanomas arising in other sites. Anaplastic spindled or epithelioid cells, arranged in loose nests, fascicles or sheets, display variable cytoplasmic melanin [216, 1863]. Melanomas may contain large cells with bizarre nuclei, numerous typical and atypical mitotic figures, significant pleomorphism, and large, often red nucleoli; others are densely cellular and less pleomorphic, usually consisting of tightly packed spindle cells with high nuclear to cytoplasmic ratios. Melanomas are more pleomorphic, have more anaplastic nuclei and have a higher cell density than melanocytoma, and will often demonstrate unequivocal tissue invasion or coagulative necrosis. Meningeal melanomatosis may arise from diffuse spreading of a primary malignant meningeal melanoma through the subarachnoid space.

Immunohistochemistry

Most tumours react with the anti-melanosomal antibodies HMB-45 or MART-1 (Melan-A), and microphthalmia transcription factor. They also express S-100 protein. Staining for vimentin and neuron-specific enolase are variable.

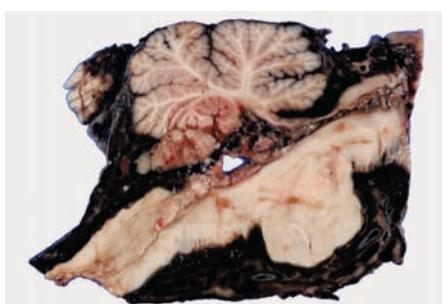


Fig. 10.32 Malignant melanoma infiltrating the meninges around brain stem and cerebellum.

There is no expression of GFAP, neurofilament proteins, cytokeratins and EMA; Ki-67 labelling indices are typically <1–2% in melanocytomas and average around 8% in primary melanomas [216].

Electron microscopy

The cells of melanocytoma lack junctions and contain melanosomes at varying stages of development. In contrast to Schwann cell tumours, a well-formed pericellular basal lamina is lacking, but groups of melanocytoma cells may be ensheathed [30]. In contrast to meningioma, no desmosomes and no interdigitating cytoplasmic processes are encountered.

Differential diagnosis

Melanocytic lesions of the nervous system are to be distinguished from metastatic malignant melanoma and from histogenetically different nervous system tumours undergoing melanization, such as schwannoma, medulloblastoma, paraganglioma and various gliomas [30, 216]. There is little evidence to support the existence of a true melanotic meningioma, although rare melanocytic colonization of meningiomas has been documented [1580]. Melanotic neuroectodermal tumour of infancy (retinal anlage tumour) has also been reported at intracranial locations [1042].

Genetic susceptibility

Neurocutaneous melanosis (neurocutaneous melanocytosis) is a combination of diffuse melanocytosis with giant or numerous congenital melanocytic nevi of the skin, usually involving midline, head and neck, and with various malformative lesions, e.g. Dandy Walker malformation, syringomyelia, lipomas, etc. [449, 468]. A genetic trait has not been unequivocally established. Approximately 25% of

patients with diffuse meningeal melanocytosis have significant concomitant cutaneous lesions. On the other hand, about 10–15% of patients with large congenital melanocytic nevi of the skin clinically present with CNS melanocytosis [449], although radiologic evidence of CNS involvement is noted in up to 23% of asymptomatic children with giant congenital nevi [595]. Diffuse melanocytosis may also be associated with congenital naevus of Ota [91].

Histogenesis

Melanocytic lesions of the nervous system and its coverings are thought to arise from leptomeningeal melanocytes that are derived from the neural crest. In the normal CNS, melanocytes are preferentially localized at the base of the brain, around the ventral medulla oblongata, and along the upper cervical spinal cord.

Prognostic and predictive factors

Diffuse melanosis carries a poor prognosis even in the absence of histologic malignancy [1863]. Melanocytoma lacks anaplastic features, but a few undergo local recurrences; the intermediate grade melanocytic tumours typically invade the CNS, although too few have been reported to predict the biology of these tumours [216]. A rare example of malignant transformation of a melanocytoma has also been reported [1934]. Malignant melanoma is a highly aggressive and radioresistant tumour with poor prognosis and may metastasize to remote organs. Nevertheless, the prognosis of the primary meningeal melanoma appears to be better than metastatic examples, particularly if localized and complete resection is possible [611].

Haemangioblastoma

K.D. Aldape
K.H. Plate
A.O. Vortmeyer
D. Zagzag
H.P.H. Neumann

Definition

A slowly growing, highly vascular tumour of adults, occurring in the cerebellum, brain stem or spinal cord; histologically comprised of stromal cells and small blood vessels; occurring in sporadic forms and in association with von Hippel-Lindau (VHL) syndrome.

ICD-O code 9161/1

Grading

Haemangioblastoma corresponds to WHO grade I.

Synonyms and historical annotation

Haemangioblastoma is also referred to as capillary haemangioblastoma. In 1931, Lindau {1325} hypothesized that these tumours may be derived from a "congenital anlage" and that the histological picture revealed an "...embryological type of the tumour cells". Stein *et al.* {2148} suggested an angio-mesenchymal origin of haemangioblastoma, based on original, developmental biologic observations made by Sabin in 1917 {1967}.

Incidence

Haemangioblastomas are uncommon tumours that occur as sporadic as well as familial forms associated with von Hippel-Lindau disease. Accurate incidence rates are not available.

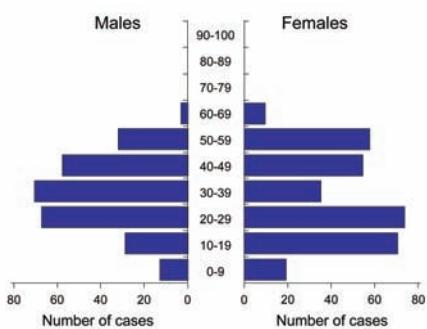


Fig. 10.33 Age and sex distribution of haemangioblastoma, based on 185 patients treated at the Universities of Freiburg (Germany) and Helsinki (Finland).

Age and sex distribution

Haemangioblastomas usually occur in adults. VHL syndrome-associated tumours may present in significantly younger patients than do sporadic tumours {1382}. The male:female ratio is approximately equal.

Localization

Haemangioblastomas may occur in any part of the nervous system. Sporadic tumours occur predominantly in the cerebellum, usually in the hemispheres, whereas VHL-associated haemangioblastomas may be multiple and affect the brain stem, spinal cord and nerve roots in addition to the cerebellum. Supratentorial and peripheral nervous system lesions are rare.

Clinical features

Symptoms generally arise from impaired CSF flow due to a cyst or solid tumour mass, resulting in an increase of intracranial pressure and hydrocephalus. Haemangioblastomas produce erythropoietin, and this may cause secondary polycythaemia.

Imaging studies typically demonstrate a gadolinium-enhancing mass with associated cyst in approximately 75% of cases. The solid component is usually peripheral in location within the cerebellar hemisphere. Flow voids may be seen within the nodule due to enlarged feeding/draining vessels. Angiography is useful to identify small lesions, showing a mass with a dense tangle of vessels, sometimes resembling an arteriovenous malformation. Evidence of calcification on imaging is usually absent. Spinal cord examples are often associated with a syrinx.

Macroscopy

Macroscopically, haemangioblastomas are well-circumscribed, highly vascularized red nodules, often in the wall of large cysts. At places, the tumour may appear yellow owing to its rich lipid content.

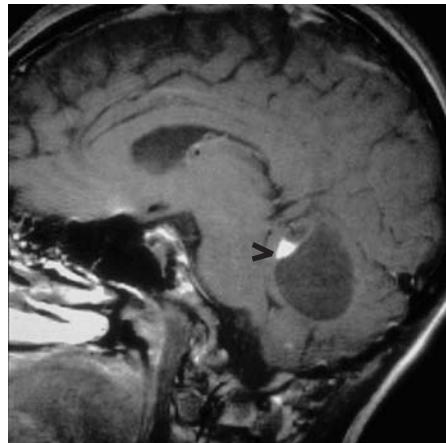


Fig. 10.34 Lateral MRI view of a cerebellar haemangioblastoma showing the hyperdense tumour nodule (arrow) and a large adjacent cyst.

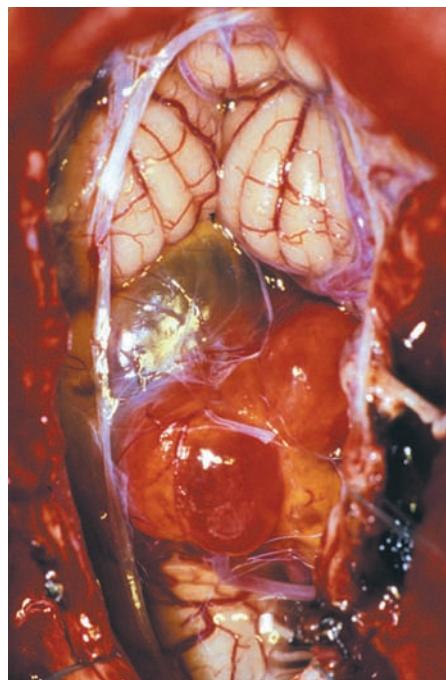
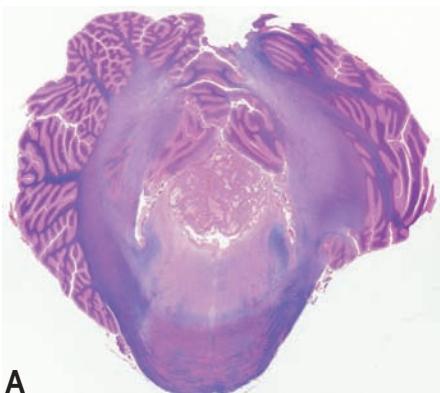


Fig. 10.35 Intraoperative view of a cystic haemangioblastoma in the region of the fourth ventricle and dorsal medulla oblongata.

Histopathology

Haemangioblastomas are characterized histologically by two main components: stromal cells that are characteristically large and vacuolated, but can reveal highly considerable cytologic variation,



A

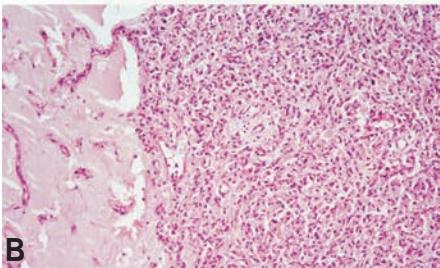


Fig. 10.36 Section of a cerebellar haemangioblastoma extending into the fourth ventricle (A). Higher magnification shows the typical distribution of tumour cells within a network of small capillaries (B). Note the hyalinised vascular stroma (left).

and abundant vascular cells. Cellular and reticular variants are distinguished on the basis of the abundance of the stromal cell component. Numerous thin-walled vessels are apparent and are readily outlined by a reticulin stain. In accordance with the highly vascular nature of haemangioblastoma, intratumoural haemorrhage may occur. Some tumours show extensive sclerosis. In adjacent reactive tissues, particularly in cyst and syrinx walls, astrocytic gliosis and Rosenthal fibers are frequently observed. The tumour edge is generally well-demarcated, and infiltration into surrounding neural tissues rarely occurs. Mitotic figures are rare. The stromal cells represent the neoplastic component of the tumour. Their nuclei may vary in size, with occasional atypical and hyperchromatic nuclei. However, their most characteristic and distinguishing morphological feature is represented by numerous lipid-containing vacuoles, resulting in the typical 'clear cell' morphology of haemangioblastoma, which may resemble metastatic renal cell carcinoma. Adding to the complexity of this differential diagnosis is the fact that patients with VHL syndrome are prone to

renal cell carcinoma. There are also reports of tumour-to-tumour metastasis (renal cell carcinoma metastatic to haemangioblastoma) in this setting [759].

Immunohistochemistry

The stromal and capillary endothelial cells differ significantly in their expression patterns. Stromal cells lack endothelial cell markers, such as von Willebrand factor and CD34, and do not express endothelium-associated adhesion molecules such as CD31 (PECAM) [191, 2422]. Unlike endothelial cells, stromal cells variably express neuron-specific enolase, neural cell adhesion molecule, S-100, CD56 and ezrin [191, 193, 923]. Vimentin is the major intermediate filament expressed by stromal cells. Stromal cells express a variety of molecules, including CXCR4 [1316, 2477], aquaporin 1 [1344], several carbonic anhydrase isoenzymes [1803], as well as EGFR [190], but do not usually express glial fibrillary acidic protein [2422]. Vascular endothelial growth factor (VEGF), a prime regulator of physiological and pathological angiogenesis, is highly expressed in stromal cells [1187], with corresponding endothelial expression of its receptors VEGFR-1 and -2 [2421], and the endothelial cell receptor Tie-1 [791]. The endothelial cells of haemangioblastomas also express receptors for other angiogenic growth factors, including platelet-derived growth factors [190].

Immunohistochemistry is useful to distinguish haemangioblastoma from renal cell carcinoma. Renal cell carcinoma is positive for epithelial markers, such as EMA, while haemangioblastomas are negative. Additional potentially useful markers include the D2-40 antibody [1945] and inhibin A [847], which are positive in haemangioblastoma but generally negative in renal cell carcinoma. CD10 staining, in contrast, shows the opposite results [1018].

Electron microscopy

Ultrastructurally, the most prominent feature of the stromal cells is an abundant electron-lucent cytoplasm containing lipid droplets. Some studies have demonstrated electron-dense bodies, reminiscent of Weibel-Palade bodies, and small granules, reminiscent of neuroendocrine granules.

Proliferation

Proliferation rates tend to be low, in the range of 0–2%, as measured by the MIB-1 antibody [1493].

Genetic susceptibility

While most cases of haemangioblastoma are sporadic, a proportion of cases are associated with VHL syndrome (see Chapter 13).

Genetics

Sequencing of constitutional DNA from

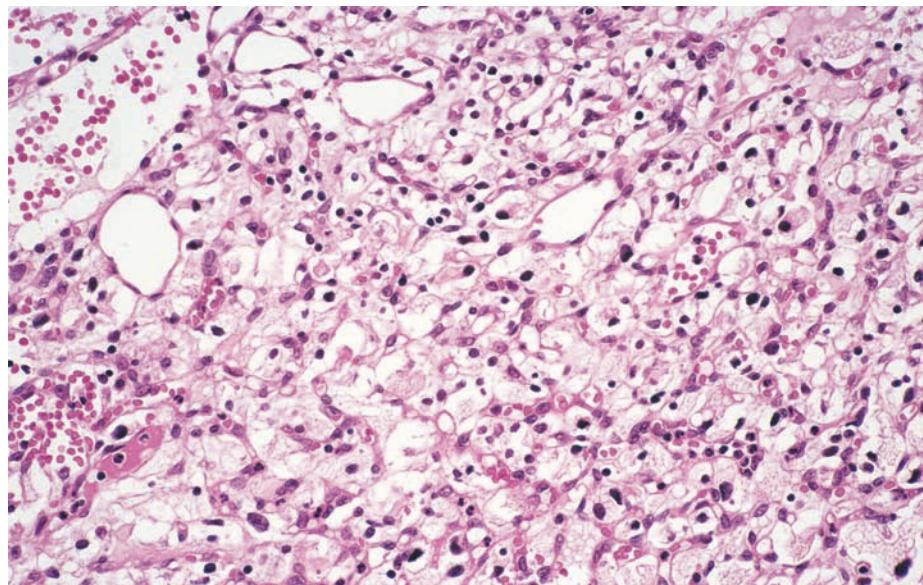


Fig. 10.37 Haemangioblastoma with accumulation of lipid droplets within stromal cells.

patients with haemangioblastoma reveals *VHL* mutations in a proportion of cases, as a recent study identified 5 germline mutations among patients from 16 families {1834}. Among 14 haemangioblastoma patients without evidence of a family history or additional clinical manifestations of VHL syndrome, 2 germline mutations in the *VHL* gene were identified {299}. While biallelic inactivation of the *VHL* gene is a frequent occurrence in familial cases, it is not common in sporadic tumours. Studies on sporadic tumours, including somatic mutation analyses, assessment of allelic loss, and hypermethylation studies have revealed loss or inactivation of the *VHL* gene area only in approximately 20% to 50% of the cases {694, 1277}. One study using comparative genomic hybridization indicated that multiple chromosomal aberrations, including those on 3p and elsewhere, are observed in sporadic tumours {682}. Loss of heterozygosity studies demonstrate allelic imbalance at chromosome 6q in the majority of cases, with a reported minimally deleted region at 6q23-24 {1291}.

Histogenesis

The histogenesis of haemangioblastoma is uncertain. Tissue microdissection,

combined with deletion analysis of the *VHL* gene locus, have identified the stromal and not the vascular cells as neoplastic {1277, 2348}. More controversial, however, has been the identification of the nature of the stromal cell. A series of immunohistochemical studies has been performed to elucidate the origin of the stromal cell resulting in identification of markers that are consistently, frequently or only occasionally immunoreactive with the stromal cells. Neural cell adhesion molecule (NCAM/CD56) is consistently immunoreactive {192, 923}. Positive immunoreactivity for S-100 protein is frequently but not always observed {856, 1245}. Factor XIIIa has been reported to be expressed by haemangioblastoma stromal cells {1245, 1644}, while other studies found it exclusively expressed by the reactive vascular component {397, 2214}. Similarly, factor VIII has been found in the stromal cells by some authors {1020, 1035, 1644}, whereas others report expression to be limited to vascular cells {2214}. GFAP positivity is variable {923, 963} and it is unclear whether GFAP marks entrapped reactive astrocytes, stromal cells with glial differentiation or stromal cells with intracytoplasmic GFAP from phagocytic activity. It is therefore not surprising that

the histogenesis of the stromal cell is controversial. Suggested origins include glial cells {45}, endothelial cells {1020}, arachnoid cells {1501}, embryonic choroid plexus {176}, neuroendocrine cells {123}, fibrohistiocytic cells {1579}, cells of neuroectodermal derivation {12} or heterogeneous cell populations {2214}. It was noted that stromal cells of haemangioblastoma express proteins common to embryonal haemangioblast progenitor cells {696}. It was further noted that one such protein, Scl, has a distribution of expression in the developing nervous system that is similar to the topographical distribution of haemangioblastoma tumours in patients.

Prognostic and predictive factors

The prognosis of CNS haemangioblastoma is excellent if surgical resection can be achieved, which is often possible. Permanent neurological deficits are rare {375} and can be avoided when CNS haemangioblastomas are diagnosed and treated early {695}. Patients with sporadic tumours have an improved outcome compared to patients with VHL syndrome, probably because the latter group tends to develop multiple lesions {1493}.



CHAPTER 11

Tumours of the Haematopoietic System

Malignant lymphomas

Extranodal malignant lymphomas arising in the CNS in the absence of lymphoma outside the nervous system at the time of diagnosis; these tumours need to be differentiated from secondary involvement of the nervous system in systemic lymphomas.

Histiocytic tumours

A heterogeneous group of tumours and tumour-like masses composed of histiocytes that are commonly associated with histologically identical extracranial lesions; Langerhans cell histiocytosis (LCH) shows features of dendritic Langerhans cells whereas most of the various non-LCH show macrophage differentiation.

Malignant lymphomas

M. Deckert
W. Paulus

Definition

Extranodal malignant lymphomas arising in the CNS in the absence of lymphoma outside the nervous system at the time of diagnosis; these tumours need to be differentiated from secondary involvement of the nervous system in systemic lymphomas.

ICD-O code

9590/3

Synonyms and historical annotation

Primary CNS lymphomas (PCNSL) were first described by Bailey in 1929 as "perithelial sarcoma". Until their lymphoid lineage and correct designation as lymphoma were generally accepted, at least 12 synonyms have been used, including adventitial sarcoma, reticulum cell sarcoma and microglioma.

Incidence

The incidence of PCNSL has markedly increased world-wide: from 0.8–1.5% up to 6.6% of primary intracranial neoplasms {1476}, mainly as the consequence of the AIDS epidemic. In immunocompetent patients, the incidence has increased in some but not all series and populations {384}. Prior to the introduction of highly effective antiviral therapy (HAART), the incidence in AIDS patients (4.7 per 1000 person-years) was about 3600-fold higher than in the general population {387}, with 2–12% of AIDS patients developing primary CNS lymphomas,

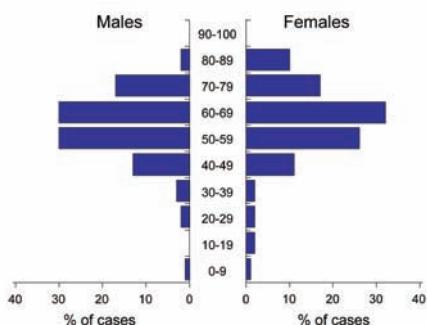


Fig. 11.01 Age and sex distribution of primary CNS lymphomas in immunocompetent patients.

mainly during late-stage AIDS {280}. HAART has reduced the occurrence of all non-Hodgkin's lymphomas with an incidence rate of 0.4 for primary and secondary brain lymphomas in AIDS patients {1968}. CNS involvement occurs in 22% of post-transplant lymphomas, about 55% being confined to the CNS {1711}.

Age and sex distribution

PCNSL affect all ages, with a peak incidence in immunocompetent subjects during the sixth and seventh decade of life, and a male: female ratio of 3:2. In immunocompromised patients, the age at manifestation is lowest in individuals who have an inherited immunodeficiency (10 years), followed by transplant recipients (37 years) and AIDS patients (39 years, 90% males).

Etiology

Inherited or acquired immunodeficiency predisposes to development of PCNSL. This includes immunodeficiency produced by Wiskott-Aldrich syndrome, AIDS and immunosuppressive therapy following organ transplantation and, to a lesser degree, therapy for Hodgkin disease and autoimmune disorders such as rheumatoid arthritis and Sjögren syndrome.

The Epstein-Barr virus (EBV) plays a major role in immunocompromised patients with PCNSL. The EBV genome is present in tumour cells in more than 95% of immunocompromised patients, but in 0–20% of immunocompetent patients. Lymphoma cells latently infected with EBV variably express EBNA 1–6, LMP1, the major EBV oncprotein {2493}, 2a, 2b, and EBER1 and EBER2. Expression of these proteins has a wide variety of effects, including activation of the NF- κ B pathway.

Data on viruses other than EBV are scarce. DNA sequences corresponding to the JCV early genome and the late agnoprotein were present in 22 samples and the JCV late genome encoding the viral capsid proteins in 8 samples of 27 PCNSL investigated {459}. The partial

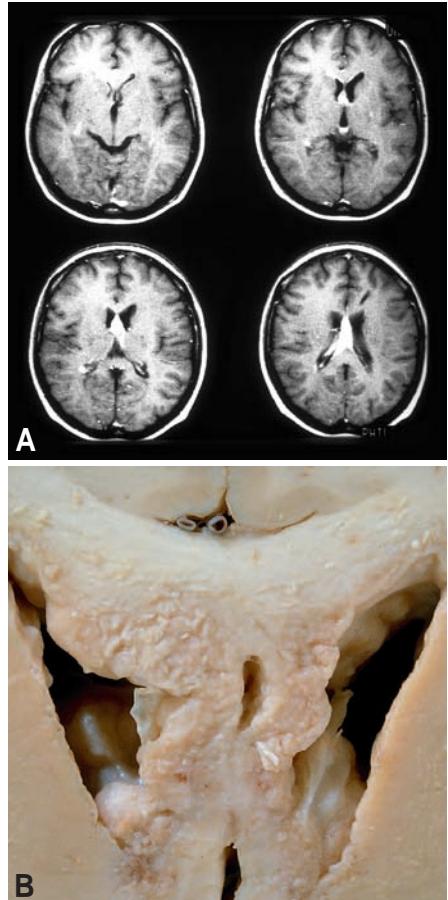


Fig. 11.02 A Malignant lymphoma. T1-weighted MRI and (B) macroscopic appearance of malignant lymphoma with diffuse infiltration of the ventricular walls.

co-expression of JCV T antigen with EBV LMP1 suggested JCV to be a cofactor or to provide one of several additional "hits" required for transformation in some PCNSL {459}. The involvement of various other viruses in the pathogenesis of PCNSL has been largely ruled out, including HHV-6 {1700}, HHV-8 {1515}, polyomaviruses SV40 and BKV {1514, 1538}.

Localization

About 60% of PCNSL involve the supratentorial space, including the frontal (15%), temporal (8%), parietal (7%) and occipital (3%) lobes, basal ganglia/periventricular regions (10%) and corpus

callosum (5%); posterior fossa (13%), and spinal cord (1%) are less commonly involved. Approximately 25–50% are multiple (60–85% in AIDS and post-transplant subjects). Secondary meningeal spread is seen in 30–40% of PCNSL, while primary leptomeningeal lymphoma may account for up to 8% of these tumours [729]. Primary dural and epidural malignant lymphomas are very rare [1485]. Ocular disease (which may antedate intracranial lesions) is present in 15–20% of cases, and distant metastases in 6–10% [232].

Since occult lymphoma has been reported in up to 8% of patients presenting with brain lymphoma, complete systemic staging is recommended [6]. Secondary CNS lymphomas occur preferentially in the dura and leptomeninges, but parenchymal lesions may also occur. Rare instances of lymphoma restricted to peripheral nerve may be designated as neurolymphomatosis.

Clinical features

Symptoms and signs

Around 50–80% of PCNSL patients present with focal neurological deficits, 20–30% with neuropsychiatric symptoms, 10–30% with signs of increased intracranial pressure, and 5–20% with seizures. Eye symptoms resulting from uveitis or vitrous lymphoma are seen in 5–20% of cases. For PCNSL, the interval between initial symptoms and diagnosis ranges from days to two years, with an average of two months. Angiotropic lymphoma often manifests as rapidly progressing dementia with multifocal neurological deficits [320, 1335]. About 50% of transplantation-associated primary CNS lymphomas appear within a year after transplantation (mean, 32 months) [1711].

Neuroimaging

MRI is the most sensitive radiologic procedure to detect PCNSL, which is isointense to hyperintense on T2, fluid inversion recovery or diffusion weighted images MRI images, densely enhancing on post-contrast images [112, 1227, 1709]. Bilateral symmetrical subependymal high-signal foci are suggestive of PCNSL. Peritumoural edema is less severe than in malignant gliomas and metastases. FDG-PET scan [852] or Thallium-201-SPECT [57] are helpful in the differential diagnosis of ring-enhancing mass lesions that are frequently seen in AIDS-related

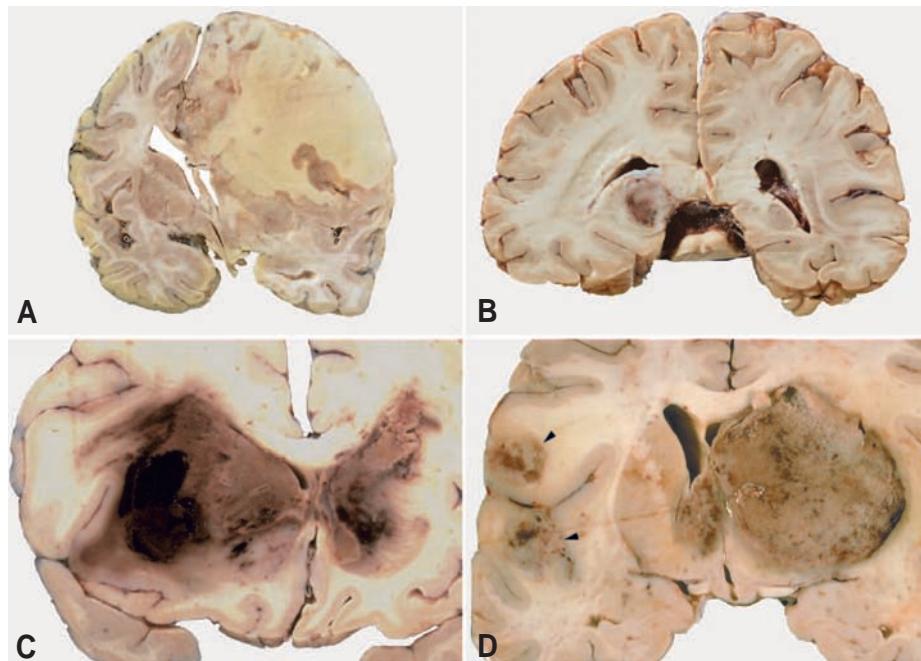


Fig. 11.03 Macroscopic features of primary malignant CNS lymphomas. A Large, necrotizing B-cell lymphoma in a HIV-1-infected seven month old infant. B B-cell lymphoma involving the medial temporo-occipital lobe. C,D Primary malignant CNS lymphomas of the basal ganglia with extension into the contralateral hemisphere. D Note the additional foci in the left insular region (arrows).

PCNSL, which are difficult to distinguish from toxoplasmosis and other non-neoplastic conditions by CT or MRI. Meningeal infiltration may present as hyperdense corticomeningeal structures, but CT and MRI can fail to detect meningeal or eye lesions. Steroid-treated lesions may disappear within hours. FDG-PET seems to be suitable for early therapeutic monitoring after chemotherapy [1673].

CSF cytology

Pleocytosis is found in 35–60% of PCNSL patients, but despite the presence of tumour cells in the CSF, cell counts may be normal. Cytology is of diagnostic value in 5–30% of PCNSL and in 70–95% of metastatic malignant lymphomas, particularly if immunocytochemistry is used to determine monoclonality [581]. The combination of flow cytometry and morphologic examination may enhance the detection of lymphoma cells in the CSF [583]. PCR analysis to identify monoclonal immunoglobulin (IG) heavy chain rearrangement may identify a clonal population in the CSF [700], but may require repeat puncture [511]. The predictive value of PCR assays for EBV DNA in CSF in AIDS patients is controversial [353, 933].

Stereotactic biopsy

Surgery is restricted to stereotactic biopsy to establish the histological diagnosis of PCNSL; partial resection is even associated with worse survival [128]. Unless herniation is imminent, corticosteroids should be withheld before biopsy as steroid application may result in non-diagnostic biopsies without detectable tumour cells. The typically dramatic response of primary CNS lymphomas to corticosteroids is usually temporary, but can occasionally be long-term [1753].

Macroscopy

PCNSL occur as single or multiple masses in the cerebral hemispheres.

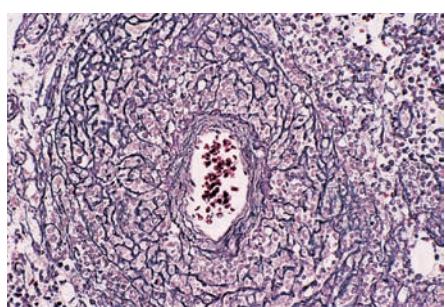


Fig. 11.04 Perivascular accumulation of lymphoma cells embedded in a concentric network of reticulin fibers.

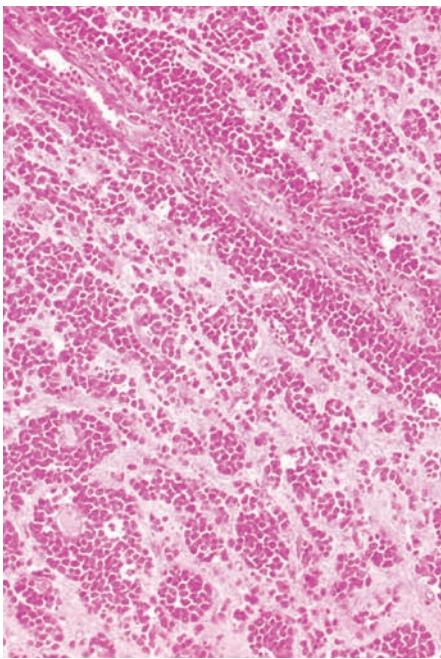


Fig. 11.05 Primary malignant CNS lymphoma, with characteristic perivascular spread of tumour cells.

While they are often deep-seated and adjacent to the ventricular system, superficial tumours may also be encountered. The tumours can be firm, friable, granular, centrally necrotic, focally haemorrhagic, grey-tan, yellow or virtually indistinguishable from the adjacent neuropil. Demarcation from surrounding parenchyma is variable. Some tumours appear well-delineated, like a metastasis. When diffuse borders and architectural effacement are present, the lesions resemble gliomas. Diffusely infiltrating forms without evidence of a cohesive mass lesion have been referred to as "lymphomatosis cerebri" [1912]. AIDS patients tend to have more necrotic areas, which may simulate necrotizing cerebral toxoplasmosis. PSNSL and toxoplasmosis may manifest concomitantly in AIDS patients [2152]. Meningeal lymphoma mimics meningioma or meningitis, or appears macroscopically normal.

Classification systems and their relevance to primary CNS lymphomas

According to the Revised European-American Lymphoma (REAL) classification and the WHO classification [955], the vast majority of CNS lymphomas is classified as diffuse large B cell lymphoma (DLBCL); however, PCNSL are not specifically included.

Histopathology

Low-power microscopy of PCNSL at the periphery often demonstrates the typical angiocentric infiltration pattern where tumour cells form collars within concentric perivascul ar reticulin deposits. From these perivascul ar cuffs, tumour cells invade neural parenchyma, either with compact cellular aggregates and a well-delineated invasion front, or with single diffusely infiltrating tumour cells resembling encephalitis. Virtually all PCNSL show a diffuse growth pattern. Large geographic necroses are common, with perivascul ar islands of viable tumour cells surrounded by large regions of coagulative necrosis. A focally prominent astrocytic and microglial response, large CD68-positive macrophages, and reactive lymphocytic infiltrates with a predominance of small CD4- as well as CD8-positive T-cells are common.

B-cell lymphoma

B-cell non-Hodgkin lymphomas constitute 92–98% of primary CNS lymphomas. Accordingly, they show immunohistochemical expression of pan-B markers such as CD19, CD20 and CD79a.

Diffuse large B-cell lymphoma

More than 95% of primary CNS B-cell lymphomas are DLBCL. They consist of blastic cells with large pleomorphic nuclei and distinct nucleoli (corresponding to centroblasts or immunoblasts). All morphological variants of DLBCL, i.e. centroblastic, immunoblastic, T-cell/histiocyte-rich and anaplastic, may occur in the CNS. In addition to pan-B markers, the majority of PCNSL express BCL-6, albeit not in all tumour cells [279, 391, 2043]. In 90–100%, tumour cells are MUM-1+. In the majority of tumours, cells express the BCL-2 protein, which is not indicative of a t(14;18) [279, 361, 391, 447].

Low-grade B-cell lymphoma

Low-grade B-cell lymphomas of the CNS correspond to their systemic counterparts [955]. A retrospective multi-centre series compiled 32 low-grade B-cell lymphomas, the most common type being lymphoplasmacytic lymphoma [959]. While age distribution and perivascul ar infiltration were similar to the much more frequent DLBCL, low-grade lymphomas differed from DLBCL with respect to better long-term outcome and the common occurrence of atypical neuroimaging features, such as hyperintensity on T2-weighted images,

lack of periventricular localization, absent or inhomogeneous contrast enhancement [959].

Marginal zone B-cell lymphoma

Intracranial low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type or marginal zone B-cell lymphoma (MZBCL), probably representing the most common primary low-grade intracranial lymphoma, usually presents as a dural-based mass mimicking meningioma [2277]. Intracerebral or intraventricular locations are exceptional [1073]. MZBCL is composed of small lymphocytes with clear cytoplasm, an irregular, centrally located nucleus and variable degrees of plasmacytic differentiation. Lymphoid follicles and massive deposition of amyloid may occur. Tumour cells express CD19, CD20 and CD79a but not CD3, CD10 or CD23 and only occasionally CD5. Trisomy 3 is most commonly detected. Female predilection (4:1) and long-term survival following therapy are typical [2277].

Plasmacytoma

In its purely extraosseous form, intracranial plasmacytoma most often appears as a nodular or plaque-like dural mass, with variable infiltration of the underlying brain. Although rare, exclusively intraparenchymal tumours have also been described. Furthermore, secondary cerebral involvement may be an unusual complication in multiple myeloma [1693].

Intravascular B-cell lymphoma

This lesion is also termed angiotropic lymphoma and affects multiple organ systems. The CNS, including the entire neuraxis, is involved in more than 30% of cases. Accumulations of large B-cells, exceptionally T-cells, NK cells or histiocytic cells, within small and medium vessels lead to vascular occlusion and disseminated small infarcts [1777]. Cerebral mass lesions may develop on the basis of intravascular B-cell lymphoma [912].

Other types of B-cell lymphoma

Single cases of a variety of other primary CNS B-cell lymphomas have been reported, such as follicular lymphoma [140], Burkitt lymphoma [1511], lymphomatoid granulomatosis [1684], precursor B-cell lymphoblastic lymphoma [4] and post-transplant lymphoproliferative disorders [296].

T-cell lymphoma

T-cell lymphomas constitute about 2–5% (Western countries), 8–14% (Japan) and 17% (Korea) of all PCNSL {341}. They are peripheral T-cell lymphomas, and have been seen mainly in the immunocompetent, although single cases in AIDS patients are on record {74}. They occur as solitary or multiple intraparenchymal masses with a higher male: female ratio. The largest study on 45 patients revealed that age distribution, localization and outcome corresponded to those of primary CNS B-cell lymphomas {2076}, while other reviews have noticed a more frequent posterior fossa localization, particularly in the cerebellum, a propensity to arise in the leptomeninges, younger age and an either better or worse prognosis {341}. Molecular genetic demonstration of T-cell monoclonality can be important for excluding T-cell rich B-cell lymphoma and inflammation {1336}.

Anaplastic large-cell lymphoma (ALCL)

ALCL is defined by its composition of large, pleomorphic, CD30 (Ki-1)-positive lymphocytes. In an analysis of 9 primary CNS cases, seven tumours involved the dura or leptomeninges, 7 were T cell, two were null cell, and 5 showed immunohistochemical expression of the ALK-1 antigen (anaplastic lymphoma kinase), which is highly sensitive and specific for ALK translocations, most commonly the (2;5) translocation {659}. Like in systemic ALCL, age less than 18 years and ALK-1 positivity were associated with a better prognosis {659}. Most patients are immunocompetent, while one AIDS patient has been described {1944}.

NK/T-cell lymphoma

Extranodal natural killer (NK)/T-cell lymphomas most commonly involve the nasal cavity. Less than 3% of cases invade or metastasize to the CNS {1360}. A single case of primary cerebral NK / T-cell lymphoma is on record {1029}. The typical immunophenotype is CD2+, CD56+, surface CD3-, CD3ε+ and EBV+.

Hodgkin disease

The diagnosis of Hodgkin disease rests upon the identification of Hodgkin and Reed-Sternberg cells in the appropriate background of non-neoplastic haemopoietic cells (lymphocytes, plasma cells, histiocytes, eosinophils), where tumour

cells are ringed by T-lymphocytes in a rosette-like manner {955}. The entity is rare in the CNS, and is most often seen in the setting of grade III or IV systemic disease, but primary CNS presentation has also been described {446}. Lesions are typically dural-based, but firm and well-demarcated intraparenchymal tumours do occur {819, 1125}.

Proliferation and apoptosis

Proliferative activity in primary CNS lymphoma of the DLBCL type is generally high with Ki-67/MIB-1 labelling indices of 50–70% or even >90% {21, 361, 447}. A variable number of apoptotic cells was detected in the majority (77%) of tumours and may be markedly increased upon corticosteroid treatment {447}.

Genetic susceptibility

With the exception of inherited immunodeficiency, no genetic predisposition to primary CNS lymphoma has been described to date. A previous or concomitant malignant neoplasm is present in about 8% of immunocompetent primary CNS lymphoma patients, most commonly leukaemia or adenocarcinoma {1860}. Associations of primary CNS lymphoma in individual patients with other brain tumours such as meningioma and glioma {575} or with hereditary

tumour syndromes such as neurofibromatosis type 1 {2489} are likely to be coincidental.

Genetics

Classical cytogenetics performed on single cases of primary CNS lymphoma revealed clonal abnormalities of chromosomes 1, 6, 7 and 14, as well as translocations (1;14), (6;14), (13;18) and (14;21) {931}. In contrast to systemic lymphomas, the molecular pathogenesis of primary CNS lymphomas is less well defined. The presence of somatically mutated *IG* genes with evidence for ongoing mutation and the expression of the *BCL6* gene suggested that PCNSL is derived from germinal centre B cells {1516, 2043, 2243}. Further maturation steps of the tumour cells appear to be inhibited as they express IgM without evidence for immunoglobulin class switch due to internal switch micro region deletions {1517}. Recurrent translocations of the *IG* and the *BCL6* gene loci were found in approximately one third of PCNSL {1519, 2043}. For the *BCL6* gene, *IGH*, *IGL*, histone 1*H4I*, *GAPD*, *HSPCA* (*HSP90A*), and *LPP* have been identified as translocation partners with subsequent promoter substitution and a block of normal down-regulation of the *BCL6* gene {1513, 1741, 2043}. *TP53* mutations are rare {361}. FISH revealed gains of the

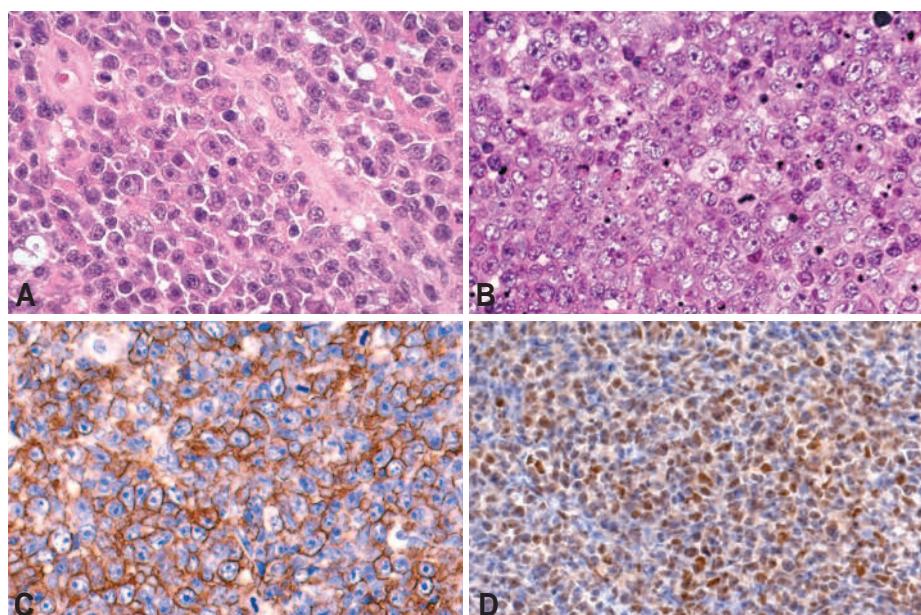


Fig. 11.06 Histological features of primary malignant lymphomas. A Malignant, diffuse large B-cell lymphoma. B Highly anaplastic malignant lymphoma with numerous mitotic figures and extensive apoptosis. C Tumour cells express the pan-B-cell marker CD20. D Expression of the *BCL6* protein by the tumour cells.

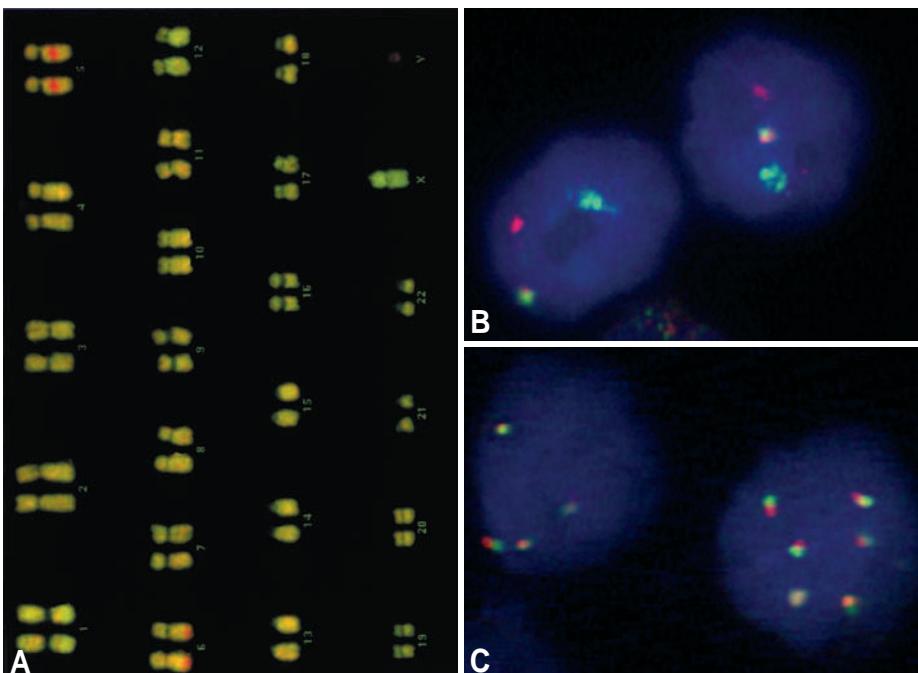


Fig. 11.07 A The fluorescence image of comparative genomic hybridization (CGH), showing chromosomal gains on 1q, 12q, 22q and losses on 5q and 6q. Interphase FISH analyses using differentially labeled probes flanking the IGH (B) and MALT (C) loci, respectively, demonstrating a breakpoint in the IGH locus (B) and multiple co-localized red and green signals indicating amplification of the MALT locus.

MALT1 and *BCL2* in 18q21 as the most common genetic alteration [1519], which may cause NF- κ -B activation. Genes of the NF- κ -B pathway are expressed [391] and may contribute to the sustained high proliferative activity and the inhibition of apoptosis of the tumour cells. FISH and CGH studies detected gains more frequently than losses of genetic material. Frequently, losses affected 6q21-22 and 6p21, while gains involved 18q, 1q, 9p, 11q, 12p, 12q, 16p, 17q20q and 22q [198, 768, 1519, 1873, 2380]. Loss of chromosome 6q was correlated with shorter survival [1560, 1873]. A candidate gene in 6q22-23 may be *PTPRK* [1560]. The oncogenes *MYC*, *PAX5*, *PIM-1*, and *RhoH/TTF* are also targeted by aberrant hypermutation in PCNSL [1518]. Aberrant methylation of *DAPK* (84%), *TSP1* (68%), *CRBP1* (67%), *p16^{INK4a}* (64%), *p14^{ARF}* (59%), *MGMT* (52%), *RARBeta2* (50%), *TIMP3* (44%), *TIMP2* (42%), *p15^{INK4b}* (40%), *p73* (28%), *hMLH1* (12%), *RB1* (8%) and *GSTP1* (8%), *HRK* (31%) was observed [348, 361, 708, 1559, 2494]. Reduced folate carrier gene expression by promoter methylation may be of prognostic and therapeutic relevance [569]. Functional polymorphisms of genes regulating the methionine metabolism may either be

protective or confer a high risk for therapy-associated white matter changes [1329, 1330]. A cDNA microarray analysis found PCNSL to be distributed among the spectrum of activated B cell-like and germinal centre type DLBCL [1946]. A gene cluster was differentially expressed between CNS and nodal DLBCL including genes involved in apoptosis and proliferation pathways [1946].

Histogenesis

It is not known whether primary CNS lymphomas arise within or outside the brain. Three hypotheses have been put forward. B-cells may be transformed at a site elsewhere in the body and then develop adhesion molecules specific for cerebral endothelia. However, no adhesion molecules, chemokines or their receptors that would distinguish PCNSL from systemic DLBCL have been identified [958, 1699, 2112].

Lymphoma cells may be systematically eradicated by an intact immune system but may escape the immune system within the CNS. Astrocyte-derived B cell-activating factor of the tumour necrosis factor family (BAFF) may support survival of the malignant BAFF-receptor expressing B cells [1209].

A polyclonal intracerebral inflammatory lesion may expand clonally within the brain and progress to the monoclonal neoplastic state. Evidence in support of this idea includes the demonstration in a few patients of transient symptomatic contrast-enhancing brain lesions ('sentinel lesions'), which regress spontaneously or with corticosteroid treatment and ultimately lead to primary CNS lymphoma within one year; histological features are non-specific and include inflammatory T-cell infiltrates, demyelination and gliosis [38]. Possibly, intracerebral antigens or superantigens may stimulate persistence and intracerebral expansion of B-cells. On the other hand, infectious or inflammatory CNS diseases have only exceptionally been described to antedate the development of primary CNS lymphoma [62].

Prognostic and predictive factors

Radiotherapy alone is insufficient to provide durable remission or cure. Patients developed long-term treatment-related neurotoxicity with combined systemic and intraventricular chemotherapy and whole brain irradiation [7] with severe leukencephalopathy and cortical/subcortical atrophy being more frequent in elderly patients (>60 years) [7]. In the largest polychemotherapy trial including methotrexate as the most efficient cytostatic drug, the Bonn protocol achieved a median overall survival of 50 months, with the best treatment results in patients younger than 61 years (5-year survival: 75%) [1710]. The inclusion of autologous stem cell transplantation may be an option for recurrent tumour in patients less than 60 years and salvage therapy in relapsing or refractory tumour [9, 910, 2126]. The dismal prognosis of HIV-infected patients with primary CNS lymphoma before the era of HAART has improved upon radiotherapy and HAART (median survival: 36 months) [853].

Histiocytic tumours

W. Paulus
A. Perry

Definition

A heterogeneous group of tumours and tumour-like masses composed of histiocytes that are commonly associated with histologically identical extracranial lesions; Langerhans cell histiocytosis (LCH) shows features of dendritic Langerhans cells whereas most of the various non-LCH show macrophage differentiation.

Synonyms and historical annotation

In 1997, the WHO Committee on Histiocytic/Reticulum Cell Proliferations and the Reclassification Working Group of the Histiocyte Society proposed classifying histiocytic disorders as: (1) dendritic cell-related disorders of varied biological behaviour, such as LCH and juvenile xanthogranuloma; (2) macrophage-related disorders of varied biological behaviour, such as haemophagocytic lymphohistiocytosis and Rosai-Dorfman disease; and (3) malignant histiocytic disorders, such as monocytic leukaemia and histiocytic sarcoma [555]. A minor revision of this classification has more recently been proposed, with group (1) now termed dendritic cell-related disorders, of which LCH is by far the most common.

LCH was previously referred to as histiocytosis X, a term embracing eosinophilic granuloma, Hand-Schüller-Christian disease, Abt-Letterer-Siwe disease and Hashimoto-Pritzker disease, 'X' being the unknown etiological factor [1319]. Because there is much overlap between these subgroups, LCH is currently classified on the basis of extent as unifocal, multifocal (usually polyostotic) and disseminated disease. Historical descriptions of cerebral LCH with principal involvement of the hypothalamus and posterior pituitary were made under terms such as hypothalamic granuloma, Gagel's granuloma and Ayala disease [1078].

A wide variety of neoplastic and non-neoplastic intracranial masses containing high numbers of macrophages or other foamy ('xanthomatous') cells have previously been referred to as 'xanthogranuloma'

or 'xanthoma', including LCH, dural or osseous masses in hyperlipoproteinaemia and Weber-Christian panniculitis, pleomorphic xanthoastrocytoma ('fibroxanthoma') and inflammatory malignant fibrous histiocytoma ('malignant xanthogranuloma'). Benign and malignant fibrous histiocytomas are mesenchymal tumours and no longer regarded as true histiocytic lesions.

Incidence

In children under 15 years of age, the incidence of LCH is estimated at 0.5 per 100 000 children per year, while non-LCH is even rarer with an incidence of about 1:1 000 000 per year [147].

LCH typically occurs in children (mean, 12 years), without sex preference. The most common form of LCH (about two third of cases) is a solitary osteolytic lesion of the skull or spine (eosinophilic granuloma). Multifocal LCH lesions of the bone with hypothalamic involvement have been referred to as Hand-Schüller-Christian disease, while Abt-Letterer-Siwe disease involves skin, lymph nodes, viscera and rarely the CNS. Extension from osseous foci to hypothalamus and pituitary gland in multifocal or disseminated LCH is responsible for most cases with CNS involvement, but unifocal or multifocal infiltrates may occur primarily within or even restricted to the hypothalamus, infundibulum, optic chiasm, choroid plexus and cerebral hemispheres [1902].

Etiology

The etiology of the histiocytic lesions is largely unknown. In most patients with histiocytoses, there is either a mild or no underlying defect in immunologic integrity and the clinical course is benign. Nevertheless, an abnormal immune response is felt to play a potentially important aetiological role. For example, data suggest defective interactions between T-cells and macrophages in LCH, Erdheim-Chester disease and haemophagocytic lymphohistiocytosis [399, 921, 1253]. In haemophagocytic lymphohistiocytosis, natural killer cell activity is

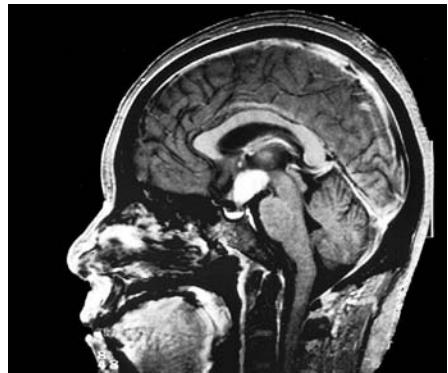


Fig. 11.08 Gadolinium-enhanced MRI of a Langerhans cell histiocytosis in the hypothalamic region (Hand-Schüller-Christian disease).

also diminished [913]. Whether such immune deficits are triggered by genetic predisposition or infectious agents remains unclear in most, although there has been limited support for the latter to date, with one exception: the two major forms of haemophagocytic lymphohistiocytosis include familial and infection-associated, the latter most commonly associated with viruses, especially EBV [1542]. The pathogenesis of the LCH-associated neuro-degenerative disorder is also poorly understood [725, 1492].

Langerhans cell histiocytosis (LCH)

Clinical features

The most common neurological signs of LCH are diabetes insipidus (25% of children with multifocal or disseminated disease) with or without associated signs of hypothalamic dysfunction (obesity, hypogonadism, growth retardation), signs of raised intracranial pressure, cranial nerve palsies, seizures, visual disturbances (visual field defect, optic atrophy), ataxia and rare progressive tetra- and paraparesis [126]. MRI changes of cranial and intracranial structures include: 1) lesions of the craniocervical bone and skull base (56%) with or without soft-tissue extension; 2) intracranial, extra-axial changes of the hypothalamic-pituitary region (50%), meninges (29%) or choroid plexus (6%); 3) intracranial, intra-axial changes of white matter and gray matter (36%); and 4) cerebral atrophy (8%) [1785].

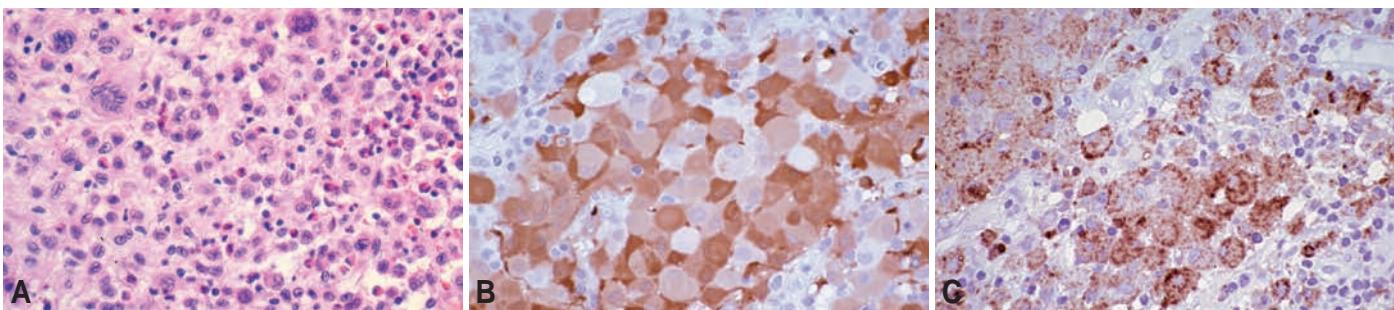


Fig. 11.09 Langerhans cell histiocytosis. A Mixed infiltrate composed of histiocytes, lymphocytes, eosinophils and multinucleated cells. B Immunolabelling with S-100 protein. C Expression of the macrophage marker CD 68.

Macroscopy

Intracranial LCH lesions are often yellow or white and vary from discrete dural-based nodules to granular parenchymal infiltrates. CNS lesions may be well-delineated or ill-defined.

Histopathology

Infiltrates are composed of Langerhans cells, macrophages, lymphocytes, plasma cells and a variable fraction of eosinophils. The nuclei of Langerhans cells are typically slightly eccentric, ovoid, reniform or convoluted with linear grooves and inconspicuous nucleoli. The cytoplasm is large (15–25 µm in diameter) and pale to eosinophilic. Touton giant cells may occur. Abundant deposition of collagen is often seen. LCH occasionally presents with demyelination and no or sparse infiltration of Langerhans cells [724, 1764]. Eosinophils may form into aggregates and undergo necrosis to produce granulomas or abscesses.

Immunohistochemically, Langerhans cells consistently express S-100 protein, vimentin and certain histiocyte markers including CD1a, Langerin (CD207), HLA-DR, β2-microglobulin and variably CD68, rarely L1 antigen (clone MAC387) and almost never CD45, CD15 and lysozyme [1423]. CD1a expression, being very characteristic but not absolutely specific to LCH, can be demonstrated even on small and routinely processed materials [555, 1423]. The ultrastructural hallmark of Langerhans cells are Birbeck granules (Langerhans cell granules), which are 34-nm wide rod-shaped or tennis-racket-shaped intracytoplasmic pentalaminar structures with cross-striation and a zipper-like central core, possibly originating from the cell membrane and/or Golgi apparatus [530]. Either expression of CD1a or presence of Birbeck granules

are currently required for definite diagnosis of LCH.

Neurodegenerative lesions lacking infiltration of CD1a+ cells may also occur. These mainly affect the cerebellum and brain stem, exhibit a profound inflammatory process dominated by CD8-reactive lymphocytes, and are associated with axonal destruction, secondary demyelination, microglial activation and gliosis, resembling paraneoplastic encephalitis [725].

Proliferation

Immunohistochemical Ki-67/MIB-1 proliferation indices of neoplastic Langerhans cells range from 4% to 16% [752].

Prognosis and predictive factors

The overall survival rates of all LCH patients at 5, 15, and 20 years are 88%, 88%, and 77%, respectively, with an event-free survival rate of only 30% at 15 years [2412]. While unifocal LCH may spontaneously recover or requires minimal treatment, e.g. surgical resection, multi-systemic disease with organ dysfunction may resist systemic chemotherapy. The mortality rate in this latter subgroup of LCH reaches 20%. Of all patients with LCH, late sequelae are seen in 64%, including skeletal defects in 42%, diabetes insipidus in 25%, growth failure in 20%, hearing loss in 16%, and other CNS dysfunction in 14% [2412]. Concerning histopathologic features of LCH, no prognostic significance of cytologic atypia and mitotic activity was found in most studies [555, 1892], but it has been suggested that a distinct clinical entity of malignant LCH, characterized morphologically by malignant-appearing Langerhans cells and clinically by male predominance, atypical organ involvement, and an aggressive clinical course, does exist [132].

Non-Langerhans cell histiocytoses

This group of diseases differs from LCH by the absence of features of dendritic Langerhans cells. Most but not all exhibit macrophage differentiation.

Rosai-Dorfman disease

Rosai-Dorfman disease of lymph nodes is most common in children and young adults, but intracranial disease is usually seen in adults. Intracranially, it typically shows dural-based solitary or multiple masses; parenchymal or intrasellar lesions and intracranial extension from an orbital mass or from nasal and paranasal cavities may also occur. Clinically, the disease most often presents as an intracranial space-occupying mass. The ‘classical’ signs of cervical lymphadenopathy, fever and weight loss (sinus histiocytosis with massive lymphadenopathy) are absent in 70% of these patients, and 52% have no associated systemic disease [1808]. The radiological appearance of intracranial Rosai-Dorfman disease usually mimics meningioma and carries a favourable prognosis after complete resection or after corticosteroid treatment [1439]. Histopathology shows sheets or nodules of histiocytes with vacuolated or eosinophilic cytoplasm (CD1a-, CD11c+, CD68+, MAC387+, lysozyme -/+, S-100 protein +), foci of lymphocytes and plasma cells, and fibrosis. Emperipoleisis, i.e. well-preserved lymphocytes and plasma cells within the cytoplasm of histiocytes, is typical, but may be inconspicuous; it is missing in 30% of leptomeningeal cases [1808].

Erdheim-Chester disease

The disease typically manifests in adults (mean, 55 years). Intracranial lesions may involve brain (preferentially cerebellum), spinal cord, cerebellopontine angle, choroid plexus, pituitary, meninges and



Fig. 11.10 Electron microscopy of Langerhans cell histiocytosis showing several Birbeck granules, apparently originating from cell membrane.

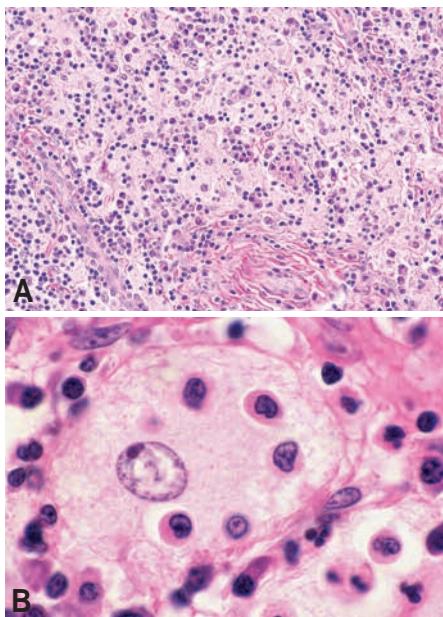


Fig. 11.11 Rosai-Dorfman disease. A Heterogeneous dural-based cellular infiltrate composed of lymphocytes, plasma cells, and large pale histiocytic cells with emperipoleisis. B Histiocyte with emperipoleisis of lymphocytes and plasma cells.

orbit {2386}. Retention of MRI gadolinium enhancement for several days may occur {77}. Patients occasionally present with non-specific neurological signs without indication of systemic disease (bones, visceral organs, adipose tissue). Diabetes insipidus and progressive cerebellar dysfunction are common symptoms {2449}. Histopathologically, lesions are composed of lipid-laden histiocytes (CD1a-, CD68+, S-100 protein -) with small nuclei, Touton-like multinucleated giant cells, a scant amount of lymphocytic infiltrates, a minimal number of eosinophils and fibrosis {17}. Elongated, microglia-type cells may be seen in cases with more diffuse brain infiltration.

Haemophagocytic lymphohistiocytosis

This autosomal recessive systemic disease of early infancy (mean, 3 months) diffusely involves leptomeninges and, multifocally, the brain. Neuroimaging is characterized by focal hyperintense lesions in white and grey matter, diffuse abnormal T2 signal intensity in white matter, delayed myelination and parenchymal atrophy {1152}. Cardinal symptoms are prolonged fever, hepatosplenomegaly and cytopenias. Biochemical markers include elevated triglyceride and ferritin, high levels of the alpha chain of the soluble interleukin-2 receptor and low fibrinogen. Impaired function of natural killer cells and cytotoxic T-cells is characteristic {970}. CNS involvement is seen in almost all patients, in 73% of patients already at time of diagnosis. Isolated CNS involvement has also been reported {2087}. Neurologic symptoms include irritability, bulging fontanelle, neck stiffness, seizures, cranial nerve palsies, ataxia and hemiplegia {812, 1152}. The outcome is lethal without allogeneic stem cell transplantation. Histopathology shows non-malignant diffuse infiltrations of lymphocytes and macrophages with haemophagocytosis. The antigenic profile of the macrophages is CD11c+, CD68+, while staining for CD1a and S-100 protein is variable. Intracranial lesions consist of lymphohistiocytic meningeal and cerebral infiltrations and multifocal cerebral necroses {812}.

Juvenile xanthogranuloma (JXG) and xanthoma disseminatum

Juvenile xanthogranuloma, now classified among the secondary dendritic-cell processes {147}, preferentially manifests in young children as solitary cutaneous nodule, but may arise in the brain or the meninges, either with or without cutaneous lesions; multicentric intracerebral cases have been reported {1294}. Xanthoma disseminatum occurs preferentially in young adults. Intracranial structures involved typically include hypothalamus, pituitary gland and dura mater {2479}. Pituitary and hypothalamic symptoms are most common (up to 40% of patients), while extracranial signs are related to involvement of skin, eyes, oral and respiratory mucosa. Both lesions are composed of histiocytes (CD1a-, CD11c+, CD68+, factor XIIIa+, MAC387-/, lysozyme -, S-100 protein -),

scattered Touton giant cells, lymphocytes and eosinophils {1701}.

Malignant histiocytic disorders

Malignant histiocytic tumours of the nervous system are extremely rare, and only a very few bona fide cases with rigorous immunohistochemical and molecular genetic characterization have been described. Histiocytic sarcoma, a malignant tumour positive for histiocytic markers (CD68, CD163, lysozyme, CD11c, CD14) and negative for myeloid markers, dendritic markers, CD30, ALK1 or other lymphoid markers, may primarily involve brain and meninges {2175}. Intracranial follicular dendritic cell (FDC) sarcoma has also been described {784}. Because vesicular nuclei, whorl formation and positivity for vimentin and EMA may mimic meningioma, immunohistochemistry for follicular dendritic cell markers (CD21, CD23, CD35) is essential.

Genetic susceptibility

Occurrence of multifocal LCH in monozygotic twins, in part with simultaneous onset of disease, has been repeatedly reported and suggests genetic susceptibility in at least some cases {1376}. The primary gene responsible for familial haemophagocytic lymphohistiocytosis is the perforin 1 (PRF1) gene on chromosome 10q22, although other genes have similarly been implicated in smaller subsets {921,1024}.

Genetics

PCR-based X-chromosome inactivation assays of female tissues provided evidence in support of a clonal origin and a neoplastic nature of LCH {2414}, whereas Rosai-Dorfman disease was shown to be polyclonal {1694}. In contrast, clonality studies have yielded mixed

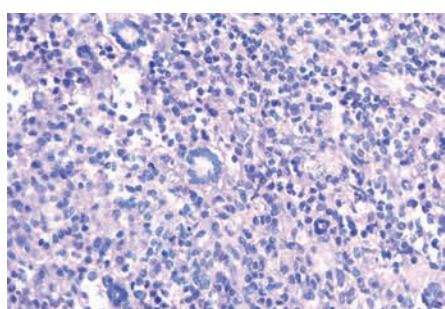


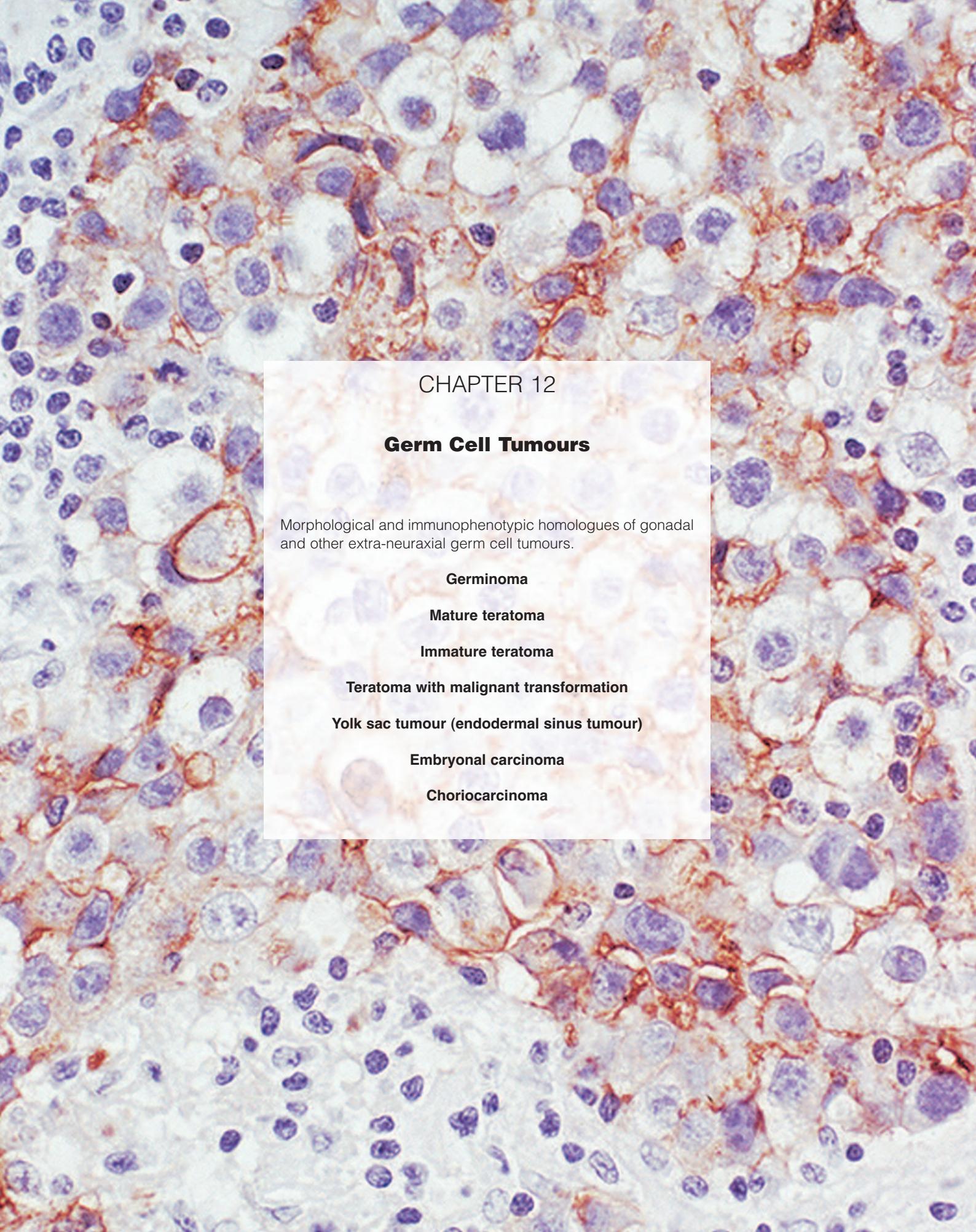
Fig. 11.12 Juvenile xanthogranuloma composed of histiocytes, multinucleated Touton cells and lymphocytes.

results in Erdheim-Chester disease {27, 329}. Monoclonal rearrangement of T-cell receptor genes was found in haemophagocytic lymphohistiocytosis {1656}, but not in LCH {2414}. *TP53* mutations were not detected in LCH {2389}, while karyotypes and the involvement of oncogenes and tumour suppressor genes are virtually unknown in the histiocytic disorders described in this chapter.

Histogenesis

Data suggest that LCH cells represent immature, partially activated dendritic Langerhans cells {1253}, whereas non-LCH disorders arise from bone marrow derived mononuclear phagocytes (macrophages) at various stages of development and activation. For example, JXG displays a phenotype similar to that of plasmacytoid monocytes {1186}. Microglial cells are the

intrinsic histiocytes of the brain, and although single tumours of possible microglial origin are on record {889}, there is no indication that microglia give rise to any one of the histiocytic disorders discussed in this chapter. Nevertheless, they may participate in the genesis of secondary neuronal damage, such as the encephalitis-like neuro-degenerative disorder of the cerebellum and basal ganglia associated with LCH {725}.



CHAPTER 12

Germ Cell Tumours

Morphological and immunophenotypic homologues of gonadal and other extra-neuraxial germ cell tumours.

Germinoma

Mature teratoma

Immature teratoma

Teratoma with malignant transformation

Yolk sac tumour (endodermal sinus tumour)

Embryonal carcinoma

Choriocarcinoma

CNS germ cell tumours

M.K. Rosenblum
Y. Nakazato
M. Matsutani

Definition

Morphological and immunophenotypic homologues of gonadal and other extra-neuraxial germ cell tumours.

ICD-O codes

Germinoma	9064/3
Teratoma	9080/1
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Yolk sac tumour	9071/3
Embryonal carcinoma	9070/3
Choriocarcinoma	9100/3

Incidence

Geographic incidence varies considerably. Most prevalent in far-east Asia, CNS germ cell tumours accounted for 2–3% of primary intracranial neoplasms, and for 8–15% of specifically paediatric examples, in series from Japan, Taiwan and Korea {842, 1416, 2173}. The highest of these figures emerge from Japan, where one population-based survey revealed an overall, age-adjusted incidence of 0.17 cases per 100 000 person-years (M=0.30, F=0.07) {1232}. In the West, these neoplasms constitute only 0.3–0.6% of primary intracranial tumours and approximately 3–4% of those affecting children {173, 1954, 2030}. An age-adjusted incidence of 0.09 cases per 100 000 person-years (M=0.12, F=0.06) has been reported in the United States {305}.

Age and sex distribution

Approximately 80–90% of CNS germ cell tumours afflict subjects younger than 25 years of age, incidence peaking in 10–14 year-olds, and a clear excess of cases involve males {173, 209, 842, 2000, 2172}. Analysis of the largest registry on record, totalling 1463 Japanese patients, showed that 70% of cases occur in the 10–24 year-old cohort and 73% affect males {209}. Only 2.9% of patients were below 5 years of age and 6.2% were older than 35 years of age in this analysis, but congenital examples (typically teratomas) are well-recognized,

as are exceptional instances of late adult onset. Male:female ratios vary with tumour location and histology. While the great majority of pineal region examples involve boys, an excess of suprasellar germ cell tumours are encountered in girls. All histologic variants exhibit a predilection for males, but this is especially decided with regard to teratomas. In the Japanese registry cited above, 89% of teratomas, 78% of germinomas and 75% of other germ cell tumour types arose in males.

Etiology

The predilection of CNS germ cell tumours for peripubertal subjects, localization to diencephalic centres regulating gonadal activity and increased incidence in the setting of Klinefelter syndrome have been taken as evidence that elevated circulating gonadotropin levels may factor in their pathogenesis. The link to Klinefelter syndrome is presumed also to reflect chromosome X overdosage, a relatively common genetic feature of intracranial germ cell tumours.

Localization

Like other extragonadal germ cell tumours, CNS variants preferentially affect the midline: 80% or more arise in structures about the third ventricle, with the region of the pineal gland being their most common site of origin, followed by the

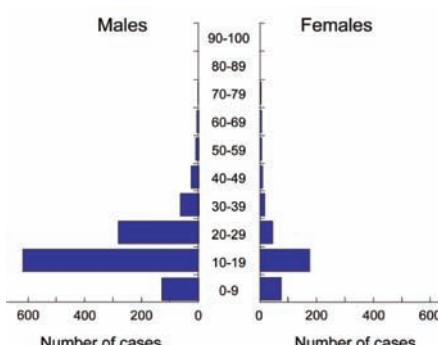


Fig. 12.01 Age and sex distribution of 1463 CNS germ cell tumours. Data from report of Brain Tumour Registry of Japan (1969–1996).



Fig. 12.02 MRI of a solid, contrast-enhancing germinoma of the pineal region, with a smaller CSF-borne metastasis in the suprachiasmatic cistern.

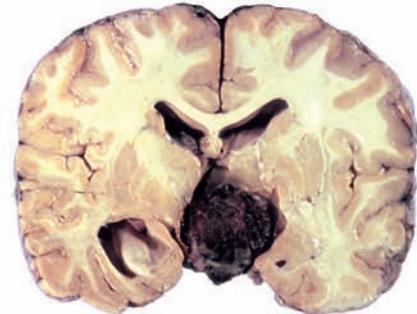


Fig. 12.03 Germinoma of the suprasellar region in a 7-year-old girl.

suprasellar compartment {850, 2000, 2030}. Suprasellar examples originate in the neurohypophyseal axis. Intraventricular, diffuse periventricular, basal ganglionic, thalamic, cerebral hemispheric, cerebellar, bulbar, intramedullary and intrasellar variants may be encountered, as may congenital holocranial examples (usually teratomas) and lesions that involve the brain extensively in complex with the orbit, cervical or cephalic soft tissues. Germinomas are the prevalent tumour type in the suprasellar compartment and basal ganglionic/thalamic regions, with non-germinomatous germ cell tumours dominating at other sites. Multifocal germ

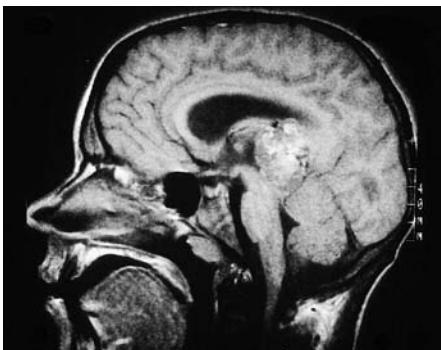


Fig. 12.04 Sagittal T1-weighted MRI of a teratoma in the pineal region, occupying the dorsal aspect of the third ventricle.

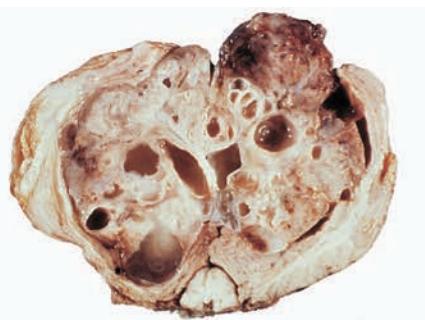


Fig. 12.05 Large teratoma of the cerebellum in a four-week-old infant, with characteristic cysts and chondroid nodules.

cell tumours usually involve the pineal region and suprasellar compartment simultaneously or sequentially. Bilateral basal ganglionic and thalamic lesions are also well recognized. Ventricular endoscopy (neuro-endoscopy) is emerging as especially sensitive in the localization of intracranial germ cell tumours, and can disclose minute tumour nodules on or beneath the ependyma that are not detectable on MRI [239].

Clinical features

Symptoms and signs

The presenting clinical manifestations of CNS germ cell tumours and their duration vary with histological type and location. Only the more common signs and symptoms are addressed here. In general, germinomas are associated with a more protracted symptomatic interval than other types. Tumours of the pineal region often compress and obstruct the cerebral aqueduct, resulting in progressive hydrocephalus with intracranial hypertension. Lesions so situated are also prone to compress and invade the tectal plate, producing a characteristic paralysis of upwards gaze and convergence known

as Parinaud syndrome. Neurohypophyseal-suprasellar germ cell tumours typically impinge on the optic chiasm, causing visual field defects, and often disrupt the hypothalamo-hypophyseal axis as evidenced by the occurrence of diabetes insipidus and manifestations of pituitary failure which include retarded growth and sexual maturation. CNS germ cell tumours may also cause "precocious puberty" by elaborating human chorionic gonadotropin (HCG), a stimulant of testosterone production that is secreted by neoplastic syncytiotrophoblasts. While the latter mechanism would account for cases of precocious sexual development encountered in boys (the overwhelming majority of those encountered in practice), the additional tumour expression of cytochrome P450 aromatase, which catalyses the conversion of C19 steroids to oestrogens, has been suggested to explain rare instances of precocious puberty affecting girls with HCG-producing intracranial germ cell neoplasms [1611]. In the latter context, HCG has also been suggested to have some intrinsic follicle stimulating hormone-like activity [2142].

Neuroimaging

The neuroradiological profiles of CNS germ cell tumours are largely non-specific, and definitive histological subclassification requires tissue examination. Nevertheless,

a few useful generalizations can be offered [618, 1315]. On CT and MRI, germ cell tumours other than teratomas usually appear as solid masses that are iso- or hyperdense relative to grey matter and show prominent contrast enhancement. Basal ganglia germinomas, which are commonly associated with ipsilateral basal ganglionic atrophy early in their evolution, occasionally exhibit little MRI abnormality in T1-weighted sequences, only ill-defined T2-hyperintensity and no, or faint, contrast enhancement. A diagnosis of teratoma should be considered for a lesion that can be shown to contain intratumoural cysts admixed with calcified regions and foci having the low signal-attenuation characteristics of fat. Intratumoural haemorrhage is particularly characteristic of choriocarcinoma and of mixed neoplasms with choriocarcinomatous elements, but may also be encountered in germinomas associated with HCG elevation (i.e. having syncytiotrophoblastic components). Finally, MRI studies are of considerable value in demonstrating hydrocephalus, invasion of regional structures and CSF-borne metastases, the latter visualized as linear or nodular foci of contrast enhancement along ventricular surfaces or in the craniospinal subarachnoid space.

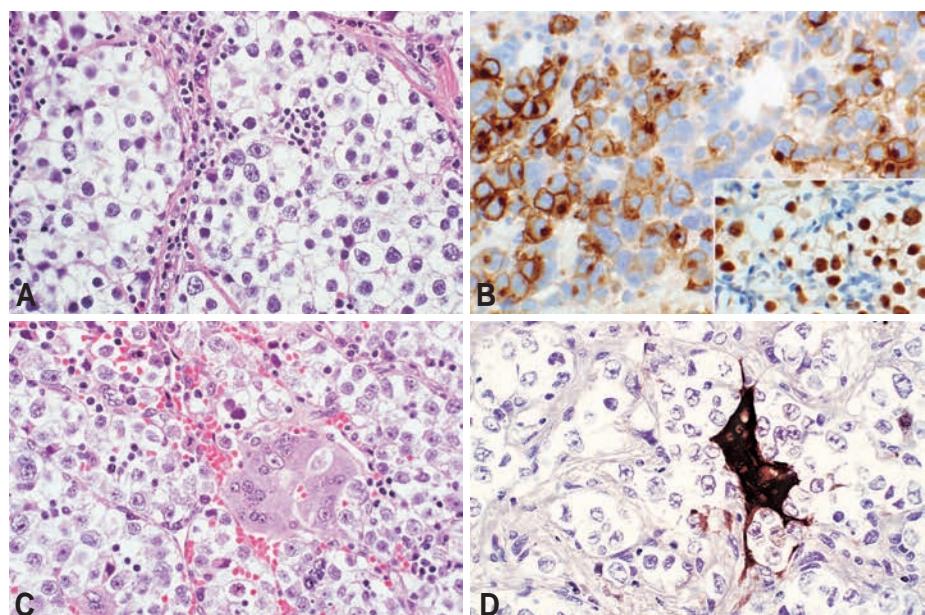


Fig. 12.06 Histological features of germinoma. A Tumour cells with abundant clear cytoplasm, round nuclei and prominent nucleoli. Note the lymphocytic infiltrates along fibrovascular septae. B Membranous and Golgi region immunolabelling for c-kit and nuclear expression of OCT4 (inset, lower right). C Syncytiotrophoblastic giant cell in an otherwise typical germinoma. D Immunostaining for human choriongonadotrophic hormone (β-HCG).

Tumour markers in serum and CSF

Assay of serum and CSF for α -fetoprotein (AFP; normally synthesized by yolk sac endoderm, foetal hepatocytes and intestinal epithelium) and β -HCG (normally secreted by syncytiotrophoblast) is now routine in the presurgical assessment of suspected germ cell tumours. Elevations of either oncoprotein constitute compelling evidence of germ cell neoplasia, the pattern of marker elevation being somewhat predictive of tumour histology [842, 850]. High AFP levels typically signal the presence of yolk sac tumour elements, but modest increases of this marker may result from expression by the enteric components of teratomas. Marked elevations of β -HCG strongly suggest that components of choriocarcinoma are present, though increases in this oncoprotein may be associated with tumours, including germinomas, that simply harbour syncytiotrophoblastic giant cells. Isolated elevation of placental alkaline phosphatase (PLAP; a cell-surface glycoprotein normally elaborated by syncytiotrophoblast and primordial germ cells) has been correlated with pure germinomatous histology, but this assessment has not been generally employed. Soluble c-kit concentrations in the CSF have been explored as a germinoma marker as well [1498]. Sampling artefact must be presumed to account for the scenario in which tissue morphology and immunohistochemical assays are at odds with serum and CSF profiles.

Macroscopy

Germinoma is generally solid, although it may show small foci of cystic change, and is composed of soft and friable tan-white tissue. Conspicuous necrosis and haemorrhage are usually absent, but when present suggest the presence of more malignant components. Choriocarcinoma is especially prone to extensive haemorrhagic necrosis, while the accumulation of myxoid material lends a gelatinous appearance and consistency to some yolk sac tumours. Teratomatous elements manifest as mucous-laden cysts, fat, chondroid nodules or bony spicules. Rarely, CNS teratomas contain teeth or well-formed hairs.

Histopathology

The accurate histological identification and subclassification of CNS germ cell

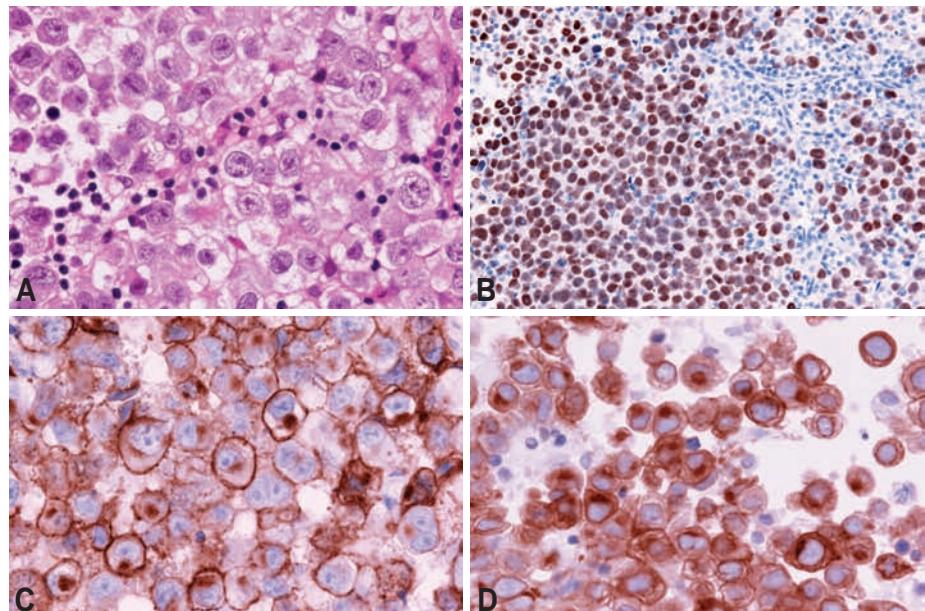


Fig. 12.07 Histological features of germinoma. A Large tumour cells with round vesicular nuclei, prominent nucleoli and clear cytoplasm. B Germinoma showing OCT4 immunoreactivity. C Cytoplasmic and membranous reactivity for PLAP. D Expression of c-kit protein in tumour cells.

tumours are critical to current treatment planning and prognostication. While the various entities collected under the generic designation of CNS germ cell tumour are here described in their pure forms, intracranial germinal neoplasms are often of mixed histologic composition. In fact, only the germinoma and teratoma are likely to be encountered as pure tumour types [173, 842, 850, 1954, 2000, 2030]. The pathologist confronted by a mixed CNS germ cell tumour is obliged to specifically enumerate its individual elements and should communicate the relative representation of each component present. Immunohistochemical studies may be required to delineate these entities.

Germinoma

The pure germinoma, the most common CNS germ cell tumour, is populated by large cells that appear undifferentiated and that resemble primordial germinal elements (of which, in theory, they represent the neoplastic counterparts). These are disposed in monomorphic sheets, lobules or, in examples characterized by a desmoplastic stromal response, regimented cords and trabecula. Promptly fixed specimens are typified by round, vesicular and centrally positioned nuclei, prominent nucleoli, discrete cell membranes and relatively abundant

cytoplasm that is often strikingly clear due to glycogen accumulation. These cytological features are basically retained in lumbar puncture or ventricular CSF samples that must be screened for tumour cells. Mitoses are usually identified without difficulty and may be conspicuous, but necrosis is uncommon. Delicate fibrovascular septa variably infiltrated by small lymphocytes—principally T cells of both helper/inducer and cytotoxic/suppressor types—are a usual feature [1999, 2385]. The identification of a biphasic population of mature lymphocytes and larger germinoma cells permits cytological diagnosis of these tumours in smear preparations. Some germinomas show a lymphoid or lymphoplasmacellular reaction so florid as to confound the identification of their neoplastic elements in biopsy material. Germinomas may also masquerade as sarcoidosis or tuberculosis by virtue of an obscuring granulomatous response [1162]. Still other germinomas are extensively overgrown by fibrous tissue.

The most constant immunohistochemical attributes of germinomas are strong cell membrane labelling for c-kit [1556] and nuclear reactivity for OCT4 [789]. Cytoplasmic and cell membrane labelling for PLAP is somewhat less common [173, 562, 789, 842, 1954] and may be particularly difficult to demonstrate in inflammatory-

looking examples and in specimens previously frozen. A minority of germinomas show patchy foci of cytoplasmic labelling for cytokeratins {562, 842}. Together with demonstrations of intercellular junctional complex and true lumen formation at the ultrastructural level {1478}, this has been taken as evidence of differentiation along somatic epithelial lines or towards embryonal carcinoma. Such differentiation, to which no clinical significance has yet been attached, would appear to be a more frequent event in the germinoma than in its testicular counterpart, the seminoma. Otherwise typical germinomas may contain syncytiotrophoblastic giant cells that manifest cytoplasmic immunolabelling for β -HCG as well as for human placental lactogen (HPL) and cytokeratins. Germinomas with syncytiotrophoblastic elements certainly do not manifest the virulence of choriocarcinomas and should not be confused with them, but emerge from some studies as more prone to recurrence than pure germinomas following radiation therapy (see below).

Teratoma

Teratomas differentiate along ectodermal, endodermal and mesodermal lines (e.g. they recapitulate somatic development from the three embryonic germ layers). Mature and immature variants require distinction.

Mature teratoma

Mature teratomas are composed exclusively of fully differentiated, 'adult-type' tissue elements. Mitotic activity is low or absent. The more common ectodermal components encountered in such tumours include skin, brain and choroid plexus. Mesodermal representatives include cartilage, bone, fat and muscle (both smooth and striated). Cysts lined by epithelia of respiratory or enteric type are the usual endodermal participants, with some examples also containing pancreatic or hepatic tissue. Not infrequently, gut-like structures are formed, replete with mucosa and muscular coats. Advanced organogenesis and somatic organization may result in the phenomenon of intracranial foetus-in-foetu {1572}, though incorporation of a dizygotic twin via epithelial or neural tube defects that disrupt the amniotic septum has also been suggested to account for some cases of this pathological curiosity {1954}.

Immature teratoma

This teratoma variant contains incompletely differentiated components resembling foetal tissues. Such incompletely differentiated areas mandate classification of the lesion as an immature teratoma even if they constitute only minor elements in an otherwise differentiated tumour. Particularly common are a hypercellular and mitotically active "stroma" reminiscent of embryonic mesenchyme and primitive neuroectodermal elements that may fashion neuroepithelial rosettes and canalicular arrays mimicking the developing neural tube. Clefts lined by melanotic neurepithelium are often encountered, these representing abortive retinal differentiation. Immature intracranial teratomas have been reported to undergo spontaneous differentiation into fully mature somatic-type tissues over time {2059}. However, re-resection

specimens composed solely of mature teratoma usually derive from patients whose immature teratomas or mixed germ cell tumours have been subjected to therapy {614}. The apparent tumour "maturation" in such cases presumably reflects the selective radio- or chemoablation of their more actively proliferating components. The enlargement of these residual, differentiated lesions is termed "growing teratoma syndrome" {149, 614}.

Teratoma with malignant transformation

These are generic designations for the occasional teratomatous neoplasm that contains as an additional malignant component a cancer of conventional somatic type. The latter is most often a rhabdomyosarcoma or undifferentiated sarcoma {173, 1954}, less commonly a squamous cell carcinoma or enteric-type adenocarcinoma {173}. Yolk sac tumour elements have also been put forward as the progenitors of select enteric-type adenocarcinomas arising from intracranial germ cell tumours {609}. Curiosities in this setting include the development of erythroleukemia {803}, leiomyosarcoma {2108} and carcinoid {917}. The pathologist detecting evidence of such "malignant transformation" should state the specific histological form that this takes.

On immunohistochemical investigation, the constituent elements of the teratoma can be expected to express those antigens that are appropriate to their native somatic counterparts. Elaboration of AFP by teratomatous glandular epithelium may result in elevated levels of this important marker in the serum and CSF {173, 562, 842, 1954}. Limited immunoexpression of c-kit by included mesenchymal and epithelial elements, as well as increased CSF c-kit levels, has been described {1498}.

Yolk sac tumour

This neoplasm is composed of primitive-appearing epithelial cells—putatively representing yolk sac endoderm—set in a loose, variably cellular and often conspicuously myxoid matrix resembling extra-embryonic mesoblast. The epithelial elements may proliferate in solid sheets but are more commonly disposed about an intervening meshwork of irregular tissue spaces ('reticular' pattern) or line anastomosing sinusoidal channels as a cuboidal epithelium draped, in some cases, over delicate fibrovascular projections to

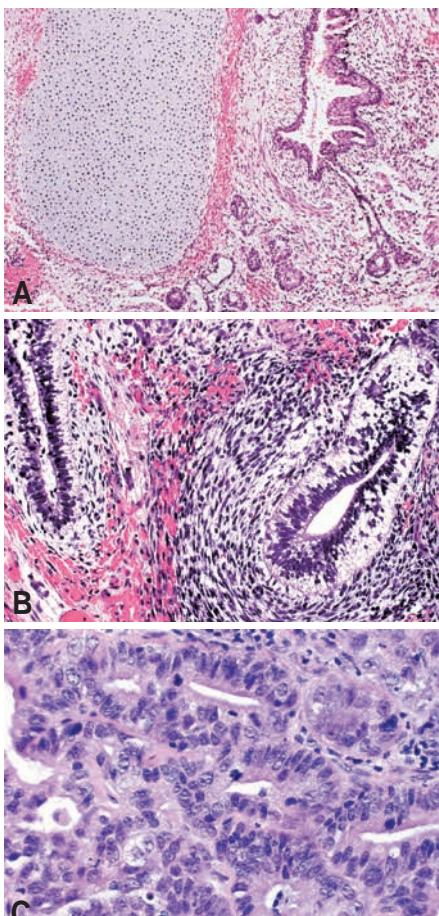


Fig. 12.08 A Mature teratoma with differentiated glands, smooth muscle bundles and a nodule of moderately hypercellular cartilage. B Immature teratoma with foetal-type glands and embryonic mesenchyme-like stroma. C Teratoma with malignant transformation into an enteric-type adenocarcinoma.

form distinctive papillae known as Schiller-Duval bodies. Yolk sac tumours may also contain eccentrically constricted cysts delimited by flattened epithelial elements ("polyvesicular vitelline" pattern), enteric-type glands lined partially by goblet cells, and foci of apparent hepatocellular differentiation ("hepatoid" variant). A diagnostic, though inconstant, feature of the yolk sac tumour is the presence of brightly eosinophilic, PAS-positive and diastase resistant hyaline globules that may appear to lie within the cytoplasm of epithelial cells or to be free in the adjoining stroma. Mitotic activity varies considerably and may be conspicuous, but necrosis is uncommon.

Cytoplasmic immunoreactivity for AFP of the epithelial component of the yolk sac tumour is characteristic {173, 562, 842, 1954} and may be of considerable value in distinguishing its solid variant from germinoma and embryonal carcinoma. Furthermore, yolk sac tumours are characteristically non-reactive for c-kit and OCT 4. The hyaline globules of this tumour are also AFP-immunoreactive.

Embryonal carcinoma

The embryonal carcinoma is composed of large cells that proliferate in cohesive nests and sheets, form abortive papillae or line irregular, gland-like spaces. Tumour cells may exceptionally replicate the structure of the early embryo, forming

"embryoid bodies" replete with germ discs and miniature amniotic cavities. Markedly enlarged nucleoli, abundant clear to somewhat violet-hued cytoplasm, a high mitotic rate and zones of coagulative necrosis complete the histological picture. The constituent cells uniformly show dense and diffuse cytoplasmic labelling for cytokeratins, attesting to their differentiation along epithelial lines and distinguishing these neoplasms from most germinomas (with which they share PLAP and OCT 4 immunoreactivity) {562, 842}. In addition, c-kit expression is not seen in embryonal carcinoma {1556}.

Choriocarcinoma

The choriocarcinoma is characterized by extra-embryonic differentiation along trophoblastic lines. The diagnosis requires the identification of syncytiotrophoblastic elements, as well as syncytiotrophoblastic giant cells. The latter may achieve enormous proportions and typically contain multiple, densely hyperchromatic nuclei, often clustered in a knot-like fashion, lying within a large expanse of basophilic or violaceous cytoplasm. The neoplastic syncytiotrophoblast surrounds or partially drapes cohesive masses of large mononucleated cells with vesicular nuclear features and clear or acidophilic cytoplasm, which represent the cytotrophoblastic component. Ectatic stromal vascular channels, blood lakes and

extensive haemorrhagic necrosis are the rule. Cytoplasmic immunolabelling of syncytiotrophoblastic giant cells for β -HCG and HPL are characteristic {173, 562, 842, 1954}.

Genetic susceptibility

CNS germ cell tumours typically afflict otherwise healthy individuals. An increased risk of intracranial germ cell neoplasia is associated with Klinefelter syndrome, which is characterized by a 47 XXY genotype and an array of anomalies that includes testicular atrophy, gynaecomastia, eunuchoid habitus and elevated serum gonadotrophins {1023}. Such patients are also predisposed to mediastinal germ cell tumours. As discussed below, CNS (and other) germ cell tumours commonly exhibit extranumerary X chromosomes. The susceptibility of Klinefelter syndrome patients to such tumours could reflect increased dosage of a chromosome X-associated gene. Noteworthy are descriptions of intracranial germ cell tumours affecting individuals with Down syndrome {334, 779}, which has been associated with an increased risk of testicular germ cell tumourigenesis. Isolated accounts also document CNS germ cell tumours arising in the setting of neurofibromatosis type 1 {2439}, in siblings {61} and in the foetus (intracranial teratoma) of a woman with independent ovarian teratoma {1779}. Rarely, patients with germ cell tumours of the CNS have been reported to develop second gonadal or mediastinal germ cell neoplasms {779, 938, 2374}; one such patient suffered from Down syndrome {779}.

Genetics

The karyotypic and molecular genetic data communicated to date indicate that pure intracranial teratomas presenting as congenital or infantile growths differ fundamentally from the more common CNS germ cell tumours arising beyond early childhood. Whereas the former resemble teratomas of the infant testis in their typically diploid status and general chromosomal integrity, the latter, irrespective of histologic composition, share with their testicular counterparts in young men characteristically aneuploid profiles, complex chromosomal anomalies and clearly overlapping patterns of net genetic imbalance {1633, 1879, 1882, 2034}. These primarily include gains

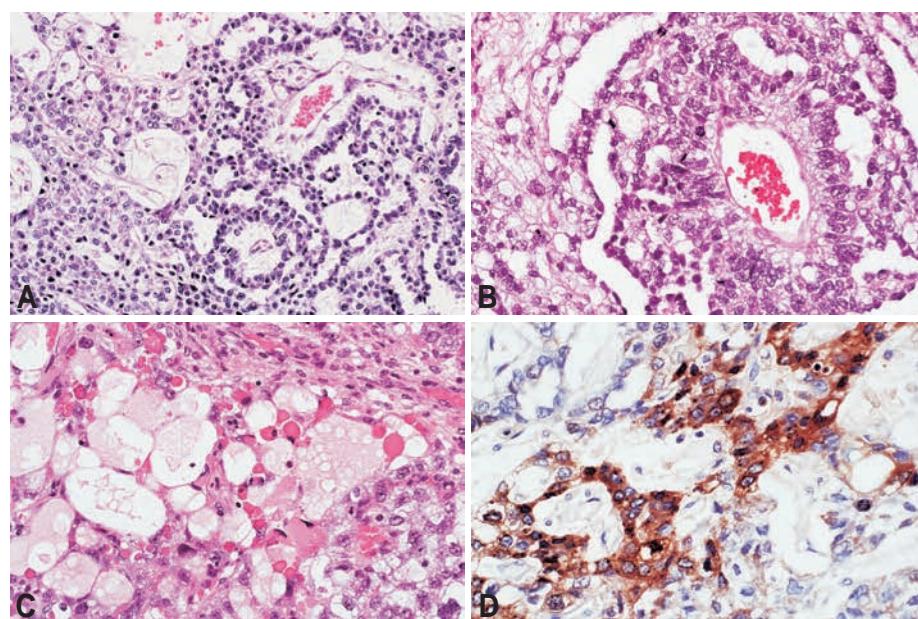


Fig. 12.09 Yolk sac tumour showing (A) typical sinusoidal growth pattern and numerous mitoses, (B) Schiller-Duval body, (C) reticular growth pattern with numerous hyaline globules and (D) α -fetoprotein immunolabelling.

involving chromosomes 12p, 8q, 1q and X as well as losses (generally less frequent) of 11q, 13 and 18q [1633, 1882, 2034]. Whether 12p gain and isochromosome 12p formation, especially characteristic of testicular and mediastinal germ cell tumours, occur at comparably high frequency in the CNS setting is debated [1633, 1882, 2034]. Similar considerations apply to the prevalence of X duplication in these locales [1633, 2034]. At the single gene level, there has been limited study of CNS germ cell tumours. The *TP53* and *CDKN2A* genes do not appear to be common targets of mutation in this setting [1607, 1633]. A subset of germinomas share with testicular and mediastinal seminomas mutations involving c-kit [1032].

Histogenesis

Germ cell tumours of the central neuraxis have long been assumed to represent the neoplastic offspring of primordial germ cells that either migrate in aberrant fashion, or purposefully ‘home’, to the embryonic CNS rather than the developing genital ridges. In support of a germinal origin for these neoplasms is the fact that they exhibit non-random genetic alterations comparable to those of their morphologic homologues in the gonads. However, studies of the human CNS, including the immunohistochemical screen of foetal pineal glands with antibodies to the primordial germ cell marker PLAP, have never shown it to harbour primitive germ cell elements [562]. Noteworthy in this regard is speculation that germ cells might differentiate into deceptively “somatic” forms

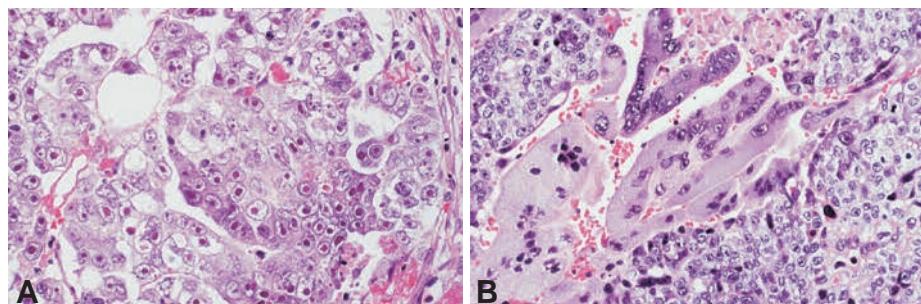


Fig. 12.10 A Embryonal carcinoma composed of large epithelial cells forming abortive papillae and glandular structures with macronuclei. B Choriocarcinoma with syncytiotrophoblastic giant cells and cytotrophoblasts.

on entering the CNS. Specifically, an enigmatic population of skeletal muscle-like cells native to the developing pineal gland has been proposed as possibly descending from primitive germinal elements attracted to this organ during neuroembryogenesis [1680]. Cited in support of this seemingly far-fetched notion is the fact that striated muscle-type cells of unknown function also populate the thymus, another organ ostensibly devoid of germ cells yet a favoured site of extragonadal germ cell tumourigenesis [1680].

An alternative to the unifying primordial germ cell hypothesis postulates an origin for CNS germ cell tumours in a variety of displaced embryonic tissues that come to be misincorporated in the developing neural tube [1984]. In this scenario, only the germinoma would derive from misrouted primordial germ cells and so qualify as a true germ cell neoplasm, while intracranial choriocarcinomas would arise from misplaced trophoblast, yolk sac tumours from malpositioned

elements of the secondary yolk sac proper, embryonal carcinomas from primitive constituents of the triploblastic embryo and teratomas from differentiating tissues of the later embryonic period. This theory, too, is based on the existence of ectopic progenitors that have not been detected in the developing human CNS. Furthermore, this scheme must postulate the co-ordinated neoplastic transformation of diverse cell types to account for mixed intracranial germ cell tumours and is difficult to reconcile with the finding of similar genetic abnormalities in neoplasms of different histologic composition. Another speculative proposal would implicate toti- or pluri-potent stem cells in the histogenesis of CNS germ cell tumours [2305]. As such cells are native to all three primitive embryonic layers, defective migration is not requisite to this hypothesis. Implicit in this formulation, however, is the selective genetic programming of uncommitted precursors along the germ cell differentiation pathway, as well as

Table 12.01 Immunohistochemical profiles of CNS germ cell tumours.

	α -Fetoprotein	Human chorionic gonadotropin	Human placental lactogen	Placental alkaline phosphatase	Cytokeratins (CAM 5.2, AE 1/3)	c-kit (CD 117)	OCT4	CD30
Germinoma	-	- ²	- ²	+	- ³	+	+	-
Teratoma	+ ¹	-	-	-	+ ⁴	+/- ⁶	-	-
Yolk sac tumour	+	-	-	+/-	+	-	-	-
Embryonal carcinoma	-	-	-	+	+	-	+	+
Choriocarcinoma	-	+	+	+/-	+ ⁵	-	-	-

¹ α -Fetoprotein is usually restricted to enteric-type glandular components.
² Syncytiotrophoblastic giant cells that may be found in otherwise pure germinomas (or in any of the other CNS GCT types) will be immunoreactive for human chorionic gonadotropin and human placental lactogen.
³ A minority of germinomas exhibit cytokeratin reactivity that is usually distributed in patchy fashion.
⁴ Cytokeratin reactivity is a feature of epithelial components.
⁵ Immunoreactivity is a regular feature of syncytiotrophoblastic giant cells, while cytotrophoblast is often negative.
⁶ Limited immunoexpression by some mesenchymal and epithelioid components may be seen.

their neoplastic transformation. A modified version of this hypothesis suggests a stem cell origin for the pure, diploid teratomas of congenital/infantile onset, reserving a primordial germ cell lineage for the peri- and post-pubertal neoplasms characterized by aneuploidy, over-representation of chromosome 12p and the presence of primitive germ cell-like or mixed histologic components. The differences in these tumour types could, however, reflect the mechanisms of their initiation rather than divergent cellular origins. Also invoked in the histogenesis of CNS teratomas are parthenogenetic mechanisms and the inclusion of blighted twins [1954]. Especially controversial is the nature of teromatous tumours of the spinal cord. While some have viewed these as complex malformations [1148], others contend that they are bona fide neoplasms of germ cell origin [29].

Prognostic and predictive factors

Histological subtype is the single factor most predictive of CNS germ cell tumour outcome [850, 2030]. Mature teratomas are potentially curable by gross total resection. Pure germinomas exhibit a remarkable radiosensitivity foreign to other germ cell tumour types, 10-year survival rates bettering 85% following craniospinal irradiation alone [1616, 2000]. The addition of chemotherapy to germinoma treatment regimes may effect comparable disease control at reduced radiation doses and field volumes [205, 1415]. One report excepted [2081], germinomas harbouring syncytiotrophoblastic cells or associated with elevated β -HCG levels have carried an increased risk of local failure and modest decrement in survival compared to their pure counterparts after irradiation alone [2000]. Most virulent are yolk sac tumours,

embryonal carcinomas, choriocarcinomas and mixed lesions in which these subtypes are prominently represented, while immature teratomas and mixed tumours dominated by teratoma or germinoma and containing high-grade non-germinomatous components in relatively limited amounts appear to occupy an intermediate position in terms of biologic potential [1415, 1617, 2000]. The historically dismal prognosis for patients with these malignant, non-germinomatous tumour subtypes has been improved with vigorous adjuvant chemotherapy strategies [1415, 1617] that continue to be investigated. While local recurrence and CSF-borne dissemination are the usual patterns of disease progression, abdominal contamination via ventriculoperitoneal shunts and hematogenous spread (principally to lung and bone) may be encountered.

CHAPTER 13

Familial Tumour Syndromes involving the Nervous System

The elucidation of the molecular basis of inherited cancer syndromes has greatly contributed to the understanding of carcinogenesis in general. The major syndromes with manifestations in the nervous system are listed below.

Syndrome	Gene	Chromosome	Nervous system	Skin	Other tissues
Neurofibromatosis type 1	<i>NF1</i>	17q11	Neurofibroma, MPNST, optic nerve glioma, astrocytoma	Café-au-lait spots, axillary freckling	Iris hamartomas, osseous lesions, phaeochromocytoma, leukaemia
Neurofibromatosis type 2	<i>NF2</i>	22q12	Bilateral vestibular schwannoma, peripheral schwannoma, meningiomas, meningoangiomyomatosis, spinal ependymoma, astrocytoma, glial hamartias, cerebral calcification	–	Posterior lens opacities, retinal hamartoma
von Hippel-Lindau	<i>VHL</i>	3p25	Haemangioblastoma	–	Retinal haemangioblastoma, renal cell carcinoma, phaeochromocytoma, visceral cysts
Tuberous sclerosis	<i>TSC1</i> <i>TSC2</i>	9p34 16p13	Subependymal giant cell astrocytoma, cortical tubers	Cutaneous angiofibroma ('adenoma sebaceum'), <i>peau chagrin</i> , subungual fibroma	Cardiac rhabdomyoma, adenomatous polyps of the duodenum and the small intestine, cysts of the lung and kidney, lymphangioleiomyomatosis, renal angiomyolipoma
Li-Fraumeni	<i>TP53</i>	17p13	Astrocytomas, PNET	–	Breast carcinoma, bone and soft tissue sarcoma, adrenocortical carcinoma, leukaemia
Cowden	<i>PTEN</i>	10q23	Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos), megalencephaly	Multiple trichilemmoma, fibroma	Hamartomatous polyps of the colon, thyroid neoplasms, breast carcinoma
Turcot	<i>APC</i> <i>hMLH1</i> <i>hPSM2</i>	5q21 3p21 7p22	Medulloblastoma Glioblastoma	Café-au-lait spots	Colorectal polyps Colorectal polyps
Naevus basal cell carcinoma syndrome (Gorlin)	<i>PTCH</i>	9q31	Medulloblastoma	Multiple basal cell carcinomas, palmar and plantar pits	Jaw cysts, ovarian fibroma, skeletal abnormalities
Rhabdoid tumour predisposition syndrome	<i>INI1</i>	22q11.2	AT/RT	–	Bilateral renal malignant rhabdoid tumours

Neurofibromatosis type 1

A. von Deimling
A. Perry

Definition

An autosomal dominant disorder characterized by neurofibromas, multiple café-au-lait spots, axillary and inguinal freckling, optic gliomas, osseous lesions and iris hamartomas (Lisch nodules); caused by mutations of the *NF1* gene on chromosome 17q11.2.

MIM No. 162200 {1433}.

Synonyms

Von Recklinghausen disease, von Recklinghausen neurofibromatosis, peripheral neurofibromatosis.

Incidence

Although the prevalence in most populations is estimated to be 1:3000 {2360}, higher frequencies have been reported for Arab-Israeli subpopulations {650}.

Diagnostic criteria

The diagnostic criteria for neurofibromatosis type 1 (NF1) are given in Table 13.01.

Nervous system neoplasms

Neurofibromas

The neurofibromas that occur in NF1 patients differ in part from those commonly observed in their sporadic counterparts

(see Chapter 9). Among the major subtypes of neurofibromas, the dermal and plexiform variants are characteristic of NF1.

Dermal neurofibroma is a well-circumscribed, non-encapsulated benign tumour variably composed of Schwann cells and fibroblast-like cells, with an admixture of endothelial cells, lymphocytes, and an unusually large number of mast cells. Deep-seated nodular neurofibromas arise less commonly {897}, have a more solid consistency, and may cause neurological symptoms.

Plexiform neurofibromas produce diffuse enlargement of major nerve trunks and their branches, sometimes yielding a rope-like mass and are almost pathognomonic of NF1. Plexiform neurofibromas may develop during the first one or two years of life as a single subcutaneous swelling with ill-defined margins. They may also cause severe disfigurement later in life, affecting large areas of the body. If these tumours arise in the head or neck region, they can impair vital functions. Plexiform neurofibromas have about a 10% lifetime risk of malignant progression. In contrast, malignant transformation is a very rare event for other neurofibromas.

Malignant peripheral nerve sheath tumours

The malignant peripheral nerve sheath tumours that arise in NF1 patients usually occur at a younger age, may be multiple, and may include rhabdomyoblastic and other heterologous elements. Such lesions, referred to as malignant Triton tumours {2442}, are highly characteristic of NF1. In addition, the glandular variant of malignant peripheral nerve sheath tumour is also a lesion indicative of NF1. Malignant peripheral nerve sheath tumours reduce life expectancy significantly.

Gliomas

The majority of gliomas in NF1 patients are pilocytic astrocytomas that are located within the optic nerve {1306}. Bilateral growth, when present, is characteristic of NF1. Optic nerve gliomas in NF1 patients



Fig. 13.01 Pilocytic astrocytoma of the optic nerve (optic nerve glioma) in a NF1 patient.



Fig. 13.02 Macroscopic preparation of a bilateral optic nerve glioma in a patient with NF1.

may remain static for many years and some may regress. Other gliomas observed at an increased frequency in NF1 patients include diffuse astrocytomas and glioblastomas {1292A}.

Other CNS manifestations

The following features are more frequent in NF1 patients: macrocephaly {898}, learning disabilities and attention-deficit-hyperactivity disorder {1418}, epilepsy {1868}, hydrocephalus, aqueductal stenosis and neuropathy {202}.

Extraneuronal manifestations

Abnormalities of pigmentation

Café-au-lait spots, freckling and Lisch nodules all involve alterations of melano-

Table 13.01 Diagnostic criteria for NF1.

The presence of two or more of the following signs identifies the NF1 patient:	
1.	Six or more café-au-lait macules (1.5 cm or larger in post-pubertal individuals, 0.5 cm or larger in pre-pubertal individuals)
2.	Two or more neurofibromas of any type or one or more plexiform neurofibromas
3.	Freckling of armpits or groin
4.	Pilocytic astrocytoma of optic pathway ("optic glioma")
5.	Two or more Lisch nodules (iris hamartomas)
6.	Dysplasia/absence of the sphenoid bone or dysplasia/thinning of long bone cortex
7.	First-degree relative with NF1

From Gutmann et al. {739}.

cytes. Café-au-lait spots are often the first manifestation of NF1 in the newborn child. Their number and size increase during infancy, but may remain stable or even decrease in adults. Histopathologically, the ratio of melanocytes to keratinocytes is higher in the unaffected skin of NF1 patients, and this is more marked in the café-au-lait spots [610]. Axillary and/or inguinal freckling occurs

Table 13.02 Manifestations of NF1.

Tumours
Neurofibromas
Dermal
Nodular
Plexiform
Gliomas
Optic glioma
Astrocytoma
Glioblastoma
Sarcomas
Neurofibrosarcoma (MPNST)
Rhabdomyosarcoma
Triton tumour
Gastrointestinal stromal tumour (GIST)
Neuroendocrine/neuroectodermal tumours
Phaeochromocytoma
Carcinoid tumour
Medullary thyroid carcinoma
C-cell hyperplasia
Haematopoietic tumours
Juvenile chronic myeloid leukaemia
Juvenile xanthogranuloma
Other features
Osseous lesions
Scoliosis
Height reduction
Macrocephaly
Pseudoarthrosis
Sphenoid wing dysplasia
Nervous system
Intellectual handicap
Epilepsy
Neuropathy
Hydrocephalus (aqueductal stenosis)
Vascular lesions
Fibromuscular dysplasia/hyperplasia of renal artery and other arteries
Skin
Café-au-lait spots

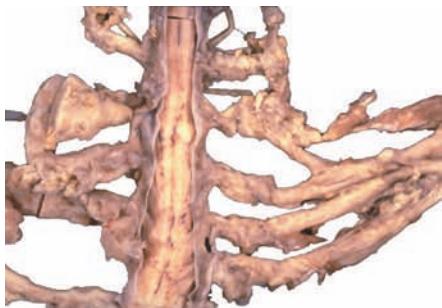


Fig. 13.03 Multiple neurofibromas of the spinal roots and the brachial plexus in a patient with NF1.

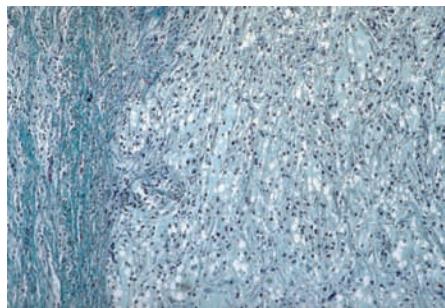


Fig. 13.04 Bilateral optic nerve glioma in a patient with NF1. The histology shows enlargement of the compartments of the optic nerves and collar-like extension into the subarachnoid space.

in about two thirds of NF1 patients, but may have a higher prevalence in young adults [739]. The histopathological features of these freckles are indistinguishable from those of café-au-lait spots. Lisch nodules are small, elevated pigmented hamartomas on the surface of the iris. The presence of Lisch nodules is a particularly useful diagnostic criterion, as they occur in nearly all adults with NF1.

Osseous and vascular lesions

In NF1, the orbits are often affected by sphenoid wing dysplasia. In addition, spinal deformities often result in severe scoliosis that may require surgical intervention. Thinning, bending and pseudoarthrosis may affect the long bones (predominantly tibial), and short stature may also be a component of NF1 [2270]. Fibromuscular dysplasia of the renal and other arteries, including the large cervical vessels, has also been reported as being associated with NF1.

Tumours

NF1 patients have an increased risk of developing rhabdomyosarcomas, juvenile chronic myeloid leukaemia, juvenile xanthogranulomas, gastrointestinal stromal tumours (GIST), duodenal carcinoids, C-cell hyperplasia/medullary thyroid carcinomas, other carcinomas and phaeochromocytomas [2508].

Genetics

The *NF1* locus is on chromosome 17q11.2 [2046].

Gene structure

The *NF1* gene is large, containing 59 exons and spanning roughly 350 kb [1947]. One of the two extensive introns, 27b, includes coding sequences for

three embedded genes that are transcribed in a reverse direction: *EVI2A*, *EVI2B* and *OMGP*. There are 12 non-processed *NF1* pseudogenes localized on 8 chromosomes. None of these pseudogenes extends beyond exon 29.

Gene expression

The *NF1* transcript is approximately 13 kb long and includes three alternatively spliced isoforms (exons 9a, 23a, and 48a), variably expressed based on tissue type and differentiation [1947].

The product of the gene, neurofibromin, is a cytoplasmic protein that can be found in two major isoforms of 2818 amino acids (type 1) and 2839 amino acids (type 2) of 220–250 kD. The protein harbours a GAP-related domain (GRD) and thus belongs to the group of mammalian RasGTPase-activating proteins. In addition to the homology between the GAP domains, it has large segments that show moderate homology to the two *Saccharomyces cerevisiae* inhibitors of Ras protein, IRA1 and IRA2. While several features of these domains, including alternative splicing and the presence of mutations, suggest that they may be functionally important, their exact role is as yet unknown. Nevertheless, data suggest that neurofibromin loss may selectively activate RAS isoforms, thereby stimulating downstream signalling cascades and mitogenic mediators, such as cAMP, AKT, ERK1/2, RAF, PI3K, mTOR, and S6K [1947]. There is also some evidence for growth-regulatory functions outside of the neurofibromin GRD. Although neurofibromin is expressed almost ubiquitously in most mammalian tissues, the highest levels have been found in the central and peripheral nervous system and in the adrenal gland.

Gene mutations

Mutation screening of the *NF1* gene is difficult due to its large size, the presence of pseudogenes, and the fact that mutations do not appear to cluster in hot spots, perhaps with the exception of exons 10a-10c [1463]. Over 300 mutations have been previously reported (<http://www.ncbi.nlm.nih.gov/entrez/dispmim.cgi?id=162200>). Using comprehensive screening techniques that may include various strategies, such as long range RT-PCR, protein truncation testing, cDNA sequencing and FISH, up to 95% of mutations may be detected in individuals fulfilling NIH criteria for NF1 [1463]. More than 80% of mutations are predicted to encode truncated proteins or none at all.

Genotype/phenotype correlation

No convincing genotype-phenotype correlations have so far been established, with the exception of the "NF1 microdeletion syndrome"; the latter is encountered in roughly 5–10% of patients and is caused by unequal homologous recombination of *NF1* repeats resulting in the loss of approximately 1.5 Mb of DNA on 17q, including the entire *NF1* gene (<http://www.ncbi.nlm.nih.gov/entrez/dispmim.cgi?id=162200>). Such patients tend to have a more severe phenotype, including facial dysmorphism, mental retardation, developmental delay, increased burden of neurofibromas and enhanced risk of MPNST development [439]. However, the latter observation was not substantiated by another group studying 30 MPNSTs

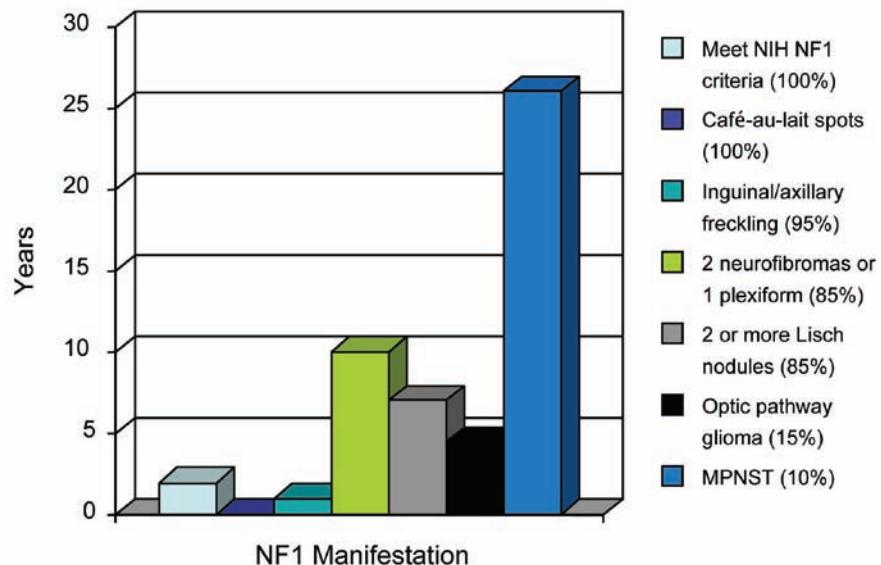


Fig. 13.05 Mean ages of onset for common clinical manifestations in patients with NF1. Estimated frequencies for each manifestation within the NF1 population are given in parentheses.

from NF1 patients [2291]. Genotype-phenotype correlations are also complicated by the unusually high degree of variable expressivity (intrafamilial variability of expression) within NF1 families. Evidence favouring a role for modifying non-allelic genes has been provided by the correlation between clinical manifestations and the degree of relatedness of patients [2191].

Genetic alterations in NF1-associated tumours

Several observations in sporadic and NF1-associated tumours indicate that neurofibromin acts as a tumour suppressor. Either loss of heterozygosity (LOH) or the

presence of a mutation of the second allele has been demonstrated in neurofibromas, MPNSTs, optic gliomas, and other NF1-associated tumours [1286, 1619, 2290]. Only the subpopulation of Schwann cells in neurofibromas exhibited loss of the *NF1* gene [1135], supporting the hypothesis that Schwann cells are the progenitor cells of neurofibromas. Animal models suggest that a heterozygous state of *NF1* inactivation within adjacent non-neoplastic cells is critical to the formation of both neurofibromas and optic pathway gliomas [88, 2504]. MPNSTs contain many other genetic alterations during malignant progression from precursor lesions, such as plexiform

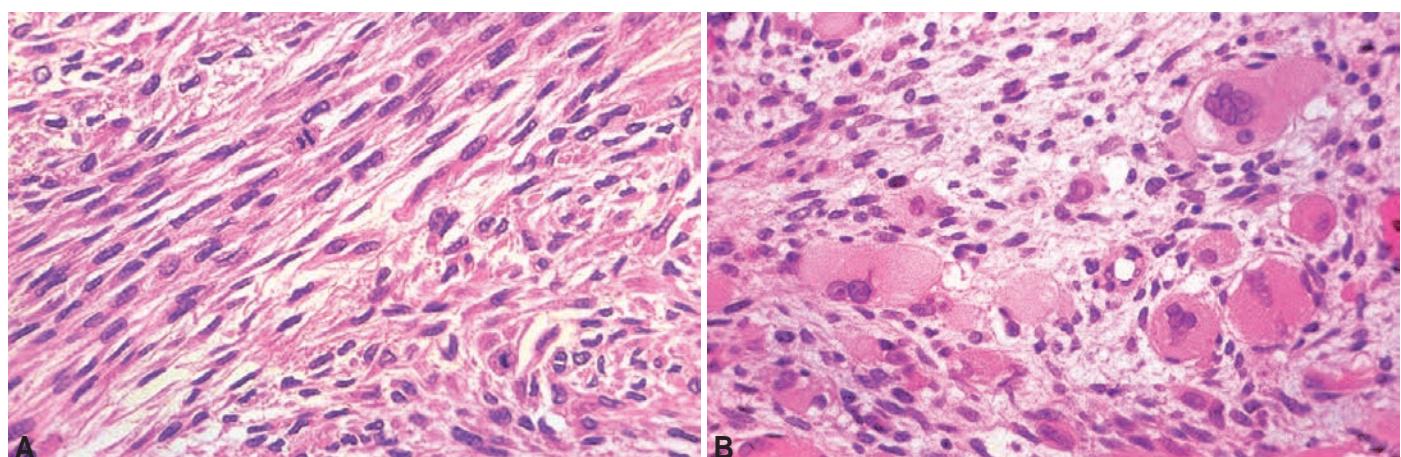


Fig. 13.06 Histological features of malignant Triton tumour. A Spindle cell component with brisk mitotic activity. B Rhabdomyosarcomatous component.

neurofibroma; commonly reported ones include *TP53* mutation, *CDKN2A* or 9p21 losses, p27 loss, EGFR protein overexpression and occasional gene amplification, topoisomerase II- α (TOP2A) overexpression, and dysregulation of numerous growth factors including neuregulin-1 and the ErbB receptors, as well as hepatocyte growth factor and the c-met receptor [290, 1180, 1591, 1728, 2107]. Karyotypes are often remarkably complex, and there are multiple regions of recurring chromosomal gains and losses for which the target genes are unknown.

NF1 variants

Variants of NF1 that do not co-segregate with the *NF1* gene locus are known [1167, 2450]. Even the autosomal dominant 'café-au-lait-spots only' variant exists as both *NF1*-gene-linked and unlinked entities [3, 234]. Similarly, patients who meet diagnostic criteria for both NF1 and NF2 have occasionally been described, although the vast majority qualify as one or the other and the existence of a 'mixed' form remains controversial. The

occurrence of a segmental form of NF1, caused by somatic mosaicism at the *NF1* gene locus, further extends the range of variability [1334, 1955]. Such patients often have only pigmentary manifestations within the affected limb or region; however, others develop classic tumours, such as plexiform neurofibromas, optic pathway gliomas, etc. Although some cell lines derived from malignant peripheral nerve sheath tumours respond to neurofibromin deficiency by dramatically increased levels of RasGTP, their tumourigenicity may depend at least as much on the inactivation of the *TP53* gene as on the loss of function of *NF1* [1456]. The generation of mice deficient in neurofibromin [213, 945] has aided the identification of potential cell-type specific functions of neurofibromin. Loss of the murine *NF1* gene product results in lethality at day 13.5 of embryogenesis due to abnormal cardiac development, a phenotype that has been linked to abnormal regulation of Ras activity [1251]. Mice heterozygous for the *Nf1* knockout allele develop rare tumours

associated with human NF1 [945] and display learning and memory defects [2099]. Loss of heterozygosity at the *NF1* locus can be demonstrated in the observed tumours [945], indicating that the condition in heterozygous mice is similar to the human disease. Schwann cells derived from neurofibromin-deficient embryos are angiogenic, highly invasive and hyperproliferative [1106]. Neurofibromin-deficient sensory neurons survive in the absence of neurotrophins via activation of a Ras-dependent pathway [1131]. Additionally, loss of neurofibromin in fetal liver cells renders the cells hypersensitive to the proliferative effects of multiple haematopoietic cytokines through constitutive activation of Ras signalling [2496]. Several instances in which biological responses to neurofibromin deficiency or overexpression are not accompanied by changes in the level of RasGTP suggest that neurofibromin may have additional functions that are independent of its RasGAP activity, and which may or may not depend on its interaction with the Ras proteins.

Neurofibromatosis type 2

A.O. Stemmer-Rachamimov
O.D. Wiestler
D.N. Louis

Definition

An autosomal dominant disorder characterized by neoplastic and dysplastic lesions that primarily affect the nervous system; bilateral vestibular schwannomas are the hallmark, with other manifestations, including schwannomas of other cranial nerves, spinal and cutaneous schwannomas, intracranial and spinal meningiomas, gliomas, meningioangiomatosis, glial hamartomas, ocular abnormalities and neuropathies, caused by mutations of the *NF2* gene on chromosome 22q12.

MIM No. 101000 {1433}.

Synonyms

Historical terms include central neurofibromatosis and bilateral acoustic neurofibromatosis. The term “von Recklinghausen neurofibromatosis” is associated with NF1 and should not be used for neurofibromatosis type 2 (NF2).

Incidence

The incidence of the disease has been reported as 1 per 40 000 newborns, however recent data suggest that may be an underestimate, and the disorder may be more common (1:25 000) {543}. About half of all cases occur in individuals with

Table 13.03 Diagnostic criteria for NF2.

Definite NF2

1. Bilateral vestibular schwannomas; or
2. First-degree family relative with NF2 and either
 - a) Unilateral vestibular schwannoma at <30 years; or
 - b) Any two of the following: meningioma, schwannoma, glioma, posterior subcapsular lens opacity.

Probable NF2

1. Unilateral vestibular schwannoma at <30 years and at least one of the following: meningioma, schwannoma, glioma, posterior subcapsular lens opacity; or
2. Multiple meningiomas and either
 - a) Unilateral vestibular schwannoma at <30 years; or
 - b) One of the following: schwannoma, glioma, posterior lens opacity.

no family history of NF2, and are caused by newly acquired germline mutations.

Diagnostic criteria

The original clinical diagnostic criteria for NF2 (NIH meeting in 1987 {2165}) underwent several revisions. The revised classifications expanded the criteria aiming to identify patients with multiple NF2 features that do not present with bilateral vestibular schwannomas and have no family history of NF2 (NIH Consensus Panel 1991, Manchester criteria, NNFF criteria) {540, 739}.

Nervous system neoplasms

Schwannoma

NF2-associated schwannomas are WHO grade I tumours that are comprised of neoplastic Schwann cells, but which differ from sporadic schwannomas in a number of ways. NF2 schwannomas present at an earlier age (third decade) than sporadic tumours (sixth decade), and many NF2 patients develop the diagnostic hallmark of the disease, bilateral vestibular schwannomas, by their fourth decade of life {540, 1410}. NF2 vestibular schwannomas may entrap seventh cranial nerve fibres {942} and have higher proliferative activity {55}, although these features do not necessarily connote more aggressive behaviour. In addition to the vestibular



Fig. 13.07 Bilateral vestibular schwannomas, diagnostic for NF2.

division of the eighth cranial nerve, other sensory nerves may be affected, including the fifth cranial nerve and spinal dorsal roots. However, motor nerves such as the twelfth cranial nerve may also be involved {540, 1352}. Cutaneous schwannomas are common and may be plexiform {540, 1410}. NF2 schwannomas may appear multilobular (“cluster of grapes”) on both gross and microscopic examination {2403}, and multiple schwannomatous tumourlets may develop along individual nerves, particularly on spinal roots {1352, 2151}.

Meningioma

Multiple meningiomas are the second hallmark of NF2 and occur in half of NF2 patients {1352}. NF2 meningiomas occur earlier in life than sporadic meningiomas

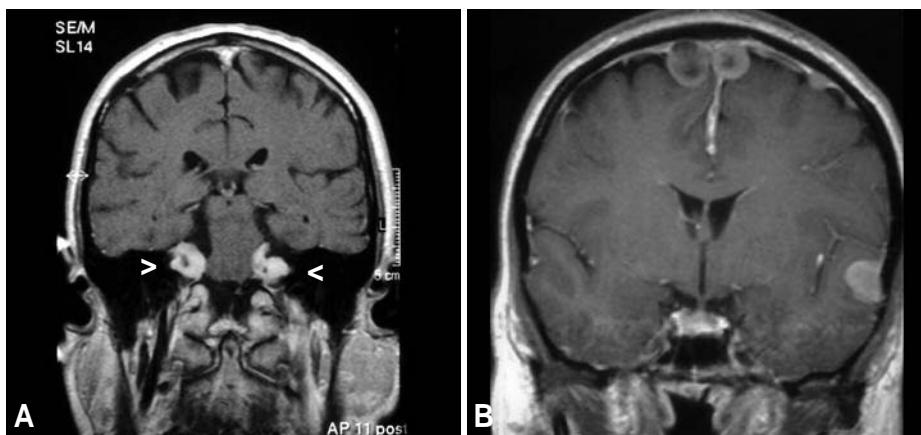


Fig. 13.08 T1-weighted, contrast-enhanced MR images from patients with NF2. A Bilateral acoustic schwannomas (arrows), the diagnostic hallmark of NF2. B Multiple meningiomas presenting as contrast-enhanced masses.

and may be the presenting feature of NF2, especially in the paediatric population [538, 540, 1410]. Although most of NF2-associated meningiomas are usually WHO grade I tumours, several studies suggest that NF2-associated meningiomas have a higher mitotic index and a more aggressive clinical behaviour than sporadic meningiomas [54, 1724]. All major subtypes of meningioma occur in NF2 patients [54, 1352].

Glioma

Approximately 80% of gliomas in NF2 patients are spinal intramedullary or cauda equina tumours, with an additional 10% of gliomas occurring in the medulla [1904]. Ependymomas account for approximately 65–75% of all histologically diagnosed gliomas in NF2, and for almost all spinal gliomas [1904, 1959]. In most cases, NF2 spinal ependymomas are multiple intramedullary masses [1904, 1959]. Diffuse and pilocytic astrocytomas also occur in NF2, but are less common.

Neurofibroma

Cutaneous neurofibromas have been reported in NF2. On histological review, however, many ‘neurofibromas’ prove to be schwannomas, including plexiform schwannomas misdiagnosed as plexiform neurofibromas.

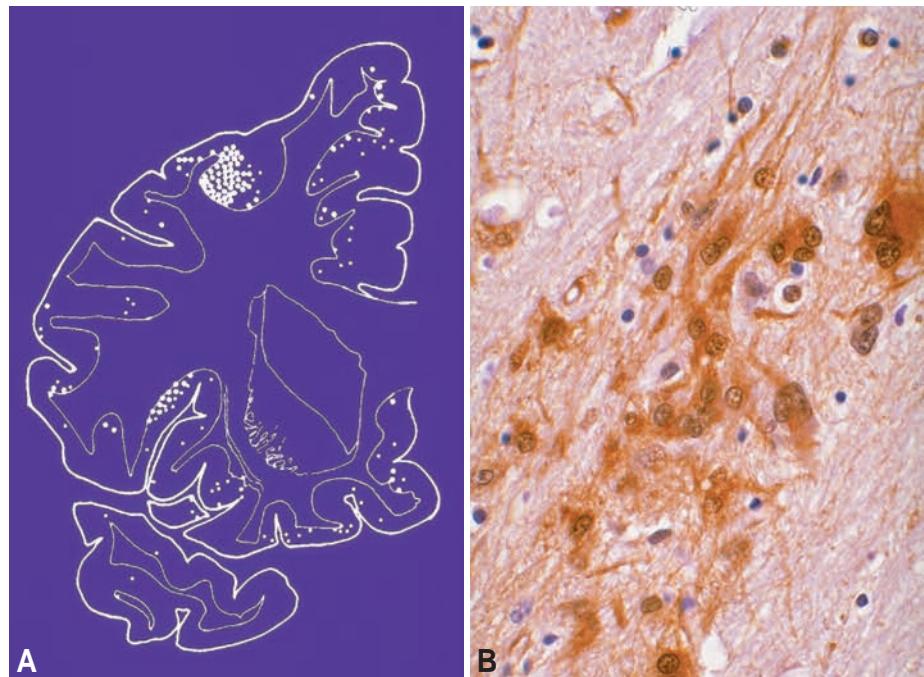


Fig. 13.09 A and B Distribution of cerebral microhamartomas in a patient with NF2. These lesions are scattered throughout the cortex and basal ganglia and show strong immunoreactivity for S-100 (B). Reproduced from Wiestler *et al.* [2410].

Other nervous system lesions

Schwannosis This is a proliferation of Schwann cells, sometimes with entangled axons, but without frank tumour formation. In NF2 patients, schwannosis is often found in the spinal dorsal root entry zones,

sometimes associated with a schwannoma of the dorsal root, or in the perivascular spaces of the central spinal cord, where the nodules appear more like small traumatic neuromas [1949, 1959]. Less robust, but otherwise identical, schwannosis has been reported in reactive conditions.

Meningioangiomatosis This cortical lesion is characterized by a plaque-like proliferation of meningothelial and fibroblast-like cells surrounding small vessels, and occurs both sporadically and in NF2. Meningioangiomatosis is usually a single, intracortical lesion, although multifocal examples occur as do non-cortical lesions [1949, 1959]. It may be predominantly vascular, resembling a vascular malformation, or predominantly meningothelial, sometimes with an associated meningioma. Sporadic meningioangiomatosis is a single lesion that usually occurs in young adults or children who present with seizures or persistent headaches. In contrast, NF2-associated meningioangiomatosis may be multifocal and is often asymptomatic and diagnosed only at autopsy [2150].

Glial hamartia Glial hamartias (or microhamartomas) of the cerebral cortex are circumscribed clusters of cells with medium-to-large atypical nuclei and



Fig. 13.10 Numerous schwannomas of the cauda equina in a patient with NF2.

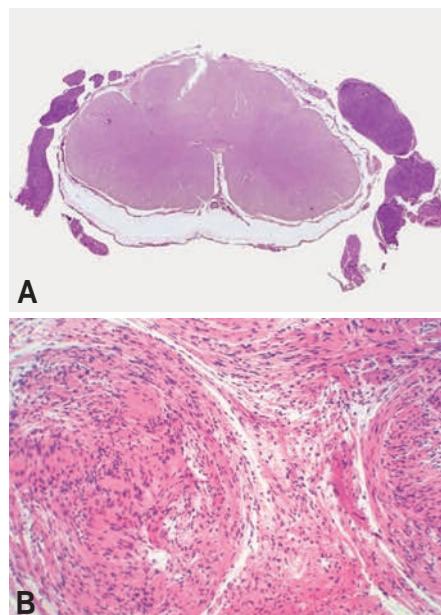


Fig. 13.11 A Multiple schwannomas of spinal roots. The histology (B) shows a nodular schwannoma in NF2 patient.

Table 13.04 Major manifestations of NF2

Schwann cell lesions:	
Schwannomas (including bilateral vestibular)	
Schwannosis	
Meningeal lesions:	
Meningiomas	
Meningioangiomatosis	
Glial lesions:	
Spinal ependymomas	
Astrocytomas	
Glial hamartias	
Other lesions:	
Posterior lens opacities	
Cerebral calcifications	

scant, sometimes stellar, eosinophilic cytoplasm. The cells stain strongly for S-100 protein, but only focally for GFAP. Glial hamartias are common in and pathognomonic of NF2 [1949, 2410], and are not associated with mental retardation or astrocytomas. The hamartias are usually intracortical, with a predilection for the molecular and deeper cortical layers, but have also been observed in the basal ganglia, thalamus and cerebellum [2410]. Merlin expression is retained in glial hamartias, raising the possibility that haplo-insufficiency during development underlies these malformations [2149].

Cerebral calcification Intracranial calcifications have been noted frequently in neuroimaging studies of patients with NF2. Preferred localizations are the cerebral and cerebellar cortices, periventricular areas and choroid plexus. The histopathological correlates remain unclear.

Peripheral neuropathy Peripheral neuropathies, not related to tumour masses, are increasingly recognized as a common

feature of NF2 [385, 1352, 3525]. Mono-neuropathies may be the presenting symptom in children [538], while progressive polyneuropathies are more common in adults. Sural nerve biopsies from NF2 patients suggest that NF2 neuropathies are mostly axonal and may be secondary to focal nerve compression by tumourlets or onion-bulb-like Schwann cell or perineurial cell proliferations without associated axons [2133, 2242].

Extraneuronal manifestations

Posterior lens opacities are common and highly characteristic of NF2. A variety of retinal abnormalities (including hamartomas, tufts and dysplasias) may also be found [314]. Skin lesions other than cutaneous nerve sheath tumours, primarily café-au-lait spots, have been reported.

Genetics

The *NF2* gene is located at chromosome 22q12 [1941, 2266].

Gene structure

The *NF2* gene [1941, 2266] spans 110 kb, and comprises 17 exons. *NF2* mRNA transcripts encode at least two major protein forms generated by alternative splicing at the carboxyl terminus. Isoform 1, encoded by exons 1-15 and 17, has intramolecular interactions similar to the ERM proteins (see below); isoform 2, encoded by exons 1-16, exists only in an unfolded state [737, 2453].

Gene expression

The *NF2* gene is expressed in most normal human tissues studied, including brain [1941, 2266]. The predicted protein product shows a strong similarity with the highly conserved protein 4.1 family of cytoskeleton-associated proteins, which includes protein 4.1, talin, moesin, ezrin, radixin and protein tyrosine phosphatases.

The similarity of the NF2-encoded protein to moesin, ezrin and radixin (ERM), resulted in the name merlin [2266]; the alternative name schwannomin has also been suggested [1941]. Members of the protein 4.1 family link the cell membrane to the actin cytoskeleton. These proteins consist of a globular amino terminal domain, an α -helical domain containing a praline rich region, and a charged carboxyl terminal domain. The amino terminus interacts with cell membrane proteins such as CD44, CD43, ICAM-1 and ICAM-2, while the carboxy terminal domain contains the actin binding site. The highest degree of structural similarity between merlin and the ERM proteins is in the amino terminal domain. Merlin lacks the actin binding site in the carboxy terminus but may have an alternative actin binding site [2453]. ERM proteins and merlin may be self-regulated by head-to-tail intramolecular associations which result in folded and unfolded states. The folded state of merlin is the functionally active molecule and is inhibited by phosphorylation of the COOH-terminal on serine residues [2075]. Although the precise mechanism of tumour suppression by merlin is still unknown, the structural similarity of merlin to the ERM protein suggests that merlin provides regulated linkage between membrane-associated proteins and the actin cytoskeleton; the tumour suppressor activity may be exerted by regulation of signal transmission from the extracellular environment to the cell [1427]. Many merlin binding partners have been identified [1117, 1539].

Gene mutations

Numerous germline and somatic *NF2* mutations have been detected, supporting the hypothesis that *NF2* functions as a tumour suppressor gene [736, 1352].

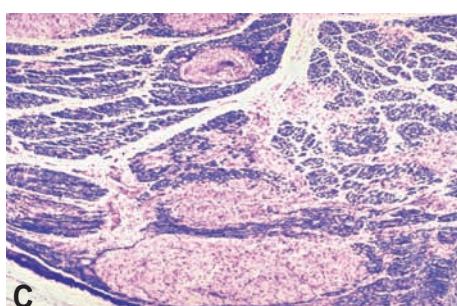
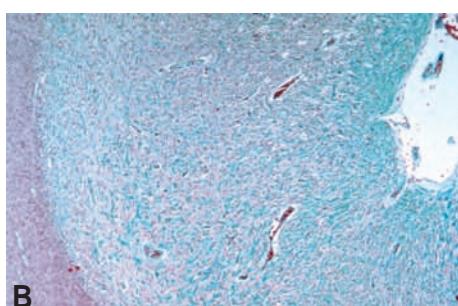
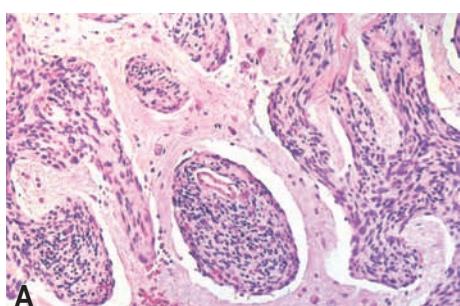


Fig. 13.12 Histological features of lesions associated with NF2. A Meningioangioma with predominance of meningothelial cells. B Diffuse cortical meningoangioma (trichrome stain). C Luxol fast blue staining of a section of the cauda equina with multiple early stages of schwannomas (tumourlets) and characteristic absence of myelin.

Germline *NF2* mutations differ somewhat from somatic mutations identified in sporadic schwannomas (see Chapter 9) and meningiomas (see Chapter 10). The most frequent germline mutations are point mutations that alter splice junctions or create new stop codons {207, 1352, 1367, 1460, 1941, 1970, 2266}. While germline mutations are found in all parts of the gene, with the exception of the alternatively spliced exons, they occur preferentially in exons 1 to 8 {1460}. A possible hot spot for mutations appears to be position 169 in exon 2, in which a C to T transition at a CpG dinucleotide results in a stop at codon 57 {207, 1460}; other CpG dinucleotides are also commonly targets for C to T transitions {1970}.

Prognostic and predictive factors

The clinical course in patients with *NF2* varies widely between families and, to a lesser extent, within families {540, 1410}. Some families feature early onset with diverse tumours and high tumour load (Wishart type), while others present later with only vestibular schwannomas (Gardner type). An effect of maternal inheritance on severity has been noted, as have families with genetic anticipation. All families with *NF2* show linkage of the disease to chromosome 22 {1570}, implying a single responsible gene, and correlations of genotype with phenotype have therefore attempted to predict clinical course on the basis of the type of the underlying *NF2* mutation. Nonsense

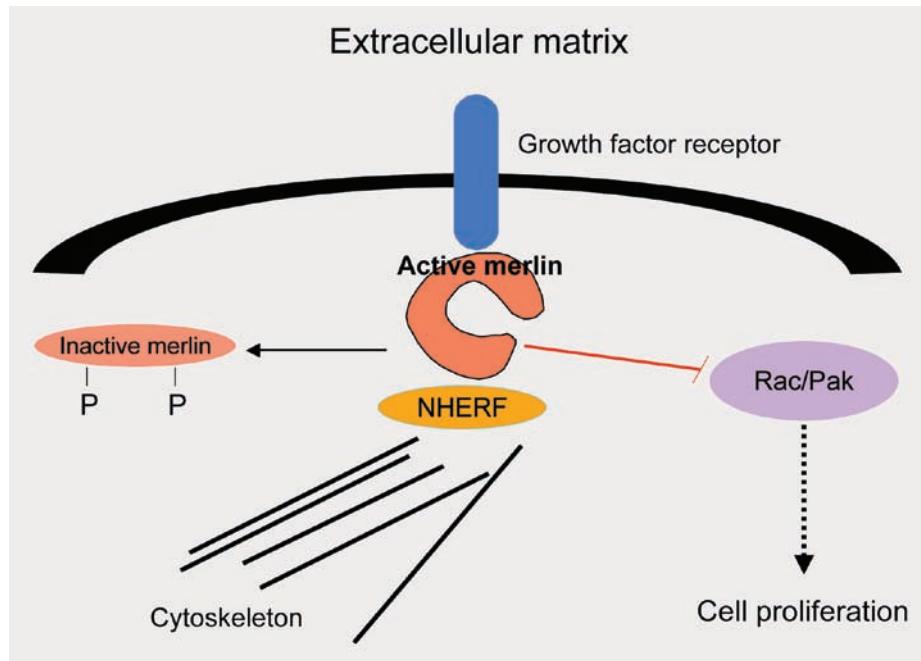


Fig. 13.13 In its active (hypophosphorylated) state merlin suppresses cell proliferation and motility by inhibiting the transmission of growth signals from the extracellular environment to the Pak/Rac signaling system. Inactivated (phosphorylated) merlin dissociates from its protein scaffold thus disinhibiting Rac/Pak signaling and cell proliferation and motility.

and frameshift mutations are often associated with a more severe phenotype, regardless of their position in the gene, while missense mutations that preserve the carboxyl terminus of the protein result in milder phenotypes {1460}. Phenotypic variability is observed in splice site mutations, with more severe phenotypes observed in mutations upstream from exon 7 {1137}. Large deletions and somatic mosaicism have been associated with mild disease {111, 544, 1138}. Clinical predictors associated with increased risk of mortality in *NF2* patients include early age at diagnosis, presence of intracranial meningiomas and treatment at non-specialty centres {110}.

MIM No.

162091.

Synonyms

Terms used to describe the disorder include "neurilemmatosis", "multiple schwannomas" and "multiple neurilemmomas".

Incidence

In several reports, schwannomatosis was found to be almost as common as neurofibromatosis type 2, with an estimated incidence 1:40 000 -1:80 000 {56, 2050}. Familial schwannomatosis is rare; representing only 10–15% of all cases {1369, 2050}.

Diagnostic criteria

Reports of patients with multiple non-vestibular schwannomas date back to 1984 {2090}, but it was long debated whether the condition represents a form of attenuated *NF2* or a separate entity. A consensus panel of experts has recently developed standardized clinical diagnostic criteria for schwannomatosis {1366}. Essential for the diagnosis of schwannomatosis is the exclusion of *NF2* by clinical criteria and by imaging of the vestibular nerves. The distinction may be particularly challenging in paediatric patients, as vestibular schwannomas may

Table 13.05 Diagnostic criteria for schwannomatosis

Definite schwannomatosis	
- Two or more (pathologically proven) schwannomas and lack of vestibular schwannomas on MRI study at >30 years and no known constitutional <i>NF2</i> mutation; or	
- One (pathologically proven) schwannoma and first degree relative with schwannomatosis.	
Probable schwannomatosis	
- Two or more schwannomas and age under 30 years and no evidence of vestibular schwannomas on MRI scan and no known constitutional <i>NF2</i> mutation; or	
- Two or more schwannomas and age over 45 years and no symptoms of cranial nerve VIII dysfunction and no known constitutional <i>NF2</i> mutation; or	
- Radiographic evidence of one schwannoma and first-degree relative with schwannomatosis.	

Schwannomatosis

Definition

A usually sporadic and sometimes autosomal dominant disorder characterized by multiple spinal, cutaneous and cranial nerve schwannomas, without vestibular schwannomas or other manifestations of neurofibromatosis type 2 (*NF2*) or neurofibromatosis 1 (*NF1*); associated with inactivation of the *NF2* gene in tumours but not in the germline.

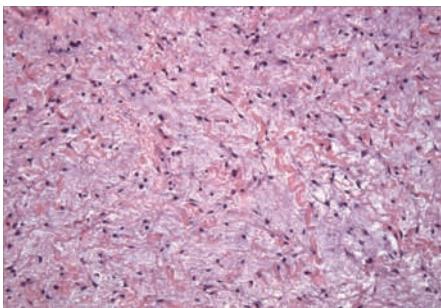


Fig. 13.14 Histopathological features of schwannomas in a schwannomatosis patient. Note a marked myxoid stroma.

develop only later in the course of the disease {542}.

Nervous system neoplasms

Schwannomas

Schwannomatosis patients develop multiple schwannomas. These tumours may develop in spinal roots, cranial nerves and in skin, but not in the vestibular nerves. Cutaneous schwannomas may be plexiform. The tumours have a segmental distribution in 30% of schwannomatosis patients {1066, 1298}. In contrast to NF2 patients, patients with schwannomatosis

often suffer from severe pain from their tumours, whereas neurological deficits and polyneuropathy are rare {1366}. Schwannomatosis tumours may display prominent myxoid stroma and an intra-neuronal growth pattern {1366} and are sometimes misdiagnosed as neurofibromas {542, 1366}.

Other nervous system lesions

There is no association of schwannomatosis with ependymomas or ocular abnormalities, but a rare association with single or multiple meningiomas has been reported {920, 1618, 1918}.

Extraneuronal manifestations

There are no extraneuronal manifestation associated with schwannomatosis.

Genetics

NF2 mutations are found in schwannomatosis-associated schwannomas, but are not found in non-tumour tissue, suggesting that *NF2* mutations are somatic rather than germline. In addition, several studies have excluded germline *NF2* mutations in familial schwannomatosis; analysis of multiple tumours from affected individuals showed no shared *NF2* mutations within the tumours or within families precluding an underlying *NF2* germline mutation {948, 1066, 1368}. This suggests that schwannomatosis is caused by another gene, which remains unknown. Linkage analysis studies suggest that the gene resides on chromosome 22 {1368}.



Fig. 13.15 Coronal MRI (STIR) showing multiple, bright, discrete tumours in a schwannomatosis patient.

Von Hippel-Lindau disease and haemangioblastoma

K.H. Plate
A.O. Vortmeyer
D. Zagzag
H.P.H. Neumann

Definition

Von Hippel-Lindau is an autosomal dominant disorder caused by germline mutations of the *VHL* gene on chromosome 3p25–26 and characterized by the development of haemangioblastomas of the nervous system and retina, clear cell renal carcinoma, phaeochromocytoma, epididymal cystadenoma, neuroendocrine tumours and microcystic adenomas of the pancreas and endolymphatic sac tumours.

MIM No. 193300 {1433}.

Synonyms and historical annotation

Lindau {1324} described capillary haemangioblastoma, and also noted its association with retinal vascular tumours, previously described by von Hippel {2343}, and tumours of the visceral organs.

Incidence

Von Hippel-Lindau (VHL) disease is estimated to occur at rates of 1:36 000 {1380} to 1:45 500 population {1375}.

Diagnostic criteria

The clinical diagnosis of VHL disease is based on the presence of capillary haemangioblastoma in the CNS or retina, and the presence of one of the typical VHL-associated tumours, or a previous family history. In VHL disease, germline *VHL* mutations can virtually always be identified {2155}.

Haemangioblastoma

VHL-associated tumours typically occur in young adults, with a mean age of 29 {1382}. Sporadic haemangioblastomas occur predominantly in the cerebellum, whereas VHL-associated haemangioblastomas are localized in the cerebellum, brain stem and spinal cord and nerve roots. Supratentorial and peripheral nervous system lesions are rare. VHL patients often have multiple haemangioblastomas at various sites; multiple tumours are almost exclusively found in VHL patients (See Chapter 10).

Histogenesis

Haemangioblastomas are composed of vascular and stromal cells. Tissue microdissection, combined with deletion analysis of the *VHL* gene locus, have identified the stromal cells as neoplastic {1277}, but their origin remains enigmatic. Suggested origins include glial cells {45}, endothelial cells {1020}, arachnoid cells {1501}, embryonic choroid plexus {176}, neuroendocrine cells {123}, fibrohistiocytic cells {1579}, cells of neuroectodermal derivation {12, 918, 1086, 2214} or heterogeneous cell populations {2214}. To address this issue, numerous immunohistochemical and ultrastructural studies have been performed. For example, neural cell adhesion molecule (NCAM/CD56) is consistently immunoreactive {190, 192} and there is frequent positive immunoreactivity for S-100 protein {886, 1245, 1579, 1644, 2214}. Factors VIII and XIIIa have been reported in stromal cells {1020, 1035, 1245, 1644}, but some studies have found these molecules

exclusively in the vascular component {397, 2214}. GFAP staining of stromal cells has been found only in some reports {923, 963}, and it is unclear whether scattered GFAP-positive cells represent entrapped reactive astrocytes {397, 445, 1579}, stromal cells with glial differentiation {397, 445, 923, 1086} or stromal cells with intracytoplasmic GFAP from phagocytic activity {445, 1020}. Some ultrastructural studies have found overlapping features between stromal and vascular cells {282, 323, 791, 843, 985, 1020, 1069}, including Weibel-Palade body formation in the cytoplasm of the stromal cells {1245, 2132}, raising the possibility that stromal cells may differentiate into vascular components, but other electron microscopic reports found distinct stromal and vascular cellular constituents {123, 191, 1579, 2214}. In this regard, an intriguing hypothesis is, as originally suggested by Lindau in 1931 {1325}, that these tumours are derived from embryonal cell types with divergent

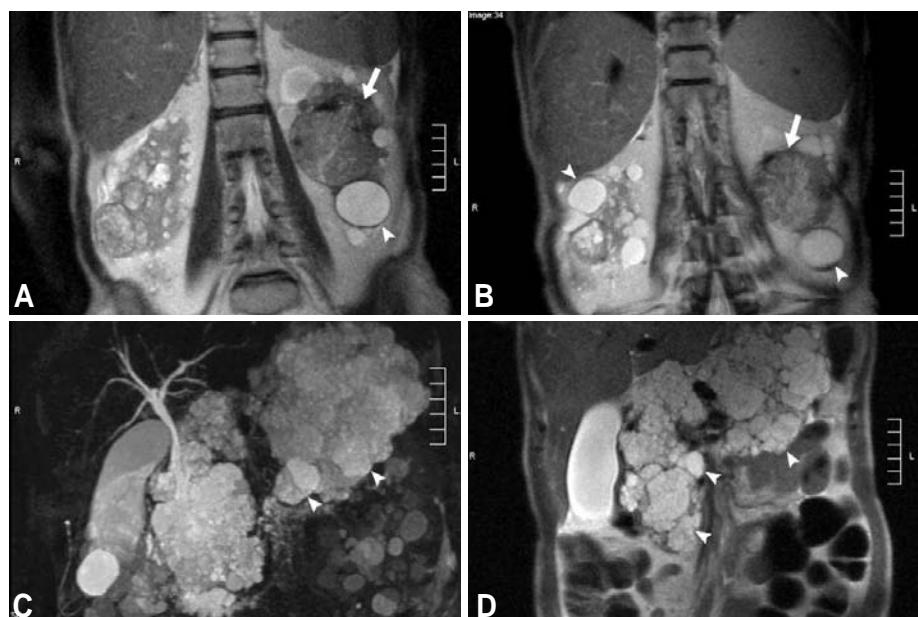


Fig. 13.16 Abdominal MRI in a patient with VHL disease. A,B Numerous renal cystic structures (arrowheads) and a solid renal mass (arrows). Coronal T2-weighted MRI images. C,D Numerous pancreatic cysts (arrowheads). Coronal T2-weighted MRI images.

Table 13.06 Extracranial manifestations of VHL disease.

Organ	Lesion
Retina	Haemangioblastoma
Peripheral nerve	Haemangioblastoma
Kidney	Cysts Renal cell carcinoma
Pancreas	Cysts Microcystic adenoma Neuroendocrine tumours
Adrenal gland/paraganglia	Phaeochromocytoma/paraganglioma
Endolymphatic sac/duct	Endolymphatic sac tumour
Epididymis	Epididymal cystadenoma
Adnexae	Cystadenoma
Other organs	Cysts

differentiation potentials. For example, one ultrastructural study {323} found features characteristic of embryonic cells and concluded that stromal cells and vasoformative elements share a common ancestry, possibly of angioblastic lineage. Decades ago, Stein *et al.* {2148} had suggested an angiomesenchymal origin of haemangioblastoma, based on original, developmental biologic observations made by Florence Sabin in 1917 {1967}. Haemangioblastomas appear capable of blood island formation with potential extramedullary haematopoiesis analogous to embryonic haemangioblastic stem cells {1943, 2148, 2347, 2488}. Furthermore, haemangioblastomas express the erythropoietin-receptor (EpoR) {2347}, which is also observed during early embryonic blood island formation at mouse embryonic day 8.0–9.5 {1279}; in addition, stromal cells express some proteins that characterize embryonic progenitor cells with haemangioblastic differentiation potential (Scl, brachyury, Csf-1R, Gata-1, Flk-1 and Tie-2) {696}. Furthermore, tumour growth occurs from highly vascularized, VHL-deficient, poorly differentiated precursor structures {2349, 2350}. Therefore, embryonic progenitor cells with haemangioblastic differentiation potential represent a likely cytologic equivalent of the stromal cell. However, the capacity of neuroectodermal cells to differentiate along a haematopoietic

lineage remains to be more convincingly demonstrated.

Extraneuronal manifestations

A variety of neoplasms are known to occur in patients with VHL disease. A common tumour is the retinal von Hippel tumour or angioma, which is histologically identical to capillary haemangioblastoma {1592, 2381}. Many of the other tumours and tumour-like lesions associated with VHL are concentrated in the visceral organs. Of the visceral tumours, clear cell renal carcinomas and phaeochromocytomas are most common {1254, 1328, 1381}. The endolymphatic sac tumour of the inner ear is a hypervascular neoplasm that arises from the temporal petrous region {342, 994, 1381}. Pancreatic involvement with VHL disease includes true cysts, serous cystadenomas, neuroendocrine tumours, or combined lesions {763}. Cystadenomas of the broad ligament are extremely rare {2395}.

Genetics

The *VHL* gene is located at chromosome 3p25-26 {1266}. The *VHL* tumour suppressor gene has three exons and a coding sequence of 639 nucleotides {1266}. It is expressed ubiquitously including in the CNS {382, 1548, 1973}.

Function of the *VHL* protein

Mutational inactivation of the *VHL* gene in affected family members is responsible for their genetic susceptibility to capillary haemangioblastoma of the CNS including the retina, renal clear cell carcinoma, phaeochromocytoma, pancreatic islet

cell tumour and endolymphatic sac tumour of the inner ear. The mechanisms by which the gene product, the *VHL* protein (pVHL), causes neoplastic transformation, has remained enigmatic. Several signalling pathways appear to be involved {1628}, one of which points a role of pVHL in protein degradation and angiogenesis. The α domain of pVHL forms a complex with elongin B, elongin C, Cul-2 {1343, 1706, 2144} and Rbx1 {1036} which has ubiquitin ligase activity {935}, thereby targeting cellular proteins for ubiquitination and proteasome-mediated degradation. The domain of the *VHL* gene involved in the binding to elongin is frequently mutated in VHL-associated neoplasms {2144}.

The β -domain of pVHL interacts with the α subunits of transcription factor, hypoxia-inducible Factor (HIF), which mediates cellular responses to hypoxia. Under normoxic conditions and in the presence of functional pVHL, the α subunits are rapidly degraded. Under hypoxic conditions and in VHL deficient cells, HIF α is stabilised, with a concomitant induction of hypoxia-regulated genes, including vascular endothelial growth factor (VEGF) {1421}. Constitutive overexpression of VEGF through this signalling pathway could explain the extraordinary capillary component of VHL-associated neoplasms {1421}. The capillaries of CNS haemangioblastomas are believed to be under the control of overexpressed VEGF and related angiogenic factors, which are secreted by stromal cells and are considered non-neoplastic.

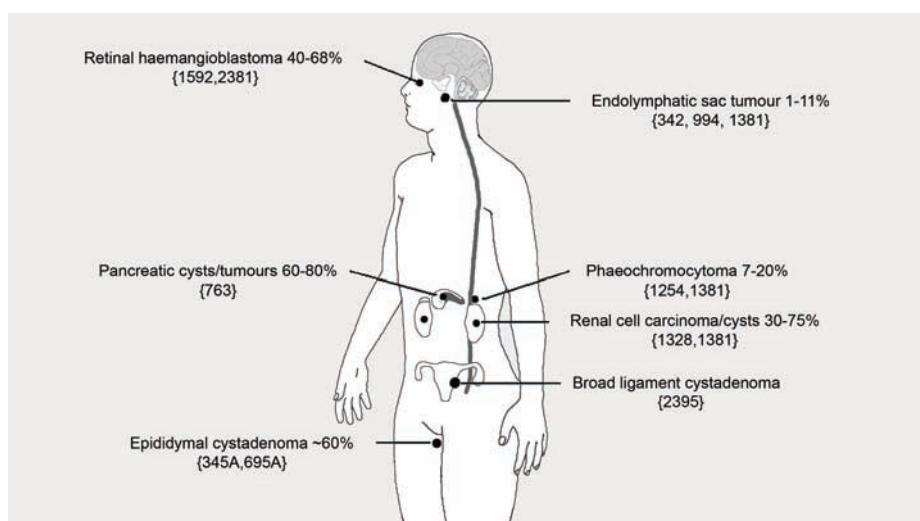


Fig. 13.17 Extraneuronal manifestations of VHL disease.

Additional functions of the VHL protein may contribute to malignant transformation and the evolution of the phenotype of VHL-associated lesions. Some of these may or may not be mediated by HIF. Studies in renal cell carcinoma cell lines suggest that pVHL is involved in the control of cell cycle exit, i.e. transition from the G2 phase, possibly by preventing accumulation of the cyclin-dependent kinase inhibitor p27 {1705}. Wild-type but not tumour-derived pVHL binds to fibronectin. As a consequence, VHL-deficient renal cell carcinoma cells show a defective assembly of extracellular fibronectin matrix {1629}. Through down-regulation of the response of cells to hepatocyte growth factor/scatter factor and reduced levels of tissue inhibitor of metalloproteinase 2 (TIMP-2), pVHL-deficient tumour cells exhibit a significantly higher capacity for invasion {1164}. Further, inactivated pVHL causes an overexpression of transmembrane carbonic anhydrases that are involved in pH regulation {932} but the biological significance of this dysregulation remains to be assessed.

Based on the discovery of VHL-deficient immature cell deposits in target tissues {2349, 2350}, the capacity of stromal cells to differentiate into red blood cells {2347}, and common protein expression profiles between stromal cells and embryonic progenitor cells with haemangioblastic differentiation potential (Scl, brachyury, Csf-1R, Gata-1, Flk-1, Tie-2) {696}, developmental effects of loss of VHL function have been suggested.

Gene mutations and VHL subtypes

Germline mutations of the *VHL* gene are spread throughout the three exons. Missense mutations are most common, but nonsense mutations, microdeletions/

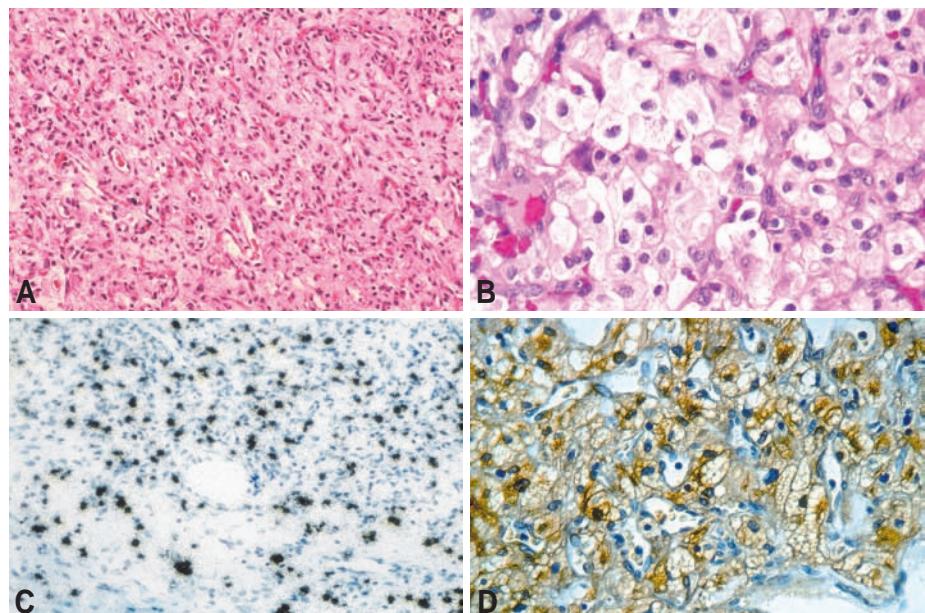


Fig.13.18 Histopathological features of haemangioblastomas. A Cellular variant showing many stromal cells. B Cellular variant showing densely packed tumour cells. C *In situ* hybridization showing expression of VEGF mRNA in stromal cells. D Immunostaining for VHL protein in stromal but not endothelial cells.

insertions, splice site mutations and large deletions also occur {1581, 1641, 2487}. The spectrum of clinical manifestations of VHL reflects the type of germline mutation displaying a more or less tight genotype-phenotype correlation. The clinical classification is based on the manifestation of phaeochromocytoma {1346}. Phaeochromocytoma is very rarely found in VHL type 1, whereas this tumour type is the prominent feature in VHL type 2. VHL type 2 is subdivided into type 2A, if both renal cell carcinoma and phaeochromocytoma are present in a given family, and type 2B, if renal cancer is absent or very rare. VHL type 2C has been established for patients who carry a VHL germline mutation but where only phaeochromocytomas occur {71, 325,

698,1582}. VHL types 2B and 2C are usually associated with missense mutations. *VHL* gene mutations are also common in sporadic haemangioblastomas and renal cell carcinomas {1040, 1612}.

Prognostic and predictive factors

While the morbidity and local tumour recurrence rates in sporadic haemangioblastoma are low, many patients with VHL ultimately develop multiple CNS haemangioblastomas. Thus, CNS involvement remains an important cause of morbidity and mortality for VHL patients {1381} in which CNS haemangioblastoma and renal cell carcinoma are the major causes of death {1381, 1872}. The average life expectancy of VHL patients is 40–50 years {1051, 1582, 1592}. In order to detect VHL-associated haemangioblastomas, analysis for germline mutations of the *VHL* gene has been recommended in every patient with CNS haemangioblastoma, particularly those of younger age and with multiple lesions. Yearly lifetime screening of VHL patients by MRI should also start after the age of ten years. This should occur in conjunction with familial screening and counseling {693}.

Table 13.07 Correlation between different VHL phenotypes and *VHL* mutations.

VHL Type	Phenotype	Examples of mutations
Type 1	Predominantly without phaeochromocytoma	<i>VHL</i> 75 del Phe <i>VHL</i> Arg 161 Stop
Type 2	Predominantly with phaeochromocytoma but not with renal cell carcinoma	<i>VHL</i> Arg 161 Pro <i>VHL</i> Tyr 98 His
Type 2B	Predominantly with phaeochromocytoma and renal cell carcinoma	<i>VHL</i> Arg 167 Trp <i>VHL</i> Arg 167 Gln
Type 2C	Predominantly with only phaeochromocytoma	<i>VHL</i> Leu 188 Val

Tuberous sclerosis complex and subependymal giant cell astrocytoma

M.B.S. Lopes
O.D. Wiestler
A.O. Stemmer-Rachamimov
M.C. Sharma

Definition

A group of autosomal dominant disorders characterized by hamartomas and benign neoplastic lesions that affect the central nervous system as well as various non-neuronal tissues; major CNS manifestations include cortical hamartomas (tubers), subcortical glioneuronal hamartomas, subependymal glial nodules and subependymal giant cell astrocytomas; major extraneuronal manifestations include cutaneous angiofibromas ('adenoma sebaceum'), peau chagrin, subungual fibromas, cardiac rhabdomyomas, intestinal polyps, visceral cysts, pulmonary lymphangioleiomyomatosis and renal angiomyolipomas; caused by a mutation of the *TSC1* gene on 9q or the *TSC2* gene on 16p.

MIM No.

TSC1	191100.
TSC2	191092 {1433}.

Synonyms

Tuberous sclerosis; Bourneville disease; Bourneville-Pringle disease.

Incidence

Variability of clinical manifestations previously led to under diagnosis. Recent data indicate that the disorder affects as many as 25 000 to 40 000 individuals in the United States and about 1 to 2 million individuals worldwide, with an estimated prevalence of 1/6000 newborns.

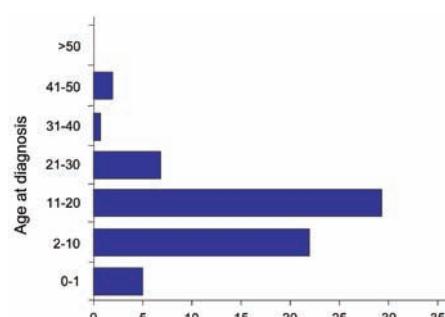


Fig. 13.19 Age distribution of subependymal giant cell astrocytoma (SEGA) at the time of clinical manifestation. Combined data for male and female patients.

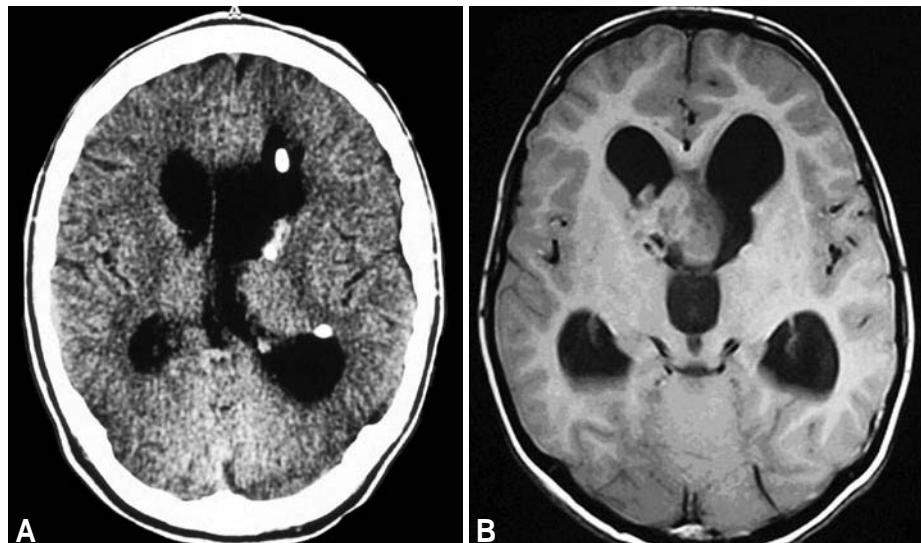


Fig. 13.20 A CT of typical subependymal calcifications in a patient with tuberous sclerosis. B A T1-weighted MRI showing mixed iso- and hypodense mass.

(http://www.ninds.nih.gov/disorders/tuberous_sclerosis/detail_tuberous_sclerosis.htm).

Diagnostic criteria

Diagnosis of tuberous sclerosis complex (TSC) is based on clinical features and may be challenging due to great variability of phenotypes. The diagnostic criteria for TSC were revised in 1998 at the Tuberous Sclerosis Consensus Conference [1894, 1895]. Clinical manifestations have been divided into major and minor features and the diagnostic categories defined as Definite, Probable and Suspect [1894]. Most patients have manifestations of TSC before the age of 10 years [20]. Confirmatory testing for *TSC1* and *TSC2* mutations may be helpful when a patient does not meet clinical criteria for definite diagnosis. Prenatal diagnosis by mutation analysis is possible when the mutation in other family members is known.

Clinical features

Neurological symptoms are the most frequent and serious manifestations. Initial signs in a majority of TSC patients tend to be epilepsy and autistic withdrawal

[20]. Mental retardation and behavioural abnormalities are usually present [706]. Infantile spasms represent another characteristic neurological manifestation in TSC.

Subependymal giant cell astrocytoma

Definition

Subependymal giant cell astrocytoma (SEGA) is a benign, slowly growing tumour typically arising in the wall of the lateral ventricles and composed of large ganglionoid astrocytes.

ICD-O code

9384/1

Grading

Subependymal giant cell astrocytoma corresponds to WHO grade I.

Incidence

Although it is debatable whether SEGA occurs outside TSC, it is the most common CNS neoplasm in TSC patients [20, 706, 2078]. Its incidence ranges from 6%–14% in patients with confirmed TSC [20, 1895, 2078], and SEGA is one of the major criteria for the diagnosis of TSC [902, 1894].

Age and sex distribution

This tumour typically occurs during the first two decades of life, although cases involving infants have been reported [1440]. A congenital case diagnosed by antenatal MRI at 24 weeks of gestation has been described [899].

Clinical features

Most patients show either a worsening of epilepsy or symptoms of increased intracranial pressure. Leptomeningeal dissemination with drop metastases has been described [2233]. Calcifications and signs of previous haemorrhage may also be present. Massive spontaneous haemorrhage has been observed. Some patients of SEGA develop manifestations of TSC in the follow-up period [2064].

Histopathology

Lesions are circumscribed, often calcified tumours composed mainly of large, plump cells resembling astrocytes. Clustering of tumour cells and perivascular pseudopalisading are common features. The tumour cells show a wide spectrum of astroglial phenotypes. Typical appearances

range from polygonal cells with abundant, glassy cytoplasm (resembling gemistocytic astrocytes) to smaller, more elongate elements within a variably fibrillated matrix. Giant pyramidal cells with a ganglionic appearance are common. The nuclei display a finely granular chromatin pattern with distinct nucleoli. Considerable nuclear pleomorphism and multinucleated cells are frequent. SEGA may demonstrate increased mitotic activity. However, these features do not appear to denote an adverse clinical course. Similarly, the occasional presence of endothelial proliferation and necrosis are not indicative of anaplastic progression. The rare examples of SEGA that recur have not been reported to show malignant transformation [2455]. Infiltration of mast cells and lymphocytes, predominantly T-lymphocytes, is a constant feature [2069].

Proliferation

Proliferative index as measured by Ki-67 (MIB-1) is generally low (mean, 1.5–7.4%), providing further support for the benign nature of these neoplasms [402, 536, 744, 1111, 2064]. Topoisomerase II labelling index is also reportedly low (mean, 2.9%) [2064]. Though extremely uncommon, craniospinal dissemination has been reported in SEGA with increased MIB-1 LI without malignant features [2233].

Immunohistochemistry

SEGA has been designated as a distinctive well-circumscribed astrocytoma, but due to its usually mixed glioneuronal phenotype, it has also been termed subependymal giant cell tumour [1261]. Tumour cells demonstrate variable immunoreactivity for GFAP and S-100 protein. Neurofilament proteins and neuronal-associated class III β -tubulin are also demonstrated [1347]. Class III β -tubulin appears more widespread in its distribution than any other neuronal epitope. Neurofilament is more restricted and mainly highlights cellular processes and a few ganglionic cells. Likewise, SEGA are rarely immunoreactive for synaptophysin in the ganglionic component [2069]. Variable immunoreactivity for neuropeptides has also been detected. These findings suggest cellular lineages with a variable capacity for divergent phenotypes, including glial, neuronal and neuroendocrine differentiation. Ultrastructural features of neuronal differentiation,

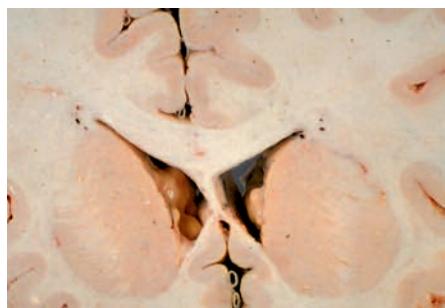


Fig. 13.21 Multiple small subependymal giant cell astrocytomas at the walls of the lateral ventricles.

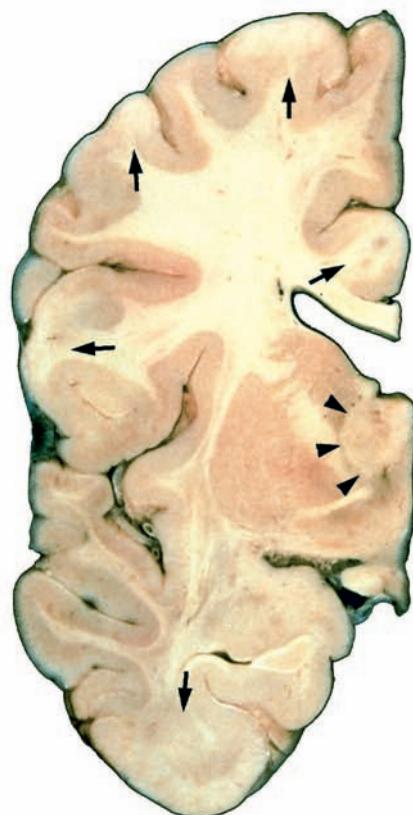


Fig. 13.22 Coronal section of the left hemisphere of a patient with tuberous sclerosis, showing a subependymal giant cell astrocytoma (arrowheads) and multiple cortical tubers.

including microtubules, occasional dense-core granules, and, rarely, synapses may be detectable [830, 1015].

Other CNS manifestations

CNS lesions include cerebral cortical tubers, white matter heterotopias, and subependymal hamartomatous nodules (candle guttering or drippings). Cortical tubers in TSC may be detected by either CT or MRI [2077]. These malformative lesions have a strong association with the development of

Table 13.08 Diagnostic criteria for Tuberous Sclerosis Complex. Modified from Roach *et al.* (1894).

Major features
Facial angiofibromas or forehead plaque
Nontraumatic ungual or periungual fibroma
Hypomelanotic macules (more than 3)
Shagreen patch (connective tissue nevus)
Multiple retinal nodular hamartomas
Cortical tuber
Subependymal nodule
Subependymal giant cell astrocytoma
Cardiac rhabdomyoma, single or multiple
Lymphangiomatosis
Renal angiomyolipoma
Minor features
Multiple randomly distributed pits in dental enamel
Hamartomatous rectal polyps
Bone cysts
Cerebral white matter migration lines
Gingival fibromas
Nonrenal hamartomas
Retinal achromic patch
"Confetti" skin lesions
Multiple renal cysts
Definite TSC: either 2 major features or 1 major feature with 2 minor features
Probable TSC: 1 major feature and 1 minor feature
Possible TSC: either 1 major feature or 2 or more minor features

epilepsy, especially infantile spasms and generalized tonic-clonic seizures. Microscopically, they consist of giant cells (like those seen in SEGA) and dysmorphic neurons, disrupted cortical lamination, gliosis, calcification of blood-vessel walls and/or parenchyma, and myelin loss. The surrounding cortex usually demonstrates a normal cytoarchitecture [900]. Dysmorphic neurons

and giant cells may be seen in all cortical layers and underlying white matter. Dysplastic neurons show altered radial orientation in the cortex, aberrant dendritic arborization and accumulation of perikaryal fibrils, and abnormal somatic morphology with abundant eosinophilic cytoplasm (balloon cells) [568, 830, 900]. Although neurons express neuronal-associated proteins, they display cytoarchitectural features of immature or poorly differentiated neurons, such as reduced axonal projections and spine density [830, 900]. Giant cells in cortical tubers show a cellular and molecular heterogeneity similar to that seen in SEGA, and immunohistochemical markers characteristic of glial as well as neuronal phenotypes suggest a mixed glioneuronal origin. Many giant cells in tubers express both nestin mRNA and protein [394]. While some giant cells demonstrate immunoreactivity for GFAP [830], others with an identical morphological phenotype express neuronal markers including connexins 26 and 32, neurofilaments, class III β -tubulin, MAP2, and α -internexin [394, 830]. Formation of well-defined synapses between giant cells and adjacent neurons is not, however, a consistent finding. Cortical hamartomas morphologically indistinguishable from tubers, may occur in chronic focal epilepsies without clinical evidence for an underlying TSC condition [180]. The pathogenesis of these sporadic lesions is unresolved.

Subependymal hamartomas are elevated, often calcified nodules and are composed of cells indistinguishable from cortical tubers, but are smaller in size.

Extraneuronal manifestations

Extraneuronal manifestations of TSC and the frequencies at which they occur are summarized in Table 13.09.

Genetics

Inheritance and genetic heterogeneity

Approximately 50% of TSC patients have a positive family history, indicating a high rate of *de novo* mutations. In affected kindreds, the disease follows an autosomal dominant pattern of inheritance, with high penetrance, but considerable phenotypic variability [2093]. Neuroradiological observations suggest that first-degree relatives of affected patients may have minor clinical signs or a forme fruste of the disease.

Molecular genetics

Genetic linkage studies have provided evidence for two distinct *TSC* loci on chromosome 9q (*TSC1*), and on chromosome 16p (*TSC2*) [371, 1038]. These are likely tumour suppressor genes, as analyses of TSC lesions from affected individuals have demonstrated loss of heterozygosity [284, 720]. It has not been possible to associate *TSC1* and *TSC2* with distinct clinical phenotypes, suggesting that both genes may be involved in the same regulatory pathway. It has been reported that the two *TSC* genes products interact within the cell [1759]. Mutations in *TSC2* are much more common than those in *TSC1* [43], and *TSC1* mutations are significantly underrepresented in sporadic cases [409, 1006]. Several studies suggest that patients with *TSC1* mutations are less severely affected than patients with *TSC2* mutations [409, 1006]. The mildest phenotype is seen in patients in whom mutations were not identified [1980].

The *TSC1* gene

The *TSC1* gene maps to chromosome 9q34 [371], and contains 23 exons, spanning 45kb of genomic DNA [2307]. Of these, 21 appear to carry coding information.

Gene expression. *TSC1* encodes an 8.6 kb mRNA. Its gene product, hamartin, has a molecular weight of 130 kD. The protein is located in cytoplasmic vesicles of cultured cells without assigning a specific function to the molecule [1759]. Hamartin is strongly expressed in brain, kidney and heart, all tissues frequently affected in TSC. Immunohistochemically, significant hamartin staining was reported in cortical neurons, kidney epithelia, pancreatic islets, bronchial epithelia and alveolar macrophages [1758]. Its pattern of expression overlaps with that of tuberin, the product of the *TSC2* gene. Tuberin and hamartin were shown to directly interact stably *in vitro* and *in vivo* [1759]. This may explain the similar clinical manifestations of the two forms of TSC.

Gene mutations. Screening in 225 unrelated patients yielded *TSC1* mutations in 29 cases (13%). Virtually all mutations resulted in a truncated gene product, and more than half of the changes affected exons 15 and 17 [2308]. Genotype-phenotype correlations were not apparent.

Table 13.09 Major manifestations of the TSC.

Manifestation	Frequency
Central nervous system	
Cortical tuber	90-100%
Subependymal nodule	90-100%
White matter hamartoma & white matter heterotopias	90-100%
Subependymal giant cell astrocytoma	6-16%
Skin	
Facial angiofibroma (adenoma sebaceum)	80-90%
Hypomelanotic macule	80-90%
Shagreen patch	20-40%
Forehead plaque	20-30%
Peri and subungual fibroma	20-30%
Eyes	
Retinal hamartoma	50%
Retinal giant cell astrocytoma	20-30%
Hypopigmented iris spot	10-20%
Kidney	
Multiple, bilateral angiomyolipomas	50%
Renal cell carcinomas	1.2%
Polycystic kidney disease	2-3%
Isolated renal cysts	10-20%
Heart	
Cardiac rhabdomyoma	50%
Digestive system	
Microhamartomatous rectal polyps	70-80%
Liver hamartoma	40-50%
Hepatic cysts	24%
Adenomatous polyp of the duodenum and small intestine	rare
Lung	
Lymphangioleiomyomatosis	1-2.3%
Pulmonary cysts	40%
Micronodular pulmonary hyperplasias of type 2 pneumocytes	rare
Others	
Gingival fibromas	50-70%
Pitting of dental enamel	30%
Bone cysts	40%
Arterial aneurysms-intracranial arteries, aorta and axillary artery	rare

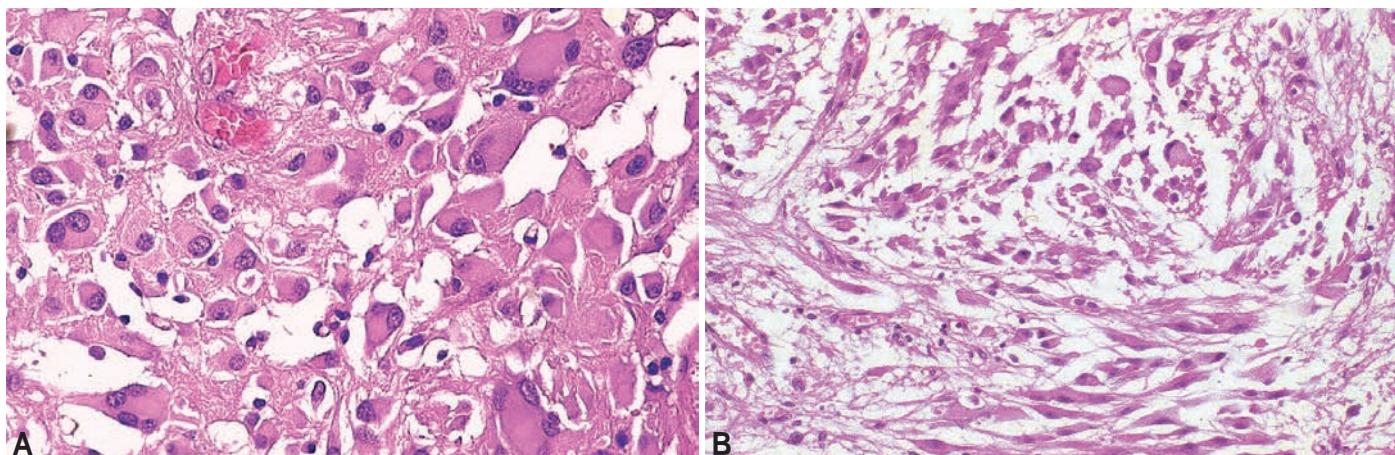


Fig. 13.23 Histological features of subependymal giant cell astrocytoma. A Pleomorphic multinucleated eosinophilic tumour cells. B Elongated tumour cells forming streams.

The TSC2 gene

The *TSC2* gene maps to chromosome 16p13.3 {1038} and contains 40 exons. **Gene expression.** *TSC2* encodes a large transcript of 5.5 kb which shows widespread expression in many tissues, including the brain and other organs affected in TSC. Alternatively spliced mRNAs have been reported {2452}. A portion of the 180 kD protein product, tuberin, bears significant homology with the catalytic domain of the GTPase-activating protein, Rap1-GAP, a member of the ras family. Studies in the Eker rat, a strain with hereditary kidney cancer, demonstrated mutations of the rat *TSC2* homologue, providing support for the hypothesis that *TSC2* acts as a tumour suppressor. Immunohistochemical and *in situ* localization studies of tuberin and *TSC2* mRNA revealed expression in normal neurons and glia.

Gene mutations. The mutational spectrum of *TSC2* is wider and includes large deletions, missense, nonsense, frameshift deletions/insertions and splice

junction mutations {409, 1006, 1980}; genotype-phenotype correlations have not emerged. Loss of heterozygosity for the *TSC1* or *TSC2* loci has been reported in many types of TSC-associated hamartomas and tumours, but are less common in brain lesions than in kidney tumours {811}, raising the possibility that some lesions in TSC may be due to haploinsufficiency {1594, 2415}. Furthermore, neuroglial lesions that are almost indistinguishable from TSC hamartomas have been observed in the brains of patients with chronic focal epilepsies. A molecular analysis for LOH on chromosomes 9q and 16p failed to detect any involvement of the *TSC1* and *TSC2* loci in these sporadic malformative lesions {2426}. This finding appears to exclude the possibility that some of these patients are afflicted with a forme fruste of TSC.

Signalling pathways involving tuberin and hamartin

The tuberin-hamartin complex integrates and transmits cellular growth factor and

stress signals to the PI3K/PKB signalling pathway and negatively regulates mTOR activity in Drosophila and mammalian cells {646, 2230}. Inactivating phosphorylation of tuberin upon insulin or growth factor stimulation causes the disruption of the hamartin/tuberin complex and activation of the mTOR pathway {70}. mTOR signalling increases proliferation and cell growth through two effector molecules: the eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and ribosomal protein S6 kinase 1 (S6K1) {2230} that are essential for G1 to S phase transition. The mTOR inhibitor, rapamycin, is a logical potential therapeutic agent for TSC. Rapamycin induces apoptosis and reduced proliferation of tuberin null cells, and reduction of tumour size in the Eker rat model of TSC {70}. Oral rapamycin therapy induces regression of astrocytomas associated with TSC {604}. The therapeutic effects of rapamycin and chemical analogs are currently being evaluated in human cancers in preclinical and clinical trials.

Li-Fraumeni syndrome and TP53 germline mutations

H. Ohgaki
M. Olivier
P. Hainaut

Definition

An autosomal dominant disorder characterized by multiple primary neoplasms in children and young adults, with a predominance of soft tissue sarcomas, osteosarcomas, breast cancer, brain tumours, and adrenocortical carcinoma; most commonly caused by a germline mutation in the *TP53* gene on chromosome 17p13 {606, 1390, 2318}.

MIM No.

Li-Fraumeni syndrome 151623.
TP53 mutations (germline and somatic)
191170 {1433}.

Synonyms

Sarcoma family syndrome of Li and Fraumeni.

Incidence

From 1990 to 2005, a total of 315 families with a *TP53* germline mutation were reported, representing 573 individuals who are confirmed as carriers of a *TP53* germline mutation (IARC *TP53* Database <http://www-p53.iarc.fr> {1638}).

Diagnostic criteria

The clinical criteria used to identify an affected individual in a Li-Fraumeni family are: (i) occurrence of sarcoma before the age of 45 and (ii) at least one first-degree relative with any tumour before age 45 and (iii) a second (or first) degree relative with cancer before age 45 or a sarcoma at any age {1310}.

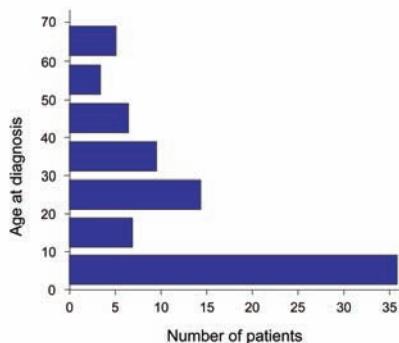


Fig. 13.24 The age distribution of patients with brain tumours associated with *TP53* germline mutations showing bimodal distribution with peaks in children and young adults (n=80, IARC *TP53* database, July 2006).

Criteria for the diagnosis of a LFS variant (Li-Fraumeni like, LFL) have been proposed to better identify *TP53* germline mutation carriers: Criteria of LFL-E2 (2nd definition by Eeles) {1639} are: sarcoma at any age in the proband with two of the following (two of the tumours may be in the same individual), breast cancer at <50 years and/or brain tumour, leukaemia, adrenocortical tumour, melanoma, prostate cancer, pancreatic cancer at <60 years or sarcoma at any age. Criteria of LFL-B (Birch definition) {171} are: proband with any childhood cancer or sarcoma, brain tumour or adrenocortical carcinoma at <45 years, with one first or second degree relative with typical LFS cancer (sarcoma, breast cancer, brain tumour, leukaemia, or adrenocortical carcinoma) at any age, plus one first or

second degree relative in the same lineage with any cancer diagnosed under age 60.

Nervous system neoplasms

In the 573 confirmed individuals carrying a *TP53* germline mutation that are included in the IARC *TP53* Database (July 2006), a total of 708 tumours were reported; 93 of these (13.1%) were located in the nervous system.

Age and sex distribution

Male female ratio of patients with brain tumours associated with *TP53* germline mutation is 1.86, slightly higher than the one of sporadic brain tumours excluding meningiomas (1.6) {1260}.

As with sporadic brain tumours, the age of patients with nervous system neoplasms associated with *TP53* germline mutations shows a bimodal distribution. The first peak of incidence is in children (mainly medulloblastomas and related primitive neuroectodermal and choroid plexus tumours), and the second (mainly astrocytic brain tumours) in the 3rd and 4th decades of life.

Familial clustering

Among 139 families with at least one case of brain tumour, the mean number of CNS tumours per family is 1.55. Several reported families showed a remarkable clustering of brain tumours. This raises the question of whether some mutations carry an organ- or cell-specific risk. A recent analysis of the IARC *TP53* Database of germline mutations showed that brain tumours were more likely to be associated with missense mutations located in the DNA-binding surface of p53 protein that make contact with the minor groove of DNA {1639}. The type of mutation was also associated with the age at onset of brain tumours, truncating mutations being associated with early onset brain tumours {1639}. Familial clustering may also be due to gene-environment interactions, e.g. exposure of families to similar environmental carcinogens or lifestyle factors has been suggested for stomach and breast cancer {1124}.

Table 13.10 Brain tumours associated with *TP53* germline mutations

Histology	No. of tumours	Mean age of patients (years)
Histologically classified (75 cases)		
Astrocytic brain tumour	45 (48%)	34
Medulloblastoma/PNET	10 (11%)	6
Choroid plexus tumour	14 (15%)	3
Ependymoma	3 (3%)	9
Oligodendrogloma	2 (2%)	21
Meningioma	1 (1%)	24
Unclassified (18 cases)	19%	
All (93 cases)	100%	

Histopathology of CNS tumours

Of the 93 brain tumours reported in confirmed carriers of a germline *TP53* mutation, 75 had been classified histologically, and of these, 45 (60%) were of astrocytic origin, including low-grade astrocytoma, anaplastic astrocytoma and glioblastoma. Paediatric brain tumours, including medulloblastoma and related primitive neuroectodermal tumours and choroid plexus tumours were less frequent. This correlates with the occurrence of *TP53* mutations in sporadic brain tumours, which prevail in astrocytoma and are considerably less frequent in medulloblastoma {1621, 1622}. Histopathologically, CNS tumours associated with *TP53* germline mutations are considered indistinguishable from their sporadic counterparts.

Extraneuronal manifestations

Breast cancer, sarcomas (osteosarcomas and soft tissue sarcomas), and brain tumours are the most frequent manifestations and account for 72% of all tumours in patients carrying a *TP53* germline mutation. The sporadic counterparts of these tumours also show a high frequency of *TP53* mutations, suggesting that in these neoplasms, *TP53* mutations are capable of initiating the process of malignant transformation {1124}. In general, tumours associated with a *TP53* germline mutation develop earlier than their sporadic counterparts, but there are marked organ-specific differences. Adrenocortical carcinoma associated with a *TP53* germline mutation develops almost exclusively in children, in contrast to sporadic adrenocortical carcinoma, which has a broad age distribution with a peak beyond age 40 {109}.

Genetics

In approximately 80% of LFS cases, and 65% of LFL cases, affected family members carry a germline mutation of one allele of the *TP53* tumour suppressor gene (IARC *TP53* Database, July 2006). Conversely, of 244 reported families with *TP53* germline mutations, approximately 45% and 35% meet the criteria of LFS and LFL syndromes respectively. However, the extent of the overlap may be greater, as in some families with *TP53* germline mutations only one tumour was analysed or data were available for only one generation. Two LFS and 3 LFL families have been reported to carry a *CHEK2*

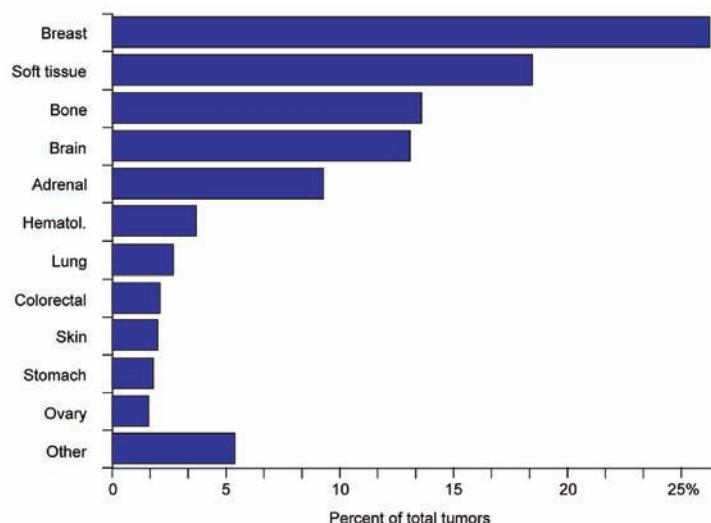


Fig.13.25 Target organs for tumourigenesis in patients carrying a *TP53* germline mutation (n=708, IARC *TP53* Database July 2006). Breast cancer, bone and soft tissue sarcomas, and brain tumours are most frequent neoplasms associated with *TP53* germline mutations.

germline mutation {172, 1280, 2294}. This gene codes for a protein involved in G2 checkpoint control which prevents cells with damaged DNA to enter mitosis {184}. However, it is now considered that *CHEK2* does not predispose to LFS/LFL, but only to the breast cancers that have occurred in the context of these families.

Gene

The *TP53* gene on chromosome 17p13 has 11 exons that span 20 kb. Exon 1 is non-coding, and exons 5 to 8 are highly conserved among vertebrates.

TP53 protein

The *TP53* tumour suppressor gene encodes a 2.8 kb transcript encoding a

393 amino-acid protein which is widely expressed at low levels. This protein is a multi-functional transcription factor involved in the control of cell cycle progression, of DNA integrity and of the survival of cells exposed to DNA-damaging agents as well as several non-genotoxic stimuli such as hypoxia. DNA damage or hypoxia induces a transient nuclear accumulation and activation of the *TP53* protein, with transcriptional activation of target genes that are responsible for induction of cell cycle arrest or apoptosis {1143, 1301}. A number of these properties are consistent with a tumour suppressor function. *TP53* mutant proteins differ from each other in the extent to which they have lost suppressor function and in their

Table 13.11 Tumour type, age at diagnosis and gender distribution in patients carrying a *TP53* germline mutation.

	Median age at diagnosis (years) <i>TP53</i> carriers	% of male patients	
		Sporadic*	<i>TP53</i> carriers
Breast cancer	36	63	0
Soft tissue sarcoma	18	61	48
Bone sarcoma	17	43	49
Brain tumour	22	57	65
Adrenocortical carcinoma	6	42	25
Haematopoietic and lymphoid tumours	24	65	65
Lung cancer	44	69	47
Colorectal cancer	37	72	50
Skin cancer	56	-	10
Stomach cancer	37	73	69
Ovarian cancer	39	64	0
Other tumour	-	-	-

* Data based on cancer registries from US, France and UK compiled in Cancer Incidence in Five Continents V.7, 1997 (1680A).

capacity to inhibit wild-type TP53 in a dominant-negative manner {1054}. In addition, some *TP53* mutants appear to exert an oncogenic activity of their own, but the molecular basis of this gain-of-function phenotype is still unclear {175}. The functional characteristics of each mutant TP53 protein may depend, at least in part, on the degree of structural perturbation that the mutation imposes on the protein.

Distribution of *TP53* mutations

TP53 germline mutations associated with the development of brain tumours are located in highly conserved regions of exons 5 to 8, with major hotspots at codons 175, 245, 248 and 273. These codons are also hot spots in sporadic brain tumours as well as other tumours. Mutations observed at these codons are missense mutations that result in mutant proteins with complete loss of function, dominant-negative phenotypes and oncogenic activities.

It is of interest to note that 3 codons (Cys 176, His 179 and Arg 249) that are commonly mutated in tumours with somatic *TP53* mutations have never been reported as germline mutation {1639}. Residues 176 (Cys) and 179 (His) are involved in the co-ordination of a zinc atom that forms a bridge between domain 1 and domain 3, and which is crucial in stabilizing the architecture of the whole DNA-binding domain. Residue 249 (Arg) makes essential contacts with

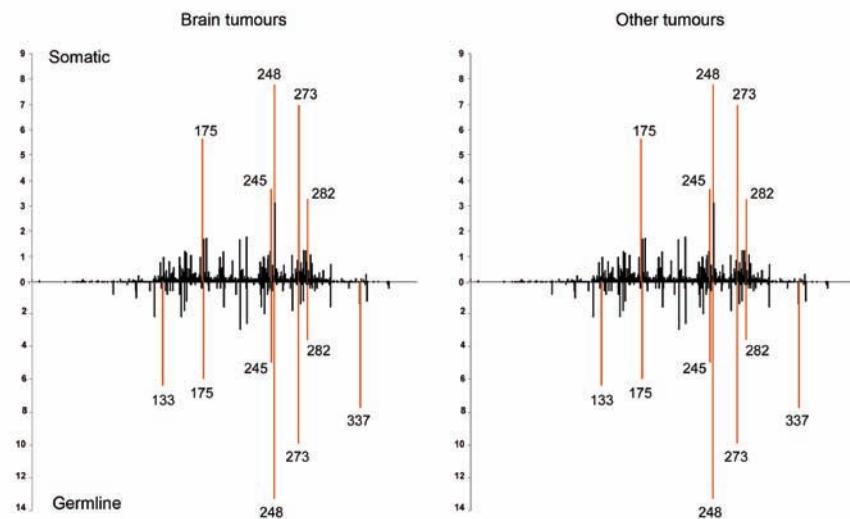


Fig. 13.26 Somatic and germline *TP53* mutations share the major hotspot codons 175, 248 and 273 within the DNA-binding domain (exons 5-8). Germline mutations associated with brain tumours prevail at codons 245 and 248. Based on 82 tumours reported in 77 individuals carrying a single base substitution in *TP53* (<http://www-p53.iarc.fr/1638>).

several residues of the scaffold through hydrogen bridges {339}. These substitutions may thus result in mutant TP53 proteins that are not tolerated when present in the germline. Two hot spots (codons 133 and 337) are specific to *TP53* germline mutations, but are not associated with brain tumour development. The mutation at codon 133 (M133T), very rarely observed in sporadic neoplasms, has been found in families with clustering of

early onset breast cancers (3–6 cases by family with a mean age at onset of 34 years; IARC *TP53* Database), whereas a mutation at codon 337 (R337H) has been frequently found in Brazilian children affected by adrenocortical carcinomas {1867} and in Brazilian LFL families {10}.

Type of *TP53* mutations

The proportion of G:C->A:T transitions at CpG sites is higher but that of G:C->A:T transitions at non-CpG sites and G:C->T:A transversions is lower in *TP53* germline than in somatic mutations. G:C->A:T transitions at CpG sites are considered to be endogenous, e.g. formed as a result of deamination of 5-methylcytosine, which occurs spontaneously in almost all cell types but which is usually corrected by DNA repair mechanisms. The difference observed may thus be explained by the fact that non-CpG G:C->A:T and G:C->T:A mutations are associated with exogenous carcinogen exposure while germline mutations appear to result mainly from endogenous processes {1640}.

Table 13.12 Type of germline and somatic *TP53* mutations in human neoplasms.

Mutation type	Brain tumours		Other neoplasms	
	Germline ¹ (n=96)	Somatic ² (n=1418)	Germline ³ (n=622)	Somatic ⁴ (n=19 352)
Missense mutations in DNA binding motifs	55%	56%	45%	49%
Missense mutations outside DNA binding motifs	25%	26%	27%	24%
Deletions/insertions	11%	10%	11%	12%
Nonsense mutations	4%	3%	7%	8%
Other mutations	4%	4%	10%	7%
Point mutations	(n=85)	(n=1259)	(n=542)	(n=16 701)
A:T->C:G	7%	5%	4%	5%
A:T->G:C	8%	14%	13%	13%
A:T->T:A	4%	3%	5%	6%
G:C->A:T not at CpG	15%	20%	12%	22%
G:C->A:T at CpG	48%	44%	55%	28%
G:C->C:G	7%	6%	6%	9%
G:C->T:A	11%	9%	6%	18%

¹ Brain tumours reported in confirmed carriers of a *TP53* germline mutation. ² Mutations reported in sporadic brain tumours. ³ Tumours other than brain tumours reported in confirmed carriers of a *TP53* germline mutation. ⁴ Mutations reported in sporadic neoplasms other than brain tumours. Data from IARC *TP53* Database (July 2006).

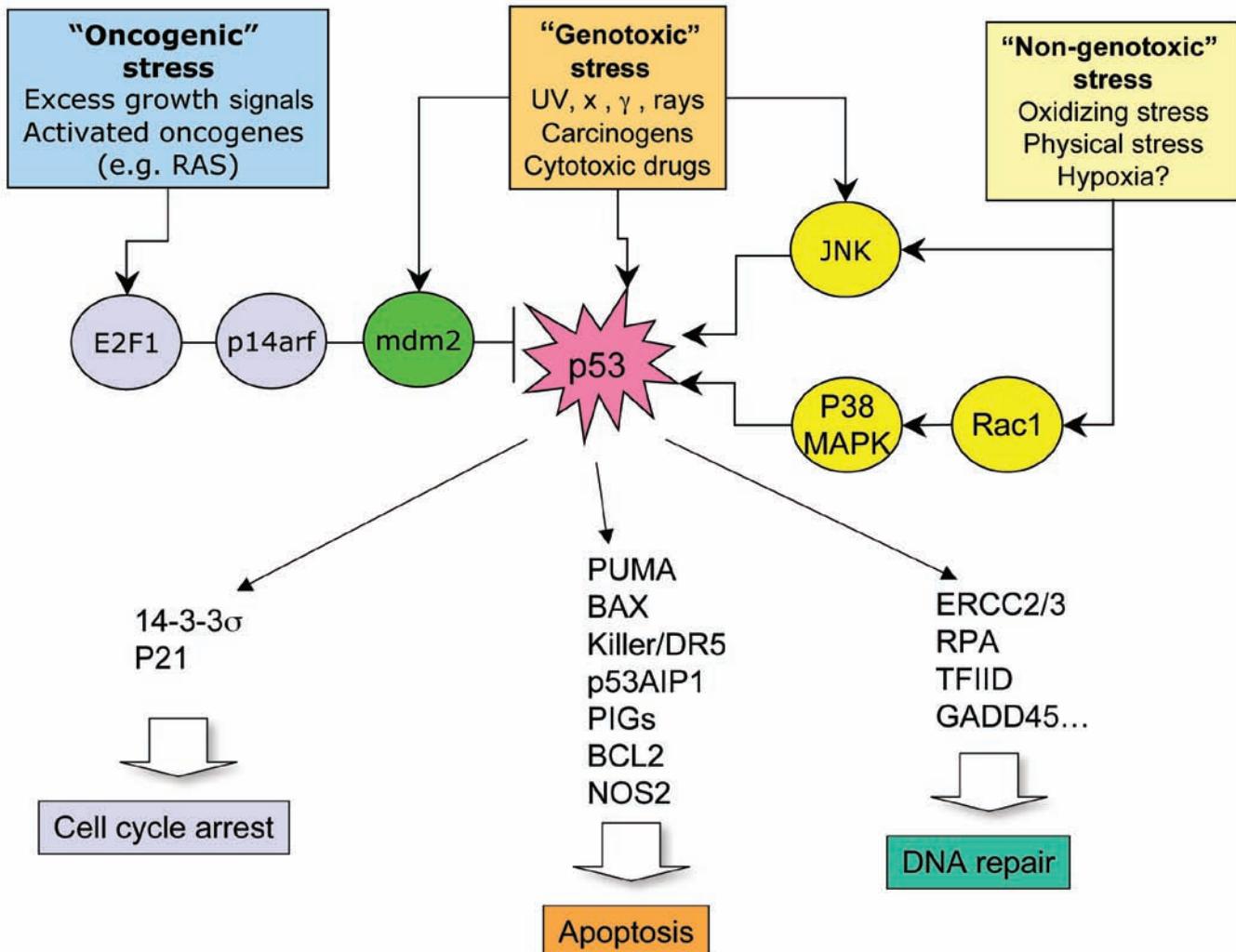


Fig. 13.27 TP53 signaling pathway. The p53 protein is activated and stabilized in response to several genotoxic and non-genotoxic forms of stress. Active p53 acts on downstream effectors through transcriptional repression and protein-protein interactions. Several effectors of p53 are involved in the control of cell cycle progression in G1/S and in G2, in DNA replication, transcription and repair, and in the regulation of apoptosis. Together, this set of cellular responses allows p53 to act as an anti-proliferative agent in cells exposed to various forms of stress. MDM2 is a transcriptional target of p53 involved in a negative, feedback loop to control p53 levels and activity. The extent and consequences of the biological response elicited by p53 vary according to stress and cell type.

Cowden disease and dysplastic gangliocytoma of the cerebellum/Lhermitte-Duclos disease

C.G. Eberhart
O.D. Wiestler
C. Eng

Definition

An autosomal dominant disorder characterized by multiple hamartomas involving tissues derived from all three germ cell layers and a high risk of breast, non-medullary thyroid and endometrial cancers; the classic hamartoma is the trichilemmoma and is pathognomonic; caused by germline mutations in *PTEN* (Phosphatase and TENSin homologue deleted on chromosome TEN). Adult-onset Lhermitte-Duclos disease (LDD)/dysplastic gangliocytoma of the cerebellum is also considered pathognomonic.

MIM No. 158350 {1433}.

Synonyms and historical annotation

The condition was originally described in 1963 by Lloyd and Dennis in the family of Rachel Cowden {1339}. Weary *et al.* {2376} gave a more detailed description of clinical features and proposed the term multiple hamartoma syndrome.

Incidence

The incidence of Cowden syndrome (CS) before the identification of *PTEN* was estimated to be 1 in a million {1578}. After gene identification, this figure was revised to approximately 1 in 250 000 {1577}. Although the exact proportion of isolated and familial cases is not known, the majority of CS cases appear to be isolated {521, 1405, 2357}. The precise incidence of LDD is unknown although it is viewed as rare {523, 1664}.

Diagnostic criteria and clinical features

A set of operational clinical diagnostic criteria has been established for purposes of identifying families [www.nccn.org] {1748}. Because of a study which found *PTEN* mutations in 15 of 18 unselected patients with the pathologic diagnosis of dysplastic gangliocytoma of the cerebellum {2499}, adult-onset LDD was revised from a major diagnostic criterion to a pathognomonic criterion. Of note, all 15 patients with mutations had adult-onset LDD, while the remaining 3 without

mutations were diagnosed in children less than 12. Thus, the presence of adult-onset LDD, irrespective of other clinical features or family history, can be considered highly predictive of identifying a germline *PTEN* mutation in that patient.

Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease)

Definition

A benign cerebellar mass composed of dysplastic ganglion cells.

ICD-O code 9493/0

Grading

It is not clear whether this lesion is neoplastic or hamartomatous. If neoplastic, it corresponds histologically to WHO grade I.

Synonyms and historical annotation

Dysplastic gangliocytoma of the cerebellum was first described in 1920 by Lhermitte and Duclos {1307} and by Spiegel {2134}. The disease has also been termed cerebellar granule cell hypertrophy, diffuse hypertrophy of the cerebellar cortex and gangliomatosis of the cerebellum. Over 100 patients have been reported since. However, the association of Cowden disease with dysplastic gangliocytoma of the cerebellum has only recently been recognized {523, 1664, 2327, 2328}.

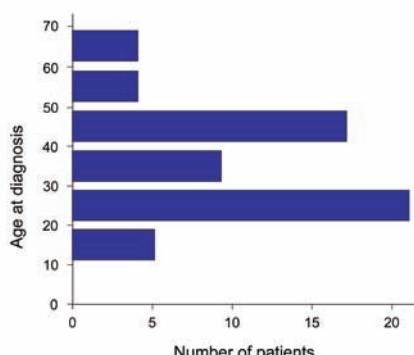


Fig.13.28 Age distribution of dysplastic gangliocytoma of the cerebellum, based on 60 cases.

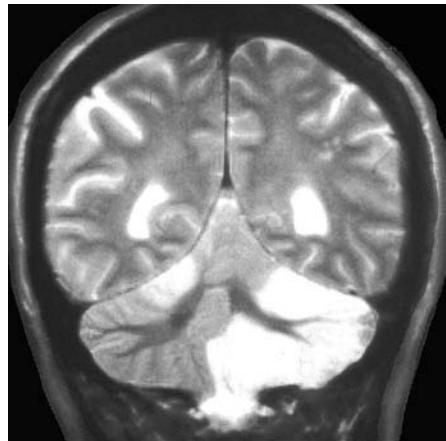


Fig. 13.29 T2-weighted MRI showing the characteristic broadening of the cerebellar cortex (hyperintense signal) on the right side, with a smaller focus in the left cerebellar hemisphere. From Sonier *et al.* {2123A}.

Age distribution

Because of the rarity of LDD, there has not been a systematic study to determine the distribution of age of onset. Most cases have been identified in adults, but a review of the literature reveals that LDD can be diagnosed in infancy, e.g. 3 years old, and as late as in the 70s {523, 1345, 2499}. *PTEN* mutations have been identified in virtually all adult-onset LDD but not in childhood-onset cases {2499}, suggesting the biology of the two is different.

Clinical features

Signs and symptoms. The most common clinical presentations of LDD include dysmetria, other cerebellar signs, and signs and symptoms of mass effect. Macrocephaly and seizures are also often present in LDD patients. Variable periods of preoperative symptoms have been noted, with a mean interval of approximately 40 months {2327}. As cerebellar lesions may develop before the appearance of other features of Cowden disease, patients with Lhermitte-Duclos should be monitored for the development of additional tumours, including breast cancer in females.

Neuroimaging. Neuroradiological studies demonstrate a distorted architecture of

the affected cerebellar hemisphere with enlarged cerebellar folia and cystic changes in some cases; MRI is particularly sensitive in depicting the enlarged folia {1472}.

Macroscopy

The affected cerebellum displays a discrete region of hypertrophy and a coarse gyral pattern that extends into deeper layers. Usually, the gangliocytoma is confined to one hemisphere, but they can occasionally be multifocal.

Histopathology

The dysplastic gangliocytoma of LDD causes diffuse enlargement of the molecular and internal granular layers of the cerebellum, which are filled by ganglionic cells of varying sizes {2}. An important diagnostic feature is the relative preservation of the cerebellar architecture, in which folia are enlarged and distorted but not obliterated. A layer of abnormally myelinated axon bundles in parallel arrays is often observed in the outer molecular layer. Scattered cells morphologically consistent with granule neurons are also sometimes found under the pia or in the molecular layer. The resulting structure of these dysmorphic cerebellar folia has been referred to as inverted cerebellar cortex. Purkinje cells are reduced in number or absent. Calcification and ectatic vessels are commonly present within the lesion. Vacuoles are sometimes observed in the molecular layer and white matter {2}.

Immunohistochemistry

The dysplastic neuronal cells are immunopositive for synaptophysin. Antibodies to the Purkinje cell antigens Leu-4, L7, PEP19 and calbindin labelled a minor subpopulation of large atypical ganglion cells, but did not react with the majority of the neuronal elements, suggesting that only a small fraction of neurons are derived from a Purkinje cell source {756, 2091}. Immunohistochemistry also demonstrates loss of PTEN protein expression in most dysplastic cells and increased expression of phosphorylated Akt and S6, reflecting aberrant signalling which is predicted to result in increased cell size and lack of apoptosis {2, 2499}.

Proliferation

Undetectable or very low proliferative activity has been reported in the few

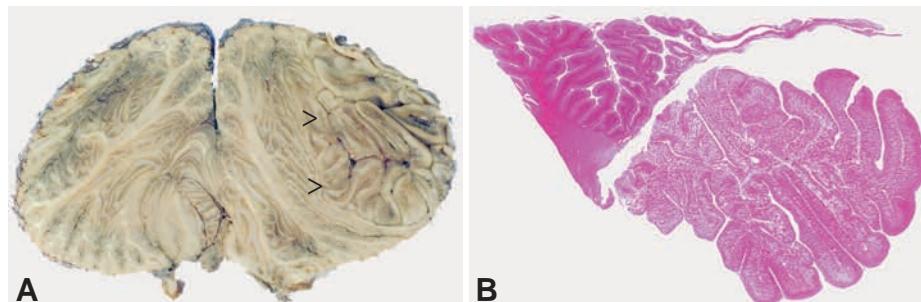


Fig.13.30 A Macroscopic aspect of Lhermitte-Duclos disease (arrows). Note the delineated enlargement and coarsening of the cerebellar folia. B Low-power view showing moderate distortion of the cerebellar cortex.

cases analysed with proliferation markers {2, 756}.

Histogenesis

It remains unclear whether Lhermitte-Duclos is hamartomatous or neoplastic in nature. Malformative histopathological features, a very low or absent proliferative activity and the absence of progression support a classification as hamartoma. However, recurrent growth has occasionally been noted and dysplastic gangliocytomas may develop in adult patients with previously normal MRI scans {2, 756, 1395}. It has been suggested that the primary cell of origin is the cerebellar granule neuron {756}, and that a combination of aberrant migration and hypertrophy of granule cells is responsible for formation of the lesions {2}. Murine

transgenic models based on localized PTEN loss support this hypothesis {1241}.

Other CNS manifestations

Additional cerebral manifestations include megalencephaly in 20–70% of cases, as well as heterotopic grey matter, hydrocephalus, mental retardation and seizures {766, 1664}. Although such tumours as meningiomas and glioblastomas have been said to be associated with CS and have been the topic of single case reports {1345, 1391}, there is currently no rigorous epidemiologic evidence that they are true component neoplasias {1748}.

Genetics

Cowden syndrome is an autosomal dominant disorder, with age-related

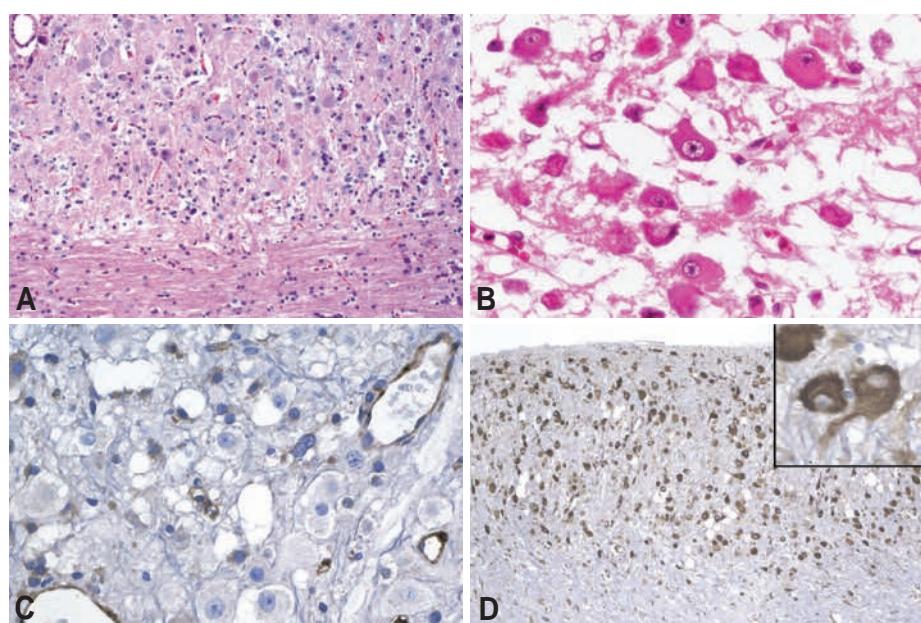


Fig. 13.31 Histological features of dysplastic gangliocytoma of the cerebellum. A The internal granule layer of the cerebellum, present at the top of the image, is filled with dysplastic ganglion cells. B A higher-power view of ganglion cells. C Immunohistochemical stains for PTEN show loss of expression in the enlarged neurons, with preserved staining in vessels. D The dysplastic ganglion cells are strongly immunopositive for phosphorylated S6.

penetrance and variable expression [522]. *PTEN* is the susceptibility gene for this syndrome [1318].

Gene structure and function

PTEN/MMAC1/TEP1 on 10q23, is comprised of 9 exons spanning 120–150 kb of genomic distance and encodes a 1.2 kb transcript and a 403 amino acid lipid dual-specificity phosphatase (it dephosphorylates both protein and lipid substrates), which has homology to the focal adhesion molecules tensin and auxilin [1309, 1312, 2145]. A classic phosphatase core motif is encoded within exon 5, which is the largest exon, constituting 20% of the coding region [1309, 1312]. *PTEN* is the major 3-phosphatase acting in the phosphoinositol-3-kinase (PI3K)/Akt apoptotic pathway [1377, 2138]. Overexpression of

PTEN results, for the most part, in phosphatase-dependent cell cycle arrest at G1 and/or apoptosis, depending on cell type. 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 [522, 2357]. Recently, non-traditional means of *PTEN* inactivation such as nuclear-cytoplasmic partitioning and transcriptional or degradative mechanisms have been found [349, 350, 2212, 2213, 2236].

Gene mutations

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 [522, 2357]. Approximately 30–40% of germline

PTEN mutations are found in exon 5, although exon 5 represents only 20% of the coding sequence. Further, approximately 65% of all mutations can be found in one of exons 5, 7 or 8 [522, 1405]. Germline *PTEN* mutations spanning exons 1–9 and the promoter have been found in 85% of all CS probands [2500]. To date, all individuals with adult-onset LDD, irrespective of other features, have *PTEN* mutations [2499]. Although *PTEN* is the major susceptibility gene for CS, one CS family without *PTEN* mutations, was found to have a germline mutation in *BMPR1A*, which is one of the susceptibility genes for juvenile polyposis syndrome [2501]. Whether *BMPR1A* is a minor CS susceptibility gene or whether this family with CS features actually has occult juvenile polyposis is as yet unknown.

Turcot syndrome

W.K. Cavenee
P.C. Burger
S.Y. Leung
E.G. van Meir

Definition

Distinct autosomal dominant disorders having adenomatous colorectal polyps or colon carcinomas and malignant neuroepithelial tumours, especially medulloblastomas or glioblastomas. Most cases occur within the setting of hereditary non-polyposis colorectal carcinoma (HNPCC) or familial adenomatous polyposis (FAP); a small proportion of patients have biallelic germline DNA mismatch repair (MMR) gene mutations which augments disease penetrance [92, 1652].

MIM No. 276300 {1433}.

Incidence

Approximately 170 cases have been reported since it was recognized in 1949.

Diagnostic criteria

There are at least two clinical entities encompassed under the Turcot syndrome (TS) [1676]. The first, Turcot syndrome type 1, consists of glioblastoma in patients without FAP, but often with HNPCC and corresponding germline mutations in the DNA mismatch repair genes *PMS2*, *MLH1* and *MSH2*. This type can now be distinguished into two subtypes. One occurs in families with classical HNPCC caused by germline mutation of one allele of the *MSH2* or *MLH1* genes. Another rare form is characterized by homozygous or compound heterozygous mutations, resulting in germline inactivation of both alleles of a MMR gene. The most frequent biallelic germline mutation

reported so far involves the *PMS2* gene, but mutations involving the *MLH1*, *MSH6* and *MSH2* have also been reported. Turcot Syndrome type 2 comprises medulloblastoma in patients with FAP and corresponding mutations in the *APC* gene. The CNS tumours are similar to their sporadic counterparts except that the medulloblastomas often occur after age 10 and the glioblastomas usually occur before age 30.

Nervous system neoplasms

Medulloblastoma, glioblastoma and anaplastic astrocytoma account for about 95% of brain tumours reported [1676]. Glioblastoma in TS generally occurs in a younger age group than sporadic glioblastoma [2304]. Patients

Table 13.13 Summary of clinical phenotypes and genetic alterations in Turcot cases.

	Turcot syndrome type 1: Glioma-polyposis	Turcot syndrome type 2: Medulloblastoma-polyposis
Intestinal phenotype	Small number of polyps (<100) Large sized polyps (>3cm) No family history of polyposis Colorectal cancer at young age (56%)	Numerous (>100) small polyps Family history of polyposis Colorectal cancer (21%)
Brain tumour types	Astrocytoma or glioblastoma at young age (<20 years)	Medulloblastoma
Skin phenotype	Frequent skin lesions (53%) and café-au-lait spots (38%)	Occasional skin lesions (21%)
Family history	Usually siblings affected No family history of polyposis or brain tumours Finding of glioblastoma at young age might indicate underlying Turcot syndrome type 1 Family history of colorectal cancer	Family history of polyposis
Consanguinity	Frequent (22%)	None
Mode of inheritance	Autosomal dominant with low penetrance behaving like autosomal recessive	Autosomal dominant
Constitutive genetic defect	Mutations in mismatch repair genes: Carry an <i>MLH1</i> or <i>MSH2</i> germline mutation or Biallelic germline mutation of <i>PMS2</i> (occasionally of <i>MLH1</i> , <i>MSH6</i> and <i>MSH2</i>)	Adenomatous polyposis coli (<i>APC</i>) gene mutations
Related genetic disorder	Hereditary non-polyposis colorectal cancer (HNPCC) Muir-Torre syndrome (sebaceous tumours) Neurofibromatosis type 1 (café-au-lait spots, neurofibromas)	Familial adenomatous polyposis (FAP), Gardner syndrome

with biallelic germline *MMR* gene mutations tend to develop glioma during childhood [92, 1652], and apart from astrocytomas grades II-IV, oligodendrogloma and supratentorial primitive neuroectodermal tumours have been recorded in some families. It is unclear whether other patients with colonic polyposis and other CNS tumours (lymphoma, pituitary adenoma, meningioma, craniopharyngioma, ependymoma, cervical spinal astrocytoma) are part of the heterogeneity.

Extraneuronal manifestations

There are two major variants of colorectal manifestations. TS type 1 presents with small numbers of large polyps, and patients develop colorectal cancer at a young age in 56% of cases. Other cancers within the HNPCC spectrum, including cancers arising from the endometrium, stomach, ovary, small intestine, pancreatico-biliary or urinary tracts, as well as sebaceous tumours of Muir-Torre syndrome, may be present in patients or their family members. It has been noted that café-au-lait spots occur in 38% of type 1 patients [1676]. TS patients with café-au-lait spots more likely belong to the group of patients with germline biallelic *MMR* gene mutations [2265]. This syndrome is characterized by very early-onset (usually in the paediatric age group) of colorectal adenomas and cancers, glioblastomas and hematological malignancies (leukaemia and lymphoma). Mild features of neurofibromatosis type 1, especially café-au-lait spots are present in the majority of patients. A minority also have axillary freckles and neurofibromas [92, 1652, 2265].

TS type 2 presents with innumerable adenomatous polyps and 21% of such cases will develop colorectal cancer. Skin lesions occur in approximately 20% of type 2 Turcot patients, usually in forms of epidermoid cysts. Craniofacial exostosis and congenital hypertrophic retinal pigmented epithelium occur in a minority of patients.

Genetics

Genetic heterogeneity

The association of neuroepithelial neoplasms with colorectal polyps was first noted by Crail [393] and genetic predisposition was later suggested by Turcot [2279]. Lewis [1304] proposed three

groups: type (I) those with two or more siblings with multiple colonic polyps and a malignant brain tumour, with neither the parents nor other generations being affected; type (II) affected individuals having an autosomal dominant colonic polyposis and with polyps occurring in several generations of their family; and, type (III) isolated non-familial cases. This led to the proposal that TS was sometimes a variant of the FAP syndrome. Lasser [1265] demonstrated genetic linkage to *APC*, the gene responsible for FAP, in a TS family with medulloblastomas. This was followed by the identification of germline *APC* mutations in three unrelated cases [1523], two of which presented with medulloblastoma, the other with a malignant astrocytoma. Hamilton and colleagues [762] analysed 14 TS families and found that 10 of the 14 families had germline *APC* mutations and that the predominant tumour was medullo-blastoma.

Mismatch repair associated Turcot syndrome (type 1)

Mismatch repair-associated TS is characterized by an inherited DNA replication error defect that leads to genomic instability. **Gene structure.** The major genes involved in *MMR* are: *MLH1* at chromosome 3p21.3, *MSH2* at 2p16, *MSH3* at 5q11-q13, *MSH6/GTBP* at 2p16, *PMS1* at 2q32 and *PMS2* at 7p22. The *PMS2* gene has many paralogous genes with over 90% sequence homology, and these can interfere with mutation detection [441, 1552].

Gene expression. Recognition and repair of base-pair mismatches in human DNA is mainly mediated by heterodimers of *MSH2* and *MSH6*, which form a sliding clamp on DNA. Cells that are deficient for *MSH2* or *MSH6* expression are defective in repair of mispaired bases and insertions/deletions of single nucleotides resulting in high mutation rates and microsatellite instability. The carboxy-terminal region of *PMS2* interacts with *MLH1*, and this complex binds to *MSH2/MSH6* heterodimers to form a functional strand-specific mispair recognition complex.

Most HNPCC families have either *MSH2* or *MLH1* mutations. Replication-error-driven microsatellite instability is rare in adult-on-set brain tumours in the absence of TS but was reported in 27% to 33% of paediatric astrocytoma grades III-IV [49, 1037, 1295]. Overall, a family history of colorectal cancer or other HNPCC-related cancers in young or

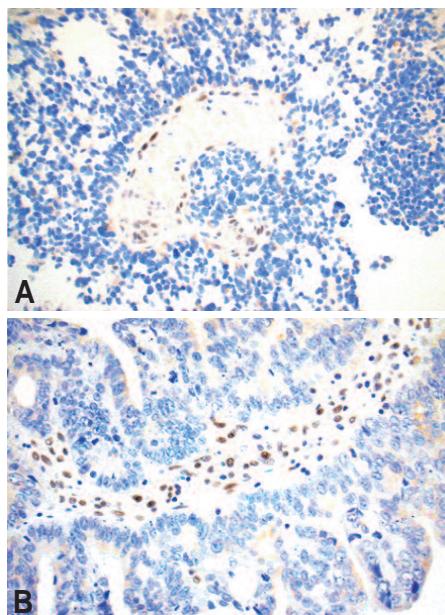


Fig. 13.32 A Turcot patient with heterozygous germline *MSH2* mutation. Immunohistochemical staining shows absence of *MSH2* protein expression in the glioblastoma (A) and the colonic adenocarcinoma (B) arising from the same patient. Note the positive nuclear staining in the endothelial cells and stromal fibroblasts. Modified from Leung et al. [1295].

paediatric glioblastoma patients should raise the suspicion of HNPCC. Screening for lack of expression of mismatch repair genes is possible by immunohistochemistry.

Gene mutations. So far, heterozygous mutations have been found in the germlines of TS families in *MSH2* (4 cases) [1295, 2319] and *MLH1* (two cases) [762, 1037]. These families commonly show a family history of HNPCC with autosomal dominant mode of inheritance. The tumours found in these patients showed evidence of replication errors that lead to genomic instability. This mutator phenotype induces somatic mutations in gatekeeper genes *TP53* and *APC* in the tumours of these patients [1297, 1496]. Notably, these families each had astrocytoma, oligodendrogloma or glioblastoma as the inclusive brain tumour.

The most commonly mutated *MMR* gene reported in TS families is the *PMS2* gene. While the first reported *PMS2* mutation in a TS family affected only one allele, subsequent analysis revealed a mutation in the second allele of the gene [441, 762]. Emerging data suggest that most *PMS2* mutations are in forms of homozygous or compound heterozygous

mutations, resulting in replication errors even in the normal tissue of the affected individuals [92,1652]. These families with biallelic germline mutation may manifest an autosomal recessive inheritance pattern, with frequent history of consanguinity in the parents. It is hypothesized that replication errors in normal cells during development may lead to inactivation of the *NF1* gene and lead to the clinical phenotype of mild neurofibromatosis type 1. The lack of cancer history in their parents who are heterozygous *PMS2* mutation carriers suggests that monoallelic germline *PMS2* mutation may confer only a very low risk of cancer. Germline biallelic mutation of *MLH1* (9 families), *MSH2* (3 families) and *MSH6* (3 families) have also been reported in some families with café-au-lait spots and clustering of cancers including gliomas, colon cancers or hematological malignancies. These families usually have more prominent features of HNPCC compared with those with *PMS2* mutation.

FAP-associated Turcot syndrome (type 2)
The APC gene responsible for FAP-associated TS lies on chromosome 5q21. **Gene expression.** The APC gene encodes an ubiquitously expressed protein of about 300 kDa which interacts with the β-catenin protein and mediates its degradation. β-catenin links the cytoplasmic tail of the cell-cell homotypic adhesion molecule cadherin to the actin cytoskeleton. Alteration of APC function may modify the movement/adhesion of epithelial stem cells in the colonic crypt. It is unclear whether it fulfills a similar function for cerebellar precursor cells, and in the absence of TS, the APC gene is rarely mutated in sporadic brain tumours [762, 1265]. About 10% of sporadic medulloblastomas show loss of heterozygosity or mutations in the β-catenin gene [2517] and APC missense point mutations occur in less than 5% of cases [881]. β-catenin has a role in signalling mediated by the nuclear translocation of transcription factors of

the lymphoid enhancing factor (LEF-1) family. The loss of the APC gene product results in increased binding of β-catenin to LEF-1 and an increase in the transcription of the cell cycle activator cyclin D1 and other genes.

Gene mutations. Truncating germline APC mutations are found in most families with FAP-associated TS [1676]. Rare cases show no mutations in the APC gene and no evidence for DNA replication errors, suggesting other underlying causes, adding to the aetiological heterogeneity of the syndrome. The association of brain tumours and colon cancer can also occur in the setting of germline TP53 mutations [1240].

Prognostic and predictive factors

The median age for occurrence of glioblastoma in TS type 1 was found to be 18 years, while the peak incidence in the general population is 40–70 years of age [2304]. These patients showed an average survival of over 27 months, which is remarkably longer than the 12 month survival for sporadic cases. Although mutation data is not available in most of these families, it is interesting to note that many of the long survivors belong to the group of patients with biallelic germline *PMS2* mutation, some of whom were still alive more than 10 years after treatment of their gliomas [440, 762, 2265]. In Turcot type 2, the median age for occurrence of medulloblastomas was 15 years which is later than the peak occurrence for sporadic medulloblastoma (7 years of age). In FAP families, the appearance of medulloblastoma at young age in patients having no evidence of polyps is of poor prognosis [2304].

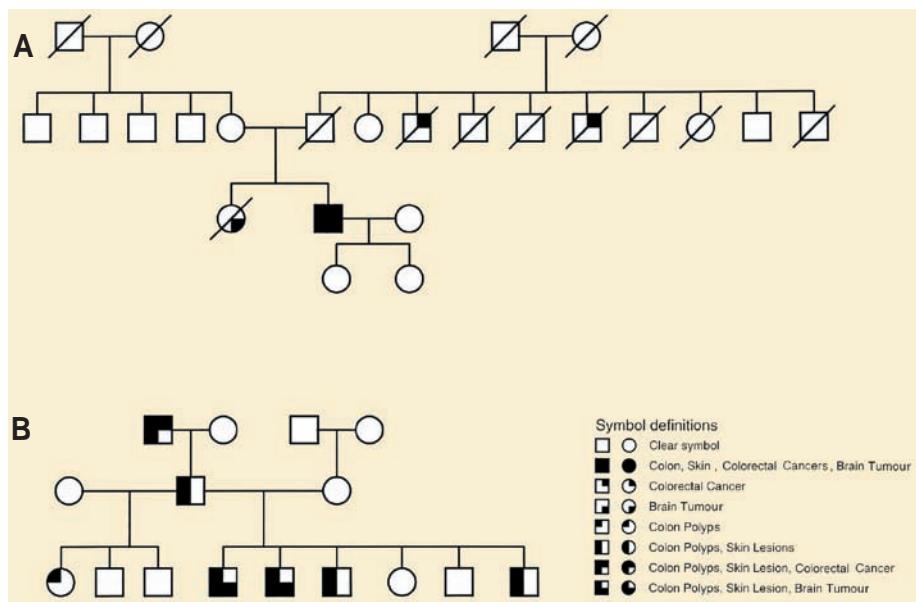


Fig. 13.33 Typical pedigrees of Turcot families. A Turcot type 1 (non-polyposis colon cancer and predominantly glioblastomas, frequently associated with mutations in DNA mismatch repair genes). B Turcot type 2, characterized by familial adenomatous polyposis, colon carcinomas, and medulloblastomas, caused by an APC germline mutation.

Naevoid basal cell carcinoma syndrome

C.G. Eberhart
W.K. Cavenee
T. Pietsch

Definition

An autosomal dominant disease associated with a broad spectrum of developmental disorders and predisposition to benign and malignant tumours, including basal cell carcinomas of the skin, odontogenic keratocysts, palmar and plantar dyskeratotic pits, intracranial calcifications, macrocephaly and medulloblastomas; caused by germline mutations of the *PTCH* gene on 9q22.

MIM No. 109400 {1433}.

Synonyms

Naevoid basal cell carcinoma syndrome (NBCCS) is also known as Gorlin syndrome, Gorlin-Goltz syndrome, basal cell nevus syndrome and fifth phacomatosis.

Incidence

A prevalence of 1 in 57 000 has been reported in a population-based study {539}. Of carriers with germline *PTCH* mutations, about 5% develop medulloblastoma and about 1–2% of medulloblastoma patients carry *PTCH* germline mutation {539}.

Diagnostic criteria and clinical features

The most common manifestations of NBCCS are multiple basal cell carcinomas, as well as odontogenic keratocysts of the jaw, which in one study were found together in more than 90% of affected individuals by the age of 40 {541}. Other major criteria for the syndrome include calcification of the falx cerebri, palmar and plantar pits, bifid or fused ribs, and first degree relatives with NBCCS {1112, 2063}. Minor criteria include medulloblastoma, ovarian fibroma, macrocephaly, congenital facial abnormalities (cleft lip or palate, frontal bossing, hypertelorism), skeletal abnormalities such as digit syndactyly, and radiologic bone abnormalities including bridging of the sella turcica {51, 1112}. A diagnosis of NBCCS is made when two or more major or one major and two or more minor criteria are present {51}. Several other tumour types have been reported in individual NBCCS

patients, including meningioma, melanoma, chronic lymphocytic leukaemia, non-Hodgkin lymphoma, ovarian dermoid, as well as breast and lung carcinoma. However, the statistical association of these neoplasms with NBCCS has yet to be shown {2063}. Radiation treatment of NBCCS patients, e.g. craniospinal irradiation for the treatment of cerebellar medulloblastoma, induces multiple basal cell carcinomas of the skin as well as various other tumour types within the radiation field {316, 1610, 2143}.

NBCCS-associated medulloblastoma

In a recent review of 33 medulloblastoma cases associated with NBCCS, all but one tumour developed in a child less than 5 years of age, and 22 cases (66%) presented prior to age 2 {51}. Medulloblastoma associated with NBCCS appear to be exclusively of the desmoplastic/nodular variant {51, 2035}. It has therefore been proposed that the identification of desmoplastic medulloblastoma in children younger than 2 serve as a major criteria for the diagnosis of NBCCS {51}. The prognosis of NBCCS-associated medulloblastoma appears to be better than that of sporadic cases, and it has been suggested that radiation therapy protocols be altered in NBCCS patients younger than 5 to ameliorate the formation of secondary tumours {51, 2143}.

Other CNS manifestations

There is no statistically proven evidence for an increased risk of other CNS neoplasms in naevoid basal cell carcinoma syndrome. Nevertheless, several instances of meningioma arising in NBCCS patients were reported {35, 2063}. Various malformative changes of the brain and skull including calcification of the falx cerebri and/or tentorium cerebelli at a young age, dysgenesis of the corpus callosum, congenital hydrocephalus, and macrocephaly may occur in affected family members.

Genetics

The condition follows an autosomal

dominant pattern of inheritance, with full penetrance but variable clinical phenotypes. The rate of new mutations has not been precisely determined. It has been estimated that a high percentage (14–81%) of the cases represent new mutations {541, 710, 2063, 2408}.

Molecular genetics

NBCCS results from inactivating germline mutations in the human homologue of the *Drosophila* segment polarity gene *patched* (*PTCH*) {753, 1005}. The *PTCH* gene maps to chromosome band 9q22.3 {1005}.

Gene structure

The *PTCH* gene spans approximately 50 kb of genomic distance. It has at least 23 exons {753, 1005} with alternative usage

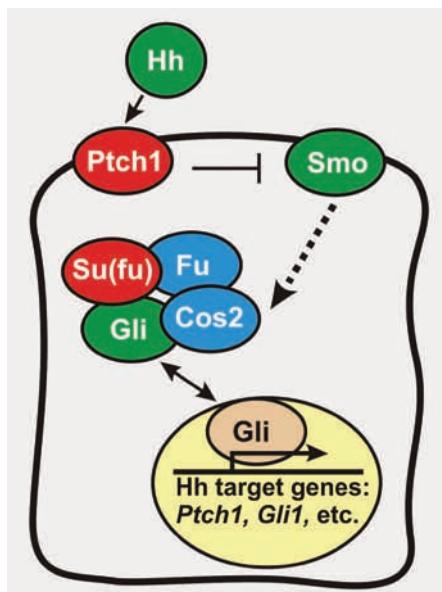


Fig. 13.34 Hedgehog signaling is activated in normal development by interaction of a secreted hedgehog ligand (Hh) with the multipass transmembrane receptor Ptch. Ligand binding relieves the repressive effects of Ptch on Smo, and permits the activation and nuclear translocation of Gli transcription factors. Gli activation is also promoted by Fu, and suppressed by Su(fu). Cos2 proteins are thought to serve as a scaffold for these interactions. Once in the nucleus, Gli factors induce the transcription of various pathway targets, including feedback loops involving Ptch1 and Gli1.

of 5 different first exons [1546]. By extensive splicing events tissue-specific expression pattern of various PTCH isoforms occur, including mRNA species encoding dominant negative forms of PTCH [1545, 1546, 2281].

Gene function

The *PTCH* gene codes for a 12-transmembrane protein (Ptch) expressed on many progenitor cell types. It functions as receptor for members of the secreted hedgehog protein family of signalling molecules [1400, 2156]. In humans, this family consists of three members designated as Sonic hedgehog, Indian hedgehog, and Desert hedgehog. The *PTCH* gene product has homology to bacterial transporter proteins [2198] and controls another transmembrane protein, Smoothened (Smo) [37, 2156]. In the absence of ligand, Ptch inhibits the activity of Smo [37, 2156]. Binding of hedgehog proteins to Ptch can relieve this inhibition of Smo, which results in signal transduction finally leading to translocation of Gli transcription factors into the cell nucleus and transcription of a set of specific target genes controlling survival, differentiation and proliferation of progenitor cells. In vertebrates, this pathway is critically involved in the development of various tissues and organ systems, such as limbs, gonads, bone, and CNS [709, 916]. Germline mutations in the Sonic hedgehog (*SHH*) and *PTCH* genes were found to cause holoprosencephaly [131, 1483, 1908].

Gene mutations

So far, 132 different *PTCH* germline mutations associated with NBCCS have been reported [1327]. However, mutations are not detected in all cases [1404]. Mutations are distributed over the entire *PTCH* coding sequence without demonstrating any mutational hot spots, and

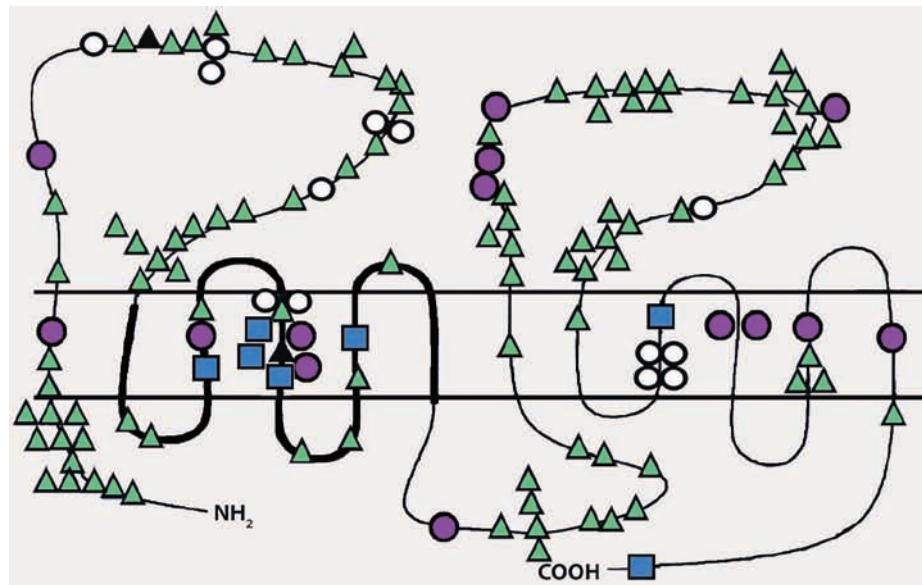


Fig. 13.35 Germline mutations of the *PTCH* gene in 132 NBCCS patients. Green triangle, nonsense mutation; open circle, splice mutation; purple circle, familial missense mutation; black triangle, *de novo* missense mutation; blue square, germline conserved missense mutation. The thick line indicates the location of the sterol sensing domain. Modified from Lindstrom *et al.* [1327].

there appears to be no clear genotype-phenotype correlation [2409]. Missense mutations cluster in a highly conserved region, the sterol sensing domain, especially in transmembrane domain 4. Somatic mutations of *PTCH* have been demonstrated in various sporadic human tumours (for review see [1327], including basal cell carcinoma [639, 753, 1005], trichoepithelioma [2346], oesophageal squamous cell carcinoma [1378], invasive transitional cell carcinoma of the bladder [1431], and medulloblastoma [1327, 1747, 1816, 2345]. Similar to the germline mutations, the vast majority of mutations detected in sporadic tumours result in truncations at the protein level. There is no obvious clustering of mutation sites. One study of 68 sporadic medulloblastomas, *PTCH* mutations were exclusively detected in the desmoplastic

variant, but not in 57 tumours with classical morphology [1747]. In line with these data, LOH analyses of sporadic medulloblastomas demonstrated frequent allelic loss at 9q22.3-q31 in desmoplastic medulloblastomas (up to 50%), but not in classic medulloblastomas [36, 2035]. These data would be consistent with the observation that medulloblastomas associated with NBCCS are predominantly of the desmoplastic variant, indicating a strong association between desmoplastic phenotype and pathological hedgehog pathway activation [51]. However, other studies also reported *PTCH* mutations in classic medulloblastomas [1816, 2345]. *PTCH2*, a *PTCH* homologue located at chromosome band 1p32, can also carry somatic mutations in single cases of medulloblastoma and basal cell carcinomas [2118].

Rhabdoid tumour predisposition syndrome

P. Wesseling
J.A. Biegel
C.G. Eberhart
A.R. Judkins

Definition

A disorder characterized by a markedly increased risk to develop malignant rhabdoid tumours (MRTs), generally due to constitutional loss or inactivation of one allele of the *INI1* gene.

MIM No. 609322.

Synonyms

Rhabdoid predisposition syndrome; Familial posterior fossa brain tumour syndrome of infancy.

Incidence

Germline *INI1* mutations in patients with atypical teratoid/rhabdoid tumours (AT/RTs), i.e. the central nervous system representative of MRTs, are estimated to occur in up to one third of patients [153]. Because of this risk, it is important to investigate the *INI1* status in all newly diagnosed cases by molecular genetic analysis. Individuals with a germline *INI1* mutation are more likely to present with a tumour in the first year of life. Children with multiple MRTs or with affected siblings or other relatives almost certainly are afflicted by the rhabdoid tumour predisposition syndrome (RTPS). Familial cases have only occasionally been reported [564, 971, 1275, 1364, 1804, 2057, 2225].

Diagnostic criteria and clinical features

As discussed in the chapter on AT/RTs (see Chapter 8), the histopathological diagnosis of these tumours can be challenging. In most cases, immunohistochemical analysis is very helpful, as the biallelic inactivation of the *INI1* gene in AT/RTs results in lack of INI1 expression in the tumour cell nuclei, while normal cells and almost all other neoplasms show unequivocal nuclear staining [1017]. Demonstration of a germline *INI1* mutation is sufficient for the diagnosis of RTPS. However, a recent study indicates that an alternate locus can cause RTPS as well [616]. As the RTPS was only relatively recently recognized, study of additional affected individuals and families is required to better define this syndrome [971].

Nervous system neoplasms

Individuals with RTPS frequently present with the central nervous system (CNS) manifestation of MRT, i.e. AT/RT (see Chapter 8). These neoplasms were called "rhabdoid" because of the presence of tumour cells with eccentrically placed nuclei containing vesicular chromatin and prominent nucleoli, as well as abundant cytoplasm with eosinophilic globular cytoplasmic inclusions, features that were

originally felt to be reminiscent of skeletal myoblasts. However, the cell of origin of MRTs is not known [153]. Patients with germline mutations or deletions of *INI1* may develop isolated AT/RTs, or an AT/RT with a synchronous renal or extra-renal MRT. AT/RTs generally occur in early childhood, but are occasionally found in adults as well [1823]. Other CNS tumours that have been reported to be associated with the RTPS include choroid plexus carcinoma [660], medulloblastoma, and supratentorial primitive neuroectodermal tumour [2057]. However, as the histopathological distinction of these tumours from AT/RTs can be challenging, and because the rhabdoid component may be missed due to sampling effects, the occurrence of such other tumours in the context of the RTPS is controversial [747, 1016, 1017, 2289]. Meningiomas may harbour *INI1* mutations [2033]. However, it is not known whether the exon 9 missense mutation described in these tumours is an inactivating mutation. The vast majority of the so-called composite rhabdoid tumours (i.e. meningiomas, gliomas, melanomas, carcinomas with rhabdoid features) retain nuclear INI1 staining [1723], strongly suggesting they do not contain the same genetic alterations as classic MRT. These composite lesions are therefore unlikely to be part of the RTPS.

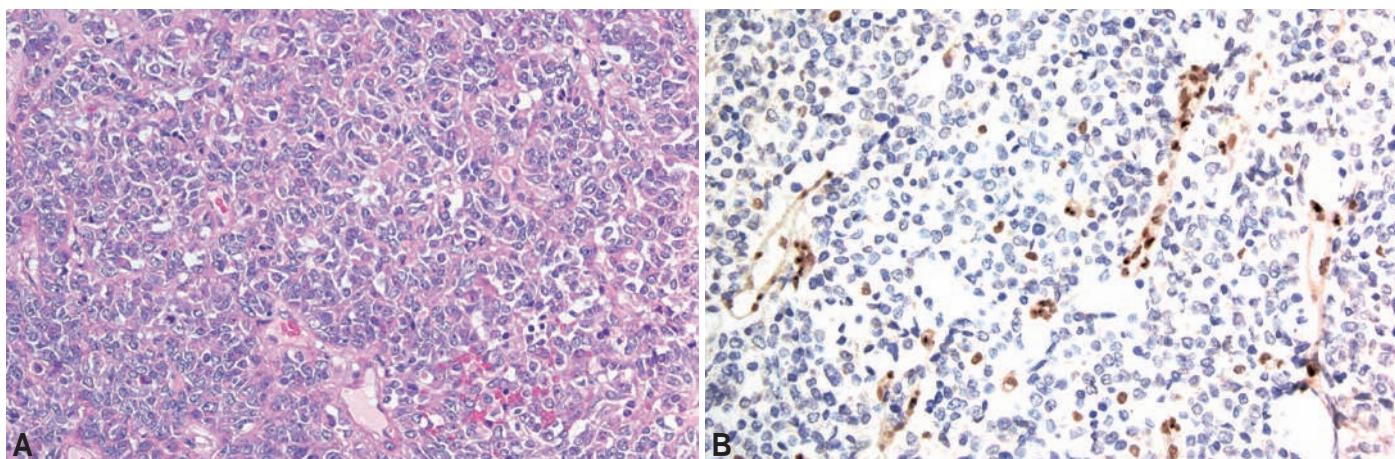


Fig.13.36 A Renal rhabdoid tumour with marked nuclear pleomorphism, prominent nucleoli and eosinophilic cytoplasmic inclusions. B INI1 immunohistochemical staining demonstrating loss of expression in neoplastic cells with retained expression in intratumoral blood vessels.

Extraneuronal manifestations

By far the most frequent extra-CNS location of MRT is the kidney. Bilateral renal MRTs are almost always associated with a germline *INI1* mutation, but infants with an isolated MRT may also carry germline mutations. Occasionally, MRTs have been reported to originate in the head and neck region, paraspinal soft tissues, heart, mediastinum and liver [2402]. Recent reports indicate that *INI1* mutations may occasionally underlie the oncogenesis of other neoplasms such as the proximal type of epithelioid sarcoma [1503], but to date these sarcomas have not been described in association with the RTPS.

Genetics

Gene

MRTs can occur sporadically or as part of the RTPS [153]. In most cases of both sporadic and RTPS-associated MRTs, *INI1* (*hSNF5*, *SMARCB1*, *BAF47*) can be identified as the causative gene. *INI1* is located at chromosome 22q11.2, has 9 exons and a coding sequence of about 1.2 kb [1028].

The *INI1* protein

The *INI1* protein is a member of the ATP-dependent SWI-SNF chromatin-remodelling complex, and is recruited to promoters of genes that regulate the cell cycle, growth, and differentiation. *INI1* functions as a tumour suppressor gene, implying

that two successive hits are needed for malignant transformation, and that in familial cancer one hit is inherited [914, 1897].

Gene mutations

The types of mutations observed in sporadic MRTs are similar to the spectrum of germline mutations reported to date. However, single base deletions in exon 9 appear most often in AT/RTs in patients without detectable germline alterations [153]. The second inactivating event is most frequently a deletion of the wild-type allele, often due to monosomy 22. Prior to the identification of *INI1* as the causative gene, several reports described siblings being affected by AT/RT and/or MRT [1364, 1804]. Subsequently, affected siblings were reported to carry the same germline *INI1* mutation [564, 1275, 2057]. Very few reports exist on involvement of two or more generations of a family [971, 2225]; in these two reported families, germline mutations of *INI1* were transmitted to the affected offspring by a non-affected carrier mother. Alternatively, new mutations can occur during oogenesis/spermatogenesis (gonadal mosaicism), or post-zygotically during the early steps of embryogenesis [2057]. For individuals carrying a germline *INI1* mutation, a developmental window seems to exist wherein MRTs occur with sharply increased susceptibility during the first years of life [971]. Such infants generally do not pass the trait to offspring because almost all die before the reproductive age.

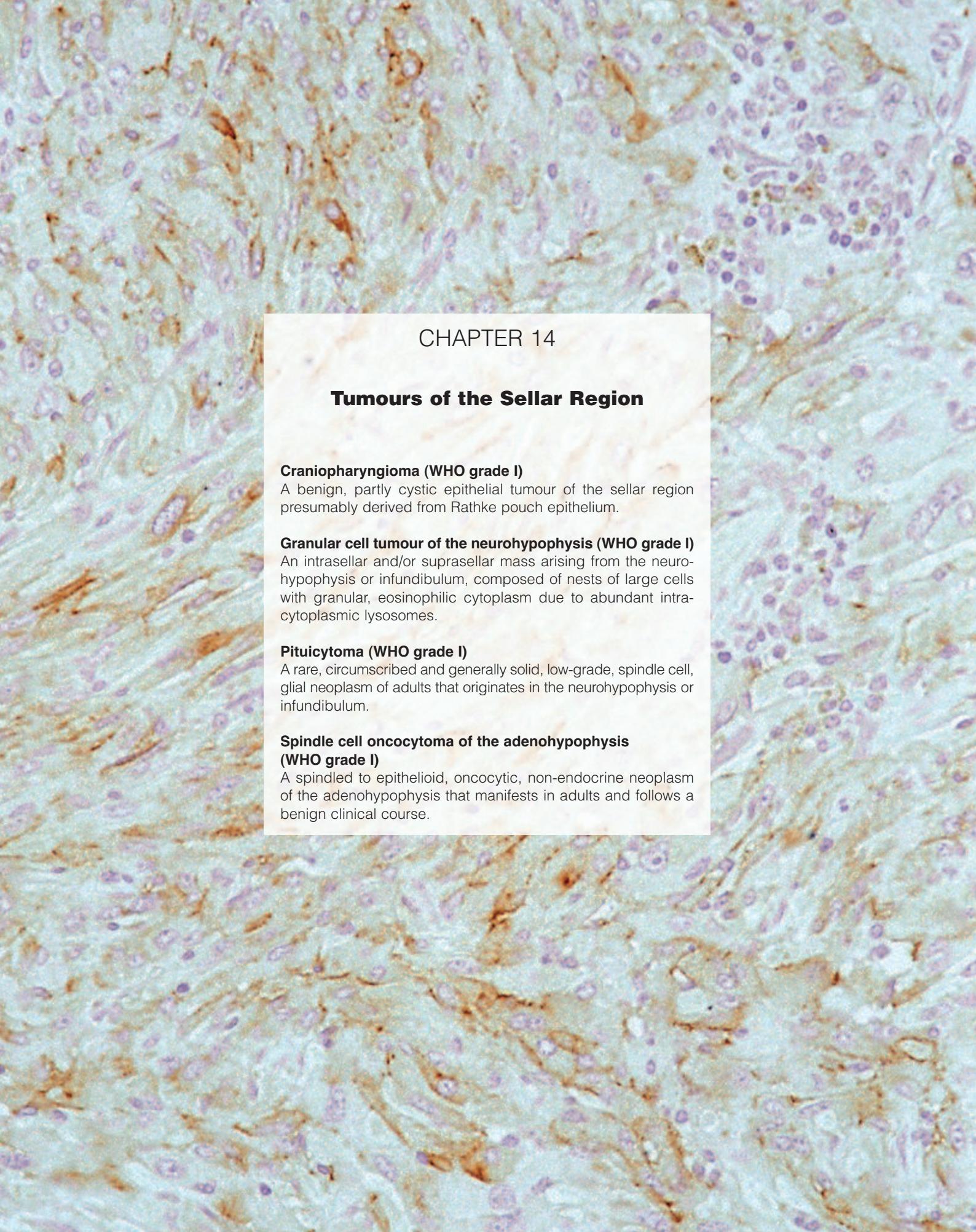
Prognostic factors

MRTs are highly aggressive cancers that most frequently occur in young children and are generally lethal within months or a few years. No clear correlation between the type of *INI1* germline alteration and biological behaviour in RTPS patients has been established.

Table 13.14 Distribution and nature of *INI1* germline mutations and tumour locations associated with rhabdoid tumour predisposition syndrome.

Exon	Codon	Mutation	Tumour Location
1-9	All	Gene deletion	brain, kidney
1-9	All	Gene deletion	kidney
1-9	All	Gene deletion	brain
1	donor splice site	G -> C	brain
2	47,48	141/4 ins C	kidney
2	51	G152A	brain
2	53	C157T	kidney
2	53	C157T	brain, kidney
2	53	C157T	brain
2	66	C197A	brain, kidney
3	91	271/2 delT	brain, kidney
4	123	C367T	brain
4	126	373 ins 4bp	brain
4	144	430 delG	brain
4	144	430 delG	brain
4	158	C472T	kidney
4	158	C472T	kidney
4	158	C472T	brain, soft tissue
4	158	C472T	brain, lung, kidney
5	197	591 delG	brain
5	198	C592T	brain, kidney
5	198	C592T	brain, kidney
5	201	C601T	brain
5	201	C601T	brain, lung
5	201	C601T	brain, kidney
5	206	G617A	kidney
6	250	750insC	bladder
6	257	C769T	brain, kidney
7	266	797 del 10 bp	kidney
7	297	889 del 7bp	brain, kidney
7	326	C978A	brain, kidney
7	326	C978A	brain
7	326	C978A	epidural
7	donor splice site	G -> A	brain

Data from 34 cases reported in the literature [153, 205A, 564, 622A, 971, 1239A, 1275, 1997A, 2057, 2225, 2409A]. Cases in bold represent families with tumour growth in two or more siblings, cases in italics and bold represent families with tumour development in multiple generations.



CHAPTER 14

Tumours of the Sellar Region

Craniopharyngioma (WHO grade I)

A benign, partly cystic epithelial tumour of the sellar region presumably derived from Rathke pouch epithelium.

Granular cell tumour of the neurohypophysis (WHO grade I)

An intrasellar and/or suprasellar mass arising from the neurohypophysis or infundibulum, composed of nests of large cells with granular, eosinophilic cytoplasm due to abundant intracytoplasmic lysosomes.

Pituicytoma (WHO grade I)

A rare, circumscribed and generally solid, low-grade, spindle cell, glial neoplasm of adults that originates in the neurohypophysis or infundibulum.

Spindle cell oncocytoma of the adenohypophysis (WHO grade I)

A spindled to epithelioid, oncocytic, non-endocrine neoplasm of the adenohypophysis that manifests in adults and follows a benign clinical course.

Craniopharyngioma

E.J. Rushing
F. Giangaspero
W. Paulus
P.C. Burger

Definition

A benign, partly cystic epithelial tumour of the sellar region presumably derived from Rathke pouch epithelium.

ICD-O codes

Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1

Grading

Craniopharyngiomas correspond histologically to WHO grade I.

Incidence

Craniopharyngiomas account for 1.2–4.6% of all intracranial tumours, corresponding to 0.5–2.5 new cases per million population per year [246], being more frequent in Nigerian (18% of all CNS tumours) [939] and Japanese children with an annual incidence of 5.25 cases per million in the paediatric population [1231]. They are the most common non-neuroepithelial intracerebral neoplasm in children, accounting for 5–10% of intracranial tumours in this age group [14].

Age and sex distribution

A bimodal age distribution of adamantino-

matous craniopharyngioma is observed [246], with peaks in children aged 5–15 years and adults aged 45–60 years. Rare neonatal and intrauterine cases have been reported [1150]. Papillary craniopharyngiomas occur virtually exclusively in adults, at a mean age of 40–55 years [14, 395]. Craniopharyngiomas show no obvious sex predilection.

Localization

The most common site is suprasellar with a minor intrasellar component. Unusual locations such as sphenoid sinus have been reported [1166].

Clinical features

Symptoms and signs

Clinical features are non-specific and essentially include visual disturbances (observed in 62–84% of the patients, more frequently in adults than in children) and endocrine deficiencies (observed in 52–87% of patients, more frequently in children) [2462]. Endocrine deficiencies include those for GH (75%), LH/FSH (40%), ACTH (25%) and TSH (25%). Diabetes insipidus is noted in up to 17% of children and up to 30% of adults. Cognitive impairment and personality changes are observed in about half of patients [2462]. Signs of increased

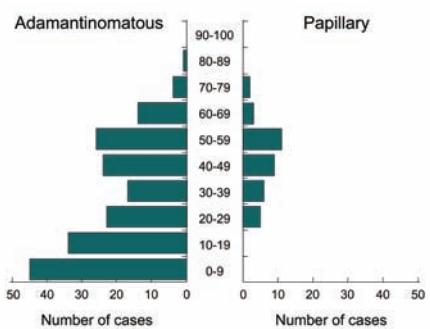


Fig. 14.01 Age distribution of adamantinomatous and papillary craniopharyngioma, based on 224 cases.

intracranial pressure are frequent, especially in cases with compression or invasion of the third ventricle.

Neuroimaging

For adamantinomatous craniopharyngioma, radiography provides an accurate depiction of the configuration of the sella and the typical calcifications. CTs show contrast enhancement of the solid portions and the cyst capsule, as well as the typical calcifications. On T1-weighted MRI, cystic areas appear as well-delineated homogeneous hyperintense structures, whereas the solid components and mural nodules are isointense, with a

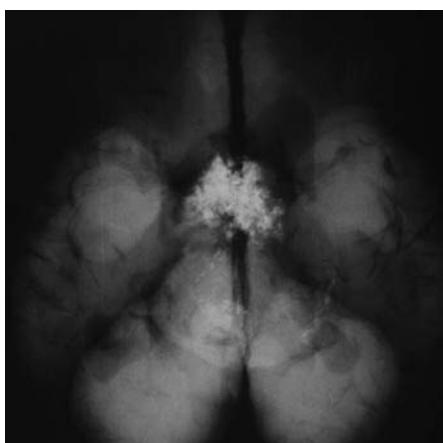


Fig. 14.02 Large adamantinomatous craniopharyngioma extending into the third ventricle. Note the dorsal portion resembling 'machine oil'. Postmortem X-ray showed extensive calcification.

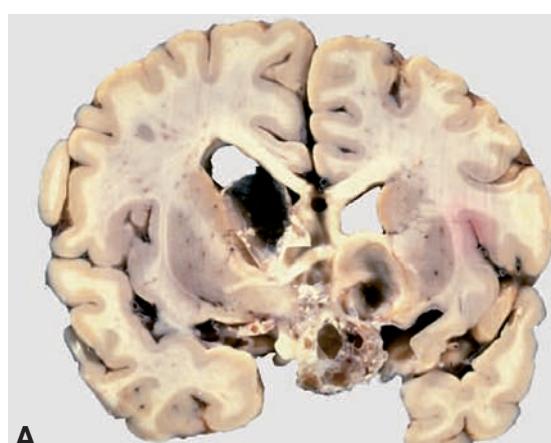


Fig. 14.03 A Cystic craniopharyngioma invading the third ventricle and the basal ganglia. B Adamantinomatous craniopharyngioma extending towards the cerebral peduncles. Note the colloid material and calcifications.



slightly heterogeneous quality. In enhanced MRI images, the cystic portion is iso-intense with an enhancing ring, whereas the solid parts are hyperintense {1936}. The papillary craniopharyngioma is non-calcified and has a more uniform appearance in CT and MRI images {395, 1992}.

Macroscopy

Typically a lobulated solid mass, on closer inspection, adamantinomatous craniopharyngiomas often demonstrate a spongy quality as a result of a variable cystic component. On sectioning, the cysts may contain dark greenish-brown liquid resembling machinery oil. The gross appearance also reflects the extent of secondary changes such as fibrosis, calcification, ossification and the presence of cholesterol-rich deposits. They often extend beyond their apparent gross confines, superficially penetrating neighbouring brain and adhering to adjacent blood vessels and nerves. By contrast, papillary craniopharyngiomas are well-circumscribed, solid or rarely cystic tumours. An additional distinction from the adamantinomatous variety is the absence of cholesterol-rich machinery oil and calcification.

Histopathology

Adamantinomatous craniopharyngioma is recognized by the presence of squamous epithelium disposed in cords, lobules and irregular trabeculae bordered by palisaded columnar epithelium. These islands of densely packed cells merge with loosely cohesive aggregates of squamous cells known as stellate reticulum. Nodules of "wet keratin" representing remnants of pale nuclei embedded within an eosinophilic keratinous mass are found in either the compact or looser areas. Cystic cavities containing squamous debris are lined by flattened epithelium. Granulomatous inflammation associated with cholesterol clefts and giant cells may be seen, but this is more typical of the xanthogranuloma. Piloid gliosis with abundant Rosenthal fibers is often seen at the infiltrative interface of the tumour and should not be mistaken for pilocytic astrocytoma. The question of "malignant transformation" of craniopharyngioma has been raised in the literature {1191}, but this appears to be very rare.

The essential features of papillary crano-

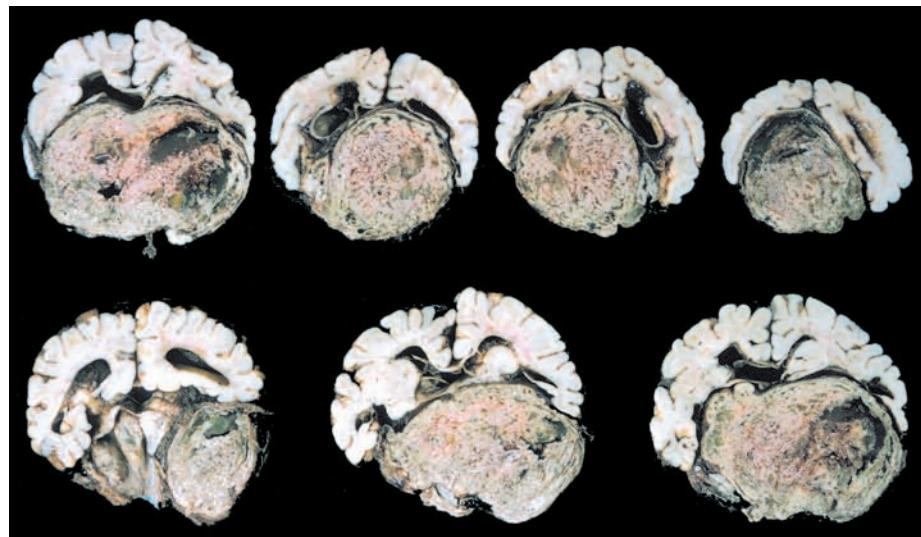


Fig. 14.04 Congenital case of an unusually large, partly cystic craniopharyngioma causing compression and shift of basal brain structures.

pharyngioma include a monomorphous mass of well-differentiated squamous epithelium lacking surface maturation, the picket-fence-like palisades and wet keratin. As noted, another contrasting point is the absence of calcification. Rarely, ciliated epithelium and goblet cells are encountered.

Electron microscopy

Although electron microscopy can serve

as a diagnostic adjunct, it is seldom needed given the rather typical features in most cases. In addition to glycogen and the usual organelles, the constituent epithelial cells contain tonofilaments and are joined by desmosomes. Fenestrated capillary endothelium, amorphous ground matrix and collagen fibrils characterize the connective tissue stroma. Mineral precipitates appear to arise in membrane-bound vesicles {1996}.

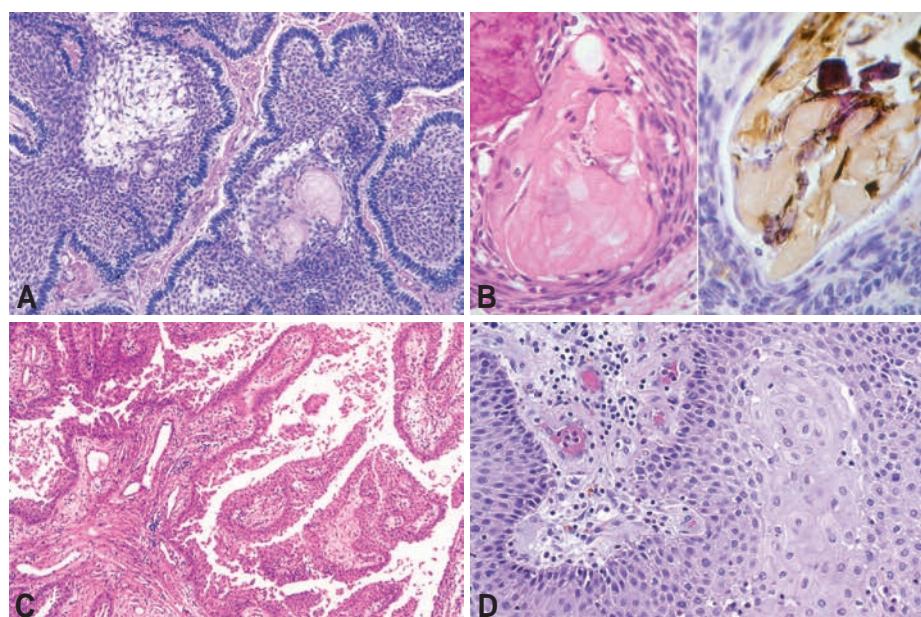


Fig. 14.05 A Adamantinomatous craniopharyngioma with focal keratinization. B Higher magnification shows wet keratin structure (left) and immunoreactivity for cytokeratin (right). C Papillary craniopharyngioma with well-differentiated epithelium. D Well-differentiated squamous epithelium.

Differential diagnosis

Xanthogranuloma of the sellar region {1697} is histologically composed of cholesterol clefts, macrophages (xanthoma cells), chronic inflammatory cellular reaction, necrotic debris and haemosiderin deposits. Although the entity is not yet fully defined and transitional cases do occur, xanthogranuloma of the sellar region is clinico-pathologically distinct from adamantinomatous craniopharyngioma with respect to location, tumour size, age distribution, symptoms and prognosis. Non-adamantinomatous squamous or cuboidal epithelium as well as small tubuli may be focally encountered, while typical adamantinomatous epithelium is usually absent or amounts to less than 10% of tissue {1697}. In contrast to adamantinomatous craniopharyngioma, epithelial cells encountered in xanthogranuloma do not exhibit nuclear accumulation of β -catenin {267}.

Although the histological appearance of adamantinomatous craniopharyngioma is characteristic, epidermoid and Rathke's cleft cysts are sometimes raised in the differential diagnosis. A reliable distinction of both entities is feasible if attention is paid, in the case of the former, to the presence of a uniloculated cyst lined by squamous epithelium and filled with flaky, "dry keratin". Rathke's cleft cysts rarely pose a significant challenge and only enter into the differential diagnosis when they show extensive squamous metaplasia. More commonly, Rathke's cleft cysts consist of a single layer of flattened, either ciliated or mucin-producing epithelium, occasionally accompanied by a xanthogranulomatous reaction {906}.

Proliferation

MIB-1 immunoreactivity is concentrated in the peripherally palisaded cells in the adamantinomatous type, and is more randomly distributed in the papillary lesions {470, 496}. Reported indices vary considerably from case to case, and, overall, are considerably higher than might be expected given the indolence of the neoplasms {470, 496}. No relationship between indices and recurrence has been established.

Genetics

Multiple chromosomal abnormalities have been reported in two cases by classic cytogenetic analysis; both tumours had

abnormalities involving chromosomes 2 and 12 {711, 1049}.

More than 70% of craniopharyngiomas of the adamantinomatous type harbour a mutation of the β -catenin gene {267, 1053, 1632, 2047}. Most of the mutations affect exon 3, which encodes the degradation targeting box of β -catenin compatible with an accumulation of nuclear β -catenin protein {267}. In few cases of adamantinomatous craniopharyngiomas, the same β -catenin mutations occurring in the epithelial cells have been identified in mesenchymal cells. Such observation suggests a biphasic nature of a subgroup of adamantinomatous craniopharyngiomas {2047}. In contrast, no mutations have been demonstrated in papillary craniopharyngiomas. Comparative genomic hybridization (CGH) studies on two large series of craniopharyngiomas have failed to show significant chromosomal imbalances in adamantinomatous and papillary-type craniopharyngiomas {1880, 2473}. Another CGH study in nine adamantinomatous craniopharyngiomas revealed at least one genomic alteration in 67% of cases {1888}.

Histogenesis

Several observations indicate that craniopharyngiomas arise from neoplastic transformation of ectodermal-derived epithelial cell remnants of Rathke's pouch and the craniopharyngeal duct. Epithelial cell rests have been reported to occur between the roof of the pharynx and the floor of the third ventricle, most frequently along the anterior part of the infundibulum and the anterior-superior surface of the adenohypophysis, sites of the previous Rathke's pouch and the involuted duct that links these structures. Metaplasia of cells derived from the tooth primordia gives rise to the adamantinomatous variety, whereas metaplastic changes in cells derived from buccal mucosa primordia give rise to the squamous papillary variety {1782}.

Further support for the assumption that craniopharyngiomas originate from Rathke's pouch is provided by the occasional occurrence of mixed tumours with characteristics of craniopharyngioma and Rathke's cleft cyst, and by the report of a unique congenital craniopharyngioma {2454} with ameloblastic as well as tooth bud and adenohypophyseal primordia components.

The hypothesis that craniopharyngiomas

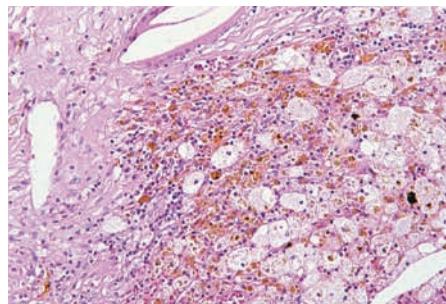


Fig. 14.06 Xanthogranuloma of the sellar region, showing xanthoma cells, lymphocytic infiltrates, haemosiderin deposits, cholesterol clefts and occasional multinucleated giant cells.

contain a neuroendocrine lineage is supported by the finding that scattered tumour cell groups may express one or more pituitary hormones {2190}, chromogranin A {2454} and human chorionic gonadotropin {2193}. Also in support is the observation of a tumour that arose from a Rathke cleft cyst and contained cells that were transitional between squamous, mucus-producing and anterior pituitary lobe secretory cells {1077}.

Prognostic and predictive factors

In large series, 60–93% of patients had a 10-year recurrence-free survival and 64–96% an overall 10-year survival {395, 1824, 2462}. The most significant factor associated with craniopharyngioma recurrence is the extent of surgical resection {1982, 2387, 2462}, with lesions greater than 5 cm in diameter carrying a markedly worse prognosis {2462}. After incomplete surgical resection, the recurrence rate is significantly higher {2387, 2462}. Histological evidence for brain invasion, more frequently documented in the adamantinomatous than in the papillary type, is not correlated with a higher recurrence rate in cases with gross surgical resection {2387}. Some authors have documented a better prognosis for the papillary than for the adamantinomatous type of craniopharyngioma {14, 2224}, while others failed to demonstrate significant differences {395, 2387}. Dissemination in the subarachnoid space {927, 1273} or implantation along the surgical track or path of needle aspiration {100, 1338} is rare. Malignant transformation of craniopharyngioma to squamous carcinoma after irradiation is exceptional {730, 2241}.

Granular cell tumour of the neurohypophysis

G.N. Fuller
P. Wesseling

Definition

An intrasellar and/or suprasellar mass arising from the neurohypophysis or infundibulum, composed of nests of large cells with granular, eosinophilic cytoplasm due to abundant intracytoplasmic lysosomes.

ICD-O code 9582/0

Grading

Granular cell tumours correspond to WHO grade I.

Synonyms

Abrikossoff tumour, choristoma, granular cell myoblastoma, granular cell neuroma, pituicytoma. The term pituicytoma is now reserved for a distinct, circumscribed glial neoplasm originating in the neurohypophysis or infundibulum (see Pituicytoma chapter).

Incidence

Symptomatic granular cell tumours (GCTs) are relatively rare and present in adulthood, with only exceptionally rare childhood cases [133]. There is a clear female predominance of greater than 2:1. The peak incidence is slightly later in men than in women (sixth and fifth decade, respectively). Asymptomatic

microscopic clusters of granular cells, termed granular cell tumorettes [2062] or tumorlets [1358], are more common than the larger, symptomatic tumours, and have been documented at an incidence up to 17% in postmortem series [1358, 2062, 2255].

Localization

GCTs arise along the anatomic distribution of the neurohypophysis, including the posterior pituitary and pituitary stalk/infundibulum. They exhibit a preference for the pituitary stalk and thus most frequently arise in the suprasellar region, but may also arise from the posterior pituitary and present as an intrasellar mass. GCTs with identical morphologic and immunophenotypic features as those seen in the neurohypophyseal tumours have rarely been reported in other anatomic locations within the central nervous system, including the spinal meninges [1402], cranial meninges [2316], third ventricle [2286] and cerebral hemisphere [472].

Clinical features

Symptoms and signs

The most common presenting symptom is visual field deficit secondary to compression of the optic chiasm [367].

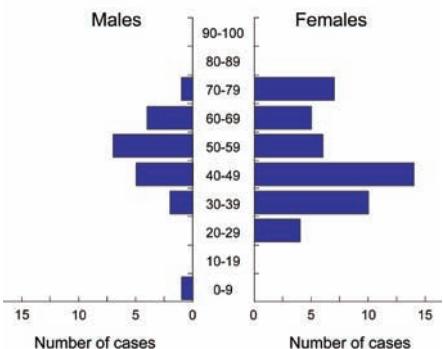


Fig.14.07 Age and sex distribution of neurohypophyseal granular cell tumours based on 66 symptomatic cases published in the literature (M:F = 1:2.3).

Other presenting complaints include panhypopituitarism, galactorrhea, amenorrhea, decreased libido and neuropsychological changes. Diabetes insipidus has been reported, but is relatively uncommon [367]. Symptoms usually develop slowly over a period of years, although acute presentation with sudden-onset diplopia, confusion, headache and vomiting can occur [367]. There are no disease-specific signs or symptoms that reliably distinguish GCT from other suprasellar mass lesions. Several cases have been found in association with pituitary adenoma [105, 367, 1348, 2255].

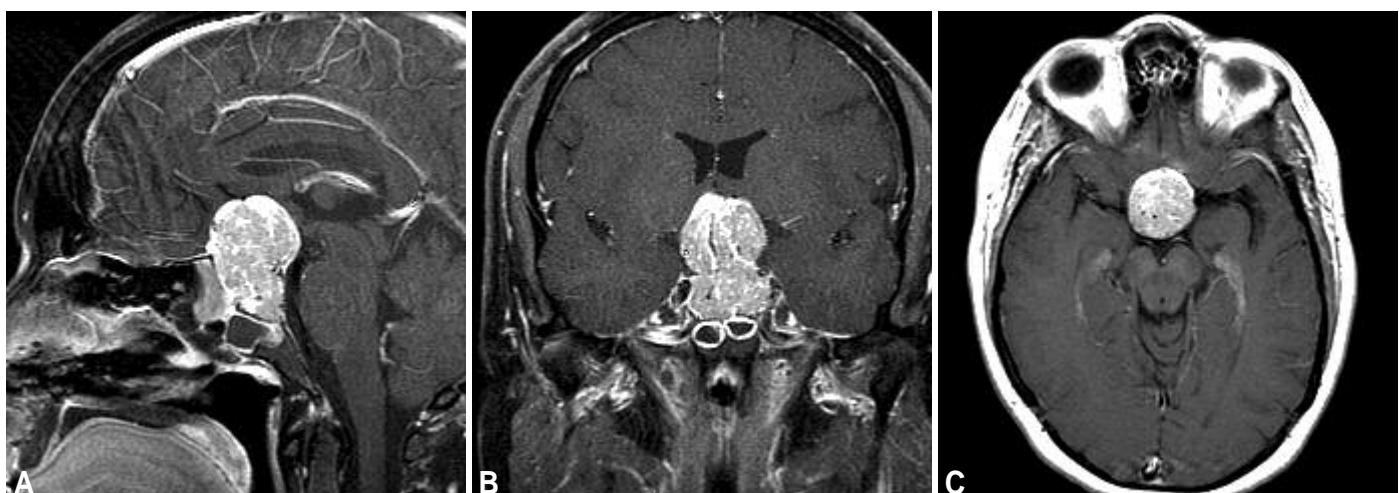


Fig. 14.08 T1-weighted post-contrast MRI of a granular cell tumour in the sagittal (A), coronal (B), and axial (C) planes showing prominent contrast enhancement. Note the characteristic sellar/suprasellar anatomic location.

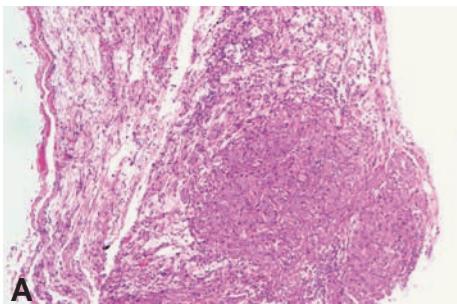
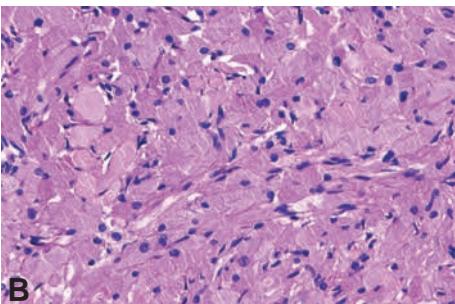
**A****B**

Fig. 14.09 Granular cell tumorlet (tumorette) of the infundibulum. A Hematoxylin-eosin whole mount section. B High-power magnification showing discrete cellular borders and granular cytoplasm.

Neuroimaging

MRI typically shows a well-circumscribed suprasellar mass that most frequently displays homogeneous or heterogeneous contrast enhancement. Tumour size typically ranges from 1.5 to 6.0 cm [367]. Calcification is unusual and thus helps to distinguish GCT from craniopharyngioma. Similarly, lack of a dural attachment ("dural tail") and the anatomic location centred around the pituitary stalk help to distinguish GCT from most regional meningiomas. Although there are no pathognomonic imaging features, cases in which the tumour can be clearly seen to be separated from the pituitary by the inferior end of the pituitary stalk are suggestive of GCT [63]. Nevertheless, similar to the situation with suprasellar pituicytomas, due to the relative rarity of the tumour, the diagnosis is rarely anticipated prior to surgical resection.

Macroscopy

The tumours are usually lobulated and well-circumscribed, with a soft but rubbery consistency that is firmer than pituitary adenoma. The cut surface is typically grey-to-yellow. Necrosis, cystic degeneration and/or haemorrhage are uncommon. The tumour may infiltrate surrounding structures such as the optic chiasm and cavernous sinus; these features may prevent gross total surgical resection.

Histopathology

GCTs consist of densely packed polygonal cells with abundant granular eosinophilic cytoplasm. The architecture is typically nodular; sheets and/or spindled/fascicular patterns can also be seen. PAS staining of cytoplasmic granules is resistant to diastase digestion. Small foci of foamy cells may be observed. Tumour cell nuclei are small, with inconspicuous nucleoli and evenly distributed chromatin. Perivascular lymphocytic aggregates are common. Mitotic activity is usually inconspicuous, and proliferative activity is usually very low. Some lesions are characterized by nuclear pleomorphism, prominent nucleoli, multinucleated cells and increased mitotic activity (up to 5 mitoses per 10 HPF and Ki-67 labelling index of 7%); these tumours have been referred to as "atypical" GCTs by some authors, although clinical and biological significance is uncertain [1052, 2331].

Immunohistochemistry

GCTs are variably positive for CD68 (KP1), S-100, α -1-antitrypsin, α -1-antichymotrypsin and cathepsin B, and negative for neurofilament proteins, cytokeratins, chromogranin A, synaptophysin, desmin, smooth muscle actin and the pituitary hormones. Most tumours are negative for GFAP, although variable immunoreactivity has been noted in a subset of GCTs.

Electron microscopy

The cytoplasm of the granular tumour cells is filled with phagolysosomes containing unevenly distributed electron-dense material and membranous debris. A few other organelles and intracytoplasmic filaments may be observed, but neurosecretory granules are absent [122].

Histogenesis

GCT is a descriptive term of a histogenetically heterogeneous group of neoplasms in various anatomic sites throughout the body. Neurohypophyseal GCTs most likely arise from pituicytes, the glial element in the posterior lobe and stalk of the pituitary gland. The conflicting results of immunohistochemical studies of these pituitary GCTs may be explained by the presence of different types of pituicytes in the normal neurohypophysis [2203]. GCTs occasionally occur in the CNS outside the pituitary gland (meninges, cerebral hemisphere, third ventricle, cranial nerves); these may be derived from glial cells, Schwann cells or macrophages [367, 1878, 2316].

Genetics

Comparative genomic hybridization analysis of one tumour did not reveal chromosomal imbalances [1878]. In a case of atypical GCT, 95% of the tumour cells showed nuclear accumulation of p53 protein; 15% expressed bcl-2 [2331].

Prognostic and predictive factors

Most GCTs are clinically benign, with slow progression and lack of invasive growth. Surgical removal is the preferred therapy for larger tumours, but the firm and vascular nature of pituitary GCTs, sometimes combined with absence of an obvious dissection plane from the adjacent brain, may hamper gross total resection.

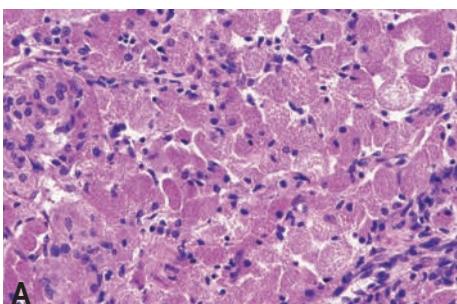
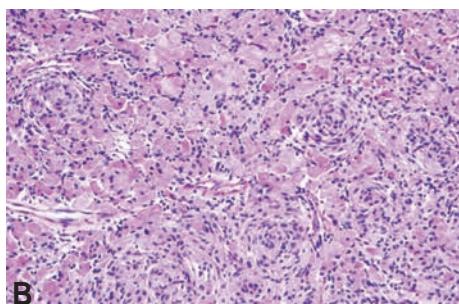
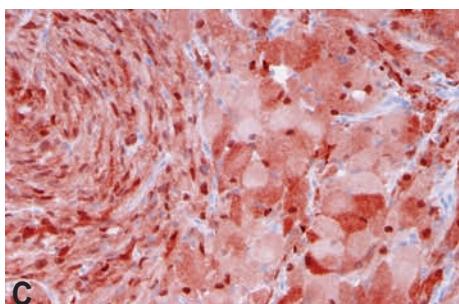
**A****B****C**

Fig. 14.10 Histological features of granular cell tumour of the neurohypophysis. A Characteristic abundant eosinophilic cytoplasm with prominent granularity. B Spindled and whorling cellular architecture. C S-100 protein expression in granular cell tumour.

Pituicytoma

P. Wesseling
D.J. Brat
G.N. Fuller

Definition

A rare, circumscribed and generally solid, low-grade, spindle cell, glial neoplasm of adults that originates in the neurohypophysis or infundibulum.

ICD-O Code

The provisional code proposed for the fourth edition of ICD-O is 9432/1.

Grading

Pituicytomas correspond to WHO grade I.

Synonyms and historical annotation

While the term pituicytoma was historically also used for other tumours in the sellar and suprasellar region (granular cell tumours, pilocytic astrocytomas), this term is now reserved for low-grade glial neoplasms that originate in the neurohypophysis or infundibulum and that are distinct from pilocytic astrocytomas. Less preferred terms for pituicytoma include posterior pituitary astrocytoma and, for lesions arising in the pituitary stalk, infundibuloma.

Incidence

Pituicytomas are extremely rare. To date, less than 30 bona fide examples have been described, often as case reports. The largest series reported to date describes 9 tumours pooled from the consultation cases of two large institutions [221].

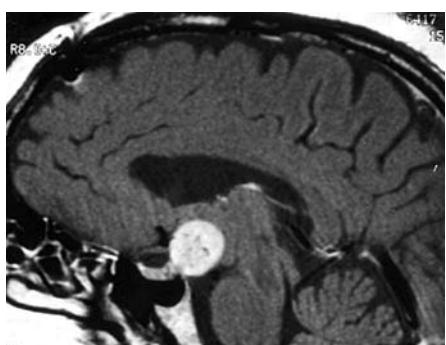


Fig. 14.11 Pituicytoma showing solid, circumscribed growth and diffuse contrast-enhancement on T1-weighted MRI.

Age and sex distribution

All pituicytomas reported to date have occurred in adult patients. In a compiled series of 26 cases, the male to female ratio is 1.6:1 {135, 221, 302, 326, 576, 893, 1065, 1181, 1569, 2041, 2061, 2283, 2285}. Three quarters of these males presented between 40 and 60 years of age; in women, no age peak is observed.

Localization

Pituicytomas arise along the distribution of the neurohypophysis, including the pituitary stalk and posterior pituitary. Accordingly, they may be located within the sella, in the suprasellar region, or occupy both the intrasellar and suprasellar compartments [221, 576, 2061, 2285].

Clinical features

Symptoms and signs

The most common presenting signs and symptoms of pituicytoma resemble those of other slowly expanding, non-hormonally active primary tumours of the sellar/suprasellar region that compress the optic chiasm, infundibulum and/or pituitary gland, and include visual disturbance, headache and various features of hypopituitarism such as amenorrhea, decreased libido and mildly elevated serum prolactin ("stalk effect") [221, 2285]. Rarely, asymptomatic cases have been found only at autopsy [2201].

Neuroimaging

Pituicytomas typically are homogeneous, well-demarcated, uniformly contrast-enhancing masses as seen on preoperative CT or MRI studies. Occasional tumours show heterogeneous contrast enhancement, and rare examples exhibit a cystic component [221].

Macroscopy

Pituicytomas are solid, well-circumscribed masses that have a firm, rubbery texture and can measure up to several centimeters. Only rarely has a cystic component been reported [221, 2285]. Radiographic studies may give the impression of a

smoothly contoured tumour, yet they can be firmly adherent to adjacent structures in the suprasellar space.

Histopathology

Pituicytomas have a solid, compact architecture and consist almost entirely of elongate, bipolar spindle cells arranged in interlacing fascicles or in a storiform pattern [221, 2285]. Tumours can show dense adherence to adjacent structures. Individual tumour cells contain abundant eosinophilic cytoplasm, and cell shapes range from short and plump to elongate and angulated. Cell borders are readily apparent, especially on cross sections of fascicles. There is no significant cytoplasmic granularity or vacuolization, and PAS staining shows only minimal reaction. Nuclei are of moderate size, oval-to-elongate, with little or no atypia. Mitotic figures are rare. Reticulin stain shows a perivascular distribution, intercellular reticulin being sparse. Important for the differential diagnosis with pilocytic astrocytoma and normal neurohypophysis, pituicytomas show no Rosenthal fibers or eosinophilic granular bodies. Herring bodies (axonal dilatations for neuropeptide storage in the histologically similar neurohypophysis) may be seen at the periphery. In contrast to spindle cell oncocyctoma, oncocyctomatous change is lacking.

Immunohistochemistry

Pituicytomas are generally positive for vimentin, S-100 protein, and GFAP [221, 576], although the latter ranges from faint and focal to moderate and patchy. Only rarely is GFAP strongly and diffusely positive. Strong staining is more often seen with S-100 protein and vimentin. Pituicytomas show no reactivity for neuronal or neuroendocrine markers, such as synaptophysin and chromogranin, or for pituitary hormones. Neurofilament protein immunoreactivity is limited to axons in peritumoural neurohypophyseal tissue and is not present within the tumour. Stains for cytokeratins are negative, while those for EMA may show a patchy, cytoplasmic rather than membranous pattern.

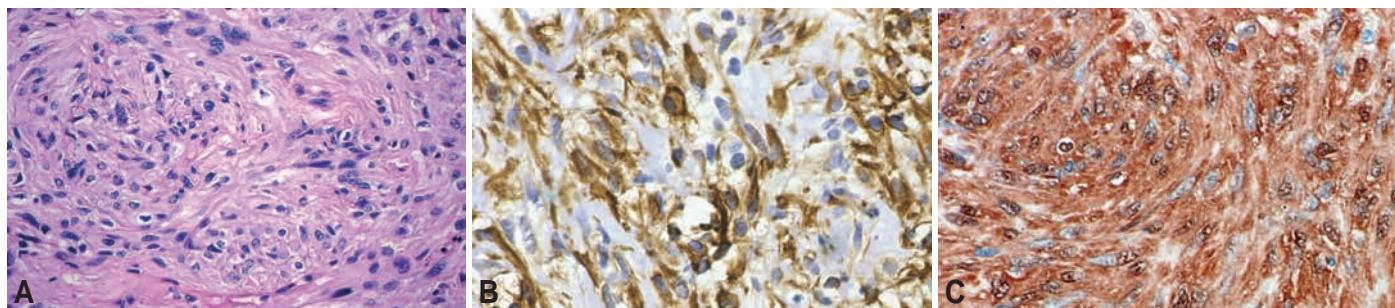


Fig. 14.12 Histological features of pituicytoma. A Elongate and plump tumour cells arranged in a fascicular pattern. B Patchy staining for GFAP. C Diffuse staining for S-100 protein.

Proliferation

Proliferation indices (Ki-67) are low and range from 0.5 to 2.0% [221, 1181]. No correlation of proliferation with outcome has been established.

Histogenesis

Pituicytomas presumably arise from pituicytes, specialized glial cells of the neurohypophysis [221, 988, 1332, 2008]. This origin accounts for the anatomic

distribution of pituicytomas and is consistent with the tumour's immunophenotypic characteristics. Although this is widely accepted, an alternative theory of origin from the folliculostellate stromal cells of the adenohypophysis has also been proposed [302]. Another primary neurohypophyseal tumour of presumed pituicyte origin is the granular cell tumour. This may be explained by the possible existence of multiple pituicyte subtypes [2203].

Prognostic and predictive factors

Pituicytomas are slowly enlarging, localized tumours that are treated by surgical resection. Subtotal resection may be accompanied by gradual regrowth over a period of several years. No instances of malignant transformation or distant metastasis have been reported.

Spindle cell oncocytoma of the adenohypophysis

G.N. Fuller
B.W. Scheithauer
F. Roncaroli
P. Wesseling

Definition

A spindled to epithelioid, oncocytic, non-endocrine neoplasm of the adenohypophysis that manifests in adults and follows a benign clinical course.

ICD-O code

The provisional code proposed for the fourth edition of ICD-O is 8291/0.

Grading

Spindle cell oncocytoma of the adenohypophysis corresponds to WHO grade I.

Synonyms and historical annotation

Spindle cell oncocytoma (SCO) was reported as a distinct entity by Roncaroli *et al.* in 2002 [1915]. The descriptive term SCO was used instead of one indicating a suspected derivation from folliculo-stellate cells of the anterior pituitary. It is possible that the term folliculo-stellate cell tumour of the pituitary will eventually be applied to this entity.

Incidence

SCO is a rare tumour and its actual incidence is difficult to determine. In the experience of one institution, SCOs represented 0.4% of all sellar tumours [1915].

Age and sex distribution

Based on the limited number of cases reported, SCO is a tumour of adults. The age of the reported patients ranges between 26 and 71 years (mean 56 years). The distribution is equal between the sexes [410, 1134, 1915, 2298].

Localization

SCO is a pituitary tumour. At presentation, five lesions showed suprasellar extension and three extended to the cavernous sinus [410, 2298]. One example invaded the sellar floor [1134].

Clinical features

Symptoms and signs

The clinical presentation and neuroimaging characteristics of patients with SCO are indistinguishable from those with a non-

functioning pituitary adenoma. The patients often exhibit pituitary hypofunction and visual field defects, less frequently headache, nausea and vomiting [410, 1134, 1915, 2298]. One patient with a recurrent SCO and involvement of the skull base presented with epistaxis [1134].

Neuroimaging

On MRI, SCO is generally seen as a sharply demarcated, solid, contrast-enhancing intra- and suprasellar mass with or without sellar or skull base destruction.

Macroscopy

On gross inspection, SCOs are indistinguishable from pituitary adenomas. Most are of macroadenoma dimension, but an exceptional 6.5 cm sellar/parasellar example has been reported [410]. They vary from soft, creamy and easily dissectable lesions to firm tumours that adhere to surrounding structures and infrequently show destruction of the sellar floor [410]. A clear margin with the adjacent normal pituitary is usually absent.

Histopathology

Spindle cell oncocytomas are typically composed of interlacing fascicles of spindled to epithelioid cells with eosinophilic, variably oncocytic cytoplasm. Mild to moderate nuclear atypia and even focal marked pleomorphism may be seen. A minor infiltrate of mature lymphocytes is seen in many lesions. Mitotic counts are typically less than one per 10 HPF. Recurrent lesions may or may not show increased mitotic activity [1134].

Electron microscopy

Ultrastructural examination is useful in the diagnosis of SCO [1134, 1915]. Neoplastic cells appear spindled or polygonal in configuration and are often filled with mitochondria. Well-formed desmosomes and junctions of intermediate type are encountered and, in addition to a lack of secretory granules, are the hallmarks of this tumour, distinguishing it from pituitary adenoma.

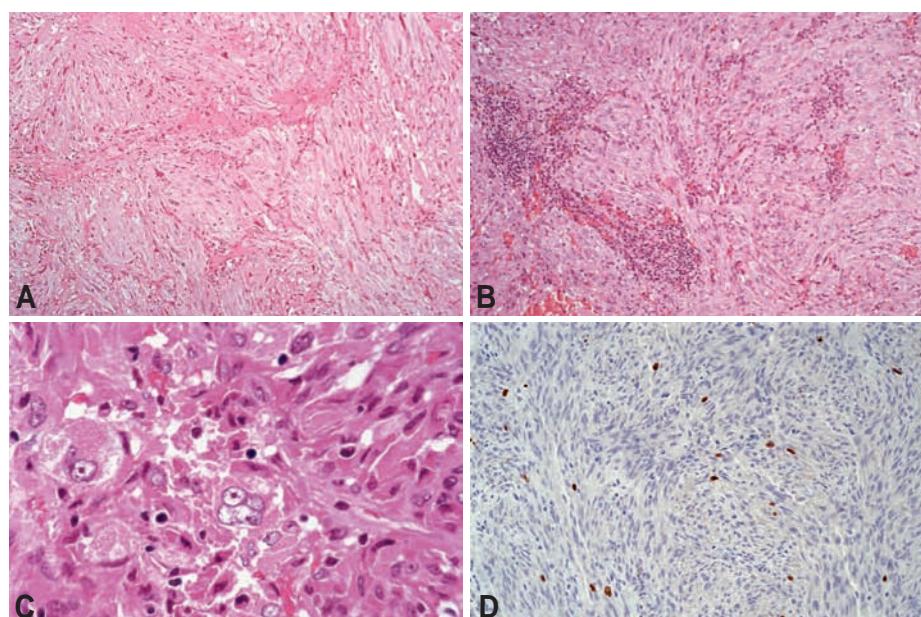


Fig. 14.13 Histological features of spindle cell oncocytoma. A The lesion is composed of interlacing fascicles of spindle cells with eosinophilic cytoplasm and mildly to moderately atypical nuclei. B Some examples show mild to moderate lymphocytic infiltrates. C A minority of tumour cells have pleomorphic nuclei and (D) low Ki-67 labelling index.

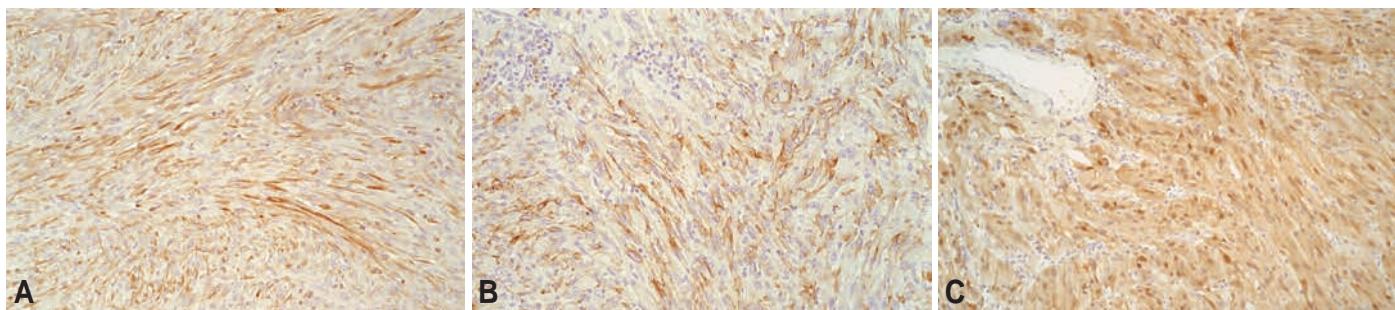


Fig. 14.14 Immunohistochemical features of spindle cell oncocytoma. Neoplastic cells characteristically express vimentin (A), EMA (B) and S-100 protein (C).

Immunohistochemistry

While negative for pituitary hormones, SCOs typically express vimentin, EMA, S-100 protein, and the anti-mitochondrial antibody 113-1. Staining for galectin-3 is seen and, although non-specific, initially suggested a link to the folliculo-stellate cell. A variety of other molecules,

including GFAP, cytokeratins, CD34, synaptophysin, chromogranin, bcl-2, smooth muscle actin and desmin have not been shown to be expressed.

Proliferation

The MIB-1 labelling index is usually low. In all but one reported case, labelling

has ranged from 1% to 8% (mean 2.8%). One recurrent example featured a MIB-1 labelling index of 20%, no data being available on the proliferation rate of the primary tumour {1134}.

Histogenesis

The cellular origin of SCO is uncertain. The original description {1915} postulated a derivation from folliculo-stellate cells of the anterior hypophysis. This was suggested by similarities between the cells of SCO and folliculo-stellate cells, including the expression of S-100 protein, vimentin and galectin-3, as well as the finding of desmosomes and intermediate junctions.

Prognostic and predictive factors

All five patients in the initial report on SCOs had a benign clinical course after 3 years of follow-up {1915}. Moderate tumour volume and lack of invasion into surrounding structures generally facilitates complete surgical resection. After incomplete removal, some tumours may (after several years) pursue a more aggressive course and show increased MIB-1 labelling indices and necrosis {1134}. Additional clinical follow-up is needed before the prognostic significance of these features can be assessed.

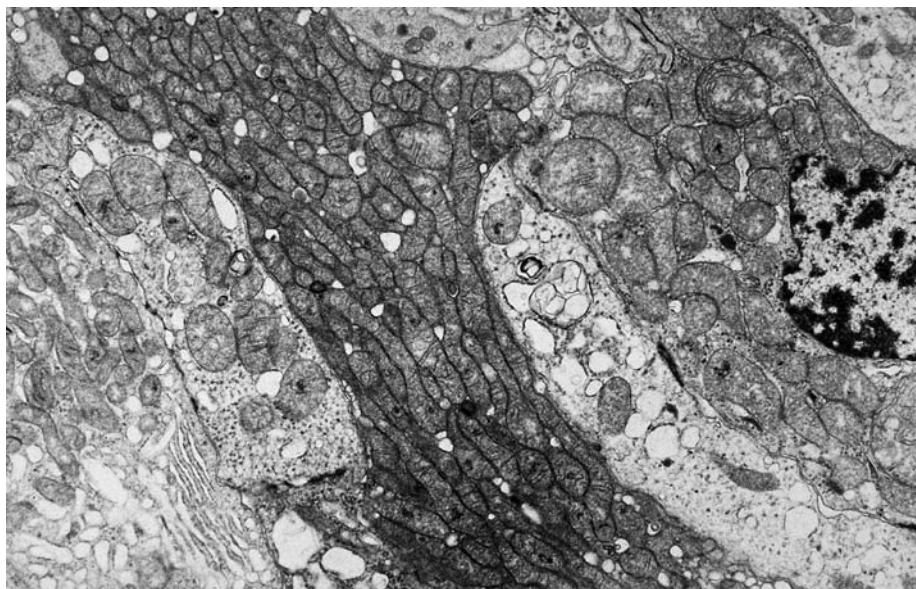
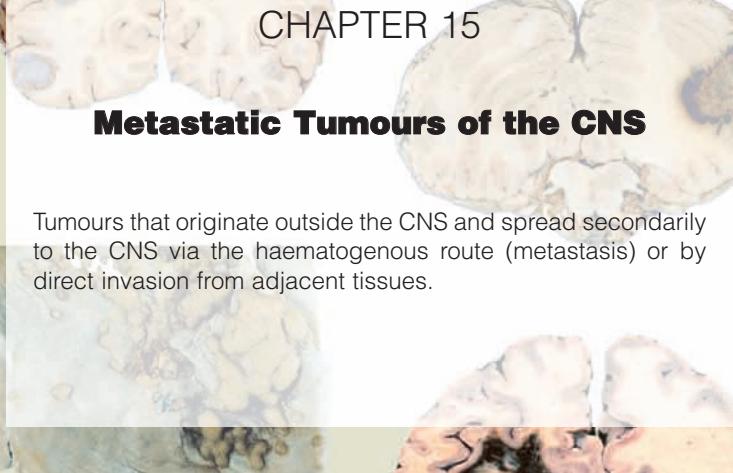


Fig. 14.15 Ultrastructurally, the tumour cells of spindle cell oncocytoma show numerous mitochondria (oncocytic change) as well as several cell-to-cell junctions, mainly short desmosomes.



Tumours that originate outside the CNS and spread secondarily to the CNS via the haematogenous route (metastasis) or by direct invasion from adjacent tissues.

Metastatic tumours of the CNS

P. Wesseling
A. von Deimling
K.D. Aldape

Definition

Tumours that originate outside the CNS and spread secondarily to the CNS via the haematogenous route (metastasis) or by direct invasion from adjacent tissues.

Incidence

Metastatic tumours are the most common CNS neoplasms. Due to underdiagnosis and inaccurate reporting, the incidence rates found in the literature for brain metastases (up to 11 per 100 000 population per year) probably underestimate the true incidence [2174]. Autopsy studies revealed that CNS metastases occur in about 25% of patients who die of cancer [654]. Leptomeningeal metastases occur in 4–15% of patients with solid tumours [2197] and dural metastases in 8–9% of cancer patients with advanced cancer [1250]. Spinal epidural metastases are found in 5–10% of all patients with cancer and are much more frequent than spinal leptomeningeal or intramedullary metastases [1541]. Direct intracranial extension from local primary tumours is rare [1129].

Age and sex distribution

The incidence of CNS metastases increases from less than one per 100 000 below 25 years of age to greater than 30 per 100 000 at age 60 years [2174]. Up

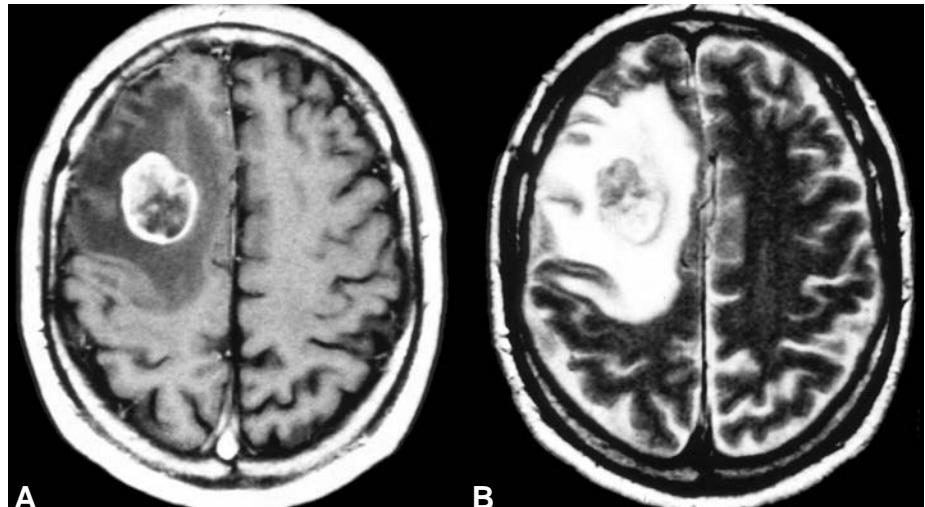


Fig. 15.01 Metastasis of an adenocarcinoma in the right frontal lobe. A Gadolinium-enhanced T1-weighted MRI showing a large area of hyperintensity corresponding to a perifocal edema that (B) shows bright hyperintensity on T2-weighted MRI.

to 30% of adults and 6–10% of children with cancer will develop brain metastases [1096]. The relative proportions of various primary tumours are different for the two sexes, but for most tumours gender lacks a significant independent effect on the occurrence of CNS metastasis [104, 2174].

Origin of CNS metastases

The most common sources of brain metastases in adults are, in descending order, lung cancer (especially small cell and adenocarcinoma), breast cancer, melanoma, renal cancer and colon cancer; in children, in descending order, leukaemia, lymphoma, osteogenic sarcoma, rhabdomyosarcoma and Ewing sarcoma [2174]. Prostate, breast and lung cancer are the most common origin of spinal epidural metastasis, followed by non-Hodgkin lymphoma, multiple myeloma and renal cancer [1541]. Tumours vary in their propensity to metastasize to the CNS [104, 404, 2036]. In up to 10% of the patients with brain metastases no primary tumour is found at presentation [1096]. Primary neoplasms in the head and neck region (e.g. squamous cell carcinoma, esthesioneuroblastoma) may extend intracranially by direct invasion

and occasionally present as an intracranial tumour [257].

Localization

More than 80% of brain metastases are located in the cerebral hemispheres, especially in arterial border zones and at the junction of cerebral cortex and white matter. Approximately 15% are found in the cerebellum. Of the brain metastases, less than half are single (i.e. the only metastasis in the brain), and very few are solitary (i.e. the only metastasis detected in the body) [654]. Other intracranial sites include the dura and leptomeninges; in these sites, extension from or to other compartments is common [1128, 1250]. The vast majority of metastases affecting the spinal cord expand from the vertebral body or paravertebral tissues into the epidural space [1541]. Occasionally, metastatic CNS tumours seed along the walls of the ventricles or are located in the pituitary gland, choroid plexus, or a pre-existing lesion like a meningioma. The posterior fossa is relatively frequently involved in patients with colorectal and renal carcinoma and tumours of the pelvic organs. Dural metastases are relatively common in cancer of the

Table 15.01 Origin of brain metastases.

Primary tumour site	% of brain metastases
Respiratory tract	50%
Breast	15%
Skin/melanoma	11%
Unknown primary site	11%

Table 15.02 Origin of metastases causing epidural spinal cord compression.

Primary tumour site	Percentage
Breast	22%
Lung	15%
Prostate	10%
Malignant lymphoma	10%

prostate, breast, lung, and in haematological malignancies {1250}; leptomeningeal metastasis in patients with lung and breast cancer, melanoma, and haematopoietic tumours {2174, 2197}; spinal epidural metastasis in cancer of prostate, breast, lung, kidney, non-Hodgkin lymphoma and multiple myeloma; and intramedullary spinal cord metastasis in small cell lung carcinoma {1541}.

Clinical features

Symptoms and signs

The neurological signs and symptoms of intracranial metastases are generally caused by increased intracranial pressure or local effect of the tumour on the adjacent brain tissue. They may progress gradually and include headache, altered mental status, paresis, ataxia, visual complaints, nausea or sensory disturbances. Some patients present acutely with seizure, infarct or haemorrhage {1096}. Many patients with leptomeningeal metastasis have multiple, varied neurological symptoms and signs at presentation, including headache, mental alteration, ataxia, cranial nerve dysfunction and radiculopathy. Cytological examination reveals malignant cells in the initial CSF sample in about 50% of such patients; this figure may increase to 90% when CSF sampling is repeated and adequate volumes (10 mL) are available for cytological analysis {699}. Spinal metastases generally result in compression of the spinal cord or nerve roots and may cause back pain, weakness of the extremities, sensory disturbances, and incontinence in the course of hours, days or weeks {2017}.

Neuroimaging

On MRI, intraparenchymal metastases are generally circumscribed and show mild T1-hypointensity, T2-hyperintensity, and diffuse or ring-like contrast-enhancement with a surrounding zone of parenchymal edema. Haemorrhagic metastases and metastatic melanomas containing melanin-pigment may demonstrate hyperintensity on non-contrast MRI or CT {2475}. In patients with leptomeningeal metastasis, MRI can reveal focal or diffuse leptomeningeal thickening and contrast-enhancement (sometimes with dispersed tumour nodules in the subarachnoid space); in addition, enhancement and enlargement of the cranial nerves and communicating hydrocephalus may be

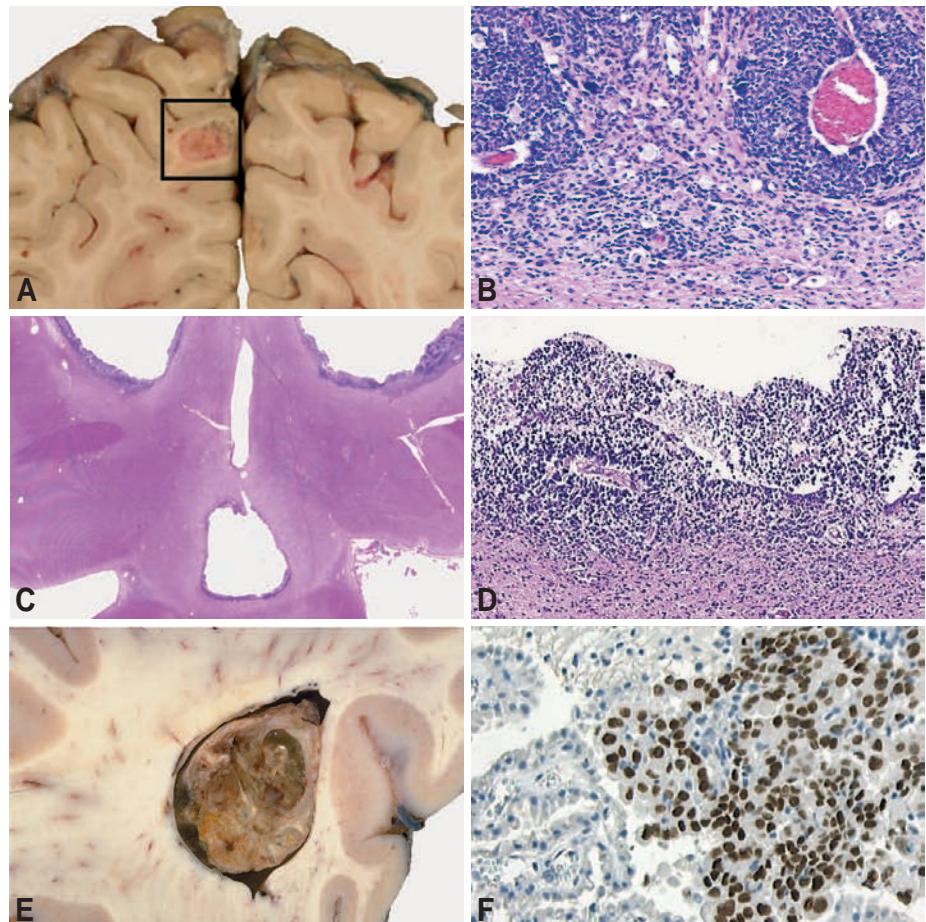


Fig. 15.02 A,B Intracerebral subcortical metastasis of small cell lung carcinoma. C, D Extensive spread of small cell lung carcinoma cells along the walls of both lateral ventricles and the third ventricle. D Higher magnification of ventricular wall. E,F Intraventricular/choroid plexus metastasis of lung adenocarcinoma. Note the TTF1 staining of tumour cell nuclei (F).

found {699, 1541}. MRI can depict dural metastases as nodular masses or dural thickening along the bone structures, while metastases in vertebral bodies are visualised as discrete, confluent or diffuse areas of low signal intensity. CT scan may be useful for detection of bone involvement {1250}.

Macroscopy

Metastases in the brain and spinal cord

parenchyma often form grossly circumscribed and rounded, grey white or tan masses with variable central necrosis and peritumoural edema. Metastases of adenocarcinomas may contain collections of mucoid material. Haemorrhage is relatively frequent in metastases of choriocarcinoma, melanoma and renal cell carcinoma. Melanoma metastases with abundant melanin-pigment have a brown to black colour. Leptomeningeal

Table 15.03 Cumulative incidence of brain metastasis from the most common primary sites.

Primary tumour site	Cumulative incidence of brain metastasis with interval after diagnosis of primary tumour		
	< 1 month	< 1 year	< 5 years
Lung	7.8%	14.8%	16.3%
Breast	0.4%	1.0%	5.0%
Melanoma	0.7%	4.0%	7.4%
Renal	1.7%	5.2%	9.8%
Colorectal	0.1%	0.6%	1.2%

Adapted from Schouten *et al.* (2036).

metastasis may produce diffuse opacification of the membranes or present as multiple nodules {1866}. Dural metastases can grow as localized plaques or nodules and as diffuse lesions {1128}. Primary neoplasms in the head and neck region that extend intracranially by direct invasion generally cause significant destruction of the skull bones. In some cases, however, the skull is penetrated by relatively subtle perivascular or perineural invasion without major bone destruction {257}.

Histopathology

The histological, ultrastructural, and immunohistochemical features of secondary CNS tumours are as diverse as in the primary tumours from which they arise. Most intraparenchymal metastases are histologically relatively well demarcated. Rather than by infiltration of single cells in the neuropil, these tumours often expand by growth of groups of tumour cells in the Virchow-Robin spaces, ultimately resulting in destruction of the neuroglial tissue and a variety of reactive changes including gliosis, inflammation and florid microvascular proliferation. Tumour necrosis may be extensive, leaving recognizable tumour tissue only at the periphery of the lesion and around blood vessels {1866}. Metastases of some carcinomas, particularly small cell carcinomas of the lung, may show relatively

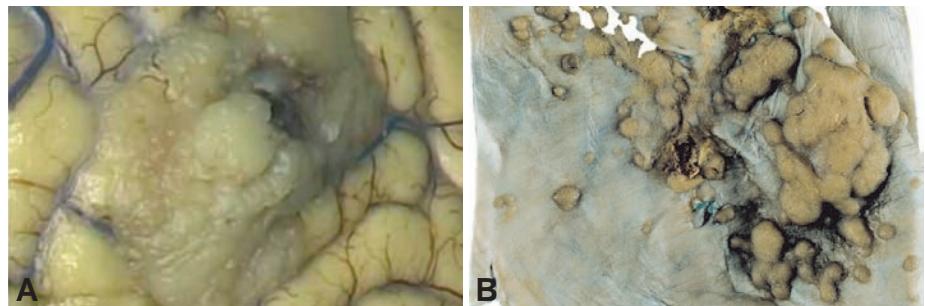


Fig. 15.03 A Leptomeningeal metastasis of non-Hodgkin lymphoma. B Dural metastasis of mammary carcinoma.

diffuse ("pseudogliomatous") infiltration in the neuropil {116, 1583}. In leptomeningeal metastasis, the tumour cells are dispersed in the subarachnoid and Virchow-Robin spaces and may invade the adjacent CNS parenchyma and nerve roots {2197}.

Immunohistochemistry

The immunohistochemical characteristics in secondary CNS tumours are generally similar to those in the tumours from which they originate. Immunohistochemical analysis is often helpful for distinguishing primary from secondary CNS tumours and, in case of an unknown primary tumour, for assessment of the exact nature and origin of the metastatic neoplasm {118, 143A, 485}.

Proliferation

Metastatic CNS tumours show variable

and often marked mitotic activity. The proliferation index may be higher than in the primary neoplasm {338}.

Pathogenesis

Before they present as haematogenous metastases in the CNS, tumour cells must successfully complete a series of steps: escape from the primary tumour, entry and survival in the blood stream, arrest and extravasation in the CNS, and survival and growth in the CNS micro-environment {1571}. Secondary CNS tumours may also develop by direct extension from primary tumours in adjacent anatomic structures (e.g. paranasal sinuses, bone), but such tumours are not considered metastases in a strict sense because they remain in continuity with the primary neoplasm. Once in contact with the CSF containing compartments, cells of those tumours may disseminate ("seed") around the CNS {2168}.

Genetics

Using comparative genomic hybridization, a high degree of conformity was found between brain metastases and the corresponding primary tumours outside the CNS {1740}. Detailed information on genes that are crucial in the metastatic process {1571} is not yet used for diagnostic, prognostic or therapeutic purposes.

Prognostic and predictive factors

Based on the data of Radiation Therapy Oncology Group (RTOG) trials, three classes for predicting outcome in patients with brain metastases were suggested: class 1, with the best outcomes (median survival after whole brain radiotherapy 7.1 months), includes patients with Karnofsky performance status (KPS) of 70 or higher, of age younger than 65, and with controlled

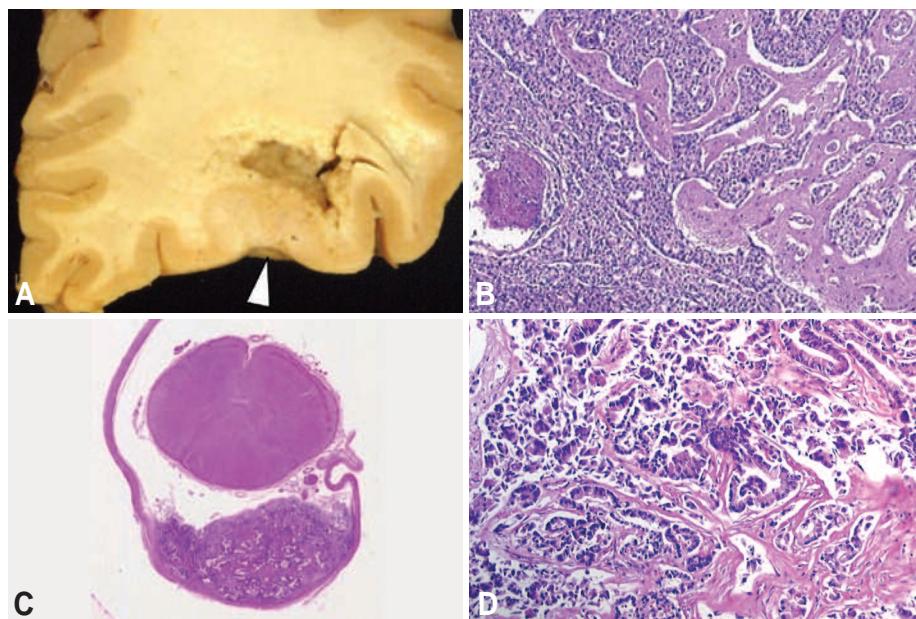


Fig. 15.04 Leptomeningeal metastasis of colon carcinoma (A,B). Note the perivascular infiltration of the cerebral cortex (B). Intraspinal dural metastasis of lung adenocarcinoma (C,D).

primary tumour and no extracranial metastases; class 3 (median survival 2.3 months) includes patients with KPS < 70; class 2 (median survival 4.2 months) encompasses all other patients. Other

prognostic factors include the sensitivity of the tumour to therapy and the number and location of CNS metastases. In general, patients with one brain metastasis have improved quality of life and

probable survival benefit from surgical resection or radiosurgery of the lesion {651, 1100, 2330}.

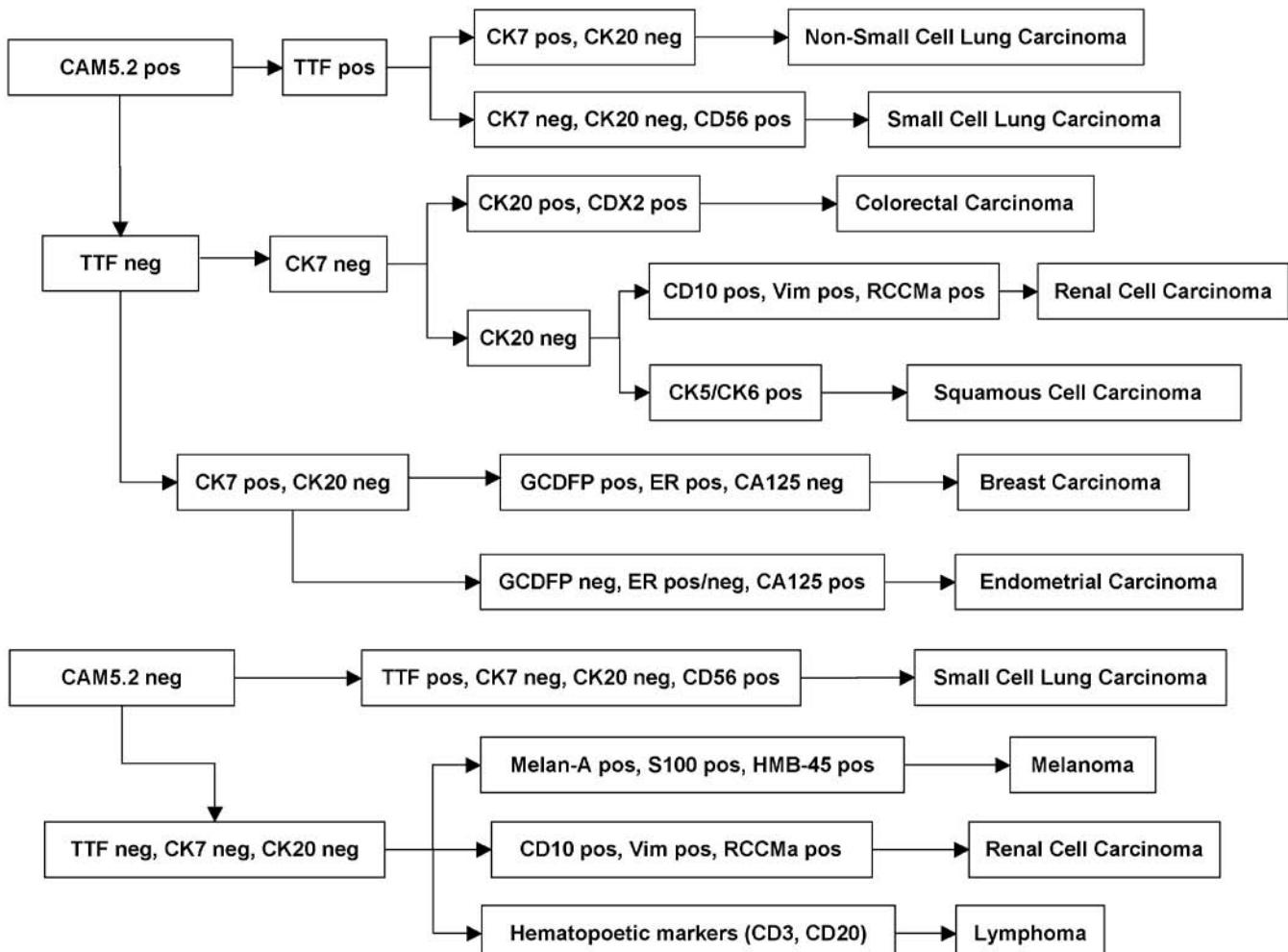


Fig. 15.05 Diagram illustrating how immunohistochemical analysis is helpful for indication of the origin of the common metastatic tumours of the CNS. From Becher *et al.* {143A}, reproduced with permission of the *Journal of Neuropathology and Experimental Neurology*. CDX2, caudal type homeobox transcription factor 2; GCDFP, gross cystic disease fluid protein; RCCMa, renal cell carcinoma marker; TTF, thyroid transcription factor.

Contributors

Dr. Kenneth D. ALDAPE*

Department of Pathology
MD Anderson Cancer Center
Box 85, 1515 Holcombe Blvd.
Houston, TX 77030
USA
Tel. +1 713 792 7935
Fax. +1 713 745 1105
kaldape@mdanderson.org

Dr. Darell D. BIGNER

Department of Pathology
Duke University Medical Center, Box 3156
Research Drive 177 MSRB
Durham, NC 27710
USA
Tel. +1 919 684 5018
Fax. +1 919 684 458
bigne001@mc.duke.edu

Dr. Herbert BUDKA

Institute of Neurology
University of Vienna
Währinger Gürtel 18-20, Postfach 48
1097 Vienna
AUSTRIA
Tel. +43 1 40400 5501
Fax. +43 1 40400 5511
herbert.budka@meduniwien.ac.at

Dr. Cristina R. ANTONESCU

Department of Pathology
Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10021
USA
Tel. +1 212 639 5905
Fax. +1 212 717 3203
antonesc@mskcc.org

Dr. Ingmar BLÜMCKE

Department of Neuropathology
Friedrich-Alexander University of
Erlangen-Nuremberg
91054 Erlangen
GERMANY
Tel. +49 9131 85 26031
Fax. +49 9131 85 26033
Ingmar.bluemcke@neuropatho.med.uni-erlangen.de

Dr. Peter C. BURGER*

Pathology Building, Room 706
Johns Hopkins University
36 Whitfield Road
Baltimore, MD 21210
USA
Tel. +1 410 955 8378
Fax. +1 410 614 9310
pburger@jhmi.edu

Dr. Albert J. BECKER

Department of Neuropathology
Bonn University Medical Center
Sigmund-Freud Strasse 25
53105 Bonn
GERMANY
Tel. +49 228 287 11352
Fax. +49 228 287 14331
albert_becker@uni-bonn.de

Dr. Fredrik T. BOSMAN*

Institute of Pathology
University of Lausanne Medical School
Rue du Bugnon 25
1011 Lausanne
SWITZERLAND
Tel. +41 21 314 7202
Fax. +41 21 314 7205
fred.bosman@chuv.hospvd.ch

Dr. Webster K. CAVENEE*

Ludwig Institute for Cancer Research
University of California, San Diego
9500 Gilman Drive
La Jolla, CA 92093-0660
USA
Tel. +1 858 552 4920 ext. 7805
Fax. +1 858 534 7750
wcavenee@ucsd.edu

Dr. Jacklyn A. BIEGEL

Division of Human Genetics
Department of Pediatrics
University of Pennsylvania School of Medicine
Philadelphia, PA 19104
USA
Tel. +1 215 590 3856
Fax. +1 215 590 3764
biegel@mail.med.upenn.edu

Dr. Sebastian BRANDNER

Division of Neuropathology and
Department of Neurodegenerative Disease
Institute of Neurology, Queen Square
London WC1N 3BG,
UK
Tel. +44 20 7676 2188
Fax. +44 20 7676 2157
s.brandner@ion.ucl.ac.uk

Dr. Leila CHIMELLI

Department of Pathology
University Hospital CFF - UFRJ
Ilha de Fundao,
CEP 21941 590 Rio de Janeiro RJ,
BRAZIL
Tel. +55 21 2562 2450
Fax. +55 21 2562 2450
chimelli@hucff.ufrj.br

Dr. Wojciech BIERNAT

Department of Neuropathology
and Molecular Pathology
Medical University Gdansk
80-210 Gdansk
POLAND
Tel. +48 58 349 1650
Fax. +48 58 349 1650
biernat@amg.gda.pl

Dr. Daniel J. BRAT*

Department of Pathology and Lab. Medicine
Emory University Hospital, H-176
1364 Clifton Rd. NE
Atlanta, GA 30322,
USA
Tel. +1 404 712 1266
Fax. +1 404 712 0148
dbrat@emory.edu

Dr. V. Peter COLLINS*

Department of Pathology
University of Cambridge
Tennis Court Road
Cambridge CB2 1QP
UK
Tel. +44 1223 336072 / 217164
Fax. +44 1223 216980
vpc20@cam.ac.uk

*The asterisk indicates participation in the Working Group Meeting on the WHO Classification of Tumours of the Nervous System that was held in Heidelberg, Germany, November 17-18, 2006

Dr. Catherine DAUMAS-DUPORT
Pathology Department
Saint-Anne Hospital Center
1 rue Cabanis
75014 Paris
FRANCE
Tel. +33 1 45 65 82 05
Fax. +33 1 45 65 87 28
c.daumas@ch-sainte-anne.fr

Dr. Gregory N. FULLER*
Department of Pathology
MD Anderson Cancer Center
Unit 085, 1515 Holcombe Blvd.
Houston, TX 77030
USA
Tel. +1 713 792 2042
Fax. +1 713 792 3696
gfuller@mdanderson.org

Dr. Volkmar H. HANS
Institute of Neuropathology
Evangelisches Krankenhaus Bielefeld
Remterweg 2
33617 Bielefeld
GERMANY
Tel. +49 521 772 790 10
Fax. +49 521 772 790 14
Volkmar.Hans@evkb.de

Dr. Martina DECKERT
Department of Neuropathology
University of Cologne
Kerpener Strasse 62
50324 Köln
GERMANY
Tel. +49 221 478 5265
Fax. +49 221 478 7237
martina.deckert@uni-koeln.de

Dr. Felice GIANGASPERO*
Department of Experimental Medicine
University of Rome La Sapienza
& IRCCS Neuromed, Pozzilli (IS)
Viale del Policlinico 155
00161 Roma,
ITALY
Tel. +39 0649 979 175
Fax. +39 0649 979 175
felice.giangaspero@uniroma1.it

Dr. Cynthia HAWKINS
Division of Pathology
Department of Paediatric Laboratory Medicine
The Hospital for Sick Children
Toronto, Ontario M5G 1X8
CANADA
Tel. +1 416 813 5938
Fax. +1 416 813 5974
cynthia.hawkins@sickkids.ca

Dr. Charles G. EBERHART*
Department of Pathology
Johns Hopkins University
720 Rutland Avenue, Ross Bldg 558
Baltimore, MD 21205
USA
Tel. +1 410 502 5185
Fax. +1 410 955 9777
ceberha@jhmi.edu

Dr. Caterina GIANNINI
Anatomic Pathology
Mayo Clinic College of Medicine
200 1st Street SW
Rochester, MN 55905
USA
Tel. +1 507 538 1181
Fax. +1 507 284 1599
giannini.caterina@mayo.edu

Dr. Stephen HUNTER
Department of Pathology
Emory University School of Medicine
1364 Clifton Road, N.E.
Atlanta, GA 30322
USA
Tel. +1 404 712 4278
Fax. +1 404 712 0714
stephen_hunter@emory.org

Dr. David W. ELLISON
Dept. Pathology
St.Jude Children's Research Hospital
332 N. Lauderdale St.
Memphis, TN 38105
USA
Tel. +1 901 495 5438
Fax. +1 901 495 3100
david.ellison@stjude.org

Dr. Hannu HAAPASALO
Department of Pathology
Tampere University Hospital
POB 2000
SF-33521 Tampere
FINLAND
Tel. +358 3 247 6560
Fax. +358 3 247 5503
hannu.haapasalo@pshp.fi

Dr. Anne JOUVET*
Laboratory of Neuropathology
Neurology Hospital
59 boulevard Pinel
69003 Lyon
FRANCE
Tel. +33 4 72 35 76 34
Fax. +33 4 72 35 70 67
jouvet@laennec.univ-lyon1.fr

Dr. Charis ENG
Genomic Medicine Institute
Cleveland Clinic Lerner Research Institute
9500 Euclid Avenue, Mailstop NE-50
Cleveland, OH 44195
USA
Tel. +1 216 444 3440
Fax. +1 216 636 0655
engc@ccf.org

Dr. Pierre HAINAUT
International Agency for
Research on Cancer (IARC)
69008 Lyon,
FRANCE
Tel. +33 4 72 73 85 32
Fax. +33 4 72 73 83 22
hainaut@iarc.fr

Dr. Alexander R. JUDKINS
Department of Pathology
University of Pennsylvania School of
Medicine and Children's Hospital of
Philadelphia
Philadelphia, PA 19104
USA
Tel. +1 215 590 1728
Fax. +1 215 590 1605
judkins@mail.med.upenn.edu

Dr. Dominique FIGARELLA-BRANGER*
Department of Pathology and Neuropathology
La Timone Hospital
13385 Marseille cedex 05
FRANCE
Tel. +33 4 91 32 44 43 / 45 88
Fax. +33 4 91 25 42 32
Dominique.Figarella-
Branger@medecine.univ-mrs.fr

Dr. Johannes A. HAINFELLNER*
Institute of Neurology
Medical University of Vienna
Waehringer Guertel 18-20
1097 Vienna
AUSTRIA
Tel. +43 1 40400 5507
Fax. +43 1 40400 5511
Johannes.Hainfellner@meduniwien.ac.at

Dr. Paul KLEIHUES*
Department of Pathology
University Hospital
Schmelzbergstr. 12
8091 Zurich
SWITZERLAND
Tel. +41 44 255 3516
Fax. +41 44 255 2525
Kleihues@pathol.unizh.ch

Dr. Andrey KORSHUNOV
Department of Neuropathology
NN Burdenko Neurosurgical Institute
Fadeeva Str. 5
125047 Moscow
RUSSIAN FEDERATION
Tel. +7 495 972 85 60
Fax. +7 495 250 29 44
akorshunov@nsi.ru

Dr. Johan M. KROS*
Division of Pathology/Neuropathology
Erasmus Medical Center
Dr. Molewaterplein 50
3015 Rotterdam
THE NETHERLANDS
Tel. +31 10 4087905
Fax. +31 10 4087905
j.m.kros@erasmusmc.nl

Dr. Arielle LELLOUCH-TUBIANA
Department of Neuropathology
René Descartes-Paris 5 University
Necker Hospital for Sick Children
149 rue de Sèvres, 75015 Paris,
FRANCE
Tel. +33 1 44 49 49 92
Fax. +33 1 44 49 49 99
arielle.lellouch@orange.fr

Dr. Suet Yi LEUNG
Department of Pathology
The University of Hong Kong
Queen Mary Hospital
Pokfulam Road
Hong Kong,
SAR CHINA
Tel. +852 285 54401
Fax. +852 287 25197
suetyi@hkucc.hku.hk

Dr. Paweł LIBERSKI
Department of Molecular Pathology
and Neuropathology
Medical University of Lodz
ul. Czechosłowacka 8/10
92-216 Lodz
POLAND
Tel. +48 42 679 1477
Fax. +48 42 679 1477
pplib@csk.am.lodz.pl

Dr. M. Beatriz S. LOPES
Department of Pathology
Box 800214 - HSC
University of Virginia Health System
Charlottesville, VA 22908-0214
USA
Tel. +1 434 924 9175
Fax. +1 434 924 9177
msl2e@virginia.edu

Dr. David N. LOUIS*
James Homer Wright Pathology Laboratories,
Massachusetts General Hospital and
Harvard Medical School
55 Fruit Street, WRN225
Boston, MA 02114,
USA
Tel. +1 617 726 2966
Fax. +1 617 726 7533
dlouis@partners.org

Dr. Masao MATSUTANI
Department of Neurosurgery
Saitama Medical School
Moroyamamachi Morohongo 38
350-04 Saitama
JAPAN
Tel. +81 492 76 1551
Fax. +81 492 76 1551
matutani@saitama-med.ac.jp

Dr. Roger E. MCLENDON*
Department of Pathology
Duke University Medical Center
Box 3712
Durham, NC 27710
USA
Tel. +1 919 684 6940
Fax. +1 919 681 7634
mclem001@mc.duke.edu

Dr. Yoichi NAKAZATO*
Department of Human Pathology
Gunma University Graduate School of
Medicine
3-39-22 Showamachi,
Maebashi Gunma 371-5811
JAPAN
Tel. +81 27 220 7970
Fax. +81 27 220 7978
nakazato@med.gunma-u.ac.jp

Dr. Hartmut P.H. NEUMANN
Department of Nephrology and Hypertension
Albert-Ludwigs University
Hugstetterstr. 55, 79106 Freiburg
GERMANY
Tel. +49 761 270 3578
Fax. +49 761 270 3778
hartmut.neumann@uniklinik-freiburg.de

Dr. Ho-Keung NG*
Department of Anatomical and Cellular
Pathology
Prince of Wales Hospital
The Chinese University of Hong Kong
Shatin, Hong Kong
SAR CHINA
Tel. +852 2632 3337
Fax. +852 2637 6274
hkng@cuhk.edu.hk

Dr. Hiroko OHGAKI*
International Agency for
Research on Cancer (IARC)
150, cours Albert Thomas
69008 Lyon
FRANCE
Tel. +33 4 72 73 85 34
Fax. +33 4 72 73 86 98
ohgaki@iarc.fr

Dr. Magali OLIVIER
International Agency for
Research on Cancer (IARC)
150, cours Albert Thomas
69008 Lyon
FRANCE
Tel. +33 4 72 73 86 69
Fax. +33 4 72 73 83 22
molivier@iarc.fr

Dr. Werner PAULUS*
Institute of Neuropathology
University Hospital Münster
Domagkstr. 19
48129 Münster
GERMANY
Tel. +49 251 83 56966
Fax. +49 251 83 56971
werner.paulus@uni-muenster.de

Dr. Arie PERRY*
Division of Neuropathology
Washington University School of Medicine
Campus Box 8118, 660 South Euclid Ave.
St Louis, MO 63110
USA
Tel. +1 314 362 7426
Fax. +1 314 362 7765
aperry@wustl.edu

Dr. Torsten PIETSCH*
Department of Neuropathology
University of Bonn Medical Center
Sigmund-Freud Str. 25
53105 Bonn
GERMANY
Tel. +49 228 287 16606
Fax. +49 228 287 14331
t.pietsch@uni-bonn.de

Dr. Karl H. PLATE
Neurology Institute (Edinger Institute)
Johann Wolfgang Goethe-University
Deutschordenstr. 46
60528 Frankfurt/Main
GERMANY
Tel. +49 69 63016042
Fax. +49 69 679487
karl-heinz.plate@kgu.de

Dr. Matthias PREUSSER

Institute of Neurology and Department of Internal Medicine
Medical University of Vienna
Waehringer Guertel 18-20
1097 Vienna
AUSTRIA
Tel. +43 1 40400 4457
Fax. +43 1 40400 6088
matthias.preusser@meduniwien.ac.at

Dr. Guido REIFENBERGER*

Department of Neuropathology
Heinrich-Heine University
Moorenstrasse 5
NRW 40225 Düsseldorf
GERMANY
Tel. +49 211 8 11 86 60
Fax. +49 211 8 11 78 04
reifenberger@med.uni-duesseldorf.de

Dr. Federico RONCAROLI

Department of Neuropathology
Imperial College of London
Faculty of Medicine, Charing Cross Campus
London W6 8RP
UK
Tel. +44 20 8846 7178
Fax. +44 20 8846 7794
f.roncaroli@imperial.ac.uk

Dr. Marc K. ROSENBLUM

Department of Pathology
Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10021
USA
Tel. +1 212 639 8410
Fax. +1 212 772 8521
rosenbl1@mskcc.org

Dr. Elisabeth J. RUSHING

Department of Neuropathology and Ophthalmic Pathology
Armed Forces Institute of Pathology
Washington, DC 20306-6000
USA
Tel. +1 202 782 3603
Fax. +1 202 782 4099
elisabeth.rushing@gmail.com

Dr. Chitra SARKAR

Department of Pathology
All India Institute of Medical Sciences
110029 New Delhi
INDIA
Tel. +91 11 26593371
Fax. +91 11 26588663 / 26588641
drchitrasarkar@yahoo.com

Dr. Bernd W. SCHEITHAUER*

Department of Laboratory Medicine and Pathology
Mayo Clinic
200 First St. SW, Rochester, MN 55905 USA
Tel. +1 507 284 8350
Fax. +1 507 284 1599
scheithauer.bernd@mayo.edu

Dr. Davide SCHIFFER

Foundation Policlinico di Monza
University of Turin
Via Cherasco 15
C.so Massimo D'Azeglio 51
PIEM 10126 Turin,
ITALY
Tel. +39 011 663 62 66
Fax. +39 011 696 34 87
davide.schiffer@unito.it

Dr. Sursala K. SHANKAR

Department of Neuropathology
National Institute of Mental Health and Neurosciences
560 029 Bangalore
INDIA
Tel. +91 80 2699 5130
Fax. +91 80 0265 64830
shankar@nimhans.kar.nic.in

Dr. Mehar C. SHARMA

Department of Pathology
All India Institute of Medical Sciences
Ansari Nagar
110029 New Delhi
INDIA
Tel. +91 11 2659 3371
Fax. +91 11 2658 8663
sharmamehar@yahoo.co.in

Dr. Dov SOFFER

Department of Pathology
Hadassah University Hospital
Kiryat Hadassah, POB 12000
IL-91120 Jerusalem
ISRAEL
Tel. +972 2 675 8207
Fax. +972 2 642 6268
soffer@cc.huji.ac.il

Dr. Figen SÖYLEMEZOGLU

Department of Pathology
Haceteppe University
Tip Fakultesi, Patoloji Anabilim Dalı
06100 Ankara
TURKEY
Tel. +90 312 241 9951
Fax. +90 312 212 9006
figensoylemez@yahoo.com

Dr. Anat O. STEMMER-RACHAMIMOV

Molecular Neuro-Oncology Laboratory, CNY6
Massachusetts General Hospital
Building 149
Charlestown, MA 02129
USA
Tel. +1 617 726 5510
Fax. +1 617 726 5079
astemmerachamimov@partners.org

Dr. Ana Lia TARATUTO

Department of Neuropathology/FLENI
Referral Center for CJD and other TSEs
Institute for Neurological Research
C1428AQK Buenos Aires
ARGENTINA
Tel. +54 11 5777 3200 / 2325
Fax. +54 11 5777 3209
ataratuto@fleni.org.ar

Dr. Tarik TIHAN

Department of Pathology
University of California at San Francisco
Brain Tumor Research Center
M551, 505 Parnassus Avenue
San Francisco, CA 94143-0102
USA
Tel. +1 415 476 5236
Fax. +1 415 476 7963
tarik.tihan@ucsf.edu

Dr. Erwin G. VAN MEIR

Winship Cancer Institute
Emory University School of Medicine
1365-C Clifton Rd., N.E., Suite C 5078
Atlanta, GA 30322
USA
Tel. +1 404 778 5563
Fax. +1 404 778 5550
evanmei@emory.edu

Dr. Scott R. VANDENBERG

University of California San Francisco
513 Parnassus Avenue
HSW 408
San Francisco, CA 94143-0511
USA
Tel. +1 415 502 7796
Fax. +1 415 476 7963
scott.vandenberg@ucsf.edu

Dr. Andreas VON DEIMLING*

Departement of Neuropathology
Institute of Pathology
Im Neuenheimer Feld 220/221
69120 Heidelberg
GERMANY
Tel. +49 6221 56 2603 / 2604
Fax. +49 6221 56 4566
Andreas.vonDeimling@med.uni-heidelberg.de

Dr. Alexander O. VORTMEYER

Surgical Neurology Branch
National Institute for Neurological Disorders
and Stroke (NINDS)
Bldg. 10, Rm. 5D37, Bethesda, MD 20892
USA
Tel. +1 301 594 29 14
Fax. +1 301 402 03 80
vortmeyera@mail.nih.gov

Dr. Otmar D. WIESTLER*

German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
GERMANY
Tel. +49 6221 42 28 50
Fax. +49 6221 42 28 40
o.wiestler@dkfz.de

Dr. David ZAGZAG

Department of Pathology
NYU Medical Center and School of Medicine
550 First Avenue, New York, NY 10016
USA
Tel. +1 212 263 6449
Fax. +1 212 263 8994
dz4@nyu.edu

Dr. Pieter WESSELING

Department of Pathology
Radboud University Nijmegen Medical Center
6500 HB Nijmegen
THE NETHERLANDS
Tel. +31 24 3614323
Fax. +31 24 3668750
p.wesseling@pathol.umcn.nl

Dr. James M. WOODRUFF

P.O. Box 1200
73 North Longyard Rd
Southwick, MA 01077
USA
Tel. +1 413 569 6878
woodrufj@earthlink.net

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6.25A	Figarella-Branger D.		Dept. of Pathology		Dept. of Radiology,
6.25B	Libersti P.		Turku University Central		Massachusetts General
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	Inst. of Neuropathology	13.19	Wiestler O.D.		School of Medicine,
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11.10	Fartasch M.		Massachusetts General		
	Dept. of Dermatology,		Hospital, Boston, USA		

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