Chapter V.4

Squamous Cell Carcinoma Including Actinic Keratosis, Bowen's Disease, Keratoacanthoma, and Its Pigmented Variants

V.4

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V.4.1 Definition

Invasive squamous cell carcinoma is the second most common skin cancer after basal cell carcinoma and causes the majority of deaths among the non-melanoma skin malignancies. When detected and treated early squamous cell carcinoma has a 95% cure rate [1]; however, if neglected, squamous cell carcinoma may cause local tissue destruction and may metastasize [2, 3]. Moreover, after the diagnosis of an initial squamous cell carcinoma, the 3-year cumulative risk for developing a second lesion is approximately 18% [4], emphasizing the need for ongoing clinical surveillance. In its pathogenesis, chronic ultraviolet (UV) irradiation plays a major role, responsible for DNA mutations (usually in the p53 tumor suppressor gene) in transformed epidermal keratinocytes [5]. This explains why squamous cell carcinoma typically develops on chronic sun-exposed body sites such as the face or forearms of fair-skinned individuals. Besides fair skin phototype, male gender, and age over 40 years, organ-transplant recipients represent a major risk group for squamous cell carcinoma, having up to a 65-fold increased risk for development compared with the general population [6]. In this particular patient group, 22% of squamous cell carcinomas will develop on sun-protected body sites such as the trunk or lower extremities.

So-called precursor lesions of squamous cell carcinomas include actinic keratosis, Bowen's disease, and erythroplasia of Queyrat, although a common etiological background is questioned, based on differences in clinical, histopathological, and pathogenic profile. However, since these lesions are all epidermal neoplasias with a certain potential of malignant progression, they are commonly grouped within the spectrum of squamous cell carcinoma [7].

Actinic keratoses are considered to be the earliest form of squamous cell carcinoma, with the risk of an individual lesion progressing to invasive squamous cell carcinoma reported to vary from 0.1% up to a considerable 20% [8, 9]. Nevertheless, even with a low individual rate of

progression, patients with multiple actinic keratoses (i.e., more than 10) may have a 14% cumulative probability of developing squamous cell carcinoma, either within the actinic keratosis or de novo, within 5 years. This underscores the need for regular follow-up in these patients [8].

Bowen's disease is a peculiar variant of squamous cell carcinoma in situ that frequently occurs in locations not exposed to solar irradiation. Consequently, some controversy exists regarding a common etiological background of Bowen's disease and squamous cell carcinoma. Bowen's disease differs significantly from actinic keratosis and squamous cell carcinoma in its clinical and histopathological features as well in its pathogenesis, which is related to human papilloma virus infection, prior arsenic exposure, radiation therapy, and internal malignancies, in addition to chronic UV exposure. In contrast, chronic UV irradiation is the primary carcinogen associated with actinic keratosis and squamous cell carcinoma [10, 11]. If left untreated for a variable period of time, Bowen's disease may progress to a variant of invasive squamous cell carcinoma known Bowenoid carcinoma, in 3–20% of cases [12, 13]. Remarkably, Bowenoid carcinoma may metastasize in up to one-third of cases, thus conferring a relatively poor prognosis[12].

In further contrast, keratoacanthoma is also often cited as a "self-healing" variant of squamous cell carcinoma, because it typically shows a self-limiting course. Therefore, there is some question as to whether keratoacanthoma is a true malignancy, or should be best regarded it as a benign "pseudocarcinoma" [14–16]. However, reports which describe local tissue destruction and metastasis keratoacanthoma have led to a consideration of this tumor as a variant of squamous cell carcinoma [17, 18]. Consequently biopsy and definitive treatment of keratoacanthoma is generally recommended.

V.4.2 Clinical Features

Although the majority of these epidermal tumors are usually non-pigmented, pigmented variants may also occur.

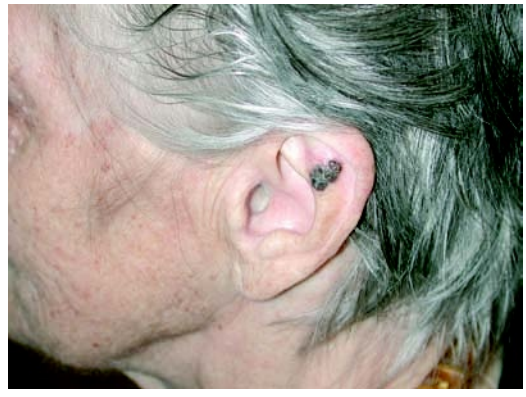

Fig. V.4.1. Clinically, this invasive squamous cell carcinoma presented as a pigmented and keratotic nodule located on the ear (antihelix) of a 78-year-old woman. Clinical differential diagnoses included of basal cell carcinoma, nodular–verrucous melanoma, and seborrheic keratosis. However, the lesion also had a history of recent change, which increased the index of suspicion for malignancy and led to a punch biopsy of the lesion. Histopathology revealed a pigmented invasive a squamous cell carcinoma and the lesion was subsequently excised

V.4.2.1 Invasive Squamous Cell Carcinoma

Invasive squamous cell carcinoma typically occurs along with the presence of multiple actinic keratoses. The initial, in-situ lesion is characterized by a reddish, ill-defined plaque that may be difficult to distinguish from hyperkeratotic actinic keratosis. If left untreated, squamous cell carcinoma in situ may progresses to invasive squamous cell carcinoma, which typically appears as a firm, infiltrating, and often ulcerated nodule, which enlarges fairly rapidly over a number of week or months. In addition, pigmented invasive squamous cell carcinoma may presents as a blue-to-black nodule with a scaly surface (Fig. V.4.1).

V.4.2.2 Actinic Keratosis

Actinic keratoses appear as multiple macules, papules, or plaques surmounted by an adherent surface scale, with some degree of erythema ranging from pale pink to dark red. Sometimes

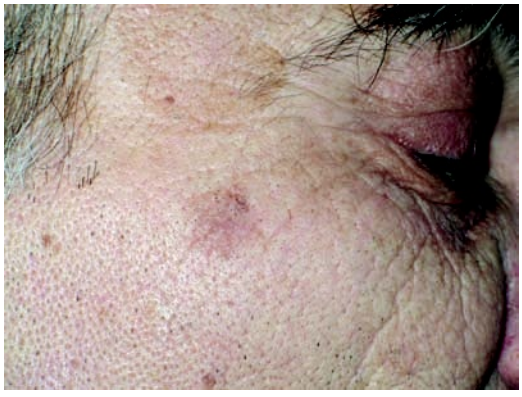

Fig. V.4.2. This pigmented actinic keratosis located on the cheek of a 65-year-old man was clinically difficult to distinguish from solar lentigo and lentigo maligna, especially since it is a solitary pigmented macule lacking the typical surface scales or the neighboring sign with other lesions

actinic keratoses reveal a hyperkeratotic surface with crusts or erosions and may cause sensations of burning or itching. Pigmented actinic keratoses are less frequent but occur as light- to dark-brown irregular plaques or macules, usually with a scaly surface. Pigmented actinic keratoses may clinically mimic solar lentigo, seborrheic keratoses, pigmented Bowen's disease, or lentigo maligna (Fig. V.4.2).

V.4.2.3 Bowen's Disease

The clinical appearance of classical non-pigmented Bowen's disease is represented by a slowly growing, erythematous, well-demarcated plaque with a scaly or crusted surface that may be eroded. Clinical differential diagnoses include a variety of non-pigmented skin tumors or erythemato-squamous skin disorders, such as actinic keratosis, basal cell carcinoma, amelanotic melanoma, clear cell acanthoma, psoriasis, viral warts, and eczema, to name but a few. In contrast, pigmented Bowen's disease is less common and presents clinically as a non-uniformly pigmented plaque with a scaly or verrucous surface which should be differentiated from seborrheic keratosis, pigmented actinic keratosis, solar lentigo, basal cell carcinoma, blue nevus, melanocytic nevi, and melanoma.

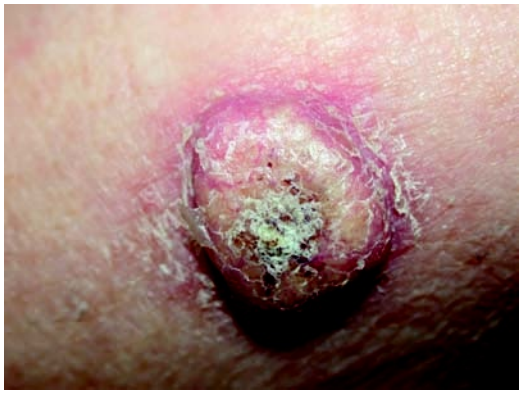

Fig. V.4.3. Keratoacanthoma typically develops rapidly and presents clinically as a dome-shaped nodule with a central plug of keratin, as seen in this image

V.4.2.4 Keratoacanthoma

The clinical course of keratoacanthoma is typified by a rapid enlargement within a few weeks until a stabilization of growth is reached. After a variable time, a spontaneous involution results in the regression of the lesion. The typical appearance of keratoacanthoma is that of a dome-shaped nodule of variable size characterized by a central crater filled with a mass of keratin. The diameter of a common solitary keratoacanthoma can range from a few millimeters up to a considerable 3 cm. Multiple lesions can occur spontaneously in the Gryzbowski variant, or in Muir–Torre syndrome (Fig. V.4.3) [19–21].

V.4.3 Dermoscopic Criteria

V.4.3.1 Squamous Cell Carcinoma

Dermoscopically, non-pigmented invasive squamous cell carcinoma frequently exhibits linear-irregular, hairpin, or dotted vessels, or combinations thereof (the so-called polymorphous or atypical vascular pattern) [22]. Typically, these vessels are surrounded by a whitish halo, which is a dermoscopic hallmark of all keratinizing tumors. Ulceration and blood crusts, if present, appear as irregularly distributed reddish to brownish to black blotches on the surface of the tumor.

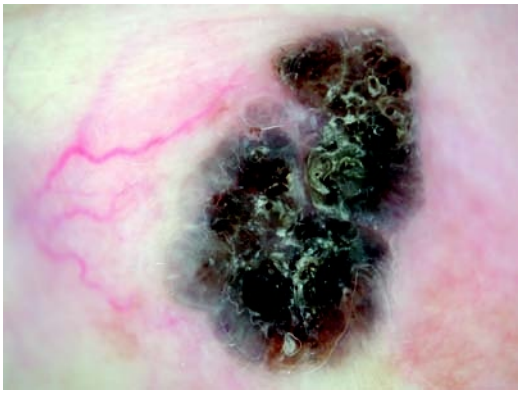

Fig. V.4.4. Dermoscopy of the pigmented invasive squamous cell carcinoma, as shown in Fig. V.4.1. reveals surface scale, a blue-white veil and irregular brown-to-black blotches. Clear-cut criteria for the diagnosis of a melanocytic skin lesion, basal cell carcinoma, or seborrheic keratosis are lacking. As a general rule, it is advisable to biopsy such lesion which lacks specific dermoscopic criteria, in order to obtain a histopathologic diagnosis

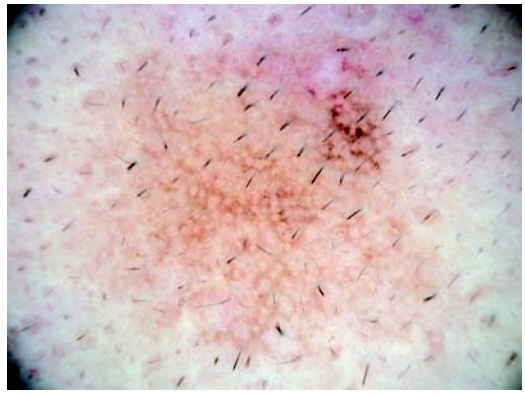

Fig. V.4.5. Dermoscopy of the pigmented actinic keratosis depicted in Fig. V.4.2 reveals the same features as lentigo maligna, characterized by rhomboidal structures and an annular granular pattern, and having a notable gray color. These common dermoscopic criteria do not allow an accurate discrimination of these two different entities. However, dermoscopy in this case helped to select the most representative area for biopsy, which in this lesion corresponds to the dark area in the upper right part of the image

Pigmented invasive SCC may reveal dermoscopically a scaly surface diffuse or homogeneous blue pigmentation and/or distinct, irregularly distributed, blue-gray granular structures. If ulcerated, dark-brown to black blood crusts may be visible. Due to the pigmentation, vessels are usually not seen (Fig. V.4.4) [23].

V.4.3.2 Actinic Keratosis

Facial non-pigmented actinic keratoses reveal four essential dermoscopic features, represented by erythema, with a marked pink-to-red "pseudonetwork" surrounding the hair follicles; white-to-yellow surface scale; fine, linear-wavy vessels surrounding the hair follicles; and hair follicle openings surrounded by a white halo and often filled with a yellowish keratotic plug. These features combine to produce a peculiar "strawberry" appearance. By contrast, actinic keratosis on extra-facial sites typically lack this "strawberry" pattern but frequently display surface scale and dot vessels; however, hyperkeratotic scale in actinic keratosis may obscure underlying vascular structures, which may challenge the specificity of the dermoscopic features [24].

Pigmented actinic keratosis located on facial sites can represent both clinical and dermoscopic mimic of lentigo maligna, since both tumors may reveal the same dermoscopic patterns of asymmetric pigmented follicles, annular–granular pattern, and rhomboidal structures [25]. Besides surface scale, a further possible clue for the diagnosis of pigmented actinic keratosis in these cases may be the presence of a superficial, prominent, "broken-up" pseudonetwork, which is not usually seen in lentigo maligna or seborrheic keratosis. However, the presence of this latter feature alone should be considered insufficient to rule out lentigo maligna. (Fig. V.4.5)

V.4.3.3 Bowen's Disease

Non-pigmented Bowen's disease displays a peculiar dermoscopic pattern characterized by a scaly surface and glomerular vessels. The latter have a highly convoluted morphology reminiscent of the renal glomerulus, and are typically arranged in clusters throughout the lesion. In pigmented Bowen's disease, small brown globules regularly packed in a patchy distribution, and structureless gray-to-brown pigmentation can also be observed (Fig. V.4.6) [26].

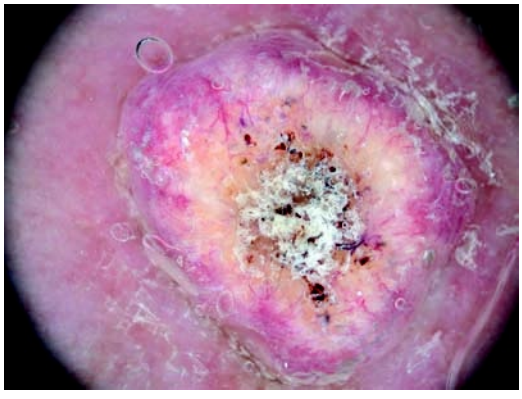

Fig. V.4.6. Dermoscopy of the keratoacanthoma, as seen in Fig. V.4.3. There is a polymorphous vascular pattern (i.e., more than one type of vascular structure) occuring on a white background, which surrounds a central mass of keratin. A polymorphous vascular pattern should always raise the index of suspicion for a malignant tumor

V.4.3.4 Keratoacanthoma

Dermoscopically, keratoacanthoma is characterized by a central yellowish to brownish structureless mass of keratin surrounded by typically elongated hairpin vessels (with whitish halos), occurring within a whitish background [22, 27].

V.4.4 Relevant Clinical Differential Diagnosis

Most of these non-pigmented keratinizing tumors may clinically mimic a variety of skin disorders; however, the dermoscopic pattern will allow the clinician, in most cases, to distinguish not only these various keratinizing tumors, but to differentiate them from inflammatory skin lesions. To this end, it is advisable to establish, as the first step in the diagnosis, whether the lesion belongs to the tumoral or inflammatory spectrum. Once the given lesion is categorized as a possible skin tumor (primarily a single lesion), the evaluation of the morphological type of vessels (step 2), their distribution within the lesion(s) (step 3), and the presence of additional dermoscopic features (step 4) allows one to reach a diagnostic conclusion (step 5). Certainly, this algorithm should be a simple guide and has its limitations, such as in the case of actinic keratosis which are usually multiple in number [28].

For pigmented tumors, a differential diagnosis in a wide spectrum of other skin tumors must be considered. For pigmented squamous cell carcinoma the differential diagnosis includes nodular melanoma, basal cell carcinoma, or blue nevus. In the case of pigmented actinic keratosis and Bowen's disease, lentigo maligna and seborrheic keratosis should be considered.

V.4.5 Histopathology

V.4.5.1 Squamous Cell Carcinoma

Invasive squamous cell carcinoma is characterized histopathologically by the presence of nests of keratinocytes arising from the epidermis with extension to the dermis. The tumor nests show varying degrees of anaplasia and keratinization. A variety of histological growth patterns can be found, including spindle cell, pleomorphic, adenoid, acantholytic, and clear-cell variants. In the surrounding epidermis residual actinic keratosis-like changes are frequently found.

Pigmented invasive squamous cell carcinoma exhibit an accumulation of melanin in the cytoplasm of keratinocytes, particularly in the upper spinous layer. Additionally, collections of melanophages intermingled with variably dense infiltrates of lymphocytes can be seen in the papillary dermis. Histopathologically, the homogeneous blue pigmentation seen on dermoscopy correlates with abundant melanin, melanophages, and/or melanin-laden tumor cells within the papillary dermis [23]. In addition, focal collections of dermal melanophages are seen dermoscopically as blue-gray granules.

V.4.5.2 Actinic Keratosis

In actinic keratoses atypical keratinocytes are present within the epidermis in varying proportions, but by definition are not in a full-thickness distribution. Focal parakeratosis with loss of the underlying granular layer is a constant

feature, while in the upper dermis solar elastosis is usually seen. There are hypertrophic, atrophic, and pigmented variants of actinic keratoses. In pigmented actinic keratoses melanin can be detected in keratinocytes of the lower epidermis and occasionally melanophages are found in the papillary dermis.

V.4.5.3 Bowen's Disease

As a form of carcinoma in situ, Bowen's disease shows histopathologically, by definition, a full-thickness involvement of the epidermis by atypical keratinocytes with increased mitotic figures. The overlying stratum corneum often shows parakeratosis or hyperkeratosis. There are convolutions of grouped and frequently dilated capillaries in the papillary dermis and dermal papillae, which correspond to the glomerular vessels seen with dermoscopy (Fig. V.4.7). In addition, there is an accompanying inflammatory, mostly lymphocytic, infiltrate in the superficial dermis.

In pigmented Bowen's disease, focal collections of melanophages in the upper dermis and/or an increased number of pigmented basal keratinocytes appear to correlate with the brown globules observed dermoscopically [26].

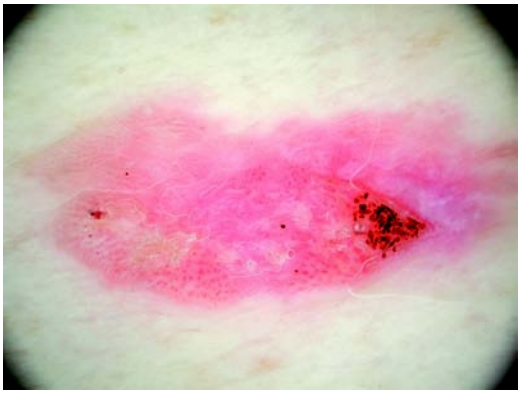

Fig. V.4.7. Dermoscopy of Bowen's disease reveals glomerular vessels (variation of dotted vessels) arranged in clusters on a whitish to pink background, in addition to surface scales

V.4.5.4 Keratoacanthoma

Keratoacanthoma is an exoendophytic tumor with distinct borders, consisting of a keratin-filled crater centrally, which is surrounded by masses of well-differentiated squamous epithelium at the sides and base of the lesion. Epithelial dysplasia and mitotic figures are usually not seen. Pigmented keratoacanthoma is an extremely rare condition.

V.4.6 Management

V.4.6.1 Squamous Cell Carcinoma

Invasive squamous cell carcinoma is usually excised with 4- to 6-mm margins, to ensure adequate tumor removal and to reduce the risk of metastasis [1, 29]. High-risk lesions include those which are large (>2 cm), poorly differentiated, have perineural invasion, or those located on high-risk facial sites such as the ear or lip. In this situation, Mohs' micrographic surgery achieves the highest cure rates [10, 30]. Sentinel lymph node biopsy is currently not a routine procedure for the management of invasive squamous cell carcinoma but may yet prove useful in the evaluation of high-risk squamous cell carcinoma [31]. Because pigmented invasive squamous cell carcinoma may clinically and dermoscopically mimic a variety of benign as well as other malignant skin tumors, such as seborrheic keratosis, blue nevus or melanoma, biopsy of any changing blue lesion is advisable.

V.4.6.2 Actinic Keratosis

The management choices for actinic keratosis are numerous, including local or minimally invasive treatments such as cryotherapy, curettage, laser treatment, topical photodynamic therapy, diclofenac in hyaluronan gel, and 5-fluorouracil or imiquimod cream. Sunscreen use and other sun-protective measures are also recommended. In the case of pigmented actinic keratosis, biopsy prior to any treatment should be performed [32].

V.4.6.3 Bowen's Disease

The management of Bowen's disease includes cryotherapy with a prolonged (20–30 s) freezing time, or other minimally invasive treatment options such as imiquimod or 5-fluorouracil cream, or photodynamic therapy. Some authors also recommend surgical excision, particularly for larger lesions, to reduce the risk of prolonged wound healing after destructive treatments, as well as to reduce the risk of recurrence or invasion [32].

V.4.6.4 Keratoacanthoma

Although considered a "benign" variant of squamous cell carcinoma, keratoacanthoma is usually surgically removed. Curettage and electrodesiccation is an alternative treatment modality. In the case of multiple keratoacanthomas, systemic retinoids (such as etretinate) are a promising treatment option [32].

Core Messages

- Squamous cell carcinoma and its variants are a diagnostic and therapeutic challenge for the clinician.
- The diagnosis should be based on all available information, including patient history and clinical and dermoscopic features.
- Doubtful lesions should be biopsied in order to rule out invasive squamous cell carcinoma.

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