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EPITHELIAL TUMORS

This chapter deals with the large morphologic and biologic spectrum of epithelial tumors presenting in the skin. A discussion of cutaneous epithelial neoplasms showing epidermal differentiation is first. Most of these tumors show squamous differentiation, and an epidermal component is frequently present. Cutaneous epithelial neoplasms consist of benign squamous proliferations, including solar lentigines, seborrheic keratosis, and rarer acanthomas; dysplastic squamous lesions; and malignant tumors, such as squamous cell carcinoma and its variants. Also included in this chapter are basal cell carcinoma and Merkel cell carcinoma.

A discussion of neoplasms with skin adnexal differentiation follows. This is further divided into tumors of sweat duct/gland, hair follicular, and sebaceous differentiation. Sweat duct/gland tumors are characterized by the formation of duct or glandular structures in the form of well-formed ducts or as intracytoplasmic lumens. They show characteristic refractile cuticles, which are highlighted immunohistochemically by staining for epithelial membrane antigen (EMA) or carcinoembryonic antigen (CEA). Hair follicular tumors show differentiation toward different aspects of the normal hair follicle, including infundibular, isthmic, trichilemmal, and matrical differentiation. Sebaceous tumors are defined by the presence of sebaceous differentiation. Recognition of mature sebaceous cells with abundant pale and finely vacuolated cytoplasm and indented, “scalloped” nuclei is necessary for the correct diagnosis. The group of skin adnexal tumors is large, with a broad morphologic spectrum, making recognition and reliable diagnosis challenging.

EPIDERMAL TUMORS

Solar Lentigo

Definition. *Solar lentigo* is a benign intraepidermal proliferation of keratinocytes, closely

linked to ultraviolet light (UV) exposure and related to seborrheic keratosis.

Clinical Features. Solar lentigines present as uniformly pigmented and well-demarcated tan to brown macules on sun-exposed skin of middle-aged to elderly adults with fair skin. They are frequently multiple and are an indicator of chronic UV exposure (1). The so-called “ink-spot” lentigo is characterized by its intense dark brown pigmentation (2).

Microscopic Findings. Solar lentigines are well-demarcated and characterized by elongated narrow rete ridges with budding at the tips in a background of dermal solar elastosis (fig. 1-1). In addition, there is basal cell layer hyperpigmentation and occasional fusion with adjacent rete ridges; mildly increased numbers of single melanocytes may be present at the dermoepidermal junction (fig. 1-2). Ink-spot lentigines

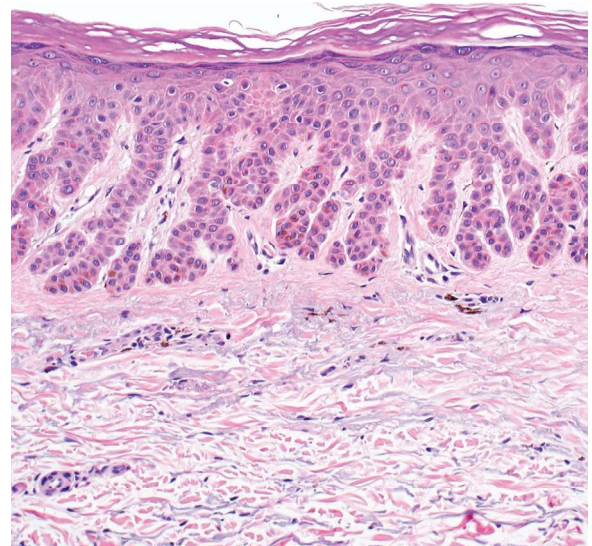


Figure 1-1

SOLAR LENTIGO

The elongated rete ridges show budding and hyperpigmentation at the base.

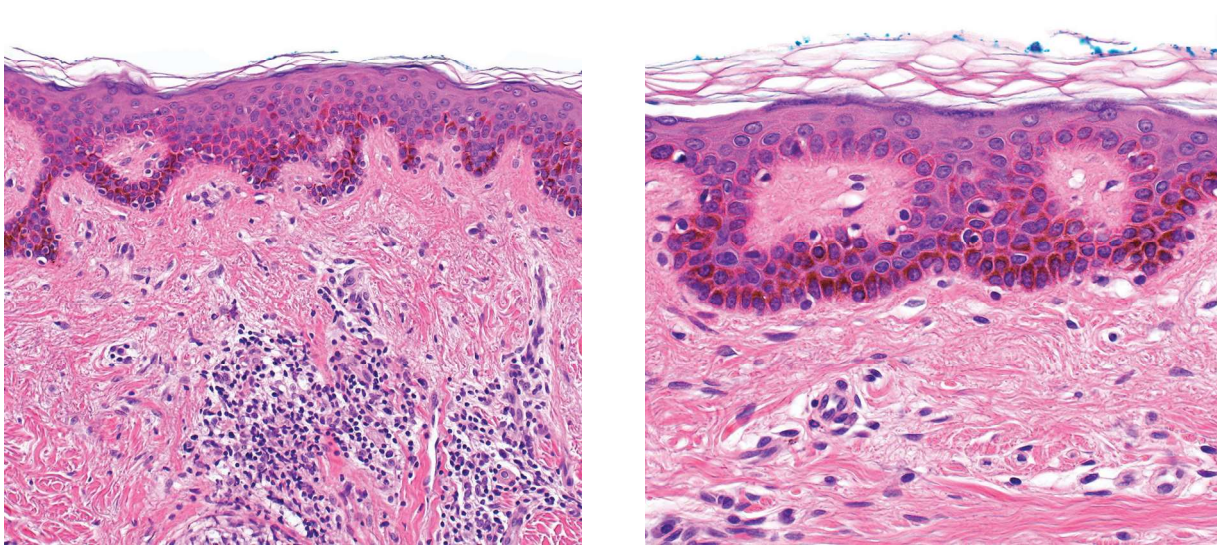


Figure 1-2

SOLAR LENTIGO

Left: Marked basal cell layer hyperpigmentation and a background of a superficial dermal chronic inflammatory cell infiltrate are seen.

Right: There is fusion of the rete ridges. The numbers of small melanocytes are mildly increased.

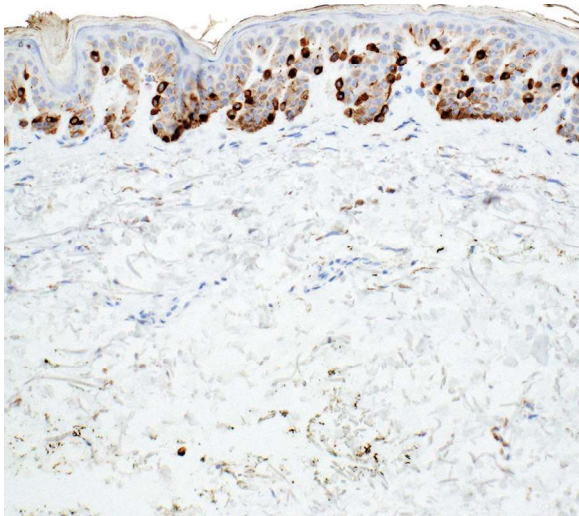


Figure 1-3

SOLAR LENTIGO

Melan A immunohistochemistry highlights the mildly increased numbers of small single melanocytes at the junction. There is no contiguous growth of junctional melanocytes.

are characterized by exuberant basal cell layer hyperpigmentation.

Differential Diagnosis. Pigmented actinic keratosis is differentiated from solar lentigo by

the presence of keratinocyte atypia. Lentigo maligna shows a contiguous growth of atypical melanocytes with epidermal atrophy and flattening. Evaluation of melan A or SOX10 immunohistochemistry may help assess melanocyte density (fig. 1-3) (3).

Treatment and Prognosis. No specific treatment is required. Solar lentigines are benign.

Large Cell Acanthoma

Definition. *Large cell acanthoma* is a benign intraepidermal proliferation of keratinocytes in the spectrum of solar lentigo and seborrheic keratosis.

Clinical Features. Large cell acanthomas are well-circumscribed, tan to brown macules or plaques arising on chronically sun-damaged skin, with a predilection for the face and arms of middle-aged or elderly adults (4,5).

Microscopic Findings. The well-circumscribed lesions are characterized by mild epidermal thickening and flattening. They contain enlarged keratinocytes with abundant cytoplasm and nuclei approximately twice the size of those seen in adjacent nonlesional keratinocytes (fig. 1-4). There is basal cell layer hyperpigmentation and overlying basket-weave

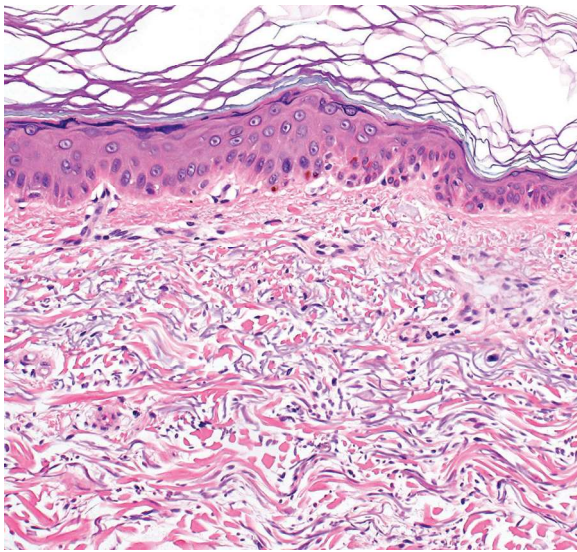


Figure 1-4

LARGE CELL ACANTHOMA

There is abrupt transition from the normal epidermis to epidermal acanthosis containing enlarged keratinocytes. Also seen is basket-weave orthohyperkeratosis.

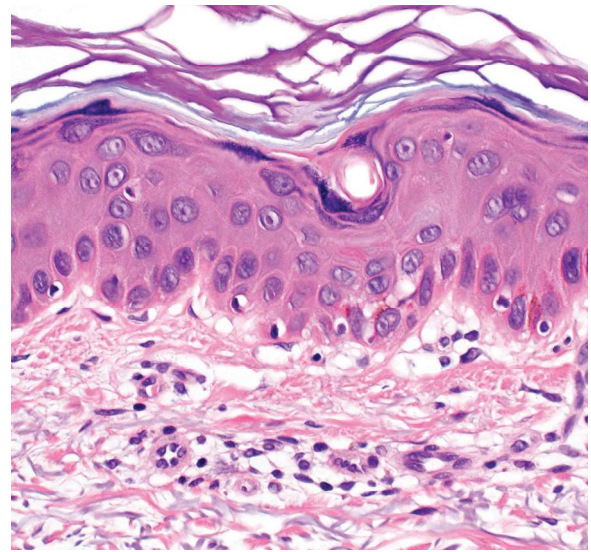


Figure 1-5

LARGE CELL ACANTHOMA

Enlarged keratinocytes contain abundant cytoplasm, with no nuclear pleomorphism. Basal cell layer hyperpigmentation is focally present.

hyperkeratosis (fig. 1-5). Cytologic atypia is not seen and mitoses are rare.

Differential Diagnosis. Actinic keratosis is characterized by the presence of squamous dysplasia and overlying parakeratosis. Lentigo maligna shows contiguous junctional growth of atypical epithelioid melanocytes, which can be highlighted by melan A or SOX10 immunohistochemistry.

Treatment and Prognosis. No specific treatment is necessary. Large cell acanthoma is benign

Clear Cell Acanthoma

Definition. *Clear cell acanthoma* is a sharply demarcated intraepidermal squamous proliferation with pale cytoplasmic changes.

Clinical Features. Clear cell acanthoma presents as solitary, well-delineated pink to red papules or nodules measuring 0.5 to a few centimeters, with an overlying scale crust (6). The lower extremities of adults are typically affected.

Microscopic Findings. The well-circumscribed lesions show psoriasiform epidermal hyperplasia with elongated and fused rete ridges and thinning of the papillary plates (fig. 1-6). Prominent pale cell change of the keratinocyte cytoplasm is seen, with an abrupt transition

from the adjacent normal epidermis (fig. 1-7). An overlying parakeratotic scale and intraepidermal and intracorneal neutrophils are present (fig. 1-8). A mixed inflammatory cell infiltrate is seen in the superficial dermis accompanied by prominent vascularity.

Differential Diagnosis. The diagnosis is straightforward if the entire lesion is sampled. Psoriasis may show identical features, but the sharp demarcation and the clinical context are helpful distinguishing features. Similarly, lichen simplex chronicus is not as sharply delineated and shows irregular epidermal hyperplasia with hypergranulosis. Seborrheic keratosis shows a papillomatous architecture with the formation of “horn cysts” and it lacks the pale cell change.

Treatment and Prognosis. No specific treatment is necessary. Clear cell acanthoma is benign.

Seborrheic Keratosis

Definition. *Seborrheic keratoses* are benign epidermal squamoproliferative lesions that show an increasing incidence with age (7).

Clinical Features. Seborrheic keratoses present as tan to brown keratotic papules or plaques with a stuck-on appearance. They may be solitary or multiple, with a predilection for the head

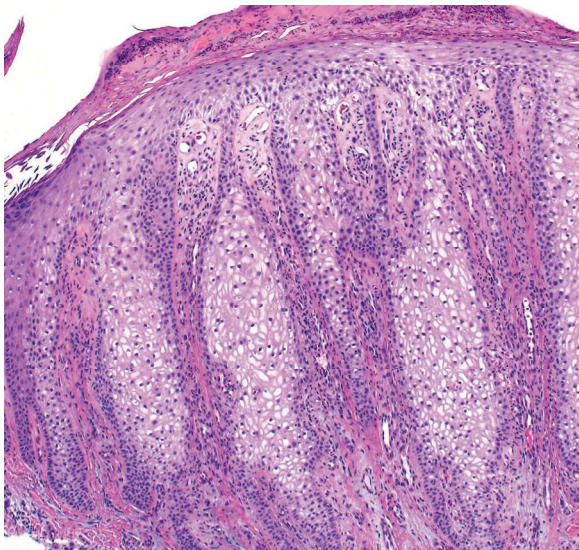


Figure 1-6

CLEAR CELL ACANTHOMA

Above: Marked epidermal hyperplasia with abrupt clear cell change.

Right: Regular psoriasiform epidermal hyperplasia is seen.

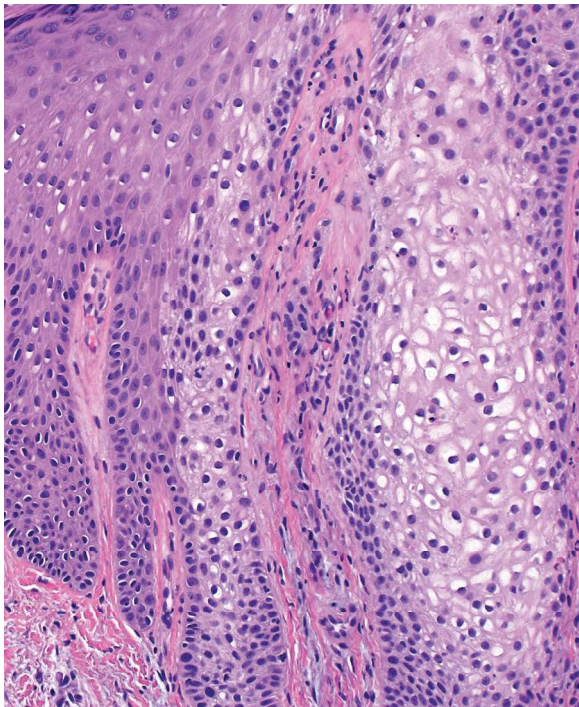
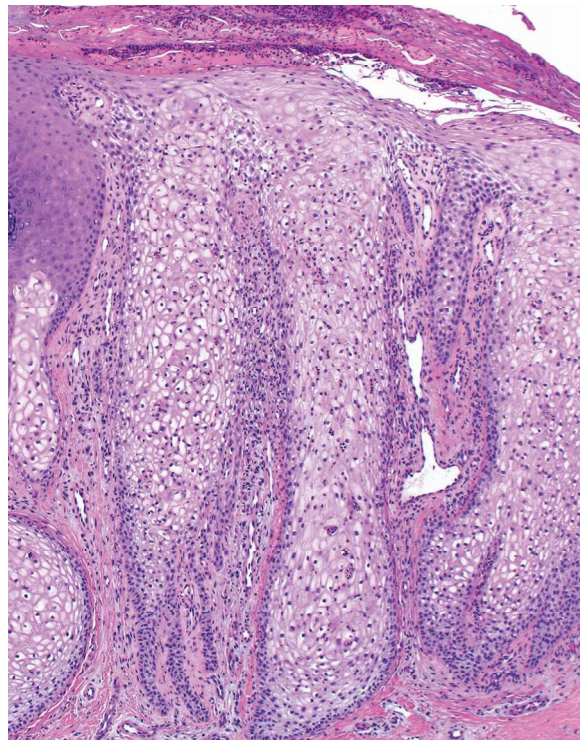


Figure 1-7

CLEAR CELL ACANTHOMA

There is abrupt transition from normal-appearing keratinocytes to those with pale to clear staining cytoplasm.

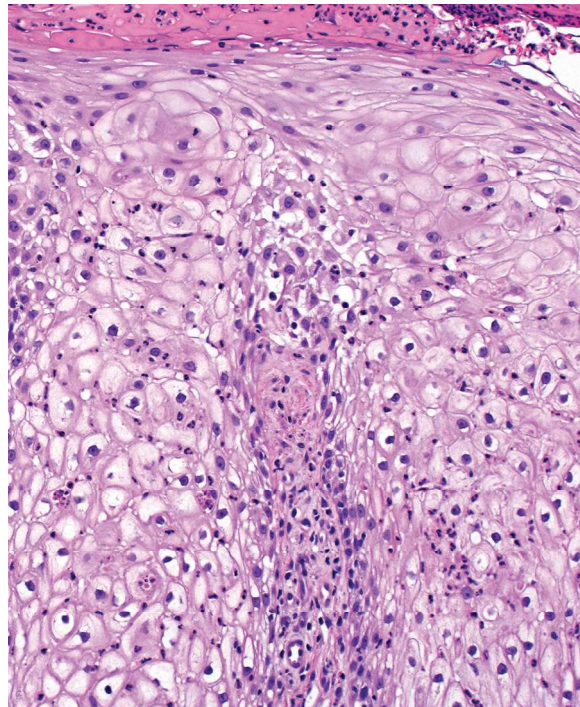


Figure 1-8

CLEAR CELL ACANTHOMA

Intraepidermal neutrophils are present.

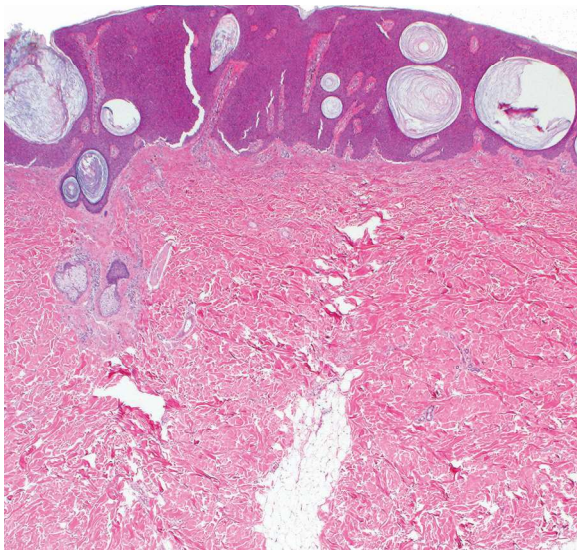


Figure 1-9

SEBORRHEIC KERATOSIS

Acanthotic seborrheic keratosis is characterized by epidermal thickening with a flat base.



Figure 1-10

SEBORRHEIC KERATOSIS

Multiple "horn cysts" are present.

and neck, trunk, and skin folds of middle-aged to elderly adults. An eruptive onset of multiple seborrheic keratoses in the setting of an internal malignancy is known as the Leser-Trélat sign (8).

Microscopic Findings. Seborrheic keratoses are well-circumscribed intraepidermal papillomatous proliferations of basaloid keratinocytes with a flat base (fig. 1-9). There is overlying orthohyperkeratosis; tangential sectioning of the squamous invaginations leads to the formation of the horn cysts (fig. 1-10). Basal cell layer hyperpigmentation is a common feature but cytologic atypia and nuclear pleomorphism are not seen (fig. 1-11).

The most frequent *acanthotic variant* is characterized by the formation of regular, broad, solid keratinocytic columns (fig. 1-10). The *keratotic (papillomatous) variant* shows a florid papillomatous architecture with marked hyperkeratosis (fig. 1-12). The *reticulated (adenoid) variant* is composed of interconnecting elongated rete ridges with small horn cysts (fig. 1-13). The *irritated type* shows a chronic inflammatory cell infiltrate, areas of squamatization, squamous eddy formation, and overlying parakeratosis (fig. 1-14).

Inverted follicular keratosis is characterized by invaginated growth and areas of squamatization. These tumors are well circumscribed and

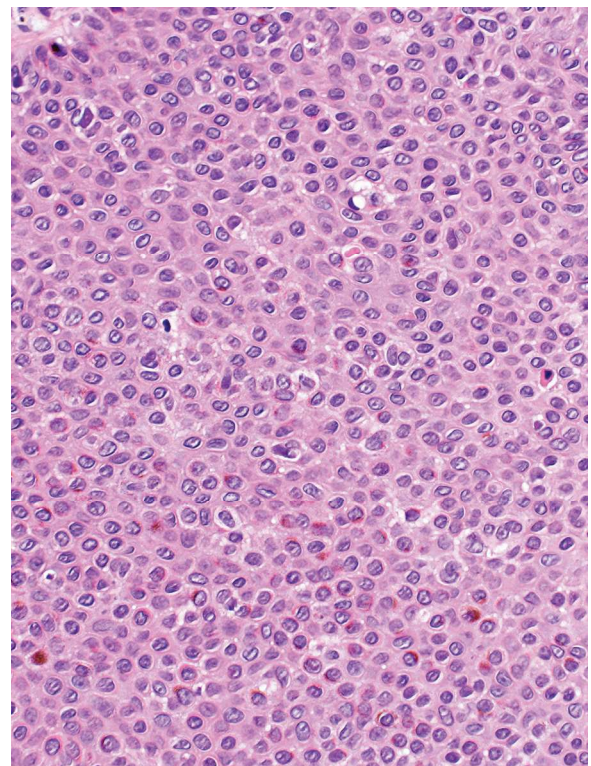


Figure 1-11

SEBORRHEIC KERATOSIS

The proliferation of uniform and small keratinocytes has no cytologic atypia.

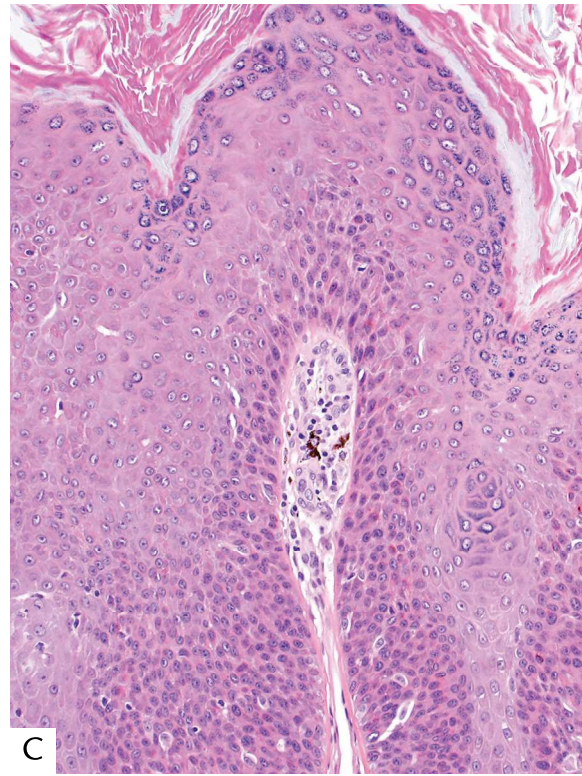
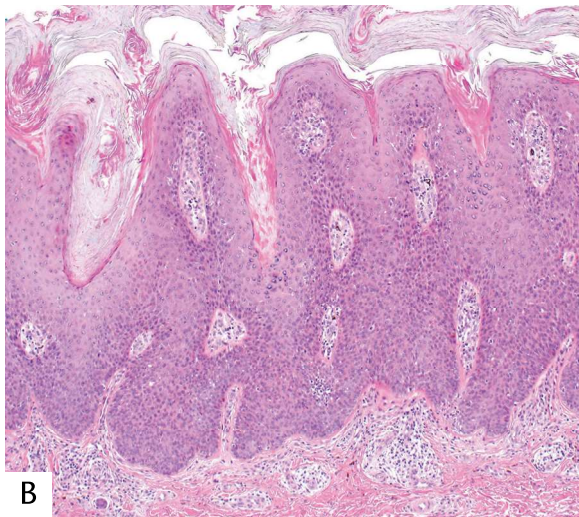
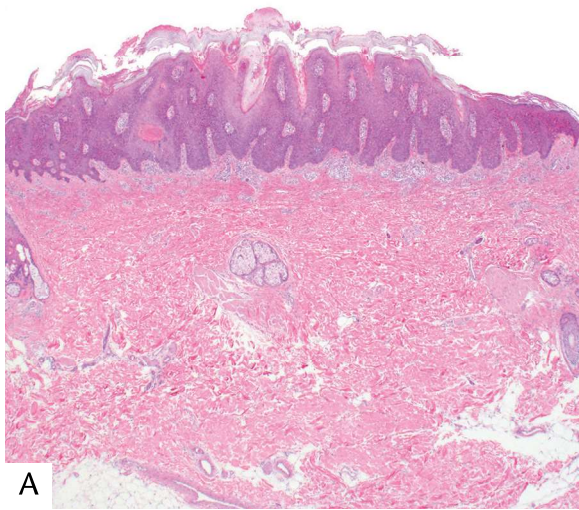


Figure 1-12

SEBORRHEIC KERATOSIS

A: The keratotic variant shows a papillomatous architecture. Lesional circumscription and a flat base are also seen.

B: High-magnification view highlights the papillomatous architecture and marked overlying hyperkeratosis.

C: Uniform small keratinocytes show hypergranulosis and hyperkeratosis.

show an exophytic papillomatous architecture and an endophytic growth component into the dermis (fig. 1-15). They are composed of strands and lobules of bland and uniform polygonal basaloid epithelial cells with areas of squamatization showing numerous “squamous eddies,” similar to irritated seborrheic keratoses (fig. 1-16). Tangential sectioning may give rise to a pseudoinvasive appearance (fig. 1-17).

The formation of distinctive intraepidermal cellular nests (Borst-Jadassohn pattern) is encountered in the *clonal type* (fig. 1-18). Tumors with increased cytoplasmic melanin pigmentation and associated pigmentary incontinence are referred to as the *pigmented variant* while those colonized by pigmented dendritic cells are regarded as *melanoacanthomas* (fig. 1-19).

Differential Diagnosis. Reactive atypia in seborrheic keratosis may be difficult to separate from squamous dysplasia in actinic keratosis or squamous cell carcinoma, especially on superficial and small samples. Rarely, squamous dysplasia and even squamous cell carcinoma develop in association with a seborrheic keratosis.

Treatment and Prognosis. No specific treatment is required. Seborrheic keratoses are benign.

Lichenoid Keratosis

Definition. *Lichenoid keratoses (lichen planus-like keratoses)* are benign intraepidermal squamoproliferative lesions characterized by a lichenoid chronic inflammatory cell infiltrate and interface change, likely representing active

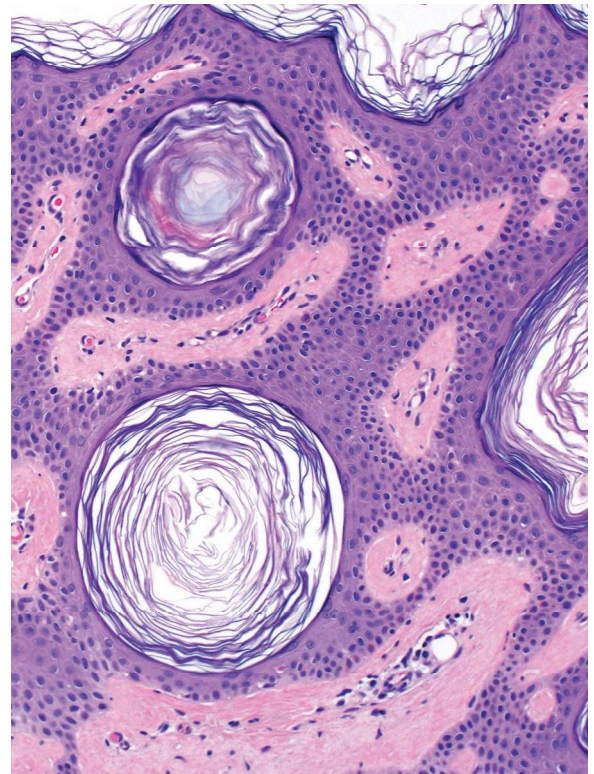
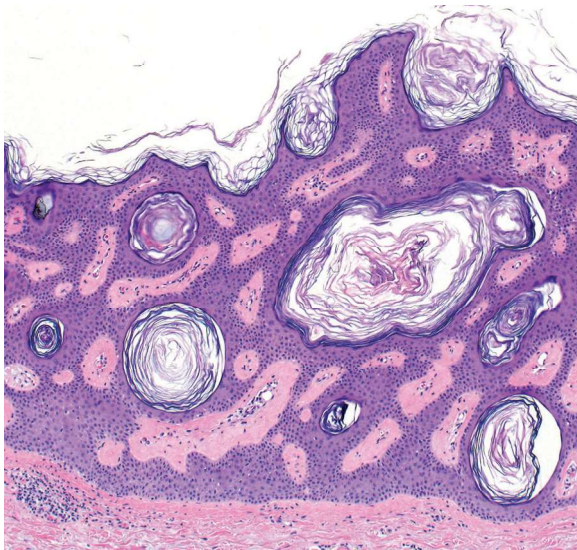


Figure 1-13

SEBORRHEIC KERATOSIS

Above: Adenoid seborrheic keratoses are composed of a reticular growth of epidermal strands.

Right: There is prominent "horn cyst" formation.

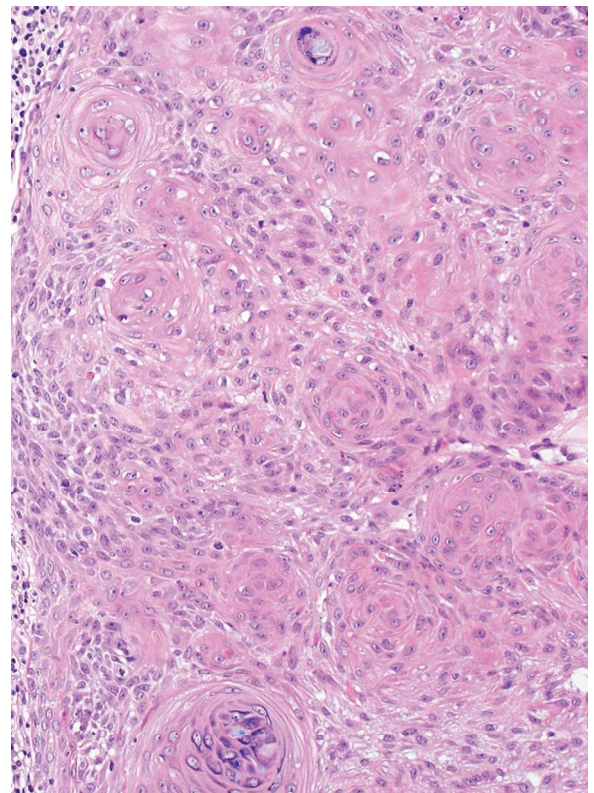
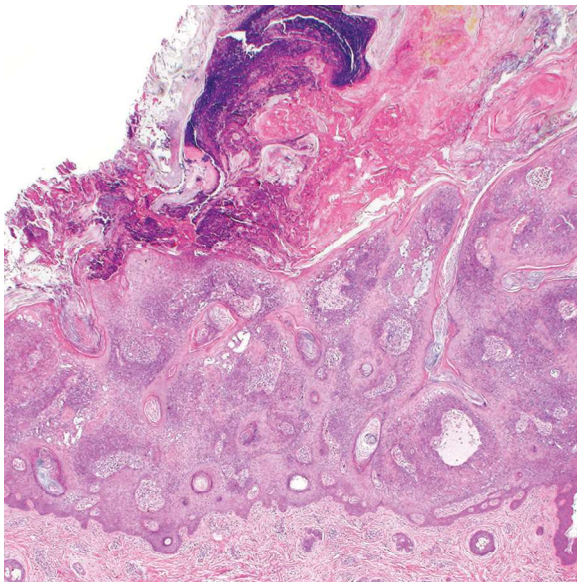


Figure 1-14

SEBORRHEIC KERATOSIS

Above: This irritated seborrheic keratosis is well circumscribed and shows a prominent overlying keratotic scale.

Right: High magnification highlights abundant squamous eddies.

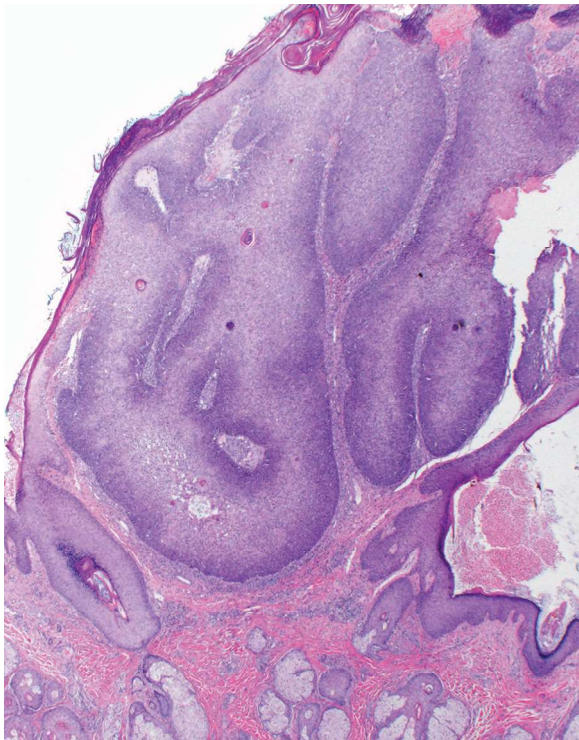


Figure 1-15

INVERTED FOLLICULAR KERATOSIS

The tumors are well circumscribed but show an endophytic growth component.

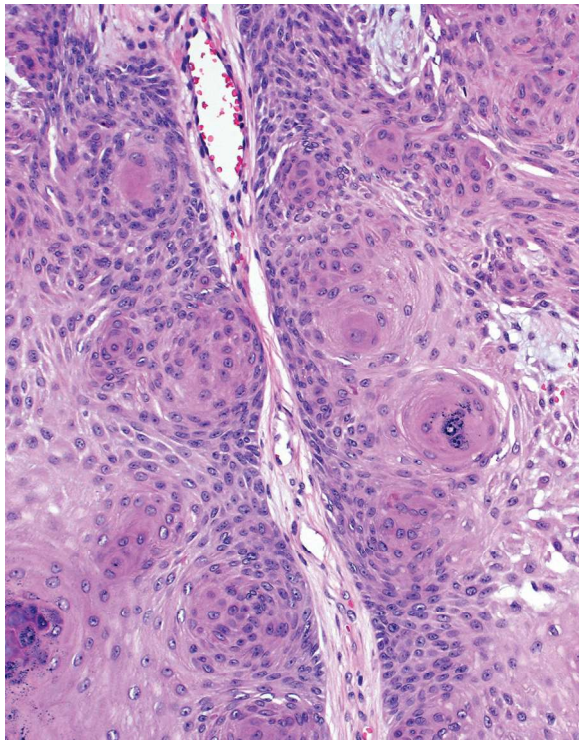


Figure 1-16

INVERTED FOLLICULAR KERATOSIS

Similar to irritated seborrheic keratoses, there are multiple squamous eddies in inverted follicular keratosis.

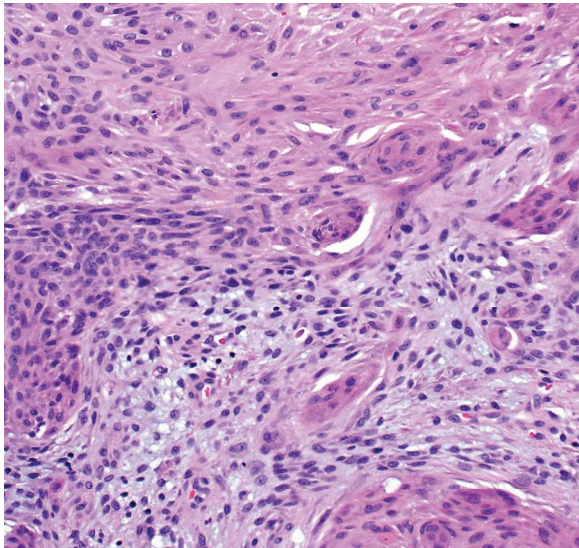


Figure 1-17

INVERTED FOLLICULAR KERATOSIS

Tangential sectioning gives rise to a pseudoinvasive appearance.

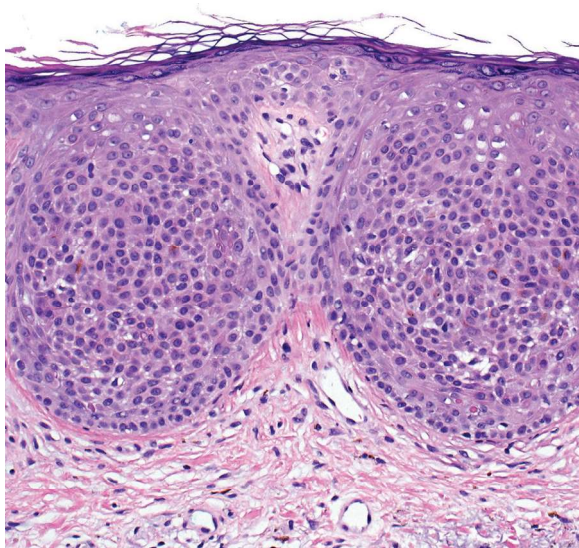


Figure 1-18

SEBORRHEIC KERATOSIS

Intraepidermal nests of uniform basaloid keratinocytes are characteristic of the clonal variant.

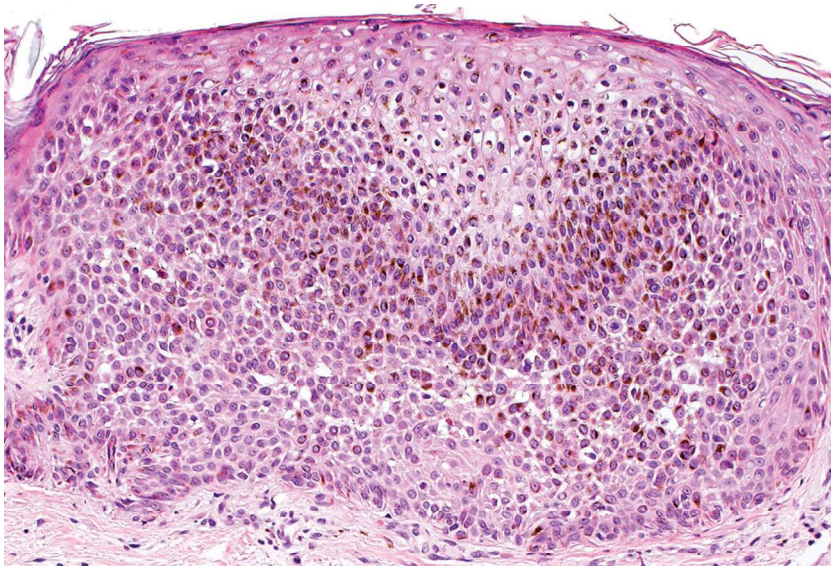


Figure 1-19

SEBORRHEIC KERATOSIS

Pigmented seborrheic keratoses show abundant melanin pigment within the cytoplasm of lesional keratinocytes.

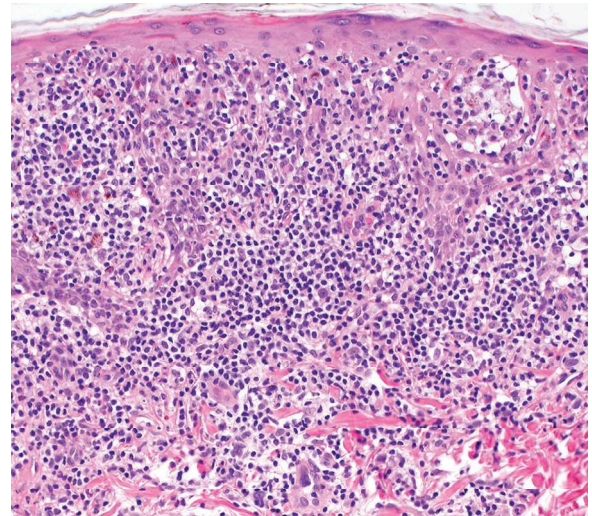
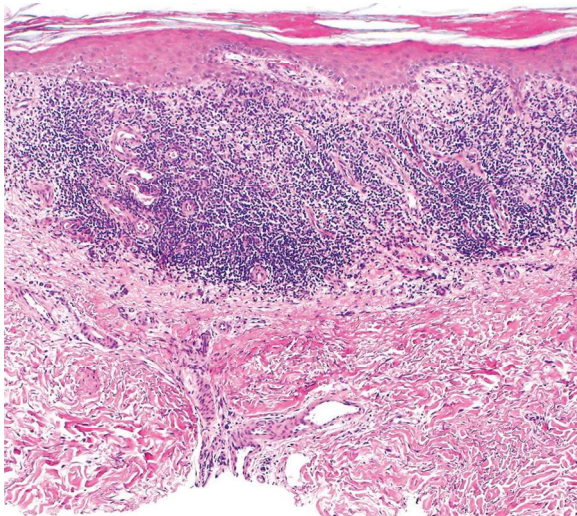


Figure 1-20

LICHENOID KERATOSIS

Left: There are alternating areas of epidermal hyperplasia and atrophy, with overlying hyperkeratosis and a dense band-like inflammatory infiltrate in the superficial dermis.

Right: Higher magnification of the band-like chronic inflammatory cell infiltrate shows pigment incontinence in areas. There is epidermotropism reminiscent of the “tagging” is more typically associated with epidermotropic cutaneous T-cell lymphoproliferative disorders.

regression. They are closely related to solar lentigines and seborrheic keratoses.

Clinical Features. Lichenoid keratoses are fairly common. They present as solitary and well-circumscribed erythematous to violaceous or brown papules and plaques. The trunk is most frequently affected, followed by the extremities of adult Caucasians; there is a female predilection

(9,10). The head and neck is rarely involved. Lichenoid keratoses are frequently mistaken for basal cell carcinoma clinically (9,11).

Microscopic Findings. Lichenoid keratoses are well-demarcated and show variable epidermal hyperplasia with overlying hyperkeratosis and parakeratosis (fig. 1-20). A superficial dermal lichenoid chronic inflammatory cell infiltrate

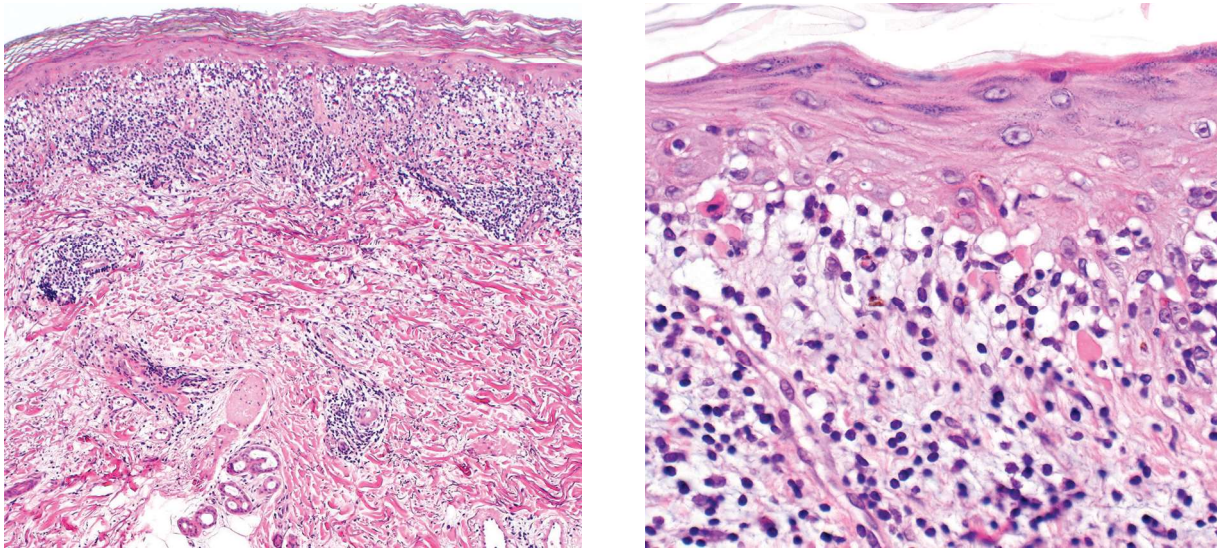


Figure 1-21

LICHENOID KERATOSIS

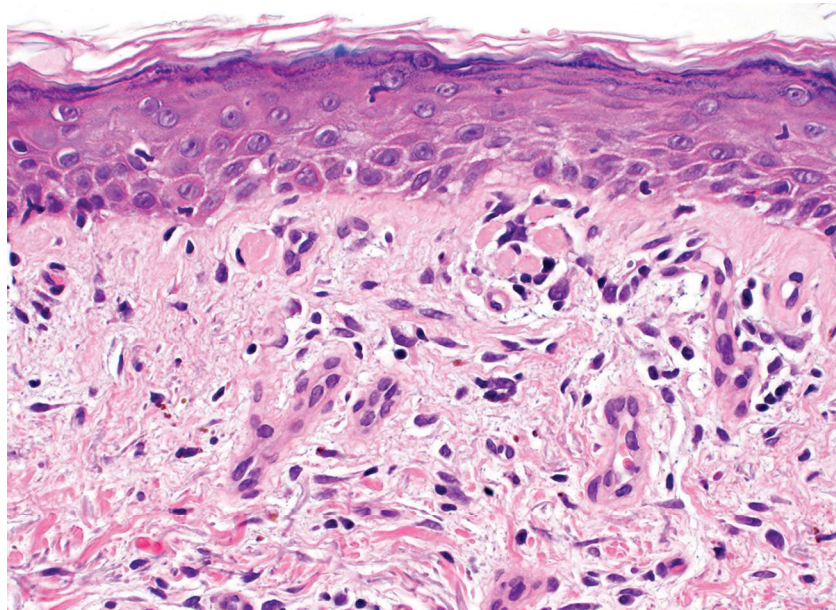
Left: Prominent lichenoid interface change resembles lichen planus.

Right: On higher magnification, the chronic inflammatory cell infiltrate results in prominent interface change with apoptotic keratinocytes and colloid bodies.

Figure 1-22

LICHENOID KERATOSIS

In the later stages of evolution the chronic inflammatory infiltrate has largely disappeared and there are several colloid bodies in the superficial dermis.



with vacuolar degenerative change and necrotic keratinocytes of the overlying epidermis is typical (fig. 1-21). The inflammatory cell infiltrate is composed of lymphocytes, histiocytes, and eosinophils; plasma cells may be admixed. Additional findings include colloid bodies, pigmentary incontinence, and superficial dermal

fibrosis (fig. 1-22). A subepidermal cleft with bulla formation may be the result of extensive vacuolar degeneration (fig. 1-23). Late-stage lesions are characterized by epidermal atrophy and marked superficial dermal fibrosis. A background of a solar lentigo or seborrheic keratosis is sometimes present.

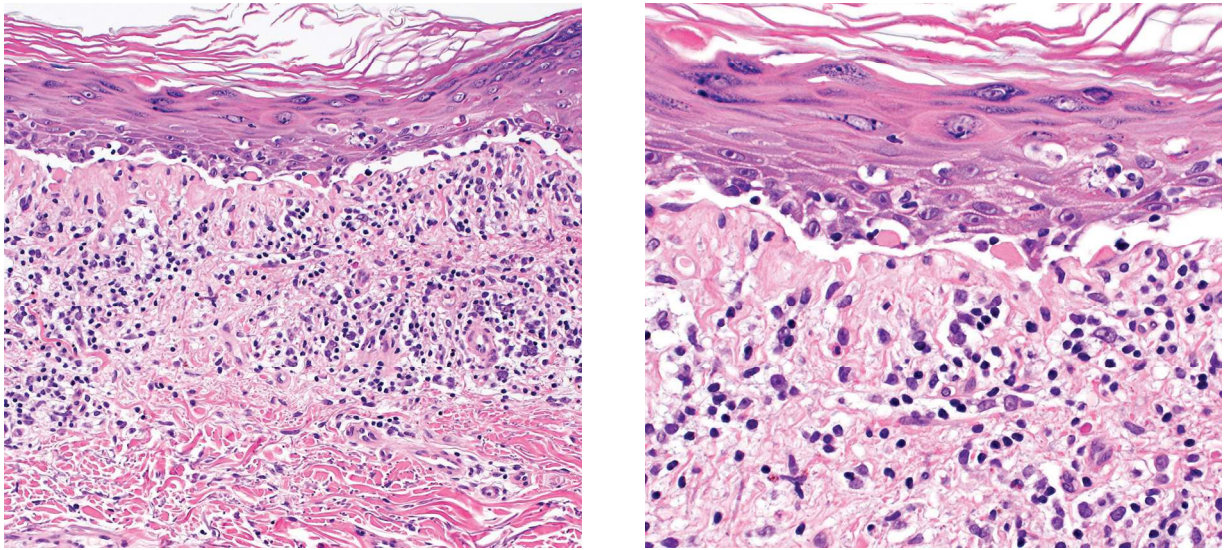


Figure 1-23

LICHENOID KERATOSIS

Left: Marked interface change may lead to bulla formation with subepidermal tissue separation.

Right: Higher magnification of the subepidermal split is shown. Apoptotic keratinocytes are evidence of the interface tissue reaction.

Differential Diagnosis. Separation from regressing or regressed melanocytic lesions is most important. Immunohistochemical staining for SOX10 and melan A as well as examination of deeper levels are helpful in identifying a residual melanocytic lesion. Absence of melanocytes in the context of prominent dermal melanophages may favor a completely regressed melanocytic lesion (fig. 1-24) (12). Basilar squamous dysplasia is seen in lichenoid actinic keratoses. Although differentiation from lichen planus may be difficult histologically, the clinical presentation of a single lesion on the trunk is suggestive of lichenoid keratosis.

Treatment and Prognosis. No specific treatment is required. Lichenoid keratoses are benign.

Warty Dyskeratoma

Definition. *Warty dyskeratoma* is a benign solitary squamous proliferation characterized by endophytic growth, acantholysis, and dyskeratosis.

Clinical Features. The tumors present as umbilicated papules or small nodules with a predilection for the head and neck of adults (13).

Microscopic Findings. The tumors arise from the epidermis as invaginated exophytic and endophytic squamoproliferations with well-cir-

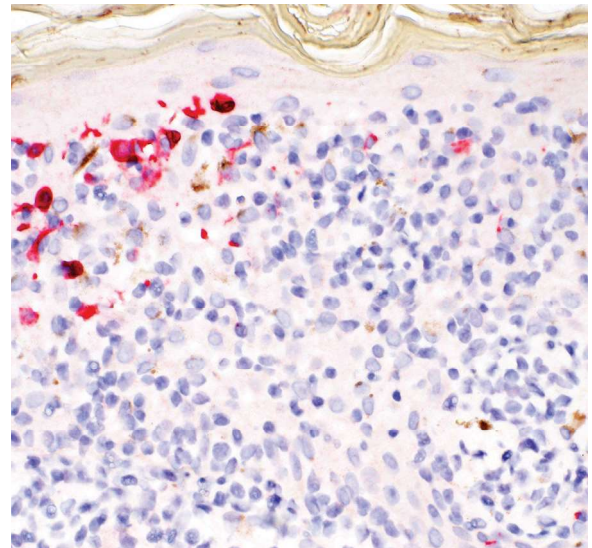


Figure 1-24

LICHENOID KERATOSIS

Melan A highlights residual junctional melanocytes in contrast to regressed melanocytic lesions.

cumscribed, cup-shaped outlines (fig. 1-25). The squamous epithelium is acanthotic and shows acantholysis with suprabasilar clefting and dyskeratosis (fig. 1-26). Corps ronds, corps

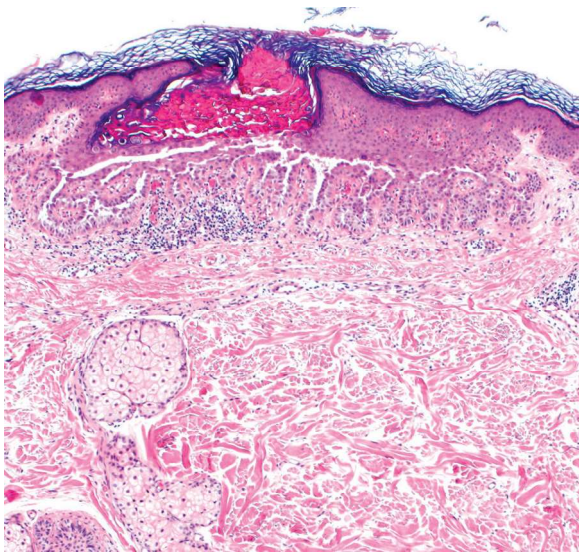


Figure 1-25

WARTY DYSKERATOMA

This endophytic well-circumscribed squamoproliferative lesion shows prominent suprabasilar clefting and a keratinaceous plug.

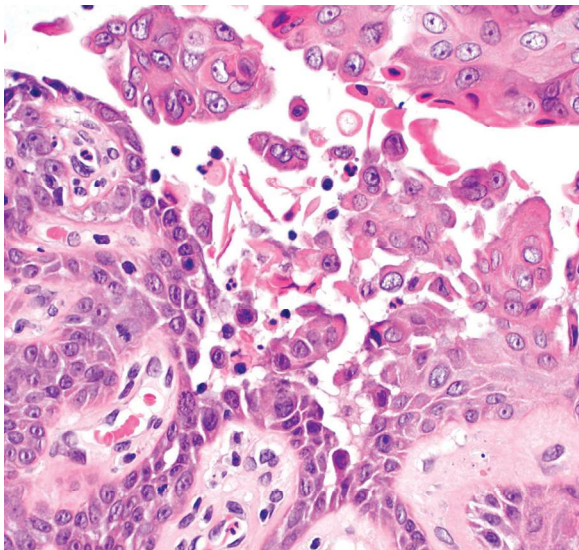


Figure 1-26

WARTY DYSKERATOMA

In addition to a suprabasilar split, there are several acantholytic and dyskeratotic cells.

grains, and parakeratotic plugging are also seen (fig. 1-27). A connection with a pilosebaceous unit is frequently present.

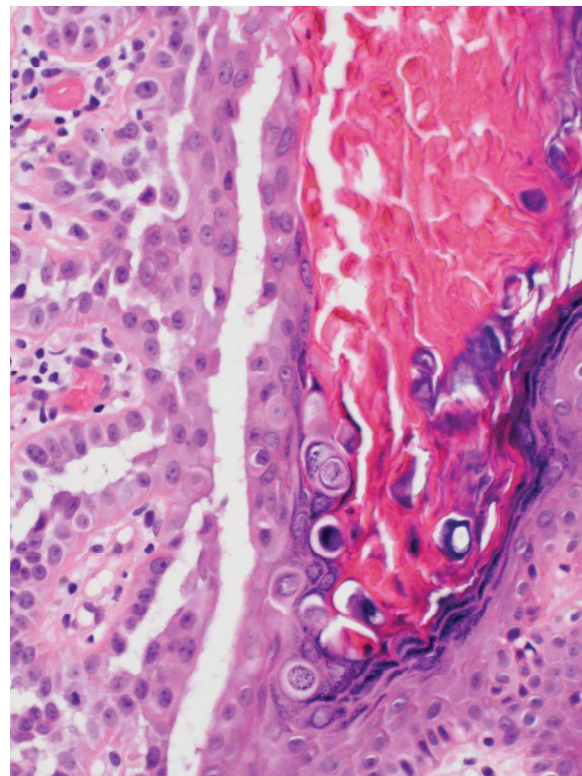


Figure 1-27

WARTY DYSKERATOMA

A keratotic column and "corps ronds" are present.

Differential Diagnosis. In contrast to the lesions of Darier or Grover disease, warty dyskeratomas are solitary.

Treatment and Prognosis. No specific treatment is required. Warty dyskeratomas are benign.

Actinic Keratosis

Definition. *Actinic keratoses* are UV-related intraepidermal squamoproliferative lesions characterized by squamous dysplasia. They may progress to squamous cell carcinoma or spontaneously regress.

Clinical Features. Actinic keratoses most commonly affect sun-exposed sites of fair-skinned individuals; there is an increasing incidence with age and a male predominance. They are seen in 37.5 percent of whites over the age of 50 years (14–16). They are frequently multiple and confluent, presenting as scaly, erythematous plaques measuring few millimeters to a centimeter on a background of chronically sun-damaged skin. The scalp, face, ear, lips, neck, forearms, and

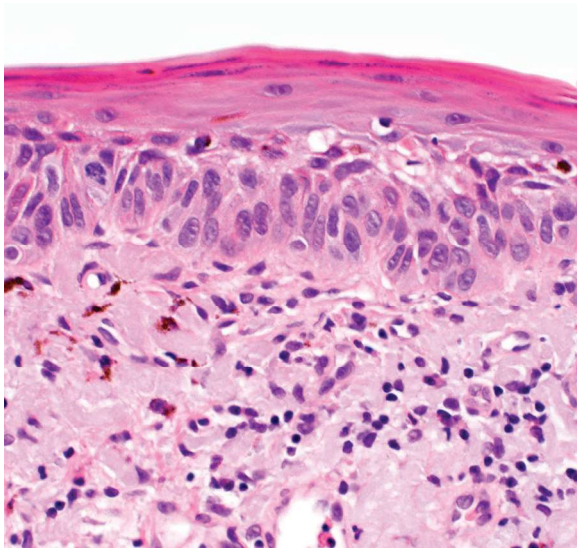


Figure 1-28

ACTINIC KERATOSIS

Squamous dysplasia involves the lower aspects of the epidermis. There is overlying parakeratosis, and a chronic inflammatory infiltrate is present within the sun-damaged dermis.

hands are particularly affected. Similar lesions are also seen after psoralen and ultraviolet A (PUVA) treatment (*PUVA keratoses*) and exposure to arsenic (*arsenical keratoses*). Arsenical keratoses show a predilection for hands and feet and occur decades after the arsenic exposure.

Microscopic Findings. Actinic keratoses are characterized by squamous dysplasia involving the basal to mid-epidermal layers (fig. 1-28). The keratinocytes contain large and irregular, hyperchromatic to vesicular nuclei with prominent and often multiple nucleoli. Mitotic figures are common (fig. 1-29). There is overlying parakeratosis, with absence of a granular layer, but, in contrast to squamous cell carcinoma in situ, no full-thickness squamous dysplasia is seen (fig. 1-30). The acrosyringeal structures and hair follicles are spared.

There is a background of solar elastosis and superficial dermal chronic inflammation. The dermal inflammation may be band-like, resulting in vacuolar degeneration of the dysplastic epidermis, suggestive of active regression (*lichenoid actinic keratosis*) (fig. 1-31). *Hypertrophic actinic keratoses* are characterized by epidermal hyperplasia and marked overlying hyperpar-

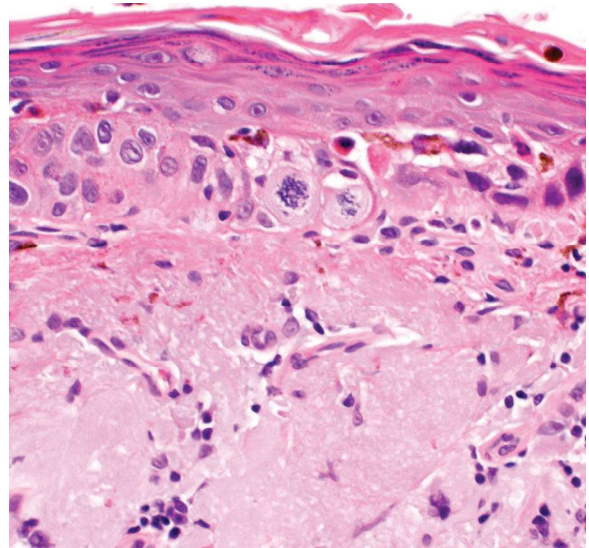


Figure 1-29

ACTINIC KERATOSIS

The dysplastic keratinocytes display irregular and enlarged nuclei with frequent mitotic figures.

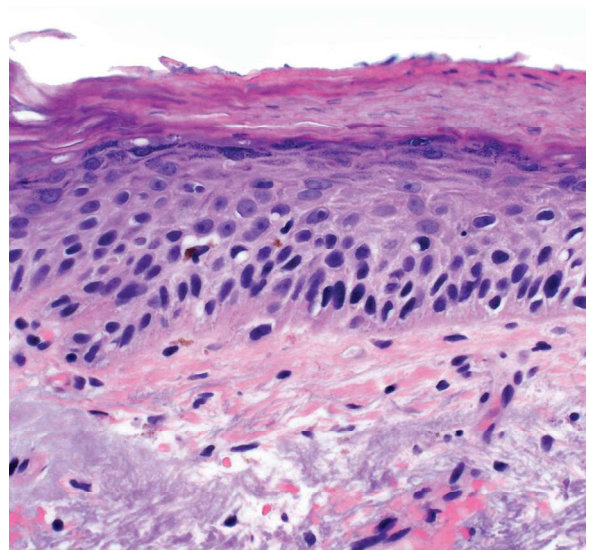


Figure 1-30

ACTINIC KERATOSIS

The absence of full-thickness dysplasia distinguishes actinic keratosis from squamous cell carcinoma in situ.

akeratosis (fig. 1-32). Atypical epithelial nests budding from the epidermis and extending into superficial dermis are observed in the *proliferative variant* (fig. 1-33). The *atrophic variant* shows pronounced epidermal atrophy, while

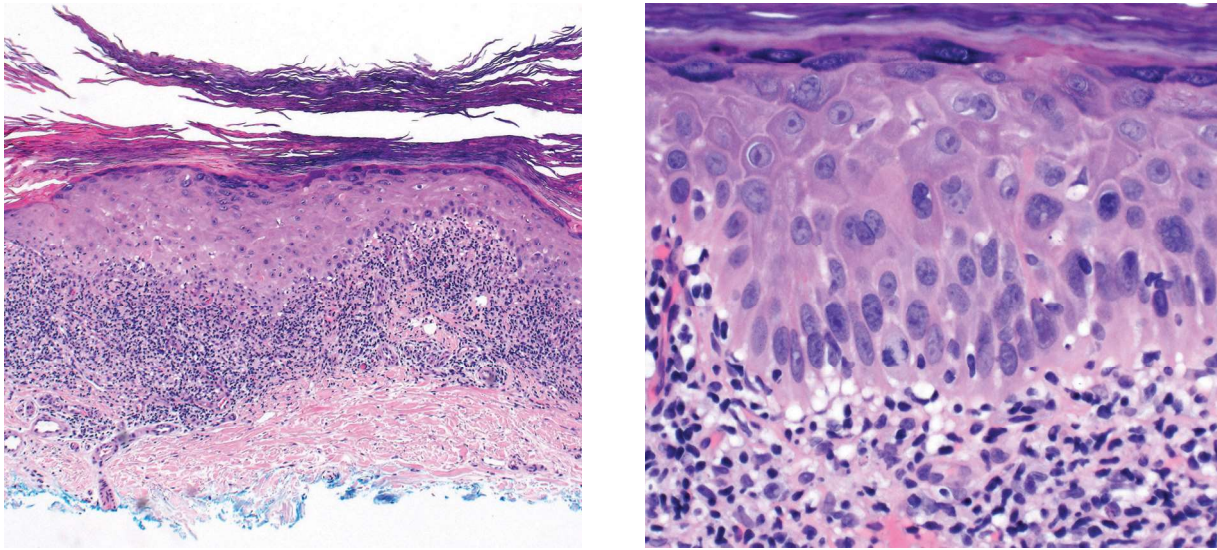


Figure 1-31

ACTINIC KERATOSIS

Left: An associated dense band-like chronic inflammatory infiltrate is characteristic of lichenoid actinic keratosis.

Right: Lichenoid actinic keratosis is characterized by squamous dysplasia and vacuolar interface change at the dermal-epidermal junction.

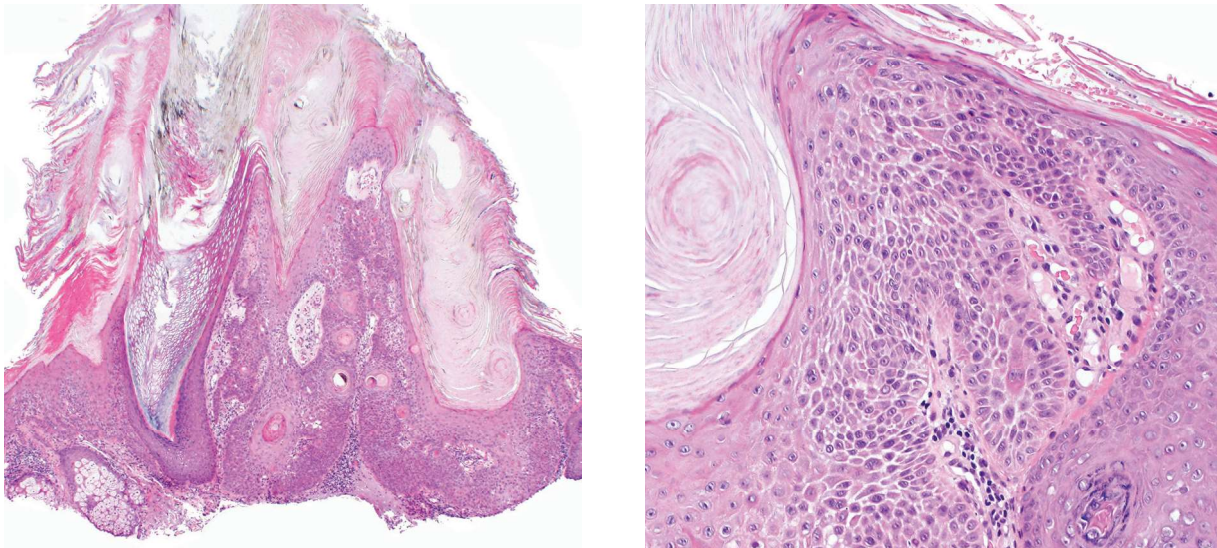


Figure 1-32

ACTINIC KERATOSIS

Left: Epidermal hyperplasia and overlying hyperparakeratosis are typical of hypertrophic actinic keratosis.

Right: The squamous dysplasia does not involve the full thickness of the epidermis.

suprabasilar acantholysis and dyskeratosis are features of the *acantholytic variant* (fig. 1-34). *Pigmented actinic keratoses* contain increased

melanin pigment in the dysplastic keratinocytes of the basal cell layer; overlying parakeratosis is often absent in this variant (fig. 1-35).

Actinic keratoses may arise in a background of other keratoses, such as solar and seborrheic keratoses. They may be associated with in situ or invasive squamous cell carcinoma.

Differential Diagnosis. The diagnosis is usually straightforward, and the presence of squamous dysplasia allows separation from solar, lichenoid, and seborrheic keratoses. Squamous cell carcinoma shows full-thickness squamous dysplasia. Proliferative actinic keratoses may be mistaken for superficially invasive squamous cell carcinoma, especially on tangential sections and superficial biopsies. Pigmented actinic keratosis may closely resemble lentigo maligna histologically. SOX10 or melan A immunohistochemistry is helpful in this setting. While there may be background lentiginous melanocytic hyperplasia in pigmented actinic keratosis, there is no confluent growth or cytologic atypia of junctional melanocytes (fig. 1-36).

Treatment and Prognosis. Actinic keratoses may be followed clinically or treated by cryotherapy, surgery, topical 5-fluoruracil or imiquimod, or photodynamic therapy depending on the extent of the disease. Actinic keratoses are benign. They may spontaneously regress but progression to squamous cell carcinoma is also possible (15–17). The precise incidence of progression to squamous cell carcinoma is unknown.

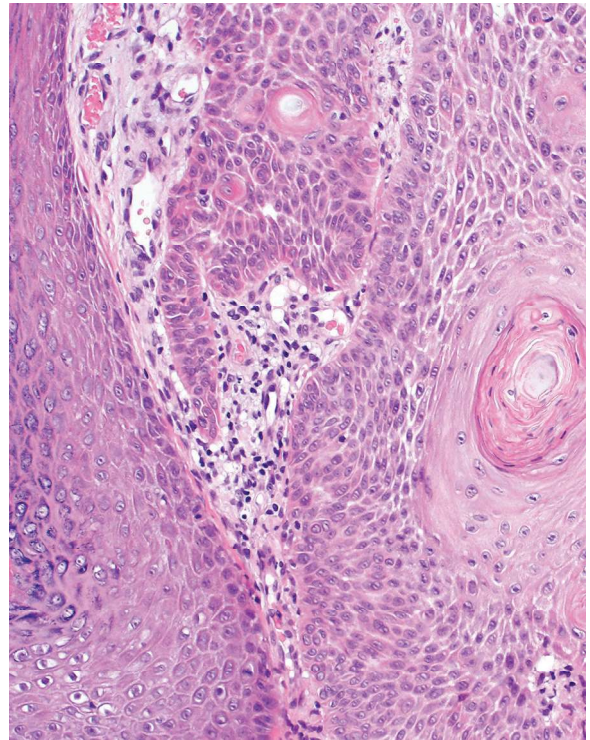


Figure 1-33

ACTINIC KERATOSIS

Dysplastic epithelial buds extend into the underlying dermis in this proliferative actinic keratosis.

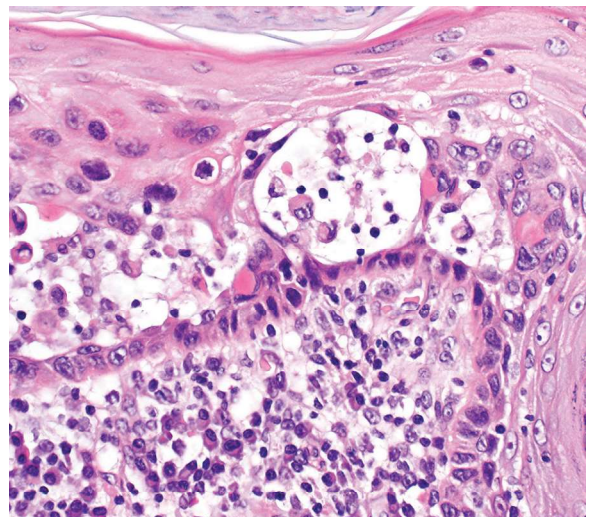
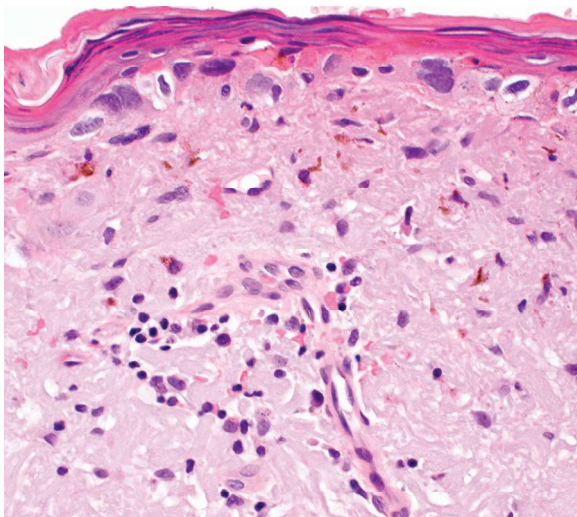


Figure 1-34

ACTINIC KERATOSIS

Left: Atrophic actinic keratosis shows marked epidermal thinning and squamous dysplasia.

Right: Acantholysis with suprabasilar clefting of dysplastic keratinocytes is seen in this acantholytic actinic keratosis.

Figure 1-35

PIGMENTED ACTINIC KERATOSIS

Melanin pigment is present in the cytoplasm of dysplastic basal layer keratinocytes. Parakeratosis may be absent in this variant.

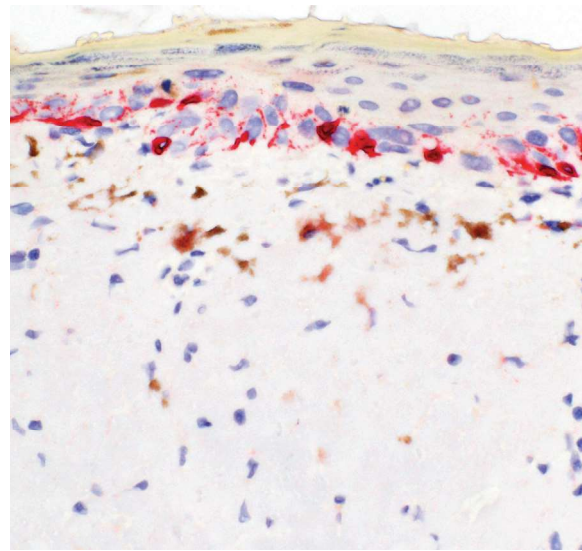
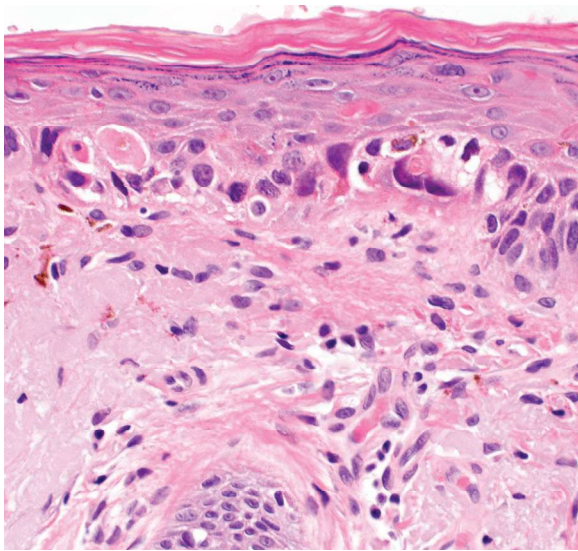
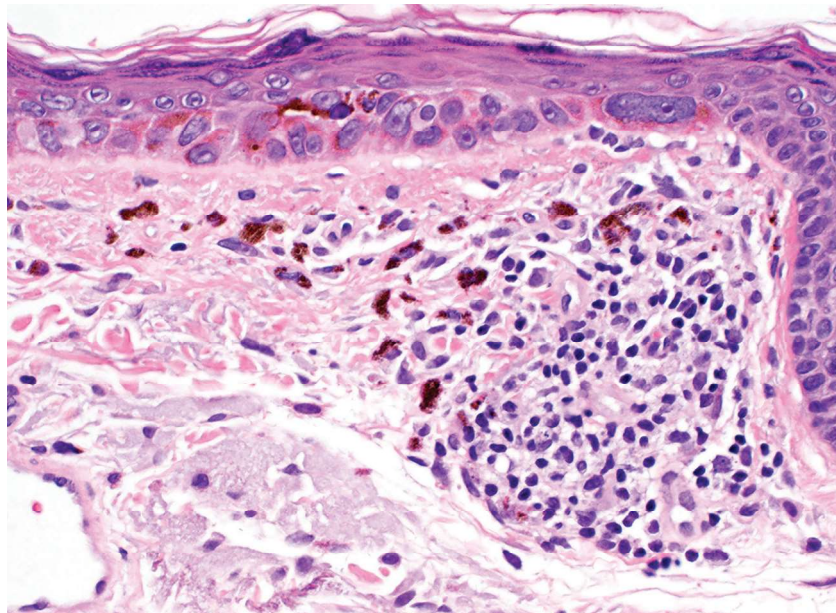


Figure 1-36

PIGMENTED ACTINIC KERATOSIS

Left: Pigmented actinic keratoses histologically may closely resemble lentigo maligna.

Right: Melan A immunohistochemistry of this pigmented actinic keratosis demonstrates hyperplasia of single melanocytes but there is no contiguous growth of melanocytes.

Squamous Cell Carcinoma in Situ

Definition. *Squamous cell carcinoma in situ* is an intraepidermal neoplasm characterized by dysplastic squamous cells involving the full thickness of the epidermis. The term *Bowen disease* is now used interchangeably, although it

originally only referred to full-thickness epidermal squamous dysplasia on sun-protected skin.

Clinical Features. Most tumors are seen on sun-exposed skin of middle-aged to elderly whites (18). They present as solitary or multiple, slowly enlarging, scaly, erythematous plaques with a predilection for the head and neck,

hands, and lower extremities. The periungual and subungual skin and genital and perineal areas may also be affected. The tumors may also appear pigmented or verrucous (19).

Squamous cell carcinoma in situ is closely linked to chronic UV damage and immunosuppression. Immunocompromised patients, especially in the setting of organ transplantation, are at a high risk for developing multiple tumors, often at a younger age. Arsenic exposure is a further risk factor. An association with high-risk human papillomavirus (HPV) infection is established, particularly in genital and nail tumors.

Microscopic Findings. Squamous cell carcinoma in situ is characterized by full-thickness epidermal squamous dysplasia with loss of polarity and absent maturation of the tumor cells (fig. 1-37). There may be involvement of skin adnexal structures, but no dermal invasion is seen. The epidermis is acanthotic, with a frequently absent granular cell layer and overlying and variably prominent hyperparakeratosis (fig. 1-38, left). The individual squamous cells show marked nuclear pleomorphism, with increased and atypical mitotic activity (fig. 1-38, right).

The *pagetoid variant* is characterized by a nested arrangement of tumor cells within the epidermis with areas of pagetoid scatter

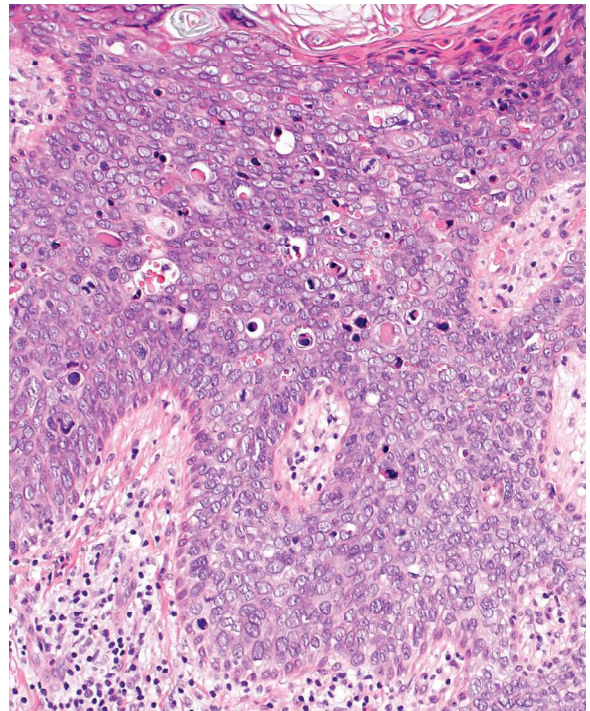


Figure 1-37

SQUAMOUS CELL CARCINOMA IN SITU

The tumor is characterized by full-thickness intra-epidermal dysplasia with loss of polarity of the tumor cells and frequent mitotic activity.

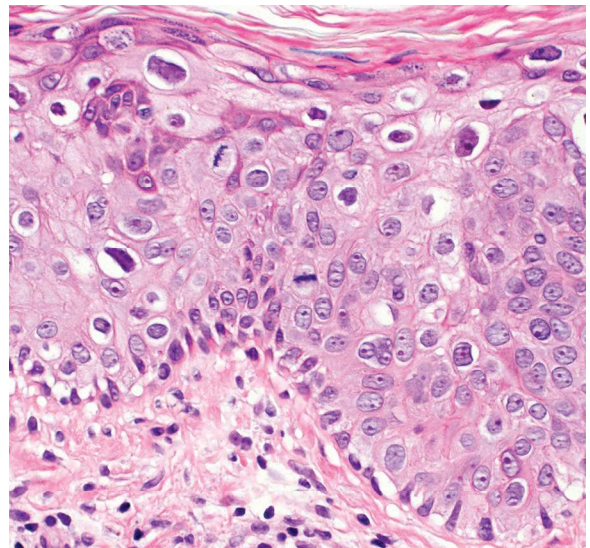
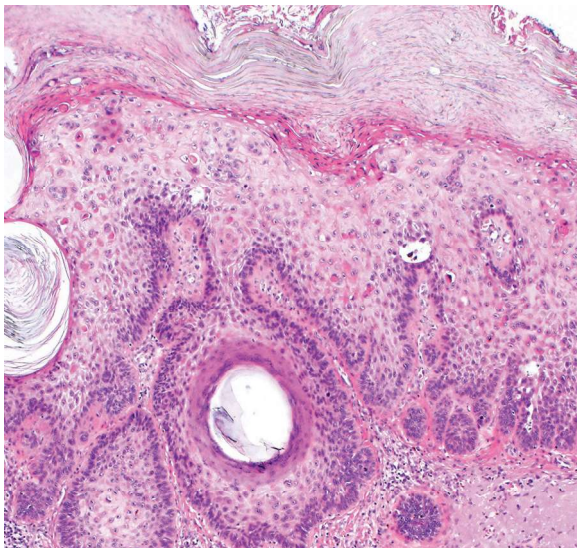


Figure 1-38

SQUAMOUS CELL CARCINOMA IN SITU

Left: The epidermis is acanthotic and there is overlying hyperkeratosis.

Right: Higher-magnification image shows the nuclear pleomorphism and mitotic activity of dysplastic keratinocytes.

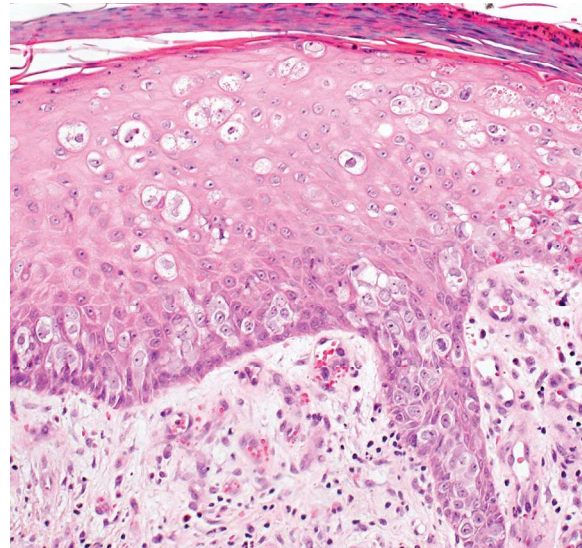
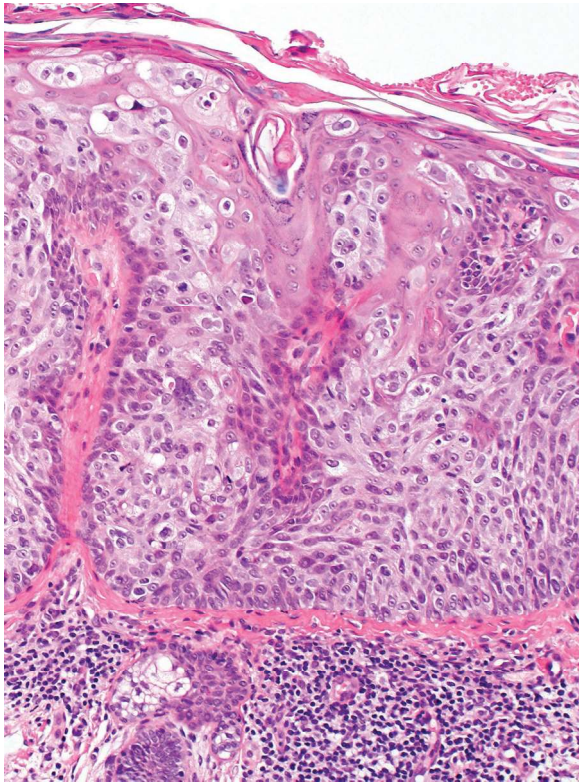


Figure 1-39

SQUAMOUS CELL CARCINOMA IN SITU

Left: The tumor cells may be scattered across the epidermis in nests or singly, giving rise to a pagetoid growth.

Above: Pagetoid scatter of single tumor cells within the epidermis.

of single tumor cells (fig. 1-39). The tumors may also show varying degrees of acantholysis and basaloid, verrucous, and atrophic growth patterns (fig. 1-40). In addition, there may be prominent clear cell change due to cytoplasmic glycogen deposition (*clear cell variant*) (fig. 1-41). Viral cytopathic change and koilocytosis may be seen in tumors associated with HPV infection (fig. 1-42).

Differential Diagnosis. The pagetoid variant closely resembles melanoma in situ or extramammary Paget disease. In these instances, immunohistochemistry for S-100 protein and melan A or CEA, respectively, may be necessary for reliable separation. Distinction from clonal and irritated seborrheic keratosis is notoriously difficult, especially on superficial samples.

Treatment and Prognosis. Topical and photodynamic treatments as well as surgery are therapeutic options. In the absence of invasive disease, the behavior is indolent following appropriate treatment. A small subset of tumors may progress to invasive squamous cell carcinoma.

Squamous Cell Carcinoma

Definition. *Squamous cell carcinoma* is a malignant invasive tumor of epidermal keratinocytes, morphologically ranging from well- to poorly differentiated. In addition to conventional squamous cell carcinoma, a number of morphologic variants are recognized, which are discussed separately.

Clinical Features. Squamous cell carcinoma is the second most common skin cancer after basal cell carcinoma (20,21). It shows a strong predilection for sun-damaged skin of fair-skinned elderly adults and a male predominance (20,21). The tumors show a preference for the head and neck area, particularly the scalp, face, lip, and ear. The extremities are also commonly involved. Tumors associated with HPV infection or immunosuppression are also found on sun-protected sites, with involvement of genital areas and the distal extremities. Chronic scarring, previous radiation, and environmental exposure to a number of substances including arsenic, tar, nitrosamines, and alkylating agents predisposes to the development of squamous

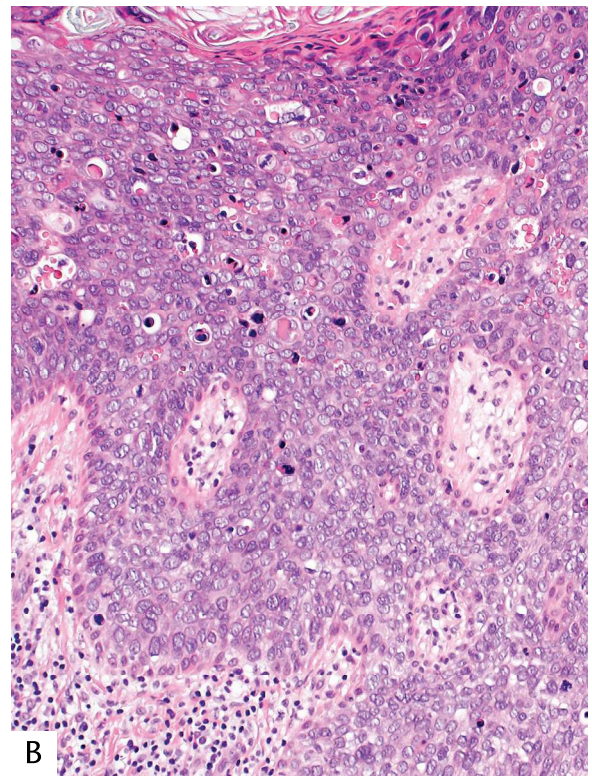
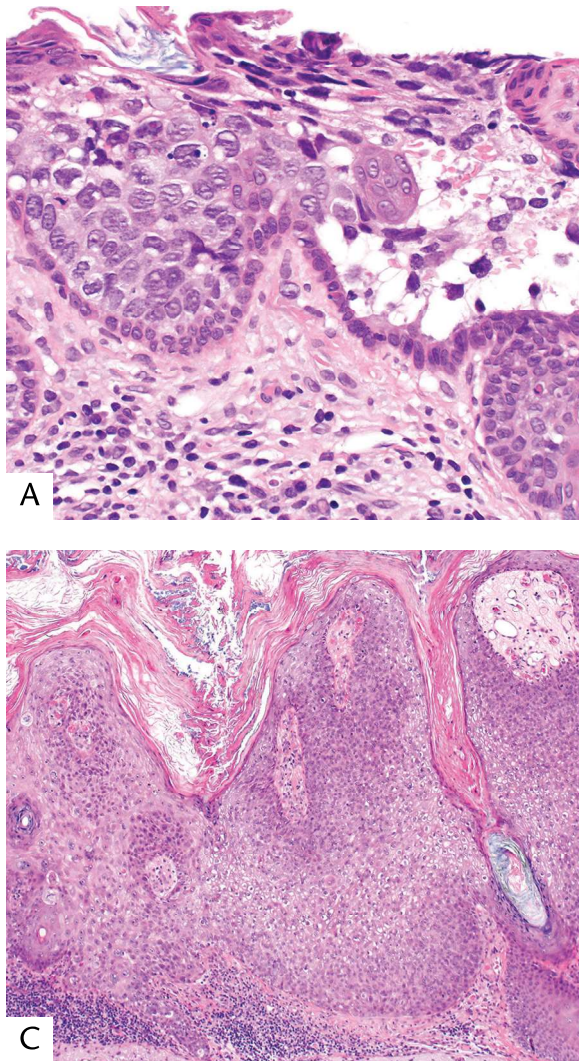


Figure 1-40

SQUAMOUS CELL CARCINOMA IN SITU

A: Acantholysis and a suprabasilar cleft are seen in some tumors.

B: Prominent basaloid differentiation is shown here.

C: Marked epidermal hyperplasia with a papillomatous architecture may be a prominent finding.

cell carcinoma (20). The tumors may present in childhood and adolescence in patients with xeroderma pigmentosum. Cutaneous squamous cell carcinoma presents as hyperkeratotic nodules and plaques, which may ulcerate.

Microscopic Findings. The tumors have a multifocal connection with the overlying epidermis, which may be ulcerated (fig. 1-43). A background of actinic keratosis or squamous cell carcinoma in situ is frequently present (fig. 1-44). The tumors are asymmetric and invade dermis and underlying subcutaneous tissues (fig. 1-45). They may be relatively circumscribed, with pushing borders, or show a diffusely infiltrative growth pattern composed of cords, strands, and islands (fig. 1-46). Perineural infiltration, lymphovascular invasion, and tumor necrosis may be present (fig. 1-47).

Well-differentiated tumors show recognizable areas of squamous differentiation, with intracellular bridges, areas of keratinization, and limited nuclear pleomorphism (fig. 1-48). Moderately differentiated tumors are characterized by more pronounced cytologic atypia; overt squamous differentiation is less prominent (fig. 1-49). Poorly differentiated tumors are largely devoid of obvious squamous differentiation (fig. 1-50). Focal areas of keratinization are helpful diagnostic clues, but immunohistochemistry is often necessary to confirm the diagnosis (fig. 1-51).

A subset of poorly differentiated squamous cell carcinomas show basaloid features (*basaloid squamous cell carcinoma*). They are composed of lobules and strands composed of large pleomorphic epithelial cells with a basaloid appearance

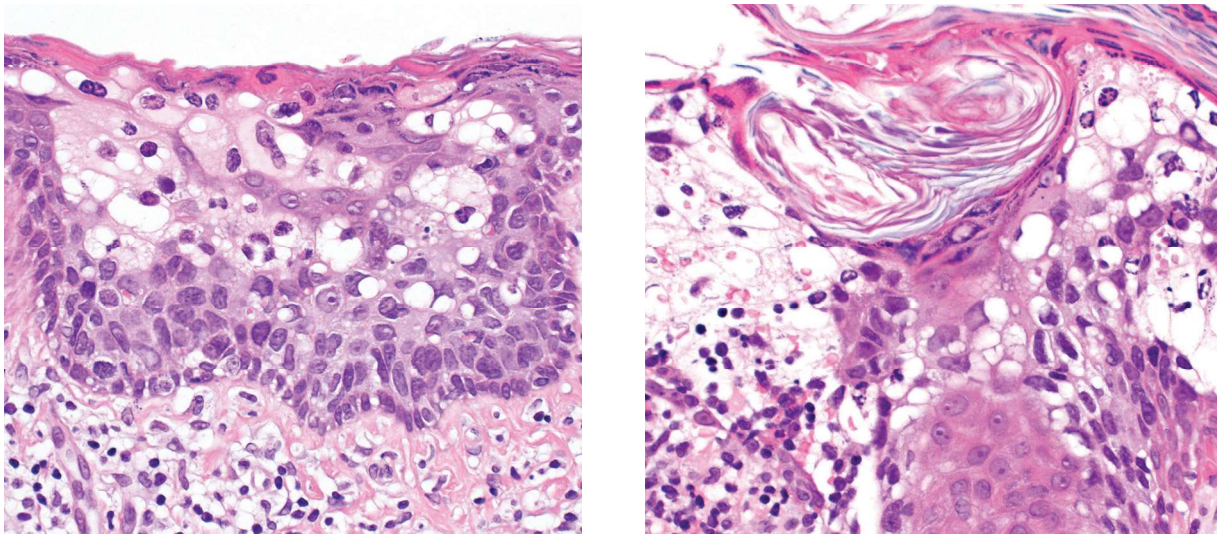


Figure 1-41

SQUAMOUS CELL CARCINOMA IN SITU

Left: Focal clear cell change is present.

Right: Tumors with marked clear cell change may closely resemble intraepidermal sebaceous carcinoma.

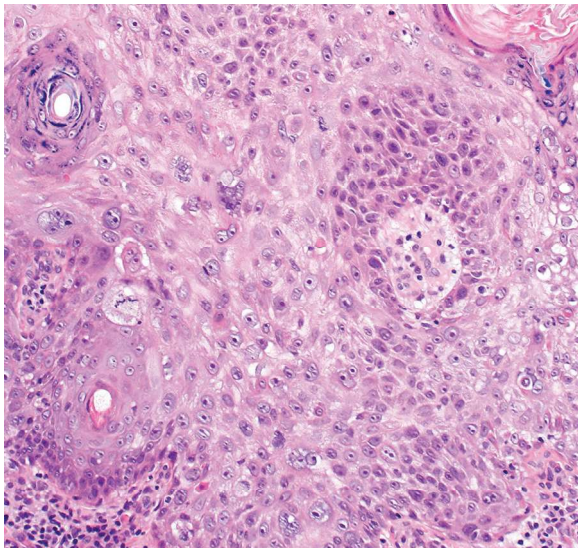


Figure 1-42

SQUAMOUS CELL CARCINOMA IN SITU

Viral cytopathic change is present in the form of multinucleation and koilocytosis.

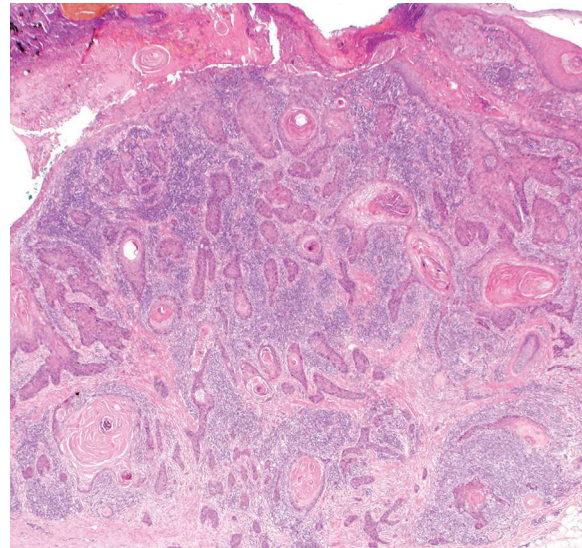


Figure 1-43

SQUAMOUS CELL CARCINOMA

This ulcerated tumor shows an epidermal connection and diffusely infiltrative growth within the dermis.

in a diffusely infiltrative growth pattern (fig. 1-52). Mitotic activity is brisk and tumor necrosis may be present. The presence of more conventional squamous cell carcinoma, at least focally, is a clue to the diagnosis (fig. 1-53).

Immunohistochemical Findings. Immunohistochemistry is particularly useful for poorly differentiated tumors, which show expression of high molecular weight cytokeratins (CK5/6, MNF116), p63, p40, and EMA (fig. 1-54).

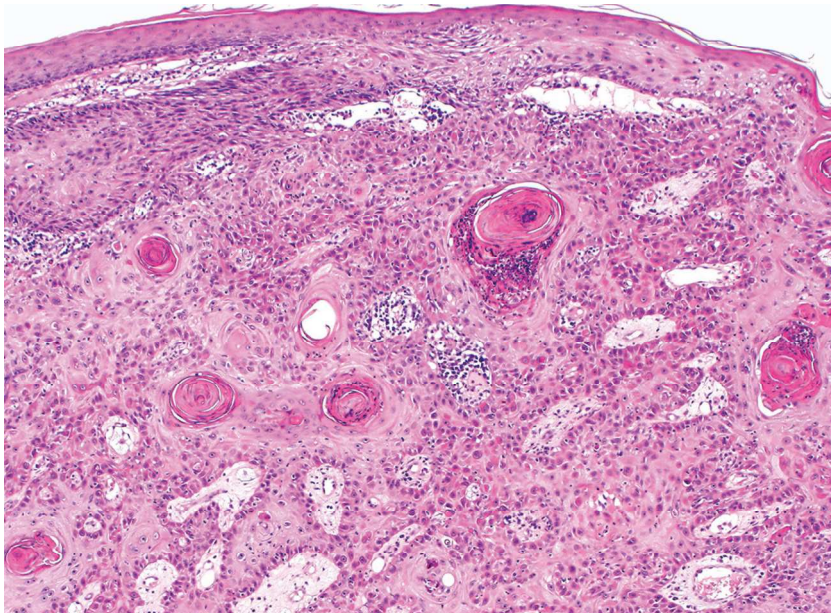


Figure 1-44

SQUAMOUS CELL CARCINOMA

The tumor arises multifocally from dysplastic overlying epidermis.

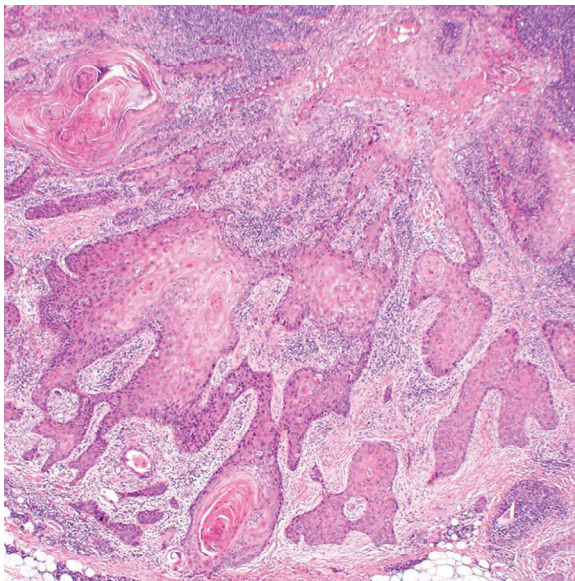
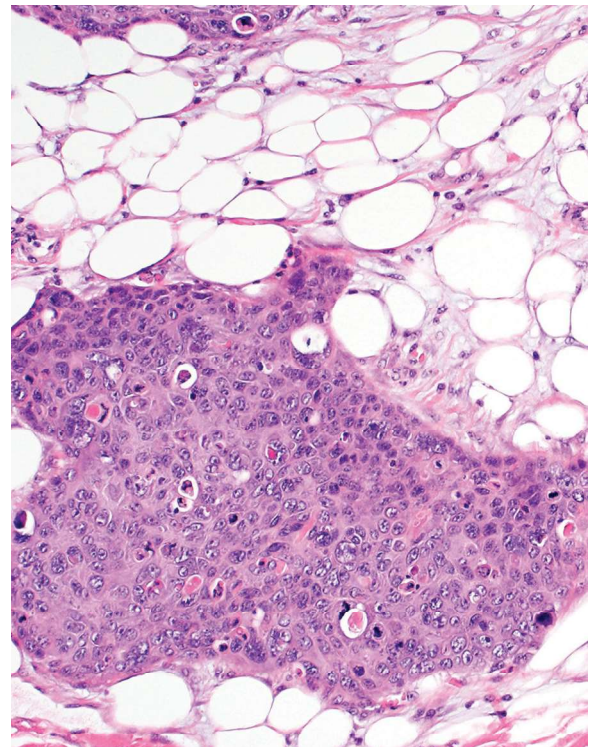


Figure 1-45

SQUAMOUS CELL CARCINOMA

Above: Invasion of the dermis and superficial subcutis.
Right: Invasion of subcutaneous adipose tissue.



Molecular Genetic Findings. Most cutaneous squamous cell carcinomas are closely linked to UV exposure, and mutations in the *TP53* gene are common (22). Other frequently mutated genes include *CDKN2A*, *KRAS*, *HRAS*, and *NOTCH 1* and *2* (20,23,24).

Differential Diagnosis. Well-differentiated squamous cell carcinoma may be difficult to distinguish from reactive epidermal hyperplasia, benign keratoses, and hypertrophic lichen planus, especially on superficial biopsies. Clinical correlation with consideration for repeat

Figure 1-46

SQUAMOUS CELL CARCINOMA

The invasive component has a diffusely infiltrative growth pattern.

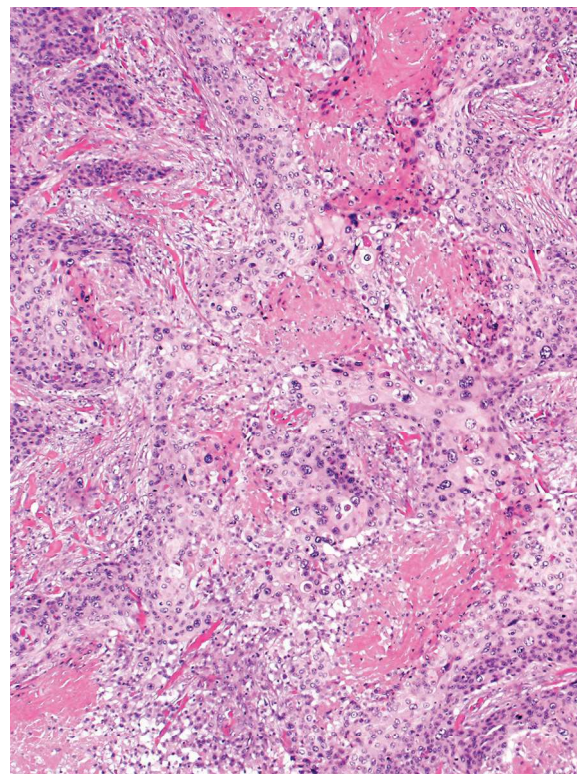
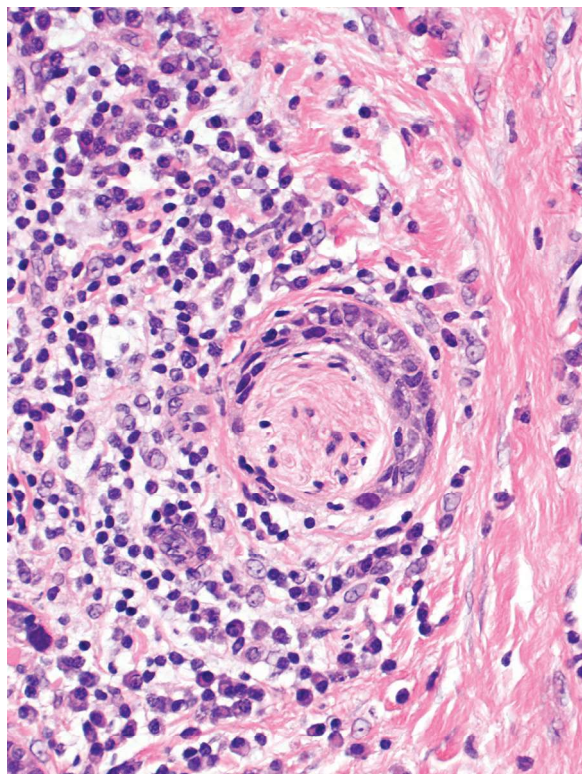
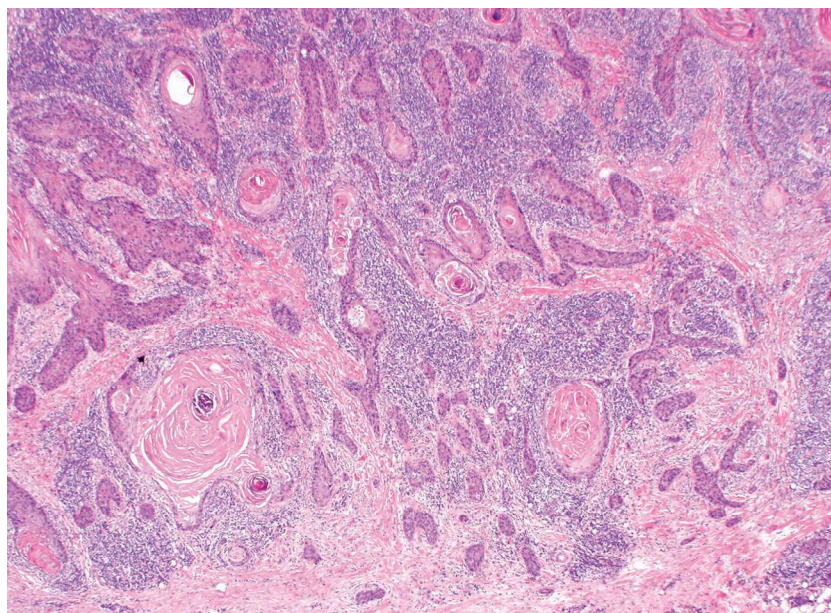


Figure 1-47

SQUAMOUS CELL CARCINOMA

Left: Perineural infiltration.

Right: Areas of geographic tumor necrosis.

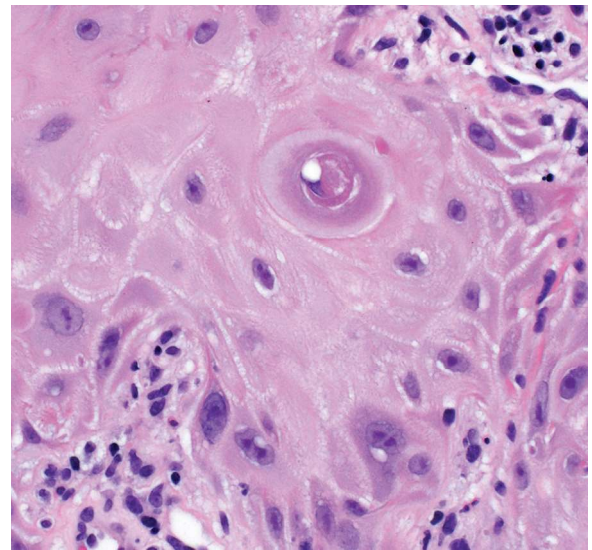
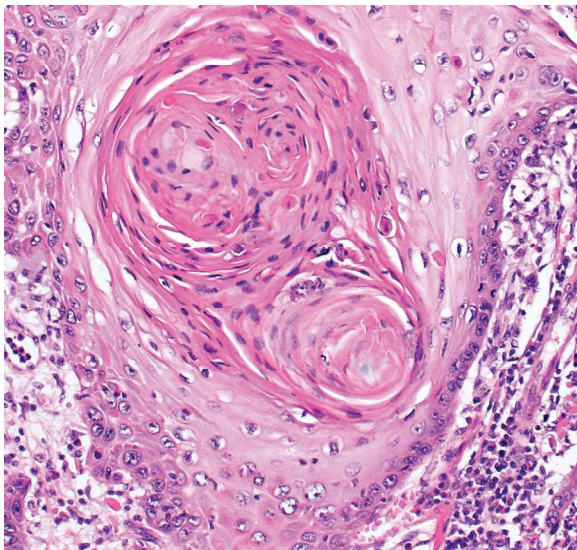


Figure 1-48

SQUAMOUS CELL CARCINOMA

Left: Well-differentiated tumors show overt squamous differentiation with keratinization.
Right: The neoplastic keratinocytes retain eosinophilic cytoplasm and intercellular bridges.

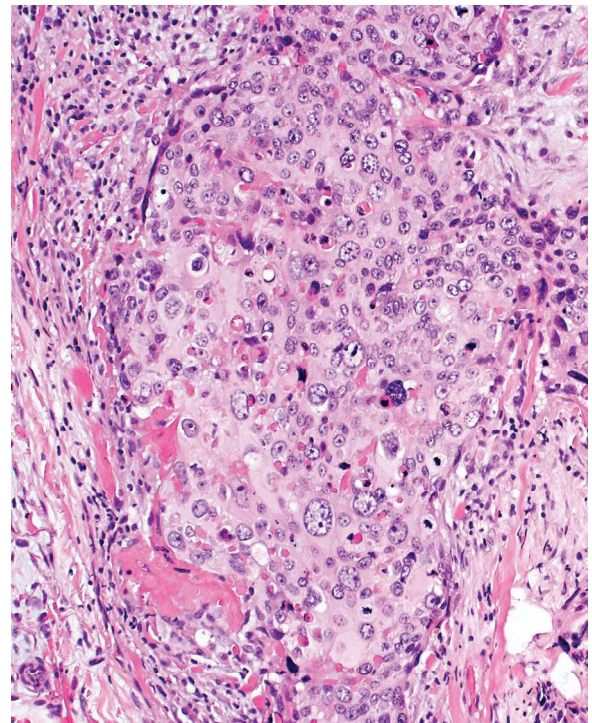
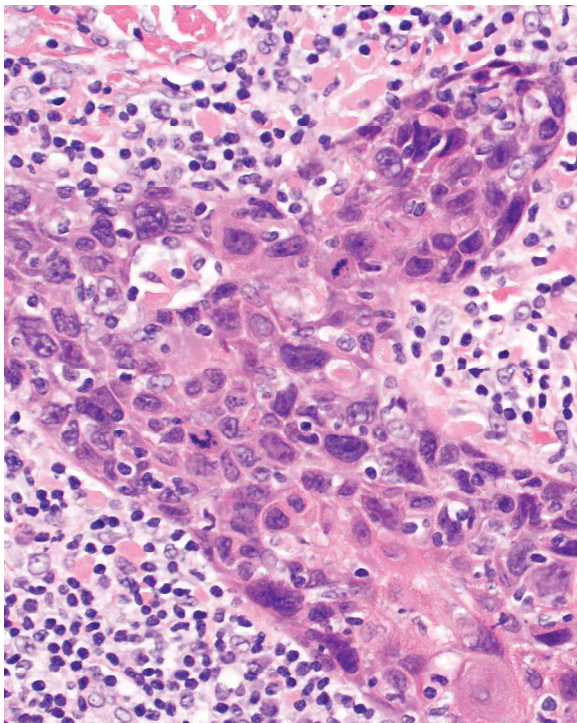


Figure 1-49

SQUAMOUS CELL CARCINOMA

Moderately differentiated tumors show pronounced cytologic atypia and nuclear pleomorphism, but areas of squamous differentiation are still evident.

Figure 1-50

SQUAMOUS CELL CARCINOMA

Poorly differentiated tumors may be difficult to classify since they show marked nuclear pleomorphism with loss of the overt features of squamous differentiation.

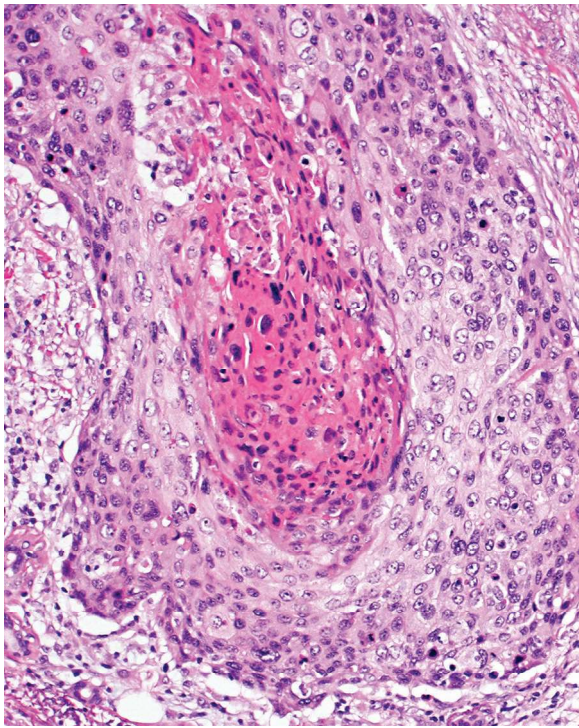


Figure 1-51

SQUAMOUS CELL CARCINOMA

Focal areas of keratinization help in the recognition of poorly differentiated tumors.

biopsy is necessary in these instances to exclude squamous cell carcinoma. Poorly differentiated tumors require immunohistochemical workup to allow separation from melanoma, atypical fibroxanthoma/pleomorphic dermal sarcoma, and angiosarcoma, which also arise on sun-damaged skin of the elderly. Basaloid squamous cell carcinoma can be separated from basal cell carcinoma by the presence of overt atypical squamous differentiation and the absence of peripheral palisades and cleft artifacts. BerEP4 is frequently expressed in at least parts of the tumor and is of little diagnostic use in this setting (25,26).

Treatment and Prognosis. Complete excision is the recommended treatment. Adjuvant radiation treatment may be helpful if surgical clearance cannot be achieved.

The tumors are associated with a risk for local recurrence and metastasis to lymph nodes, liver, lung, bone, and brain. Risk factors for aggressive behavior are tumor size greater than 2 cm, tumor thickness over 2 mm, invasion of anatomic level V, perineural or lymphovascular invasion, and presentation on the temple, ear, or lip (27–30). Squamous cell carcinoma developing on previously irradiated skin or in the setting

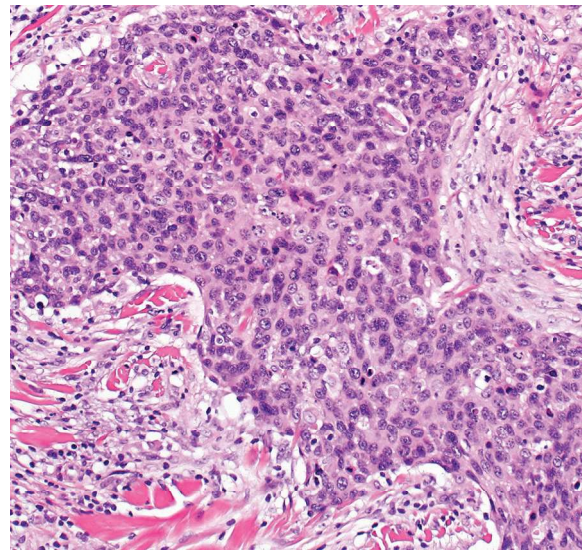
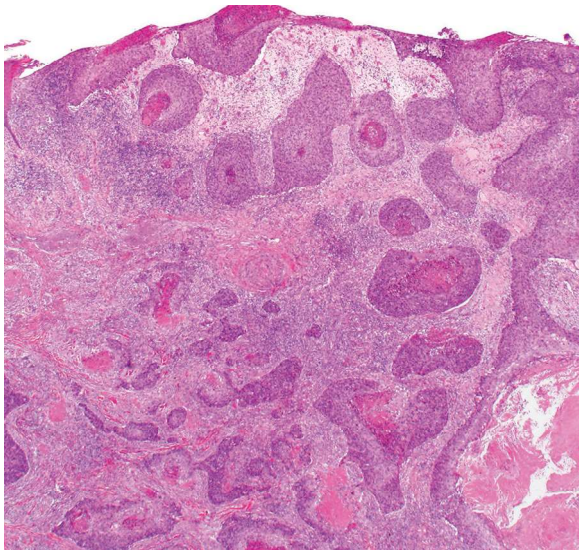


Figure 1-52

SQUAMOUS CELL CARCINOMA

Left: This basaloid variant is composed of basaloid nests, islands, and strands, and a diffusely infiltrative growth pattern. Right: Higher magnification demonstrates the basaloid appearance of the neoplastic cells.

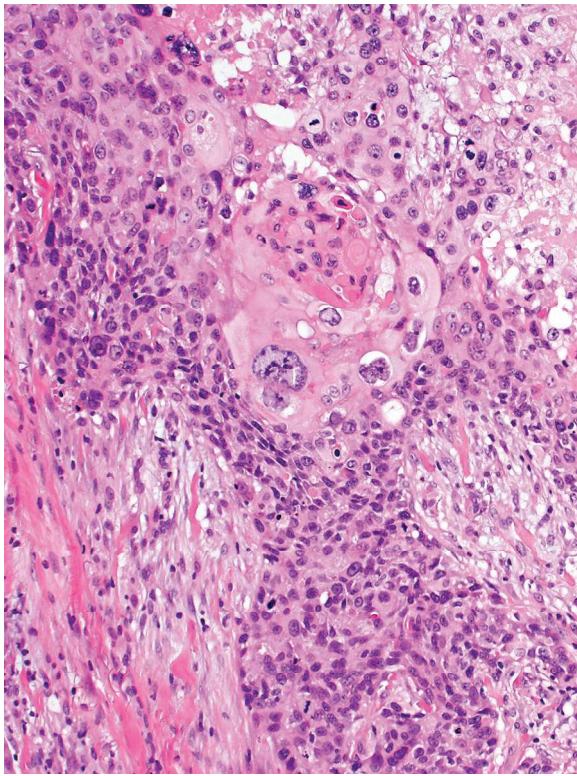


Figure 1-53

SQUAMOUS CELL CARCINOMA

The identification of better-differentiated areas is helpful in the diagnosis of basaloid tumors.

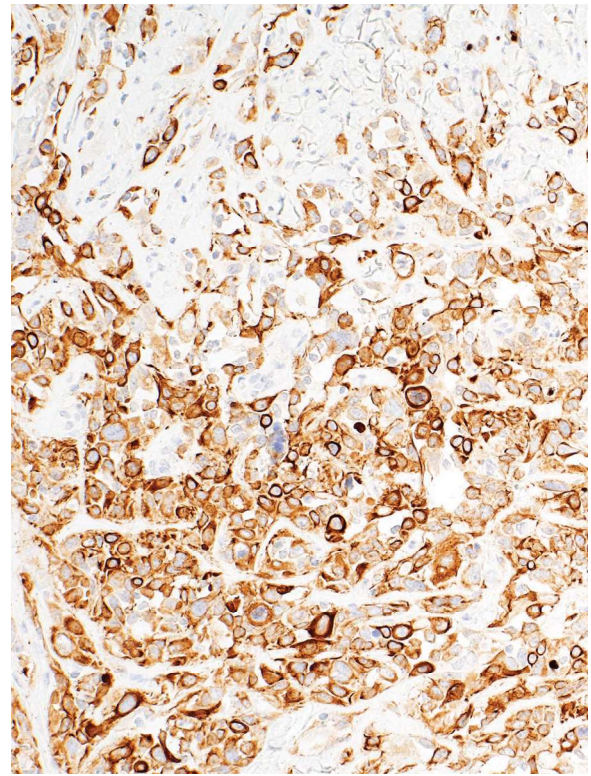


Figure 1-54

SQUAMOUS CELL CARCINOMA

Cytokeratin AE1/3 expression helps diagnose poorly differentiated squamous cell carcinoma.

of chronic scarring or immunosuppression is associated with more aggressive behavior (28).

Clear Cell Squamous Cell Carcinoma

Definition. *Clear cell squamous cell carcinoma* is squamous cell carcinoma showing abundant clear cell differentiation due to intracellular glycogen.

Clinical Features. The tumors show a clinical presentation similar to conventional squamous cell carcinoma. They occur most commonly on the sun-damaged skin of the head and neck of elderly men (31,32).

Microscopic Findings. Similar to conventional squamous cell carcinoma, these tumors are arranged in islands, cords, and strands within the dermis. They connect with the overlying epidermis and invade underlying tissues in a pushing or diffusely infiltrative growth pattern. The hallmark of the tumor is extensive cytoplasmic clear cell differentiation due to

intracytoplasmic glycogen. In areas, the nucleus may be compressed, reminiscent of signet ring cell change (fig. 1-55).

Immunohistochemical Findings. The staining pattern is identical to conventional squamous cell carcinoma. A special stain for periodic acid-Schiff (PAS) shows a diastase-sensitive reaction.

Differential Diagnosis. Due to the extensive clear cell change the tumors may be mistaken for trichilemmal carcinoma. A peripheral palisade and pilar keratinization favor trichilemmal carcinoma but reliable separation is not always possible. Sebaceous carcinoma shows a vacuolated cytoplasm with indentation of the nucleus. Lack of true duct differentiation excludes sweat duct carcinomas, absence of S-100 protein expression excludes balloon cell melanoma, and lack of CD31 and ERG staining argues against angiosarcoma with signet ring cell change. Clear cell atypical fibroxanthoma is cytokeratin negative.