

Chapter 6

Squamous Cell Carcinoma: Variants and Challenges

Michael B. Morgan

EPIDEMIOLOGY: Second most common skin cancer, rare in the dark-skinned races.

ETIOLOGY: Ultraviolet light, HPV infection.

PATHOGENESIS: p53 tumor suppressor gene mutation.

CLINICAL: Rapidly growing keratotic papule or shallow ulcer in sun-exposed site of elderly.

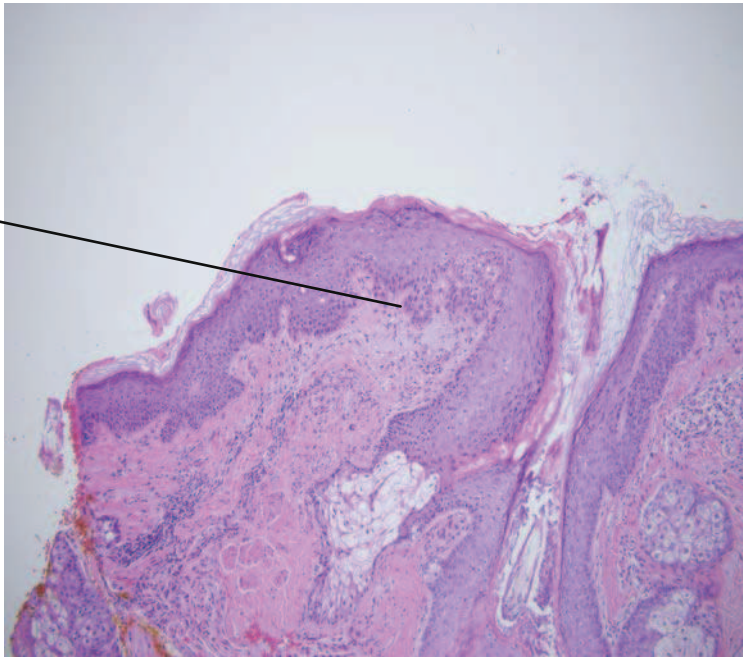
HISTOLOGY: In situ lesions with full thickness or pagetoid scatter of dysplastic keratinocytes, invasive infiltrating keratinizing neoplasm may be **pigmented**, **warty (verrucous)**, **acantholytic**, heavily inflamed (**lymphoepithelioma**) or **spindled**.

Squamous cell carcinoma (SCC) is the second most frequent form of skin cancer superseded by only basal cell carcinoma. Like basal cell carcinoma, SCC is predisposed for by excessive ultraviolet exposure, hence its association with advancing age and cumulative sun exposure, exposed anatomic sites and highest incidence in sunny geographic locales. The most important pathogenic mechanisms involve aberration of the p53 tumor suppressor gene via ultraviolet-induced mutation or HPV-encoded interdiction. The latter mechanism is thought to be the most important factor in the development of these malignancies in the setting of epidermodysplasia verruciformis and solid organ iatrogenic immunosuppression where multicentric tumor may present in a metachronous or synchronous fashion. Less common associations have been ascribed to chronic inflammatory or scarring conditions such as in the setting of burns, so called Marjolin's ulcer, osteomyelitic sinuses and lichen sclerosis et atrophicus, among others. The typical clinical presentation entails a rapidly growing keratotic papule or shallow ulcer on an exposed anatomic site in the elderly. These tumors may be broadly divided into intraepithelial malignancy and invasive tumors. The intraepithelial form synonymously referred to as Bowen's disease or squamous cell carcinoma-in-situ, may histologically present in the guise of transepidermal keratinocytic dysplasia or

as scattered dysplastic (pagetoid) keratinocytes found throughout all levels of the epithelium and extending into adjacent adnexal epithelium. These forms of the disease may exist in continuity with focal keratinocytic dysplasia confined to the basilar layer of the epithelium (actinic keratosis) or focal to full-thickness dysplasia without adnexal extension (bowenoid actinic keratosis). The relationship of these lesions to squamous cell carcinoma remains contentious, particularly in regard to their potential as precursors of SCC. Invasive squamous carcinoma can be histologically and prognostically stratified. Prognostic subcategorization can be accomplished on the basis of their degree of differentiation (well, moderate and poor) with increasing de-differentiation representative of a worse prognosis. Additional prognostic attributes that may be sought after include the depth of dermal invasion, the presence of vascular permeation or perineural extension. Deeper dermal extension, vascular permeation and perineural involvement have all been shown to portend a worse outcome. Histologic variants include a pigmented form associated with benign intra-tumoral melanocytes, an acantholytic form with dyshesive neoplastic keratinocytes, a spindled form which may be readily confused with melanoma or other spindled tumors, a lymphoepithelioma type with a rich endowment of lymphocytes, and a warty-like verrucous variant.

Precursor Lesion
Actinic Keratosis (AK)

Actinic
Keratosi



MEDIUM

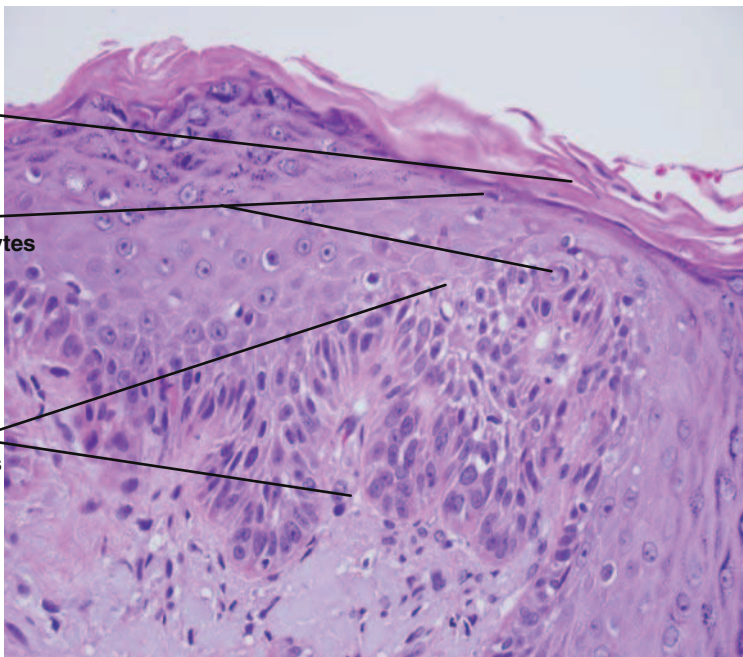
6-1

- Focal keratinocyte dysplasia confined to the basilar area of the epithelium

Parakeratosis

Normal
Keratinocytes

Dysplastic
Keratinocytes



HIGH

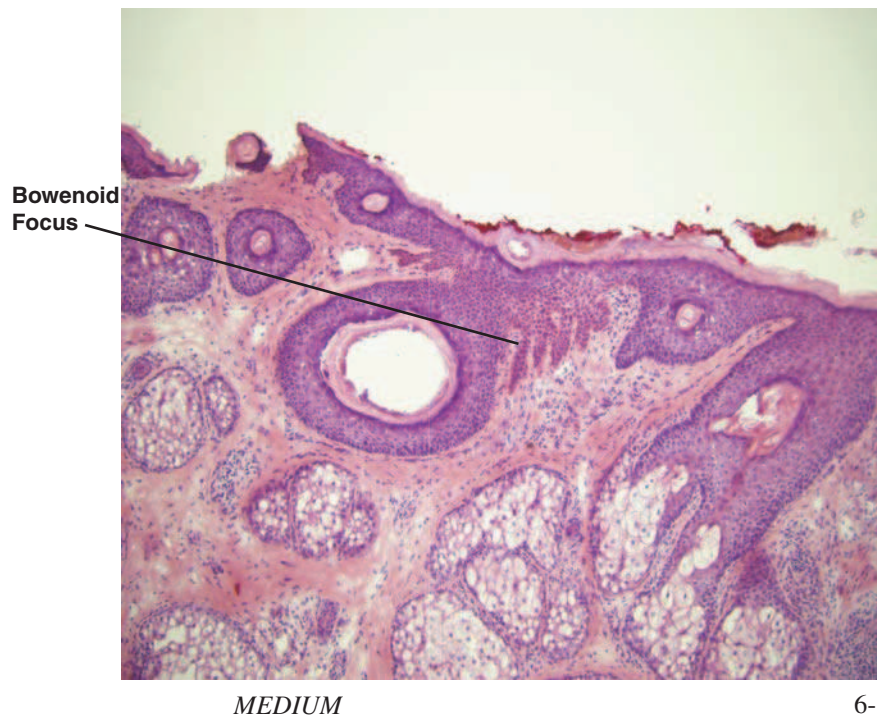
6-2

- Dysplasia defined by enlarged hyperchromatic keratinocyte nuclei

Note: Surface keratinocyte maturation

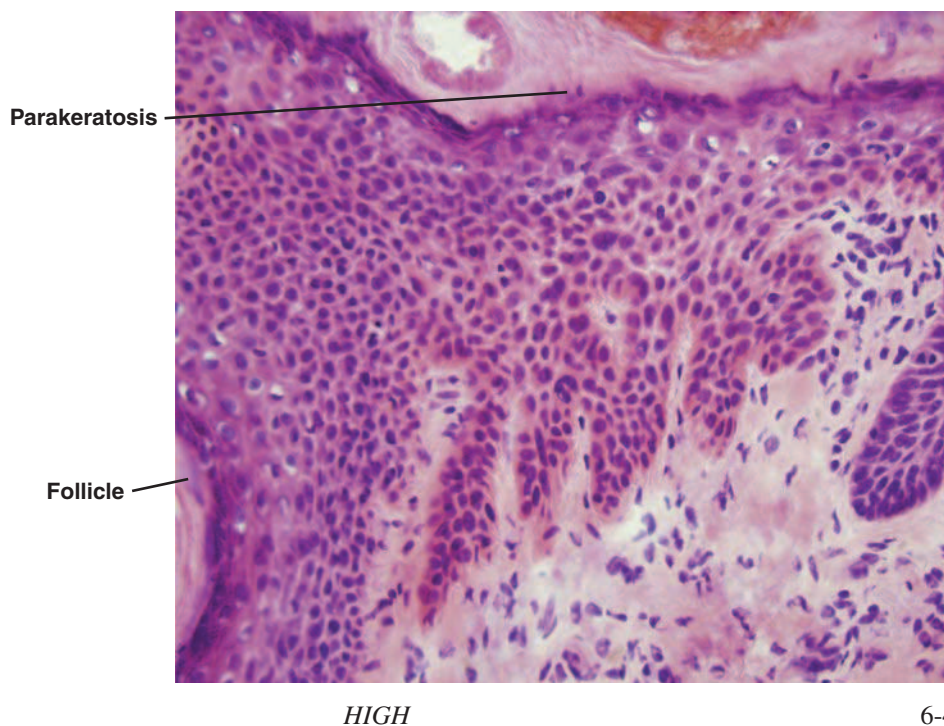
Note: Focal parakeratosis overlying dysplastic foci

Precursor Lesion Bowenoid Actinic Keratosis



- Focal full thickness dysplasia

Note: Eosinophilia of cytoplasm (Dyskeratosis)



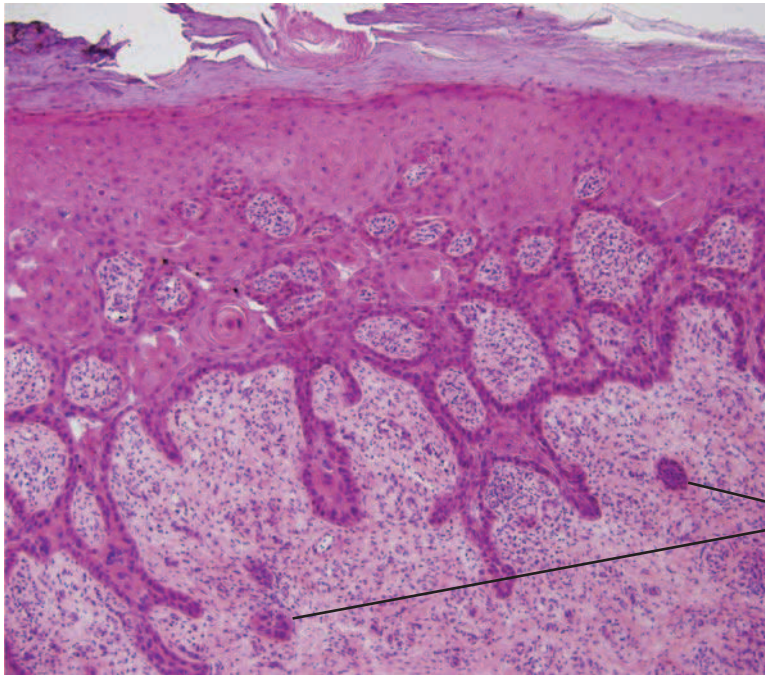
- Dysplastic keratinocytes defined by hyperchromatic enlarged nuclei
- No extension down adjacent follicle

Note: Parakeratosis

6-3

6-4

Squamous Cell Carcinoma In-Situ

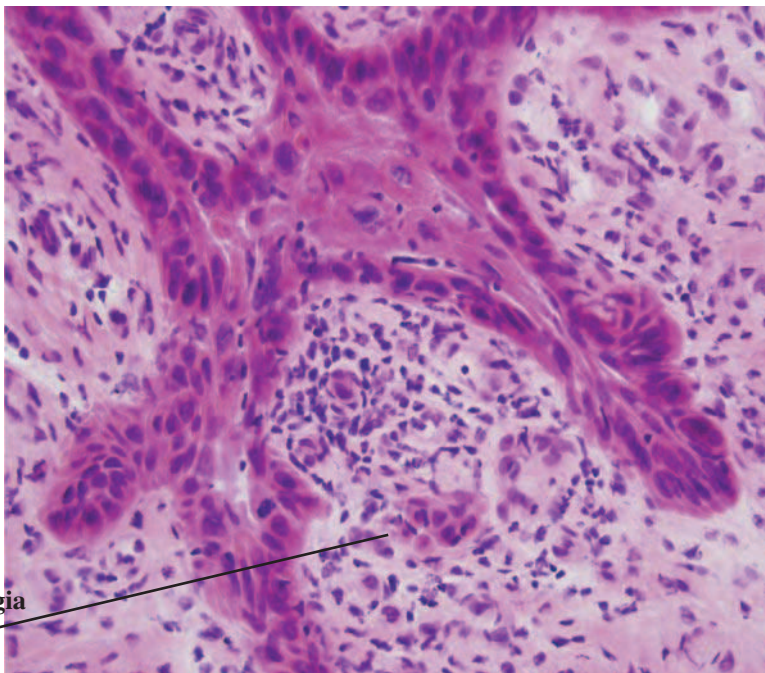


- Transepidermal keratinocyte dysplasia
- Extension down adnexal structures, (Acrosyringia)

Eccrine ducts
(Acrosyringia)

MEDIUM

6-5



Acrosyringia

- Eccrine (Acrosyringeal) extensions

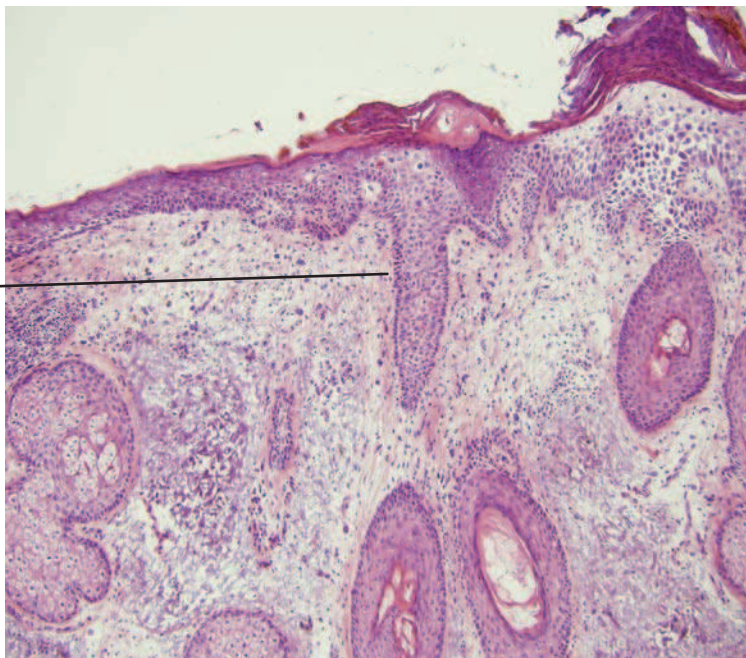
HIGH

6-6

Variants

Squamous Cell Carcinoma In-Situ with Follicular Extension

Follicle

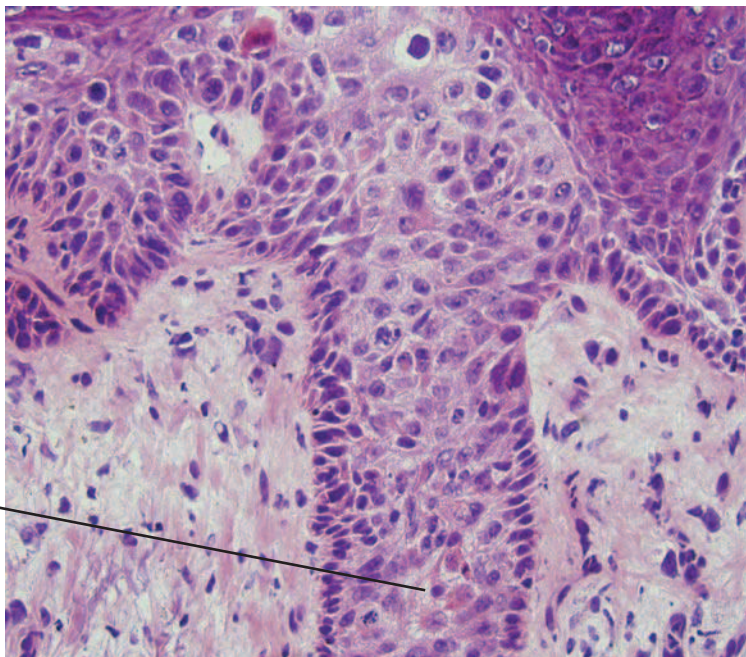


MEDIUM

6-7

- SIS with follicular extension

Dyskeratosis



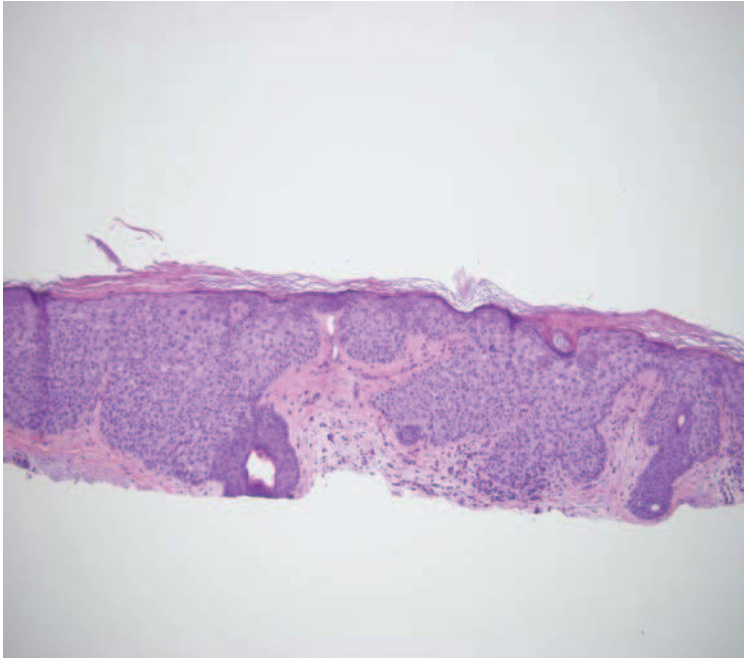
HIGH

6-8

- Follicle effaced by dysplastic keratinocytes

Note: Dyskeratosis

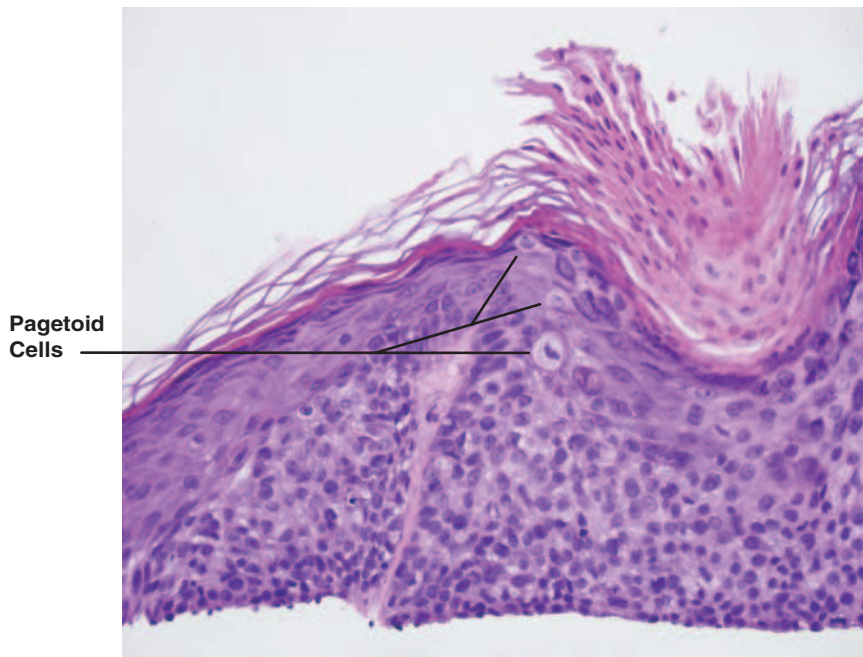
Clear Cell Bowens Disease



MEDIUM

6-9

- Multifocal transepidermal dysplasia



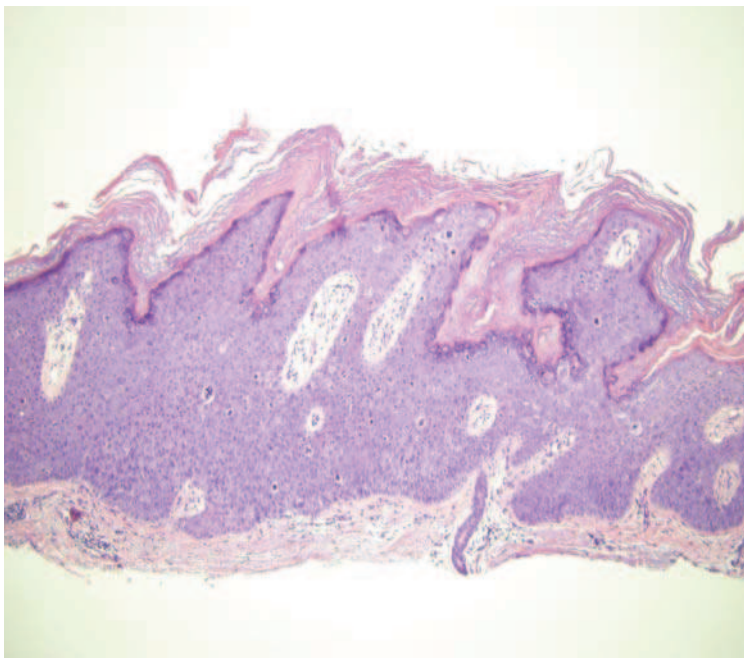
Pagetoid
Cells

HIGH

6-10

- Note:* Cytoplasmic pallor (clear cells)
Note: Pagetoid scatter of dysplastic keratinocytes

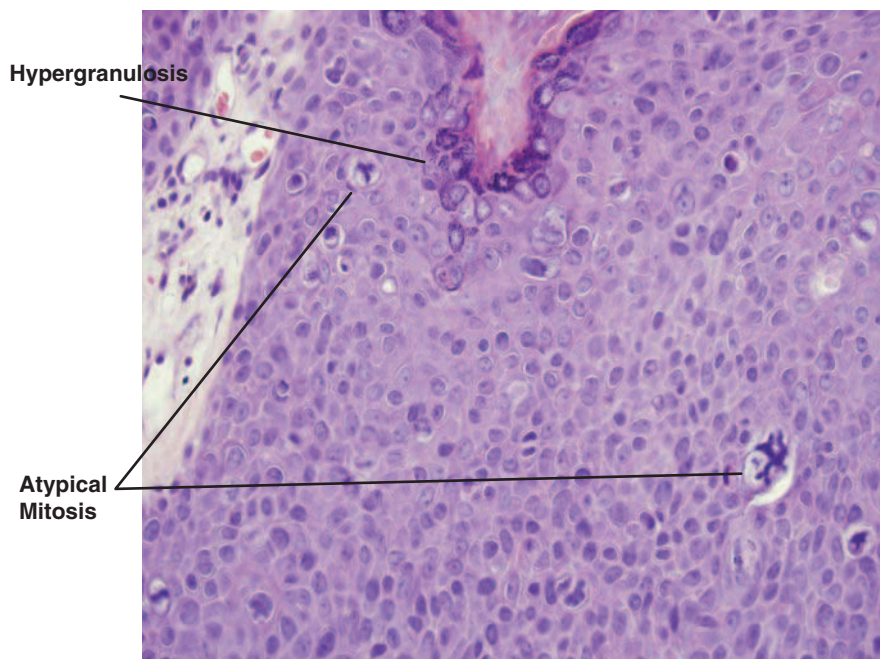
SCC-In-Situ Arising in Verruca (HPV Effect) Bowens Disease



MEDIUM

6-11

- Warty silhouette
- Transepidermal keratinocyte dysplasia



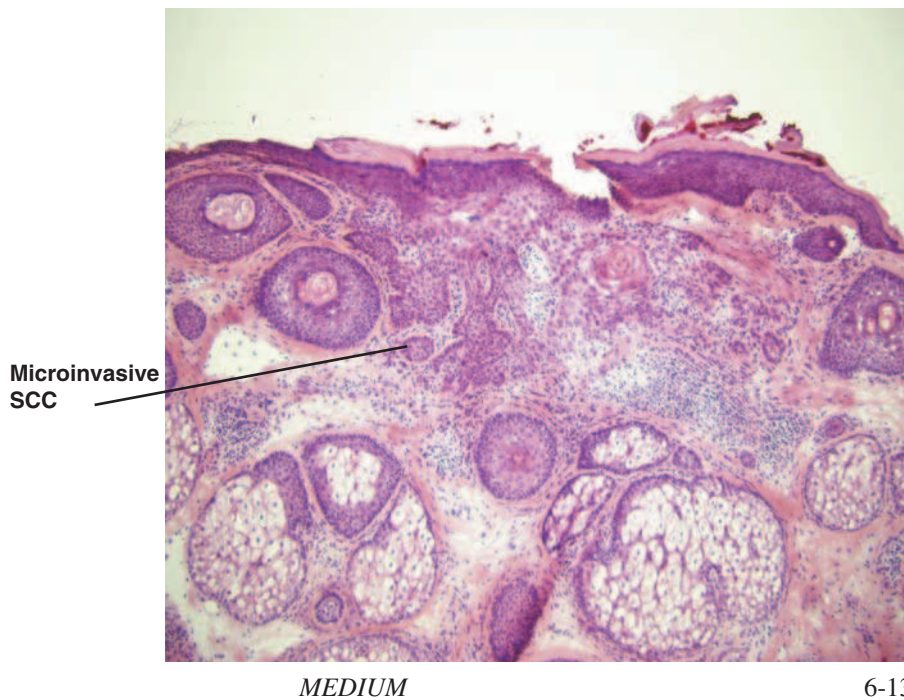
HIGH

6-12

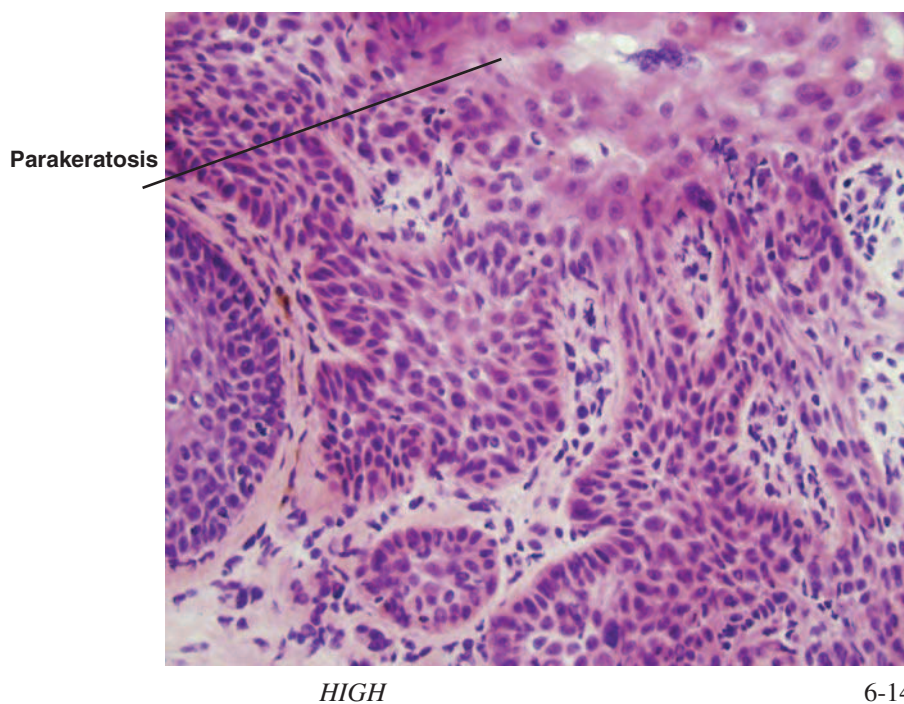
- Hypergranulosis (HPV effect)

Note: Severe dysplasia and atypical mitotic figures

Variants
Microinvasive Well-differentiated SCC



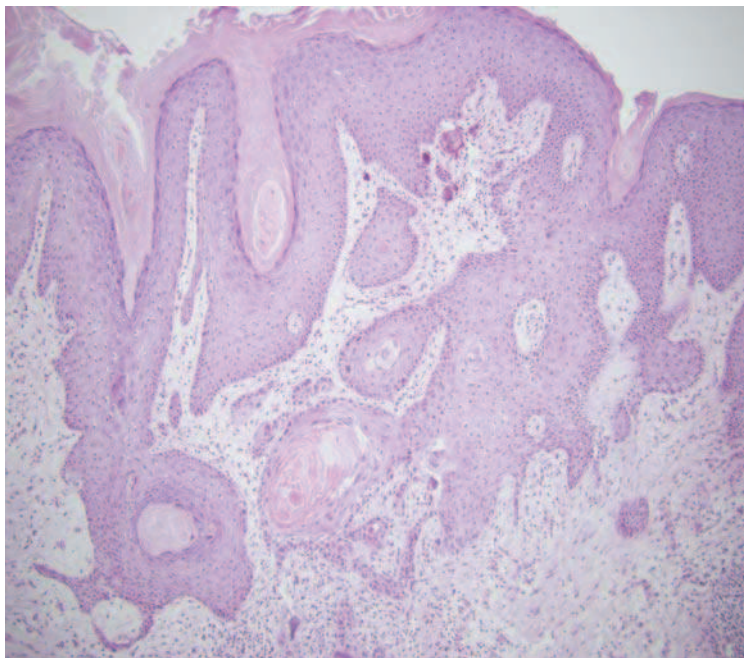
- Irregular infiltration by SCC confined to superficial dermis



- Irregular infiltration defined by jagged silhouette

Note: Coarse parakeratosis

Histologic Grade Well-differentiated SCC

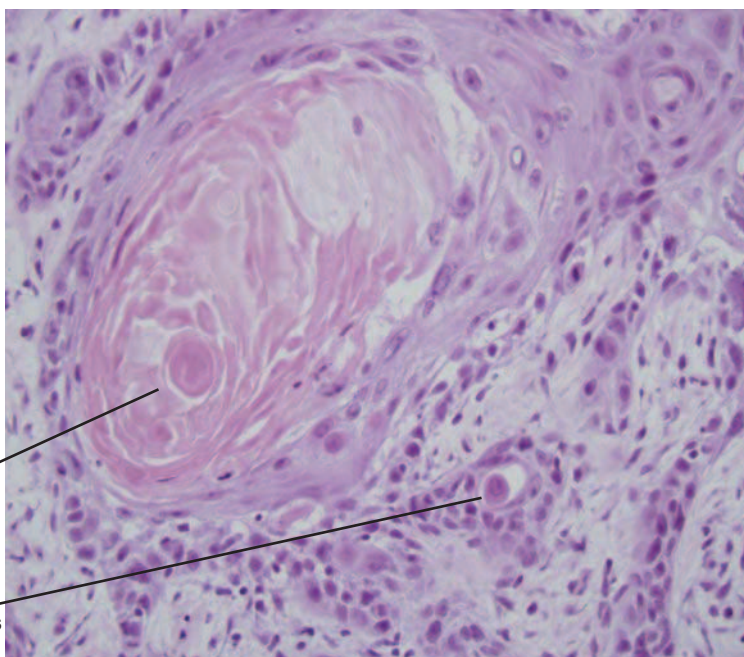


MEDIUM

6-15

- Invasive well-differentiated SCC

Note: Irregular infiltrating foci



Squamous
Pearl

Dyskeratosis

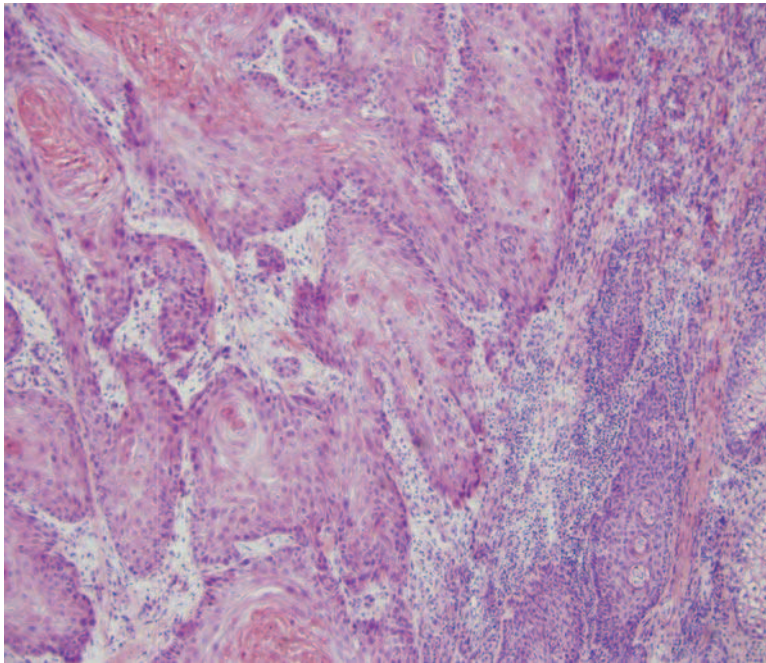
HIGH

6-16

- Well-differentiated SCC with dysplastic keratinocytes

Note: Squamous pearls and dyskeratosis

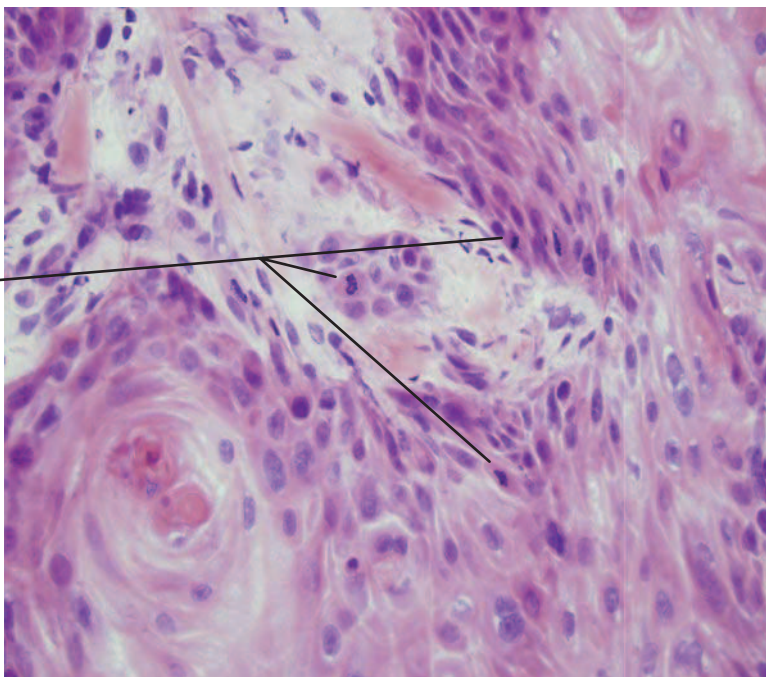
Histologic Grade Moderately Differentiated SCC



MEDIUM

6-17

- Irregular infiltrating SCC



Mitosis

HIGH

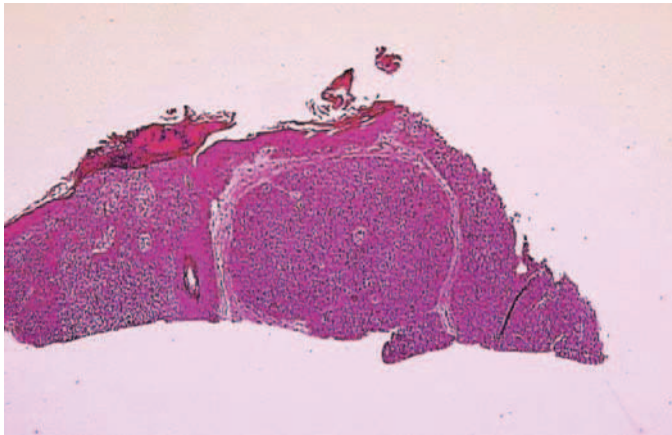
6-18

- Moderate degree of differentiation

Note: Enlarged nuclei with altered nuclear/cytoplasm ratio

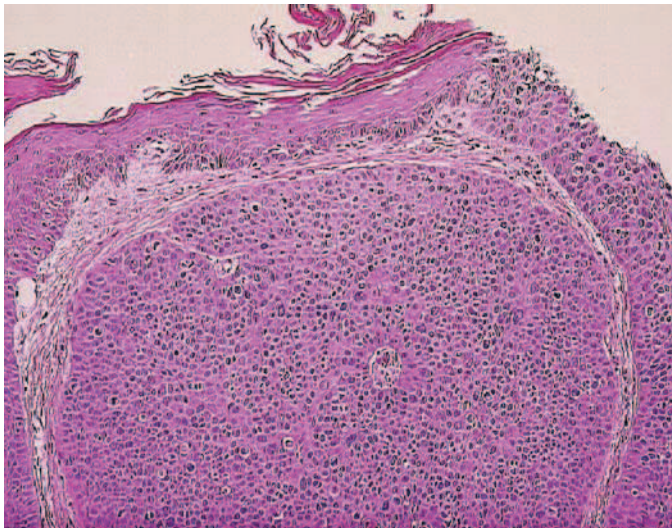
Note: Scattered mitosis

Histologic Grade Poorly Differentiated SCC

*LOW*

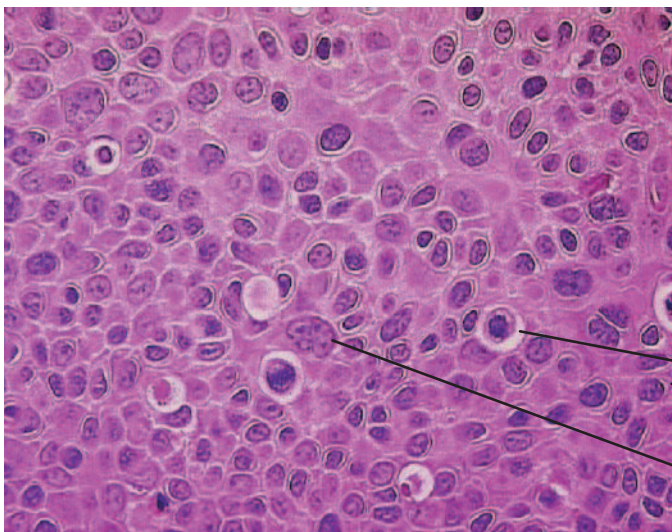
6-19

- Irregular nodular expansion of epithelium

*MEDIUM*

6-20

- Detail of squamous tumor with superficial parakeratosis and underlying nodular growth

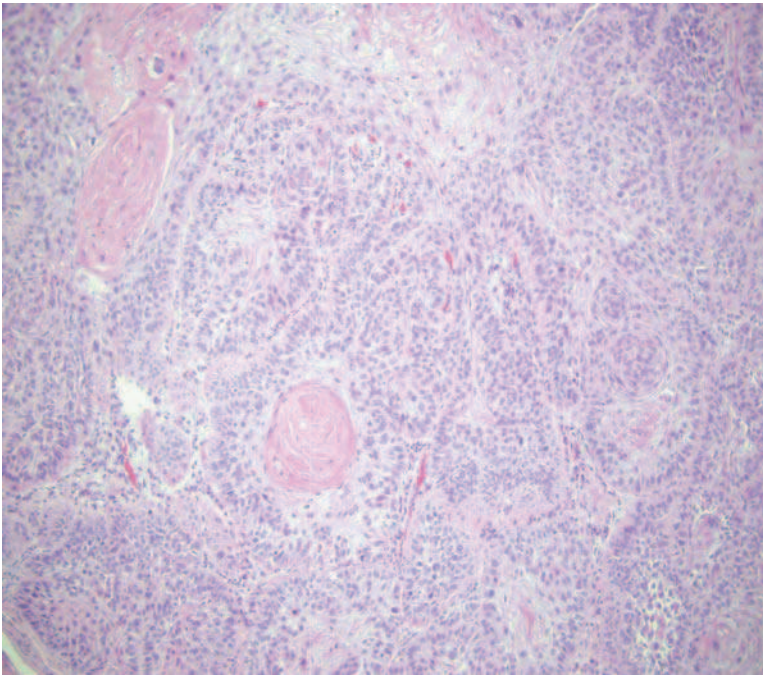
*HIGH*

6-21

- Detail of non-keratinizing meno- and multinucleate cells with dyskeratosis and increased number of mitosis

Mitosis**Multinucleate Cells**

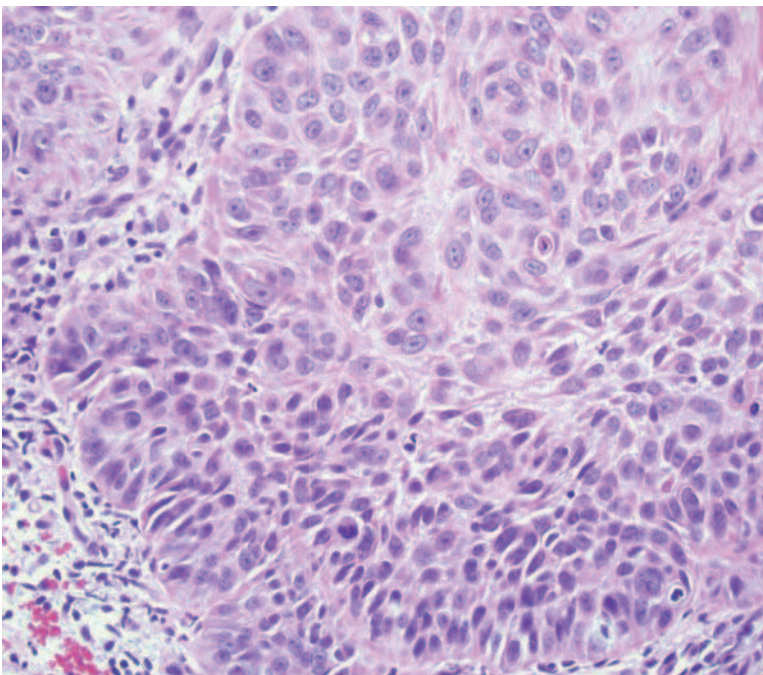
Histologic Grade Poorly Differentiated SCC



MEDIUM

6-22

- Irregular infiltrative neoplasm with keratinized foci



HIGH

6-23

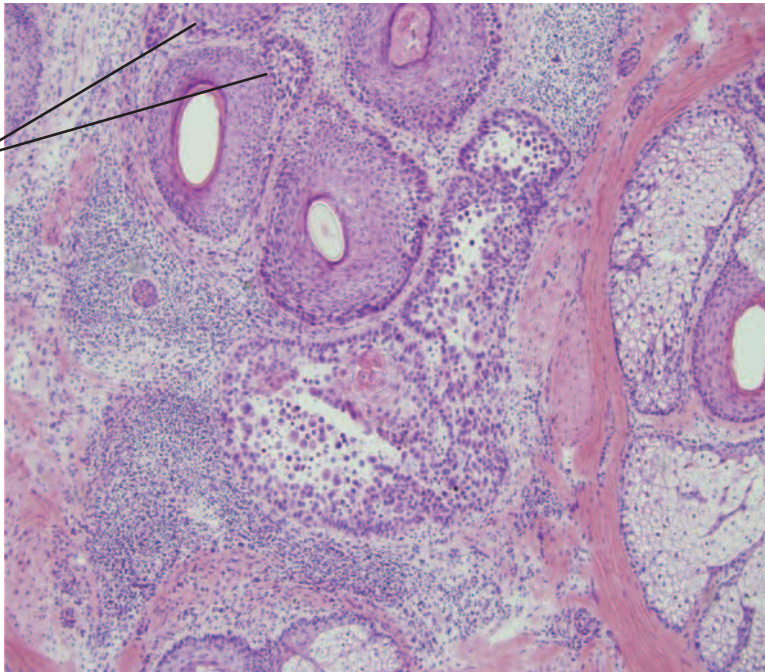
- Detail of a poorly differentiated SCC

Note: High Nuclear/Cytoplasmic Ratio

Note: Hyperchromatic enlarged nuclei

Variants Acantholytic SCC

Follicular
Extension



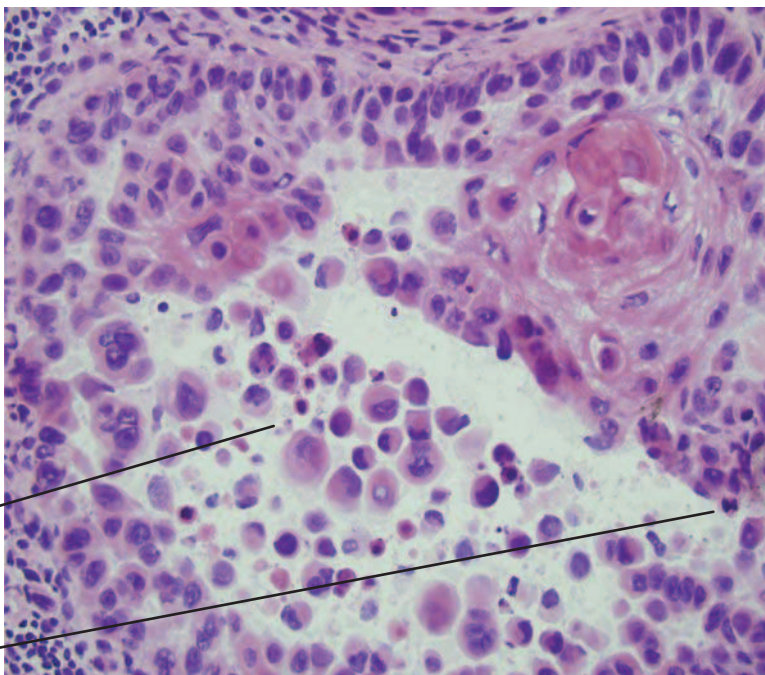
- Acantholytic SCC seen within dermis and extending around follicle

MEDIUM

6-24

Free-Floating
Keratinocytes

Mitotic
Figure



- Acantholysis defined by dyshesive keratinocytes

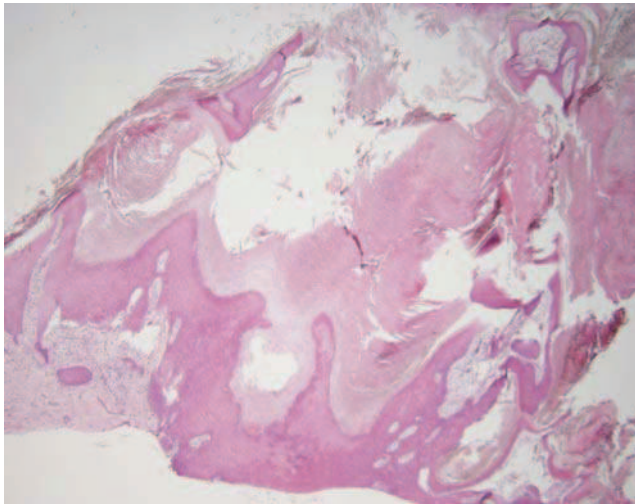
Note: Free floating keratinocytes forming a cavity

Note: Dyskeratosis and mitotic figures

HIGH

6-25

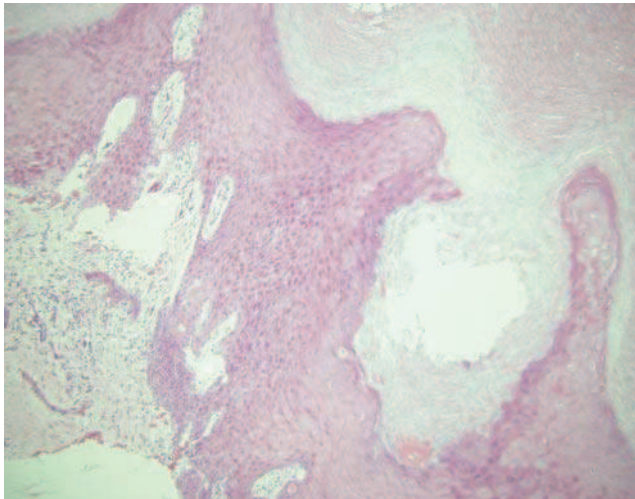
Keratoacanthoma Type Squamous Cell Carcinoma



LOW

6-26

- Endophytic neoplasm with hyperkeratosis and digitate epidermal extensions

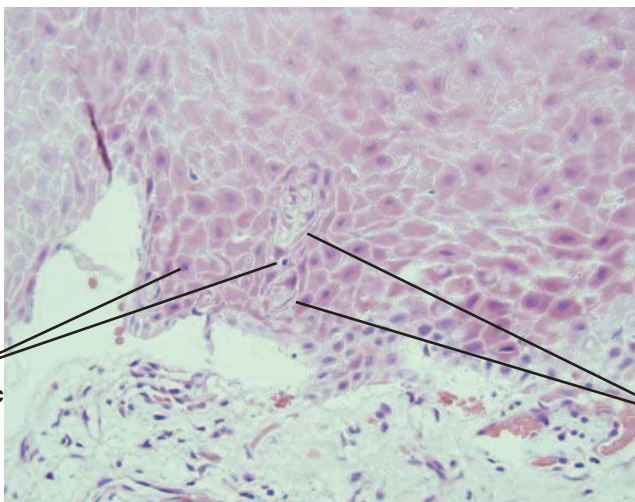


MEDIUM

6-27

- Detail of digitate extensions

Note: Irregular dermal extensions



Dysplastic
Keratinocytes
with
Hyperchromatic
Nuclei

Perforating
Strands of
Elastin

HIGH

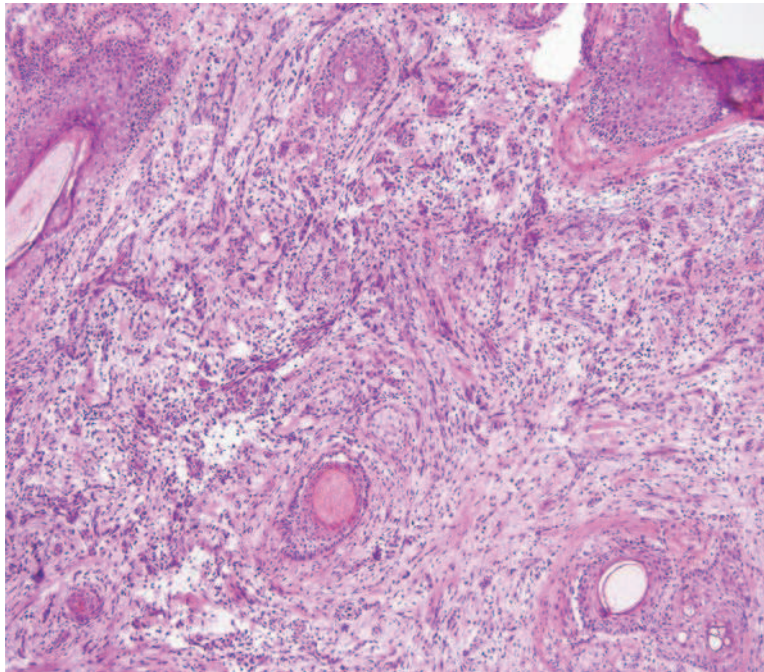
6-28

- High power showing epidermal keratinocyte pallor

Note: Basilar layer dysplasia and perforating strands of elastin

Variants

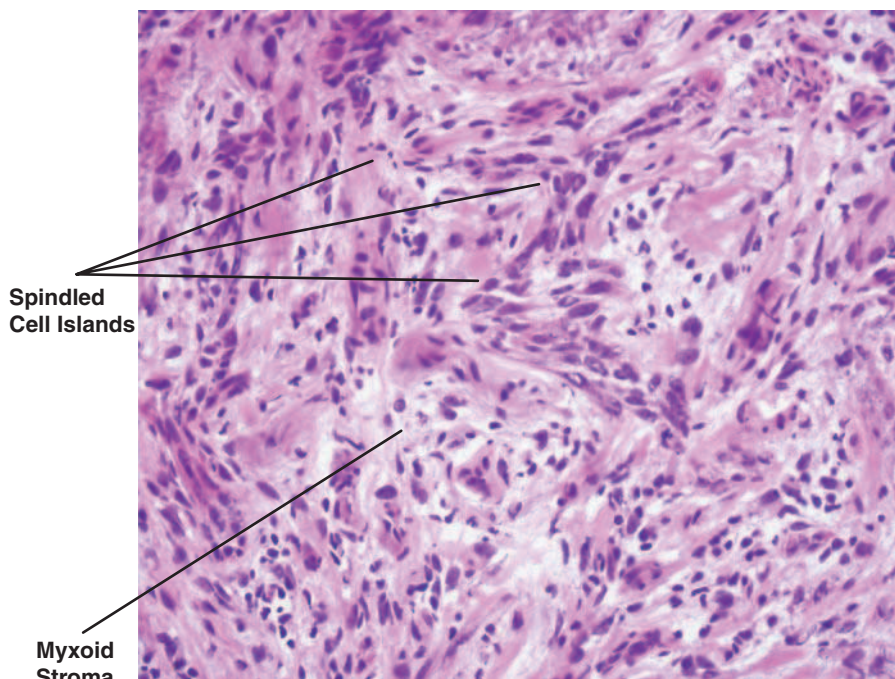
Spindle Cell SCC



- Irregular spindle cell proliferation

MEDIUM

6-29



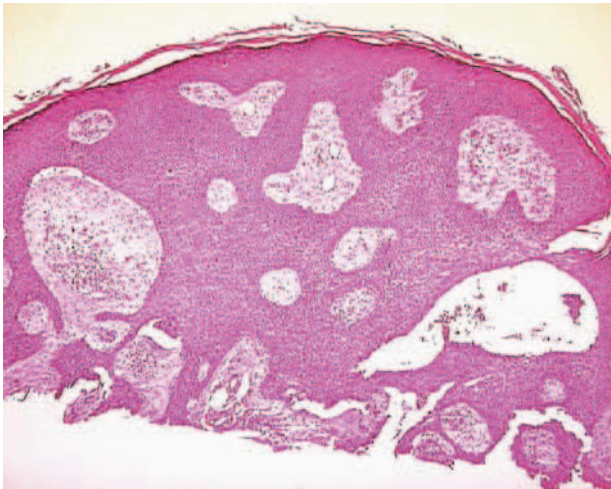
- Spindled cells coalesced to form vague outlined islands

Note: Myxoid and inflamed stroma

HIGH

6-30

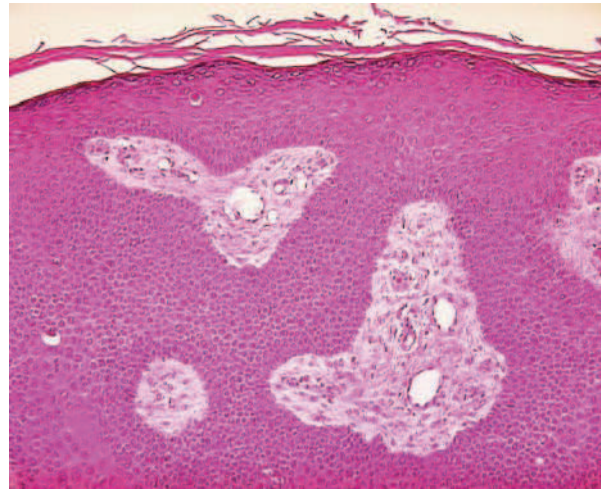
Challenges: SCC Simulant Poroma



LOW

6-31

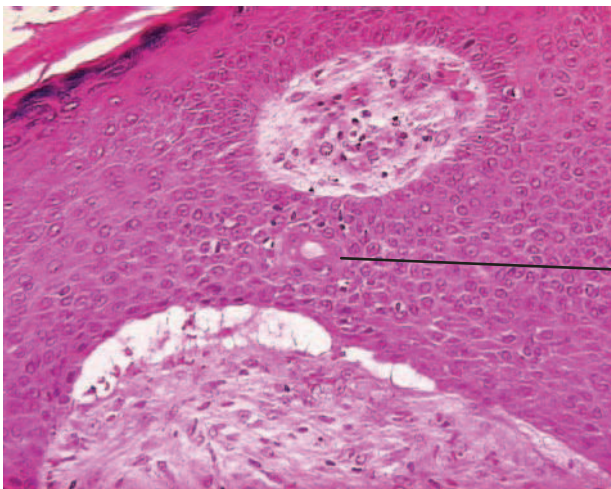
- Plate like horizontal arrangement of epithelial cells



MEDIUM

6-32

- Sheets of uniform epithelial cells with prominent fibrovascular cores

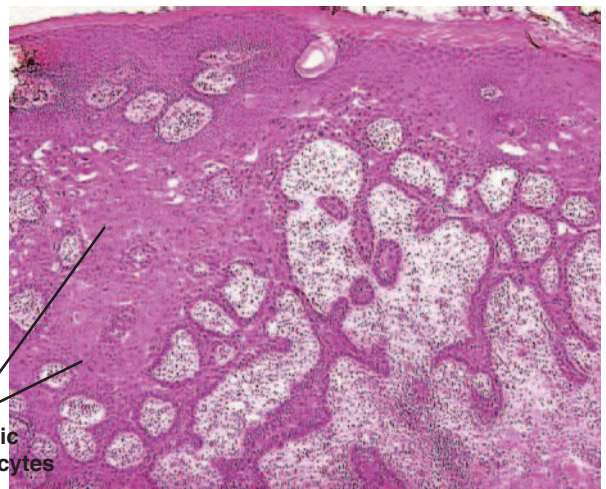


HIGH

6-33

- Intraepithelial pores or ducts

Ducts

Dysplastic
Keratinocytes

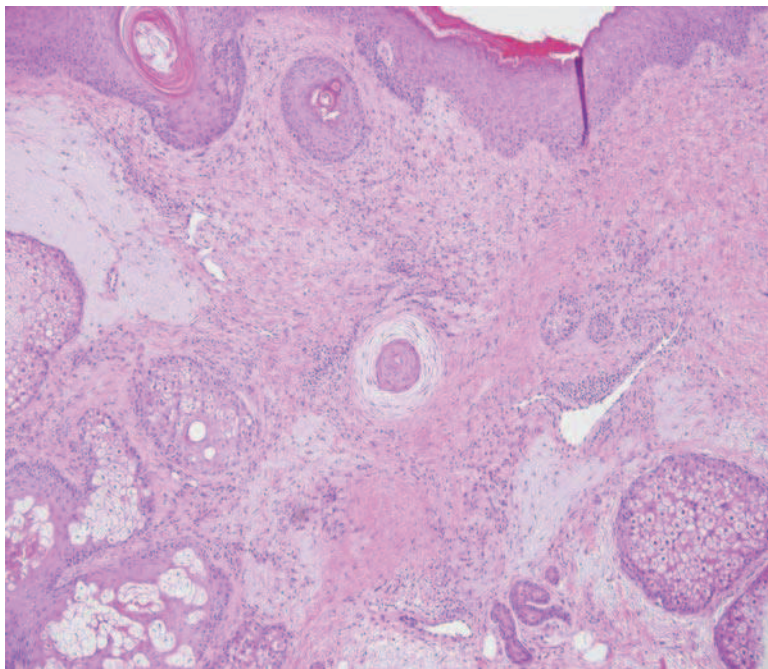
ACRAL SQUAMOUS CELL CARCINOMA

6-34

- Acral SIS often confused with poroma

Note: Keratinocyte dysplasia and lack of pores

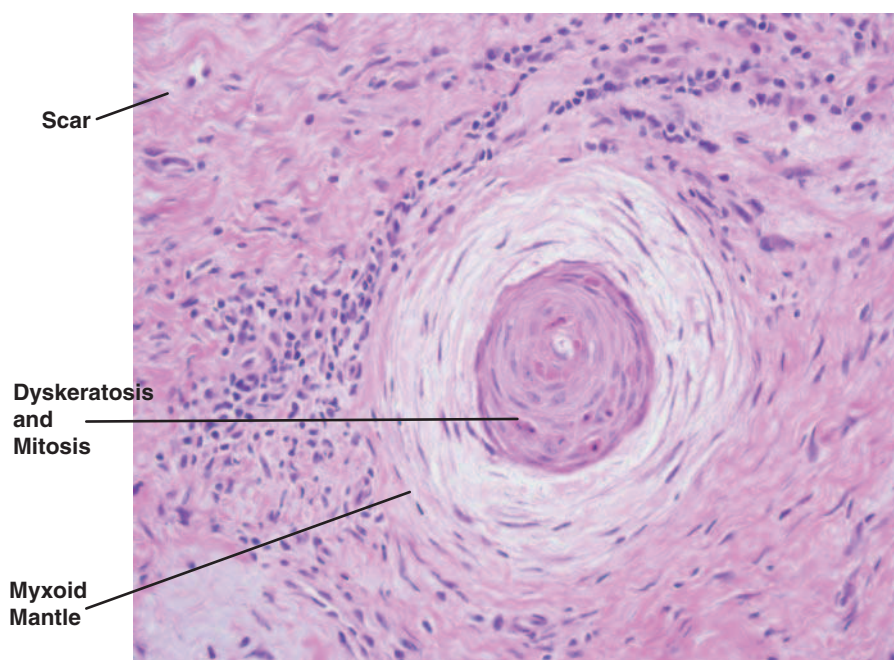
Challenges: SCC Simulant Eccrine Syringometaplasia



MEDIUM

6-35

- Rounded and oval squamous islands seen within scar



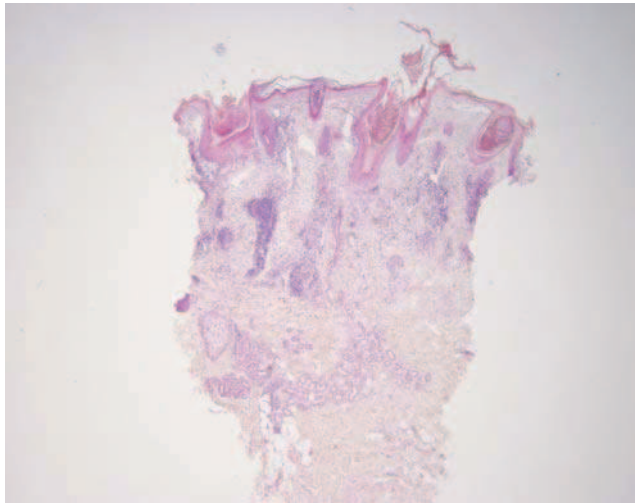
HIGH

6-36

- Rounded silhouette despite dyskeratosis and mitosis

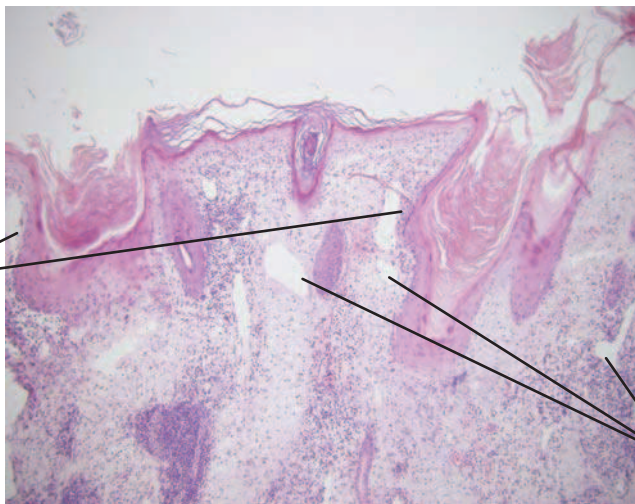
Note: Myxoid mantle

Challenges Discoid Lupus Erythematosus

*LOW*

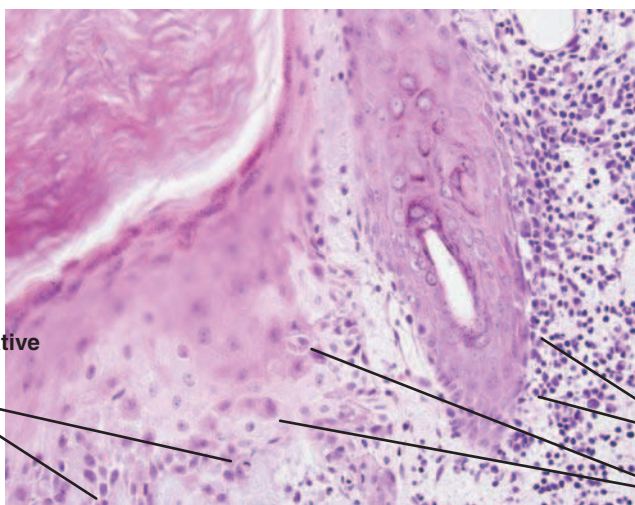
6-37

- Variably thickened and thinned epidermis with superficial and deep dermal inflammation

**Follicular Plugs****Telangiectasia***MEDIUM*

6-38

- Follicular plugs with capillary ectasia (telangiectasia)

**Pseudo-Infiltrative Appearance****Interface Dermatitis****Dyskeratosis/Dysplasia***HIGH*

6-39

- Interface dermatitis
- Ragged basilar epidermis with deskeratosis, dysplasia and pseudo-infiltrative appearance

Bibliography

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2. Epstein J. Photocarcinogenesis, skin cancer, and aging. *J Am Acad Dermatol*. 1983;9:487.
3. Lohmann C, Solomon A. Clinicopathologic variants of cutaneous squamous cell carcinoma. *Adv Anat Pathol*. 2001;8:27.