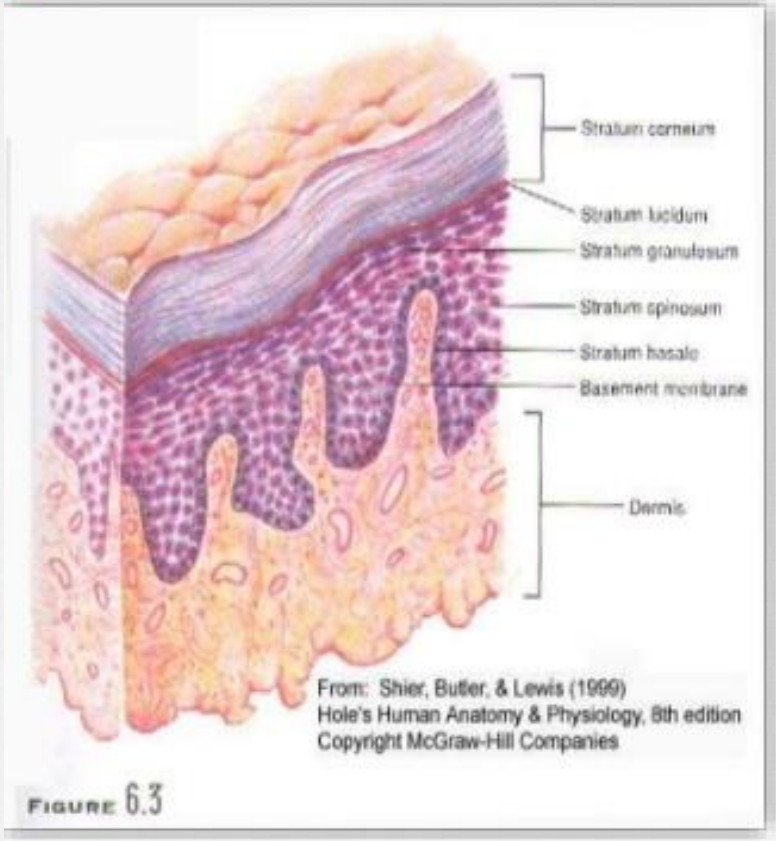
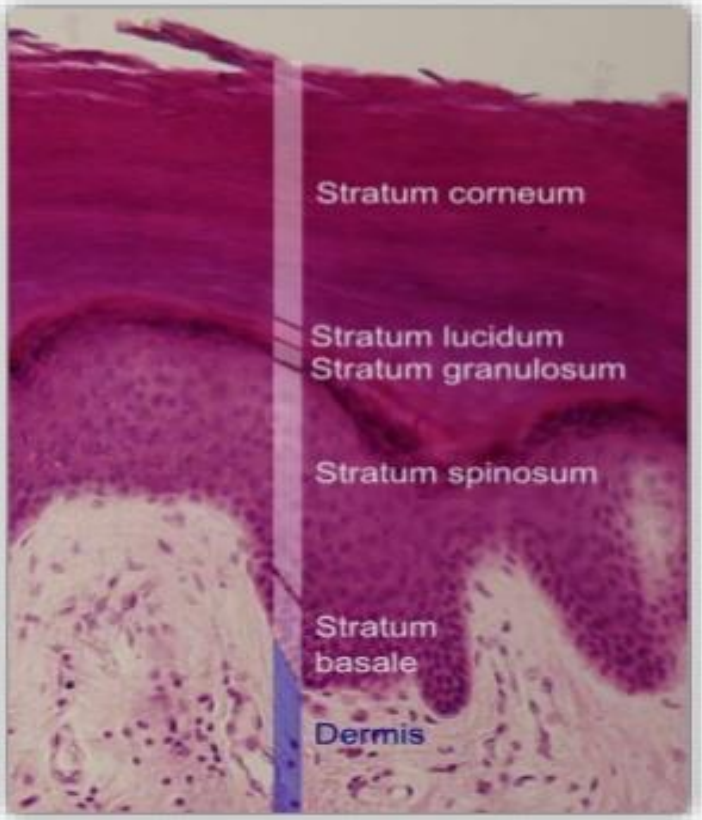
Premalignant lesions /SCC/BCC

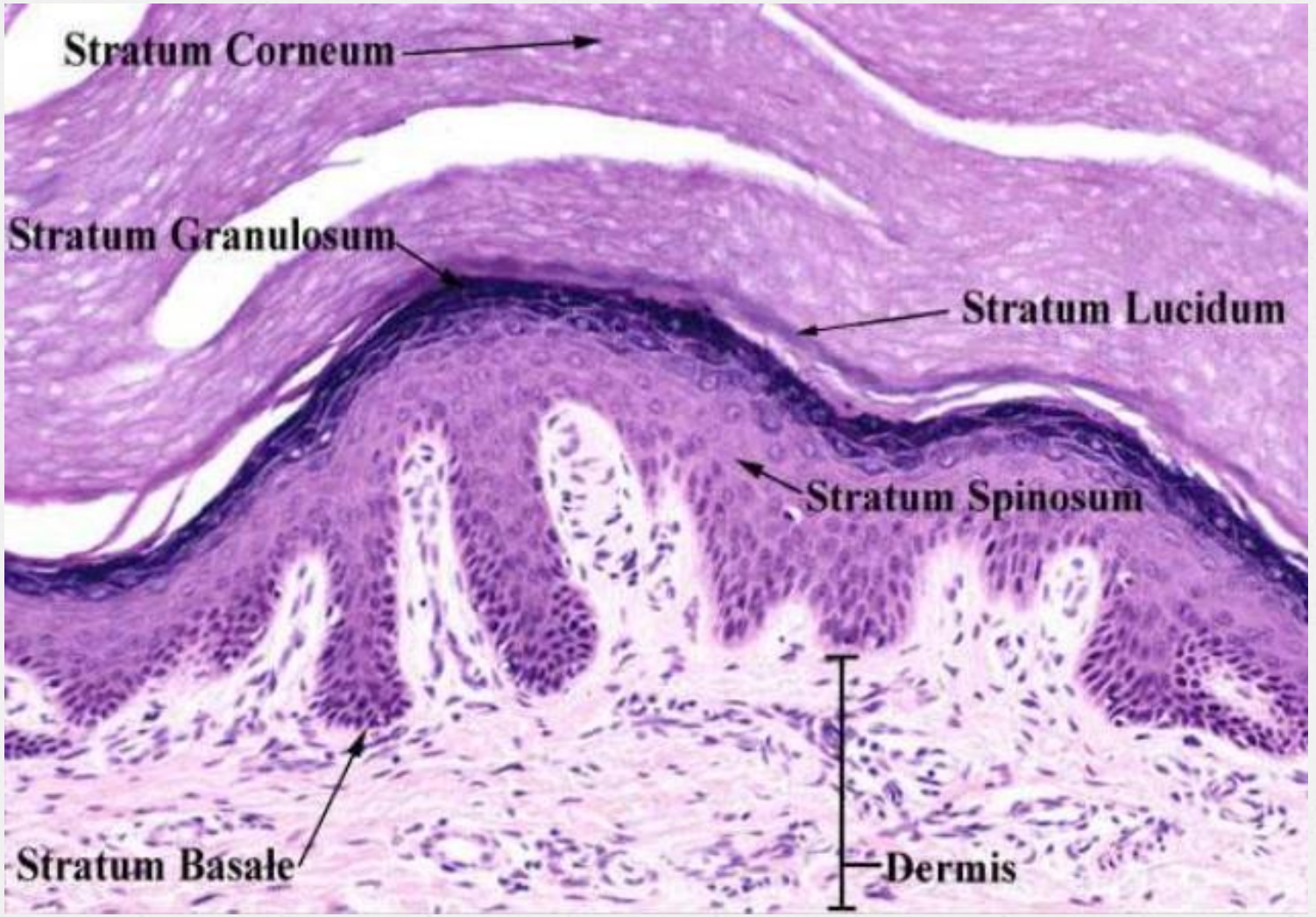
Dr Saima Nadeem
Assist Professor
Pathology

LEARNING OBJECTIVES

- List the pre-malignant epithelial lesions
- List the predisposing factors for Squamous cell carcinoma of skin
- Differentiate Squamous cell carcinoma from basal cell carcinoma on the basis of morphology and clinical features


Stratum corneum
Stratum lucidum
Stratum granulosum
Stratum spinosum
Stratum basale
Basement membrane
Dermis
From: Shier, Butler, & Lewis (1999)
Hole's Human Anatomy & Physiology, 8th edition
Copyright McGraw-Hill Companies
FIGURE 6.3


Stratum corneum
Stratum lucidum
Stratum granulosum
Stratum spinosum
Stratum basale
Dermis


Stratum Corneum
Stratum Granulosum
Stratum Lucidum
Stratum Spinosum
Stratum Basale
Dermis

Premalignant Epidermal lesions

- The most important premalignant skin lesions are

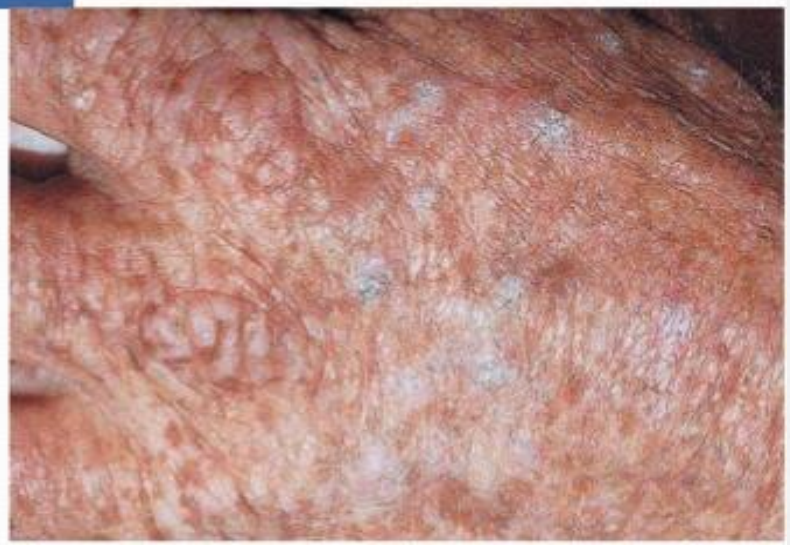
1) Actinic keratosis.
2) Bowen‘s disease
3) Xeroderma pigmentosum
4) Cutaneous Horn
5) keratoacanthoma

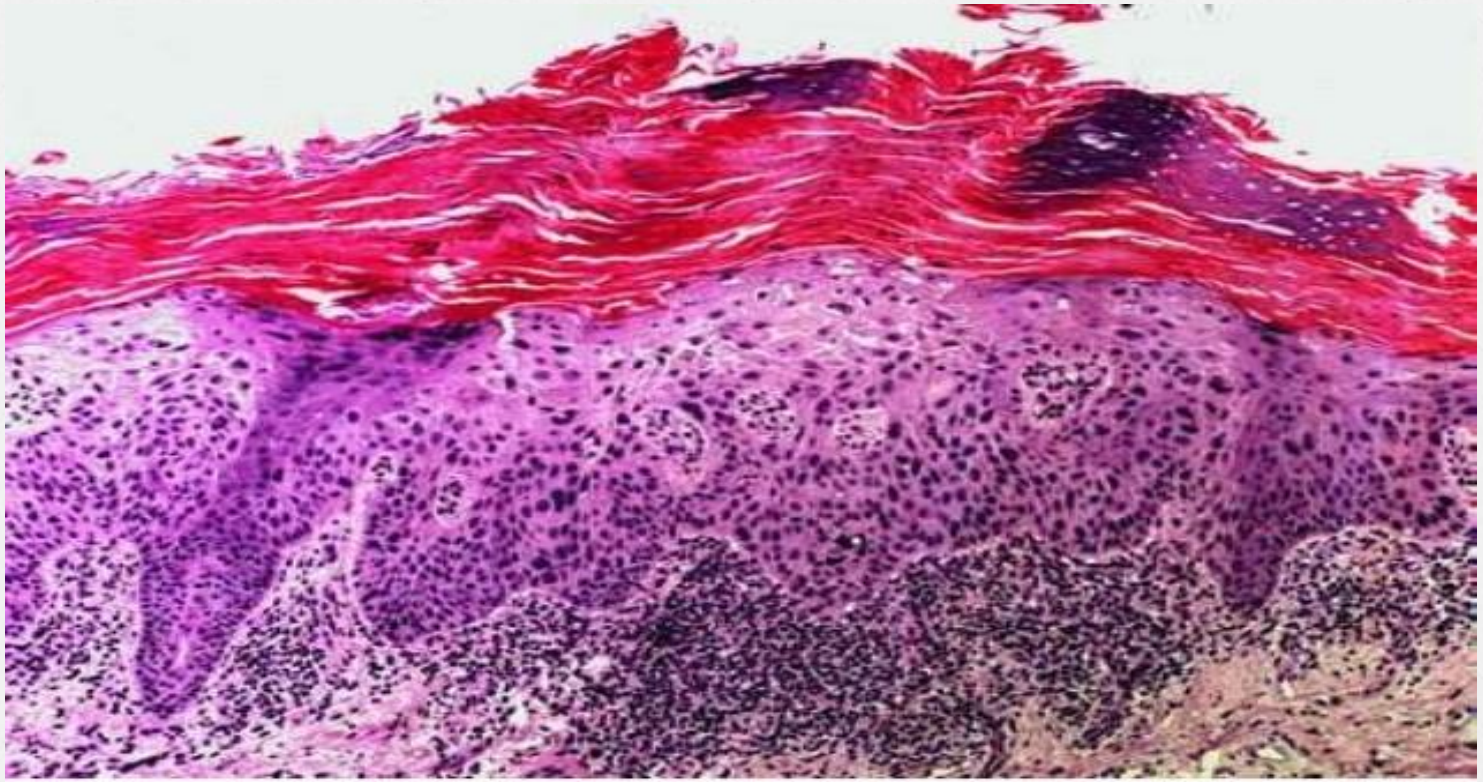
Actinic keratosis

- Seen as multiple lesions in sun-exposed areas
- Excessive exposure to sunlight over many years and inadequate protection against it are the essential predisposing factors
- Seen most commonly on the face and the dorsa of the hands and in the bald portions of the scalp in men

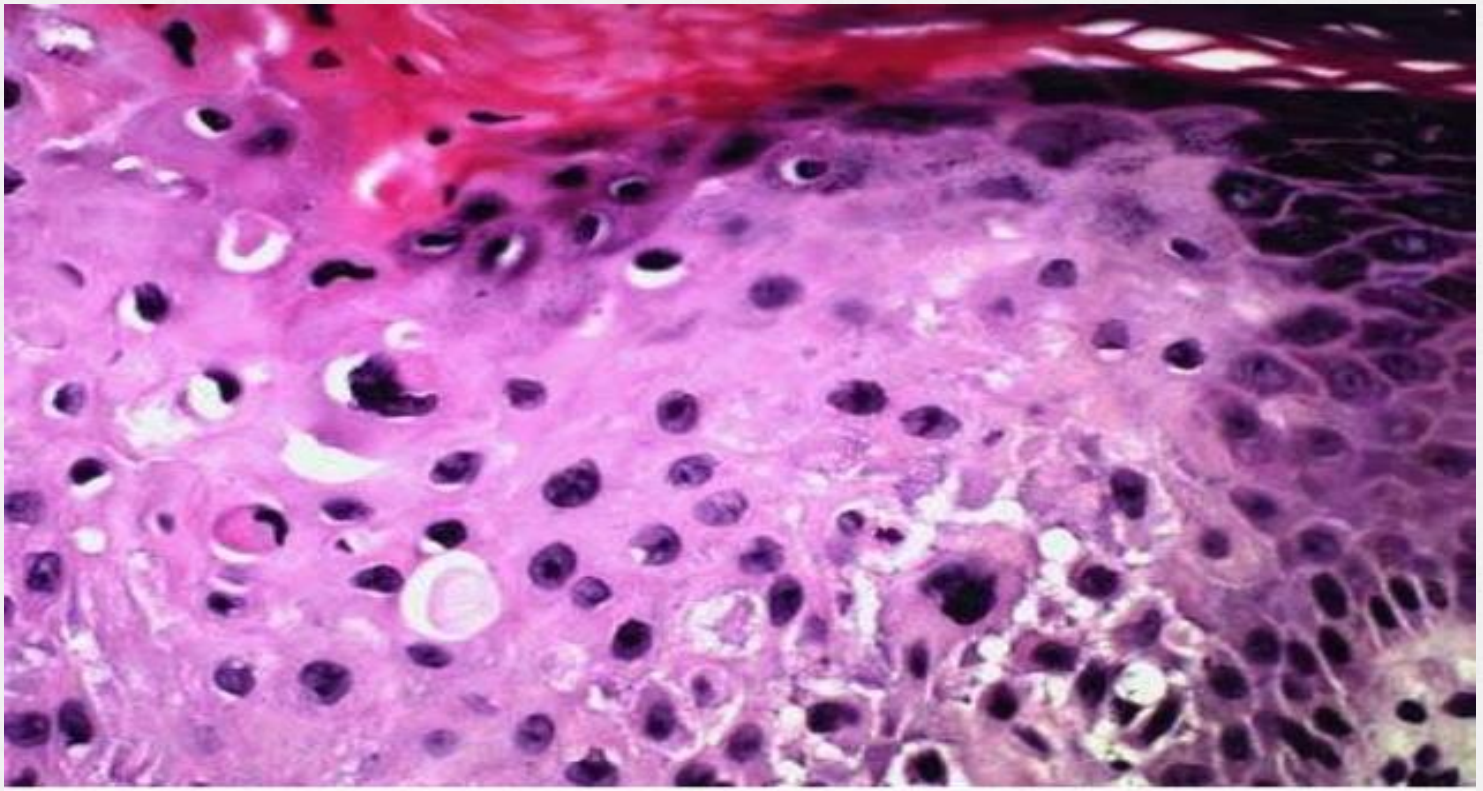
- lesions measure less than 1 cm in diameter
- erythematous, are often covered by adherent scales
- May pigmented and show peripheral spreading
- Occasionally, lesions show marked hyperkeratosis and then have the clinical aspect of cutaneous horns.

- Analogous lesion on the vermilion border of the lower lip as solar cheilitis and may show areas of erosion and hyperkeratosis
- Both can develop into squamous cell carcinoma
- Incidence of this transformation varies but It has been estimated that in 20% of patients have SCC in one or more of the lesions .
- SCC arising either in actinic keratoses or de novo in sun-damaged skin do not metastasize





Actinic keratosis. Tall columns of parakeratotic keratin alternate with bands of orthokeratotic keratin with moderate atypia of the underlying keratinocytes

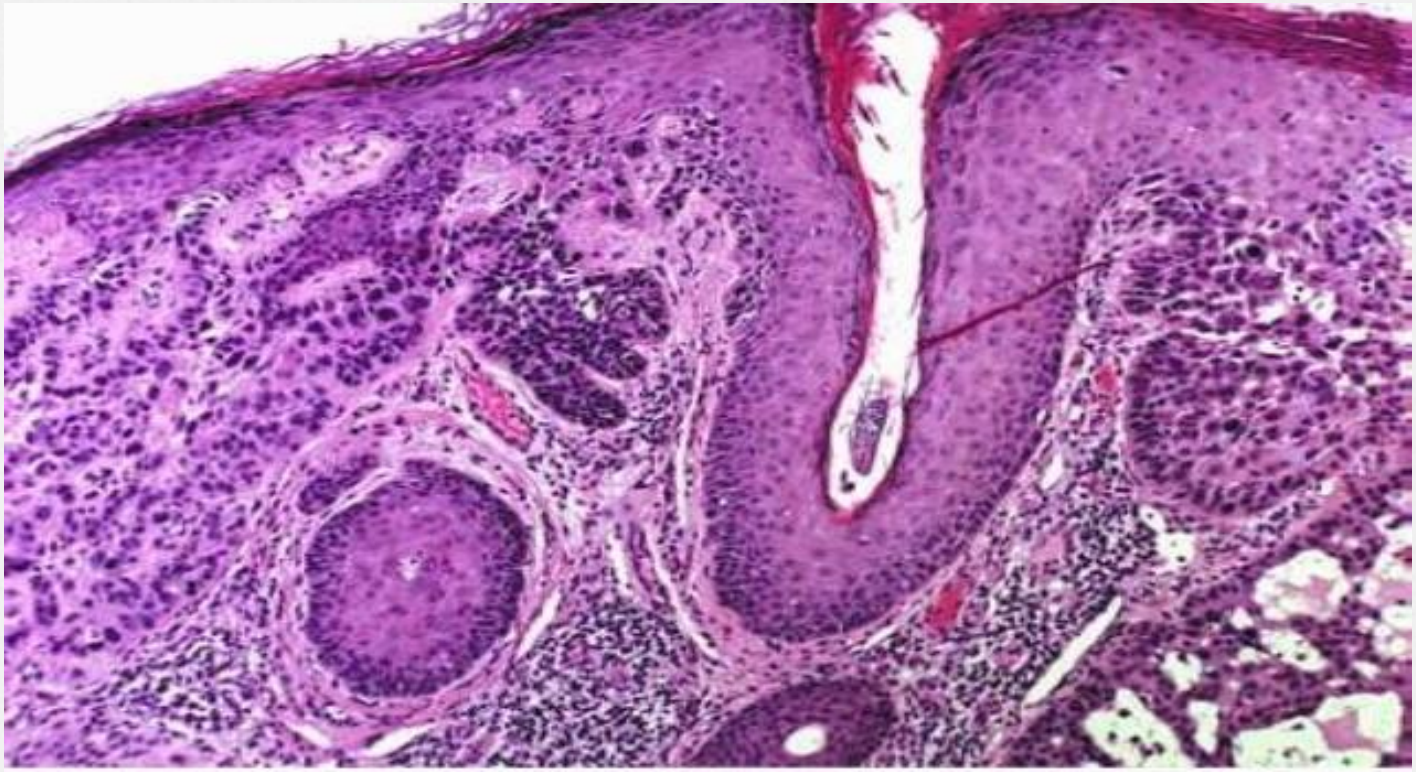


Actinic keratosis. Beneath a thick layer of parakeratotic keratin the epidermis shows cytologic atypia.

- Actinic keratoses are keratinocytic dysplasias or squamous cell carcinomas in situ
- Types- I) Hypertrophic,
  II) Atrophic,
  III) Bowenoid,
  IV) Acantholytic,
  V) Pigmented

Hypertrophic type of actinic keratosis

- Hyperkeratosis is pronounced and is usually intermingled with areas of parakeratosis
- Mild or moderate papillomatosis may be present
- The epidermis is thickened in most areas and shows irregular downward proliferation that is limited to the uppermost dermis and does not represent frank invasion
- Stratum malpighii show a loss of polarity and a disorderly arrangement
- Lichenoid actinic keratosis –a well known variant



Actinic keratosis, Hypertrophic type. The lesion shows hyperkeratosis and papillomatosis with prominent cytologic atypia. There is a moderate lymphocytic infiltrate in the underlying papillary dermis.

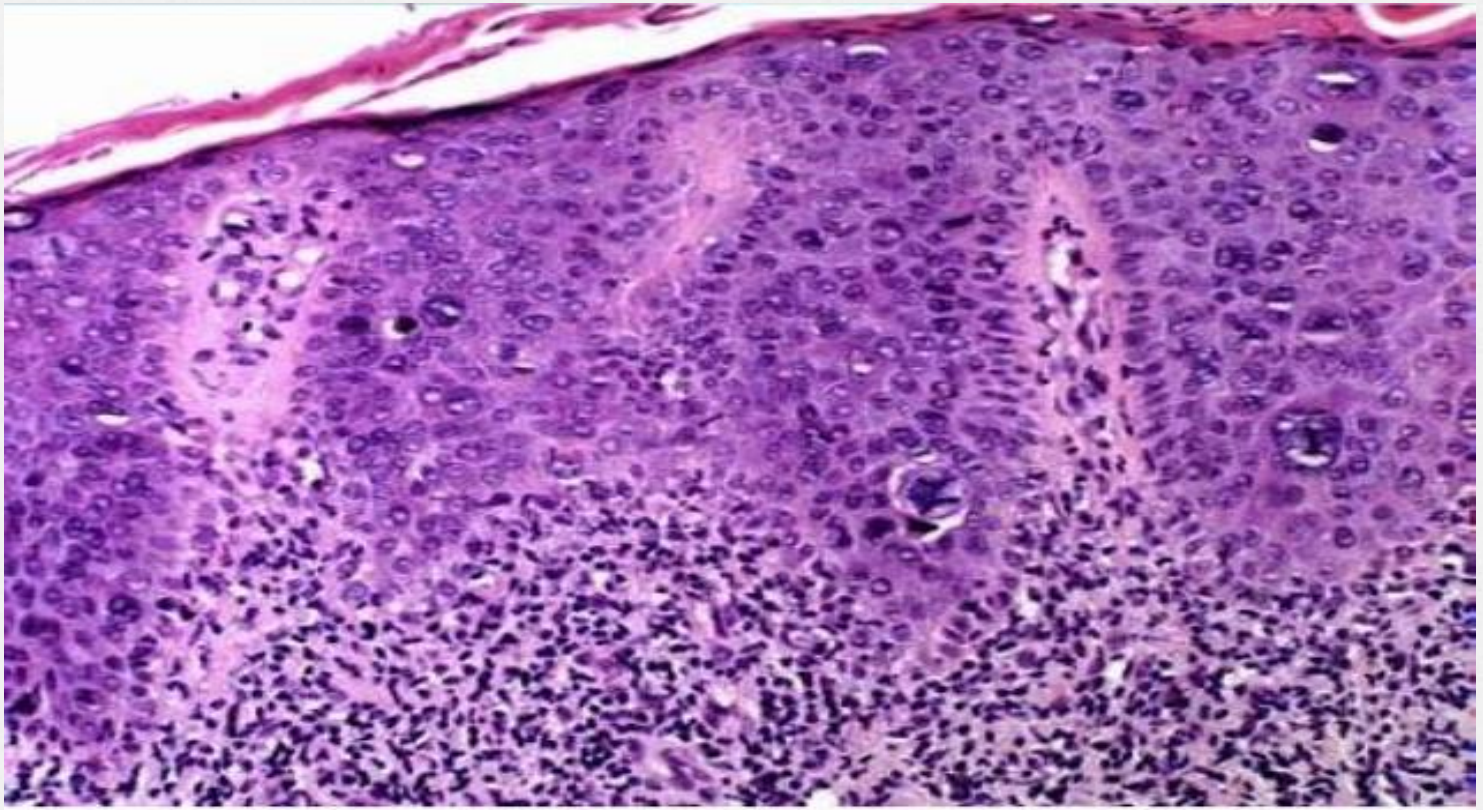
Atrophic type of actinic keratosis

- Hyperkeratosis usually is slight
- Epidermis is thinned and devoid of rete ridges
- Atypicality of the cells is found predominantly in the basal cell layer
- Atypical basal layer may proliferate into the dermis as buds and duct-like structures

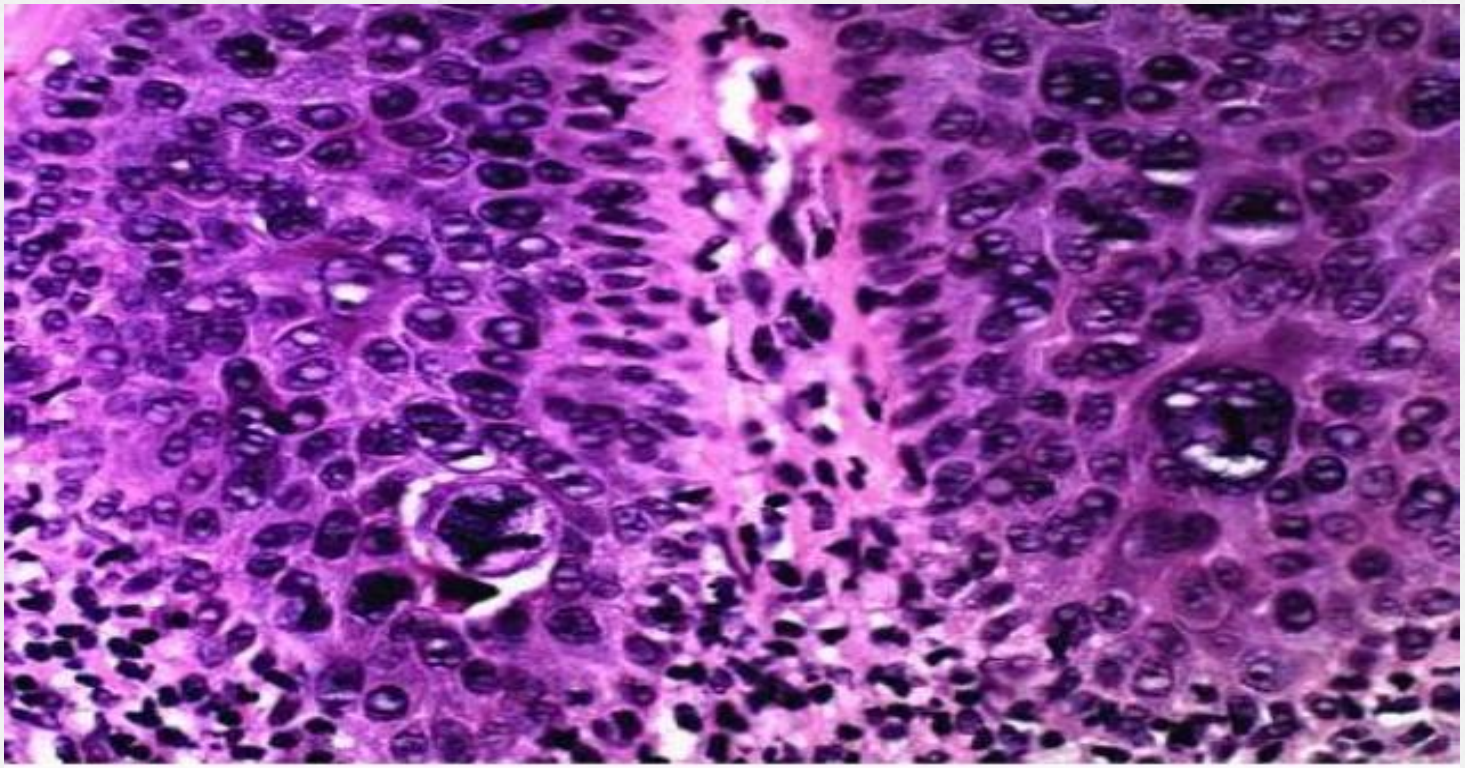
Bowenoid type of actinic keratosis

- Histologically indistinguishable from Bowen's disease
- Also be referred to as squamous cell carcinoma in situ
- As in Bowen's disease, there is within the epidermis considerable disorder in the arrangement of the nuclei, as well as clumping of nuclei and dyskeratosis

Actinic keratosis, Bowenoid type (squamous cell carcinoma in situ). Low magnification. Beneath a thick layer of parakeratotic keratin the epidermis shows cytologic atypia.



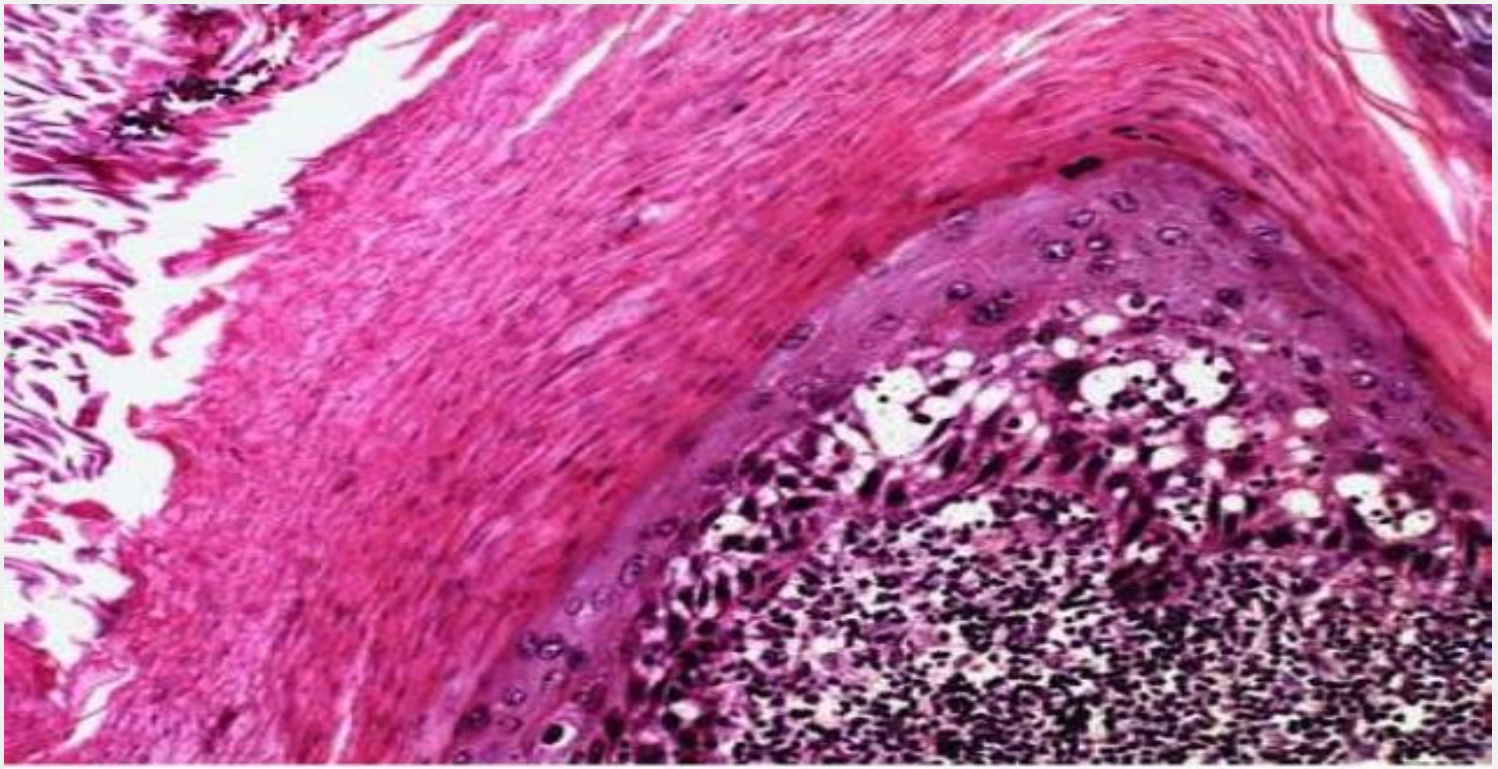
Actinic keratosis, Bowenoid type (squamous cell carcinoma in situ). Medium magnification. Marked cellular and nuclear pleomorphism are present together with frequent and atypical mitoses



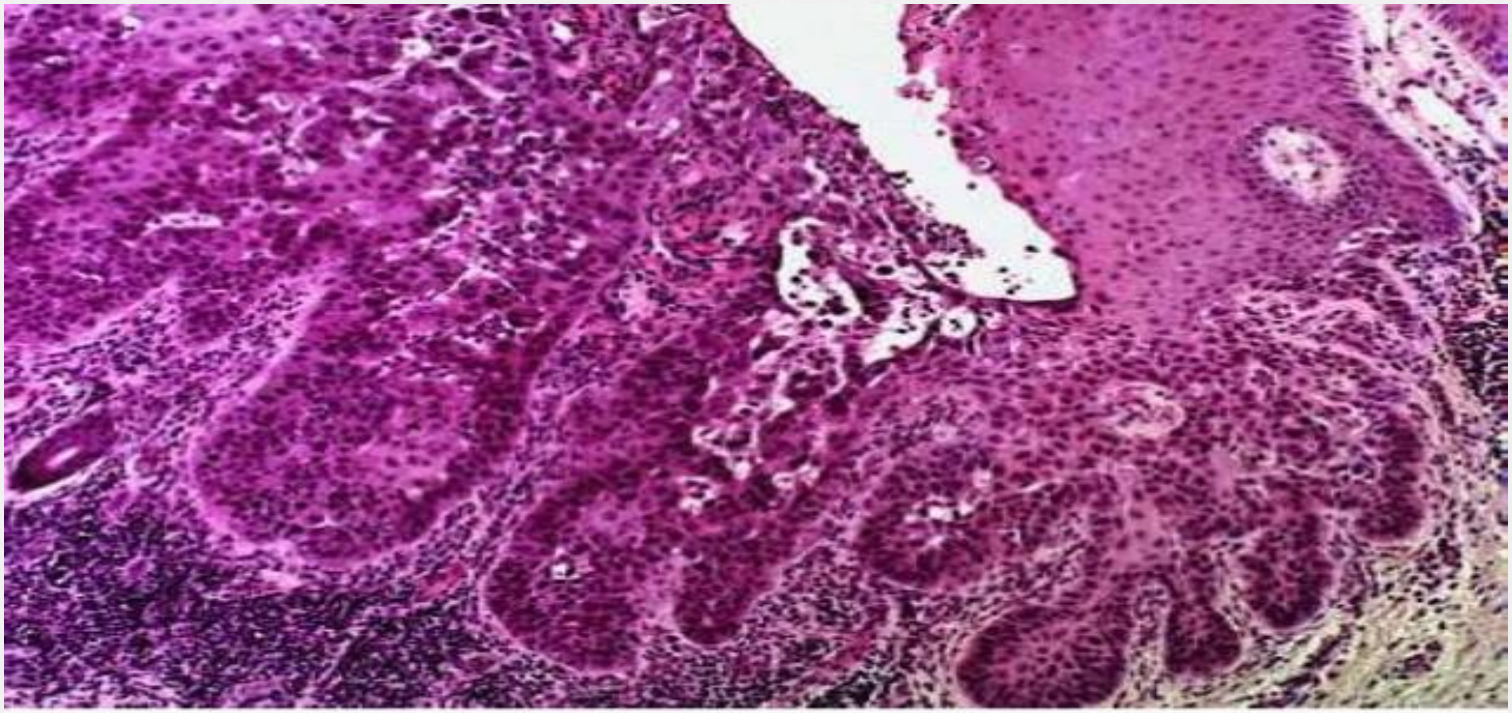
Actinic keratosis, Bowenoid type (squamous cell carcinoma in situ). High magnification. Large atypical mitoses are prominent in this Bowenoid actinic keratosis

Acantholytic type of actinic keratosis

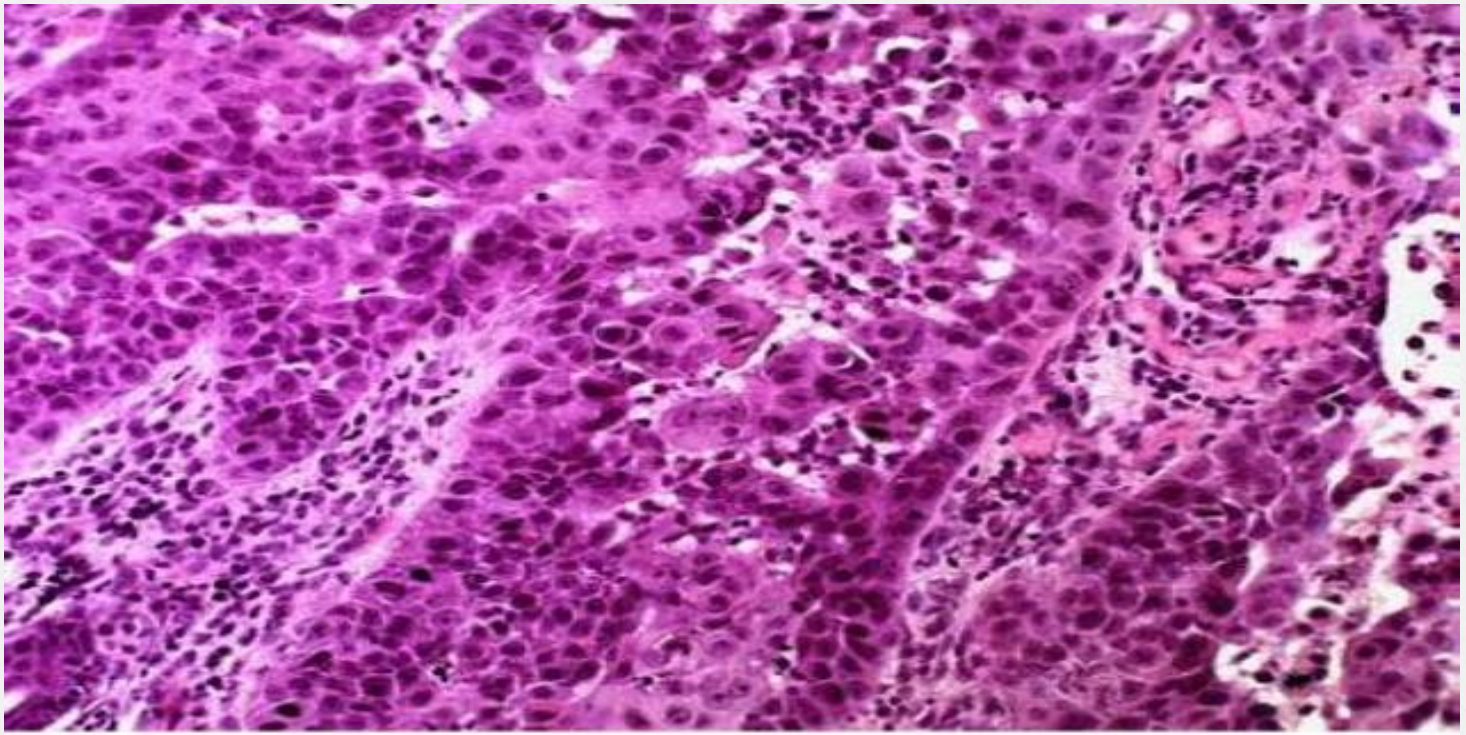
- Immediately above the atypical cells composing the basal cell layer there are clefts or lacunae
- Result of anaplastic changes in the lowermost epidermis, resulting in dyskeratosis and loss of the intercellular bridges
- Above the acantholytic clefts, the epidermis shows varying degrees of atypicality but generally less atypicality than basal layer
- When atypia is full-thickness or high-grade, the term acantholytic squamous cell carcinoma in situ may be applied.



Actinic keratosis, acantholytic type. Low magnification. The epidermis is markedly hyperkeratotic. In the dermis, there is a dense lichenoid inflammatory infiltrate. The keratosis shows focal acantholytic change



Actinic keratosis, acantholytic type. Medium magnification. In the dermis, there is a dense lichenoid inflammatory infiltrate. The keratosis shows focal acantholytic change



Actinic keratosis, acantholytic type. High magnification. Keratinocytes in the basal layer are crowded, with an ↑ N:C ratio, and tend to become separated from one another and to adopt a rounded configuration

Pigmented type of actinic keratosis

- Excessive amounts of melanin are present, especially in the basal cell layer
- Almost all the melanin is retained within the cell bodies and dendrites of the melanocytes, indicating some block in melanin transfer
- Numerous melanophages are seen in most cases in the superficial dermis

- In all five types of actinic keratosis, the upper dermis usually shows a fairly dense, chronic inflammatory infiltrate composed predominantly of lymphoid cells but often also containing plasma cells
- Solar cheilitis, more frequently than actinic keratosis of the skin, shows an inflammatory infiltrate in which plasma cells predominate

CLINICAL VARIANTS OF AKs

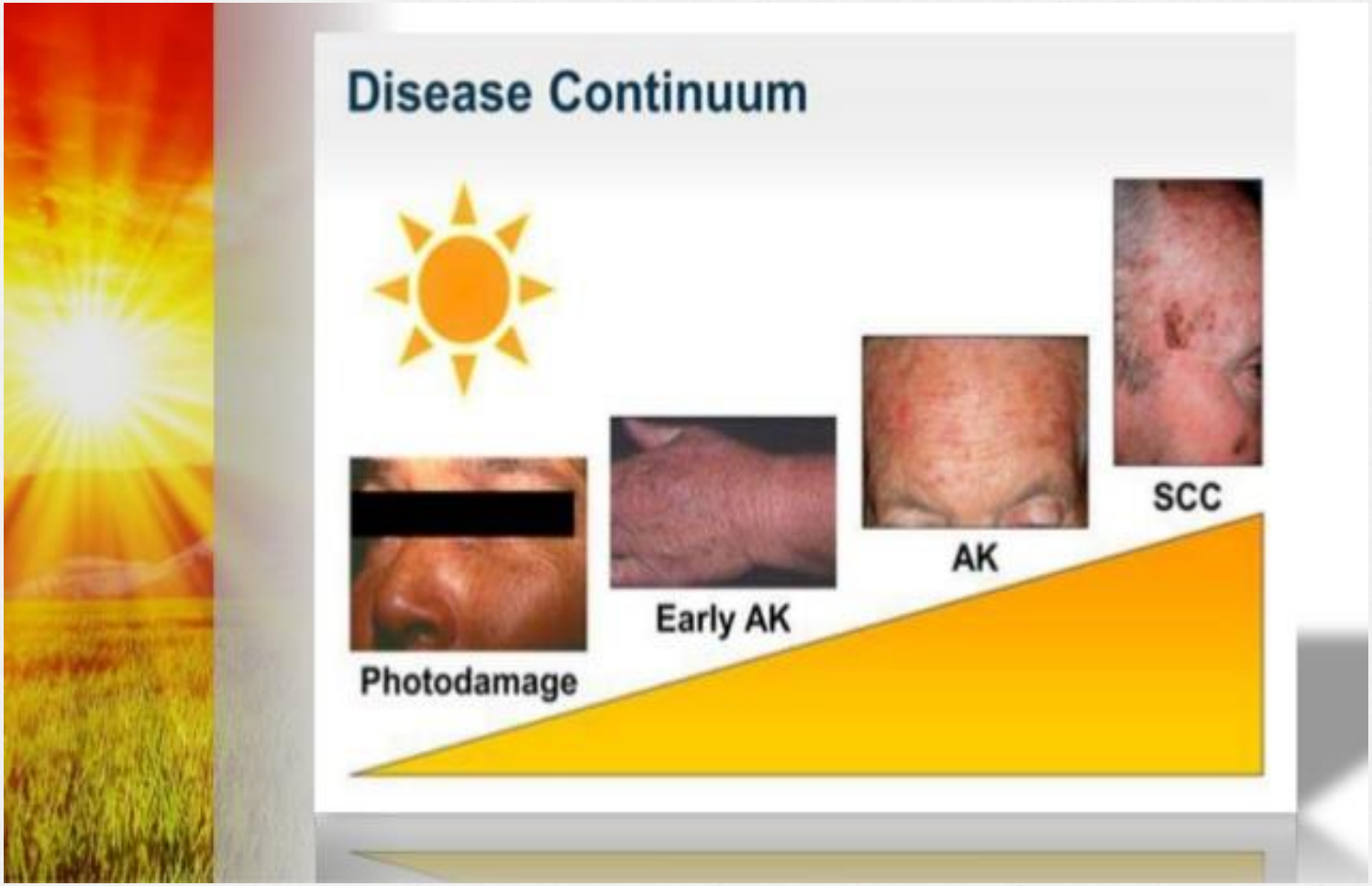
1. Hypertrophic (HAK)

2. Pigmented

3. Lichenoid

4. Atrophic

5. Actinic cheilitis

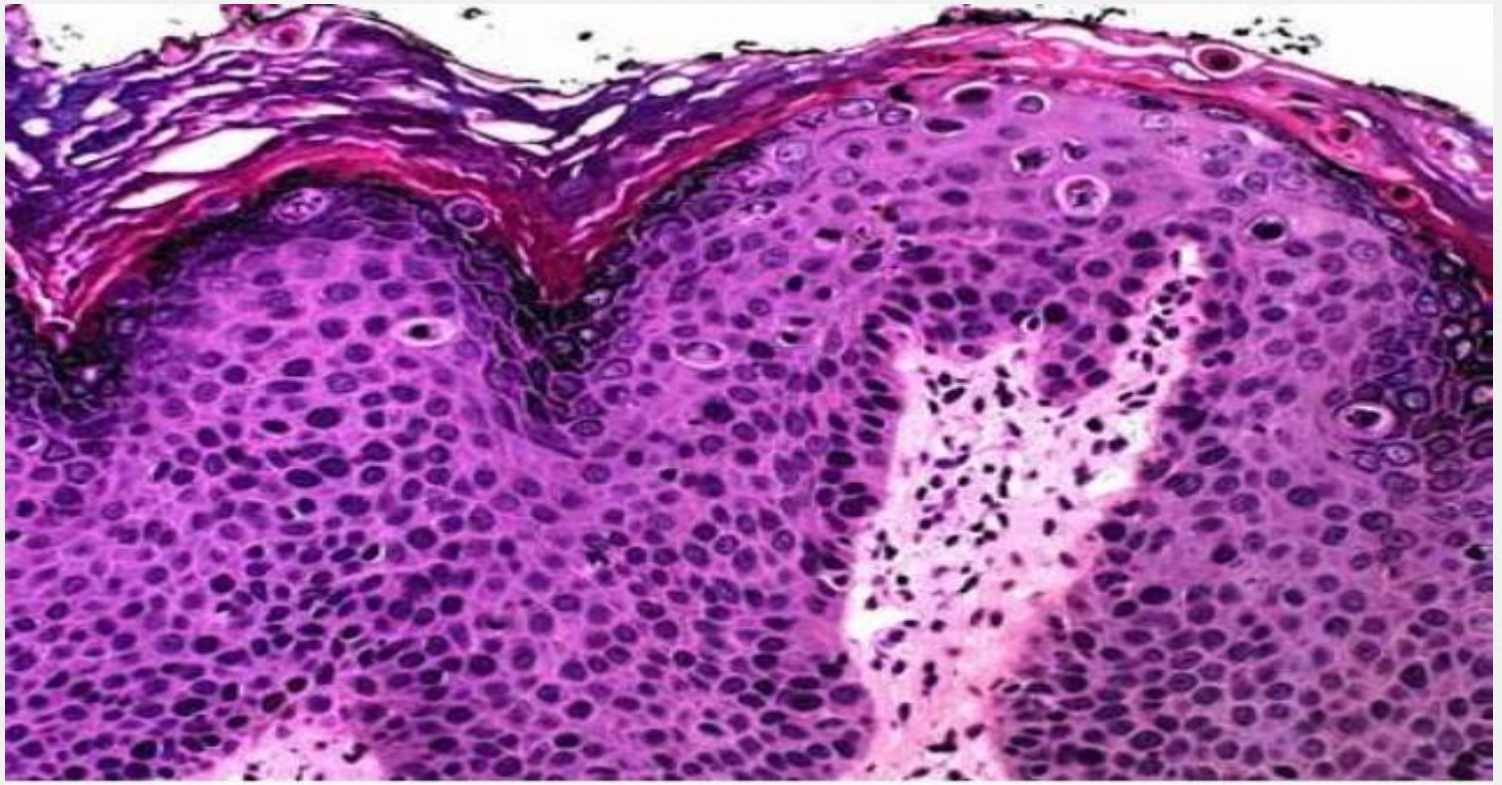

Disease Continuum
Photodamage
Early AK
AK
SCC

BOWEN'S DISEASE

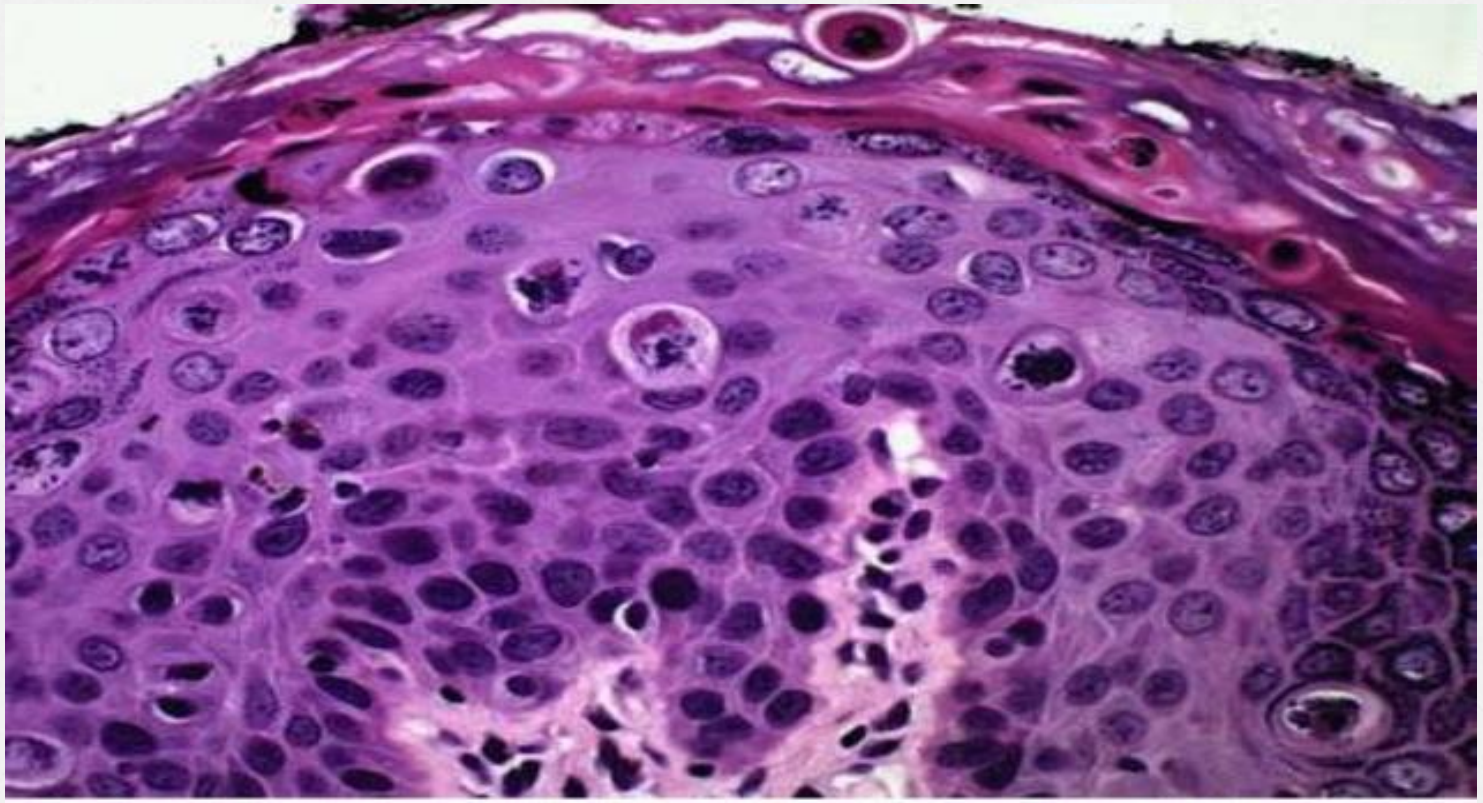
- Solitary lesion
- May occur on exposed or on unexposed skin
- Exposed skin by exposure to the sun and on unexposed skin by the ingestion of arsenic
- Can form in lesions of epidermodysplasia verruciformis caused by HPV-5
- Slowly enlarging erythematous patch of sharp but irregular outline, showing little or no infiltration.
- Within the patch are generally areas of scaling and crusting

- An intraepidermal squamous cell carcinoma referred to also as squamous cell carcinoma in situ
- Epidermis shows acanthosis with elongation and thickening of the rete ridges,
- Cells lie in complete disorder, resulting in a windblown appearance
- Horny layer usually is thickened and consists largely of parakeratotic cells with atypical, hyperchromatic nuclei

- Atypical individual cell keratinization
- Dyskeratotic cells are large and round and have a homogeneous, strongly eosinophilic cytoplasm and a hyperchromatic nucleus
- Border between the epidermis and dermis everywhere appears sharp, and the basement membrane remains intact
- Occasionally vacuolization of the cells, especially in the upper portion of the epidermis seen
- So long as Bowen's disease remains in its intraepidermal stage, metastases do not occur



Bowen's disease. The epidermis is irregularly thickened. The normal maturation pattern is effaced



Bowen's disease. Throughout the epidermis, the cells lie in disarray, with frequent large atypical mitoses

XERODERMA PIGMENTOSUM

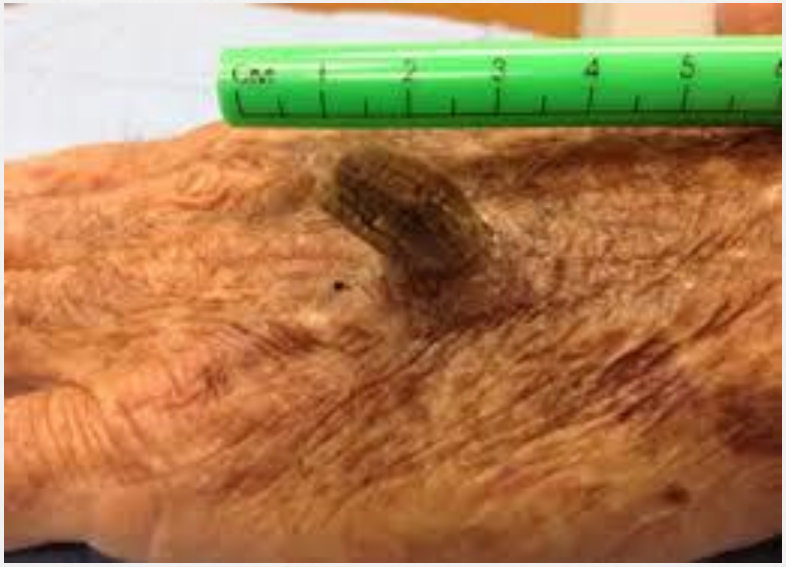
- An autosomal recessive disorder
- Neucleotide excision repair enzymes are mutated
- Lesions occur chiefly in areas of the skin habitually exposed to sunlight
- Three stages – I) Diffuse erythema is associated with scaling
  II) Atrophy of the skin, mottled pigmentation, and telangiectases
  III) Various types of malignant tumors of the skin appear, often causing death

- Hyperkeratosis, thinning of the stratum malpighii with atrophy of some of the rete ridges
- Squamous cell carcinoma, basal cell epithelioma, and, rarely, fibrosarcoma and malignant melanoma

Cutaneous Horn

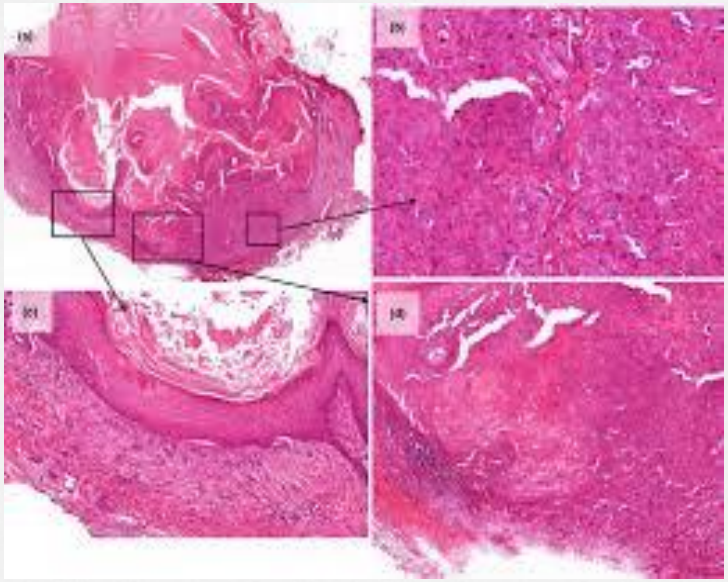
- **Cutaneous horns** are conical, circumscribed protuberances formed by densely layered **keratin**.
- These lesions originate from basal keratinocytes and may manifest as benign, **premalignant**,or malignant **cutaneous** pathology in chronically sun-damaged areas.

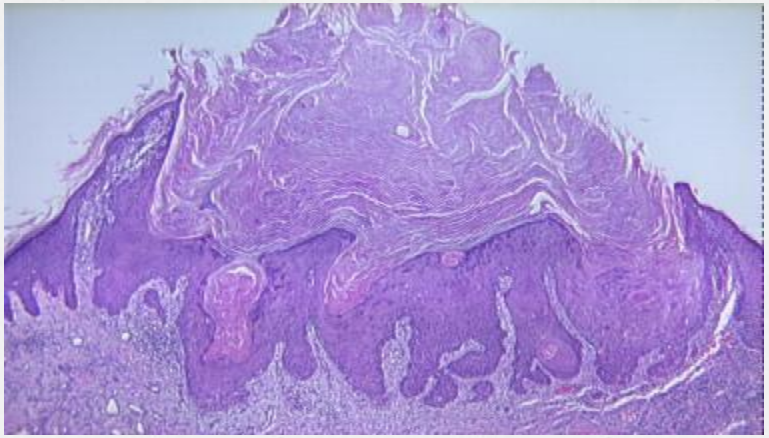

A
B



keratoacanthoma

- Keratoacanthoma (KA) is a special lesion, a pseudo cancer, occurring as an isolated nodule, usually on the face,
- mimicking **squamous cell carcinoma**. Unique features are its rapid growth rate, much faster than that of an SCC, and also its spontaneous remission over a period of several months.





Squamous Cell Carcinoma

- Squamous cell carcinoma is *a common tumor arising on sun exposed sites in older people.*
- *These tumors have a higher* incidence in men than in women.
- In addition to sunlight, predisposing factors include industrial carcinogens (tars and oils), chronic ulcers, old burn scars, ingestion of arsenicals, and ionizing radiation.
- As with squamous cell carcinomas at other sites, those in the skin may be preceded by in situ lesions.

PATHOGENESIS

- The most common exogenous cause of cutaneous squamous cell carcinoma is UV light exposure, which causes DNA damage .

- *TP53 mutations caused by UV light*– induced DNA damage are common, as are activating mutations in *HRAS and loss-of-function mutations in Notch* receptors, which transmit signals that regulate the orderly differentiation of normal squamous epithelia.

.

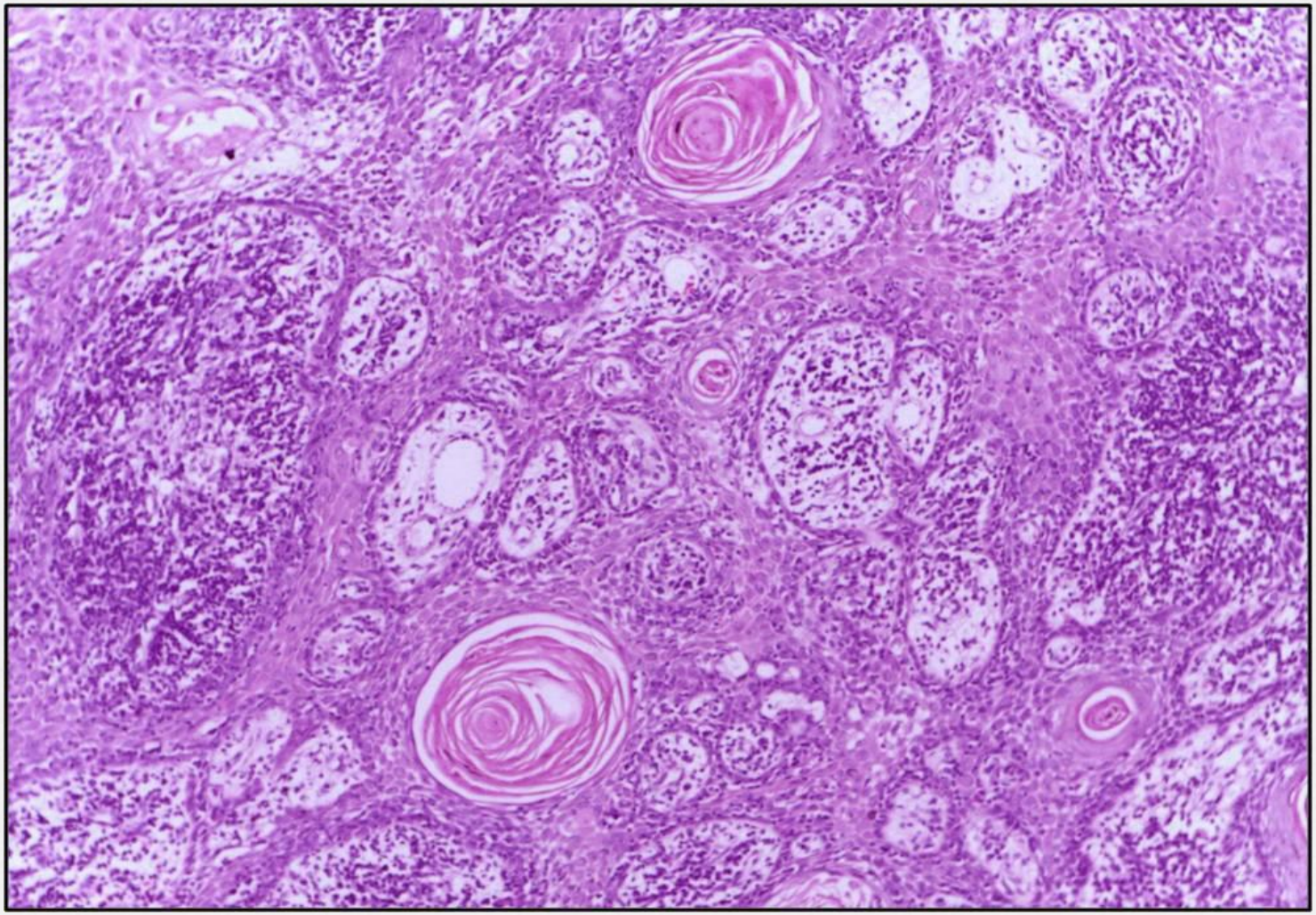
PATHOGENESIS

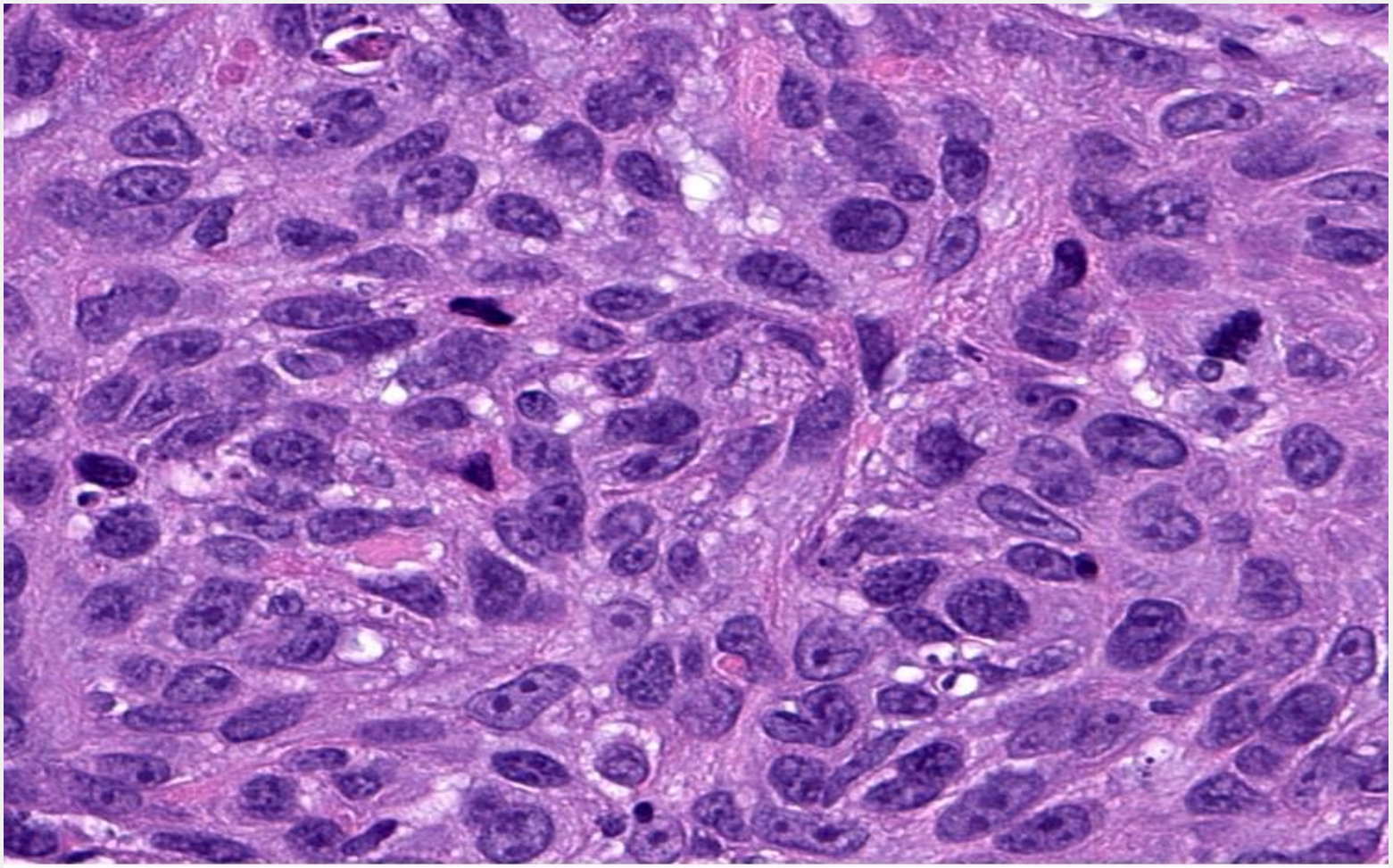
- In addition to inducing mutations, UV light (UVB in particular) may have a transient immunosuppressive effect on skin by impairing antigen presentation by Langerhans cells.
- This effect may contribute to tumorigenesis by weakening immunosurveillance

- Patients who are immunosuppressed as a result of chemotherapy or organ transplantation, or who have xeroderma pigmentosum, are at increased risk.
- Tumors in immunosuppressed persons, particularly organ transplant recipients, are likely to be associated with HPV infection.

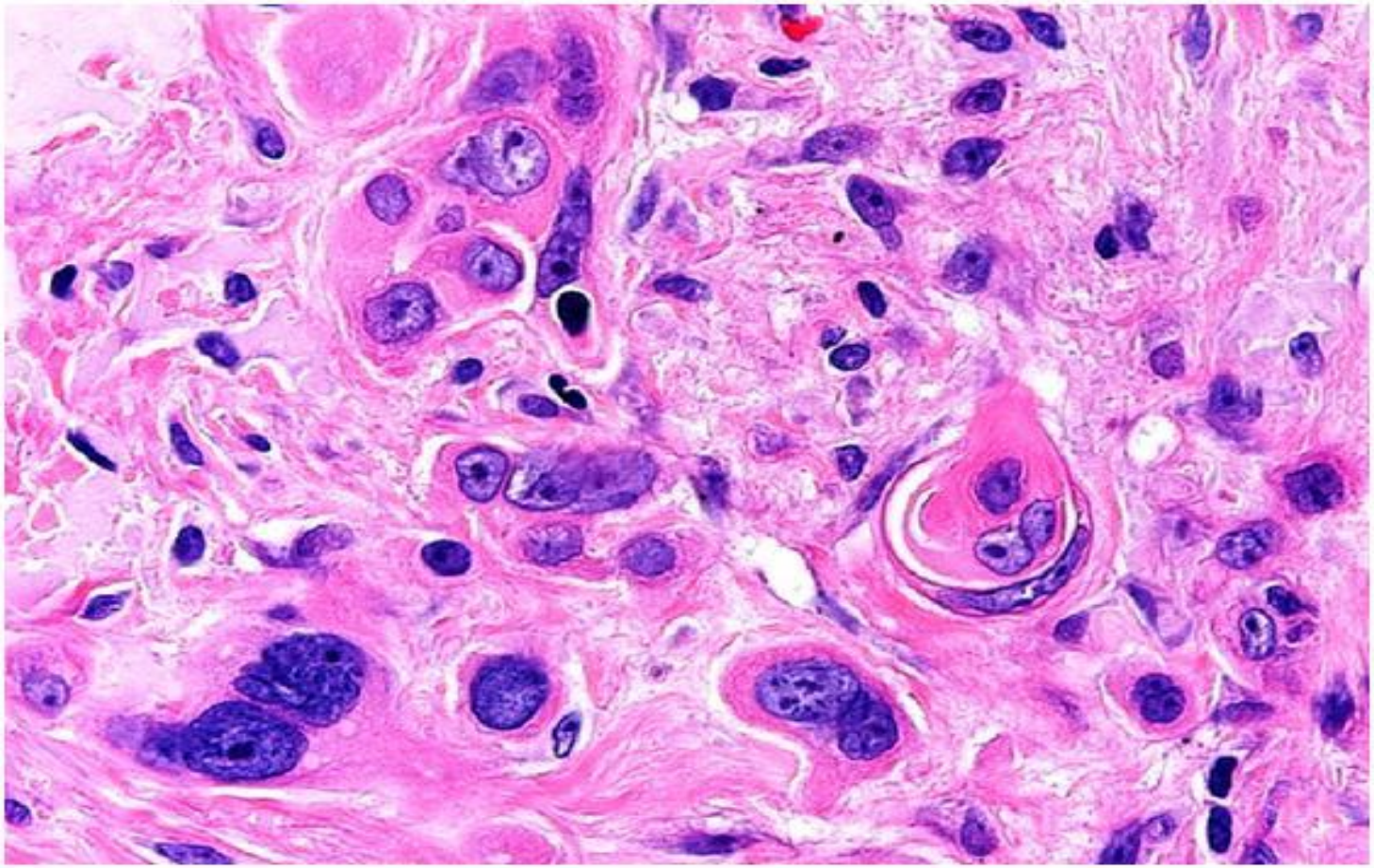
MORPHOLOGY

- Squamous cell carcinomas in situ appear as sharply defined, red, scaling plaques; many arise from prior actinic keratoses.
- More advanced, invasive lesions are nodular, show variable scale, and may ulcerate .
- *Microscopically, squamous* cell carcinoma in situ is characterized by highly atypical cells at **all levels of the epidermis, with nuclear crowding** and disorganization.
- Invasive tumors, defined by penetration of the basement membrane , *show variable* degrees of differentiation, ranging from tumors with cells arranged in orderly lobules that exhibit extensive keratinization
- to neoplasms consisting of highly anaplastic cells with foci of necrosis and only abortive, single-cell keratinization (dyskeratosis).



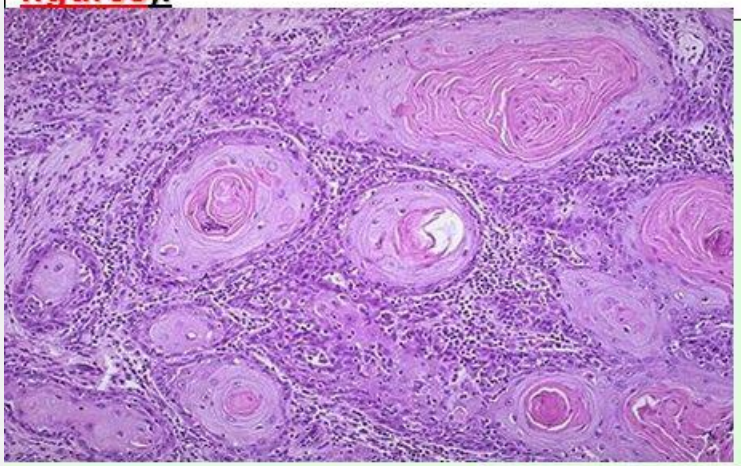


Squamous cell carcinoma, moderately differentiated: there is more obvious pleomorphism but the squamous nature of the tumor is still apparent

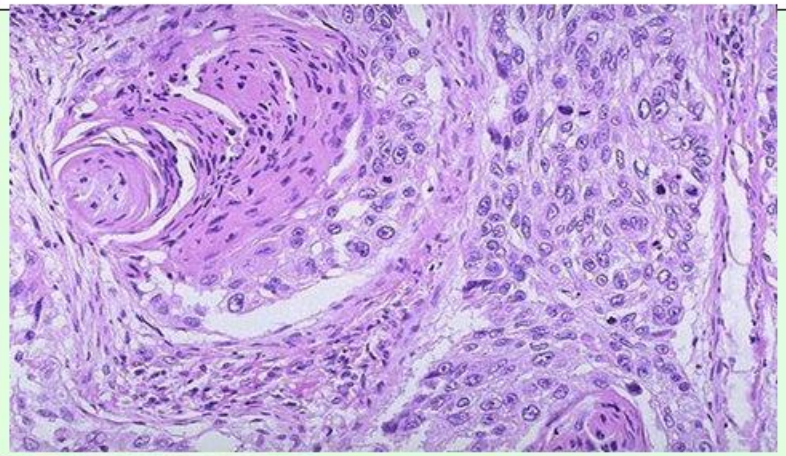


Microscopic Picture of Squamous cell carcinoma:

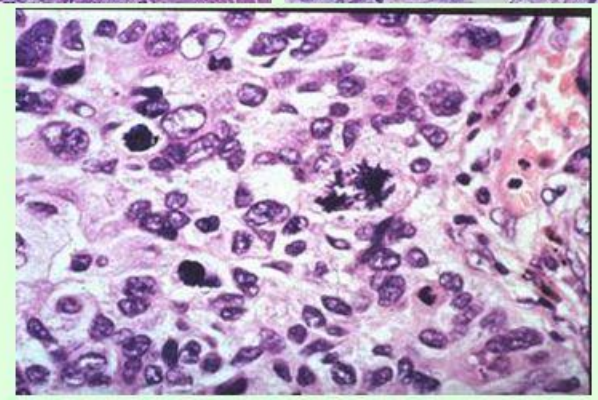
It ranges from well differentiated squamous cell carcinoma showing central keratin pearls and intercellular bridges to poorly differentiated squamous cell carcinoma. (Grading of the tumour is based on the cytological diff.& no. of mitotic figures).



Well diff sq c c



Mod diff sq c c



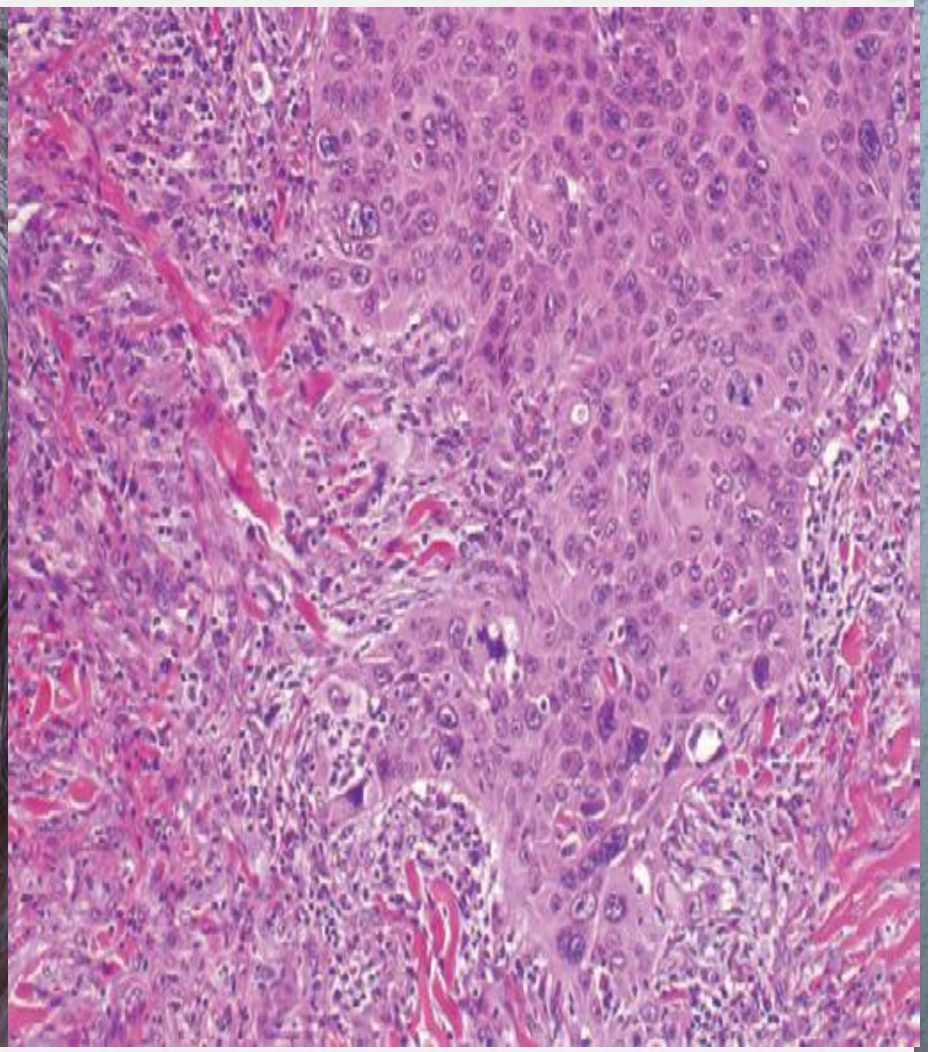
Poorly diff sq c c

Clinical Features

- Invasive squamous cell carcinomas of the skin often are discovered while small and resectable.
- Less than 5% have metastasized to regional nodes at diagnosis.
- The likelihood of metastasis is related to the thickness of the lesion and degree of invasion into the subcutis.

Clinical Features

- Tumors arising in the context of actinic keratoses may be locally aggressive but generally metastasize only after long periods of time, while those arising in burn scars, ulcers, and non–sun-exposed skin behave less predictably.
- Mucosal squamous cell carcinomas (oral, pulmonary, esophageal, etc.) generally are much more aggressive.



Basal Cell Carcinoma

- Basal cell carcinoma is a common *slow-growing cancer that rarely metastasizes.*
- *It tends to occur at sites subject to chronic* sun exposure and in lightly pigmented individuals.

PATHOGENESIS

- **Basal cell carcinoma is associated with dysregulation of the Hedgehog pathway.**
- **Inherited defects in the *PTCH*** gene, a tumor suppressor that regulates Hedgehog pathway signaling, cause familial basal cell carcinomas in Gorlin syndrome.

PATHOGENESIS

- The Hedgehog pathway is an important regulator of embryonic development, and subtle developmental anomalies are also often noted in affected persons.
- Some component of the hedgehog pathway is mutated in the great majority of sporadic basal cell carcinomas as well.
- Mutations in *TP53* are also common in both familial and sporadic tumors.

Key components in the Hedgehog signaling pathway

The Hedgehog ligand, Hedgehog (Hh)

Initiates signal transduction of the Hedgehog pathway

The Hedgehog ligand receptor, Patched (PTCH)

Normally suppresses the activity of SMO

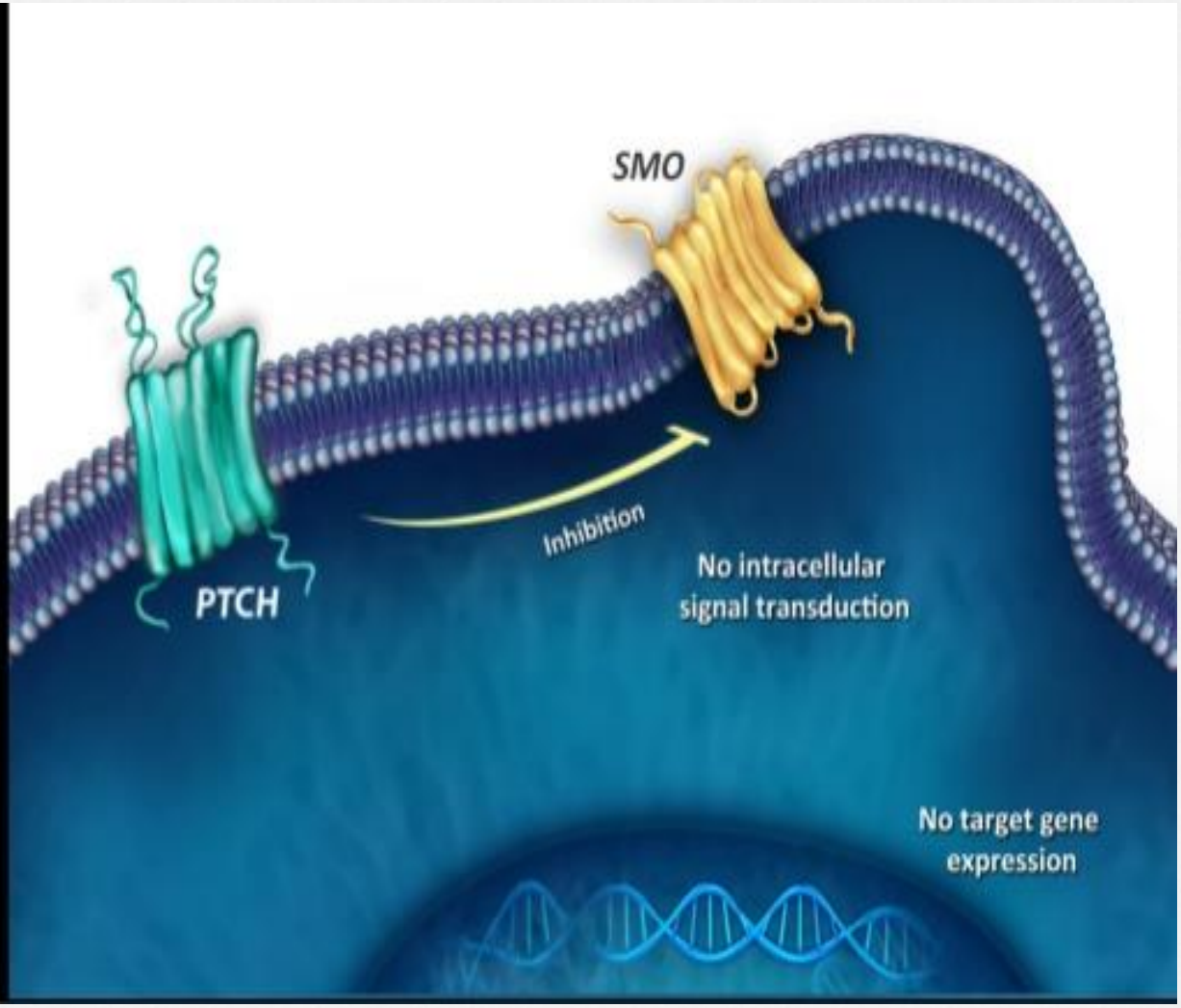
The cell surface signal transducer, Smoothened (SMO)

Normally suppressed by PTCH, preventing its activation of the Hedgehog signalling cascade

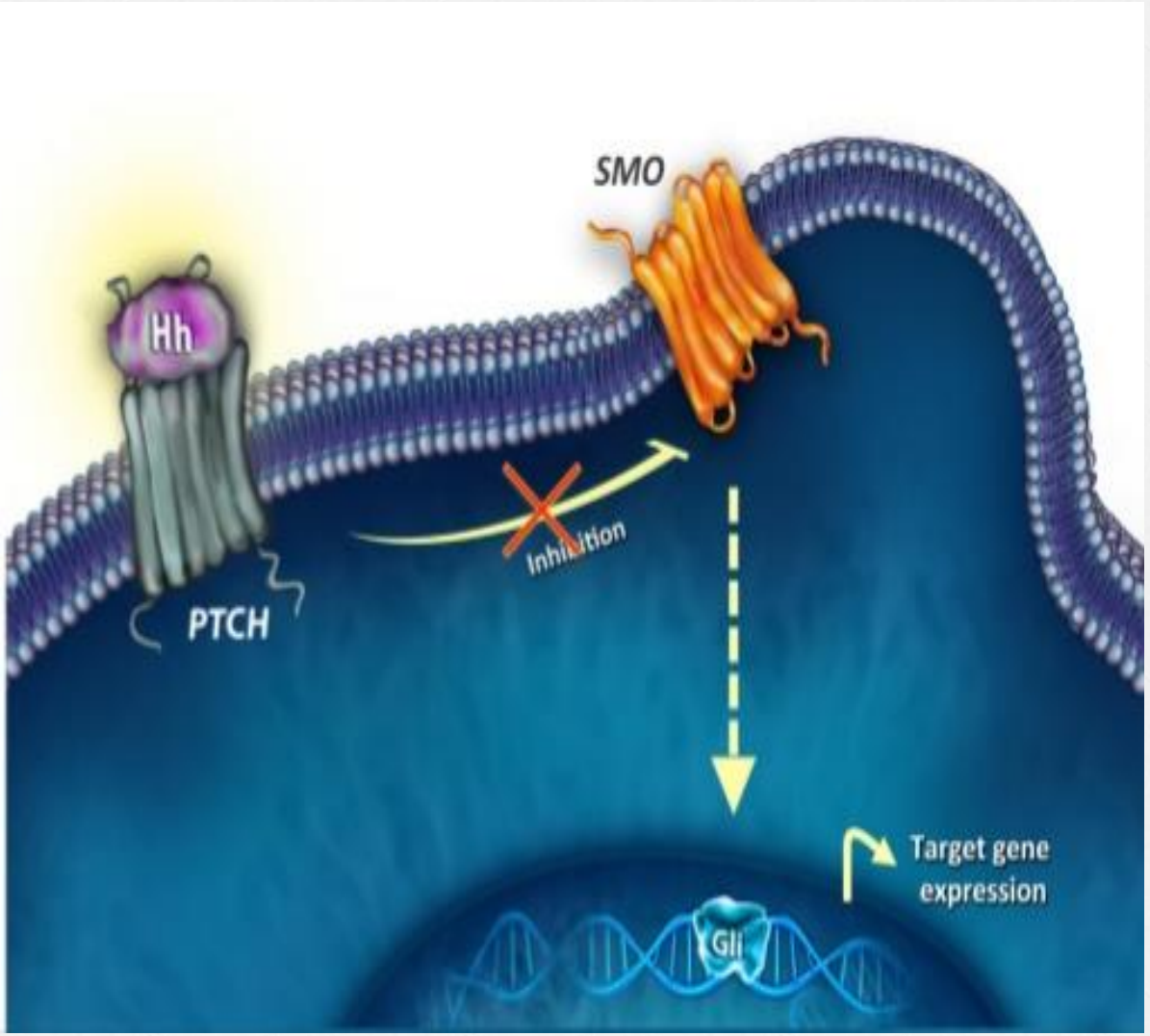
The downstream effectors, the Gli transcription factors

Cytosolic complex of proteins including the Gli family of transcription factors. Activation leads to expression of specific genes that promote cell proliferation and differentiation

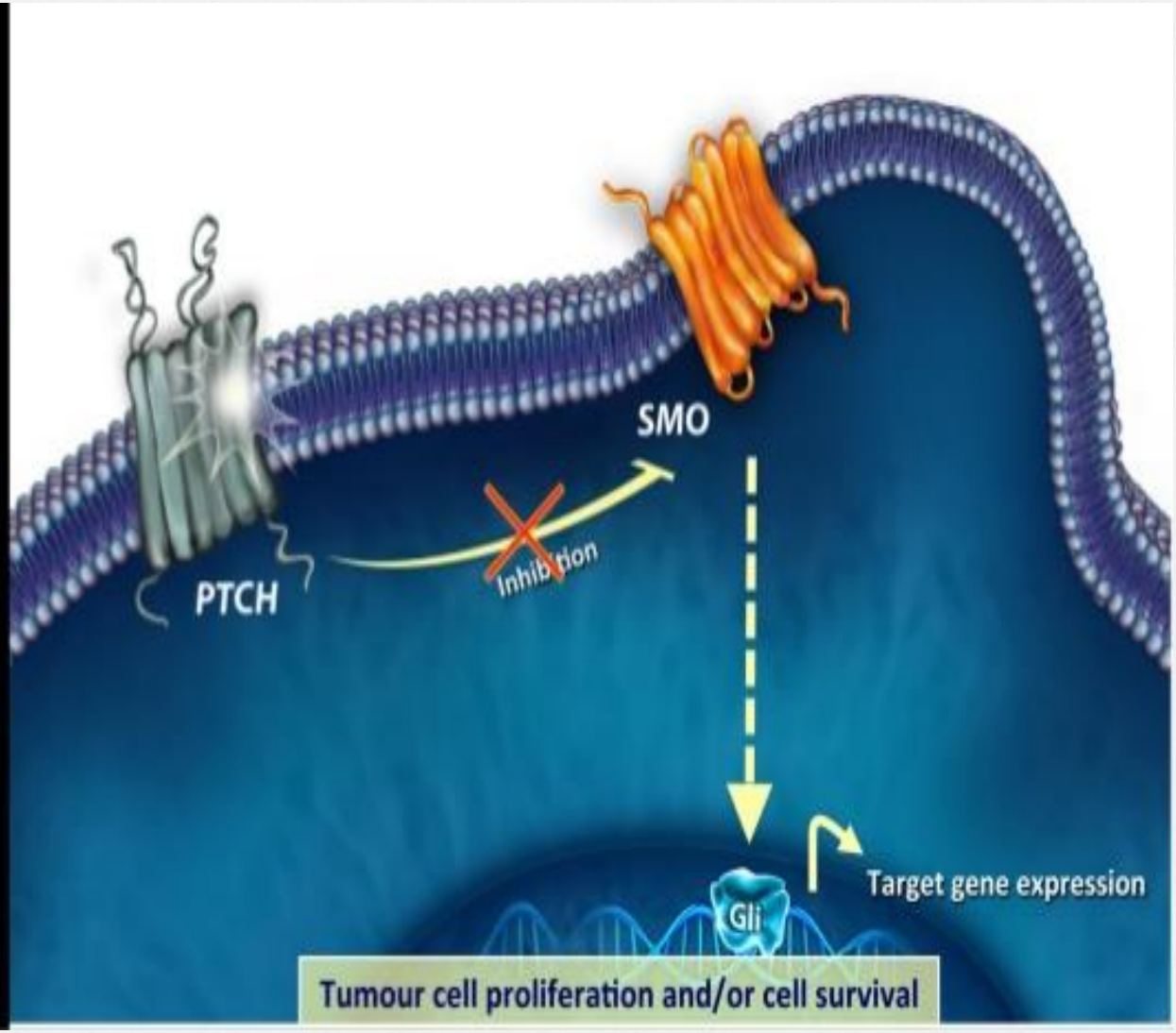
When the Hedgehog pathway is **inactive**, **PTCH inhibits SMO** activity and there is **no** target gene **expression**



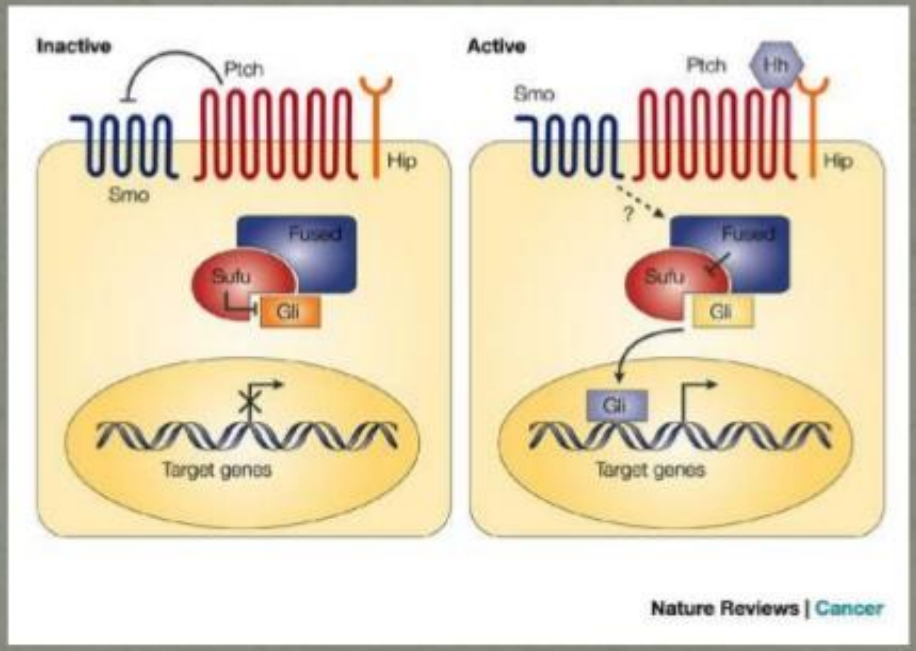
When the **Hh ligand activates** the Hedgehog pathway the cell responds by **activating expression** of target genes



Inactivating mutations of **PTCH** result in constitutive pathway **activation** via **removal** of PTCH **inhibition** on **SMO**



SONIC HEDGEHOG PATHWAY



MORPHOLOGY

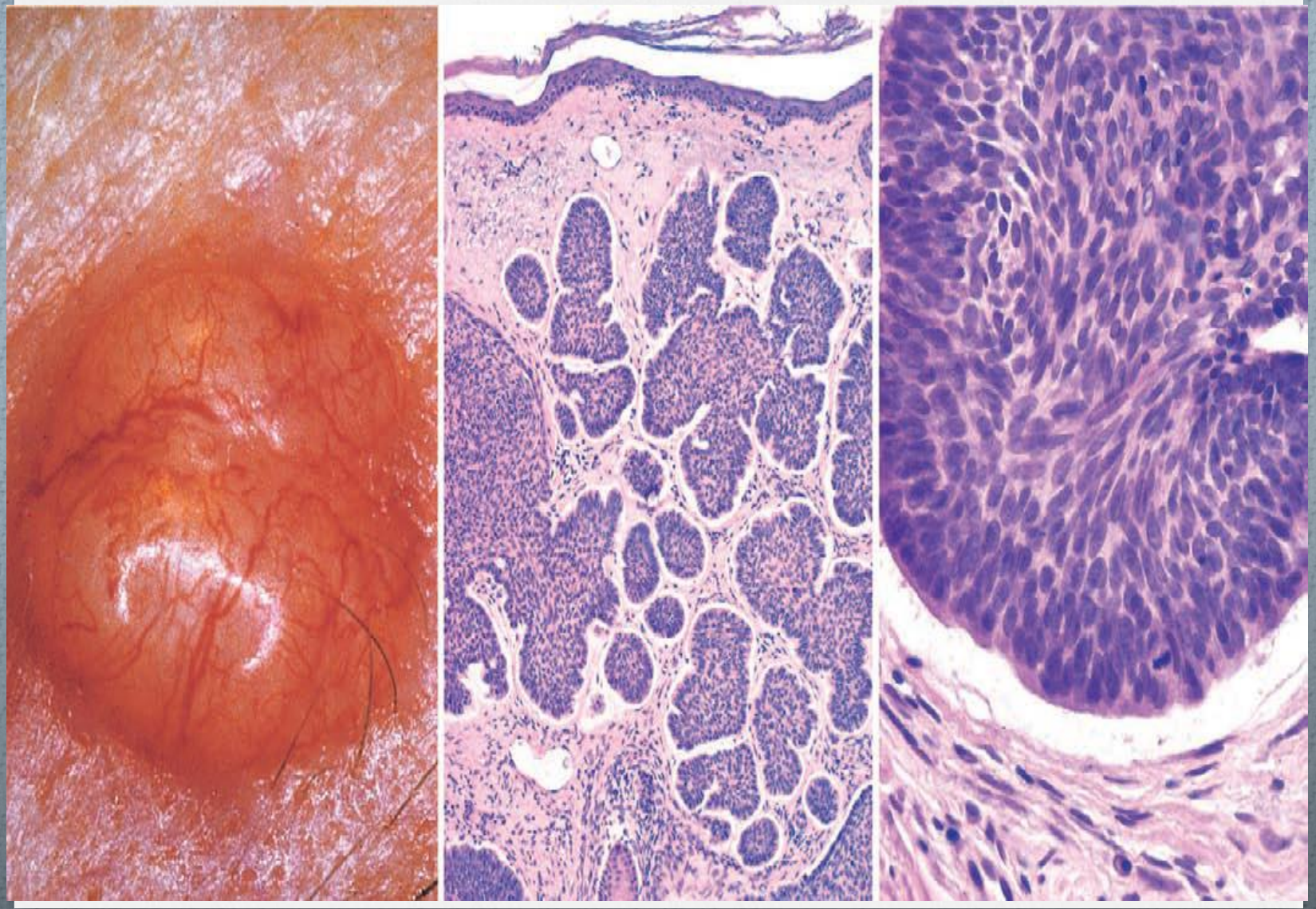
- Grossly, basal cell carcinomas manifest as **pearly papules, often with prominent, dilated subepidermal blood vessels (telangiectasia) .**
- ***Some tumors*** contain melanin pigment and thus appear similar to melanocytic nevi or melanomas.
- Microscopically, the tumor cells resemble the normal epidermal basal cell layer from which they are derived.
- Because they may arise from either the epidermis or the follicular epithelium, they are not encountered on mucosal surfaces.

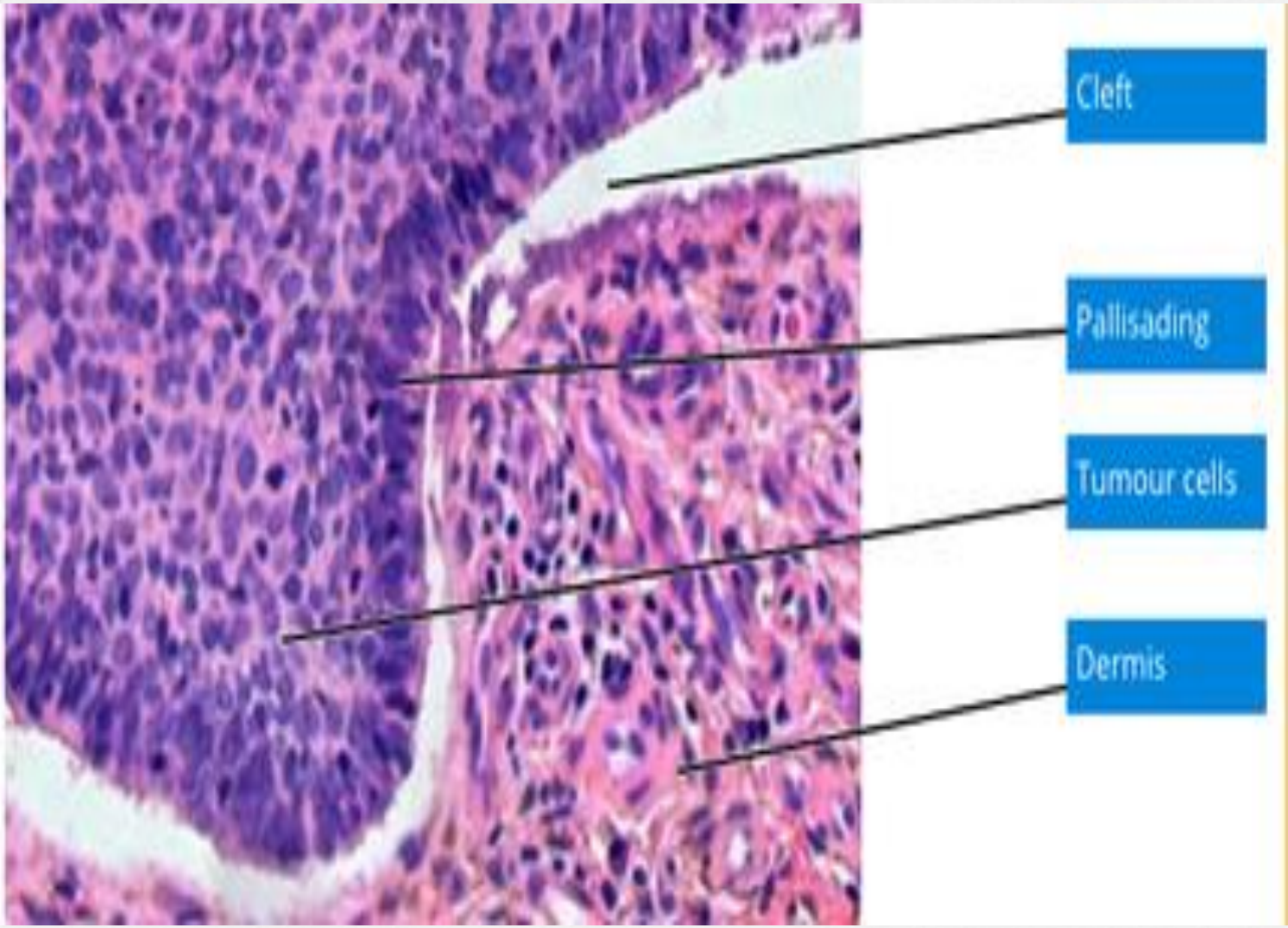
MORPHOLOGY

- Two common patterns are seen: multifocal growths originating from the epidermis (superficial pattern), or
- nodular lesions growing downward into the dermis as cords and islands of variably basophilic cells with hyperchromatic nuclei, embedded in a fibrotic or mucinous stromal matrix.
- Peripheral tumor cell nuclei align in the outermost layer (a pattern termed palisading), which often separates from the stroma, creating a characteristic cleft

Clinical Features

- It is estimated that in excess of 1 million basal cell carcinomas are treated in the United States annually.
- By far the most important risk factor is sun exposure;
- basal cell carcinoma is more common in warm southern regions of the United States, and its incidence is 40-fold higher in sunny climates near the equator, such as Australia, than it is in Northern European locales.
- Individual tumors usually are cured by local excision, but approximately 40% of patients will develop another basal cell carcinoma within 5 years.
- Advanced lesions may ulcerate, and extensive local invasion of bone or facial sinuses may occur if the lesions are neglected for many years.



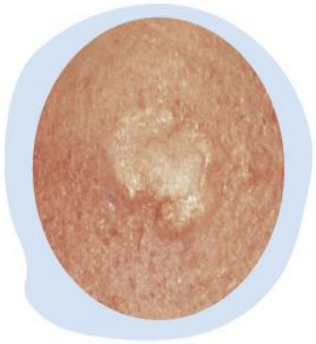

Cleft
Pallisading
Tumour cells
Dermis

BASAL CELL CARCINOMA TYPES (BCC)

Nodular BCC

Superficial BCC

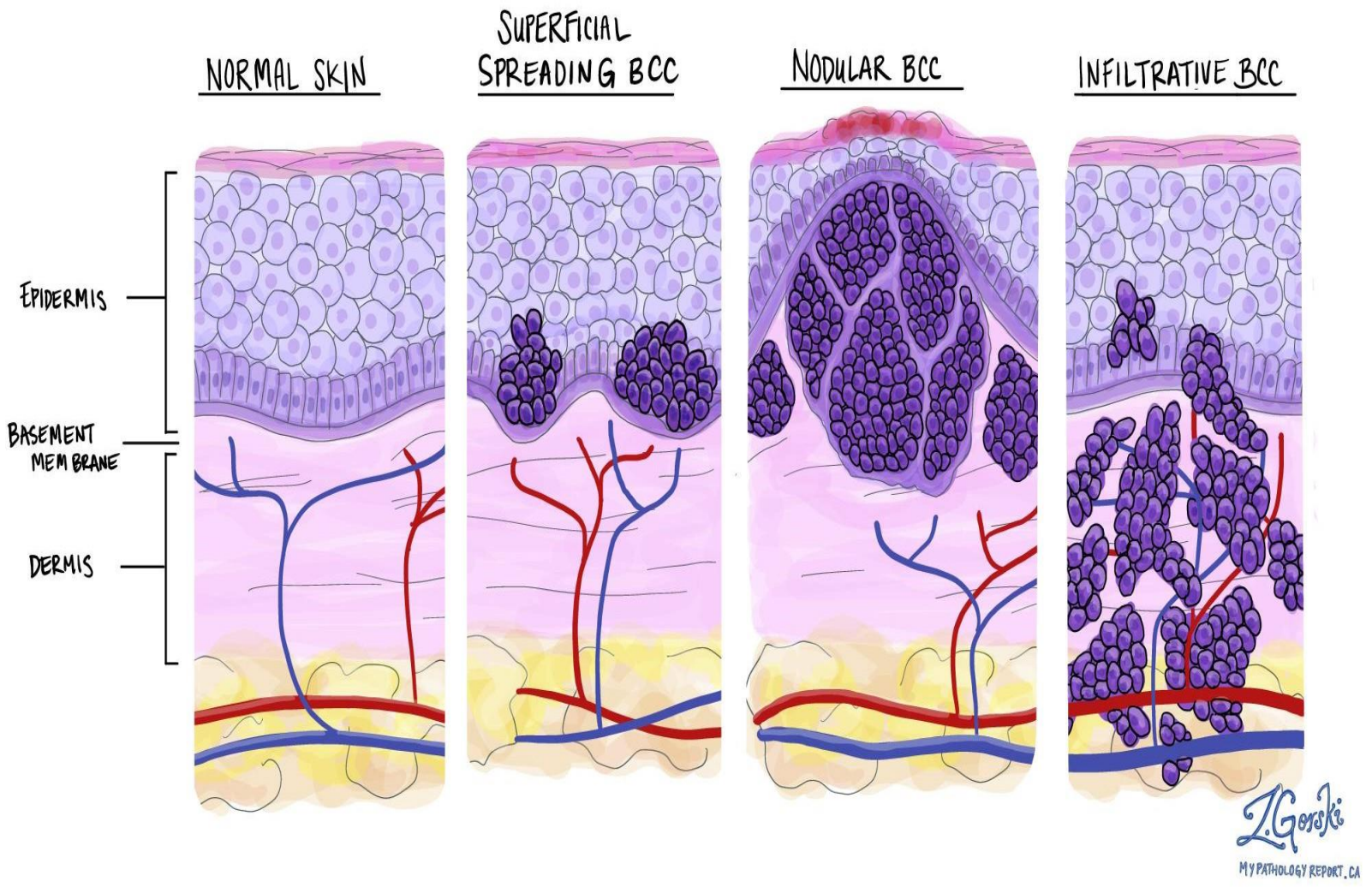
Pigmented BCC



Morphoeic BCC

Basosquamous BCC

miiskin


NORMAL SKIN
SUPERFICIAL SPREADING BCC
NODULAR BCC
INFILTRATIVE BCC
EPIDERMIS
BASEMENT MEMBRANE
DERMIS
L.Gorski
MYPATHOLOGYREPORT.CA

Classification	Definition
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor $\leq$ 2 cm in greatest dimension
T2	Tumor $>$ 2 cm in greatest dimension but $\leq$ 5 cm in greatest dimension
T3	Tumor $>$ 5 cm in greatest dimension
T4	Tumor invading deep extradermal structures (e.g., cartilage, skeletal muscle, or bone)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Histopathologic grade (G)	
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Notes: Staging excludes eyelid, vulva, and penis.
In the case of multiple simultaneous tumors, the tumor with the highest T category will be classified, and the number of separate tumors will be indicated in parentheses [e.g., T2(5)].
Source: Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. Reprinted from ID Fleming, JS Cooper, DE Henson, et al. (eds), *AJCC Cancer Staging Manual* (5th ed). Philadelphia: Lippincott-Raven, 1997:157–161.

Characteristics	BCC	SCC
Also called	Rodent ulcer	Epidermoid ca
Incidence	80% most common of all skin tumor	20% of all skin tumors
Common site	Inner canthus of eye	Sun exposed areas
Gross appearance	Red, pale or pearly in color	Thickened red spot may bleed, crust or ulcerate.
Histological feature	Geographic appearance with palisading pattern	Keratin pearls
Behavior	Less aggressive	Very aggressive
Spread	Non metastasizing Locally invasive	metastasize

Characteristics	BCC	SCC
Progress	Slow growing	Rapid growing
Treatment	Highly radiosensitive	Less radiosensitive wide local excision done
Diagnosis	biopsy	biopsy
Risk factors	White races. UV exposure. Gorlin syndrome	UV exposure. Xeroderma pigmentosum. Actinic keratosis. Bowen's disease. Chronic ulcers. Old scars. HPV infections.

Summary

Premalignant lesions	• Actinic keratosis • Bowen's disease • Xeroderma pigmentosum • Cutaneous horns • keratoacanthoma
SCC	• Aggressive metastasizing tumor accounts for 20% of skin Cancers • Keratin pearls
BCC	• Locally invasive non metastasizing 80% of skin cancers. • Peripheral palisading .


THANK
YOU