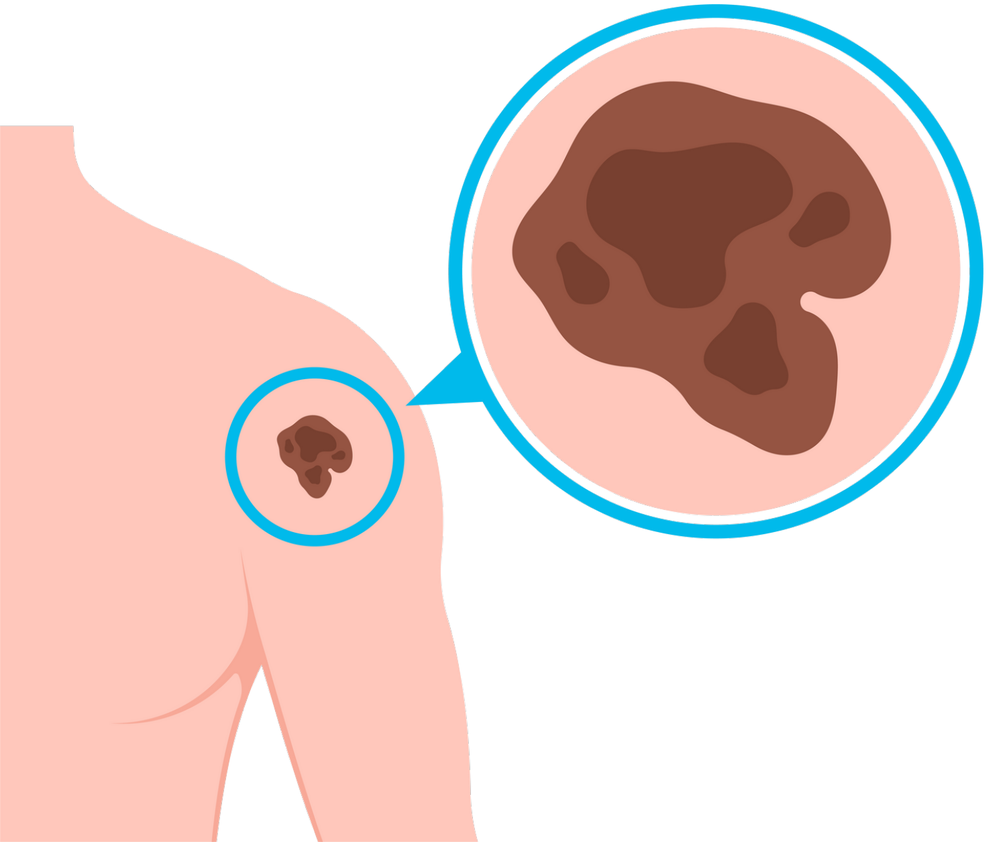
Pathology of skin tumor

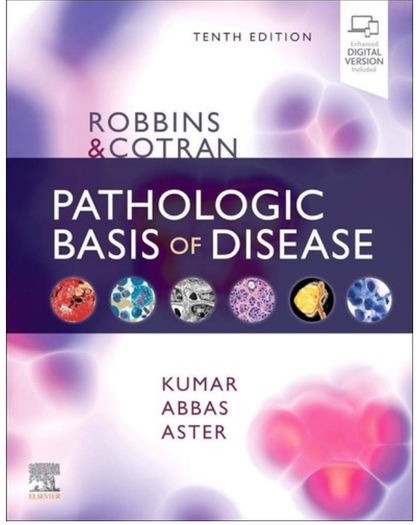
Sirawich Jessadapattarakul, MD, FRCPath

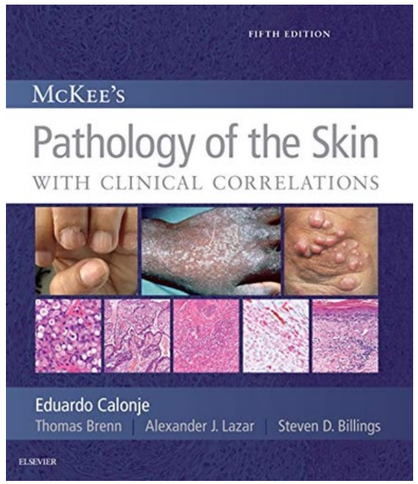
Department of Pathology, Faculty of Medicine, Khon Kaen University
Contact: siraja@kku.ac.th

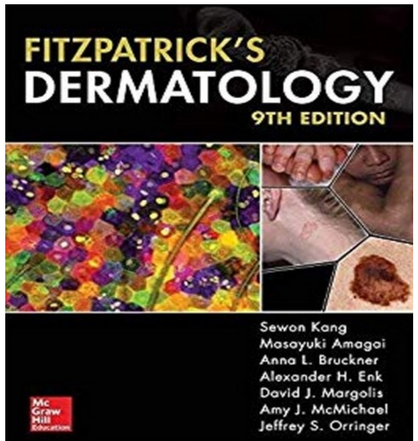
Learning Objectives



1. Learn descriptive terms used in understanding skin diseases and pathology of skin
2. Learn etiology and pathogenesis of common and interesting skin tumors
3. Learn pathology and clinical manifestations of common and interesting skin tumors
4. Learn pathology, pathogenesis, and clinical features of skin cysts, calluses, and corns







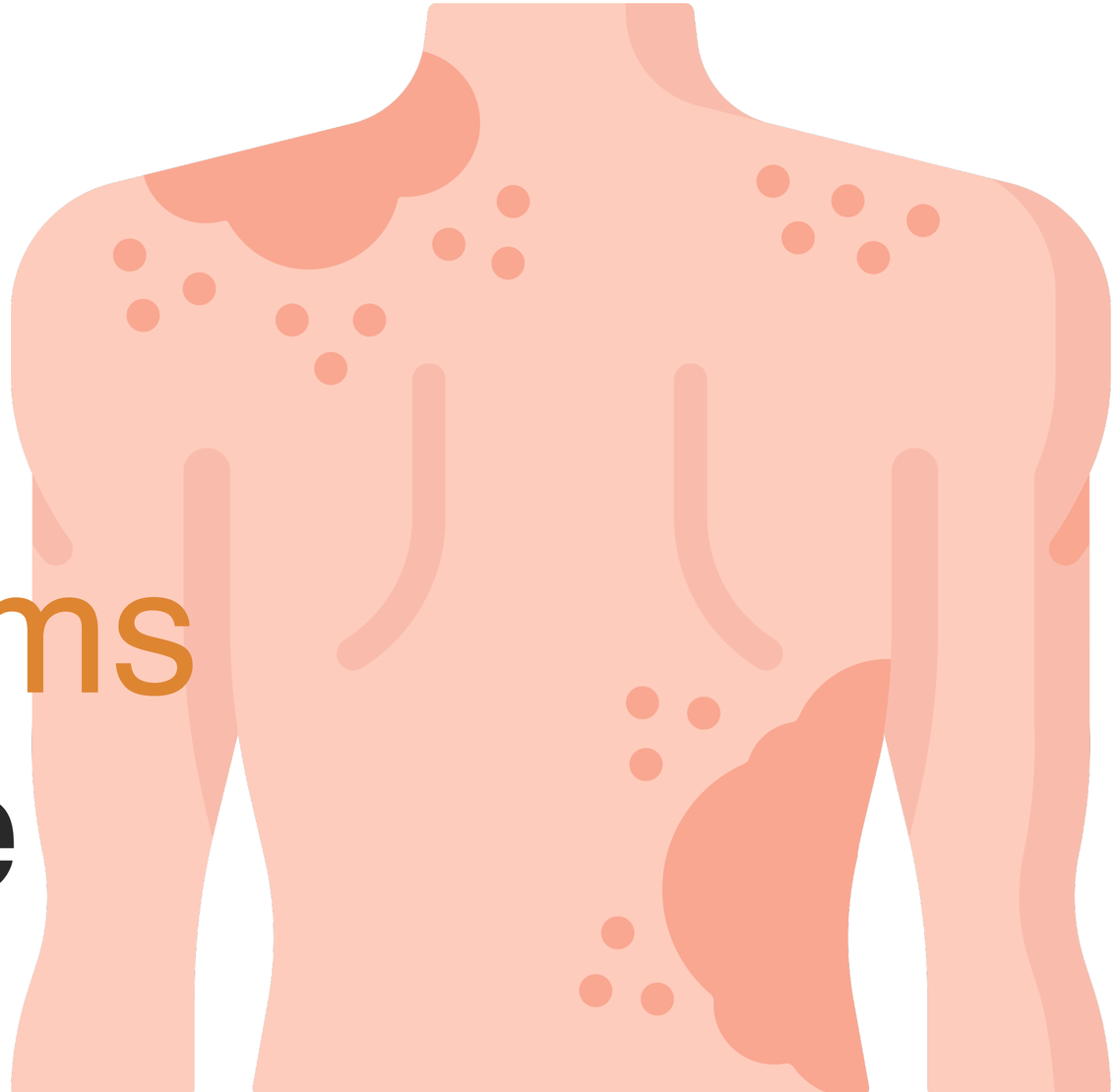
References & suggested readings

Robbins and Cotran pathologic basis of disease,10th edition, 2021, Kumar et al, Saunder Elsevier.

McKee's Pathology of skin with clinical correlation, 4th edition, 2012, McKee et al, Elsevier Health Sciences.

Fitzpatrick's Dermatology 9th edition. McGraw-Hill, 2018.

Macroscopic descriptive terms in skin disease



Macroscopic descriptive terms

1. **Macule**
   Circumscribed flat lesion with discoloration, size ≤ 5 mm (≤ 1 cm)

2. **Patch**
   Circumscribed flat lesion with discoloration, size > 5 mm (> 1 cm)

3. **Papule**
   Elevated dome-shaped or flat-topped lesion, size ≤ 5 mm (≤ 1 cm)

4. **Nodule**
   Elevated dome-shaped lesion, size > 5 mm (> 1 cm)

5. **Plaque**
   Elevated flat-topped lesion, size > 5 mm (> 1 cm)

Macroscopic descriptive terms

6. Vesicle

Fluid-filled raised lesion, size ≤ 5 mm (≤ 1 cm)

7. Bulla

Fluid-filled raised area, size > 5 mm (> 1 cm)

8. Blister

Common term used for “vesicle” or “bulla”

Usually seen in blistering skin diseases
(abnormality in epidermal keratinocyte adhesion)

9. Pustule

Discrete pus-filled raised area

10. Wheal (urticaria)

Itchy transient elevated area resulting from dermal edema

Macroscopic descriptive terms

11. Erosion

Superficial defect (loss) of epidermis only

12. Ulcer

Defect (loss) of epidermis and portion of dermis or even subcutaneous fat

13. Scale

Increased dead cells (keratin) on surface of the skin (stratum corneum):

- Epidermal keratinocyte proliferation and/or increased keratin production (mostly from neoplasm (tumor) of epidermal keratinocytes):
  - Benign tumor: Seborrheic keratosis
  - Premalignant lesion: Actinic keratosis
  - Malignancy: Squamous cell carcinoma
- Defective desquamation: Hereditary ichthyoses

Macroscopic descriptive terms

14. Crust

Air-dried remnants of blood, oozing serum, or pus

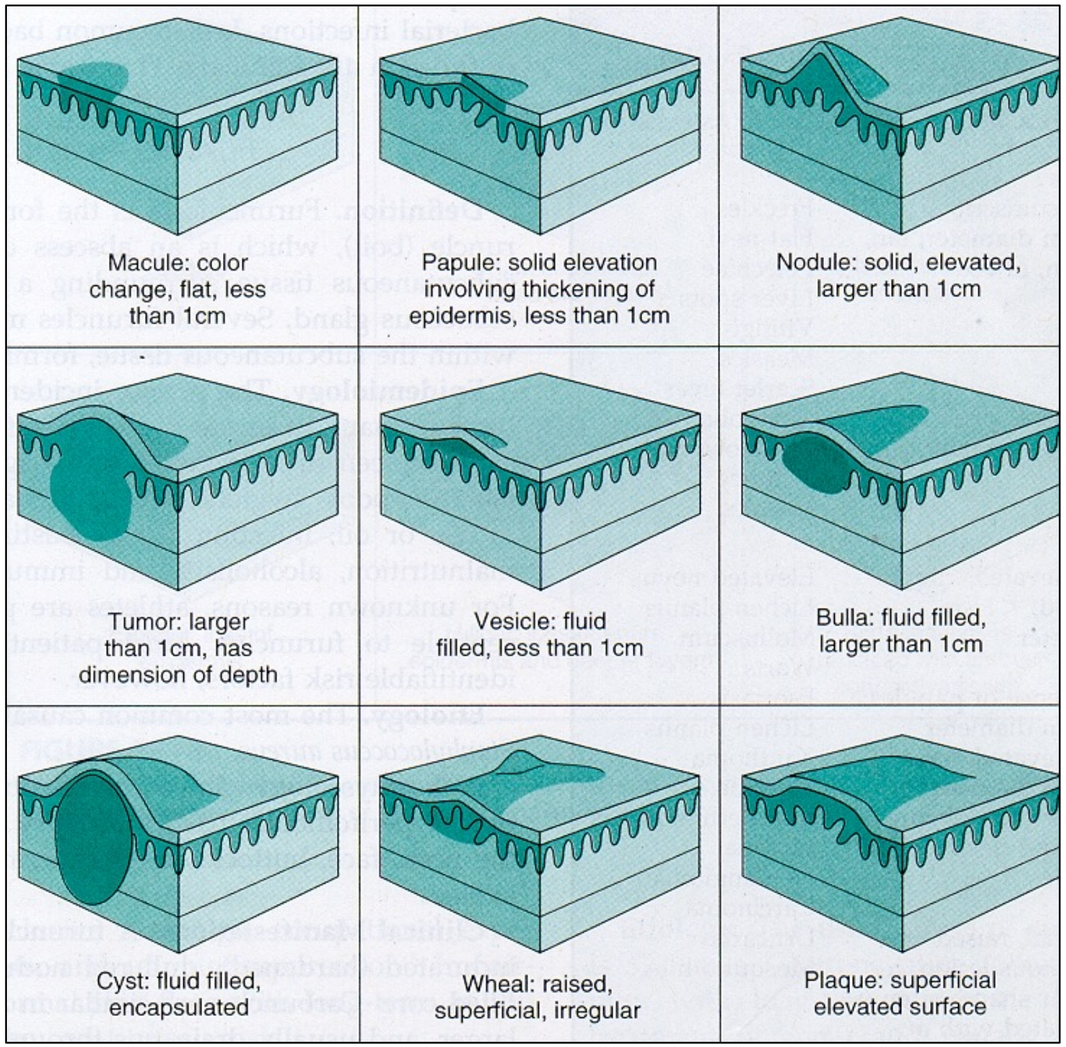
15. Fissure

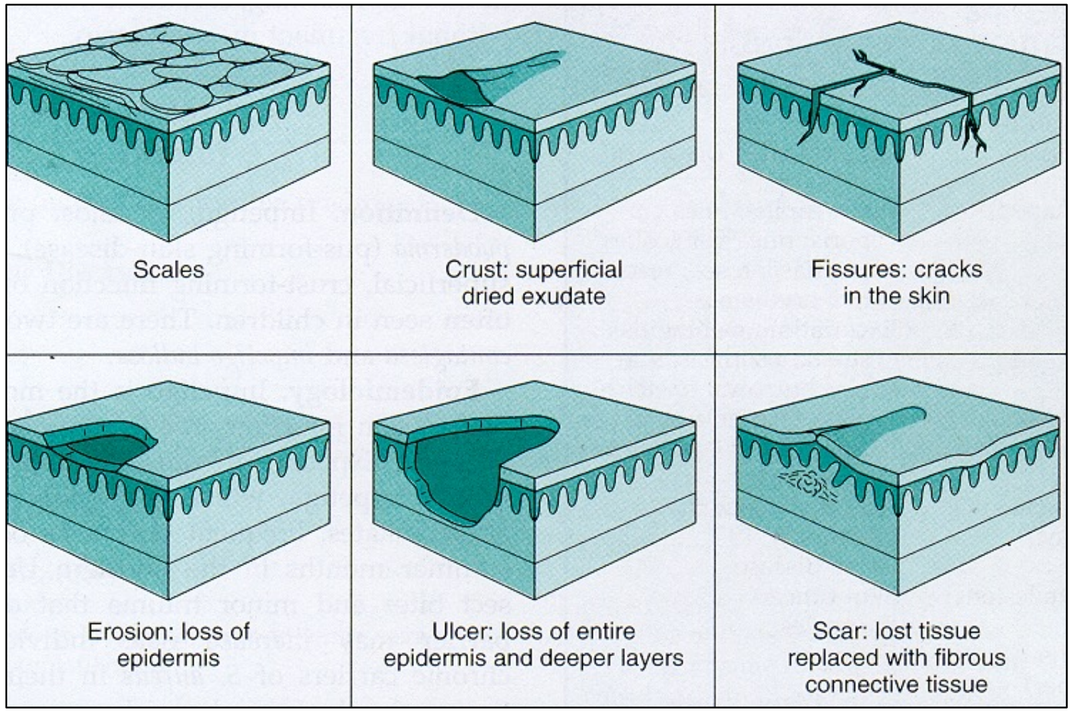
Small cleft penetrating into dermis

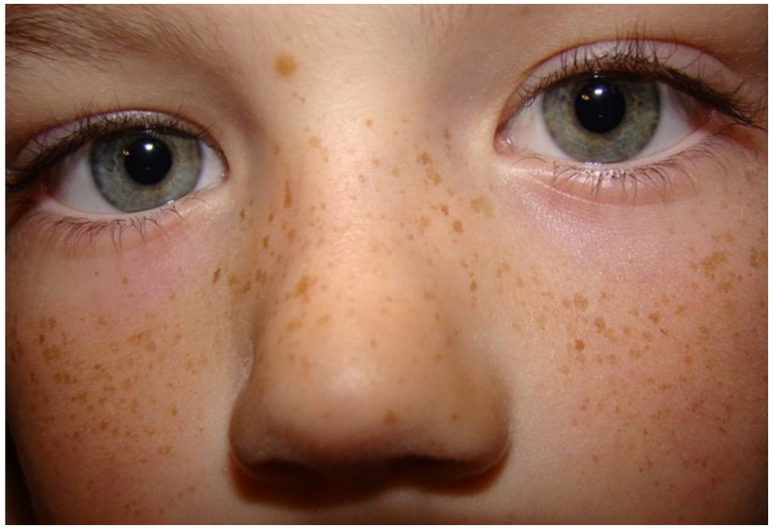
16. Cyst

Dome-shaped encapsulated lesion that contains fluid or semi-fluid material

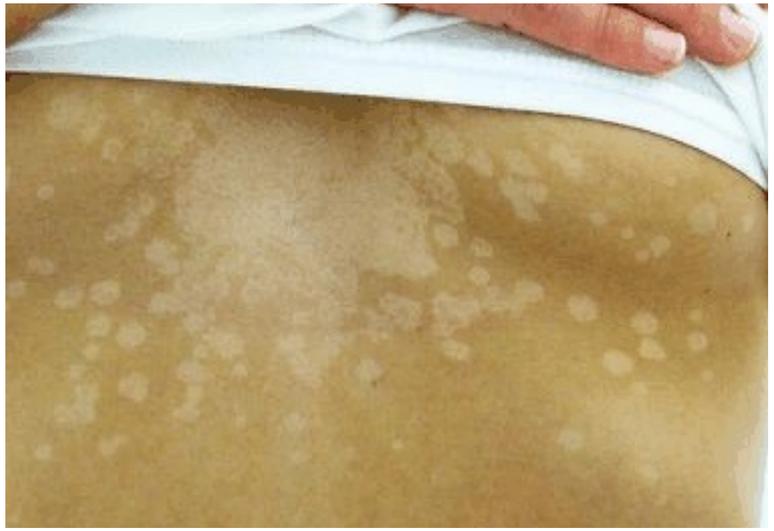
Macroscopic descriptive terms





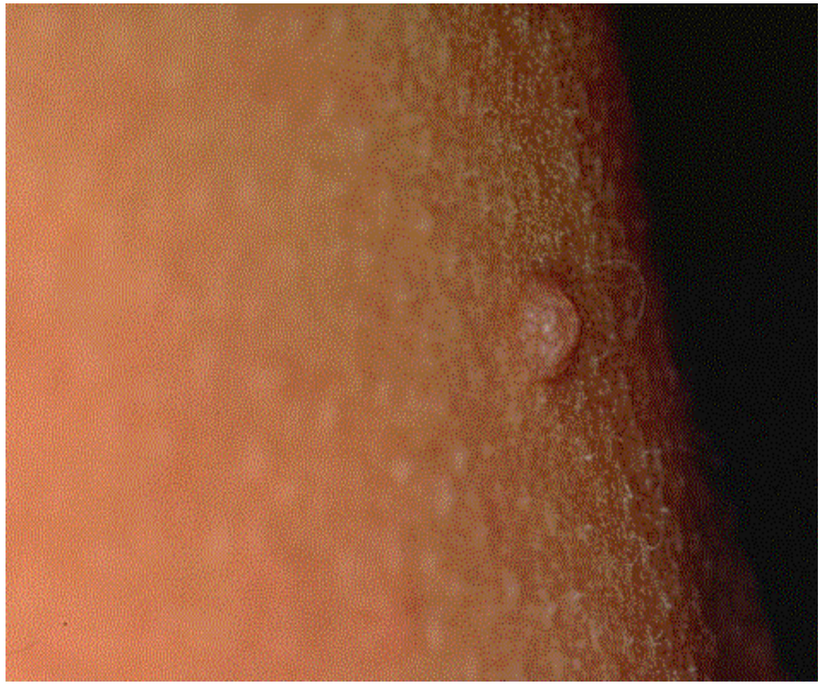


Macules

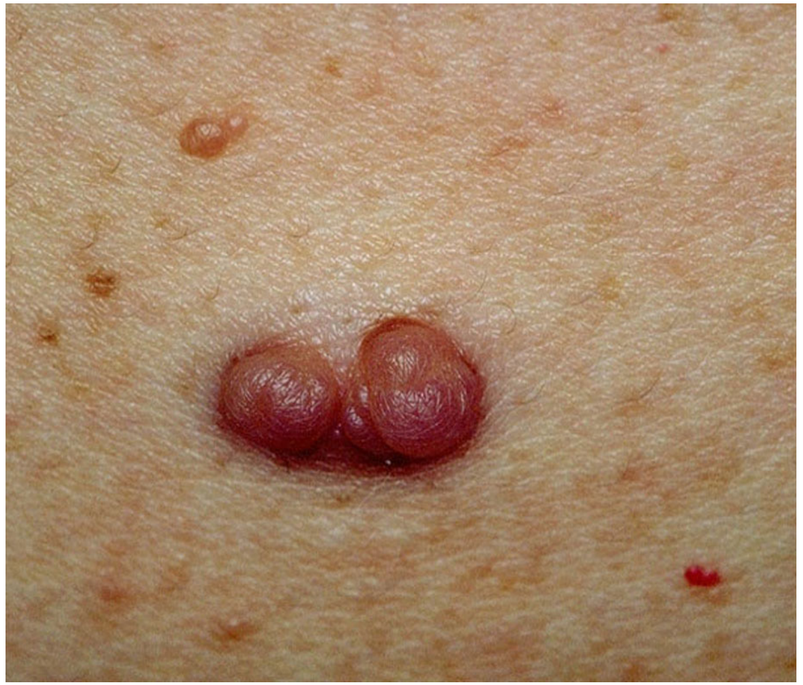


Macules and patches

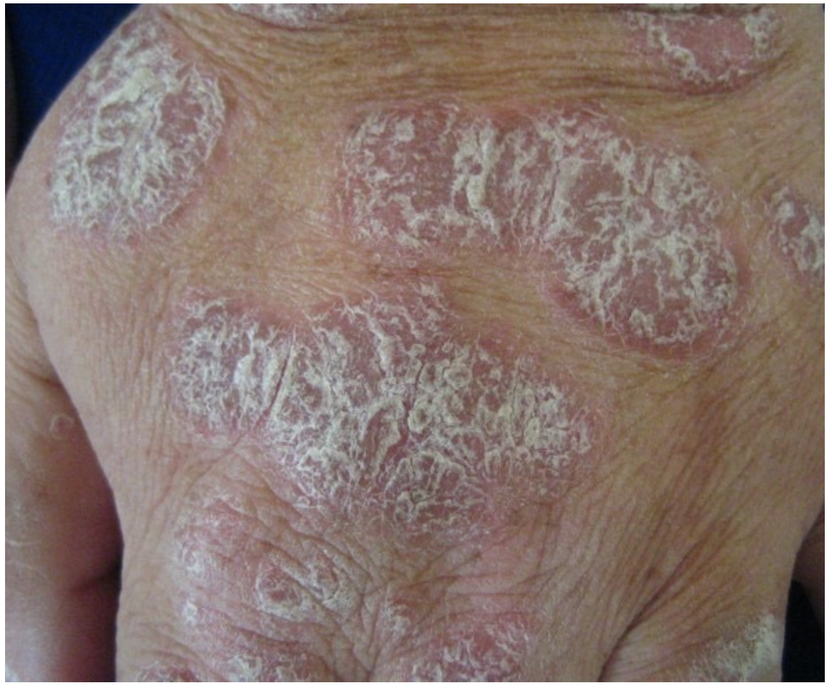
Patches



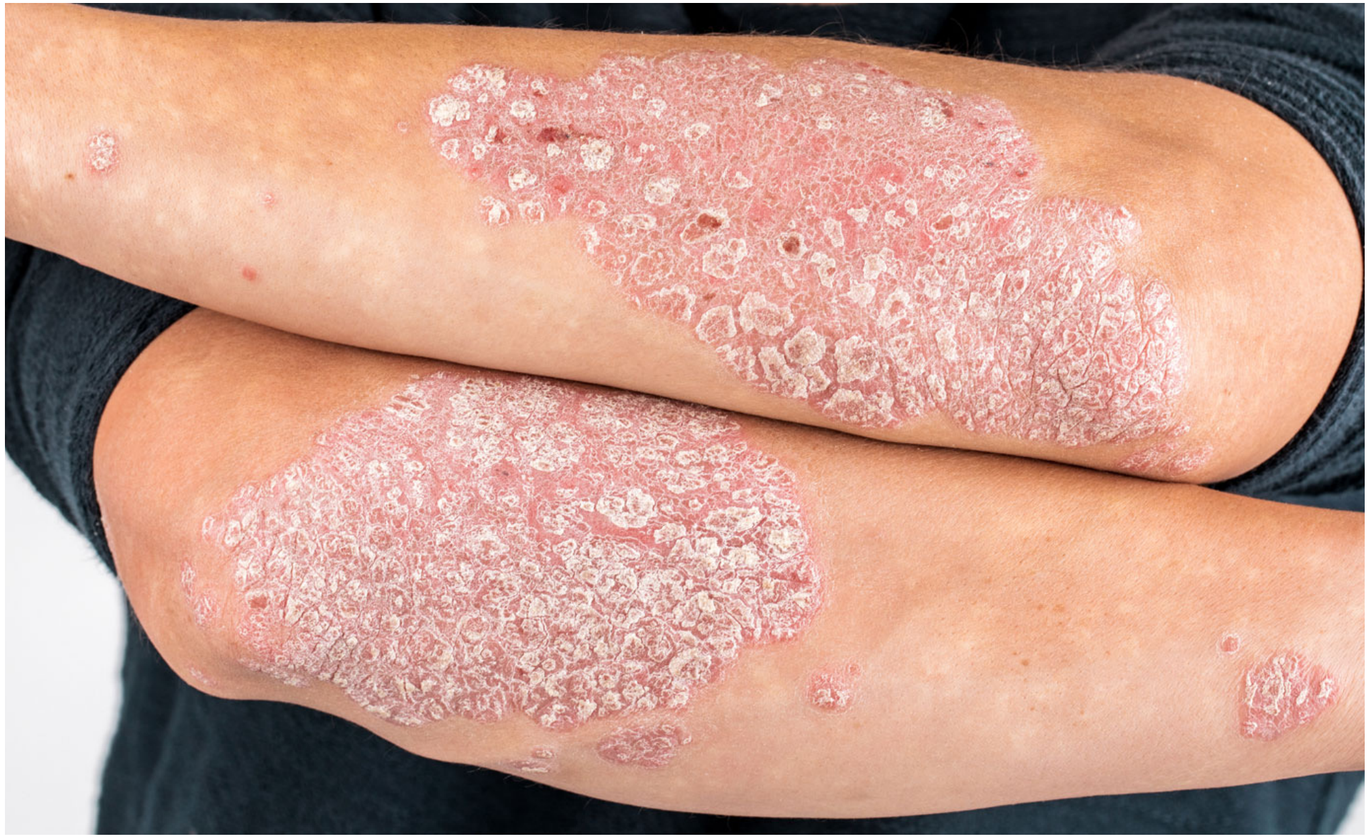
Papule



Nodule

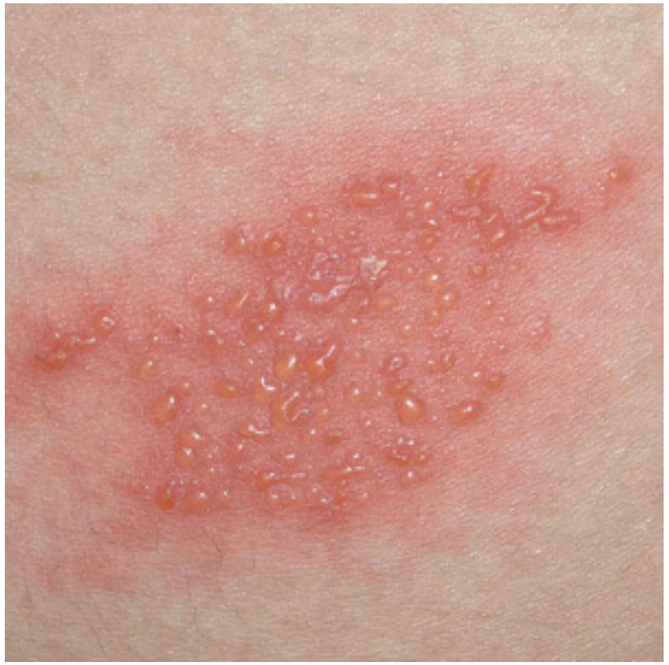


Plaque

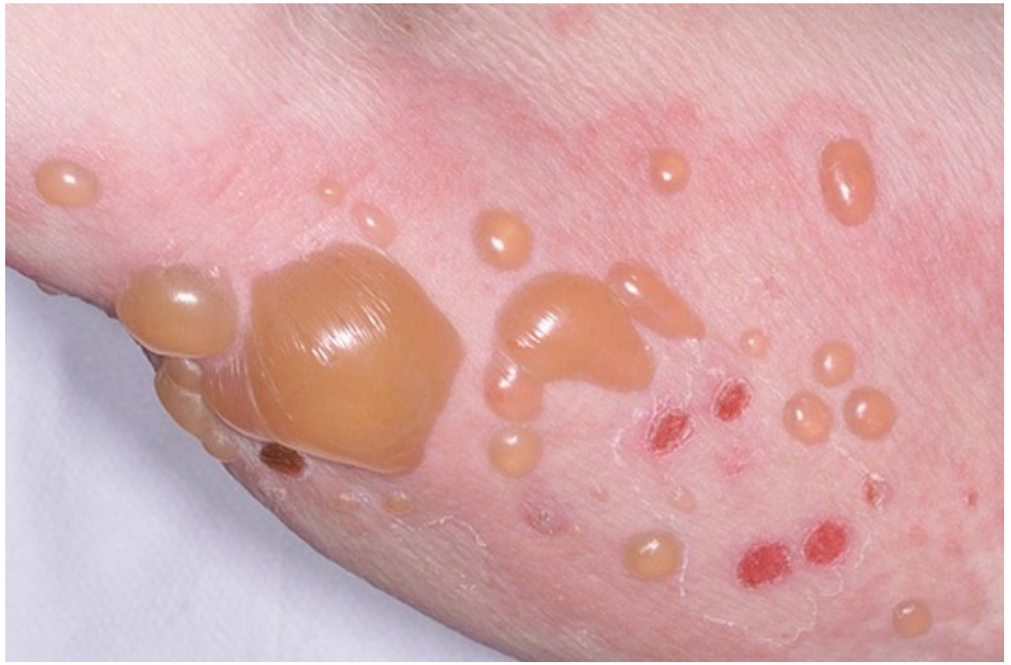


Scale

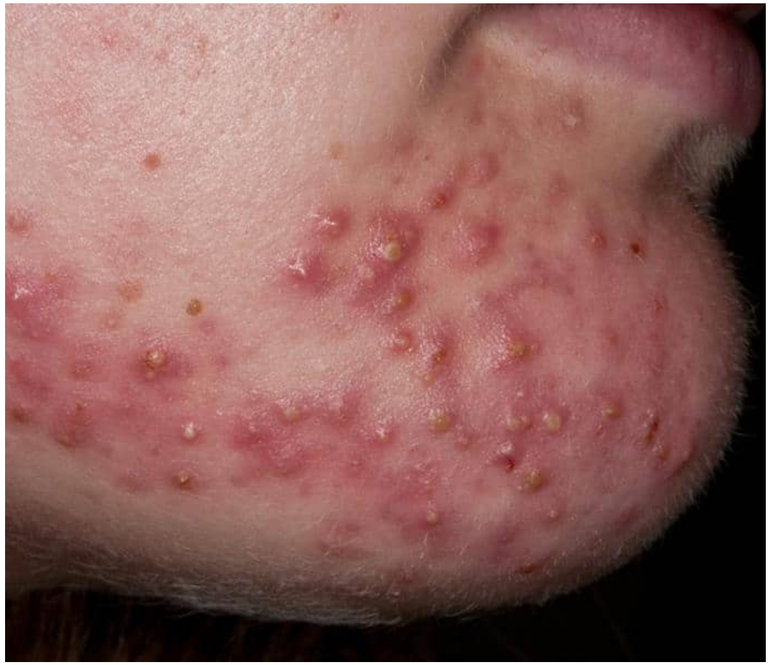
Crust



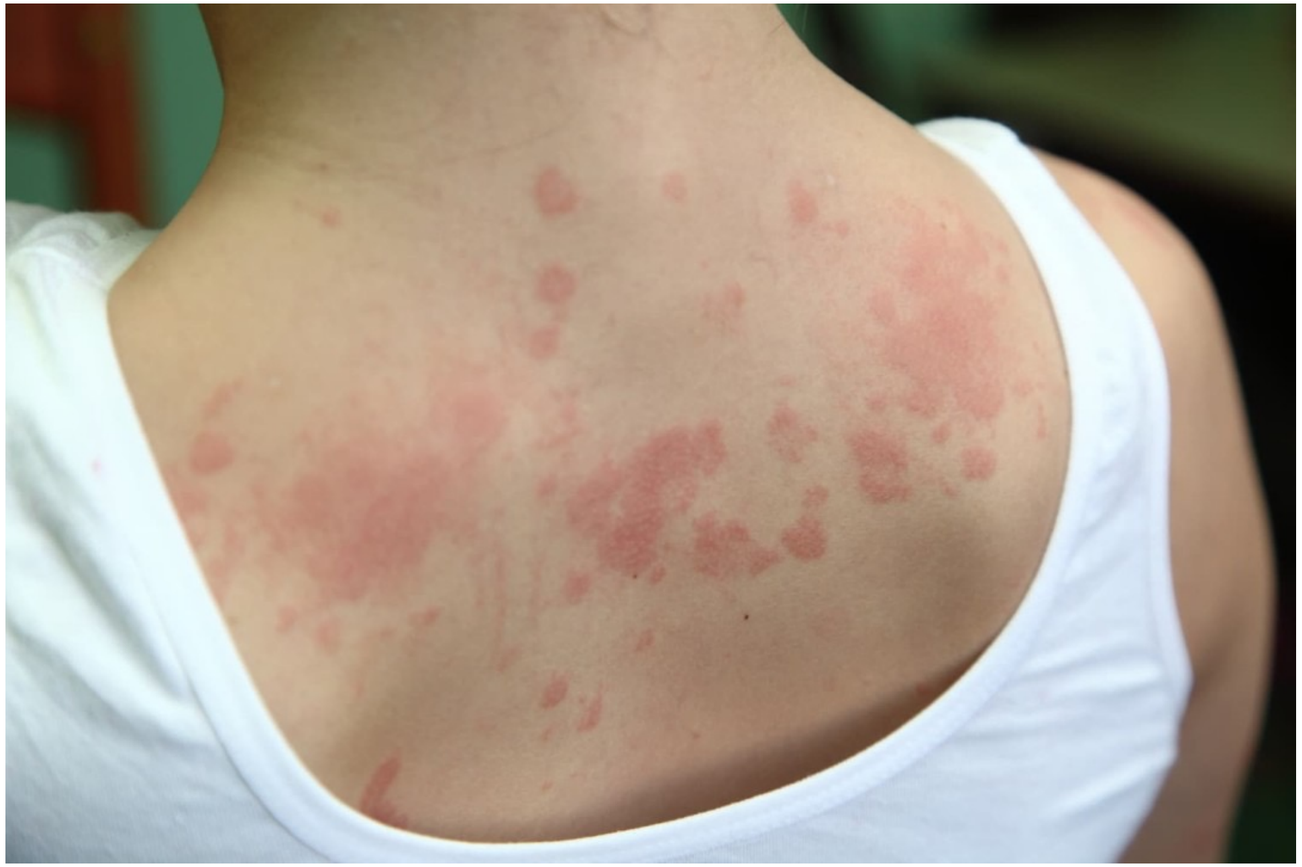
Vesicles



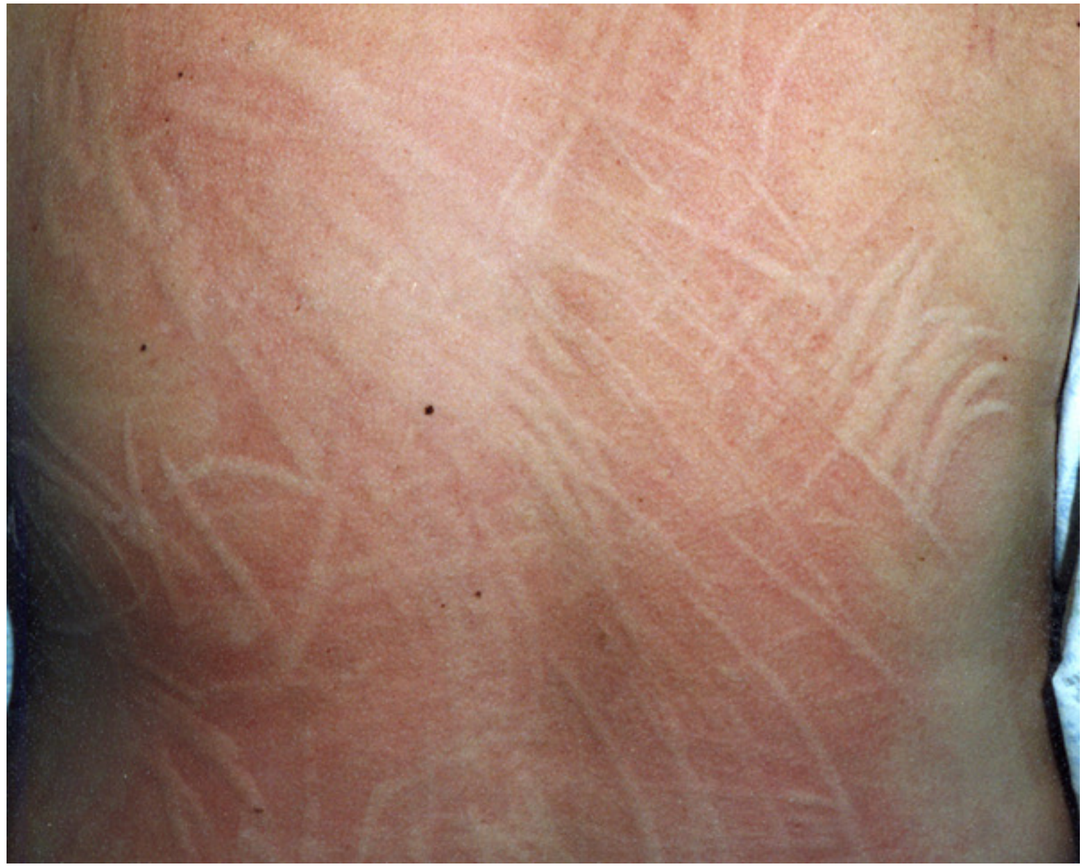
Bullae



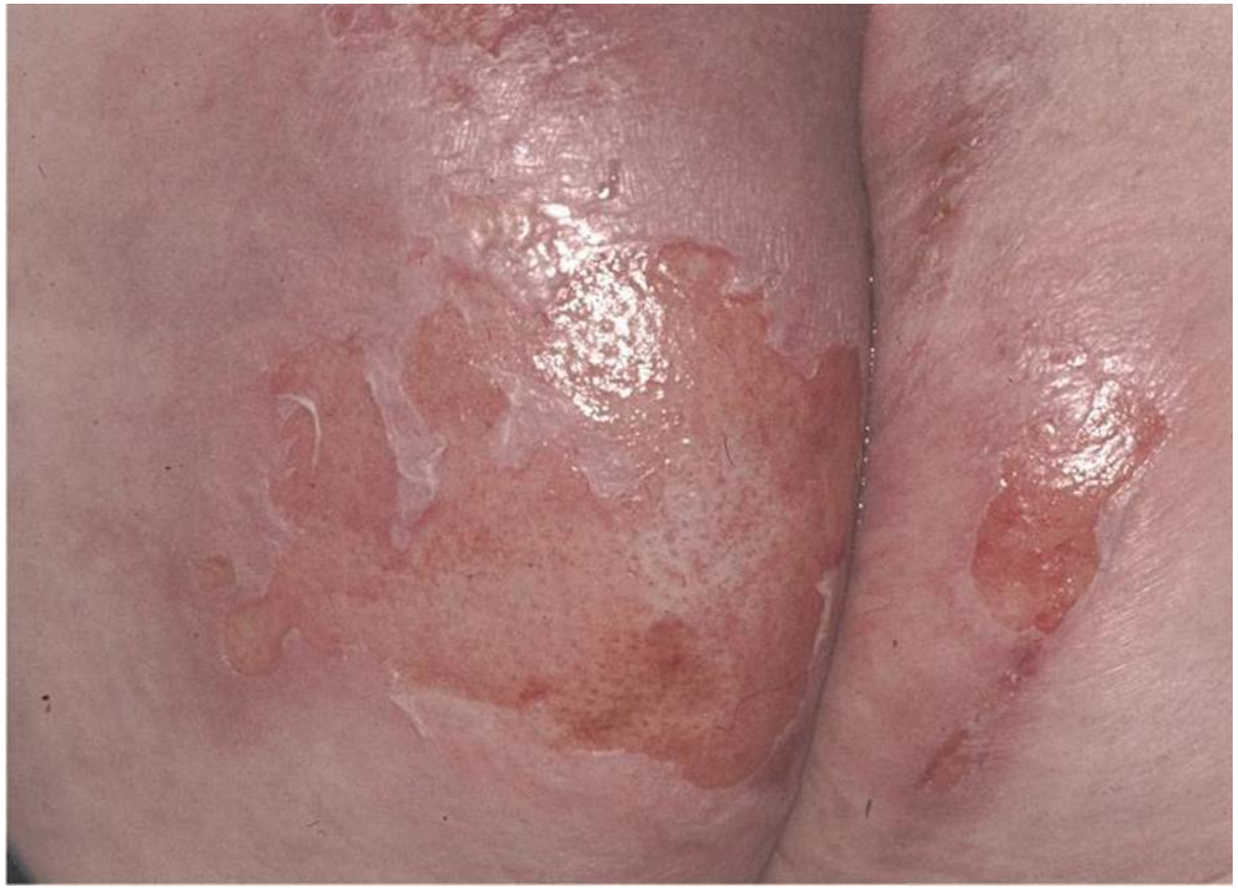
Pustules



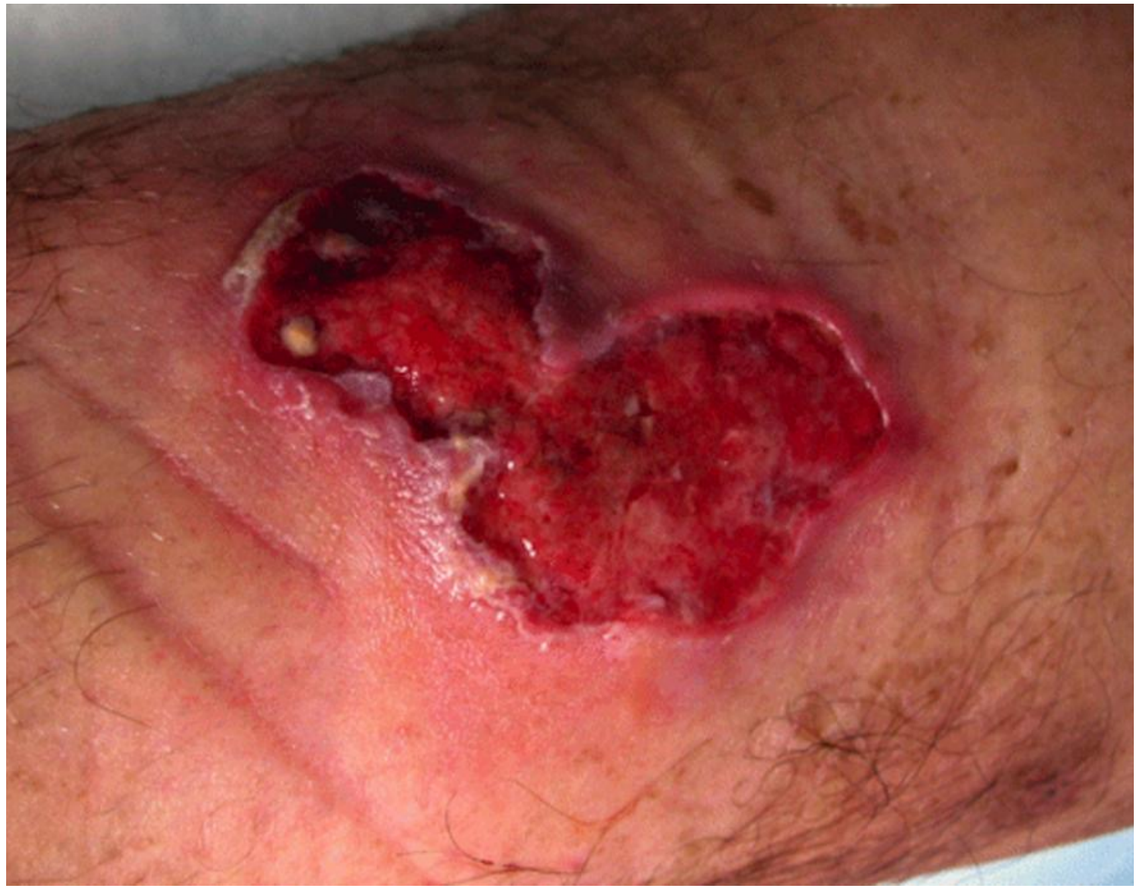
Wheal and flare



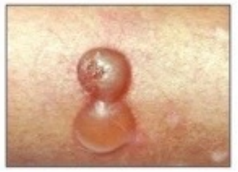
Dermographism



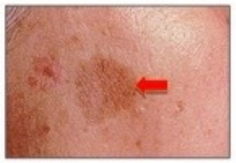
Erosion



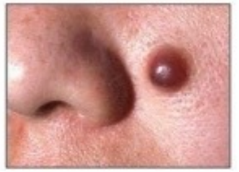
Ulcer



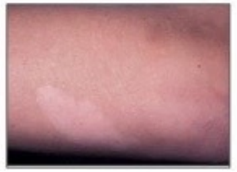
Bulla
Circumscribed collection of free fluid > 1 cm



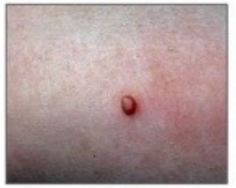
Macule
Circular flat discoloration
< 1cm
brown, blue, red or hypopigmented



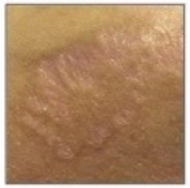
Nodule
Circular, Elevated, Solid Lesion
>1 cm



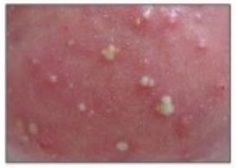
Patch
Circumscribed Flat Discoloration
> 1cm



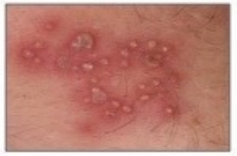
Papule
Superficial solid elevated, ≤ 0.5 cm, color varies



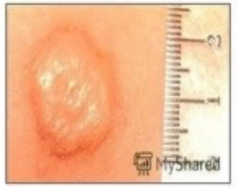
Plaque
Superficial elevated solid flat topped lesion
> 1 cm



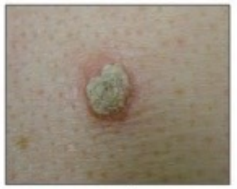
Pustule
Vesicle containing puss (inflammatory cells)



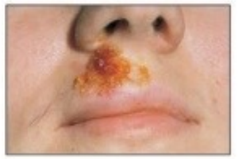
Vesicle
Circular collection of free fluid
≤ 1 cm



Wheal
Edematous, transitory, plauqe, may last few hours

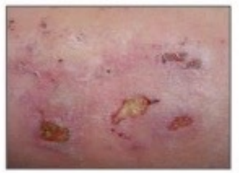


Scale
Epidermal thickening; consists of flakes of plates of compacted desquameted layers of stratum corneum

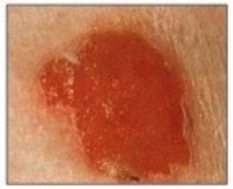


Crust
Dried serum or Eexudate on skin

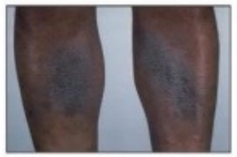
Fissure
Crack or split



Excoriation
Linear erosion



Erosion
Loss of epidermis superficial; part or all of the epidermis has been lost



Lichenification
Thickening of the epidemis seen with exaggeration of Normal skin lines

Scar
Thickening; permanent fibrotic changes that occur on the skin following damage of the epidermis

Microscopic descriptive terms in skin disease

Microscopic descriptive terms

1. **Hyperkeratosis:** Thickened stratum corneum, caused by:
    - Incomplete keratinization: Actinic keratosis
    - Rapid keratinocyte proliferation: Psoriasis
        - **A. Orthokeratosis:** Devoid of nuclei (preserved keratinocyte maturation)
        - **B. Parakeratosis:** Retained nuclei (delayed keratinocyte maturation)

2. **Acanthosis:**
    - Epidermal hyperplasia and thickening,
    - Elongated rete ridges usually extend into dermis
    - Can be regular (all rete pegs at the same level) or irregular (rete pegs at different levels of the papillary dermis)

Microscopic descriptive terms

3. Acantholysis:

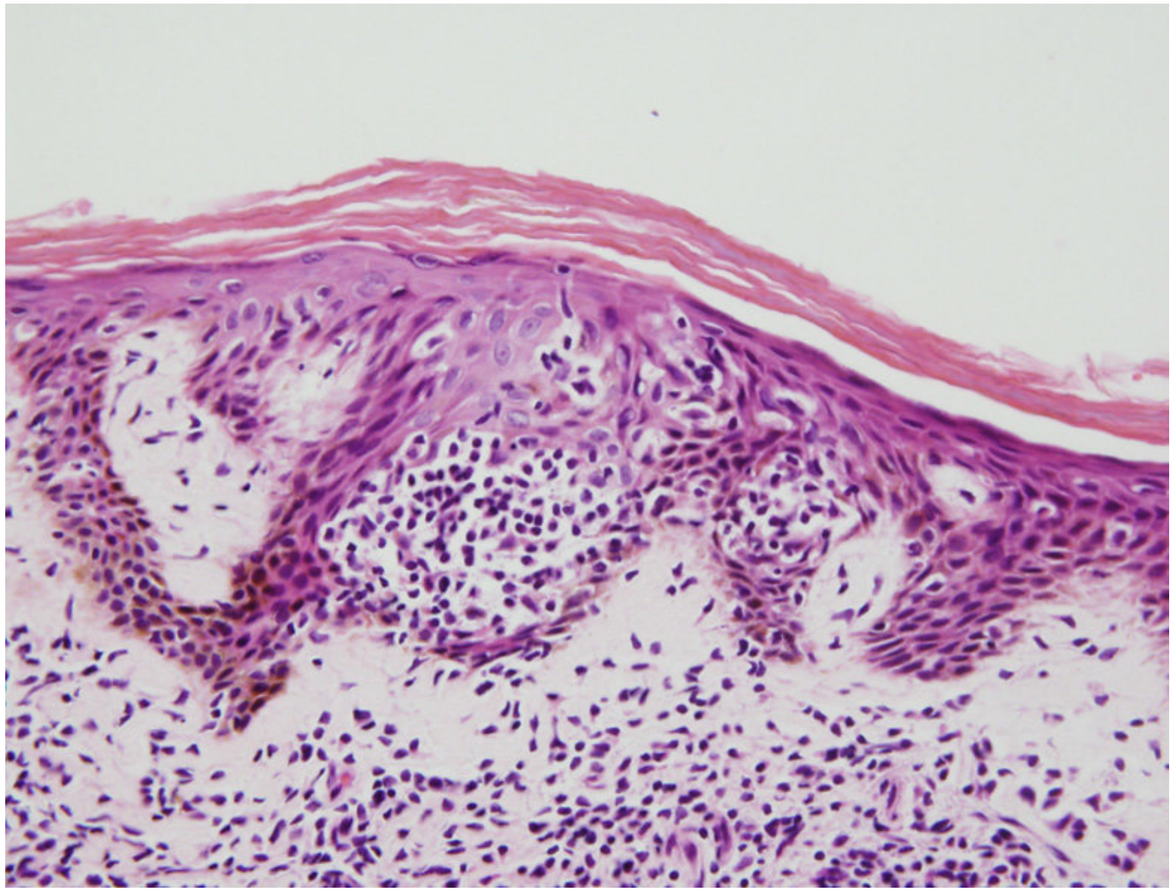
- Loss of intercellular cohesion between keratinocytes (cell-to-cell connections; desmosomes) leading to single and rounded keratinocytes
- Seen in blistering skin disorders

4. Spongiosis:

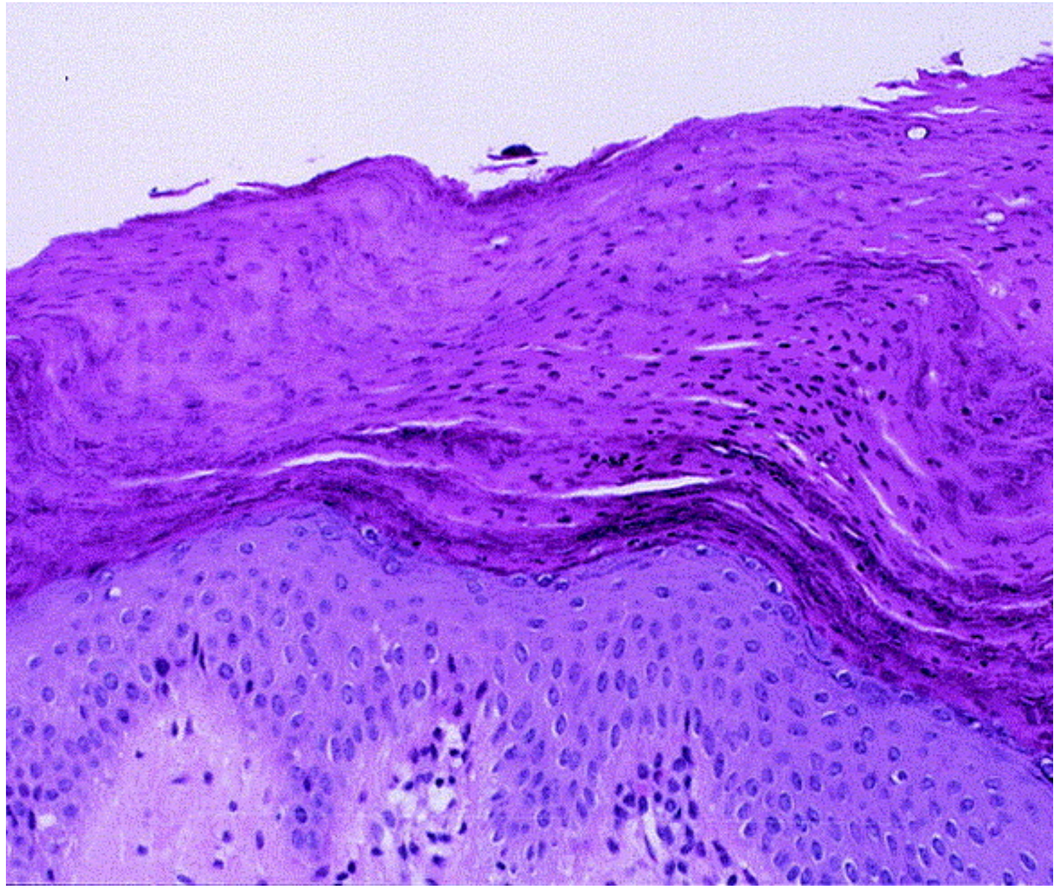
- Intercellular edema of epidermis
- Seen in several inflammatory skin disorder (e.g. eczema)

5. Papillomatosis:

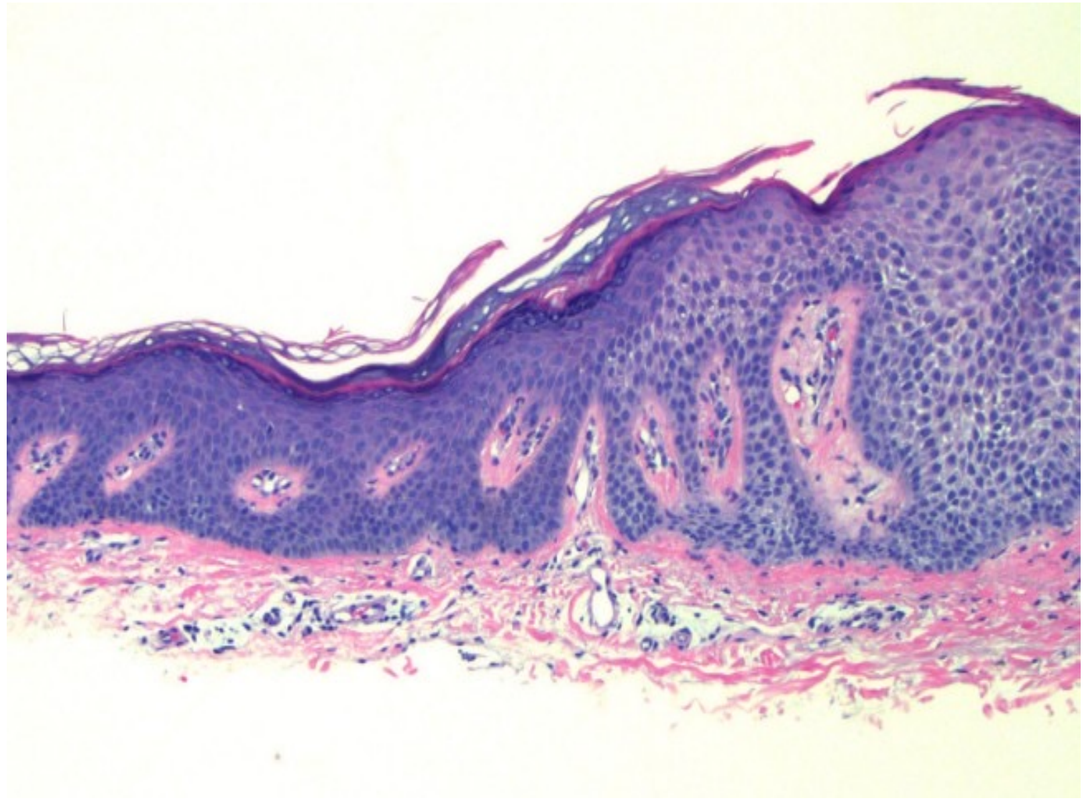
- Finger-like undulation of the epidermis with upward expansion of hyperplastic long and/or wide dermal papillae
- May have associated epidermal hyperplasia



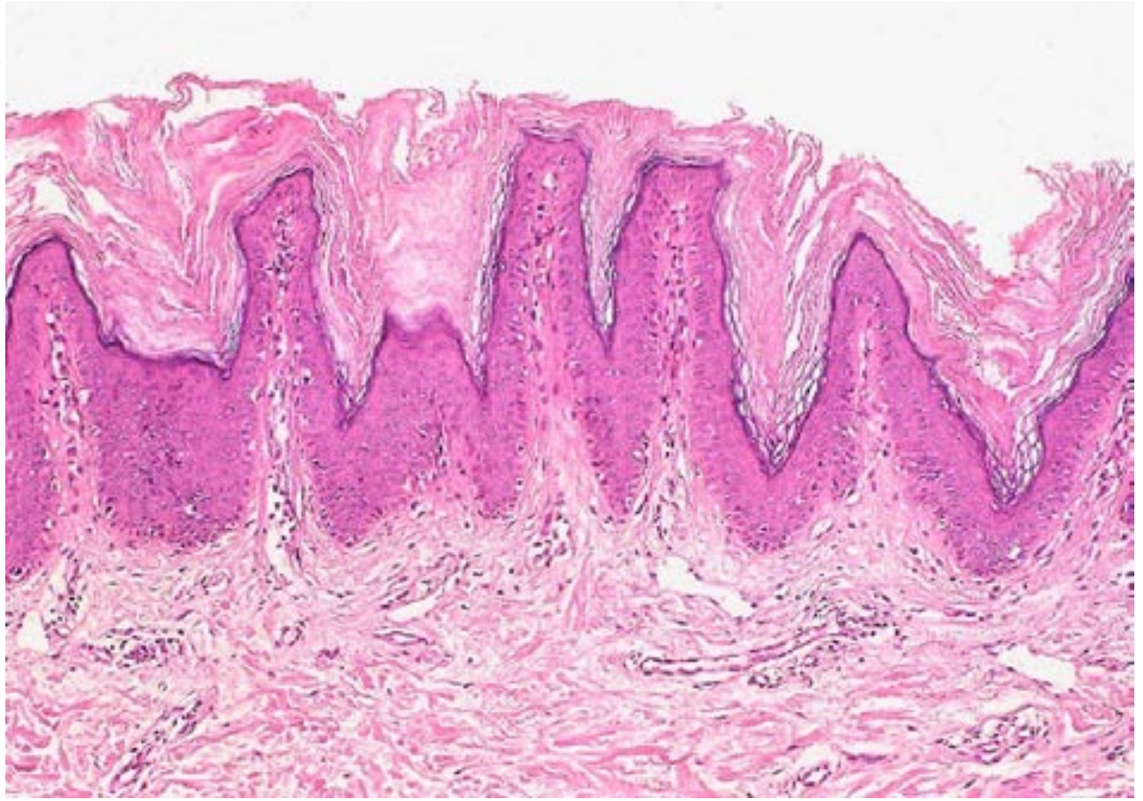
Orthokeratosis (orthokeratotic hyperkeratosis)



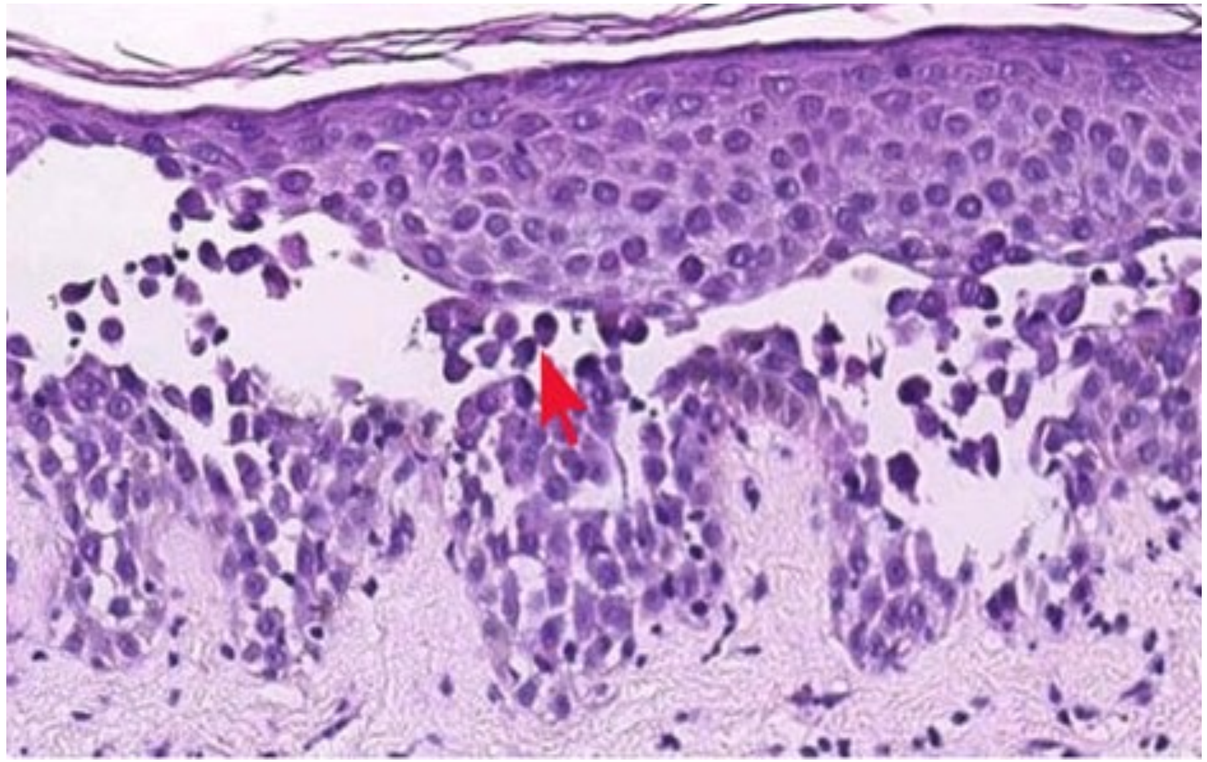
Parakeratosis (parakeratotic hyperkeratosis)



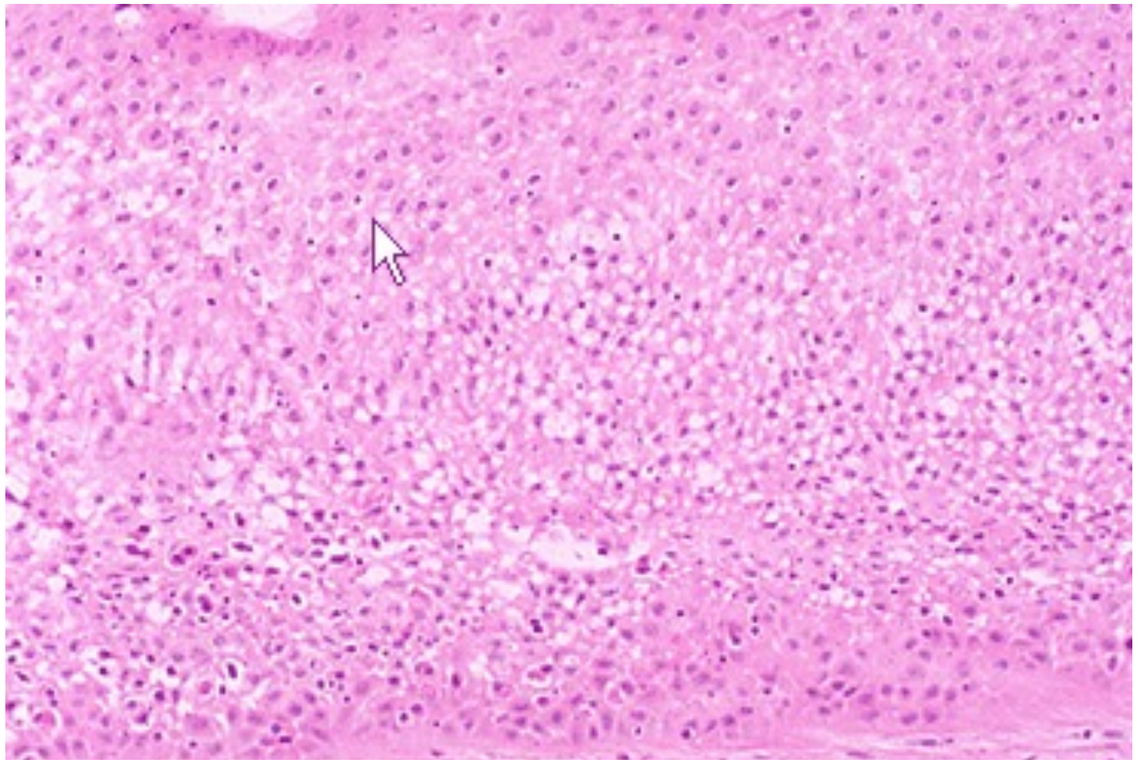
Acanthosis : epidermal hyperplasia



Papillomatosis : finger-like hyperplasia of papillary dermis

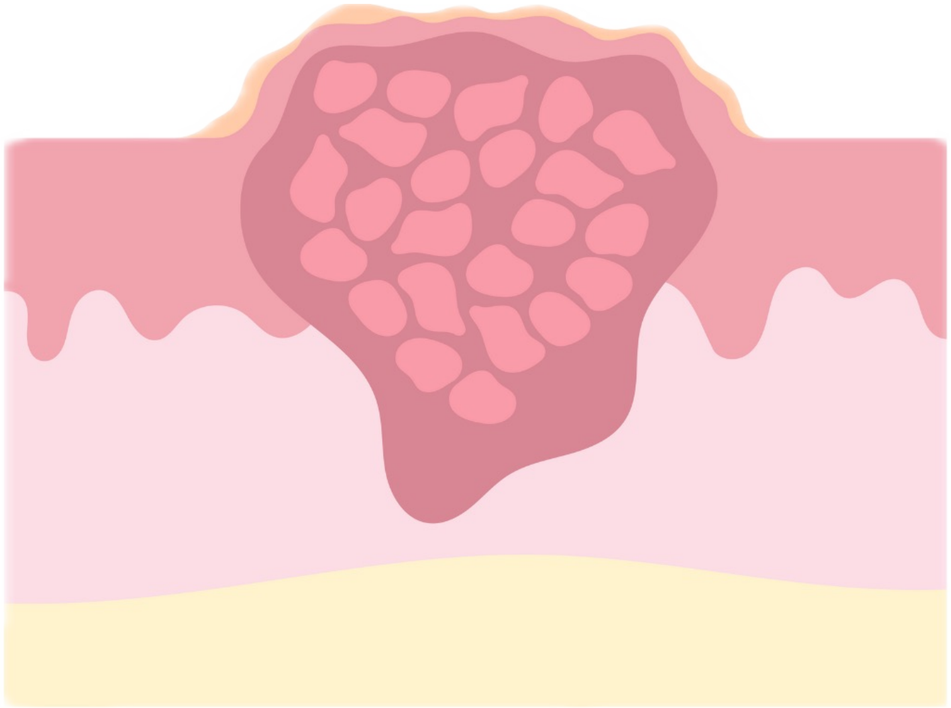


Acantholysis : loss of intercellular cohesion between keratinocytes



Spongiosis : intercellular edema of epidermis

Pathology of skin tumor & related connective tissue



1 Epidermal (keratinocytic) tumors

Benign epidermal tumor

Premalignant epidermal tumor

- Actinic keratosis

Malignant epidermal tumor

- Squamous cell carcinoma in-situ (Bowen disease)
- (Invasive) squamous cell carcinoma (invasive)
- Basal cell carcinoma

2 Melanocytic tumors

Benign melanocytic tumor

- (Melanocytic) nevus

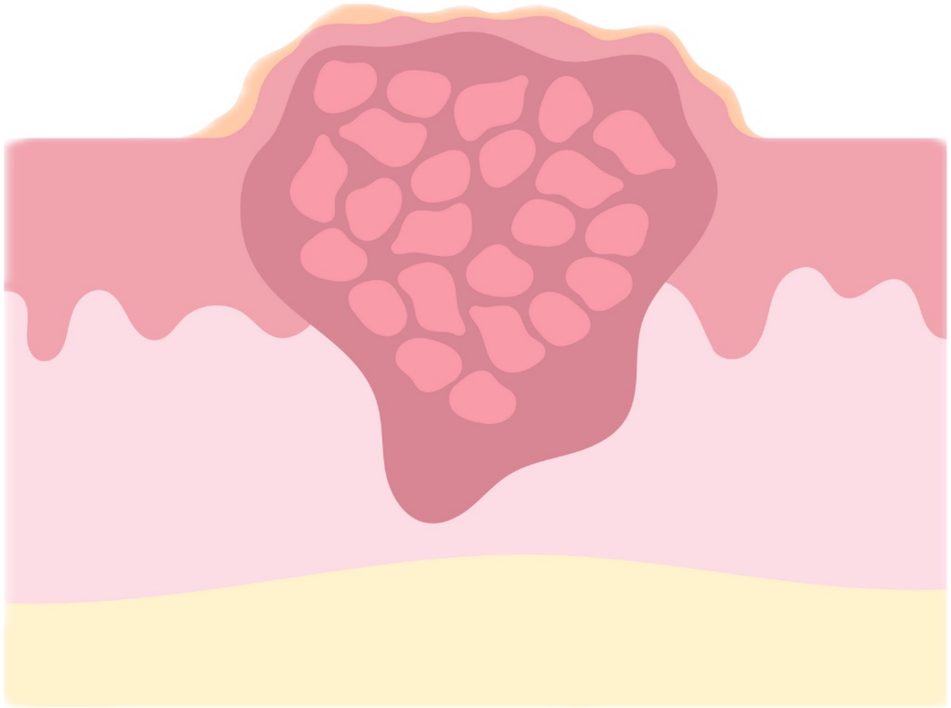
Premalignant melanocytic tumor

- Dysplastic (atypical) nevus

Malignant melanocytic tumor

- (Malignant) melanoma

Pathology of skin tumor & related connective tissue



3 Skin appendageal (adnexal) tumors

Benign and malignant tumors of
sweat glands, sebaceous glands,
and hair follicles

4 Dermal (connective tissue) tumors

Benign tumor:

- Fibrous histiocytoma (dermatofibroma)

Malignant tumor:

- Dermatofibrosarcoma protuberans

Etc.

Epidermal (keratinocytic) tumors

Benign epidermal tumors

1. **Viral-associated tumor-like lesions**
   - Verrucae (warts)
   - Molluscum contagiosum

2. **Seborrheic keratosis**

3. **Fibroepithelial polyp (skin tag, acrochordon):**
   Benign non-epithelial tumors arising from mesodermal (mesenchymal) tissue

4. **Keratoacanthoma:** controversy - benign or malignant ?

Verrucae (warts)

- **Cause:** Human papillomavirus (HPV), low-risk types: (1, 2, 4, 6, 11, 42, 44, etc.)

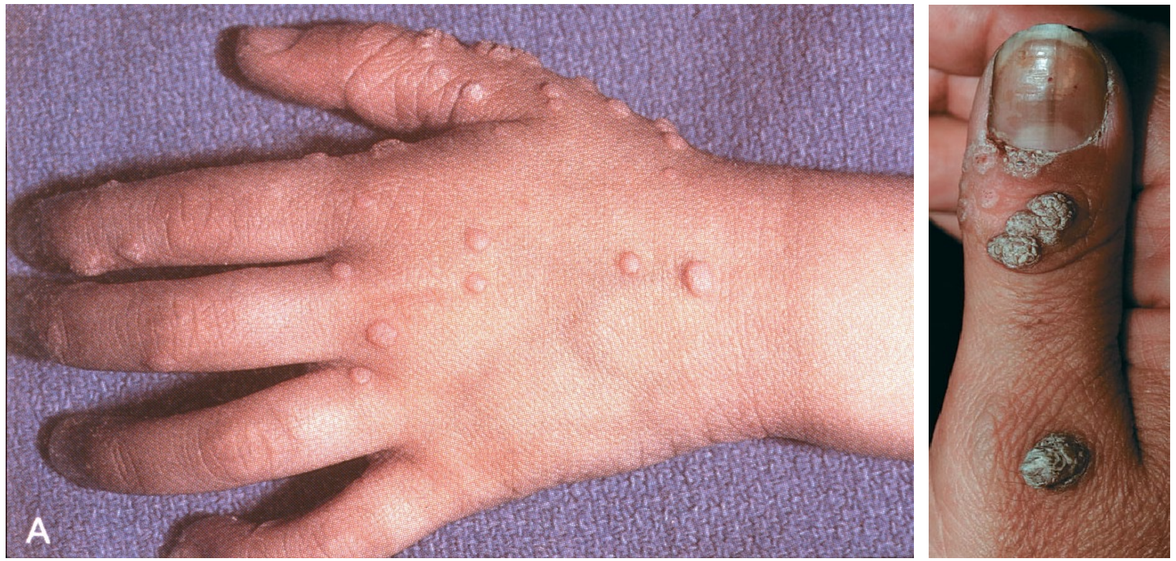
- **Transmission:** Direct contact

- **Clinical:**
  - Common in children and adolescents (**except:** condyloma acuminata, more common in active reproductive age)
  - Usually self-limiting and regress within 6 months to 2 years

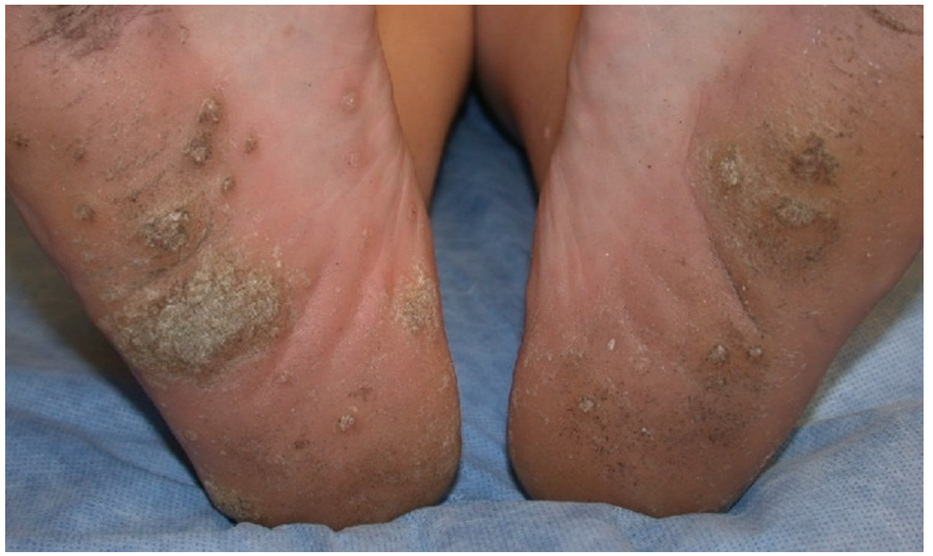
- **Pathogenesis:**
  - HPV affects cell cycle control causing increased proliferation of epithelial cells and production of viruses.

Verrucae (warts)

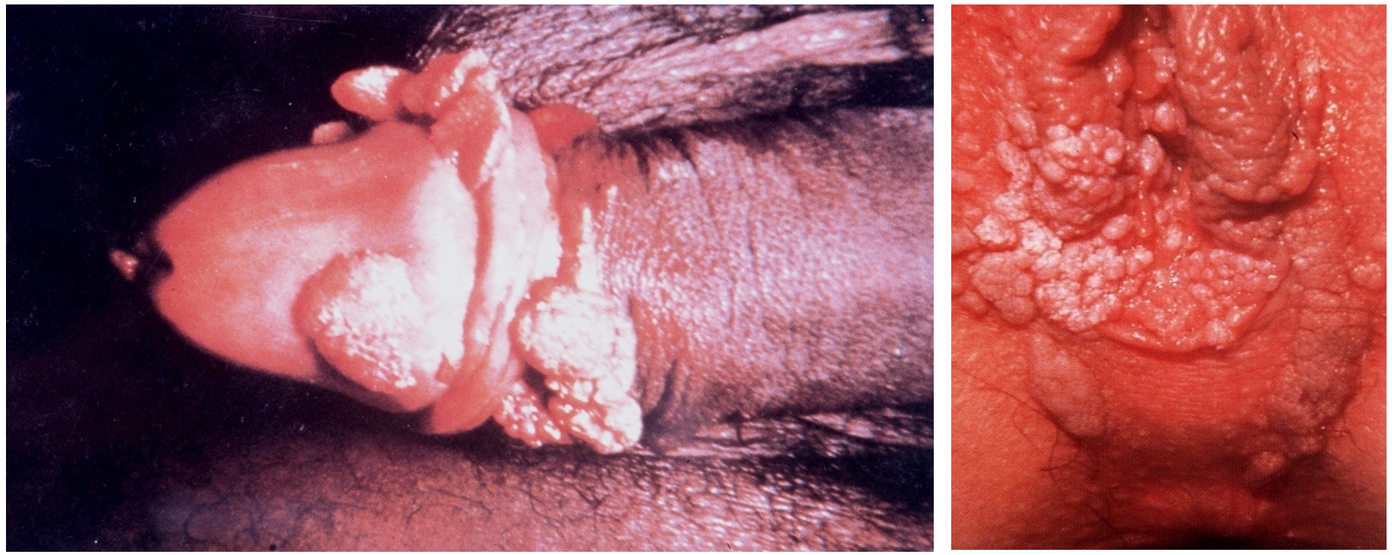
- **Classification:** based on clinical morphology and location
  1. Verruca vulgaris (most common)
     - Occurs anywhere. Usually dorsum & periungual area of hand
     - Gray-white, dome-shaped, 0.1 to 1-cm papule, with rough surface
  2. Verruca plantaris
     - Occurs on sole
     - Rough scaly coalesce plaque
  3. Verruca palmaris
     - Occurs on palm
     - Rough scaly coalesce plaque
  4. Condyloma acuminata (venereal / genital wart)
     - Occurs in anogenital regions (usually associated with HPV type 6 and 11)
     - Soft tan cauliflower-like masses



Verruca vulgaris: papules with rough surface



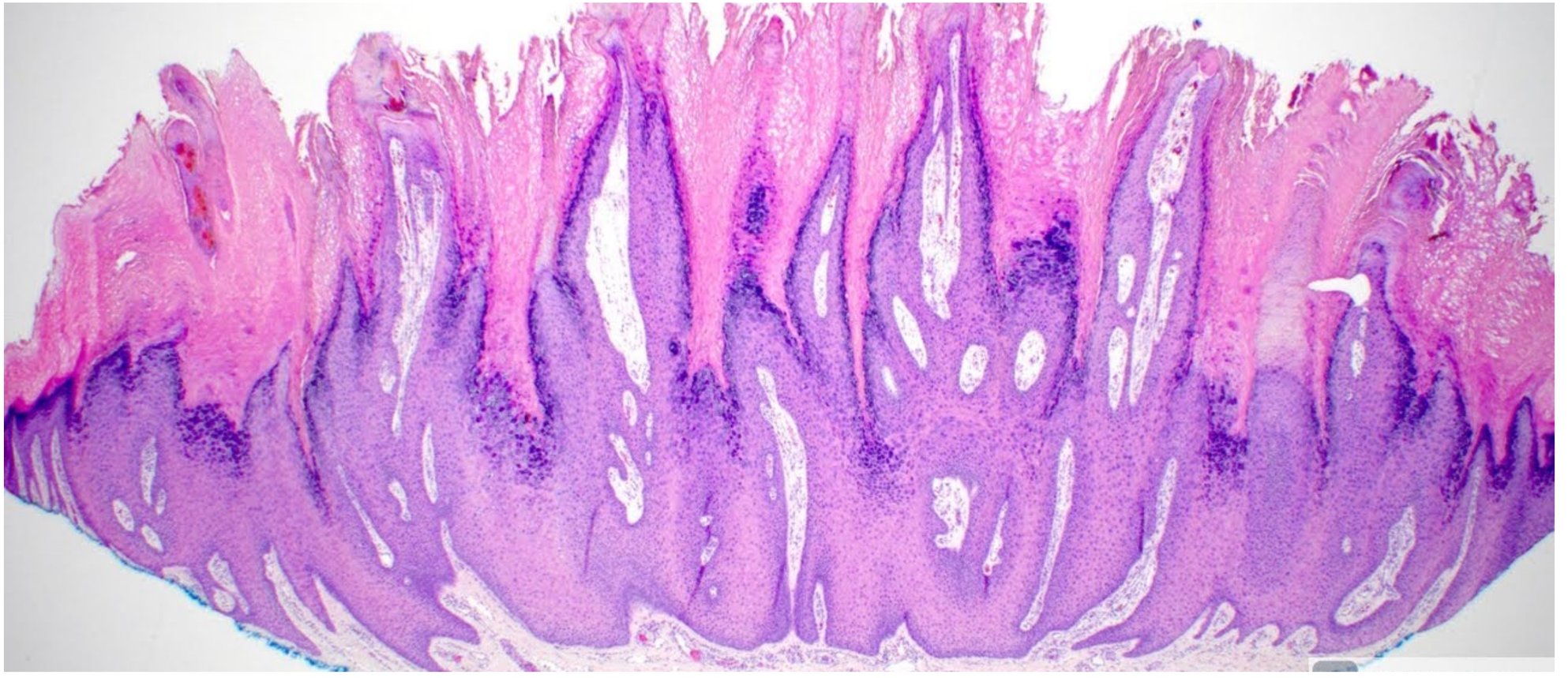
Verruca plantaris: rough scaly coalesce plaque



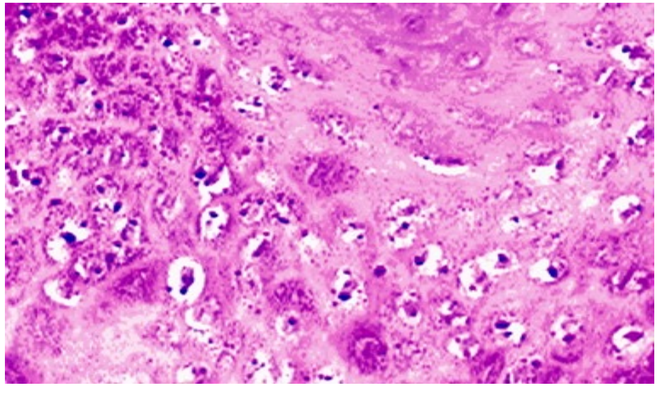
Condyloma acuminata: venereal / genital wart

Verrucae (warts)

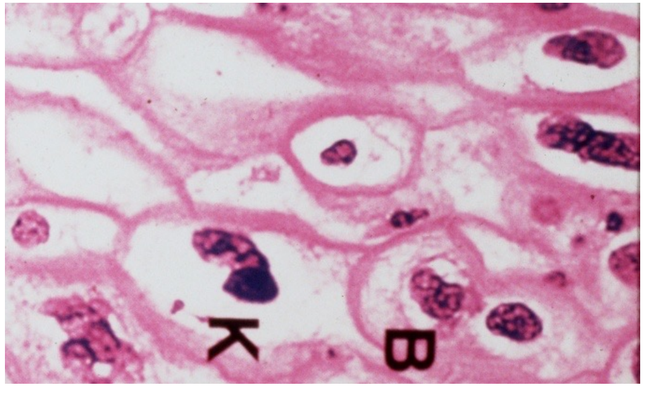
- **Histopathology:**
  - Marked **hyperkeratosis**
  - **Acanthosis:** epidermal hyperplasia
  - **Prominent papillomatosis:** papillary dermis hyperplasia with long delicate dermal papillae
  - **Hypergranulosis:** cells with condensed keratohyaline granules
  - **Koilocytosis (koilocytic atypia):** viral cytopathic changes with perinuclear halo, hyperchromatic nuclei with irregular nuclear membrane, may be binucleated



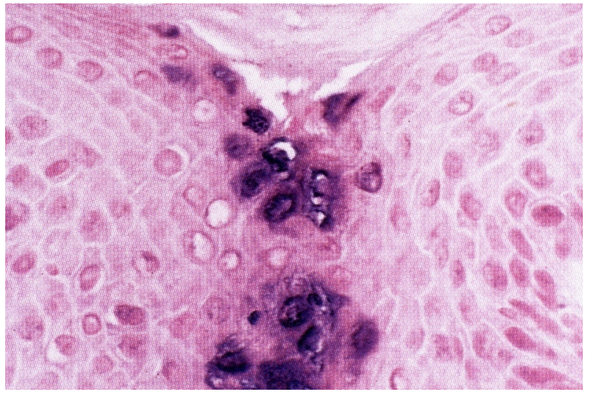
Hyperkeratosis, papillomatosis, acanthosis



Hypergranulosis



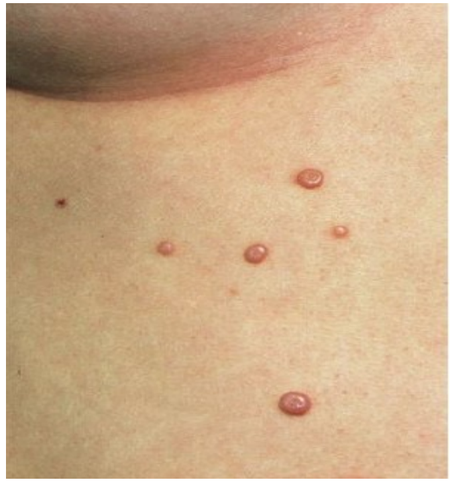
Koilocytosis

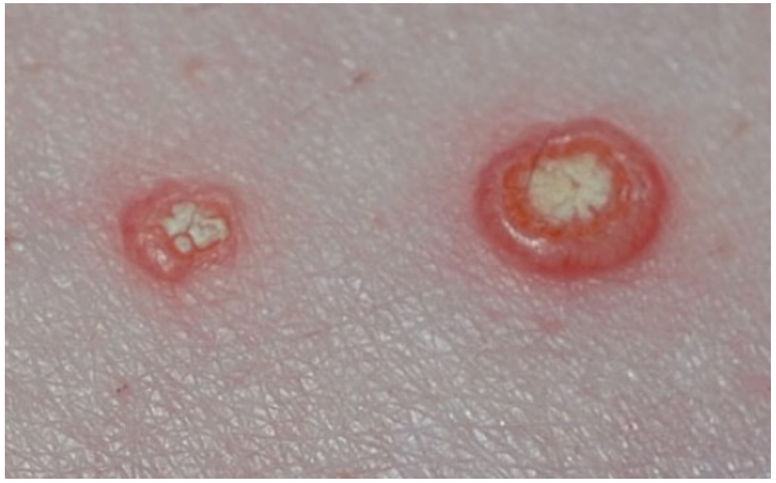


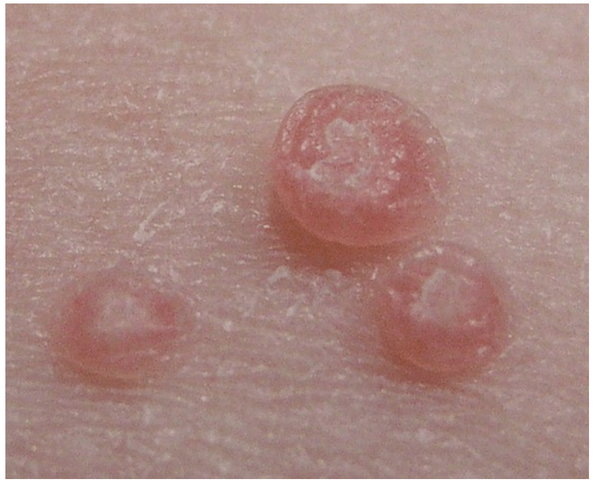
In-situ hybridization with HPV

Molluscum contagiosum

- **Cause:** Poxvirus mollusci (Molluscum contagiosum virus)
- **Transmission:** Direct contact
- **Clinical:**
  - Common in children and young adults
  - Firm, pruritic, umbilicated small papules, 0.2 to 0.4 cm
  - Curd-like or cooked rice-like whitish material at central umbilication
  - Usually self-limiting

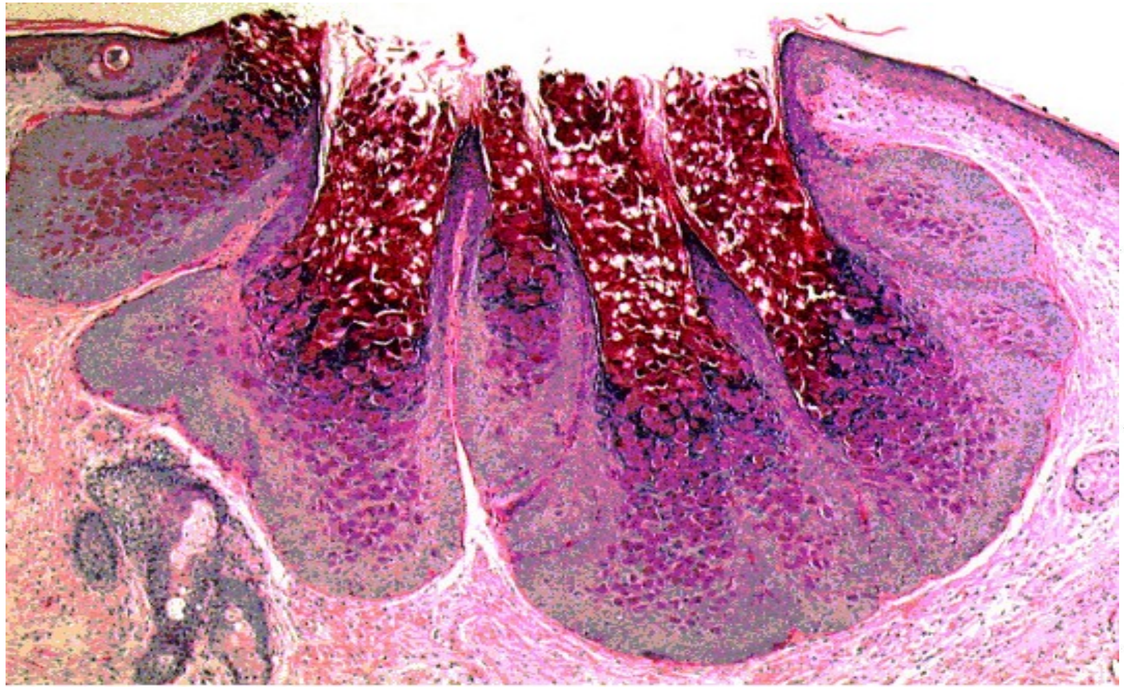






Molluscum contagiosum

- **Histopathology:**
  - Cup-like (verrucous) epidermal hyperplasia containing molluscum bodies within stratum granulosum and corneum
  - Molluscum bodies: large homogenous eosinophilic cytoplasmic inclusions



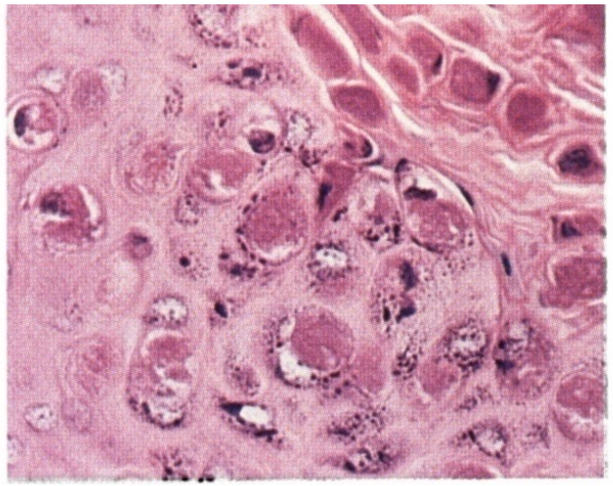
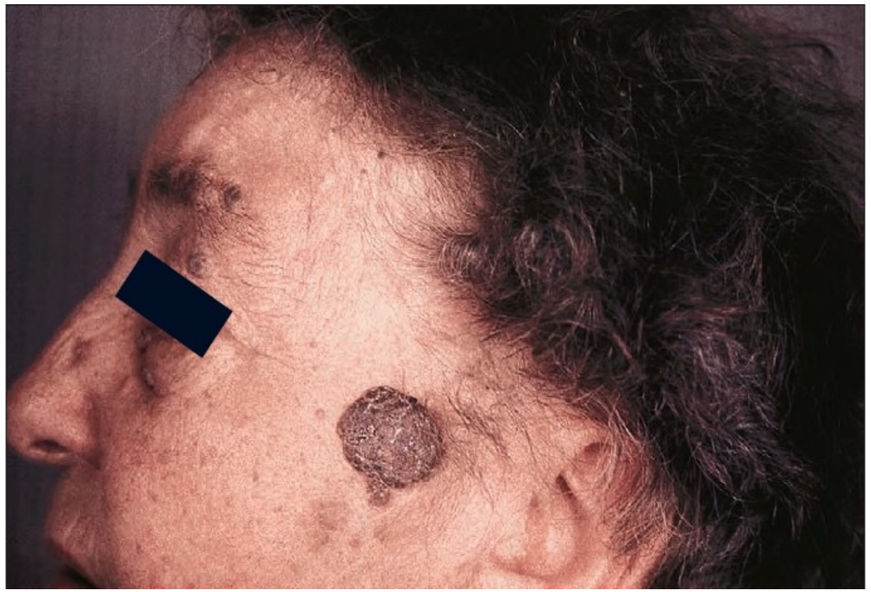


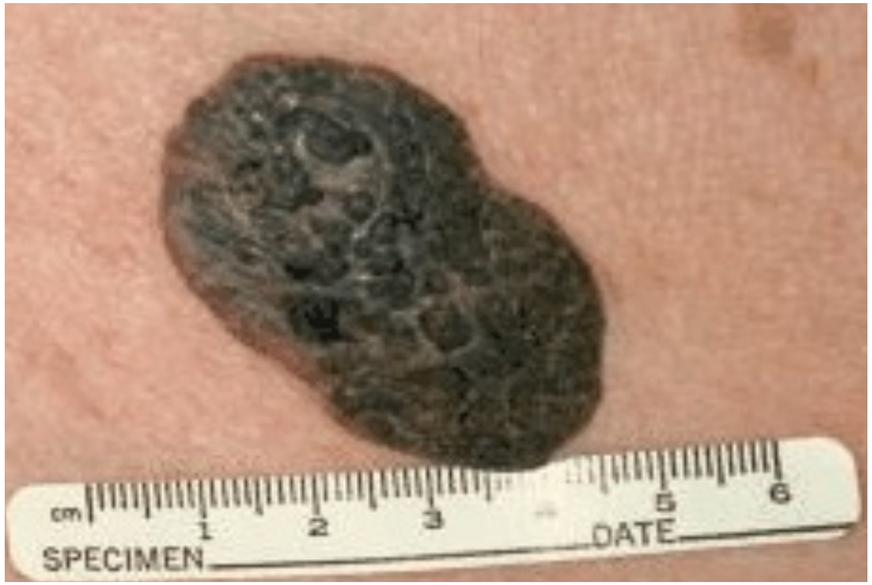
Figure 27–45 ■

Molluscum contagiosum. A focus of verrucous epidermal hyperplasia contains numerous cells with ellipsoid cytoplasmic inclusions (molluscum bodies) within the stratum granulosum and stratum corneum.

Seborrheic keratosis

- Benign keratinocytic tumor with hyperkeratosis
- **Pathogenesis:**
  - Activating mutation in **fibroblast growth factor receptor-3 (FGFR-3)* gene** in 40-85% of patients
- **Clinical:**
  - Common in middle-aged to older patients
  - Common in head, neck, trunk, and extremities
  - Well-demarcated, round, flat, coin-like (stuck-on appearing) plaques, vary in size (mm to cm)
  - Uniformly tan to dark-brown color with granular surface
- **Prognosis:** Usually benign

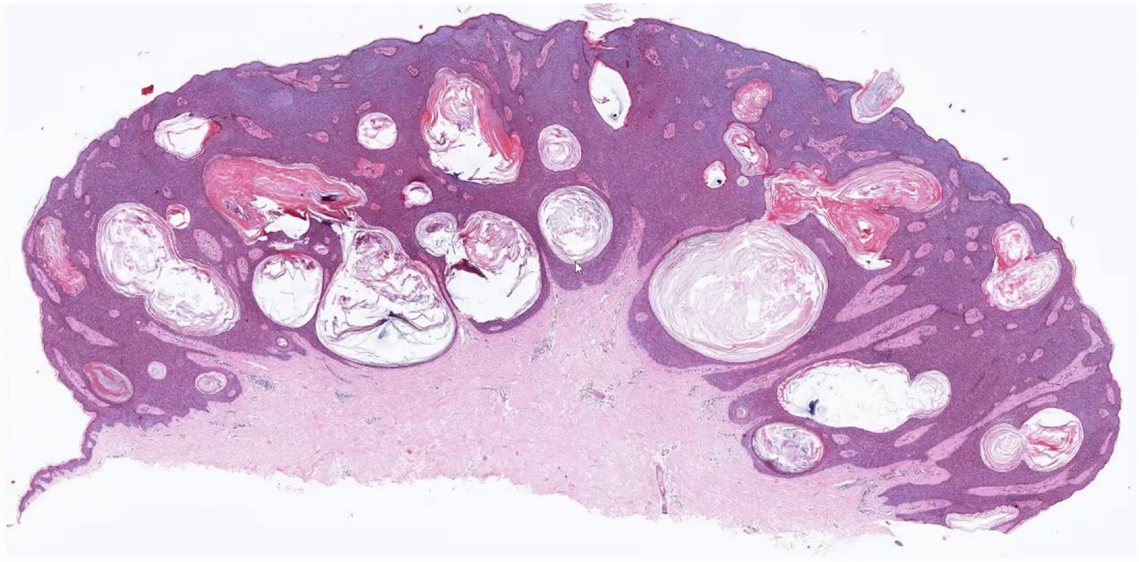


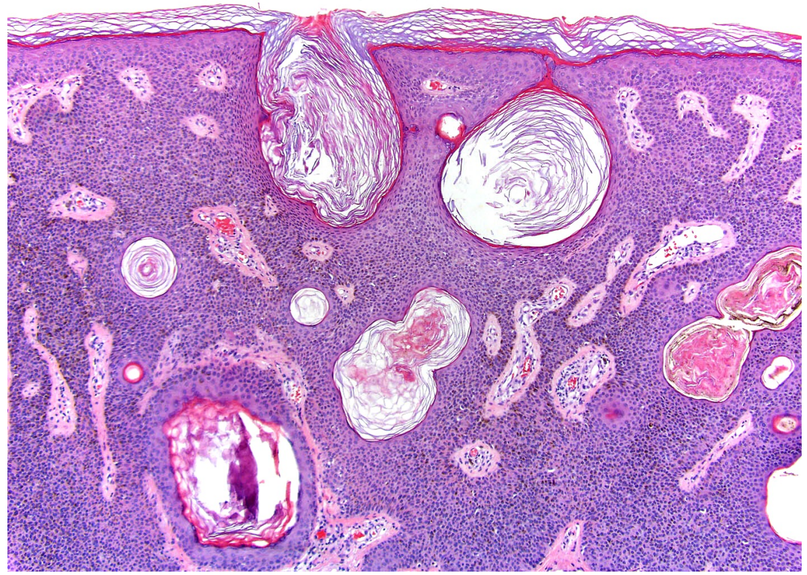


* FGFR3: transmembrane tyrosine kinase receptor (TRK) involving in signal transduction regulating **cell growth and differentiation**

Seborrheic keratosis

- **Histopathology:**
  - Exophytic and well-demarcated sharply from adjacent epidermis
  - Acanthosis and marked hyperkeratosis at surface
  - Benign-appearing epidermal keratinocytes (small size) with variable melanin pigments
  - Small keratin-filled cysts (horn cysts) within the tumor



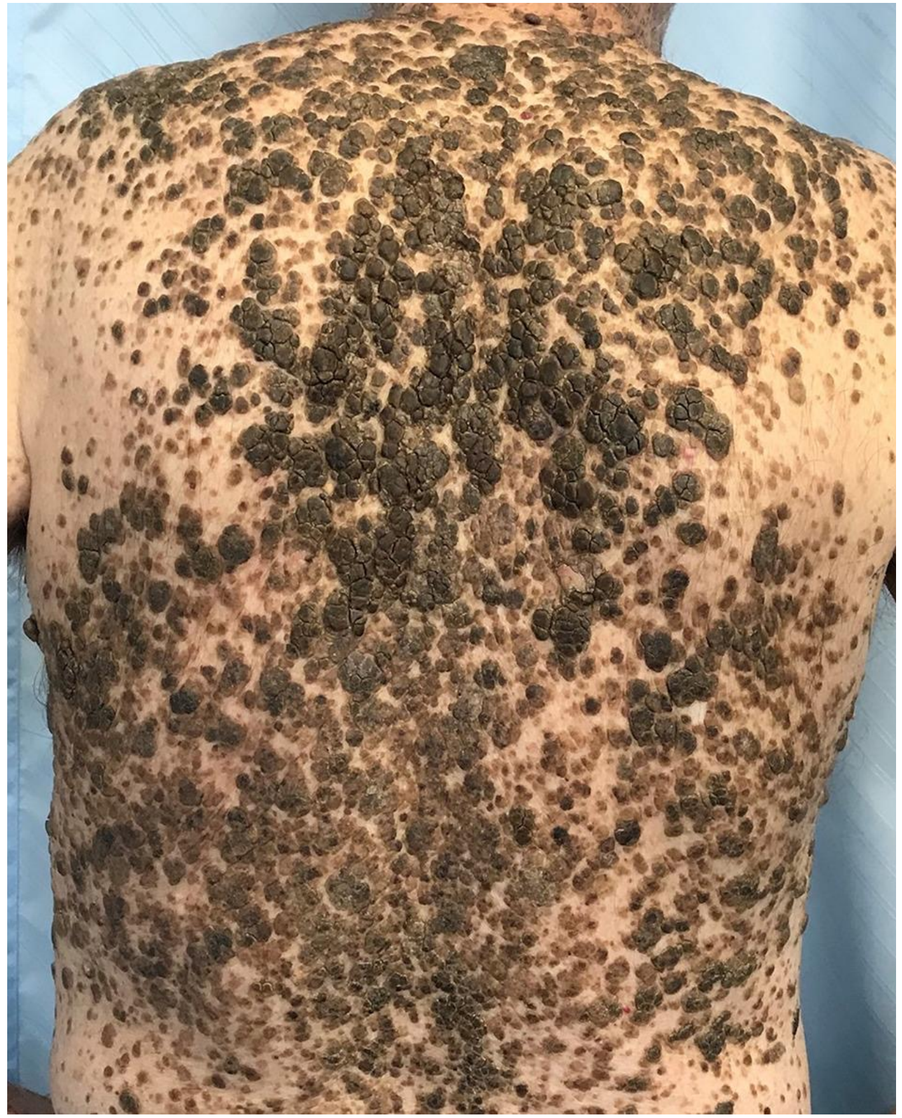


Seborrheic keratosis

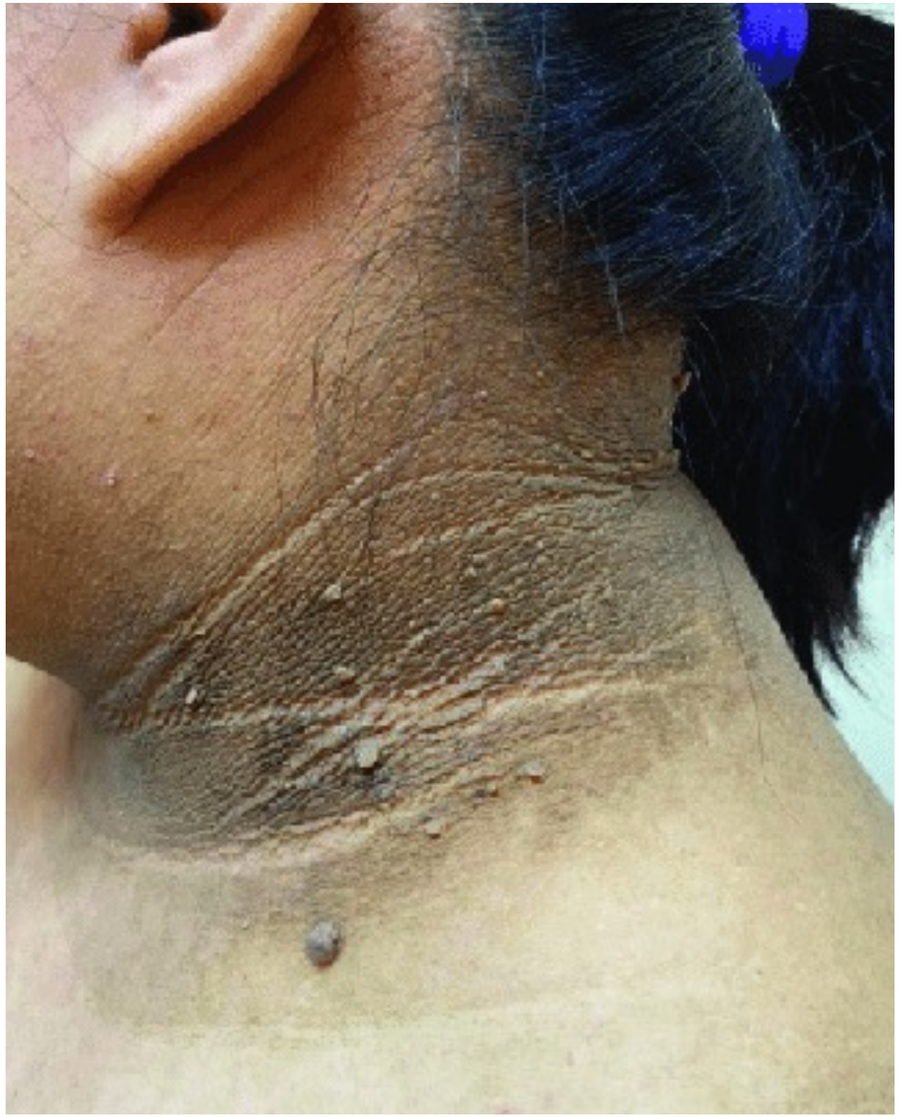
- **Leser-Trelat sign**
  - Sudden explosive onset of many seborrheic keratosis
  - Often produced by other malignant tumors (e.g. GI tract, lung, or breast cancers): – paraneoplastic syndrome
  - Caused by increased production of growth factor (e.g. TGF-α) or growth factor receptor (e.g. EGFR) by other malignant tumors
  - May associated with **acanthosis nigricans**

Acanthosis nigricans

- Brown-to-black velvety hyperpigmentation of skin, usually found at body folds (axilla, groin, posterior neck)
- May associated with obesity or endocrinopathy (DM): **benign acanthosis nigricans**
- May associated with other malignant tumors (e.g. adenocarcinoma of GI tract, lung, uterus): **malignant acanthosis nigricans**



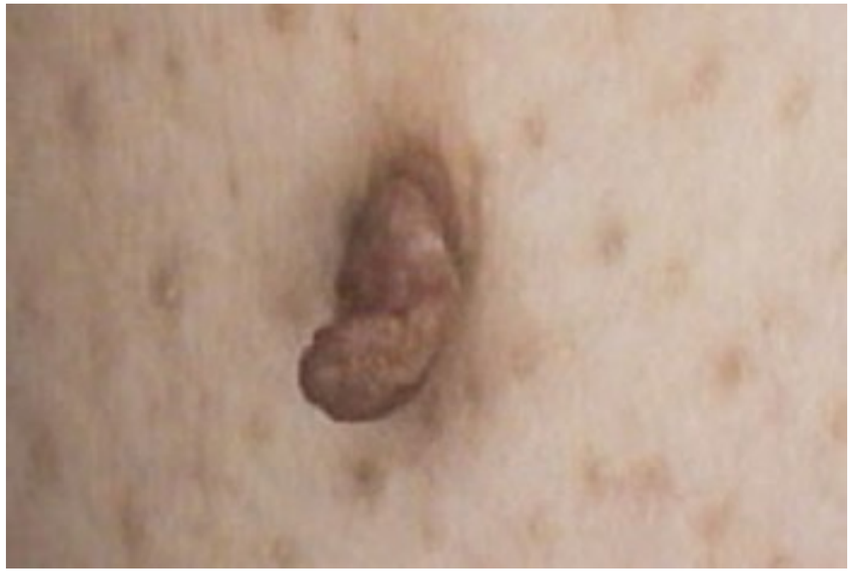
Leser-Trelat sign

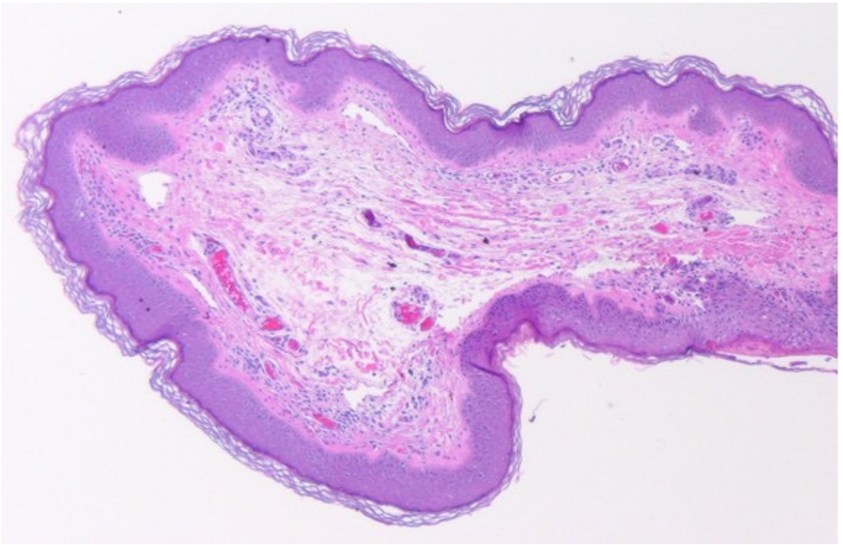


Acanthosis nigricans

Fibroepithelial polyp

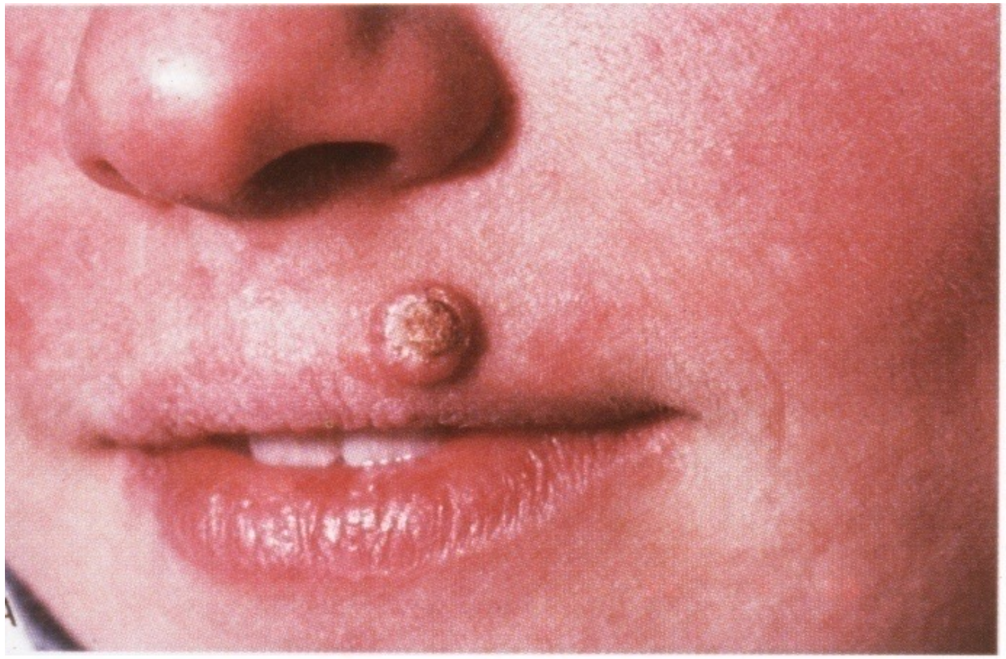
- **Synonyms:** Skin tag, squamous papilloma, acrochordon
- **Clinical:**
  - Common in middle-aged and older patients, usually at skin crease areas (neck, groin, perigenital areas)
  - Soft, flesh-colored, bag-like tumor with small pedunculated stalk (sometimes can be very large in size, called “giant skin tag”)
  - Usually not harmful
  - May associated with DM and intestinal polyposis
- **Histopathology:**
  - Pedunculated exophytic lesion with fibrovascular core covered by benign squamous epidermis

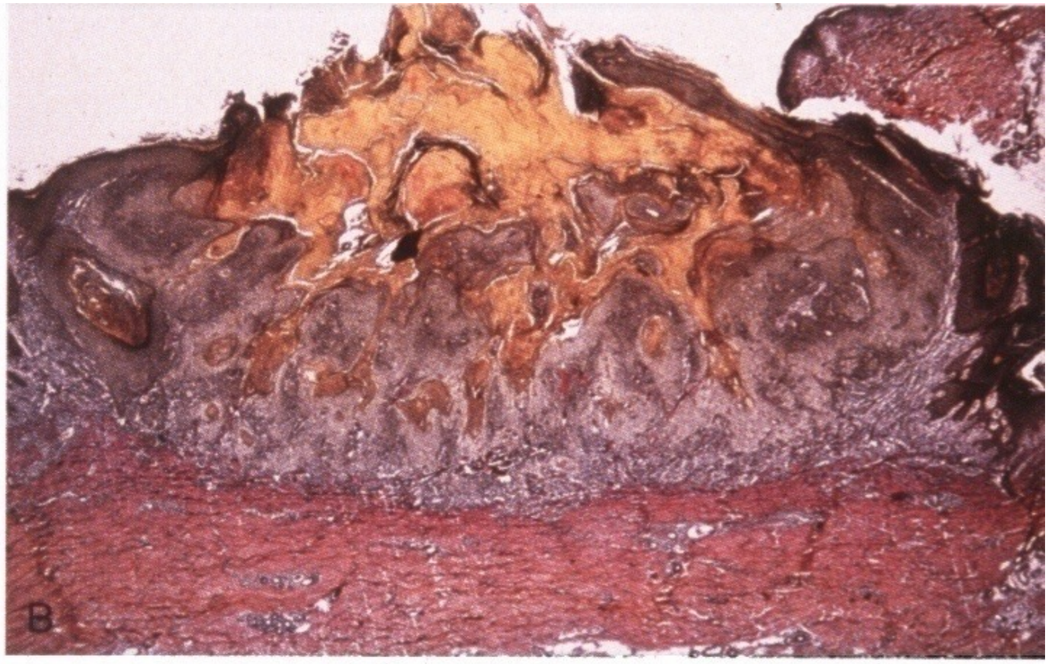




Keratoacanthoma

- Controversy whether benign tumor, pseudomalignancy or variant, of well-differentiated squamous cell carcinoma?
- At present, it is recommended to be called **“keratoacanthoma-like squamous proliferation”** or **“squamoproliferative tumor of uncertain malignant potential, keratoacanthoma-like”**.
- **Clinical:**
  - Rapid-growing skin tumor, usually at sun-exposed areas
  - Flesh-colored, dome-shaped nodule with central keratin-filled plug (crater-like appearance), size 1-2 cm in diameter
  - Giant keratoacanthoma: a large tumor usually > 3 cm in size)
  - Clinically mimicking well-differentiated squamous cell carcinoma; therefore, biopsy for pathologic diagnosis may be needed.
- **Prognosis:** Self-limiting and heal spontaneously without treatment (usually within 4-6 months)





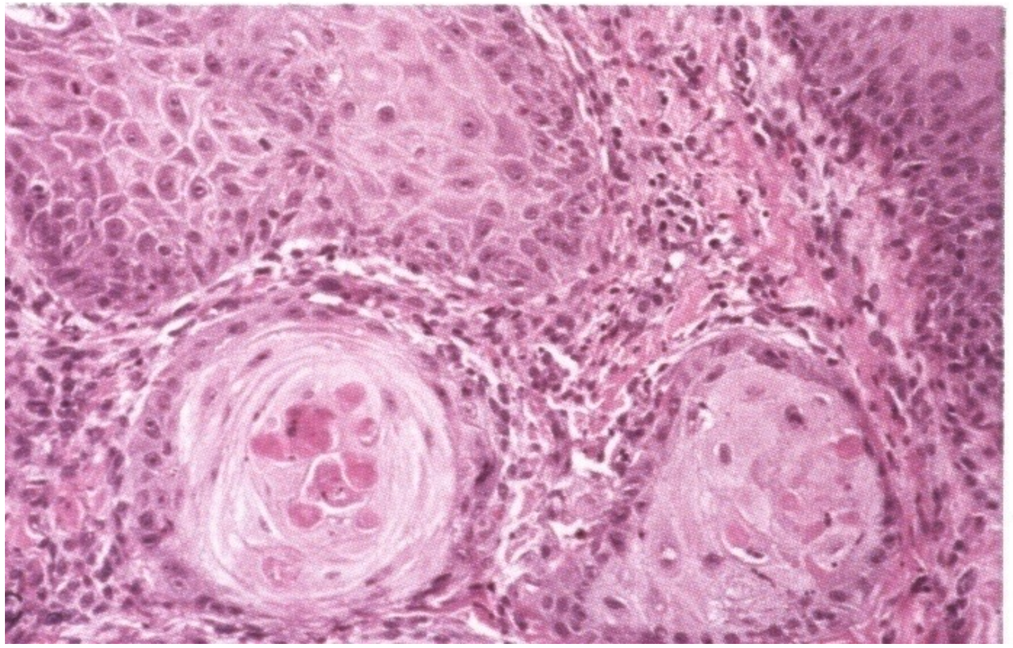


Figure 27–10 ■

Keratoacanthoma. *A*, This symmetric crater-like nodule has a prominent central keratin plug. *B*, At low power, the crater-like architecture may be appreciated with an elastic tissue stain where the dermis is red, epithelial elements are gray, and the central keratin plug is yellow. *C*, Higher power view shows keratoacanthoma to be composed of large, glassy squamous cells and central islands of eosinophliic keratin. (*A* and *B* from Murphy GF, Herzberg AJ: Atlas of Dermatopathology. Philadelphia, WB Saunders, 1996, pp 143 and 144.)

Premalignant & malignant epidermal tumors

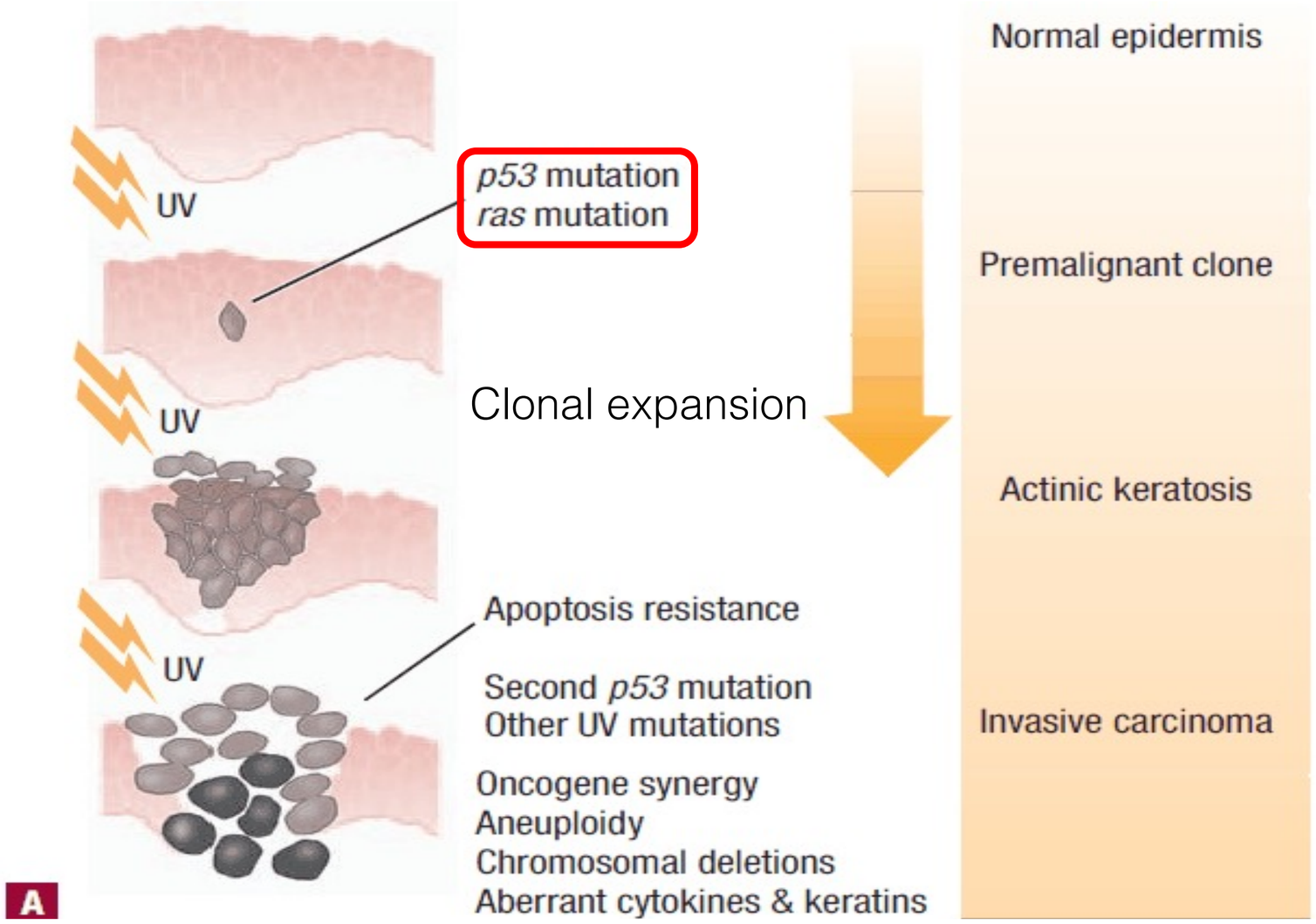
1. **Actinic (solar) keratosis**

2. **Squamous cell carcinoma in-situ / Bowen disease**

3. **Squamous cell carcinoma (invasive) ***

4. **Basal cell carcinoma ***

Ultraviolet (UV) carcinogenesis



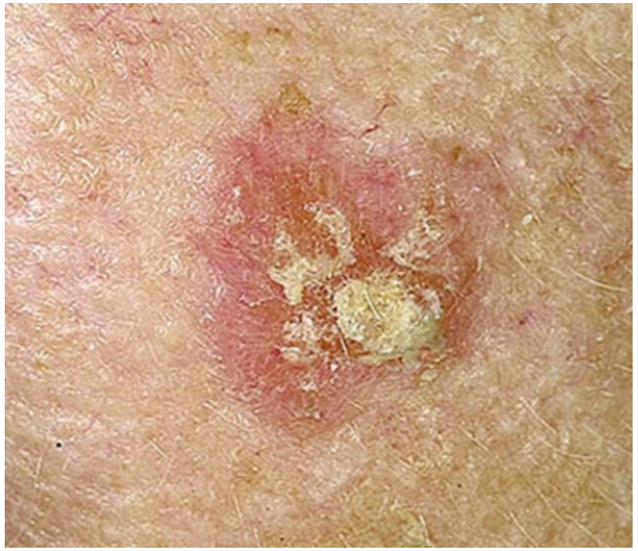
Actinic (solar) keratosis

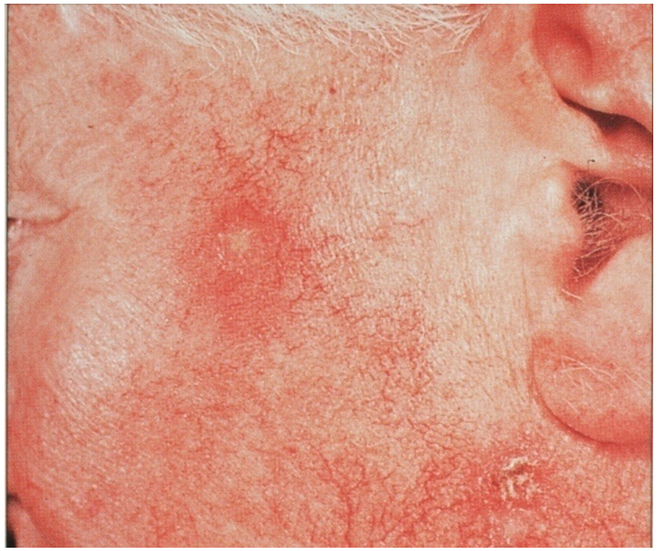
- **Definition:**
  - A skin lesion caused by excessive exposure to UV (especially UV-B)
  - A potential pre-malignant lesion of squamous cell carcinoma (although some regress or remain stable)
  - Risk of malignant change to invasive squamous cell carcinoma is 6-10% (13-20% in some studies)

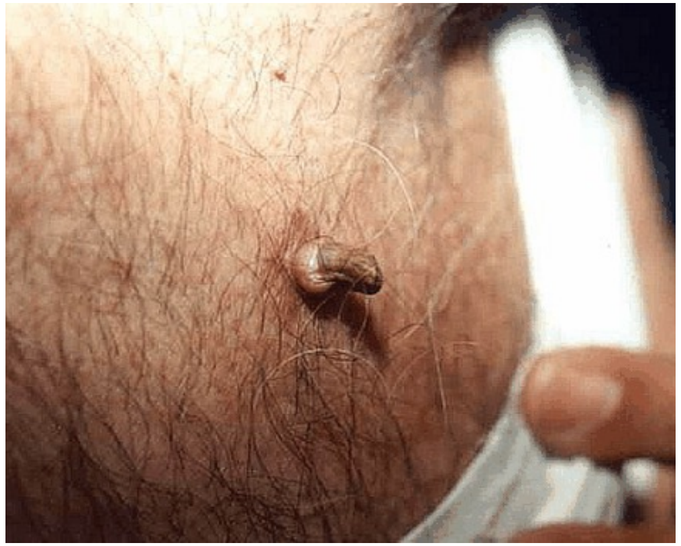
- **Clinical:**
  - Middle-aged and elderly patient (usually in lightly-pigmented skin, especially Caucasoid)
  - Location: usually at sun-exposed areas (face, arm, dorsum of hands)

Actinic (solar) keratosis

- **Clinical:**
  - Lesion usually less than 1 cm, red (from angiogenesis) or tan-brown patch or plaque with rough sandpaper-like consistency
  - May have telangiectasia (dilated superficial capillaries)
  - May have yellow-white scale (due to increased keratin at surface
  - May form a “cutaneous horn” (reaction pattern with marked hyperkeratosis)

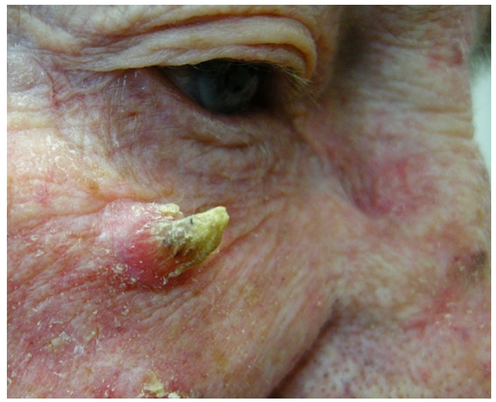


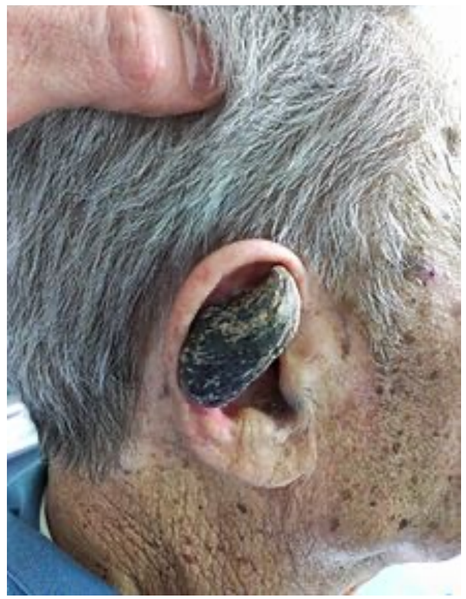




Cutaneous horn (cornu cutaneum)

- A descriptive clinical findings of hyperkeratotic epithelial lesion resembling an animal horn, characterized by height more than half of diameter of its base
- **A reaction pattern caused by other lesions:**
  - Actinic keratosis (38-40%)
  - Squamous cell carcinoma
  - Keratoacanthoma
  - Seborrheic keratosis
  - Verruca vulgaris
  - Others





Actinic (solar) keratosis

- **Histopathology:**
  - Mild acanthosis with occasional downward buds with dysplastic keratinocytes displaying cytologic atypia* with hyperkeratosis (particularly parakeratosis)
  - **Early lesion:** Dysplastic (atypical) keratinocytes with loss of polarization, crowding, and overlapping begin at basal layer (lower portion of epidermis).
  - **Later lesion:** Dysplastic keratinocytes can progress to involve mid to upper epidermal layers, can extend along adnexal structures (typically limited to infundibular extension), but never involve full epidermal thickness.

*** Cytologic atypia:**

- Increased nuclear size
- Increased nuclear-to-cytoplasmic ratio
- Hyperchromatic nuclei (nuclear hyperchromasia)
- Nuclear pleomorphism
- Increased mitosis, may have atypical/abnormal mitotic figure

Actinic (solar) keratosis

- **Histopathology:**
  - Dermis usually contains thickened fibrillary faint basophilic elastic fibers (called **solar elastosis**), caused by dermal collagen degradation and replacement with de novo synthesis of elastotic materials (elastin, fibrillin, and glycosaminoglycans) by sun-damaged fibroblasts

Solar elastosis

- Histologic evidence of skin damaged severely by UV (representing photoaging)
- Inflammatory cells (lymphocytes, histiocytes) reactions at dermis
- Angiogenesis (due to VEGF produced by UV-damaged keratinocytes)
- Telangiectasia (dilated small capillaries)

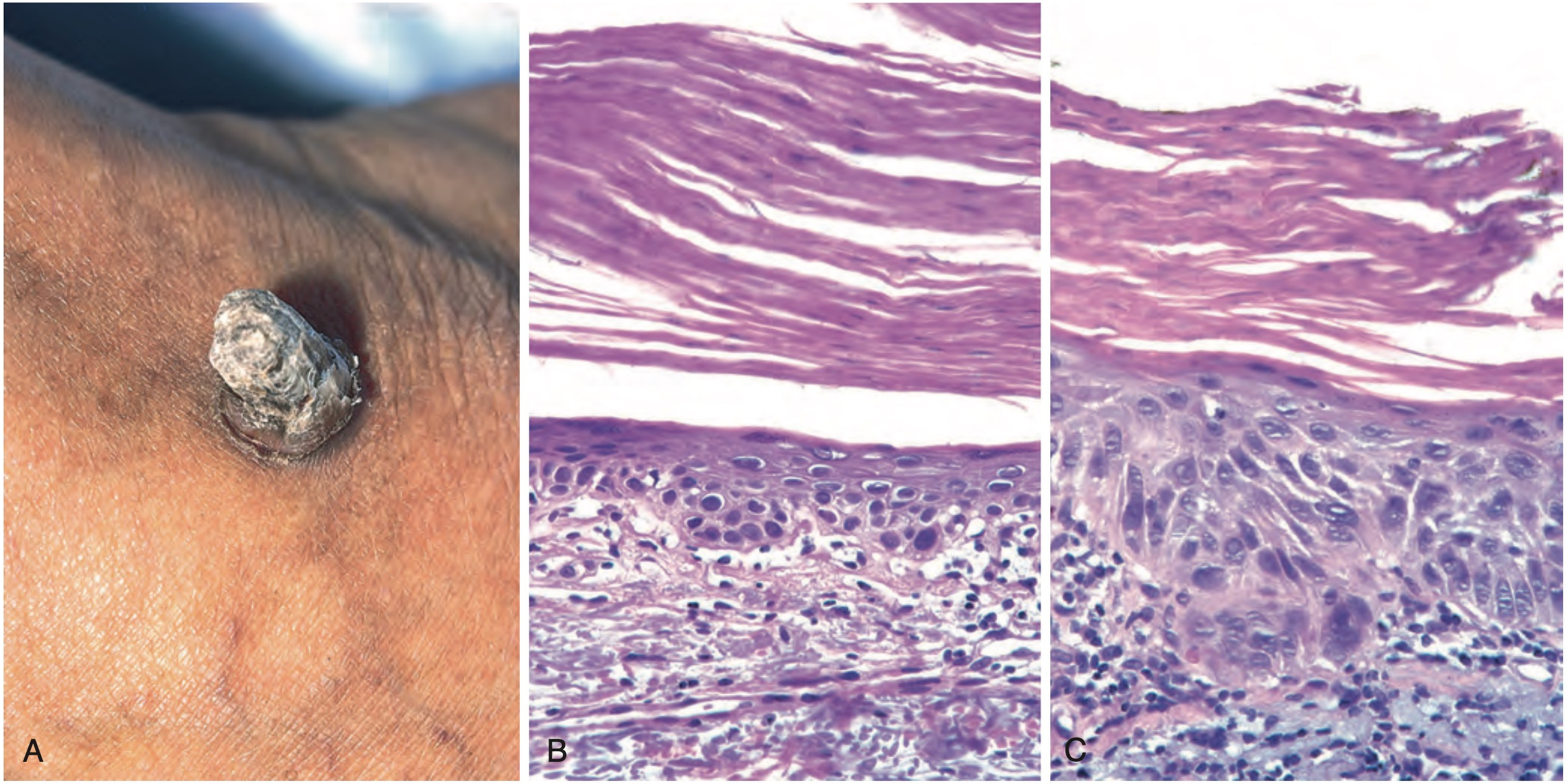
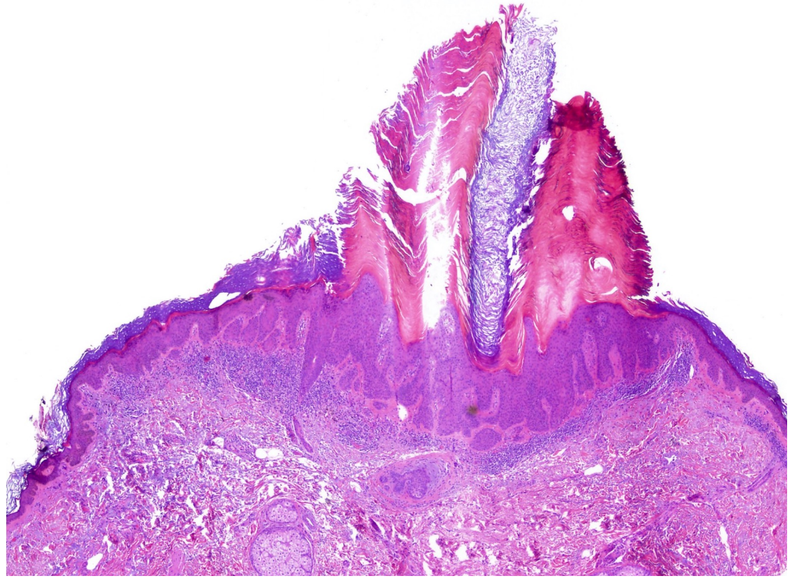
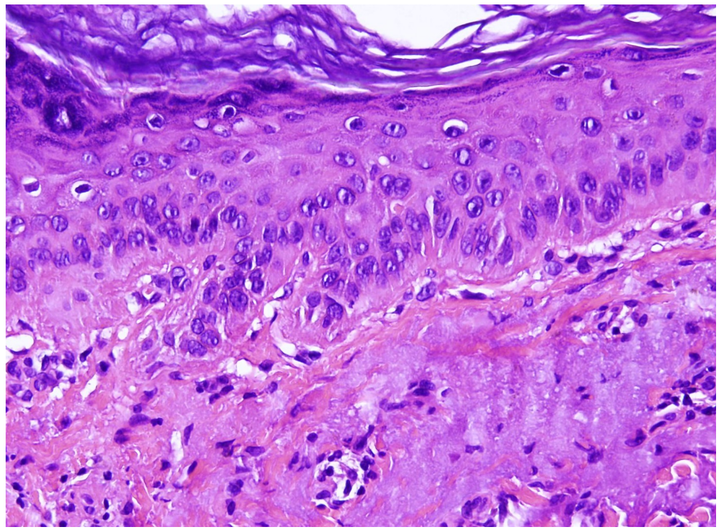


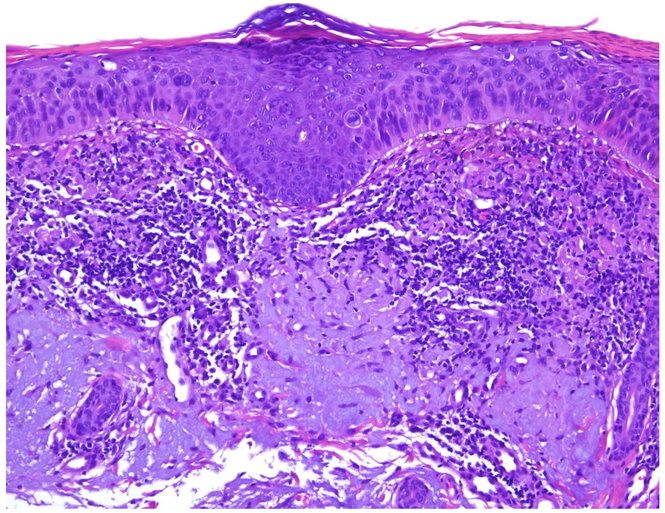
Figure 25.12 Actinic keratosis. (A) Excessive keratotic scale in this lesion has produced a "cutaneous horn." (B) Basal cell layer atypia (dysplasia) is associated with marked hyperkeratosis and parakeratosis. (C) Progression to full-thickness nuclear atypia, with or without the presence of superficial epidermal maturation, heralds the development of squamous cell carcinoma in situ.



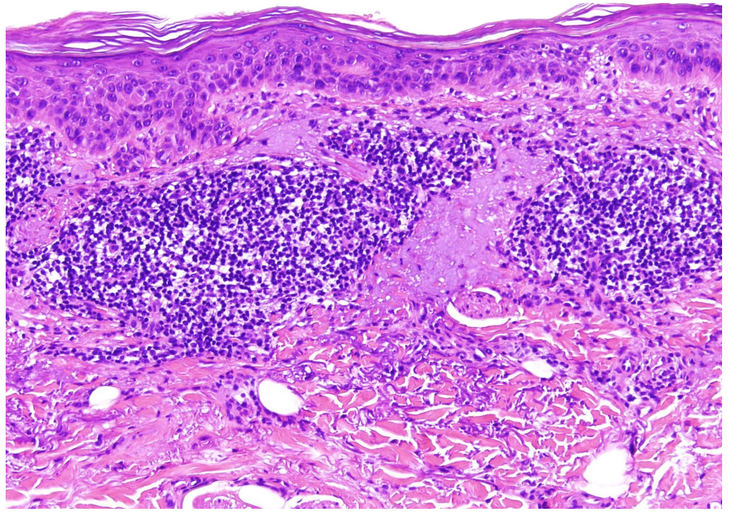
Acanthotic epidermis, papillomatosis and thick hyperkeratosis. A Freudenthal funnel is present in the central portion.



Epidermis with basal atypia, hyperkeratosis and marked solar elastosis with slight lymphocytic infiltrate in the dermis (early lesion)



Keratinocytic atypia spares the acrosyringial epithelium.



Keratinocytic atypia (loss of polarity in lower half of epidermis with nuclear pleomorphism and hyperchormasia), solar elastosis, and abundant lymphocytic infiltrate

Actinic Keratosis: *Pathogenesis and clinical findings*

Authors:
Darrin Wiebe
Reviewers:
Heena Singh
Amanda Eslinger
Yan Yu
Matthew Harding
Laurie Parsons*
** MD at time of publication*

Genetics → Unknown mechanism

UV Exposure → Tumor suppressor mutation → ↓ KC response to signals of apoptosis

Immunosuppression → ↓ ability to control damaged cell proliferation

↑ KC proliferation

↑ production of keratin → Keratin deposited on the outer surface of epidermis

- **Crusted texture**
- ↑ keratin deposition leaves nuclei in outer keratin layer → **Parakeratosis** (Nuclei in stratum corneum on histology)

Release of inflammatory cytokines → FB stimulated to produce elastin → Elastin deposition in the dermis → **Dermal Thickening**

Attraction of lymphocytes into dermis → Lymphocytes release inflammatory cytokines

- Stimulation of local nociceptive receptors → **Burning**; **Itching**
- Vasoactive cytokines cause dilation of local microvasculature → **Erythema**

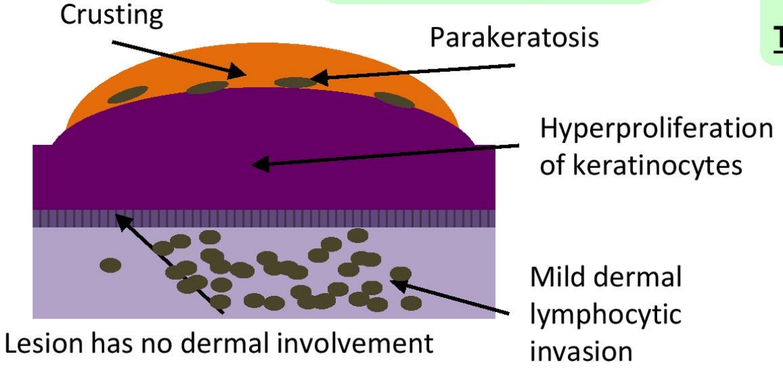
Risk of progression to SCC is 0.1% to 20% per year

Typically found on sun exposed areas

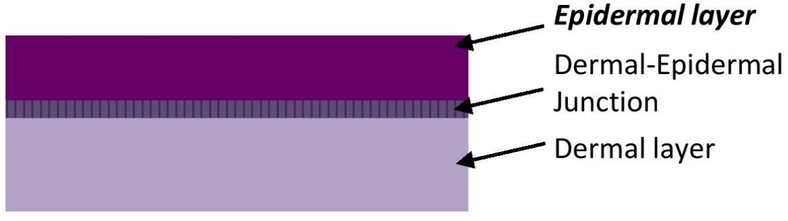
Present in 11-26% of North Americans
Risk factors: Sun exposure, fair skin

Abbreviations:
SCC = squamous cell carcinoma
KC = keratinocyte
FB = fibroblast
CK = cytokines

Actinic Keratosis



Normal Skin



Squamous cell carcinoma in-situ / Bowen disease

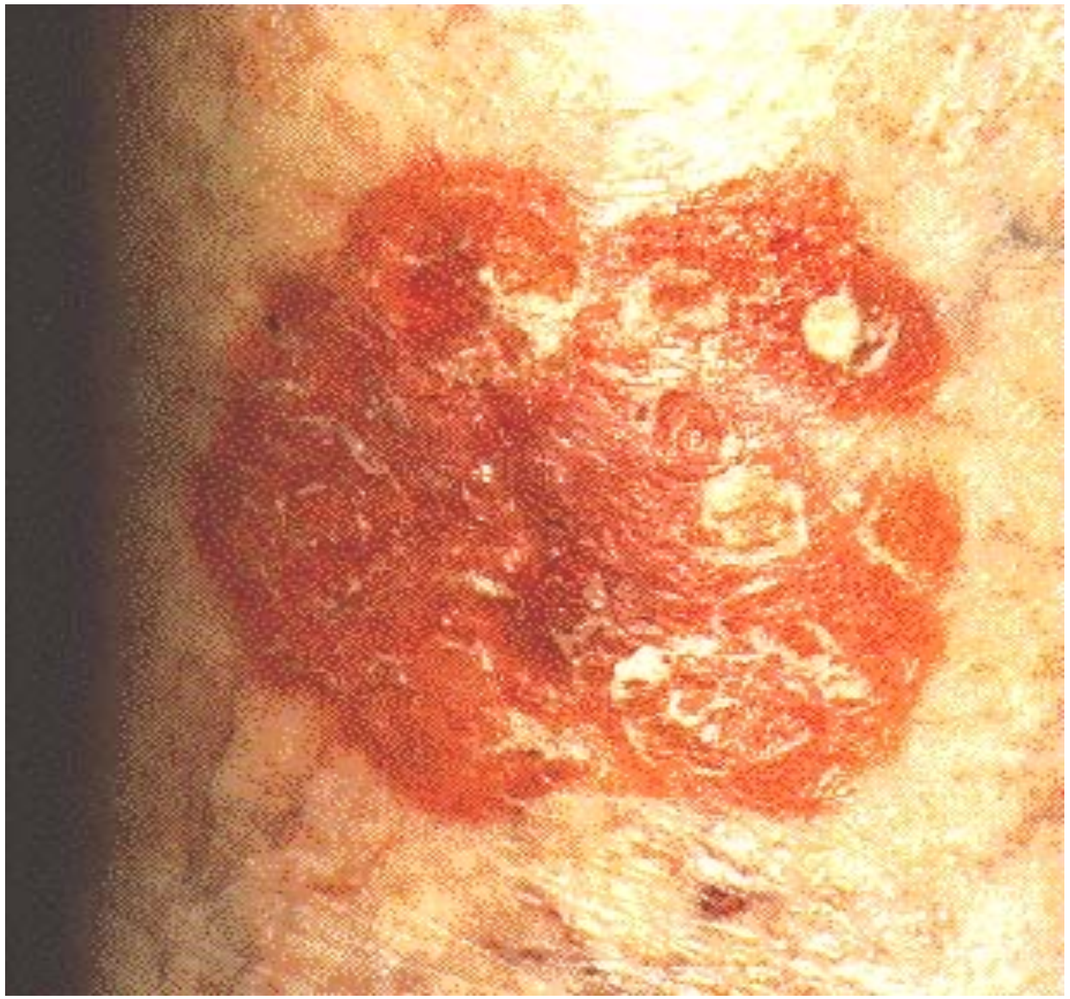
- An early stage of squamous cell carcinoma that limits in the epidermis, but not yet invades beyond the basement membrane

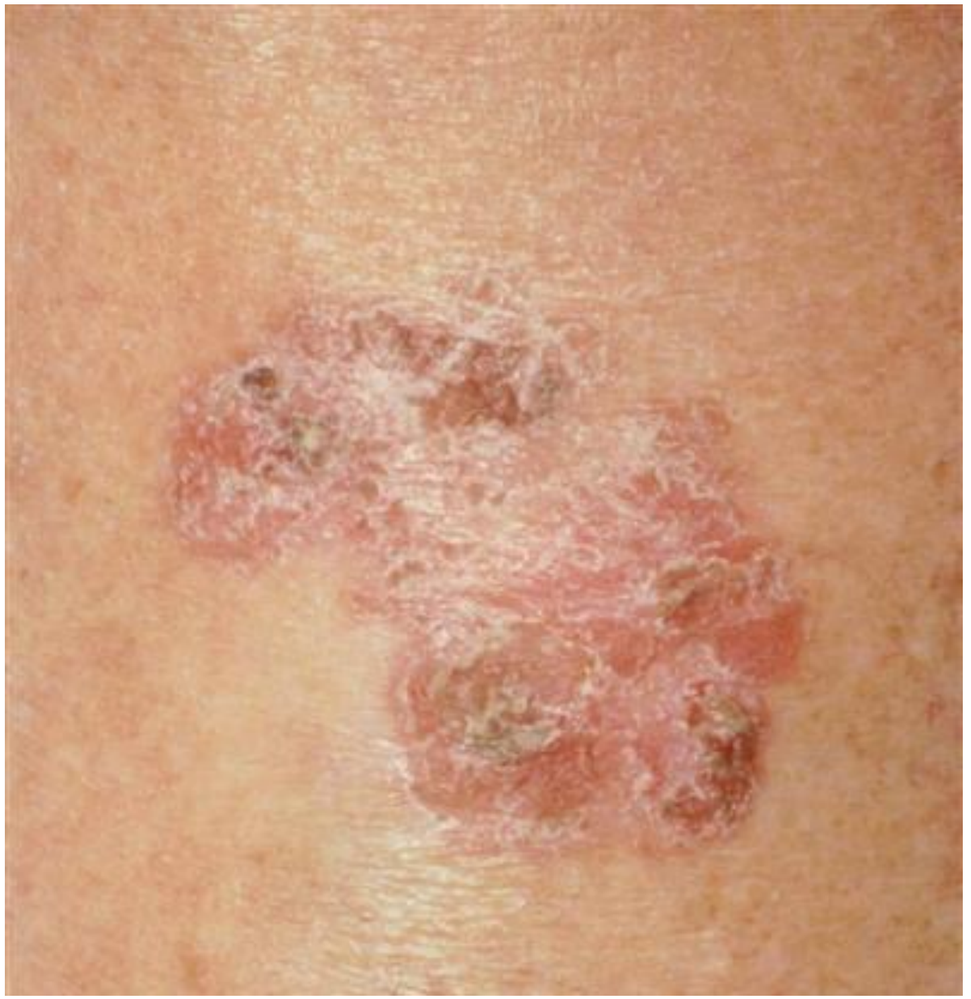
- **Etiology and risk factors:**
  - UV light (particularly UV-B)
  - Chemicals (arsenic)
  - Immunosuppression
  - High-risk HPV (type 16 and 18) at anogenital lesions

- **Pathogenesis:**
  - Sun-exposed areas: DNA damage induced by UV light exposure
  - Anogenital area: HPV viral proteins E6 and E7 interfere with the activity of tumor suppressor proteins that regulate cell growth and cell survival.

Squamous cell carcinoma in-situ / Bowen disease

- **Clinical:**
  - Mostly middle-aged and elderly patients
  - Usually in lightly-pigmented skin with history of chronic sunlight exposure
  - Single or multiple slow-growing, well-circumscribed, irregular, erythematous, scaly or crusted plaques, size ranging from few mm to many cm
  - Approximately 50% develop invasive component, and 30% have metastatic potential



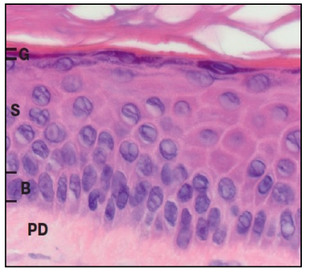


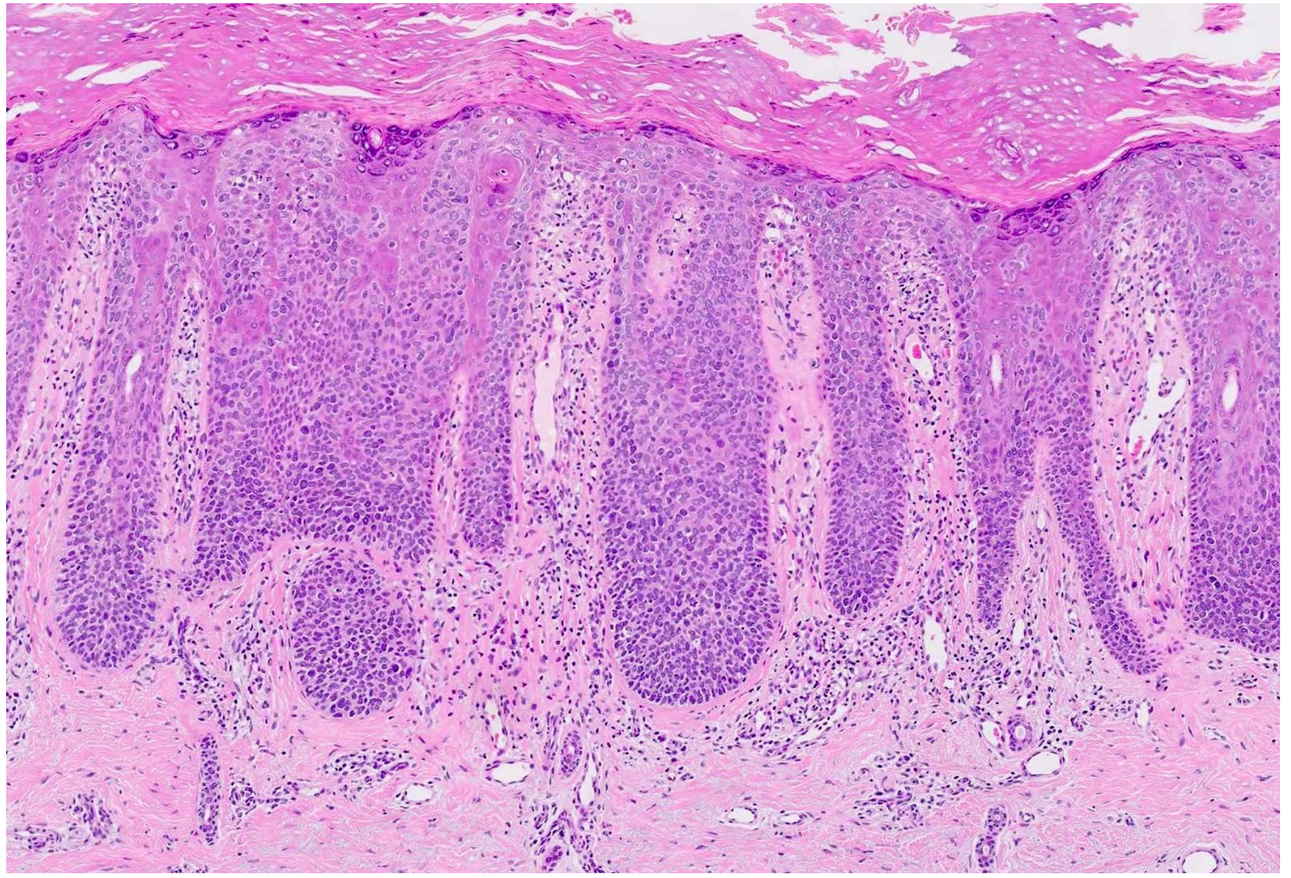
Squamous cell carcinoma in-situ (Bowen disease):
well-circumscribed, irregular, erythematous, scaly plaques

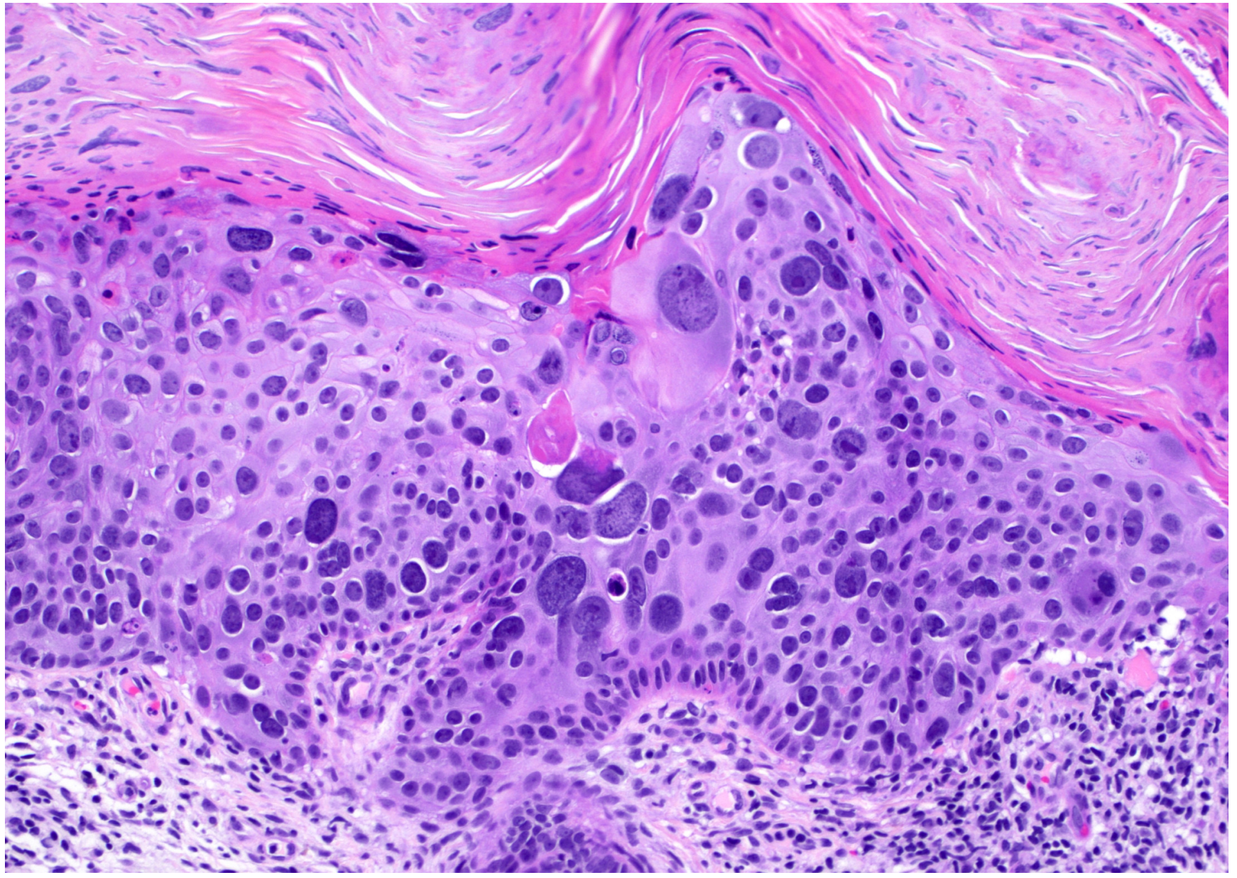
Squamous cell carcinoma in-situ / Bowen disease

- **Histopathology:**
  - Epidermal full-thickness involvement by dysplastic (atypical) keratinocytes (although may be surrounded by normal keratinocytes), but not extend beyond basement membrane
  - Architectural and cellular atypia, apoptotic cells, individual cell dyskeratosis
  - Markedly altered maturation (Some surface keratinization (parakeratosis) and intercellular bridges may be seen.)
  - Marked nuclear atypia, including nuclear hyperchromasia and multinucleation, numerous mitotic figures, atypical mitotic figures
  - May extend into eccrine sweat glands (not considered invasive disease)

Normal skin histology



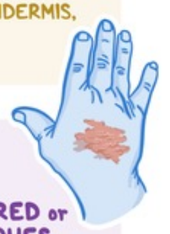




Squamous cell carcinoma in-situ / Bowen disease: Epidermis shows acanthosis and hyperkeratosis (commonly parakeratosis) and is completely disorganized with full-thickness atypical keratinocytes displaying overt cytologic atypia.

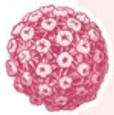
BACKGROUND

* **EARLY FORM of SKIN CANCER** with POTENTIAL to DEVELOP into INVASIVE SQUAMOUS CELL CARCINOMA
  - ~ 2nd MOST COMMON TYPE of SKIN CANCER
  - ~ IN SITU: CANCER CELLS FOUND in EPIDERMIS, but HAVE NOT YET INVADED BASEMENT MEMBRANE



CAUSES

* **EXPOSURE to UV RADIATION**
  - ~ SUN or TANNING BOOTHS
* **RISK FACTORS:**
  - ~ FAIR SKINNED INDIVIDUALS CONSIDERED ↑↑ RISK (RISK INCREASES with SUN EXPOSURE OVER TIME)
  - ~ WEAKENED IMMUNE SYSTEM (e.g. SECONDARY to SOLID ORGAN TRANSPLANTATION, HIV INFECTION, LONG-TERM GLUCOCORTICOID USE)
  - ~ ARSENIC EXPOSURE
  - ~ HPV INFECTION



SIGNS & SYMPTOMS

* **SMALL, WELL-CIRCUMSCRIBED, RED or BROWN PATCHES with SCALY PLAQUES on TOP**
  - ~ MOST OCCURS on SUN-EXPOSED SKIN REGIONS (PARTICULARLY FACE, EARS, NECK, & HANDS)
  - ~ CAN DEVELOP on SUN-PROTECTED AREAS like LEGS & GENITALS
  - ~ GROWS SLOWLY OVER MONTHS & YEARS
* **PROGRESSION to INVASIVE SQUAMOUS CELL CARCINOMA:**
  - ~ RAPID GROWTH of LESION, ULCERATION, BLEEDING, or PAIN

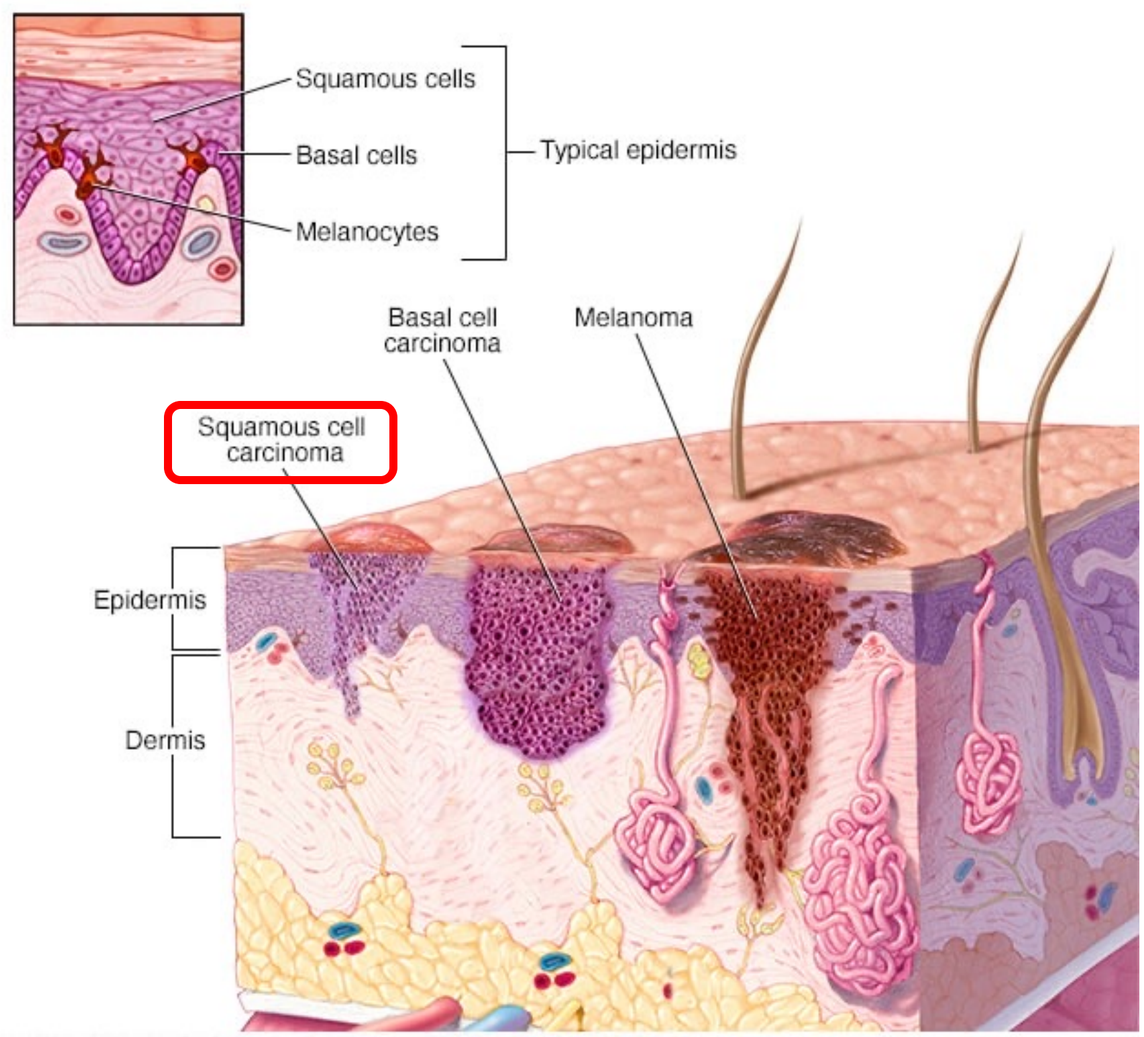
TREATMENT

* **SURGICAL (PREFERRED)**
  - ~ STANDARD SURGICAL EXCISION
  - ~ MOHS SURGERY
    - VERY PRECISE TECHNIQUE USED on HIGH-RISK SITES such as FACE or GENITALIA
* **NON-SURGICAL**
  - ~ CURETTAGE & ELECTRODESICCATION
    - SIMPLE, SAFE, EFFECTIVE, but ONLY PERFORMED on SMALL, SOLITARY LESIONS with LOW RISK of PROGRESSION to INVASIVE DISEASE
  - ~ CRYOTHERAPY
    - TUMOR FROZEN OFF with LIQUID NITROGEN, TYPICALLY USED for INDIVIDUALS MULTIPLE LESIONS
  - ~ PHOTODYNAMIC THERAPY
    - PHOTOSENSITIZING AGENTS ACTIVATED with LIGHT to TREAT CANCER CELLS
  - ~ TOPICAL MEDICATIONS
    - FLUOROURACIL or IMIQUIMOD CREAMS, ESPECIALLY for LESIONS > 3CM in DIAMETER & where HEALING from OTHER METHODS WOULD BE COMPROMISED
  - ~ FOLLOW UP (EVERY 3 - 6mo)
  - ~ MINIMIZE SUN EXPOSURE, USE BROAD SPECTRUM SUNSCREENS DAILY, WEAR PROTECTIVE CLOTHING

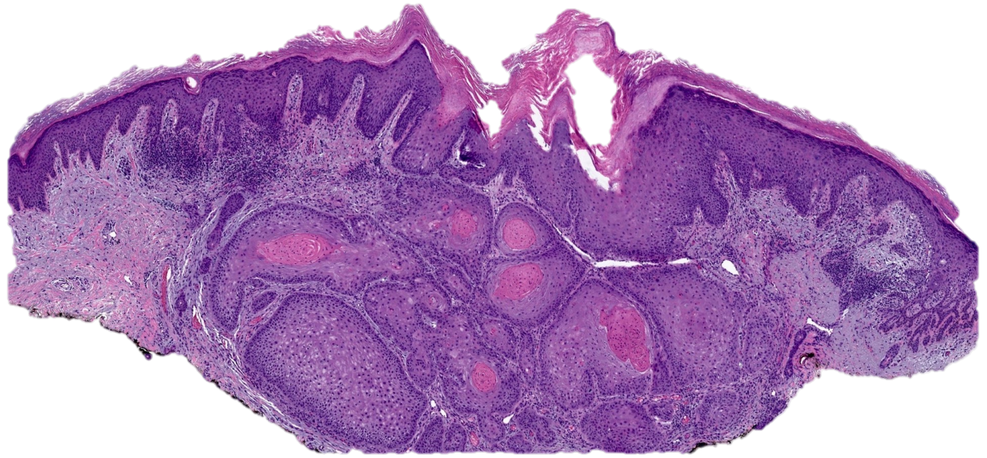
DIAGNOSIS

* **SKIN EXAMINATION**
* **DETAILED HISTORY**
  - ~ TIME of ONSET, DURATION, LOCATION, EVOLUTION
* **DERMOSCOPY**
  - ~ MAGNIFYING LENS to VISUALIZE SKIN STRUCTURES NOT VISIBLE to NAKED EYE
* **TISSUE BIOPSY**
  - ~ ATYPICAL KERATINOCYTES that INVOLVE FULL THICKNESS of EPIDERMIS without INFILTRATION into DERMIS
* **ANOGENITAL AREA**
  - ~ DISTINGUISHED from BOWENOID PAPULOSIS: PREMALIGNANT LESION PRESENTING as SOLITARY or MULTIPLE SMALL PINK, BROWN, or VIOLACEOUS PAPULES that RESEMBLE GENITAL WARTS

Squamous cell carcinoma

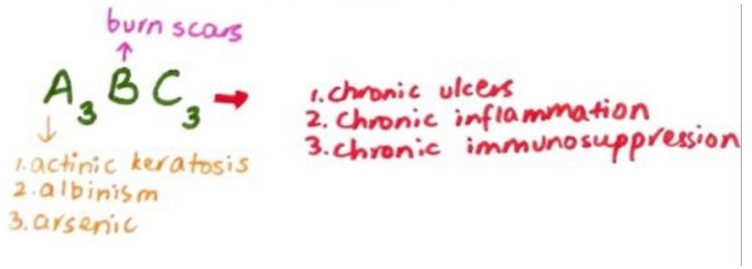


- The second most common malignant skin tumors (mostly arising on sun-exposed sites in older people)
- Usually discovered while they are small and resectable (less than 5%; deeply invasive and involve the subcutis, and metastasize to regional lymph node)



Squamous cell carcinoma

- **Etiology and risk factors** (resembling those of Bowen disease)**:**
  - Premalignant lesions: actinic keratosis, arsenic Keratosis, Bowen disease
  - Ultraviolet radiation
  - Ionizing radiation
  - HPV high-risk types: type 16, 18 (anogenital); type 5, 8
  - Immunosuppression: chemotherapy, transplantation
  - Chemical carcinogens: arsenic. hydrocarbon (oils, tars)
  - Persistent chronic inflammation: chronic ulcer, chronic osteomyelitis, old burn scar, varicose ulcers
    - Squamous cell carcinoma arising in such conditions is called **Marjolin's ulcer.**
  - Hereditary skin disorders (genodermatoses):
    - Albinism: tyrosinase defect (no melanin pigment to protect UV)
    - Xeroderma pigmentosa: inherited defect in DNA repair gene by nucleotide excision repair pathway



Squamous cell carcinoma

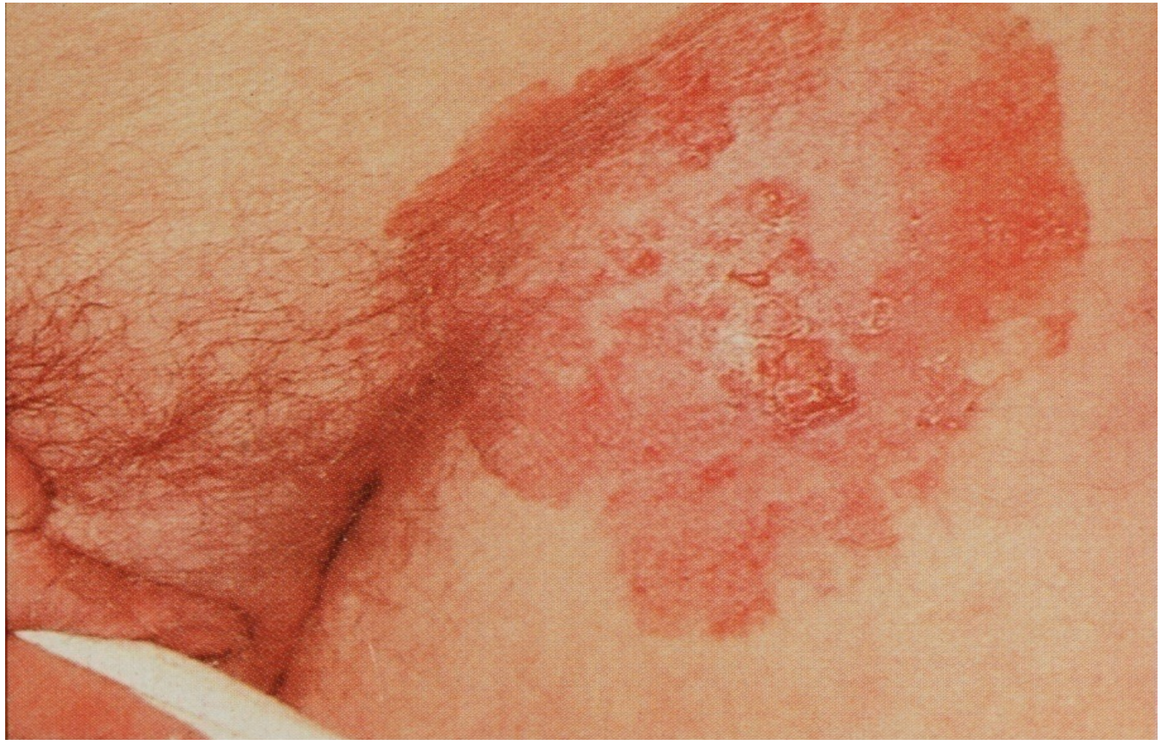
- **Pathogenesis:**
  - **UV light exposure:** subsequent unrepaired DNA damage
  - **Deactivating mutation of** TP53 (tumor suppressor gene) associated with UV exposure
    - p53 aids in cell cycle control (G1 arrest) and DNA repair (apoptosis)
  - **Activating mutation of** RAS (proto-oncogene) associated with UV exposure
  - **Immunosuppression (chemotherapy or organ transplantation):** become easily infected with oncogene viruses HPV types 5 and 8

Squamous cell carcinoma

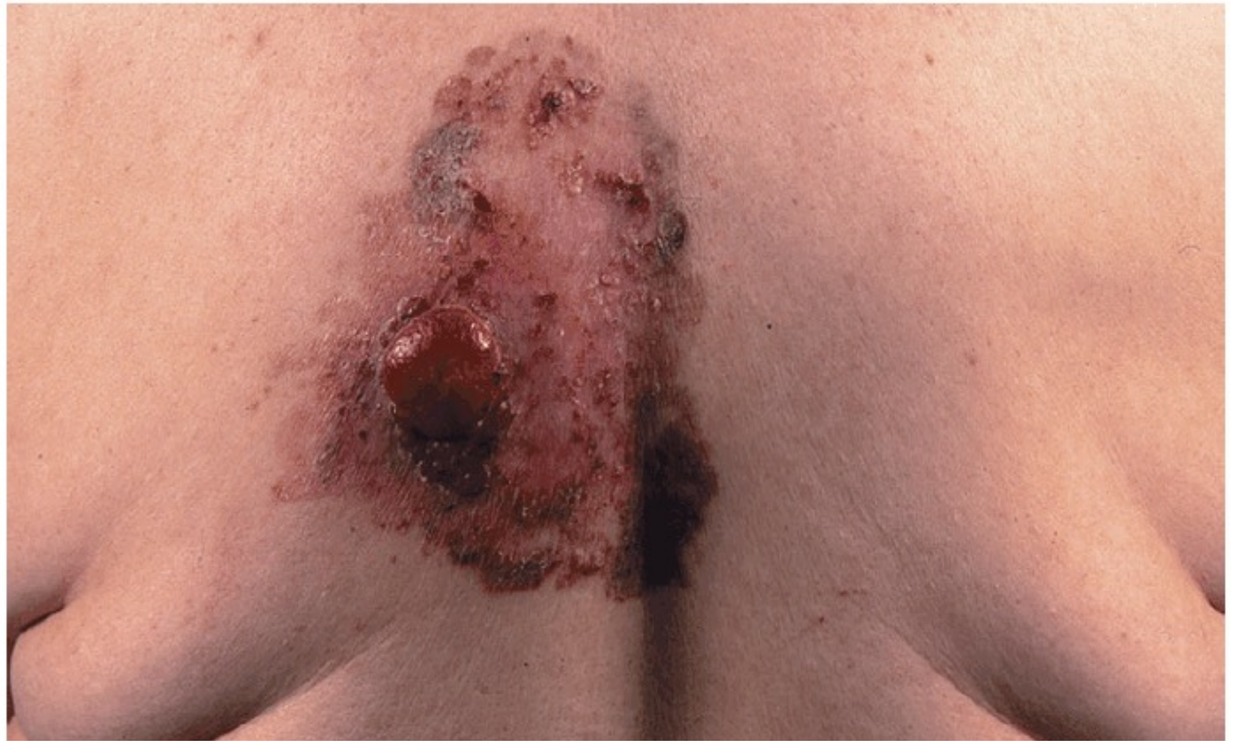
- **Location:**
  - **Sun-exposed areas:** head and neck, arm, hand, foot (UV-related)
  - **Anogenital area** (high-risk HPV-related)

- **Clinical:**
  - Usually erythematous papule, plaque, or nodule, and may be ulcerated

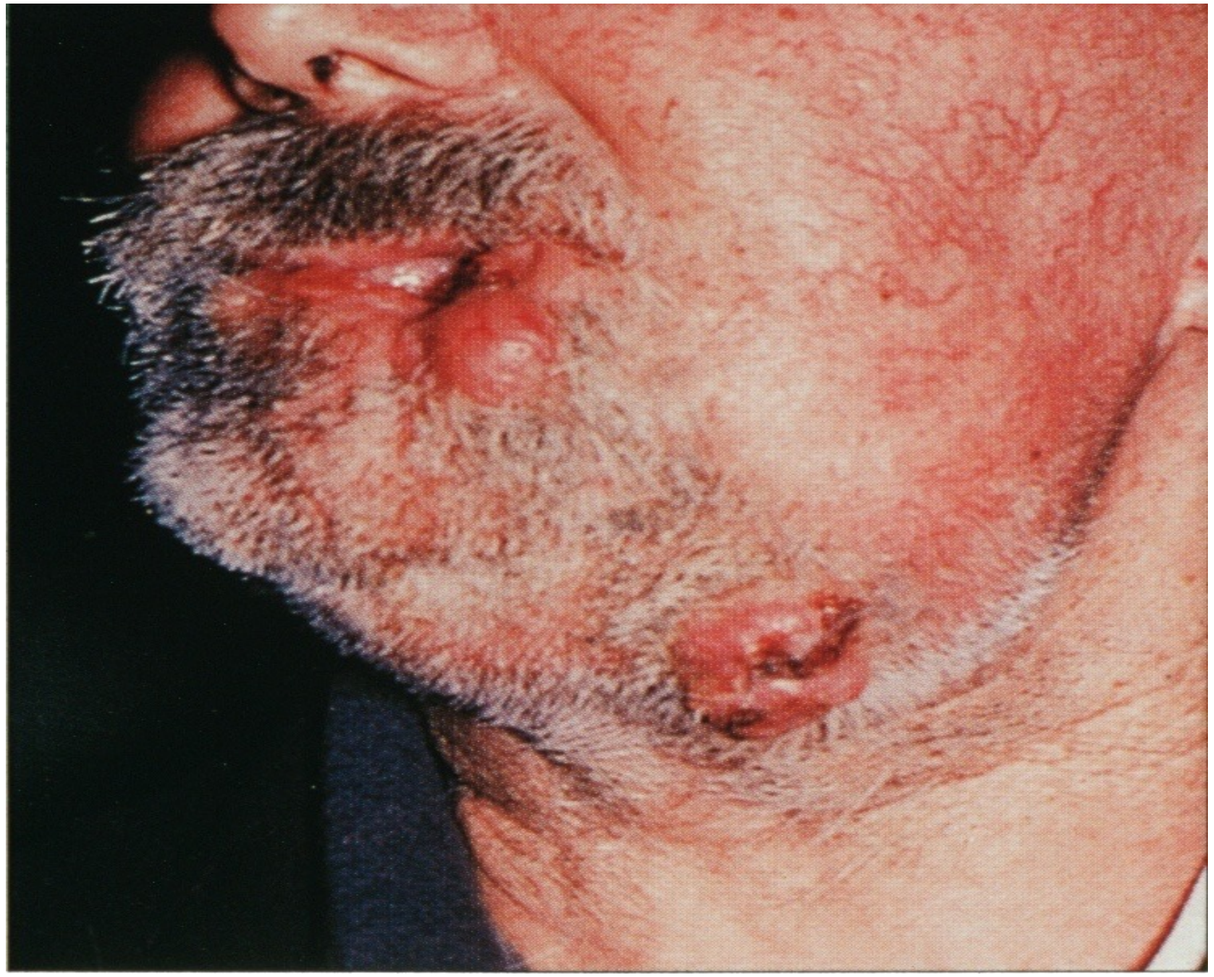
- **Prognosis:**
  - Depends primarily on **staging**
  - Rate of recurrence and metastasis depends on **tumor size** and **depth of invasion**
  - 40% of recurrence rate within 2 year
  - Better prognosis than melanoma, but worse than basal cell carcinoma



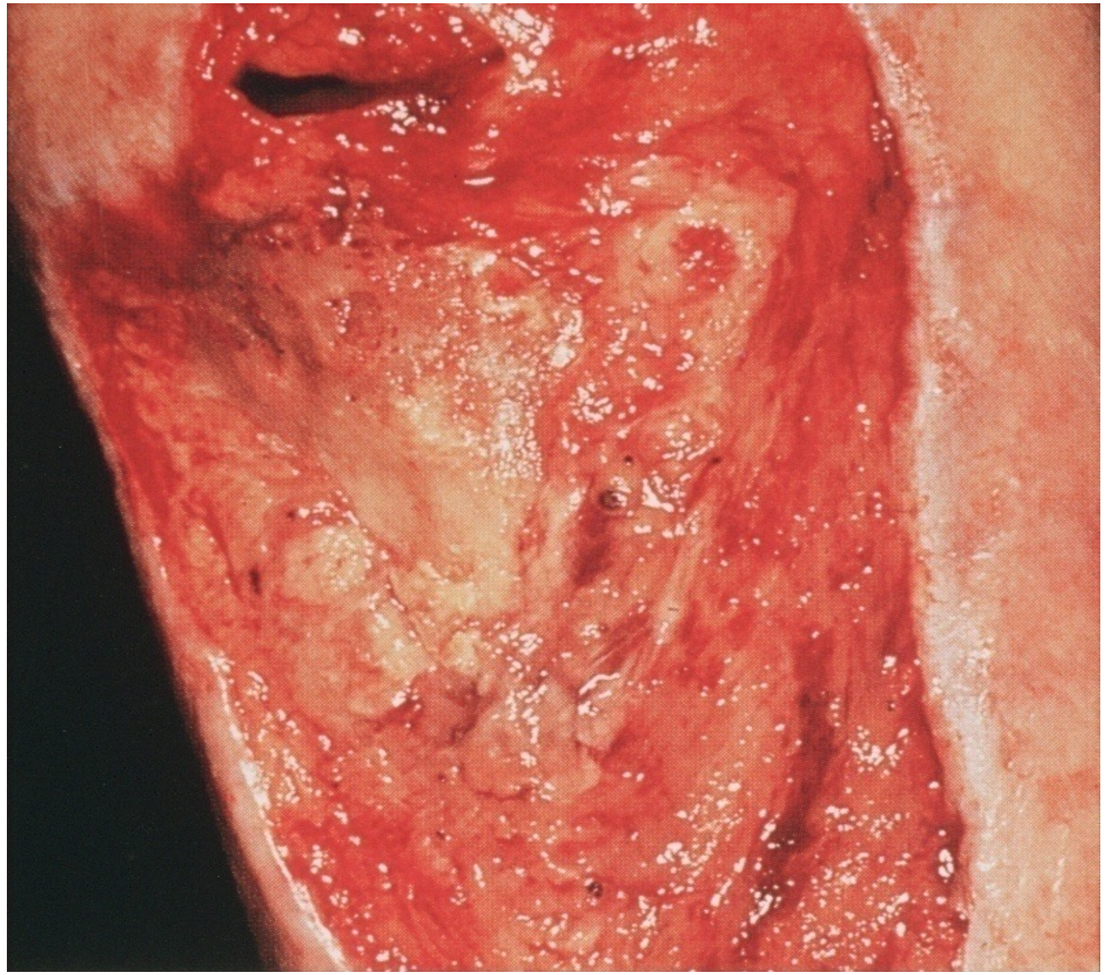
Bowen disease with invasive squamous cell carcinoma:
extensive erythematous scaly plaque with multiple nodules



Bowen disease with invasive squamous cell carcinoma:
large variegated orange, brown-to-gray plaque, sharply defined,
with irregular outline (representing Bowen disease),
and a red nodule (representing invasive squamous cell carcinoma)



Squamous cell carcinoma: large nodular tumors on lip and jaw of an elderly patient

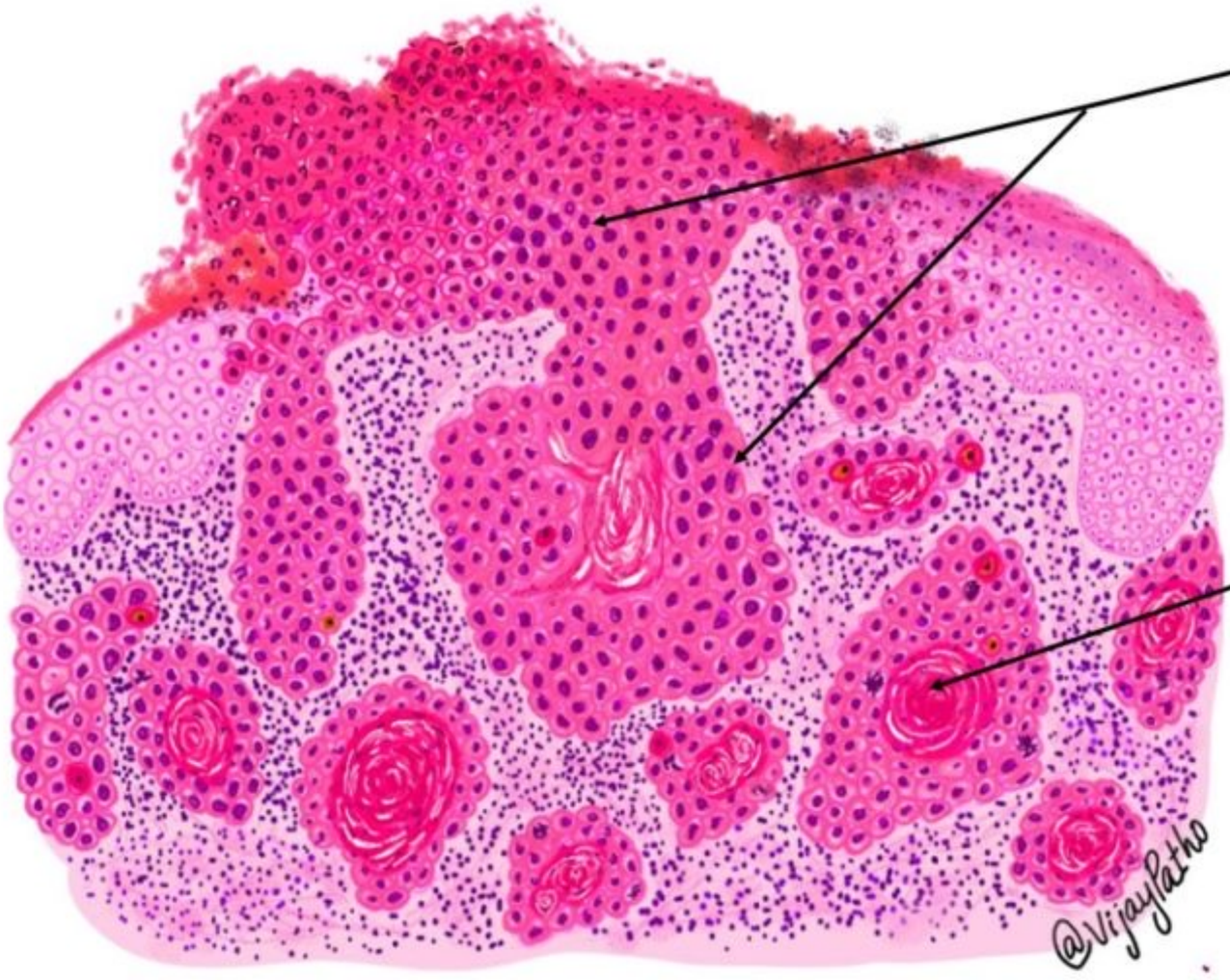


Squamous cell carcinoma arising in long-standing ulcer **(Marjolin's ulcer)**

Squamous cell carcinoma

- **Histopathology:**
  - Infiltrative sheets and nests of dysplastic/malignant squamous (keratinocytic) cells beyond basement membrane into underlying dermis or other nearby tissue
  - The neoplastic cells display nuclear hyperchromasia and pleomorphism, increased mitoses (presence of atypical forms)
  - Evidence of keratinization: keratin pearls, intercellular bridges (usually in well- and moderately-differentiated tumors)
  - Histologic grading: well-, moderately-, and poorly-differentiated

Squamous cell carcinoma



Pleomorphic **squamous** epithelial **cells** arising from the epidermis and extending into the dermis

Central keratinization surrounded by concentric layers of abnormal squamous cells

KERATIN PEARL

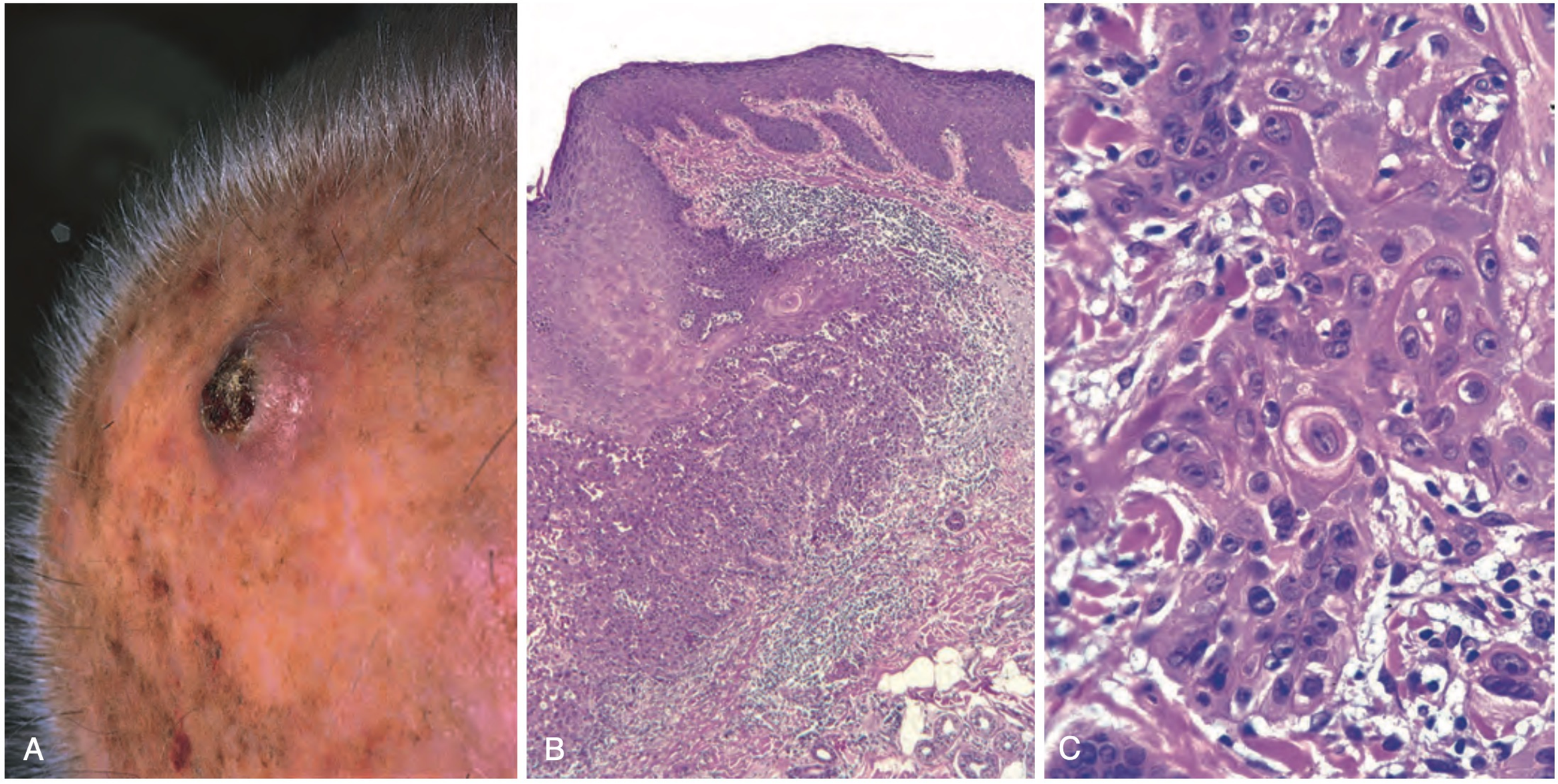
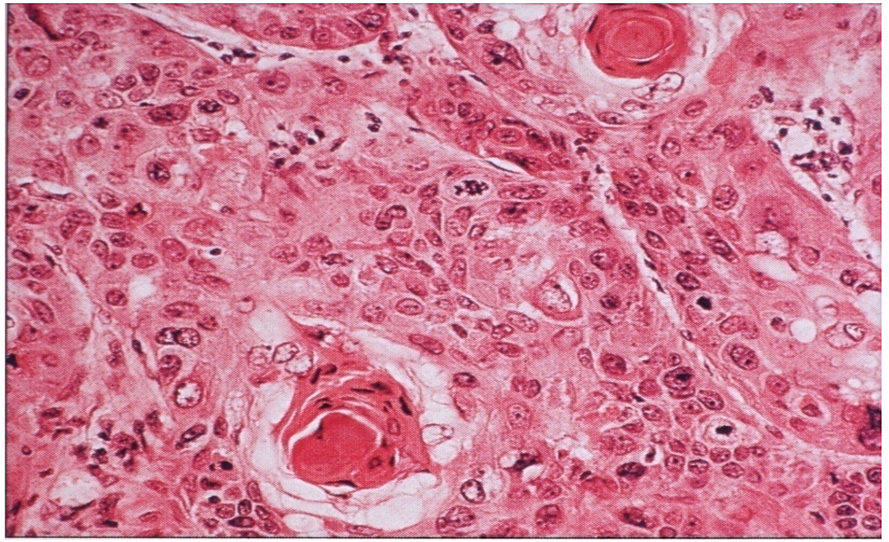
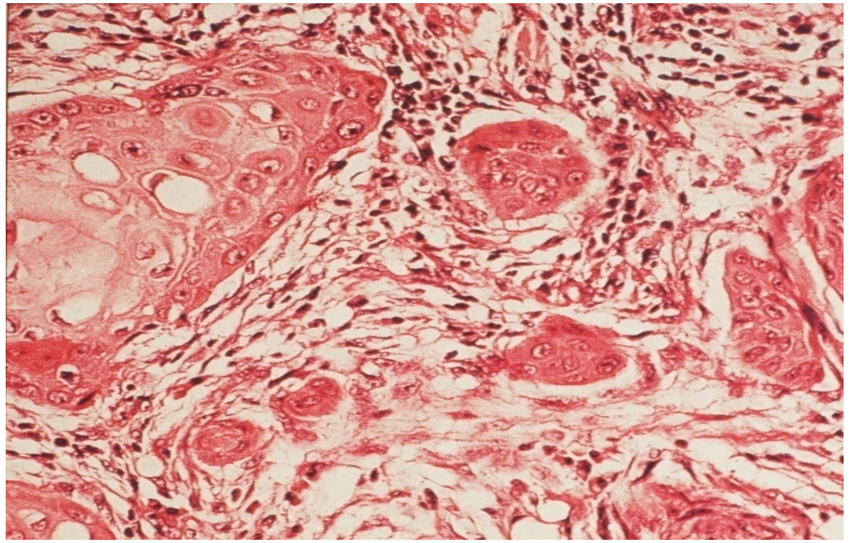


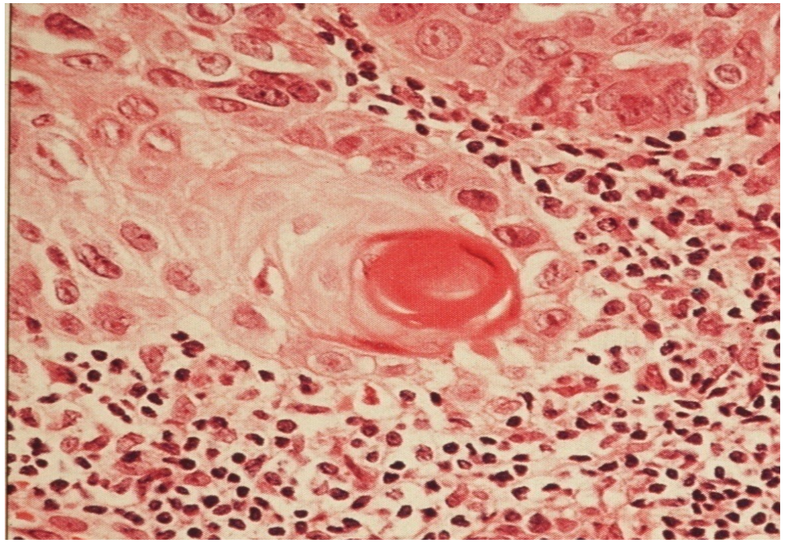
Figure 25.13 Invasive squamous cell carcinoma. (A) Lesions are often nodular and ulcerated, as seen in this scalp tumor. (B) Tongues of atypical squamous epithelium have transgressed the basement membrane and invaded deeply into the dermis. (C) Invasive tumor cells show enlarged nuclei with angulated contours and prominent nucleoli.



Squamous cell carcinoma (well-differentiated): nulear pleomorphism and mitoses, including abnormal form, identified keratinization



Squamous cell carcinoma (well-differentiated): minimal pleomophism, conpicuous intercellular bridges



Squamous cell carcinoma (well-differentiated): typical keratin pearl formation

Squamous Cell Carcinoma (SCC) : *Pathogenesis and clinical findings*

Author:
Danny Guo
Reviewers:
Yan Yu
Jason Baserman
Laurie Parsons*
Régine Mydlarski*
** MD at time of publication*

UV radiation causes mutations in epithelial squamous cells

Epithelial squamous cells enters uncontrolled proliferation and reduced apoptosis

- **Invasion of deep tissue layers**

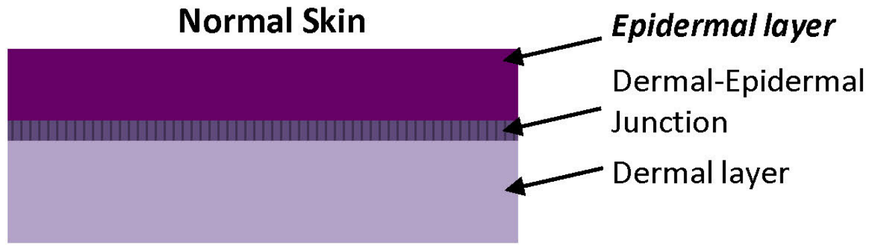
Increased number of squamous cells lead to accumulation and overproduction of keratin

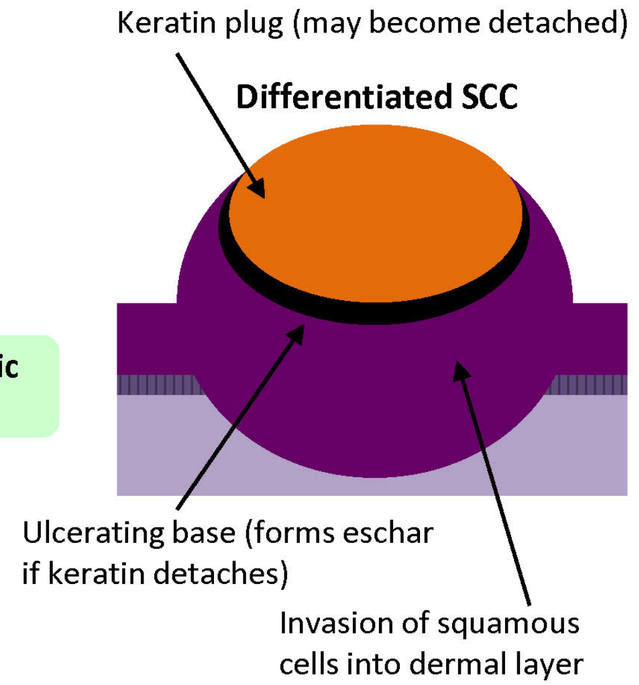
- Adherent keratotic scale or keratin plug
  - **Hard on palpation**
  - **Yellowish appearance**

Keratin plug and cell proliferation disrupts vascular supply

- **Underlying tissue necrosis**
  - **Crater-like centre**
  - **Eschar (intact necrotic tissue) formation**

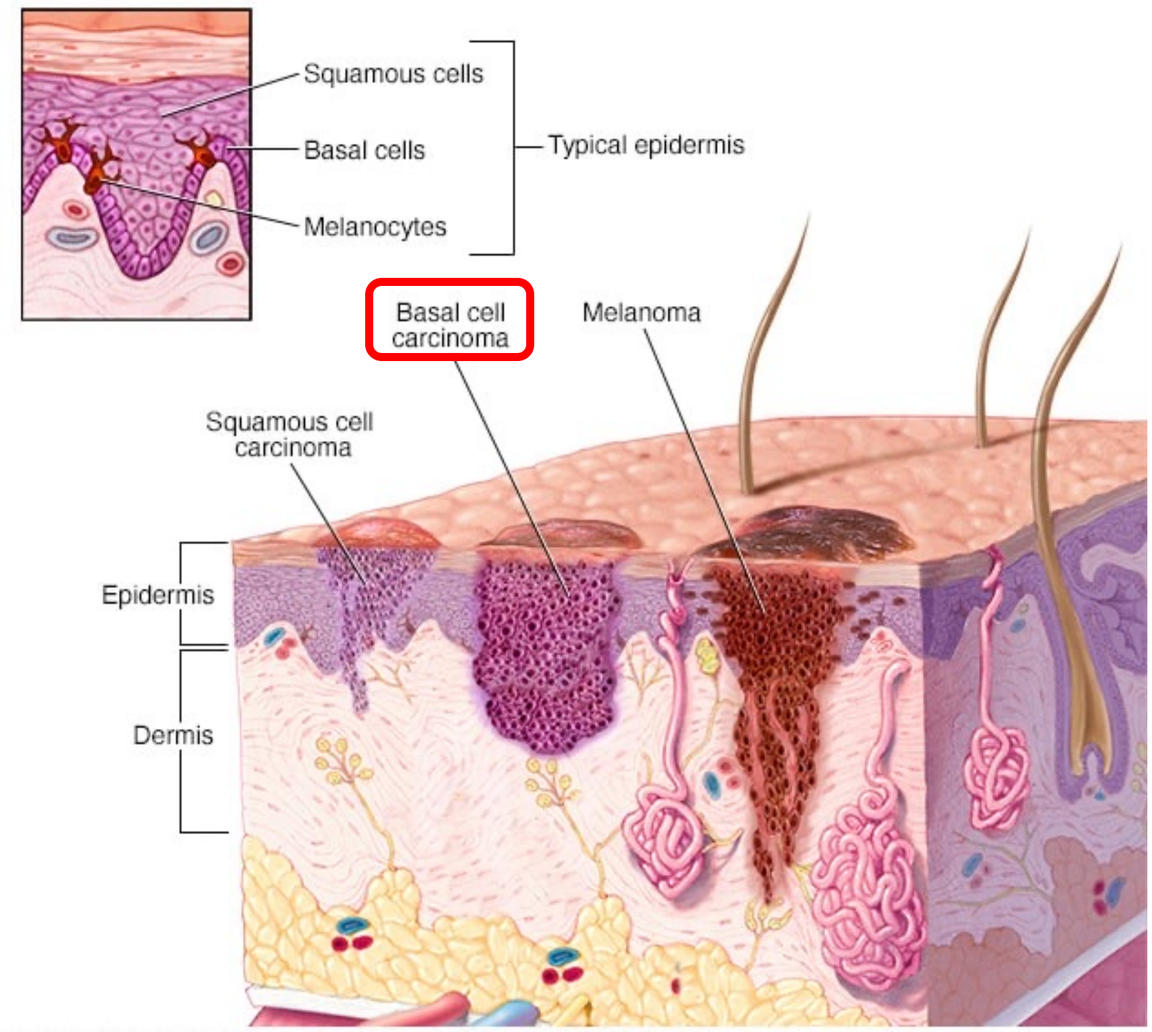
If untreated, SCC cells will eventually metastasize to other parts of the body



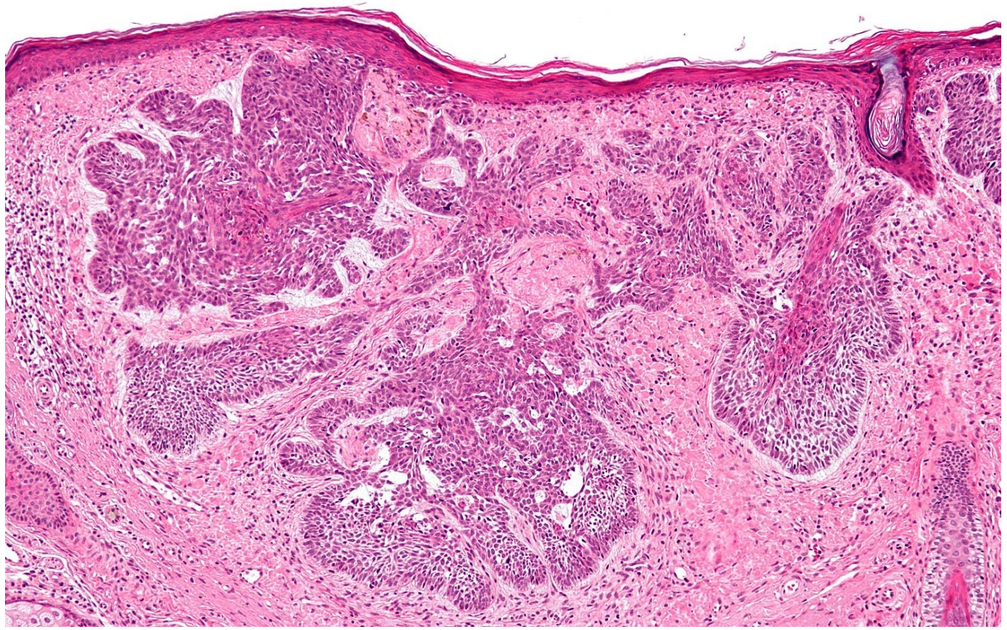


Note: *SCC's are not limited to the skin and have very different morphologies in other parts of the body.*

Basal cell carcinoma



- The most common skin malignant tumor
- Slow-growing and locally aggressive malignant tumor with histologically **resembling basal cell**



Basal cell carcinoma

- **Etiology and risk factors** (similar to those of SCC)**:**
  - Chronic sun (UV) exposure
  - Lightly-pigmented people
  - Immunosuppression: post-transplantation with immunosuppressive therapy, AIDS
  - Hereditary (genodermatosis):
    - Basal cell nevus syndrome (Nevoid basal cell carcinoma syndrome / Gorlin syndrome):
      - ✓ Rare, autosomal dominant inheritance, variable clinical expressivity
      - ✓ PATCH (tumor suppressor gene) mutation
      - ✓ Associated with many basal cell carcinoma in early life with abnormalities of bone (vertebrae and ribs), nervous system, eyes, and reproductive organs (thecoma-fibroma)
    - Xeroderma pigmentosa: autosomal recessive

Basal cell carcinoma

- **Etiology and risk factors** (continued)**:**
  - Hereditary (genodermatosis):
    - Basal cell nevus syndrome (Nevoid basal cell carcinoma syndrome / Gorlin syndrome):
      - ✓ Rare, autosomal dominant inheritance, variable clinical expressivity
      - ✓ PATCH (tumor suppressor gene) mutation
      - ✓ Associated with many basal cell carcinoma in early life with abnormalities of bone (vertebrae and ribs), nervous system, eyes, and reproductive organs (thecoma-fibroma)
    - Xeroderma pigmentosa: autosomal recessive

Hereditary cancer syndromes with cutaneous manifestations

Disease	Inheritance	Chromosomal Location	Gene/Protein	Normal Function/Manifestation of Loss
Ataxia-telangiectasia	AR	11q22.3	*ATM*/ATM	DNA repair after radiation injury/neurologic and vascular lesions
Nevoid basal cell carcinoma syndrome	AD	9q22	*PTCH*/PTCH	Developmental patterning gene/multiple basal cell carcinomas; medulloblastoma; jaw cysts
Cowden syndrome	AD	10q23	*PTEN*/PTEN	Lipid phosphatase/benign follicular appendage tumors (trichilemmomas); internal adenocarcinoma (often breast or endometrial)
Familial atypical mole and melanoma syndrome	AD	9p21	*CDKN2A*/p16, INK4 *CDKN2A*/p14, ARF	Inhibits CDK4/6 phosphorylation of RB, promoting cell cycle arrest/melanoma; pancreatic carcinoma Binds MDM2, promoting p53 function/melanoma; pancreatic carcinoma
Muir-Torre syndrome	AD	2p22 3p21	*MSH2*/MSH2 *MLH1*/MLH1	Involved in DNA mismatch repair/sebaceous neoplasia; internal malignancy (colon and others)
Neurofibromatosis 1	AD	17q11	*NF1*/neurofibromin	Negatively regulates RAS signaling/neurofibromas
Neurofibromatosis 2	AD	22q12	*NF2*/merlin	Integrates cytoskeletal signaling/neurofibromas; acoustic neuromas
Tuberous sclerosis	AD	9q34 16p13	*TSC1*/hamartin *TSC2*/tuberin	Work together in a complex that negatively regulates mTOR/angiofibromas; intellectual disability
Xeroderma pigmentosum	AR	9q22 and others	*XPA*/XPA and others	Nucleotide excision repair/melanoma; nonmelanoma skin cancers

AD, Autosomal dominant; *AR,* autosomal recessive.

From Tsai KY, Tsao H: The genetics of skin cancer, *Am J Med Genet C Semin Med Genet* 131C:82, 2004.

Basal cell carcinoma

- **Etiology and risk factors** (continued)**:**
  - Chemical carcinogens: arsenic
  - Smoking
  - Ionizing radiation
  - Radiotherapy
  - Family history of skin cancer

Basal cell carcinoma

- **Pathogenesis:**
  - **UV light exposure:** subsequent unrepaired DNA damage
  - **TP53 (tumor suppressor gene) mutations**: associated with UV exposure
  - **PTCH (tumor suppressor gene) mutations**: associated with UV exposure

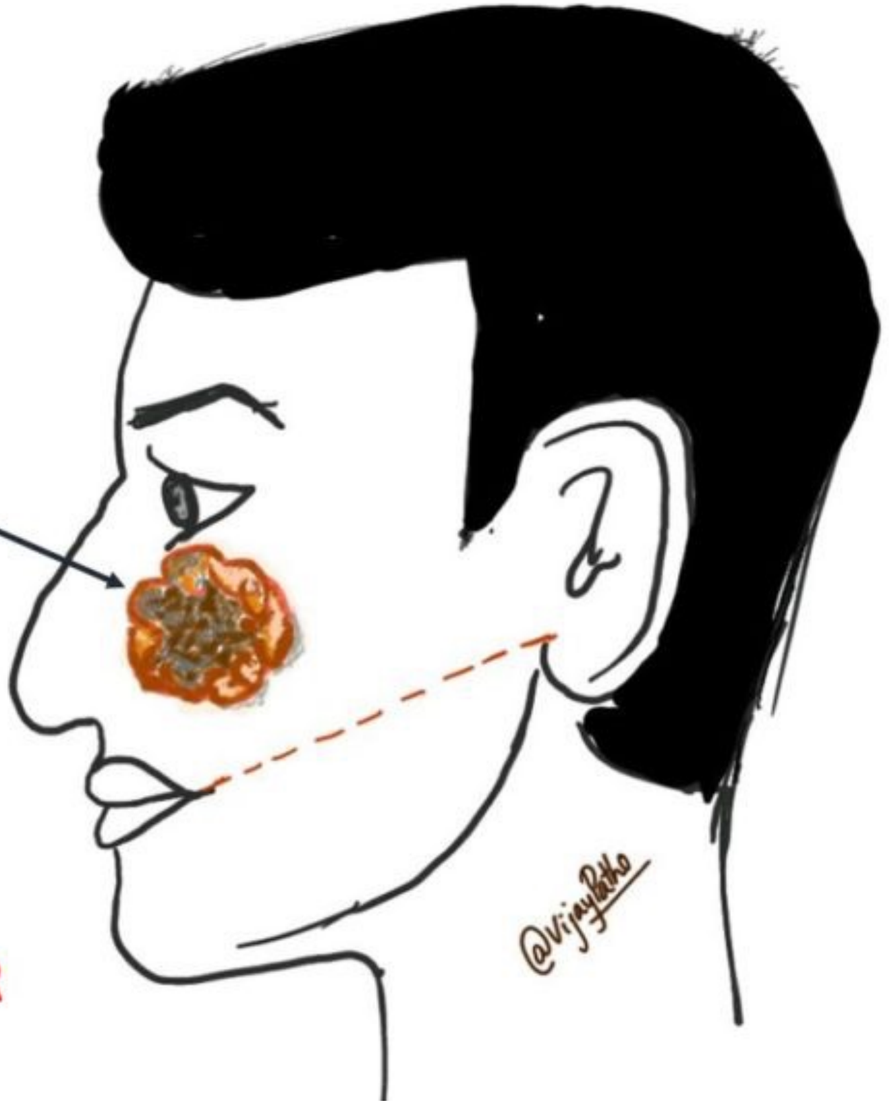
- **Clinical:**
  - Mostly arise at sun-exposed skin (especially face)
  - Slow growing tumor, rarely metastasis, but can be extensive local invasion of bone, orbit, or sinuses (if left untreated)
  - **Early lesion:**
    - Pearly papule/nodule, often contains telangiectasia (dilated subepidermal blood vessels) on surface, some contains melanin pigment (pigmented type)
  - **Advanced lesion:**
    - Increased size with central ulceration and raised rolled edge (“rodent ulcer”)

BASAL CELL CARCINOMA

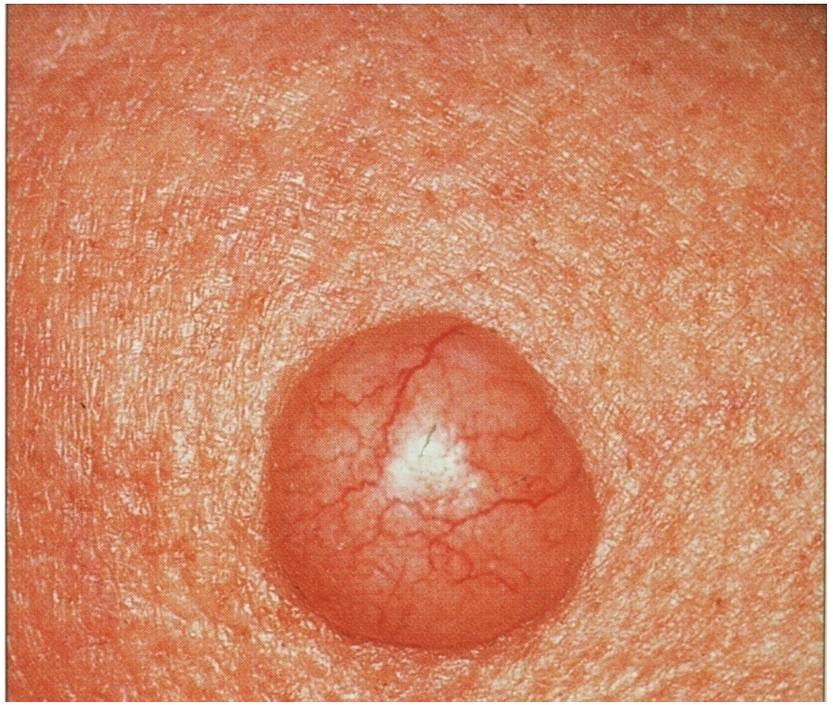
Nodulo- ulcerative lesion situated above the line drawn from the angle of the mouth to pinna

The ulcer is invasive and destructive and the tumor nibbles away the skin (like a rodent!)

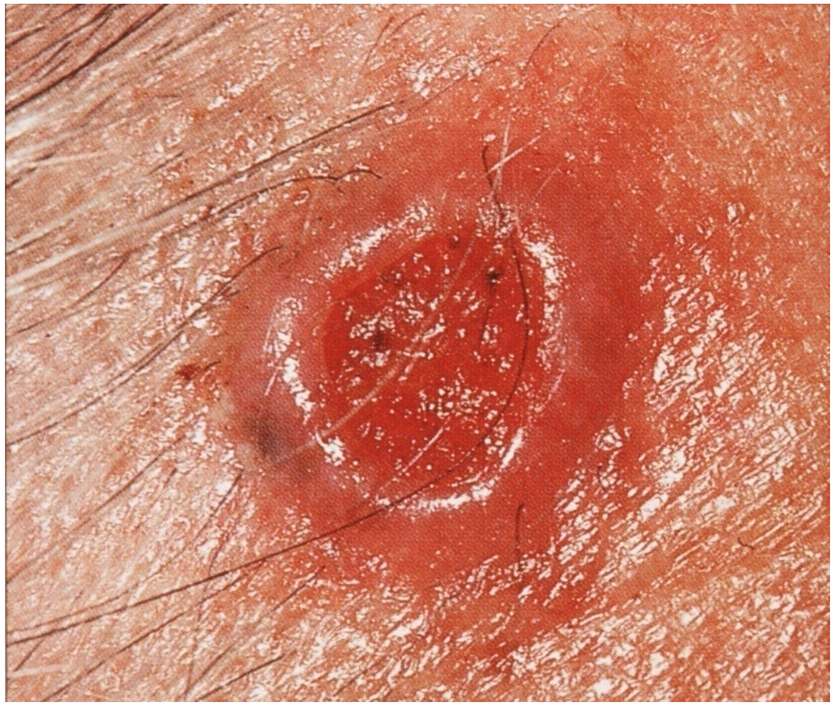
RODENT ULCER



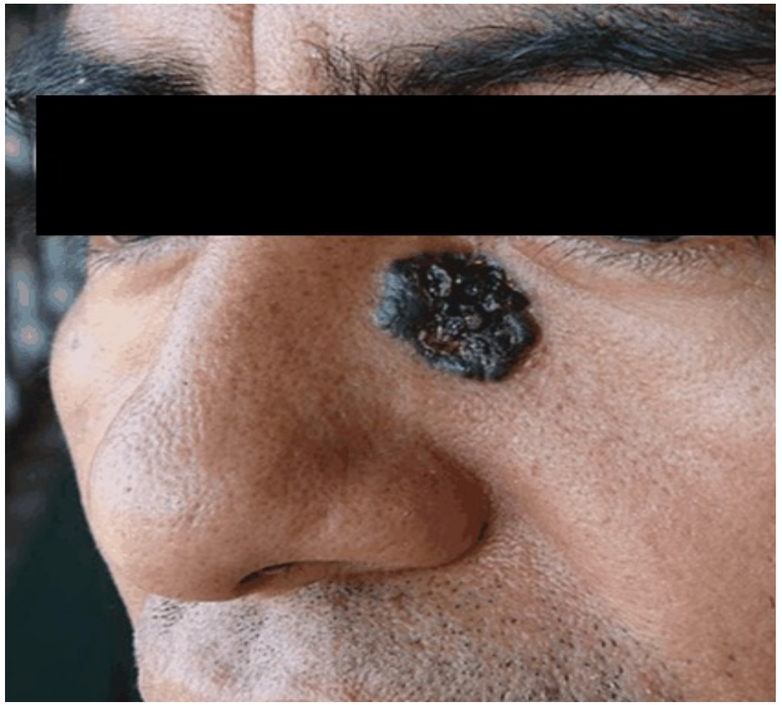
Majority of the basal cell carcinoma occur **in head and neck region.**
The most common location would be above the line which is drawn from the angle of mouth to the pinna of the ear.



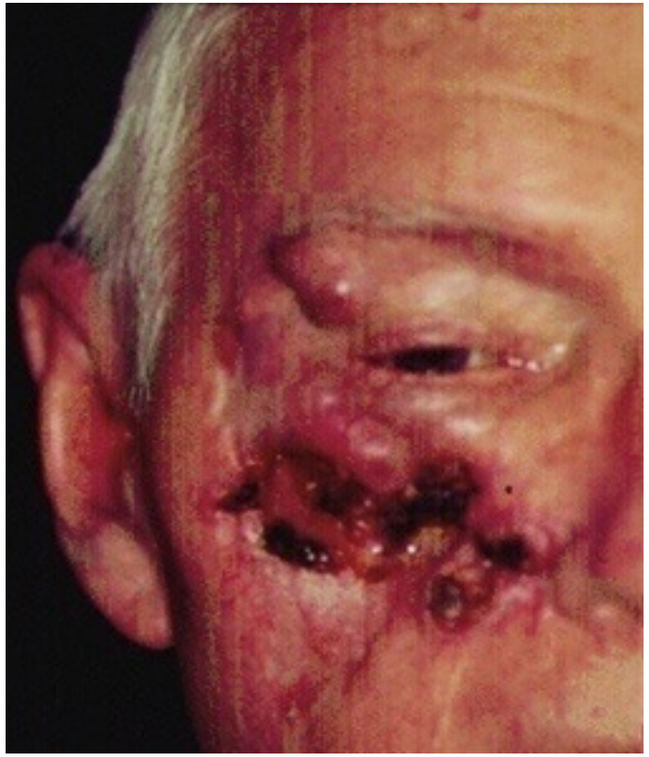
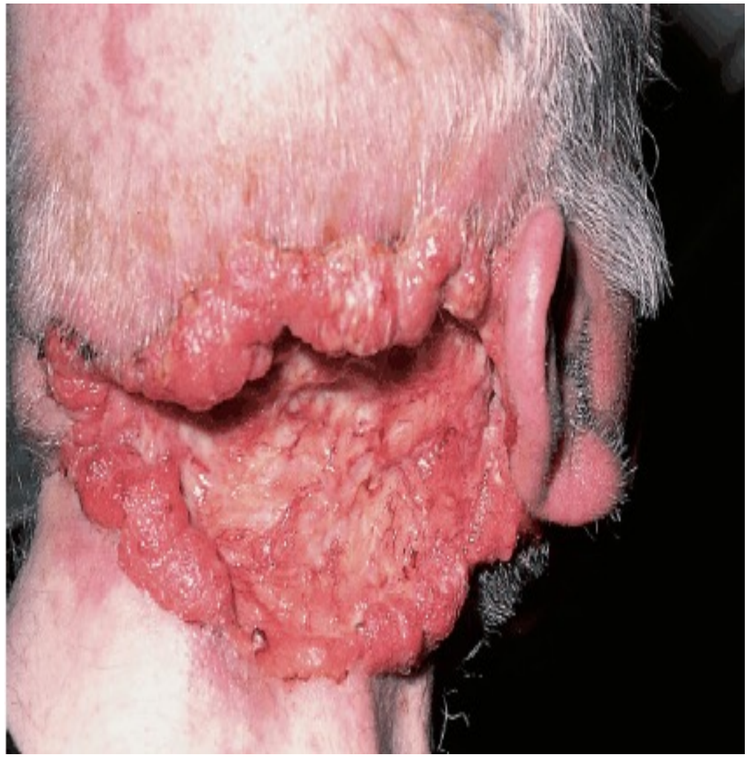
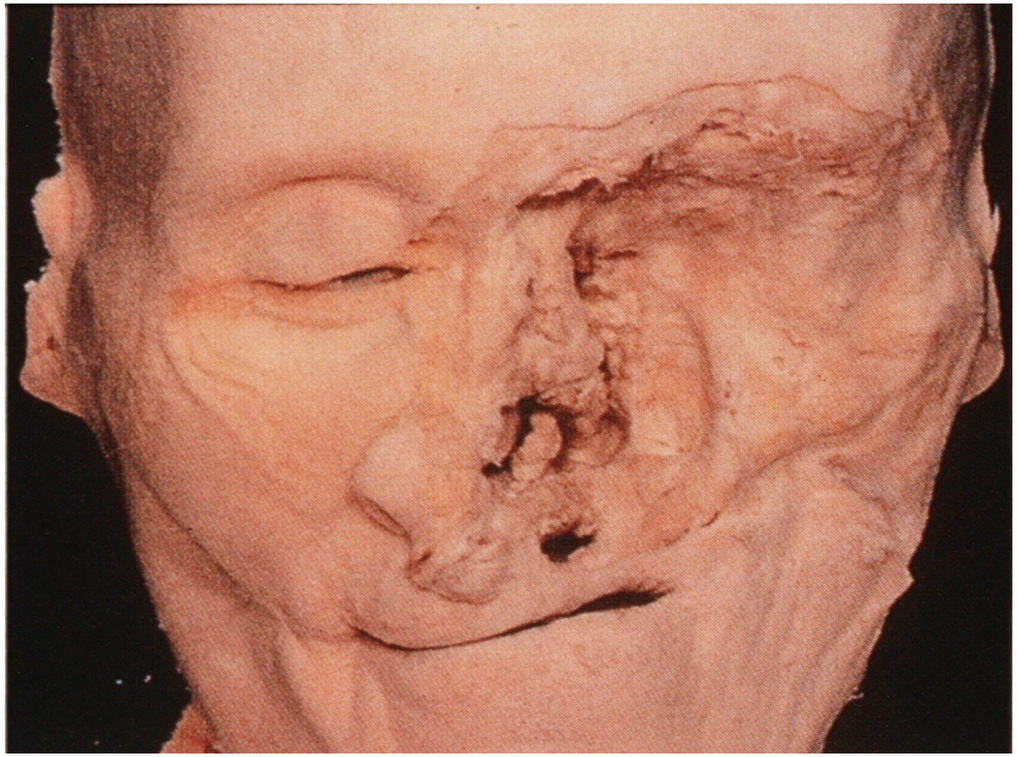
Basal cell carcinoma (early lesion):
characteristic telangiectatic vessels coursing over the surface of nodulcystic-type tumor



Basal cell carcinoma (advanced lesion):
central ulceration and characteristic raised rolled border



Basal cell carcinoma (pigmented type):
increased functional melanocyts and melanin transfer to the neoplastic cells and increased dermal melanophages, clinically resembling malignant melanoma

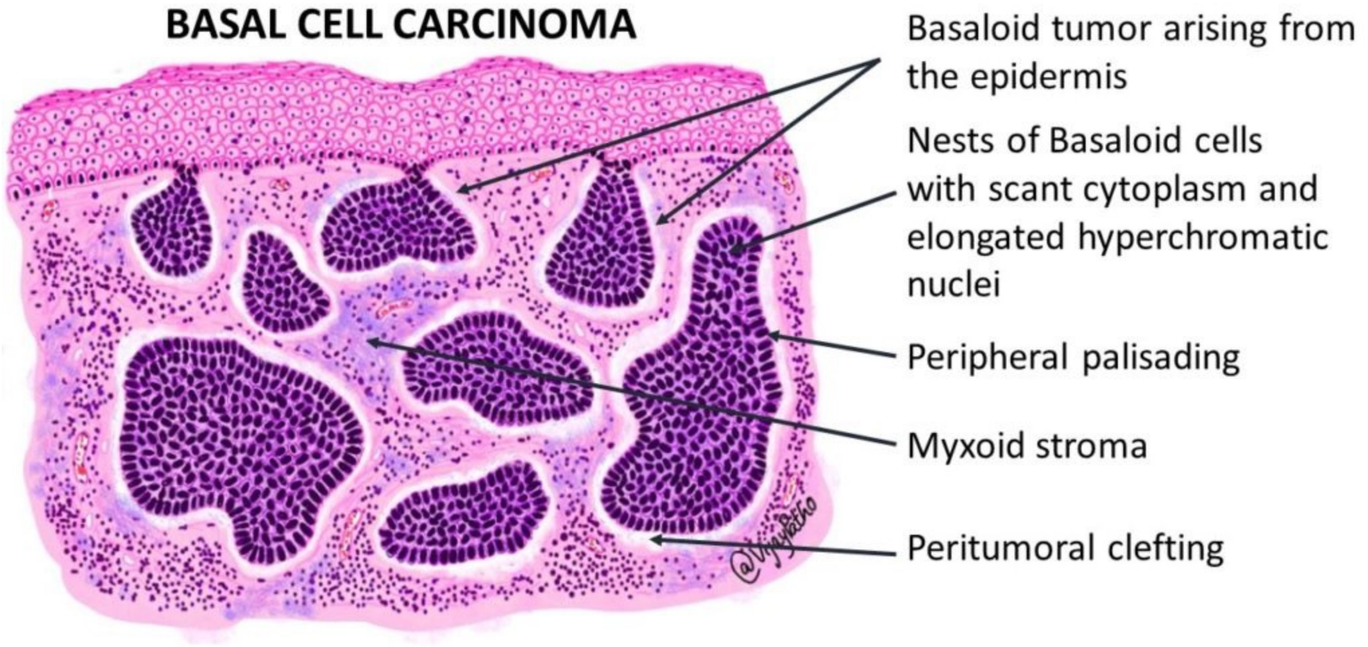
Basal cell carcinoma (advanced and locally aggressive lesion): can be extensive local invasion of bone, orbit, or sinuses (if left untreated)

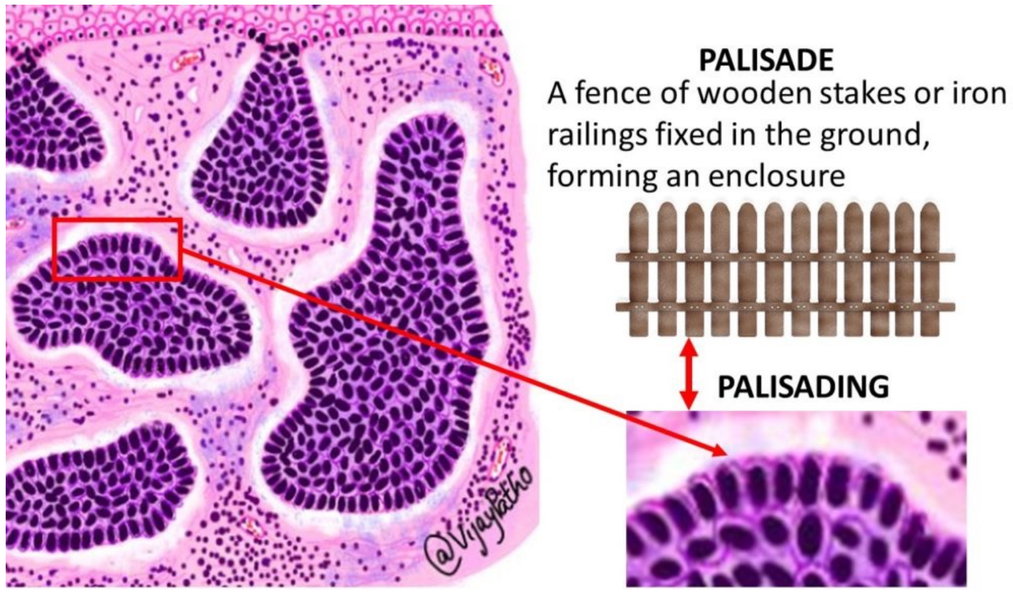
Basal cell carcinoma

- **Histopathology:**
  - Infiltrative sheets and nests of neoplastic cells resembling basal cell layer of the epidermis (basaloid appearance)
  - Characteristic peripheral nuclear palisading at the tumor border and peritumoral myxoid stroma (clefting)
  - Evidence of solar damage in the dermis (solar elastosis)

- **Prognosis:**
  - Recurrence rate varies from 1 to 8.7%, depending on location, size, histologic subtypes, and form of primary treatment
  - Rarely metastasize (less than 1%)

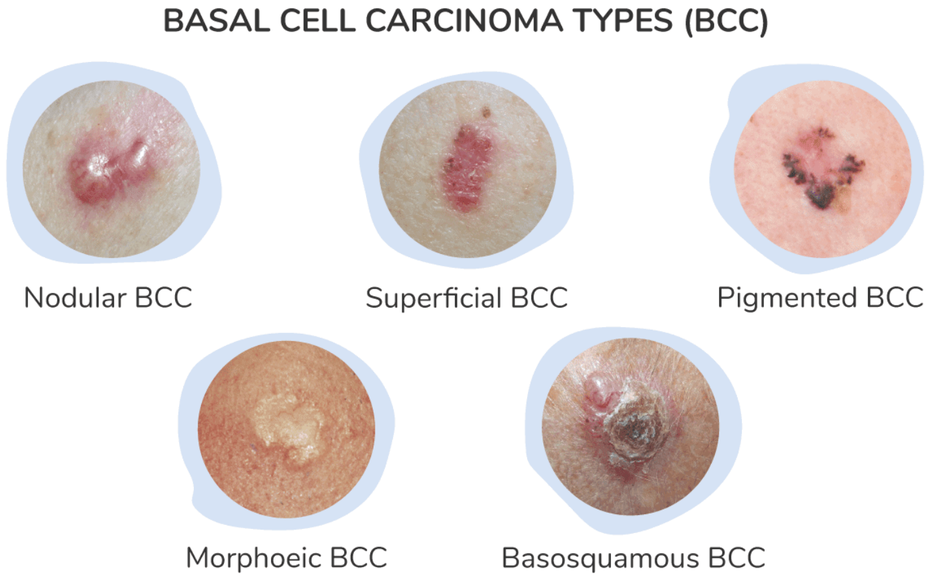
Basal cell carcinoma

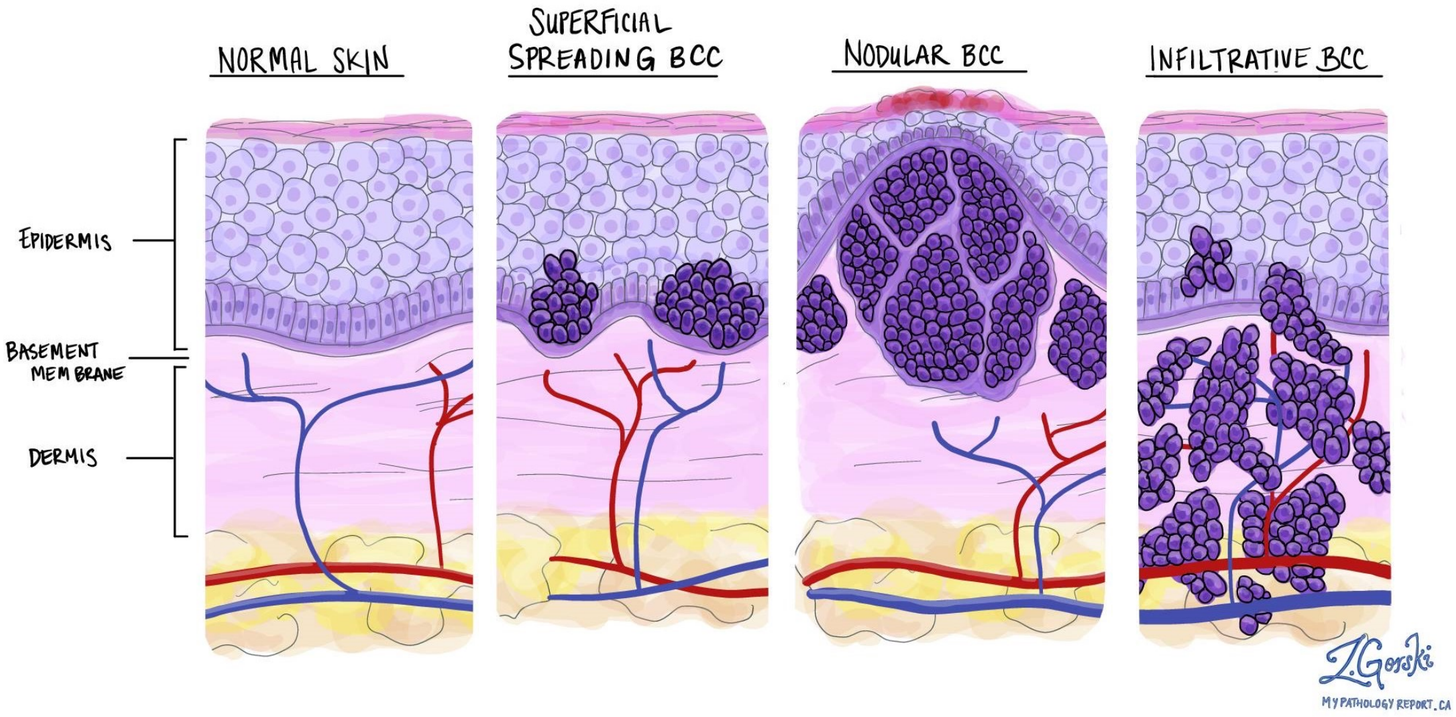




Clinically, the appearance of the tumor vary and they can be **nodular, cystic, ulcerated, sclerotic (morphoeic), superficial, pigmented, basasquamous (metatypical),** or **infiltrating types.**
While the ulcerated type is the one which is commonly referred to as rodent ulcer.

Types (variants) of basal cell carcinoma





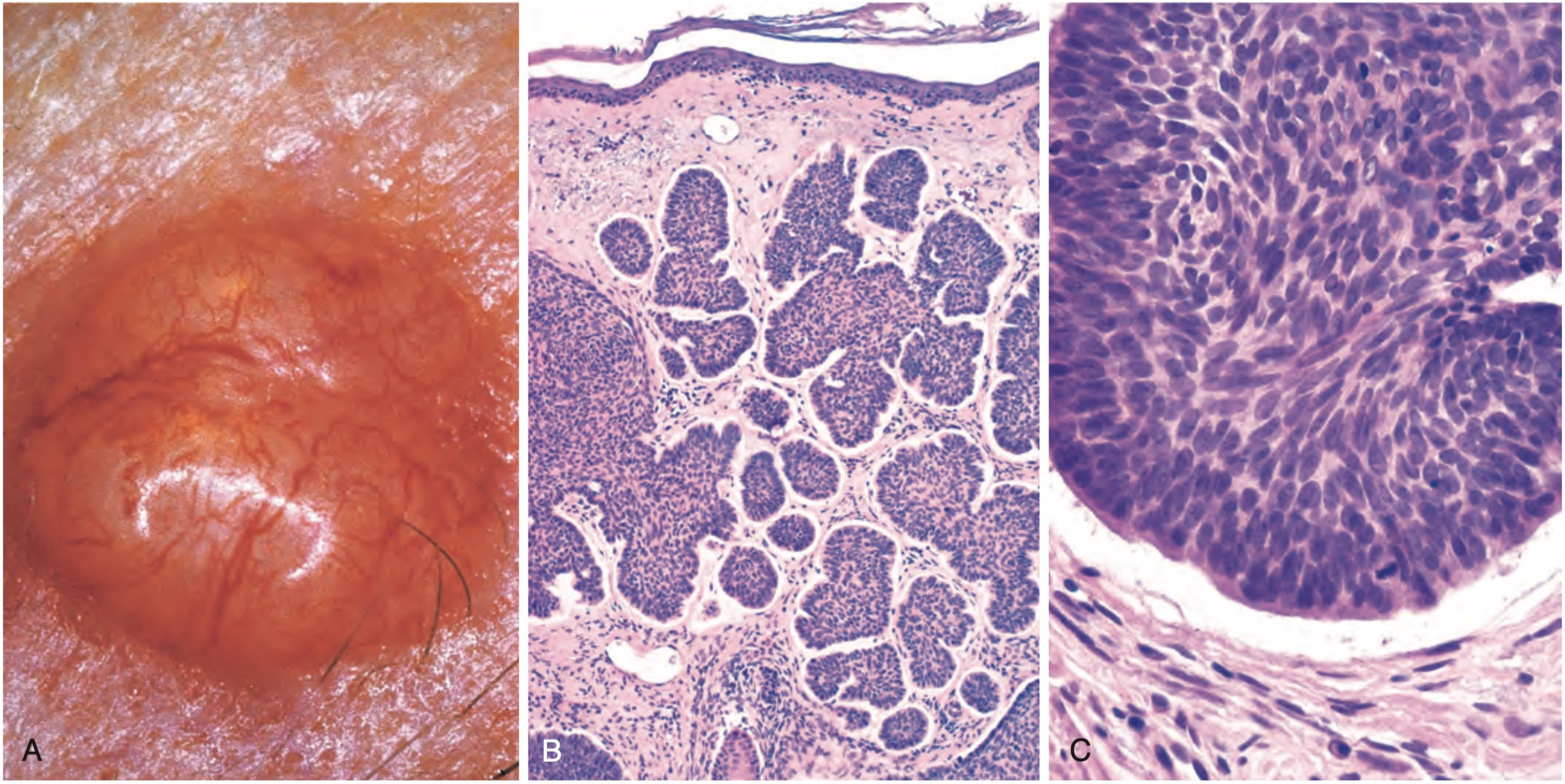
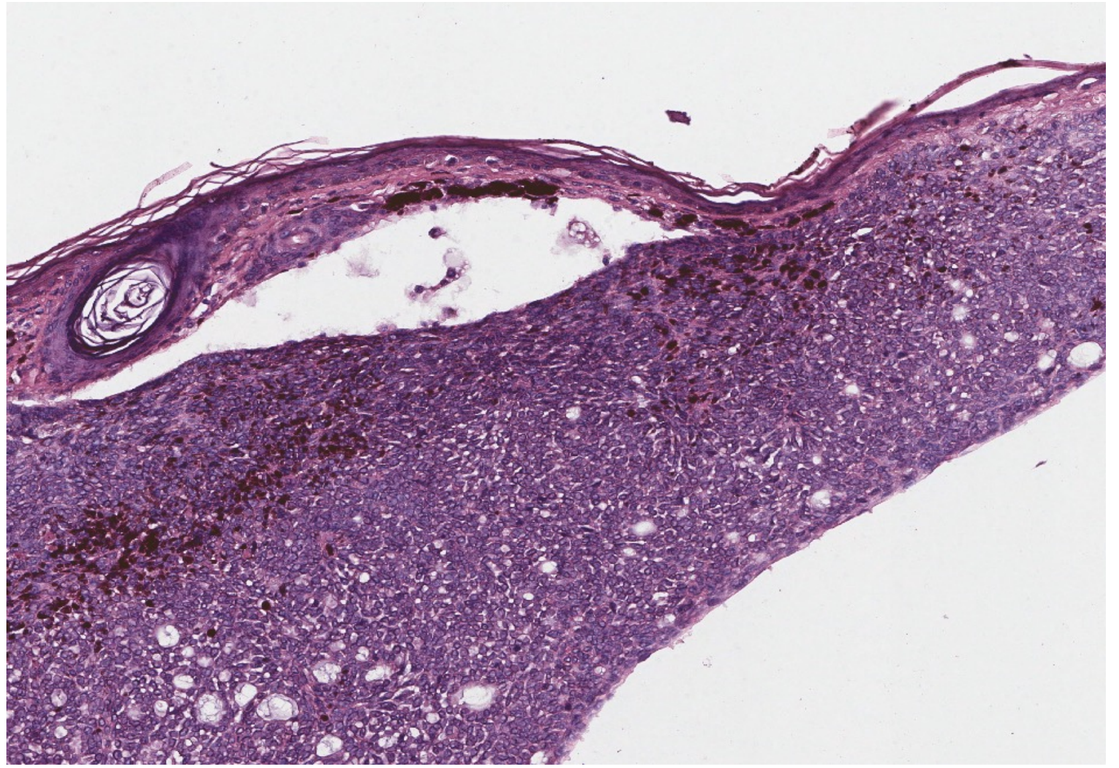
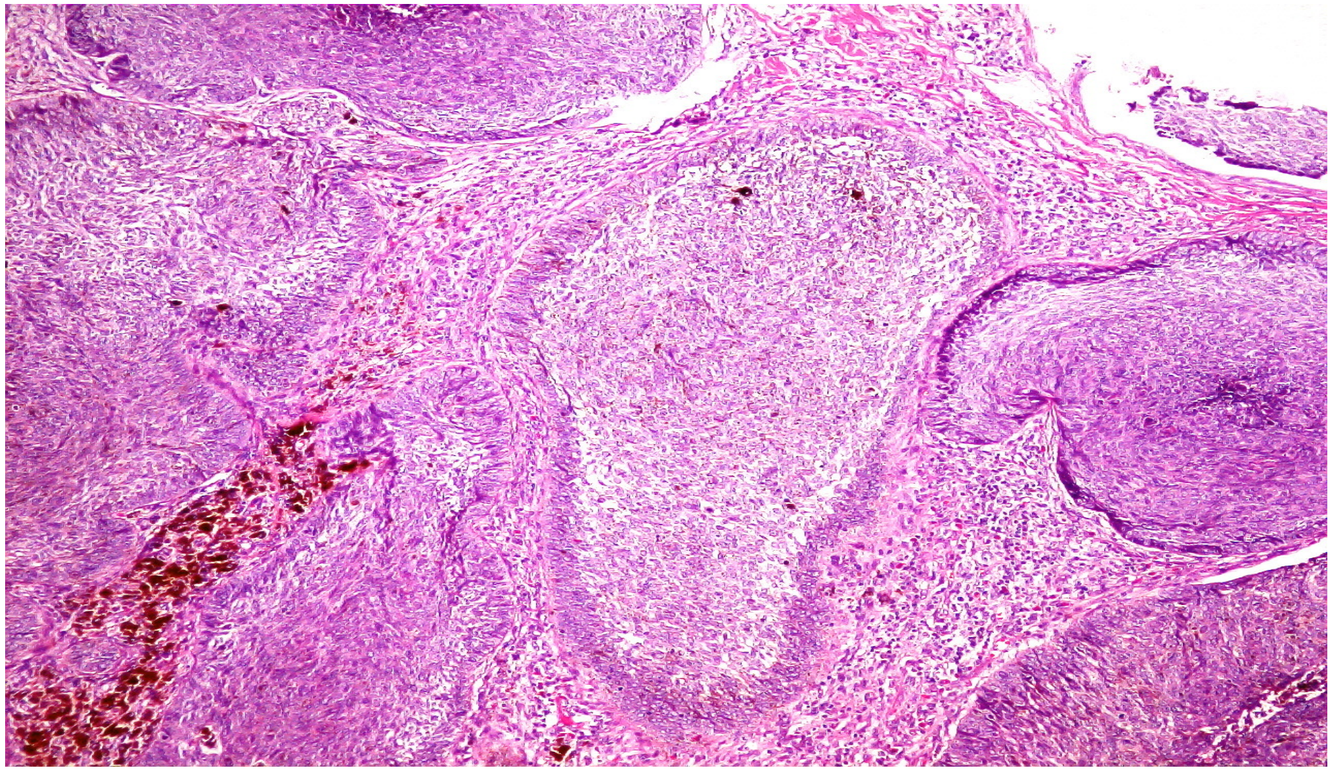


Figure 25.15 Basal cell carcinoma. Pearly, telangiectatic nodules (A) are composed of nests of uniform basaloid cells within the dermis (B) that are often separated from the adjacent stroma by thin clefts (C), an artifact of sectioning.





Basal cell carcinoma, pigmented type: melanin pigments in the neoplastic cells transferred from functional melanocytes, seen dermal macrophages with melanin pigments (melanophages)

Basal Cell Carcinoma (BCC): *Pathogenesis and clinical findings*

Authors:
Danny Guo
Yan Yu
Reviewers:
Jason Baserman
Laurie Parsons*
Régine Mydlarski*
** MD at time of publication*

Note: Nodular and ulcerating are only 2 subtypes of BCC's.

UV radiation causes basal cells of the skin to accumulate genetic abnormalities

↓

Basal cell growth and division becomes dysregulated

↓

Rapid growth and expansion of genetically abnormal basal cells, which normally have a palisading pattern

- Stretching of overlying epidermal layer → **Pearly surface**
- Uncontrolled and disharmonious neoangiogenesis in tumor tissue → **Arborizing telangiectasia**
- Reproduction of abnormal palisades in tumor → **Palisades (*on histology*)**

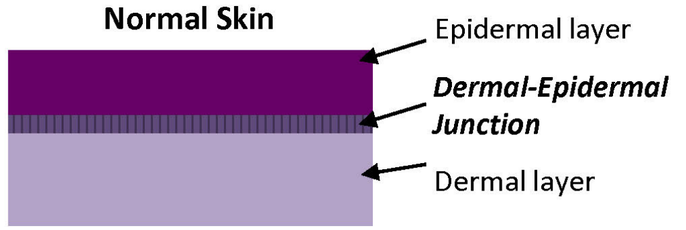
↓

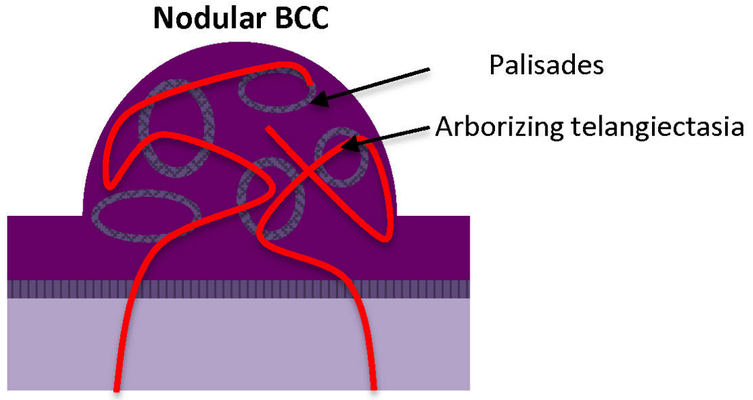
Rate of tissue expansion > rate of neoangiogensis

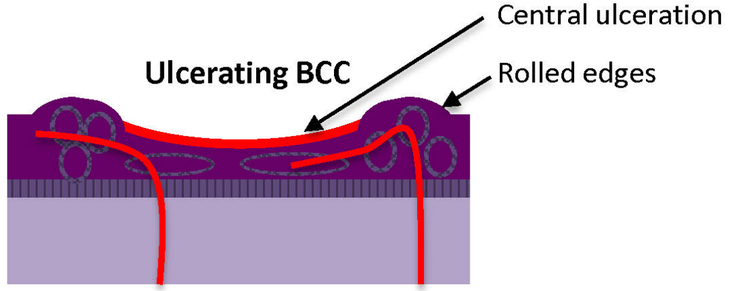
- Tissue ischemia and necrosis in central tumor → **Central Ulceration**
- Peripheral tumor maintains blood supply from neighbouring tissue → **Rolled edges**

↓

If untreated, the tumor will continue to invade local tissue

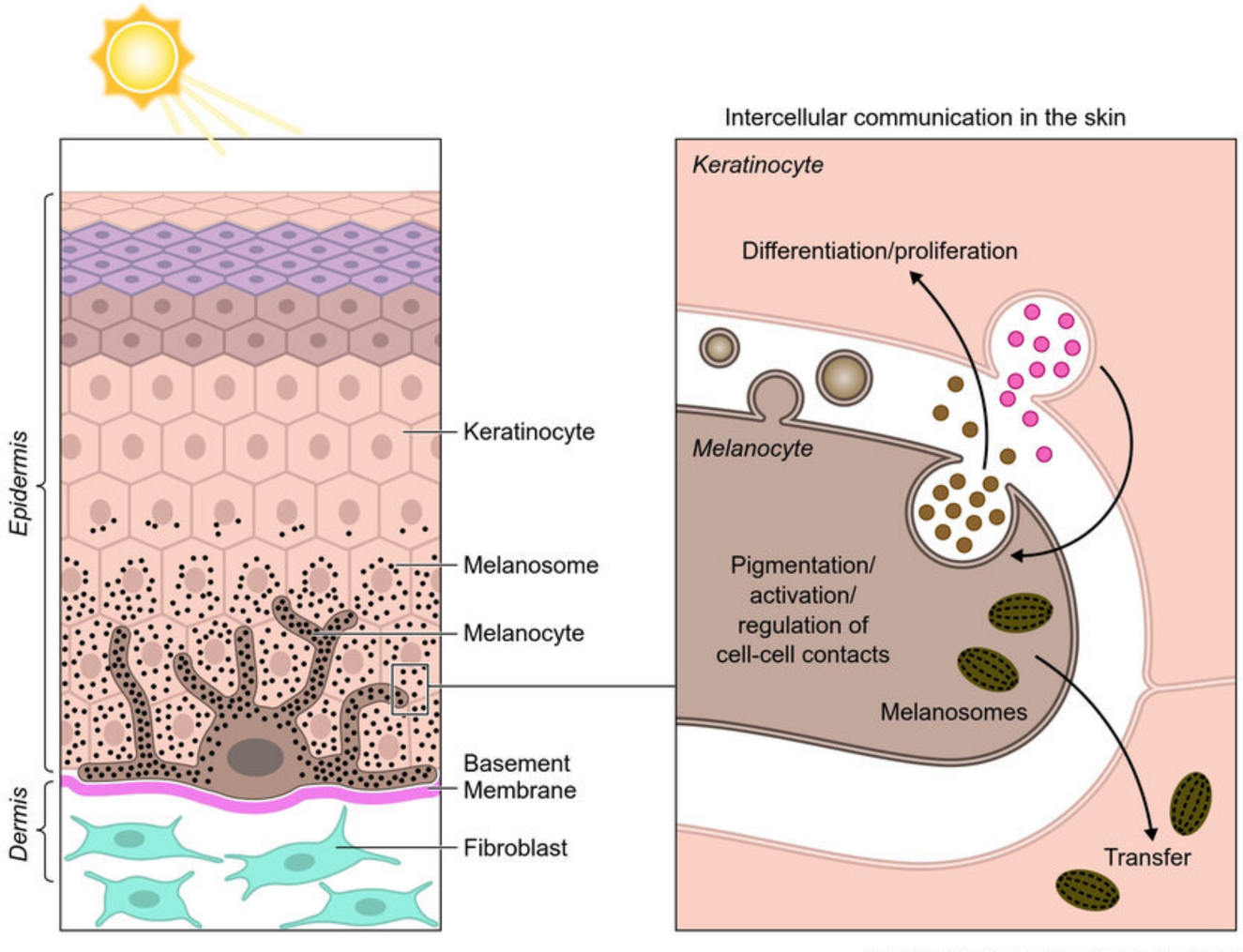


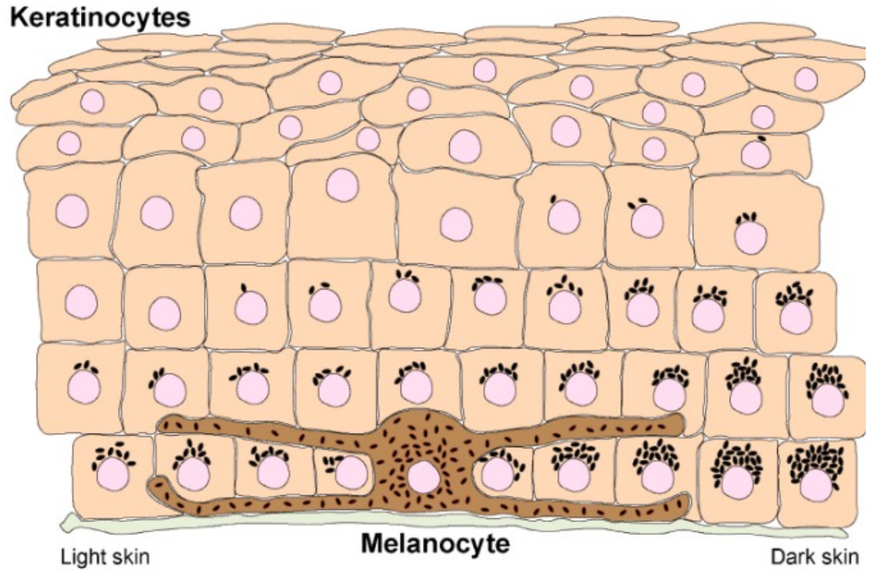


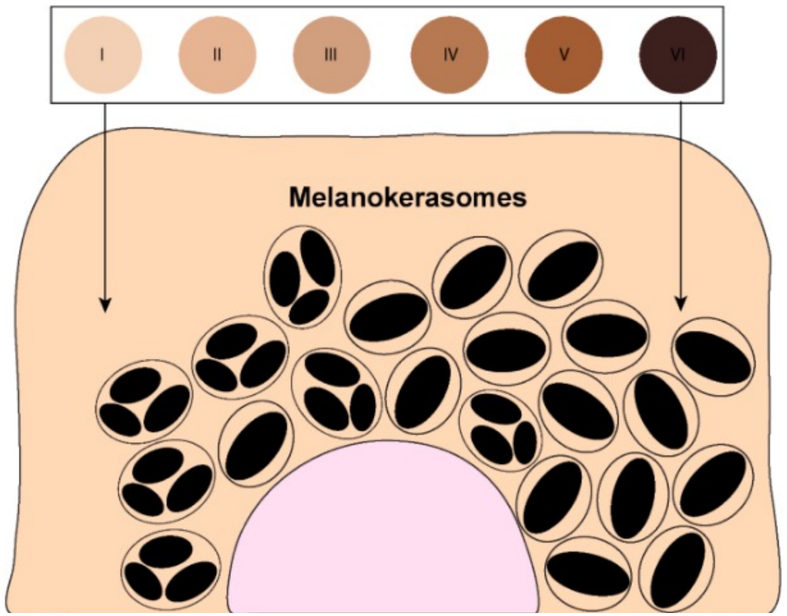


Melanocytic tumors

Melanocyte


Epidermis
Dermis
Keratinocyte
Melanosome
Melanocyte
Basement Membrane
Fibroblast
Intercellular communication in the skin
Keratinocyte
Differentiation/proliferation
Melanocyte
Pigmentation/ activation/ regulation of cell-cell contacts
Melanosomes
Transfer


Keratinocytes
Light skin
Melanocyte
Dark skin


I
II
III
IV
V
VI
Melanokerasomes

Melanocytic nevus

- A benign melanocytic neoplasm of melanocytes, also called “**nevus**” or “**mole**”

- **CInical:**

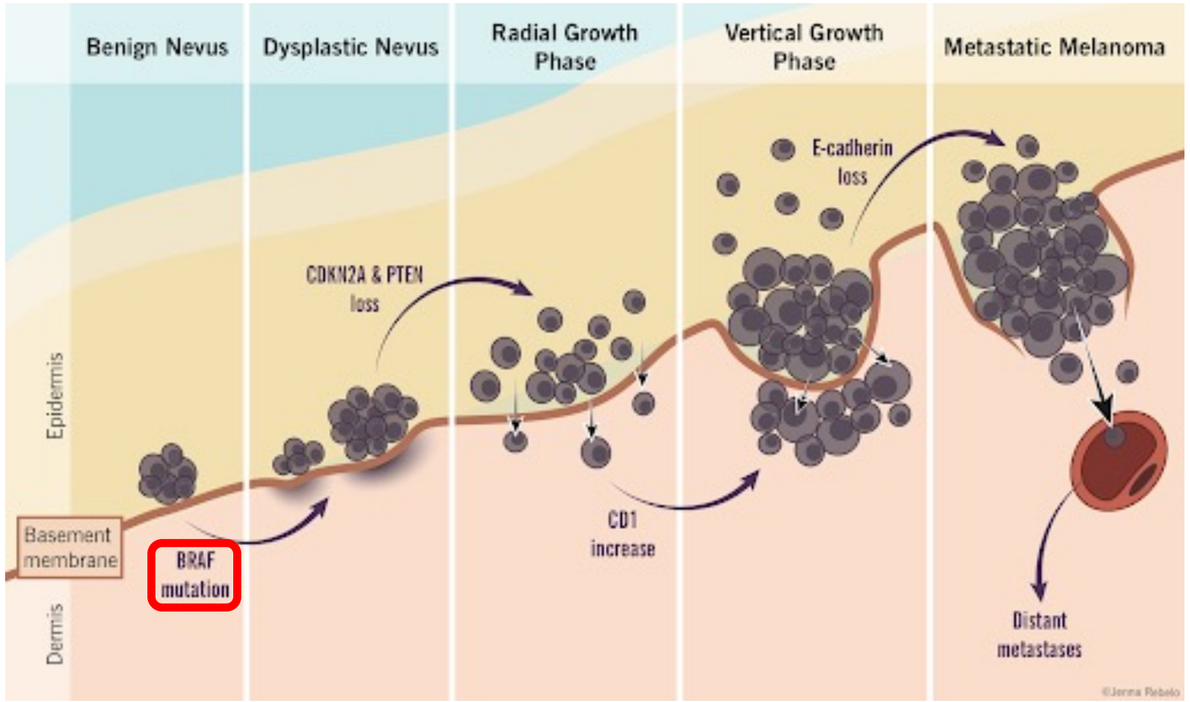
  1. Congenital nevus
  - Present at birth
  - May increase risk of melanoma in giant congenital melanocytic nevus (> 20 cm)

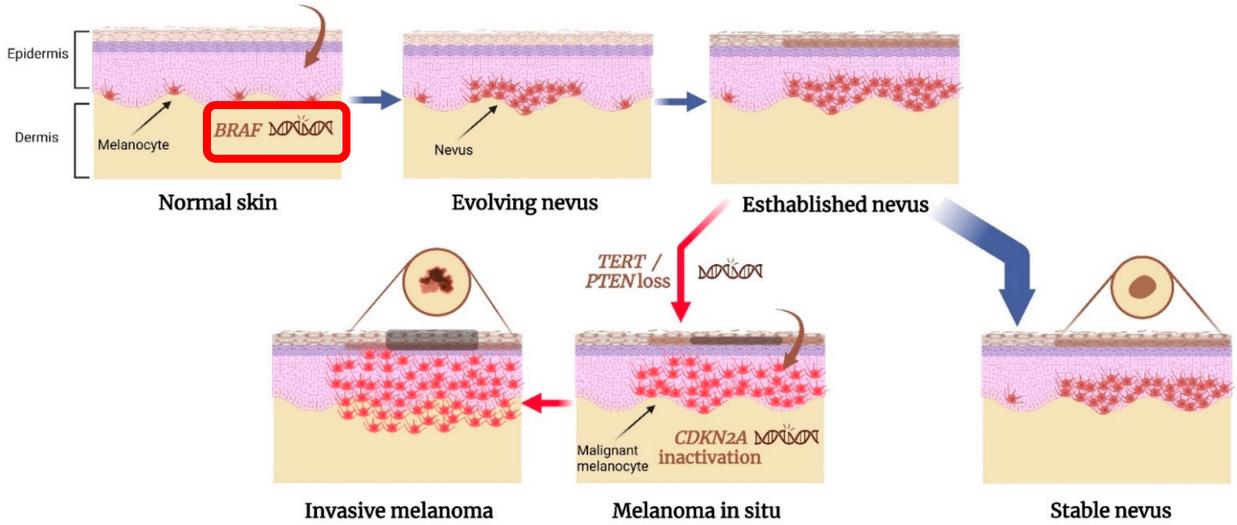
  2. Acquired nevus:
  - More common type and found in virtually all individuals
  - Occurs after 6 months old, and maximum at age of 20-30 years
  - Small macule, usually < 6 mm (junctional nevus)
  - Some subsequently become raised domed-shaped papule (compound and intradermal nevus)

Melanocytic nevus

- **Pathogenesis:**
  - A majority of nevi have recently been found to have an activating mutation of **BRAF (oncogene)** and RAS, which can lead to growth stimulation through the mitogen-activated protein kinase (MAPK) pathway.
  - After initial period of growth, nevi are stable lesions that may regress or senesce, mediated by increased activity of **p16** protein (which is encoded by CDKN2A gene on chromosome 9p21), acting as a potent inhibitor of several cyclin-dependent kinases, including cyclin-dependent kinase 4 and 6 (CDK4 and CDK6), resulting in suppressed cell proliferation and promoting end-stage differentiation of the nevus cells.

Molecular pathogenesis of melanocytic tumor





Melanocytic nevus

- **Histopathology** (classification reflecting their evolution / maturation sequence)**:**
  - **Junctional nevus**
    - Melanocytes form **nests** at the tips of epidermal rete ridges (dermoepidermal junction)
    - Tend to lose dendritic morphology, but retained pigment in cytoplasm
  - **Compound nevus**
    - **Nests** of melanocytes are seen in the epidermis and some of the cells have migrated into the dermis
  - **Dermal (intradermal) nevus**
    - Intraepidermal melanocytic growth has ceased and melanocytes are present **only in the dermis**
    - Pigment tends to be lost at this stage, but still presence of **residual nested architecture** (important clue to the diagnosis of nevus versus another tumor)

Maturation sequence of melanocytic nevus

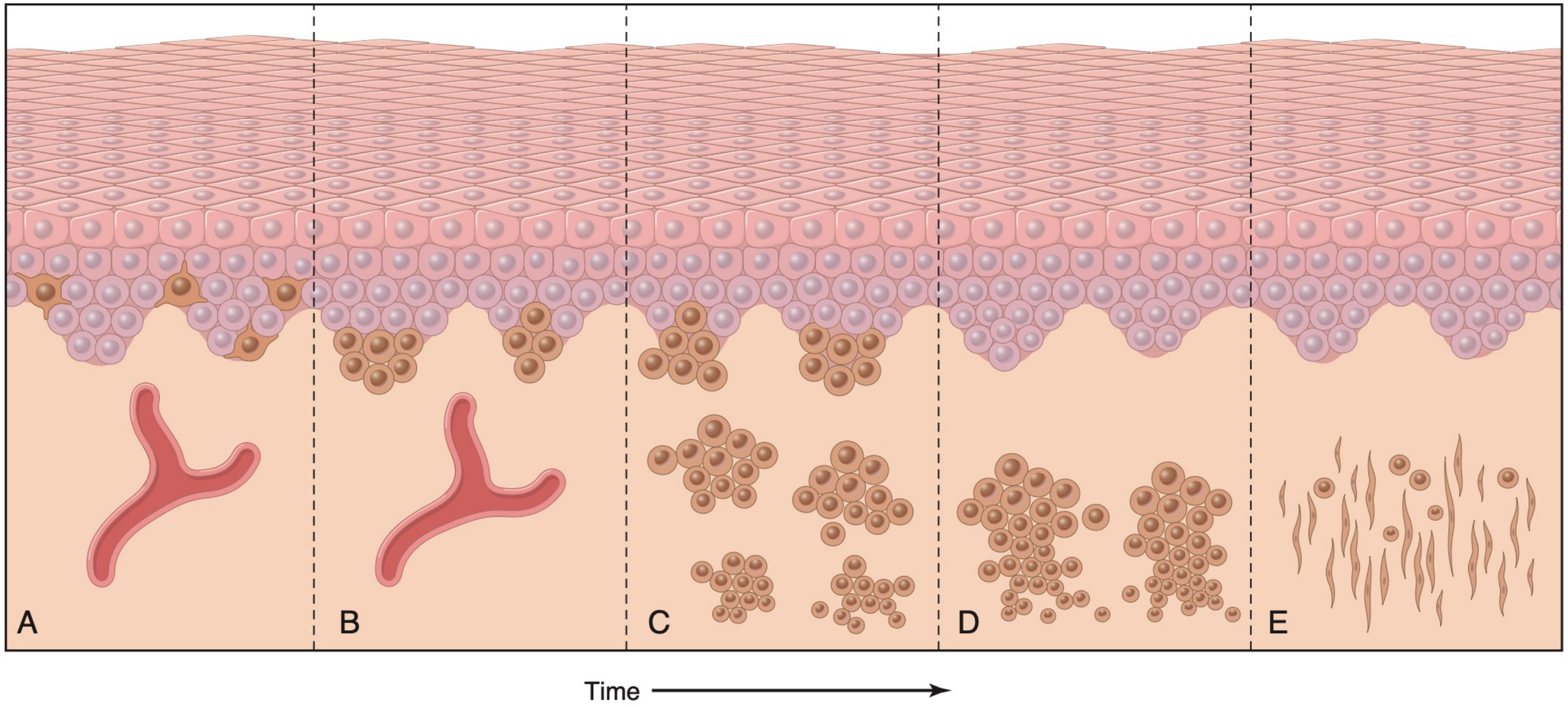
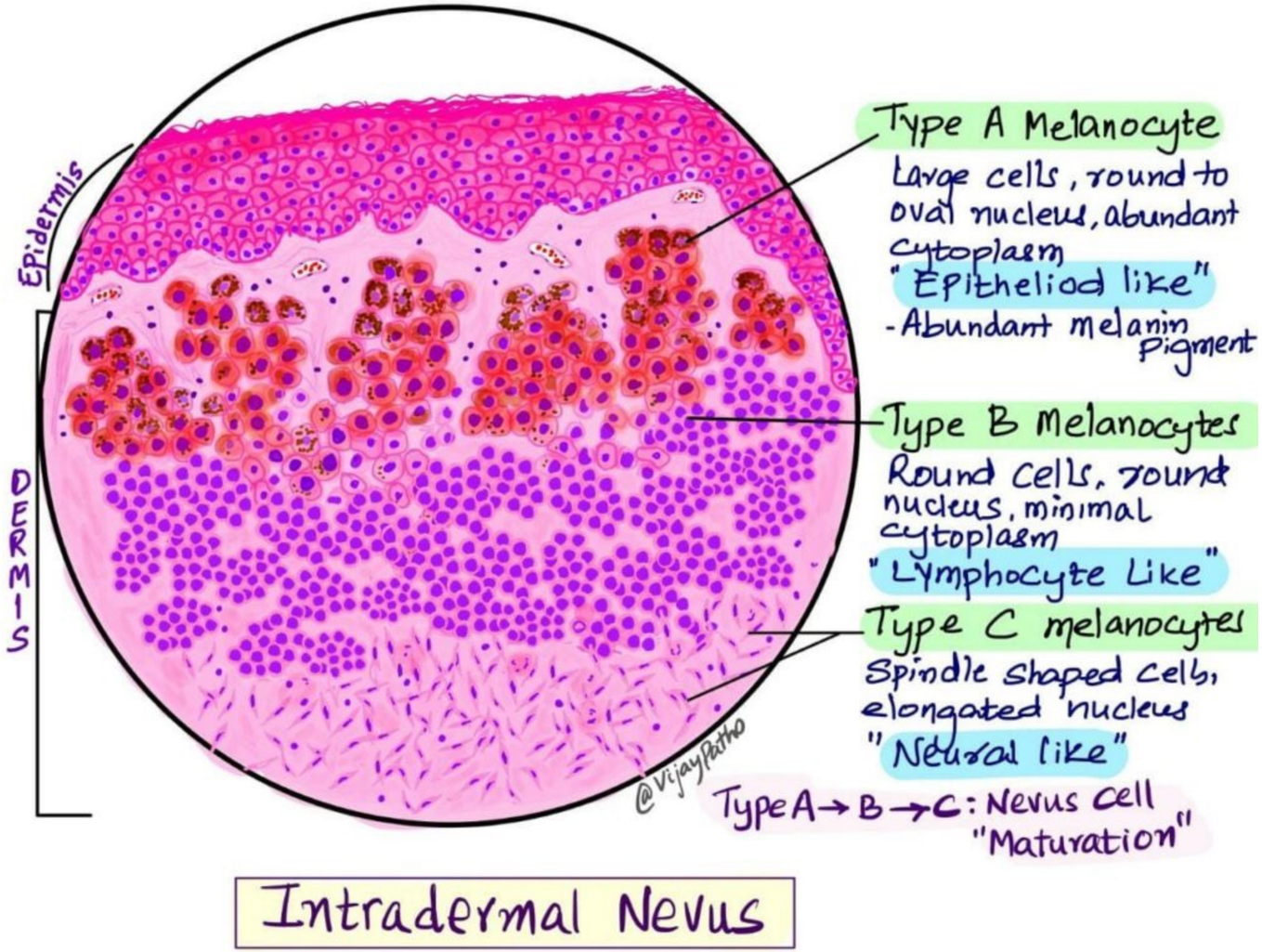
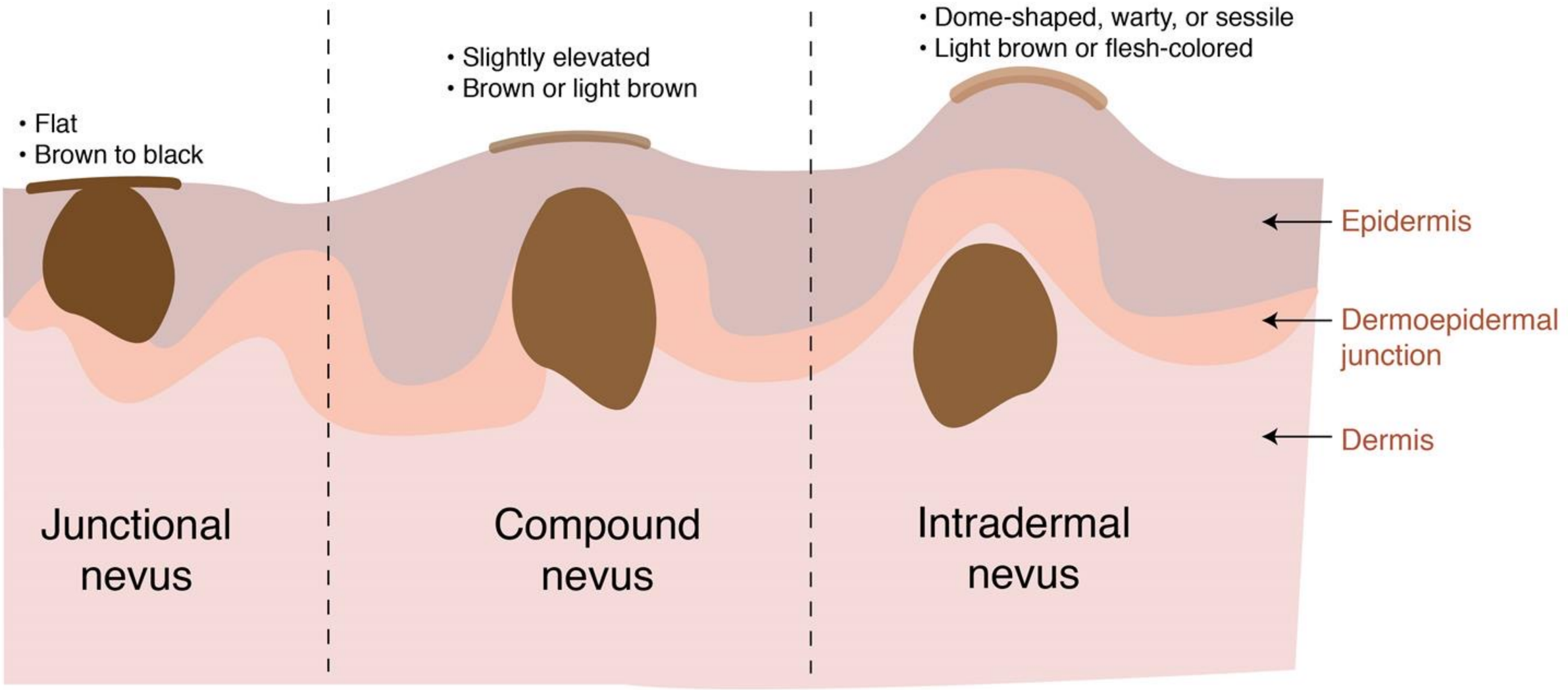


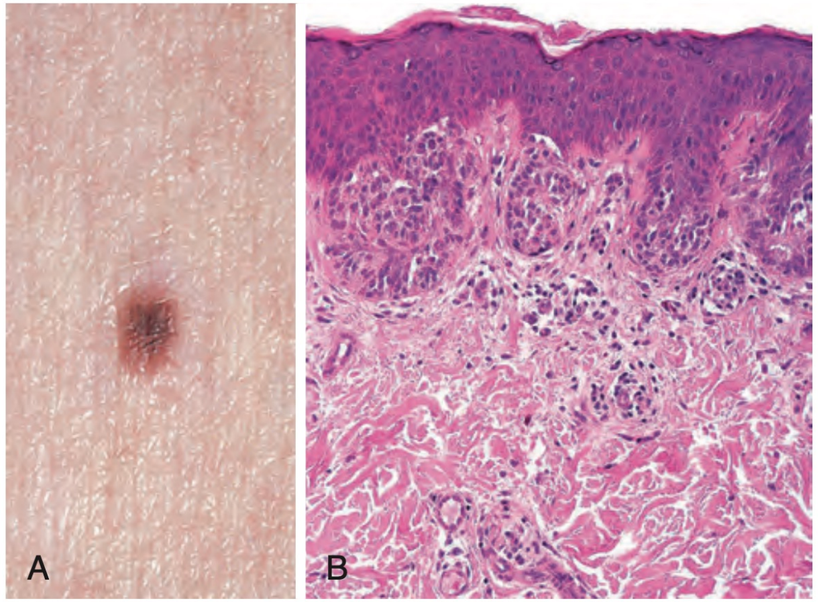
Figure 25.4 Maturation sequence of nondysplastic melanocytic nevi. (A) Normal skin shows only scattered dendritic melanocytes within the epidermal basal cell layer. (B) Junctional nevus. (C) Compound nevus. (D) Dermal nevus. (E) Dermal nevus with neurotization, a change that is also referred to as maturation. Nevi may exist at any stage in this sequence for variable periods of time, although many are believed to progress through this sequence.

Maturation sequence of melanocytic nevus

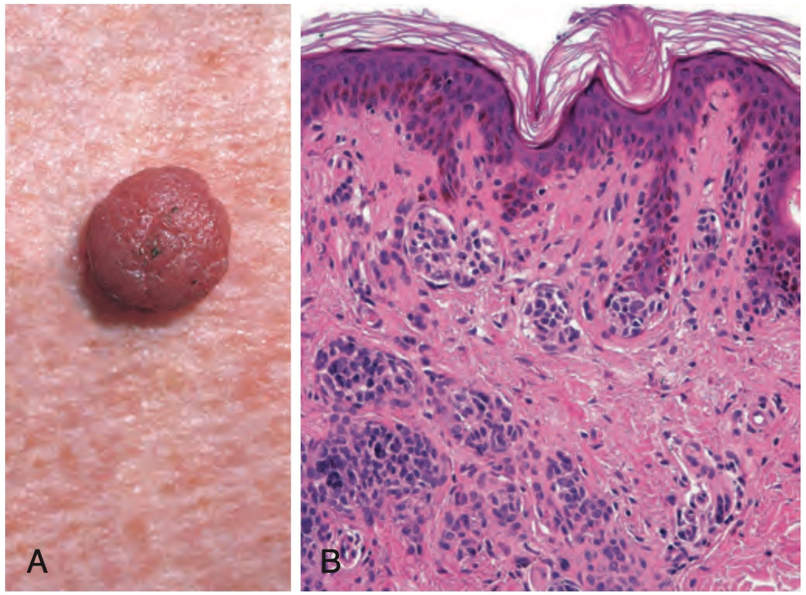


Types of melanocytic nevus

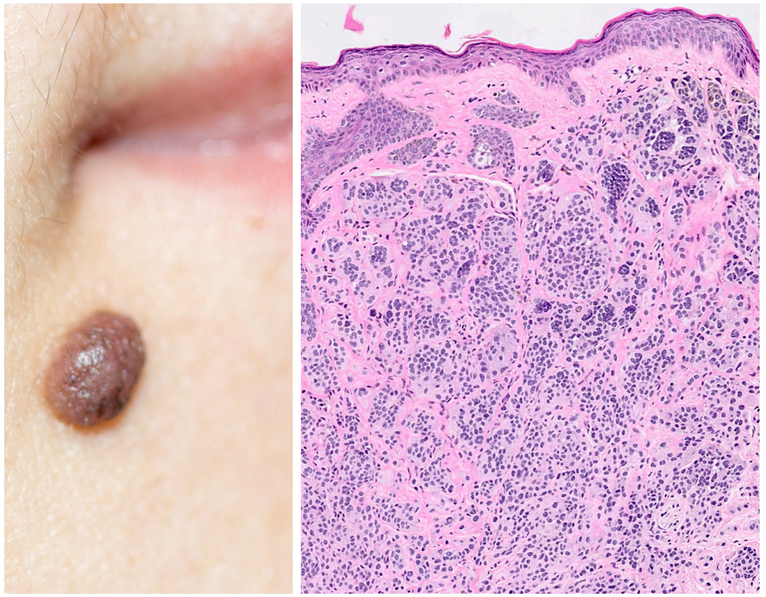




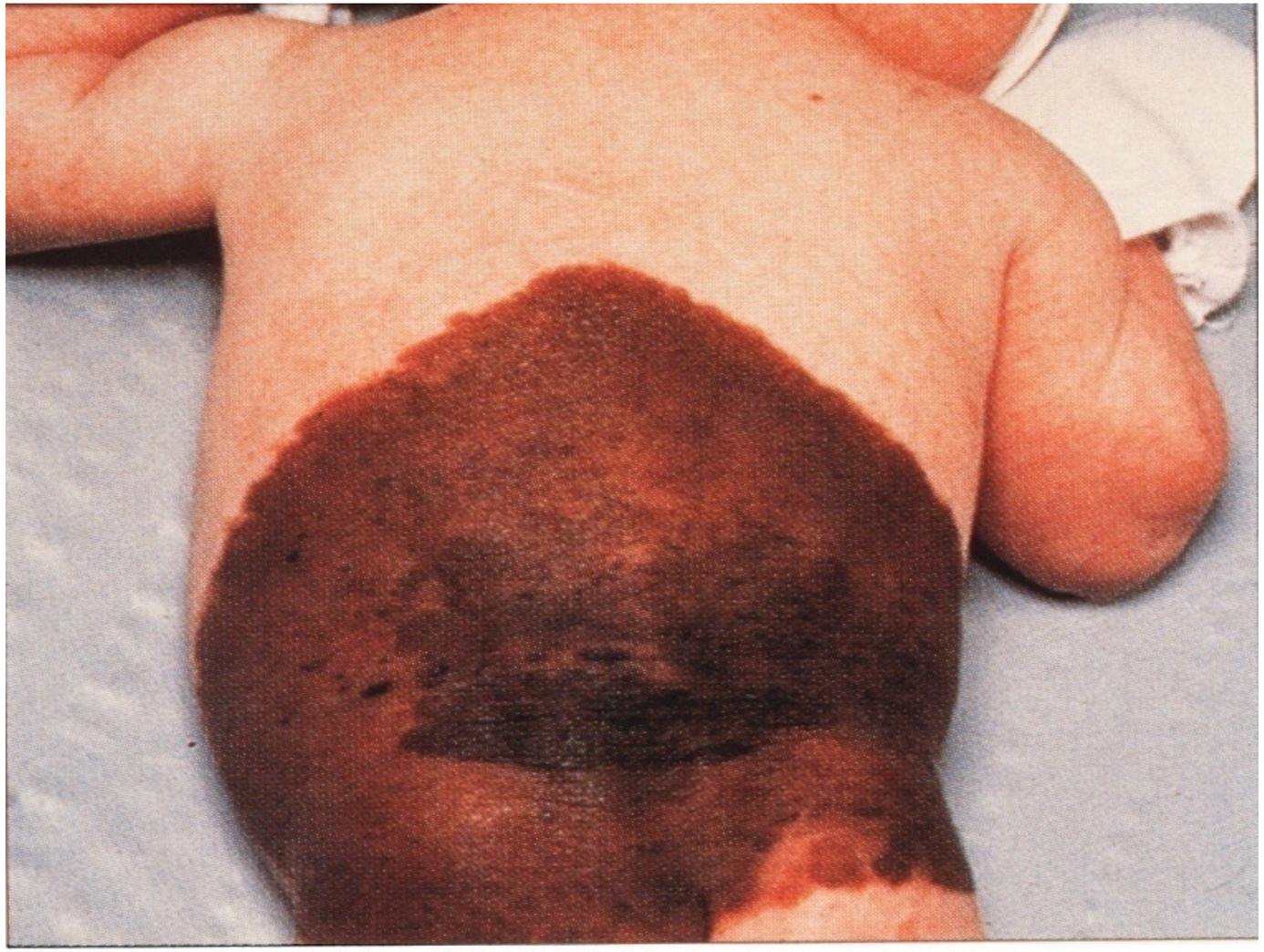
Junctional melanocytic nevus:
(clinical) small flat symmetrical, and uniform pigmented macule or patch
(histopathology) rounded nests of nevus cells originating at the tips of rete ridges along dermoepidermal junction



Compound melanocytic nevus:
(clinical) raised, dome-shaped, symmetrical and uniform pigmented papule
(histopathology) rounded nests of nevus cells at both dermoepidermal junction and in the dermis



Intradermal melanocytic nevus:
(clinical) raised, dome-shaped, symmetrical and uniform pigmented papule, difficult to distinguish from compound type
(histopathology) nests of nevus cells entirely confined within the dermis



Giant congenital melanocytic nevus: In addition to cosmetic importance, the lesion has a high risk of malignant transformation.

Dysplastic nevus

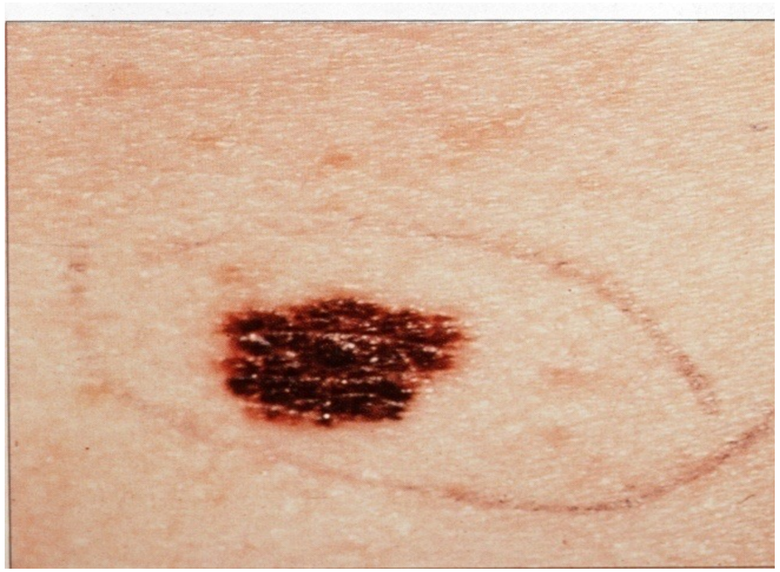
- A nevus with potential being precursor of (malignant) melanoma (also called **atypical mole**), especially in families prone to development of melanoma (familial dysplastic nevus syndrome)

- Patients with **familial dysplastic nevus syndrome** have probability greater than 50% to develop melanoma by age of 60 years.

- Two distinct forms of dysplastic nevus:
  1. **Sporadic form:** low risk of melanoma
  2. **Familial form (familial dysplastic nevus syndrome):**
     - High risk of melanoma (probability greater than 50% to develop melanoma by age of 60)
     - Autosomal dominant inheritance
     - **Pathogenesis:** activating mutation of RAS or BRAF, mutation of CDKN2A and CDK4

Dysplastic nevus

- **Clinical:**
  - Common in lightly-pigmented individuals (Caucasoid)
  - Usually size larger than acquired nevus (often ≥ 6 mm)
  - May have multiple (hundreds) lesions
  - Flat macules to slightly raised plaques, variegation (variability in color), irregular borders, with pebble-like surface



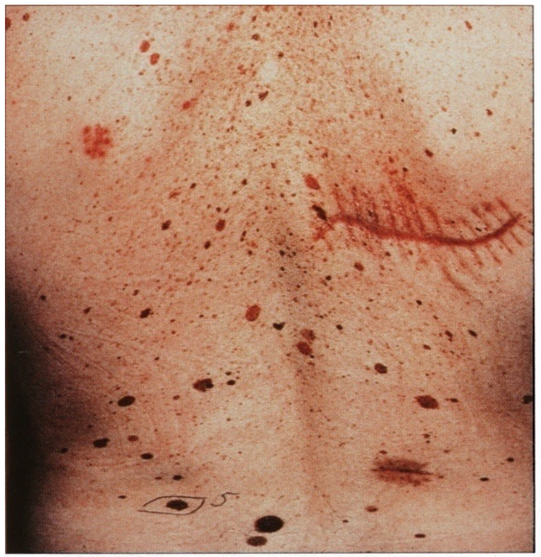
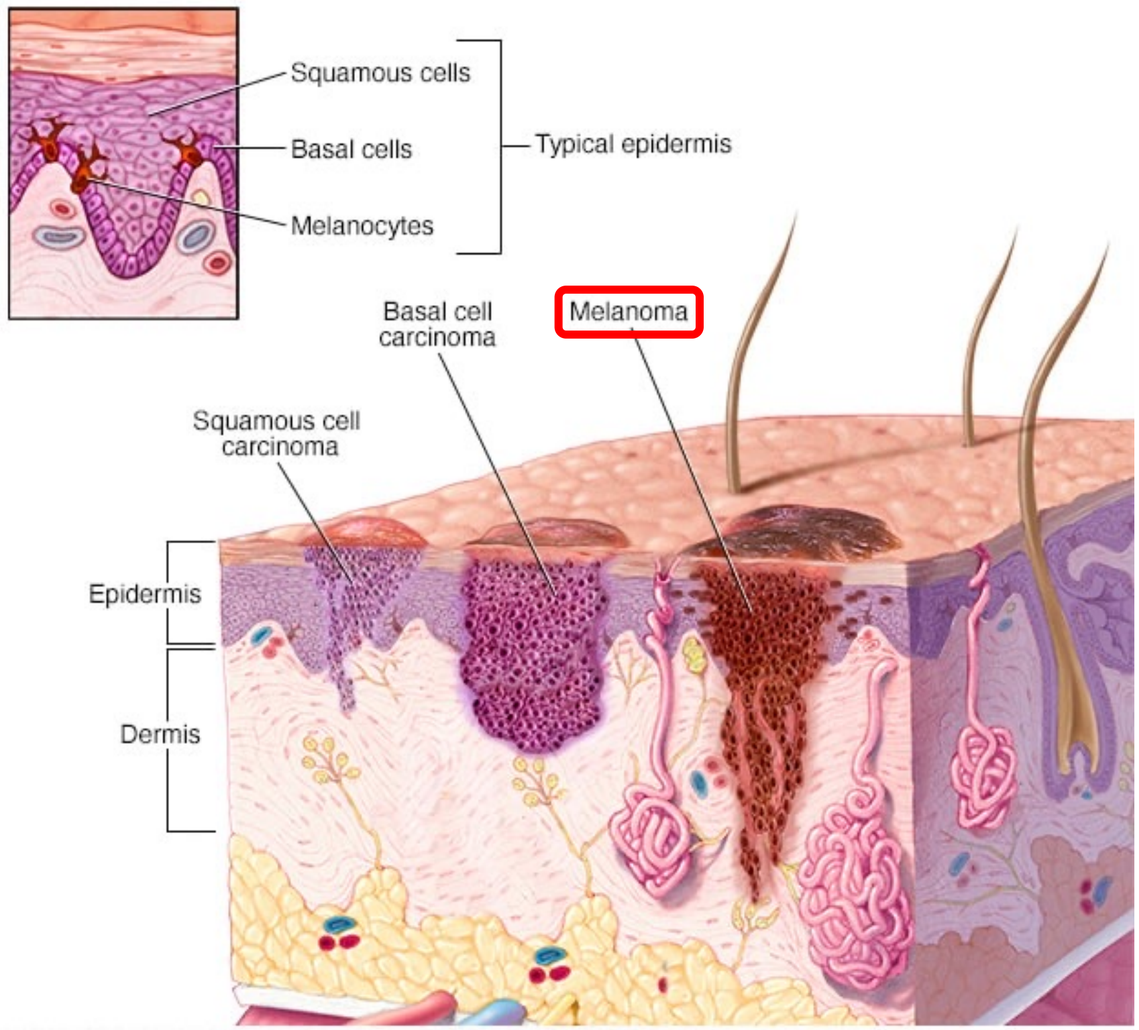
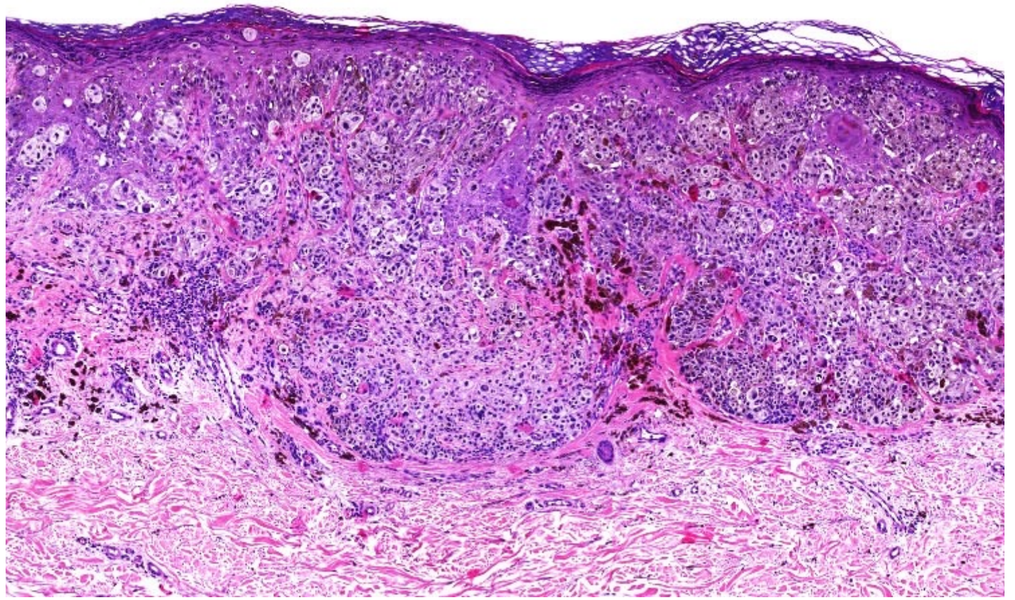


Fig. 13.102 Dysplastic naevi: (upper) there are numerous hyperpigmented naevi and the scar marks the site of an excised malignant melanoma; (lower) note the irregular border, hyperpigmentation and unaffected skin creases. By courtesy of Professor R. Mackie, University of Glasgow, UK.

Malignant melanoma



- Shortly called “**melanoma**”
- Malignant neoplasm of melanocytes
- Most aggressive and deadly skin cancer



Malignant melanoma

- Malignant neoplasm of melanocytes (most aggressive and deadly skin cancer)

- Although mostly occur at skin, may be seen at oral and anogenital mucosa, meninges, esophagus, and eye (uveal tissue)

- Mostly occur sporadically, but sparsely hereditary (5-10%)

- **Risk factors:**
  - Lightly-pigmented or fair skin (especially Caucasoid) with sunlight (UV-B) exposure
  - Patients with dysplastic nevus or giant congenital nevus
  - Familial dysplastic nevus syndrome (e.g. familial atypical multiple mole-melanoma (FAMMM) syndrome)

Malignant melanoma

- **Pathogenesis:**
  - Multi-step processes of activating mutations in oncogenes and loss of tumor suppressor genes
  - Activating mutation of BRAF (oncogenes), or less often RAS
  - Mutation of CDKN2A (tumor suppressor gene): found in 40% of familial melanoma
  - Suppression of PTEN (tumor suppressor gene): cause activation of AKT pathway that promote cell proliferation
  - Others

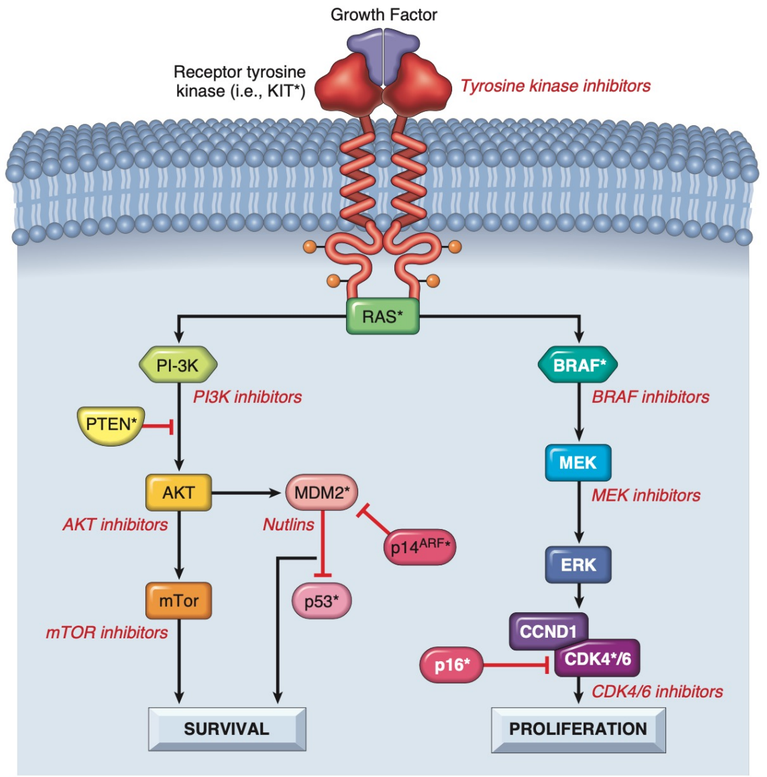
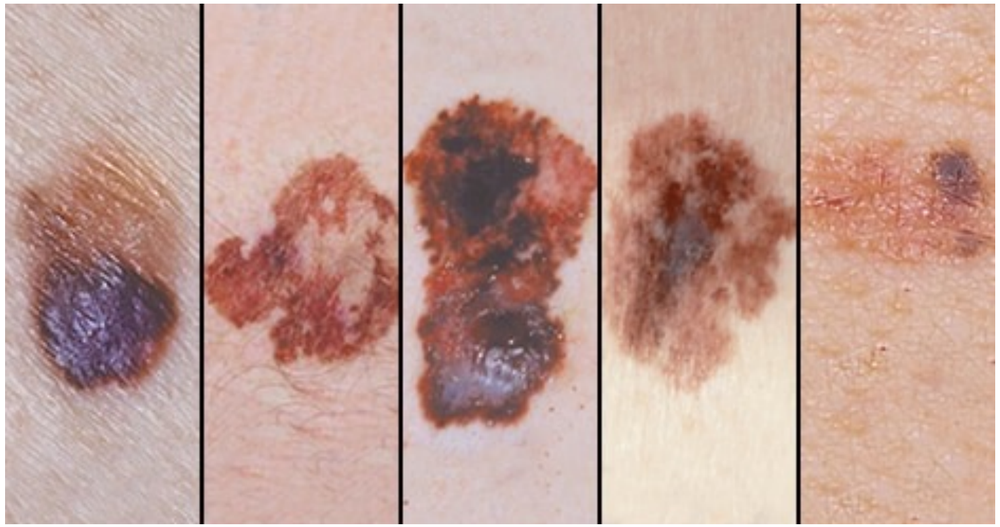


Figure 25.7 Pathways important in melanoma. Growth factors activate signaling circuits involving receptor tyrosine kinases (e.g., KIT), RAS, and two key downstream pathways that include the serine/threonine kinase BRAF and the phospholipid kinase PI3K. Proteins indicated by *asterisks* are mutated in melanoma. Components of these pathways that are being targeted by drugs are indicated.

Malignant melanoma

- **Clinical:**
  - **Early lesion**
    - Pigmented macule with change in color
    - Variegation (light brown to deep black)
    - Irregular border of pigmented lesion
    - Enlargement of pre-existing nevus
    - Itching or pain in pre-existing nevus
  - **Later (advanced) lesion**
    - Developed nodule or tumor (invading the dermis)
    - May become ulcerated or bleeding



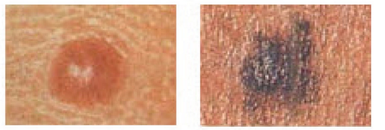
Malignant melanoma

- **Suspicious clinical features for melanoma ***
  - **A :** **A**symmetry
  - **B :** Irregular **B**order
  - **C :** **C**olor variegation
  - **D :** **D**iameter > 6 mm
  - **E :** **E**volution (changes in size and/or color), **E**levation (tumor, nodule)

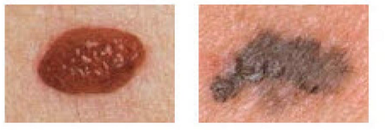
The ABCDE checklist

The ABCDE guideline is one of two commonly used strategies for early detection of melanoma.

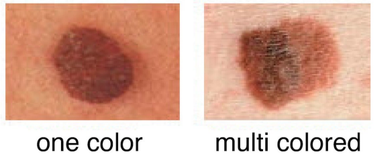
A **Asymmetry:** Moles that have asymmetrical appearance. If you draw a line through this mole, the two halves will not match.



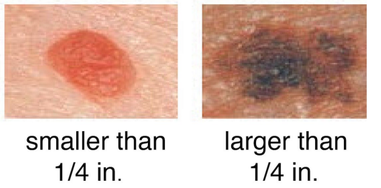
B **Border:** Uneven, scal-loped, jagged, or notched borders



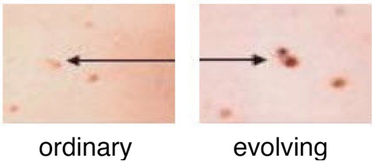
C **Color:** A mole with more than one color.



D **Diameter:** The diameter of the mole is usually larger than a pencil earaser, (1/4 inch or 6 mm). They can be smaller, though.

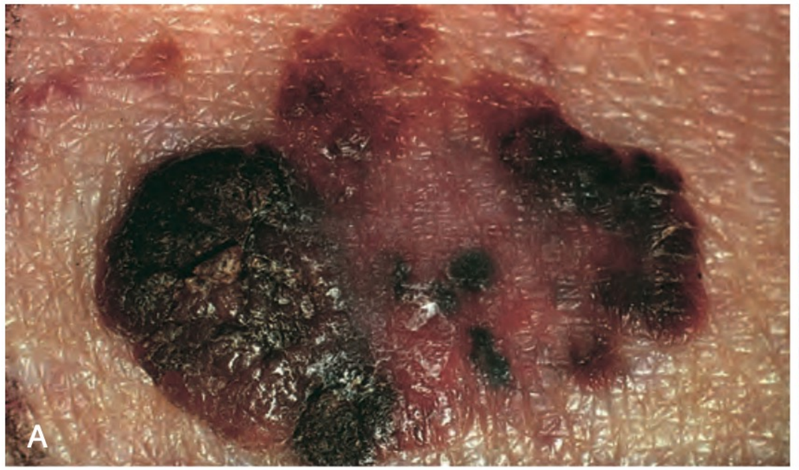


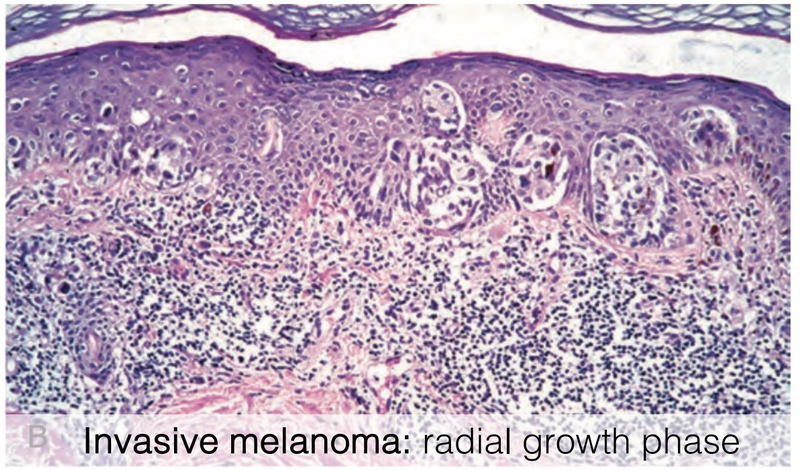
E **Evolution:** Moles that evolve suddenly in size, shape, color, elevation, crusting, itching, or other traits.

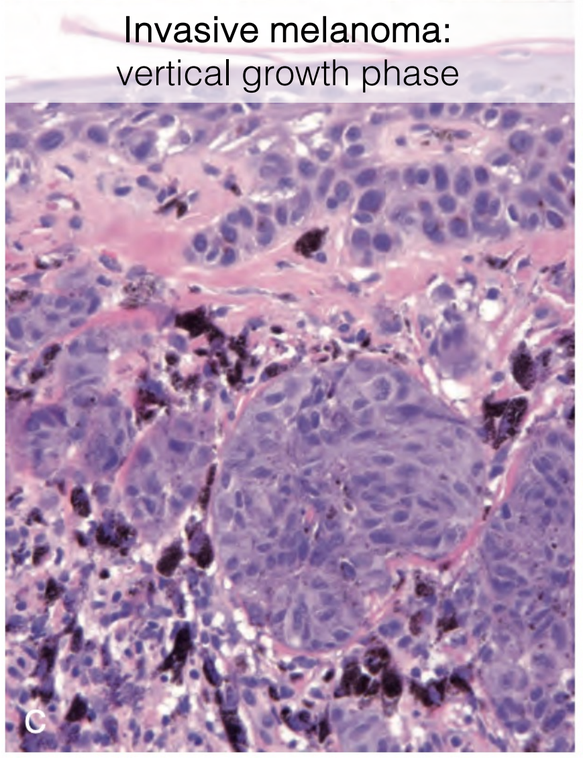


Malignant melanoma

- **Histopathology:**
  - **Early phase**
    - Nested and/or individual malignant melanocytes confined within the epidermis **(melanoma in situ)**
    - Malignant melanocytes (melanoma cells): larger than normal nevus cells with **overt cytologic atypia (prominent nucleoli, increased mitoses with atypical forms)**, and occasionally **intracytoplasmic dark brown melanin pigments**
    - Subsequently, they grow horizontally within epidermis and superficial dermis **(invasive melanoma, radial growth phase)**
  - **Later phase**
    - Melanoma cells invade downward (vertically) into the dermis **(invasive melanoma, vertical growth phase)**







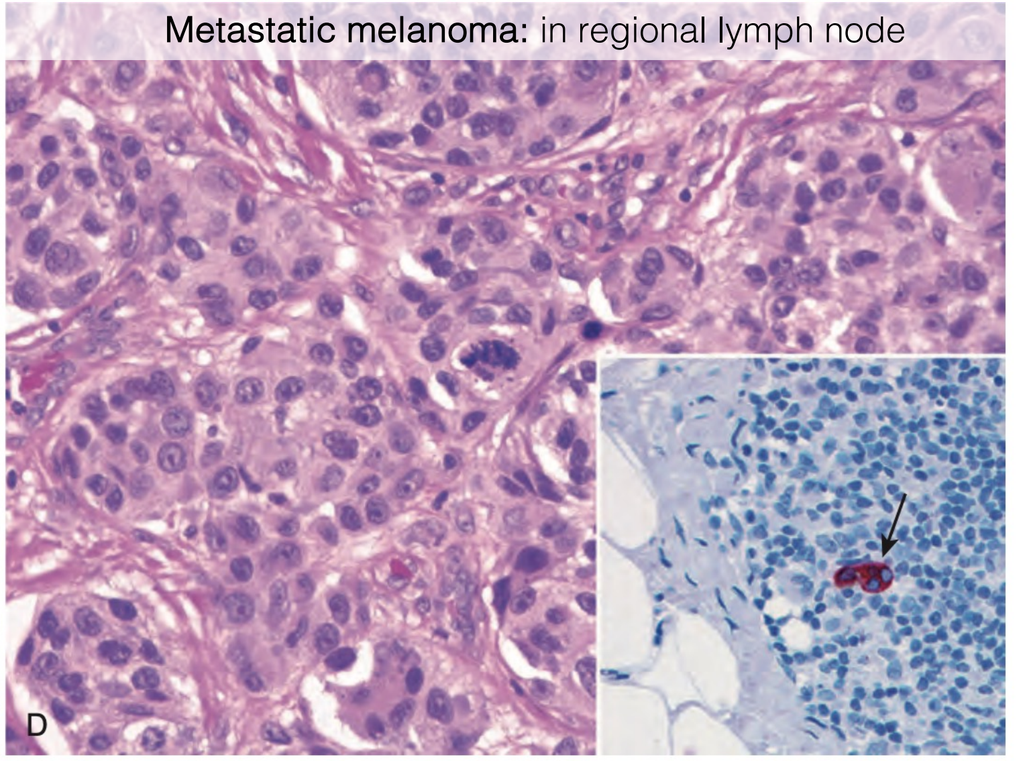
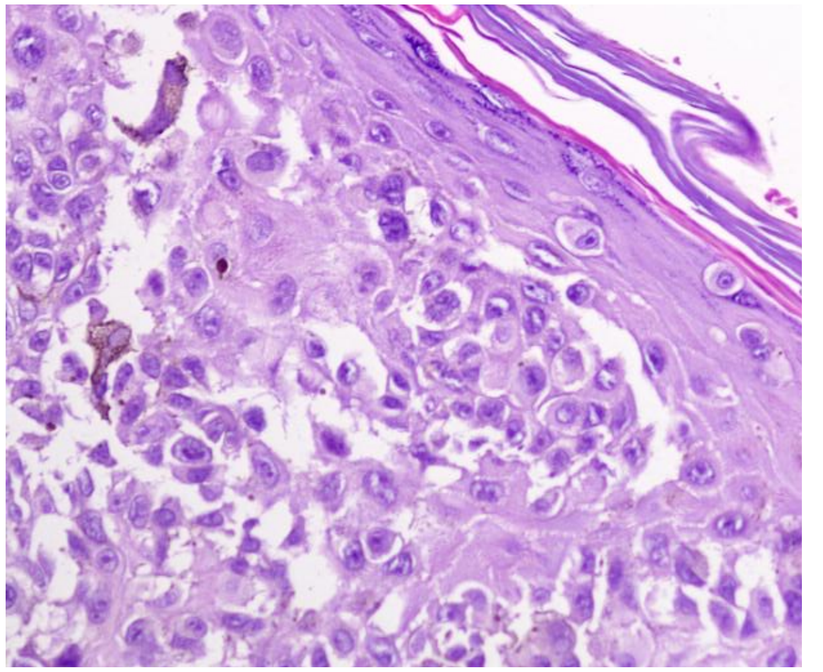
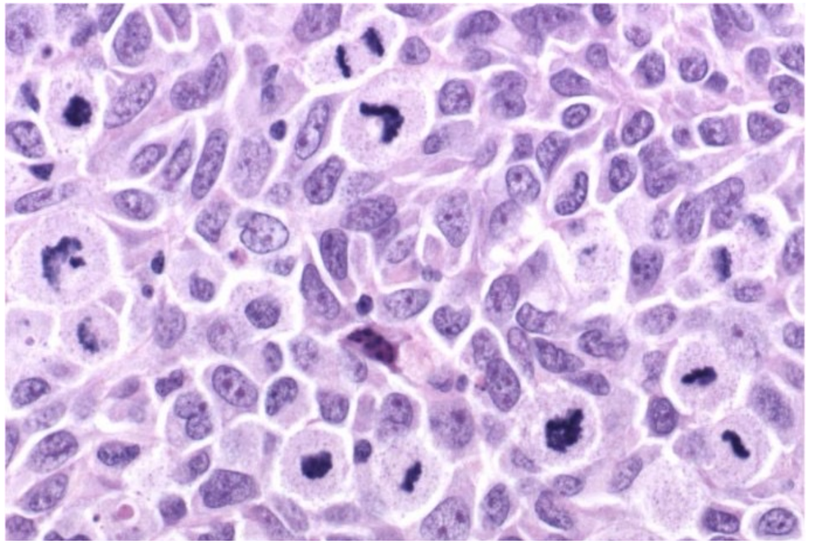


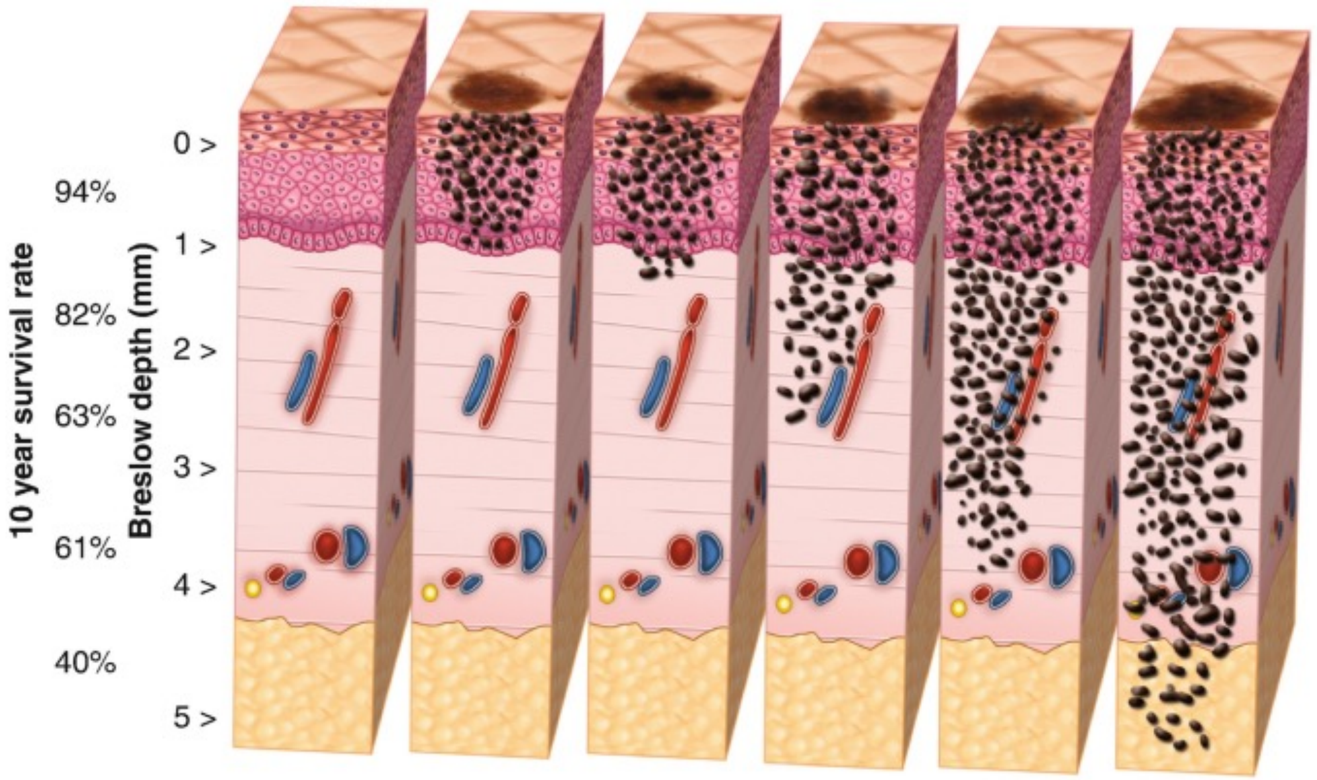
Figure 25.8 Melanoma. (A) Typical lesions are irregular in contour and pigmentation. Macular areas correlate with the radial growth phase, while raised areas correspond to nodular aggregates of malignant cells in vertical growth phase. (B) Radial growth phase showing irregular nested and single-cell growth of melanoma cells within the epidermis and an underlying inflammatory response within the dermis. (C) Vertical growth phase demonstrating nodular aggregates of infiltrating cells. (D) High-power view of melanoma cells. The *inset* shows a sentinel lymph node with a tiny cluster of melanoma cells *(arrow)* staining for the melanocytic marker HMB-45. Even small numbers of malignant cells in a draining lymph node may confer a worse prognosis.





Malignant melanocytes (melanoma cells):
overt cytologic atypia, prominent nucleoli,
increased mitoses (atypical forms)

Malignant melanoma



- **Prognosis:**
  - Depends on **the depth of vertical tumor thickness (Breslow thickness),** ulceration of overlying skin, mitotic count, tumor infiltrating lymphocytes (TIL), and evidence of tumor regression
  - **Breslow thickness:** the distances from **stratum granulosum** to **the deepest invasive portion** of the tumor
    - If < 0.75 mm; usually cured by local excision
    - If > 3 mm; high risk for lymph node or distant organ metastasis

Melanoma: *Risk factors, pathogenesis, and clinical findings*

Authors: Ayaa Alkhaleefa, Ryan T. Lewinson
Reviewers: Tara Shannon, Harjot Atwal, Gurleen Chahal, Usama Malik, Laurie Parsons*, Habib A Kurwa*
** MD at time of publication*

Oral methoxsalen (psoralen) and ultraviolet A radiation therapy used for psoriasis, vitiligo

Genetic risk factors like fair skin, multiple nevi on skin surface, extreme sun hypersensitivity

Intermittent intense sun exposure and sunburn in childhood

No/minimal sunscreen use (broad spectrum SPF 30+)

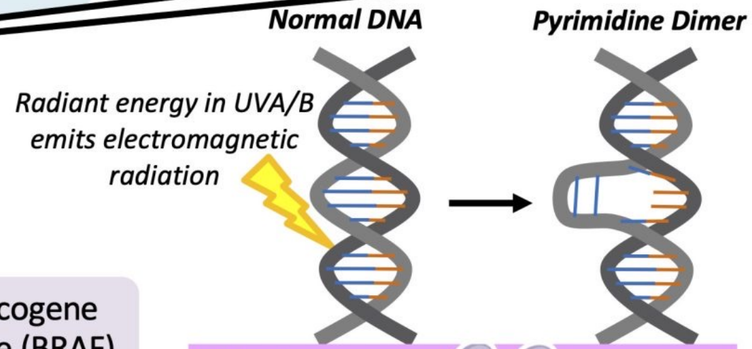
Minimal protective clothing e.g., sunglasses, hats

Geographic location e.g., equatorial regions

Tanning beds

↑ Ultraviolet A and B exposure (UVA/B)

Formation of cyclobutene pyrimidine dimers in melanocytes (see illustration)



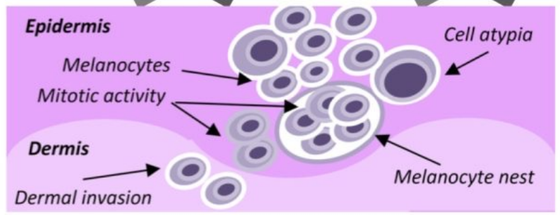
Melanin and reactive oxygen species activation in melanocytes

Mutation in tumour protein 53 (a tumor suppressor gene) in melanocytes

Accelerated proto-oncogene serine/threonine kinase (BRAF)

Oxidative DNA damage in melanocytes

↑ Cell division of mutated melanocytes



Melanoma

Rapid proliferation of abnormal melanocytes at different stages of growth

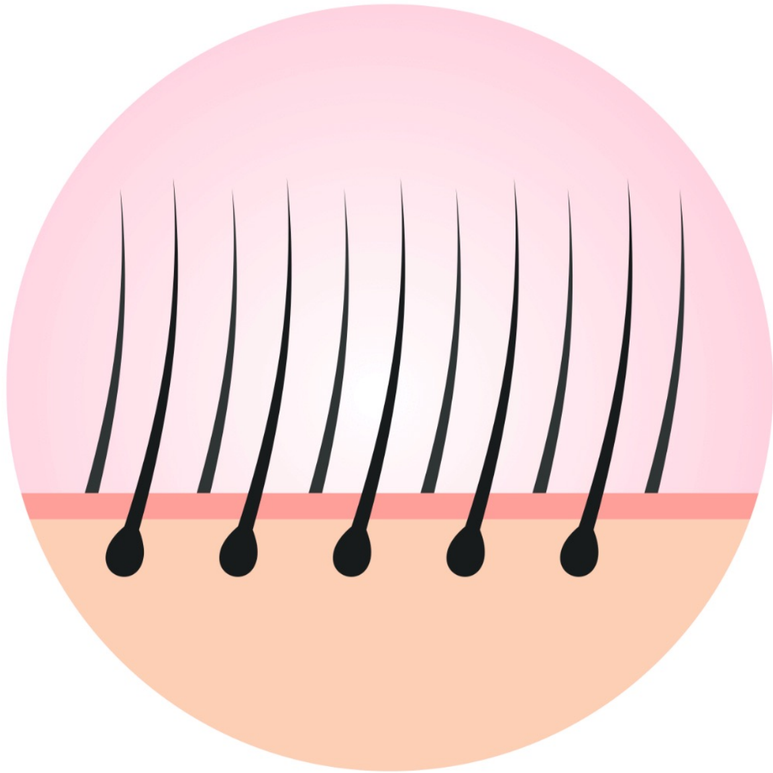
- **Asymmetry:** One half of lesion does not look like the other
- **Borders:** Irregular, poorly defined, or scalloped appearance

Growth of mutated melanocytes at irregular and uncontrolled rates

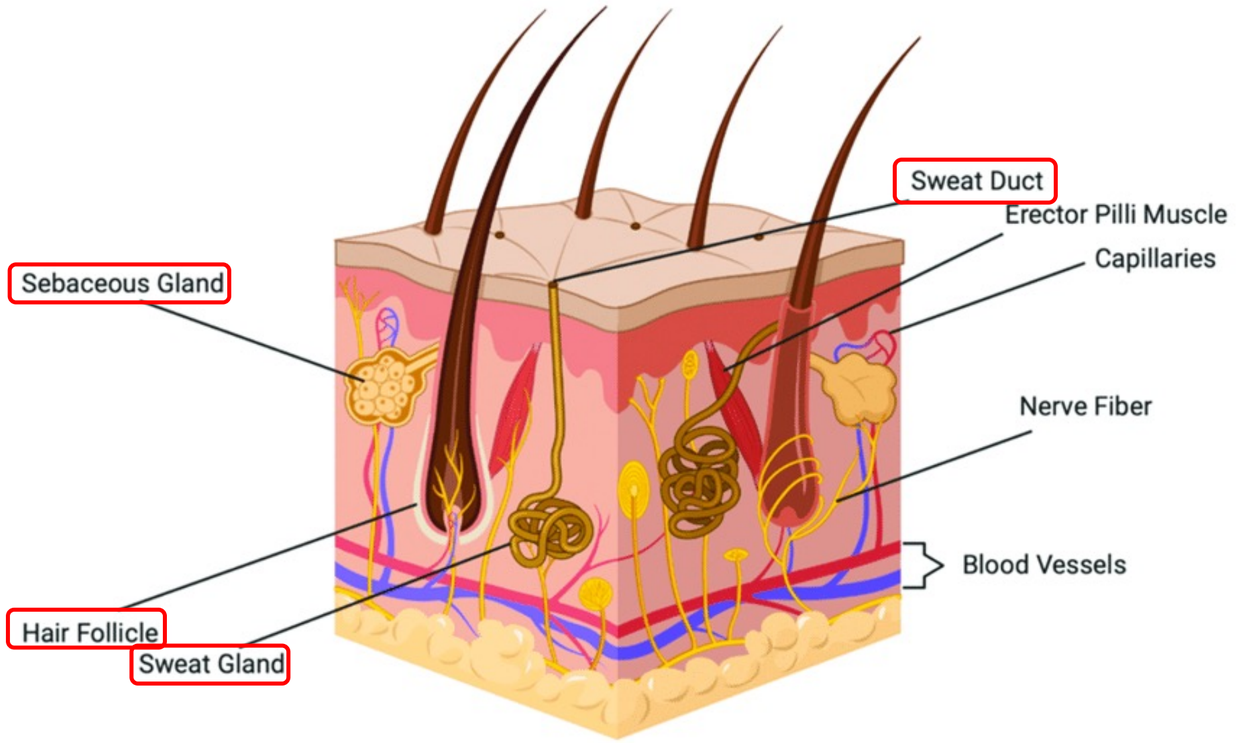
- Unregulated production of melanin by each melanocyte → **Color:** Varied throughout lesion e.g., black, blue, or red
- **Diameter:** Usually greater than 5 mm
- **Evolving:** Rapid change (few months) in shape, size, and color

- Plaque with prolonged horizontal growth phase occurring anywhere on the body → **Superficial spreading melanoma**
- Rapidly growing nodule occurring anywhere on the body → **Nodular melanoma**
- Evolving solar freckle in sun exposed areas (head, neck) found in older adults → **Lentigo maligna melanoma**
- Found in palms of hands and soles of feet → **Acral lentiginous melanoma**

Skin appendigeal (adnexal) tumors



Skin appendages (adnexae)



- **Skin appendages (adnexae):** hair follicles, sebaceous glands, sweat glands (eccrine and apocrine)
- Although there are various types of cutaneous adnexal tumors identified, the incidence of these tumors are **relatively lower than** epidermal tumors.

Benign skin appendigeal (adnexal) tumors

- **Benign follicular epithelium (hair) neoplasms:**
  - Trichoepithelioma, trichoblastoma, pilomatricoma, etc.

- **Benign sweat gland neoplasms**
  - Eccrine sweat gland: eccrine poroma, syringoma, cylindroma, etc.
  - Apocrine sweat gland: apocrine adenoma, syringocystoma papilliferum, etc.

- **Benign sebaceous gland neoplasm**
  - Sebaceous adenoma, etc.

Malignant skin appendigeal (adnexal) tumors

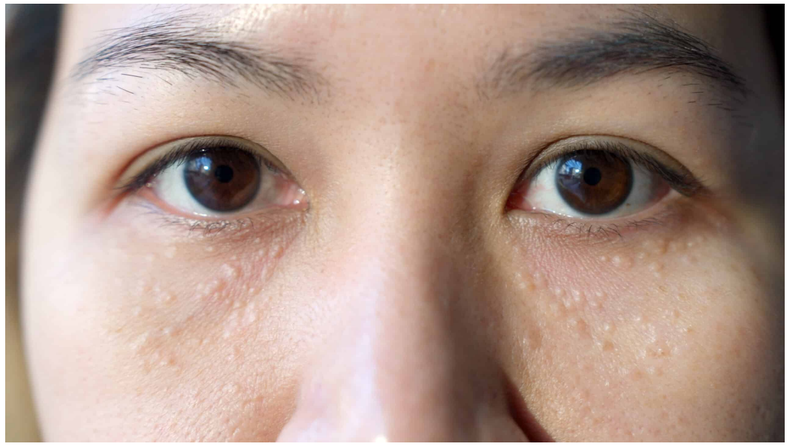
- **Malignant follicular epithelium (hair) neoplasms:**
  - Malignant trichoepithelioma, etc.

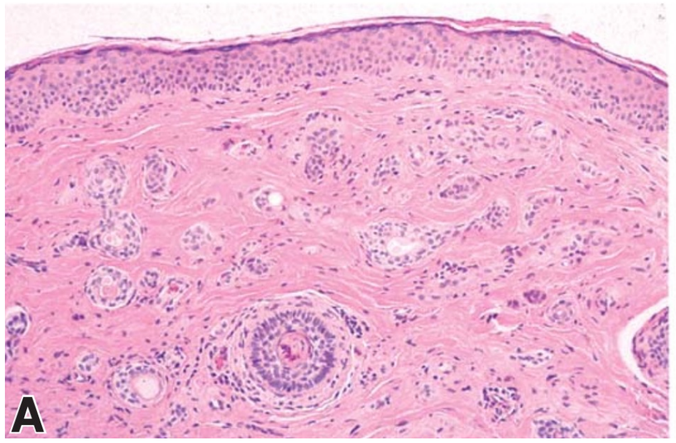
- **Malignant sweat gland neoplasms**
  - Eccrine sweat gland: eccrine carcinoma, microcystic adnexal carcinoma, etc.
  - Apocrine sweat gland: apocrine carcinoma, etc.

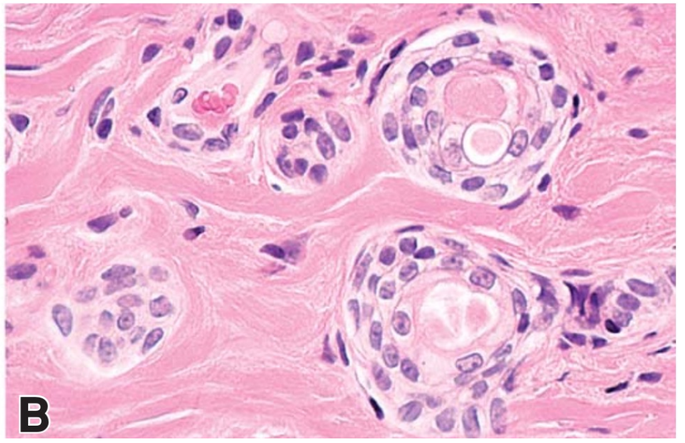
- **Malignant sebaceous gland neoplasm**
  - Sebaceous carcinoma, etc.

Syringoma

- Benign adnexal neoplasm of sweat gland (eccrine) origin, derived **sweat duct ridge**
- Mostly occurs on lower eyelids or upper cheeks of women
- **Clinical:** elevated, flesh-colored papules
- **Histopathology:**
  - Epithelial proliferation forming ducts, tubules and solid islands amid dense fibrous stroma within the upper dermis
  - Ductal differentiation closely mimics that of straight dermal eccrine duct, with central lumen and cuticle formation

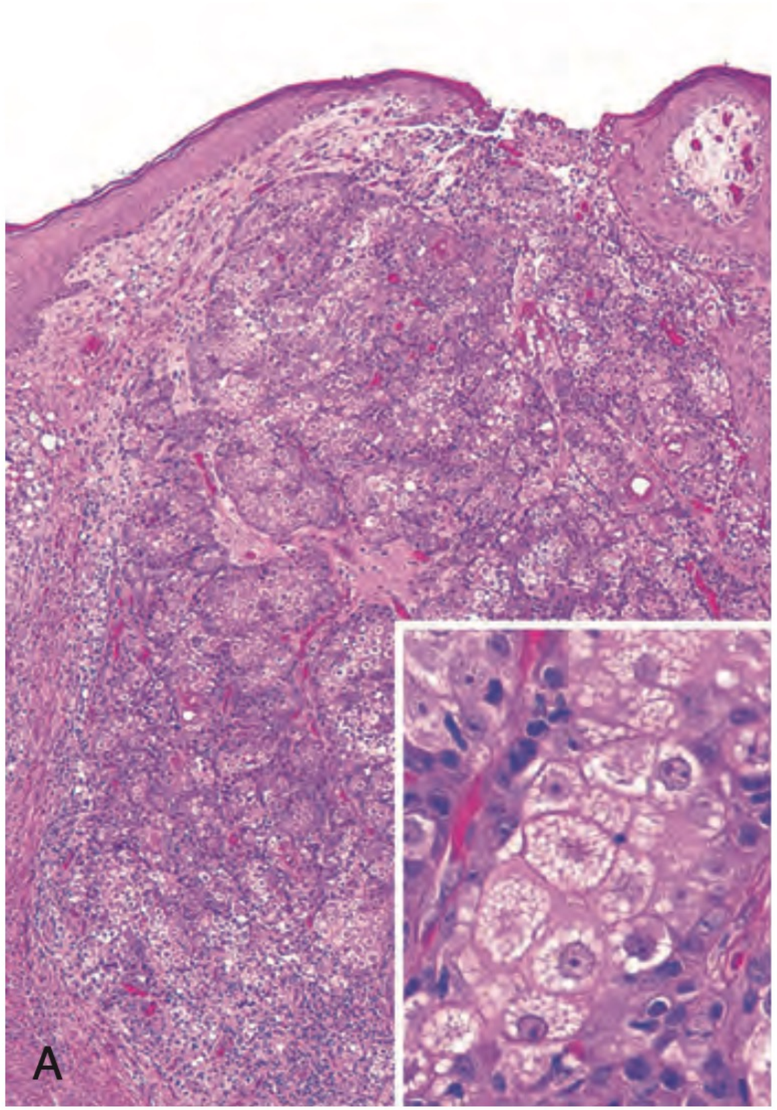






Sebaceous adenoma

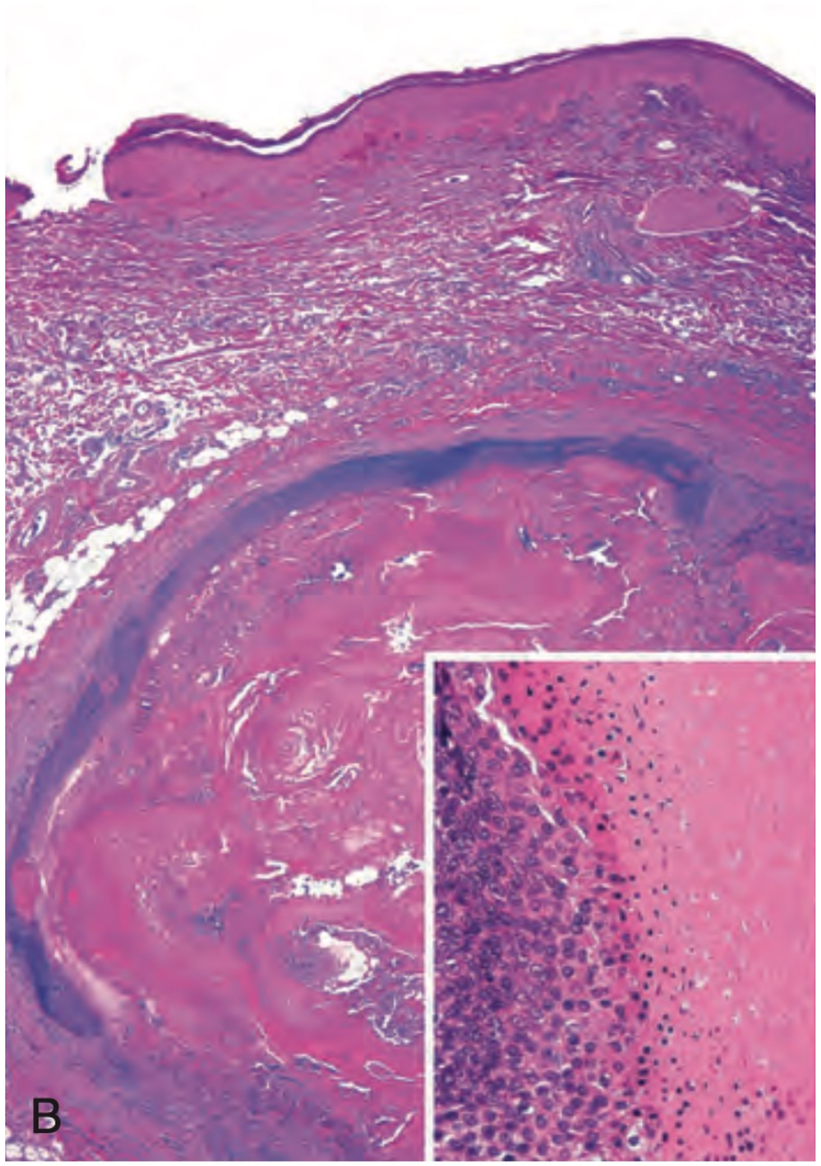
- Benign neoplasm composed of mature sebaceous lobules with the expansion of germinative basaloid cell layers at the periphery
- Associated with Muir-Torre syndrome (especially when arising outside head and neck region), a clinical variant of hereditary nonpolyposis colorectal carcinoma syndrome (Lynch syndrome), which is caused by germline defects in DNA mismatch repair genes
- **Clinical:** older people (mean age of 60 years), mostly in head and neck, particularly on the face and scalp
- **Histopathology:**
  - Well-circumscribed, nodular growth of lobules consisting of admixture of **peripheral basaloid cells** and **central mature sebocytes** (intracytopasmic lipid vacuoles)



Benign adnexal tumor demonstrating sebaceous differentiation

Pilomatricoma

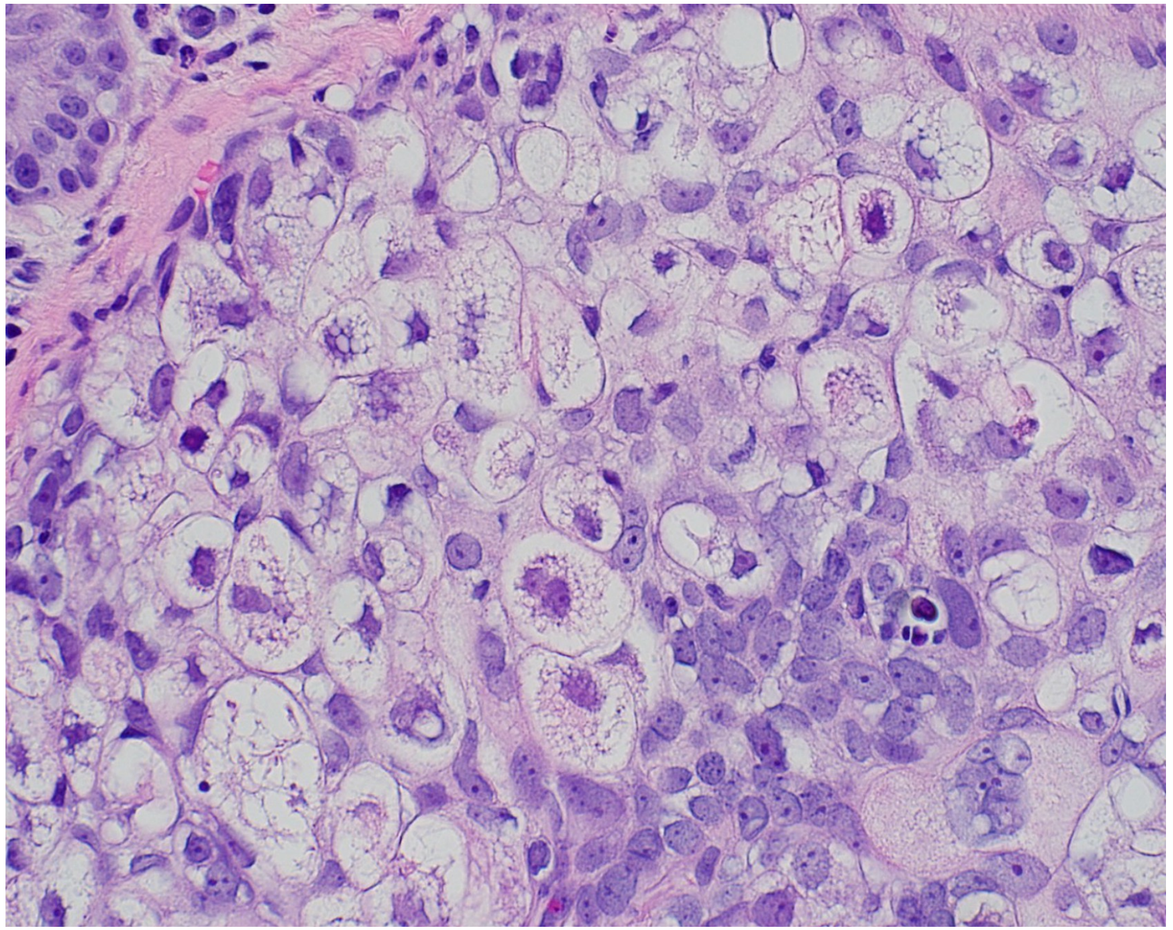
- Benign skin adnexal tumor originating from hair matrix and cortex
- Associated with activating mutations in CTNNB1 (gene encoding β-catenin) – Wnt/β-catenin signaling pathway is critical for early hair development and regulates hair growth and maintenance
- **Clinical:**
  - Commonly in head and neck, extremities, and trunk in children
  - Circumscribed hard dermal nodule with cheesy material
- **Histopathology:**
  - Basaloid cells that show trichilemmal or hair-like differentiation (hair matrix differentiation to anucleate ghost cells)



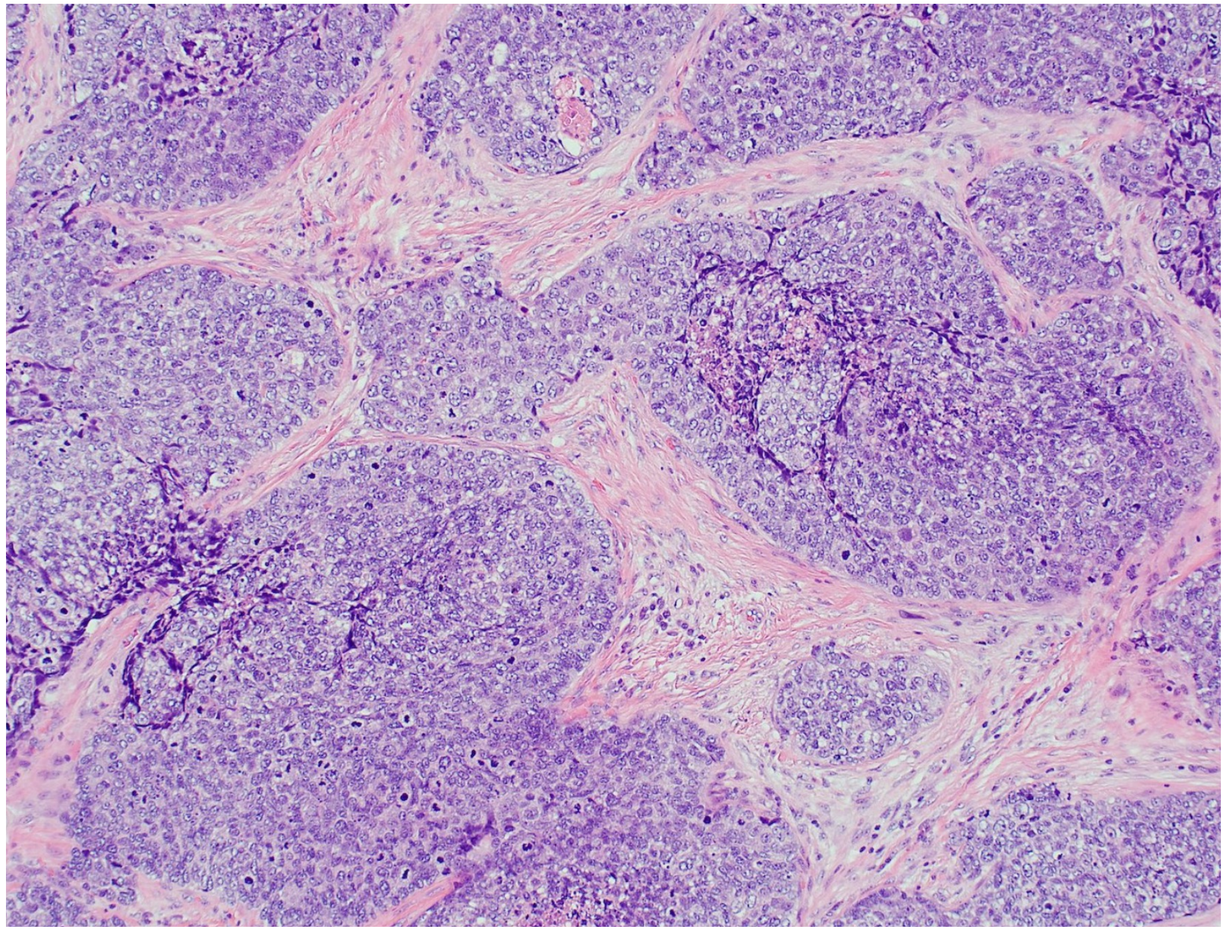
Sebaceous carcinoma

- Malignant neoplasm with sebaceous differentiation
- **Clinical:**
  - Mostly occurs sporadically in elderly patients
  - Commonly in periocular (periorbital) locations
  - Rarely occur in association with Muir-Torre syndrome
  - Aggressive tumor

  Histopathology:
  - Infiltrative sheets or lobules separated by fibrovascular stroma
  - Variable proportion of admixed mature-appearing sebocytes (multivacuolated cells) with nuclear indentation and basaloid undifferentiated cells
  - Frequent mitoses and necrosis (comedo type)

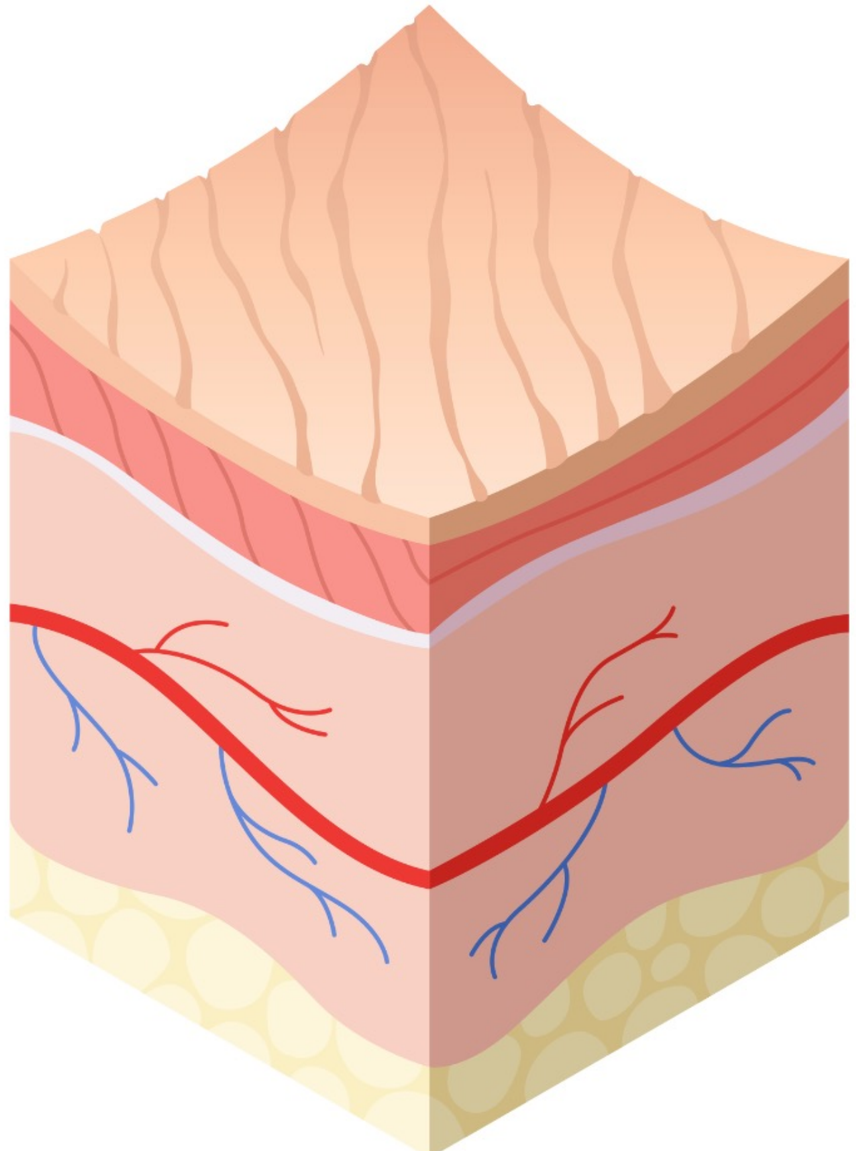


Sebaceous carcinoma (well-differentiated):
a high proportion of multivacuolated cells that exhibit nuclear indentation, pleomorphism, and mitoses

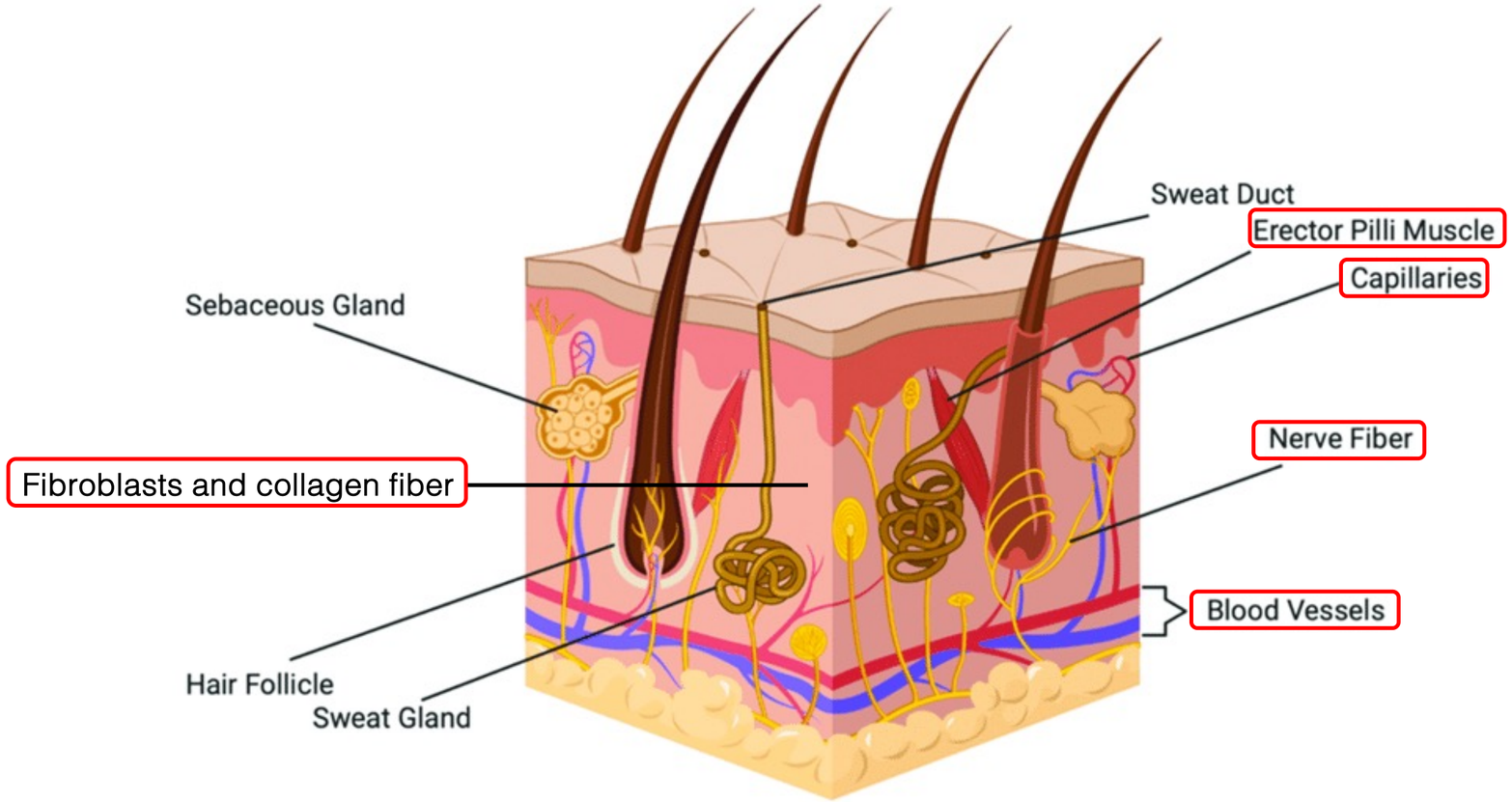


Sebaceous carcinoma (poorly-differentiated):
atypical basaloid cells exhibiting marked pleomorphism and scattered mitoses, with a small proportion of multivacuolated cells

Dermal (connective tissue) tumors



Dermis (connective tissue)



- **Dermis:** connective tissue consisting of fibroblasts (collagen fibers), blood vessels, nerve, and smooth muscle

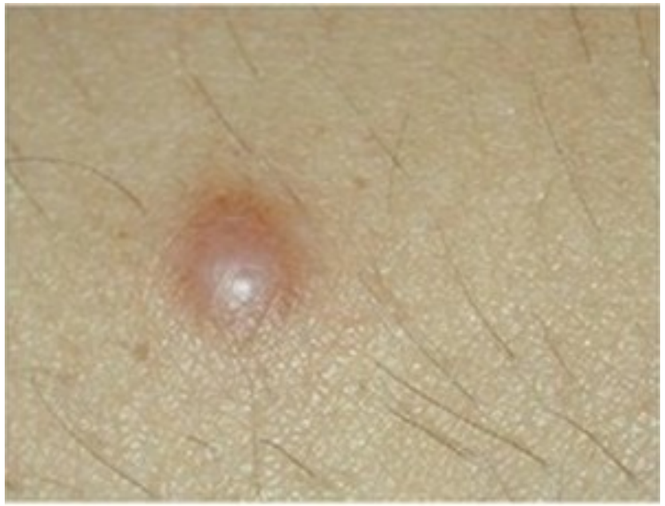
Dermal (connective tissue) tumors

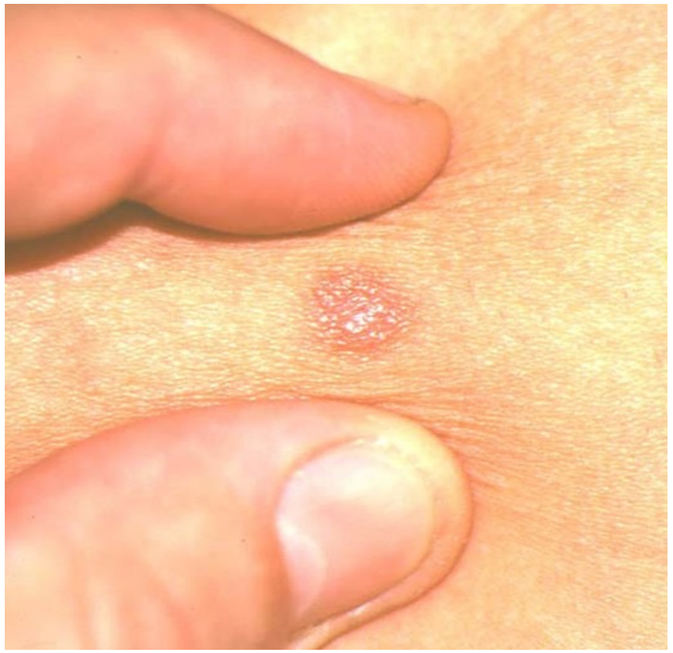
Cell of origin	Benign tumors	Malignant tumors
Uncertain lineage	• Dermatofibroma (fibrous histiocytoma)	• Dermatofibrosarcoma protuberans (DFSP)
Blood vessel	• Hemangioma	• Angiosarcoma • Kaposi sarcoma
Nerve and nerve sheath	• Neurofibroma • Schwannoma	• Malignant peripheral nerve sheath tumor (MPNST)
Smooth muscle	• Leiomyoma	• Leiomyosarcoma

Dermatofibroma

- Also called “**cutaneous fibrous histiocytoma**”
- A spectrum of benign dermal based lesion with fibroblastic and histiocytic differentiation
- There is still debate as to whether dermatofibroma:
  - Neoplastic or reactive process ?
  - Cells of origin: fibroblast (CD34+) or dermal dendrocytes (factor XIIIa+) ?

- **Clinical:**
  - Usually in young to middle-aged adults
  - Typically occurs on **distal extremities (legs, arms)** and trunk, but can occur on any part of the skin surface
  - Firm, tan papules
  - Lateral pressure on the skin nearby to the lesion produces a depression on the lesion **(dimple sign)**

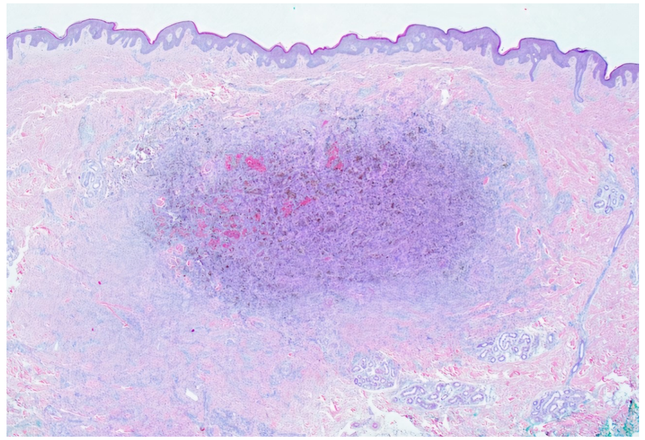


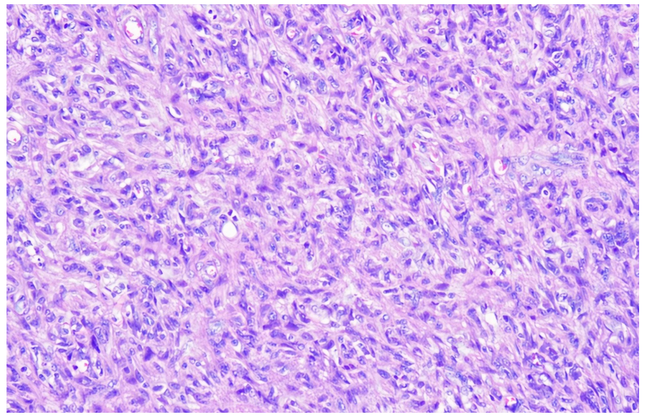


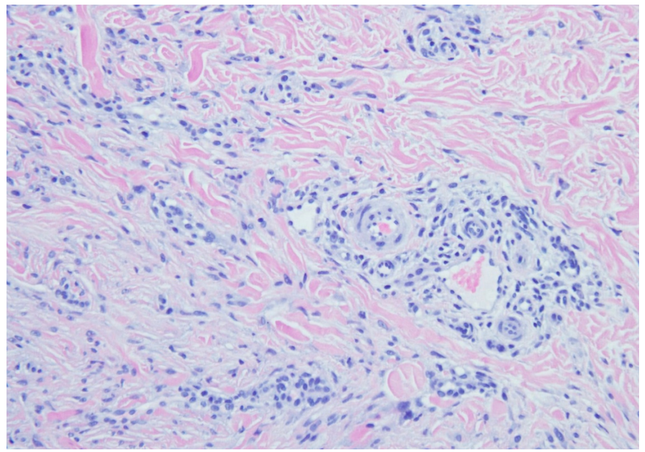
Dimple sign

Dermatofibroma

- **Histopathology:**
  - Symmetric dermal-based unencapsulated lesion
  - Made up of spindled fibroblasts (thin elongated nuclei with pointed ends and eosinophilic cytoplasm) and histiocytes (epithelioid shaped cells with abundant pale cytoplasm) arranging vague storiform, pinwheel, or curlicue pattern
  - Variable amounts of inflammatory cells and mitoses
  - Collagen trapping at periphery
  - Grenz zone (sparing of the superficial papillary dermis)
  - Occasional Touton giant cells and ringed lipidized siderophages may be present.





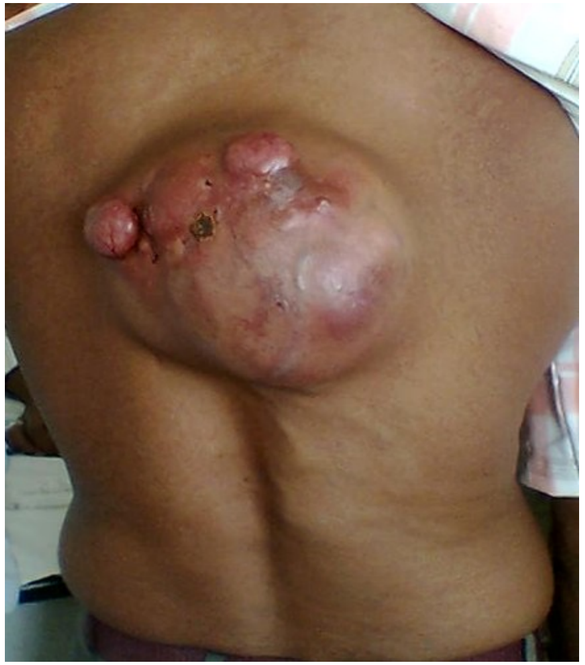


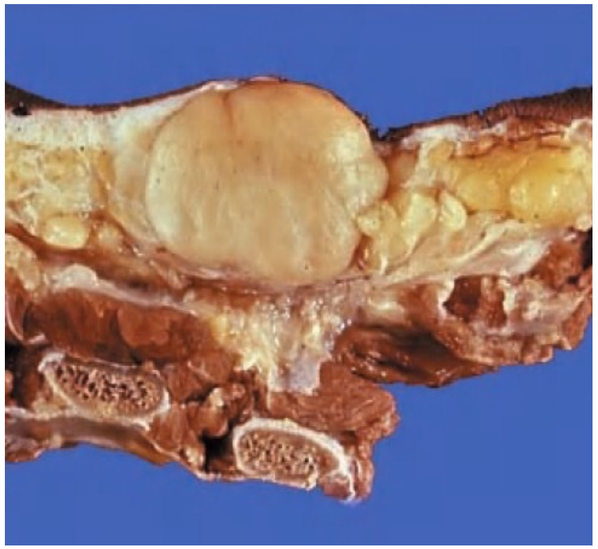
Dermatofibrosarcoma protuberans

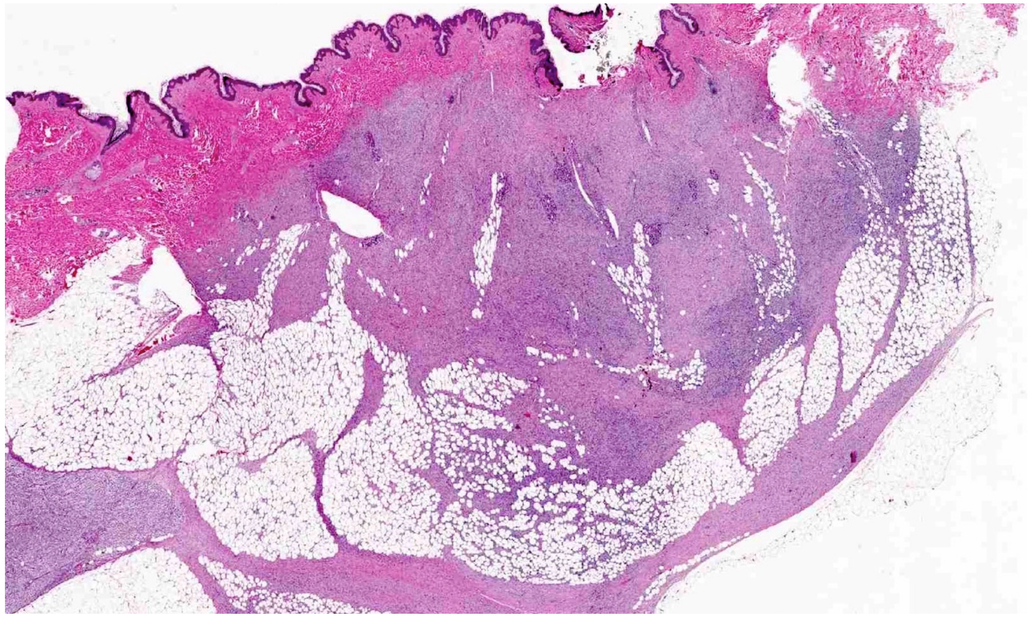
- A low to intermediate-grade malignant soft tissue tumor

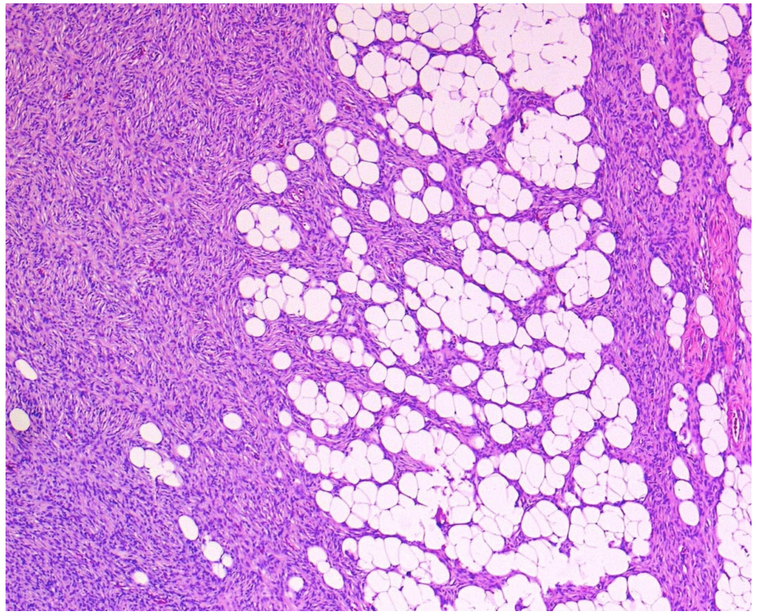
- **Clinical:**
  - Slow-growing mass, frequently on trunk
  - Locally aggressive, may recur (but rarely metastasize)
  - Firm solid nodules

- **Histopathology:**
  - Neoplastic spindle cells with prominent storiform to whorled patterns
  - Infiltrate and expand fibrous septa of subcutaneous tissue; interdigitation among lobules of fat (honeycomb pattern)
  - Diffuse and strong positive immunoreactivity to CD34

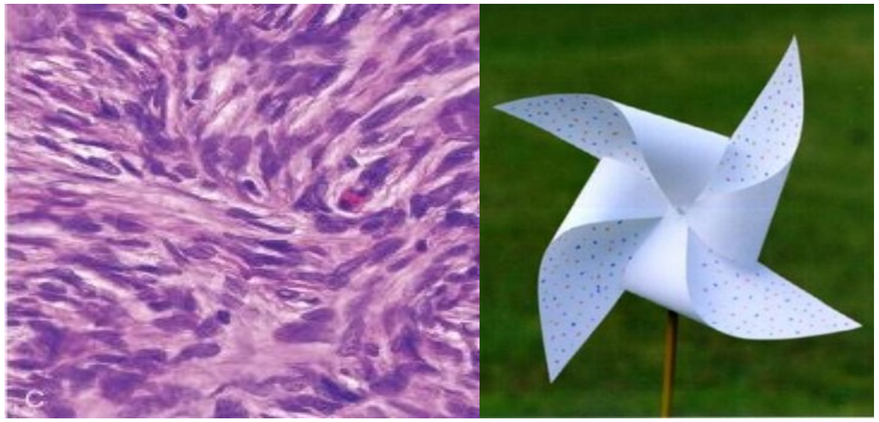




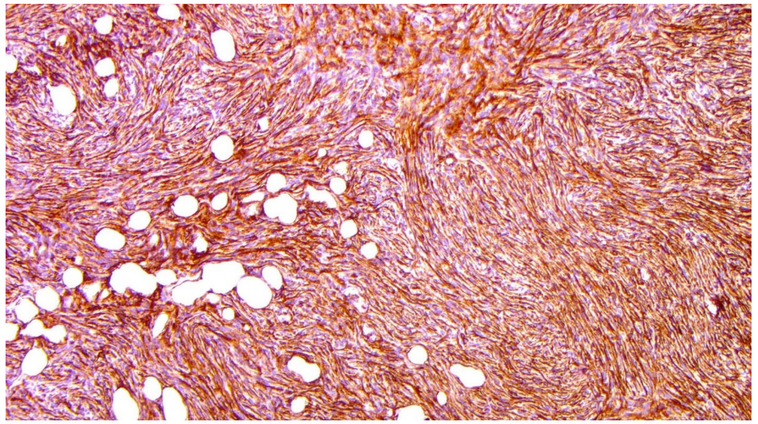




Dermatofibrosarcoma protuberans: infiltrate and expand fibrous septa of subcutaneous tissue; interdigitation among lobules of fat **(honeycomb pattern)**



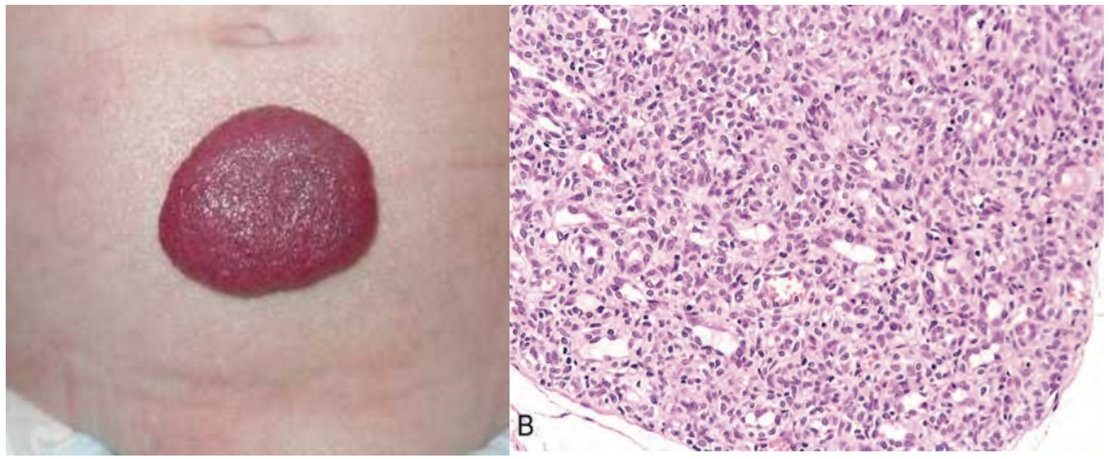
Storiform pattern



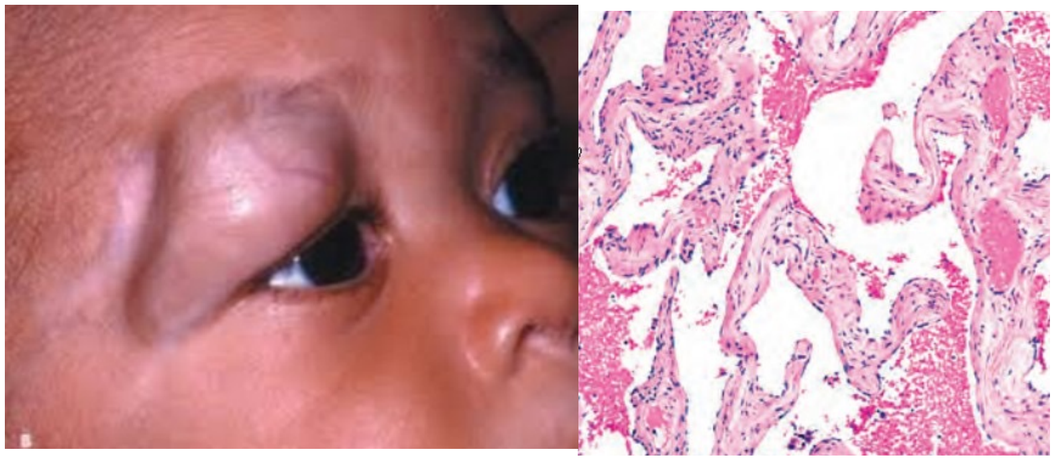
Diffuse and strong positive immunoreactivity to **CD34**

Hemangioma

- Benign tumor of endothelial-derived blood vessel
- Usually produce obvious vascular channels filled with blood cells and lined by endothelial cells
- Common benign tumors of infancy and occurs in approximately 5% - 10% of infants
- Several histologic and clinical variants
  - **Capillary hemangioma:** thin-walled capillaries
  - **Cavernous hemangioma:** large and dilated vascular channels



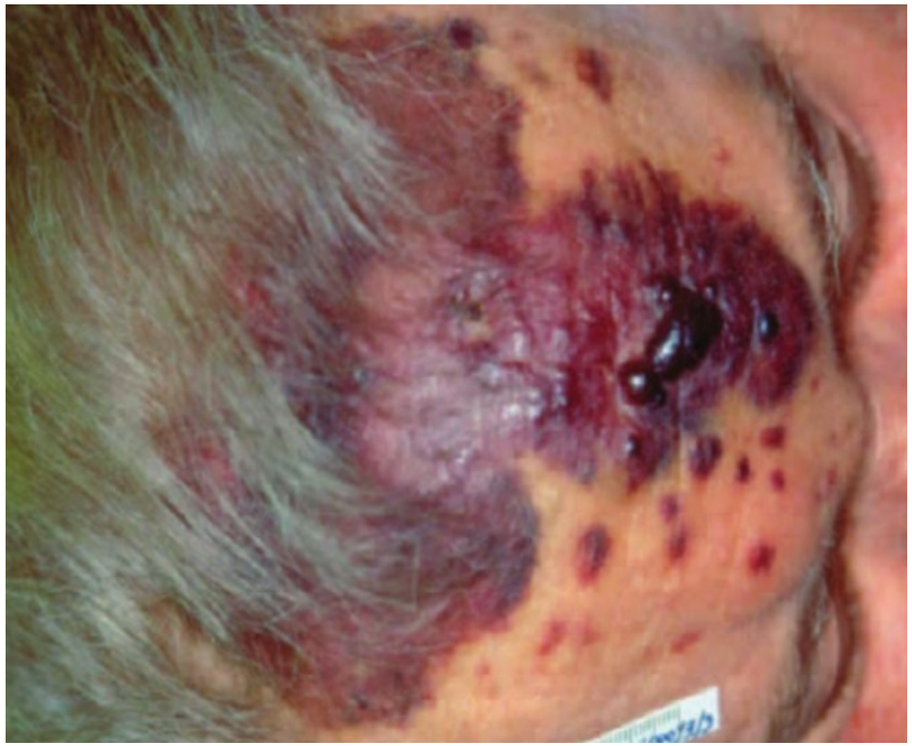
Capillary hemangioma

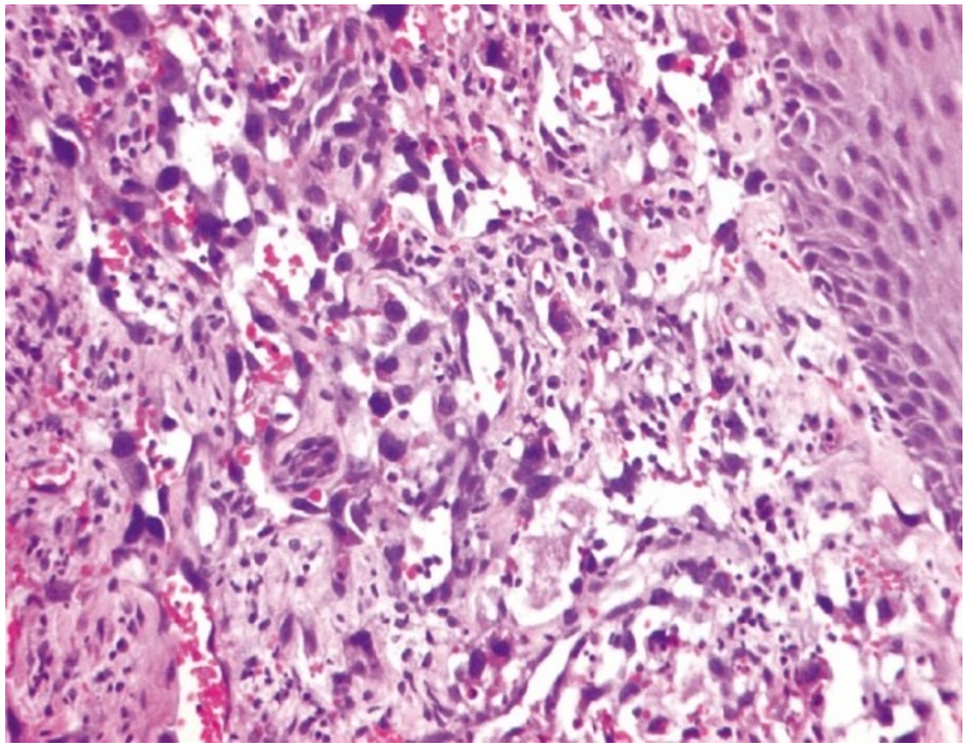


Cavernous hemangioma

Angiosarcoma

- Malignant endothelial neoplasm that primarily affects **older adults**
- Can occur in any site, but most often involves skin, soft tissue, breast, and liver



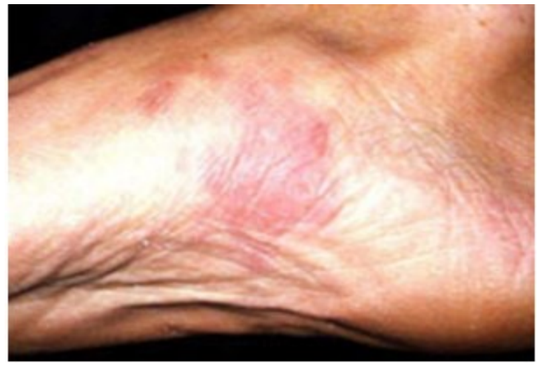


Angiosarcoma arising at scalp

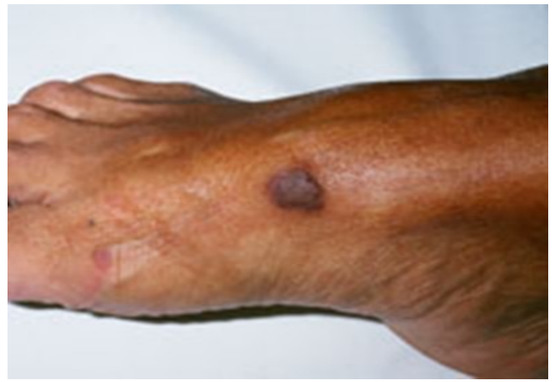
Kaposi sarcoma

- Intermediate-grade malignant vascular neoplasm

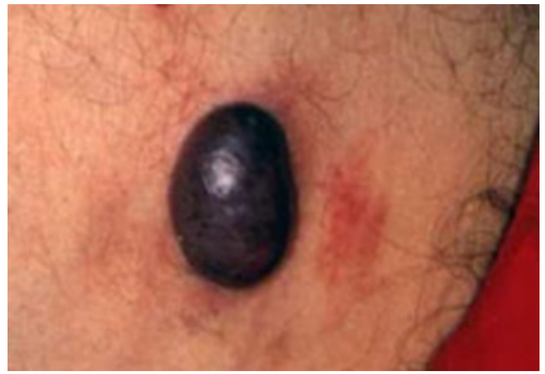
- **Clinical:** Four different settings
  1. Chronic Kaposi sarcoma (classic or European KS)
  2. Lymphadenopathic Kaposi sarcoma (African or endemic KS)
  3. Transplant-associated Kaposi sarcoma
  4. AIDS-associated (epidemic) Kaposi sarcoma *
     - Common in patients with AIDS
     - Cause: human herpesvirus-8 (HHV-8) or KS-associated herpes virus (KSHV)
     - Affected organs: skin, oral, GI, respiratory tract, lymph nodes, and others
     - Three stages of skin presentation: patch, plaque, nodule



Patch stage

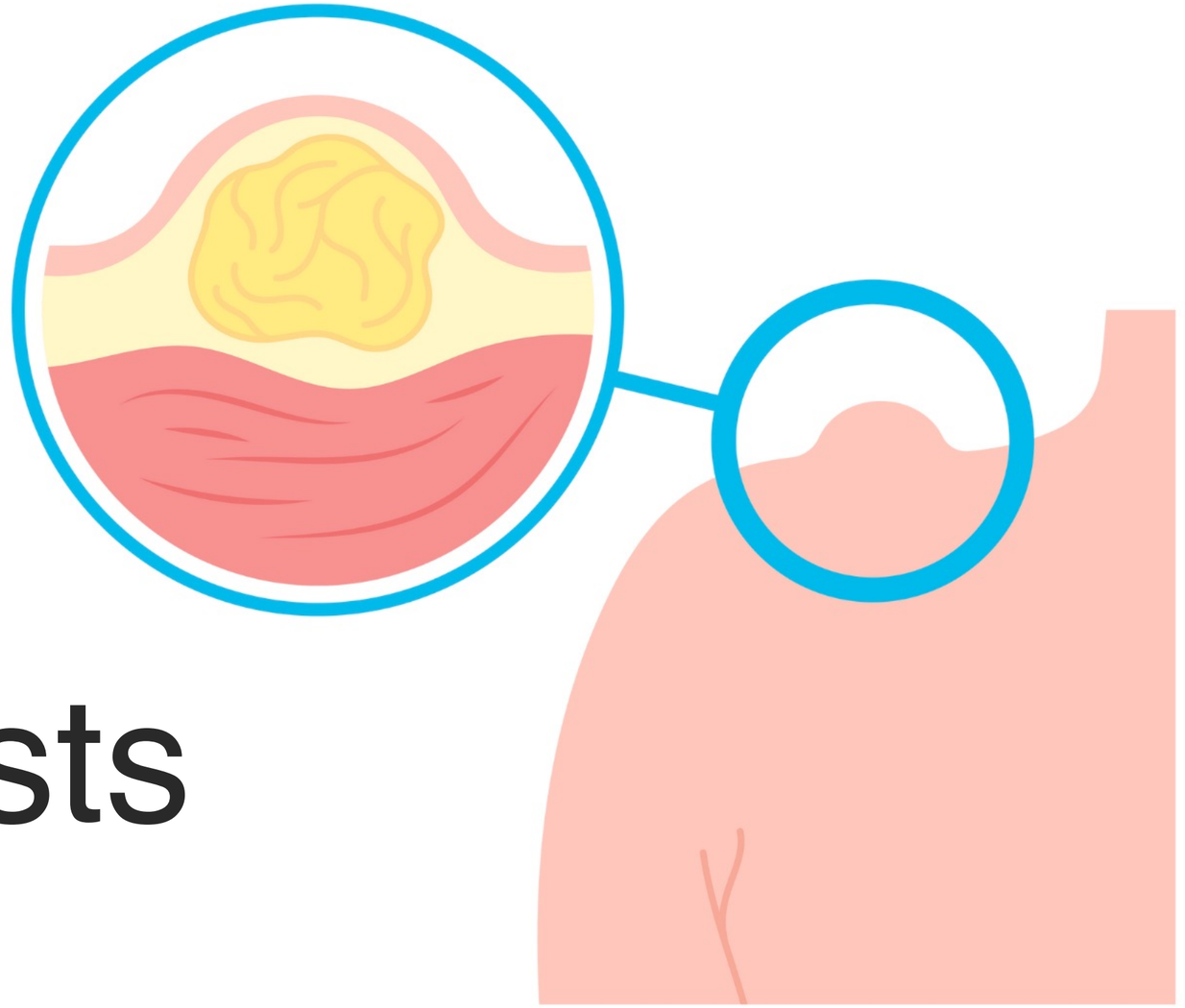


Plaque stage



Nodule stage

Cutaneous epithelial cysts



Cutaneous epithelial cyst

- Common lesions formed by downgrowth and cystic expansion of the epidermis or hair follicle (follicular) epithelium
- Cysts usually filled with keratin, proteinaceous fluid, or lipid debris

- **Clinical:**
  - Usually young and middle-aged patients
  - Well-circumscribed, firm, cystic, movable nodule at dermis or subcutaneous fat
  - If large, may be dome-shaped
  - Often painful when traumatic rupture due to secondary inflammation

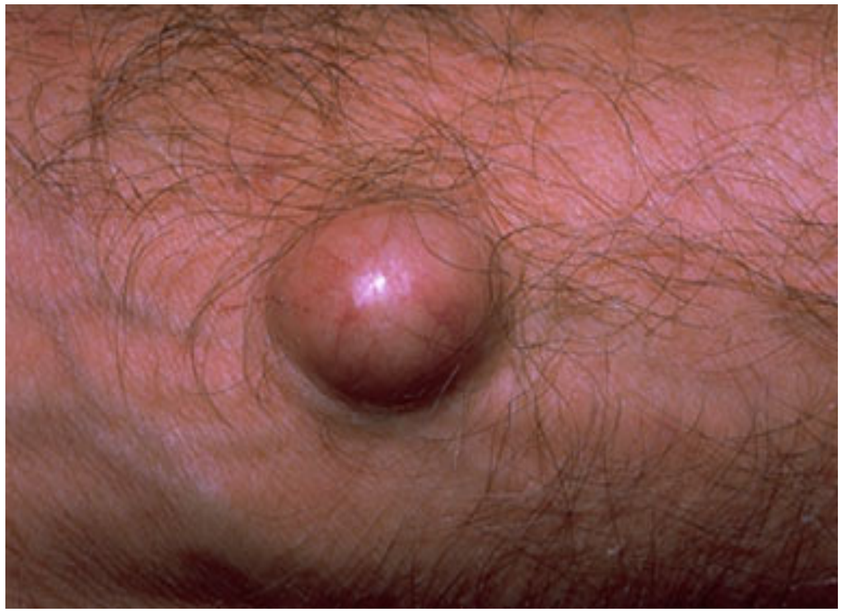
- **Classification** (based on structural/histological components of walls)**:**
  1. Epidermal (epidermoid) cyst
  2. Trichilemmal cyst (pilar cyst)
  3. Dermoid cyst

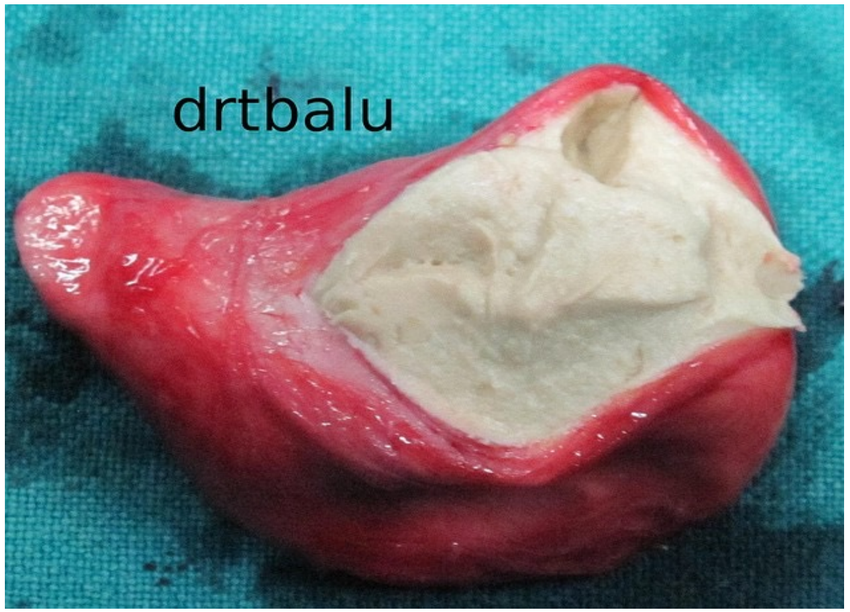
Epidermal cyst

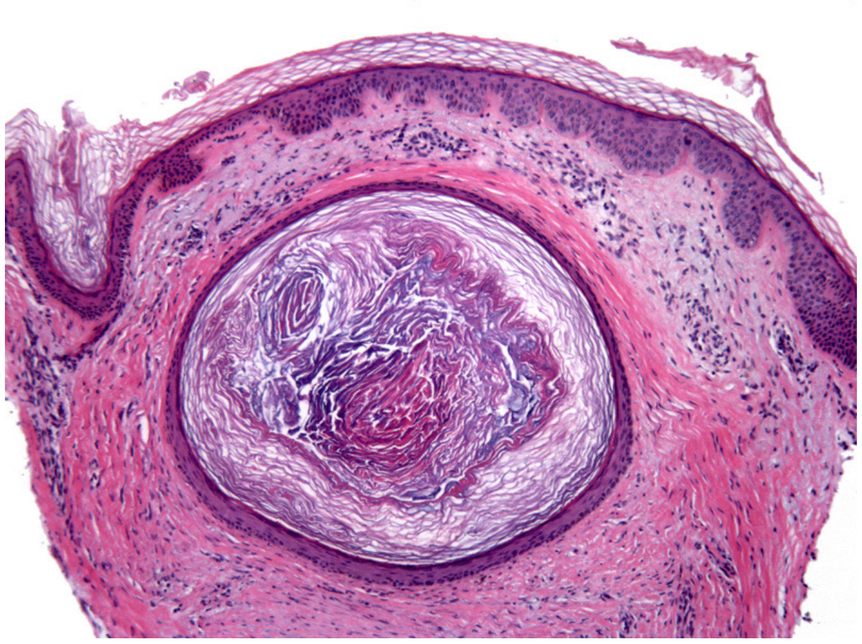
- Also called **epidermoid cyst, epidermal inclusion cyst, infundibular cyst,** or **sebaceous cyst** (misnomer)
- Most common skin cyst
- Can occur anywhere on the skin (most commonly on face, neck, upper trunk, scrotum)

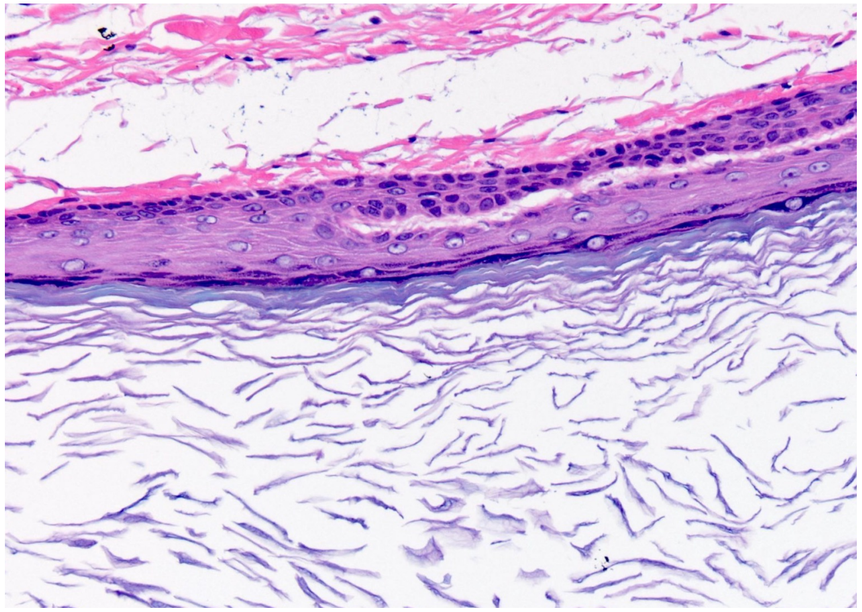
- **Gross:** well-circumscribed cyst containing cheesy materials

- **Histopathology:**
  - Subepidermal well-defined cyst lined with epithelium identical to the epidermis (stratified squamous epithelium with **presence** of granular layers)
  - Containing flaky keratinous materials







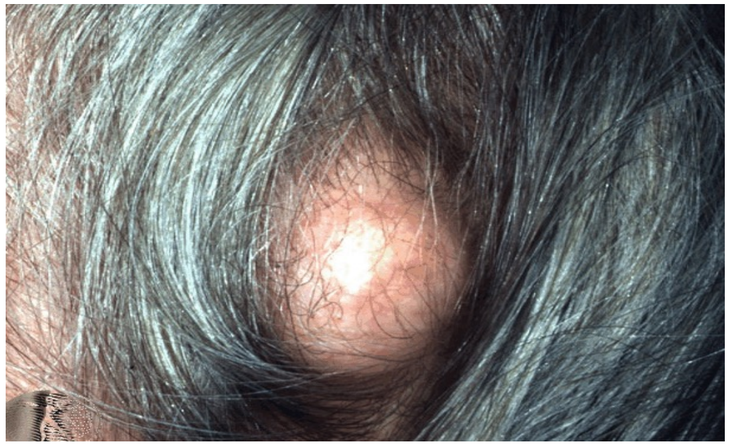


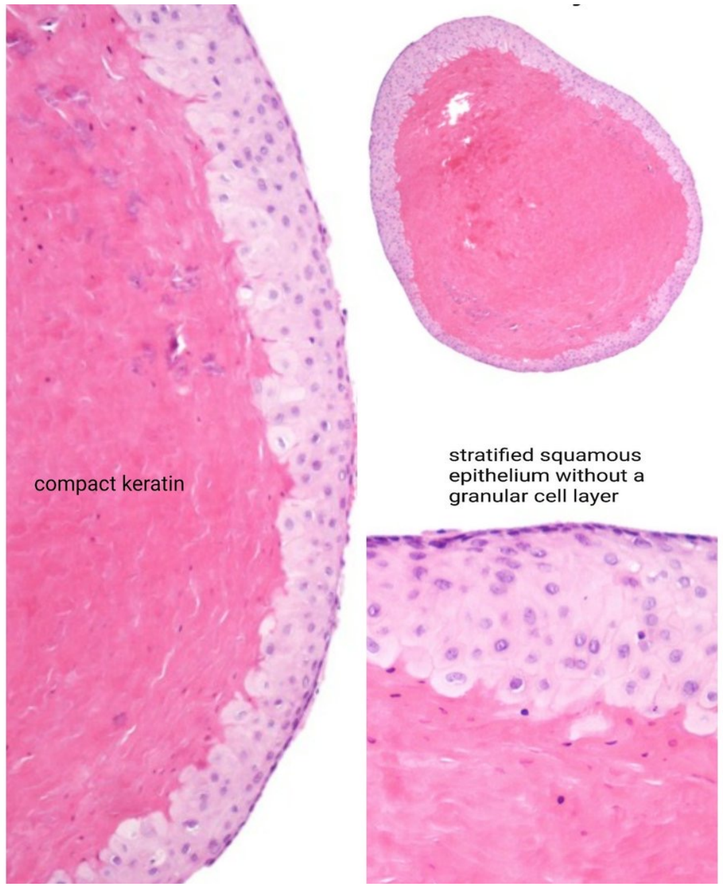
Epidermal (epidermoid) cyst

Trichilemmal cyst

- Also called **pilar cyst**
- Mostly occur on the **scalp** (90%)

- **Histopathology:**
  - Subepidermal well-defined cyst lined with epithelium identical hair follicular epithelium (stratified squamous epithelium **without** granular layers)
  - Containing dense compact laminated eosinophilic keratinous materials (may become calcified)

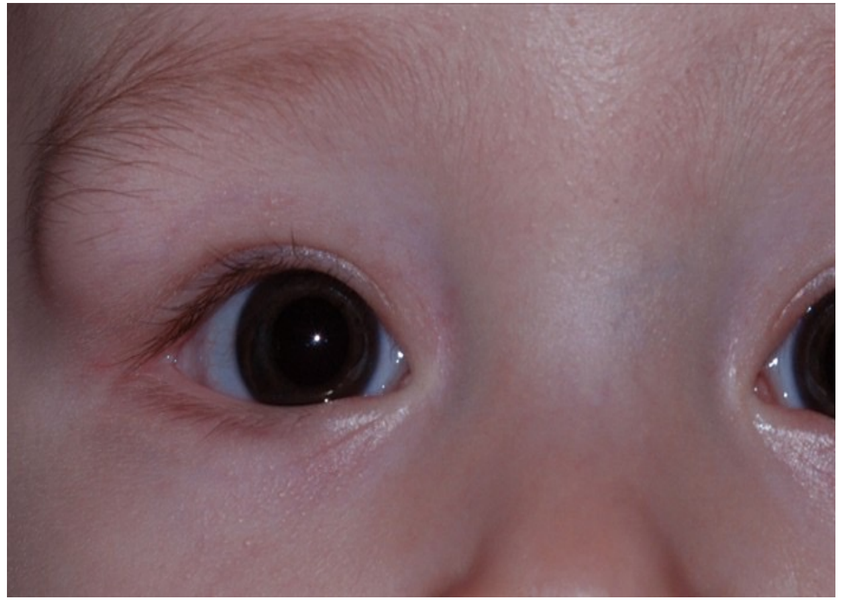


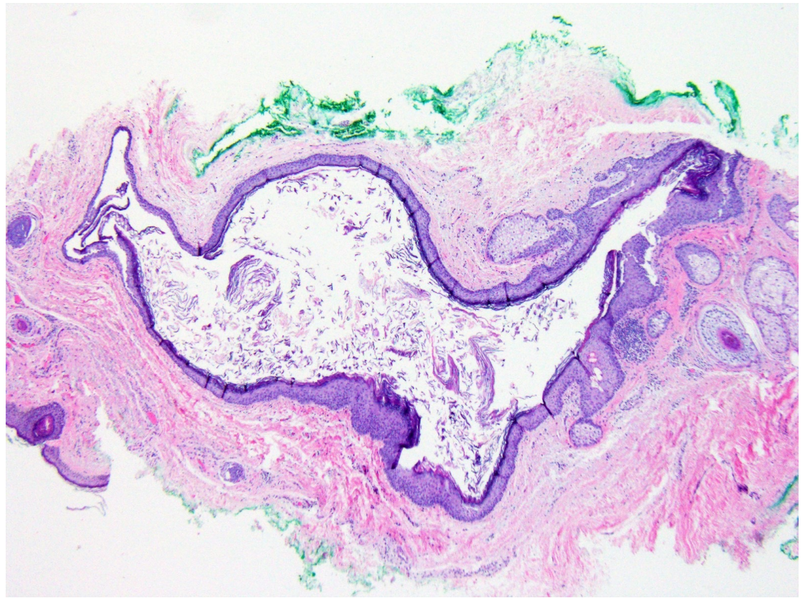


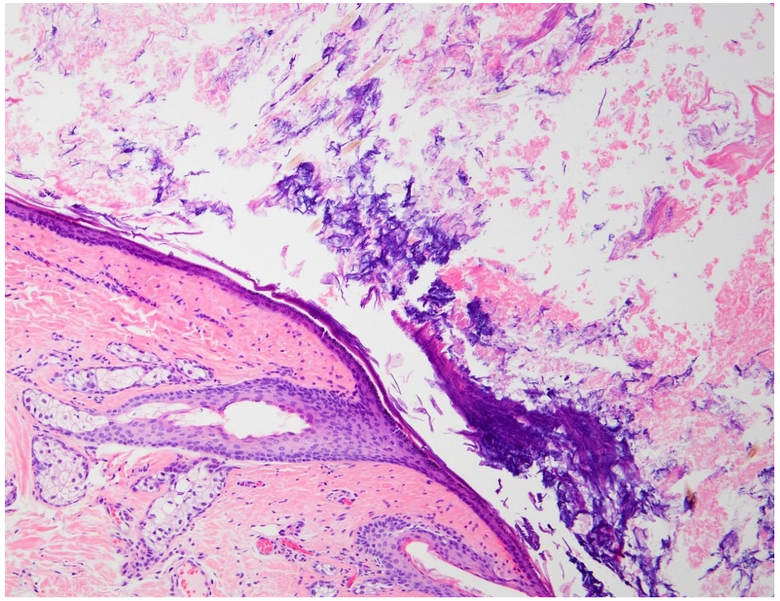
Dermoid cyst

- Frequently found on lateral eye, forehead, and neck

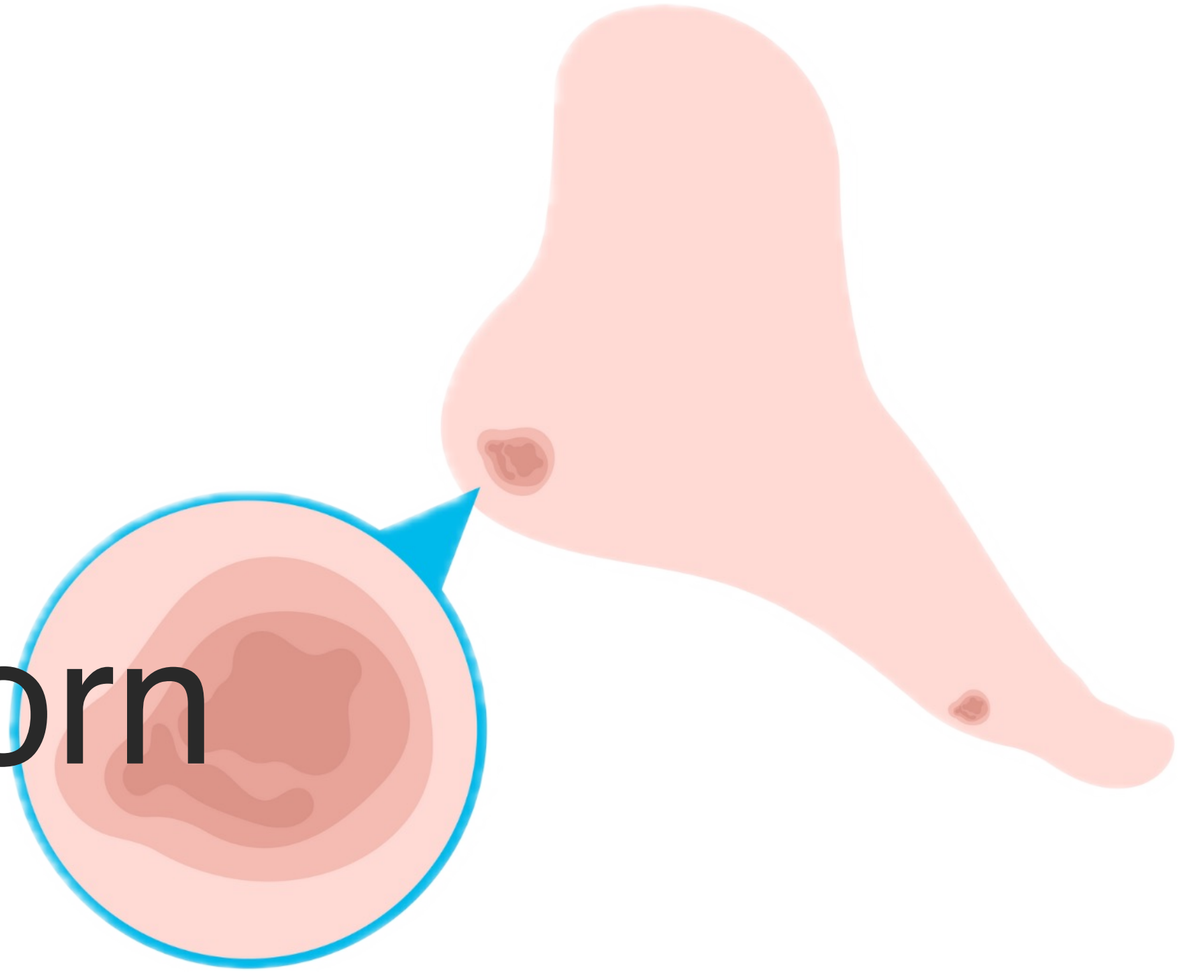
- **Histopathology:**
  - Histologically resembling epidermal cyst, but also have multiple skin appendages (hair follicles, sebaceous glands, or sweat glands)







Callus and corn

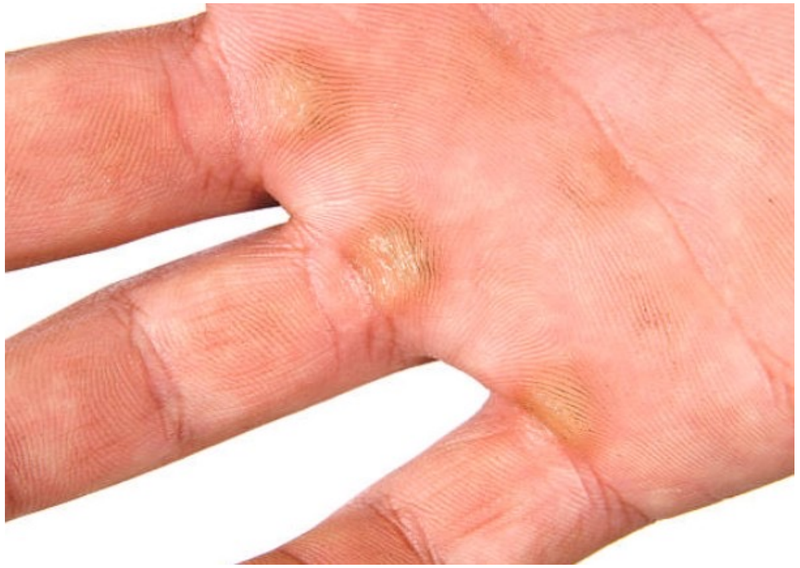


Skin callus and corn

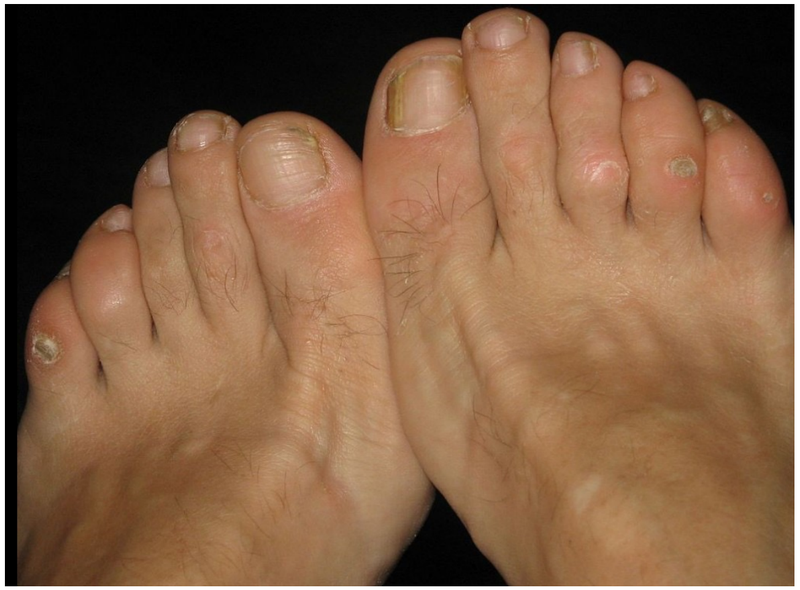
- **Callus (tyloma):** area of thickened and sometimes hardened skin, often painless

- **Corn (clavus / heloma):** cone-shaped callus that penetrates into the dermis, may result in pain and ulcer

- **Cause:**
  - Often develop on feet, toes, hands, or fingers, in response to repetitive friction, pressure, or other irritation (e.g. pressure from ill-fitting shoes, weightlifting, guitar playing, or weight bearing activity)
  - Resulting in **hyperkeratosis and acanthosis (hyperplasia)** of skin



Callus



Corn (with ulcer)

Q&A