Skin tumors

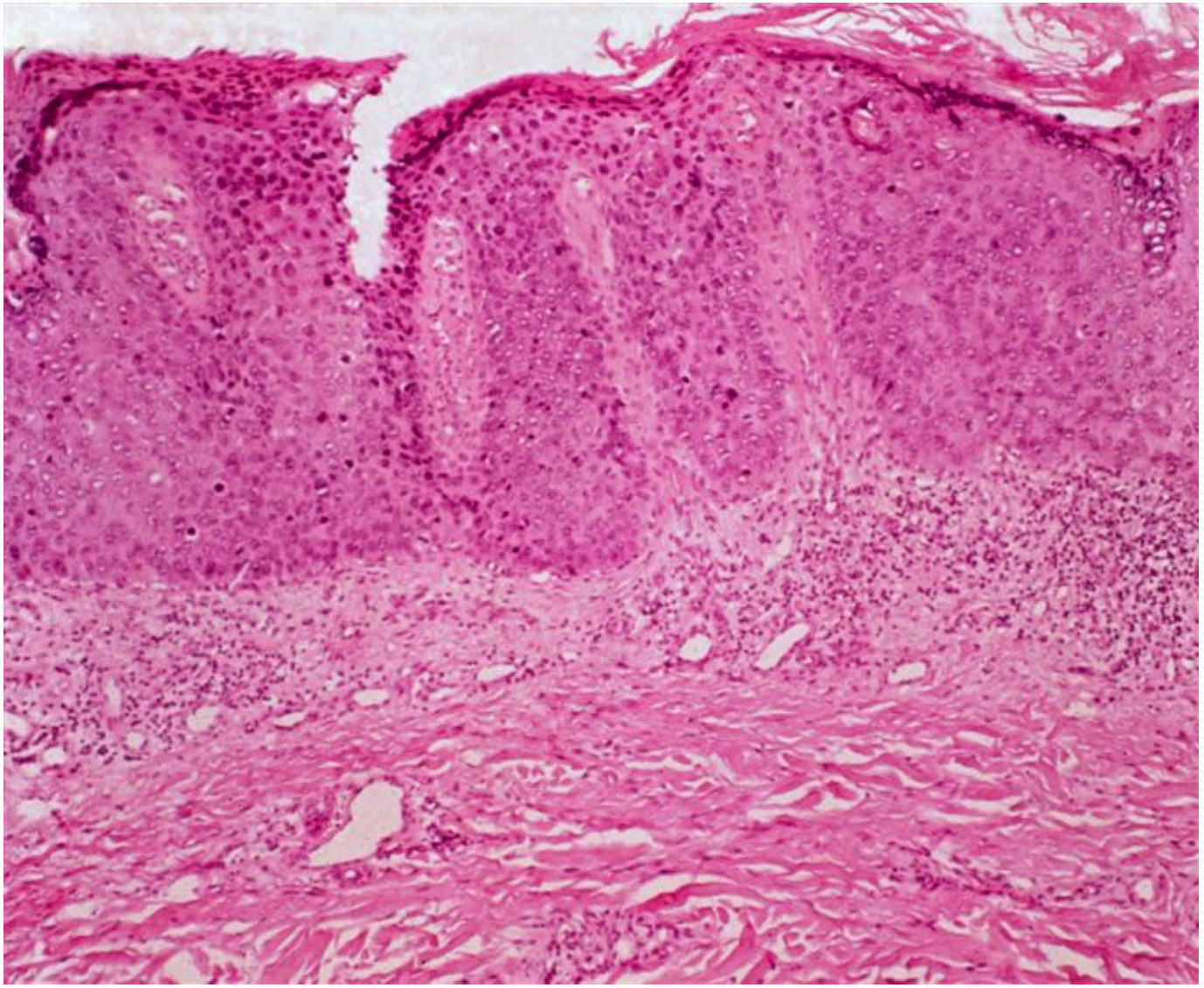
Non melanocytic and melanocytic tumors

Bowen disease

- Usually on skin NOT exposed to sunlight, such as trunk
- Called erythroplasia (of Queyrat) if at glans penis, vulva, oral cavity
- Often considered as carcinoma in situ or squamous intraepidermal neoplasia

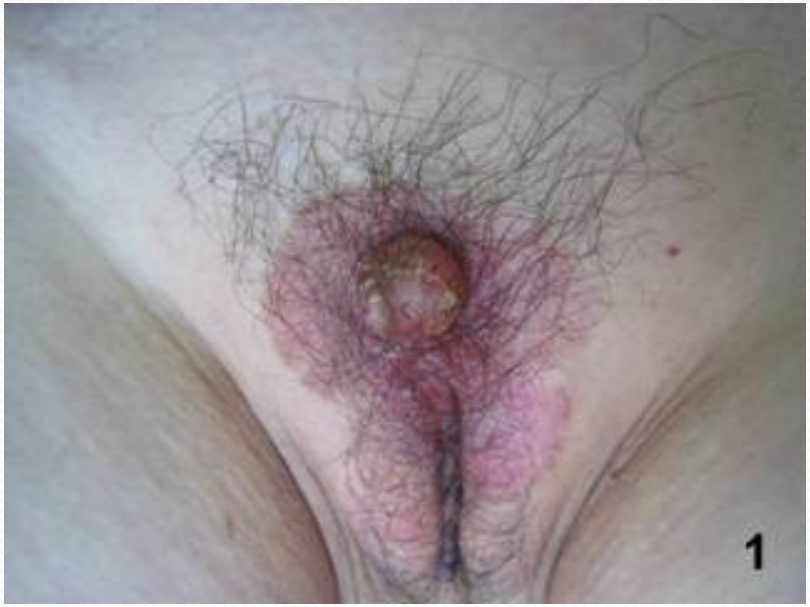
Gross description

- Slightly raised, large scaly erythematous plaque with irregular border
- Usually single patch or verrucous growth
- Atypia is prominent and throughout epidermis
- Includes nuclear hyperchromasia and multinucleation, individual cell dyskeratosis, increased mitotic figures, atypical mitotic figures
- Also cytoplasmic vacuoles, markedly altered maturation, but usually still some surface keratinization
- May extend into eccrine sweat glands (not considered invasive disease)
- Intercellular bridges present
- Rarely pagetoid cells or ground glass cytoplasm



Pagets' disease

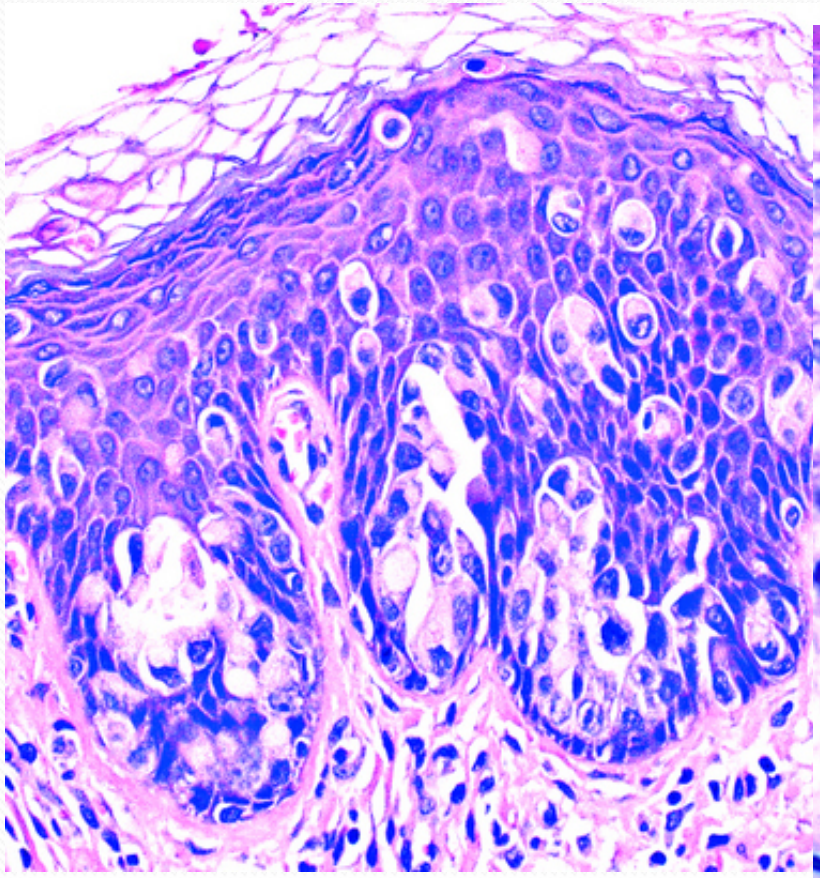
- May originate from intraepidermal portion of sweat glands or primitive basal cells with ability to differentiation towards glandular elements
- Labia majora, scrotum and perineum are most common sites
- Due to underlying carcinoma in 10 - 20% of cases of vulvar disease

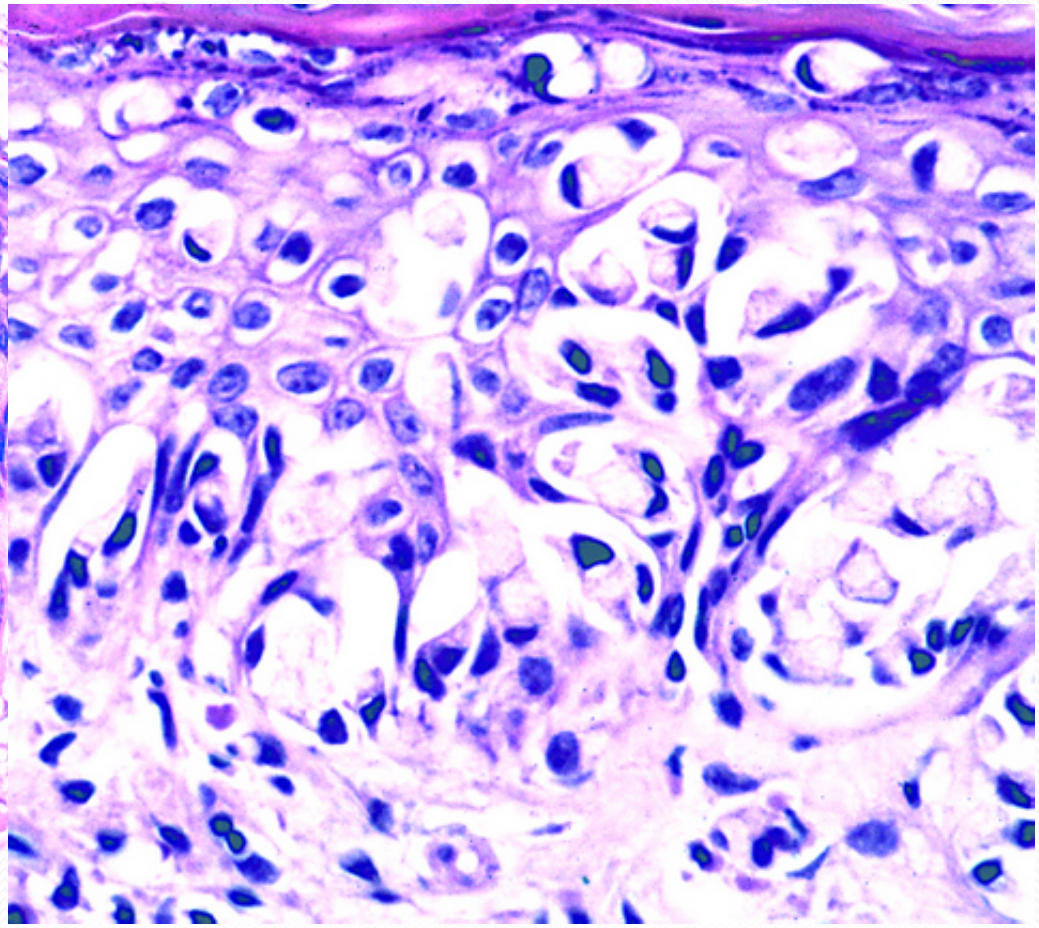


Erythematous, eczematous or ring-shaped
Often multicentric, extensive, pigmented

Histology

- Malignant cells in epidermis with differentiation towards local glandular structures
- Almost always simultaneous involvement of eccrine glands or hair follicles
- Dermal invasion is rare in vulva, more common in perianal region
- Single, clusters or glandular formations of large cells with pale, vacuolated cytoplasm, usually just above basal layer of epidermis
- May have cleft-like spaces between Paget cells and neighboring keratinocytes
- No intercellular bridges, no dyskeratosis





Basal cell carcinoma

- BCC is most common malignancy of skin, constitutes ~80% of all skin cancers
- Patients with xeroderma pigmentosum, who have a diminished capability for repairing sun induced mutations, develop a large number of basal cell and squamous cell carcinomas (SCCs) early in life
- Multiple BCCs develop early in life in patients with basal cell nevus syndrome

Epidemiology

- Occurs in all races, but much more often in fair skinned people
- Usually in patients >40 years of age
- More often in men than in women (male : female = 1.6:1)
- Mainly sun exposed skin, in any hair bearing area (e.g. head and neck)
- Also at sites with limited or no sun exposure

Clinical appearance

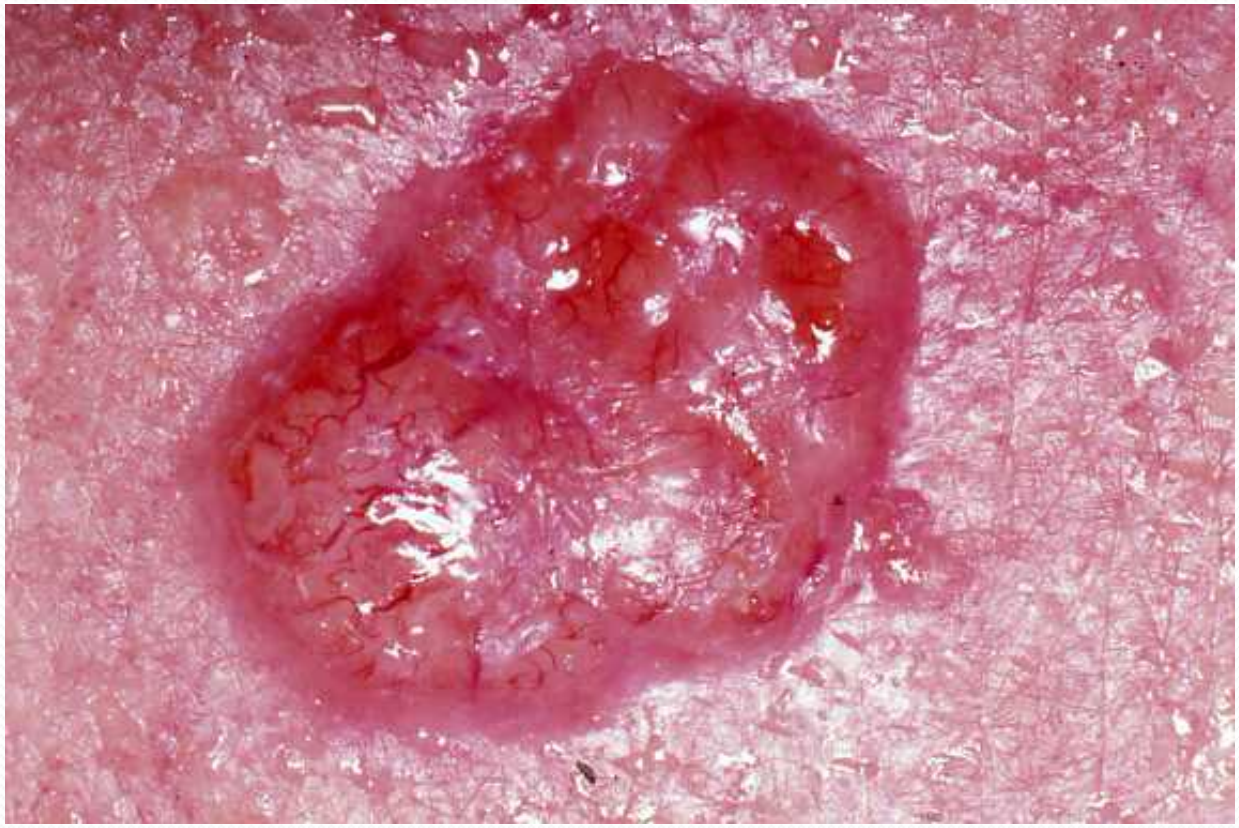
- Clinical appearance often parallels the histologic subtype
- Most common appearance is a papule or nodule with telangiectasias, which may be eroded or ulcerated (ulcus rodens / rodent ulcer)
- Papules of BCC may clinically resemble a nevus, fibroma or folliculitis
- Usually only local growth; may be locally destructive with significant morbidity depending on location and size
- Pigmented BCC may mimic a melanocytic neoplasm
- Metastases are exceedingly rare (preferred sites: lymph nodes, lung, bones)

Variants

- Nodular
- Superficial
  - Tumor nests growing multifocally from the epidermis
- Infiltrative / Morpheaform
- Basosquamous (metatypical) carcinoma

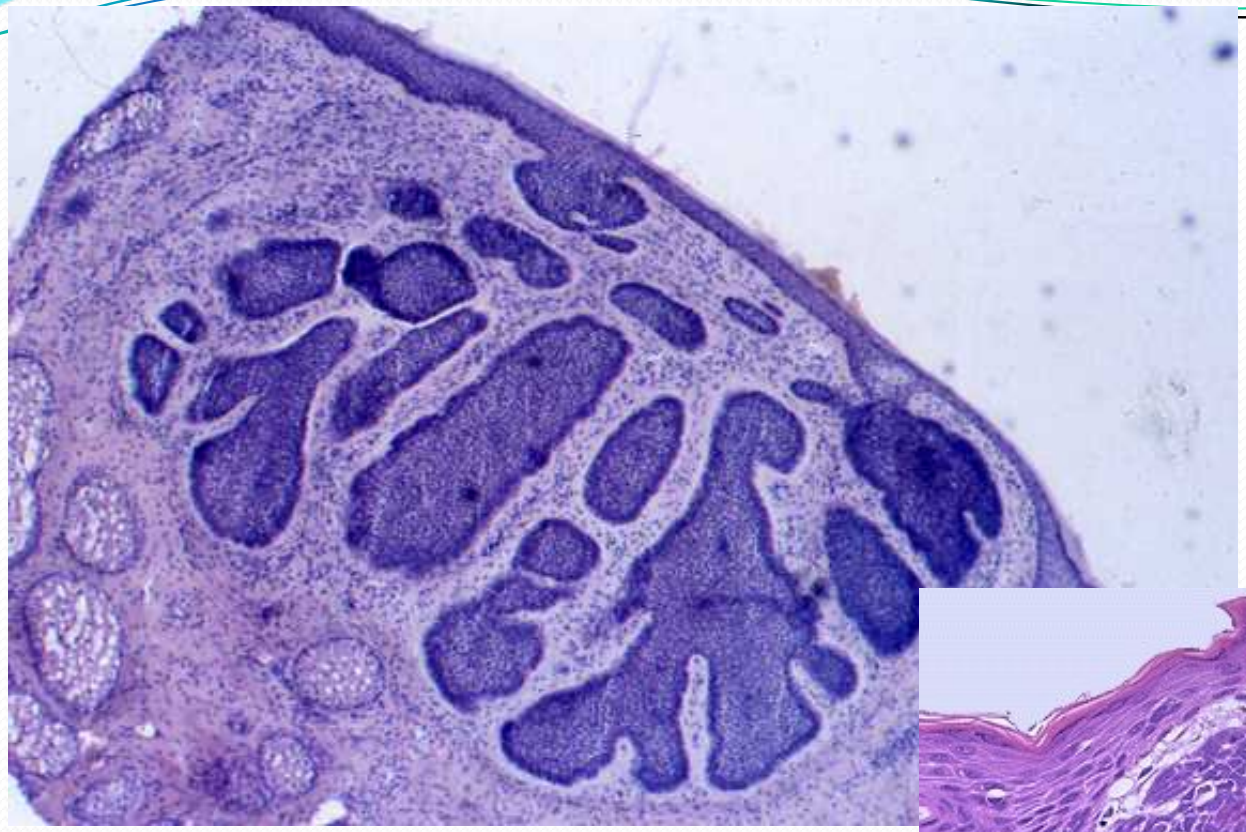
Basal cell nevus syndrome:

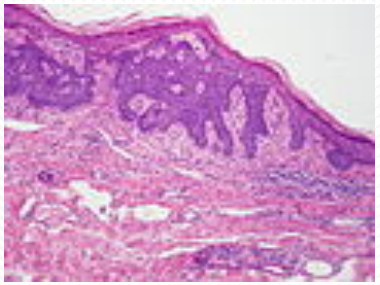
- Also called Gorlin's syndrome
- Due to mutations in PTCH (patched) gene on 9q22.3
- Autosomal dominant, young patients with multiple basal cell carcinomas (with more varied histologic types than normal, often superficial and multicentric), palmar pits (in situ basal cell carcinomas), dural calcification, keratinous cysts of jaws, skeletal abnormalities, occasional abnormalities of CNS, mesentery and endocrine organs (medulloblastoma, ovarian fibromas)

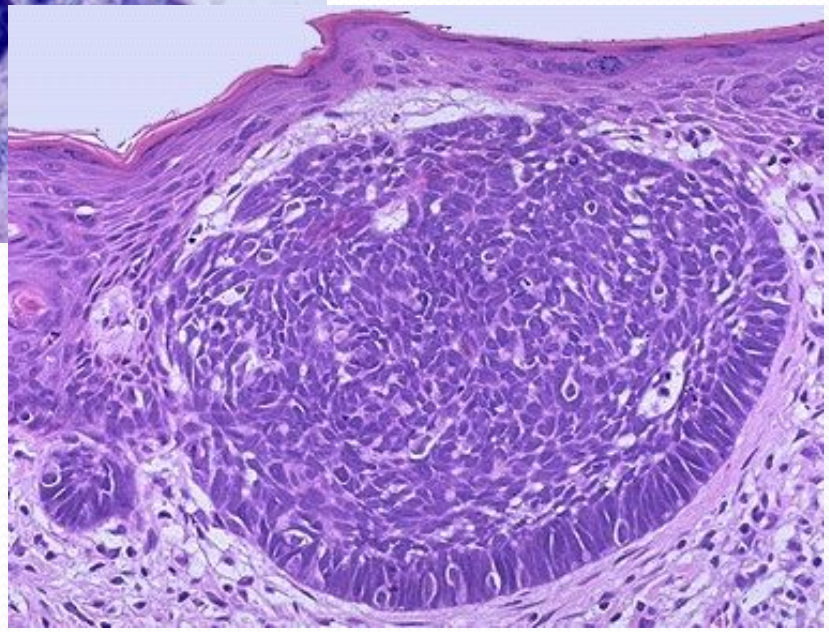


Histology

- Basaloid cells with scant cytoplasm and elongated hyperchromatic nuclei, peripheral palisading, peritumoral clefting and mucinous alteration of surrounding stroma
- Also mitotic figures, apoptotic bodies
- The presence of myxoid stroma and peripheral clefting has been suggested to be most helpful to distinguish BCC from other basaloid tumors
- Many secondary features may occur, such as dystrophic calcification, amyloid deposition or inflammatory reactions with or without partial regression







Squamous cell carcinoma

- Second most common invasive skin cancer, after basal cell carcinoma
- Derived from keratinocytes in epidermal layer

Risk factors

- Usually UV light / ionizing radiation
- **Actinic keratosis** (precursor lesion), albinism (lack of pigmentation in skin), **arsenic**
- Burn scars
- Chronic ulcers
- **Epidermodysplasia verruciformis**
- **Hidradenitis suppurativa**
- Immunosuppression (post-transplant or HIV)
- **Necrobiosis lipoidica**
- Osteomyelitis - draining sinuses
- Xeroderma pigmentosa: disorder with diminished capacity for DNA repair after UV light exposure, due to gene at 9q22.3; associated with squamous cell, basal cell carcinoma and melanoma

Grading

- Often graded somewhat subjectively based on degree of differentiation and keratinization: well, moderate, poorly differentiated
- **Well differentiated:** abundant pink cytoplasm, mild to moderate atypia, well developed keratinization
- **Moderately differentiated:** focal keratinization; features between well and poorly differentiated
- **Poorly differentiated:** no / minimal keratinization, high nuclear to cytoplasmic ratio, nuclei are markedly atypical or frankly anaplastic
- **Undifferentiated:** tumors presumed to be SCC based on prior biopsy at same site, but no keratinization identified by light microscopy; immunohistochemistry is usually necessary to exclude melanoma or sarcoma

Epidemiology

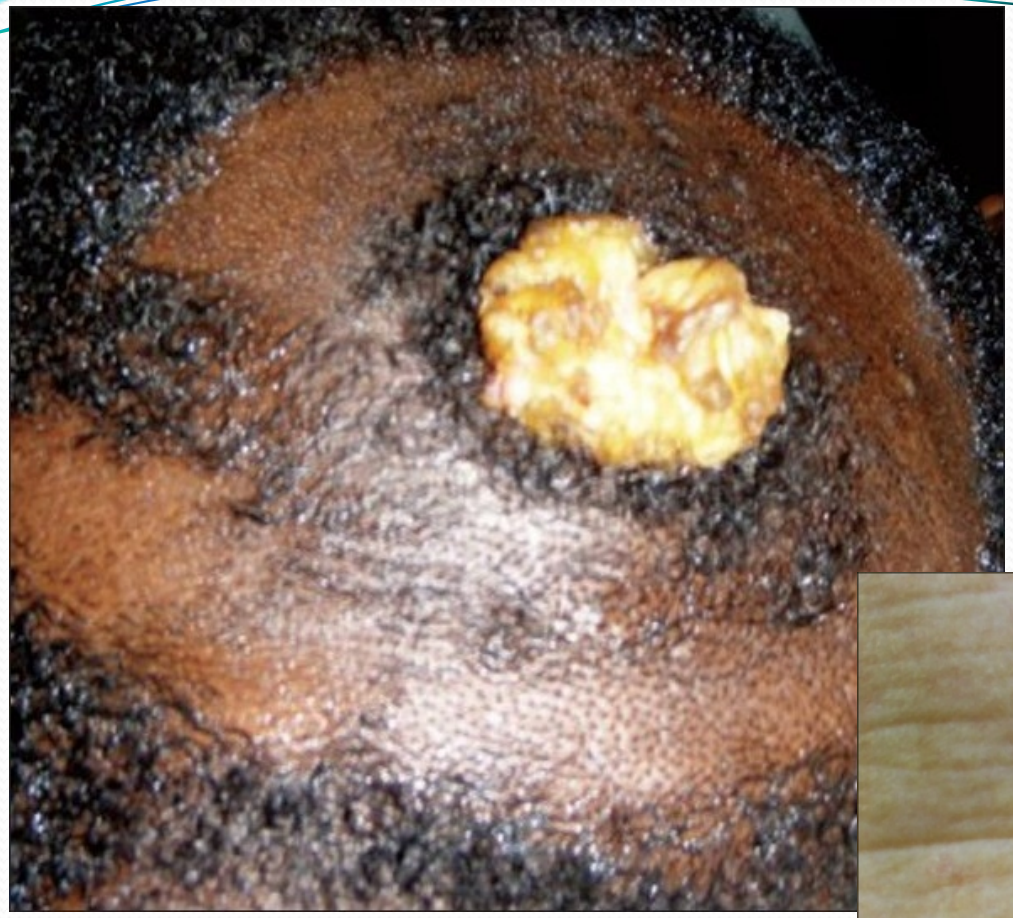
- Commonly affects men > 60 years
- Incidence: 1 per 1000 individuals

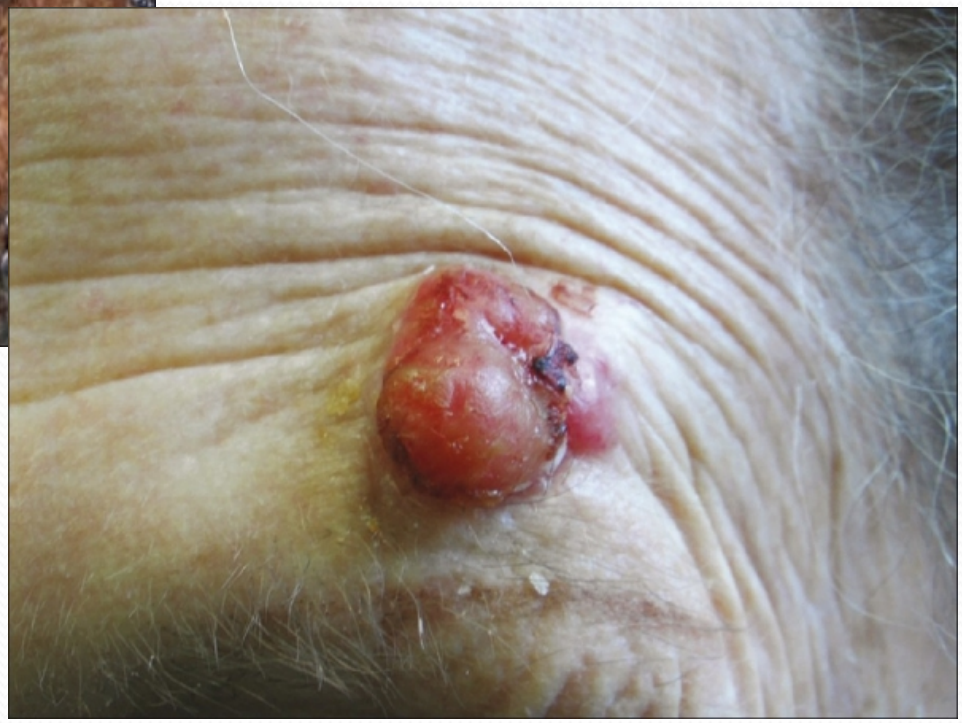
Sites

- Face, ears, scalp, dorsal hands

Prognosis

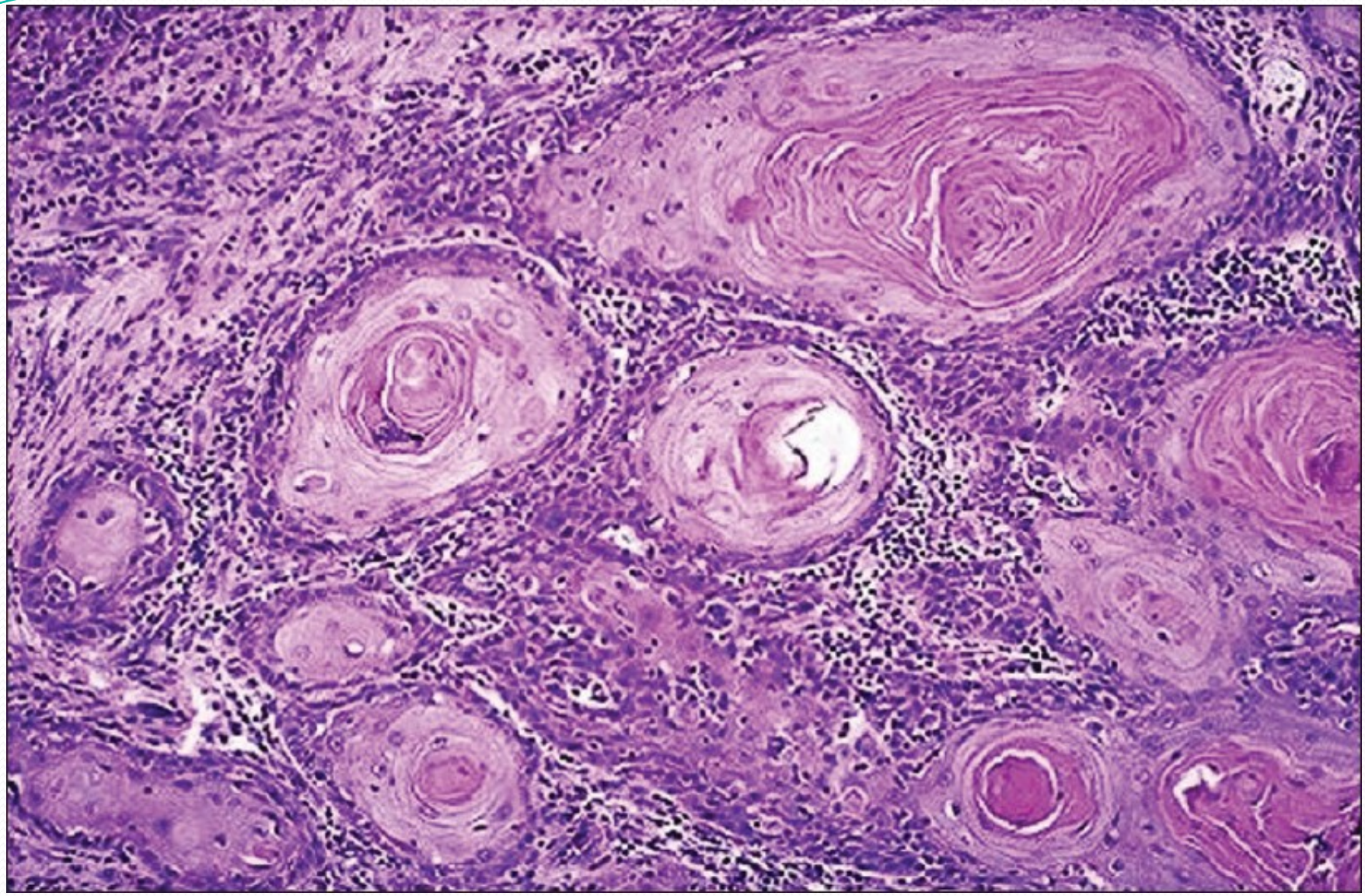
- Excellent prognosis
- < 1% die of disease
- Metastases uncommon if tumor < 1.5 cm deep
- 5% metastasize if 2 cm or more and definite dermal invasion; most common site is lung
- Metastatic rate is 5 - 10% in transplant patients, who do poorly with metastatic disease
- Metastases more likely in tumors that originate in scars or ulcers
- Most superficial tumors are indolent

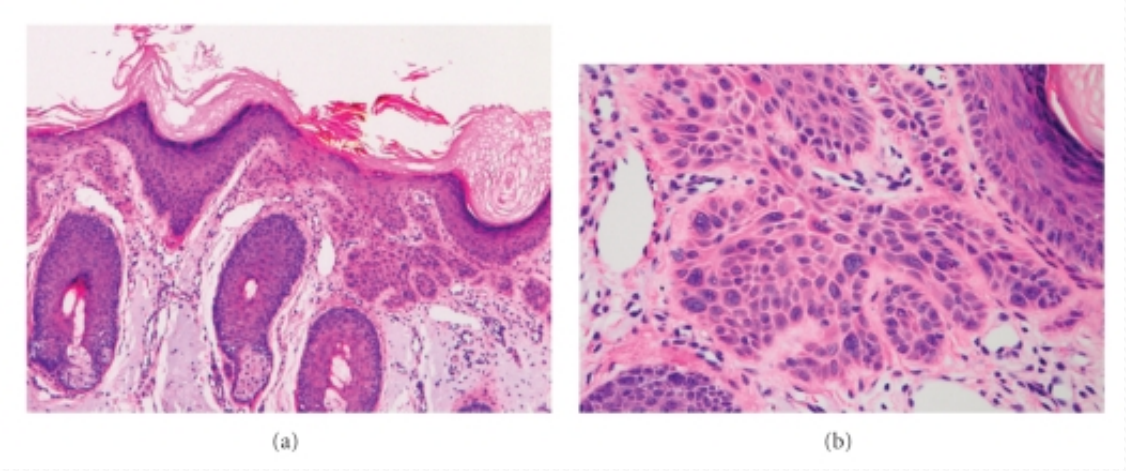


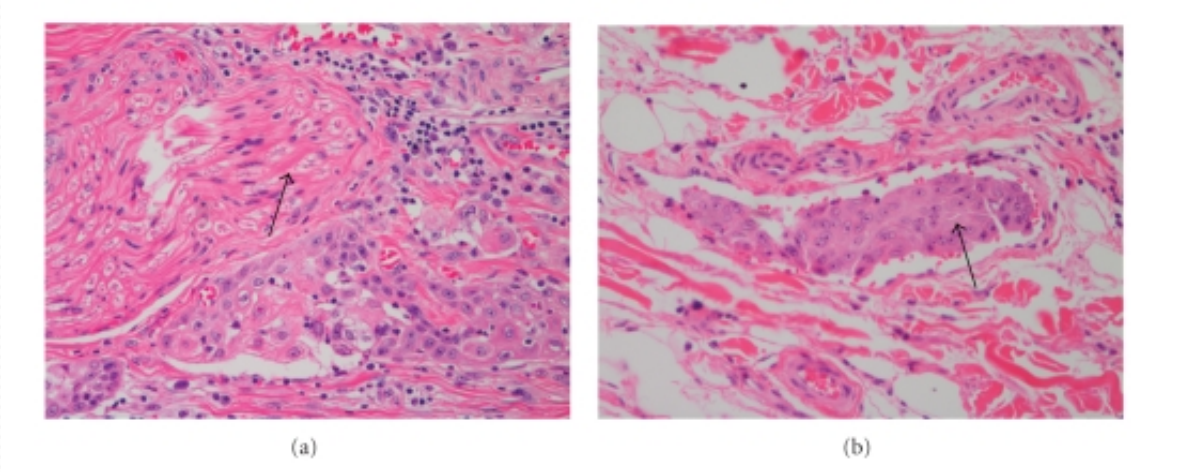


Histology

- Carcinoma that infiltrates dermis
- An associated precursor lesion (actinic keratosis / keratinocytic dysplasia / in situ squamous cell carcinoma) is often present, but may not be detectable due to ulceration
- Spectrum of histologic features, which has led to descriptions of various "types" of SCC; all share downward growth below level of adjacent or overlying epidermis







Perineural and vascular infiltration

Nevus

- Congenital or acquired benign melanocytic proliferation
- Also called melanocytic, nevocellular or pigmented lesion
- Most common melanocytic tumor
- Usually clinically evident between ages 2-6 years

Histological features

- Small size, circumscription and symmetry
- Nested proliferation with nests regularly distributed at tips of the rete ridges
- Melanocyte nuclei smaller than in adjacent keratinocytes
- Uniform cellular density throughout same level of lesion
- Melanocytes decrease in size towards base of lesion ("maturation")
- Coalescent eosinophilic globules (Kamino bodies) are associated with Spitz nevi
- Absence of mitotic activity (particularly at base of lesion), although rare mitoses may be seen in benign nevi
- Lack of necrosis and cytologic atypia

Gross description

- Papule or macule, tan-brown, uniformly pigmented and small (0.6 cm or less)

- Often erosion or ulceration if adjacent to a hair follicle, with a granulomatous response or scale crust

- **Intraepidermal component:**
  Junctional nests of melanocytes uniform in size, distributed at the tips of the rete ridges

  Dermal component:
  Type A morphology:

  - In superficial dermis
  - Pigmented epithelioid cells with well-defined cell boundaries
  - Abundant eosinophilic to amphophilic cytoplasm containing coarse melanin granules
  - Uniform round / oval nuclei slightly smaller than that of adjacent keratinocytes
  - Finely dispersed chromatin
  - Delicate nuclear membrane
  - No / small distinct eosinophilic nucleoli

- ***Type B morphology:***

  - In intermediate dermis
  - Cells more lymphoid than epithelioid
  - Decreased cytoplasm with no melanin
  - Smaller and slightly hyperchromatic nuclei with dispersed chromatin and no nucleoli

- ***Type C morphology:***

  - In deep dermis
  - Spindled, fibroblast-like or schwannian cells with oval nuclei and bland chromatin
  - Single cell infiltration of superficial reticular collagen

- ***Maturation:***

  - Deeper portion of lesion has smaller cells with less pigment and less atypia
  - Deep cells grow in smaller sized nests or single cells
  - May resemble neural tissue
  - Terminal differentiation recapitulates some aspects of Schwann cell development

Immunohistochemistry

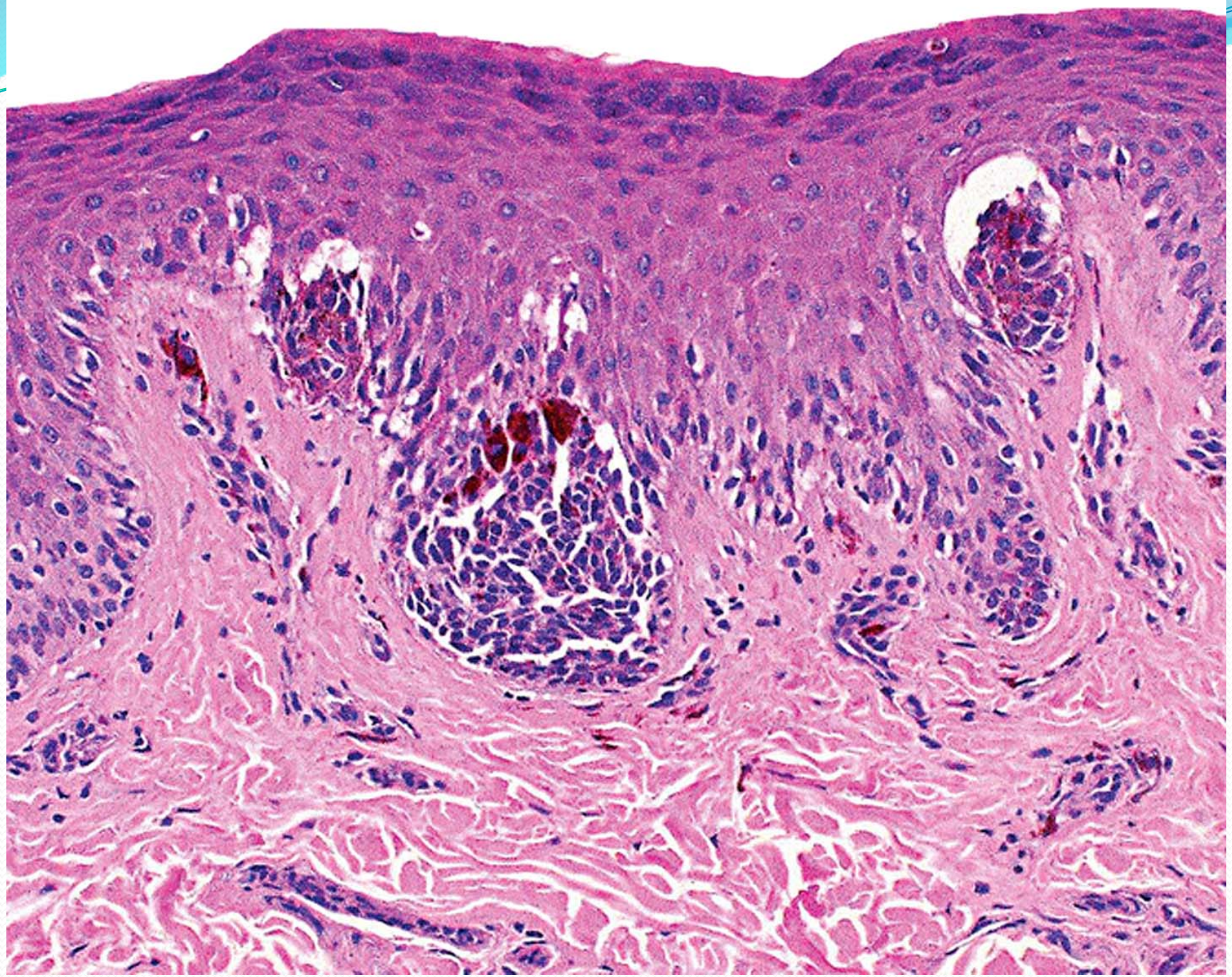
- Melan A in type A and B, but not type C cells
- S100, HMB45 in the intraepidermal and superficial dermal component

Junctional nevus

- Melanocytic proliferation restricted to basal epidermis (junctional area)
- Earliest stage of intraepidermal melanocytic proliferation
- **Lentigo simplex:**
  - Also called lentigo, lentigines
  - Often in acral sites
  - Precursor lesion to nevi, with proliferation of melanocytes (but no nests) in epidermal basal layer along rete ridges
- **Multiple lentigines:**
  - Associated with Peutz-Jeghers syndrome, centrofacial lentiginosis,

Junctional nevus

- Traditionally considered more common in children, may actually occur in all ages
- Melanomas may arise from junctional nevi
- **Sites**
  Usually non-sun exposed areas, such as palms and soles
- Small, flat or slightly elevated; non-hairy, deeply pigmented



Dermal nevus

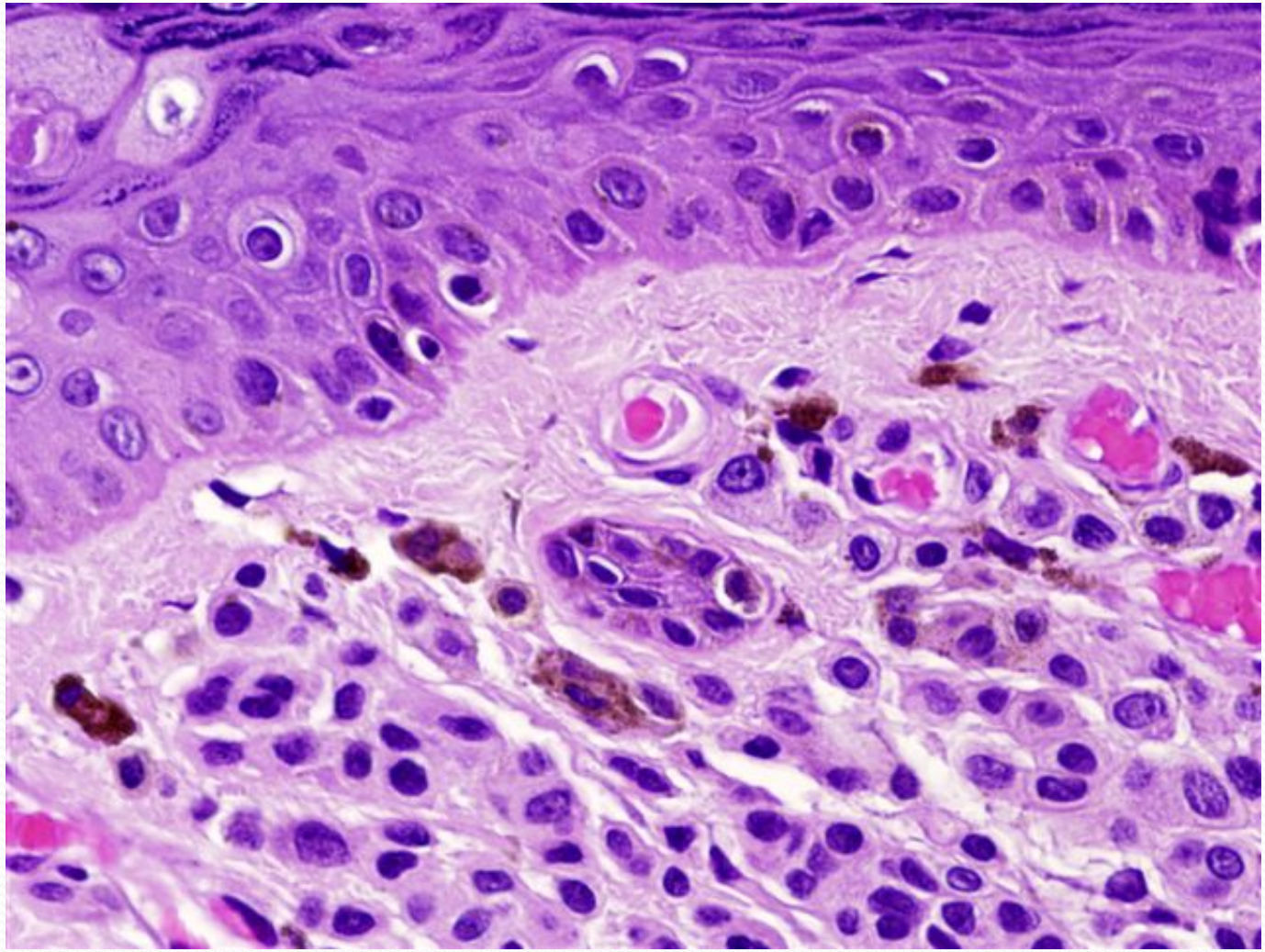
- Nevus with all melanocytes within the dermis
- Also called intradermal nevus
- Most common adult nevus
- Represents final stage in progression from junctional to compound to dermal nevus
- Seen mainly after adolescence

Clinical features

- Flat, pedunculated or papillary, often hairy
- Flesh colored or lightly pigmented (usually becomes lighter over time)
- Melanomas only rarely arise from intradermal nevi
- Rarely has cerebriform appearance - these nevi may be congenital

Histology

- Small nests of melanocytes in upper dermis, often around pilosebaceous units, with variable pigmentation and cellularity
- May have multinucleated melanocytes; deeper portion is usually less pigmented and less cellular and may have Wagner-Meissner corpuscles (representing neural portion of nevus)
- No junctional component



Compound nevus (not combined)

- Features of both junctional and intradermal nevi (i.e. epidermal and dermal components)
- Highest incidence in second decade, then decreases
- Elevated or dome shaped
- Less pigmented than junctional nevi
- Only rarely undergoes malignant transformation
- Nevogenesis may be due to ultraviolet light

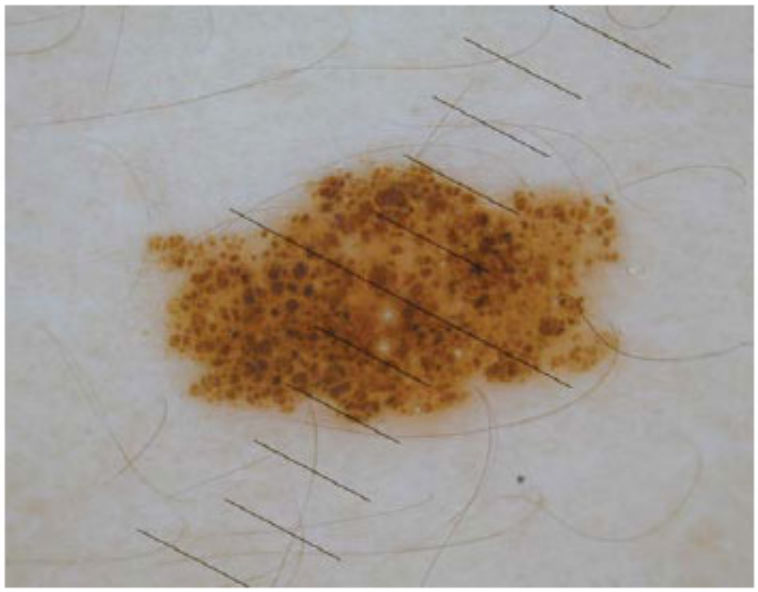


FIGURE 1: Dermaphoto (10X) of a compound melanocytic nevus with a cobblestone pattern. Observed the "fitted" distribution of globules

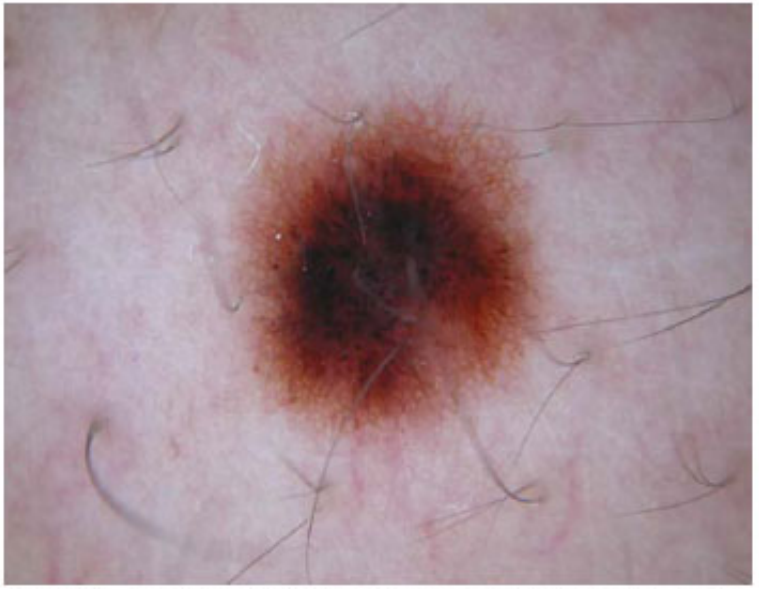
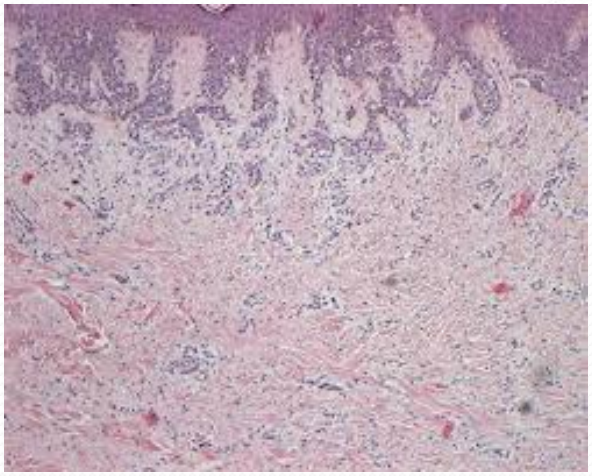


FIGURE 3: Dermaphoto (10X) of a compound melanocytic nevus. Note peripheral regular pigmented network, central homogeneous area and central black dots

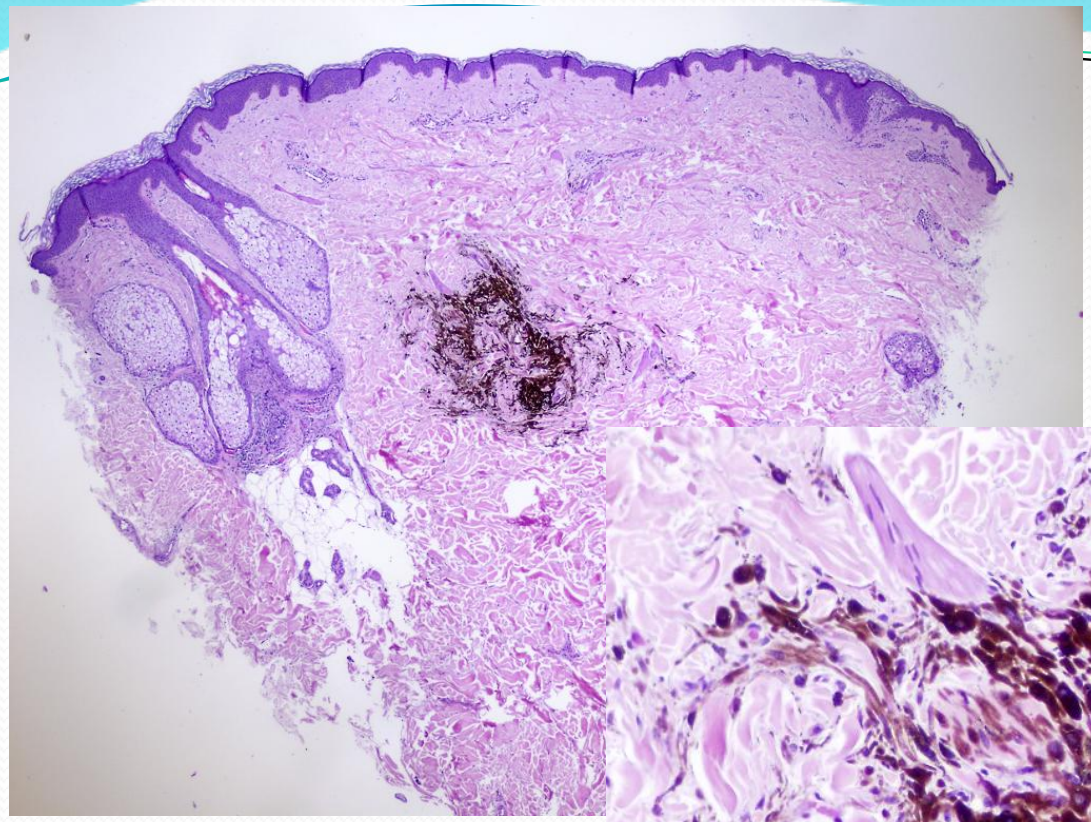


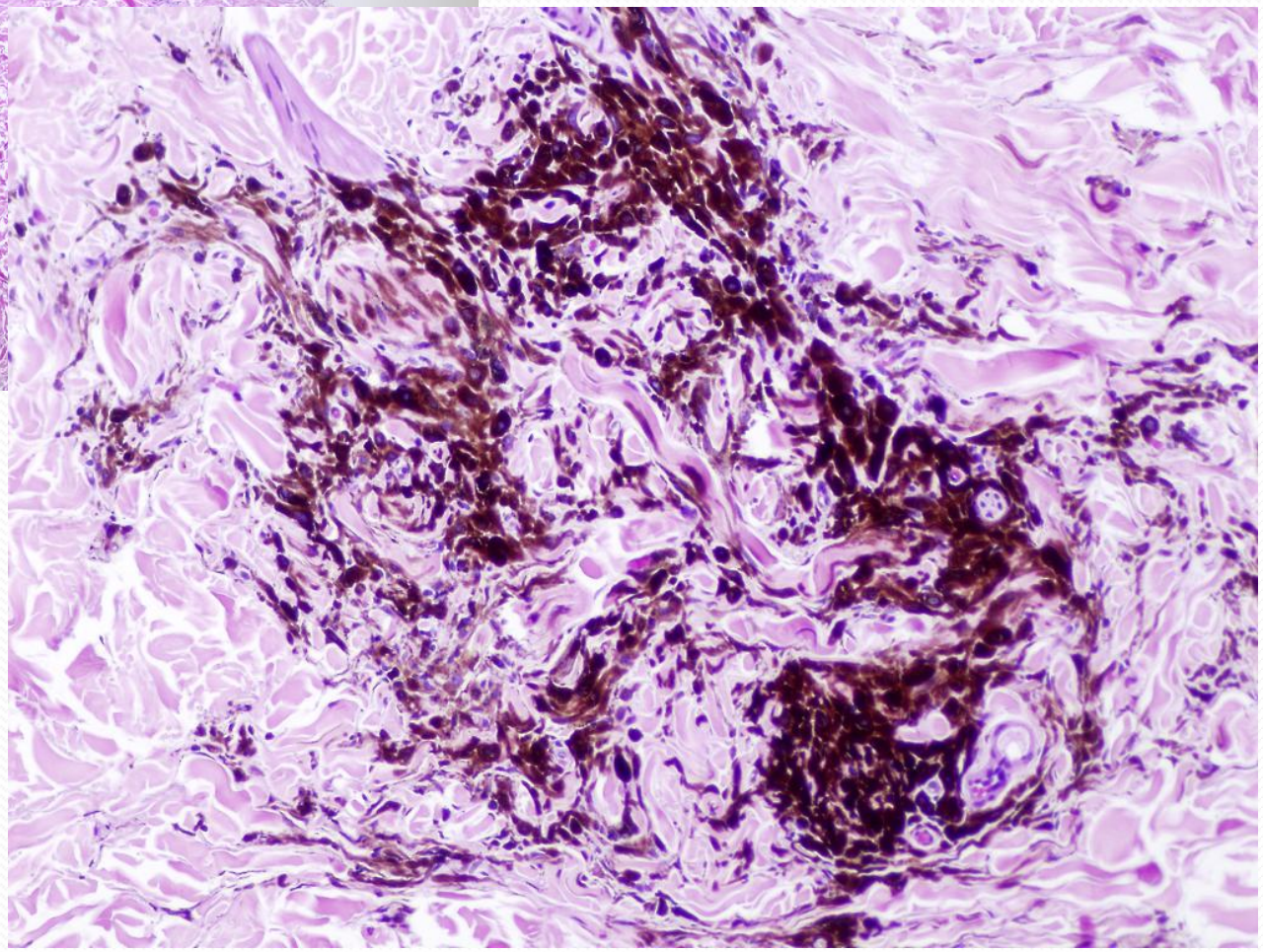
Blue nevus

- Collection of benign type C melanocytes (Schwann cell-like morphology) in dermis
- Blue color due to Tyndall effect of selective absorption of parts of the light spectrum by deeply located (dermal) melanin pigment, which is usually abundant
- May be due to arrested migration of immature melanocytes in dermis
- Numerous histologic variants and related entities (cellular, malignant)

Histology

- Ill defined deep dermal proliferation of spindled (Type C) melanocytes with abundant pigment and melanophages, dissecting dermal collagen and often extending into subcutis
- No junctional or superficial dermal involvement





Spitz nevus

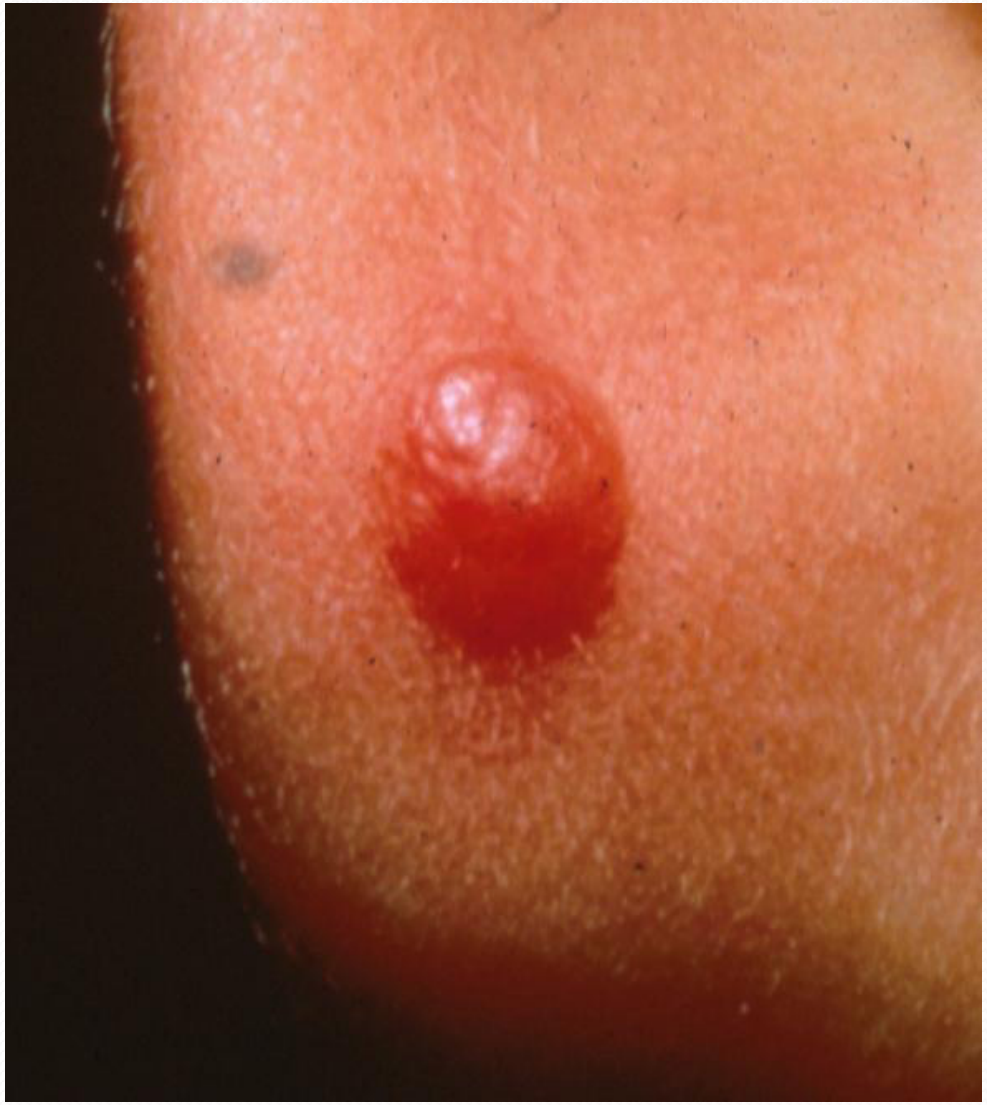
- Benign tumor of spindled and epithelioid melanocytes
- Also called spindle and epithelioid cell nevus, benign juvenile melanoma

- First described by Sophie Spitz in 1948

Usually occurs before puberty, but 2/3 were age 20+ years in one study

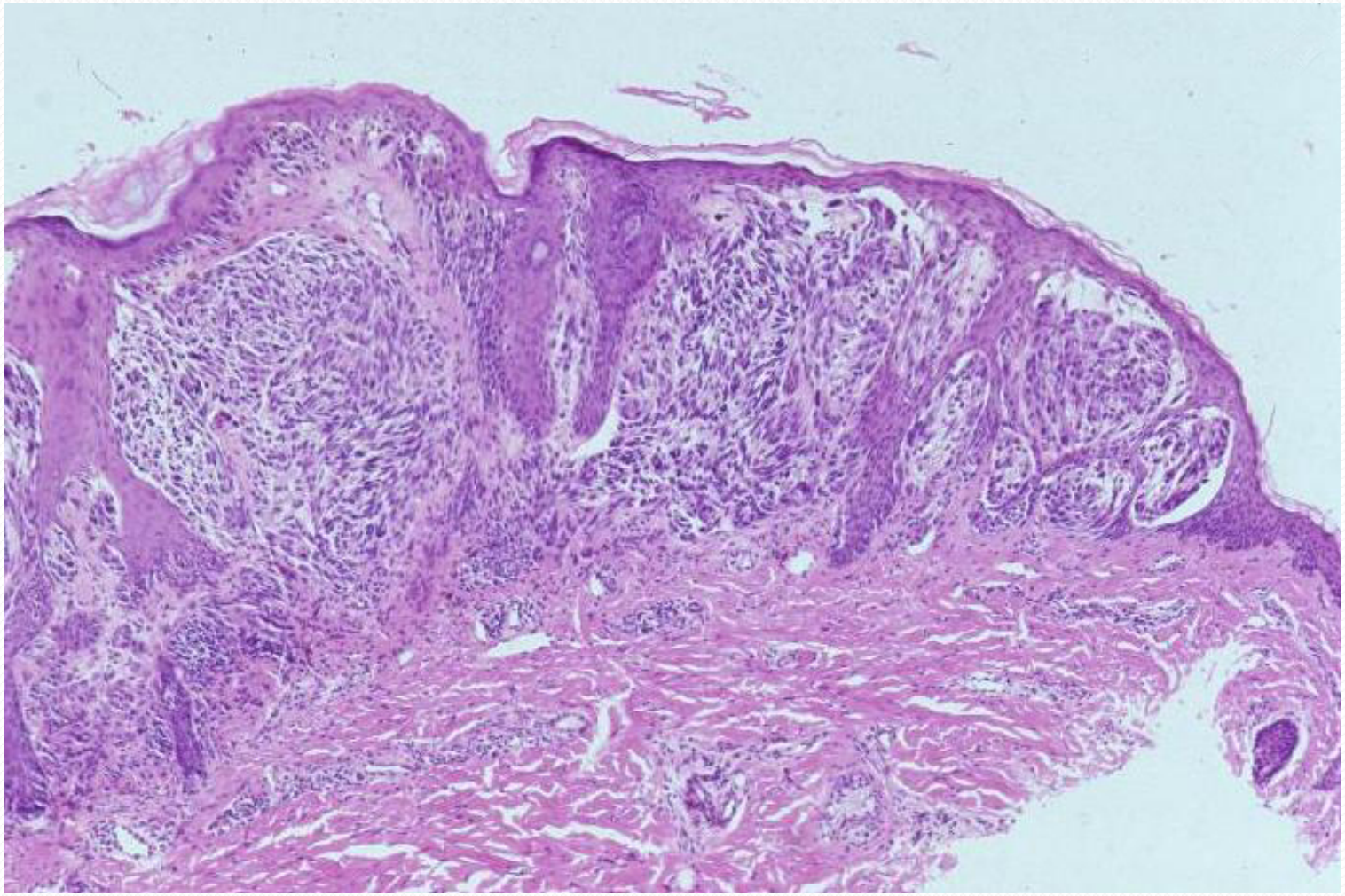
Spitz nevus

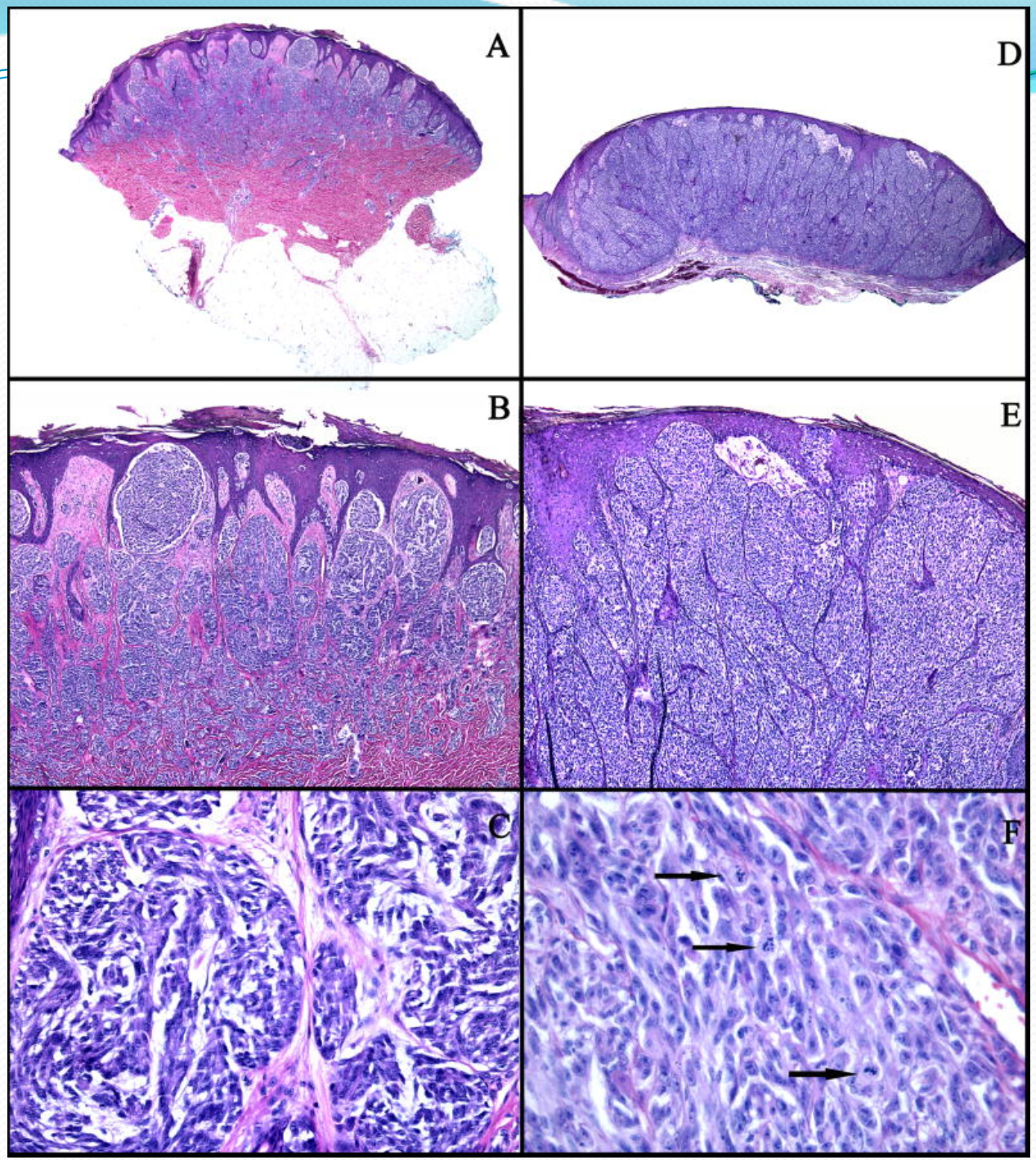
- Trunk most common; also lower extremities, head and neck
- Tongue lesions may have pseudoepitheliomatous hyperplasia and resemble malignancy
- Small, raised, pink / red or brown / black nodule
- May resemble hemangioma or pyogenic granuloma
- Usually 6 mm or smaller
- Usually single, but may be multiple and clustered or multiple and disseminated
- Benign, but may recur if incompletely excised
- May involve regional lymph nodes, particularly atypical lesions
- Common cause of malpractice claims is misdiagnosis as melanoma



Spits nevus

- Symmetric with sharp lateral borders, usually compound nevus with prominent intraepidermal component
- 5% are junctional, 20% are dermal
- Composed of spindled and epithelioid cells
- Spindle cells may be arranged in fascicles in dermal papillae, are perpendicular to epidermis, cigar-shaped with large nuclei, have prominent nucleoli
- Epithelioid cells are dispersed individually, polygonal with abundant eosinophilic cytoplasm, distinct cell borders, large nuclei and prominent nucleoli, have variable mitotic figures, occasional multinucleation and often marked atypia, although most cells appear benign
- Cell maturation occurs in deep portion of tumor
- Also large and well-formed Kamino bodies (eosinophilic hyaline bodies along dermoepidermal junction)
- Scanty pigmentation
- "Consumption of epidermis" (usually associated with melanoma) is seen in 10%, defined as thinning of epidermis with attenuation of basal and suprabasal layers and loss of rete ridges in areas of direct contact with neoplastic melanocytes




A
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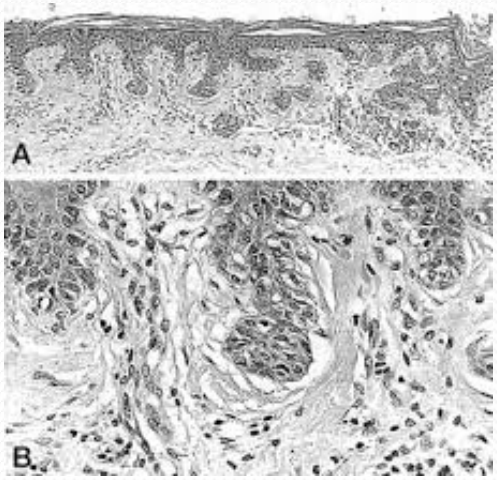
Dysplastic nevus

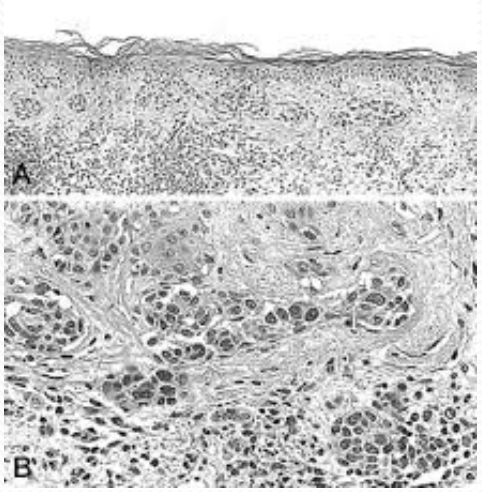
- Controversial topic, particularly for solitary lesions; better defined in dysplastic nevus syndrome (multiple dysplastic nevi and two family members with melanoma)
- Also called atypical nevus, nevus with architectural disorder, nevus with architectural disorder and cytologic atypia, Clark's nevus

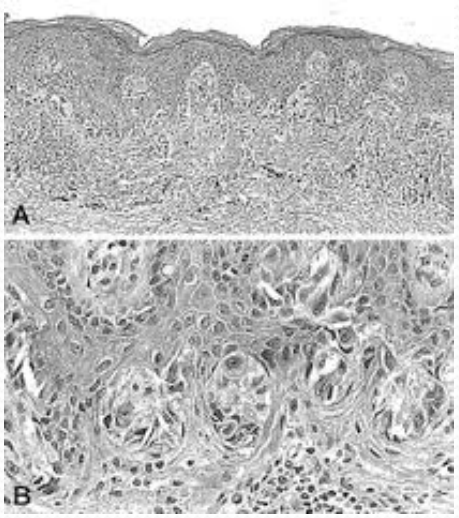
- Develop in teenager years and into adulthood
- Atypical nevi of scalp of adolescents resemble those in genitalia with apparent benign behavior
- May be intermediate step in pathway between benign nevus and melanoma
- Higher risk for melanoma with more severe atypia
- May occasionally be associated with neurofibroma

Dysplastic nevus

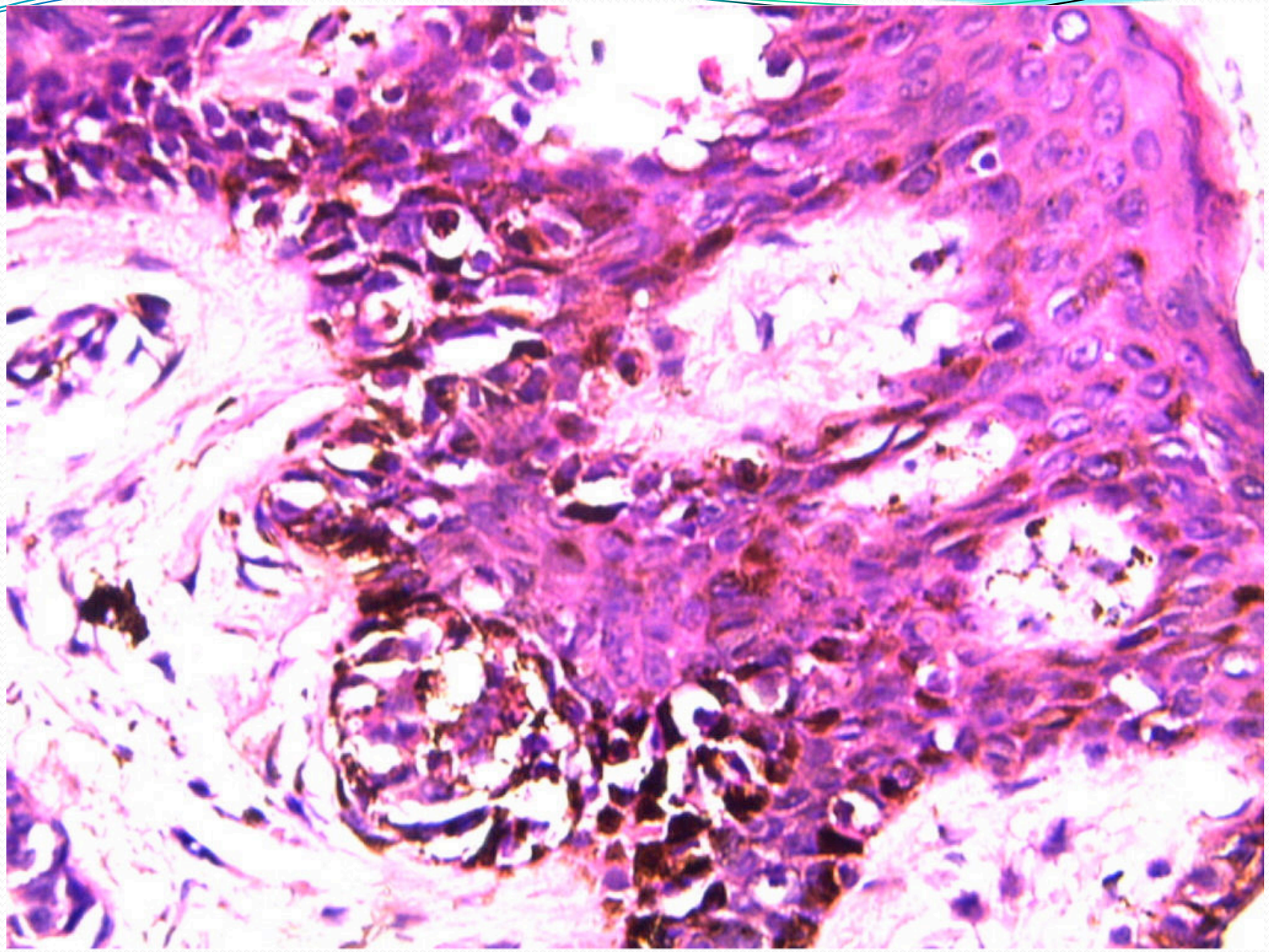
- Compound nevi with marked lentiginous proliferation of melanocytes at dermoepidermal junction, extending at least 3 rete ridges beyond lateral margins of dermal component
- Nests have cytologic and architectural atypia, including irregular sizes and shapes and bridging of adjacent rete ridges, which are irregular themselves
- Papillary dermal lamellar fibroplasia with perivascular infiltrate and vascular dilation
- Usually mild / moderate cytologic atypia (nuclear hyperchromasia, prominent nucleoli, dusty melanin pigment)
  Melanocytes are spindled and parallel to surface or epithelioid
- Epidermolytic hyperkeratosis present but not specific







MILD – MODERATE - SEVERE

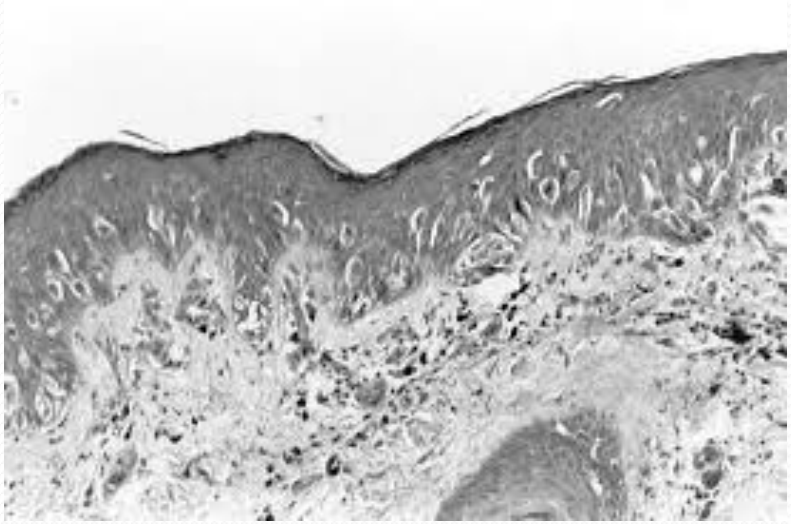


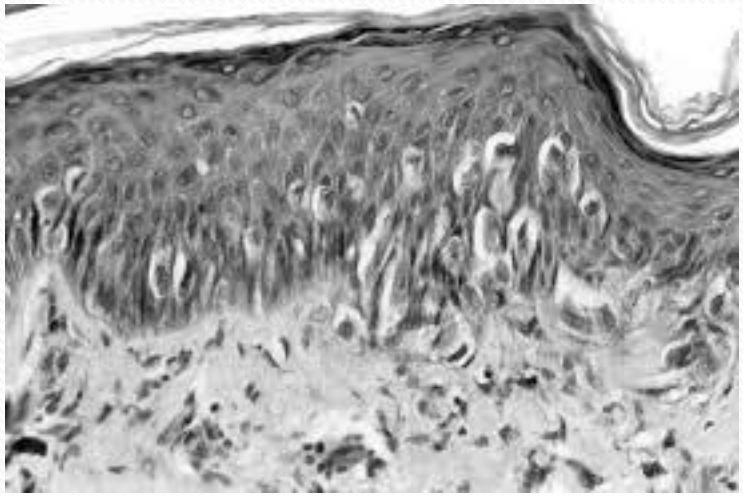
Melanoma in situ

- Malignant melanocytes in epidermis, without dermal invasion
- Variants include lentigo maligna, superficial spreading and acral melanoma
- Median age 63, males > females

Melanoma in situ

- Atypical melanocytes in epidermis with no dermal invasion
- Usually epidermal effacement (absences of rete ridges in some foci
- Predominance of individual unit melanocytes over nests
- Confluent growth of melanocytes along dermo-epidermal junction
- Pagetoid spread
- Involvement of adnexal structures





Invasive melanoma

- Malignancy of melanocytes, predominantly in skin, but also eyes, ears, GI tract, leptomeninges, mucous membranes
- Only 4% of skin cancers but majority of skin cancer deaths
- Usually due to sun (UV light) exposure
- Incidence increasing worldwide

Populations at higher risk

- Whites with fair skin, red hair, tendency to burn or freckle from sun exposure, large number of melanocytic nevi, xeroderma pigmentosum, familial dysplastic nevi, melanosis, vitiligo, frequent sunburns at any age;
- 5-10% are familial
- Possible increase in neurofibromatosis type I
- Usually occurs after puberty, occasionally children - all have same morphology
- Partial and even total regression may occur

Sites

- Head and neck, back, lower extremities (particularly in women)
- Also oral and anogenital mucosa, esophagus, meninges and eye
- Rarely subungual ("Hutchinson's sign / melanotic whitlow"), palm or sole

Clinical warning signs

- Change in color of pigmented lesion
- Enlargement of existing mole
- Itching or pain in pre-existing mole
- Development of new pigmented lesion in adult life
- Irregular borders in pigmented lesion
- Variegation of color in pigmented lesion
- Change in color of pigmented lesion

Metastases

- Regional lymph nodes, liver, lungs, GI tract, bone, CNS, heart, skin and other sites
- Isolated tumor cells or tumor deposits > 0.1 mm (within lymph nodes) that meet the criteria for histologic or IHC detection of melanoma should be scored as node positive
- Satellite tumors are considered intralymphatic metastases within 2 cm of primary tumor; termed in transit metastases if > 2 cm from primary tumor,
- Metastasis are occasionally S100-, but can still be identified as melanoma due to:
    a. Negative workup for carcinoma, lymphoma and sarcoma
    b. HMB45+, MART1+
    c. clinical history of melanoma
- Metastases may arise from unrelated clones
- Molecular analysis can distinguish a second primary from metastatic disease

Prognostic factors

- High Breslow (vertical) thickness in primary tumor
- High Clark's level
- Vascular invasion
- High stage (TNM)
- Male gender
- High mitotic rate
- Ulceration
- Microscopic satellites (tumor nests 50 microns or larger and separated from main tumor mass)
- Regression
- Tumor-infiltrating lymphocytes

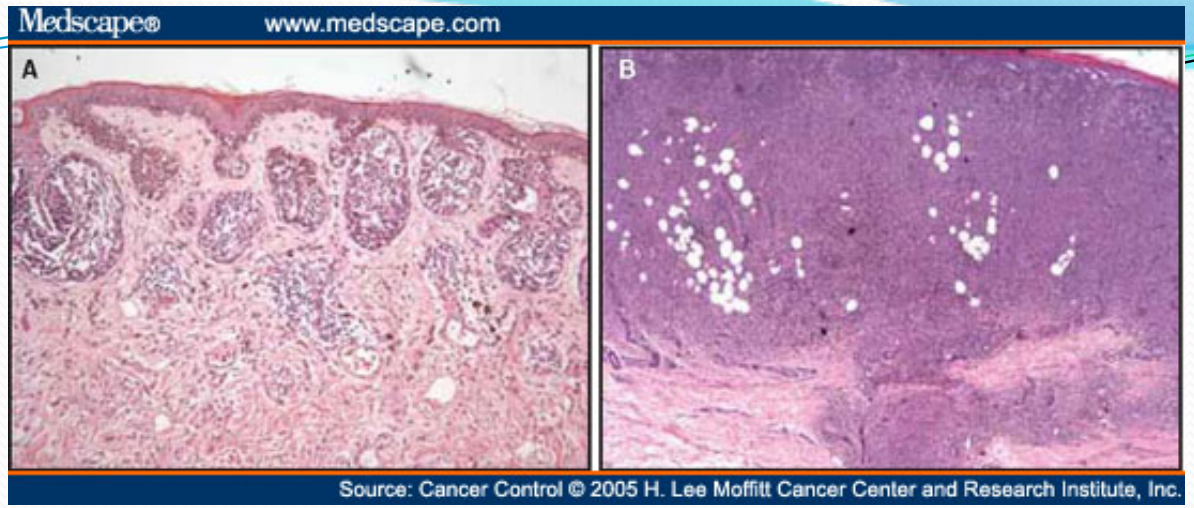
Histology

- Features of melanoma in situ + dermal involvement of atypical melanocytes with cytologic atypia and no maturation
- Classic features are junctional activity with obscured dermoepidermal junction and pagetoid spread individually and in clusters throughout epidermis
- Prominent melanin pigmentation, invasion of surrounding tissue
- Large cells with abundant eosinophilic and finely granular cytoplasm
- Nuclear pseudoinclusions, folds or grooves
- Marked atypia with pleomorphic nuclei with large eosinophilic nucleoli

Other microscopic features:

- ***Growth patterns:*** pseudoglandular, pseudopapillary, peritheliomatous (around blood vessels), hemangiopericytoma-like, Spitz nevus-like, trabecular, verrucous, nevoid
- ***Cell type:*** epithelioid, spindled or bizarre
- ***Size:*** lymphocytes to multinucleated giant cells
- ***Cytoplasm:*** eosinophilic, basophilic, foamy, signet ring, rhabdoid, oncocytic or clear
- ***Stroma:*** desmoplastic, myxoid, bone or cartilage, osteoclast-like giant cells
- ***Epithelium:*** pseudoepitheliomatous hyperplasia
- ***Other differentiation:*** Schwann cells, ganglion cells, other neural structures

- Frequent mitotic figures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A
B
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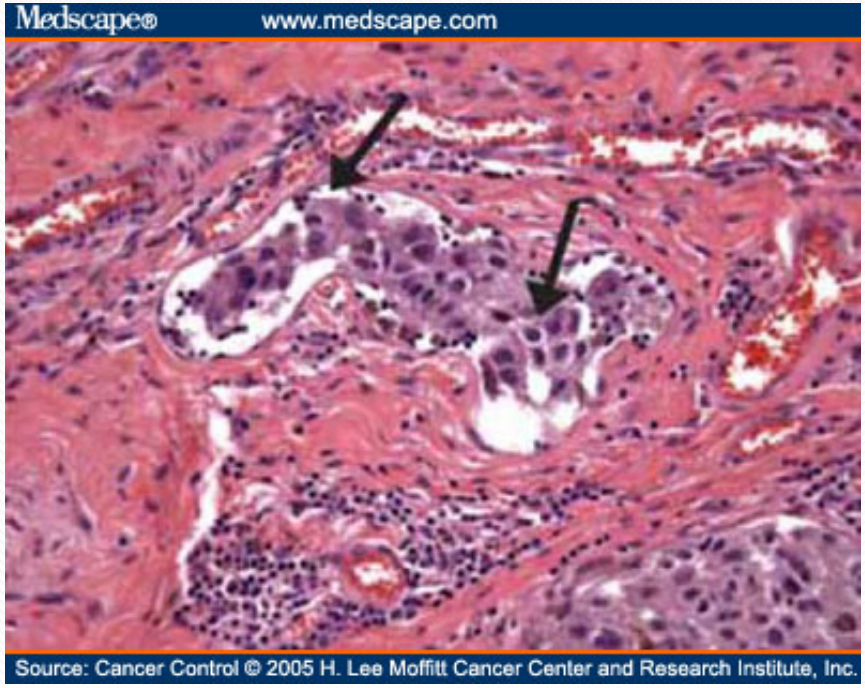
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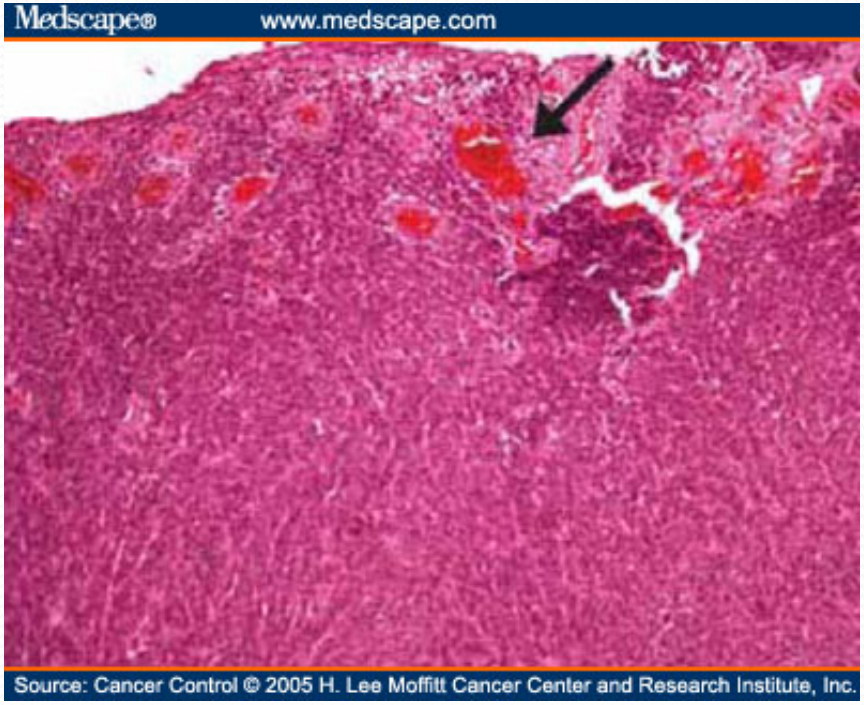
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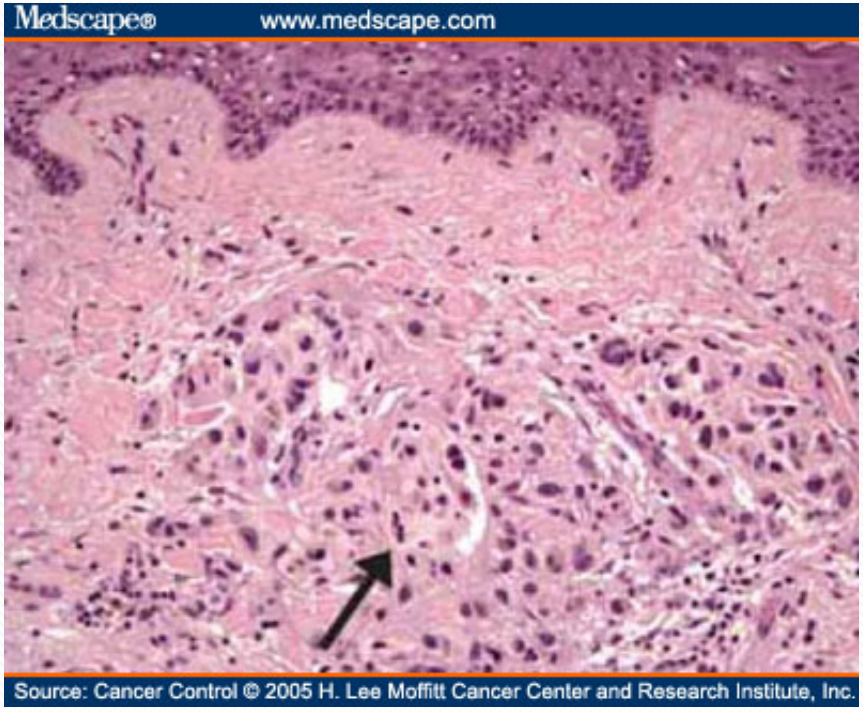
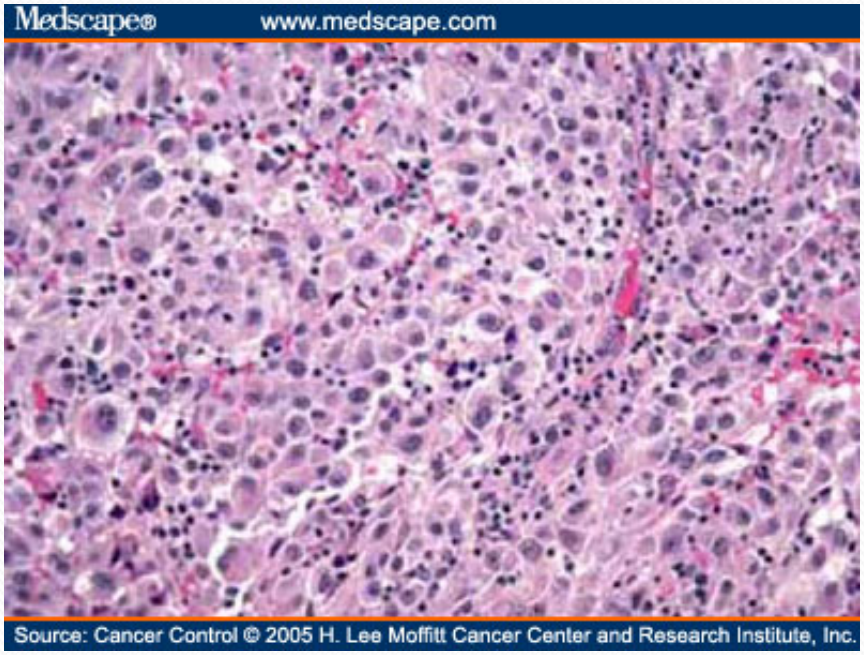


Satellite metastasis



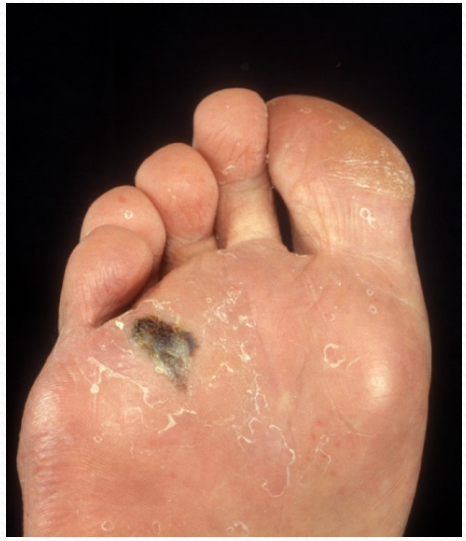
Tumor infiltrating lymphocytes

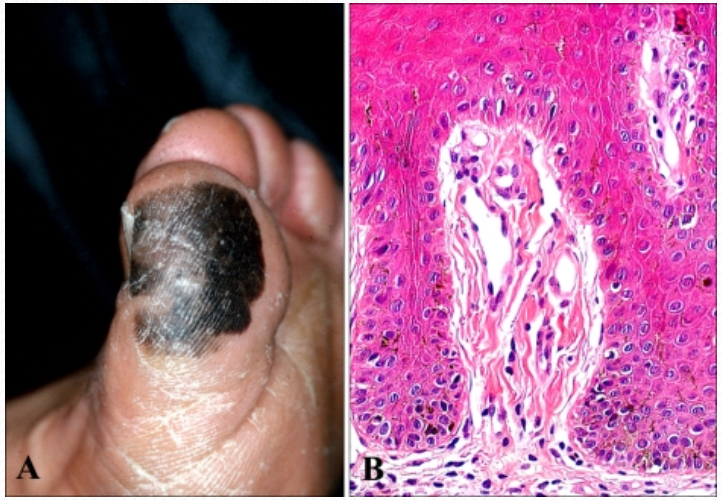
4 major subtypes

- Acral lentiginous
- Lentigo maligna
- Nodular
- Superficial spreading

Acral lentiginous

- **Acral:** relating to or affecting the glabrous (non-hair bearing) or volar skin of the soles, palms and digits as well as the nail apparatus
- Note: all melanomas of acral sites do NOT have histology of acral lentiginous melanoma



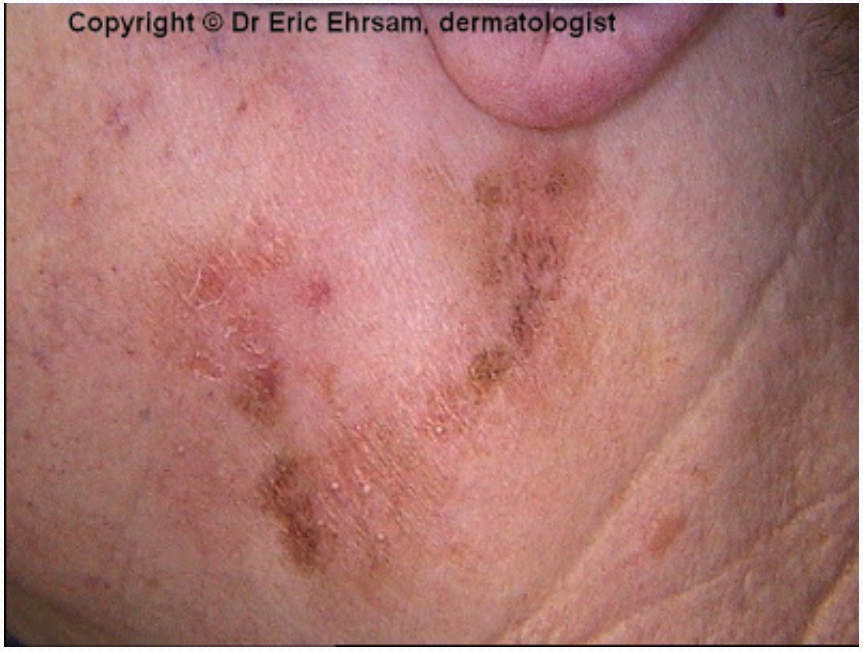


Histology

- Confluent single-cell melanocytic proliferation
- Variable cytologic atpyia of melanocytes
- Prominent acanthosis of epidermis with elongated rete ridges
- Pagetoid spread
- Proliferation of melanocytes downward along eccrine ducts
- Invasive component often composed of spindle cells, but epithelioid, small cells and pleomorphic cells are occasionally noted
- Intraepidermal lentiginous component is similar to lentigo maligna, but intraepidermal melanocytes are bizarre, epidermis is markedly hyperplastic and papillary dermis is widened and inflamed
- Consumption of epidermis present (attenuation of basal / suprabasal layers with rete ridge loss

Lentigo maligna

- Atypical melanocytes in basal layer, individually and in nests (theques), associated with sun damage
- Flat, tan to black with irregular hyperpigmentation, > 2 cm
- 5-15% of (invasive) melanoma; increasing prevalence, particularly among men age 65+ years
- Slow growing lesion of sun exposed skin of elderly whites, often cheek; partial regression is common
- Similar behavior to other melanoma subtypes when depth of invasion is considered, but unusual to die of disease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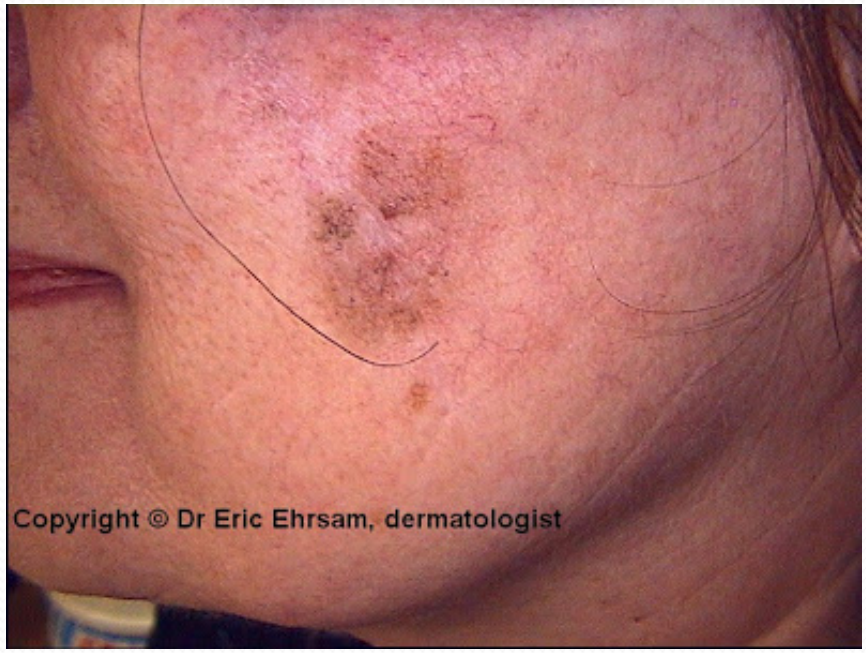
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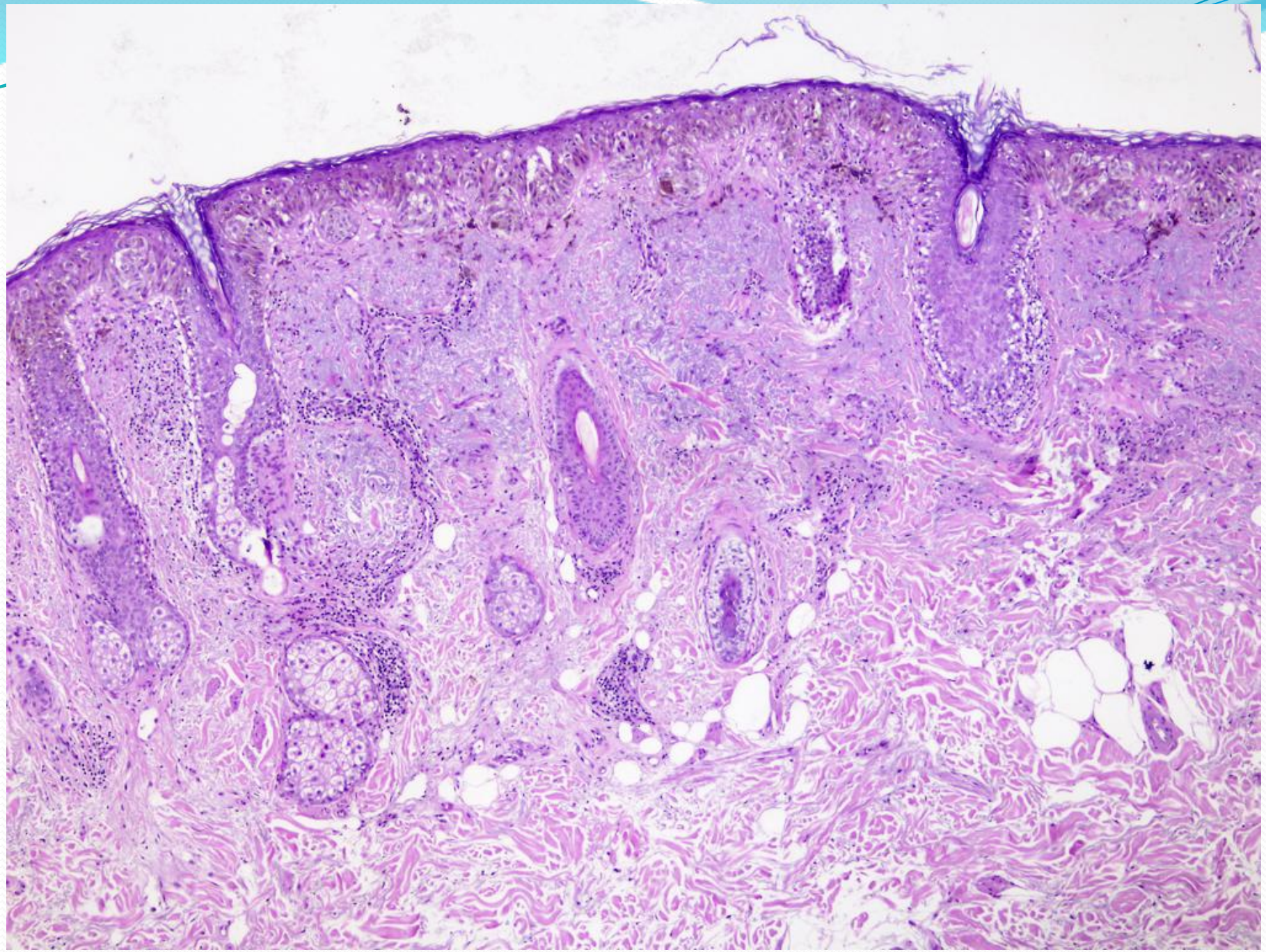
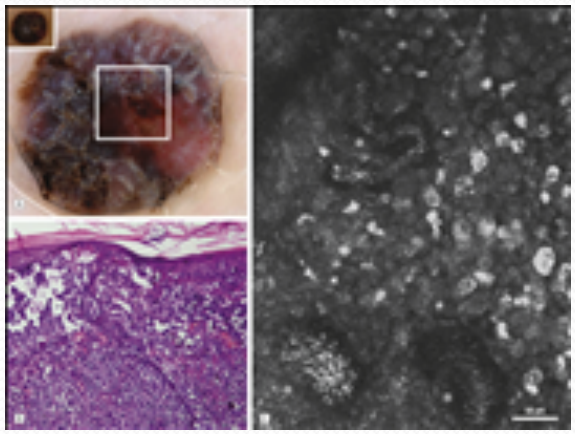
Histology

- Contiguous growth of atypical melanocytes in basal layer, individually and in nests (theques)
- Cells may be spindled, pleomorphic and have cytoplasmic retraction
- Dermis shows solar elastosis
- Also epidermal atrophy, actinic damage and basilar keratinocyte hyperpigmentation



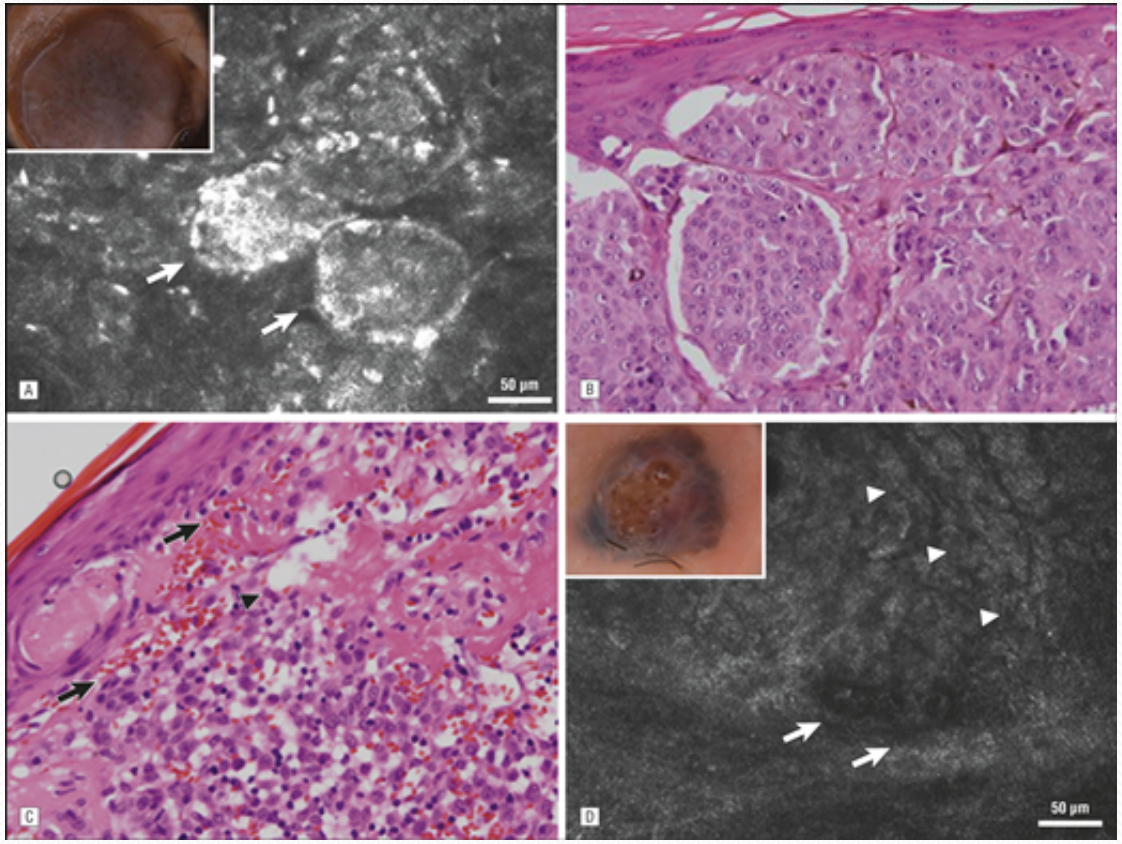
Nodular melanoma

- Aggressive subtype of melanoma with early vertical growth phase
- Median age 63 years; men > women
- Affects all body surfaces, but usually legs and trunk



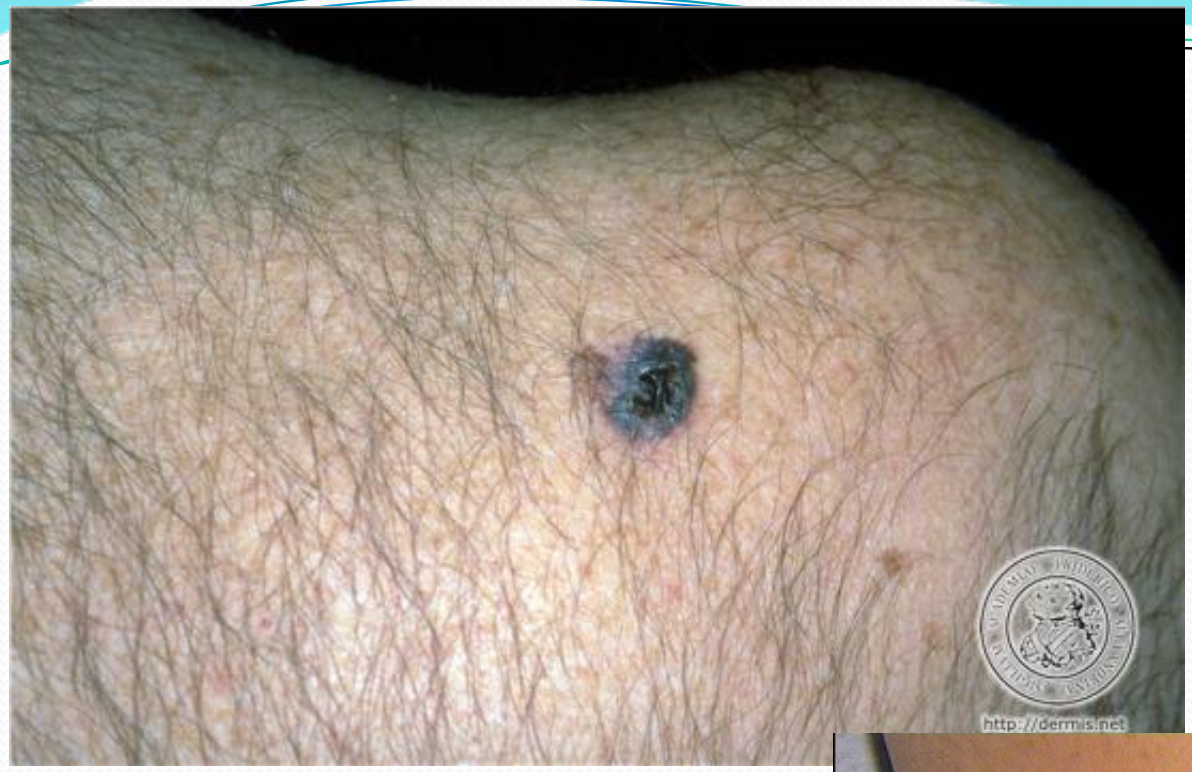
Histology

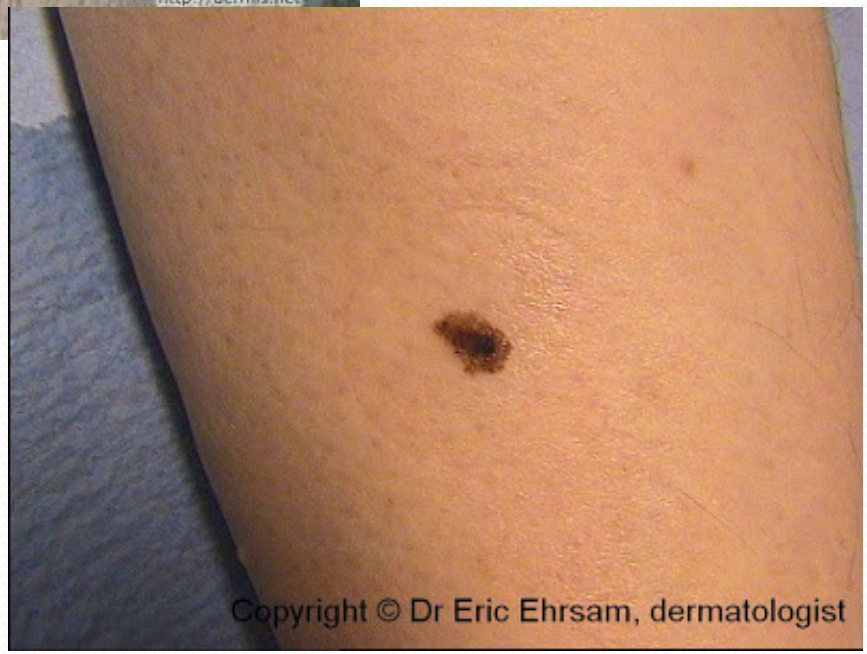
- No radial growth phase
- Epidermis is thin and may be ulcerated
- No in situ melanoma
- Dermal component consists of a cohesive nodule of tumor cells with pushing border
- Cells are most commonly epithelioid, may be spindled or small with occasional monster cells


A
50 µm
B
C
D
50 µm

Superficial spreading

- Traditional considered most common type of melanoma (50-75%), but lentigo maligna may actually be more common in patients with extensive sun exposure
- Usually affects light skinned individuals, young adults to elderly
- Often trunk and extremities


http://dermis.net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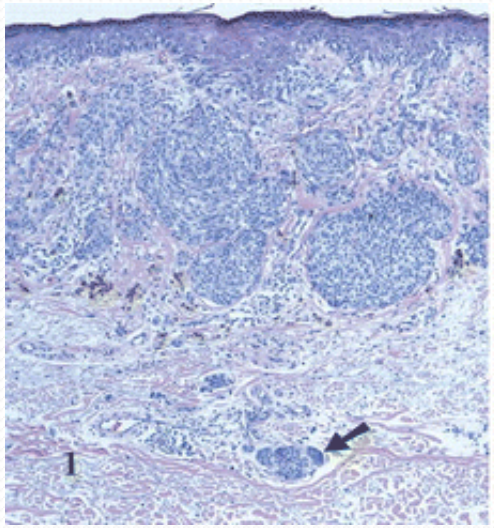
Histology

- Classified based on radial growth component
- Non-invasive areas have asymmetry and poor circumscription, irregular acanthosis, irregular lentiginous and nested proliferation, uniform atypical melanocytes with nests and pagetoid cells
- Also transdermal migration, nuclear pleomorphism, dusty pigmentation, apoptosis of individual melanocytes and pigmented parakeratosis
- Invasive component generally of epithelioid subtype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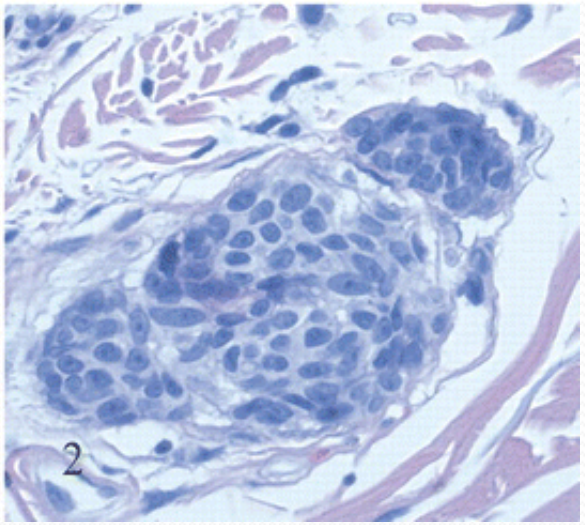
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Clark's levels of invasion

I: not penetrating basement membrane (in situ)

II: in papillary dermis (difficult to differentiate II versus III)

III: filling and expanding the papillary dermis and stopping at the interphase between the papillary and reticular dermis

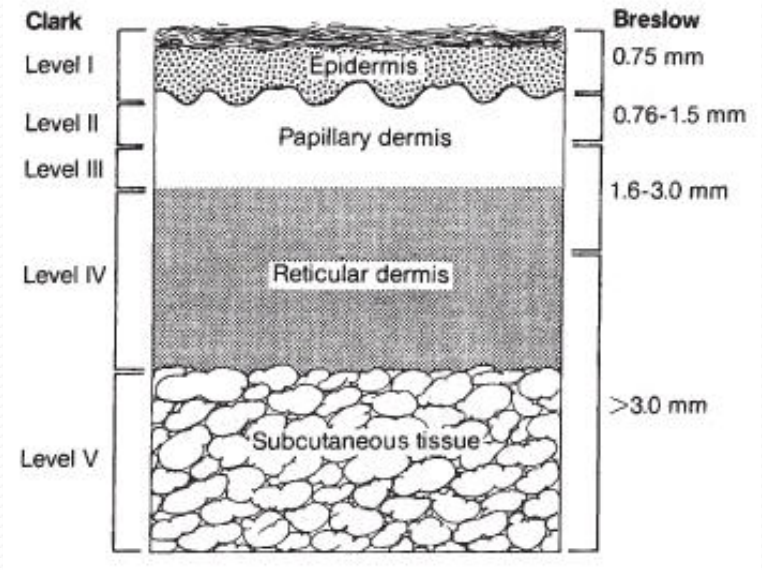
IV: in the reticular dermis

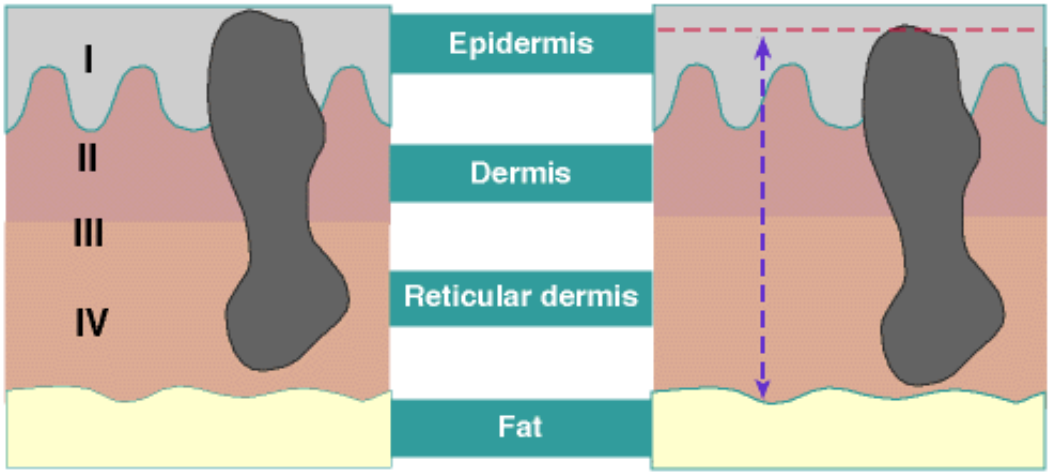
V: in the subcutaneous tissue

References: Cancer 2000;88:589

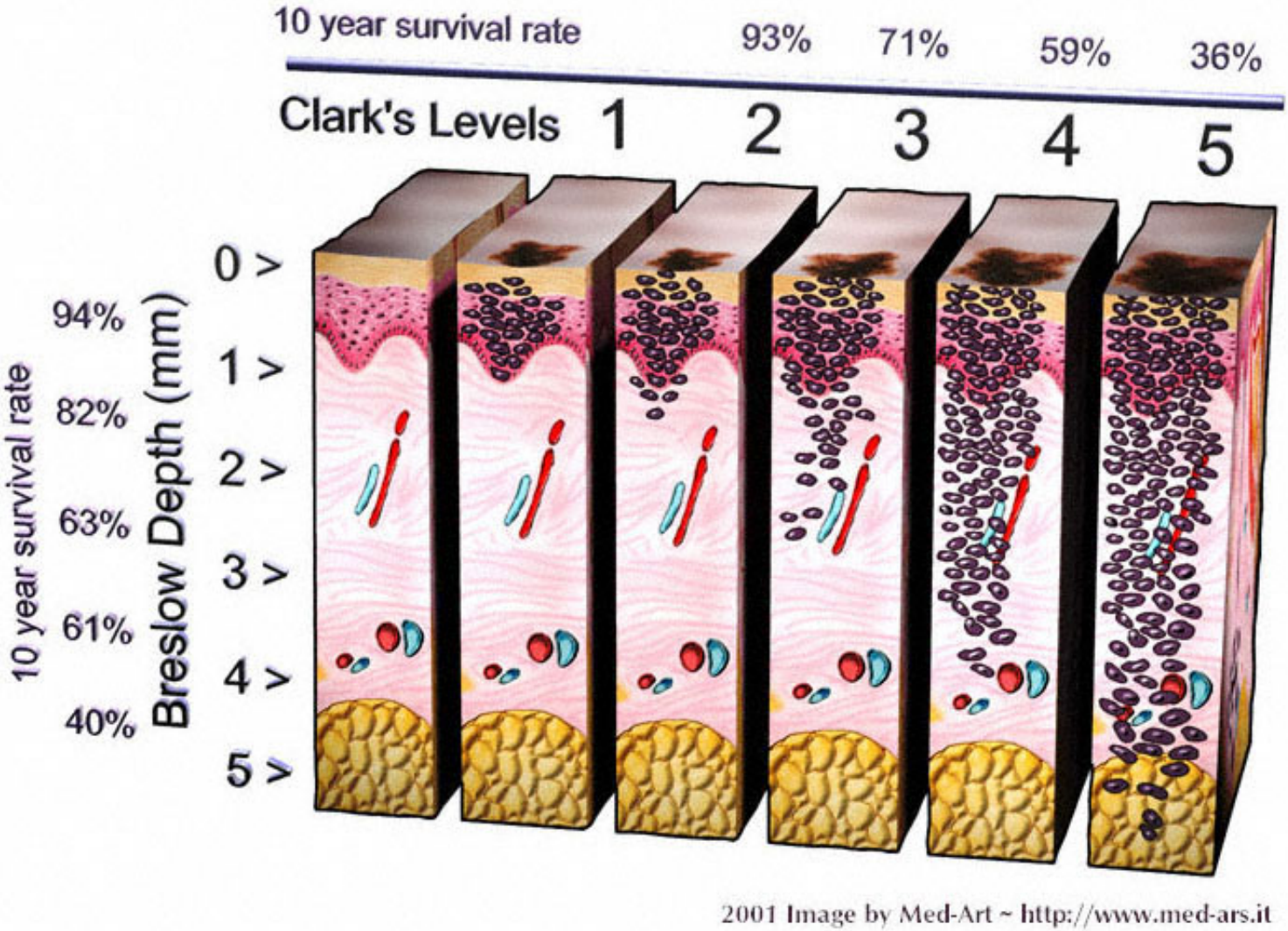
Breslow's system for tumor thickness

- Important prognostic factor first described by Breslow in 1970
- Measure tumor thickness with ocular micrometer at right angles to surface of adjacent normal skin from (a) top of granular layer of overlying epidermis OR from ulcer base over deepest point of invasion to (b) deepest invasive tumor cells
- Traditional categories are 0 to 0.76 mm, 0.76 to 1.49 mm, 1.50 mm to 3.99 mm and greater than 4.00 mm
- 2009 AJCC Staging System employs following thresholds for thickness: T1: ≤ 1.00 mm thickness, T2: 1.01 to 2.00 mm thick, T3: 2.01 to 4.00 mm thick, T4: more than 4.00 mm
- 10 year survival: 92% for melanoma < 1.00 mm thick; 80% if 1.01 to 2.00 mm thick; 63% if 2.01 to 4.00 mm thick; 50% if > 4.00 mm thick
- 5 year survival in non-ulcerated tumors is 97% for Breslow thickness of 0 to 1.0 mm, 91% for 1.01 to 2.0 mm, 79% for 2.01 to 4.0 mm and 71% for > 4.0 mm (AJCC 7th Edition, 2010)





Dr. Breslow suggested measuring from the top of the granular layer to the bottom of the melanoma using an occular micrometer within the microscope. This method is highly reproducible and now widely used.


10 year survival rate
93%
71%
59%
36%
Clark's Levels
1
2
3
4
5
10 year survival rate
94%
82%
63%
61%
40%
Breslow Depth (mm)
0 >
1 >
2 >
3 >
4 >
5 >
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