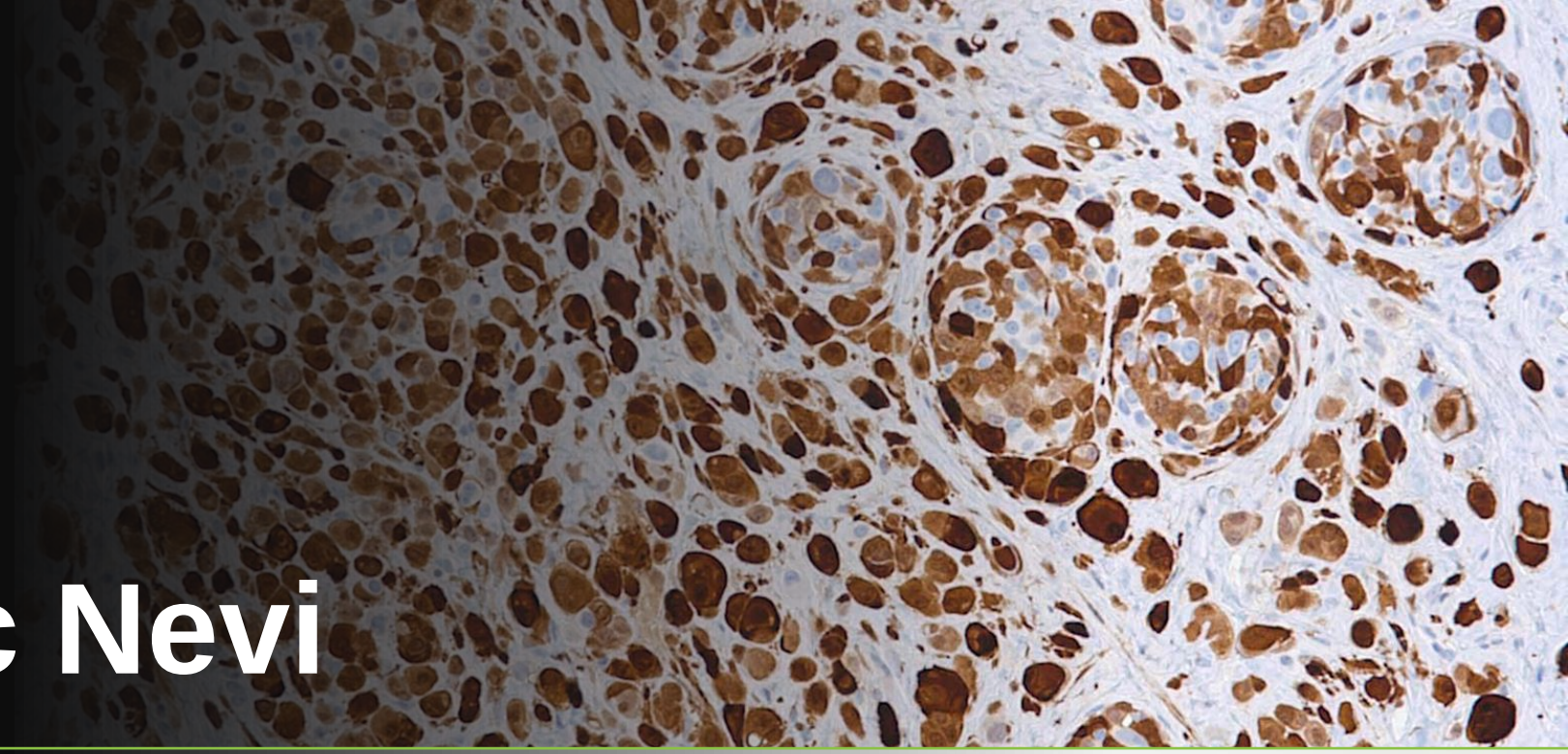


Melanocytic Nevi

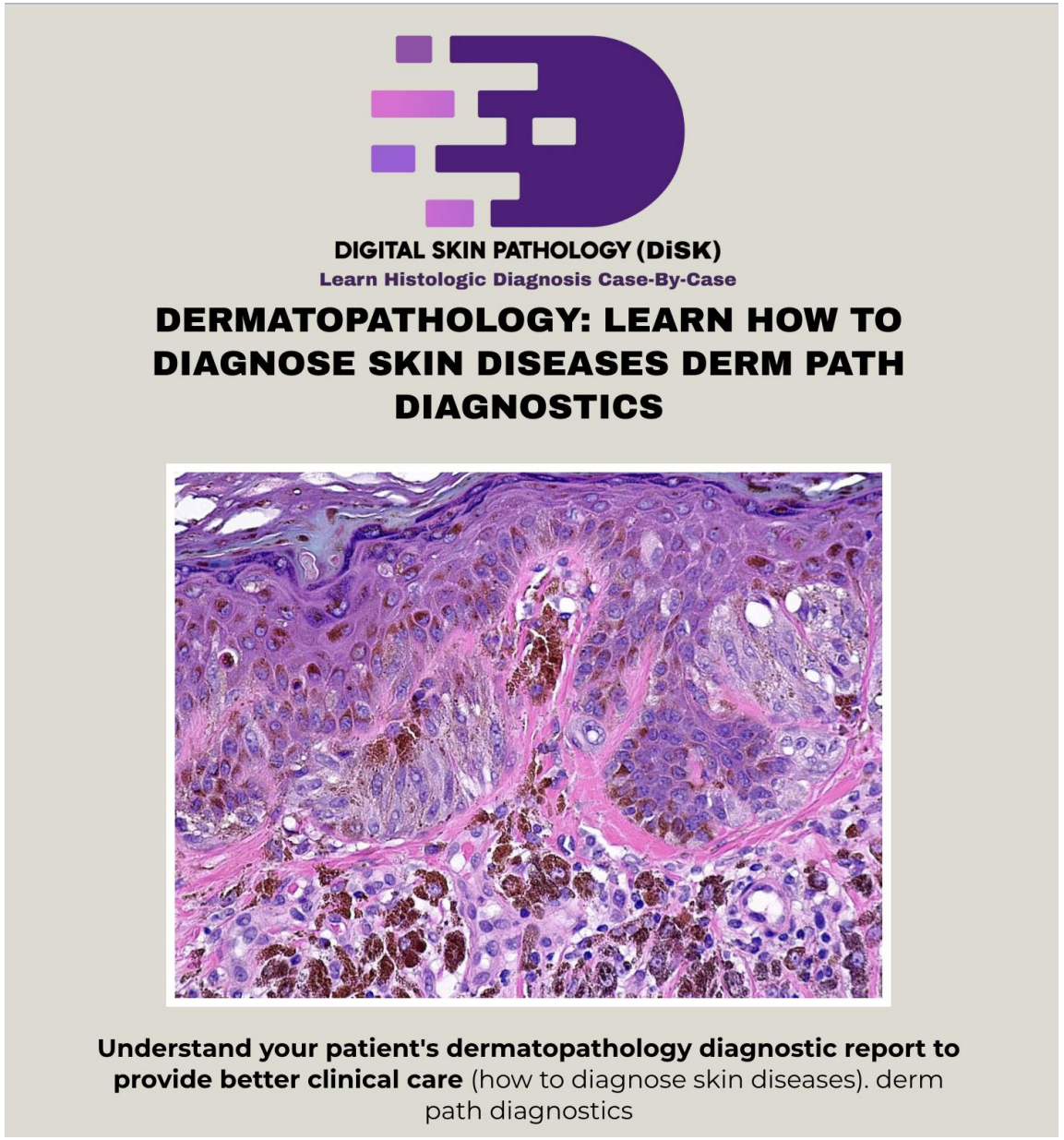
Soheil S Dadras MD-PhD

Digital Skin Pathology

https://digitalskinpathology.com/

- Meet the challenges of the growing needs for dermatopathology knowledge
- Dermatology PAs and NPs
- Primary MDs and general surgeons
- Residents of Dermatology and Pathology

- Learn skin pathology based on actual real-life cases, lectures, and quizzes
- Study quiz cases no. 110-118



Lecture objectives for melanocytic neoplasms

Understand the WHO classification (5th edition)

Learn the diagnostic principals of common melanocytic nevi

What is the histopathology of

Nevus subtypes?

Common nevus vs. dysplastic nevus?

Understand the evolving concept of melanocytoma

What are the four subtypes?

What is their genetic pathways?

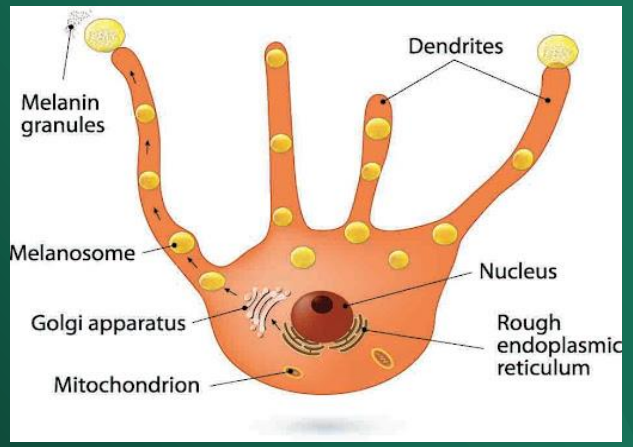
Learning tips & pitfalls

Where to begin

- Melanocytic nevus, “hamartoma” of melanocytes, a neoplasm
- Examine as many case examples as possible (reliably curated sources)
    - Digitalskinpathology.com, other websites, atlas, study sets
- Learn minimal diagnostic criteria for each entity
- Understand diagnostic principles of “benign” nevus
- Apply the principle during your dermatopathology rotation

Practical considerations

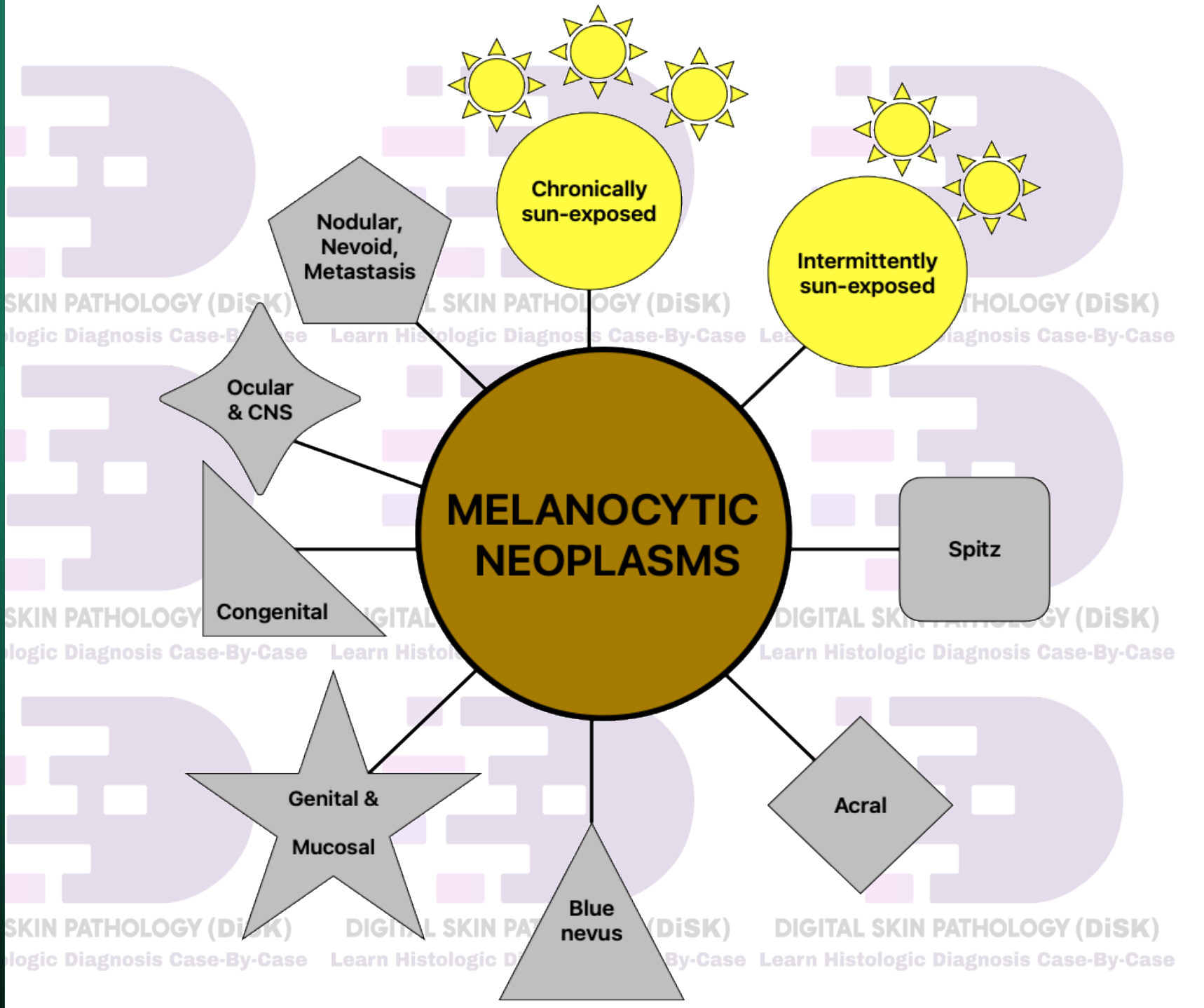
- Know the anatomic site and the reason for biopsy
    - Examples: woman for mole removal, or lesion present for a long time, “now changed”
- Consider secondary changes, e.g., rubbing (pigmented parakeratosis)
- Are you examining the entire lesion or a part of it?
- Formulate a “working” histologic diagnosis before immunohistochemistry (IHC)
- IHC is only ancillary, pitfalls:
    - MART-1/MELAN-A (over interpretation of density of epidermal melanocytes)
    - PRAME (Positive in nevi, negative in melanomas)



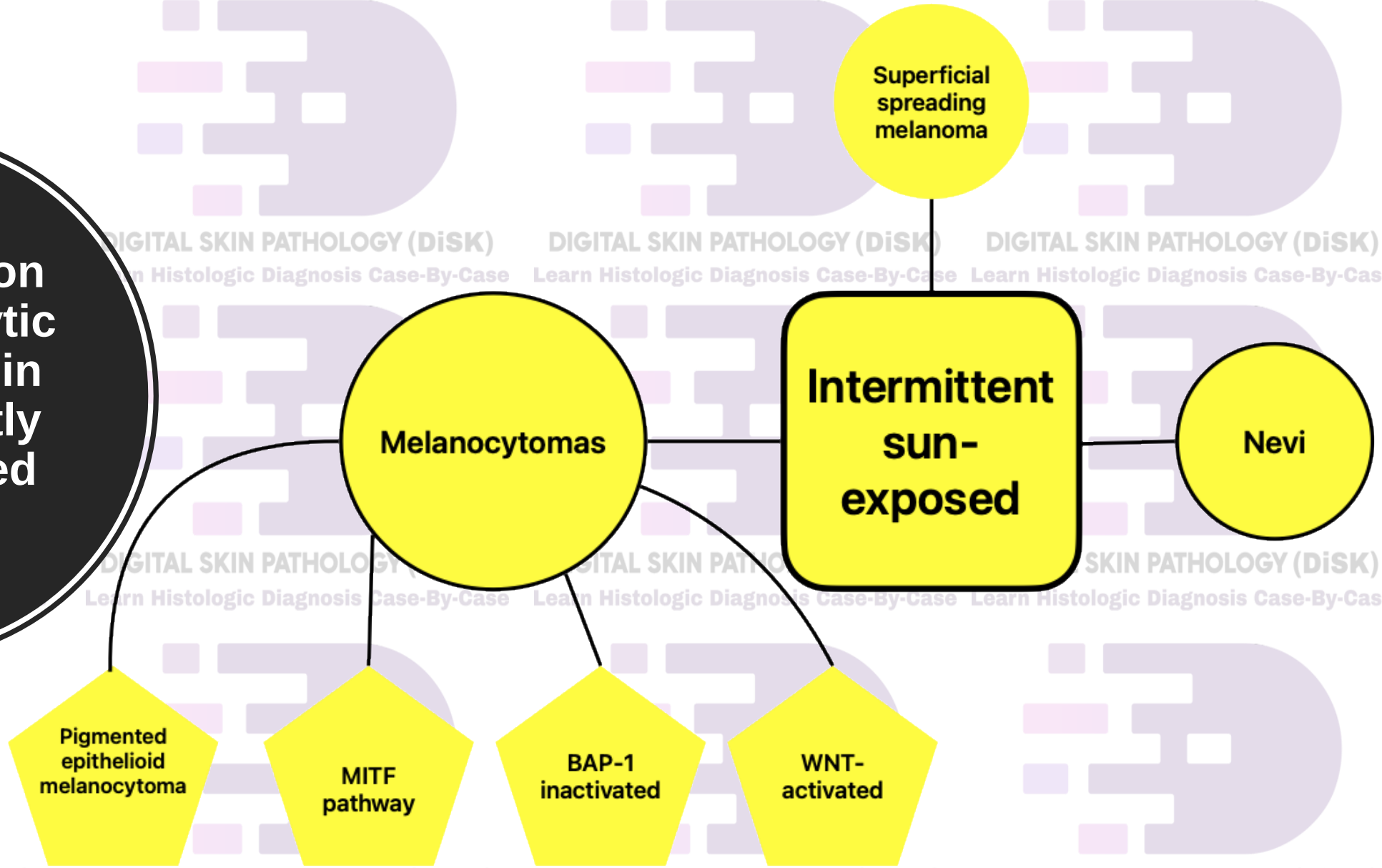
Classification of melanocytic neoplasms
(WHO 5th edition)

CSD – cumulative sun damage

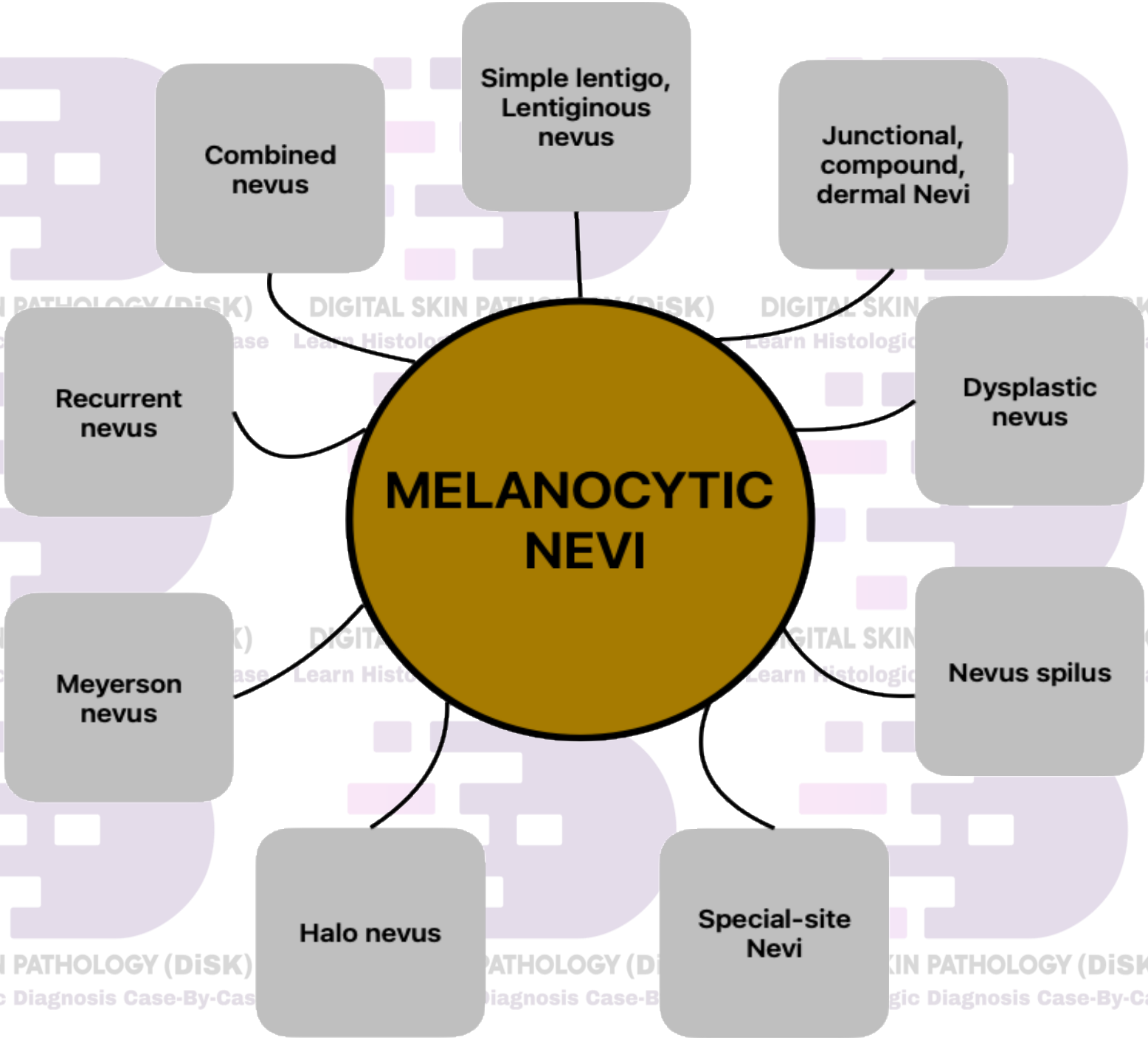
Altered genetic pathways



Classification of melanocytic neoplasms in intermittently sun-exposed skin



Classification of melanocytic nevi



Immunohistochemical markers for melanocytic neoplasms

Primary Markers (Specific)

- **S100** – Sensitive (>95%), not specific (also stains nerve cells and adipocytes)
- **SOX10** – Sensitive and not specific (also stains nerve cells and eccrine apparatus)
- **Melan-A (MART-1)** – Negative in desmoplastic and spindle cell melanomas
- **HMB-45** – Marks premelanosomes; gradient-based expression (in nevi); negative in desmoplastic and spindle cell melanomas
- **Tyrosinase** – Less commonly used
- **MITF (Microphthalmia-associated Transcription Factor)** – Nuclear marker for melanocytes (also marks histiocytes)

Secondary Markers (Supportive)

- **PRAME (PReferentially expressed Antigen in MElanoma)** – Positive in melanomas, negative in nevi (false positive and negative rate)
- **Ki-67 (Proliferation Marker)** – Higher expression in melanoma vs. nevus
- **p16 (CDKN2A)** – homozygous loss supports Loss of melanoma progression

Nevus classification scheme

Melanocytes:

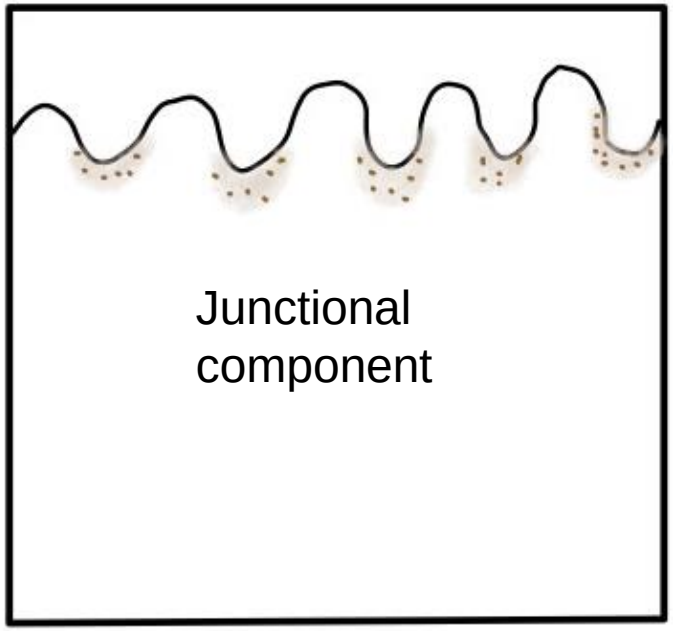
1. Location (where)

2. Morphology (what)

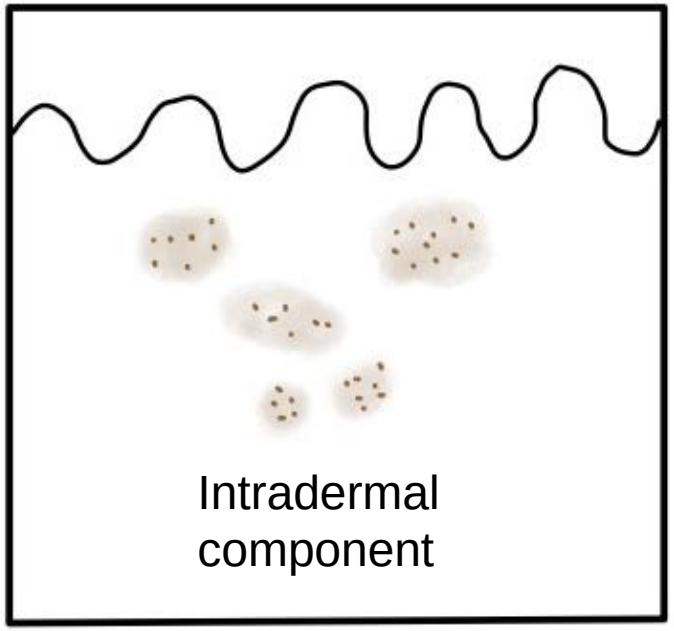
- Location in the skin
  - Superficial:
    - Intraepidermal
    - Upper half of reticular dermis
  - Deep
    - Lower half of reticular dermis
    - Subcutaneous
    - Fascial

- Cell type
  - Small round or oval
  - Fusiform or spindle
  - Epithelioid (enlarged, abundant cytoplasm)
  - Dendritic (long, delicate processes)
- Stroma: desmoplasia, sclerosis

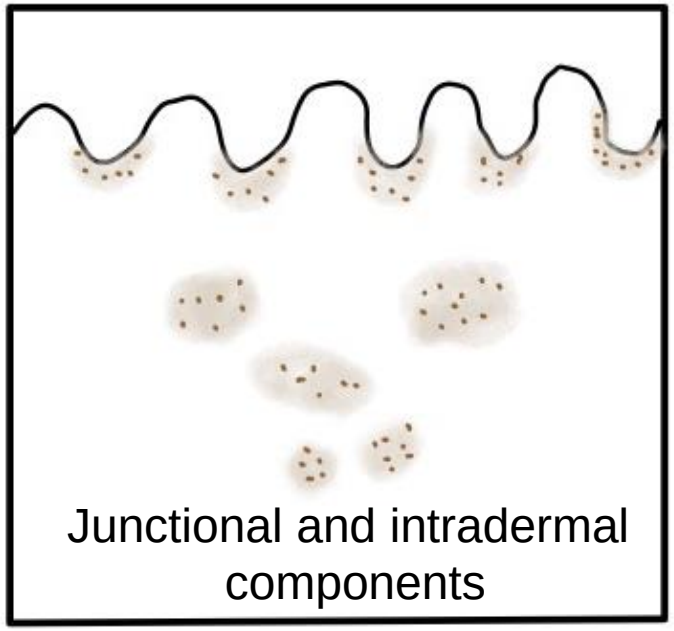
What is a compound melanocytic nevus?



Junctional nevus



Intradermal nevus



Compound nevus

What are the clinical features of a melanocytic nevus

- Onset childhood, adolescence, third decade, or later
- 2 to 6 mm diameter
- Macular, papular, or both macular and papular, dome-shaped, polypoid, or papillomatous
- Homogeneous skin color, tan, light brown, brown, dark brown
- Round, oval
- Symmetrical
- Well-defined, regular borders

What are the histologic features of a nevus?

Low magnification: Architecture

Epidermal location

- Overall symmetry/circumscription
- Nested at the tips of rete ridges (no shouldering or lateral displacement)
- Junctional nesting (not lentiginous)
- No scattering of melanocytes through the epidermis (pagetoid upward scatter)

Dermal location

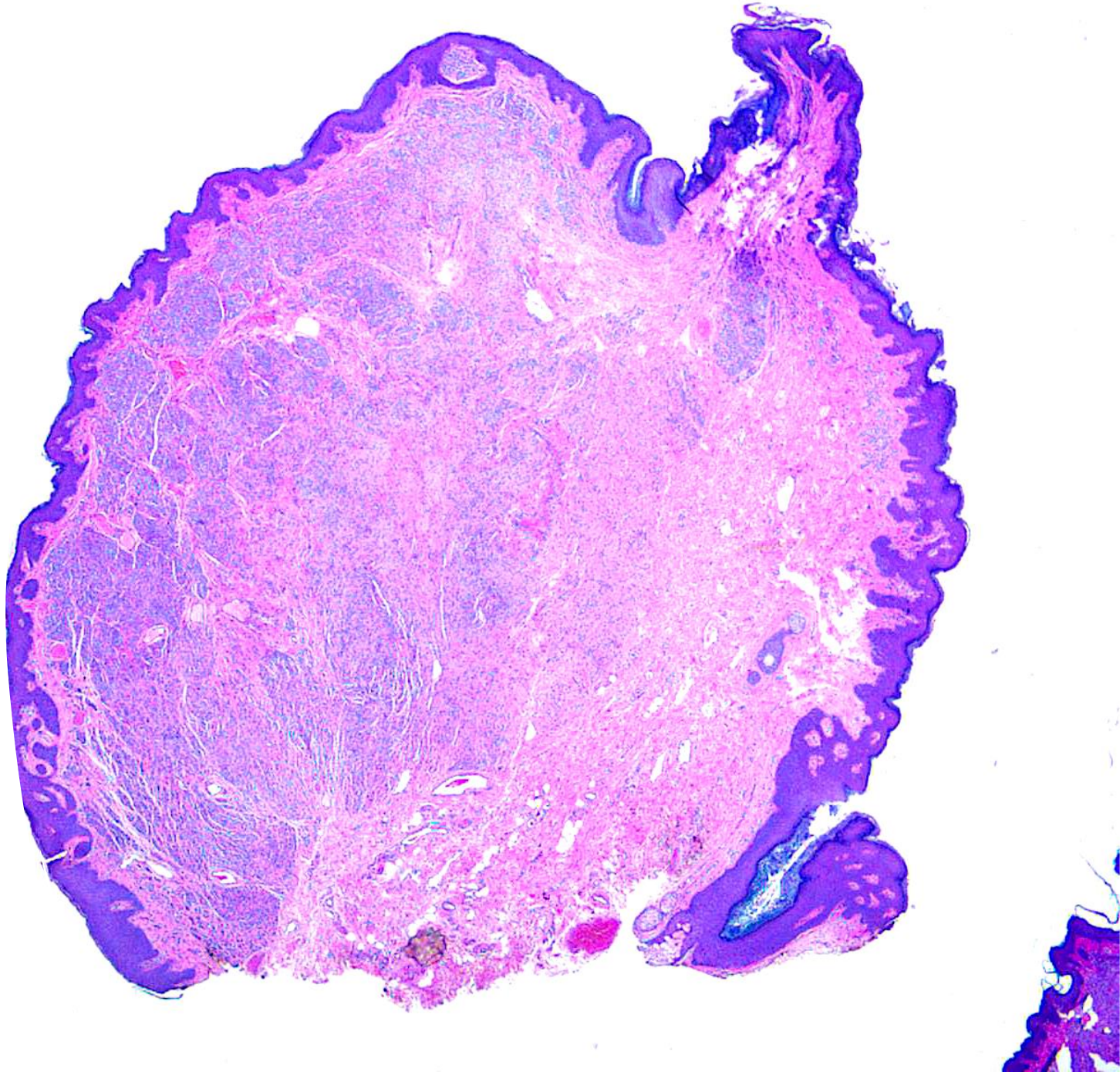
- Maturing with dermal depth (not sheeting),
- Transition: Epithelioid → Lymphocytoid → Spindled, dispersing at deep aspect
- Reaction to adnexa: co-exist and preserve
- Even distribution of melanin

High magnification: Cytology

- Nuclear membrane: thin, regular contour
- Hyperchromatic nuclei (closed chromatin)
- No prominent cherry red nucleoli
- Scanty cytoplasm (non-epithelioid)
- No more than one deep dermal mitosis
- No necrosis in larger lesions
- No ulceration (other than external trauma)
- No lymphatic or vascular invasion

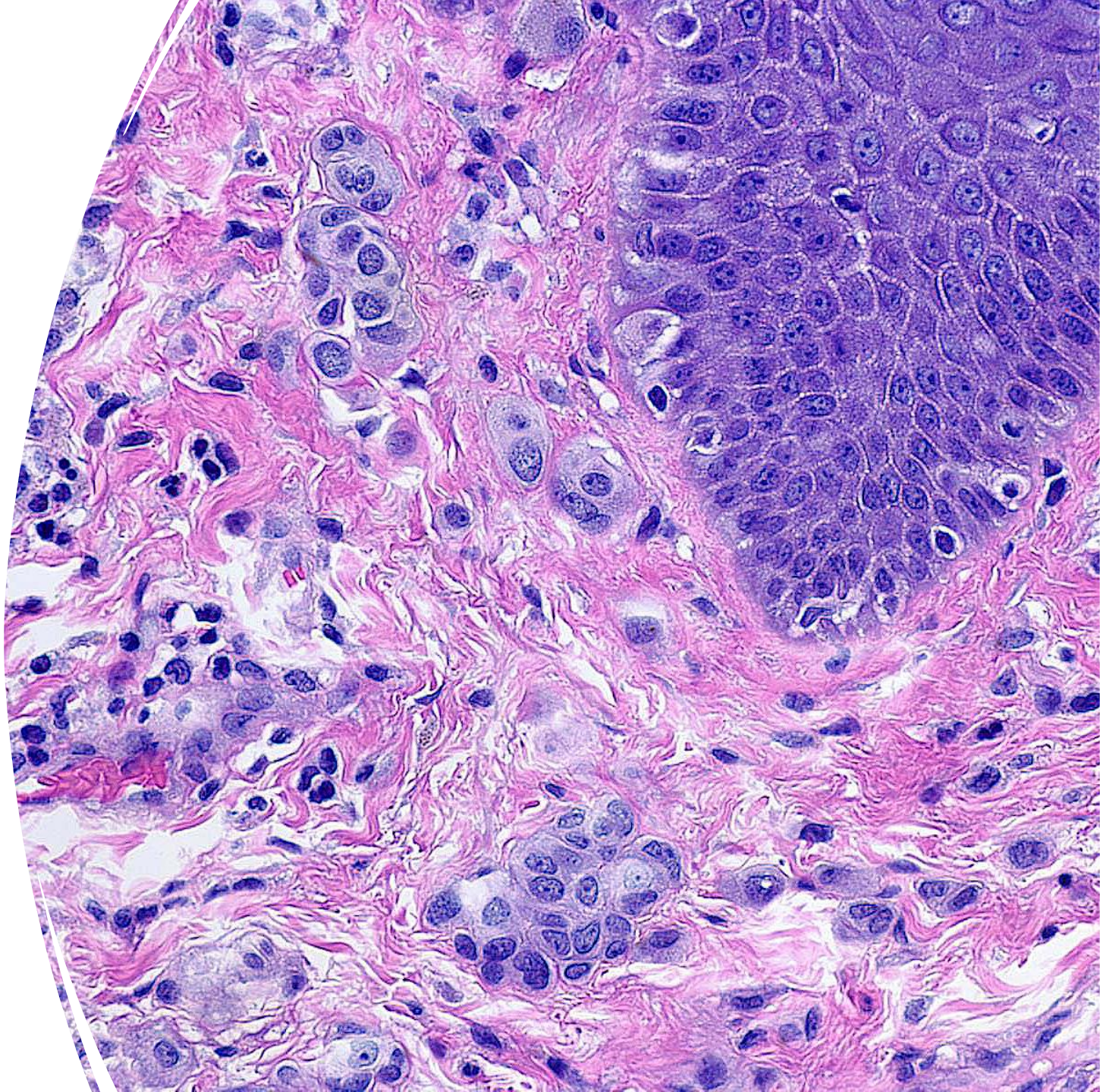
Architectural Features of Nevi: Low-Power Patterns

- **Symmetrical proliferation** of melanocytes.
- **Sharp lateral borders** (well-circumscribed lesion).
- **Nested growth pattern** (melanocytes cluster in theques at the dermoepidermal junction).
- **Maturation with depth**:
  - Superficial melanocytes are larger, more epithelioid.
  - Deeper dermal melanocytes become smaller, spindled, and resemble lymphocytes ("neurotization").
- **No pagetoid spread** (melanocytes confined to basal layer, unlike melanoma).

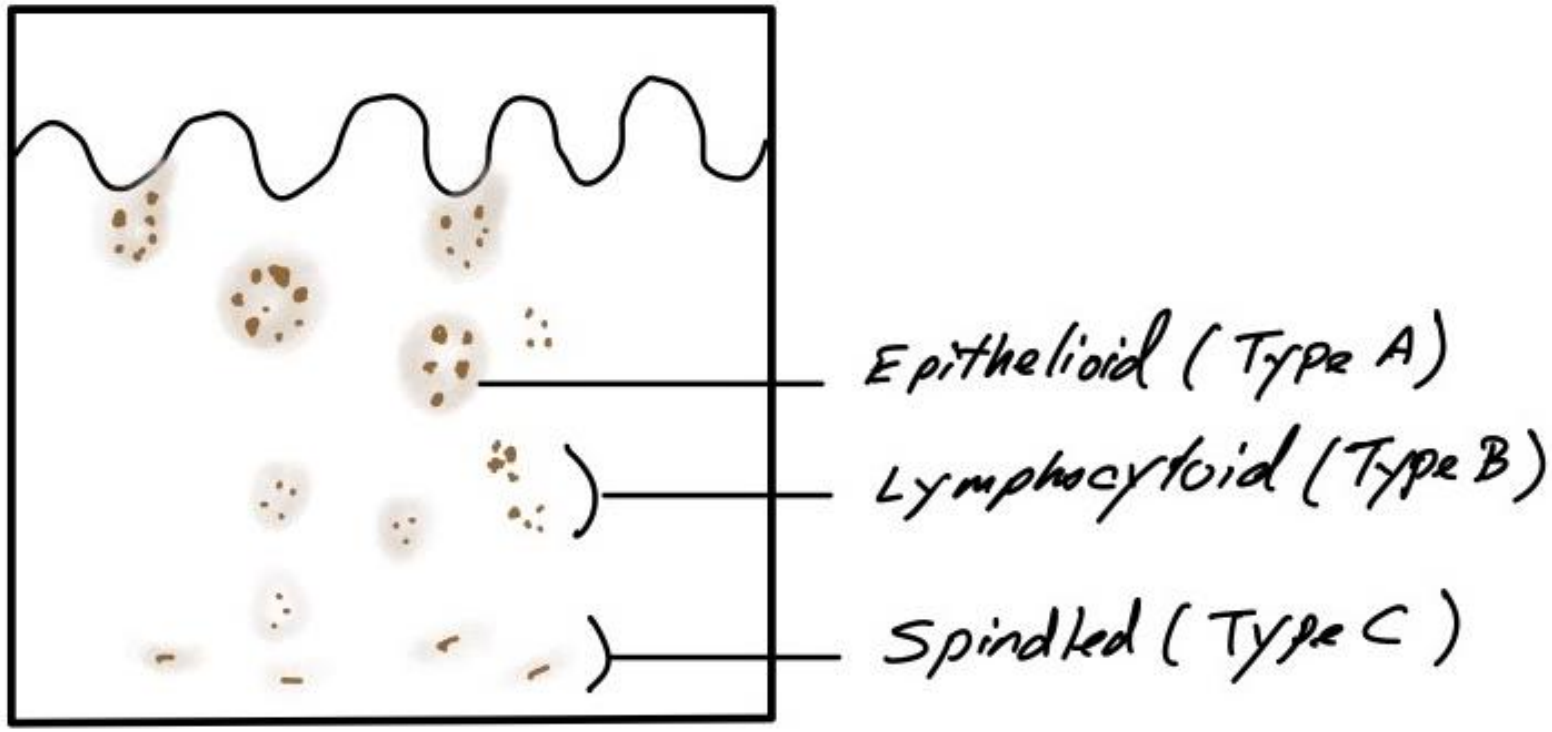


Cytologic Features Nevi: High-Power Patterns

- **Uniform melanocytes** with minimal atypia:
  - Small, round nuclei.
  - Even chromatin.
  - Inconspicuous nucleoli.
- **Absence of mitoses** (rare in benign nevi; if present, confined to superficial dermis).
- **No deep mitoses** (a red flag for melanoma).
- **Lack of necrosis** (suggests malignancy).



What is dermal maturation of a nevus?



Dispersion of cells at the base

Maturation of intradermal melanocytes: Morphologic transition from

Type A

↓

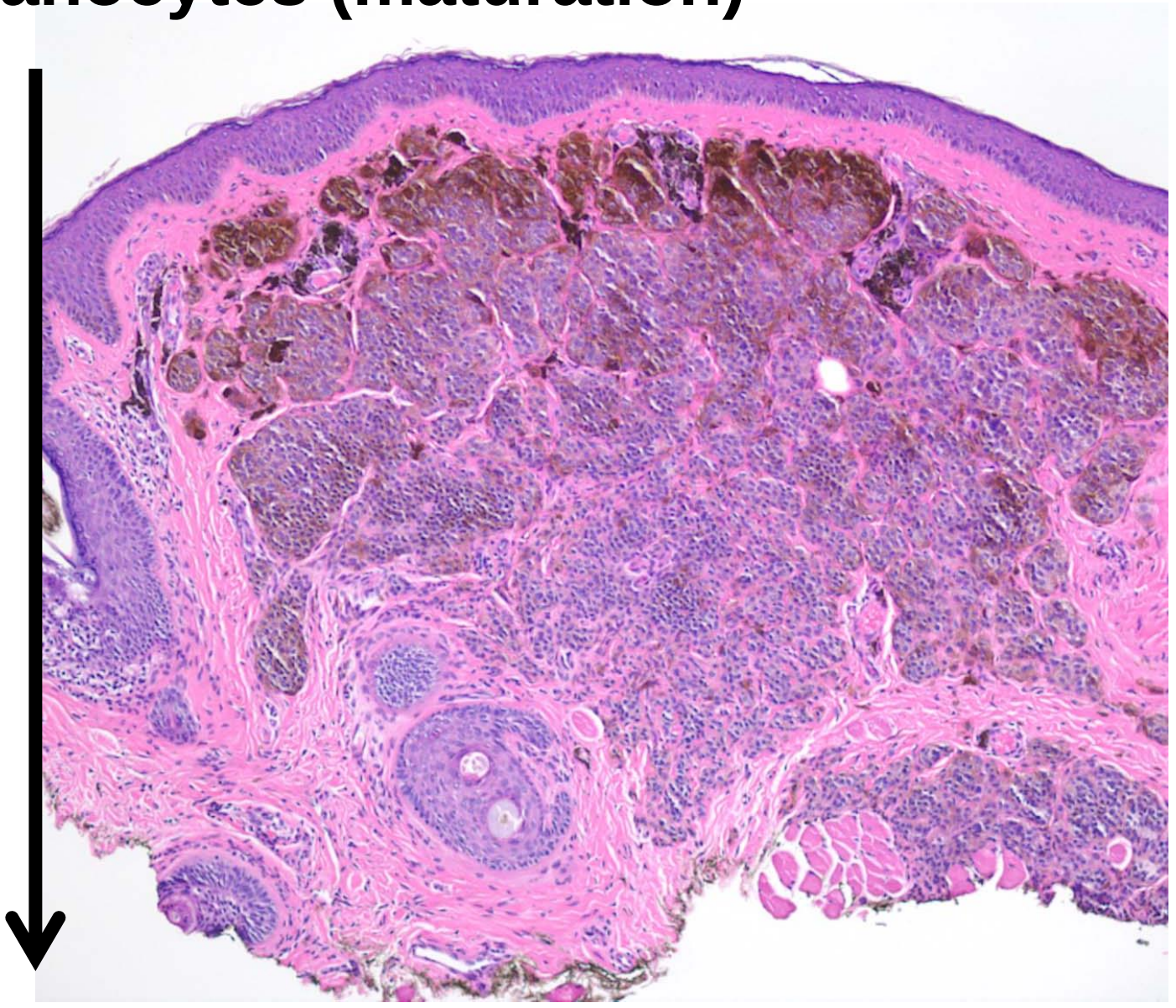
Type B

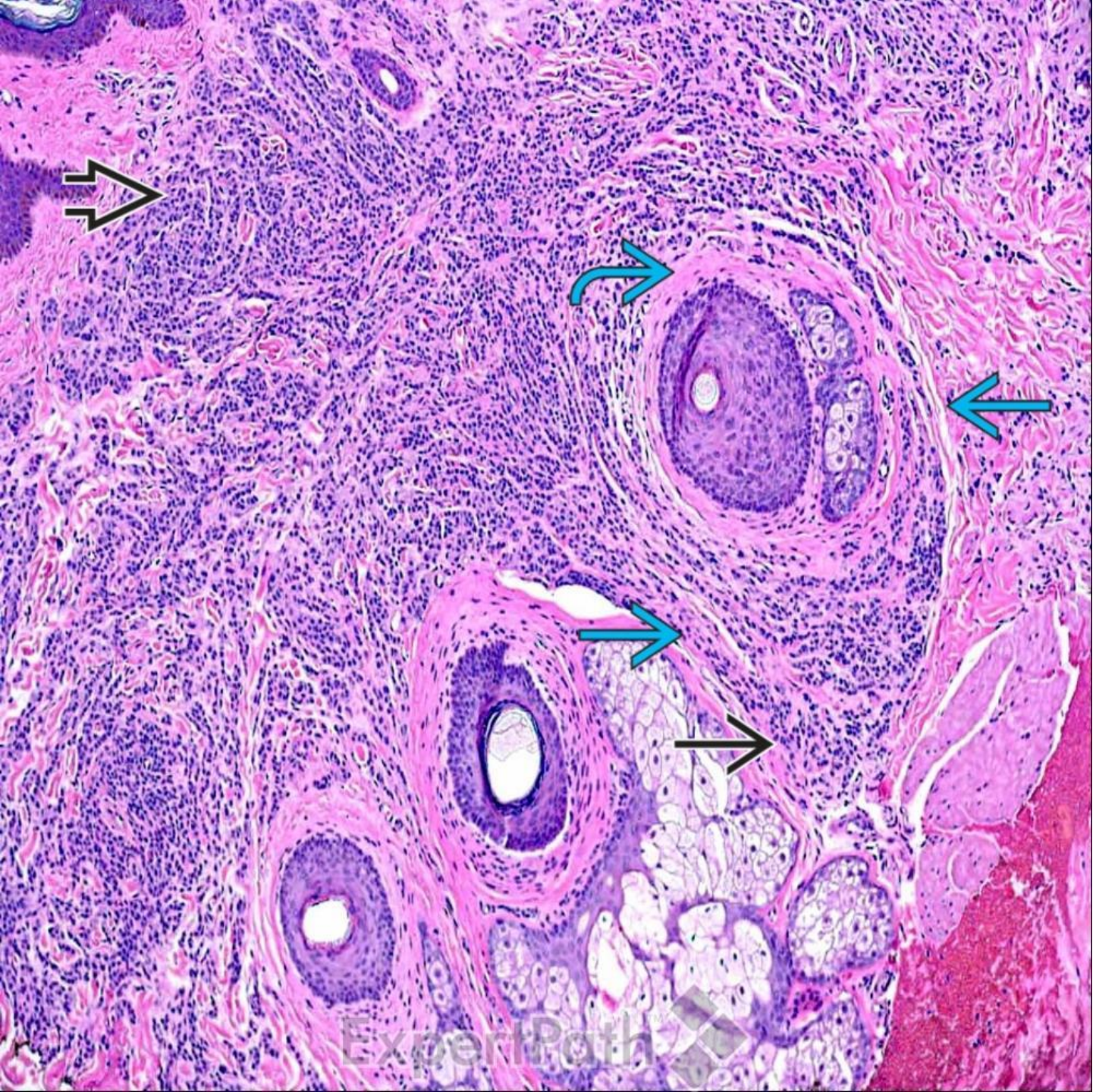
↓

Type C

Morphologic/phenotypic changes associated with dermal descent of melanocytes (maturation)

- Decreased nesting
- Less epithelioid (type-A)
- More lymphocytoid (type-B)
- Spindled (type-C)
- Less pigmented
- IHC: decreased expression of MITF and HMB-45 (gradient)
- IHC: maintained expression of SOX-10 and Melan-A (display shrinking of nuclei and cytoplasm)

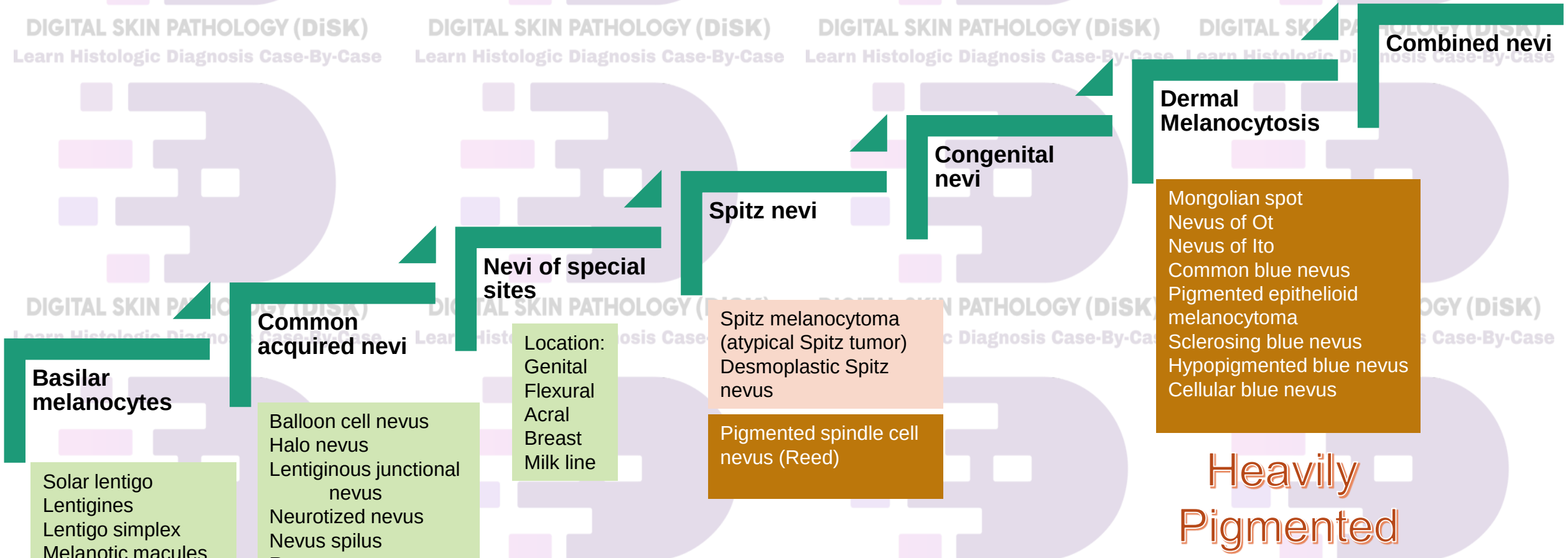


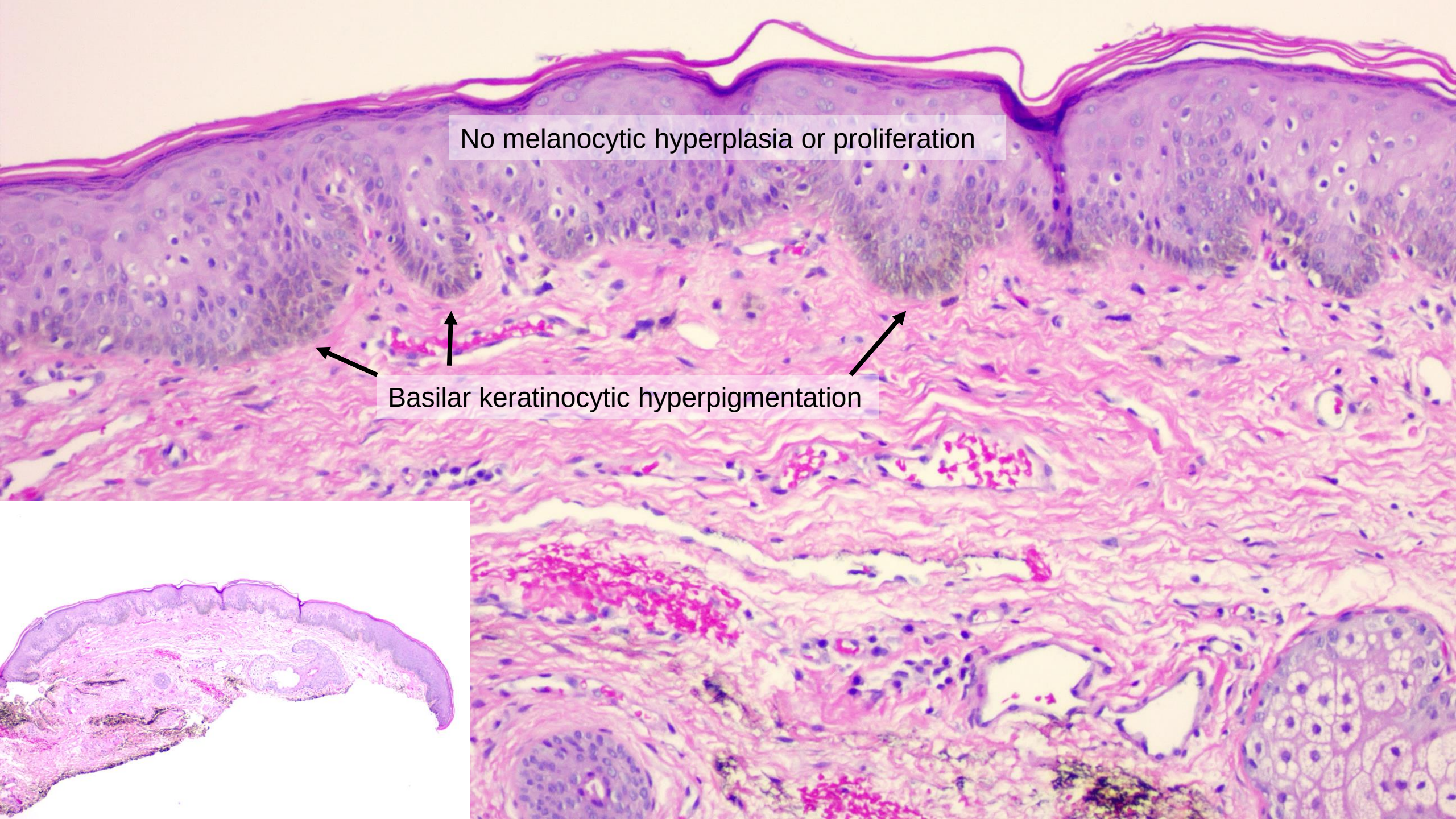


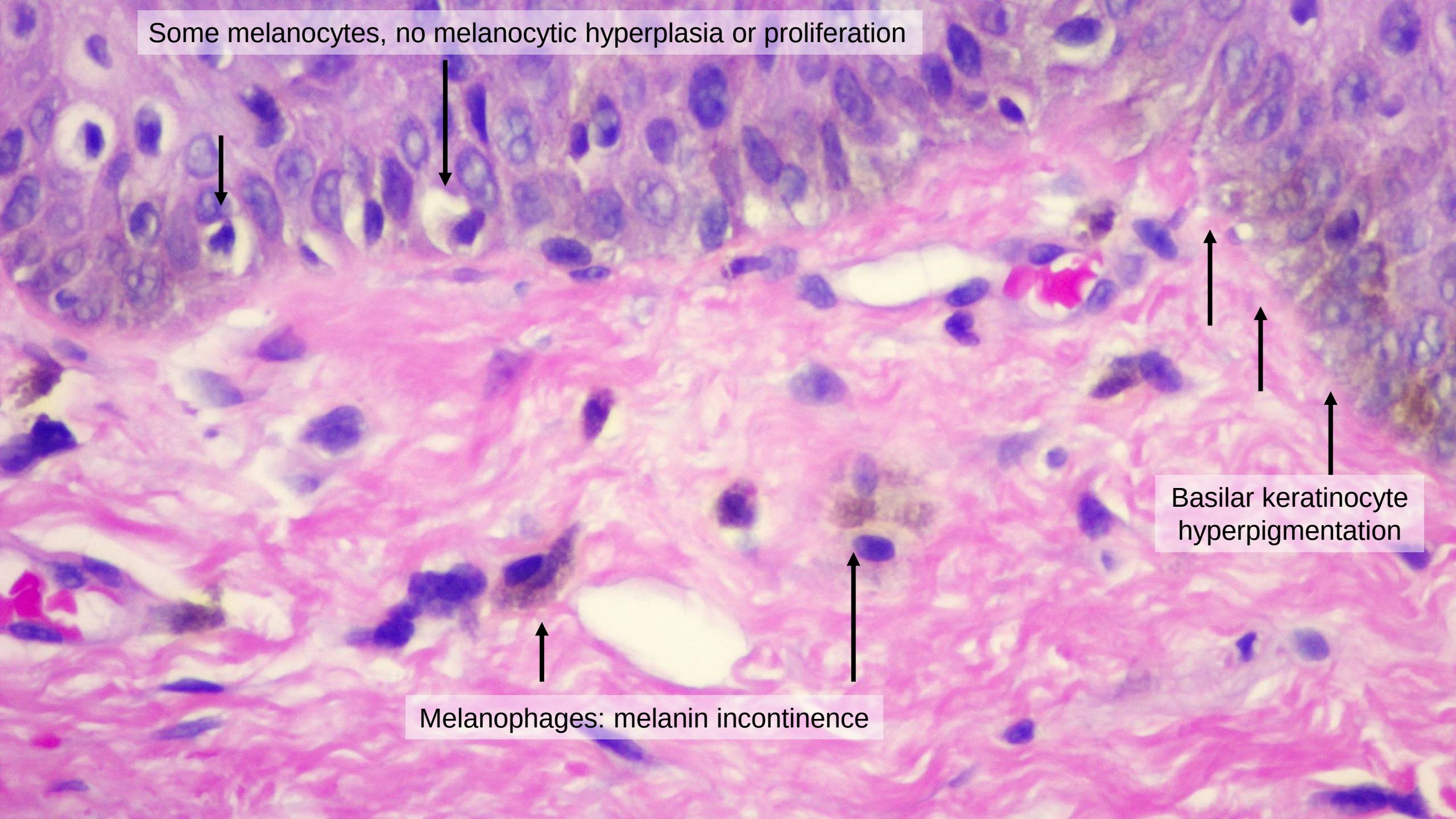
Maturation of intradermal melanocytes: morphology transition from type A → B → C

Cells extend down follicles (cyan solid arrow) and neurovascular bundles (not shown). The nevus cells tightly wrap around the fibrous sheath (cyan curved arrow) without invading it. Cells mature with increasing dermal depth. Type B nevus cells get smaller from superficial (black open arrow) to deeper (black solid arrow) dermis.

Histologic classification of melanocytic nevi based on morphologic complexity




No melanocytic hyperplasia or proliferation
Basilar keratinocytic hyperpigmentation


Some melanocytes, no melanocytic hyperplasia or proliferation
Basilar keratinocyte hyperpigmentation
Melanophages: melanin incontinence

Clinical Information: 40-year-old female. None provided.

DIAGNOSIS:

Vulva, 3:00, Biopsy:

- Genital melanotic macule.

Teaching Points:

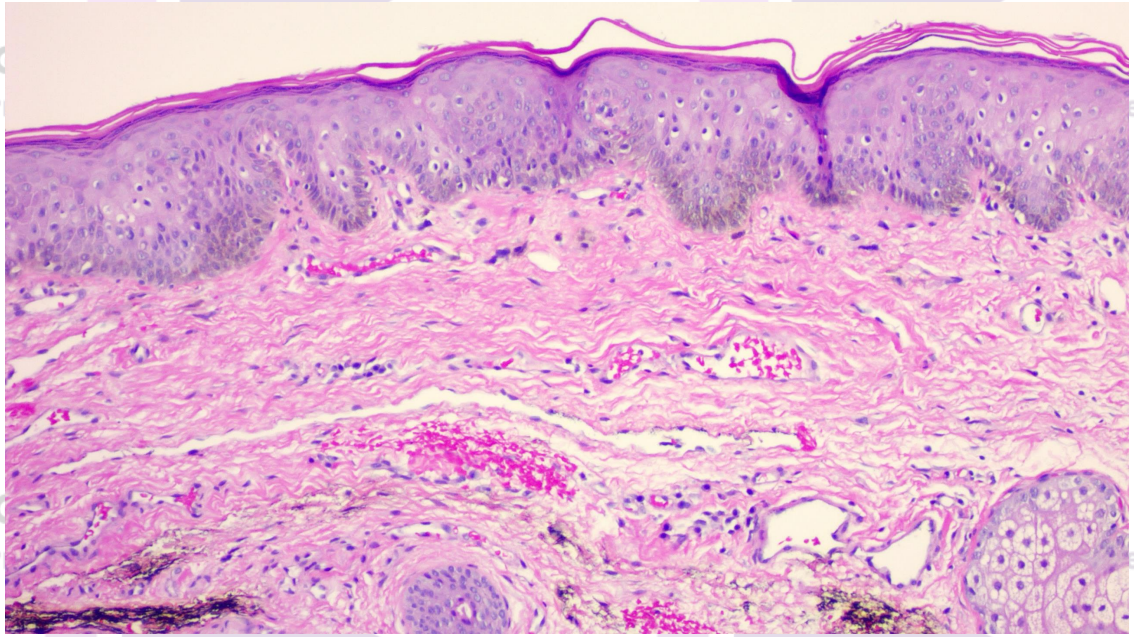
Don’t overinterpret the number of epidermal or genital epithelial melanocytes

SOX-10 IHC may be helpful, MART-1 or Melan-A may mislead to over interpret the number of melanocytes

Melanotic macule is a benign pigmented lesion due to basal layer hyperpigmentation without melanocytic proliferation.

No nests, no atypia, no dermal melanocytes → Distinguishes it from nevi/melanoma.

Biopsy may be needed if clinical suspicion for melanoma (e.g., irregular borders, recent change).



Minimal Diagnostic Criteria:

No melanocytic hyperplasia or neoplasia (proliferation)

Lentiginous hyperpigmentation of basilar keratinocytes

Dermal melanin incontinence

Differential Diagnosis:

Lentigo simplex: May look similar but shows elongated rete ridges.

Solar lentigo (sun-induced): Epidermal hyperplasia, more common in sun-exposed skin.

Early melanoma in situ (mucosal): Atypical melanocytes with pagetoid spread (requires careful evaluation).

Post-inflammatory hyperpigmentation: Clinical history of prior inflammation, dermal melanophages.

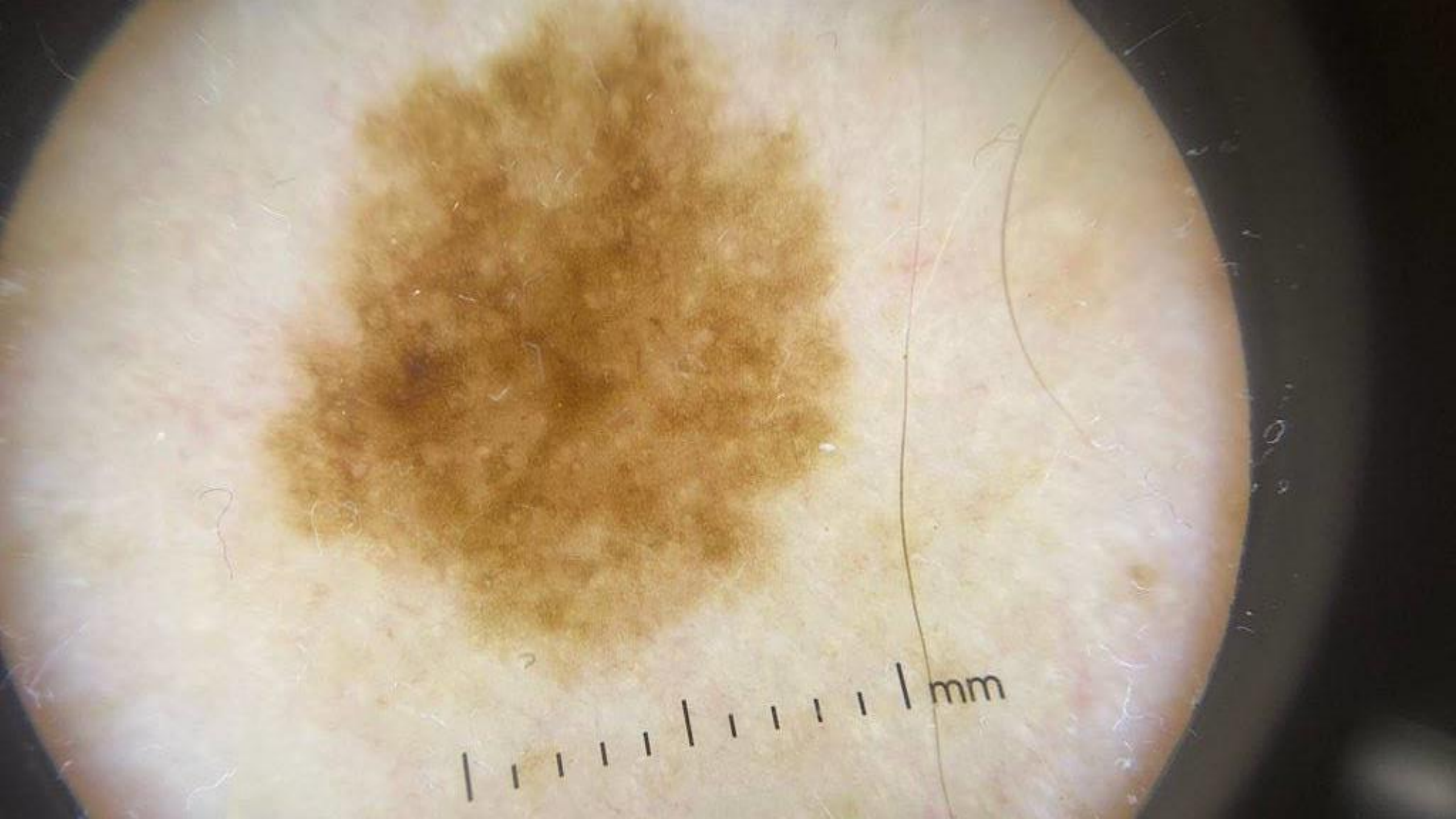
Summary: Melanotic Macule

Clinical Features

- **Appearance**:
  - Small, **solitary**, well-circumscribed **brown to black macule** (flat lesion).
  - Usually **<5 mm** but can be larger in mucosal cases.
- **Location**:
  - **Mucosal**: Lips (vermilion border), oral mucosa, genitalia (penis, vulva).
  - **Cutaneous**: Any site (less common than mucosal).
- **Demographics**:
  - Adults (most common), but can occur at any age.
  - No strong gender predilection.
- **Behavior**:
  - **Benign**, stable over time.
  - No malignant potential (unlike melanoma in situ on mucosa).

Histologic Features

- **Epidermis**:
  - **Hyperpigmentation of basal keratinocytes** (increased melanin).
  - **No melanocytic proliferation** (key difference from melanocytic lesions like nevi or melanoma).
  - **No atypia or pagetoid spread**.
- **Melanocytes**:
  - **Normal in number or slightly increased** (but not forming nests).
  - **No cytologic atypia** (small, uniform nuclei).
- **Dermis**:
  - **No dermal melanocytes** (unlike nevi).
  - **Melanin incontinence** (melanin in dermal macrophages).
  - **No stromal reaction or fibrosis** (unlike lichenoid keratosis or post-inflammatory pigmentation).
- **Special Stains (if needed)**:
  - **Fontana-Masson**: Highlights melanin.
  - **Melan-A/MART-1 or HMB45**: Confirms melanocytes are **not increased** (helps rule out melanoma in situ).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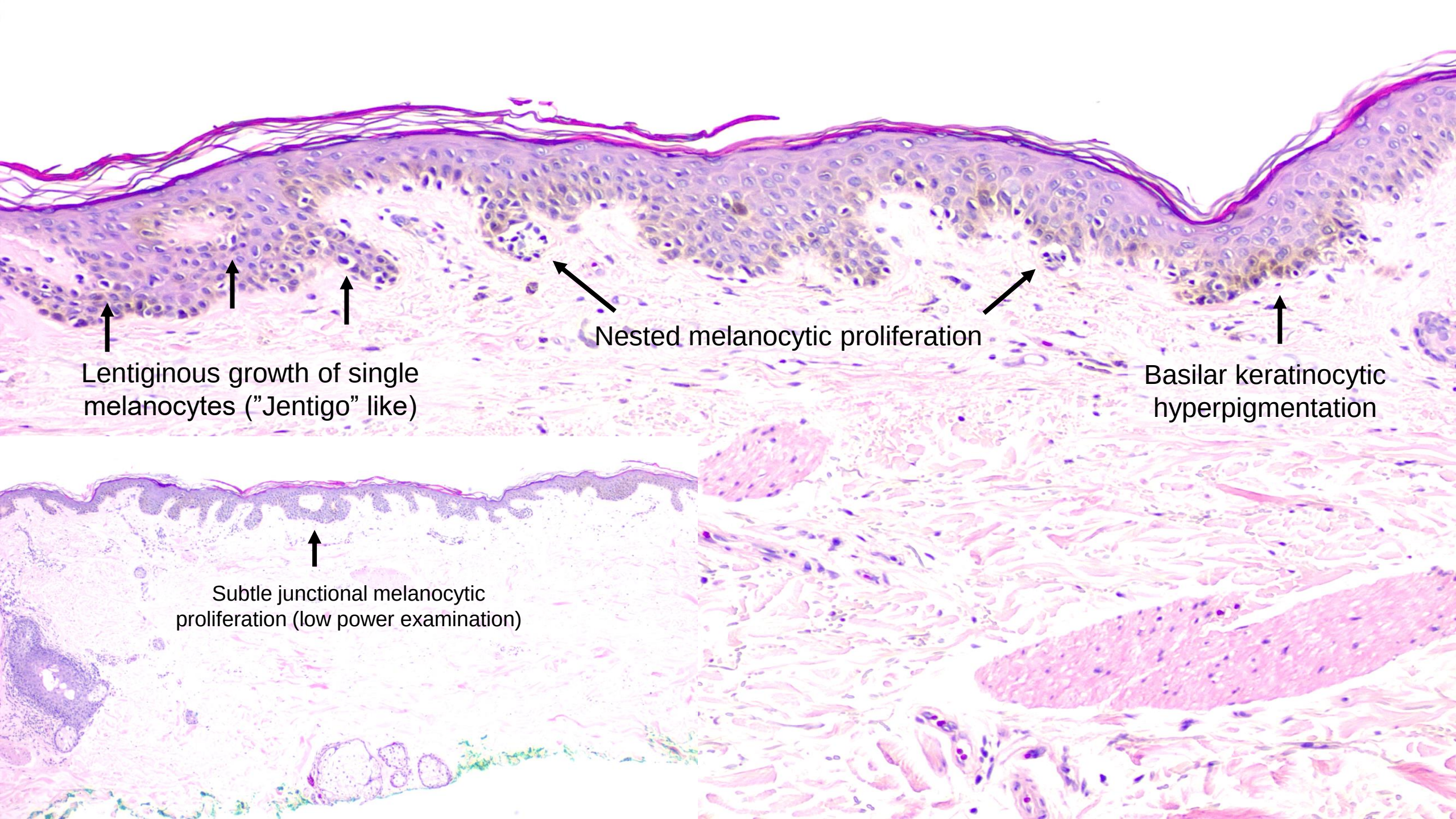
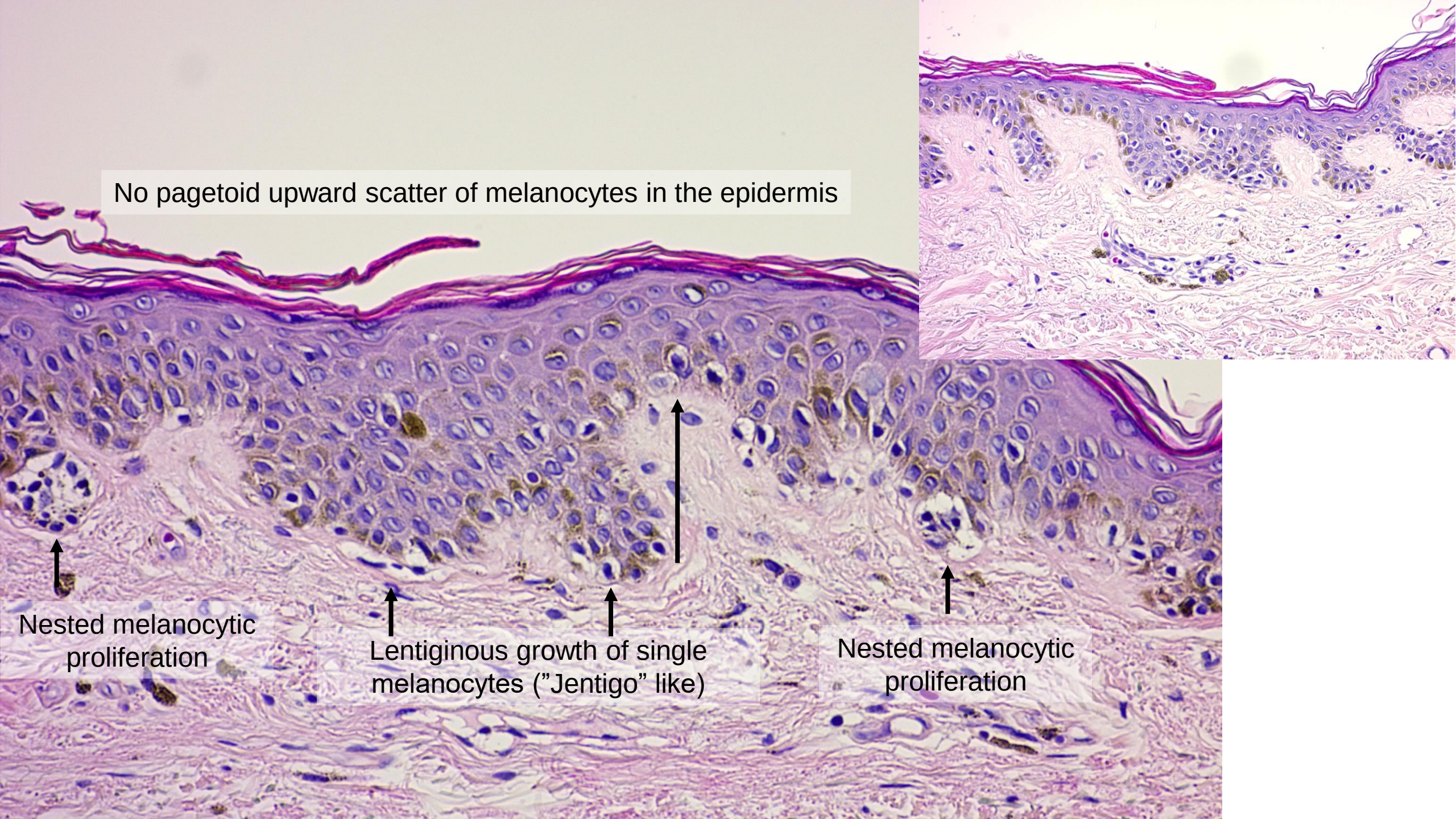
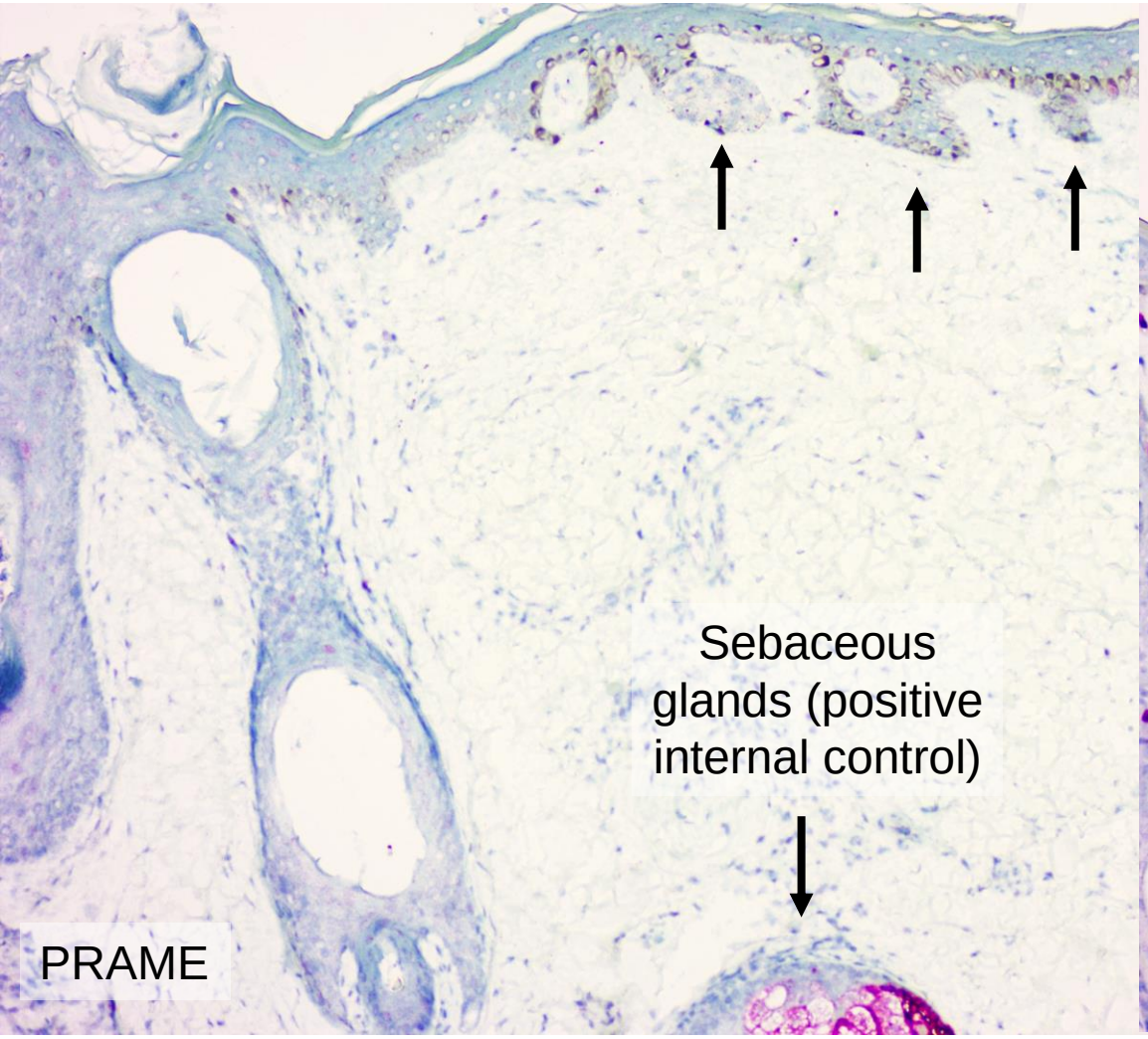
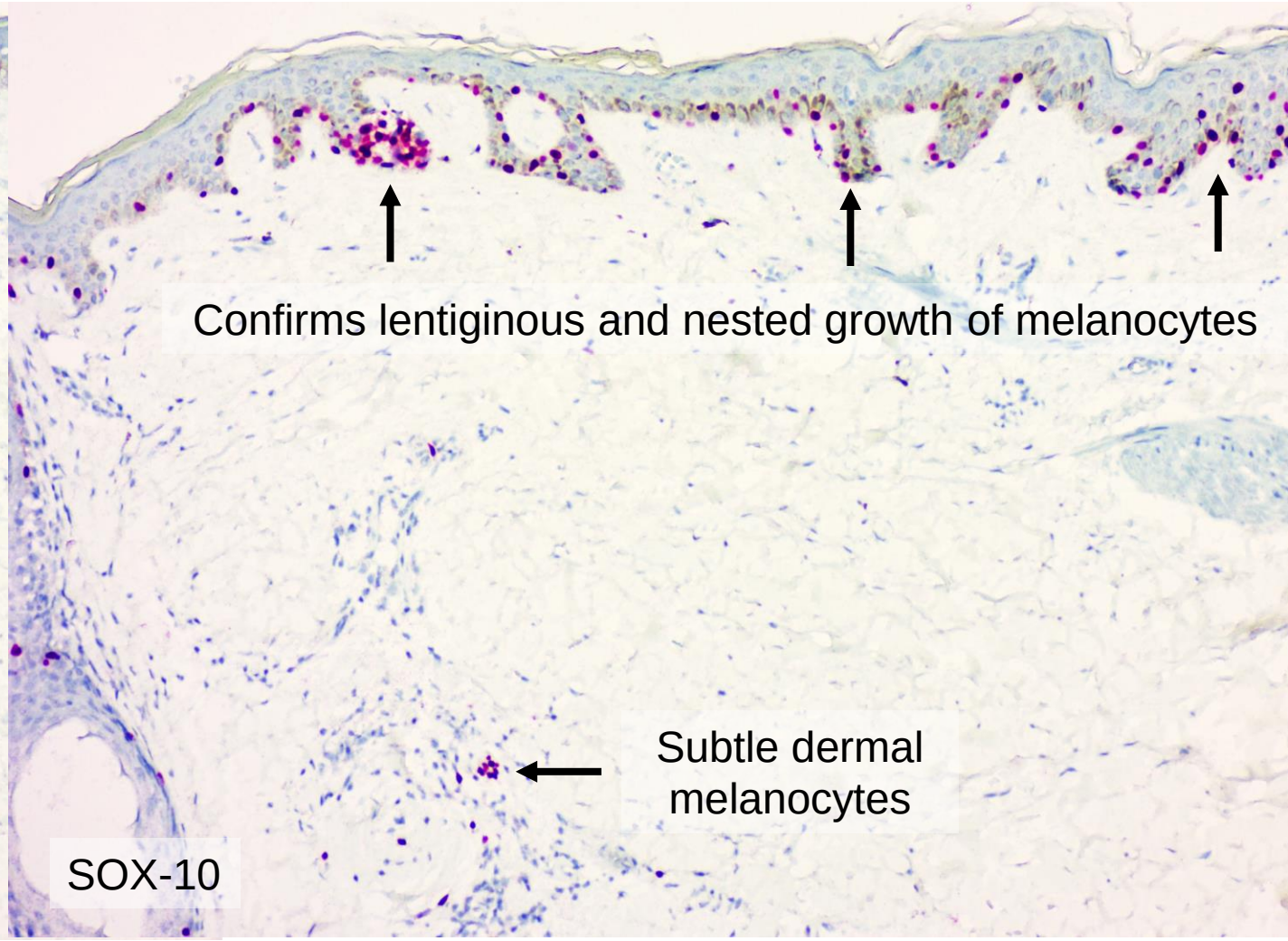

Lentiginous growth of single melanocytes (”Jentigo” like)
Nested melanocytic proliferation
Basilar keratinocytic hyperpigmentation
Subtle junctional melanocytic proliferation (low power examination)


No pagetoid upward scatter of melanocytes in the epidermis
Nested melanocytic proliferation
Lentiginous growth of single melanocytes (”Jentigo” like)
Nested melanocytic proliferation

Reassuring immunohistochemical results





Clinical Information: 72-year-old male; 14 mm x 13 mm slightly irregularly bordered tan brown patch. Solar lentigo vs. LM vs. MMIS vs. Other

DIAGNOSIS:

Skin, Right Upper Back, Shave Biopsy:

- Broad lentiginous compound melanocytic nevus, without atypia, focally extending to tissue edges.

Teaching Points:

- Lentiginous compound nevus is a benign melanocytic proliferation with lentiginous epidermal hyperplasia and dermal nests showing maturation.
- No atypia, no deep mitoses, no pagetoid spread → Helps exclude melanoma.
- If dysplastic features are present, consider dysplastic nevus (but still benign unless severe atypia).

Differential Diagnosis:

Dysplastic Nevus:

Architectural disorder, bridging rete ridges, lamellar fibrosis.

Cytologic atypia (but still has maturation).

Lentigo Maligna (Melanoma In Situ):

Atypical melanocytes with pagetoid spread.

No dermal nests (unless invasive).

Superficial Spreading Melanoma:

Asymmetry, pagetoid spread, deep mitoses, no maturation.

Junctional or Compound Nevus (Non-Lentiginous):

Lacks prominent lentiginous hyperplasia.

Summary: lentiginous compound nevus

Clinical Features

- Appearance:
  - Small, well-circumscribed, brown to black macule or slightly raised papule.
  - Typically, 5–10 mm in diameter.
- Location:
  - Most common on trunk, extremities, or face.
  - Less common on palms, soles, or mucosal surfaces.
- Demographics:
  - Usually acquired (childhood to early adulthood).
- Behavior:
  - Benign, stable over time.
  - Very low risk of malignant transformation (unless dysplastic features are present).

Histologic Features

1. Architectural Features (Low Power)

   Symmetry with sharp lateral borders.

   Lentiginous (linear) melanocytic hyperplasia along the basal layer.

   Nested melanocytes at the DEJ.

   Dermal component with maturation.

   Elongated rete ridges (due to lentiginous growth pattern).

2. Cytologic Features (High Power)

   Uniform melanocytes with small, round nuclei and inconspicuous nucleoli.

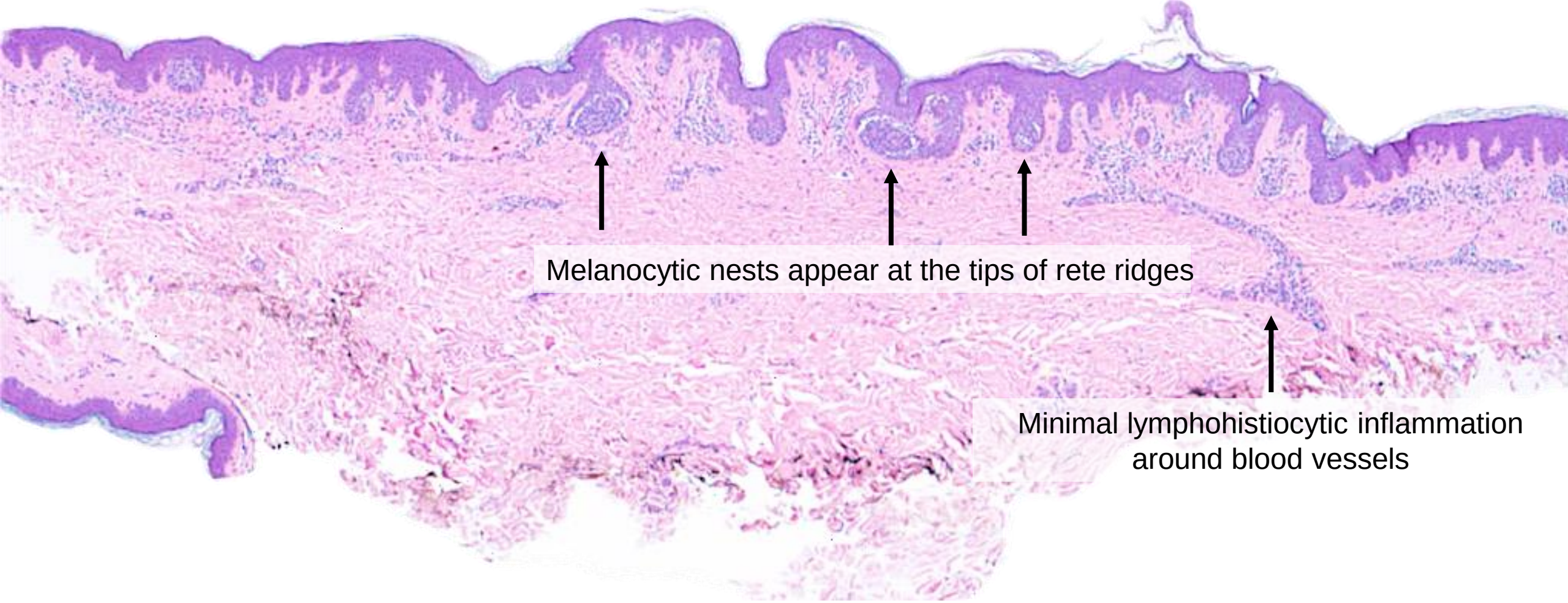
   No significant atypia or mitoses (if present, rare and superficial).

   No pagetoid spread (unlike melanoma).

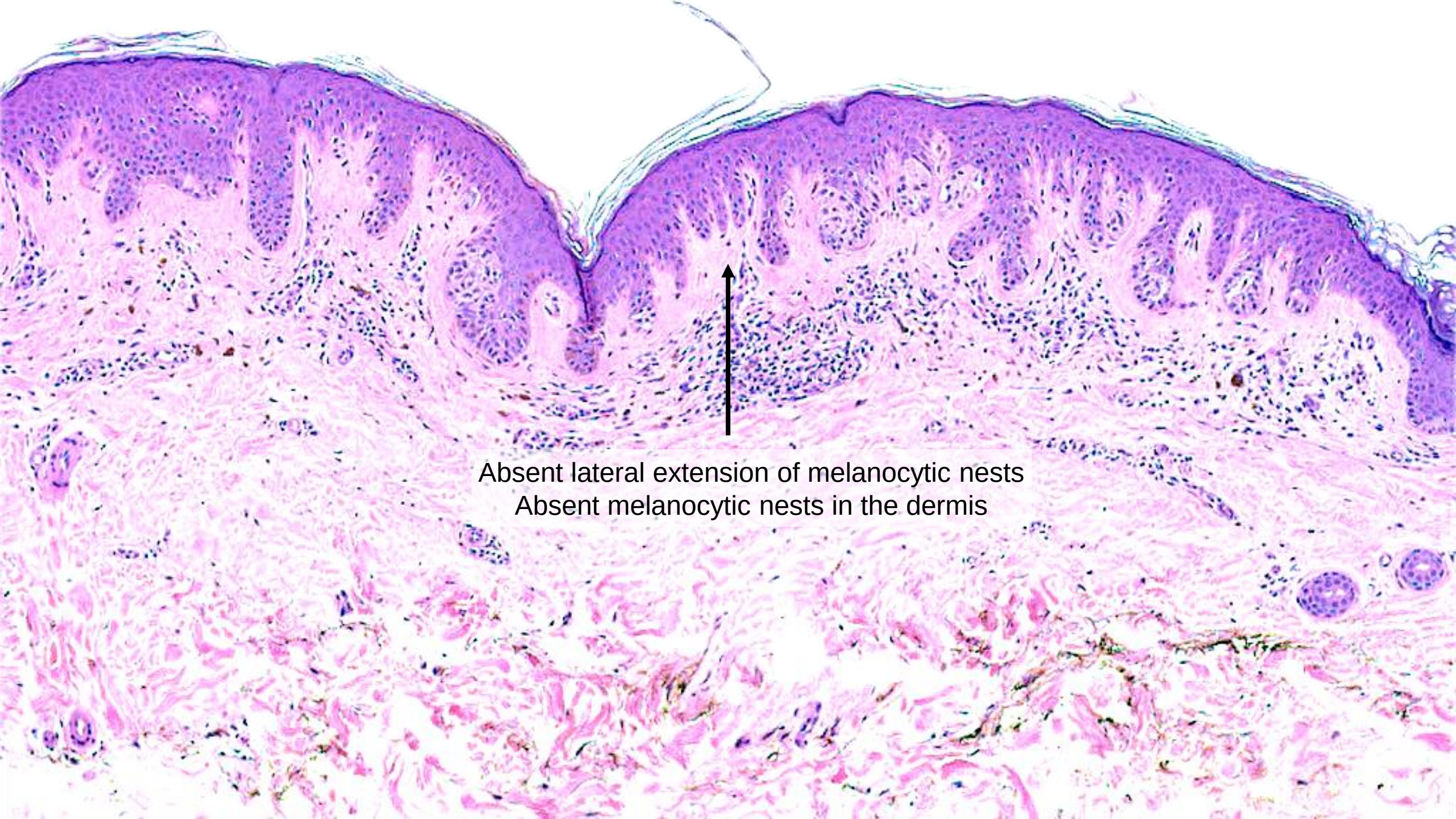
3. Stroma

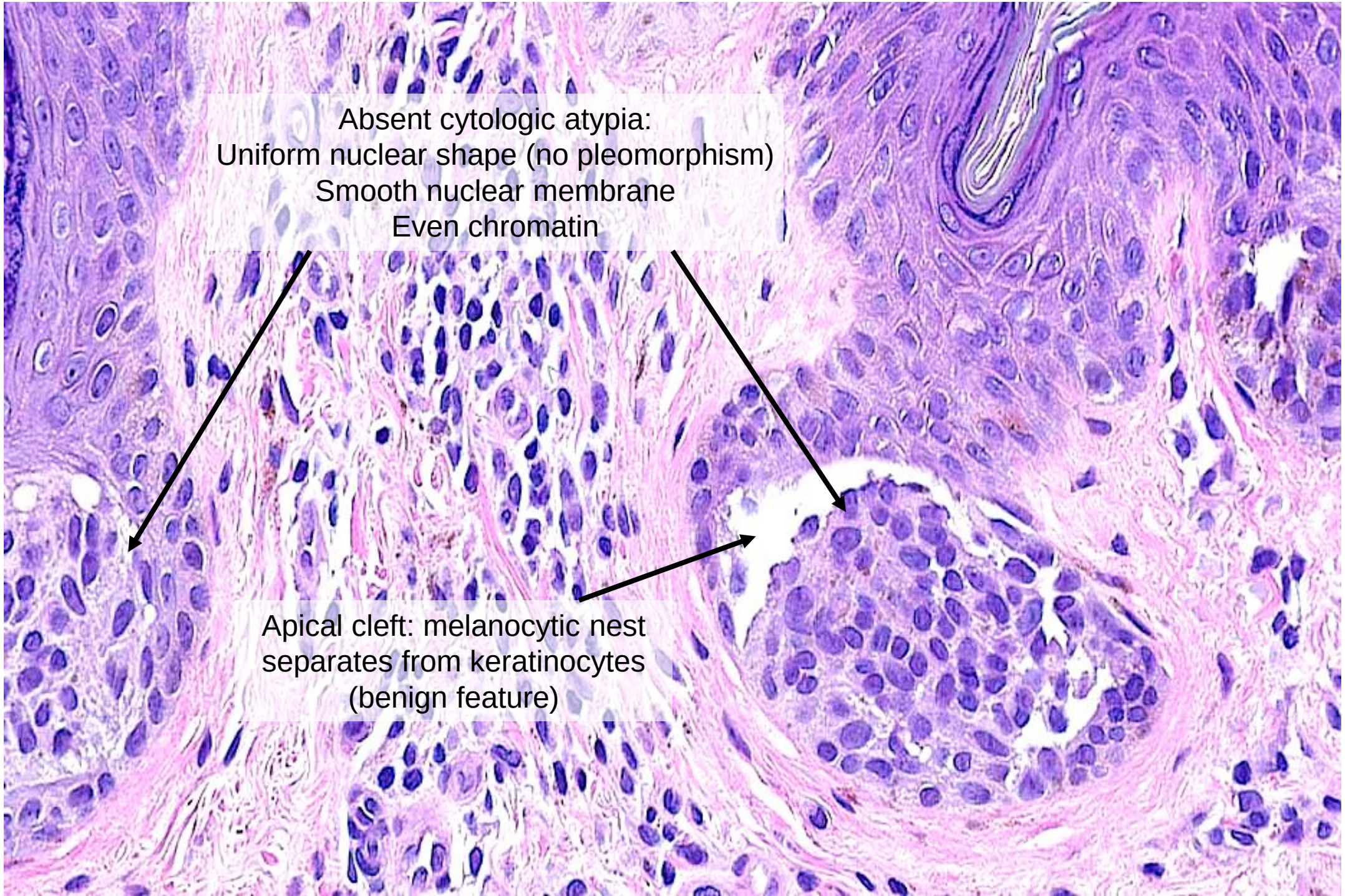
   Fibrosis or lamellar fibroplasia (especially if dysplastic features are present).

   Melanin incontinence (macrophages with pigment).

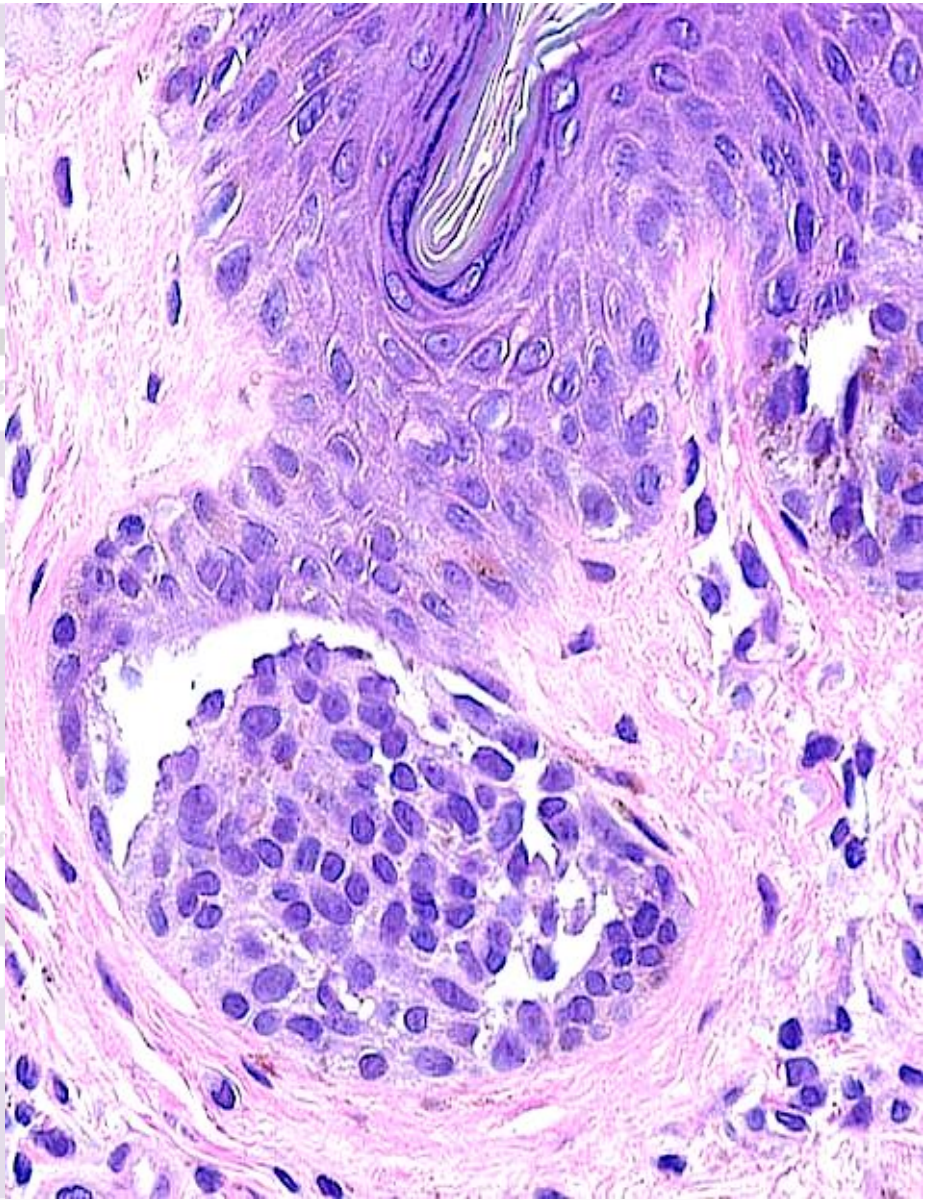


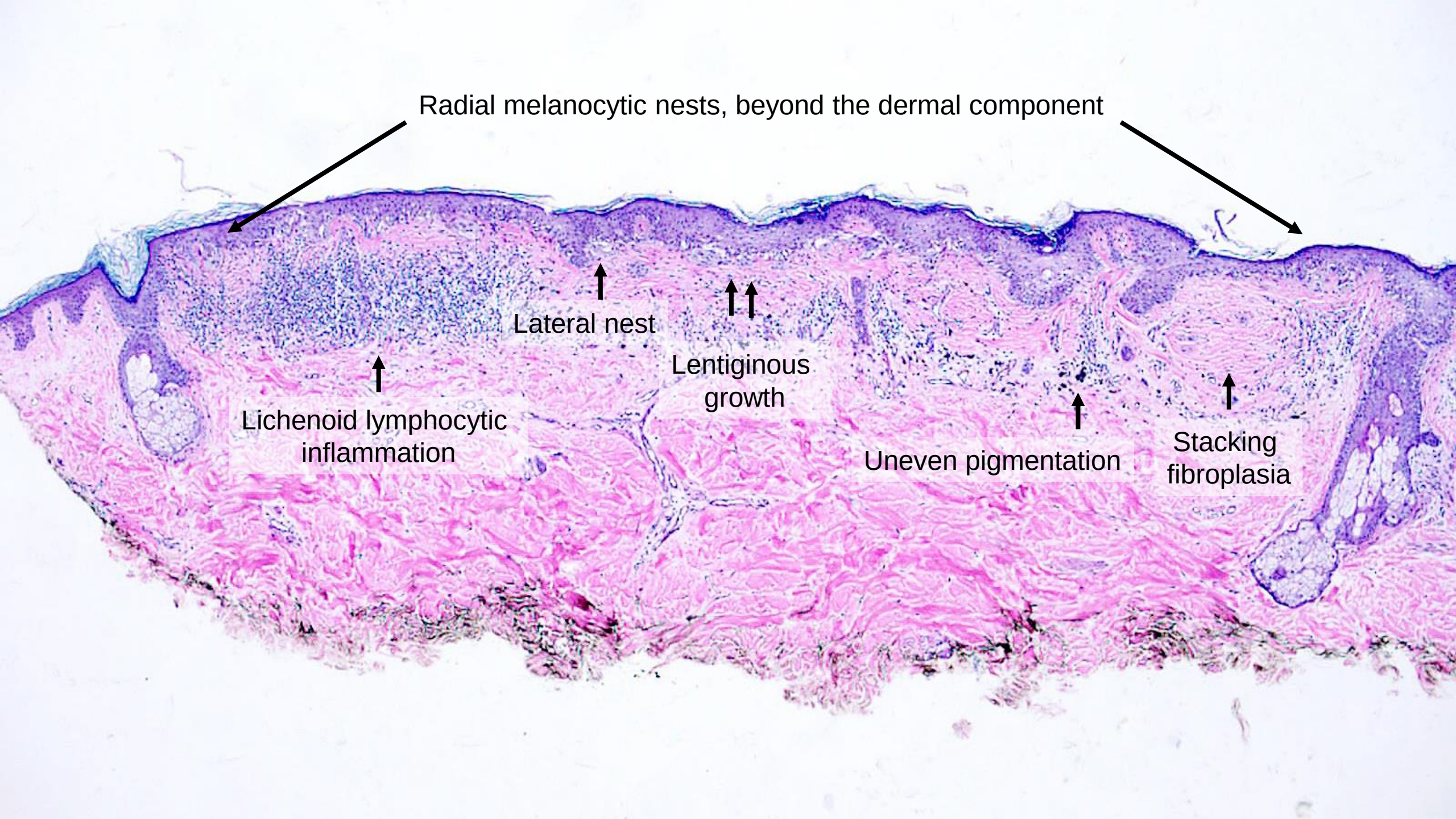
Well defined junctional melanocytic proliferation
Begins with a melanocytic nest and ends with a nest
Overall architectural symmetry

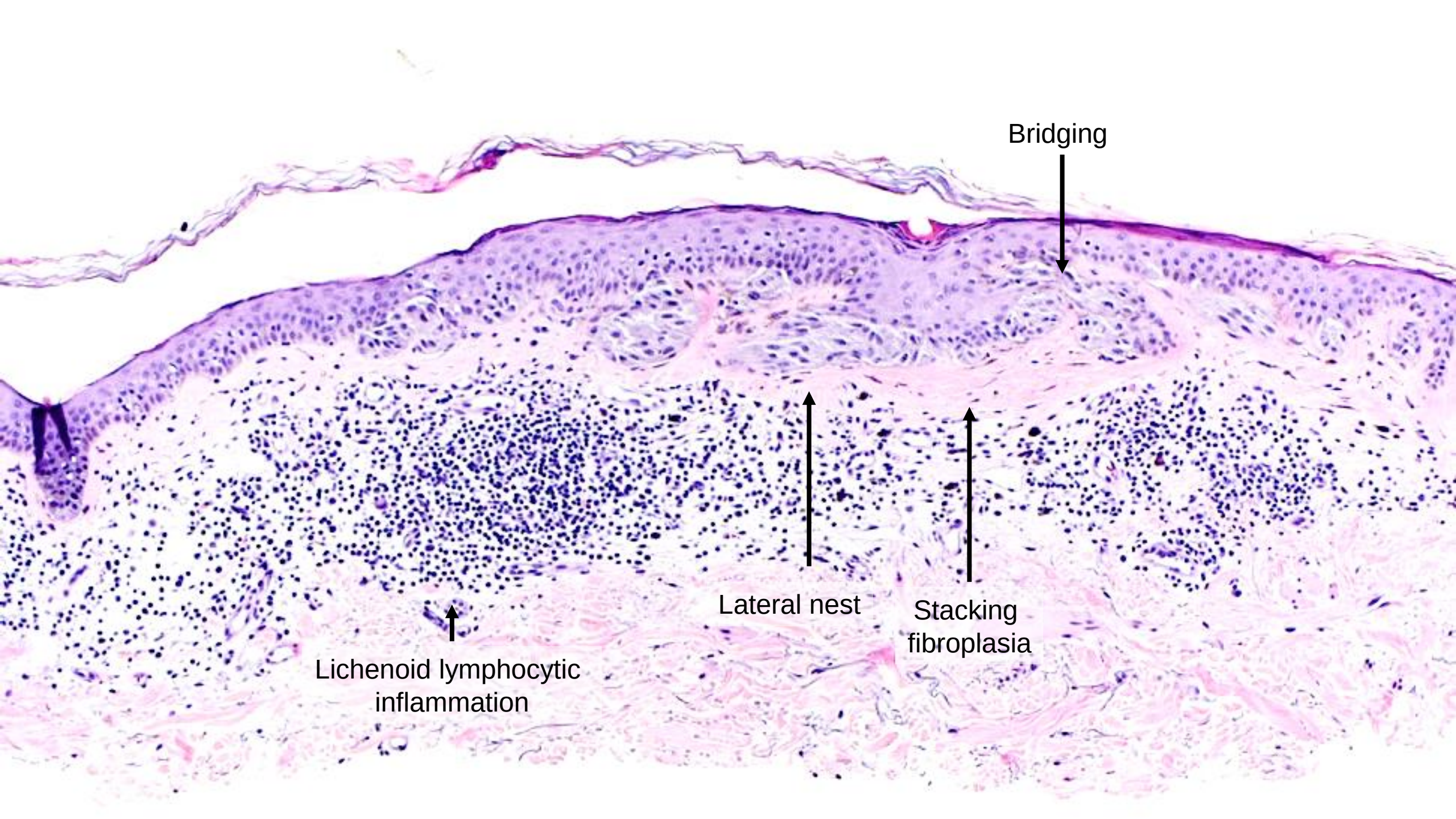

Absent lateral extension of melanocytic nests
Absent melanocytic nests in the dermis

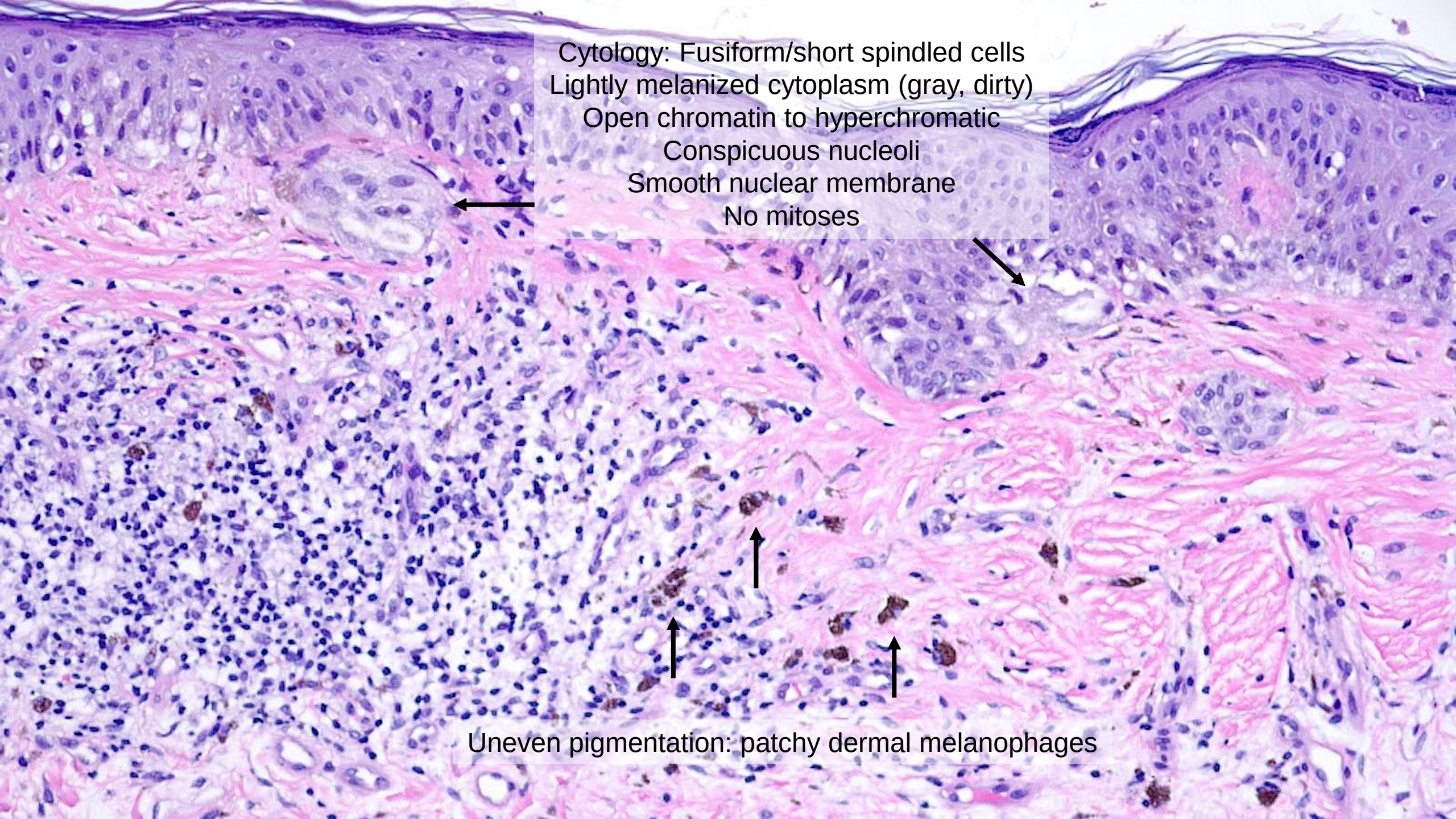

Absent cytologic atypia:
Uniform nuclear shape (no pleomorphism)
Smooth nuclear membrane
Even chromatin
Apical cleft: melanocytic nest
separates from keratinocytes
(benign feature)

- **Clinical Information:** 41F Right buttock, 6 mm dark brown, r/o atypia
- **DIAGNOSIS:**
  - SKIN, RIGHT BUTTOCK, BIOPSY:
    - JUNCTIONAL MELANOCYTIC NEVUS WITH FEATURES OF SPECIAL SITE, EDGES FREE OF INVOLVOMENT IN EXAMINED SECTIONS.
- **Teaching Points:**
  - Melanocytic nevi may show mild histologic architectural atypia
  - The atypia is not neoplastic, rather attributed to the anatomic site (Breast, axilla, ear, and scalp)
  - No further treatment is needed, if the lesion is optimally biopsied
- **Minimal Diagnostic Criteria:**
  - Mild histologic architectural atypia
  - May present as junctional or compound architecture
  - No cytologic atypia or dysplastic features
- **Differential Diagnosis:**
  - Dysplastic junctional melanocytic nevus
    (no lateral extension of nests, no bridging of nests)

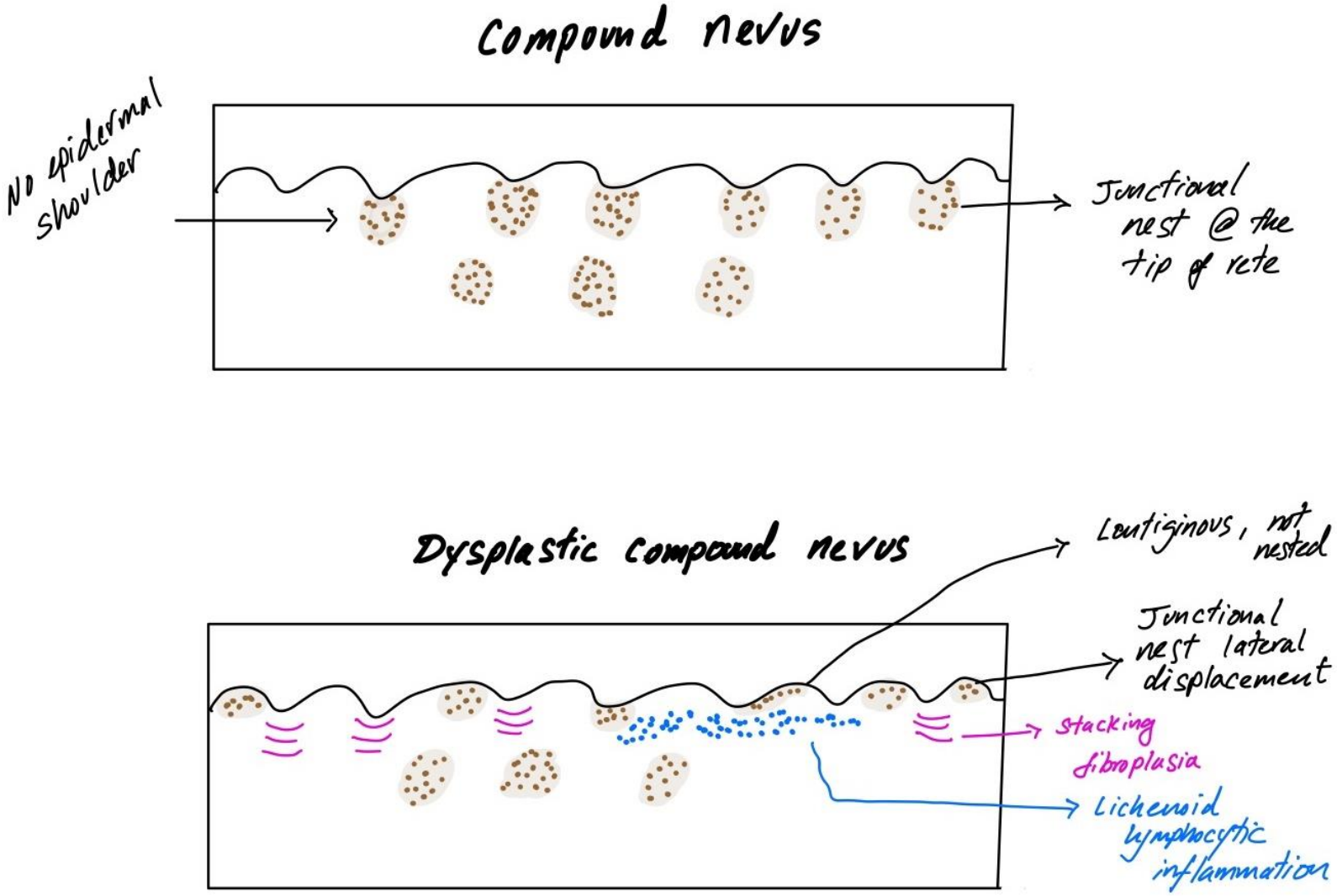



Radial melanocytic nests, beyond the dermal component
Lateral nest
Lentiginous growth
Lichenoid lymphocytic inflammation
Uneven pigmentation
Stacking fibroplasia


Bridging
Lateral nest
Stacking fibroplasia
Lichenoid lymphocytic inflammation


Cytology: Fusiform/short spindled cells
Lightly melanized cytoplasm (gray, dirty)
Open chromatin to hyperchromatic
Conspicuous nucleoli
Smooth nuclear membrane
No mitoses
Uneven pigmentation: patchy dermal melanophages

Dysplastic nevus: Architectural atypia



- Junctional nests
  - Not at the tip of rete
  - Laterally displaced
  - Bridging
- Growth pattern:
  - Lentiginous >> nested
- Stacking fibroplasia
- Lichenoid lymphocytic inflammation
- Cytology:
  - Lightly melanized cytoplasm
  - Nuclear pleomorphism

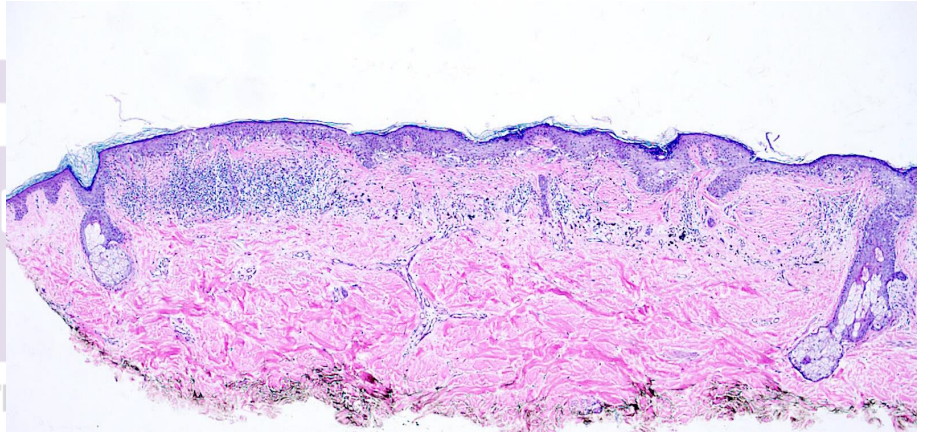
- **Clinical Information:** 38-year-old male with changing mole, rule out dysplasia.

- **DIAGNOSIS:**

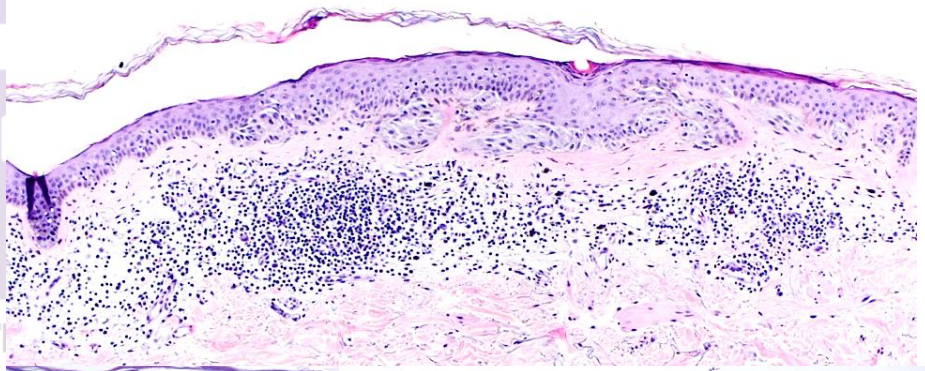
  Skin, Right Upper Back, Shave Biopsy:

  Compound dysplastic melanocytic nevus with moderate-severe atypia and regression, extending to tissue edges.

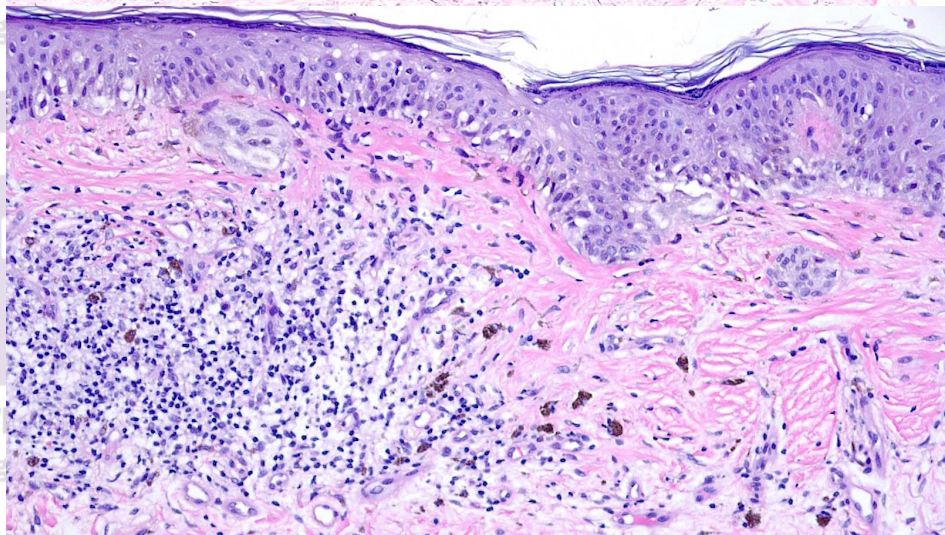
  Comment: Complete removal with clear 3-5 mm margins is recommended.



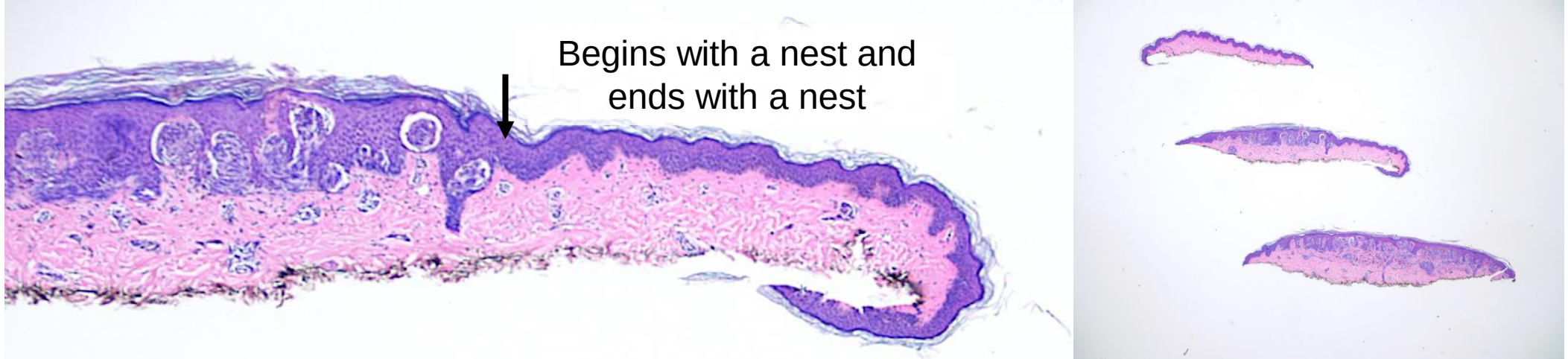
- **Teaching Points:**
  - Be concerned about partially sampled (shave or punch biopsy) nevus with atypia (partial sampling of melanoma on excision)
  - When observing atypia, be mindful of external trauma/irritation and prior biopsy at this site (i.e., recurrent nevus)



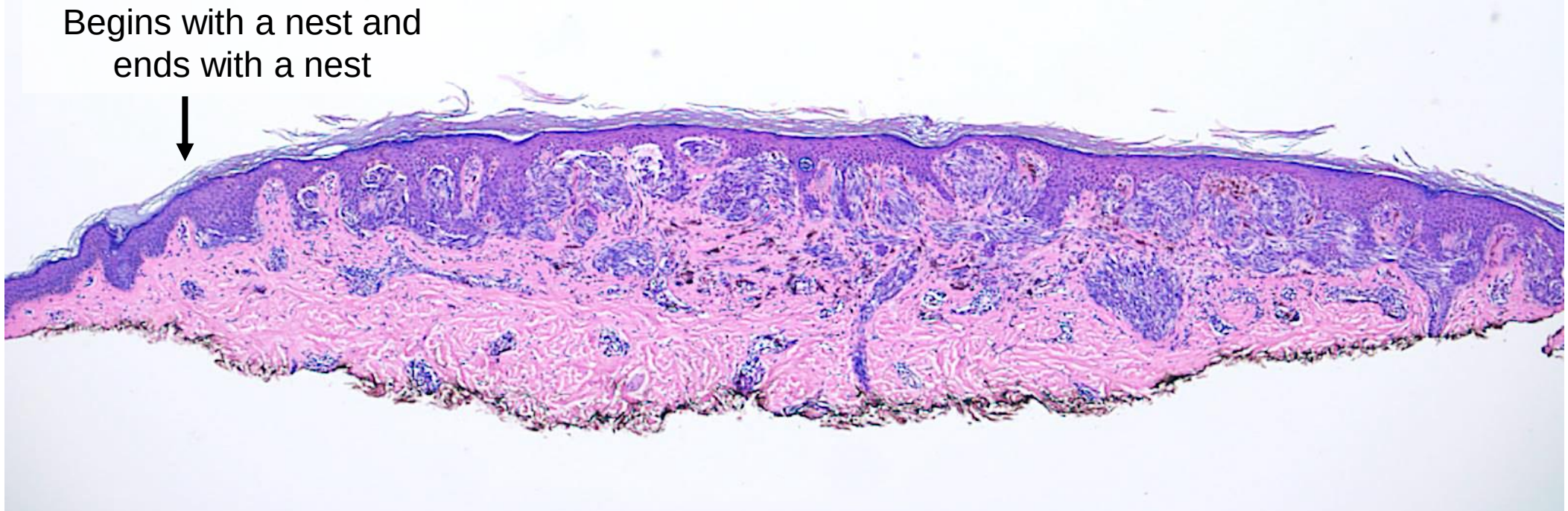
- **Minimal Diagnostic Criteria:**
  - Asymmetric junctional or compound melanocytic neoplasm
  - Radial melanocytic nests, beyond the dermal component (shoulder)
  - Lateral displacement of junctional nests, bridging or lentiginous (single cell) growth
  - Stacking fibroplasia and lichenoid lymphocytic inflammation
  - Cytology: Fusiform/short spindled cells, lightly melanized cytoplasm (gray, dirty), open chromatin to hyperchromatic, conspicuous nucleoli, smooth nuclear membrane, and No mitoses

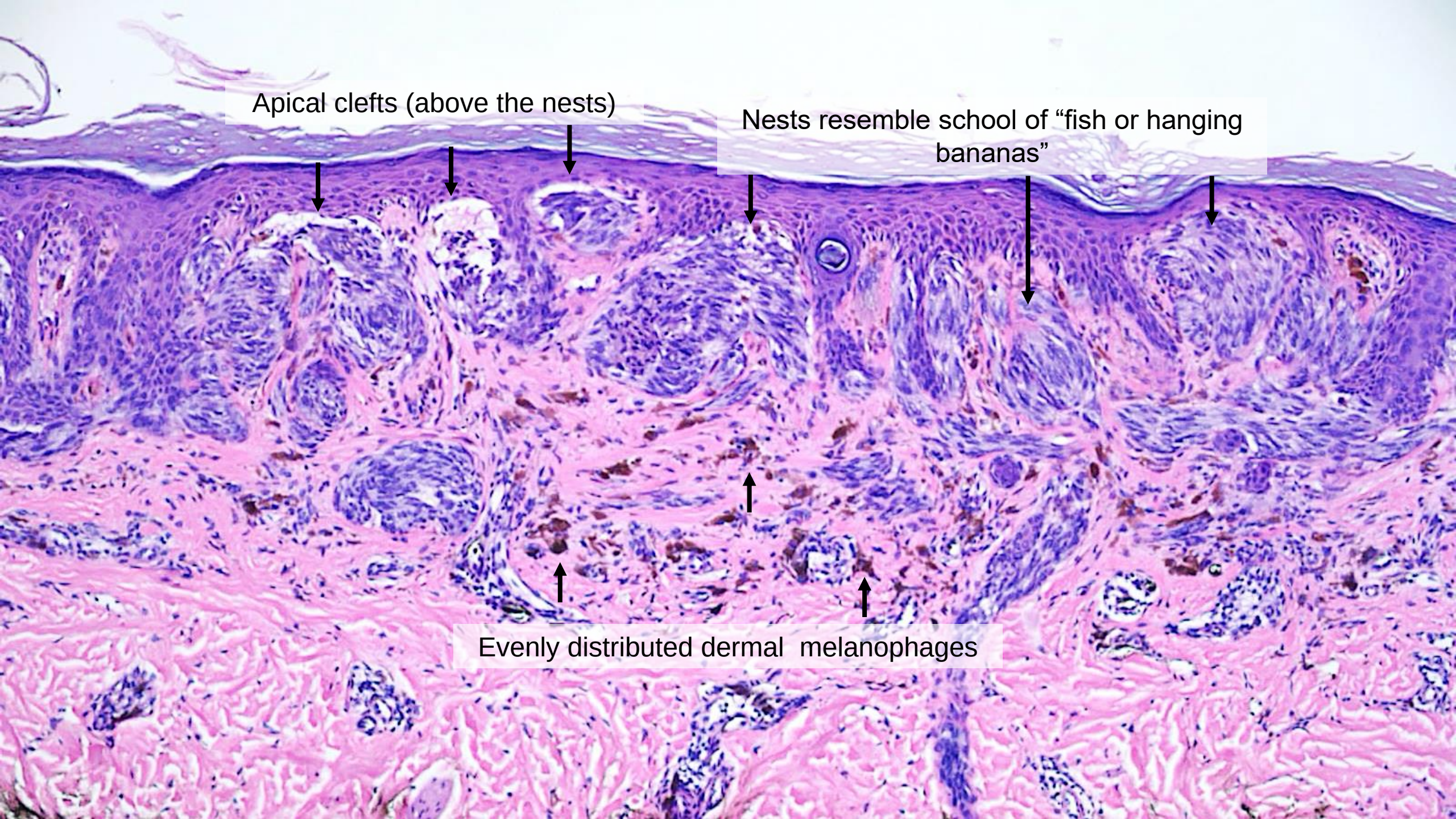


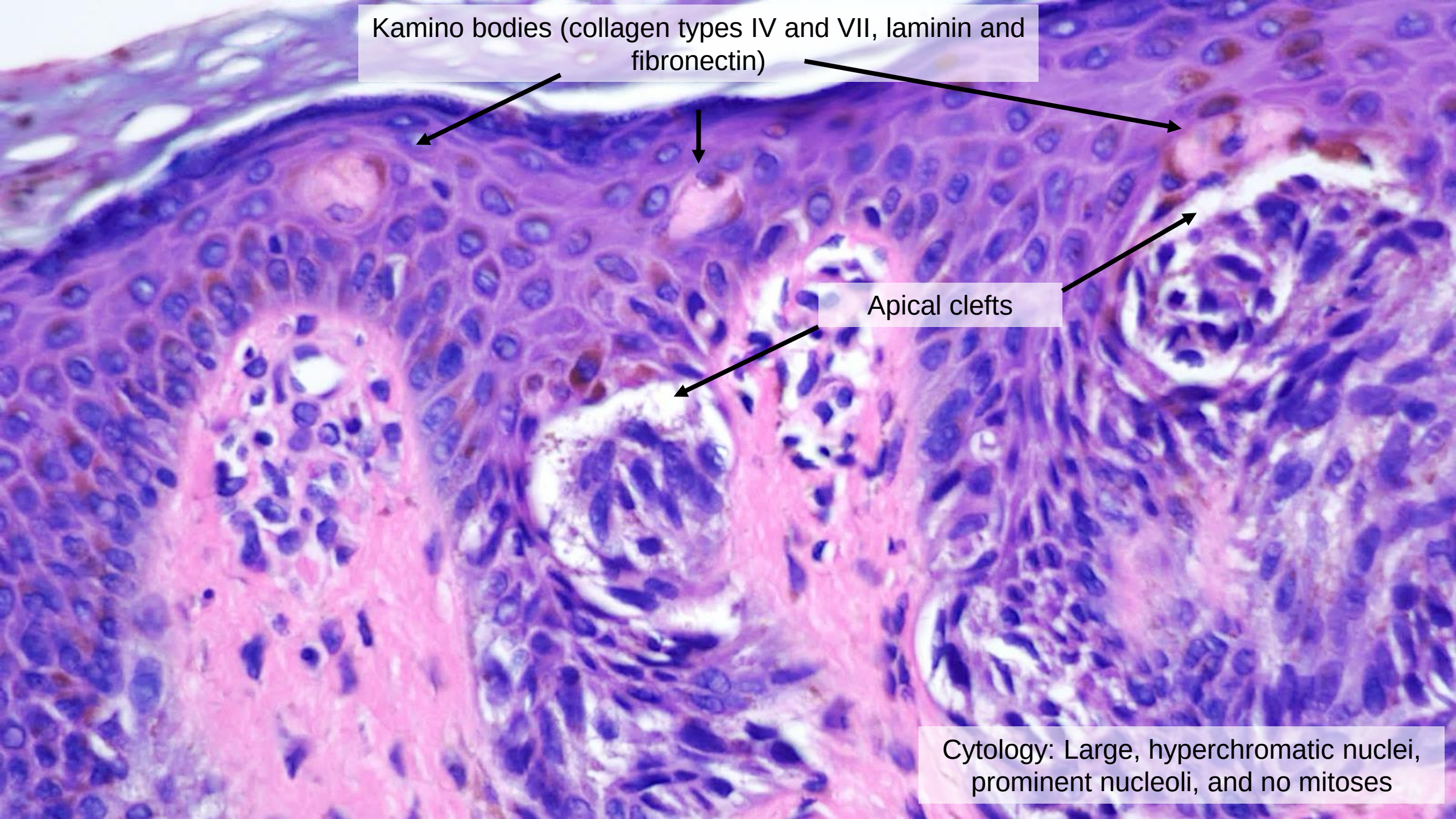
- **Differential Diagnosis:**
  - Halo nevus with atypia
  - Early evolving melanoma



Compound, hypercellular, symmetrical, and well-defined melanocytic neoplasm



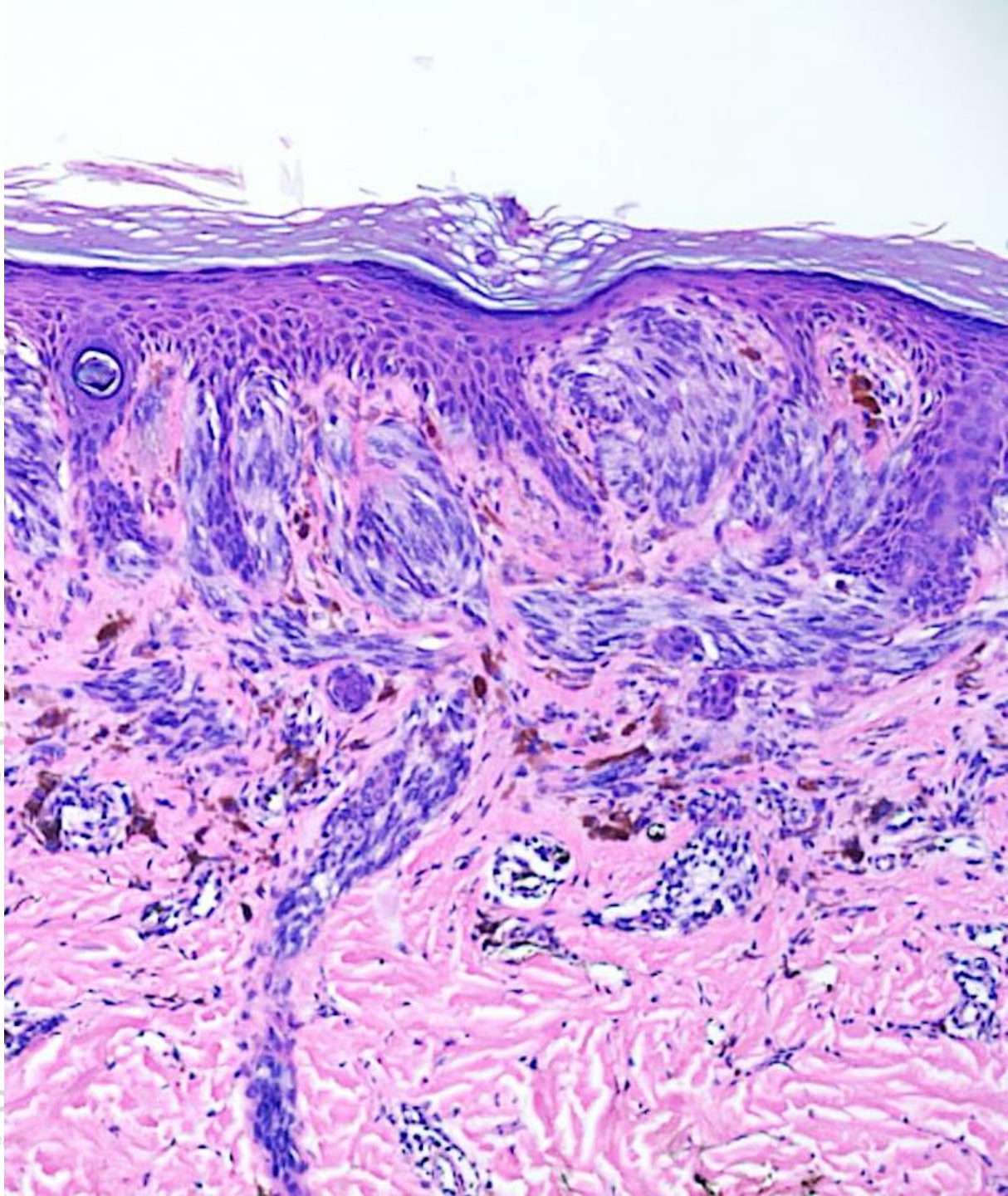

Apical clefts (above the nests)
Nests resemble school of “fish or hanging bananas”
Evenly distributed dermal melanophages


Kamino bodies (collagen types IV and VII, laminin and fibronectin)
Apical clefts
Cytology: Large, hyperchromatic nuclei, prominent nucleoli, and no mitoses

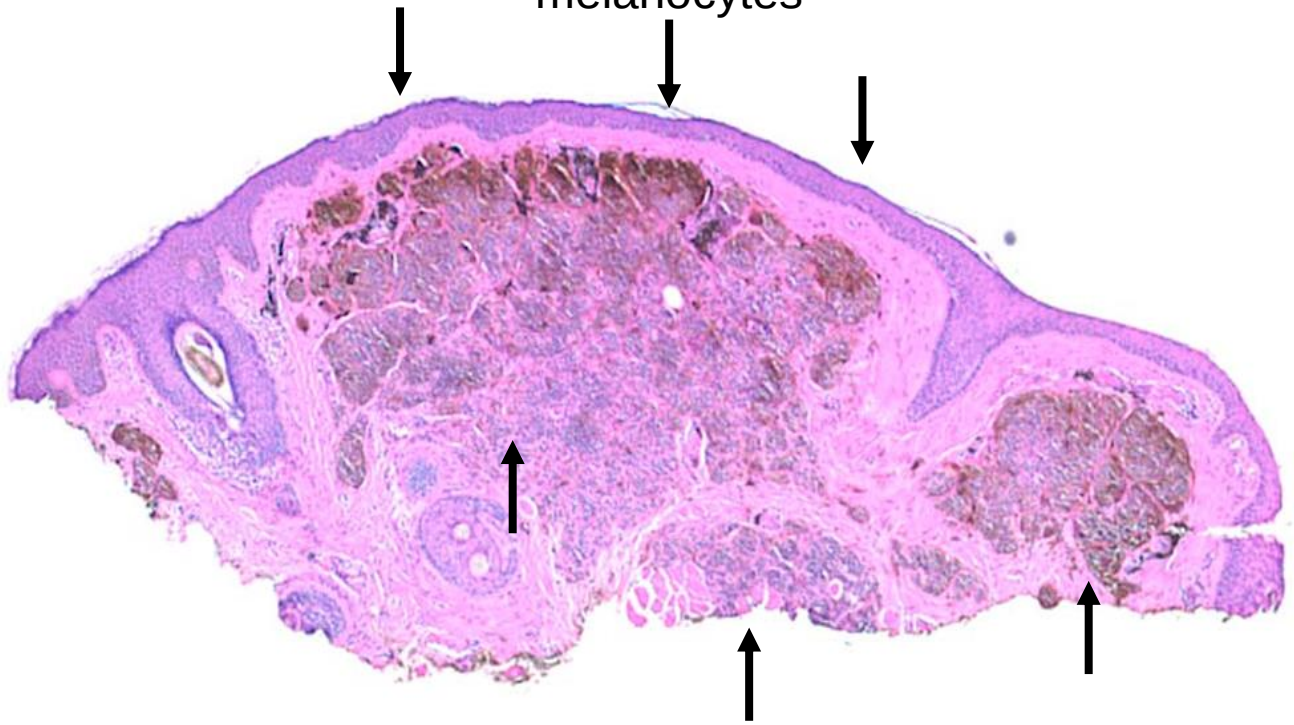
- **Clinical Information:** 5-year-old female, r/o DN
- **DIAGNOSIS:**

  Skin, Right Posterior Lower Arm, Shave Biopsy:

  - Compound Spitz melanocytic nevus, without atypia, with melanin incontinence, focally extending to tissue edges.
- **Comment:** No further treatment is generally needed for this lesion, unless clinically indicated.
- **Teaching Points:**
  - Kamino bodies found in Spitz nevi >> melanoma
  - Only 1-2 junctional mitoses are allowed
  - Spitz nevi exhibit atypical cytology
  - IHC: low ki-67 proliferative rate, PRAME^{-}, p16$^{+/-}$
- **Minimal Diagnostic Criteria:**
  - Apical clefts in melanocytic nests
  - Dome-shaped outline (silhouette)
  - Hypercellular nests, but well-defined borders
  - “schools of fish or hanging bananas”
  - Kamino bodies at the junction
  - Less apparent dermal maturation
  - Evenly pigmented via melanophages (not melanocytic cytoplasm)
  - High-grade cytology: Large, hyperchromatic nuclei and prominent nucleoli
- **Differential Diagnosis:**
  - Unusual nevus type, e.g., pigmented spindle cell nevus (of Reed)
  - Dysplastic nevus
  - Melanoma

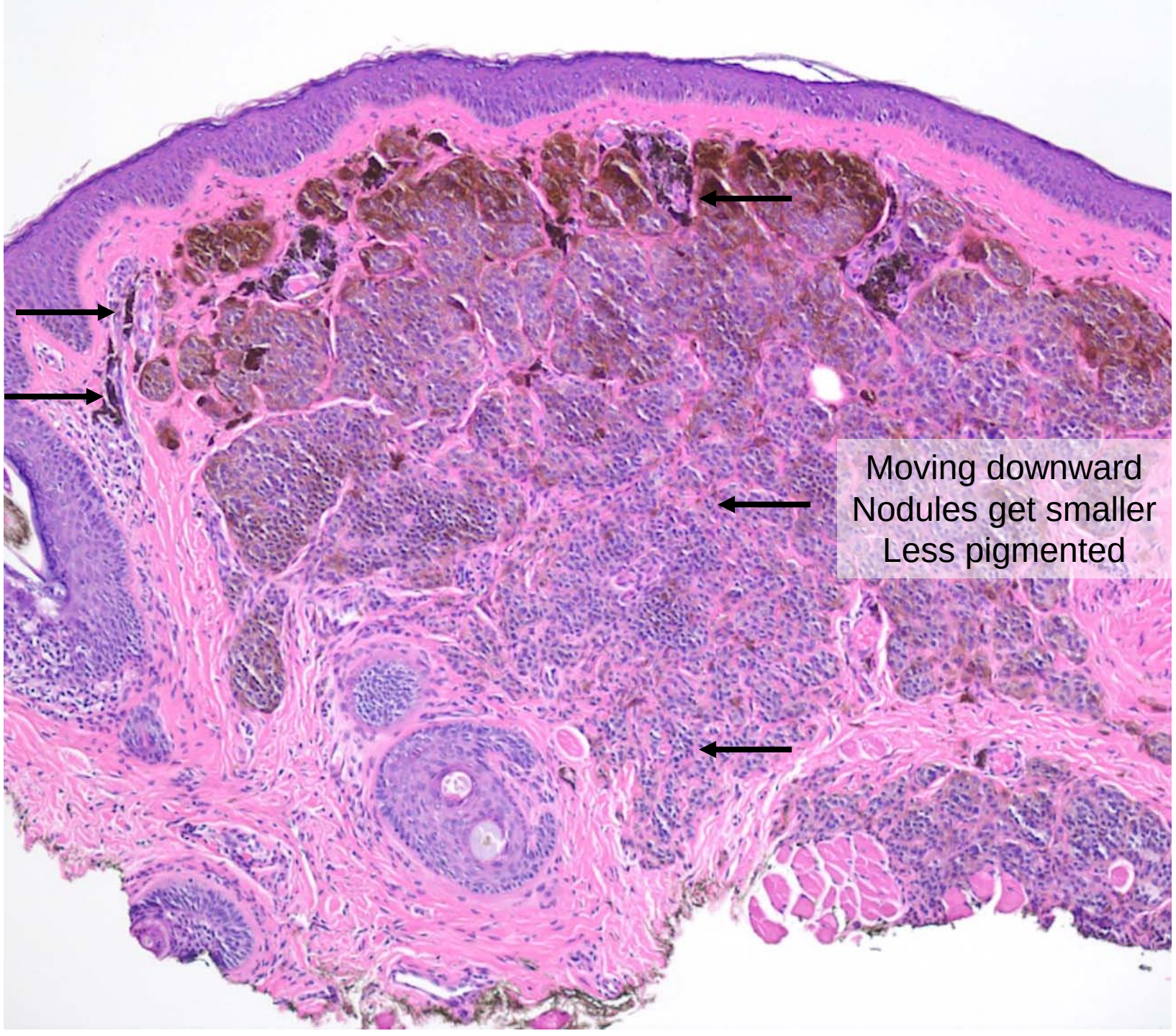


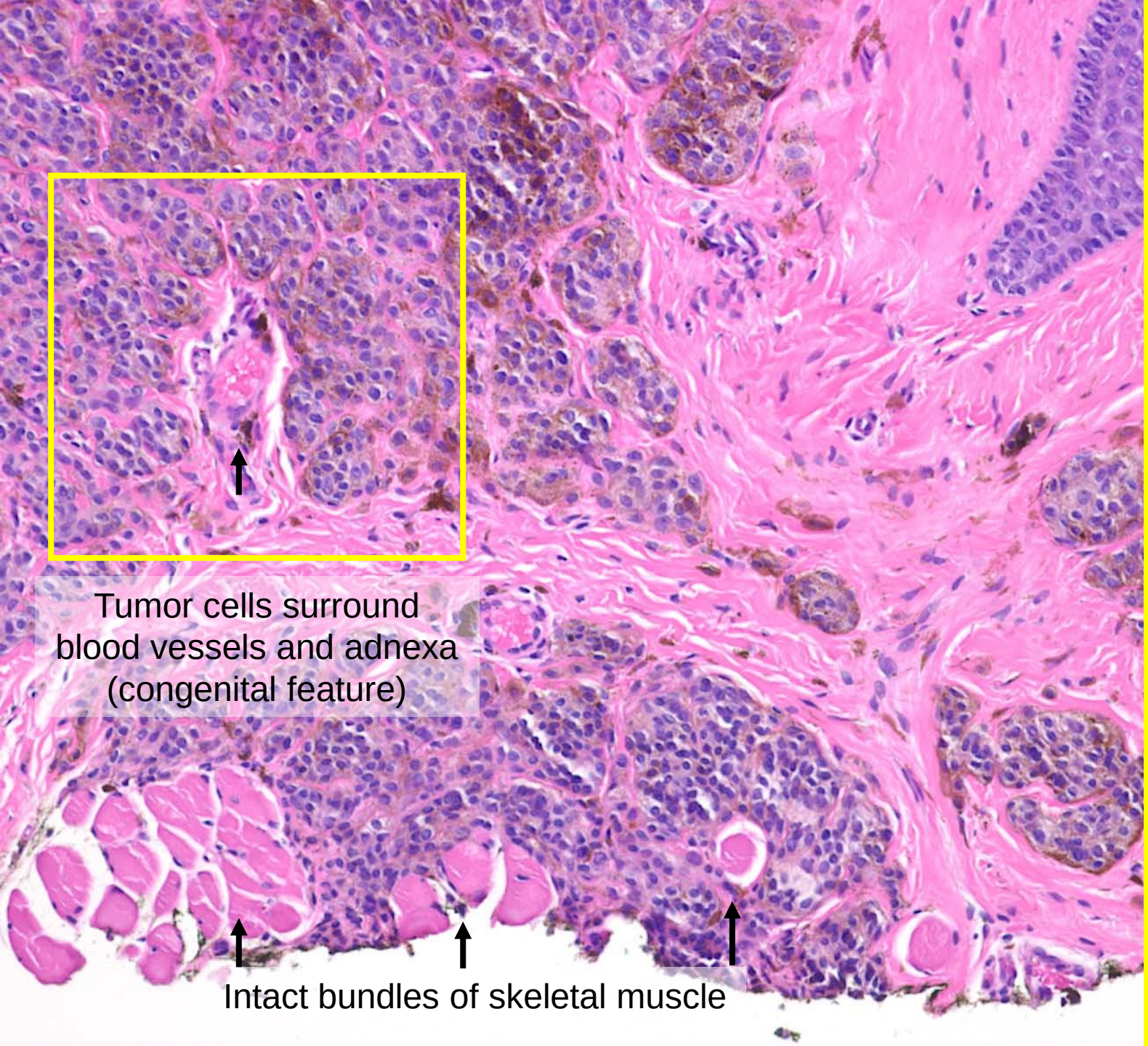
No intraepidermal or junctional melanocytes



Round, well circumscribed, evenly pigmented dermal nodular and nested growth (papule)

Melanophages: melanin incontinence (black/brown)




Tumor cells surround
blood vessels and adnexa
(congenital feature)
Intact bundles of skeletal muscle

Clinical Information: 39-Year-old female. None provided.

DIAGNOSIS:

Skin, Right lower eyelid, Biopsy:

- Intradermal melanocytic nevus, without atypia, heavily pigmented, extending to tissue base.

Teaching Points:

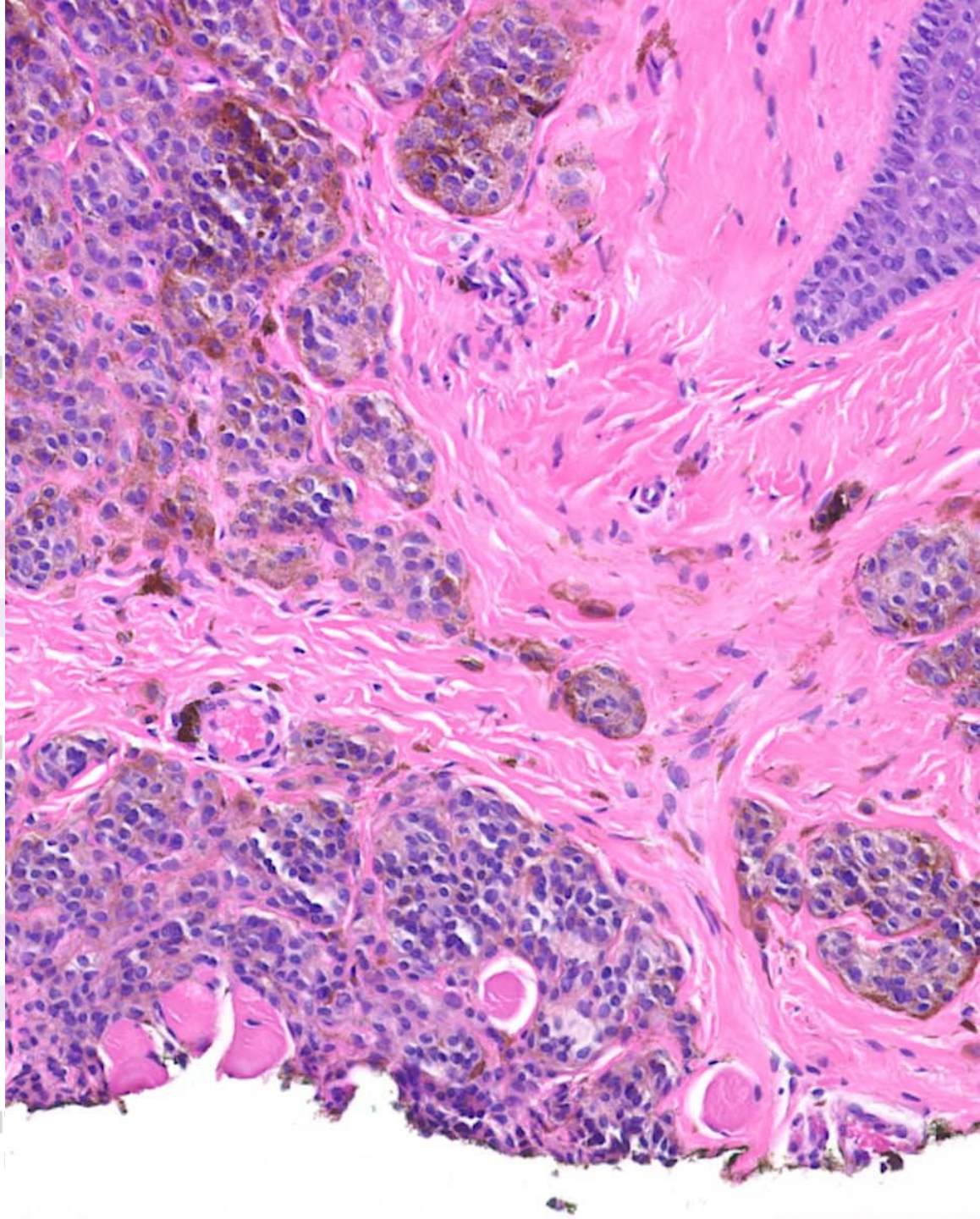
- Scan under 10x to look for dermal mitoses

Minimal Diagnostic Criteria:

- Moving downward in the dermis, nodules, nests, and cellular nuclear to cytoplasmic ratio all decrease (maturation)
- No junctional or intraepidermal component
- No dermal mitoses
- Evenly pigmented at top, pigmentation decreases by moving downward in the dermis
- No cytologic atypia

Differential Diagnosis:

- Nevoid melanoma
- Congenital nevus

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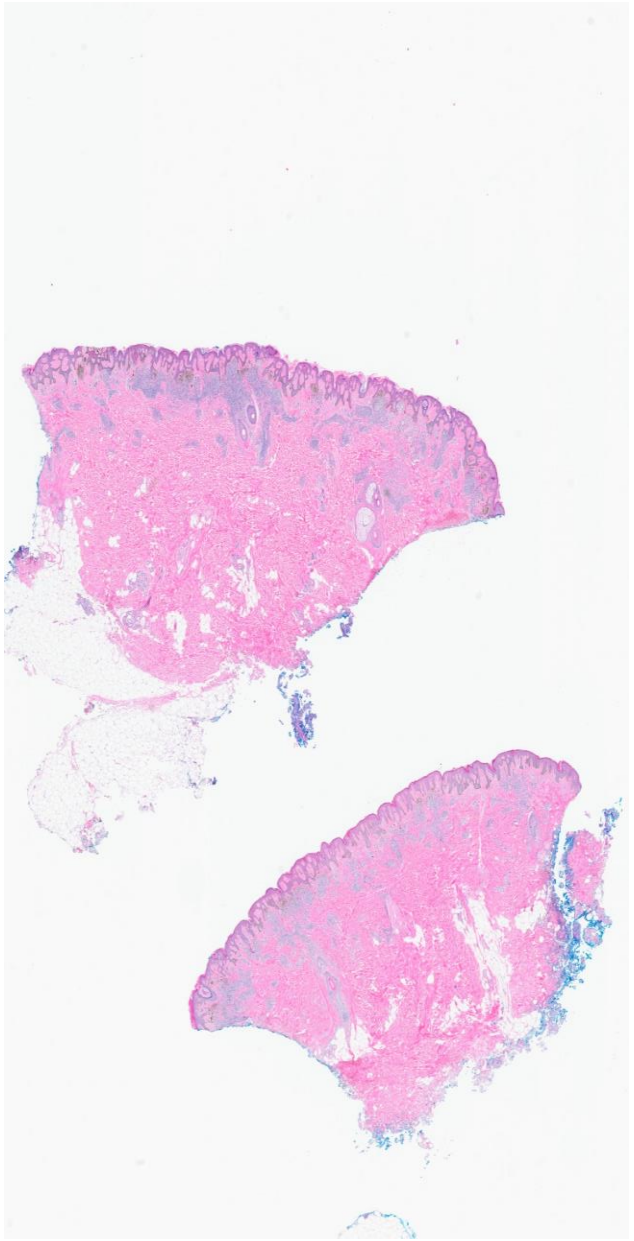
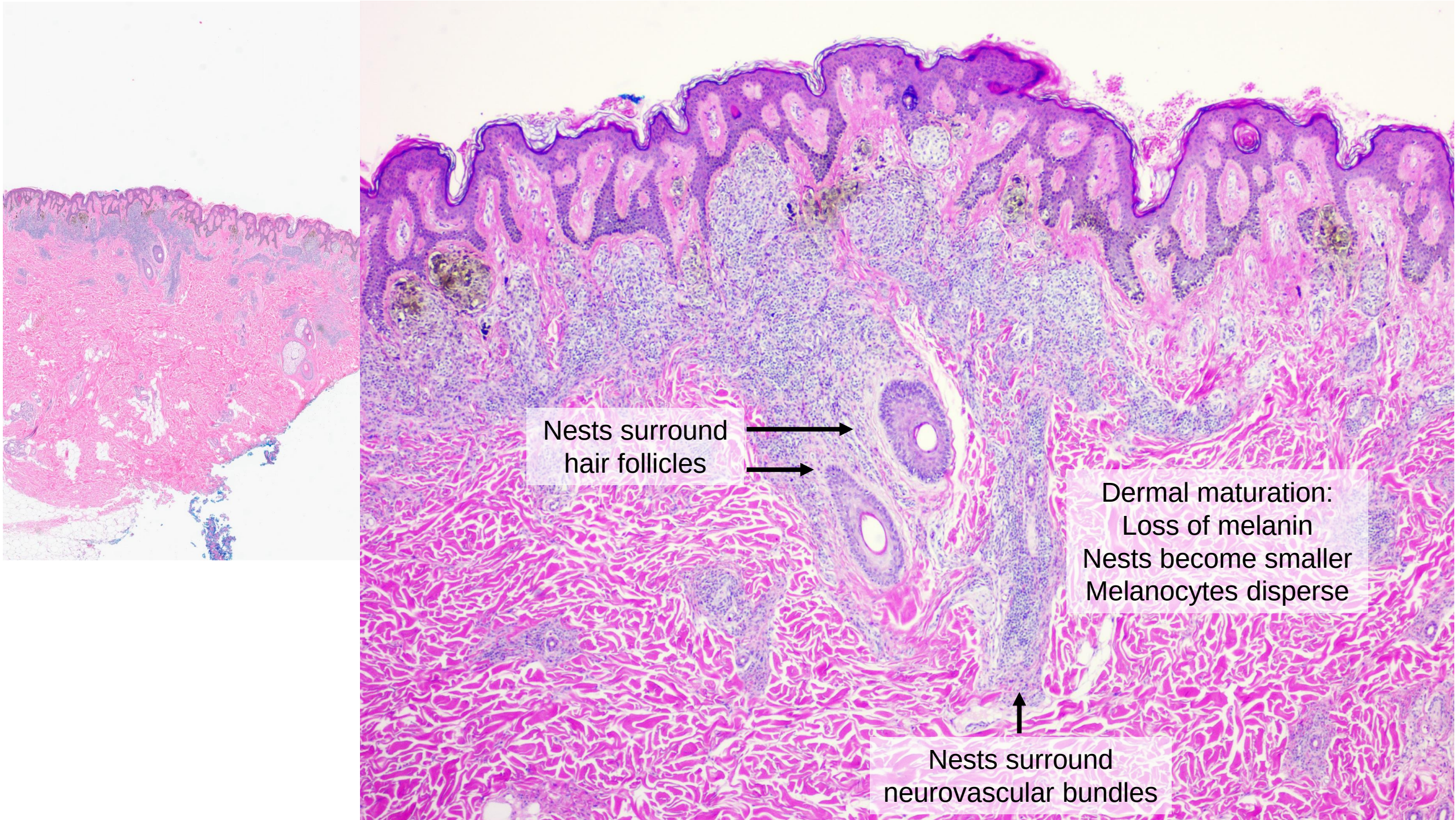
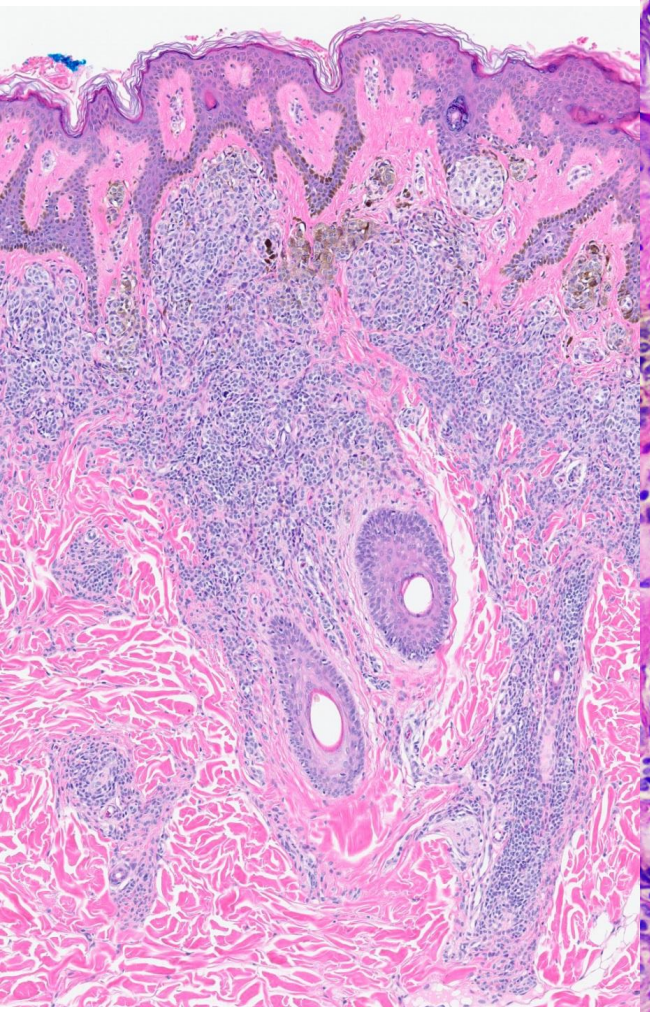


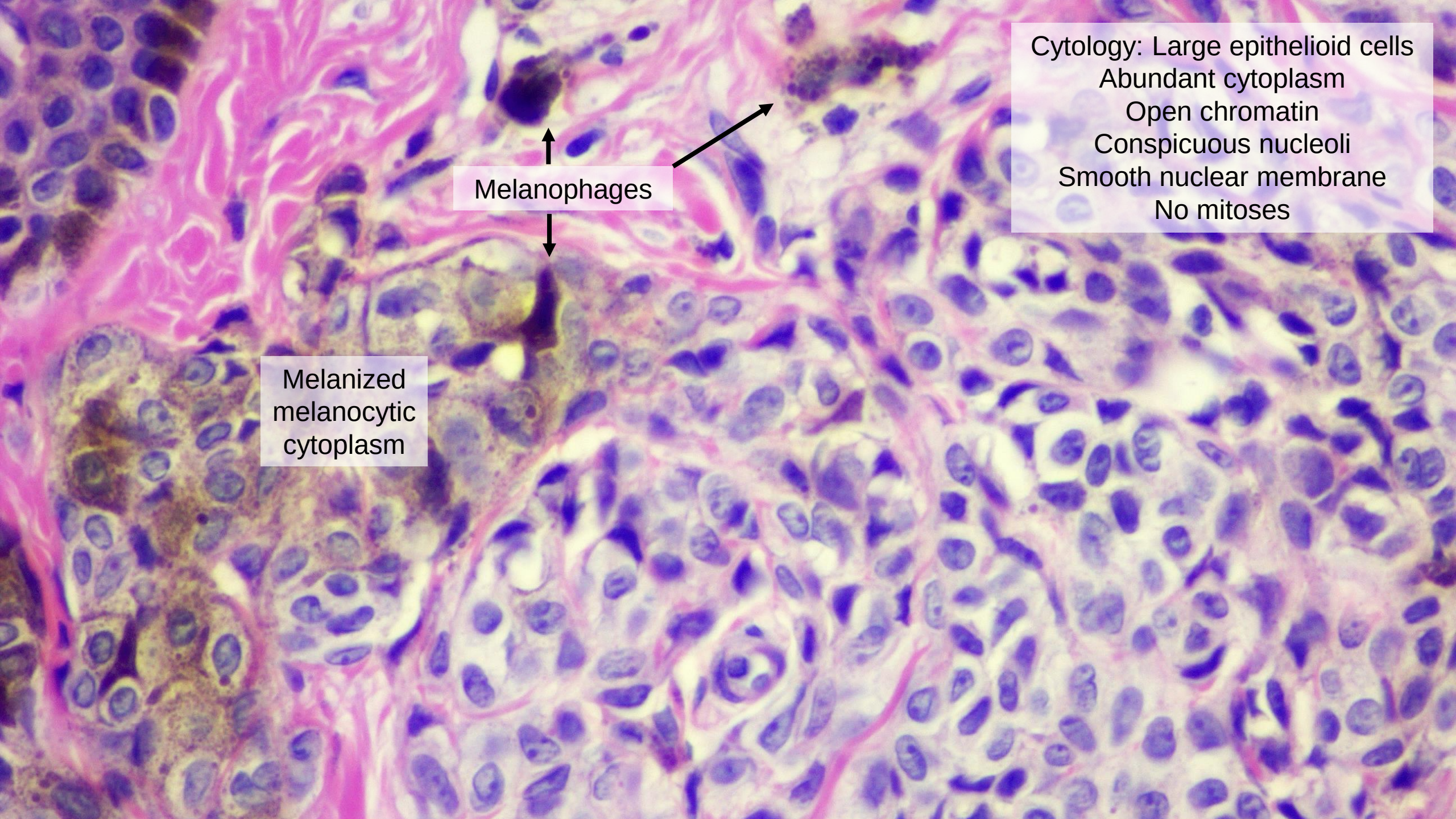
Papillomatosis: epidermal hyperplasia

Dermal nodular, nested proliferation


Nests surround
hair follicles
Dermal maturation:
Loss of melanin
Nests become smaller
Melanocytes disperse
Nests surround
neurovascular bundles



Compound melanocytic neoplasm
Hypercellular dermal nests
Dermal nests converge into nodules

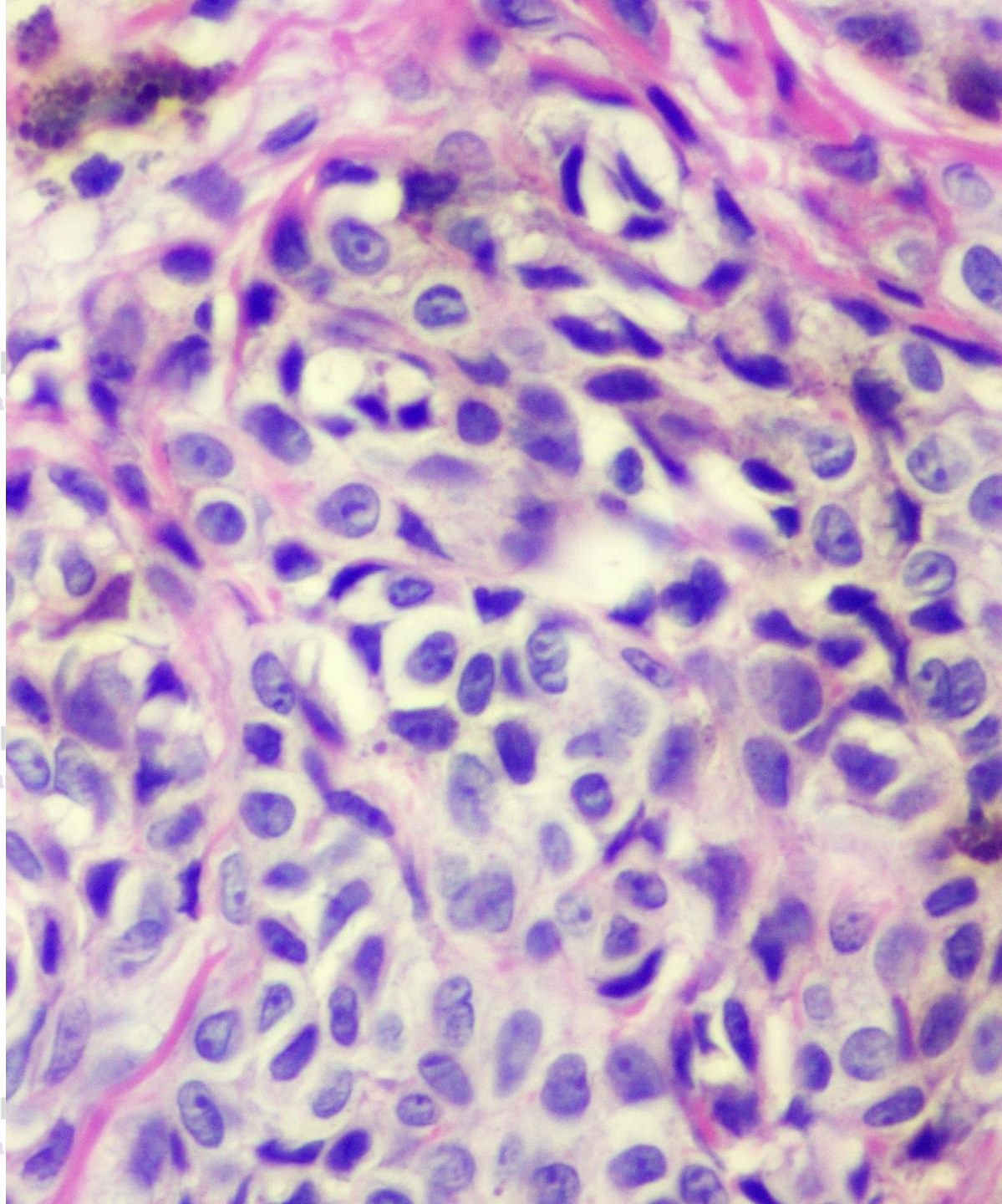

Melanophages
Melanized melanocytic cytoplasm
Cytology: Large epithelioid cells
Abundant cytoplasm
Open chromatin
Conspicuous nucleoli
Smooth nuclear membrane
No mitoses

- **Clinical Information:** 11 year-old male, Lower Back; giant congenital nevus-1st stage of serial excision (S24-22017)
- **DIAGNOSIS:**

  Skin, Lower Back, Excision:

  - Compound melanocytic nevus with congenital features, without atypia, variably pigmented, focally extending to tissue edges.

  Comment: No further treatment is generally needed for this nevus, unless clinically indicated.
- **Teaching Points:**
  - Look for mitoses in dermal nodules (proliferative nodule in giant congenital melanocytic nevi)
  - Invagination of melanocytic nests in lymphatic space (not malignant, not invasion)
  - IHC: low ki-67 proliferative rate, PRAME^{-}, p16$^{+/-}$
- **Minimal Diagnostic Criteria:**
  - Compound, hypercellular melanocytic neoplasm
  - Dermal nests converge into nodules
  - Melanocytic nests surround hair follicles and neurovascular bundles (congenital pattern or features)
  - Dermal maturation (moving from top to bottom): loss of melanin, melanocytic nests become smaller, and melanocytes disperse
  - Cytology: Large epithelioid cells with abundant cytoplasm, open chromatin, conspicuous nucleoli, smooth nuclear membrane, and no mitoses
- **Differential Diagnosis:**
  - Dysplastic nevus
  - Proliferative nodule (melanoma) arising in giant congenital melanocytic nevi

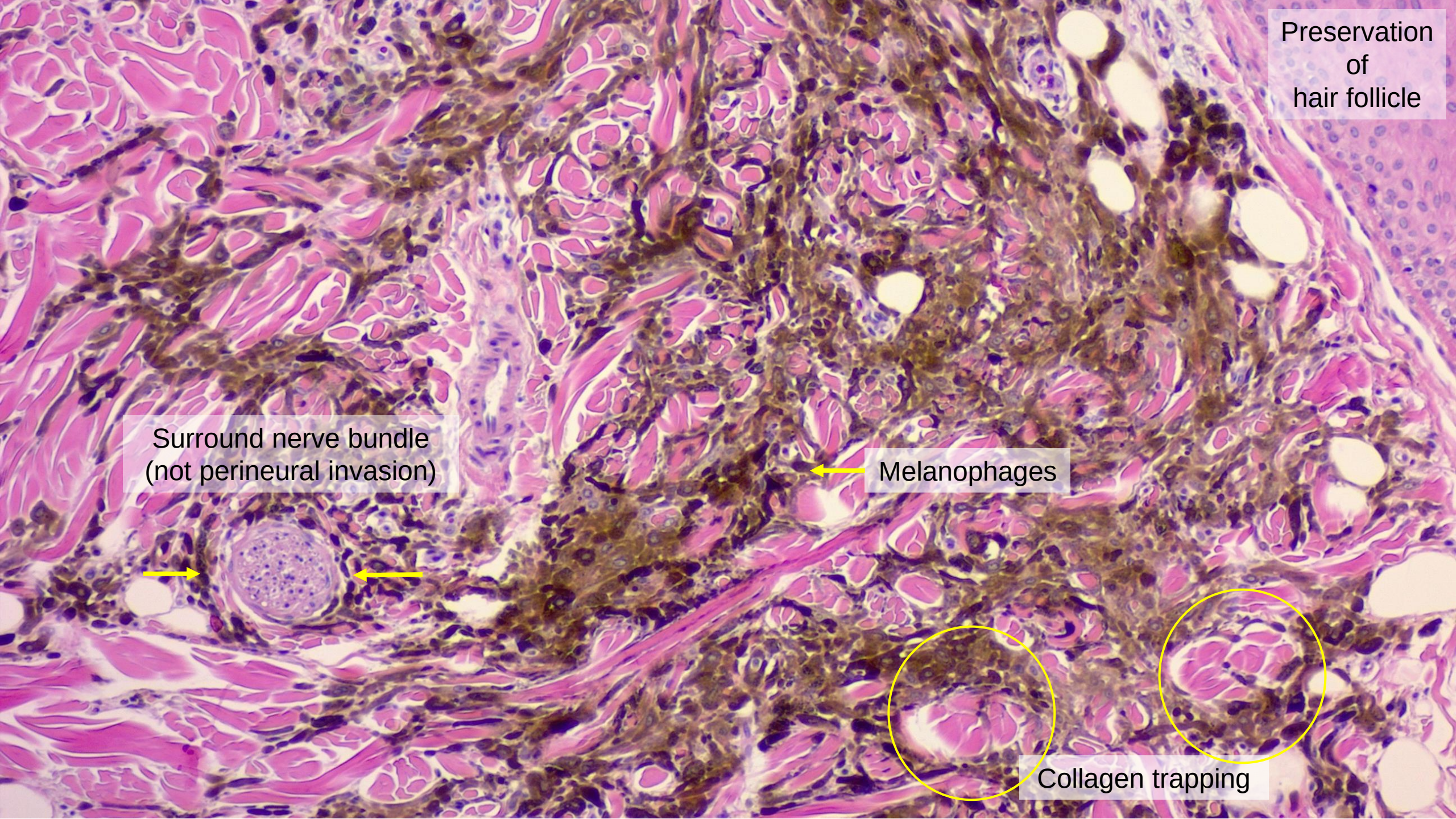


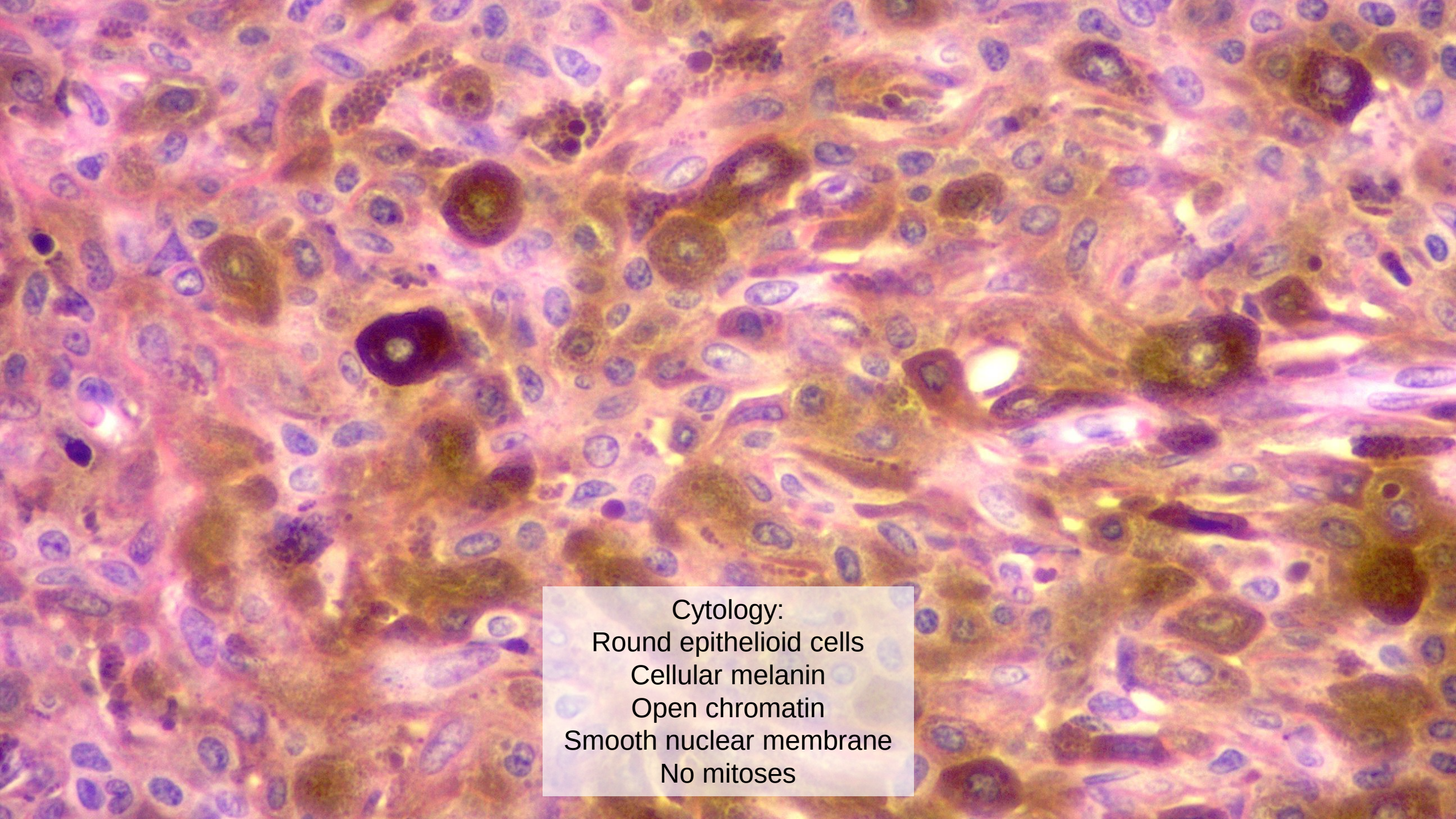
Pigmented dermal melanocytic neoplasm

Hypercellular center

Infiltration of adipose tissue

“Dumbbell” shaped
Round, smooth bottom


Preservation
of
hair follicle
Surround nerve bundle
(not perineural invasion)
Melanophages
Collagen trapping


Cytology:
Round epithelioid cells
Cellular melanin
Open chromatin
Smooth nuclear membrane
No mitoses

Clinical Information: 19-year-old female, excisional biopsy of dark blue papule.

DIAGNOSIS:

Skin, Left Frontal Scalp, Excision:

- Cellular blue nevus, edges free of involvement in examined sections.

Teaching Points:

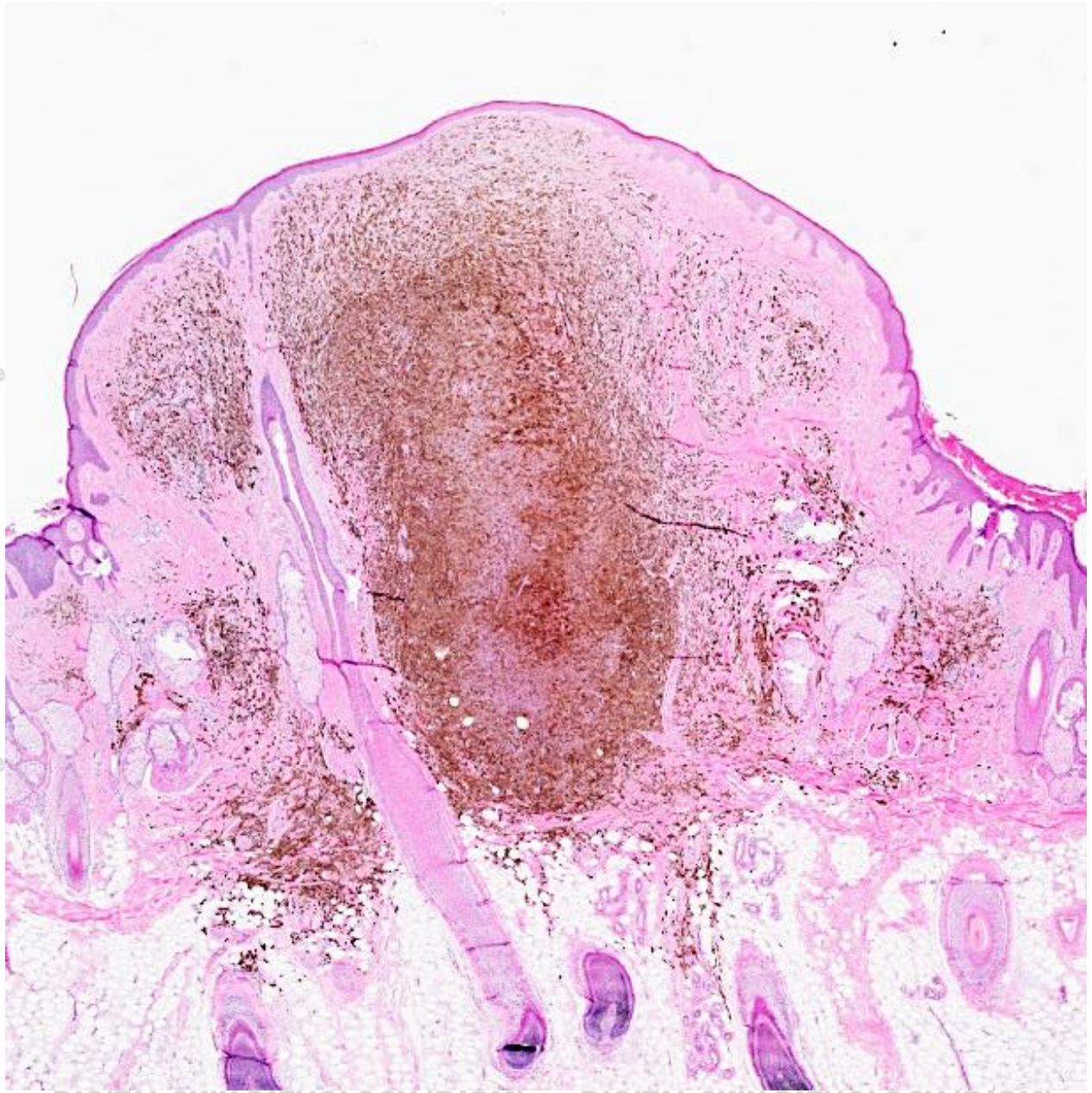
- Perform additional bleached levels, look for deep dermal mitoses
- Be concerned if partially sampled
- Double IHC: ki-67 Melan-A (<5% mitotic index)

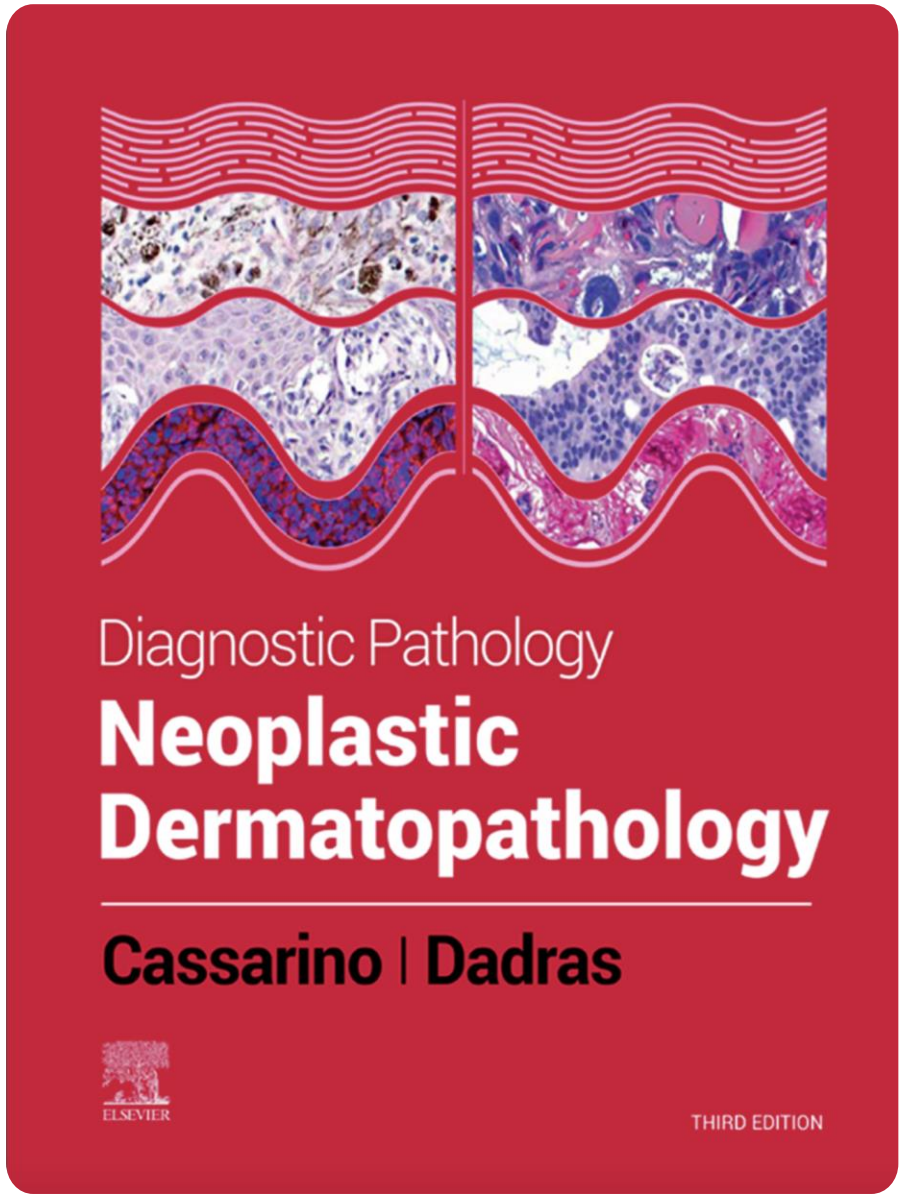
Minimal Diagnostic Criteria:

- Large pigmented dermal nodule/mass
- “dumbbell” shaped, round smooth bottom
- Can infiltrate deeply into adipose tissue
- Adnexa are preserved
- Involve neurovascular bundles (benign feature)
- Collagen trapping
- Cytology: Round epithelioid cells, cellular melanin, open chromatin, smooth nuclear membrane, no mitoses

Differential Diagnosis:

- Deep penetrating nevus
- Inverted type-A nevus
- Melanoma arising in blue nevus (malignant blue nevus)





References

- WHO Classification of Tumors online
- *Neoplastic Dermatopathology*, 4th edition (in progress)
- *https://app.expertpath.com/*
- Digitalskinpathology.com
- Personal collection