MALIGNANT MELANOMAS

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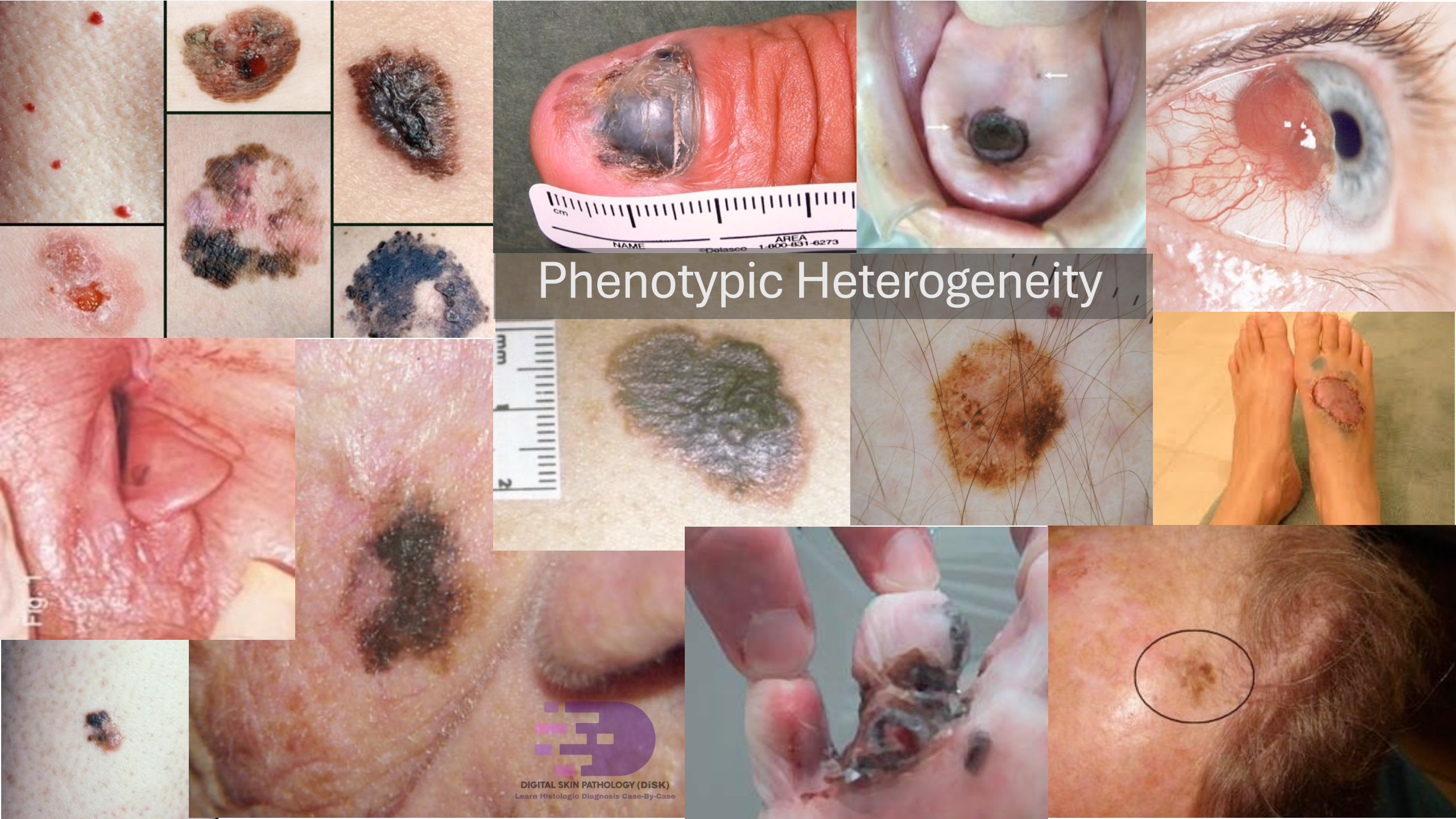
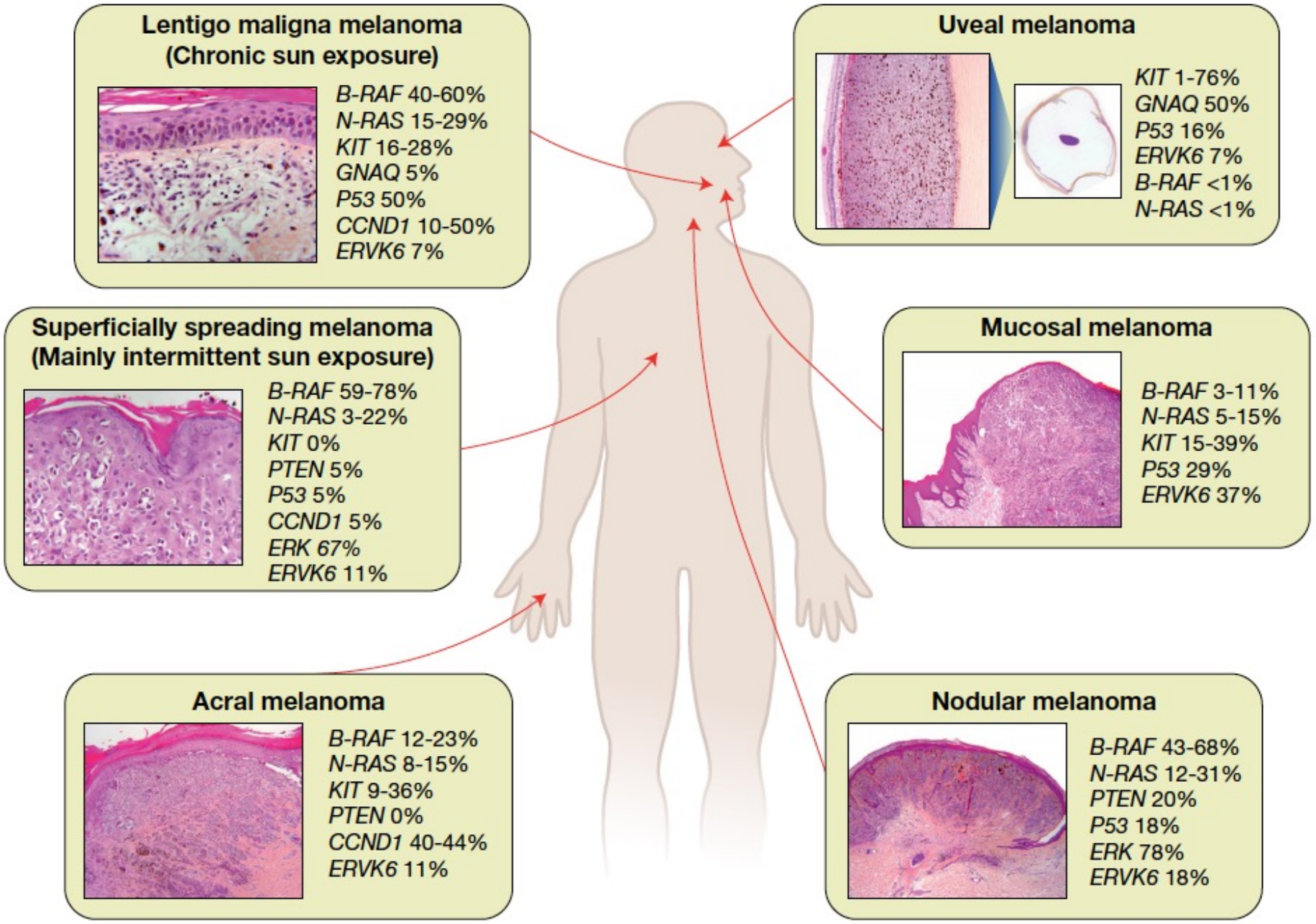
Melanoma lecture outline

- What are some diagnostic principals of (malignant) melanoma
  - How to differentiate melanoma in situ from invasive melanoma?
  - How does WHO 5th edition classify melanoma subtypes?
  - How many melanoma histologic subtypes are there?
  - What are their histopathologic features?
  - What is melanoma cytology?
- What are melanoma prognostic parameters?
  - What are CAP/AJCC criteria for pathologic staging?
- What is an “atypical” melanocytic neoplasm?
  - How to histologically define “atypia”?
  - What is borderline lesion/atypical melanocytic neoplasm/MELTUMP/melanocytoma?
  - Can histopathology determine outcome?
  - Can immunohistochemistry or molecular diagnostics assist in cases of equivocal histopathology?


Phenotypic Heterogeneity
DIGITAL SKIN PATHOLOGY (DiSK)
Learn Histologic Diagnosis Case-By-Case

Molecular Heterogeneity

- *BRAF*
- *NRAS*
- *KIT*
- *GNAQ*
- *P53*
- *CCND1*
- *ERVK6*
- *ERK*



Pacheco et al. (Tron) *Expert reviews in molecular medicine* 2011

Molecular pathogenesis of cutaneous melanoma

- Inherited mutations in (2%)
  - CDKN2A [p16 (Rb) and p14ARF (p53)], 25% of familial melanoma kindred
  - CDK4
- Constitutive activating mutations in MAPK
  - NRAS (21%)
  - BRAF (66%)
  - Found in majority of melanocytic nevi and melanomas
- Ultraviolet solar radiation

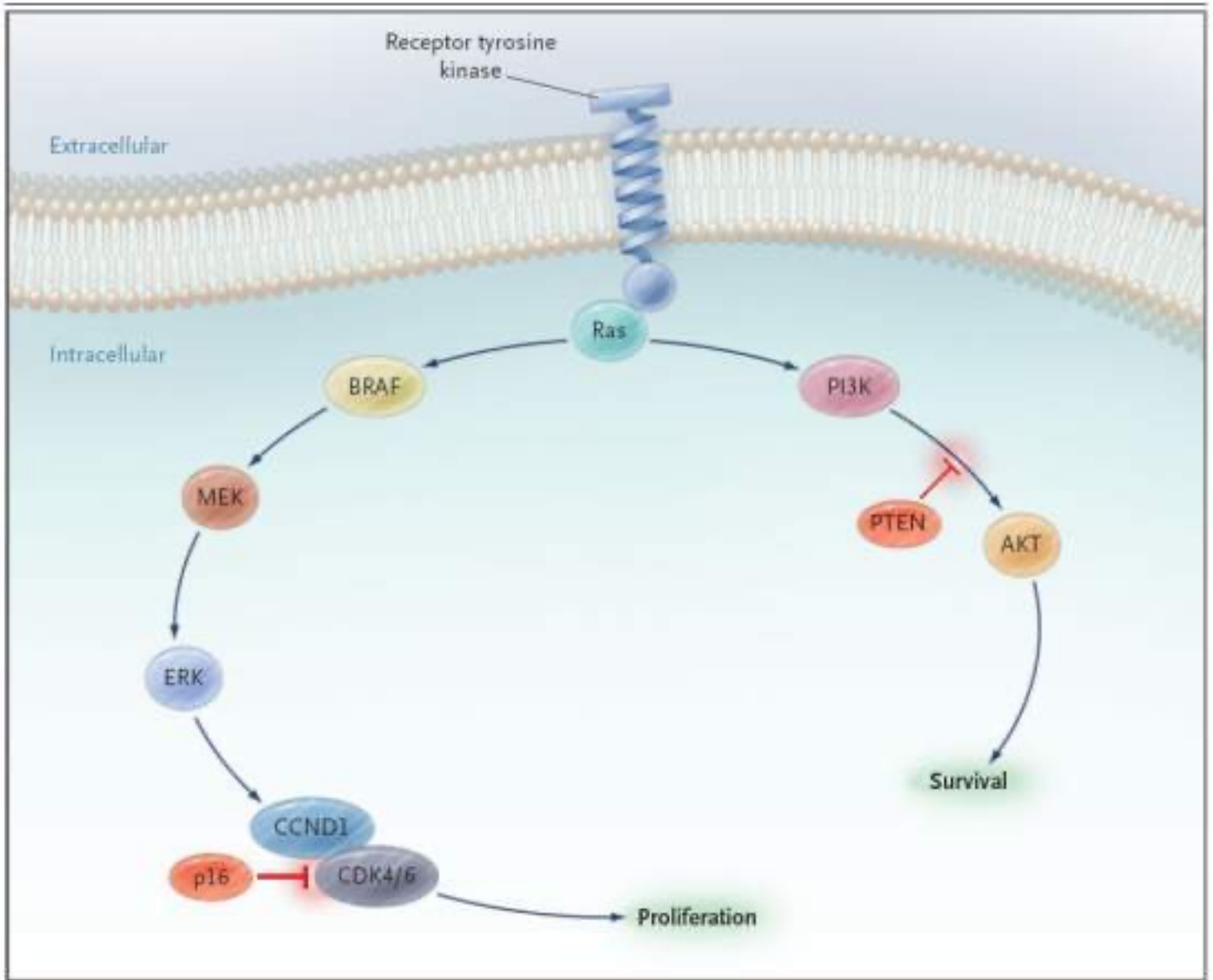
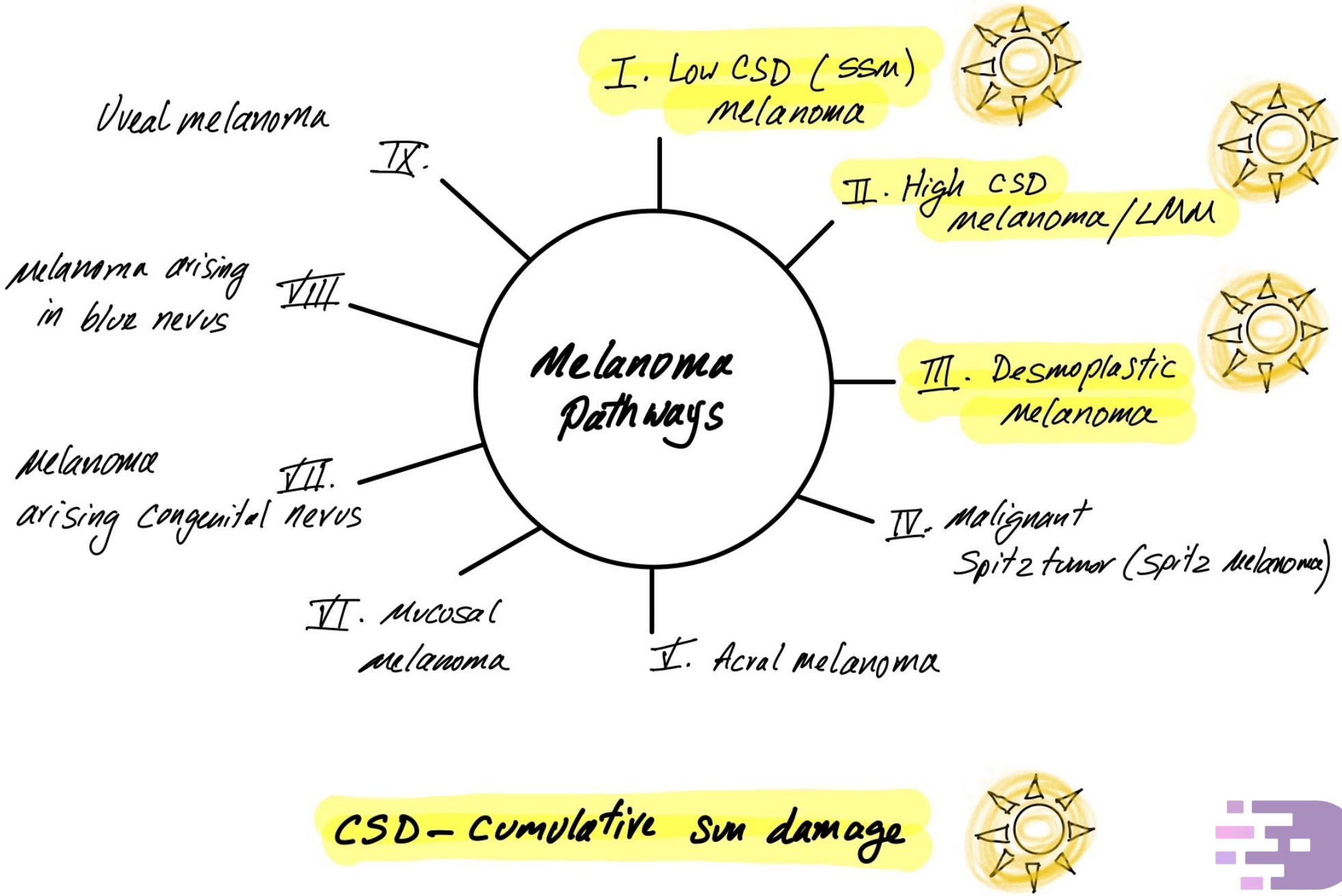


Figure 1. **The Mitogen-Activated Protein (MAP) Kinase and Phosphatidylinositol 3' Kinase (PI3K) Pathways.**
Signals from receptor tyrosine kinases can promote proliferation through the MAP kinase pathway (left branch) and survival through the PI3 kinase pathway (right branch).

Curtin JA et al. *NEJM* 2005

WHO 5th edition: Melanoma classification by genetic pathways



Distinguishing benign from malignant?

Siberian Husky Dog

Gray Wolf

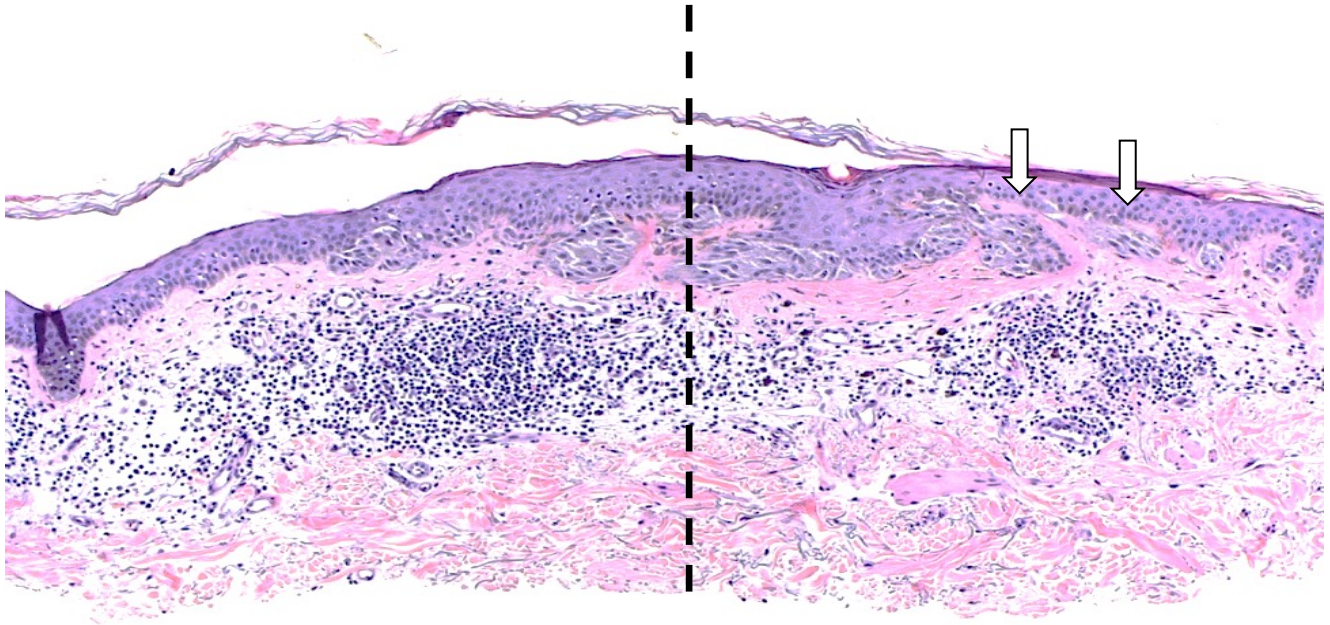
What is the clinical/anatomic context of melanocytic atypia?

- Site of trauma or friction
  - Upward scattering of epidermal melanocytes
- Anatomic location of the lesion (special site)
  - Flexural skin, genitalia, breast, knee, etc.
  - Atypia is related to the anatomy and not neoplasia
- Senescent atypia (smudged chromatin) in aging nevus
- Enlarged melanocytes in children
- Recurrent nevus (pseudomelanoma) or repigmentation in a prior biopsy site
- Reactive epidermal melanocytes in chronically sun-damaged skin (e.g. melanoma excision)

What is architectural atypia in a melanocytic neoplasm?

Low magnification: Architecture

- Epidermal location
  - Asymmetry
  - Poorly circumscribed
  - Nested, at the side (not tips) of rete ridges or shouldering
  - Lentiginous, not nested
  - Adnexal extension
  - Upward scattering of melanocytes, not nested
- Dermal location
  - Sheeting, not maturing with dermal depth
  - Epithelioid, not dispersing at deep aspect
  - Reaction to adnexa
  - Distribution of melanin

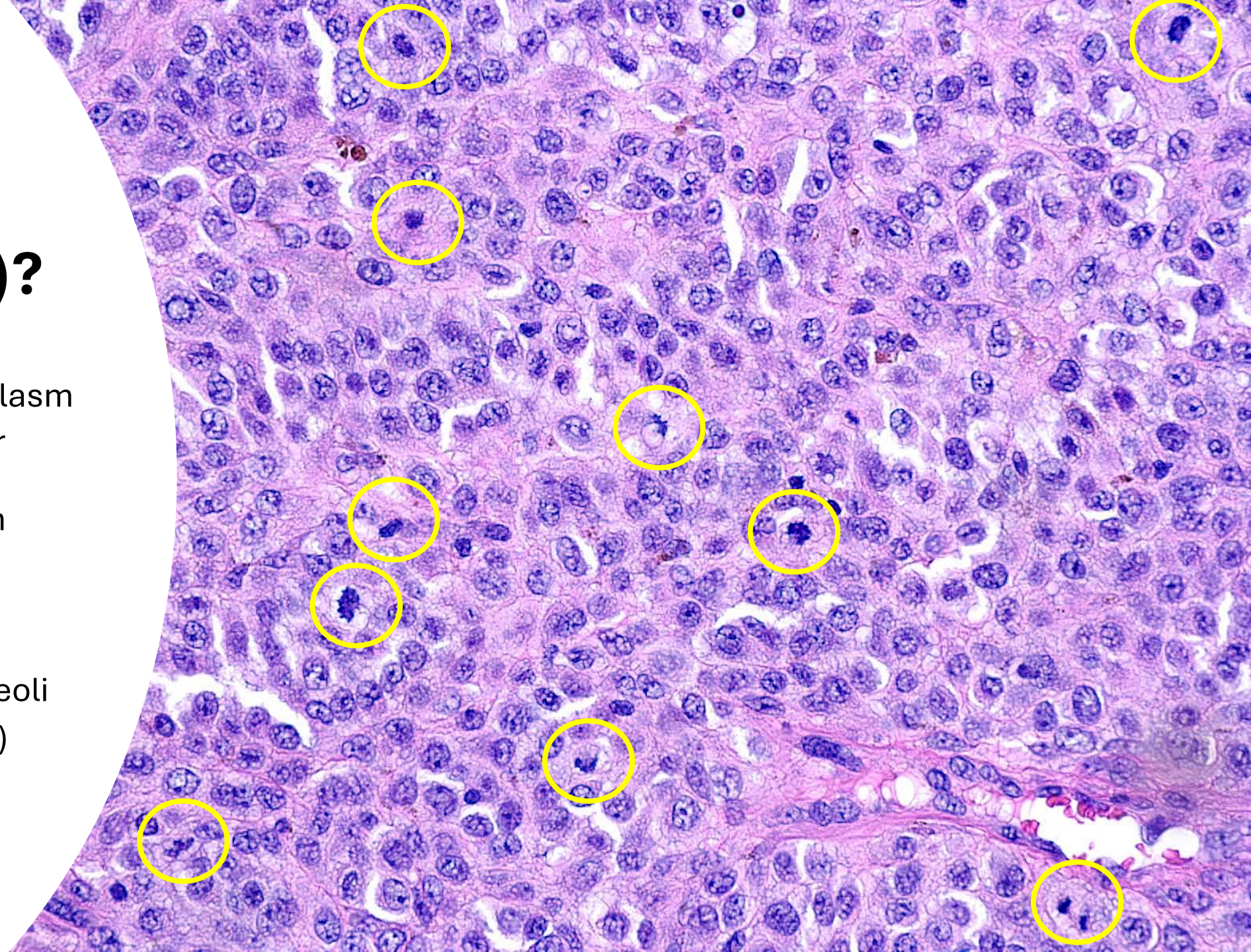


Asymmetry (vertical axis)
Poorly nested, lentiginous growth

DIGITAL SKIN PATHOLOGY (DiSK)
Learn Histologic Diagnosis Case-By-Case

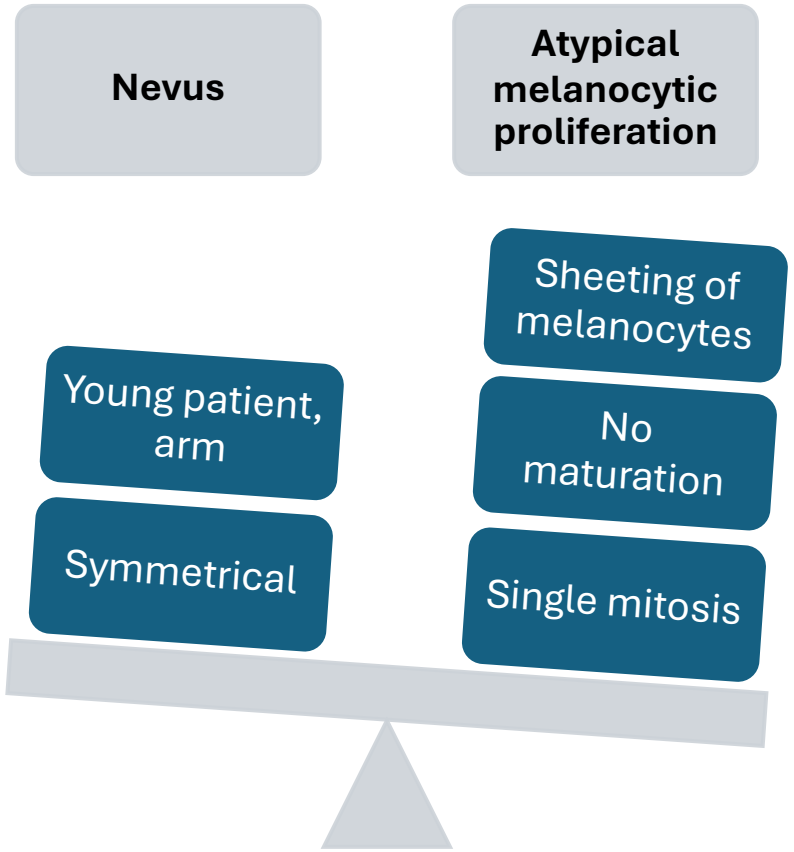
What is melanoma cytology (high magnification)?

- Large epithelioid cytoplasm
- Thick, irregular contour nuclear membrane
- Nuclear pleomorphism
- Open chromatin (or hyperchromatic)
- Prominent nucleoli
- Cherry red macro nucleoli
- Mitoses (yellow circles)



DIGITAL SKIN PATHOLOGY (DiSK)
Learn Histologic Diagnosis Case-By-Case

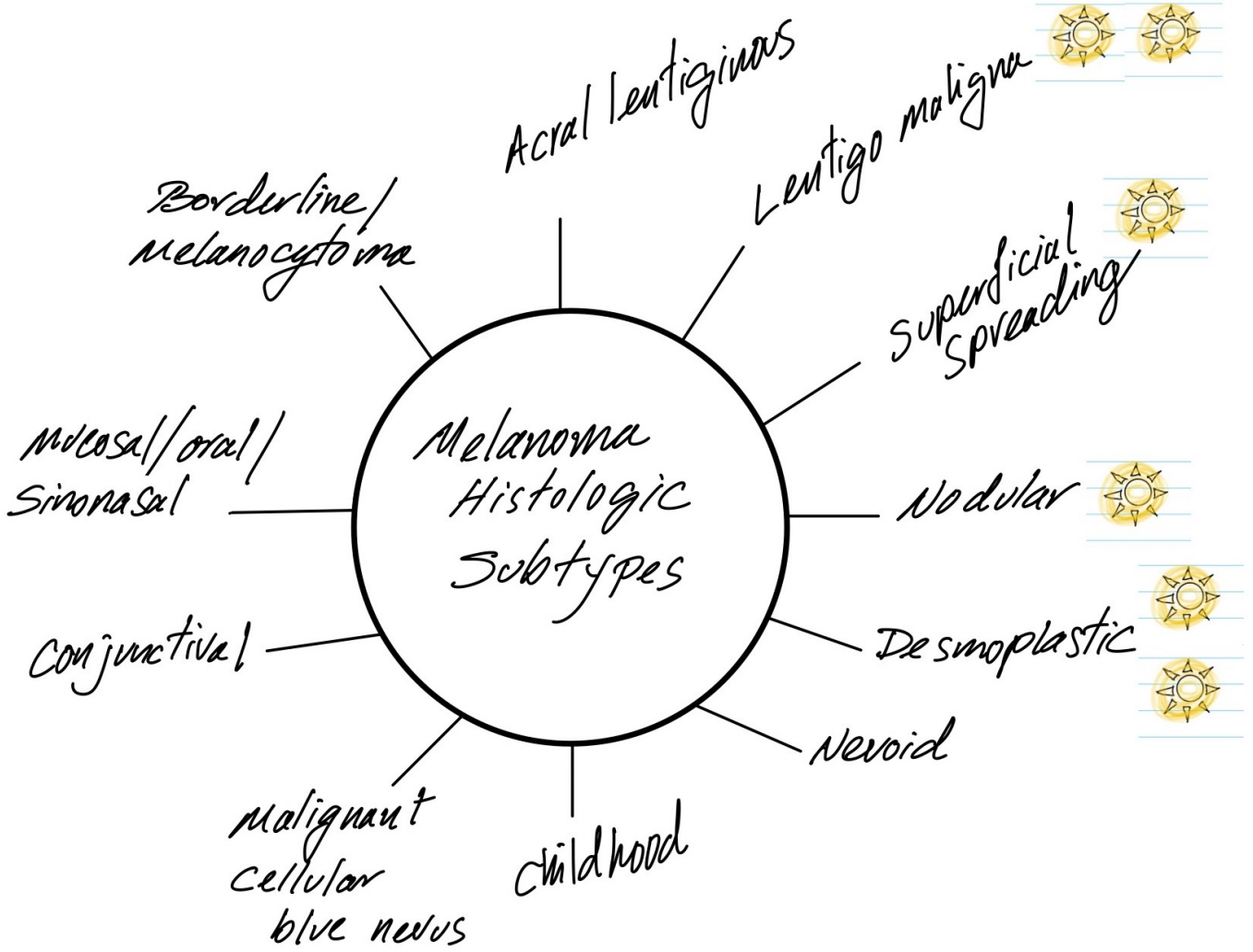
Multifactorial approach to diagnose melanocytic neoplasms



Imbalance of benignancy vs. atypia

Clinical	Histologic
Age	Symmetry
Anatomic site	Circumscription
Biopsy type: shave or punch	Melanin distribution
Size	Architectural organization
Trauma	Parakeratosis or excoriation
Prior treatment or manipulation	Arrangement of nests
History of melanoma	Cytologic details
Dysplastic nevus syndrome	Marked lichenoid inflammation

Melanoma histologic classification



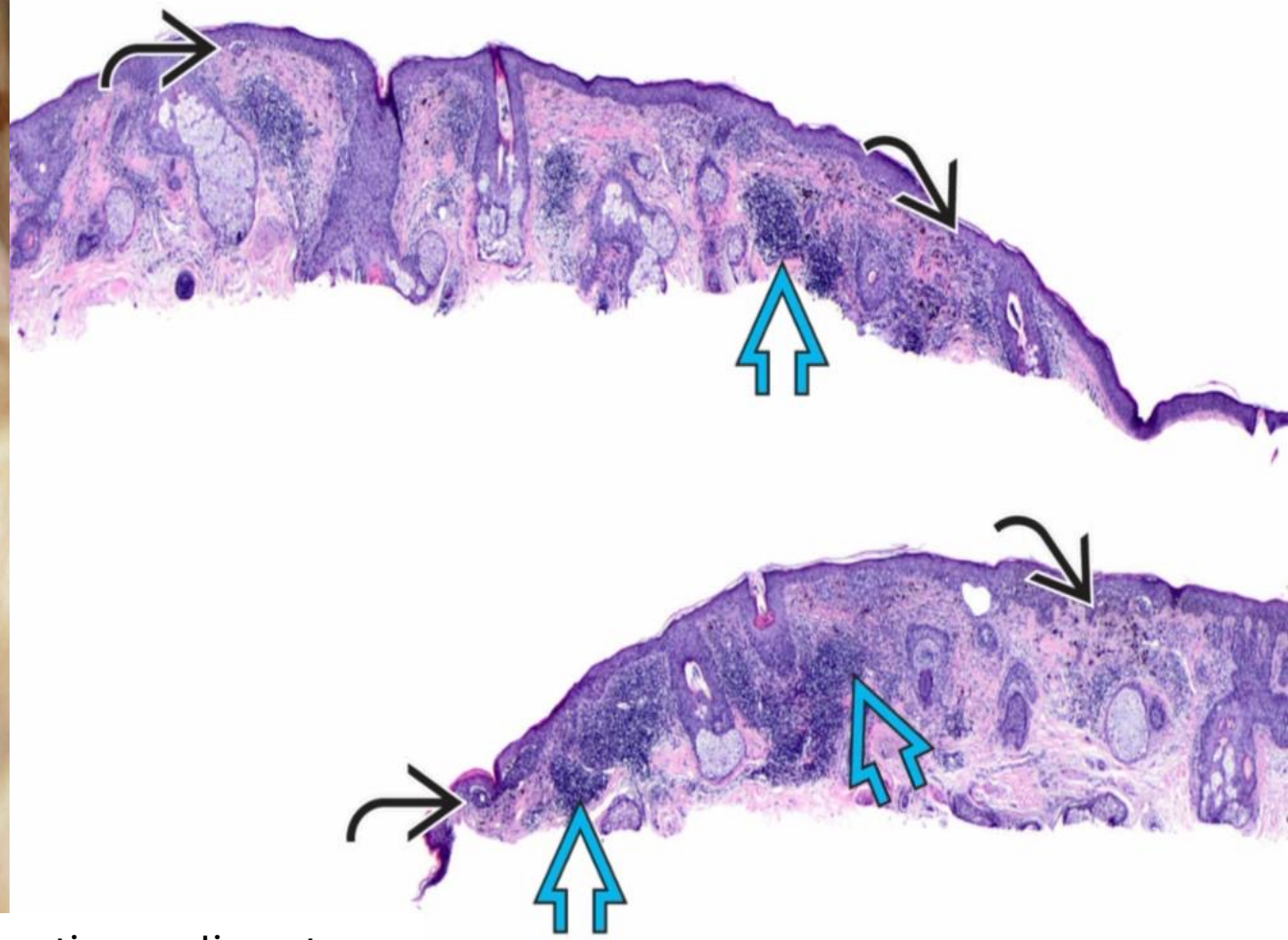
CSD – cumulative sun damage

VARIANTS OF MELANOMA IN SITU

1. Melanoma in situ, lentigo maligna type
2. Melanoma in situ, superficial spreding type
3. Melanoma in situ, acral lentiginous type

Multicolor pigmented patch on the facial cheek with regression (white curved arrow). (Courtesy J. Finch, MD.)

Atypical lentiginous junctional melanocytic proliferation (black curved arrow); dense inflammatory aggregates (cyan open arrow) in the papillary dermis.



Melanoma in situ, lentigo maligna type

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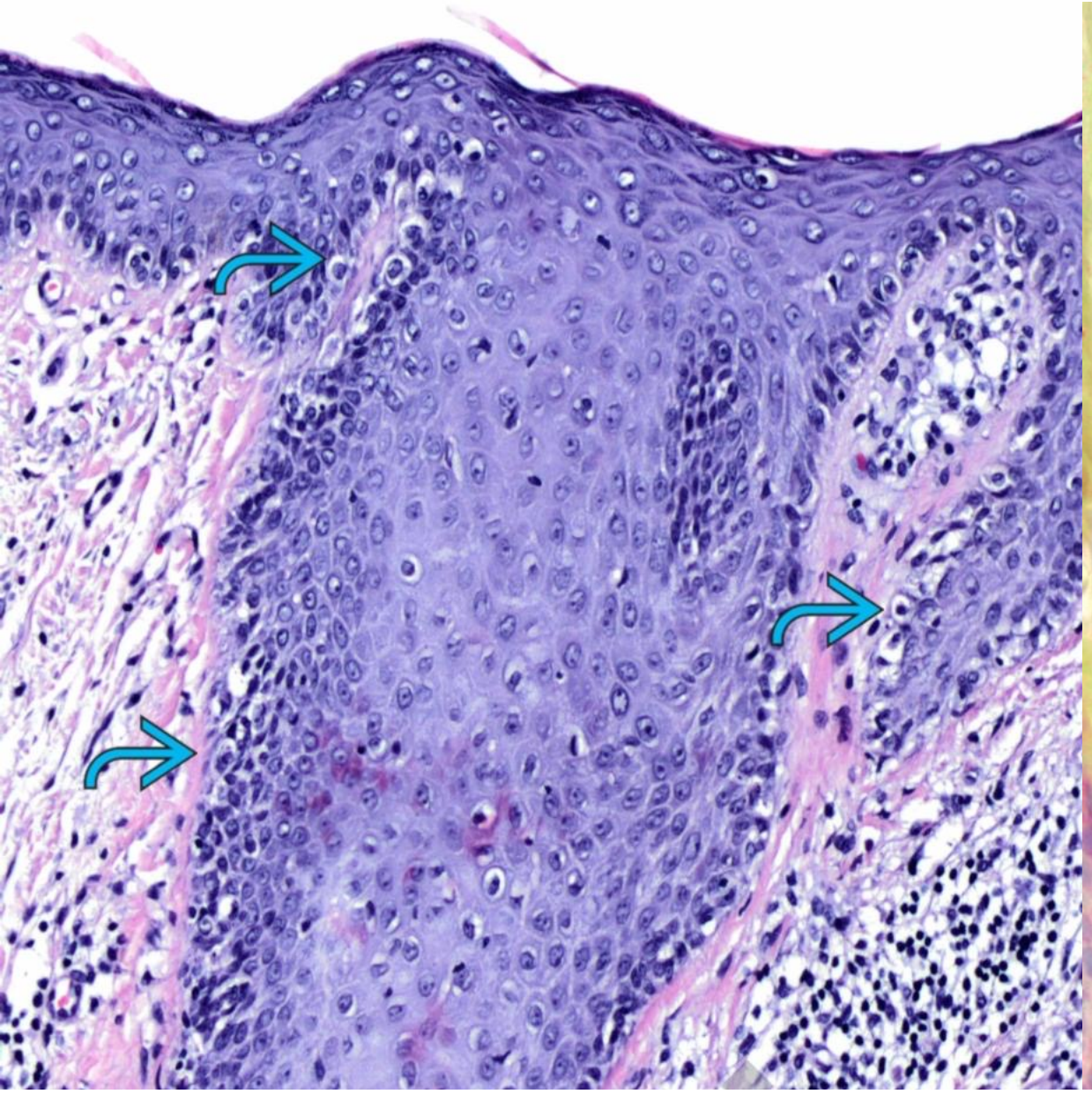
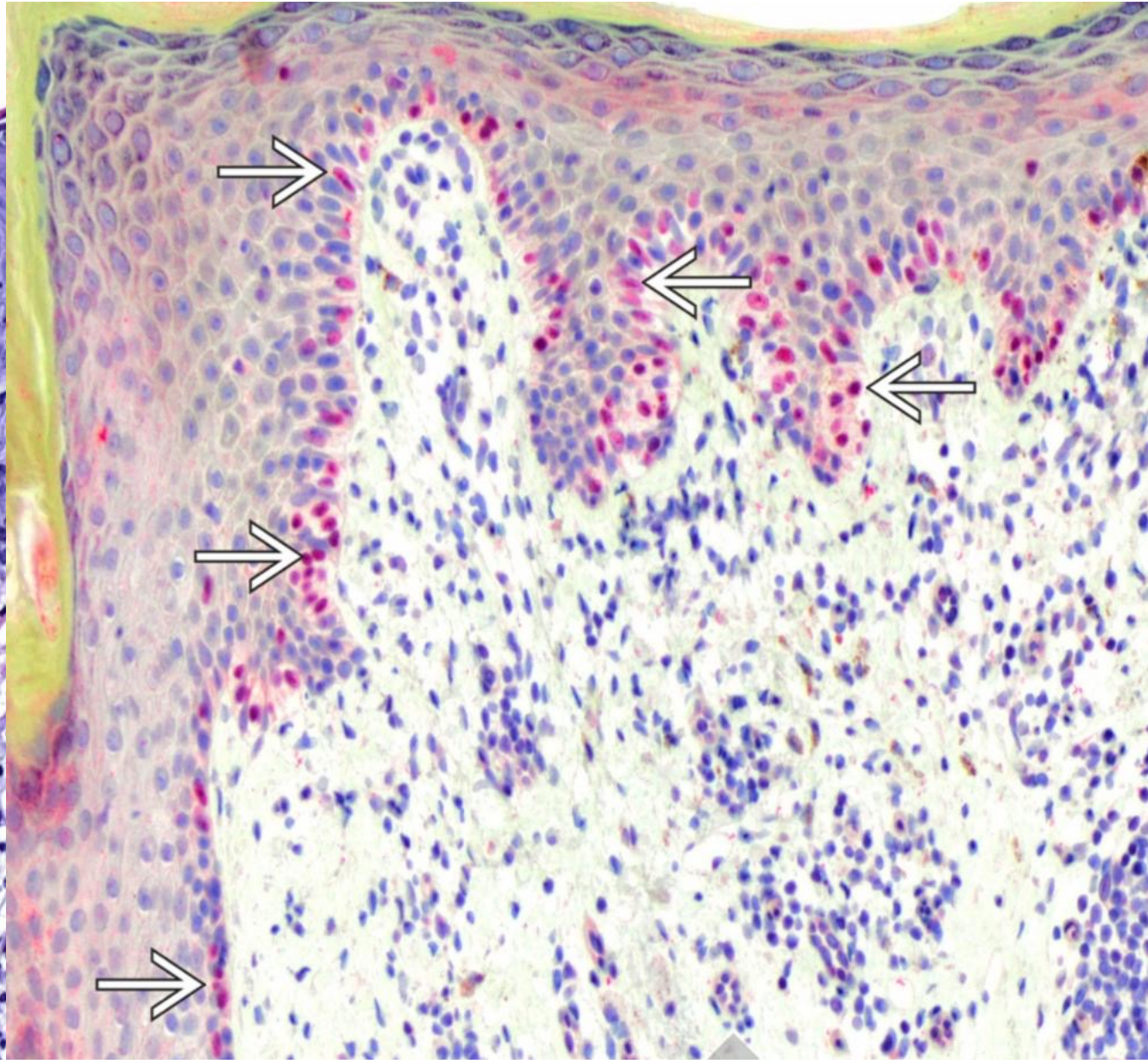
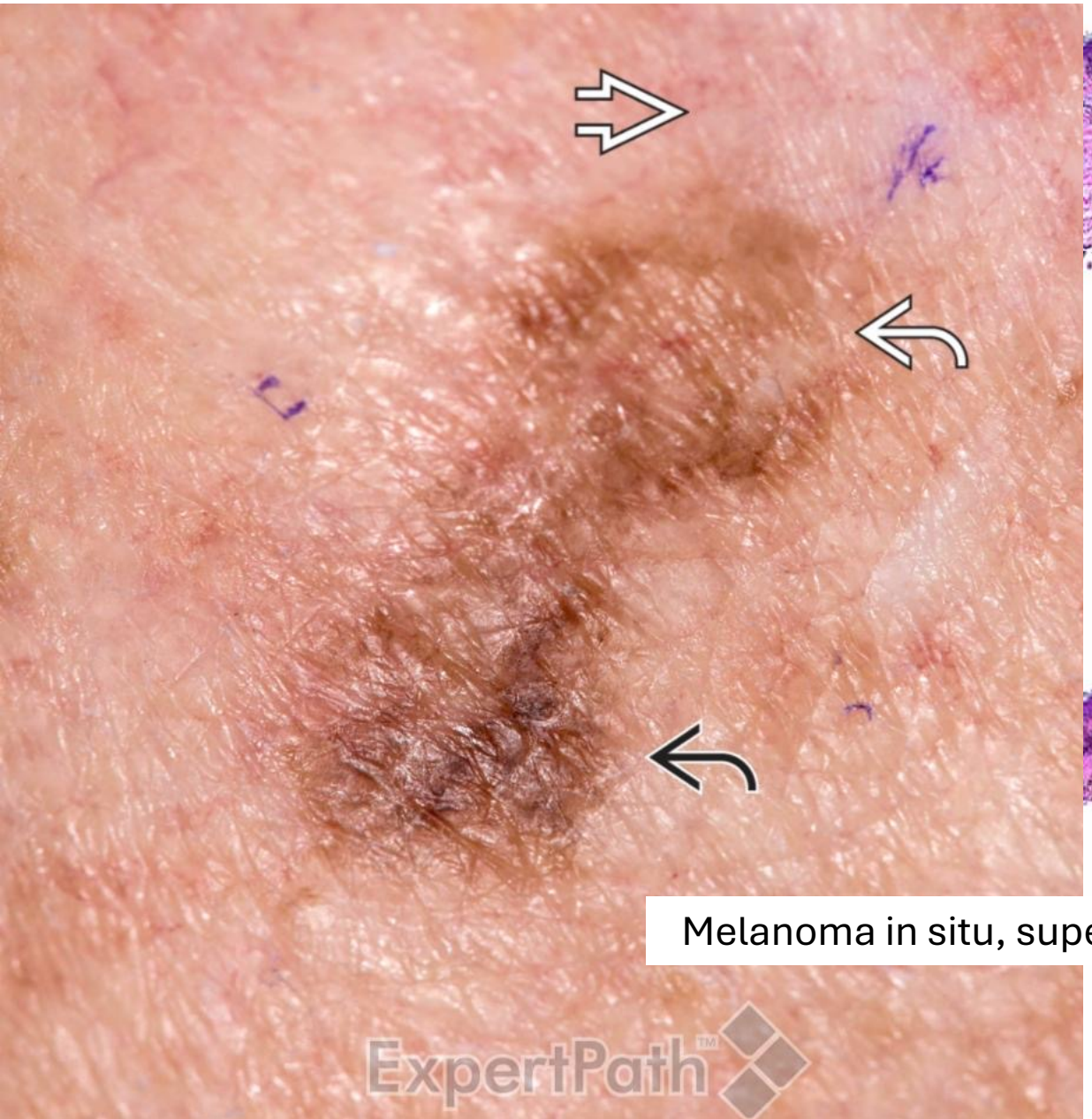


Atypical lentiginous junctional melanocytic proliferation (cyan curved arrow); exuberant follicular involvement.

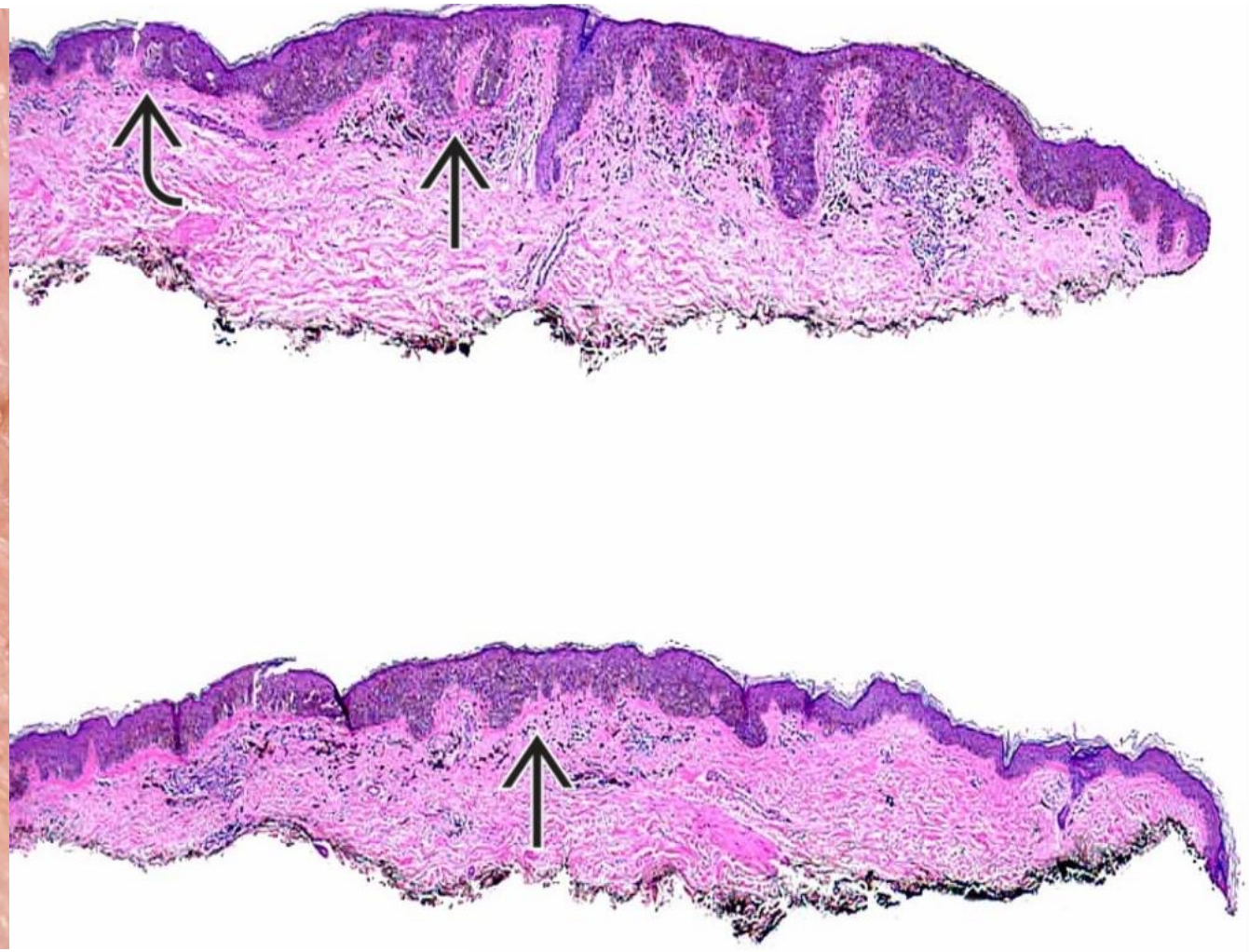


Atypical lentiginous junctional melanocytic hyperplasia is highlighted by SOX10 (red nuclei) (white solid arrow).

Asymmetric pigmented patch: hypo- (white curved arrow) and hyperpigmentation (black curved arrow) as well as depigmented area (white open arrow). (Courtesy J. Finch, MD.)

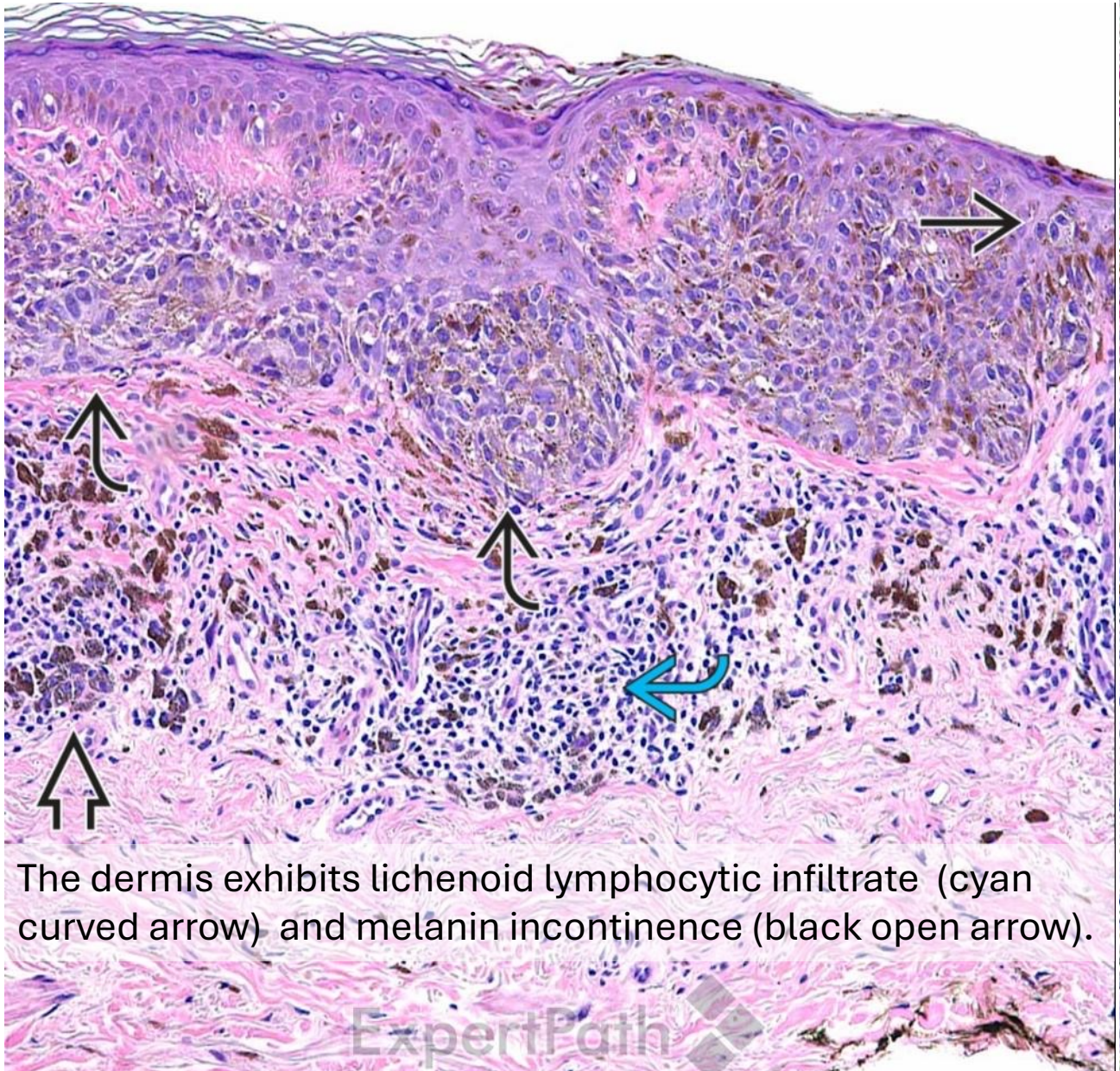


Heavily pigmented epidermal melanocytic proliferation that is lentiginous (black solid arrow) and nested (black curved arrow).



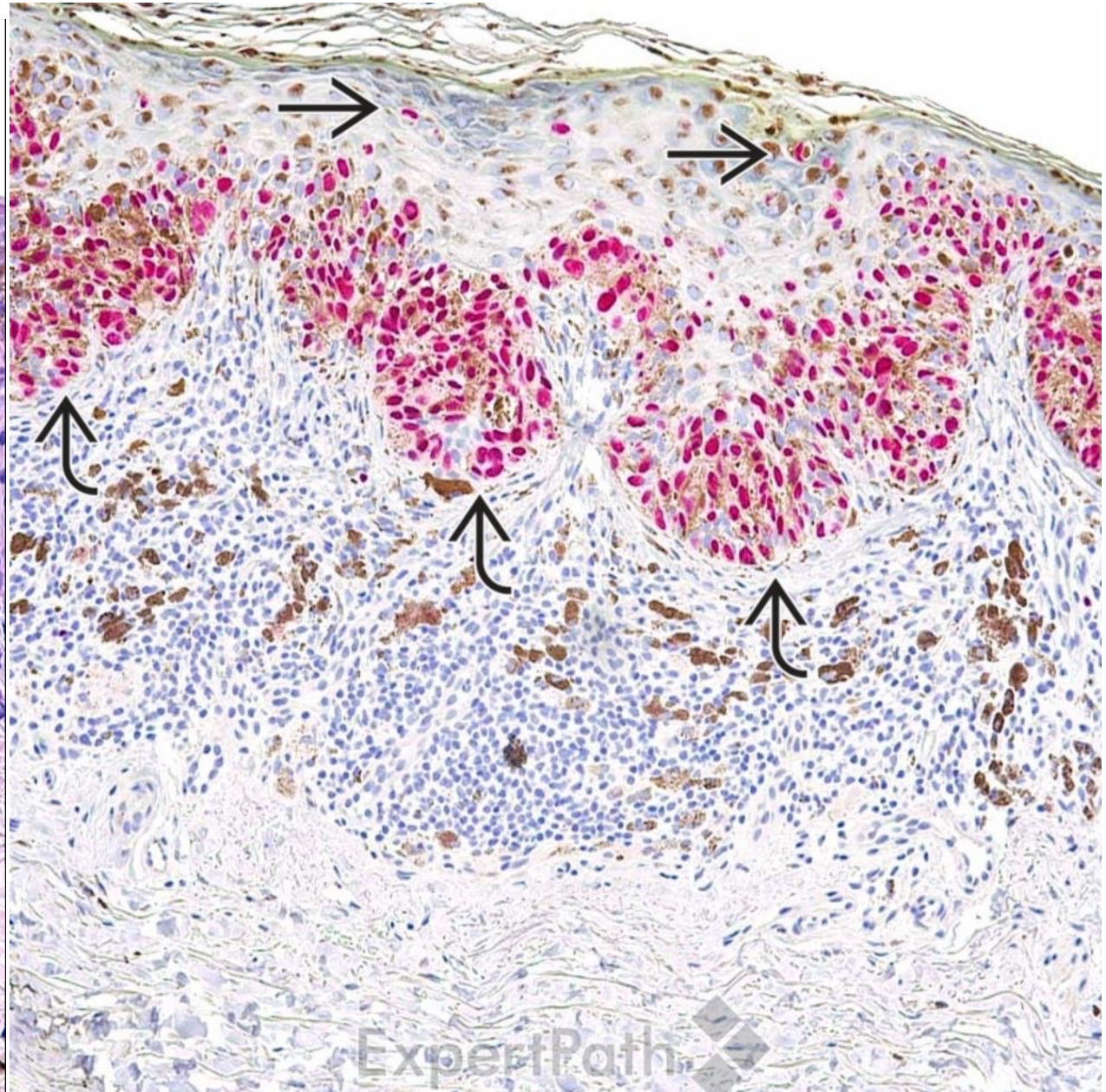
Melanoma in situ, superficial spreading type

Epidermal melanocytes replace many keratinocytes; nested (black curved arrow) and pagetoid upward scatter (black solid arrow).



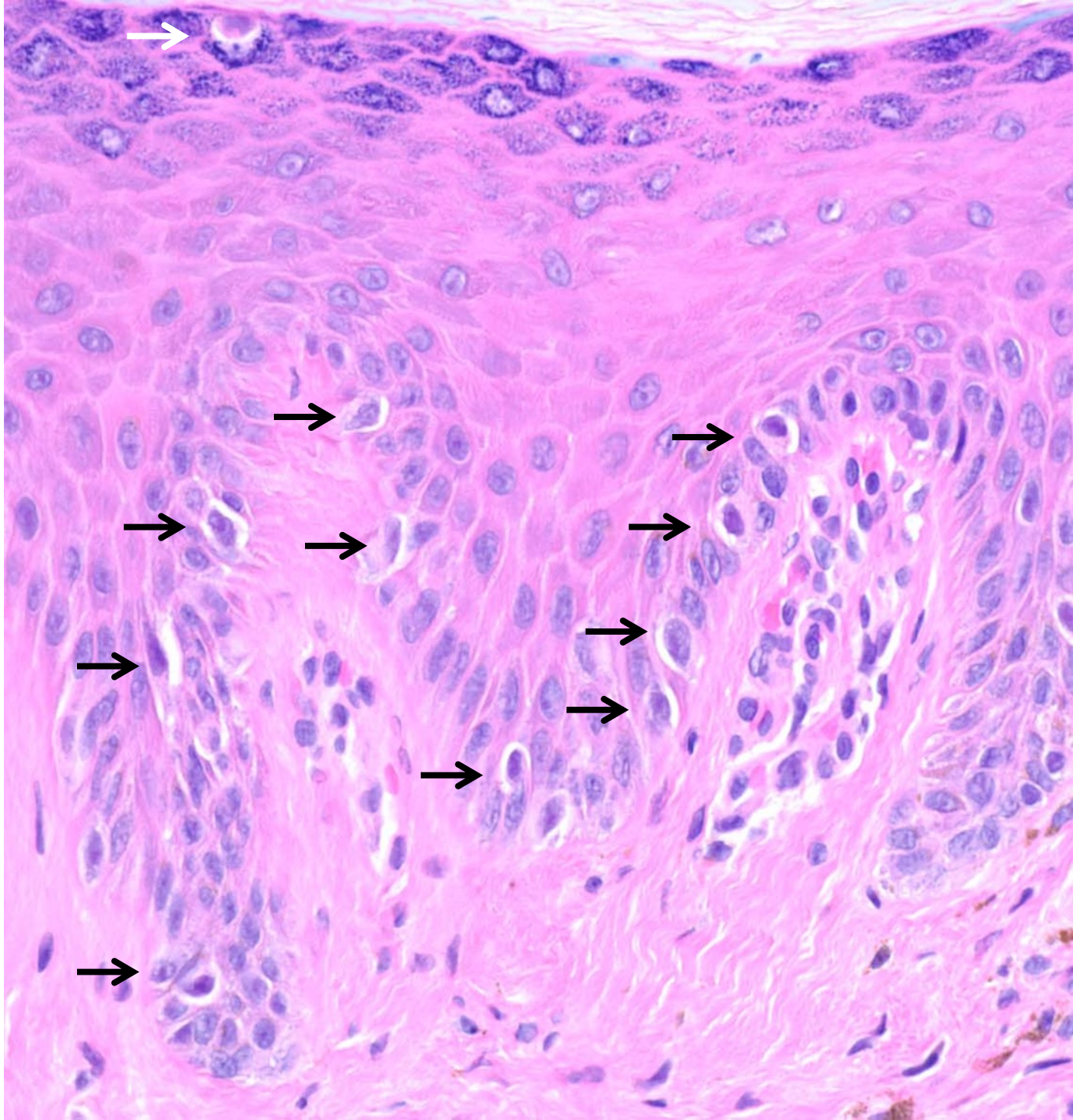
The dermis exhibits lichenoid lymphocytic infiltrate (cyan curved arrow) and melanin incontinence (black open arrow).

SOX10 confirms the presence of pagetoid (black solid arrow) and nested (black curved arrow) melanocytic growth pattern; confirms lack of dermal invasion.



ACRAL LENTIGINOUS MELANOMA IN SITU

- Angulated single melanocytes in the periphery of the lesion
- Lentiginous array
- Defies circumscription (peripheral asymmetry)



Increased density of atypical melanocytes:
Lentiginous array, limited to the basilar layer

Peri-eccrine involvement

Eccrine ducts are negative

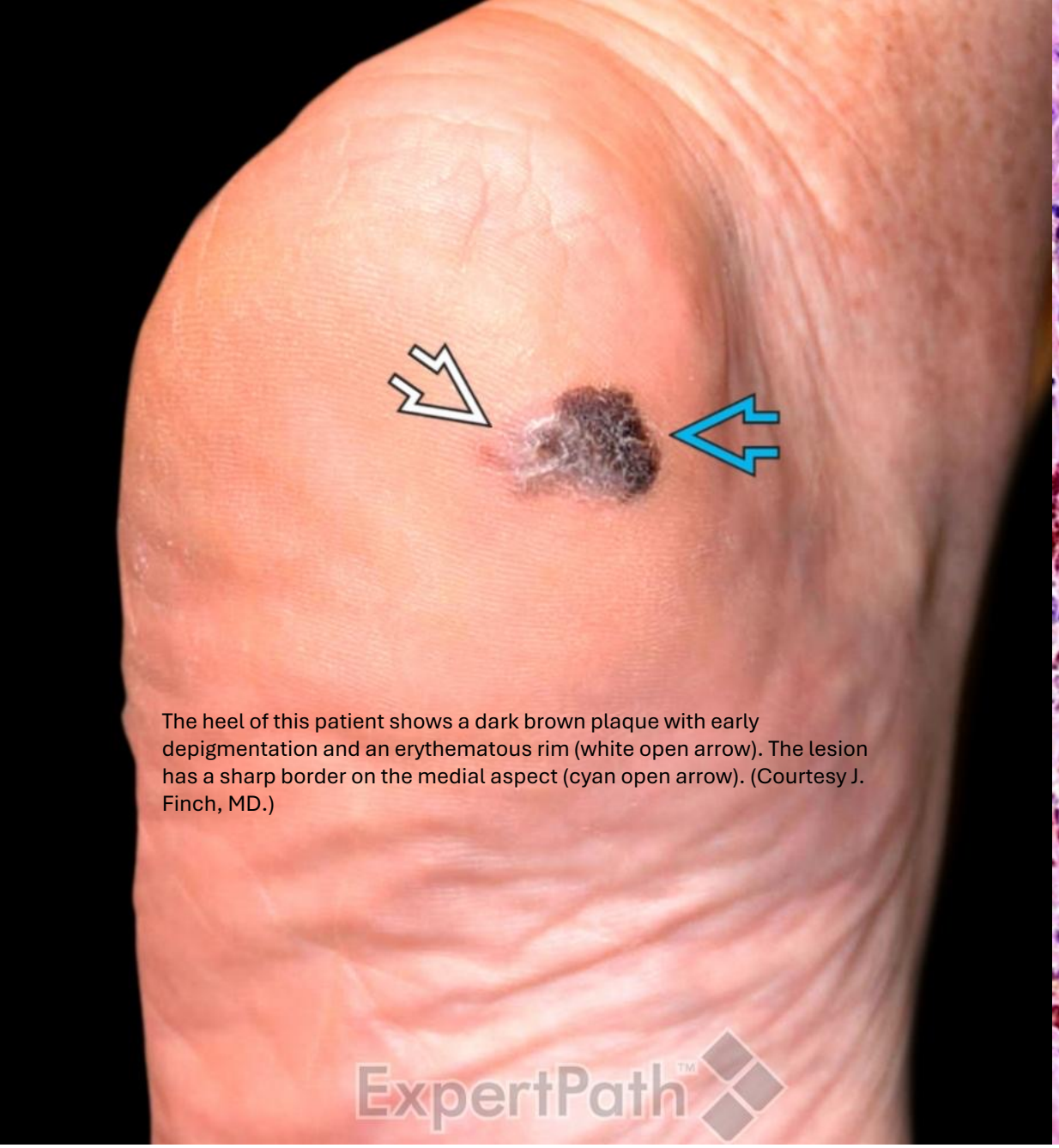
Melanoma cells in adventitia (not in dermis)

Staging pitfall: Eccrine duct involvement, not deep dermal invasion

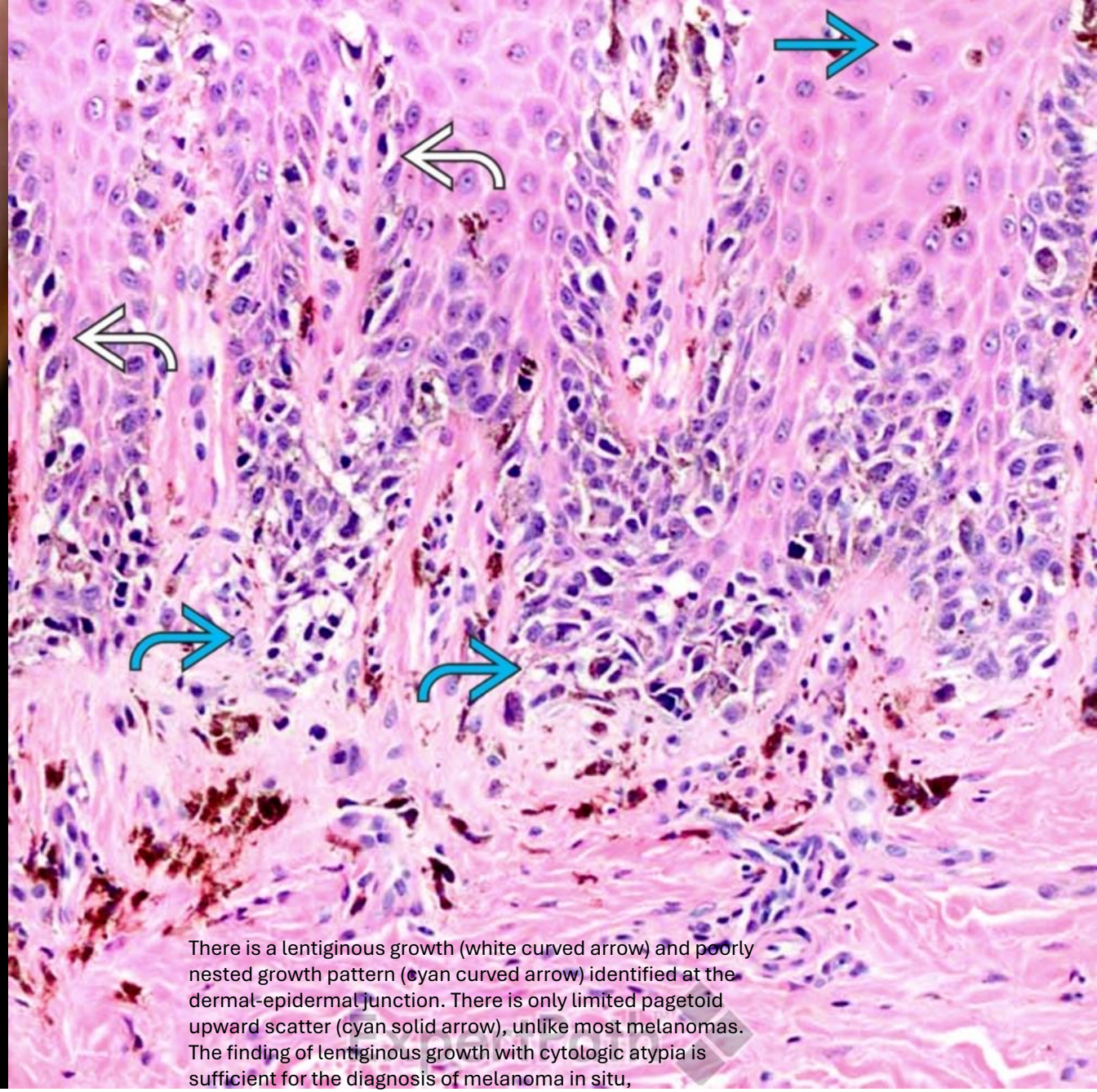
SOX-10

VARIANTS OF INVASIVE MELANOMA

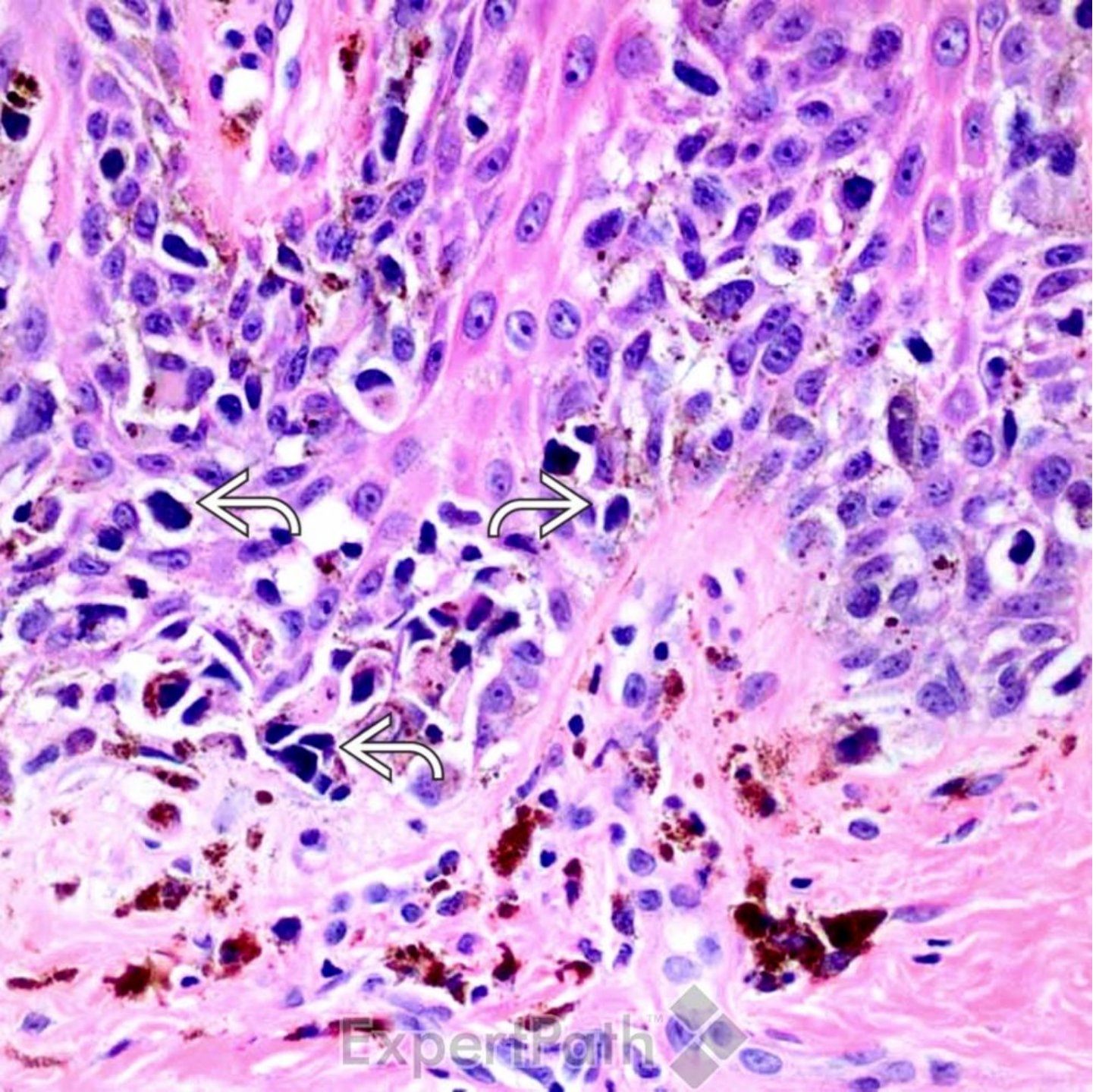
1. Melanoma, acral lentiginous type
2. Melanoma, lentigo maligna type
3. Melanoma, desmoplastic type
4. Melanoma, superficial spreading type
5. Melanoma, nodular type
6. Melanoma, nevoid type



The heel of this patient shows a dark brown plaque with early depigmentation and an erythematous rim (white open arrow). The lesion has a sharp border on the medial aspect (cyan open arrow). (Courtesy J. Finch, MD.)

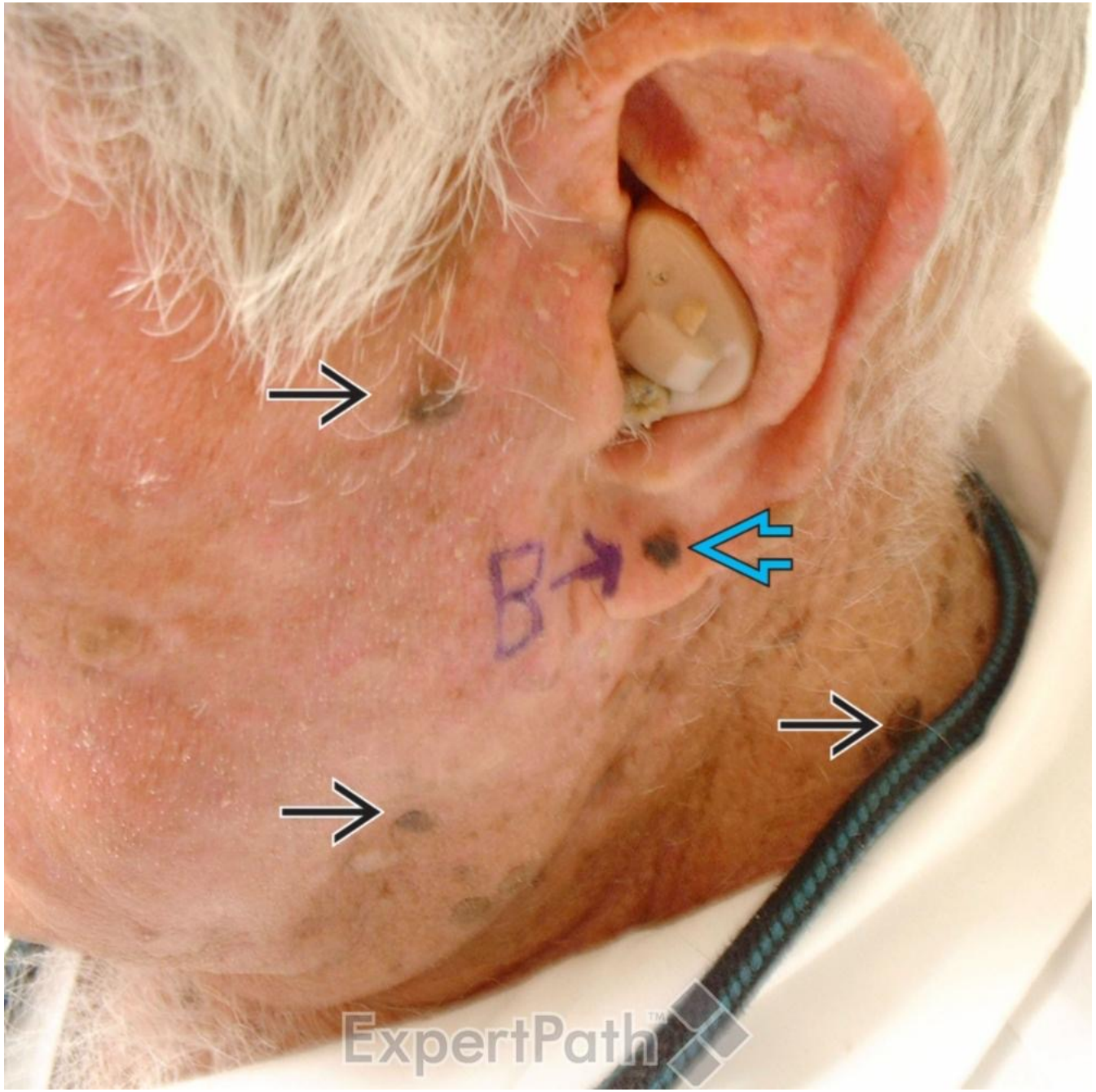


There is a lentiginous growth (white curved arrow) and poorly nested growth pattern (cyan curved arrow) identified at the dermal-epidermal junction. There is only limited pagetoid upward scatter (cyan solid arrow), unlike most melanomas. The finding of lentiginous growth with cytologic atypia is sufficient for the diagnosis of melanoma in situ, acrolentiginous type.



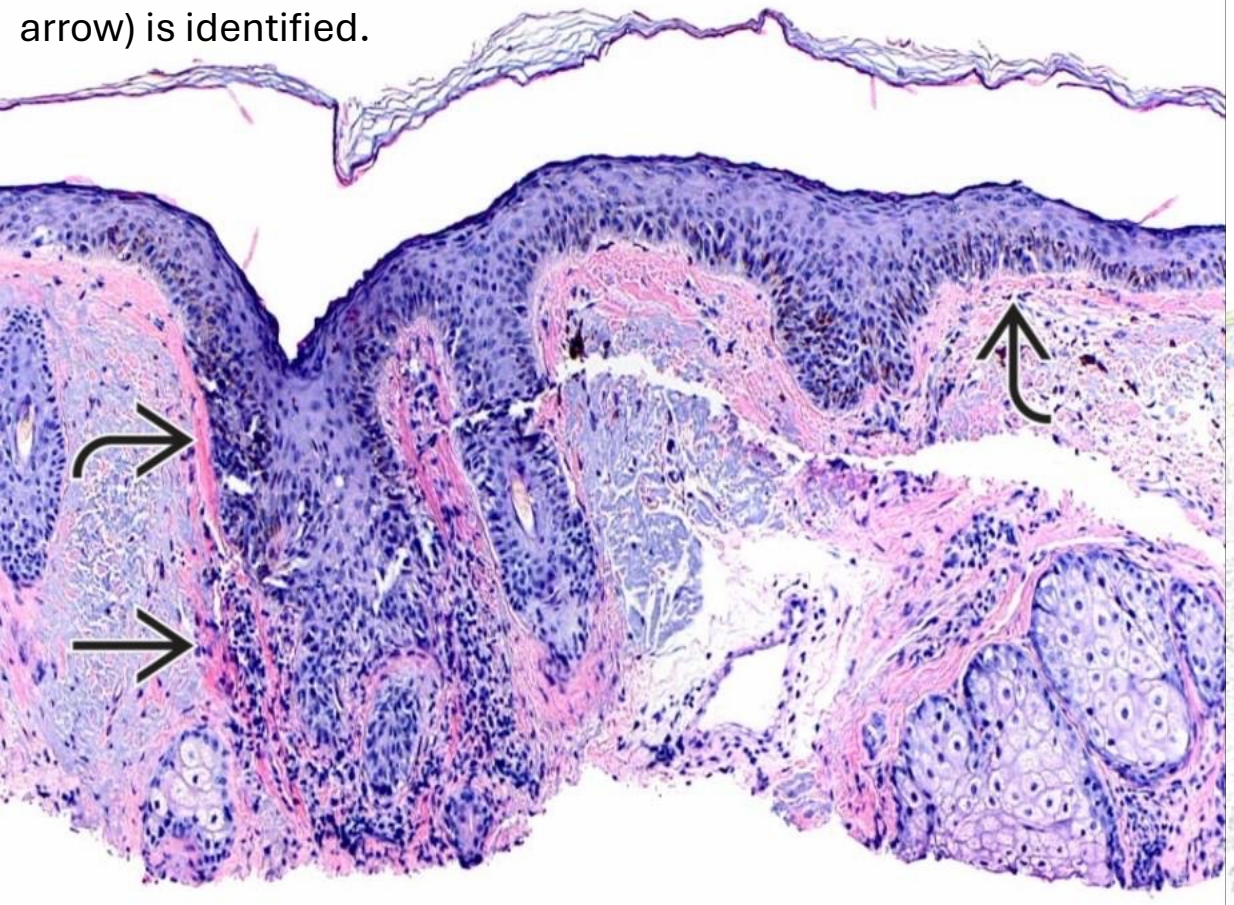
Melanoma, acral lentiginous type

Higher magnification of same lesion shows angulated, hyperchromatic-staining nuclei with scant amounts of cytoplasm (white curved arrow). Note that the melanocytic hyperplasia has replaced most of the basal keratinocytes.

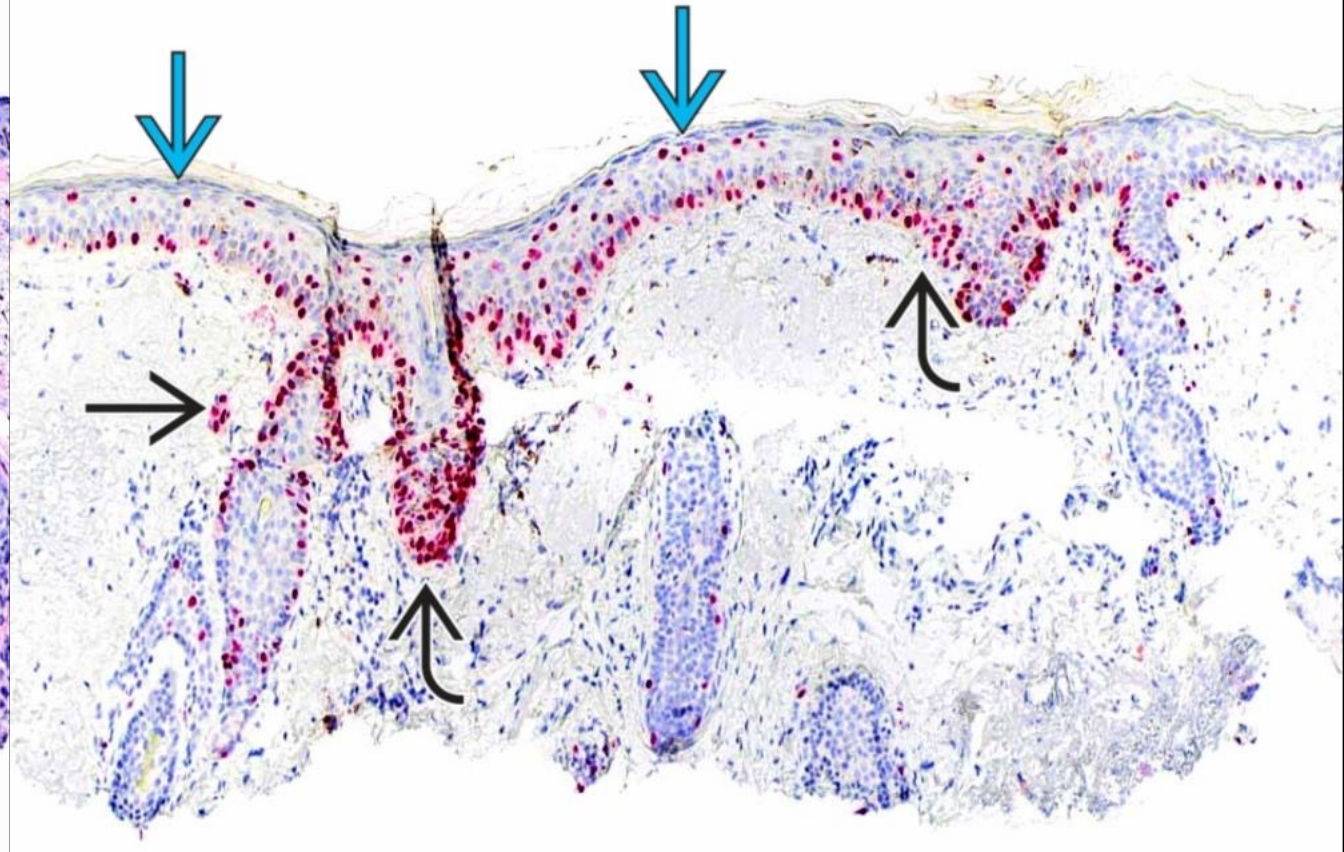


The marked lesion is concerning for melanoma (cyan open arrow). This lesion stands out among the many seborrheic keratoses (black solid arrow) on the left face and neck. (Courtesy J. Finch, MD.)

Contiguous, lentiginous growth of atypical melanocytes (black curved arrow) is characterized by cellular crowding at the basal layer of epidermis. An areas of likely microinvasion (black solid arrow) is identified.



Microinvasion with a solitary dermal nest (black solid arrow) next to the hair follicle is confirmed. Moreover, poorly nested lentiginous growth (black curved arrow) and upward scatter (cyan solid arrow) of atypical melanocytes with adnexal involvement are evident.



Melanoma, lentigo maligna type

SOX-10

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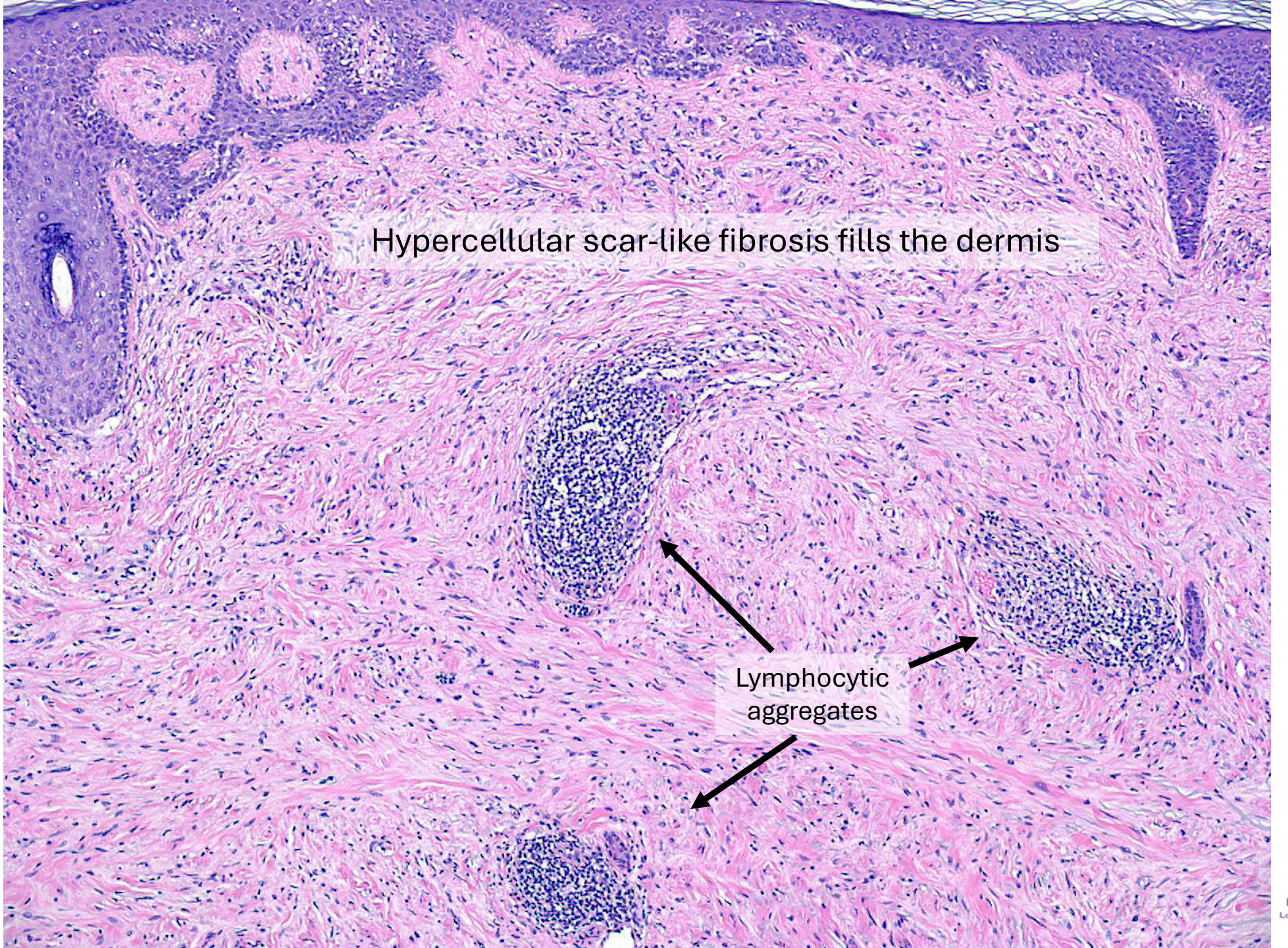
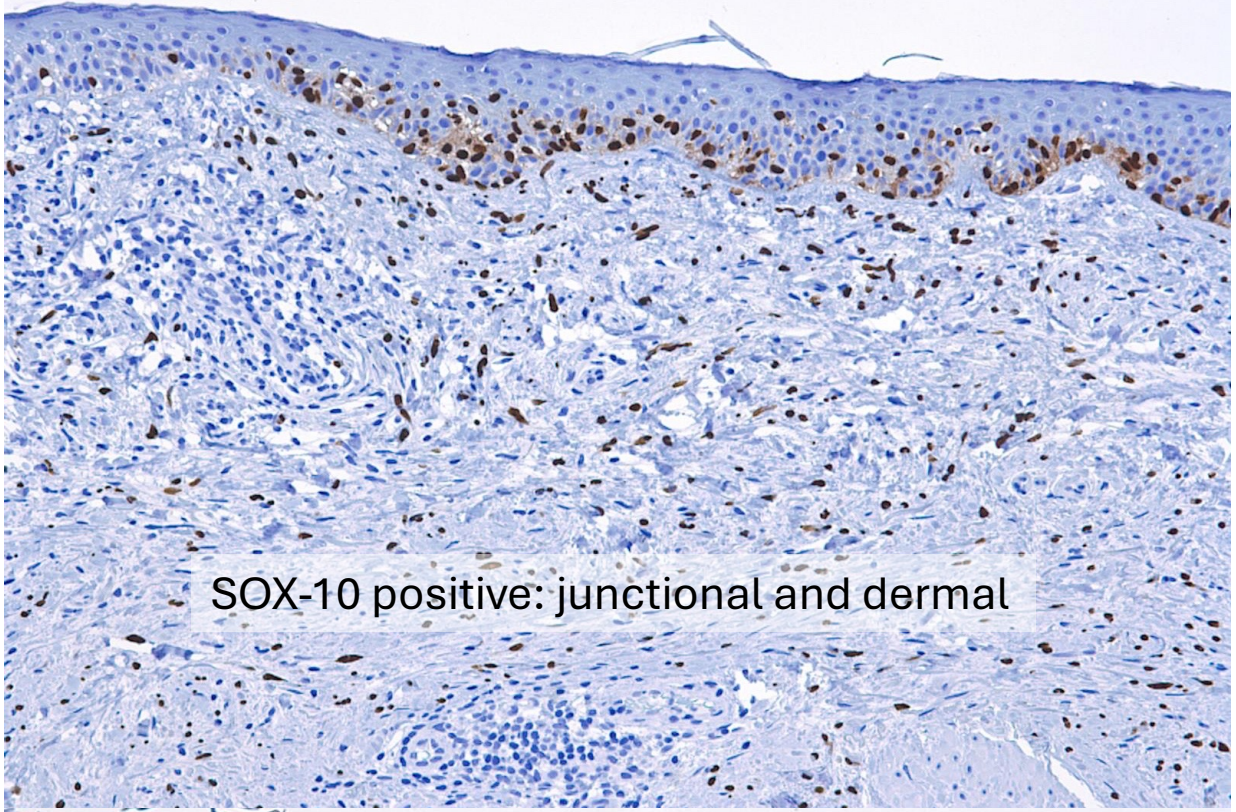
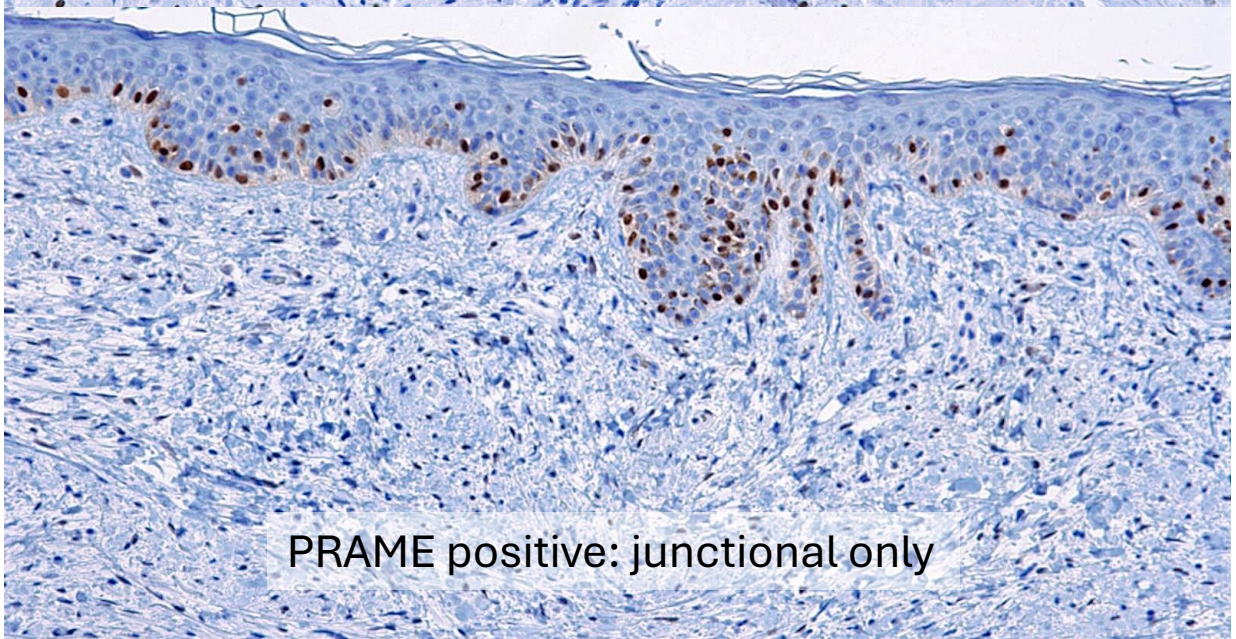
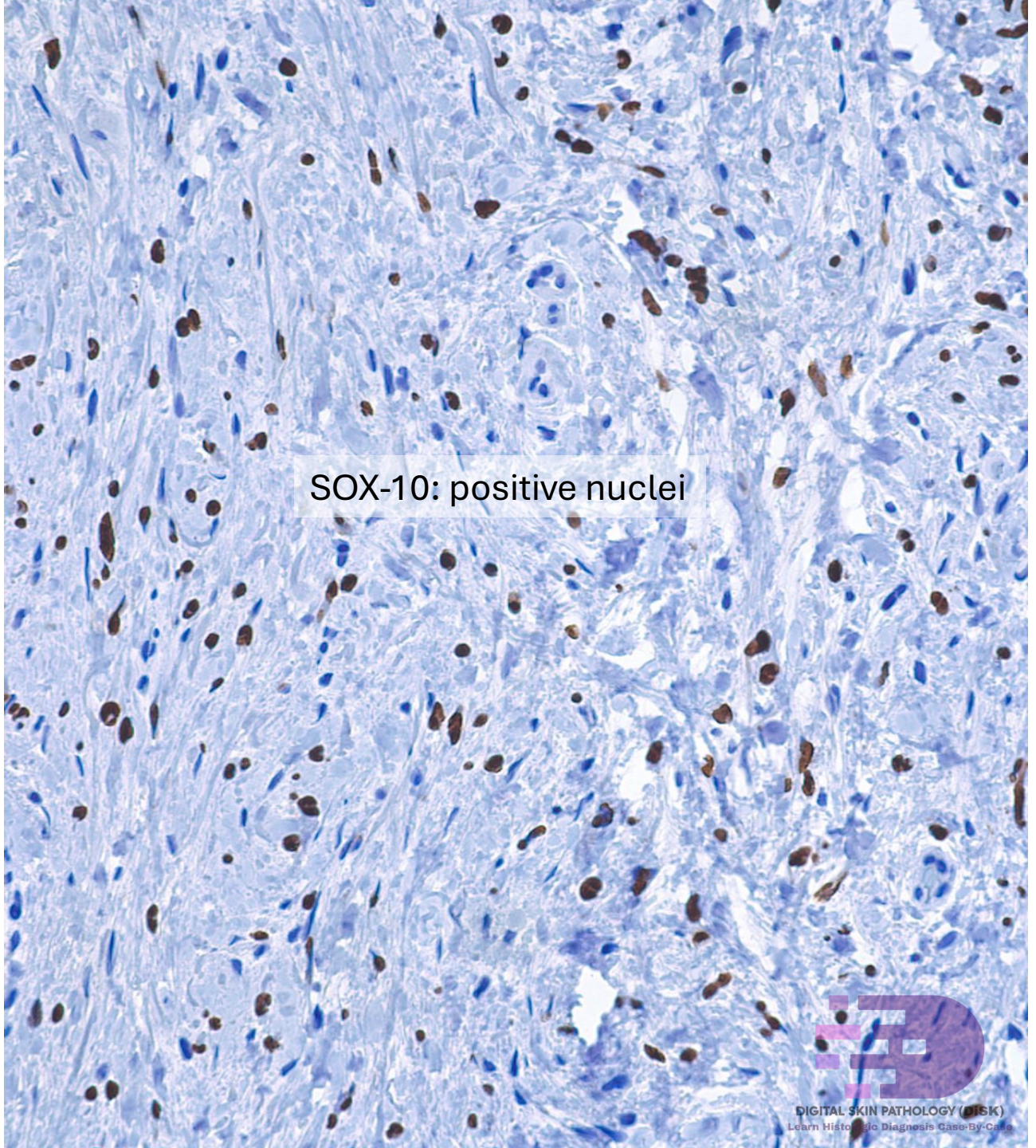
Melanoma, desmoplastic type

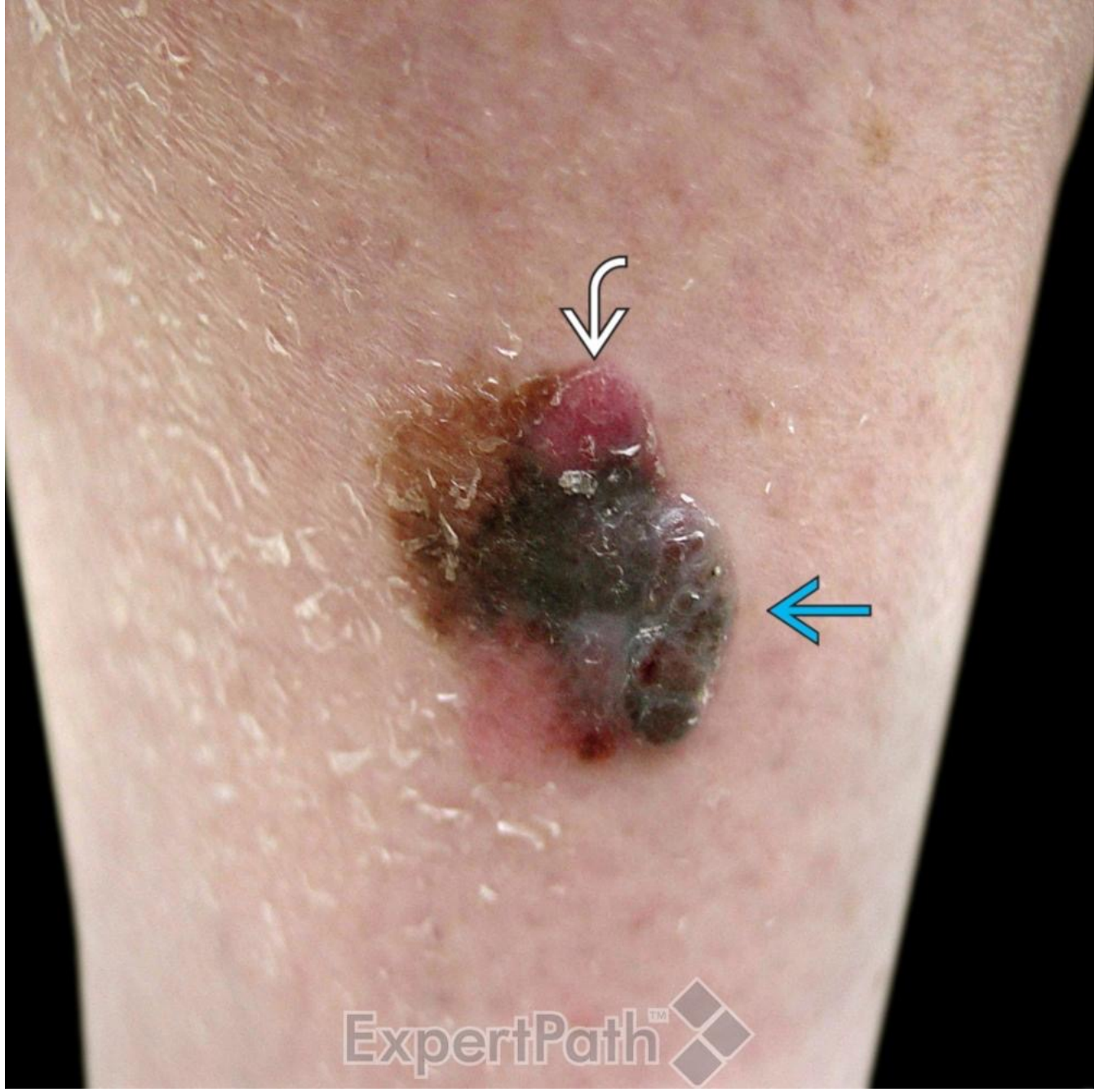


DIGITAL SKIN PATHOLOGY (DiSK)
Learn Histologic Diagnosis Case-By-Case


SOX-10 positive: junctional and dermal

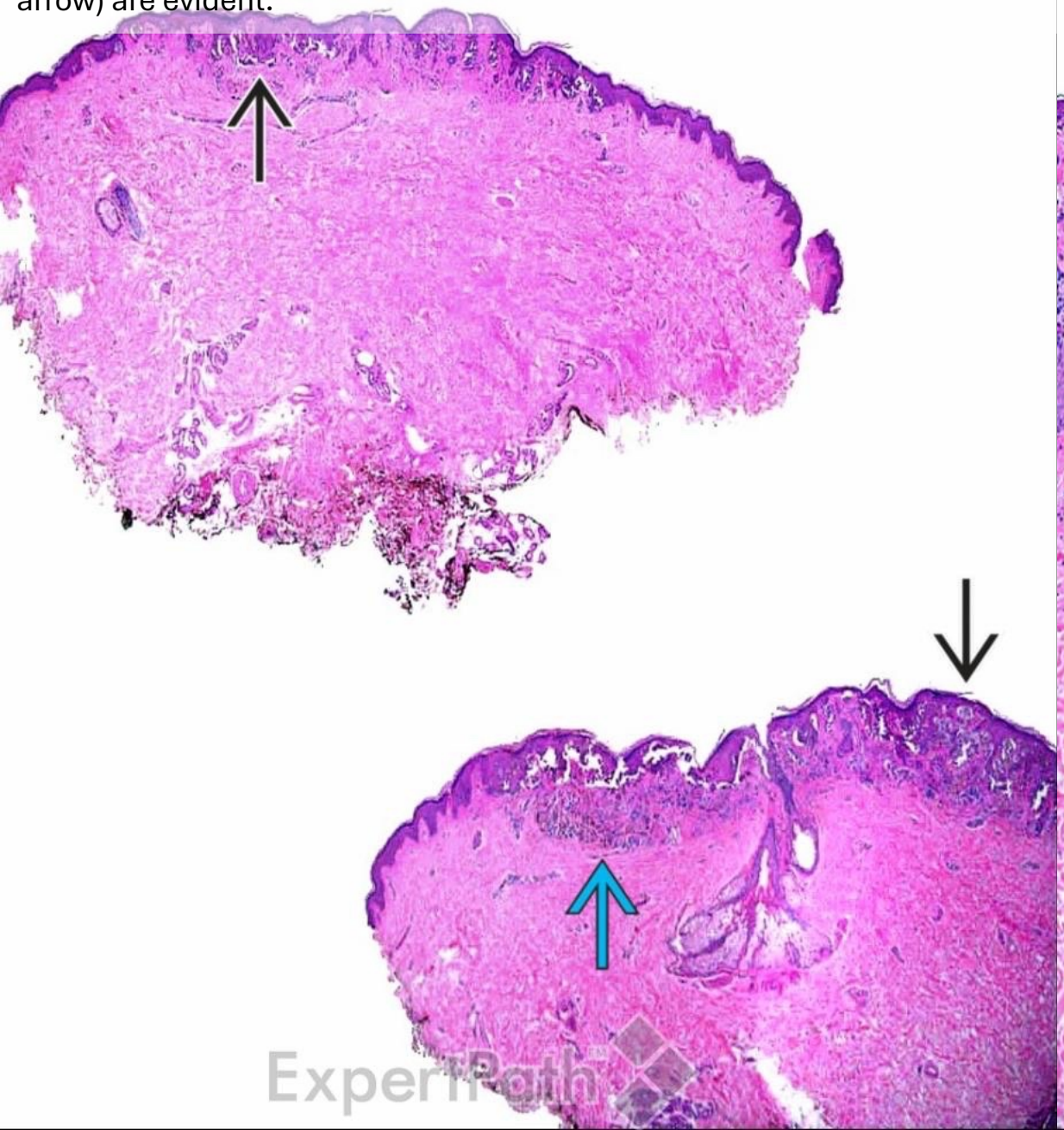

PRAME positive: junctional only


SOX-10: positive nuclei
DIGITAL SKIN PATHOLOGY (DISK)

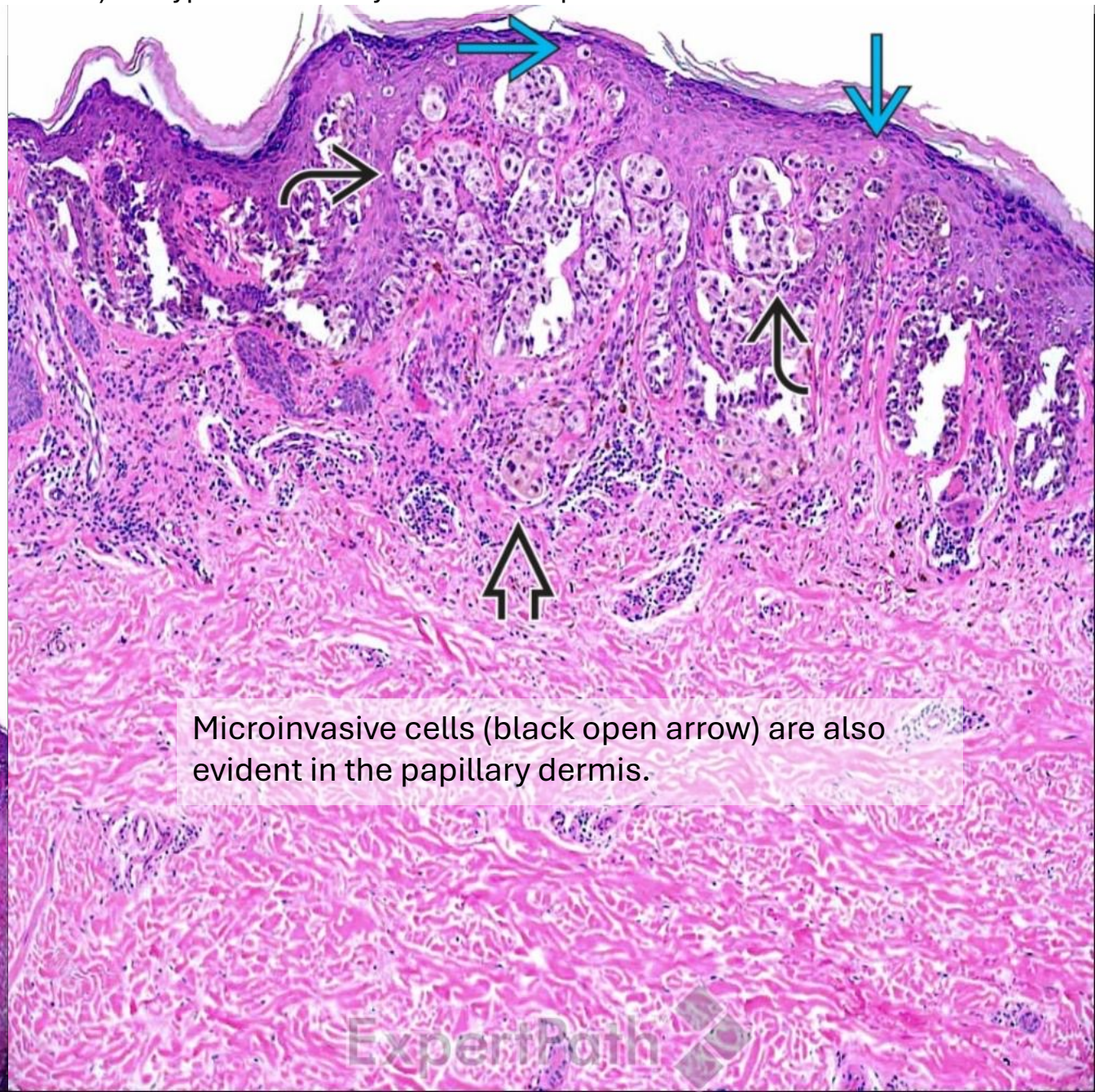


This large, growing patch with variegated colors proved to be a melanoma, superficial spreading type (MM-SST) on histologic examination. Note the patch (white curved arrow) at the edge, which represents the horizontal growth, and the plaque, which represents the invasive component (cyan solid arrow). (Courtesy J. Finch, MD.)

An asymmetric compound pigmented proliferation is evident. A nested pattern (black solid arrow) and significant dermal component (cyan solid arrow) are evident.



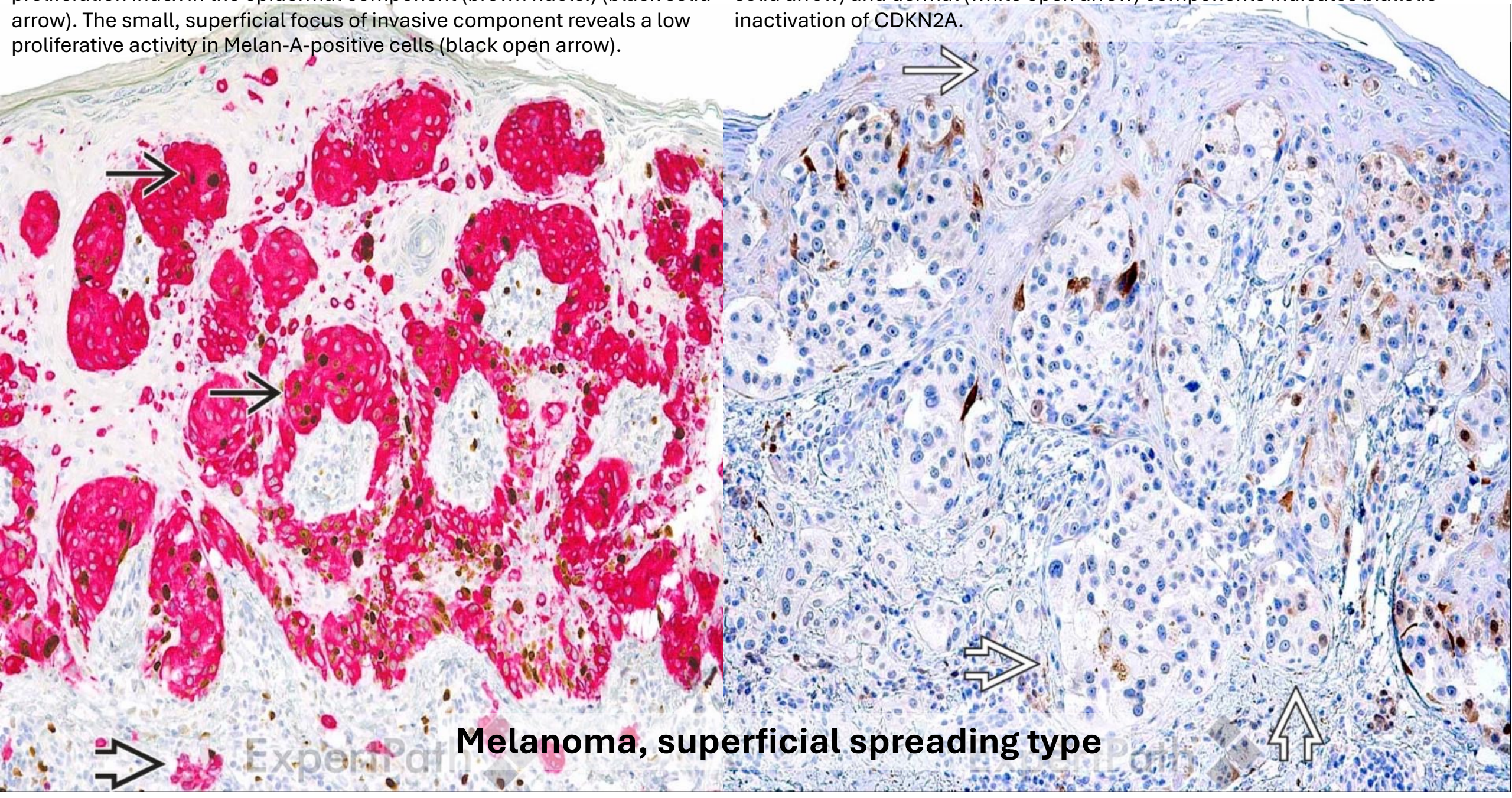
Confluent nesting (black curved arrow) and pagetoid upward scatter (cyan solid arrow) of atypical melanocytes with the epidermis are noted.



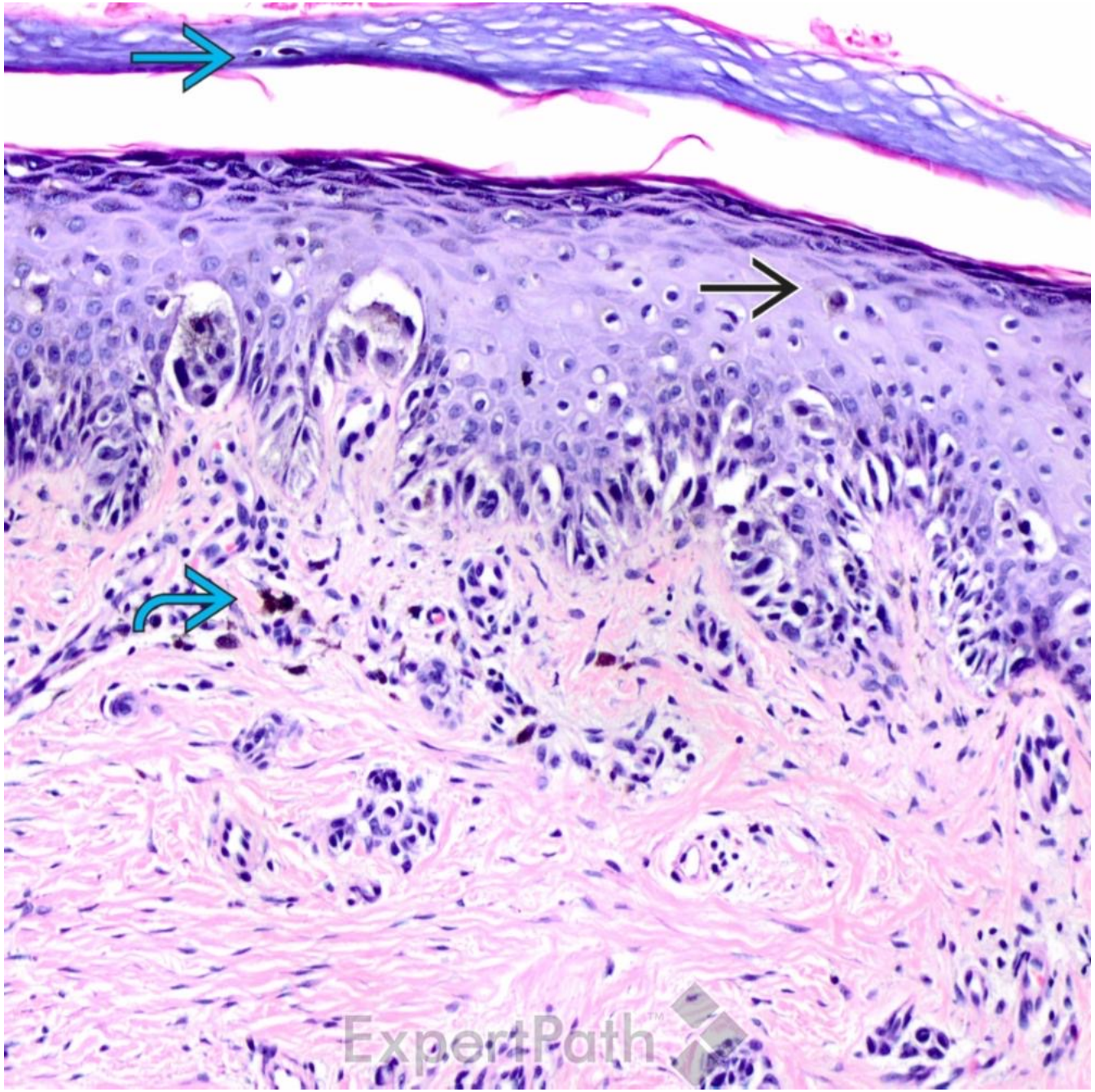
Microinvasive cells (black open arrow) are also evident in the papillary dermis.

Ki-67/Melan-A double immunostaining demonstrates increased proliferation index in the epidermal component (brown nuclei) (black solid arrow). The small, superficial focus of invasive component reveals a low proliferative activity in Melan-A-positive cells (black open arrow).

Complete loss of p16 (tumor suppressor protein) in both the epidermal (white solid arrow) and dermal (white open arrow) components indicates biallelic inactivation of CDKN2A.



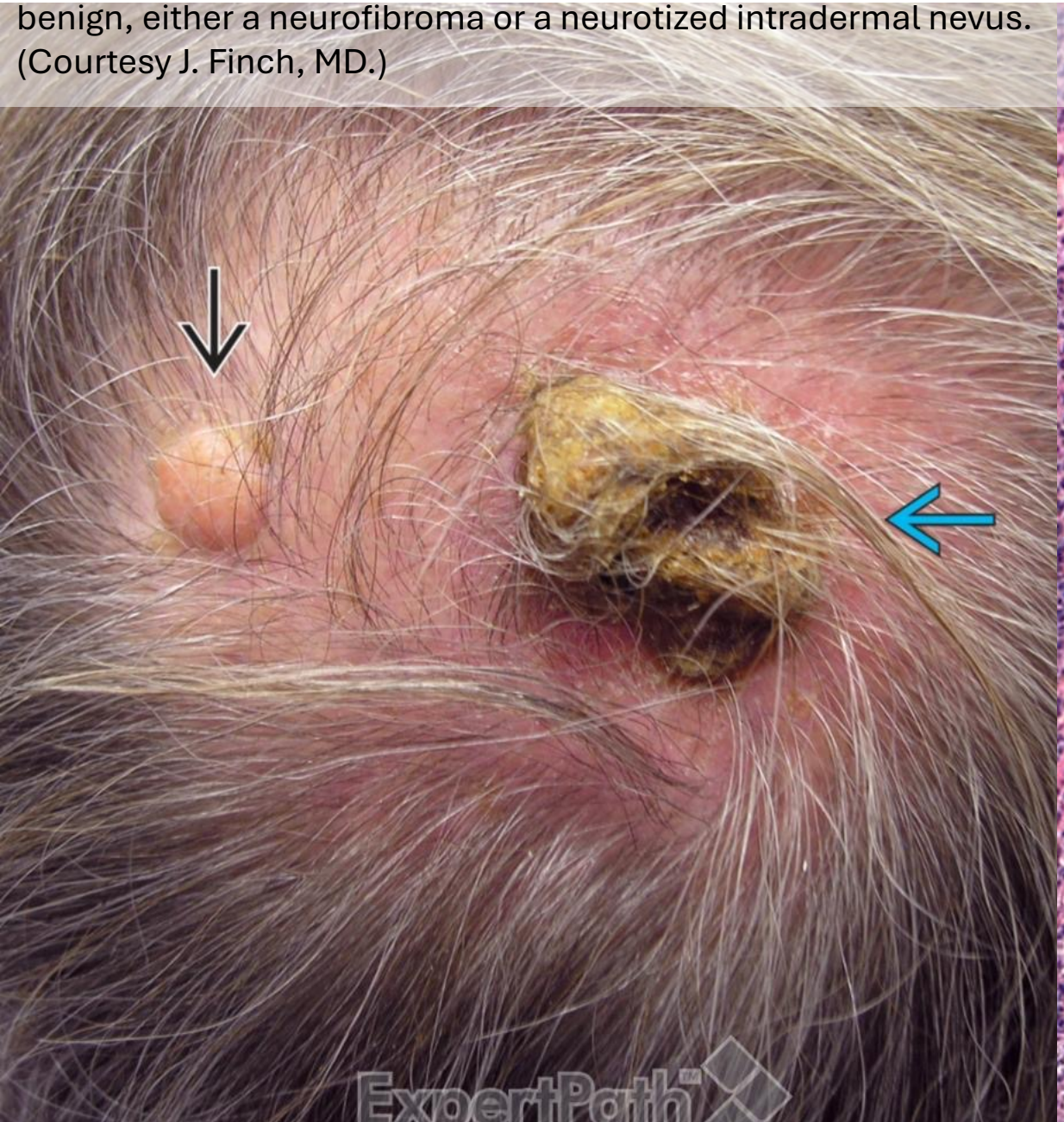
Melanoma, superficial spreading type



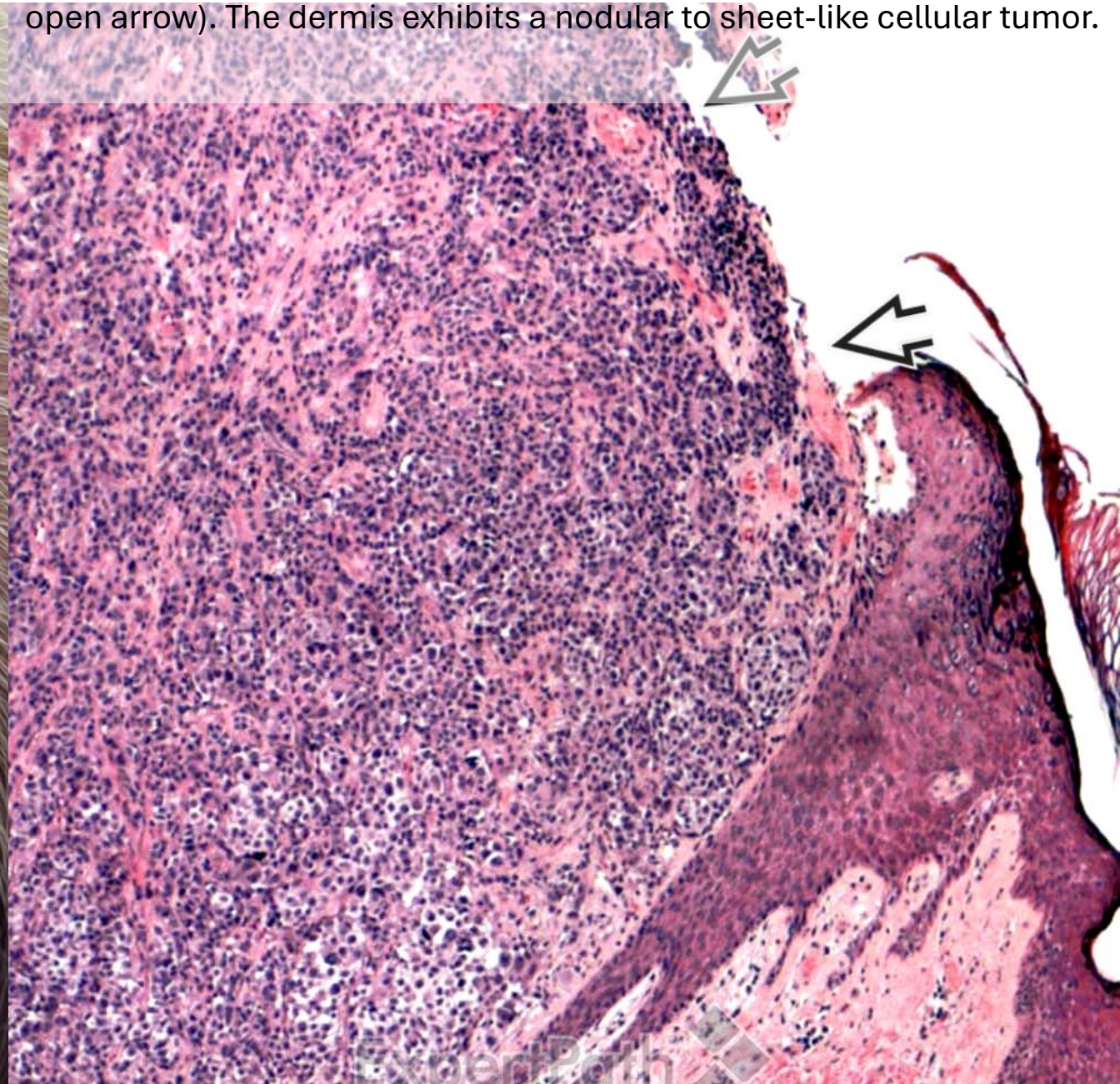
Differential diagnosis: Recurrent nevus (pseudomelanoma)

Limited pagetoid scatter (black solid arrow) may be evident. Melanin deposition in the dermis (cyan curved arrow) &/or stratum corneum (cyan solid arrow) are consistent with prior trauma (i.e., previous biopsy) in recurrent nevi.

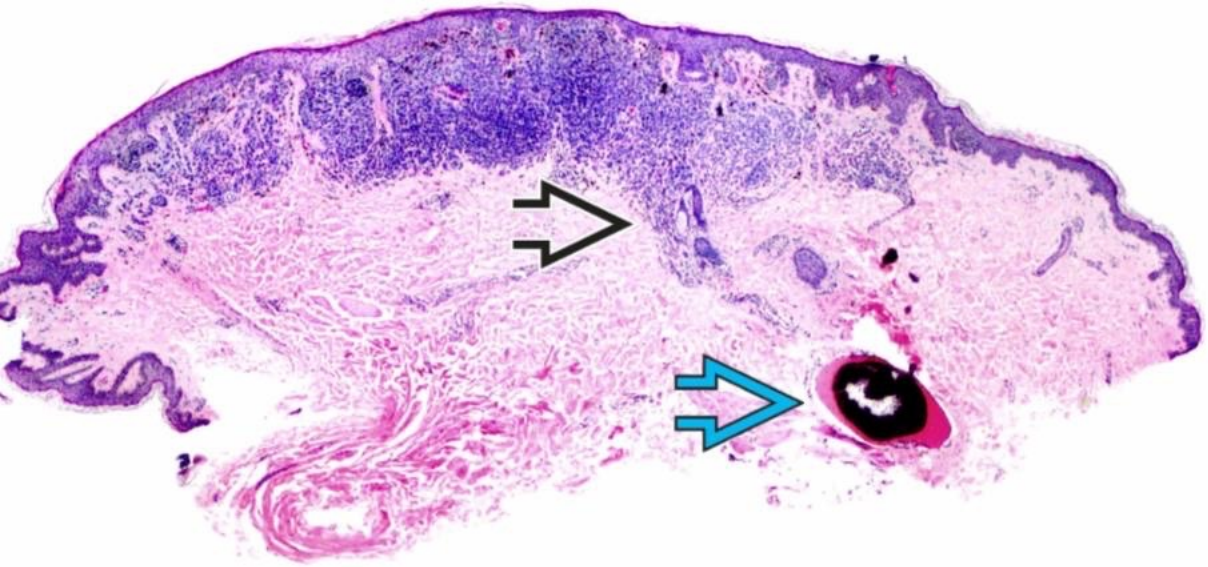
A tumor (cyan solid arrow) is crusted on the scalp of this older man. The skin-colored nodule on the left (black solid arrow) is benign, either a neurofibroma or a neurotized intradermal nevus. (Courtesy J. Finch, MD.)



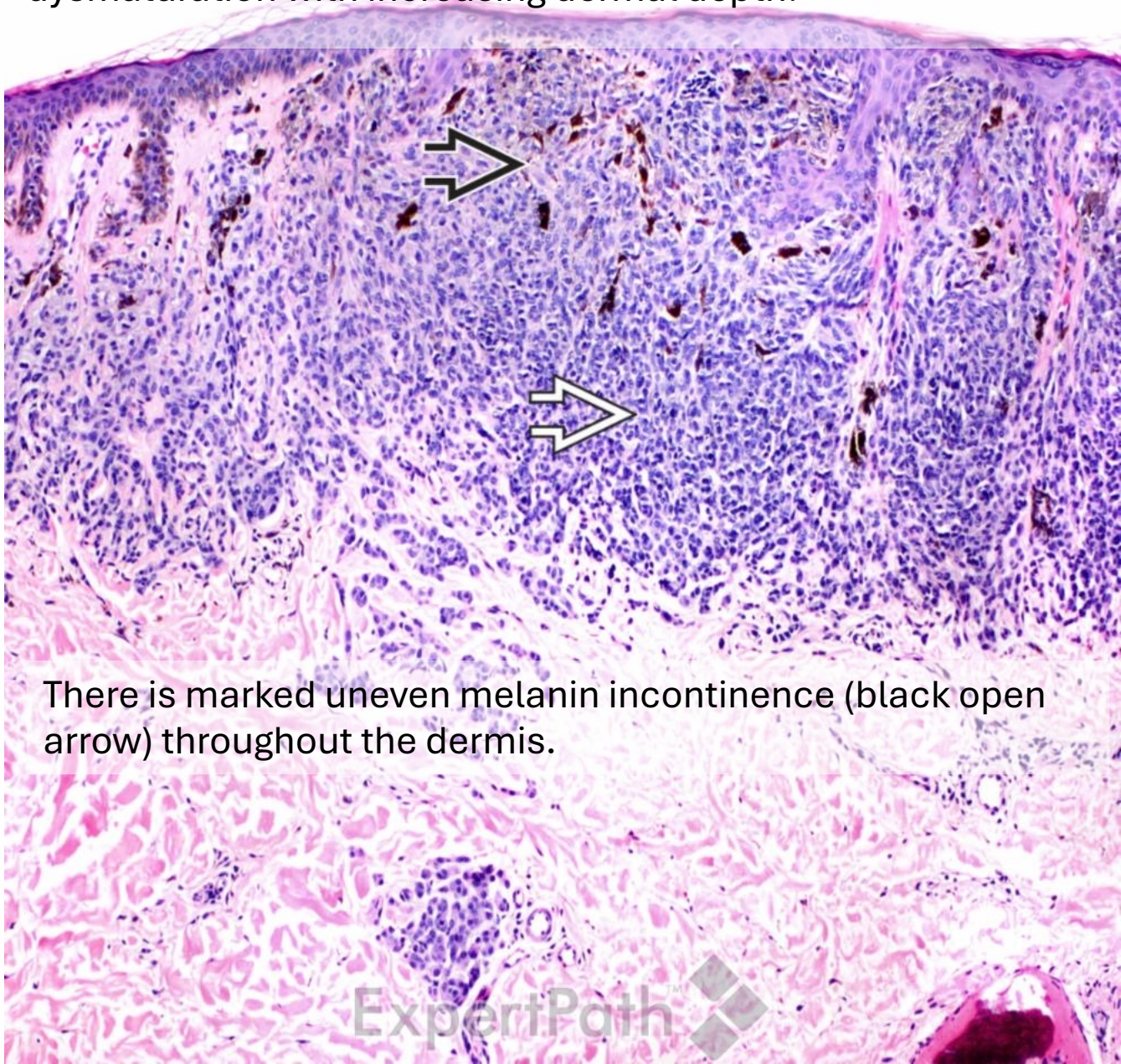
Nodular malignant melanoma shows a large, expansile dermal nodule with significant epidermal thinning and full-thickness ulceration (black open arrow). The dermis exhibits a nodular to sheet-like cellular tumor.



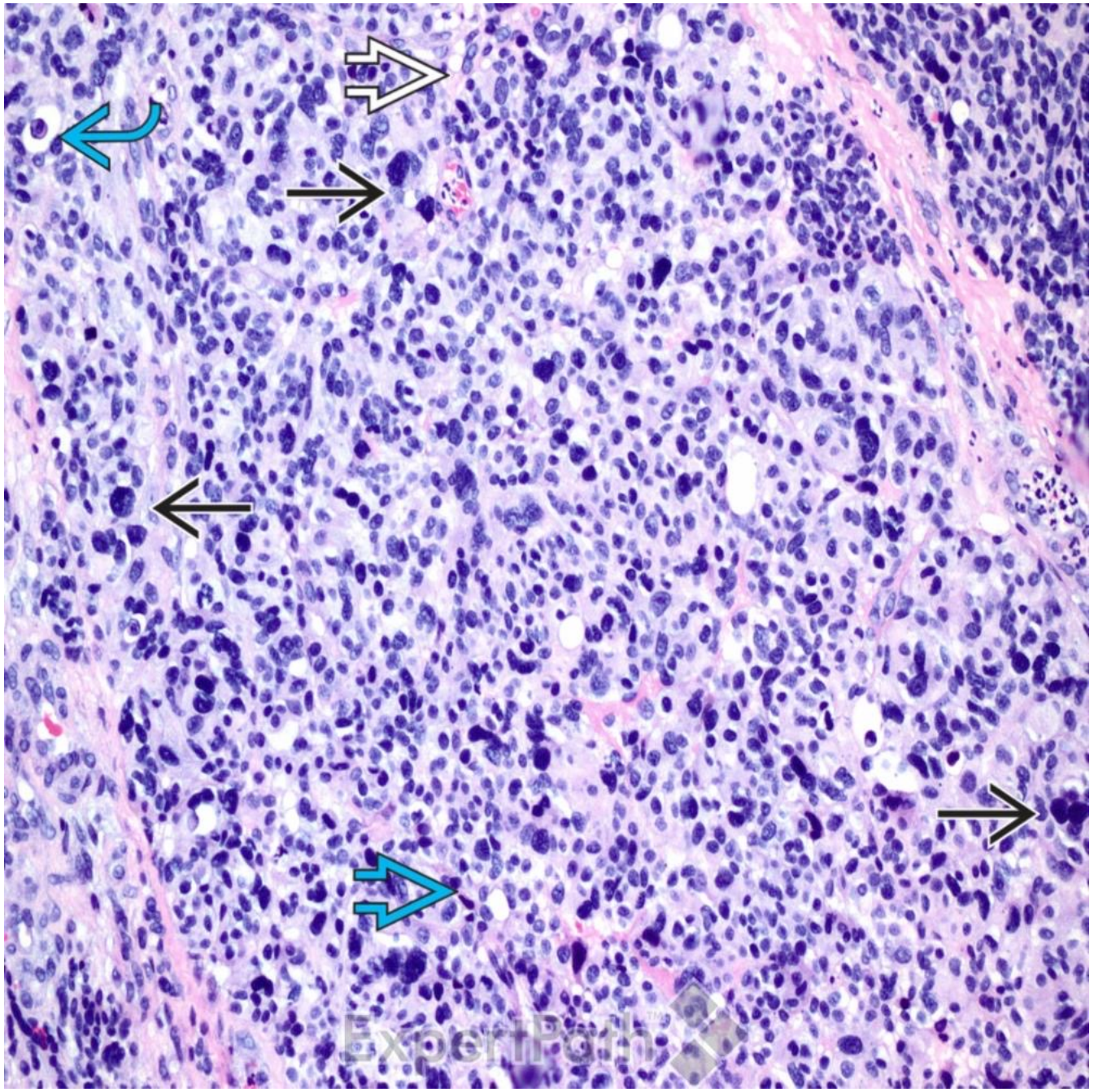
Nevoid melanoma shows a symmetrical, small melanocytic tumor with some congenital features (condensation of melanocytes around adnexa) (black open arrow). There is an incidental osteoma cutis (cyan open arrow).



Tumor shows hyperchromasia (white open arrow) and dysmaturation with increasing dermal depth.



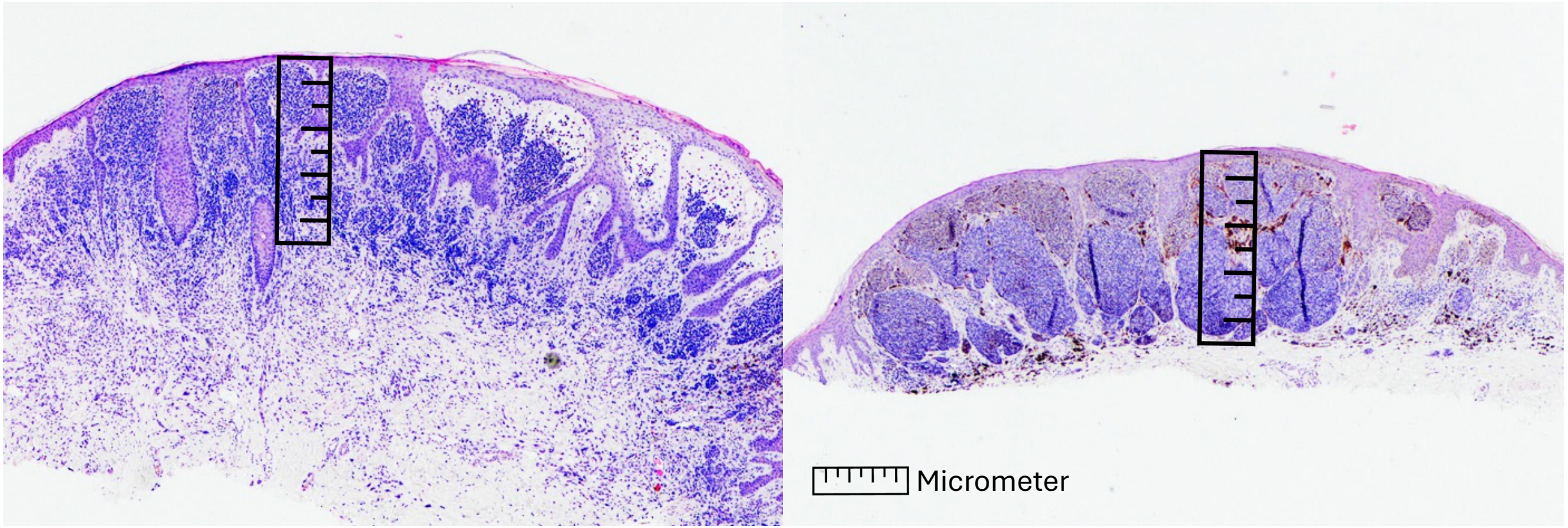
There is marked uneven melanin incontinence (black open arrow) throughout the dermis.



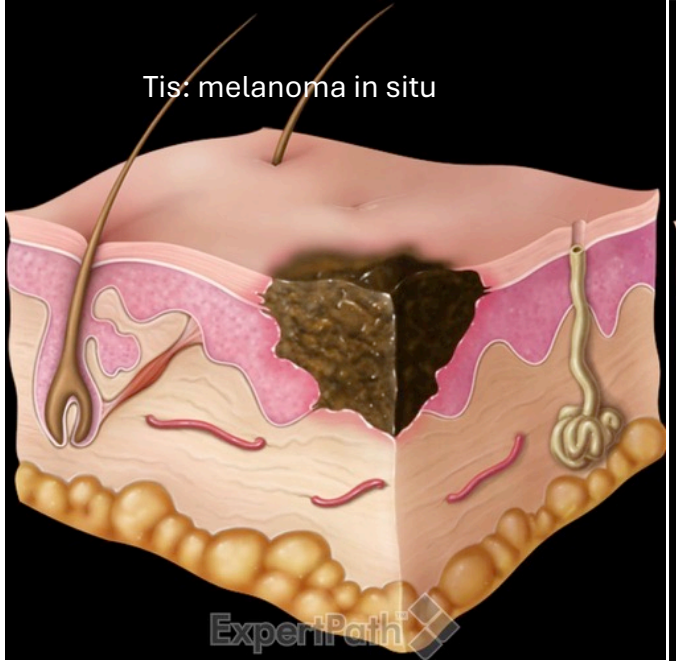
Melanoma, nevoid type

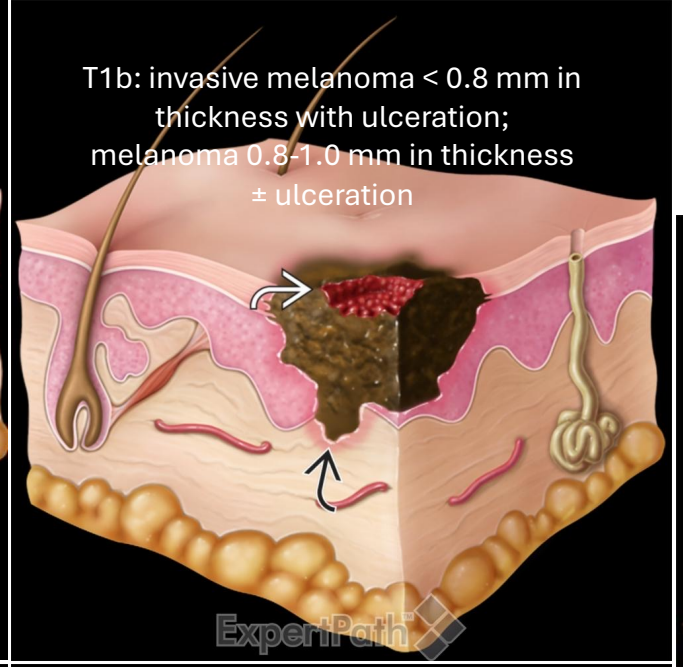
Examining the lesion from top (white open arrow) to bottom (cyan open arrow) reveals dysmaturation with increasing dermal depth. Moreover, there is significant nuclear pleomorphism (black solid arrow). Also found are apoptotic bodies (cyan curved arrow), but no sheet-like necrosis is found. There were mitotic figures in other fields (not shown).

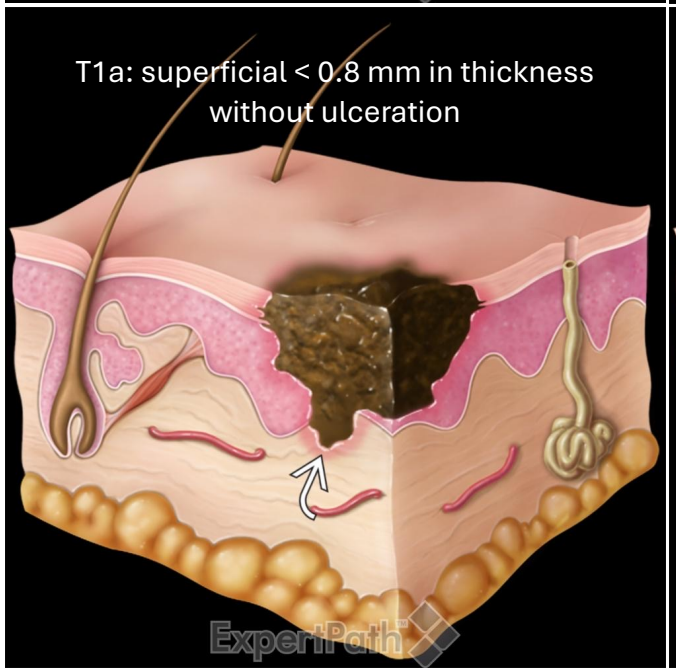
Melanoma staging: measuring invasive tumor depth and ulceration (no epidermis)

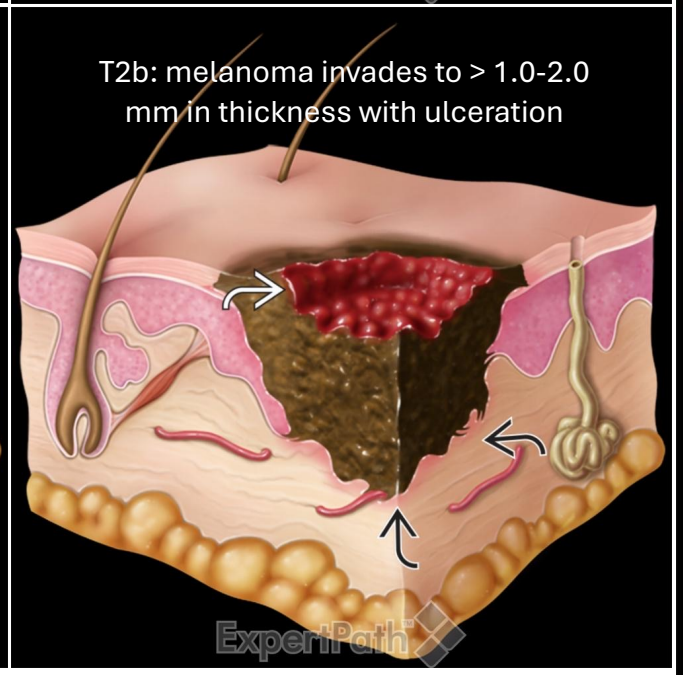


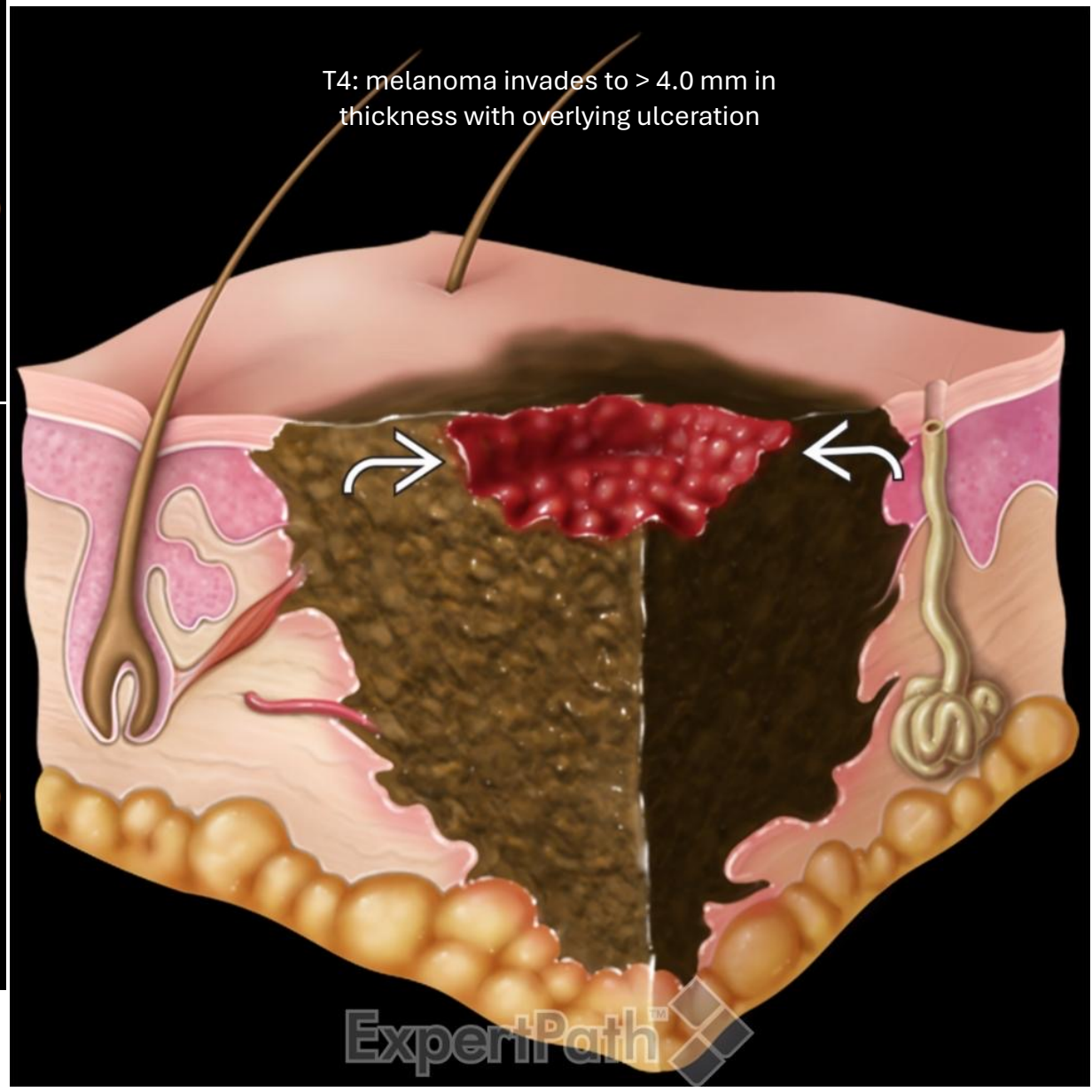
AJCC Melanoma staging











Neoplastic Dermatopathology, Cassarino, Dadras 3rd edition

Cutaneous melanoma staging according to AJCC and UICC, 8th Edition

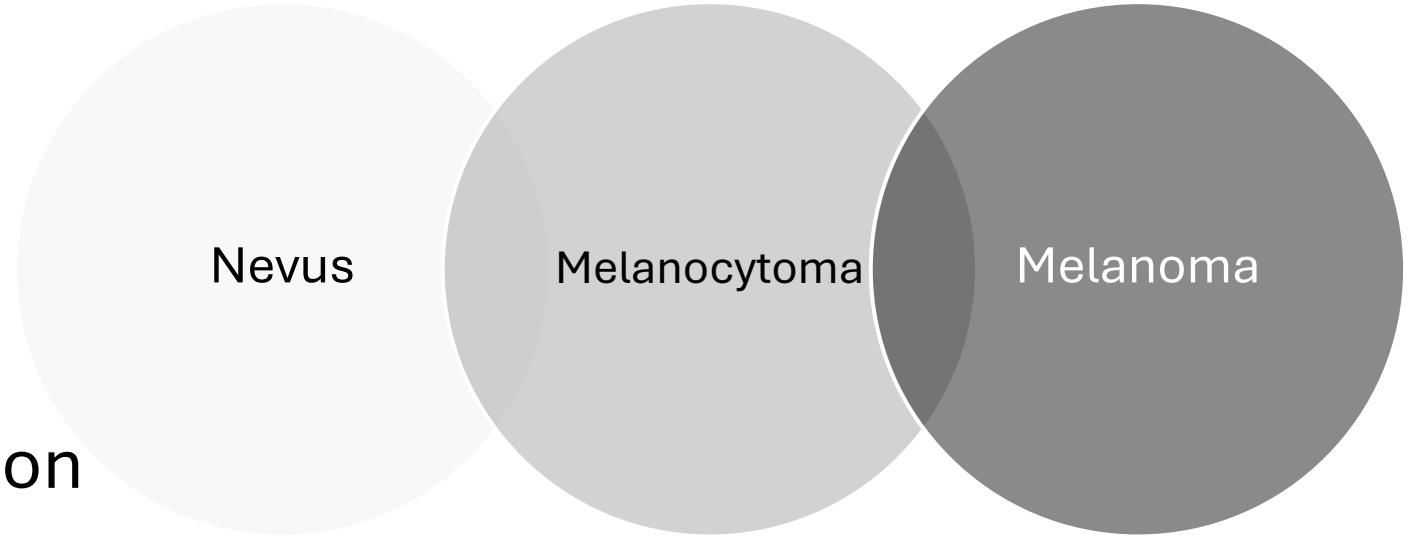
Pathologic stage	T classification	Definition	10-year survival rate
0	Tis	melanoma in situ	
IA	pT1a	thickness < 0.8 mm without ulceration	98%
IB	pT1b	thickness 0.8 – 1.0 mm or ≤ 1.0 mm with ulceration	96%
	pT2a	thickness ≥ 1.1 – 2.0 without ulceration	92%
IIA	pT2b	thickness ≥ 1.1 – 2.0 mm with ulceration	88%
	pT3a	thickness ≥ 2.1 – 4.0 mm without ulceration	88%
IIB	pT3b	thickness ≥ 2.1 – 4.0 mm with ulceration	81%
	pT4a	thickness > 4 mm without ulceration	83%
	pT4b	thickness > 4 mm with ulceration	75%

Immunostaining for Melanocytic Proliferations

Marker	Histologic Situation
Melan-A/MART-1 (Cytoplasmic)	Microinvasion Sentinel lymph node (SLN) screening
SOX-10 (also neural) (Nuclear)	Desmoplastic dermis Residual melanoma in excision scar Melanoma in situ in sun-damaged epidermis
Ki67/Melan-A	Dermal melanoma (>5% mitotic index)
S100 (also neural) (Nuclear and cytoplasmic)	Metastasis Desmoplastic dermis
p16 (*CDKN2A gene*) (Nuclear)	Melanoma (silenced, absent expression or homozygous deletion). sporadic: 26%; familial: 44%
BAP-1 (Nuclear)	BAP-1 inactivated nevus or melanocytoma (not melanoma); spitzoid or biphasic morphology
PRAME (Nuclear)	Melanoma (+92% melanoma; -84% nevi)
HMB-45 (Cytoplasmic)	Invasive melanoma (paradoxical expression), SLN screening
MITF (nuclear)	Metastatic melanoma, melanocytic differentiation

What is a melanocytoma? (not black and white, shades of grey)

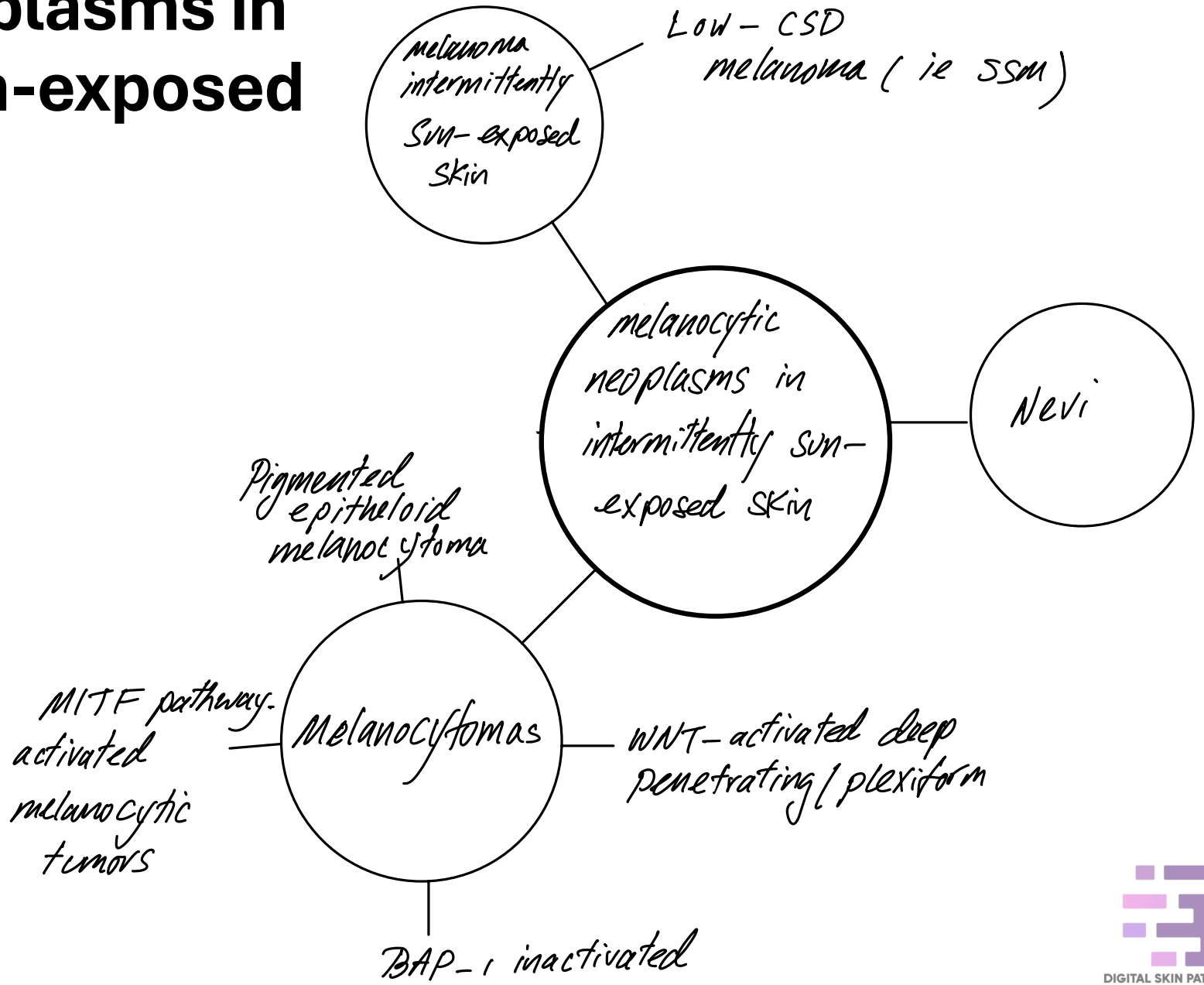
- WHO: tumorigenic melanocytic neoplasm with increased cellularity, atypia, and increased (but low) probability of neoplastic progression
- Other names: Borderline lesion or MELTUMP
- Morphology cannot predict biologic behavior

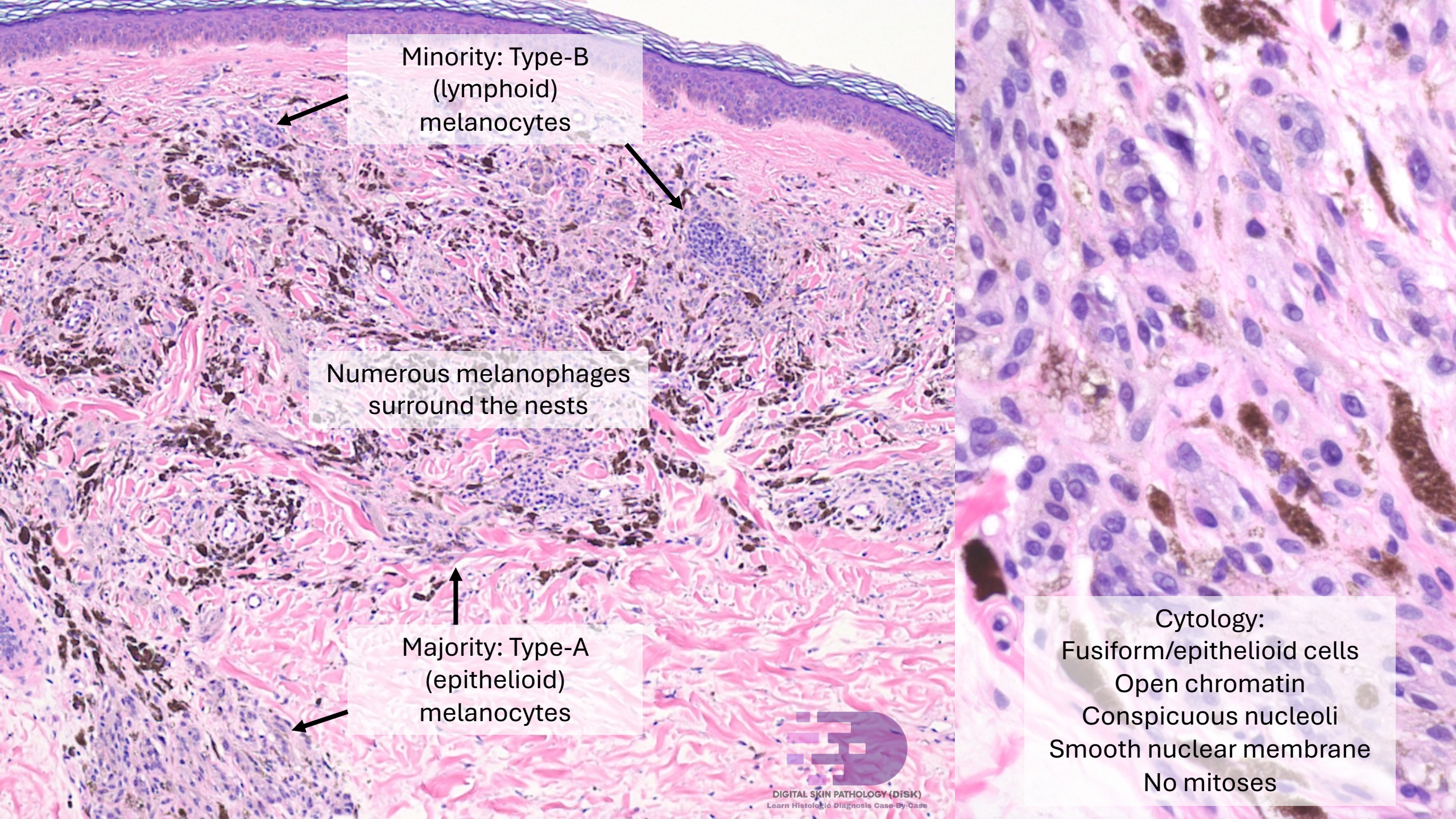


Size
Depth
Architectural asymmetry
Cytologic atypia
Mitoses
Aberrant immunophenotype

DIGITAL SKIN PATHOLOGY (DiSK)
Learn Histologic Diagnosis Case-By-Case

Melanocytic neoplasms in intermittently sun-exposed skin




Minority: Type-B (lymphoid) melanocytes
Numerous melanophages surround the nests
Majority: Type-A (epithelioid) melanocytes
Cytology:
Fusiform/epithelioid cells
Open chromatin
Conspicuous nucleoli
Smooth nuclear membrane
No mitoses
DIGITAL SKIN PATHOLOGY (DiSK)
Learn Histologic Diagnosis Case-By-Case

- **Clinical Information:** 45-year-old female; 4-mm blue black macule, new “ish”

- **DIAGNOSIS:**

  Skin, Right Upper Arm, Excision:

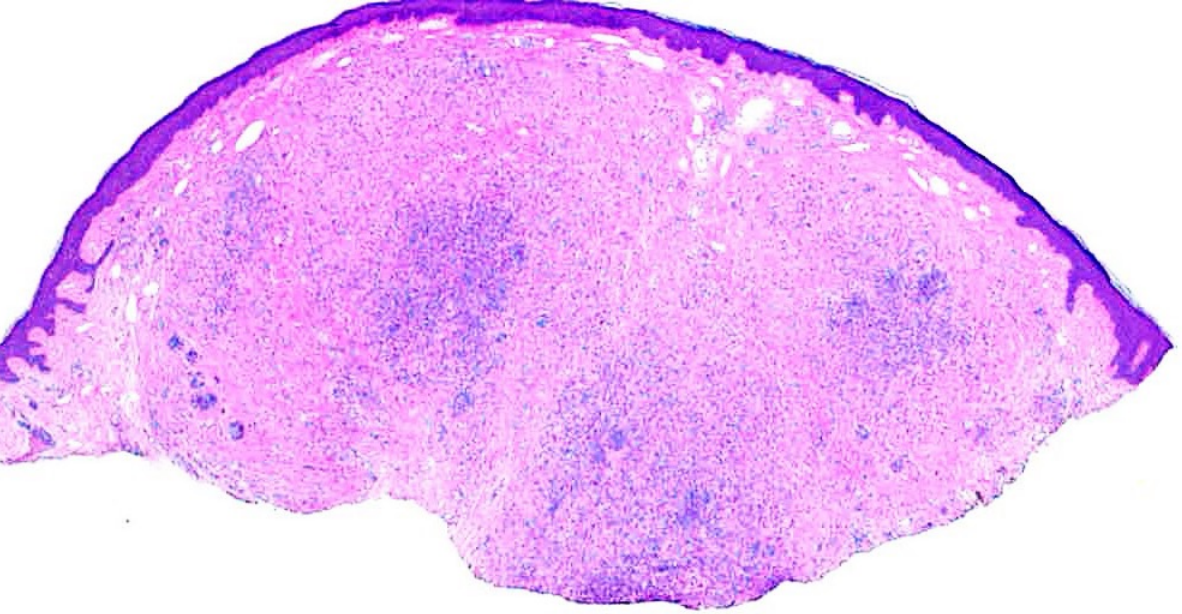
  - Inverted type-A nevus (WHO: WNT-activated deep penetrating/plexiform melanocytoma), variably pigmented, free of involvement in examine sections.

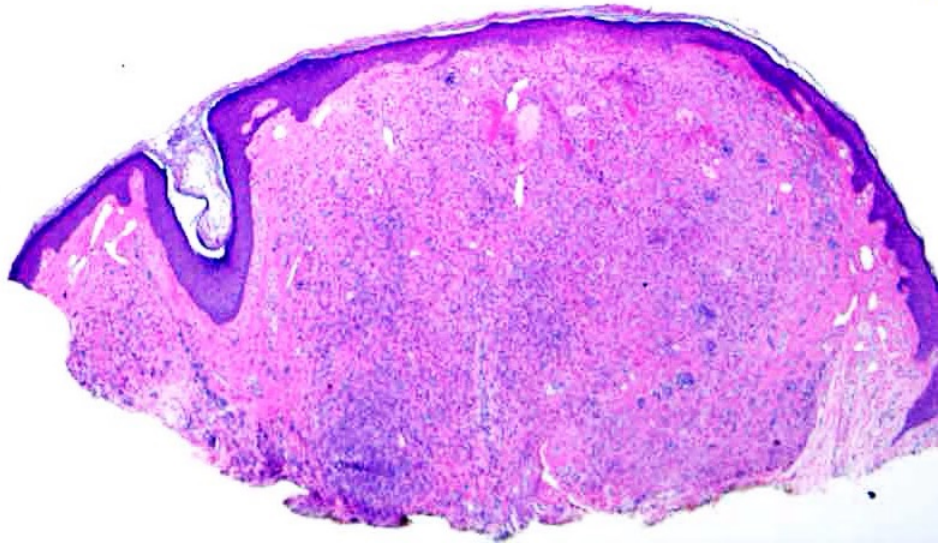
  Comment: Inverted type-A nevus is a variant of combined melanocytic nevus. No further treatment is generally needed for this nevus, unless clinically indicated.

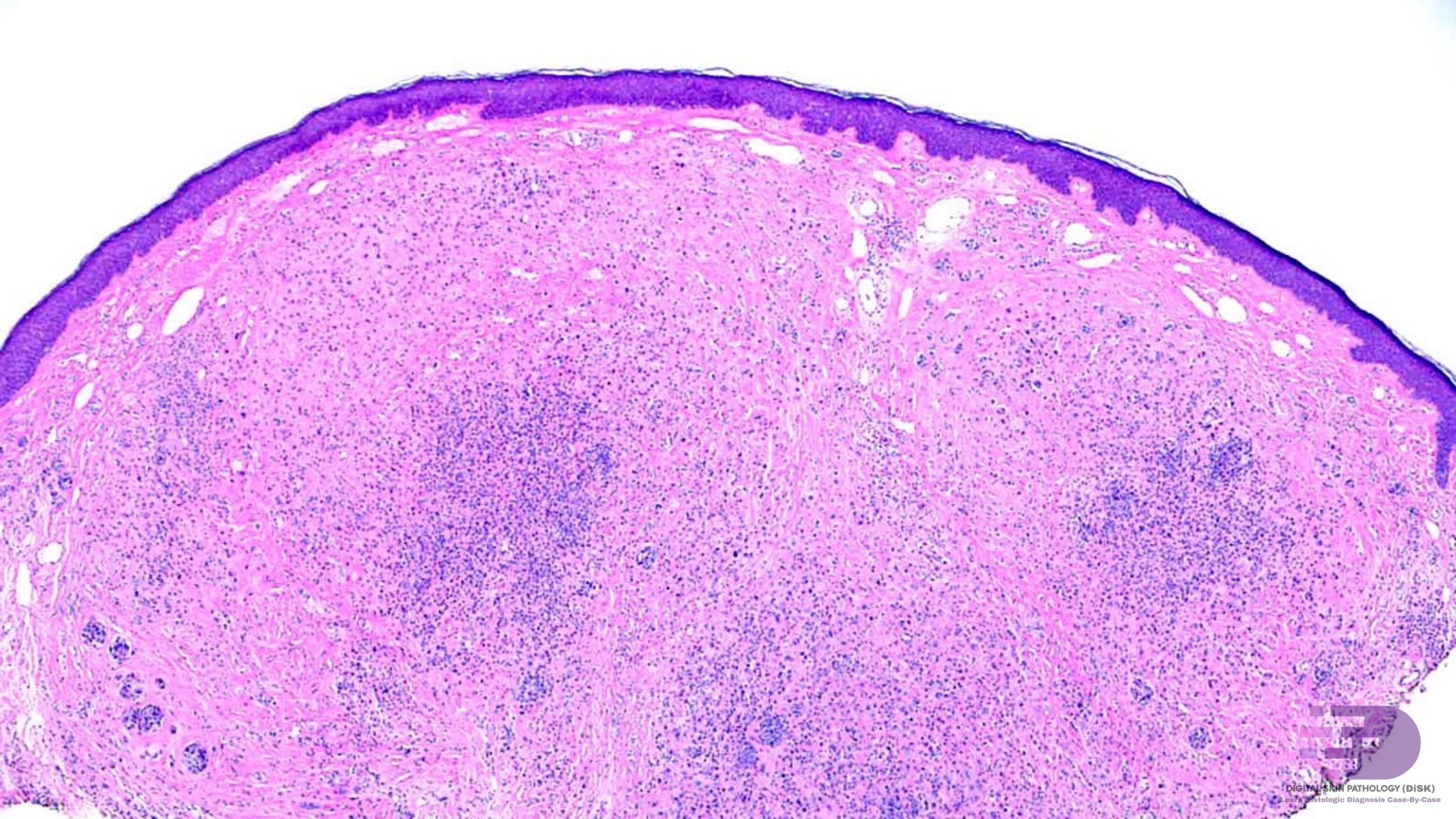
- **Teaching Points:**
  - Don’t be confused by many other names given to this nevus type
  - Perform additional bleached levels, look for deep dermal mitoses
  - Be concerned, if partially sampled
  - Double IHC: ki-67 Melan-A (<5% mitotic index)

- **Minimal Diagnostic Criteria:**
  - Mostly intradermal wedge-shaped
  - Dermal nests converge into nodules
  - Combined features (more than two different cell types)
  - Defies dermal maturation, turned upside down, type-B melanocytes at the top and type-A at the bottom
  - Cytology: Large epithelioid cells with abundant cytoplasm, open chromatin, conspicuous nucleoli, smooth nuclear membrane, and no mitoses

- **Differential Diagnosis:**
  - Deep penetrating nevus/clonal nevus
  - Melanoma arising in melanocytic nevi



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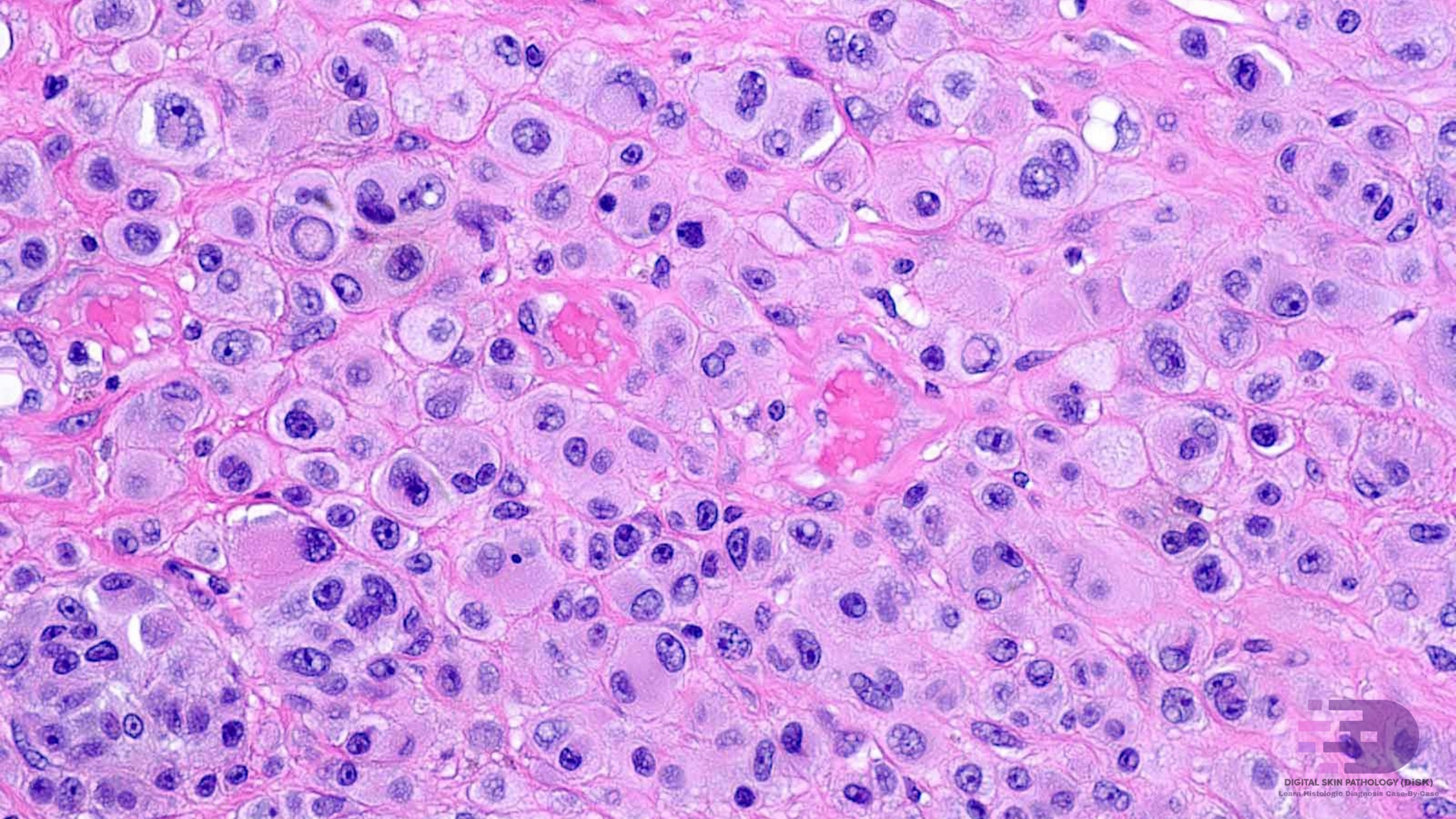
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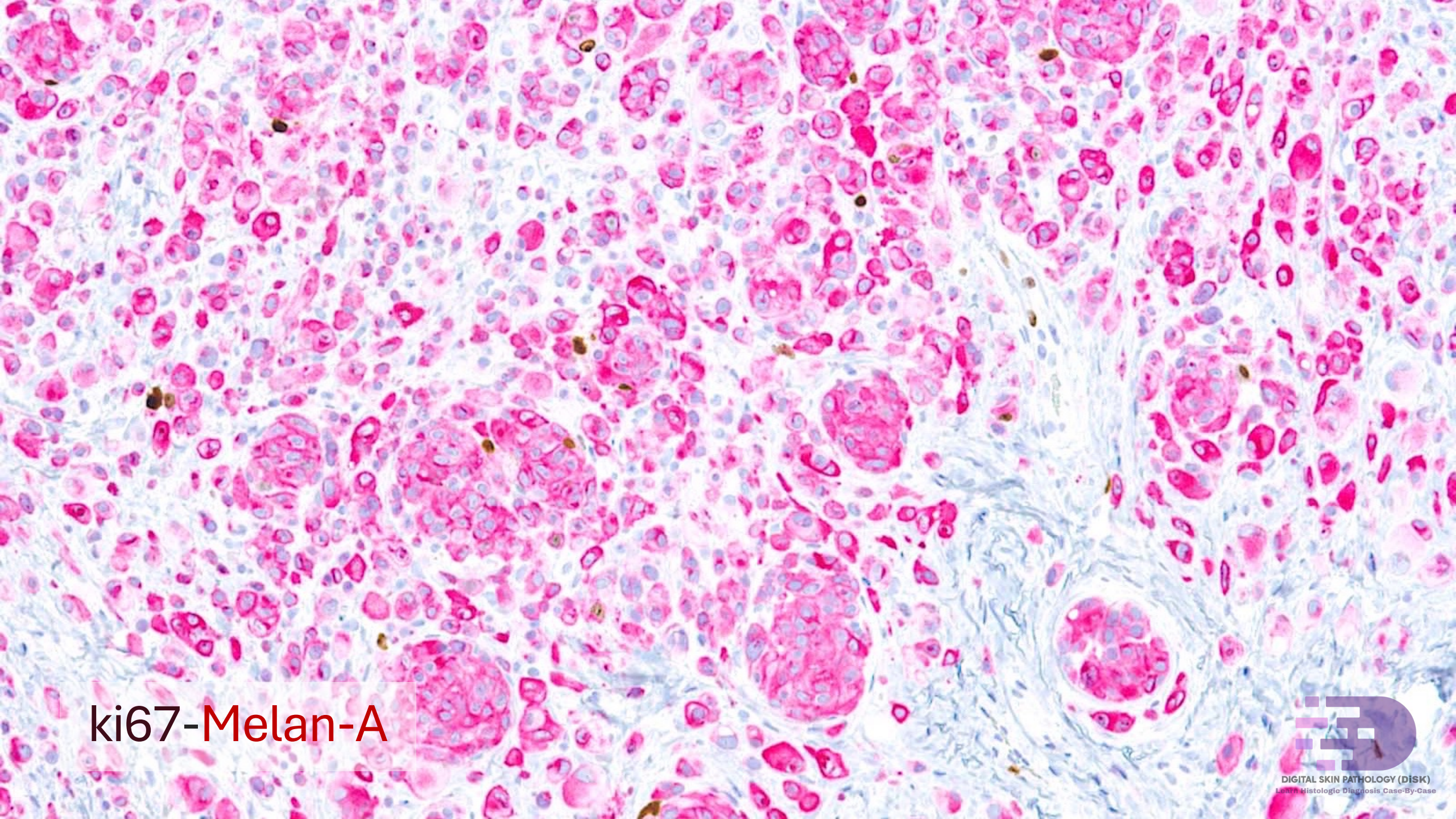
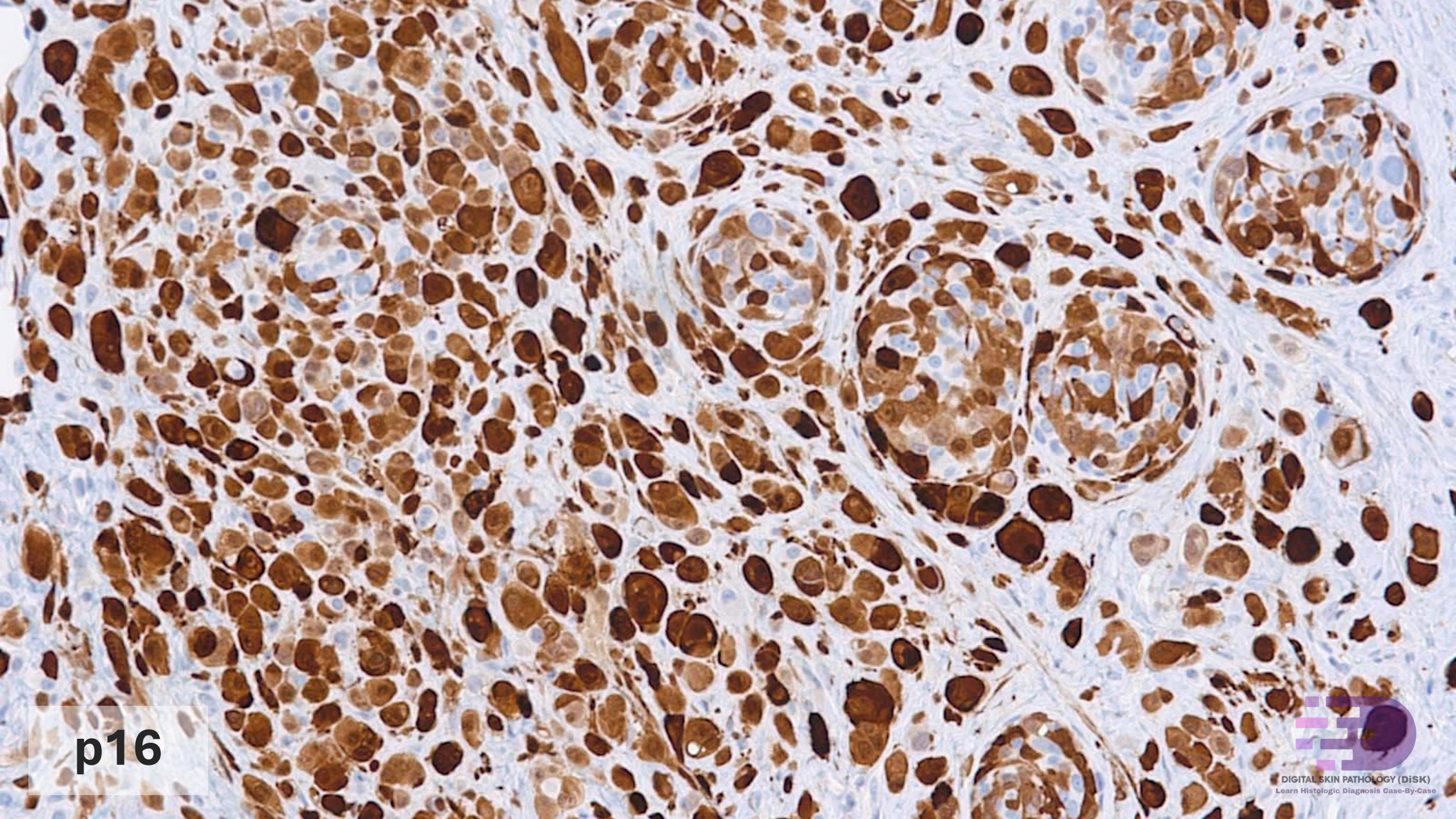
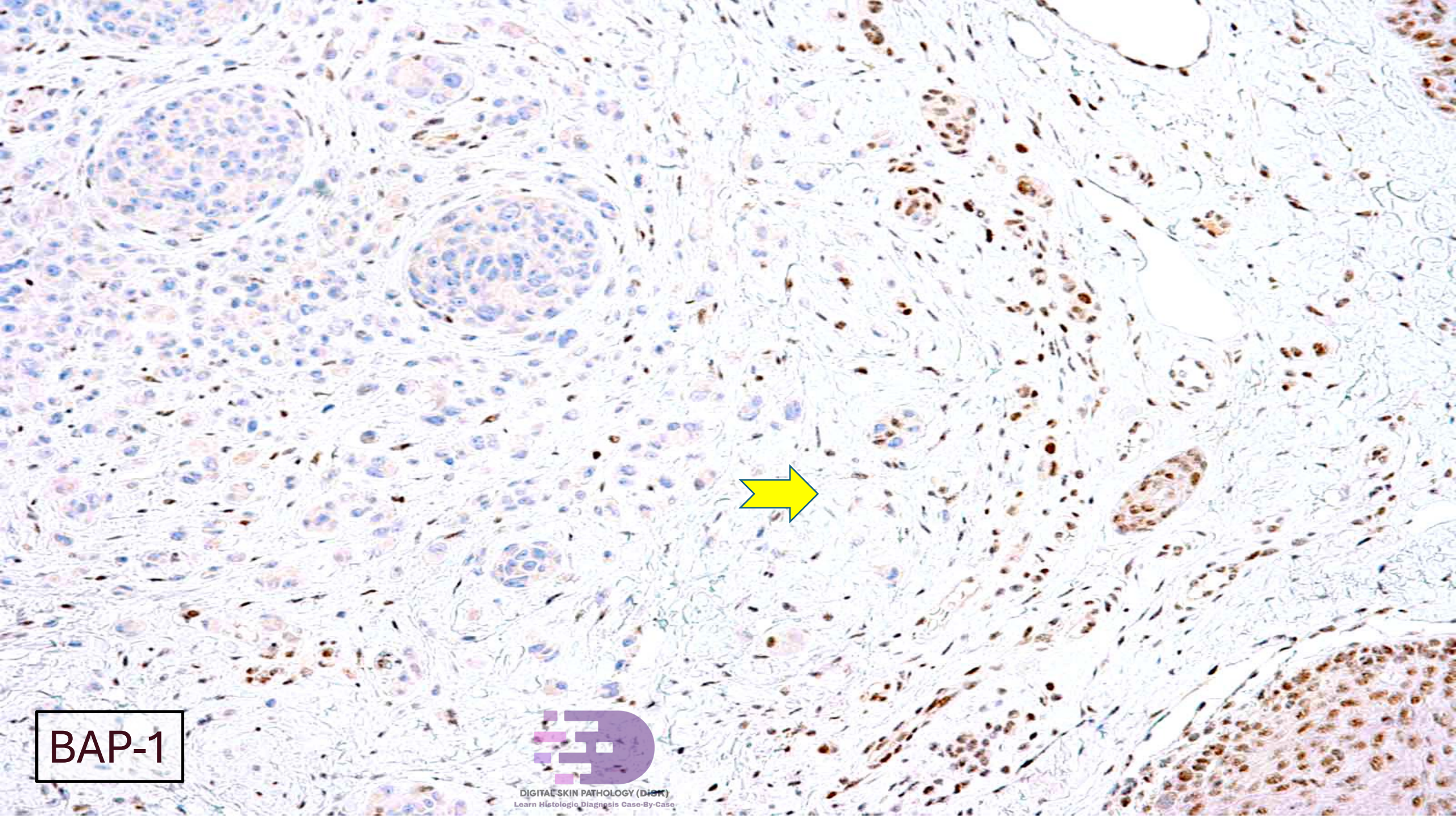




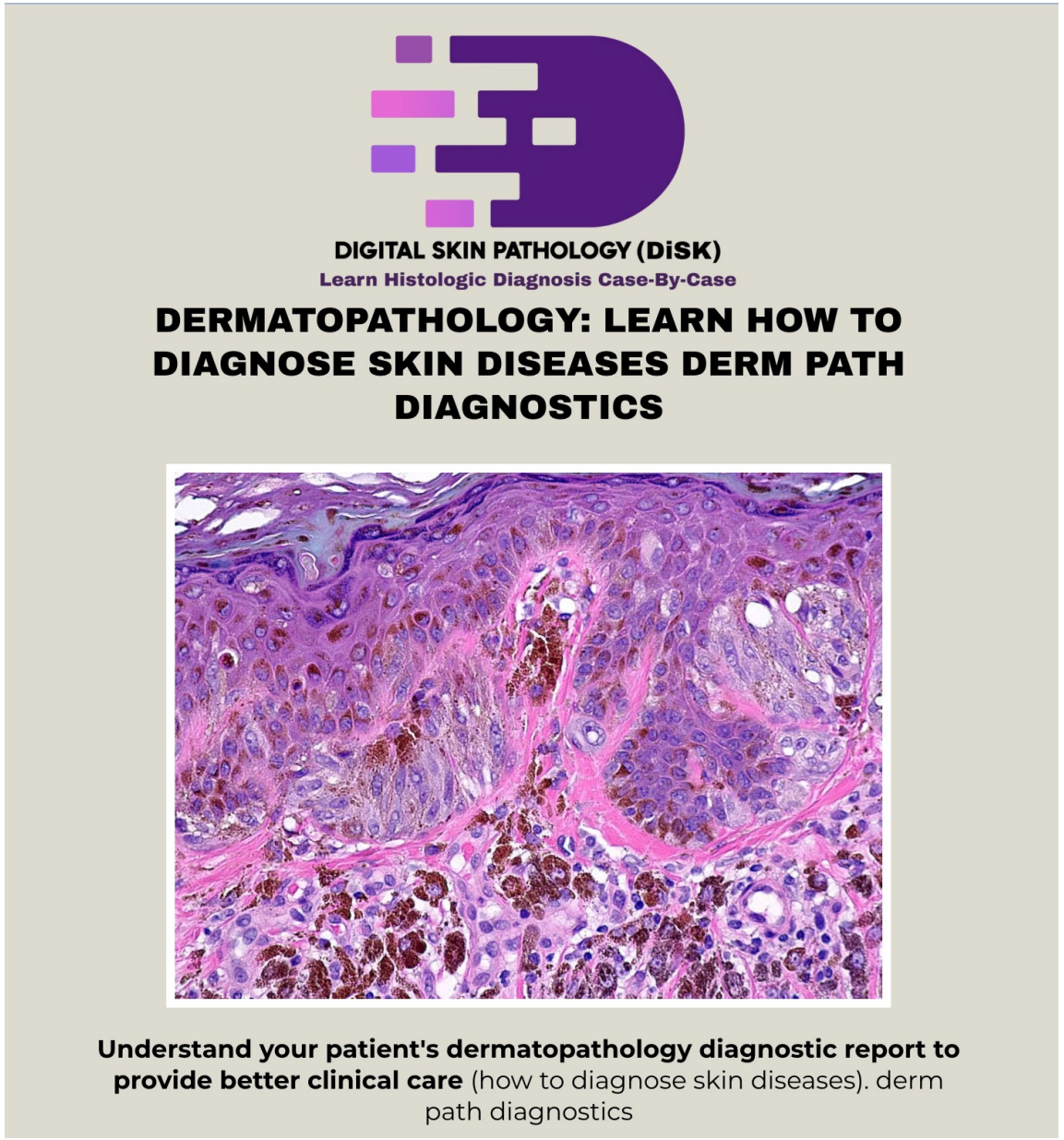

BAP-1
DIGITAL SKIN PATHOLOGY (DiSK)
Learn Histologic Diagnosis Case-By-Case

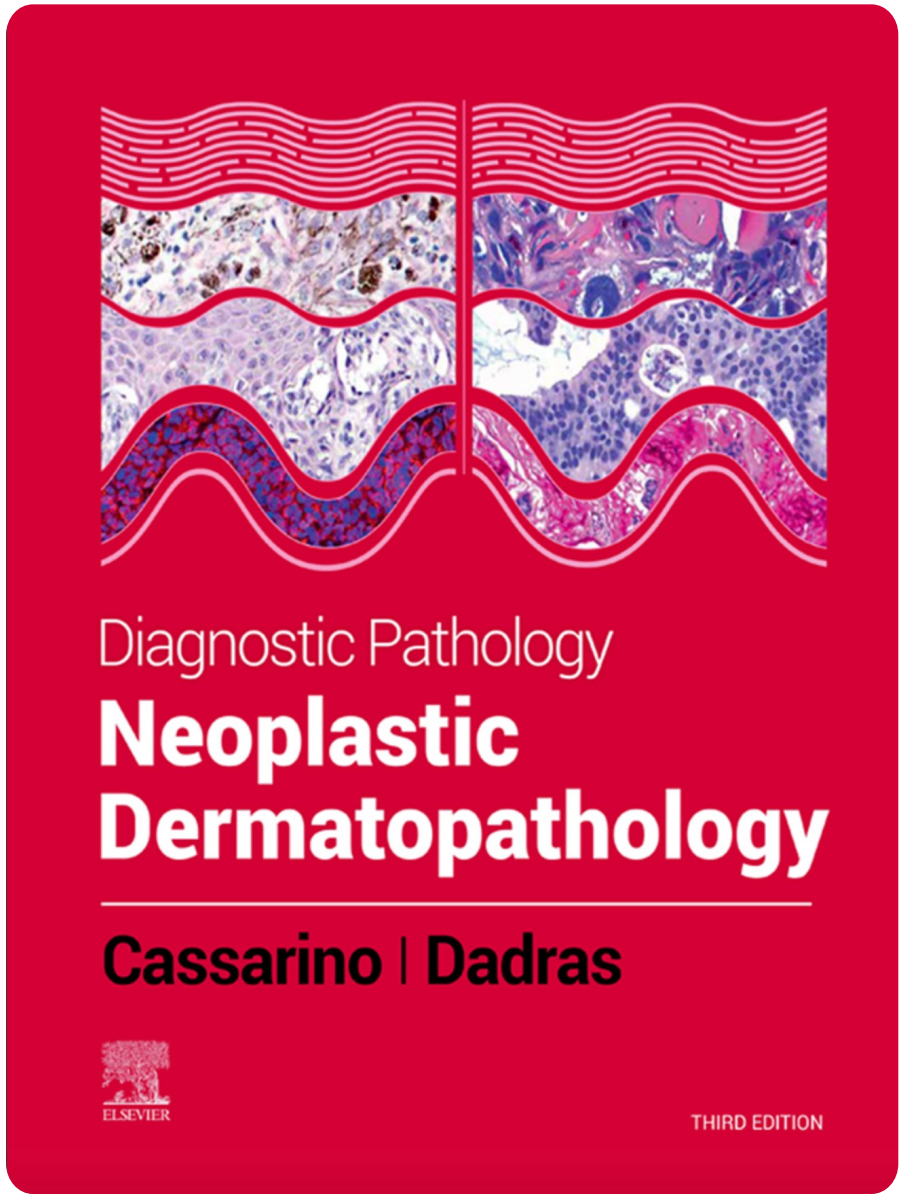
- **Clinical Information:** Clinical: 73-year-old male ?BCC, R Neck Shave.
- **DIAGNOSIS:**
  - SKIN, RIGHT NECK, SHAVE BIOPSY:
    - BAP-1 INACTIVATED MELANOCYTOMA, PRESENT AT MARGIN. SEE COMMENT.
    - ACTINIC KERATOSIS.
  - Complete excision with 2-3 mm margin is recommended. BAP-1 demonstrates loss of this tumor suppressor in most of the second population of tumor cells, suggesting that its mutation is likely. This result confirms the possibility of BAP-1 inactivated melanocytoma (BAPoma). Germline mutations in the tumor suppressor gene, BRCA-1 associated protein (BAP1), underlie a tumor predisposition syndrome characterized by increased risk for numerous cancers including uveal melanoma, melanocytic tumors and mesothelioma, among others. Case reviewed by Dr. XXX, who concurs.
  - Immunohistochemistry with appropriate control is performed. Immunostaining for p16 demonstrates retention of this tumor suppressor in some of the tumor cells in a mosaic pattern, suggesting that homozygous CDKN2A deletion is unlikely. Double immunostaining for ki-67/Melan-A shows a low proliferative index in the dermal tumor cells (~1%). BAP-1 expression is lost in the second population of dermal tumor cells. PRAME expression is retained.
- **Teaching Points:**
  - Low malignant potential e.g., Pigmented epithelioid melanocytoma
- **Minimal Diagnostic Criteria:**
  - A tumorigenic melanocytic neoplasm with increased cellularity and cytologic atypia (vs. nevus)
  - BAP-1 deficiency in sporadic melanocytic neoplasms with biphasic and epithelioid spitzoid features
- **Differential Diagnosis:**
  - Atypical Spitz tumor
  - Spitz nevus
  - Combined nevus
  - (melanoma)

Digital Skin Pathology

https://digitalskinpathology.com/

- Meet the challenges of the growing needs for dermatopathology knowledge
- Learn Dermatopathology based on actual real-life cases
- Residents of Dermatology and Pathology
- Dermatology PAs and NPs
- Primary MDs and general surgeons





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- *Neoplastic Dermatopathology*, 3rd edition