



Melanocytic neoplasms

Soheil S Dadras MD-PhD



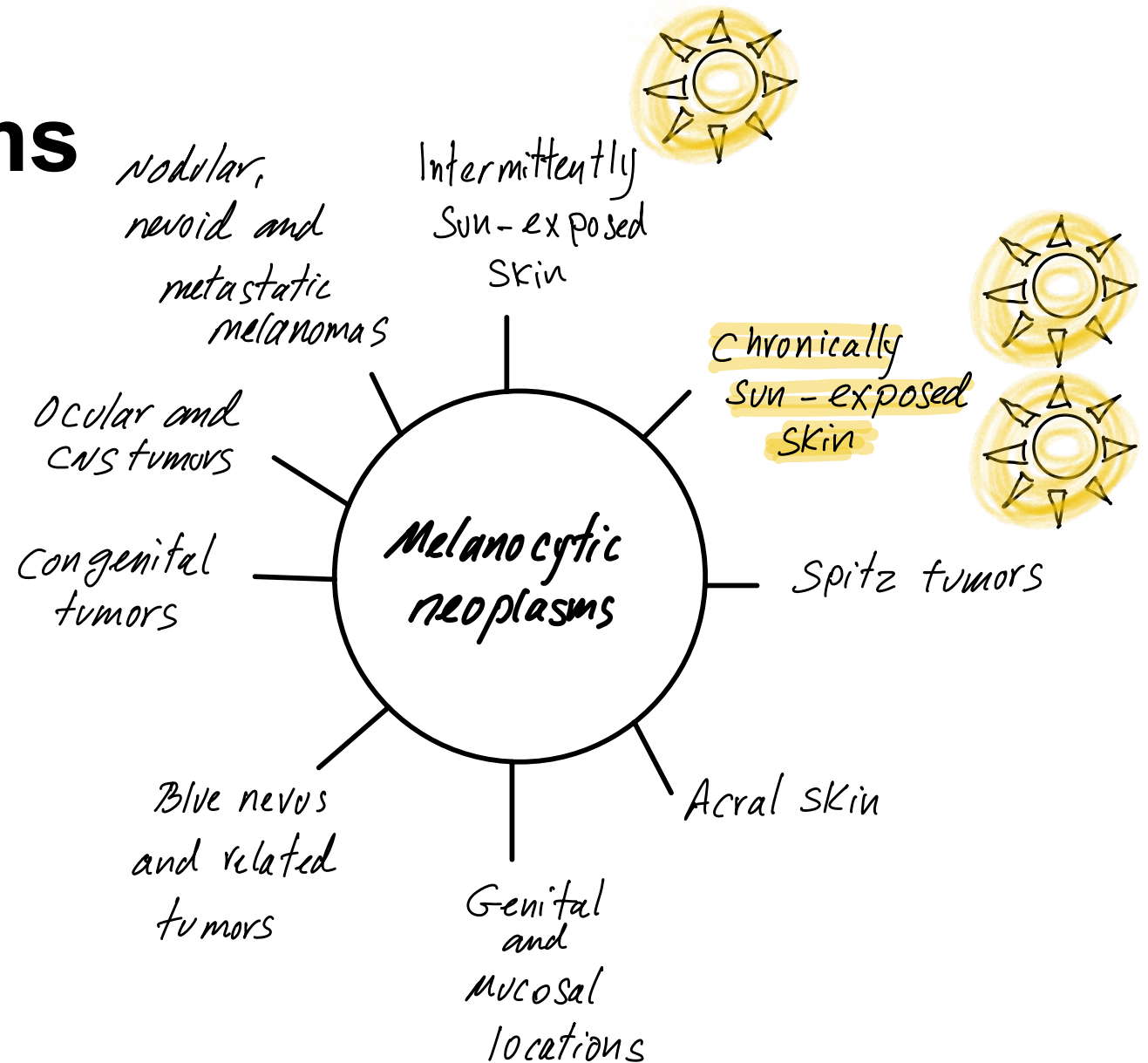
Lecture outline

- Diagnostic principals of melanocytic nevus
 - What are nevus subtypes?
 - What are histologic features of a nevus?
 - What are histologic features of a common nevus and a dysplastic nevus?
- Melanocytoma (Borderline/atypical melanocytic neoplasms)
 - Deep penetrating nevus/Inverted type A nevus
 - BAP-1 inactivated melanocytoma
- Melanoma
 - Cutaneous (hairy) skin
 - Acral, glabrous (non hairy) skin
- Melanoma prognostic parameters

WHO 5th edition: Melanocytic neoplasms

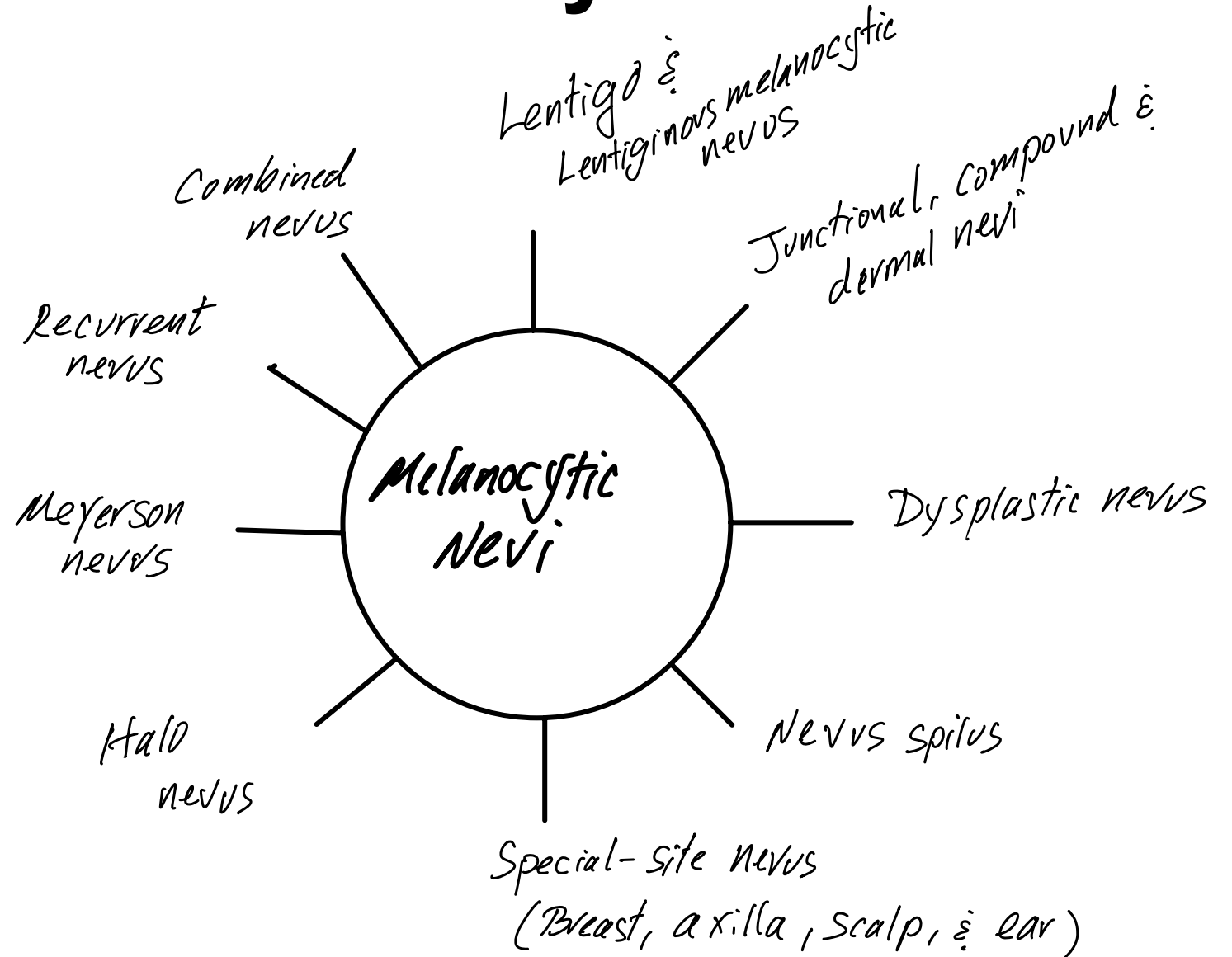
CSD – cumulative sun damage

Altered genetic pathways



WHO 5th edition: melanocytic nevus classification

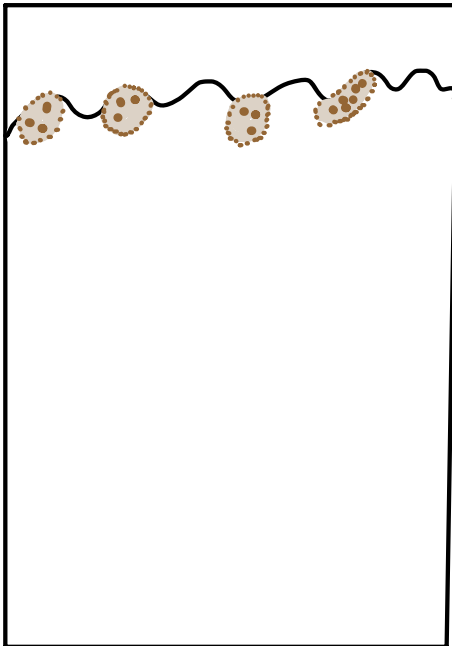
Intermittently sun-exposed skin



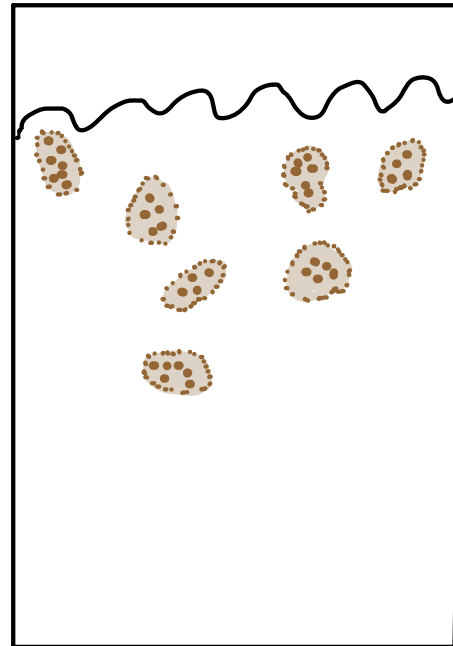
Histologic subtypes of melanocytic nevi

Nevus, a type of hamartoma (denotes any congenital tumor-like tissue malformation).

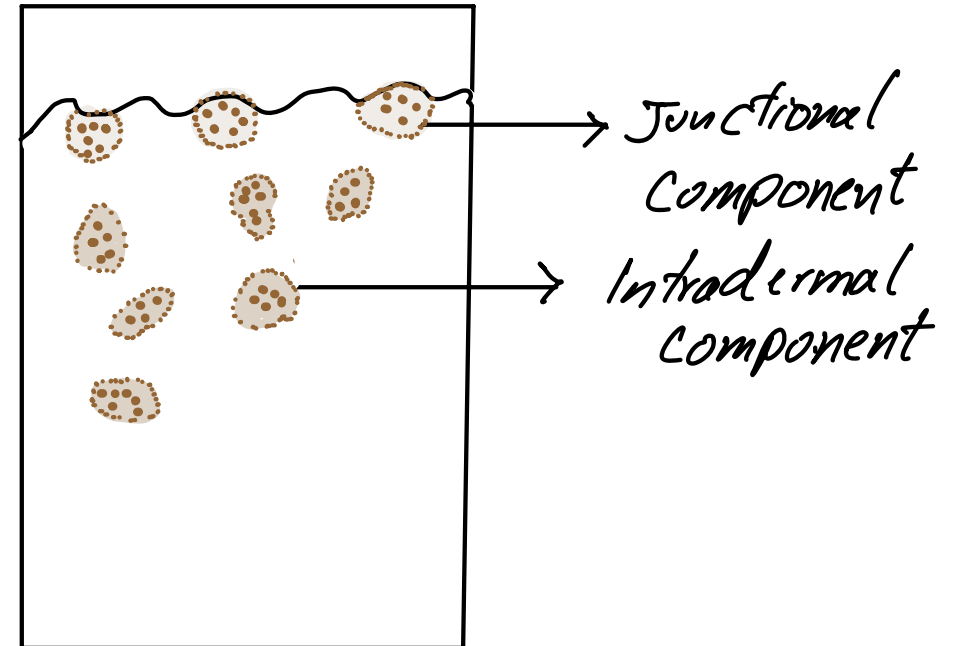
Junctional



Intradermal



Compound



What are the histologic features of a benign nevus?

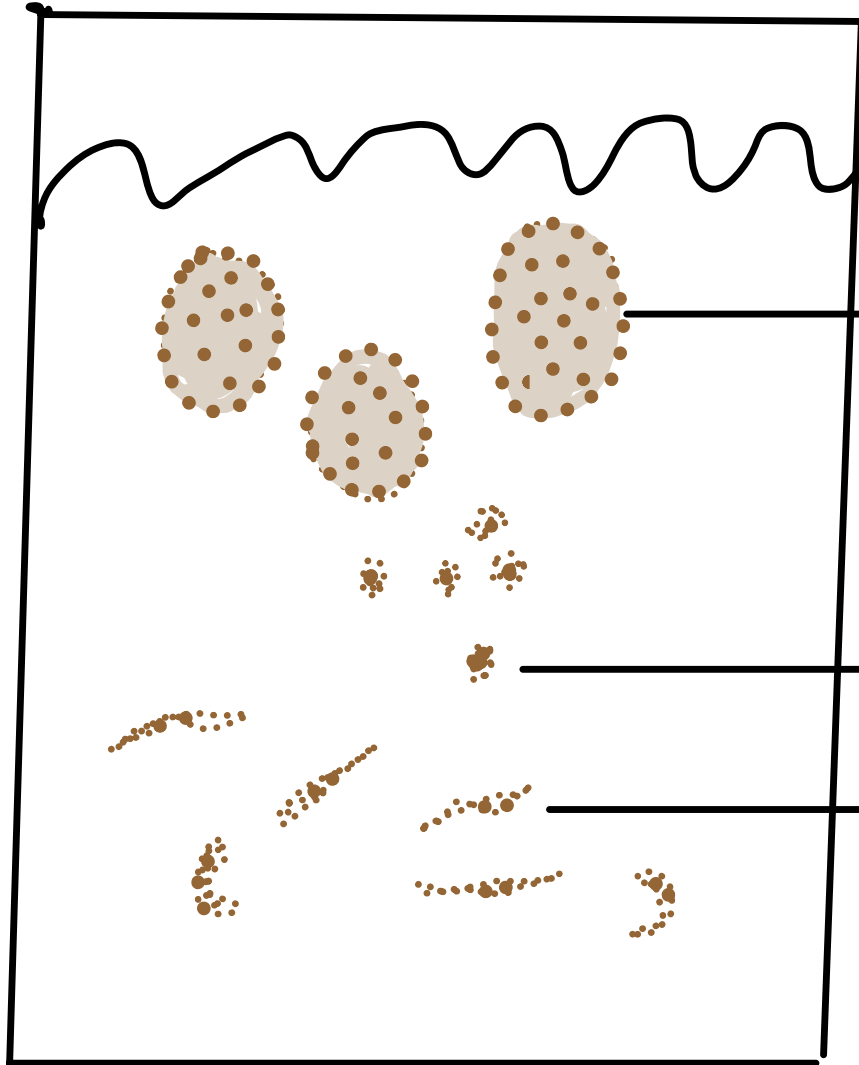
Low magnification: Architecture

- 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

Maturation of melanocytic nevus: morphology transition with increasing dermal depth

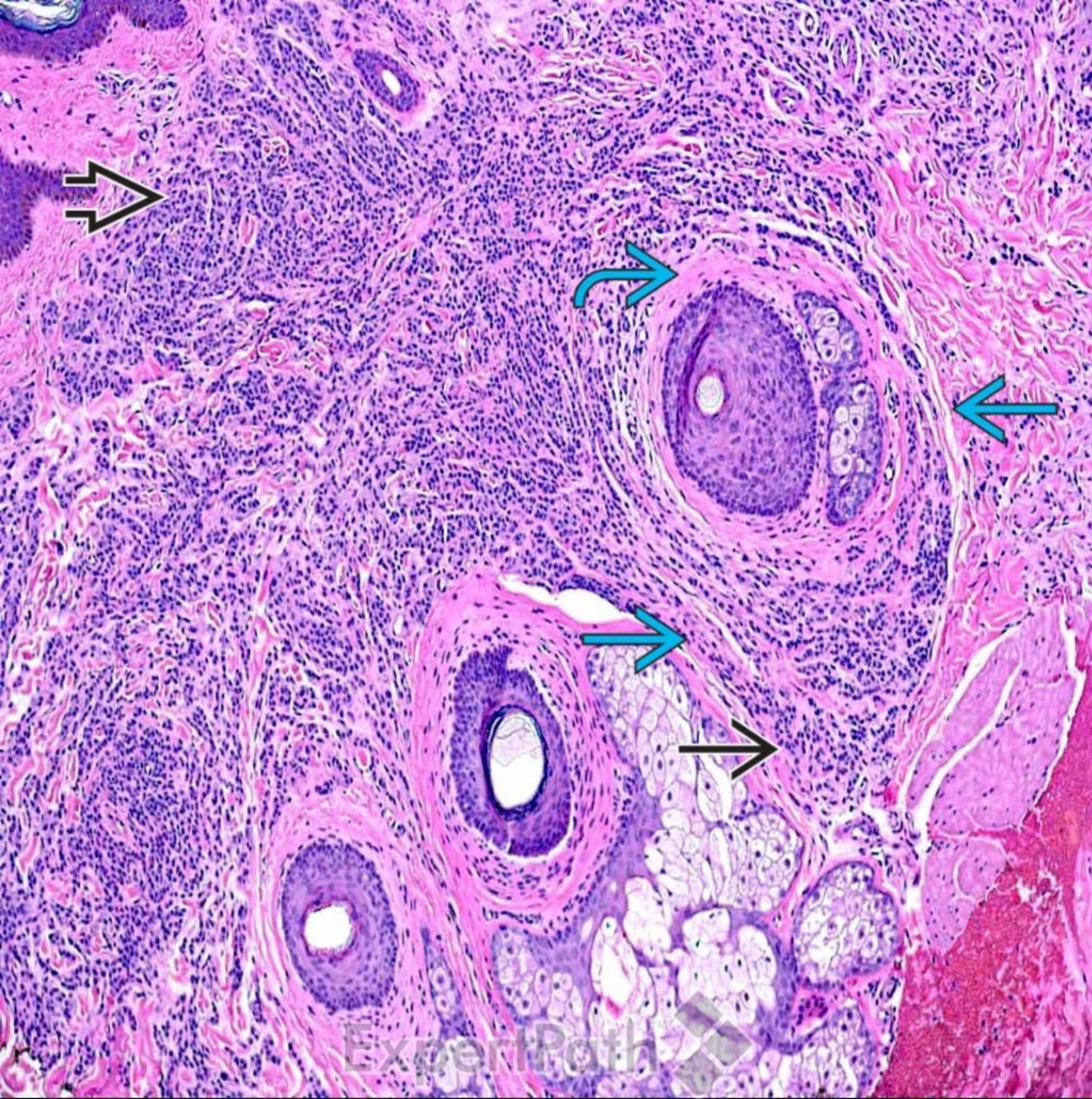


→ Epithelioid (type A)

→ Lymphocytoid (type B)

→ Spindled (type C)

Dispersion of cells at the base



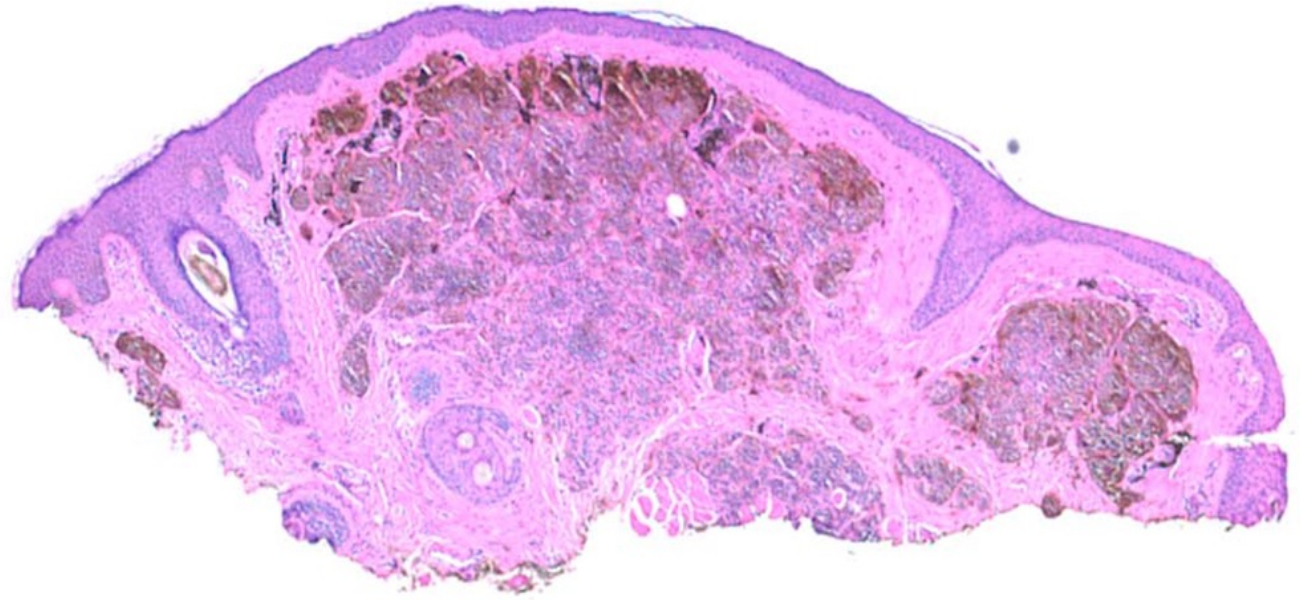
Maturation of intradermal melanocytes: morphology transition from type A → B → C

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.

Clinical features of melanocytic nevus



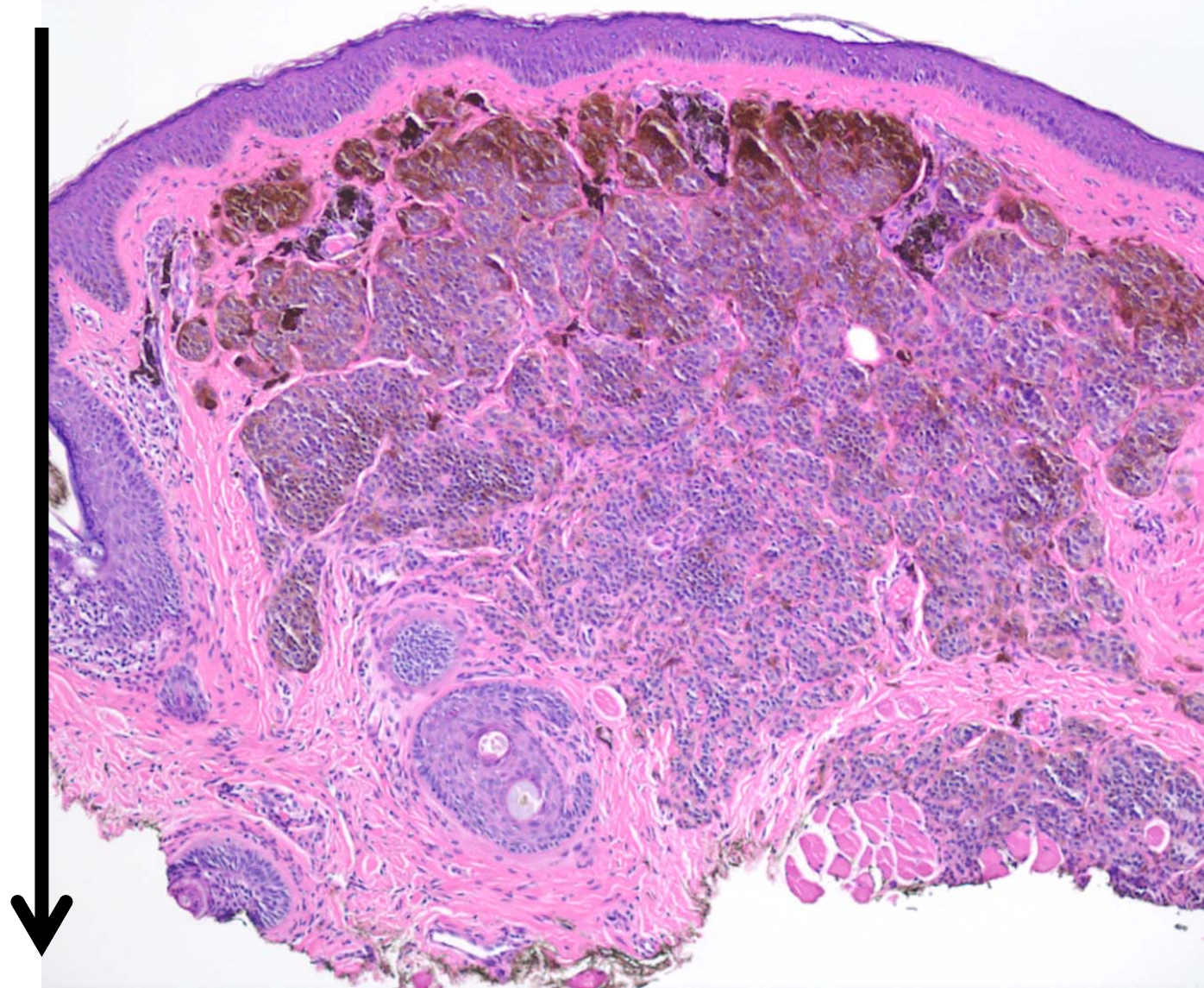
- Onset childhood, adolescence, third decade, or later
- 2 to 6 mm diameter
- Macular, papular, or both macular and papular, dome-shaped, polypoid, or papillomatous
- Homogeneous skin color, tan, light brown, brown, dark brown
- Round, oval
- Symmetrical
- Well-defined, regular borders

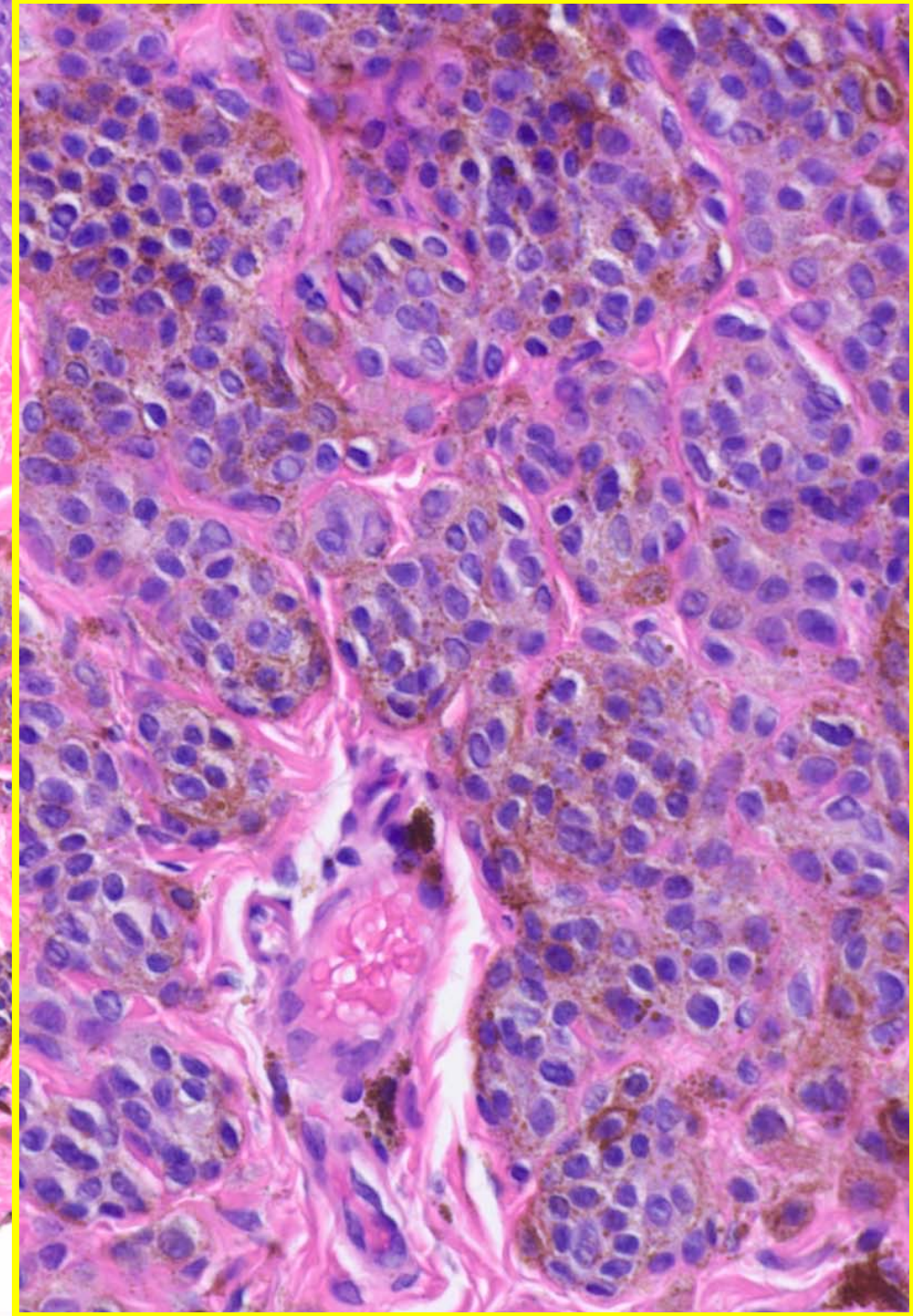
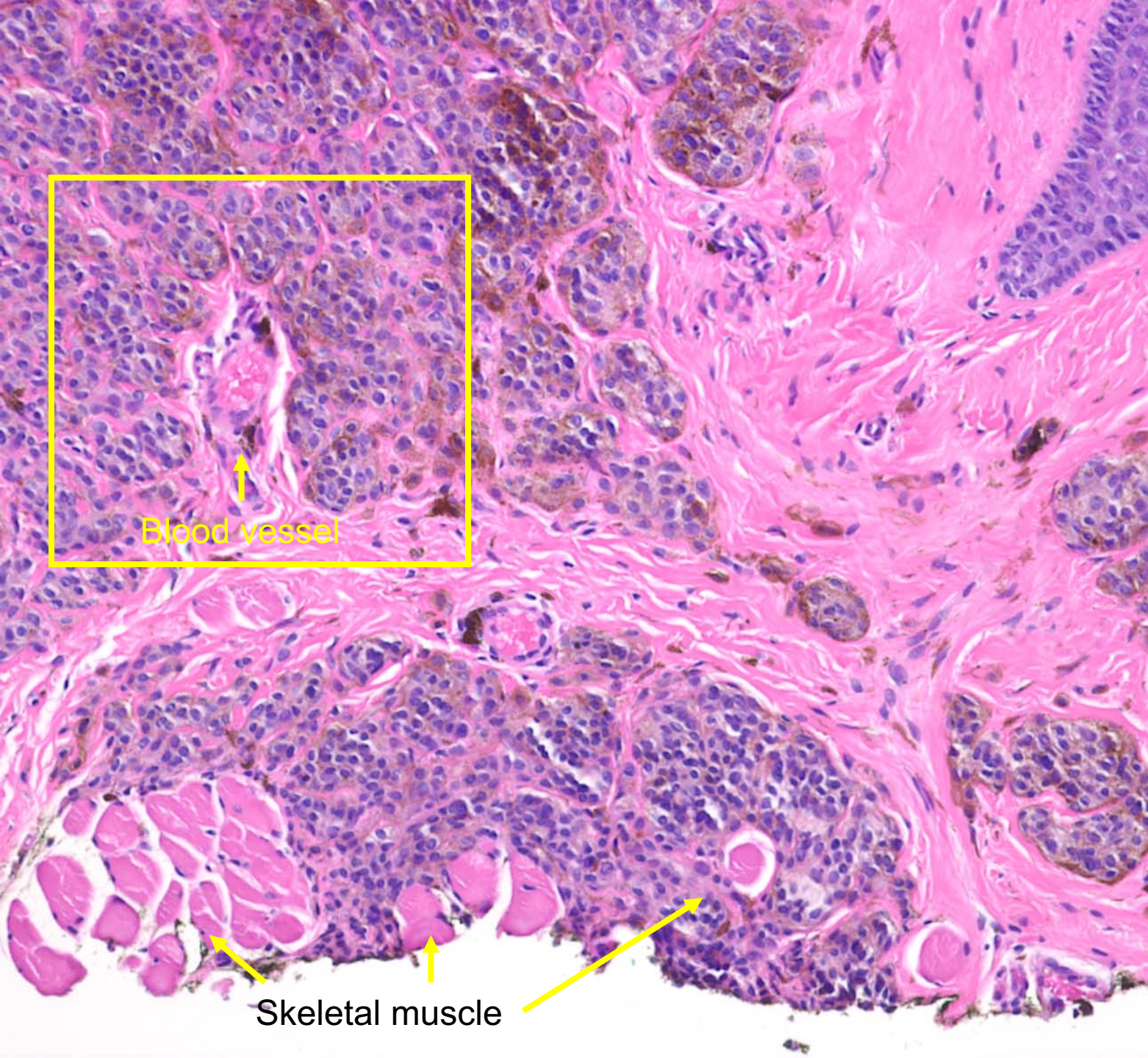


39-Year-old female
None provided
Right lower eyelid biopsy

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

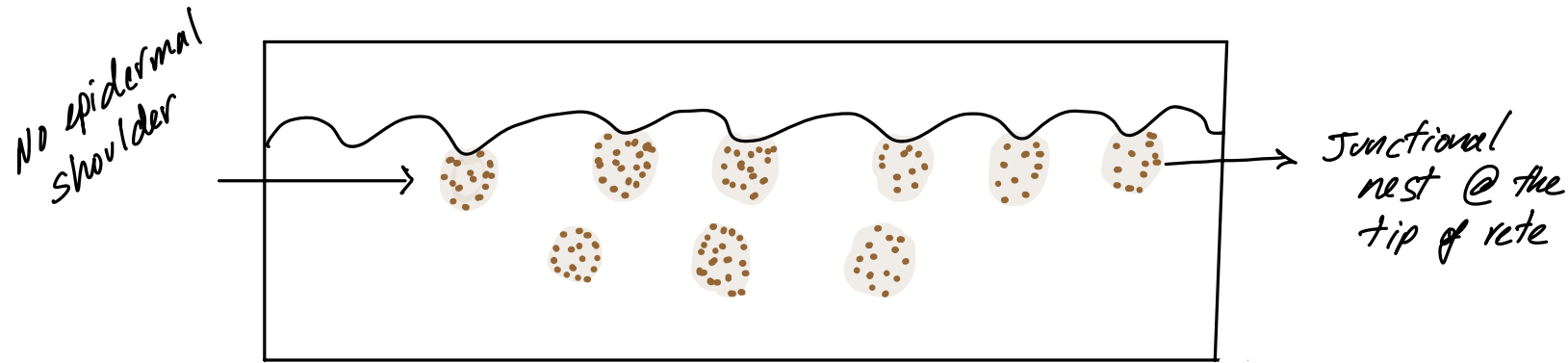
- Decreased nesting
- Less epithelioid (type-A)
- More lymphocytoid (type-B)
- Spindled (type-C)
- Less pigmented
- IHC: decreased expression of MITF and HMB-45
- IHC: maintained expression of SOX-10 and Melan-A (display shrinking of nuclei and cytoplasm)



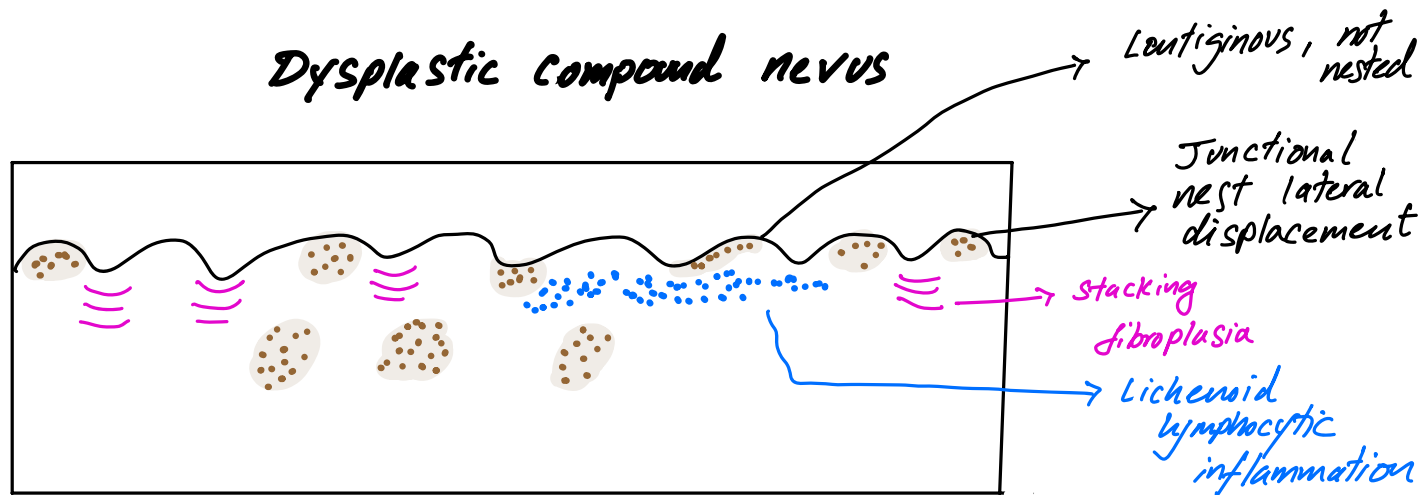


Architecture of histologic dysplasia

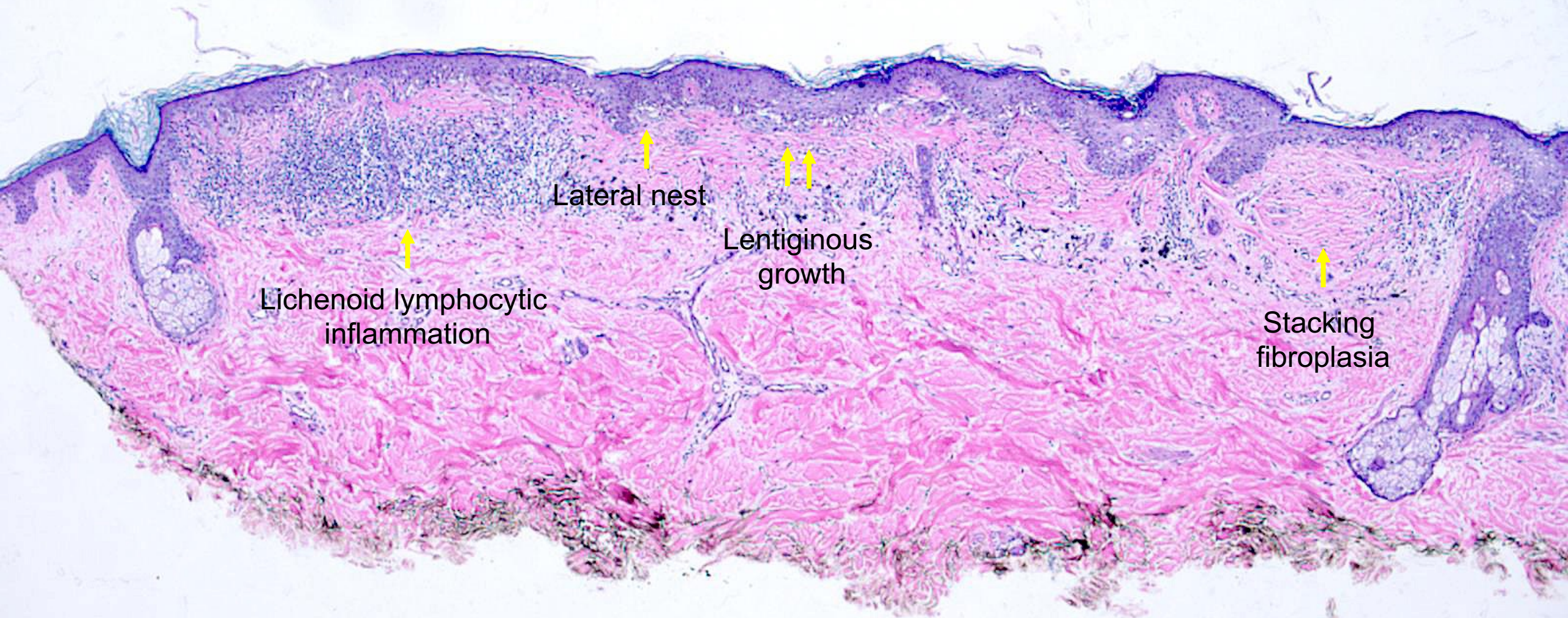
Compound nevus



Dysplastic compound nevus



- Junctional nests
 - Not at the tip of rete
 - Laterally displaced
 - Bridging
- Lentiginous, not nested, growth
- Stacking fibroplasia
- Lichenoid lymphocytic inflammation



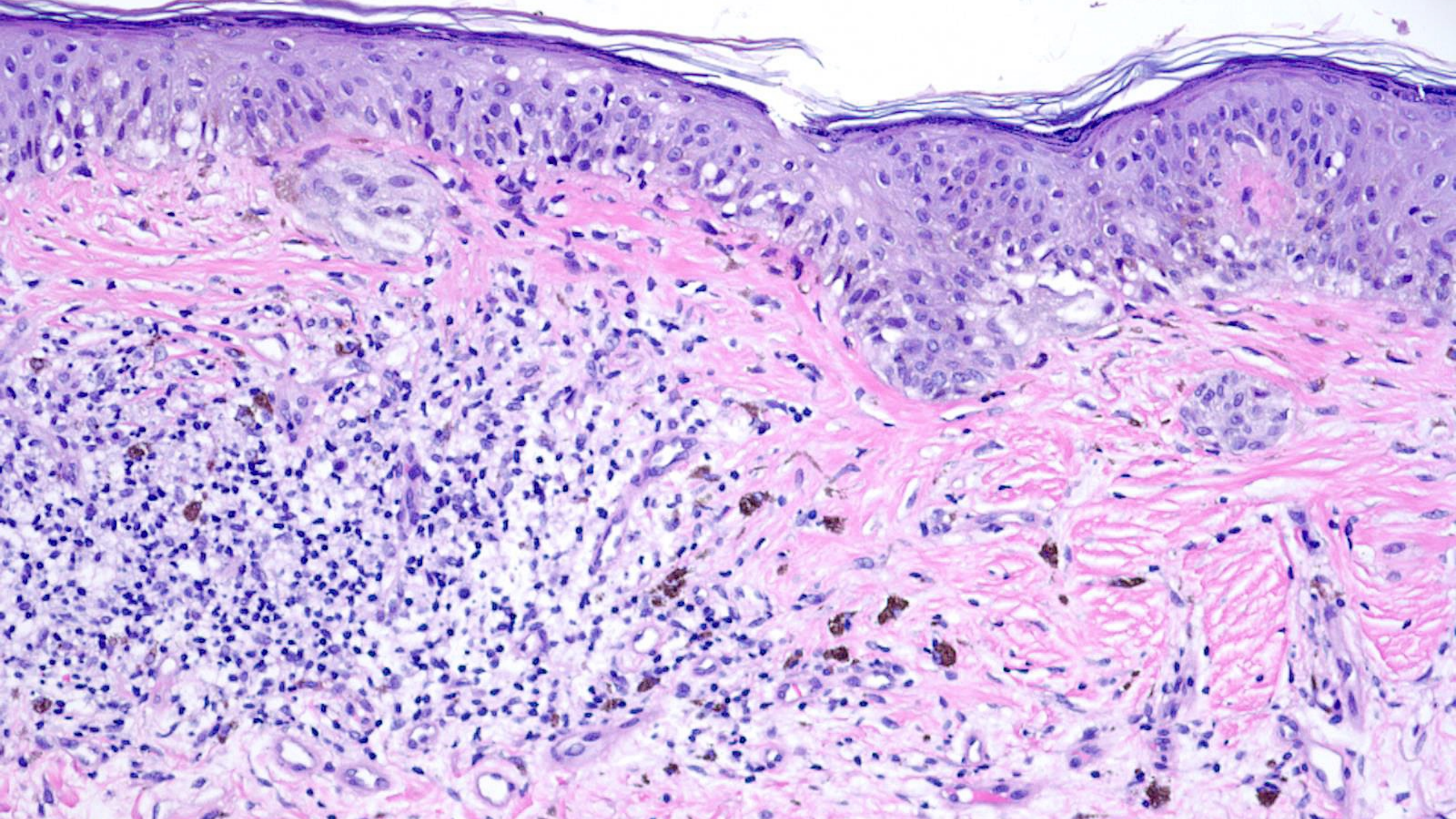
Lichenoid lymphocytic
inflammation

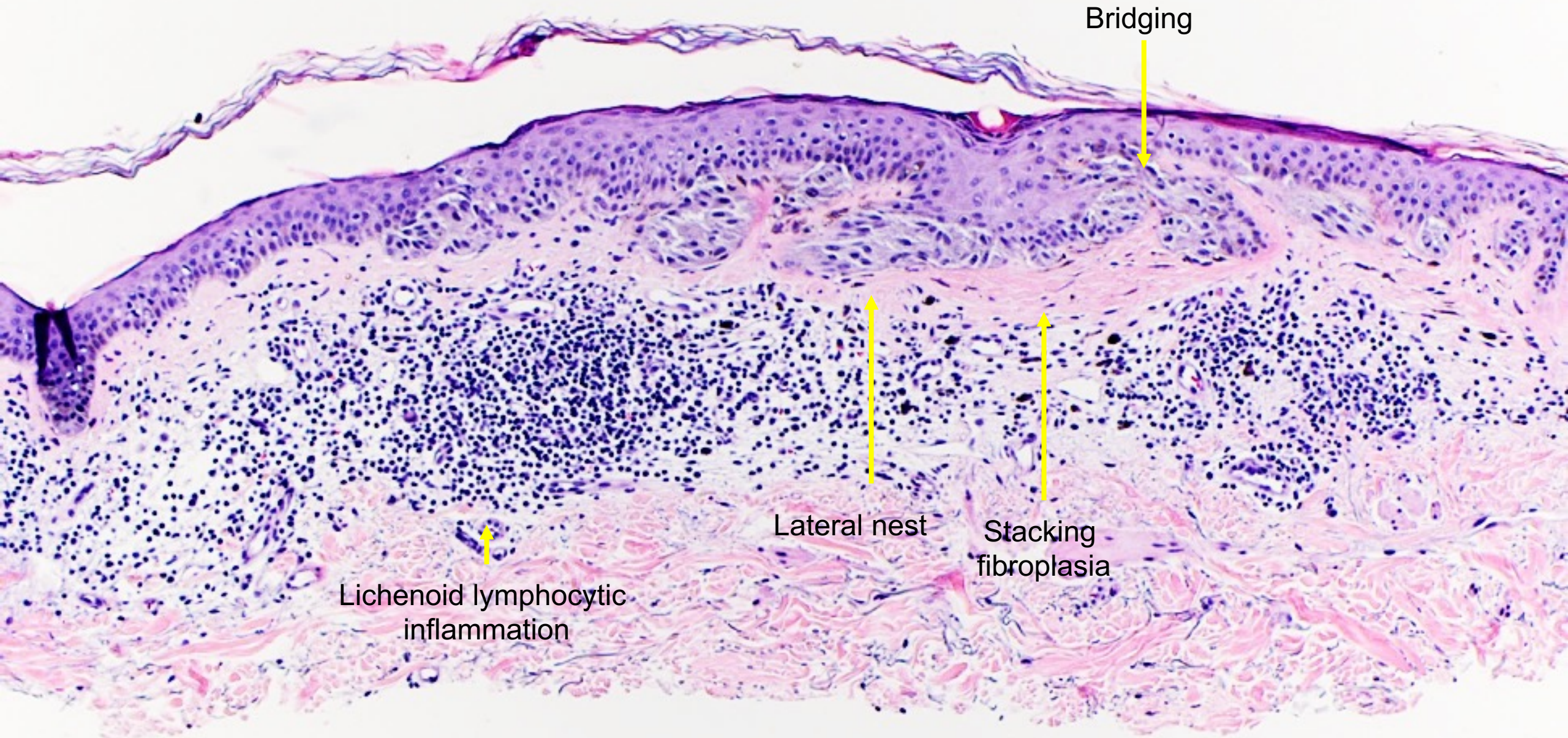
Lateral nest

Lentiginous
growth

Stacking
fibroplasia

Compound dysplastic nevus with regression





Bridging



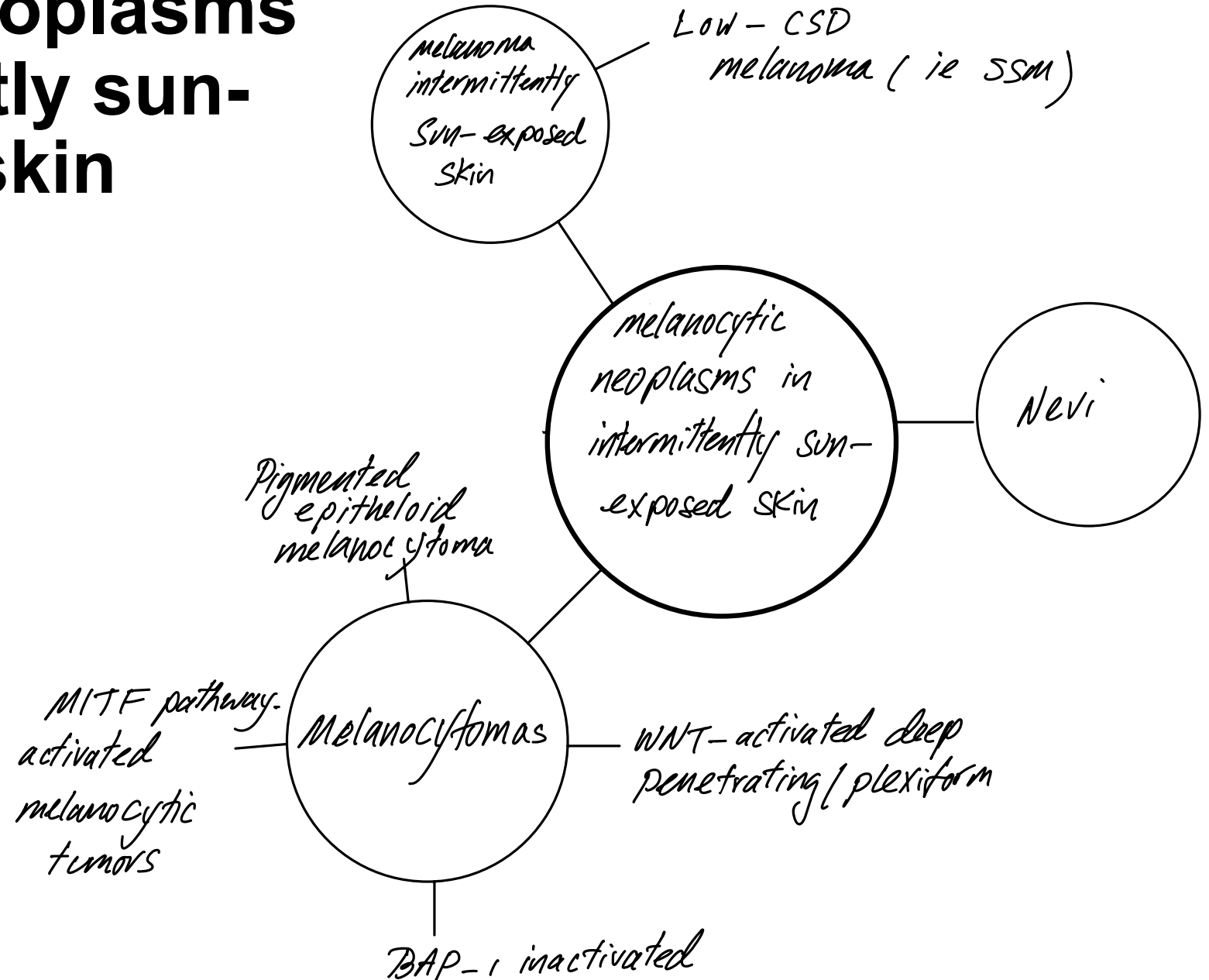
Lichenoid lymphocytic inflammation



Lateral nest

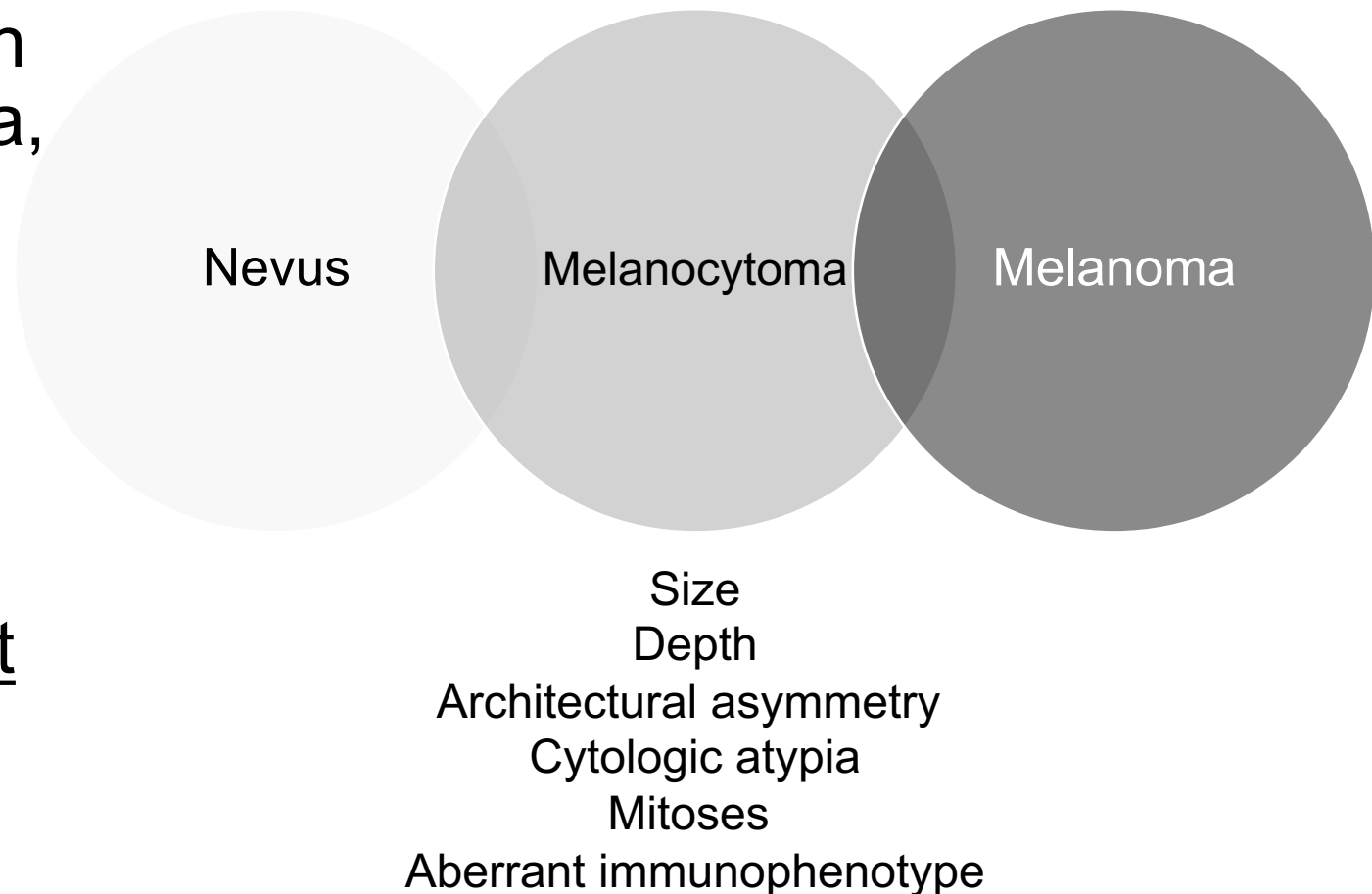
Stacking fibroplasia

Melanocytic neoplasms in intermittently sun-exposed skin

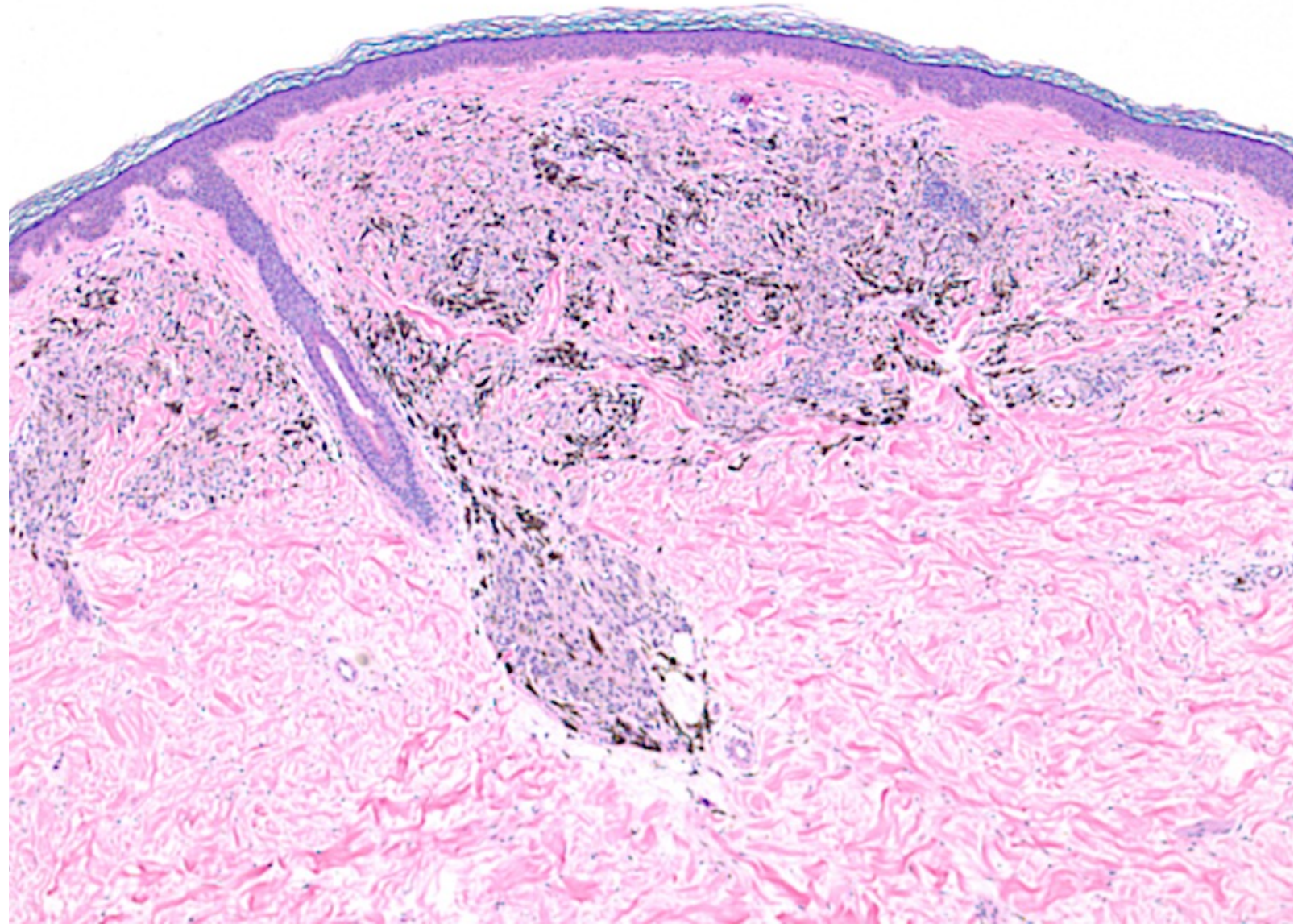


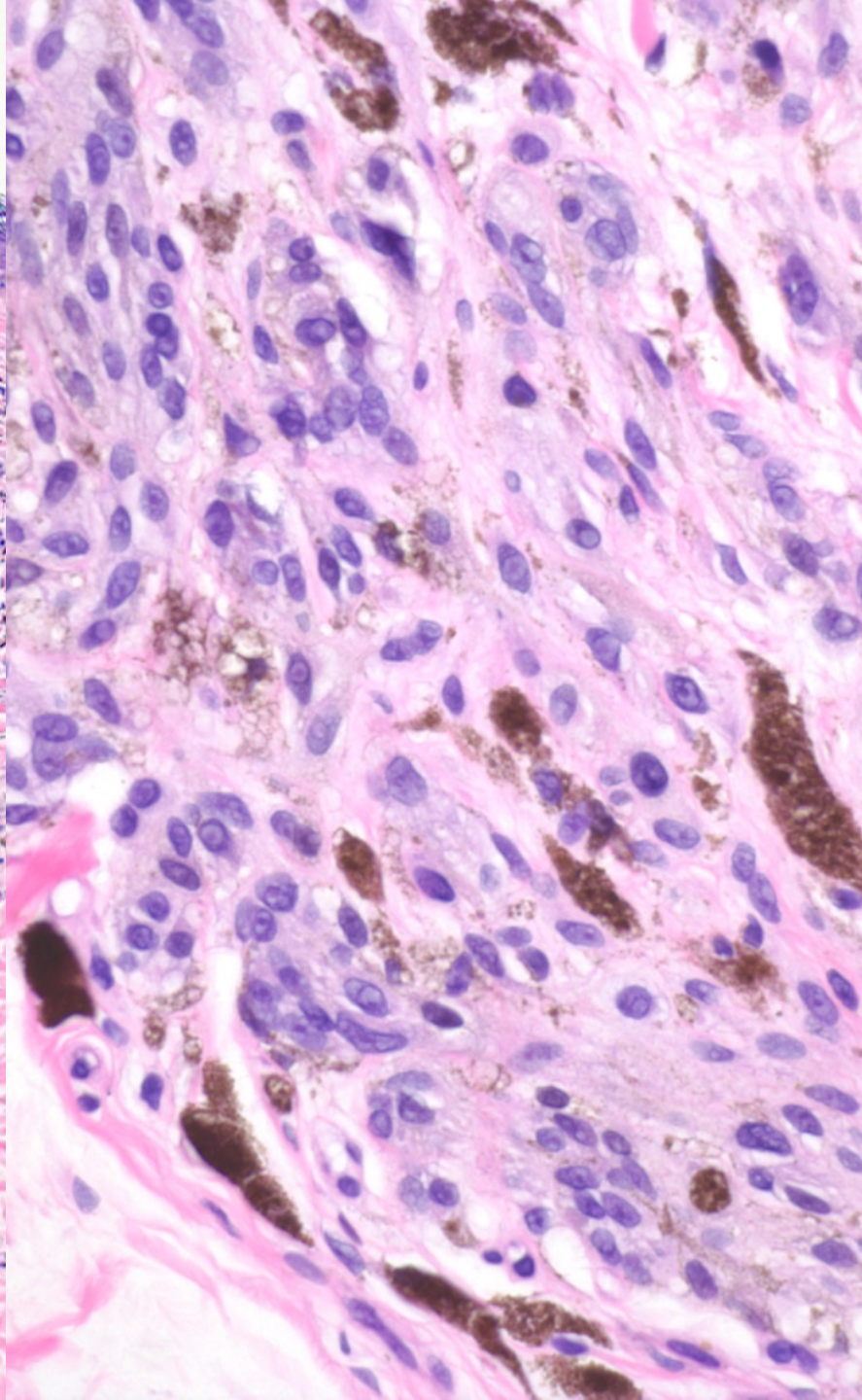
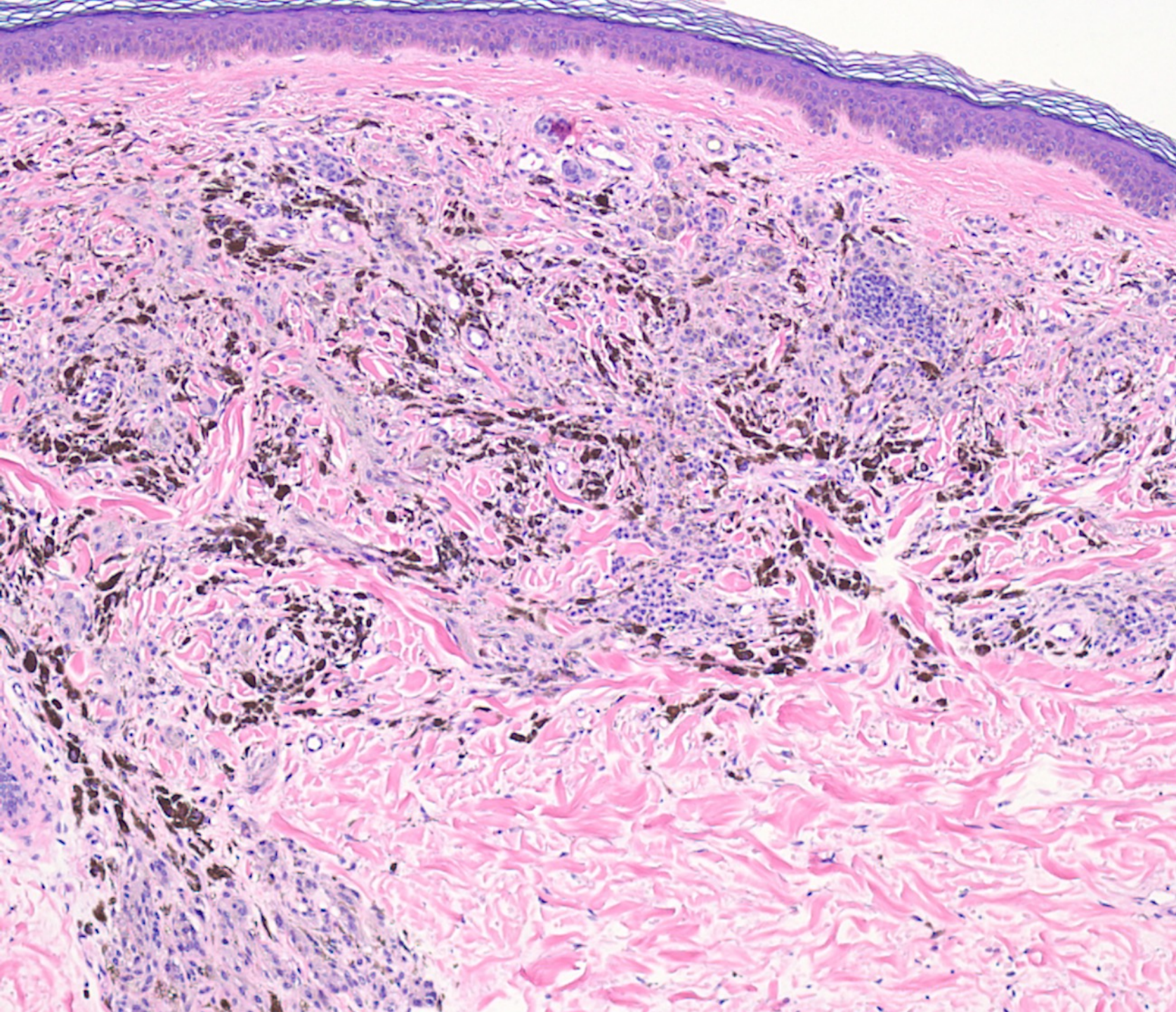
What is a melanocytoma? (not black and white, shades of grey)

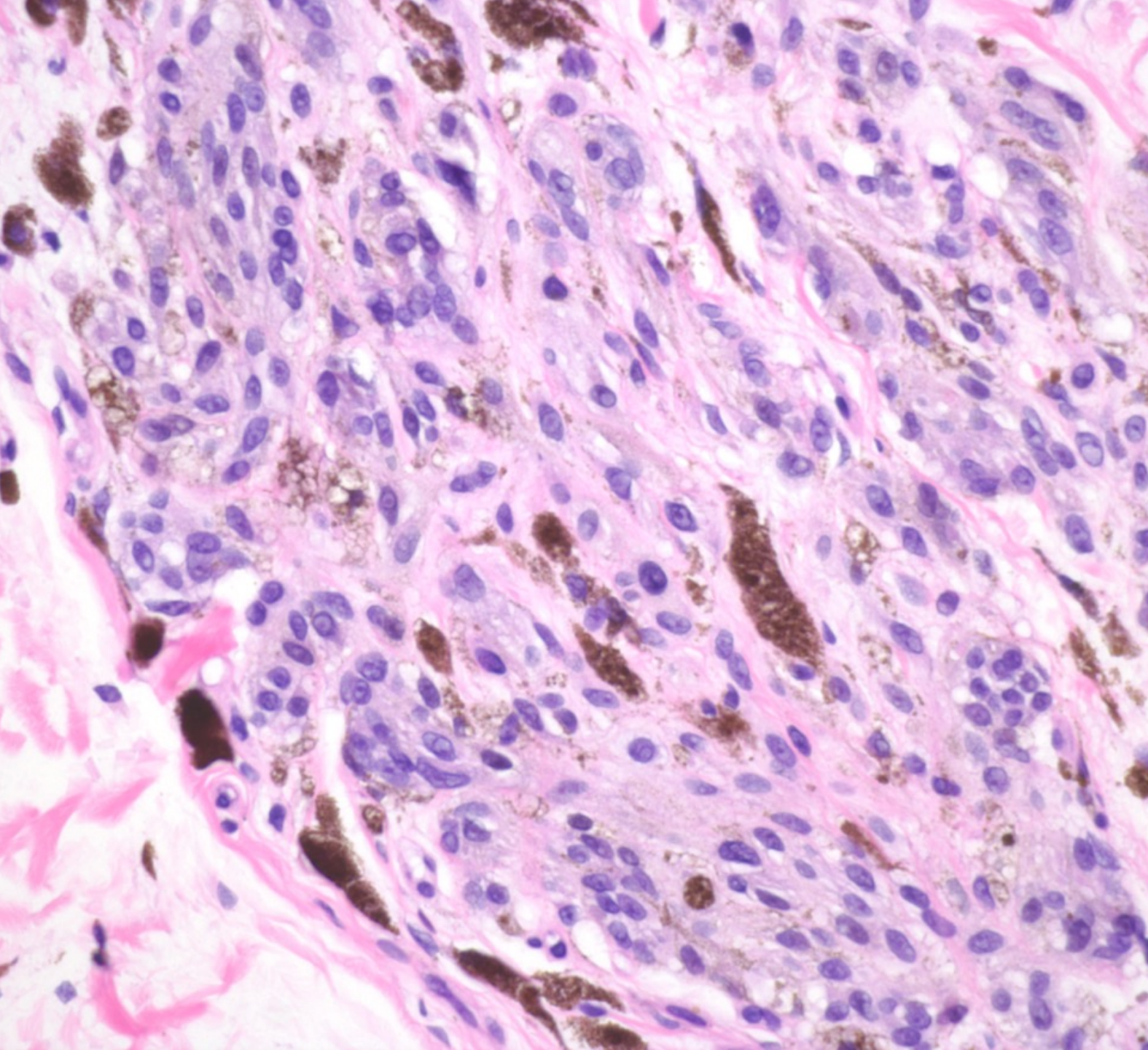
- WHO: tumorigenic melanocytic neoplasm with increased cellularity, atypia, and increased (but low) probability of neoplastic progression.
- Other names: Borderline lesion or MELTUMP
- Morphology cannot predict biologic behavior



45-year-old female
4-mm blue black
macule, new “ish”
Right upper arm
excision



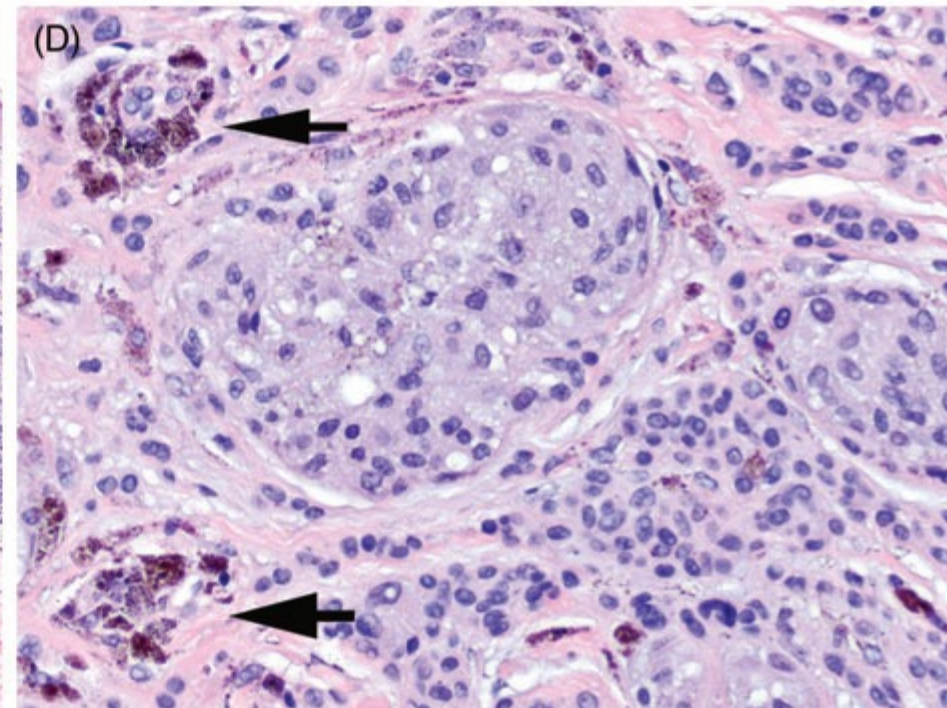
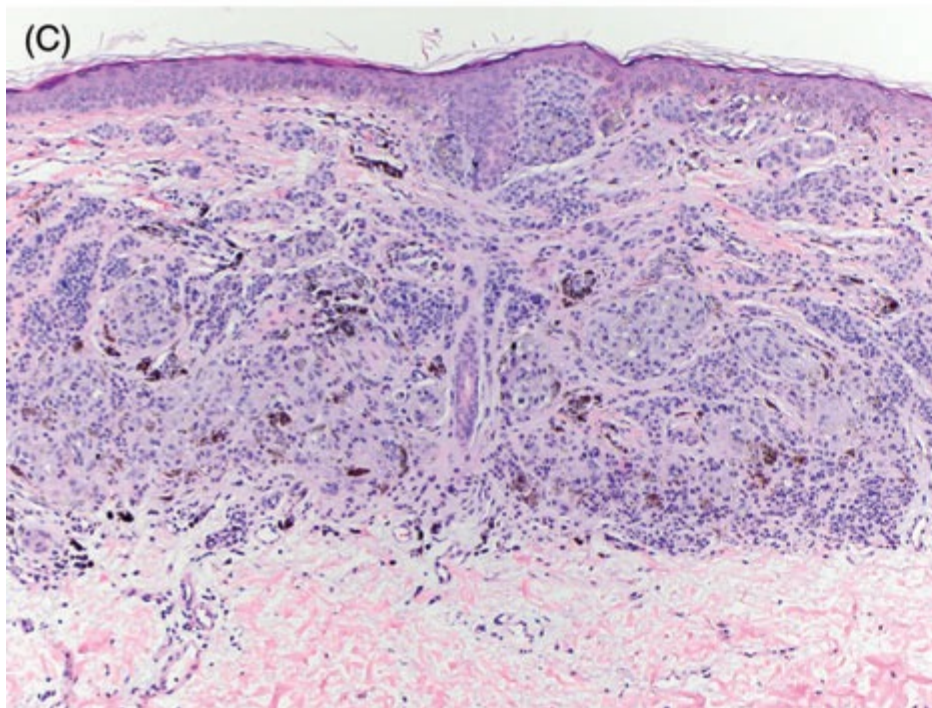
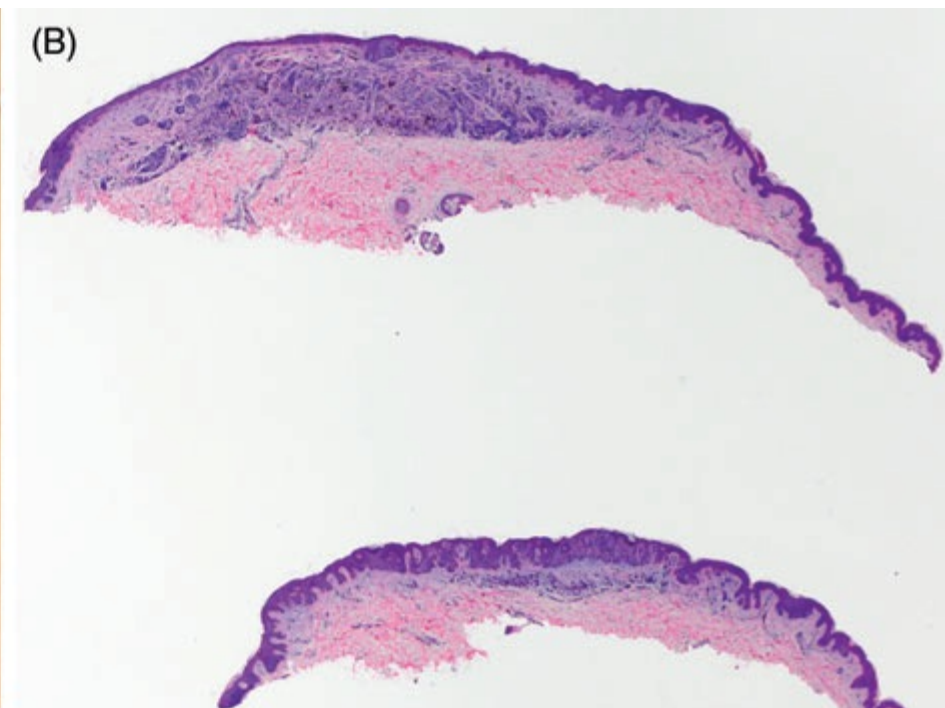
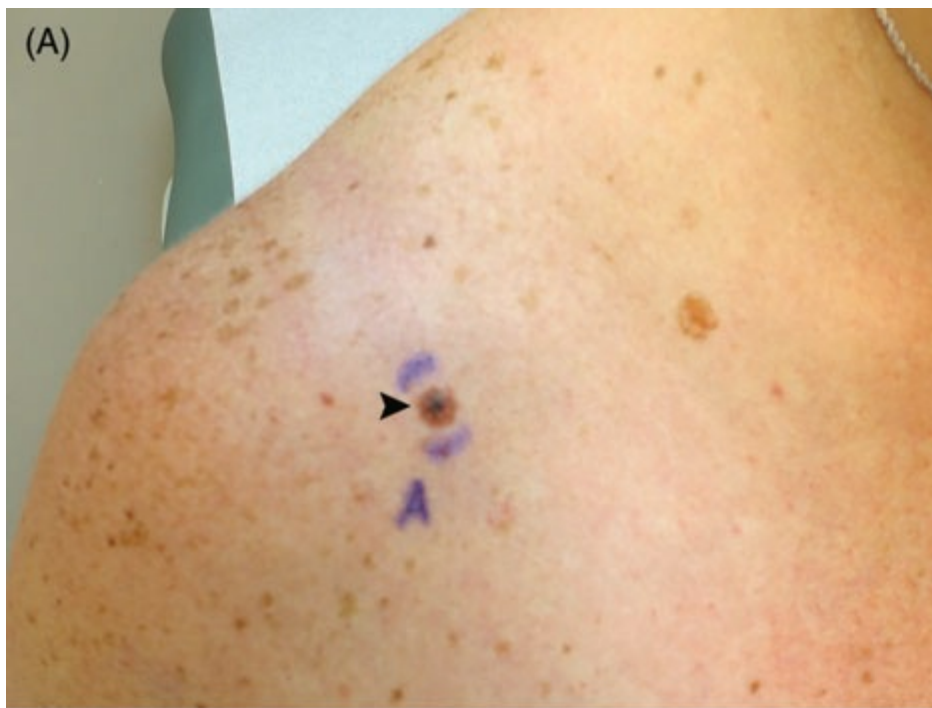





**SKIN, RIGHT UPPER ARM,
BIOPSY: INVERTED TYPE-A
NEVUS, MARGINS NEGATIVE
IN PLANES OF SECTIONS
EXAMINED.**

- Additional levels
- Melanin bleached levels
 - Nuclear pleomorphism
 - Nuclear contour
 - Nuclear membrane
 - Mitoses
- Double IHC: ki-67 Melan-A (<5% mitotic index)

Inverted type-A
melanocytoma/nevus
defies dermal
maturation



Histological features and outcome of inverted type-A melanocytic nevi

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Correspondence

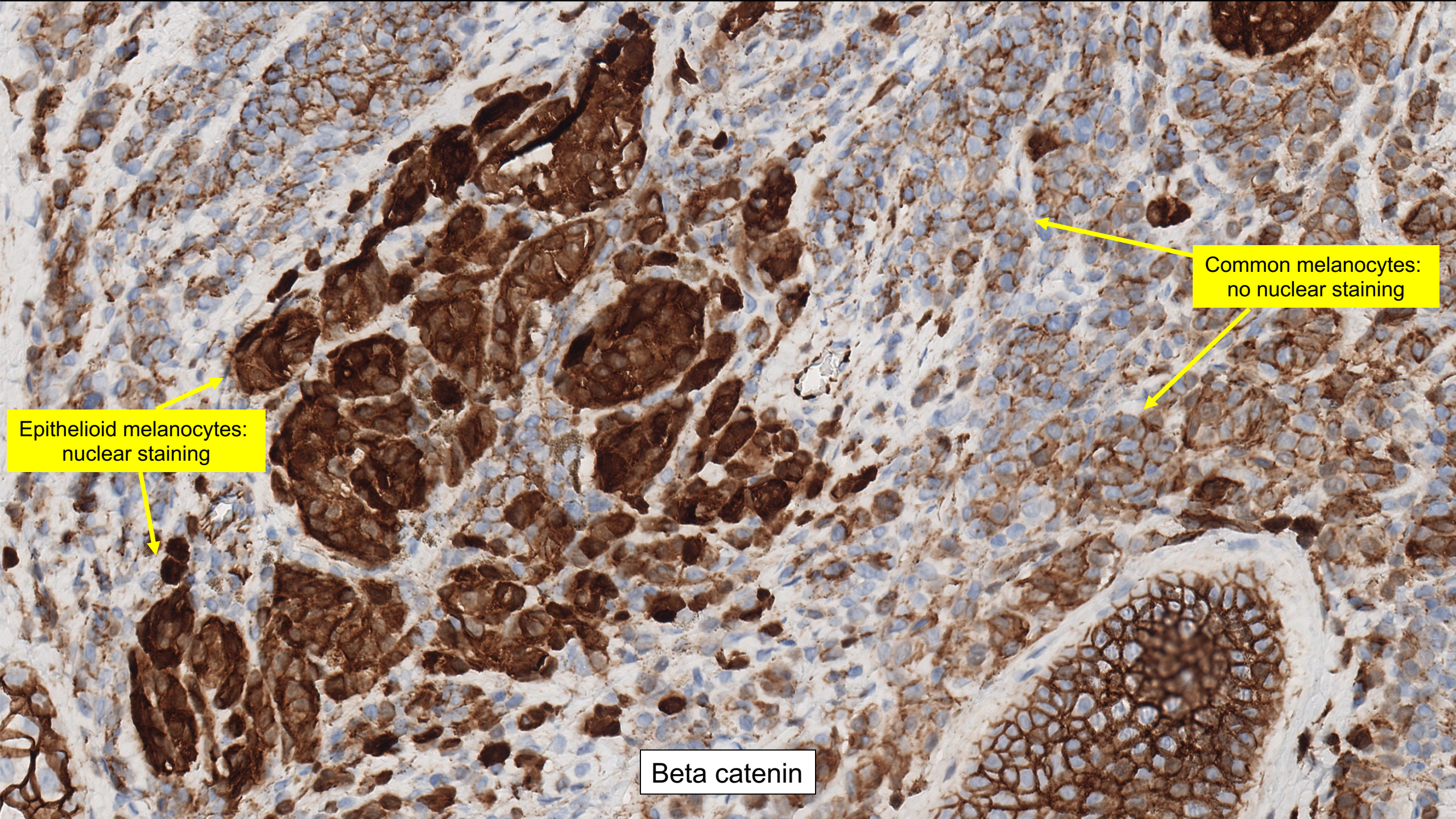
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The presence of enlarged epithelioid/spindled nests located deep in the reticular dermis of a biphasic melanocytic neoplasm can mimic melanoma arising in a pre-existing nevus, causing over-interpretation of malignancy. We aimed to define the clinicopathologic significance of epithelioid/spindled nests in melanocytic nevi. Retrospectively using clinical and histologic information, we characterized 121 patients with a single lesion showing epithelioid/spindled melanocytes in the reticular dermis or subcutaneous fat, surrounded by melanophages, sometimes blending in with the adnexa. The majority of nevi occurred in women in the ages of 10 to 39 years, where the most frequent presentation was a changing mole. While 78% of the lesions displayed an anatomic (Clark's) level of IV-V, there was no ulceration, significant regression or inflammation. Up to 2 mitoses were found in only 12% of the cases, not correlating with the severity of cytological atypia. No recurrence or metastasis occurred during 45.5 months (mean) of clinical follow up in 26 patients. Notwithstanding the deep dermal extension, these findings suggest a benign histopathology and clinical outcome. Having compared the overlapping histopathology and clinical features between deep penetrating/clonal nevus and combined nevus, we posit that "inverted type-A nevus" might be considered a variant of the two.

KEYWORDS

atypical dermal nodule in benign melanocytic nevus, combined nevus, deep penetrating nevus, melanocytic nevus with focal atypical epithelioid component (clonal nevus) nevus with phenotypic heterogeneity

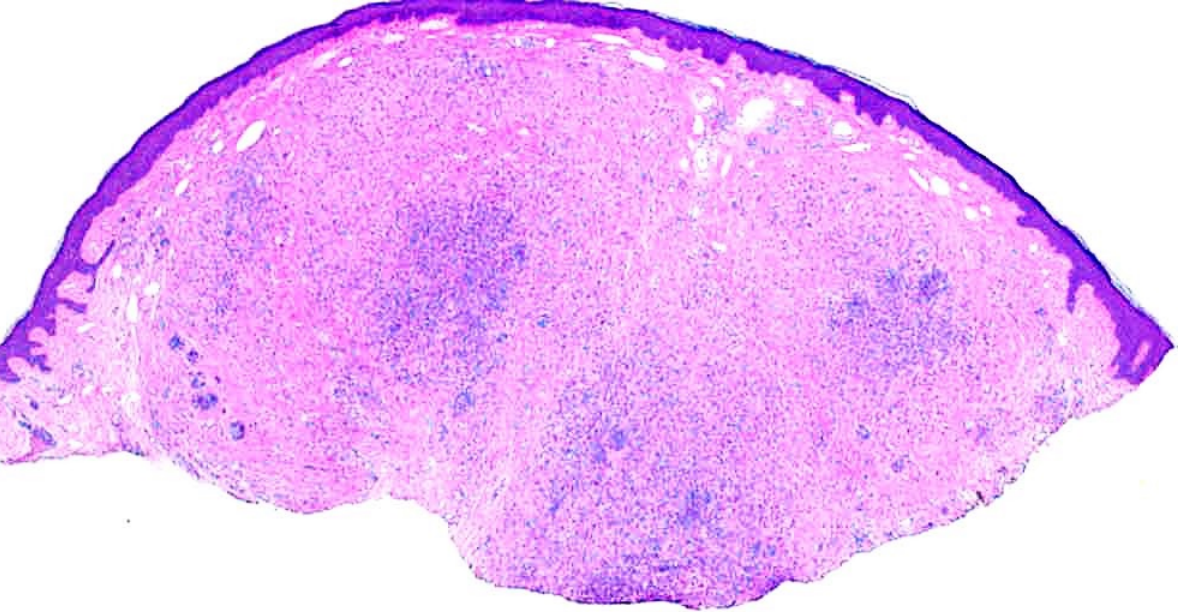
- Unifying concept: overlapping histopathology and clinical features between deep penetrating/clonal nevus and combined nevus
- Enlarged epithelioid/spindled nests mimics dermal melanoma or melanoma arising in nevus
- Arising in a pre-existing nevus
- No recurrence or metastasis occurred during 45.5 months (mean) of clinical follow up in 26 patients
- Worrisome histopathology but benign clinical outcome
- Epithelioid cells, within a pre-existing nevus, acquire activating mutation of **WNT/beta-catenin pathway**



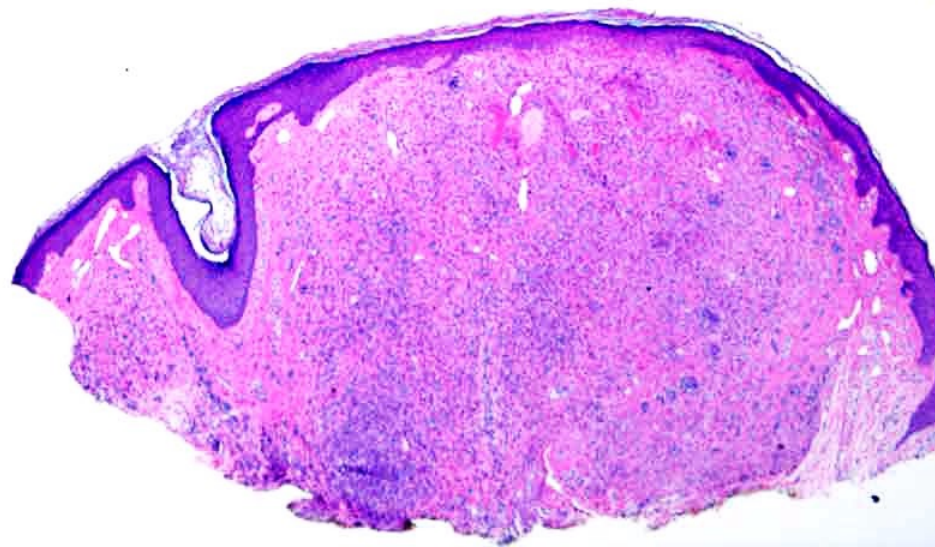
Common melanocytes:
no nuclear staining

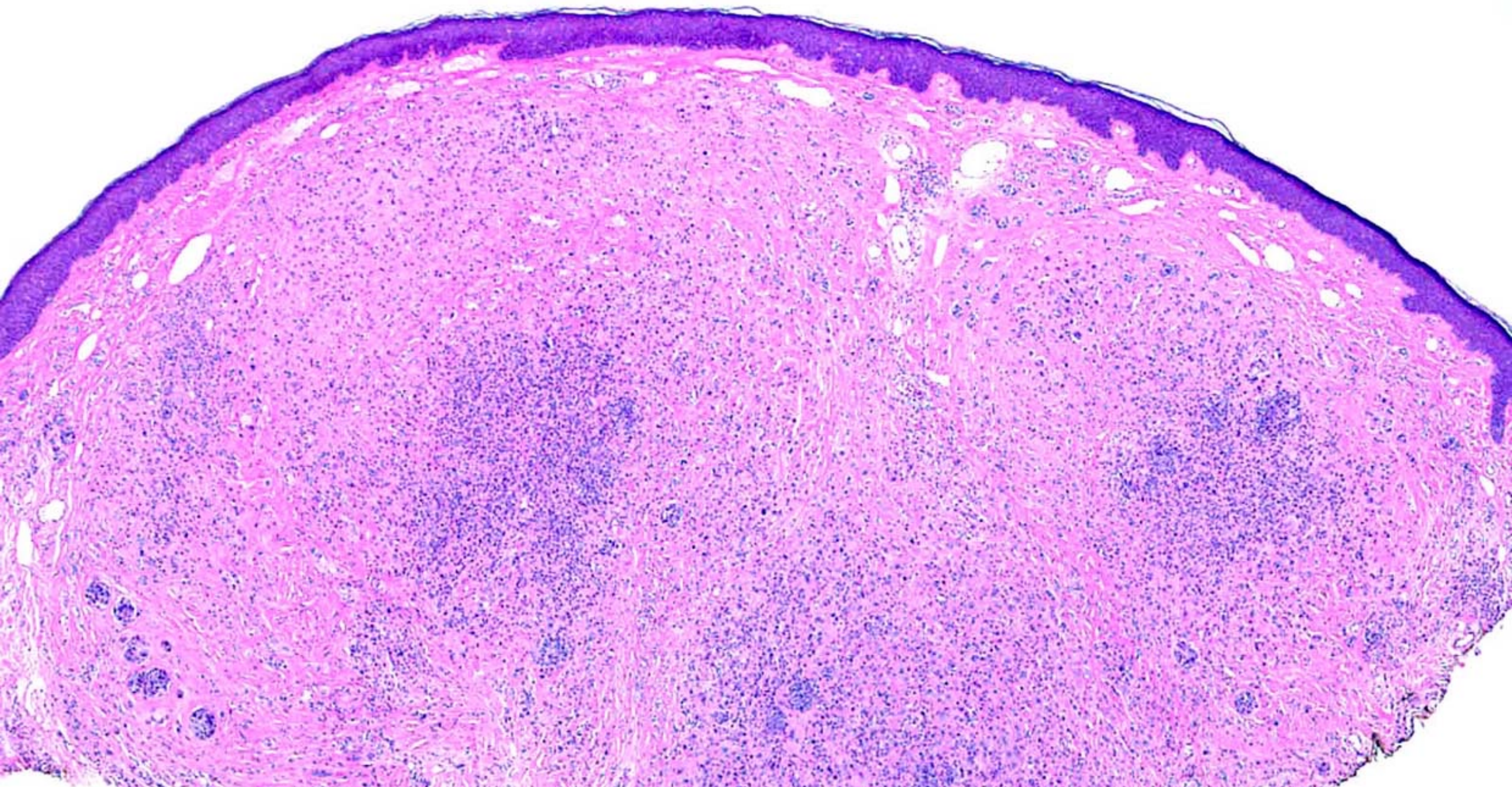
Epithelioid melanocytes:
nuclear staining

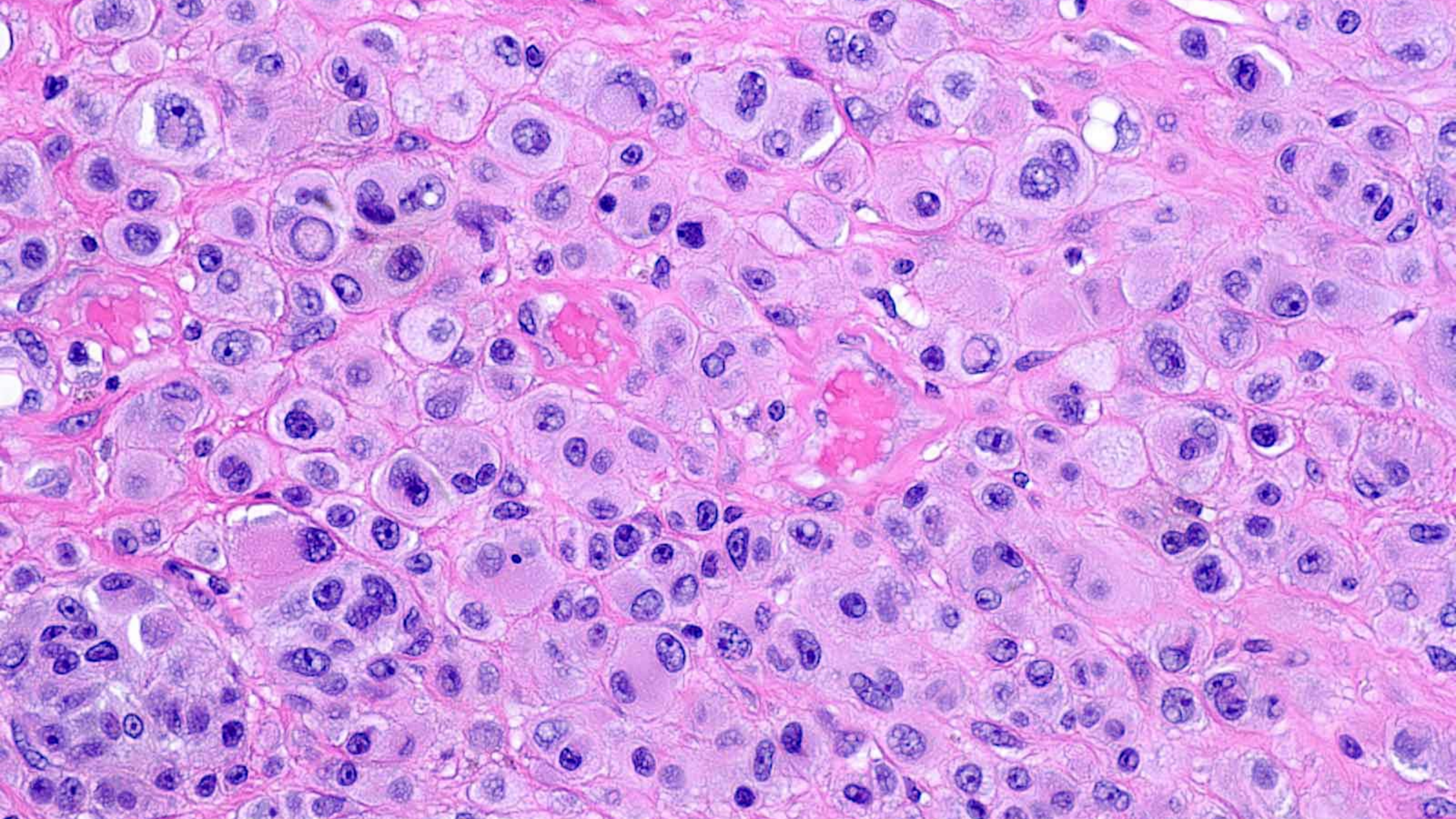
Beta catenin

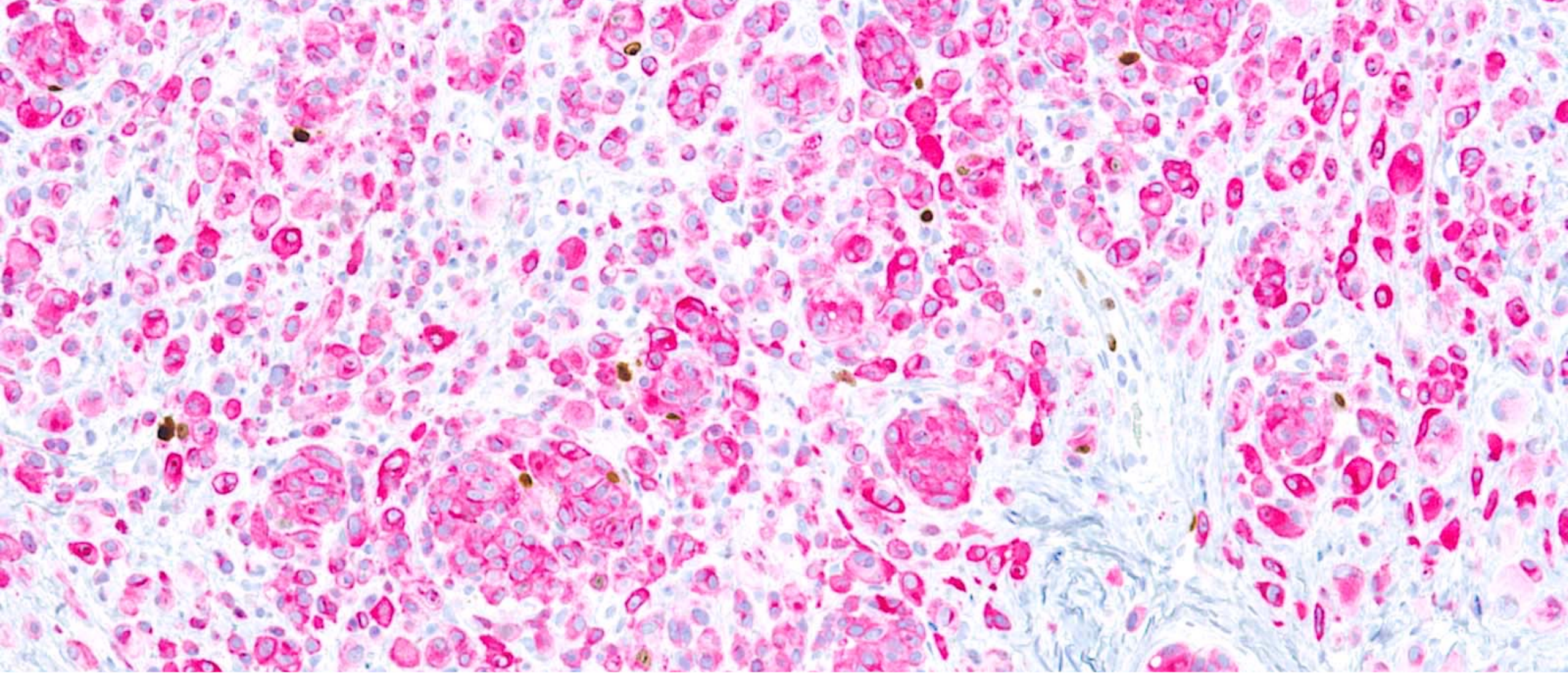


-
- Clinical: 73-year-old male
?BCC, R Neck Shave.

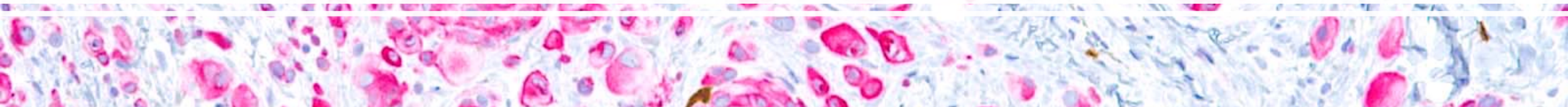


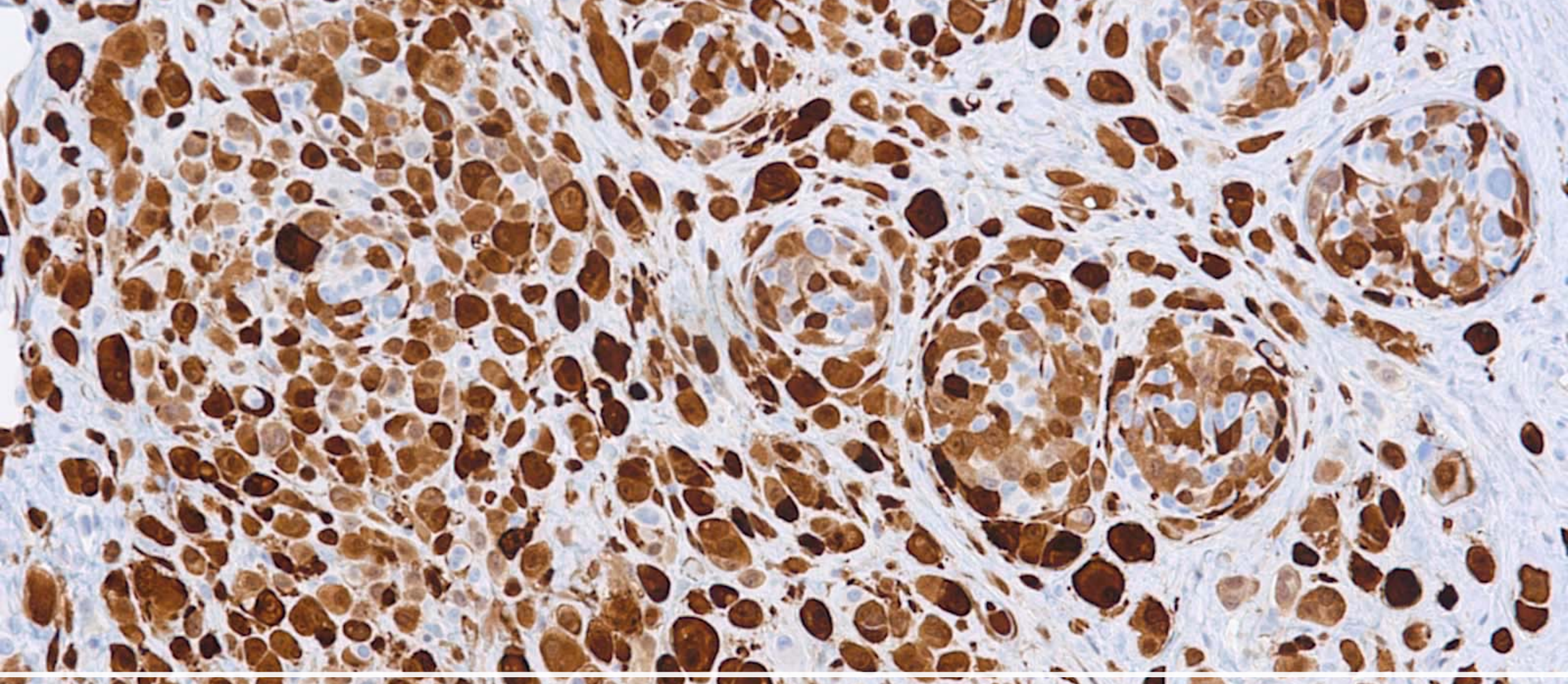




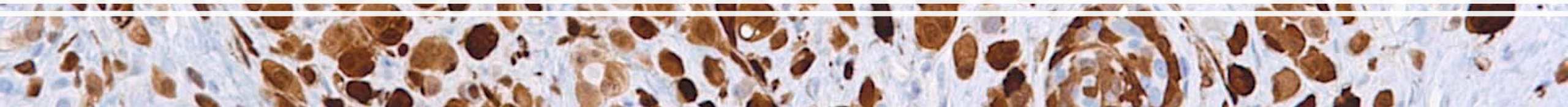


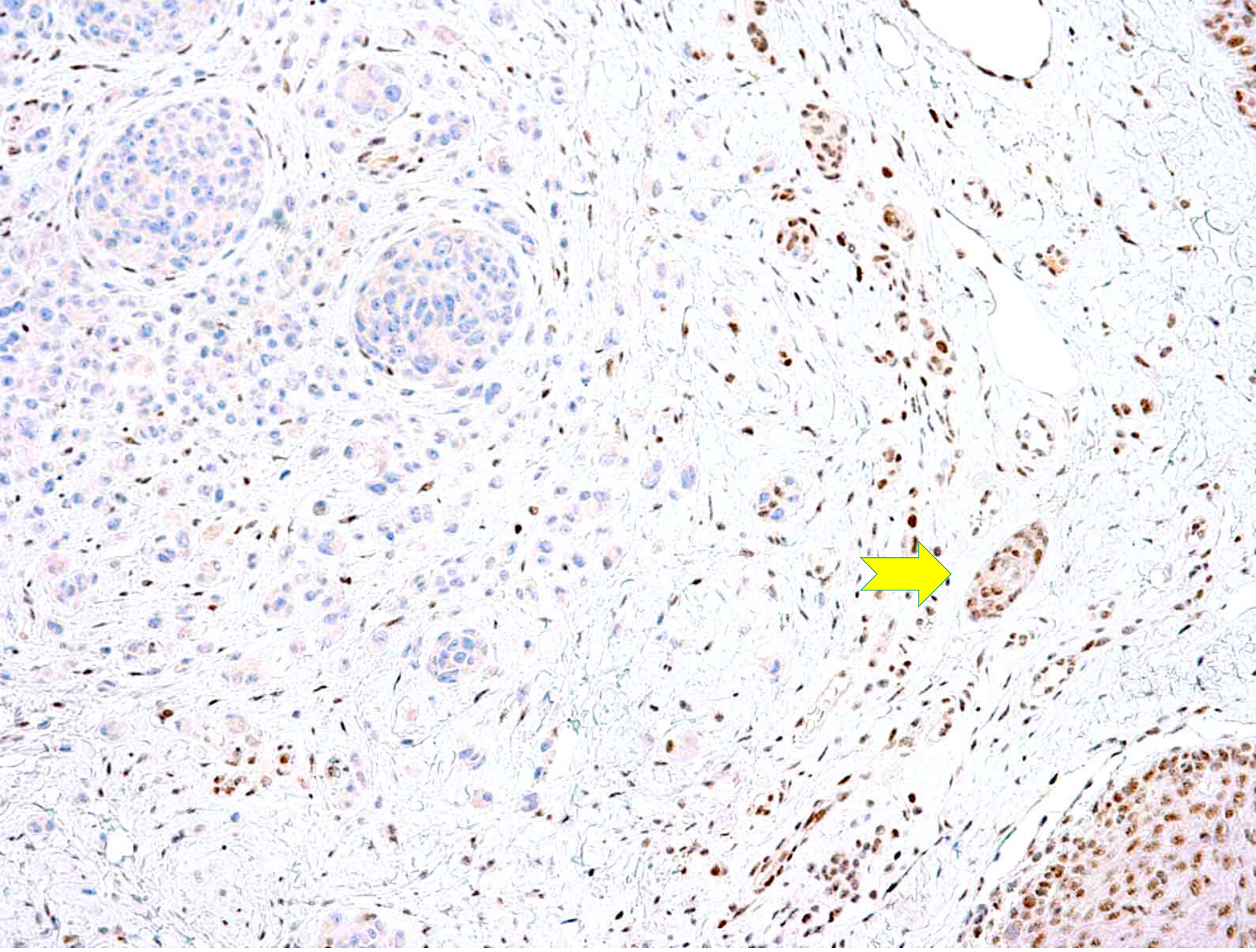
ki67-Melan-A





p16





BAP-1

Diagnosis:

SKIN, RIGHT NECK, SHAVE BIOPSY:

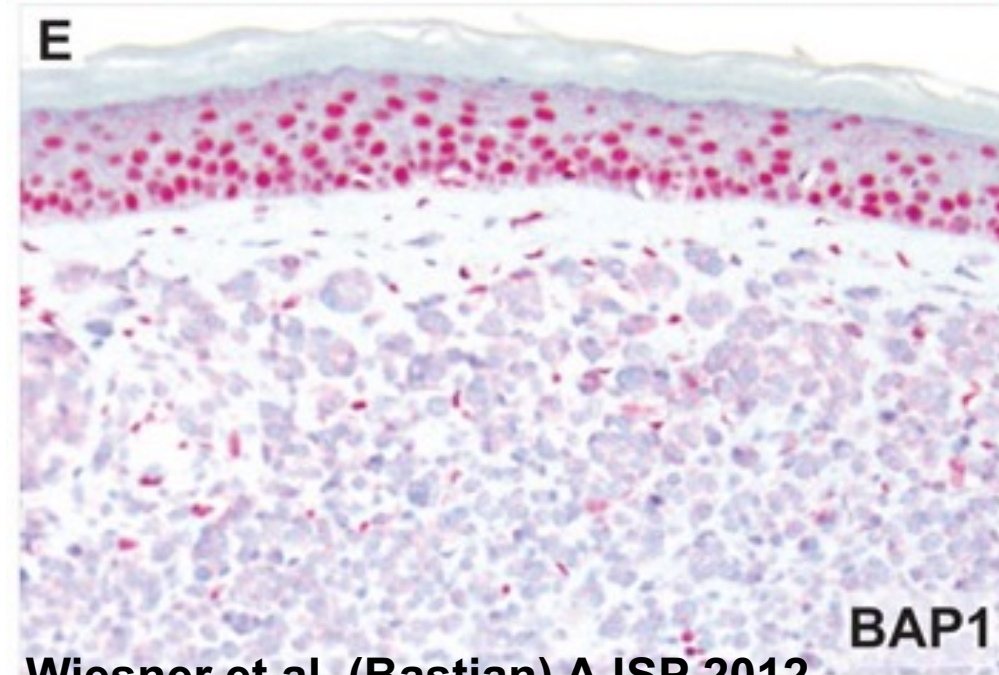
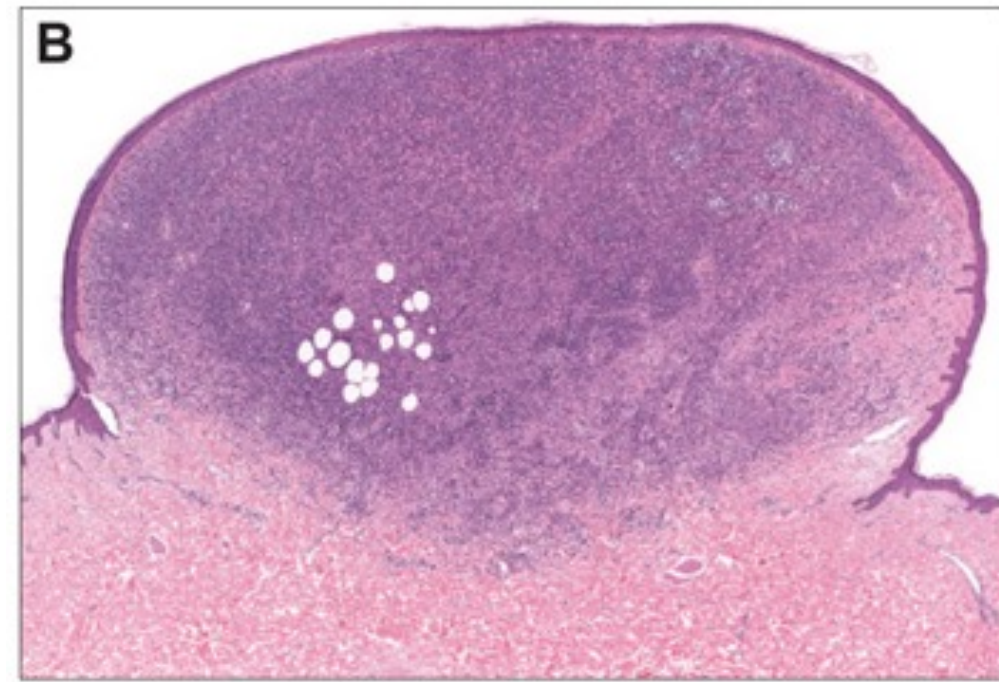
1. BAP-1 INACTIVATED MELANOCYTOMA,
PRESENT AT MARGIN. SEE NOTE.
2. ACTINIC KERATOSIS.

NOTE: 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.

BRCA1 Associated Protein-1 (BAP-1)

- Multiple (from 5 to >50) cutaneous lesions in members of two families with germline mutations in BAP1
 - Wiesner et al. *Nat Genet.* 2011
- Marker for a hereditary BAP1-associated cancer syndrome
- Elevated incidence of uveal melanoma, cutaneous melanoma and mesothelioma

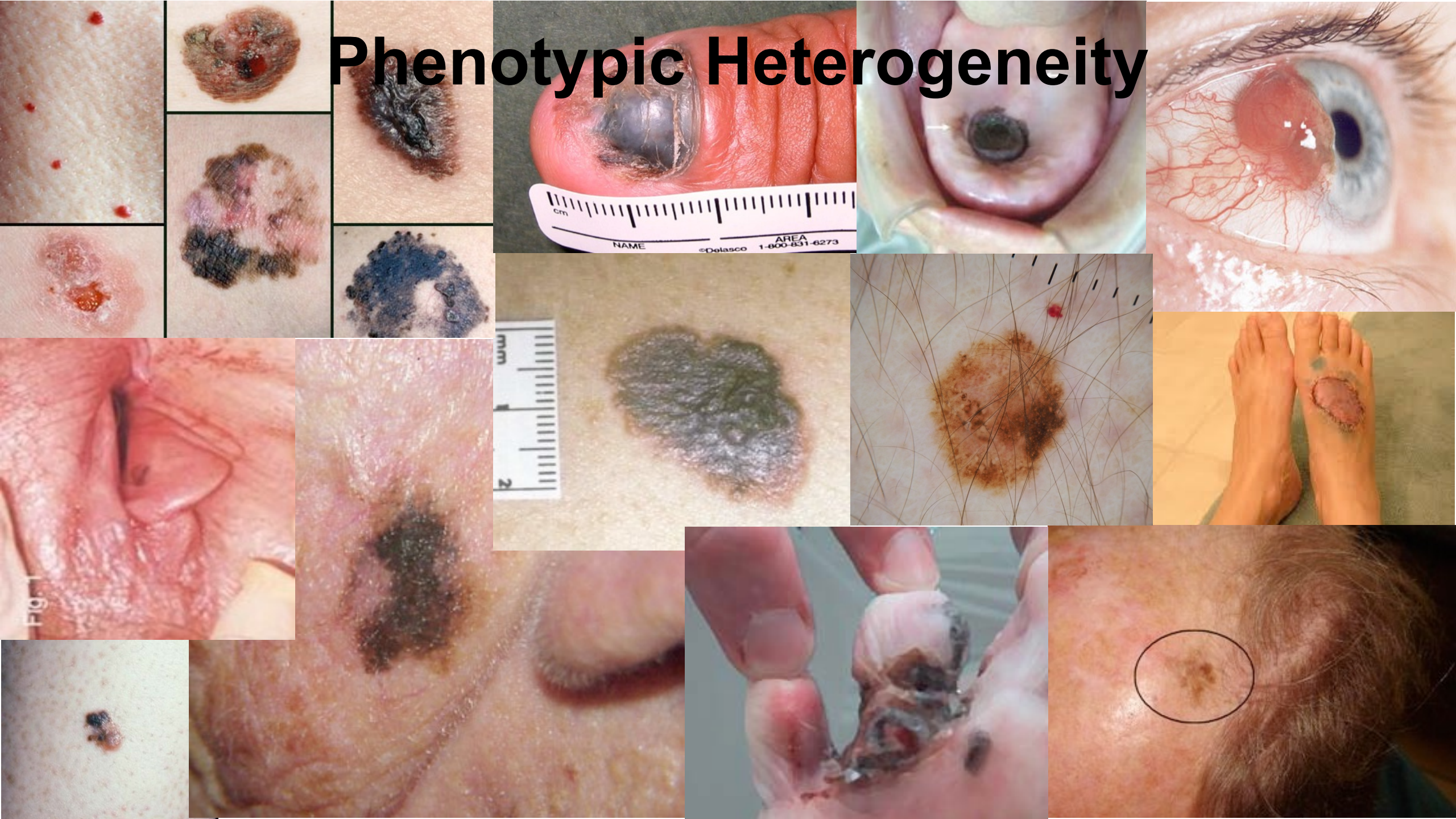


Wiesner et al. (Bastian) AJSP 2012

WHO: BAP-1 inactivated nevus or melanocytoma

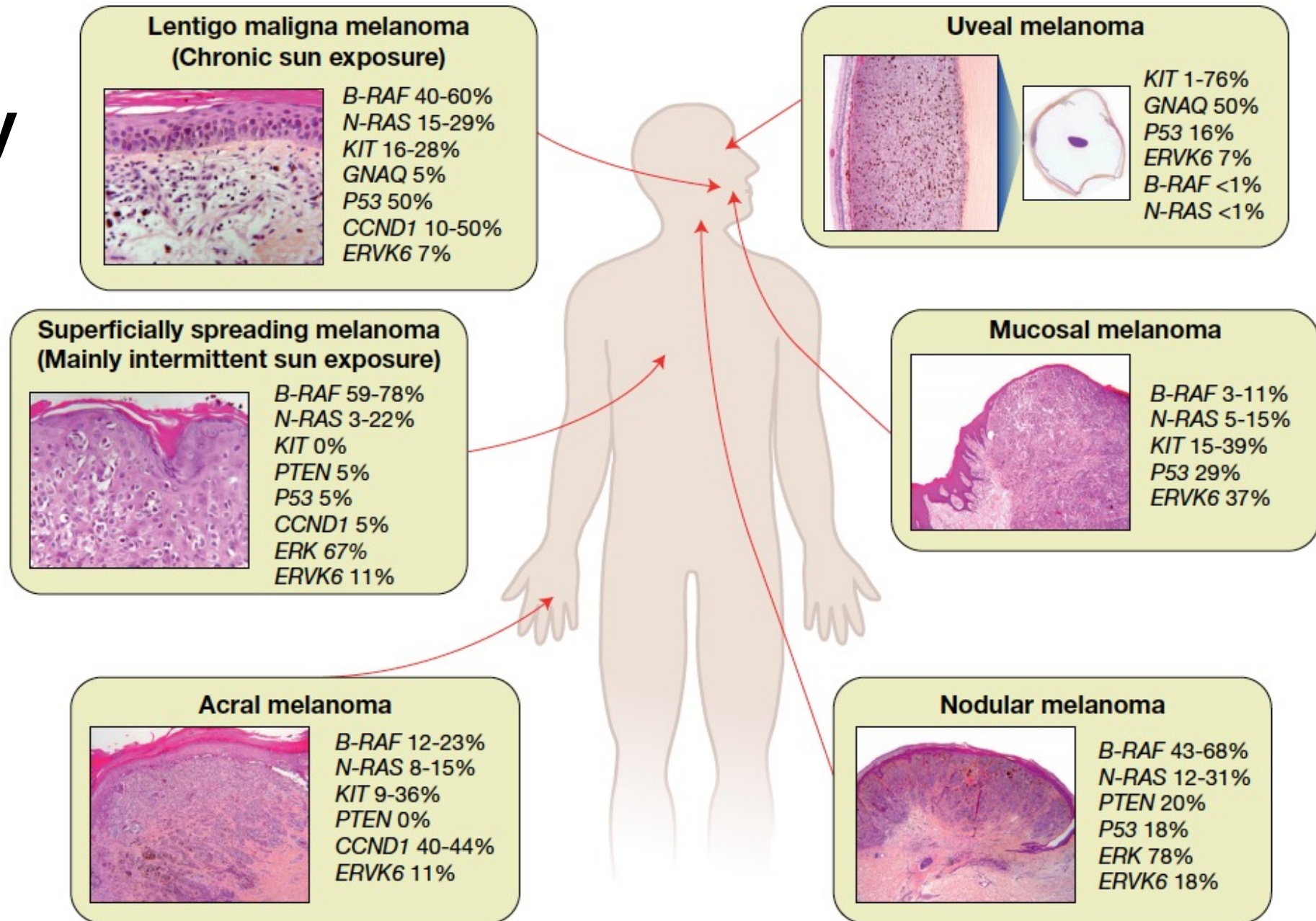
- A tumorigenic melanocytic neoplasm with increased cellularity and cytologic atypia (vs. nevus)
- BAP-1 deficiency in sporadic melanocytic neoplasms with biphasic and epithelioid spitzoid features
- Low malignant potential
 - e.g. Pigmented epithelioid melanocytoma
- Differential diagnosis
 - Atypical Spitz tumor
 - Spitz nevus
 - Combined nevus
 - (melanoma)

Phenotypic Heterogeneity

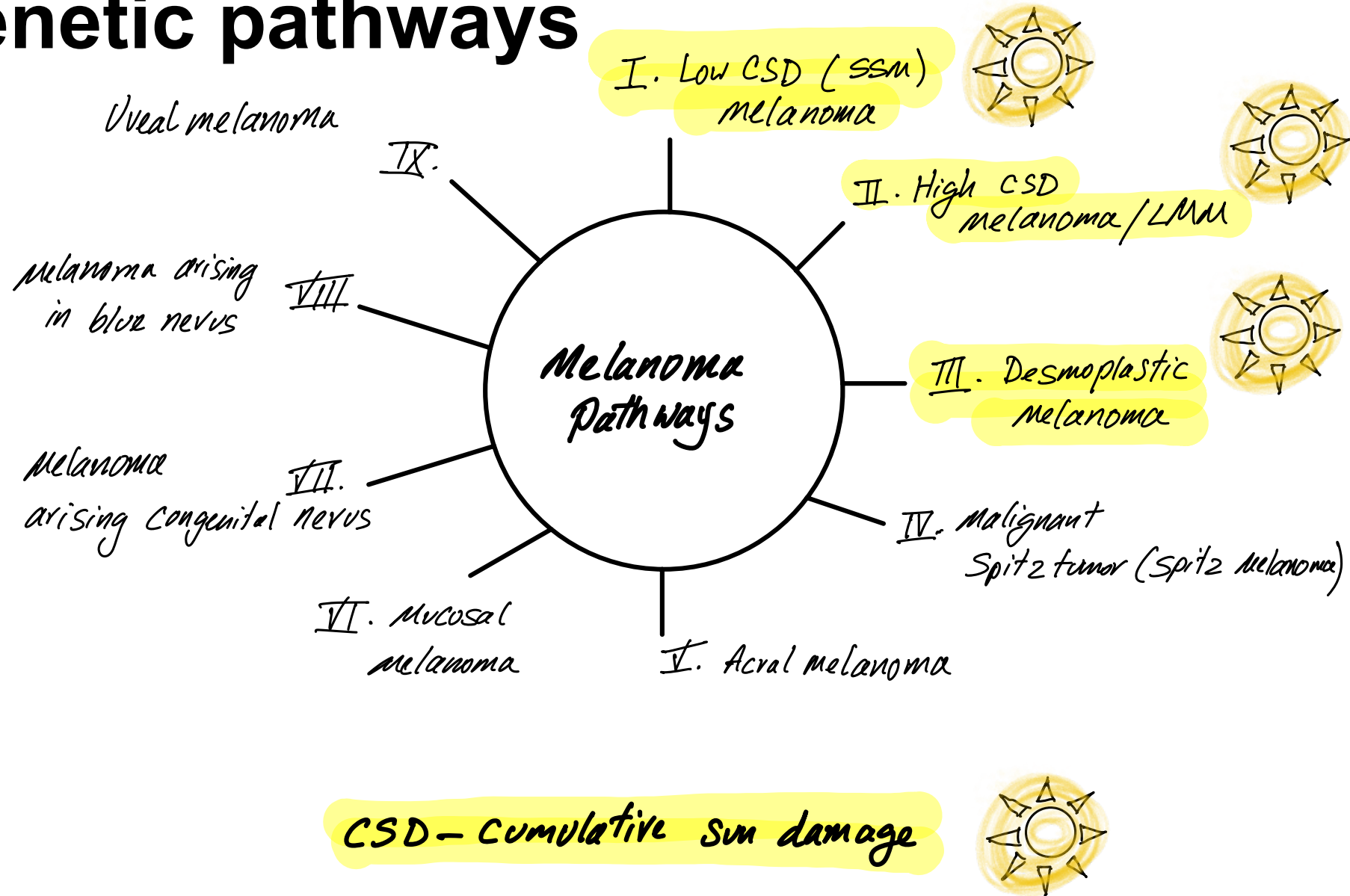


Molecular Heterogeneity

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



WHO 5th edition: Melanoma classification by genetic pathways





Left, medial

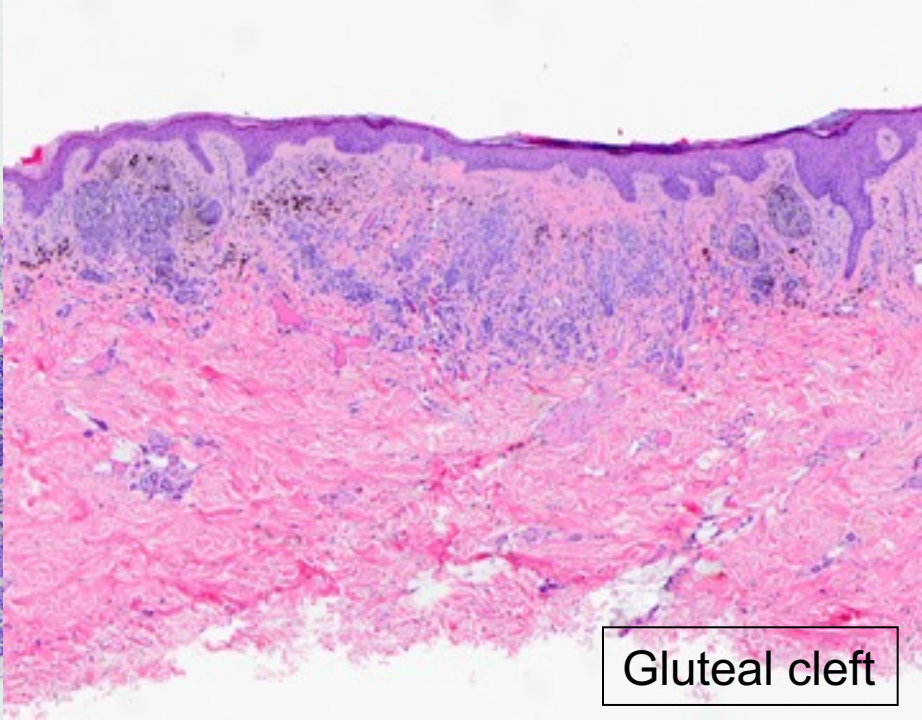
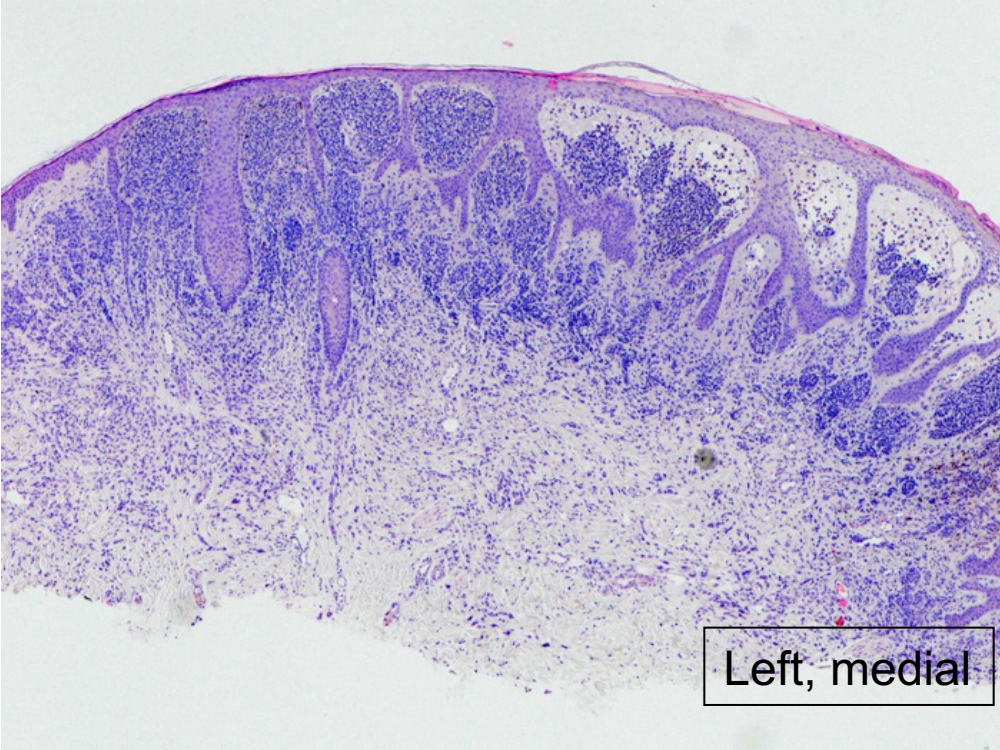


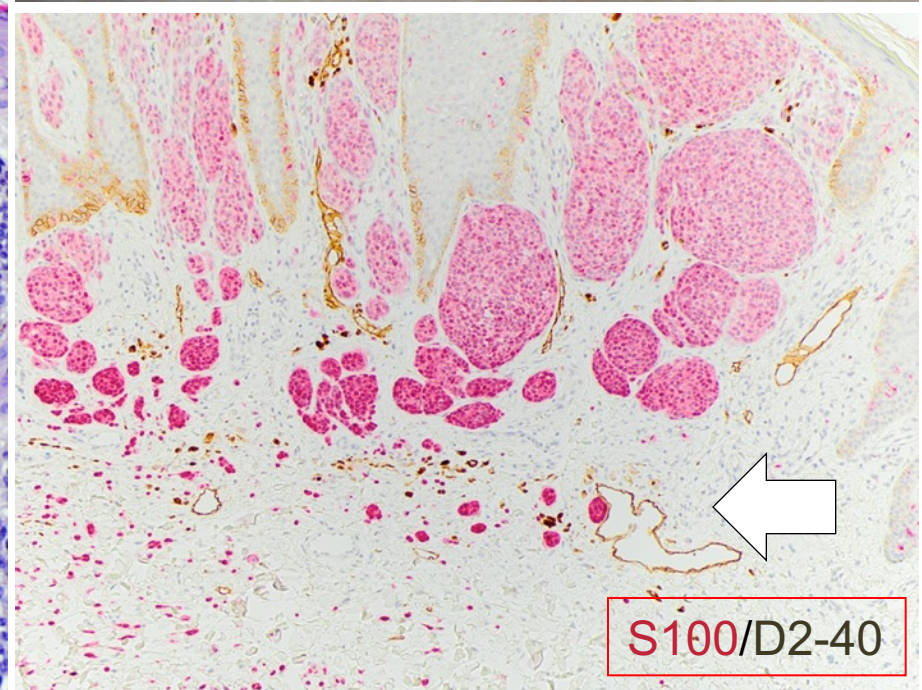
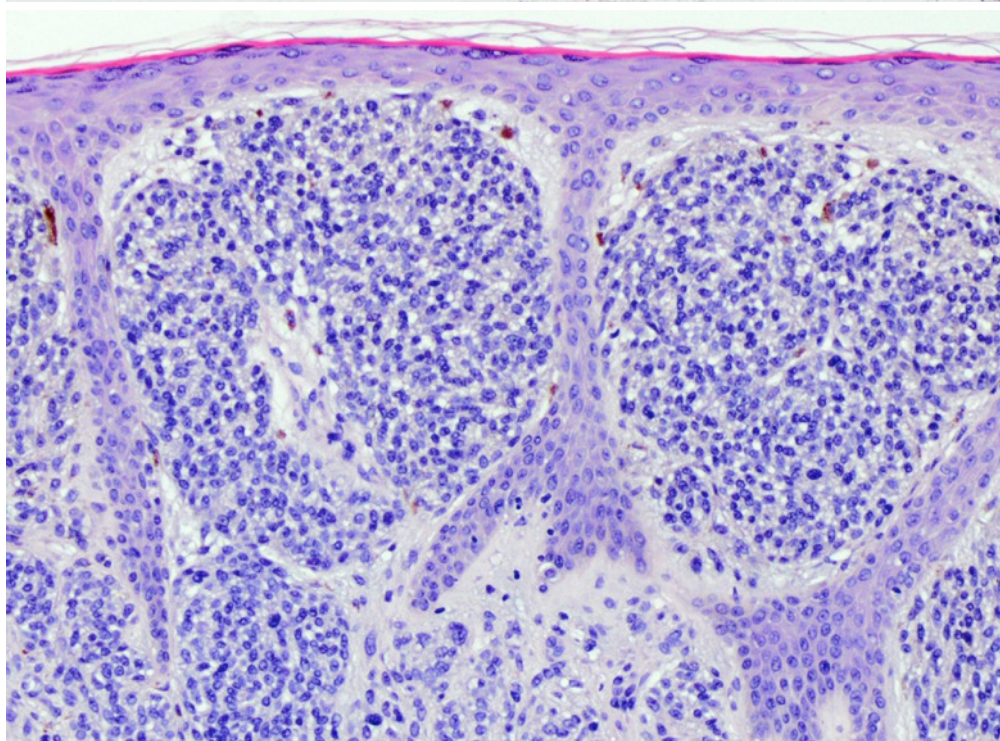
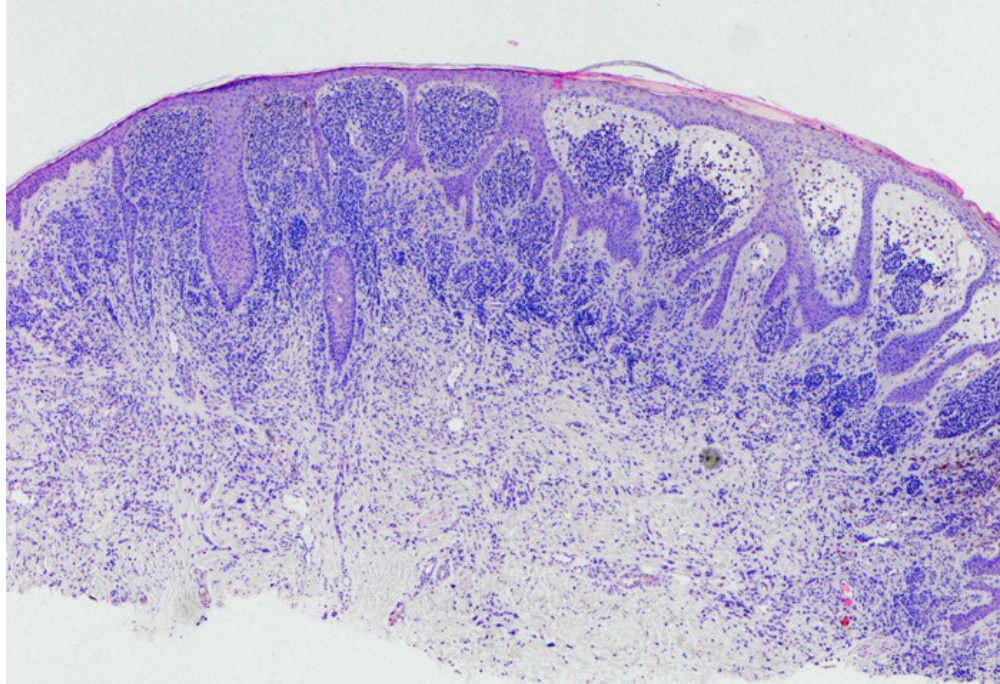
Gluteal cleft



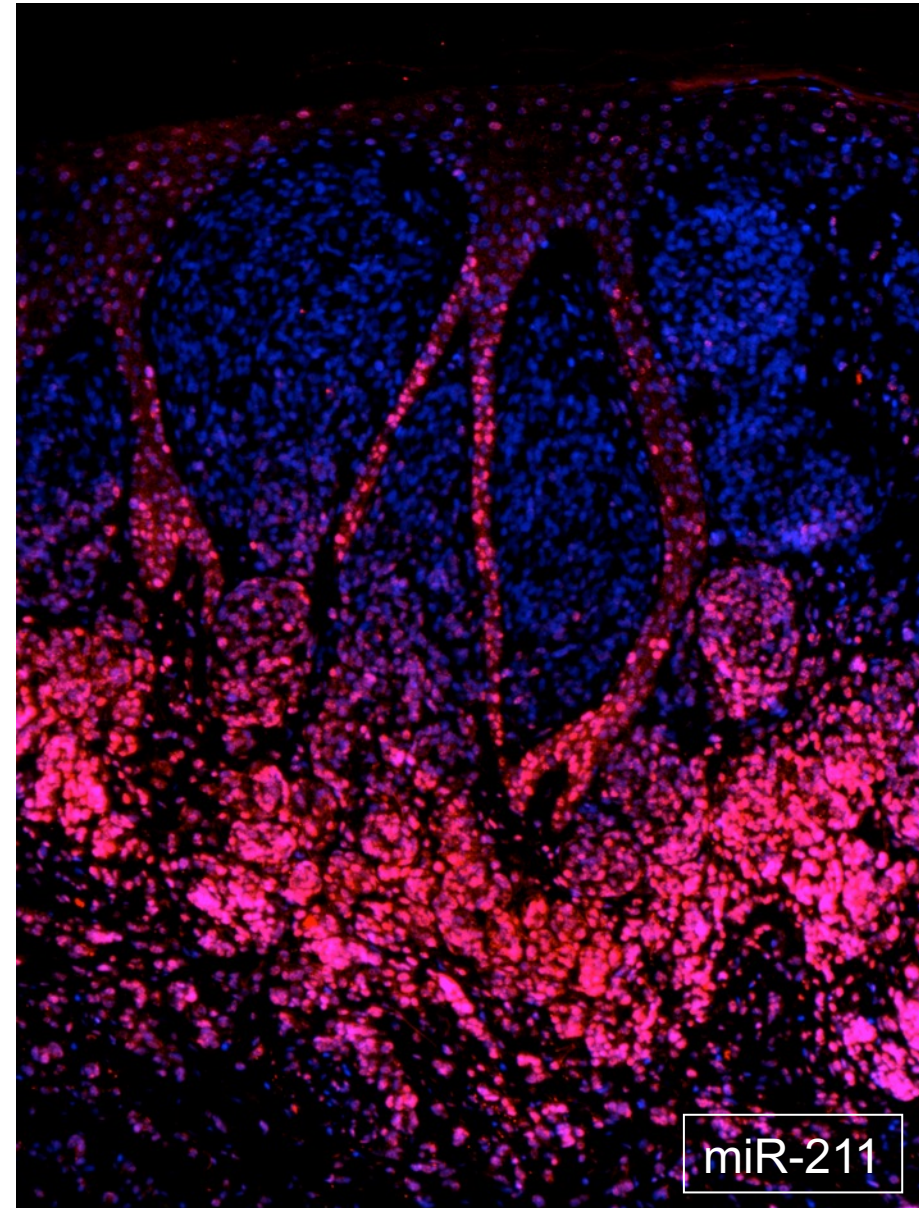
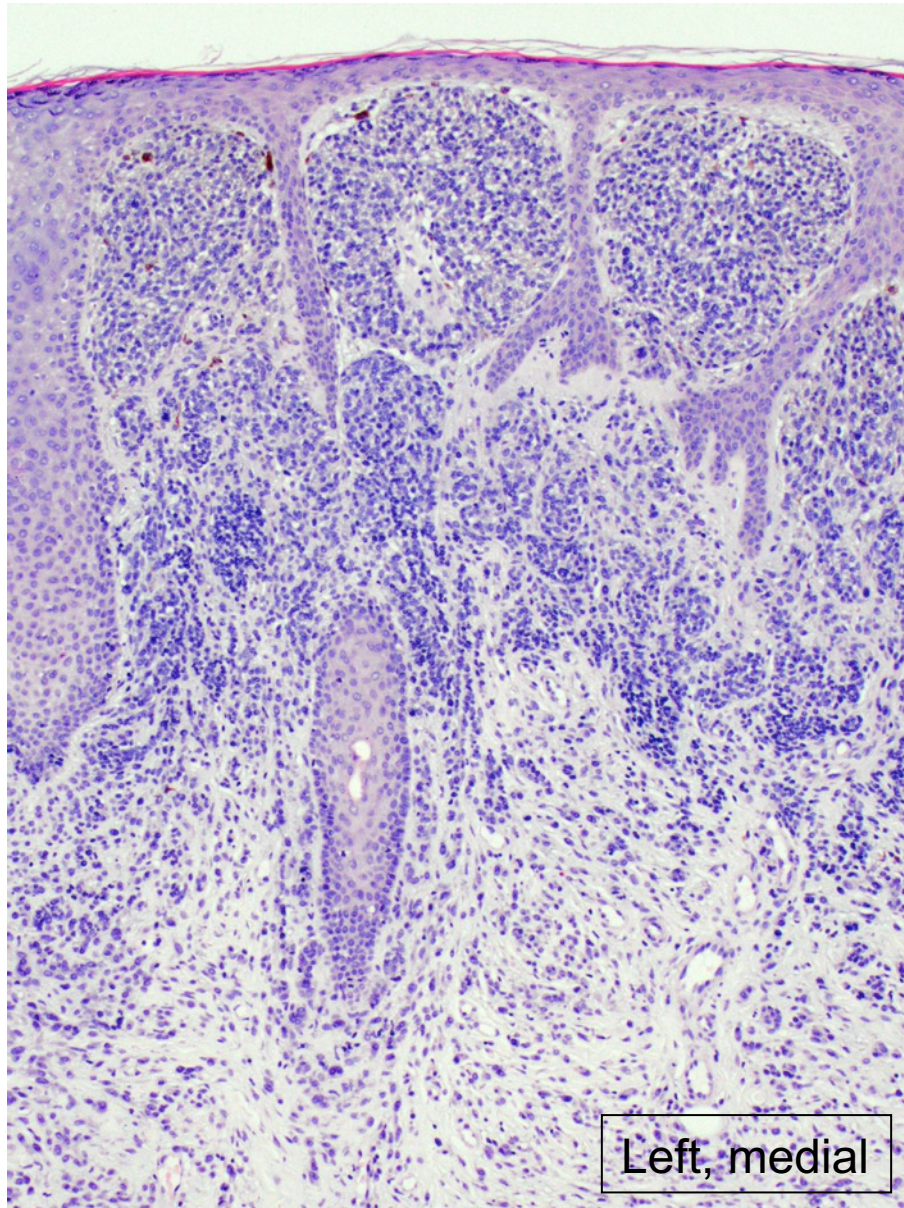
Left, lateral

- 96-year-old woman with painful growths on the buttocks
- Past dermatological history
 - Melanoma in situ, right upper arm June 2012
 - SCC, left upper face April 2012
 - Seborrheic keratoses



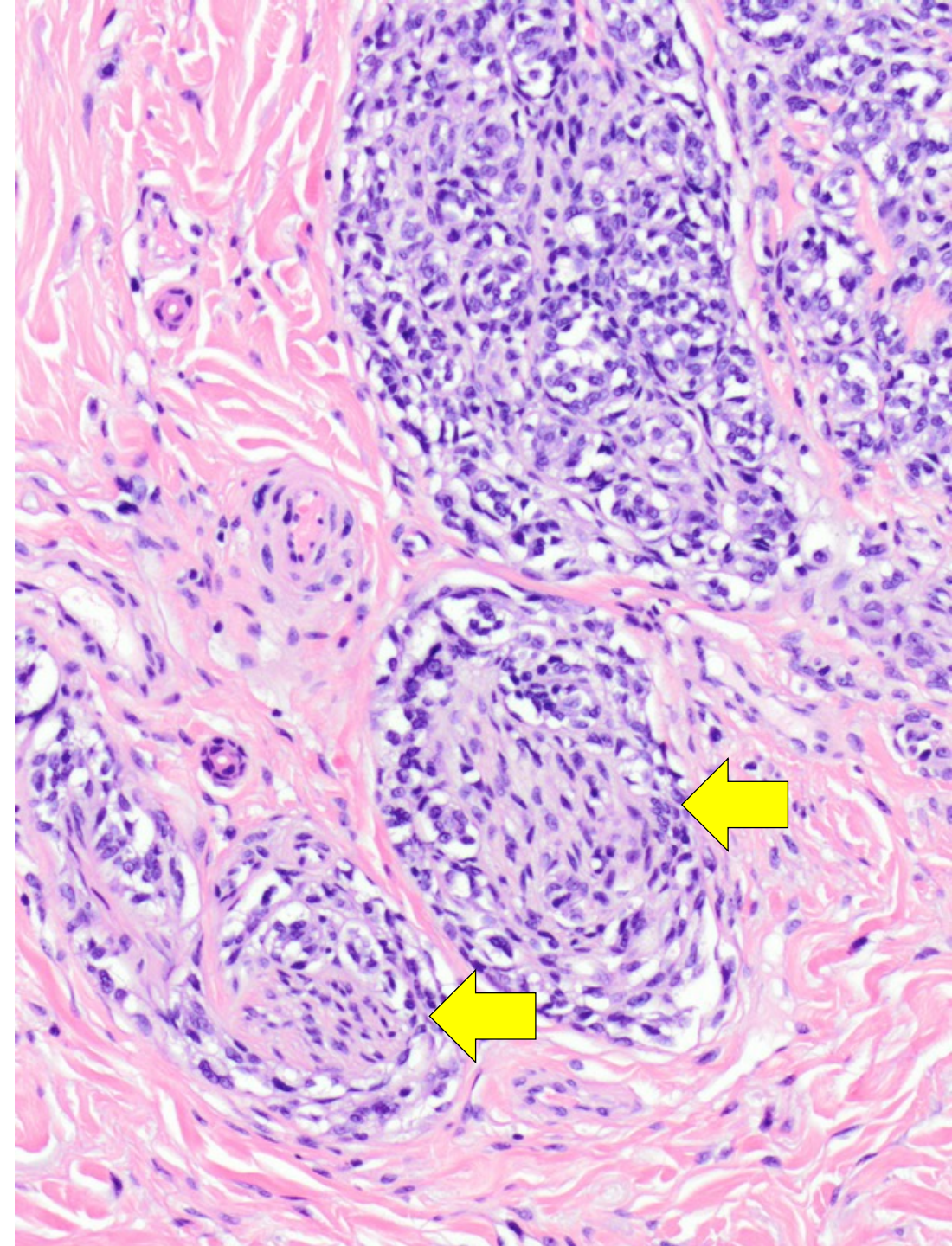


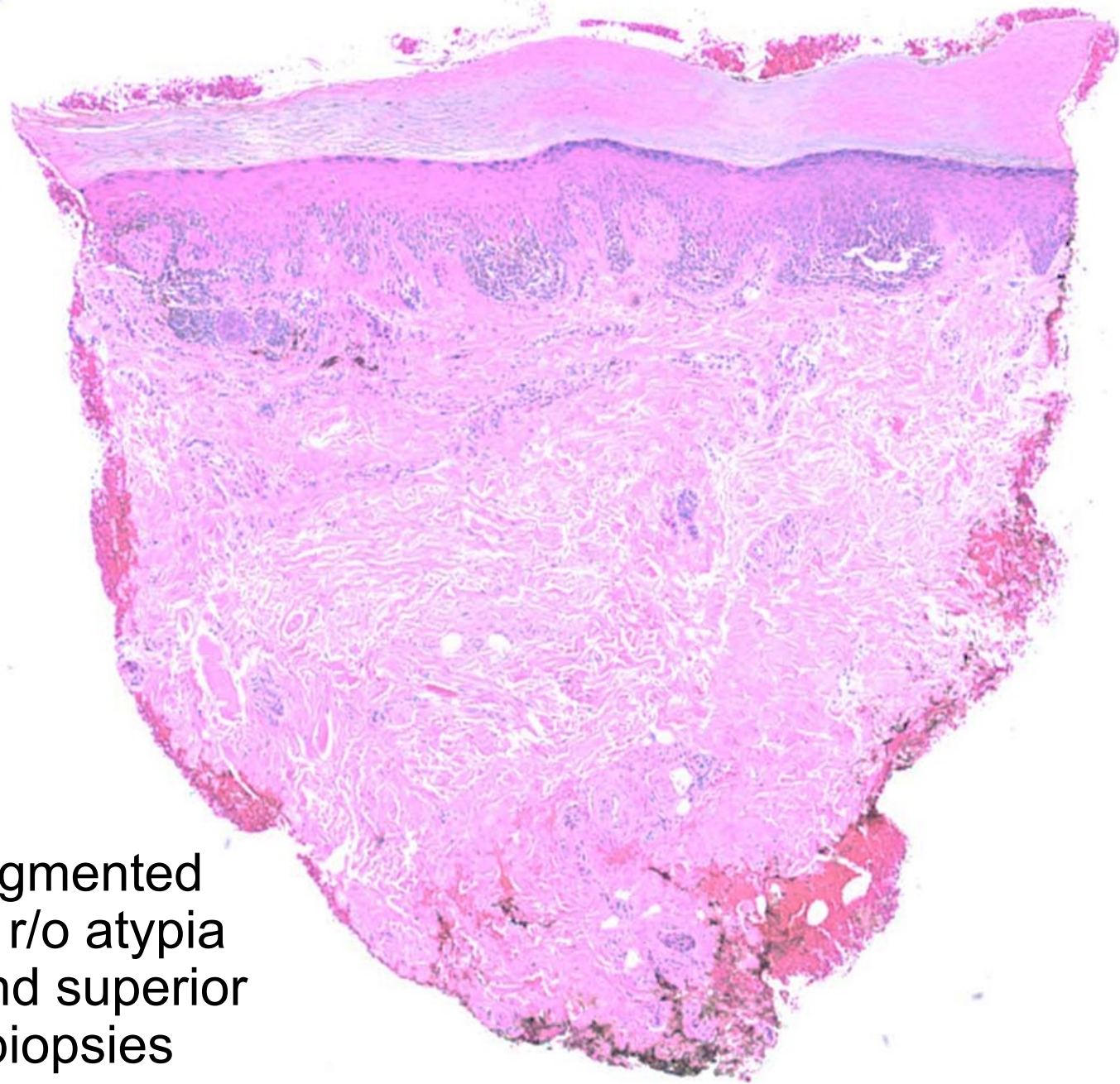
Loss of miR-211 expression from the upper atypical melanocytic nests



Clinical follow up

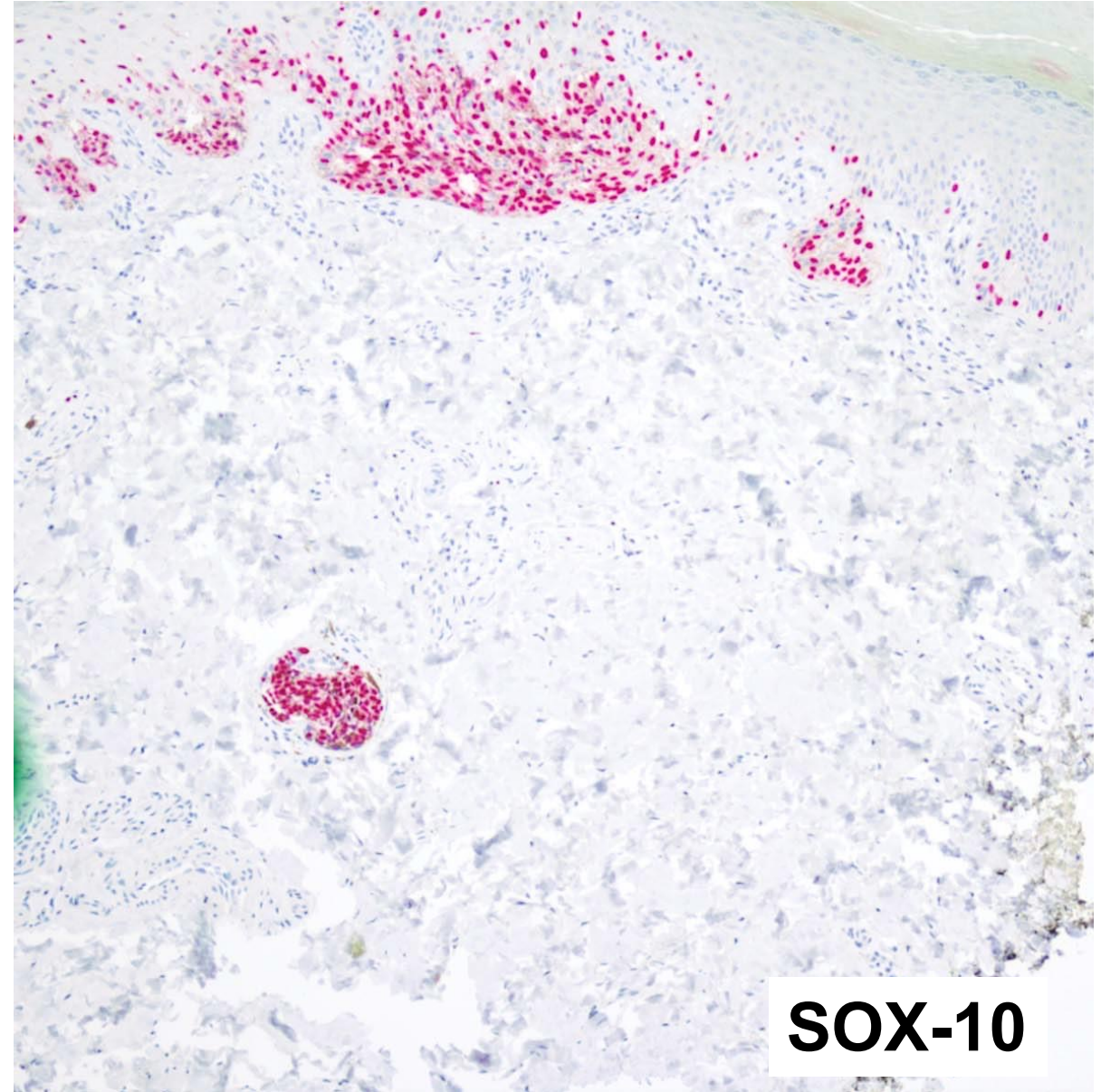
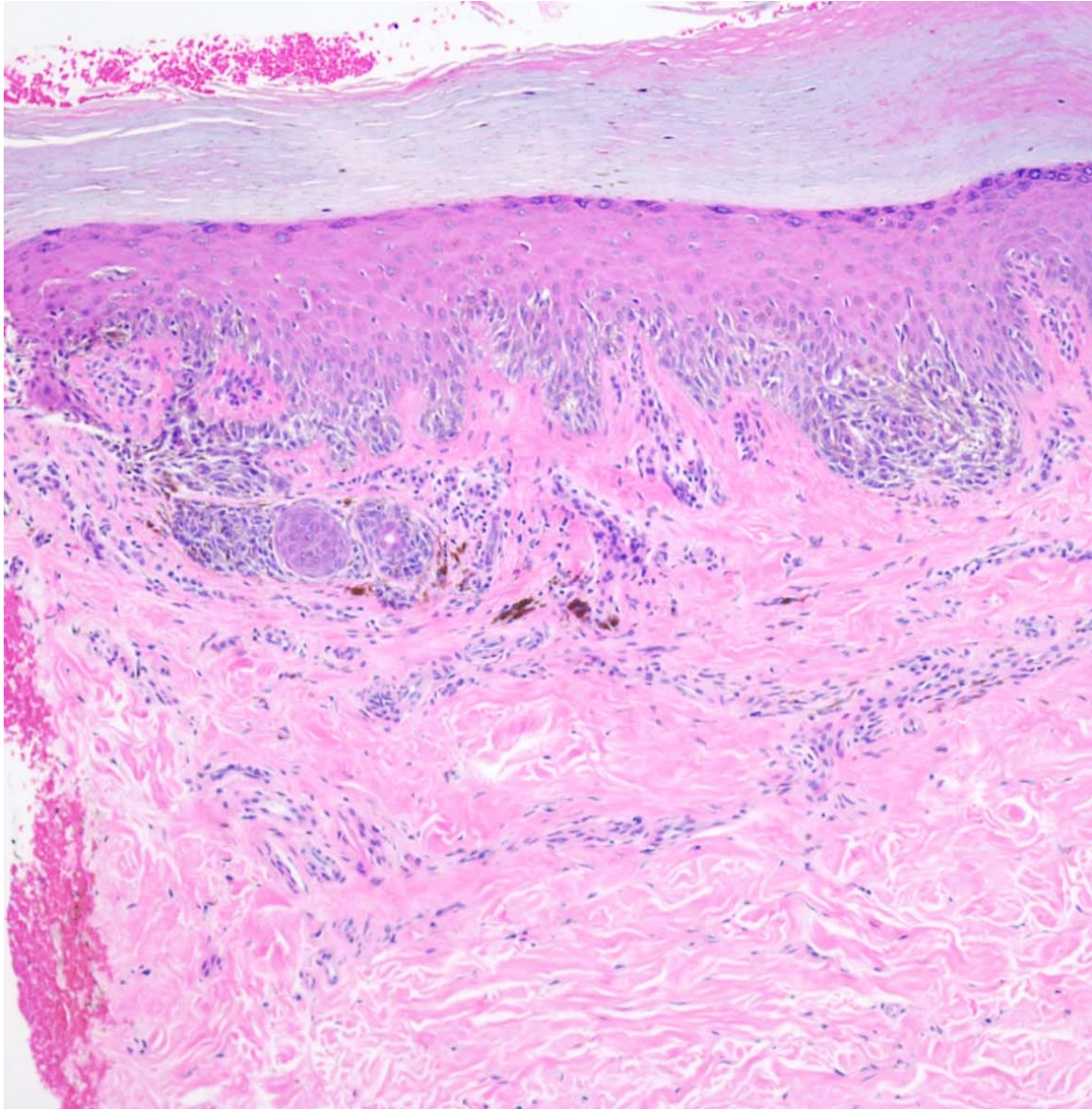
- Buttock melanomas excised
 - Gluteal cleft: 2.2 mm, IV, 2 mitoses/mm², PNI
 - Left, medial: 4.02 mm, IV, 4 mitoses/mm²
 - Left, lateral: small focus of intradermal nests
- Pathologic staging
 - pT3a N1b (N2c or N3) Mx
- Metastasis in left inguinal node
- Died of disease few months after excision





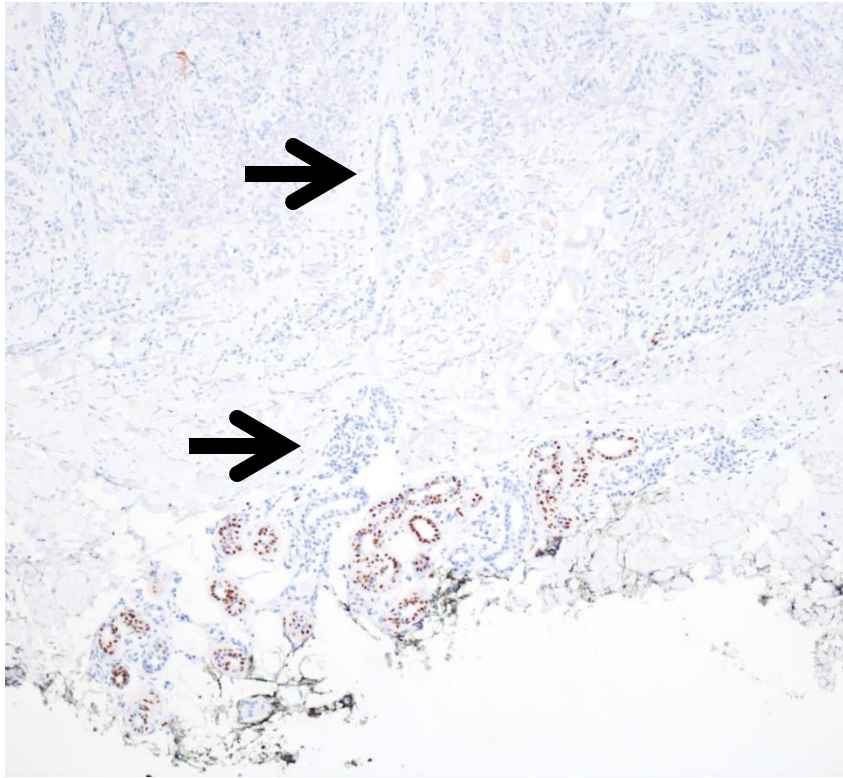
50-year-old male
1.5 cm irregular pigmented
brown patch, MM, r/o atypia
Left inferior (A) and superior
(B) 5th toe punch biopsies

Staging pitfall: Deep dermal invasion or eccrine duct involvement?

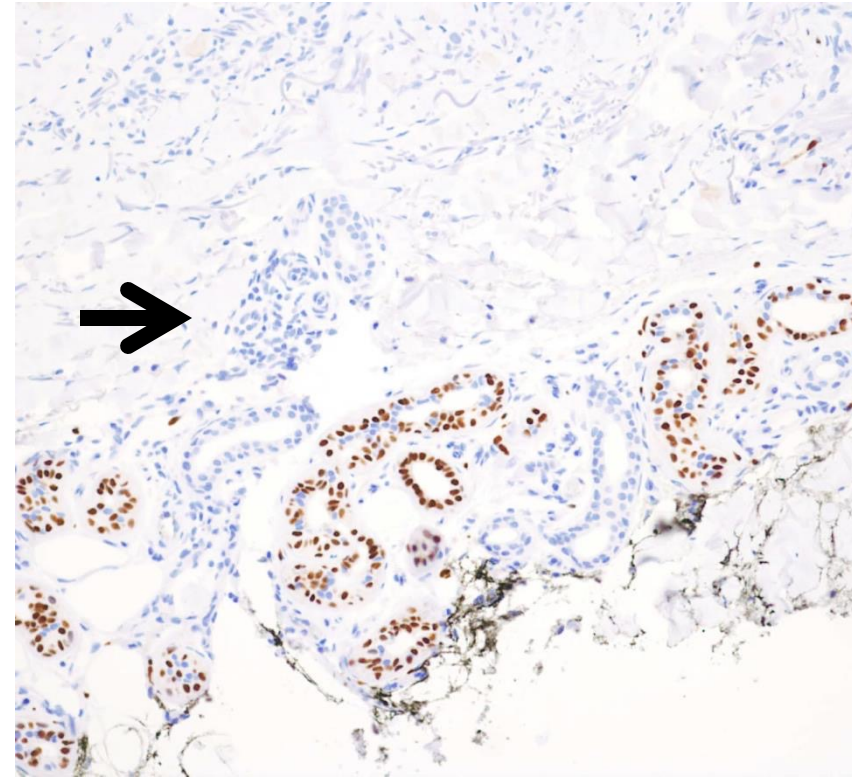


SOX-10 expression in eccrine glands not in ducts

Absent in ducts



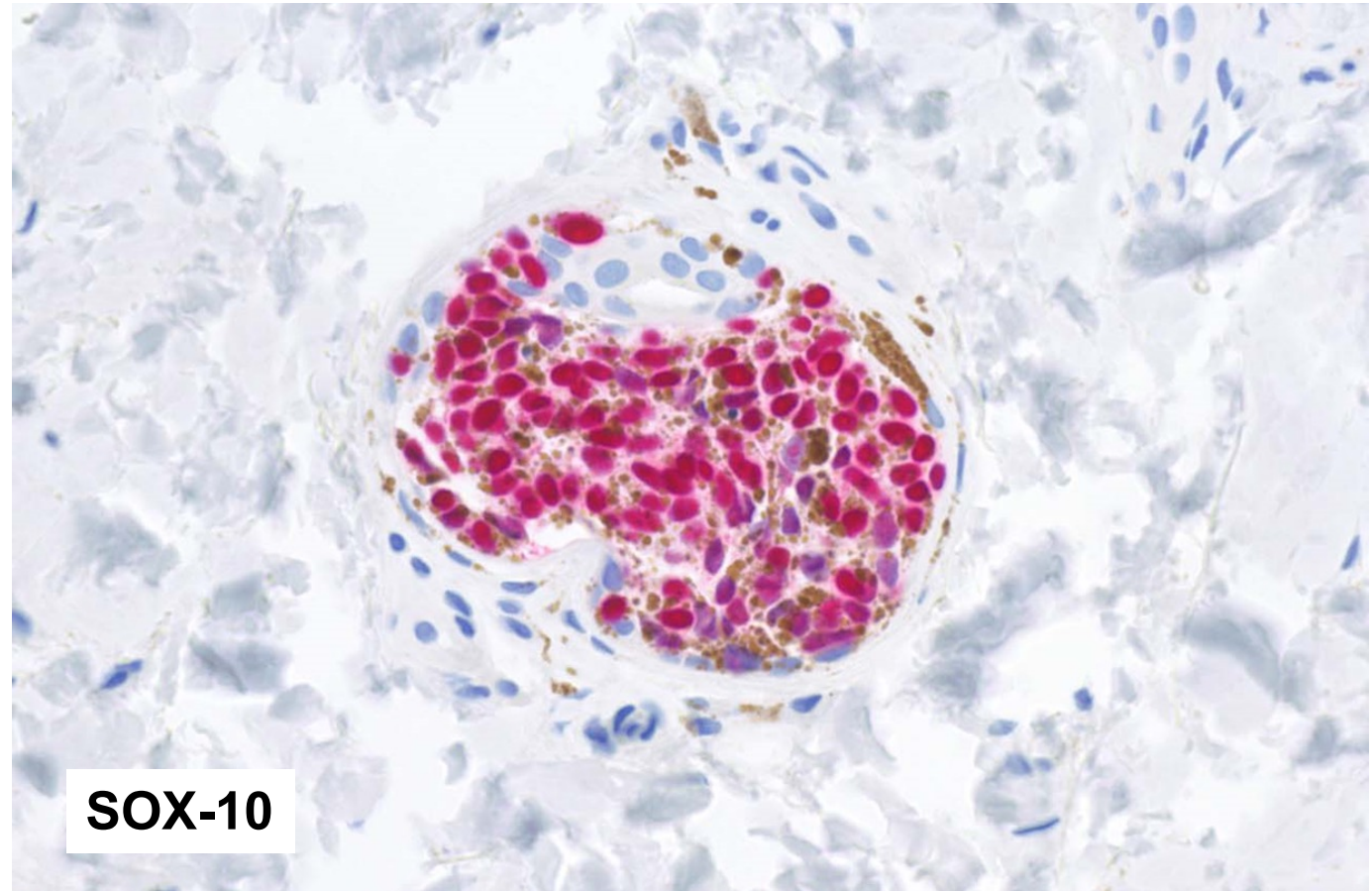
Present in glands



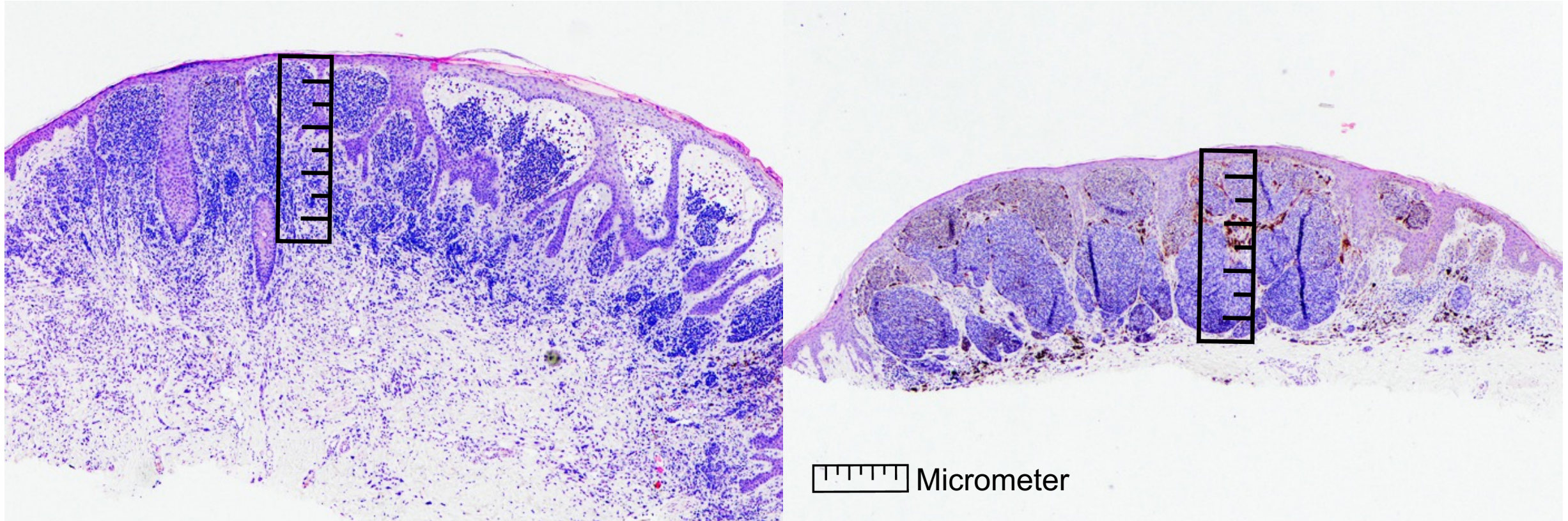
MELANOMA IN SITU,
ACRAL LENTIGINOUS
TYPE, WITH EXTENSIVE
DEEP ECCRINE DUCT
INVOLVEMENT, PRESENT
AT PERIPHERAL MARGIN
(SEE NOTE).

Extensive eccrine involvement, not
invasive. The pathologic stage is pTis
(AJCC, 8th edition).

On part A, the lesion is close to deep
margin along the eccrine structure
extension.

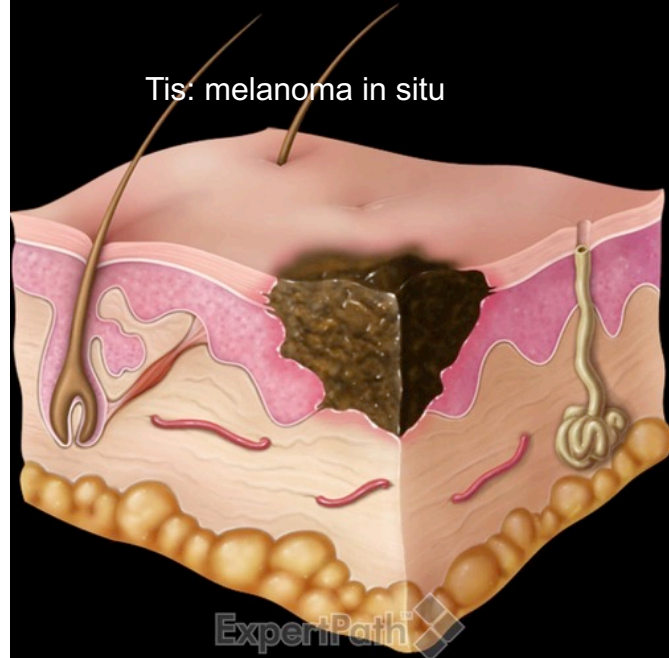


Melanoma staging: measuring invasive tumor depth and ulceration (no epidermis)

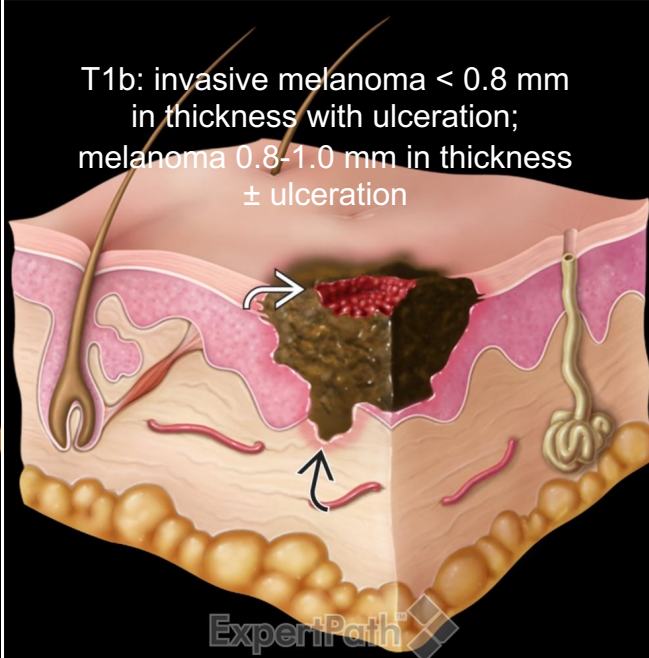


AJCC Melanoma staging

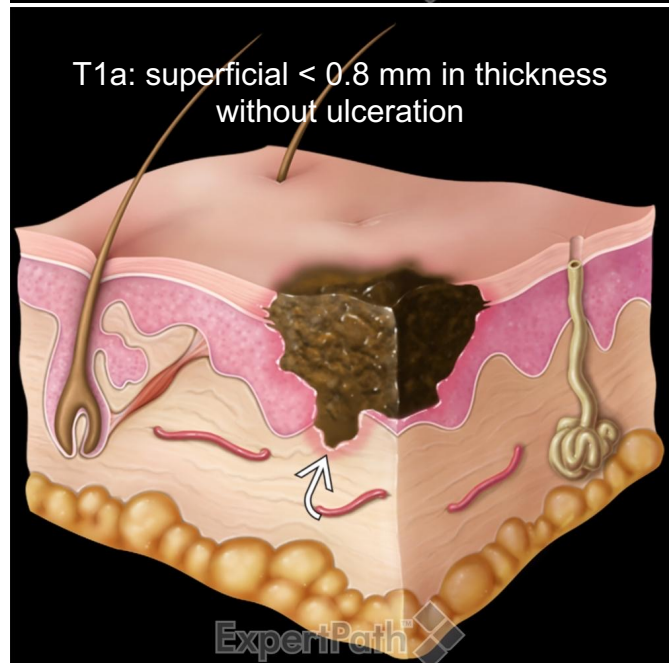
Tis: melanoma in situ



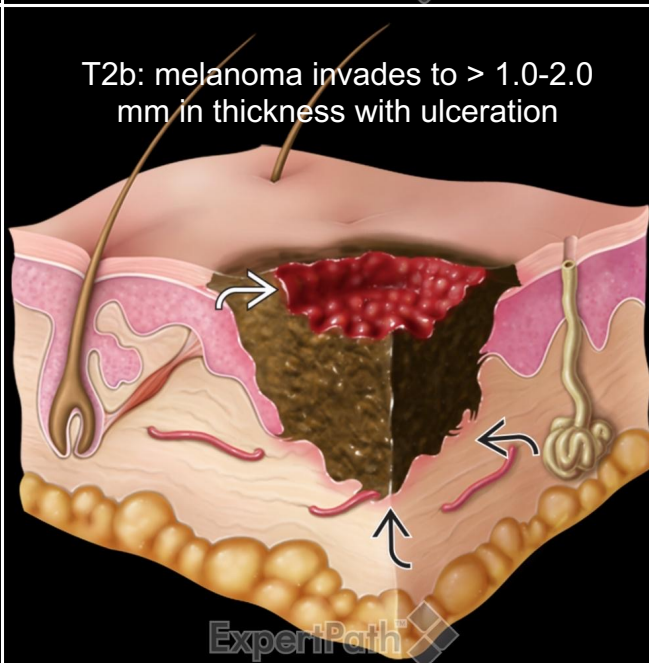
T1b: invasive melanoma < 0.8 mm in thickness with ulceration; melanoma 0.8-1.0 mm in thickness \pm ulceration



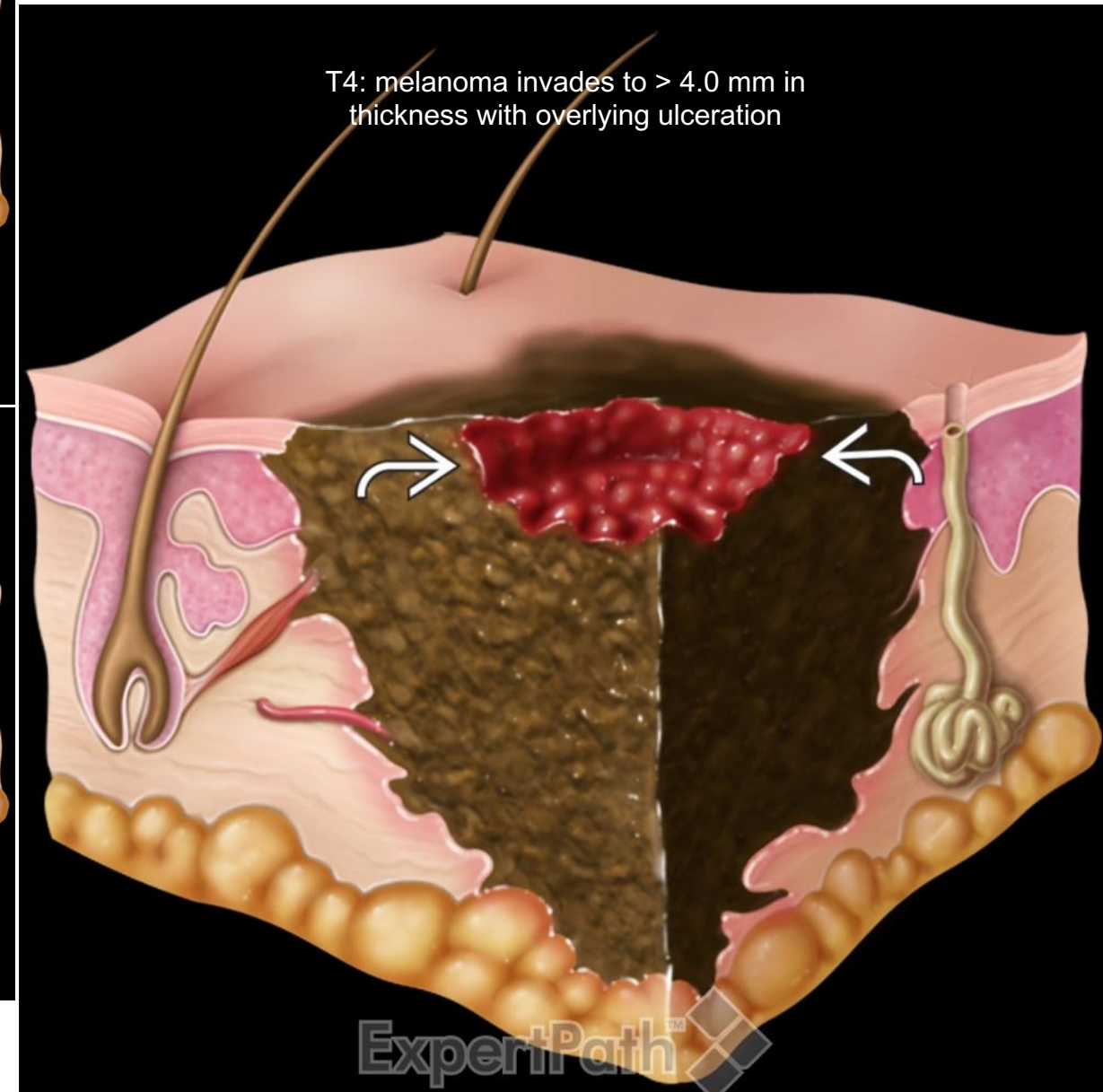
T1a: superficial < 0.8 mm in thickness without ulceration



T2b: melanoma invades to > 1.0-2.0 mm in thickness with ulceration



T4: melanoma invades to > 4.0 mm in thickness with overlying ulceration



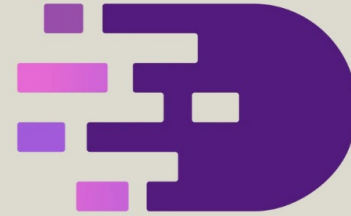
Cutaneous melanoma staging according to AJCC and UICC, 8th Edition

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%

Digital Skin Pathology

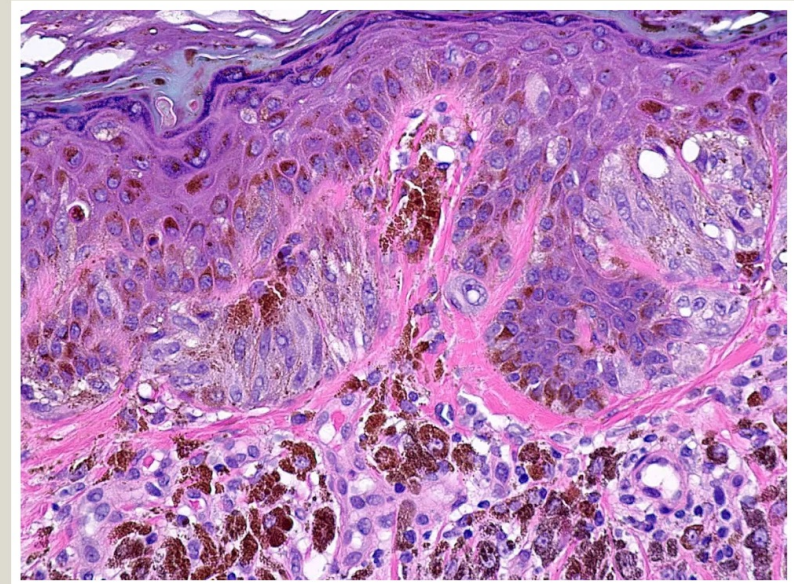
<https://digitalskinpathology.com/>

- 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

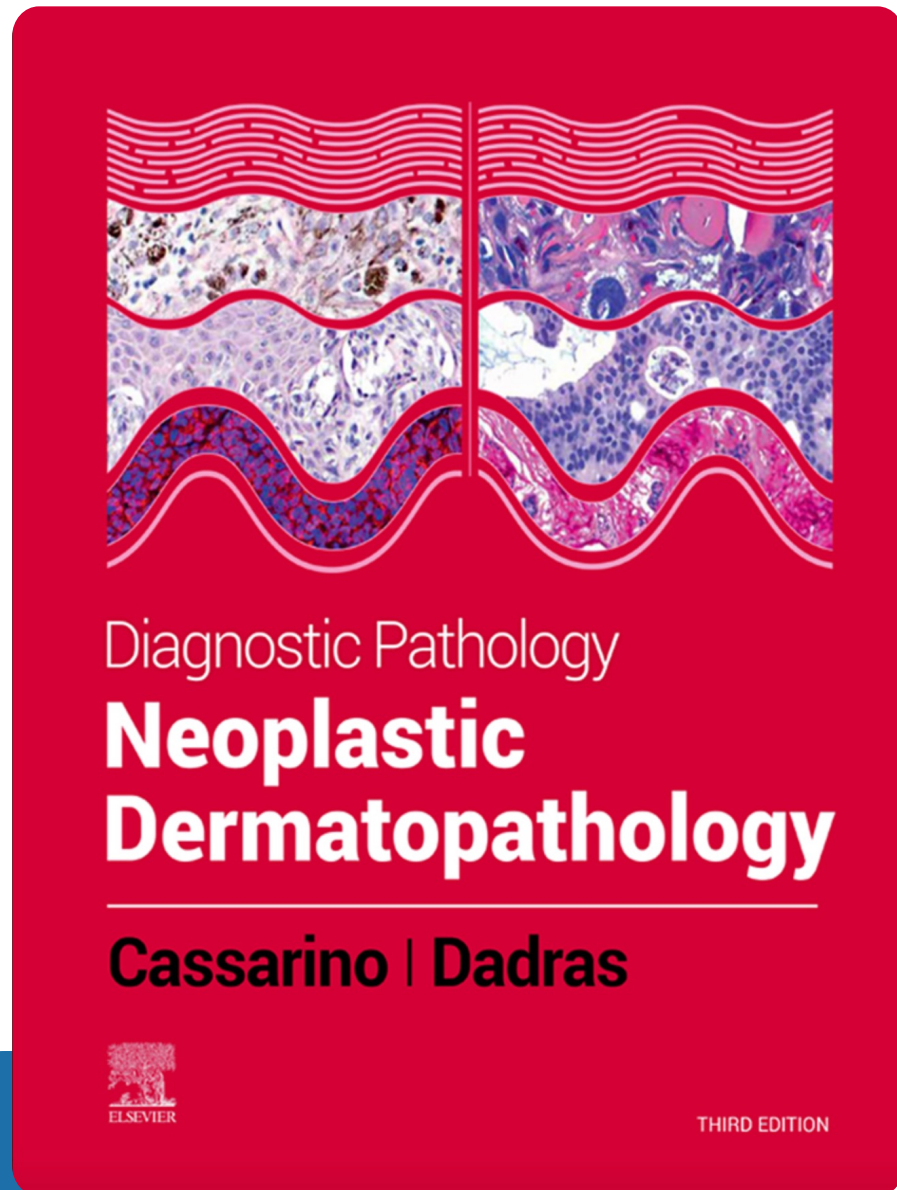


DIGITAL SKIN PATHOLOGY (DiSK)
Learn Histologic Diagnosis Case-By-Case

**DERMATOPATHOLOGY: LEARN HOW TO
DIAGNOSE SKIN DISEASES DERM PATH
DIAGNOSTICS**



**Understand your patient's dermatopathology diagnostic report to
provide better clinical care** (how to diagnose skin diseases). derm
path diagnostics



References

- WHO Classification of Tumors online
- *Neoplastic Dermatopathology*, 3rd edition