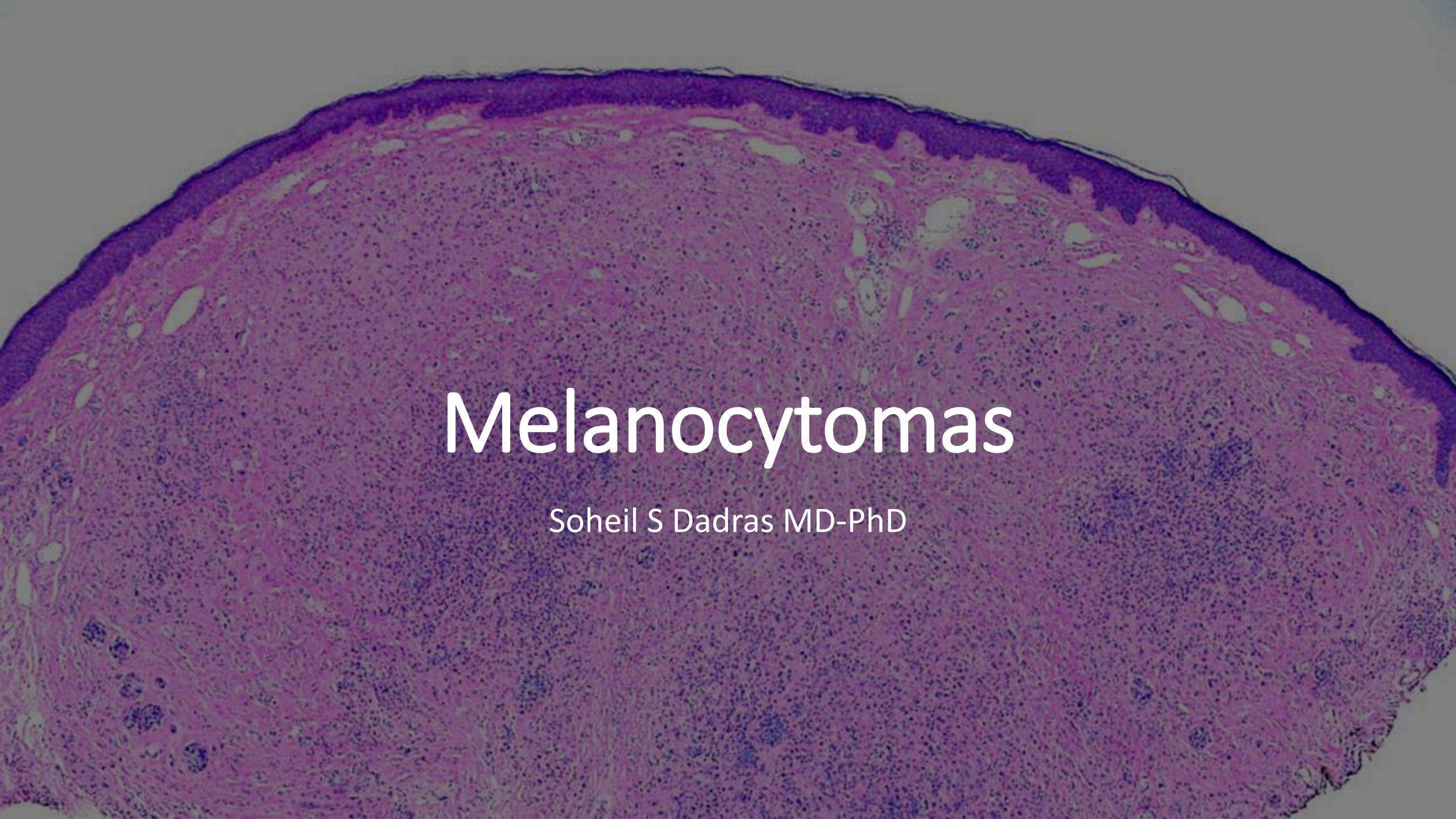


Melanocytomas

Soheil S Dadras MD-PhD

Melanocytomas

WHO 5th ed.

(MELTUMP, Borderline, Atypical melanocytic neoplasms)

1. WNT-activated deep penetrating/plexiform melanocytoma
   (Deep penetrating nevus/Inverted type A nevus)
2. Pigmented epithelioid melanocytoma
3. BAP1-inactivated melanocytoma
4. MITF pathway-activated melanocytic tumors

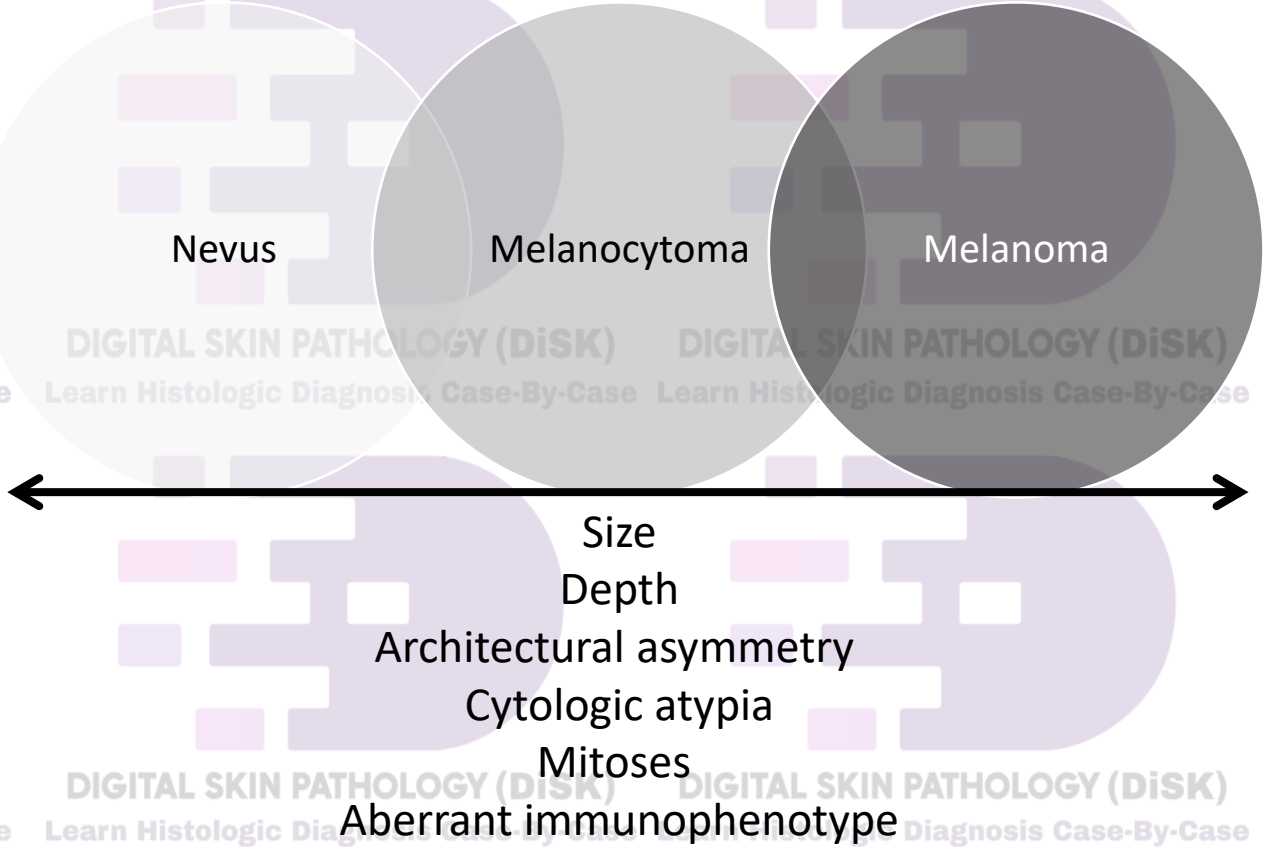
What is a melanocytoma?

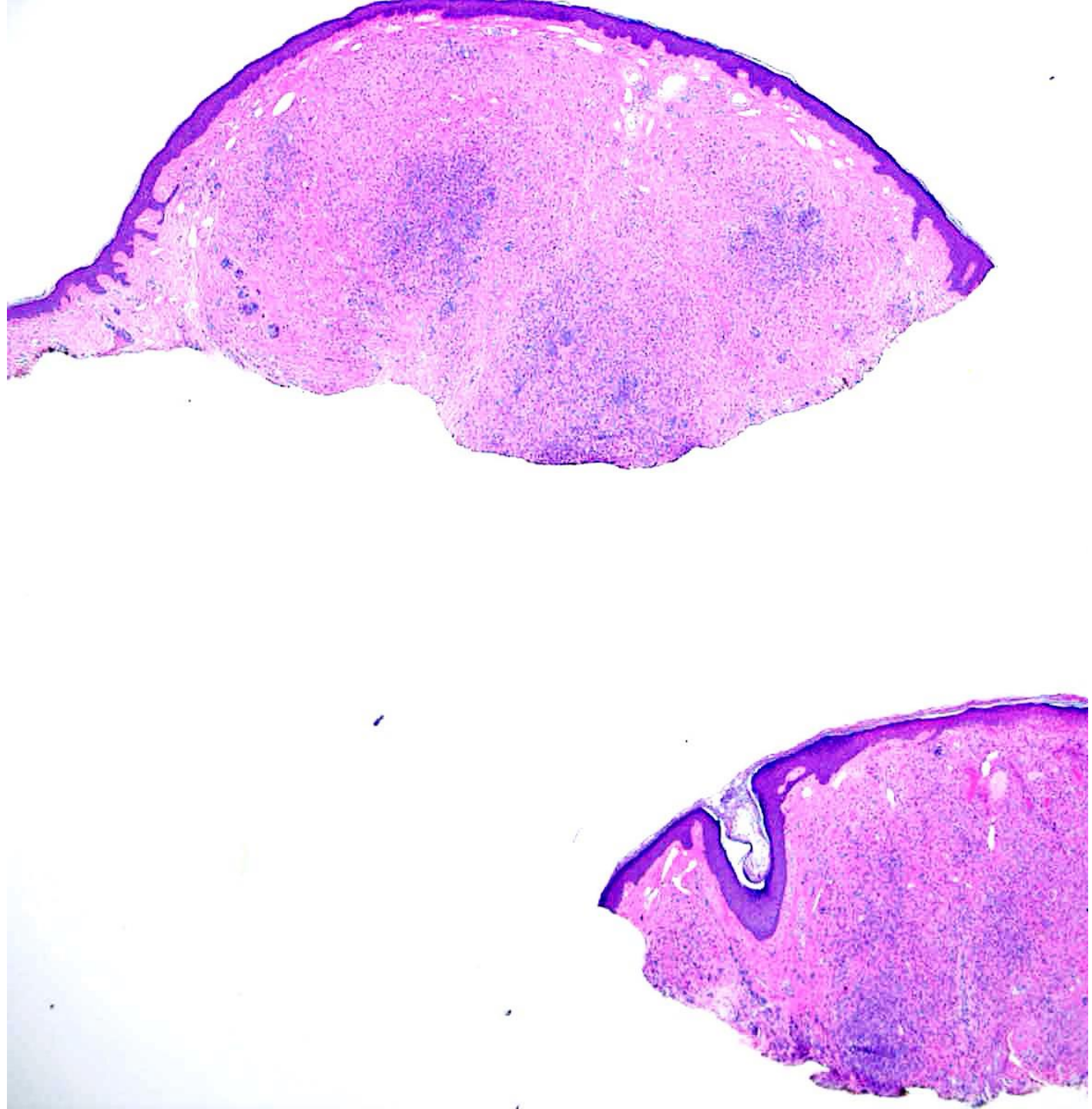
(diagnostic ambiguity and uncertainty in biologic behavior)

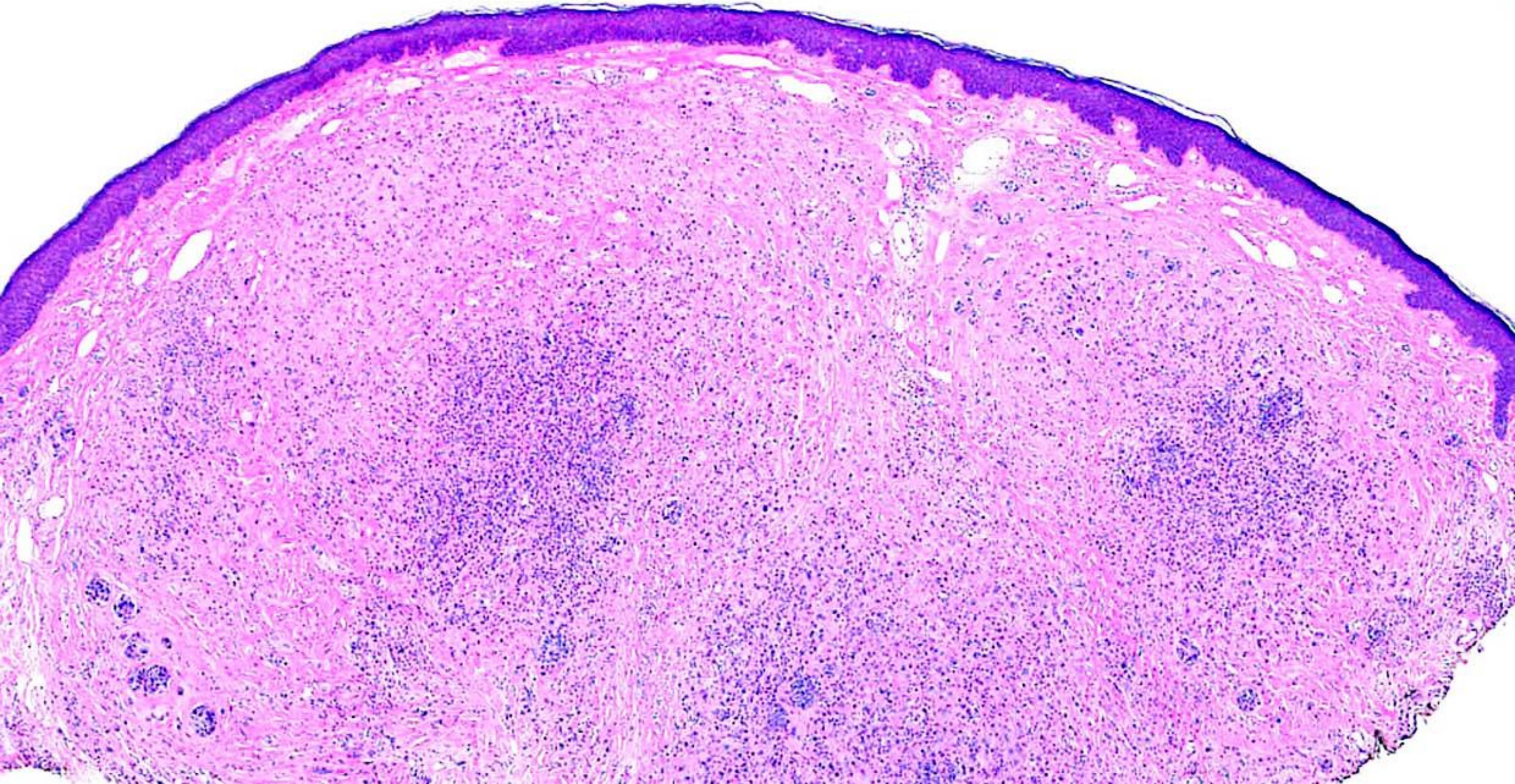
- WHO: tumorigenic melanocytic neoplasm with increased cellularity, atypia, and increased (<u>but low</u>) probability of neoplastic progression.

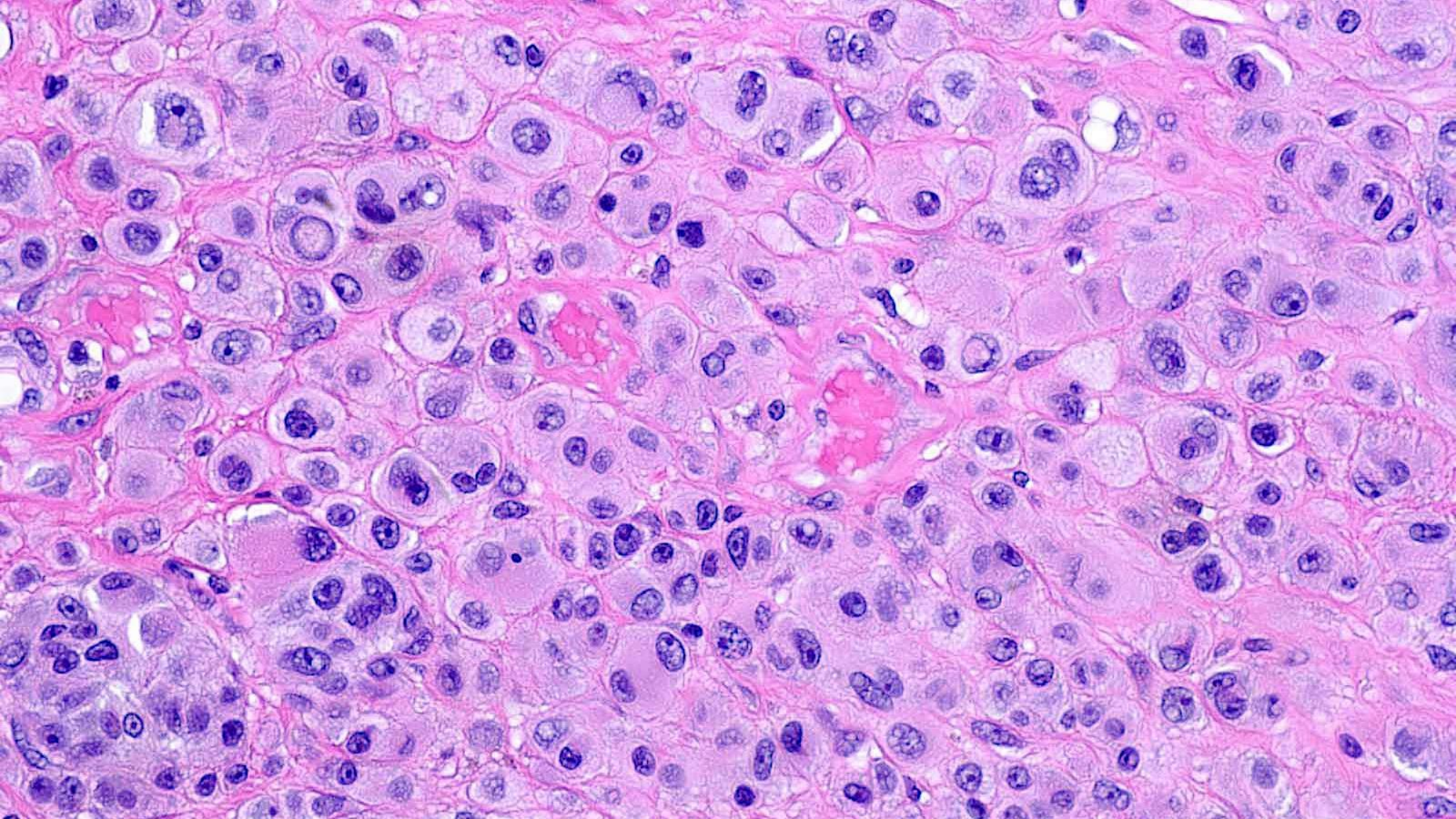
- Other names: Borderline lesion or MELTUMP

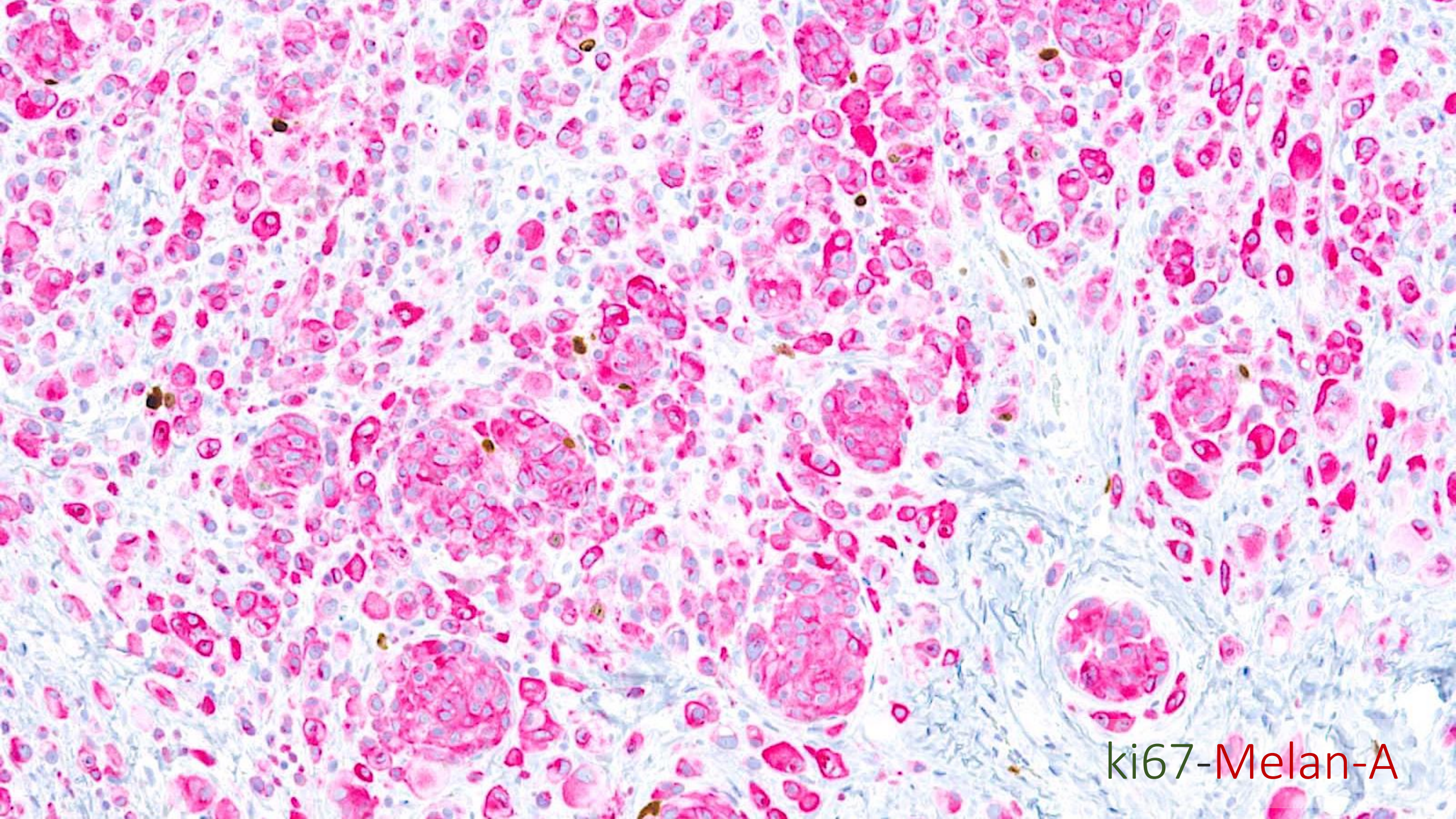
- <u>Morphology cannot predict biologic behavior</u>

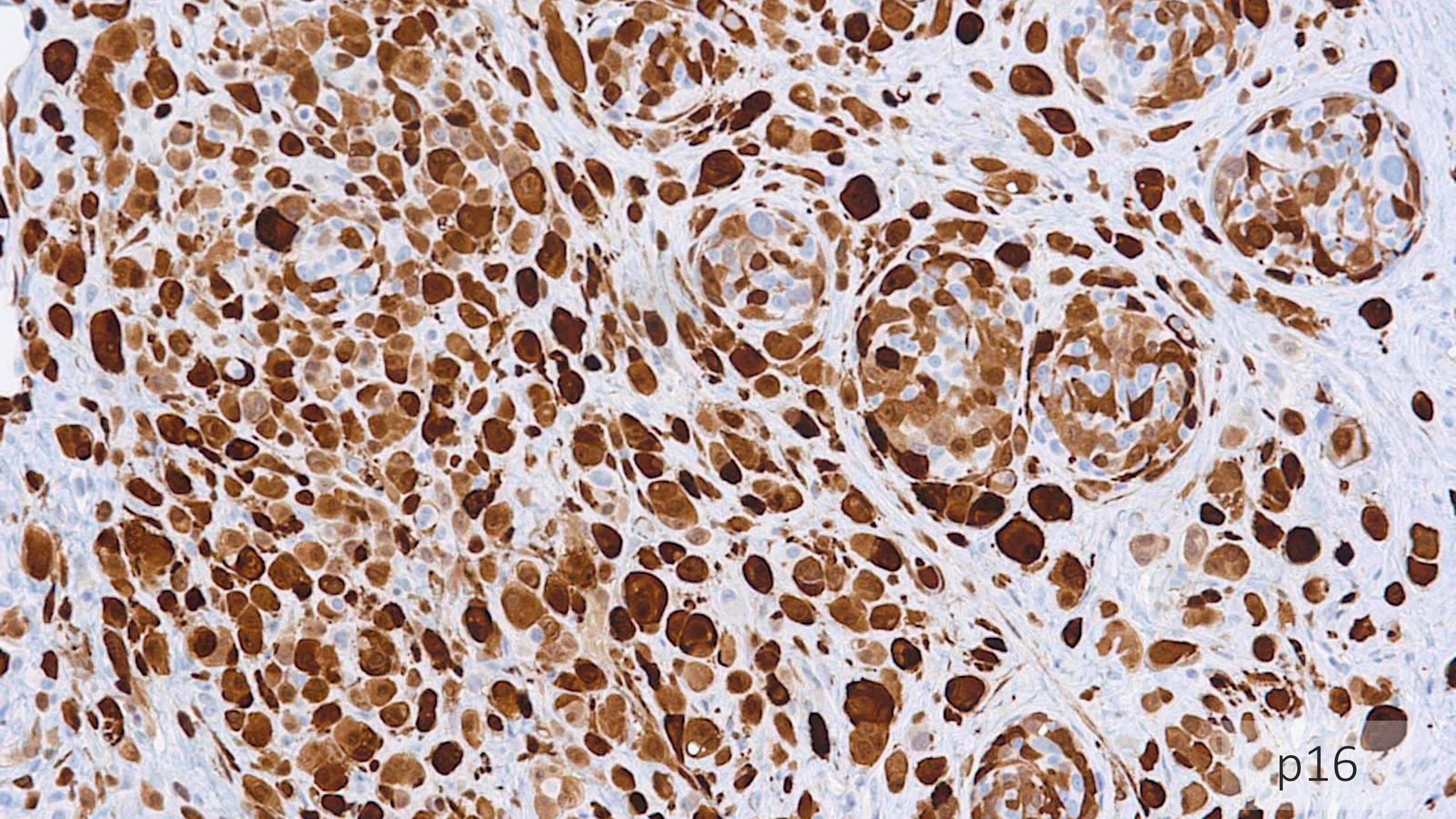


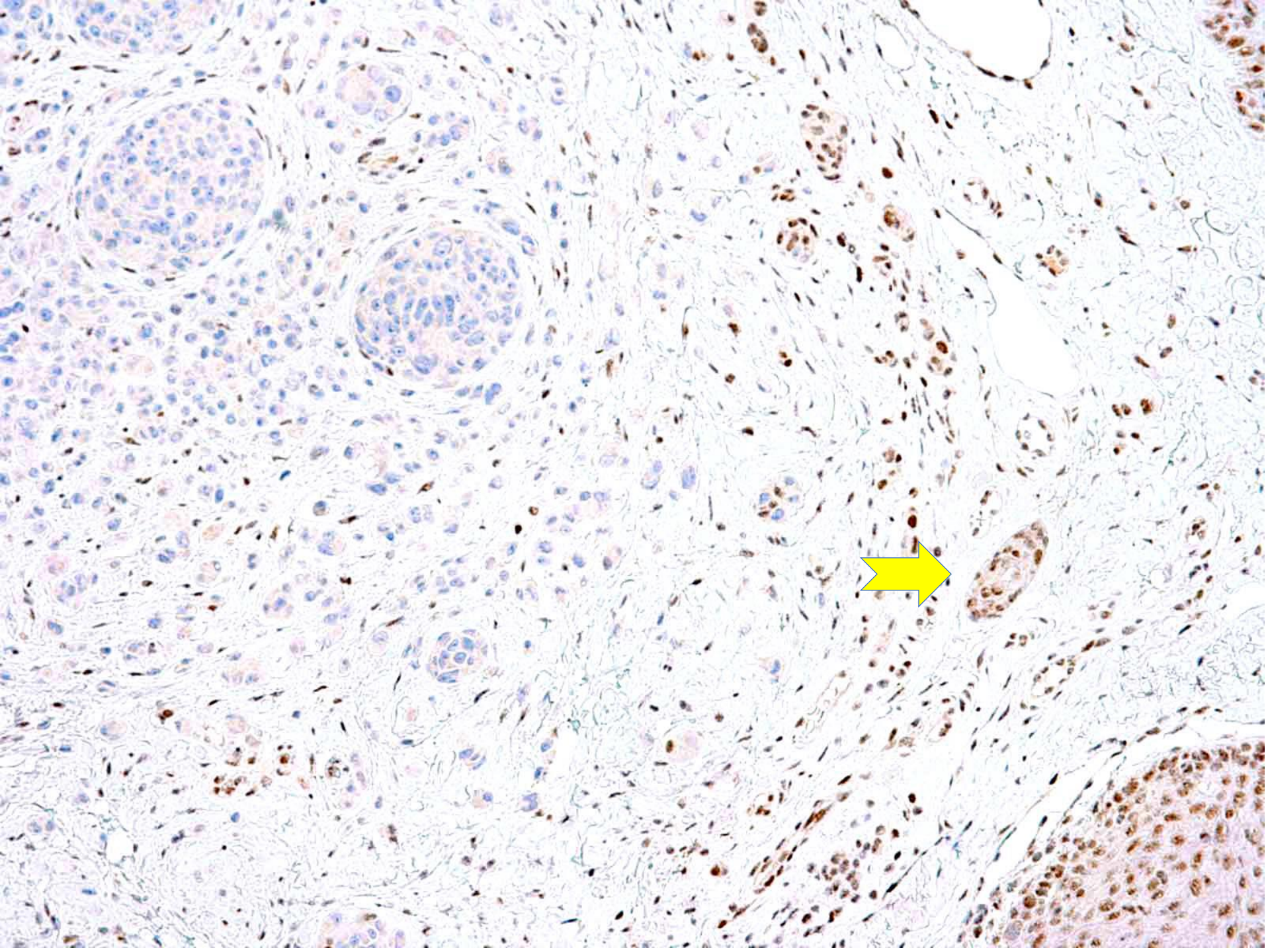







ki67-Melan-A


p16



BAP-1

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

DIAGNOSIS:

Skin, Right Neck, Shave Biopsy:
- BAP1-inactivated melanocytoma, extending to tissue base.

Teaching Points:

Loss of BAP1 nuclear staining (IHC confirmation).
No significant mitotic activity (if present, rare and superficial).
No destructive infiltrative growth (unlike melanoma).

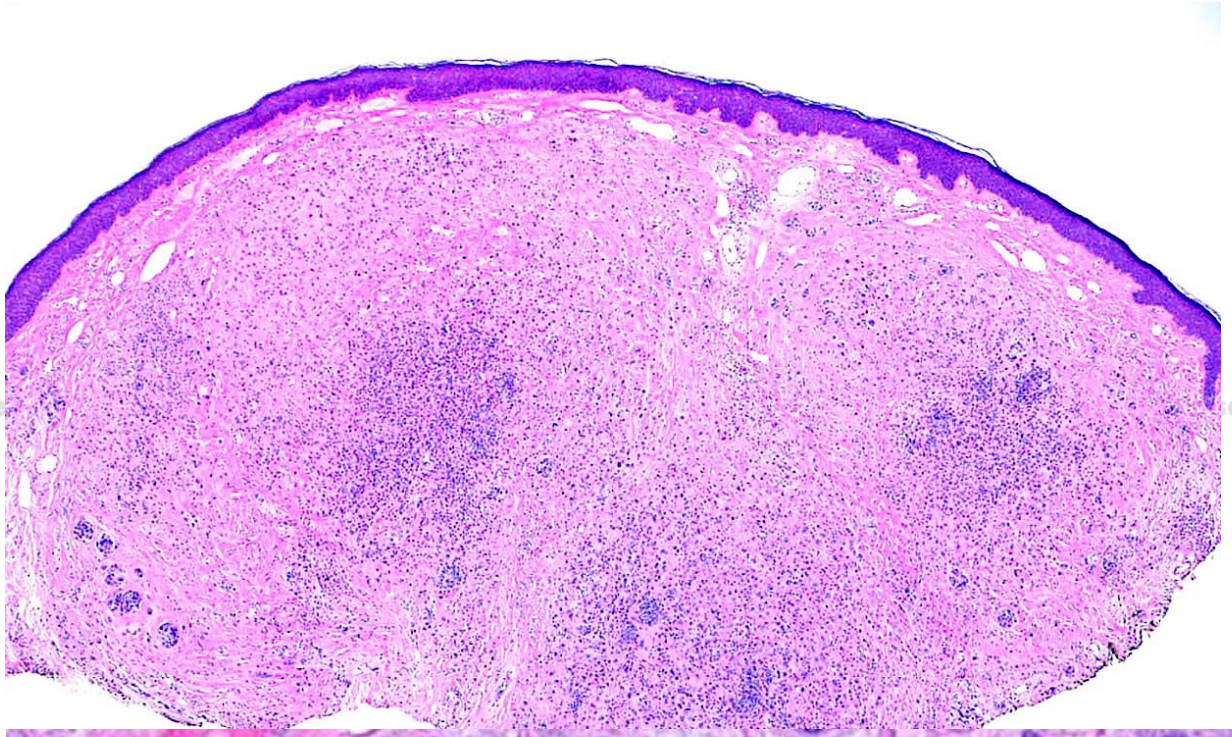
Minimal Diagnostic Criteria:

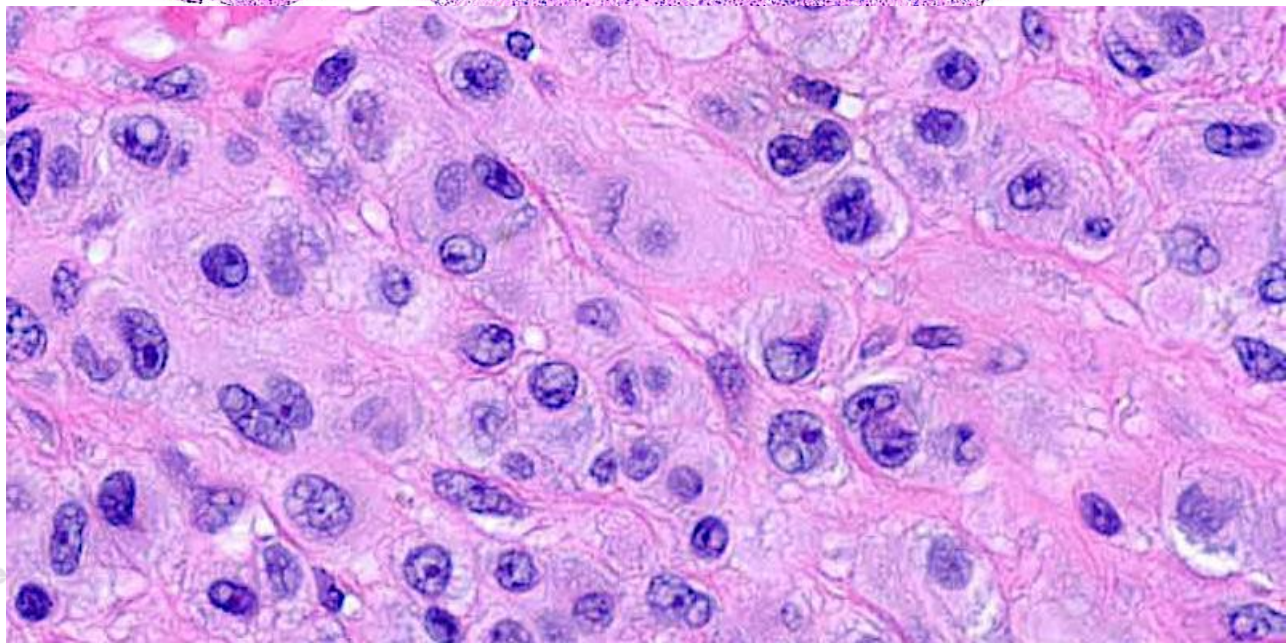
Symmetrical, well-circumscribed lesion.
Compound or dermal proliferation (often wedge-shaped).
Nested and fascicular growth (~Spitz nevus).
Cytologic Features
- Biphasic cell population
- Large epithelioid melanocytes with abundant amphophilic cytoplasm.
- Vesicular nuclei with prominent nucleoli (~melanoma).
- Nuclear pseudoinclusions (common).
- Smaller, conventional nevus-like cells (maturation present).

Benign, but may rarely progress to BAP1-inactivated melanoma.
Familial cases require screening for other BAP1-associated tumors (mesothelioma, renal cell carcinoma, uveal melanoma).

Differential Diagnosis:

Nevoid melanoma
Spitz nevus
Combined nevus
Spitz melanocytoma (AST)





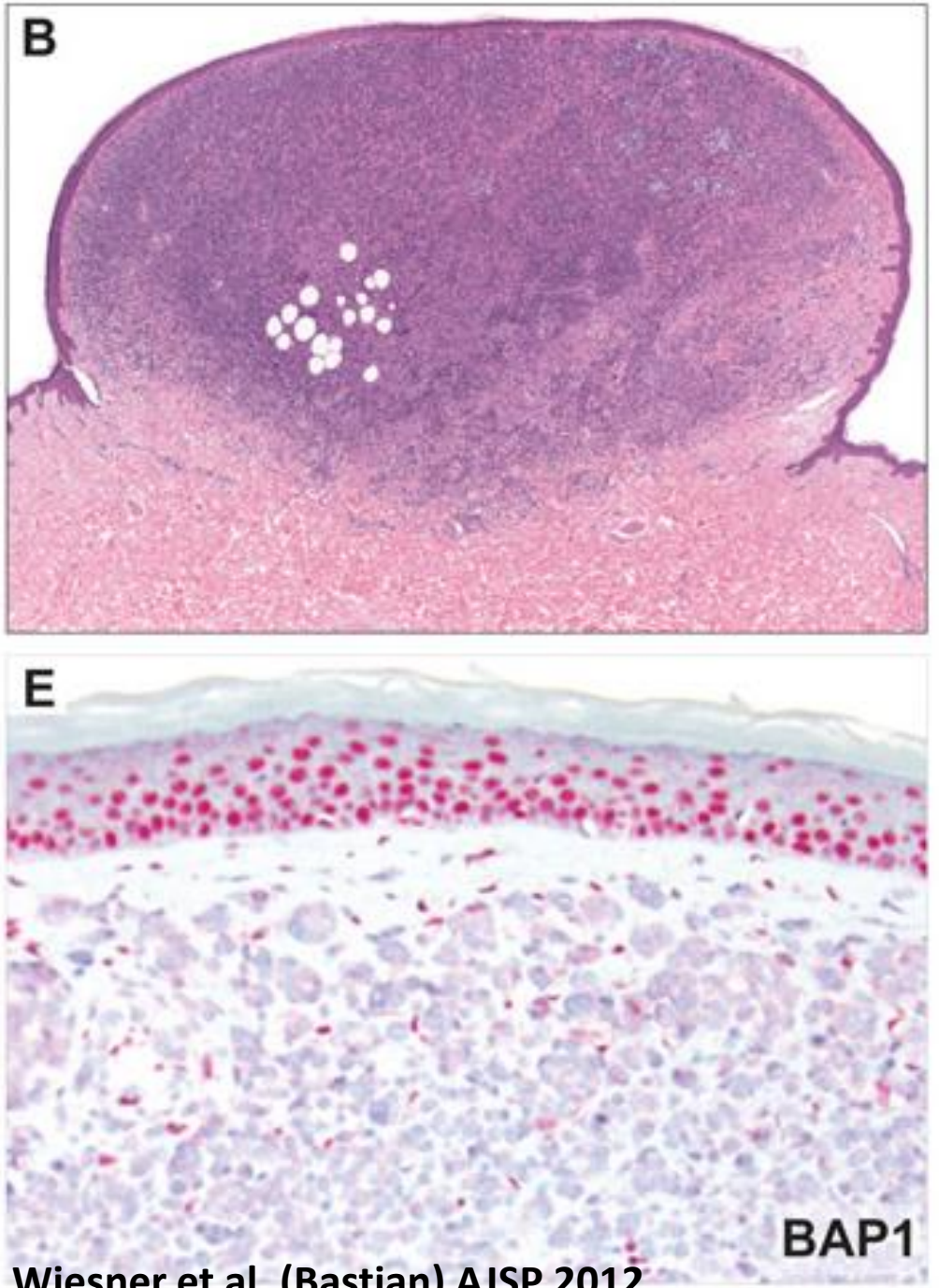
Diagnosis:
SKIN, RIGHT NECK, SHAVE BIOPSY:
1. BAP-1 INACTIVATED MELANOCYTOMA, PRESENT AT MARGIN. SEE NOTE.
2. ACTINIC KERATOSIS.

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 is negative in the majority of the tumor cells.

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

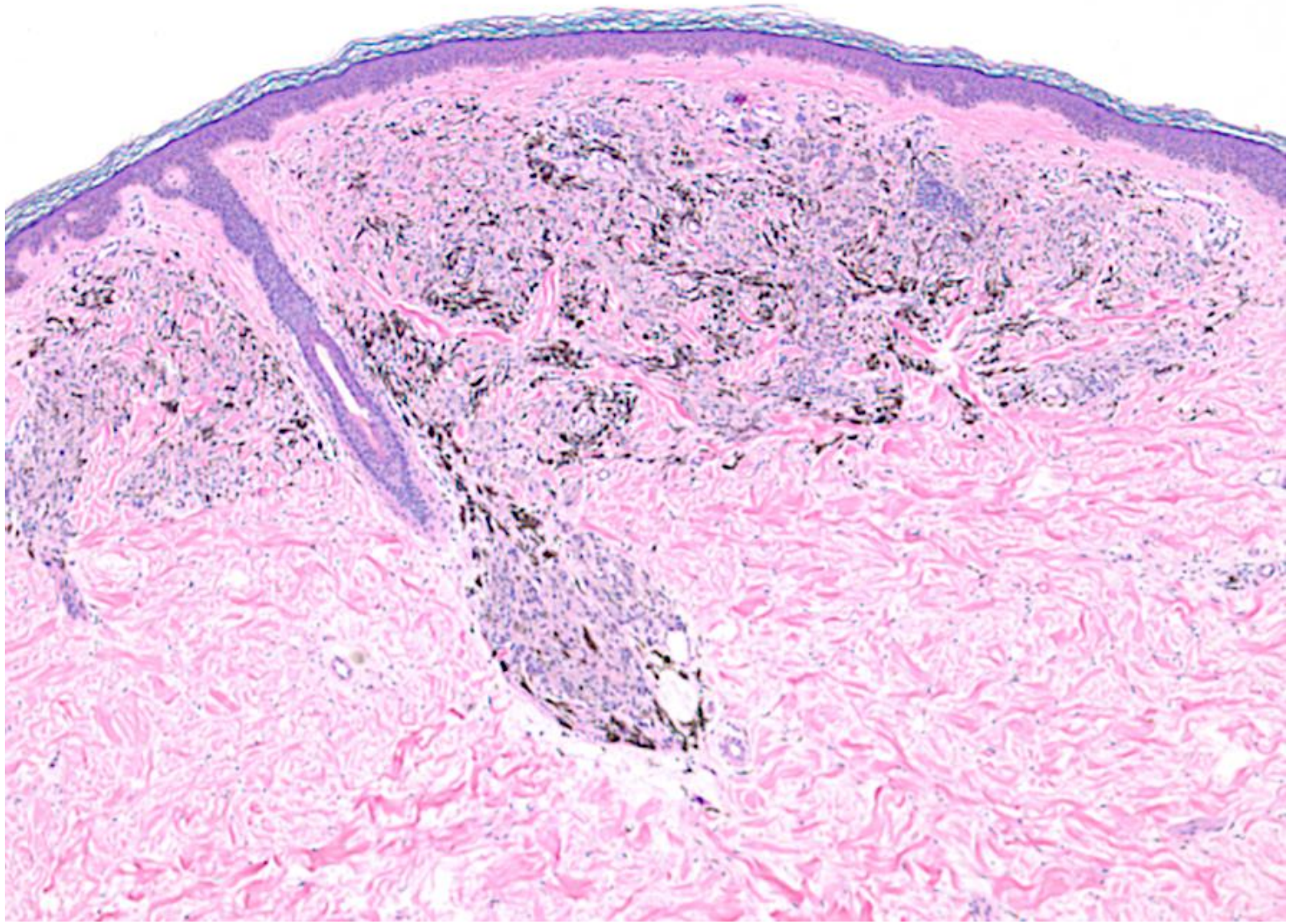


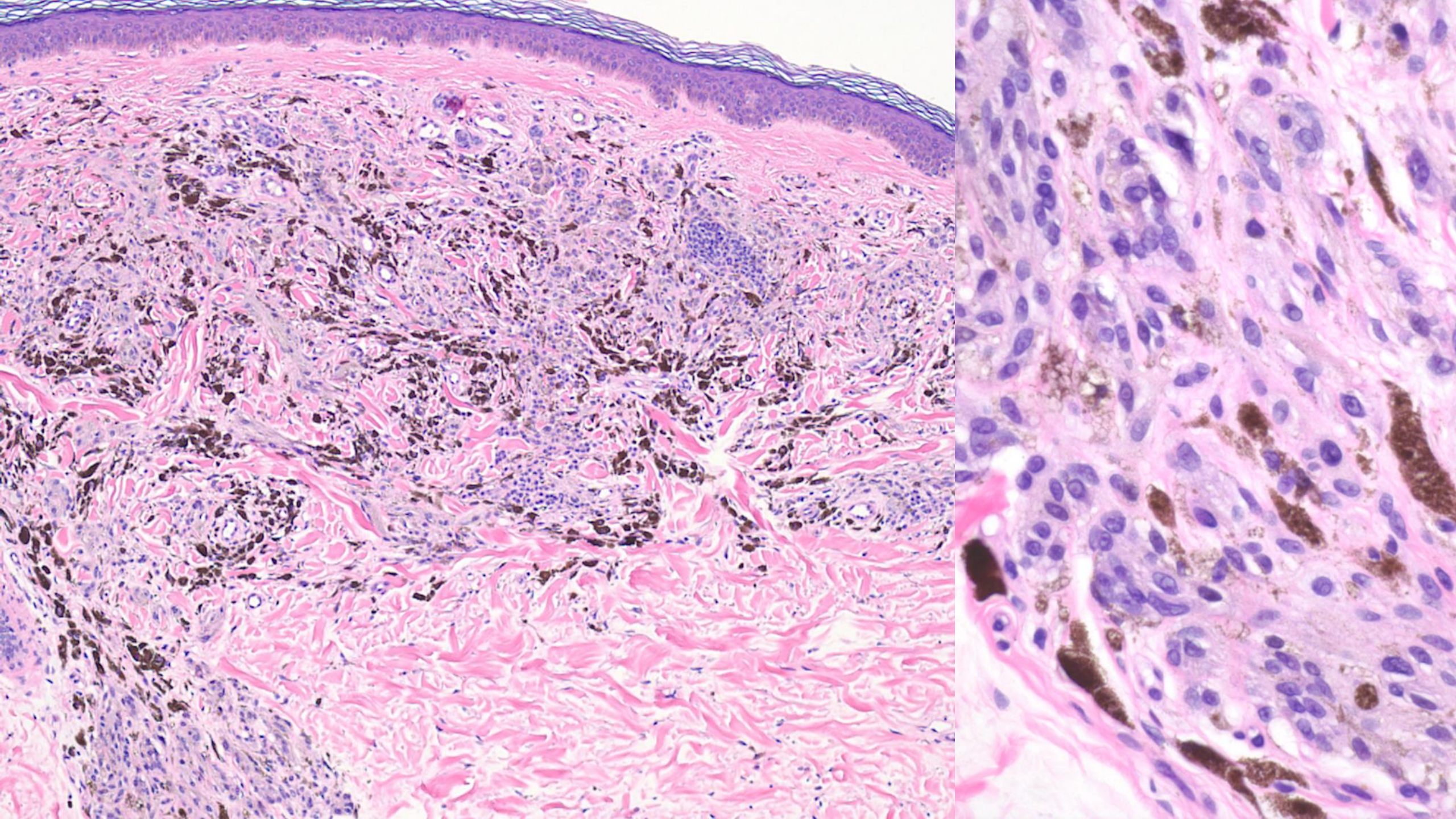
Wiesner et al. (Bastian) AJSP 2012

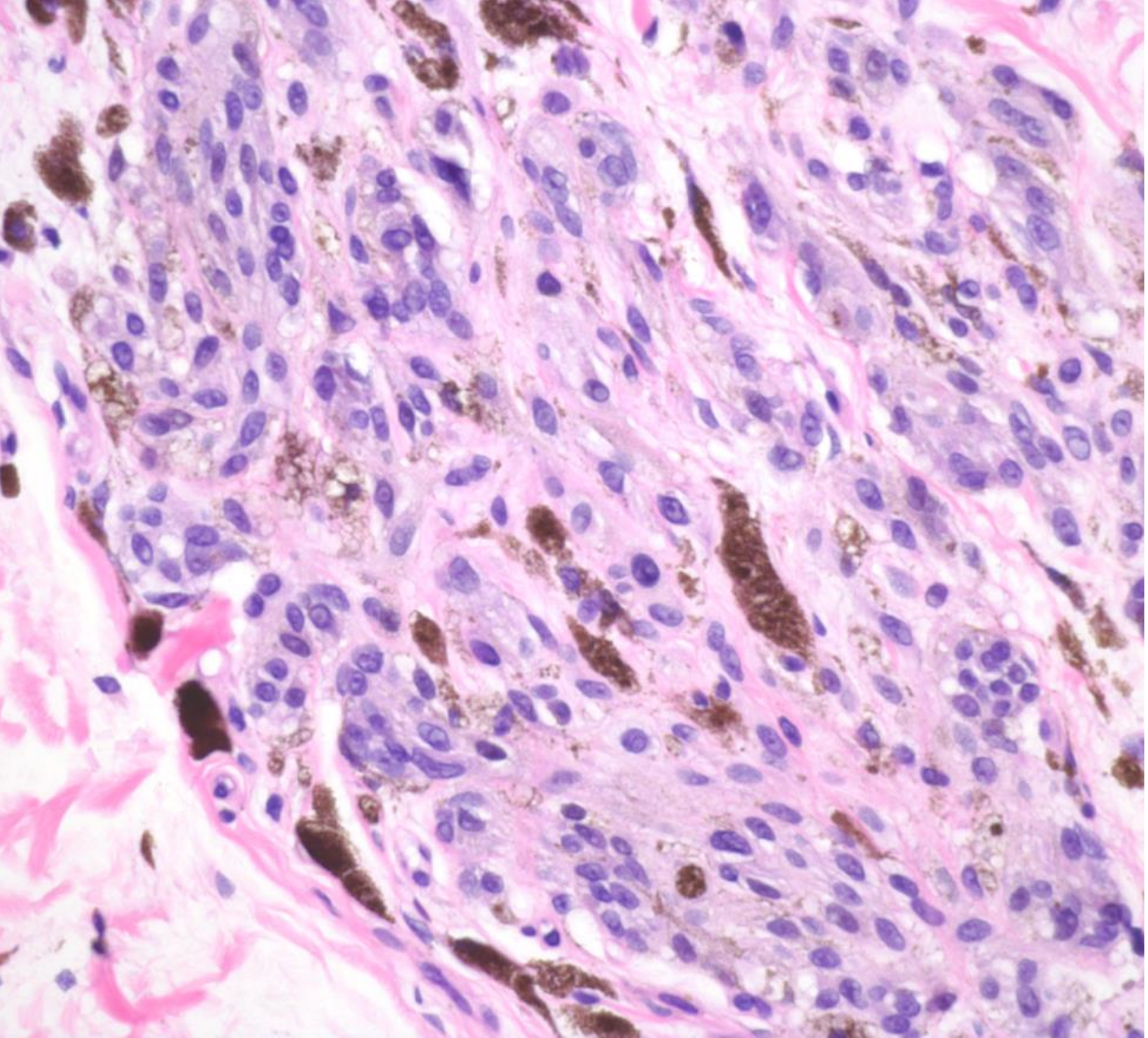
WHO: BAP-1 inactivated nevus or melanocytoma

- 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)

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

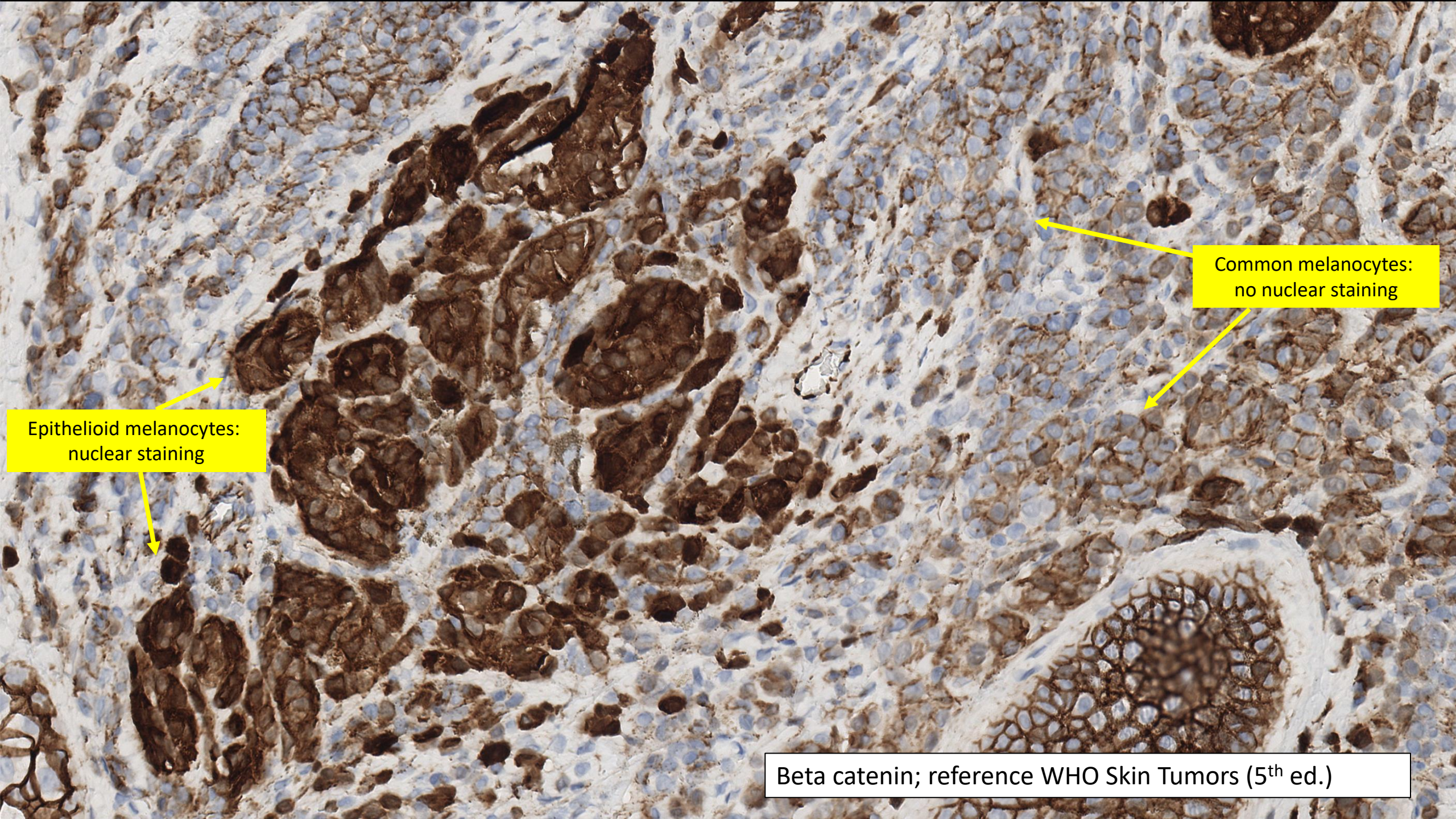




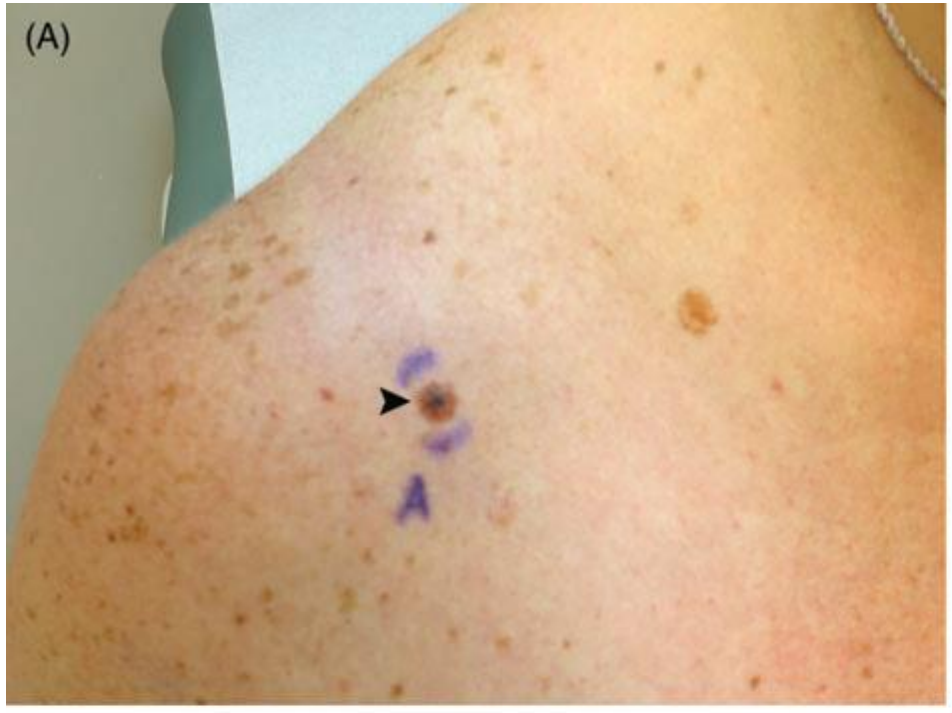


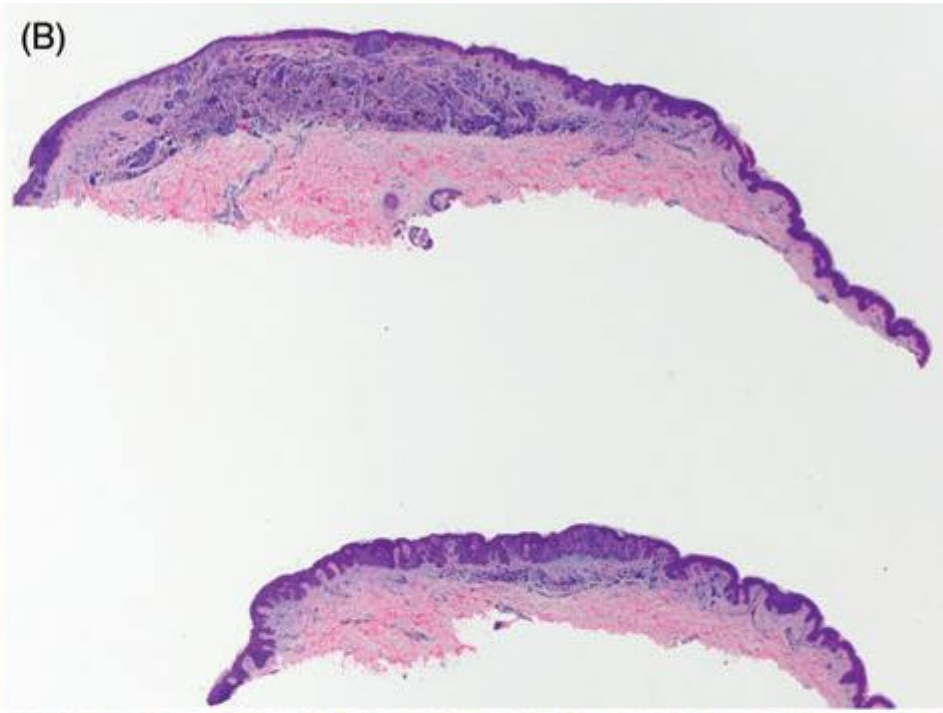
SKIN, RIGHT UPPER ARM, BIOPSY: INVERTED TYPE-A NEVUS, MARGINS NEGATIVE IN PLANES OF SECTIONS EXAMINED.

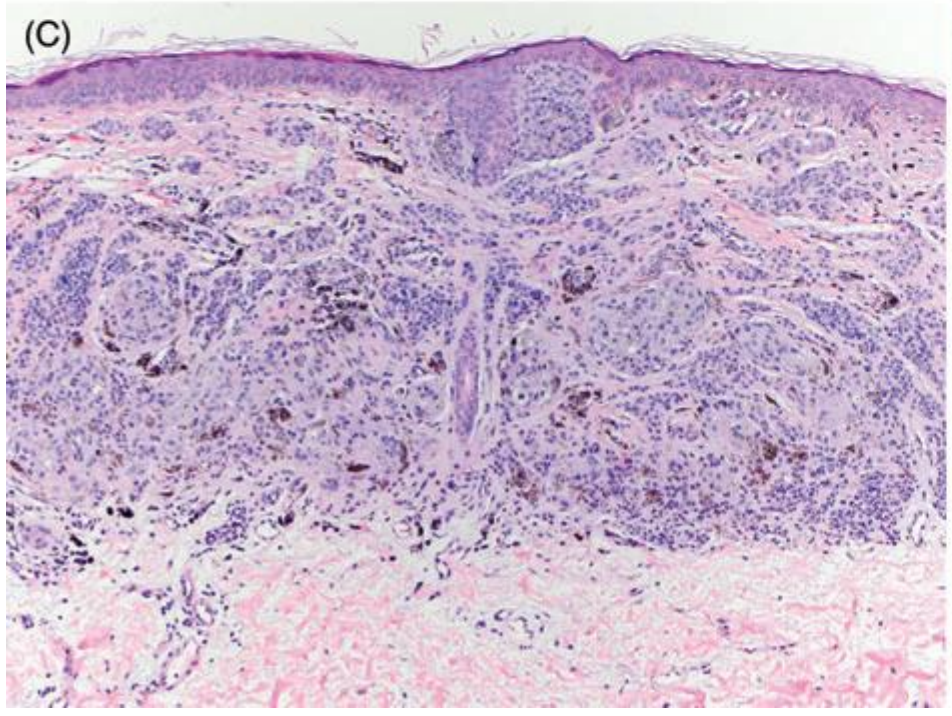
- Additional levels
- Melanin bleached levels
  - Nuclear pleomorphism
  - Nuclear contour
  - Nuclear membrane
  - Mitoses
- Double IHC: ki-67 Melan-A (<5% mitotic index)

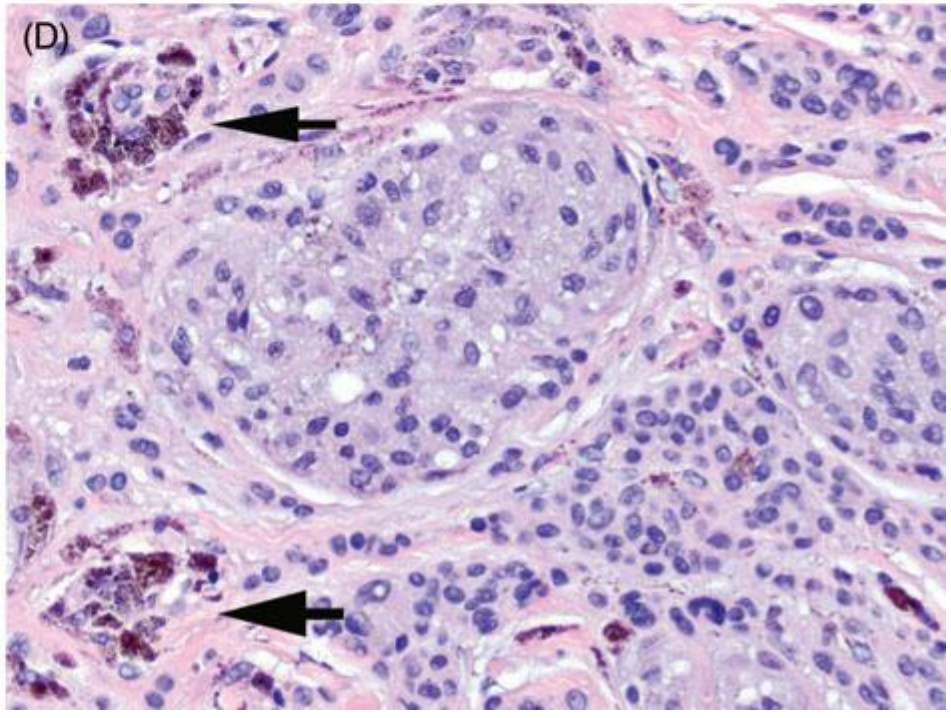

Common melanocytes:
no nuclear staining
Epithelioid melanocytes:
nuclear staining
Beta catenin; reference WHO Skin Tumors (5th ed.)

Inverted type-A melanocytoma/nevus defies dermal maturation









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ORIGINAL ARTICLE

Histological features and outcome of inverted type-A melanocytic nevi

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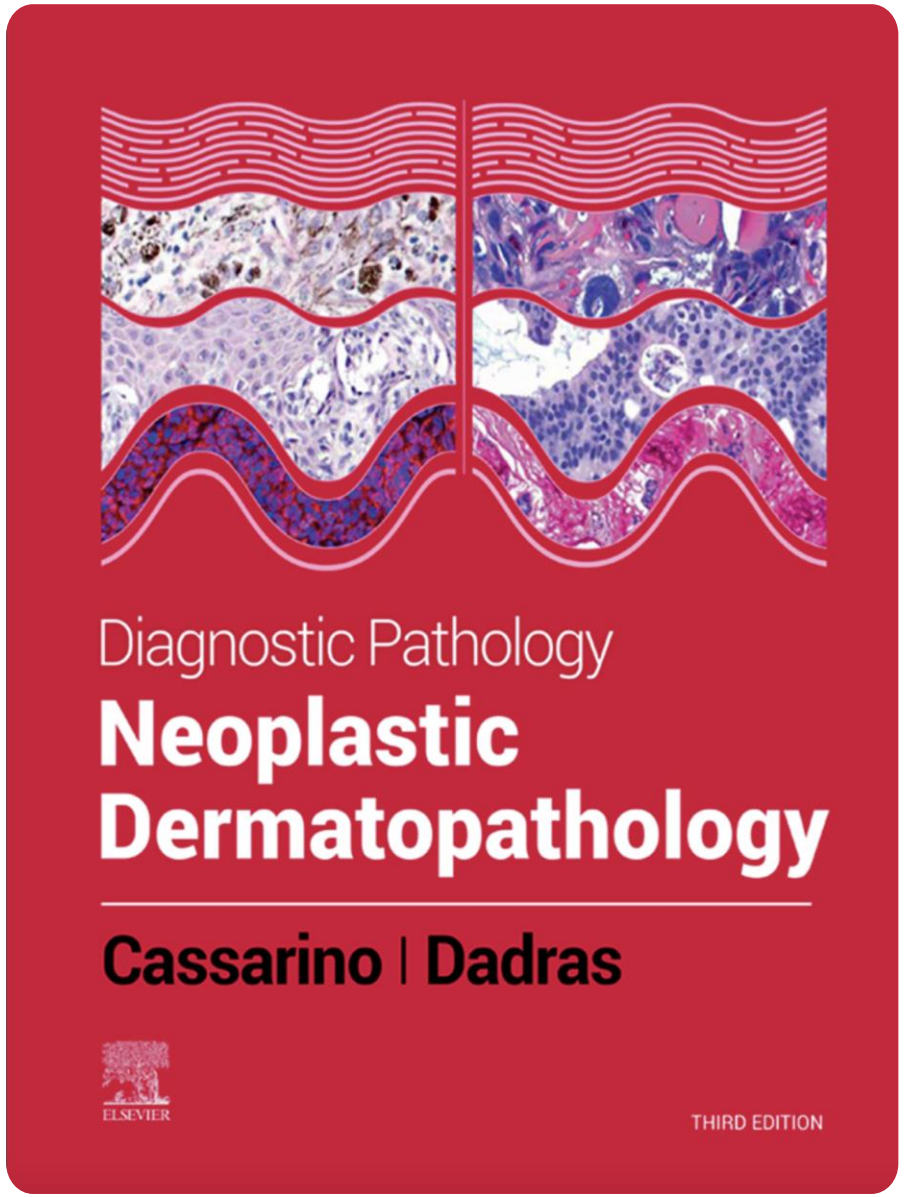
The presence of enlarged epithelioid/spindled nests located deep in the reticular dermis of a biphasic melanocytic neoplasm can mimic melanoma arising in a pre-existing nevus, causing over-interpretation of malignancy. We aimed to define the clinicopathologic significance of epithelioid/spindled nests 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



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- Personal collection