Problems in Melanocytic Pathology and Update in Dysplastic naevi

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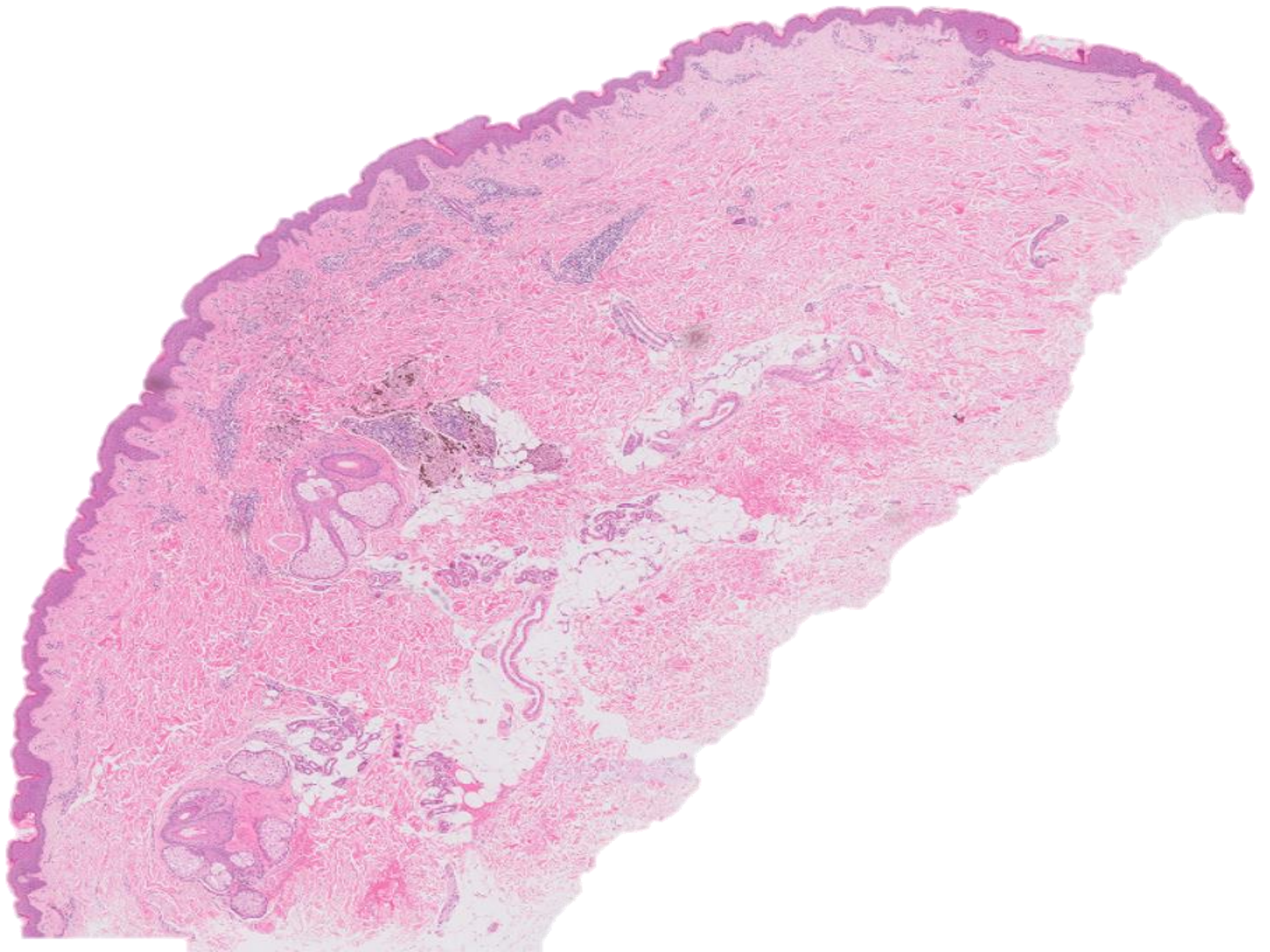
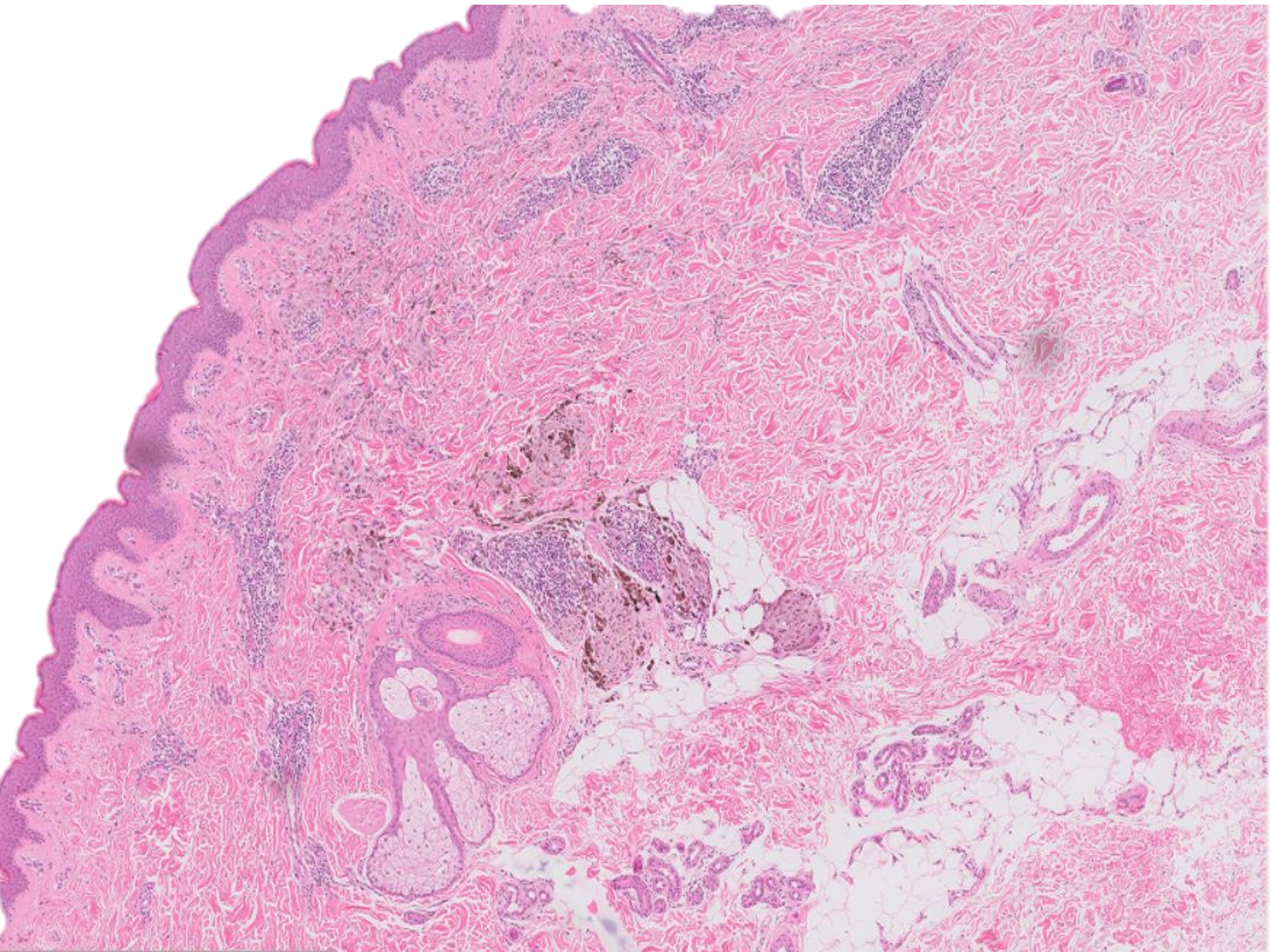
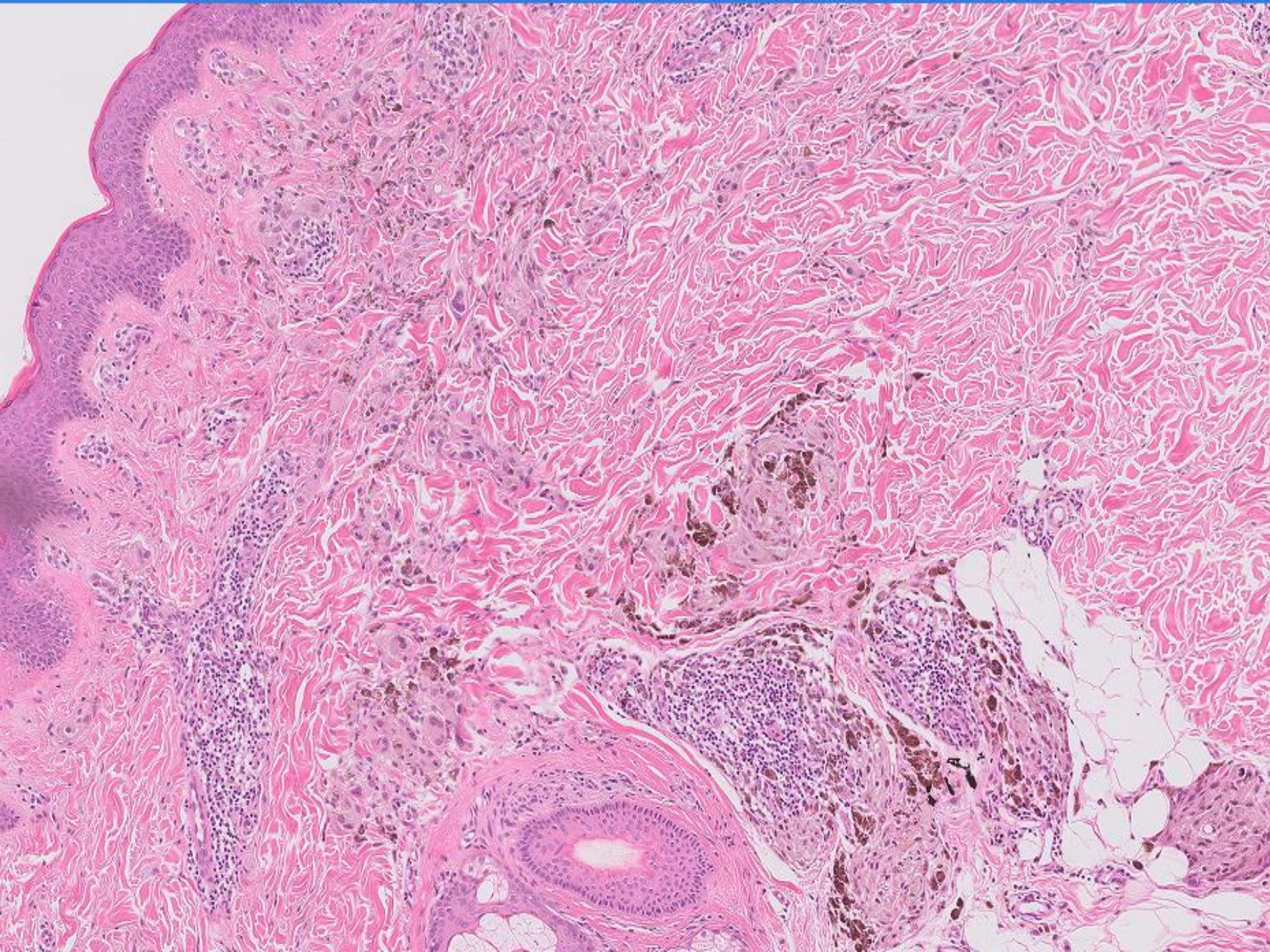
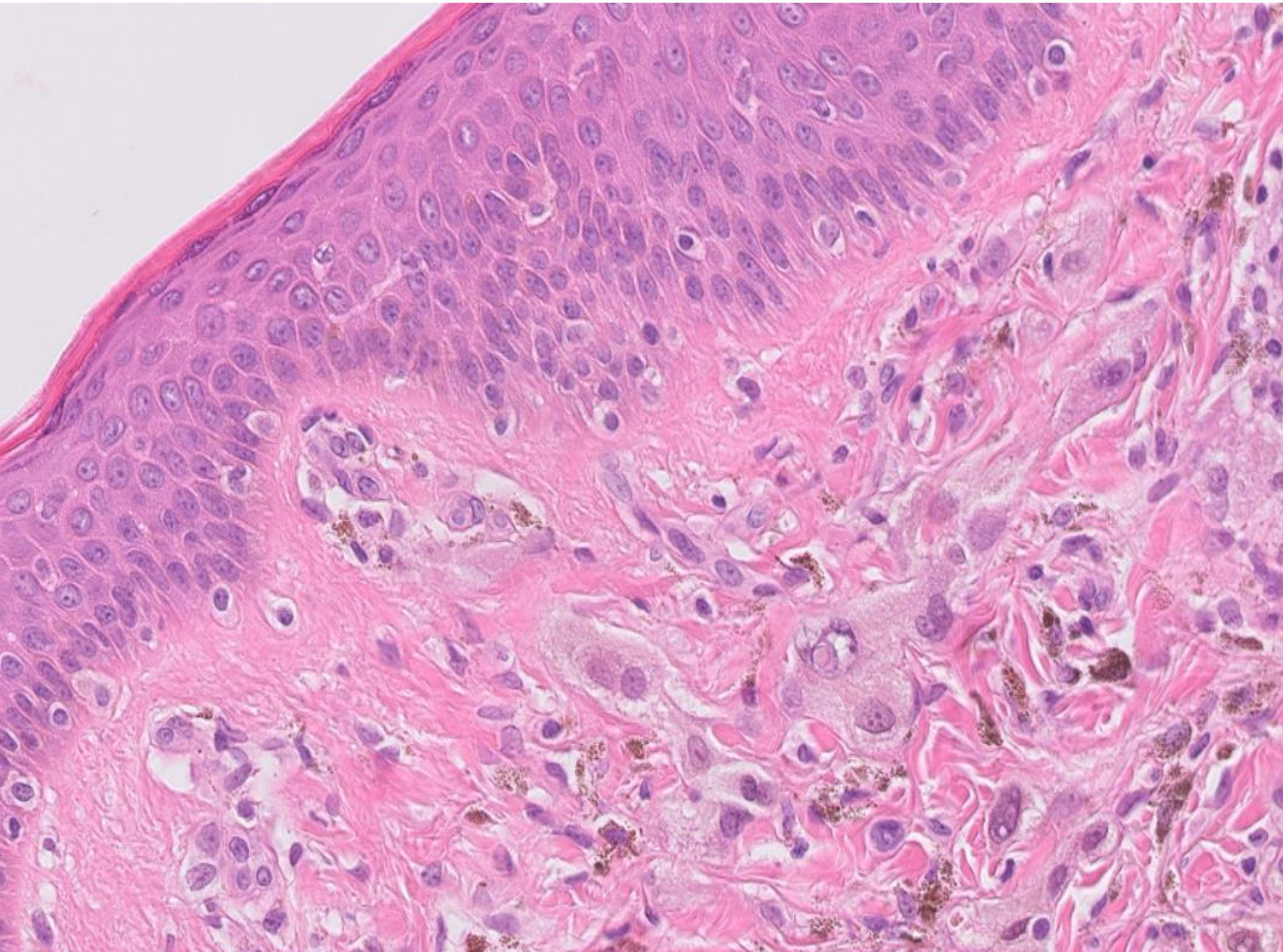
Case 1

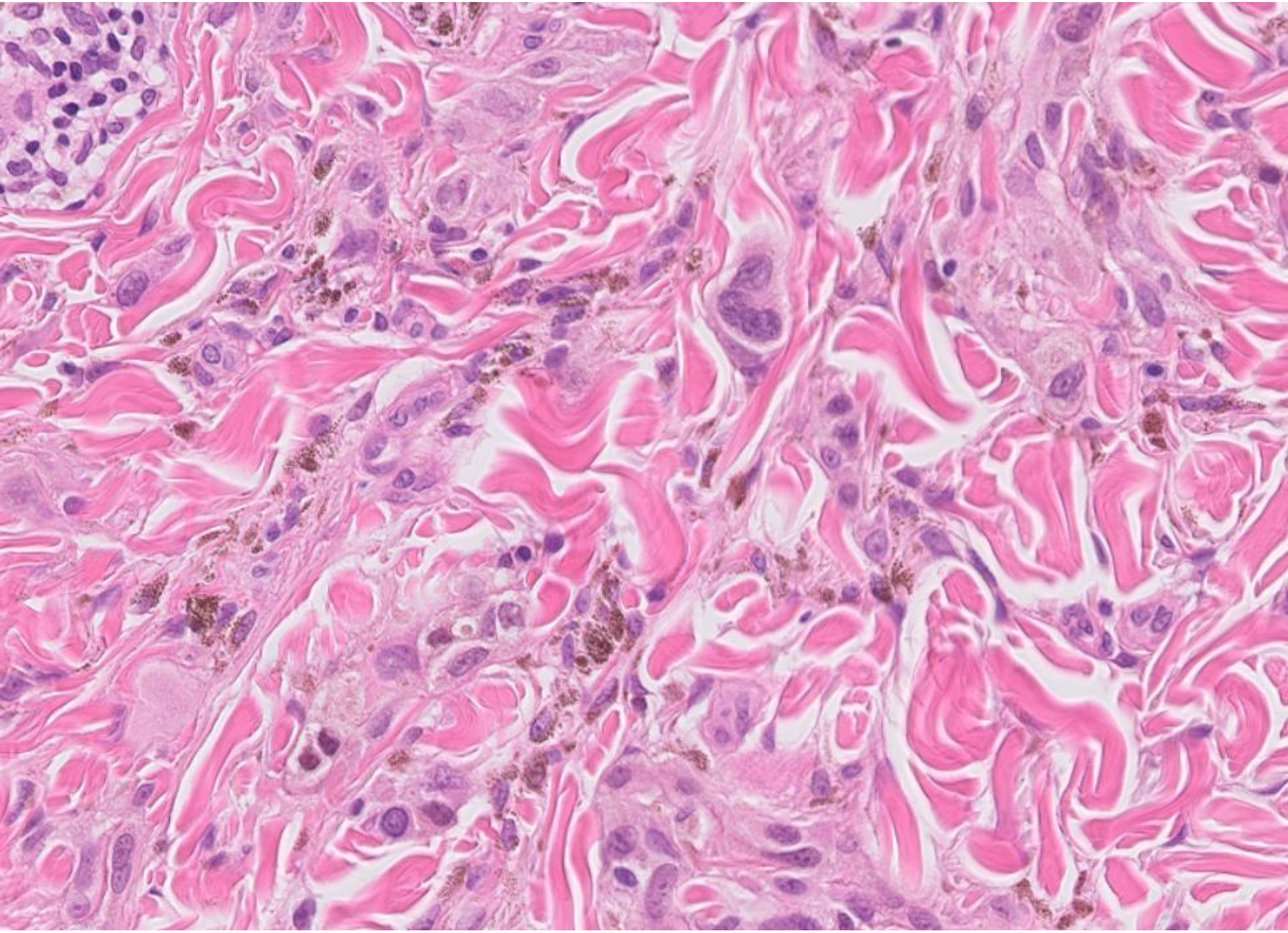
27/F, dark brown macule forearm ? Spitz ?Blue naevus

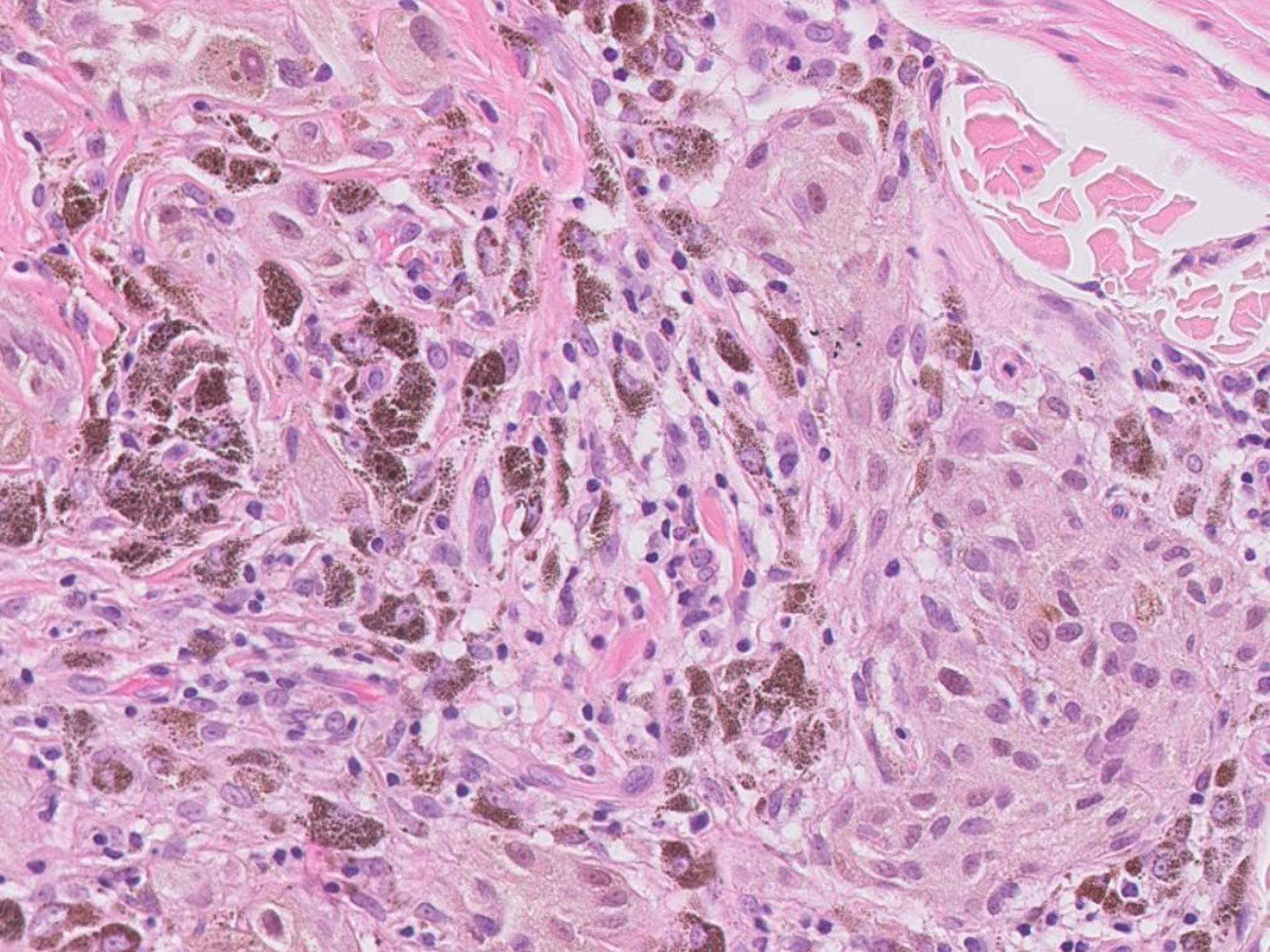


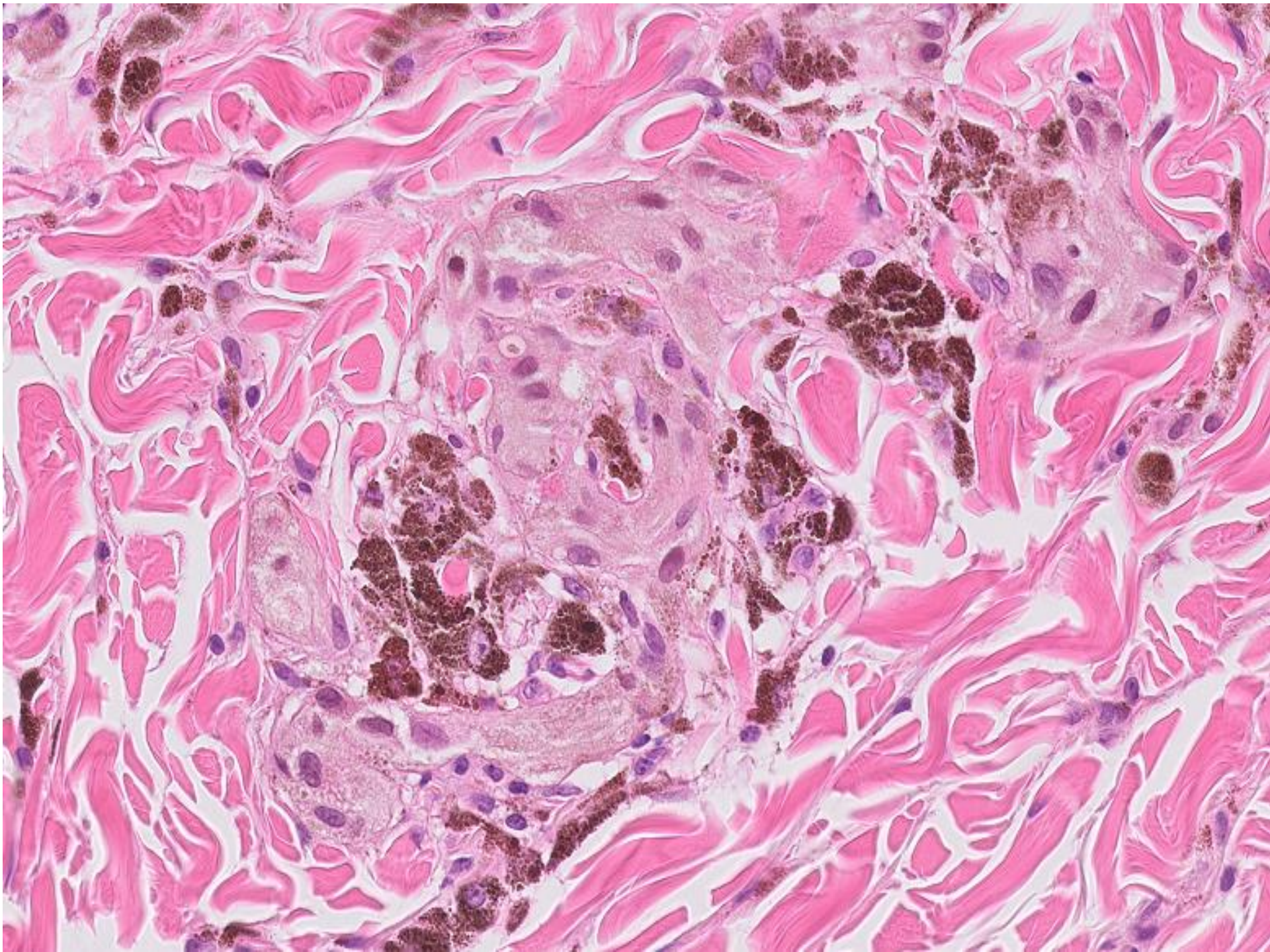


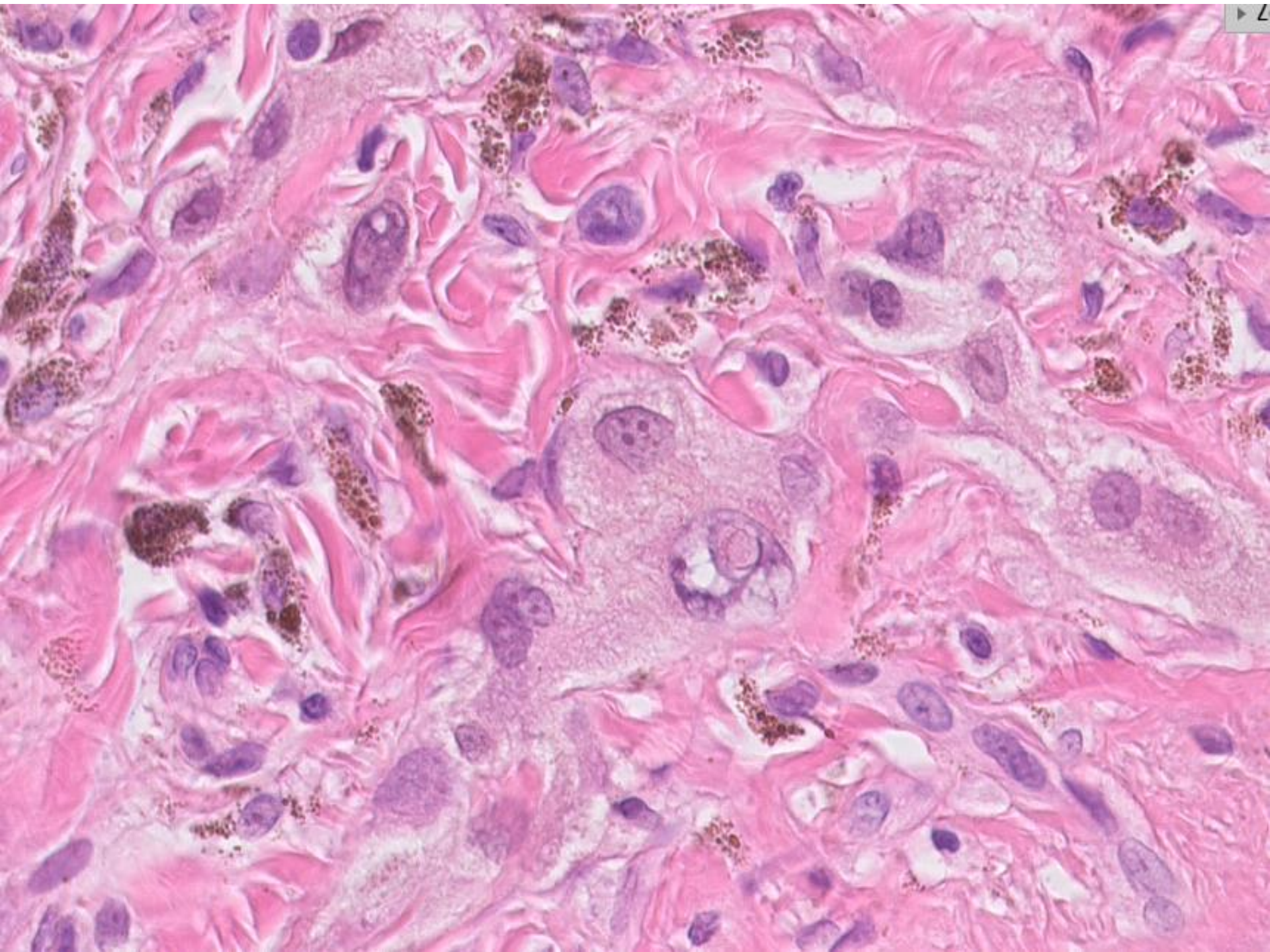












Diagnosis

Benign (left hand)

vs

Malignant (right hand)

Diagnosis?

1. Blue Naevus
2. Deep penetrating naevus
3. Intradermal Spitz/Atypical Spitz

Diagnosis

Deep Penetrating Naevus

Arch Pathol Lab Med. 2011 Mar;135(3):321-6.
Deep penetrating nevus: a review.
Luzar B[1], Calonje E.

DPN: Which family?

- Blue Naevus family
- Spitz Naevus Family
- Distinct entity

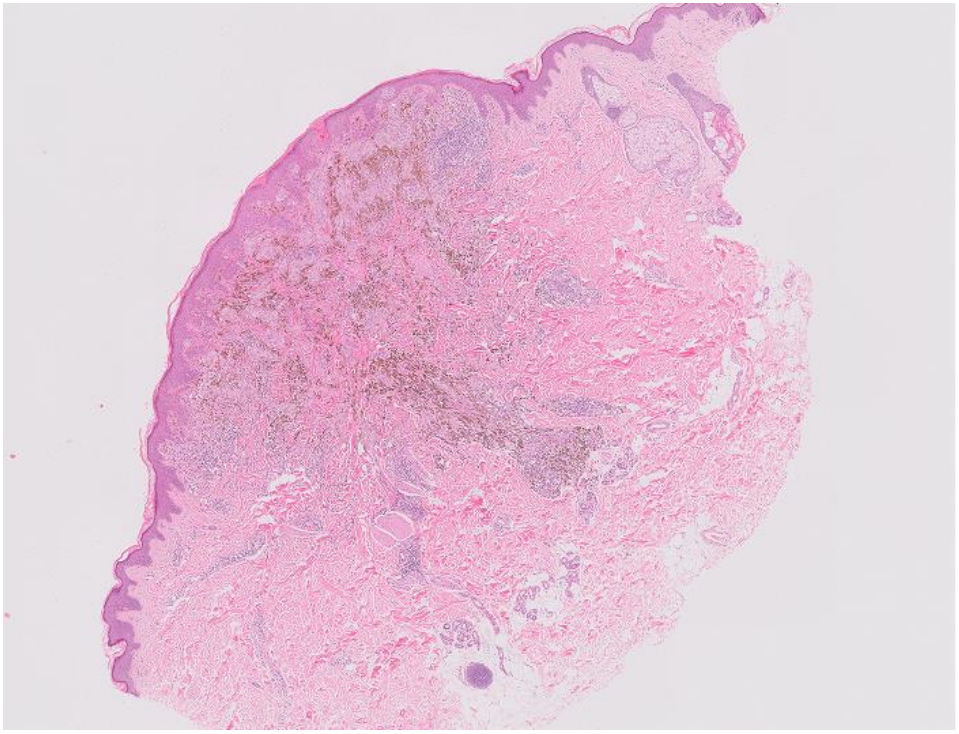
Which family?

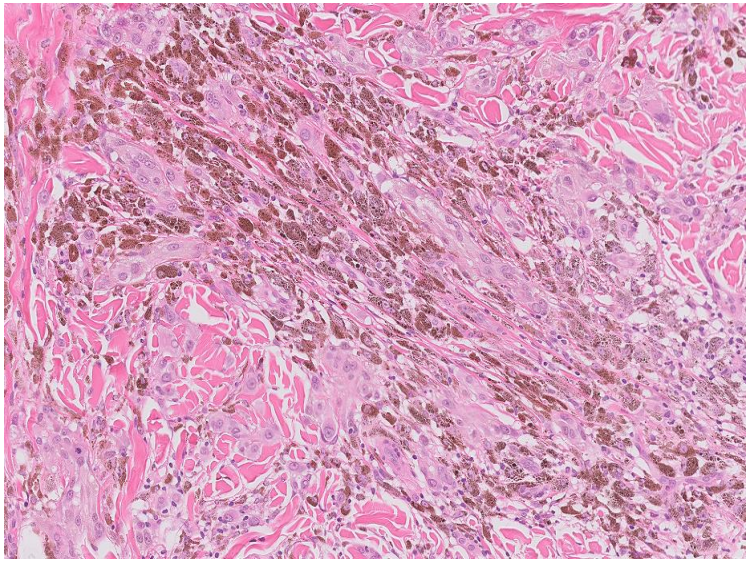
- Blue Naevus family
- Spitz Naevus Family
- Distinct entity

Recent molecular insights: Alterations in the Wnt/B-catenin pathway define DPN.

Architecture

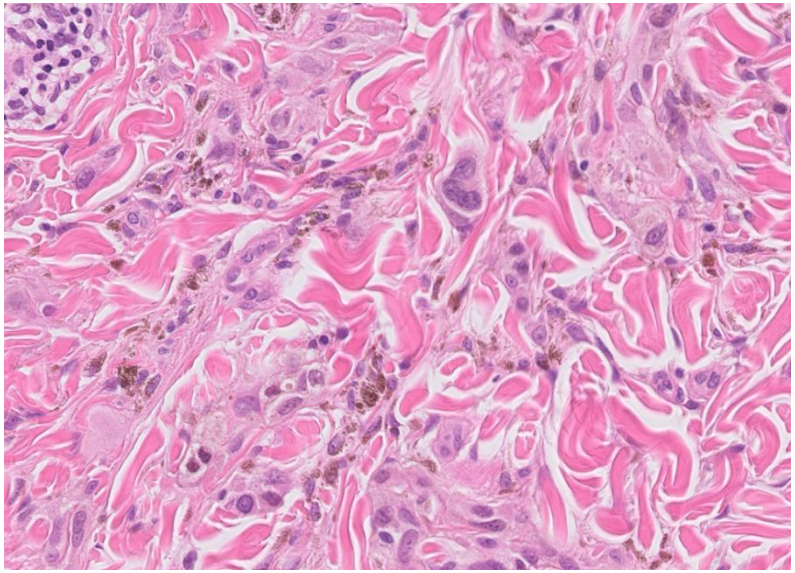
- Silhouette: inverted triangle with apex towards the subcutis
- Extension along folliculosebaceous units or neurovascular bundles
- Nests or elongated fascicles



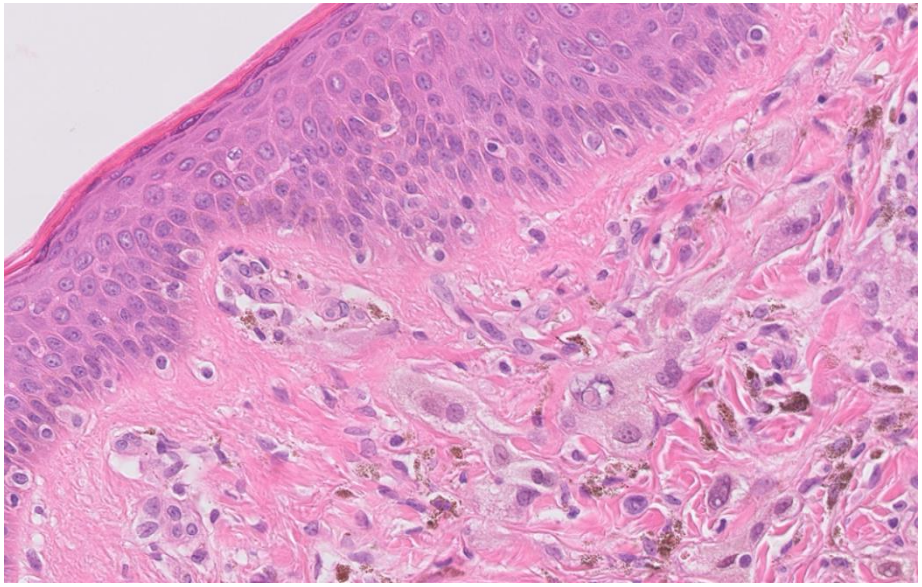


Architecture

- Splaying of collagen fibres in between nests and single cells



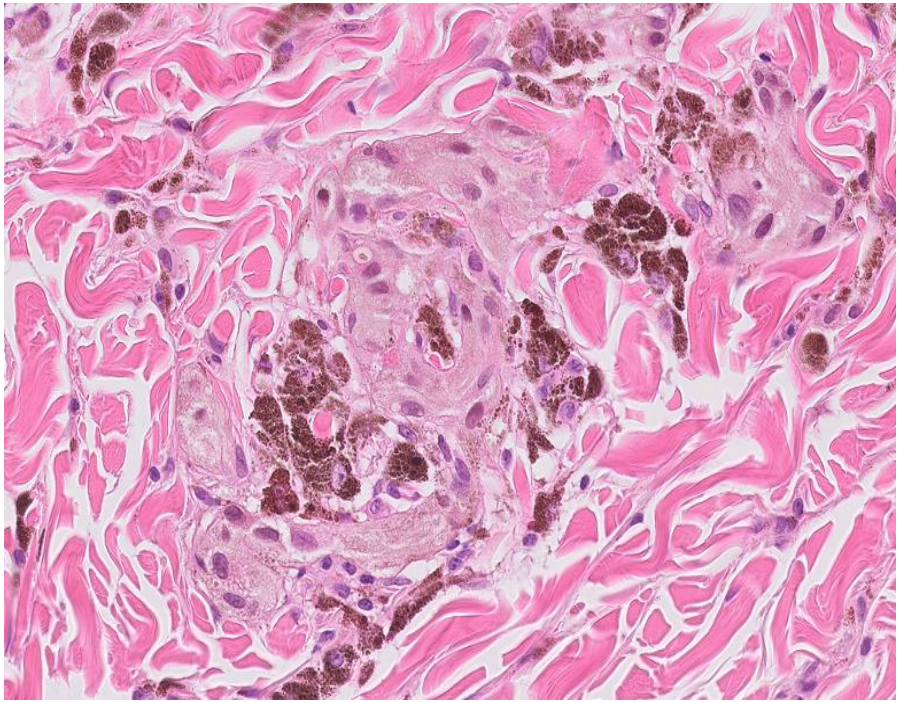
- Usually wholly intradermal with a Grenz zone



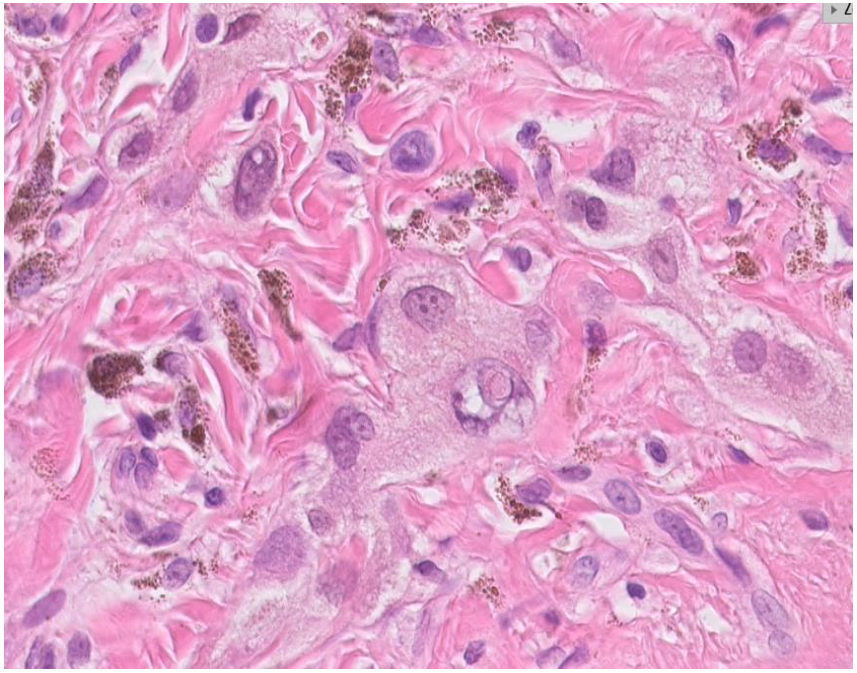
- Less commonly: scant junctional component with lentiginous pattern or rarely junctional nests

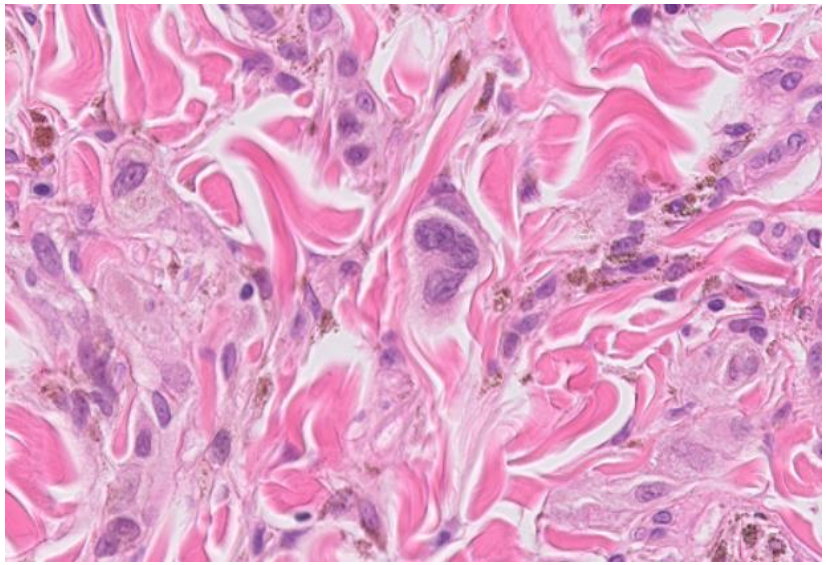
Cytomorphology

- Round, oval, fusiform or nearly spindled
- Epithelioid>spindle
- Abundant pale pink to grey cytoplasm with dusty appearing pigment



- Nuclei: small monomorphic to large and pleomorphic (random atypia)
- Intranuclear pseudoinclusions are a frequent finding
- Melanophages are present regularly scattered throughout the neoplasm
- Achromic DPN is rare but can occur before puberty
- Ocassional mitoses can be seen (including deep ones)





Virchows Arch. 2019 May;474(5)

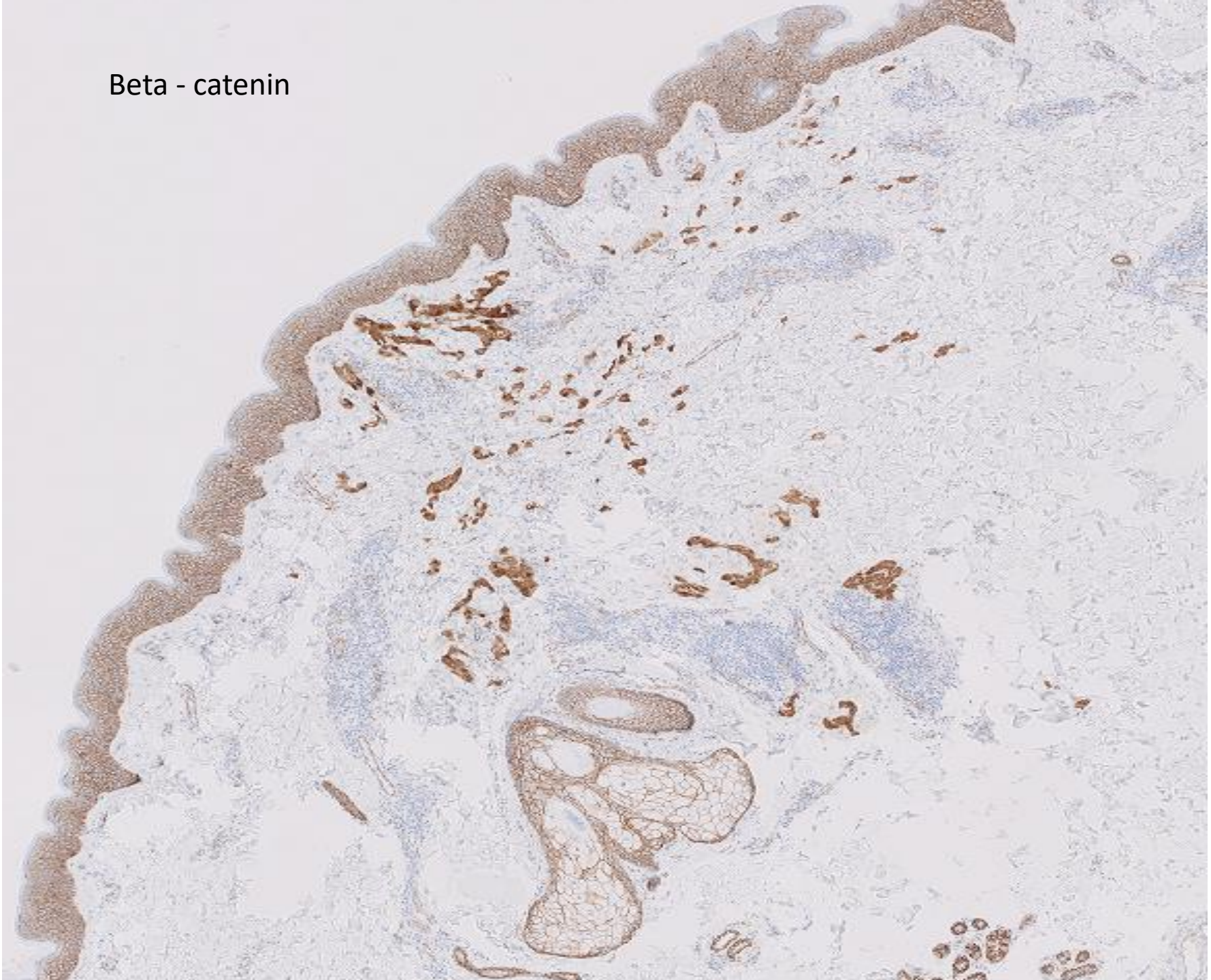
β-Catenin nuclear expression discriminates deep penetrating nevi from other cutaneous melanocytic tumors.

de la Fouchardière A[1,2], Caillot C[3], Jacquemus J[3], Durieux E[4], Houlier A[3,5], Haddad V[3], Pissaloux D[3,5].

Nuclear staining is regarded as positive, can be variable :

- 98/100 DPN +
- 2/16 melanoma +
- 0/30 Spitz +
- 0/26 Blue naevi +
- 0/5 PEM +

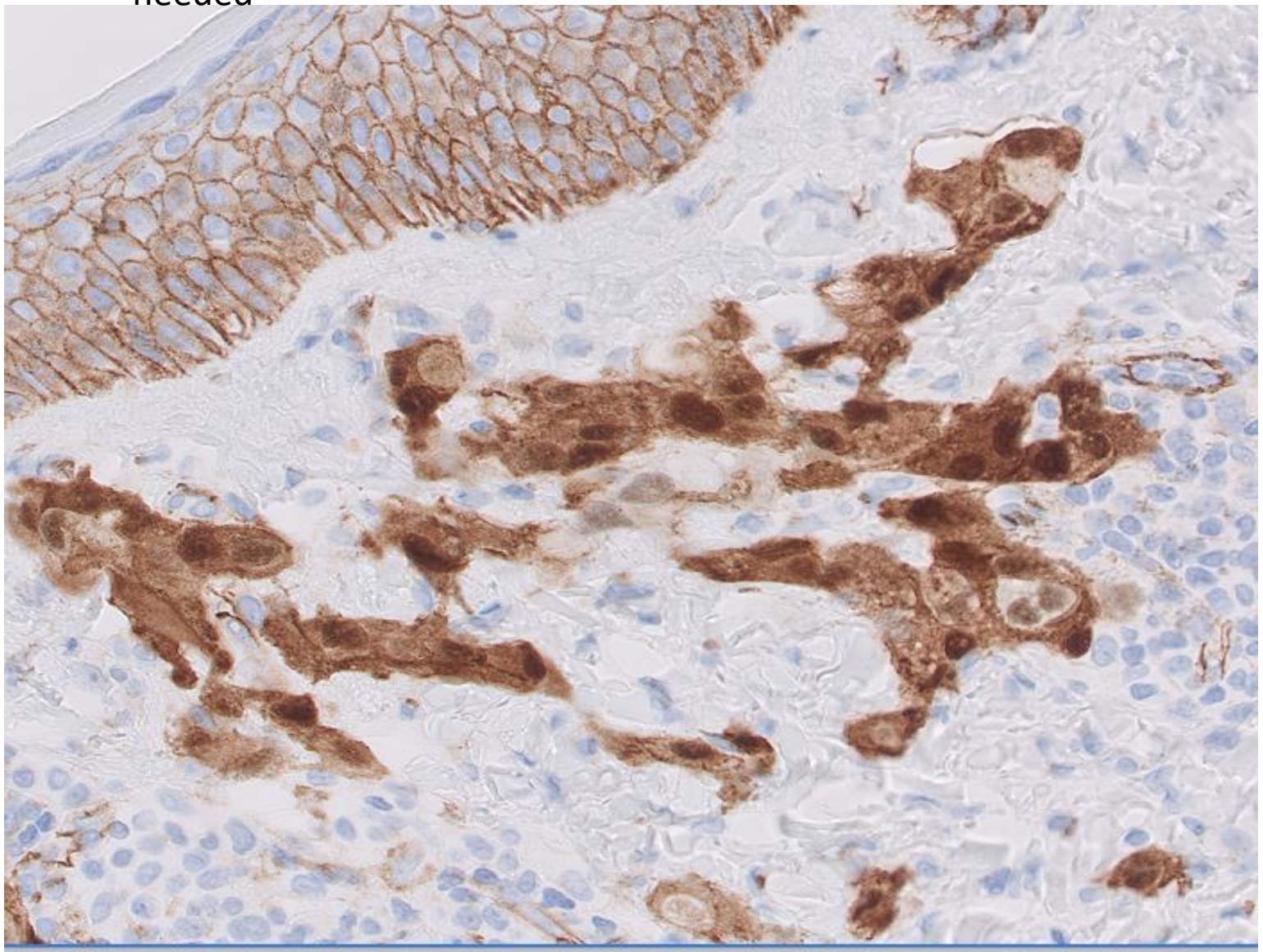
Beta - catenin



Ignore membranous and cytoplasmic staining

Look for nuclear staining. Usually patchy positivity (may be <10% of nuclei)

Negative score if 0 nuclei stain: careful high power examination needed



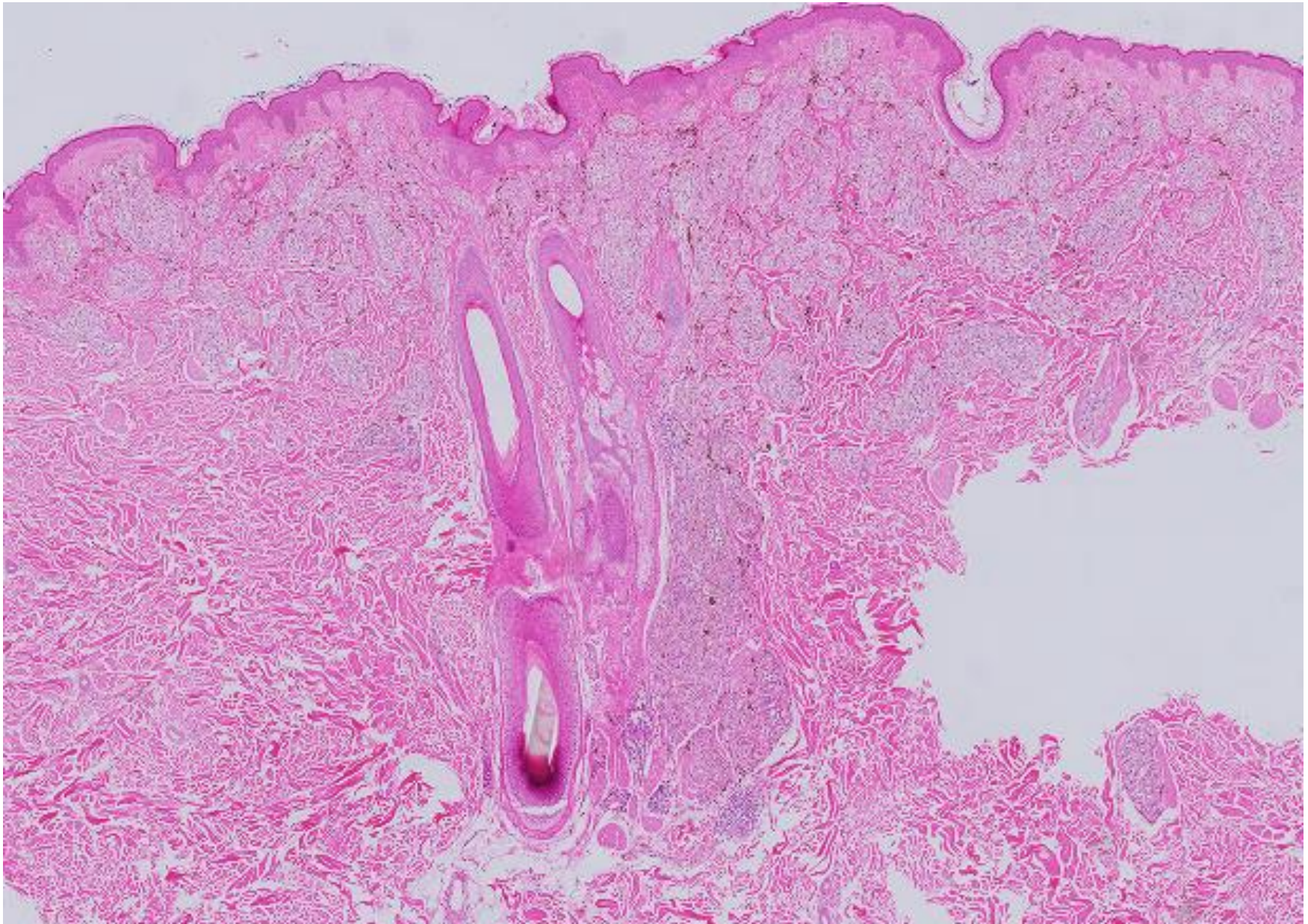
Differential Diagnosis of DPN

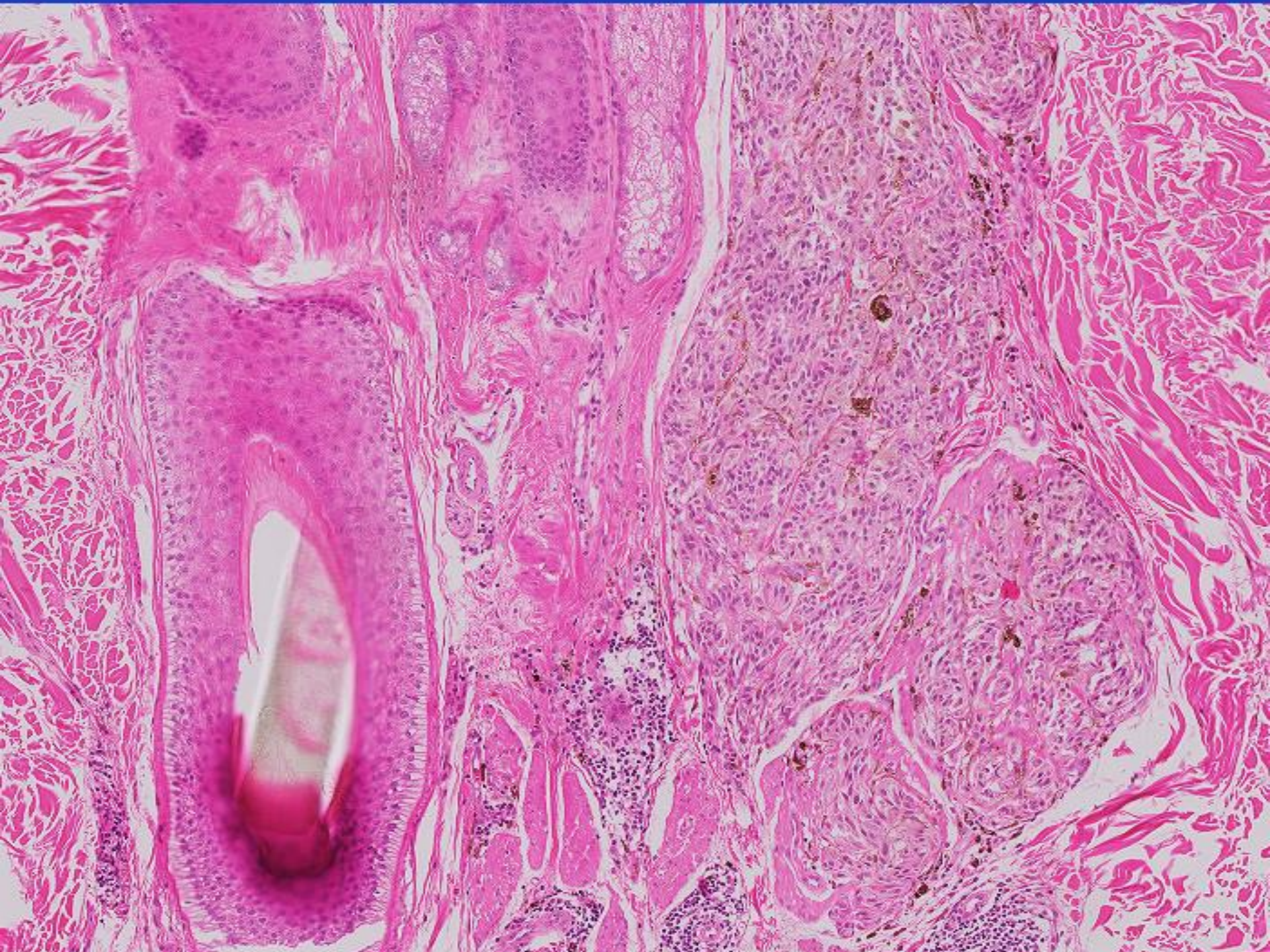
- Spitz tumours (incl Spitz, Atypical Spitz and Spitzoid melanomas)
- Cellular Blue Naevus
- DPN-like Melanoma or Plexiform Melanoma

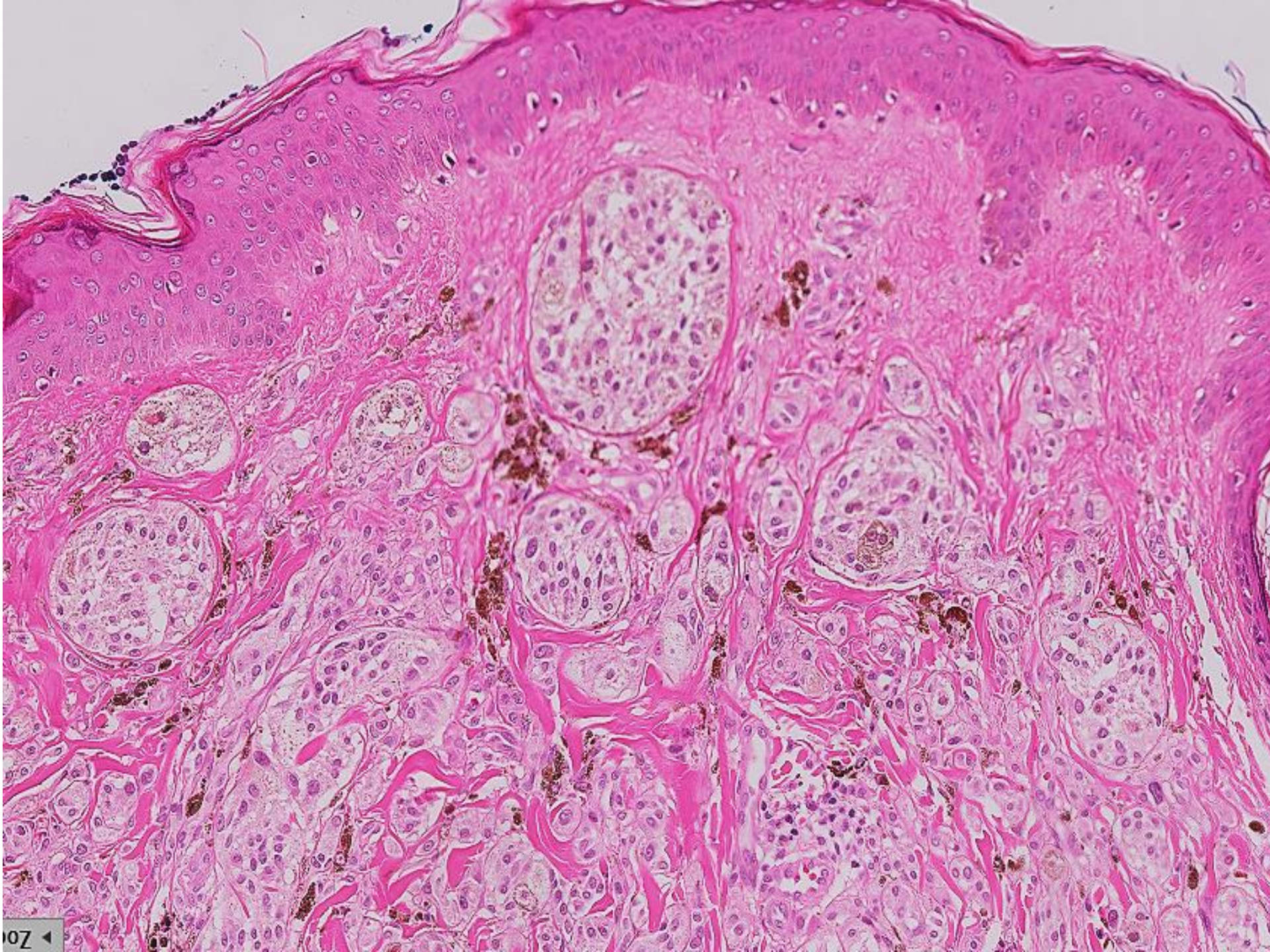
DPN vs Spitz vs Cellular Blue Naevus Why is the distinction important?

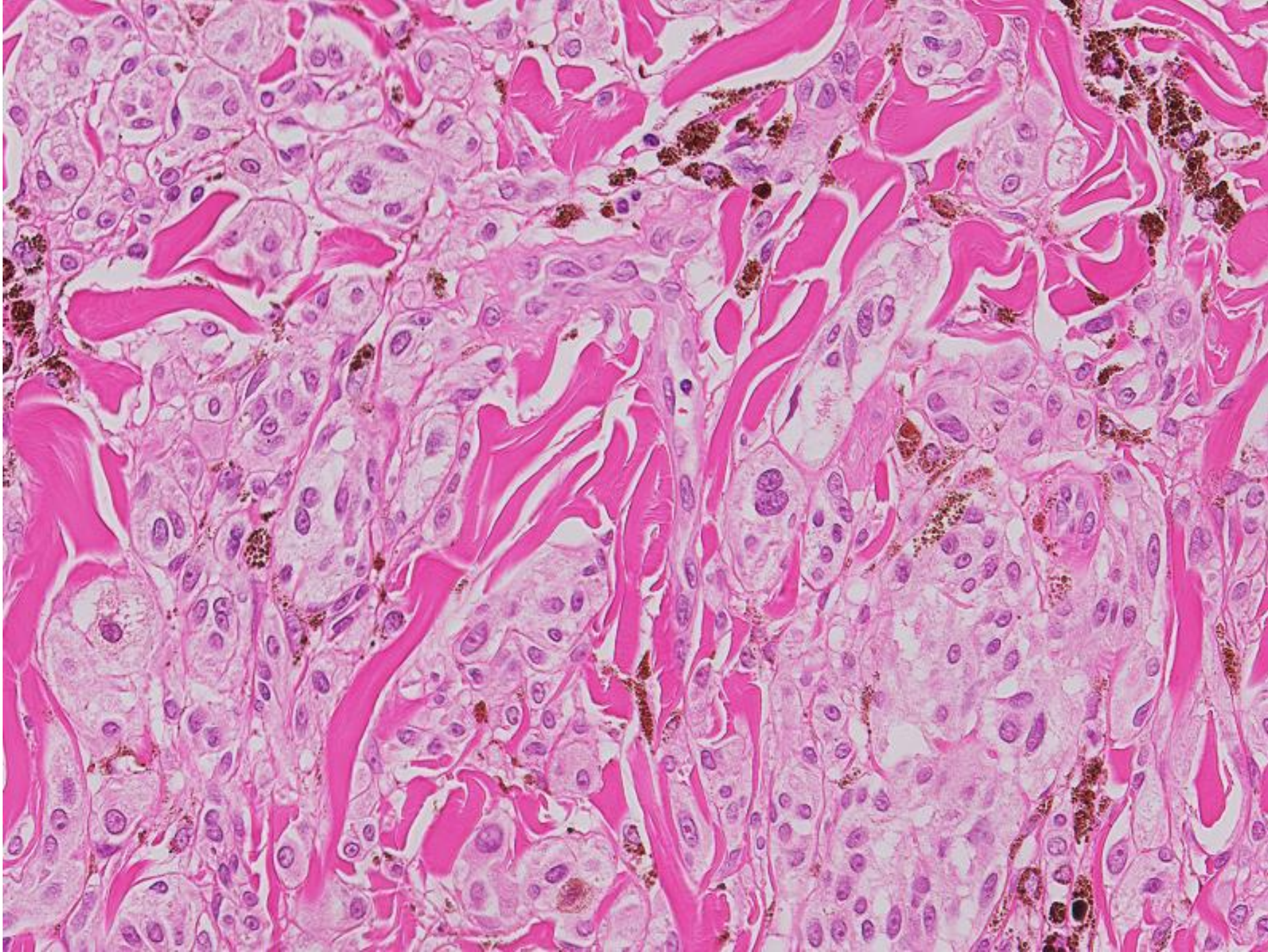
- Different diagnostic criteria for benign, borderline and malignant
- Different entities at a molecular level
- Evolving understand of lesions and future therapeutic implications

Problem Case 2: 36/M, changing dark mole





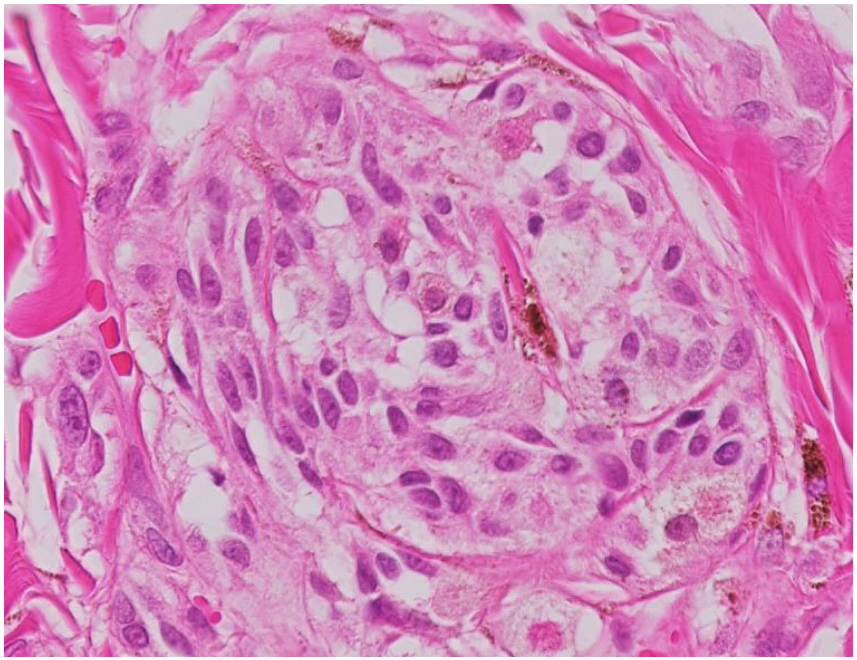


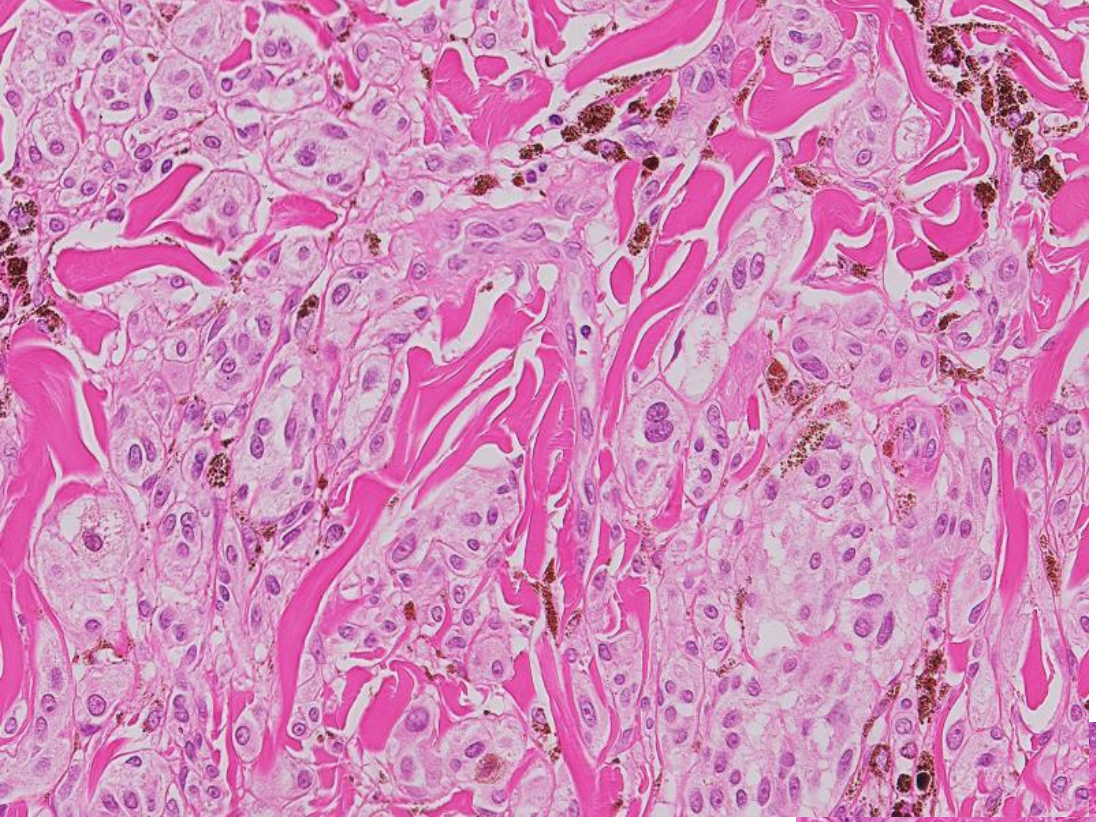


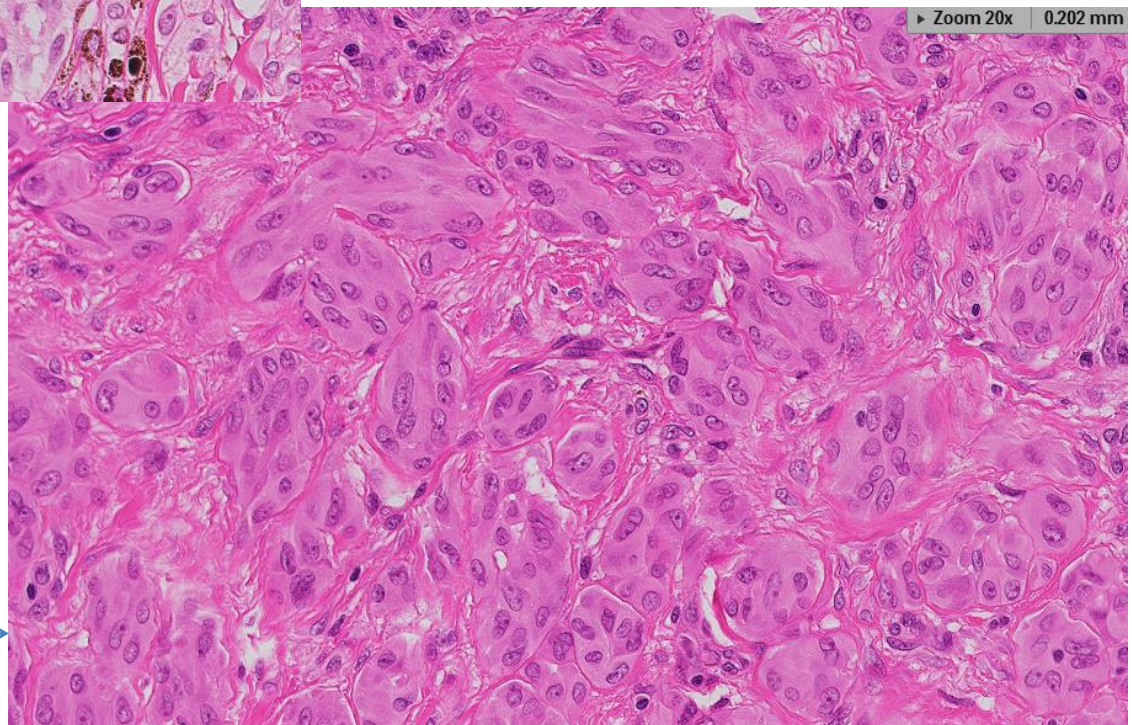
Query from referring pathologist

- No maturation with depth
- Cytological atypia +
- No mitosis

- ?DPN ?Atypical Spitz

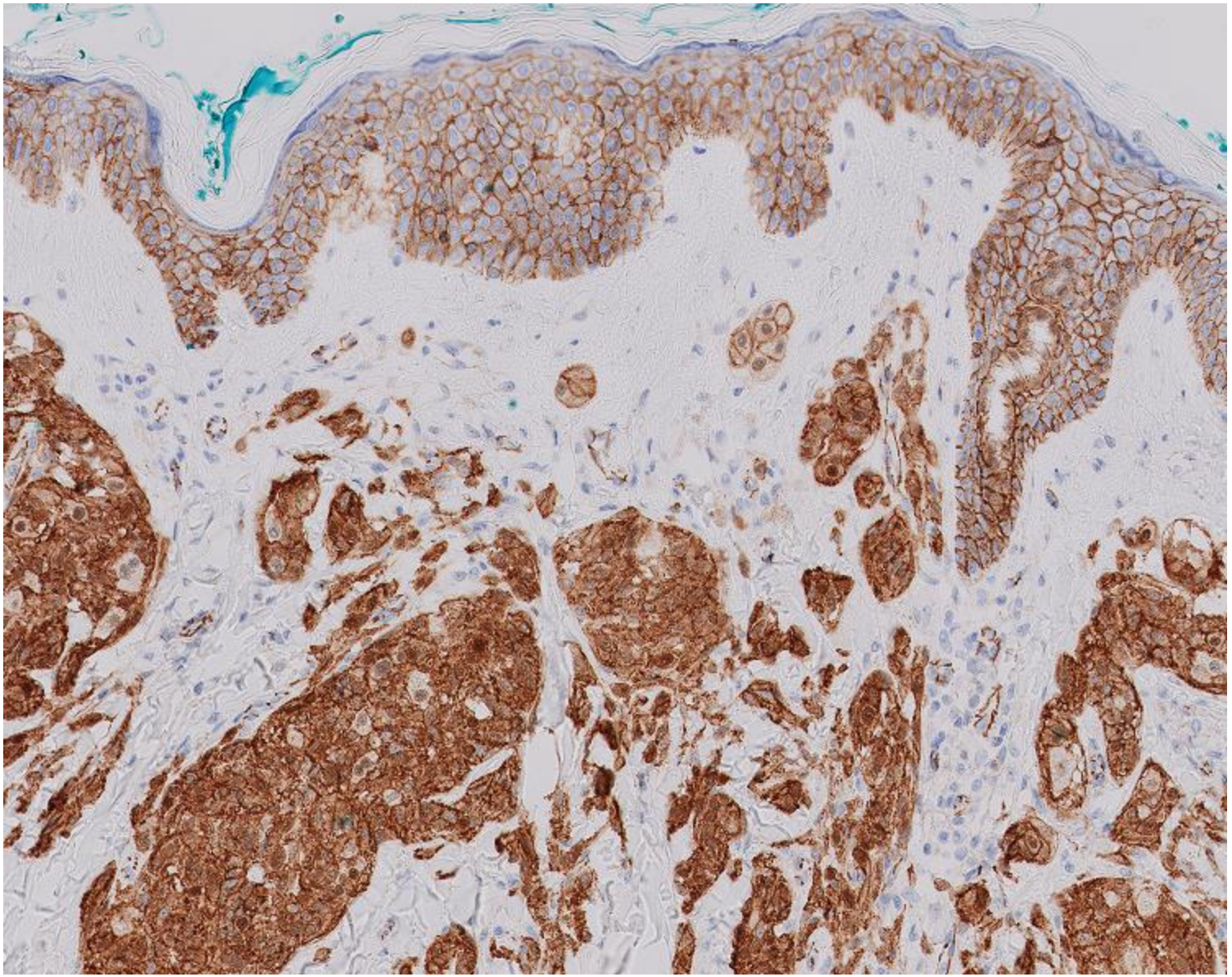


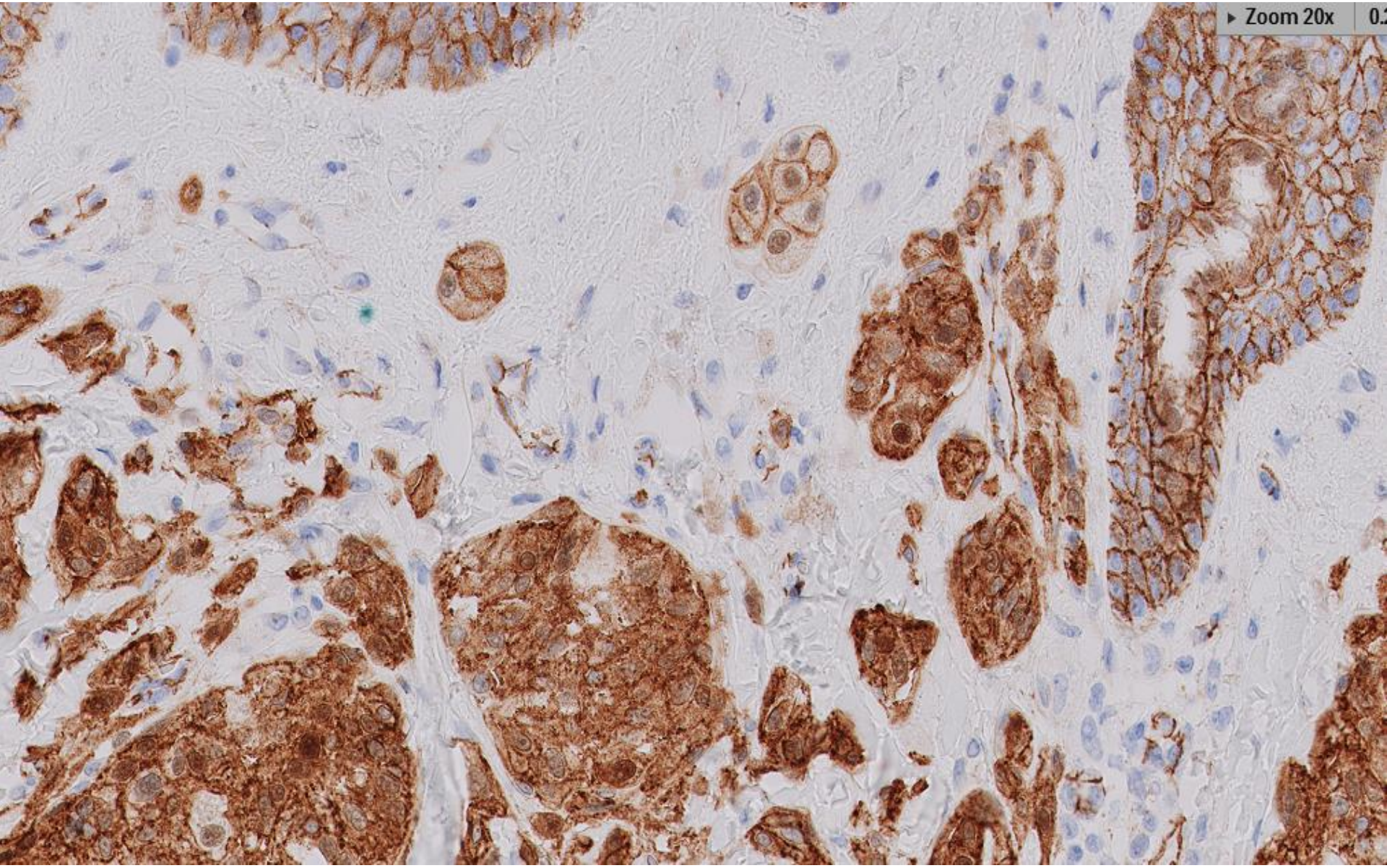


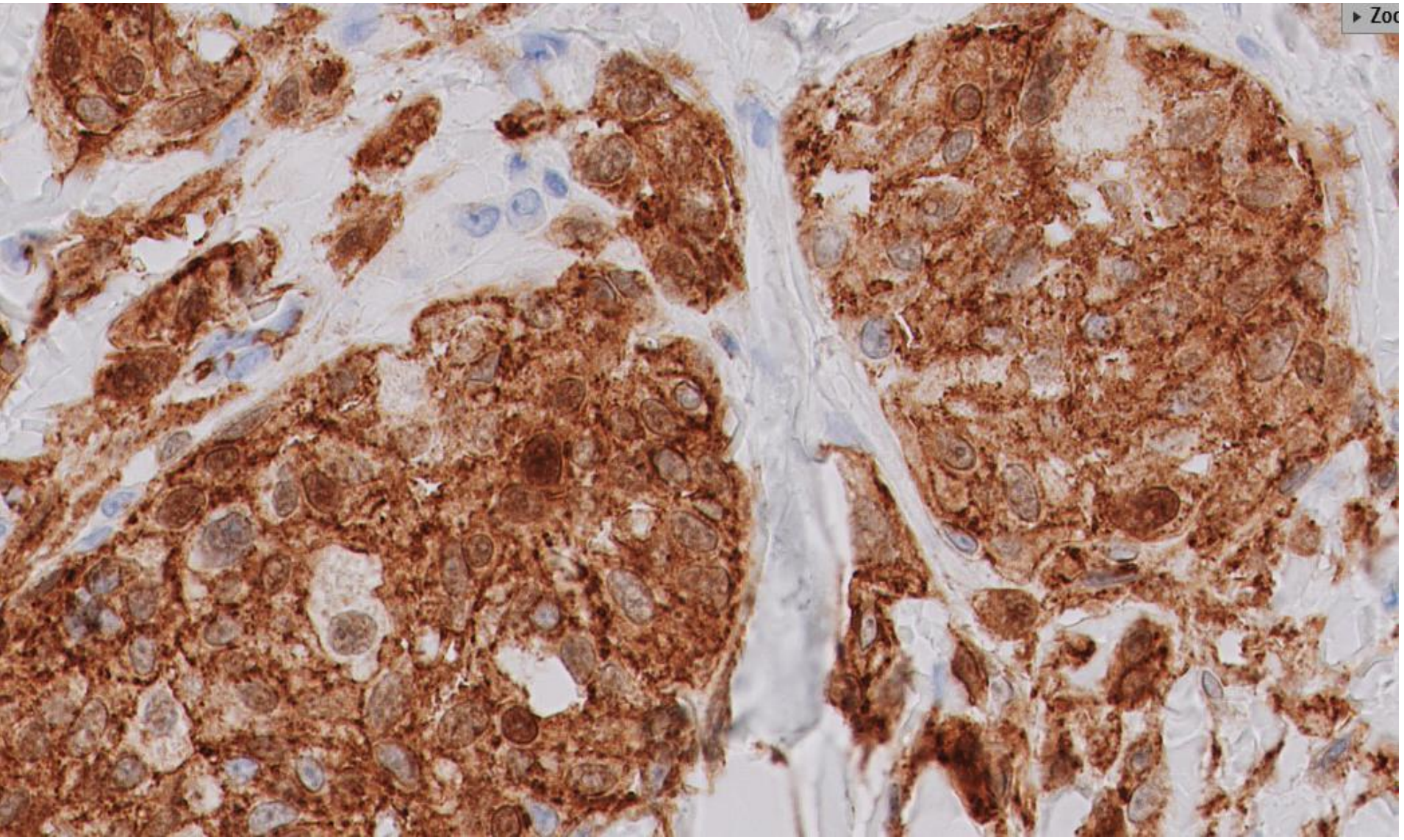


Intradermal Spitz

Beta - Catenin

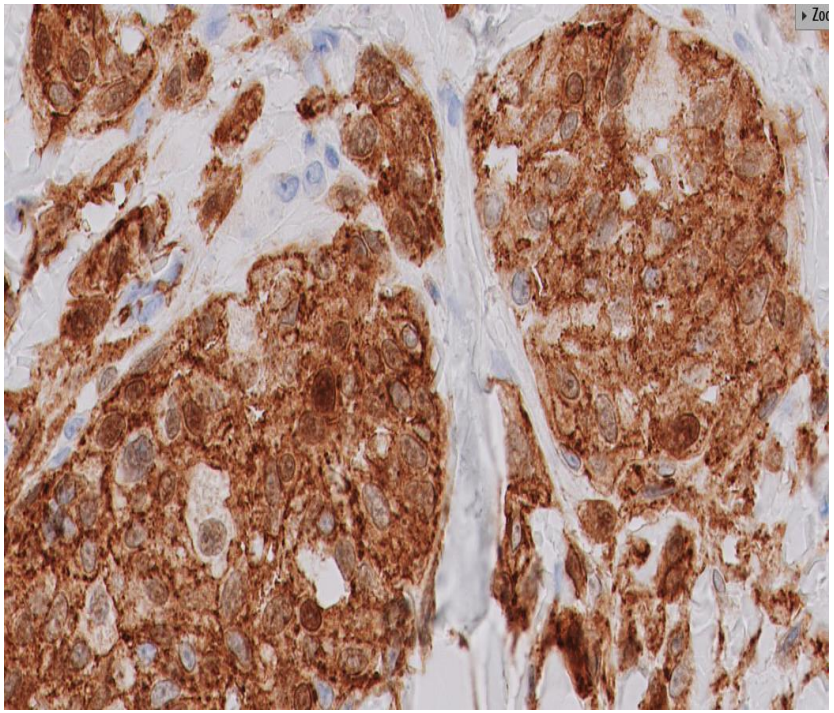



Zoom 20x

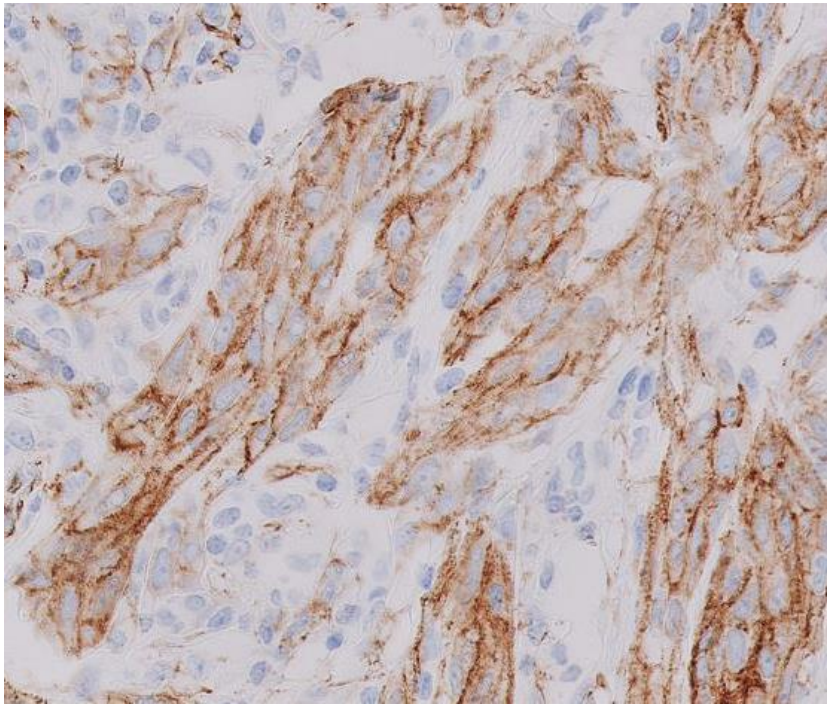

Zoo

Beta Catenin

DPN



Spitz



IHC and molecular

DPN

IHC:

- Beta catenin +
- BRAF V600E +

Molecular:

- BRAF mutation + dysregulation of WNT/Beta catenin pathway

Spitz

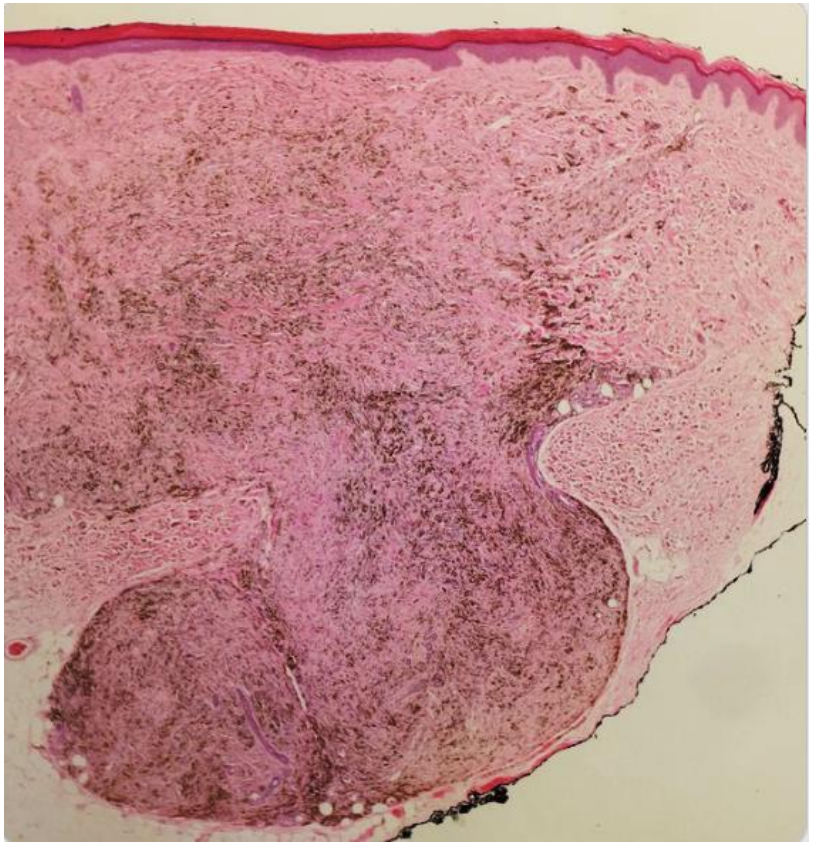
IHC

- Beat catenin –ve
- BRAF V600E usually –ve

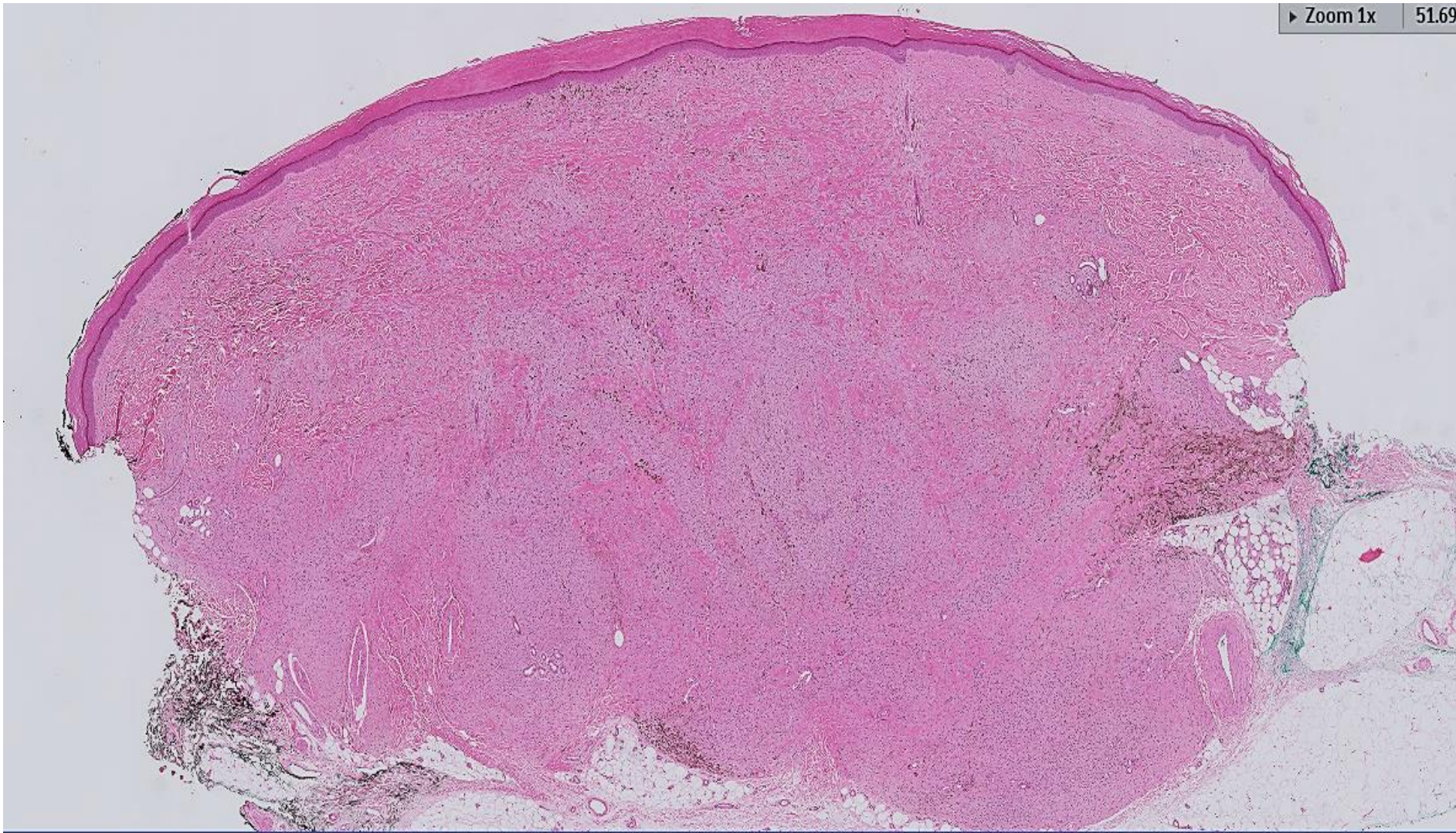
Molecular:

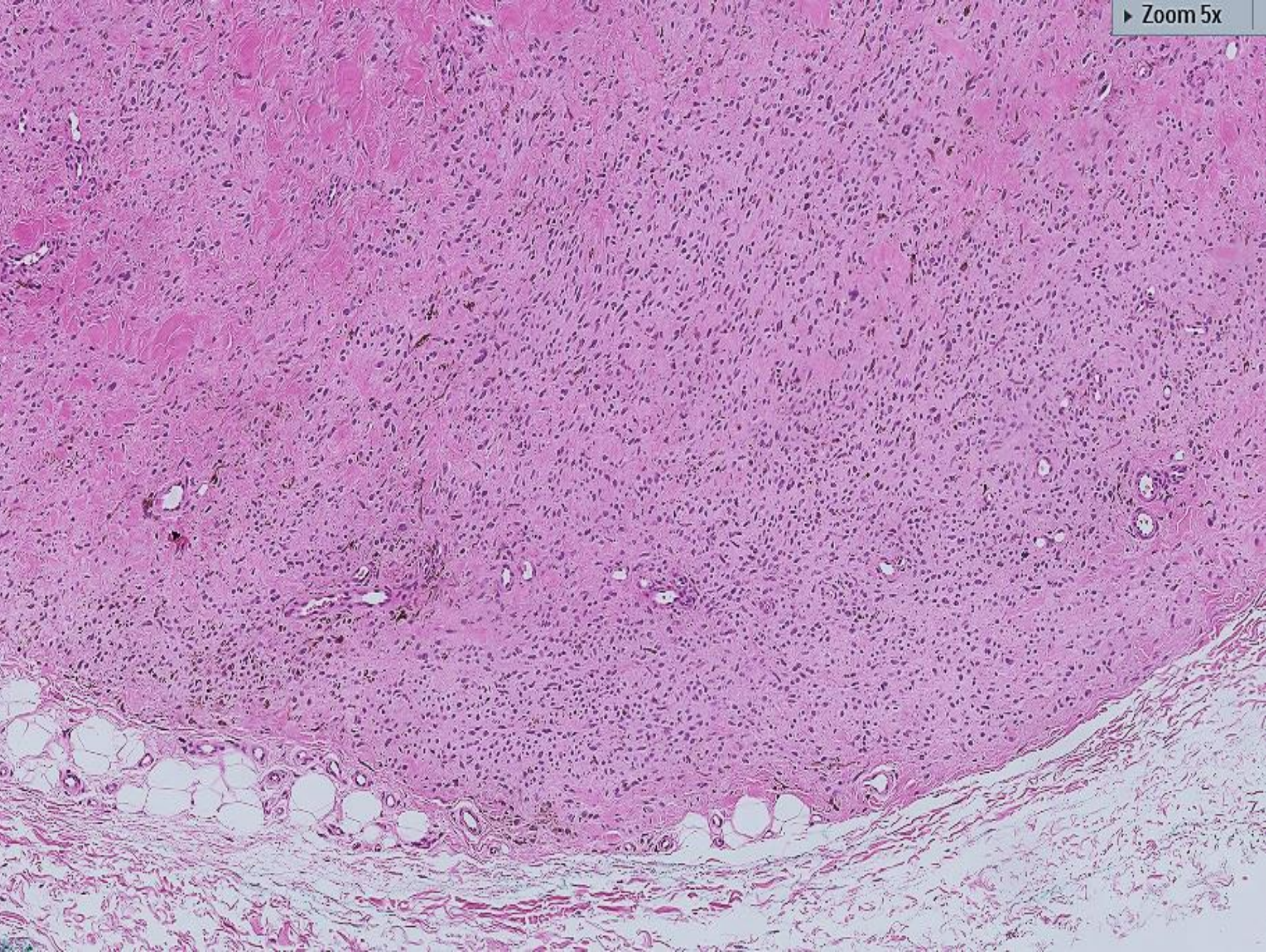
- HRAS mutations
- BAP1 loss (+BRAF)
- Kinase fusions (ALK, MET, ROS etc)

DPN vs Cellular Blue Naevus



24/M, variably pigmented lesion

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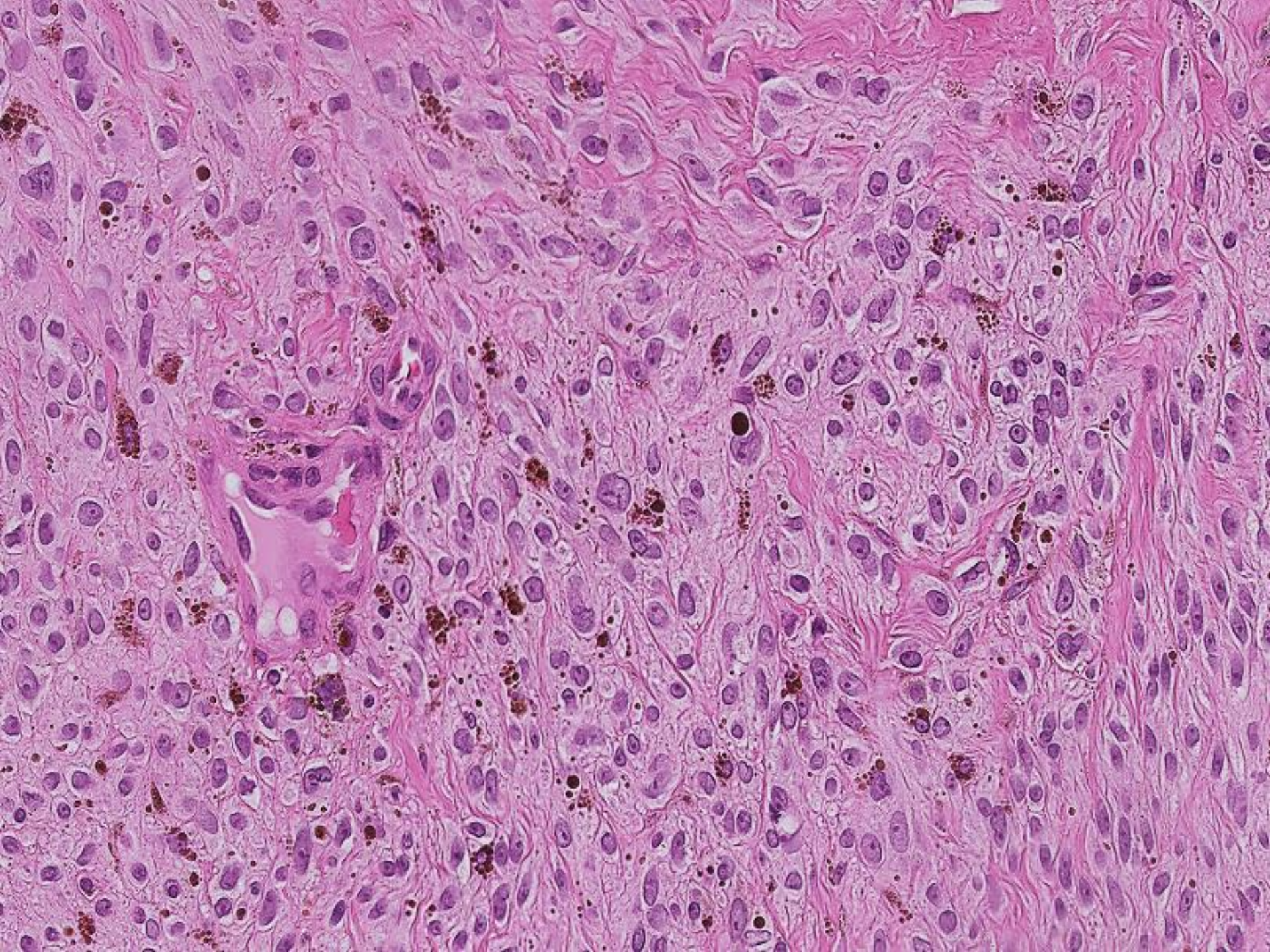
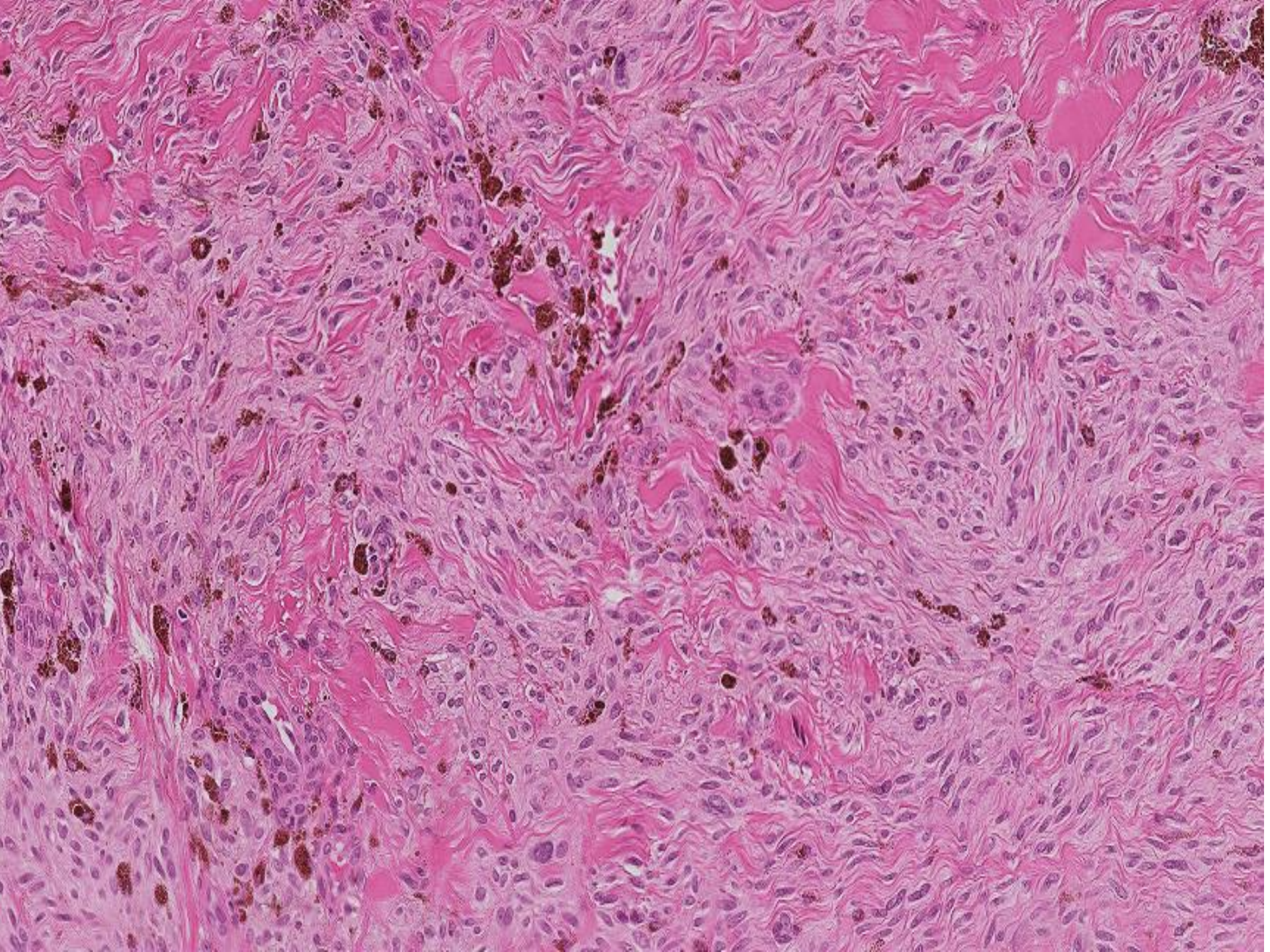
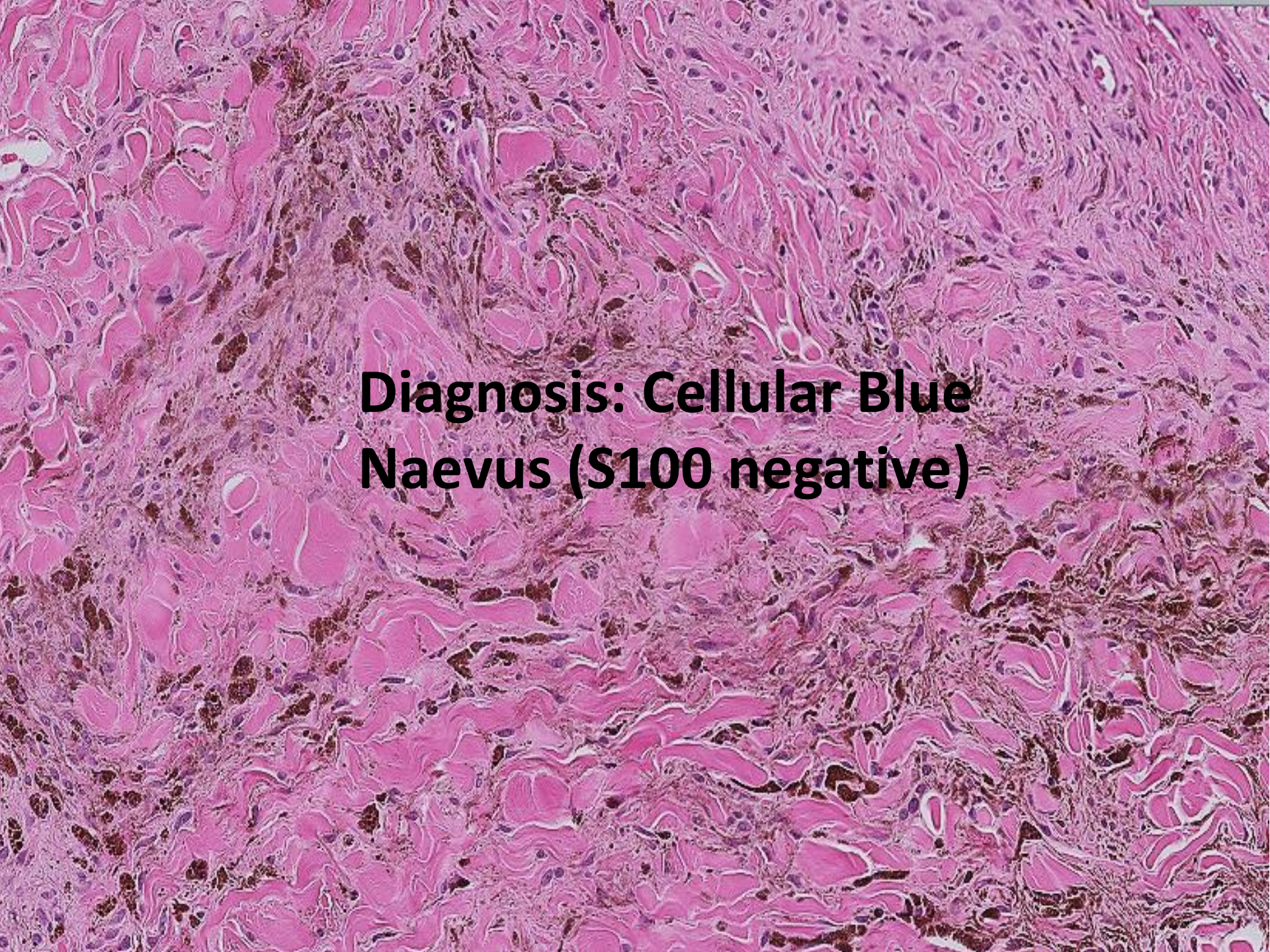





Diagnosis: Cellular Blue
Naevus (S100 negative)

	DPN	Cellular Blue Naevus
Architecture	Wedge shaped, inverted triangle	Dumbell shaped
	Nests of cells interweave in between collagen	Bulging, pushing rounded borders
Cytomorphology	Epithelioid>spindle	Spindle cell prominent, particularly at edges
	Cells have abundant pale/grey cytoplasm	Less cytoplasm
Tracking along adnexal structures	++	++
IHC and molecular	• BRAF + • Beta Catenin+ • S100 + • WNT/B-Cat dysregulation	• BRAF- • Beta Catenin- • S100 -/weak • GNAQ and GNA11 mutations

DPN: Biologiocal behaviour

WHO classification:

- Intermediate lesions (along with dysplastic naevus , PEM and BAPoma)

- Vast majority behave in a benign fashion.
- A subset has limited potential for locoregional spread but not distant metastatsis or death
- Complete excision sufficient.

DPN vs DPN-like Melanoma

What is allowed?

Architectural features

- Deep extension into subcutis (usually along adnexal and N-V bundles)
- Extension into arector pili muscles
- Perineural infiltration
- No gradient

Cytological features

- Lack of gradient in cell size, amount of cytoplasm, size of nuclei and amount of pigment deposition.
- Some degree of random nuclear pleomorphism
- Few mitoses (including deep ones): usually 1-2/mm2

What is not allowed?

Architectural features

- Expansile confluent growth of melanocytes instead of discrete nests/fascicles separated by collagen
- Aymmetry and uneven distribution of pigment or inflammatory reaction (exception: may be seen if part of a combined naevus)
- Necrosis

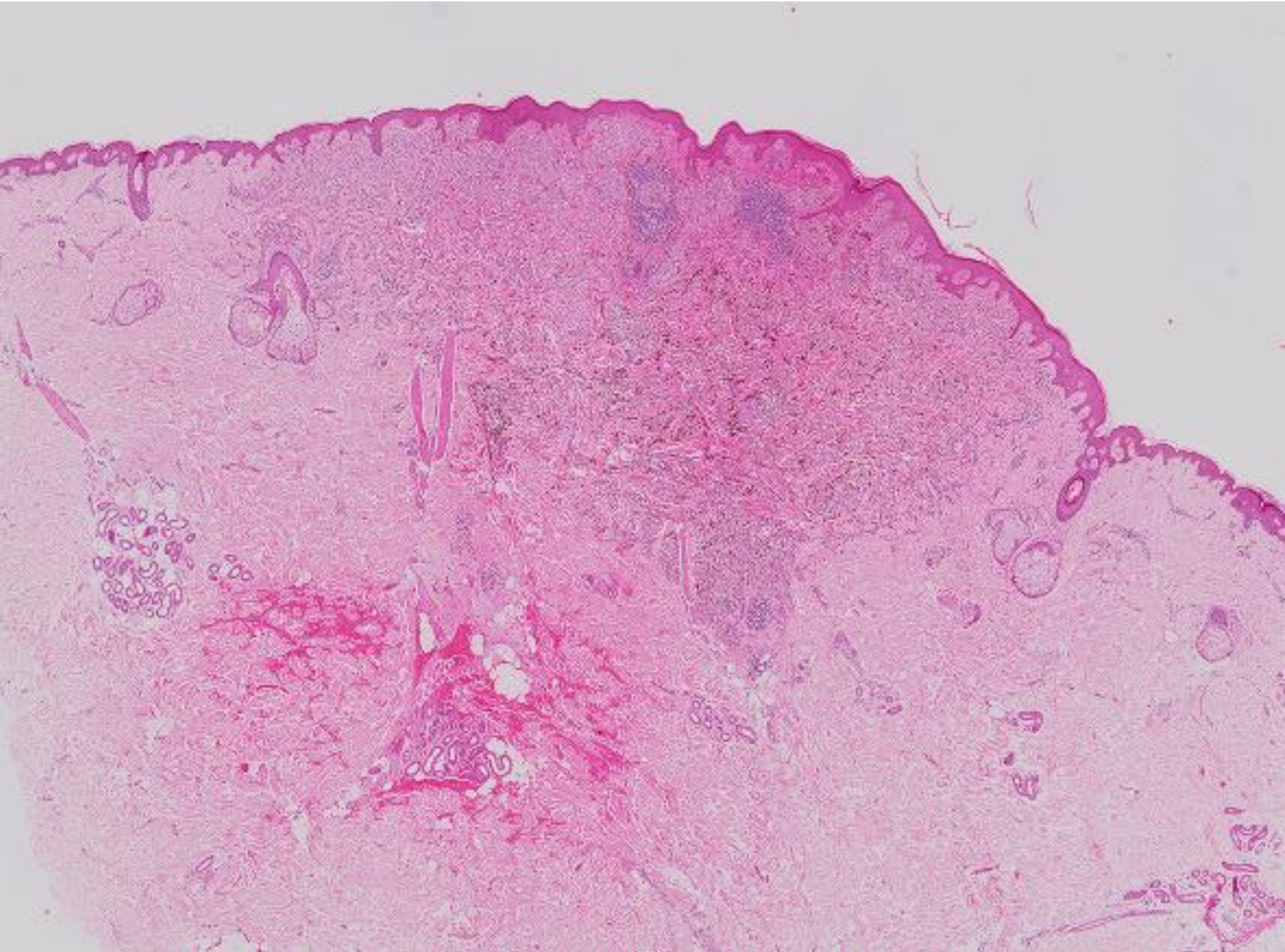
Cytological features

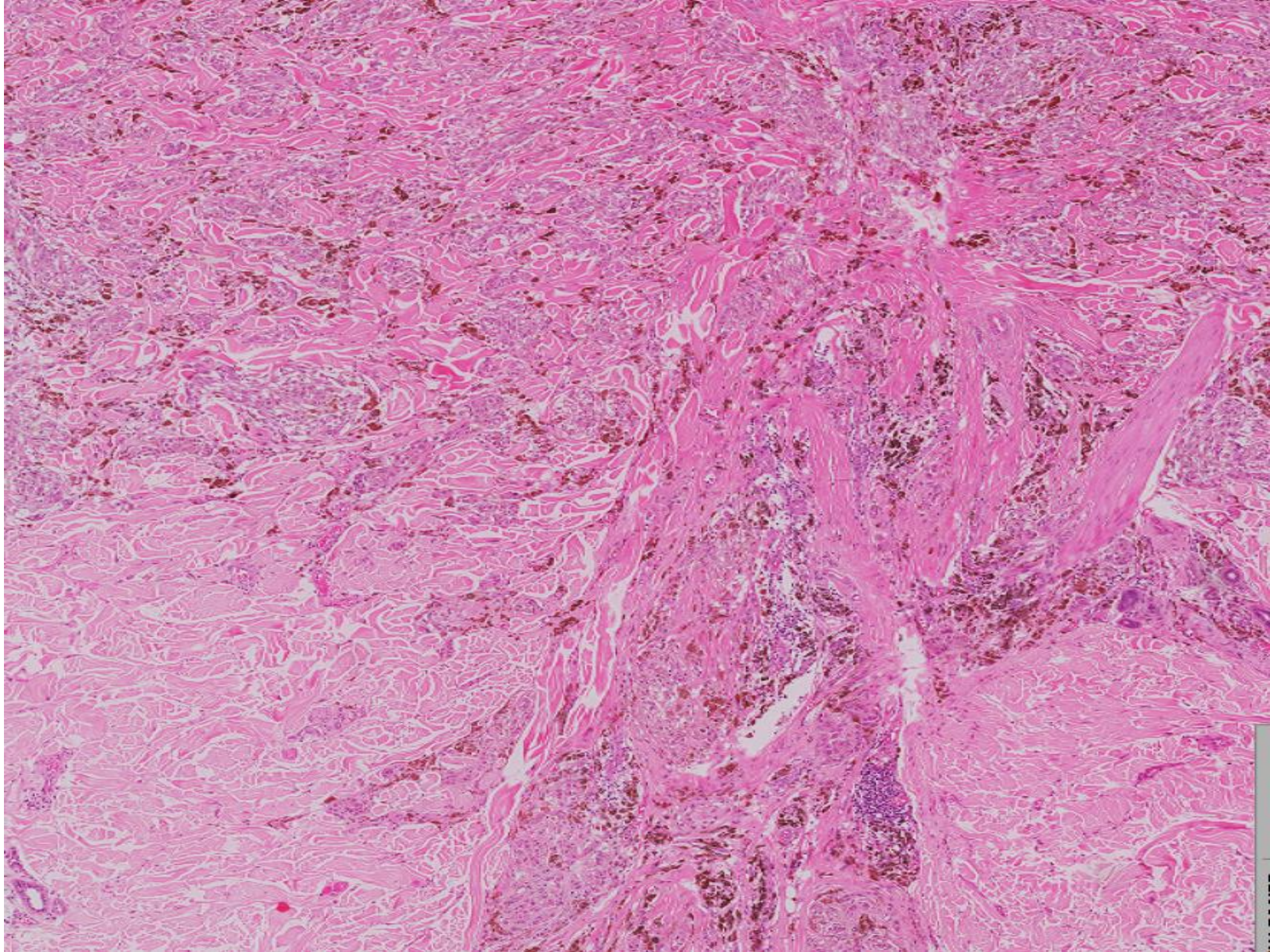
- Non random diffuse and severe atypia
- More than occasional mitoses
- Atypical mitosis

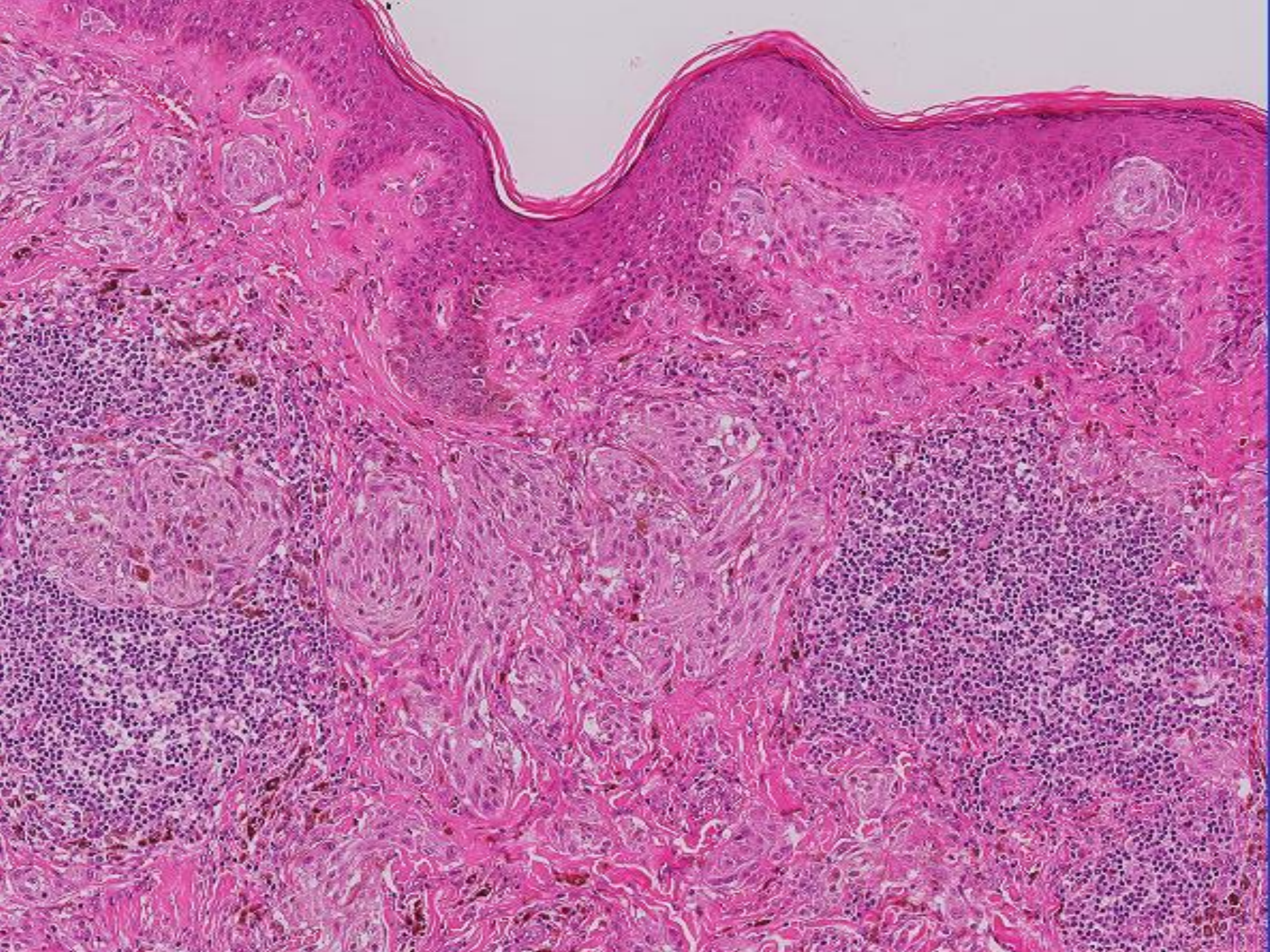
How much is TOO much!

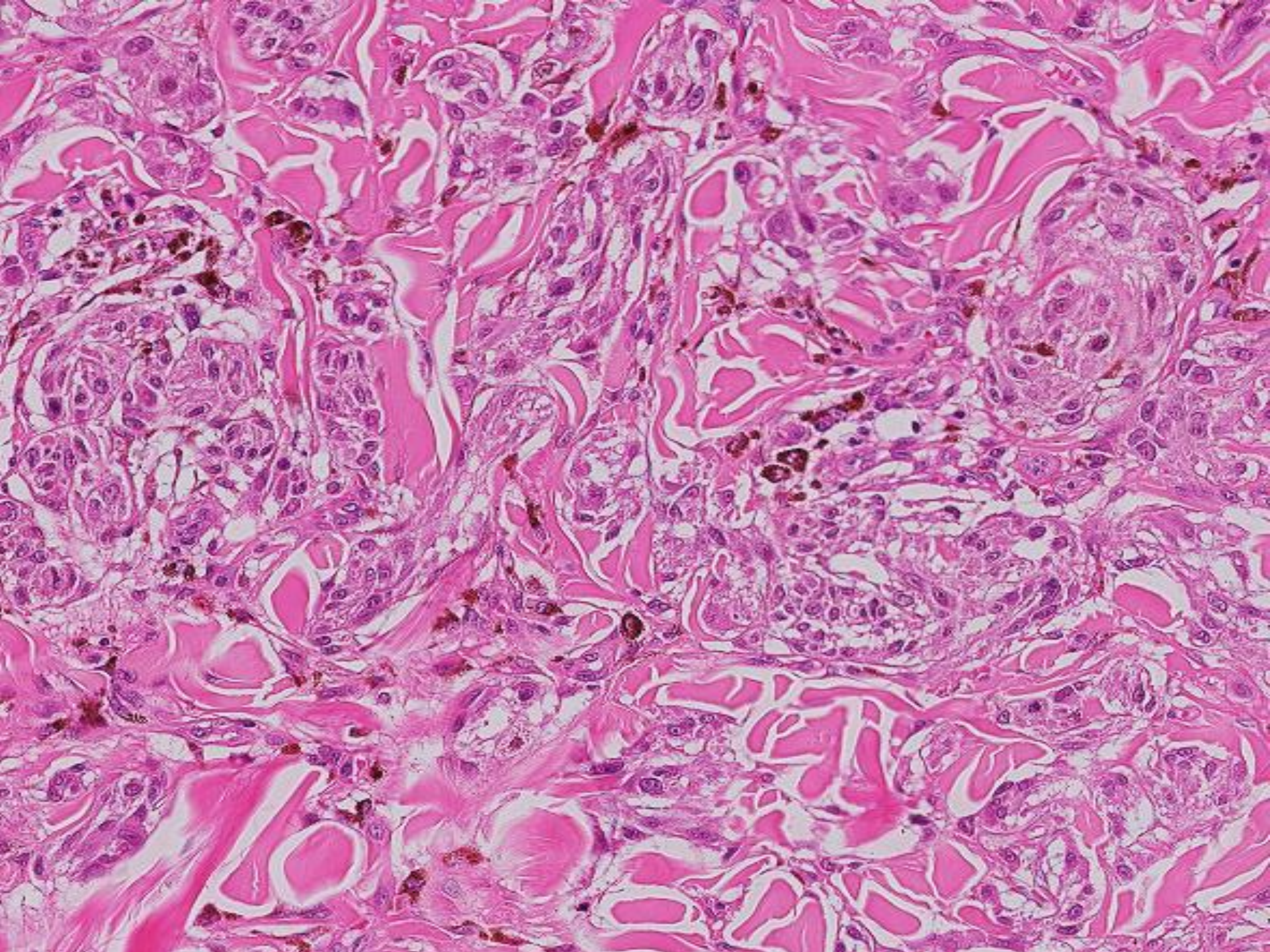
Problem Case 3

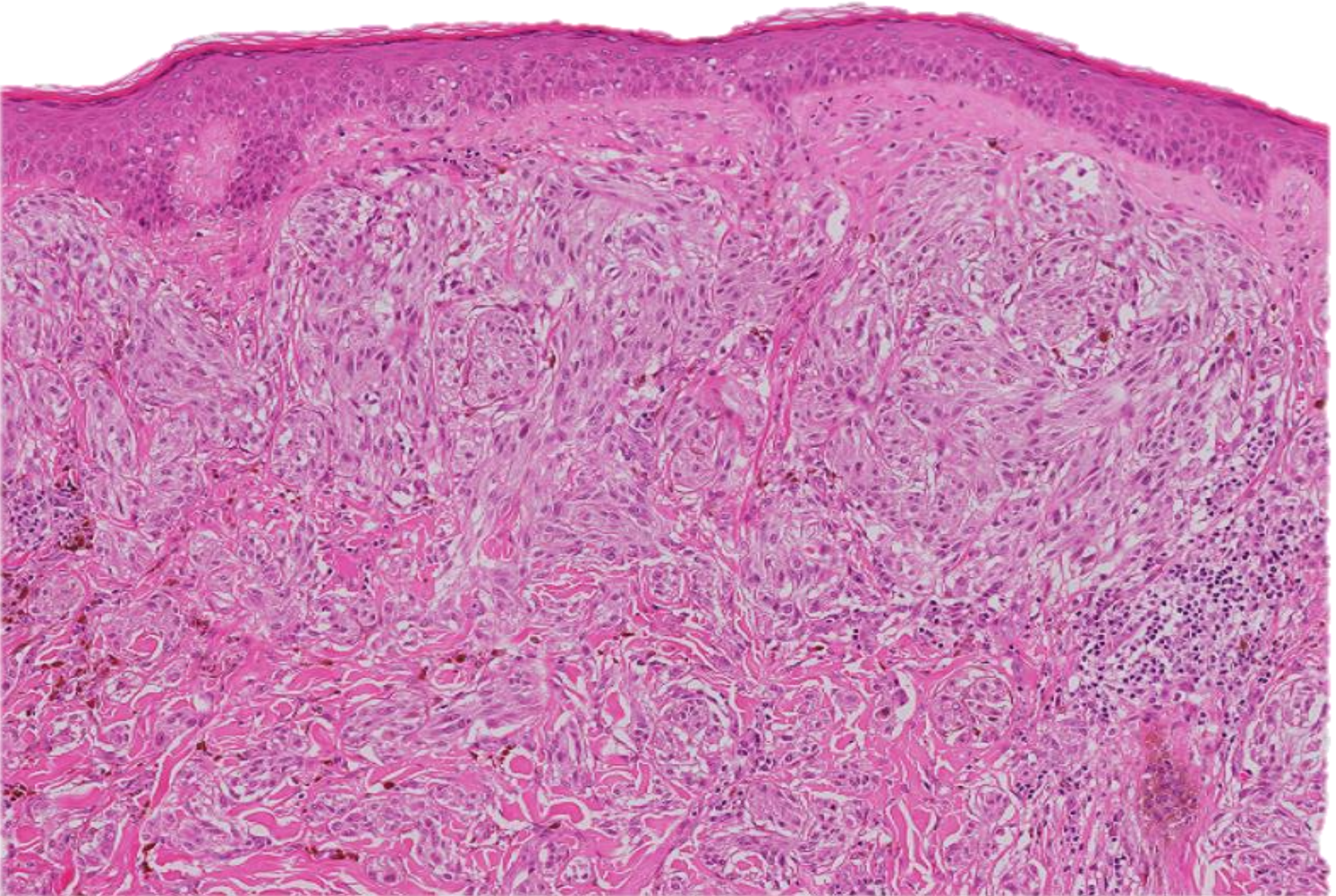
- 40/M
- Presented in 2013
- Excision of pigmented lesion from back 8x7mm
- Clin diagnosis: nodular melanoma

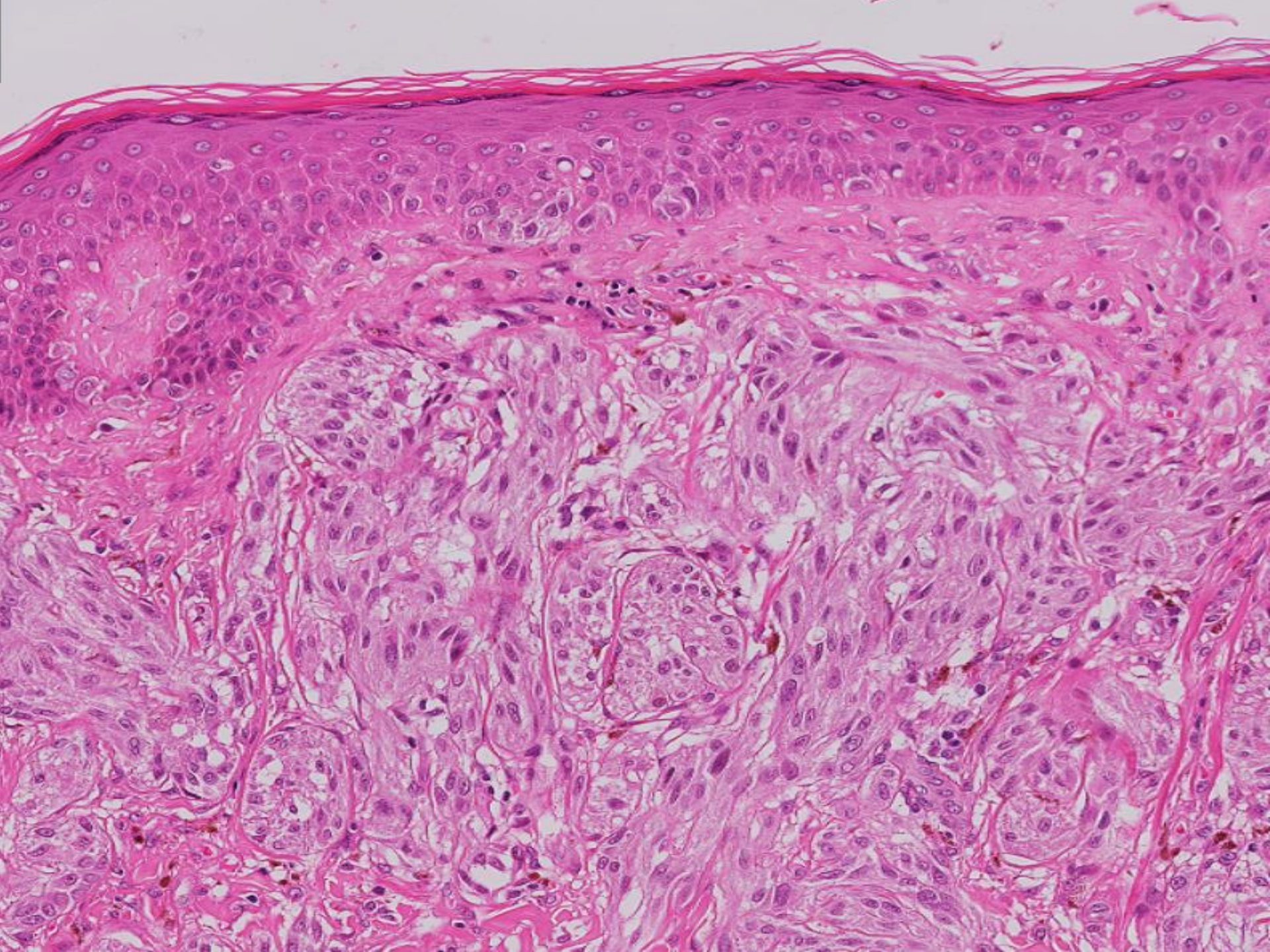


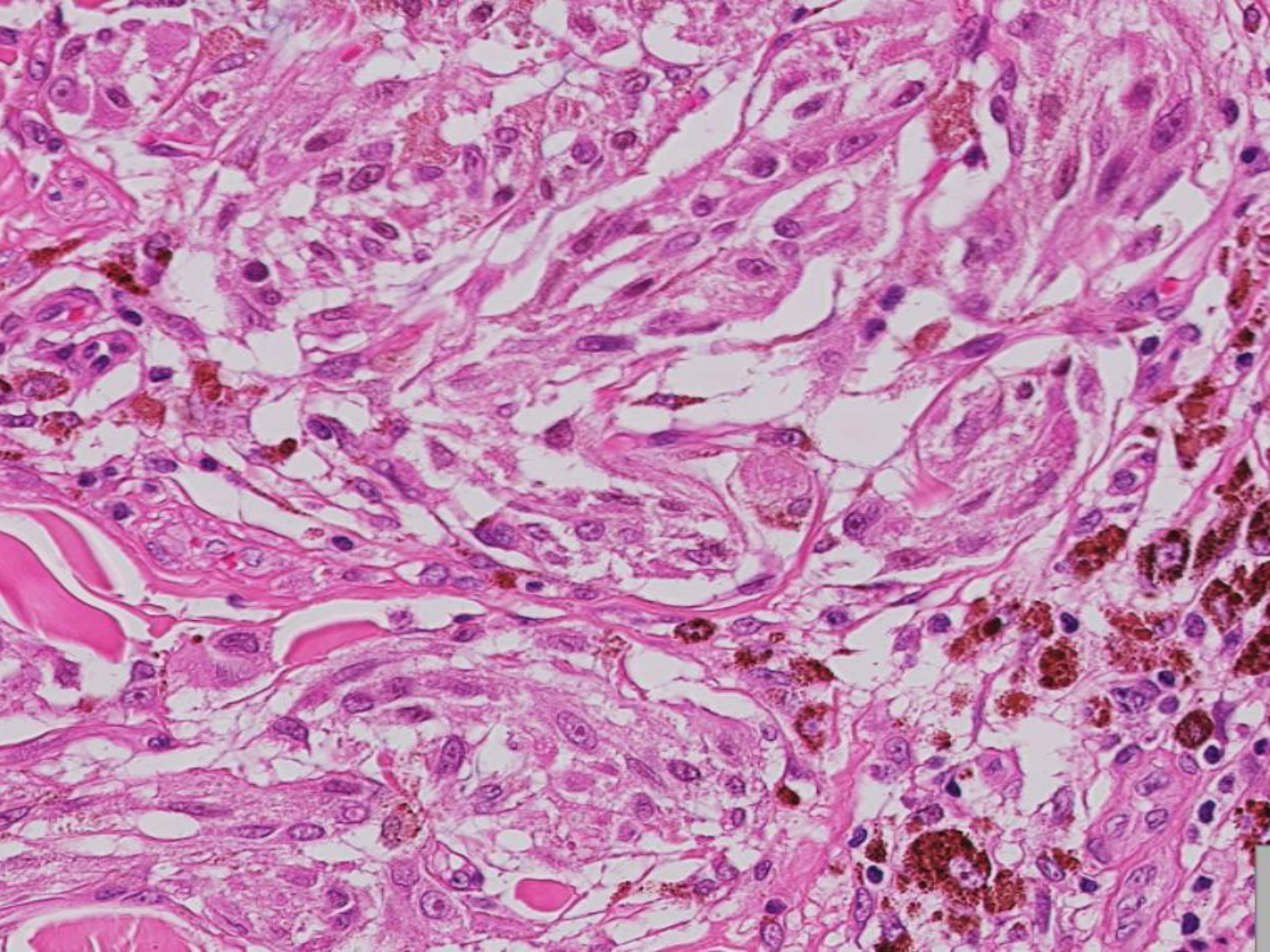


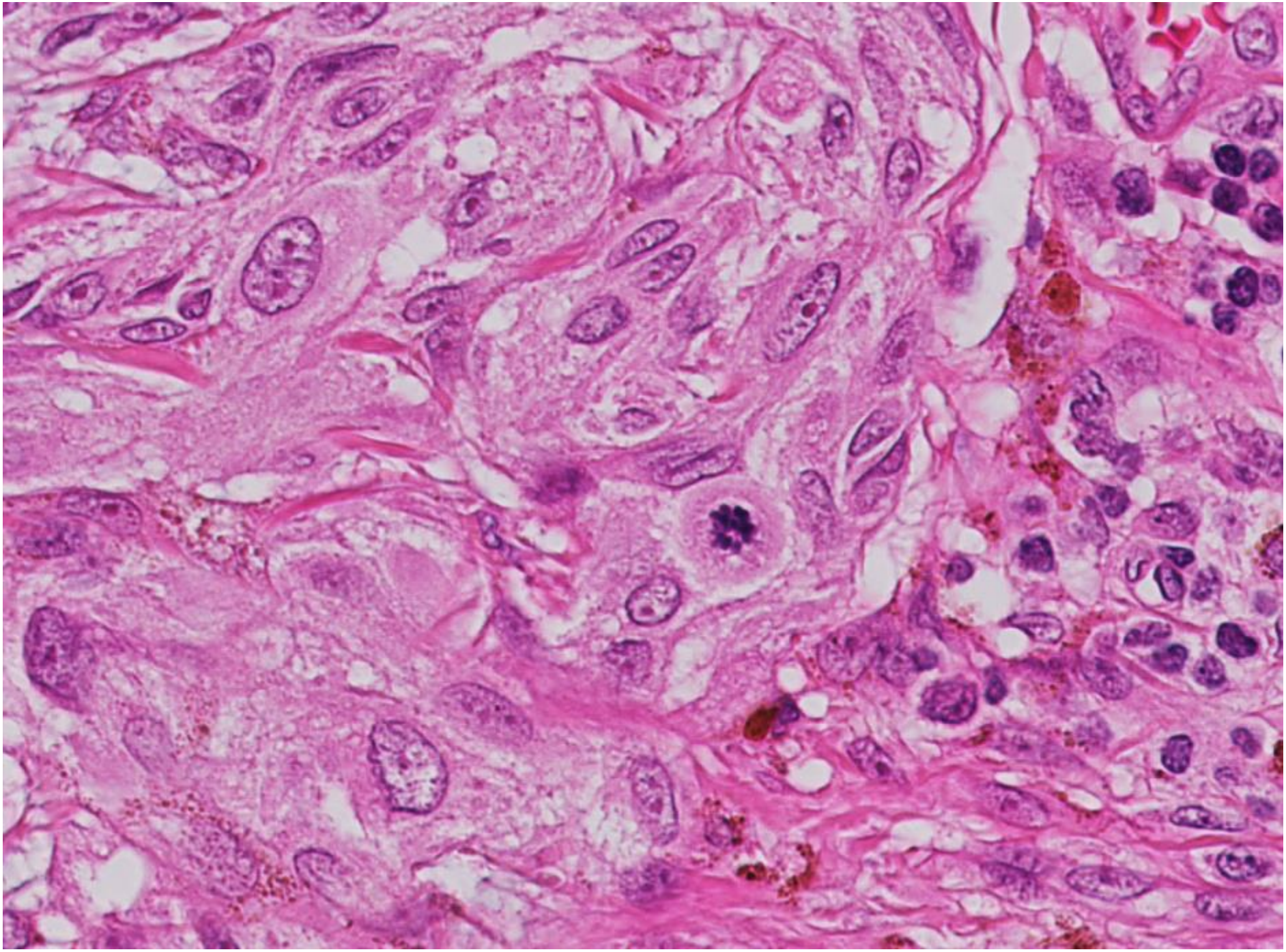












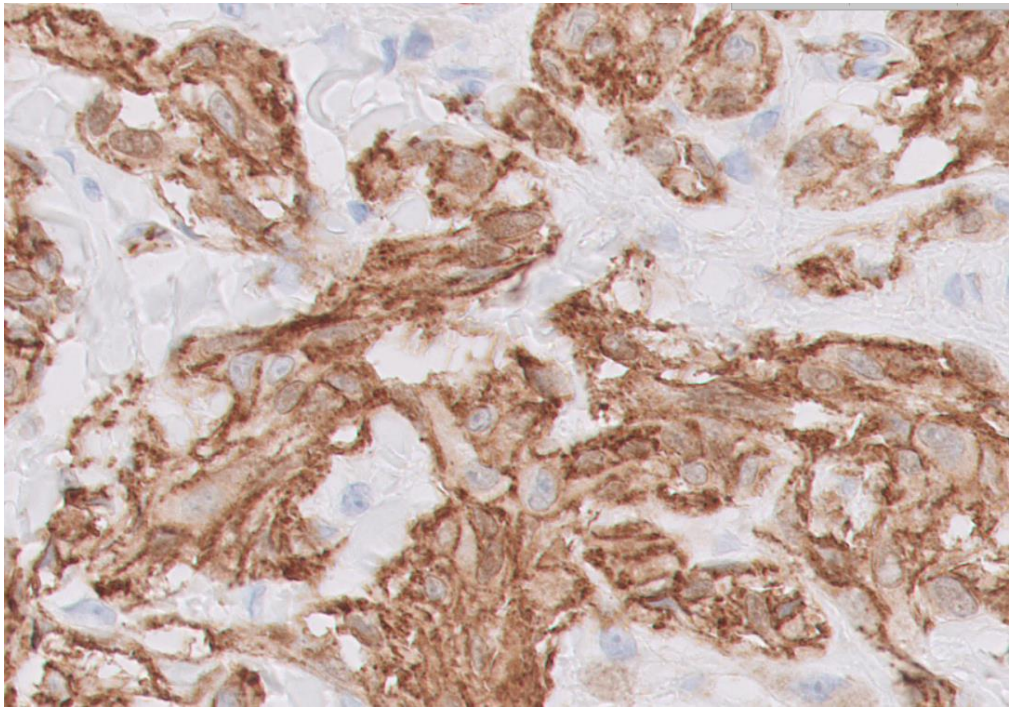
Expert opinions!

- DPN
- Atypical Spitz
- Invasive Melanoma (Breslow’s 5mm)

Management and Follow up

- Wide local excision as per 5mm thickness melanoma
- Bilateral axillary positive sentinel LN bx (subcapsular deposits) and subsequent bilateral axillary node dissection.
- 7 yrs follow up: uneventful, fit and well

Beta- Catenin



S100-ve, BRAF FISH +

Diagnosis ??

- DPN
- Atypical DPN/DPN- like borderline tumours
- DPN like Melanoma

Molecular analysis:

- Multiprobe FISH
- CGH

Take home message
DPN vs Spitz vs Blue naevi

Classical examples:

- Attention to cytomorphology and architecture can help distinguish DPN, Spitz and Blue naevi in vast majority of cases.

- Distinction important as separate set of criteria for malignancy apply to each category

Take home message
DPN vs Spitz vs Blue naevi

Challenging cases: Simple panel of 3 immunos helpful

	Blue naevus	DPN	Spitz
S100	negative/weakly positive	positive	positive
Beta catenin	negative	positive	negative
BRAF V600E	negative	positive	Usually negative

Take home message
DPN vs Spitz vs Blue naevi

Ambiguous cases

- A small subset of ambiguous cases defy classification on morphology and IHC and need molecular techniques.

The problem of a Biphenotypic Population

D/D

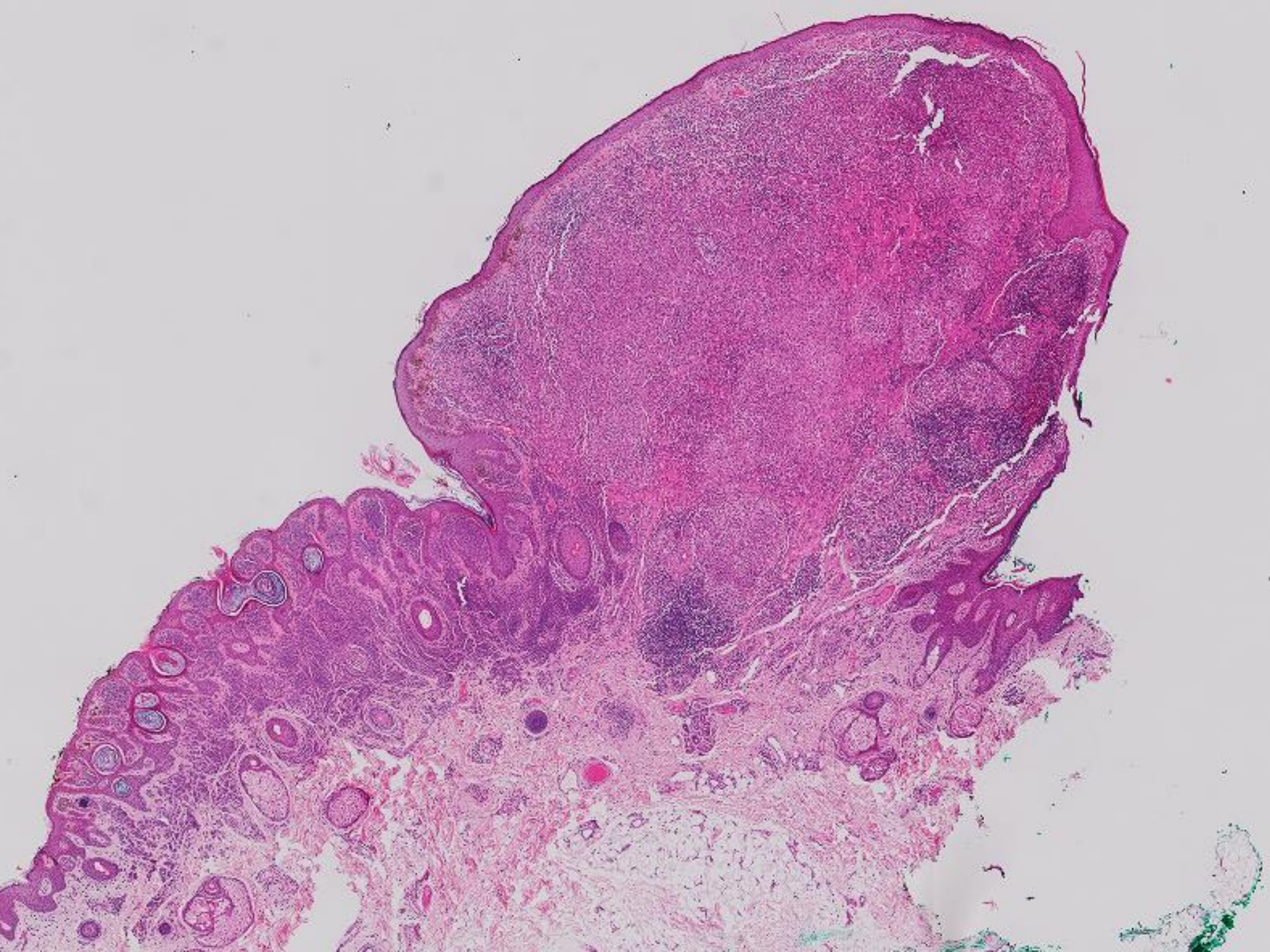
1. Combined Naevi
    - usual +blue (‘true and blue’)
    - usual + Spitz
    - usual +DPN
    - Spitz+ blue

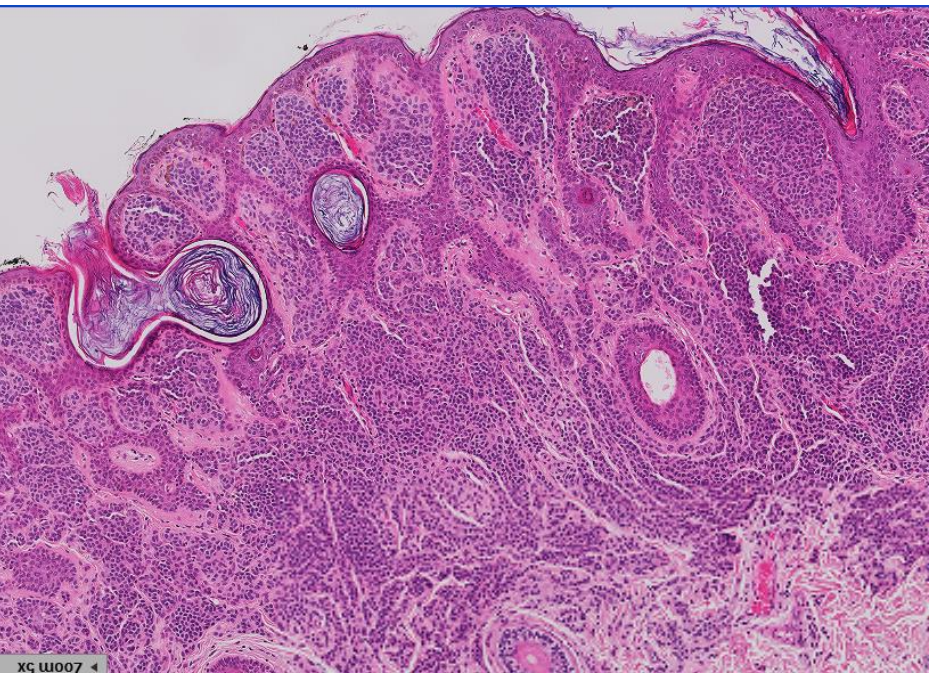
2. Proliferative nodule in a congenital naevus

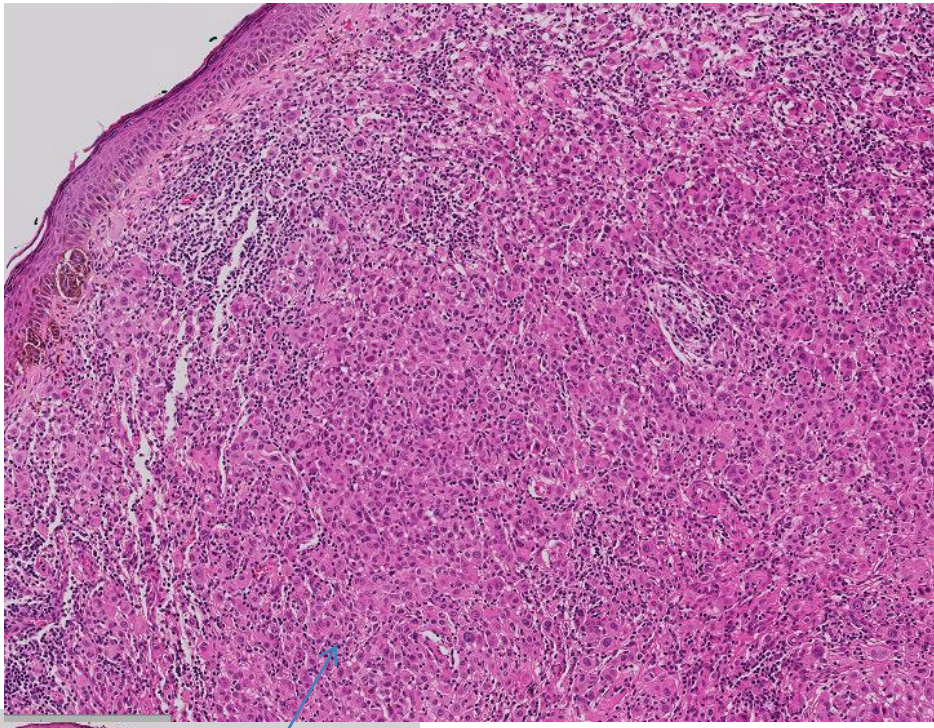
3. Melanoma arising in a naevus

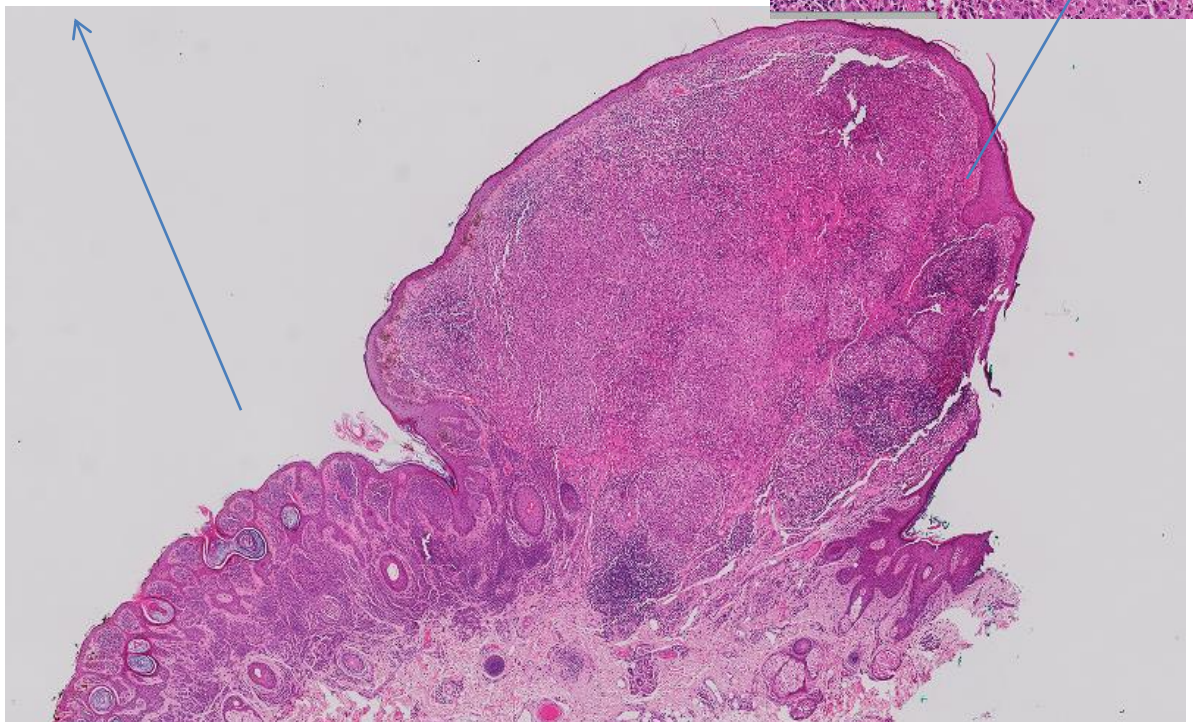
Biphenotypic pattern
Problem Case 4

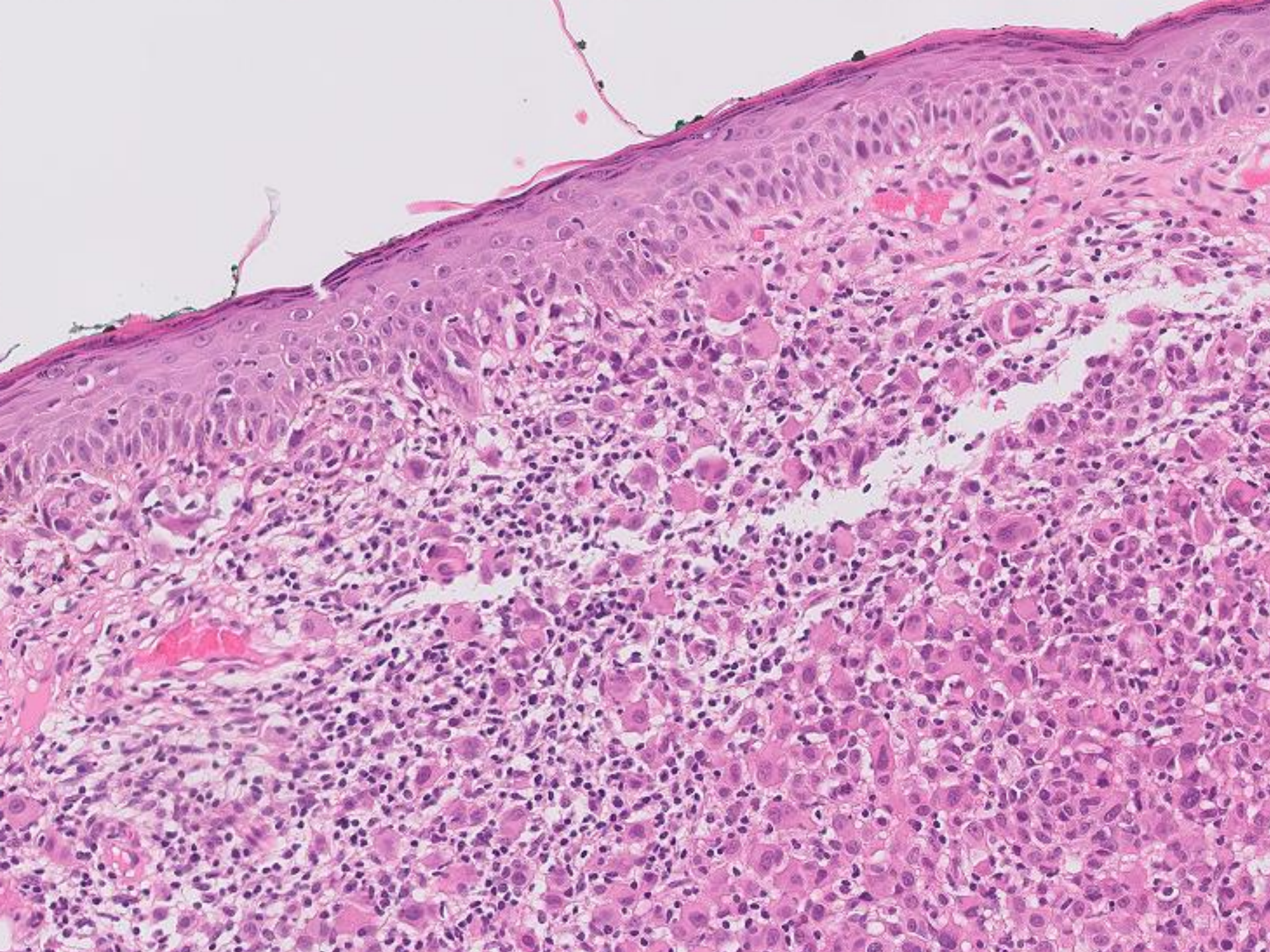
- 20/F, congenital mole, recent lump ?melanoma

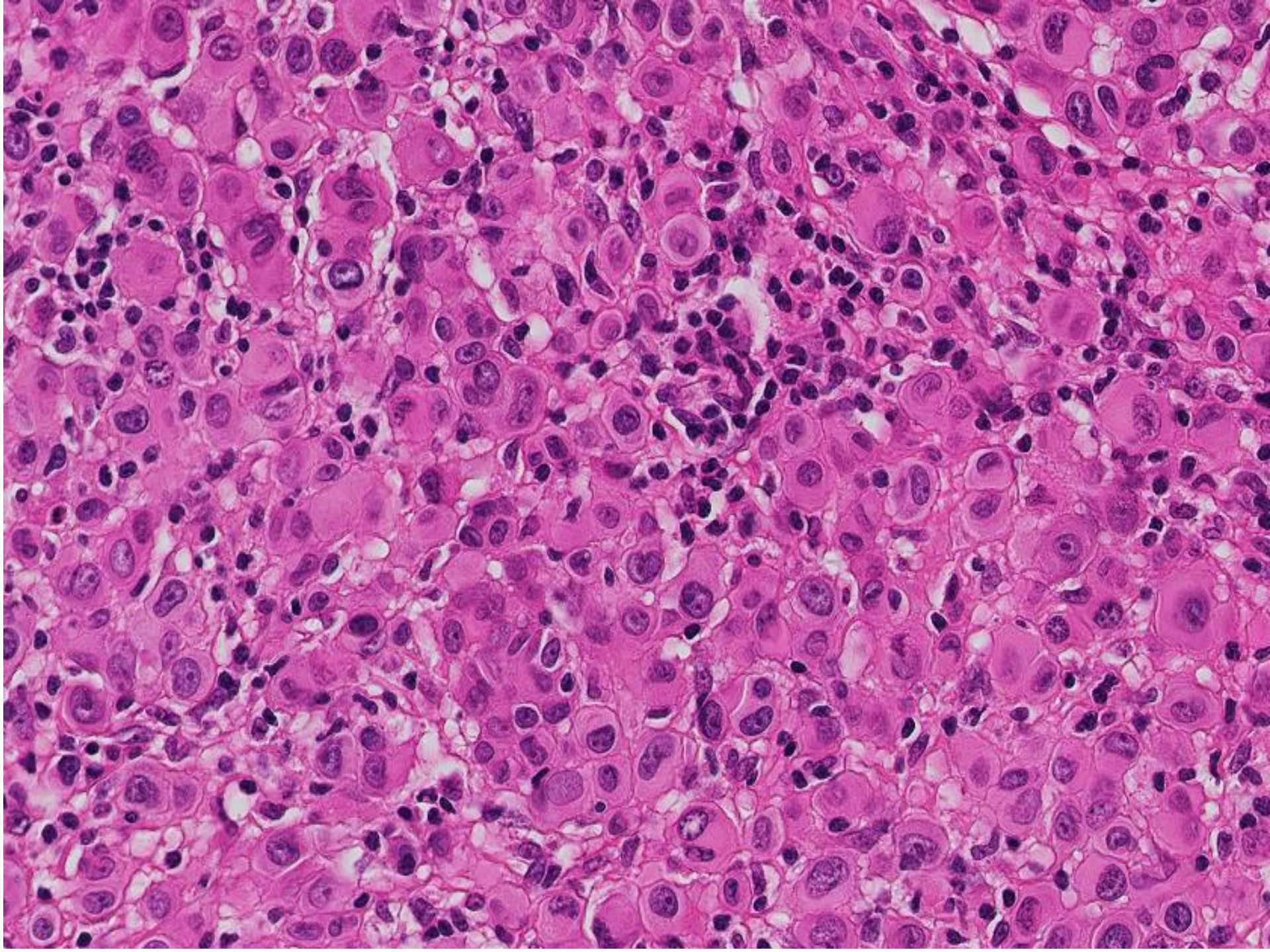


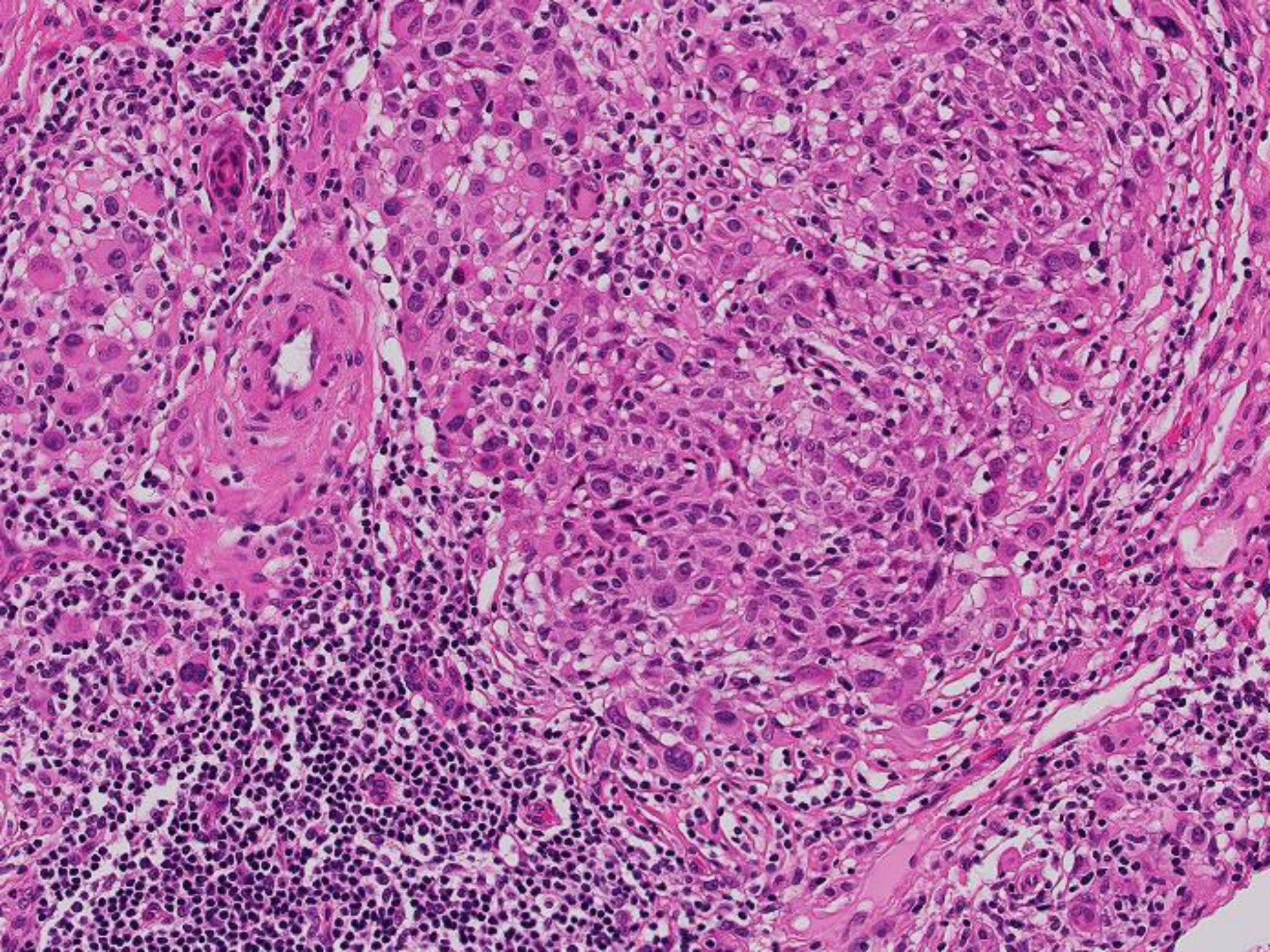

Zoom 5x



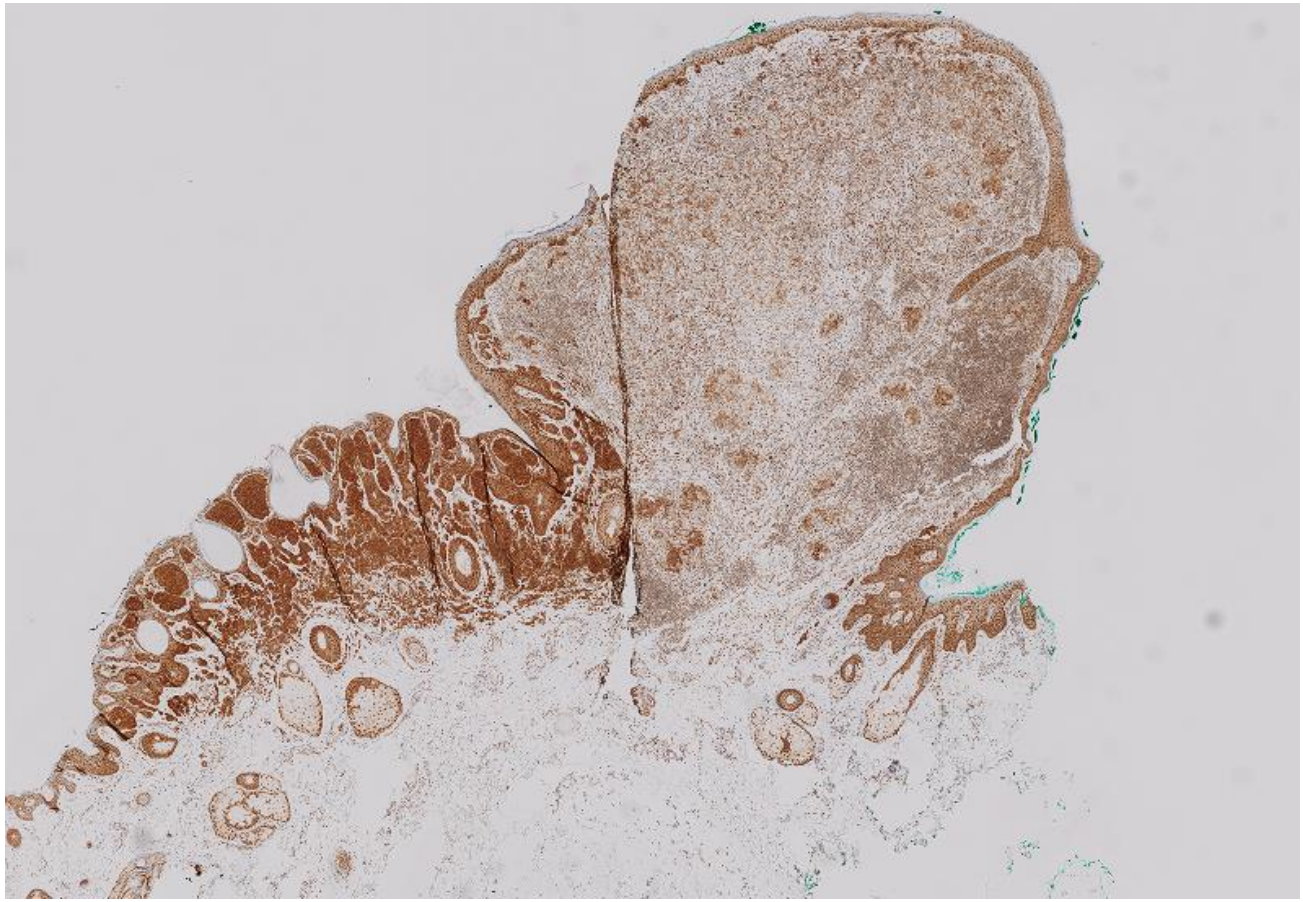


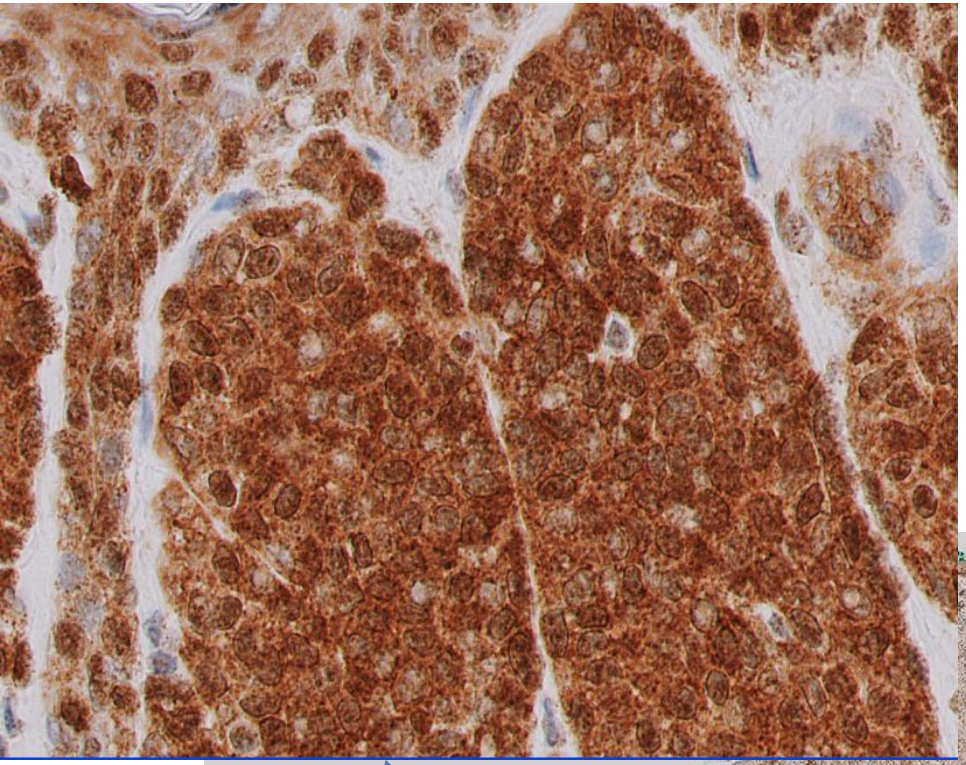


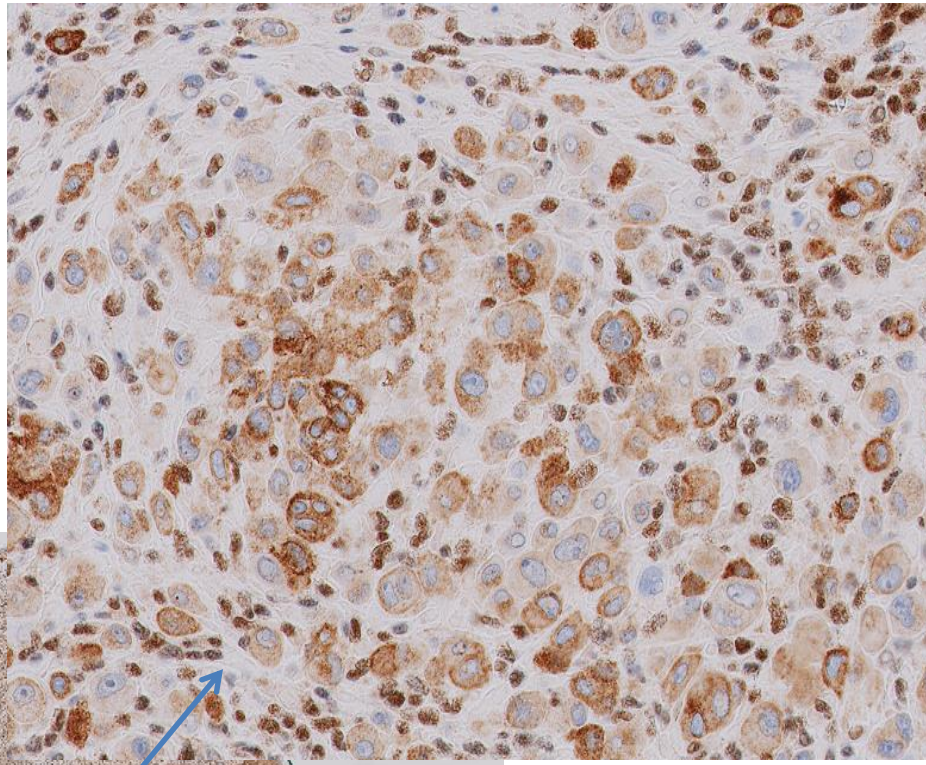


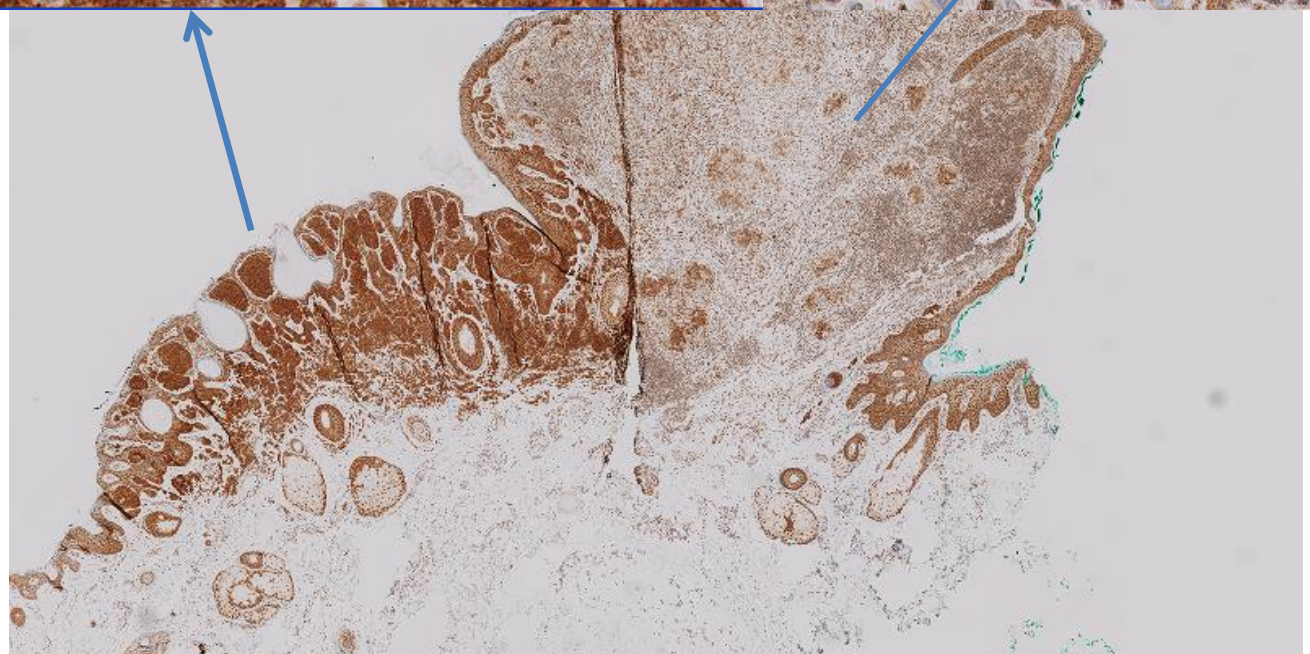


BAP1 stain









BAP 1 inactivated Tumour

- Occurs due to sporadic or germline mutation in BRCA1- associated protein 1 (BAP1) mutation

- Germline mutation associated with predisposition to malignant tumours
  mesothelioma
  uveal melanomas
  Cutaneous melanoma
  (full spectrum still not established : renal cell carcinoma, meningioma)

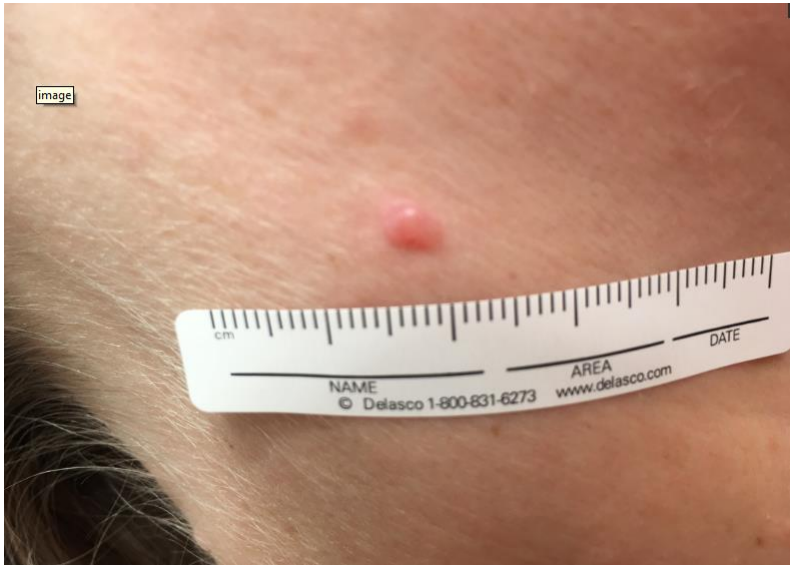
Cutaneous BIMT is a early marker of the syndrome

BAP1 inactivated melanocytic tumour (BIMT)

Synonyms:

BAPoma

Weisner's naevus



WHO 2018 recommends:

BAP1 inactivated melanocytic naevus

BAP1 inactivated melanocytoma

- **BAP1 inactivated melanocytic naevus**: naevoid cells with minimal atypia

- **BAP1 inactivated melanocytoma**: Large epithelioid cells with well defined cell borders, pleomorphic vesicular nuclei and prominent nucleoli

D/D

- Spitz tumour
- Melanoma

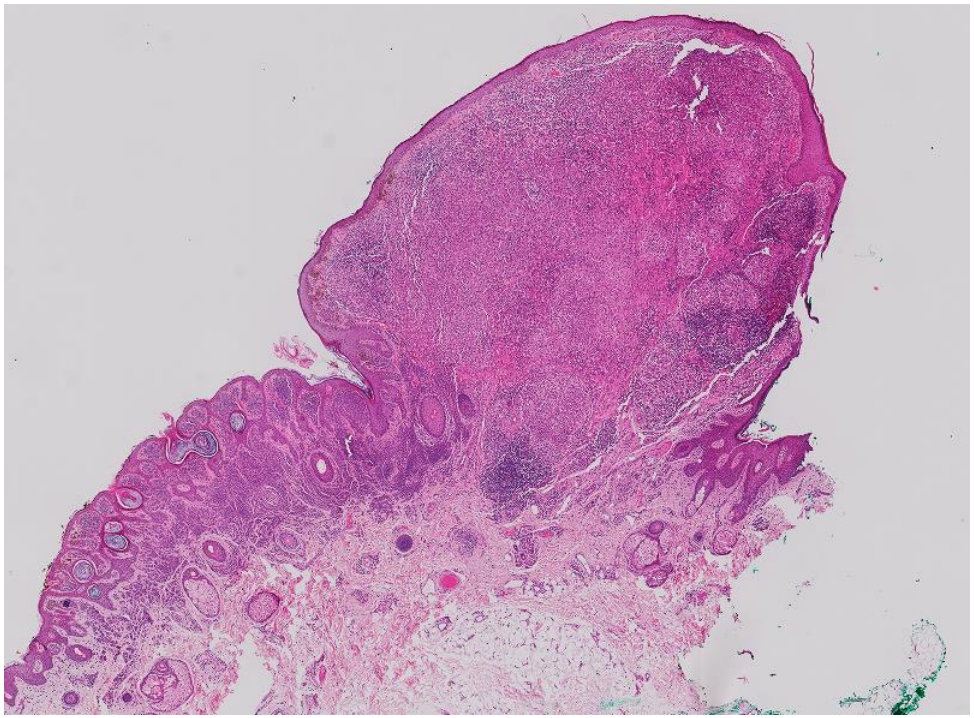
Spitzoid lesion

When to order BAP 1 ??

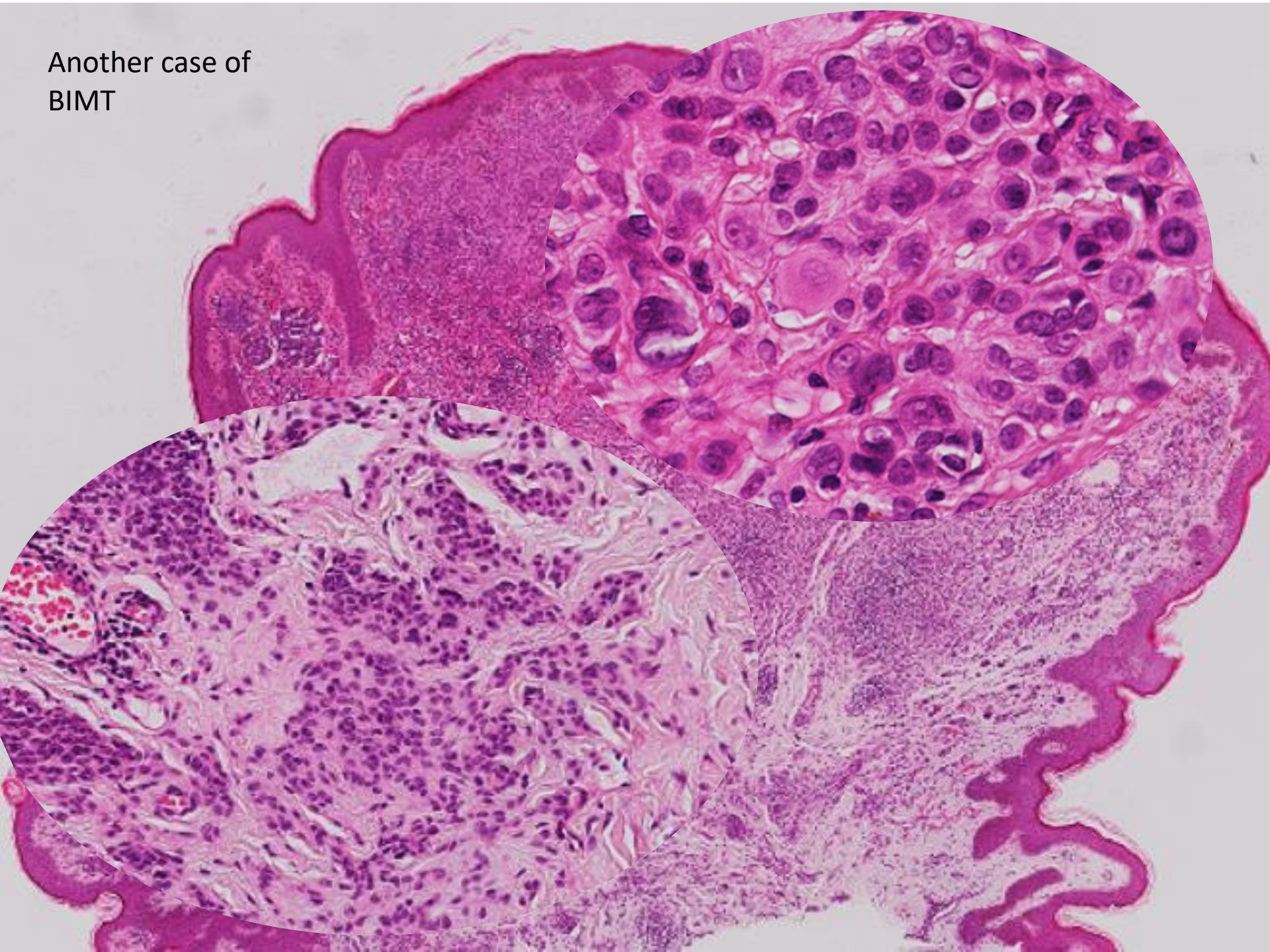
When to order BAP 1 in a Spitzoid lesion

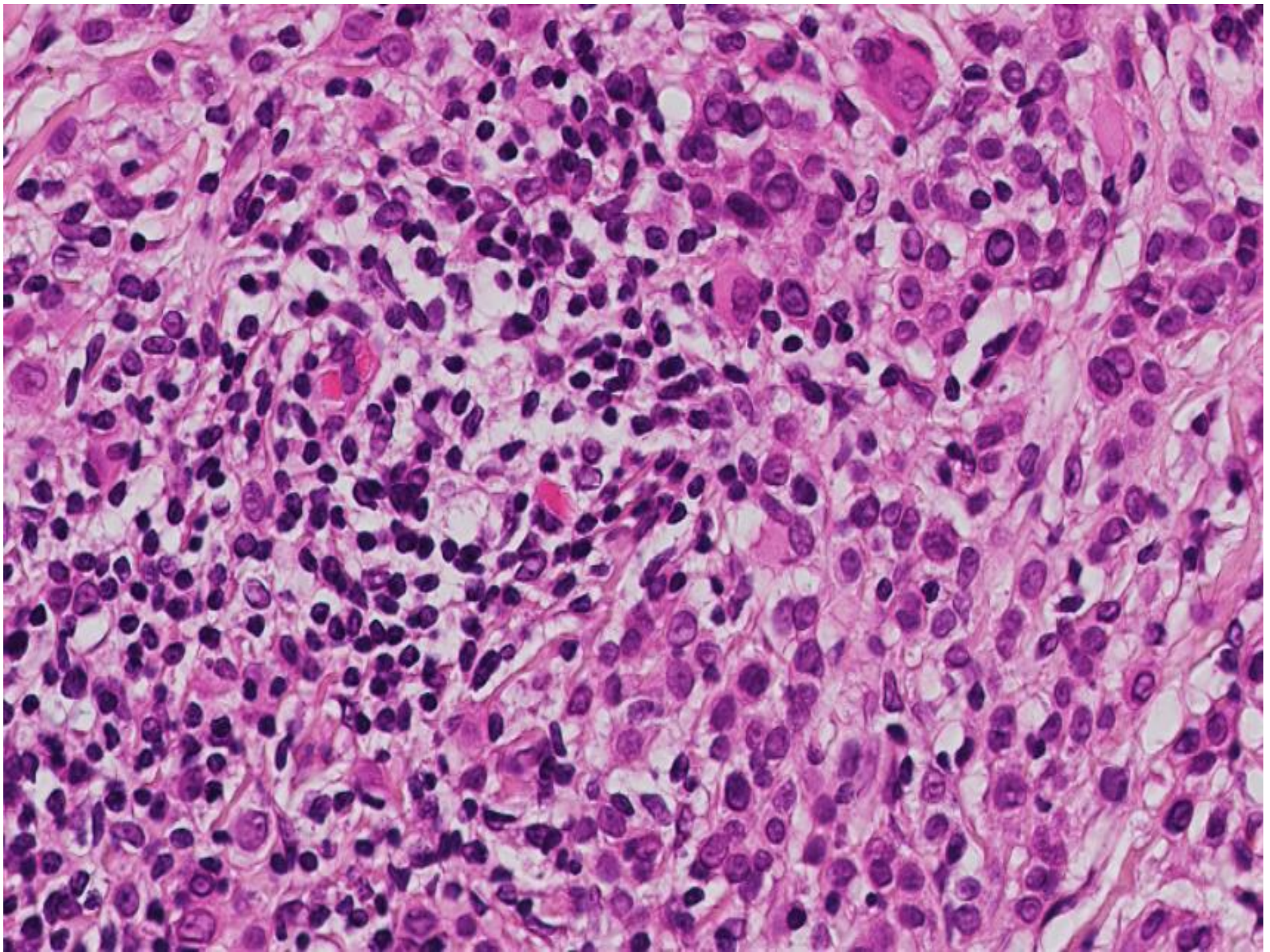
Clues to BIMT in a lesion with Spitzoid cytomorphology:

- Predominantly intradermal proliferation
- Usually occurs as part of a combined naevus
- No maturation with depth
- Nesting or cobble stone pattern
- Associated lymphocytic infiltrate
- An occasional mitosis may be seen, including deeply located

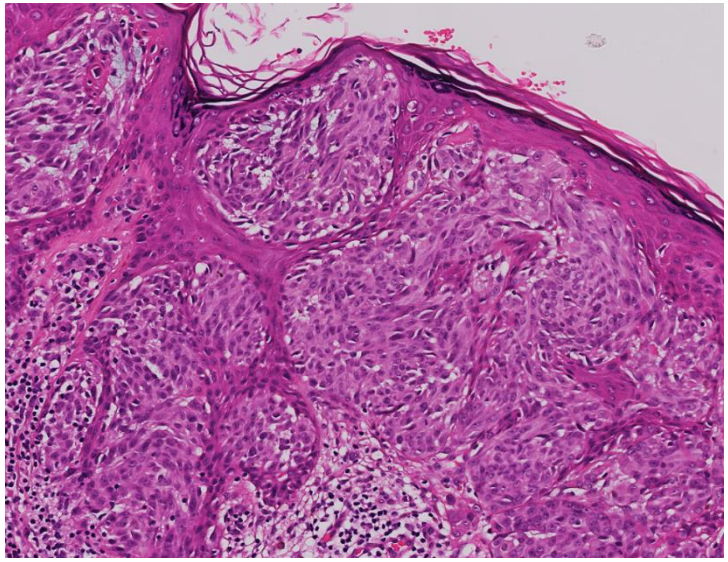


Another case of
BIMT



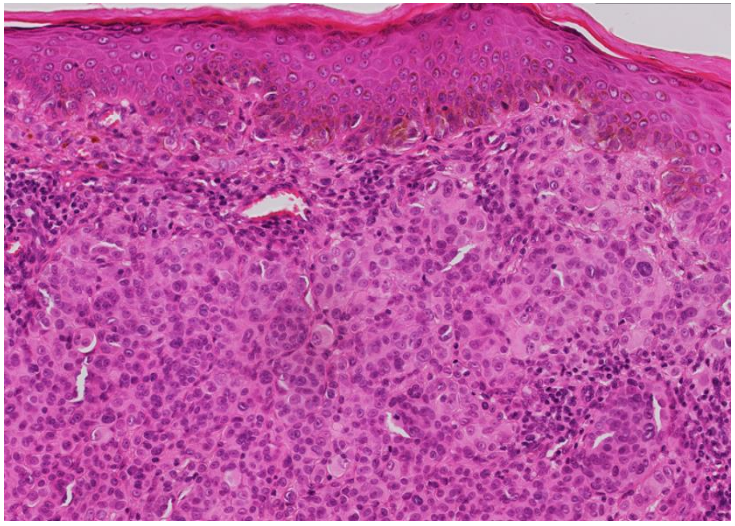


When NOT to order BAP 1!



Conventional
Spitz

BIMT



Features usually not seen in BIMT

- Prominent junctional component
- Spindled melanocytes
- Kamino bodies
- Epidermal hyperplasia.

BAP1 stain does not differentiate benign from malignant!

Features of malignancy: destructive growth, frequent mitoses, necrosis

Diagnosis: BAP 1 inactivated tm!

What to do next?

What to do next?

1. Indication for germline testing:

   2 or more cutaneous BIMT

   and/or

   Personal/Family history of mesothelioma or uveal melanoma

What to do next?

2. Management of cutaneous BIMT:

Most follow a benign course

If incompletely removed, advise complete excision (particularly for BAP1 inactivated melanocytoma)

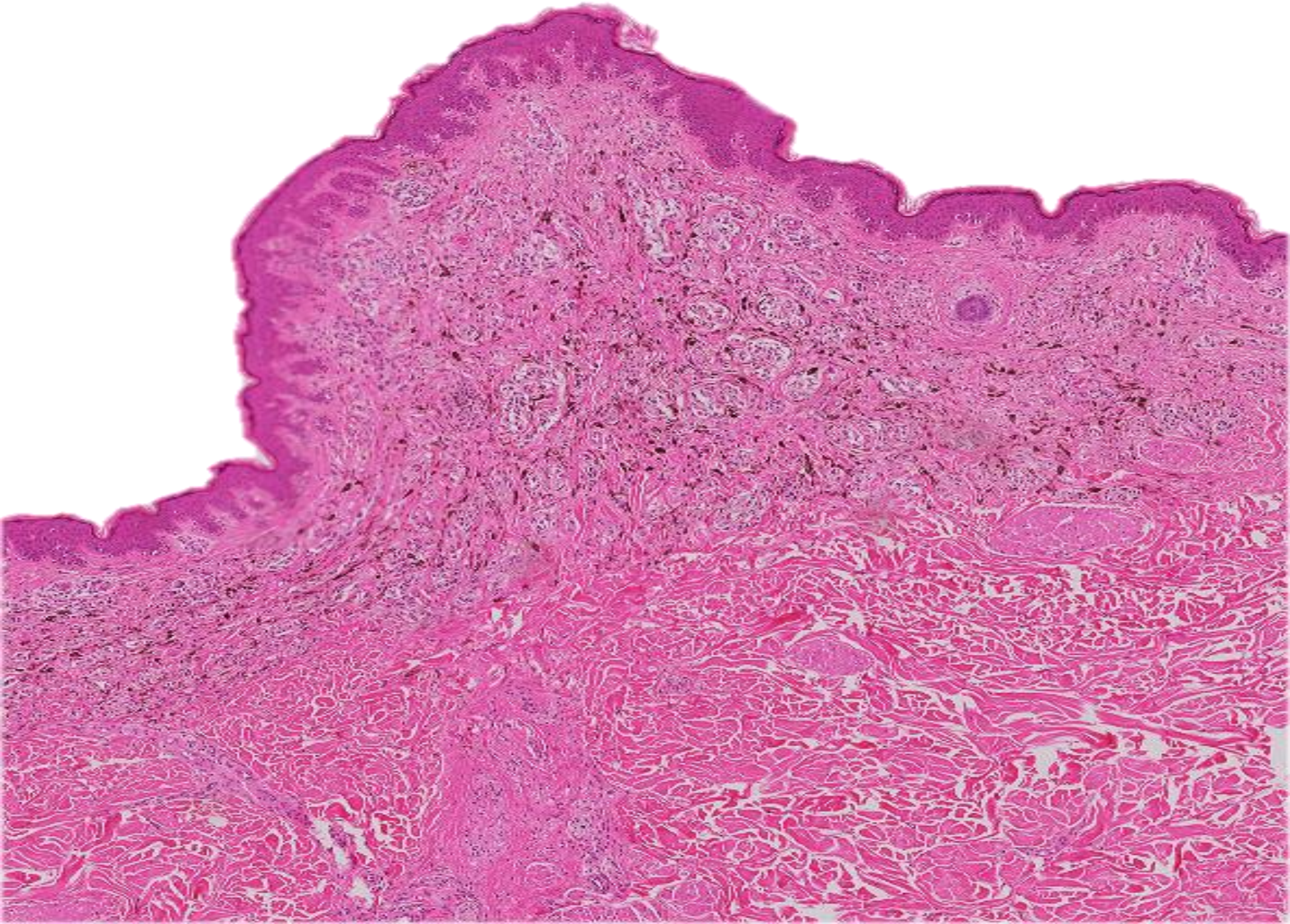
Uneventful course in most studies but paucity of studies with sufficient follow up to definitely determine outcome.

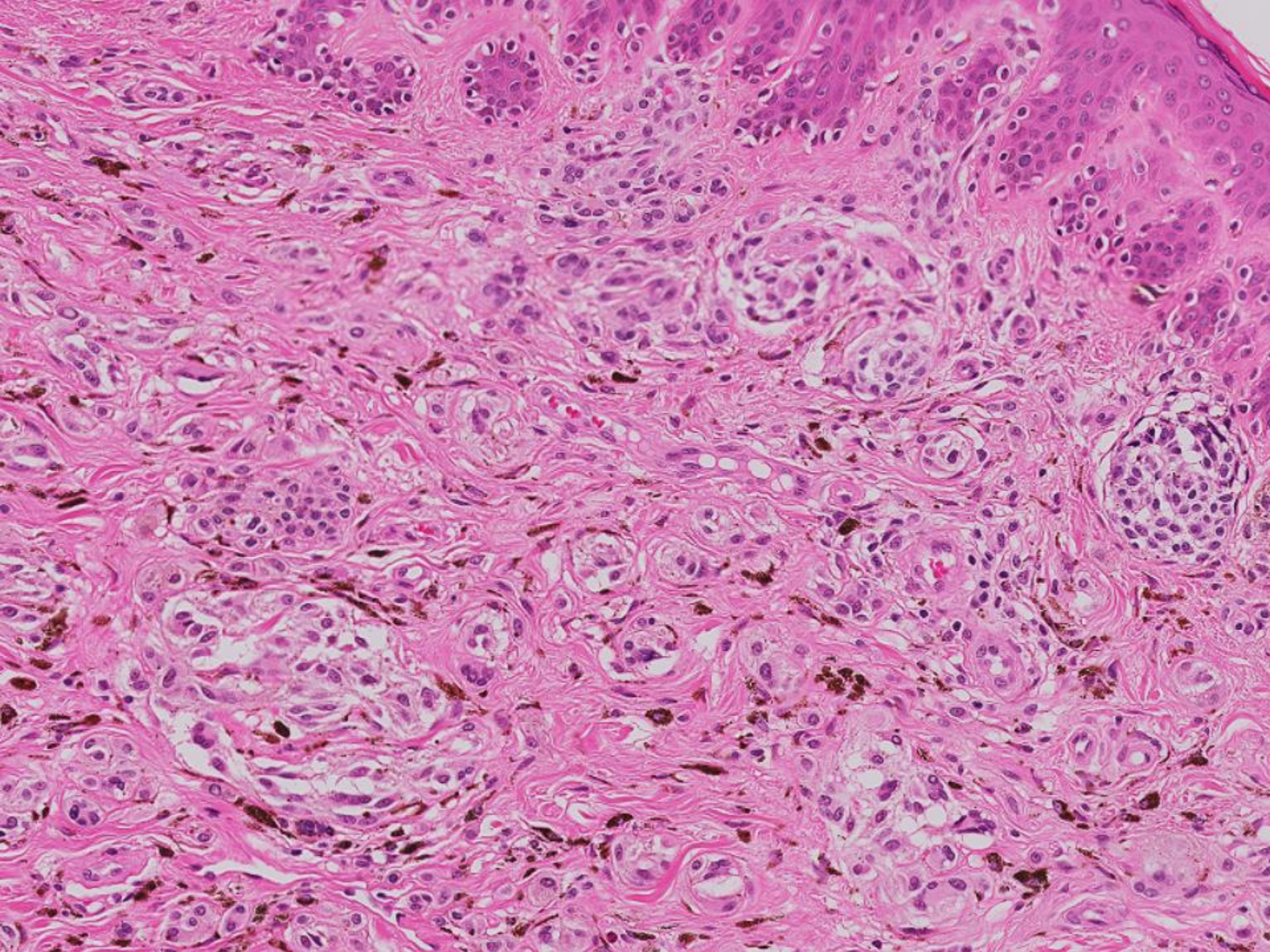
Atleast some cutaneous BIMT have the potential to become melanoma (hence categorised as intermediate in WHO classification)

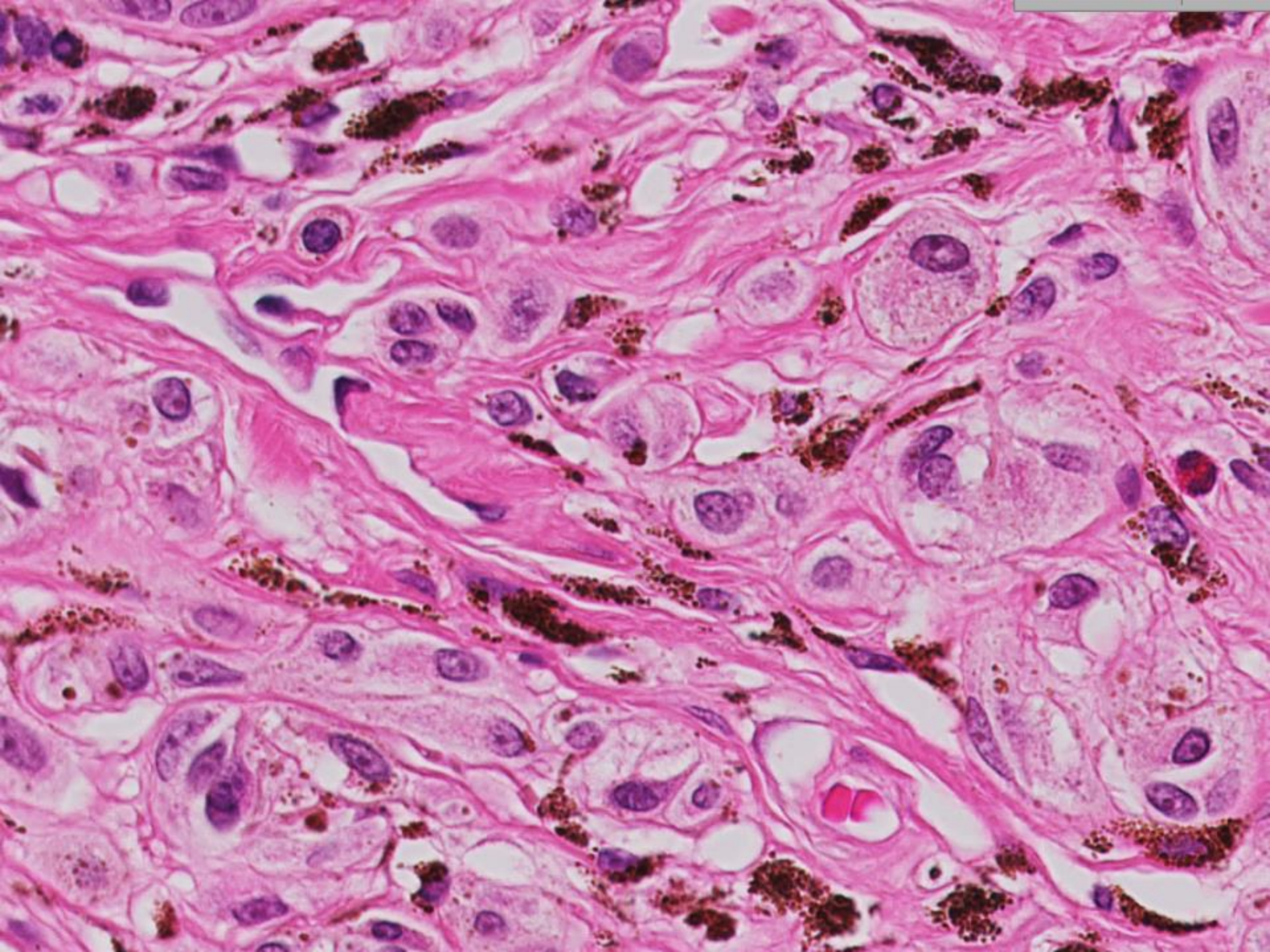
Biphenotypic Pattern
Problem Case 5

59/M

Hyperpigmented lesion mid back with veil
?melanoma





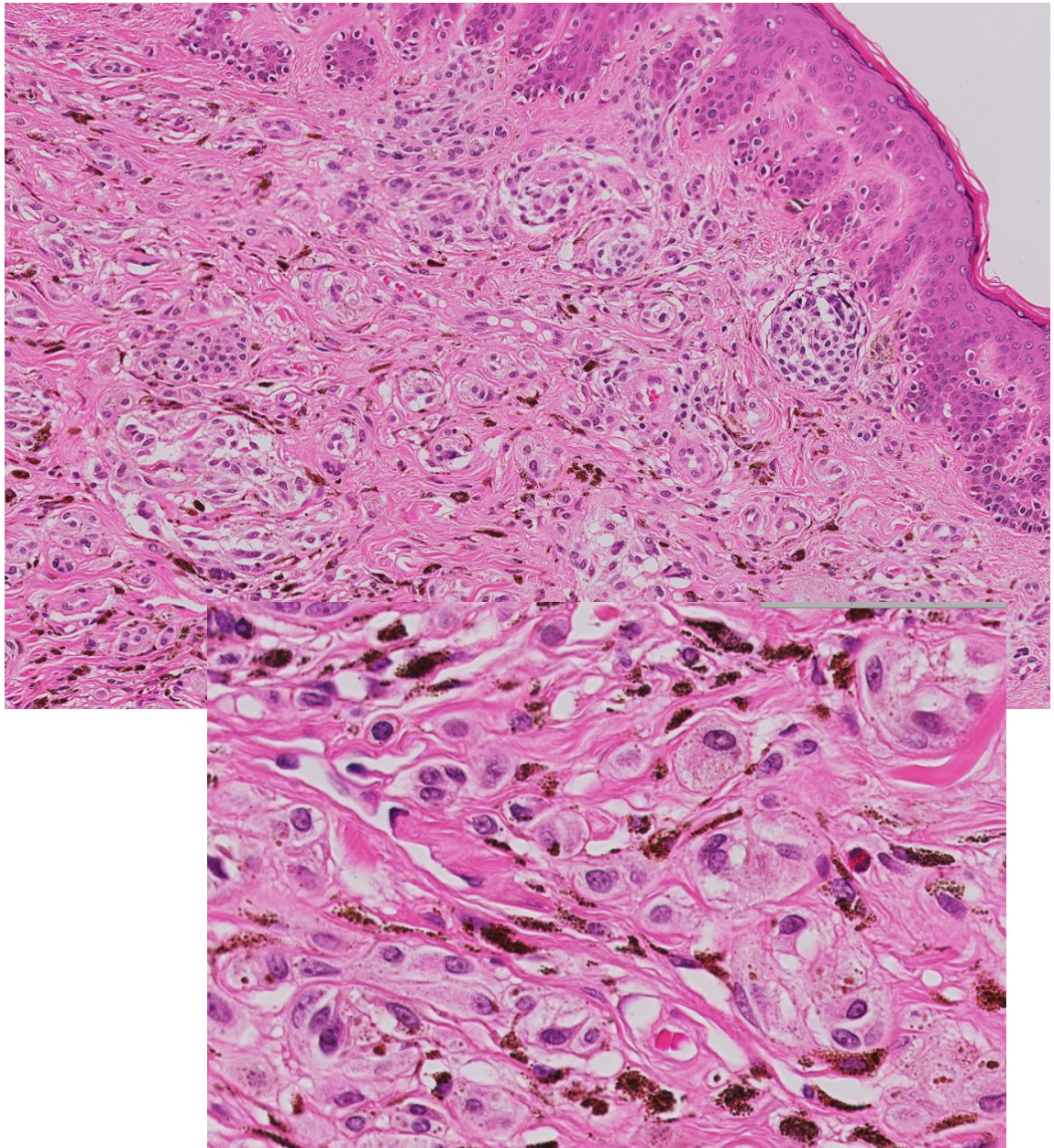


Original report

Biphenotypic lesion

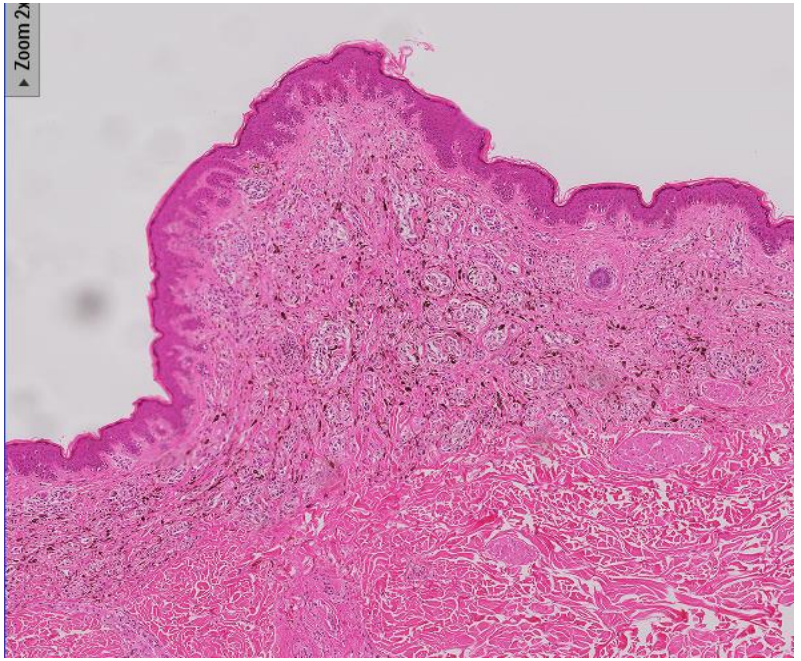
Diag: Combined Naevus (True and Blue)

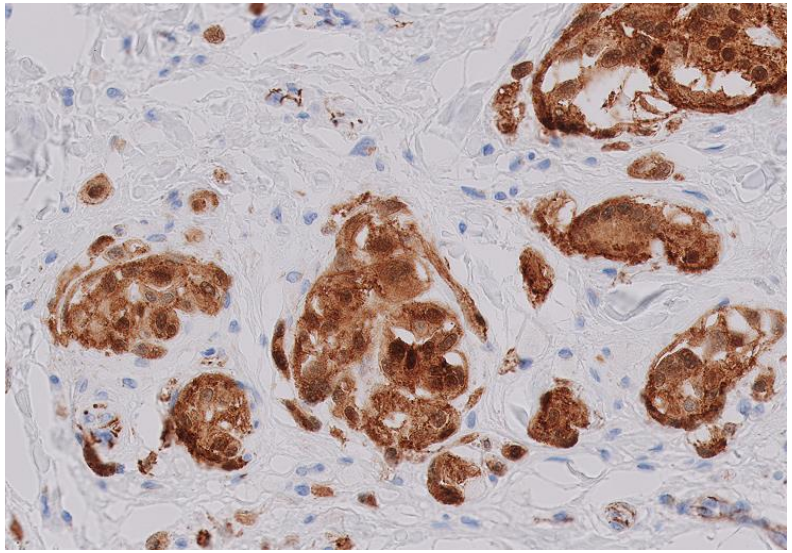
Attention to cytomorphology!!



Superficial variant of DPN

- DPN may not be ‘deep’ or ‘penetrating’!
- Often occurs as part of a combined naevus
- No blue element in index case.





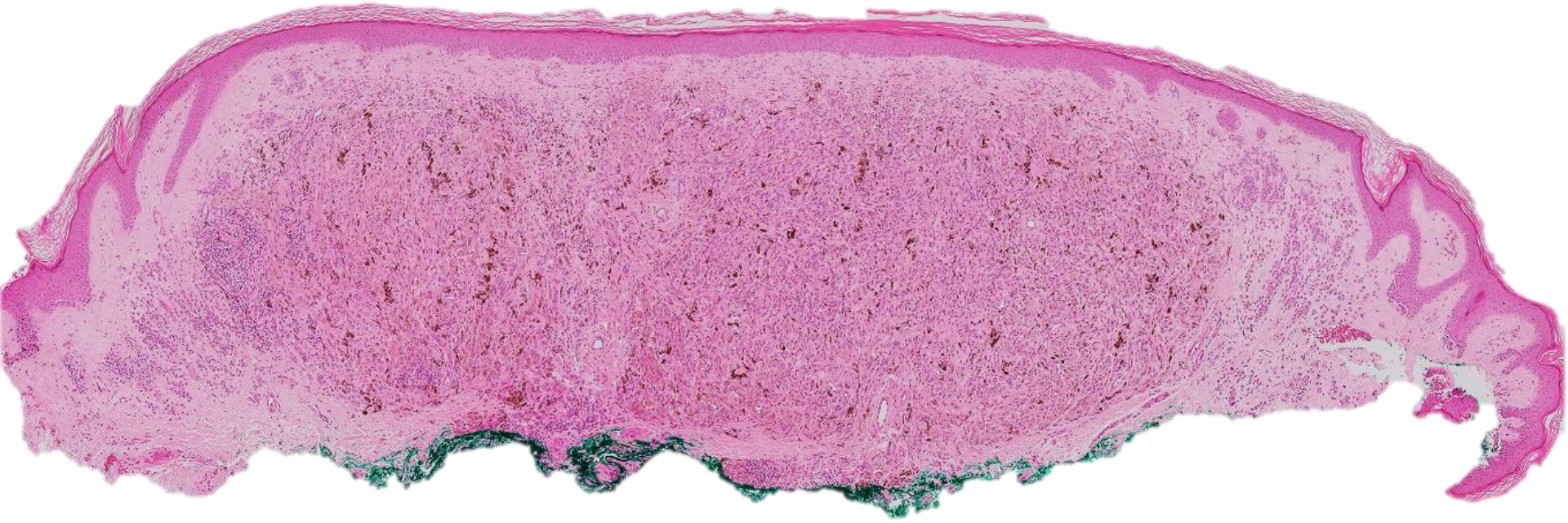
Beta catenin

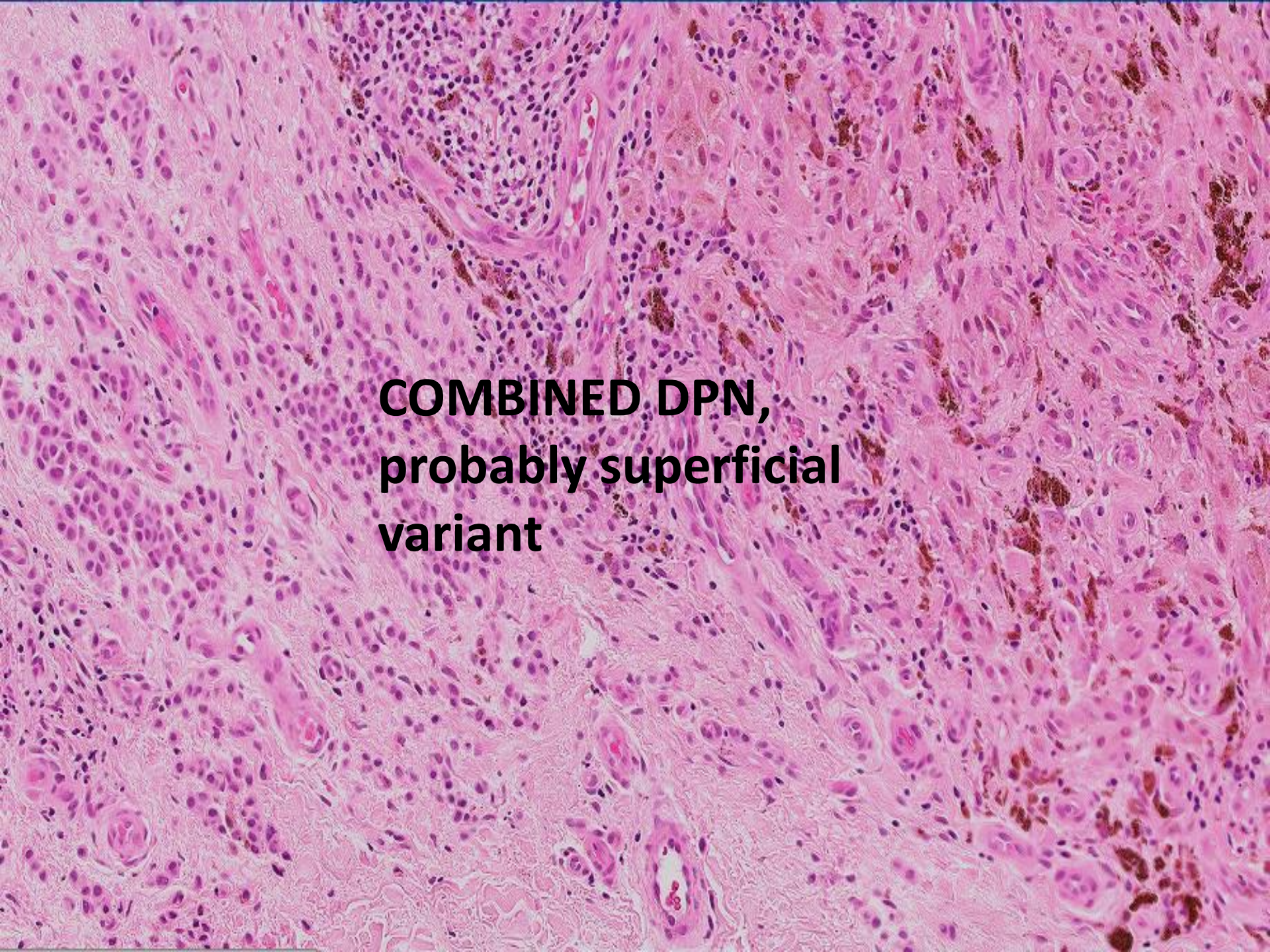
Superficial variant of DPN

Synonyms:

- Combined naevus with atypical epithelioid cell component
- Clonal naevus
- Naevus with phenotypic hetergeniety

Problem case 5: sent as ?melanoma arising in a nevus



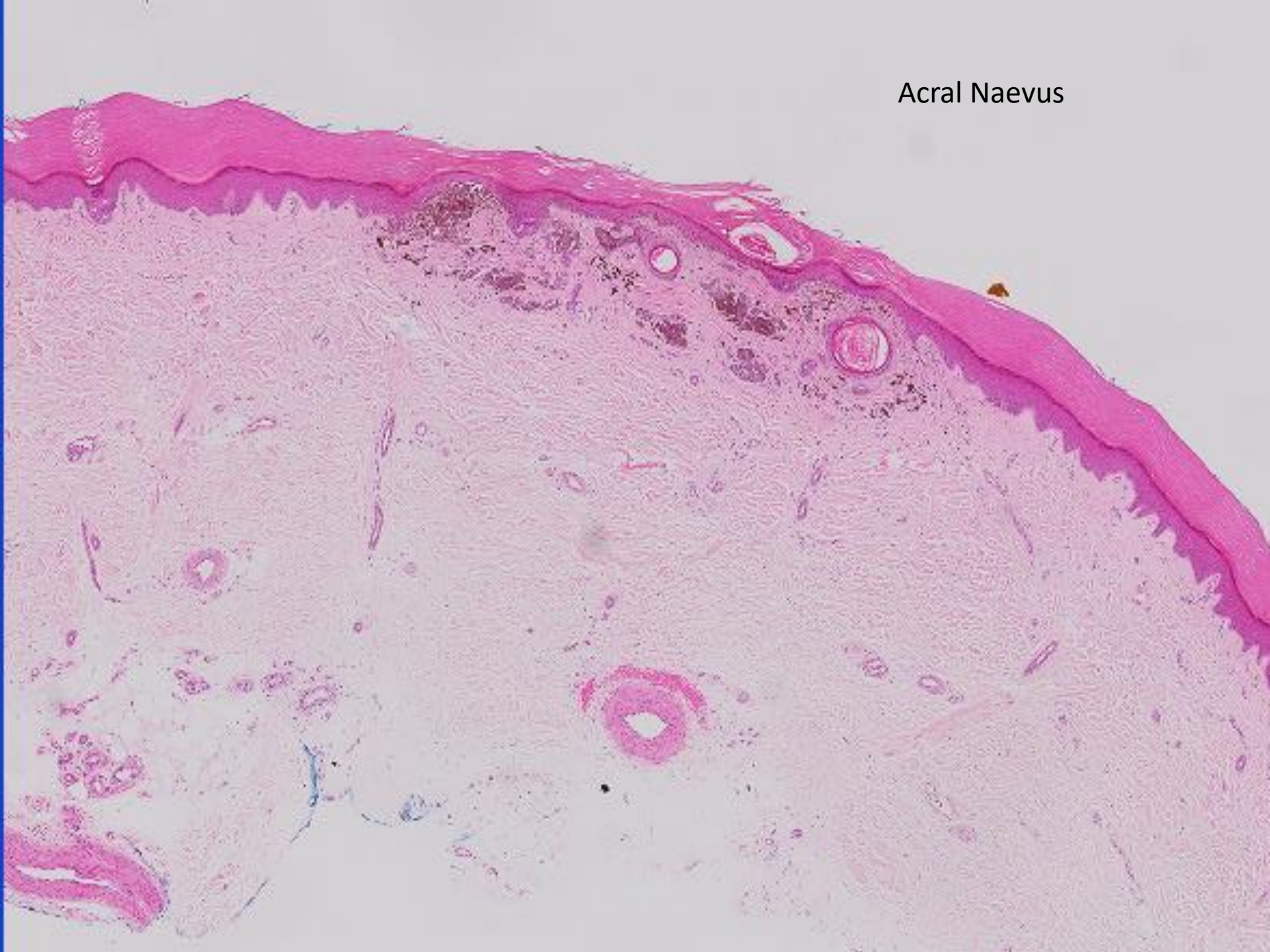

COMBINED DPN,
probably superficial
variant

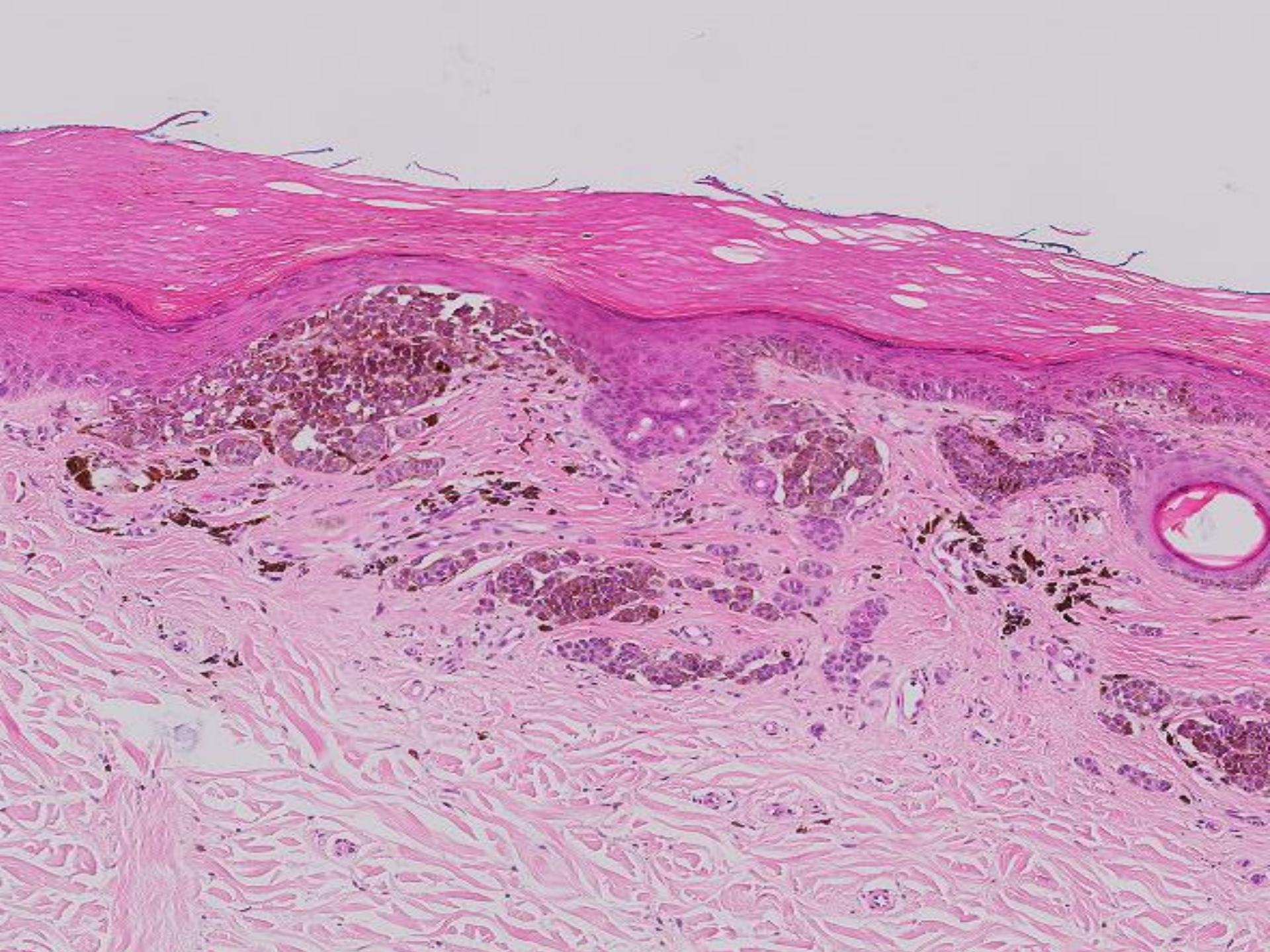
Take home message for biphenotypic pattern in melanocytic lesions

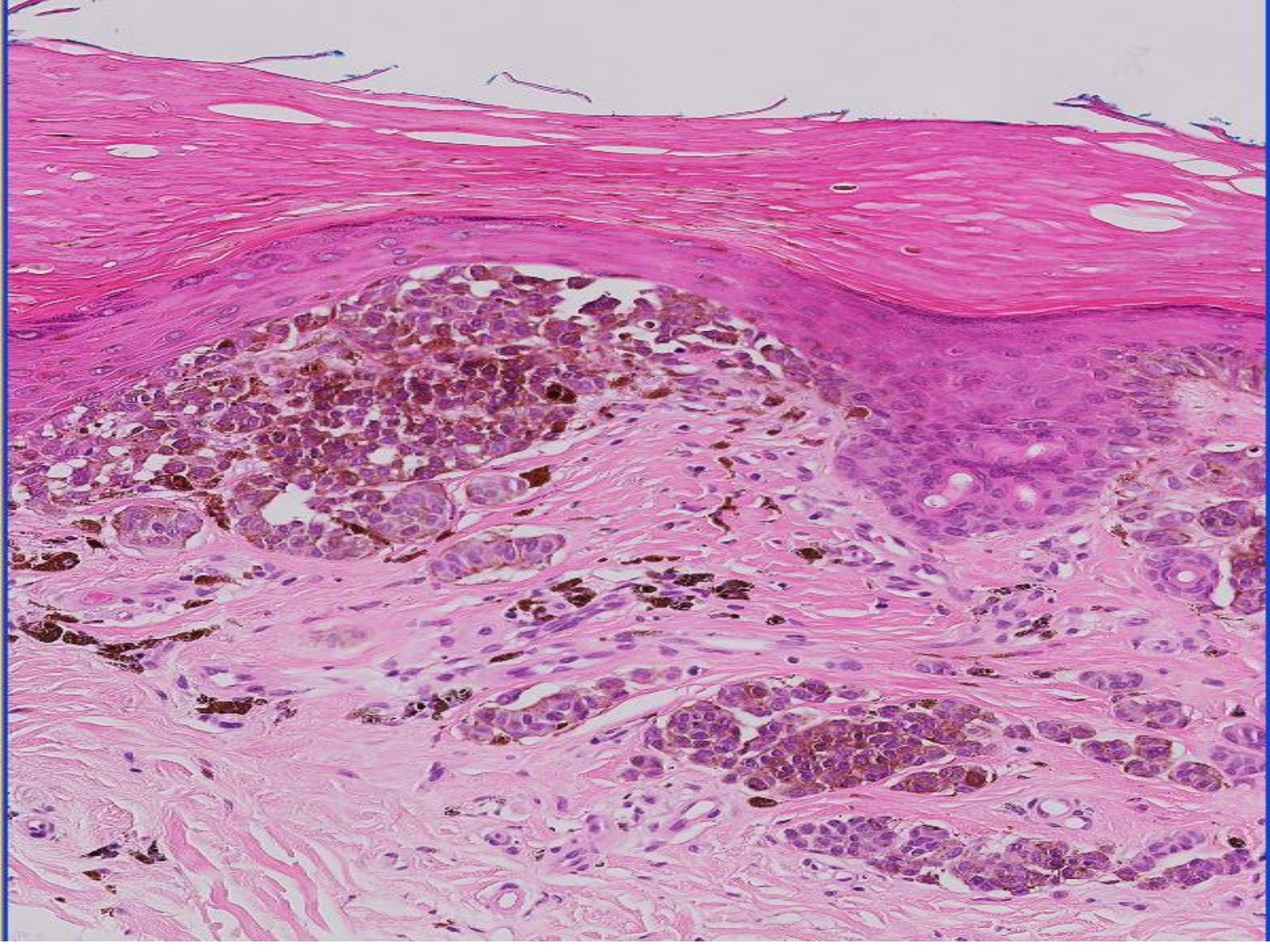
- Asymmetry is a feature and does not distinguish benign from malignant.
- Assess each component of a lesion individually.
- 2 components coexist without destructive growth in a benign combined naevus.
- In addition to usual combinations of combined naevus, keep BAP1 inactivated tumour and superficial DPN in mind.

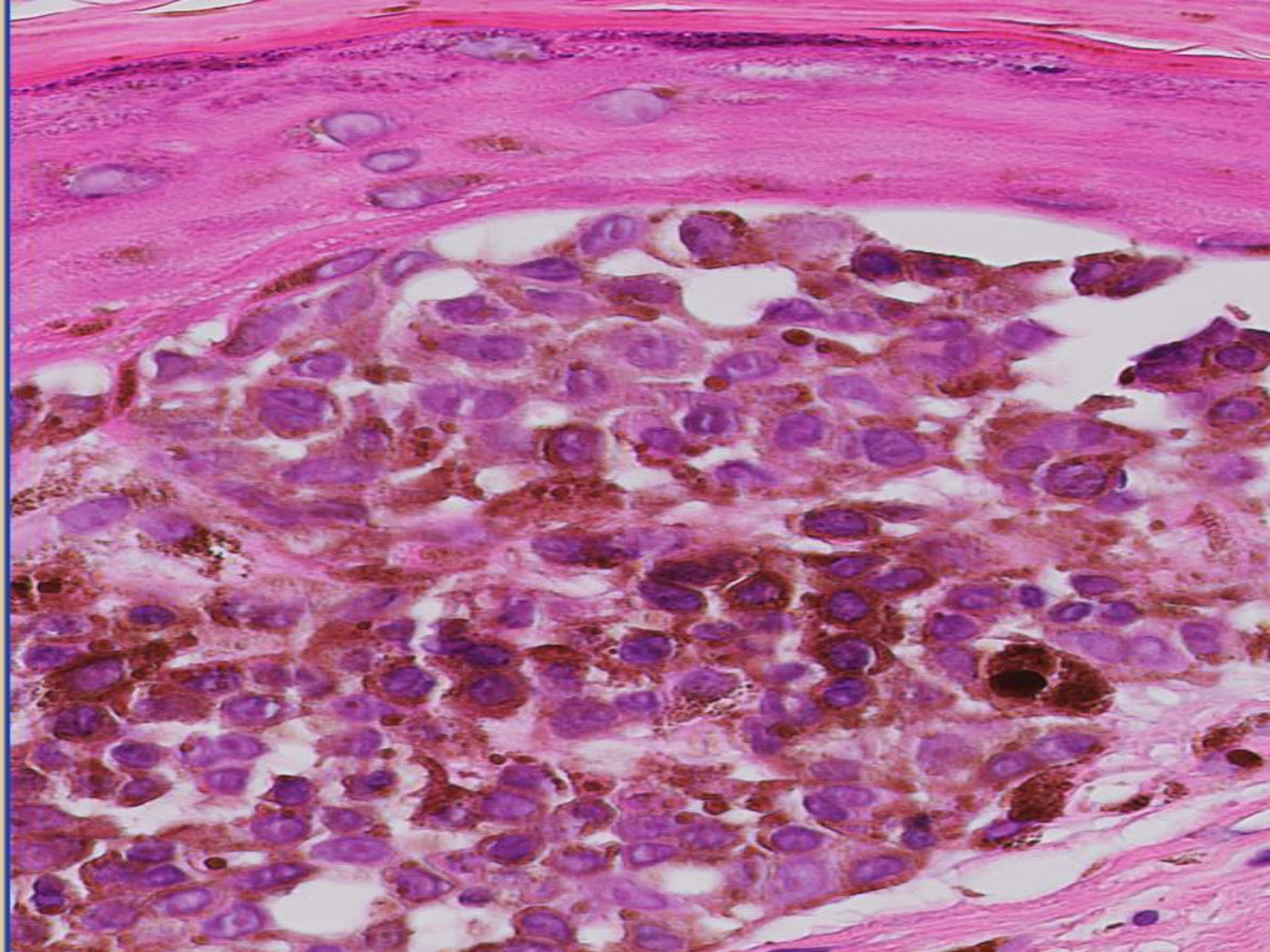
Acral Melanocytic Lesions

Acral Naevus

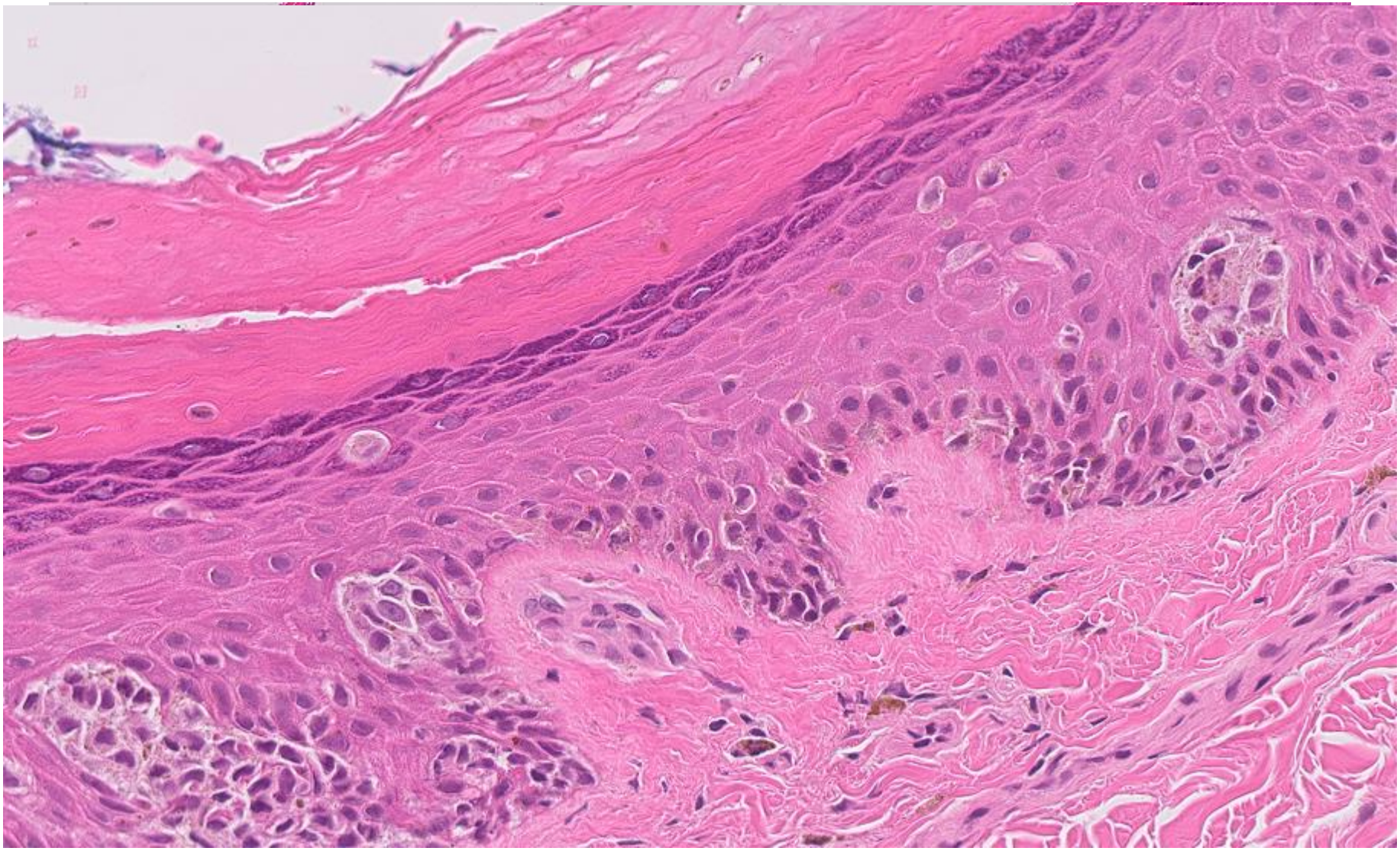








Acral naevus: Example 2

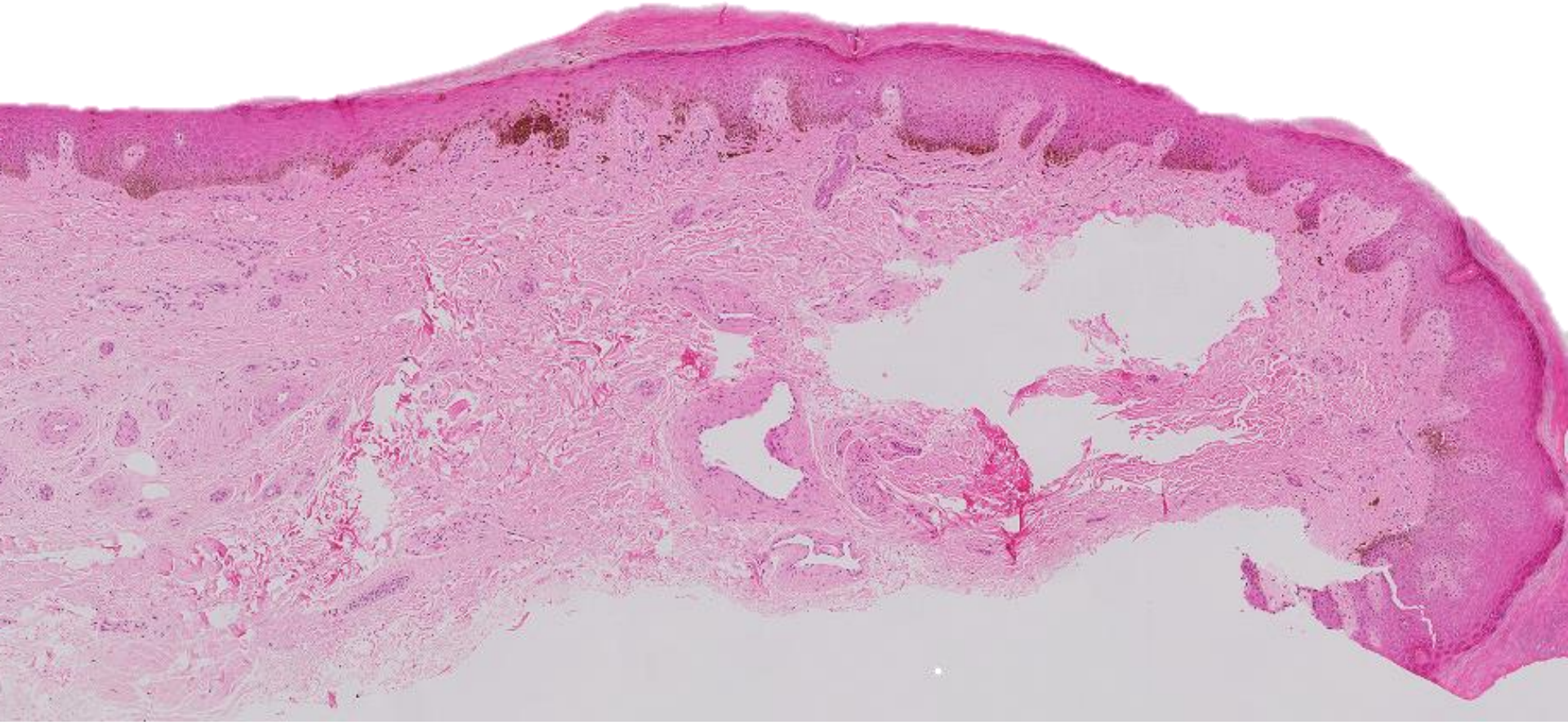


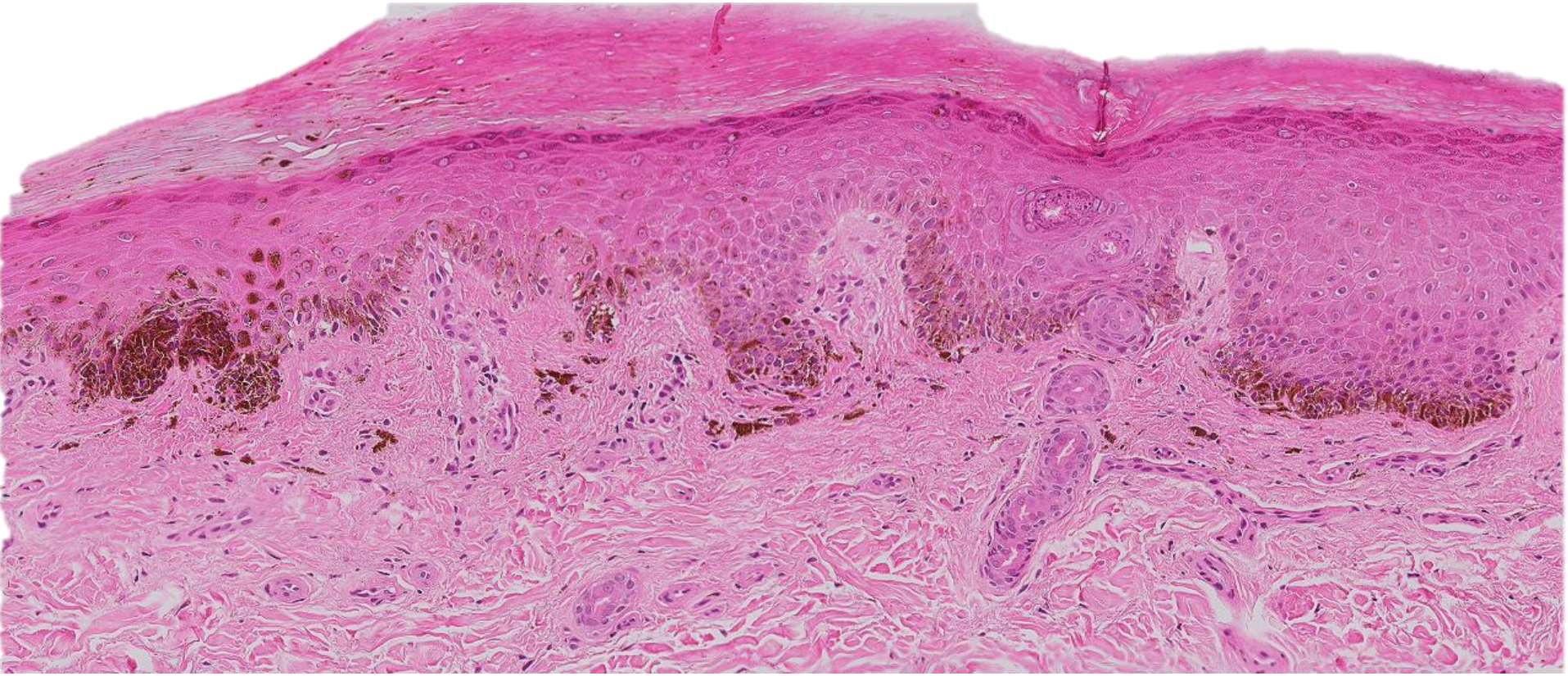
The problem of lentiginous acral melanocytic lesions

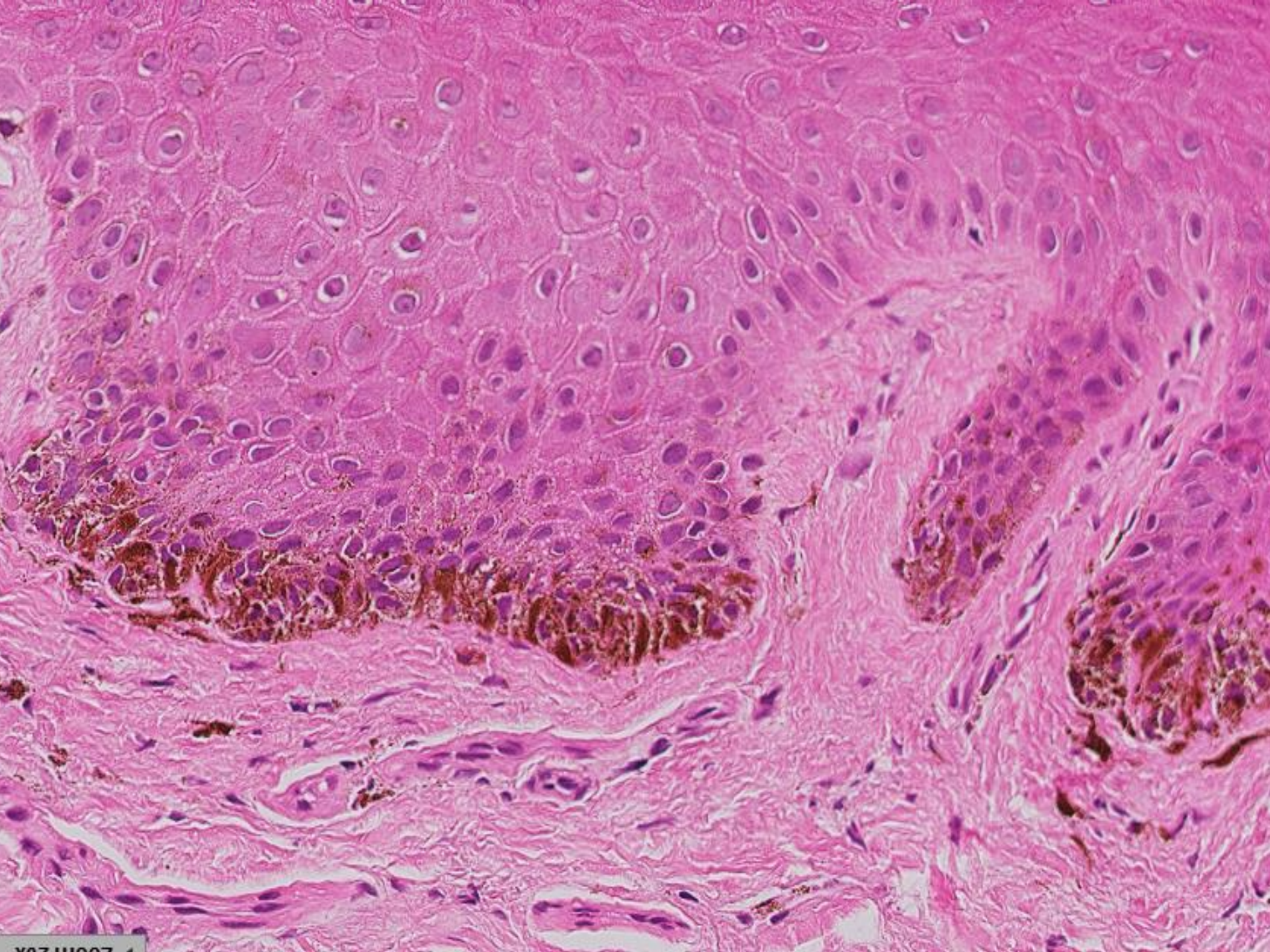
Problem Case 5

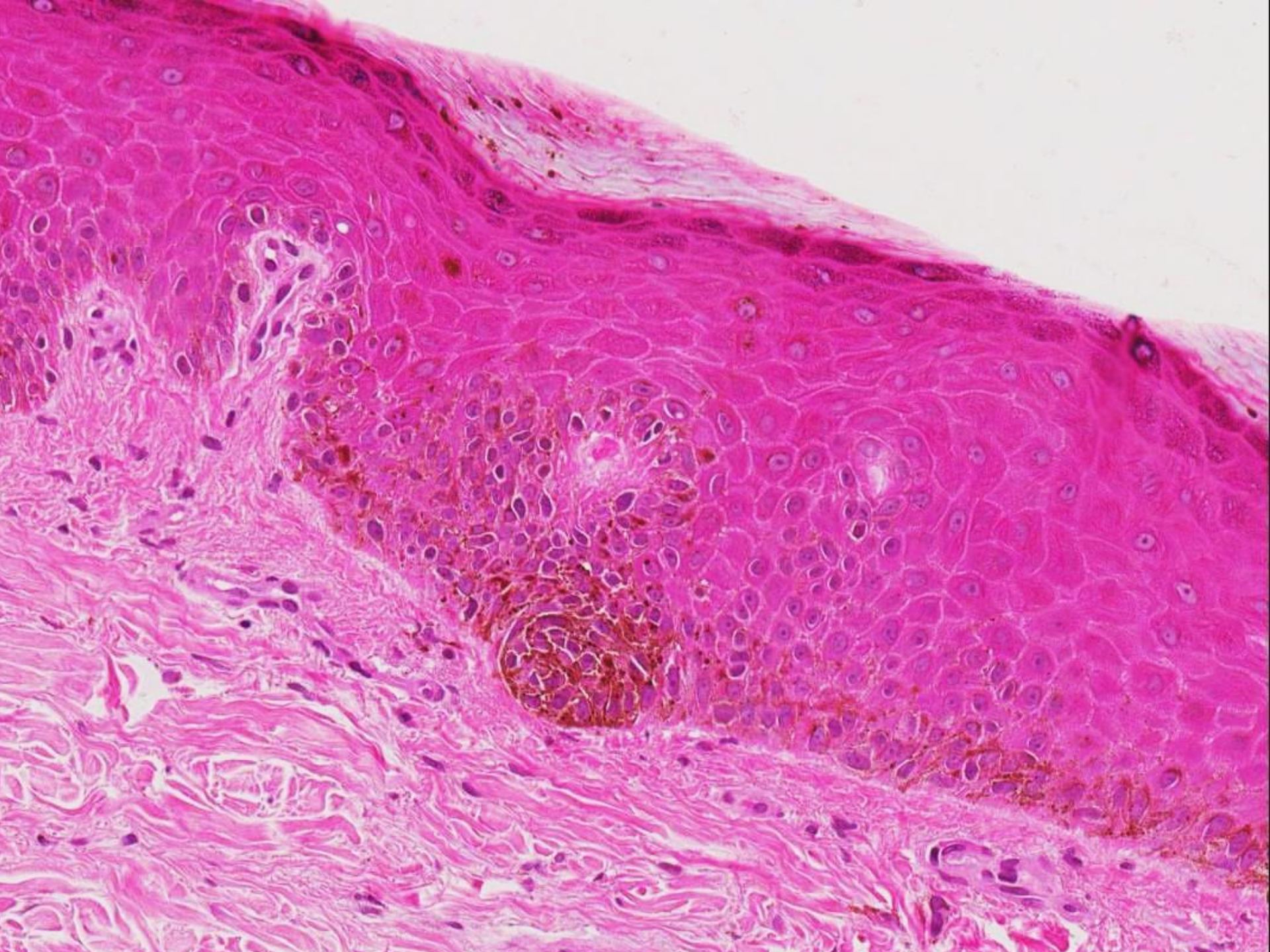
- 65/M new onset atypical flat pigmented lesion plantar surface of foot, 10mm

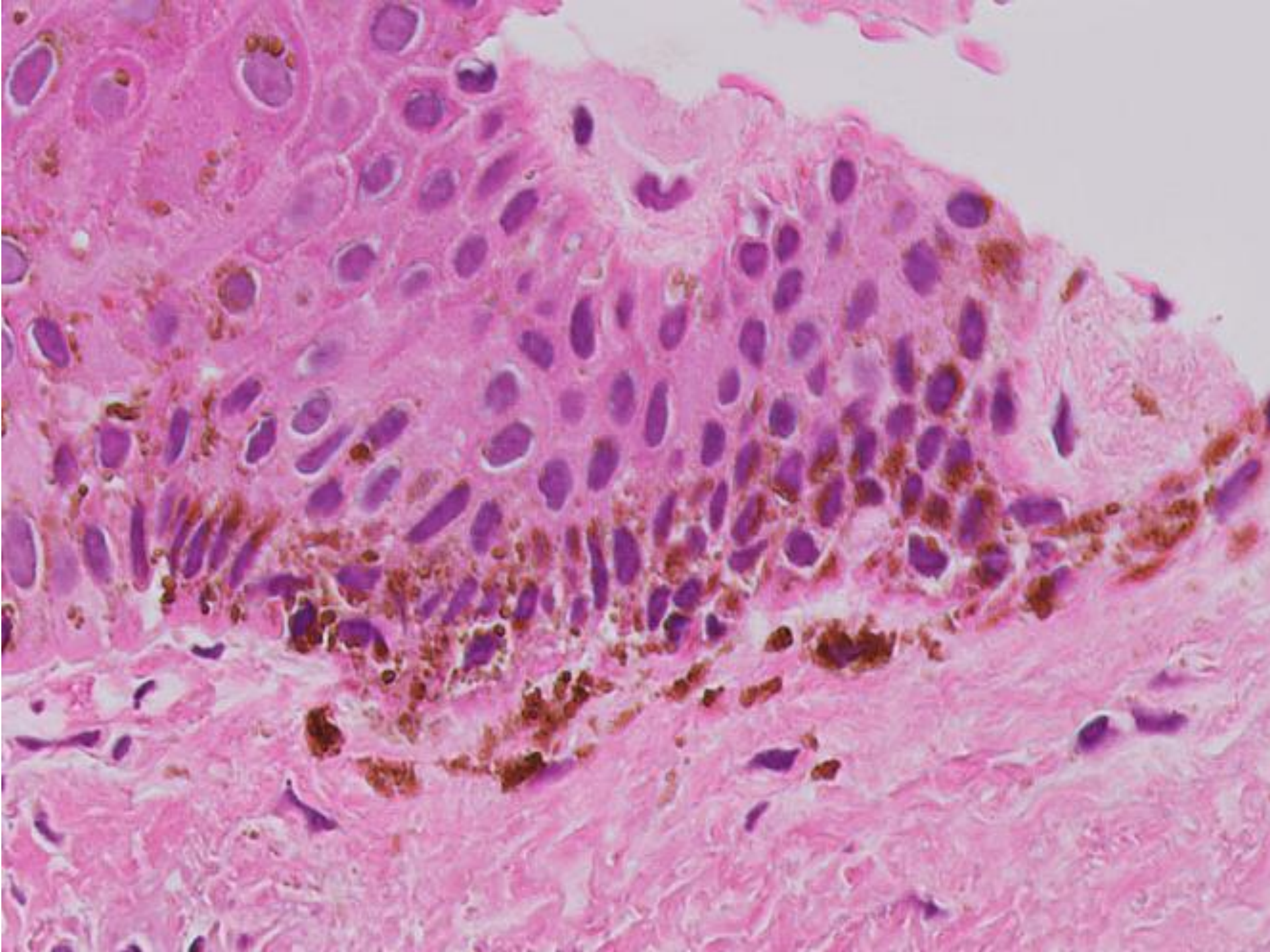
- Incisional bx

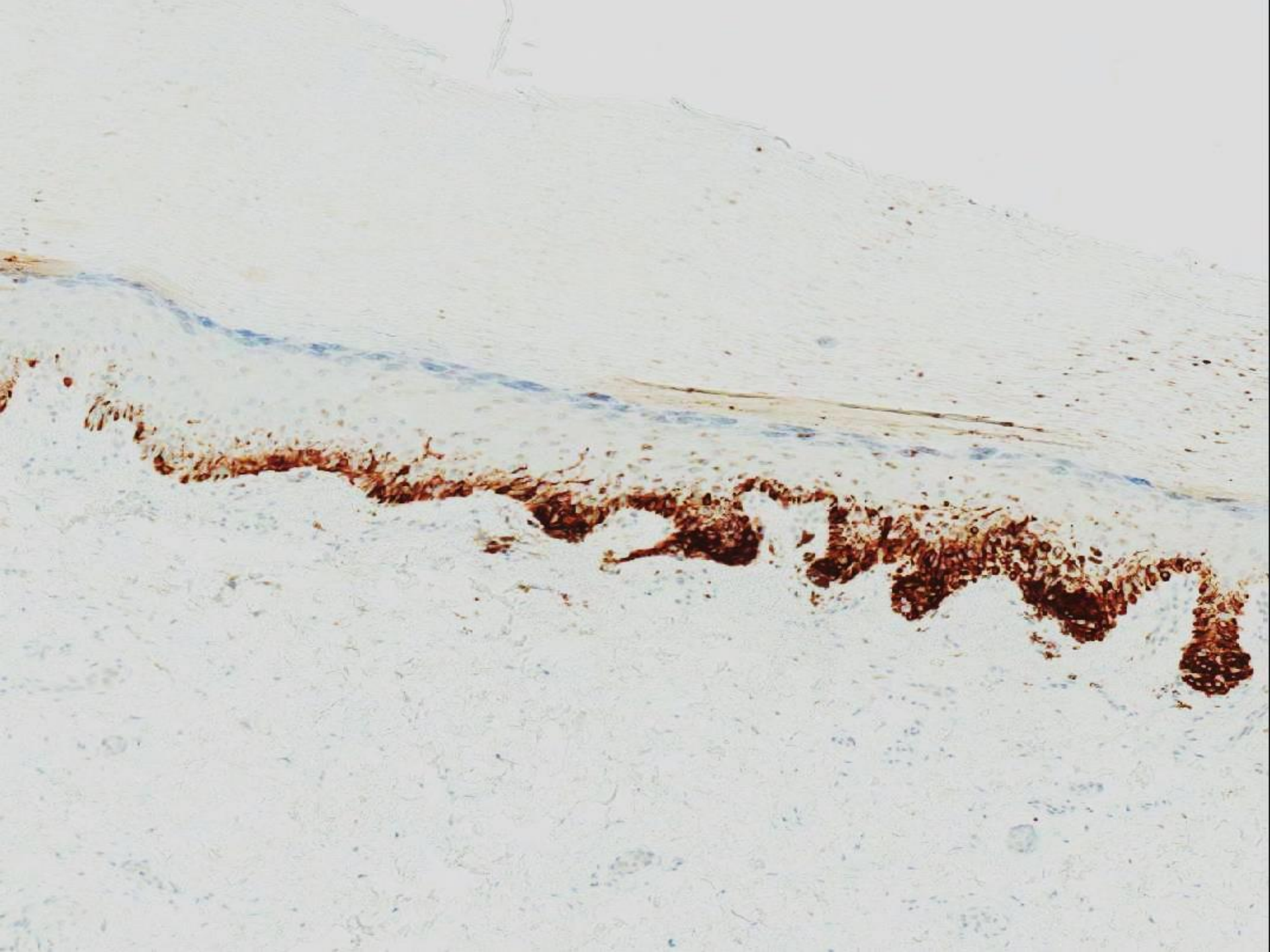












D/D

1. Acral lentiginous naevus
2. Atypical lentiginous melanocytic hyperplasia of foot
3. Acral lentiginous melanoma in situ

65/M new onset atypical flat pigmented lesion plantar surface of foot, 10mm

D/D

1. Acral lentiginous naevus
2. Atypical lentiginous melanocytic hyperplasia of foot
3. Acral lentiginous melanoma in situ

65/M new onset atypical flat pigmented lesion plantar surface of foot, 10mm

Lentiginous Acral Melanocytic Lesions

- Lentiginous Acral Naevus

- Lentiginous Acral Melanoma in situ

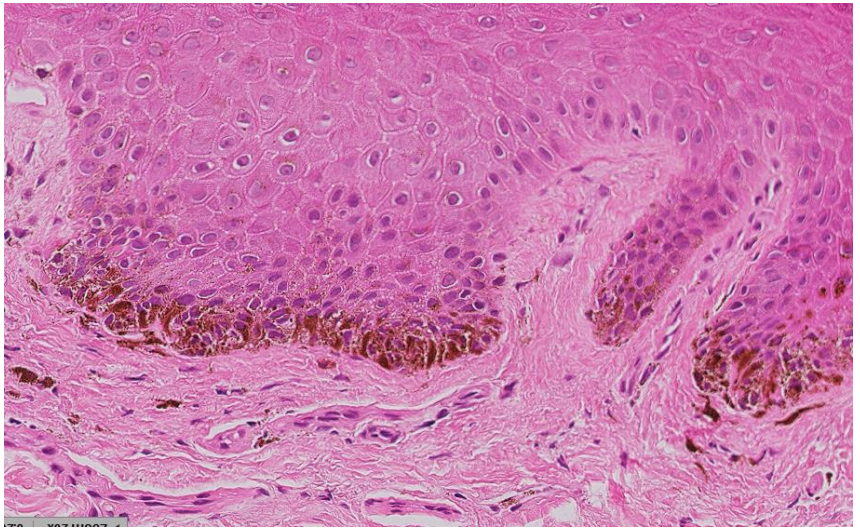
Arch Pathol Lab Med. 2011 Jul;135(7):847-52.
Acral junctional nevus versus acral lentiginous melanoma in situ: a differential diagnosis that should be based on clinicopathologic correlation.

Lentiginous Acral Melanocytic Lesions

Diagnosing Acral Melanoma In Situ:

- Misdiagnosis rate of 25-30%!
- Clinico-pathological entity
- Non congenital flat irregular black/brown lesion on acral skin >1cm
- Dermoscopy pattern important

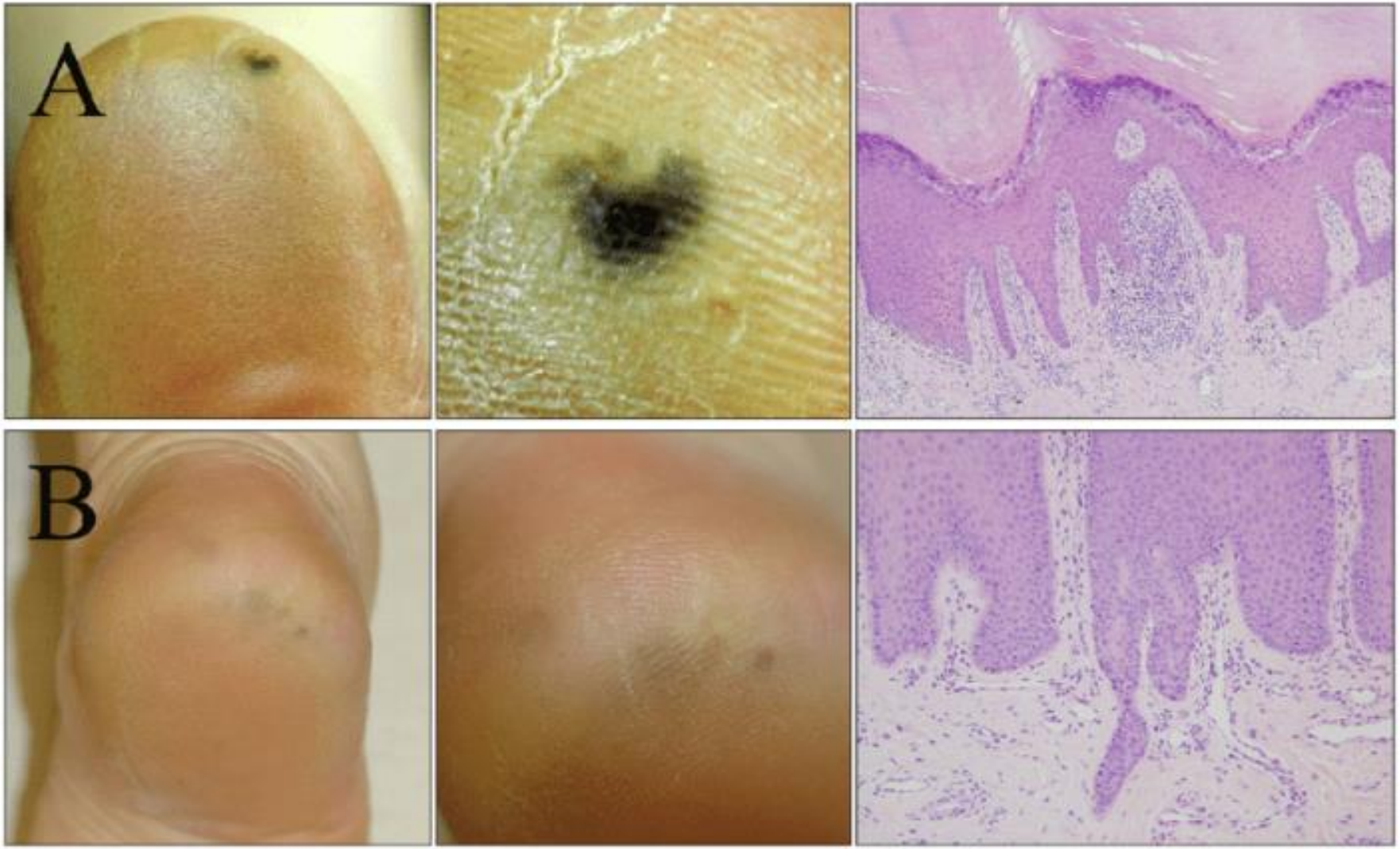
Lentiginous Acral Melanocytic Lesions



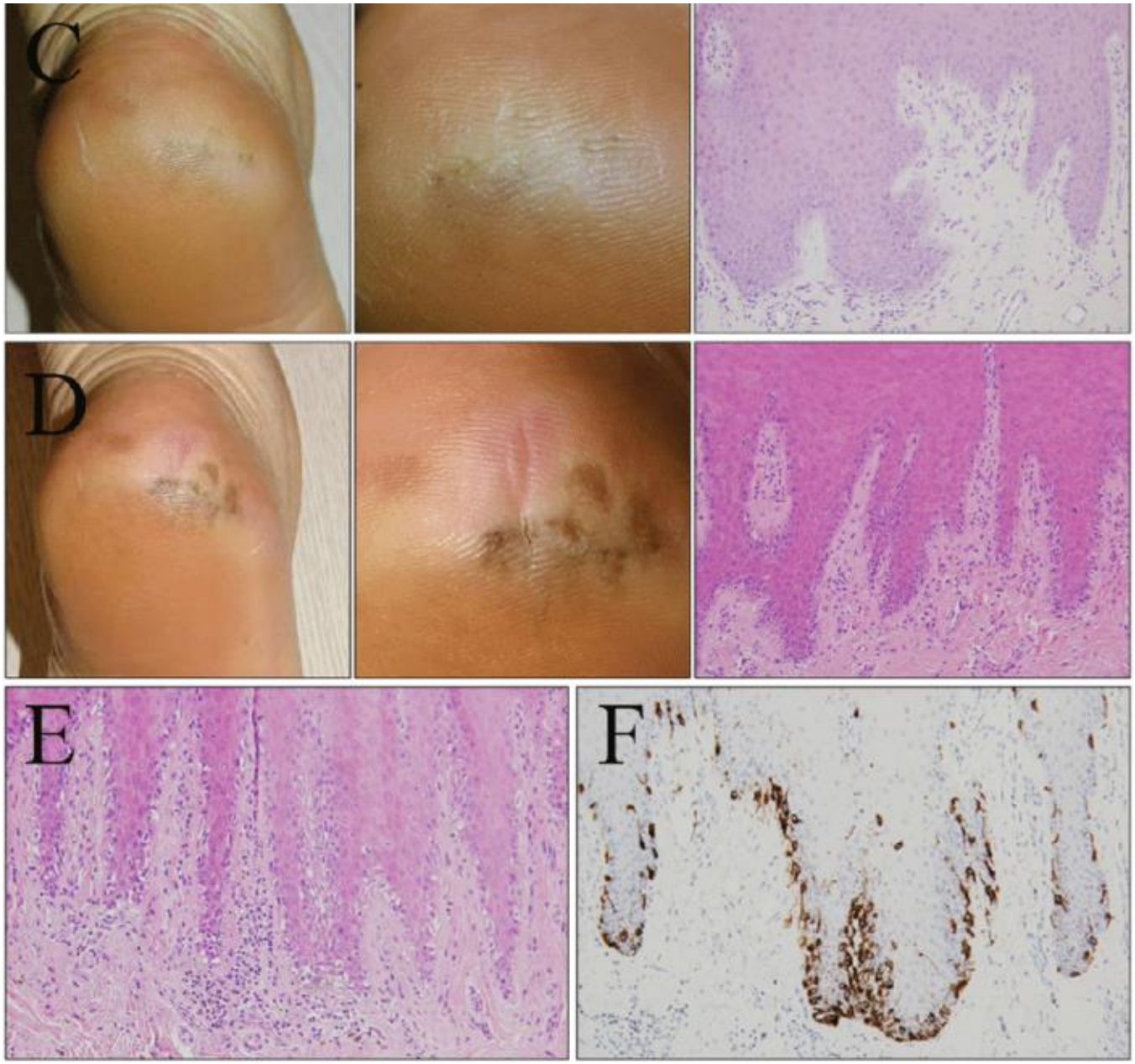
Diagnosing Acral Melanoma In Situ:

- Histology may be subtle and consist of bland lentiginous proliferation in early stage
- Cytological atypia seen in form of angulated and hyperchromatic nuclei
- Dendrites are thick, large and numerous
- Nests appear later and pagetoid spread may not be a feature till advanced stage

Annals of Dermatology 26(6):779-781 · December 2014



Annals of Dermatology 26(6):779-781 · December 2014



Top Tips for Acral lentiginous lesions

- Acral lentiginous naevus (ALN) vs Acral lentiginous melanoma (AMIS): age and size important!

  -Acral MIS exceedingly unlikely <30 yrs

  - A new onset flat pigmented acral lesion in elderly almost always MIS

- Clinico-pathological entity

- Dermoscopy important:
  parallel ridge pattern- bad
  parallel furrow pattern- good

Top Tips Acral lentiginous lesions

1. Upto a size of 4mm, acral naevi can be purely lentiginous.

2. An acral lesion >7mm with predominantly lentiginous proliferation of melanocytes is highly suggestive of acral melanoma in situ.

- If cytological atypia is present: call Acral Melanoma In Situ

- If minimal or no cytological atypia: Do serials, take second opinion, discuss in MDT, correlate with dermoscopy, if needed advise another biopsy but do not dismiss as benign.

Update on Dysplastic Naevi

- Simulants of Melanoma
- Precursors of Melanoma
- Risk markers of Melanoma

JAMA Dermatol. 2016 Dec 1;152(12):1327-1334.

Reexamining the Threshold for Reexcision of Histologically Transected Dysplastic Nevi.

Objective:

To determine long-term risk of associated melanoma in biopsied mild or moderate DN with positive histologic margins that were clinically observed vs reexcised with negative margins.

590 specimens studied.

Conclusion:

In cases of mild and moderate DN with microscopically positive margins and no concerning clinical residual lesion, observation, rather than reexcision, was a reasonable management option.

J Am Acad Dermatol. 2014 Dec;71(6)

The utility of re-excising mildly and moderately dysplastic nevi: a retrospective analysis.

J Am Acad Dermatol. 2017 Mar;76(3):527-530

Recurrence of moderately dysplastic nevi with positive histologic margins.

WHO ‘Blue’ Book on skin tumours
Dysplastic Naevus

Table 2.07 International Melanoma Pathology Study Group (IMPSG) diagnostic criteria for dysplastic naevus. Reproduced from: Shors AR et al. {2434} and Xiong MY et al. {2868}

Dysplastic naevus

- Width >4 mm in fixed sections (>5 mm clinically)
- Presence of architectural disorder, which requires both of the following:
  - Irregular (i.e. horizontally oriented, bridging adjacent rete, and/or varying in shape and size) and/or dyscohesive nests of intraepidermal melanocytes
  - Increased density of non-nested junctional melanocytes (e.g. more melanocytes than keratinocytes in an area ≥ 1 mm^2)
- Presence of cytological atypia, which is graded on the basis of the highest degree of cytological atypia present in more than a few melanocytes (see Table 2.13)

Grading of Dysplasia

Table 2.13 Nuclear features in the varying grades of dysplasia

WHO classification (2018)	Former grade	Nuclear size vs resting basal cells	Chromatism	Variation in nuclear size and shape	Nucleoli
Not a dysplastic naevus	0 (mild dysplasia)	1×	May be hyperchromatic	Minimal	Small or absent
Low-grade dysplasia	1 (moderate dysplasia[a])	1–1.5×	Hyperchromatic, or dispersed chromatin	Prominent in a small minority of cells (random atypia)	Small or absent
High-grade dysplasia	2 (severe dysplasia[a])	≥1.5×	Hyperchromatic, coarse granular chromatin, or peripheral condensation	Prominent in a larger minority of cells	Prominent, often lavender

[a] Architectural features are required for the diagnosis of dysplasia (see Table 2.07) and also contribute to grade; attributes that indicate a diagnosis of high-grade (severe) dysplasia even when cytological atypia is low-grade include pagetoid scatter above the basal layer (but to a lesser degree than in melanoma, usually not above the middle third, and focal, i.e. contained within an area < 0.5 mm^2), focal continuous basal proliferation, and intraepidermal mitoses (any dermal mitosis or anything more than a rare mitosis should raise concern for melanoma).

Naevus with Architectural disorder and minimal or mild cytological atypia

Diagnostic criteria:

- Width often <4mm
- Architectural features of dysplastic naevus
- Grade of cytological atypia and/or denisty of atypical melanocytes below the threshold for dysplastic naveus

Is this the demise of ‘Mildly dysplastic’ Naevus?

- Terminolgy is far less critical than the understanding by the clinician of implication of diagnosis.

- Communication with clinicians is key

- ‘Mildly dysplastic’ naevi do not need re-excision even if margin positive.

Moderately dysplastic naevus (low grade dysplasia WHO)

- A weak simulant of melanoma
- Association with melanoma risk +
- Probably not a high risk precursor
- If margin positive, consider re-excision, observation is also an option

Severely dysplastic naevus (high grade dysplasia WHO)

- Strong simulant of melanoma
- Association with melanoma risk+
- Probably a high risk precursor
- If margin positive , re-excision to ensure complete removal.

Thank You