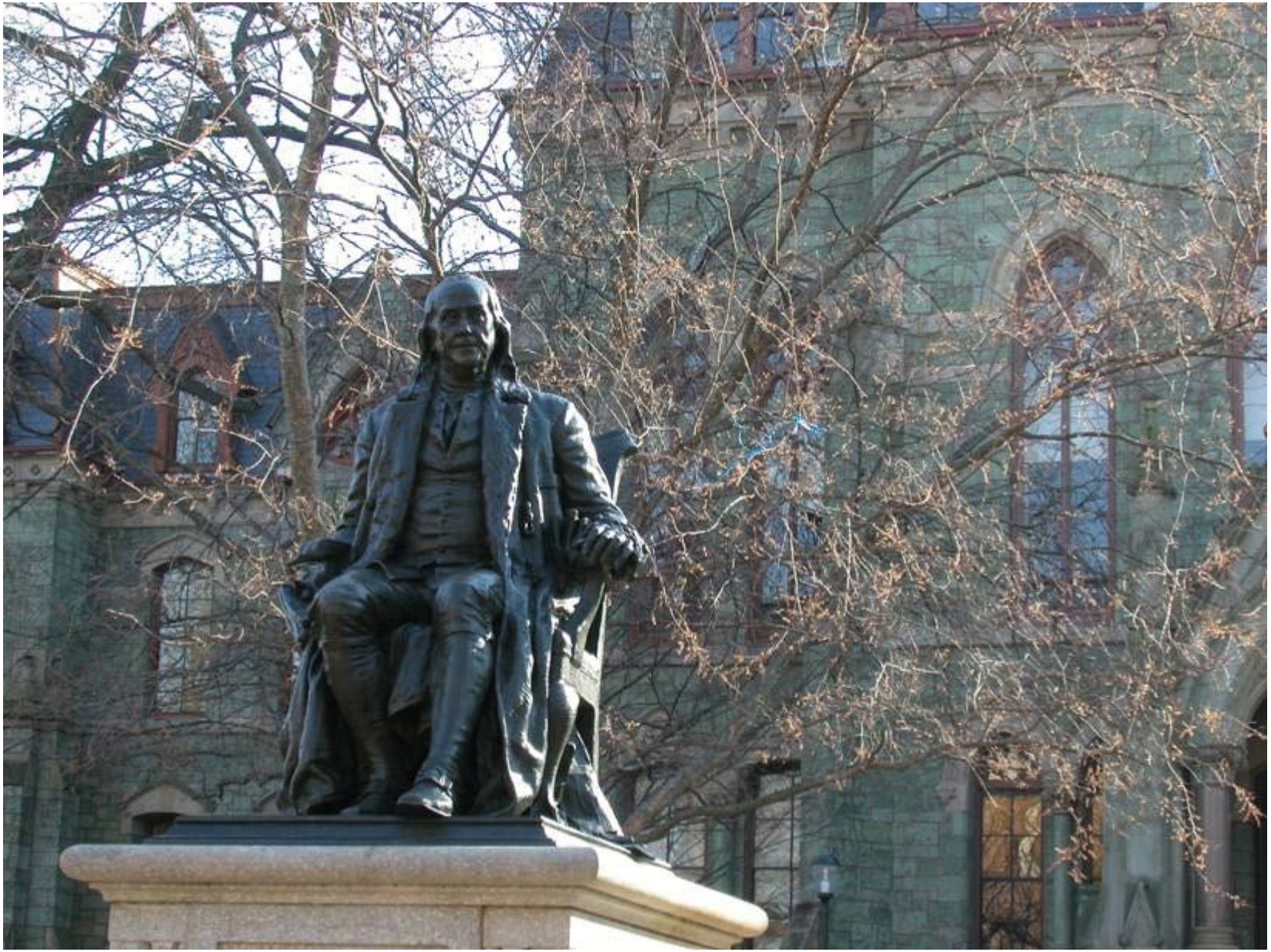


University of Pennsylvania, Founded by Ben Franklin in 1740

Acquired Melanocytic Nevi & Melanoma

David Elder, Paris 2020

Significance of Nevi

- Nevi are important almost exclusively in relation to melanoma

- Significance as

  - Simulants of melanoma
  - Markers of individuals at increased risk for melanoma
  - Potential precursors of melanoma

“Intermediate” category has more than one genetic alteration and distinctive histopathologic features.

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure/CSD				High UV radiation exposure/CSD	
Pathway	**I**				**II**	**III**
Endpoint of pathway	Low-CSD melanoma/SSM				High-CSD melanoma/LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate/low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate/high-grade dysplasias and melanocytomas	High-grade dysplasia/MIS	*BAP1*-inactivated melanocytoma/ MELTUMP	Deep penetrating melanocytoma/ MELTUMP	PEM/MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma/SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	**BRAF p.V600E** or ***NRAS*** *TERT*; *CDKN2A*; *TP53*; *PTEN*	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF* (non-p.V600E)**; ***KIT***; or *NF1* *TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET* *TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

BIN, *BAP1*-inactivated naevus; **BN**, blue naevus; **CBN**, cellular blue naevus; **CN**, congenital naevus; **CSD**, cumulative sun damage; **DPN**, deep penetrating naevus; **IAMP**, intraepidermal atypical melanocytic proliferation; **IAMPUS**, intraepidermal atypical melanocytic proliferation of uncertain significance; **IMP**, intraepidermal melanocytic proliferation without atypia; **LMM**, lentigo maligna melanoma; low/high-CSD melanoma, melanoma in skin with a low/high degree of cumulative sun damage; **MELTUMP**, melanocytic tumour of uncertain malignant potential; **MIS**, melanoma in situ; **PEM**, pigmented epithelioid melanocytoma; **SSM**, superficial spreading melanoma; **STUMP**, spitzoid tumour of uncertain malignant potential; **UV**, ultraviolet; **VGP**, vertical growth phase (tumorigenic and/or mitogenic melanoma).

CSD Melanomas (Pathways 1-III)

Bastian BC, de la Fouchardiere, A, Elder, DE, Gerami P, Lazar AJ, Massi D, Nagore E, Scolyer RA, Yun SJ. Genomic Landscape of Melanoma. *In* Elder DE, Massi D, Scolyer RA, Willemze R: WHO Classification of Skin Tumours, Lyon, 2018

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure/CSD				High UV radiation exposure/CSD	
Pathway	**I**				**II**	**III**
Endpoint of pathway	Low-CSD melanoma/SSM				High-CSD melanoma/LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate/low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate/high-grade dysplasias and melanocytomas	High-grade dysplasia/MIS	*BAP1*-inactivated melanocytoma/ MELTUMP	Deep penetrating melanocytoma/ MELTUMP	PEM/MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma/SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	***BRAF* p.V600E** or ***NRAS*** *TERT*; *CDKN2A*; *TP53*; *PTEN*	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF* (non-p.V600E)**; ***KIT***; or *NF1* *TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET* *TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

BIN, *BAP1*-inactivated naevus; **BN**, blue naevus; **CBN**, cellular blue naevus; **CN**, congenital naevus; **CSD**, cumulative sun damage; **DPN**, deep penetrating naevus; **IAMP**, intraepidermal atypical melanocytic proliferation; **IAMPUS**, intraepidermal atypical melanocytic proliferation of uncertain significance; **IMP**, intraepidermal melanocytic proliferation without atypia; **LMM**, lentigo maligna melanoma; low/high-CSD melanoma, melanoma in skin with a low/high degree of cumulative sun damage; **MELTUMP**, melanocytic tumour of uncertain malignant potential; **MIS**, melanoma in situ; **PEM**, pigmented epithelioid melanocytoma; **SSM**, superficial spreading melanoma; **STUMP**, spitzoid tumour of uncertain malignant potential; **UV**, ultraviolet; **VGP**, vertical growth phase (tumorigenic and/or mitogenic melanoma).

CSD Melanomas (Pathways 1-III)

Bastian BC, de la Fouchardiere, A, Elder, DE, Gerami P, Lazar AJ, Massi D, Nagore E, Scolyer RA, Yun SJ. Genomic Landscape of Melanoma. *In* Elder DE, Massi D, Scolyer RA, Willemze R: WHO Classification of Skin Tumours, Lyon, 2018

Nevi as Potential Precursors of Melanoma

- About 1/3rd of melanomas arise in association with a nevus, often a dysplastic nevus
- Paradoxically most dysplastic nevi, like other nevi, are stable and will not progress to melanoma
  - Reason: Dysplastic nevi are much more numerous in the community than melanomas*
- Progression is not obligate
- Other nevi (CN, DN, DPN, PEM, BIN) have even lower risk (but not zero)
- CN: compound nevus; DN Dermal nevus; DPN, Deep penetrating nevus; PEM, Pigmented epithelioid melanocytoma; BIN, BAP1 insufficiency nevus

* Tsao H, Bevona C, Goggins W, Quinn T. The transformation rate of moles (melanocytic nevi) into cutaneous melanoma: a population-based estimate. Arch Dermatol. 2003;139(3):282-8.

"The annual transformation rate of any single mole into melanoma ranges from 0.0005% or less (ie, </=1 in 200,000) for both men and women younger than 40 years to 0.003% (about 1 in 33,000) for men older than 60 years. "

Combined Nevi

- Typically a background small often congenital pattern nevus with a BRAFV600E mutation
- “Second hit” gives rise to a more cellular dermal component (two genetic abnormalities, i.e. tumor progression in a nevus))
- Second hit can involve BAP1 (BIN) or PRKAR1a (PEM) loss, or Beta catenin activating mutation (DPN), likely others …
  - these can also occur de novo, without a background nevus
- Additional hits can rarely give rise to melanoma

Combined naevus, including combined *BAP1*-inactivated naevus / melanocytoma

Wiesner T.
Mihm M.C.Jr
Scolyer R.A.

Definition
A combined naevus contains two (or more) melanocytic naevus components in the same lesion. The cellular components can be any combination of any naevus variants, but most frequently, a common naevus component is combined with a blue naevus, deep penetrating naevus (DPN), or Spitz naevus component.

ICD-O code 8720/0

Synonyms
Clonal naevus; melanocytic naevus with phenotypic heterogeneity; naevus with dermal epithelioid component; inverted type A naevus; naevus with atypical dermal nodules {2366}
Combined *BAP1*-inactivated naevus {2743}; Wiesner naevus {1578}; *BAP1*-deficient tumour {875}; melanocytic *BAP1*-mutated atypical intradermal tumours {374}

Epidemiology
The exact prevalence is unknown, but combined naevi are relatively uncommon; they have been found to account for < 1% of melanocytic naevi sampled for histopathological examination. Combined naevi can develop at any age, but typically present in young people, with a mean age of about 30 years {2366}.

Etiology
The etiology is likely heterogeneous, but is unknown in most cases {2366}. Some combined naevi may develop by divergent cell differentiation, which might be triggered by the tumour microenvironment or by alterations in genes involved in chromatin modification or cell differentiation. Other combined naevi may represent collision tumours, with two naevus cell populations that have developed independently by distinct genomic aberrations. Some combined naevi evolve by the sequential acquisition of genomic aberrations; for example, in combined *BAP1*-inactivated naevi all melanocytes usually harbour BRAF p.V600E mutations, but only the epithelioid melanocytes

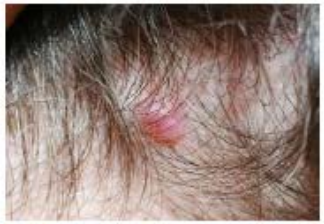


Fig. 2.42 Combined *BAP1*-inactivated naevus. A symmetrical, pink, smooth-surfaced papule.

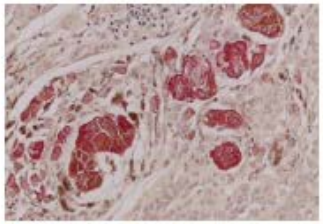


Fig. 2.43 Combined naevus. HMB45 positive staining in the DPN component; the common naevus component (bottom of field) is negative.

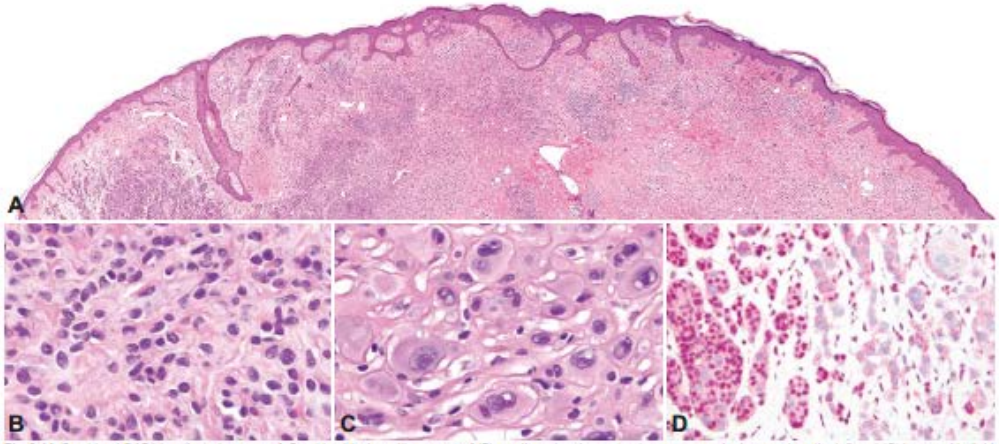
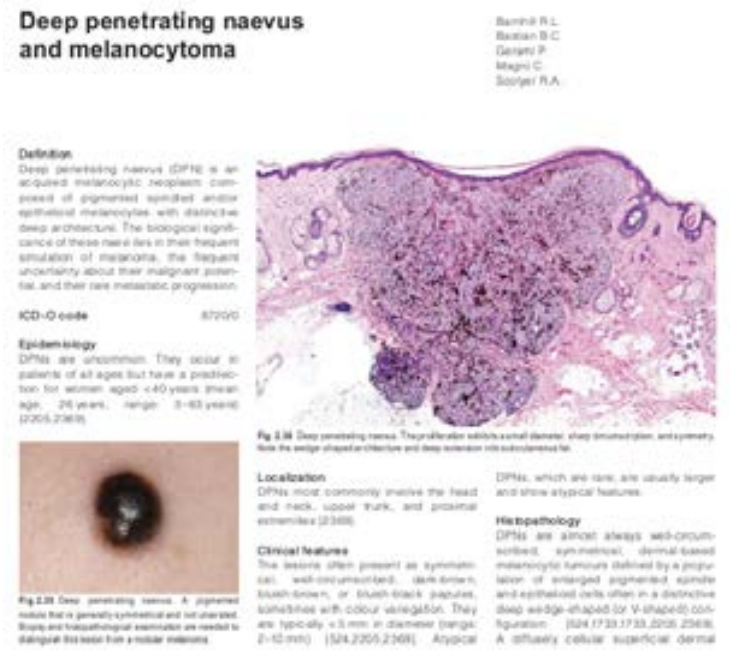


Fig. 2.44 Combined *BAP1*-inactivated naevus. **A** Combined lesion with an area of (B) small, oval melanocytes (common acquired naevus) on the left and (C) large epithelioid melanocytes with large, polymorphic nuclei, vesicular chromatin, abundant cytoplasm, distinct cell borders, and tumour infiltrating lymphocytes on the right. **D** BAP1 immunohistochemistry shows nuclear staining in the common naevus component (left) and loss of nuclear staining in the epithelioid component (right).
Reprinted with permission from: T. Wiesner et al. (2011) Nat Genet. 43:1018-21, Macmillan Publishers Ltd.

- Combined nevus contains 2 or more components, most commonly DN + BIN, DPN or PEM
  - (BN (blue) and SN (Spitz) are in different pathways)
- BAP1 loss may occur usually in a BRAFV600E mutated nevus
  - 2 (or more) genomic abnormalities
- Leads to formation of a cellular nodule of epithelioid cells



Deep penetrating naevus and melanocytoma

Barnhill R.L.
Beatson B.C.
Gerami P.
Magro C.
Scolyer R.A.

Definition

Deep penetrating naevus (DPN) is an acquired melanocytic neoplasm composed of pigmented spindled and/or epithelioid melanocytes with distinctive deep architecture. The biological significance of these naevi lies in their frequent simulation of melanoma, the frequent uncertainty about their malignant potential, and their rare metastatic progression.

ICD-O code 8770/0

Epidemiology

DPNs are uncommon. They occur in patients of all ages but have a predilection for women aged <40 years (mean age, 26 years; range, 3–63 years) (2205,2369).

Fig. 2.39 Deep penetrating naevus. A pigmented nodule that is generally symmetrical and not ulcerated. Biopsy and histopathological examination are needed to distinguish this lesion from a nodular melanoma.

Fig. 2.38 Deep penetrating naevus. The proliferation exhibits a small diameter, sharp circumscription, and symmetry. Note the wedge-shaped architecture and deep extension into subcutaneous fat.

Localization

DPNs most commonly involve the head and neck, upper trunk, and proximal extremities (2369).

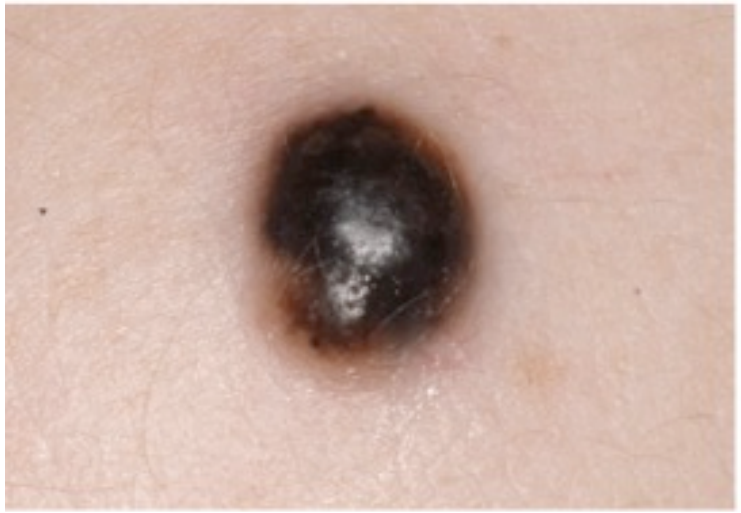
Clinical features

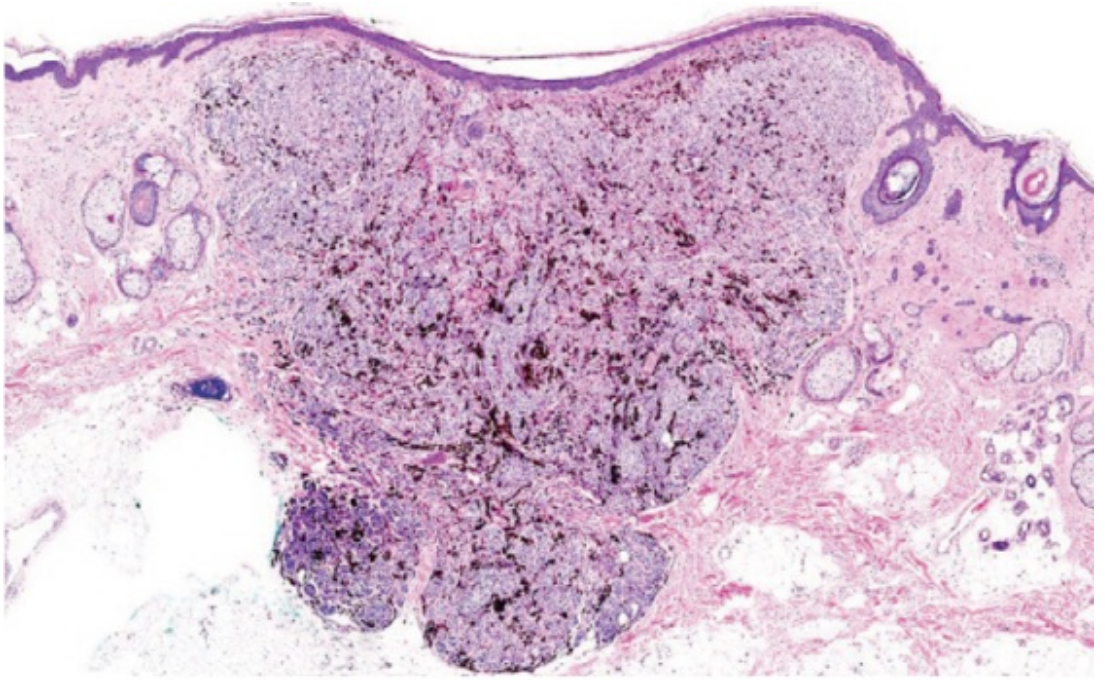
The lesions often present as symmetrical, well-circumscribed, dark-brown, bluish-brown, or bluish-black papules, sometimes with colour variegation. They are typically <5 mm in diameter (range: 2–10 mm) (524,2205,2369). Atypical DPNs, which are rare, are usually larger and show atypical features.

Histopathology

DPNs are almost always well-circumscribed, symmetrical, dermal-based melanocytic tumours defined by a proliferation of enlarged pigmented spindle and epithelioid cells often in a distinctive deep wedge-shaped (or V-shaped) configuration (524,1733,1733.2205,2369). A diffusely cellular superficial dermal

- DPN is an acquired melanocytic neoplasm composed of spindle and/or epithelioid melanocytes with distinctive deep architecture
- “Significance lies in their frequent simulation of melanoma, uncertainty about their malignant potential, and their rare metastatic progression”
- Usually have mutated BRAF and an activating mutation of beta catenin or related gene
  - i.e. two genomic abnormalities





Pigmented epithelioid melanocytoma

Zembowicz A.
Calonje E.
Mihm M.C. Jr

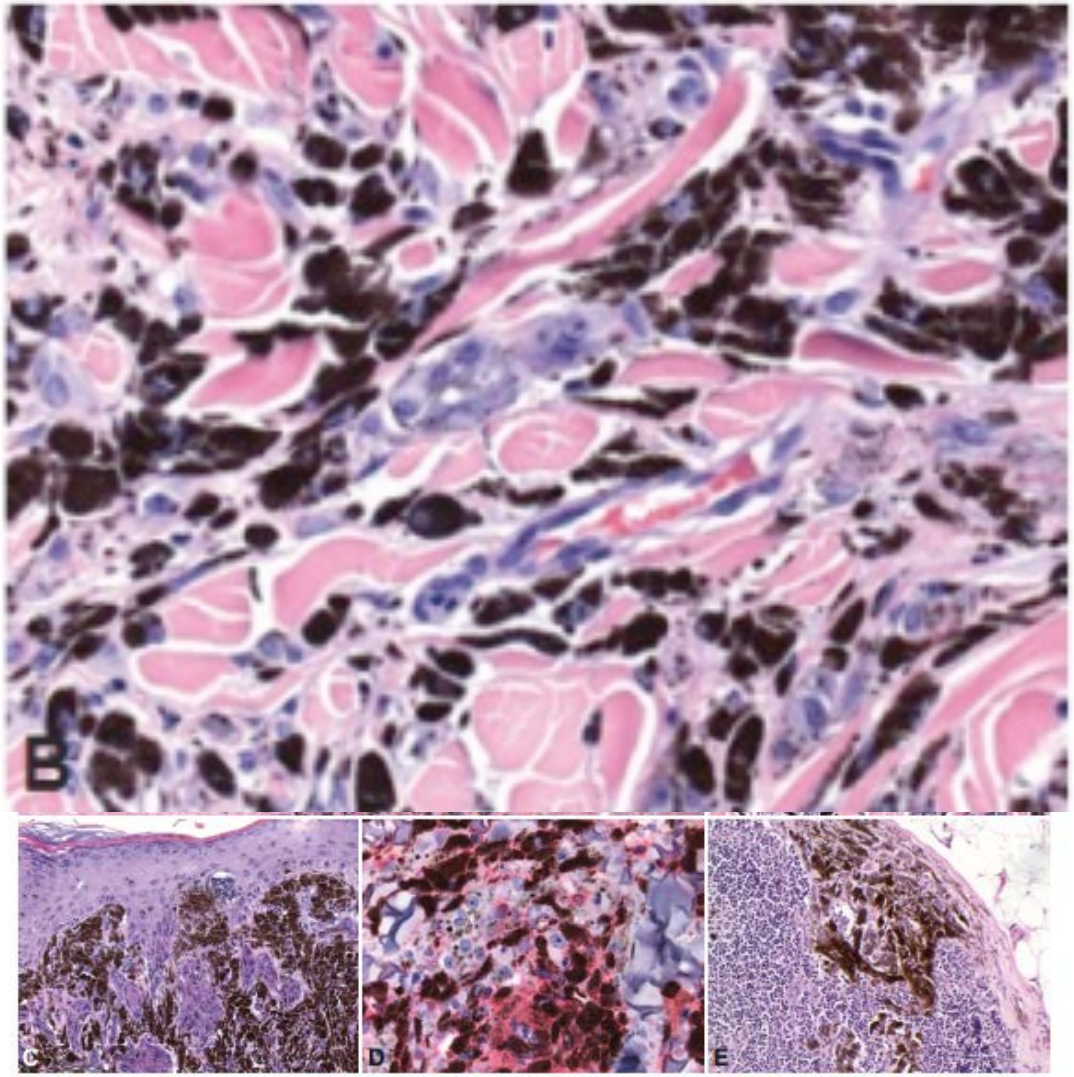


Fig. 2.38 Pigmented epithelioid melanocytoma, pure. **A** Low-magnification showing epidermal hyperplasia, a wedge-shape configuration, and an infiltrative border. **B** Cellular composition including pigmented dendritic cells, epithelioid cells, and melanophages. **C** Junctional component. **D** Loss of PRKAR1A expression in large epithelioid cells. **E** Lymph node metastasis.

- A melanocytic neoplasm comprised of heavily pigmented epithelioid and dendritic cells.
- Distinctive oval nuclei, regular nuclear membranes, pale chromatin, prominent nucleolus.
- Metastatic potential usually limited to regional nodes.
- Loss of PRKAR1a or related genes.
- MM in PEM occurs but is very rare.

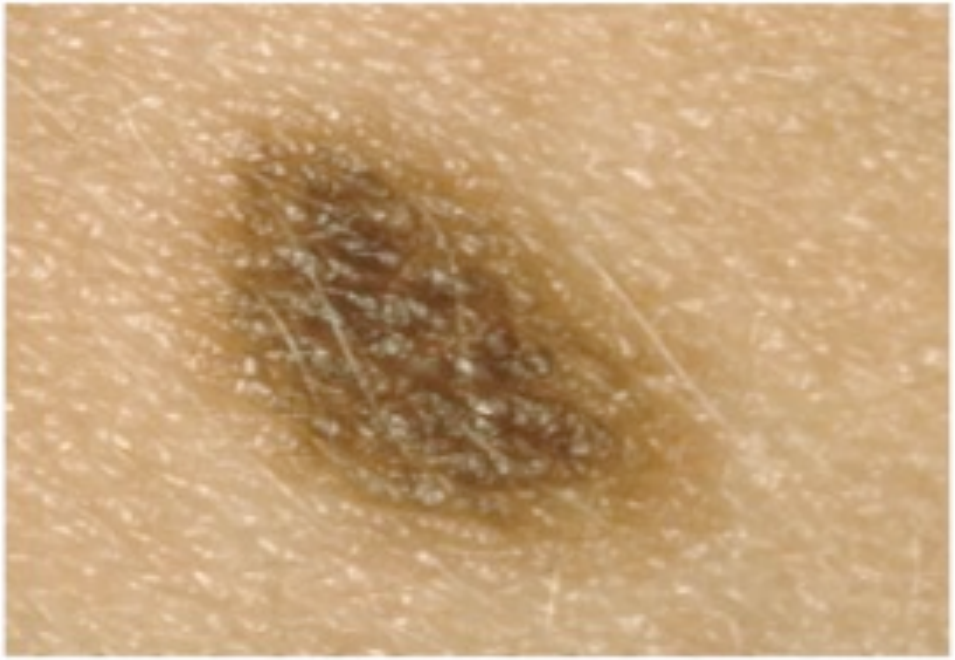
Dysplastic Nevi

The most important simulants, risk markers and potential precursors of melanoma

Dysplastic naevus

Elder D.E.
Barnhill R.L.
Bastian B.C.
Duncan L.M.
Massi D.

Mihm M.C. Jr
Piepkorn M.
Rabkin M.
Scolyer R.A.



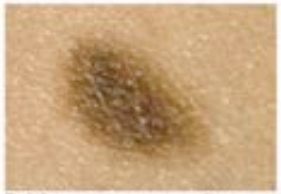


Fig. 2.13 Clinically dysplastic naevus. This lesion is broad, somewhat irregular, raised in the centre, and flat at the periphery. It has variegated shades of tan and dark brown, and an indefinite border.

cells is < 1.5x that of resting (i.e. with the smallest nuclei) basal keratinocytes, constituting moderate random cytological atypia.

effect and also due to involution [995]. In a case–control study, one or more clinically dysplastic naevi were found in 43% of 658 patients with melanoma and in 10% of 1009 control subjects; the most common number of naevi found was two among the patients and one among the controls [2667]. In a study of histological dysplasia, the prevalence of moderate or severe dysplasia was 24% in patients with melanoma and 12% in spouse controls [2434].

Etiology

Like other melanocytic tumours [160] (including melanomas), dysplastic naevi arise due to genetic, environmental, and phenotypic factors, in particular factors related to sun susceptibility and exposure. There is evidence of a genetic component to naevogenesis; genome-wide association studies of naevus counts have implicated several loci, but germline susceptibility loci unique to dysplastic naevi have not been reported [908]. It is

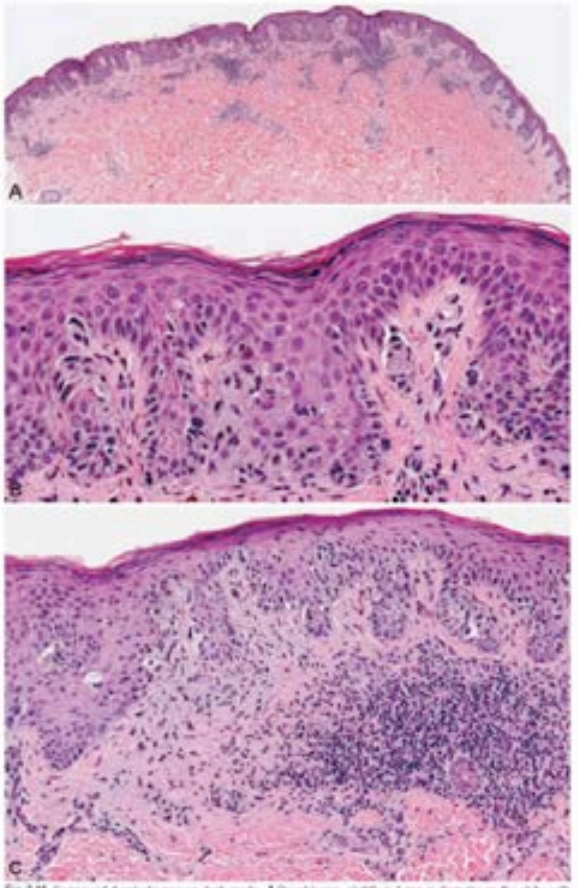


Fig. 2.15 Compound dysplastic naevus, high grade. **A** Broad lesion, slightly > 4 mm in diameter on the slide, with changes present at the left specimen edge. The rete ridges are somewhat irregularly thickened, although relatively uniformly elongated. There is a patchy to focally more dense lymphocytic infiltrate in the dermis, mostly perivascular and partly interstitial. Nests of melanocytes can be seen near the tips and sides of rete ridges, with some bridging nests. **B** Higher magnification shows that some of the lesional cells have a nuclear size > 1.5x that of resting basal keratinocytes, and have irregular hyperchromatic nuclei, constituting severe random cytological atypia. There is a focal tendency to confluence of lesional cell nests in the epidermis with only minimal evidence of upward scatter in this field. In the dermis, there are perivascular lymphocytes and melanophages, with subtle concentric fibroplasia at the tip of some rete. **C** In this focal area of the same lesion, there are changes that raise concern for evolving melanoma (at least in situ); there are large cells with similar cytology as seen in panel B, and there is a focal tendency to upward pagetoid scatter near the middle of the lesion, not beyond the mid-spinous layer. A few cells in the dermis (left of centre) resemble those in the epidermis, with an associated focus of diffuse fibroplasia. The lymphocytic infiltrate is focally band-like; there is well-developed eosinophilic fibroplasia around rete ridges on the right.

possible that stimuli from chronic ultraviolet (UV) radiation exposure and the resulting cumulative sun damage (CSD) acting on a naevus can promote the attributes of clinical and histological atypia.

Localization

The anatomical distribution of dysplastic naevi, like that of other naevi, only partially overlaps with that of melanoma, paralleling the distribution of melanoma in skin with a low degree of CSD (low-CSD melanoma) rather than that of high-CSD melanoma. Dysplastic naevi tend to arise in skin that is intermittently (rather than chronically) sun-exposed; the most common site is the back [456].

Clinical features

A widely adopted definition published by the International Agency for Research on Cancer (IARC) in 1990 (and subsequently modified) recommends the following criteria to identify atypical (dysplastic) naevi: there must be a macular component in at least one area; in addition, at least three of the following features must be present: a non–well-defined border, size ≥ 5 mm, colour variegation, uneven peripheral contour, and erythema [645]. The lesions almost always have a flat component (representing junctional proliferation), and there is often a central raised portion constituting a dermal component, resulting in a resemblance to a fried egg or a target. These criteria partially overlap with those for melanoma. Lesions with markedly atypical attributes, as well as new or changing lesions, should be submitted for histological evaluation to rule out melanoma. Dermoscopy and photographic follow-up and image analysis may be used to improve the specificity of clinical diagnosis [2840].

Histopathology

Melanocytic dysplasia comprises alterations of architectural disorder and cytological atypia [678]. The term "architectural disorder" refers to deviation from a stereotypical junctional naevus pattern (in which uniform nests of naevoid melanocytes are present at the tips of rete ridges uniformly across the lesion) and also indicates increased size of the lesions relative to common acquired naevi. There may be single cells between the nests, suggesting the evolution of a junctional naevus from a pre-existing simple lentigo and forming a lentiginous

"Dysplastic nevi are a subset of melanocytic nevi that are clinically atypical and characterized histologically by architectural disorder and cytological atypia, always involving their junctional component."

Low UV

Pathway I

Low-CSD Melanoma

Superficial Spreading Melanoma

Banal Acquired Nevus (junctional, compound, dermal)

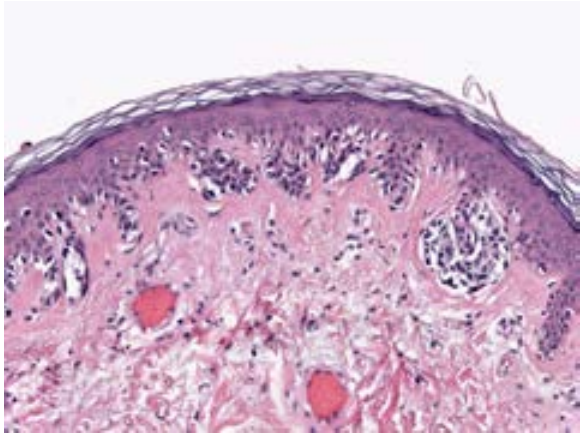
Low Grade Dysplasia

High Grade Dysplasia

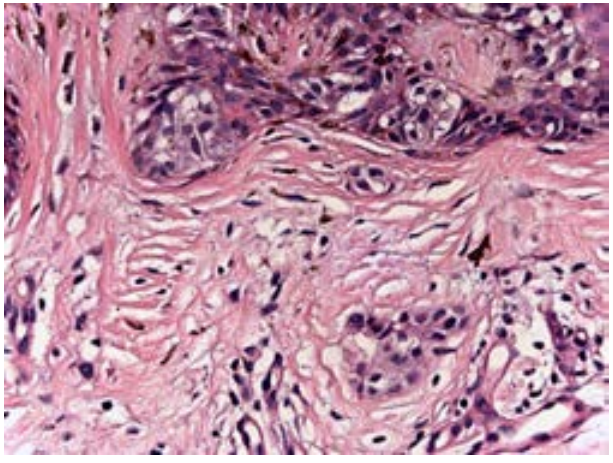
Superficial Spreading Melanoma

BRAF V600E, NRAS

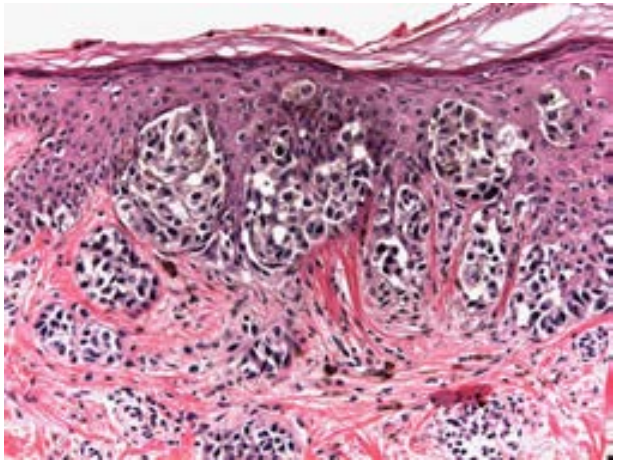
TERT, CDKN2A, TP53, PTEN



Lentiginous junctional nevus



Compound dysplastic nevus



Superficial spreading or “pagetoid” melanoma

Case 1.

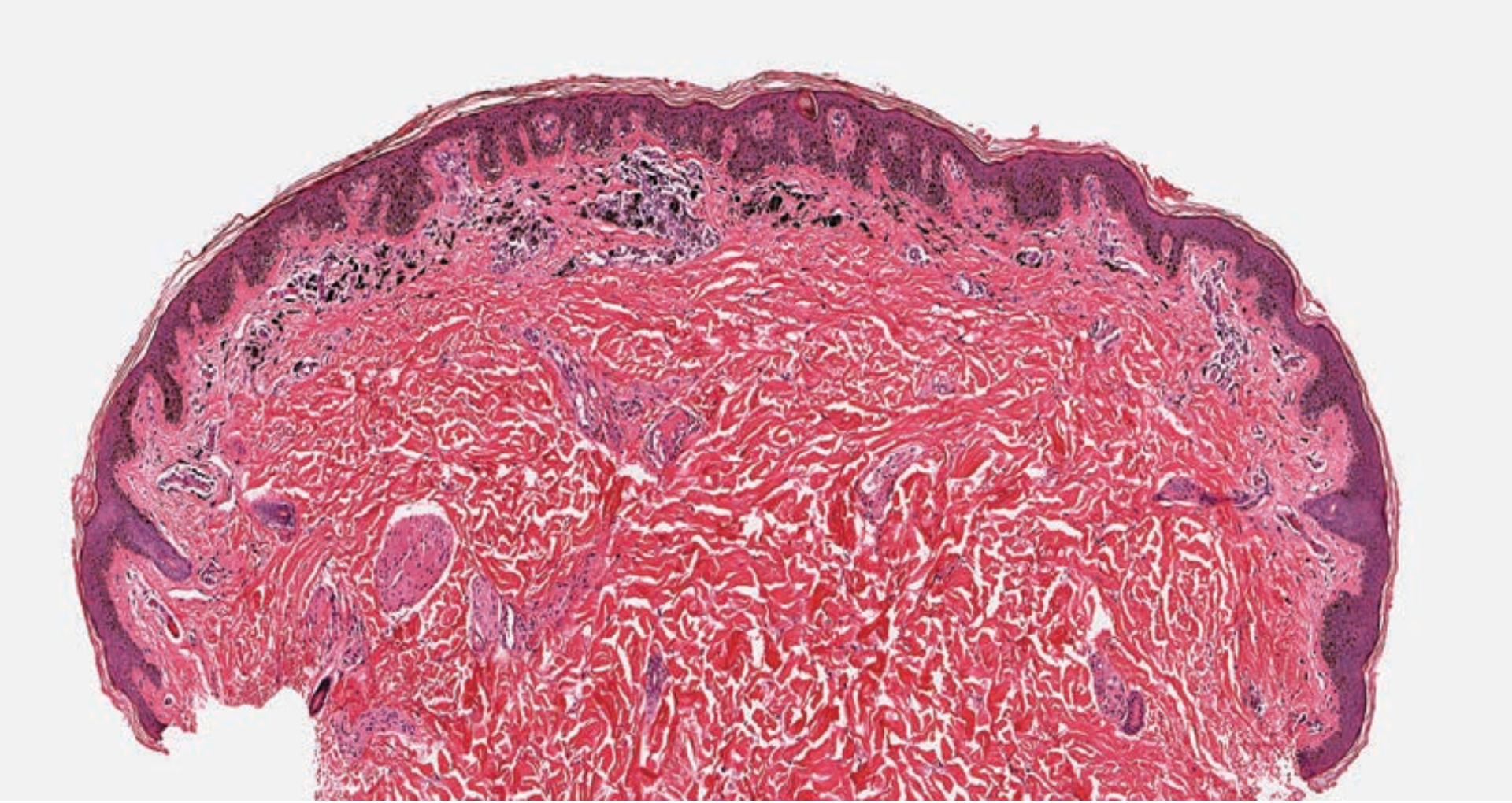
London SVS\25451.svs

Clinical Information.

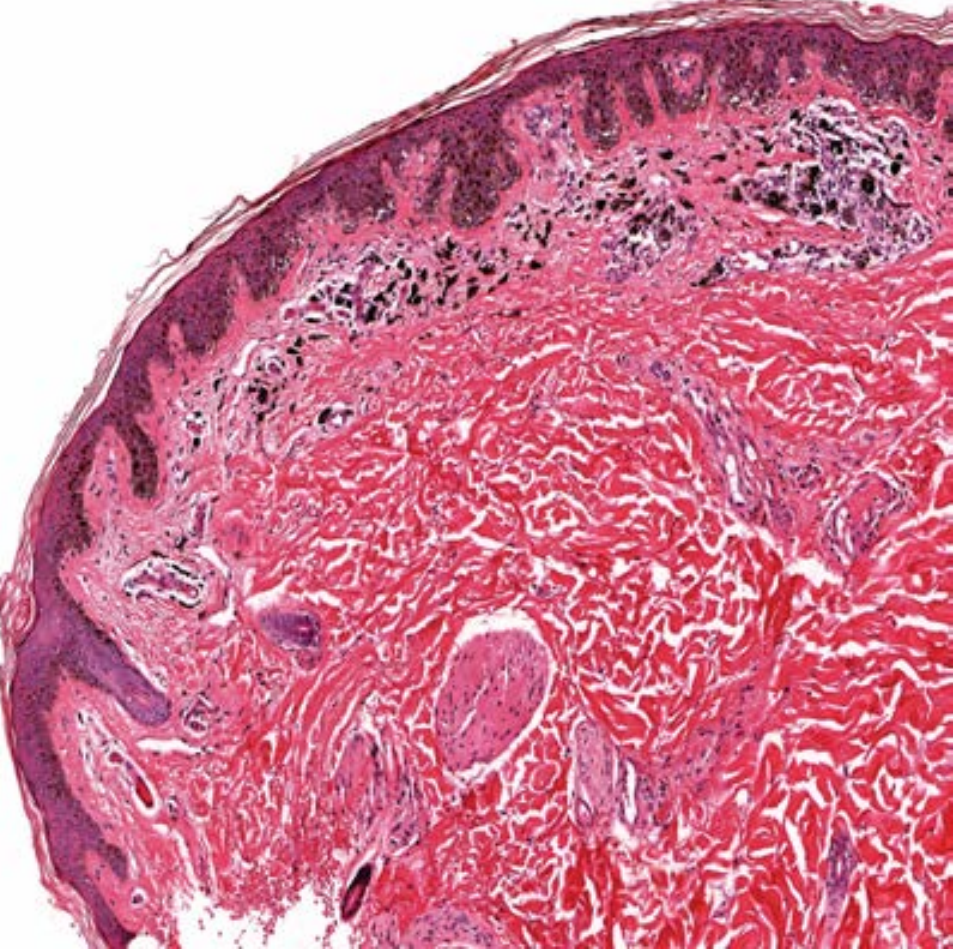
A macular slightly variegated lesion from the back of a 37-year-old woman.

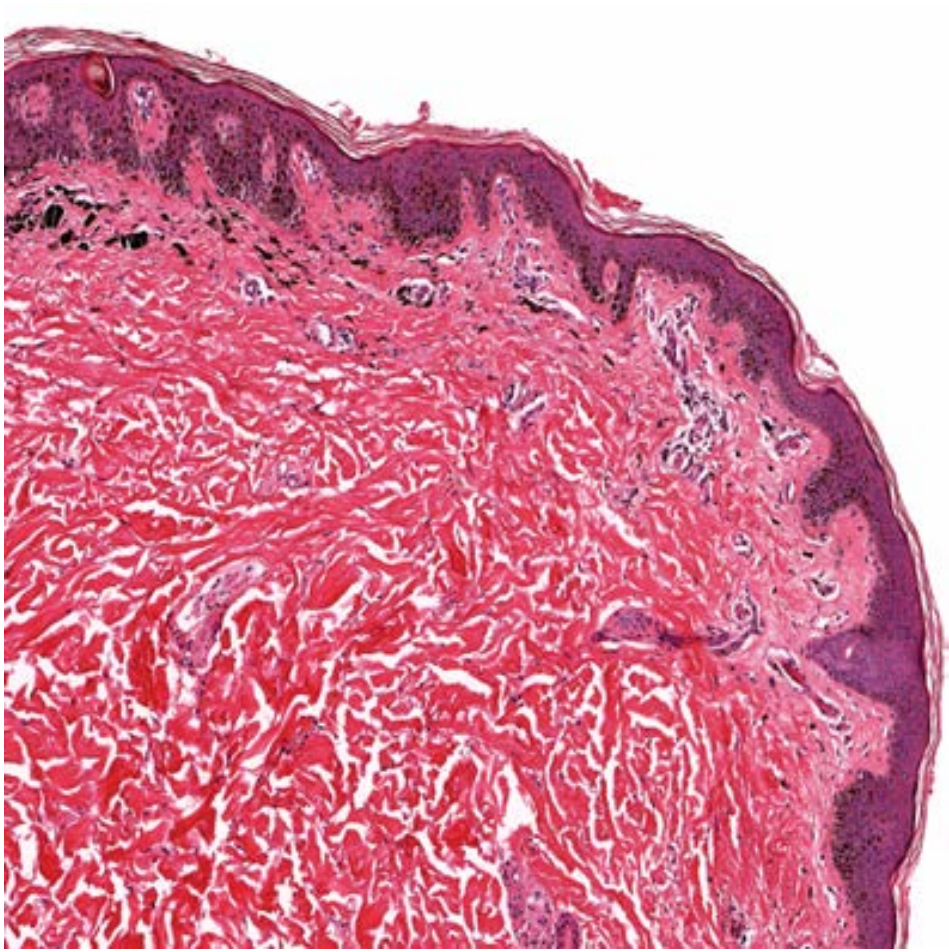
Reason for Consultation.

Is this a dysplastic nevus?

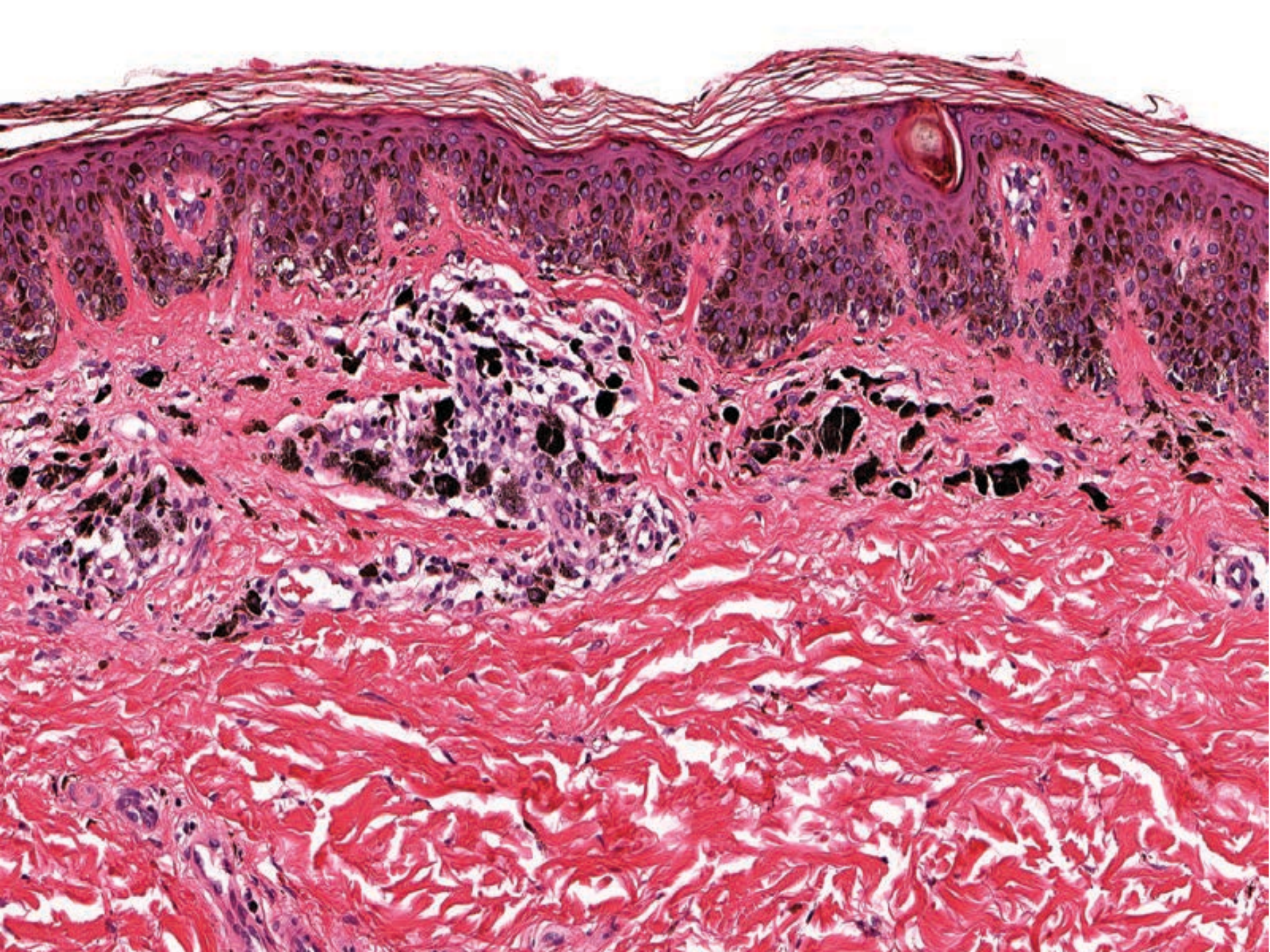


- **25451**
- ***Clinical Information.***
- A 3 mm macular slightly variegated lesion from the back of a 37-year-old woman.
- ***Reason for Consultation.***
- Is this a dysplastic nevus?

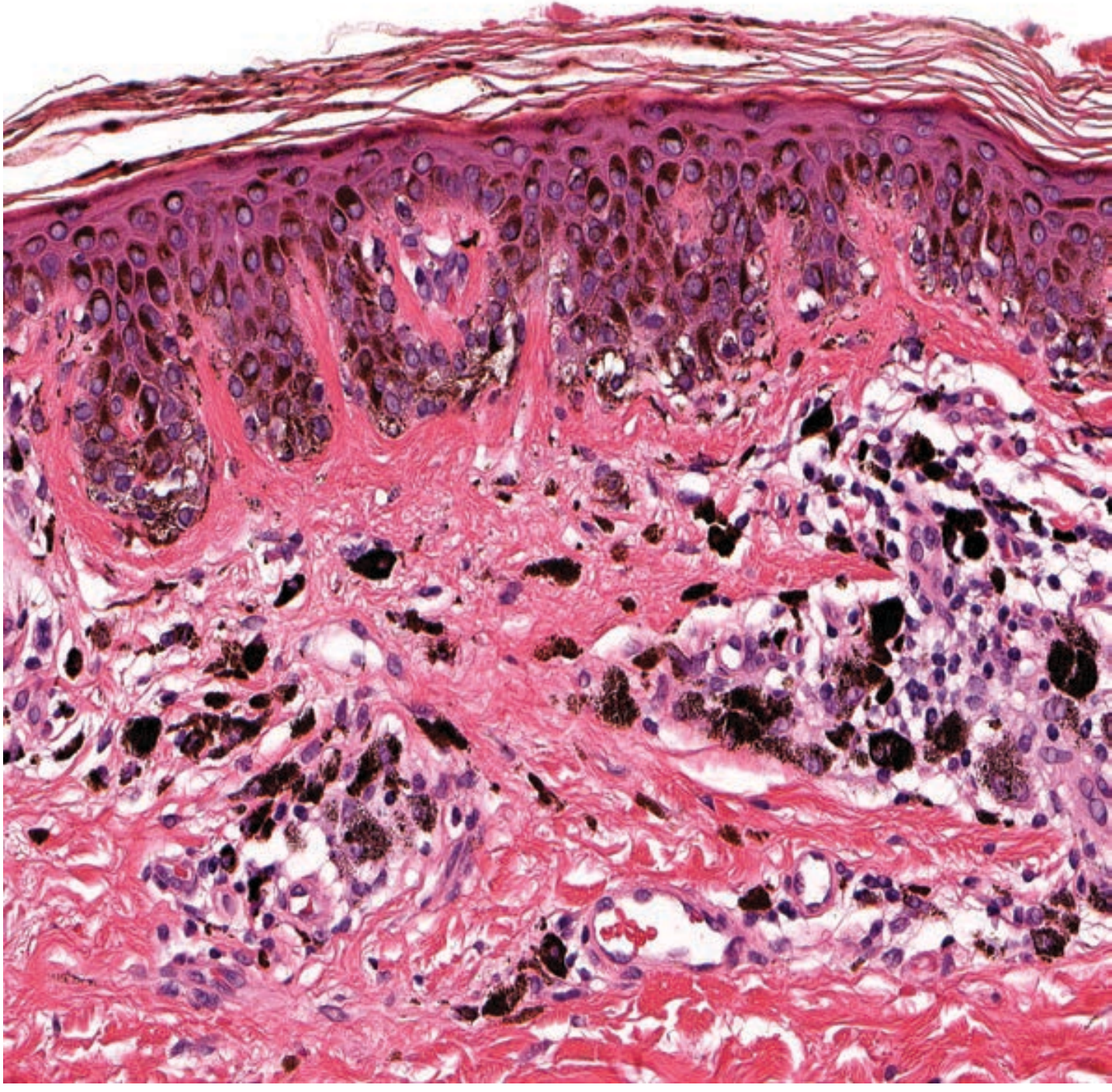




- Small
- Poorly circumscribed
- Nest predominate, discrete
- Patchy lymphocytes, scant fibroplasia, numerous melanophages (clinically atypical)



- Slight/absent cytologic atypia
- No mitoses



Your Diagnosis?

Melanoma?

Nevus?

Your Diagnosis?

Dysplastic?

Nondysplastic?

Criteria for Melanoma vs. Nevi

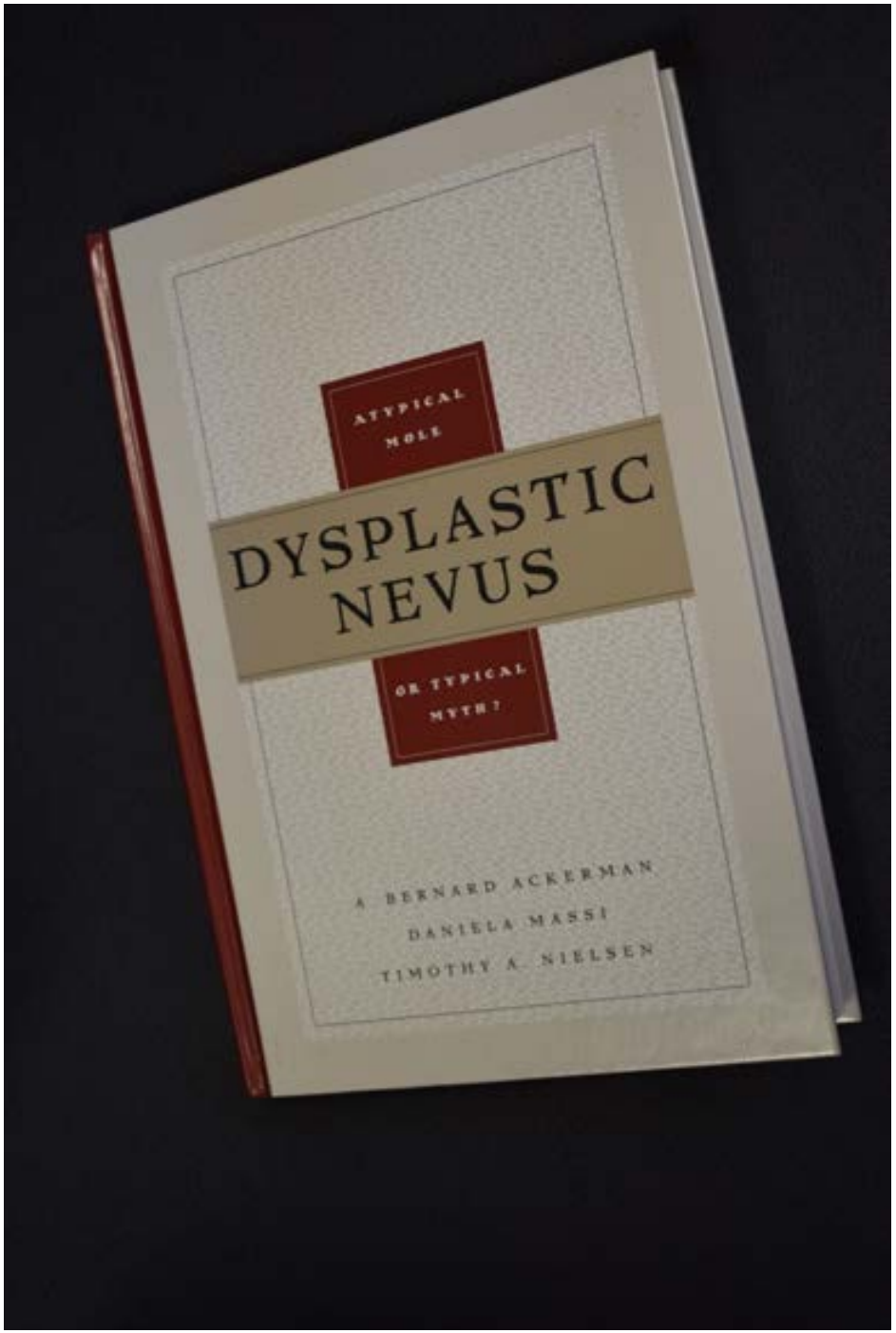
Feature	Melanoma	Dysplastic Nevus	Nevus
Size	larger	intermediate	smaller
Symmetry	poor	good	good
Rete ridges	irregular	uniformly elongated	uniform
Junctional Melanocytes	epithelioid	mixed	nevoid
Poor circumscription	cannot assess	less common	uncommon
Distribution of Nests	variable, irregular	predominant, regular	predominant, regular
Distribution of Nests	coalescent (confluent)	bridging	discrete
Size of Nests	variable	uniform	uniform
Lentiginous (single cells)	continuous	discontinuous	minimal
Pagetoid	high, extensive	low, focal, minimal	minimal
Nuclear atypia	uniform, moderate-severe (size > 1.5x)	random, mild-moderate (1-1.5x)	minimal (1x)
Mitoses – junctional/dermal	about 1/3 of cases	almost always absent	absent
Pyknosis/necrosis	common	uncommon	none
Fibroplasia	diffuse	concentric	minimal
Lymphocytes	bandlike, lichenoid	patchy, perivascular	minimal
Regression	frequent, extensive	rare, minimal	absent
Dermal Cells	uniform atypia limited maturation mitoses	random or no atypia maturation no mitoses	no atypia maturation no mitoses

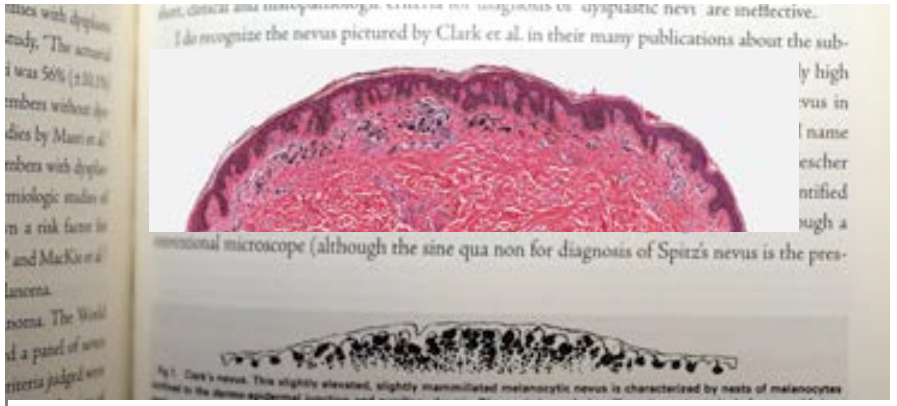
Diagnosis, Case 2, F37.

- ***Diagnosis.***

- **Skin, abdomen:**
  - **Lentiginous compound nevus (WHO, 2018)**

- This is an MPATH Category 1 lesion (no need for reexcision even if margins are positive).





Dysplastic nevi have been heavily over-diagnosed

Superficial Atypical Nevi.

- Nevi are important mainly in relation to melanoma
  - Precursors – but risk for individual lesions is low (one in thousands)
  - Risk markers – important mainly in high risk situations (patients with multiple atypical nevi, family history, high CSD etc.)
  - Simulants – important in everyday clinical decision-making.

Superficial Atypical Nevi.

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  - Risk markers – important mainly in high risk situations (patients with multiple atypical nevi, family history, high CSD etc.)
  - Simulants – important in everyday clinical decision-making.

Case 2.

Part 2-3.

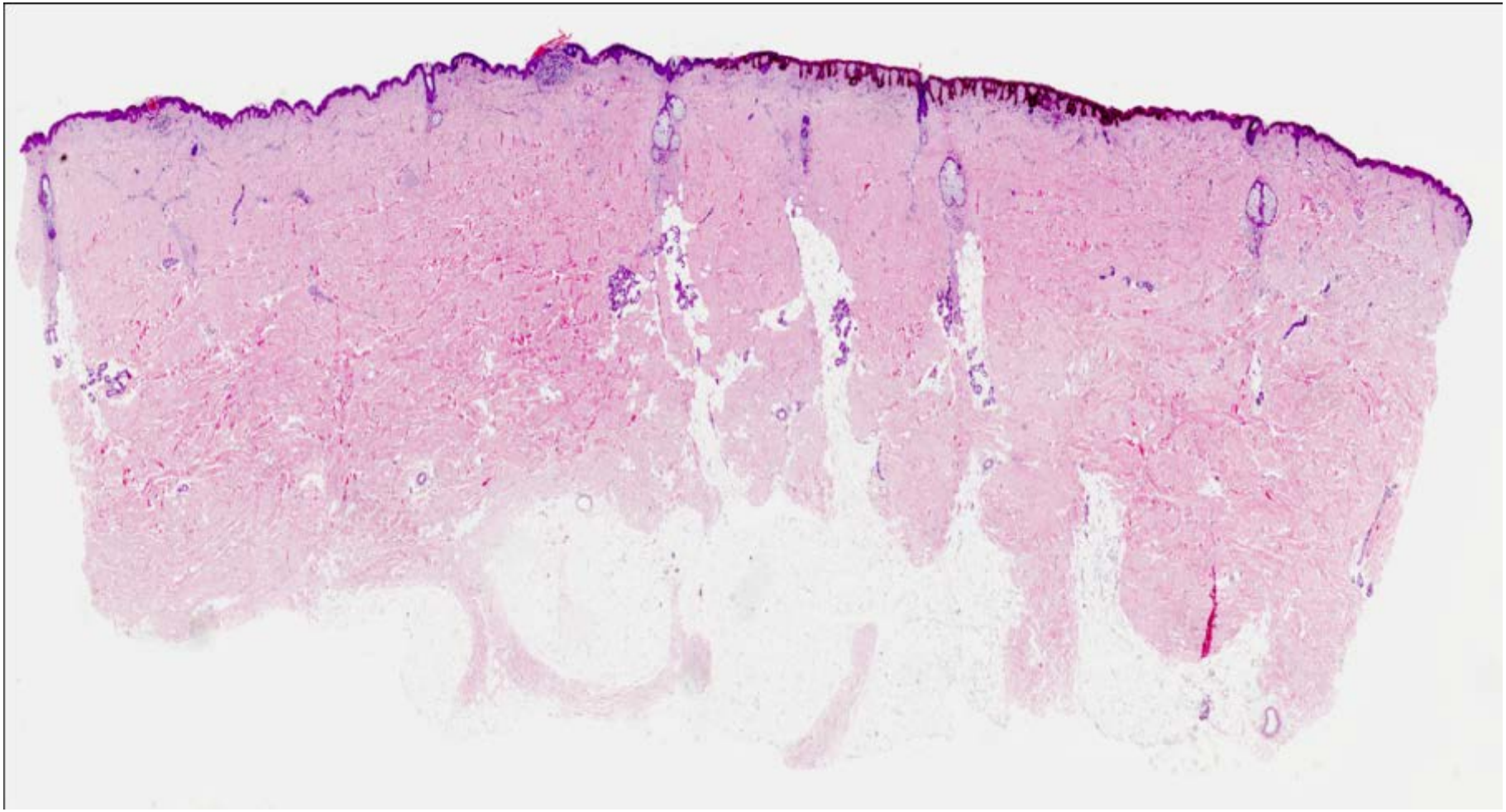
London SVS\1001309.svs

Clinical Information:

A lesion from the back of a 54 year old man

Reason for consultation:

The clinician was concerned about a melanoma but I favor a dysplastic nevus.



Description:

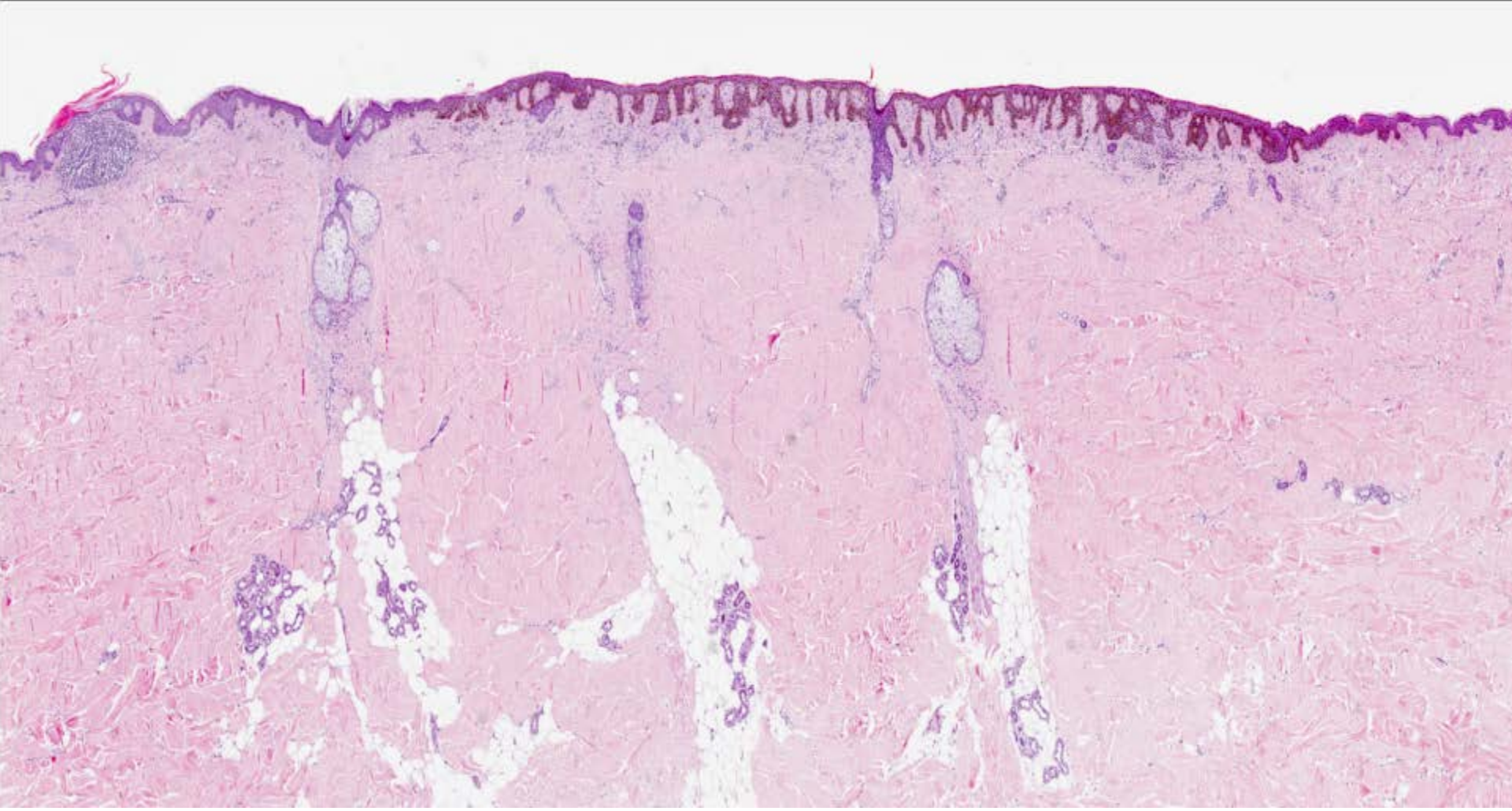
Very broad

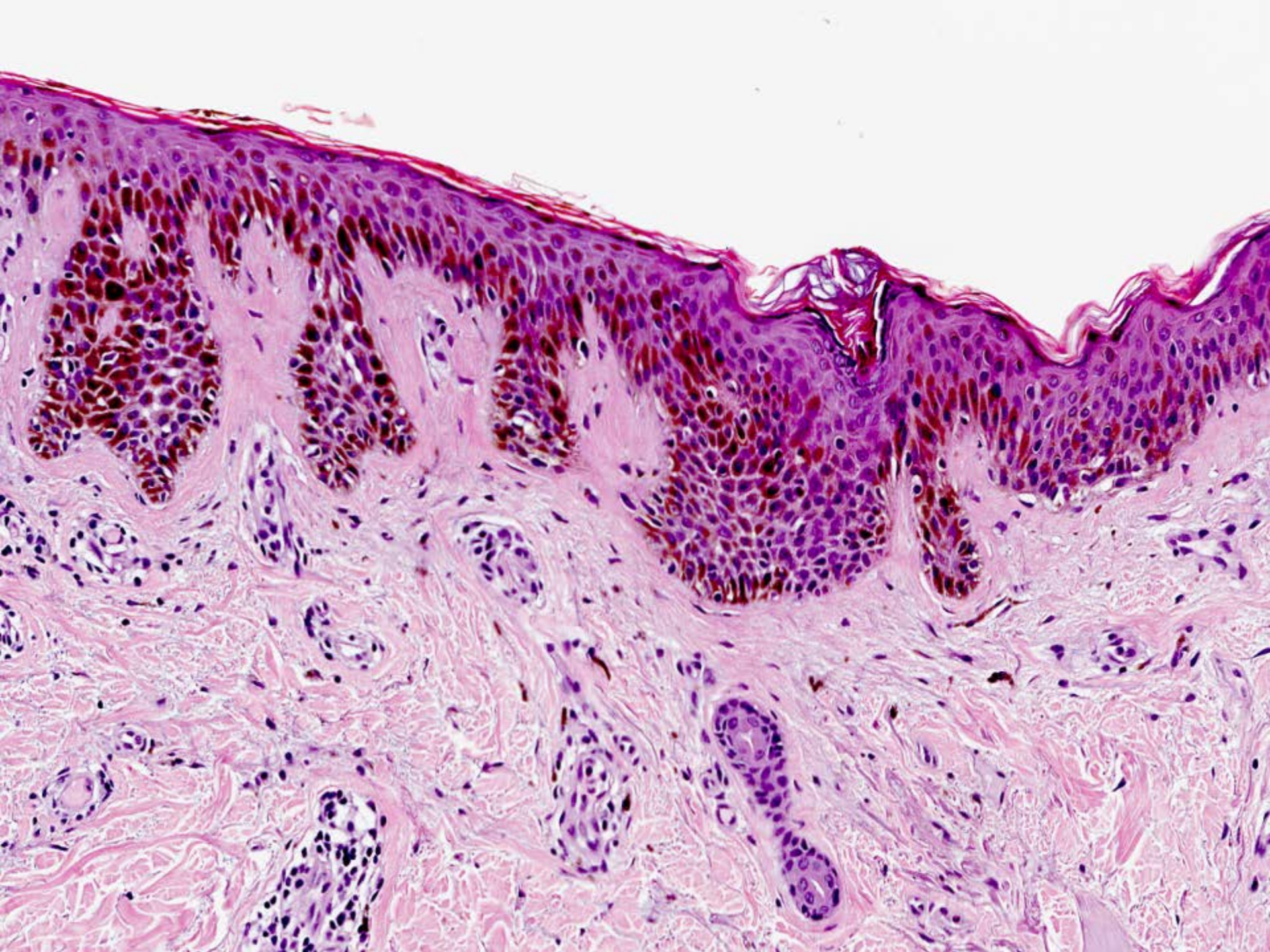
Moderately cellular

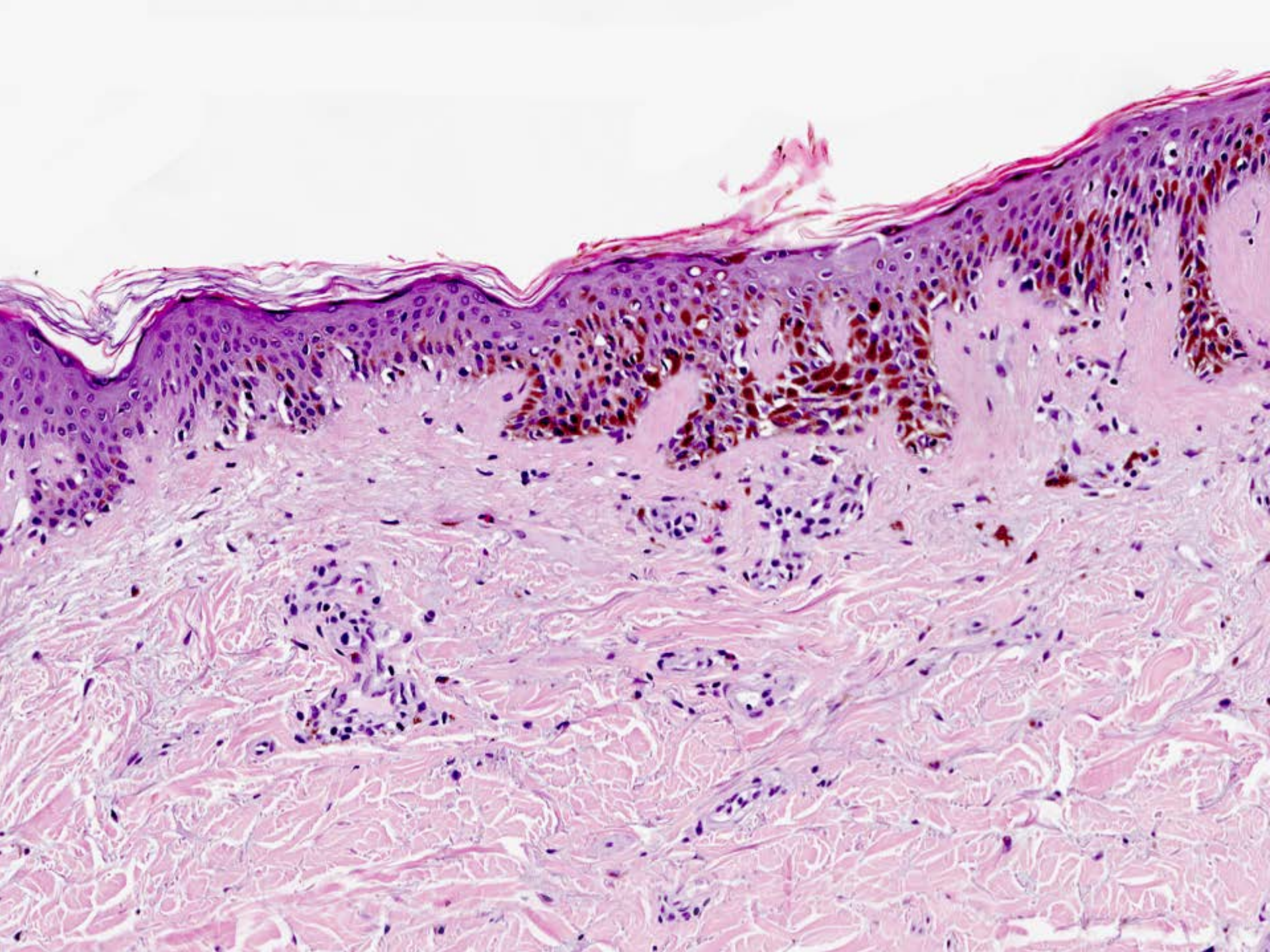
Reasonably symmetrical

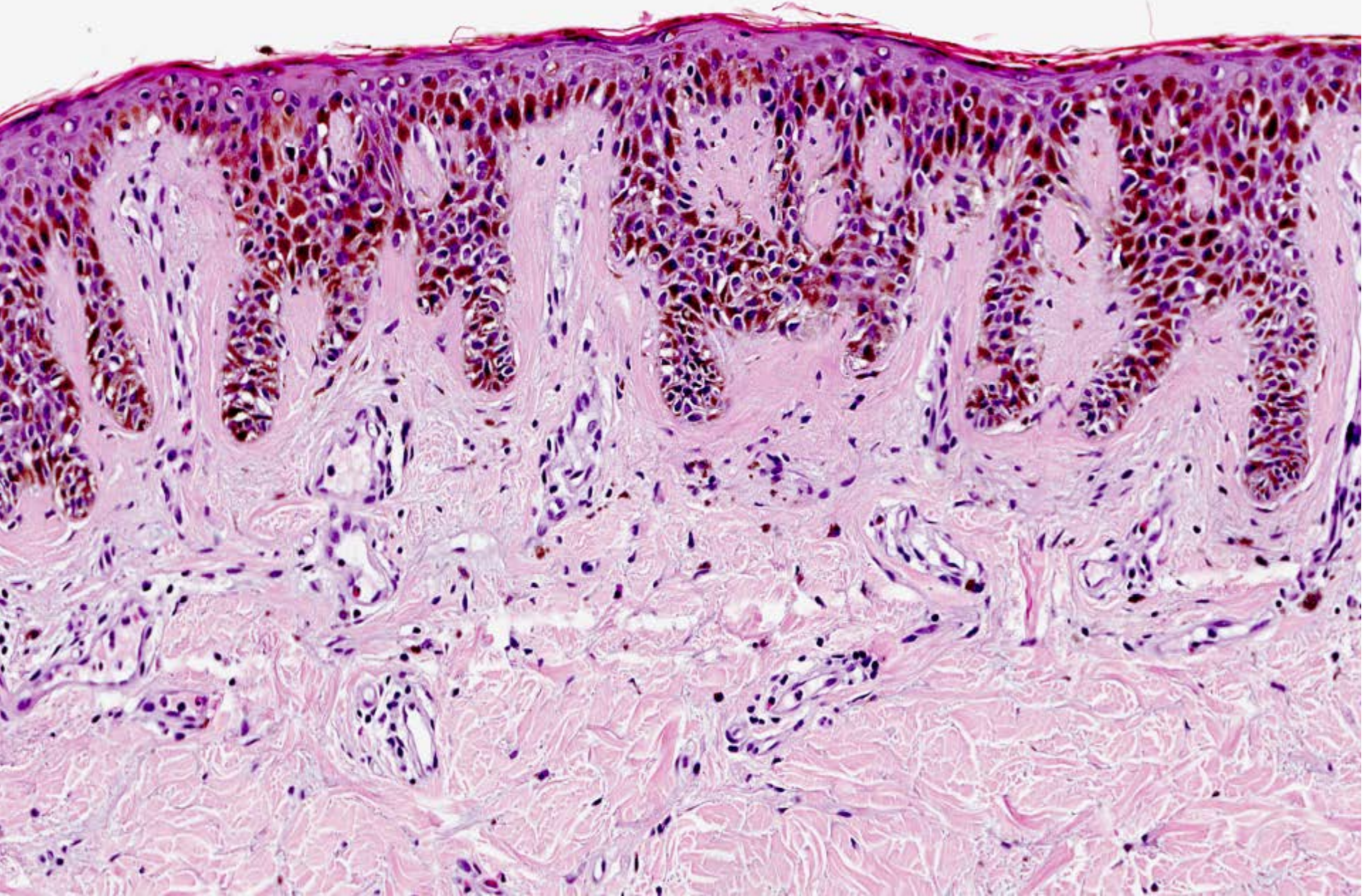
Uniformly elongated rete

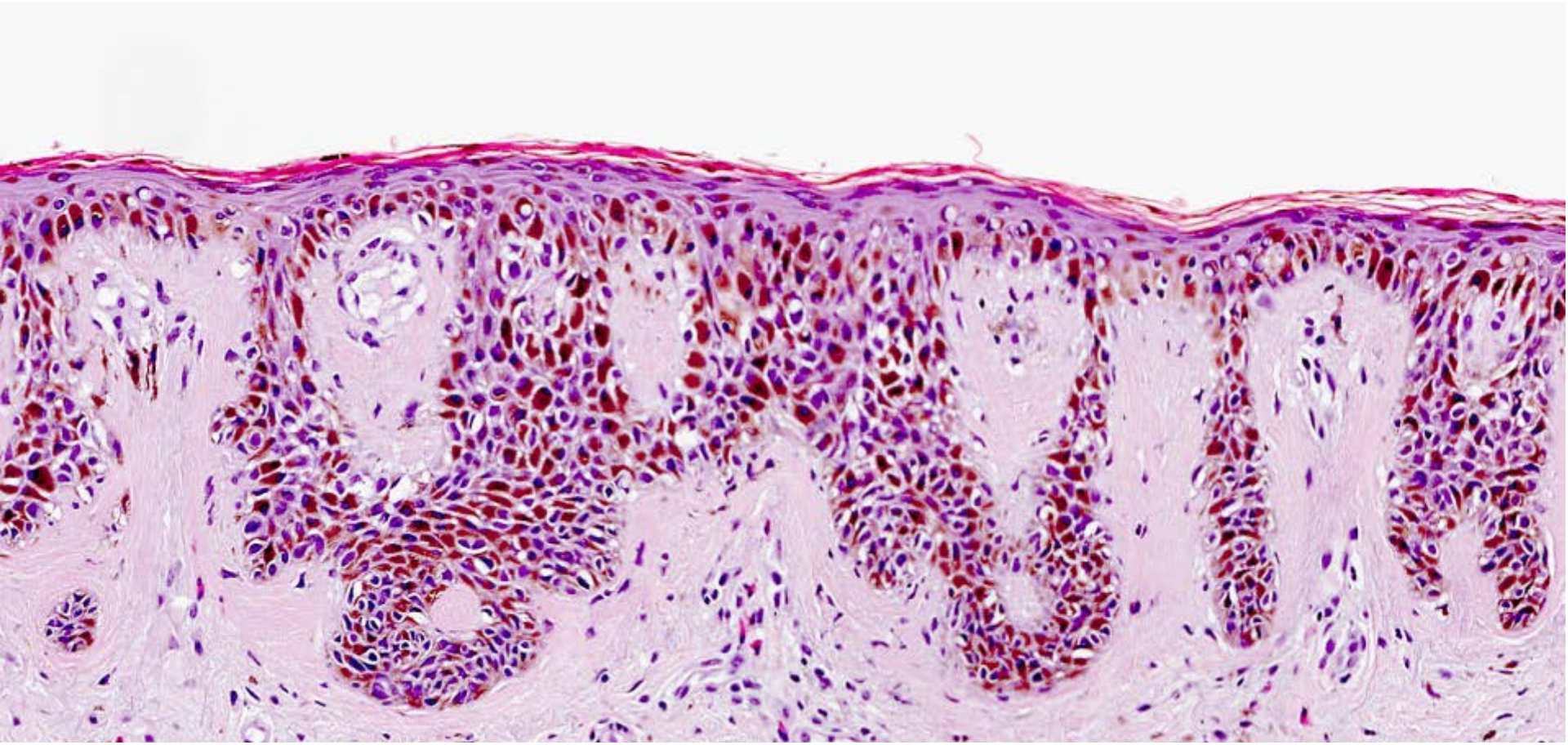
Patchy infiltrate in dermis











- ***Description***:
- Very broad level
- Moderately cellular
- Reasonably symmetrical
- Uniformly elongated rete
- Patchy infiltrate in dermis

Moderate pagetoid scatter, low

Mild to moderate cytologic atypia

Mild to moderate solar elastosis

Your Diagnosis?

Melanoma?

Nevus?

Your Diagnosis?

Dysplastic?

Nondysplastic?

Your Diagnosis?

Low Grade?

High Grade?

Compound nevus with severe dysplasia

(Severe architectural disorder, moderate cytological atypia)

Feature	Melanoma	Dysplastic Nevus	Nevus
Size	larger	intermediate	smaller
Cellularity	high	intermediate	lower
Symmetry	poor	good	good
Rete ridges	irregular	uniformly elongated	uniform
Junctional Melanocytes	epithelioid	mixed (nevoid to epithelioid)	nevoid
Poor circumscription	common	less common	uncommon
Nested	variable	predominant	predominant
Nests	coalescent (confluent)	bridging	discrete
Size of Nests	variable	uniform	uniform
Lentiginous	continuous	discontinuous	discontinuous
Pagetoid	high, extensive	low, focal, minimal	minimal
Nuclear atypia	uniform atypia, moderate-severe	random atypia, mild-moderate (1-1.5X)	minimal, mild
Mitoses - junctional	about 1/3 of cases	almost always absent	absent
Pyknosis/necrosis	common	uncommon	uncommon
Fibroplasia	diffuse	concentric	minimal
Lymphocytes	bandlike, lichenoid	patchy, perivascular	minimal
Regression	frequent, extensive	rare, minimal	absent
Dermal Cells Absent	uniform atypia limited maturation mitoses	random or no atypia maturation no mitoses	no atypia maturation no mitoses

Diagnosis, Case 2

- Junctional dysplastic nevus, high grade (WHO 2018)

- vs. Junctional nevus with severe melanocytic dysplasia
  - Completely excised
  - Diagnosis is based on “severe” architectural features (single cell predominance, low level pagetoid scatter), with mild to moderate cytologic atypia.
  - MPATH-Dx Category III (consider excision with up to 5 mm margins, if present at the margin)

Case 3.

Part 2-5. **35728**

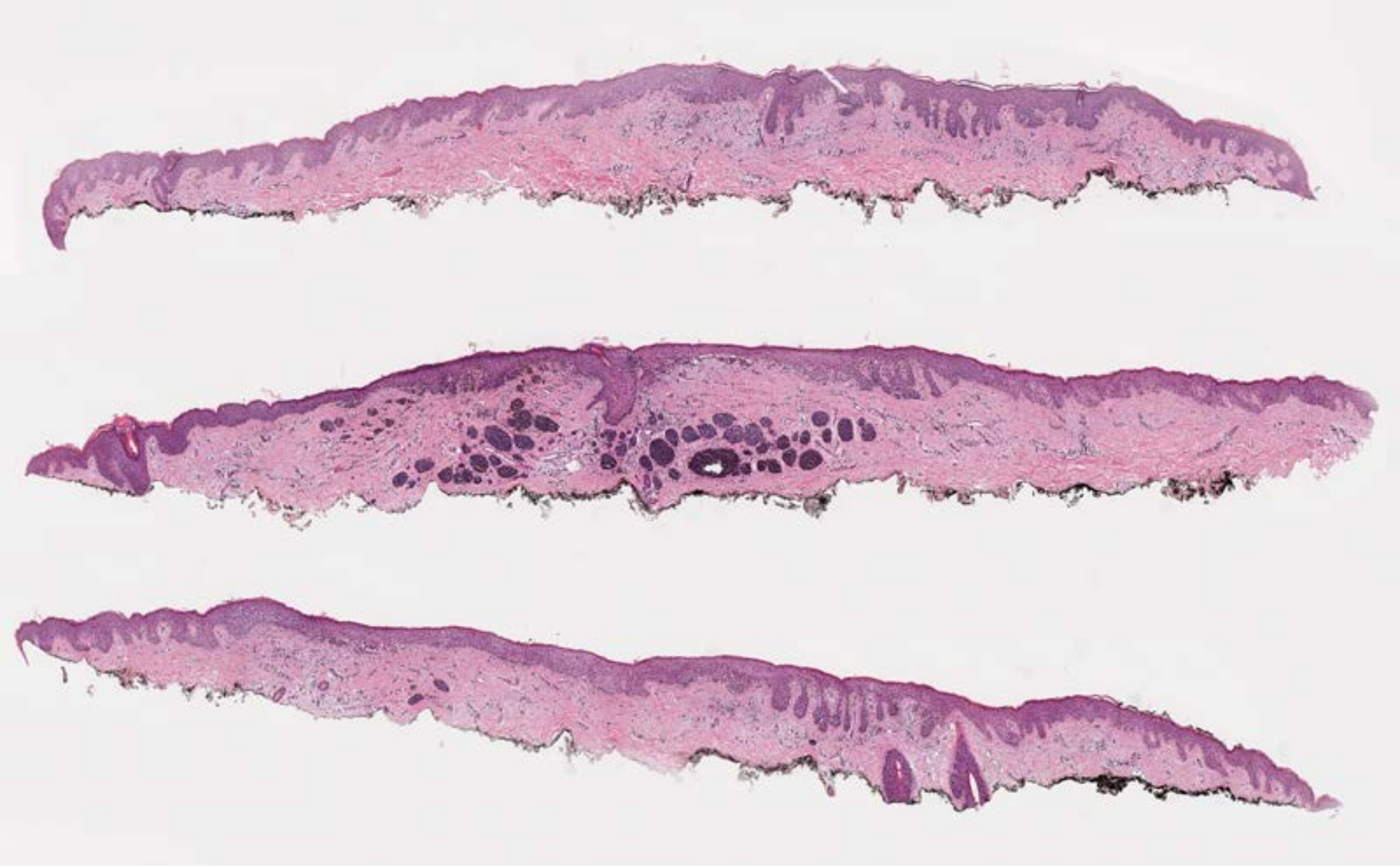
London SVS\35728.svs

Clinical Information.

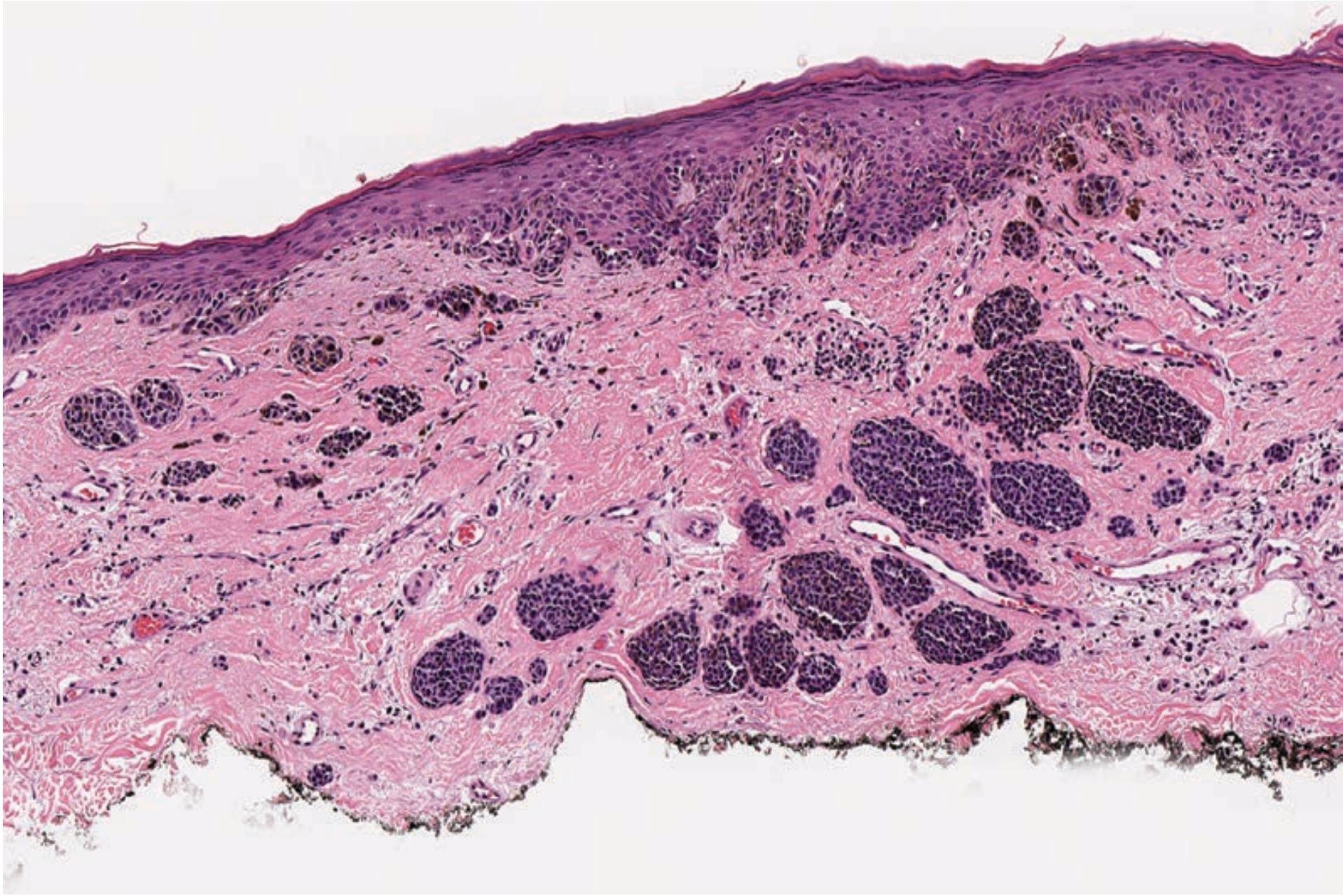
An irregular pigmented lesion on the back of a 59 year old man

Reason for Consultation.

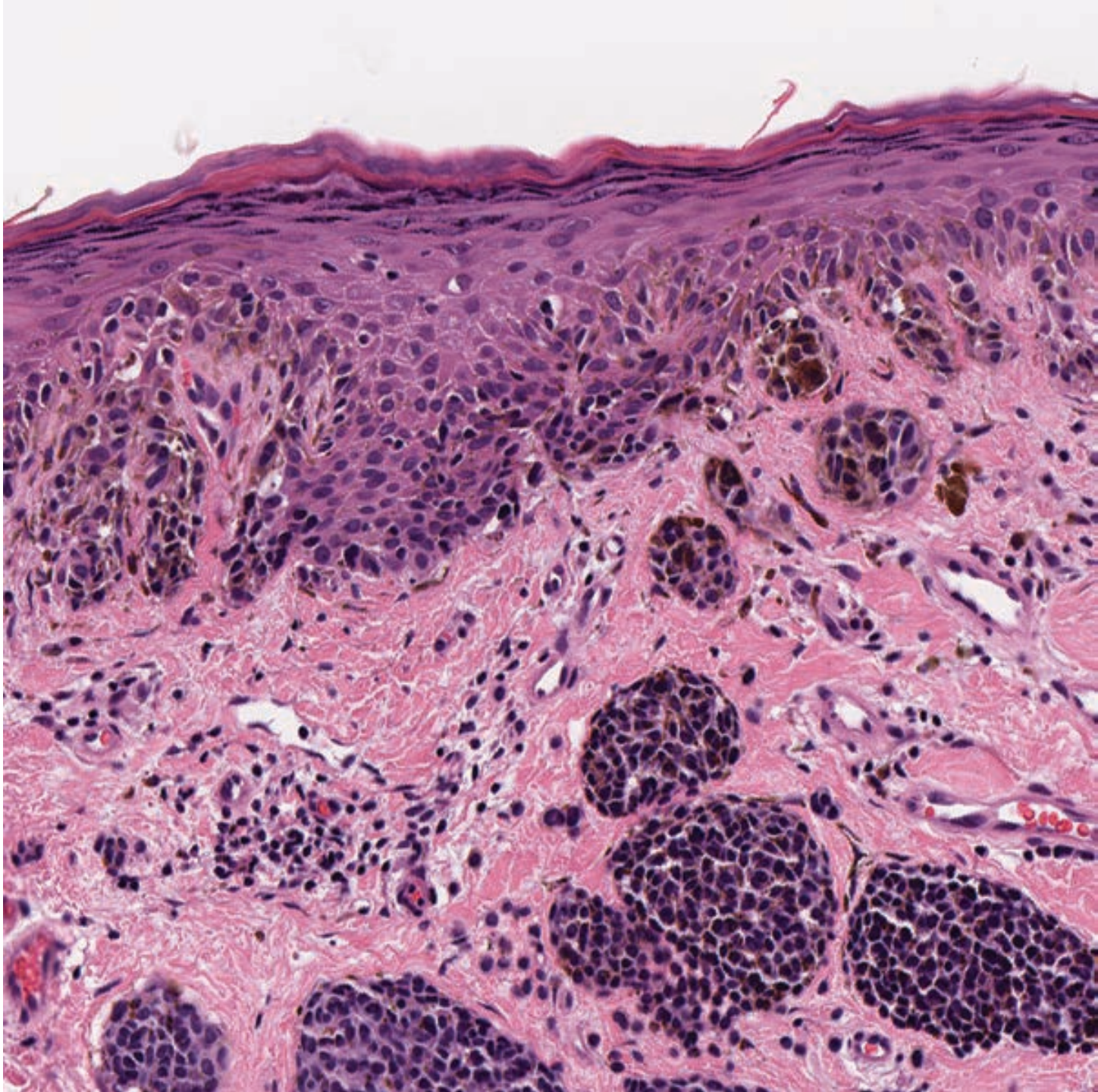
Is this a nevoid melanoma?



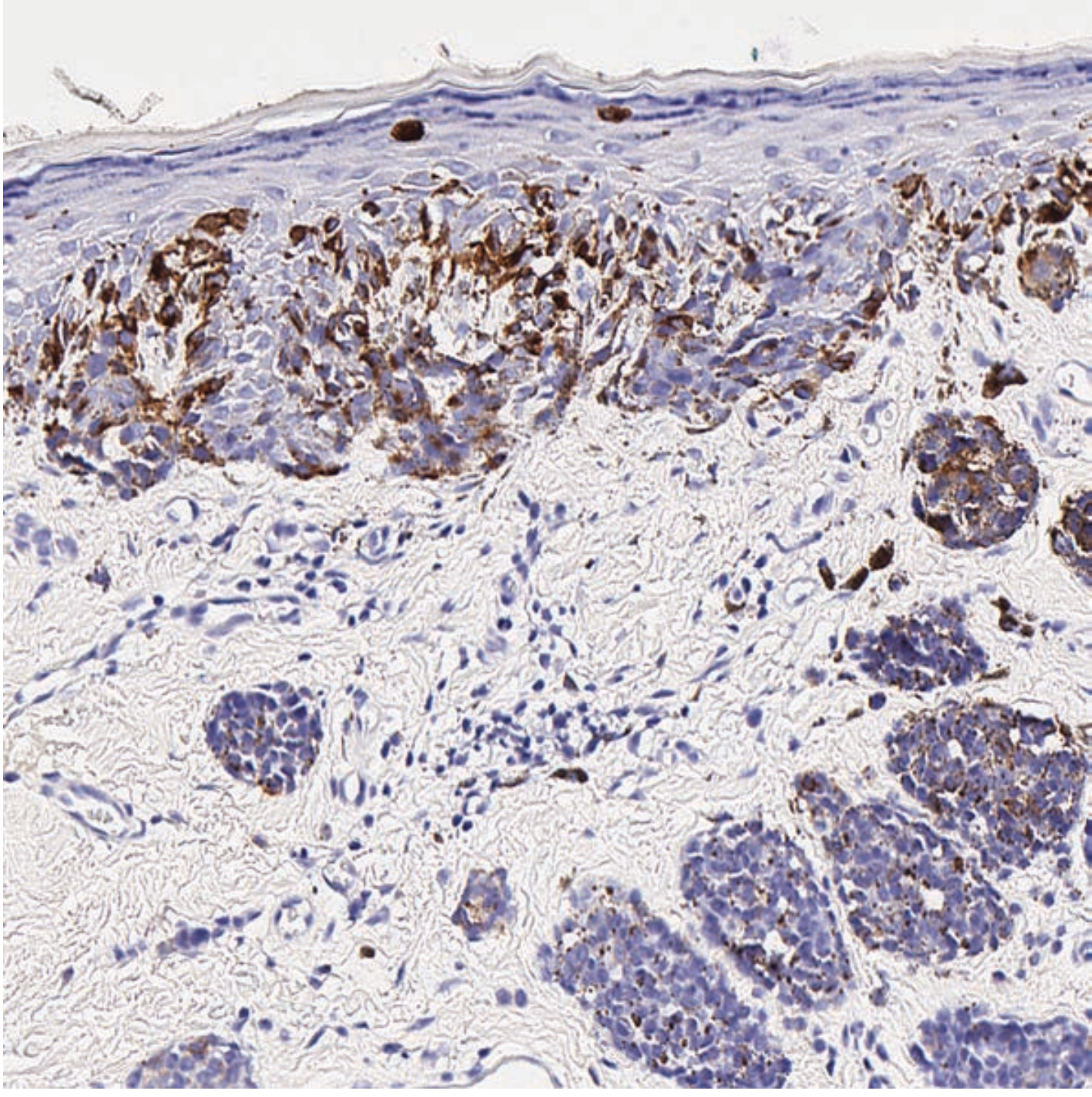
Broad, focally highly cellular, asymmetric diffuse fibroplasia and variably sized nests in dermis



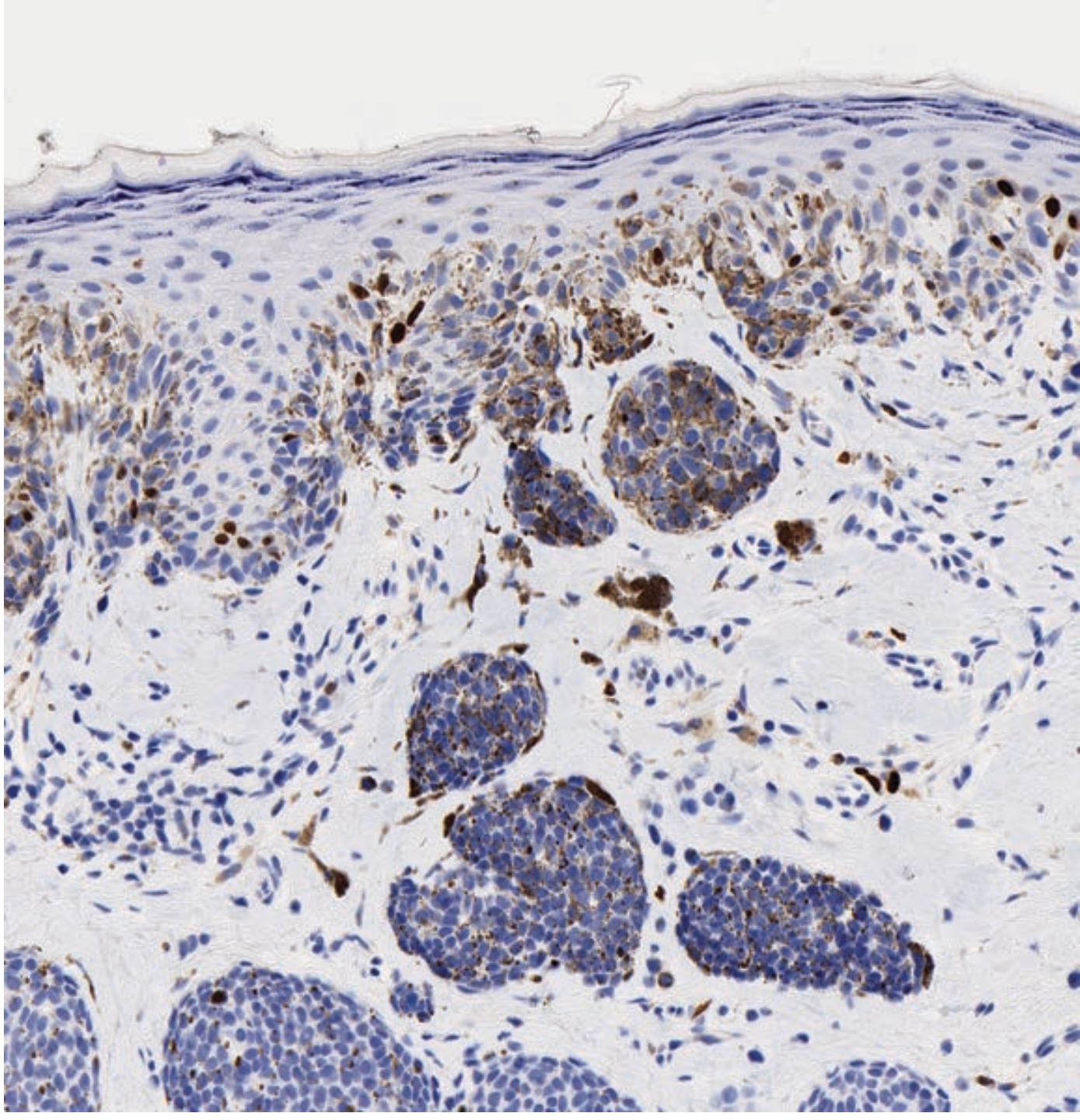
- Only minimal pagetoid scatter
- Moderate cytologic atypia
- No mitoses
- Cells in dermal nests are small, nevoid
- No confluent sheetlike growth



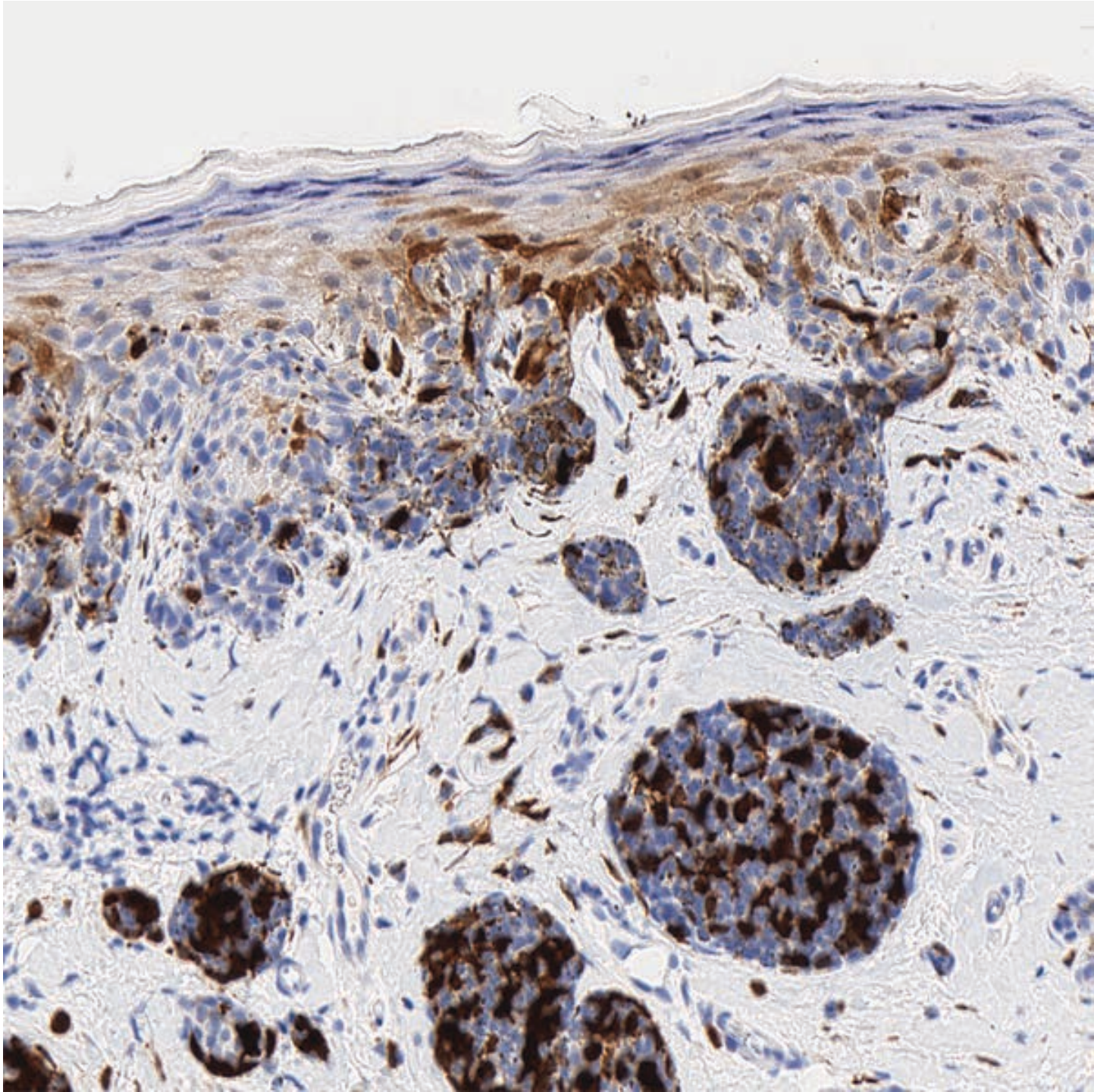
HMB45 staining is “top-heavy” (stratified)



- Ki-67 proliferation is minimal in dermis



- p16 staining is positive in a checkerboard (“mosaic”) pattern, with nuclear and cytoplasmic positivity



Helpful Markers in Nevus vs. Melanoma

- HM45 stratification
  - J Invest Dermatol. 1993 Mar;100(3):313S-317S. Immunophenotyping of compound and spitz nevi and vertical growth-phase melanomas using a panel of monoclonal antibodies reactive in paraffin sections.
    Lazzaro B1, Elder DE, Rebers A, Power L, Herlyn M, Menrad A, Johnson B.
- Low Ki-67 proliferation rate
  - A zonal comparison of MIB1-Ki67 immunoreactivity in benign and malignant melanocytic lesions.
    Li LX, Crotty KA, McCarthy SW, Palmer AA, Kril JJ.
    Am J Dermatopathol. 2000 Dec;22(6):489-95.
- Preservation of p16 protein expression
  - More problematical; presence in an atypical tumor at least precludes homozygous loss of 9p21 and is therefore reassuring but does not preclude diagnosis of melanoma
  - Absence of p16 is probably always concerning

9p21 Locus

- Contains p16, p14 and p15, all suppressor genes
- Presumably all lost together in cases of homozygous 9p21 loss
- May have special significance in Spitzoid lesions
- Also in melanoma progression (nevus vs. melanoma)

A p16-Ki-67-HMB45 immunohistochemistry scoring system as an ancillary diagnostic tool in the diagnosis of melanoma.

Uguen A, Talagas M, Costa S, Duigou S, Bouvier S, De Braekeleer M, Marcorelles P. Diagn Pathol. 2015 Oct 26;10:195

Built an immunomarker-based score to differentiate nevi from melanomas.

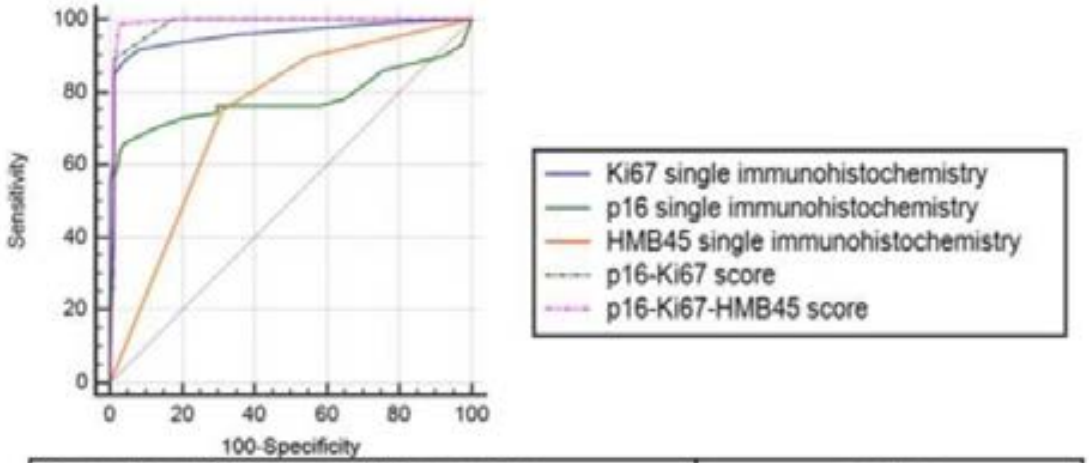
- **METHODS:**

A TRAINING SET AND A VALIDATION SET

Built a SCORING SYTSTEM

A “p16-Ki67-HMB45” score classified nevi with a sensitivity of 97.4% and a specificity of 97.3% in the training set

Sensitivity and specificity of 100% were obtained in a validation set

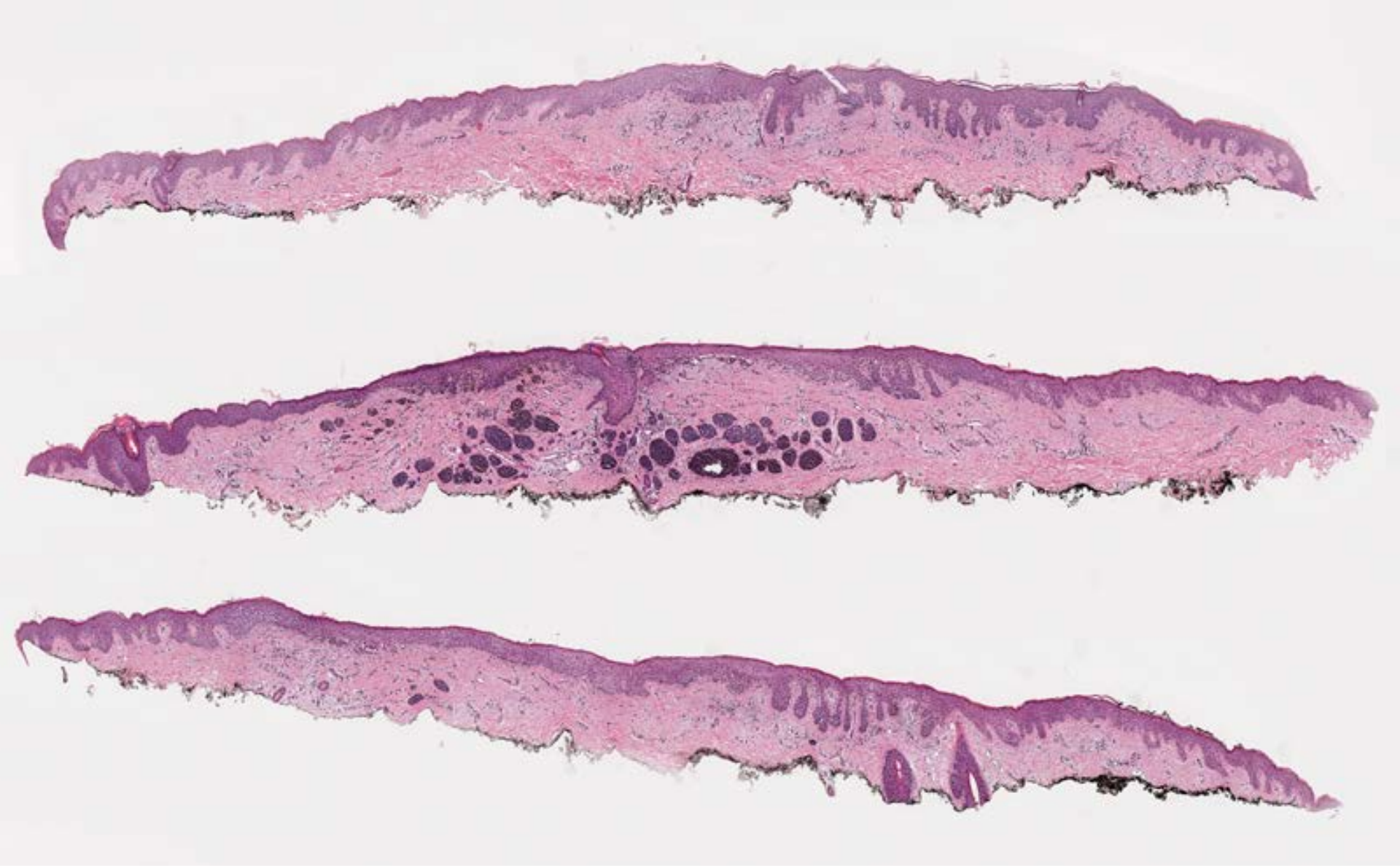


Comparison of ROC curves AUC: parameters	p-values
Ki-67 vs p16	p<0.0001
Ki-67 vs HMB45	p<0.0001
Ki-67 vs p16-Ki-67 score	p=0.0532
Ki-67 vs p16-Ki-67-HMB45 score	p=0.0220
p16 vs HMB45	p=0.4239
p16 vs p16-Ki-67 score	p<0.0001
p16 vs p16-Ki-67-HMB45 score	p<0.0001
HMB45 vs p16-Ki-67 score	p<0.0001
HMB45 vs p16-Ki-67-HMB45 score	p<0.0001
p16-Ki-67-HMB45 score vs p16-Ki-67 score	p=0.0801

Fig. 2 Receiver Operating Characteristic (ROC) curves comparison of single and combined immunohistochemical analyses and *p*-values of the Areas Under the Curves (AUC) of the Receiver Operating Characteristic curves of single and combined immunohistochemical analyses

Uguen A, Talagas M, Costa S, Duigou S, Bouvier S, De Braekeleer M, Marcorelles P. Diagn Pathol 2015 Oct 26;10:195

A p16-Ki-67-HMB45 total score from 0 to 9 permitted to classify nevi (score <4) and primary melanomas (score ≥4) with a sensitivity of 97.4% and a specificity of 97.3% in the first set of tumours.



Broad, focally highly cellular, asymmetric diffuse fibroplasia and variably sized nests in dermis

Ki-67 low, HMB45 stratified, p16+

Your Diagnosis?

Melanoma?

Nevus?

Your Diagnosis?

Dysplastic?

Nondysplastic?

Your Diagnosis?

High Grade?

Low Grade?

Case 3, M59, back

Feature	Melanoma	Dysplastic Nevus	Nevus
Size	larger	intermediate	smaller
Cellularity	high	intermediate	lower
Symmetry	poor	good	good
Rete ridges	irregular	uniformly elongated	uniform
Junctional Melanocytes	epithelioid	mixed (nevoid to epithelioid)	nevoid
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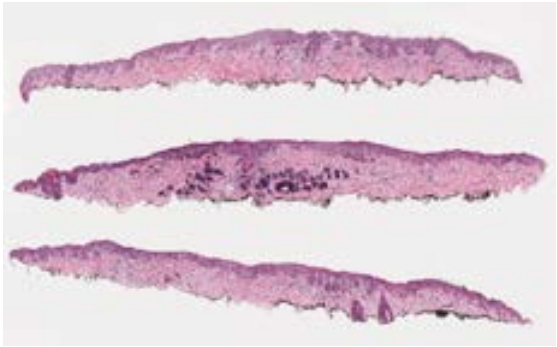
Regression	frequent, extensive or focal	rare, minimal	absent
Dermal Cells Absent	uniform atypia	random atypia	no atypia
	limited maturation	maturation	maturation
	mitoses	no mitoses	no mitoses

Diagnosis. Case 3, M59.



- **Skin, right, mid back: Compound nevus with severe dermal and epidermal dysplasia and dermal fibrosis (“sclerosing atypical nevus”, “fibrosing dysplastic nevus"), extending close or to specimen base and margins, see description and final comment.**

- **OR - Dysplastic nevus, high grade, with a sclerosing dermal component**

J Cutan Pathol 2008: 35: 995–1002
doi: 10.1111/j.1600-0560.2007.00941.x
Blackwell Munksgaard. Printed in Singapore

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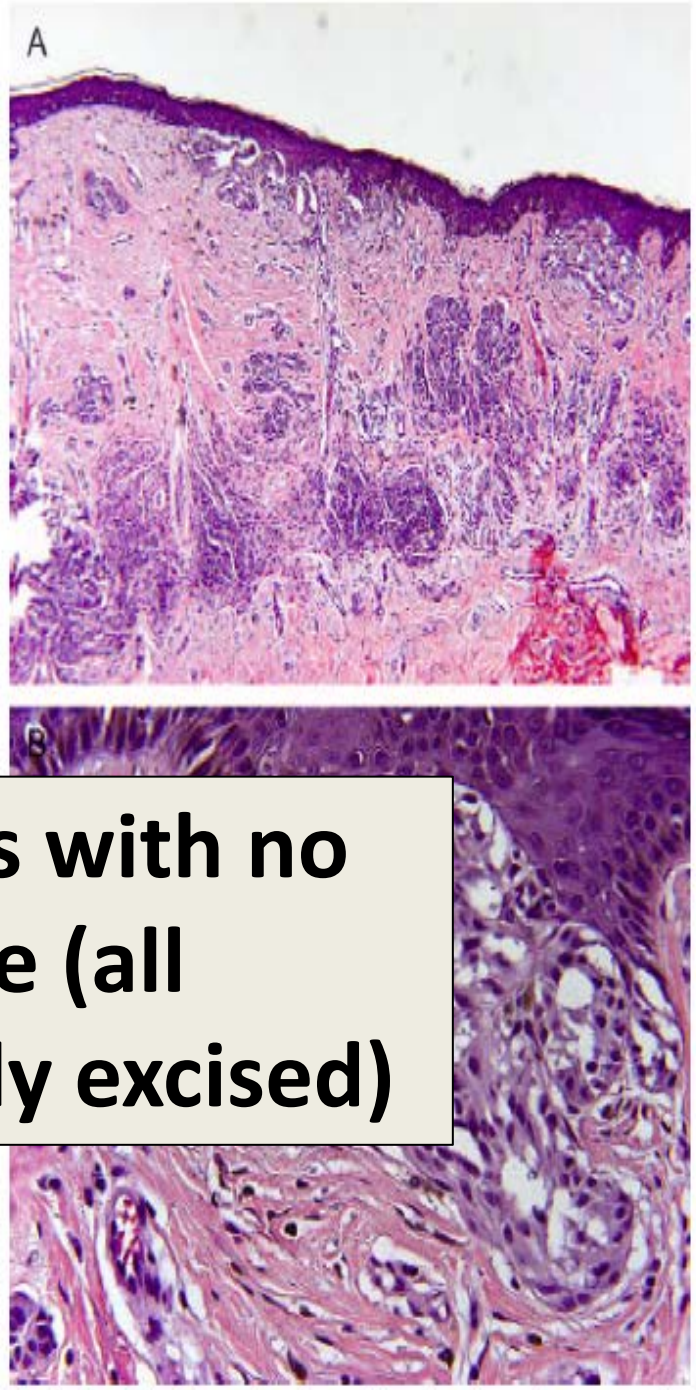
Journal of
Cutaneous Pathology

Sclerosing nevus with pseudomelanomatous features

Background: Among the pigmented lesions with a central area of scar, we found a group of cases histologically characterized by striking architectural alteration of the melanocytic component, but with no cytological atypia and mitotically quiescent. The aim of the current study was to assess the biological nature of such lesions.
Methods: We selected 19 of these melanocytic neoplasms that had the following characteristics: (a) a clinically evident whitish central area suggestive of regression (with no history of a previous surgical procedure or trauma), (b) histological features of fibrous scar-like tissue at the center of the lesion, (c) the presence of large, confluent and unusually shaped melanocytic nests at the dermoepidermal junction and in the dermis, (d) a pagetoid spread of melanocytes above the epidermal basal layer and (e) remnants of nevus tissue at the border of the scar. The lesions showed no evidence of cytological atypia, expansive nodules of melanocytes, significant numbers of mitoses or cellular necrosis.
Results: All the cases have been followed up and none have recurred or metastasized. Histologically, these neoplasms have important similarities with the so-called recurrent nevus, nevi on lichen sclerosus and nevi developed during or following cutaneous inflammatory and sclerosing processes. The origin of the scar in each case was obscure but was probably related to minor unnoticed trauma or to chronic friction on a nevus. In few cases, the fibrosis was probably the result of partial regression of the nevus or a sequel to folliculitis. The pseudomelanomatous features appear to be related to the presence of the scar, as already reported for nevi that are involved in fibrotic or scarring processes. In our study, the nevi involved in the fibrotic process were congenital nevi and common or dysplastic nevi. One case was a Spitz nevus.

Giuseppe Fabrizi[1], Ilaria Pennacchia[2], Calogero Pagliarello[1] and Guido Massi[2]

[1]Department of Dermatology, Molise University Medical School, Campobasso, Molise, Italy and
[2]Department of Pathology, Catholic University Medical School, Rome, Italy



19 Lesions with no recurrence (all completely excised)

Histopathology

Histopathology 2017 DOI: 10.1111/his.13317

New insights into naevoid melanomas: a clinicopathological reassessment

Martin G Cook,[1,2,3,4] Daniela Massi,[4,5] Willeke A M Blokx,[4,6] Joost Van den Oord,[4,7] Senada Koljenović,[4,8] Vincenzo De Giorgi,[9] Eleanor Kissin,[10] Megan Grant,[2] Amit Mandal,[2] Gabriela Gremel,[2] Caroline Gaudy,[2] Amaya Viros,[2] Nathalie Dhomen,[2] Kiarash Khosrotehrani,[11,12] Richard Marais,[2] Adele C Green[2,13] & Martin C Mihm Jr[4,14]

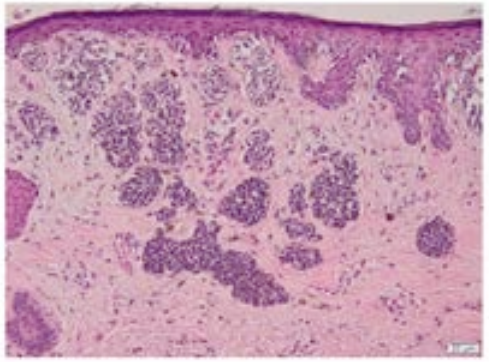


Figure 7. A different maturing naevoid melanoma showing a change from epithelioid pleomorphic nested melanocytes in the superficial dermis to, in the deeper part, smaller but still atypical cells arranged in nests surrounded by dense collagen.

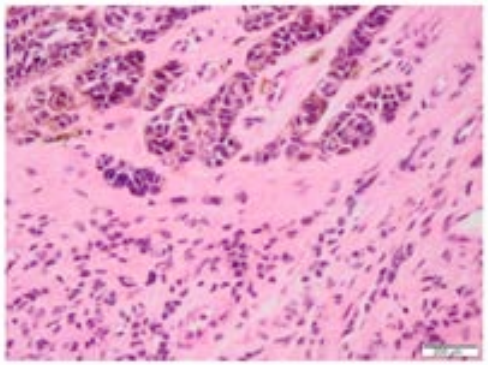


Figure 8. A maturing naevoid melanoma in which small atypical melanocytes in the superficial dermis are arranged in nests surrounded by dense collagen. A true benign naevus is present at the deep aspect of this melanoma.

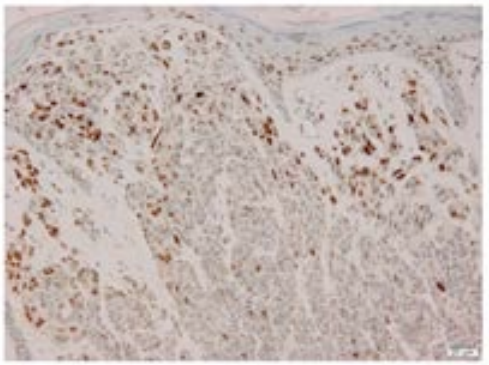


Figure 9. An example of immunohistochemical staining. p21 is seen to be positive in the junctional and superficial dermal component of another maturing naevoid melanoma, but is largely negative in the deeper small-cell component.

Papillomatous naevoid melanoma

- Papillomatous epithelial strands; dense proliferation; lack of maturation; atypia; mitoses

- In-transit or lymph node metastases occurred in 33% of patients

" … no disease progression was seen in those with maturing naevoid melanomas …"

Conclusions

- Dysplastic nevi have been heavily overdiagnosed
- Former mild dysplasia is a benign lentiginous nevus (the commonest type of nevus)
- Low grade dysplasia (former moderate dysplasia) can be observed clinically or by patients, looking for evidence of changing lesions
- High grade dysplasia is difficult to distinguish from melanoma in situ (UNCERTAINTY), may have competence for local persistence, recurrence and progression, and should be completely excised or followed carefully

- All of these are “melanocytic neoplasms of low (or no) malignant potential” which have little or no competence for metastasis

Case 4.

London SVS\Case 15 29268_nl.svs

Clinical Information.

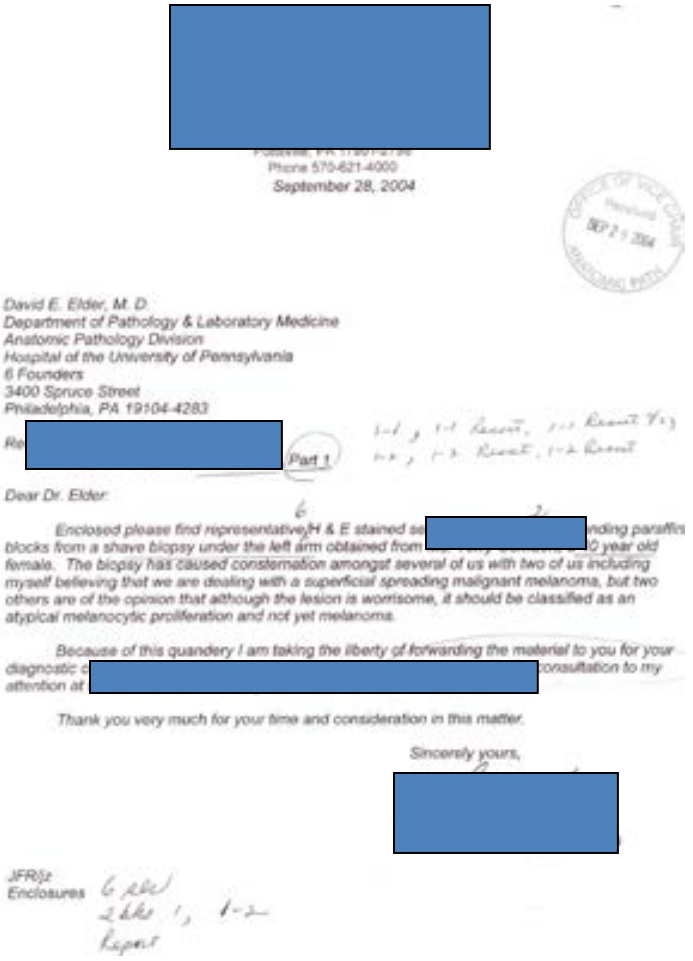
Pigmented lesion on the back of a 40 year old woman

Reason for Consultation.

Rule out melanoma?

A Lesion of the Back in a 40 Year Old Woman

- “shave biopsy under the left arm … has caused consternation … two of us believing that we are dealing with a … melanoma… two others believing that although worrisome … not yet melanoma”



[redacted]

Phone 570-621-4000

September 28, 2004

David E. Elder, M.D.
Department of Pathology & Laboratory Medicine
Anatomic Pathology Division
Hospital of the University of Pennsylvania
6 Founders
3400 Spruce Street
Philadelphia, PA 19104-4283

Re: [redacted] Part 1

Dear Dr. Elder:

Enclosed please find representative H & E stained se[redacted]nding paraffin blocks from a shave biopsy under the left arm obtained from [redacted]0 year old female. The biopsy has caused consternation amongst several of us with two of us including myself believing that we are dealing with a superficial spreading malignant melanoma, but two others are of the opinion that although the lesion is worrisome, it should be classified as an atypical melanocytic proliferation and not yet melanoma.

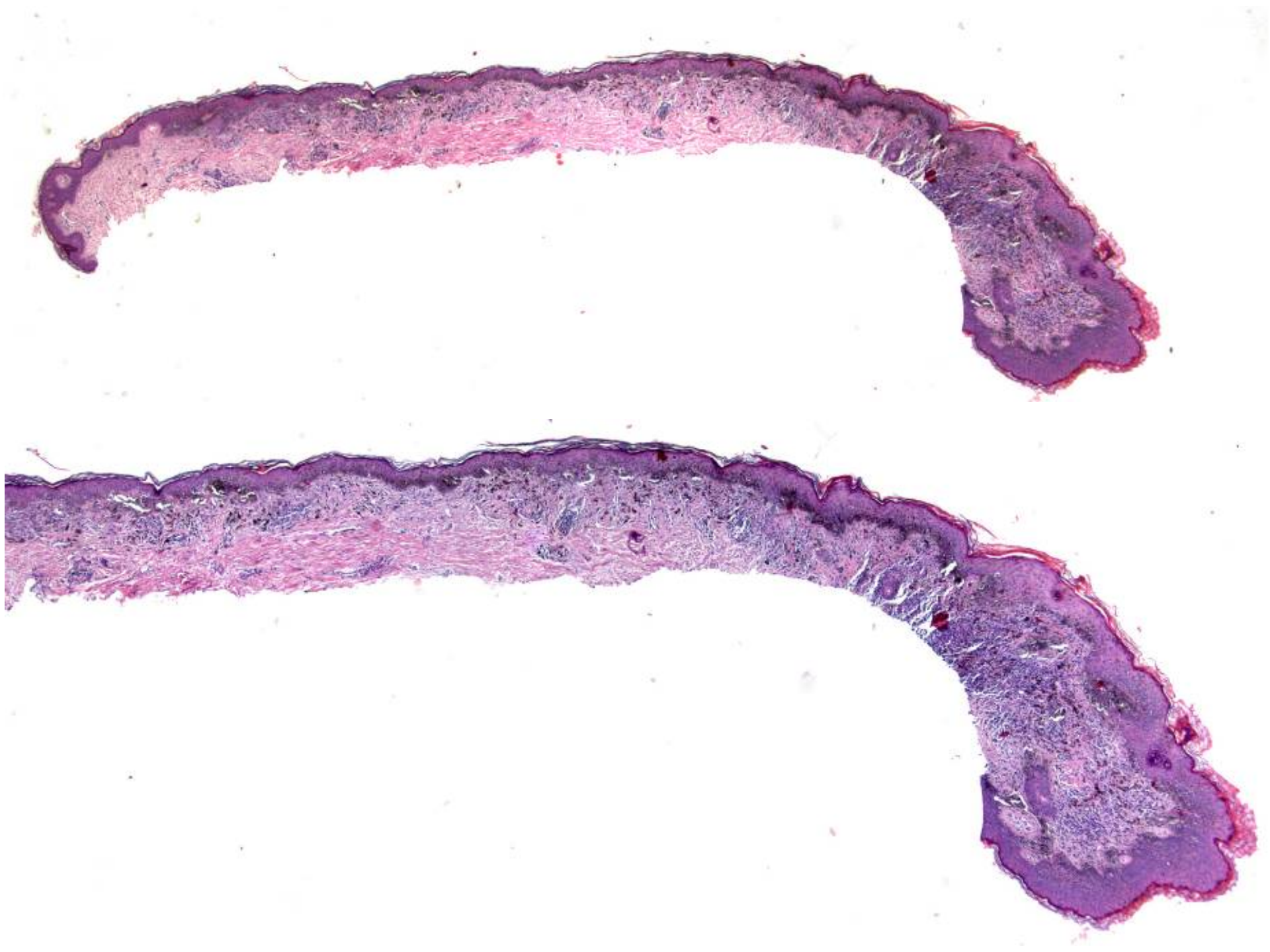
Because of this quandery I am taking the liberty of forwarding the material to you for your diagnostic c[redacted]consultation to my attention at [redacted]

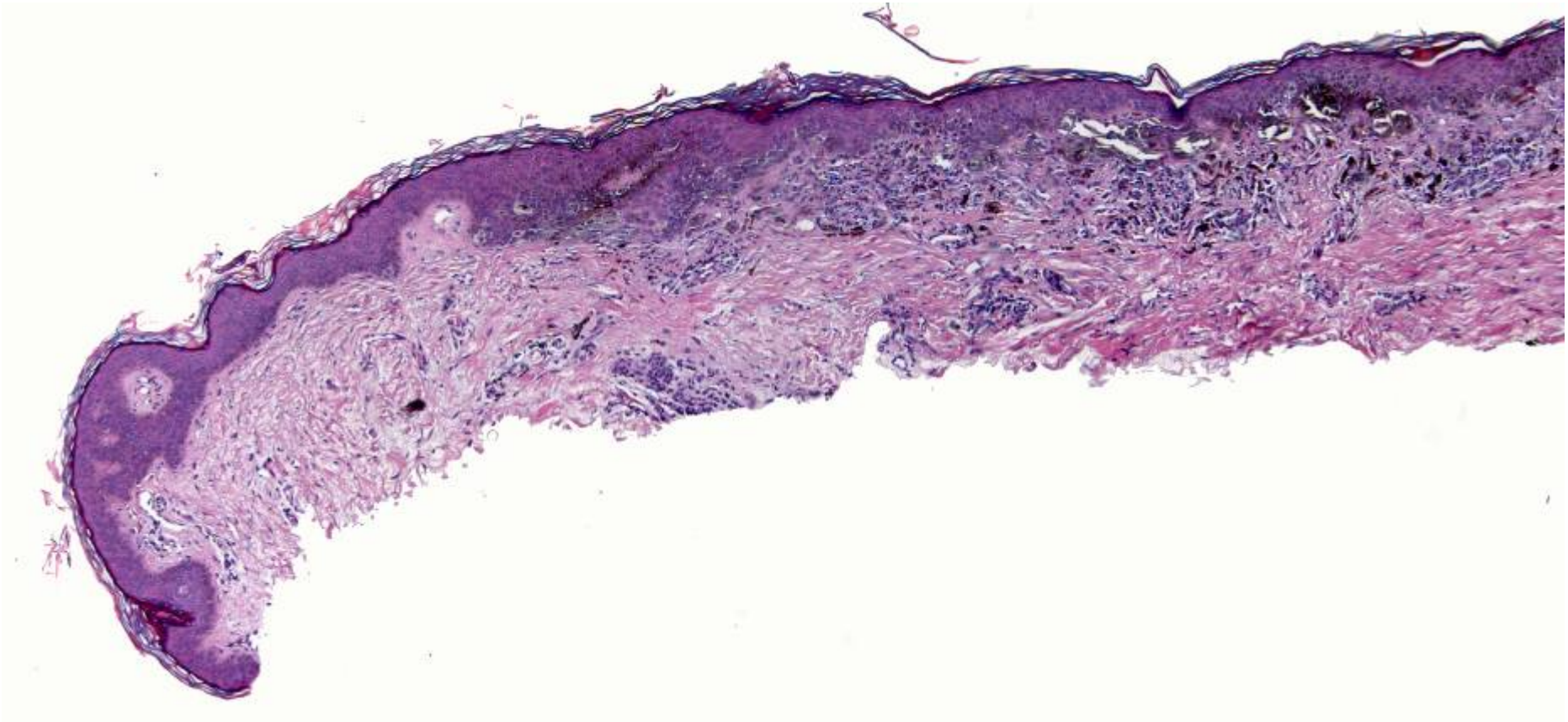
Thank you very much for your time and consideration in this matter.

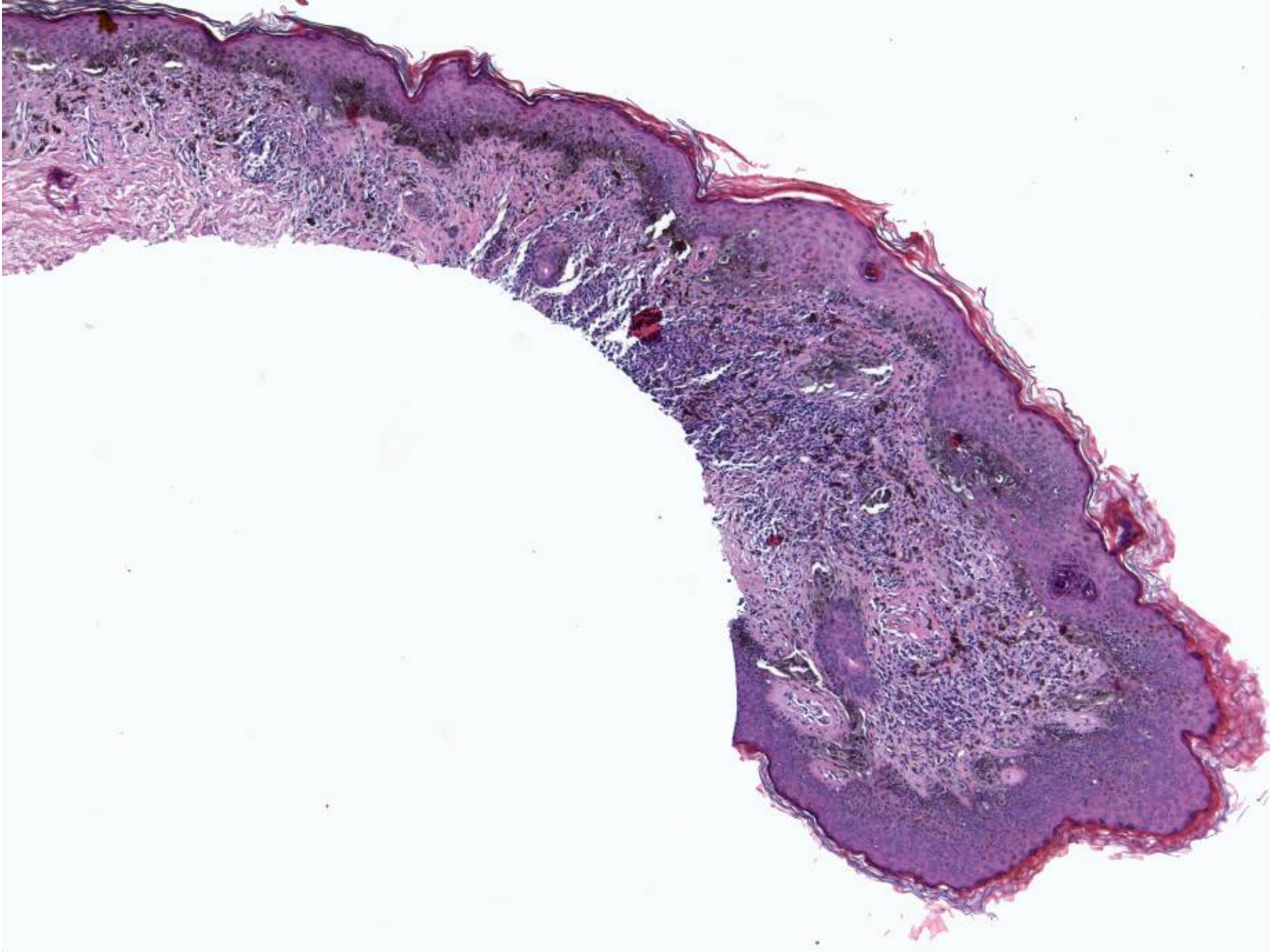
Sincerely yours,

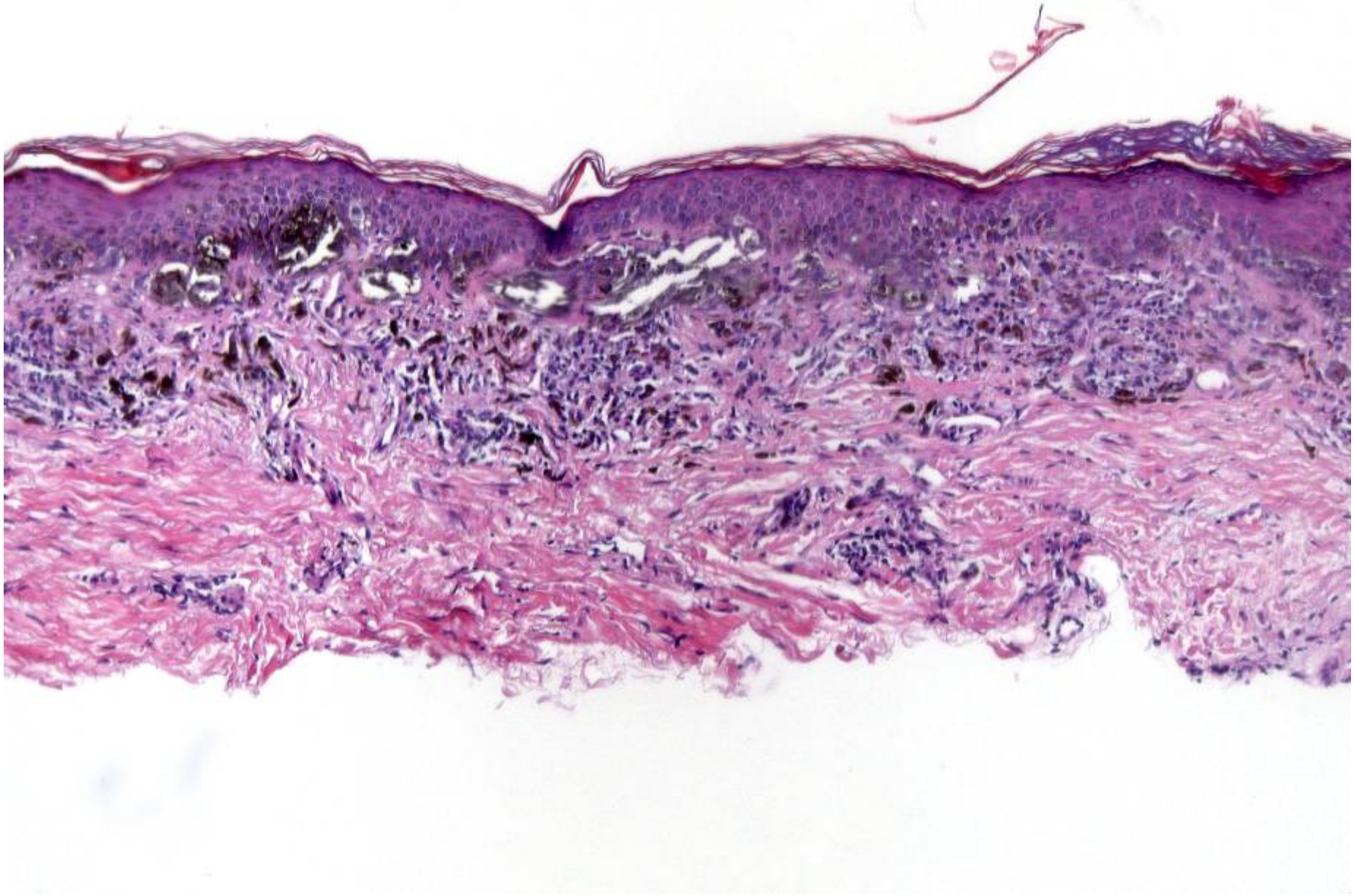
[redacted]

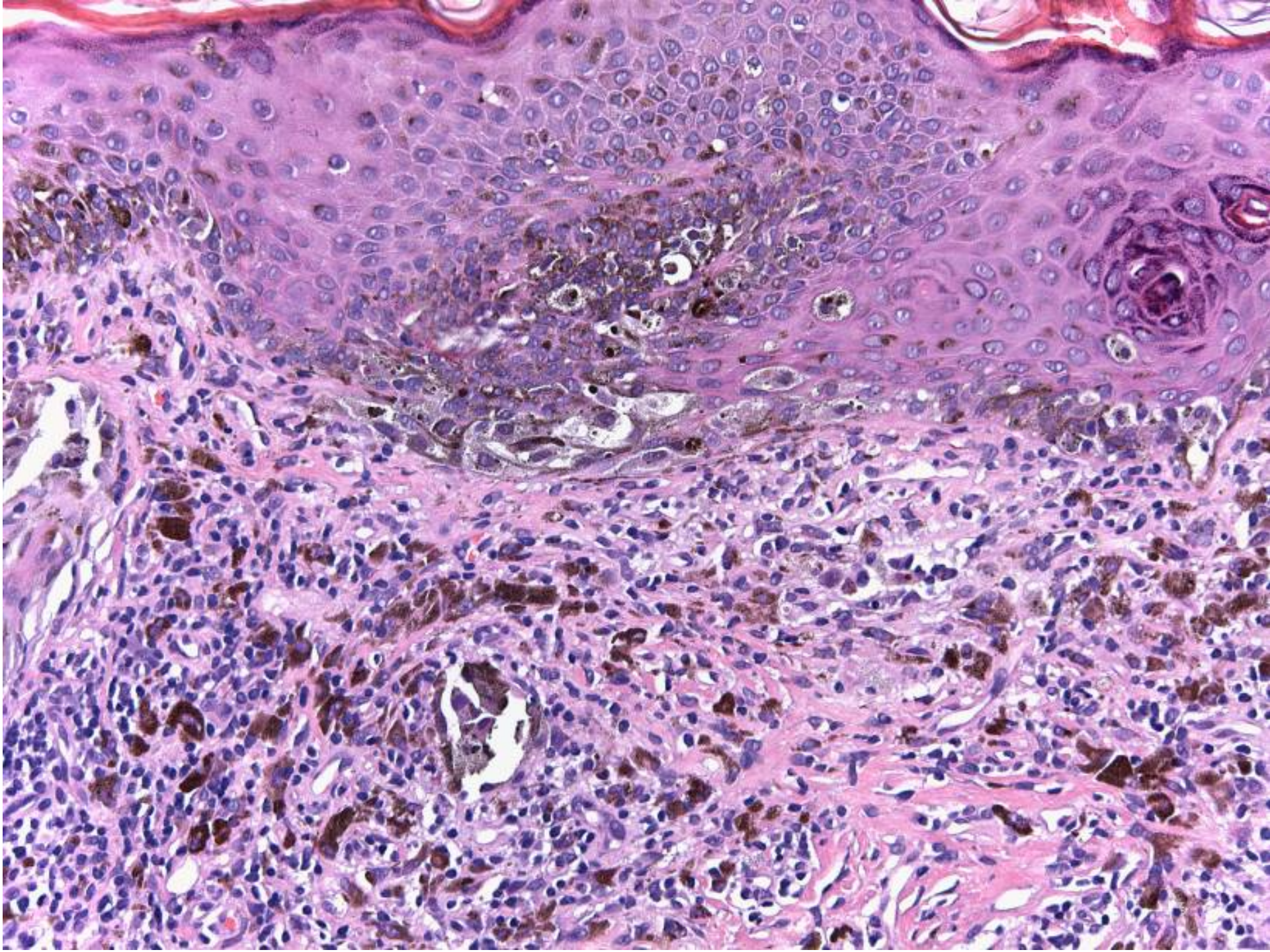
JFR/jz
Enclosures

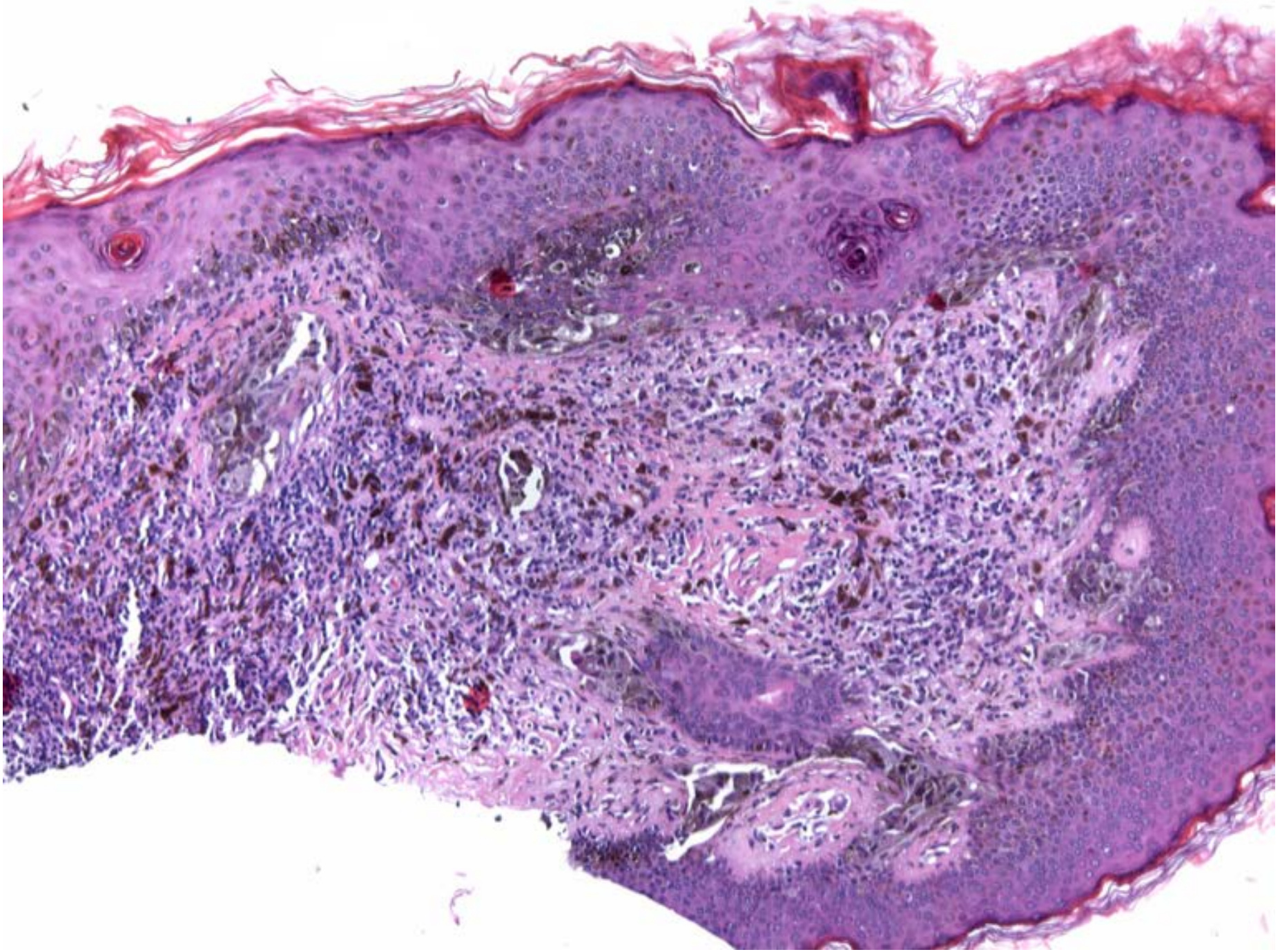


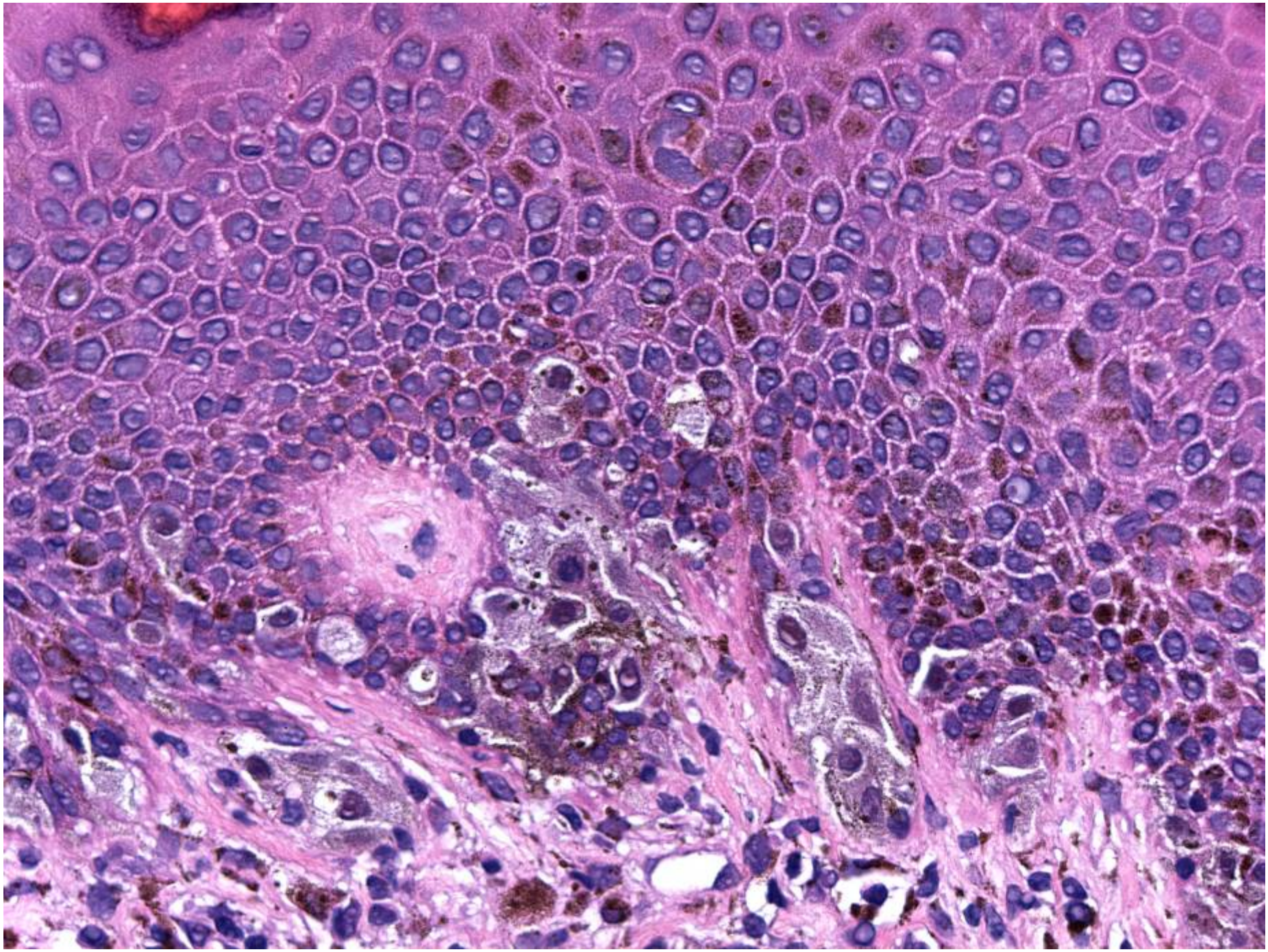


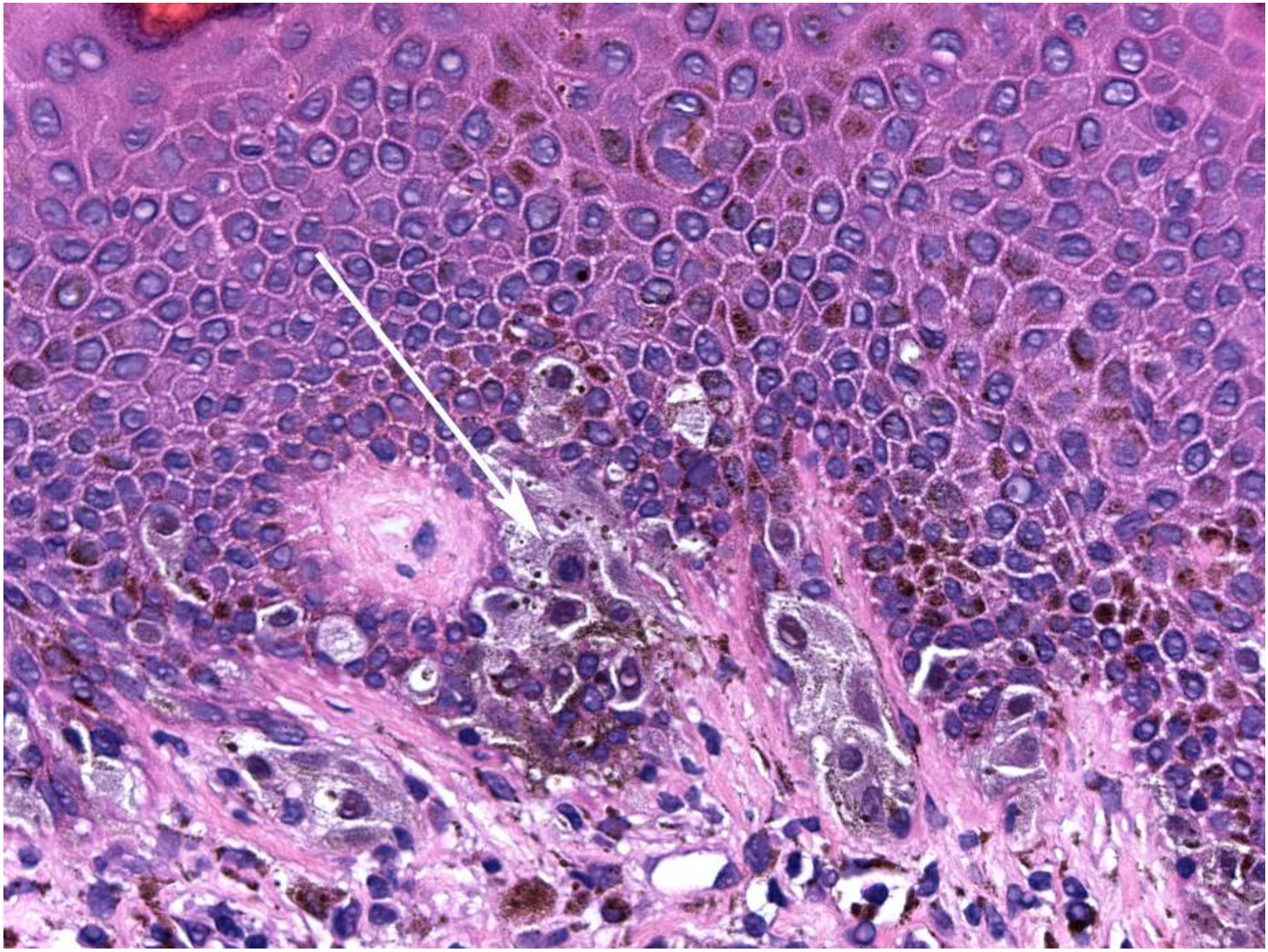


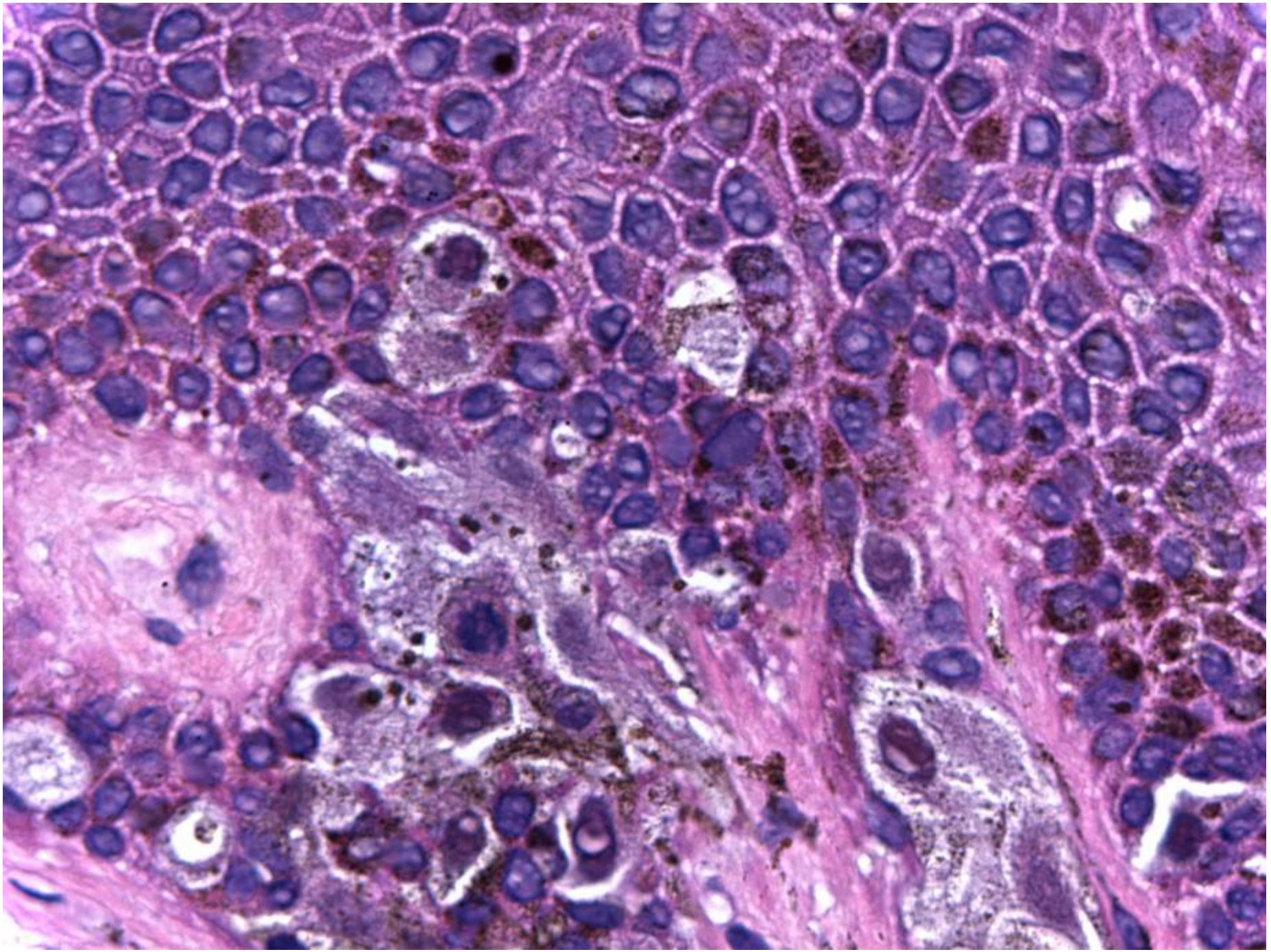












Your Diagnosis?

Melanoma?

Nevus?

Your Diagnosis?

Dysplastic?

Nondysplastic?

Your Diagnosis?

High Grade?

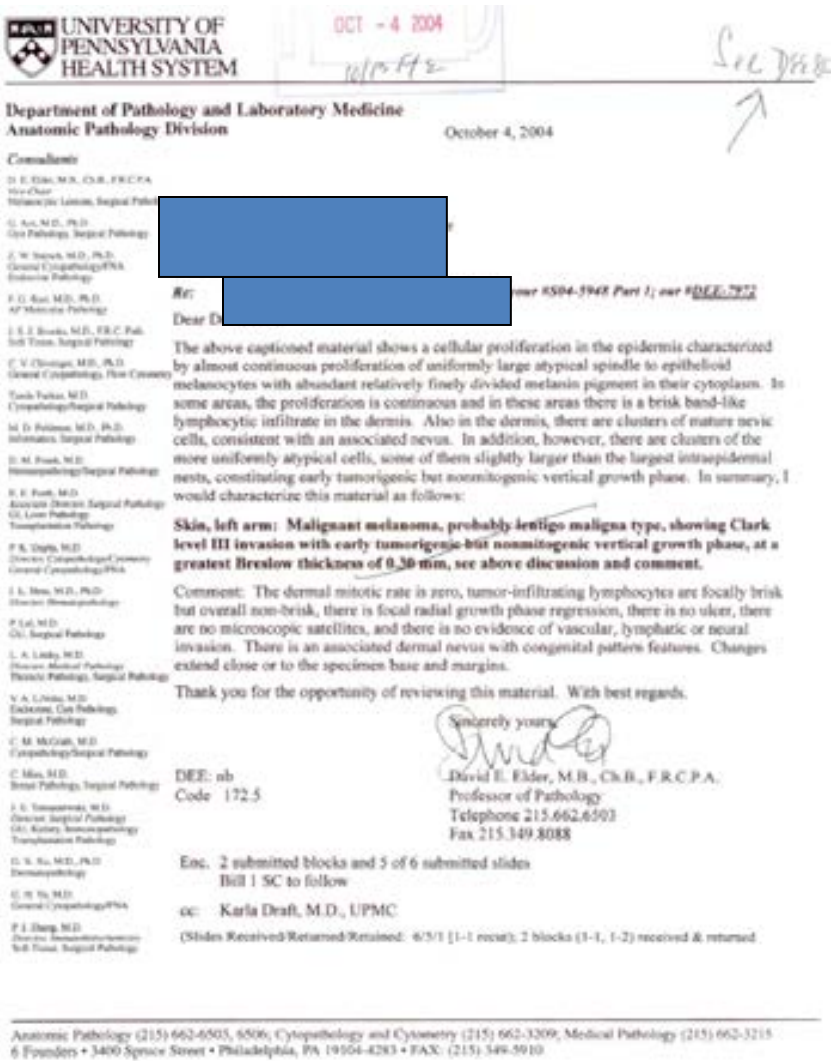
Low Grade?

Clark's Dysplastic Nevus vs. Melanoma in Situ vs. Nevus

Feature	Melanoma	Dysplastic Nevus	Nevus
Size	tend to be larger	intermediate	smaller
Symmetry	poor	good	good
Keratinocytes	irregular	uniform elongated rete	uniform
Melanocytes	epithelioid	mixed	nevoid
Nested	variable	predominant	predominant
Nests	coalescent	bridging	discrete
Lentiginous	continuous	discontinuous	discontinuous
Pagetoid	high, extensive	low, focal, minimal	minimal
Nuclear atypia	uniform atypia, severe (> 1.5x)	random atypia, mild-moderate	minimal
Mitoses	about 1/3 of cases	almost always absent	absent
Fibroplasia	diffuse	concentric	minimal
Lymphocytes	bandlike, lichenoid	patchy, perivascular	minimal
Regression	frequent, extensive	rare, minimal	absent

Diagnosis Rendered

- “malignant melanoma, probably lentigo maligna type, showing Clark level III invasion with early tumorigenic but nonmitogenic vertical growth phase, at a greatest Breslow thickness of 0.30 mm … associated nevus with congenital pattern features”



UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

OCT - 4 2004

Department of Pathology and Laboratory Medicine
Anatomic Pathology Division

October 4, 2004

Consultants

[redacted]

Re: [redacted] our #504-5948 Part 1; our #DEE-7972

Dear [redacted]

The above captioned material shows a cellular proliferation in the epidermis characterized by almost continuous proliferation of uniformly large atypical spindle to epithelioid melanocytes with abundant relatively finely divided melanin pigment in their cytoplasm. In some areas, the proliferation is continuous and in these areas there is a brisk band-like lymphocytic infiltrate in the dermis. Also in the dermis, there are clusters of mature nevic cells, consistent with an associated nevus. In addition, however, there are clusters of the more uniformly atypical cells, some of them slightly larger than the largest intraepidermal nests, constituting early tumorigenic but nonmitogenic vertical growth phase. In summary, I would characterize this material as follows:

Skin, left arm: Malignant melanoma, probably lentigo maligna type, showing Clark level III invasion with early tumorigenic but nonmitogenic vertical growth phase, at a greatest Breslow thickness of 0.30 mm, see above discussion and comment.

Comment: The dermal mitotic rate is zero, tumor-infiltrating lymphocytes are focally brisk but overall non-brisk, there is focal radial growth phase regression, there is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic or neural invasion. There is an associated dermal nevus with congenital pattern features. Changes extend close or to the specimen base and margins.

Thank you for the opportunity of reviewing this material. With best regards.

Sincerely yours,

DEE: nb
Code 172.5

David E. Elder, M.B., Ch.B., F.R.C.P.A.
Professor of Pathology
Telephone 215.662.6503
Fax 215.349.8088

Enc. 2 submitted blocks and 5 of 6 submitted slides
Bill 1 SC to follow

cc: Karla Draft, M.D., UPMC

(Slides Received/Returned/Retained: 6/5/1 [1-1 recut]; 2 blocks (1-1, 1-2) received & returned

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New Information!

"I received a call from the primary care physician of this patient asking me to review a biopsy from June of 2004, which I had signed out as a compound congenital melanocytic nevus. She told me that the lesion had developed re-pigmentation in the previous biopsy site … "


Geisinger
Health System

Heal. Teach. Discover. Serve.

Age/Sex: 40/F
Location: left flank

Dear Dr. Russo,

As we discussed on the telephone this morning, I received a call from the primary care physician of this patient asking me to review a biopsy from June of 2004, which I had signed out as a compound congenital melanocytic nevus. She told me that the patient had developed re-pigmentation in the previous biopsy site and that she had referred the patient to Dr. Harold Milstein for further evaluation. Dr. Milstein apparently did a shave biopsy of this area of re-pigmentation, which you received as your specimen S04-5945 (part 1) labeled skin of axilla-lower under left arm. You sent this case to Dr. David Elder and it was interpreted as a superficial spreading melanoma; however, neither he nor you had the history that there was a previous congenital nevus biopsied in this same area three months previously and the re-pigmentation had developed on the biopsy site. I again spoke to Dr. Rhonda Todd, the patient's primary physician this morning to re-verify the clinical history and she assured me that the pigmentation did occur in the previous biopsy site.

I am sending you our slide (S04-16990-B) for review and so that you can also send it to Dr. David Elder with this additional information for further review of the subsequent biopsy specimen that you received. I have not seen your slides or an actual copy of Dr. David Elder's report; however, I think it is almost certain that the subsequent biopsy is a pseudomelanoma based on the fact that there was no atypia in the original shave biopsy specimen, the interval between biopsy and re-pigmentation is only three months and the re-pigmentation is in the previous biopsy site. The lack of this additional clinical information at the time that you received the specimen was a handicap.

The patient's primary care physician is Dr. Rhonda Todd. Her telephone number is 570-459-9730. Her fax number is 570-459-9736. I have discussed this case with her and I explained that I have spoken to you and that I am sending the original biopsy specimen from June for both you and Dr. Elder to review. Feel free to contact Dr. Todd to discuss any clinical details. She has also discussed and explained this dilemma with the patient.

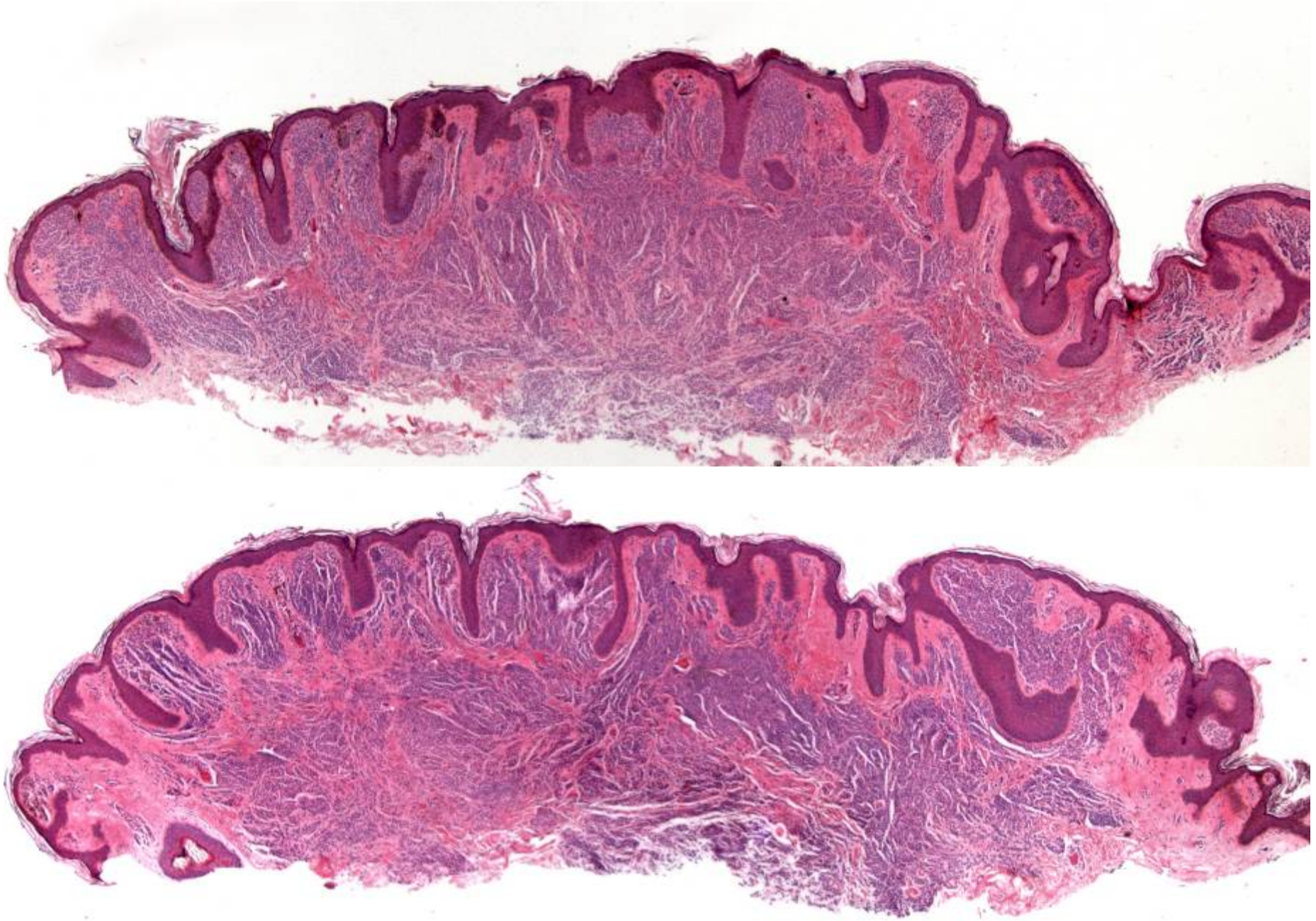
Sincerely,

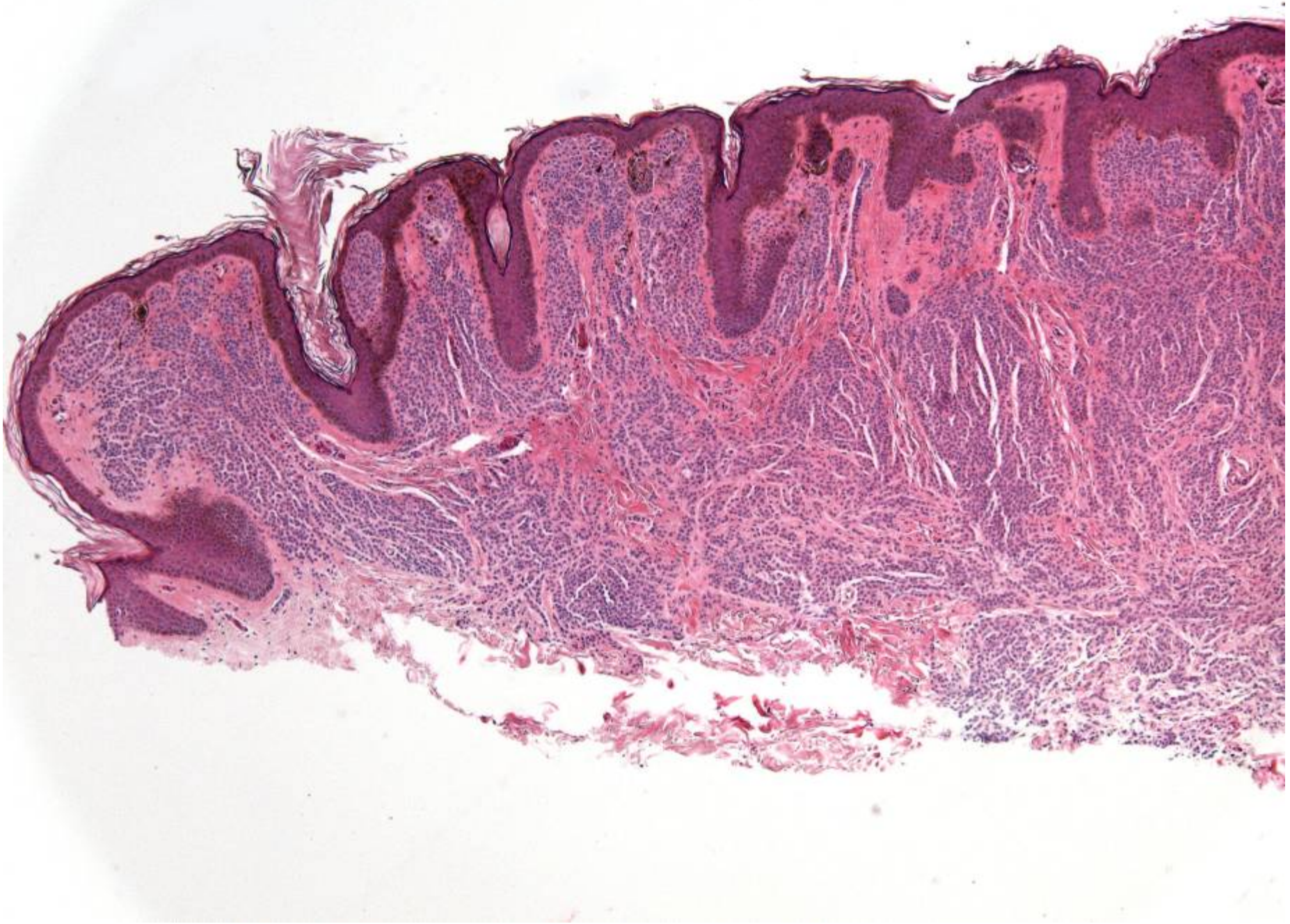
Dear Dr. [redacted]

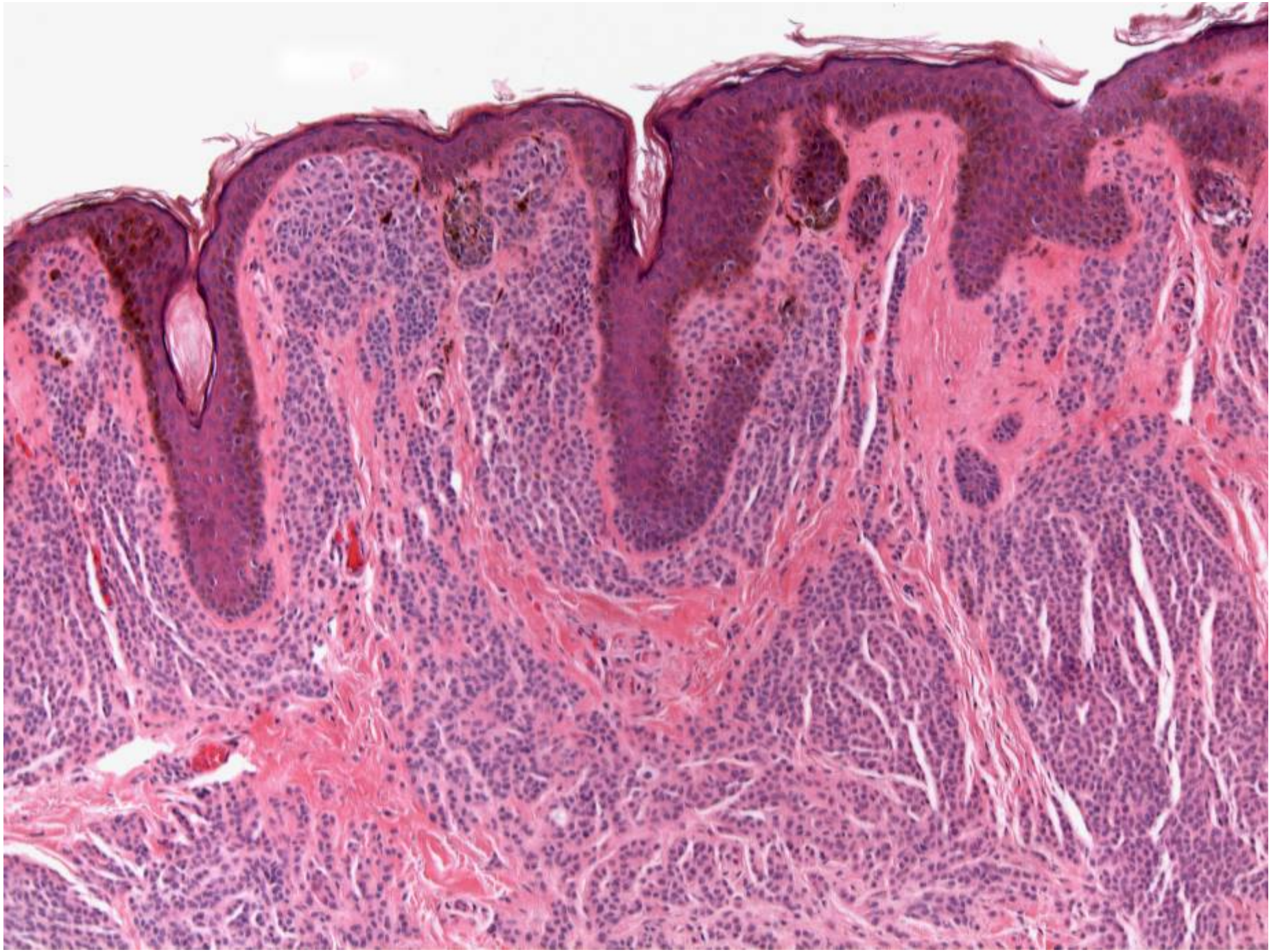
As we discussed on the telephone this morning, I received a call from the primary care physician of this patient asking me to review a biopsy from June of 2004, which I had signed out as a compound congenital melanocytic nevus. She told me that the patient had developed re-pigmentation in the previous biopsy site and that she had referred the patient to Dr. Harold [redacted] for further evaluation. Dr. [redacted] apparently did a shave biopsy of this area of re-pigmentation, which you received as your specimen S04-5948 (part 1) labeled skin of axilla-lesion under left arm. You sent this case to Dr. David Elder and it was interpreted as a superficial spreading melanoma; however, neither he nor you had the history that there was a previous congenital nevus biopsied in this same area three months previously and the re-pigmentation had developed in the biopsy site. I again spoke to Dr. Rhonda Todd, the patient's primary physician this morning to re-verify the clinical history and she assured me that the pigmentation did occur in the previous biopsy site.

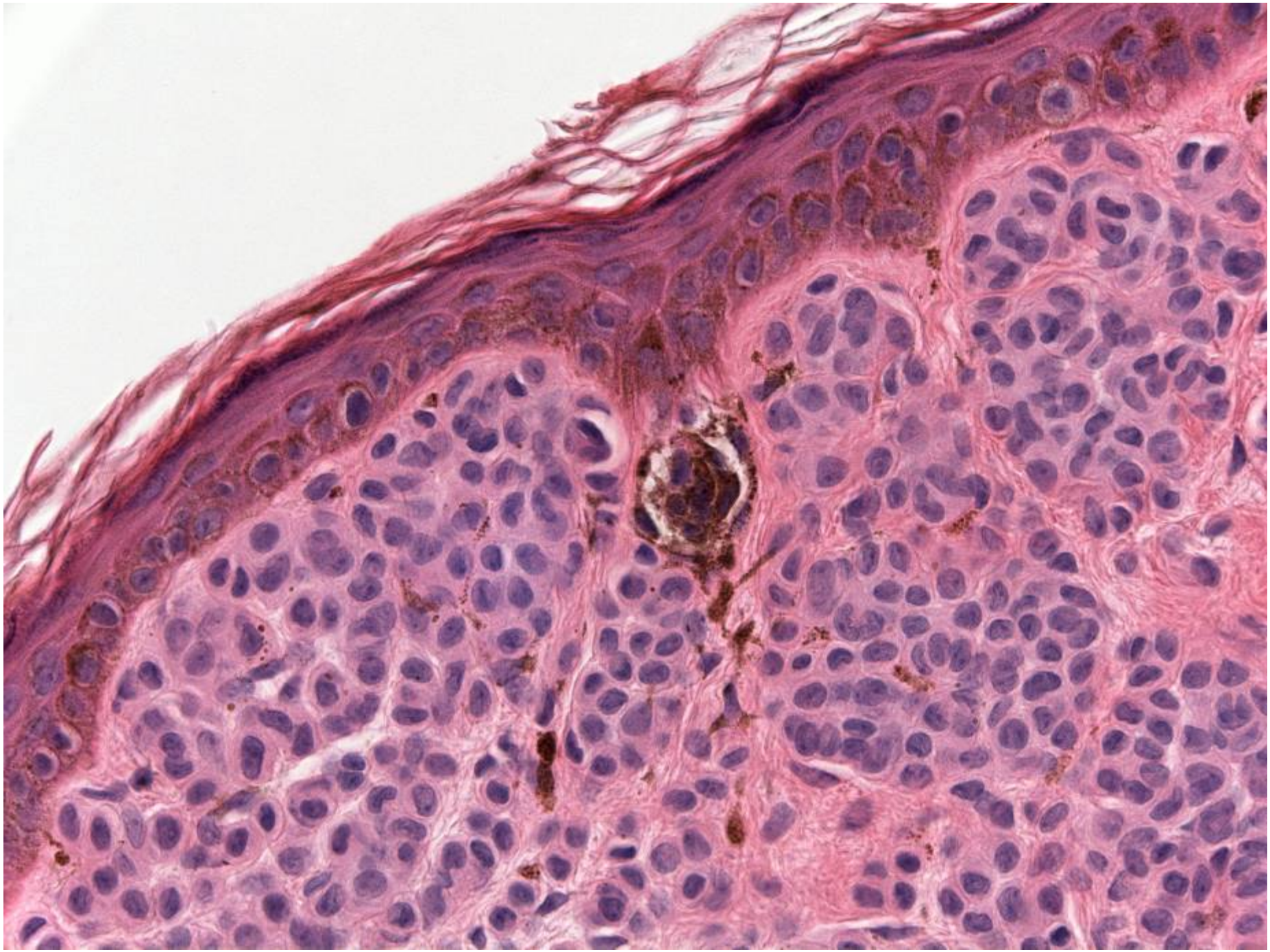
I am sending you our slide (S04-16990 B) for review and so that you can also send it to Dr. David Elder with this additional information for further review of the subsequent biopsy specimen that you received. I have not seen your slides or an actual copy of Dr. David Elder's report; however, I think it is almost certain that the subsequent biopsy is a pseudomelanoma based on the fact that there was no atypia in the original shave biopsy specimen, the interval between biopsy and re-pigmentation is only three months and the re-pigmentation is in the previous biopsy site. The lack of this additional clinical information at the time that you received the specimen was a handicap.

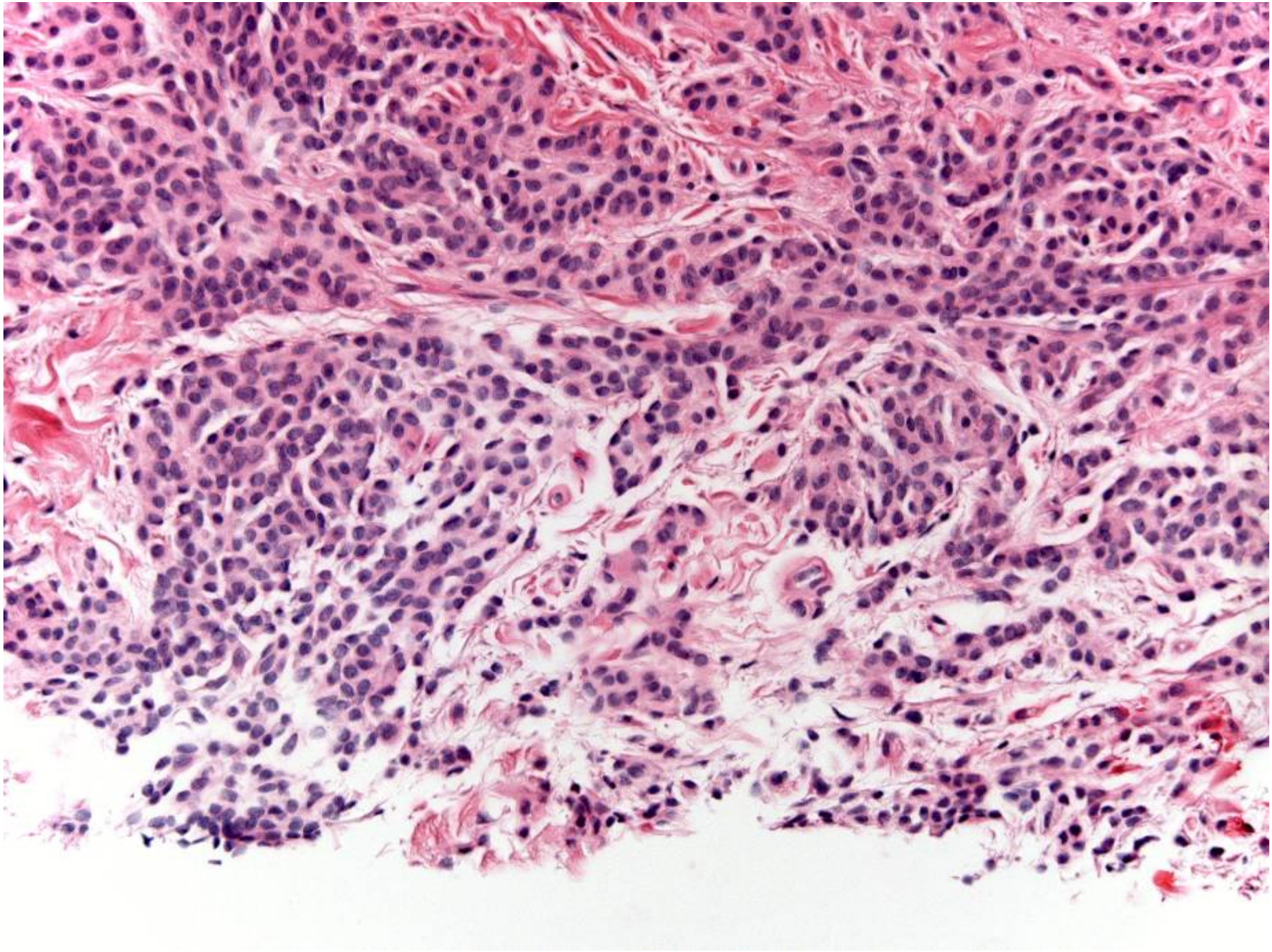
- "I think it is almost certain that the subsequent biopsy is a pseudomelanoma based on the fact that there was no atypia in the original shave biopsy specimen, the interval between biopsy and re-pigmentation is only three months, and the re-pigmentation is in the previous biopsy site. The lack of this additional information at the time you received the biopsy was a handicap"

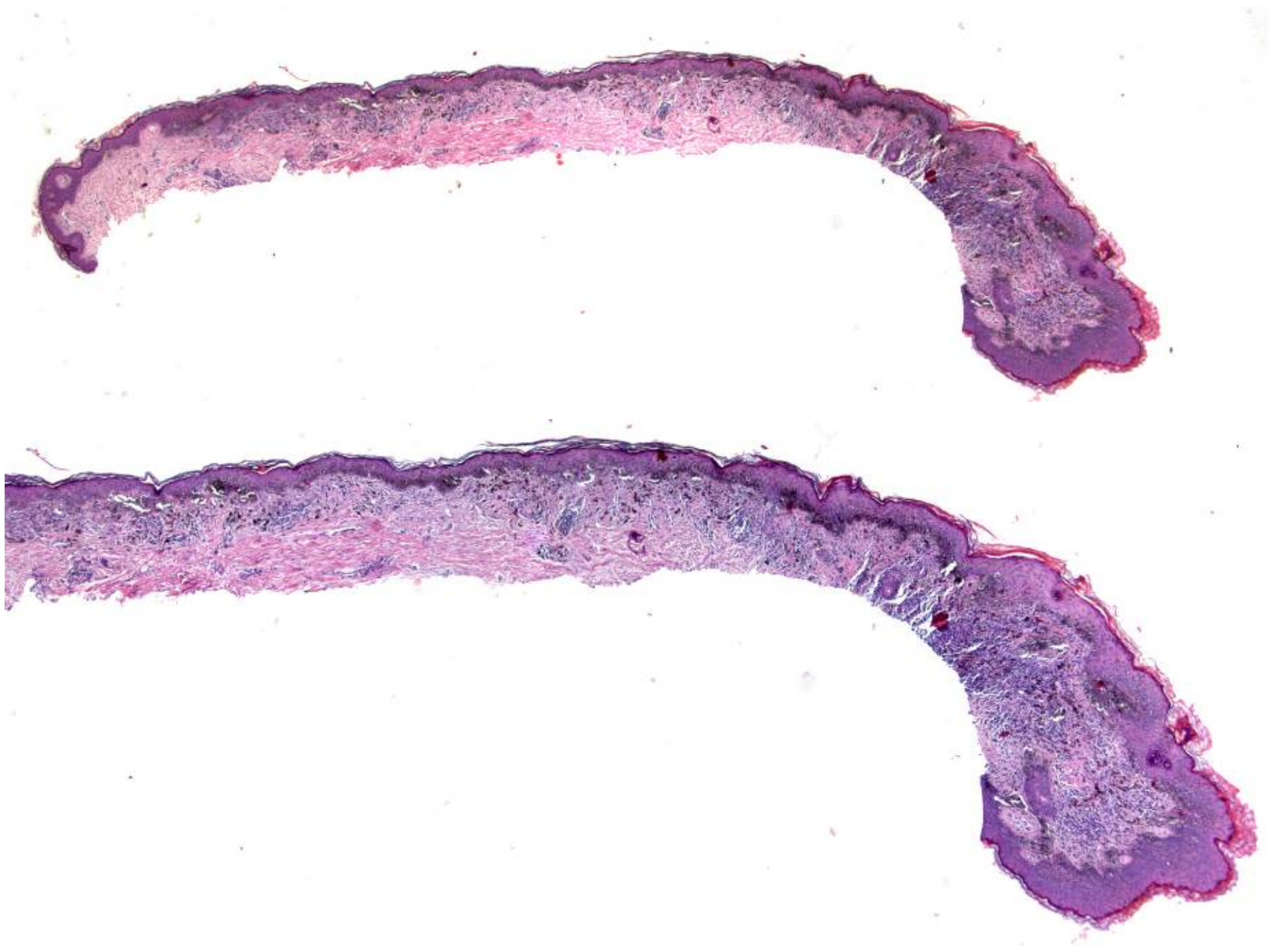






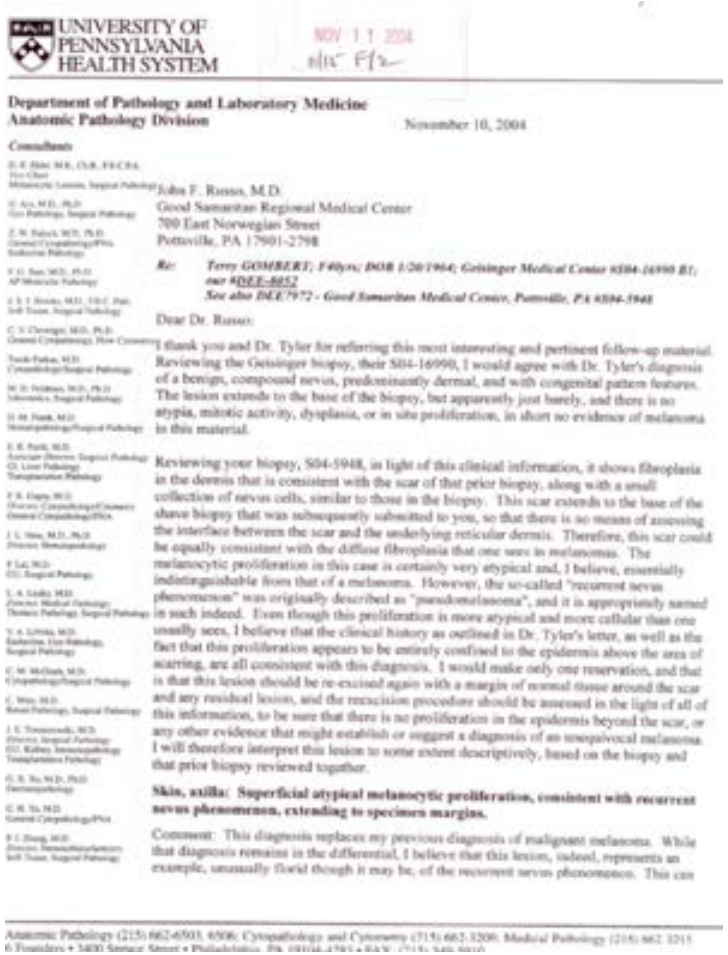






Case 4. New Report!

"superficial atypical melanocytic proliferation, c/w recurrent nevus phenomenon, extending to specimen margins" … "I would make only one reservation, and that is that this lesion should be re-excised again with a margin of normal skin around the scar and any residual lesion …"



UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

NOV 11 2004

Department of Pathology and Laboratory Medicine
Anatomic Pathology Division

November 10, 2004

Consultants

John F. Rosso, M.D.
Good Samaritan Regional Medical Center
700 East Norwegian Street
Pottsville, PA 17901-2798

Re: ***Terry GOMBERT; F40yrs; DOB 1/20/1964; Geisinger Medical Center S04-16990 E1; our #DEE-8057***
See also DEE7972 - Good Samaritan Medical Center, Pottsville, PA S04-5948

Dear Dr. Rosso:

I thank you and Dr. Tyler for referring this most interesting and pertinent follow-up material. Reviewing the Geisinger biopsy, their S04-16990, I would agree with Dr. Tyler's diagnosis of a benign, compound nevus, predominantly dermal, and with congenital pattern features. The lesion extends to the base of the biopsy, but apparently just barely, and there is no atypia, mitotic activity, dysplasia, or in situ proliferation, in short no evidence of melanoma in this material.

Reviewing your biopsy, S04-5948, in light of this clinical information, it shows fibroplasia in the dermis that is consistent with the scar of that prior biopsy, along with a small collection of nevus cells, similar to those in the biopsy. This scar extends to the base of the shave biopsy that was subsequently submitted to you, so that there is no means of assessing the interface between the scar and the underlying reticular dermis. Therefore, this scar could be equally consistent with the diffuse fibroplasia that one sees in melanomas. The melanocytic proliferation in this case is certainly very atypical and, I believe, essentially indistinguishable from that of a melanoma. However, the so-called "recurrent nevus phenomenon" was originally described as "pseudomelanoma", and it is appropriately named in such indeed. Even though this proliferation is more atypical and more cellular than one usually sees, I believe that the clinical history as outlined in Dr. Tyler's letter, as well as the fact that this proliferation appears to be entirely confined to the epidermis above the area of scarring, are all consistent with this diagnosis. I would make only one reservation, and that is that this lesion should be re-excised again with a margin of normal tissue around the scar and any residual lesion, and the resection procedure should be assessed in the light of all of this information, to be sure that there is no proliferation in the epidermis beyond the scar, or any other evidence that might establish or suggest a diagnosis of an unequivocal melanoma. I will therefore interpret this lesion to some extent descriptively, based on the biopsy and that prior biopsy reviewed together.

Skin, axilla: Superficial atypical melanocytic proliferation, consistent with recurrent nevus phenomenon, extending to specimen margins.

Comment: This diagnosis replaces my previous diagnosis of malignant melanoma. While that diagnosis remains in the differential, I believe that this lesion, indeed, represents an example, unusually florid though it may be, of the recurrent nevus phenomenon. This can

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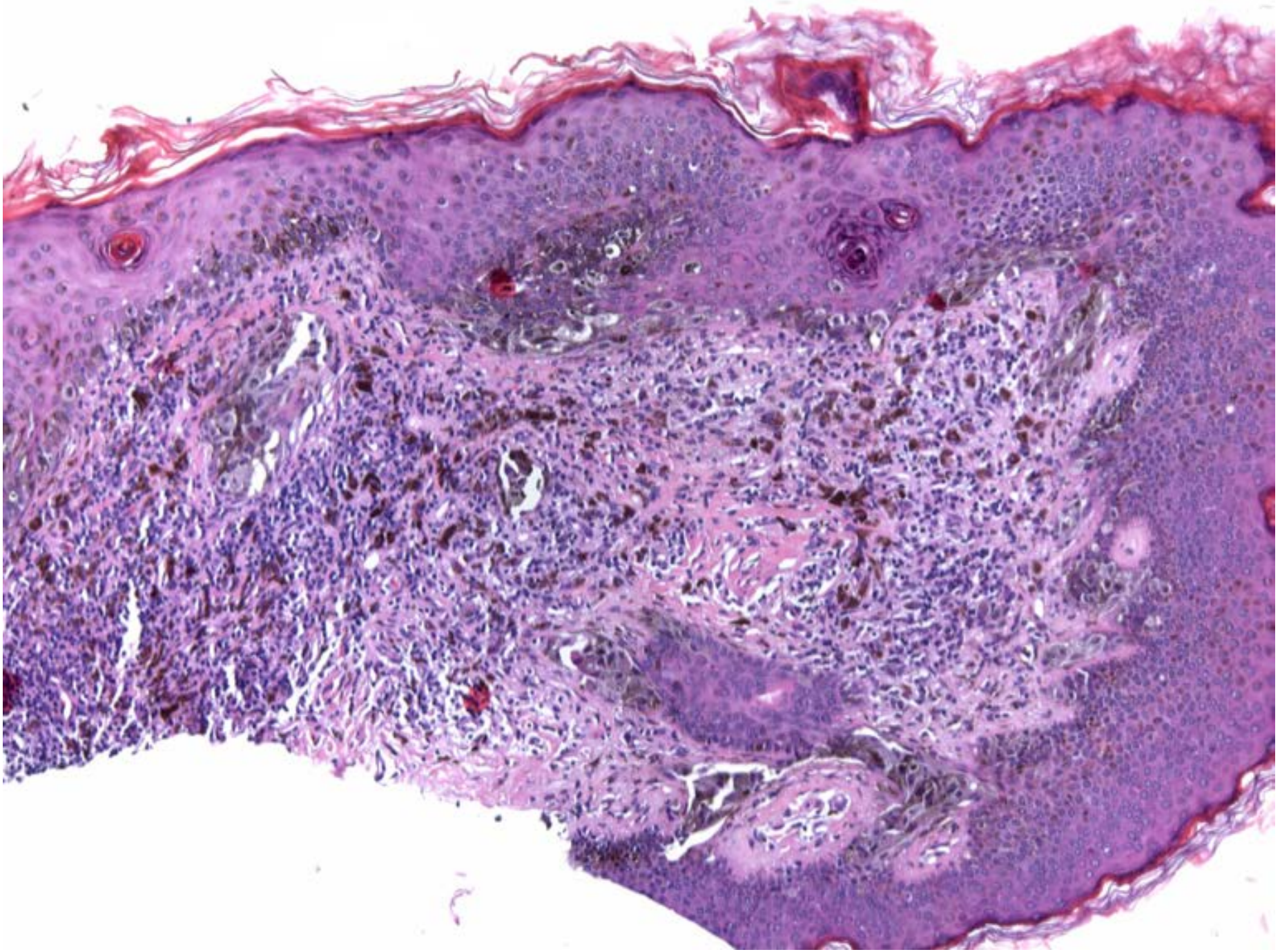


Lessons

- Atypia in recurrent nevi can be severe, yet is “reactive”.
  - Mitoses can be present
  - Dermal atypia can be present
- A superficial scar can mimic diffuse fibroplasia seen in many melanomas
- Keep a high index of suspicion
  - Consider a full differential diagnosis
  - Call for history if necessary

Conclusions

- Dysplastic nevi have been heavily over-diagnosed
- Former mild dysplasia is a benign lentiginous nevus (the commonest type of nevus)
- Low grade dysplasia (former moderate dysplasia) can be re-excised conservatively (MPATH II), or observed clinically or by patients, looking for evidence of changing lesions
- High grade dysplasia is difficult to distinguish from melanoma in situ (UNCERTAINTY), may have competence for local persistence, recurrence and progression, and should be completely excised, or carefully followed (MPATH II or III)
- Recurrent nevus is a form of “reactive atypia”

- ALL OF THESE ARE LESIONS WITH NO COMPETENCE FOR METASTASIS THAT NEED TO BE DISTINGUISHED FROM METASTATICALLY COMPETENT MELANOMAS

Grading of atypia in nevi: correlation with melanoma risk

Arumi-Uria, McNutt, Finnerty, 2003

- Grading of nevi with architectural disorder (dysplastic nevi) involves architectural and cytological features.
- Grades of atypia are related to patient history of melanoma:
  - personal history of melanoma present in 5.7% of 2,504 patients with mild, 8.1% of 1657 with moderate, and 19.7% of 320 patients with severe atypia.
- Odds ratio as a measure of association between NAD and history of melanoma:
  - 4.08 for severe versus mild,
  - 2.81 for severe versus moderate and
  - 1.45 for moderate versus mild dysplasia.
- “Melanoma risk is greater in persons whose nevi have higher grade histological atypia”

Dysplasia Grading Criteria …….

Arumi-Uria et al, Mod Pathol, 2003

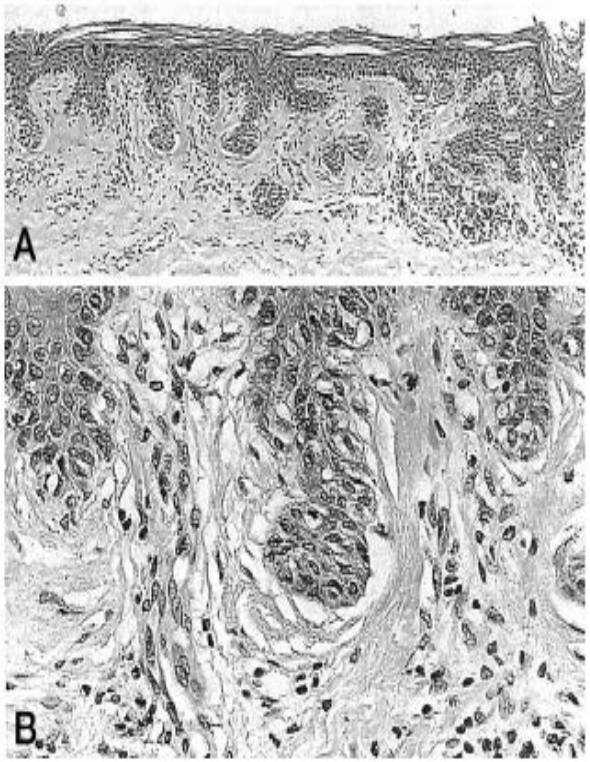


FIGURE 1. A, nevus, compound type, with architectural disorder and mild cytologic atypia of melanocytes. This region shows the extension of the junctional component beyond the dermal component, with some papillary dermal fibrosis and lymphocytic infiltration but with only slight distortion of the rete ridges and with nevus cells that generally do not have nuclei larger than the keratinocyte nuclei nearby (H&E, 10×). B, the nuclear size in the nevus cells is near that in the keratinocytes (H&E, 40×).

Mild

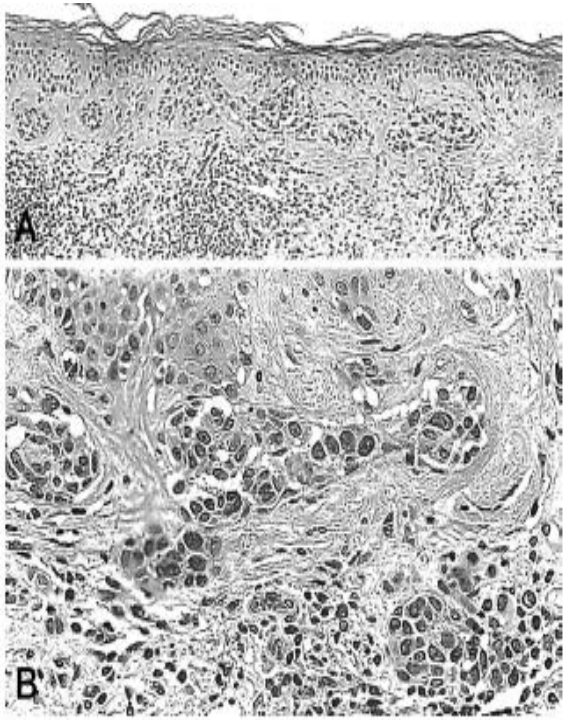


FIGURE 2. A, nevus, compound type, with architectural disorder and moderate cytologic atypia of melanocytes. This region also has extension of the junctional component beyond the dermal portion. There has been partial regression of the dermal component. The rete ridges are quite distorted, and the nuclei in the nevus cells are enlarged (H&E, 10×). B, the enlargement and hyperchromasia of the nevus nuclei is more evident at higher magnification of this lesion, which is overall at the high end of the scale of moderate atypia. A few cells in this photo have sufficient atypia to be classified as severe atypia (H&E, 40×).

Moderate

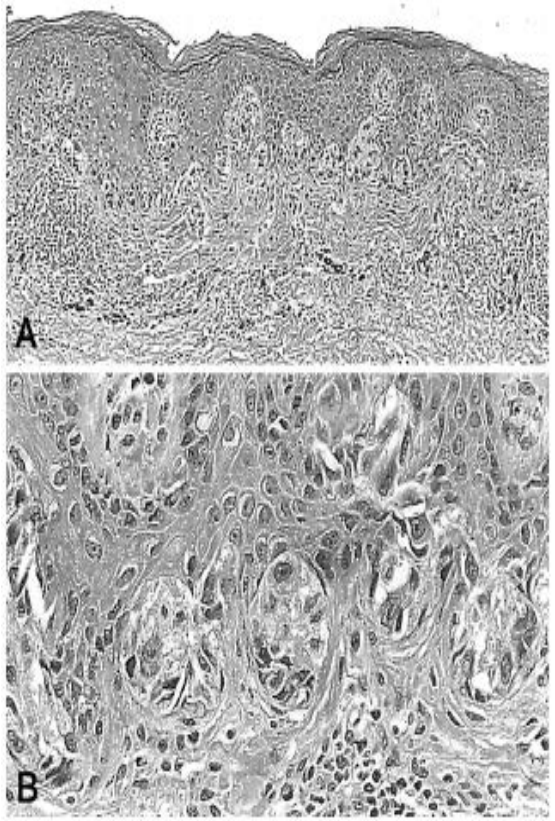


FIGURE 3. A, nevus, compound type, with architectural disorder and severe cytologic atypia of melanocytes. Rete ridge fusion is extensive with papillary dermal fibrosis and lymphocytic and melanophage infiltration. Many of the nuclei in the nevus cells are enlarged (H&E, 10×). B, the nuclei are more expanded, and nucleoli are more prominent than those in the moderate degree of atypia. The cytoplasm also is more abundant (H&E, 40×).

Severe

CLINICAL AND LABORATORY INVESTIGATIONS

Dysplastic naevi with moderate to severe histological dysplasia: a risk factor for melanoma

A.R. Shors, S. Kim, E. White,* Z. Argenyi, R.L. Barnhill,† P. Duray,‡ L. Erickson,§ J. Guitart,¶ M.G. Horenstein,** L. Lowe,†† J. Messina,‡‡ M.S. Rabkin,§§ B. Schmidt,¶¶ C.R. Shea,*** M.J. Trotter††† and M.W. Piepkorn

- Clinically most atypical macular nevus biopsied from 80 newly incident cases of melanoma and spouse controls.
- Histological dysplasia was assigned on a 0-4 point scale by 13 dermatopathologists (International Melanoma Pathology Group)
- Subjects with panel ratings > 1 had increased relative risk of melanoma:

- Odds ratio after adjustment for confounders = 3.99, 95% CI 1.02-15.71.

- kappa statistic was 0.28 for the panel histological diagnoses, indicating poor interobserver reproducibility.
  - Repeating study agreed but found size to be a good surrogate/correlate for atypia
  - Evidence-based criteria for histologic dysplasia as a risk marker

Rabkin, Piepkorn, Barnhill et al **RESEARCH LETTERS** JAAD

Diameter of dysplastic nevi is a more robust biomarker of increased melanoma risk than degree of histologic dysplasia: A case-control study

See related article on page 1071

To the Editor: While grade of dysplasia of histologically dysplastic nevi (HDN) has been associated with increased risk of melanoma,[1,2] interrater reliability of dysplasia grading among dermatopathologists is poor.[1,3] We sought to (1) improve interrater reliability of HDN grading scores by training dermatopathologists using consistent grading criteria and (2) determine whether posttraining scores better predicted melanoma.

Table II. Association between lesion diameter and melanoma

Predictor	N (%)	OR	*P* value
Diameter (mm)			
<2.40	37 (22%)	1.00	(reference)
2.40-2.90	34 (20%)	1.35	.5
2.91-3.50	36 (21%)	1.07	.9
3.50-4.40	34 (20%)	2.04	.1
>4.40	31 (18%)	5.08	.012
Total	172		

Table I. Predictors of melanoma before and after training

Predictor	OR	95% CI	*P* value
A: Before training			
Univariate model			
Average dysplasia score	1.52	0.78-2.95	.2
Multivariate model			
Diameter	1.61	1.14-2.27	.007
Average dysplasia score	1.37	0.64-2.93	.4
Age	1.06	0.96-1.17	.2
Sex	0.79	0.44-1.41	.4
B: After training			
Univariate model			
Average dysplasia score	3.79	1.32-10.86	.013
Multivariate model			
Diameter	1.46	1.03-2.07	.034
Average dysplasia score	2.80	0.91-8.64	.07
Age	1.06	0.96-1.17	.3
Sex	0.82	0.46-1.45	.5

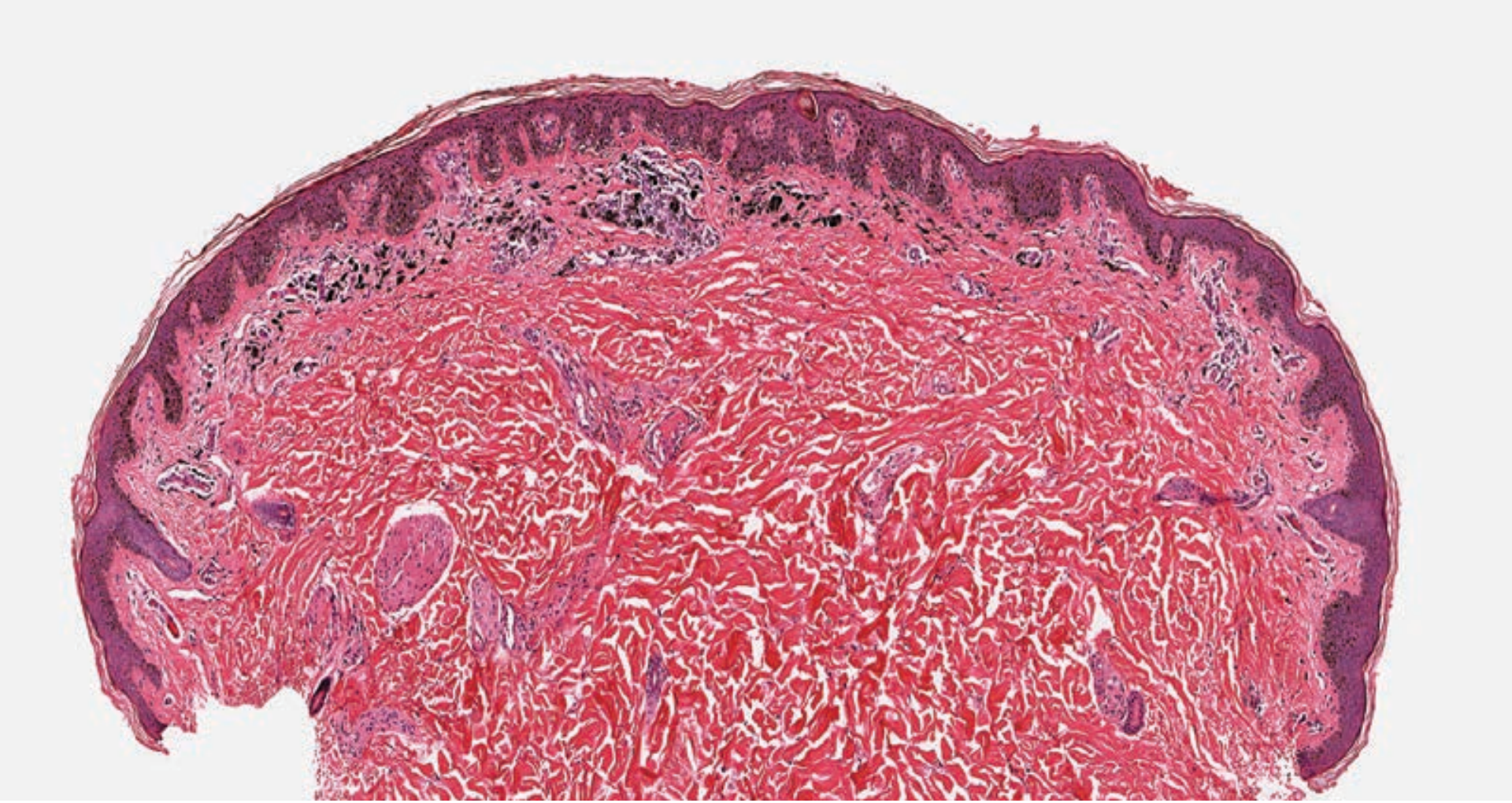
"Given that measuring diameter tends to be more objective than grading dysplasia, these results could provide increased consistency when assessing risk of melanoma among patients with dysplastic nevi"

Mild Dysplasia

- Poorly reproducible diagnosis (vs. nevus)
- Not associated with melanoma risk
- Not a high risk precursor
- Not a strong simulant of melanoma
- UNCERTAINTY vs. Moderate dysplasia, No dysplasia

- Should be considered in the spectrum of banal nevi (junctional or compound nevus, e.g. lentiginous junctional nevus)
- Complete excision is not necessary even when margins are positive

- TERM “MILD DYSPLASIA” SHOULD NO LONGER BE USED

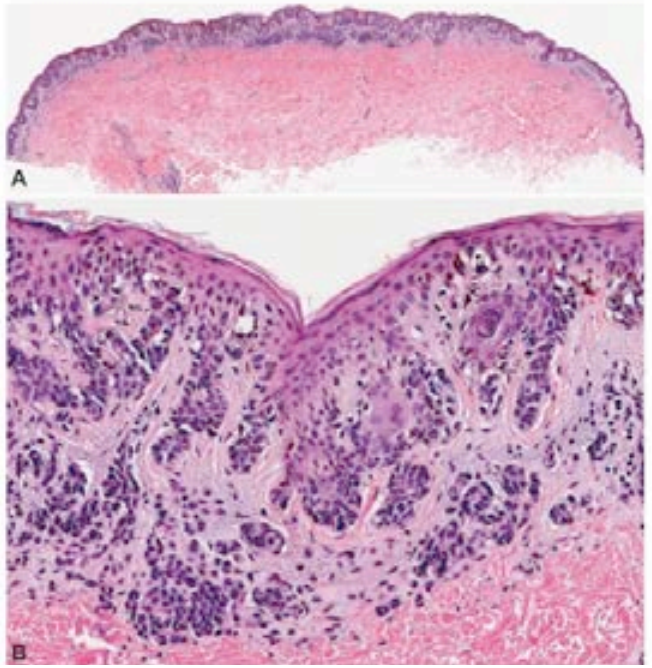


- **(Lentiginous) Junctional Nevus**
  - **< 4 mm diameter**
  - **minimal cytologic atypia**

Moderate Dysplasia

- Controversial
- Poorly reproducible diagnosis (vs mild, severe)
- UNCERTAINTY vs. Mild dysplasia, MIS
- Associated with melanoma risk
- Probably not a high risk precursor
- A weak simulant of melanoma (at least histologically)

- Complete excision is a consideration; observation is an option



JAMA Dermatology | Original Investigation

Risk of Subsequent Cutaneous Melanoma in Moderately Dysplastic Nevi Excisionally Biopsied but With Positive Histologic Margins

Caroline C. Kim, MD; Elizabeth G. Berry, MD; Michael A. Marchetti, MD; Susan M. Swetter, MD; Geoffrey Lim, MD; Douglas Grossman, MD, PhD; Clara Curiel-Lewandrowski, MD; Emily Y. Chu, MD, PhD; Michael E. Ming, MD, MSCE; Kathleen Zhu, BA; Meera Brahmbhatt, MD; Vijay Balakrishnan, BS; Michael J. Davis, BMus; Zachary Wolner, BA; Nathaniel Fleming, BA; Laura K. Ferris, MD, PhD; John Nguyen, BA; Oleksandr Trofymenko, BA; Yuan Liu, PhD; Suephy C. Chen, MD, MS; for the Pigmented Lesion Subcommittee, Melanoma Prevention Working Group

- Followed 467 patients 6.9 years (mean, SD 3.4 years.
- No cases of MM at site of prior incomplete biopsy
- 100 patients (22.8%) developed melanoma at other sites

CONCLUSIONS AND RELEVANCE This study suggests that close observation with routine skin surveillance is a reasonable management approach for moderately dysplastic nevi with positive histologic margins. However, having 2 or more biopsied dysplastic nevi (with 1 that is a moderately dysplastic nevus) appears to be associated with increased risk for subsequent CM at a separate site.

Severe Dysplasia

- Reasonably reproducible diagnosis
- UNCERTAINTY vs. MIS
- Associated with melanoma risk
- Probably a high risk precursor
- A strong simulant of melanoma (at least histologically)

- Should be managed by complete excision and consideration of follow-up, similar to MIS
  - "Complete excision for full evaluation, and to minimize any potential for local persistence, recurrence or progression"

Grading Dysplasia WHO 2018

- Junctional/compound nevus
  - Includes former mild dysplasia and “Clark’s nevus”
- Low Grade Dysplasia (LGD)
  - Former moderate dysplasia
- High Grade Dysplasia (HGD)
  - Former severe dysplasia

Dysplastic Nevus – 2018 WHO Criteria

Table 2.7 International Melanoma Pathology Study Group (IMPSG) diagnostic criteria for dysplastic naevus. Reproduced from: Shors AR et al. (2434) and Xiong MY et al. (2868).

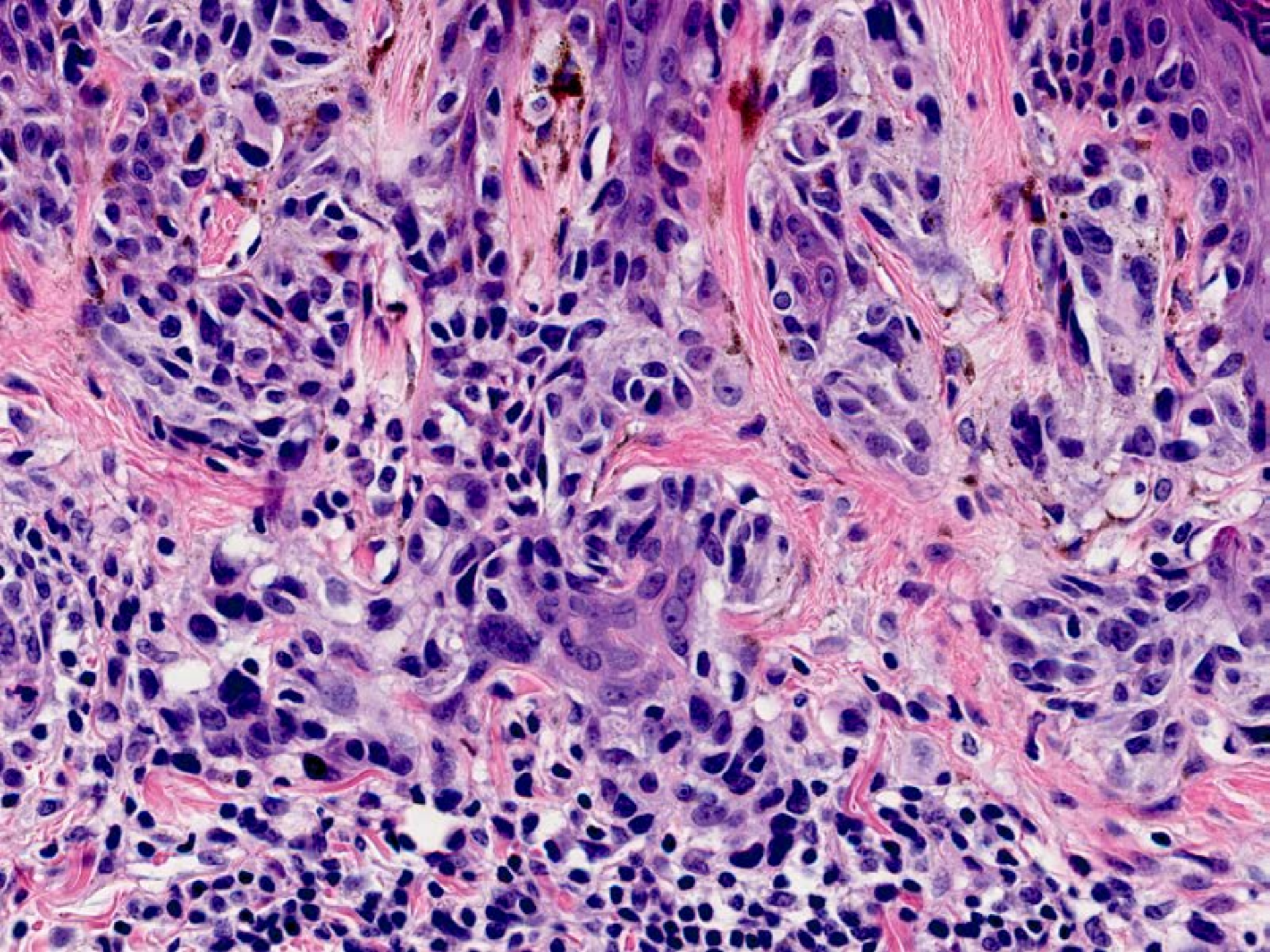
Dysplastic naevus

- 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)

2.13 Low Grade and High Grade Dysplasia

Grade (former)	2017 Grade	Nucleus size compared to resting basal cells	Chromatin	Nuclear size & shape variation	Nucleolus
0 (former mild)	Not a dysplastic nevus	1x	May be hyperchromatic	Minimal	Small or absent
1 (moderate dysplasia)	Low Grade Dysplasia	1-1.5x	Hyperchromatic or dispersed	Prominent in a minority of cells (“random atypia”)	Small or absent
2 (severe dysplasia)	High Grade Dysplasia	1.5x or more	Hyperchromatic, coarse granular, or peripheral condensation	Prominent in a larger minority of cells	Prominent, often lavender

Architectural features (including size > 4 mm) are required for the diagnosis and also contribute to the grade of dysplasia.



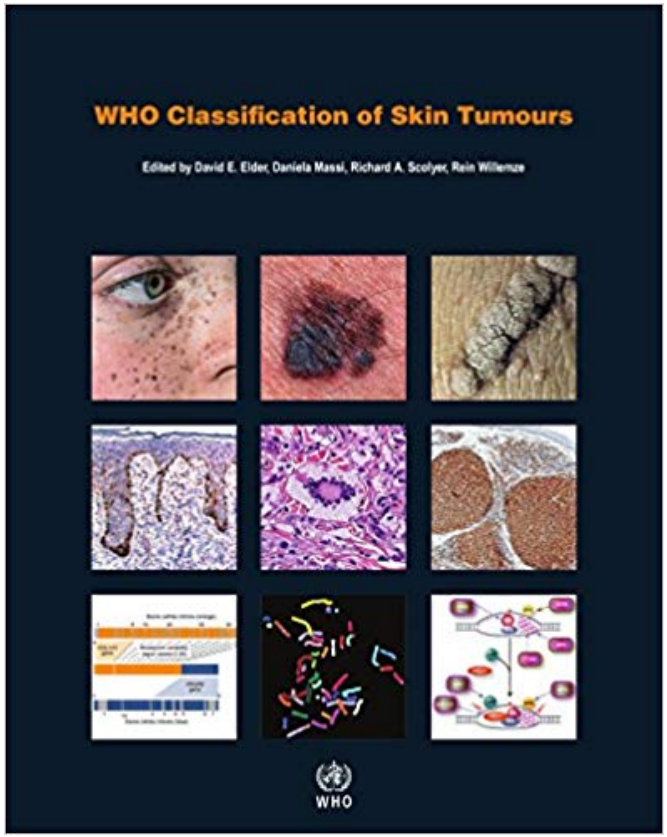
Conclusions

- Former mild dysplasia is a benign lentiginous nevus (the commonest type of nevus)
- Low grade dysplasia (former moderate dysplasia) can be observed clinically or by patients, looking for evidence of changing lesions
- High grade dysplasia is difficult to distinguish from melanoma in situ (UNCERTAINTY), may have competence for local persistence, recurrence and progression, and should be completely excised or followed

- All of these are “melanocytic neoplasms of low (or no) malignant potential” which have little or no competence for metastasis


LOVE

WHO Classification of Skin Tumours



- Edited by
- David E Elder
- Daniela Massi
- Richard A Scolyer
- Rein Willemze

- And > 100 contributors


WHO Classification of Skin Tumours
Consensus and Editorial Meeting, 24-26 September 2017, IARC, Lyon, France

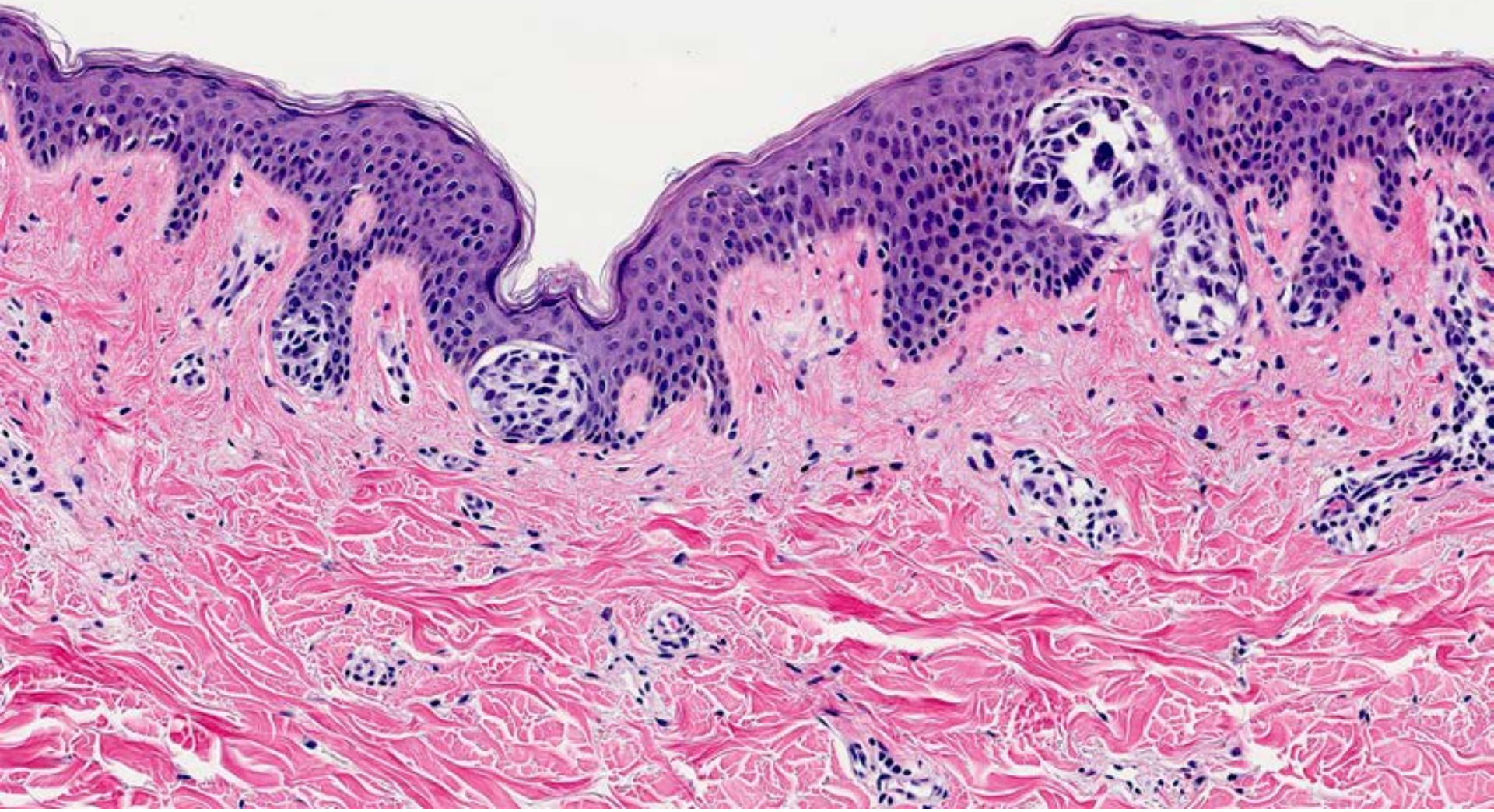
Case 4

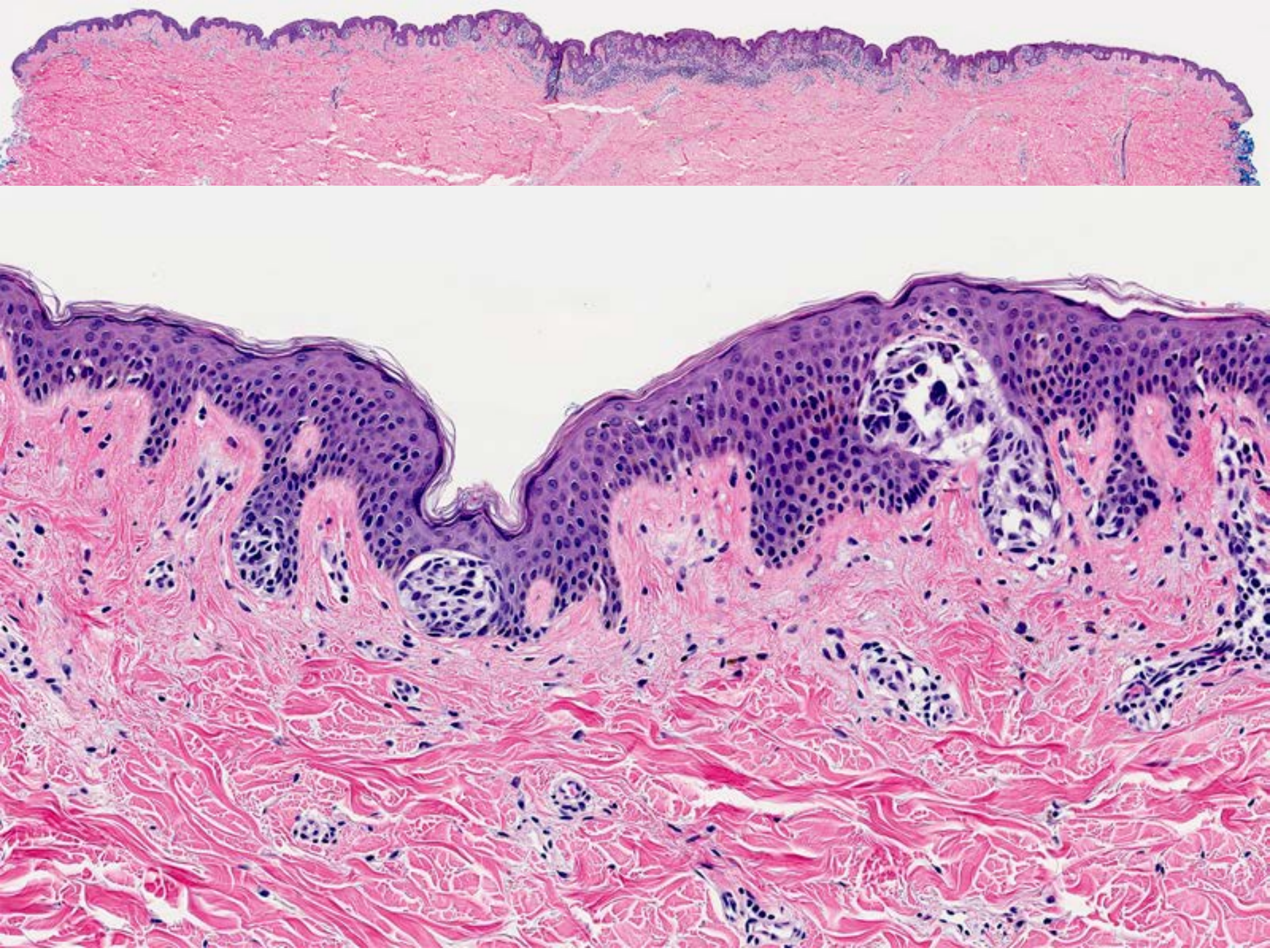
London SVS\90137.svs

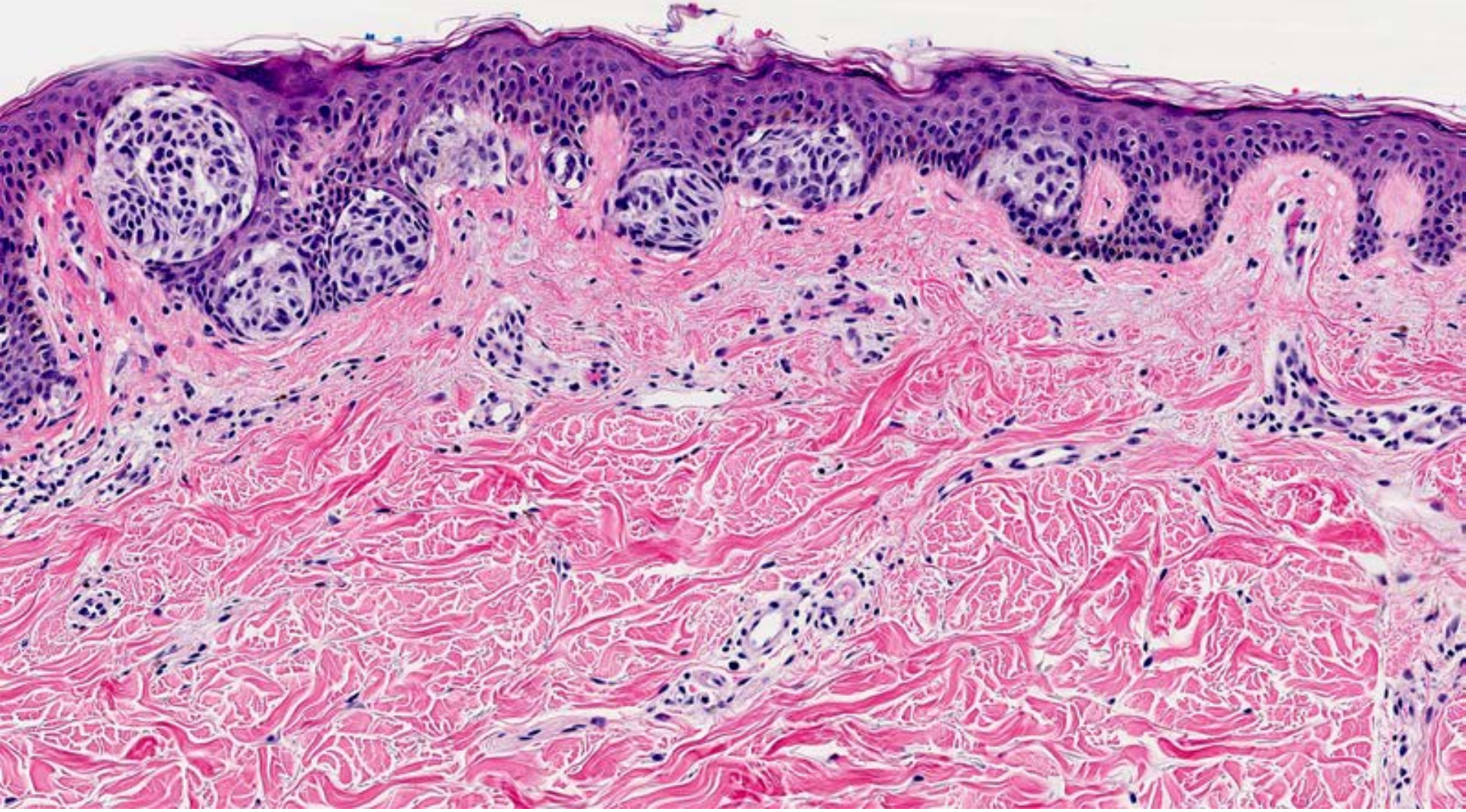
Lesion of skin of knee in a 30 y.o. woman

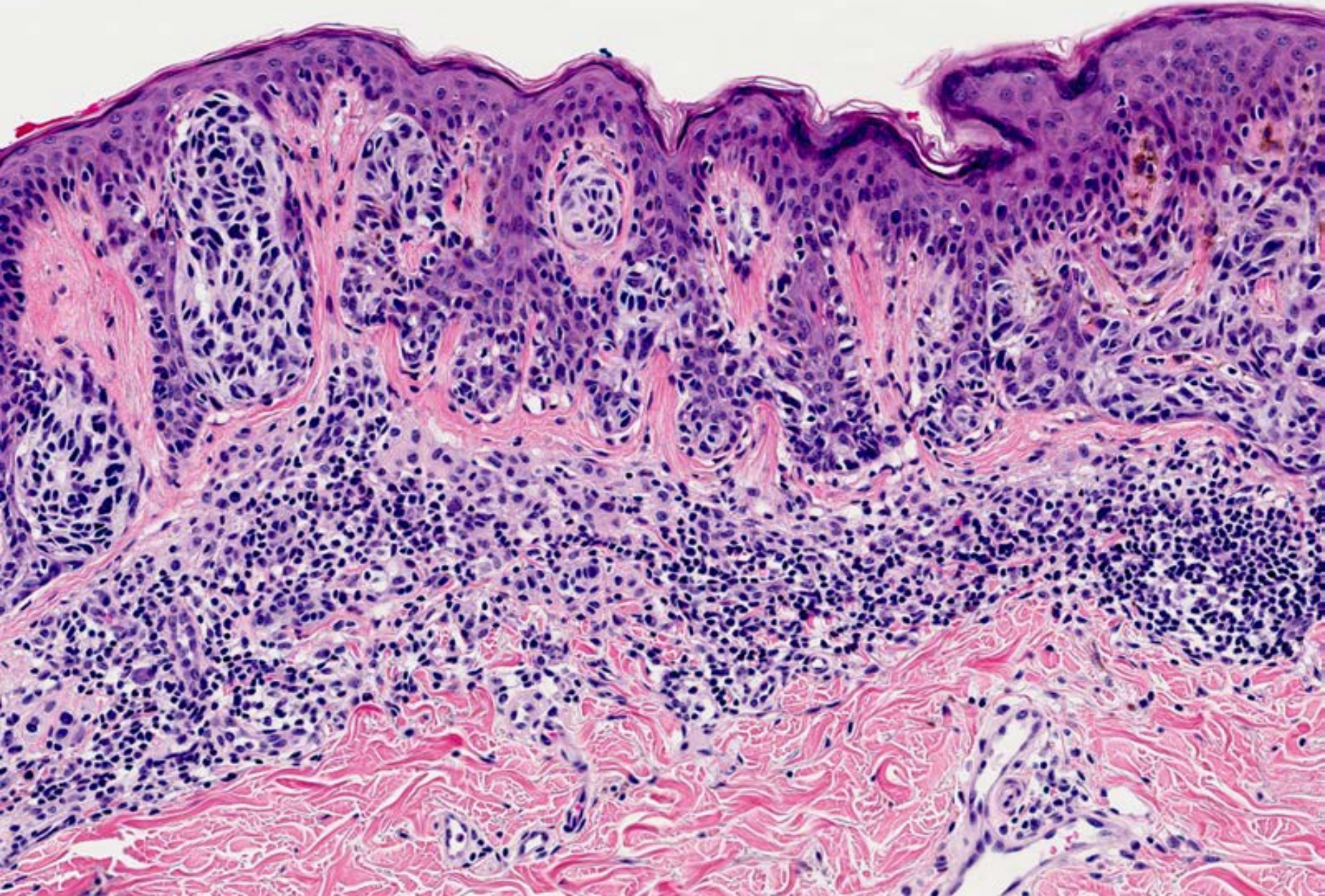
From the knee of a 30 y.o. woman

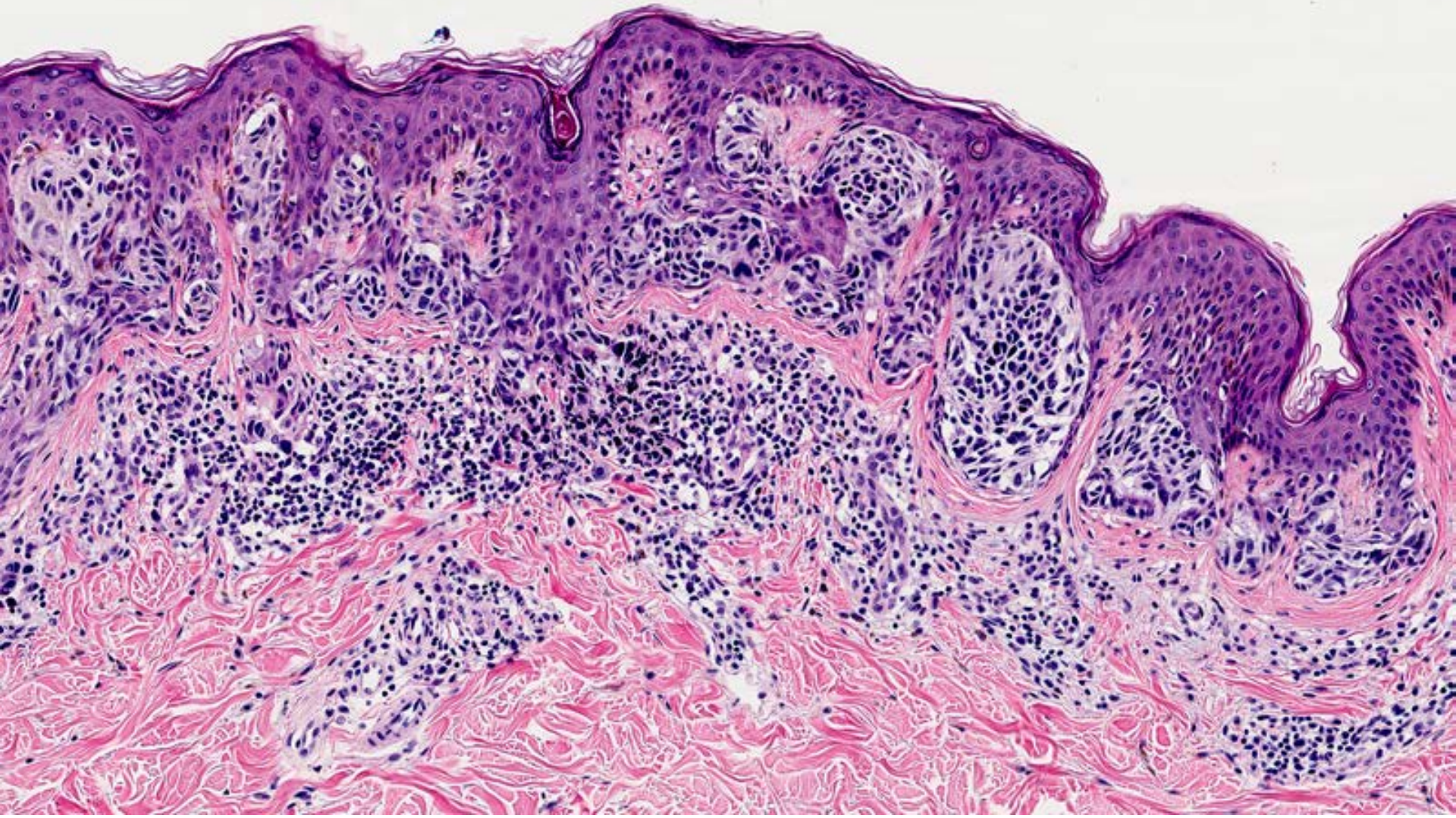
- Submitted with the following clinical information: "Changing mole, exam shows a 7-8 mm dark brown papule with pigment irregularity”.
- The lesion has been present for a "couple of months“.
- Dermoscopy shows an irregular pigmented network, irregular dots and globules and positive possible negative pigment network.
- Differential diagnosis: “Melanoma versus Nevus".

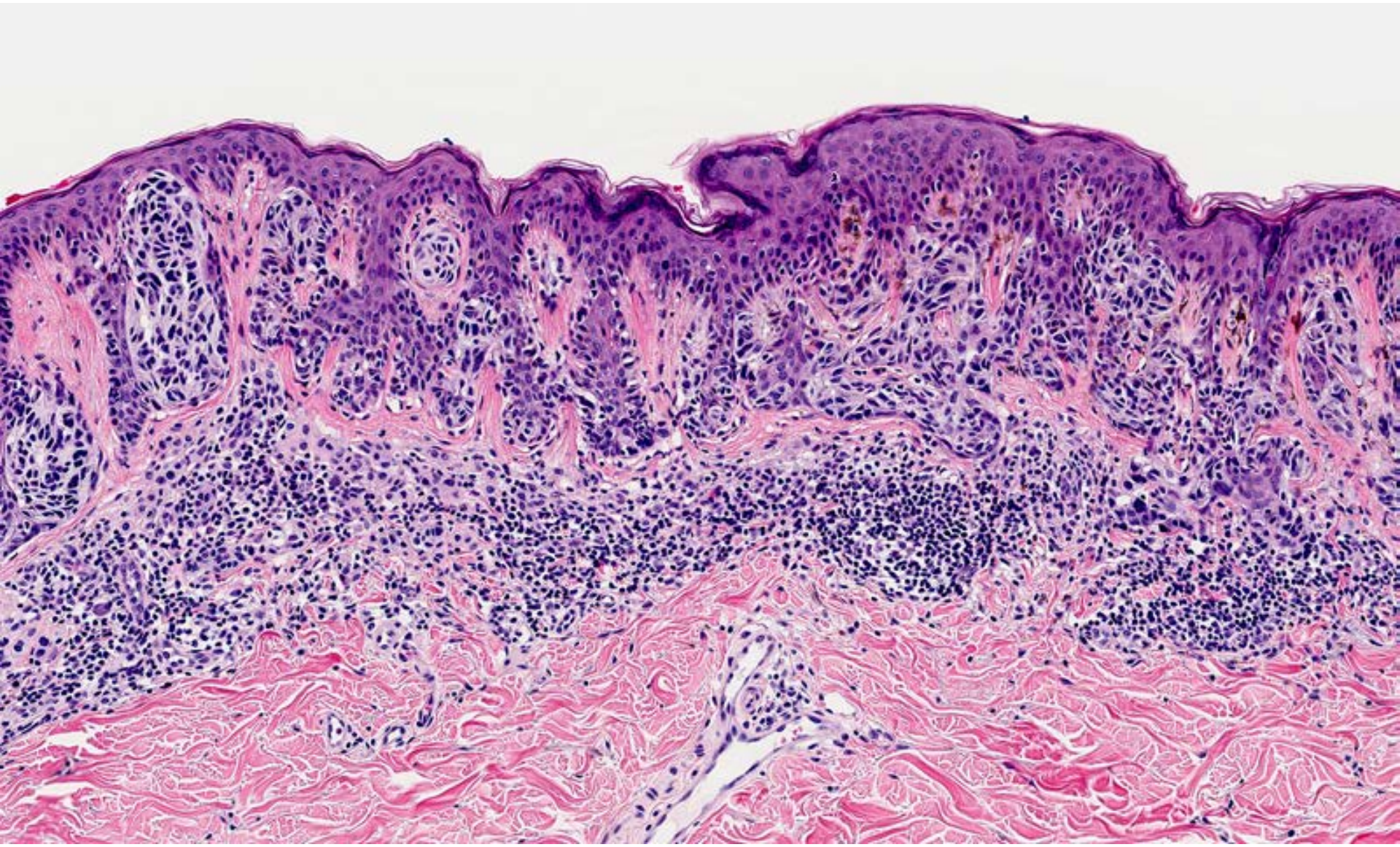


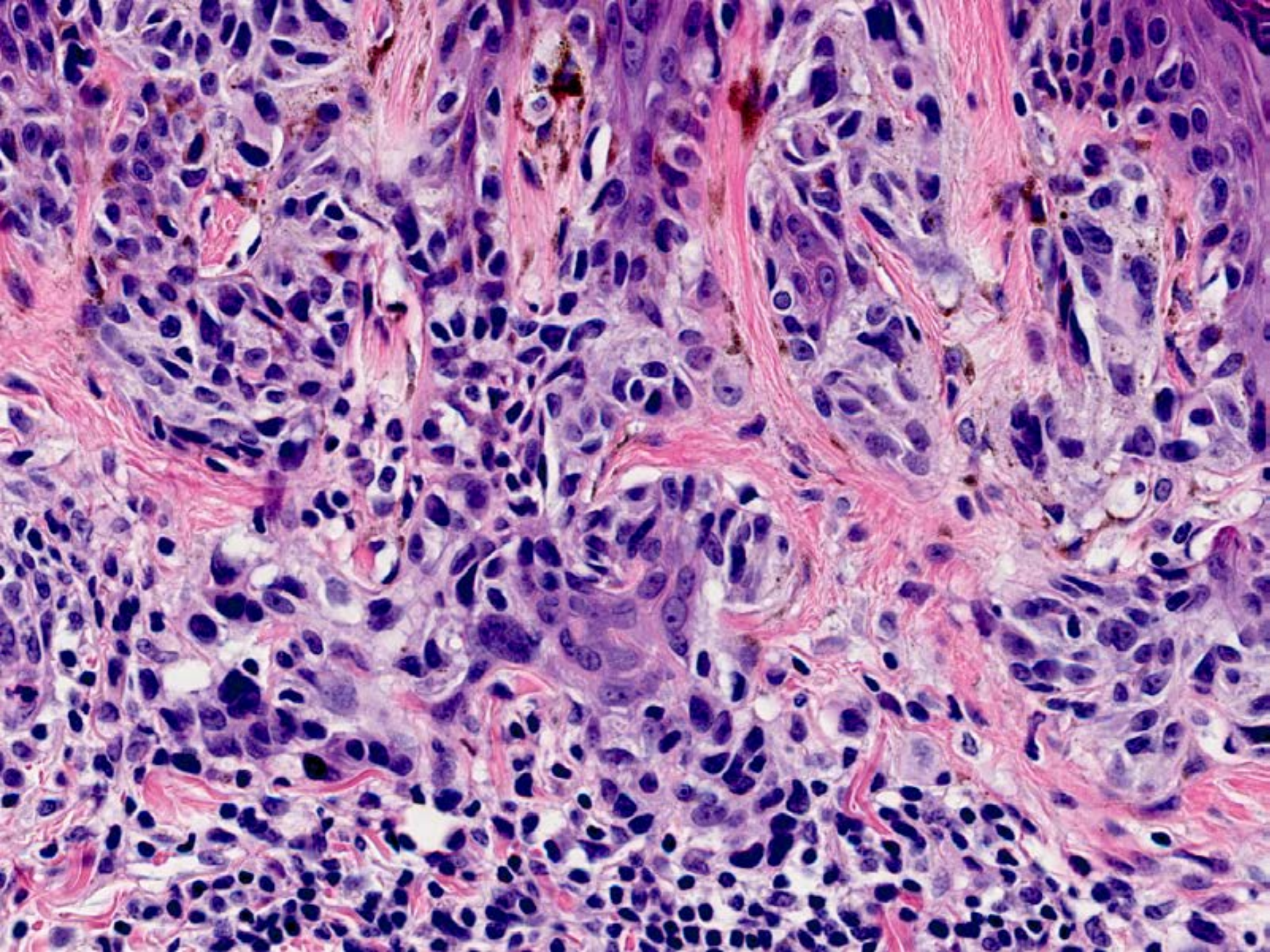


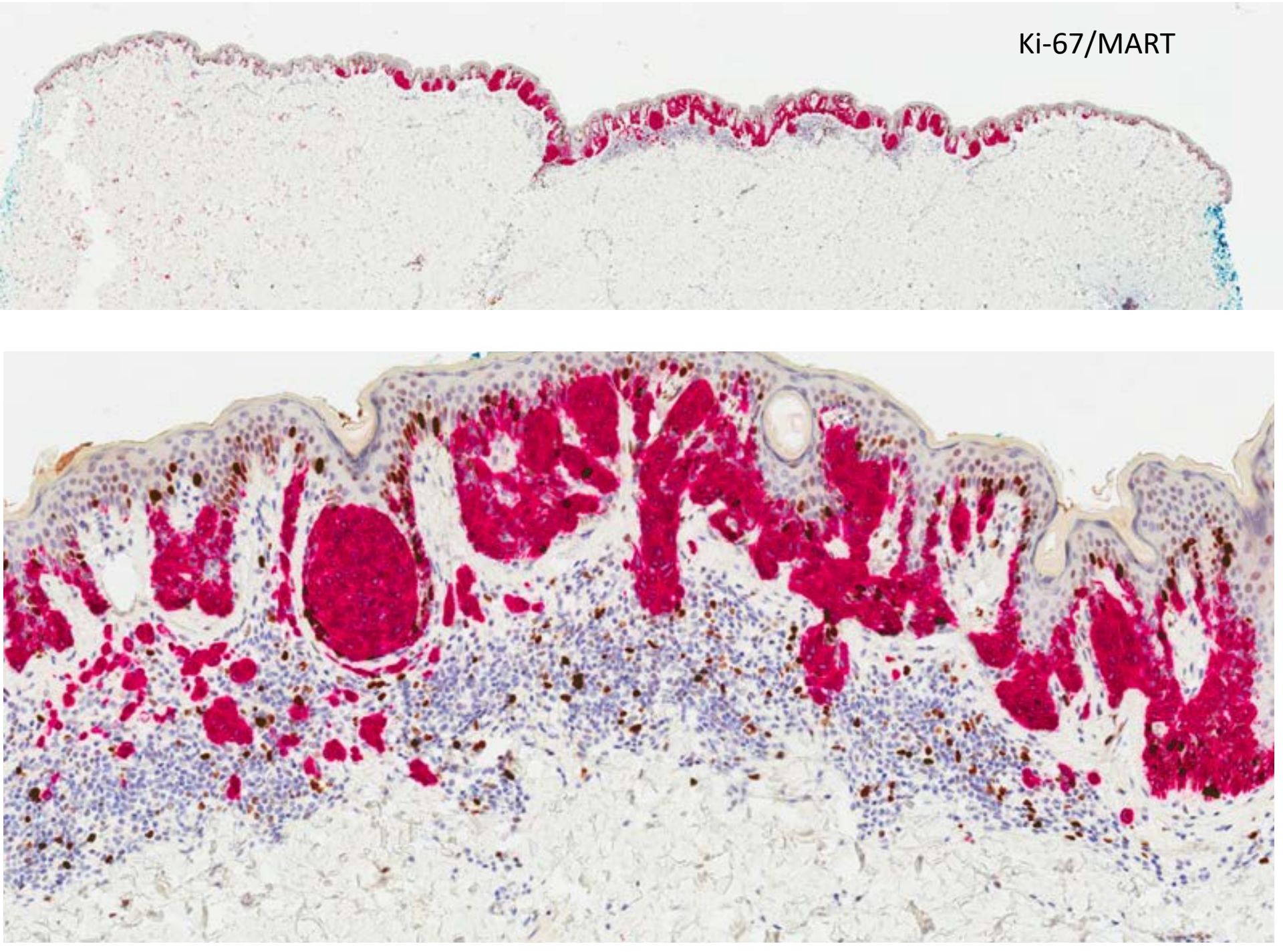








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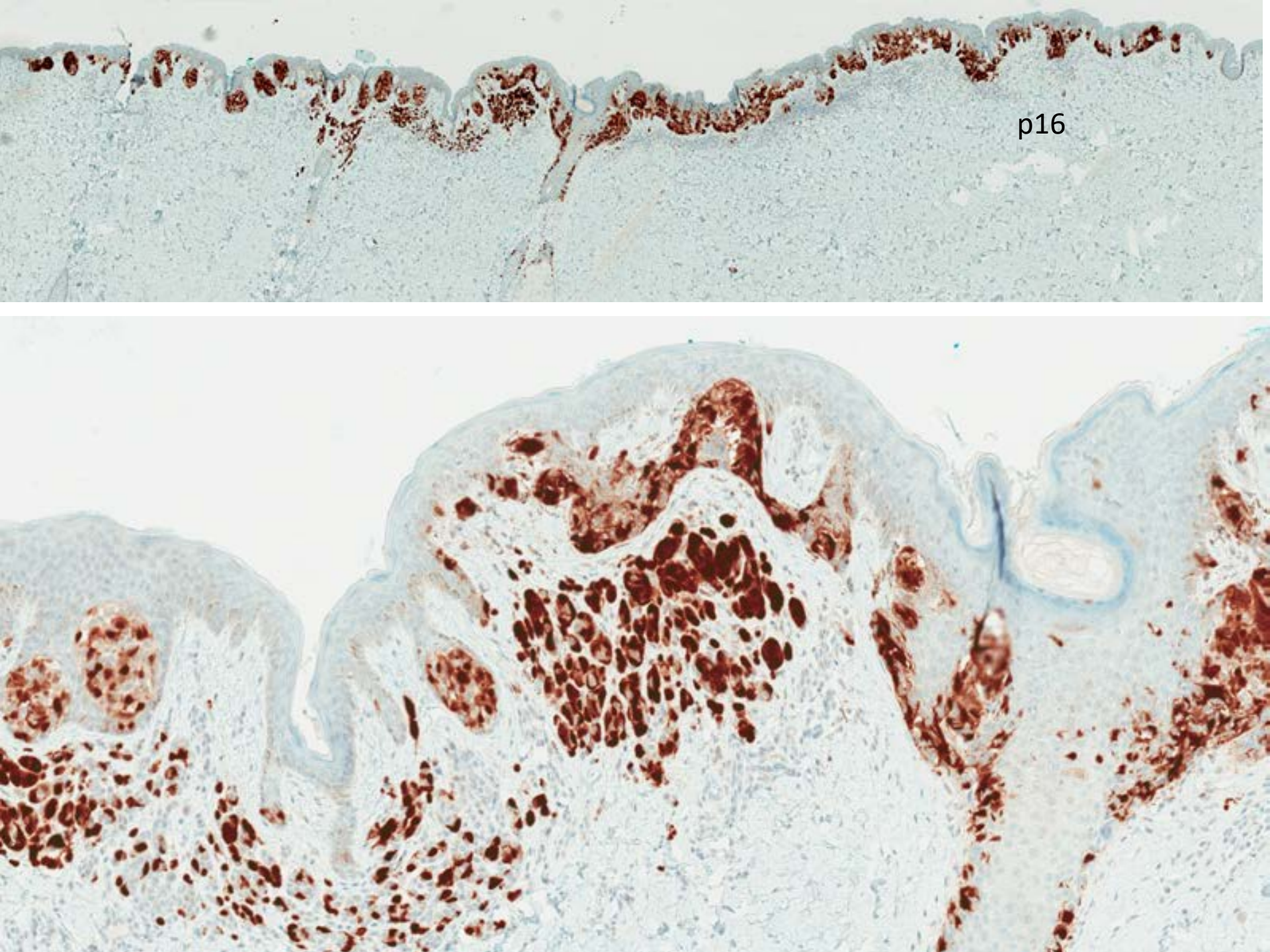
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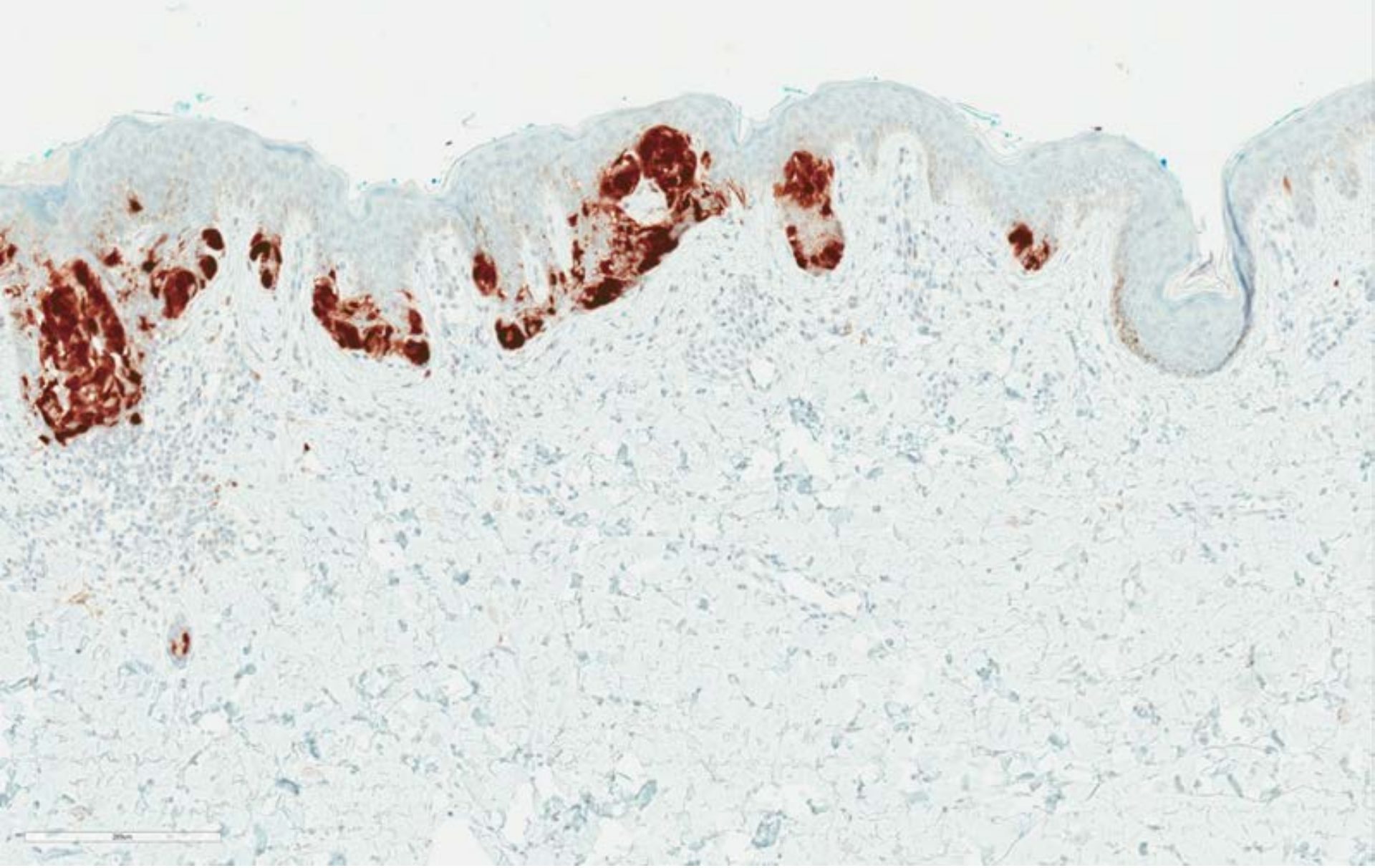

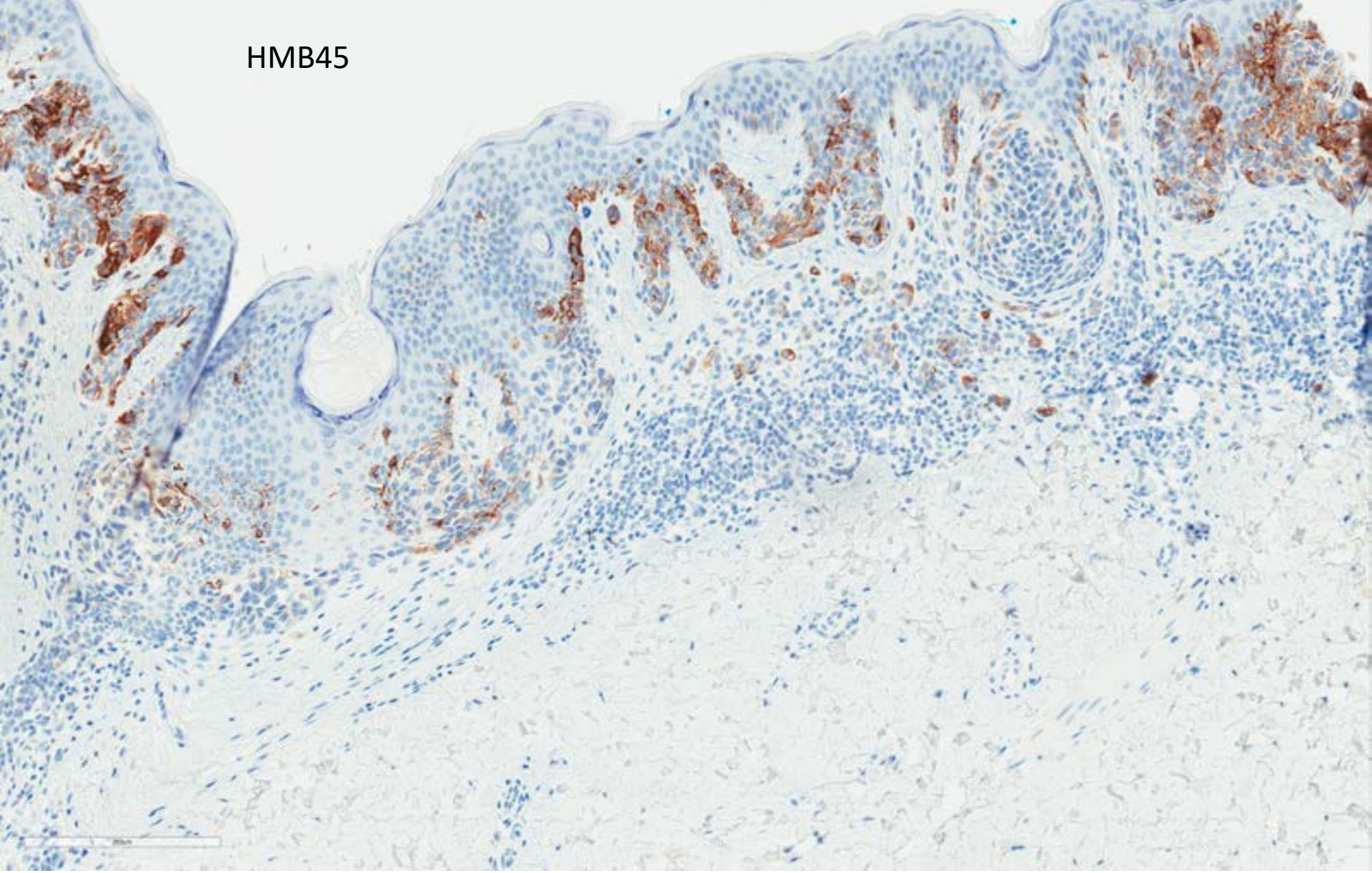
HMB45

Your Diagnosis

Melanoma?

Nevus?

Your Diagnosis

Dysplastic Nevus?

Other?

Our Diagnosis

Compound nevus with severe dysplasia

(High grade dysplasia, WHO 2018)

Compound nevus with severe dysplasia

(Moderate architectural disorder, severe cytological atypia)

Feature	Melanoma	Dysplastic Nevus	Nevus
Size	larger	intermediate	smaller
Cellularity	high	intermediate	lower
Symmetry	poor	good	good
Rete ridges	irregular	uniformly elongated	uniform
Junctional Melanocytes	epithelioid	mixed (nevoid to epithelioid)	nevoid
Poor circumscription	common	less common	uncommon
Nested	variable	predominant	predominant
Nests	coalescent (confluent)	bridging	discrete
Size of Nests	variable	uniform	uniform
Lentiginous	continuous	discontinuous	discontinuous
Pagetoid	high, extensive	low, focal, minimal	minimal
Nuclear atypia	uniform atypia, moderate-severe	random atypia, mild-moderate (1-1.5X)	minimal, mild
Mitoses - junctional	about 1/3 of cases	almost always absent	absent
Pyknosis/necrosis	common	uncommon	uncommon
Fibroplasia	diffuse	concentric	minimal
Lymphocytes	bandlike, lichenoid	patchy, perivascular	minimal
Regression	frequent, extensive	rare, minimal	absent
Dermal Cells Absent	uniform atypia limited maturation mitoses	random or no atypia maturation no mitoses	no atypia maturation no mitoses

2018 WHO Classification of Melanoma

- Melanomas are classified based on epidemiology, clinical and histologic morphology, and genomic characteristics
- Nine categories or “pathways” are defined, the first 3 of which are related to cumulative solar damage (CSD) – others have little/no relationship
- The melanomas are also classified in relation to their benign and “intermediate” potential precursor lesions, where applicable

Table 1.
Classification of Melanocytic Tumors by Epidemiologic, Clinical, Histopathologic & Genomic Attributes

Role of UV:	**Low UV**				**High UV**		**Low to No (or Variable) CSD**					
Pathway:	**I**				**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**
	Low-CSD Melanoma Superficial Spreading Melanoma				High-CSD Melanoma (LMM)	Desmoplastic Melanoma	Spitz Melanoma	Acral Melanoma	Mucosal Melanoma	Melanoma in Congenital Nevus	Melanoma In Blue Nevus	Uveal Melanoma
Benign	Nevus				? IAMP	? IAMP	Spitz Nevus	?IAMP	Melanosis	Congenital Nevus (CN)	Blue Nevus	?
Borderline Low	Low Grade Dysplasia	Bap-1 Deficiency Melanocytoma /MELTUMP	DPN Melanocytoma /MELTUMP	PEM Melanocytoma /MELTUMP	? IAMP	? IAMP	Atypical Spitz nevus	Atypical melanocytic proliferation	Atypical melanosis	Nodular proliferation in CN	Cellular Blue Nevus	Uveal nevus
Borderline High	High Grade Dysplasia				Lentigo maligna	Melanoma in situ	STUMP	Melanoma in situ	IAMPUS/ SAMPUS	? MIS in CN	Atypical CBN	?
Malignant	Superficial Spreading Melanoma	Melanoma in BPDM (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	Lentigo Maligna Melanoma	Desmoplastic Melanoma	Malignant Spitz Tumor	Acral lentiginous melanoma	Mucosal lentiginous melanoma	Melanoma in CN	Melanoma ex Blue Nevus	Uveal melanoma
Common mutations	BRAF V600E, NRAS	(BRAF or NRAS) +BAP1	(BRAF, MEK1, or NRAS) +(CTNNB1 or APC)	(BRAF +PRKAR1A) or PRKCA	NRAS, BRAFnon-V600E, KIT, NF1	NF1, ERBB2, MAP2K1, MAP3K1, BRAF, EGFR, MET,	HRAS, ALK, ROS1, RET, NTRK1, NTRK3, BRAF,MET	KIT, NRAS, BRAF, HRAS, KRAS, NTRK3, ALK, NF1	KIT, NRAS, KRAS, or BRAF	NRAS, BRAF V600E (small lesions), BRAF	GNAQ, GNA11, or CYSLTR2	GNAQ, GNA11, CYSLTR2, or PLCB4
	TERT, CDKN2A, TP53, PTEN				TERT, CDKN2A, TP53, PTEN, RAC1	TERT, NFKBIE, NRAS, PIK3CA , PTPN11	CDKN2A	CDKN2A, TERT CCND1, GAB2	NF1, CDKN2A SF3B1, CCND1, CDK4, MDM2		BAP1, EIF1AX, SF3B1	BAP1 SF3B1, EIF1AX,

Notes: Progression is not obligate and steps can be skipped

Color Code: Mutations: Red; gain of function; Blue, loss of function; Green, change of function, Black, promoter mutation. Orange, amplifications. Purple: Rearrangements.

Disclosures

Consulting:
Myriad Genetics
SciBase