



University of Pennsylvania, Founded by Ben Franklin in 1740

08.15 Introduction. [Raymond Barnhill](#)
08.20 Criteria for melanocytic lesions : an introduction.
[Raymond Barnhill](#)
08.50 Immunohistochemistry for pathologists. [Klaus Busam](#)
09.20 Molecular diagnostics for pathologists. [Boris Bastian](#)
10.00 Coffee Break
10.30 MPath classification. [Raymond Barnhill](#)
10.50 AJCC 8th edition guidelines. [David Elder](#)
11.10 Sentinel lymph nodes and prognostic factors in
melanoma, [Lyn Duncan](#)
11.30 Treatment recommendations for melanocytic lesions.
[David Elder](#)
12.00 Lunch
01.00 ^{PM} Classification of melanoma for pathologists. [Boris
Bastian](#)
01.30 ^{PM} Lentigo maligna melanoma. [Klaus Busam](#)
01.50 ^{PM} Ocular conjunctival and uveal melanocytic lesions:
Clinical aspects. [Denis Malaise](#)
02.10 ^{PM} Conjunctival melanocytic lesions: Pathological
aspects. [Ian Cree](#)
02.25 ^{PM} Uveal melanoma: Pathological aspects. [Raymond
Barnhill](#)
02.40 ^{PM} Angiotropic extravascular migratory metastasis.
[Claire Lugassy](#)
03.00 ^{PM} Coffee Break
03.30 ^{PM} Case presentations
(10 cases, 10 min/case with discussion)
05.45 ^{PM} Welcome cocktail

08.10 Acquired melanocytic nevi. [David Elder](#)
08.40 Spitz nevus, atypical Spitz tumor, Spitz melanoma.
[Raymond Barnhill](#)
09.10 Blue nevus and melanoma arising in blue nevus.
[Arnaud de la Fouchardière](#)
09.40 Site-specific nevi (including scalp, breast and milk-line,
flexural, perianal). [David Elder](#)
10.00 Coffee Break
10.30 Combined melanocytic nevi: BAP1, deep penetrating,
Pigmented epithelioid melanocytoma, etc [Arnaud de la
Fouchardière](#)
10.50 Pediatric melanocytic lesions. [Raymond Barnhill](#)
11.10 Acral melanocytic nevi and melanoma. [Richard Scolyer](#)
11.40 Melanoma of unknown primary: differential diagnosis,
[Lyn Duncan](#)
12.10 Lunch
01.10 ^{PM} Nevoid melanoma. [Klaus Busam](#)
01.30 ^{PM} Desmoplastic nevi and desmoplastic melanoma.
[Klaus Busam](#)
01.50 ^{PM} Oral and genital melanocytic lesions. [Ian Cree](#)
02.10 ^{PM} Sinonasal melanoma, [Lyn Duncan](#)
02.30 ^{PM} Gene expression profiling in melanocytic lesions: an
update, [Matthew Goldberg](#)
03.00 ^{PM} Coffee Break
03.30 ^{PM} Case presentations continued

Acquired Melanocytic Nevi & Melanoma 30 min

David Elder, Paris 2024

Nature and Significance of Nevi

- Nevi (“melanocytic nevi” are benign neoplasms of melanocytes
- 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

WHO Classification of Melanoma

- Defines 9 “pathways” to Melanoma, based on ideas of Boris Bastian.
- 3 of these pathways are related to “cumulative solar damage” (CSD); the other 6 pathways are not related or only incidentally related to sun exposure.
- Precursor lesions and “intermediate” lesions are included in the classification.

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
	<u>Low-CSD Melanoma</u> <u>Superficial Spreading Melanoma</u>				<u>High-CSD Melanoma</u> <u>(LMM)</u>	<u>Desmoplastic</u> <u>Melanoma</u>	<u>Spitz</u> <u>Melanoma</u>	<u>Acral</u> <u>Melanoma</u>	<u>Mucosal</u> <u>Melanoma</u>	<u>Melanoma in</u> <u>Congenital</u> <u>Nevus</u>	<u>Melanoma</u> <u>In Blue Nevus</u>	<u>Uveal</u> <u>Melanoma</u>
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	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.

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

The Genetic Evolution of Melanoma from Precursor Lesions.

Shain AH, Yeh I, Kovalyshyn I, Sriharan A, Talevich E, Gagnon A, et al. The Genetic Evolution of Melanoma from Precursor Lesions. N Engl J Med. 2015;373(20):1926-36.

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 <i>TERT</i> ; <i>CDKN2A</i> ; <i>TP53</i> ; <i>PTEN</i>	BRAF or NRAS + BAP1	BRAF , MAP2K1 , or NRAS + CTNNB1 or APC	BRAF + PRKAR1A or PRKCA	NRAS ; BRAF (non-p.V600E); KIT ; or NF1 <i>TERT</i> ; <i>CDKN2A</i> ; <i>TP53</i> ; <i>PTEN</i> ; RAC1	NF1 ; ERBB2 ; MAP2K1 ; MAP3K1 ; BRAF ; EGFR ; MET <i>TERT</i> ; <i>NFKBIE</i> ; 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

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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 <i>TERT;</i> <i>CDKN2A; TP53;</i> <i>PTEN</i>	BRAF or NRAS + BAP1	BRAF, MAP2K1, or NRAS + CTNNB1 or APC	BRAF + PRKAR1A or PRKCA	NRAS; BRAF (non-p.V600E); KIT; or NF1 <i>TERT;</i> <i>CDKN2A; TP53;</i> <i>PTEN;</i> RAC1	NF1; ERBB2; MAP2K1; MAP3K1; BRAF; EGFR; MET <i>TERT; NFKBIE;</i> NRAS; PIK3CA; PTPN11

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Nevi as Potential Precursors of Melanoma

Often, the “melanoma” that is diagnosed as arising in a dysplastic nevus has the characteristics of an overdiagnosed melanoma

- T1a, nontumorigenic, nonmitogenic RGP only lesions may be overdiagnosed as melanoma
- Lesions with tumorigenic and/or mitogenic VGP qualify as true melanomas

Dysplastic Nevi

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

Evolving thinking in present state of concern about overdiagnosis of melanoma

Dysplastic nevi have also been heavily overdiagnosed

Dysplastic naevus

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

Mirm M.C. Jr
Piepkorn M.
Ratkin M.
Sooyler 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 indistinct border.

Comparison of increasing lesion size at histology on naevus to epidermal dysplasia, the number of nests of melanocytes is $< 1.5\times$ that of naevus (i.e. with the smallest nests) based 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 858 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 count have implicated several loci, but germline susceptibility loci unique to dysplastic naevi have not been reported [908]. It is

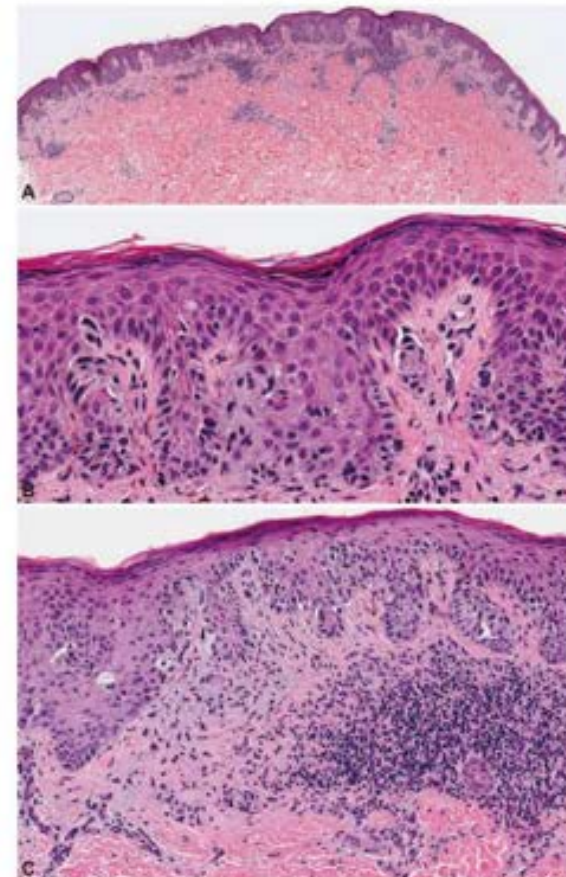


Fig 2.15 Compound dysplastic naevus, high grade. **A** Broad lesion, slightly > 4 mm in diameter on the side, with changes present at the left specimen edge. The rete ridges are somewhat irregularly thickened, although relatively uniformly elongated. There is a patchy to focally more dense lymphocytic 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 lesion's cells have a nuclear size $> 1.5\times$ 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 fibrosis at the tip of some rete. **C** In this focal area of the naevus lesion, there are changes that raise concern for evolving melanoma (at least in situ). There are large cells with nuclear cytology on some in panel B, and there is a focal tendency to upward pagetoid scatter near the middle of the lesion, not beyond the mid-epidermal layer. A few cells in the dermis (all of central) resemble those in the epidermis, with an associated focus of diffuse fibrosis. The lymphocytic infiltrate is focally band-like, there is well-developed acanthosis fibrosis 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

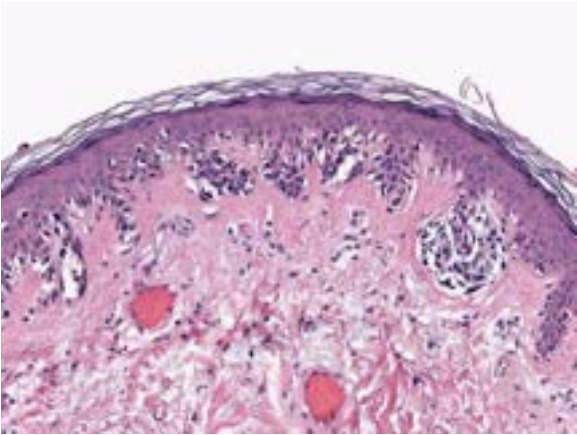
A widely adopted definition published by the International Agency for Research on Cancer (IARC) in 1990 (and subsequently modified) recommends the following criteria to identify atypical (dysplastic) naevi: there must be a macular component in at least one area; in addition, at least three of the following features must be present: a non-well-defined border, size ≥ 5 mm, colour variegation, uneven peripheral contour, and erythema [845]. 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

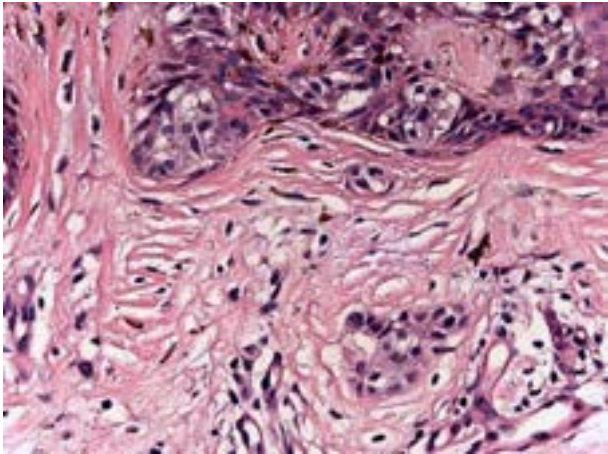
Melanocytic dysplasia comprises alterations of architectural disorder and cytological atypia [678]. The term "architectural disorder" refers to deviation from a stereotypical junctional naevus pattern (in which uniform nests of naevoid melanocytes are present at the tips of rete ridges uniformly across 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.”

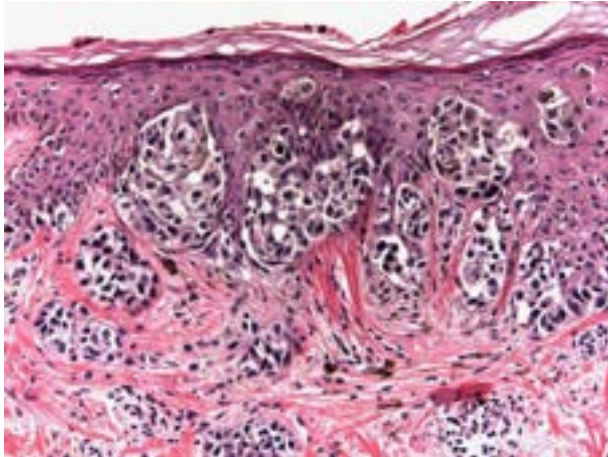
Low UV			
Pathway I			
Low-CSD Melanoma <u>Superficial Spreading Melanoma</u>			
Banal Acquired Nevus (junctional, compound, dermal)			
Low Grade Dysplasia			
High Grade Dysplasia			
Superficial Spreading Melanoma			
BRAF V600E, NRAS			
TERT, CDKN2A, TP53, PTEN			



Lentiginous junctional nevus



Compound dysplastic nevus



Superficial spreading or "pagetoid" melanoma

Case 1.

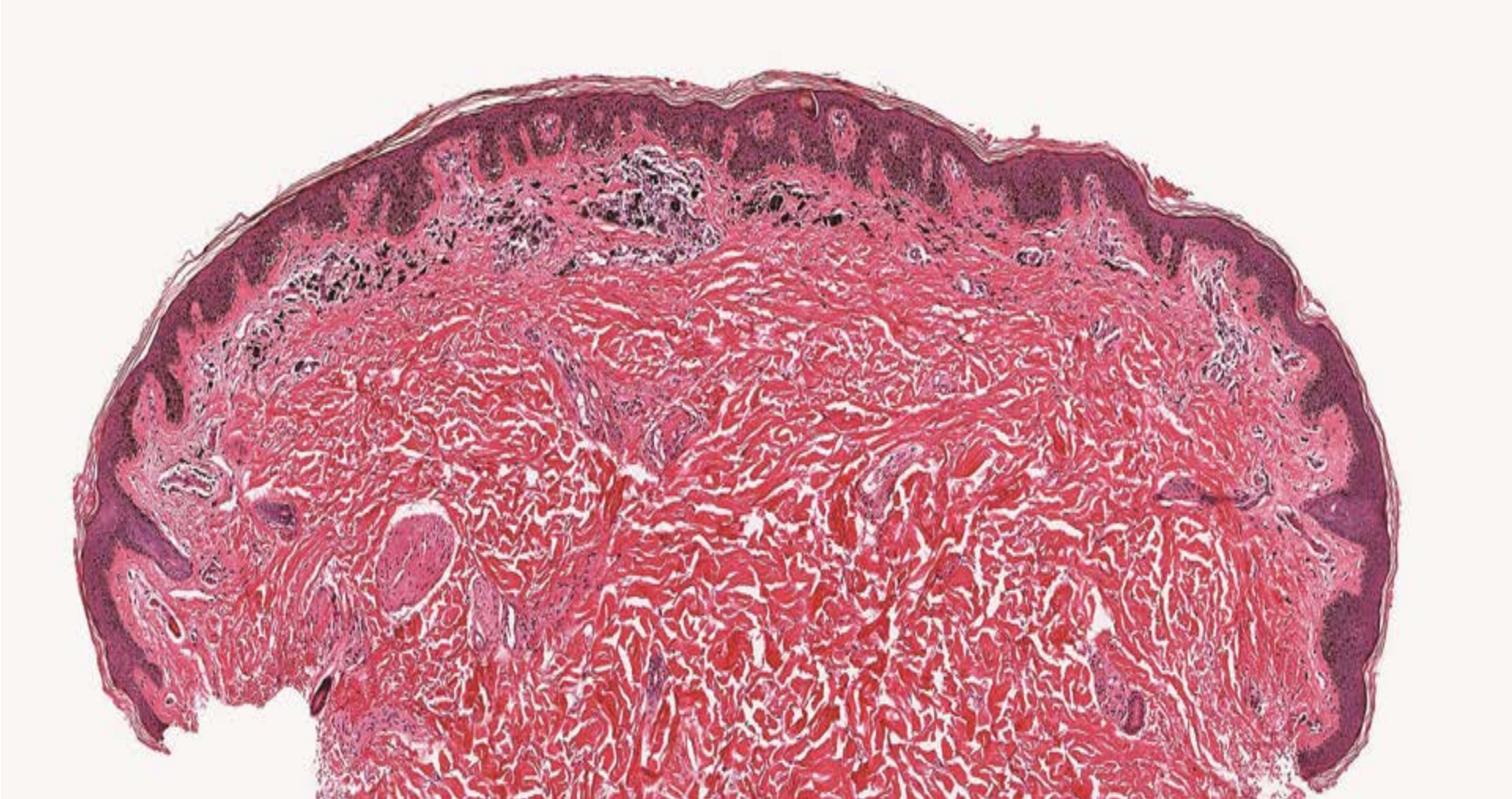
[London SVS\25451.svs](#)

Clinical Information.

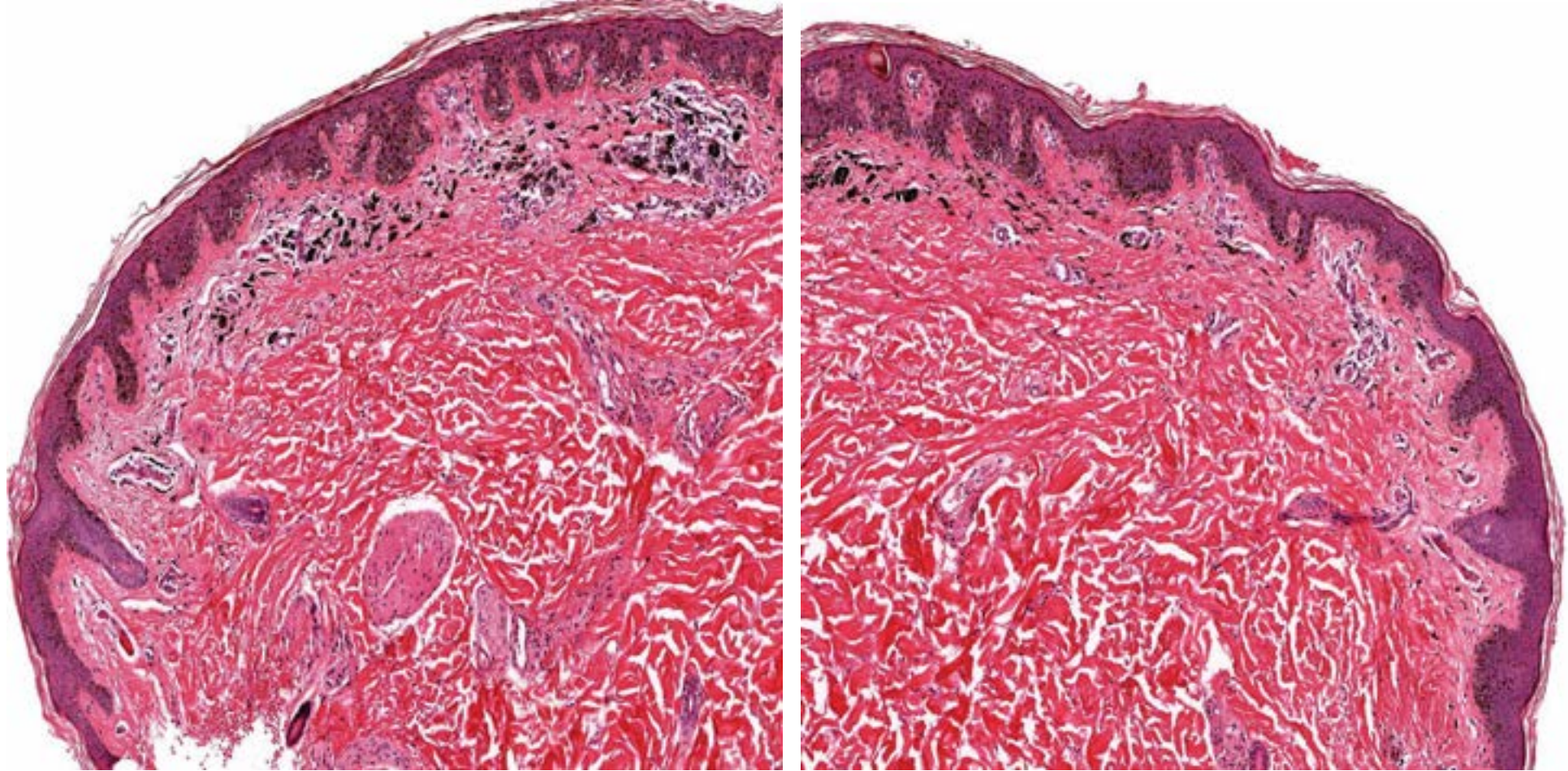
A macular slightly variegated lesion from the back of a 37-year-old woman.

Reason for Consultation.

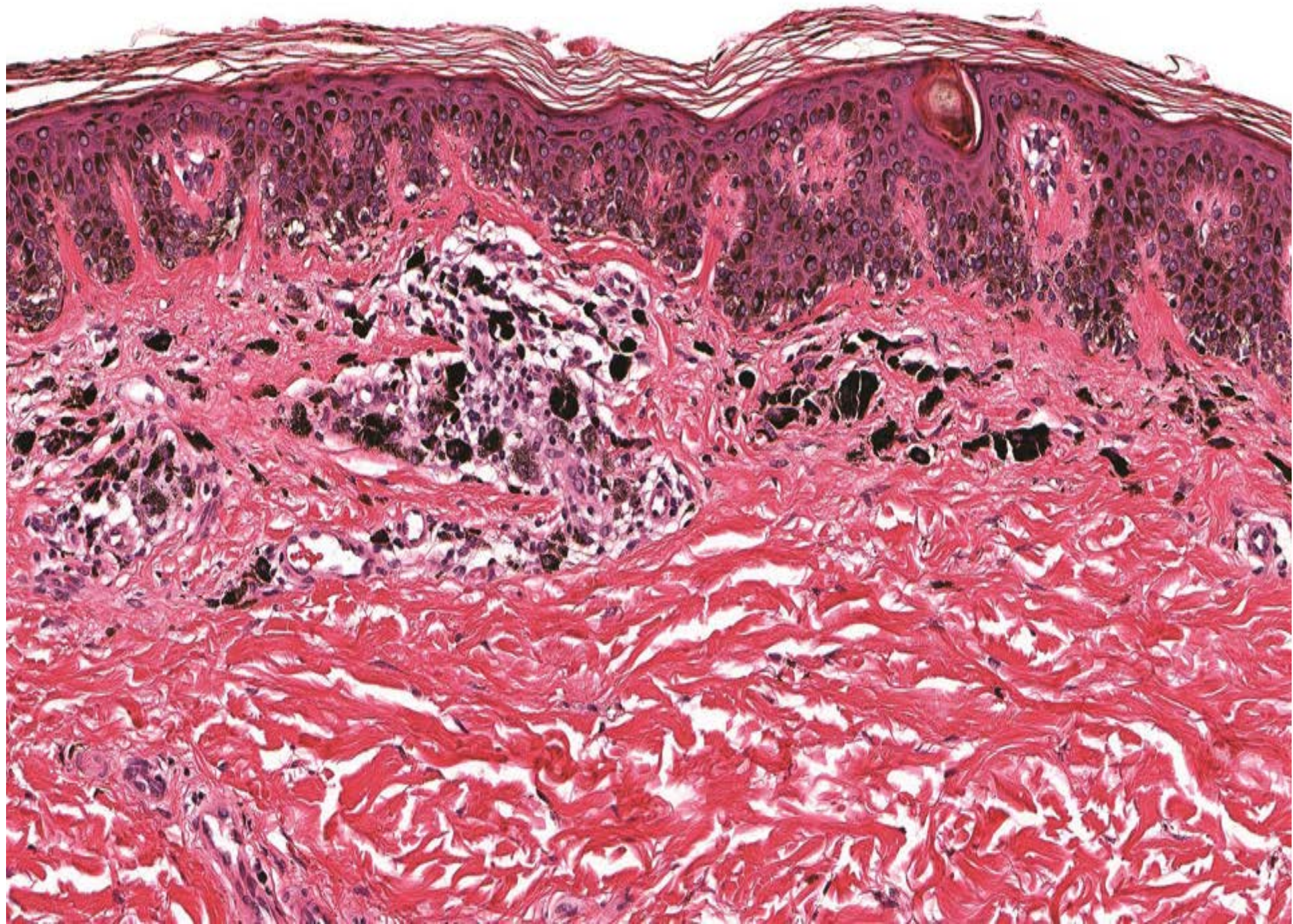
Is this a dysplastic nevus?



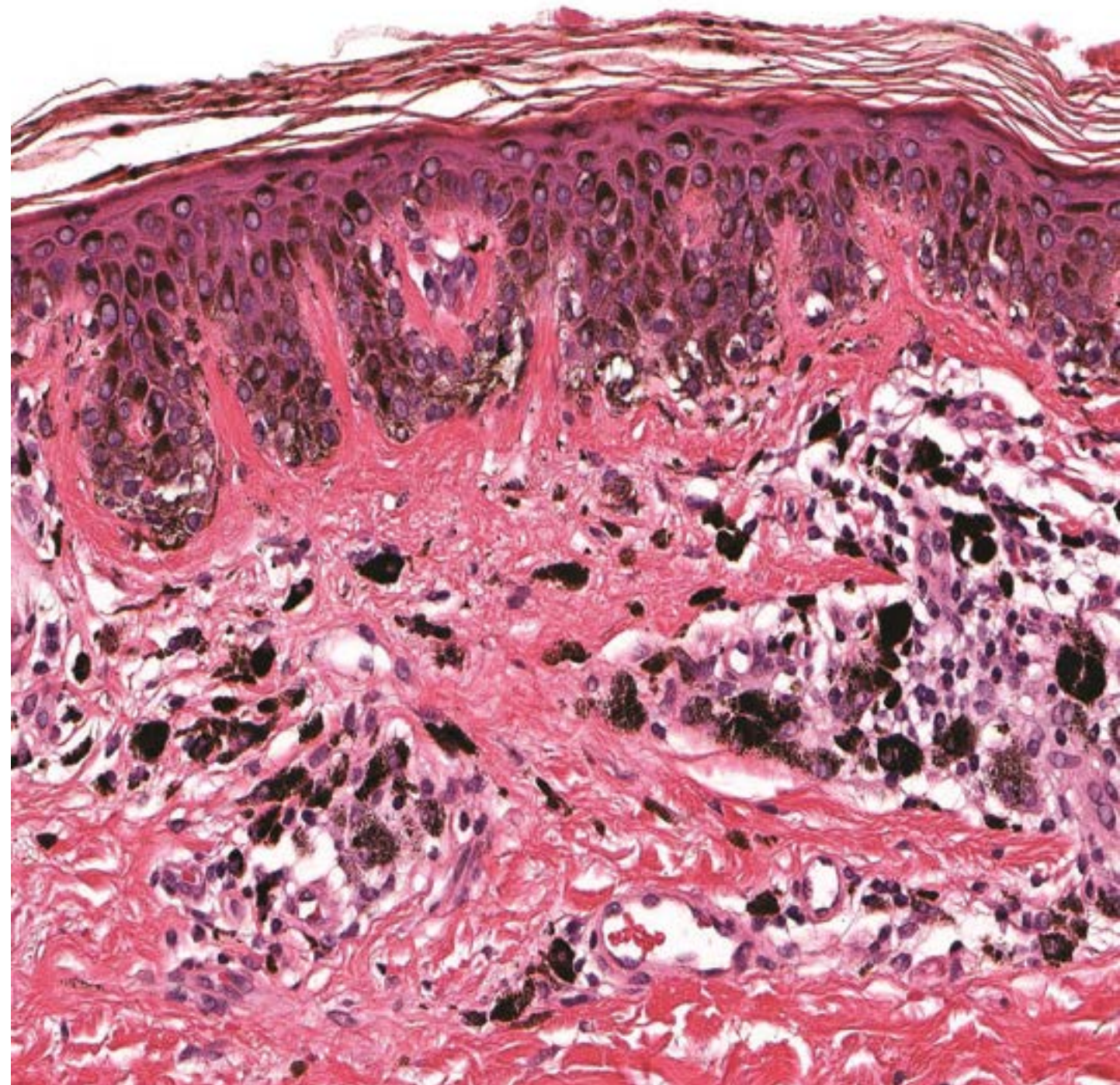
- **25451**
- ***Clinical Information.***
- A 3 mm macular slightly variegated lesion from the back of a 37-year-old woman.
- ***Reason for Consultation.***
- Is this a dysplastic nevus?



- 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?

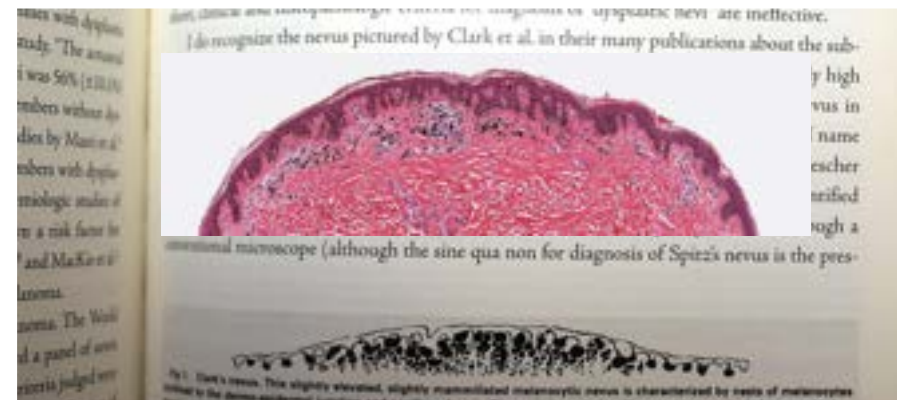
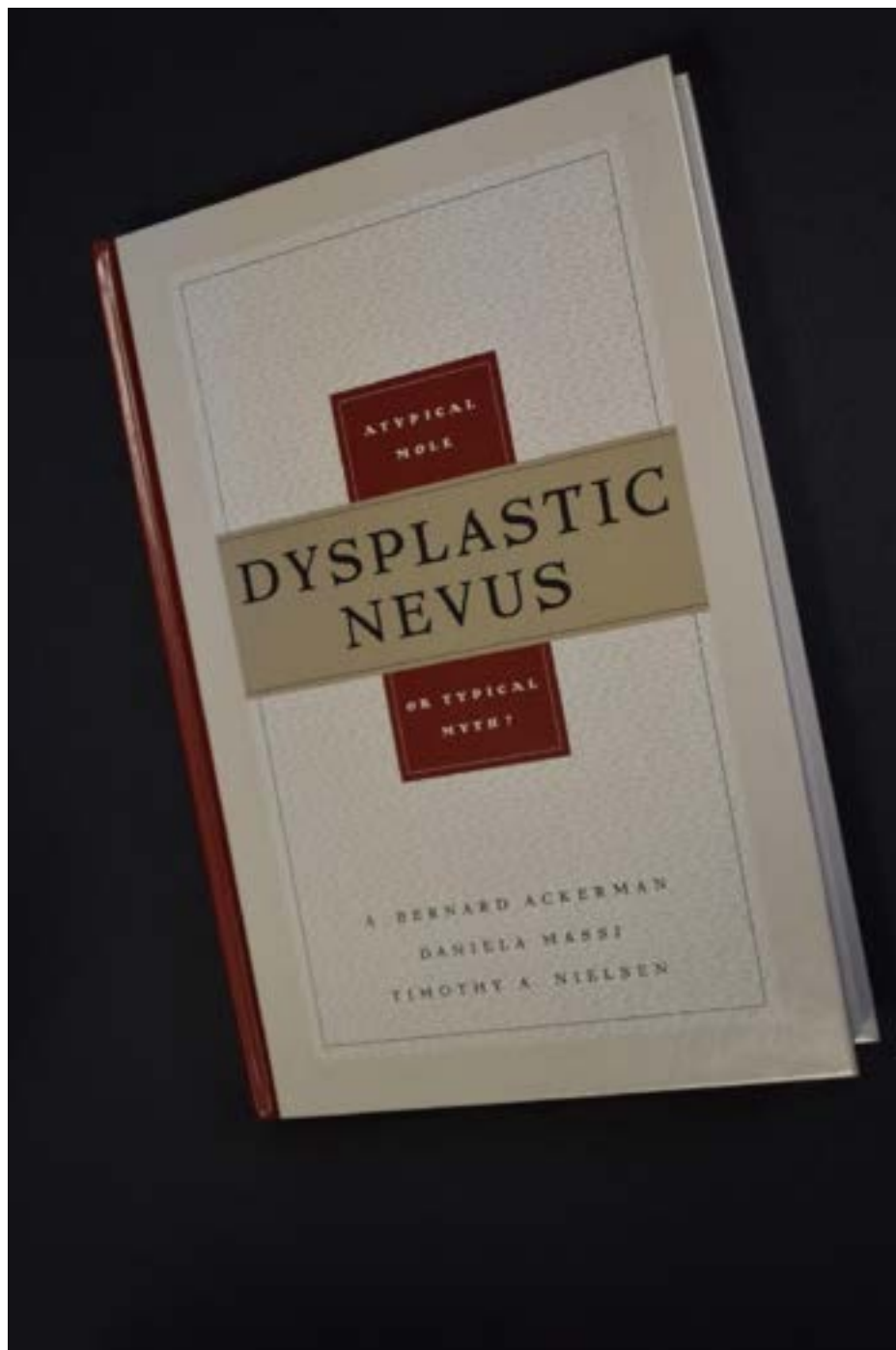
Nondysplastic?

Criteria for Melanoma vs. Nevus

Feature	Melanoma	Dysplastic Nevus	Nevus
Size	larger	intermediate	smaller
Symmetry	poor	good	good
Rete ridges	irregular	uniformly elongated	uniform
Junctional Melanocytes	epithelioid	mixed	nevroid
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	random or no atypia	no atypia
	limited maturation	maturation	maturation
	mitoses	no mitoses	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

Intermediate Lesions of Tumor Progression

- Term defined by Wallace H Clark Jr.
- Lesions that are intermediate between benign and malignant tumors
 - Includes MIS
 - Biologically benign
 - May be precursors of malignant tumors – however the rate of individual lesion progression is very low
 - Morphologically intermediate – clinically atypical and histologically dysplastic – SIMULANTS OF MELANOMA
 - Genomic profile is also intermediate

Superficial Atypical/Dysplastic 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/Dysplastic Nevi.

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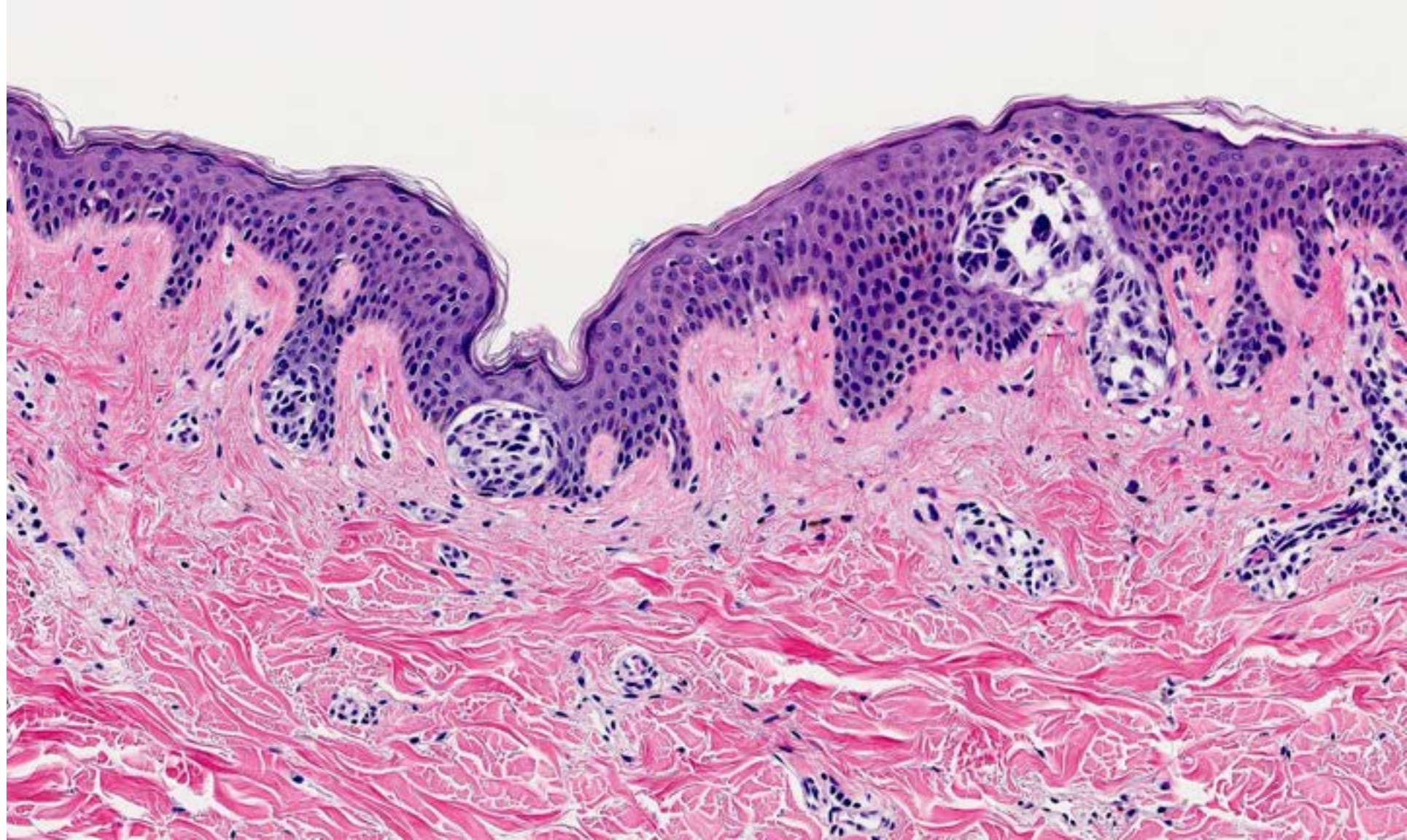
Case 4

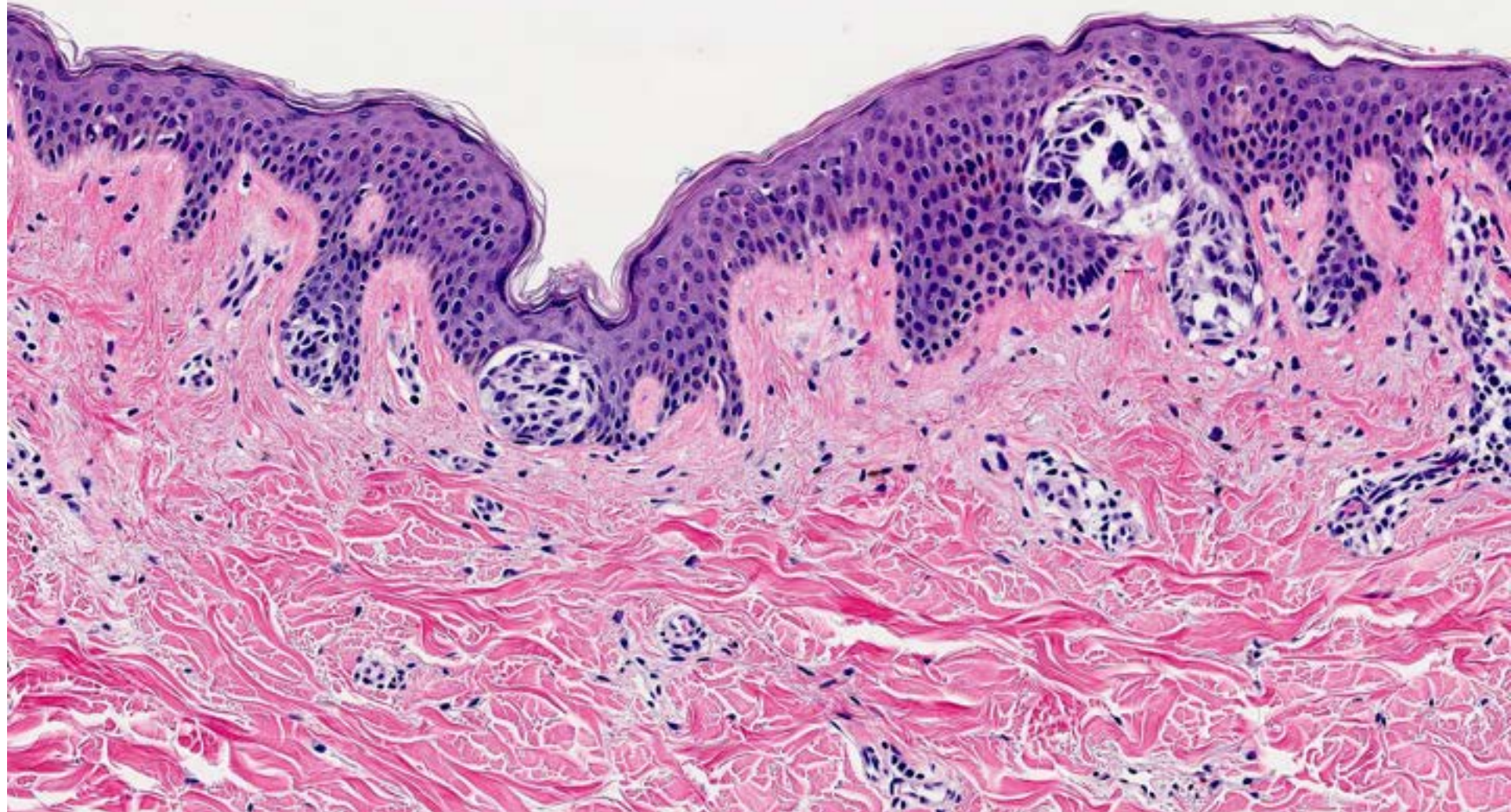
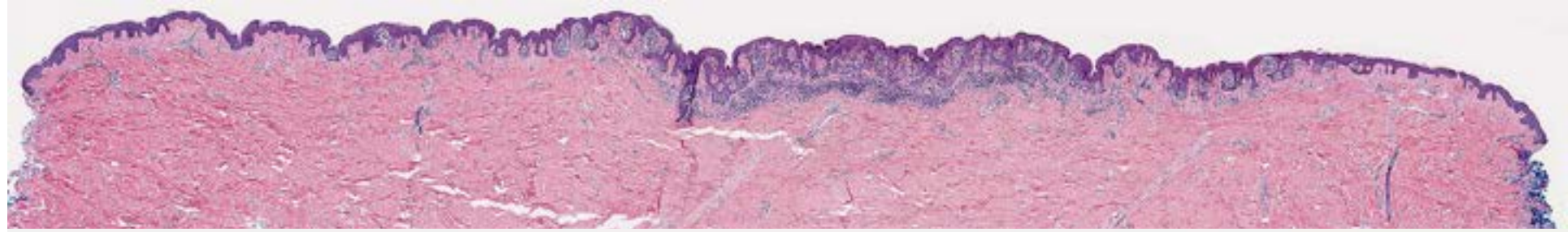
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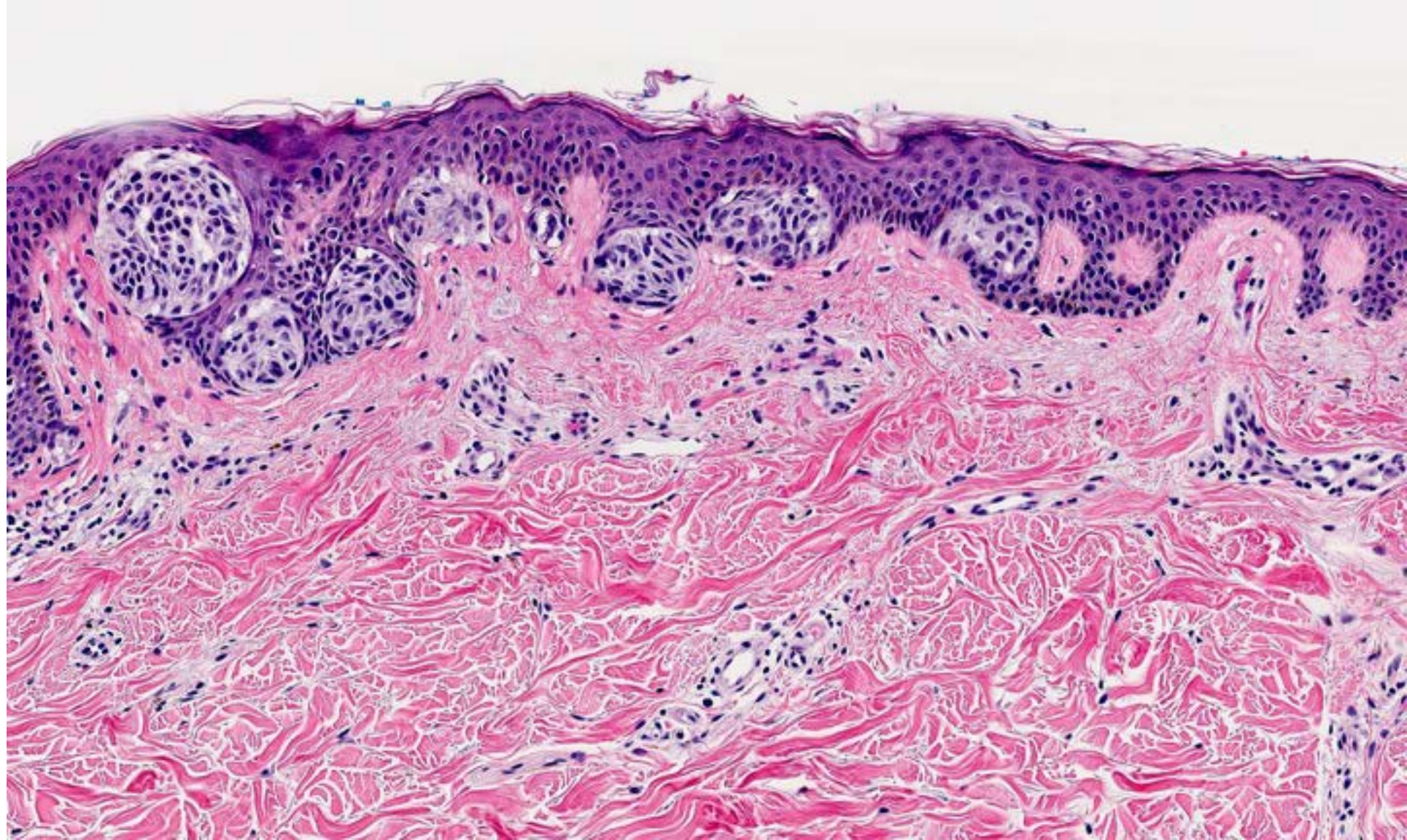
Lesion of skin of knee in a 30 y.o. woman

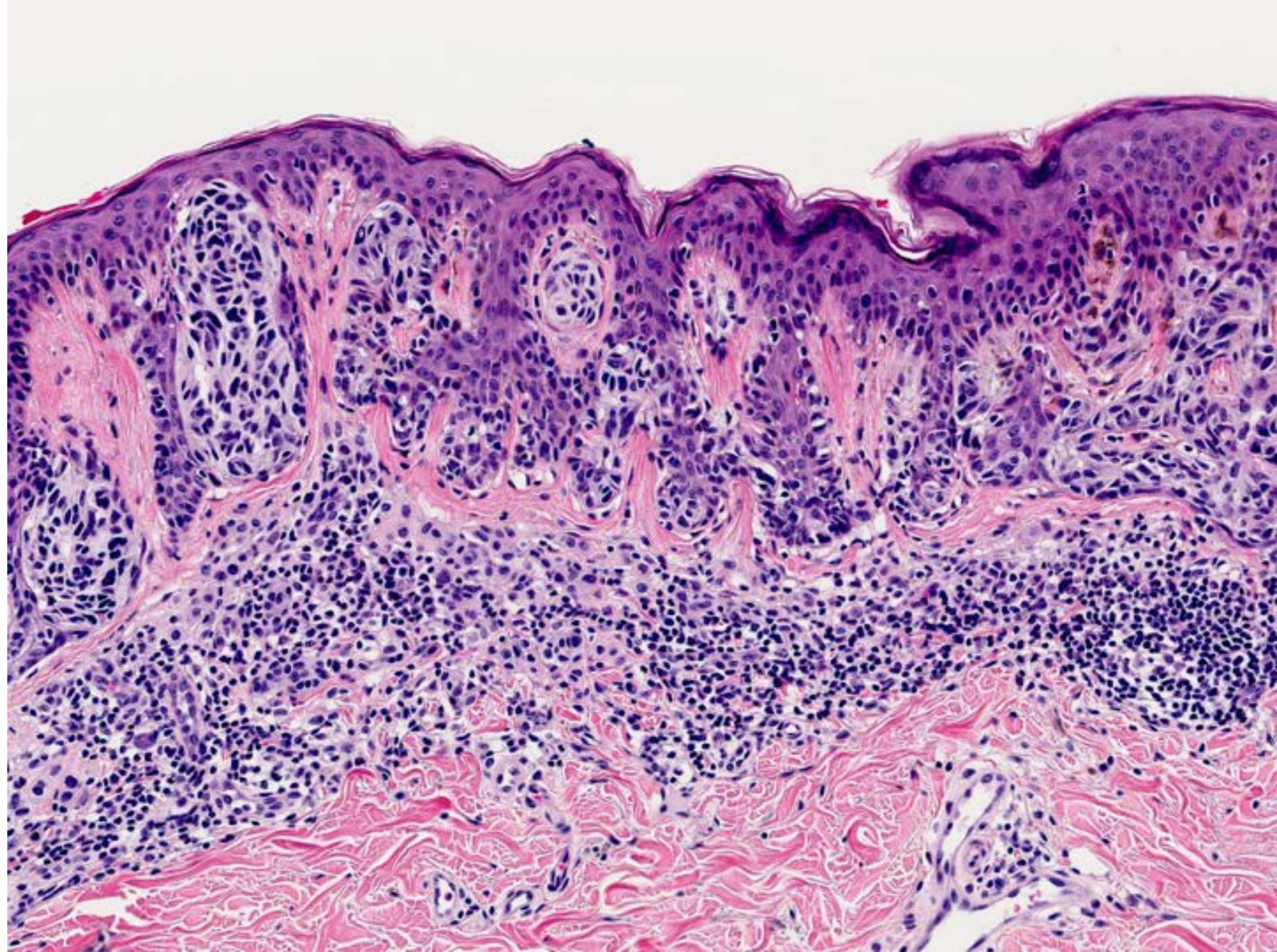
From the knee of a 30 y.o. woman

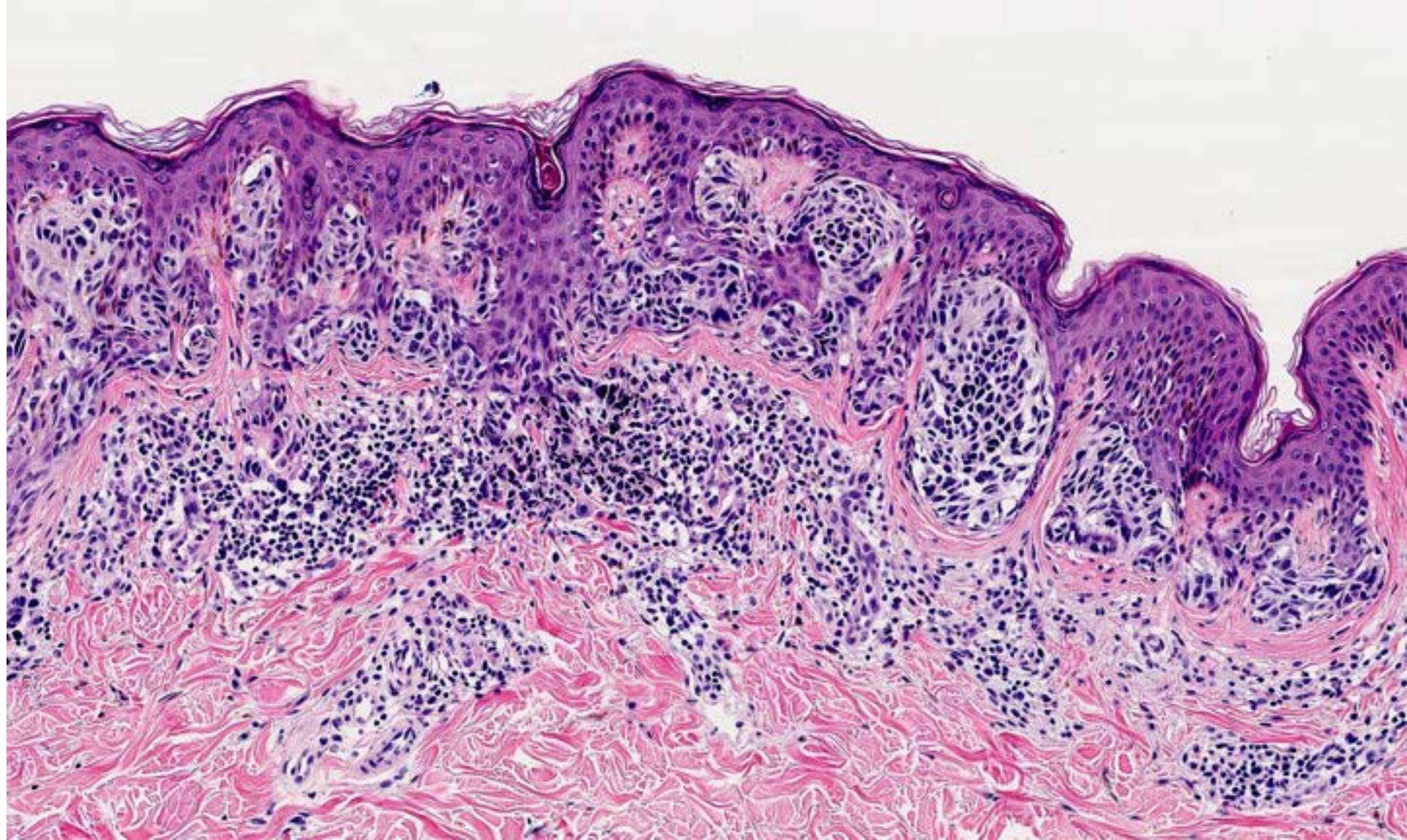
- Submitted with the following clinical information: "Changing mole, exam shows a 7-8 mm dark brown papule with pigment irregularity".
- The lesion has been present for a "couple of months".
- Dermoscopy shows an irregular pigmented network, irregular dots and globules and positive possible negative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

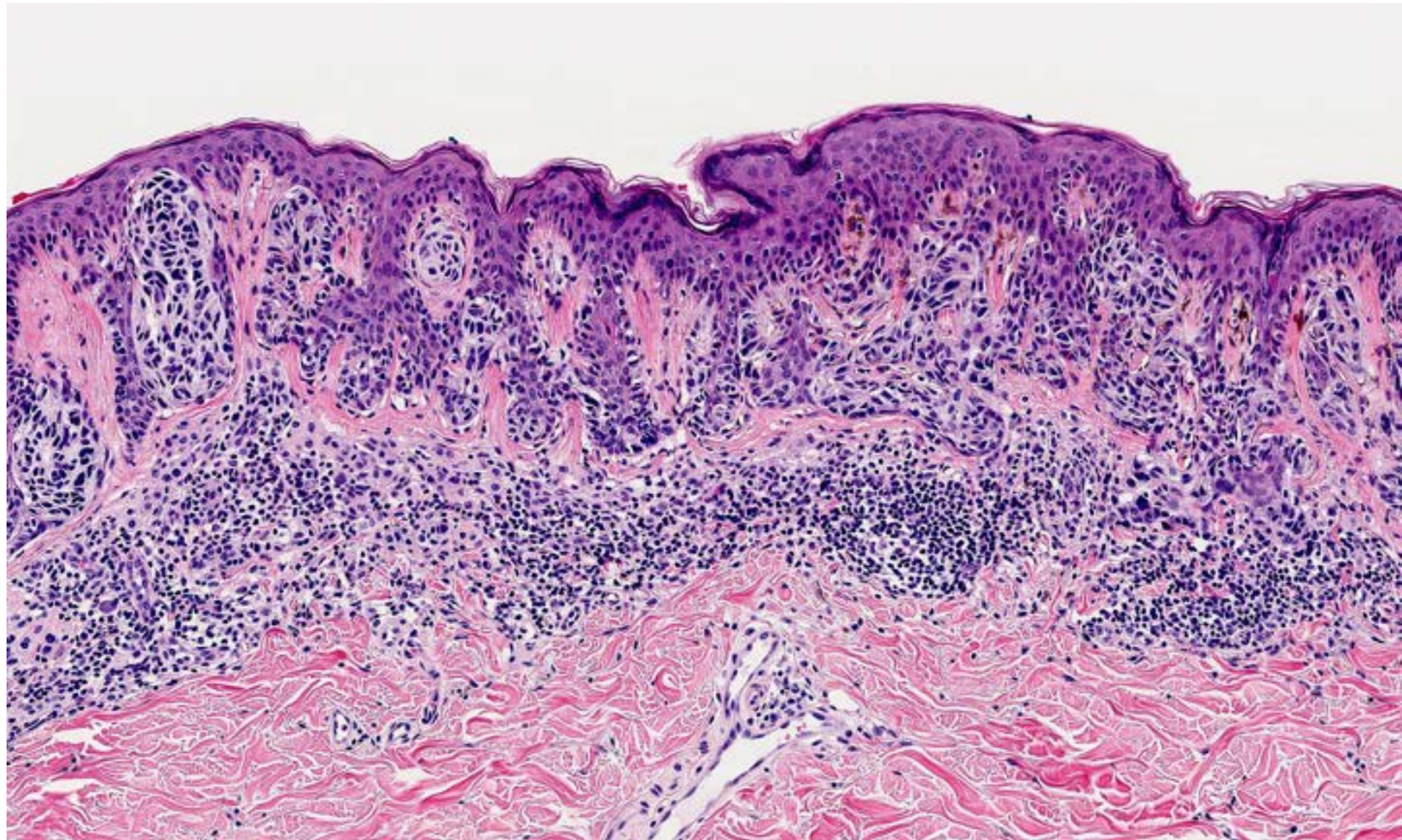


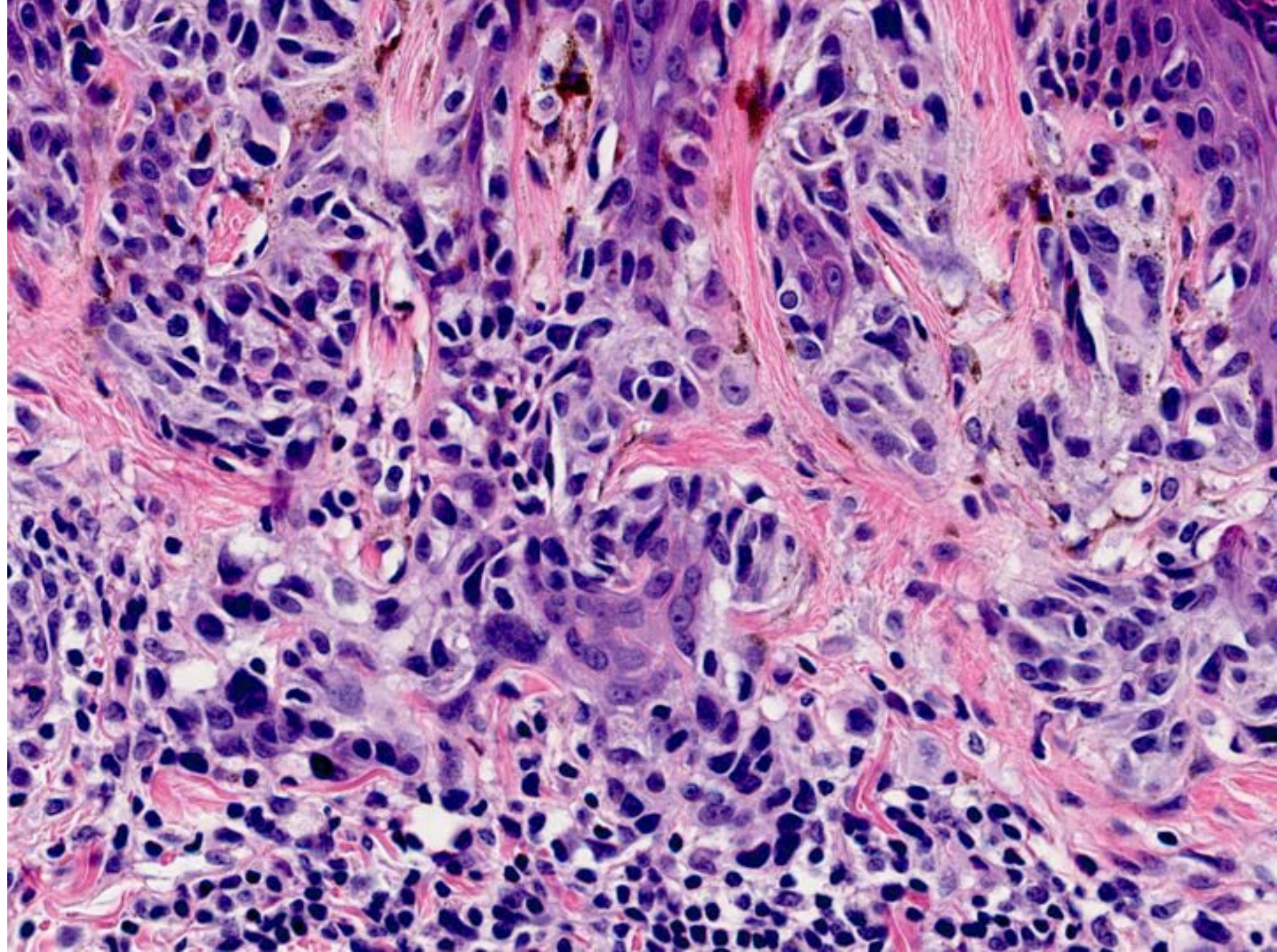










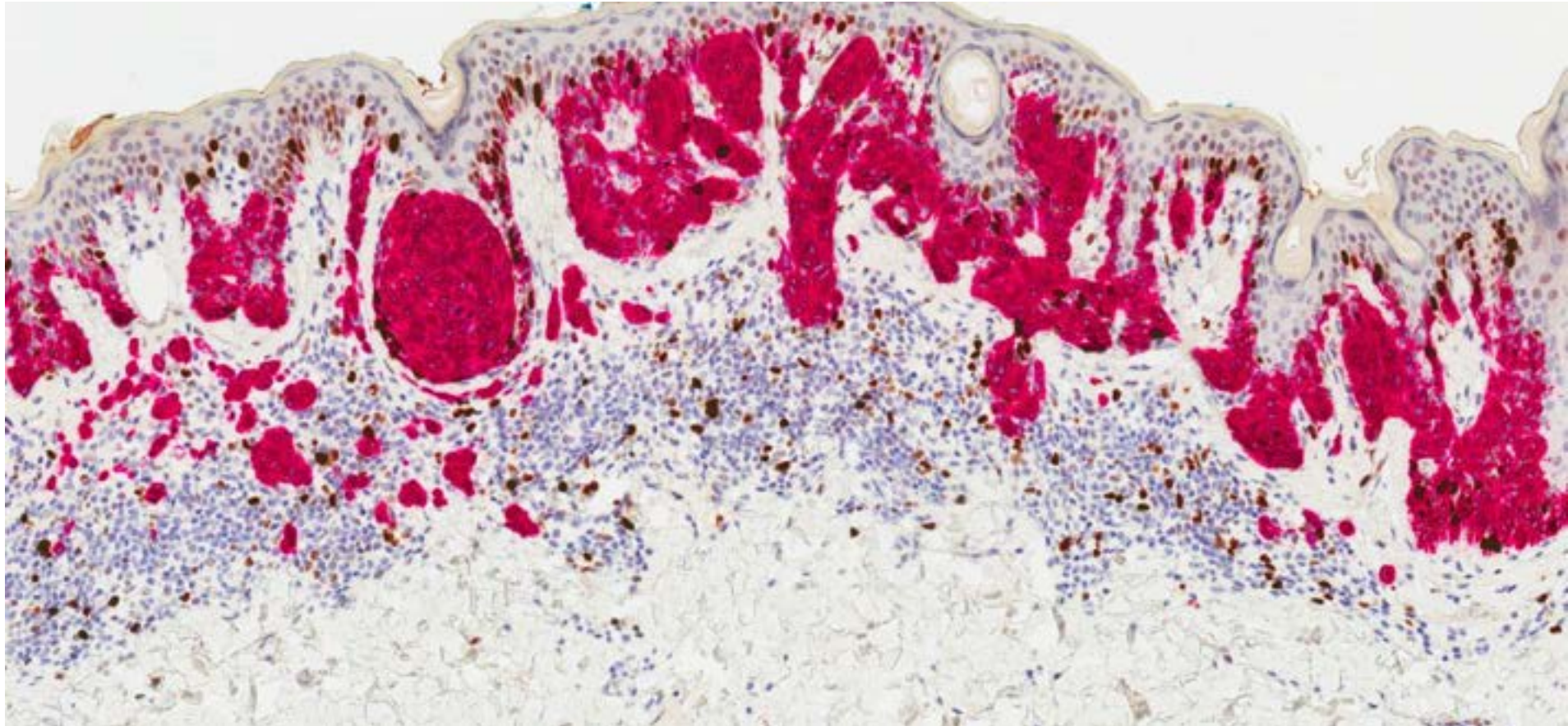


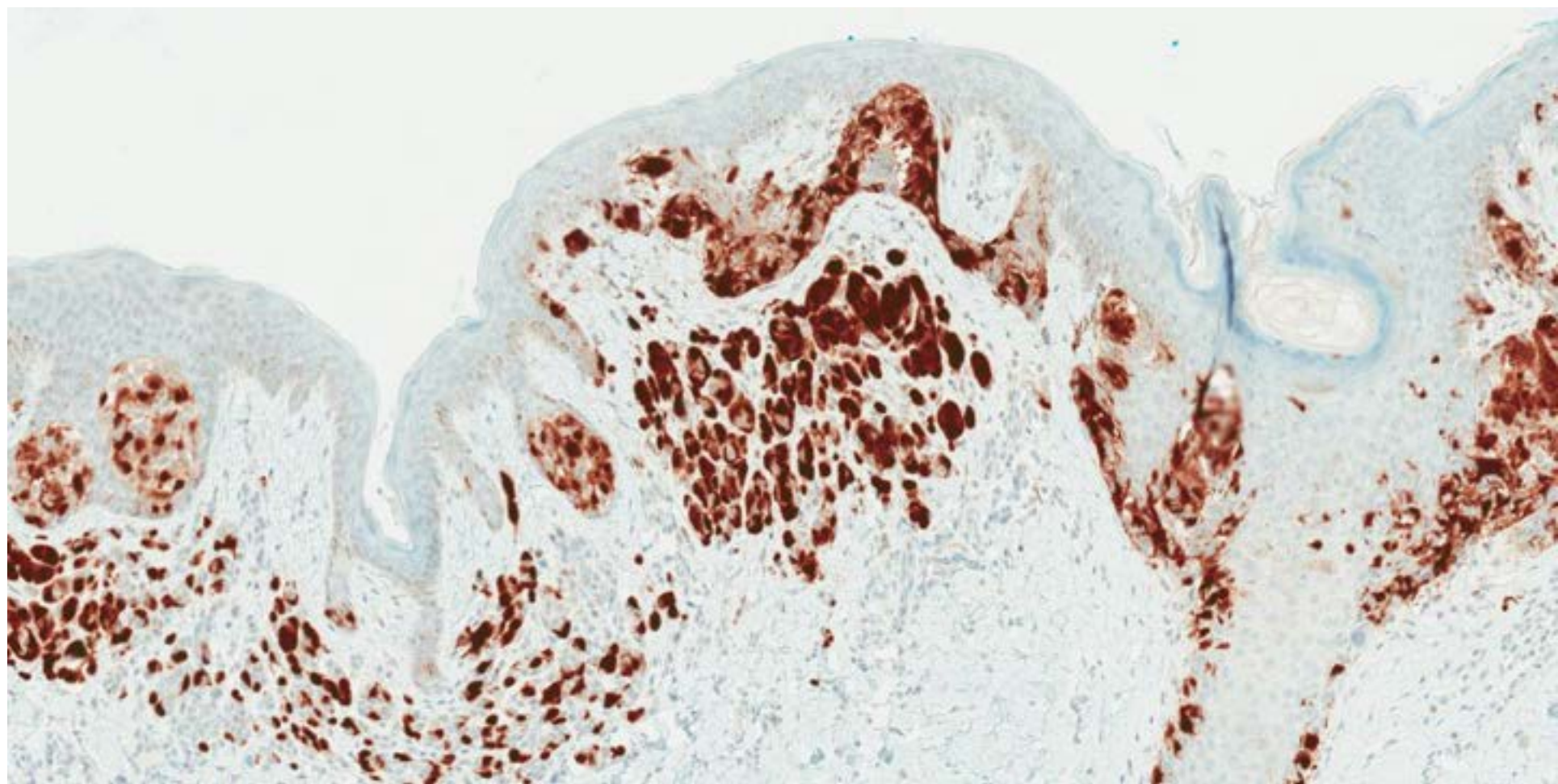
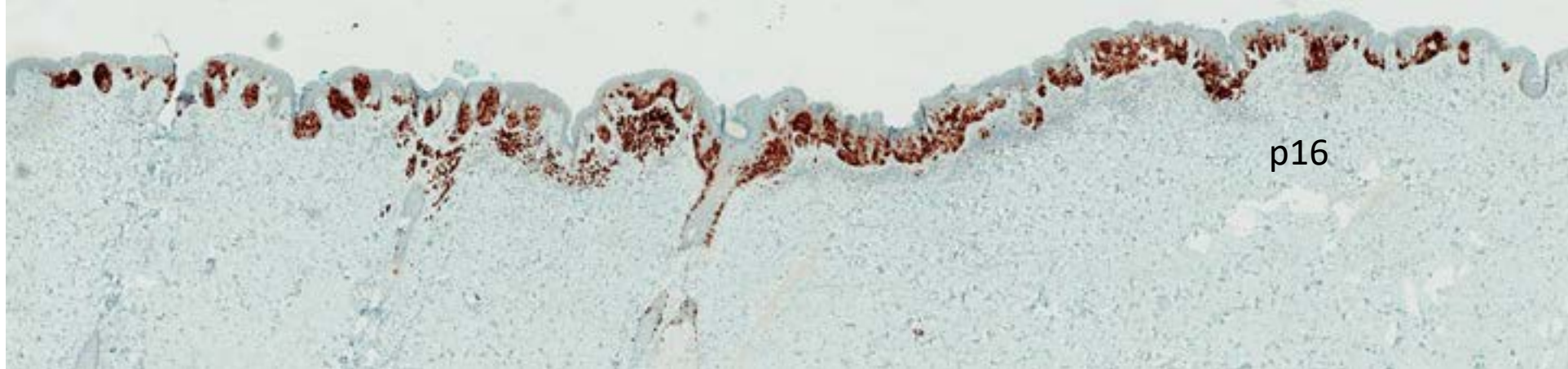
Your Diagnosis

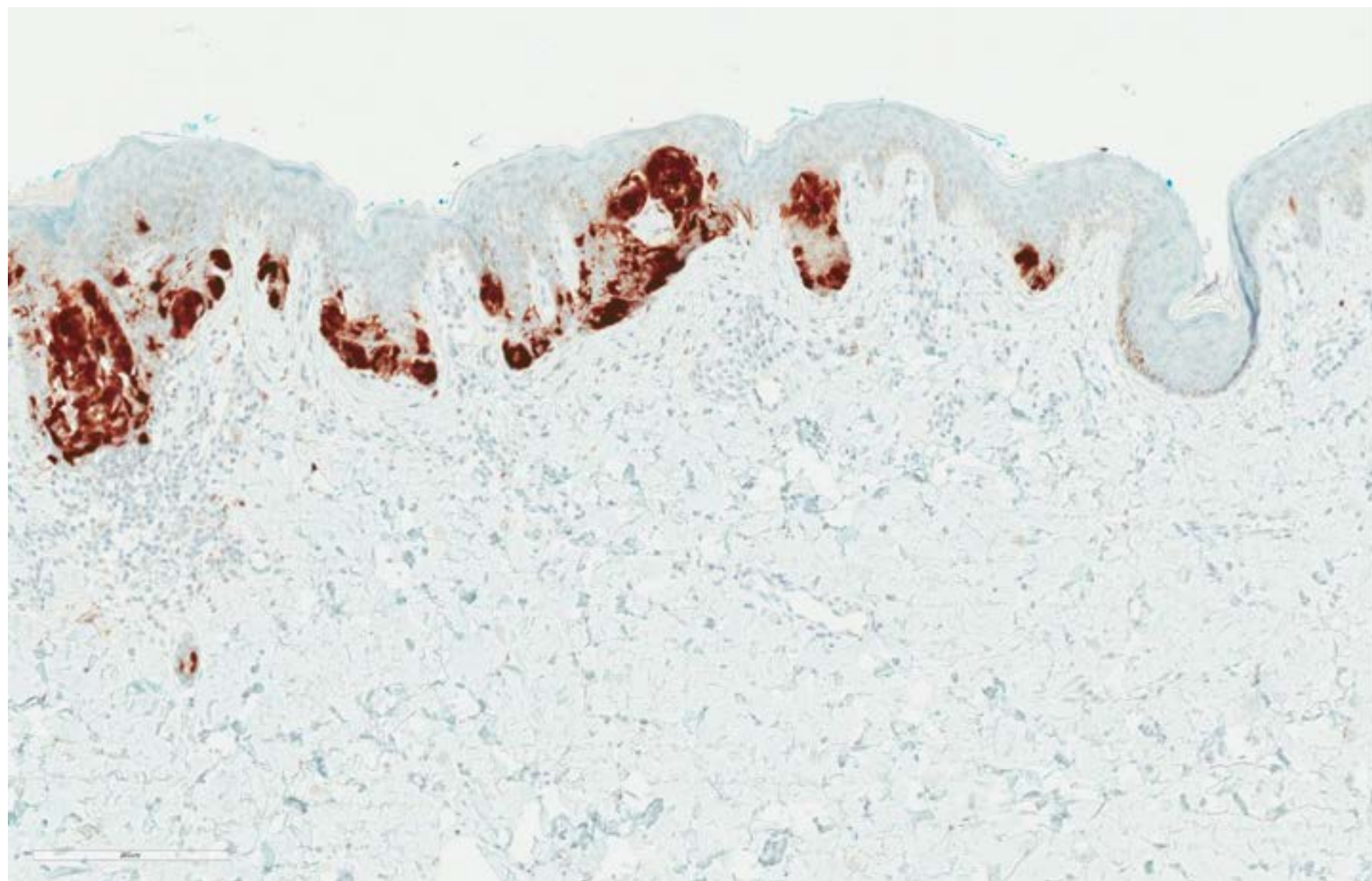
Melanoma?

Nevus?

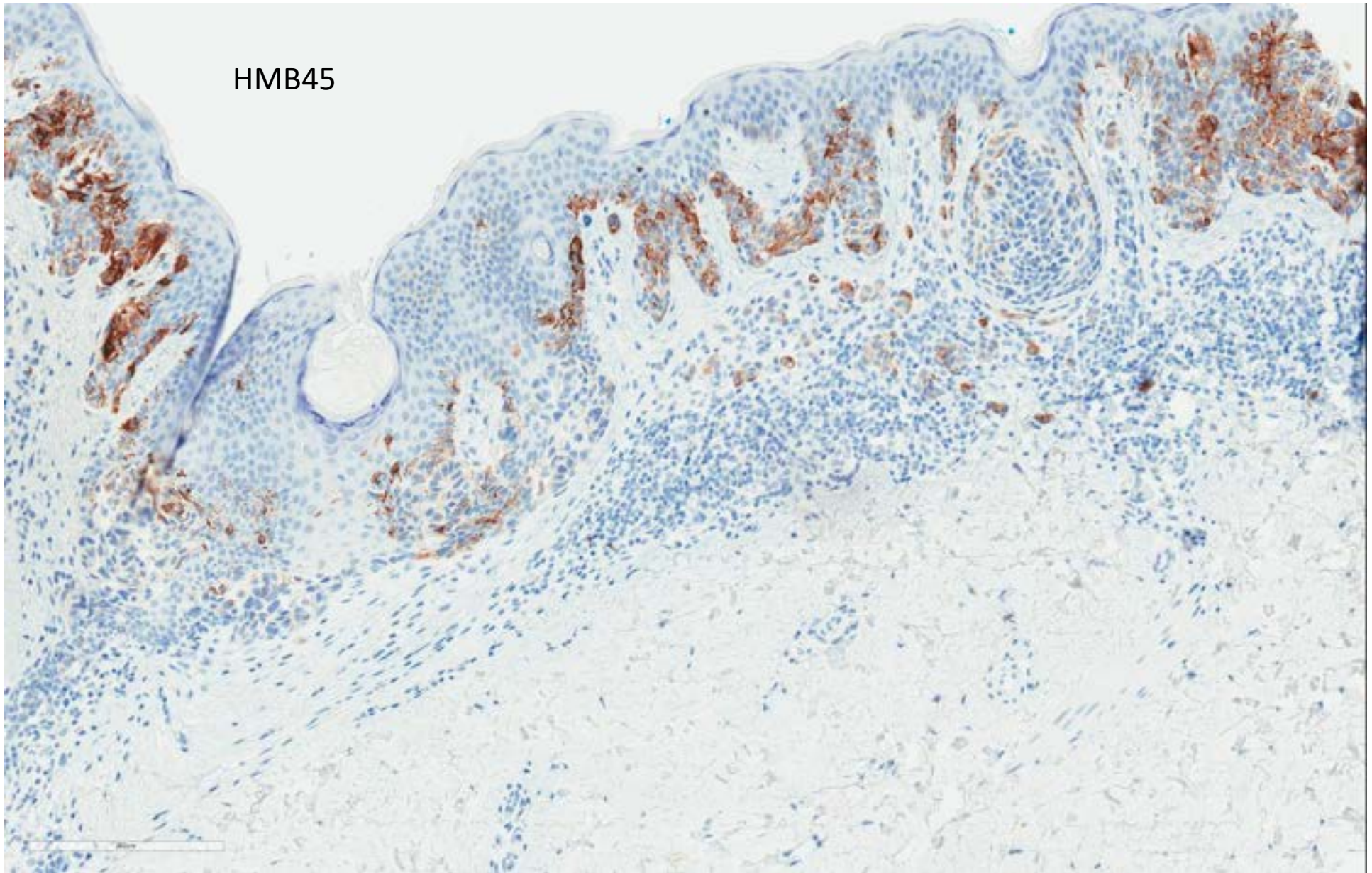
Ki-67/MART







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 (nevroid to epithelioid)	nevroid
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

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

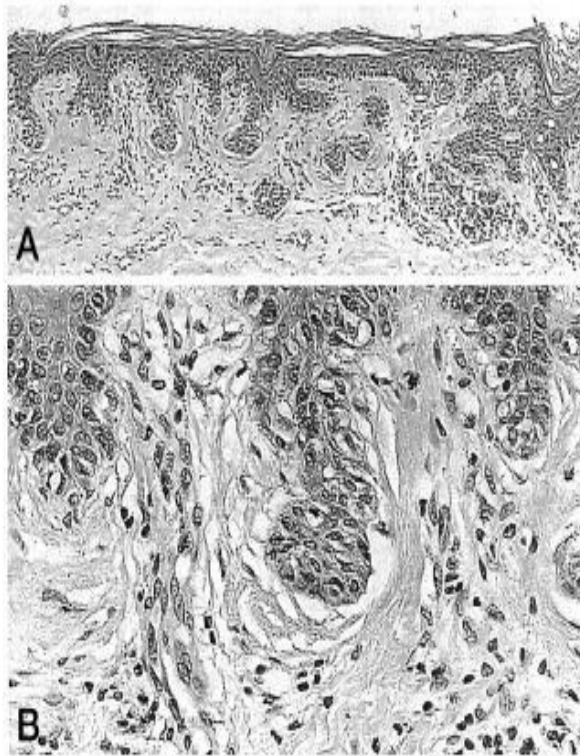


FIGURE 1. A, nevus, compound type, with architectural disorder and mild cytologic atypia of melanocytes. This region shows the extension of the junctional component beyond the dermal component, with some papillary dermal fibrosis and lymphocytic infiltration but with only slight distortion of the rete 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

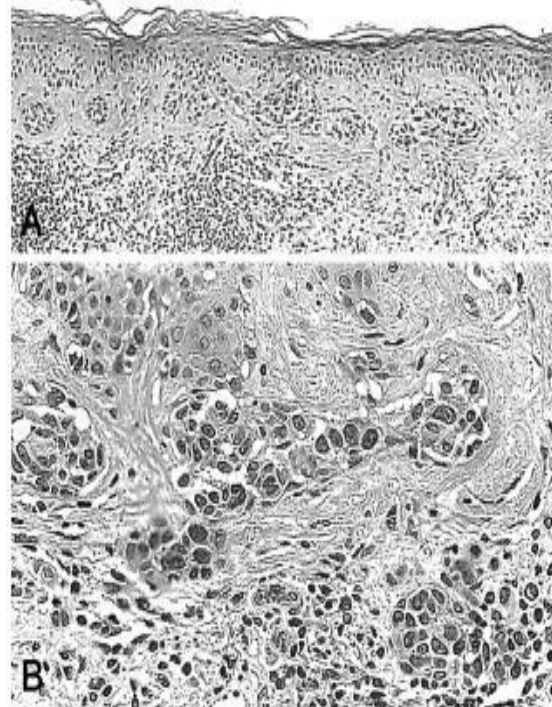


FIGURE 2. A, nevus, compound type, with architectural disorder and moderate cytologic atypia of melanocytes. This region also has extension of the junctional component beyond the dermal portion. There has been partial regression of the dermal component. The rete ridges are quite distorted, and the nuclei 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

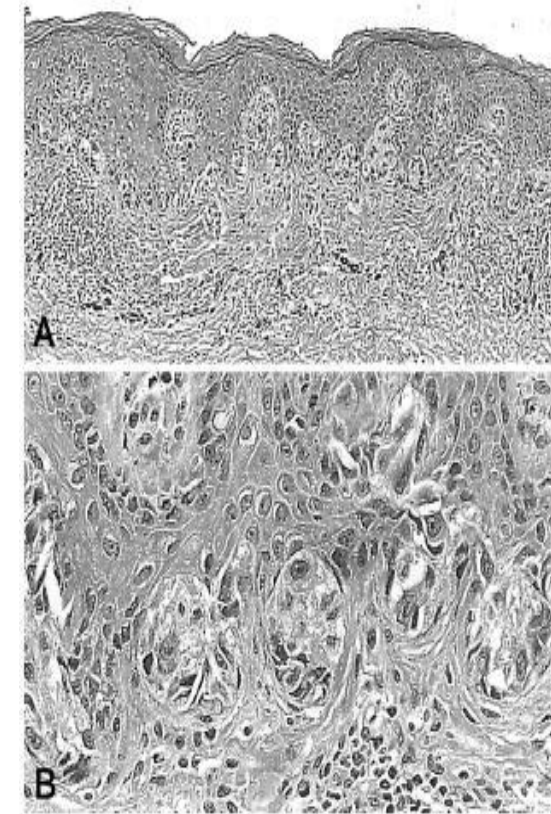


FIGURE 3. A, nevus, compound type, with architectural disorder and severe cytologic atypia of melanocytes. Rete ridge fusion is extensive with papillary dermal fibrosis and lymphocytic and melanophage infiltration. Many of the nuclei in the nevus cells are enlarged (H&E, 10×). B, the nuclei are more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

Severe

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

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		

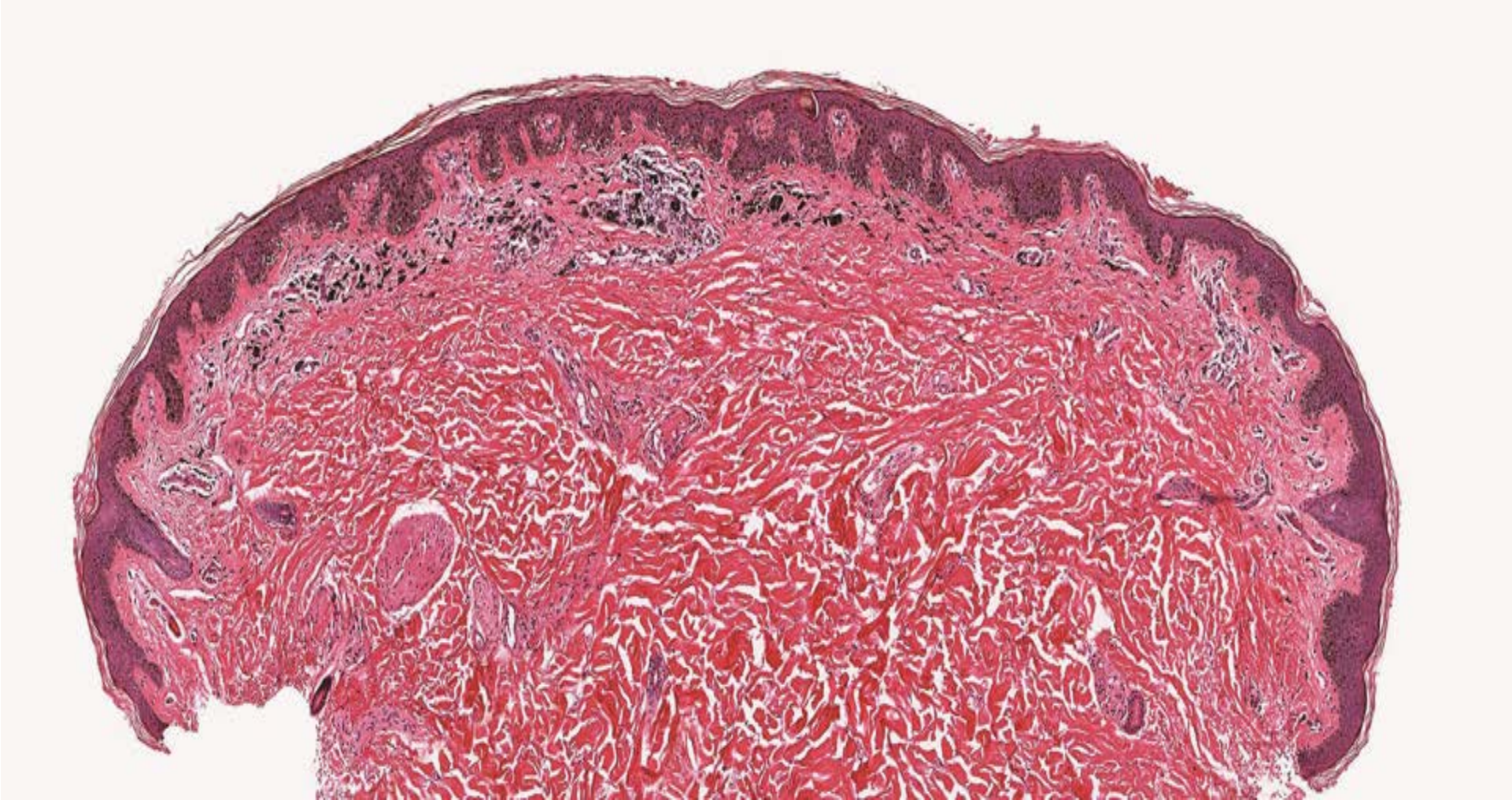
Table I. Predictors of melanoma before and after training

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

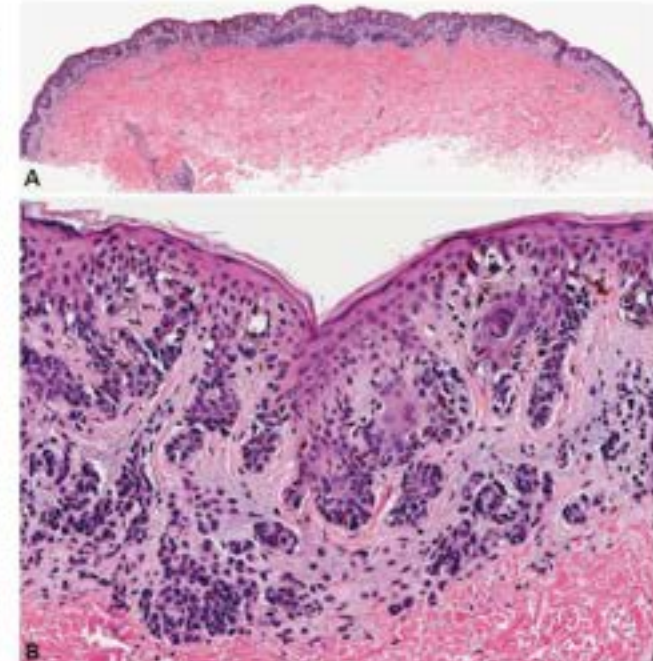
- Poorly reproducible diagnosis (vs. nevus)
- Not associated with melanoma risk
- Not a high risk precursor
- Not a strong simulant of melanoma
- UNCERTAINTY vs. Moderate dysplasia, No dysplasia
- Should be considered in the spectrum of banal nevi (junctional or compound nevus, e.g. lentiginous junctional 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



Risk of Subsequent Cutaneous Melanoma in Moderately Dysplastic Nevus 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 $\geq 1 \text{ mm}^2$)
- 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)

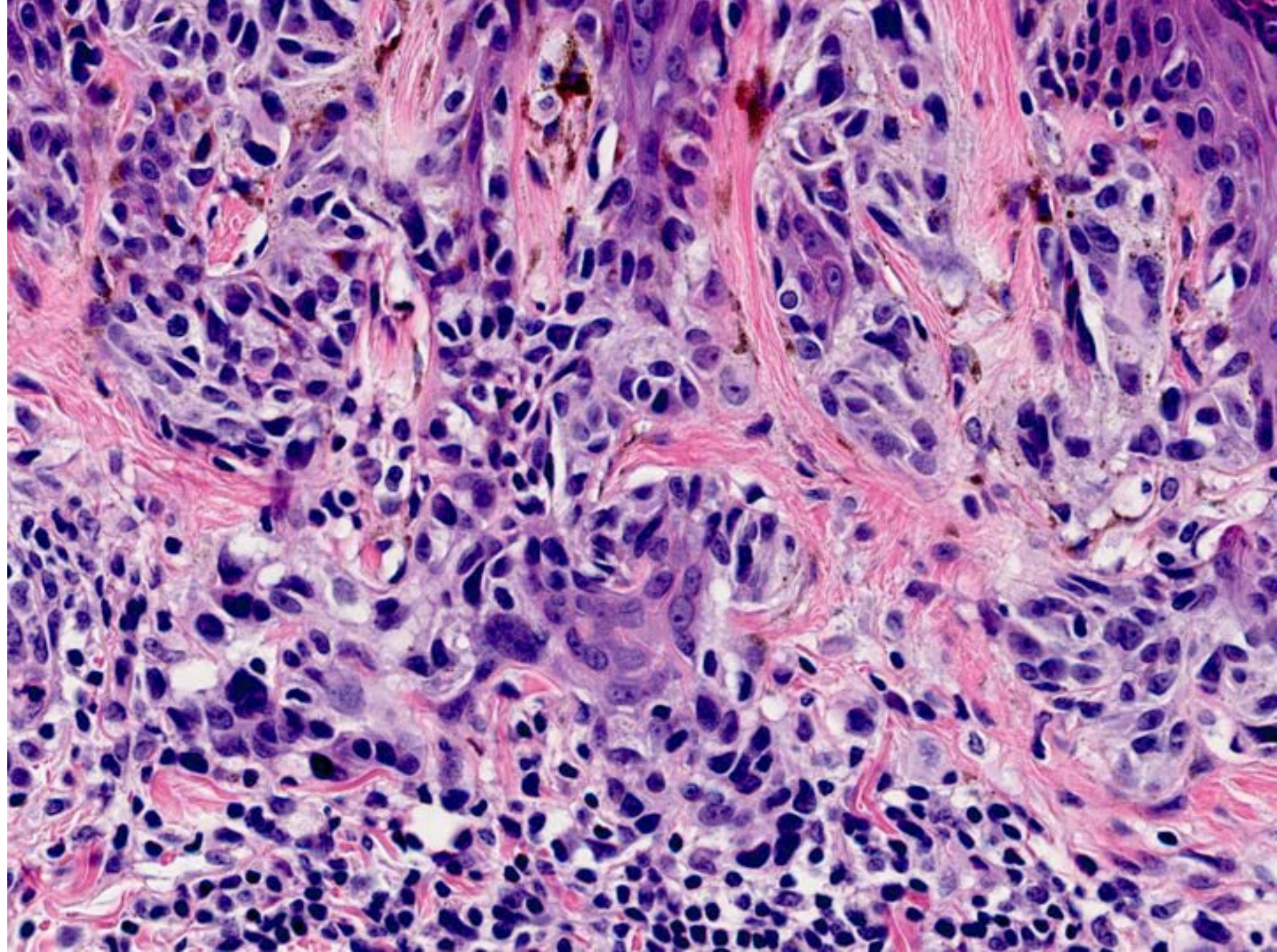
2.13 Low Grade and High Grade Dysplasia

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.

High Grade Dysplasia

- Architectural features that indicate a diagnosis of high grade (severe) dysplasia even when cytologic atypia is low grade include:
 - pagetoid scatter above the basal layer (to a lesser degree than in melanoma, usually not above the middle third, and focal i.e. < 1 HPF),
 - More than minimal continuous basal proliferation (lentiginous) proliferation
 - Intraepidermal mitoses (more than a rare mitosis and/or any dermal mitosis should raise concern for melanoma).



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 or causing death

Distinct senescence mechanisms restrain progression of dysplastic nevi

PNAS Nexus, 2024, 3, 1–8

Franziska K. Lorbeer^a, Gabrielle Rieser^a, Aditya Goel^a, Meng Wang^b, Areum Oh^c, Iwei Yeh^{b,d,e}, Boris C. Bastian^{b,d,e,*} and Dirk Hockemeyer^{a,f,g,*}

- Characterized mutations, telomere length, and p16 expression in a ... set of DN.
 - Two primary mechanisms at work in the arrest of DN: DN with strong mitogen activated protein kinase (MAPK) signaling preferentially trigger OIS*.
 - In DN where OIS* is bypassed, telomere shortening eventually triggers replicative senescence

*OIS = Oncogene induced senescence

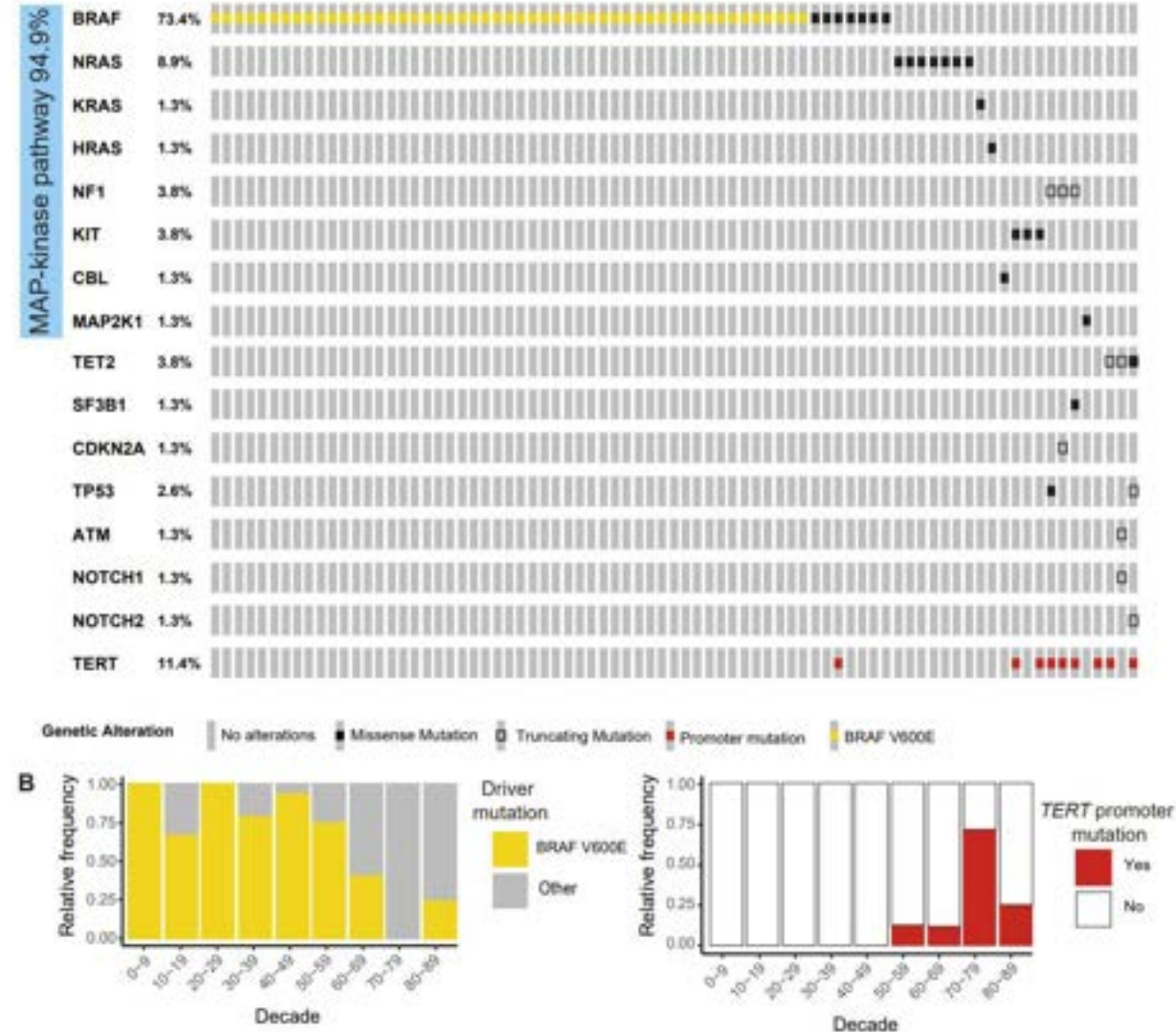


Fig. 1. Somatic mutations in DN. BRAF V600E mutations are more common in younger patients where other mutations predominate in older patients partially combined with TERT promoter mutations. A) Tiling plot of pathogenic and likely pathogenic mutations. Side bar indicates all mutations affecting the MAPK pathway. B) Relative frequency of BRAF V600E (left) and TERT promoter mutations (right) by age decade.

The Real Dysplastic Nevi?

- Are the Replicative Senescence Nevi the “Real Dysplastic Nevi”
- Or are they forme fruste melanomas?
- My opinion – probably not melanomas, but probably relatively high risk precursors of “melanomas”
- But are these “Overdiagnosed” melanomas?



Up the Creek Without a Paddle?



Or on a Pathway Forward

Case 3.

Part 2-5. **35728**

[London SVS\35728.svs](#)

Clinical Information.

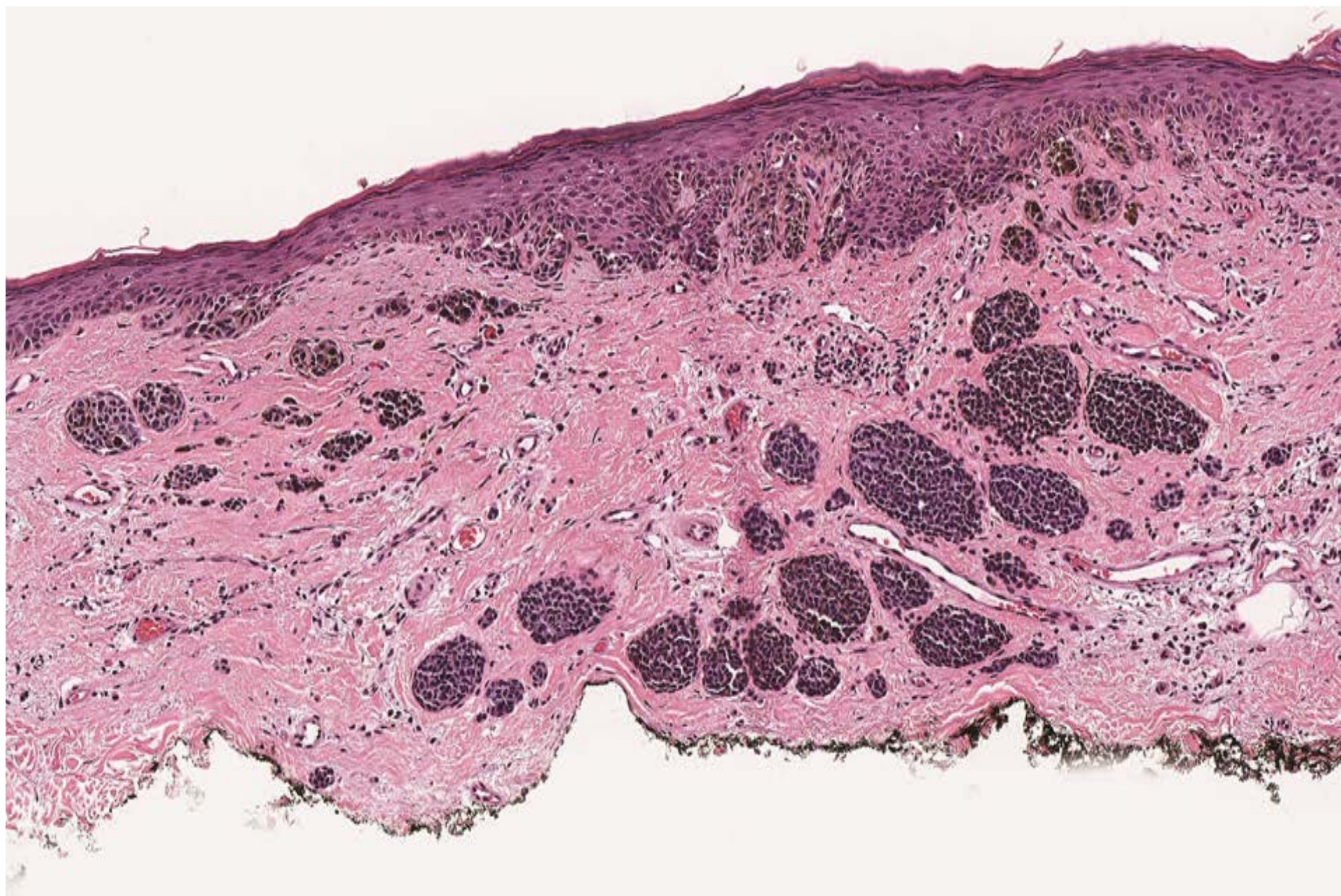
An irregular pigmented lesion on the back of a 59 year old man

Reason for Consultation.

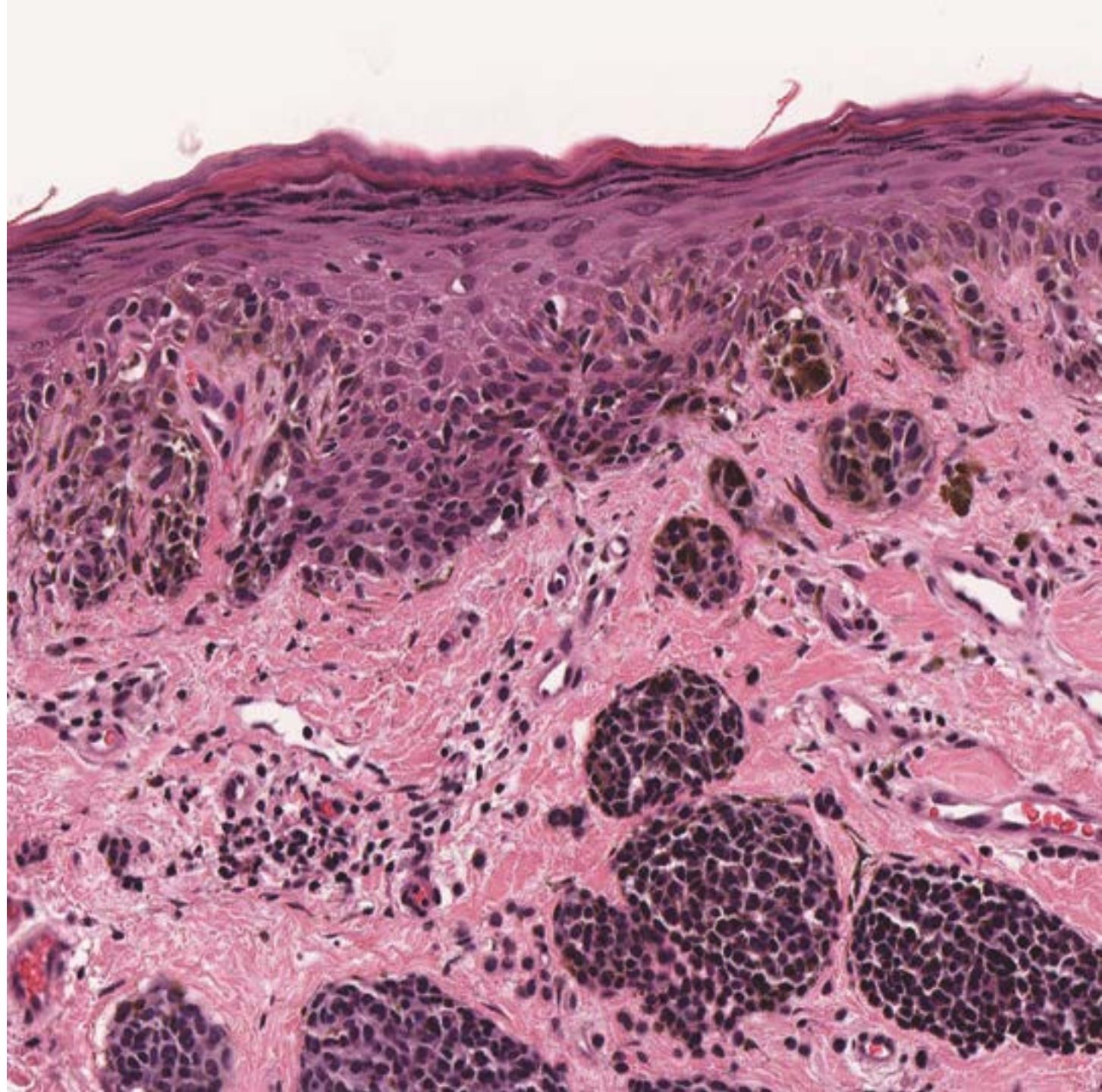
Is this a nevoid melanoma?



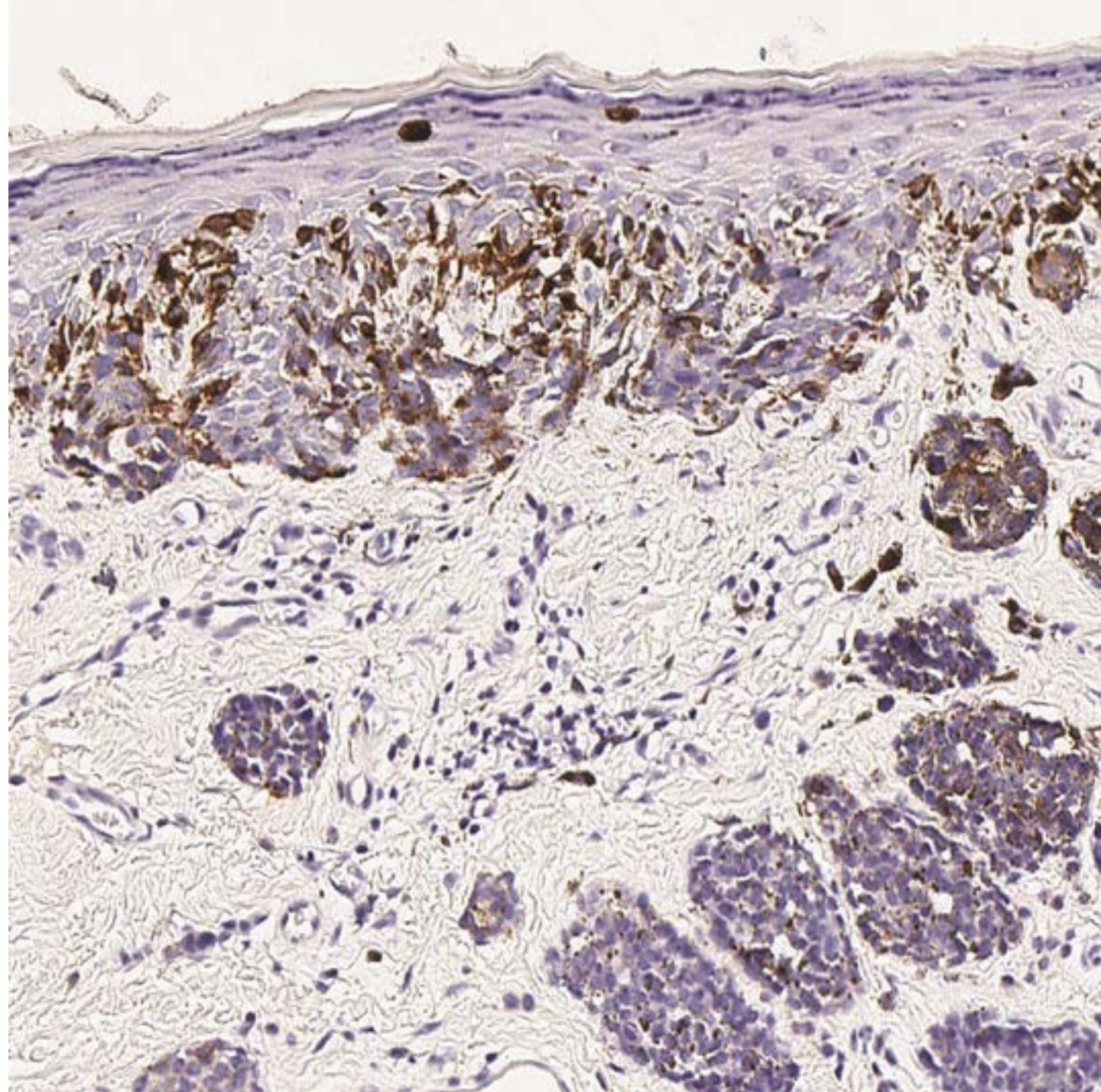
Broad, focally highly cellular, asymmetric diffuse fibroplasia and variably sized nests in dermis



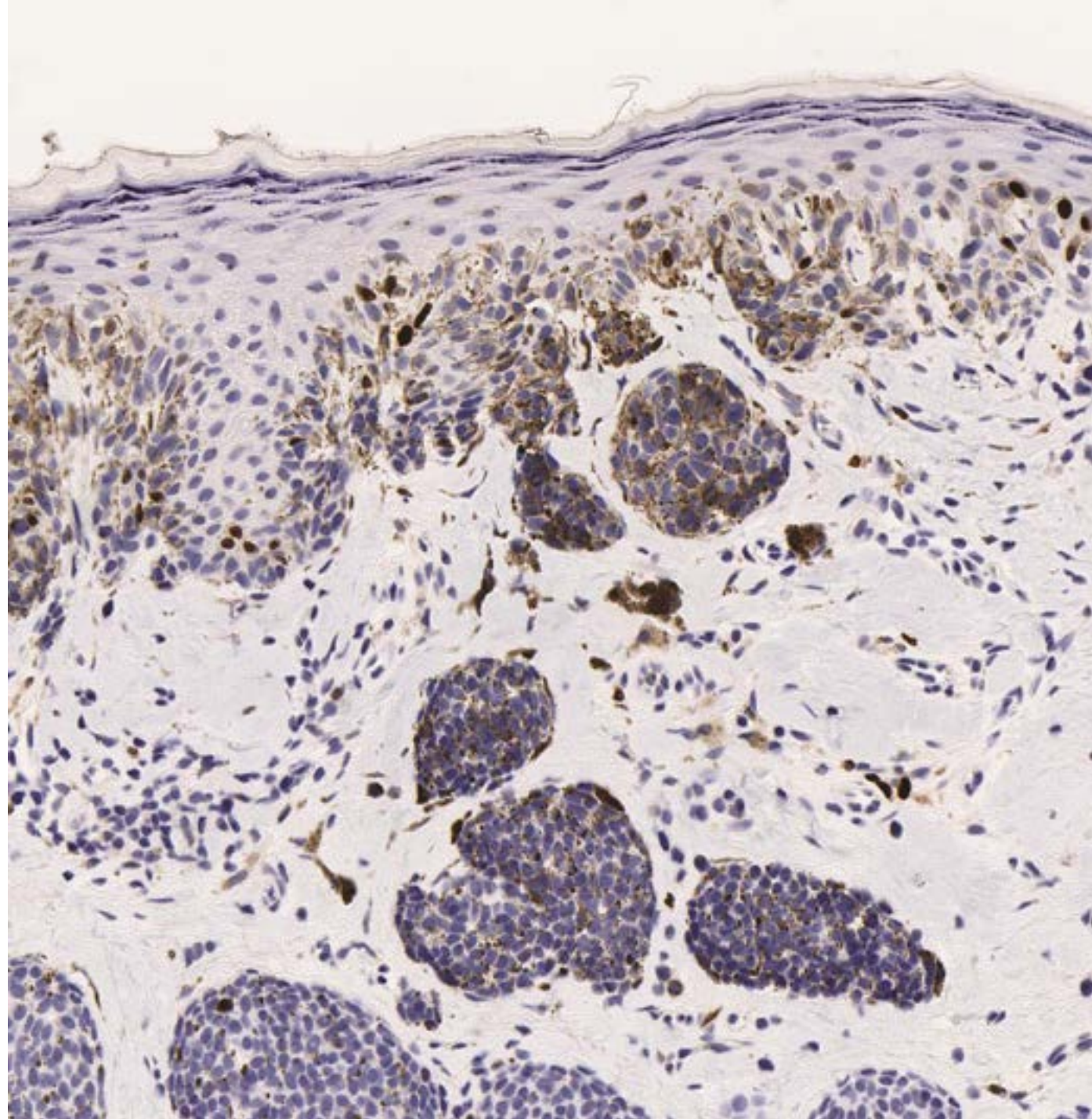
- Only minimal pagetoid scatter
- Moderate cytologic atypia
- No mitoses
- Cells in dermal nests are small, nevoid
- No confluent sheetlike growth



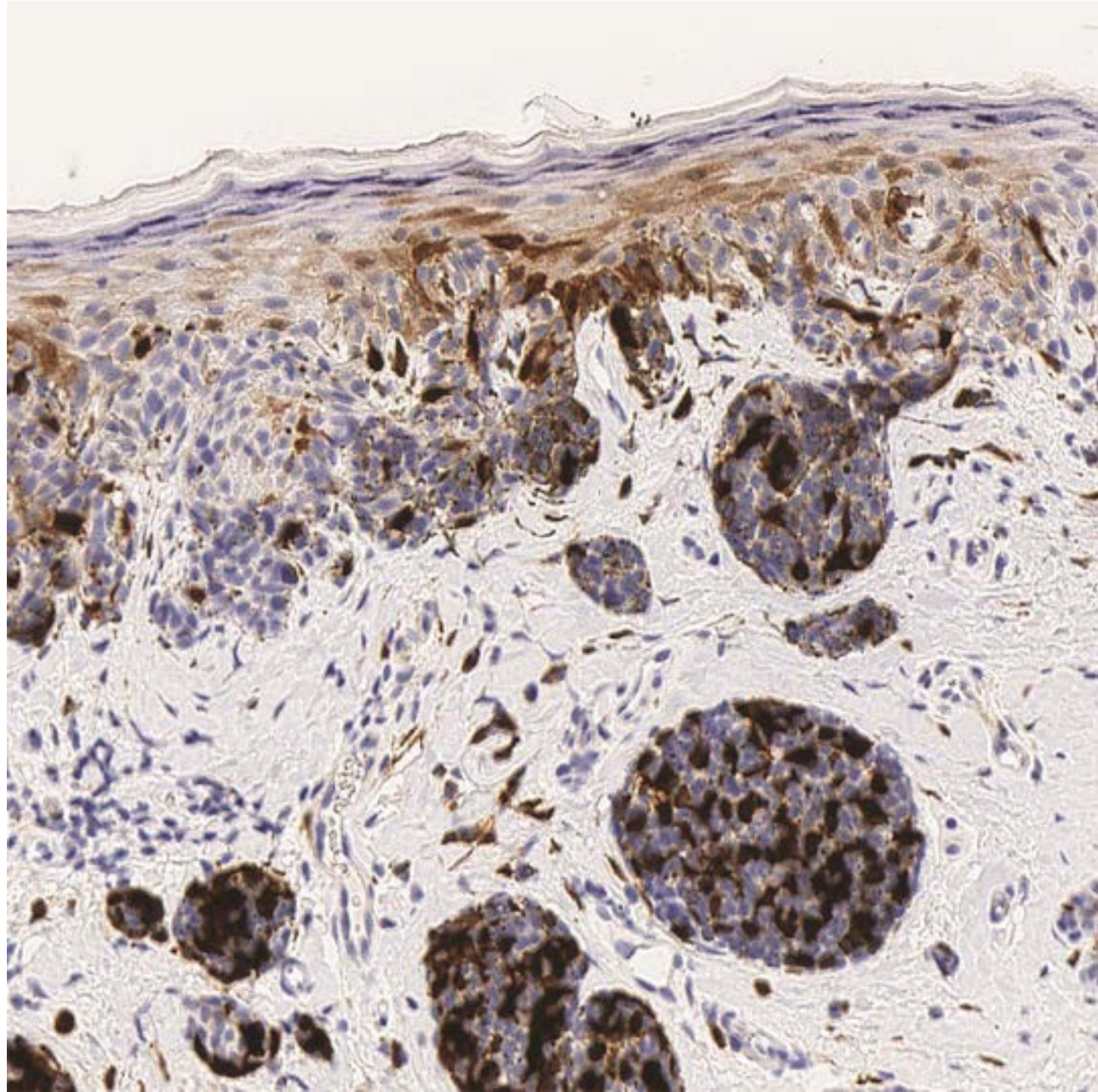
HMB45 staining
is “top-heavy”
(stratified)



- 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)
- Melanomas can express p16 and not all melanomas have lost expression

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.

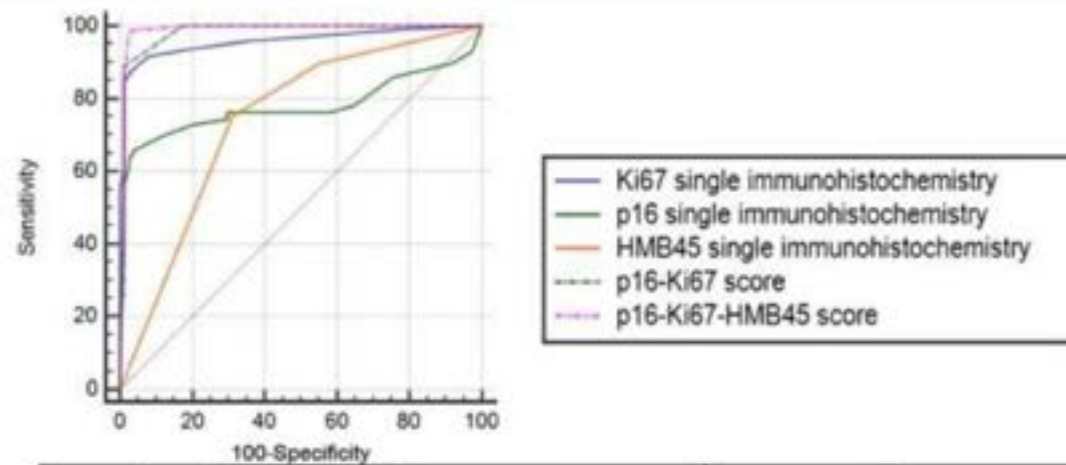
- **METHODS:**

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?

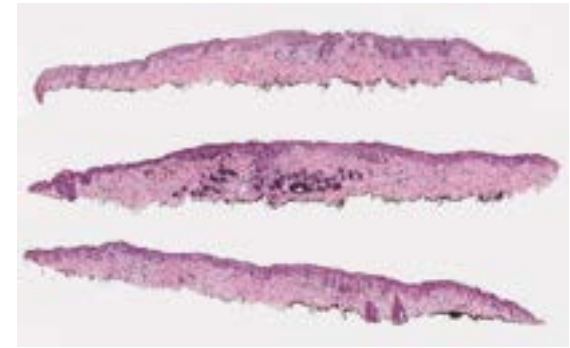
High Grade?

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 (nevroid to epithelioid)	nevroid
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 or focal	rare, minimal	absent
Dermal Cells Absent	uniform atypia limited maturation mitoses	random atypia maturation no mitoses	no atypia maturation 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

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.

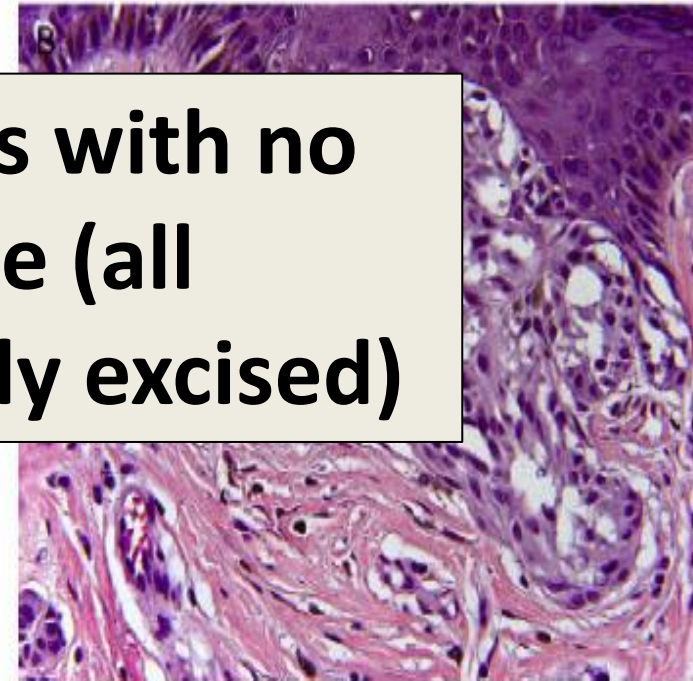
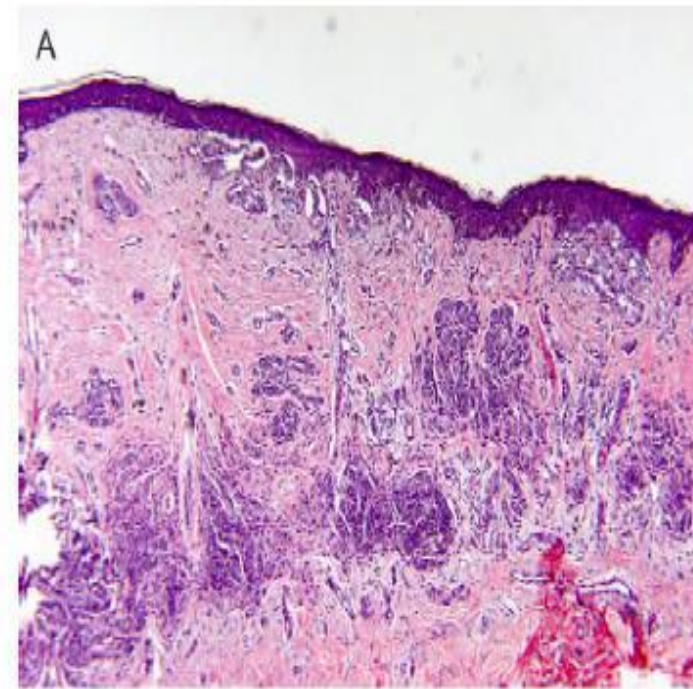
Results: All the cases have been followed up and none have recurred or metastasized. Histologically, these neoplasms have important similarities with the so-called recurrent nevus, nevi on lichen sclerosus and nevi developed during or following cutaneous inflammatory and sclerosing processes. The origin 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 Fabrizi¹,
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Molise, Italy and

²Department of Pathology, Catholic University
Medical School, Rome, Italy

**19 Lesions with no
recurrence (all
completely excised)**



New insights into naevoid melanomas: a clinicopathological reassessment

Martin G Cook,^{1,2,3,4} Daniela Massi,^{4,5} Willeke A M Blokk,^{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 Klarash Khosrotehrani,^{11,12} Richard Marais,² Adele C Green^{2,13} & Martin C Mihm Jr^{4,14}

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 ... ”

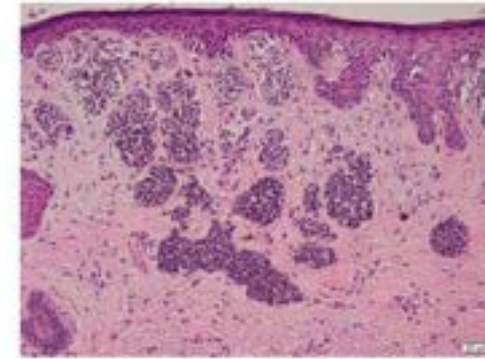


Figure 7. A different maturing naevoid melanoma showing a change from epithelioid pleomorphic nested melanocytes in the superficial dermis to, in the deeper part, smaller but still atypical cells arranged in nests surrounded by dense collagen.

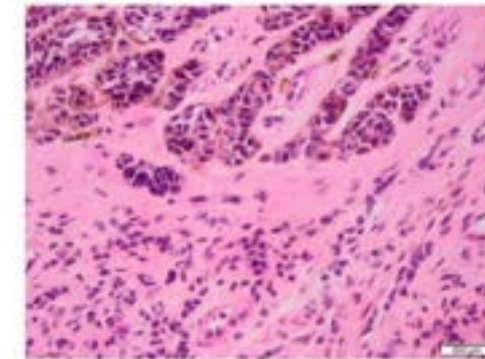


Figure 8. A maturing naevoid melanoma in which small atypical melanocytes in the superficial dermis are arranged in nests surrounded by dense collagen. A true benign naevus is present at the deep aspect of this melanoma.

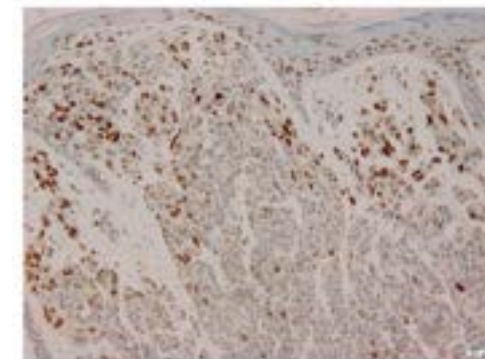


Figure 9. An example of immunohistochemical staining. p21 is seen to be positive in the junctional and superficial dermal component of another maturing naevoid melanoma, but is largely negative in the deeper small-cell component.

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



Up the Creek without a Paddle?