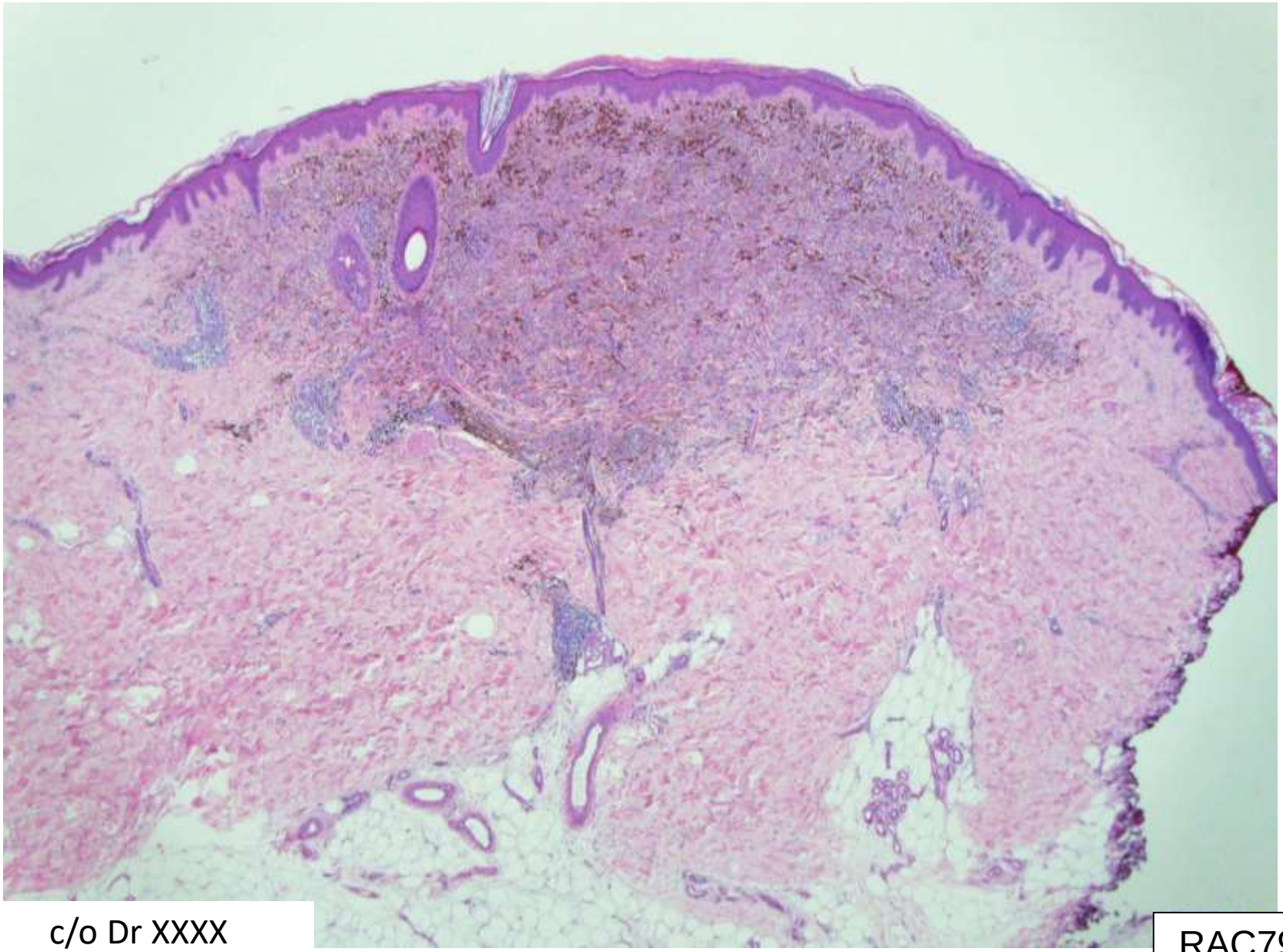
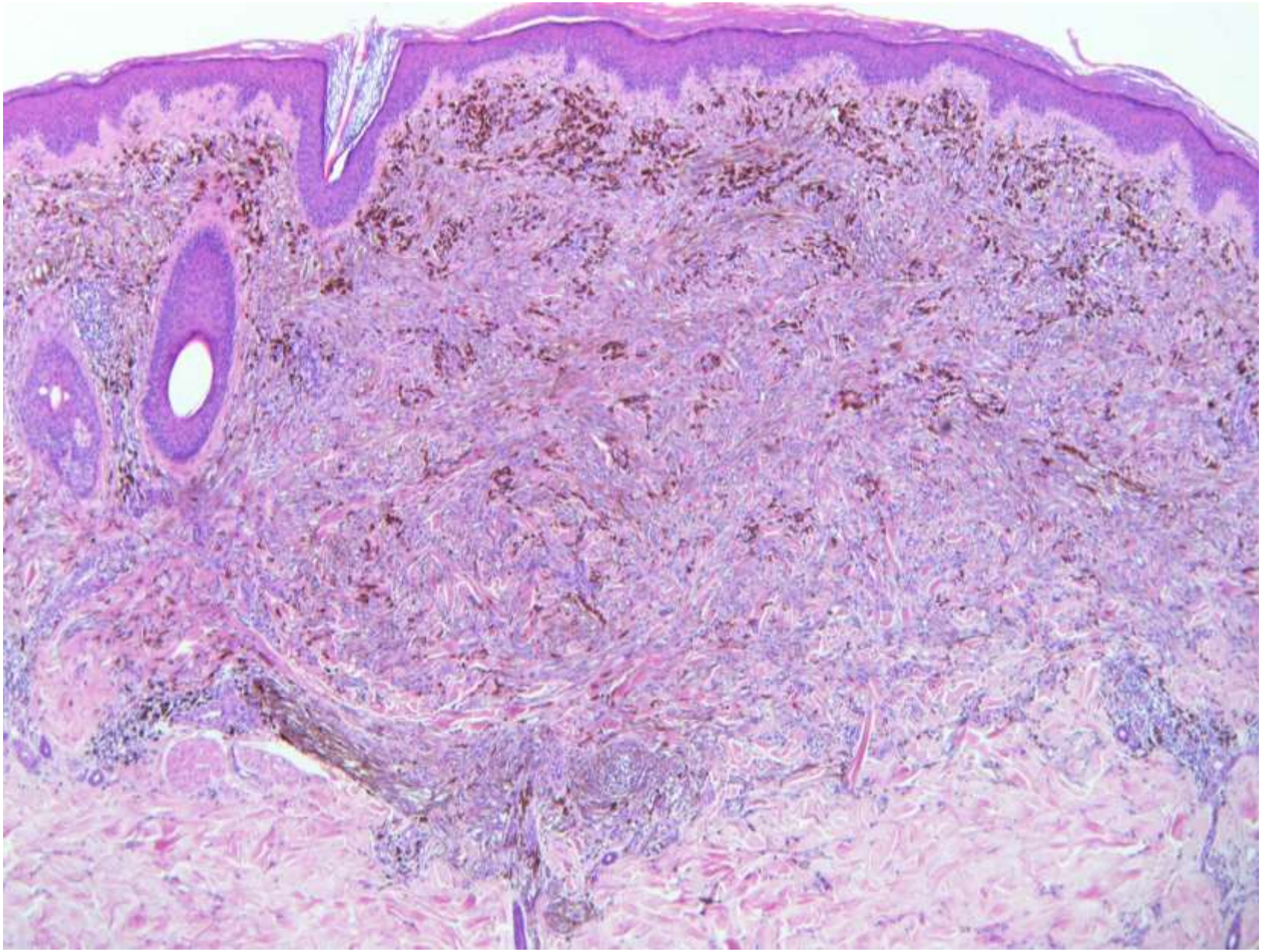
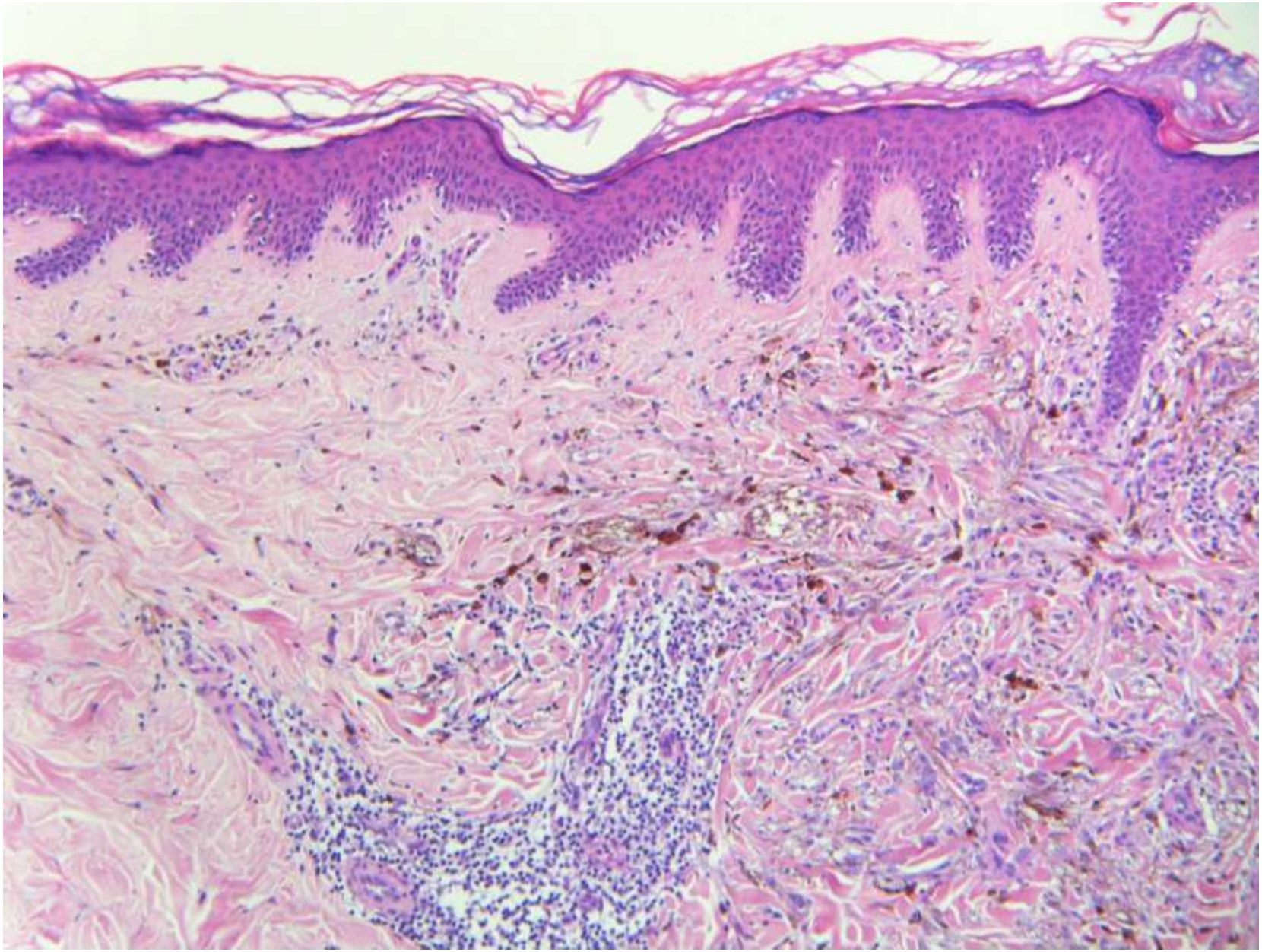
F24. Leg. Congenital naevus spilus. Developed blue nodule 1 year ago. Now flatter on examination. Blue naevus. Exclude melanoma.

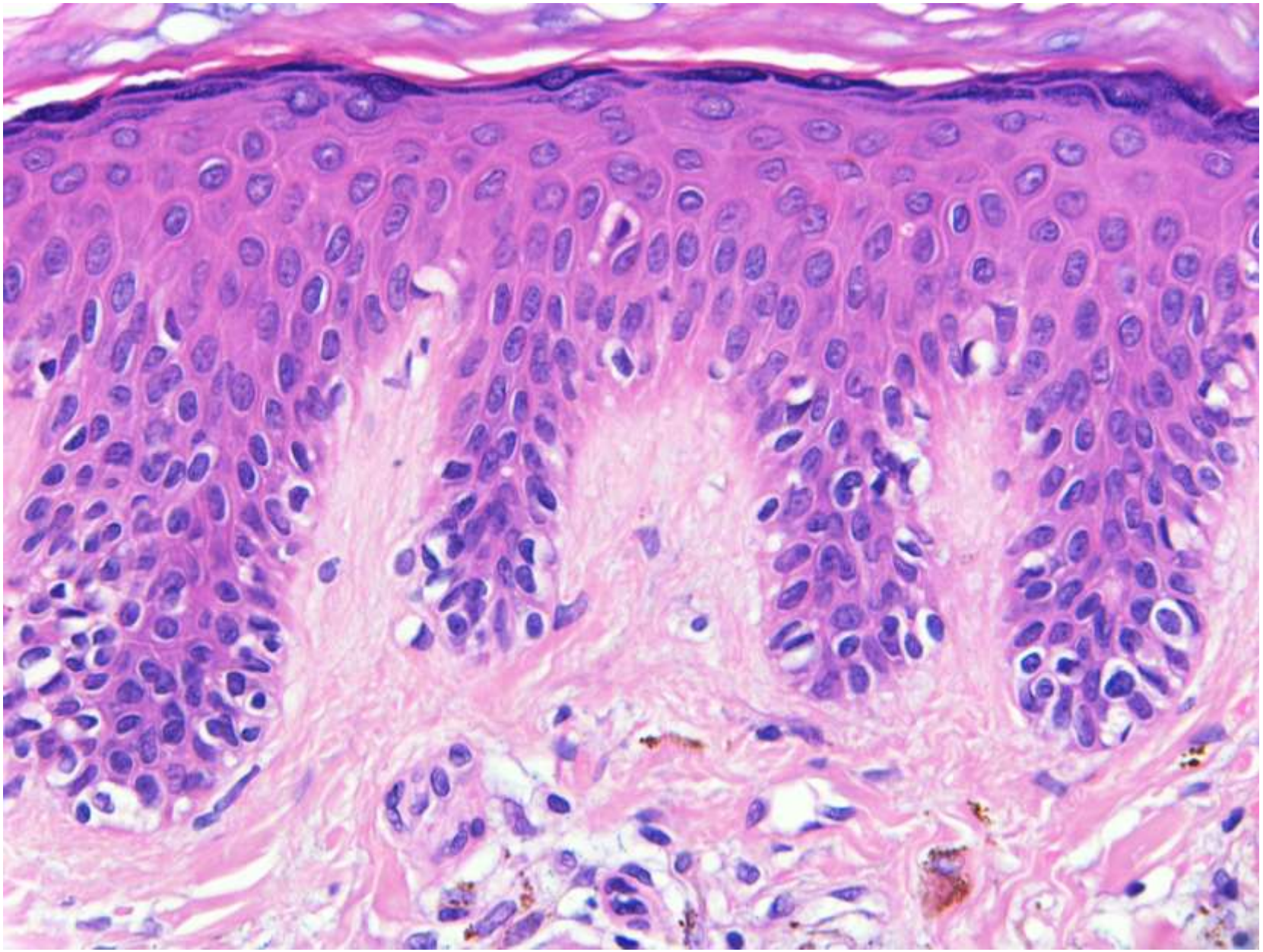


c/o Dr XXXX

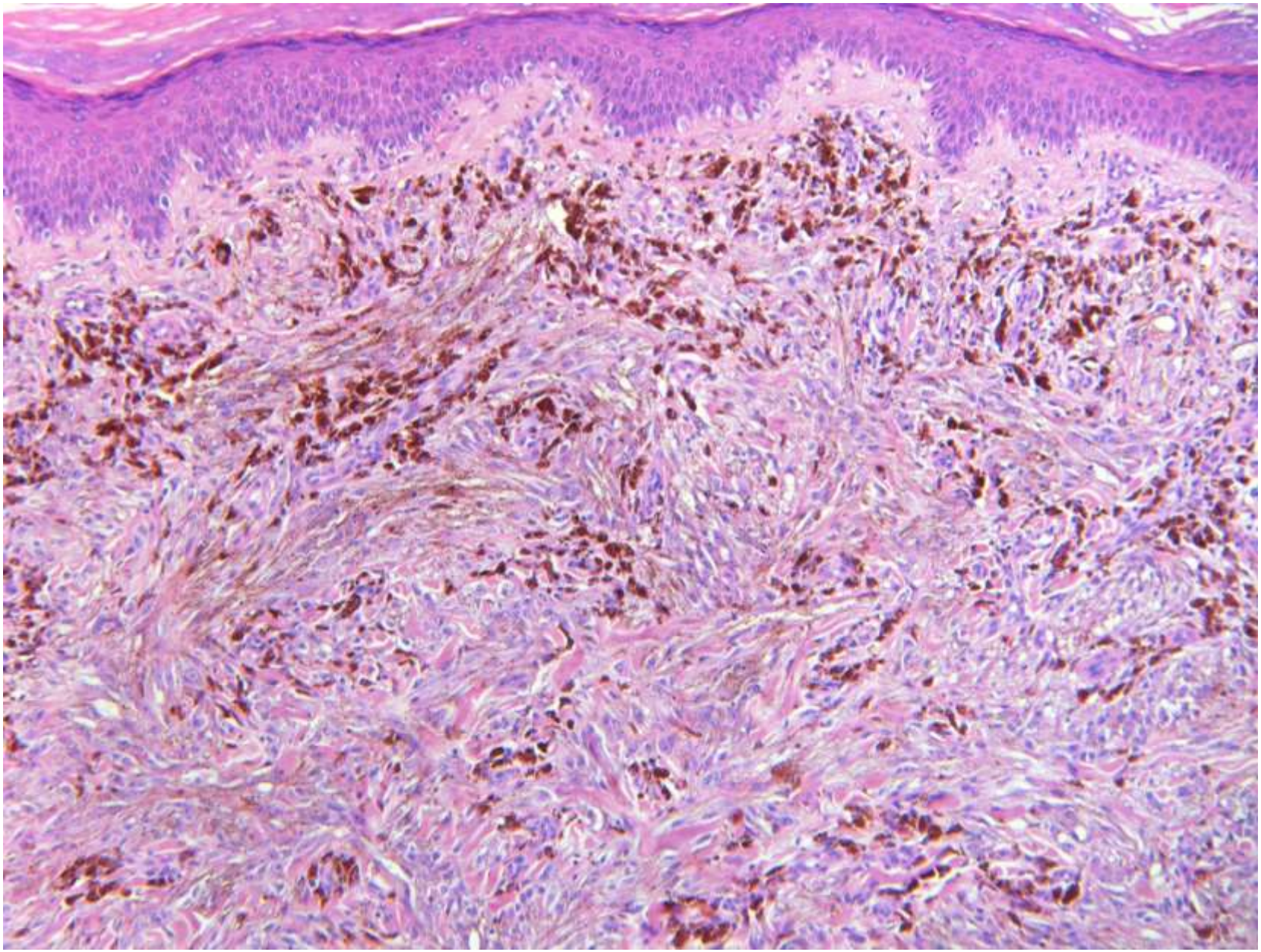
RAC7935

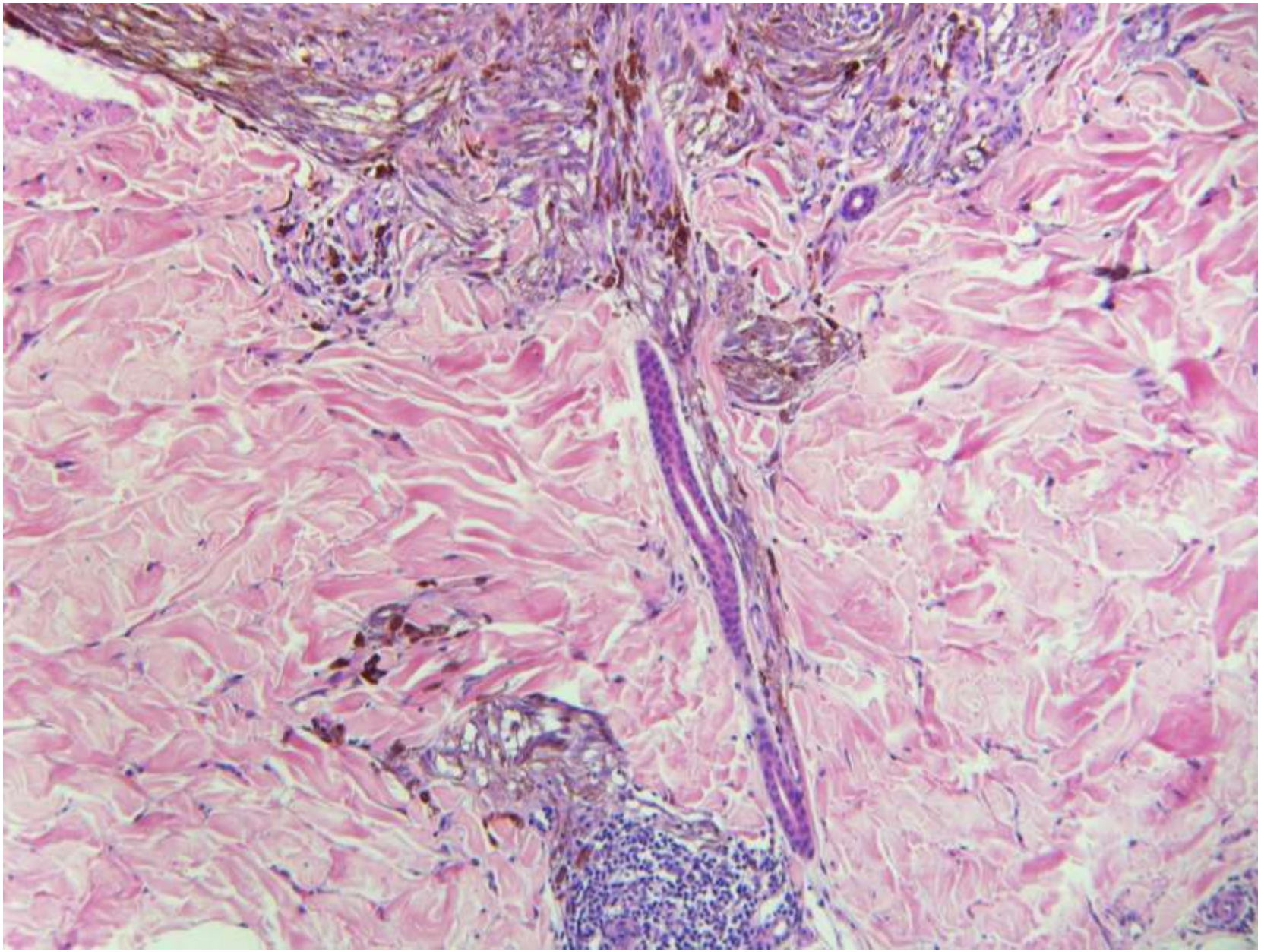


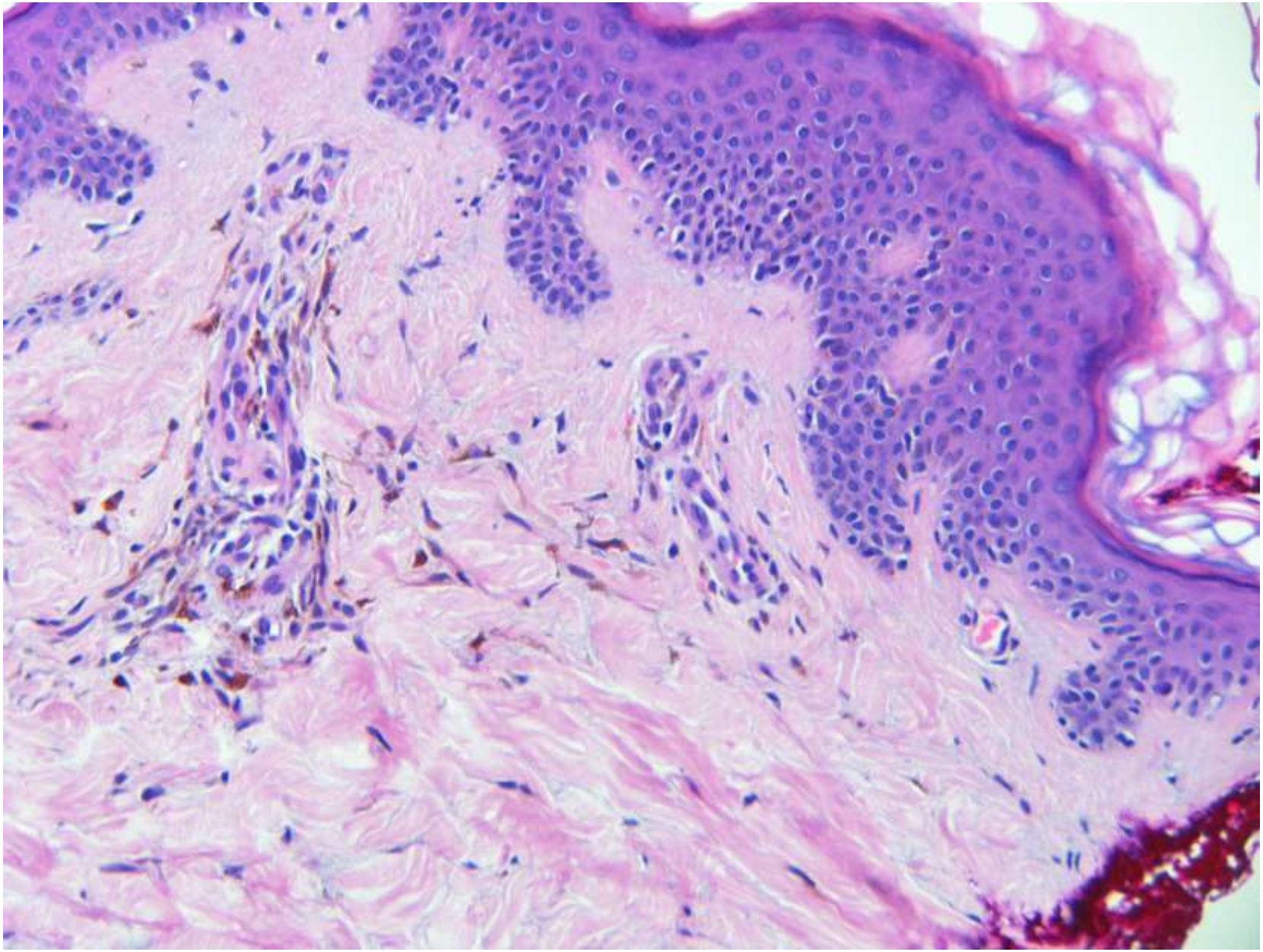




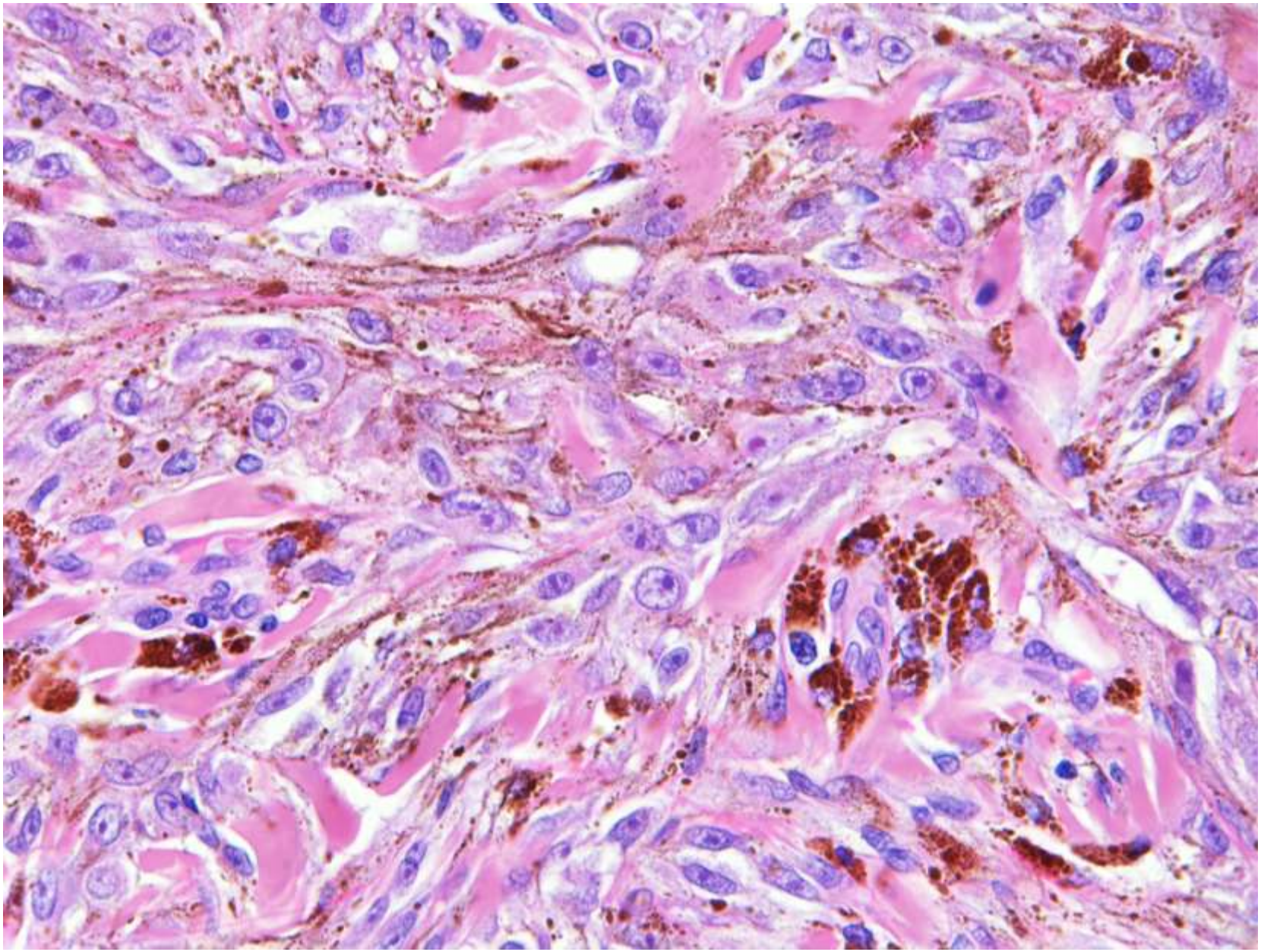
Minimal focal junctional proliferation.



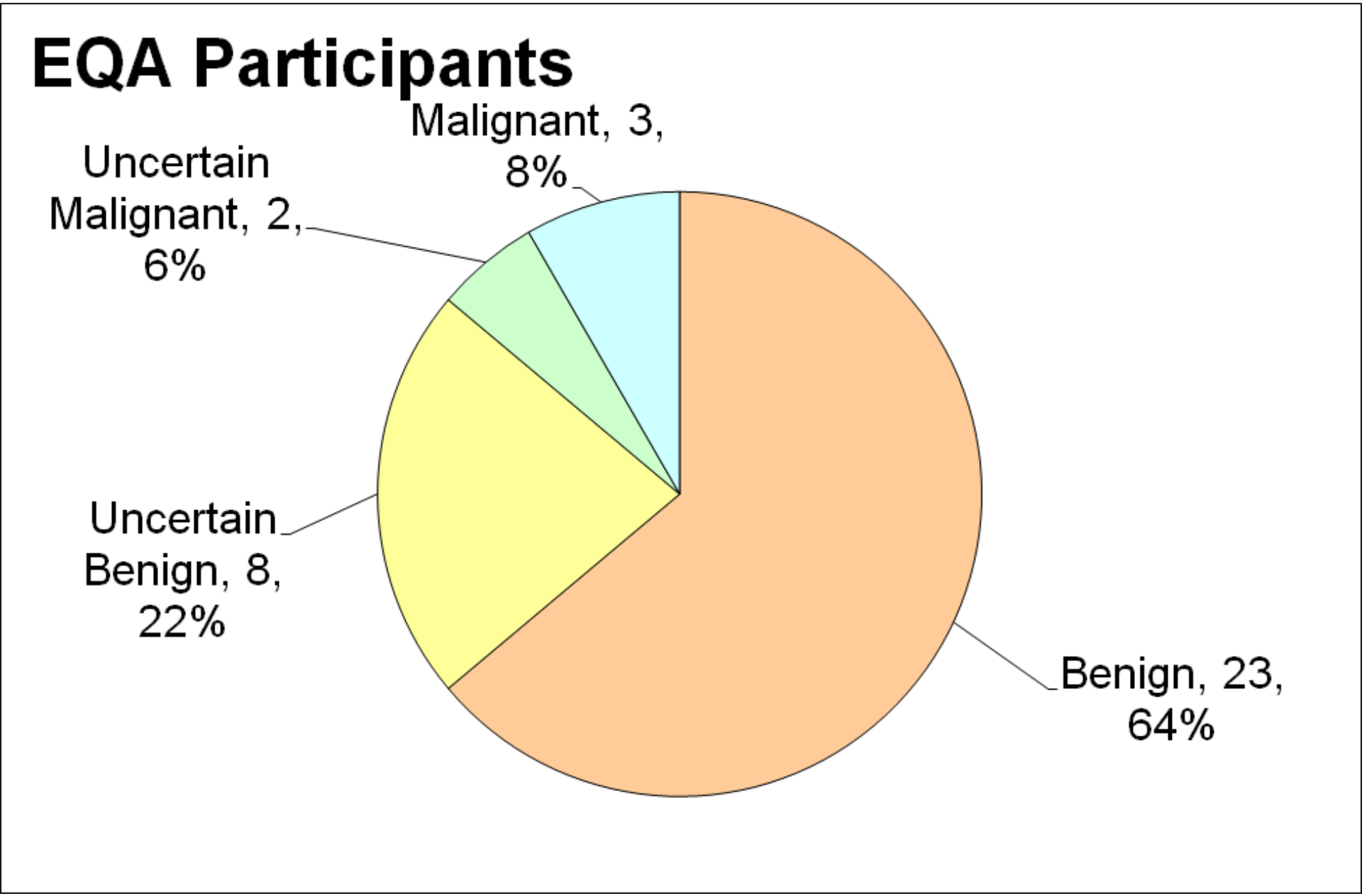




Bland dendritic cells.



N=36


EQA Participants
Malignant, 3, 8%
Uncertain Malignant, 2, 6%
Uncertain Benign, 8, 22%
Benign, 23, 64%

# Summary EQA Participant Responses

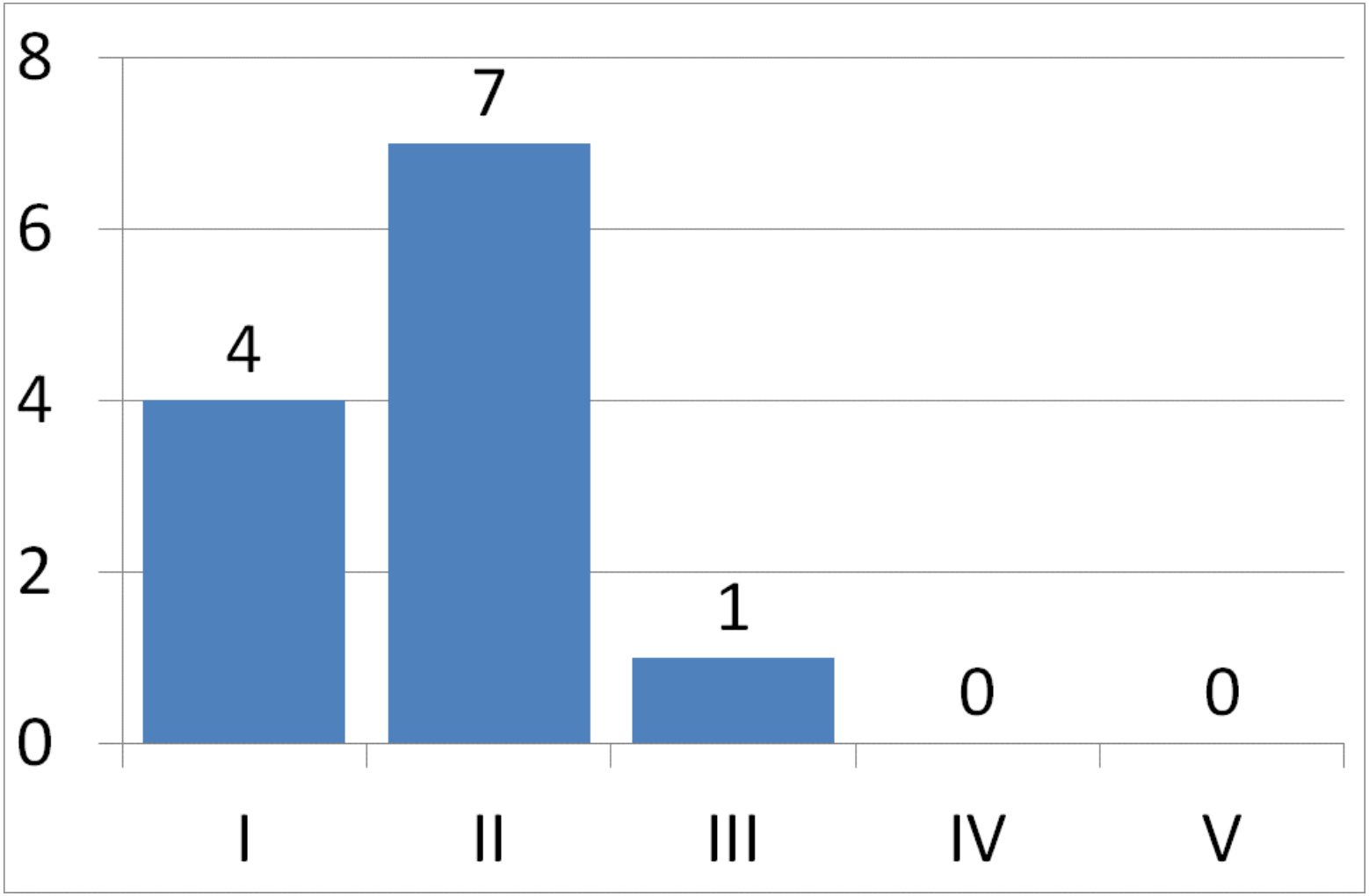
| | |
|---|---|
| Benign: | 24 |
| Blue / CBN | 20 |
| PEM | 5 |
| DPN | 5 |
| Spitz, Reed, Clonal n., Congenital n., Lentigo = 1 each | |
| Uncertain favour benign | 8 |
| Uncertain favour malignant | 2 |
| Malignant | 3 |
| Malignant blue | 2 |
| Minimal dev/naevoid | 1 |

# Malignant Responses: Parameter Summary

| EQA Participants | | | | | |
|---|---|---|---|---|---|
| Clark Level | 1 | 2 | 3 | 4 | 5 |
| | 0 | 0 | 0 | 1 | 1 |
| Breslow | Min | Max | Mean | Median | |
| | 2.0 | 2.0 | 2.00 | 2.0 | |
| Growth Phase | R | V | | | |
| | 0 | 2 | | | |
| Regression | N | Y | | | |
| | 2 | 0 | | | |
| Mitotic Rate | Absent | Low | High | | |
| | 1 | 1 | 0 | | |

# MPathDx*

Amalgamated
EQA & Slide Club




*I: Leave as is even if incompletely excised; II: Complete excision <5mm; III: 5mm; IV: as pT1a, pT1b; 1cm +/-; V: as pT2 or greater e.g. >1cm

# EQA Participants: Benign

N=24

Benign, favouring **Cellular blue naevus**

…predoinantly spitz but there is also some intersection of collagen with spindling, suggesting a blue naevus-like growth. **?BLITZ**

…almost symmetrical intradermal.. spindled elongated cells in packets and singly interspersed with dernal collagen, macrophages and skin adnexa. No high grade atypia or evident mitotic activity. In keeping with **cellular blue naevus**; …expected positive MelanA, HMB 45, p16 and S100 with low Ki67.

**Epithelioid cellular Blue naevus**

**Expansile nodule in congenital melaocytic nevus**

**clonal naevus component** developing in **naevus spilus**

**Favour CBN** v's DPN

# EQA Participants: Uncertain favour benign

N=8

**Pigmented epithelioid melanocytoma**

**Pigmented epithelioid melanocytoma** with some cytological atypia. I didn't notice mitoses.

Blue lesion with cytological atypia, **epithelioid blue naevus**

…favouring **deep penetertating naevus, …melanocytoma** category, …favourable outcome.

# EQA Participants: Uncertain favour malignant

N=2

**proliferative nodule vs malignant melanoma**. Atypia and surrounding inflammation worrying. More levels required

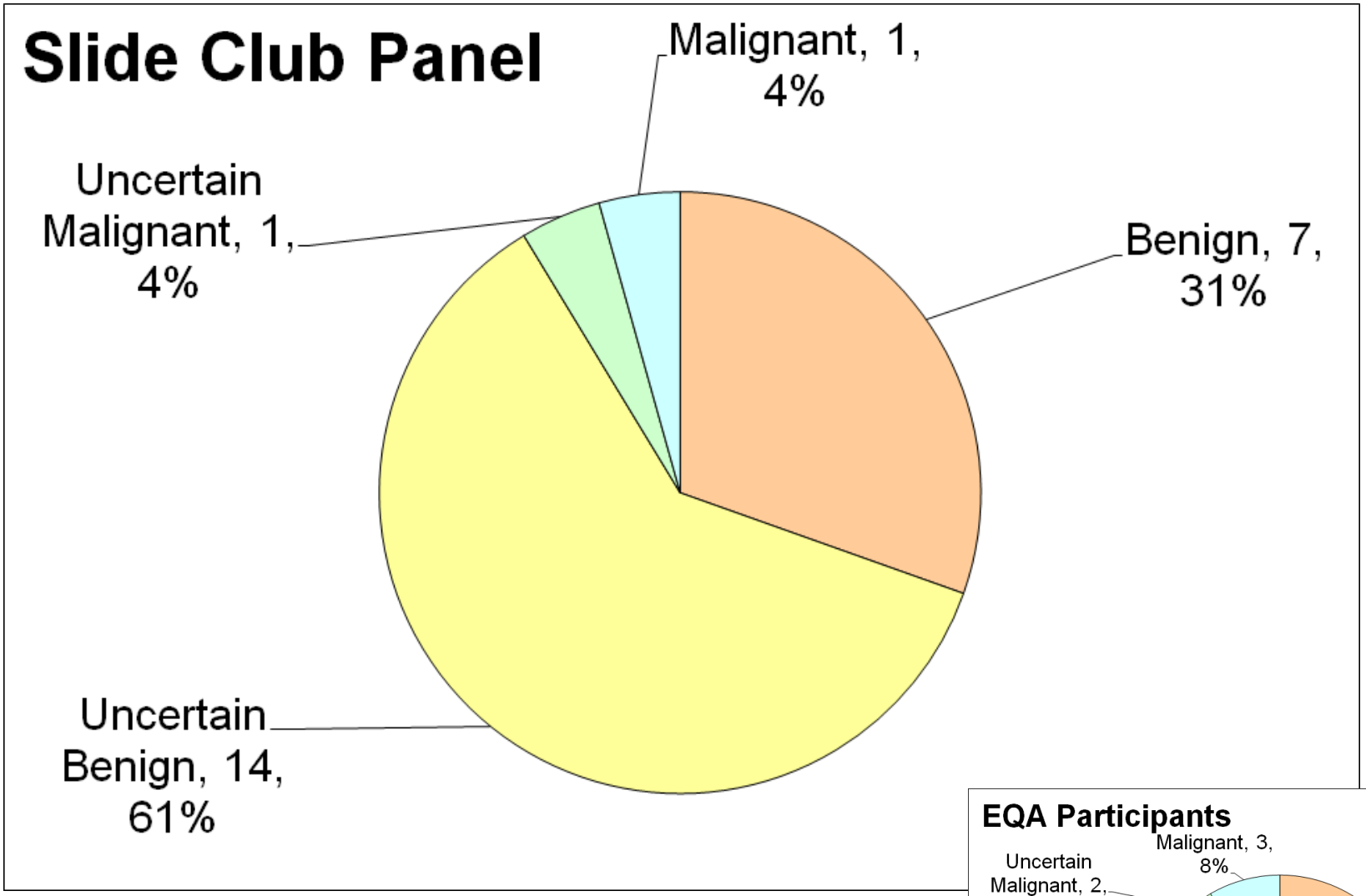
Difficult case with awful cytology but inapparant mitoses. **Favour malignant**

# EQA Participants: Malignant

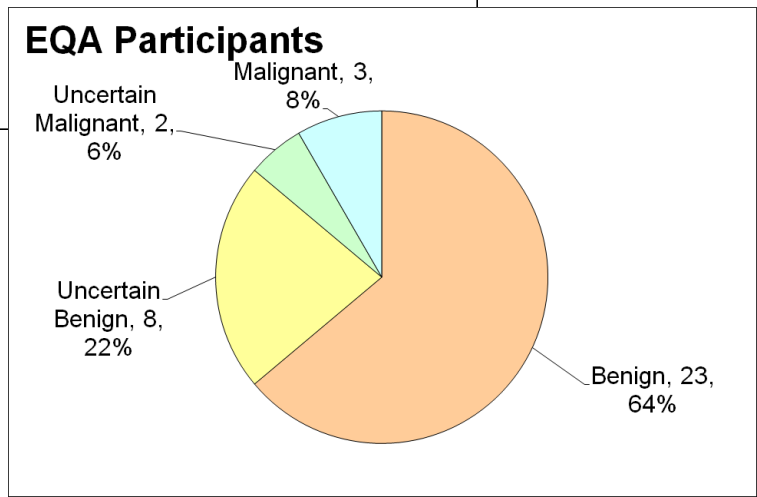
N=3

Difficult case with awful cytology but inapparant mitoses. Favour malignant

# Slide Club Panel




N=24




PEM: 13; DPN: 6; Blue: 5

# SLIDE CLUB RESPONSES

- [Benign, MPathDxII] Beta-Catenin? ?DPN
- [Benign, MPathDxIII] Atypical dermal pigmented spindle/dendritic cell and epithelioid cell melanocytic tumor, 4.6 mm diameter, 2.3 mm thickness, mitotic rate 1 -2 per mm2, favor atypical blue nevus with epithelioid cells vs PEM arising in nevus spilus, Differential diagnosis may include atypical Spitz tumor variant, deep-penetrating nevus/tumor. Further evaluation for GNAQ/GNA11, PRKAR1A, PRKCA for blue nevus variant, PEM, less likely atypical Spitz, DPN.
- [Favour Benign; MPathDxII] Relatively symmetrical and somewhat wedge-shaped heavily pigmented epithelioid and focally dendritic dermal melanocytic proliferation - best regarded as pigmented epithelioid melanocytoma. Molecular studies looking for aberrations in the PRKAR1A and fusion of PRKCA genes may be useful in this case.
- looks mostly like a **DPN**, atypia more pronounced than usual. I do not see mitoses. Perhaps small more nevoid nests on the side. Betacatenin? I do not see the nevus spilus in this excision.
- [Favour Benign] fits best with the rare entity of **PEM**. I suspect that it has arisen with a pre-existing naevus spilus although I have to say that was rather subtle in these sections. The features typical for PEM of are the large slightly epithelioid melanocytic cells with vesicular rounded nuclei and prominent central nucleoli. Large numbers of accompanying melanophages. Lesional cells at the periphery have a more dendritic morphology and to follow neurovascular bundles.

# SLIDE CLUB RESPONSES

[Favour Benign] Deep penetrating / pigmented plexiform melanocytic tumour. Mostly composed of large epithelioid melanocytes with large macronucleoli. Hard to find mitotic activity. Difficult to classify but in view of the large cells I think I would label it as "**atypical DPN / plexiform naevus**".

[Favour benign] **Melanocytoma not combined**, exclude Carney complex. If sporadic unpredicatable behaviour.

**Blue naevus** (common or CBN)

**PEM**. Somewhat more cellular than average and has a few scattered mitoses, but on balance a low risk lesion, I think.

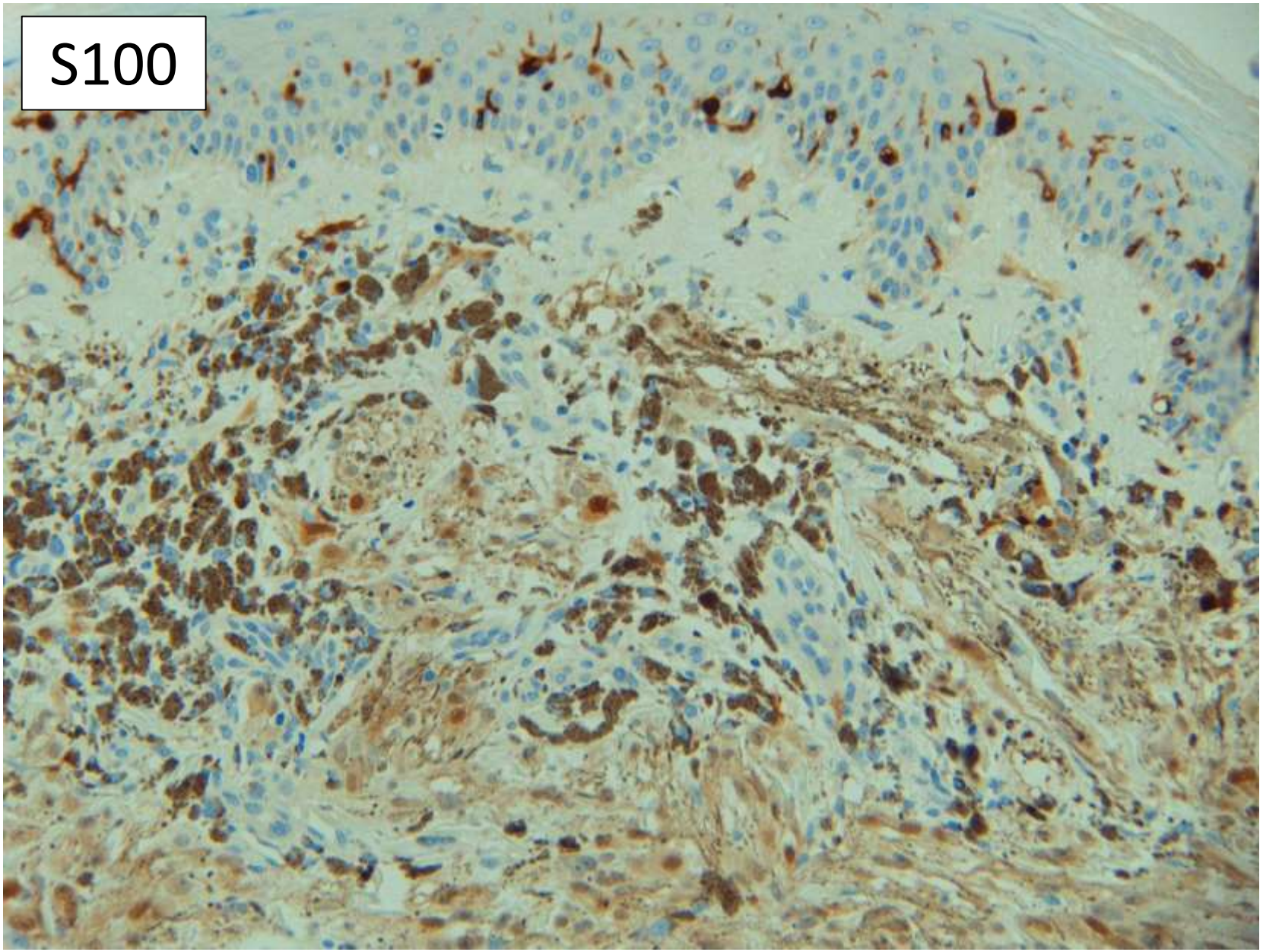
There is a slight and patchy excess of melanocytes across this biopsy but it is difficult to establish whether this really amounts to naevus spilus. Within the centre there is wedge shaped dermal melanocytic lesion composed of plump epithelioid to spindle shaped melanocytes associated with fairly prominent melanin pigment elaboration. The cells have an enlarged vesicular nucleus with a prominent acidophilic nucleolus. There is some tendency to track neurovascular bundles and adnexae and it lacks maturation. My main thought here is for **PEM** which is best considered to be of uncertain (but likely low) malignant potential.

- SLIDE CLUB RESPONSES

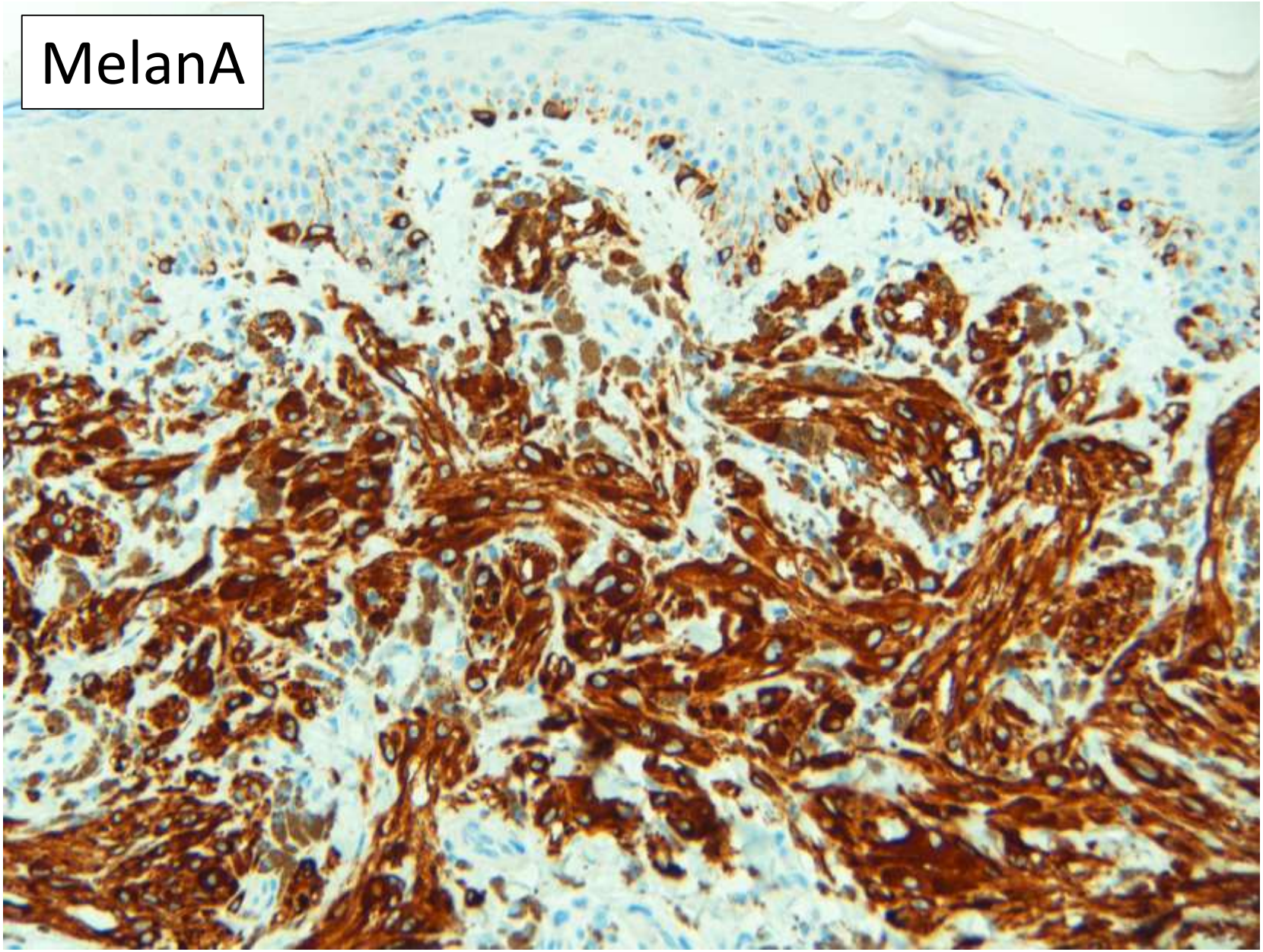
- [MPathDx II, Favour Benign] Classical **PEM**. A dermal-based, willing be wedge-shaped melanocytic tumour composed by dendritic cells and epithleioid cells, the latter with striking macronucleoli. Although cytologically worrying, these atypical epithelioid cells are relatively monomorphic and mitotically inactive (on the digital slide...); macronucleoli are often surrounded by a 'clear' halo (fried-egg?); there is some inflammation, but not truly 'brisk'. The epidermis is uninvolved; there is actually a thin but evident grenz zone. I think that this may be a pigmented epithelioid melanocytoma. Nucleoli are slightly larger and more polymorphic than expected, but overall I see no morphological feature of a 'hgh risk' atypical tumour
- [Favour benign; MPathDx II] **Atypical blue tumor**
- **PEM**. Believe the history might mislead. There are heavily pigmented cells, spindle and epithelioid, with large rounded nuclei and very prominent nucleoli, usually seen in PEM.
- [Favour benign] Overall I favour a **benign naevus** which does look like **blue naevus** although the cells look a bit epitheliod but not that much melanin to call it a pigmented melanocytoma. Not seen any mitosis. Background skin could be compatible with a neavus spilus which I am saying only because of the history otherwise may not have noticed it that much.
- **DPN**. B Catenin immunostain. Some PEM like features but cytology not typical

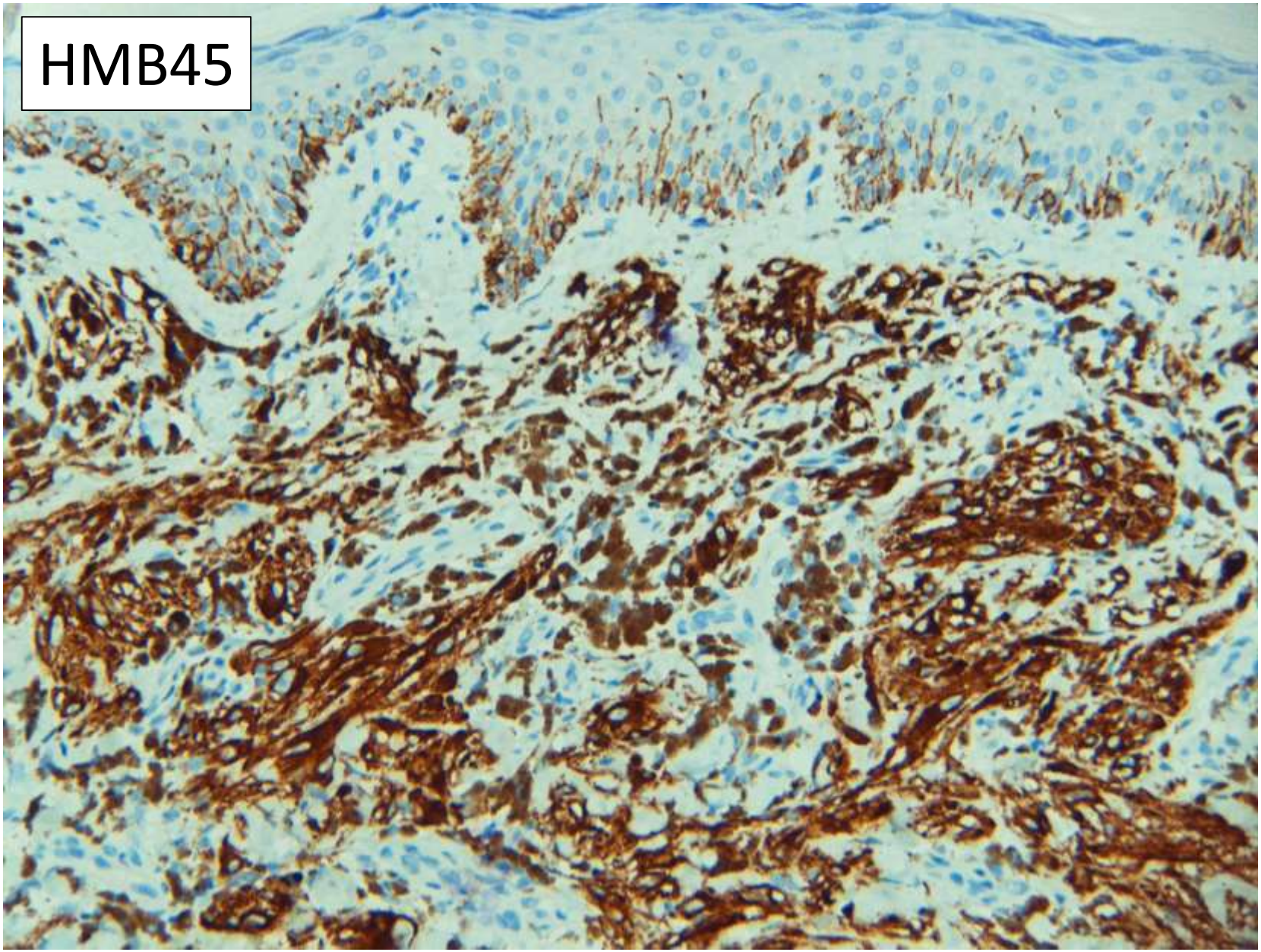
- SLIDE CLUB RESPONSES

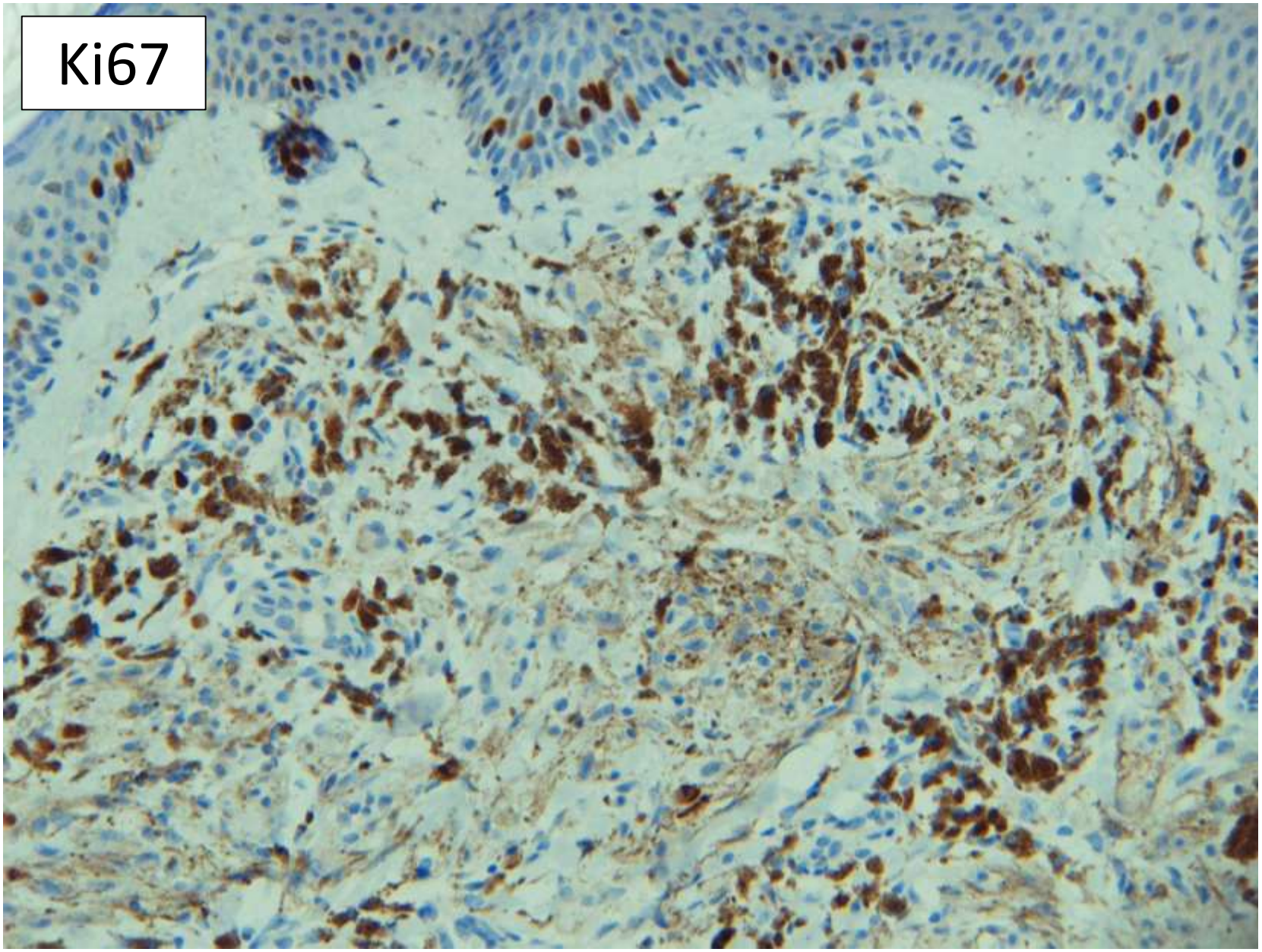
- [Favour benign, MPathDx II] Uniform enlarged melanocytes with prominent nucleoli. No convincing mitotic figures or areas or necrosis. No junctional component and no common blue naevus component. I favour a lesion in the spectrum of **epithelioid melanocytoma**. Variant of cellular blue naevus also possible. Not convinced of a definite malignant component despite the nuclear enlargement and prominent nucleoli
- Inverted wedge shaped heavily pigmented tumour, with epidermal hyperplasia. Melanophages, epithelioid/RS like melanocytes, and dendritic cells with vesicular nuclei. Mitotically inactive. Would get PRKAR1A if available & beta catenin to exclude blue naevus with epithelioid cells (unlikely). **PEM** is main consideration. Low grade tumour needing complete excision and follow up only.
- **CBN**
- [Malignant] **Pigment synthesising melanoma / PEM**
- Plump spindle cells with some pigmentation, wedge shaped, nuclear atypia without mitoses. **Favour melanocytoma, likely PEM group**.
- **PEM** v **animal melanoma**. Needs molecular.
- **deep penetrating melanocytoma**, suspect HRAS and CTNNB1 given clinical of nevus spilus
- (Jan20): **melanocytic nevus, blue Seab/so-called deep penetrating type**
- (Jul20): melanocytic nevus, dermal blue type Seab (deep penetrating)



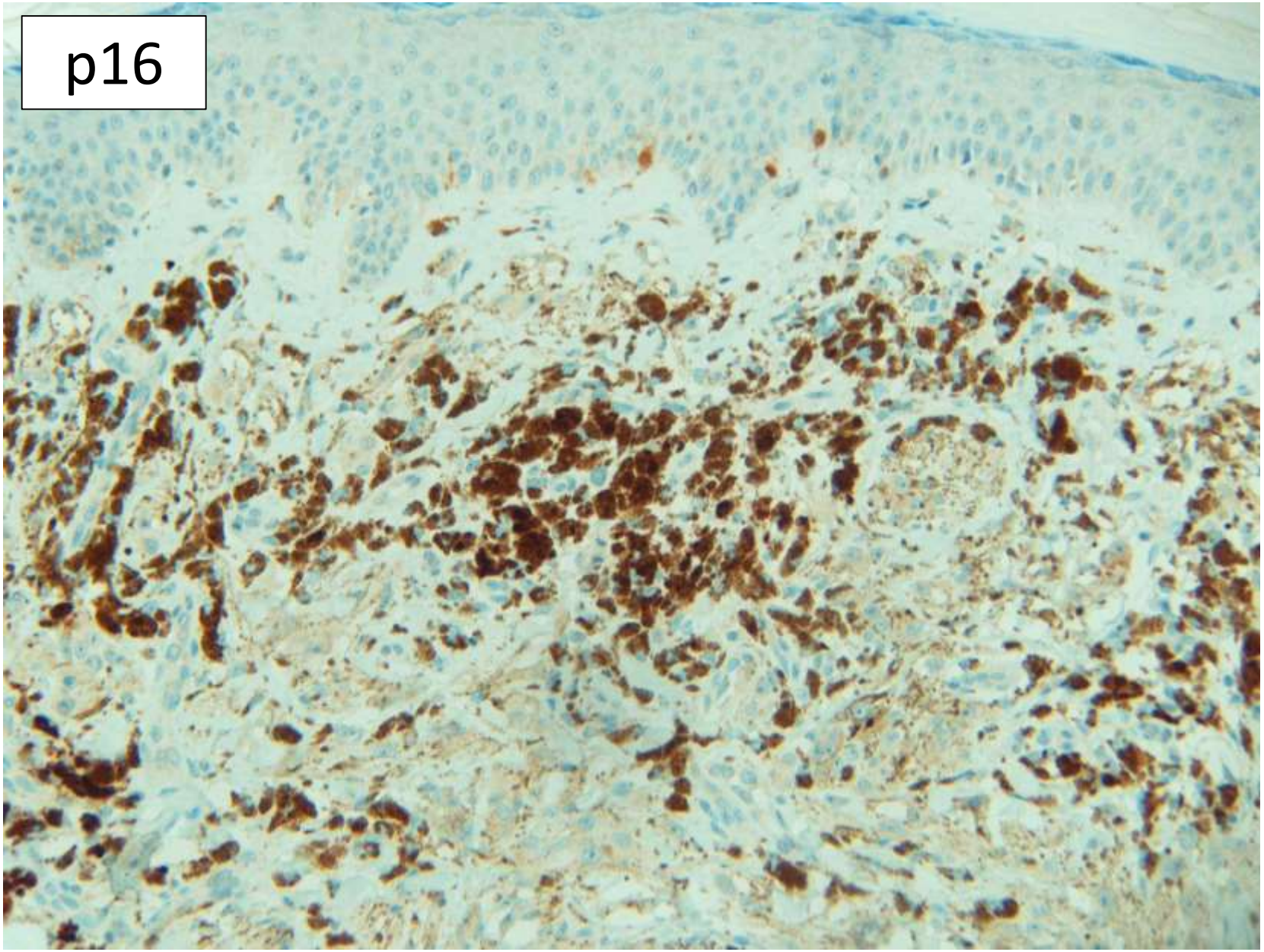

Weak / negative in lesional cells (note strong in Langerhan’s cells).


MelanA

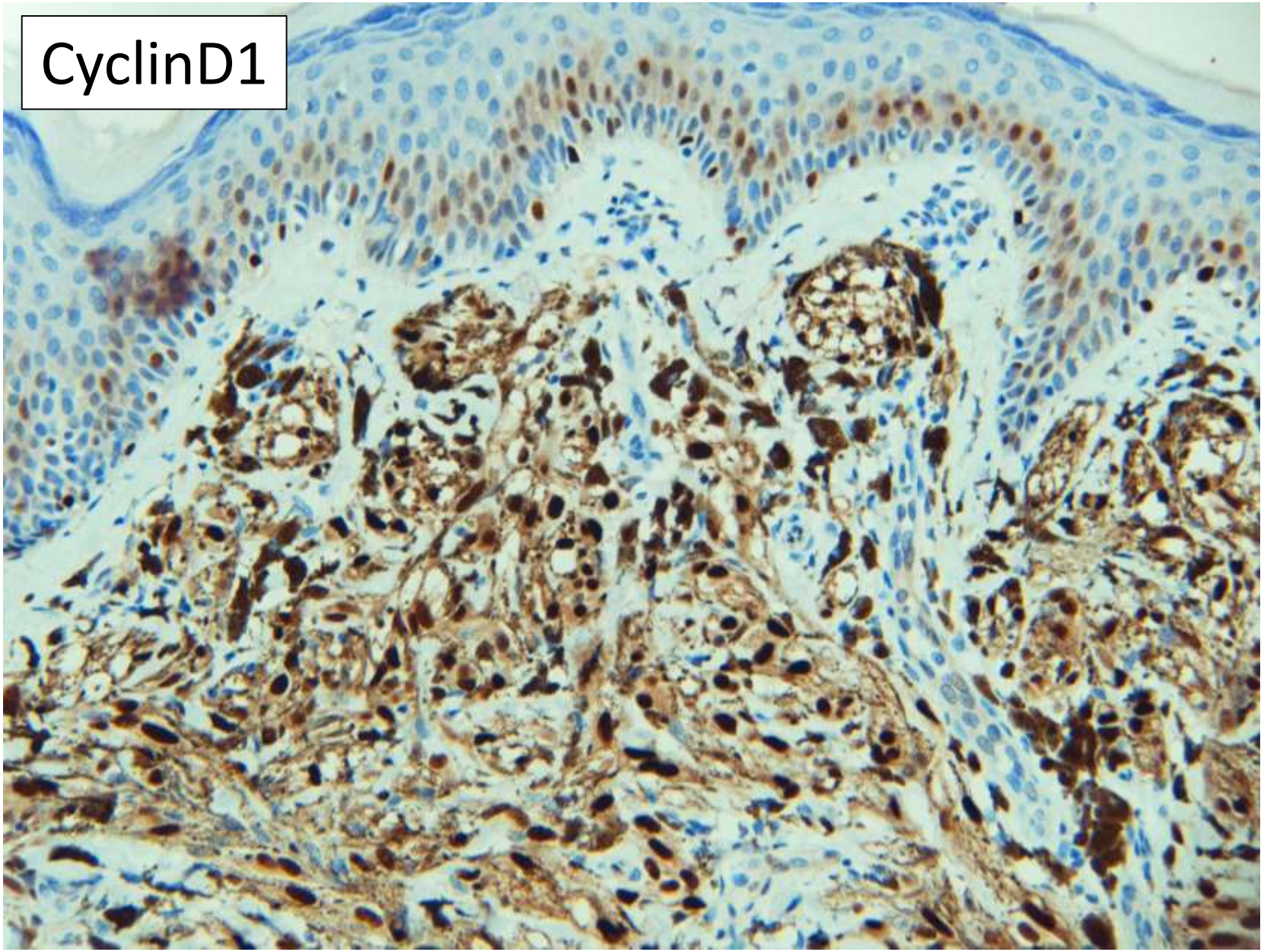

HMB45




Appears low.




Appears negative.




Increased.

DPN probably rather then PEM arising in naevus spilus
Looks like S100 weak, p16 negative, CyclinD1 high

Arnaud,

Subtle extensions up to radial margin. No frankly “atypical” features but thinking I should recommend modest re-excision.

Given it cause me some difficulty would it still interest you.

Not sure if there would be enough tissue for the club but we could enter it as a “Scanned case only”.

Regards
RAC

Dear Colleague,

**Re: RAC7935**

**Clinical Details:**

Congenital naevus spilus left leg. Developed blue nodule 1 year ago initially grew now flatter on examination. Blue naevus exclude melanoma

Many thanks for sending this case which I reviewed with Dr XXXX. In our opinion this lesion fits best with the rare entity of pigmented epithelioid melanocytoma. I suspect that it has arisen with a pre-existing naevus spilus although I have to say that was rather subtle in these sections. The features typical for PEM are the large slightly epithelioid melanocytic cells with vesicular rounded nuclei and prominent central nucleoli. Large numbers of accompanying melanophages. Lesional cells at the periphery have a more dendritic morphology and follow neurovascular bundles. Reassuring in this case is the low Ki-67 proliferation rate and sparse mitotic activity. The lesion has retained relatively good symmetry.

These lesions are now being classified in the intermediate category in regards of biological potential, although I would expect with the appearances in this case a low risk for metastasis. Given that the lesion follows a neurovascular structure to within 0.5 mm of the radial margin I would advise re-excision with a 0.5 to 1 cm margin and follow up. I should point out that some patients with these lesions, they can be associated with Carney's complex NAME and LAMB syndrome. Although I think that majority of lesions are sporadic. The underlying genetic abnormality is usually within the PKA1R1A gene and unfortunately we do not have the appropriate immunohistochemistry or molecular tools to investigate this further and certainly, this group of tumours have rather complex molecular genetics.

I have taken the liberty of sending your block and H&E slide to Dr Arnaud Fouchardiere in France following receipt of e-mail consent.

Dear Arnaud

**Re: RAC7935**

**Clinical Details: Congenital naevus spilus left leg developed blue nodule 1 year ago initially grew, now flatter on examination. Blue naevus exclude melanoma**

I would be most grateful if you could take a look at this case. I enclose copy H&E and block. Our initial impression was pigmented epithelioid melanocytoma, but I have to admit I also considered deep penetrating naevus. Given the difficulty in such cases I would greatly appreciate your thoughts on the case. I have not cut the sections for the Slide Club because the block looked a little thin, but we have permission to use the case for education.

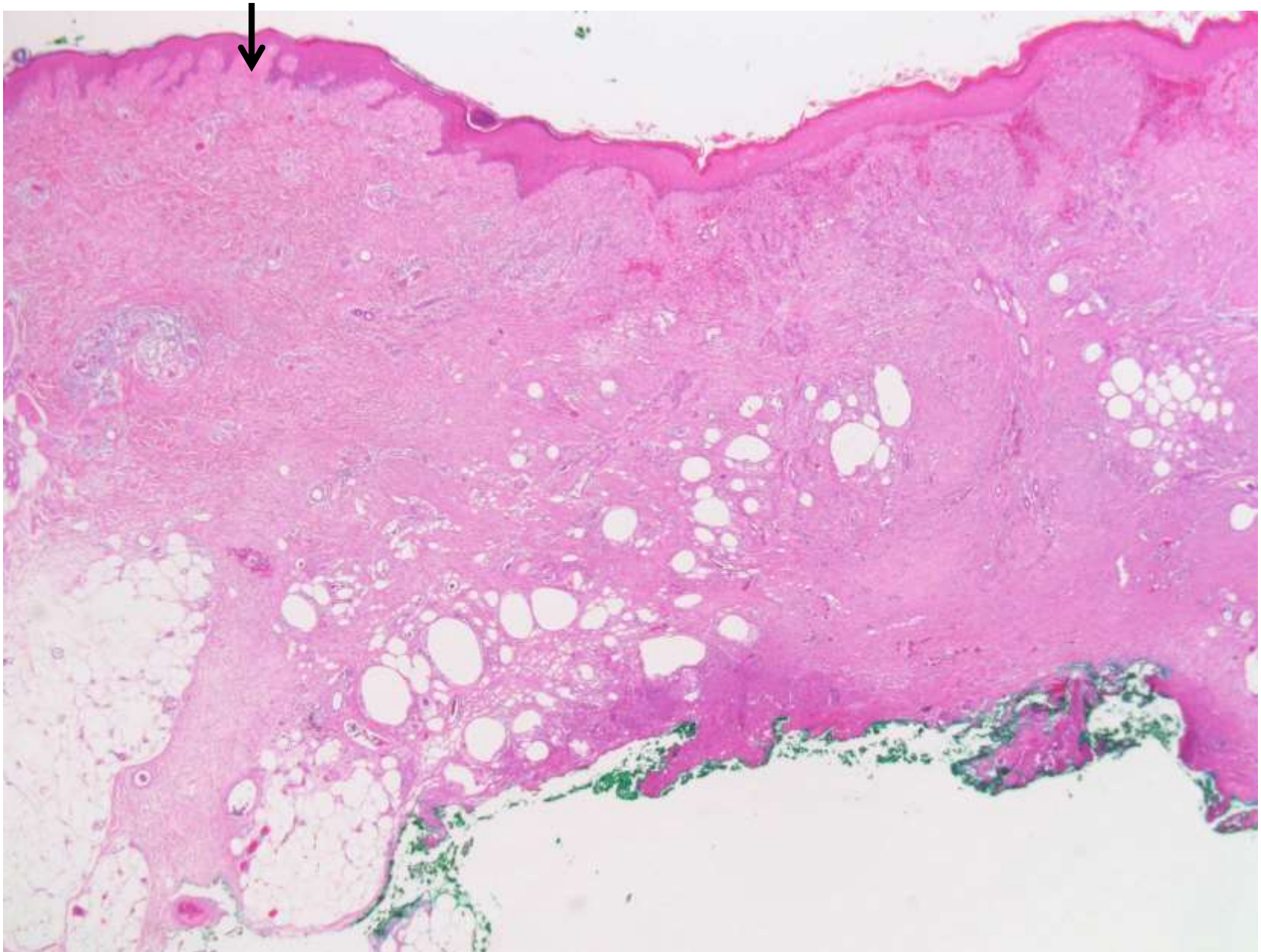
Yours sincerely

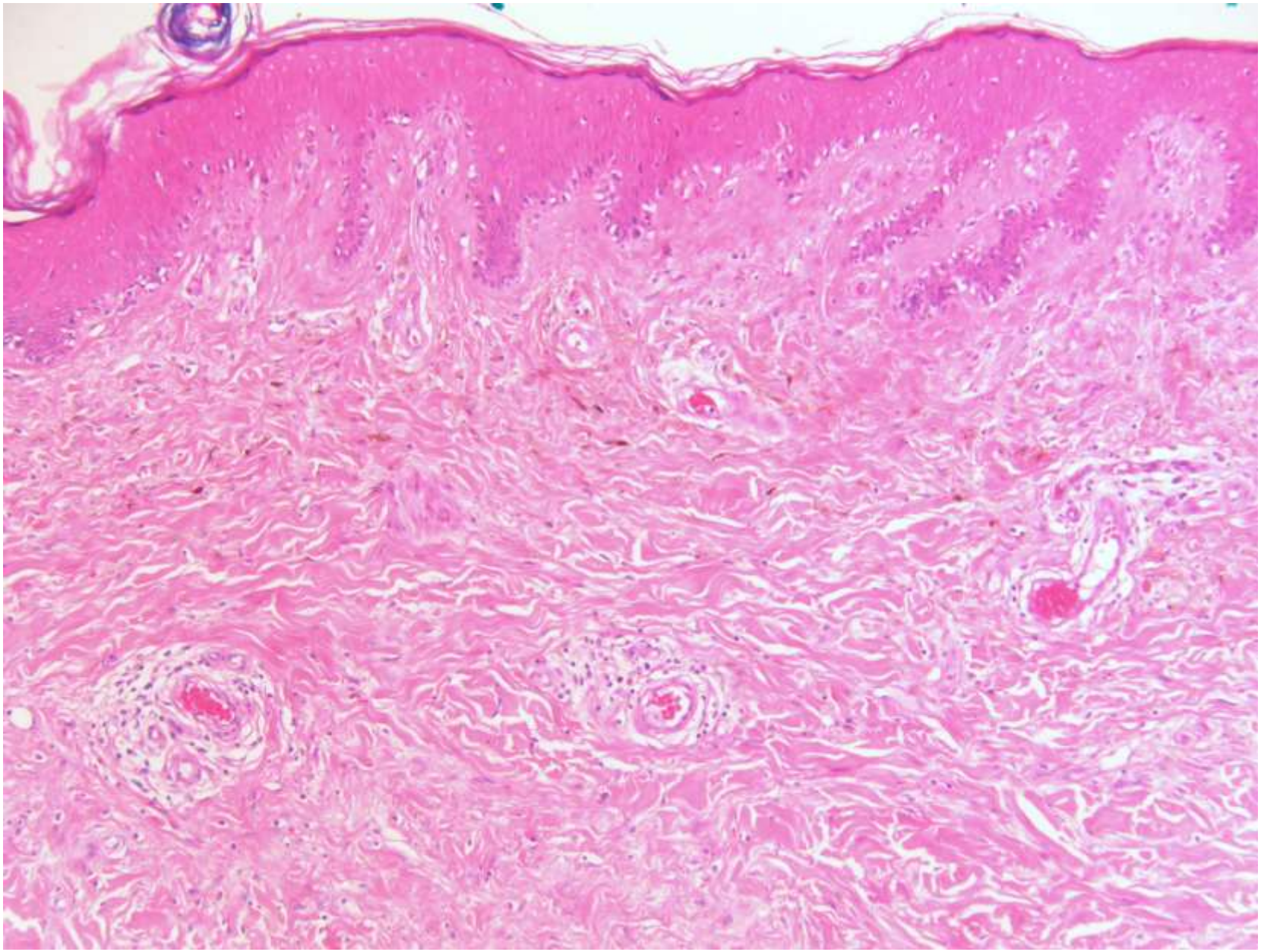
**Report c/o Dr Arnaud de la Fouchardiere (30/10/2018):**

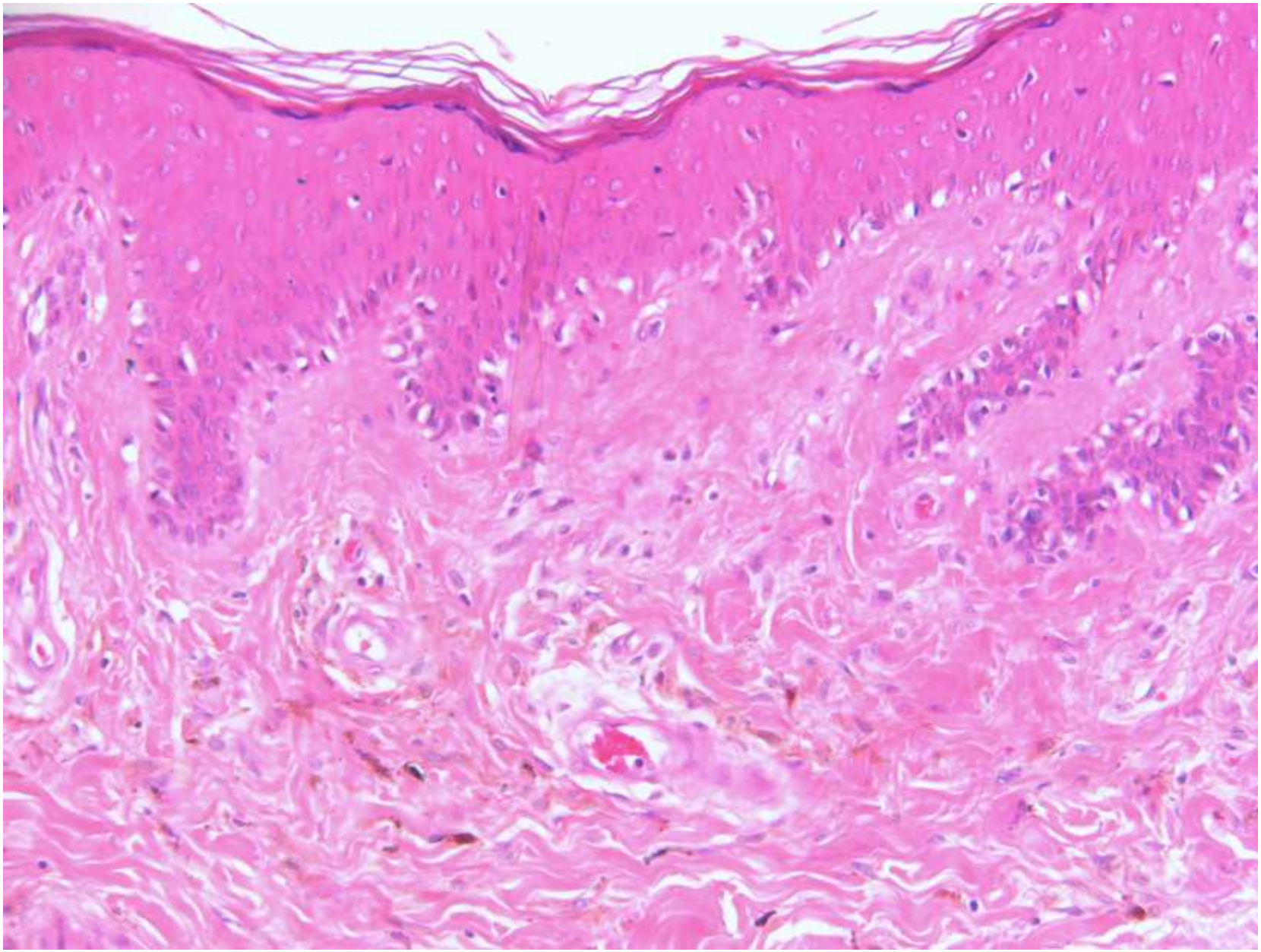
Cutaneous resection left leg
The melanocytic proliferation is mainly dermal with some lentiginous junctional melanocytes of small to medium size, mildly pigmented. There is no pagetoid spreading. In the dermis large spindled melanocytes are arranged in a fasciculated architecture extending without maturation into the reticular dermis. The bundles are made of large melanocytes with nucleated oval nuclei and a strongly pigmented cytoplasm. Many melanophages surround these fascicules. There is a discrete fibrotic background. Mitotic activity remains low. Inflammatory changes are rare with some lymphocytic infiltrates with perivascular reinforcement. The lesion extends deeply reaching the subcutis.
The immunohistochemical study carried out shows a lack of staining with the antibody directed against beta-catenin.
RNA-Seq shows the presence of a **ZNF555-DNAJA3 fusion**, not yet described in the literature, to be considered of unknown significance and pathogenicity in the current state of knowledge. Presence of the **p.S298P mutation in exon 9 of the MITF gene**, and the **p.R177W mutation in exon 7 of the PRKCSH** gene, with indeterminate diagnostic meanings. There was no identified HRAS mutation as usually found in the spilus nevi. In conclusion this lesion remains poorly classified, to be considered as of uncertain prognosis with a Breslow thickness of 2.2mm.

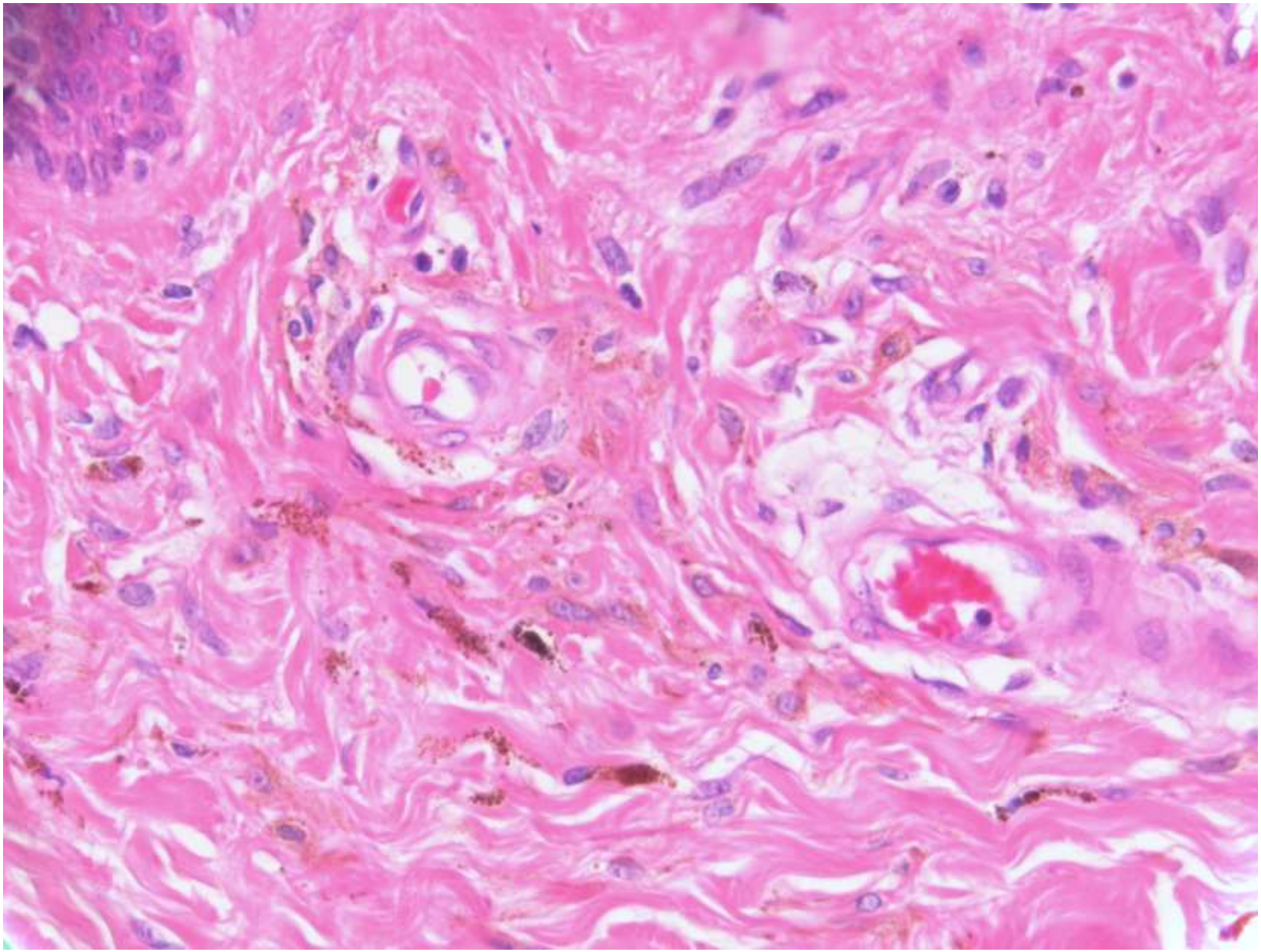
CONCLUSION:
Cutaneous resection left leg: poorly classified, predominantly dermal, fasciculated melanocytic proliferation with large hyperpigmented spindled melanocytes. This case must be considered of uncertain prognosis (MelTUMP equivalent) without evidence of malignancy. Breslow thickness measured at 2.2mm. Absence of features suggesting a link with the DPN spectrum.

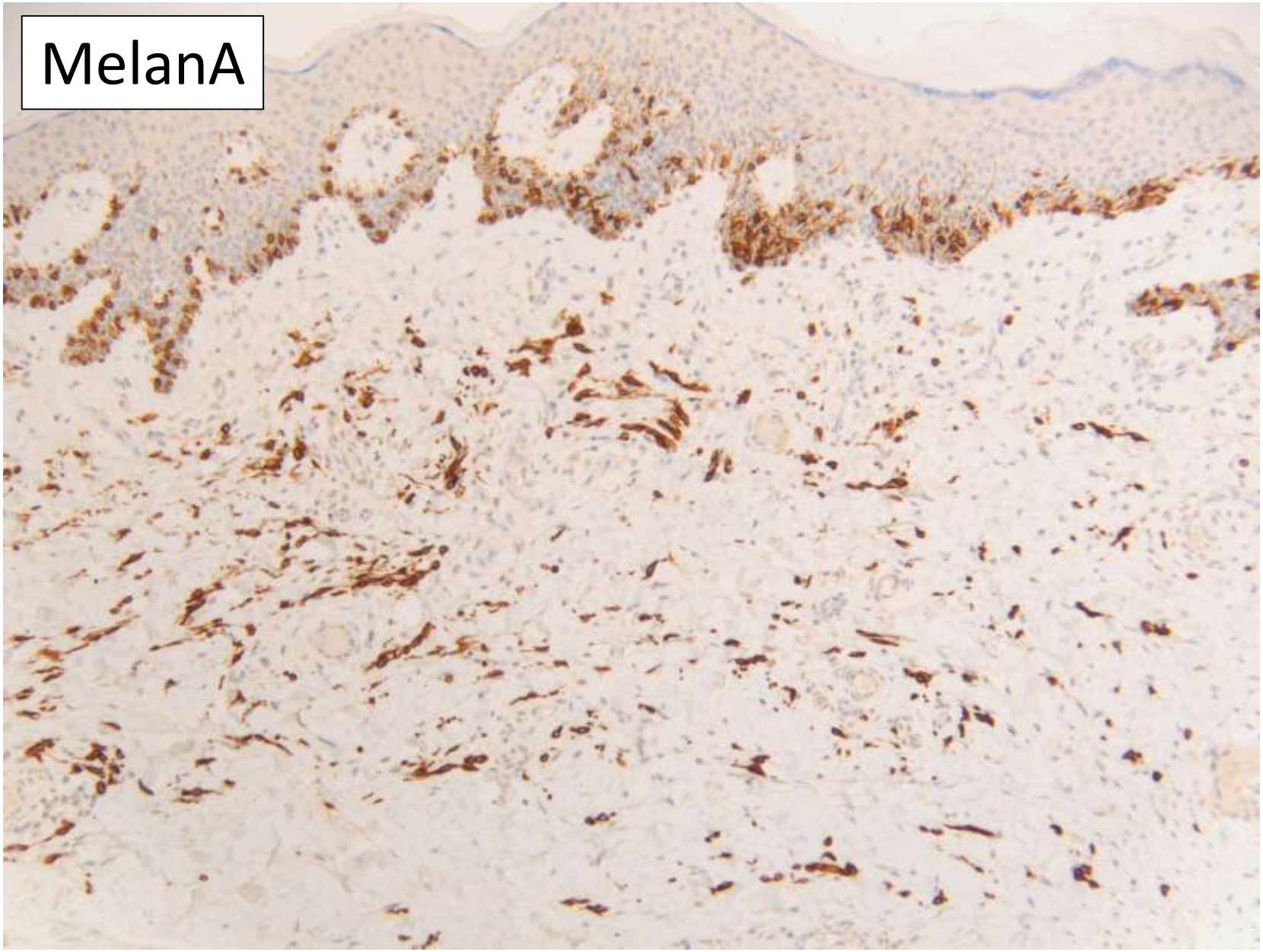
F24. Previous report suggested PEM. Residual lesion ?PEM



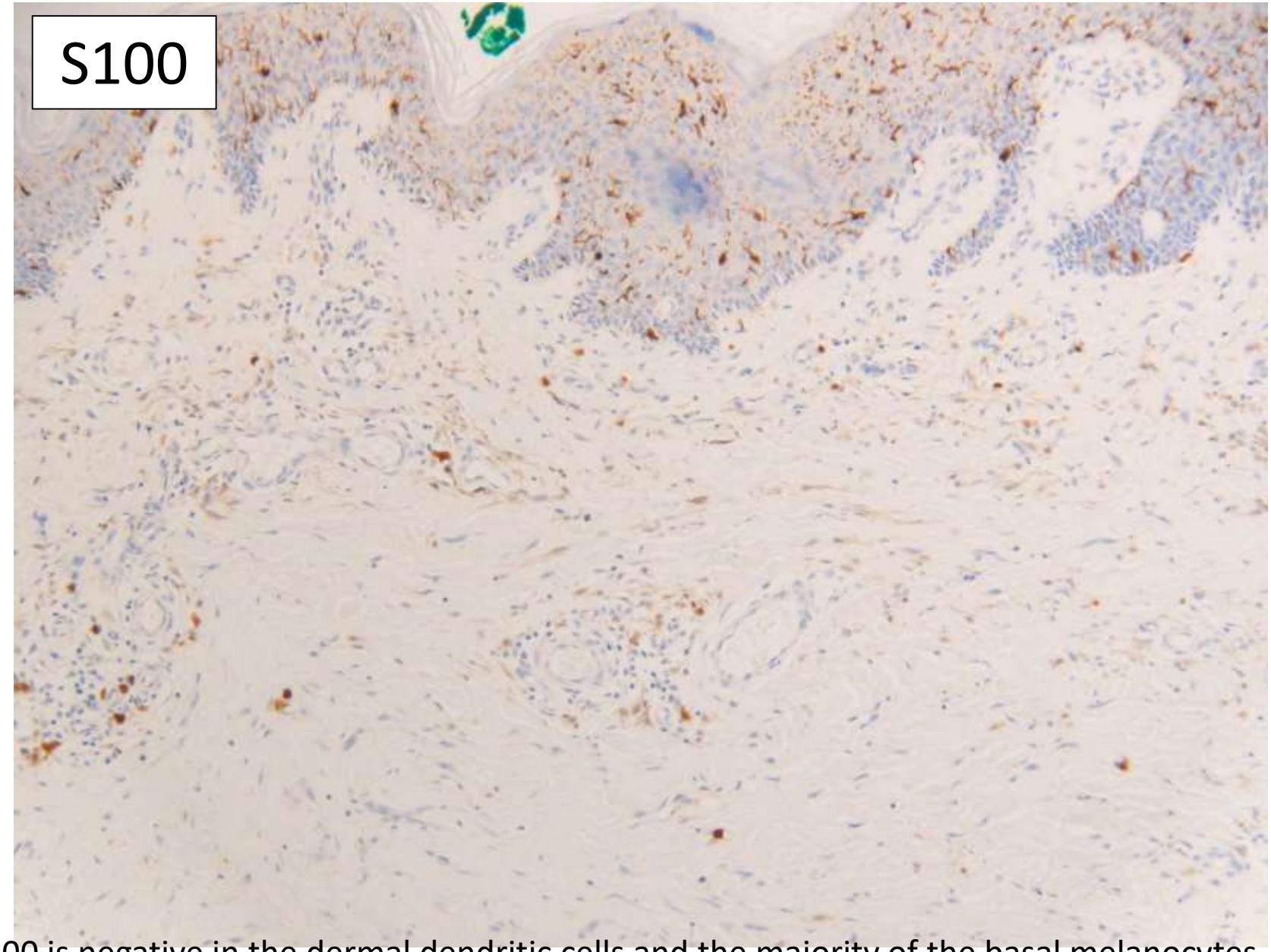









MelanA is positive in the dermal dendritic cells and prominent basal epidermal dendritic cells.




S100 is negative in the dermal dendritic cells and the majority of the basal melanocytes (c/w MelanA). Highlights mainly Langerhan's cells in the epidermis and scattered in the inflammatory infiltates in the dermis

Dear XXX,

I met Arnaud in Lisbon and he has some interesting new findings on your patient. Bx PH13863/18. It shows an underlying GNA mutation (i.e. a blue group lesion) and a PKAR1Ca loss by IHC. This is extra-ordinary indeed as most PEM are combined with BRAF or MAPK pathway driver mutations (rather than blue's).

Can I ask what happened after the re-excision (23689/18)

I presume watchful waiting?

I can't see I ever responded to you formally on the excision specimen for which I apologise.

My thoughts now on the re-excision

I note there is a very widespread hypocellular dermal spindle proliferation around the scar and extending widely in the dermis even quite close (~1mm to radial margins). The immunos MelanA+++/S100- in the dendritic cells and the dendritic basal cells in the overlying epidermis without nests is typical for a **blue naevus** in this case a **hypocellular plaque type**.

I think watchful waiting would be appropriate.

I don't think the PEM component has made it into the re-excision

Summary/Conclusion: Combined lesion comprising a congenital plaque-type blue naevus component (GNA driver mutation) with PEM (PKAR1Ca loss). I expect underlying Carney's will be unlikely.

**Oct20 Update (Arnaud):** I went back to the report, **no GNAQ mutation**. I'm afraid I got tangled up with too many cases at that time so she is not the one with that anomaly. I still don't know what she has but going back to the cluster **she is grouped with all my CYSLTR2 cases** (R474 for DP) so I need to investigate this with my bio engineer to check if she has the hotspot mutation. Do you have more precisions on clinical condition with naevus spilus. Now I am all hyped again for this case.

Daniel PISSALOUX
Hello everyone,
In this case, out of our gene list of interest we solely detected :
PRKCSH:NM_001001329:exon7:c.C529T:p.R177W
MITF:NM_000248:exon9:c.T892C:p.S298P

I went back on our unfiltered file for the detection of variants, and I found no mutation in the coding exons of GNAQ / GNA11 / CYSLTR2 / SF3B1 / EIF1AX genes.

However I was able to detect a PLCB4:NM_000933:exon1:c.G61A:p.A21T nonsynonymous SNV, but it's not the D630 hotspot and it's declared as benign for now in ClinVar…
Best regards,

Thanks so much Daniel – I guess we can say the lesion clusters with CYSLTR2 and it's interesting ?coincidence there is a PLCB4 abnormality (not yet described in the "blues")
Great we are collaborating on this case!
Warm regards
Richard

*Mod Pathol.* 2017 March ; 30(3): 350–356. doi:10.1038/modpathol.2016.201.

**Activating cysteinyl leukotriene receptor 2 (*CYSLTR2*) mutations in blue nevi**

Inga Möller[1], Rajmohan Murali[2], Hansgeorg Müller[3], Thomas Wiesner[4], Louise A

Dermatology

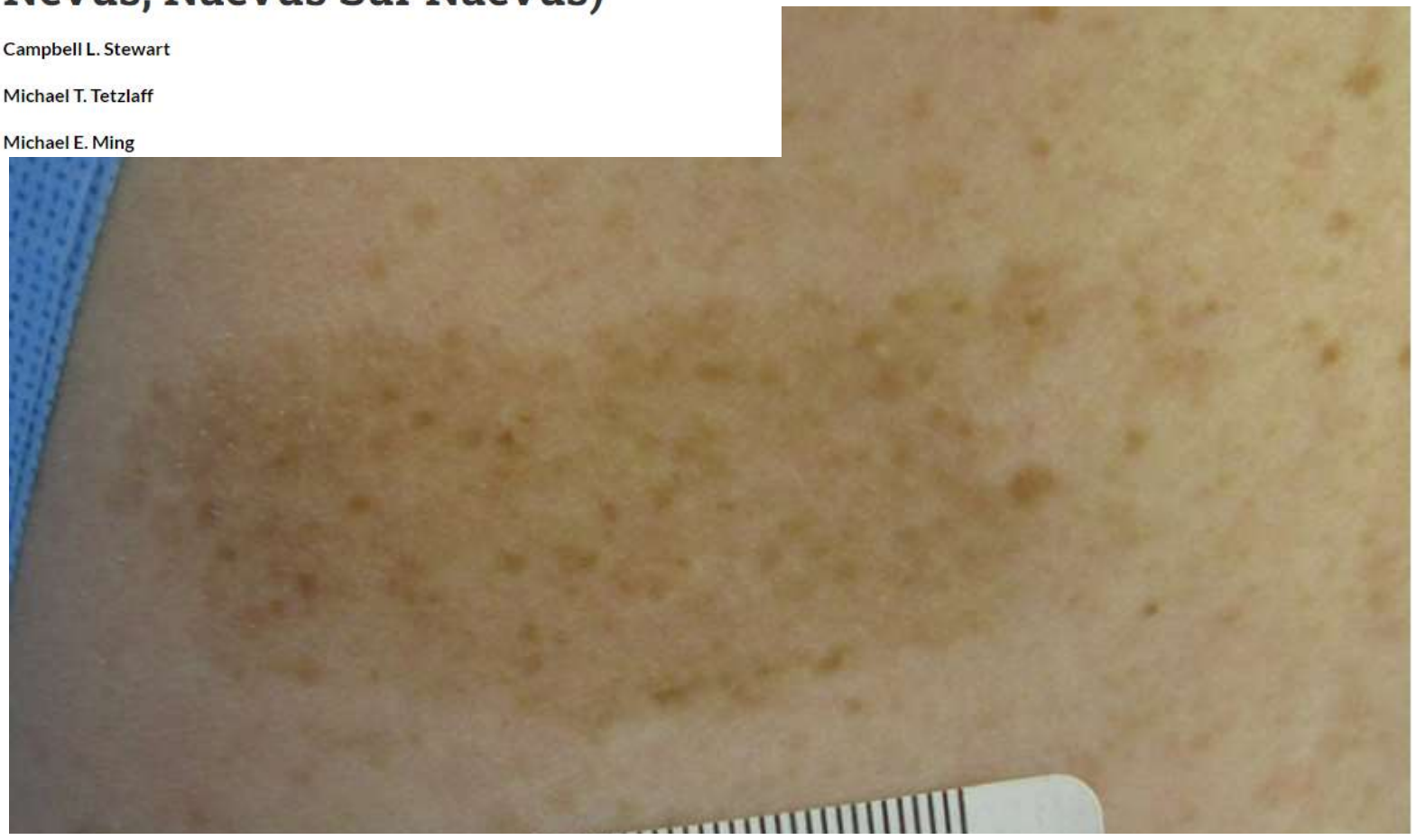
# Nevus spilus (Speckled Lentiginous Nevus, Naevus Sur Naevus)

Campbell L. Stewart

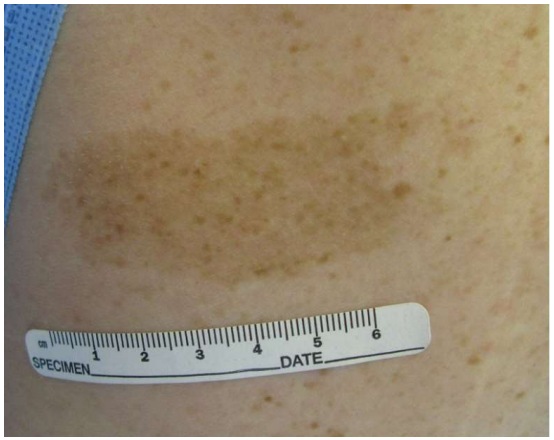
Michael T. Tetzlaff

Michael E. Ming

The etiology of NS is not entirely clear, however, mutations in HRAS have been implicated. It is generally considered to be a congenital nevus, though some authors contend that it can be acquired, due to the fact that it is often not present at birth, and more common in school aged children and adults.



A nevus spilus (NS) or speckled lentiginous nevus (SLN) typically presents before the age of 2 as a light brown macule or patch containing smaller, more darkly pigmented macules or papules within the borders (Figure 1). These smaller pigmented aspects may appear after the first background patch is noted. NS is thought by most but not all authors to represent a type of congenital melanocytic nevus.




Microscopically, the two types of clinical features appear very different.

The tan-brown background pigmentation exhibits features with lentigo simplex: the epidermis is acanthotic with elongation and hyperpigmentation of the rete ridges and an associated mild increase in the number of single melanocytes along the dermal-epidermal junction. Others have reported the appearance of melanocytic nests in these areas as well.

In contrast, the “speckled areas” within this lentiginous background can exhibit a range of reported histolopathologic appearances: from simple lentigines to ordinary nevi (junctional, compound or intradermal) to blue nevi to Spitz nevi.

When a NS is large and segmental, it may be a sign of one of the following rare congenital disorders: phacomatosis pigmentovascularis type III or phacomatosis spilorosea, phacomatosis pigmentokeratotica, or speckled lentiginous nevus syndrome (SLNS). Phacomatosis pigmentokeratotica is now understood to represent a form of a “Mosaic RASopathy” caused by post-zygomatic mutations in the RAF/RAS/MAPK pathway.

Clinically, the differential diagnosis for early NS (which presents as a solitary light brown macule or patch) includes a cafe-au-lait macule, Becker pigmented hairy nevus, agminated lentigines, congenital nevus, and other lentigines. Twenty percent of the general population can have a solitary cafe-au-lait macule, but these will consistently lack the hyperpigmented macules and papules seen in NS. Multiple cafe-au-lait macules should raise suspicion for neurofibromatosis and a cafe-au-lait macule with irregular borders may be seen in the McCune-Albright syndrome. A Becker pigmented hairy nevus may be challenging to differentiate from NS, and may not be evident until the classic hypertrichosis becomes evident in later years.

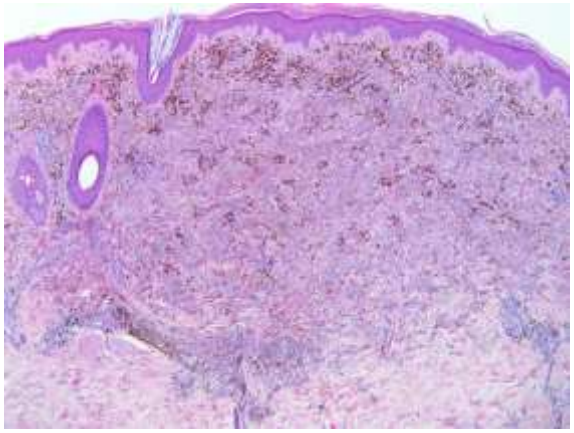
Perhaps the most challenging to differentiate clinically from NS are agminated lentigines. These lesions are defined as numerous lentigines (small pigmented macules with sharp circumscribed borders), geographically arranged either in a dermatomal distribution, a checkerboard pattern, or a midline cluster pattern, and can be uni- or bilateral. They are ultimately distinguished by having a background of normal skin, as opposed to the hyperpigmented light brown background patch seen in NS. As NS lesions develop their characteristic “speckles,” there are very few pigmented lesions that can mimic their clinical appearance.

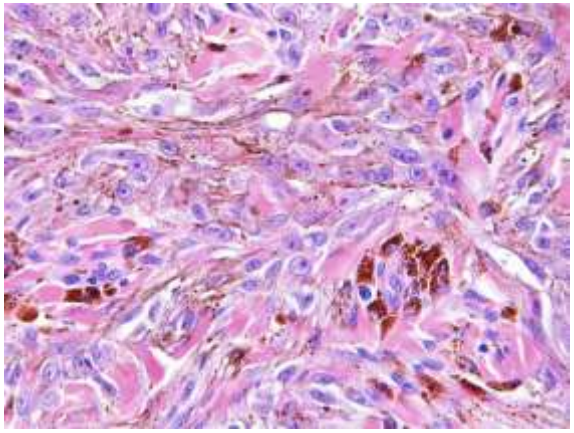
Case 237

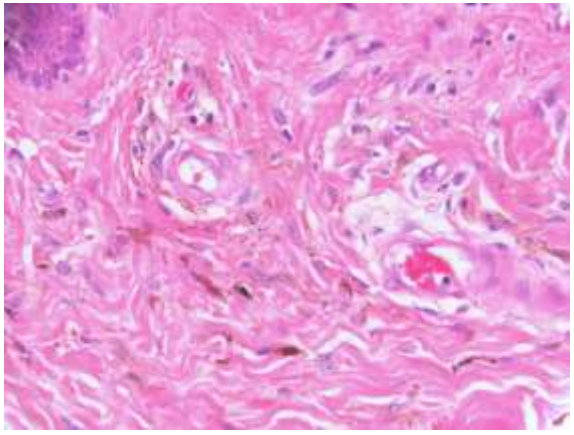
# Case Summary

- Blue nodule developed in a plaque type blue naevus – clinically naevus Spilus (characterised by S100-/MelanA+++)
- Relatively good agreement for a low risk uncertain lesion between EQA and Slide Club Experts
- Relatively novel genetics clustering with CYSLTR2 (blue) group

PRKCSH:NM_001001329:exon7:c.C529T:p.R177W
MITF:NM_000248:exon9:c.T892C:p.S298P
PLCB4:NM_000933:exon1:c.G61A:p.A21T







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