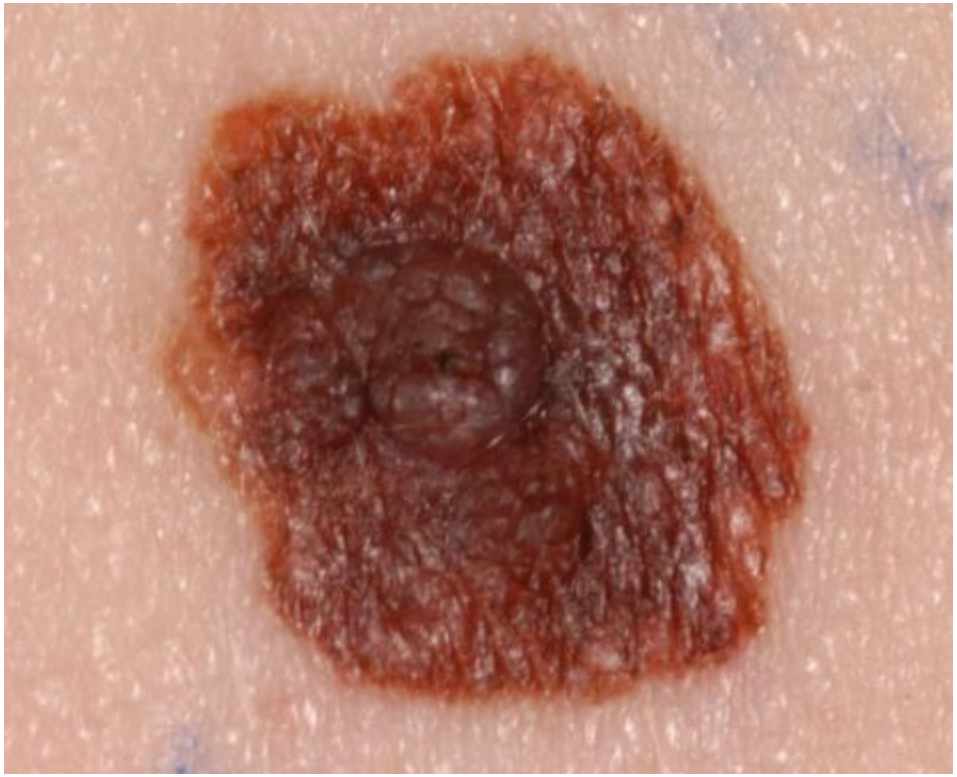
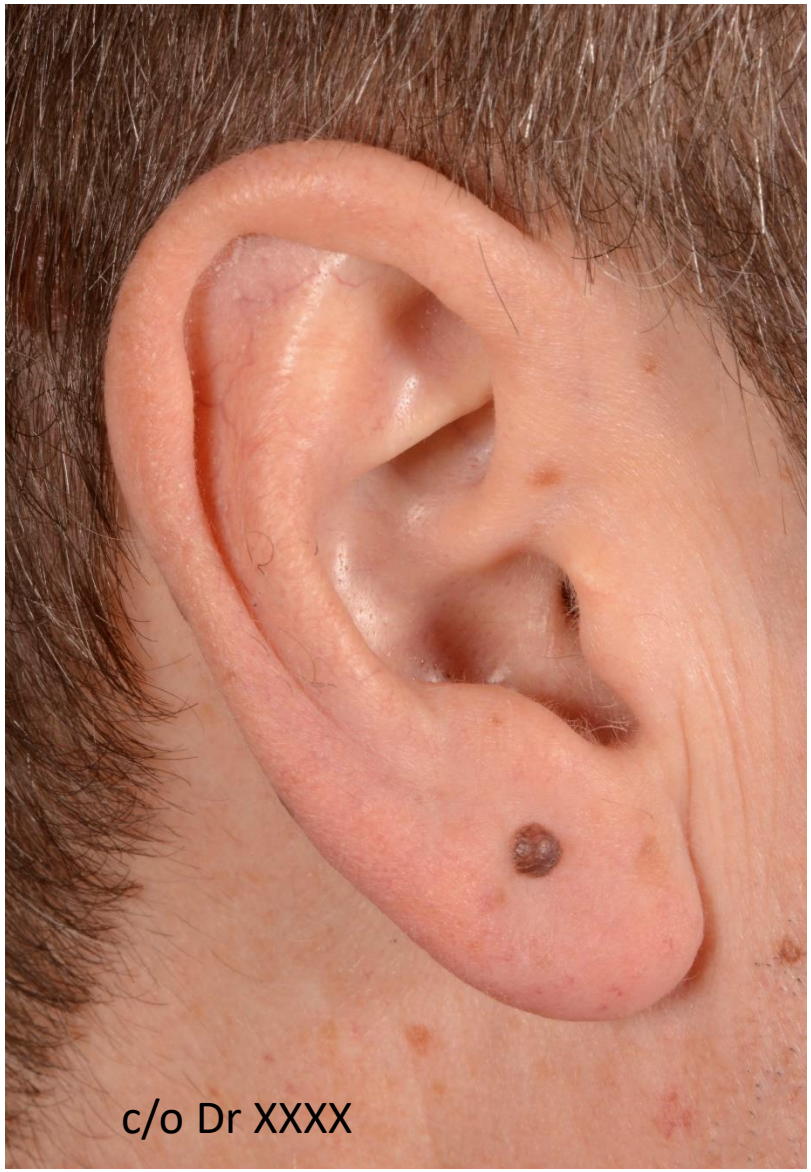
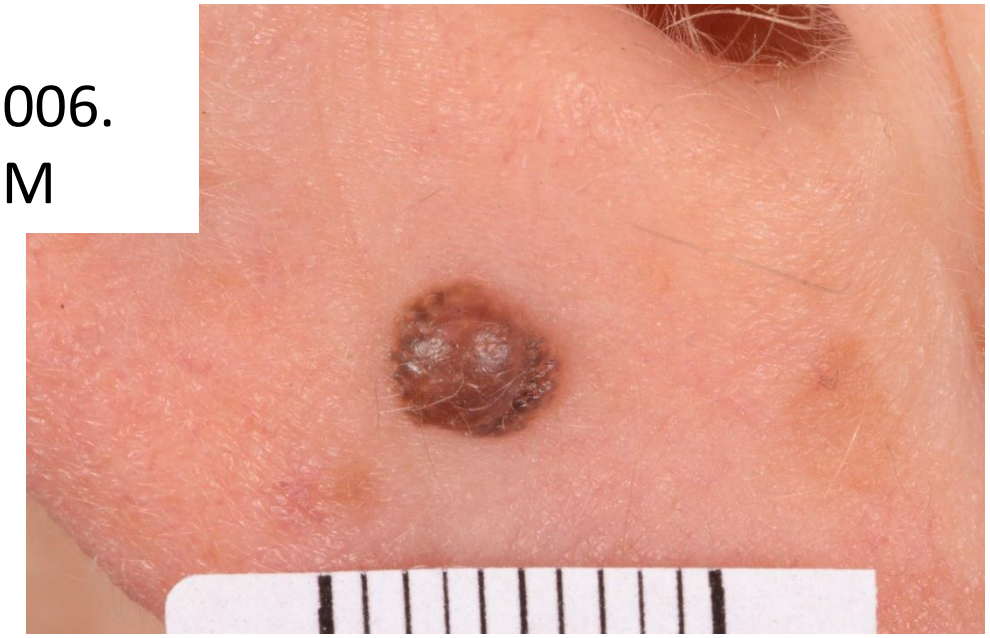
Case 238

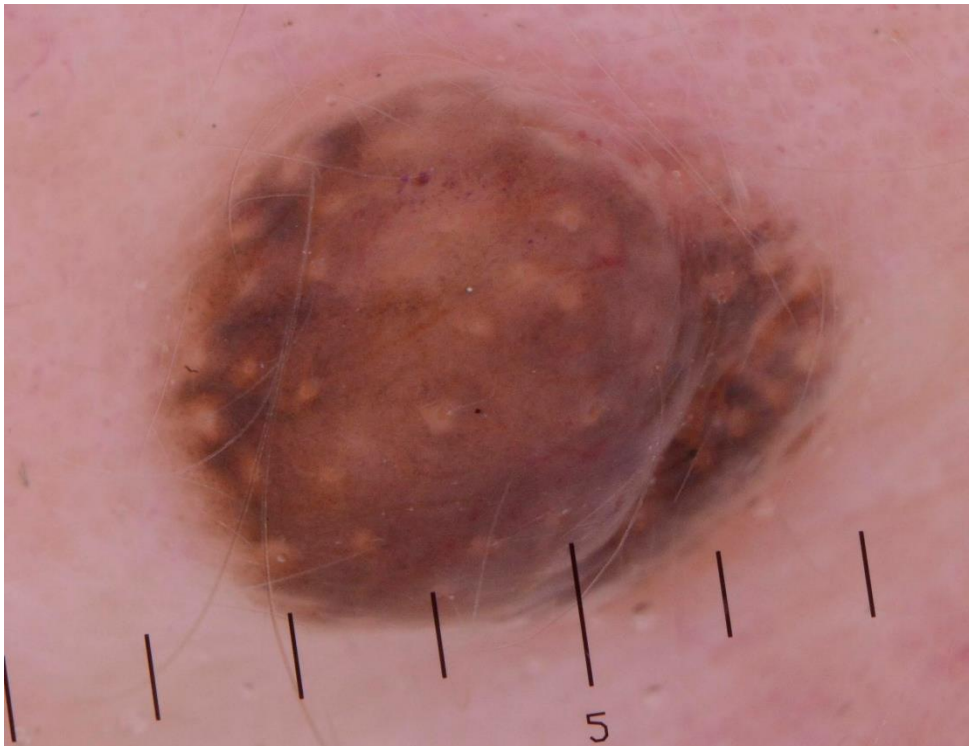
This lesion was previously diagnosed as a melanoma in 2006 (histology not available)



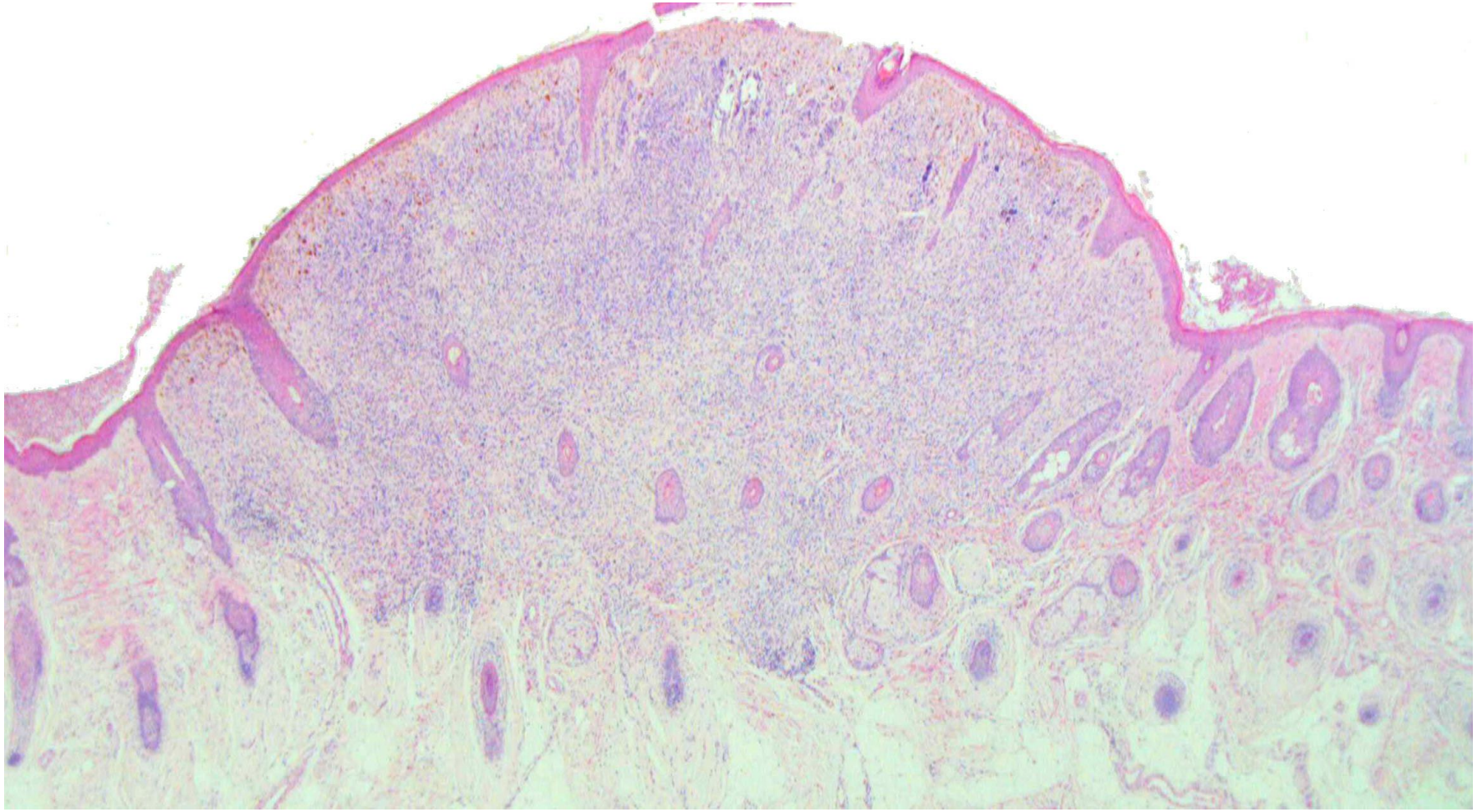
Case 238: M47. Previous h/o MM.
Breslow 1.2mm on right shoulder 2006.
Pigmented lesion right ear lobe ?MM





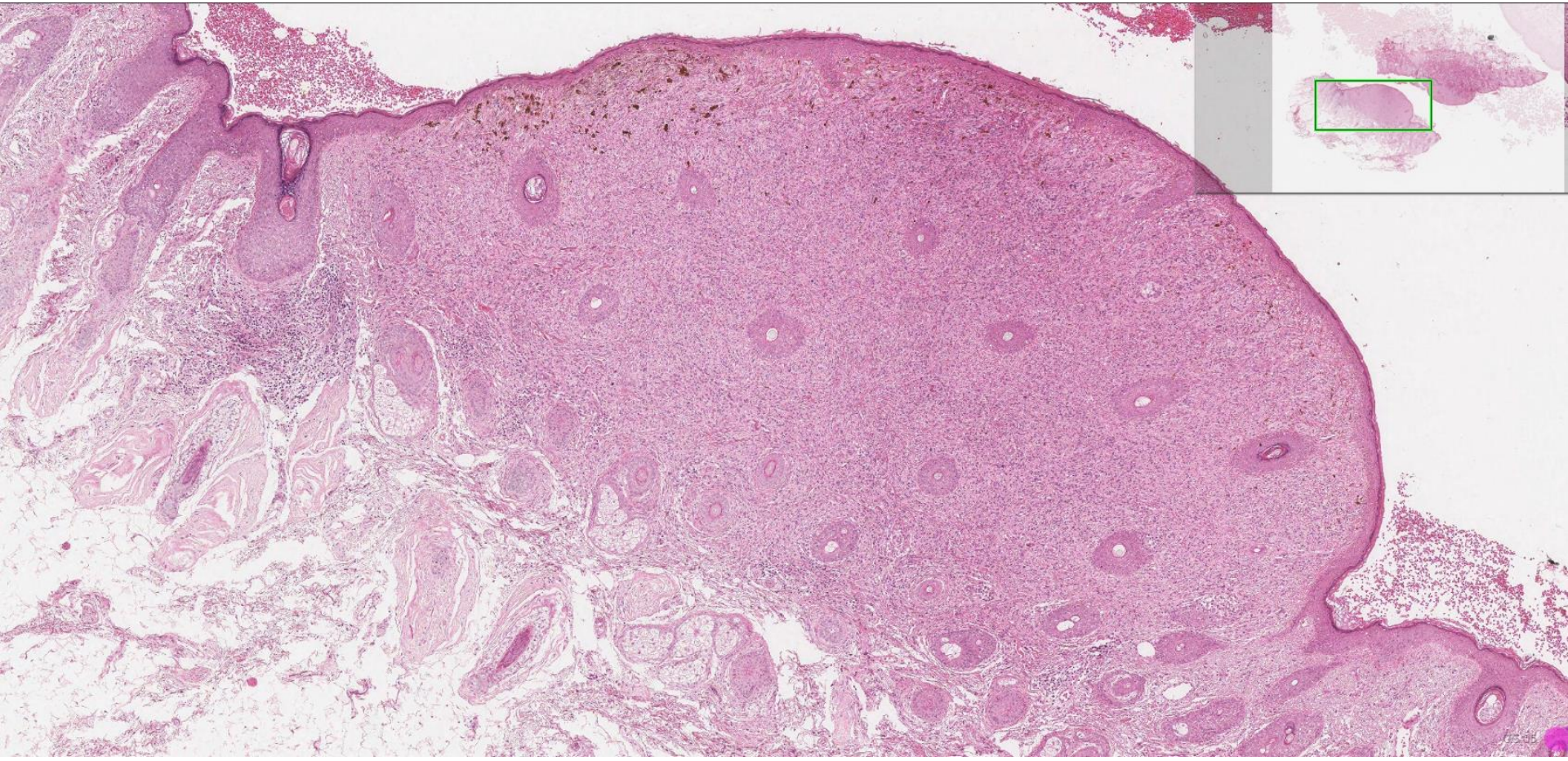


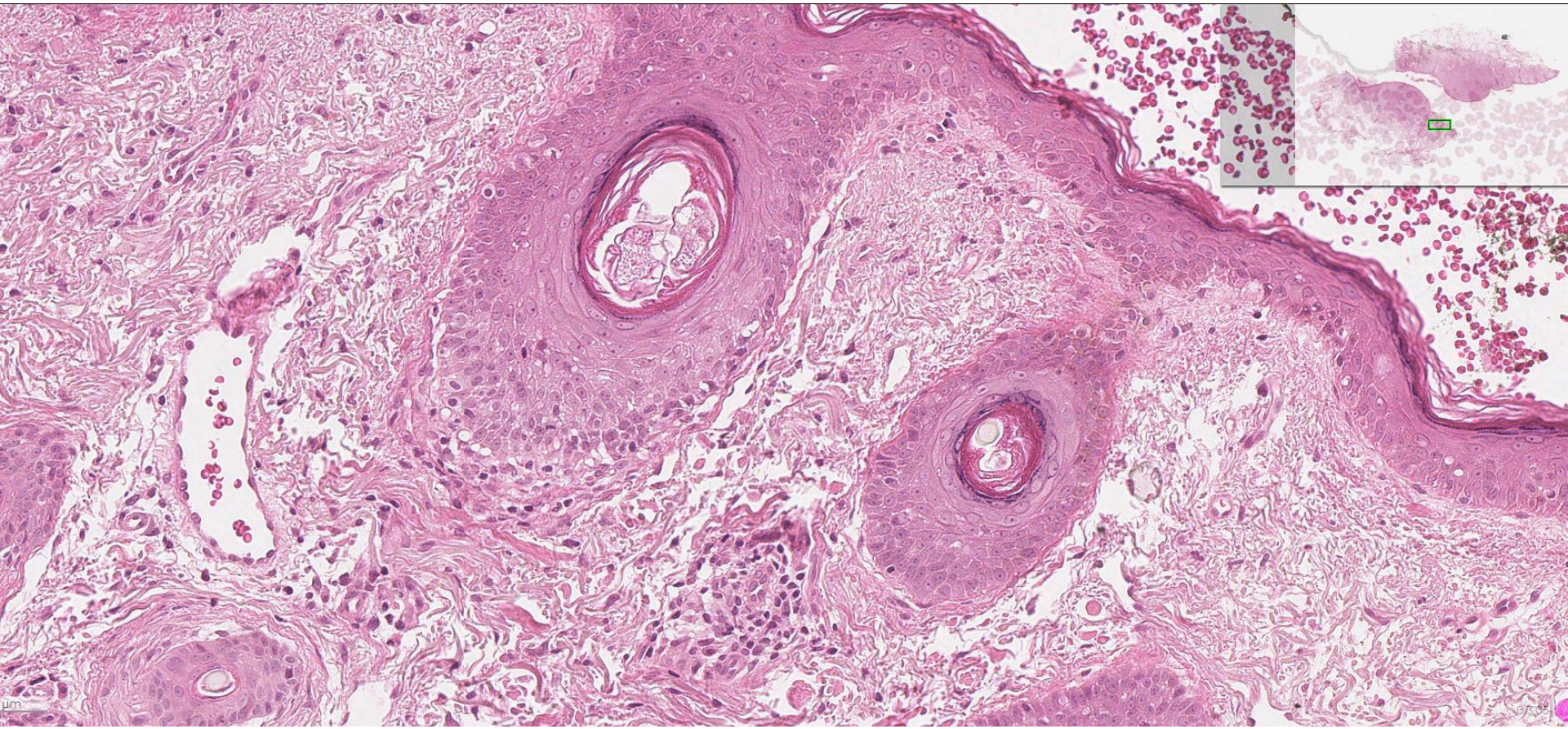
M47. Previous h/o MM. Breslow 1.2mm on right shoulder 2006.
Pigmented lesion right ear lobe ?MM



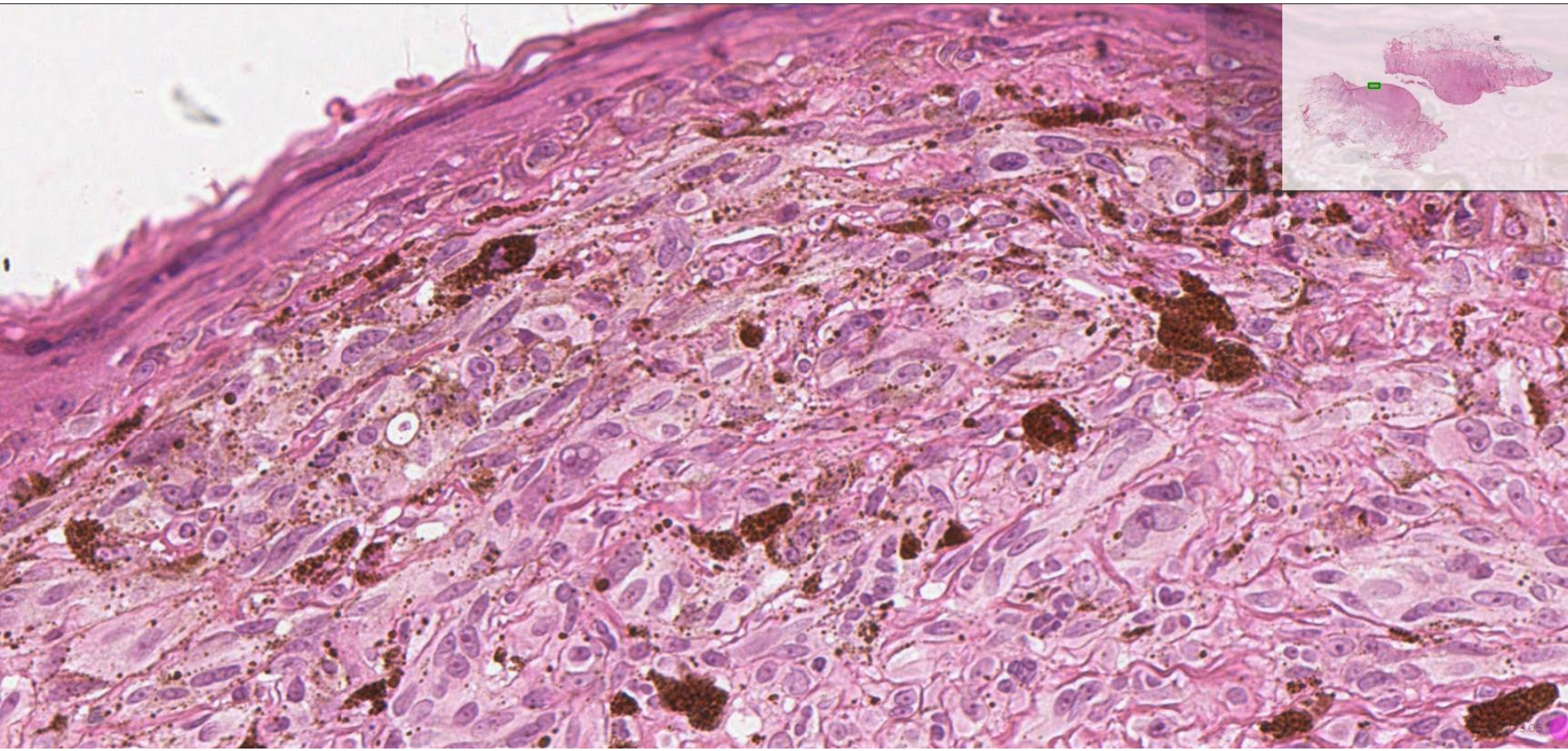
Go to digital scanned slides

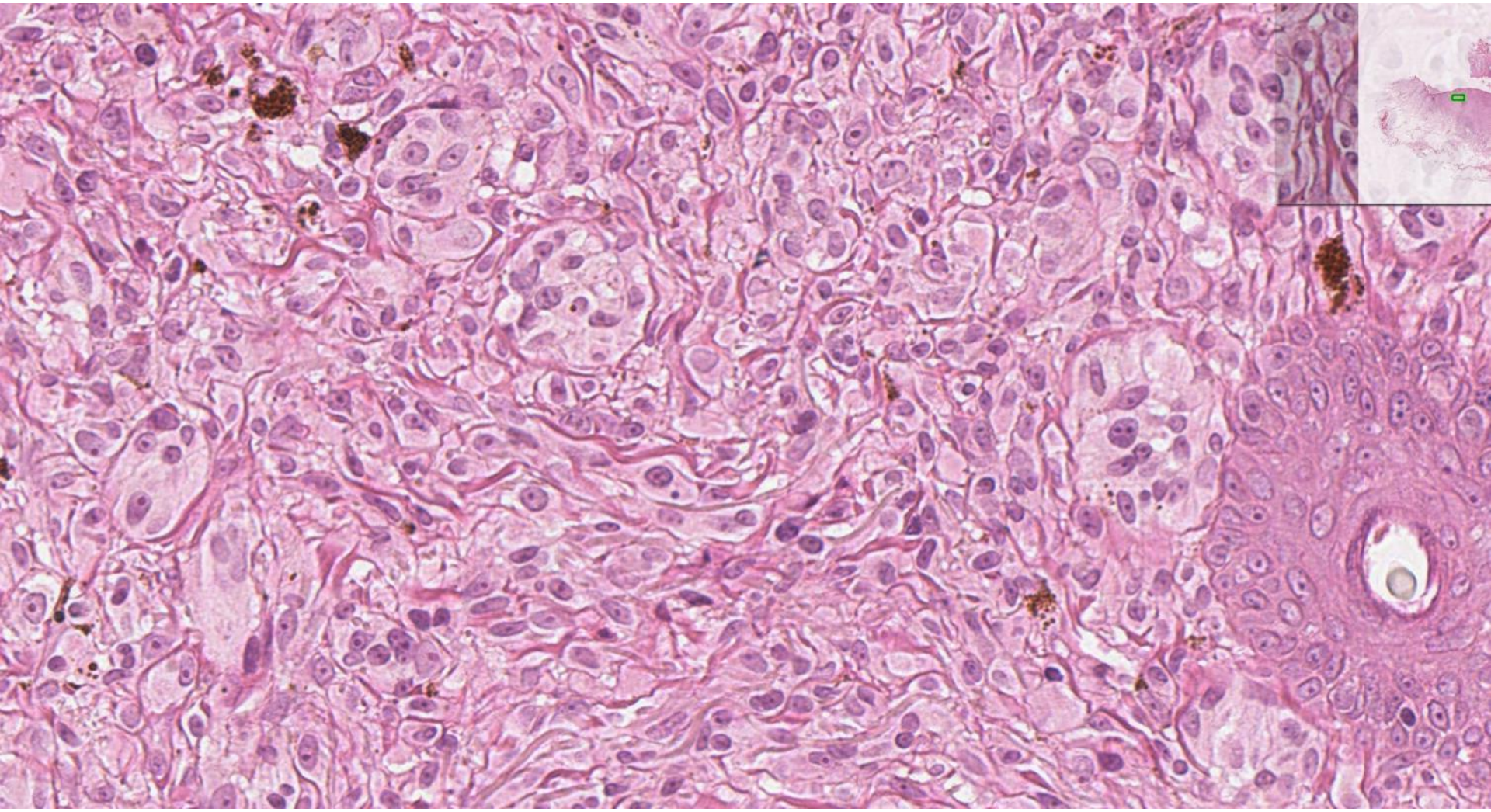
c/o Dr XXXX

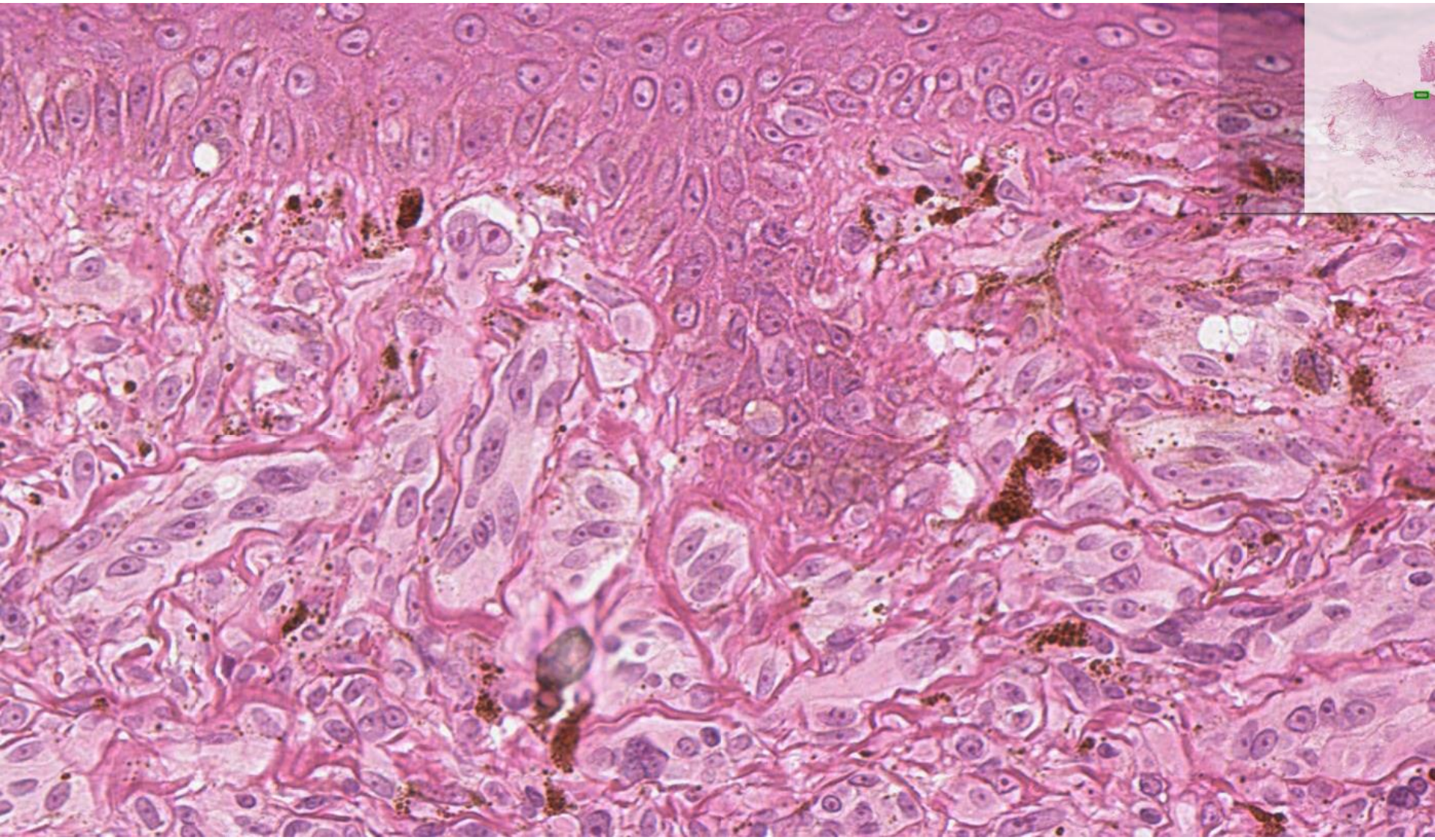




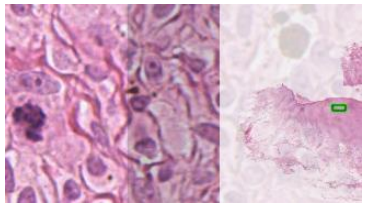
Mild solar elastosis

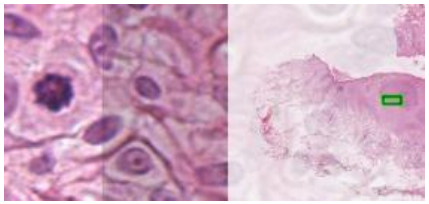


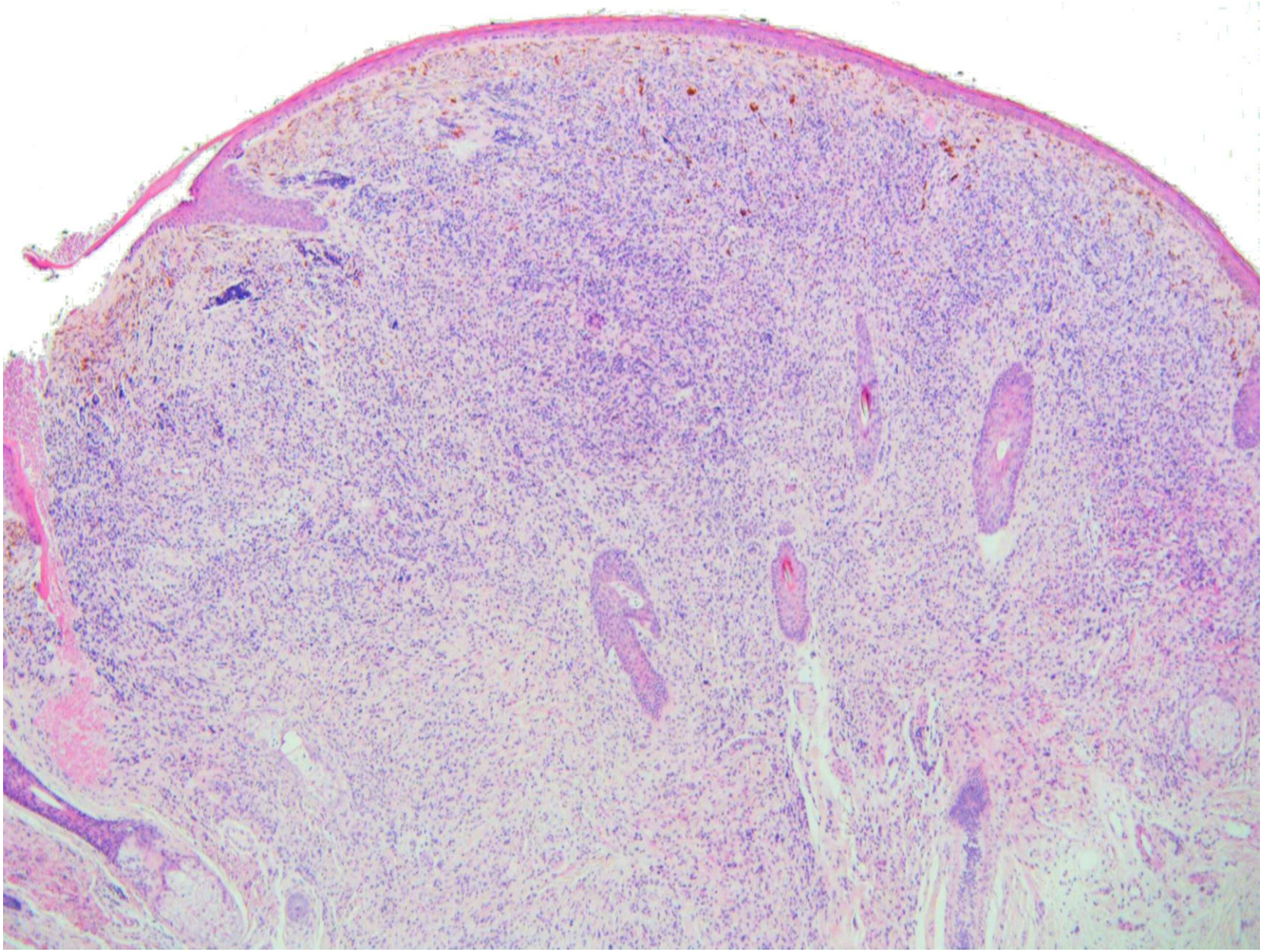


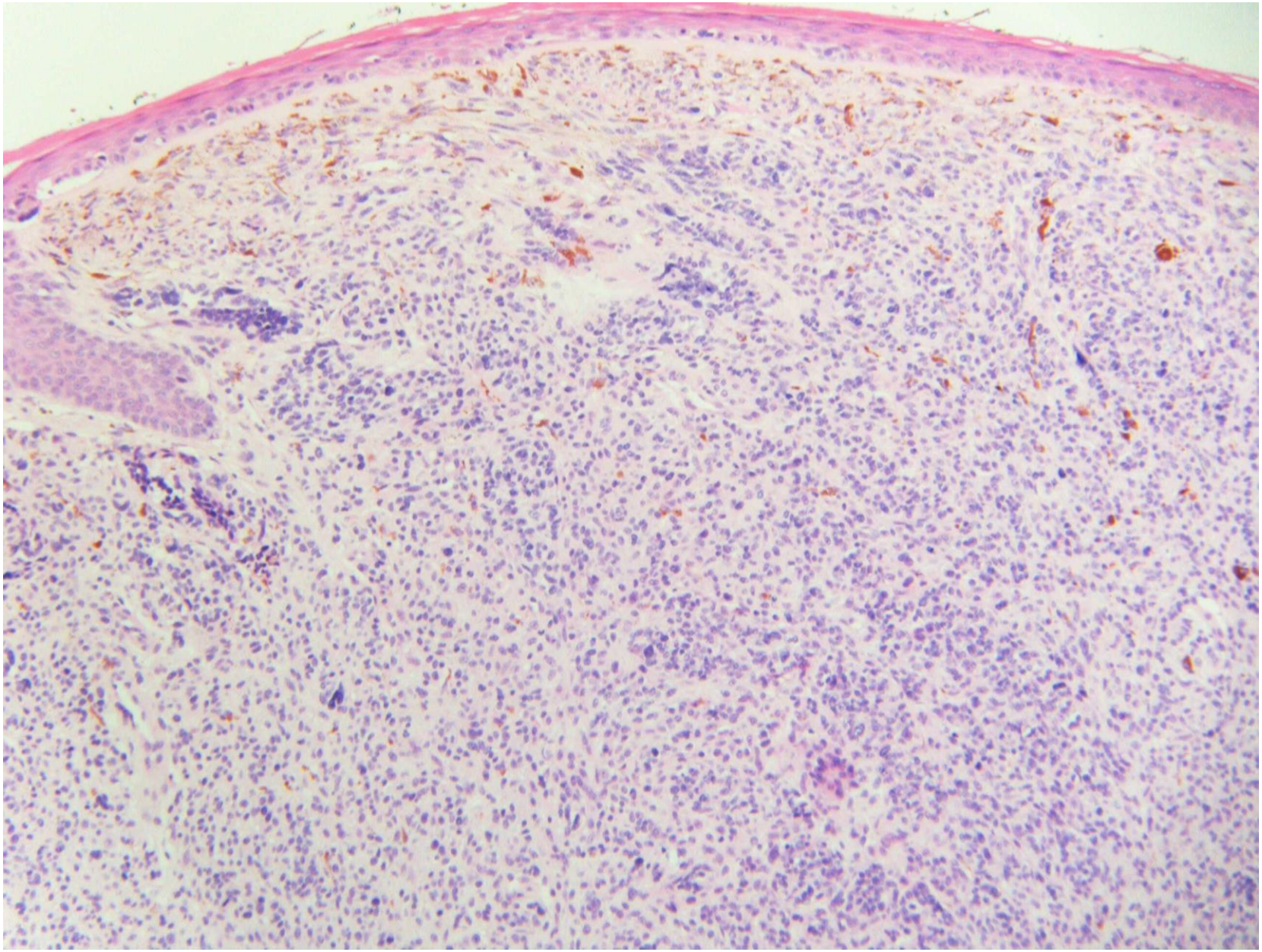


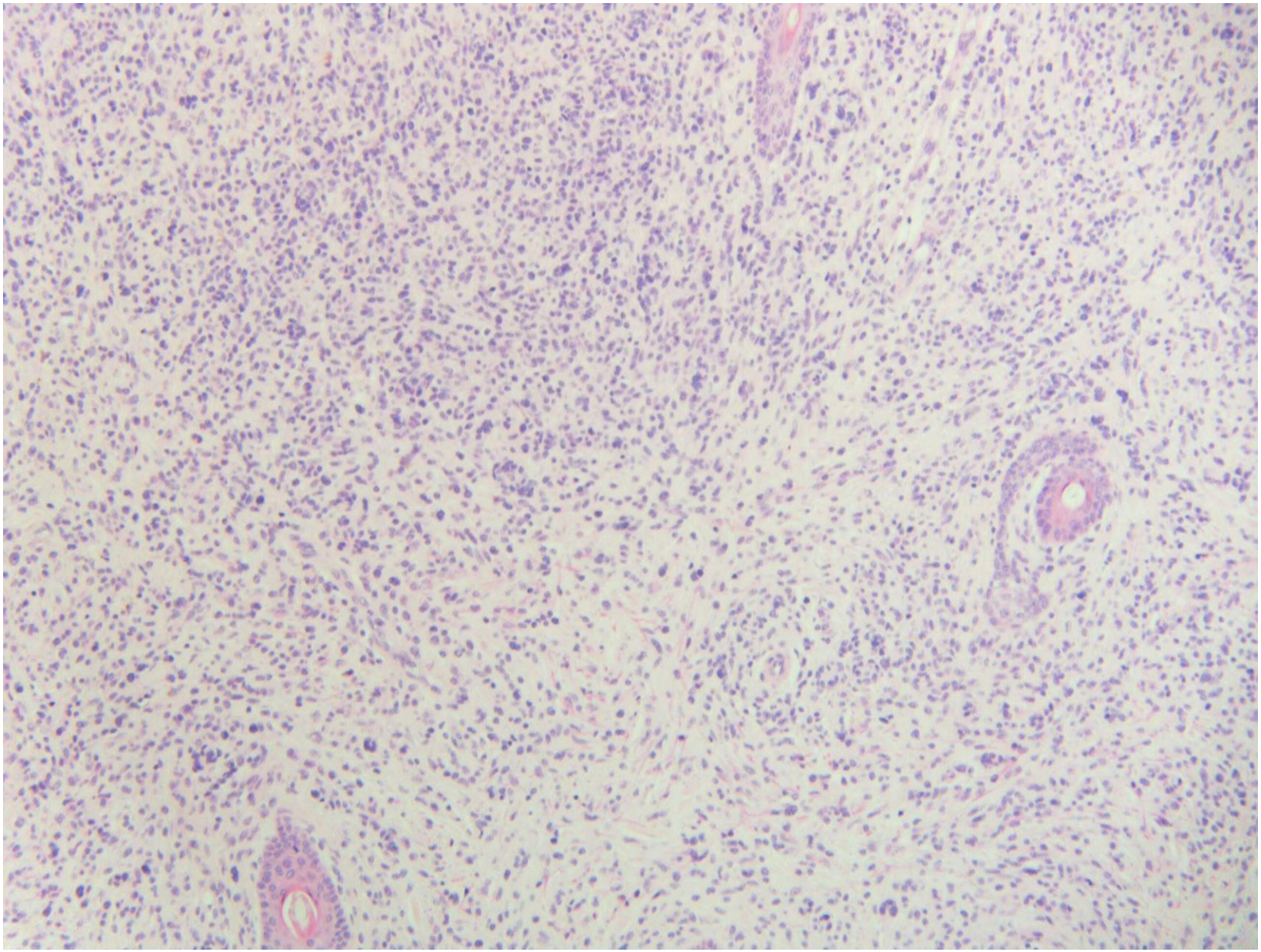
Mitoses were present in the scanned slides…

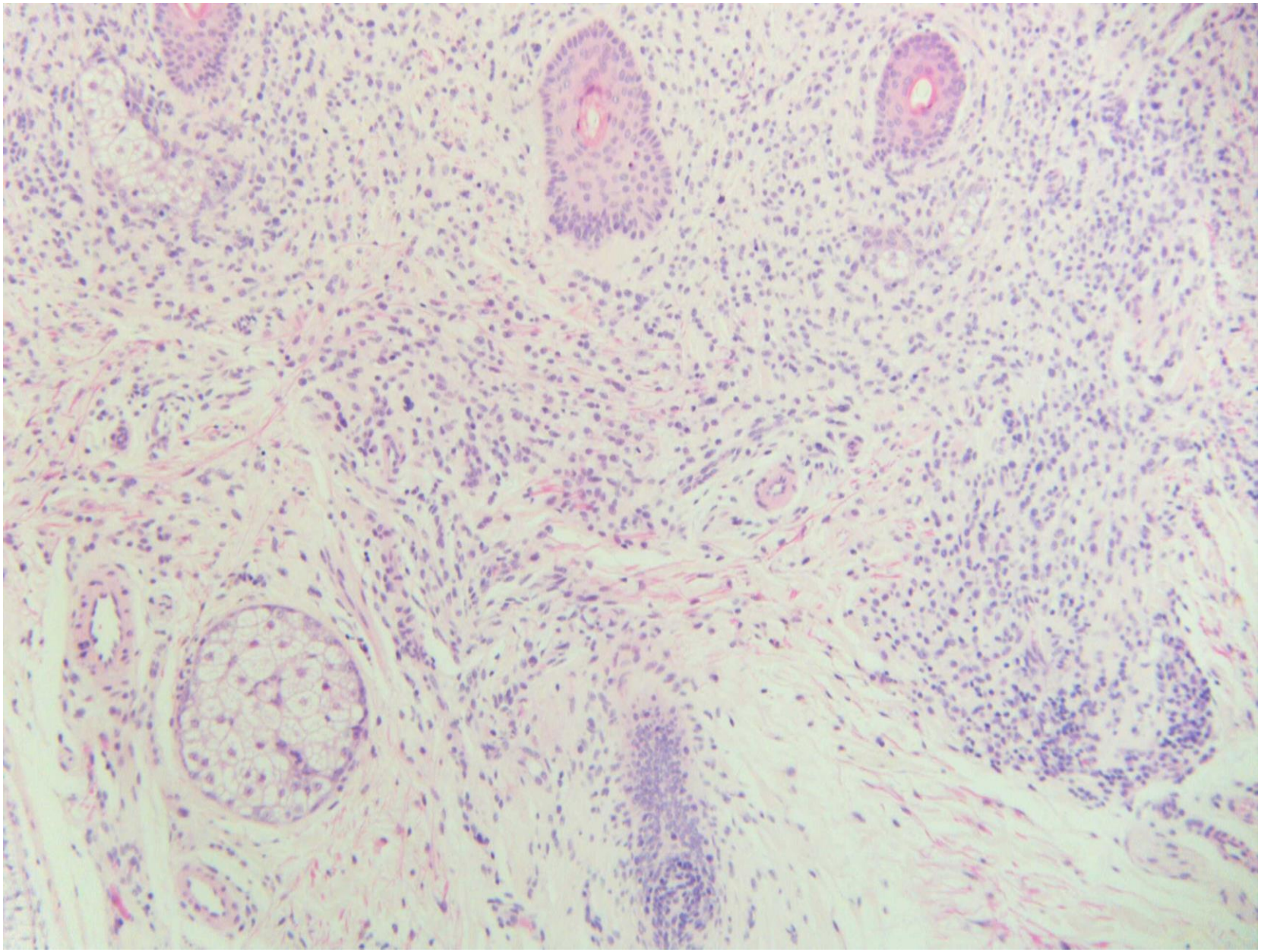


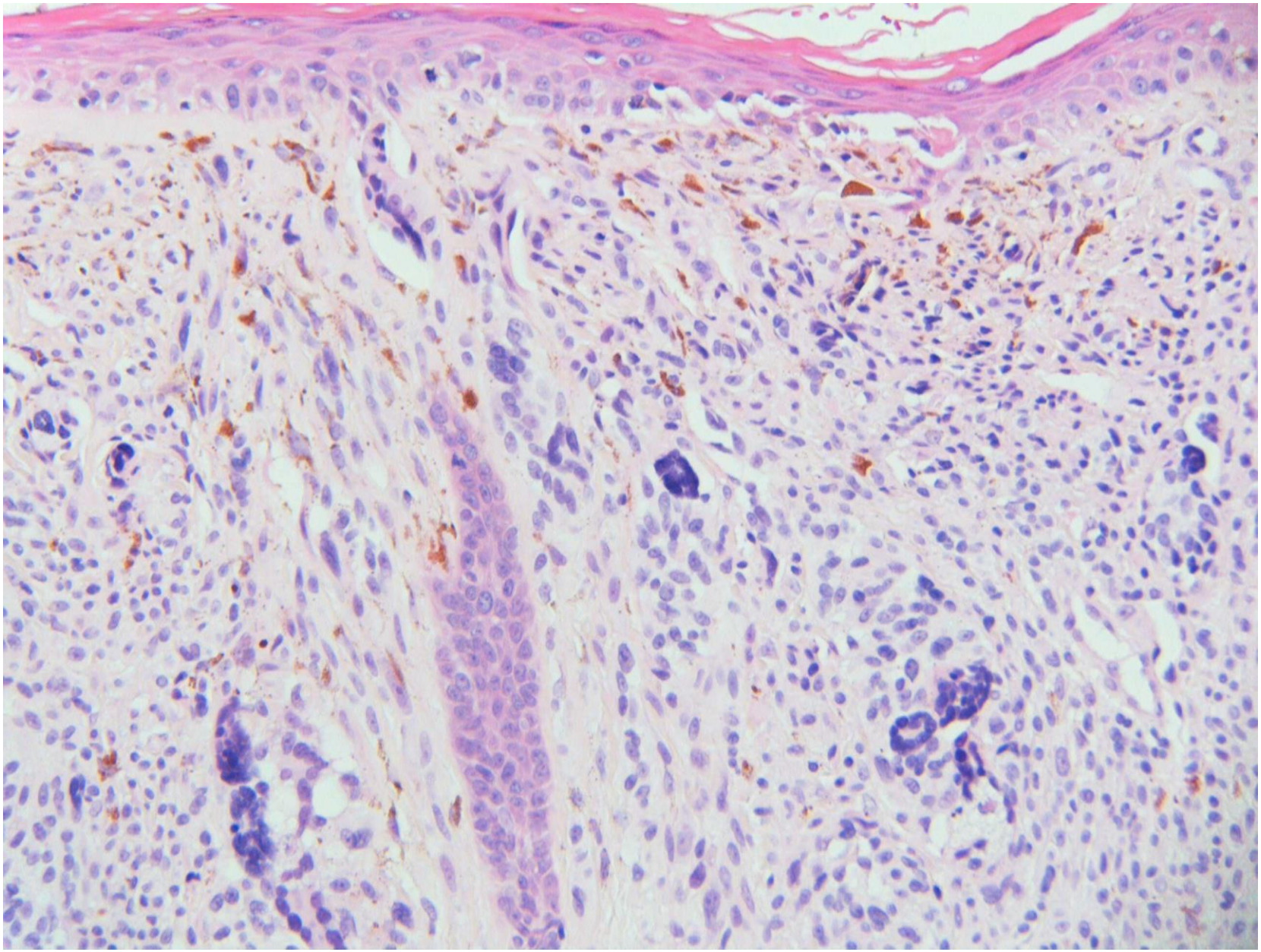


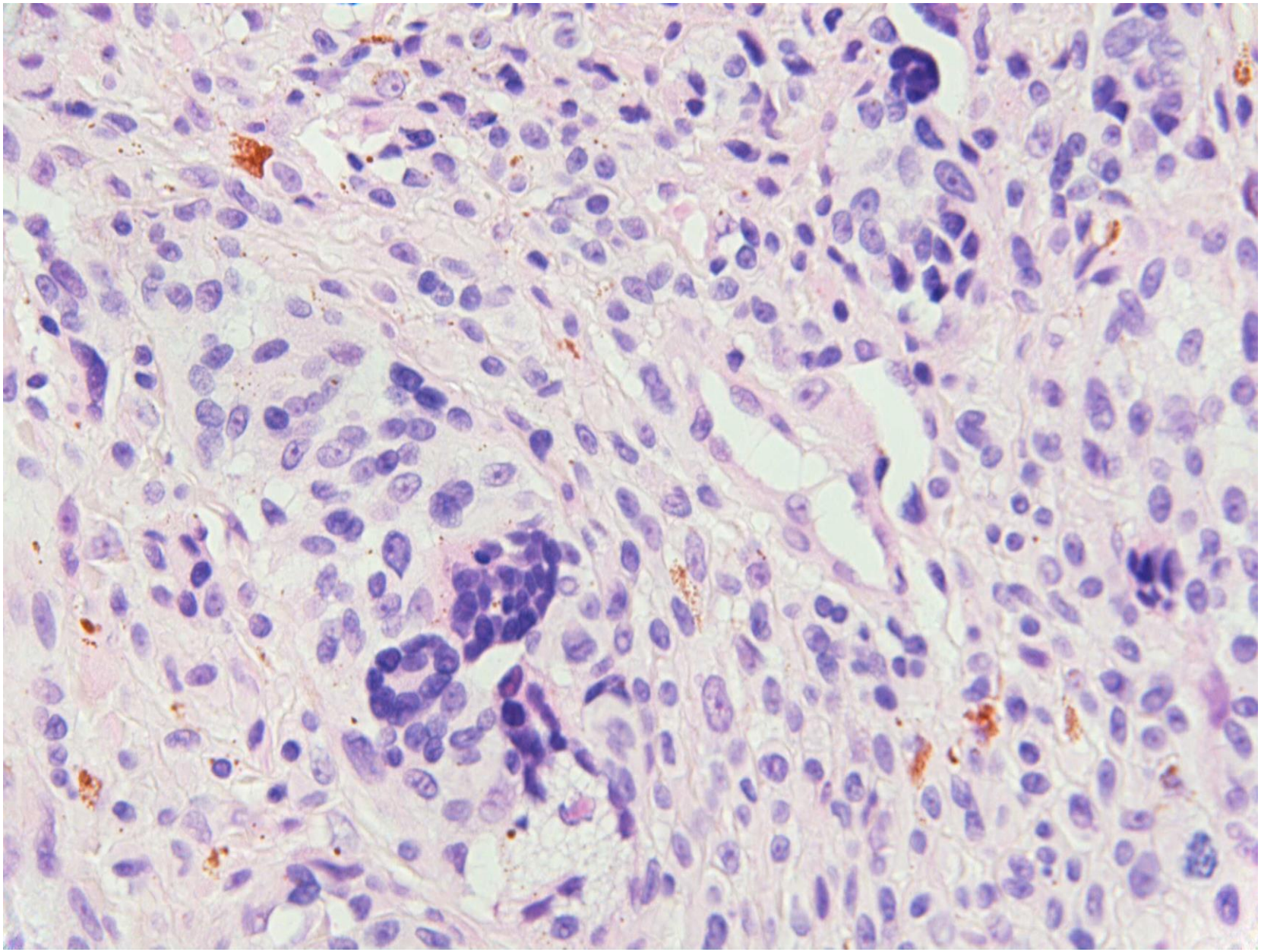


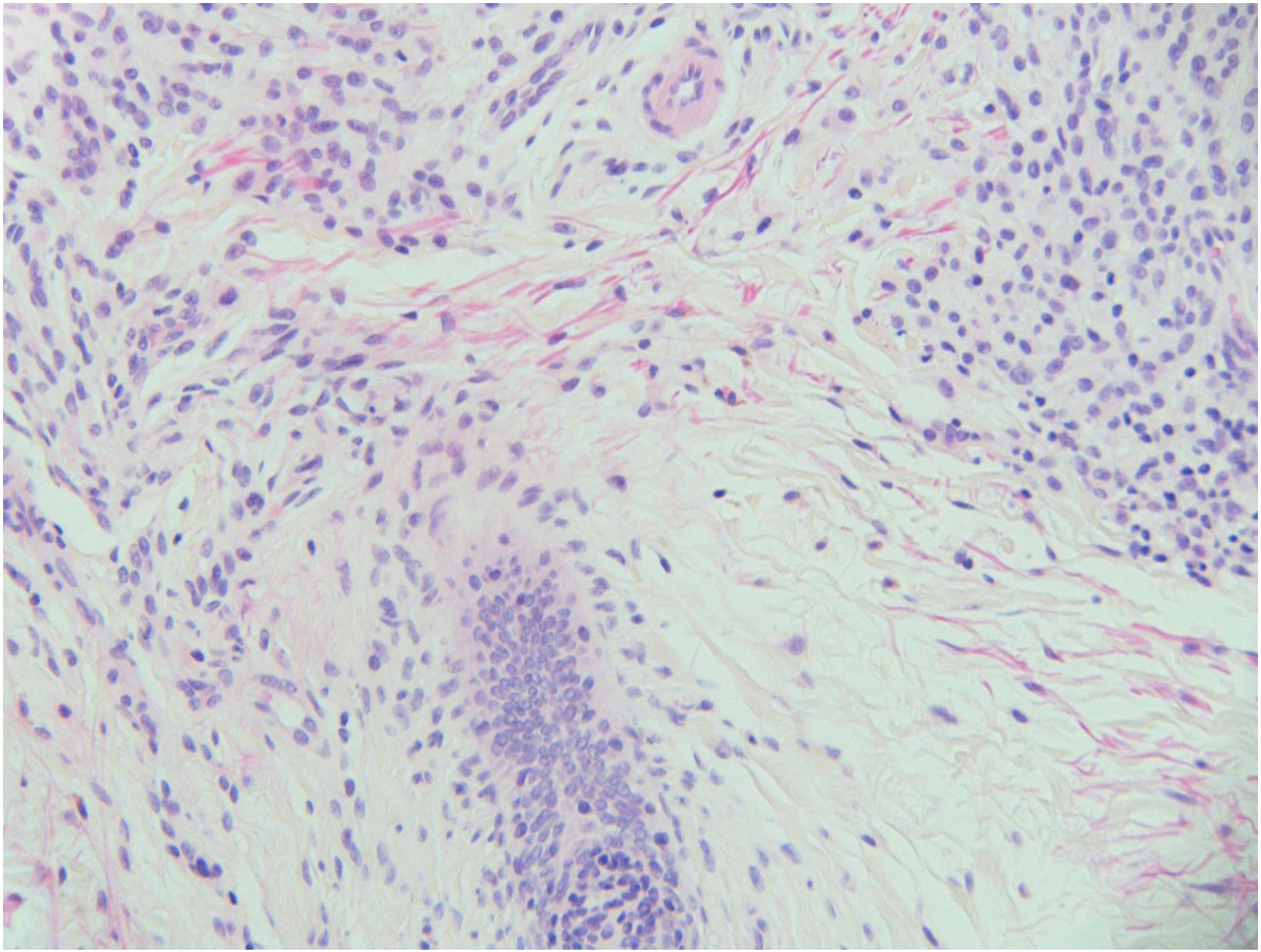


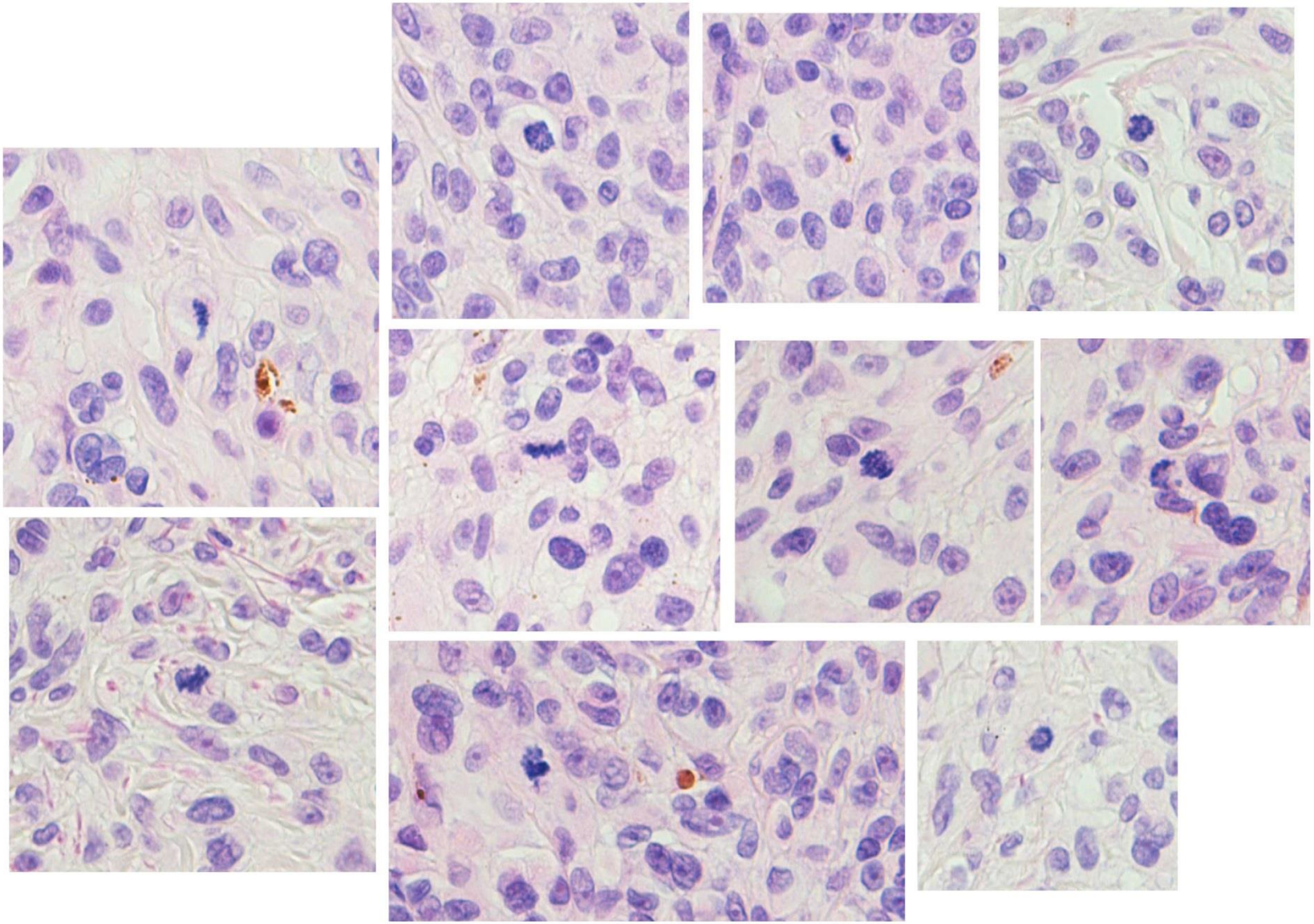






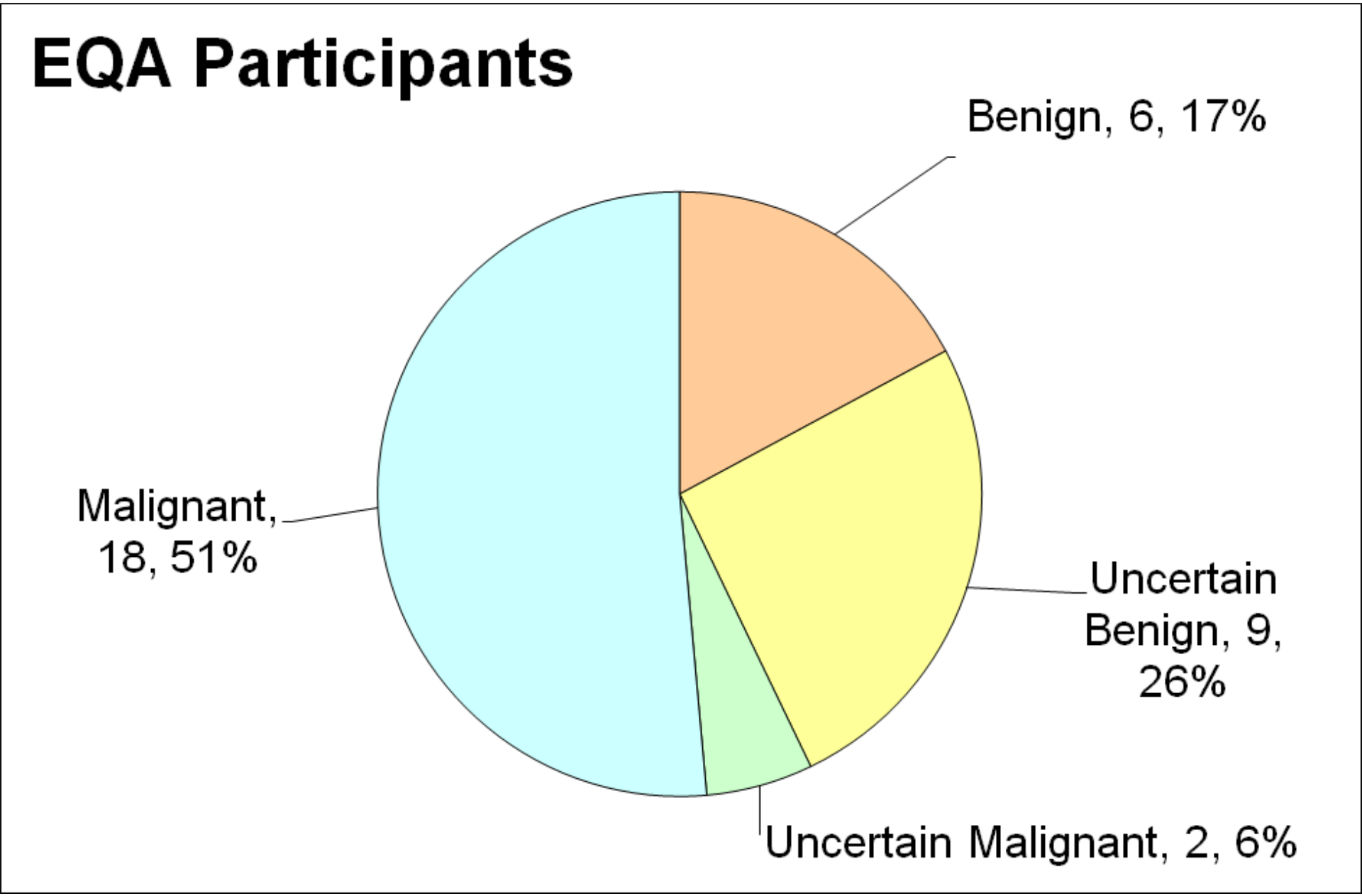






12 mitoses in 12mm^2 but pretty sure no-one saw them all on digital slide!

N=36


EQA Participants
Benign, 6, 17%
Malignant, 18, 51%
Uncertain Benign, 9, 26%
Uncertain Malignant, 2, 6%

Summary EQA Participant Responses

Benign:		6
	BAP?	4
	Spitz n.	3
	Benign unclassifiable	3
	Blue n.	2
	Compound n.; IDN; Clonal n.	1 each
Uncertain favour benign		8
Uncertain favour malignant		2
Malignant		18
	Nodular	14
	Metastasis	3
	Naevoid	2
	Spitzoid	2
	LMM, Malignant blue,	1 each

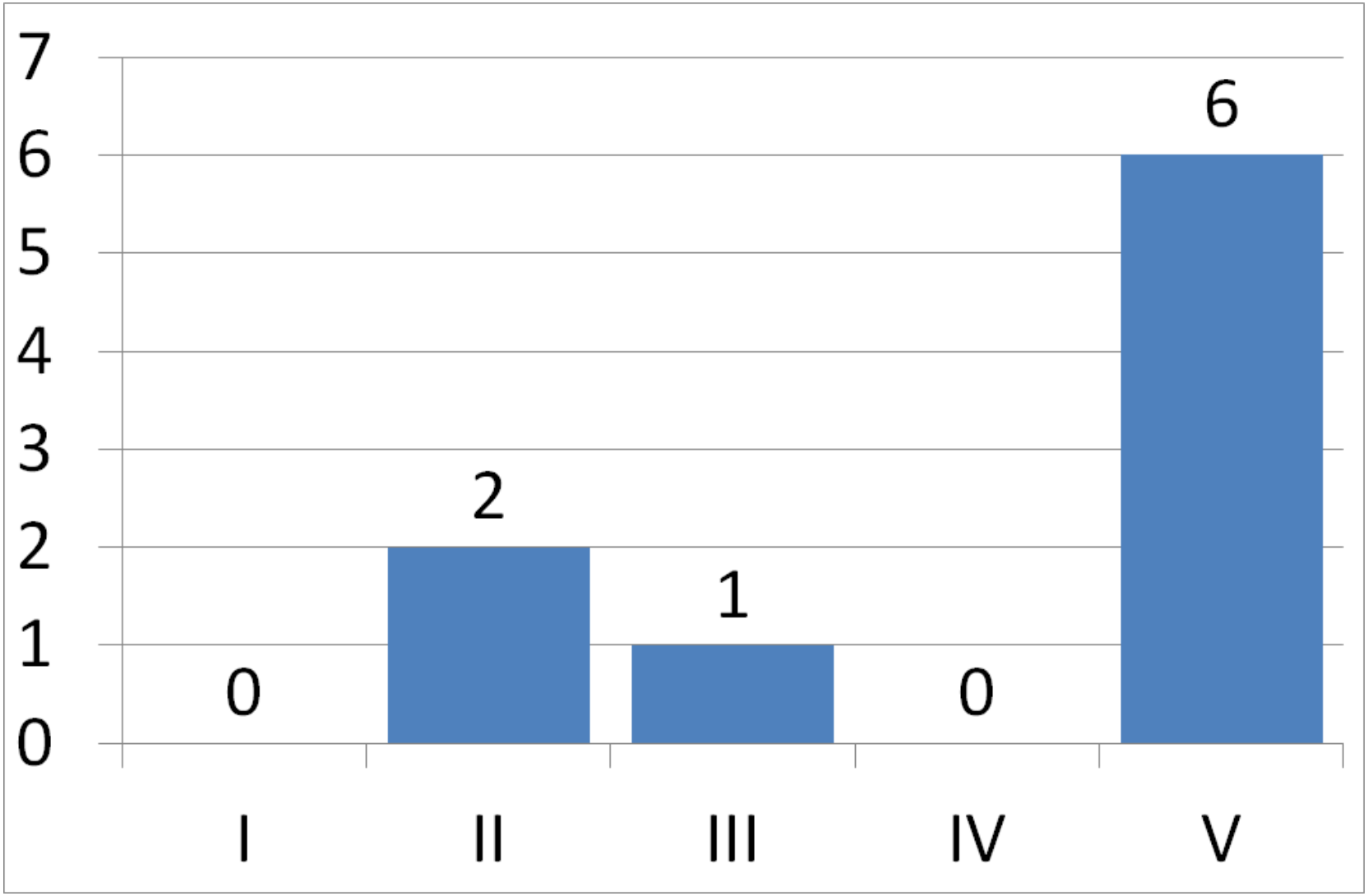
Malignant Responses: Parameter Summary

EQA Participants					
Clark Level	1	2	3	4	5
	0	0	0	16	1
Breslow	Min	Max	Mean	Median	
	1.5	3.5	2.24	2.0	
Growth Phase	R	V			
	0	17			
Regression	N	Y			
	17	0			
Mitotic Rate	Absent	Low	High		
	2	16	0		

Notes:
A few managed to give a Breslow on the digital slide but variation was wide.
Several commented they could not do a mitotic count.

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=6

a mostly intradermal (compound) and almost symmetrical melanocytic lesion with epidermal hyperplasia. Scanty junctional component of few elongated cell nests and lentiginous epithelioid melanocytes; no pagetoid or contiguous growth. Dermal melanocytes are epithelioid to spindled forming sheets and packets around skin adnexa; and have maturation changes; and lack high grade atypia orevident mitotic activity. Overall, in keeping with **Spitz naevus**.

Epithelioid Spitz naevus

Symplastic compound naevus.

Mid dermal mitosis noted. dDx: Spitz and ('special') site specific naevus.

EQA Participants: Uncertain favour benign

N=8

Atypical epithelioid melanocytic nevus, ? BAP1-deficient

symmetrical, no junctional activity, moderate atypia, mid dermal mitosis, uneven maturation **? BAP-inactivated melanocytic tumour**

despite an occasional mitosis, favour benign - **?BAP1 inactivated naevus /spitzoid variant**

This melanocytic lesion is mostly composed of dermal epithelioid melanocytes with abundant glassy cytoplasm, well-demarcated cytoplasmic border, moderately enlarged nuclei with prominent nucleoli and occasional nuclear pseudo-inclusions. Occasional mid-dermis mitotic figures are present. There appears to be a **nevocellular naevus component** at the periphery of one of the pieces. **BAP-1 inactivated naevus/melanocytoma**?

EQA Participants: Uncertain favour malignant

N=2

No comments made

EQA Participants: Malignant

N=18

This looks like a new primary than a metastasis; possible arising on a background of a pre-excisting naevus.

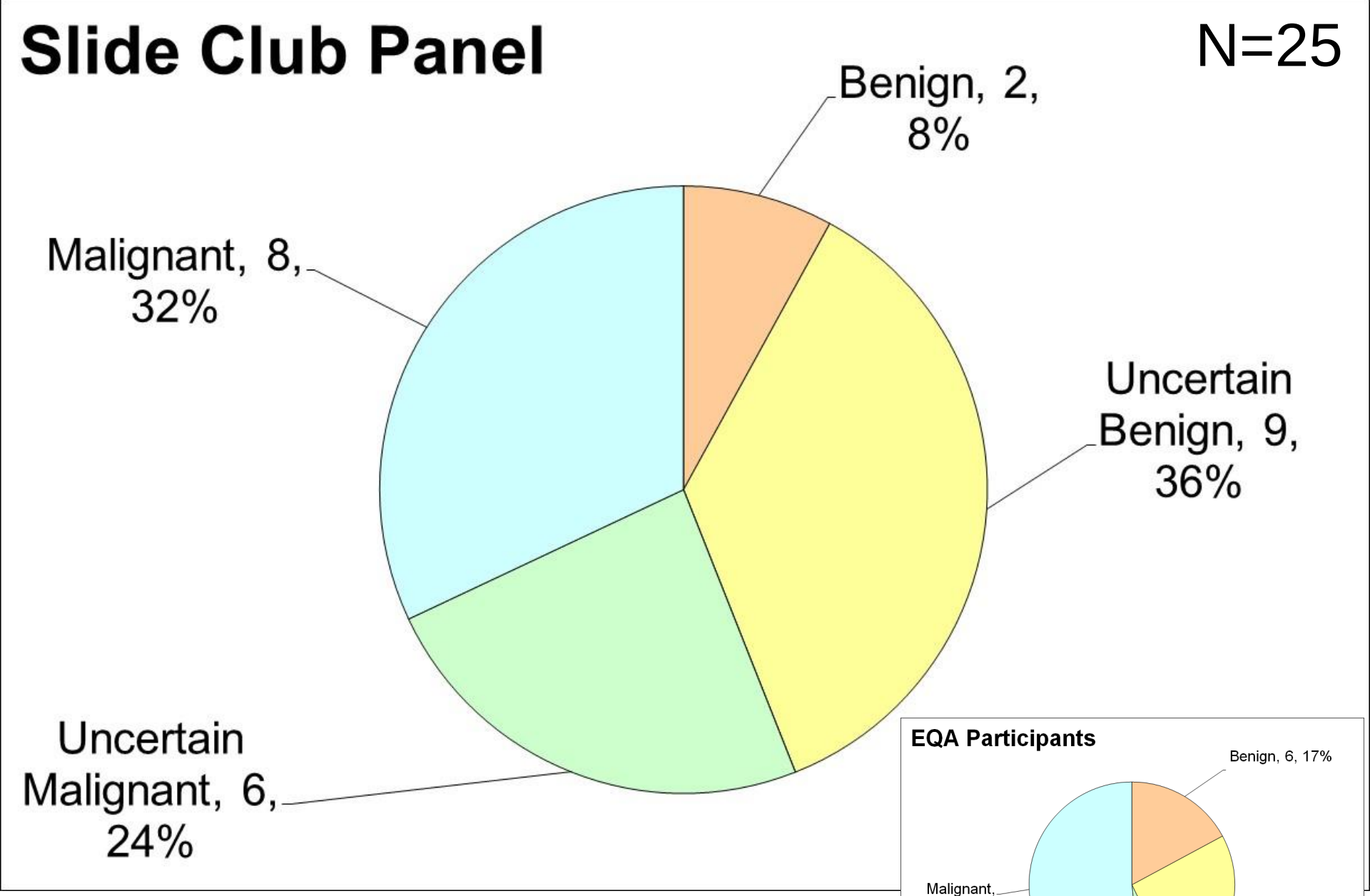
Considered Spitzoid melanoma.

Difficult on screen. Minimal junctional component but malignant cytology/growth patttern. Low/absent mitoses. Differential includes metastatic melanoma to the ear.

Difficult case…nodular melanoma v metastatic deposit. .. pagetoid spread into the overlying epidermis and dermal appendage epithelium...focal non-malignant melanocytes, reminiscent of naevus. **Favour metastatic melanoma**, no clear-cut epidermal component. Also, history is compatible.

Slide Club Panel

N=25



SLIDE CLUB RESPONSES

- [Malignant] I would ask for BAP1 in this lesion as I think it could be a **BAPOMA**
- [Favour malignant] Atypical compound spindle and epithelioid spitz-like melanocytic neoplasm with asymmetry, dermal nodular growth, ~ 3 mm diameter, thickness 2.2 mm, mitotic rate 2 per mm2, significant atypia, solar elastosis, ? precursor lesion, spitz. Must review previous "melanoma" for confirmation and comparison. DDX: second primary spitz-like melanoma arising in ?Spitz precursor; metastasis; atypical Spitz tumor with uncertain malignant potential. Based on age, solar elastosis, nodular growth, **I favor primary melanoma**. Based on evaluation of digitized images only, I continue to have some uncertainty about the lesion. Ancillary/molecular testing could help confirm melanoma and its classification.
- [Favour malignant] Hypercellular, mitotically active compound melanocytic proliferation. Although there is some suggestion of cytological maturation towards the deep aspect, I think the apearances are highly concerning for a malignant melanoma, particularly a naevoid melanoma. I note the past history of melanoma and the possibility of an unusual metastasis cannot be ruled out definitively. To start with, an immunohistochemical work up using proliferation markers like Ki67, P16 and PRAME could be used to support a diagnosis of malignancy.

SLIDE CLUB RESPONSES

- I would think of BAP1 inactivated melanocytic nevus-tumor/clone. I do not see mitoses. More pigment than usual and junctional component. BAP1 staining? Previous lesion melanoma? Both cases do not appear clear-cut malignant to me.
- **[Favour Benign]** I **favour a mitotically active naevus** (predictably as I'm "benign").
- *More anon*

SLIDE CLUB RESPONSES

- [Malignant] This looks spitzoid with expansile solid dermal growth, plemorphism and mitotic activity. I would regard this an **invasive spitzoid melanoma**. There is a junctional component but in view of previous history of invasive MM would be prudent to consider metastasis and review the previous melanoma to see if it shows similar morphology. Appears to be a small banal dermal naevus as well.
- Seems like a **MM, perhaps on nevus** (but difficult to judge whether few dermal nevoid melanocytes really represent a pre-existing nevus.
- *After feedback: Thanks - am curious to know what Arnaud says about molecular, to me location + atypia (and high cellularity) very suspicious for MM; I had spot a few mitoses by far though not 12 (together with age, location and atypia almost diagnostic...). If 12 that seals the diagnosis...*
- Pre-existing melanoma is just enough.The lesion shows slight epidermal hyperplasia with spitzoid cells and Kamino bodies. Dermal cohesive proliferation of spitzoid cells sparing adenexal structure. Deep maturation with infiltrative growth. Rare mitoses. In sum: **Atypical Spitz Tumor**. I would be surprised of an aggressive behaviour.
- Balloon cell naevus

SLIDE CLUB RESPONSES

- Demographically and morphologically **concerning for melanoma**, but very Sptzoid and difficult to identify mitoses. Would do available immunostains - MelanA/Mart, HMB45, Ki-67, p16, PRAME BRAFV600E, depending on results would possibly send out for CGH iFISH or GEP in effort at more difinitive diagnosis, would manage with complete excision.
- This portion of skin incorporates a compound and focally polypoid melanocytic tumour There is no epidermal thinning or ulceration. The dermal component is alarmingly cellular comprising epithelioid to focally more spindled melanocytes . I have located an occasional mitosis as far as the mid part of the tumour. There is incomplete basal maturation. On the basis of the cytomorphology my preference is for a compound **Spitz tumour** but on the basis of the cellularity with incomplete maturation and an occasional mitosis I would consider this to be atypical (**of uncertain potential**). In one area there is evidence of usual type naevus so given this combination of features I would suggest a BAP1 immunostain to determine if this is a bapoma. I don't feel that this lesion is likely to be related to the previous melanoma.

SLIDE CLUB RESPONSES

Very difficult. The bulk of my arguments is based on the assumption (to be entirely confirmed) that the sheets of epitheliod cells I see in the dermis are BAP1-inactivated. The 'inclusion-like' quality of the cytoplasms and the presence of a little amount of deep-lateral dermal nevocytic component may be in keeping with my idea. With the unproven asumption that the bulk of the tumour is BAP1-inactivated, this is not an 'ordinary' bapoma, becuase of the presence of compact (not loose) sheets of cells, because of the lack of a 'grenz zone', because of some epidermal/adnexal hyperplasia (these are 'indidderent' to a common BAPoma), because of the presence of a couple of mitotic figures in a single high-power field. Even more atypical is the junctional component, which is associated with asymmetrical pigmentation, epidermal atrophy, and irregular orientation of spindle cells. I don't love the concept of 'progression' (because it does not work on the vast majority of melanocytic tumours) but this case **may represent a banal dermal naevus 'complicated' by the onset of a BAP1-deficient clone, in turn complicated by a BAP1-mutated melanoma** . "I have evaluated case 238 based on the assumption that it is a BAP1 inactivated tumour. If so, it clearly demonstrates that the histopathological features of atypia depicted by the WHO 2018 for BAPomas are completely inadequate. Please find attached a recent manuscript of mine. I had to fight for its acceptance because its basic concept is that the WHO criteria are not as good as one might think. Atypical features of BAPomas are: epidermal 'response', compact sheets of cells, grouped mitotic figures. If your case 238 is BAP1 inactivated it is severely atypical (in the PPT, a screenshot of a HPF with two mitoses) and should be managed as per melanoma."(Attachments: Paper & Presentation)& follow-up discussion

SLIDE CLUB RESPONSES

- Unclassifiable atypical melanocytic tumor favor benign
- **Epithelioid Spitzoid lesion v's Metastatic Deposit**. The histopathological aspects, with epithelioid large cells, some multinucleated reminded me of a **BAP-1 loss epithelioid atypical spitzoid lesion**. Would investigate family history and proceed to BAP-1 immunohistochemistry. Would also examine previous melanoma to see if features are similar to this biopsy.
- Interesting one. At one edge there is a benign naevus and the rest is this slightly epithelioid blandish looling naevoid cells in which I did find a very occasional mitosis. No junctional activity is seen. I feel that this could be a **BAP inactivated naevus** so would definitely request a BAP on this case. Given the history of previous melanoma, and an occasional mitosis in this one, I would be a bit more worried but I am not convinced there are enough features for to call it a melanoma. However it looks like it is completely excised and as the patient has a previous melanoma the patient must be on follow up anyway. Another thing would be to see if the patient has a BAP1 syndrome
- Favour new lesion and do not think this is an epidermotropic metastasis. Has a distinct phenotype (Special site melanoma)

SLIDE CLUB RESPONSES

- The majority of this lesion has an epithelioid component with pale cytoplasm, mild nuclear variability and small prominent nucleoli. Possibly one or 2 mitotic figures. Multinucleation noted superficially. I think there is a junctional component but its difficult to seperate this from the superficial dermal component on the digital slides. There are some cells extending into the lower epidermal layers. Basic stains to assess architecure would be useful. There is a smaller component of benign cells at the periphery of the main lesion. I **favour this to be benign possibily with some site related atypia**. However, I think it is difficult to exclude a melanoma arising in a naevus and would exercise a fair degree of caution in interpretting this lesion. I think there are some features raising the possibility of BAP inactivation and would do a BAP1.Additional immunos such as Ki67, cyclinD1 and HMB45 may offer some useful information.
- Some extremely atypical cells albeit with no mitoses in several minutes screening (slow software). In this age group, with these features and that history, this is **most likely metastasis**. I would get Ki-67, and compare with previous melanoma.

SLIDE CLUB RESPONSES

BAPoma

Spitzoid lesion. Circumscribed and symmetrical but doesn't mature. Low mitotic. **Favour malignant**

nodular melanoma vs cutaneous metastasis.

Metastatic melanoma

has features of **BAP1 inactivated melanocytoma** and adjacent conventional nevus

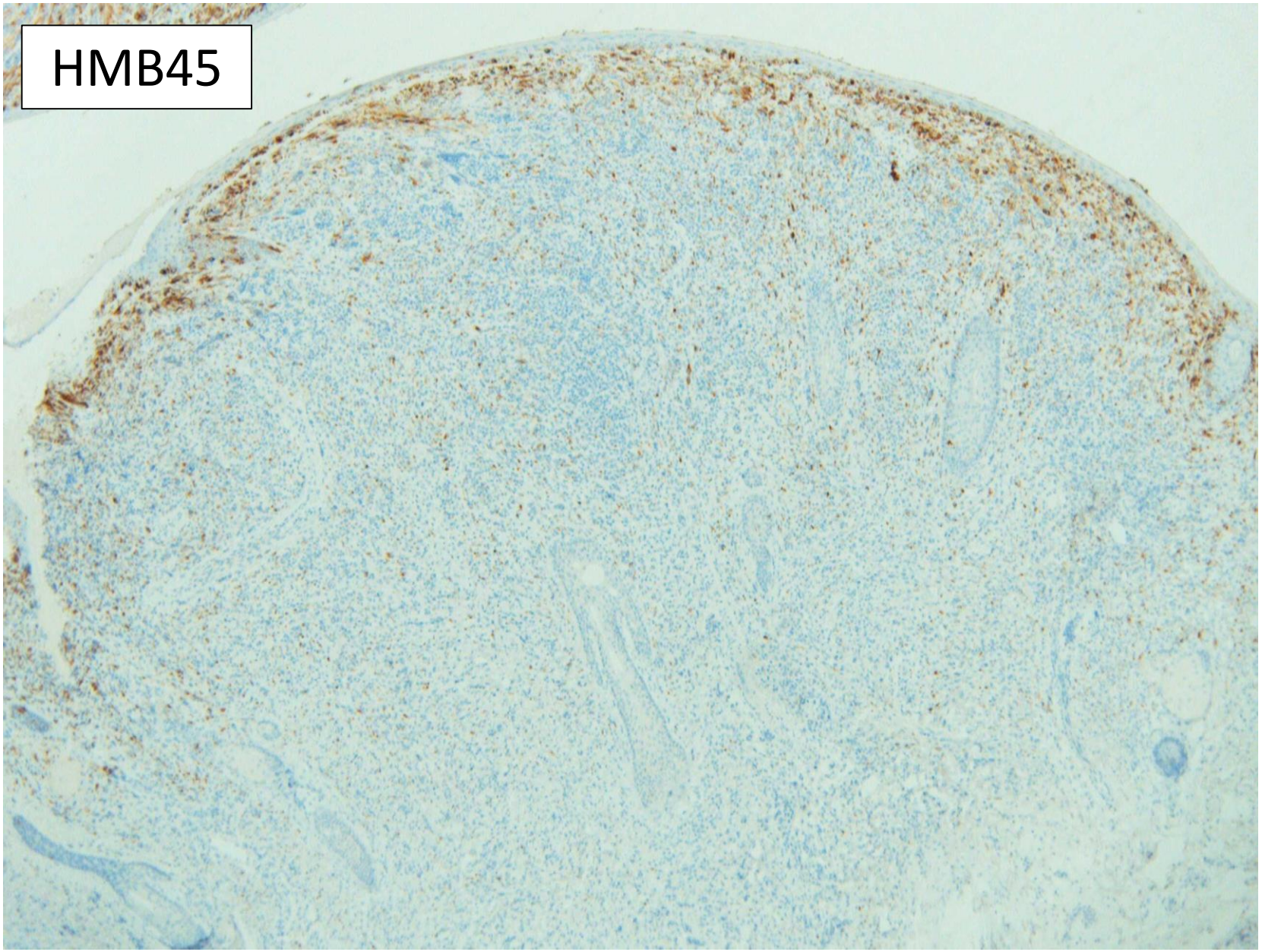
(Jan20): melanocytic nevus, Spitz type, think of **Wiesner nevus BAP?**

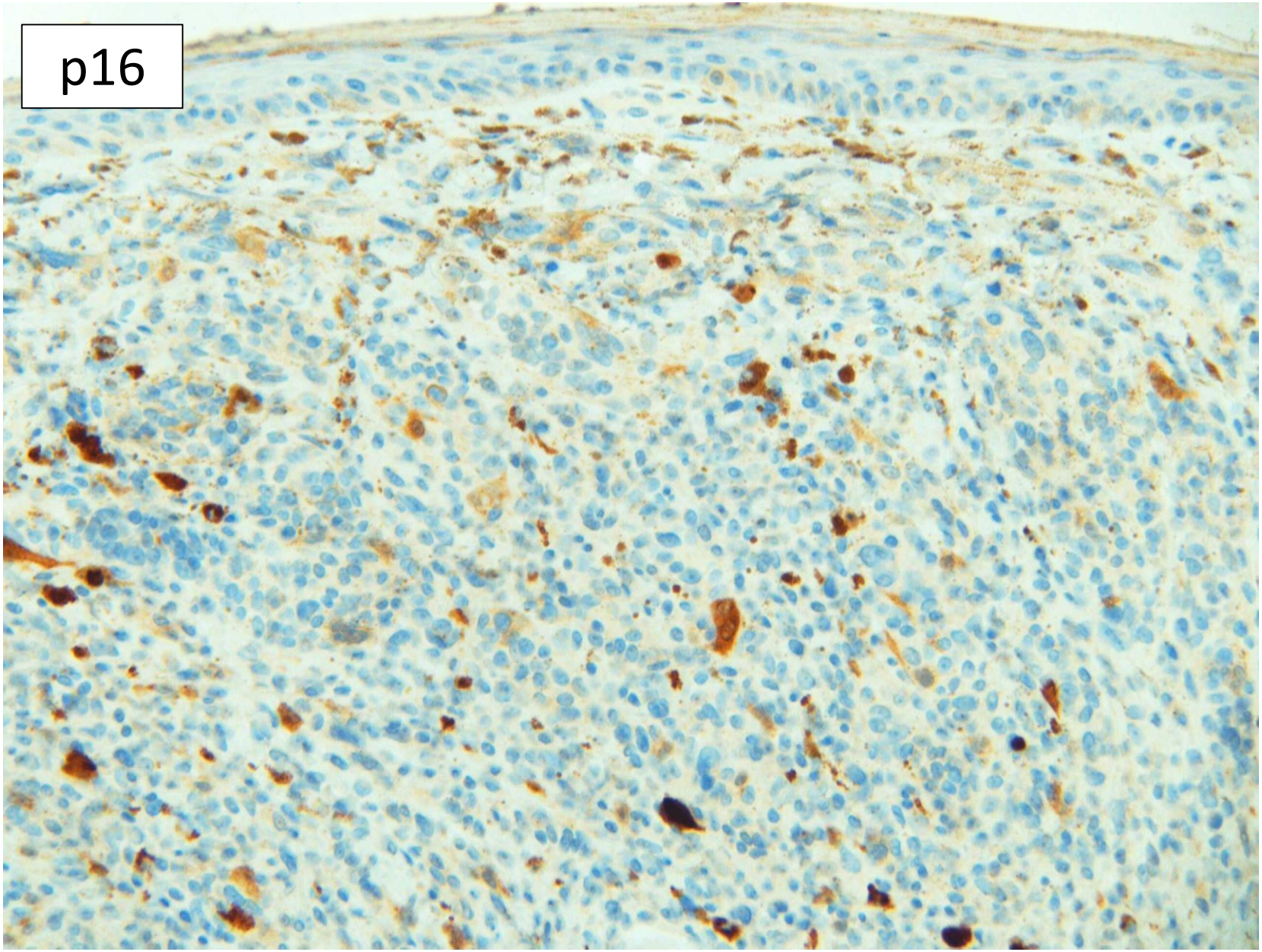
(Jul20): melanoma, nodular type with spitzoid features, Clark IV, Breslow (estimated) ca 5-6mm

Dear XXXX,
I hope you remain well. I'd like to thank you for being so helpful and kindly responding regularly to the melanocytic cases. For Cases 237 & 238 you gave a response in Jan. and a second response in Jul. I don't want to cause you any embarrassment ***but one of the tenets of the club is to be open and embrace the difficulty and uncertainty – not to mention the double jeopardy of using a digital slide.*** This case generated almost complete disagreement between experts and EQA participants so I think your two different responses are equally valid interpretations.
Are you okay if I include both your responses? Warm regards

Dear Richard

yes ok, bad intra-observer reliability, obviously Morbus Alzheimer is getting me closer. Best greetings, XXX


HMB45


p16

First Expert Review

"Your levels show a small pigmented compound melanocytic lesion with good side-to-side symmetry. The junctional component is rather indistinct and characterised by lentiginous and focally nested proliferation of melanocytes. The junction is perhaps best appreciated on the HMB immunostain and it shows focal cytonuclear atypia but no evidence of pagetoid ascent. There is a degree of thinning of the epidermis but not evidence of ulceration.

It is the dermal component that dominates and this has an approximate wedge shaped profile probably attributable to extension around appendage structures and neurovascular bundles. The upper part of the lesion is rather more cellular than the basal part and this shows areas of melanocytes with patchy pigment elaboration. The cells are of spindled to epithelioid type and occasional multinucleate giant cells are a feature. The cells possess vesicular nuclear with a small nucleolus and there is really quite widespread anisonucleosis with some severely atypical cells particularly within the upper third of the lesion. Towards the base the cellularity tends to diminish although there is still a degree of anisonucleosis even quite deep within the lesion. I agree with your comments regarding mitotic activity - these are really quite readily identified (so far I have found at least 20) and they are distributed throughout the lesion including some quite deep within the tumour. I have not been able to identify clear evidence of atypical mitoses.

This lesion is extremely difficult to categorise. I note your comment regarding possible DPN, however these lesions are generally combined in type, the cellular morphology is not typical and this degree of mitotic rate would be very high for a DPN. My main considerations here are **the possibility of the rather ill-defined entity of a mitotically active naevus**, however I remain concerned by the exact nature of this lesion given its appearance at a sun damaged site in a patient of this age and with concurrent cytonuclear atypia and slight thinning of the overlying epidermis (a feature which may reflect underlying proliferative growth). On the other hand, the lesion has the general configuration of a naevus being of small size and with good symmetry. It is difficult to give a categoric opinion regarding the exact biological potential of this, however, given the atypia and mitotic activity **I cannot exclude this being a low grade naevoid melanoma**. The lesion appears to have been removed completely, however it would be reasonable to **consider re-excision and close follow-up**. Unfortunately, I do not feel comfortable giving a definitive diagnosis and would greatly appreciate any follow-up in this case."

2nd Expert Review

I favour a mitotically active naevus (predictably as I'm "benign").
I pretty much photographed every mitosis in the main "dotted" level and have around 12 mitoses in around 12mm2 so that is a relatively low proliferation all be it very unusual for naevus.
I thought some mitotic figures were subjective or oddly mummified – like they weren't that keen!
No real deep mitoses, nice architecture, nice umbrella sign (lack of solar elastosis in the naevus – which protects the dermis from the sun).
Maybe the driver mutation is driving proliferation but I don't see enough variation in morphology to think it's taken enough "malign" steps.
Interesting the p16 looks negative but I don't have a total handle on p16 in naevoid lesions.
HMB45 nicely graded is re-assuring.
Ki67 would be helpful to show my impression of lower proliferation with depth although there are a lot of follicles so even a deep perifollicular proliferation would not be unexpected.
I'd love to see a mitotic spindle marker – suspect Arnaud might have.
To be honest when you get the multinucleation & therefore hyper-diploid cells, you are going to see some nuclear pleomorphism and even an atypical mitotic figure would not be out of the question (although none were seen).
The majority cells are rather bland and there is clear maturation with depth.
Can you review the melanoma for me?
Would be nice to have a bit more details. Was it a proper one?
Also would help if the Clinical colleagues can quiz the patient about this "naevus" further i.e. how long has he had it?
Any family history (the negative p16 is making me wonder).
I'll e-mail Alan Evans who asked for "follow-up" etc. and I'm totally sure he'd like to be kept in the loop.
This will be great case for the slide club – I've not done any additional stains or copy sections as I want Arnaud to have the maximum material for analysis.
Thanks
Note: Seen independently by Scott Sanders who agrees with me (again not surprising as we're long collaborating colleagues!)

Dr Arnaud de la Fouchardiere:

Cutaneous excision right ear lobe: The melanocytic proliferation is mainly dermal with an elevation of the overlying epidermis that appears moderately papillomatous. Some junctional melanocytes are visible, of lentiginous and mini-thecal architecture. The melanocytes are medium-sized with spindled or epithelioid nuclei and more or less pigmented cytoplasm. There is no pagetoid spreading. The dermal component is somewhat dense but without net obscuring of the grenz zone. It forms loose sheets more or less fasciculated containing some nests and clusters that prevail in the superficial part. Some large multinucleated cells are visible near the surface where there is also some degree of intra cytoplasmic pigmentation with melanophages. Deep maturation is moderate but present. Global mitotic activity remains low. The lesion extends to the hypodermis with some deep large melanocytes with hyperchromatic nuclei and weakly pigmented cytoplasm. Cytology is not clearly spitzoid. The lesion is poorly limited laterally. The immunohistochemical study performed showed negative labelling with specific mutation BRAF, V600E, NRAS Q161R, P53 is weakly expressed. Discretely heterogenous staining with melanA, rare cells labelled in HMB45 in the dermis. Weak heterogenous labelling of P16. The proliferation rate is around 19%. A complete loss of BAP1 expression is observed except in a small lateral naevic component

CONCLUSION

Cutaenous excision right ear lobe: **combined melanocytic tumour with BAP1 inactivation, (MelTUMP)**. The history of melanoma is suggestive of a germline anomaly that should be explored in an oncogenetic consultation. A re-examination of 2006 slides with BAP1 immunohistochemistry is recommended. A 0.5 to 1 cm complementary resection and clinical monitoring are recommended (best decided in a multidisciplinary staff).

Re: Management

RAC Comments: If it's out already (which I think from memory it was – but Paul please double check as I made no comment in the powerpoint I sent you) I'd be in favour of "watchful waiting" if it was my ear.

I don't personally think there is any need to re-excise an already fully excised MelTUMP with low grade histological criteria. The BAP1 familial germline would be associated with several tumours notably cutaneous and uveal melanoma, mesothelioma, multiple BCC, renal cancer, many polypoid naevi (BAPomas, MBAITs) particularly on the upper body.

CRITICAL REVIEW

(*Am J Dermatopathol* 2019;41:884–896)

"Personalized Excision" of Malignant Melanoma—Need for a Paradigm Shift in the Beginning Era of Personalized Medicine

Wolfgang Weyers, MD

although the latter tend to be more sharply confined. Extending margins of excision for the purpose of removing inapparent metastases is fallacious because the latter are rare, their localization cannot be foretold, and satellite metastases are usually associated with distant metastases, so that patients do not profit from early removal of cutaneous lesions. The

histopathologically. Because of limitations of the method, a histopathologic safety margin should be observed that must depend on the characteristics of the individual lesion. In sharply confined melanomas, a histopathologic margin of at least 1 mm is sufficient. In the case of poor demarcation, with solitary atypical melanocytes extending far beyond the bulk of the lesion, a broader histopathologic safety margin is advisable. Special caution should be exercised in the presence of regression and for desmoplastic melanomas, acral melanomas, and melanomas on the face and scalp. Instead of wide and deep excisions with standardized margins, "personalized excisions" are required for primary cutaneous melanoma. The concept of clinical safety margins is a relic of former times that has no place in modern medicine.

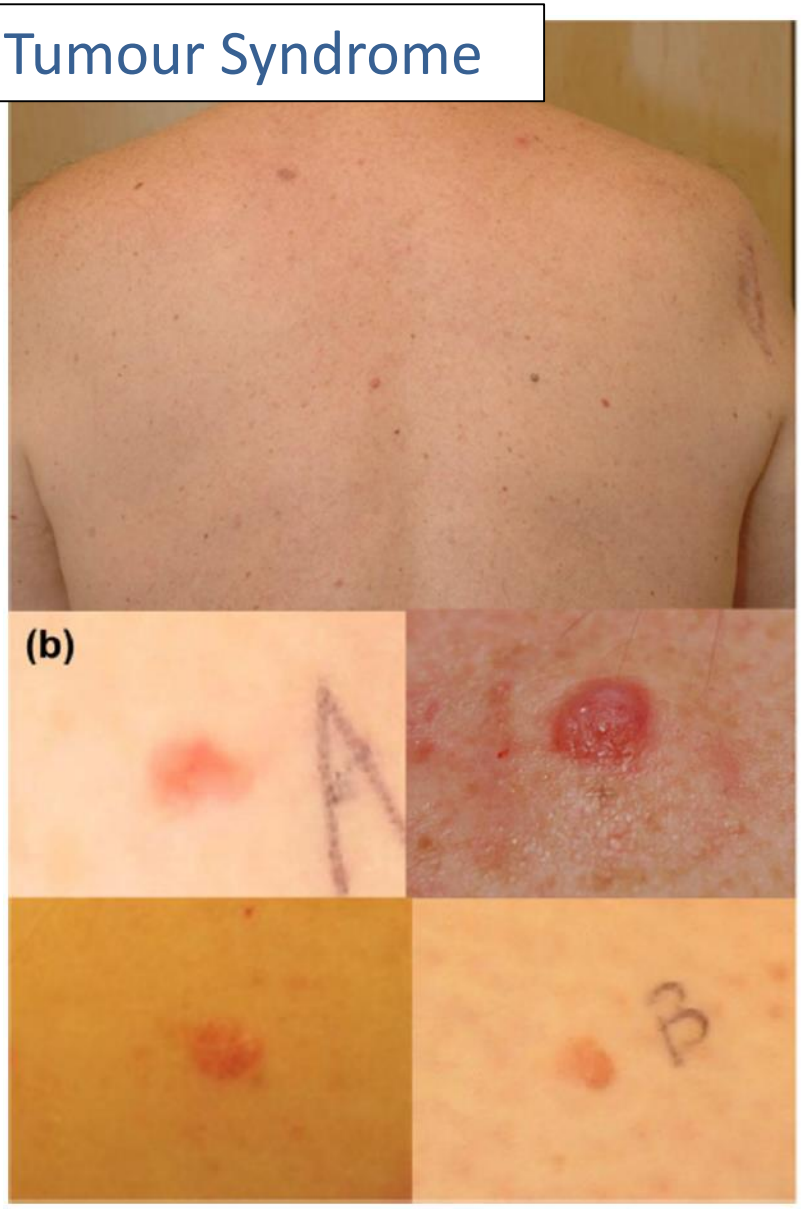
BAPOLOGY

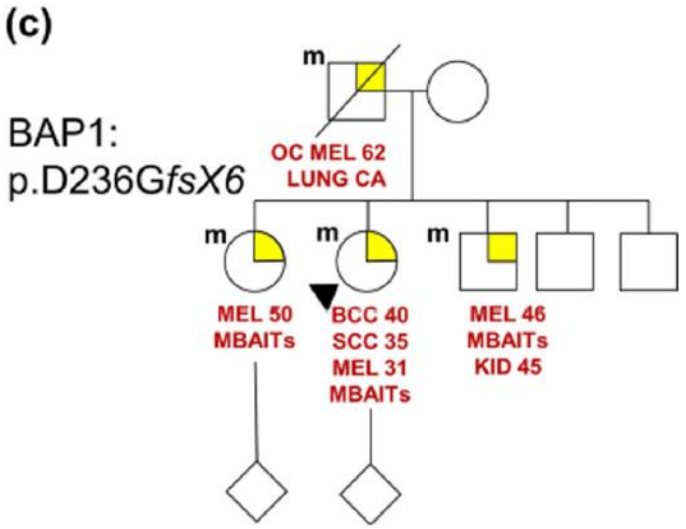
BAP1 Tumour syndrome

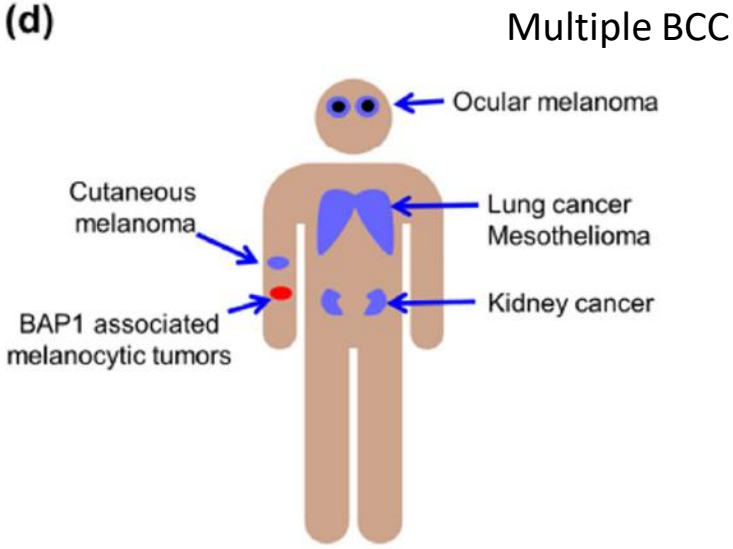
- BRCA-1 associated protein 1, *BAP1*, 3p21.3 encodes protein BAP1 (intracellular deubiquitinase)
- Cutaneous melanoma, uveal melanoma, and various internal malignancies
- Up to 67% of patients with BAP1 cancer complex present with multiple atypical melanocytic proliferations called “MBAITs” (Melanocytic BAP1 Associated Intradermal Melanocytic Tumours)
- Reddish-brown, dome shaped to pedunculated, well-circumscribed papules appearing progressively after 1st decade2 to 10mm, varying in no. from 5 to 50
- MBAITs look like AST but in addition to IHC BAP1 loss have a BRAF mutation in (89%)
- Need bi-annual check of lesions and complete removal of any that are of concern
- Patients presenting with metastatic UM or concurrent UM and cutaneous melanoma have a higher possibility of exhibiting BAP1 mutations compared to other melanoma patients

Soura et al J Am Acad Dermatol. 2016 Mar;74(3):411-20

BAP1 Tumour Syndrome







Soura E, Eliades PJ, Shannon K, Stratigos AJ, Tsao H. Hereditary melanoma: Update on syndromes and management: Emerging melanoma cancer complexes and genetic counseling. J Am Acad Dermatol. 2016 Mar;74(3):411-20

OVERVIEW OF GENETIC TESTING: FAMILIAL MELANOMA & SUBORDINATE CANCER SYNDROMES

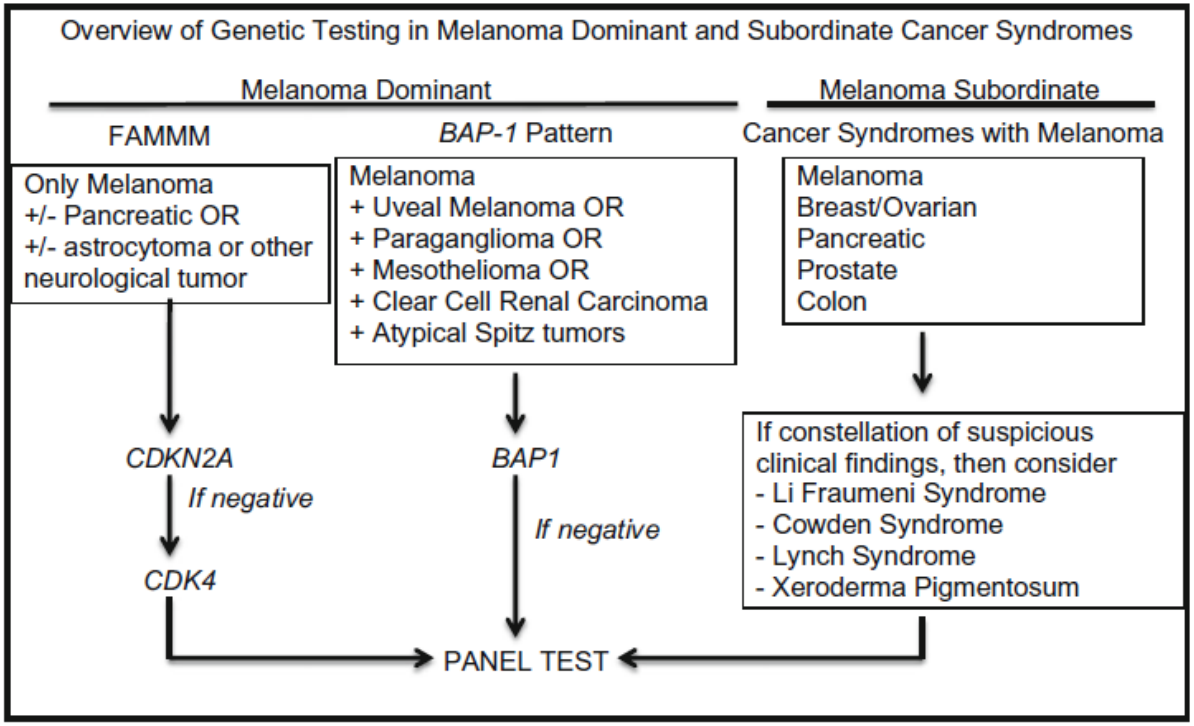


Fig. 1 Overview of genetic testing in melanoma-dominant and melanoma-subordinate cancer syndromes. This algorithm details navigation of genetic testing based on family history. It is also an option to proceed directly to panel testing. *FAMMM* familial atypical multiple mole melanoma syndrome. The *left side* of the figure depicts syndromes that contain melanoma as the dominant cancer in the syndrome whereas the *right side* of the figure depicts other cancer syndromes that contain melanoma as a subordinate cancer

Identification, genetic testing, and management of hereditary melanoma.
Cancer Metastasis Rev. 2017 Mar;36(1):77-90. doi: 10.1007/s10555-017-9661-5.
Leachman SA, Lucero OM, Sampson JE, Cassidy P, Bruno W, Queirolo P, Ghiorzo P.

BAPOLOGY

- BAPology is a fascinating new science
- Melanocytic tumors with loss of BAP1 expression can identify carriers of a germline syndrome with cancer-predisposition
- Isolated cases with somatic mutations prevail
- Exophytic combined architecture
- Large unpigmented epithelioid and nevoid dermal melanocytes +/- lymphocytes
- IHC is an excellent technique to identify loss of function
- Malignant transformations are rare

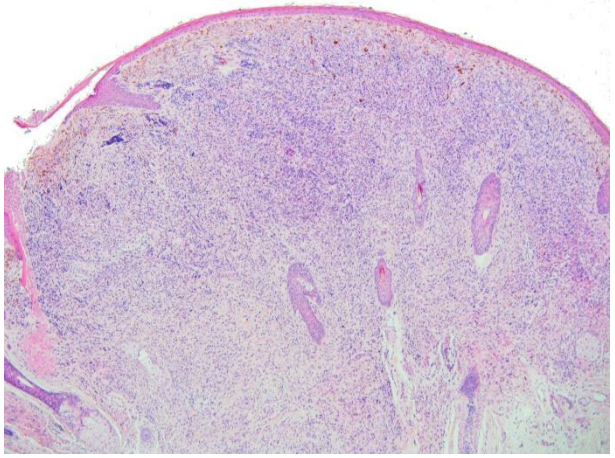
c/o Dr Arnaud De La Fouchardiere

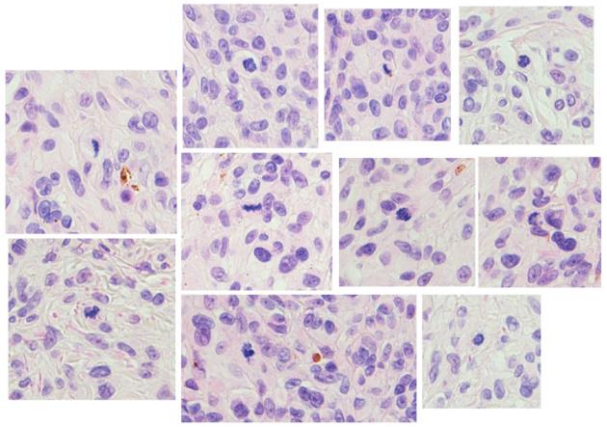
Case 238 Learning Points

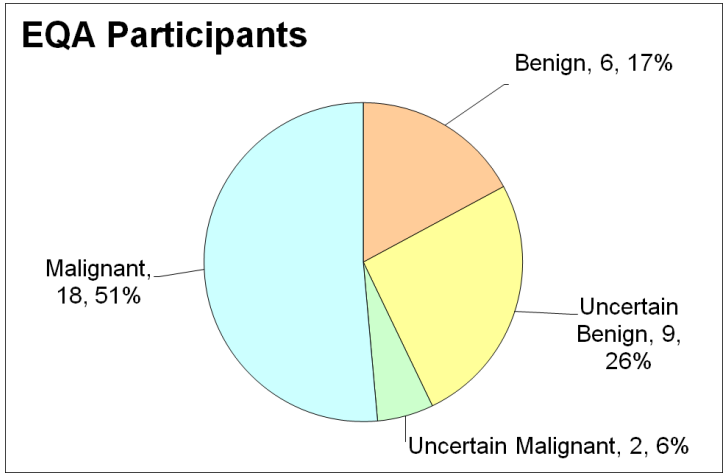
BAP Inactivated MELTUMP (unknown driver)

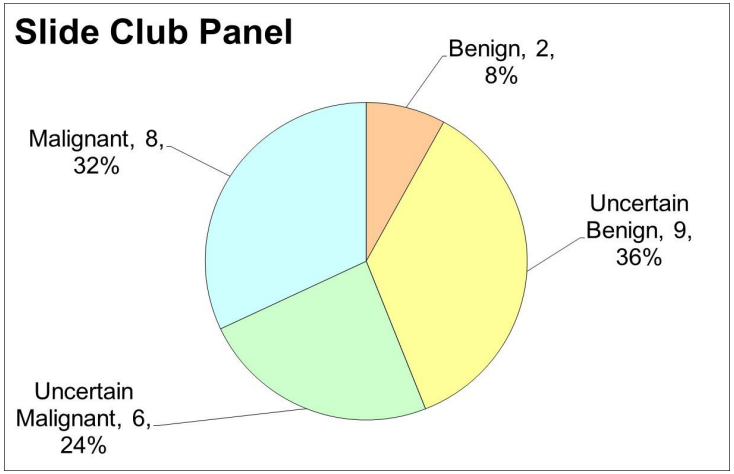
Challenging case giving a wide range of opinions

It seems okay to admit uncertainty and recommend complete removal, appropriate follow-up and genetic studies but ultimately these studies do not always provide a definitive answer.









I’d like to make a-BAPology for this awful joke!

Thanks

Paul Barrett

Alan Evans

Arnaud de la Fouchardiere

All responders from the EQA and Slide Club