MELANOMA SLIDE CLUB 245 AND 246

- Dr William Merchant
- St. James's Hospital
- Leeds
- Yorkshire
- England

- Thanks Richard Carr for assistance

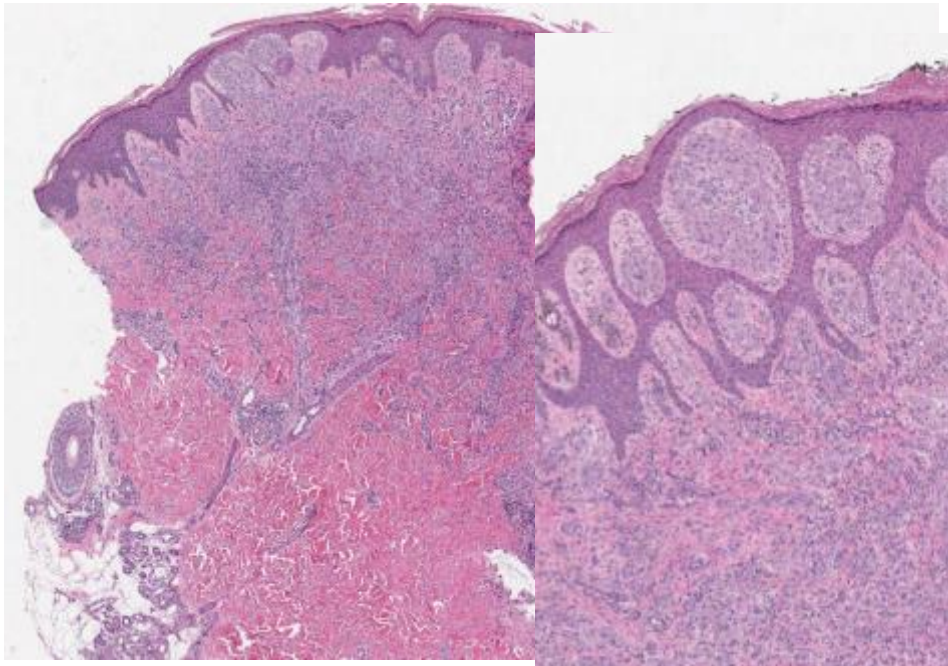
Case 245

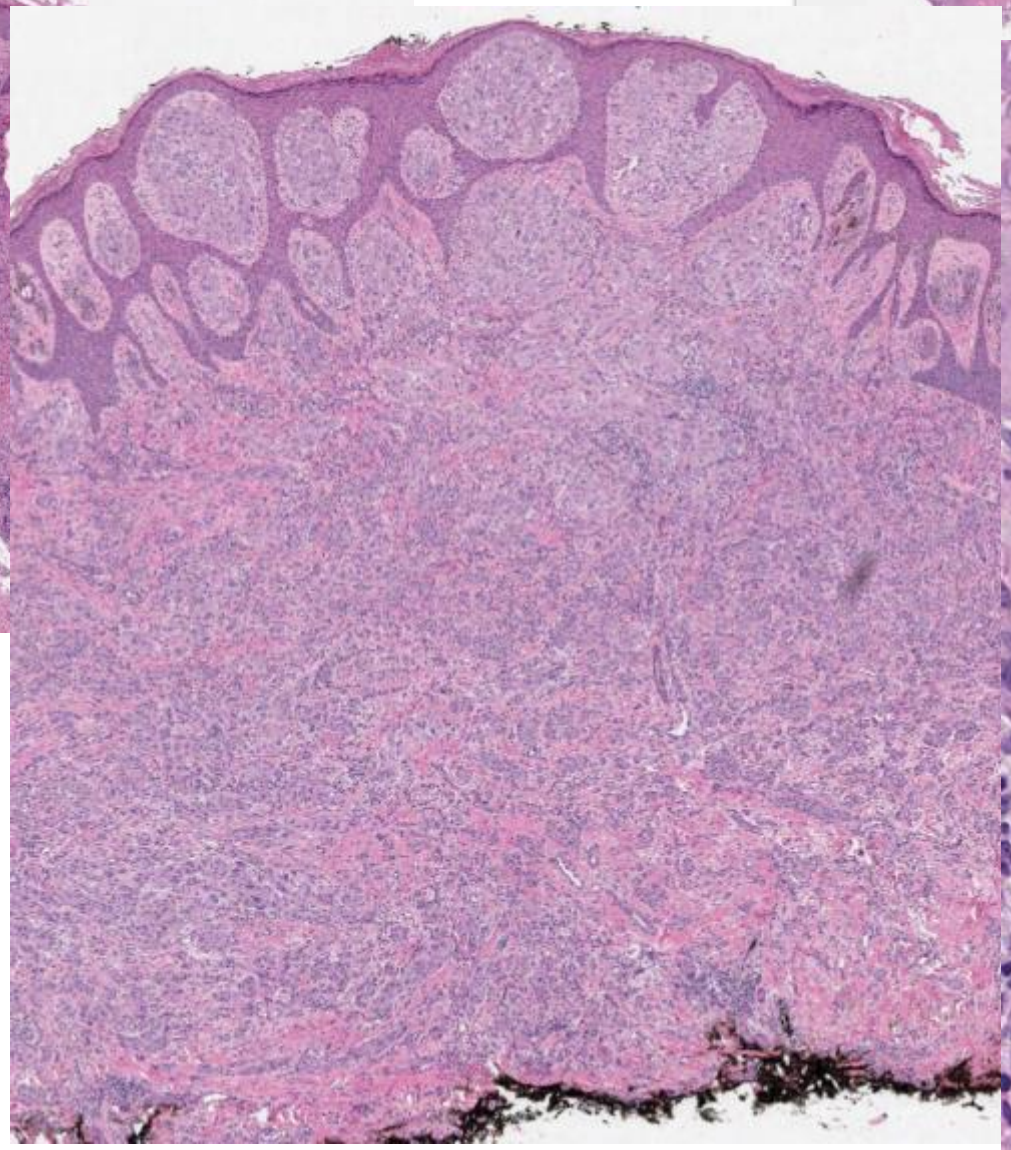
Female 21 years

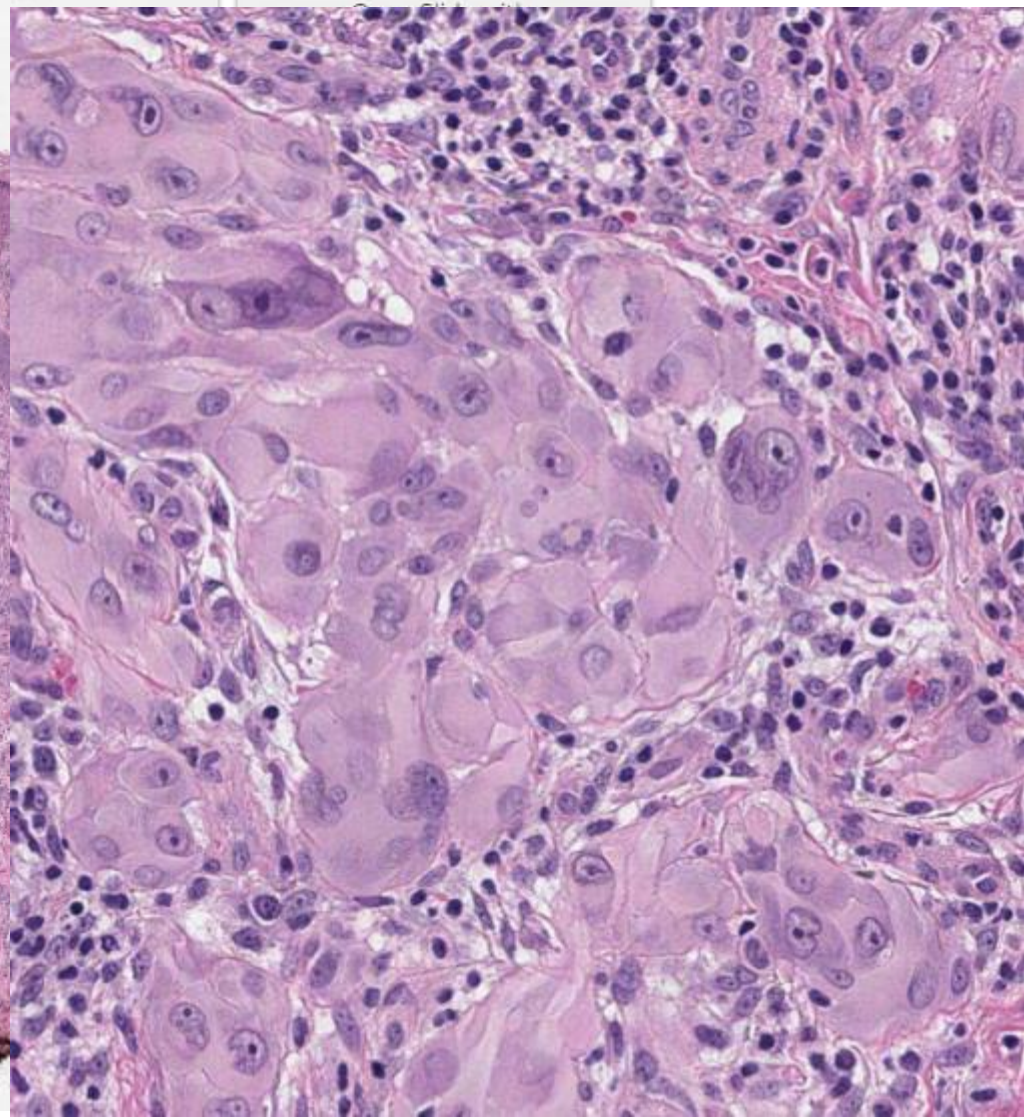
Erythematous firm nodule, ? Keloid. Left lower leg, Punch biopsy followed by excision.

H&E 542145

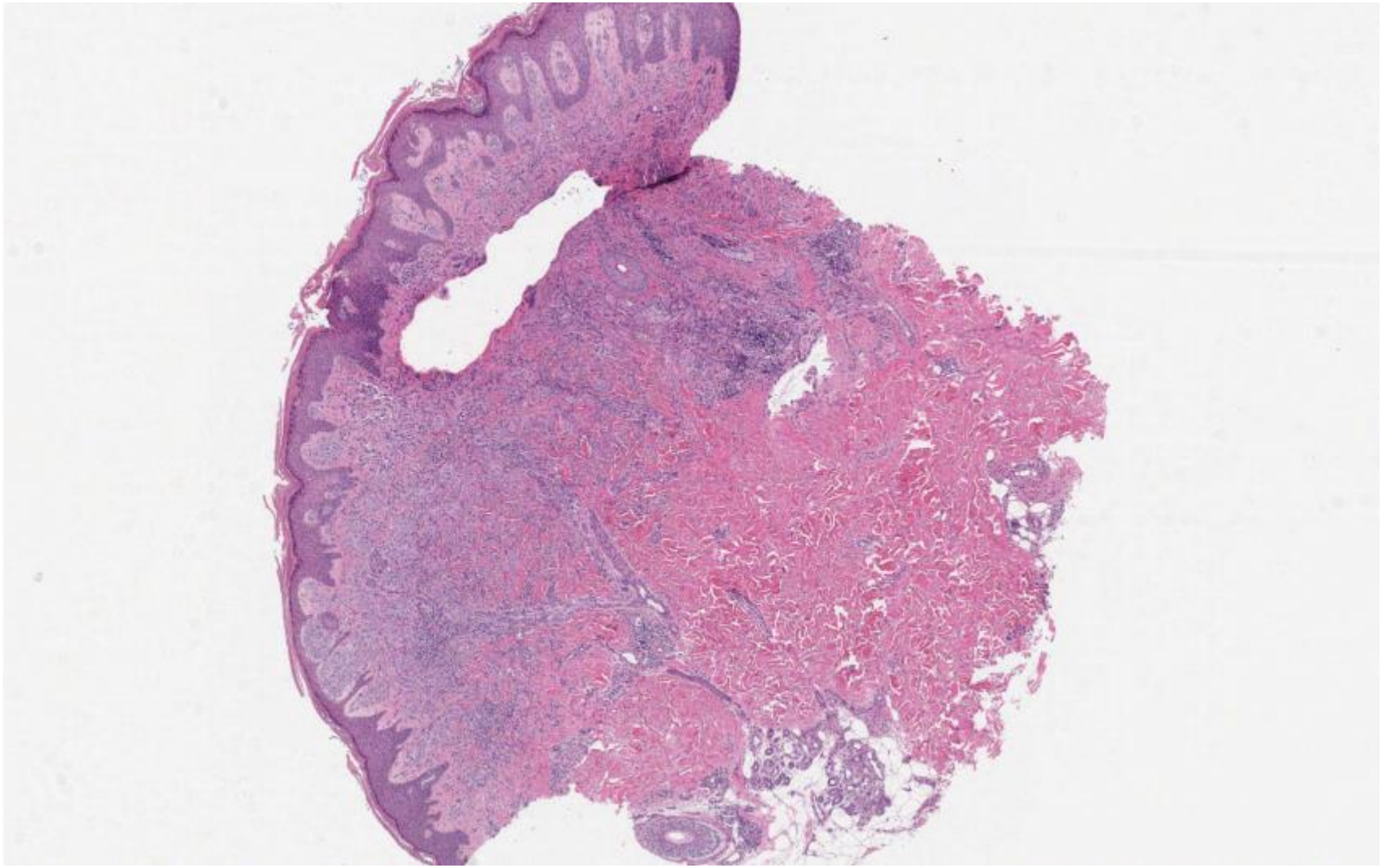
H&E 542146







Initial Punch



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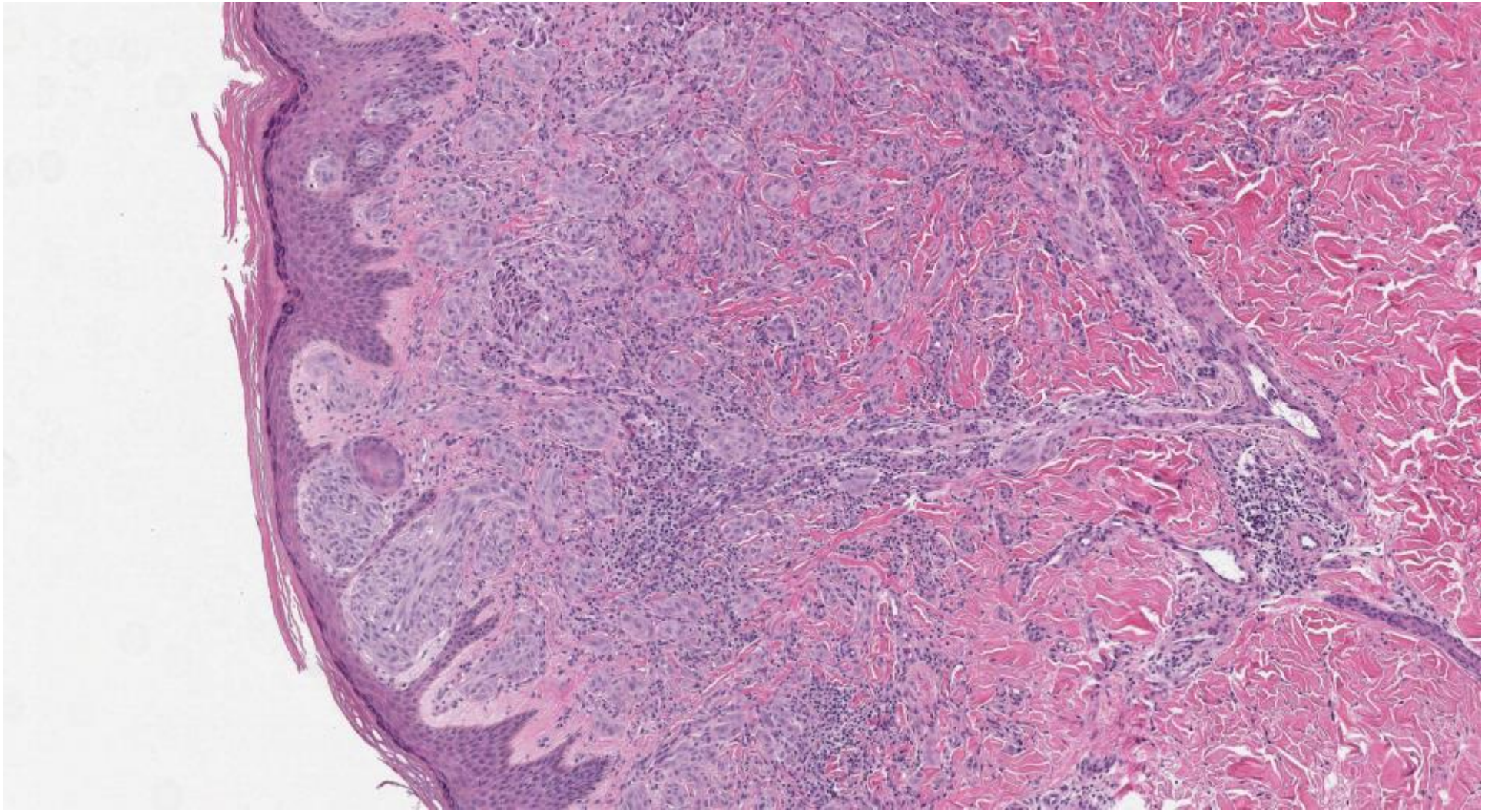

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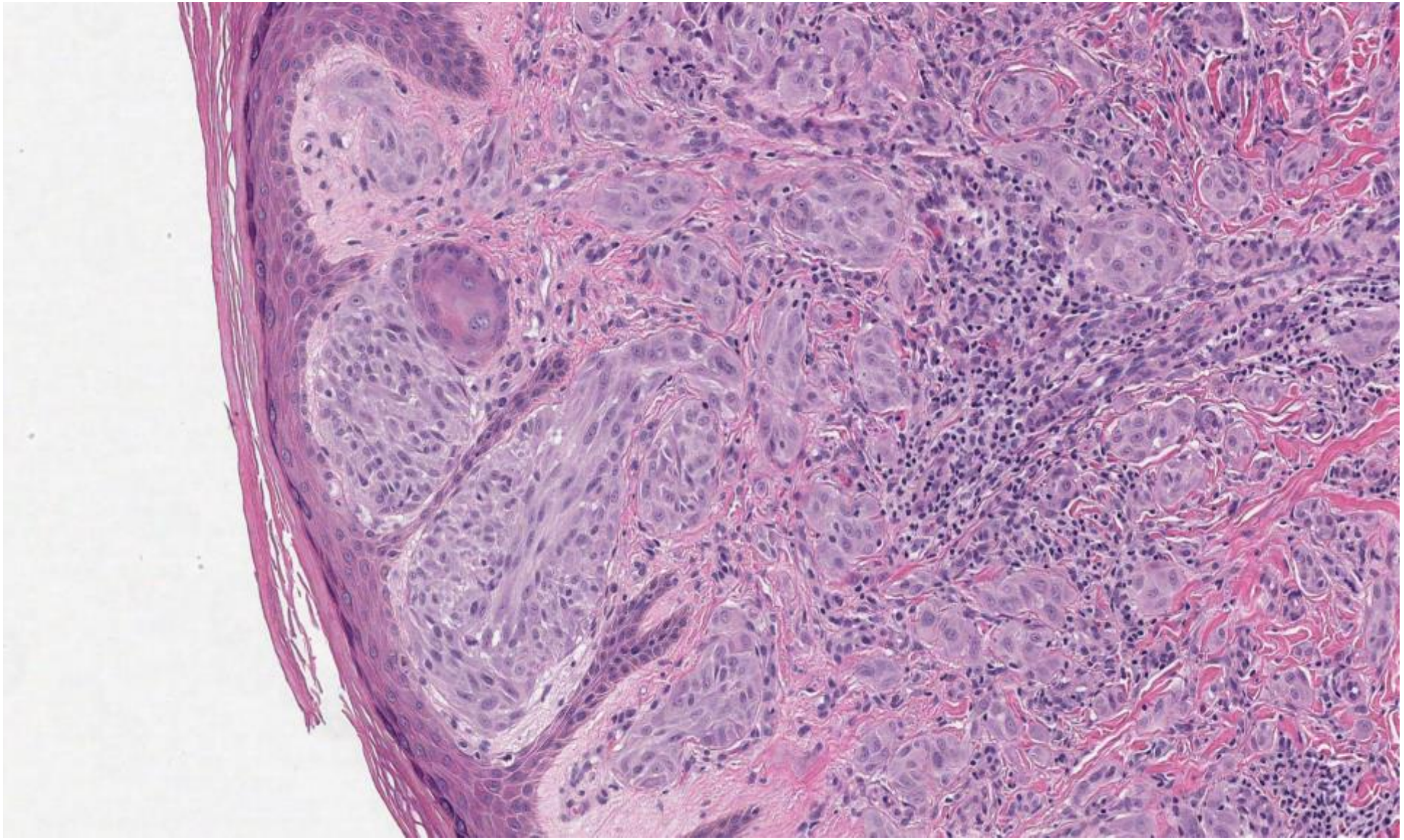
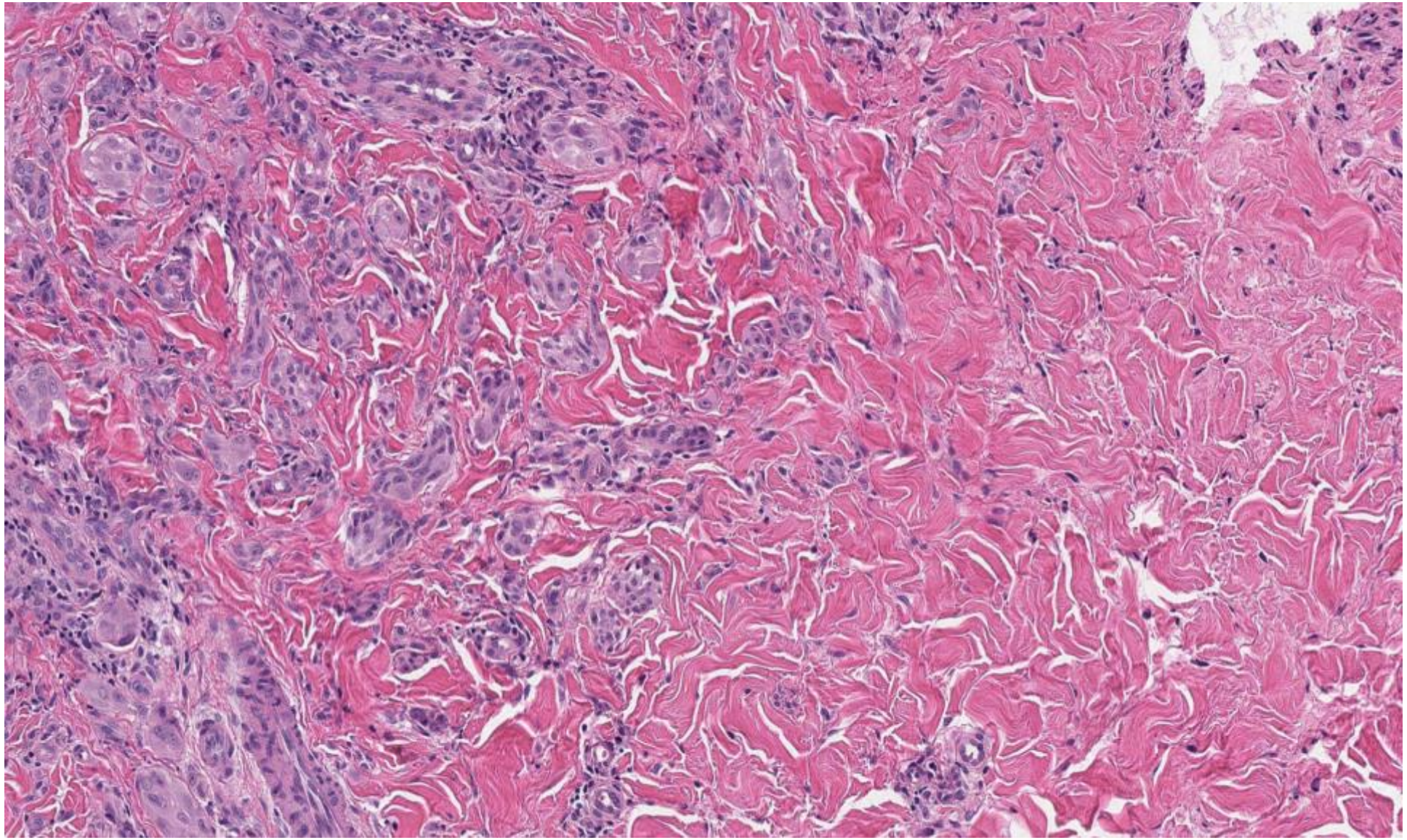
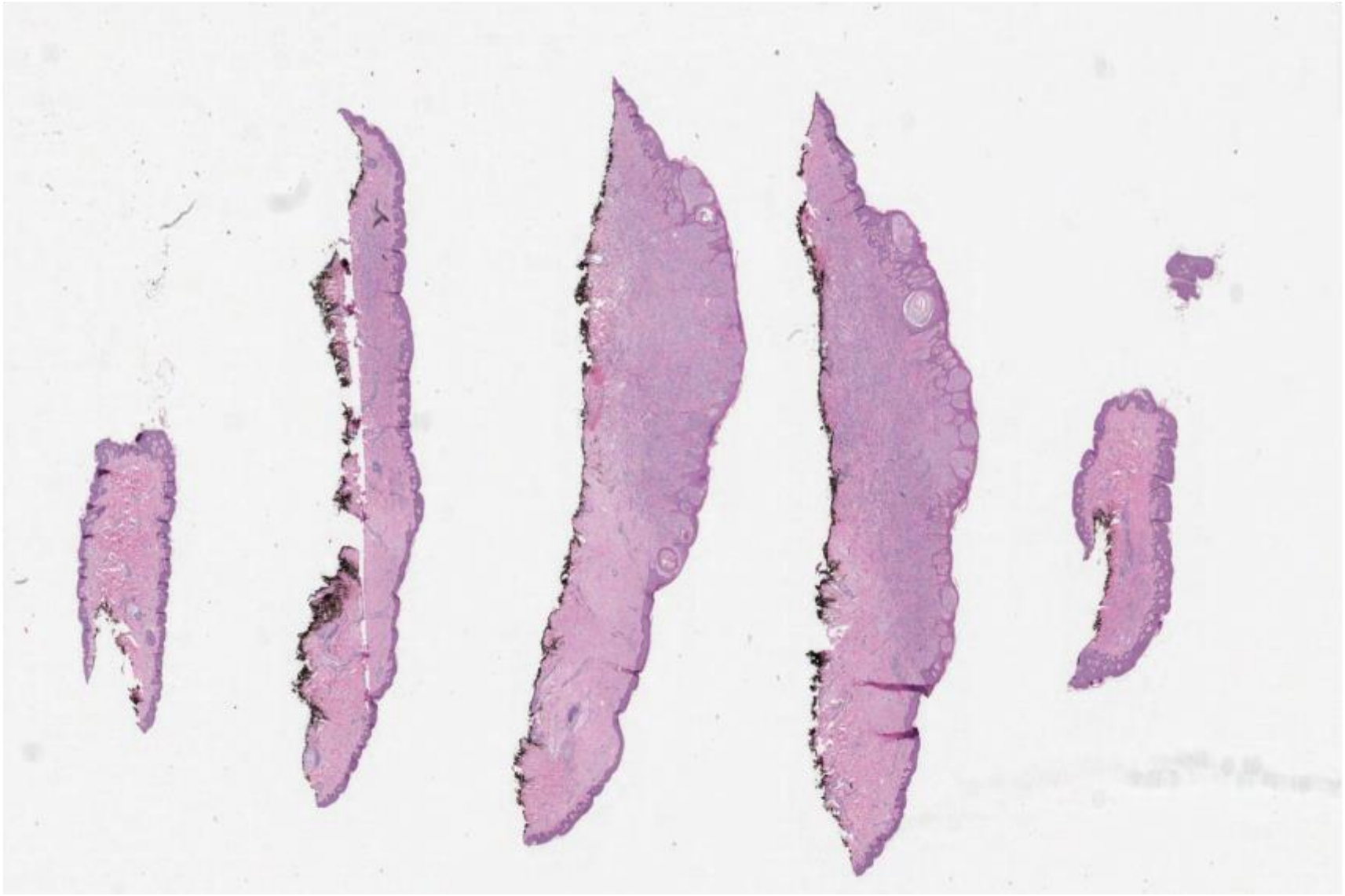


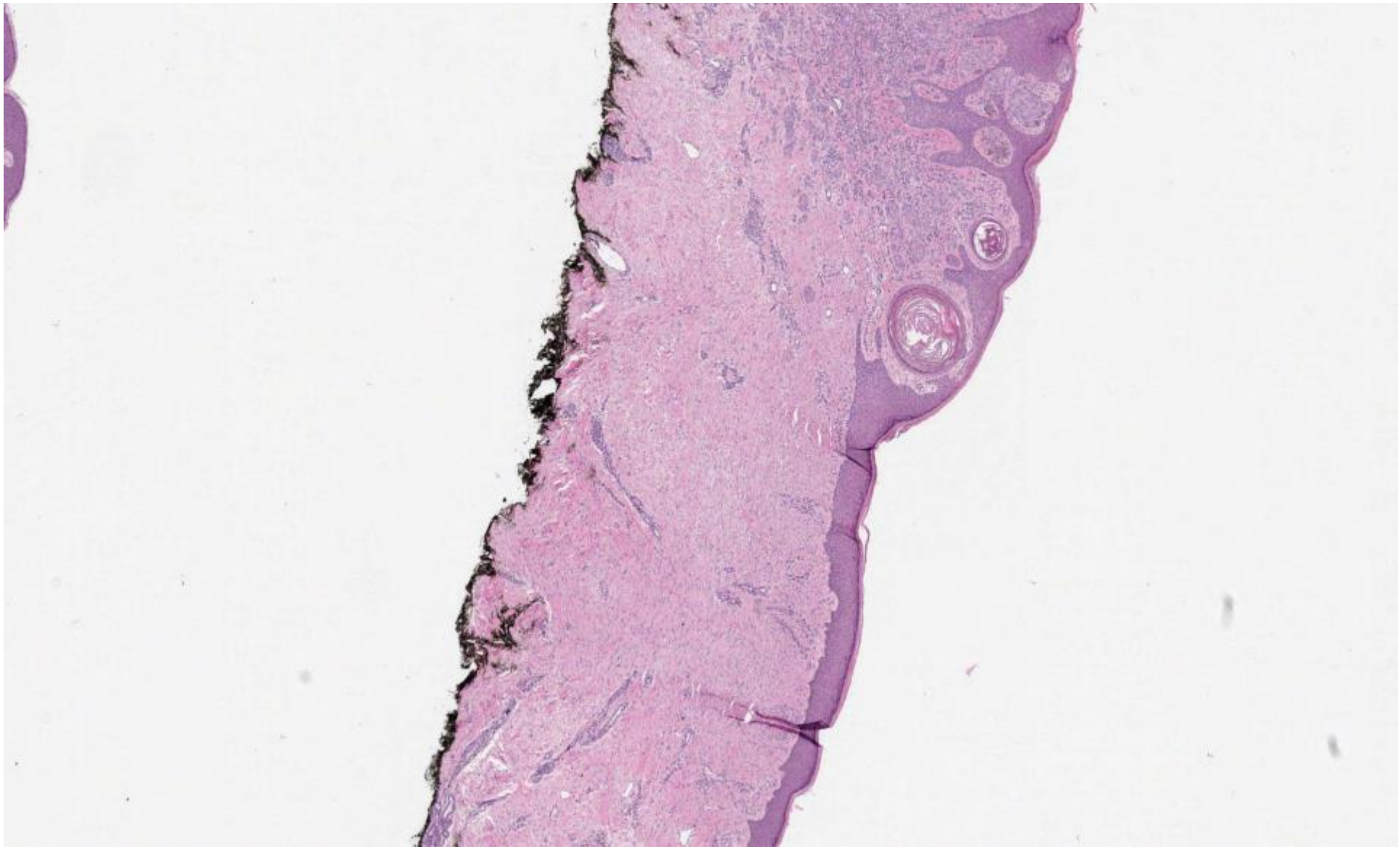
Initial Punch



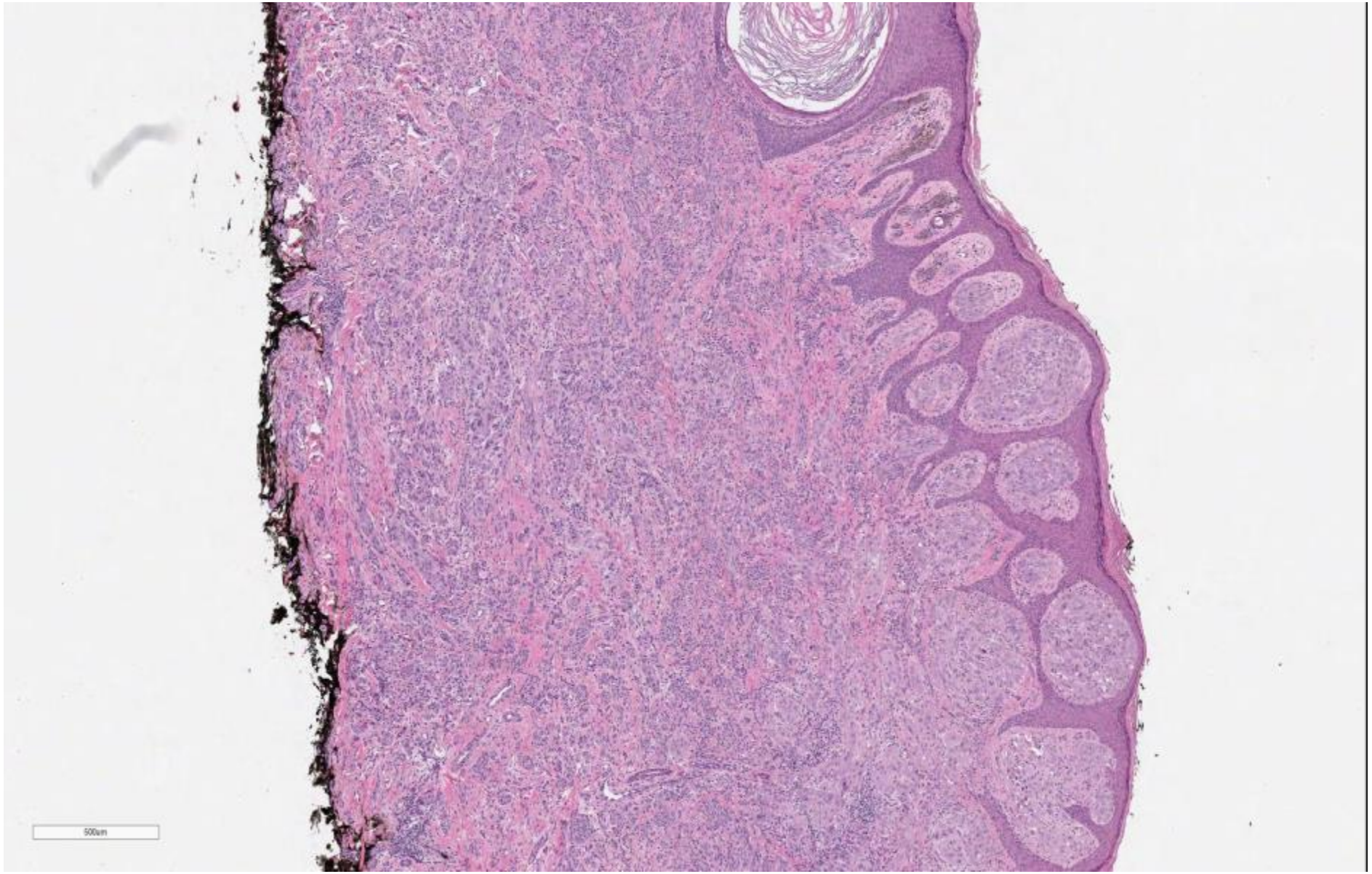
Excision
lesion 13mm



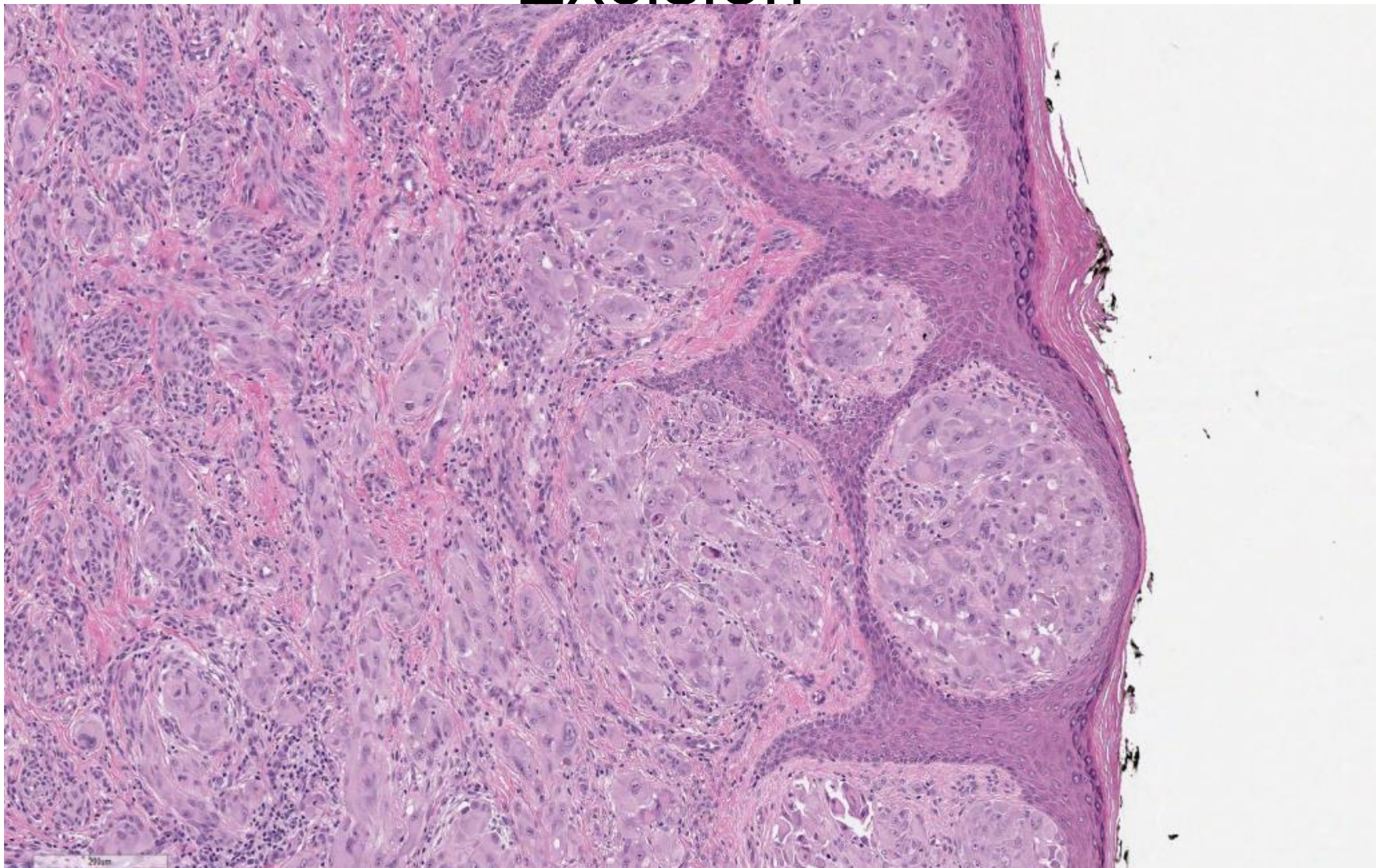
Excision, Scar



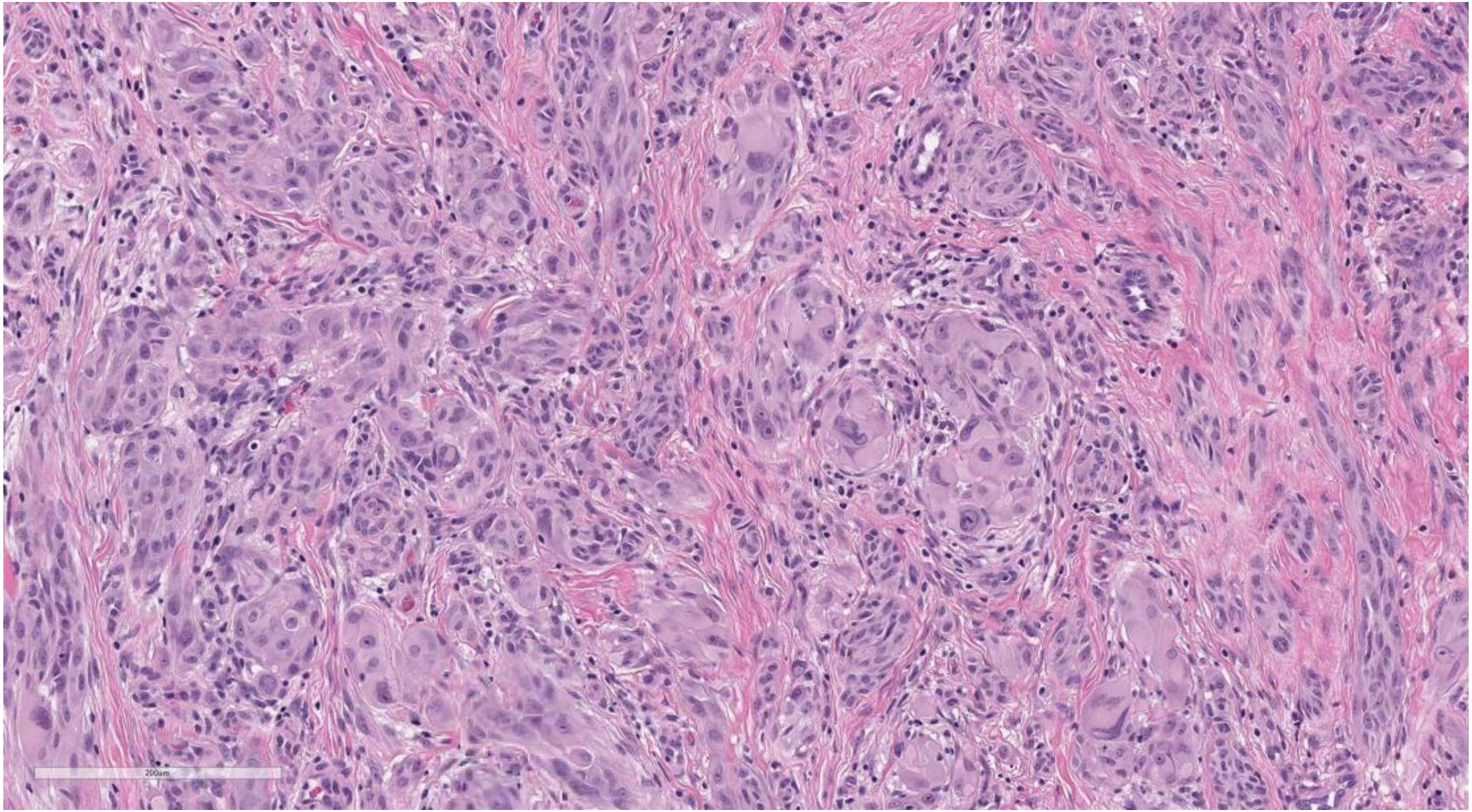
Excision



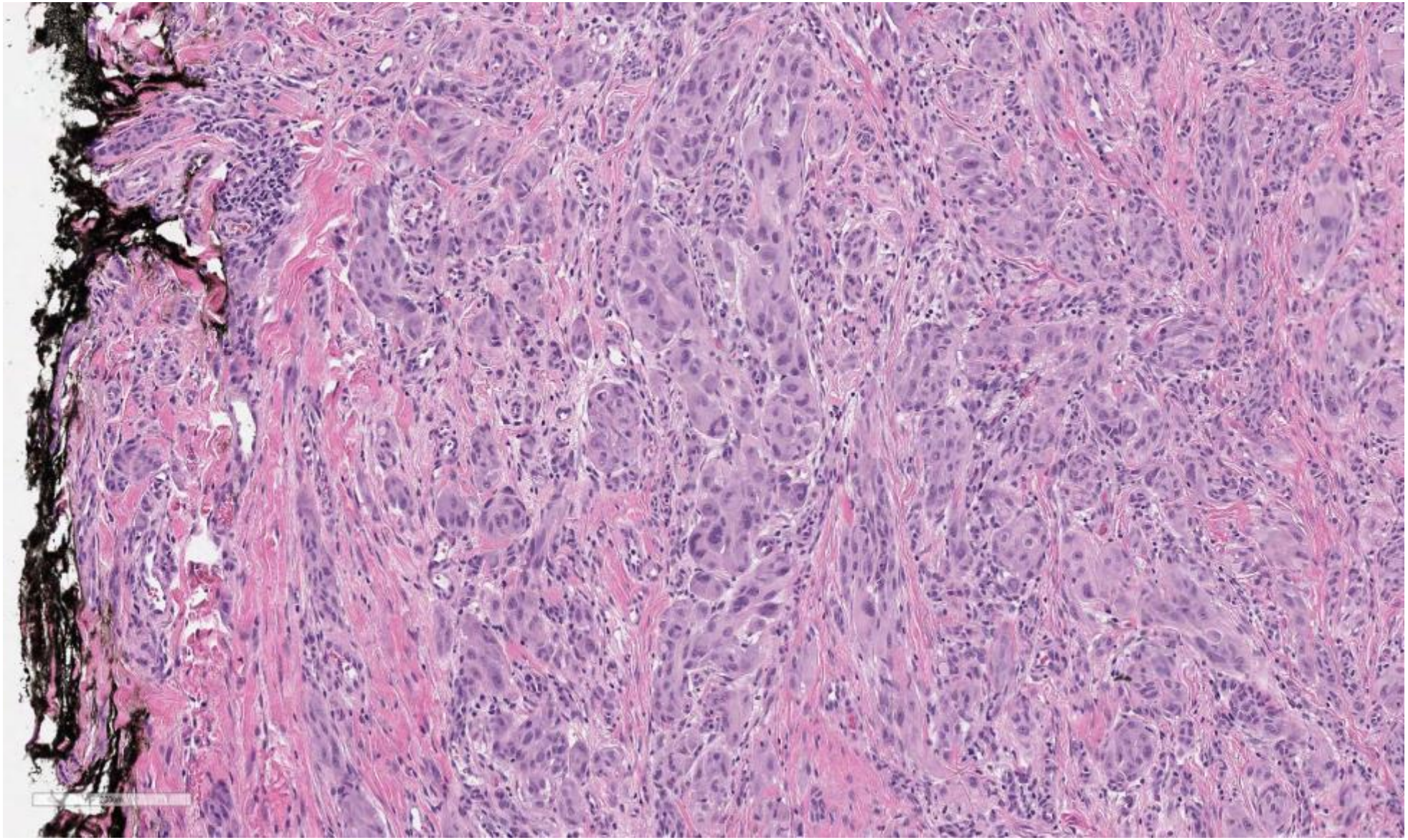
Excision



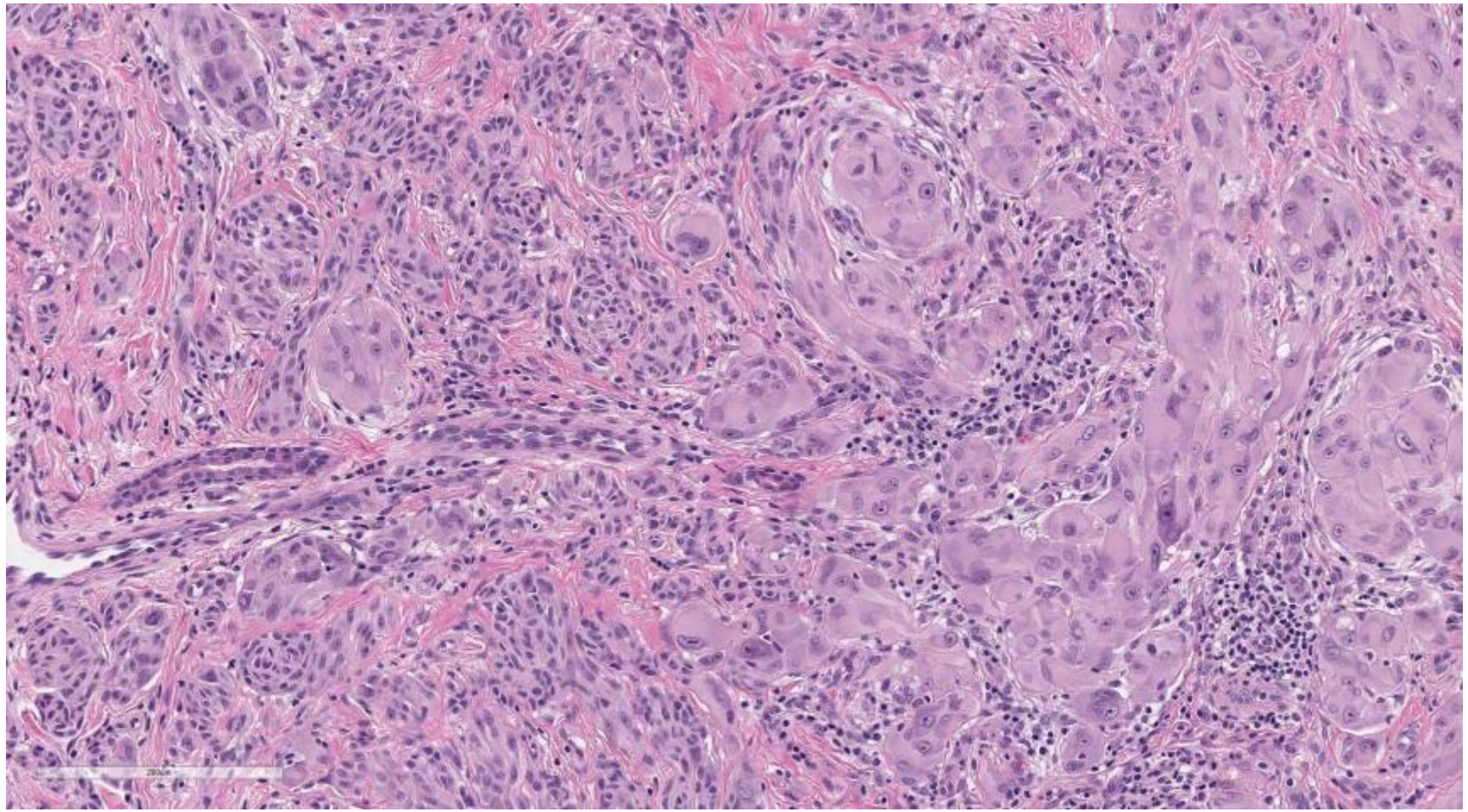
Mid lesion, variation in size



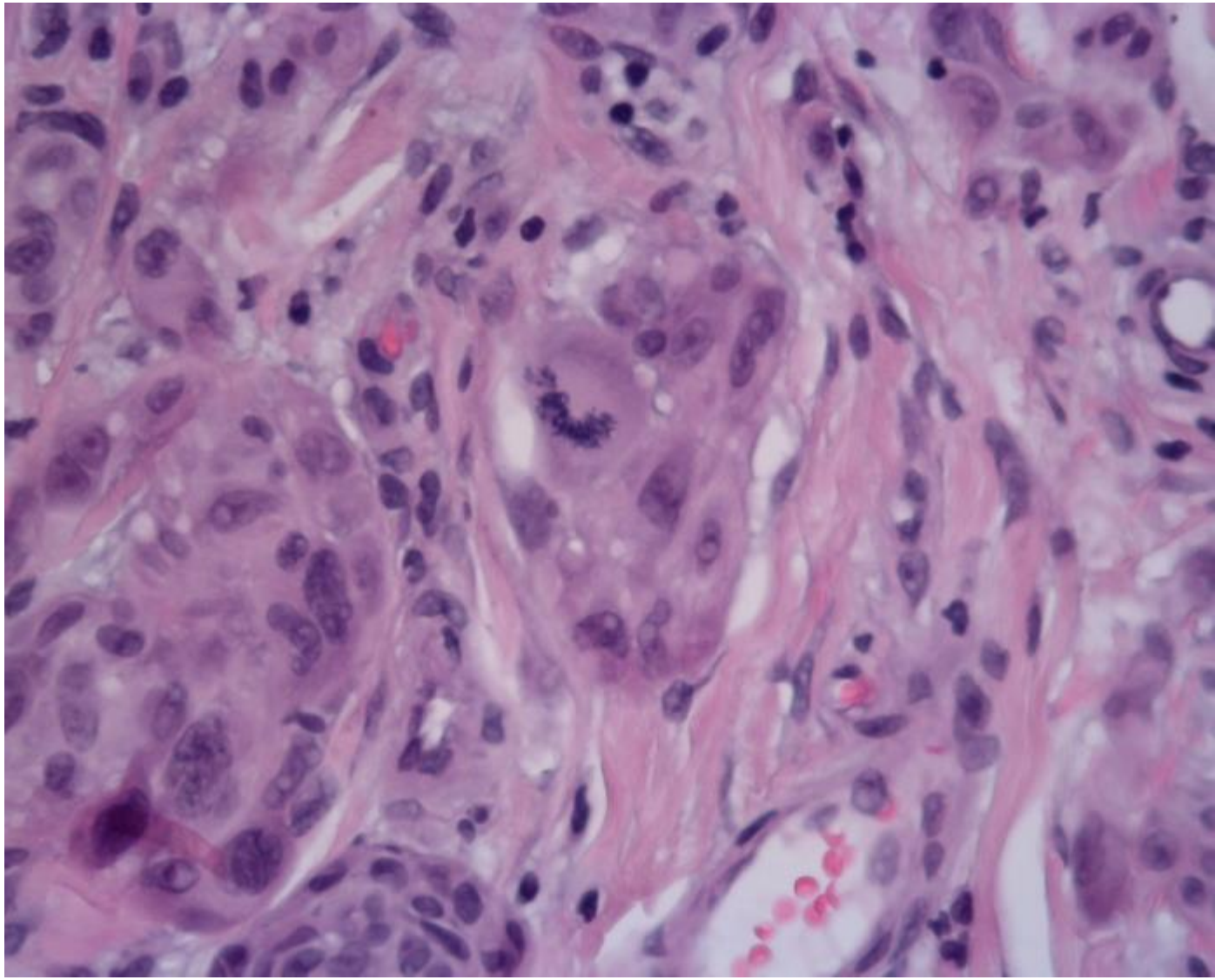
Deep aspect



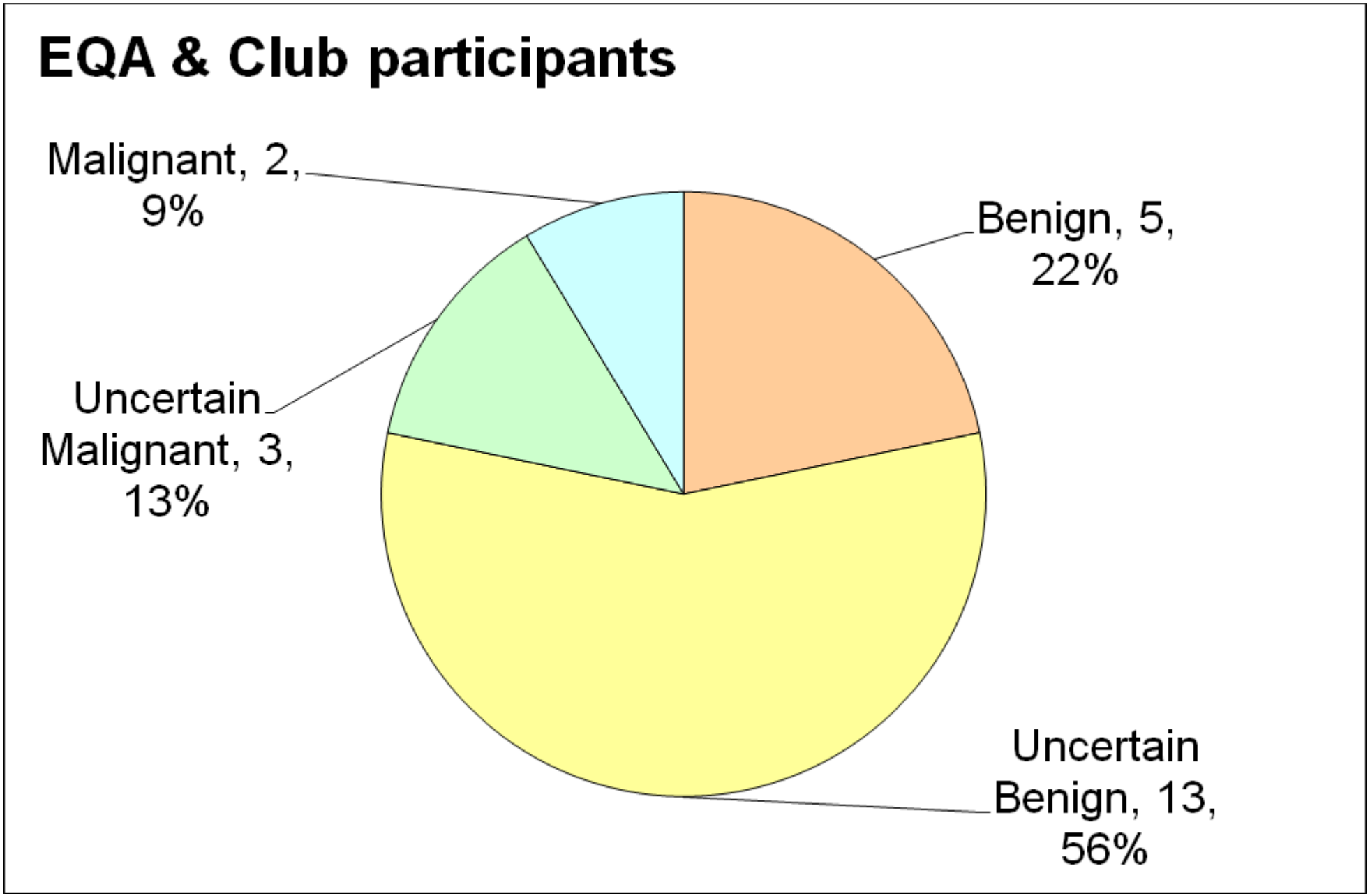
Cytology



Deep mitosis



N=25


EQA & Club participants
Malignant, 2, 9%
Benign, 5, 22%
Uncertain Malignant, 3, 13%
Uncertain Benign, 13, 56%

MPathDx*

- Unfortunately not enough responses or left blank.

*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=5

This has quite a plexiform morphology, relatively superficial. Probably a plexiform spitz naevus, usually ALK positive. I'd like a re-excision; conservative margins fine with me

This is a combined nevus, with Spitz nevus as one of the populations. Thus labelled as combined Spitz Nevus.

IHC for kinase fusions can be performed

Very spitzoid appearance.

EQA Participants: Uncertain favour benign N=13

I think it is within the Spitz family of lesions. I think it is an 'Atypical Spitz Tumour' , low risk subtype, due to the bland cytology, but it shows presence of a single atypical mitosis in superficial dermis and ,focal epidermal thinning., and asymetry. Therefore, I would classify it as MELTUMP, probably benign. Needs 0.5-1cm clearance and shorter follow up than a melanoma (5 years only).

Atypical Spitz tumour. Need further workup with molecular work up

Atypical Spoitzoid tumour favour benign needs thorough IHC and analysis using a proper digital system

Atypical favour benign: Epithelioid, retraction artefact, scattered inflam cells, no epithelial infiltration

Atypical favoure benign: quite epitheliod with maturation, no mitotic activity or pagetoid spread. Some nuclei are with open chromatin while others appear hypercromatic. Immunostains might help: P16, S100, ki-67, Braf, Bap-1,Prame

Favour atypical Spitzoid tumour of uncertain malignant potential

The morphological homogeneity of the lesion suggests to me a mutation driven lesion

Almost symmetrical compound melanocytic lesion, no Pagetoid spread or contiguous proliferation, epidermis hyperplastic. Junctional componenet mostly of nests with moderately atypical Spitzoid cells. Similar nests of atypical Spitzoid cells present in upper dermis which seem maturing with dermis depth. No significant mitoses. Overall appears Spitz Naevus but cellular atypia is worrisome.

mainly dermal lesion - epitheoild morphology with Kamino bodies, vague plexiform architecture - would do kinases (ROS and Alk-1)

EQA Participants: Uncertain favour malignant

N=3

Atypical spitzoid tumour or spitzoid melanoma - few single cell intraepithelial pagetoid spread apart from large nests, Infiltrative pattern, Mitosis

Spitzoid features but no maturation in the centre and a relatively deep mitosis. Overall would clissify as an atypical Spitz vs Spitz melanoma.

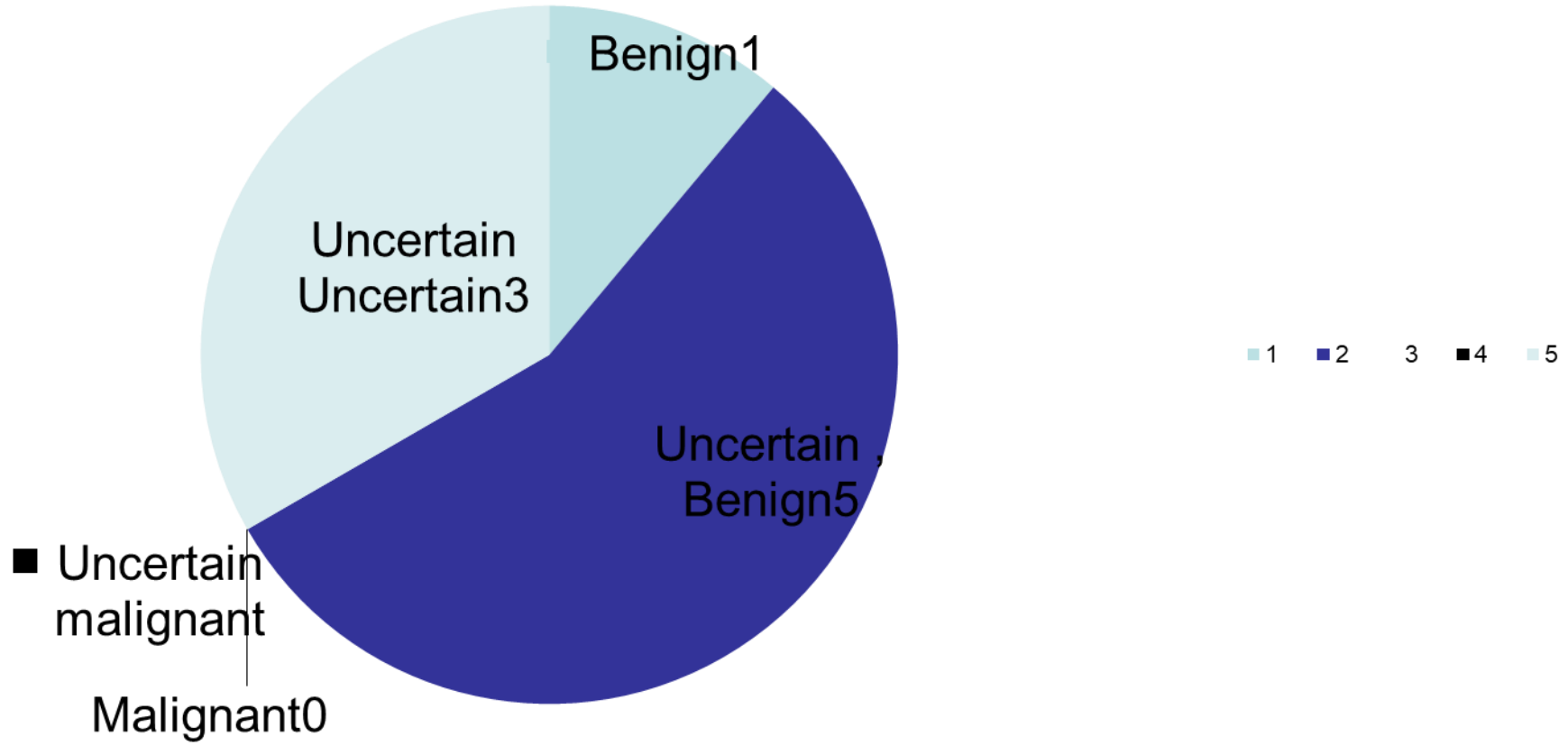
The punch biopsy shows a Compound Spitz naevus, predominantly intradermal, minimal intraepidermal component. The excision show somewhat more worrying features with epidermal thinning atypia of the superficial dermal component. Occasional mitoses were noted in the mid dermal level. The margins are involved

EQA Participants: Malignant

N=2

Melanoma: Difficult. Spitzoid lesion. Wider excision shows marked cytological atypia. I saw at least two mitoses in the mid and deep part. Borderline pre-ulcer changes. I could not find an annotation tool to do an accurate BT measurement.

Slide club Responses



SLIDE CLUB RESPONSES

Barnhill: Atypical compound spitzoid melanocytic neoplasm, **favor Atypical compound Spitz tumour**, biopsy and partial excision. [There is some uncertainty about the nature of this lesion. Complete excision is needed for further evaluation and to assure complete removal.].

Biswas:

Blokx: large lesion , ”spitzy” looking, quite variable cytonuclear aspect with epithelioid, spindle shaped and even some more nevoid cells, only focal pigmented. In some areas very large nuclei/cells. Low number of mitoses, but present also deeper. Limited junctional component. There is inflammation and some fibrosis. Based on morphology alone I would mainly consider an **atypical Spitz tumor/Spitz melanocytoma** (perhaps BRAF or MAP3K8 fused). I would certainly do additional IHC and molecular to assess signature and dignity.

Busam:

Carr: Punch Bx: Spitz naevus, ensure complete excision. Excision: Atypical Spitz naevus/tumour, favour benign (BAPOMA on steroids pattern in part of lesion). Additional studies: ALK-fusion and molecular work-up are quite re-assuring for a LOW-RISK lesion p16 loos is a concern but not sufficient for melanoma, PRAME is equivocal and does not change my recommendation to ensure complete excision with 3-5mm margin. LNs can be assessed by clinical & USSCan assessment. Follow-up recommended.

Carton:

Clarke:

Collina: **Atypical Spitz Tumor**. I would suggest complete excision and follow up

Craig:

Elder:

SLIDE CLUB RESPONSES

Evans:

Ferrara: This is a melanocytic tumour with clear-cut Spitz-like morphological features. The lesion is large, horizontally oriented, quite thick, with some inflammation, and with focally confluent pleomorphism. Although there is some tendency toward the decrease of the cell size from the surface to the depth, maturation is impaired in my eye. Cells are epithelioid and spindle, and the latter are often arranged in vertically oriented fascicles. I have noticed a few mitotic figures. Although the incision biopsy specimen showes some deep desmoplasia, I don't see unequivocal features of a 'Bastian naevus'. My provisional diagnosis is **atypical Spitz tumour, intermediate-to-low risk. May be ALK translocated**.

Jamieson:

Kempf:

Maheshwari:

Massi:

Muc: Tumour with spitz features, scattered mid dermal mitoses, some reduction in cell size with depth but overall poor maturation, and large size extending to margin. I would **favour atypical Spitz tumour** and request limited re-excision. No definite feature for melanoma. i think the genetic data is reassuring. Loss of P16 in deeper regions on IHC a bit concerning. PRAME less useful in this context. Morphology correlates to some extent with ALK rearrangment.

Mudaliar:

Oxley:

SLIDE CLUB RESPONSES

Requena: Compound Spitz nevus

Saldanha:

Scolyer: This is a difficult case. On morphology I would favour an atypical Spitz tumour/melanocytoma but would not make a diagnosis without immunostains (NTRK, ROS, ALK, BRAF, RAS) and molecular studies

Singh:

Slater:

Taibjee: "Spitzoid. Some phenotypic variation and pleomorphism as well as assymmetry. But minimal mitosis. So **atypical Spitz, but not frank melanoma,** and certainly warrants re-excision to ensure it is completely out. In real practice I would request IHC including BRAFV600E, ROS-1, ALK, NTRK, p16 and Ki67. This might help to establish Spitz pathway (and rule out a BRAFV600E melanoma). p16 loss might be a concern if present. It is the type of case which might benefit from other ancillary studies such as FISH or CGH."

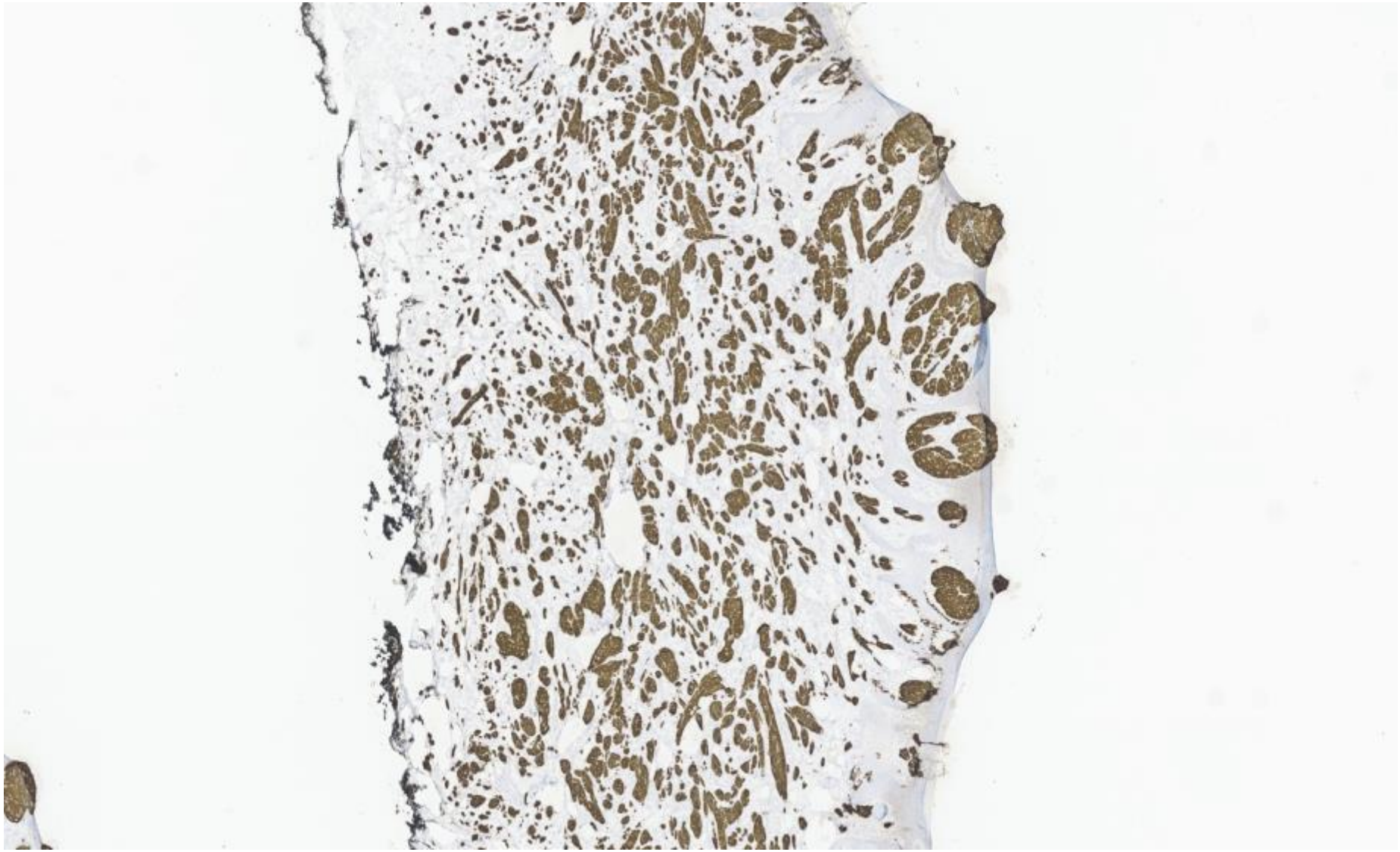
In the light of the new info:

1. With regards to IHC: ALK most likely indicates Spitz lineage underpinned by ALK fusion, so helpful. The p16 is heterogeneous, and would have prompted further ancillary (genetic) testing. That said, I am aware of recent data which suggests loss of p16 does not actually provide much prognostic utility. I am wary of interpretation of PRAME in such lesions (don't really know what it means). There seems to be some proliferation on Ki67, including deep aspect, which reinforces atypical designation.

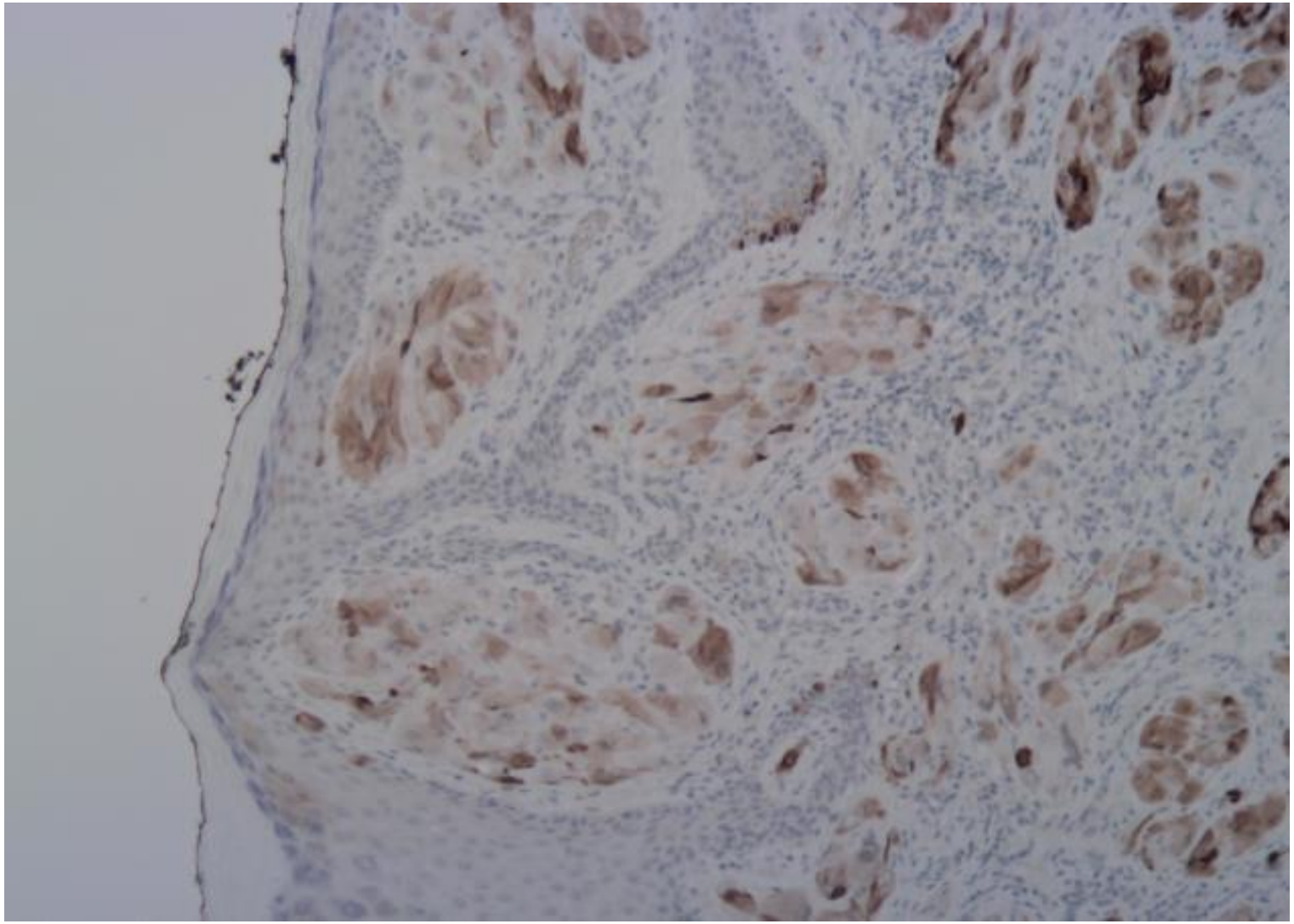
2. The absence of TERT promoter mutation and SNP array abnormalities is reassuring. So reinforces my original impression to keep as atypical Spitz, and certainly not to push into Spitz melanoma. The clinical consequence (for me) would be to recommend complete excision +/- follow up, but definitely not SLNB. The negative BRAF and NRAS is as expected for Spitz lineage i.e. mutually exclusive pathways.

Tiffin: Plexiform spitz tumour, uncertain favour benign

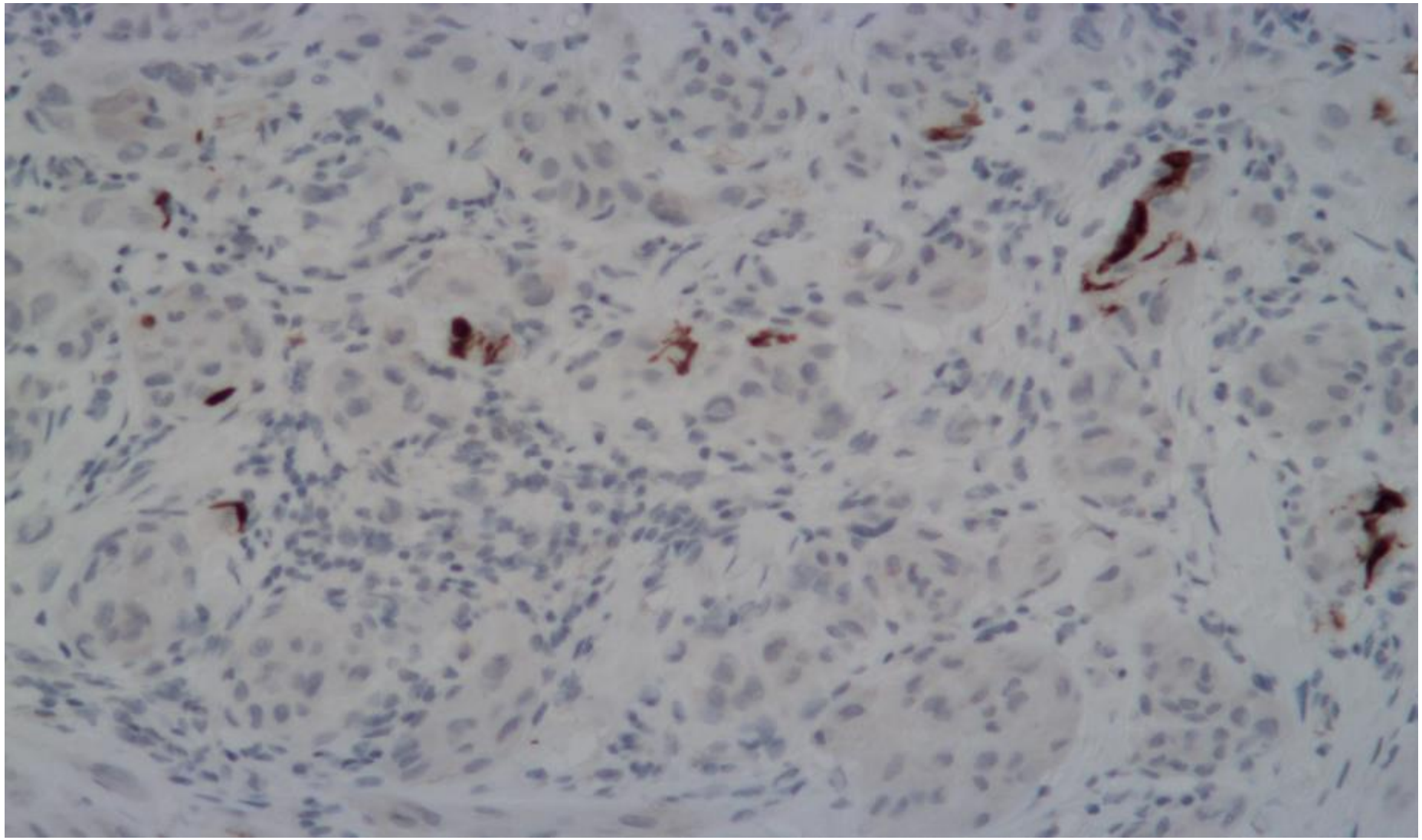
Additional tests , ALK1



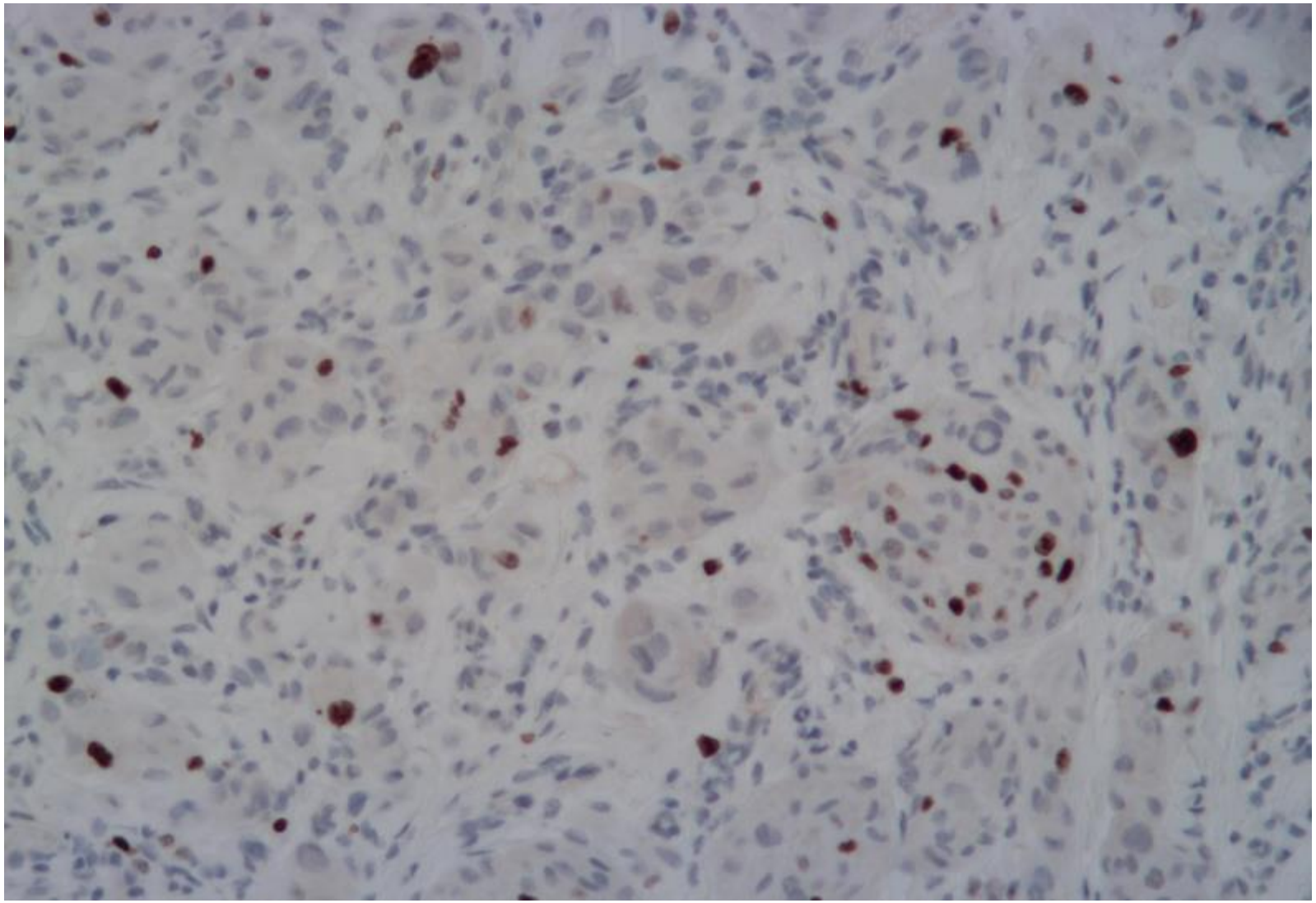
P16 , superficial



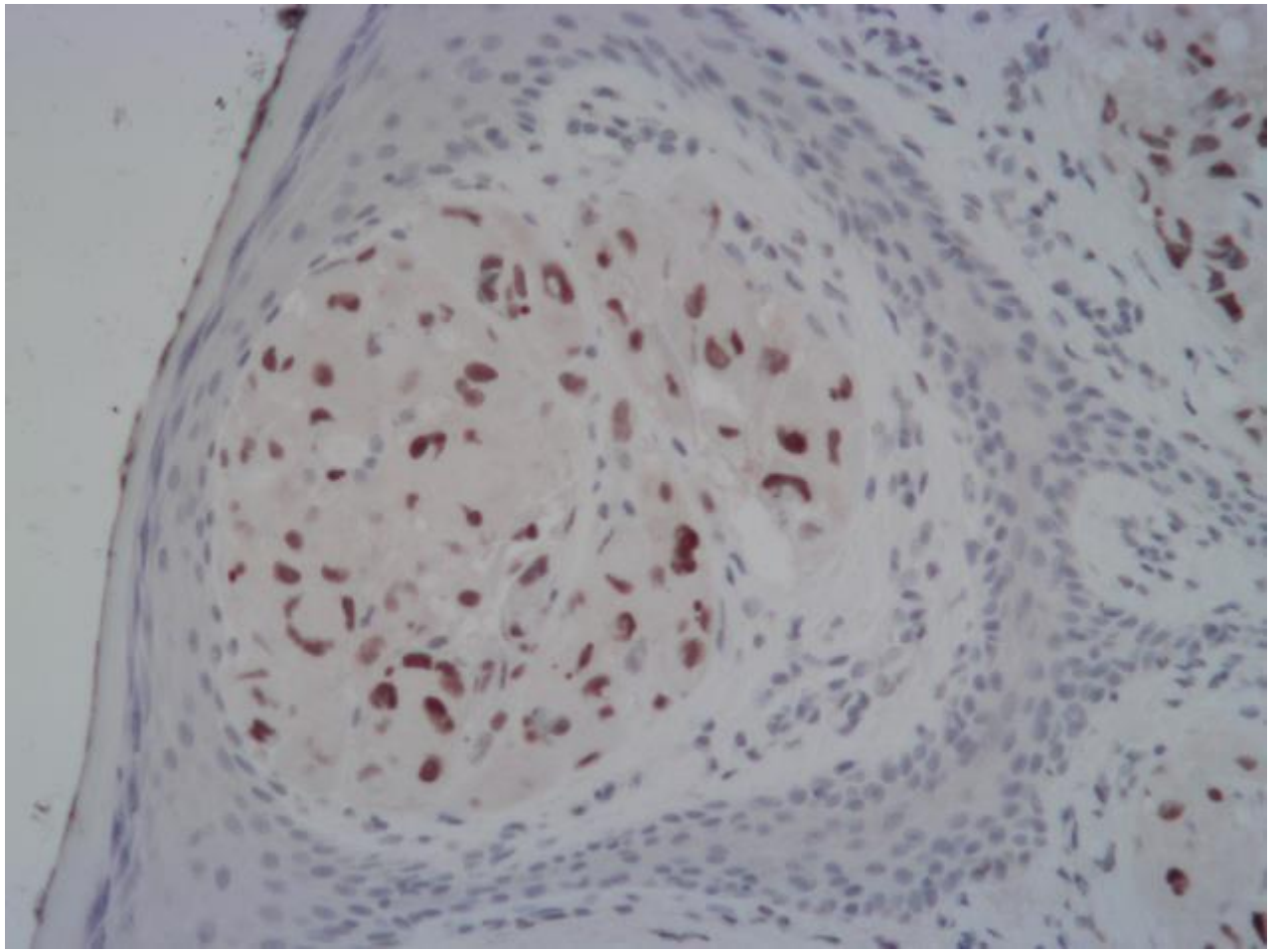
P16 Deep



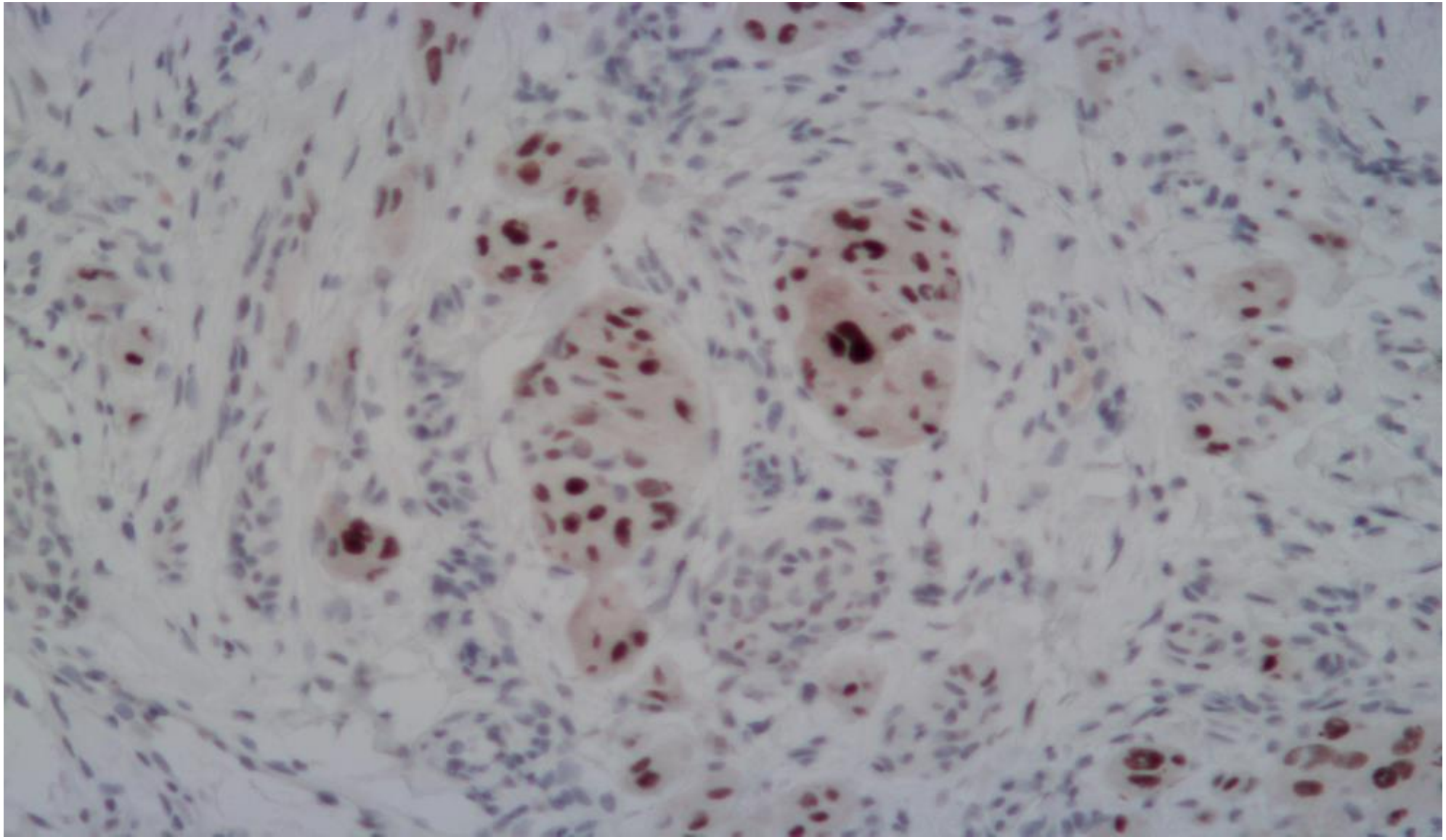
Ki67 , deep



PRAME



PRAME deep aspect



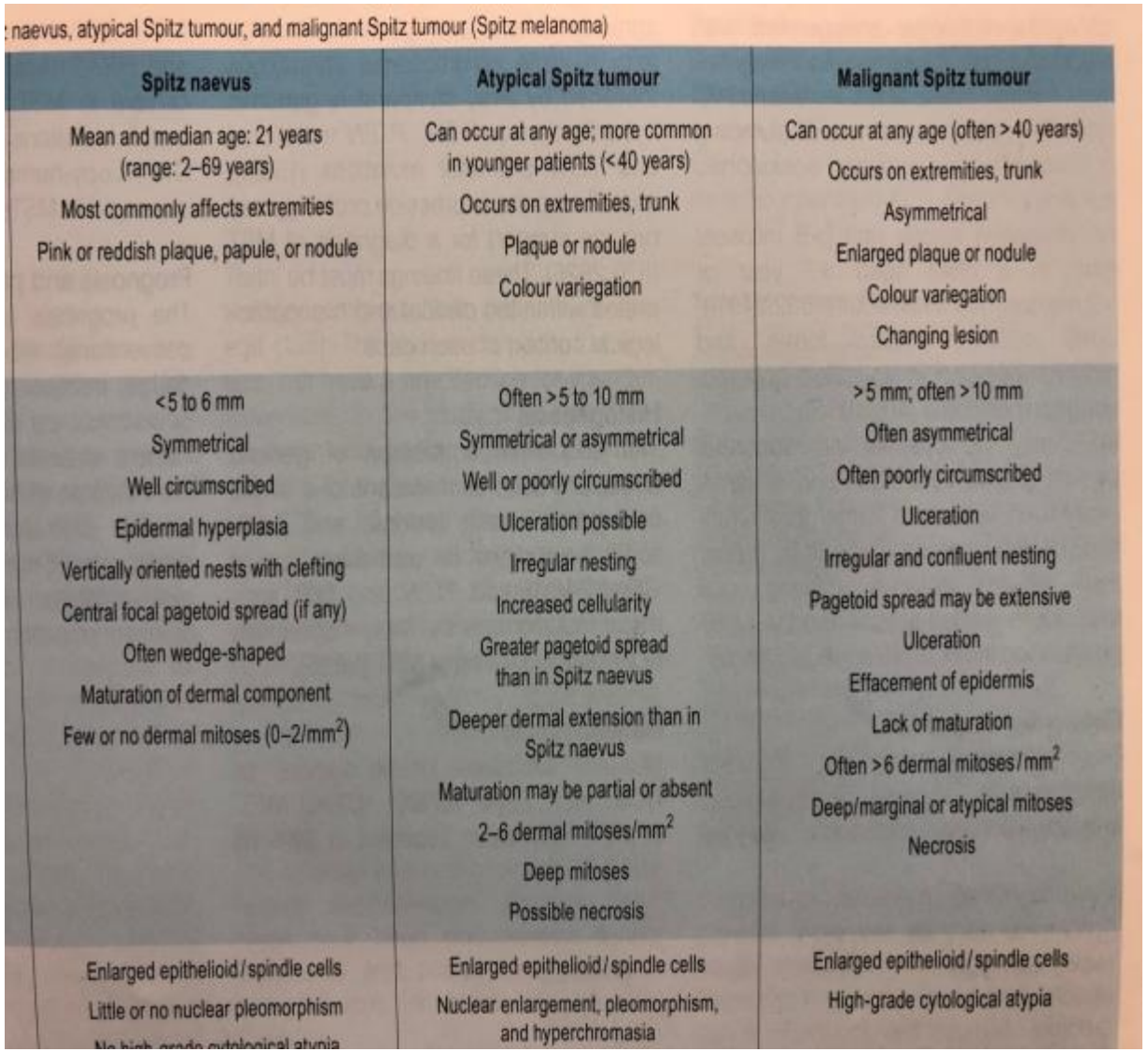
GENETICS

- Next Generation sequencer- No BRAF, NRAS or TERT promoter mutation

- FISH -CDKN2a - 40 cells Monosomy, 27 cells heterozygous loss , 20 cells homozygous loss . Variation in different fields.

- SNP array analysis – No significant copy number abnormalities or unbalanced structural chromosome abnormalities. . A negative result.

WHO Classification, 4th Ed



naevus, atypical Spitz tumour, and malignant Spitz tumour (Spitz melanoma)

Spitz naevus	Atypical Spitz tumour	Malignant Spitz tumour
Mean and median age: 21 years (range: 2–69 years) Most commonly affects extremities Pink or reddish plaque, papule, or nodule	Can occur at any age; more common in younger patients (<40 years) Occurs on extremities, trunk Plaque or nodule Colour variegation	Can occur at any age (often >40 years) Occurs on extremities, trunk Asymmetrical Enlarged plaque or nodule Colour variegation Changing lesion
<5 to 6 mm Symmetrical Well circumscribed Epidermal hyperplasia Vertically oriented nests with clefting Central focal pagetoid spread (if any) Often wedge-shaped Maturation of dermal component Few or no dermal mitoses (0–2/mm^2)	Often >5 to 10 mm Symmetrical or asymmetrical Well or poorly circumscribed Ulceration possible Irregular nesting Increased cellularity Greater pagetoid spread than in Spitz naevus Deeper dermal extension than in Spitz naevus Maturation may be partial or absent 2–6 dermal mitoses/mm^2 Deep mitoses Possible necrosis	>5 mm; often >10 mm Often asymmetrical Often poorly circumscribed Ulceration Irregular and confluent nesting Pagetoid spread may be extensive Ulceration Effacement of epidermis Lack of maturation Often >6 dermal mitoses/mm^2 Deep/marginal or atypical mitoses Necrosis
Enlarged epithelioid/spindle cells Little or no nuclear pleomorphism No high-grade cytological atypia	Enlarged epithelioid/spindle cells Nuclear enlargement, pleomorphism, and hyperchromasia	Enlarged epithelioid/spindle cells High-grade cytological atypia

- Case 245
- Age 21
- Extremity
- Plaque

- 13mm
- Asymmetrical
- ? Poorly circumscribed
- No ulceration/ effacement
- Irregular nesting
- Lacks maturation
- Mitoses 2mm
- Deep mitosis
- No necrosis
- Cytological atypia present

WHO classification 4th ed

IHC	HMB45 and Ki-67 staining diminished with depth in dermal component Low Ki-67 proliferation index (<5%)	HMB45 and Ki-67 staining diminished or variable with depth Low to intermediate Ki-67 proliferation index (5–15%)	HMB45 and Ki-67 deep staining commor Elevated Ki-67 proliferation index (>20% p16 expression may be diminished or absent
Molecular pathology	Array CGH: isolated gains of 7p and 11q, tetraploidy Activating *HRAS* mutations Kinase fusions	Array CGH: often ≥ 1 chromosomal abnormality Kinase fusions *PTEN* mutations Heterozygous or homozygous loss of 9p21 may occur	Array CGH: >1 chromosomal abnormalit Kinase fusions *BRAF* and *NRAS* mutations rare *HRAS* mutations rare *PTEN* mutations Homozygous loss of 9p21 *TERT* promoter mutations
Prognosis	Very low (almost no) risk of progression	Low risk of progression Almost always indolent Clinical recurrences occur	Regional clinical lymph node metastases occur Rare distant metastases and death

CGH, comparative genomic hybridization; IHC, immunohistochemistry.

- Ki67 deep
- 20%, focally
- P16- loss
- SNP – Neg
- Alk Fusion
- 9p21 – areas with loss
- No TERT

PRAME Expression Correlates With Genomic Aberration and Malignant Diagnosis of Spitzoid Melanocytic Neoplasms

- Pedram Gerami 1, Sarah Benton 1, Jeffrey Zhao 1, Bin Zhang 1, Nathaniel Lampley 3rd 1, Andrew Roth 1, Anastasiya Boutko 1, Shantel Olivares 1, Klaus J Busam 2

- Am J Dermatopathology , 2022 Aug 1;44(8):575-580

PRAME and SPITZ

- 59 Spitzoid tumours.
- PRAME positive in 33.3% diagnosed as malignant
- PRAME positive in 2.6% diagnosed as benign
- 4 of 8 cases with TERT promoter mutation, Positive
- 4 of 51 cases TERT negative , positive
- 3 cases metastasized – 2 PRAME positive

Pointer to atypical/malignant lesion, but with occasional false positives and negatives

SUMMARY

- Spitz lesion with ALK fusion [i.e. true Spitz]
- Has some concerning features on morphology and immunohistochemistry.
- Genetics – No features which push it into malignant category

ALK fused Spitz

- They present more commonly on extremities of young patients.
- Most lesions are amelanotic and are the largest lesions among all the translocated Spitz neoplasms.
- Typical histology : elongated nests of spindled melanocytes, in a wedge-shaped/bulbous distribution and infiltrative pattern at the periphery. No Kamino bodies are usually present.
- Overall, it appears that the category which is most represented in ALK fused lesion is AST, with a minor component represented in Spitz naevi, and Spitz melanoma categories.
- Front Oncol. 2022;

ATYPICAL SPITZ TUMOUR
[SPITZ MELANOCYTOMA]

- WHO classification of Skin Tumours, 5th Ed, online Beta version.
- Definition:
- Spitz melanocytoma (atypical Spitz tumour) is a melanocytic neoplasm characterized by one or more atypical features, and are morphologically and genetically “intermediate” between Spitz naevus and melanoma.
- No additional information compared to 4th edition at present.

ESP, EORTC, and EURACAN Expert Opinion: practical recommendations for the pathological diagnosis and clinical management of intermediate melanocytic tumors and rare related melanoma variants

- Virchows Archiv (2021) 479:3–11

Spitz melanocytoma (Atypical Spitz tumour)

- Excision with a 5–10-mm margin is recommended in AST.
- It is desirable that excision margins are tailored to individual cases based on size and depth of involvement. A SLN biopsy procedure is not currently recommended in these tumors.

Recommended for this case. No evidence of distant spread so far.

Incidence and outcome of Spitzoid tumour of unknown malignant potential (STUMP): an analysis of cases in the Netherlands from 1999 to 2014

- 0.7% of 1237 AST diagnosed in the Netherlands were reported to have developed metastases
- Br J Dermatol.. 2020 Dec;183(6):1121-1123

ESP, EORTC, and EURACAN Expert Opinion, Molecular testing of ambiguous lesions

Mutation detection by sequencing or others molecular biology methods (NGS; Sanger sequencing, real-time PCR, pyrosequencing)

- BRAF exon 11, 15; N/H/K-RAS exon 2, 3; KIT exon 11, 13, 17 and 18;, NF1;
- GNAQ exon 4 and 5; GNA11 exon 4 and 5;
- CYSLTR2 p.(L129Q);
- PLCB4; BAP1; SF3B1;
- EIF1AX; MAP2K1;
- TERT promoter mutations;
- CTNNB1.

- **Fusion detections (FISH, RT-PCR, NGS targeted RNAseq, nanostring)**
- ALK; ROS1; NTRK1; NTRK3; MAP3K8; BRAF; MET; RET; PRKCA.

- **CNV analysis (CGH array, NGS, nanostring; shallow NGS, MLPA)**
- 3p21 loss (BAP1); 9p21 loss, (CDKN2A); gain 11p, (HRAS), specific, breakpoints areas in fusion Genes, assessment of number, and type of CNV

TSO500 capability:

On TSO500 and should call successfully

On TSO500 but unreliable calling

Not on TSO500

ALK Fusion Atypical Spitz Melanocytoma

- Quite marked differences between punch biopsy and excision.
- Full work up required genetics.
- Some genetic techniques, eg CNV can take at least 4 weeks to turnaround.
- Genetic techniques can be blunt as tend to look at whole section so could potentially miss small sub-clones.