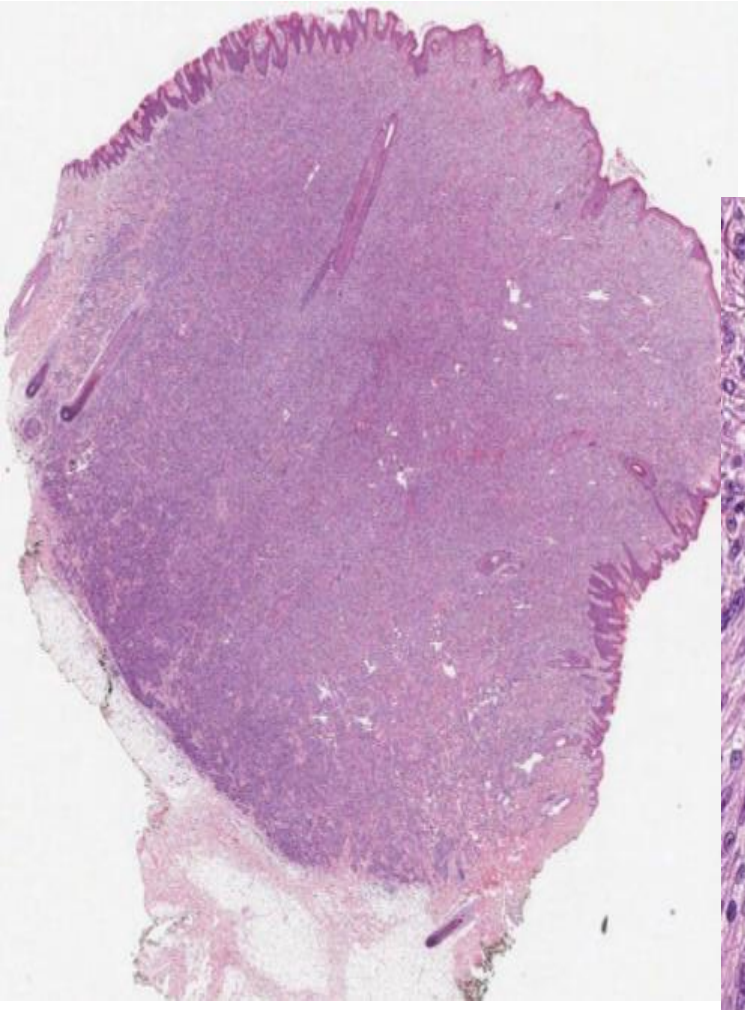
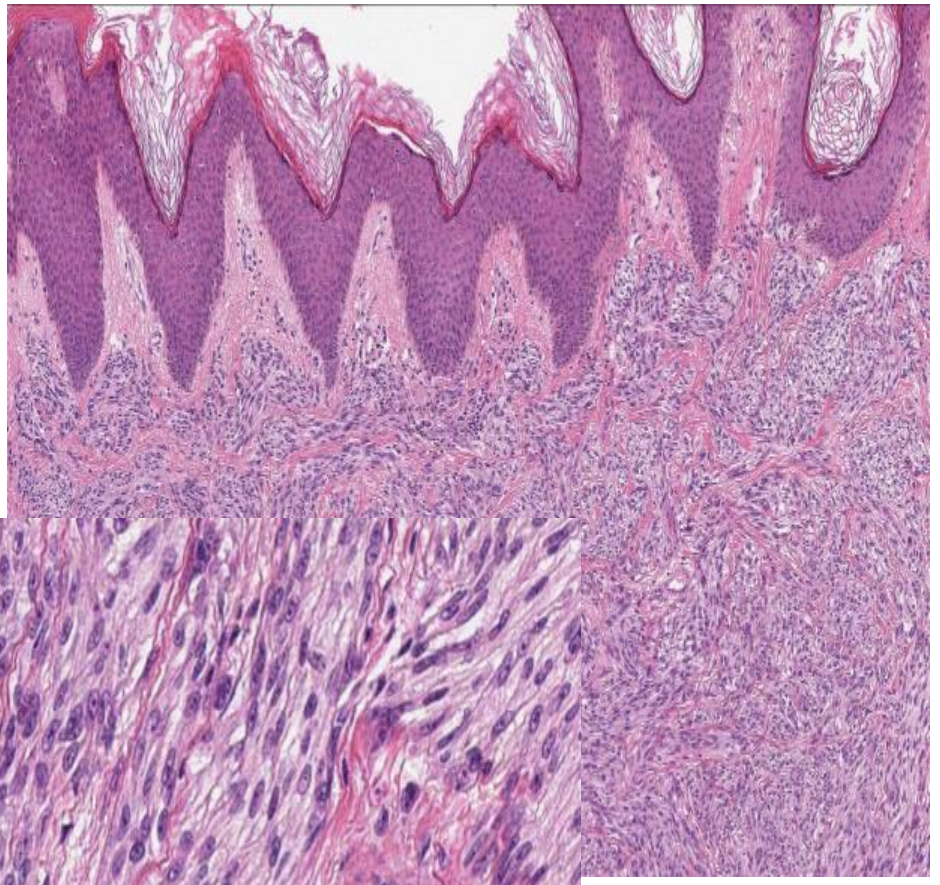
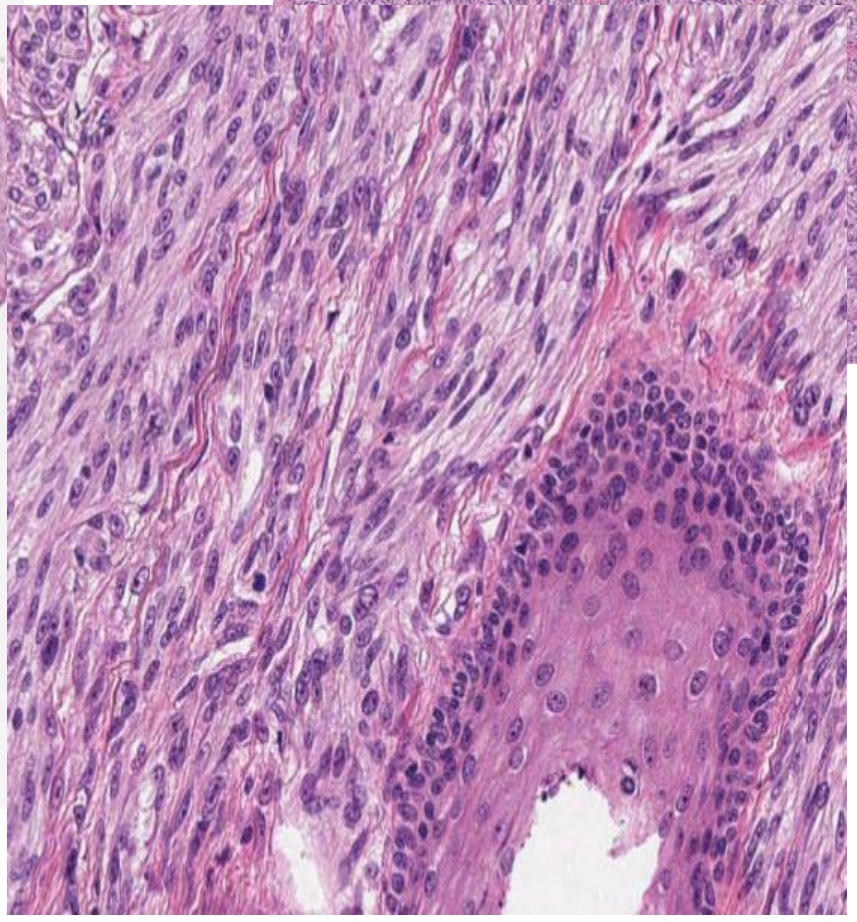
Case 246

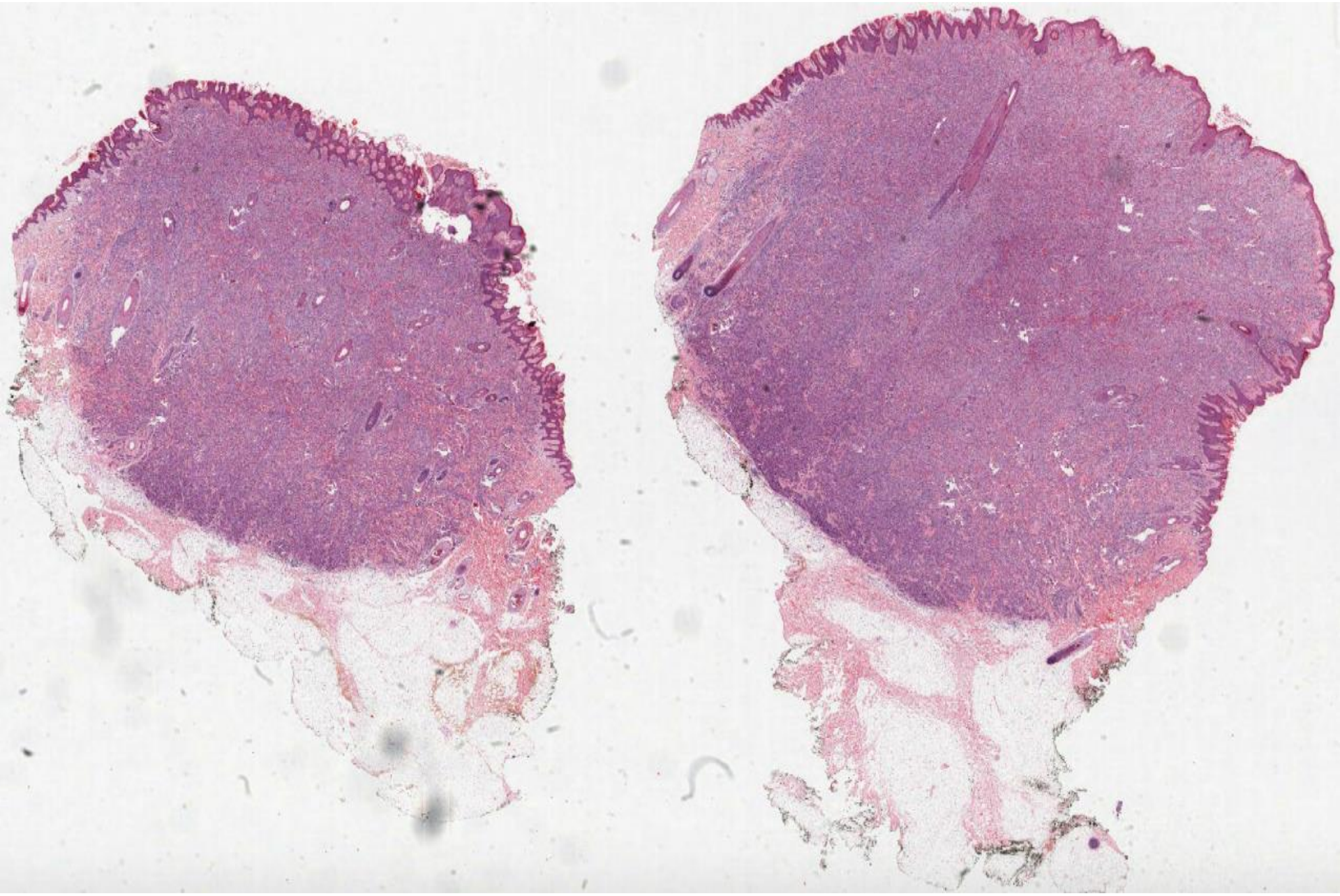
Female 22 years

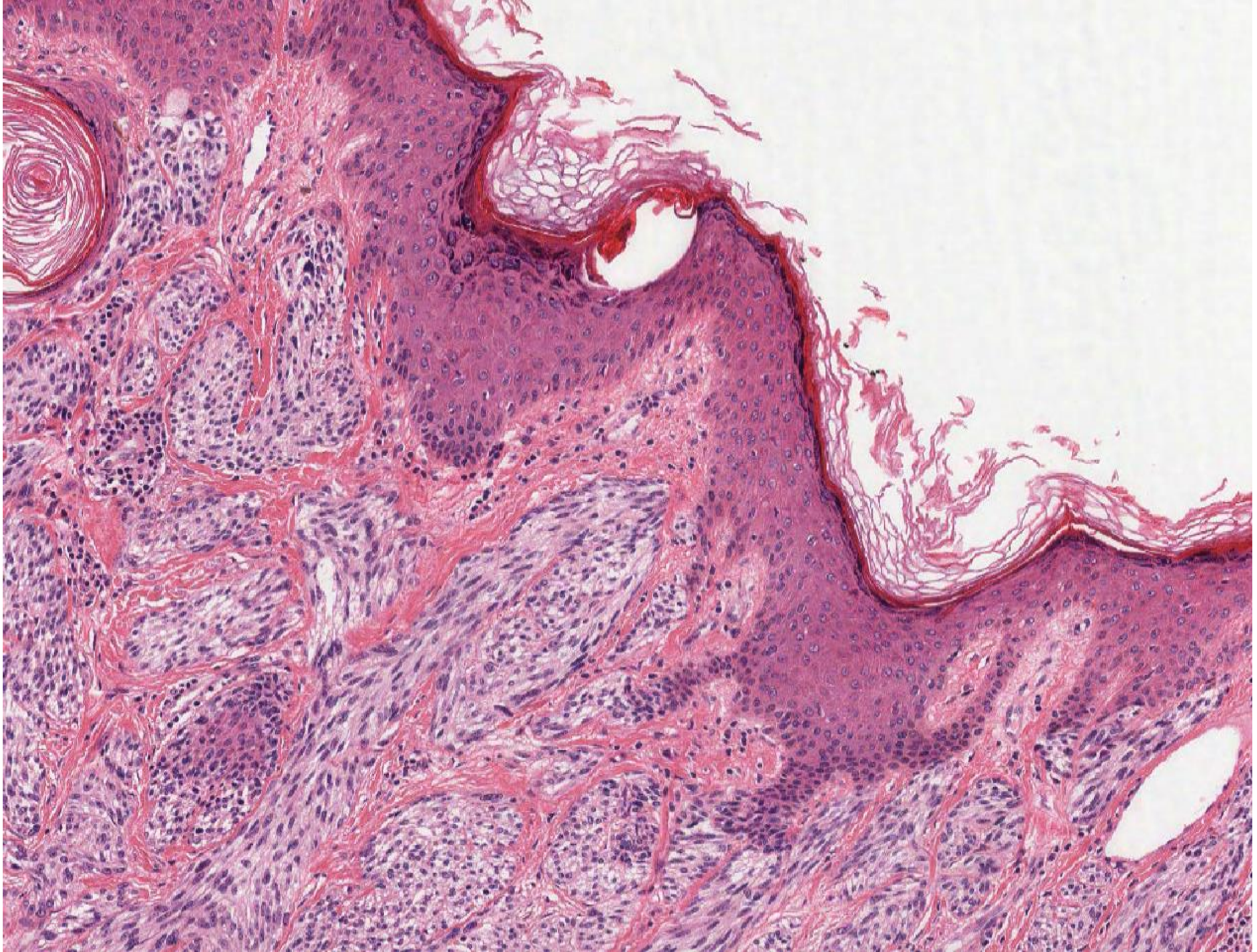
Nodular lesion left post auricular area, ? appendage tumour.

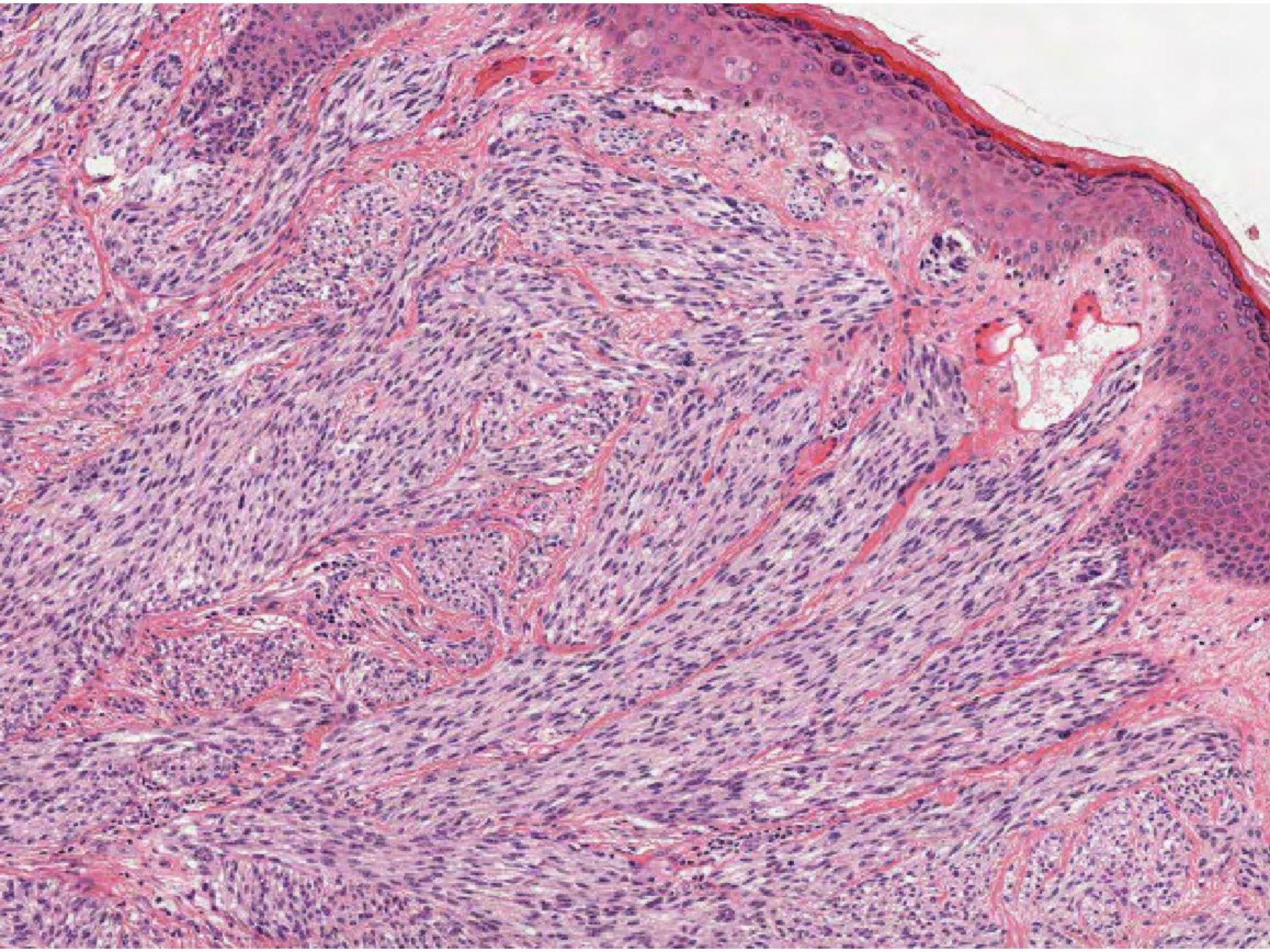


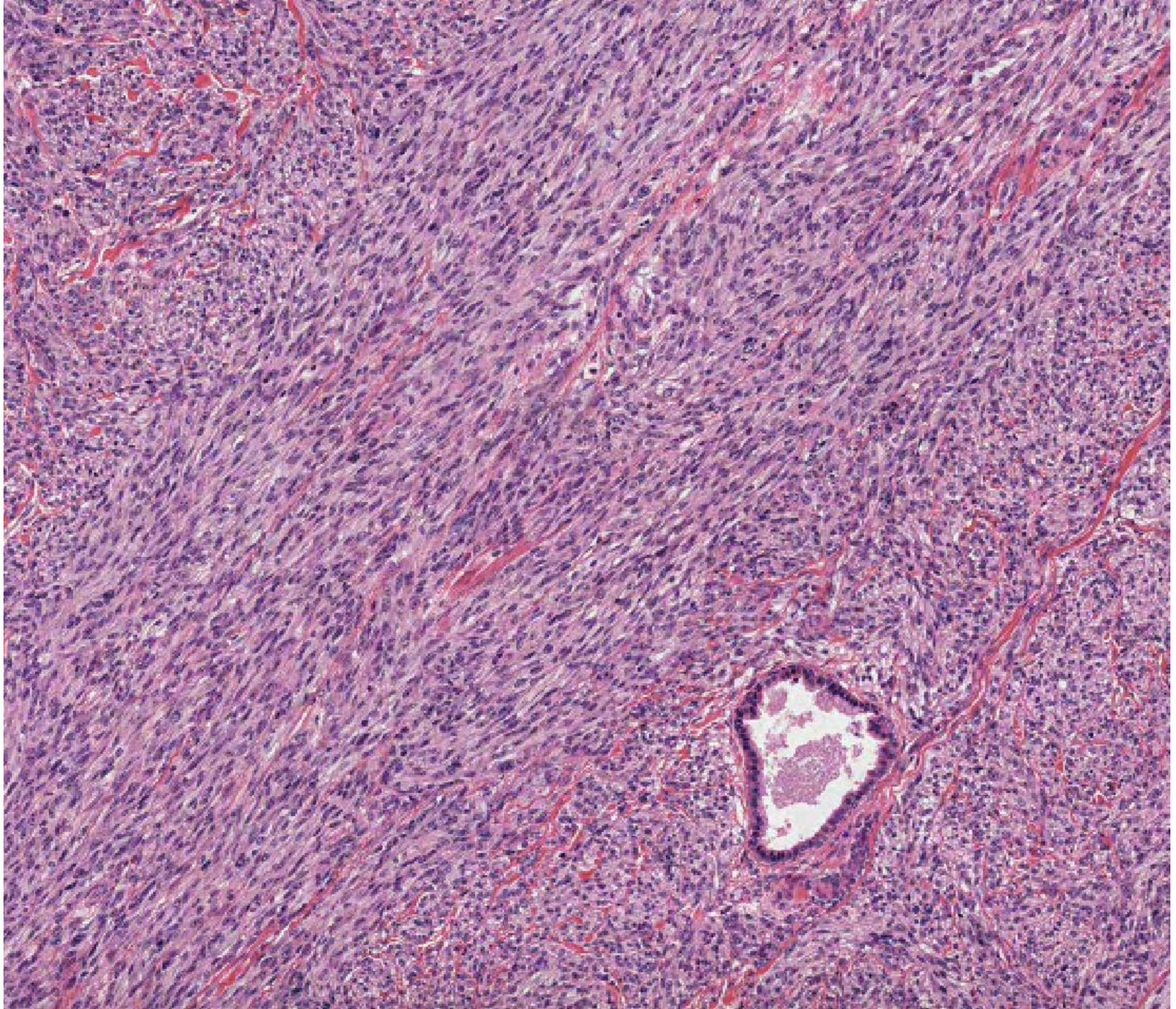


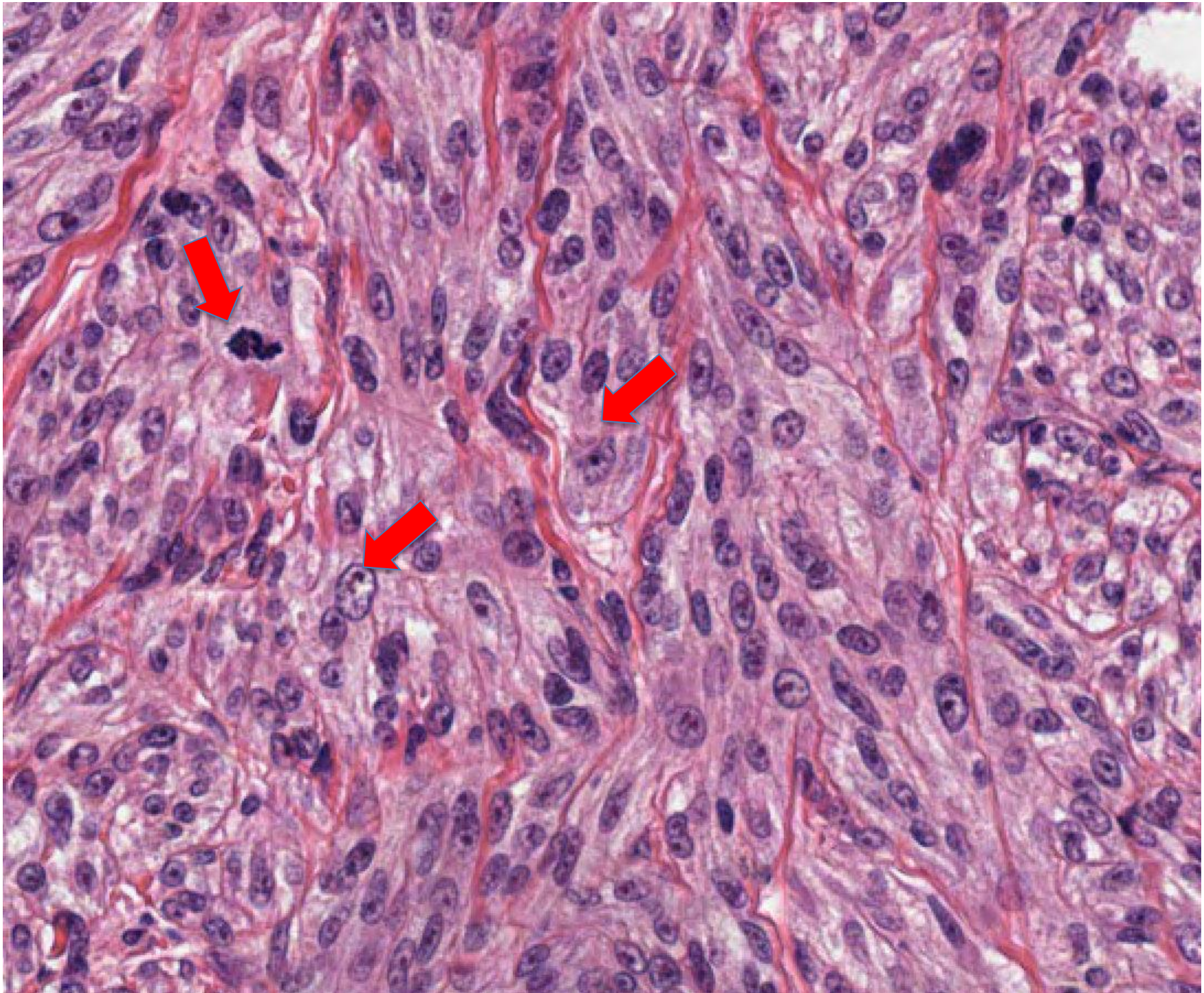


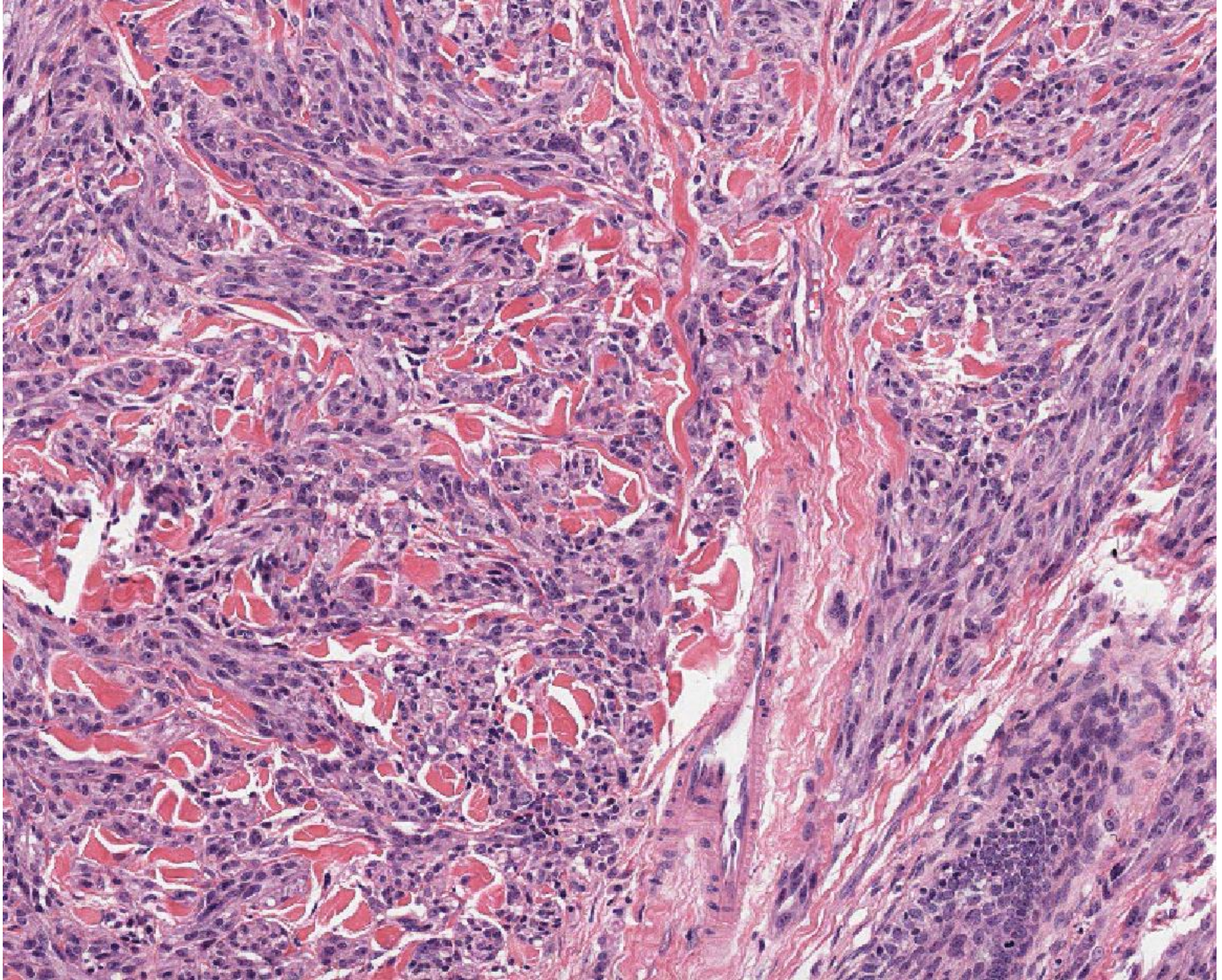


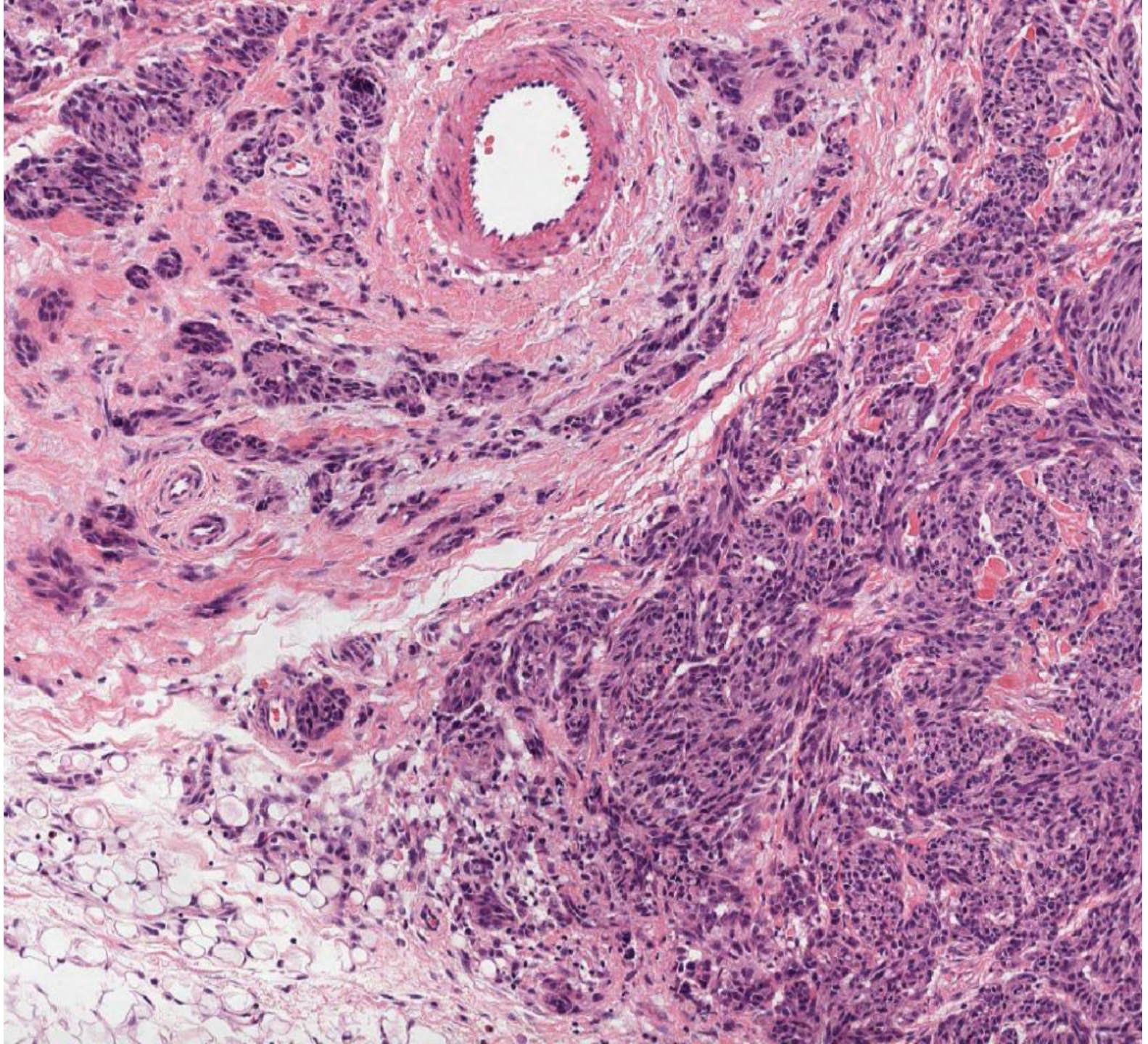


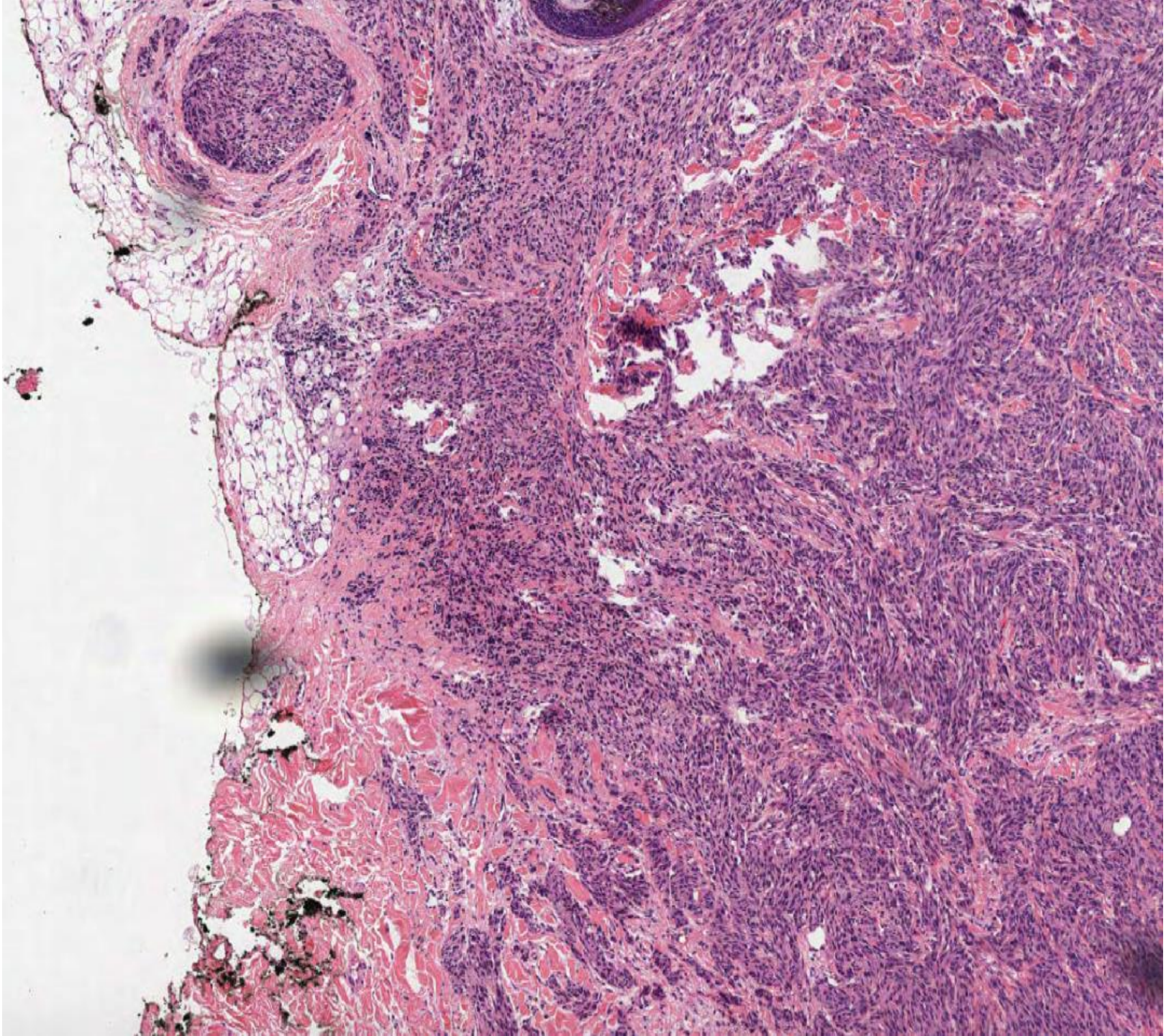




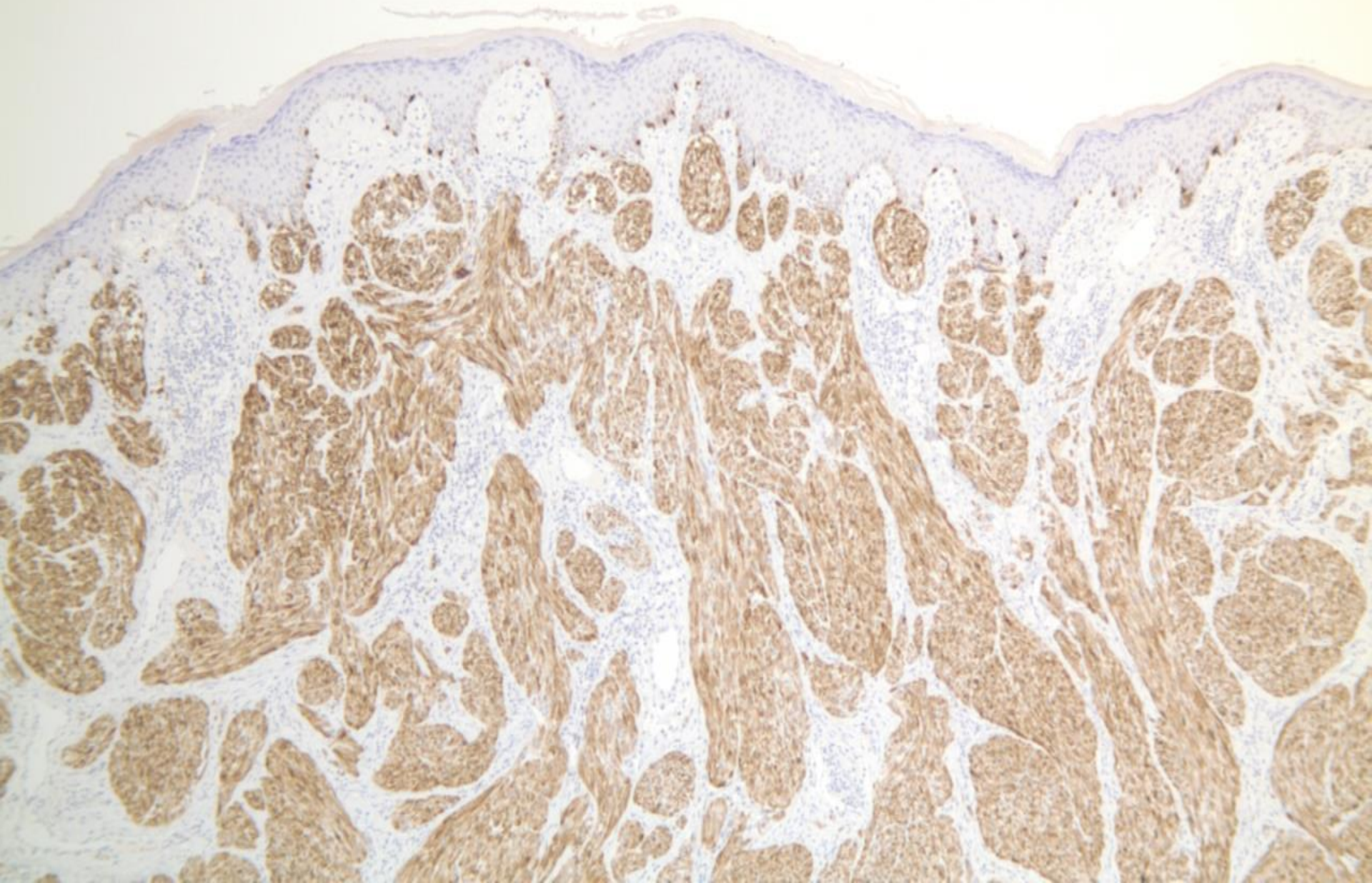


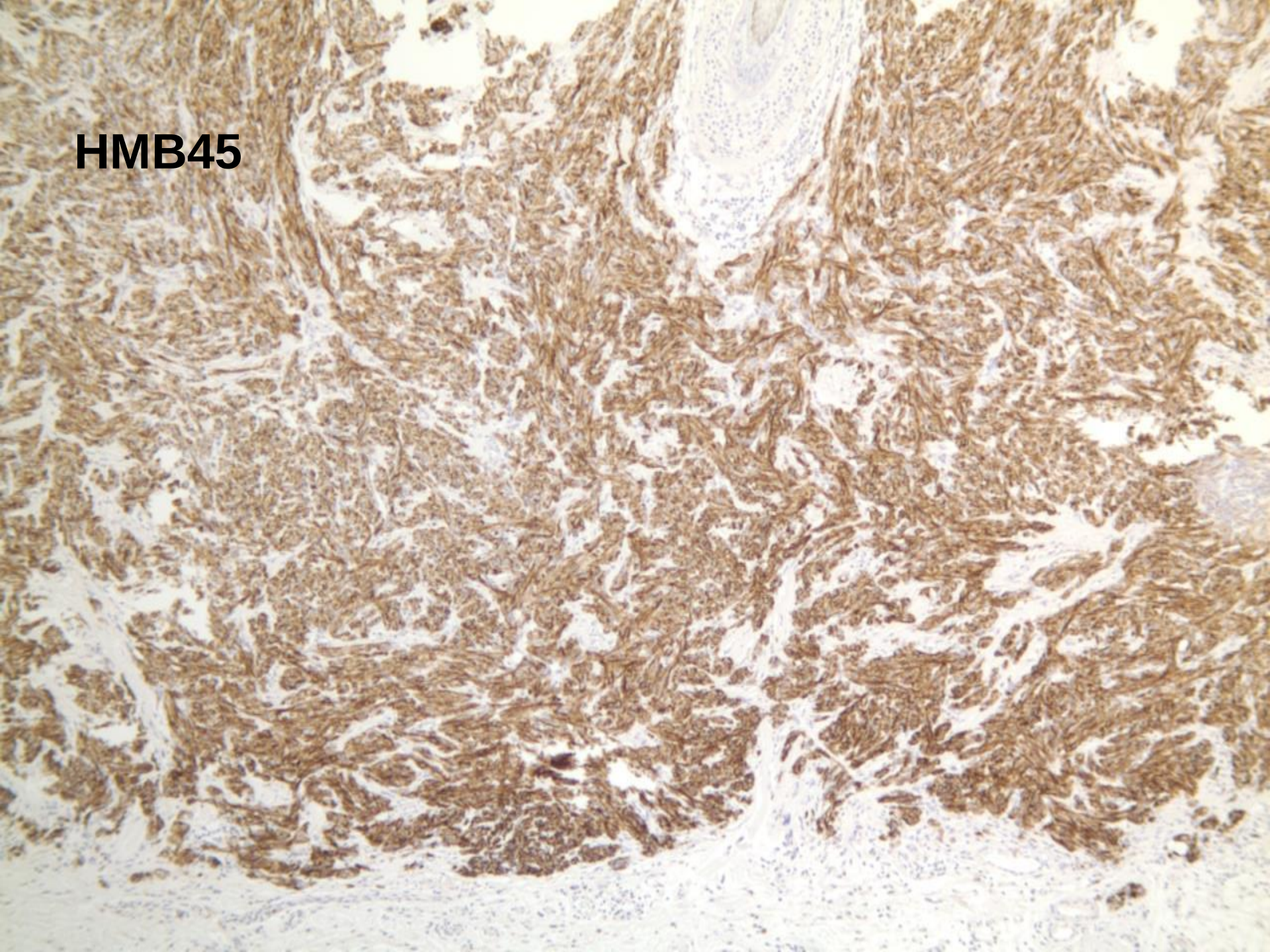




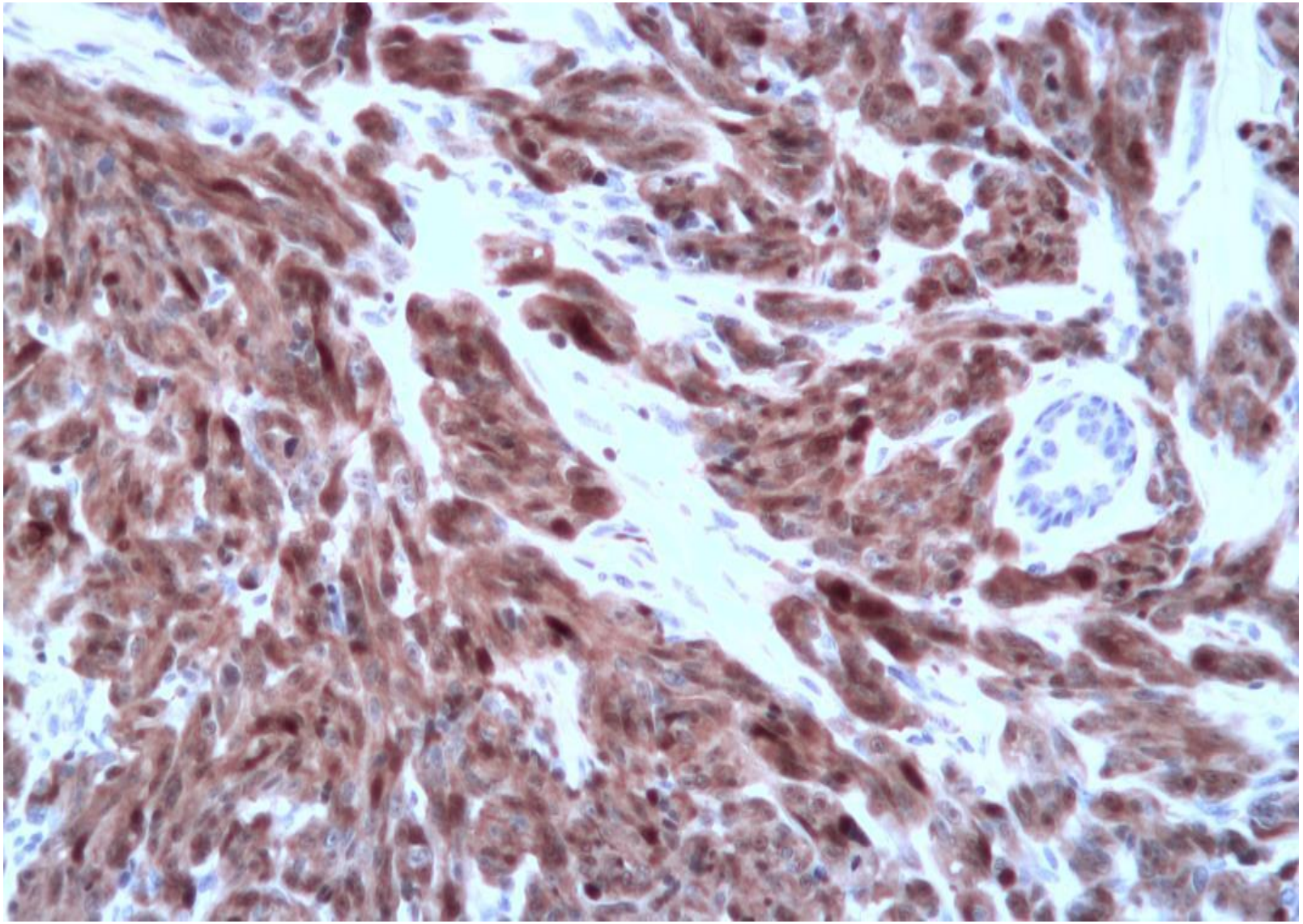


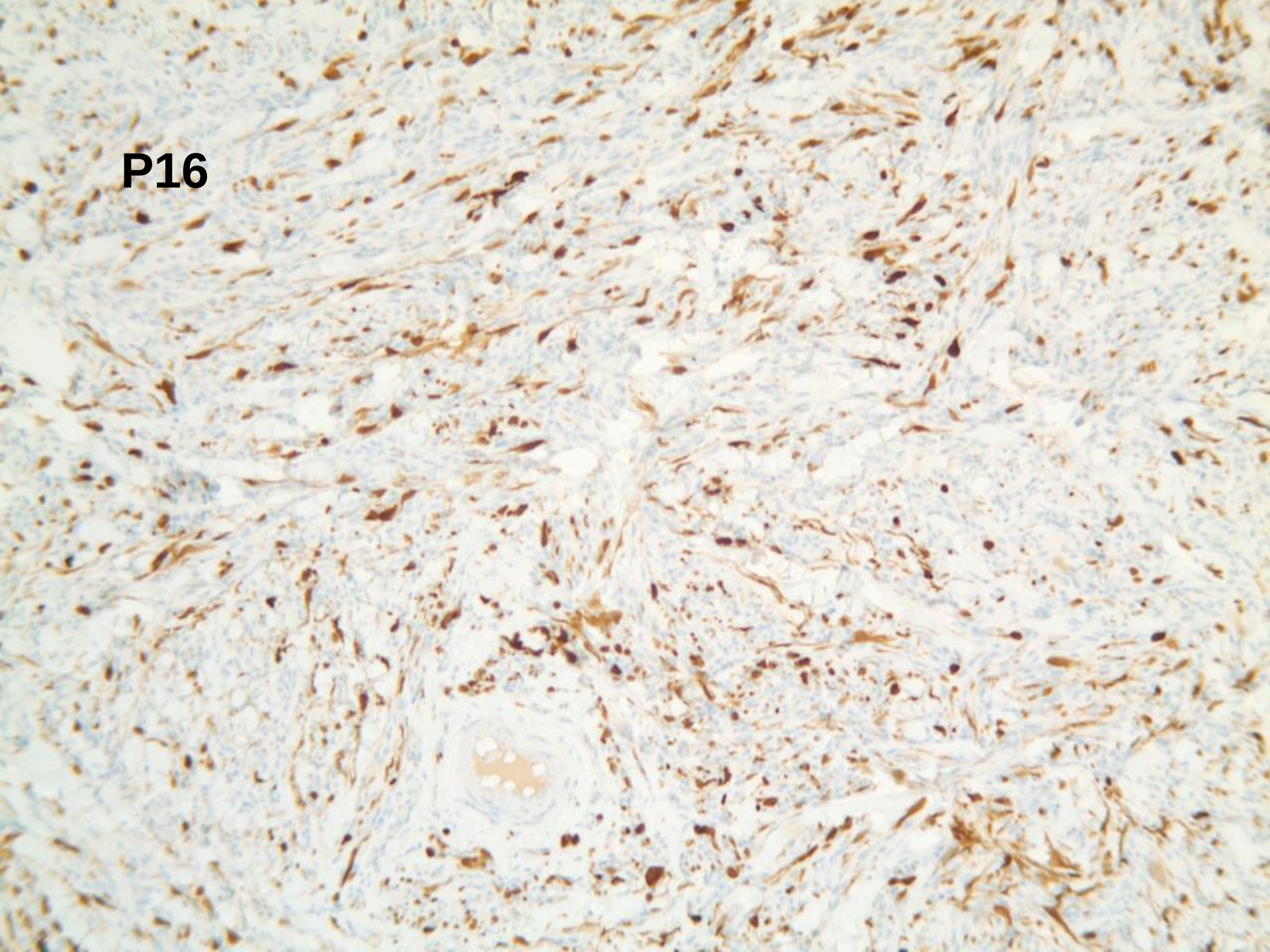
MELAN A



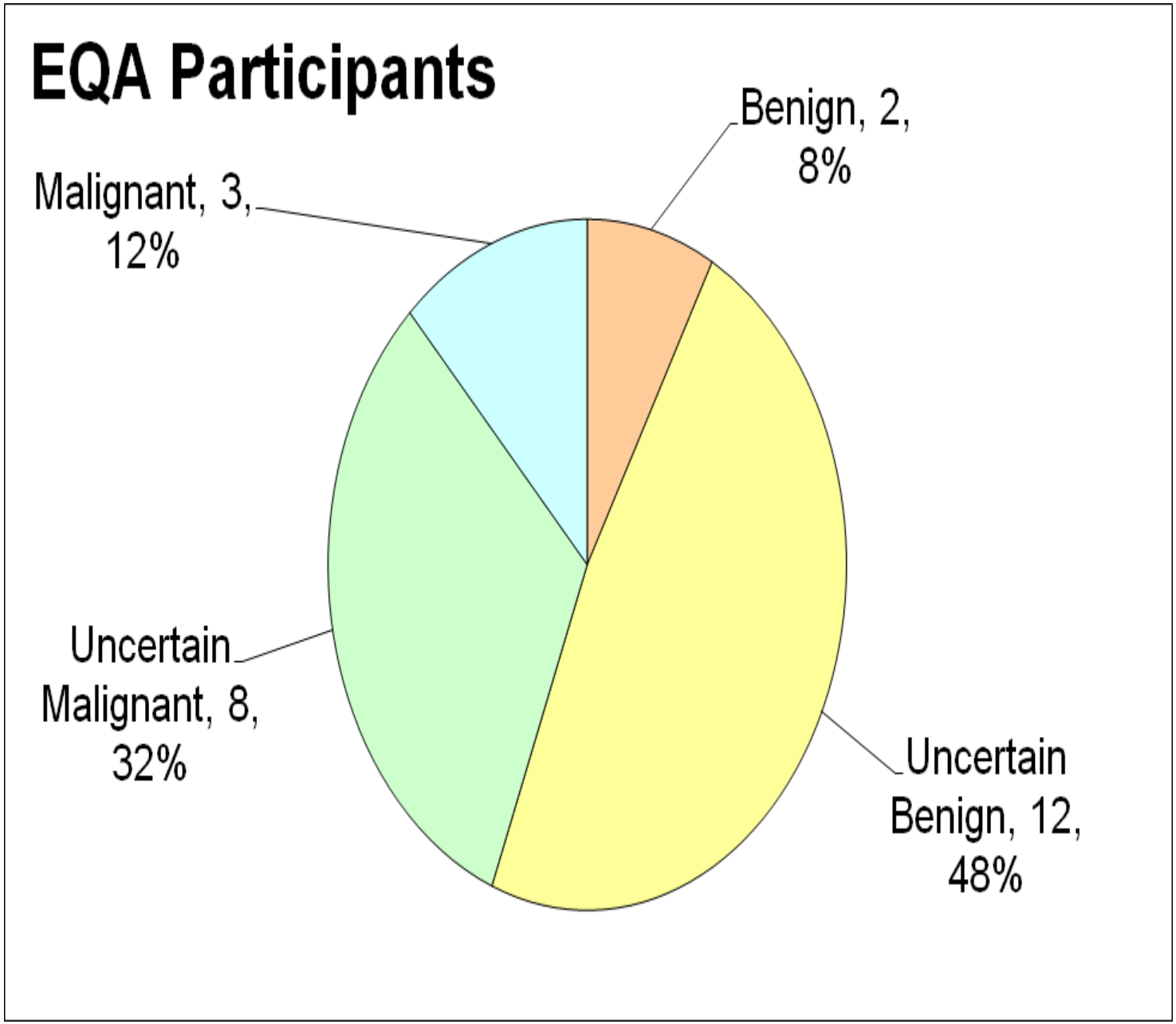

HMB45

s100




P16

N=2


EQA Participants
Benign, 2, 8%
Malignant, 3, 12%
Uncertain Malignant, 8, 32%
Uncertain Benign, 12, 48%

EQA Participants:Benign

DPN: Features of a deep penetrating naevus esp the anatomical location, the lack of maturation and the mild degree of atypia in epithelioid melanocytes

Spitz N.: Bundles of spindle melanocytes, no epithelial infiltration, no mitoses seen bbig lesion but looks Spitz

EQA Participants: Uncertain

N=X

This looks sizeable, goes deep. Don't think I see any mitoses. Again plexiform morphology but very packed. Would also do the HMB45/p16/ki67 panel, and moleculars for CDNk2/TERT promoter for better stratification. Overall on morphology alone I'd probably put this in the Atypical Spitz Category. Current margins look too close for comfort so would like 5-10 mm margins on this (plus follow up).

Cellular amelanotic blue nevus needs thorough IHC and analysis using a proper digital system

This is a nodular amelanotic atypical spitz tumour. NGS is required to confirm.

Atypical favour benign: Dense epithelioid and spindle melanocytic proliferation. No mitotic activity or pagetoid spread. Helpful immunostains: P16, S100, ki-67, Braf, Prame

Atypical favour benign: Cellular blue naevus

Atypical favour benign: the morphological homogeneity of the lesion suggests to me a mutation driven lesion

Spitzoid appearance but atypical, with limited or no obvious maturation with depth. Mitotic figures present. Favour atypical spitz tumour. Molelcular testing may be contributory - to have information about underlying molecular driver.

Favour atypical cellular blue naevus due hypercellularity, mild nuclear pleomorphism with nucleoli and occasional mitotic figures.

EQA Participants: Uncertain

N=X

I think it is within the Spitz family of lesions. I think it is an 'Atypical Spitz Tumour' , high risk subtype. due to the presence of significant cytological atypia, atypical mitoses in mid dermis, and lack of maturation. However it is symetrical and respects the adnexal structures rather than destroying these. Therefore, I would classify it as MLTUMP, high risk subtype. Needs at least 1cm clearance and shorter follow up than a melanoma (5 years only).

Possible malignant blue naevus

difficult lesion, intradermal, mainly spindle cells with focal interlacing fascicles - occasional mitoses, deep, dissects collagen - probably an atypical Spitz variant

- Difficult lesion, need IHC and probably molecular. Could be ALK positive spitz. Deep mitosis is seen, edging towards malignant.
- predominantly dermal Spitzoid spindle cell lesion with occasional mitoses. extending deep and pushing lower border into the subcutis.

EQA Participants:

N=X

Spitzoid melanoma

Compound but largely intradermal melanocytic proliferation of moderately atypical cells with densely cellular sheets, spindling and mitotic activity including deep mitoses; no maturation evident; cell remain atypical throughout. It has features of malignant tumour; and I favour it to be a nodular melanoma

MSG members

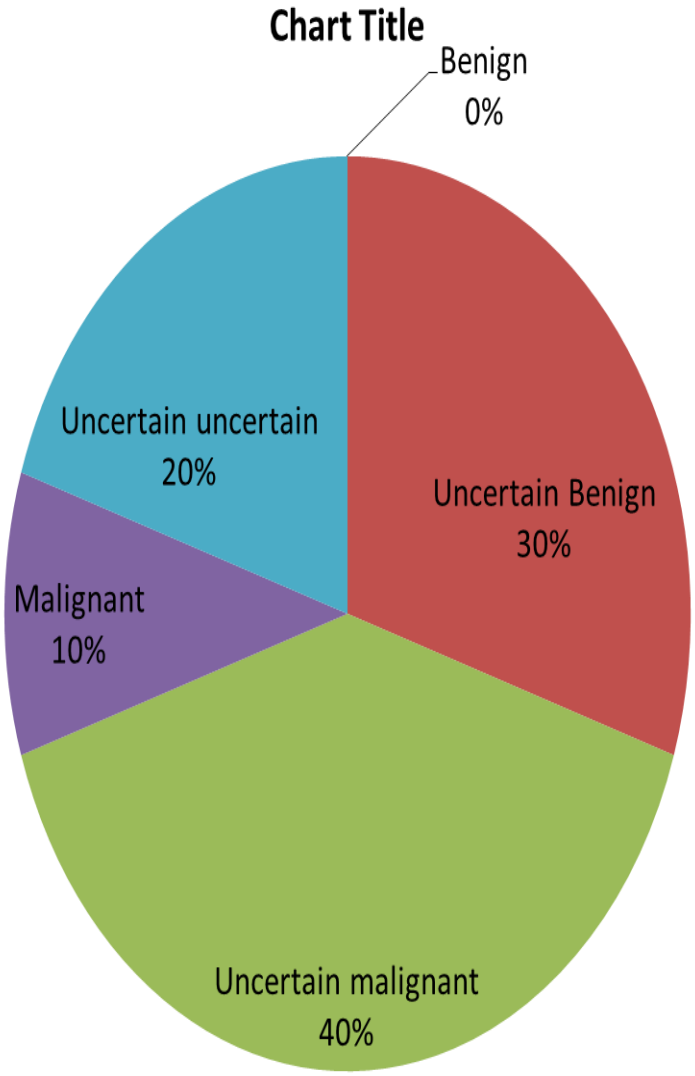


Chart Title
Benign
0%
Uncertain uncertain
20%
Uncertain Benign
30%
Malignant
10%
Uncertain malignant
40%

SLIDE CLUB RESPONSES

Abdel-Halim:

Bakshi:

Barnhill: Atypical compound nodular spindle cell tumor with focal melanin pigment, dense cellular fascicles of spindle cells, some vertically oriented,spitzoid cytomorphological features, cytological atypia, uncommon mitotic figures, ulceration absent, lack of conventional maturation, subcutaneous fat involved, > 1 cm diameter ?. Provisional: Atypical compound spindle cell melanocytic neoplasm with spitzoid features and uncertain malignant potential [Comprehensive clinical information and ancillary/molecular testing are needed to rule out or confirm malignancy as much as possible]

Biswas:

Blokx: highly cellular, nodular, compact spindle shaped lesion, severe atypia and numerous mitoses, even at the base, without maturation. Dermal based tumor. DD: AST/Spitz melanocytoma, MST/Spitz melanoma, nodular melanoma. I think it is a primary lesion and not a metastasis. Again IHC and molecular testing needed to determine signature and dignity

Busam:

Carr: Bulky, spindle Spitz fusion probably (especially ALK as the organisers usually have a theme)**,** I favour atypical Spitz, ?ALK-fusion & low risk. Ensure complete excision

Carton:

Clarke:

Collina, Malignant Spitz Tumor (Spitz melanoma):

SLIDE CLUB RESPONSES

Evans:

Ferrara: This is a melanocytic tumour with morphological features to be likely ascribed to the Spitz lineage. The lesion is nodular and very thick, with sheets of relatively monomorhic spindle cells, often arranged in tightly packed vertically oriented fascicles. There are several mitotic figures. The epdermis is hyperplastic, but only minimally involved by the neoplasm. My provisional diagnosis is atypical Spitz tumour, intermediate-to-high risk. May be ALK translocated. There are a few other possibilities; namely: cutaneous clear cell sarcoma; CRTC1-TRIM11 fused melanocytoma. However, the epidermal hyperplasia, the presence of a juncional melanocytic component, and the absence of fibrous bands speak against these alternative possibilities

Jamieson:

Kempf:

Maheshwari:

Massi:

Muc: Uncertain favour benign - Plexiform DPN-like morphology but without the pigment. No IHC provided. There is uniform low grade atypia and dermal mitoses. I think this is atyical, insufficient for melanoma, but concerned about MA. Cellular blue also possible, but again atypical and no biphasic pattern. I cannot assess further in absence of IHC, including B catenin. Would also like NGS and CGH/SNP data.

Mudaliar:

Oxley:

SLIDE CLUB RESPONSES

Requena: Atypical cellular blue nevus

Robson:

Saldanha:

Scolyer: I don’t recognise this case. Could it be a TRIM11 "melanocytoma"? Needs molecular testing

Singh:

Slater:

Sundrum:

Szakacs:

Taibjee: Rather cellular and deep Spitzoid lesion with fascicular architecture but relatively uniform cytology and minimal mitosis (on quick search). So atypical Spitz, but not frank melanoma. Given the narrow margin will probably warrant 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 (this one might be ALK positive, but other drivers are also possible). 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. I also wondered about a melanocytic tumour underpinned by a CRTC1-TRIM11 fusion, but focal junctional component makes this less likely?

Tiffin: plexiform spitz tumour, uncertain favour malignant

- Excised with clearances of 0.5 (deep) and 0.7mm (peripheral)

- Immunoprofile:
  - Strongly positive S100, Melan A and HMB45
  - Negative for AE1/3, SMA, desmin, CD34 and ALK-1
  - BAP-1 staining retained

- BRAF codon 600 (pyrosequencing) - no mutations;
- FISH - no ALK, ROS1 or NTRK rearrangements

- Due to mitotic activity and exuberant nature of the proliferation, diagnosed as *Spitz tumour of uncertain malignant potential, pending further genetic testing.*

Differential diagnosis

- Atypical Spitz Melanocytoma [AST]
- Atypical cellular Blue Naevus - but s100 diffusely positive
- Melanocytoma with CRTC1-TRIM11 fusion

Further work up

- Subsequently t(12;22) (q13;q12) translocation resulting in an *EWS-ATF1* gene fusion detected - diagnosis revised to *compound clear cell sarcoma*

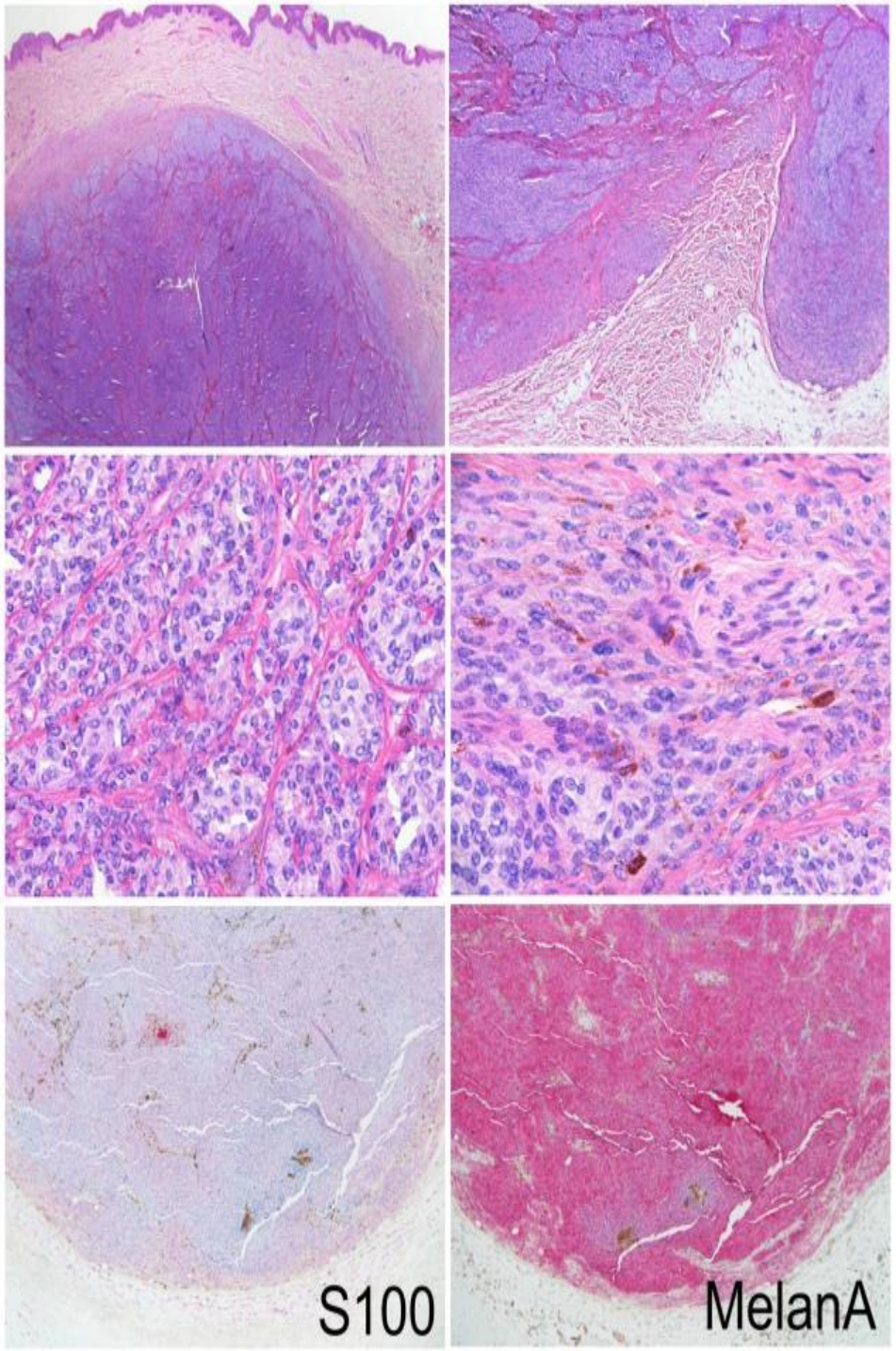
Clear cell sarcoma (melanoma of soft parts)

- Rare melanocytic soft tissue sarcoma
- Adolescents/young adults, tendons/aponeuroses of distal extremities
- Hx: (usu.) painless deep soft tissue nodule
- Diagnostically very challenging:
  - *Morphology*: spindle cells, melanin *but* reticulated stroma, monomorphic tumour cells, no pagetoid spread/increase of epidermal melanocytes.
  - *IHC*: melanocytic
  - *Genetics*: 70-90% have t(12;22) (q13;q12) *(same as* angiomatoid fibrous histiocytoma]

Main Differential diagnosis

- Spitz Tumour, especially ALK fusion
- Hypopigmented Cellular Blue
- CRTC1-TRIM1 Melanocytoma [MSG case 239]
- PEM-like blue naevus (melanocytoma) with CYSLTR2 mutation [MSG case 234]

Hypopigmented Cellular Blue Naevus
S100 Negative
No junctional component



Cutaneous Melanocytoma With *CRTC1-TRIM11* Fusion

Report of 5 Cases Resembling Clear Cell Sarcoma

Lucie Cellier, MD, Emilie Perron, MD, MSc,*†‡ Daniel Pissaloux, PhD,* Marie Karanian, MD,* Veronique Haddad, PharmD,* Laurent Alberti, PhD,* and Arnaud de la Fouchardière, MD, PhD**

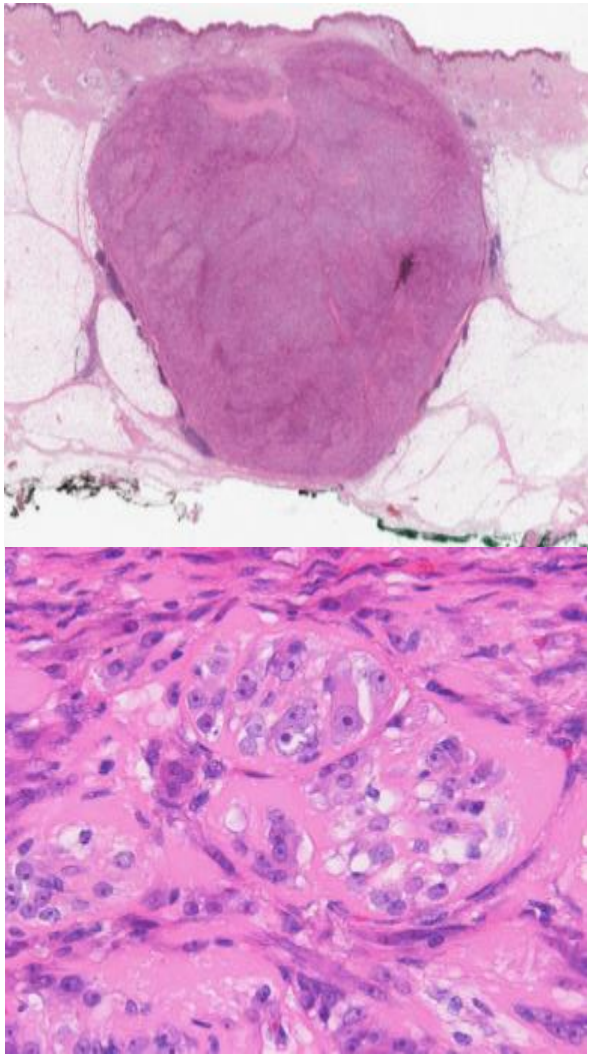
(*Am J Surg Pathol* 2018;42:382–391)

- **Take Home Messages: Case 239**

Cutaneous Melanocytoma *CRTC1-TRIM11* (CM*CT*)

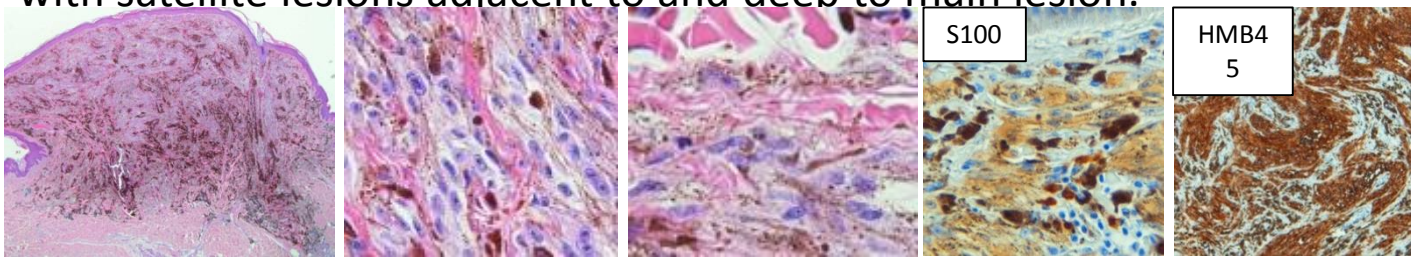
Consider when you see a circumscribed rounded dermal nodule, staining for melanocytic markers composed of epithelioid and spindle cells, lacking a pre-existing benign naevus or frankly malignant features….

- Primary dermal melanoma (PDM) is rare and their molecular profile is largely unknown, consider CM*CT*
- Paraganglioma-like dermal melanocytic tumour (PDMT) is a tumour of largely unknown molecular profile and may be examples of CM*CT*
- Hypopigmented blue naevus (S100-/Melan+++)
- Exclude clear cell sarcoma (*EWSR1* fusions)
- Exclude metastatic melanoma
- Consider referral for RNAseq; TRIM11 FISH; TRIM11 antibody



RAC8404

Case 234 Highlights: M41. Left Flank. Blue black clinically suspicious with satellite lesions adjacent to and deep to main lesion.



- Nested oval epithelioid cells and dendritic cells
- Final Diagnosis: **PEM-like blue naevus (melanocytoma) with epithelioid cells and satelitosis and CYSLTR2 mutation**
- No overtly malignant features, complete excision recommended

DISCUSSION

- Considerable challenge distinguishing PEM, DPN and Blue naevus with epithelioid cells
- Treatment same “melanocytomas” i.e. expected benign behaviour but warrenting complete excision with clear margins e.g. up to 5mm.
- PEM – require consideration of Carney’s complex

ORIGINAL ARTICLE

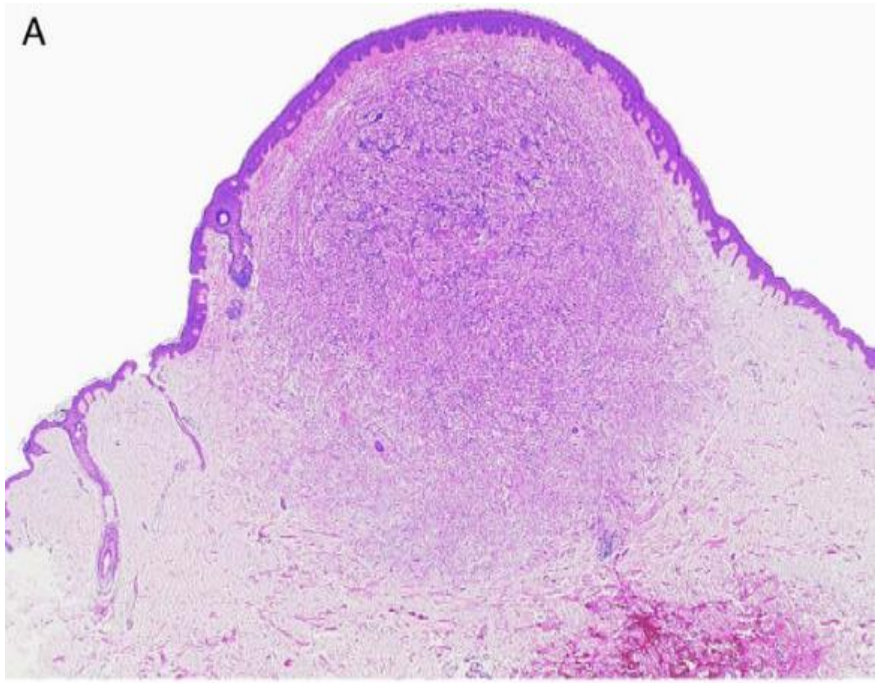
Cutaneous Clear Cell Sarcoma: A Clinicopathologic, Immunohistochemical, and Molecular Analysis of 12 Cases Emphasizing its Distinction from Dermal Melanoma

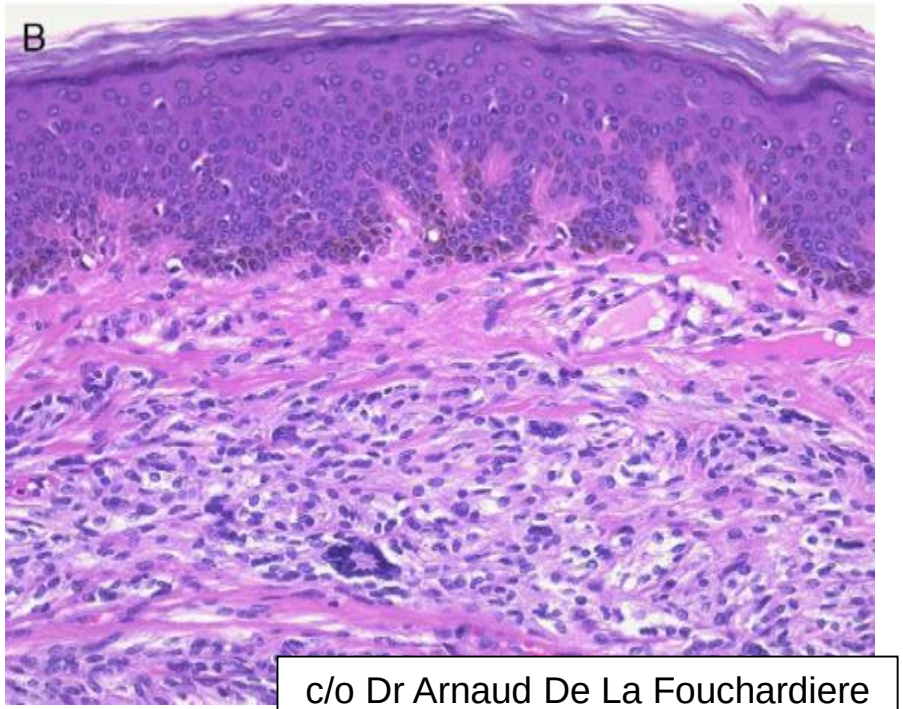
Markus Hantschke, MD, Thomas Mentzel, MD,* Arno Rütten, MD,* Gabriele Palmedo, PhD,* Eduardo Calonje, MD,† Alexander J. Lazar, MD,‡ and Heinz Kutzner, MD**

Abstract: Clear cell sarcoma (CCS) of tendons and aponeuroses/malignant melanoma (MM) of soft parts is a rare tumor and in the majority of cases presents a characteristic reciprocal translocation *t*(12;22)(q13;q12) that results in fusion of the *EWS* and *ATF1* genes. Although the melanocytic differentiation of CCS is indisputable, its precise lineage remains unclear. Typically, the slowly growing tumor affects the extremities of adolescents or young adults, especially around the ankle and cases by fluorescence in situ hybridization. Local recurrences and metastases developed in 2 and 3 patients, respectively, and 1 patient died of the disease.

Key Words: clear cell sarcoma, melanoma of soft parts, melanoma

(*Am J Surg Pathol* 2010;34:216–222)





c/o Dr Arnaud De La Fouchardiere

- **Compound Clear Cell Sarcoma of the Skin-A Potential Diagnostic Pitfall: Report of a Series of 4 New Cases and a Review of the Literature**
- Boštjan Luzar , Steven D Billings , Arnaud de la Fouchardiere , Daniel Pissaloux , Laurent Alberti , Eduardo Calonje

Am J Surg Pathol.. 2020 Jan;44(1):21-29.

Dermal clear cell sarcoma WHO 5th Ed.

- Malignant neoplasm of uncertain histogenesis displaying melanocytic differentiation and associated with a gene fusion involving EWSR1 and ATF1 or CREB1
- .Classified under Soft tissue tummours of uncertain differentiation [ie not melanoma]
- predominantly affects the extremities, especially distal extremities], but can occur elsewhere, including the head and neck region.

Dermal clear cell sarcoma WHO 5th Ed

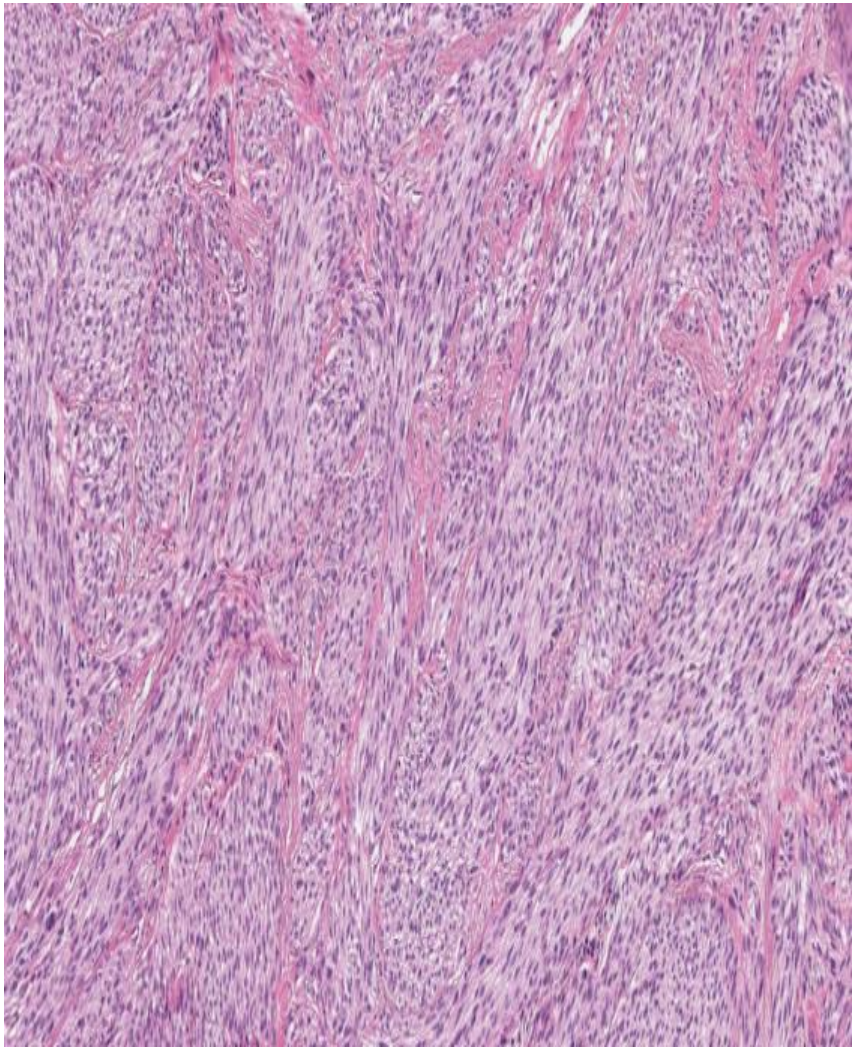
- Tends to affect young adults, most often during the third to fourth decade of life. Very rarely the tumour may also occur in children or older individuals.
- The majority (70-90%) of CCS harbour an EWSR1::ATF1 fusion secondary to the reciprocal translocation (t(12;22)(Q13;q12). The oncogenic fusion constitutively activates the promoter of microphthalmia transcription factor (MITF) resulting in melanocytic differentiation and tumour growth. A variant translocation t(2;22)(q32.3;q12), which results in an EWSR1::CREB1 fusion is rare, accounting for approximately 5% of tumours

Immunohistochemistry

- The tumour cells express S100 protein, Sox10 and melanocyte differentiation antigens like gp100, gp75, melan-A and microphthalmia transcription factor. In contrast to cutaneous melanomas, PRAME expression is usually absent or only focal

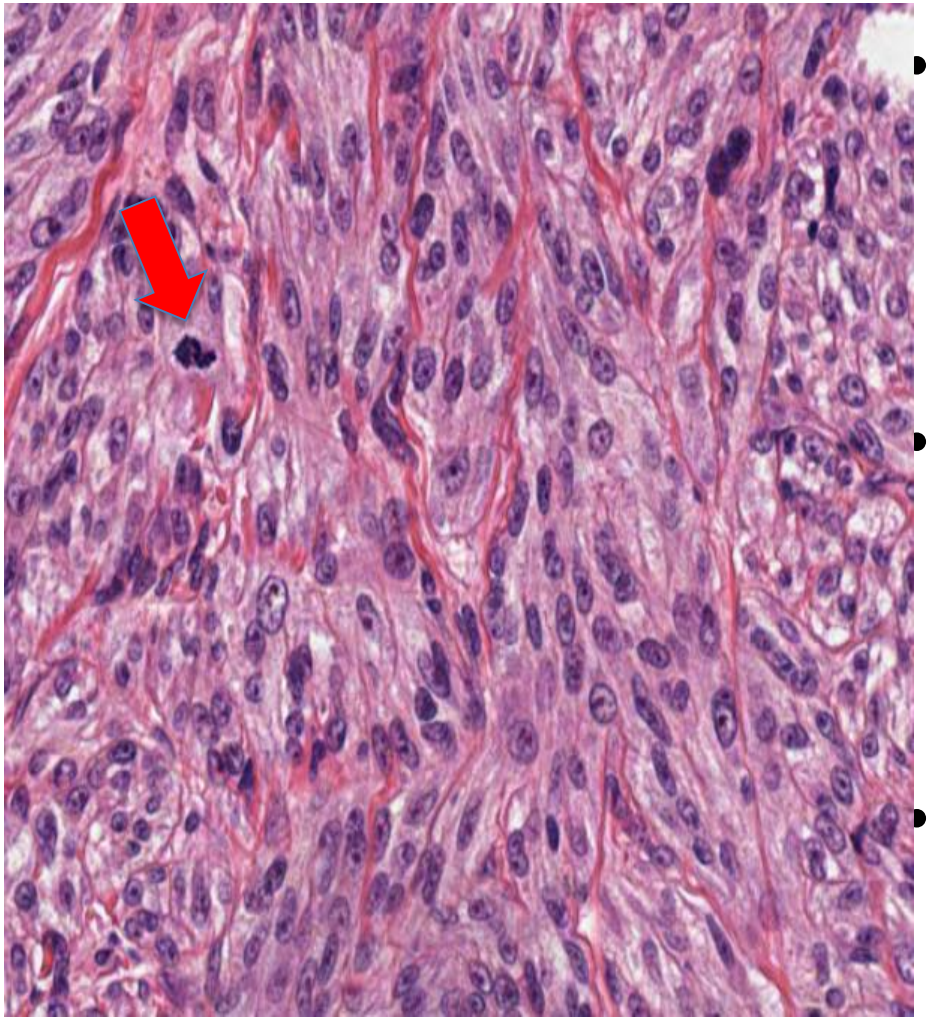
- Metastasis to regional lymph nodes and lungs
- Prognosis: tumour size (≥5cm), necrosis, local recurrence,metastasis
- Local recurrence, late metastases, can take many years
- ? Cutaneous tumours have better prognosis?
- Of 11 cases Local recurrence in 2 and Mets in 3
- Adjuvant therapy largely ineffective - aim for wide excision +/- SLN Bx

Dermal Clear Cell Sarcoma



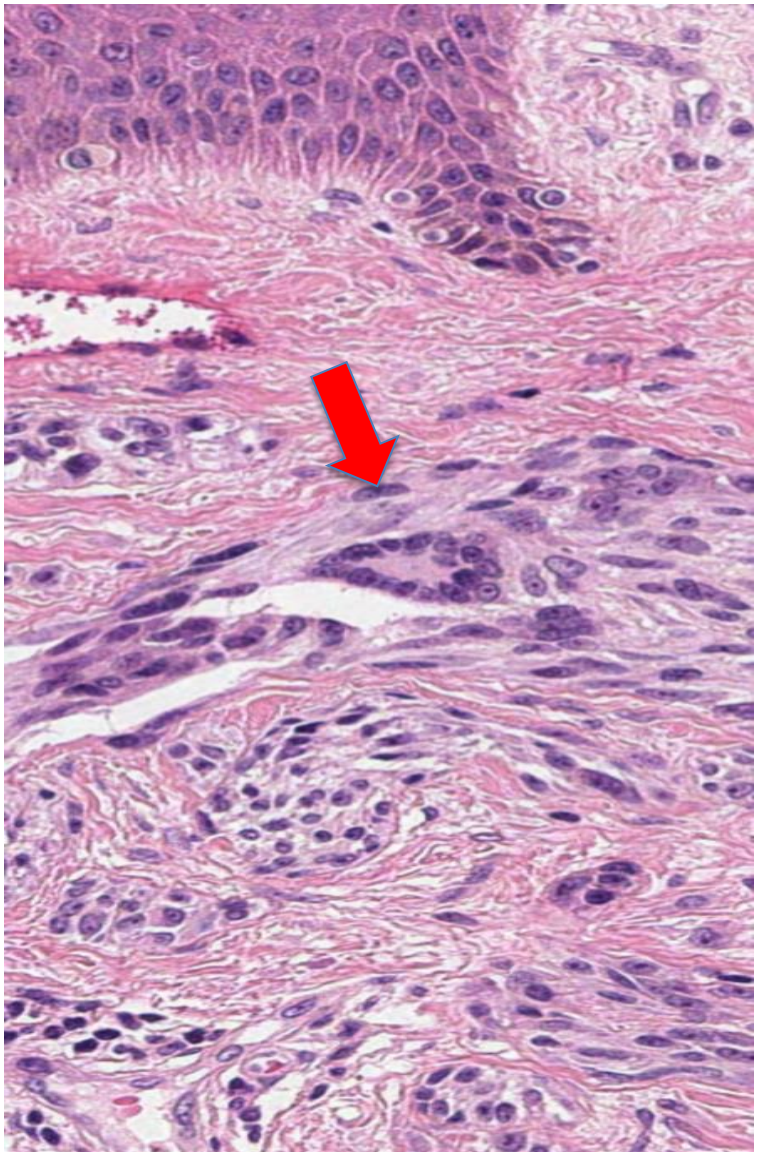
- *Essential:*
- **Characteristic nested or fascicular architectures divided by fine fibrous tissue septa and a pronounced hyalinised stroma.**
- **Plump spindle or ovoid cells with palely eosinophilic cytoplasm and prominent nucleoli**

Dermal Clear Cell Sarcoma



- Fair pleomorphism with plump spindled nuclei and prominent nucleoli.
- The mitotic activity ranged from 2 to 20 mitotic figures (MF)/10 high-power fields
- (HPF) (mean: 8MF/10 HPF)

Dermal Clear Cell Sarcoma



- Giant cells with wreath-like nuclei

Patients with cutaneous clear cell sarcoma

Case	Age (y)/Sex	Site	Size (cm)	*EWSR1*	Follow-up (mo)
1	31/F	Back	1,0	16/65	ANED 52
2	7/M	Foot	0,9	18/76	REC 12, ANED 67
3	13/F	Lower Arm	0,7	27/98	ANED 54
4	12/F	Sole	1,2	21/83	REC 12; MET; DOD 38
5	19/F	Foot	1,7	10/43	MET 2, AWD 37
6	50/F	Abdomen	0,4	16/65	ANED 40
7	15/M	Sole	0,5	18/69	ANED 17
8	61/F	Upper Leg	1,6	52/73	NA 17
9	74/F	Upper Arm	1,3	26/61	ANED 14
10	65/F	Palm	0,6	29/54	MET 1; AWD 14
11	25/F	Upper Leg	0,7	09/51	ANED 20
12	50/F	Back	1,2	11/36	ANED 12

Hantscke *et al*. Am J Surg Pathol. 2010;34:216-22.

WHO 5 ed. Prognosis and prediction

- The tumour is clinically characterized by a propensity for local recurrences with late metastases. Patients with cutaneous CCS may have a more favourable outcome than those with deep soft tissue tumours. An analysis of 23 cutaneous CCS reported an association with local recurrence in 46% (median relapse-free survival 15 months), while two patients died of disease at 38 months and 60 months, respectively. Small tumour size and negative sentinel lymph node status have been associated with longer disease-free survival

Dermal Cutaneous Clear Cell Sarcoma

- **Learning points**
- Can have a junctional component.
- Does have characteristic morphology once aware.
- Easily confused with Melanocytic tumours, especially Spitz tumours and Blue group.
- Need to include fusions in your Atypical Spitz panel.
- Genetic investigation is of paramount importance.