Superficial Pleomorphic Tumours: A Case Based Presentation
NW EQA Meeting
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Manchester

Superficial Pleomorphic Tumours - Challenges

- Wide variety of histological patterns & many entities with overlapping features
- Significant proportion difficult to classify as benign or malignant

Benign lesions which mimic sarcomas

- Atypical fibrous histiocytoma
- (Atypical fibroxanthoma)
- Ancient schwannoma
- Neurofibroma with atypia
- Symplastic haemangioma

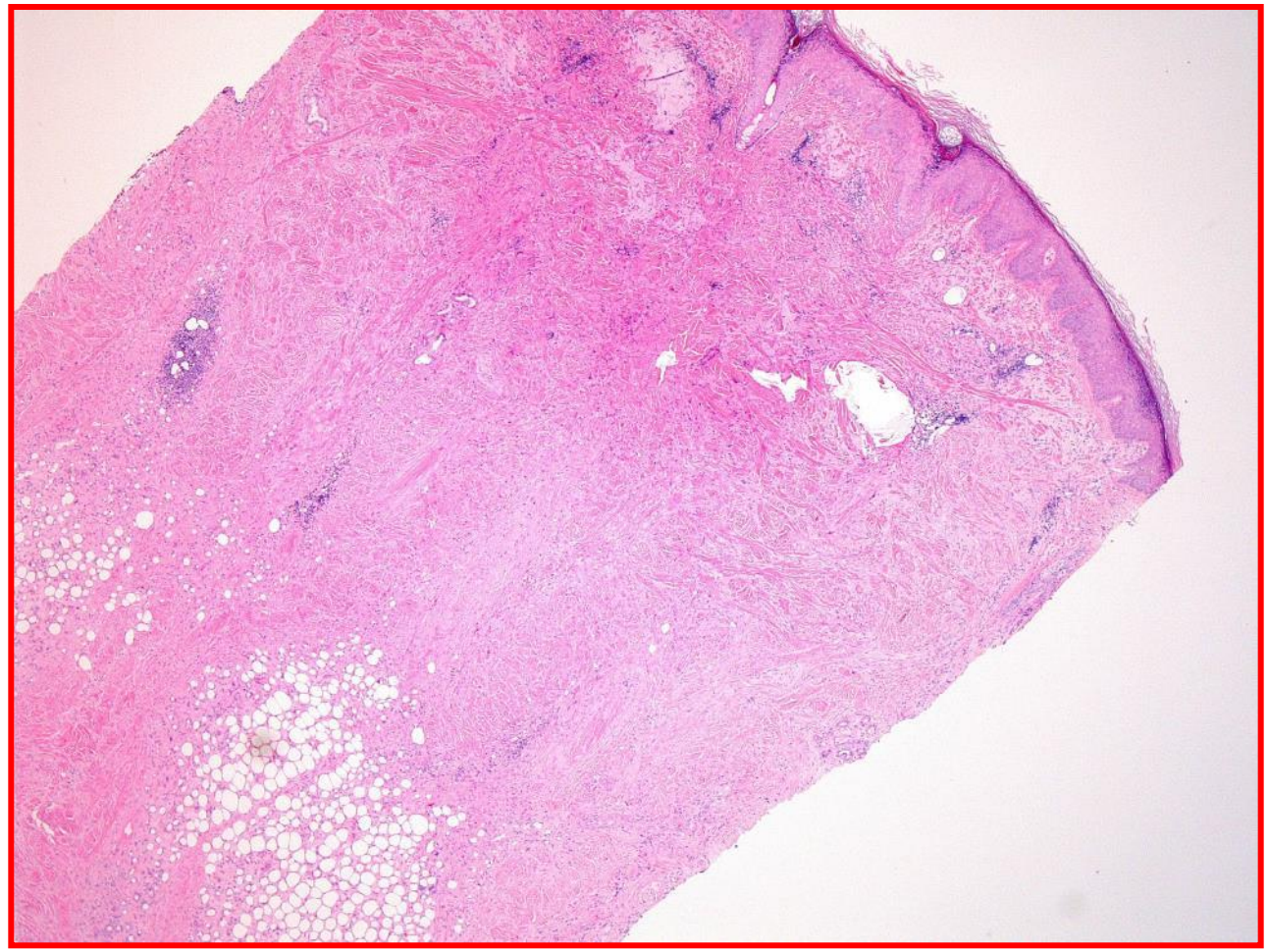
Sarcoma Vs Non-sarcoma

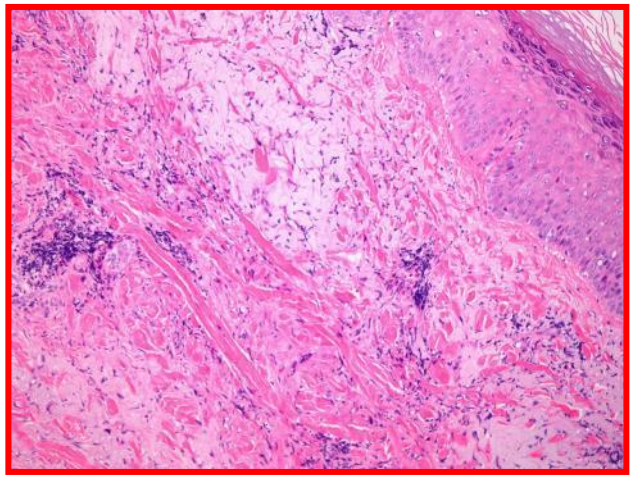
- Sarcomatoid carcinoma/ Spindle cell carcinoma
- Desmoplastic & spindle cell melanoma
- Haemolymphoid malignancies

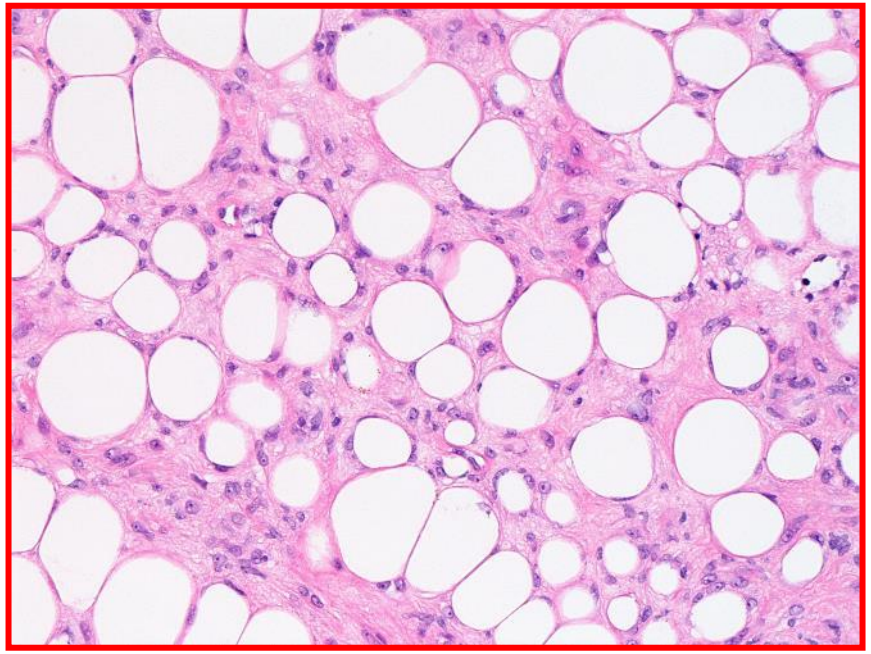
- Leiomyosarcoma
- Myofibrosarcoma
- Angiosarcoma
- Superficial CD34-positive fibroblastic tumour
- AFX & Pleomorphic dermal sarcoma

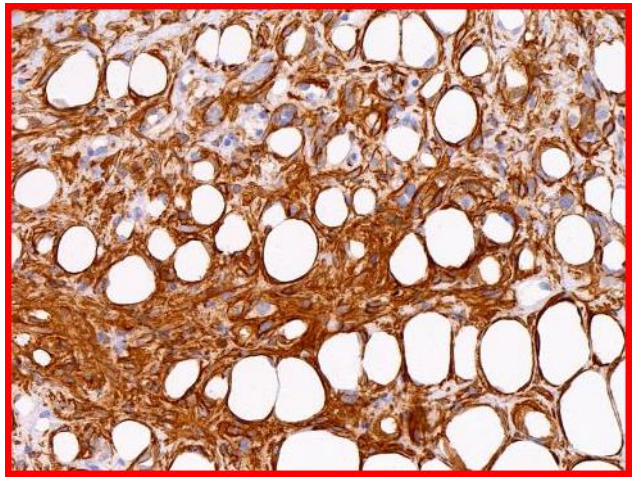
Case

- 80yr old male
- Ulcerated scalp lesion, punch biopsy



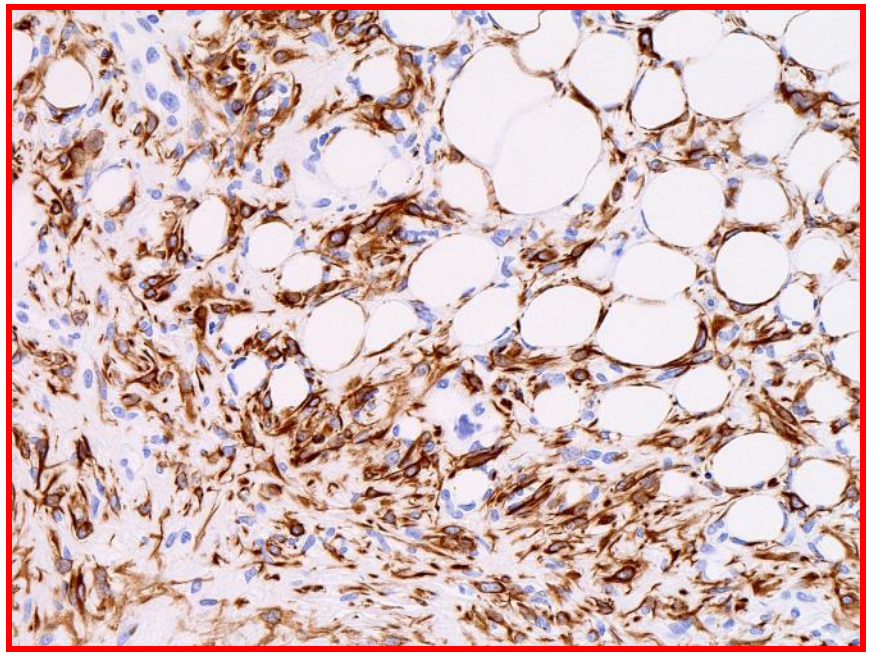




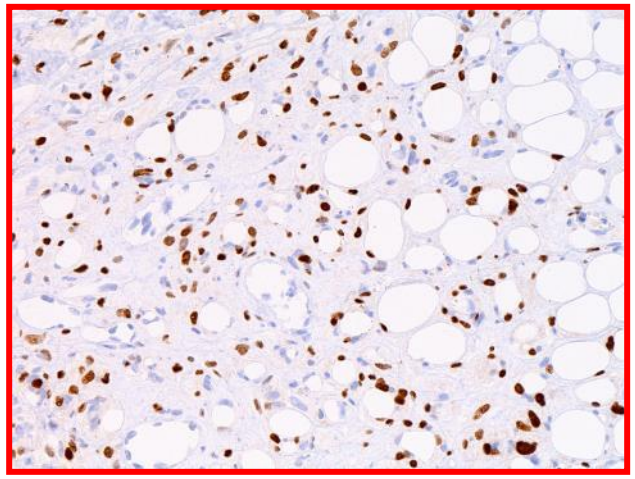


SMA

Negative for: MNF116, desmin, CD34, ERG, S100 & SOX10



34βE12



p63

Also +ve for p40, AE1/3, CK14

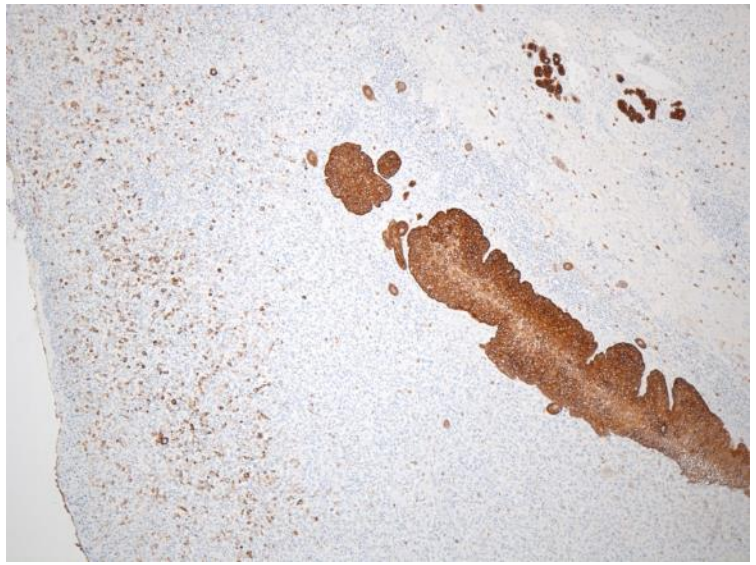
Spindle Cell Carcinoma (sarcomatoid squamous cell carcinoma)

- Almost always occur in sun damaged skin
- Head, neck, chest & upper extremities
- Elderly, predominantly Caucasian pts
- M>F
- Occur in non-sun damaged areas post radiotherapy and is more aggressive in that context

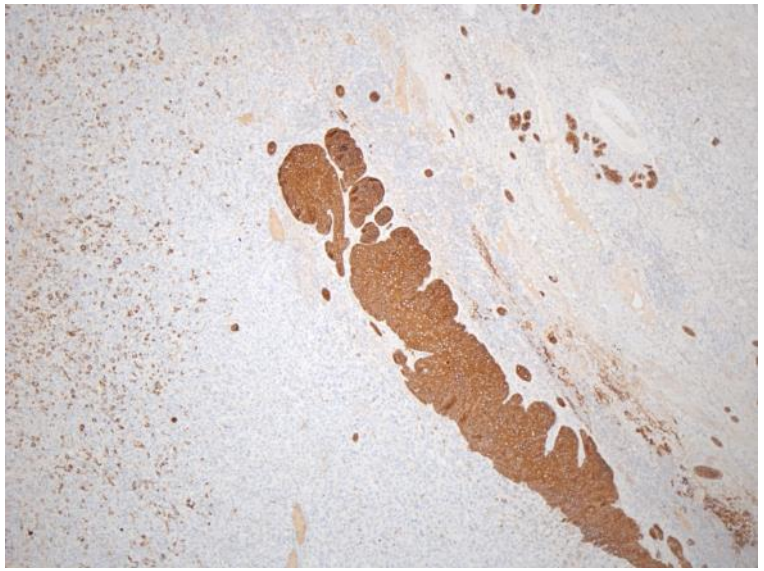
Spindle Cell Carcinoma

- Pleomorphic, mitotically active spindle cells -morphologically indistinguishable from AFX/PDS
- Foci of overt epithelial differentiation may be present (Cellular cohesion, intercellular bridges, keratinisation)
- Rarely, may exhibit foci of osteosarcomatous, chondrosarcomatous or rhabdomyosarcomatous differentiation
- Presence of actinic keratosis in the overlying/adjacent epidermis not very useful in the differential diagnosis

Sarcomatoid SCC



MNF116



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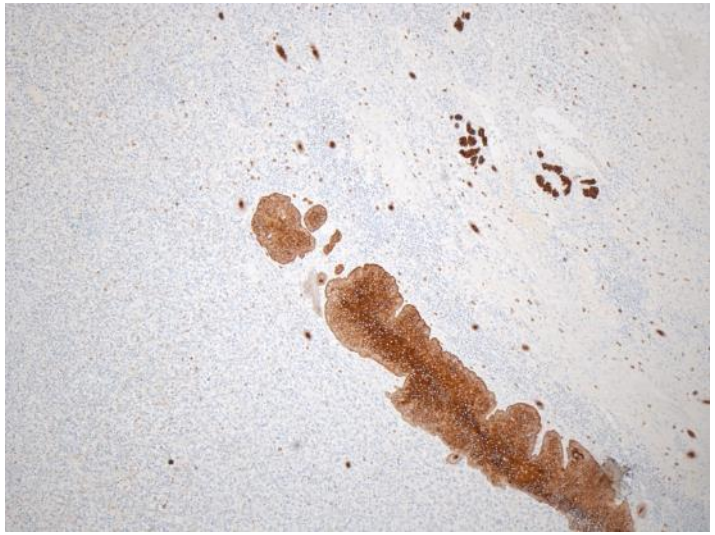
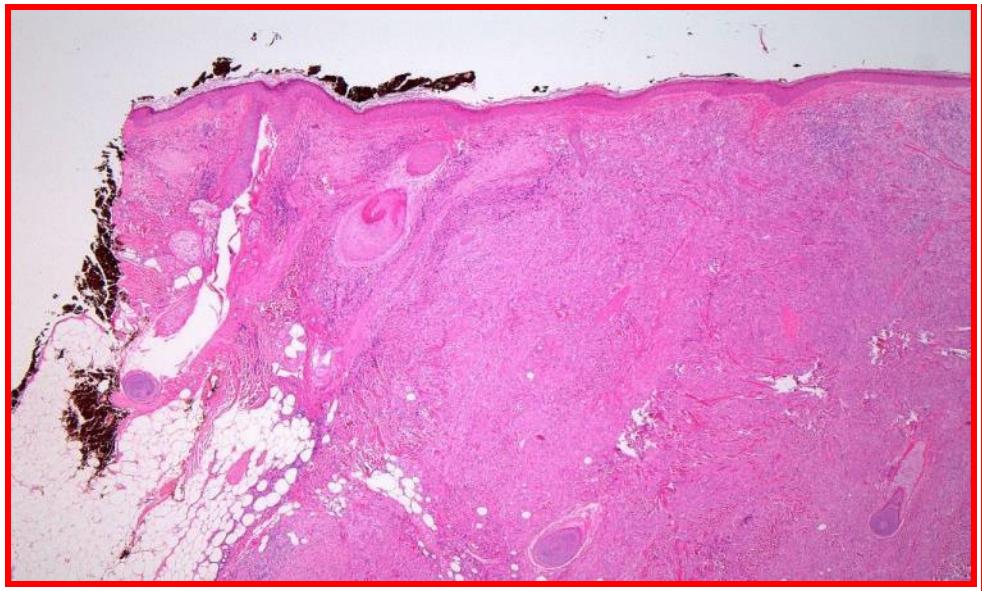


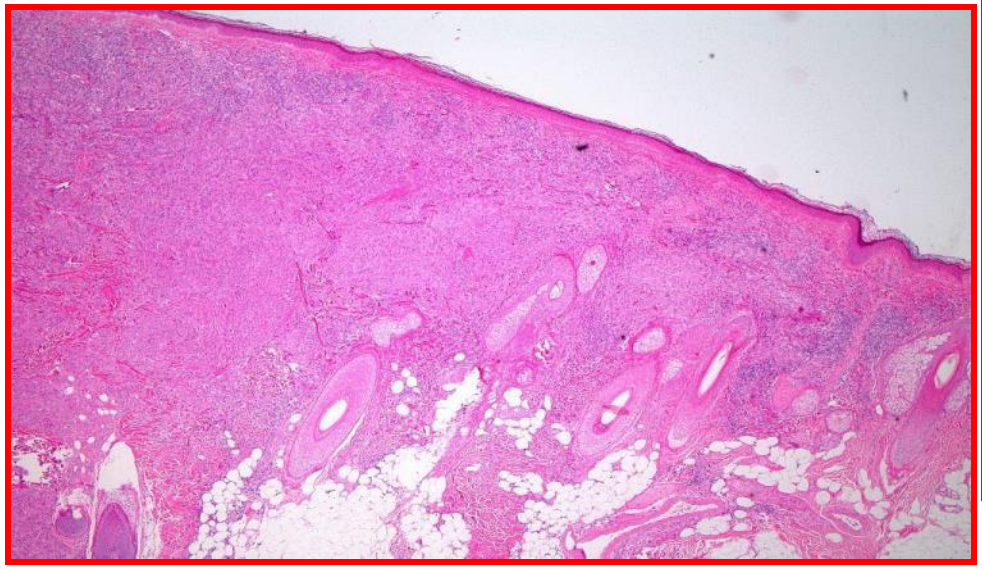
AE1/AE3

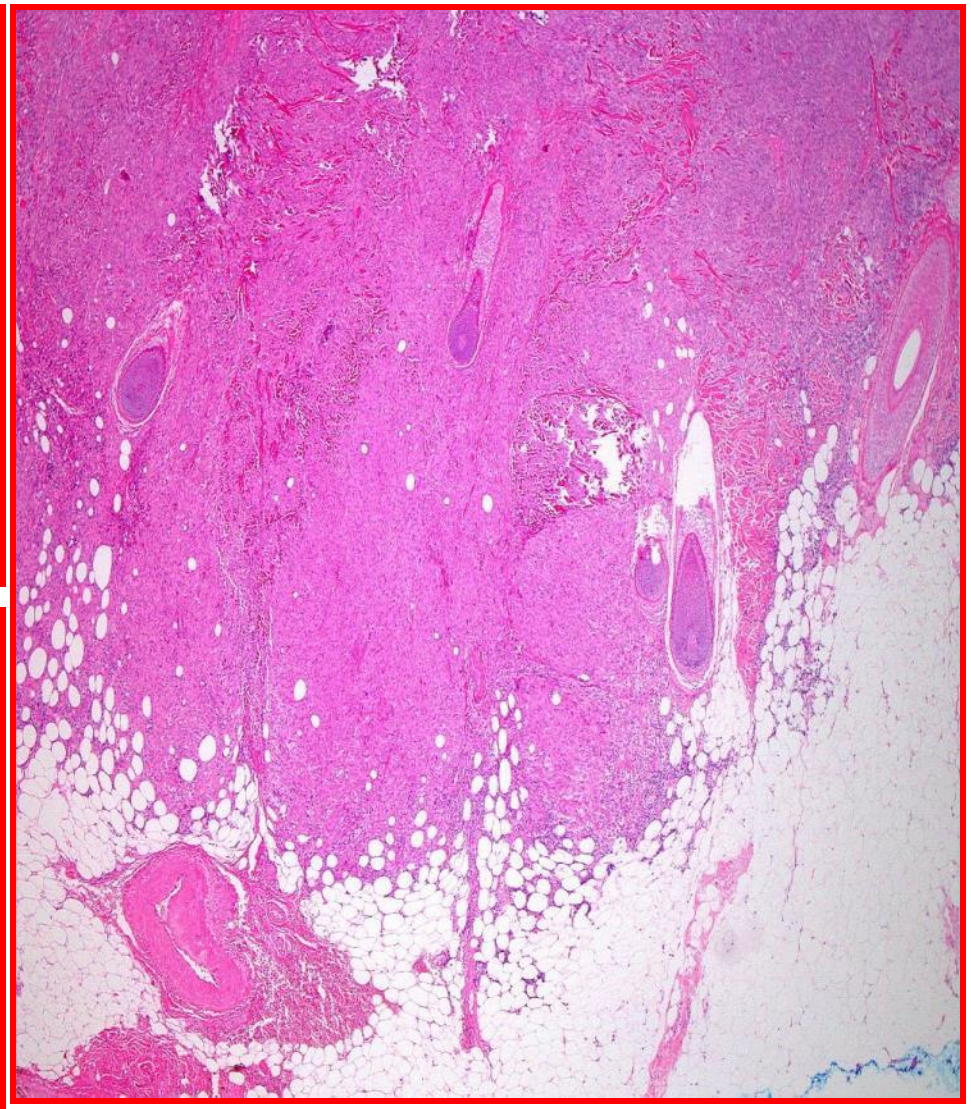
Cutaneous Spindle Cell Tumours with Cellular Pleomorphism

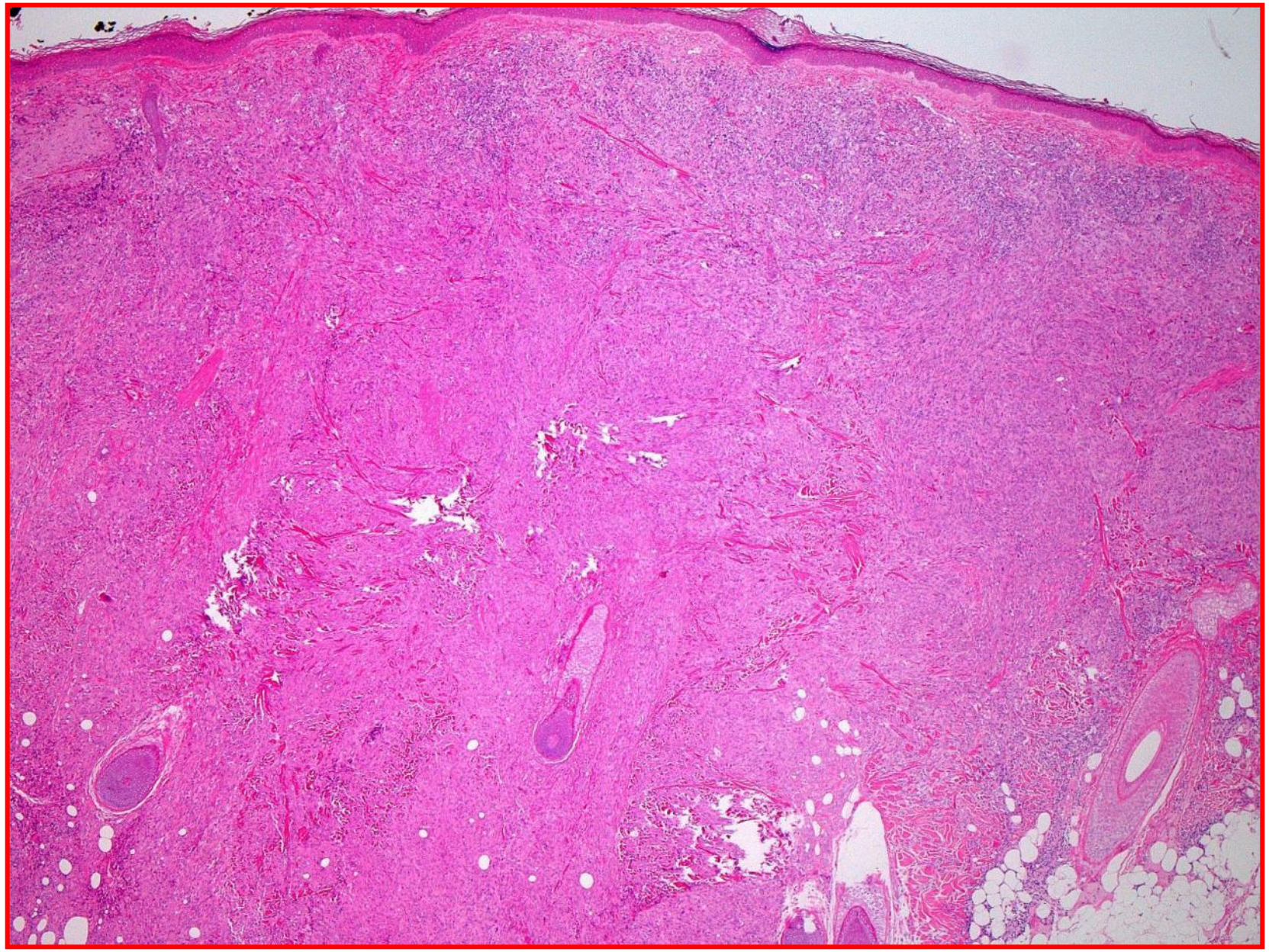
- Melanoma (desmoplastic and spindle cell MM)
- Angiosarcoma
- Leiomyosarcoma
- Atypical Fibroxanthoma
- Pleomorphic Dermal Sarcoma
- Atypical Fibrous Histiocytoma

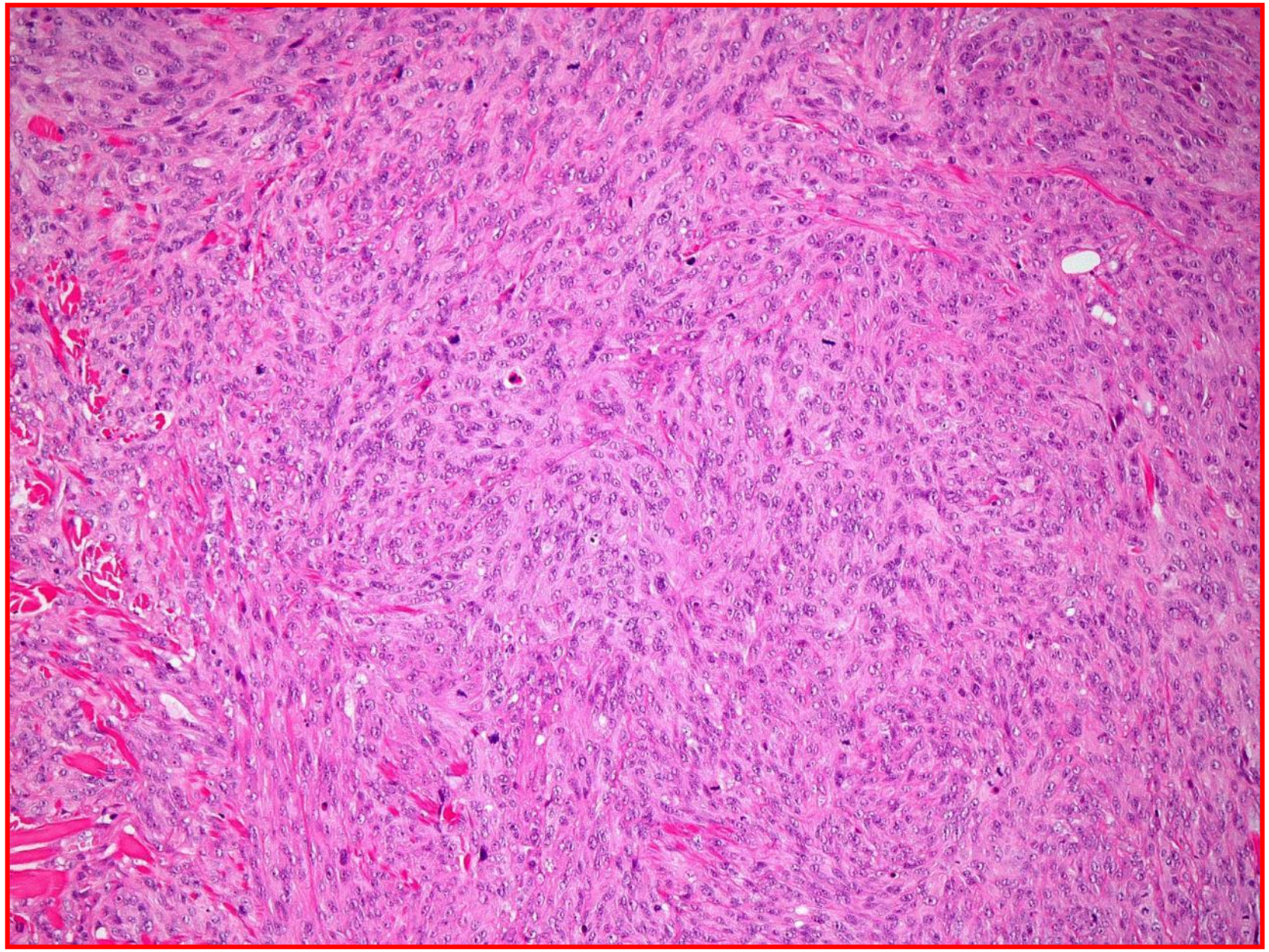
Case: 82M, Forehead lesion

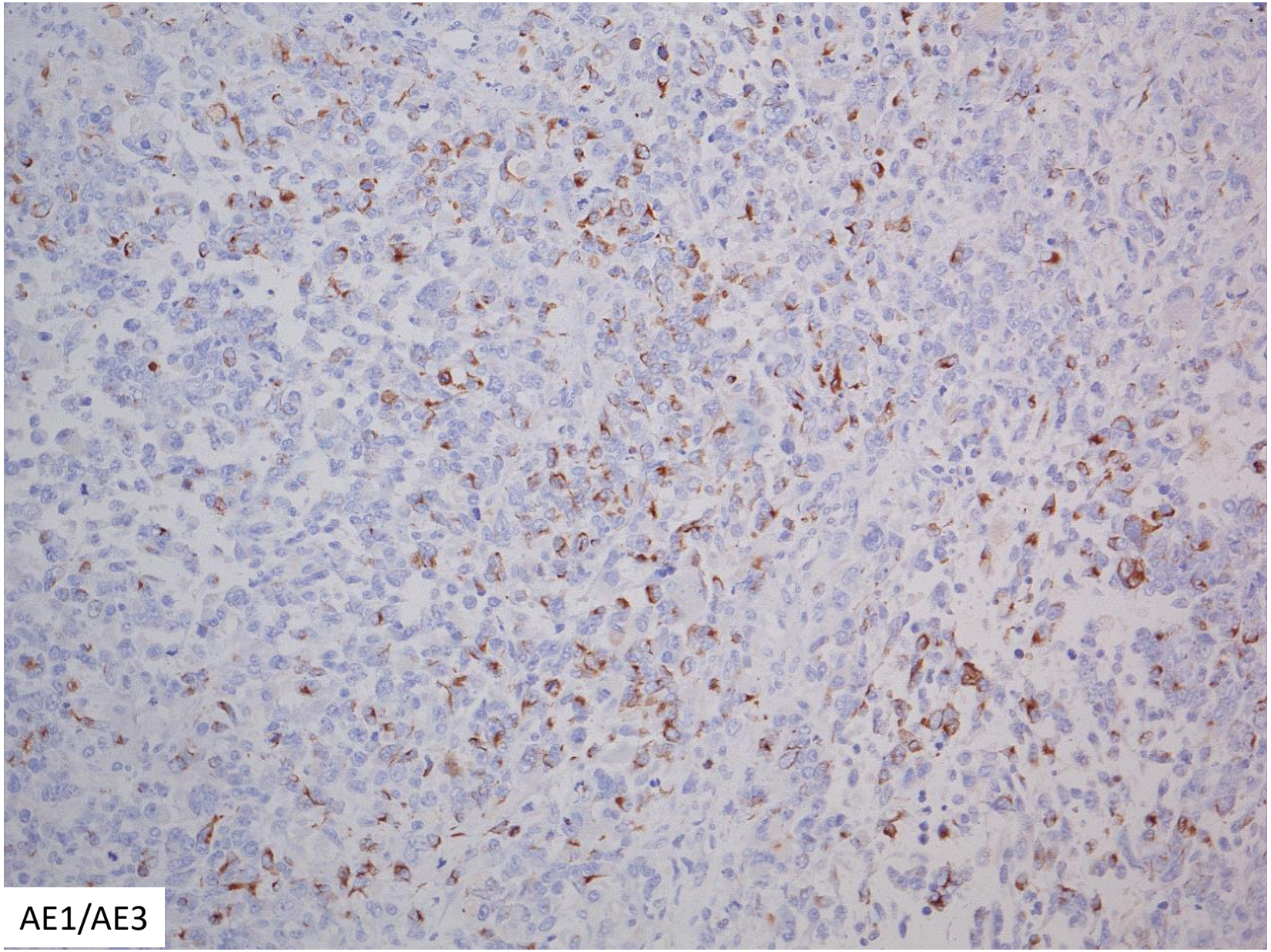






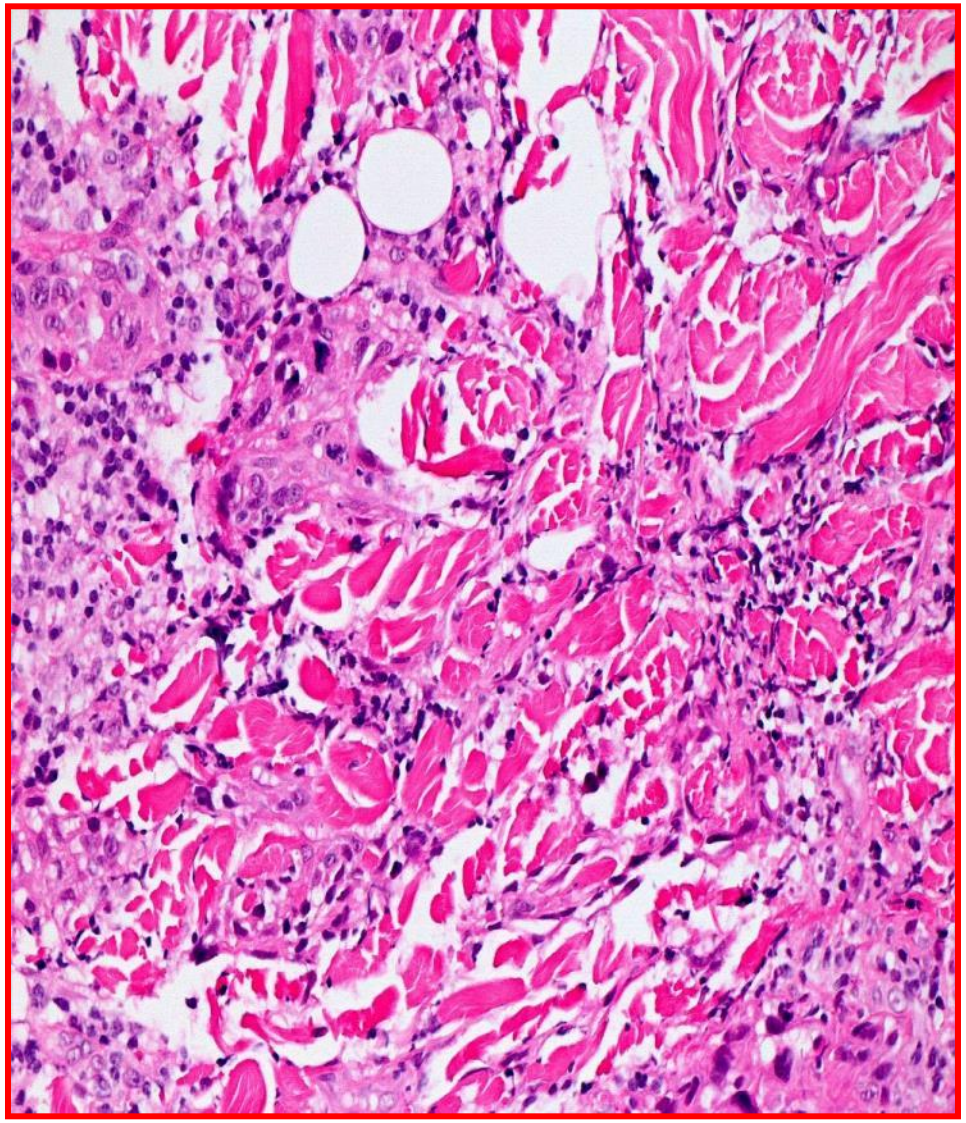


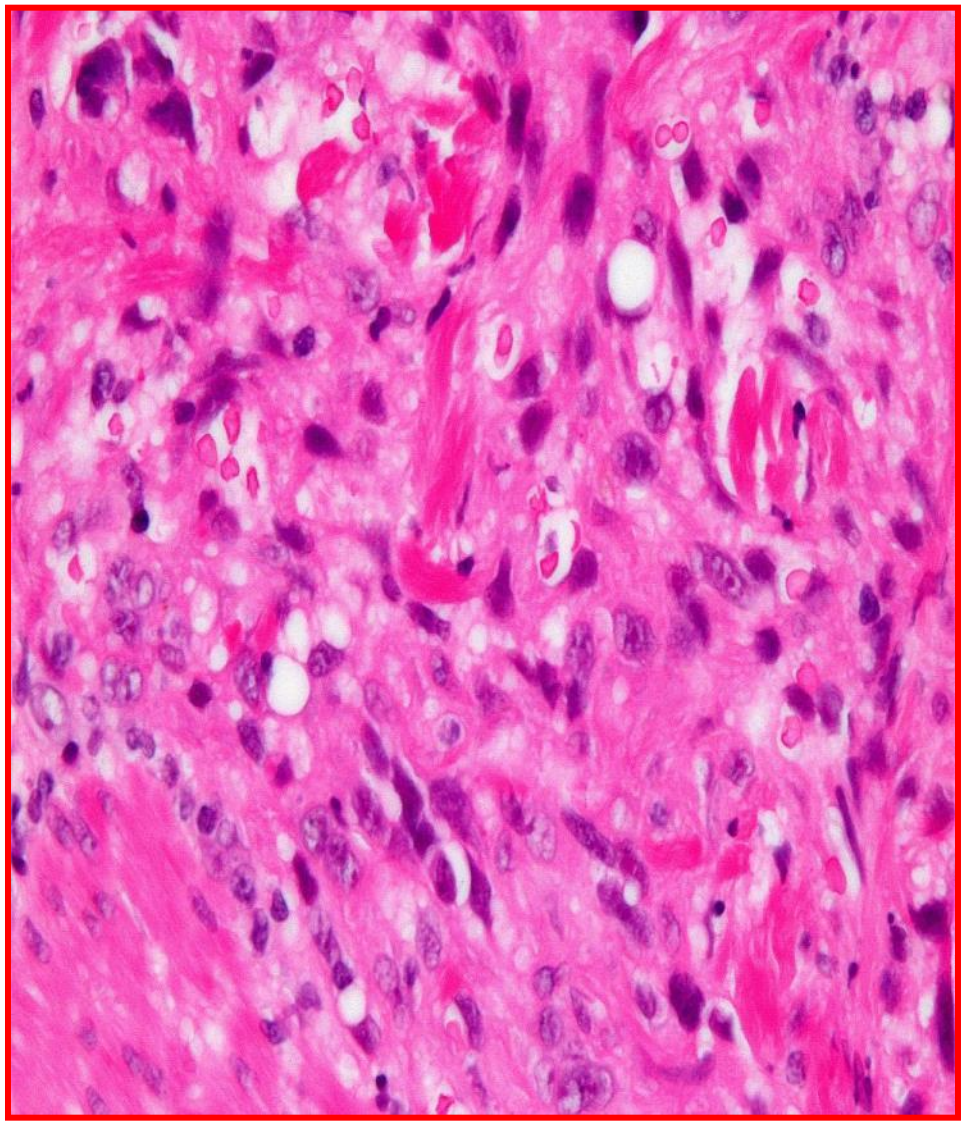




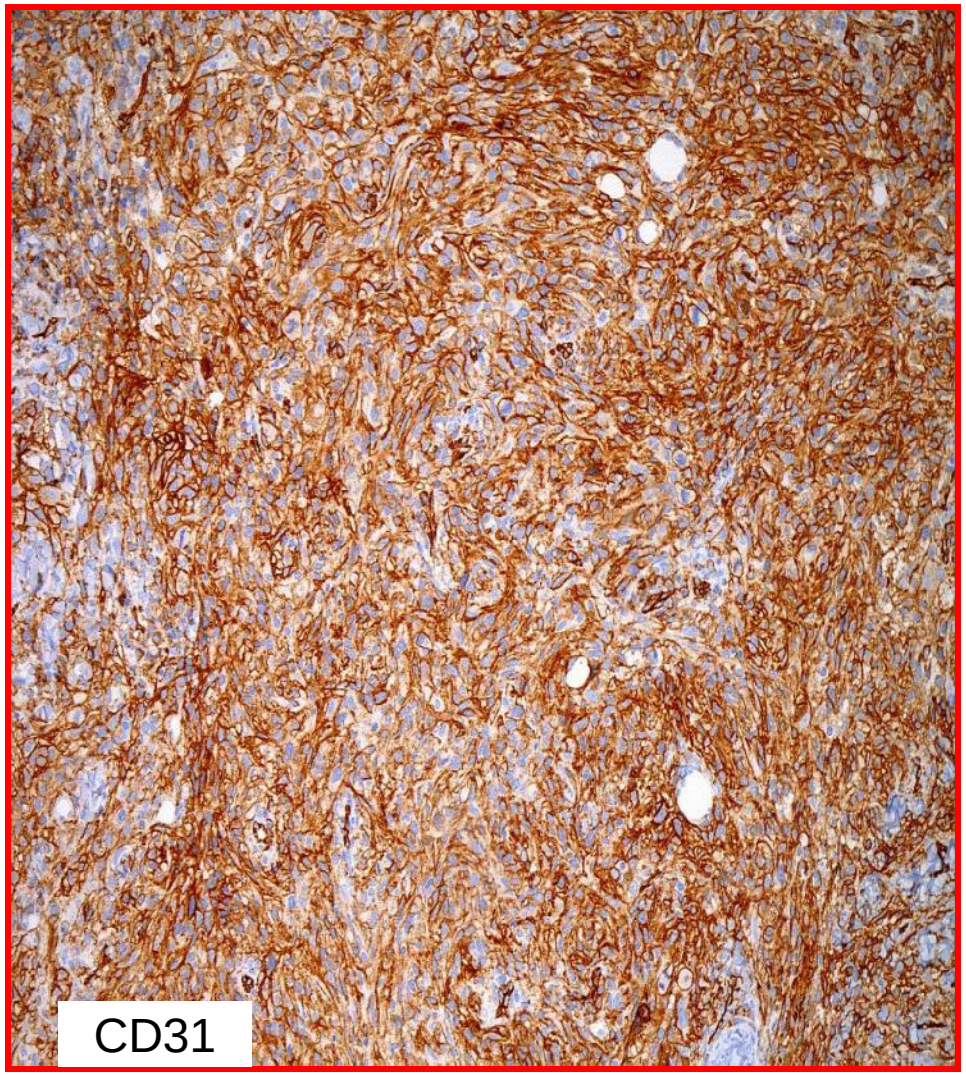
AE1/AE3

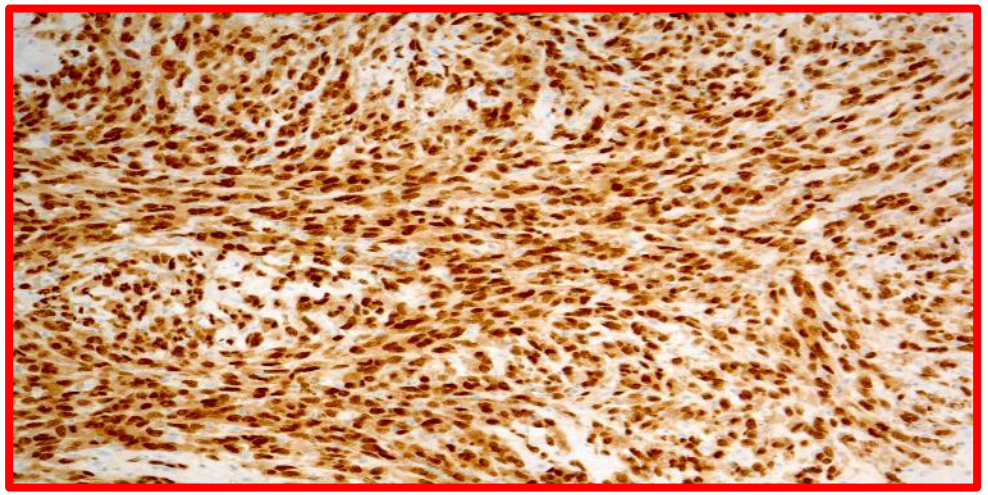
Negative for: MNF116, 34BE12, desmin, S100, SOX10





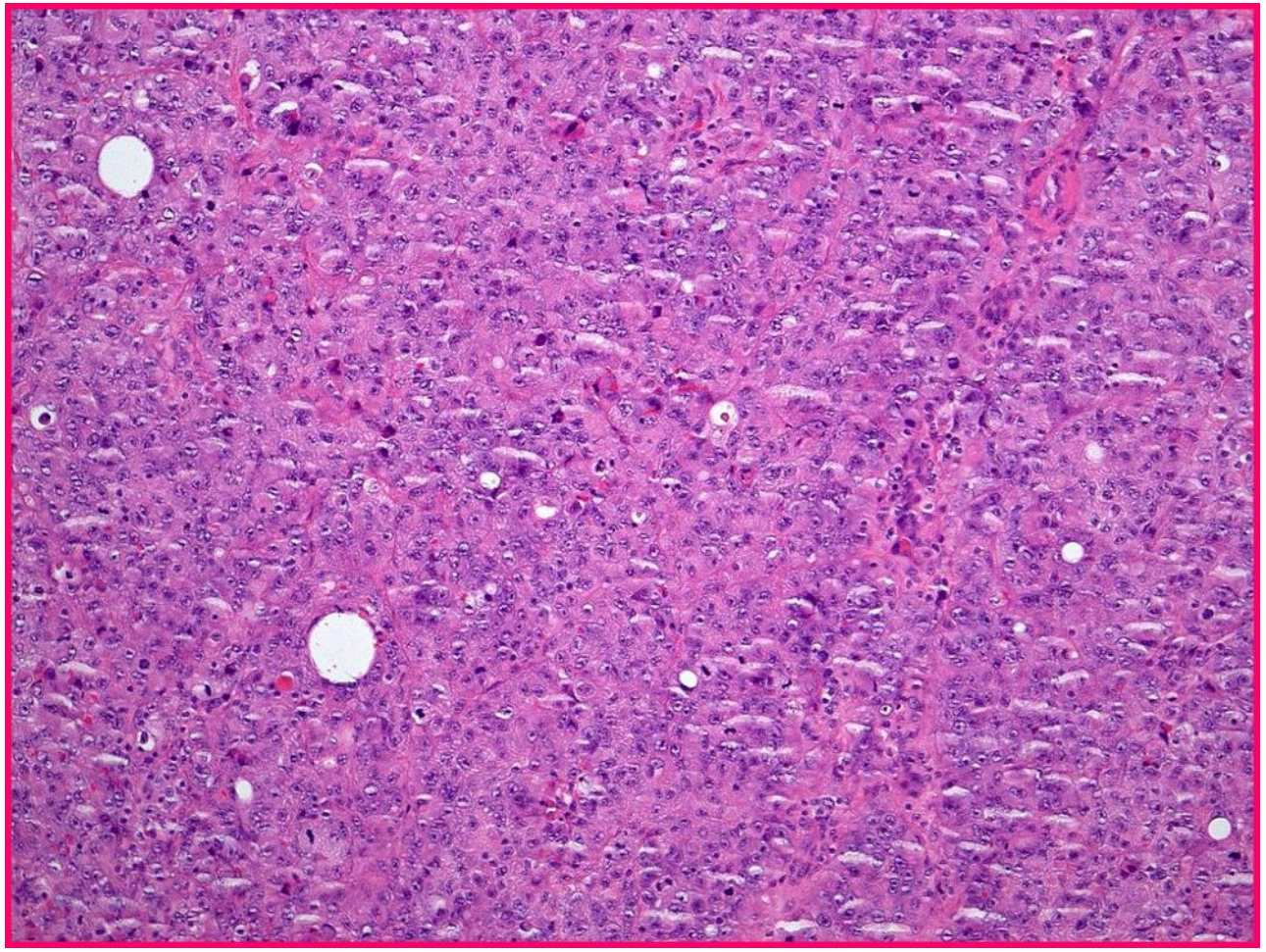
Diagnosis: Angiosarcoma

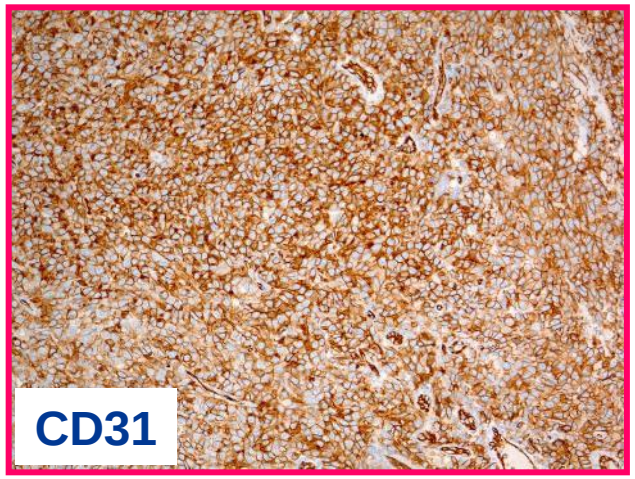


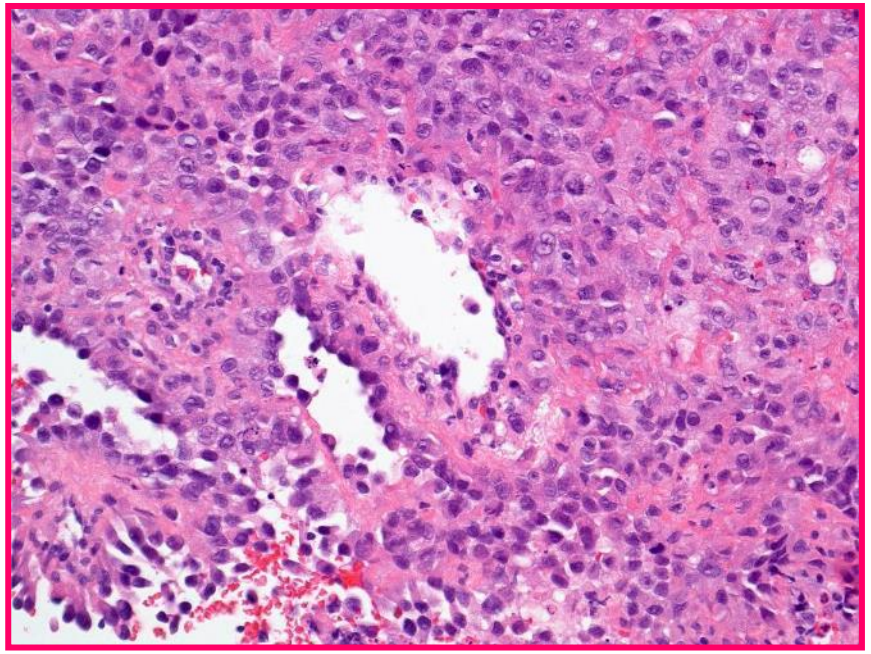


ERG

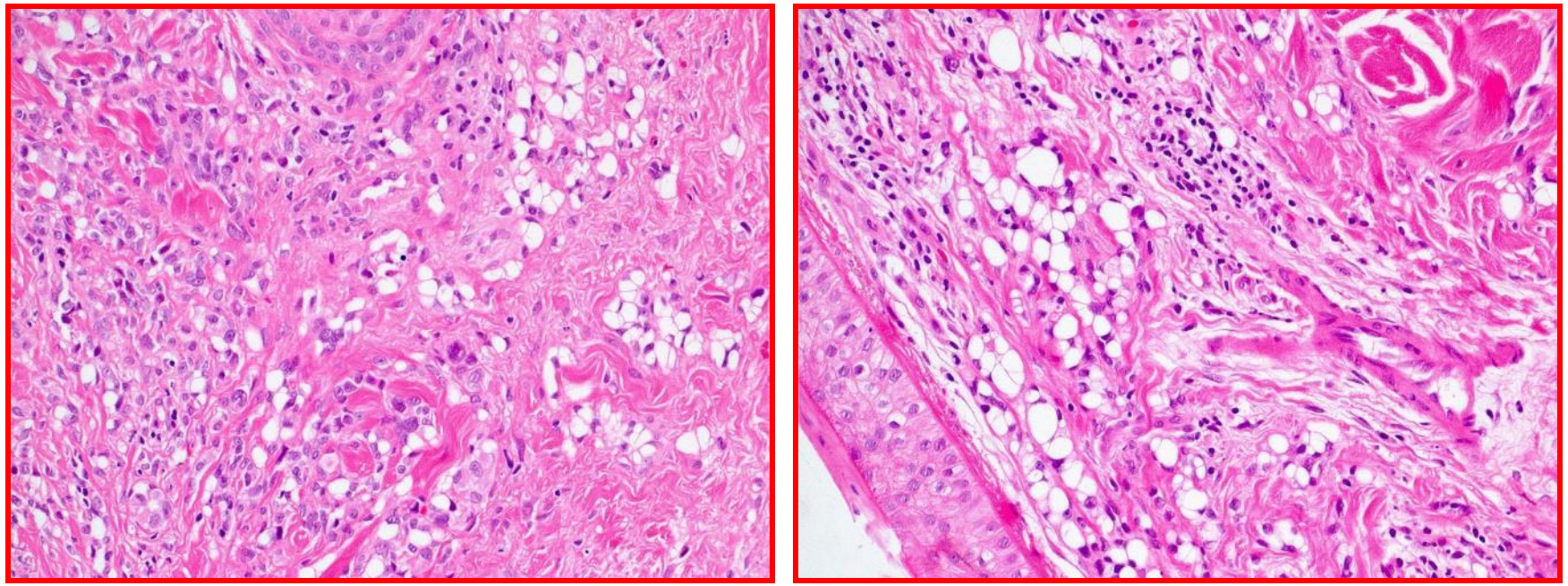
Epithelioid AS



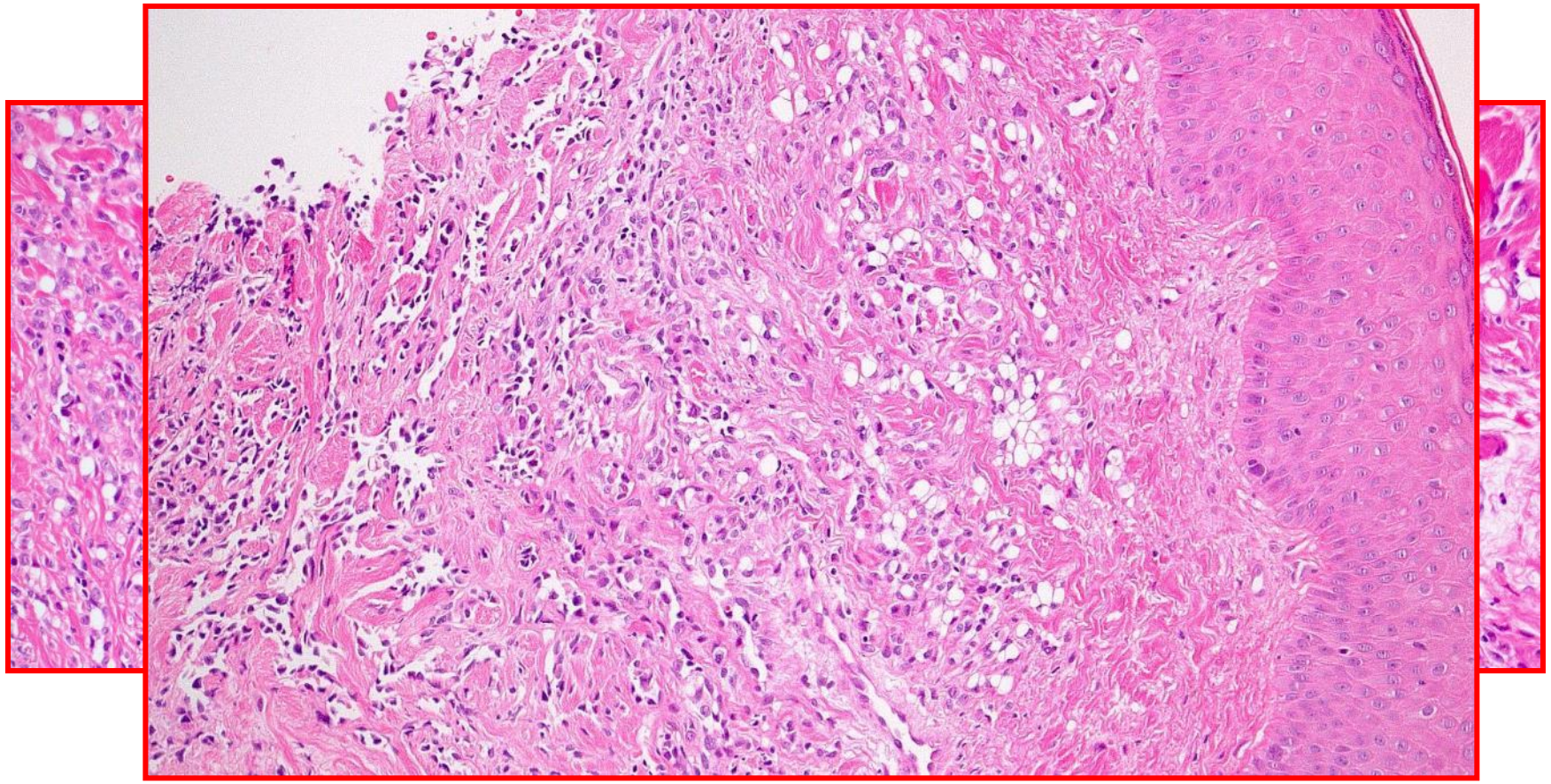




Clear Cell/Signet Ring Cell AS

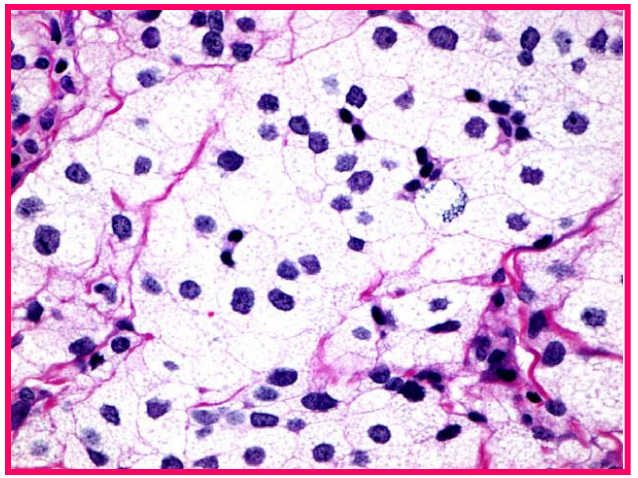


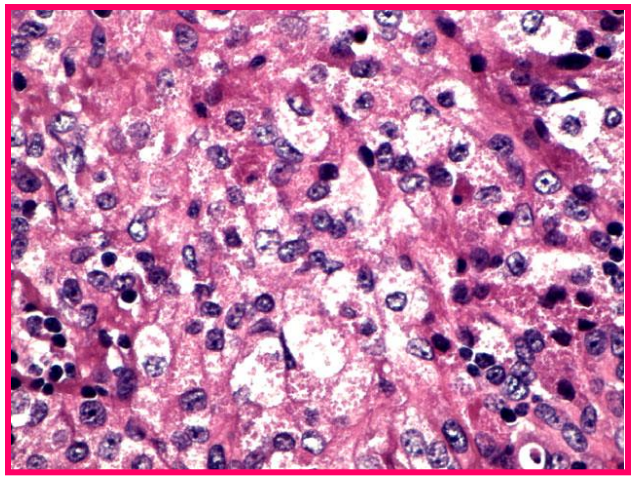
Clear Cell/Signet Ring Cell AS



Other Morphological Variants of Epithelioid AS

- Foamy cell
- Granular cell





Histopathology 2015, 66, 856–863

Dermatopathol. 2014; 36; 669–672

J. Cutan. Pathol. 2010; 37; 901–906

J. Cutan. Pathol. 2012; 39; 476–478, 475

AS

- Can be mostly epithelioid/spindled
- Vasoformation can be inconspicuous; usually seen at the periphery
- Can be easily mistaken for other tumours if index of suspicion low!

AS IHC

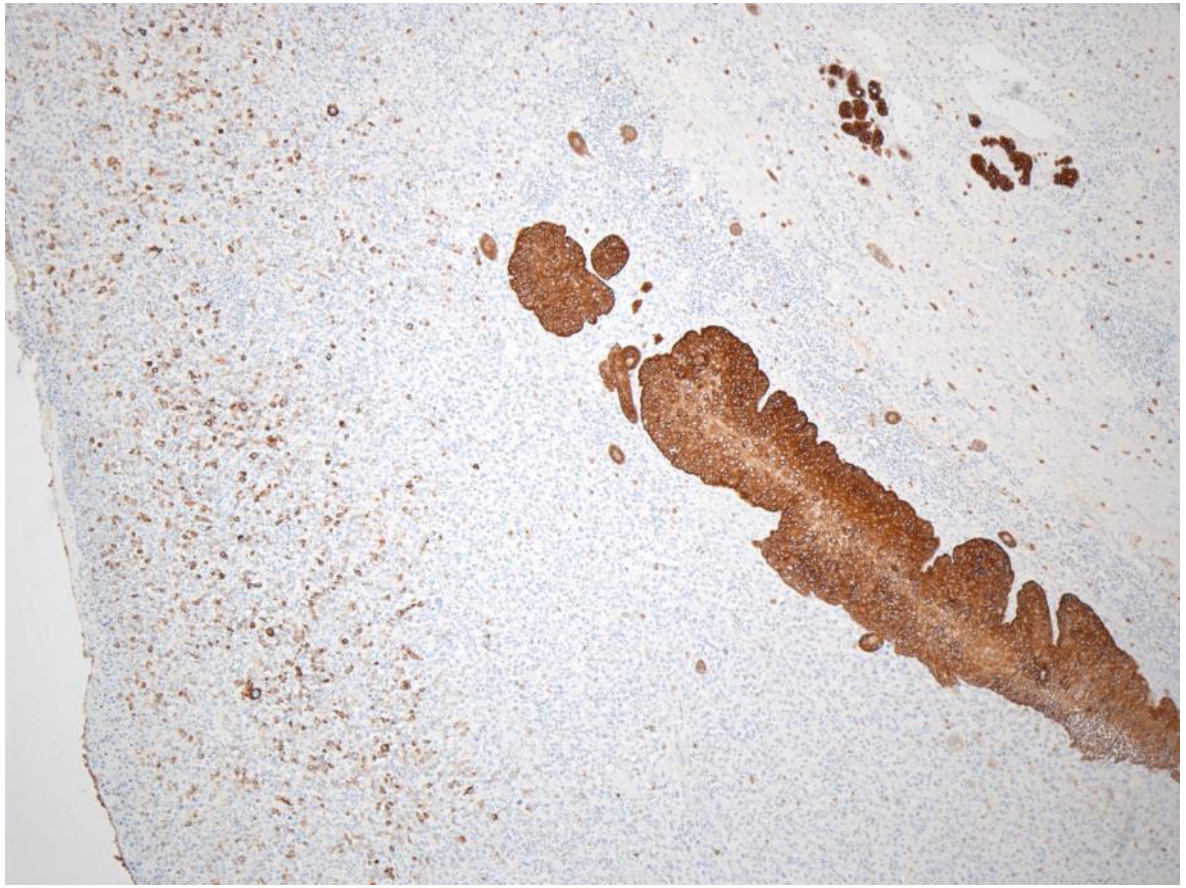
- Use more than one endothelial marker
- CD34, CD31, ERG, (*Podoplanin, FVIIIRA*)

- *CD31 – not entirely specific, also expressed by histiocytes*
- *CD34 – less sensitive than CD31 & not specific*

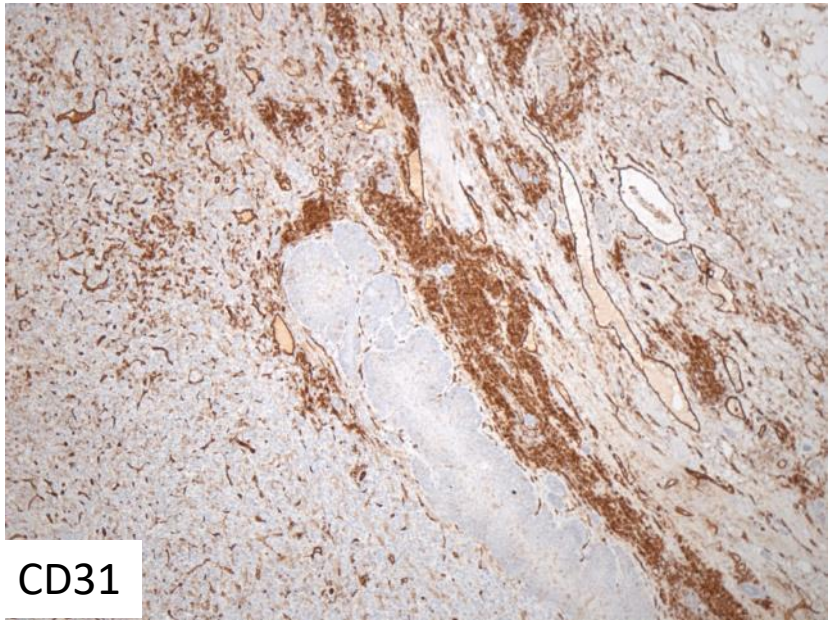
ERG

- ERG = ETS-related gene
- ETS family of transcription factor
- Expressed in normal endothelial cells
- Expressed by haemangiomas, lymphangiomas, almost all angiosarcomas, EHE and PMHE
- Also +ve in AML, subset of EWS + some prostatic adenocarcinoma

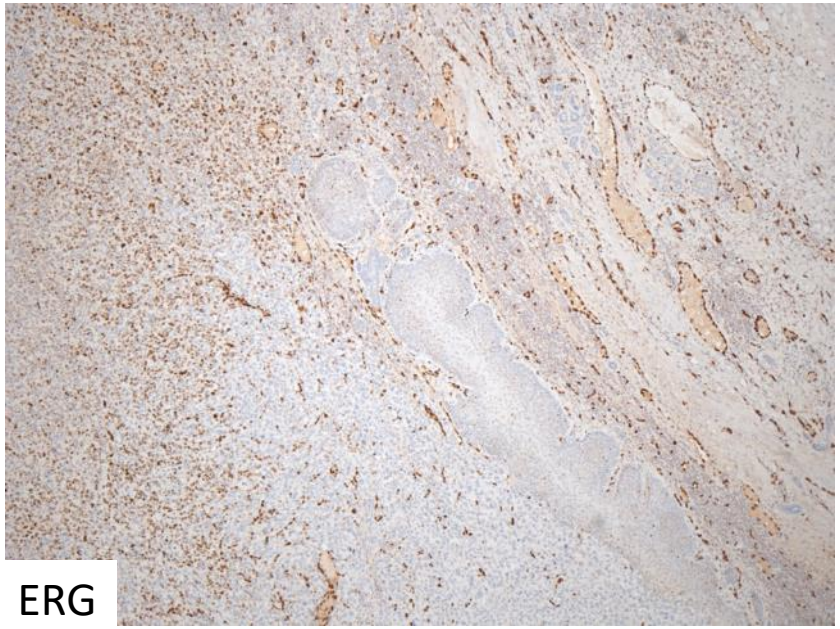
Sarcomatoid SCC



MNF116

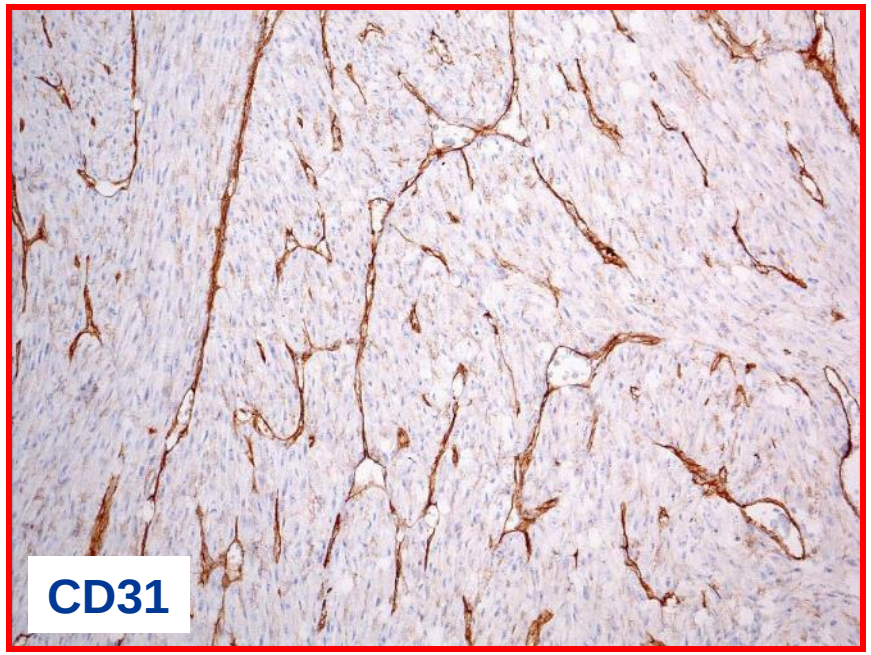


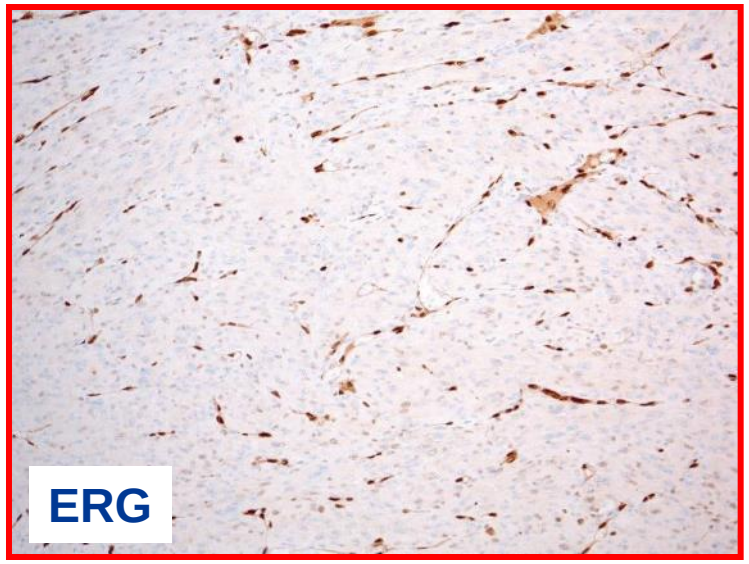
CD31

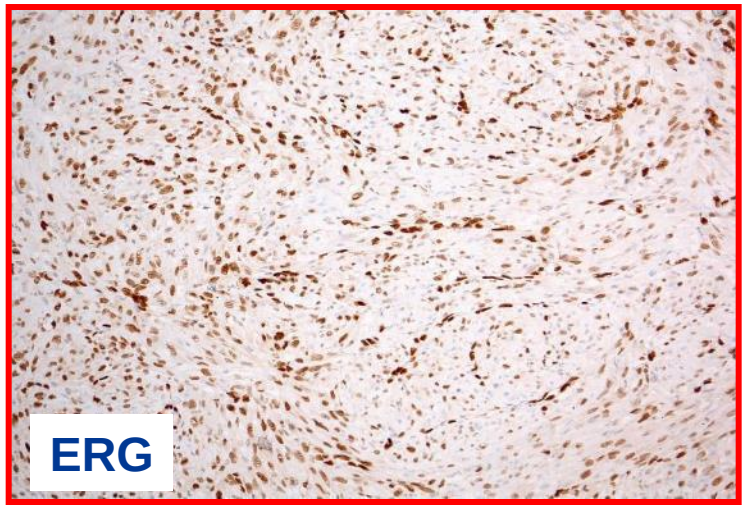


ERG

PDS

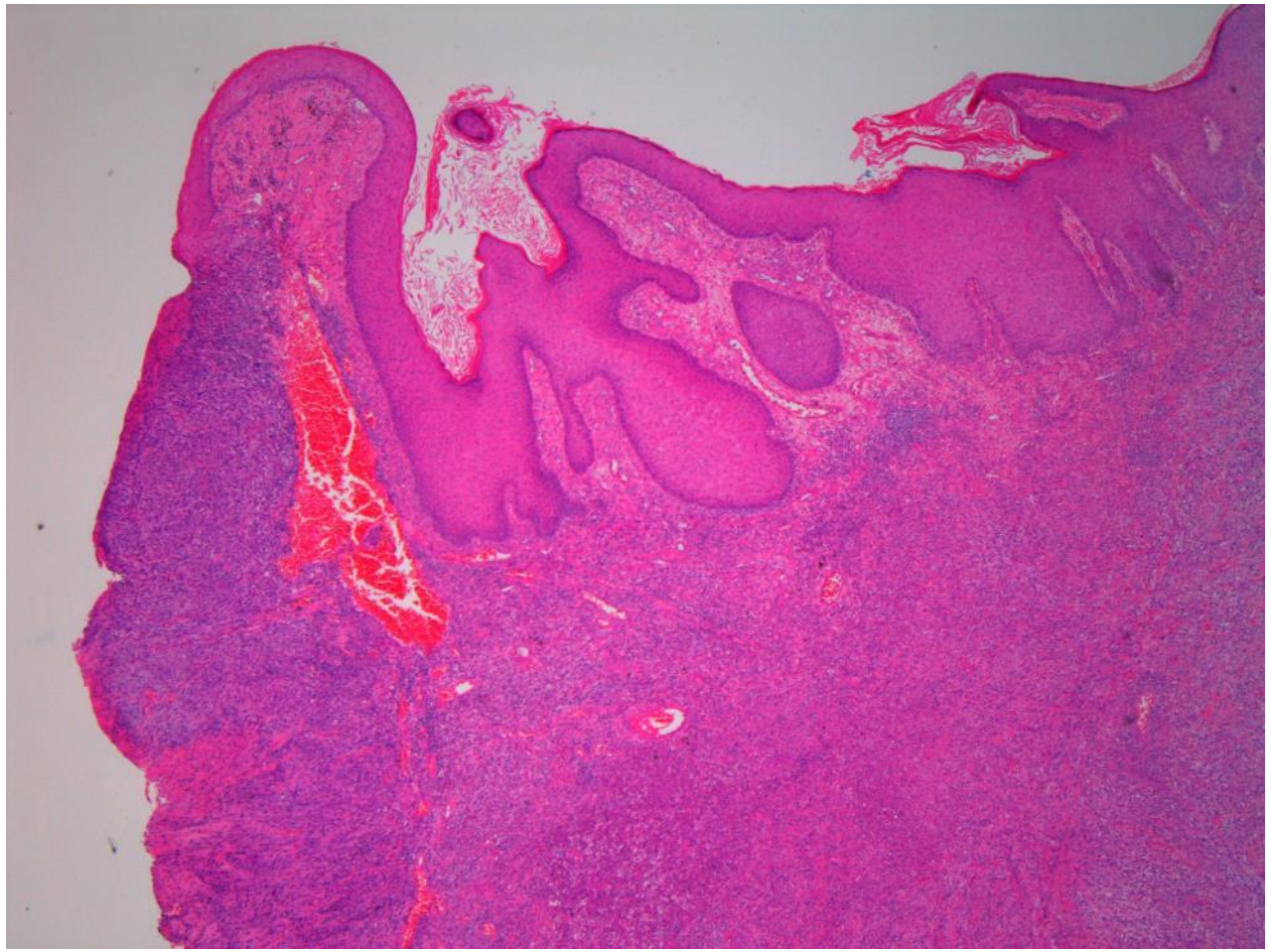


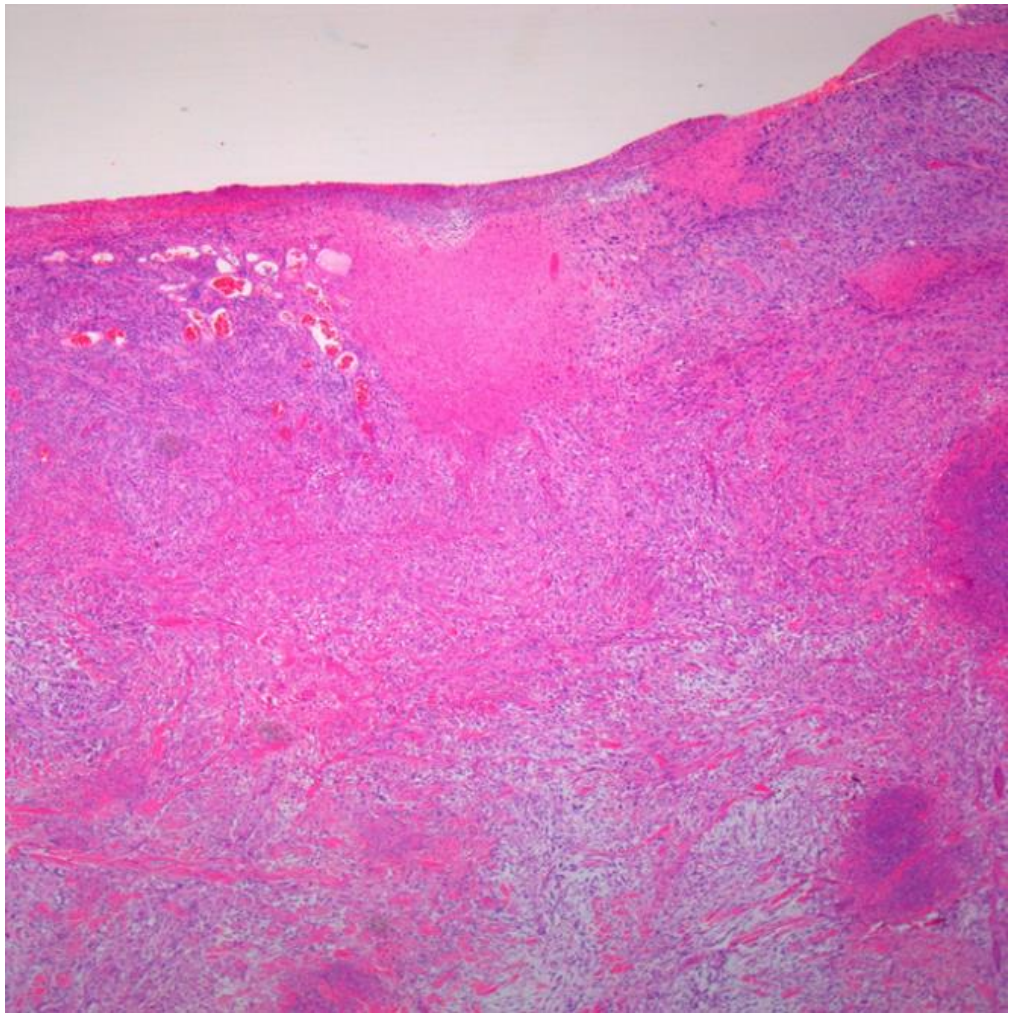


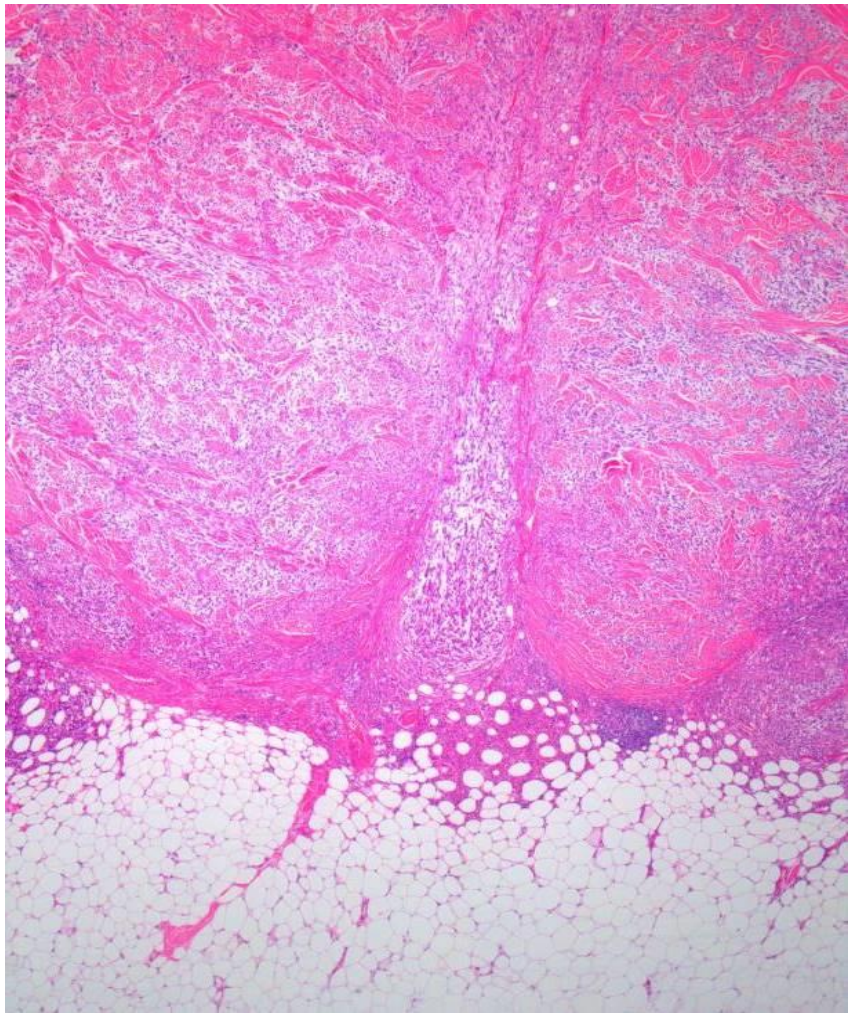


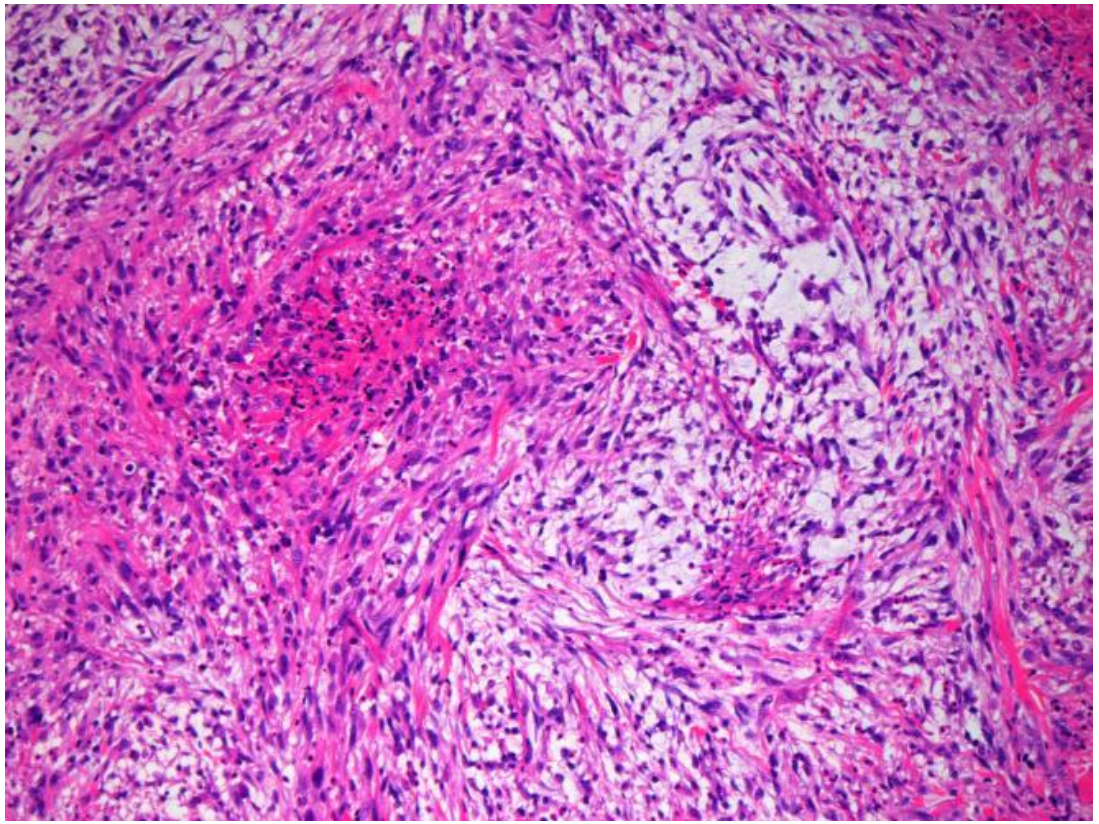
Case

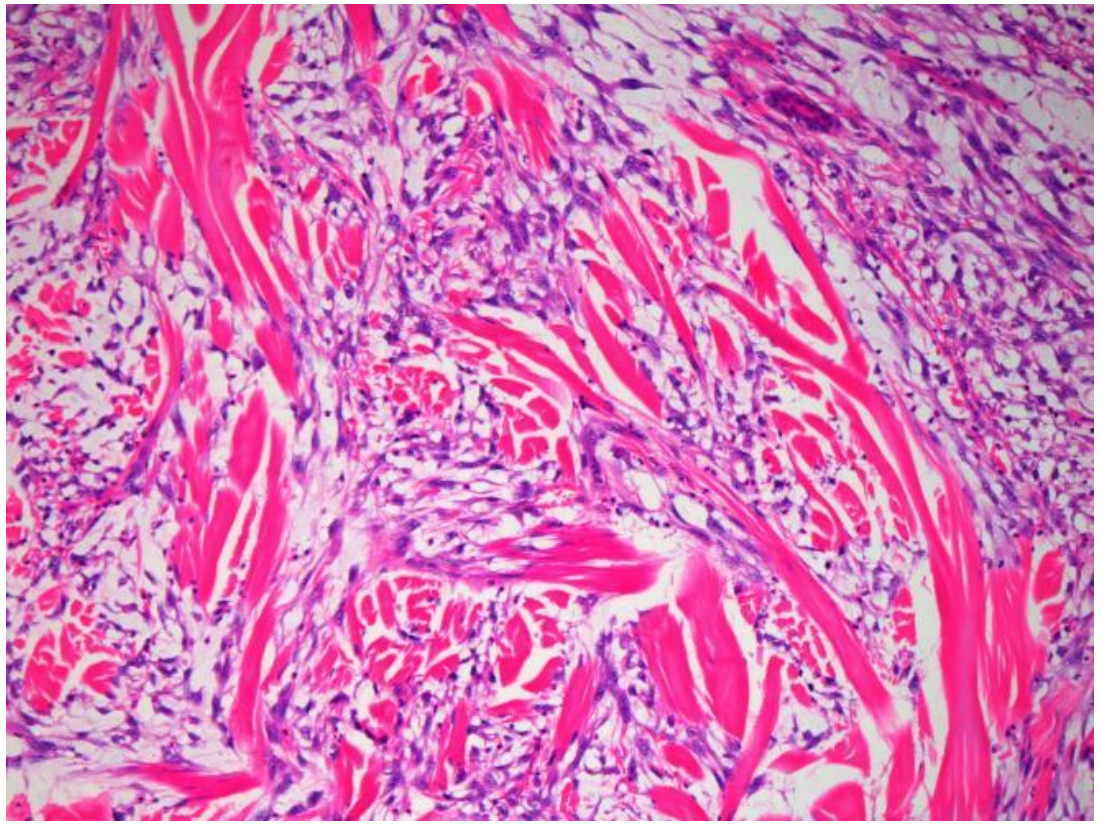
- 77M.Skin lesion, back, WLE

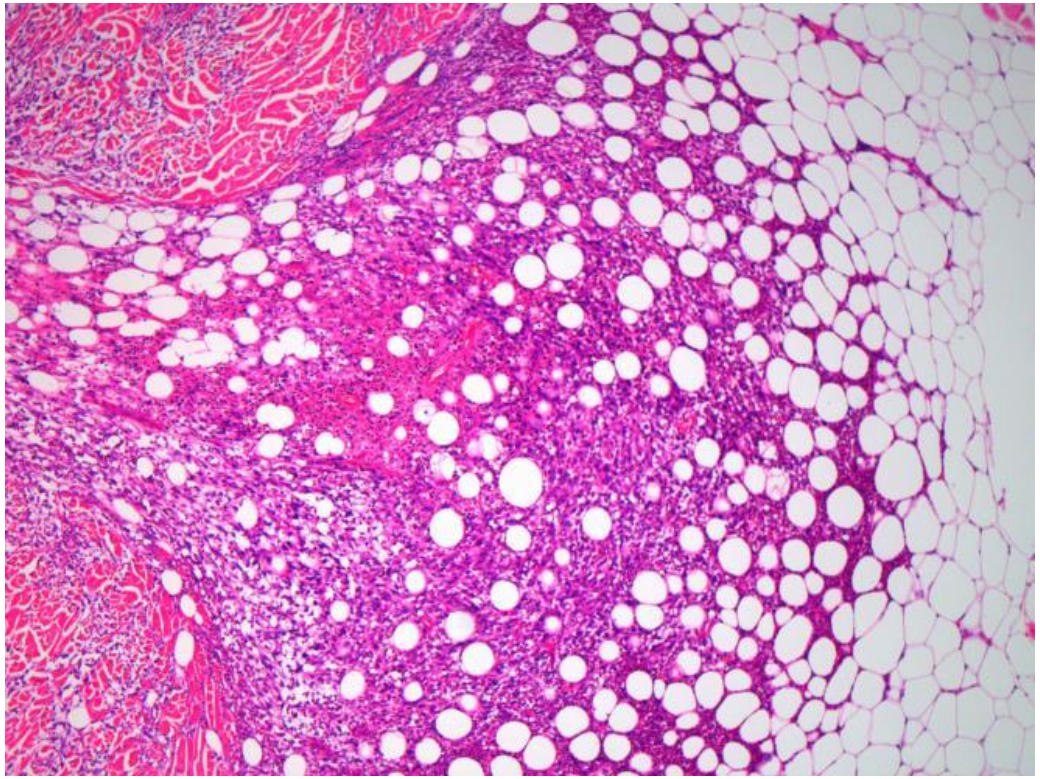


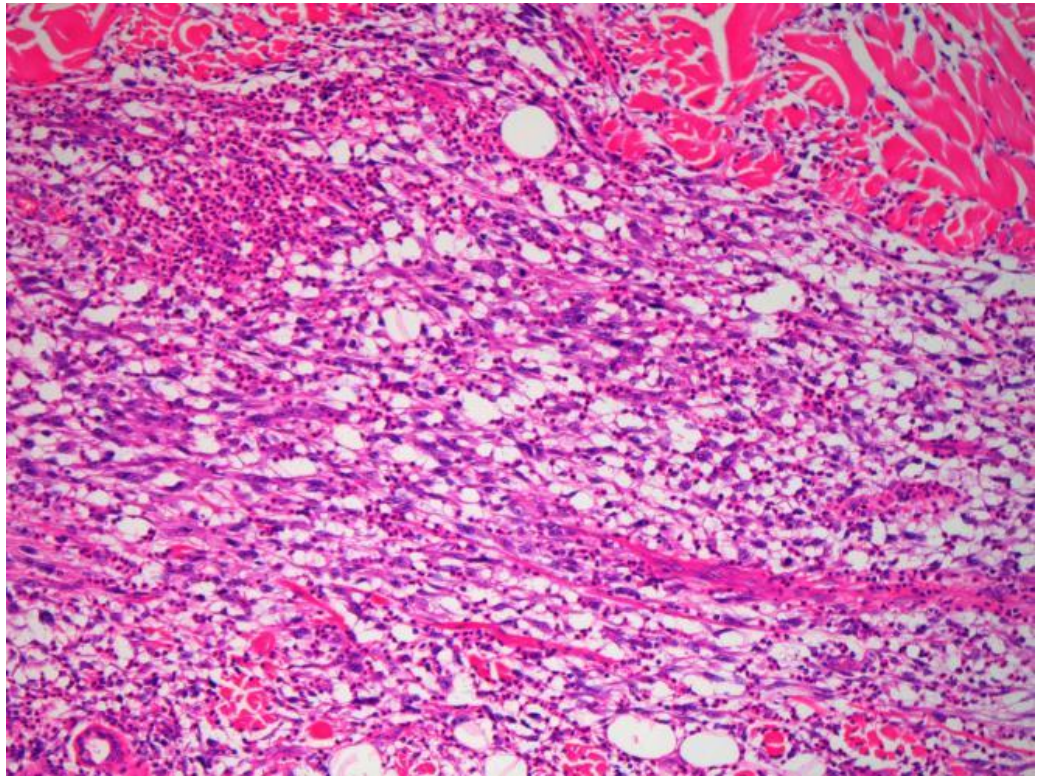


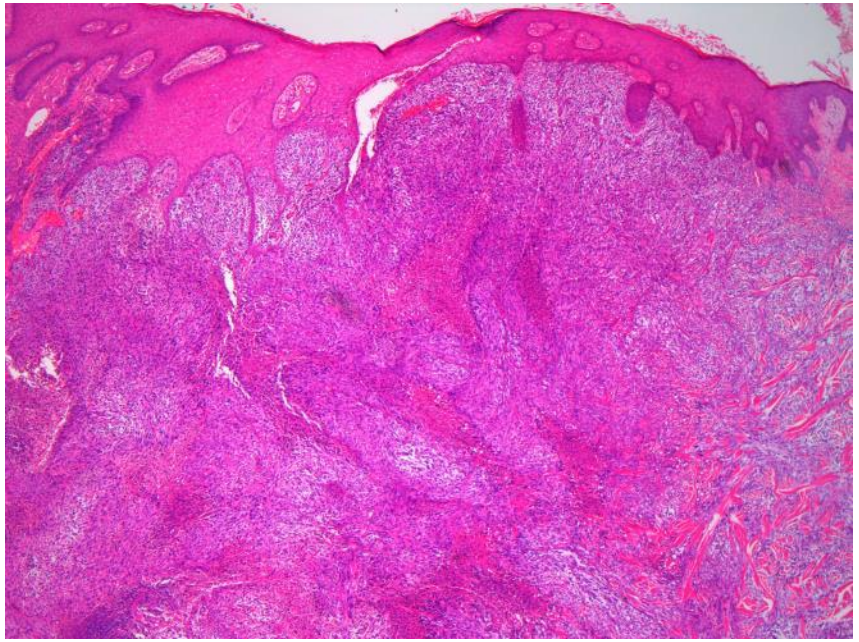


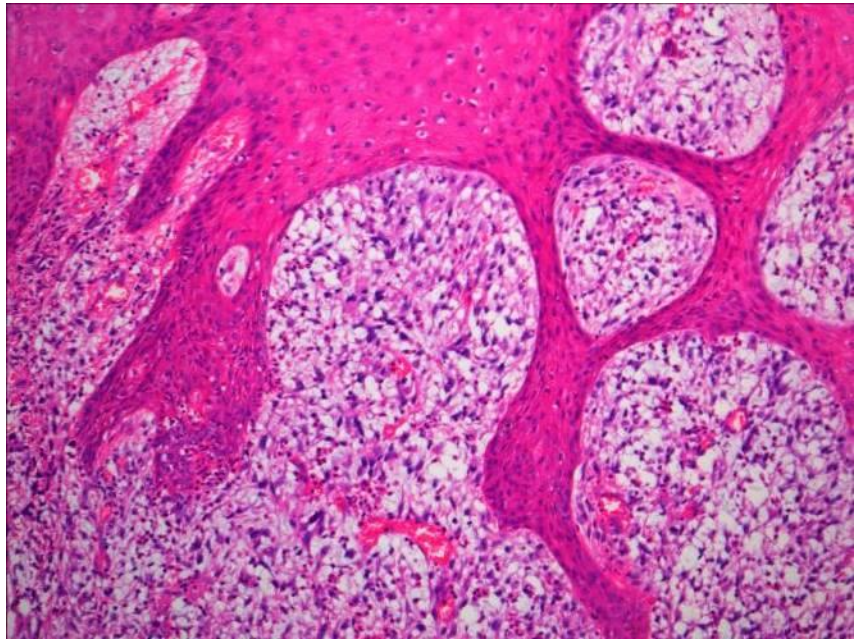


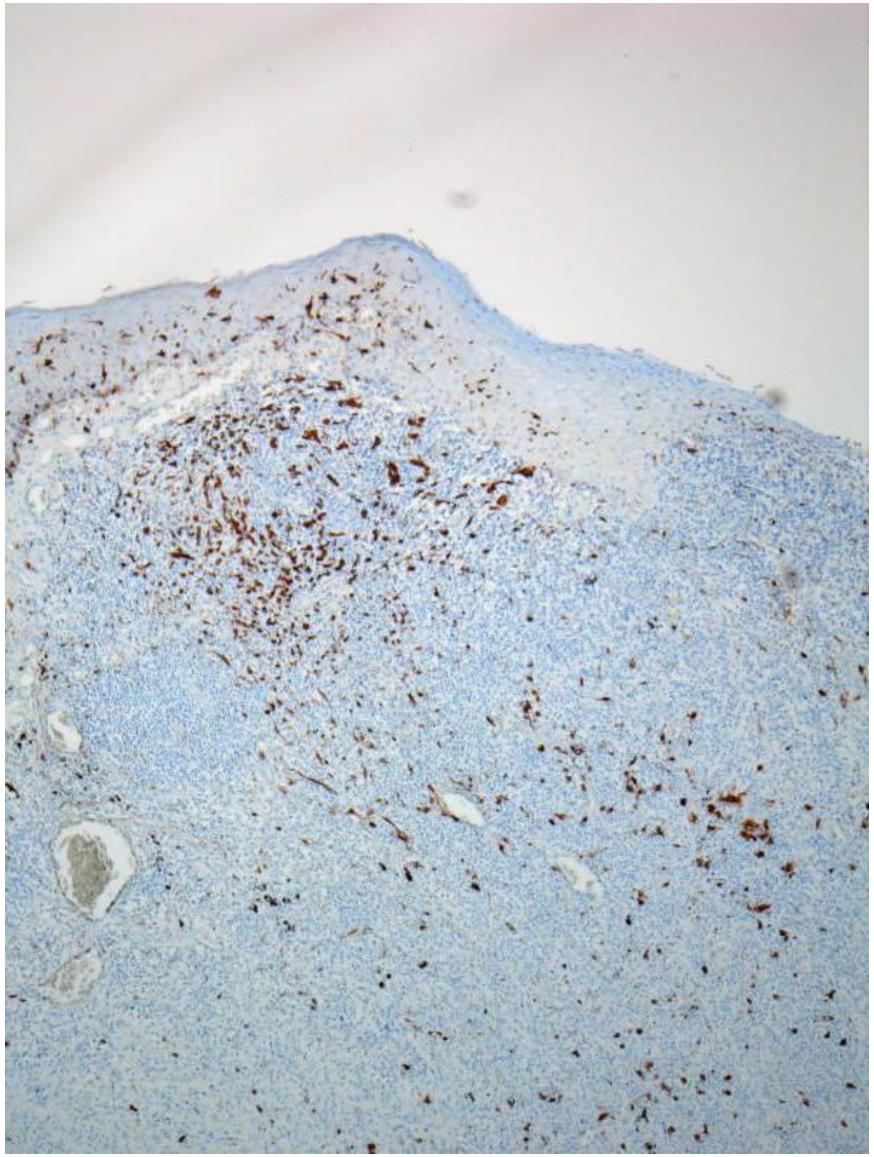




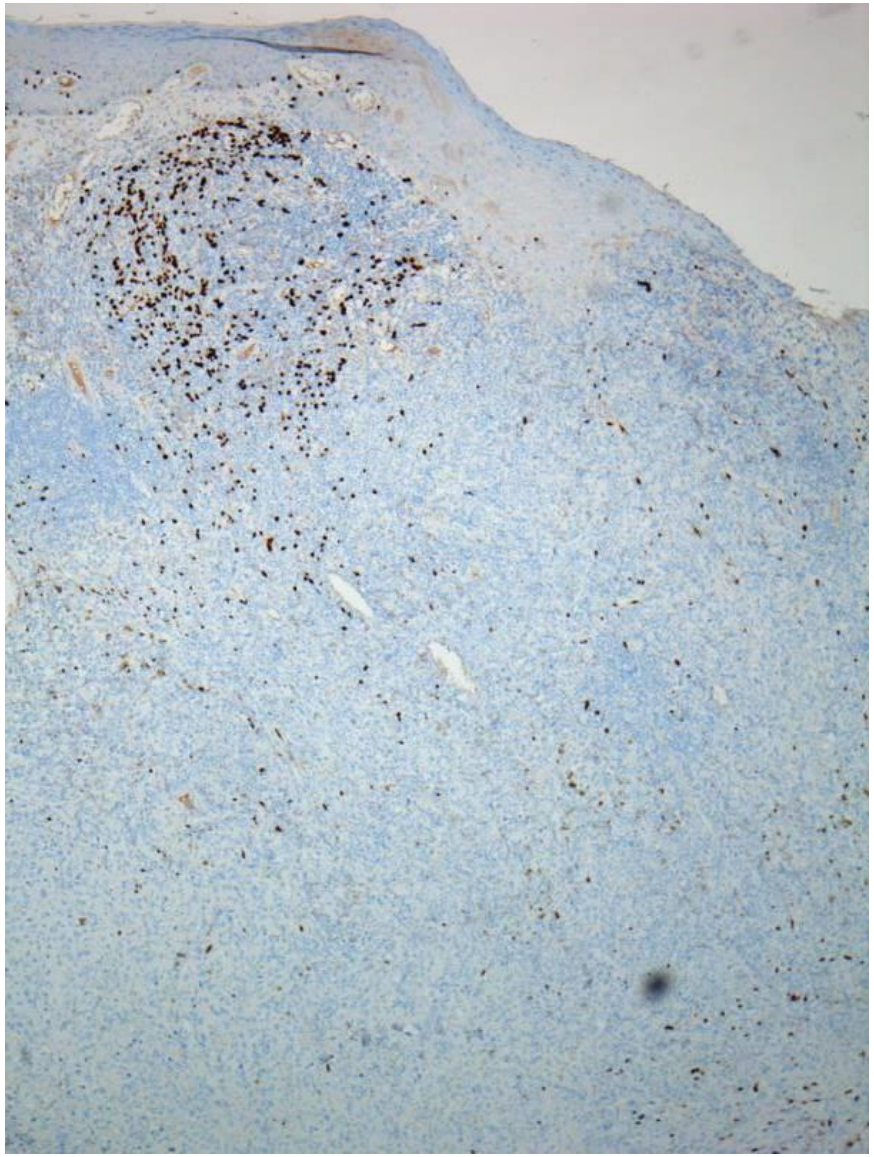




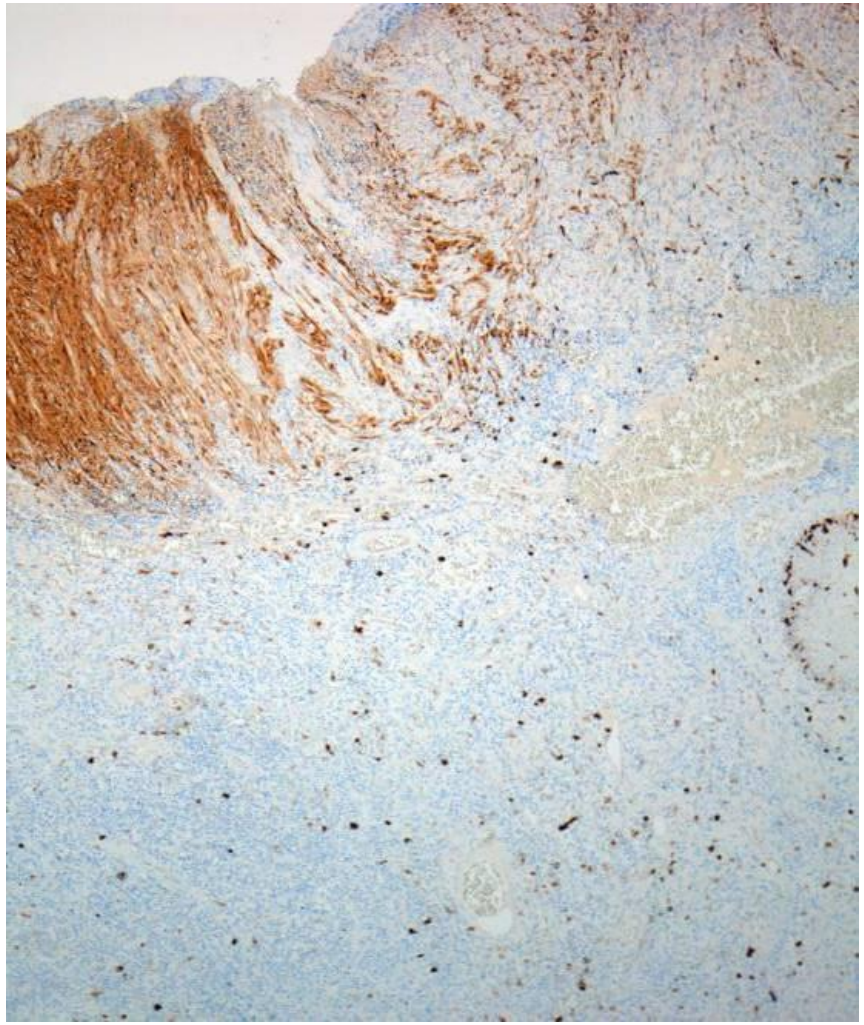




S100



SOX10



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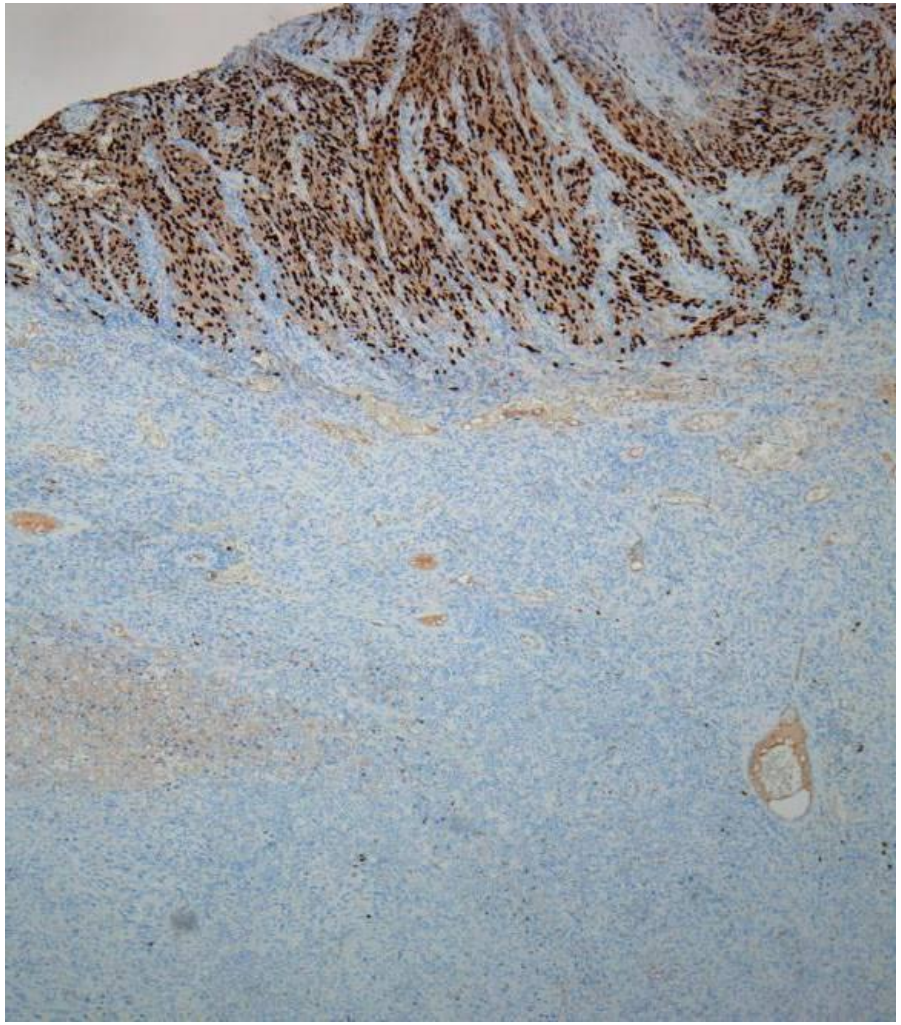

SOX10

Diagnosis

- Sarcomatoid malignant melanoma (melanoma with sarcomatoid dedifferentiation)

Desmoplastic Melanoma with Sarcomatoid De-differentiation

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Abstract

Desmoplastic melanoma (DM) is a variant of melanoma, which typically affects chronically sun-damaged skin of elderly patients. Pure DM displays a low density of fusiform melanocytes in a collagen-rich matrix. In mixed DM, tumor cell density is higher, and parts of the tumor lack abundant stromal fibrosis. Both pure and mixed DM usually express S100 protein homogeneously. We report herein an unusual bi-phenotypic tumor characterized by the association of a pure DM with an undifferentiated solid spindle cell nodule. It occurred on the scalp of a 66 year-old man. A biopsy of the undifferentiated spindle cell nodule was initially interpreted at a commercial laboratory as atypical fibroxanthoma. The pure DM was seen only in the excisional specimen. All cells of the pure DM stained for S100 protein and SOX10. The adjacent solid sarcomatoid spindle cell nodule lacked expression of S100 protein, SOX10, as well as melan-A, gp100 and microphthalmia transcription factor in more than 95% of its tumor cells. While focal expression of melanocyte differentiation antigens in the solid tumor component made us favor a combined DM with sarcomatoid de-differentiation, we also considered the possibility of a collision scenario, i.e., a pleomorphic dermal sarcoma incidentally colliding with a DM. To further assess a possible relationship of the sarcomatoid nodule with the DM, we performed next-generation sequencing analysis on each component separately. The analysis revealed shared chromosomal copy number changes and a high number of common mutations, thereby supporting the concept of a DM with a de-differentiated sarcomatoid component. An interesting finding is the presence of mutations of the neurofibromin gene in both tumor components

Am J Surg Pathol. 2014

Living on the Edge: Diagnosing Sarcomatoid Melanoma Using Histopathologic Cues at the Edge of a Dedifferentiated Tumor: A Report of 2 Cases and Review of the Literature

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*Victor G. Prieto, MD, PhD,† Alison L. Cheah, MBBS,‡ and Steven D. Billings, MD**

Abstract: Sarcomatoid melanoma is a rare type of melanoma lacking typical histologic features of melanoma and often lacks expression of S100 protein and melanocyte-specific markers. Given the rarity of this entity, its clinicopathologic findings are not well defined. We report 2 cases of sarcomatoid melanoma received in consultation: a 65-year-old woman with a right breast mass and a 62-year-old man with a left plantar heel mass. Both lesions were ulcerated, pedunculated, highly cellular proliferations of atypical spindle cells arranged as fascicles and/or sheets. The tumor cells of the breast mass expressed CD10 and vimentin diffusely but S100 protein only focally. The tumor cells of the heel mass lacked expression of melanocytic markers altogether, except for weak, very focal S100 protein expression. At the junctional edge of the breast mass and in the ulcer base of the heel mass, focal precursor melanoma was present and exhibited melanocytic differentiation. We report these cases to emphasize the importance of meticulous histologic inspection at the lesion's edge and/or ulcer base to correctly identify the conventional precursor melanoma in these rare lesions to ensure appropriate diagnosis and subsequent clinical management as treatment options may be significantly different from those offered for sarcomas.

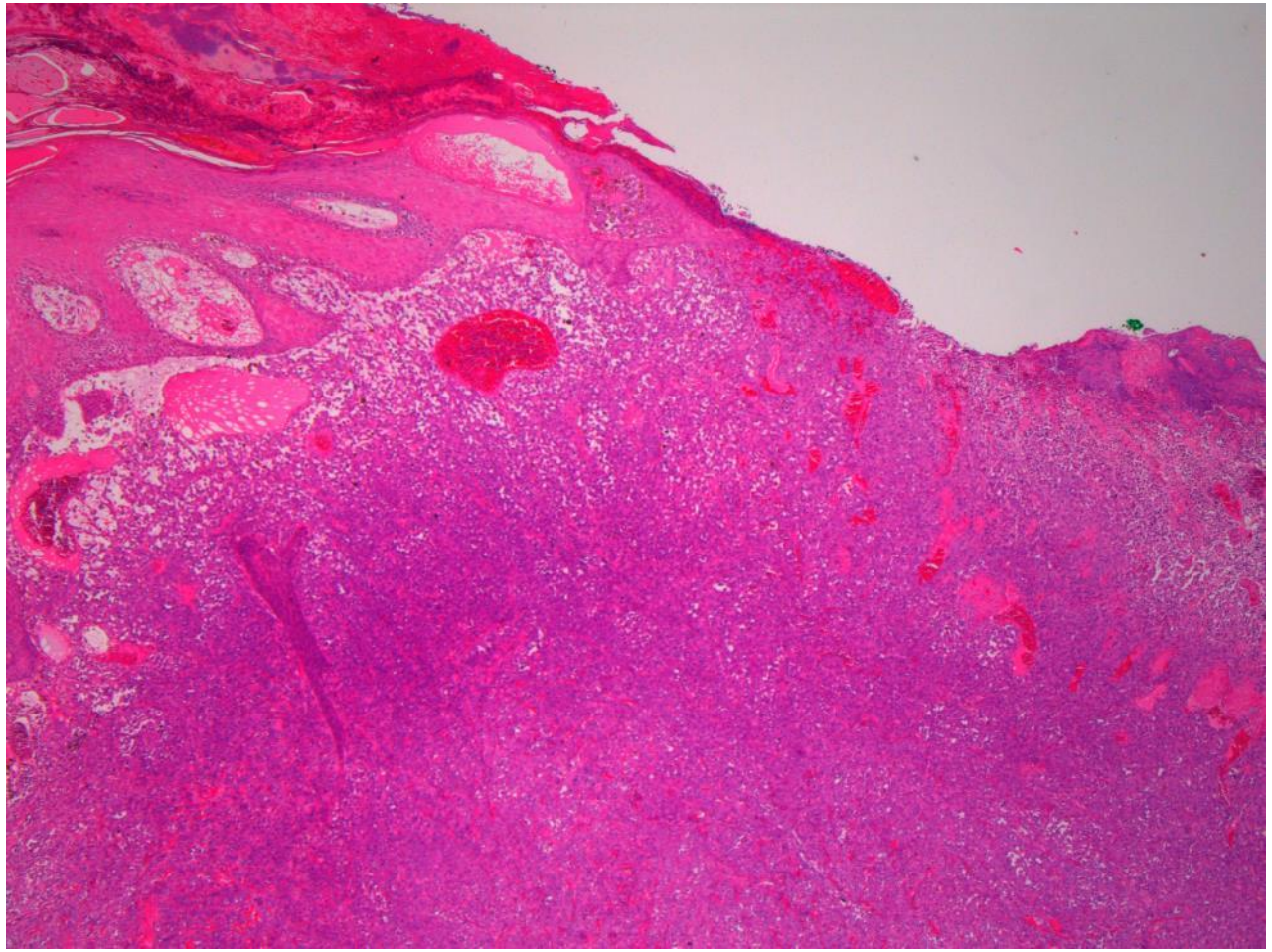
differential diagnosis of primary cutaneous pleomorphic spindle-cell neoplasms. Therefore, making a correct diagnosis of sarcomatoid melanoma is not only essential for initiating appropriate clinical management but also for contributing meaningful data to the existing scarce literature regarding its clinicopathologic behavior. Although because of its rarity, the efficacy of targeted immunotherapies recently approved for melanoma is unknown, accurate diagnosis would potentially allow a chemotherapeutic option that could positively affect patient outcome. Herein, we describe 2 cases of sarcomatoid melanoma and review of the literature.

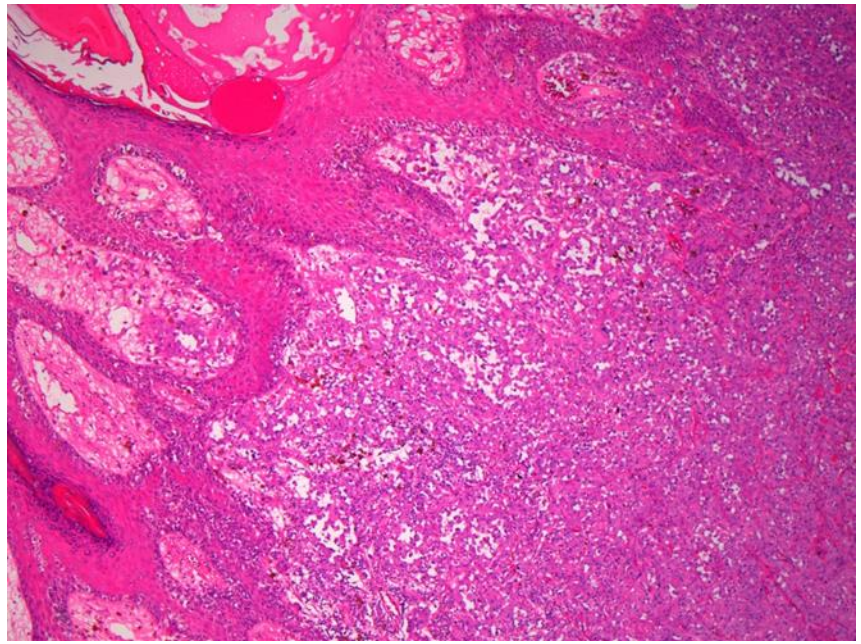
MATERIALS AND METHODS

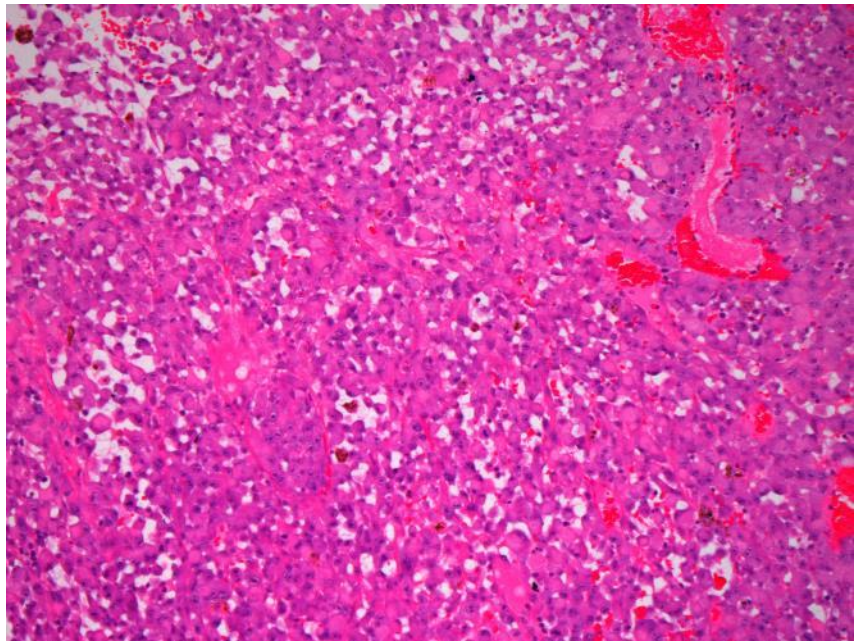
Two cases were received in consultation in 2013 and 2014 at the Cleveland Clinic Foundation, Cleveland, OH, and at The University of Texas MD Anderson Cancer Center, Houston, TX. Sarcomatoid melanoma was defined as a primary cutaneous pleomorphic spindle-cell neoplasm with focal, weak, or absence of expression of neural crest or melanocytic markers in the sarcomatoid component with an

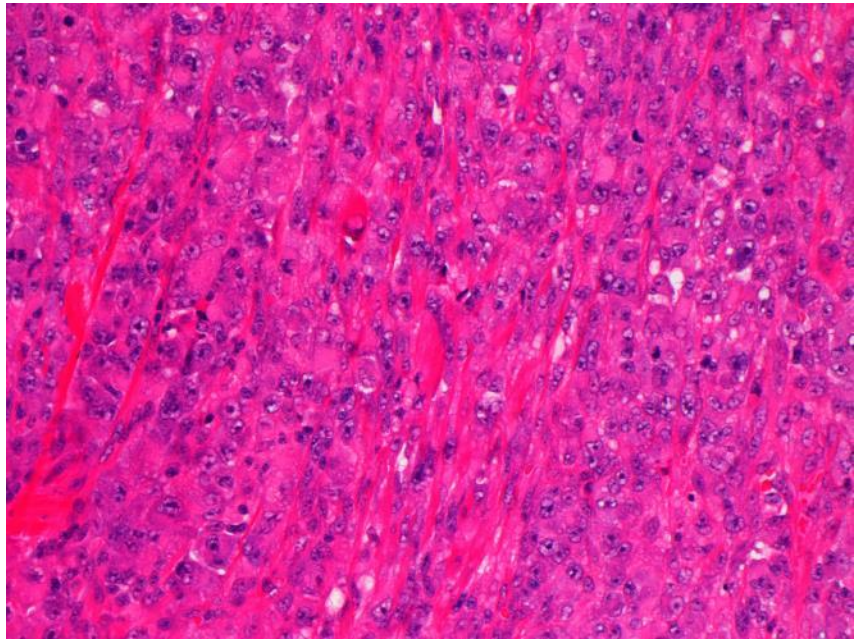
Case

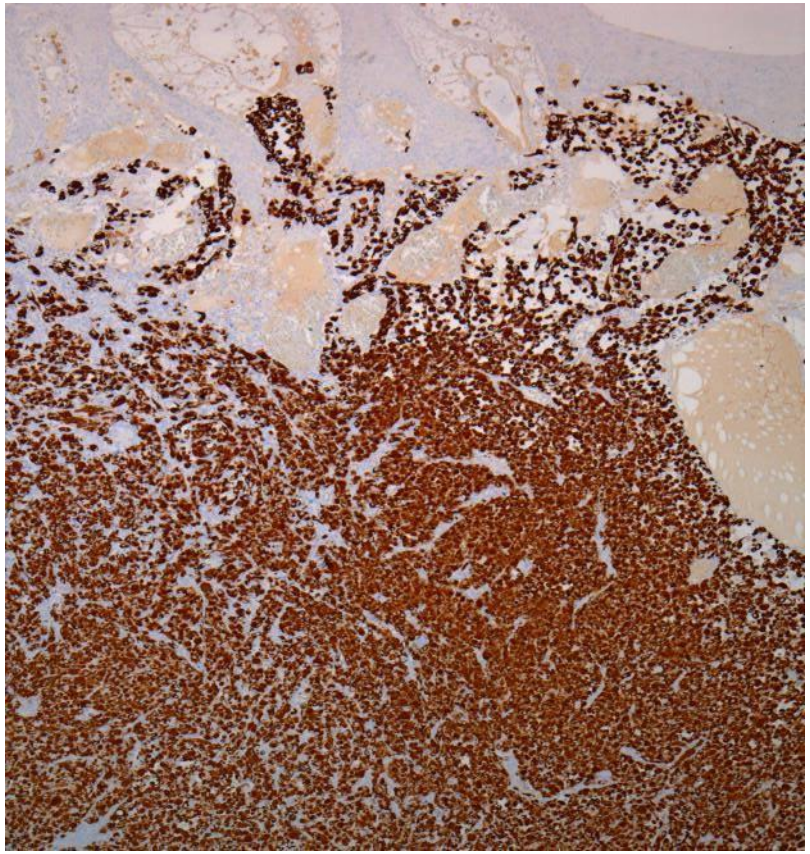
- 19M. Excision of nodular lesion Rt temple. Clinical Information: Biopsy showed discohesive sheets of tumour cells with epithelial, plasmacytoid and rhabdoid morphology ? Rhabdomyosarcoma

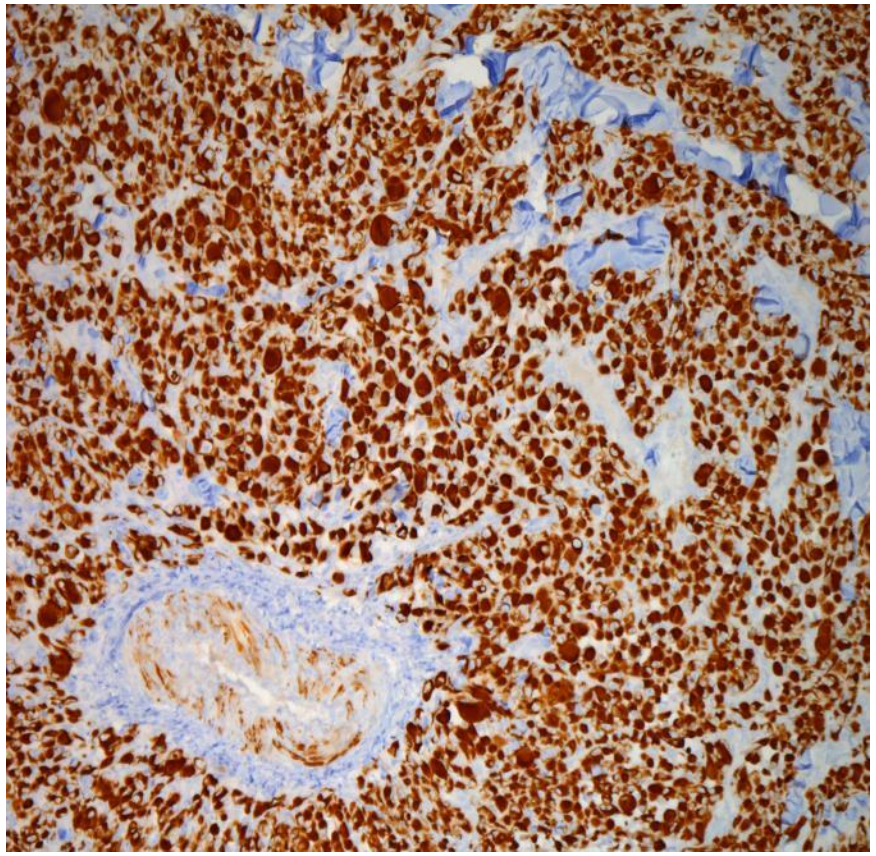




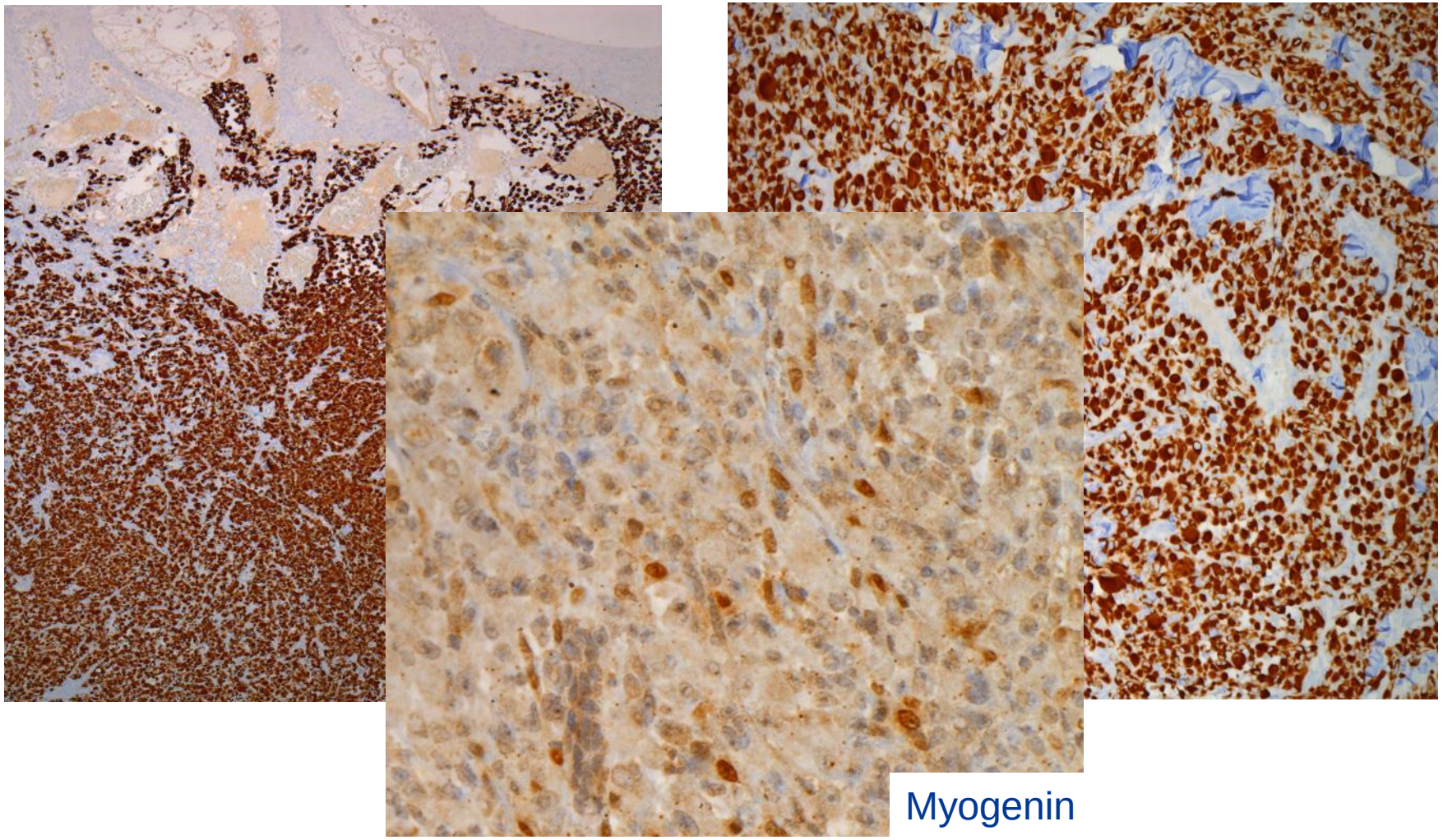




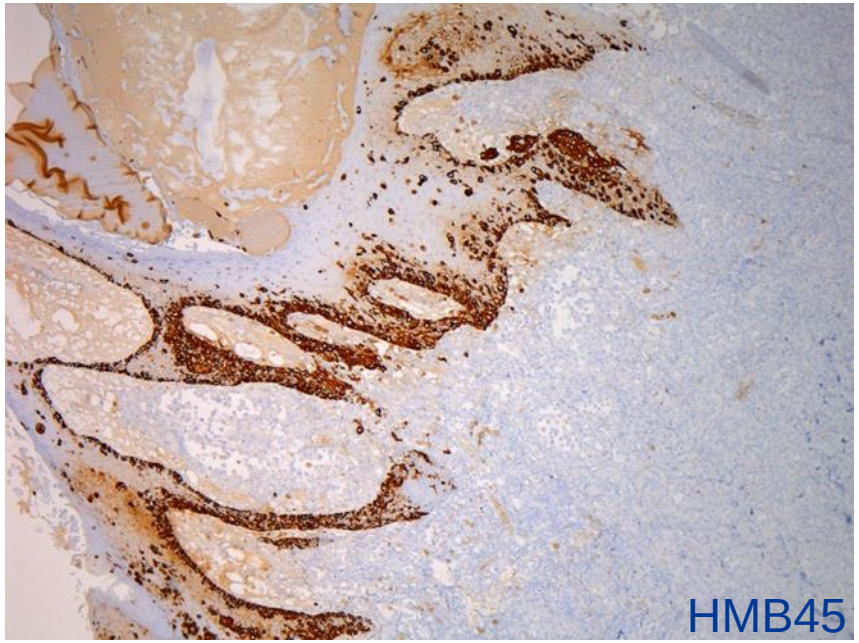


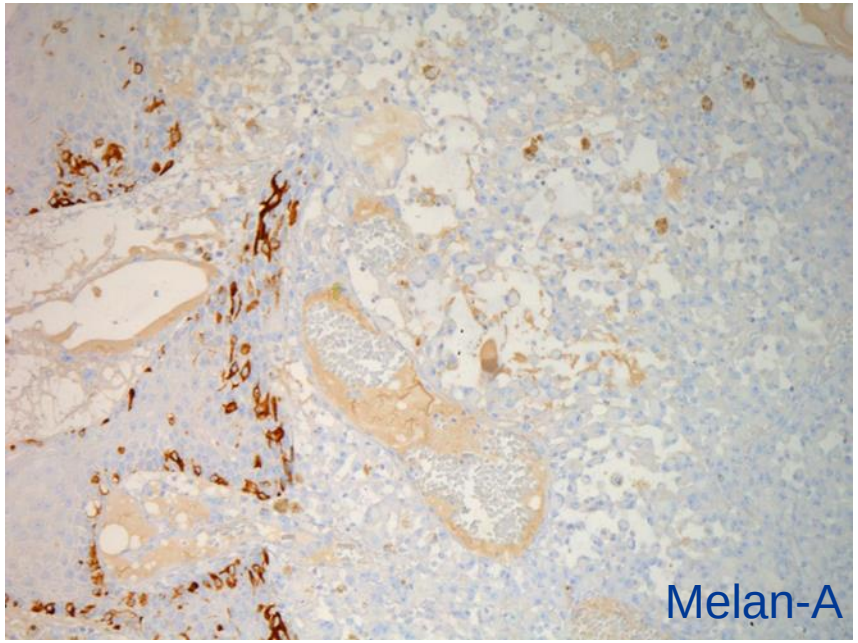


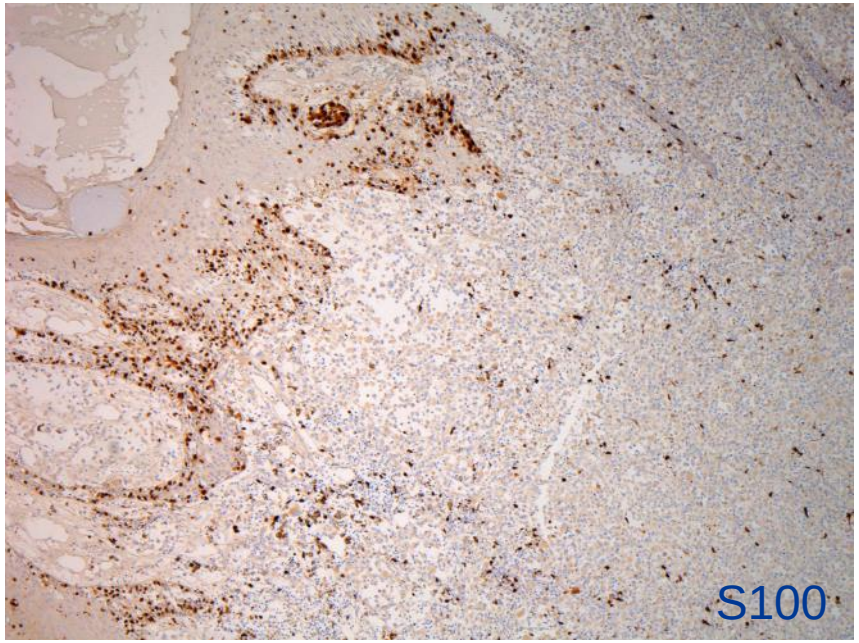
Desmin

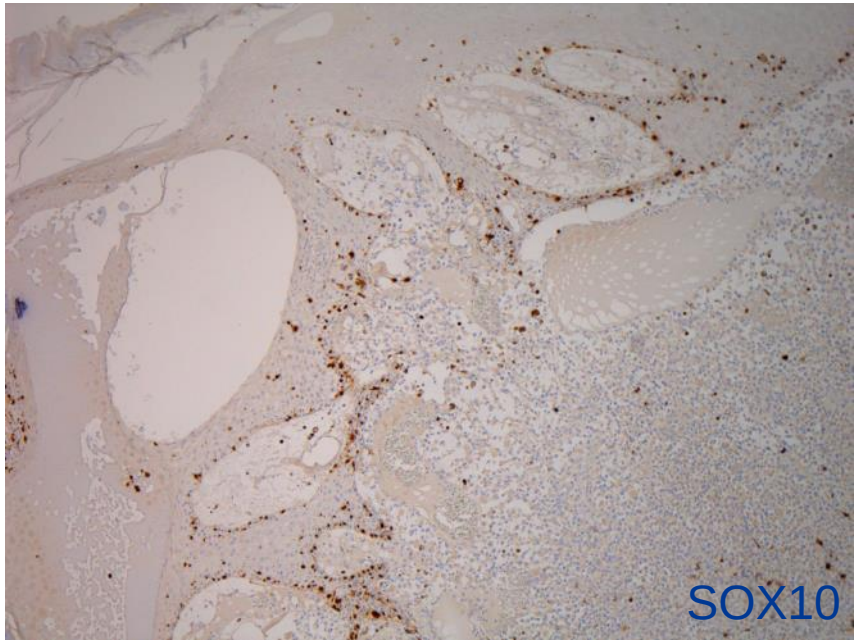


Myogenin


HMB45


Melan-A


S100


SOX10

Diagnosis

- Malignant melanoma with divergent rhabdomyosarcomatous differentiation

- Mutation analysis detected a mutation in codon 600 of *BRAF*

Definition of Divergent Differentiation in Melanomas

- Development of morphologically, immunohistochemically and or ultrastructurally recognisable non melanocytic cell or tissue components

Banerjee S S & Eyden B, Histopathology 2008;52:119 –129

Rhabdomyoblastic Differentiation

- Mainly described in congenital nevi in children with or without neurocutaneous melanosis syndrome
- Very rarely seen in melanomas occurring in adults
- IHC: Desmin, myogenin, MYO-DI ± myoglobin
- EM: Thick and thin filaments + Z-bands

Tran TAN et al. Am J Dermatopathol. 2018. Campbell K et al. J Cutan Pathol. 2018. Antonov NK et al. Am J Dermatopathol. 2016. **Shenjere P et al. Int J Surg Pathol. 2014**. Gharpuray-Pandit D et al. Int J Surg Pathol. 2007. Gattenlohner, S & Brocker, EB. N Engl J Med. 2008. Reilly, DJ et al Int J Surg Pathol. 2013. Kuwadekar A et al. BMJ Case Rep. 2018

- Should be differentiated from rhabdoid melanomas
- Other D/D: malignant Triton tumor

Different Non-melanocytic Components Detected In Malignant Melanomas

- Fibroblastic/ myofibroblastic
- Smooth muscle
- Osteocartilaginous
- Schwannian & Perineurial
- Ganglionic and ganglioneuroblastic
- Neuroendocrine
- Epithelial

- Divergent differentiation/trans-differentiation and dedifferentiation can cause diagnostic confusion:

  -awareness of the possibility important
  -sampling
  -use of panel of IHC
  -clinical context

- Prognostic significance still uncertain – more experience required

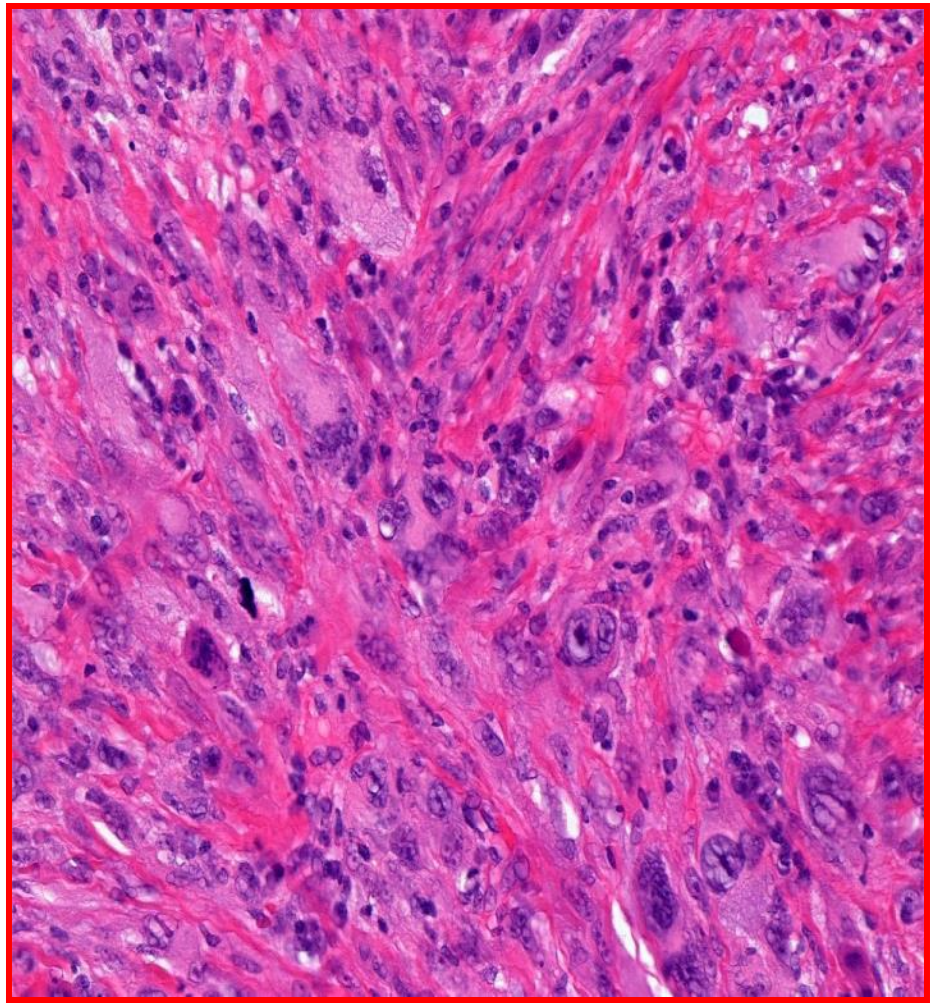
Atypical Fibroxanthoma (AFX)

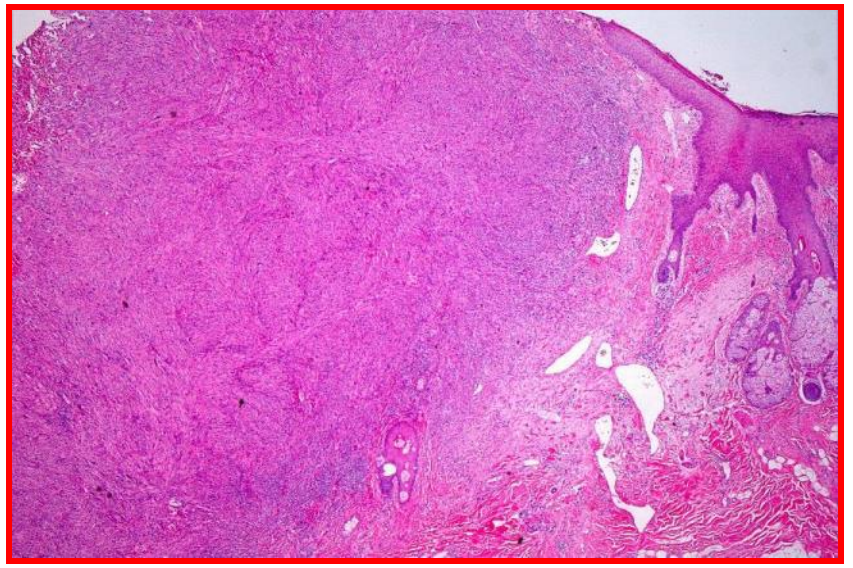
- Term coined by Helwig in 1961
- Cutaneous tumour with histologically malignant appearance but associated (in most cases) with favourable clinical behaviour
- Elderly patients & younger patients with xeroderma pigmentosa
- Sun exposed areas – head and neck and upper limbs
- UV signature mutation in p53
- ?? Immunosuppression

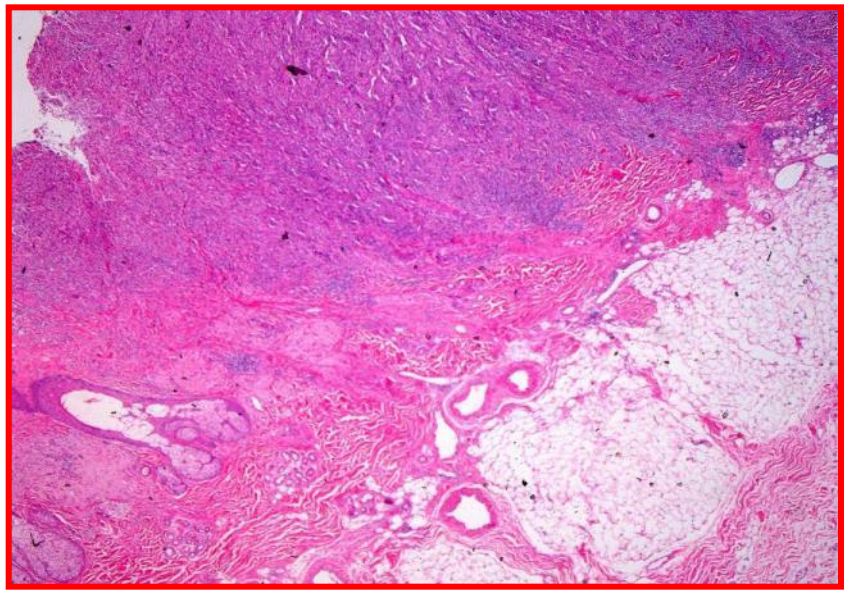
AFX

- Usually less than <1 cm in MD
- Relatively well-circumscribed
- Pushing deep edge
- Majority of cases abut the overlying epidermis
- Cellular with obvious cellular pleomorphism
- Variable morphology – Cells may be spindled, epithelioid or stellate-shaped
- Multinucleated cells and tumour giant cells frequently present
- Mitoses are frequent, including atypical forms
- Actinic keratosis common in overlying or adjacent epidermis & solar elastosis typically present in surrounding dermis

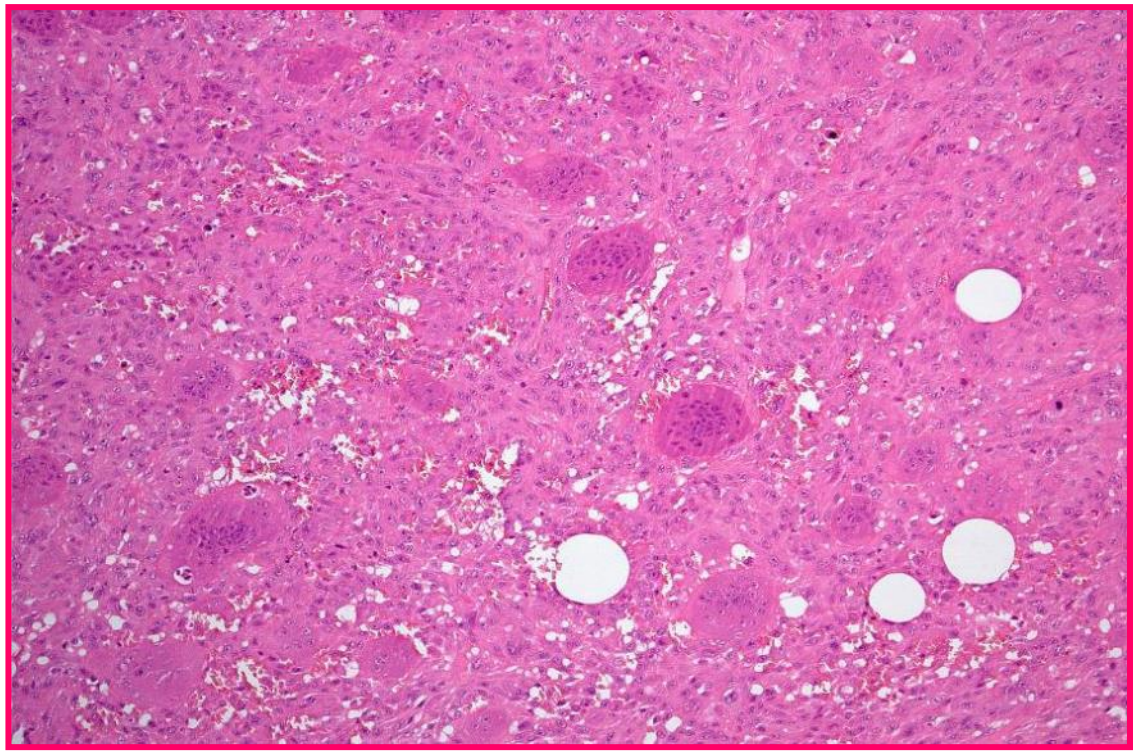
AFX



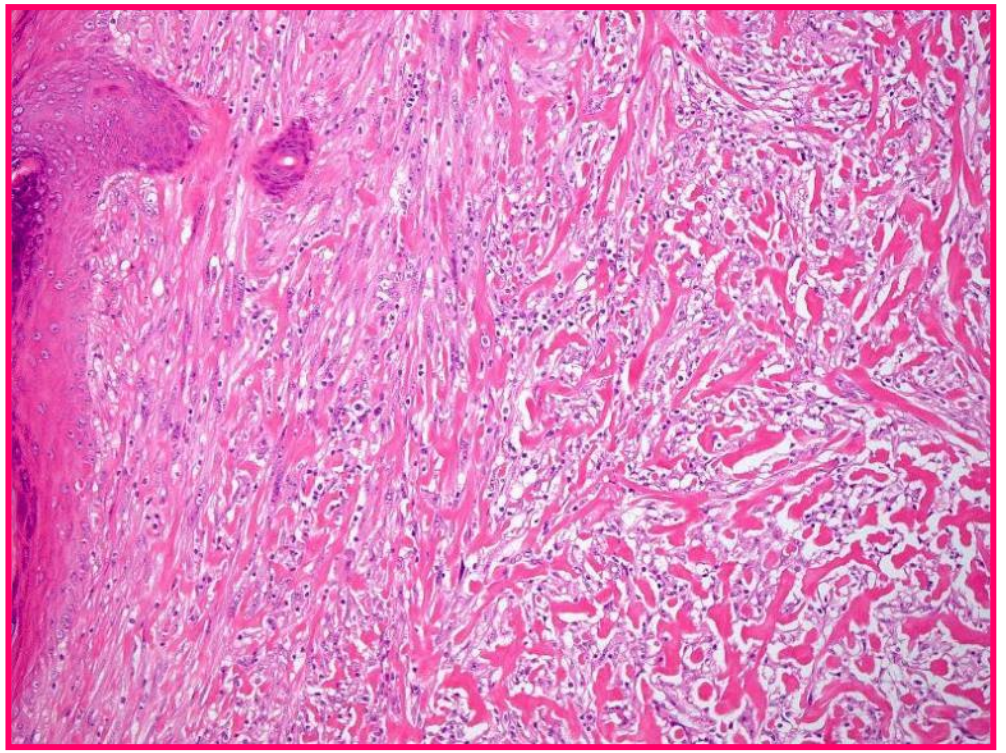




Morphological Variants

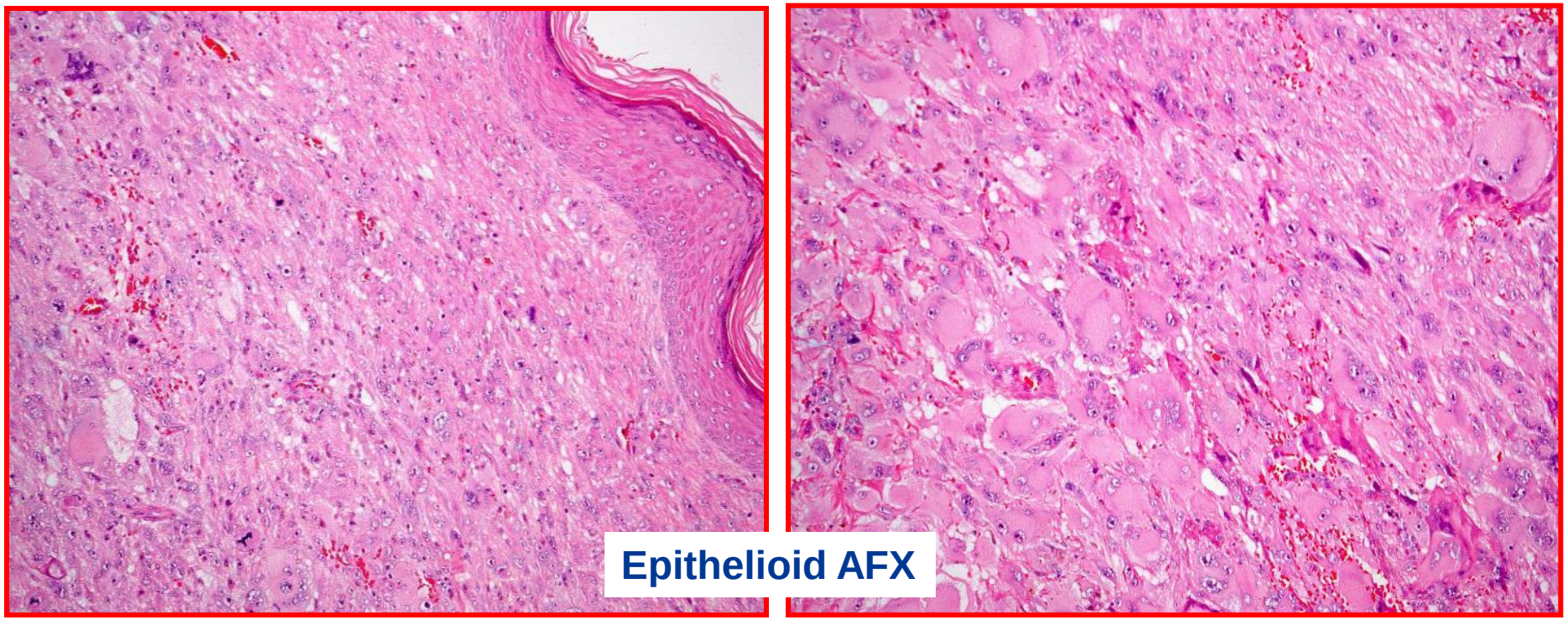


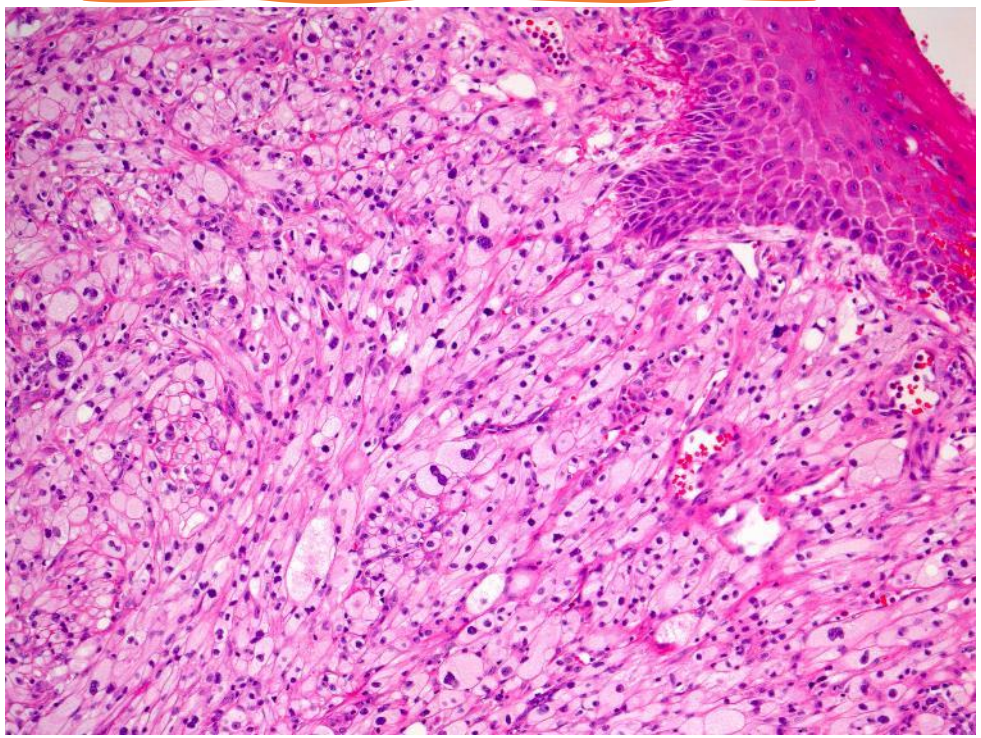
AFX with osteoclast-like giant cells



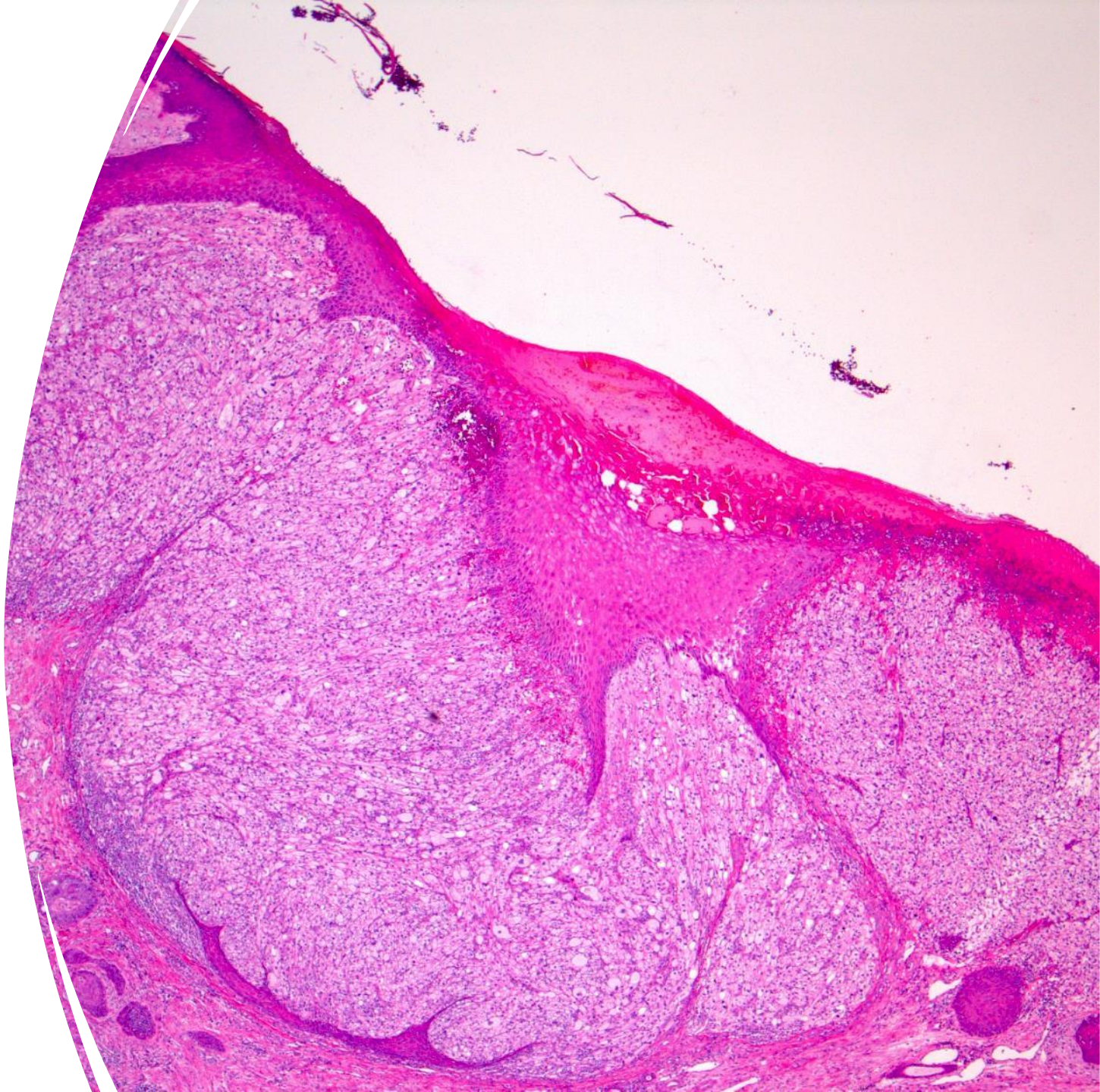
Keloidal AFX

AFX
Morphological Variants





Clear cell AFX



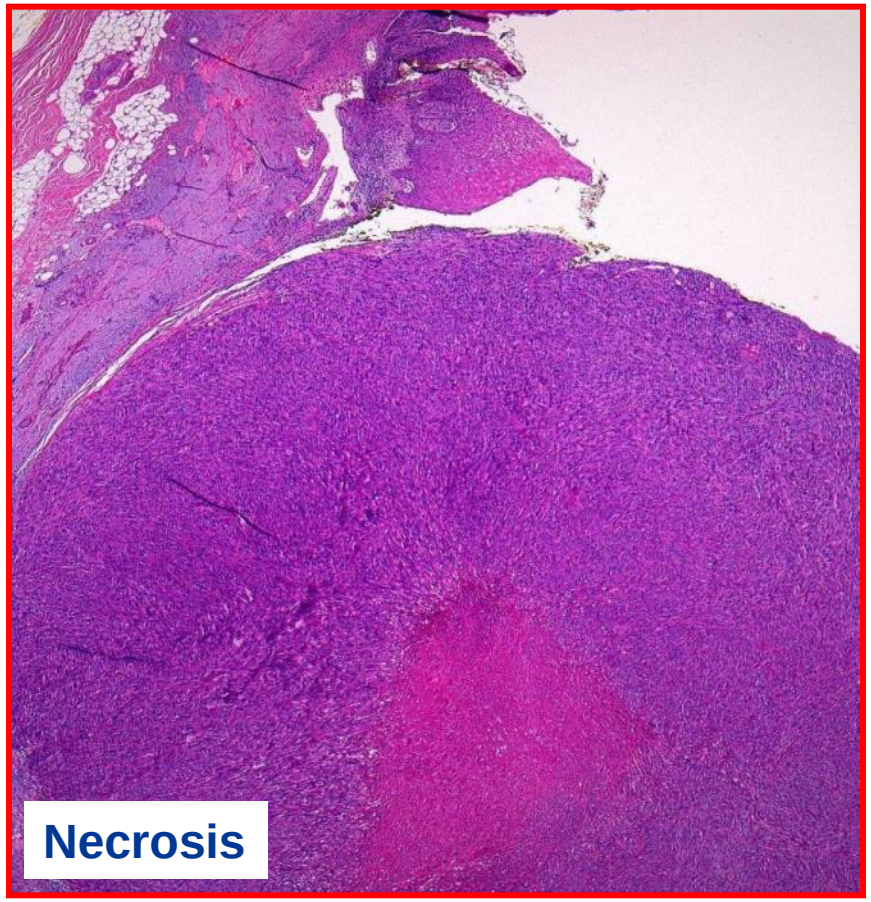
AFX
Other Morphological Variants

- Spindle cell non-pleomorphic AFX/ Monomorphic spindle cell AFX
- Granular cell AFX
- Myxoid AFX
- Pseudoangiomatous AFX
- Plaque-like
- Regressed

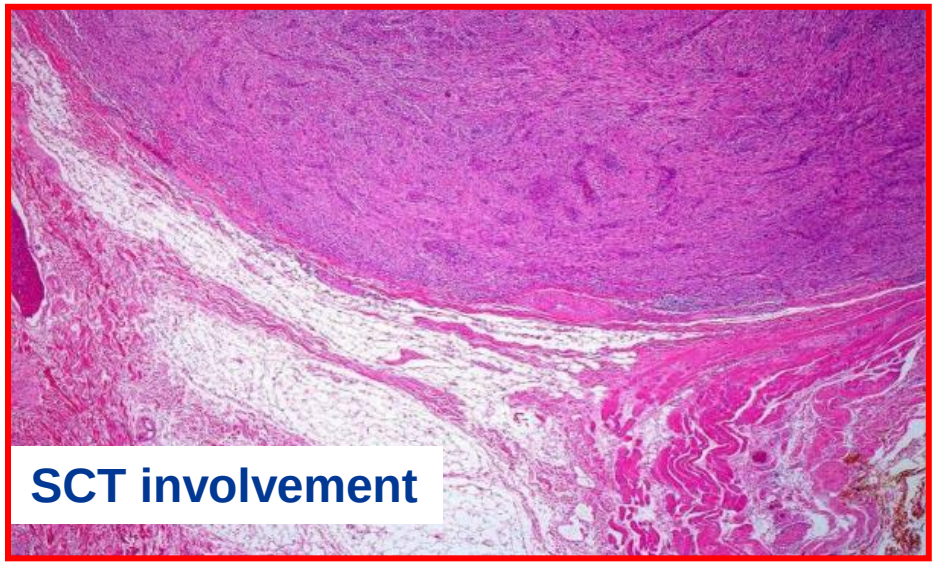
AFX

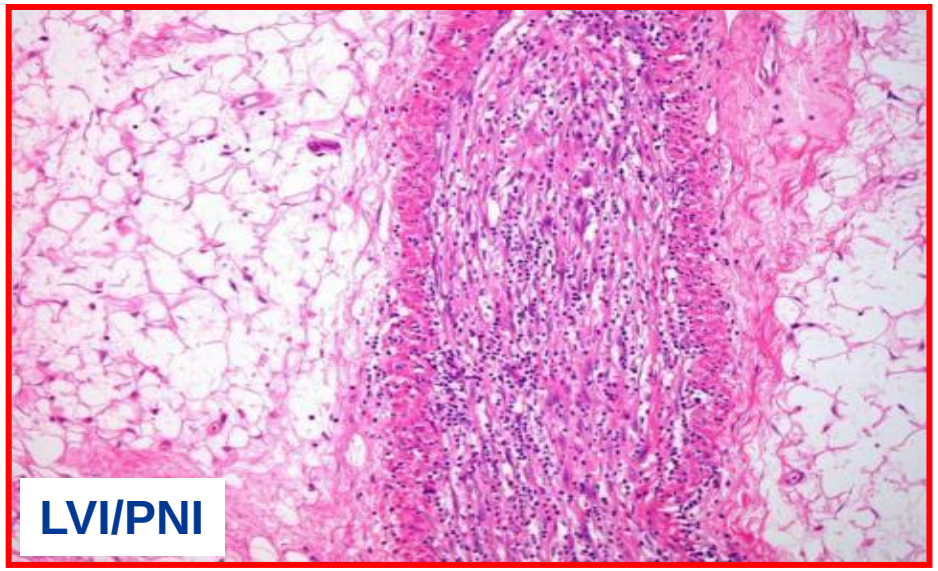
- Diagnosis of exclusion
- By definition is a superficial tumour with no / or minimal subcutaneous involvement
- No lymphovascular space or perineural invasion
- No necrosis
- Diagnosis requires complete excision

Pleomorphic Dermal Sarcoma(PDS)



-Usually >1cm in size, median 2.5cm
-Ulceration & bleeding common





AFX &PDS Immunohistochemistry

- No specific immunohistochemical markers
- Negative for: CKs, including HMW CKs

  S100

  Desmin

  CD34
- Cells usually positive for CD68, CD99, CD10, vimentin and alpha-1 antitrypsin
- SMA and CD31 may be positive

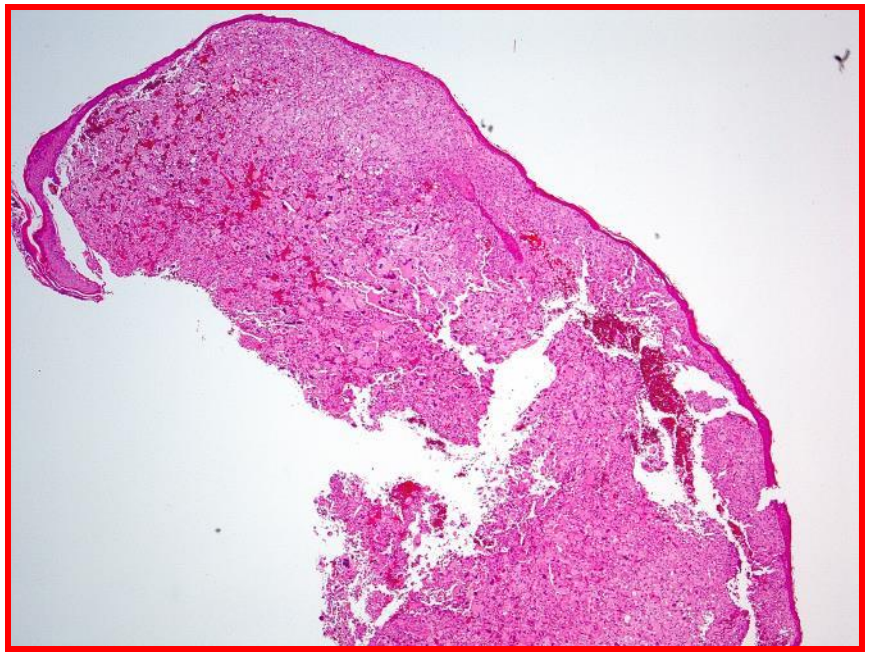
PDS vs AFX
(Clinical Behaviour)

- PDS – rarely metastasise(10%) & upto 30% of cases recur
- AFX has a recurrence rate of ≈ 5%

Miller K, et al. Am J Surg pathol.2012;36(9):1317-26

PDS vs AFX

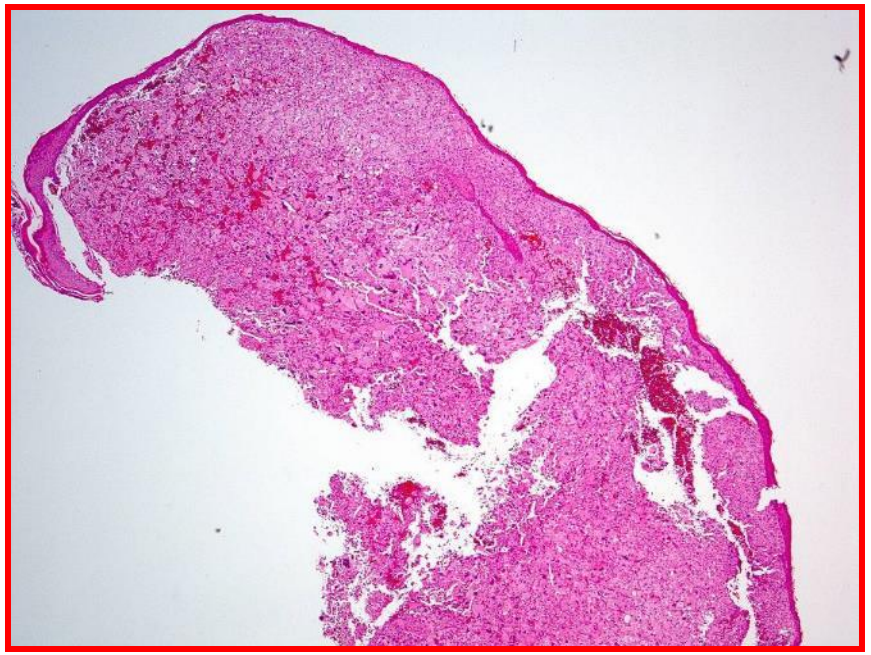
- Beware of superficial biopsies!!



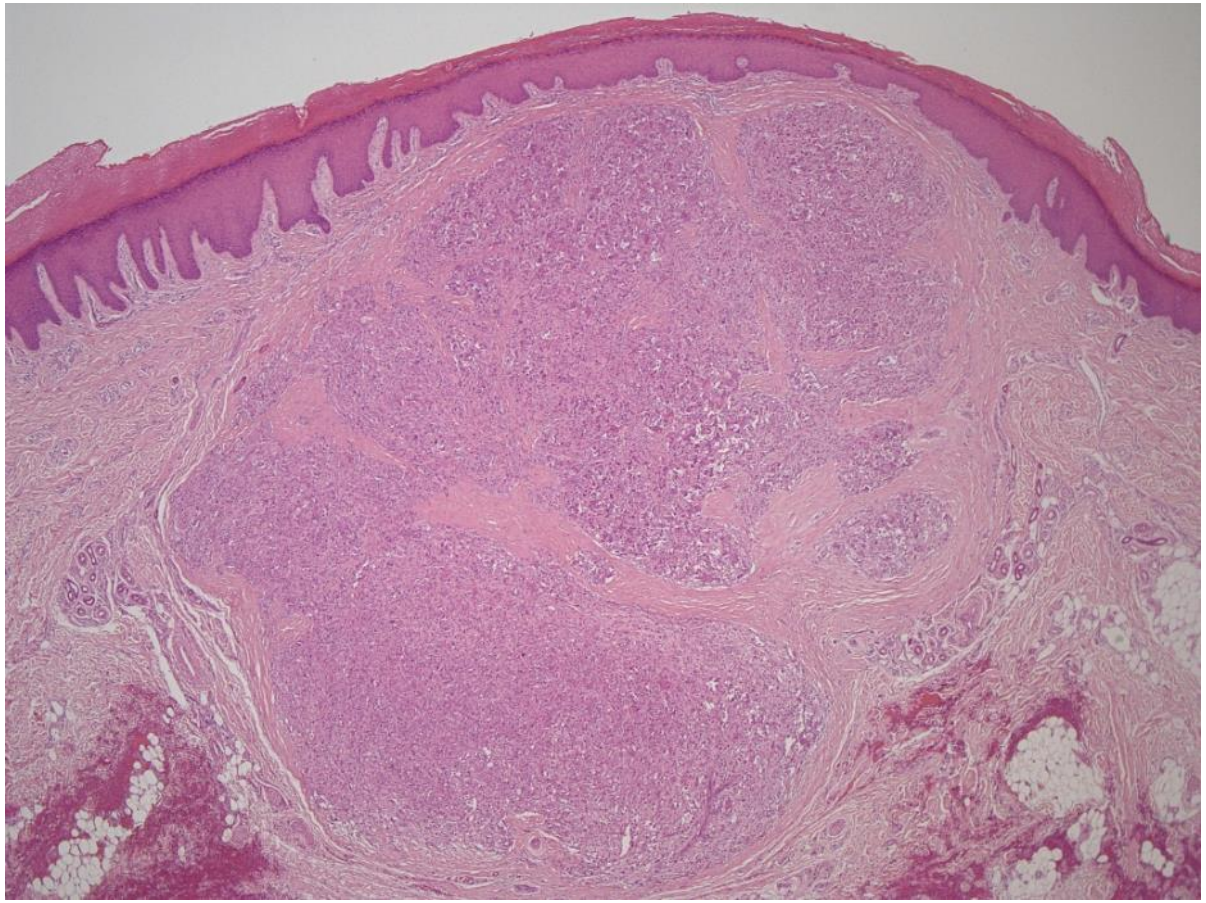
PDS vs AFX

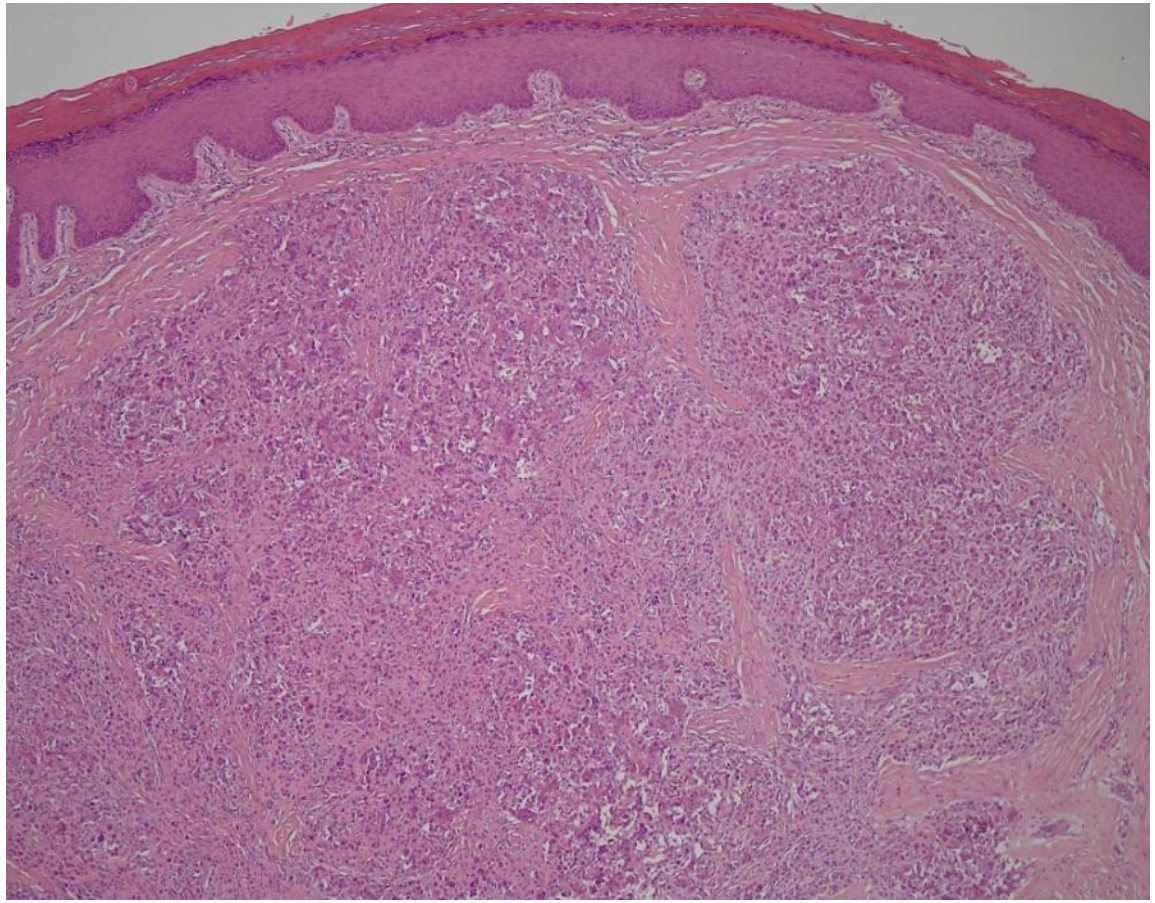
- Beware of superficial biopsies!!

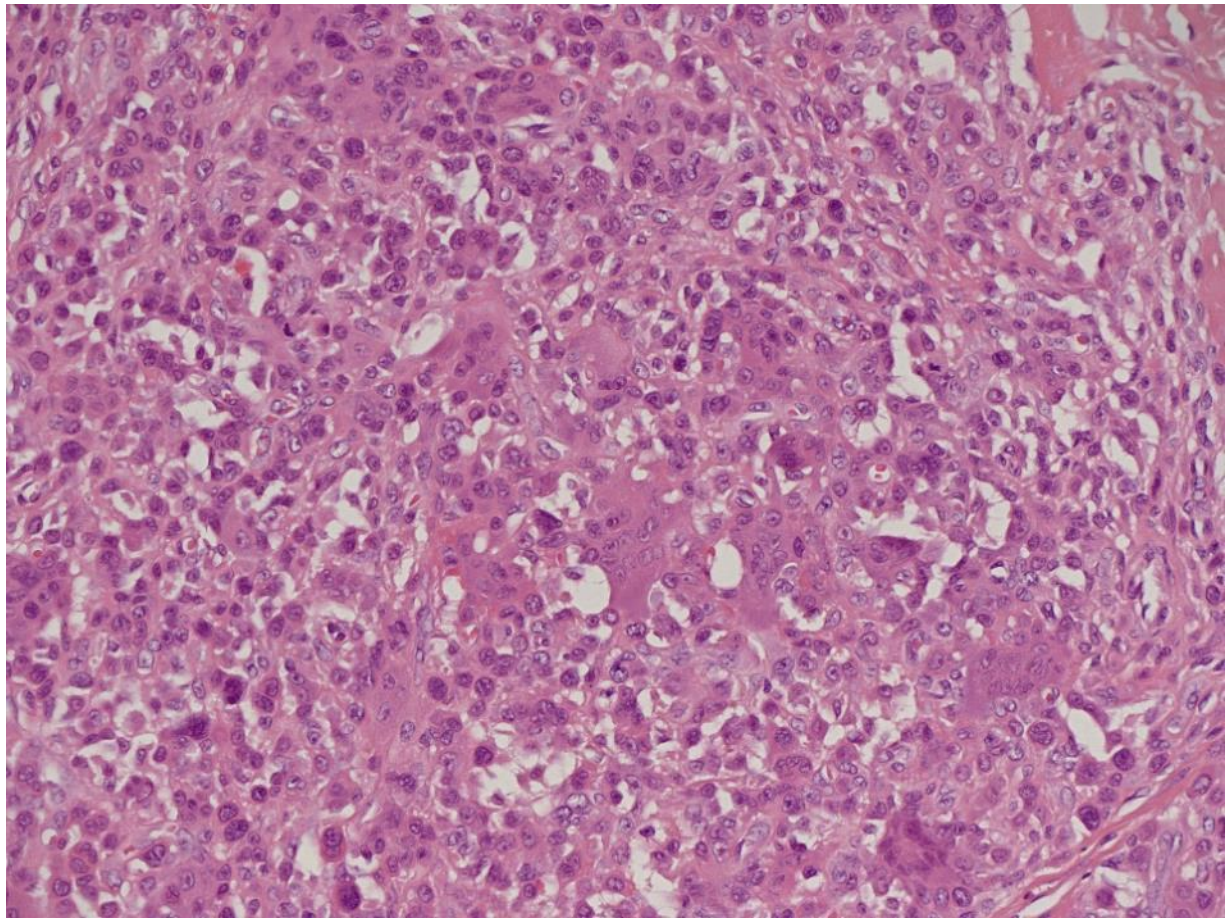
- *“Superficial pleomorphic spindle cell neoplasm, either an AFX or PDS. Nature of specimen precludes full histological interpretation, making it impossible to give a definitive diagnosis”.*

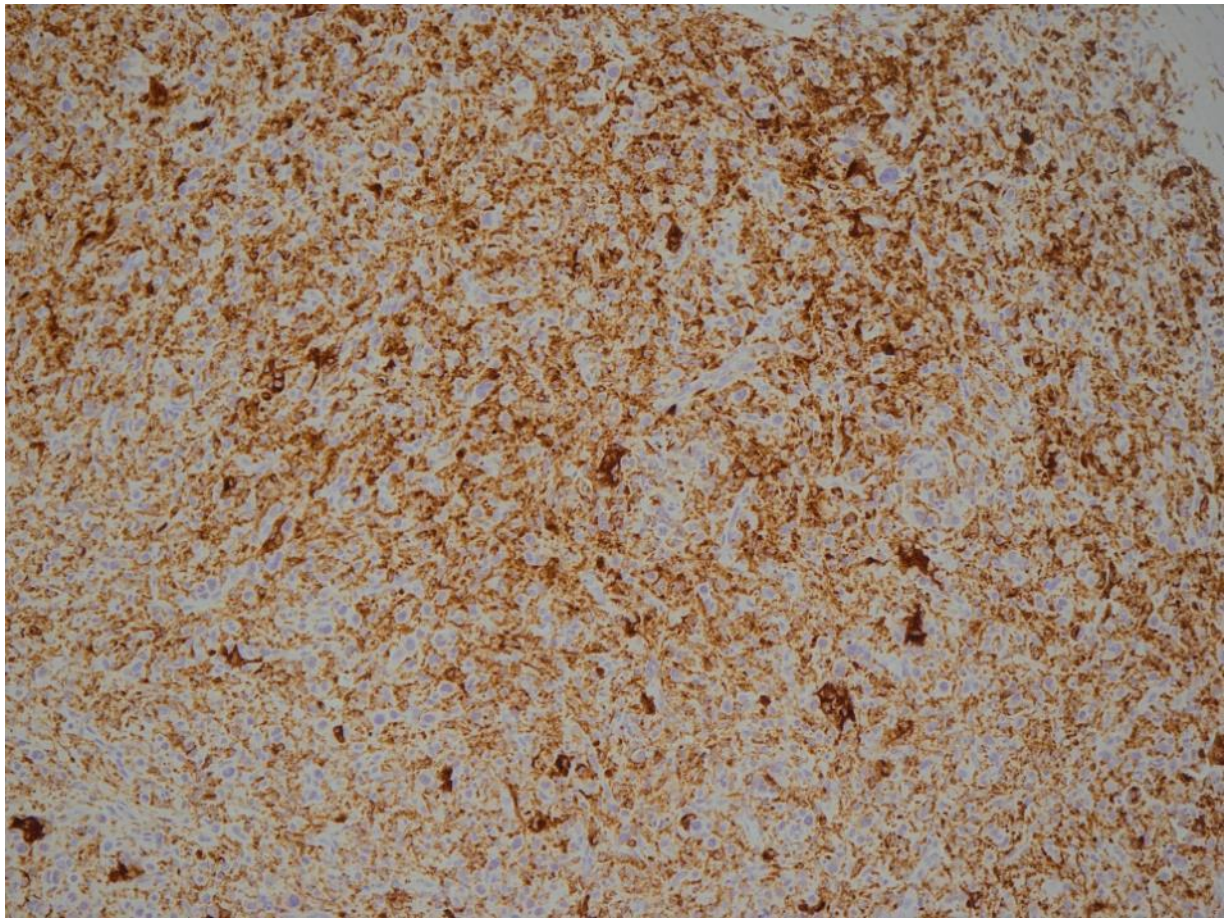


Case: 18F. Skin Lesion on wrist, excision

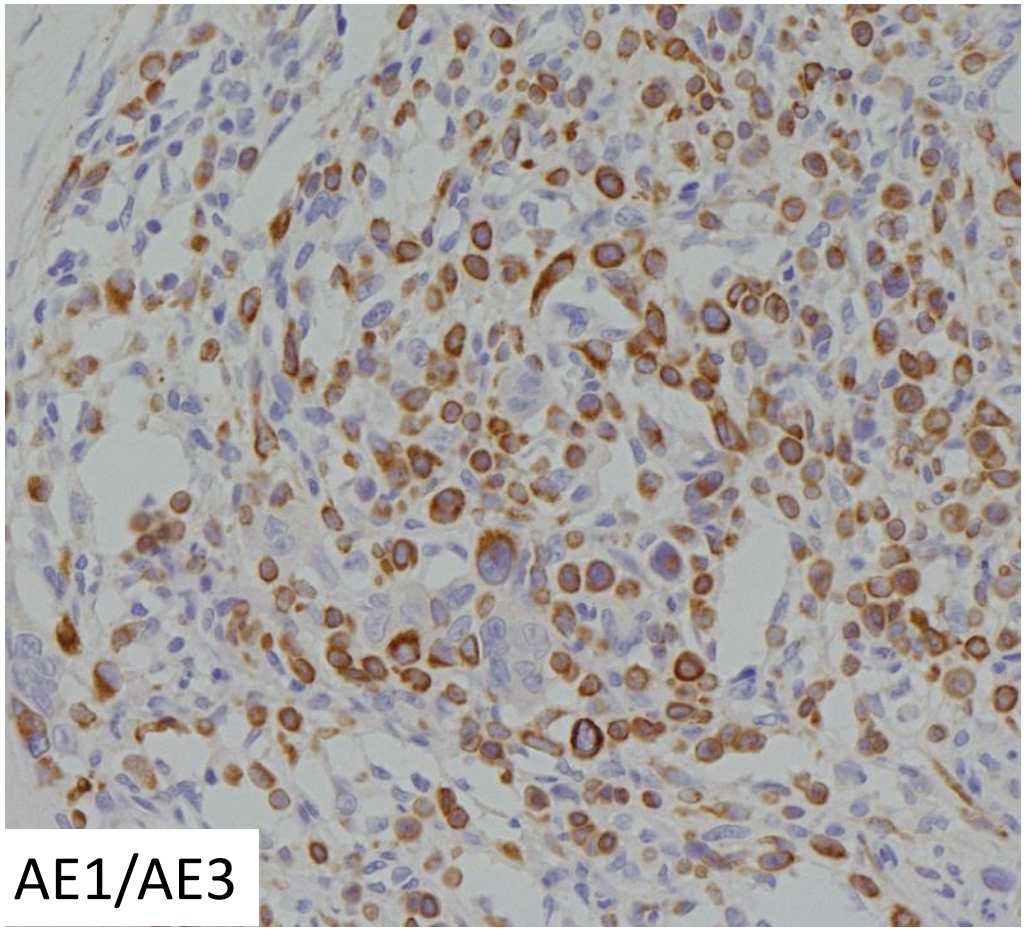




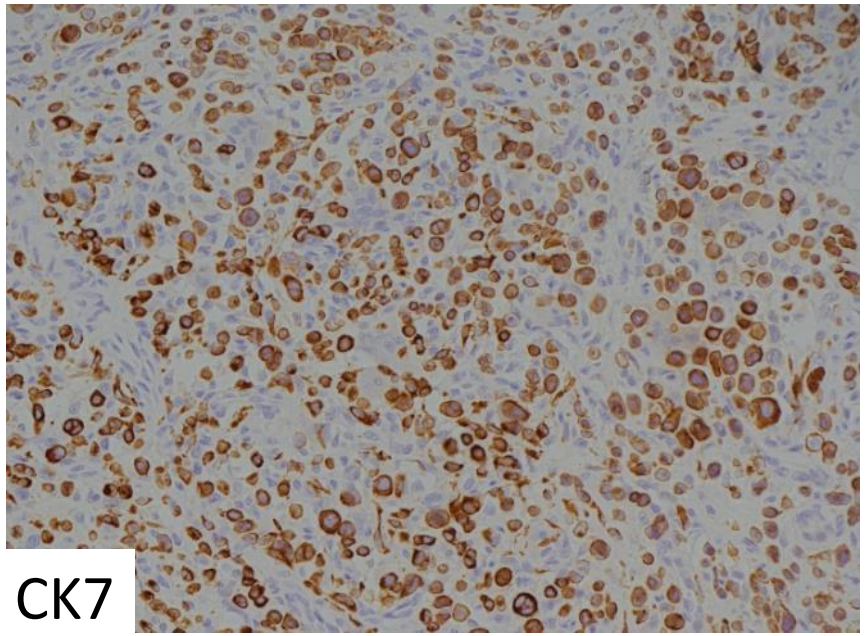




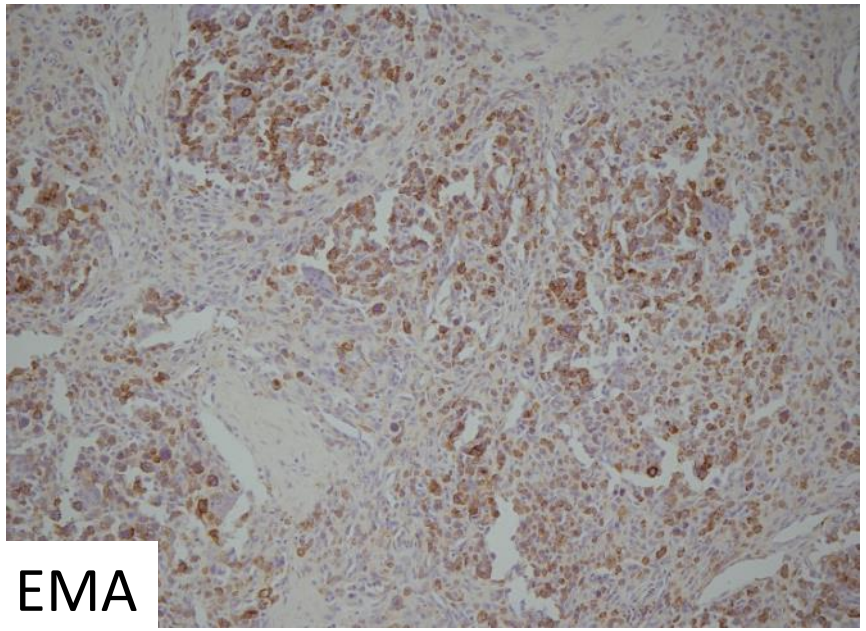
CD68



AE1/AE3

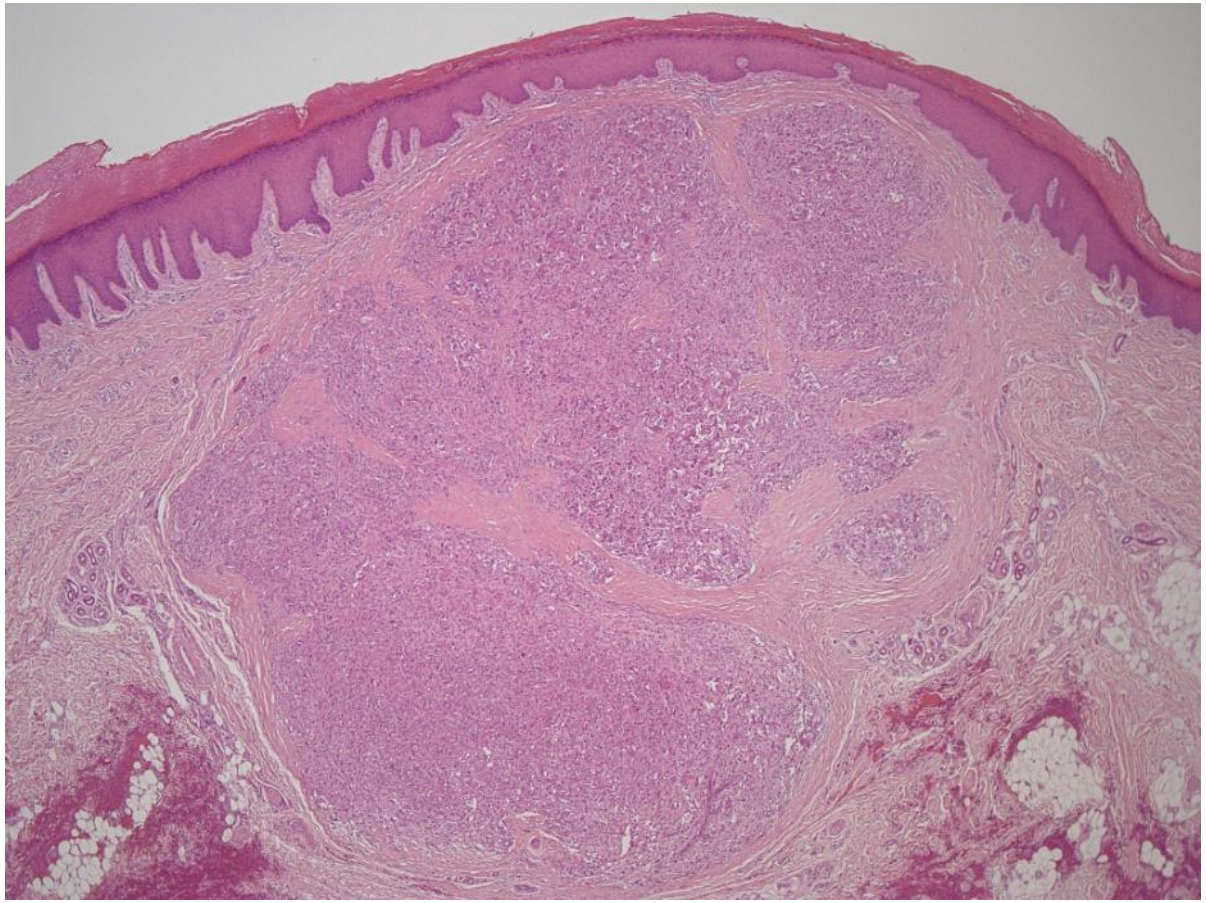


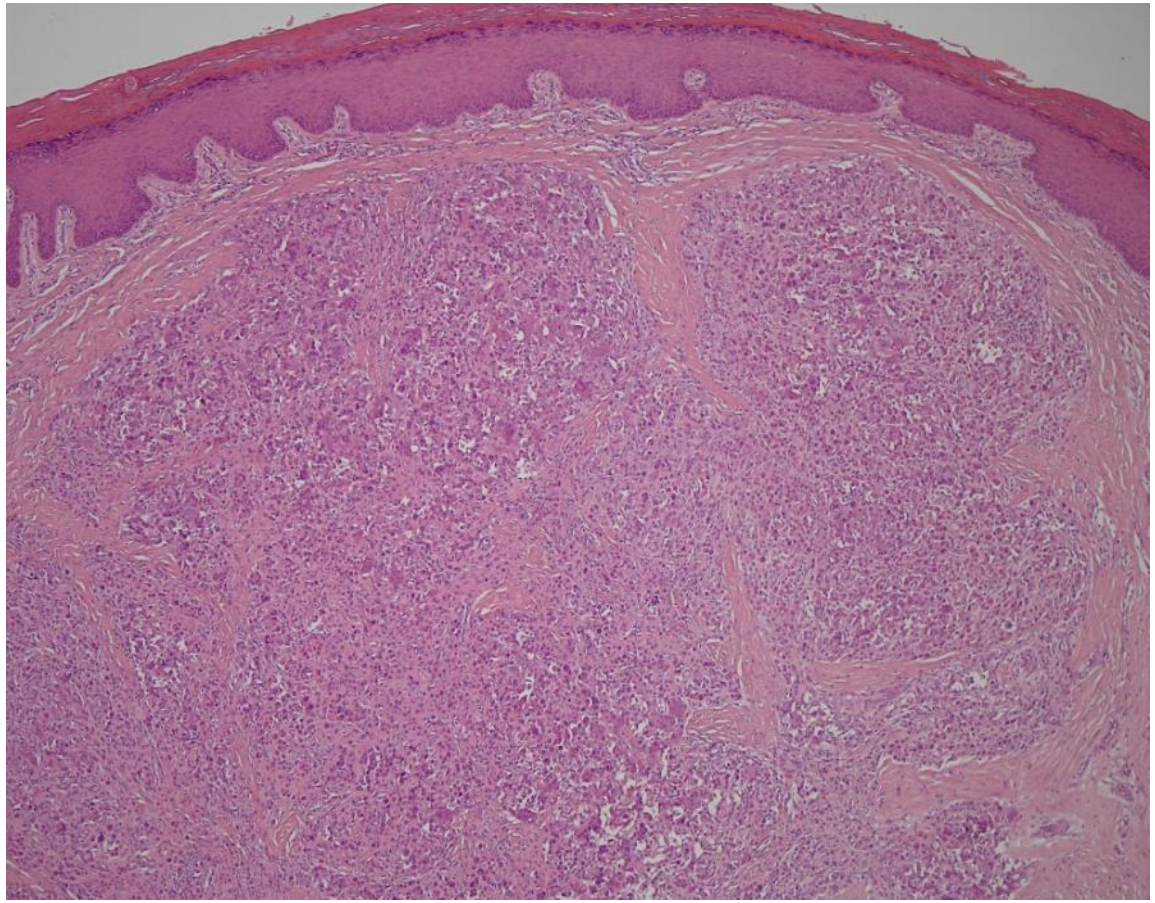
CK7



EMA

Negative for: G34W, p63, and SATB2





RNA fusion NGS sarcoma panel analysis identified an in-frame fusion transcript involving HMGA2 exon 3 and NCOR2 exon 16

Modern Pathology (2021) 34:1507–1520
https://doi.org/10.1038/s41379-021-00789-8

ARTICLE

Recurrent novel *HMGA2-NCOR2* fusions characterize a subset of keratin-positive giant cell-rich soft tissue tumors

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Received: 10 December 2020 / Revised: 20 February 2021 / Accepted: 23 February 2021 / Published online: 19 March 2021

Abstract

Giant cell tumors of soft tissue (GCT-ST) are rare low-grade neoplasms that were at one time thought to represent the soft tissue counterparts of GCT of bone (GCT-B) but are now known to lack the *H3F3* mutations characteristic of osseous GCT. We present six distinctive giant cell-rich soft tissue neoplasms that expressed keratins and carried a recurrent *HMGA2-NCOR2* gene fusion. Patients were five females and one male aged 14–60 years (median, 29). All presented with superficial (subcutaneous) masses that were removed by conservative marginal (3) or wide (2) local excision. The tumors originated in the upper extremity (2), lower extremity (2), head/neck (1), and trunk (1). Five patients with follow-up (median, 21 months; range, 14–168) remained disease-free. Grossly, all tumors were well-demarcated but not encapsulated with variable lobulation. Histologically, they were composed of bland plump epithelioid or ovoid to spindled mononuclear cells admixed with evenly distributed multinucleated osteoclast-type giant cells. Foci of stromal hemorrhage and hemosiderin were seen in

GCT with *HMGA2::NCOR2* fusion

- GCT with *HMGA2::NCOR2* fusion have recently been identified as a distinct entity
- These occur in the subcutis and dermis
- Show a striking female preponderance
- Morphologically similar to conventional ST GCTs
- Multinodular proliferation of round to ovoid mononuclear cells admixed with innumerable osteoclast-type giant cells
- Often show focal haemorrhage
- Lack shell of bone and are -ve for SATB2
- Clinically they may recur locally, but no incidence of distant metastasis have been described to date

- Soft tissue giant cell tumours are morphologically indistinguishable from giant cell tumour of bone
- They are however genetically distinct [GCT of bone harbour mutations at the Gly34 codon of *H3F3A* gene and express *H3G34W* (histone 3 G34W) immunohistochemically]
- GCT of bone also commonly express p63, RANKL and SATB2 which are not usually expressed by ST GCT
- ST GCTs are heterogeneous, with more than a single entity represented

IHC in D/D of Pleomorphic Cutaneous Spindle Cell Tumours

Tumour	AE1/3	MNF116	34BE12	CK5	p40	SMA	Desmin	S100	SOX10	CD31	ERG	CD10
SCC (10)	7(7/10)	4(4/10)	7	3(3/10)	2(2/4)	8(p/w-in 6)	1(1/10 f/w)	0(0/10)	0(0/5)	0(0/6)	2(2/5)	6(6/8)
AFX/ PDS (52)	0(0/52)	1(1/43 v.f/w)	0(0/37)	0(0/28)	0(0/15)	31(31/42 variable)	1(1/42-f/w)	0(0/52)	0(0/34)	12(12/42 – f/p/w)	6(6/33 f/w)	22 (22/22)
LMS (7)	3(3/7)	0(0/4)	0(0/2)	ND	ND	7	7	0(0/7)	0(0/3)	0(0/2)	0(0/4)	1(1/3-p/w)
MM (6)	0(0/6)	0(0/3)	0(0/4)	0(0/1)	ND	4(4/6-p/w)	1(1/3)	6(2 –f)	3(3/3)	0(0/3)	0(0/2)	2(2/2 p/w)
All (75)	**10**	**5 (5/60)**	**7**	**3**	**2(2/19)**	**50 (50/61)**	**10 (10/62)**	**6 (6/75)**	**3 (3/45)**	**12 (12/53) (23%)**	**8 (8/44) (18%)**	**31 (31/35)**

Acknowledgement: Rachael Winstanley & Sereen Wahballa

IHC in D/D of Pleomorphic Cutaneous Spindle Cell Tumours

Tumour	AE1/3 & MNF116	34BE12	CK5	SMA	Desmin	S100	SOX10	CD31	ERG
SpCC	+	+	+	+/-	-	-	-	-	-
AFX PDS	-	-	-	-/+	-	-	-	-/+	-
AS	-/+	-	-	-/+	-	-	-	+	+
LMS	-/+	-	-	+	+	-	-	-	-
MM	-/+	-	-	+/-	-	+	+	-	-

Summary

Superficial spindle cell lesions can usually be accurately classified if a systematic approach is used:

- Clinical data
- Macroscopic appearance
- Morphology
- IHC -panel
- Molecular studies