An Update on Superficial Soft Tissue Tumours
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Superficial Soft Tissue Tumours - Challenges

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

- Rarity and morphological diversity make soft tissue tumour pathology one of the most challenging fields in diagnostic surgical pathology

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

- Superficial CD34-positive fibroblastic tumour

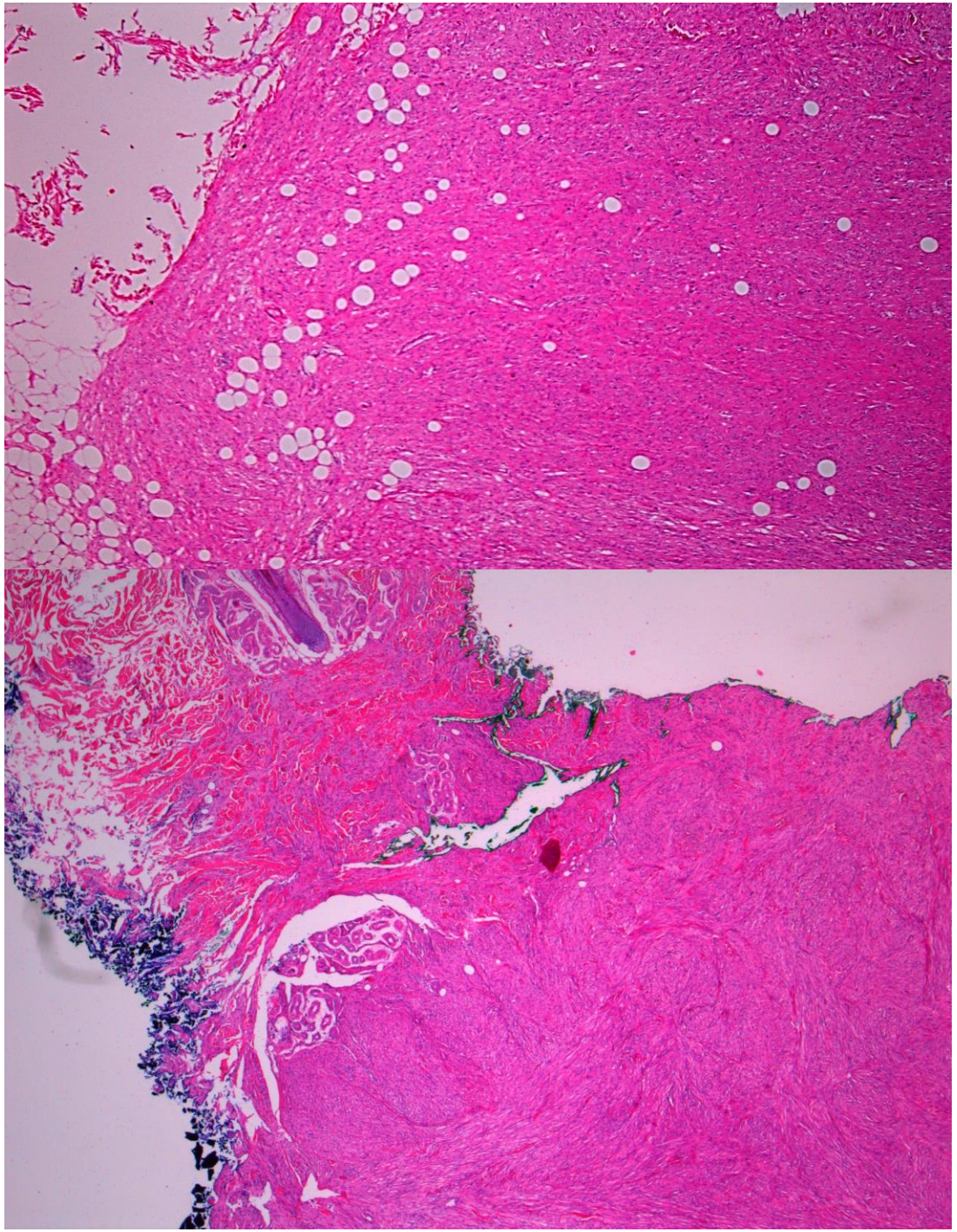
- Leiomyosarcoma
- Myofibrosarcoma
- Angiosarcoma
- AFX & Pleomorphic dermal sarcoma

Superficial CD34-positive Fibroblastic Tumour

- Low-grade tumour of the skin and subcutis
- Commonly affects young adults & middle-aged pts; M>F
- Predilection for lower extremities

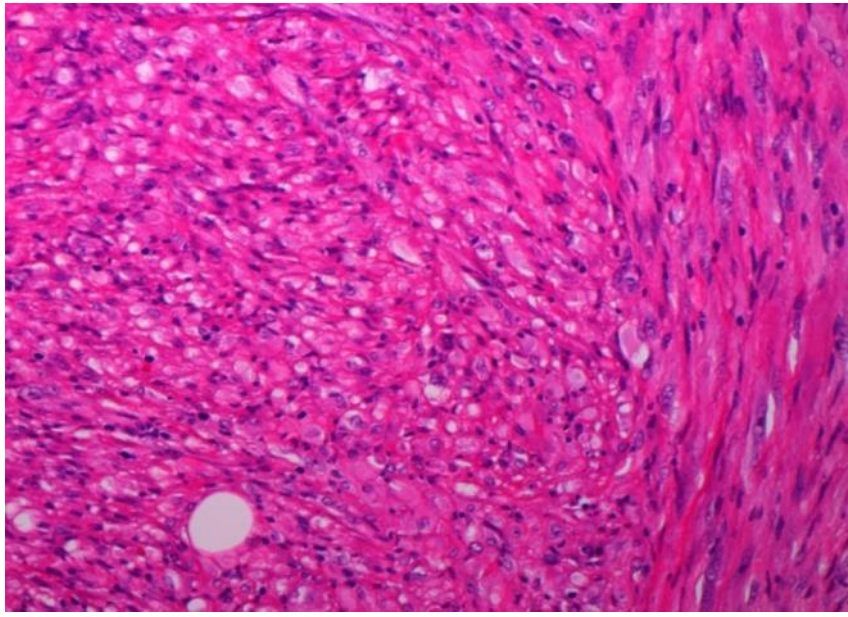
Carter JM et al Mod Pathol 2014
Lao IW et al, Histopath 2017
Puls F et al, Am J Surg Pathol 2019

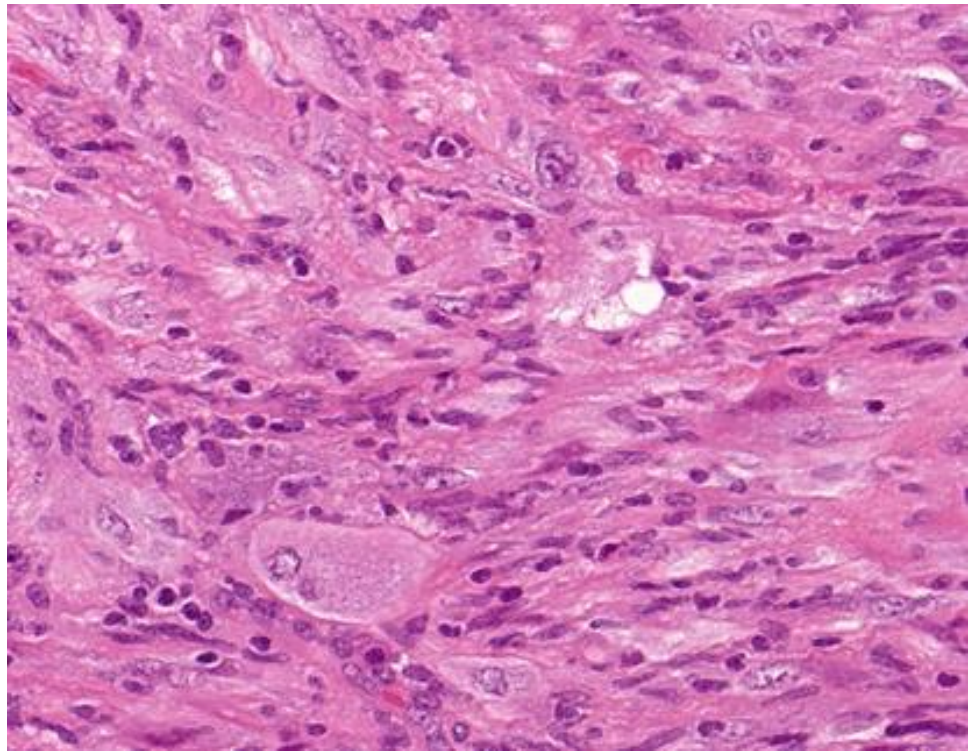
- Typically well circumscribed



Superficial CD34-positive Fibroblastic Tumour

- Low-grade tumour of the skin and subcutis
- Commonly affect middle-aged pts; M>F
- Predilection for lower extremities
- Typically well circumscribed
- Composed of spindled fibroblastic cells with ‘glassy’ cytoplasm admixed with scattered inflammatory cells and foamy histiocytes
- Presence of striking nuclear pleomorphism that occurs in the absence of significant mitotic activity or necrosis is a key feature
- Characterised by diffuse positivity for CD34 and focal positivity for keratins (mostly AE1/AE3) in ~70%
- Outcomes have so far been very favourable
- Overlap with PRDM10-rearranged soft tissue tumours





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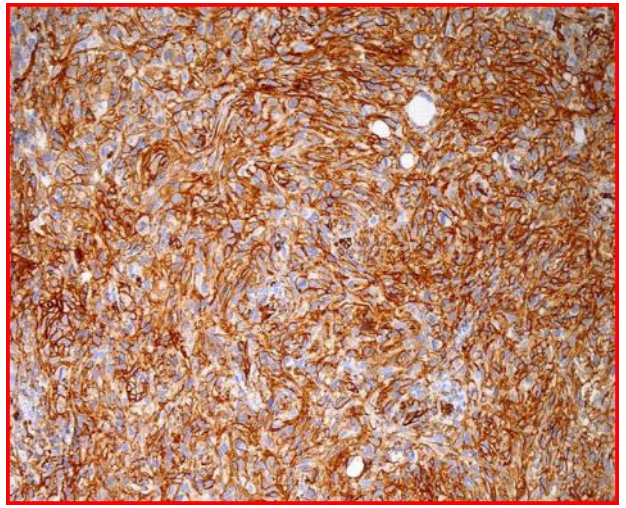

CD34

TABLE 2. Morphologic Features of *PRDM10*-rearranged Tumors

Case	Demarcation	Myxoid Areas	Multinucleated Giant Cells	Pseudovascular Spaces	Vacuolization	Mitoses/ 50 hpf*	Original Diagnosis
1	Well demarcated	Present	Absent	Absent	Absent	7	UPS, low grade
2	Focal infiltrative	Absent	Present	Absent	Absent	7	UPS, low grade
3	Focal infiltrative	Present	Absent	Present	Single cells	1	UPS, low grade
4	Well demarcated	Present	Absent	Present	Prominent	0	PLS
5	Focal infiltrative	Present	Absent	Present	Single cells	3	PHAT
6	Well demarcated	Present	Absent	Present	Prominent	4	PLS
7	Well demarcated	Absent	Present	Absent	Single cells	7	SCD34FT
8	Focal infiltrative	Present	Present	Absent	Single cells	2	SCD34FT
9	Well demarcated	Entirely myxoid	Absent	Absent	Absent	3	SCD34FT

*Mitoses were counted in 50 ×40 objective fields (field area of 0.238 mm^2).
PHAT indicates pleomorphic hyalinizing angiectatic tumor; PLS, pleomorphic liposarcoma.

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Histopathology

Histopathology 2021, **79**, 810–825. DOI: 10.1111/his.14429

Superficial CD34-positive fibroblastic tumor and *PRDM10*-rearranged soft tissue tumor are overlapping entities: a comprehensive study of 20 cases

Raul Perret,[1] Michael Michal,[2,3] Richard A Carr,[4] Valérie Velasco,[1] Marian Švajdler,[2,3] Marie Karanian,[5,6] Alexandra Meurgey,[5] Sandrine Paindavoine,[5] Isabelle Soubeyran,[1] Jean-Michel Coindre,[1,7] Romain Boidot,[8] Céline Charon-Barra,[9] Damien Geneste,[10] Noelle Weingertner,[11] Daniel Pissaloux,[5,6] Franck Tirode,[6] Jessica Baud[7,12] & François Le Loarer[1,7,12]

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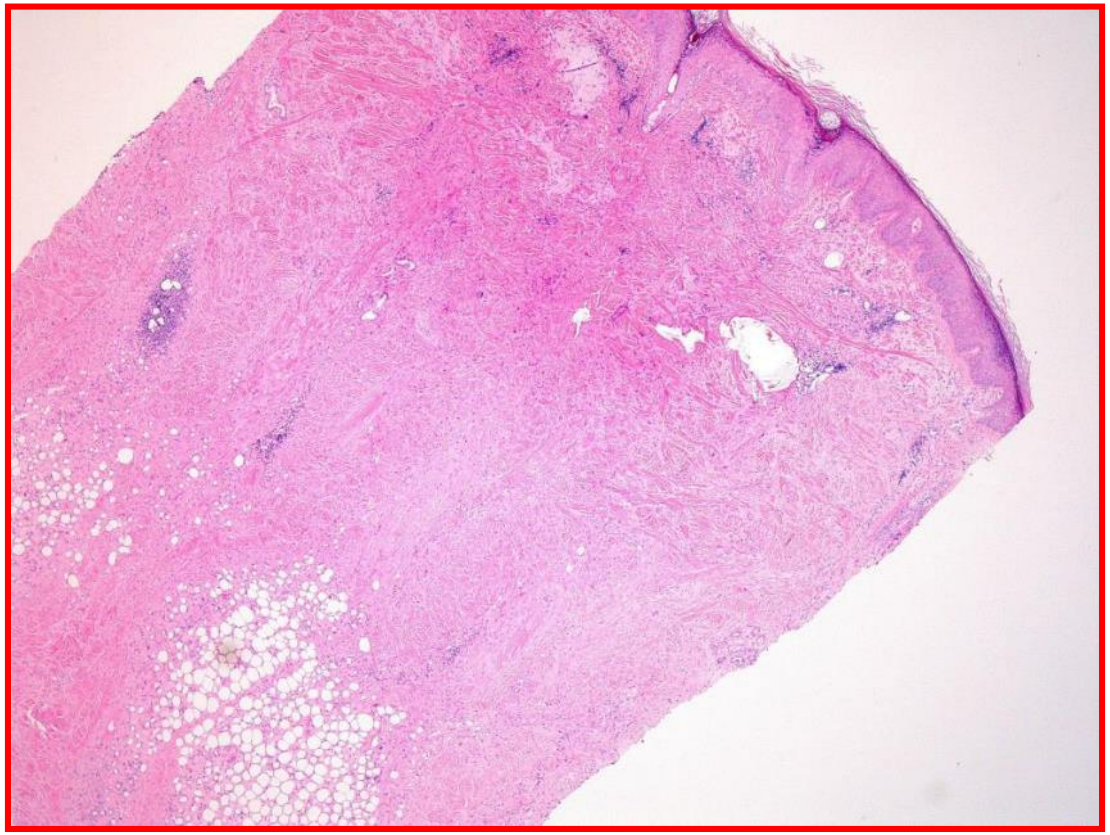
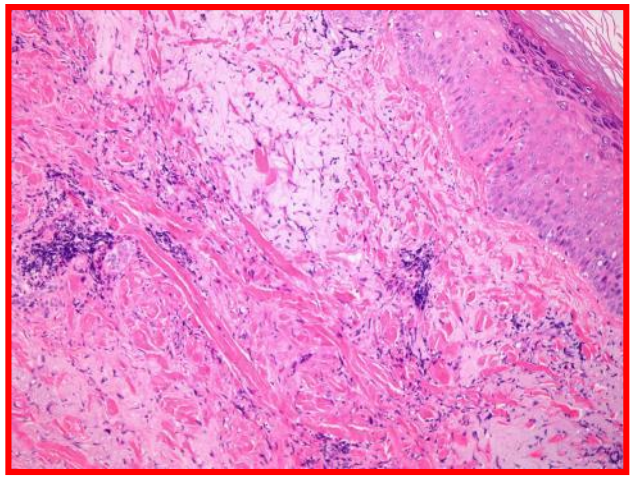
Spindle Cell Squamous Carcinoma

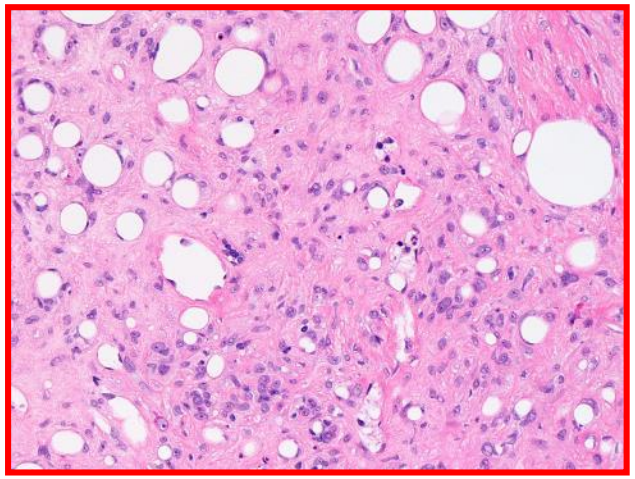
- Almost always occur in sun damaged skin
- Head, neck, chest & upper extremities
- Elderly, predominantly Caucasian pts
- M>F
- Occur in non-sun damaged areas post radiotherapy and is more aggressive in that context

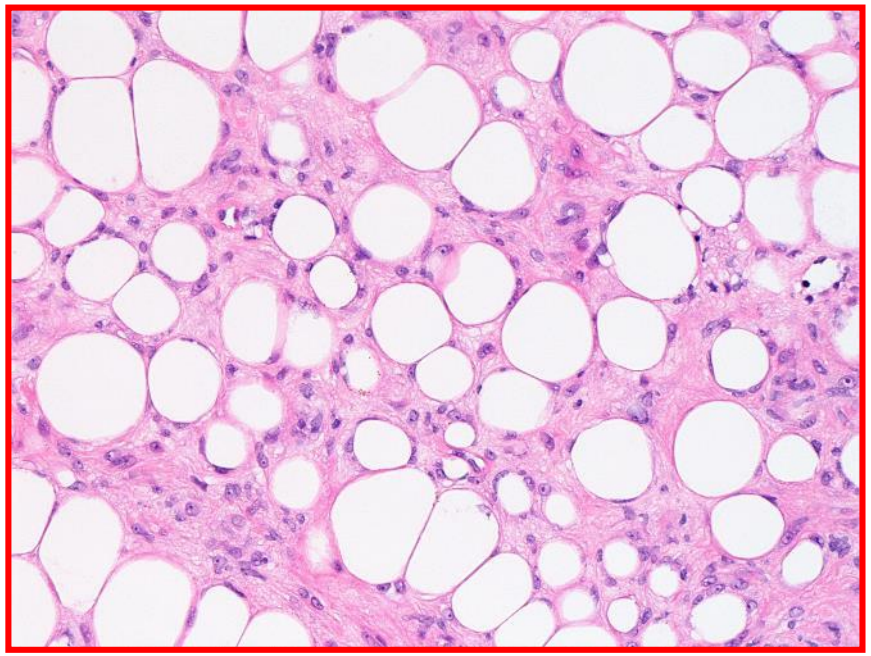
Spindle Cell Carcinoma

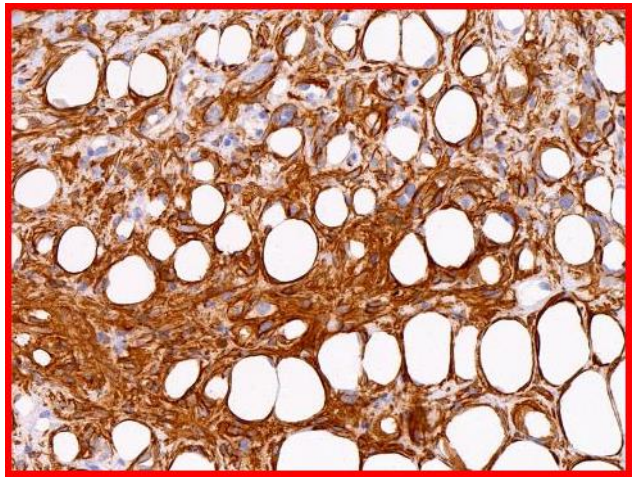
- Pleomorphic, mitotically active spindle cells -morphologically indistinguishable from AFX/PDS
- Foci of overt epithelial differentiation may be present (Cellular cohesion, intercellular bridges, keratinisation)
- Rarely, may exhibit foci of osteosarcomatous, chondrosarcomatous or rhabdomyosarcomatous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





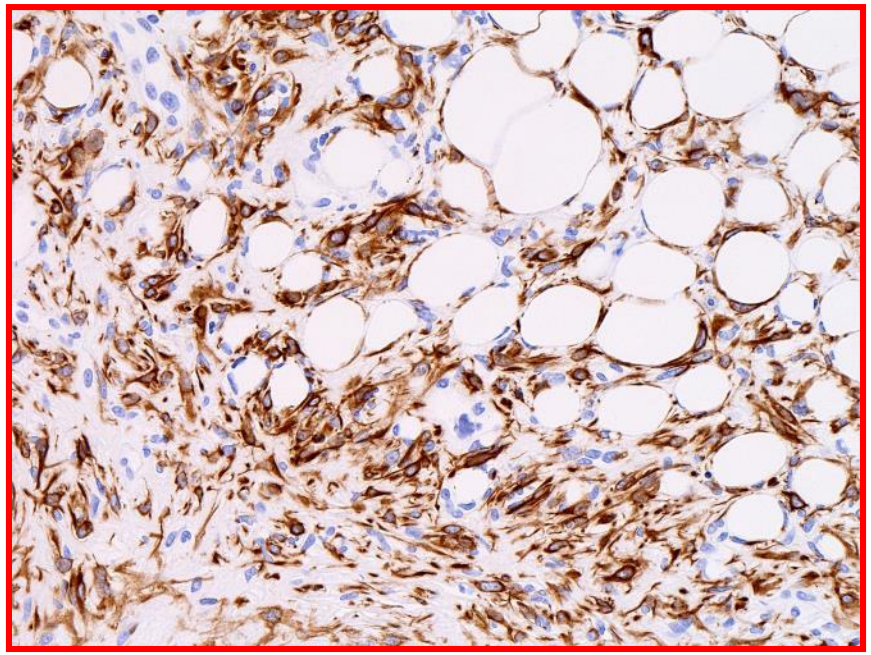




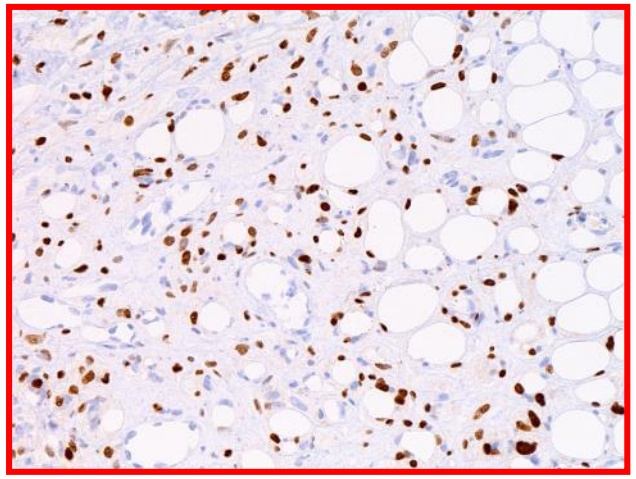


SMA

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



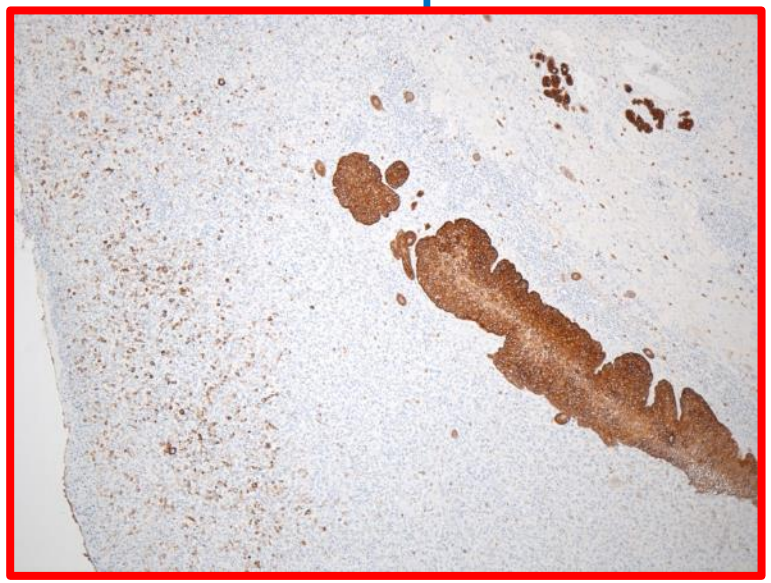
34βE12



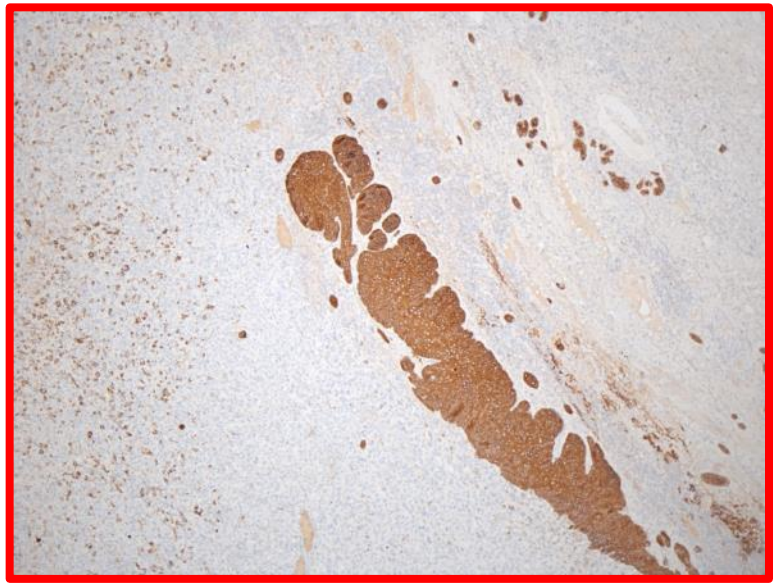
p63

Also +ve for p40, AE1/3, CK14

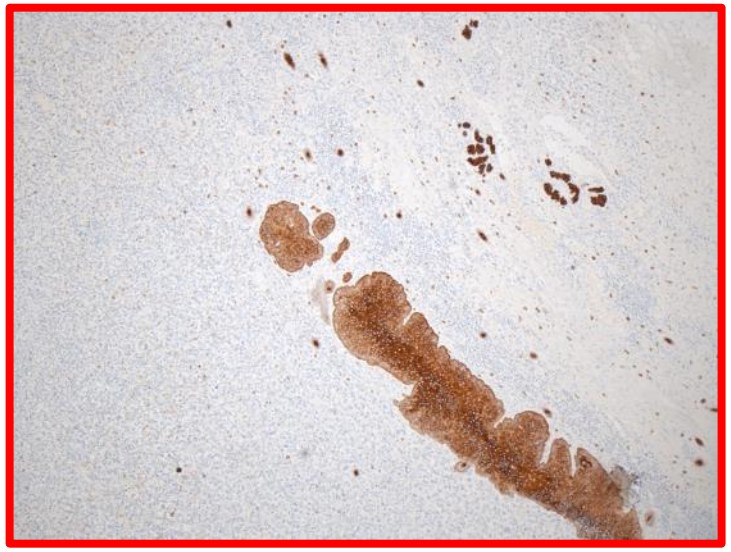
Spindle cell squamous cell carcinoma



MNF116



34BE12

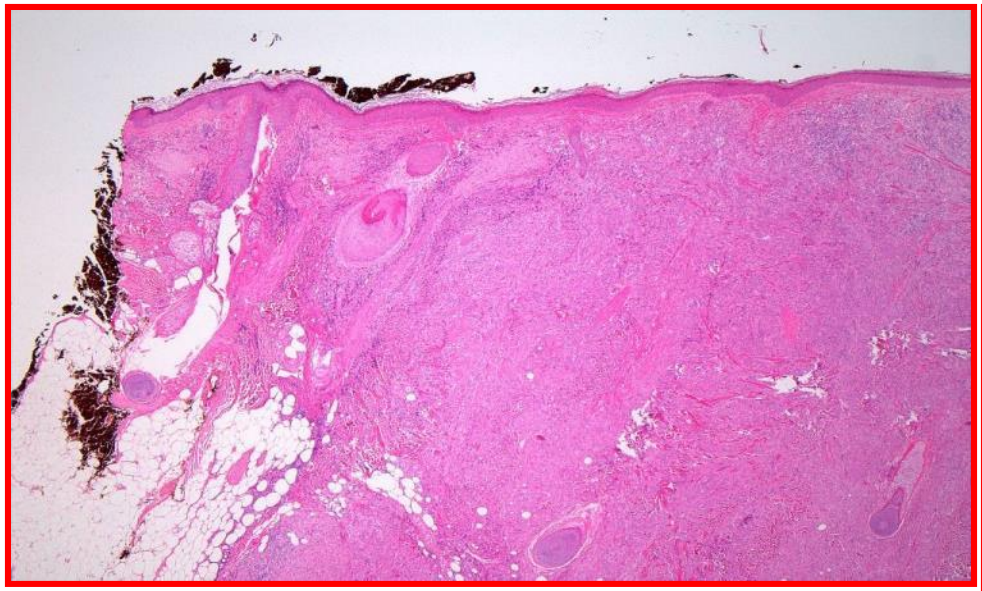


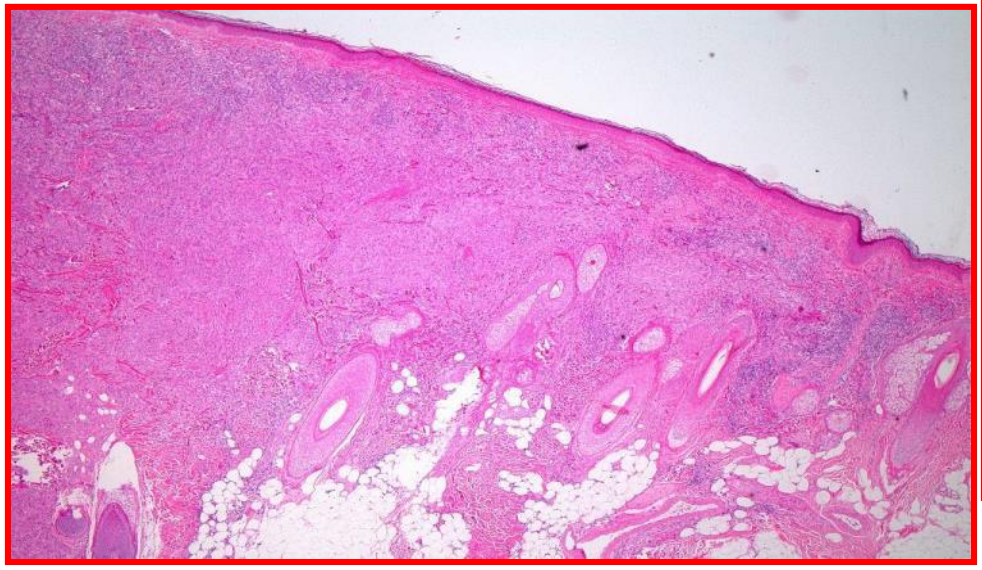
AE1/AE3

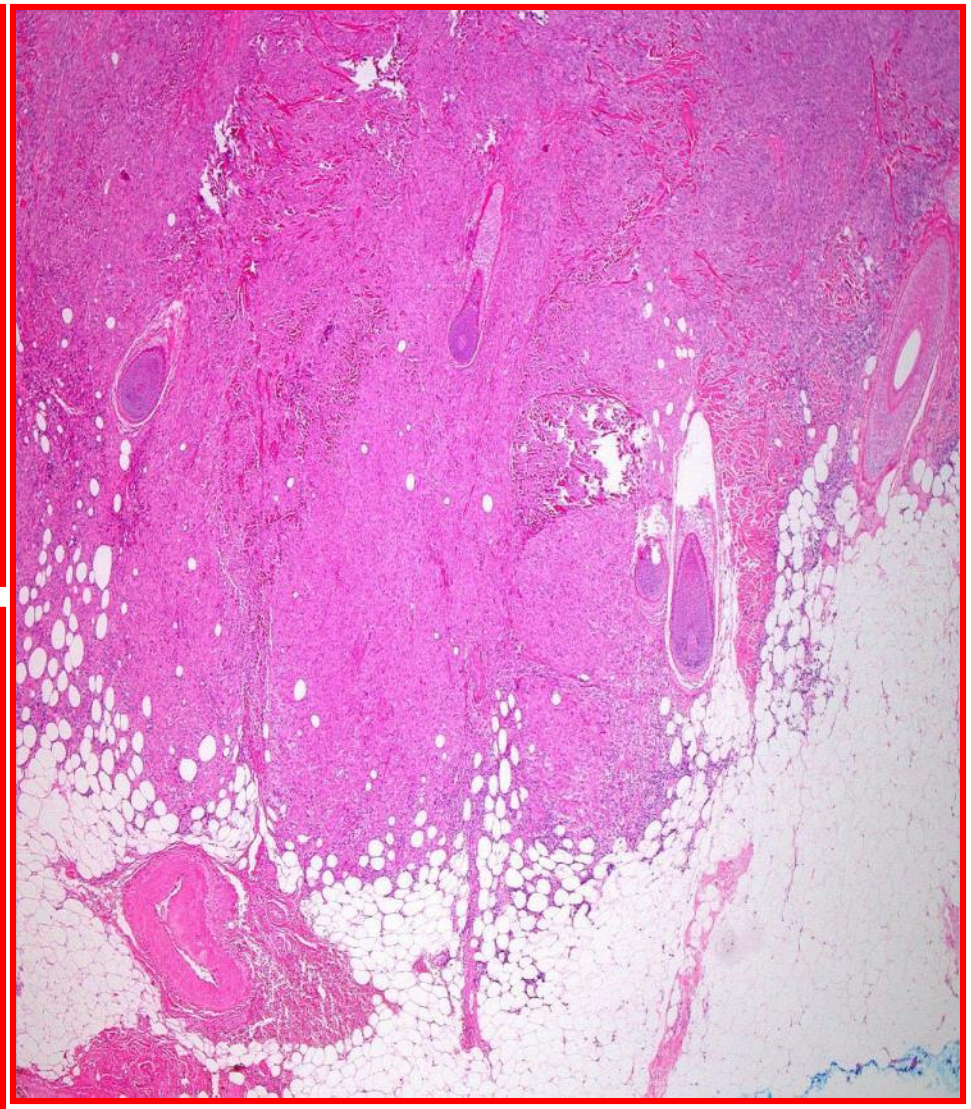
Cutaneous Spindle Cell Tumours with Cellular Pleomorphism

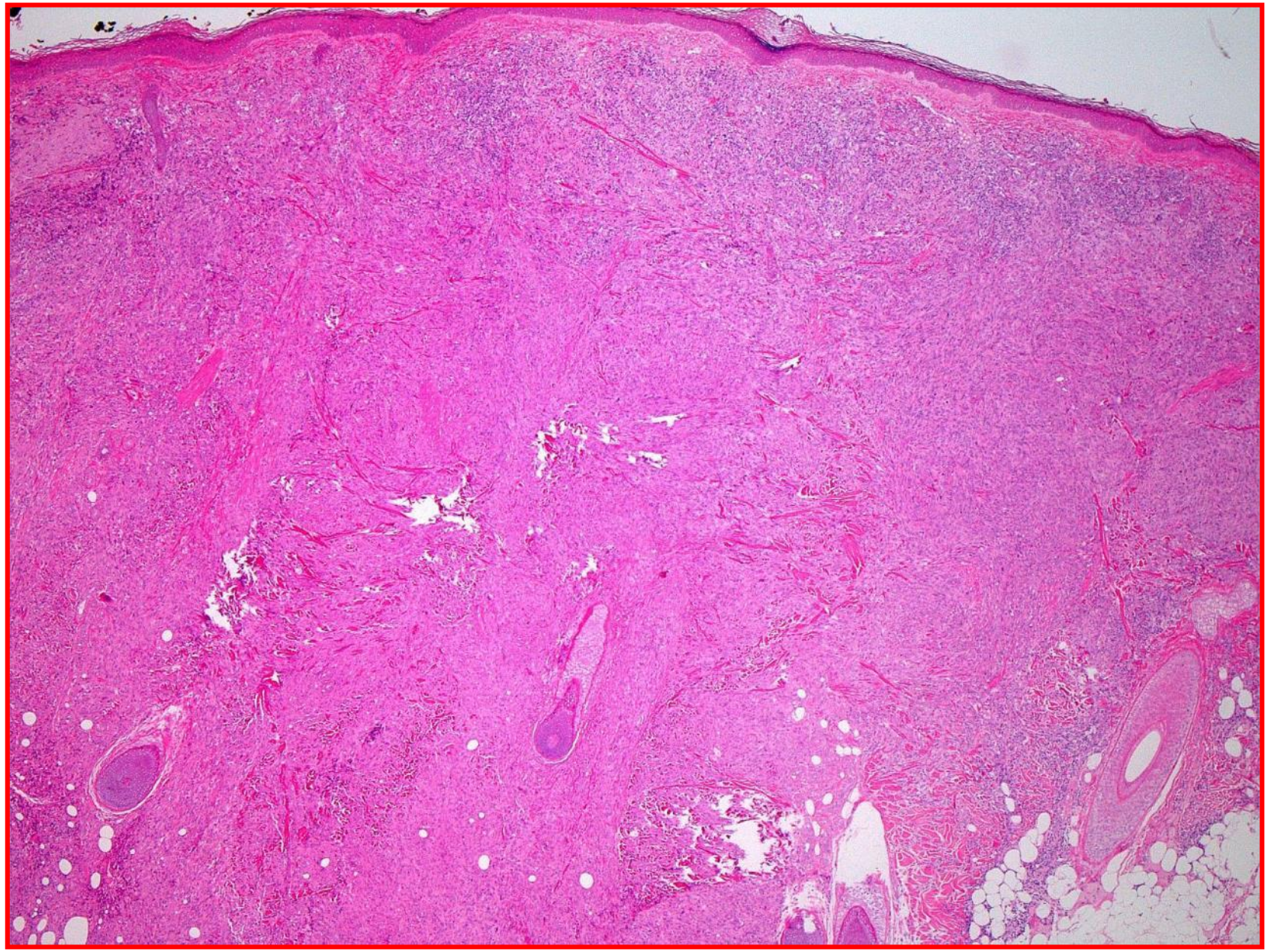
- Melanoma (desmoplastic and spindle cell MM)
- Angiosarcoma
- Leiomyosarcoma
- Atypical Fibroxanthoma
- Pleomorphic Dermal Sarcoma
- Atypical Fibrous Histiocytoma
- Superficial CD34-positive Fibroblastic Tumour

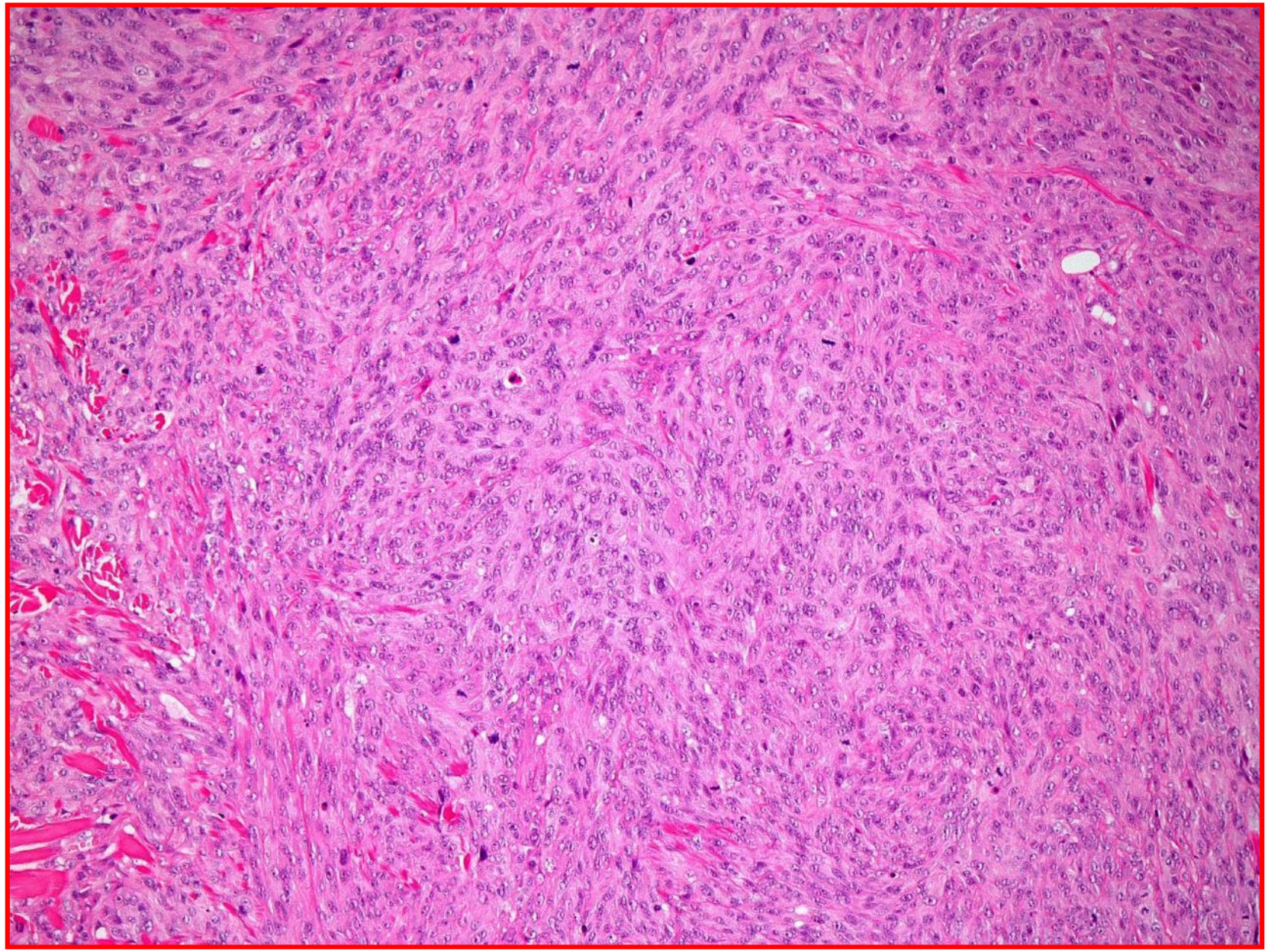
Case: 82M, Forehead lesion

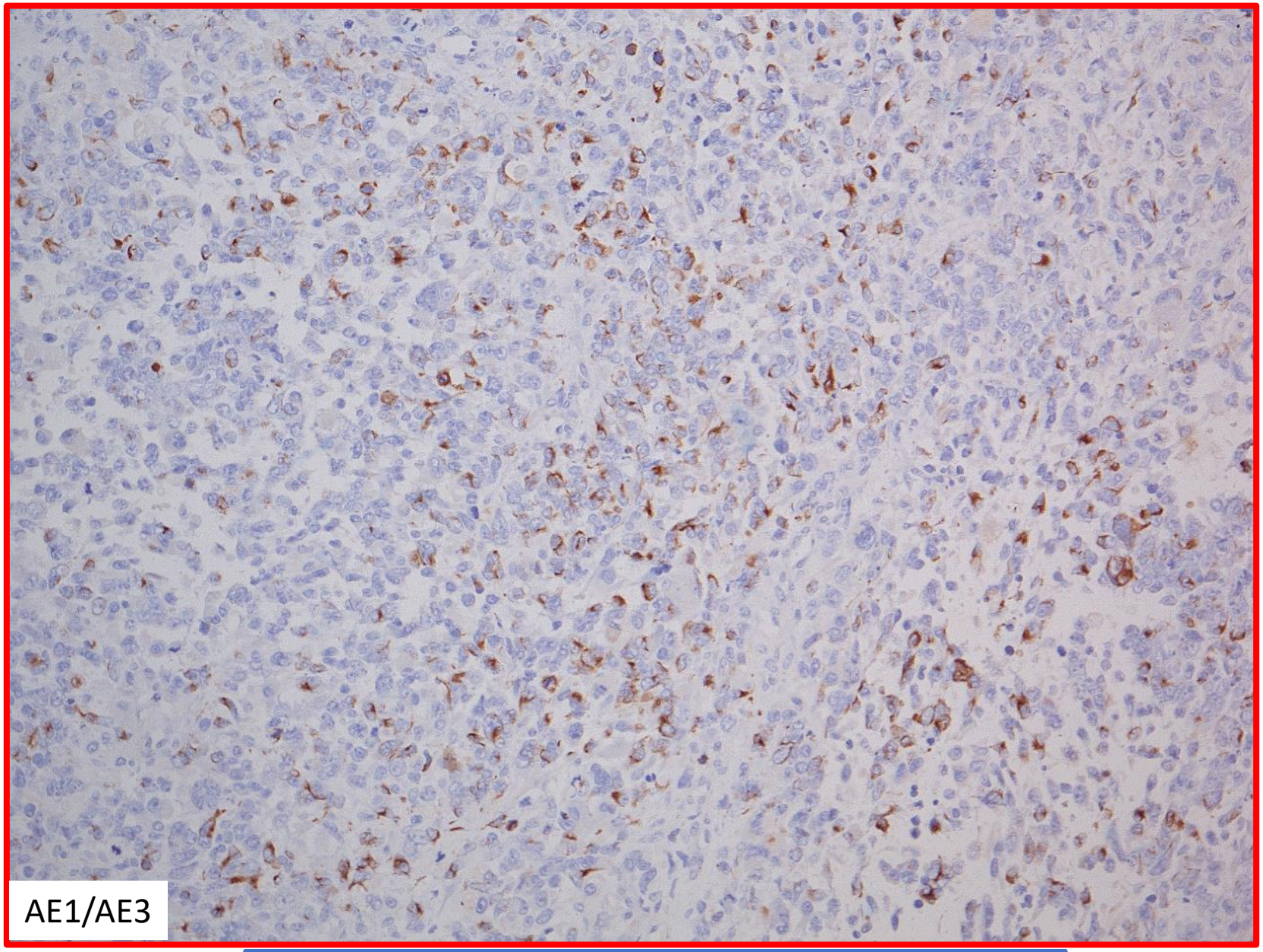




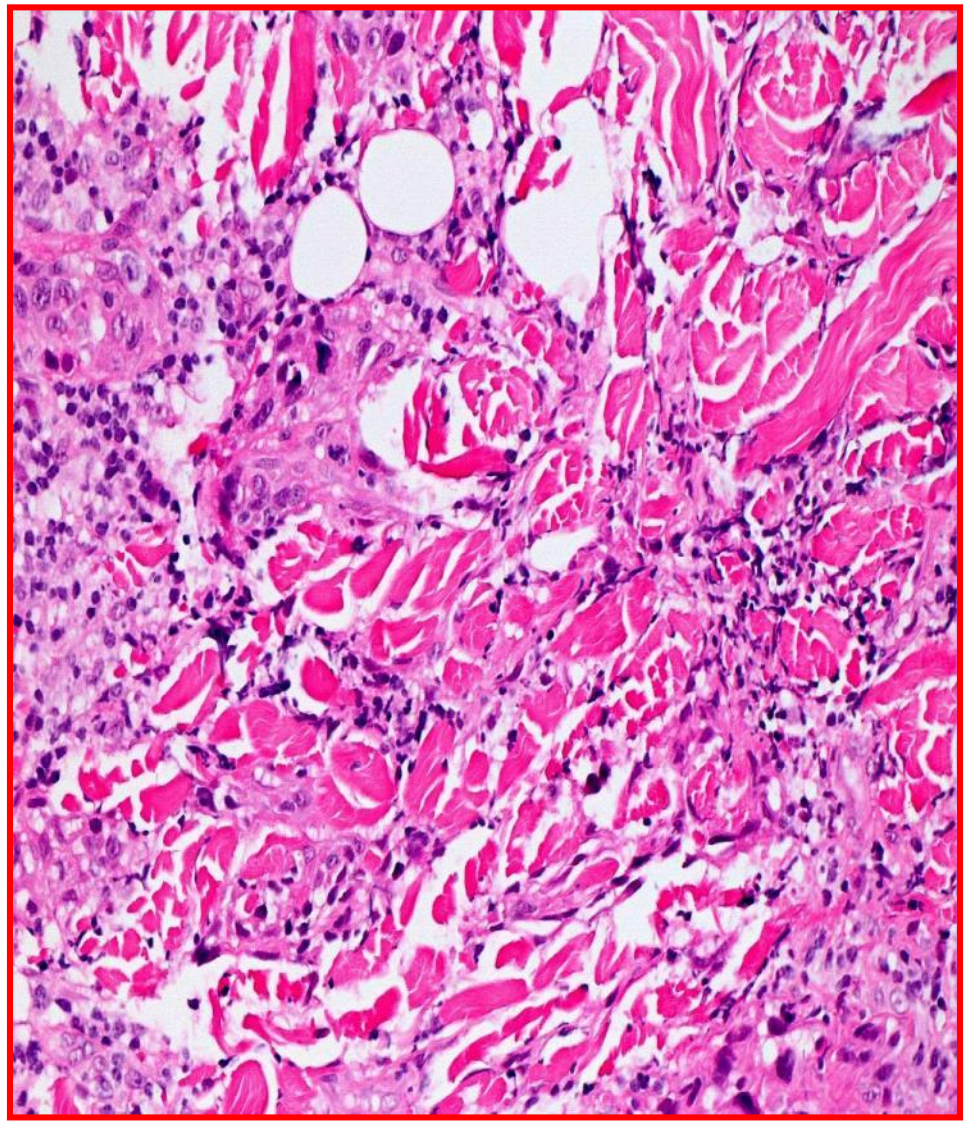


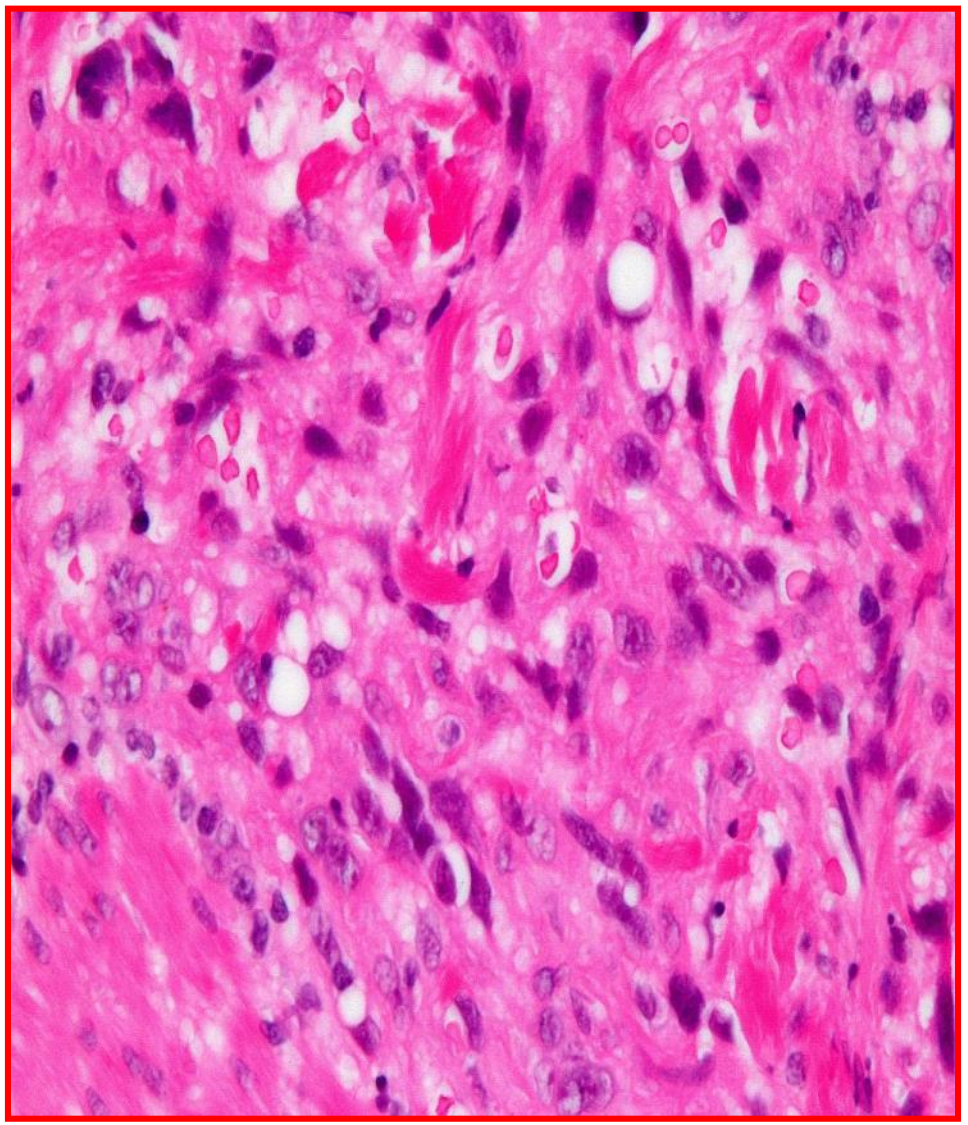




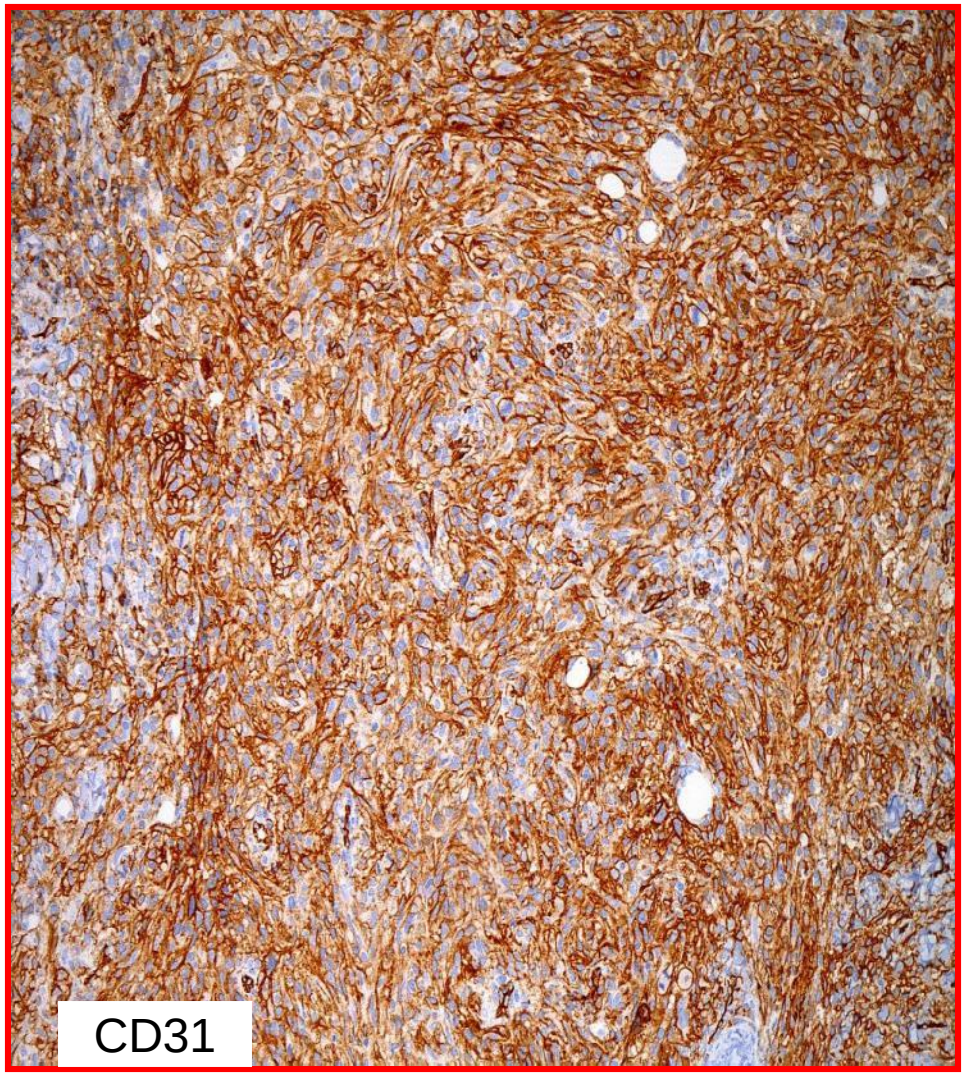


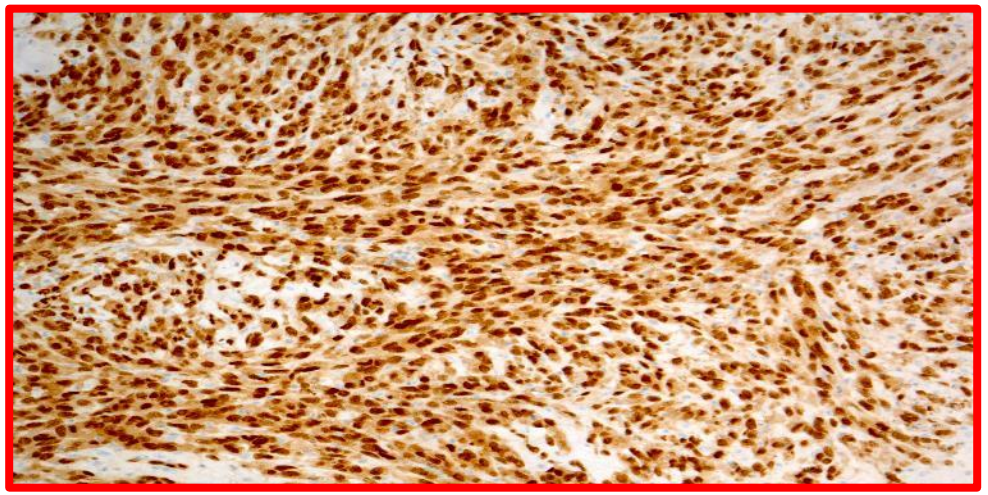
Negative for: MNF116, 34BE12, desmin, S100, SOX10





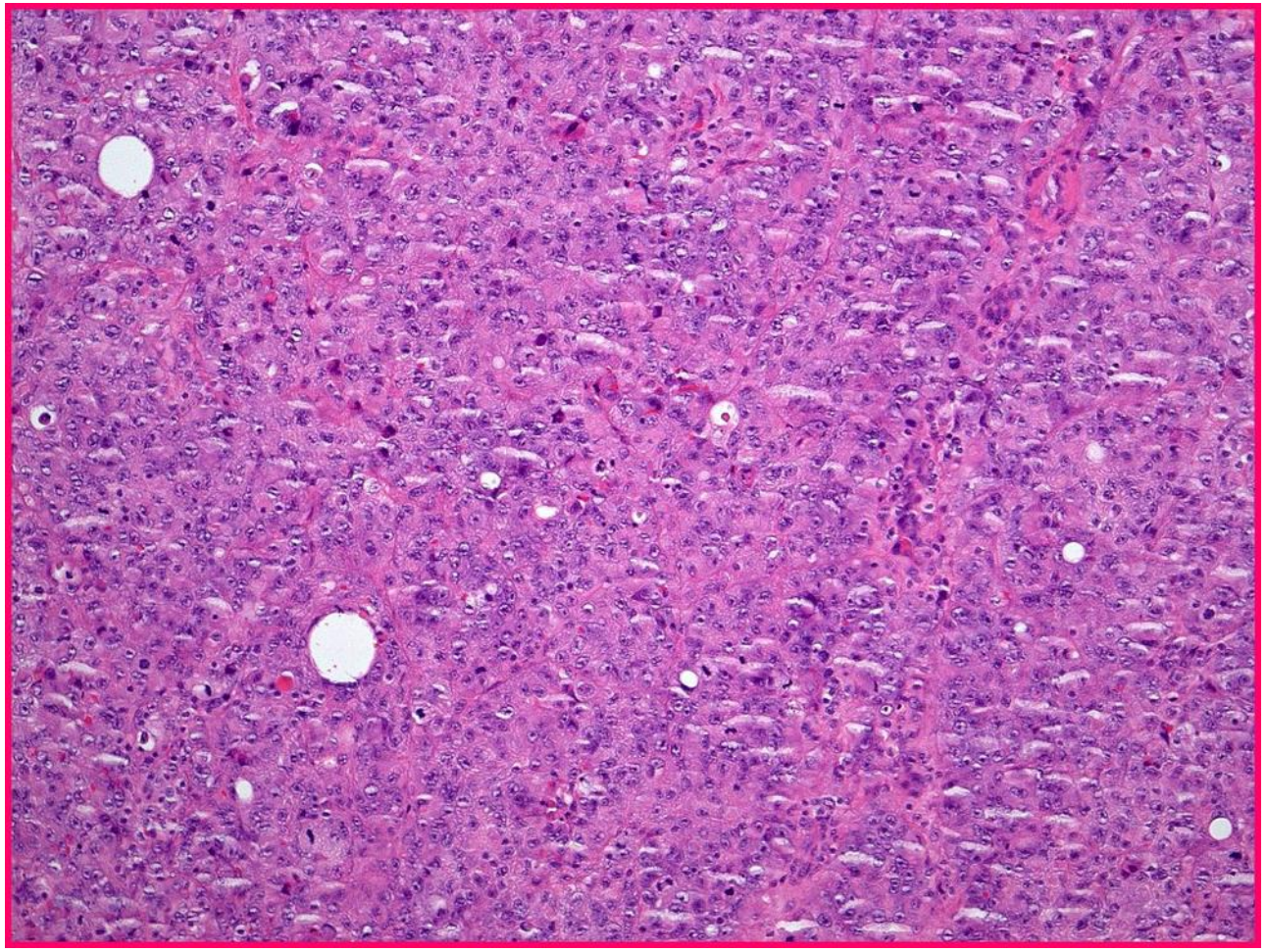
Diagnosis: Angiosarcoma(AS)

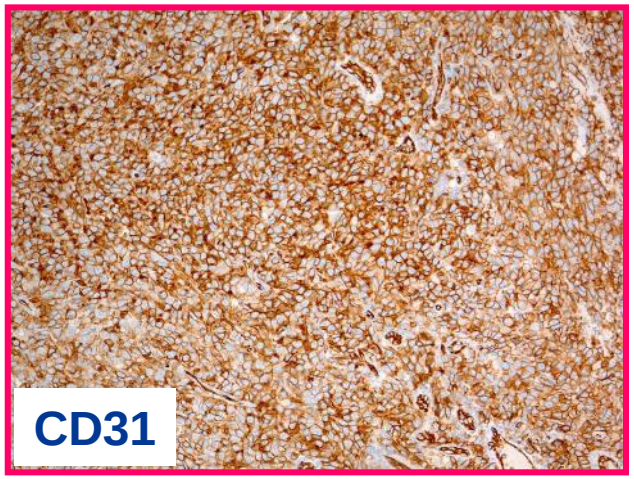


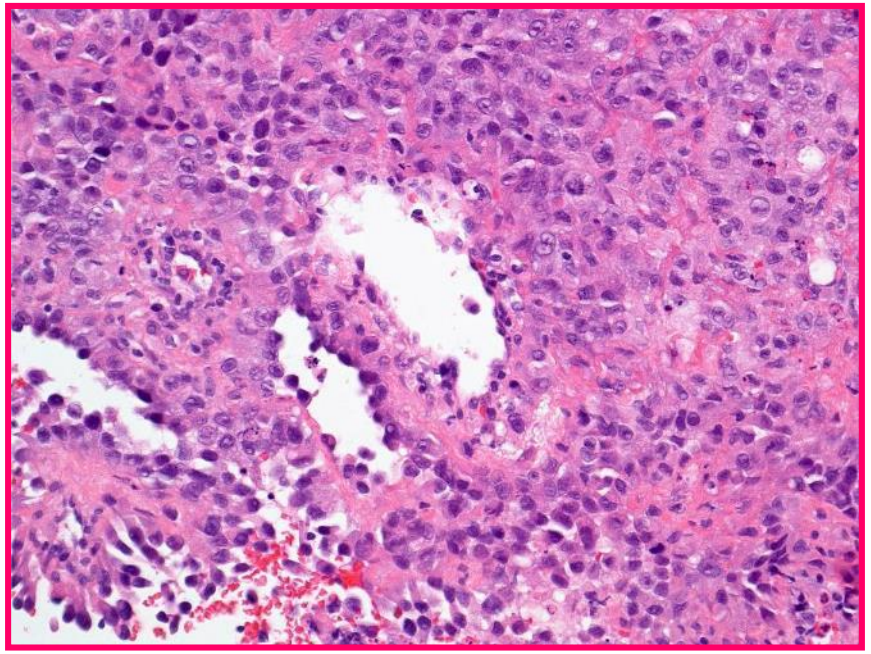


ERG

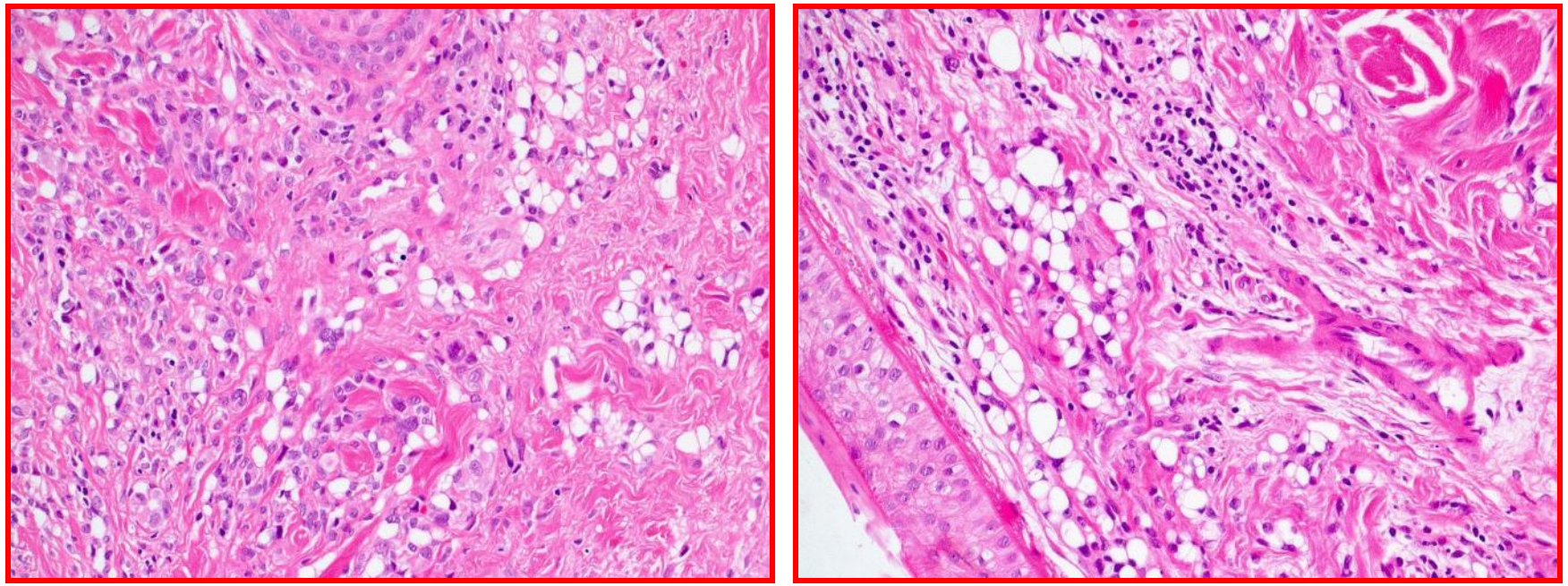
Epithelioid AS







Clear Cell/Signet Ring Cell AS



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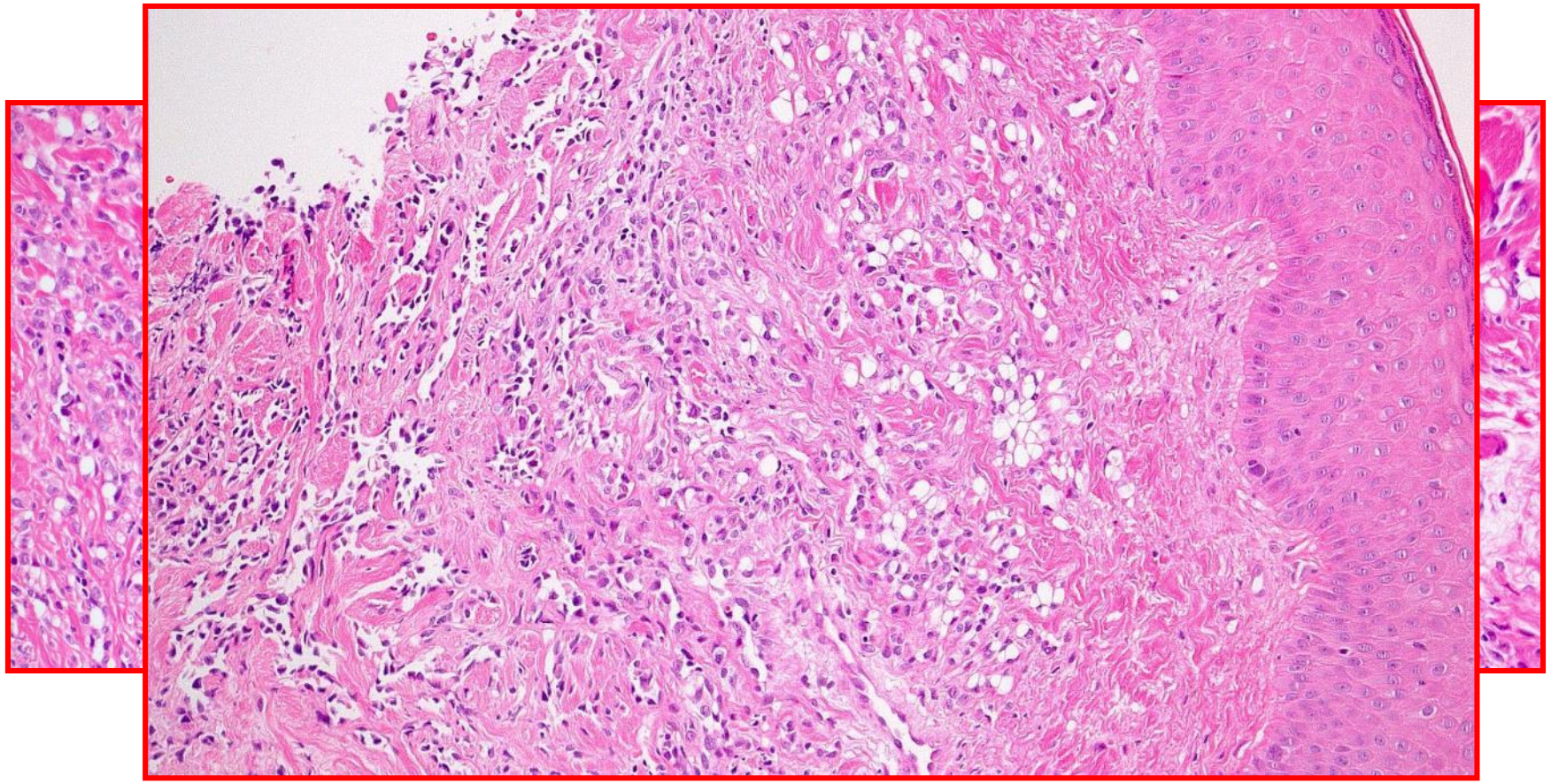
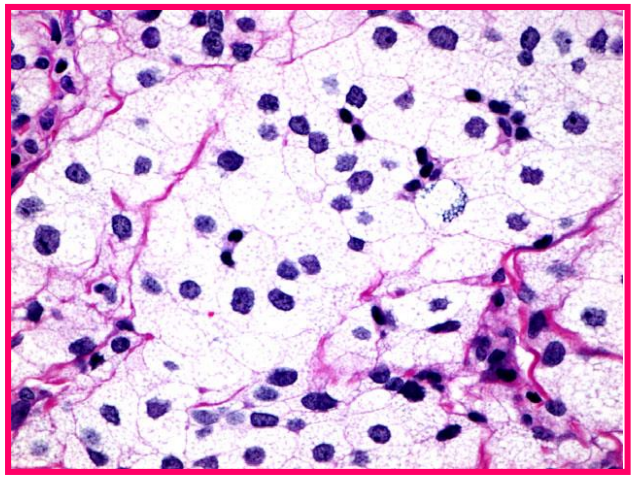
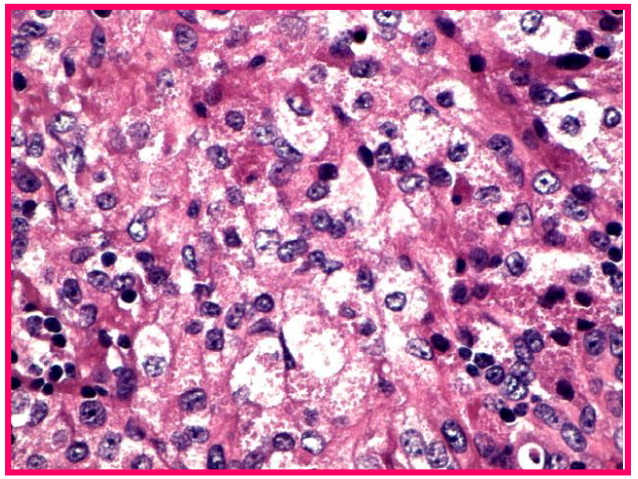


Other Morphological Variants of Epithelioid AS

- 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

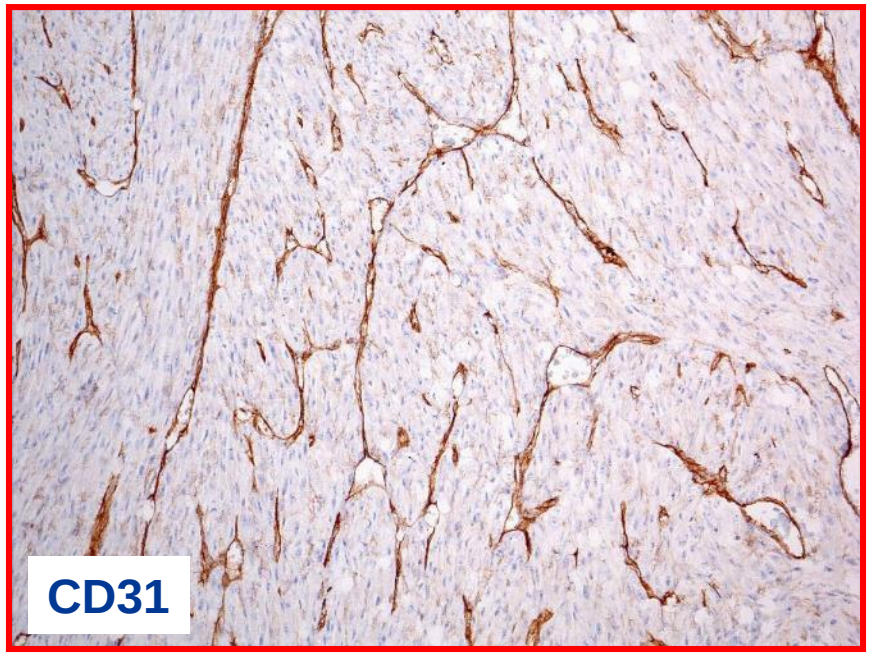
- Use more than one endothelial marker
- CD34, CD31, ERG, (*Podoplanin, FVIIIRA*)

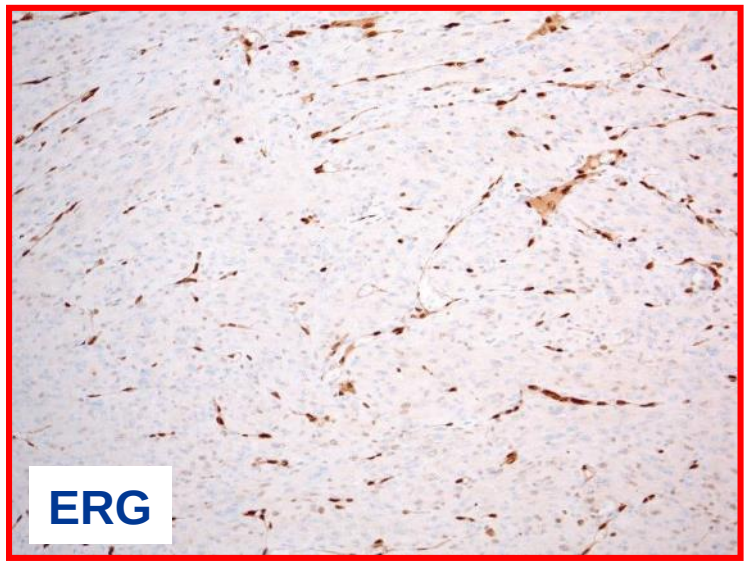
- *CD31 – not entirely specific, also expressed by histiocytes*
- *CD34 – less sensitive than CD31 & not specific*

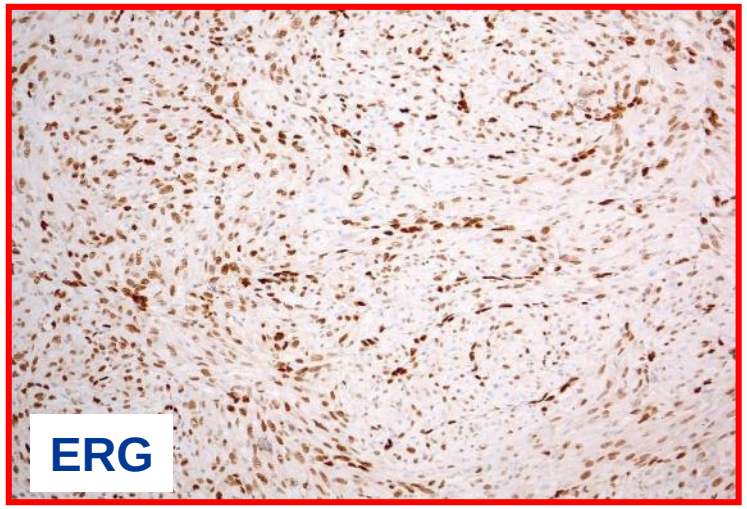
ERG

- 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

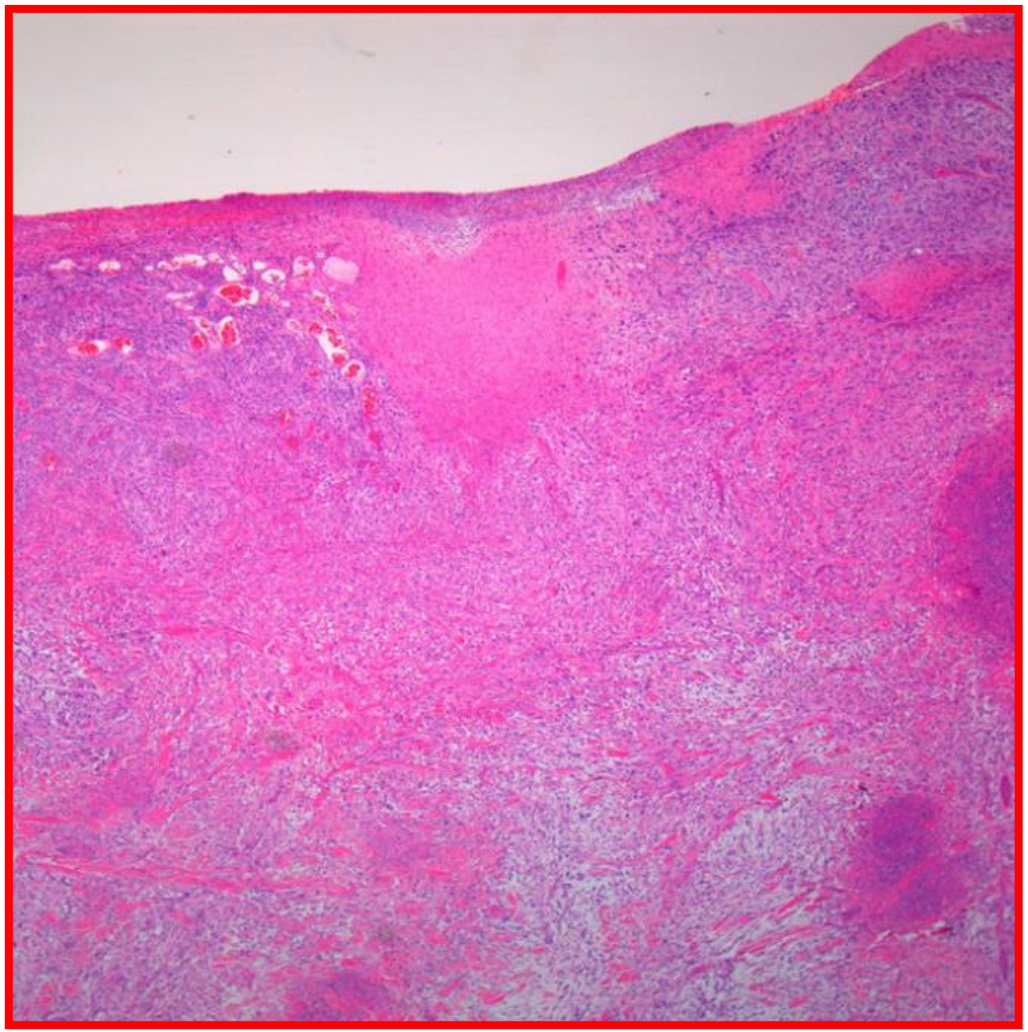
PDS

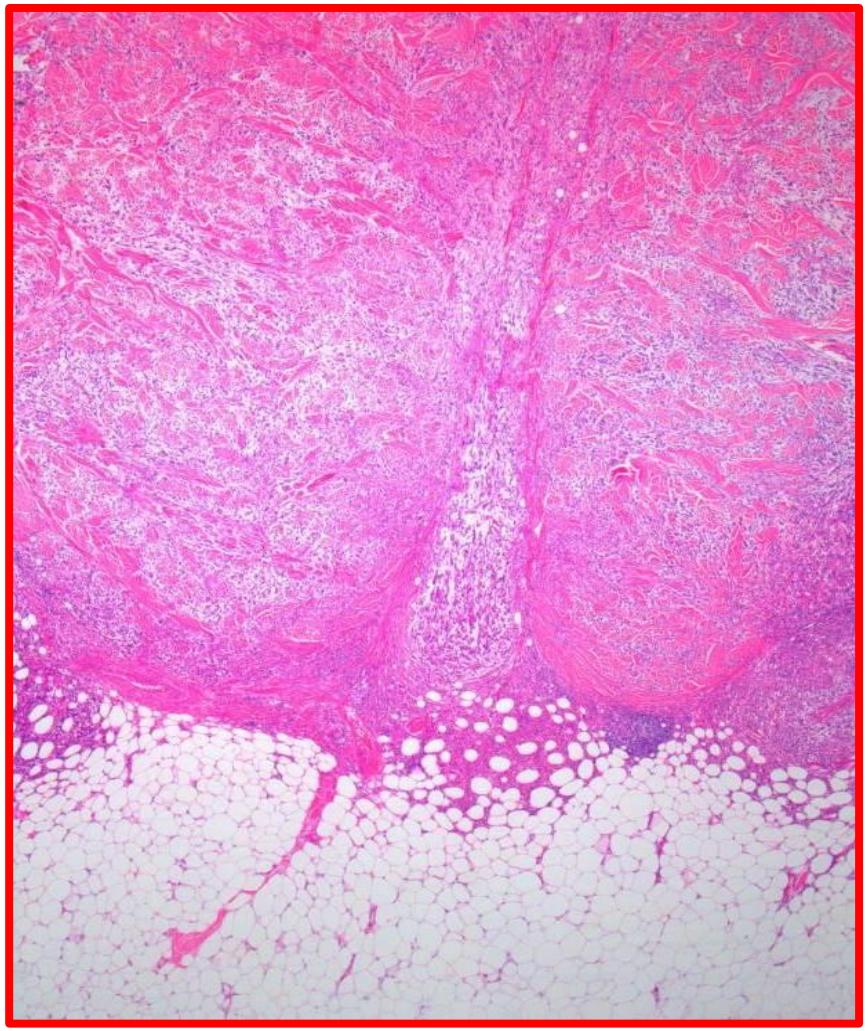


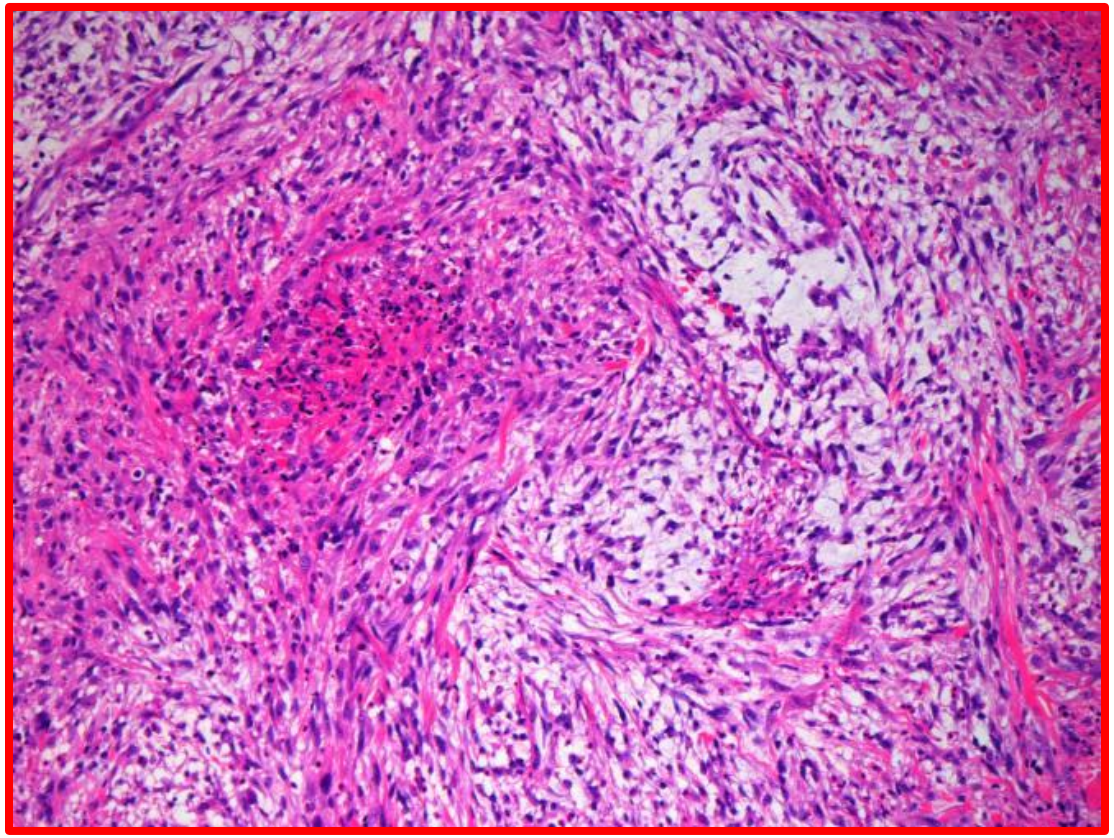


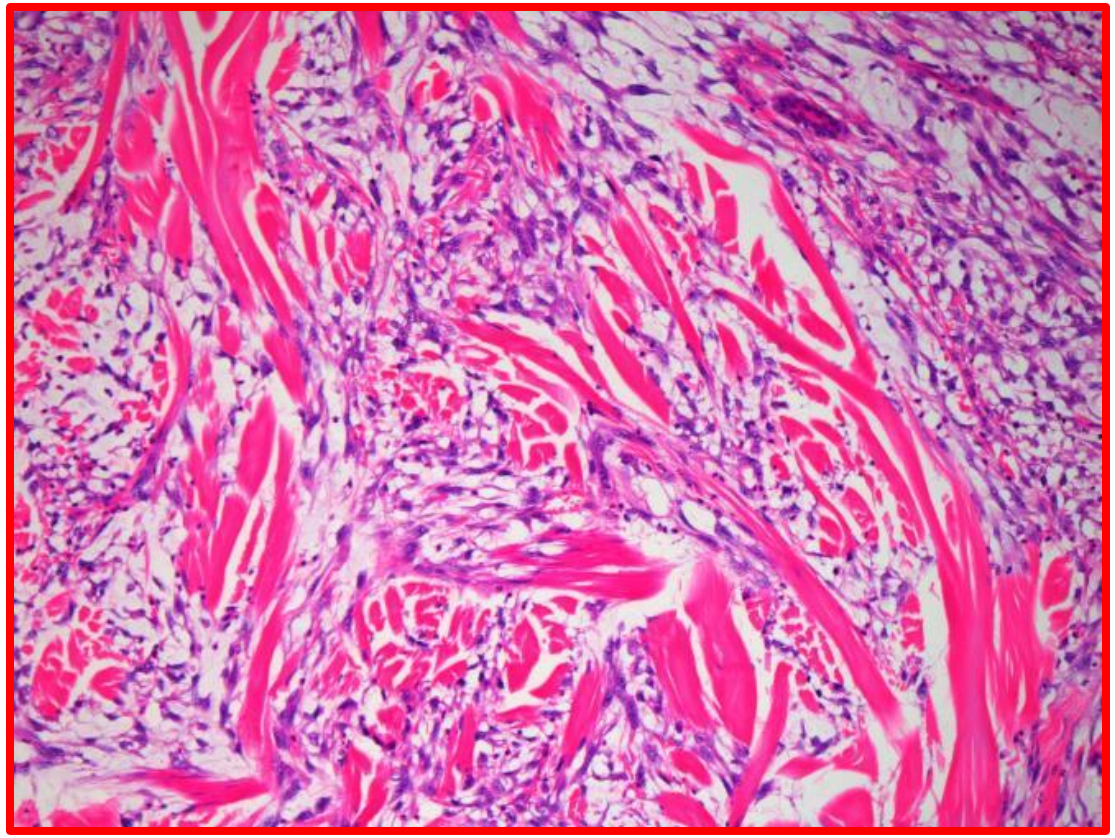


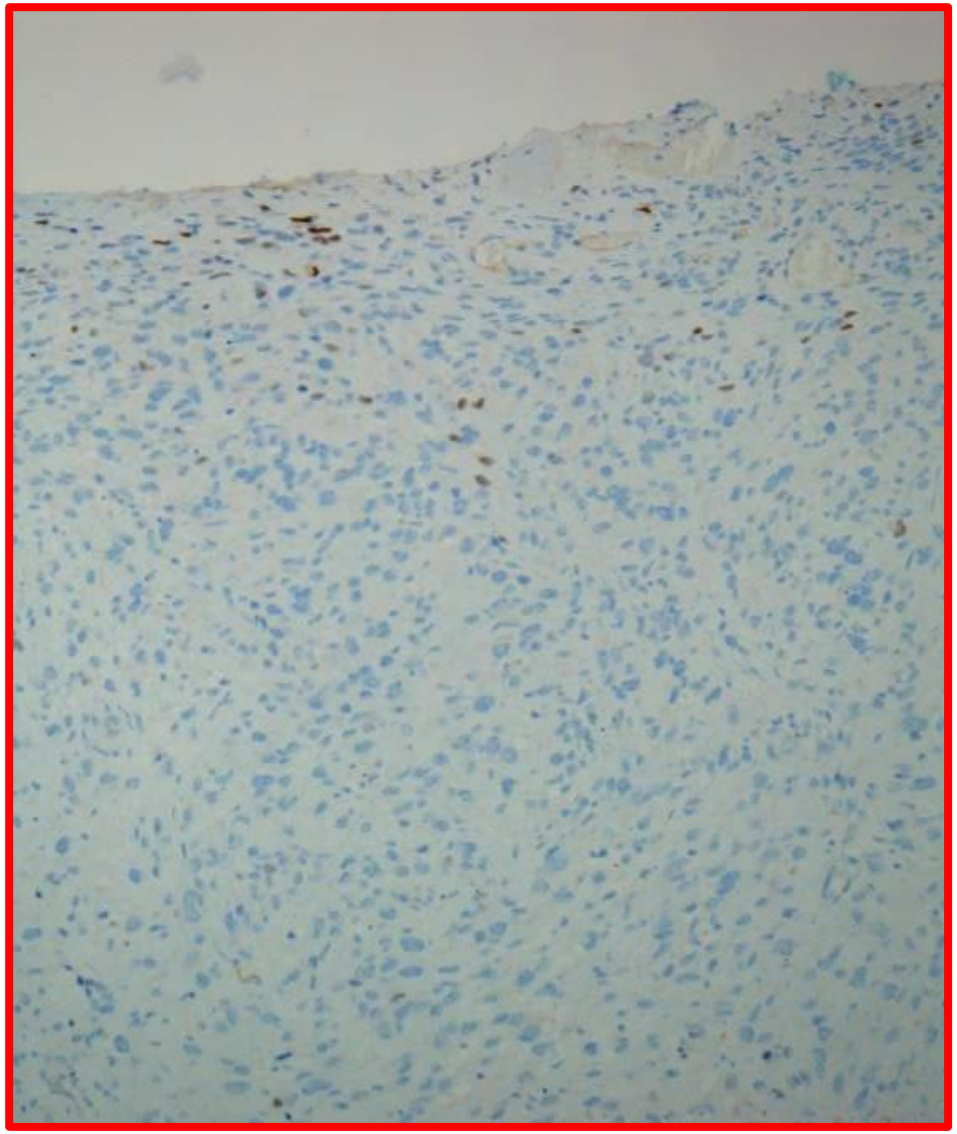
77M.Skin lesion, back. WLE





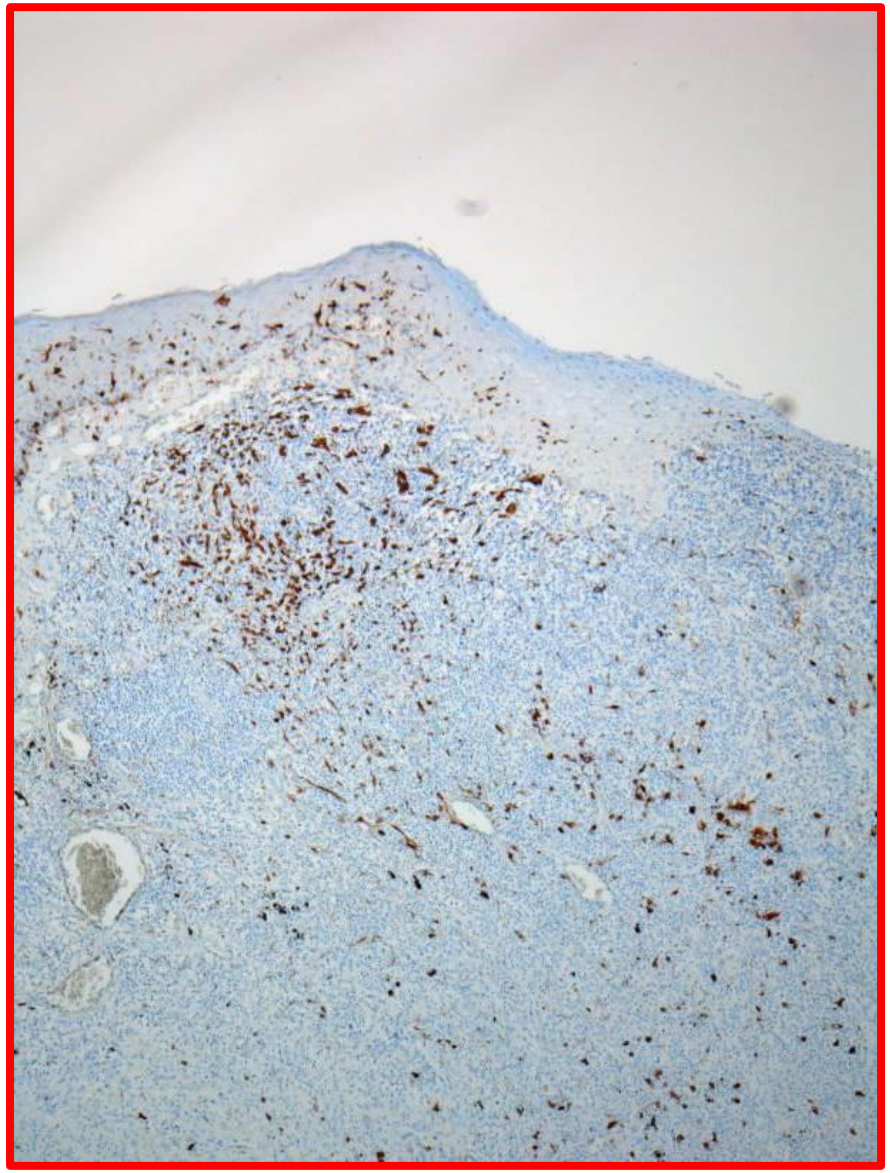




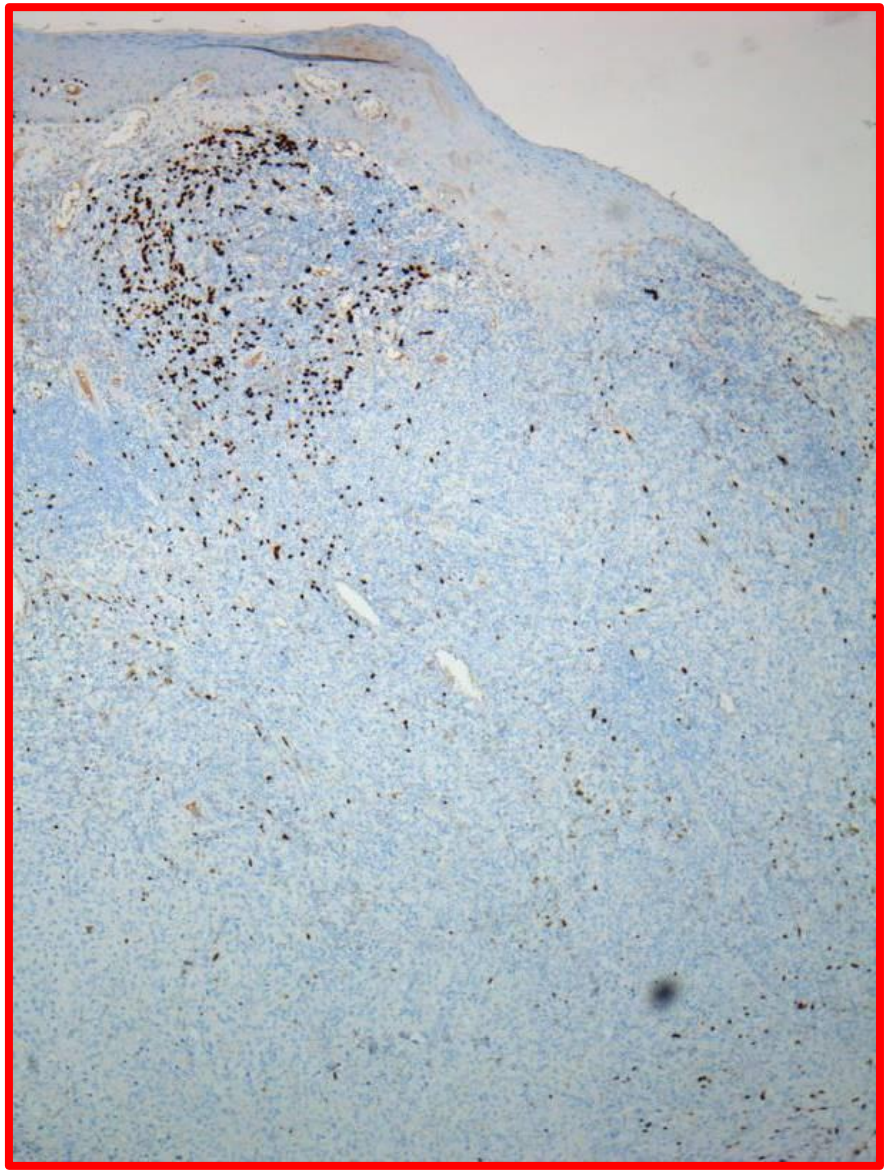


SOX10

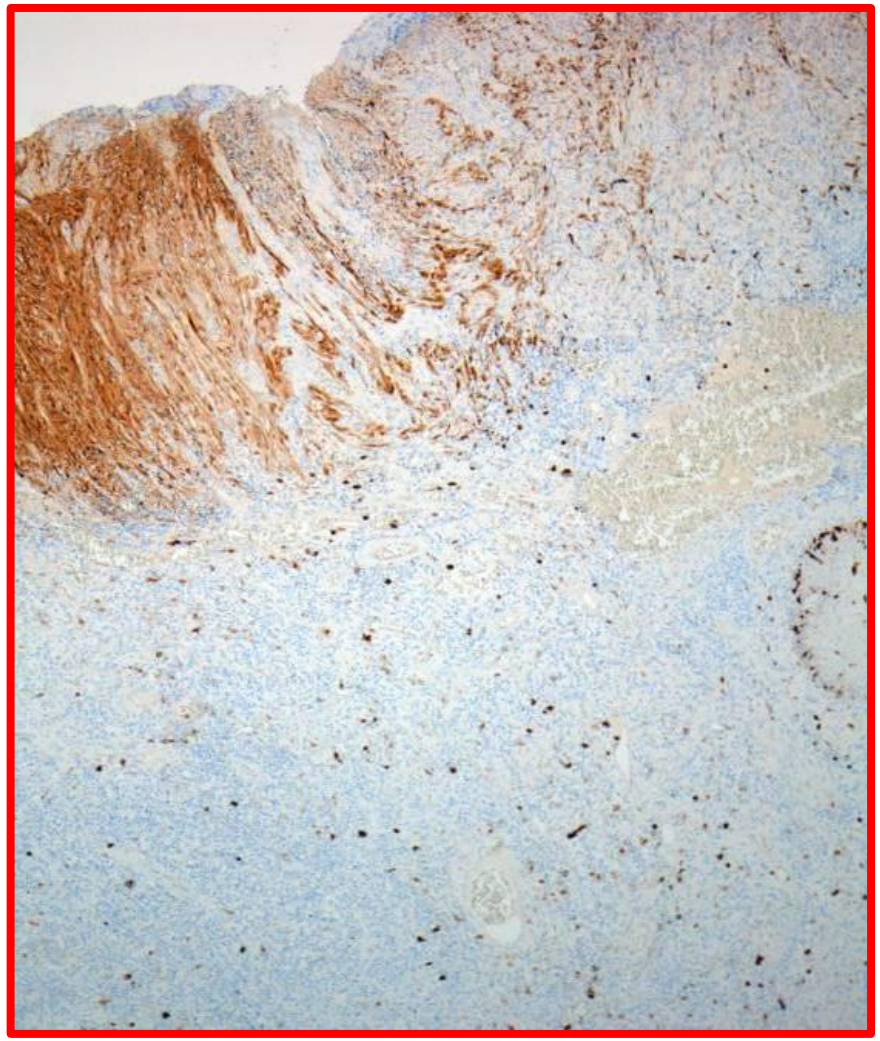
S100



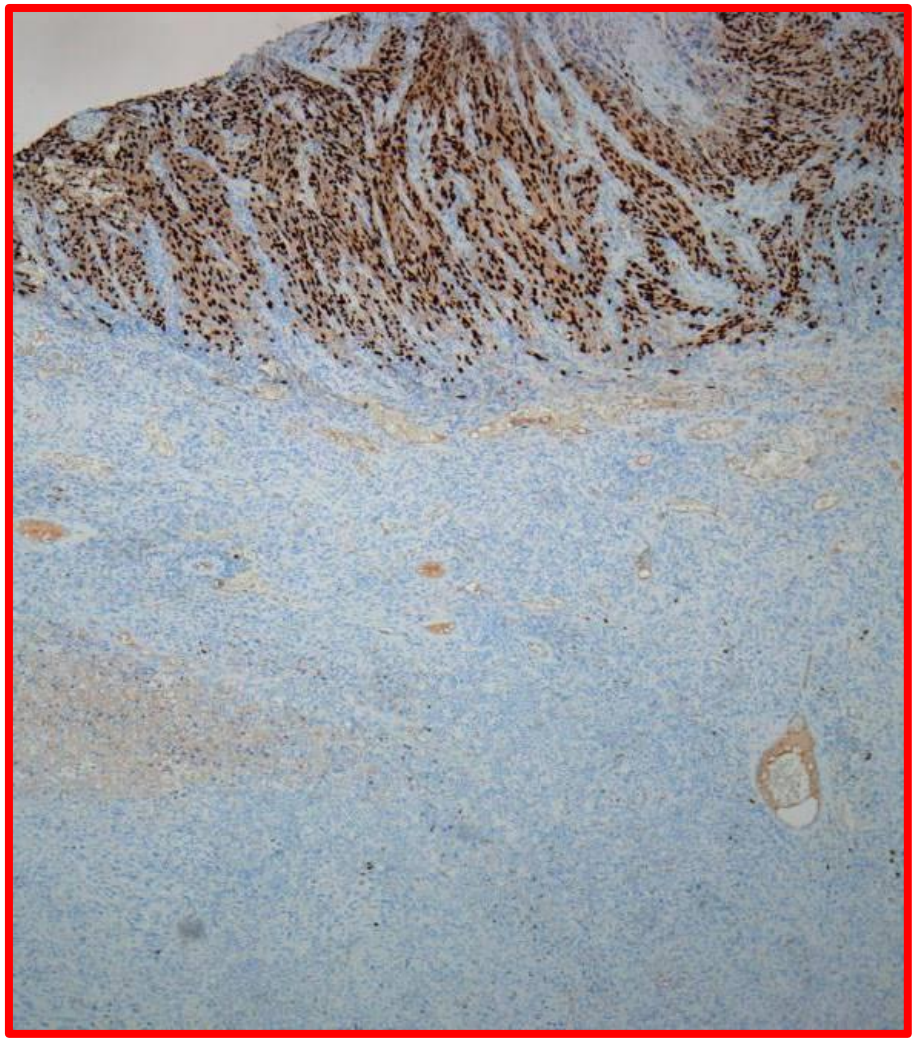
S100



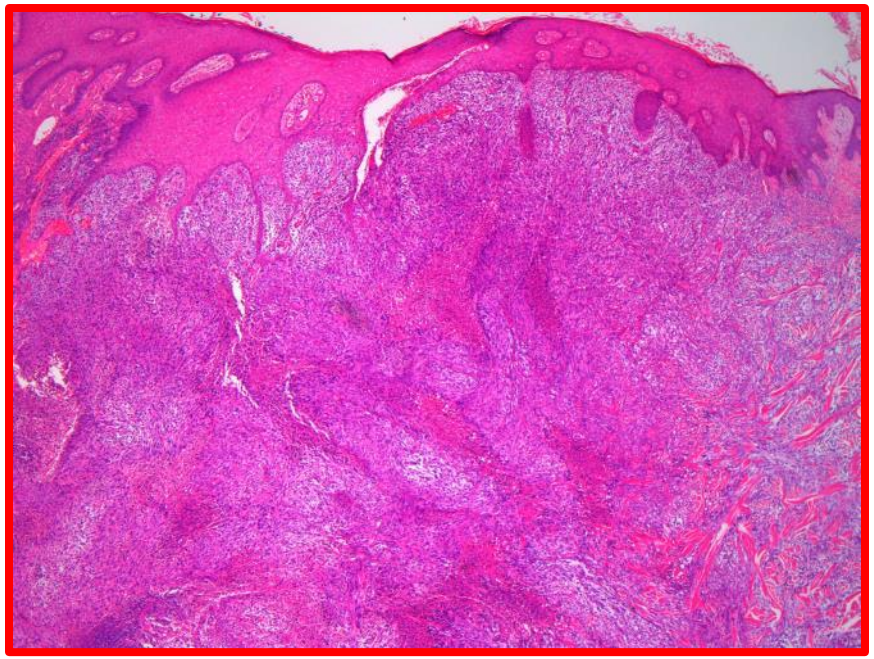
SOX10

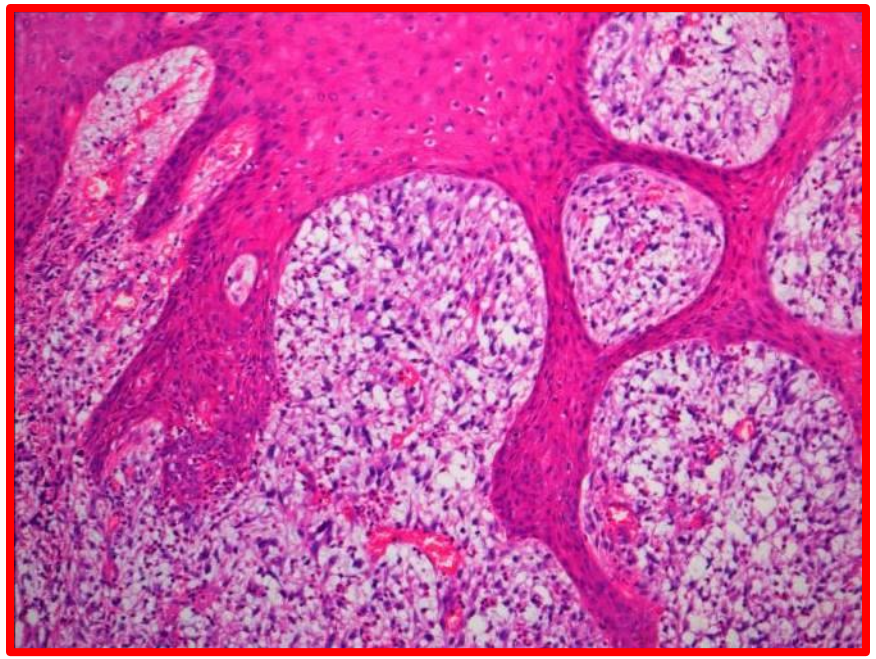


S100



SOX10





Diagnosis

- Sarcomatoid malignant melanoma (melanoma with sarcomatoid dedifferentiation)

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

Different Non-melanocytic Components Detected In Malignant Melanomas

- Fibroblastic/ myofibroblastic
- Smooth muscle
- Rhabdomyoblastic
- 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

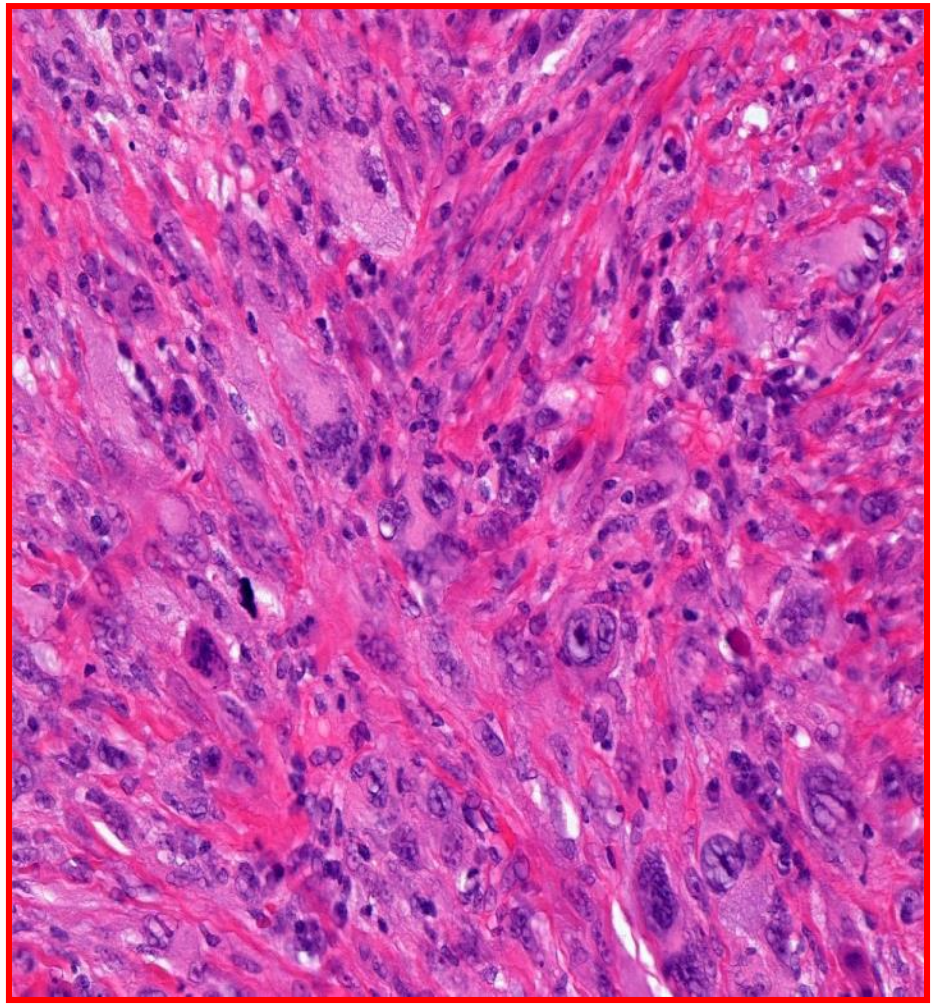
Atypical Fibroxanthoma (AFX)

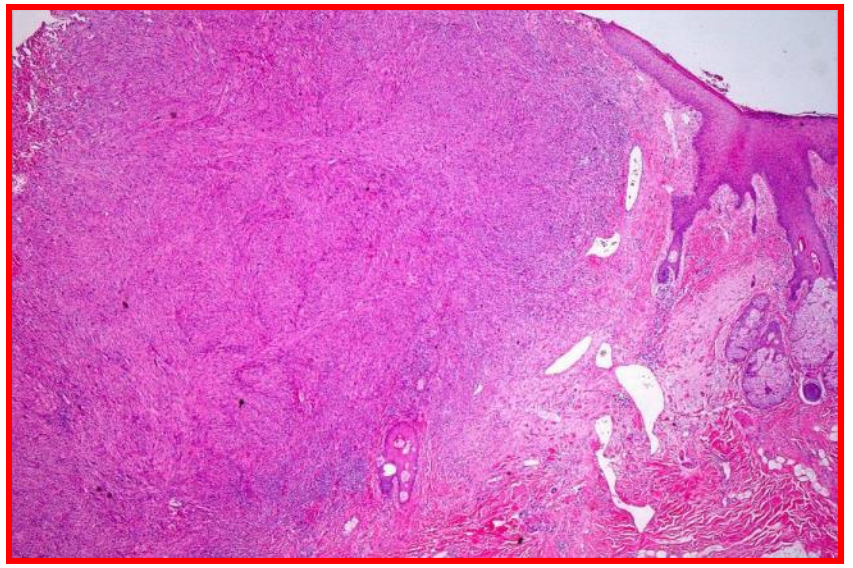
- Term coined by Helwig in 1961
- Cutaneous tumour with histologically malignant appearance but associated (in most cases) with favourable clinical behaviour
- Elderly patients & younger patients with xeroderma pigmentosa
- Sun exposed areas – head and neck and upper limbs
- UV signature mutation in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

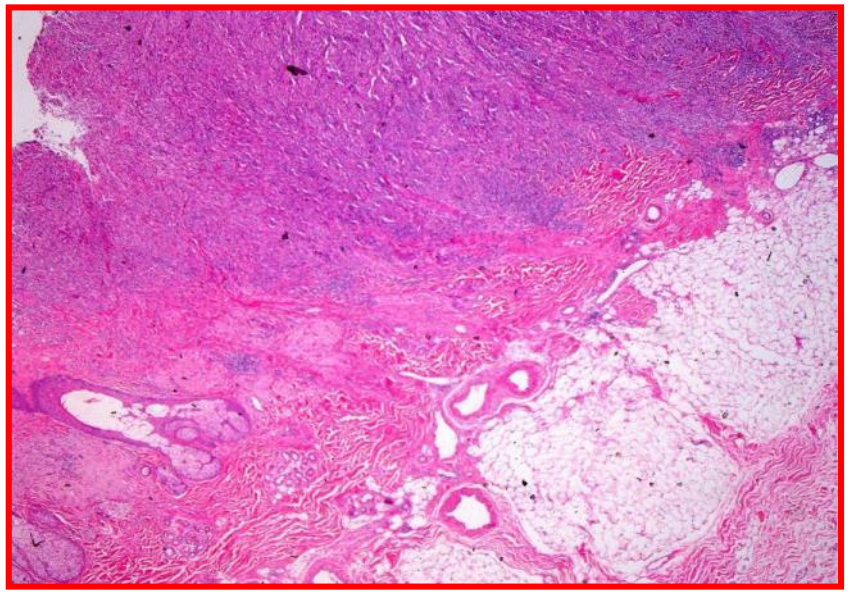
AFX

- Usually less than <1 cm in MD
- 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

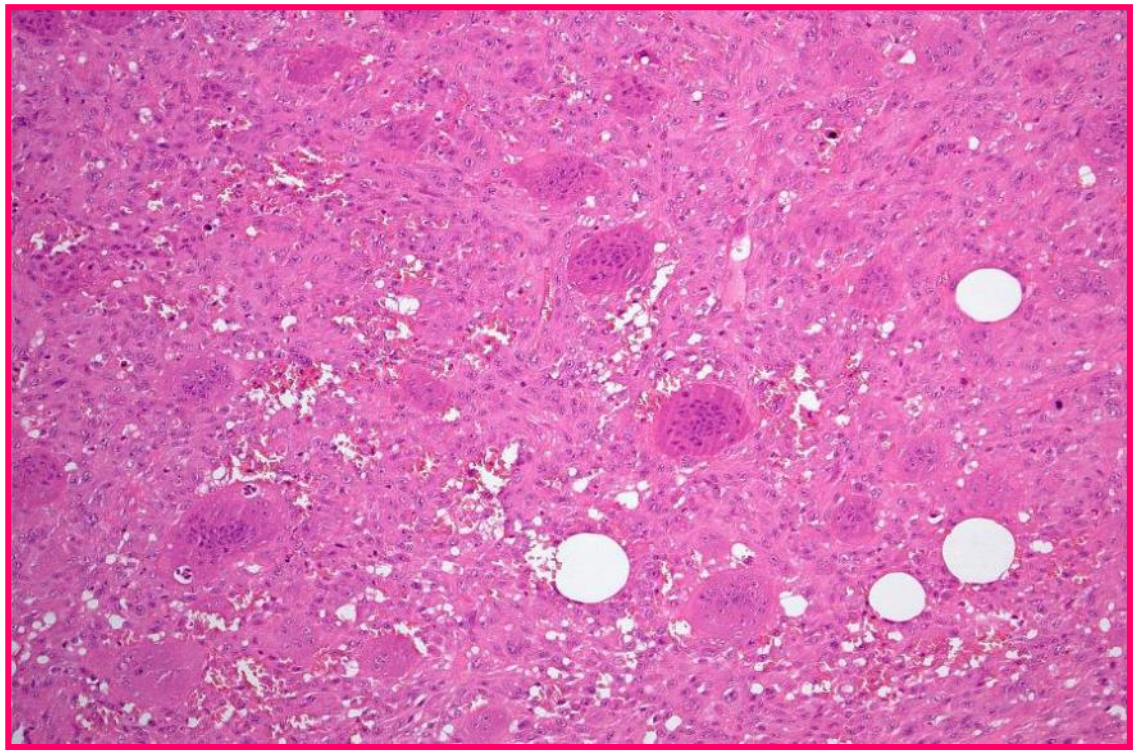
AFX



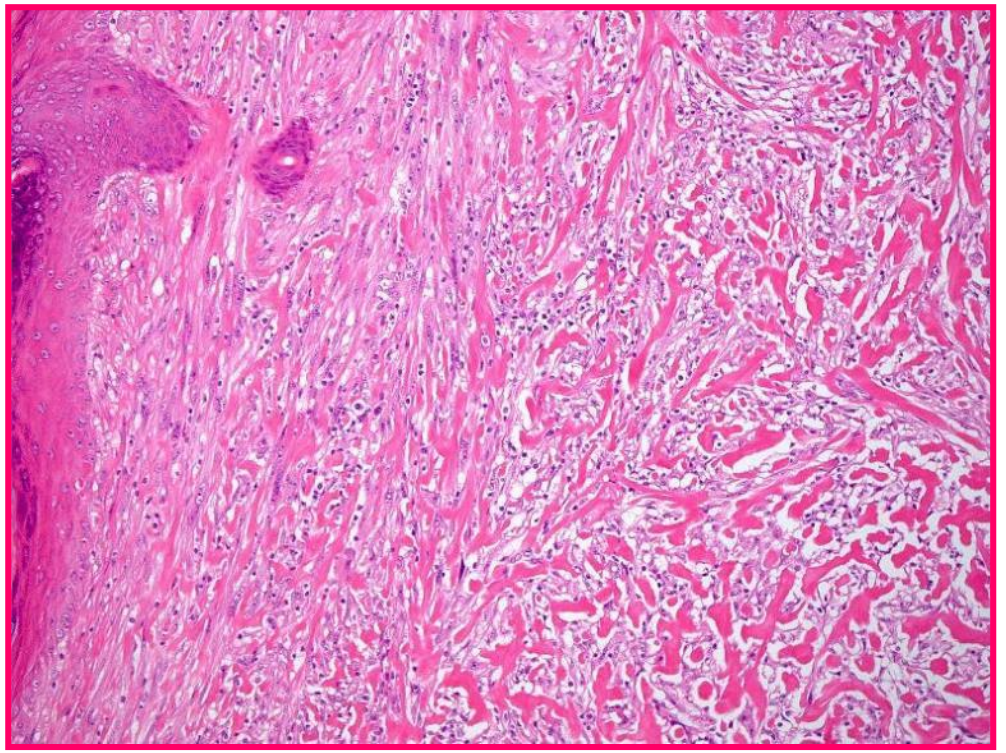




Morphological Variants

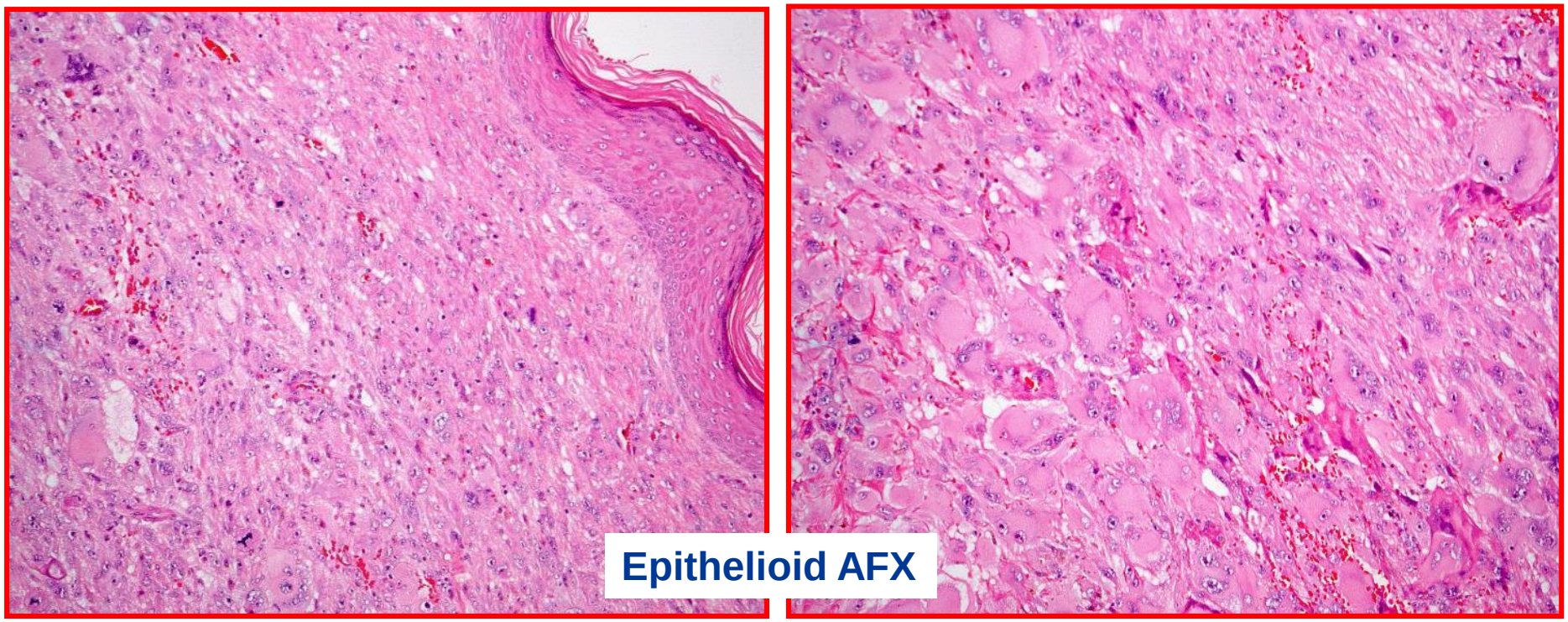


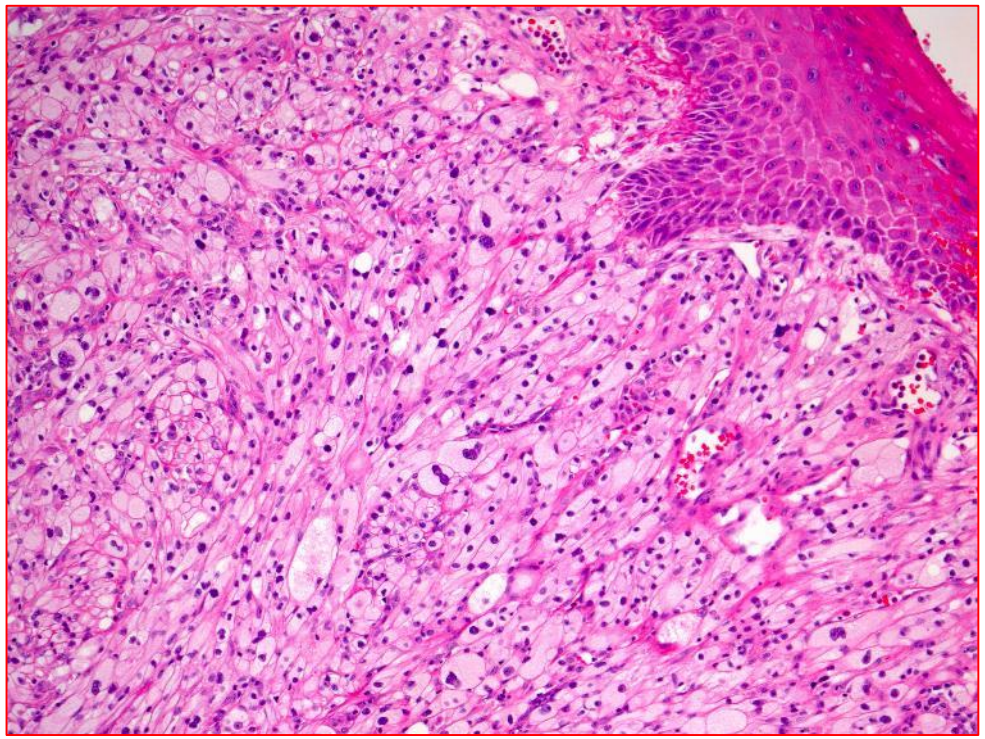
AFX with osteoclast-like giant cells

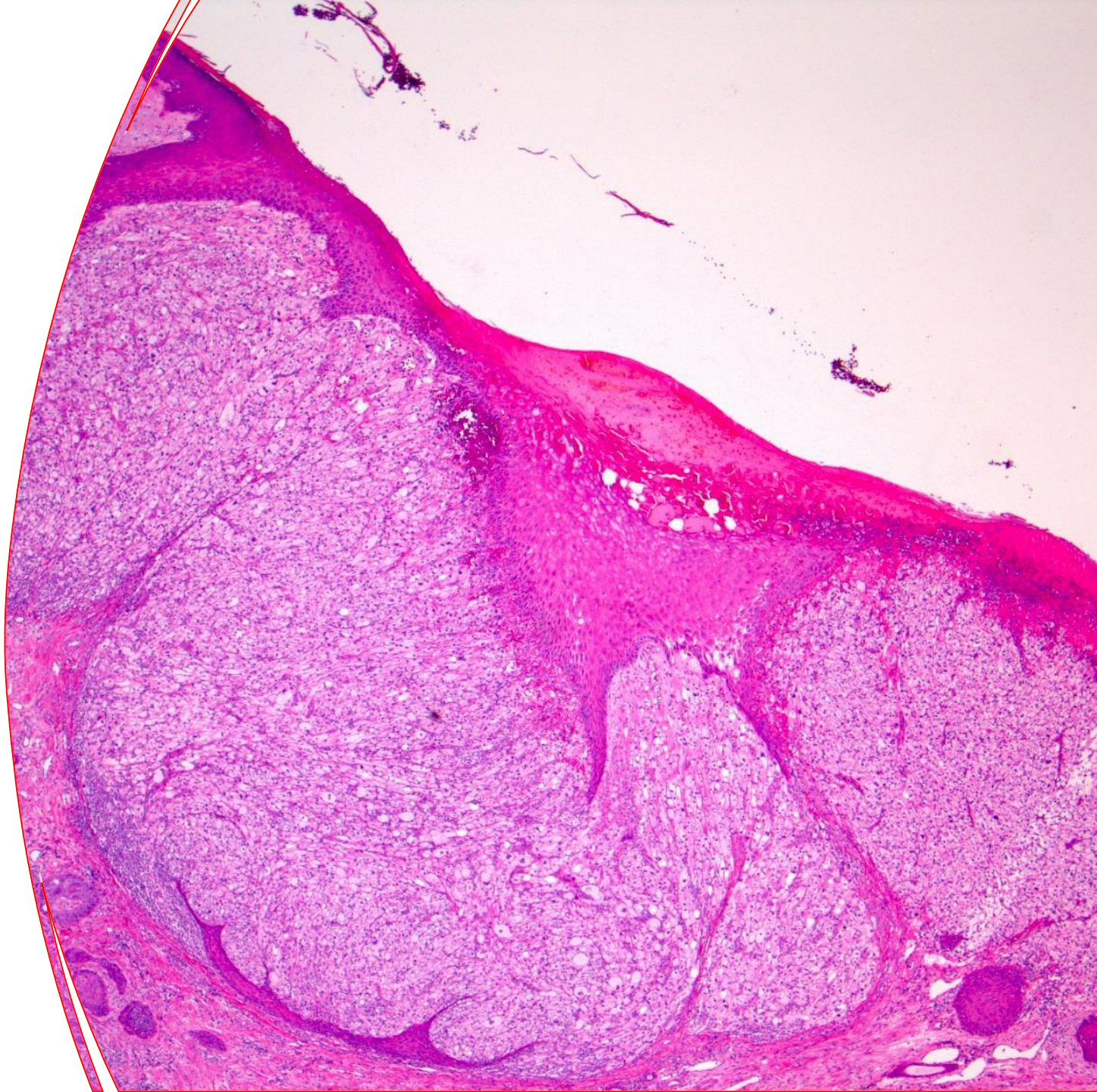


Keloidal AFX

AFX - Morphological Variants





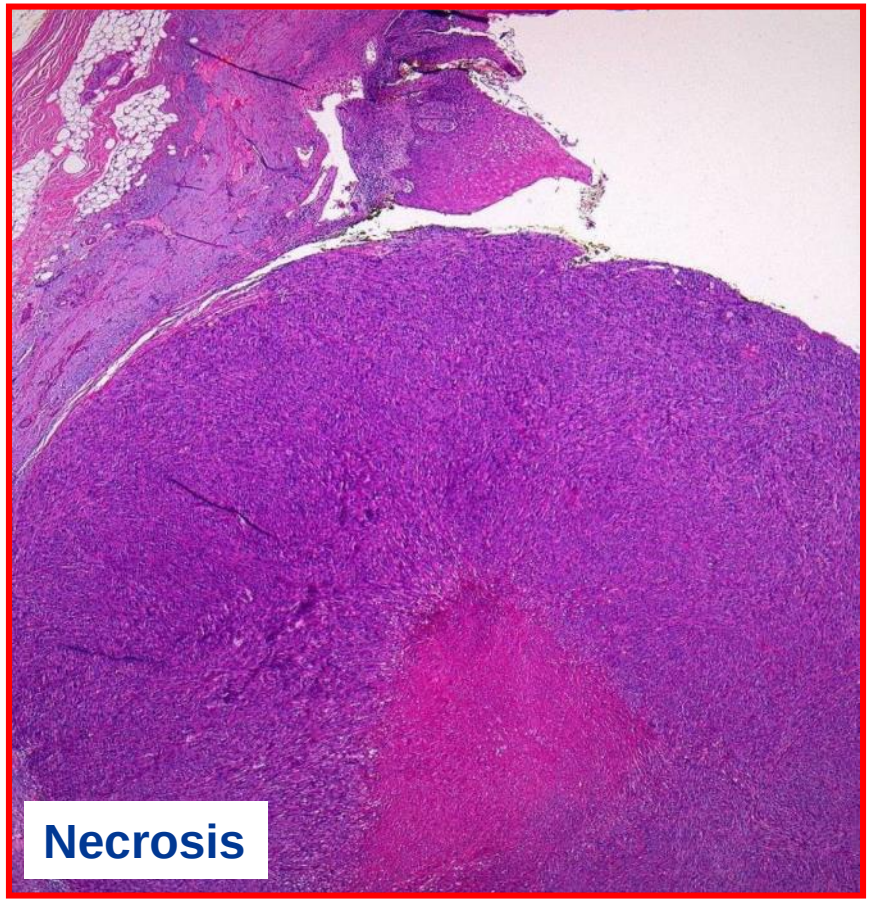


Clear cell AFX

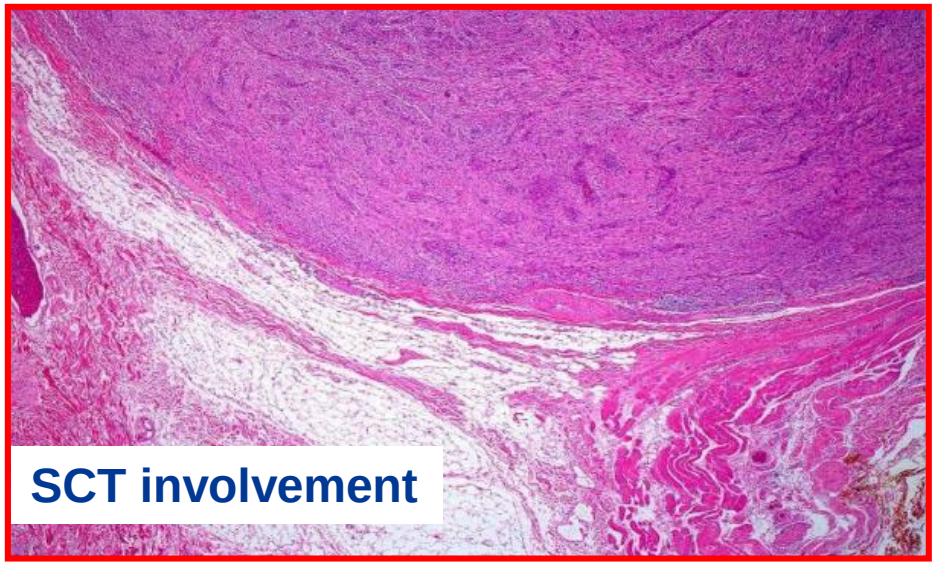
AFX - Other Morphological Variants

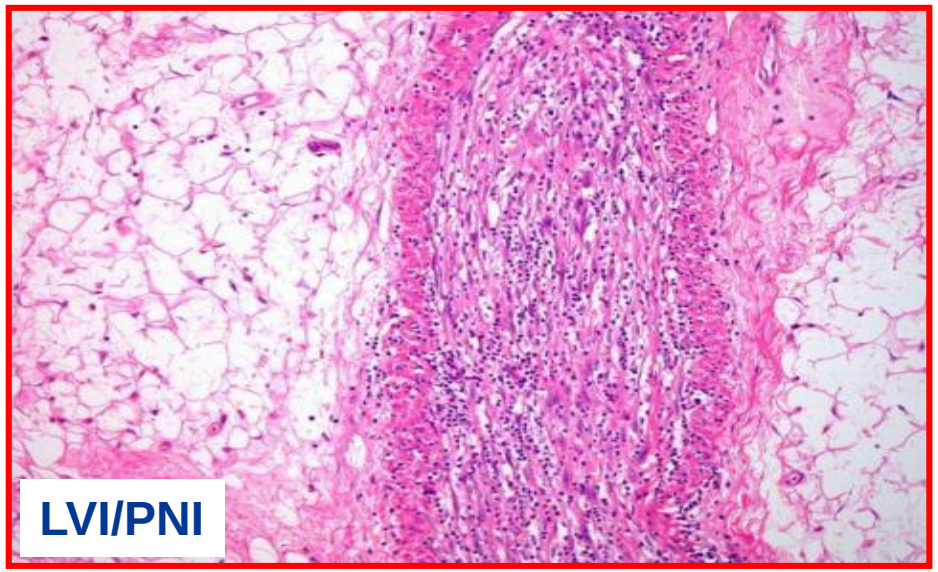
- Spindle cell non-pleomorphic AFX/ Monomorphic spindle cell AFX
- Granular cell AFX
- Myxoid AFX
- Pseudoangiomatous AFX
- Plaque-like
- Regressed

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 anti-trypsin
- SMA and CD31 may be positive

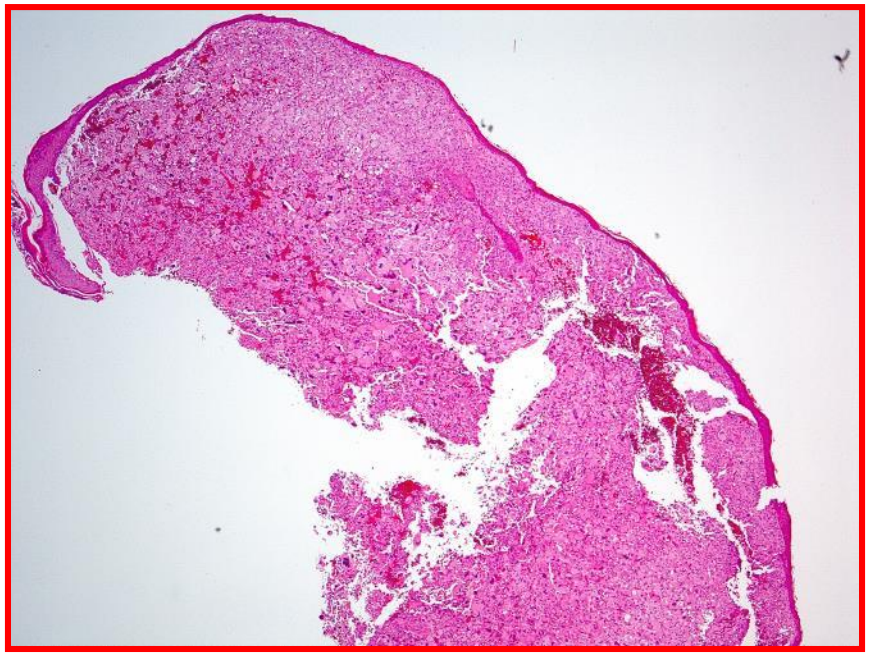
PDS vs AFX
(Clinical Behaviour)

- 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

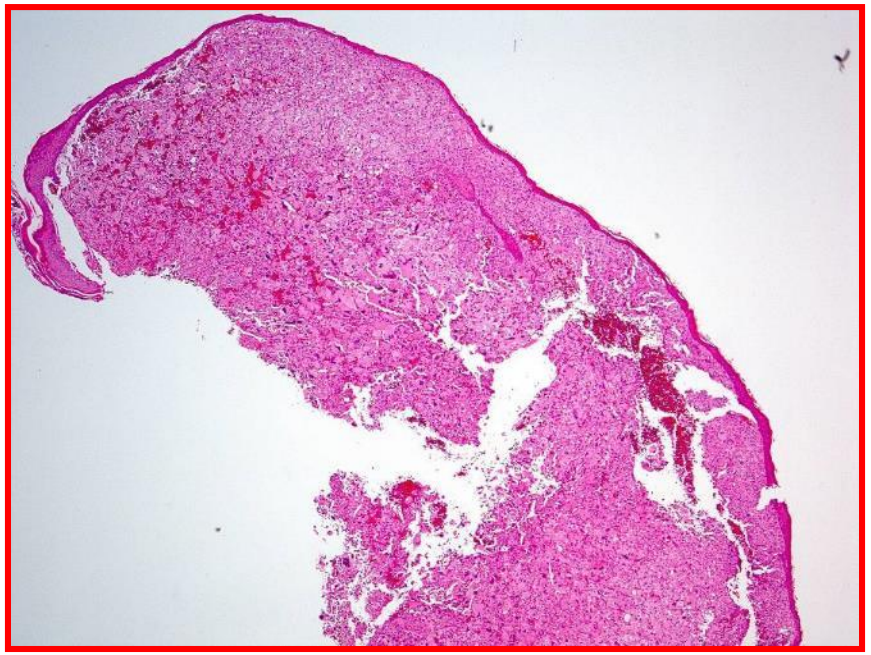
- Beware of superficial biopsies!!



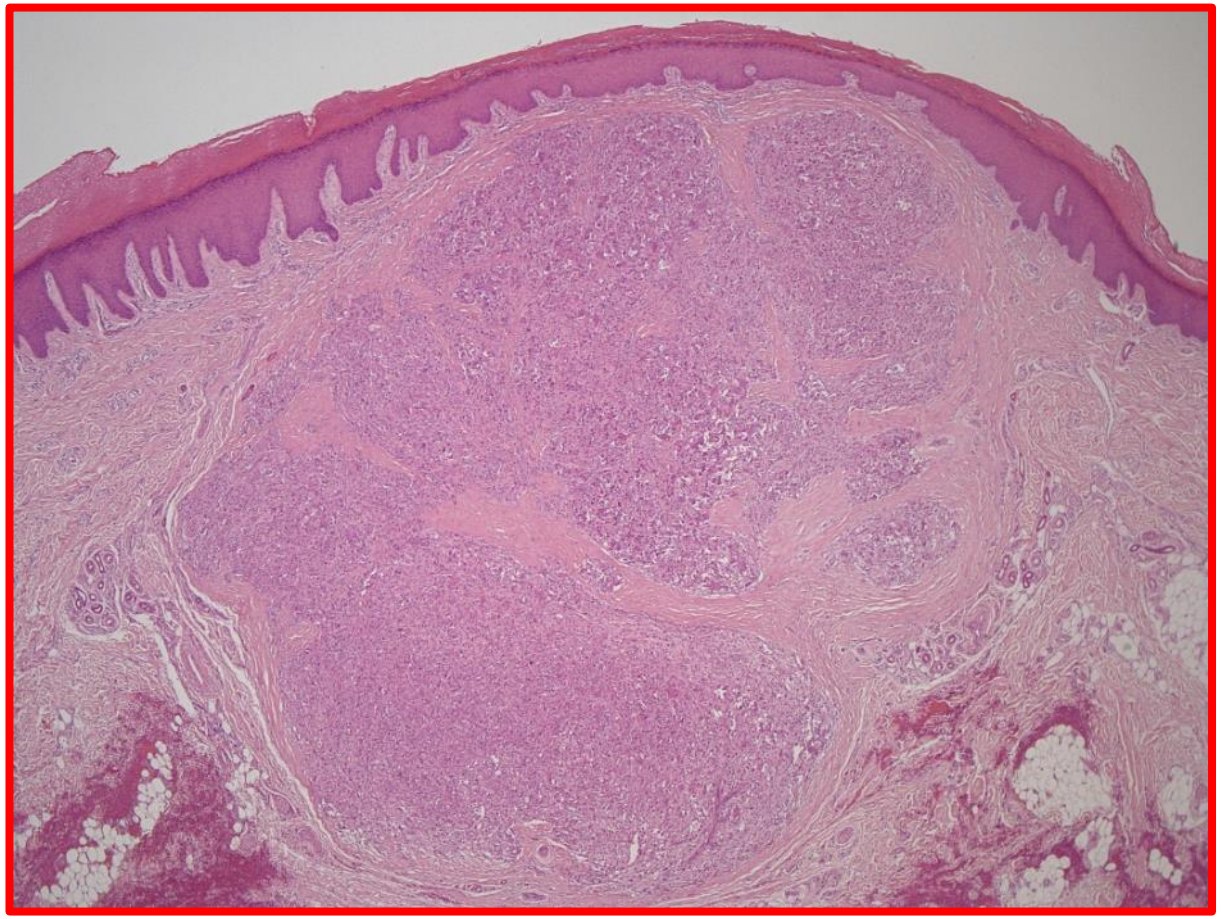
PDS vs AFX

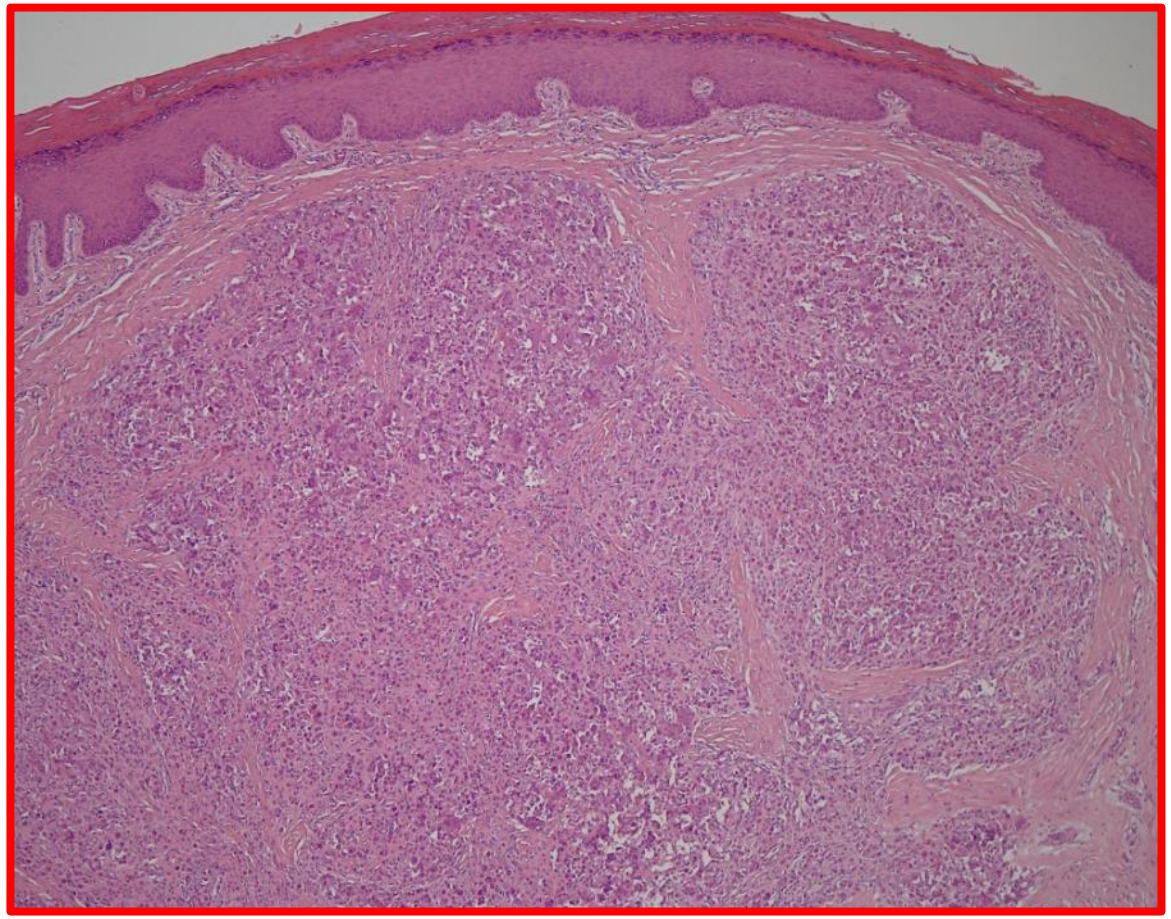
- Beware of superficial biopsies!!

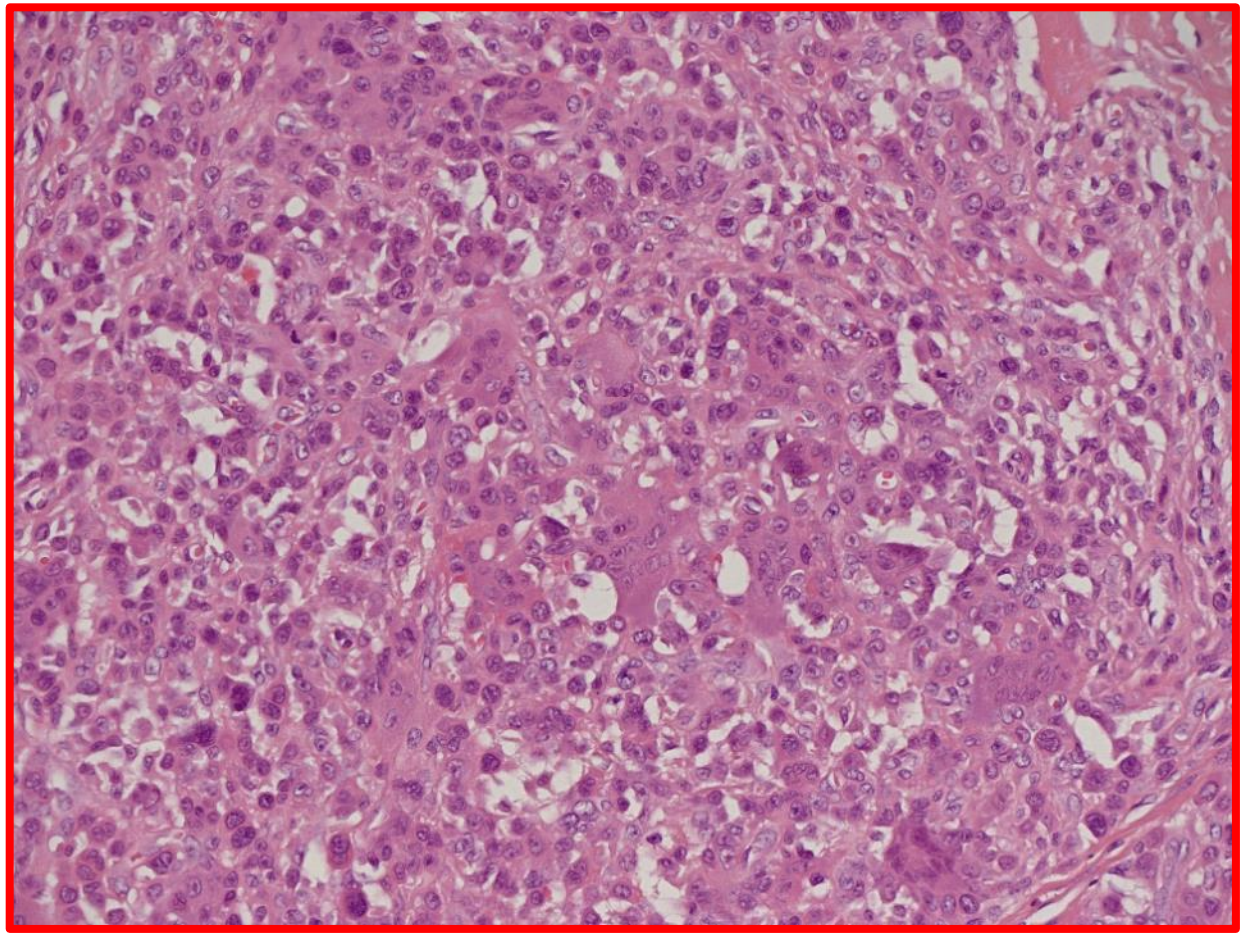
- *“Superficial pleomorphic spindle cell neoplasm, either an AFX or PDS. Nature of specimen precludes full histological interpretation, making it impossible to give a definitive diagnosis”.*

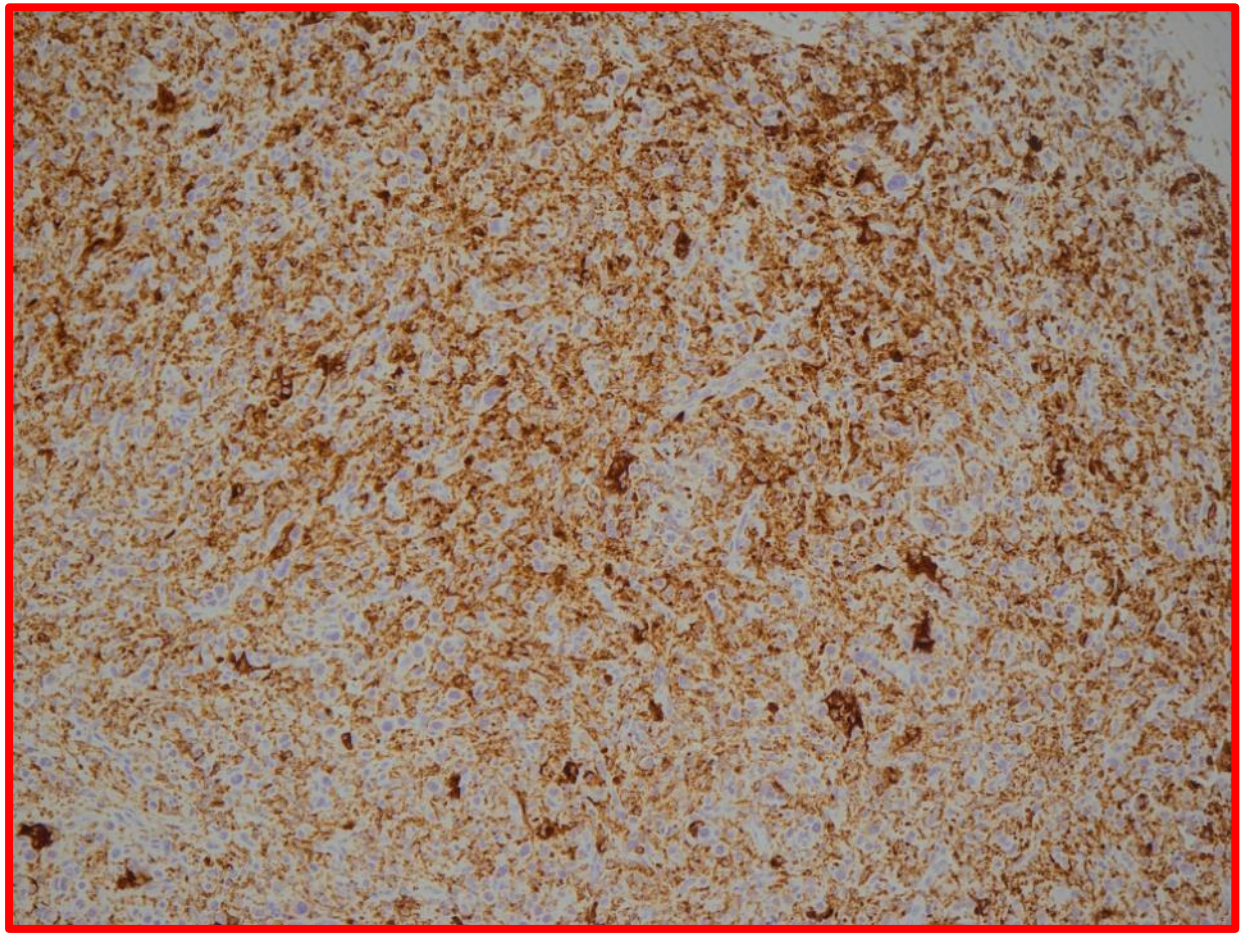


Case: 18F. Skin Lesion on wrist, excision

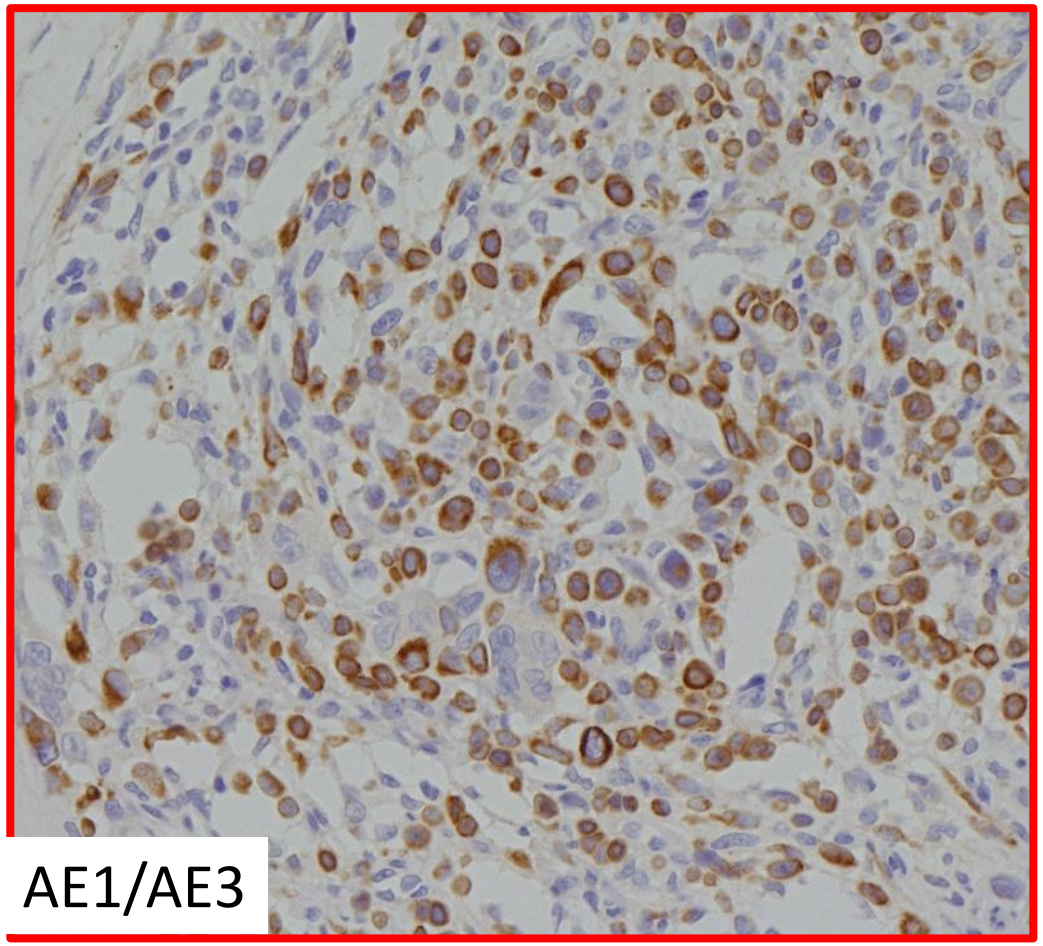




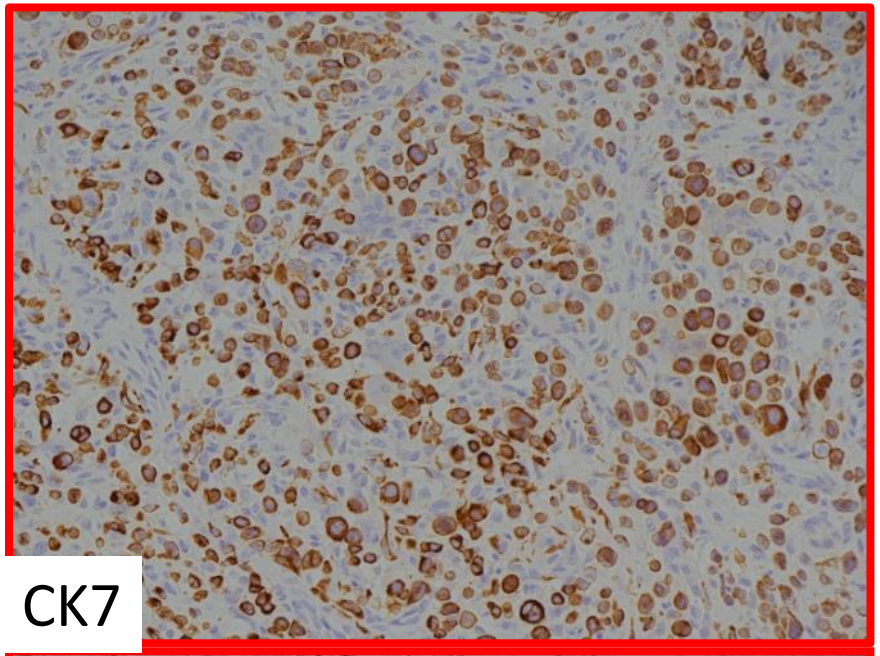




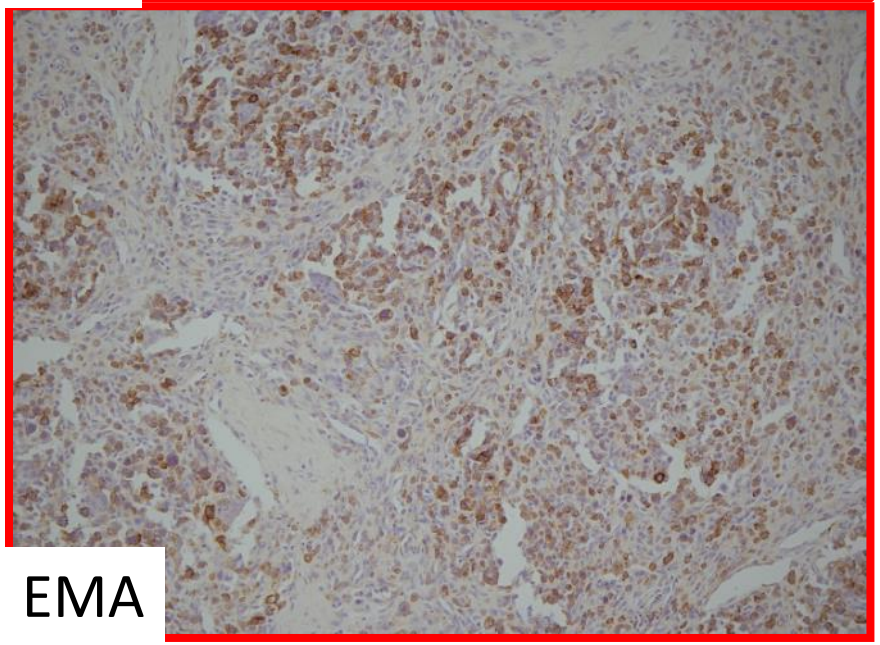
CD68



AE1/AE3

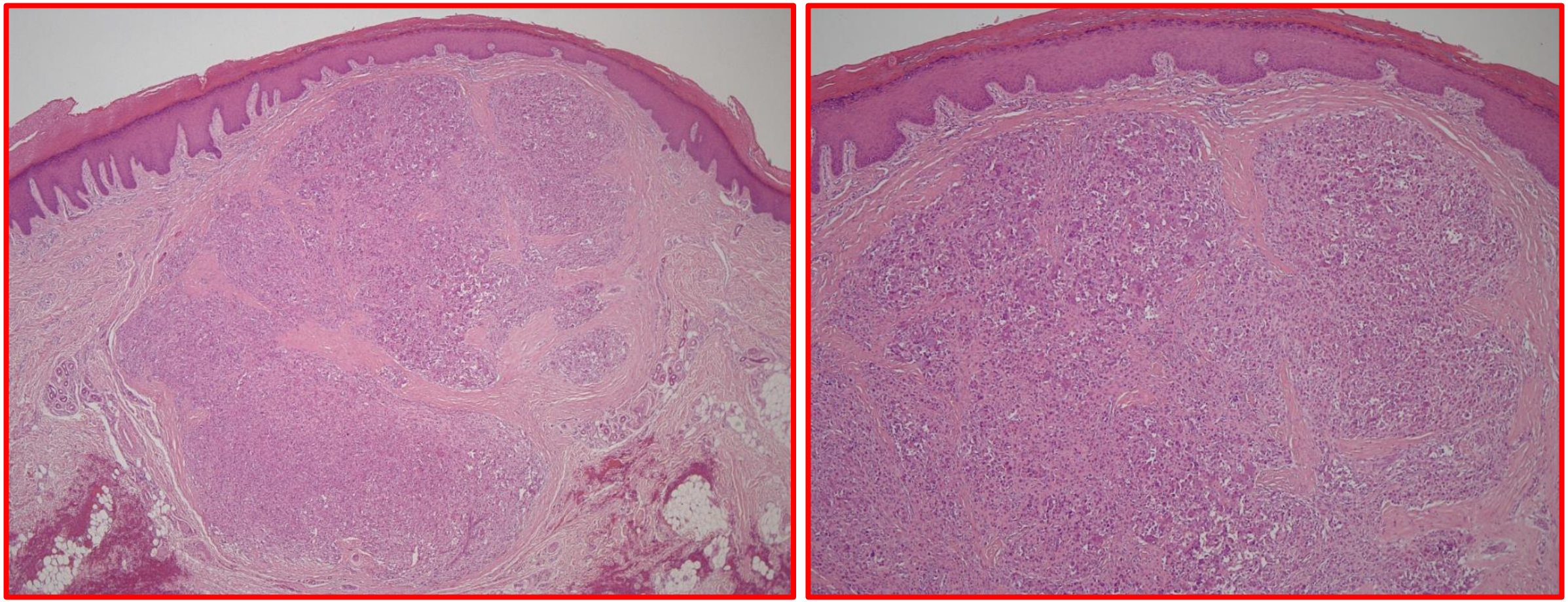


CK7



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

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
- Has overlapping features with xanthogranulomatous epithelial tumour (XGET)

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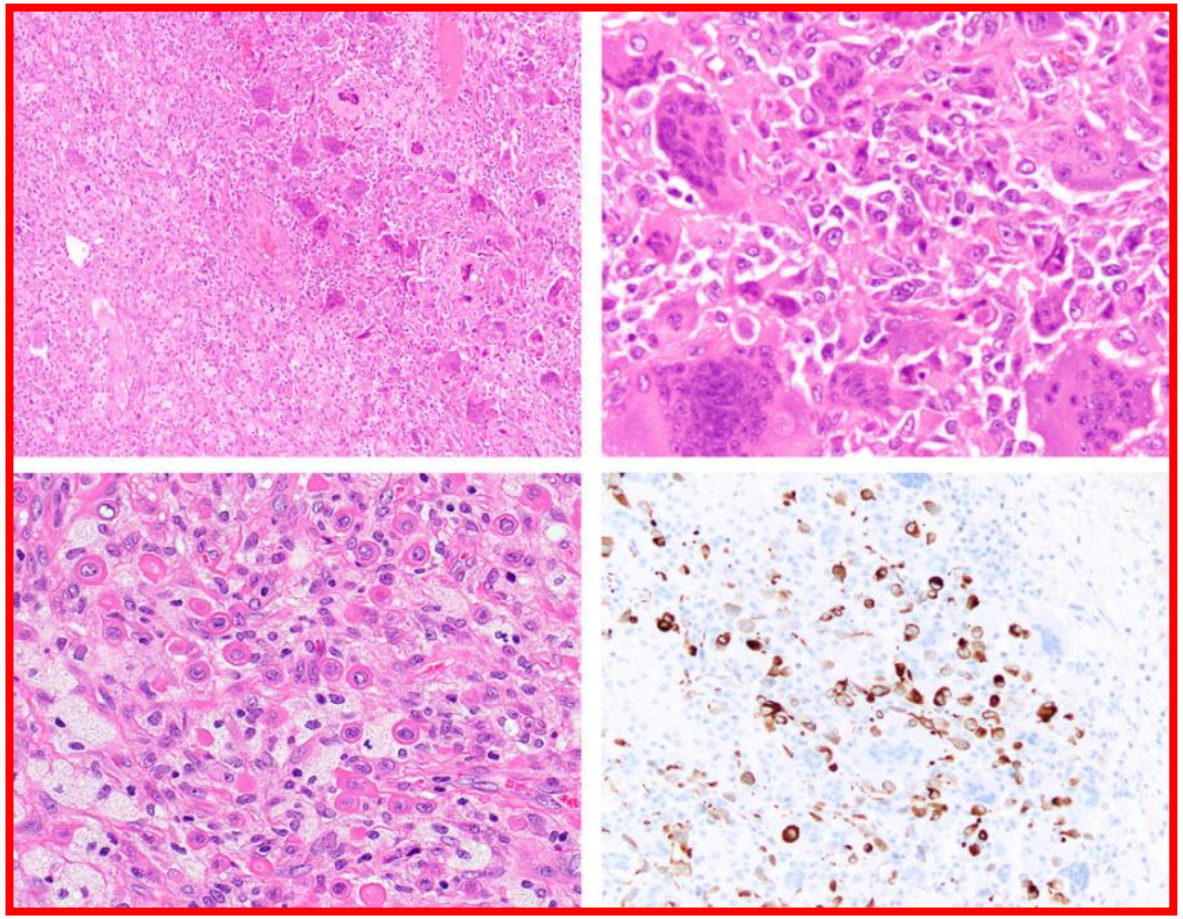
Received: 10 December 2020 / Revised: 20 February 2021 / Accepted: 23 February 2021 / Published online: 19 March 2021

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

- Fritchie et al, recently described a novel subtype of GCT of soft tissue - "xanthogranulomatous epithelioid tumour"
- Like the *HMGA2::NCOR2* GCTs, these also show cytokeratin expression and show a female predilection, but they however occur equally in bone and soft tissues
- They have variable amounts of osteoclast-like giant cells and a show a sheet like proliferation of foamy histiocytes - hence the designation "xanthogranulomatous epithelial tumours"
- They also contain Touton type multinucleated giant cells and chronic inflammatory cells
- They may have foci of necrosis and cholesterol clefts
- On high power, they show clusters of cytologically atypical epithelioid cells, some with squamoid cytoplasmic features
- The epithelioid cells are positive for broad spectrum cytokeratins and occasionally for HMWCK with retention of INI-1 and SMARCA4 expression
- The genetics of these tumour remains unknown

Mod. Pathol. 2020; 33; 1889–1895



Histopathology. 2022 Jan;80(1):54-75

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	-/+	-	-	+/-	-	+	+	-	-

EWSR1::SMAD3 Rearranged Fibroblastic Tumour

Novel *EWSR1-SMAD3* Gene Fusions in a Group of Acral Fibroblastic Spindle Cell Neoplasms

Yu-Chien Kao, MD, Uta Flucke, MD, PhD,† Astrid Eijkelenboom, PhD,† Lei Zhang, MD,‡ Yun-Shao Sung, MSc,‡ Albert J.H. Suurmeijer, MD, PhD,§ and Cristina R. Antonescu, MD‡*

Abstract: Benign/low-grade fibroblastic tumors encompass a broad spectrum of tumors with different morphologies and molecular genetic abnormalities. However, despite significant progress in recent genomic characterization, there are still tumors in this histologic spectrum that are difficult to classify, lacking known molecular characteristics. Triggered by a challenging congenital spindle cell neoplasm arising in the heel of a 1-year-old boy, we applied RNA sequencing for genetic discovery and identified a novel *EWSR1-SMAD3* gene fusion. On the basis of the index case superficial acral location and fibroblastic appearance with a nonspecific immunophenotype, we searched our files for similar cases and screened them by fluorescence in situ hybridization for these abnormalities. Thus an identical *EWSR1-SMAD3* fusion was identified in 2 additional spindle cell tumors with similar clinicopathologic features. Both cases occurred in the feet of adult women (58 and 61 y old) and were characterized by distinctive nodular growth with zonation pattern of peripheral hypercellular areas arranged in short fascicles, transitioning to hypocellular central areas of hyalinization and infarction. Focal stippled calcification in the collagenous area was present in 1 case. All 3 tumors had similar immunoprofiles, being negative for SMA, CD34, CD31, and S100, but showing consistent ERG positivity of uncertain significance. Follow-up information was available in 2 patients who developed local recurrences after incomplete initial excisions, at 5 and 14 months, respectively. None developed metastatic disease. In summary, we report a group of locally recurrent superficial acral tumors, characterized by bland spindle cell fascicular growth, occasional zonation pattern, ERG

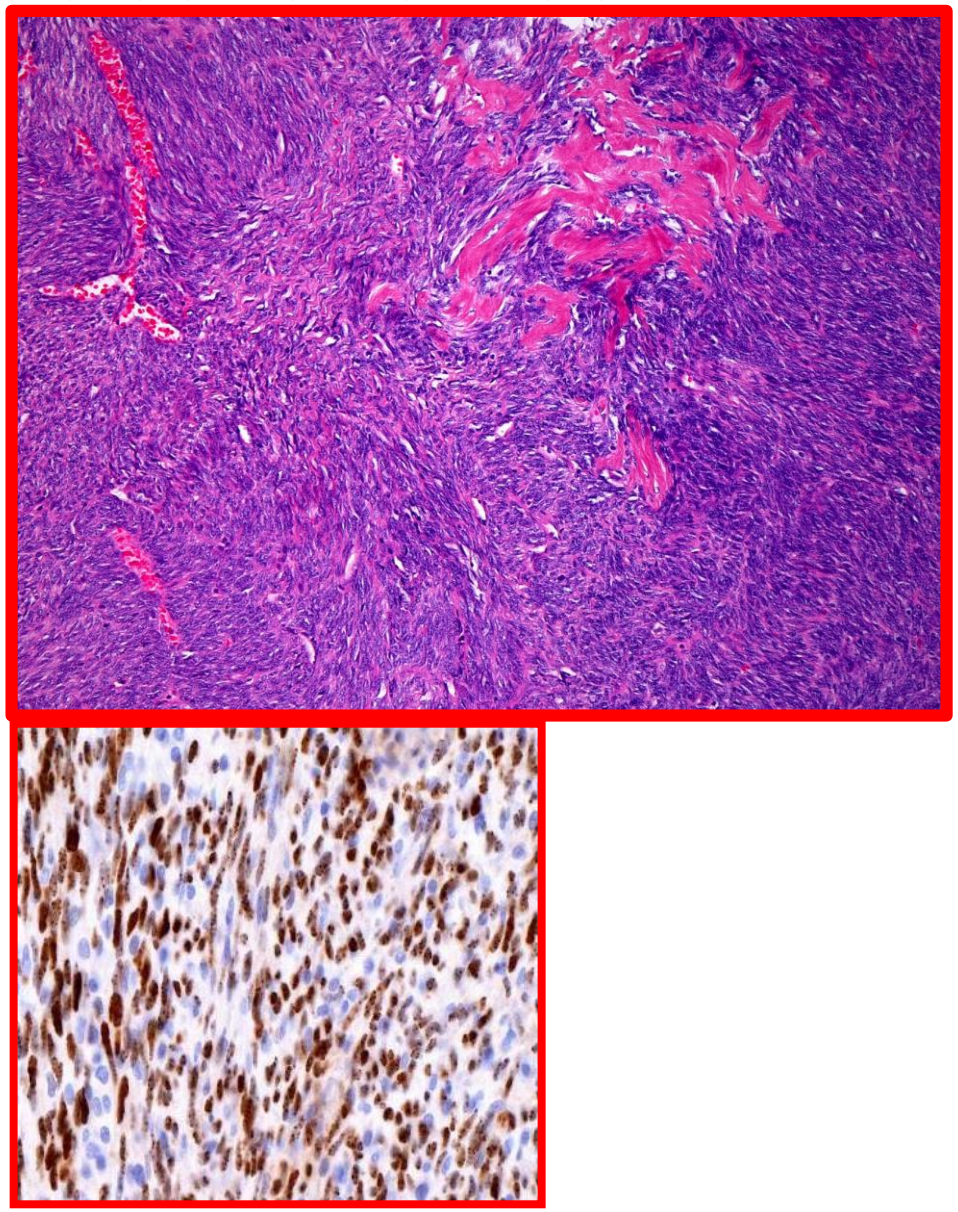
Key Words: EWSR1, SMAD3, ERG, spindle cell tumor, fibroblastic tumor, acral

(*Am J Surg Pathol* 2018;42:522–528)

Benign/low-grade fibroblastic tumors are a diverse group of tumors with overlapping morphologies and clinical presentations that can pose diagnostic challenge due to their rarity and lack of a specific immunoprofile. In recent years, with the advent of next-generation sequencing, novel genetic alterations, including mutations or recurrent gene fusions, have been unraveled, increasingly refining the classification of fibroblastic and myofibroblastic neoplasms. Few examples in this morphologic spectrum with newly described genetic abnormalities include: calcifying aponeurotic fibroma showing recurrent *FN1-EGF* fusions,[1] fibrous hamartoma of infancy with *EGFR* internal tandem duplications,[2] myofibroma/myopericytoma with *PDGFRB* mutations,[3,4] and lipofibromatosis-like neural tumors with recurrent *NTRK1*-related gene fusions.[5] Triggered by a challenging congenital fibroblastic lesion, which did not fit in any of the known pathologic entities, we have applied whole transcriptome sequencing for further genomic characterization. Thus a novel *EWSR1-SMAD3* fusion was identified and found to be recurrent in 2 additional cases with similar acral clinical presentation and immunoprofile, suggesting the possibility of a new subtype of fibroblastic lesions with propensity for local recurrence.

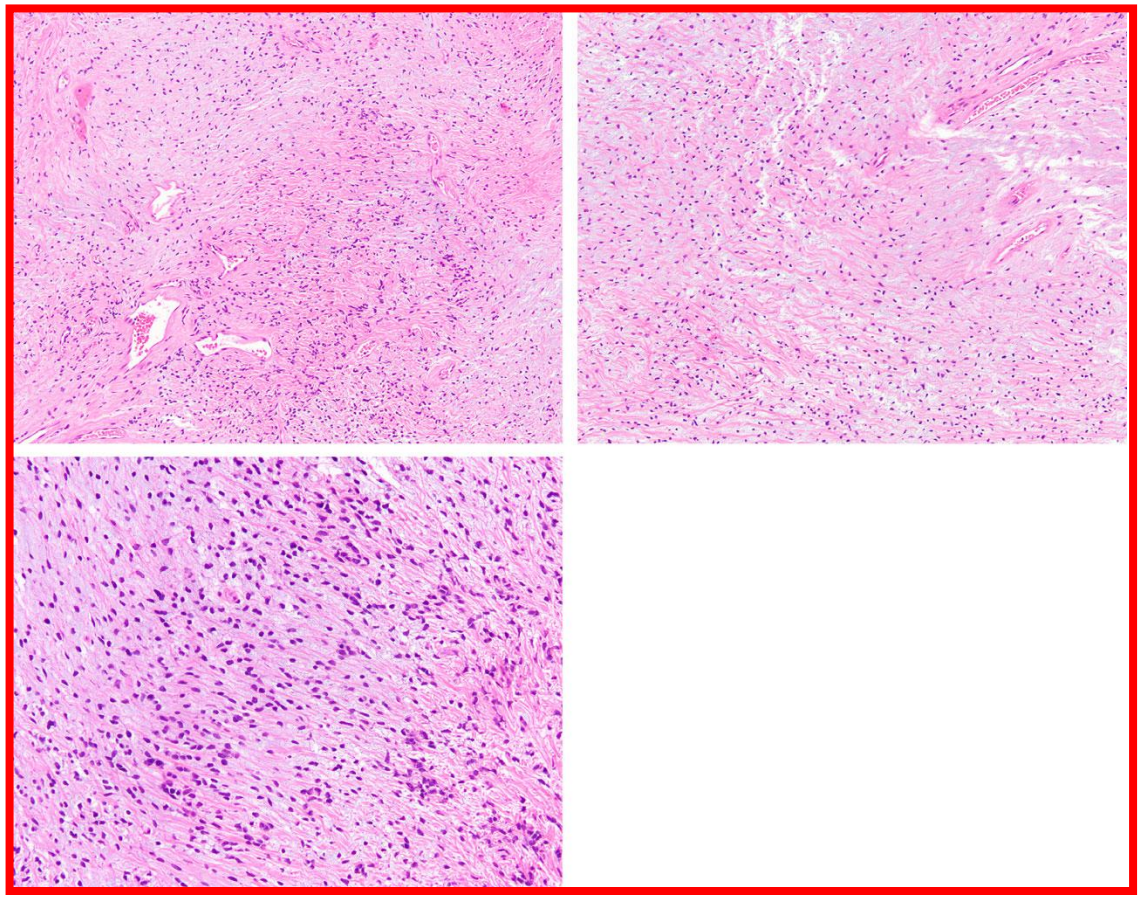
EWSR1::SMAD3 Rearranged Fibroblastic Tumour

- Rare
- Locally aggressive
- Wide age range
- M<F – M:F=1:4
- Extremities –acral sites
- Cellular spindle cell proliferation and paucicellular/acellular hyalinised areas
- Diffusely positive for ERG
- Focal to patchy staining for SATB2



“*PRRX::NCOAx* rearranged fibroblastic tumour”

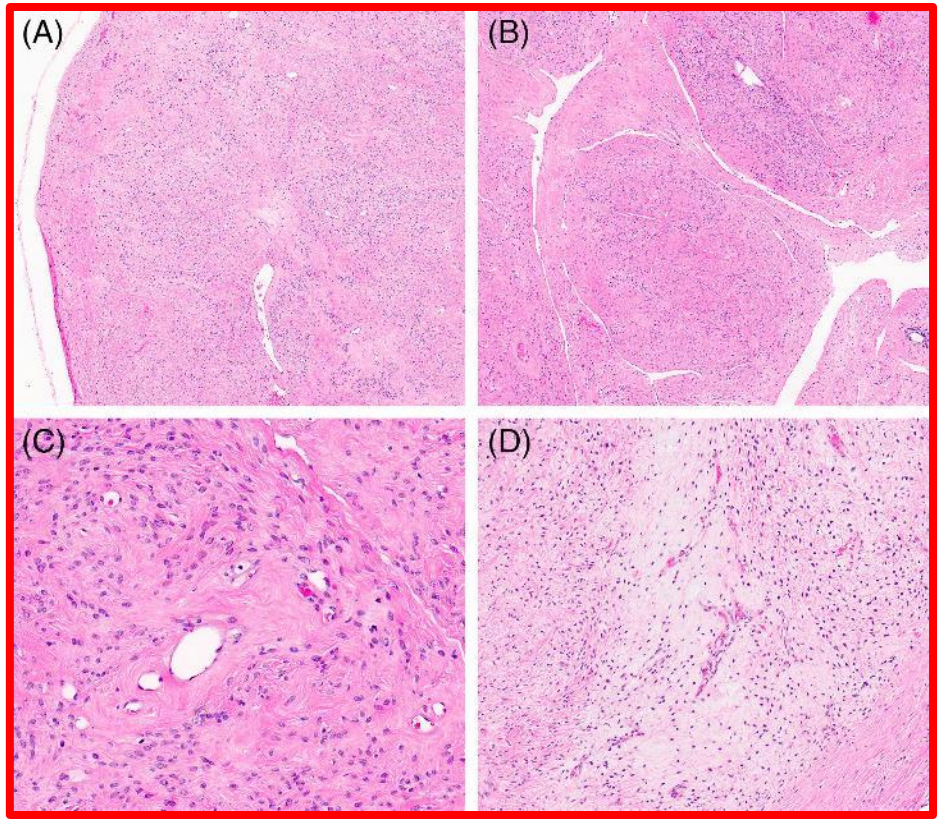
- Most commonly affects middle-aged women
- Located in subcutis
- Nodular, well-circumscribed & predominantly hypocellular
- Prominent irregular, gaping, crescent shaped or staghorn-like vessels (similar to those seen in nasal angiofibromas and SFTs)
- Cords and nests of round to ovoid cells in a predominantly hyalinised and focally myxoid stroma
- No significant cytological atypia
- Low mitotic count and no necrosis
- No specific immunophenotype - S100 &/or SOX10 focally positive in a subset of cases,
- Clinically benign (limited clinical follow-up and few cases reported so far)



Lacambra MD, et al. Genes Chromosom. Cancer 2019; 58; 705–712

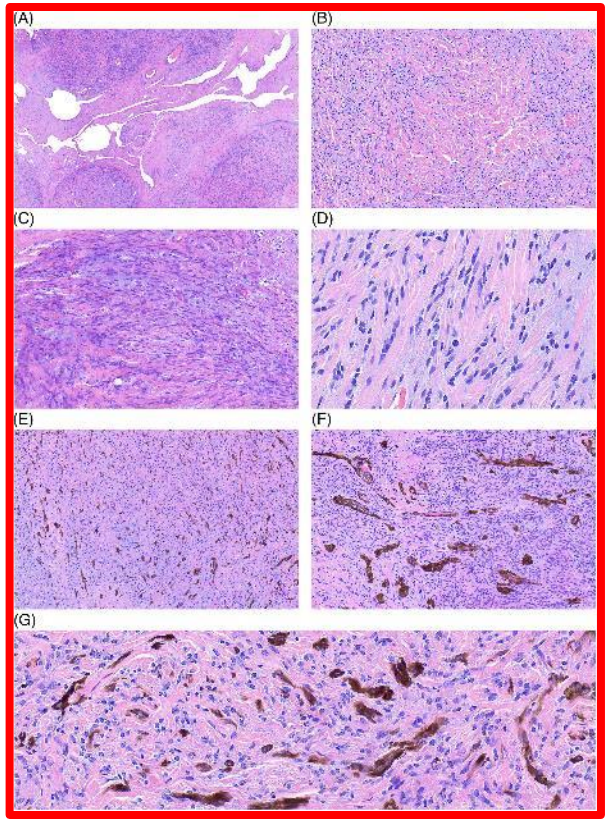
Histopathology. 2022 Jan;80(1):54-75

PRRX-NCOA1/2 rearrangement characterizes a distinctive fibroblastic neoplasm



Lacambra MD, et al. Genes Chromosom. Cancer 2019; 58; 705–712, DOI: (10.1002/gcc.22762)

Pigmented PRRX1::NCOA1-rearranged fibroblastic tumor: A rare morphologic variant of an emerging mesenchymal tumor



J Cutan Pathol, Volume: 49, Issue: 9, 802-807, DOI: (10.1111/cup.14262)

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


THANK YOU