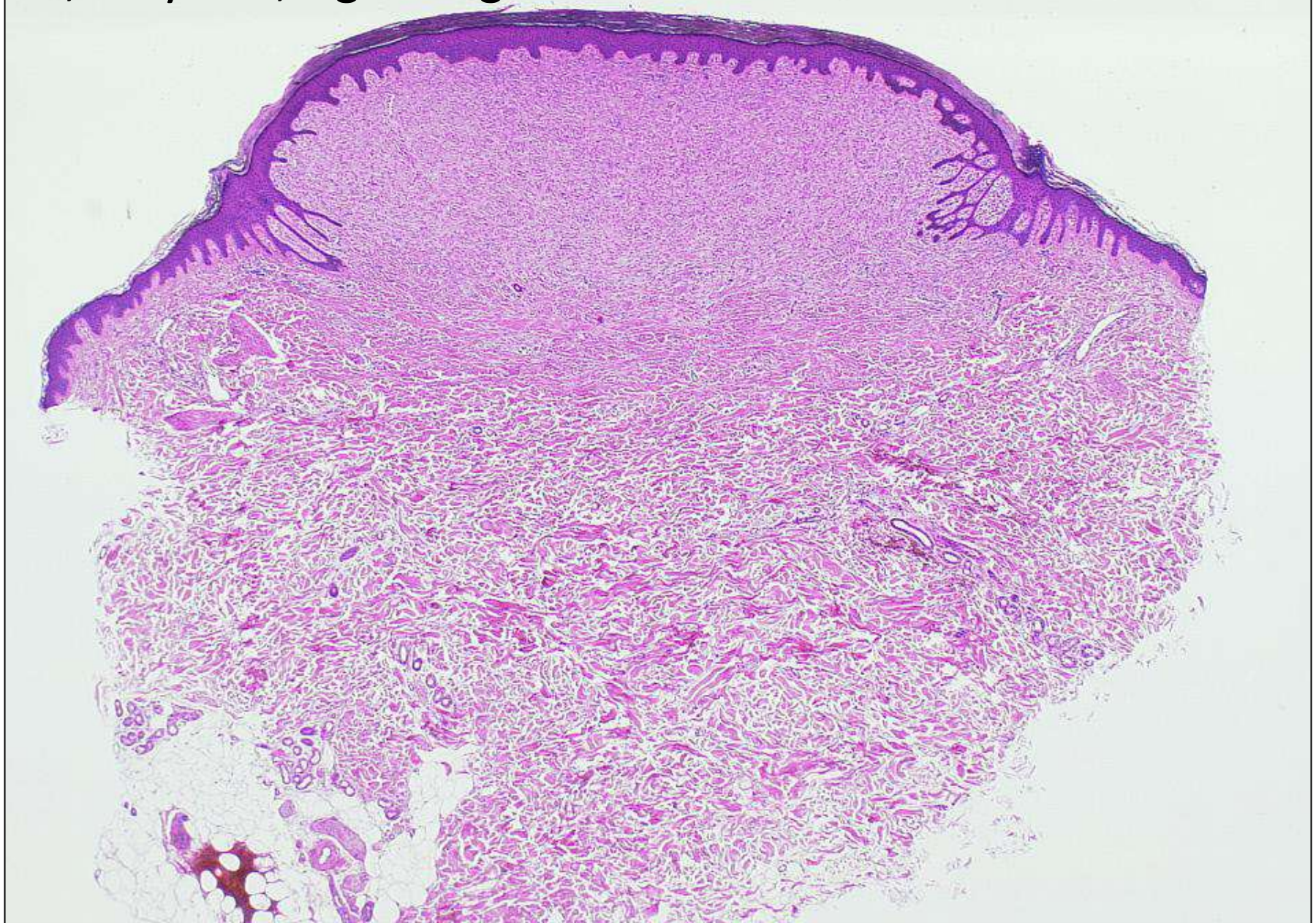
Slide Seminar

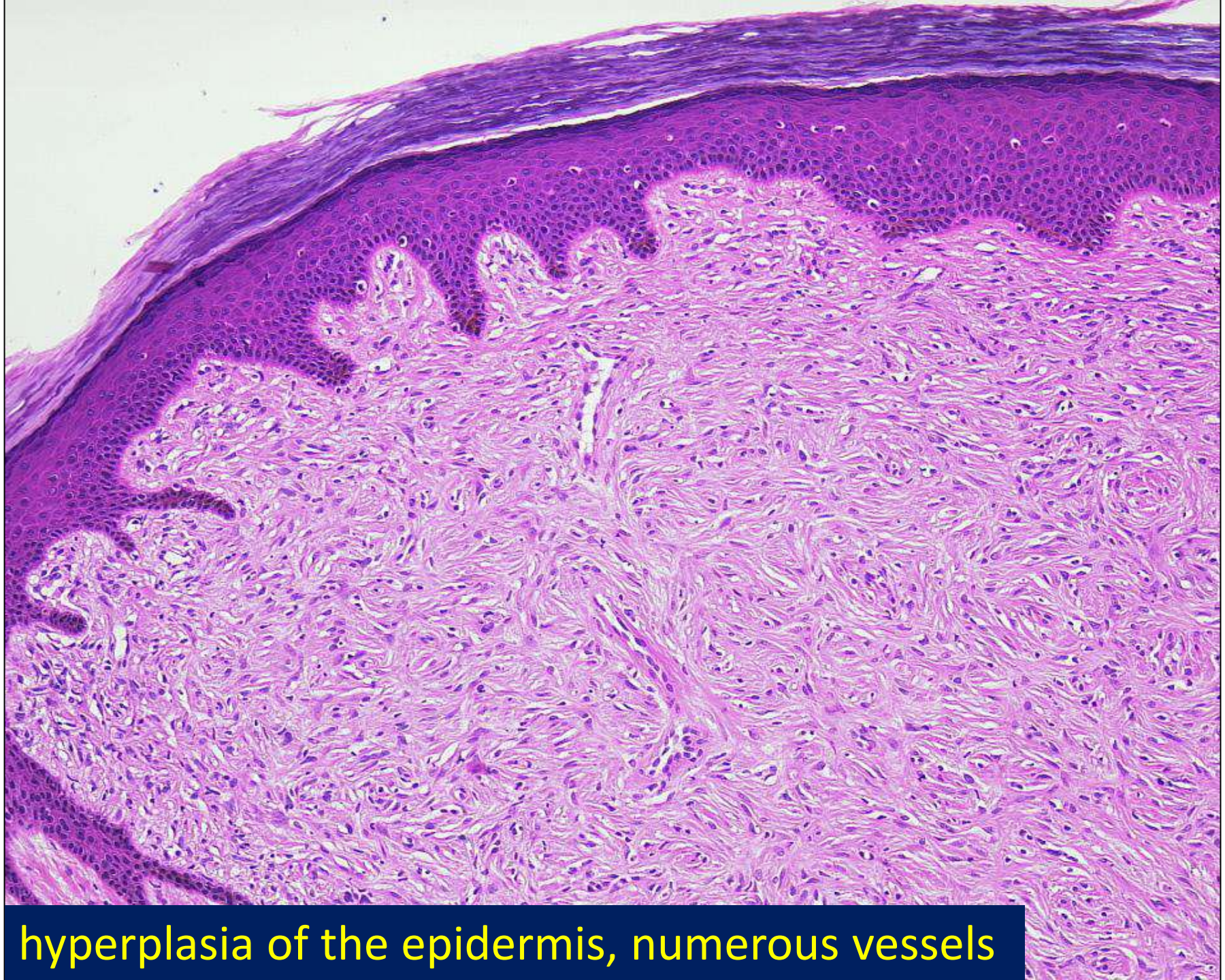
Dr. Thomas Mentzel, Friedrichshafen

MVZ Dermatopathologie Friedrichshafen / Bodensee PartG

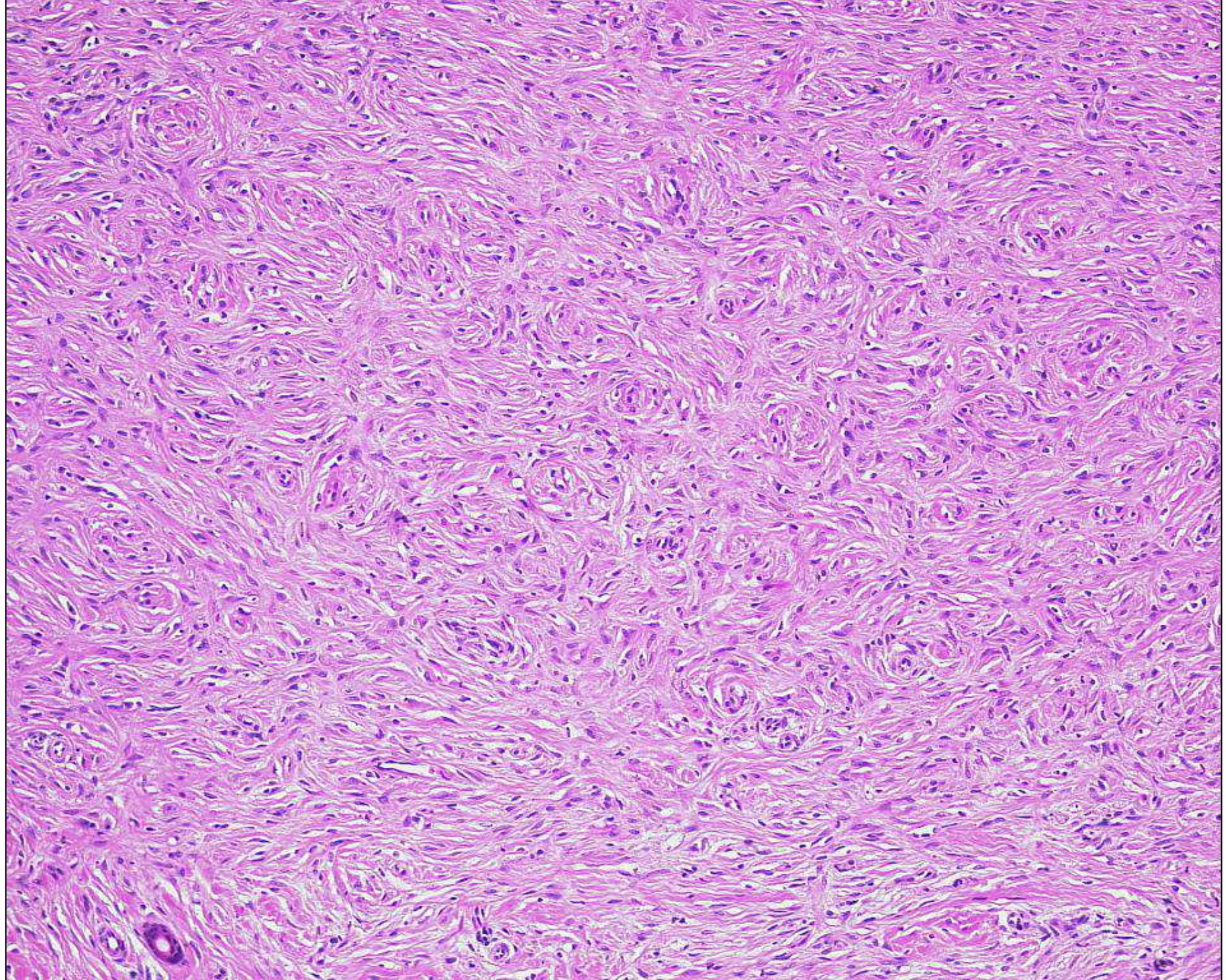
Case 1:

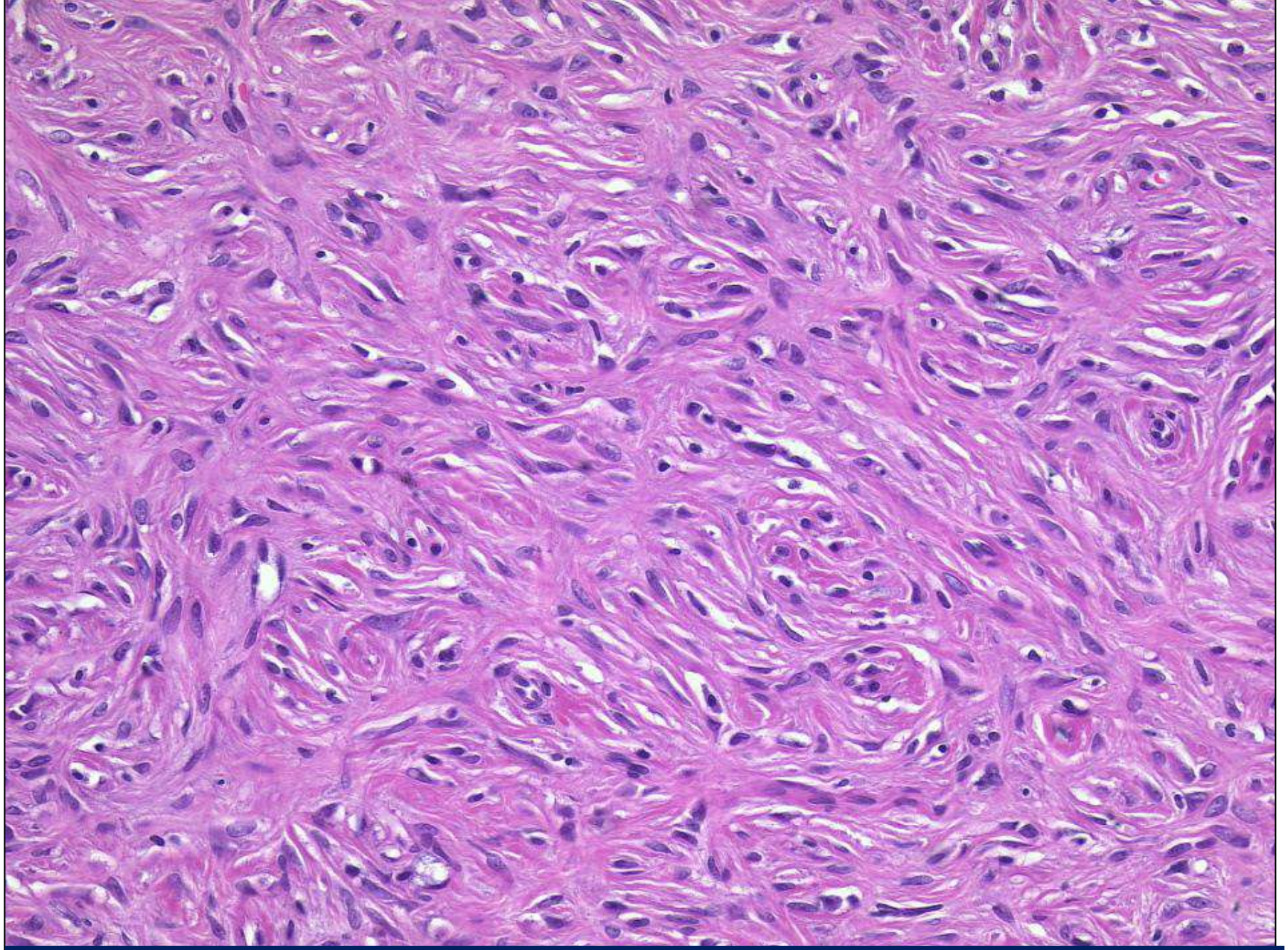
M, 55 years, right thigh



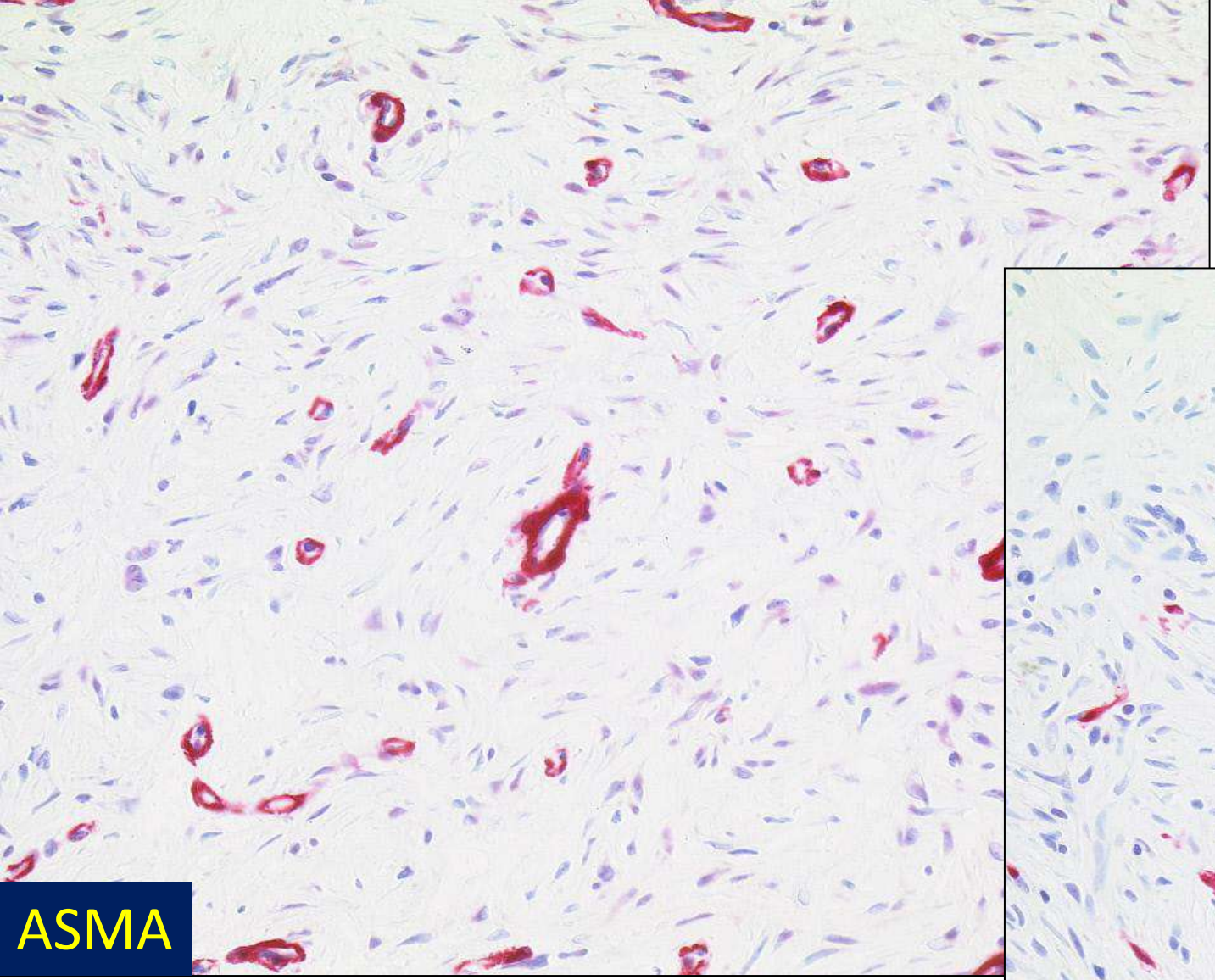


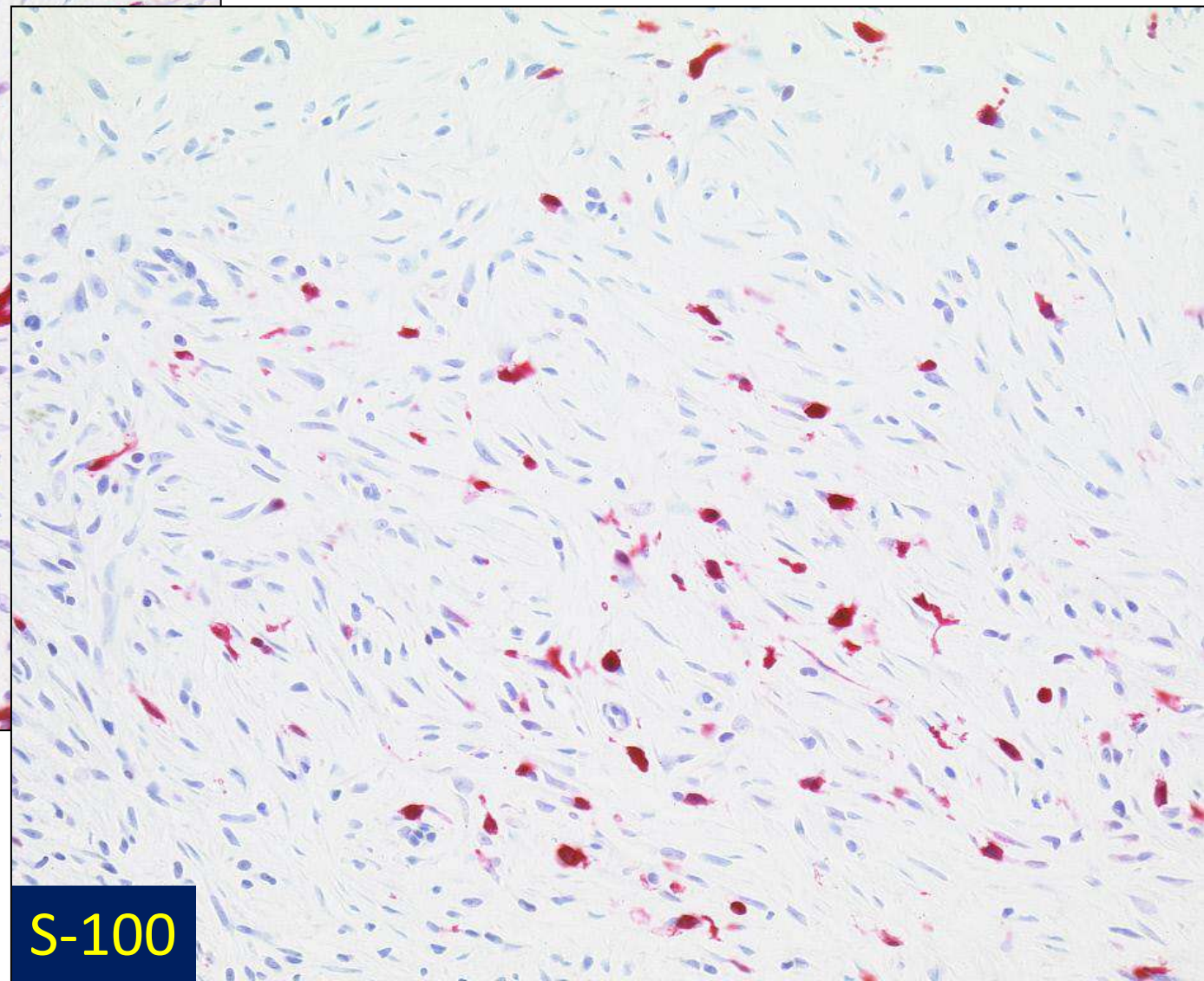
hyperplasia of the epidermis, numerous vessels

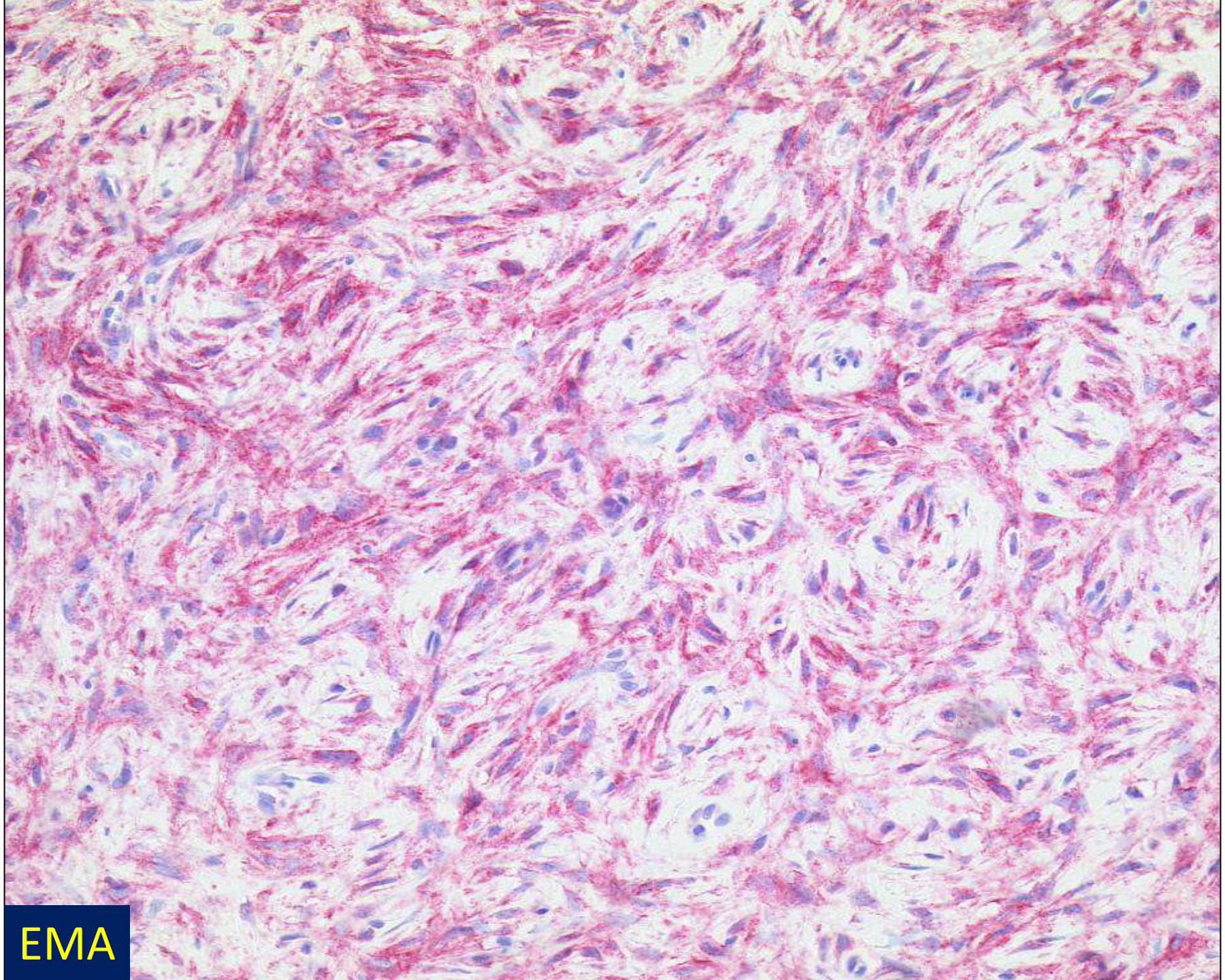


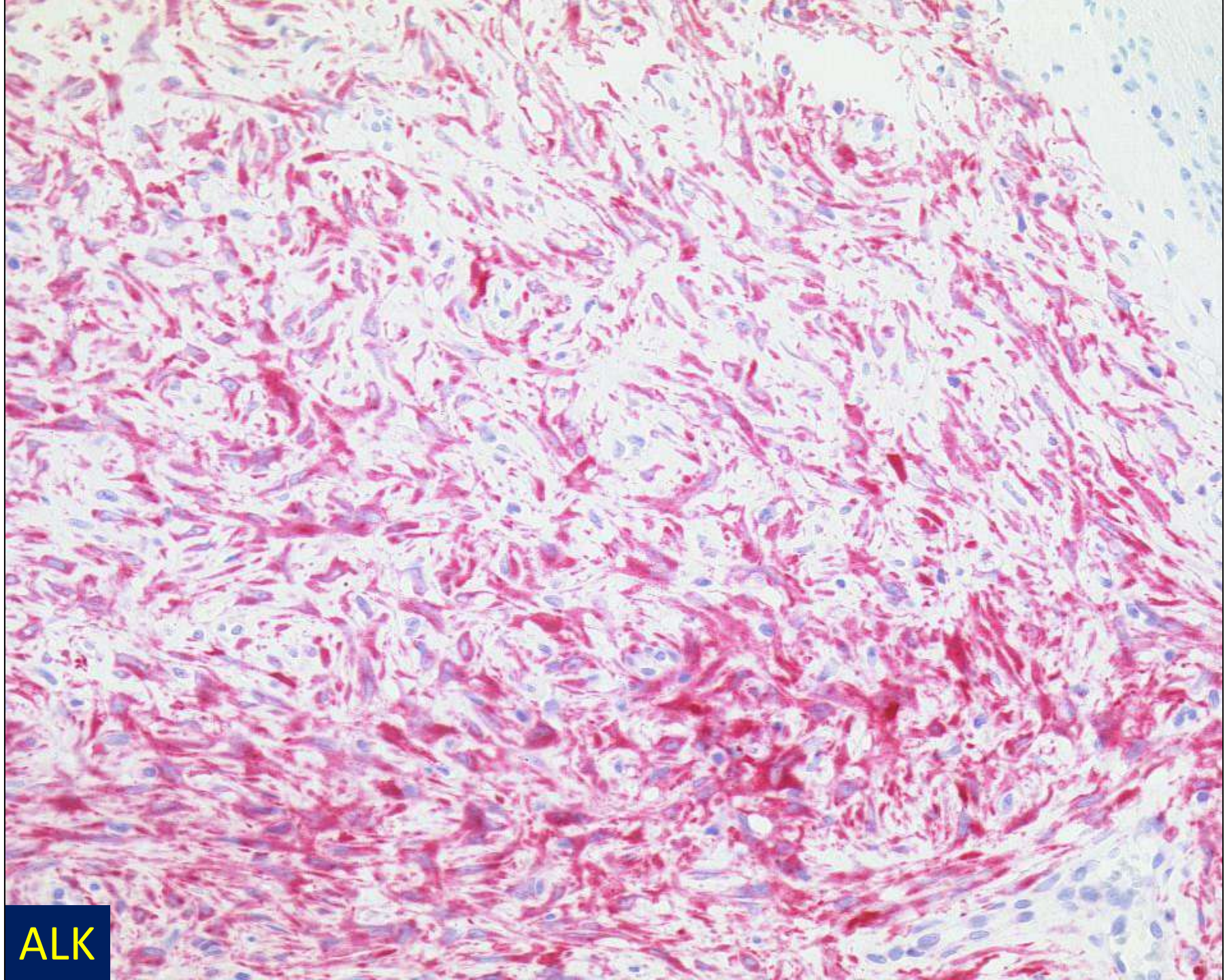


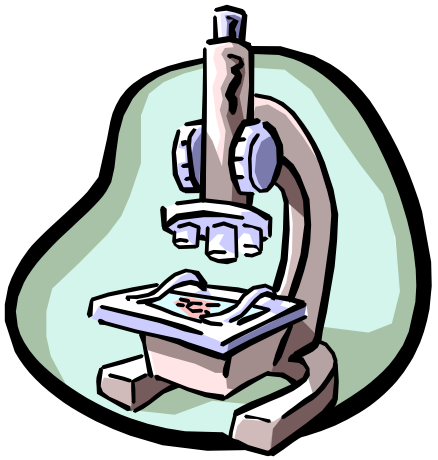
admixture of round / epithelioid and plump spindled cells


ASMA


S-100


EMA


ALK



Diagnosis Case 1

„epithelioid“ benign fibrous histiocytoma

Jones EW et al. Epithelioid cell histiocytoma: a new entity.
Br J Dermatol 1989; 120: 195-195

middle-aged adults, 11 F, 8 M, lower limbs > everywhere
asymptomatic solitary, polypoid, red, cutaneous nodule
epidermal collarette, round cells with abundant eosinophilic cytoplasm
vesicular nuclei, small nucleolus, binucleated cells
rarely transition to more spindle-shaped cells
DD: Spitz naevus, reticulohistiocytoma

Sing Gomez C et al. Epithelioid fibrous histiocytoma of skin: clinicopathological analysis of 20 cases of a poorly known entity. Histopathology 1994; 24: 123-129

12 M, 8 F, 7-80 years, local recurrence in 1 case
polygonal, rounded epithelioid tumour cells (> 50% of cells)
hyalinized collagen, many blood vessels
subcutaneous involvement in 2 cases
forms a spectrum with ordinary dermatofibroma

Jedrych J et al. Epithelioid cell histiocytoma of the skin with clonal ALK gene rearrangement resulting in *VCL-ALK* and *SQSTM1-ALK* gene fusions
Br J Dermatol 2015; 172: 1427-1429

Doyle LA et al. *ALK* rearrangement and overexpression in epithelioid fibrous Histiocytoma. Mod Pathol 2015; 28: 904-912

33 epithelioid fibrous histiocytoma (29/33 ALK +, 13 *ALK* rearrangement)
41 fibrous histiocytoma (ALK -), 10 myoepithelioma (ALK -), 5 AFX (ALK -)

Dickson BC et al. Epithelioid fibrous histiocytoma: molecular characterization of *ALK* fusion partners in 23 cases. Mod Pathol 2018; 31: 753-762

SQSTM1::ALK (52%), *VCL::ALK* (30%), *DCTN1::ALK* (1), *PPFIBP1::ALK* (1), *SPECC1L::ALK* (1), *ETV6::ALK* (1, nuclear ALK expression)

Kazakov DV et al. *ALK* gene fusions in epithelioid fibrous histiocytoma: a study of 14 cases, with new histopathological findings. Am J Dermatopathol 2018; 40: 805

SQSTM1::ALK (3), *VCL::ALK* (3), *TMP3::ALK* (2), *PRKAR2A::ALK* (1), *MLPH::ALK* (1), *EML4::ALK* (1), no correlation to morphology!

Mansour B et al. Epithelioid fibrous histiocytoma: three diagnostically challenging cases with novel *ALK* gene fusions, unusual storiform growth pattern, and a prominent spindled morphology. Virchows Archiv 2022; 481: 751-757

prominent spindle cell proliferation, storiform growth pattern

ALK +, *AP3D1::ALK, COL1A1::ALK, LRRFIP2::ALK*

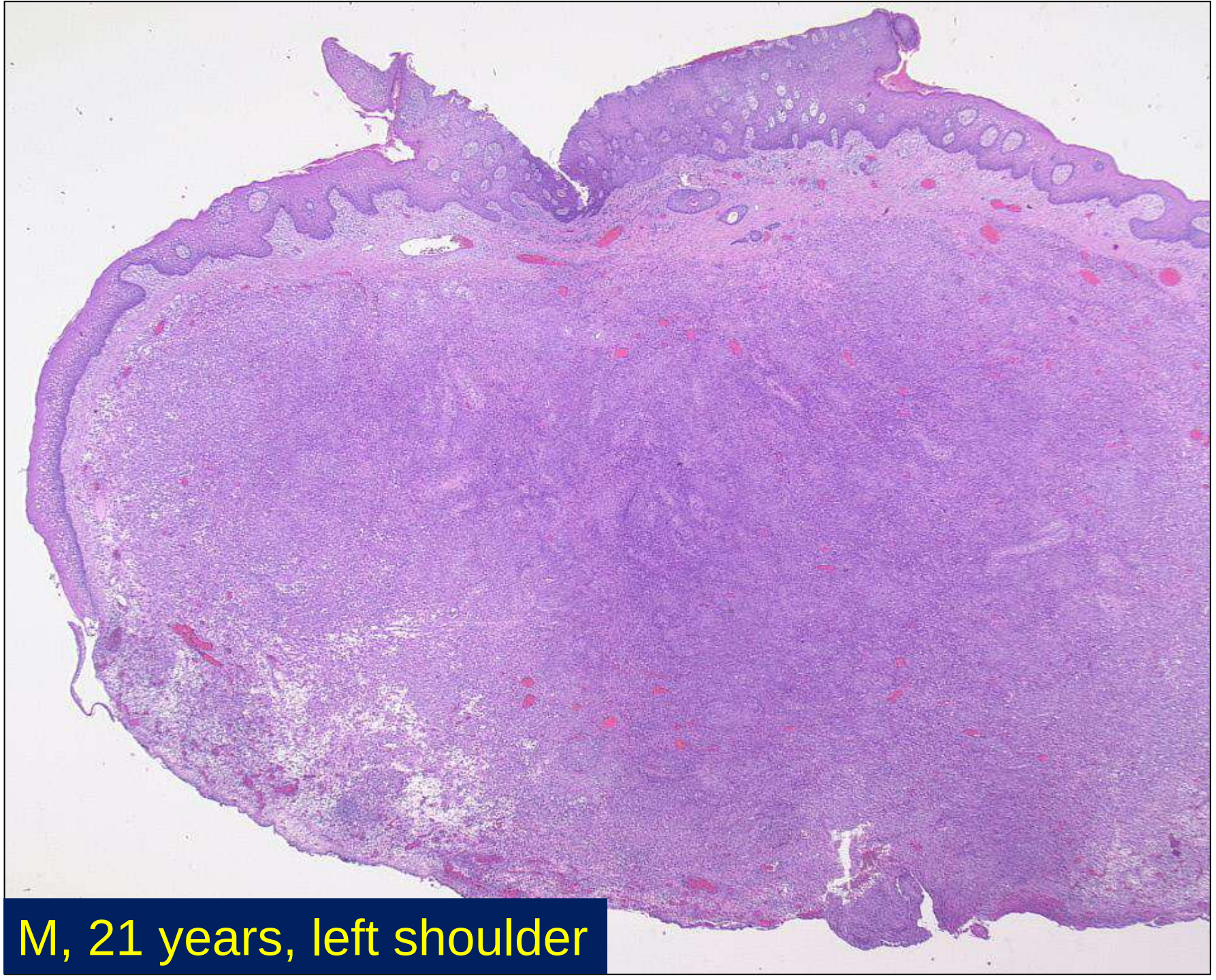
Kazlouskaya V et al. Spindle cell variant of epithelioid cell histiocytoma (spindle cell histiocytoma) with *ALK* fusions: case series and review of the literature
J Cutan Pathol 2021; 48: 837-841

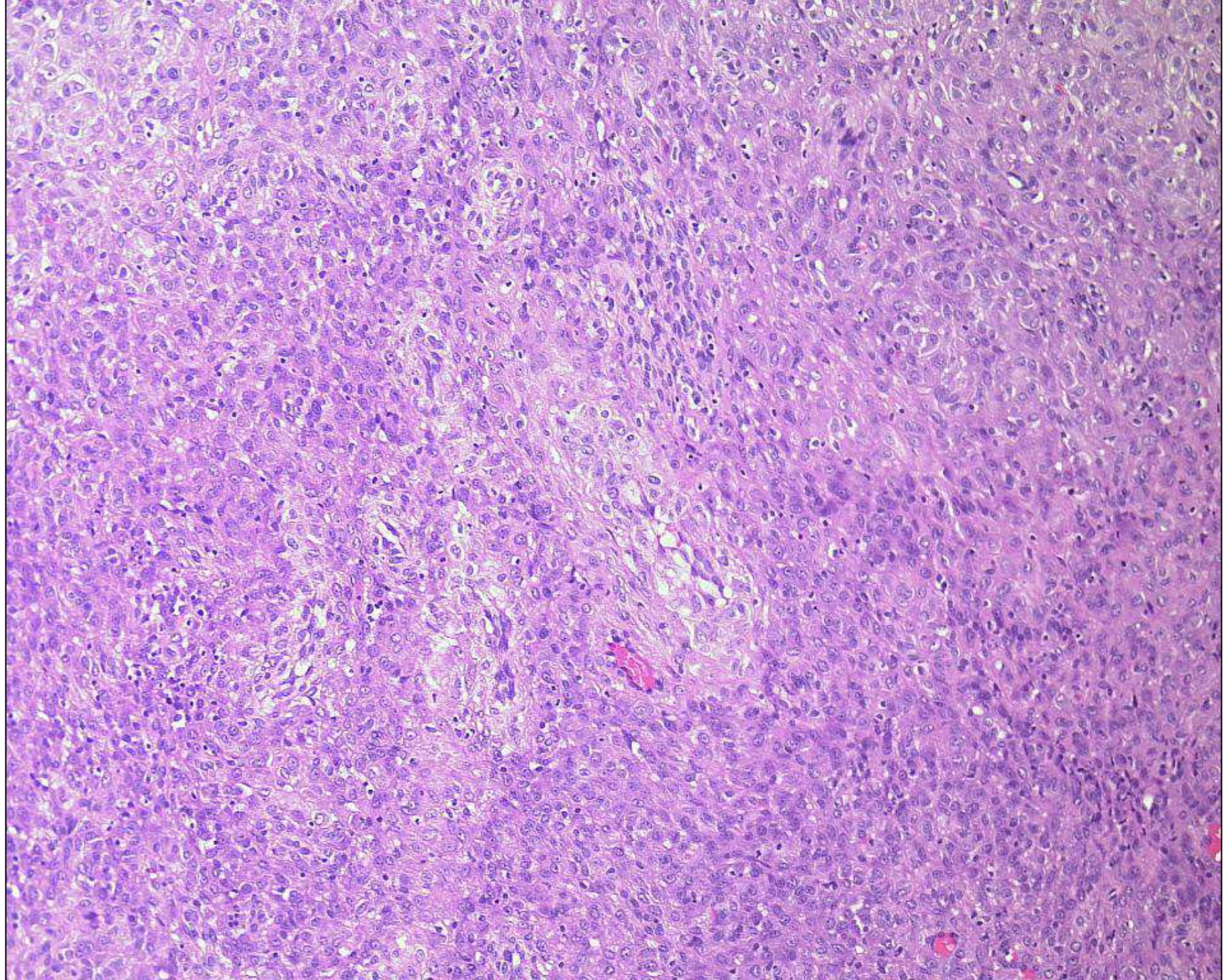
3 F, 25-55 years

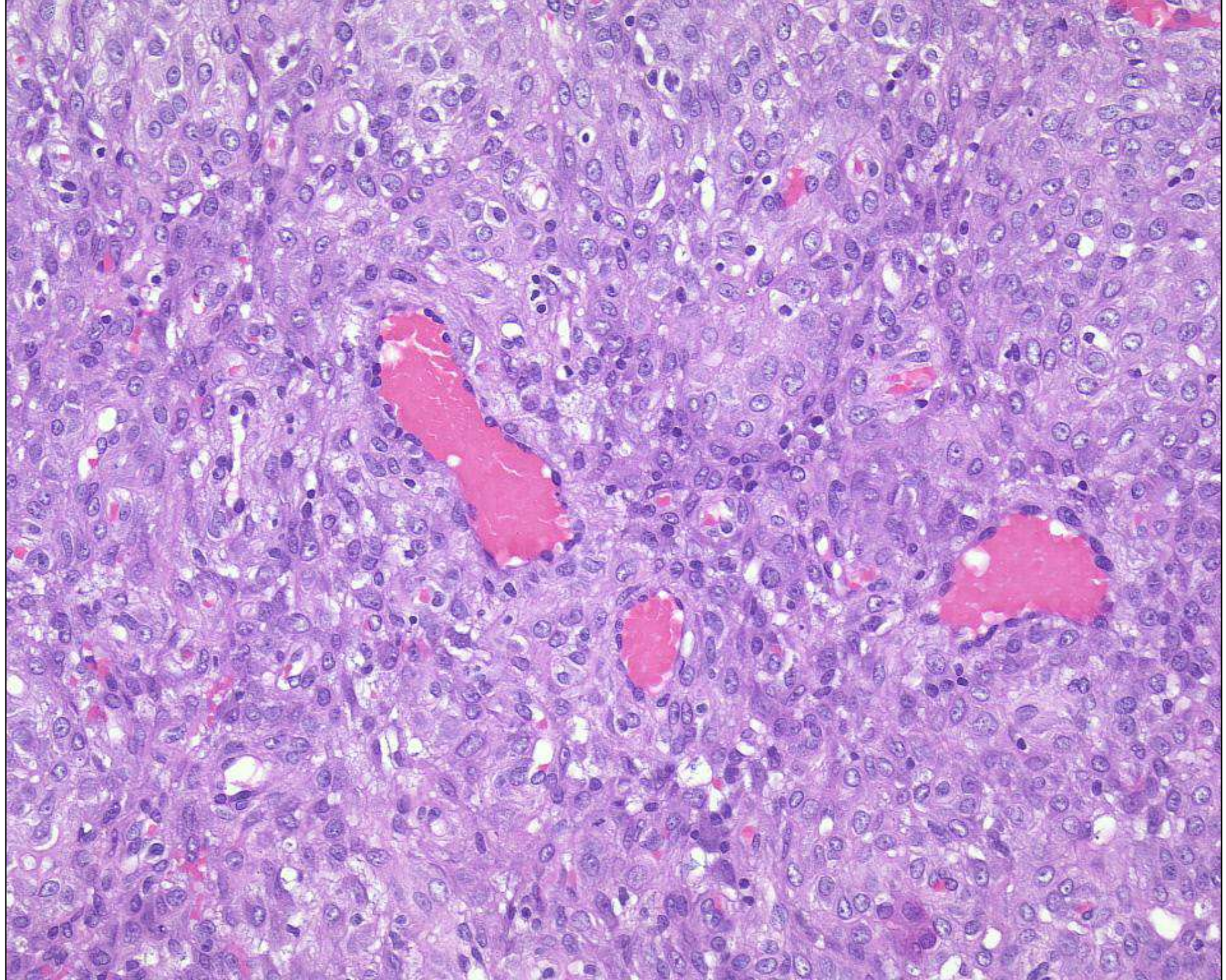
exclusively spindle cell morphology, strong ALK expression

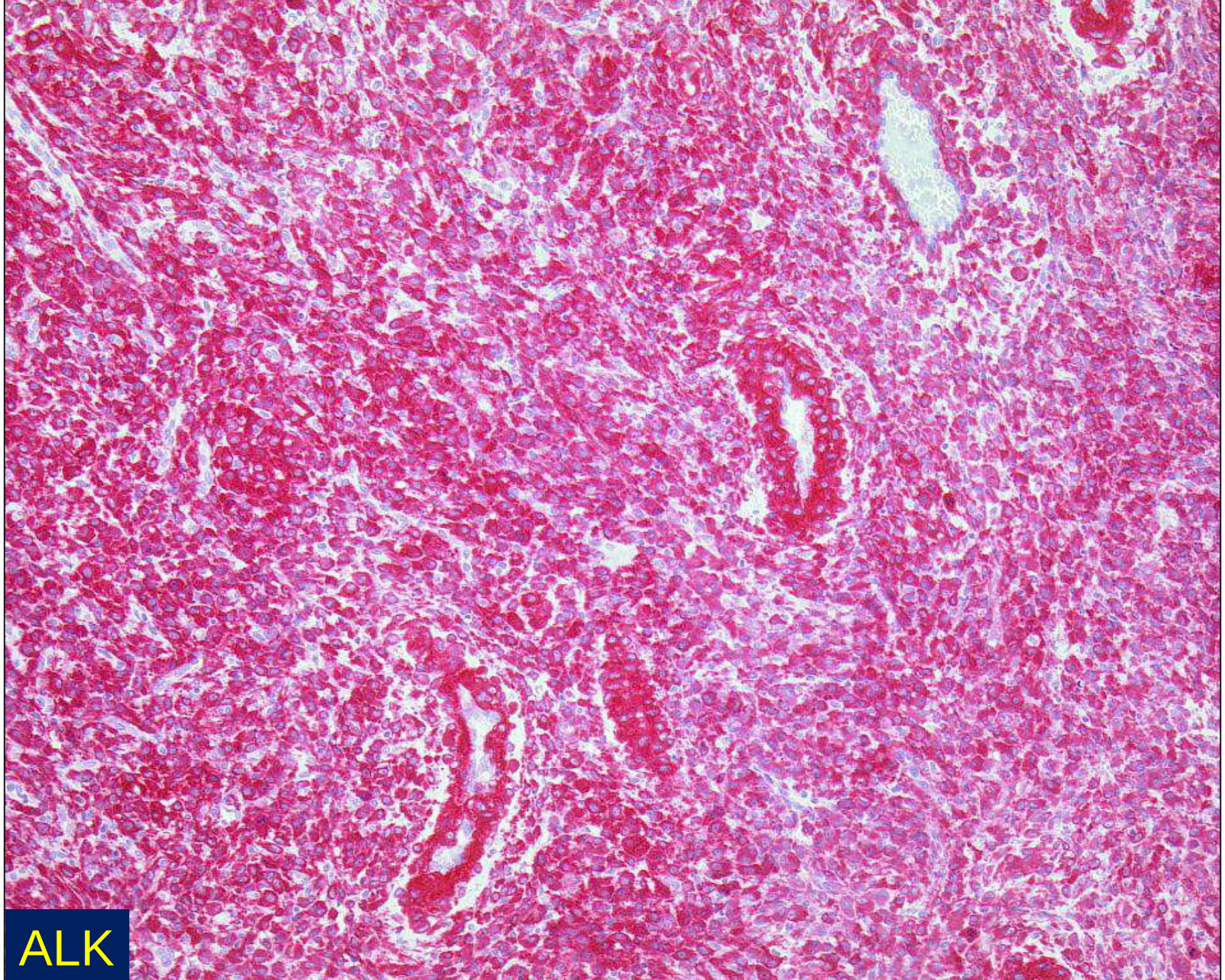
ALK rearangement (3), *DCTN1::ALK* (2)

Russell-Goldman E et al. A novel fusion partner, SP100, drives nuclear dot localization of ALK in epithelioid fibrous histiocytoma. Am J Dermatopathol 2023; 45: 539-543


M, 21 years, left shoulder






ALK

Conclusions Case 1

epithelioid fibrous histiocytoma represents a distinct entity

morphological differences to classic dermatofibroma

exophytic, epithelial collarette, many vessels, perivascular growth

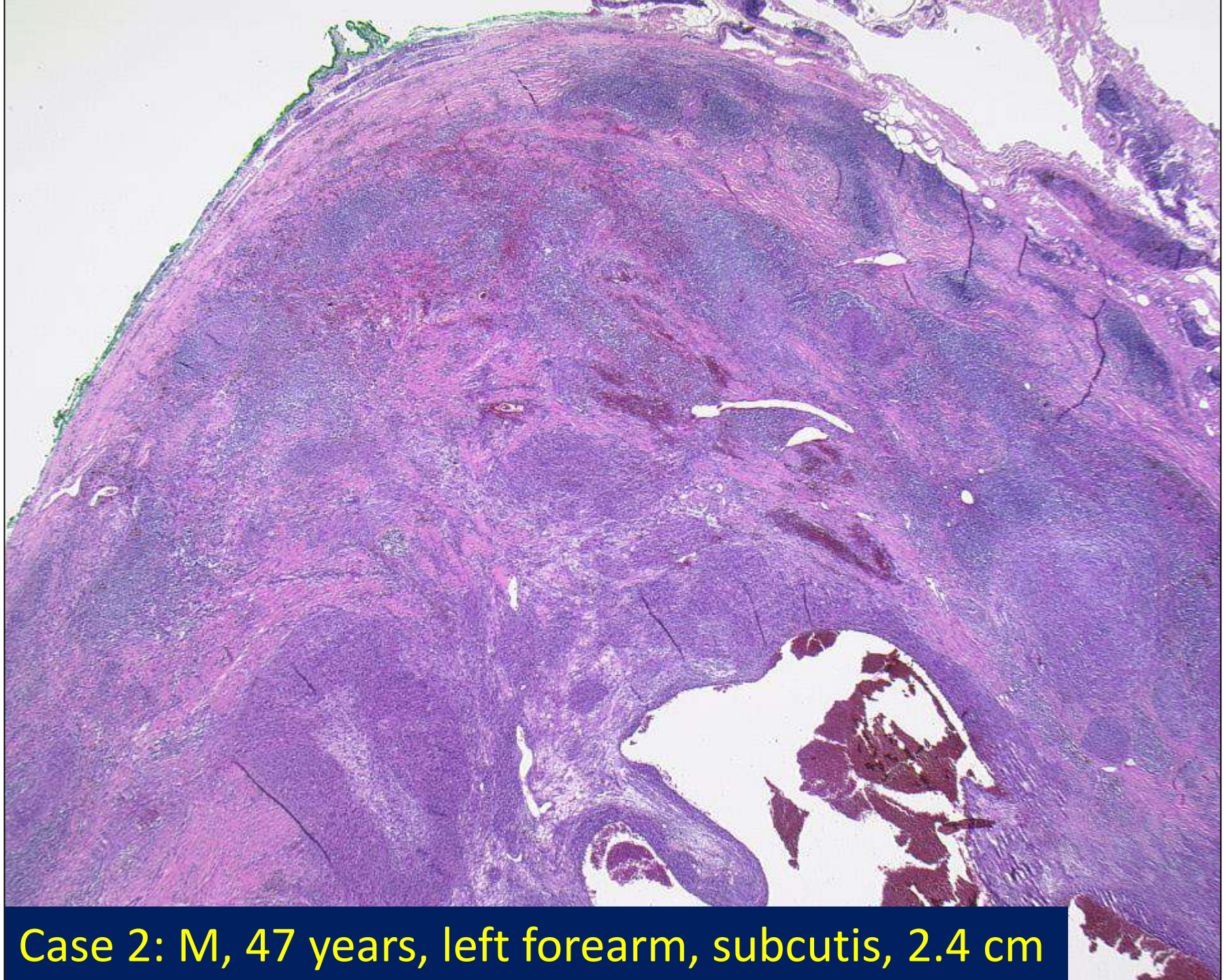
no entrapment, no multinucleated giant cells

strong ALK expression, often coexpression of EMA

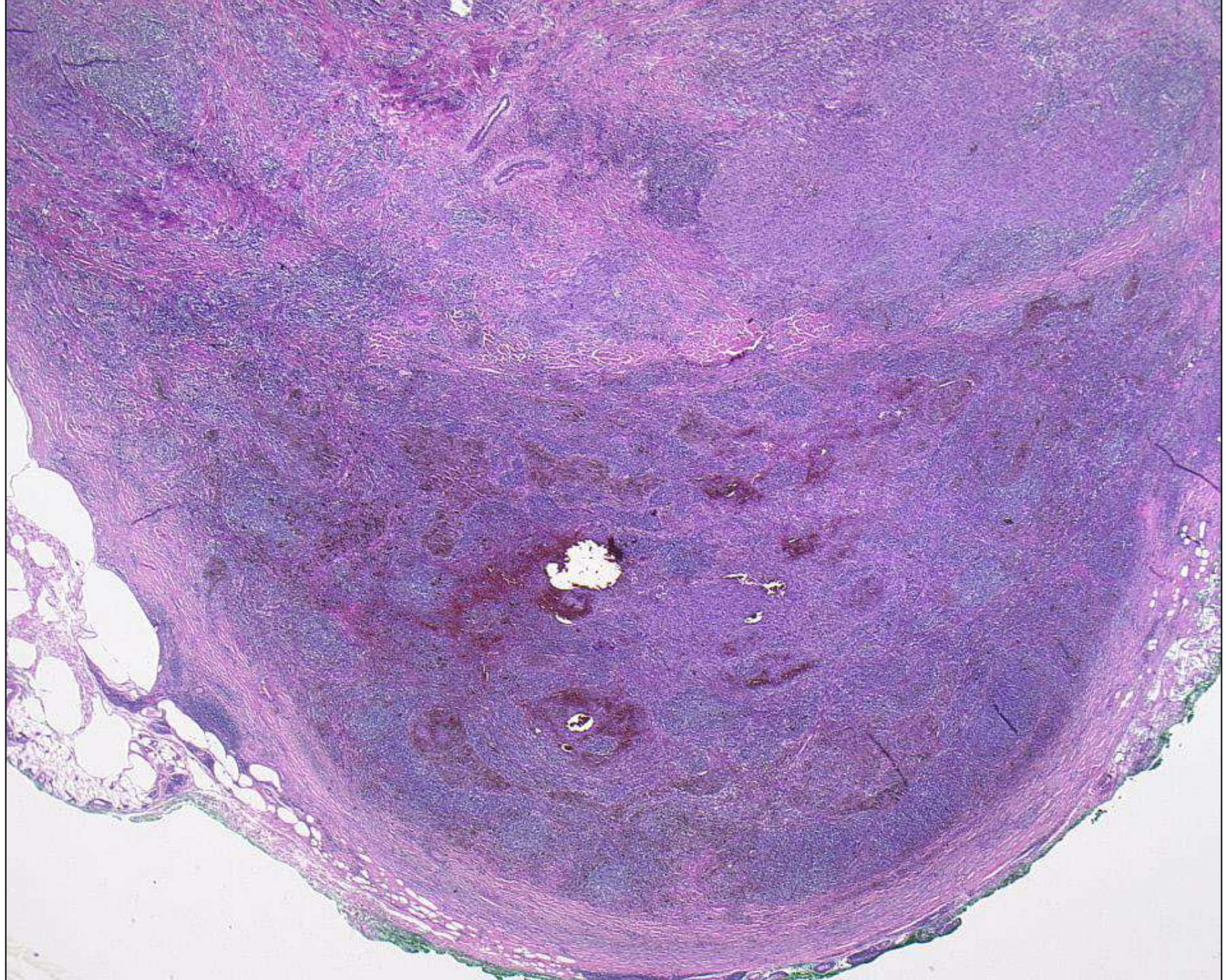
variable morphology

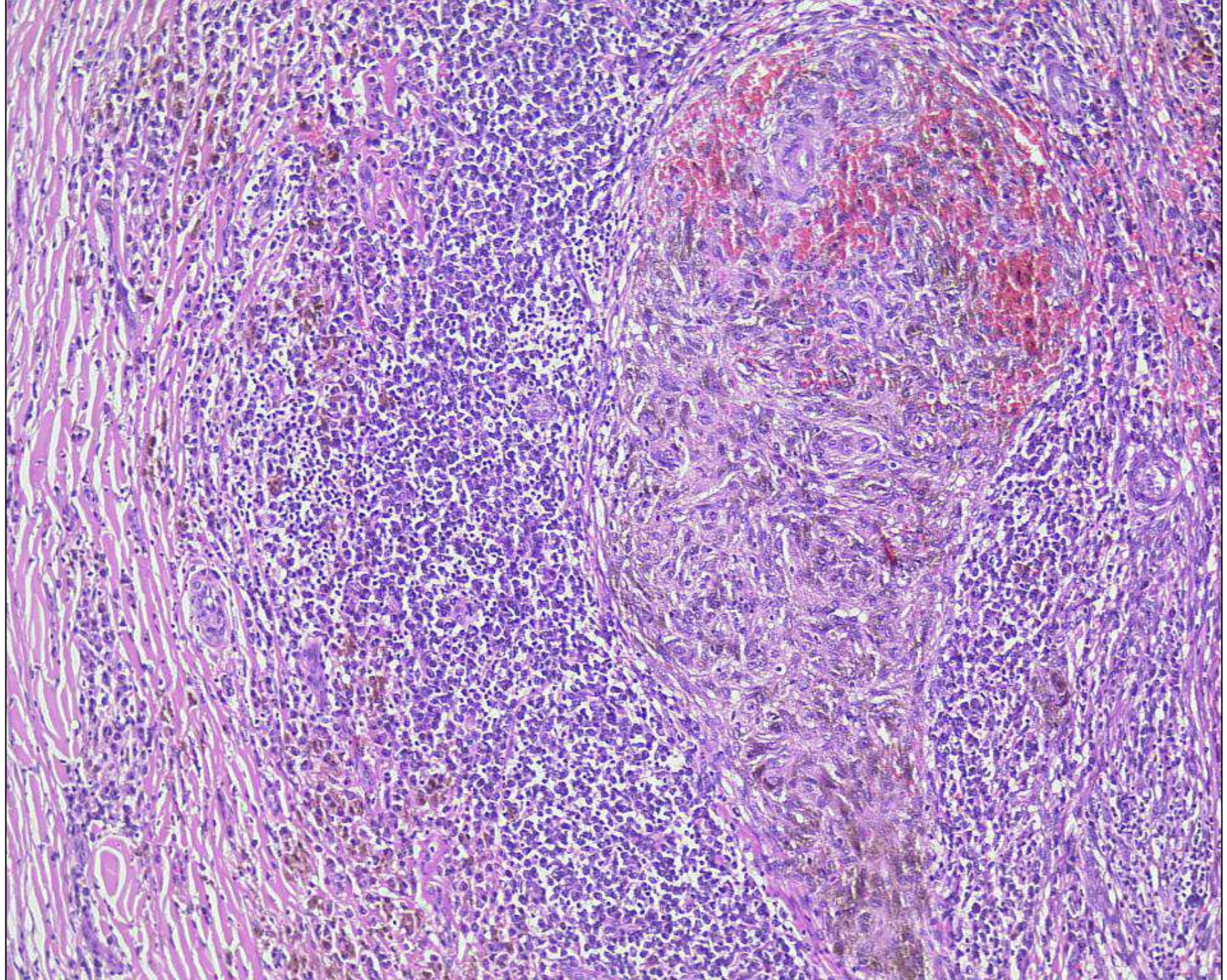
different fusion partners of *ALK* gene

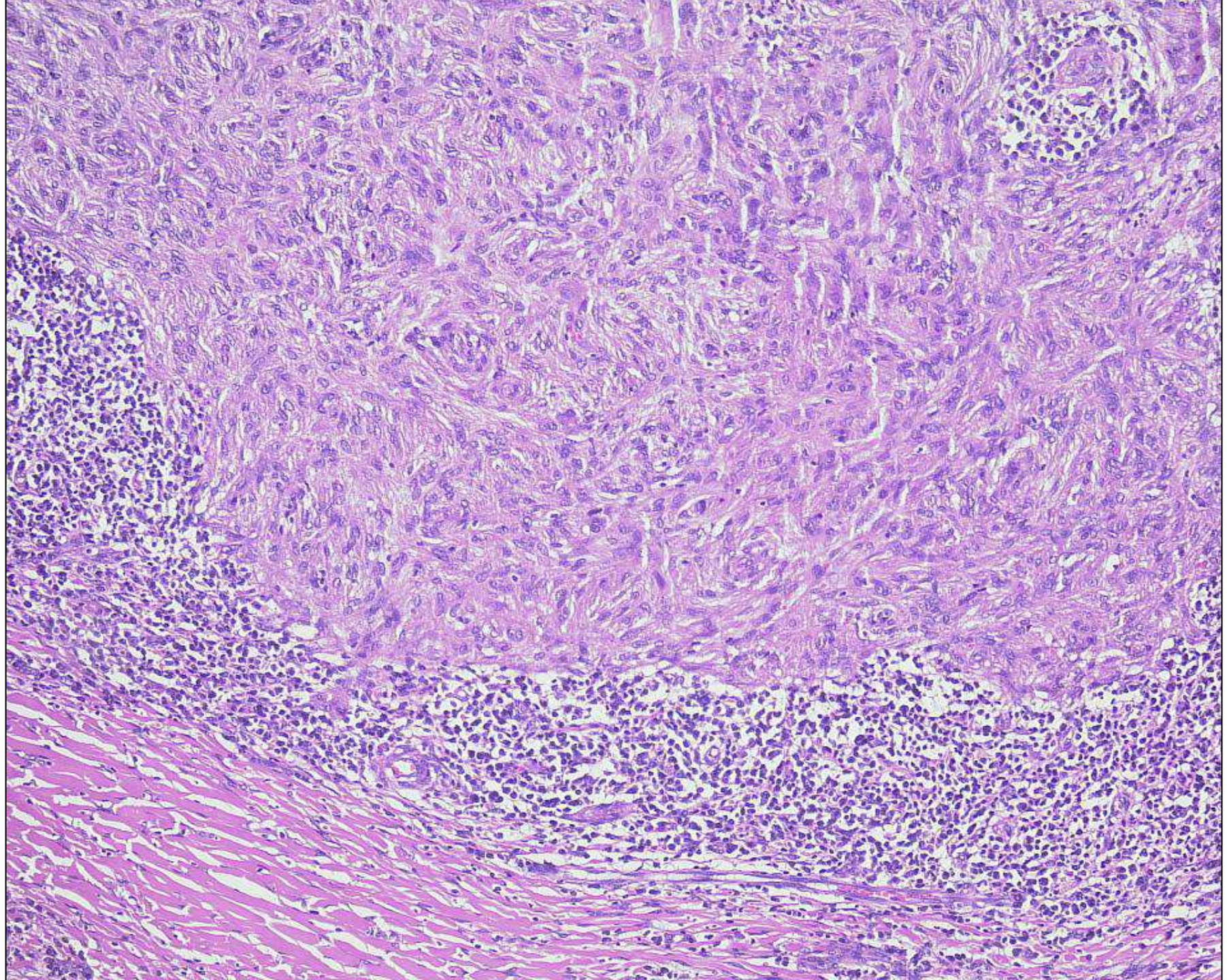
unknown line of differentiation („ALKoma“)

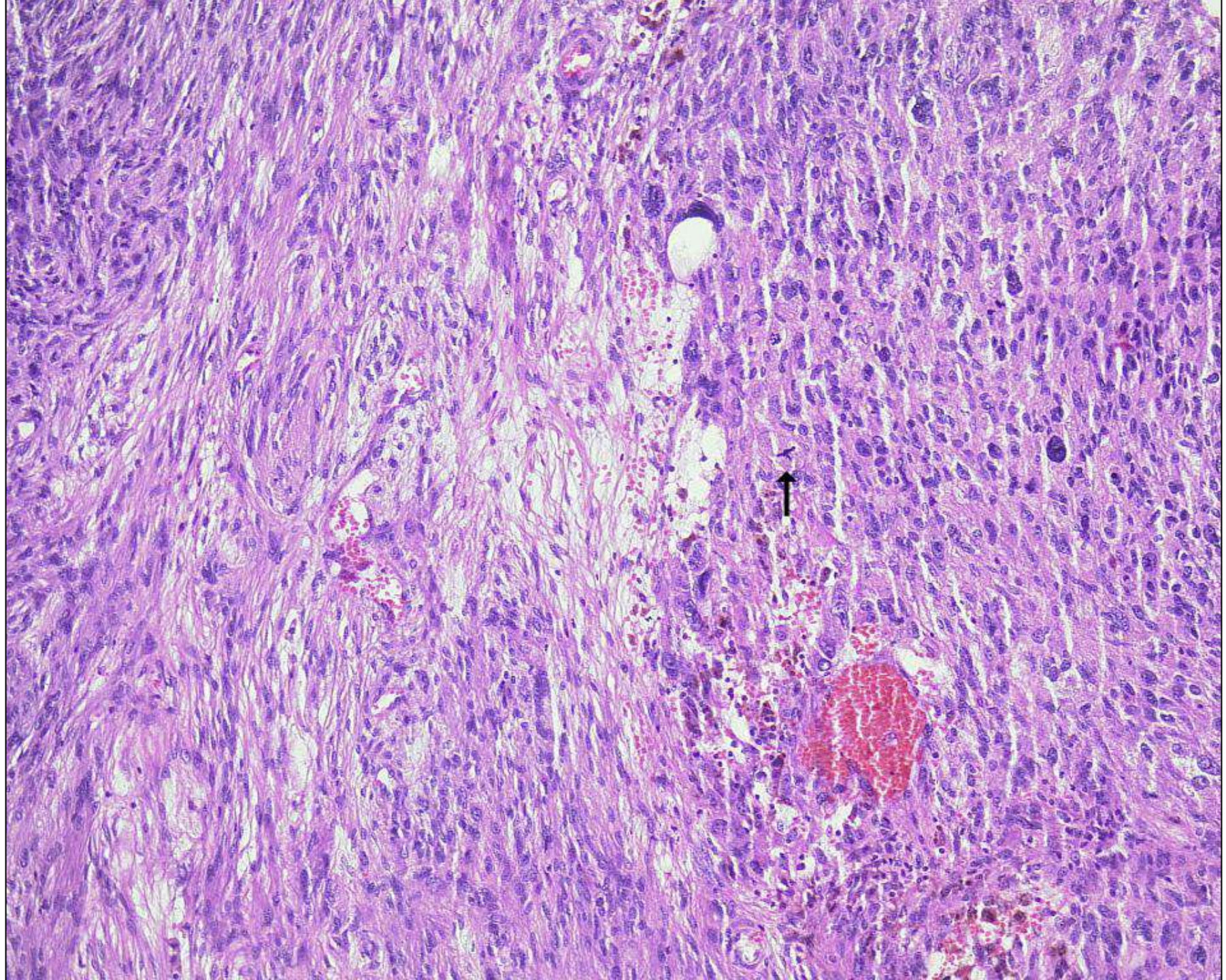


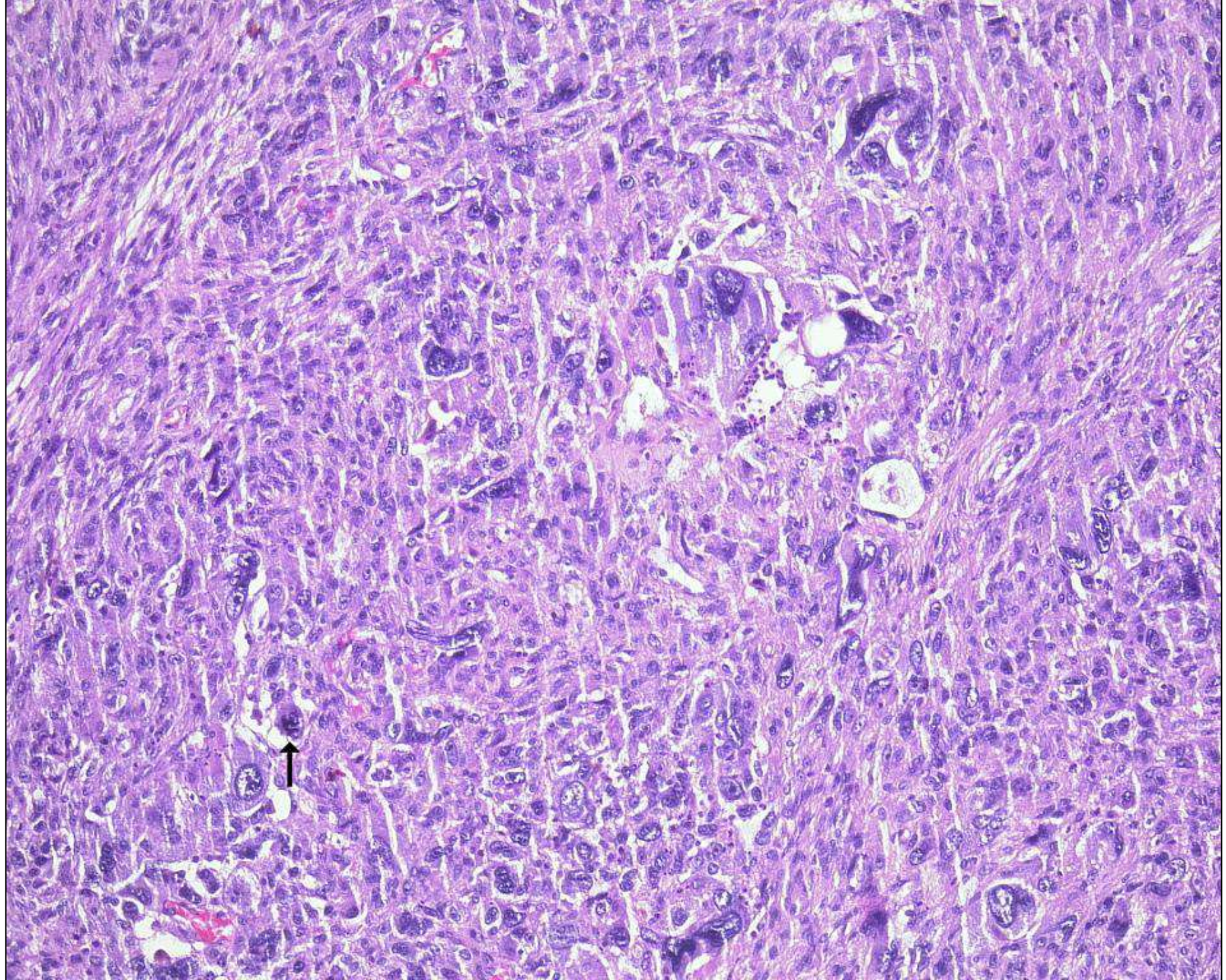
Case 2: M, 47 years, left forearm, subcutis, 2.4 cm

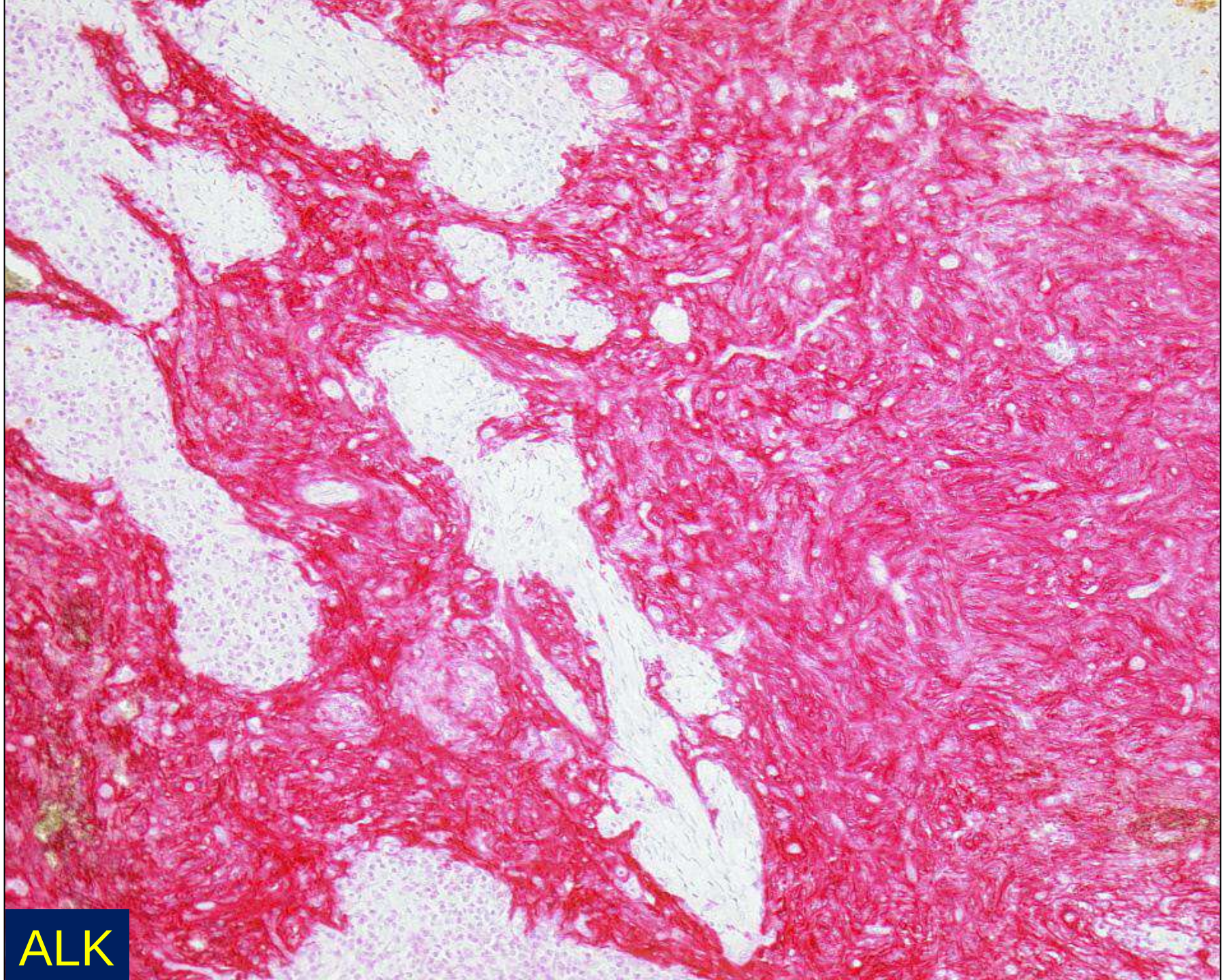


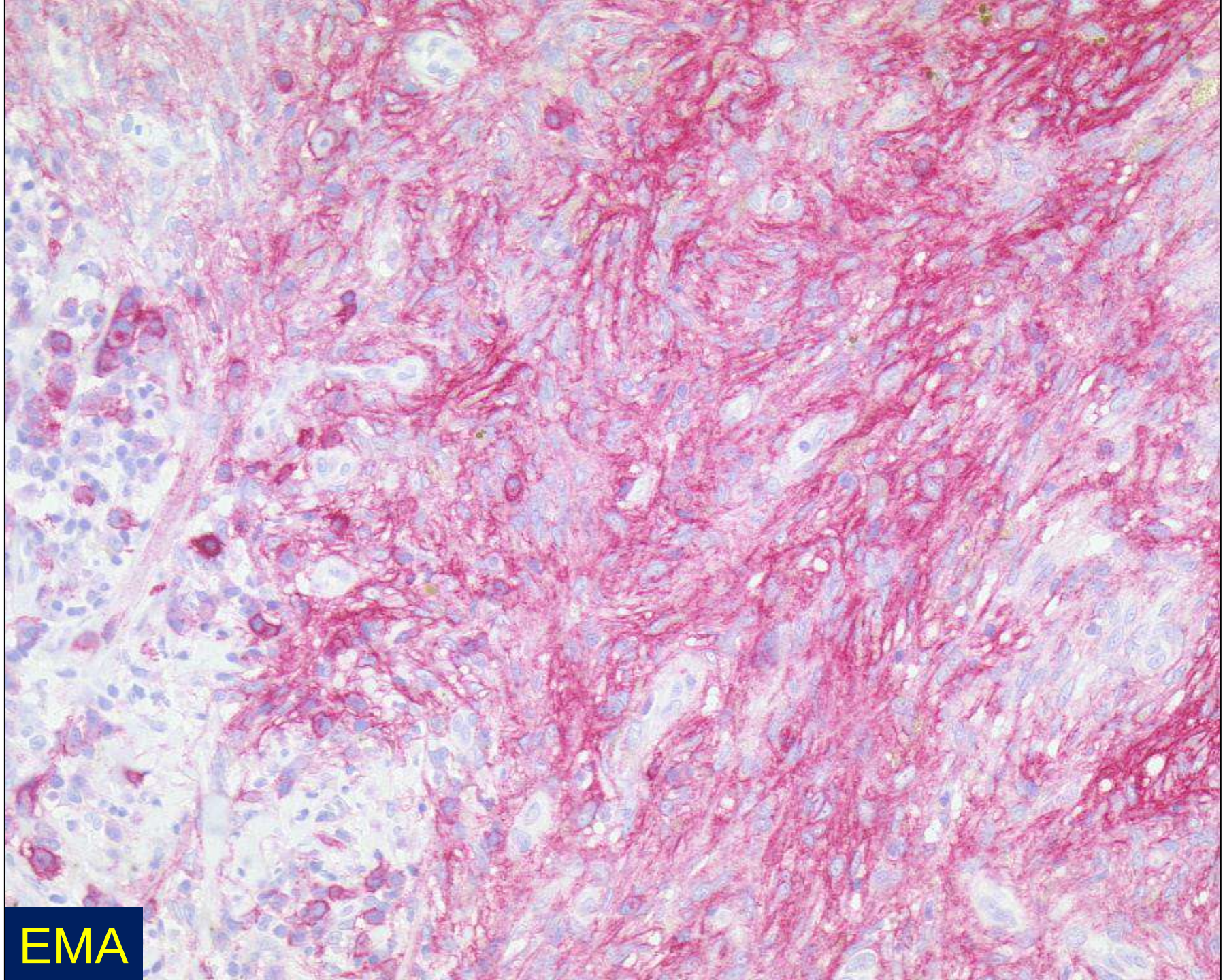









ALK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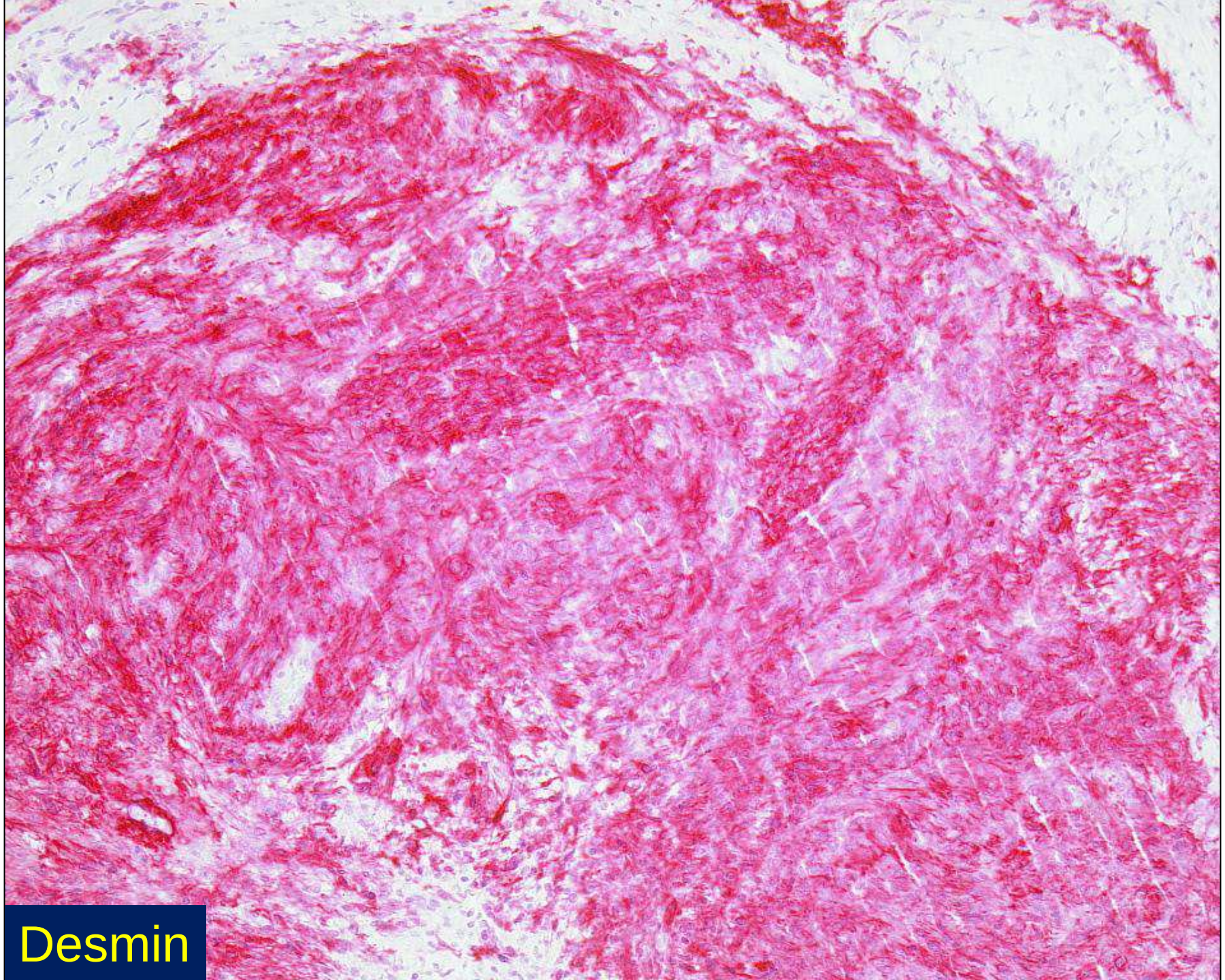
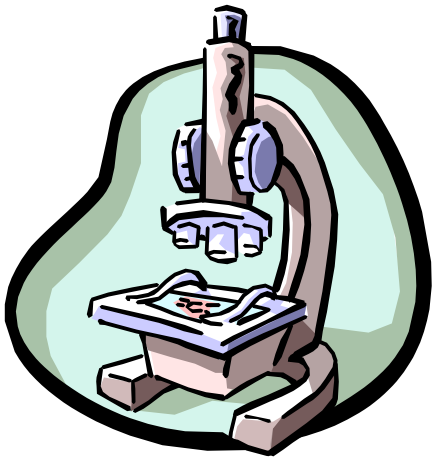

Desmin



Diagnosis Case 2

atypical angiomatoid fibrous histiocytoma

angiomatoid fibrous Histiocytoma

- Enzinger F. Angiomatoid malignant fibrous histiocytoma: a distinct fibrohistiocytic tumor of children and young adults simulating a vascular neoplasm Cancer 1979; 44: 2147
- rare neoplasm, unknown line of differentiation
  locally aggressive, rarely metastasizing
- children, young > elderly adults
  subcutis, extremities > trunk > head/neck
- often in the surrounding of lymph nodes
  often systemic symptoms (fever, anemia)

- well-circumscribed, indurated, nodular
  plump spindled / myoid / histiocytoid tumour cells
- syncytial growth
  pseudoangiomatous spaces
- capsule-like structures, haemosiderin deposits
  peripheral lymphocytes, plasma cells, germinal centres
- desmin + (60%), EMA + (50-60%), CD 99 +,
  CD 68 +, S-100 -, CD 34 -, ASMA -
- t(2;22)(q32.3;q12) with *EWSR1::CREB1*
  t(12;22)(q13;q12) with *EWSR1::ATF1*
  t(12;16)(q13;p11) with *FUS::ATF1*

Problems in the diagnosis of angiomatoid fibrous Histiocytoma

- given name (aneurysmal dermatofibroma)
- lymphnode metastasis?
- unusual anatomic locations
- unusual morphological variants

angiomatoid fibrous Histiocytoma

unusual anatomic locations:

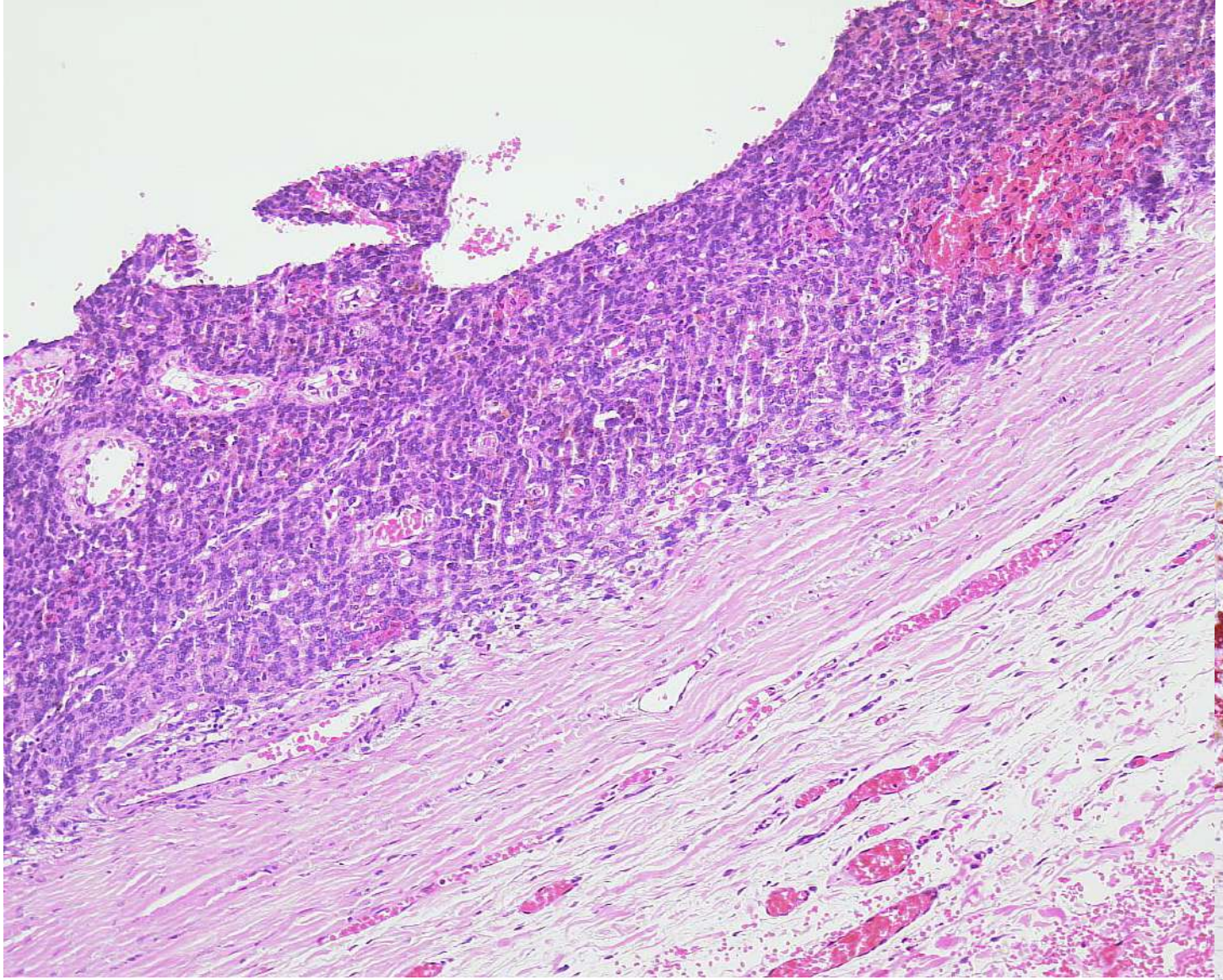
- brain (myxoid mesenchymal intraventricular brain tumour)
- lung, mediastinum
- bone
- retroperitoneum
- intraabdominal
- vulva
- ovary …

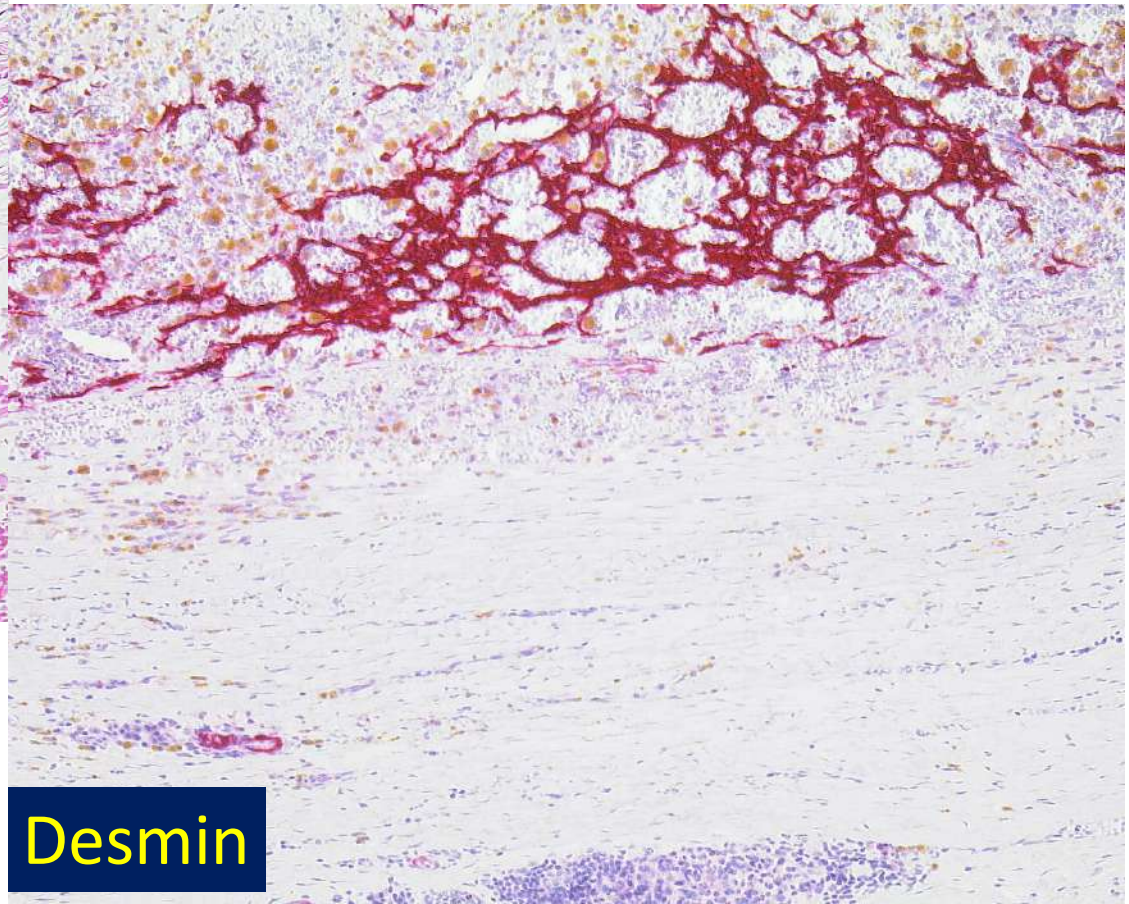
angiomatoid fibrous Histiocytoma

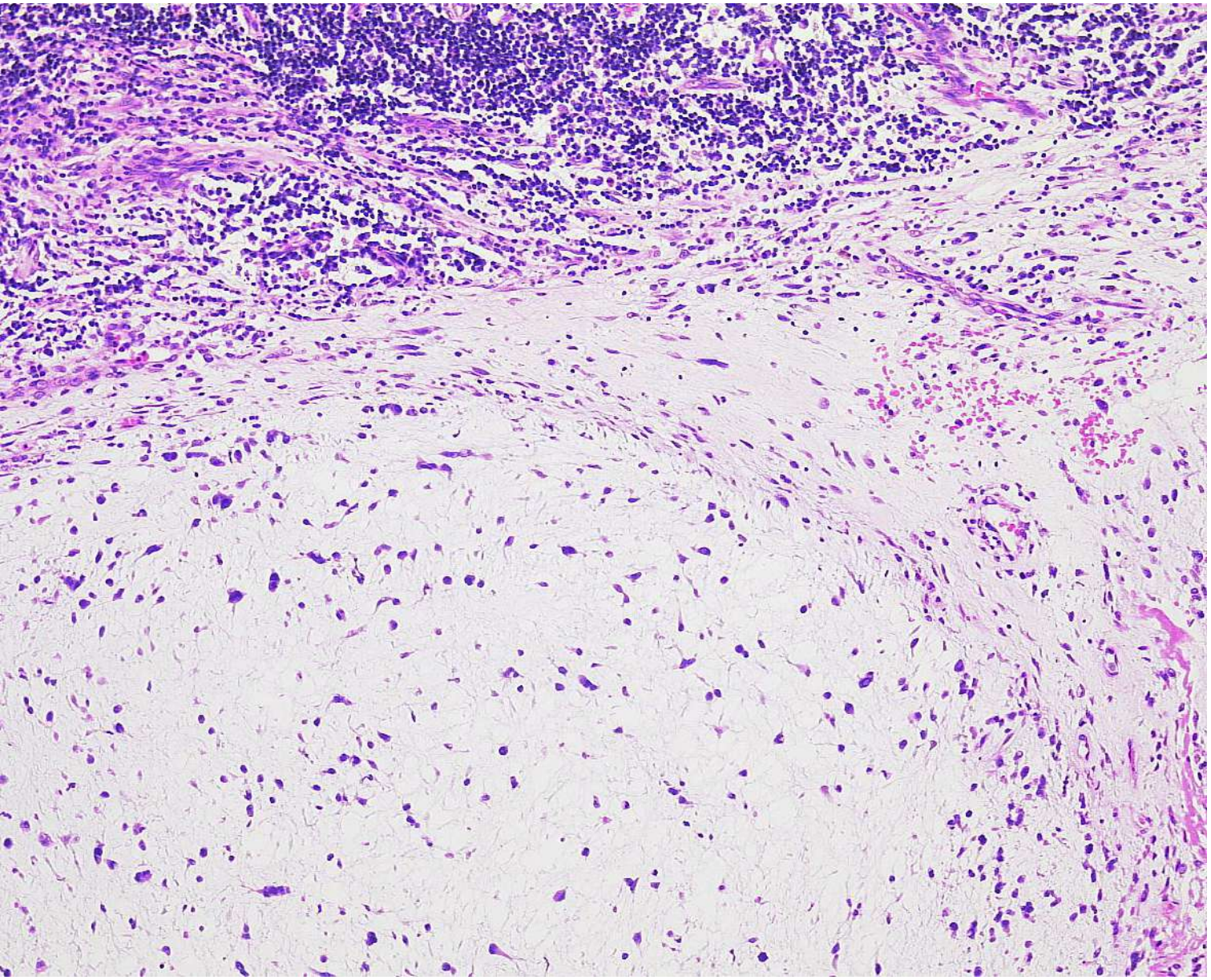
ununusual morphological variants

- composed of small- and blue cells (CD99 + !!!)
- solid angiomatoid fibrous histiocytoma
- cystic angiomatoid fibrous histiocytoma
- pleomorphic angiomatoid fibrous histiocytoma
- spindle cell angiomatoid fibrous histiocytoma
- myxoid angiomatoid fibrous histiocytoma
- clear cell angiomatoid fibrous histiocytoma
- angiomatoid fibrous histiocytoma with rhabdomyoblast-like cells…

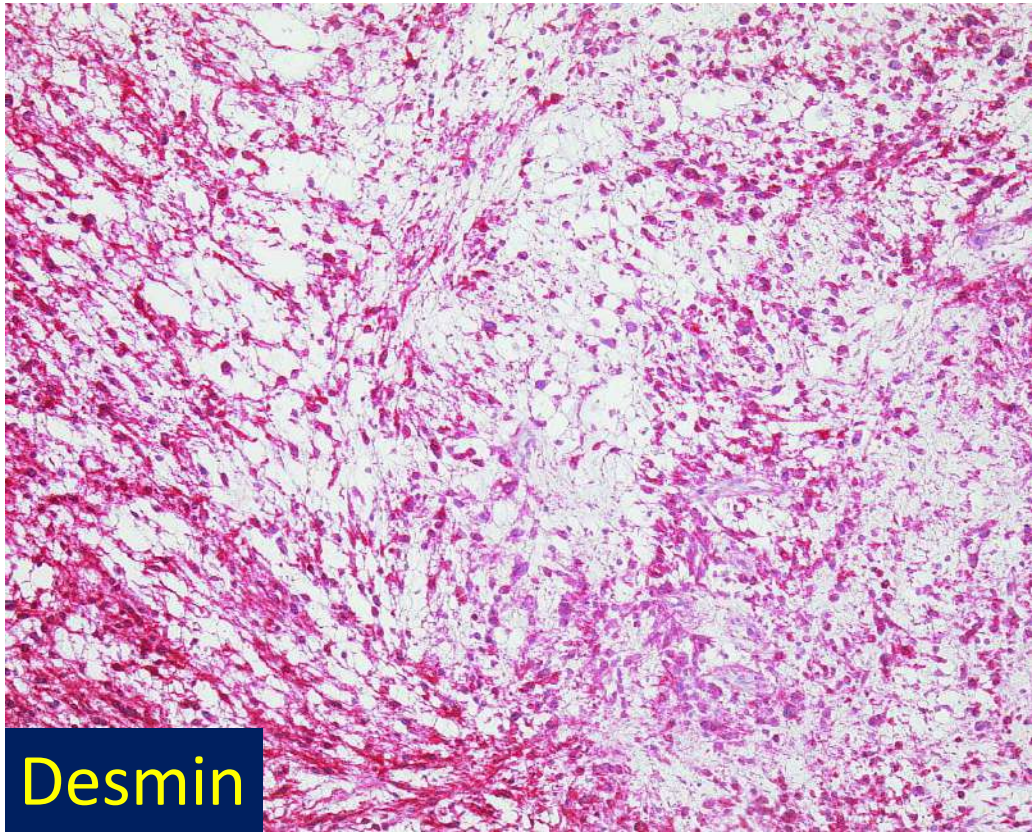
F, 4 years, back of the head

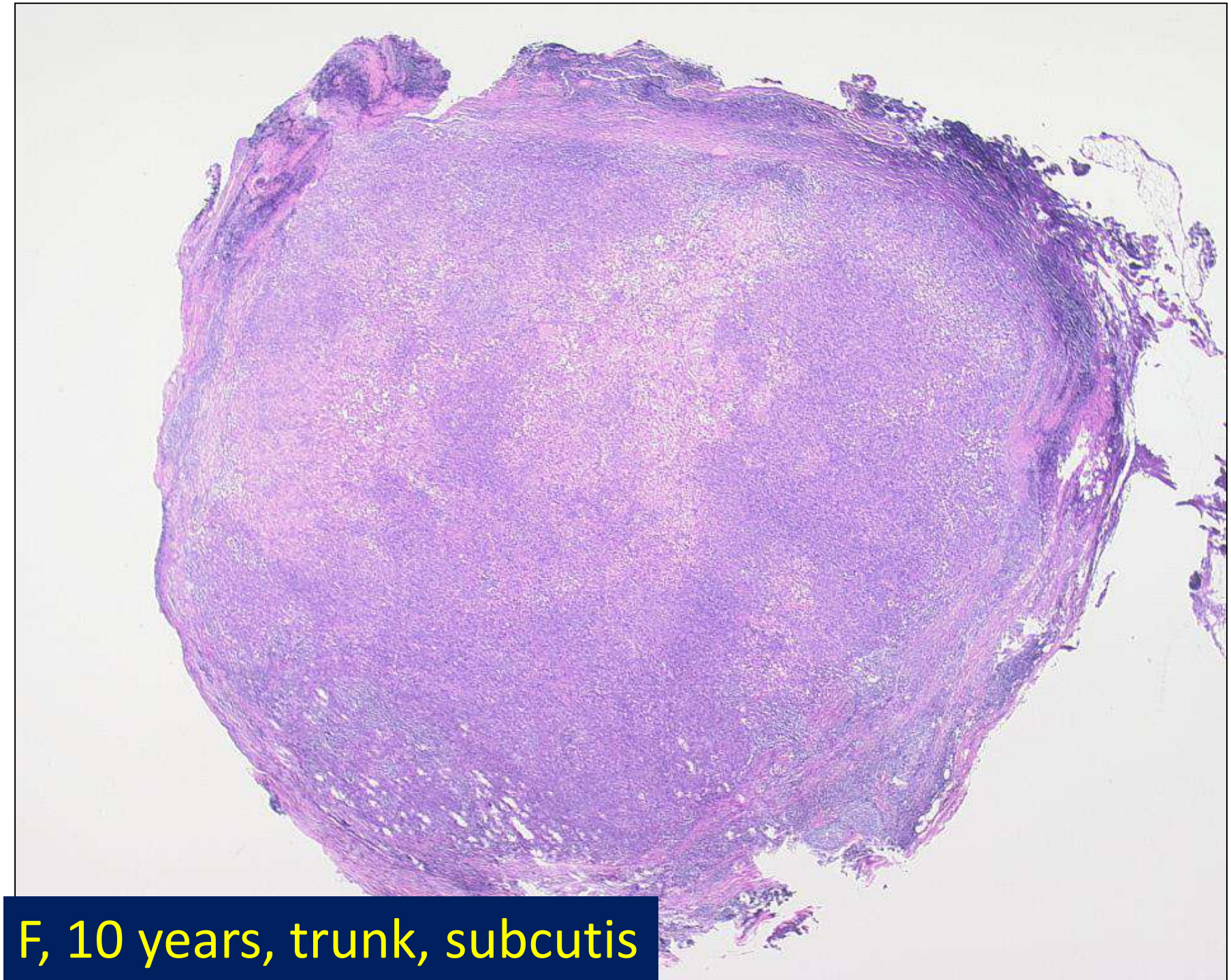



Desmin

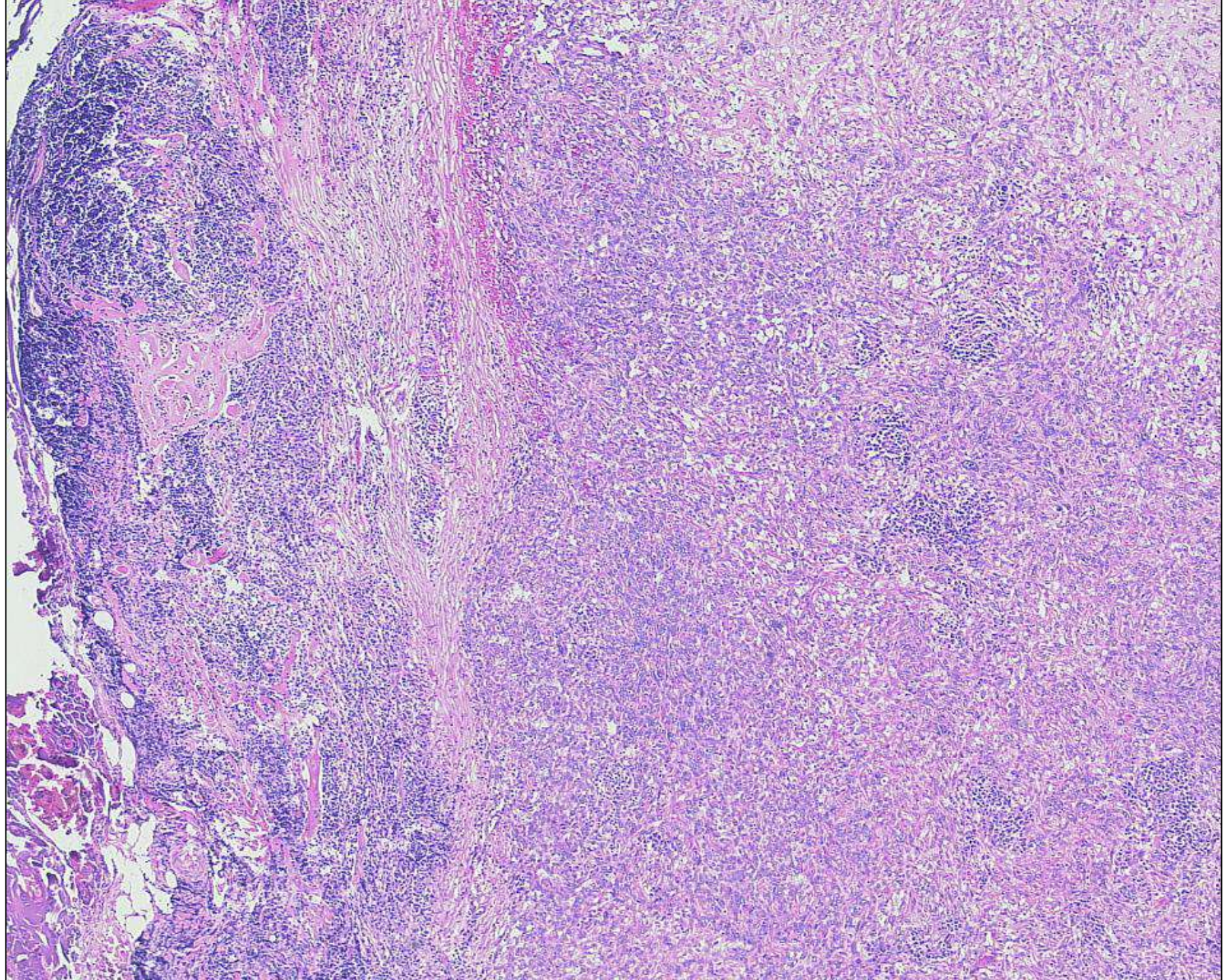


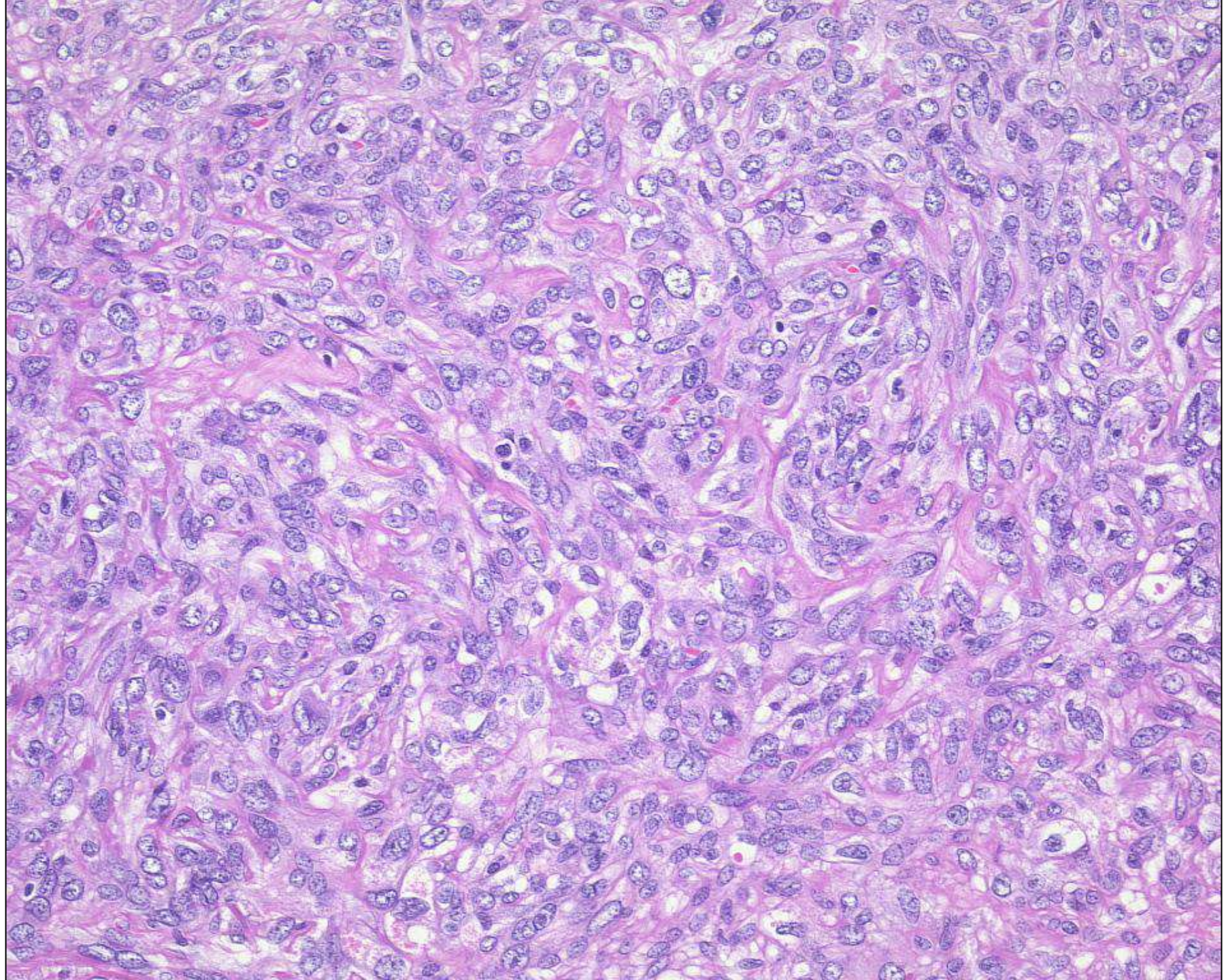
Myxoid variant of so-called angiomatoid „MFH“: clinicopathologic characterization in a series of 21 cases
Schaefer IM, Fletcher CDM
Am J Surg Pathol 2014; 38: 816

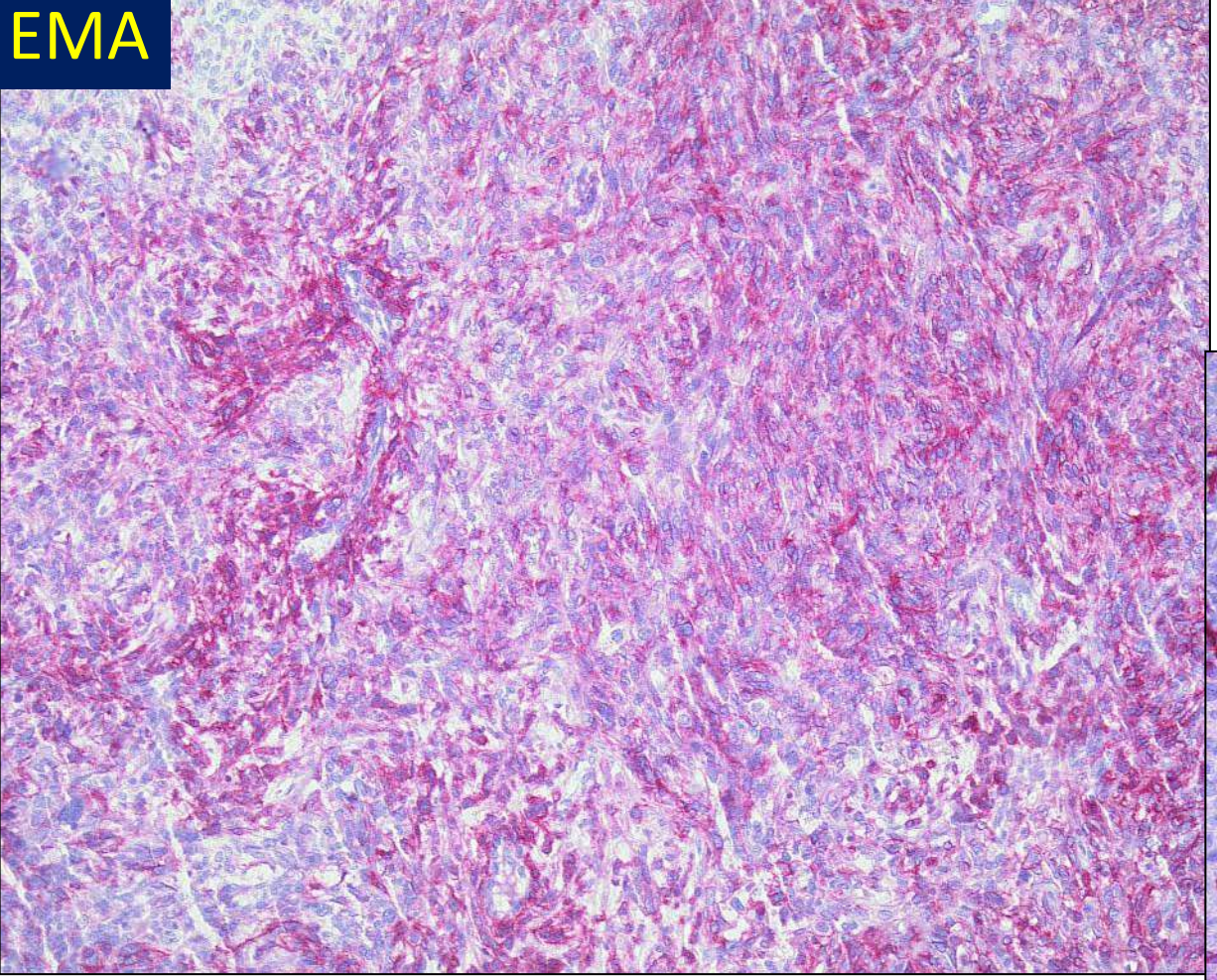


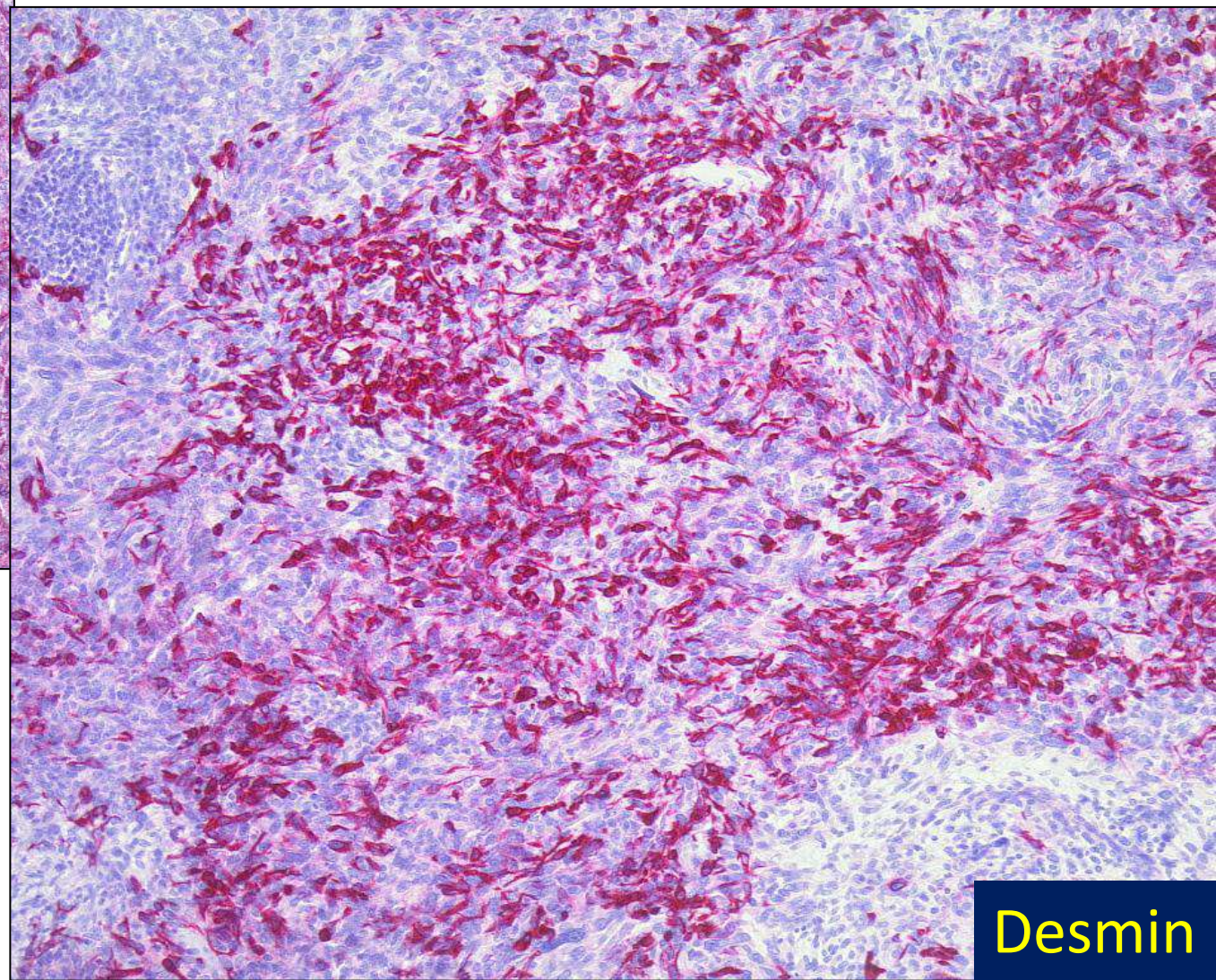


F, 10 years, trunk, subcutis

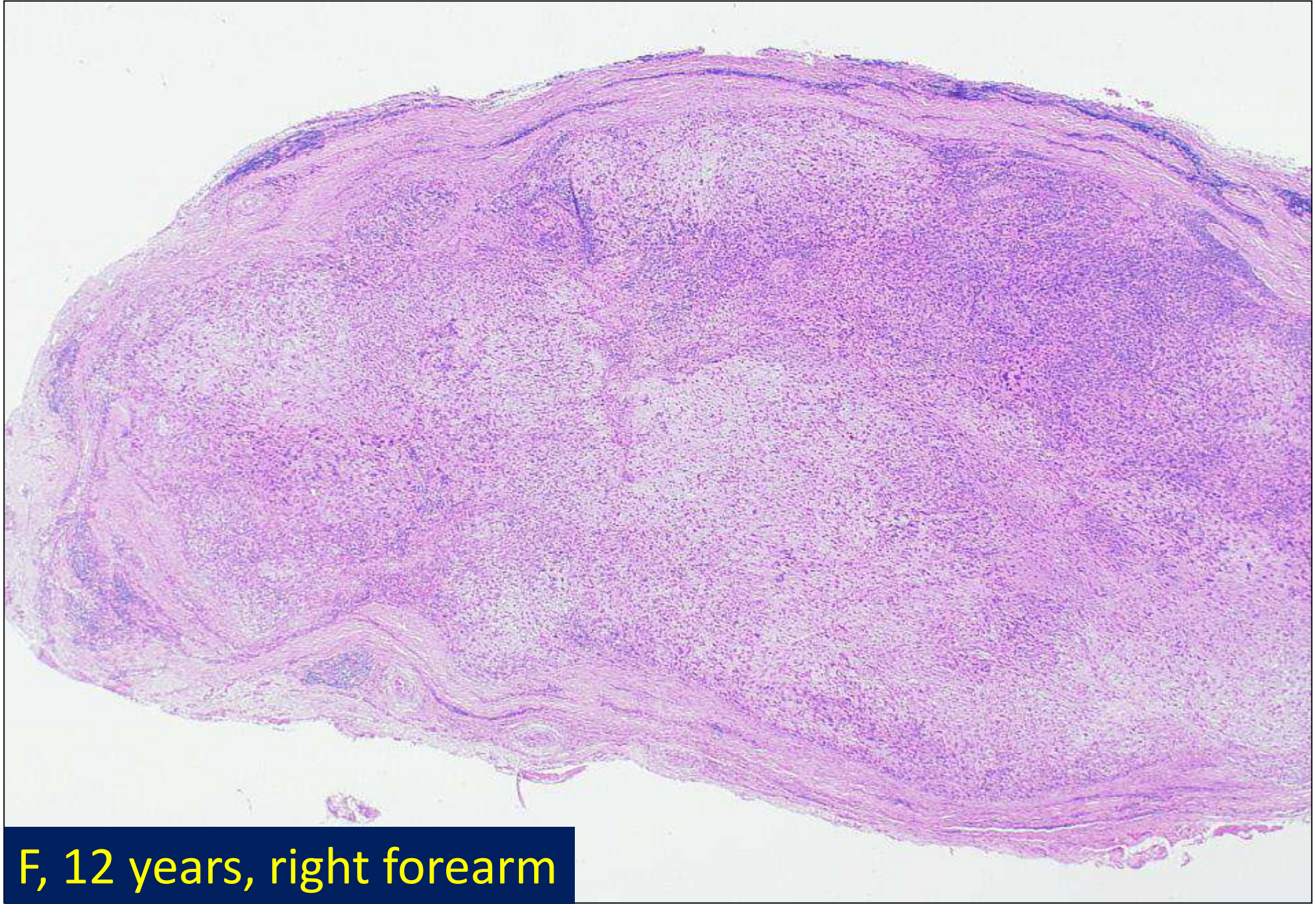


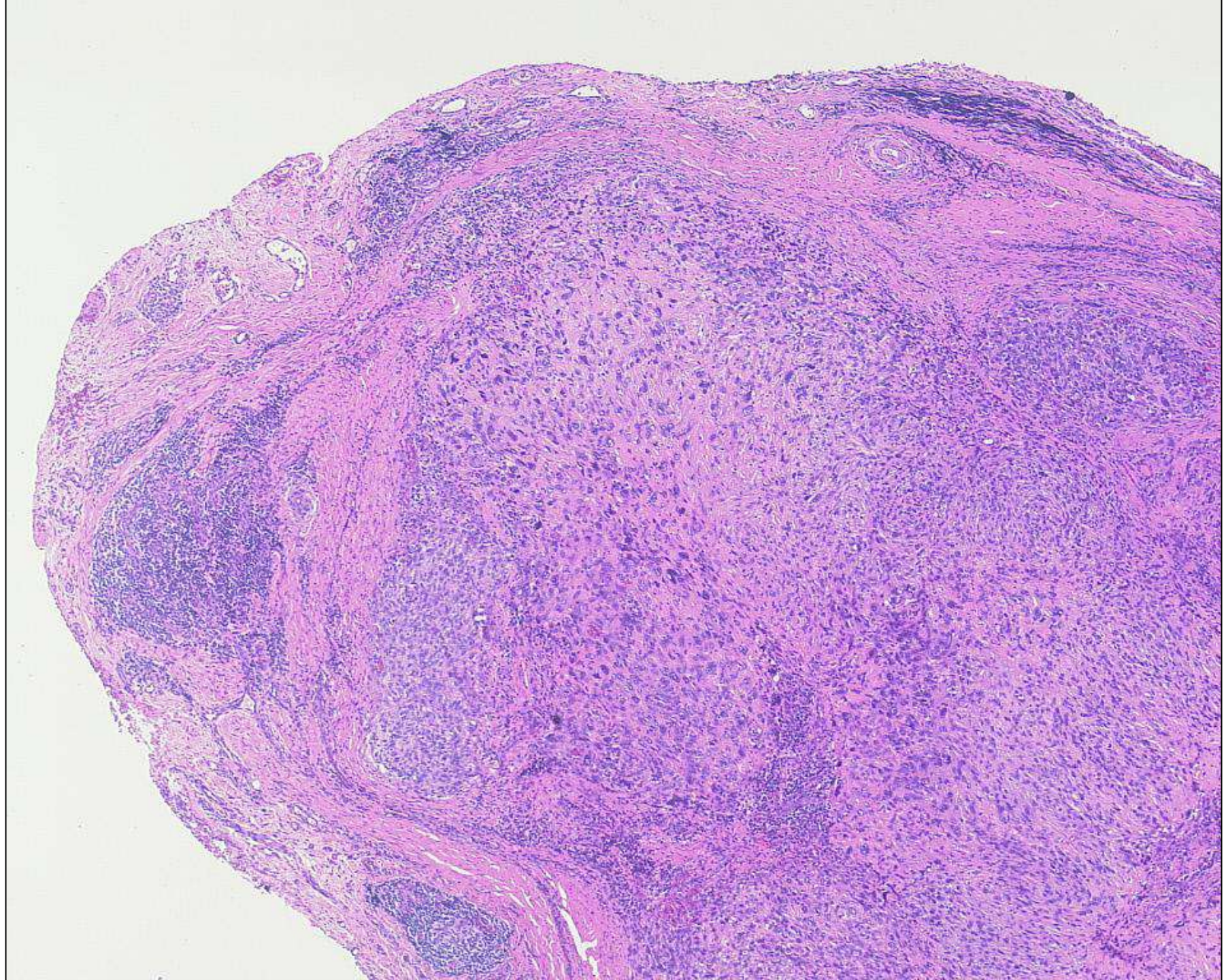


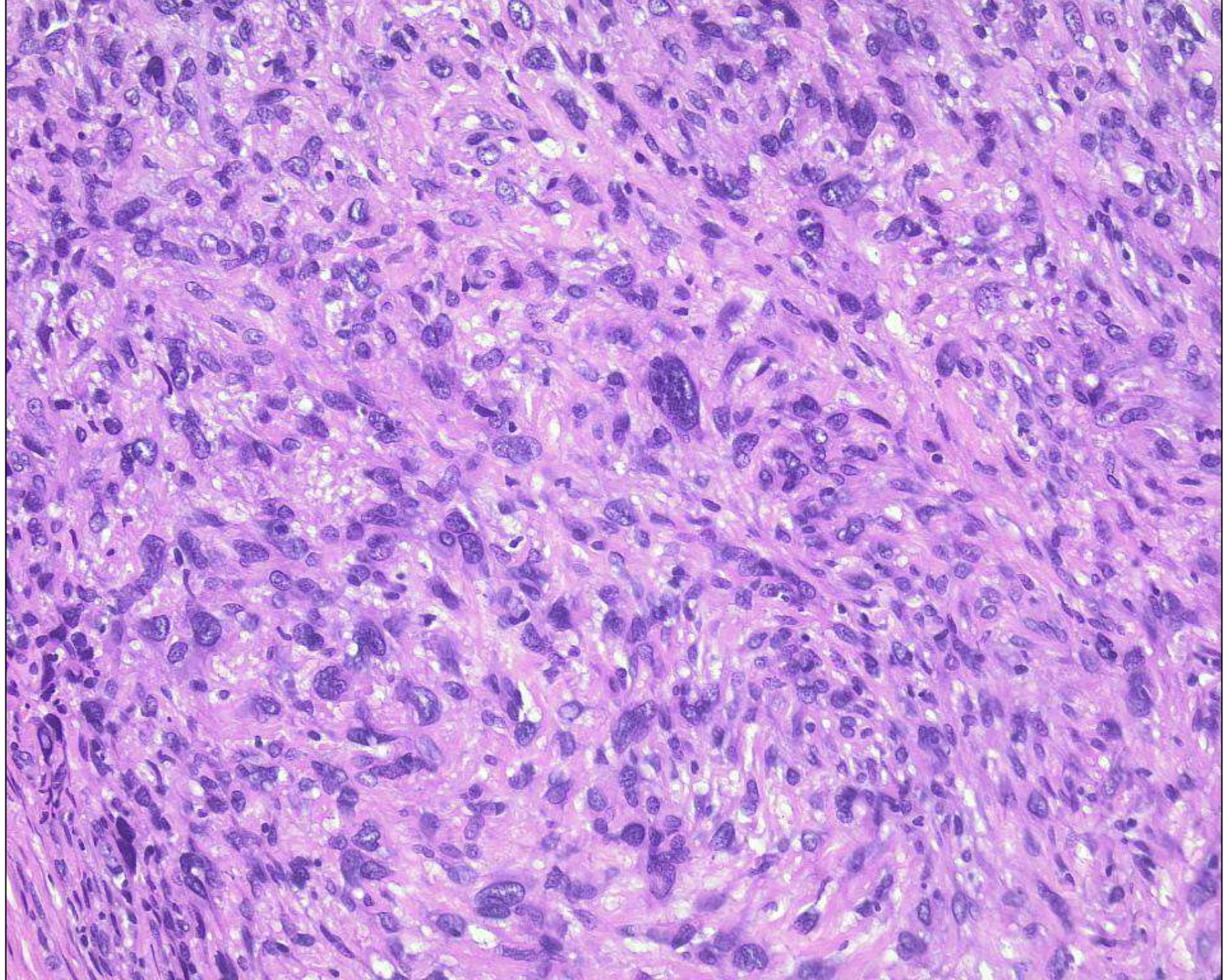


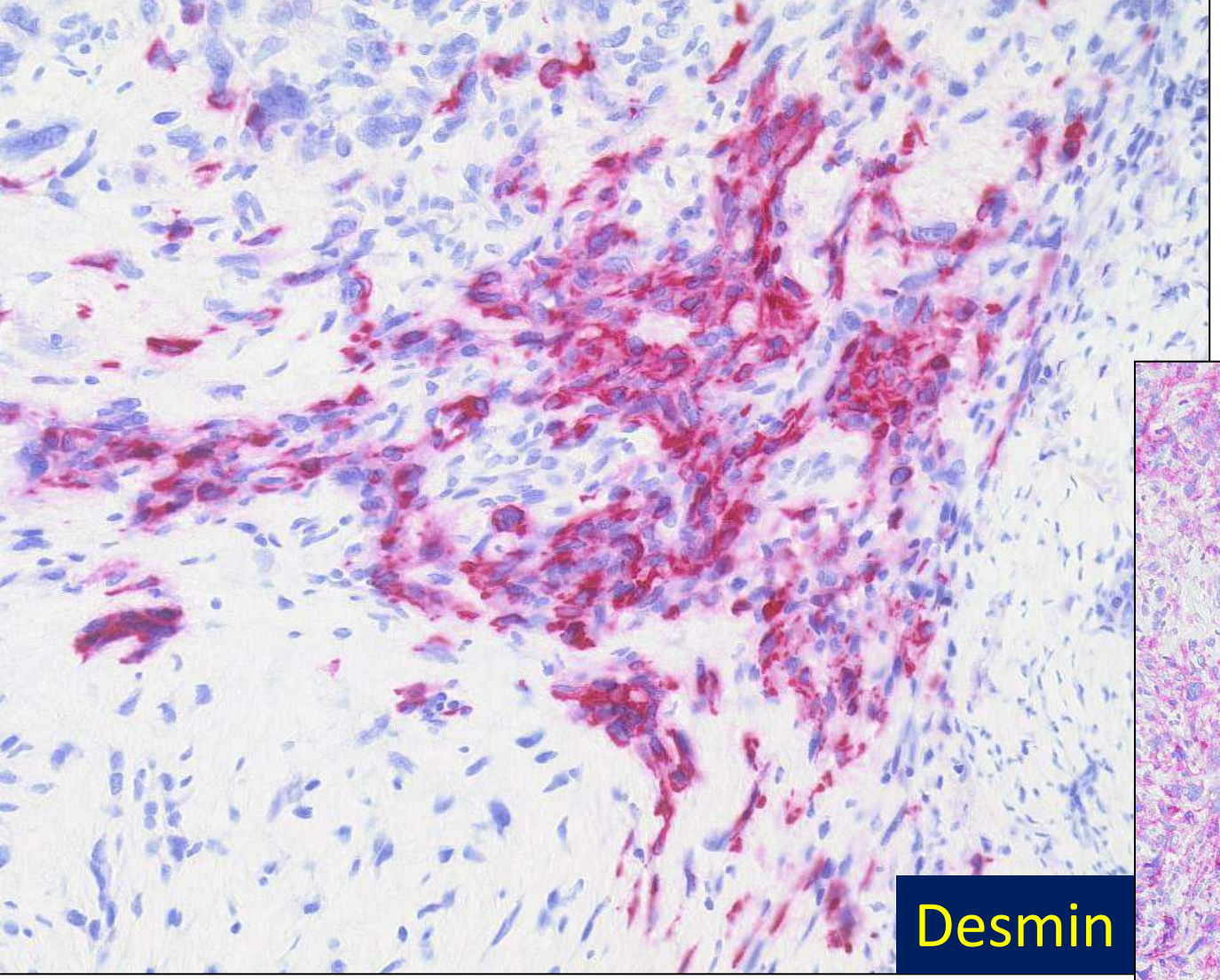


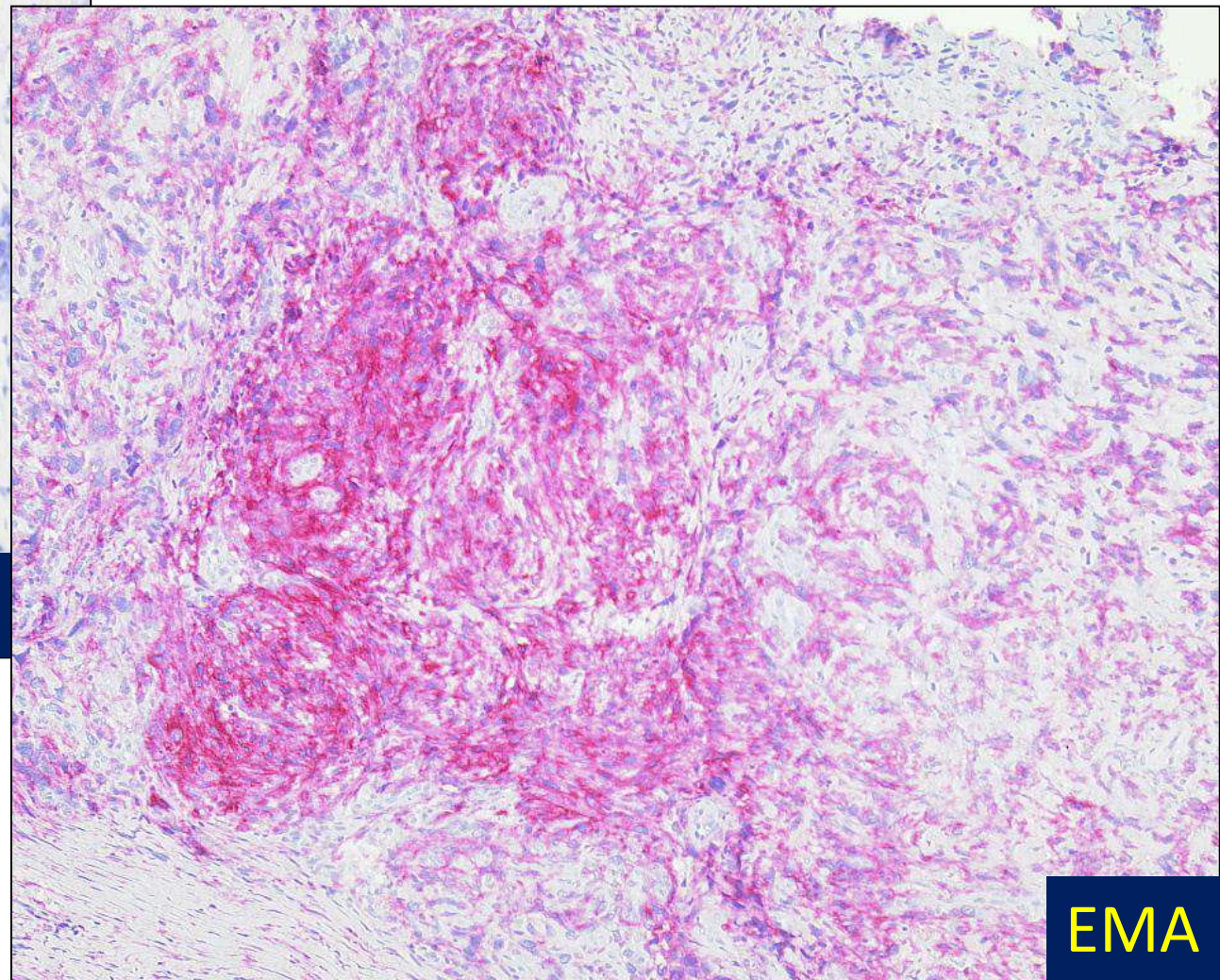
solid variant of angiomatoid fibrous histiocytoma


F, 12 years, right forearm







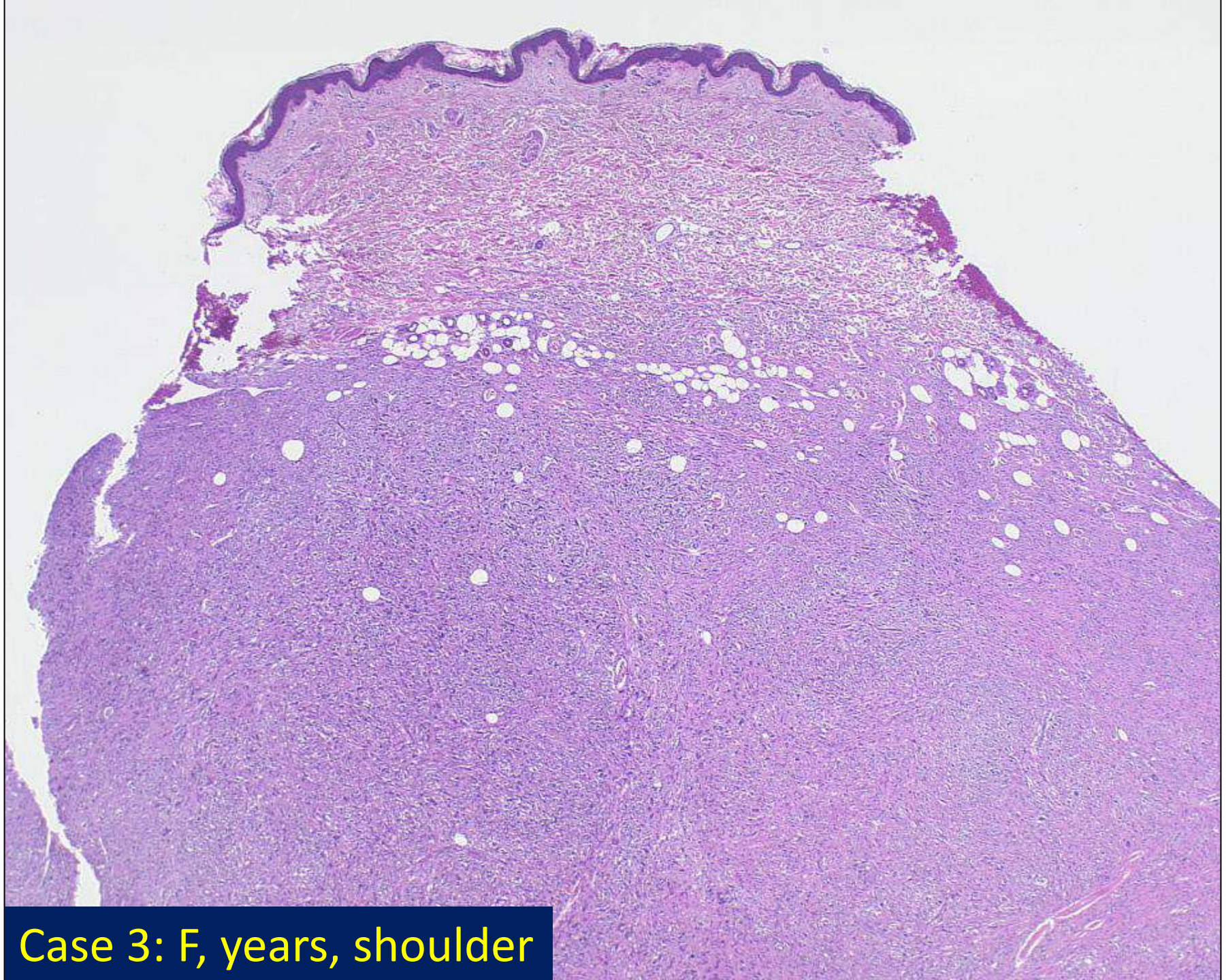


solid variant of atypical angiomatoid fibrous histiocytoma

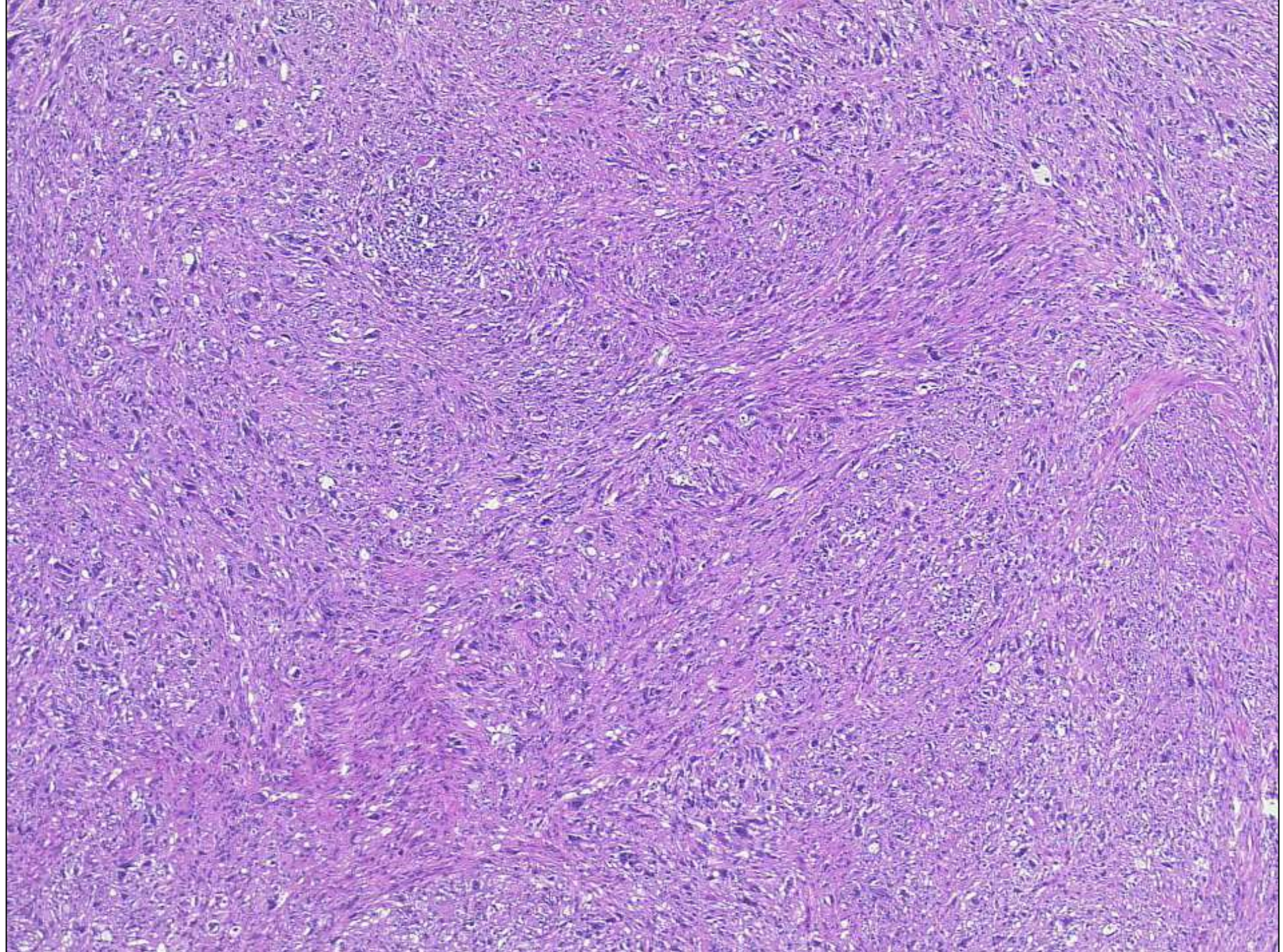
Cheah AL et al. ALK expression in angiomatoid fibrous histiocytoma: a potential diagnostic pitfall
Am J Surg Pathol 2019; 43: 93-101

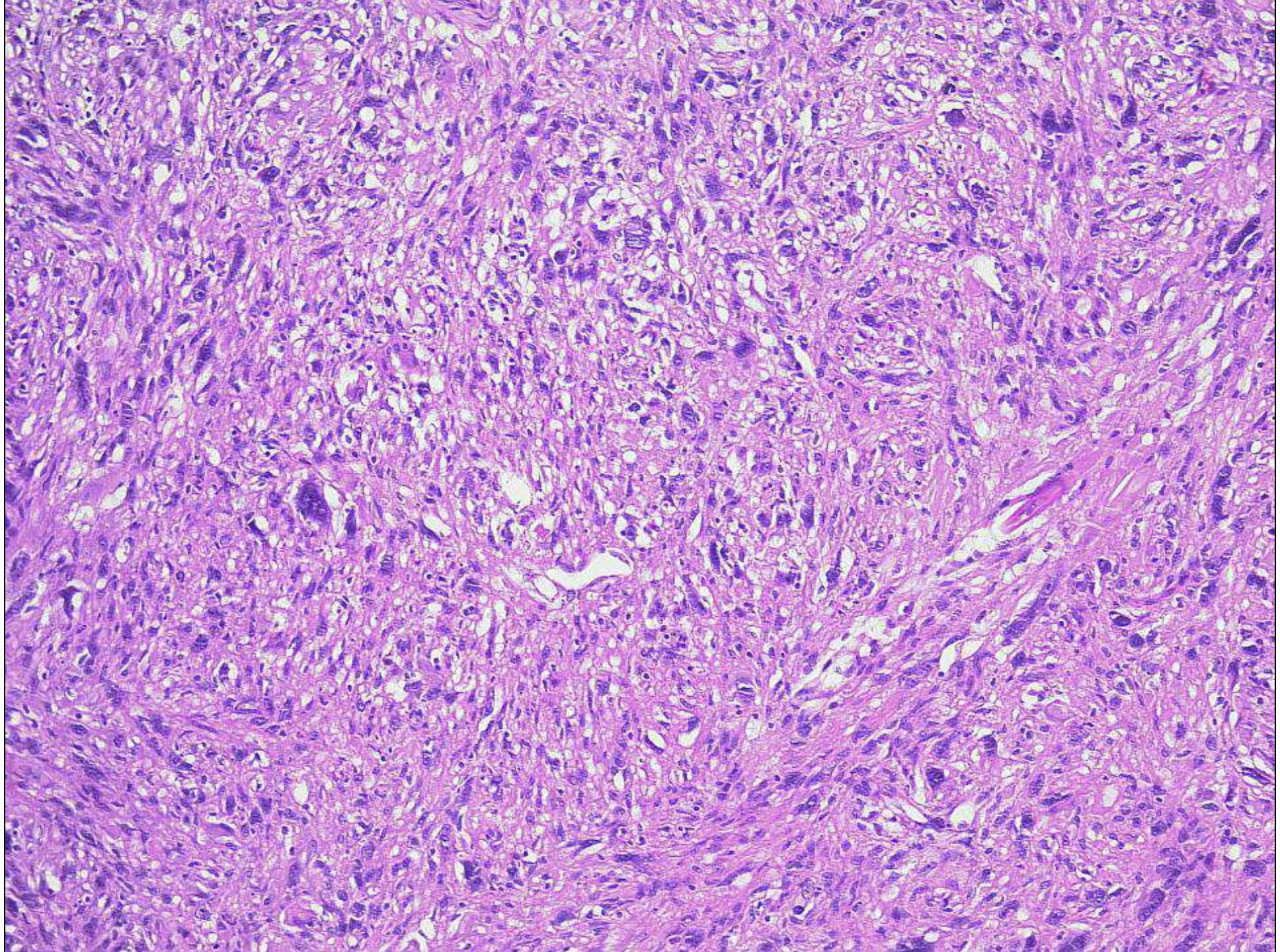
- 11 cases of angiomatoid fibrous histiocytoma
  - ALK +, no ALK rearrangement
- 15 cases of inflammatory myofibroblastic tumour
  - 67% ALK +, 9/10 ALK rearrangement
- 11 cases of follicular dendritic cell sarcoma
  - ALK -

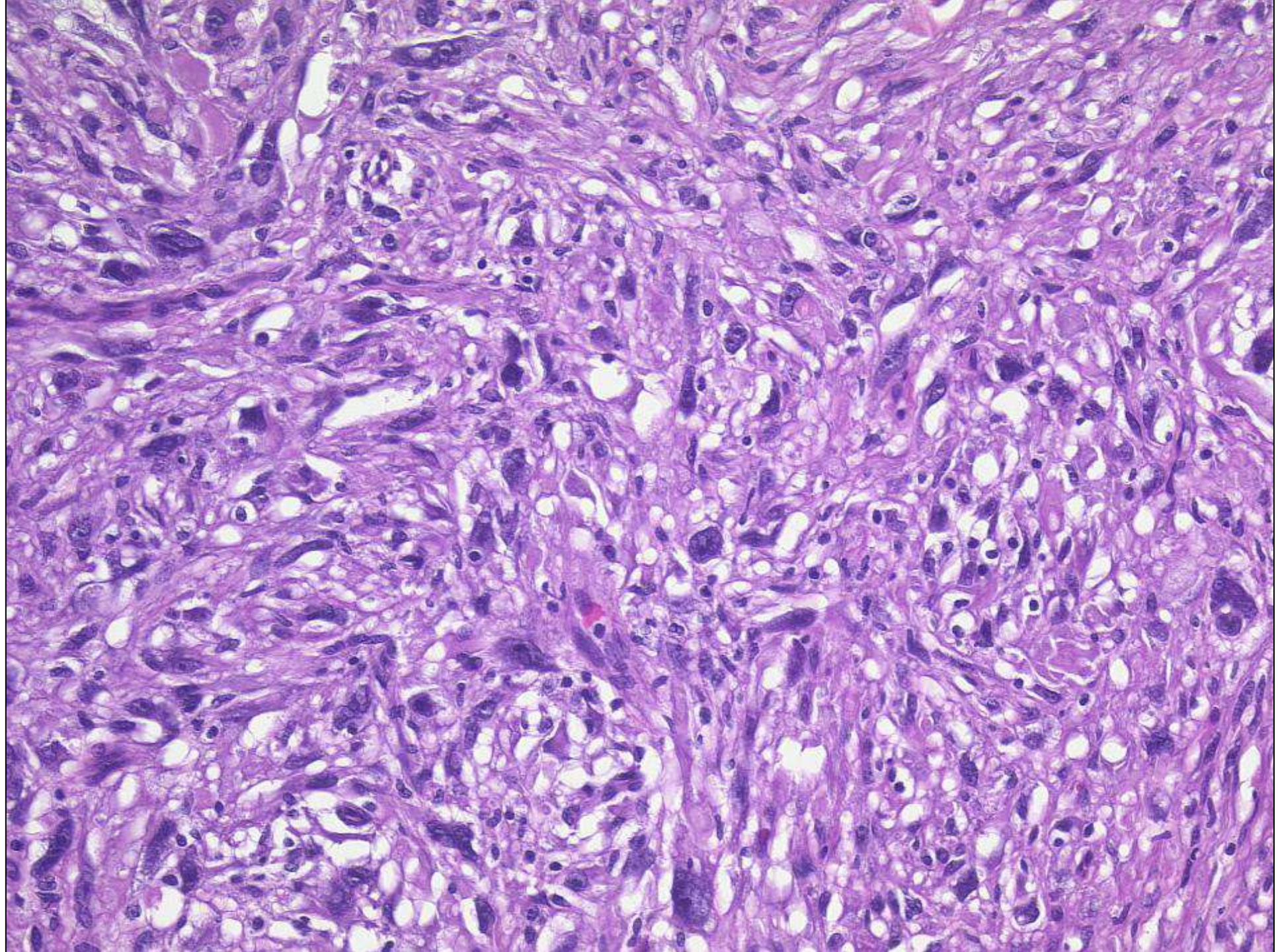
van Zwam P et al. ALK expression in angiomatoid fibrous histiocytoma: confirmation of the findings of Cheah
Am J Surg Pathol 2019; 43: 1156



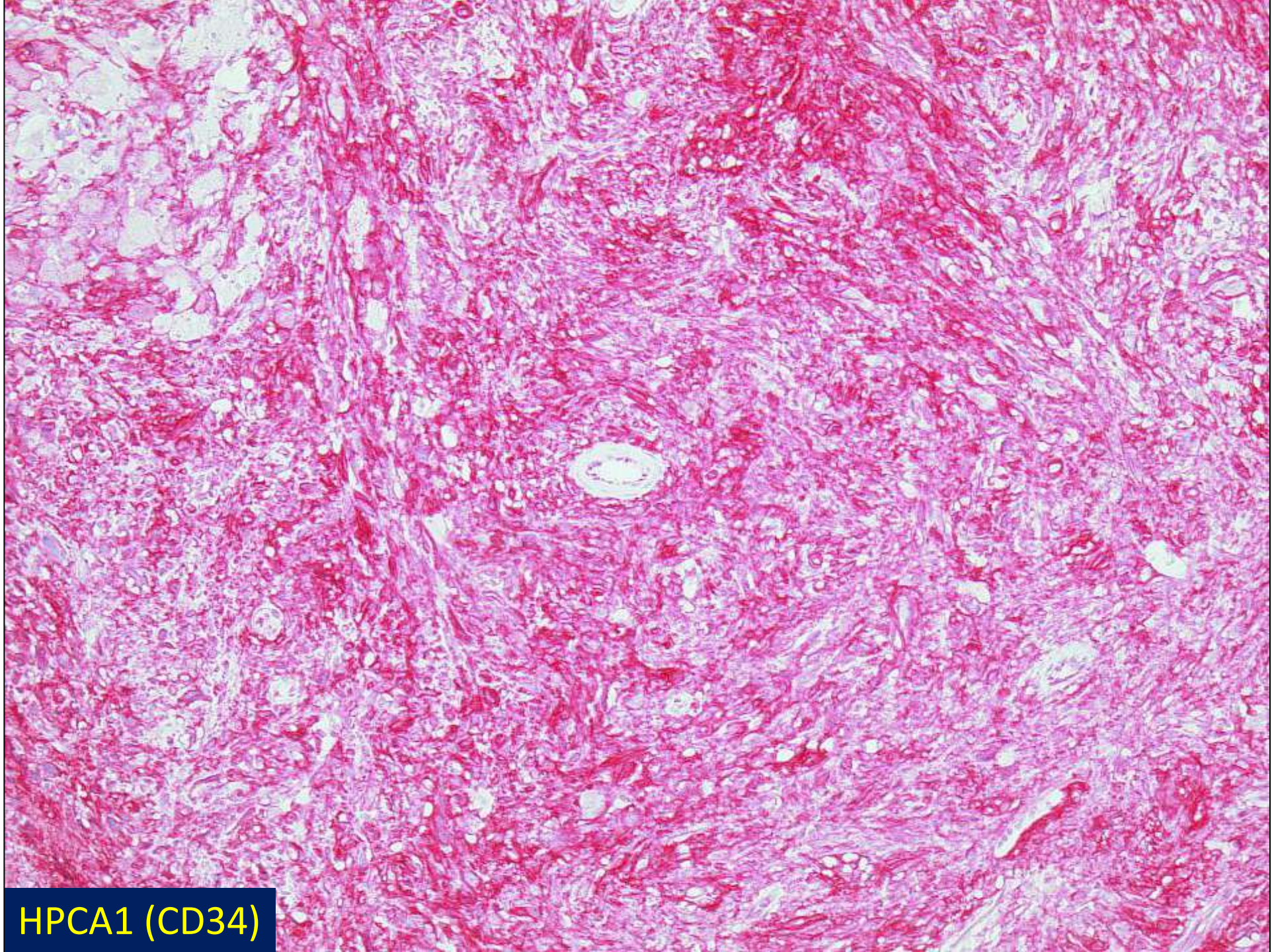
Case 3: F, years, shoulder

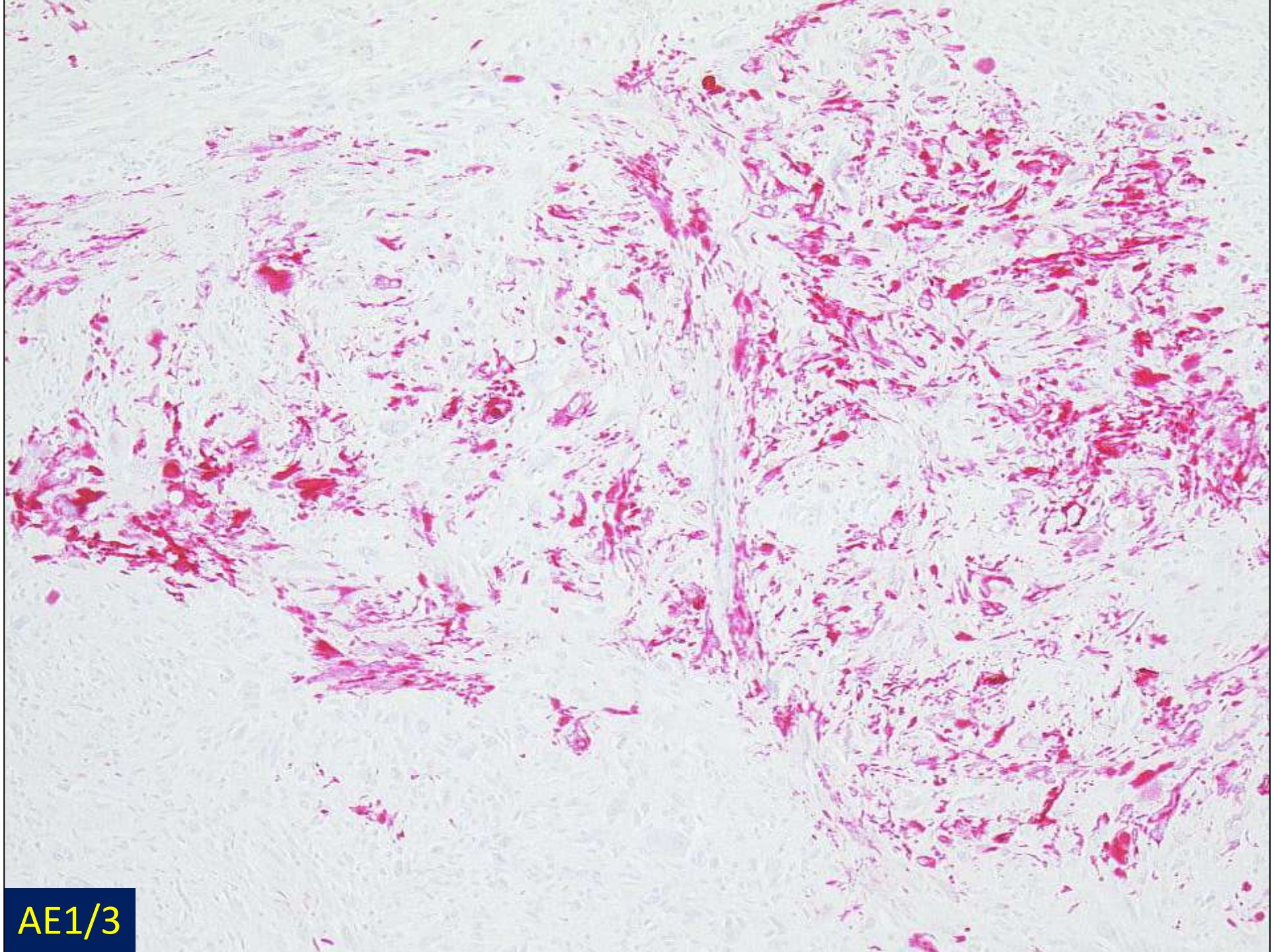


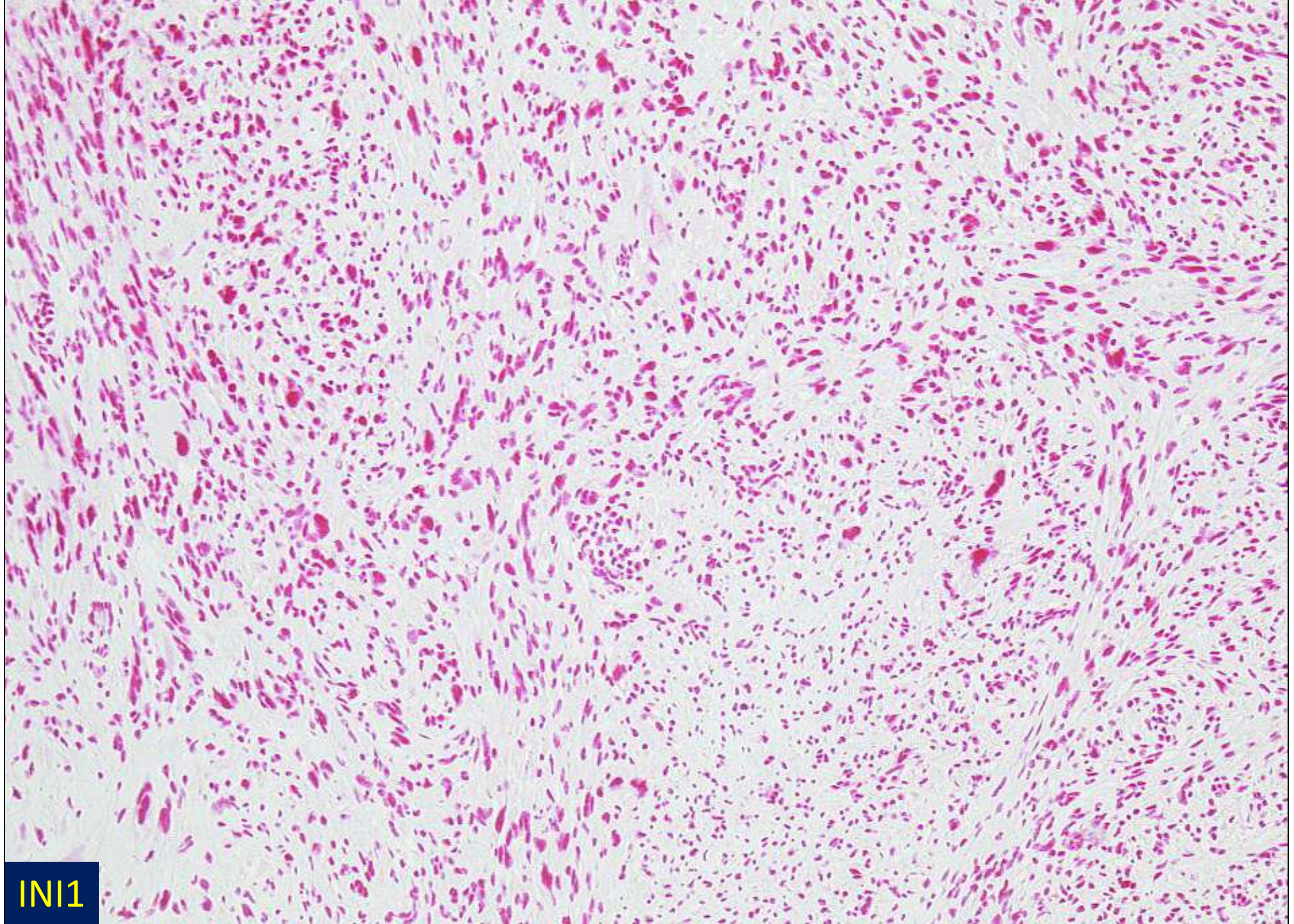


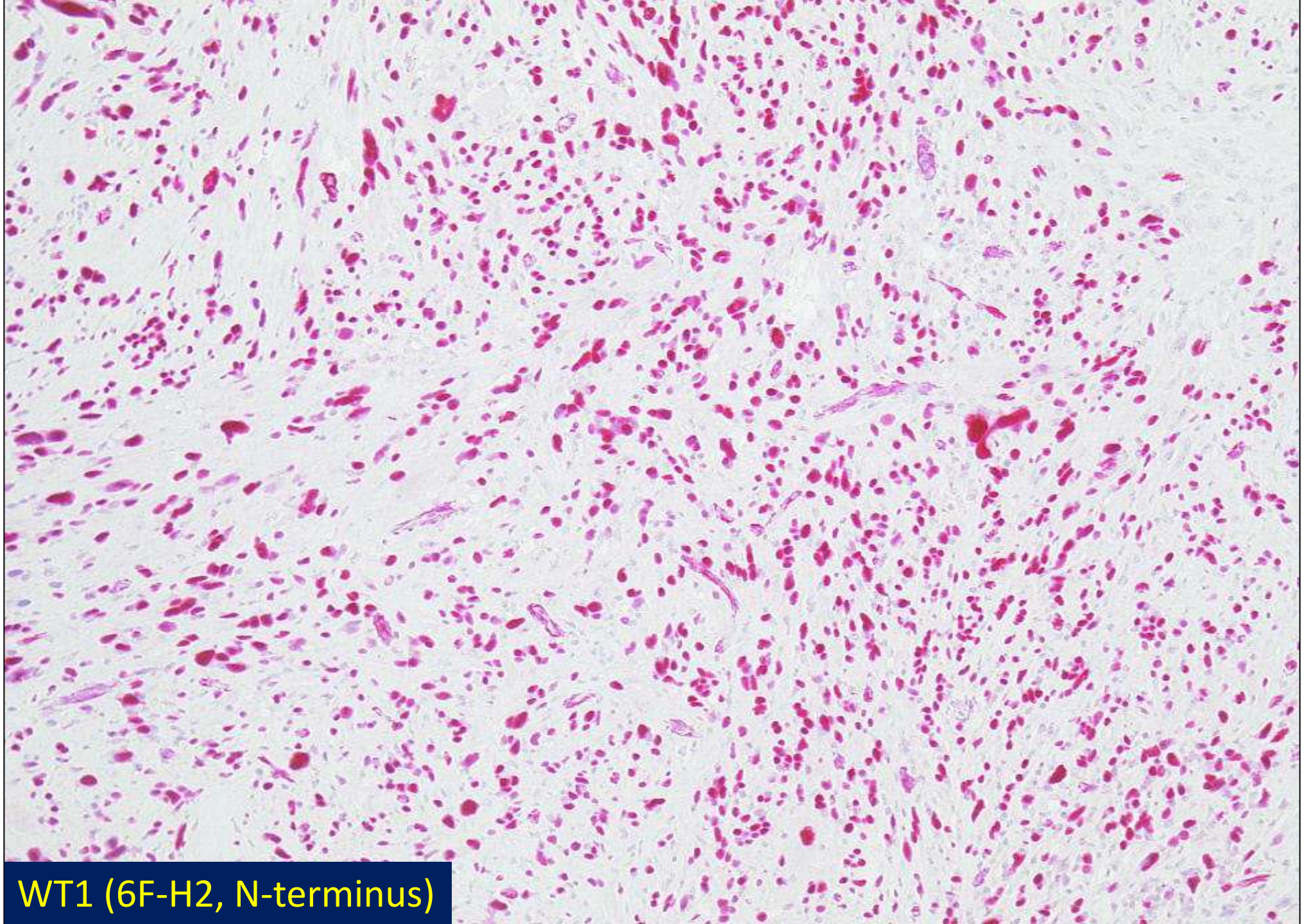


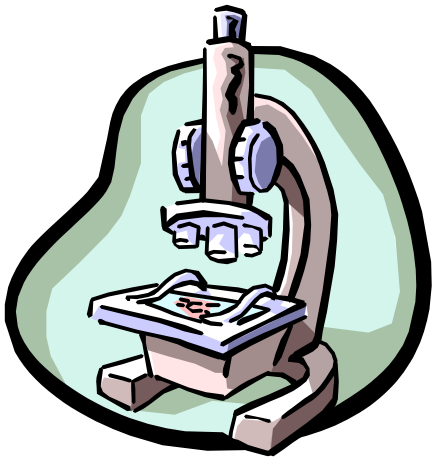
Immunohistochemistry ?


HPCA1 (CD34)


AE1/3


INI1

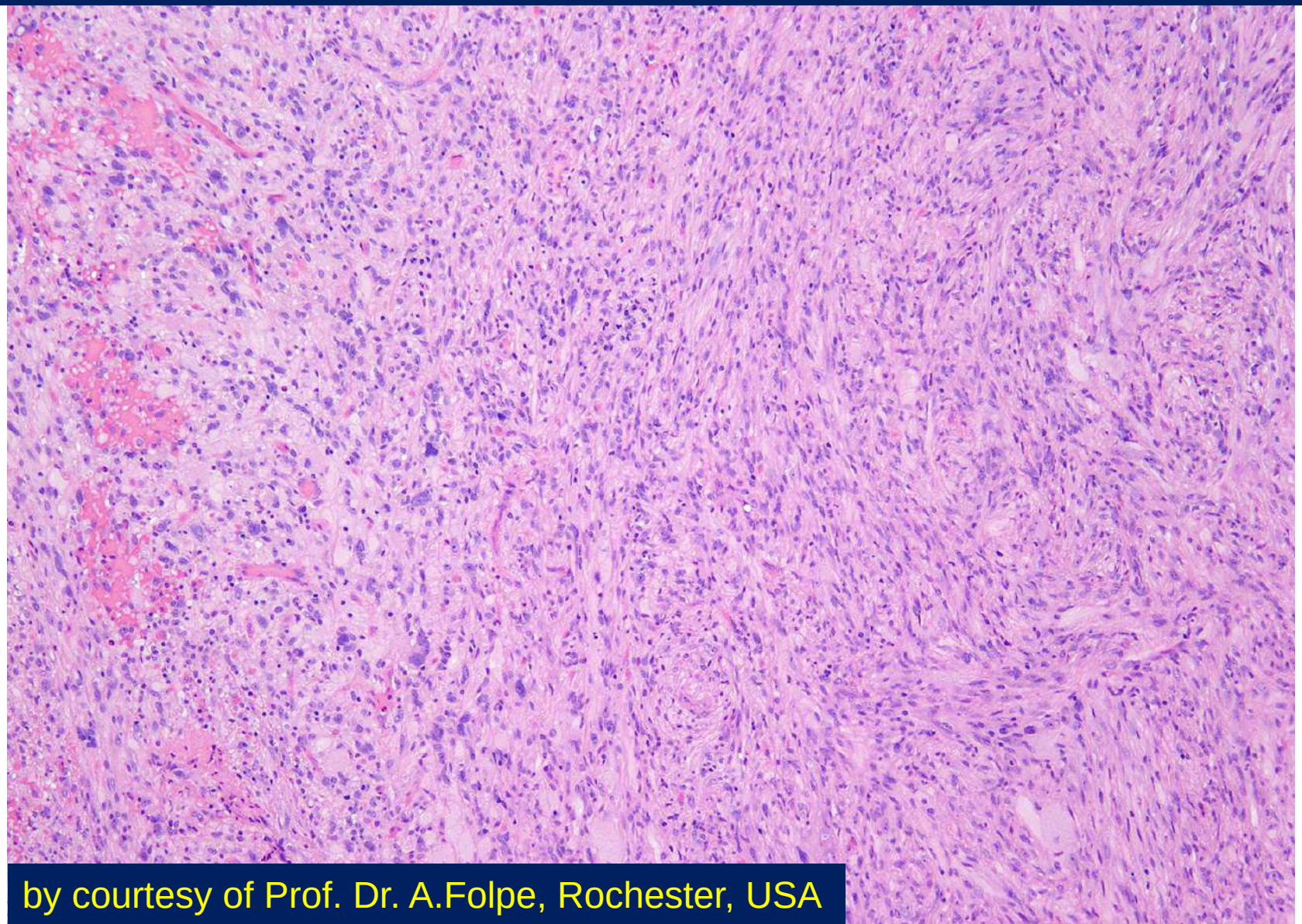

WT1 (6F-H2, N-terminus)



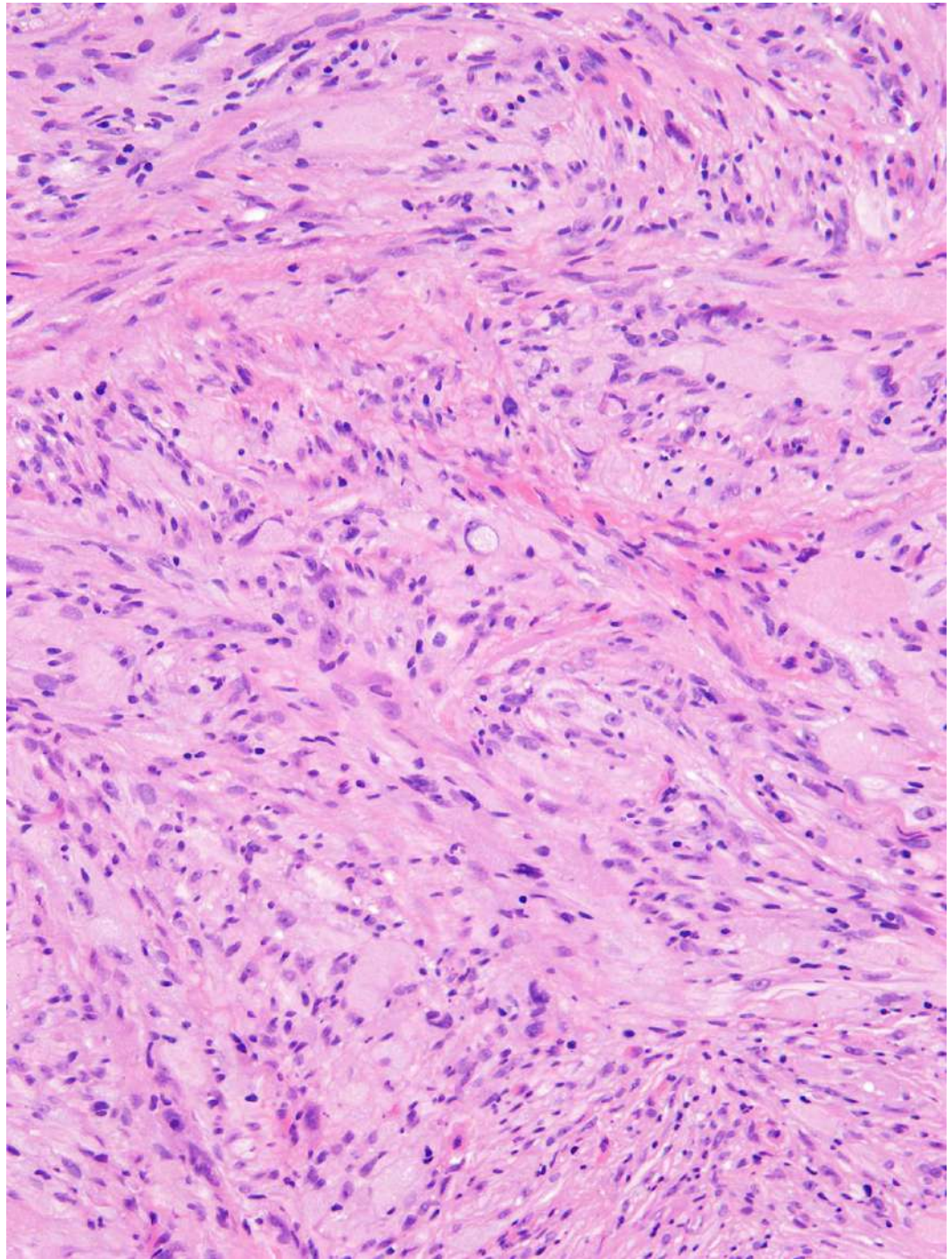
Diagnosis Case 3

superficial CD34-positive fibroblastic Tumor

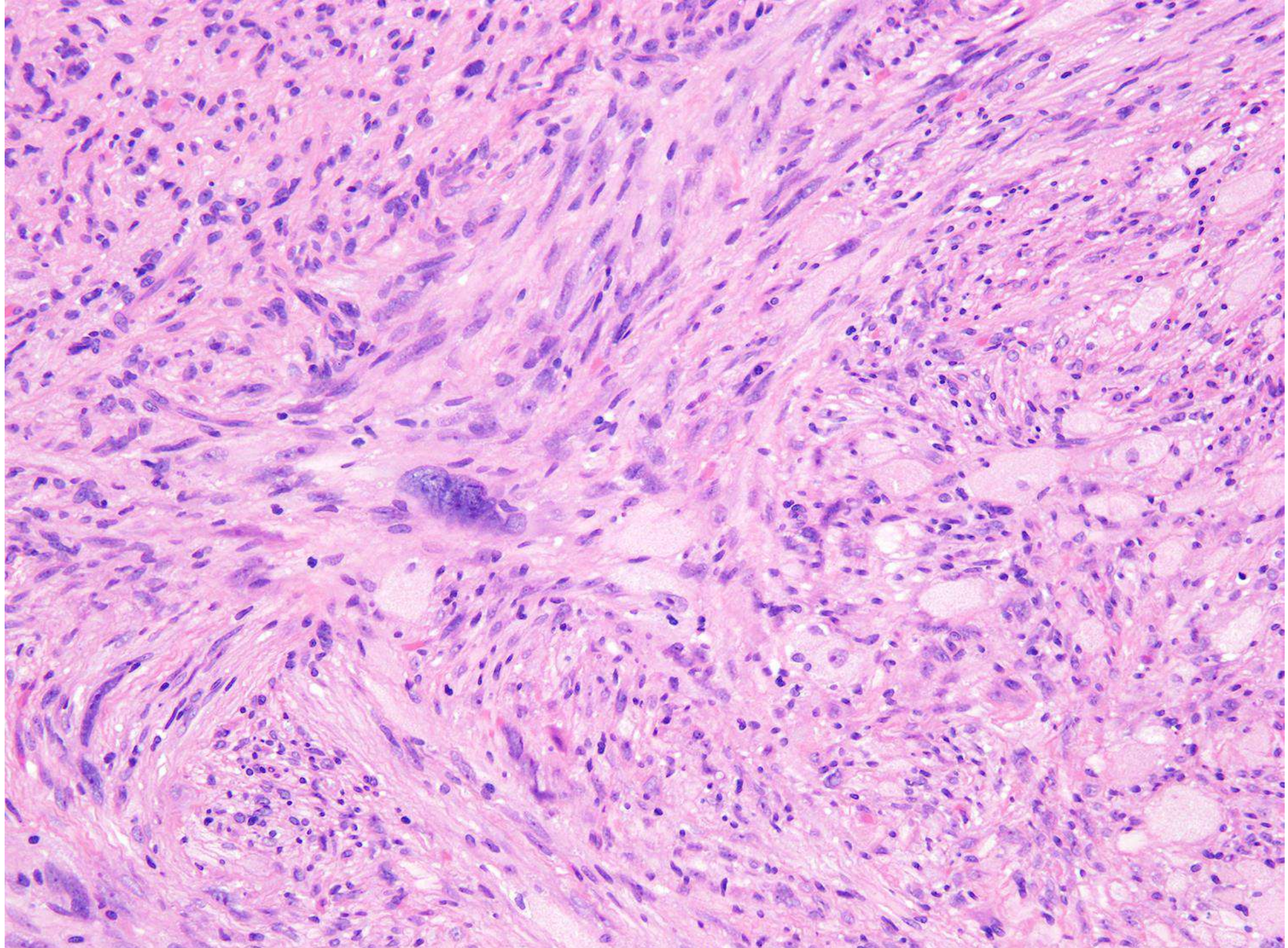
Superficial CD34-positive fibroblastic Tumour (Carter JM et al. Mod Pathol 2014; 27: 294)

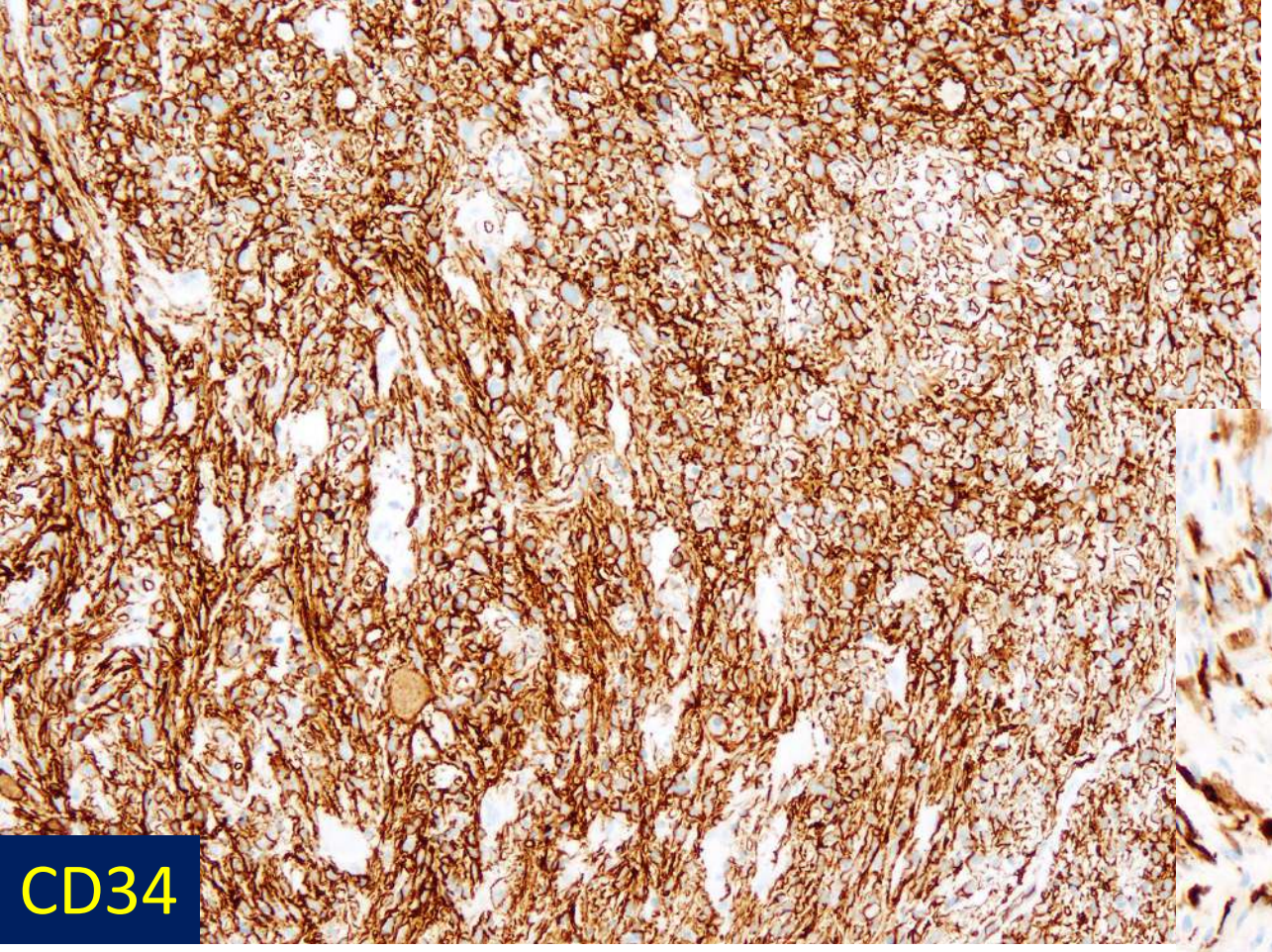


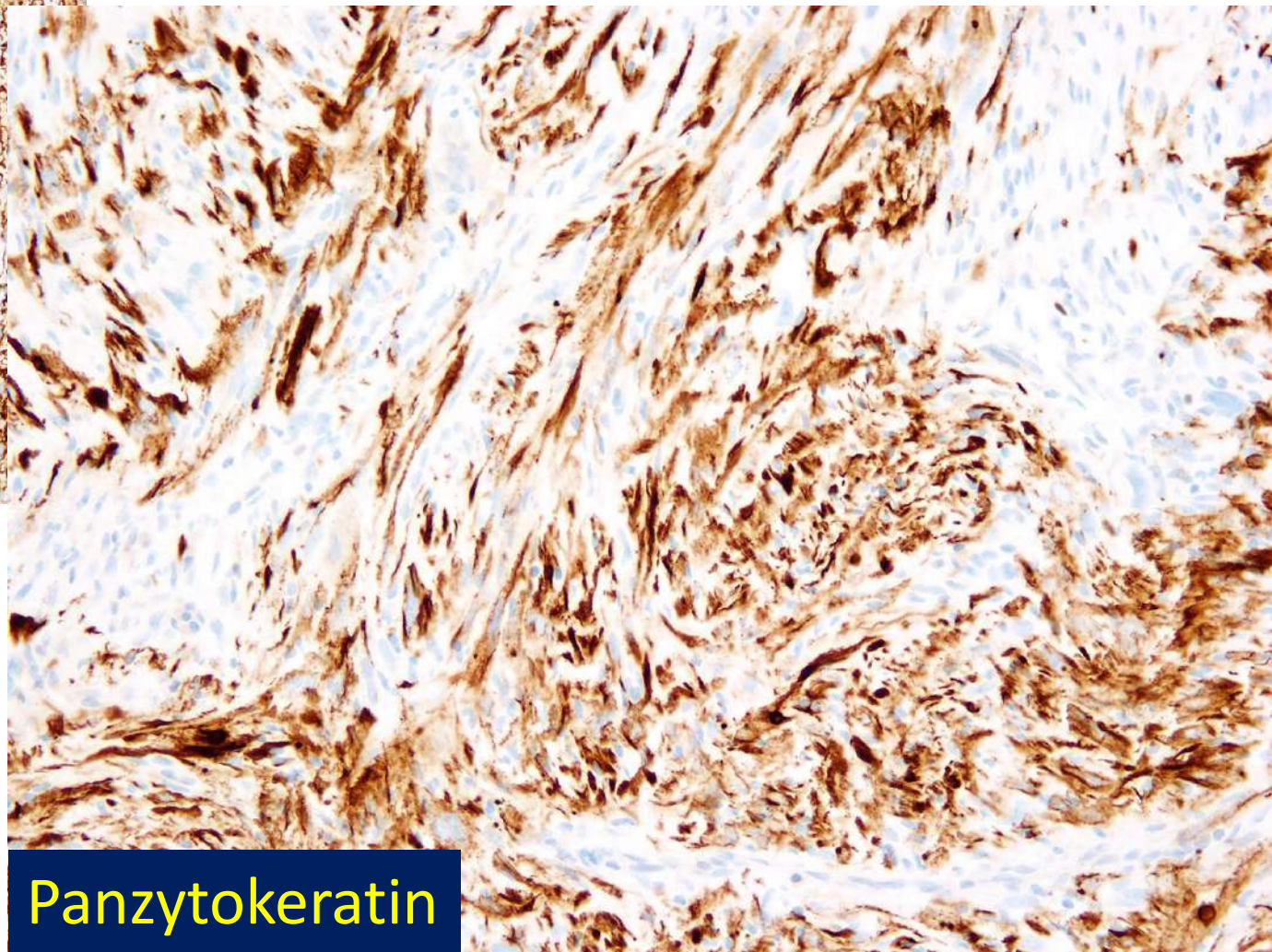
by courtesy of Prof. Dr. A.Folpe, Rochester, USA



adult patients, 10 M, 8 F
20-76 years, 1.5 – 10 cm
extremities, dermis/subcutis
ill-defined, infiltrative
spindled tumour cells
striking cellular pleomorphism
no / few mitoses
tumour necrosis in 1 case
CD34 +, CK focal +, S-100 –
Desmin -, ASMA -, ERG -
locally aggressive
MTS very rare (1/13 patients developed lymph node MTS)




CD34


Panzytokeratin

Recurrent *PRDM10* gene fusion in undifferentiated pleomorphic sarcoma
Hofvander J et al. Clin Cancer Res 2015; 21: 864-869

84 undifferentiated pleomorphic soft tissue sarcomas
3 cases showed *PRDM10* fusions (*MED12, CITED2*)

Undifferentiated pleomorphic sarcomas with *PRDM10* fusions have a distinct gene expression profile
Hofvander J et al. J Pathol 2019; 249: 425-434

upregulation of *CADM3* gene (IM CADM3 +)
PRDM10-fusions represent critical driver mutations

PRDM10-rearranged soft tissue tumor: a clinicopathological study of 9 cases
Puls F et al. Am J Surg Pathol 2019; 43: 504-513

9 cases, 5 M, 4 F, 20-61 years, 1/9 local recurrence
CD34 +, PRDM10 + (nuclear), 5/6 CK + (focal)

Superficial CD34-positive fibroblastic tumor: A clinicopathologic, immunohistochemical, and molecular study of 59 cases

Anderson WJ et al. Am J Surg Pathol 2022; 46: 1329

33 M, 26 F, 14-85 years, 1-9 cm in diameter

lower limb (73%), upper limb (8%), back (7%), trunk (3%)

local recurrence (2), lymph node metastasis (1)

spindled and pleomorphic cells

CD34 +, CADM3 + (95%), WT1 + (75%)

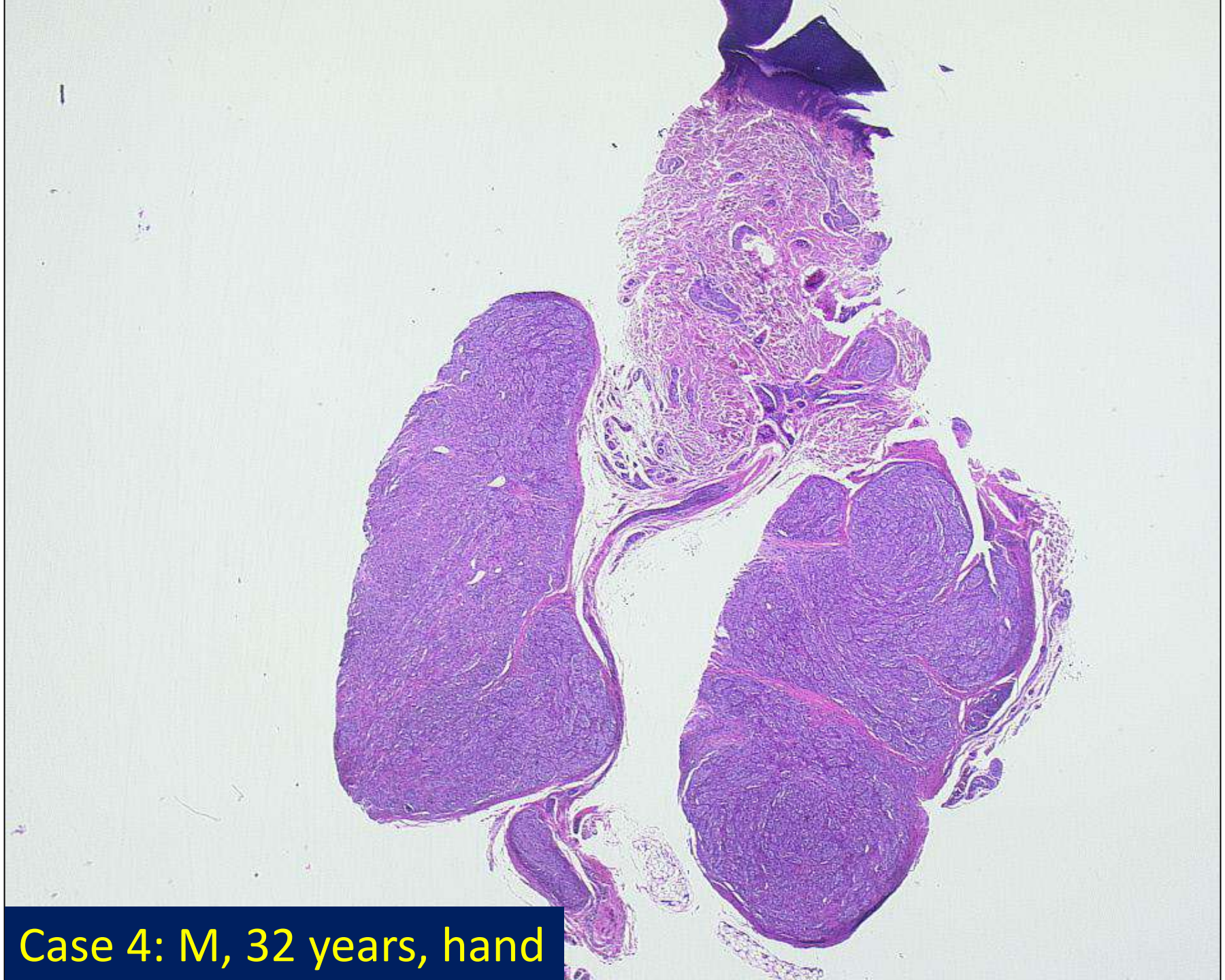
3/8 cases showed *PRDM10* rearrangement

Conclusions: indolent rarely metastasizing tumour

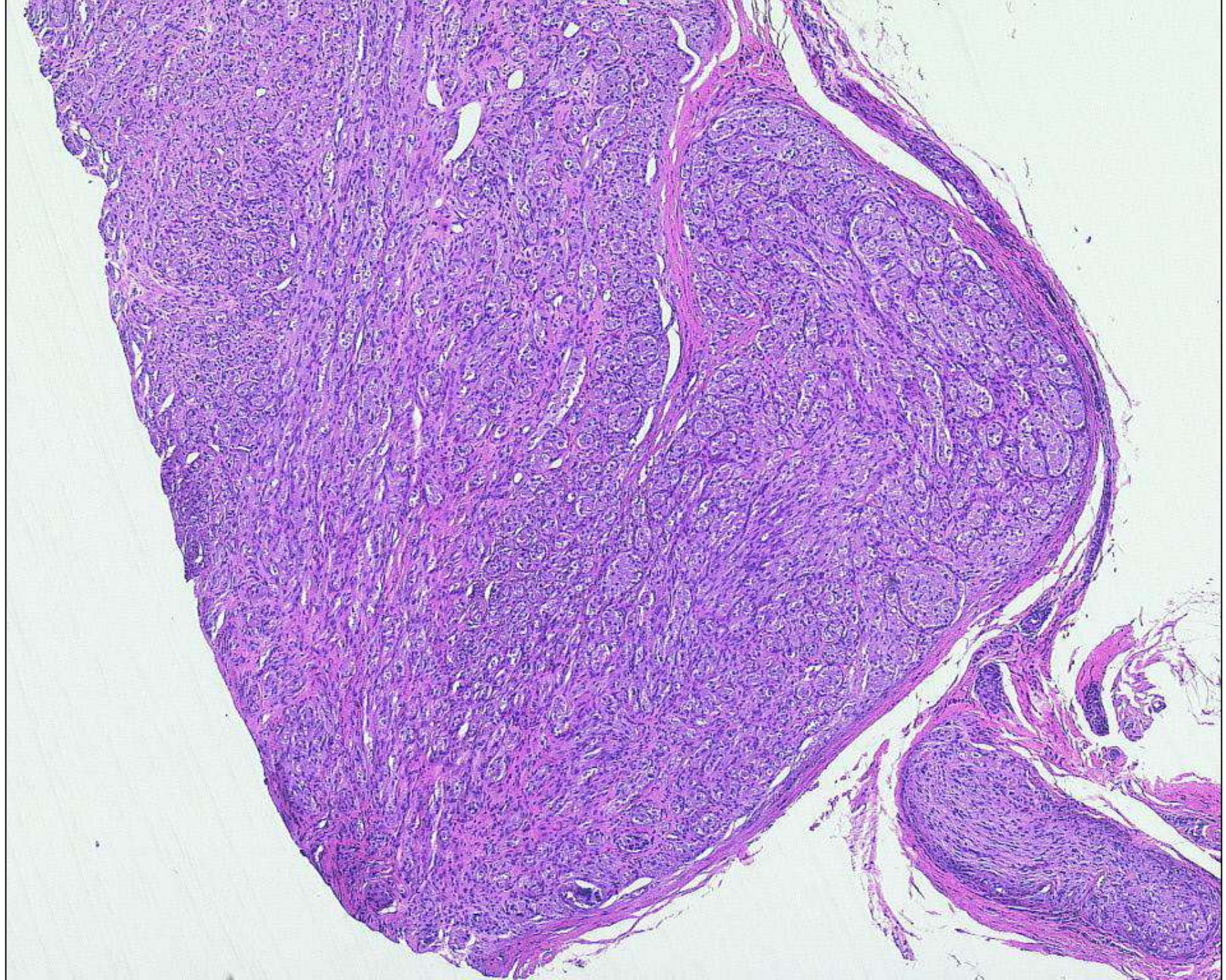
SCD34FT and PRDM10-STT are related

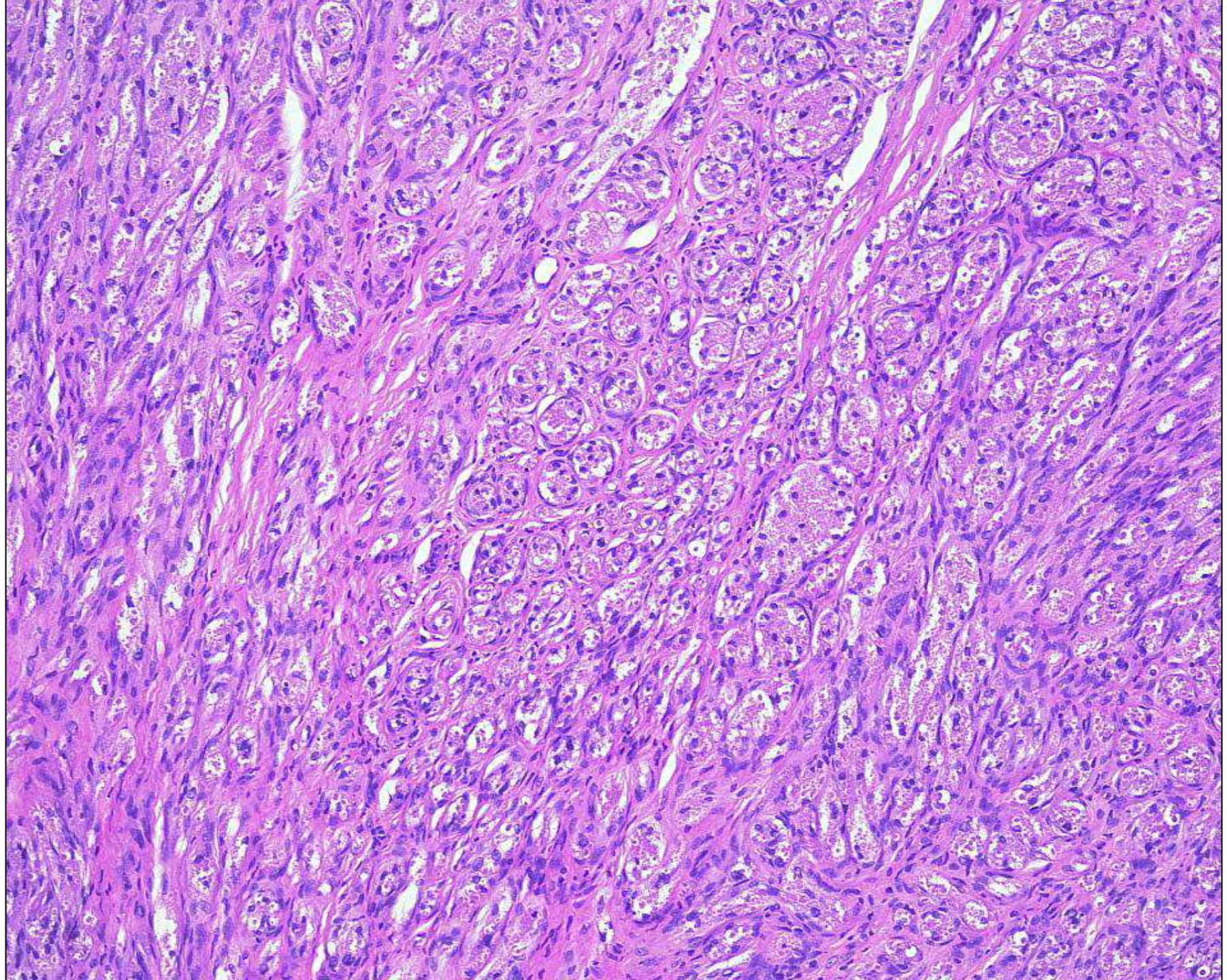
superficial CD34-positive fibroblastic tumor
Immunohistochemistry

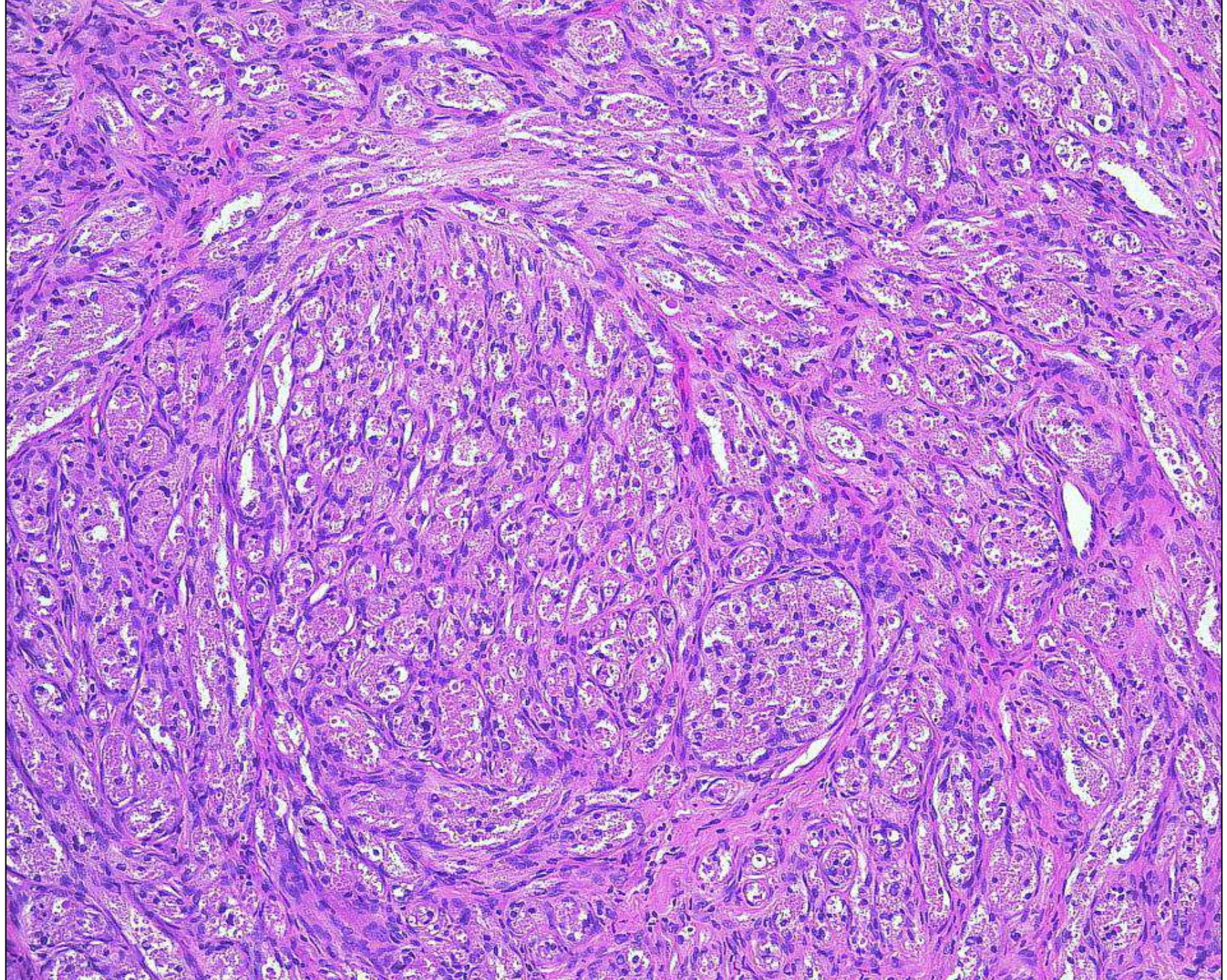
CD 34	100% positive
AE1/3	70% positive (focal)
Desmin	35% positive (focal)
CADM3	95% positive (nuclear)
WT1	75% positive (nuclear)

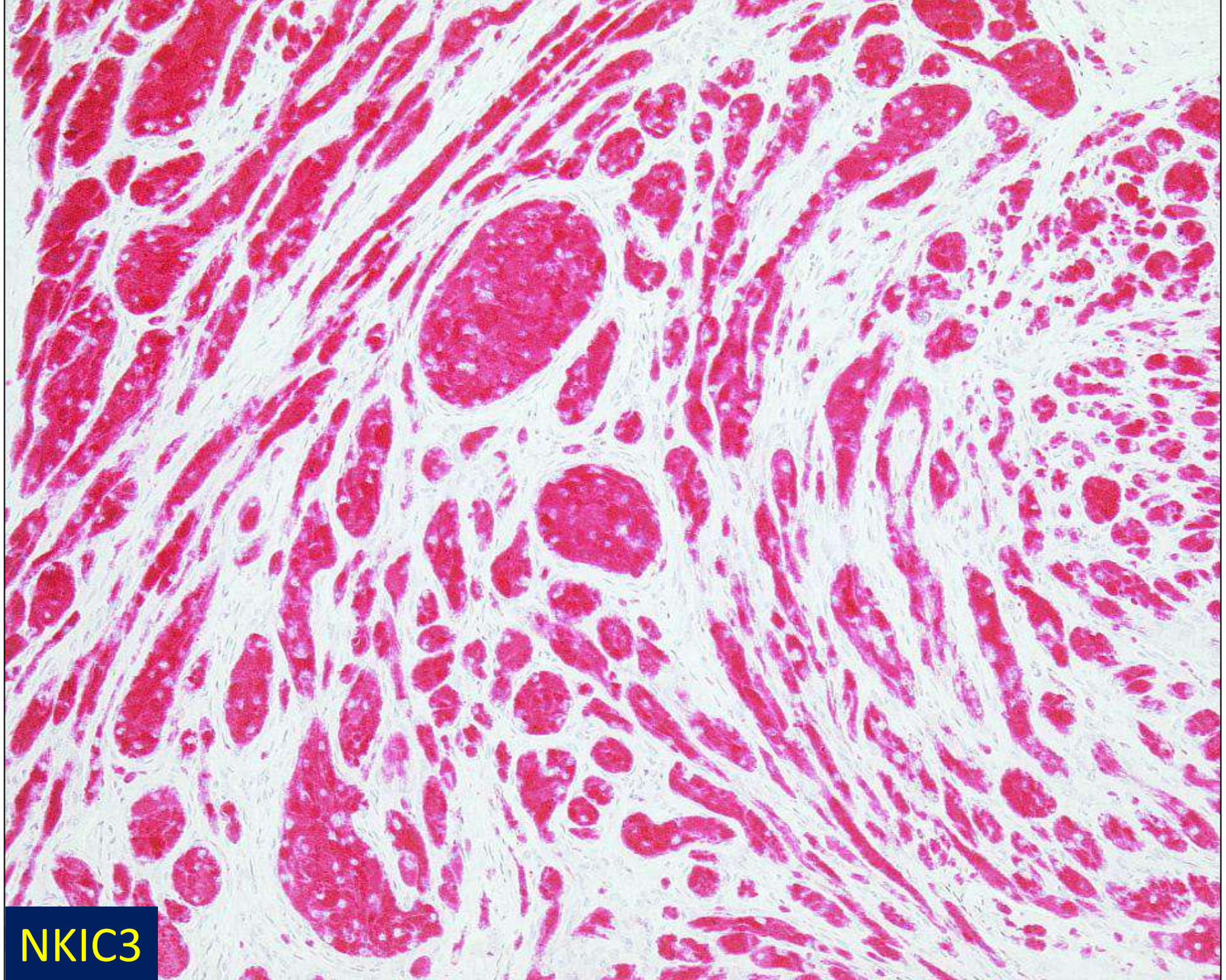


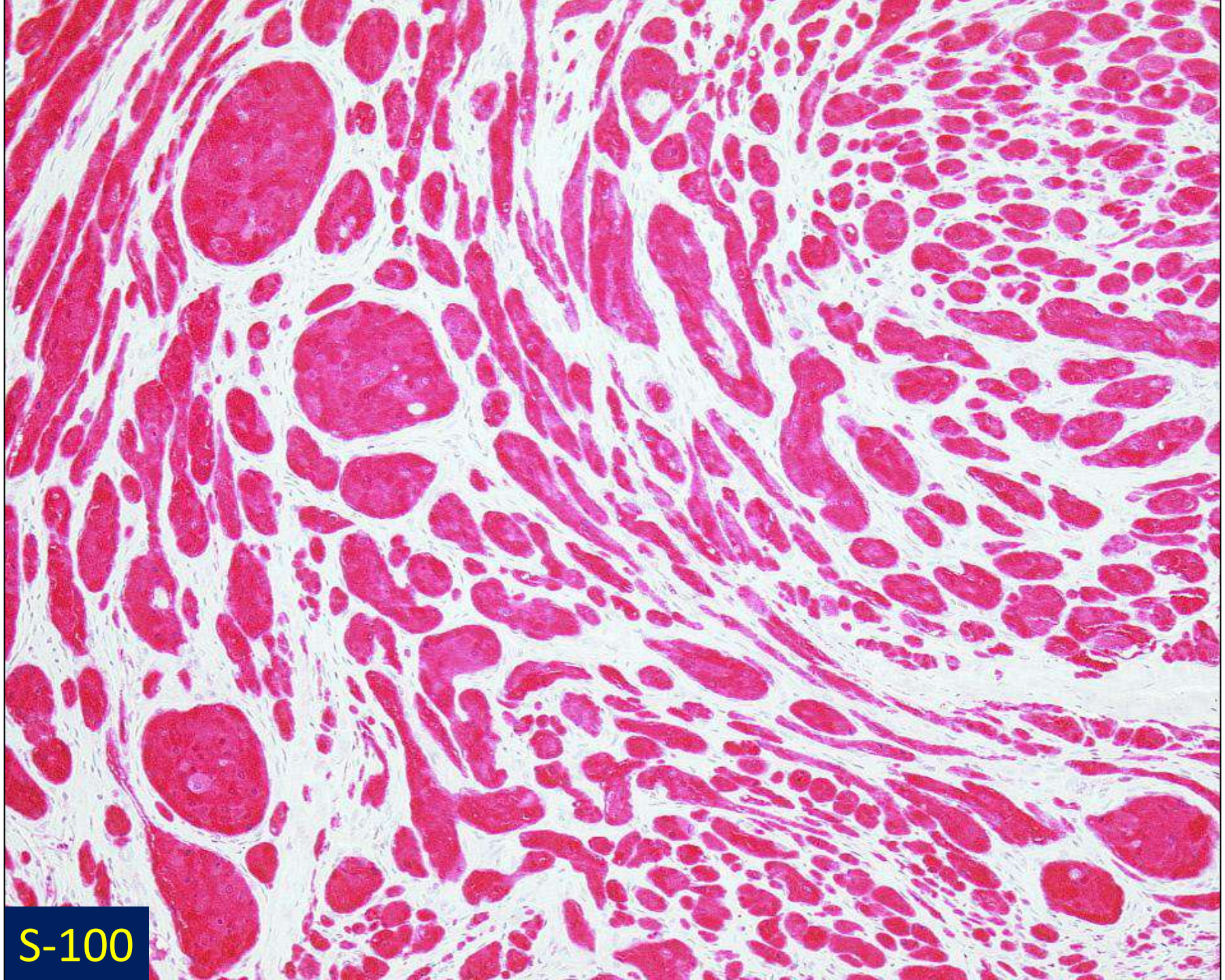
Case 4: M, 32 years, hand

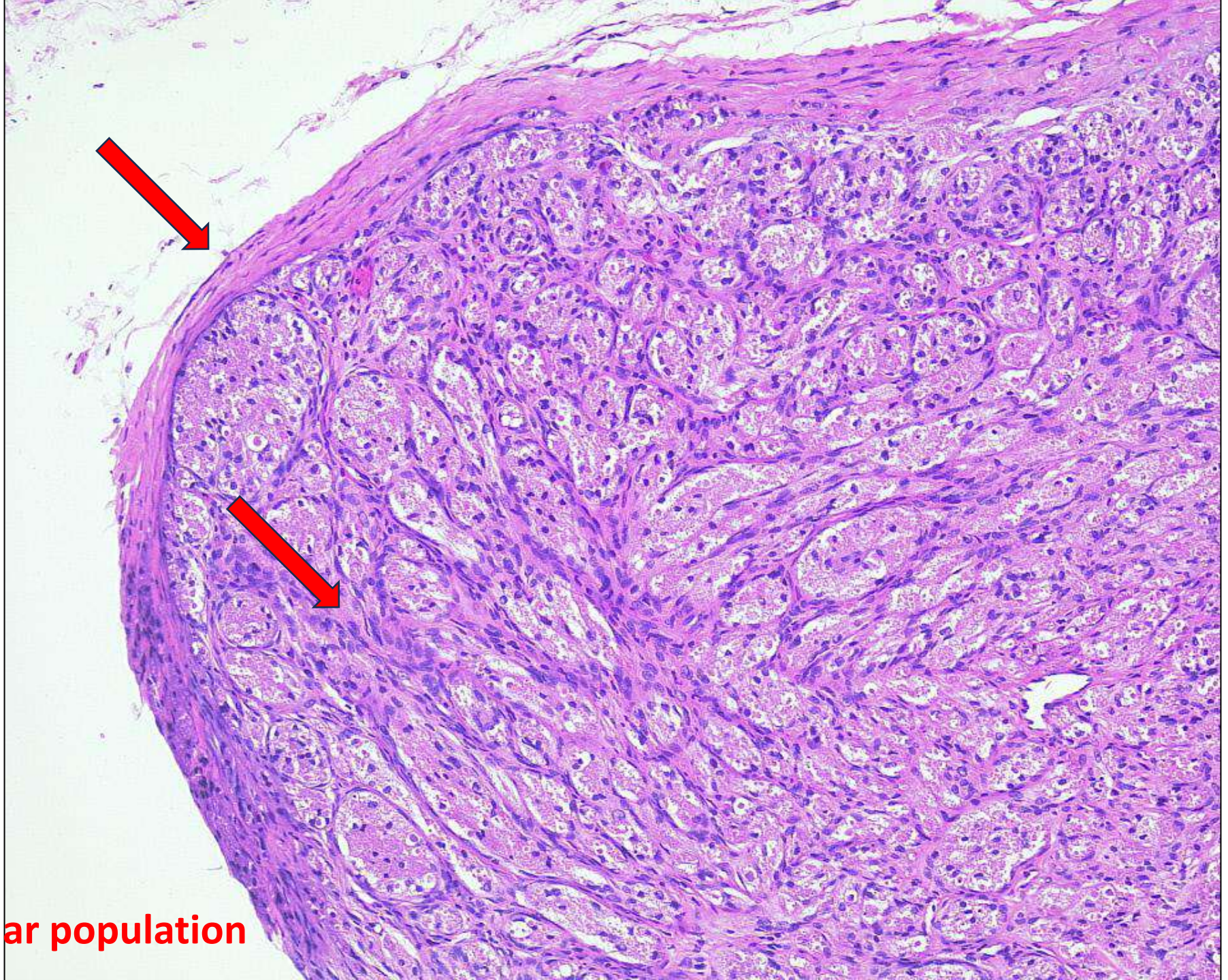






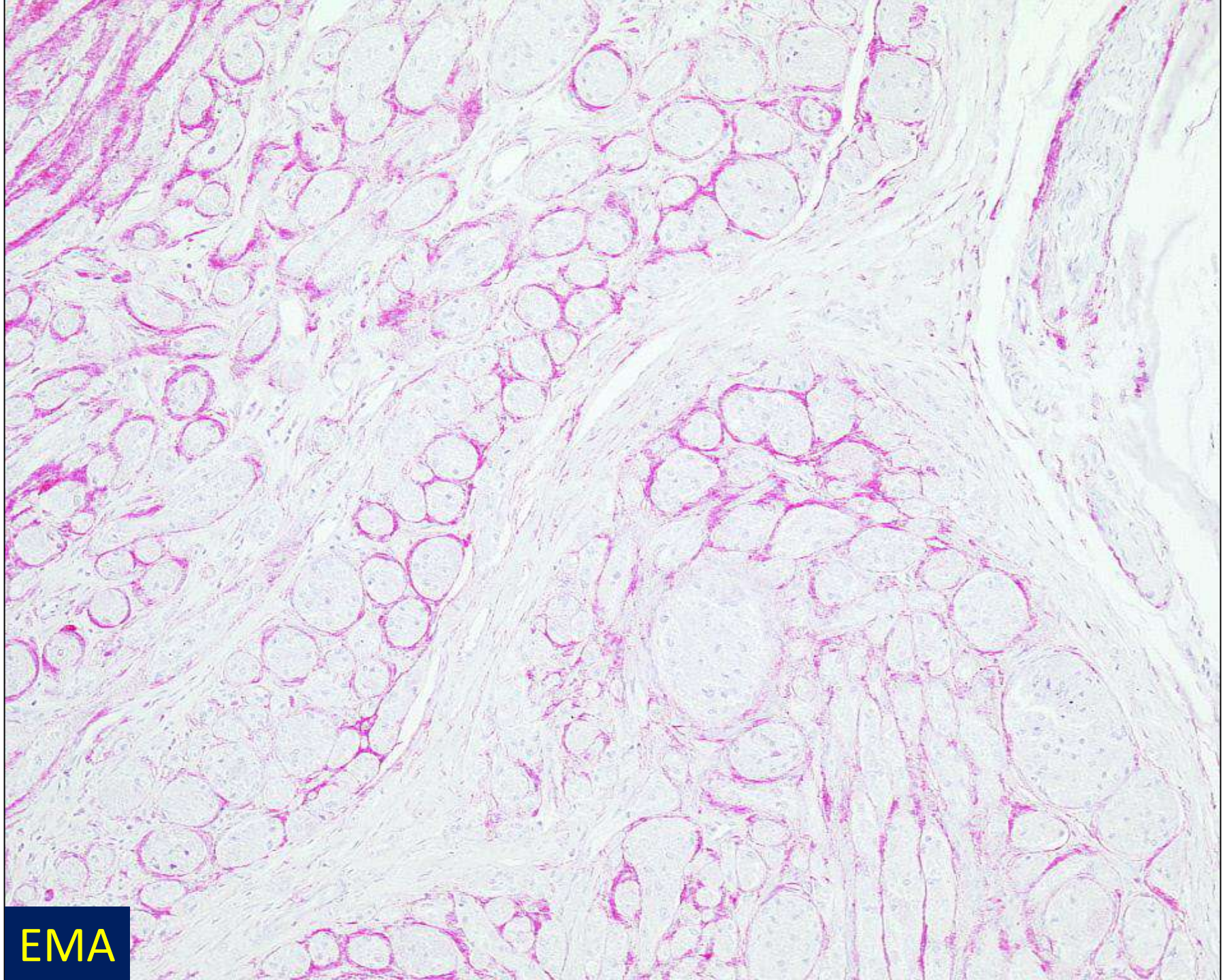

NKIC3

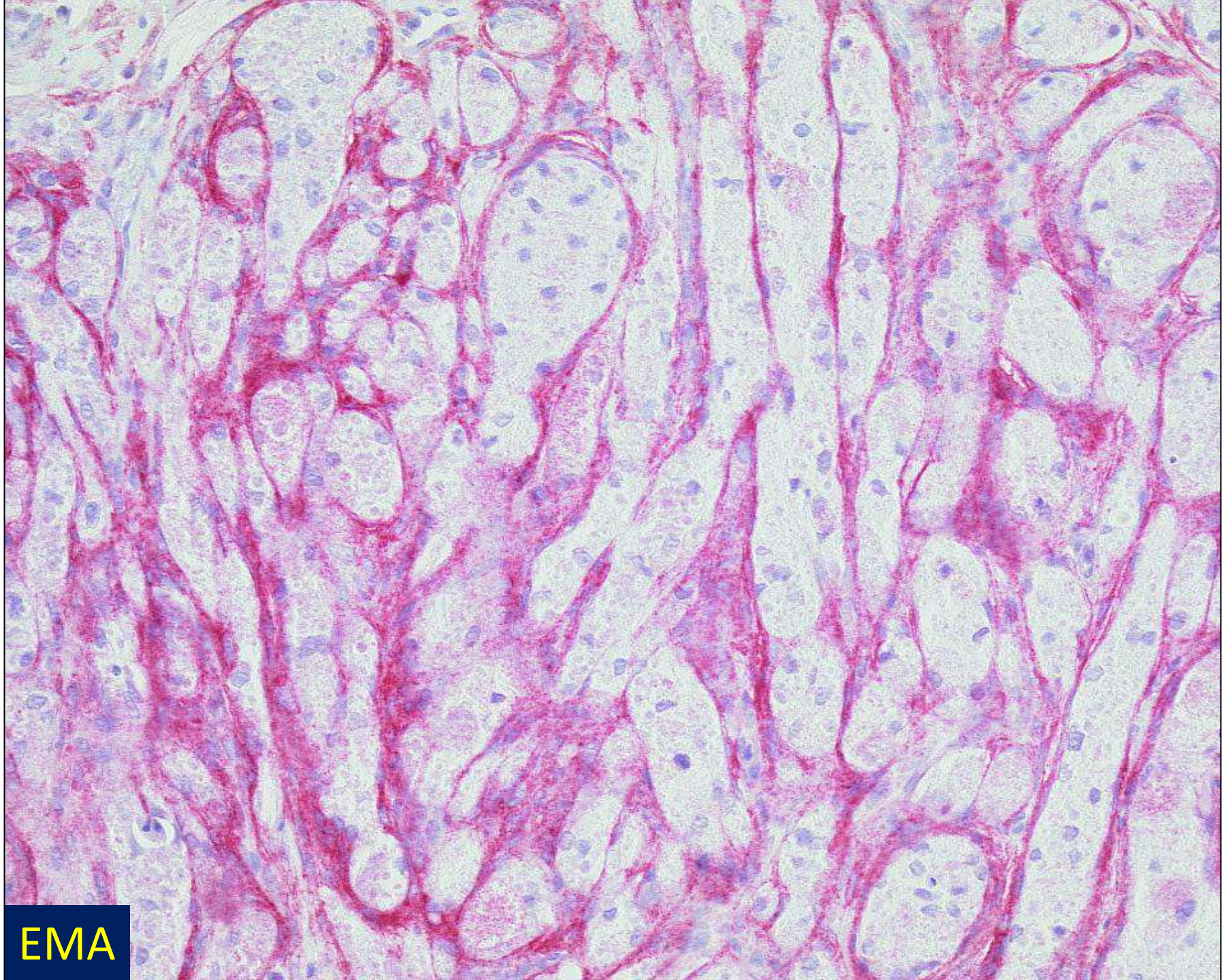

S-100



capsule

second cellular population


EMA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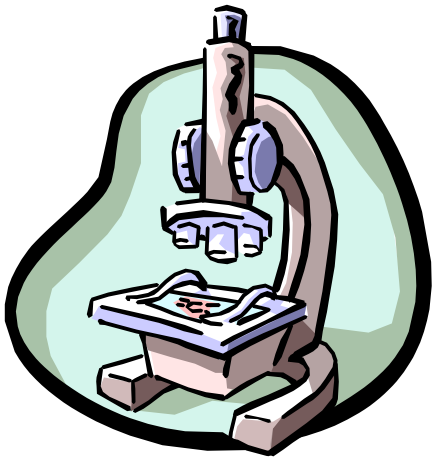


Diagnosis Case 4

granular cell hybrid peripheral nerve sheath Tumour (schwannoma / perineurioma)

Classification of benign peripheral nerve sheath Tumours

Neurofibroma: schwann cells, perineurial cell, fibroblasts
(plexiform, diffuse, epithelioid, pigmented, dendritic, atypical)

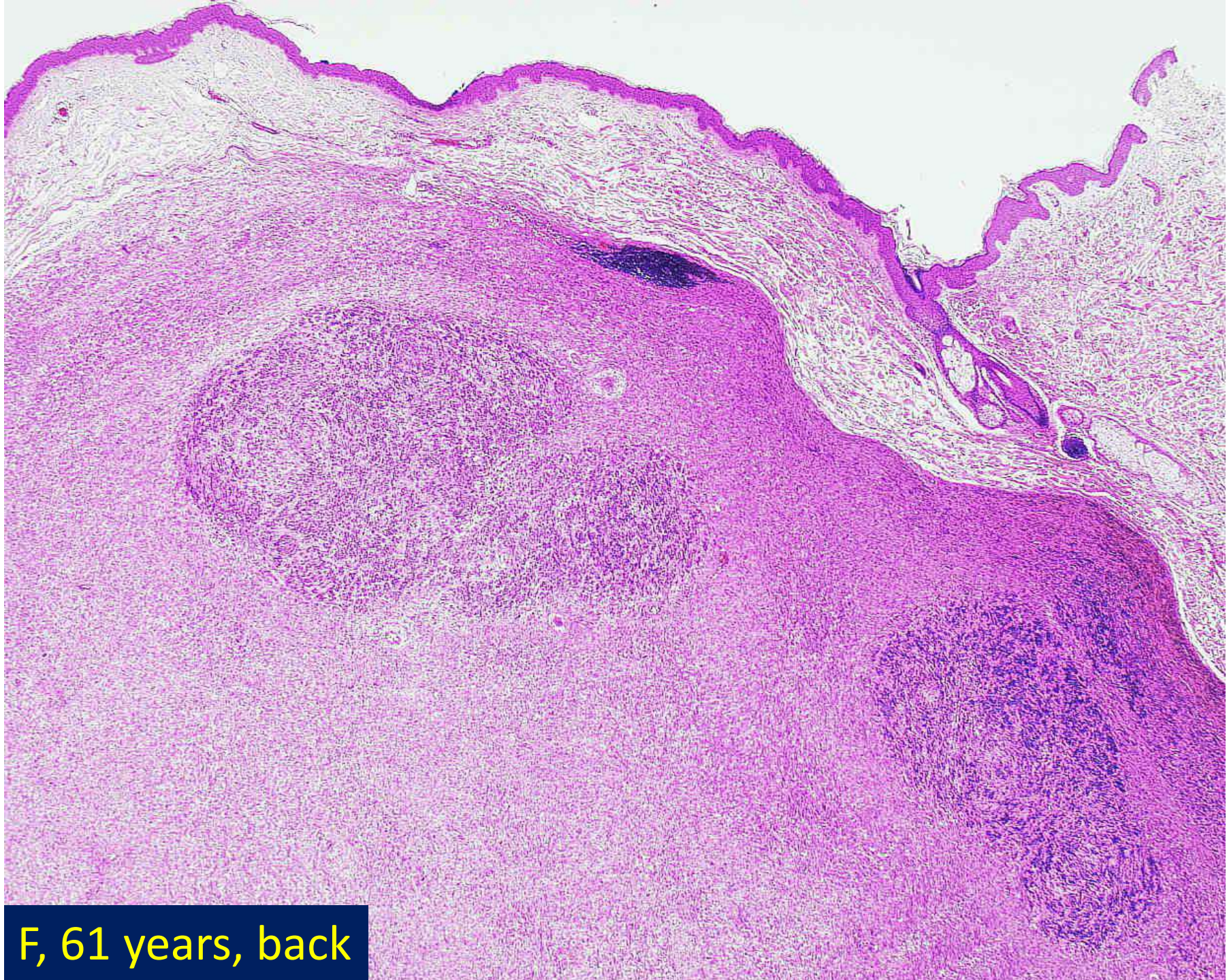
Schwannoma: schwann cells
(cellular, ancient, plexiform, epithelioid, reticular, neuroblastoma-like)

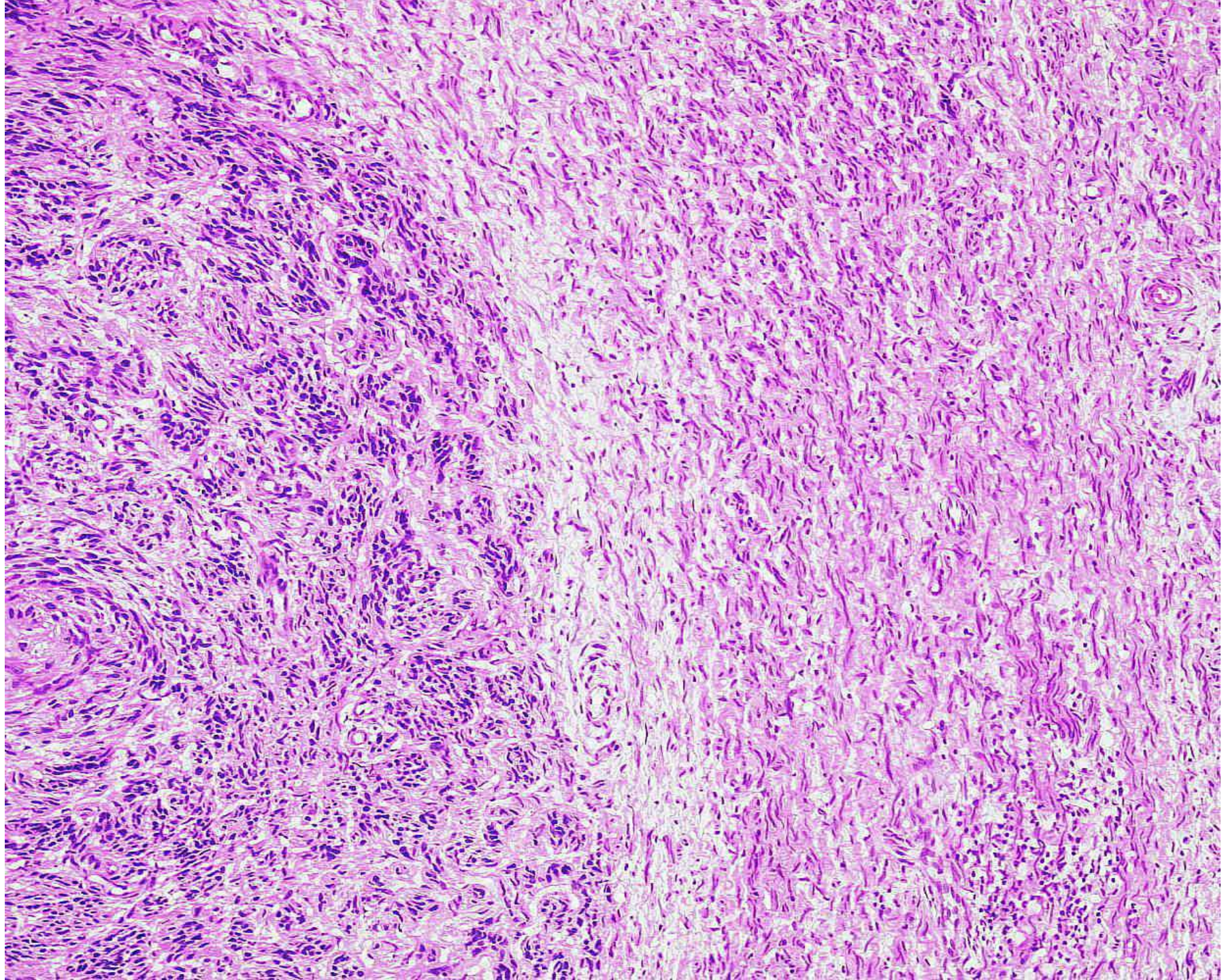
Perineurioma: perineurial cells
(intra- and extraneural spindle cell, sclerosing, reticular)

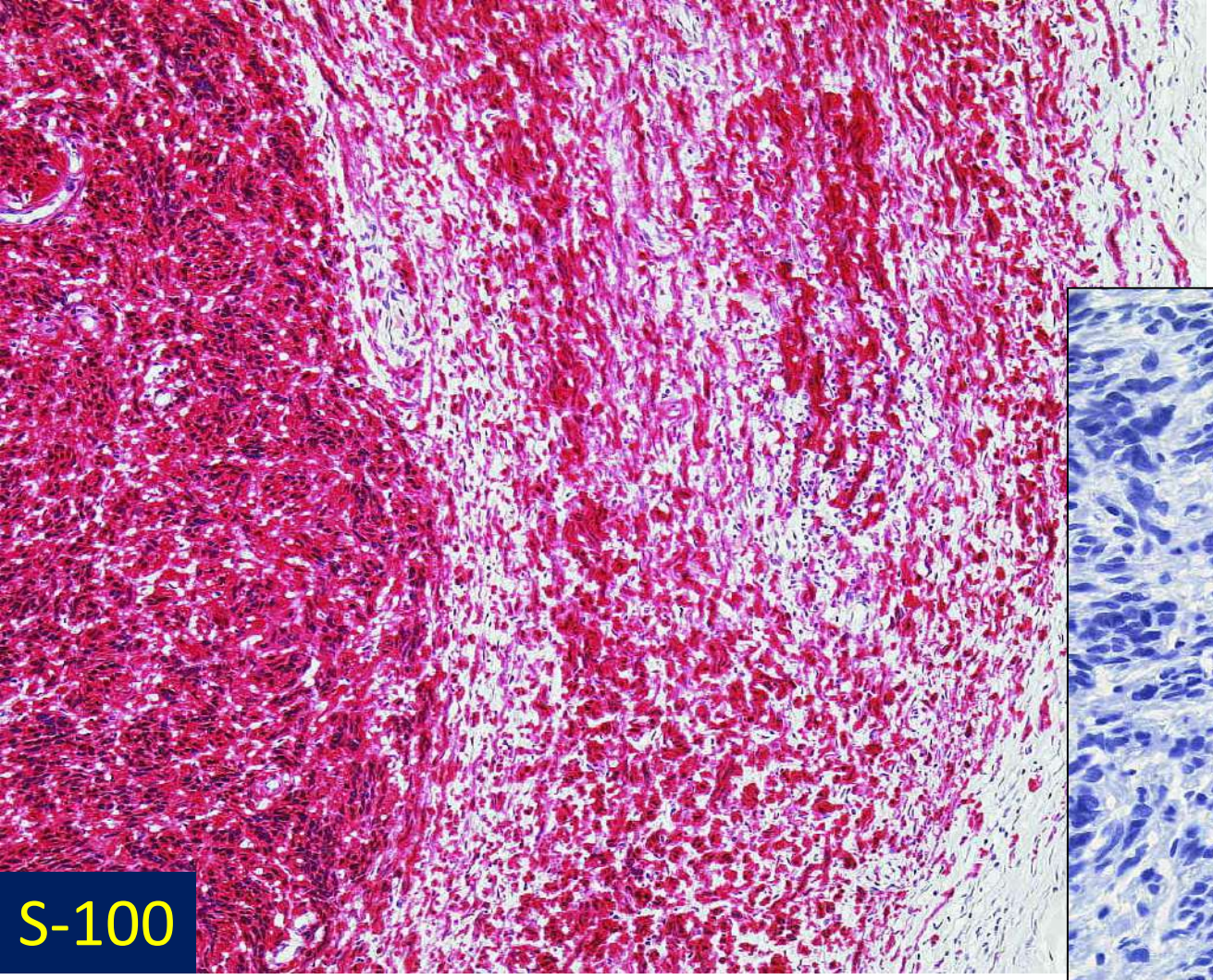
Neuroma
(traumatic, mucosal, Morton`s, Pacinian, solitary circumscribed)

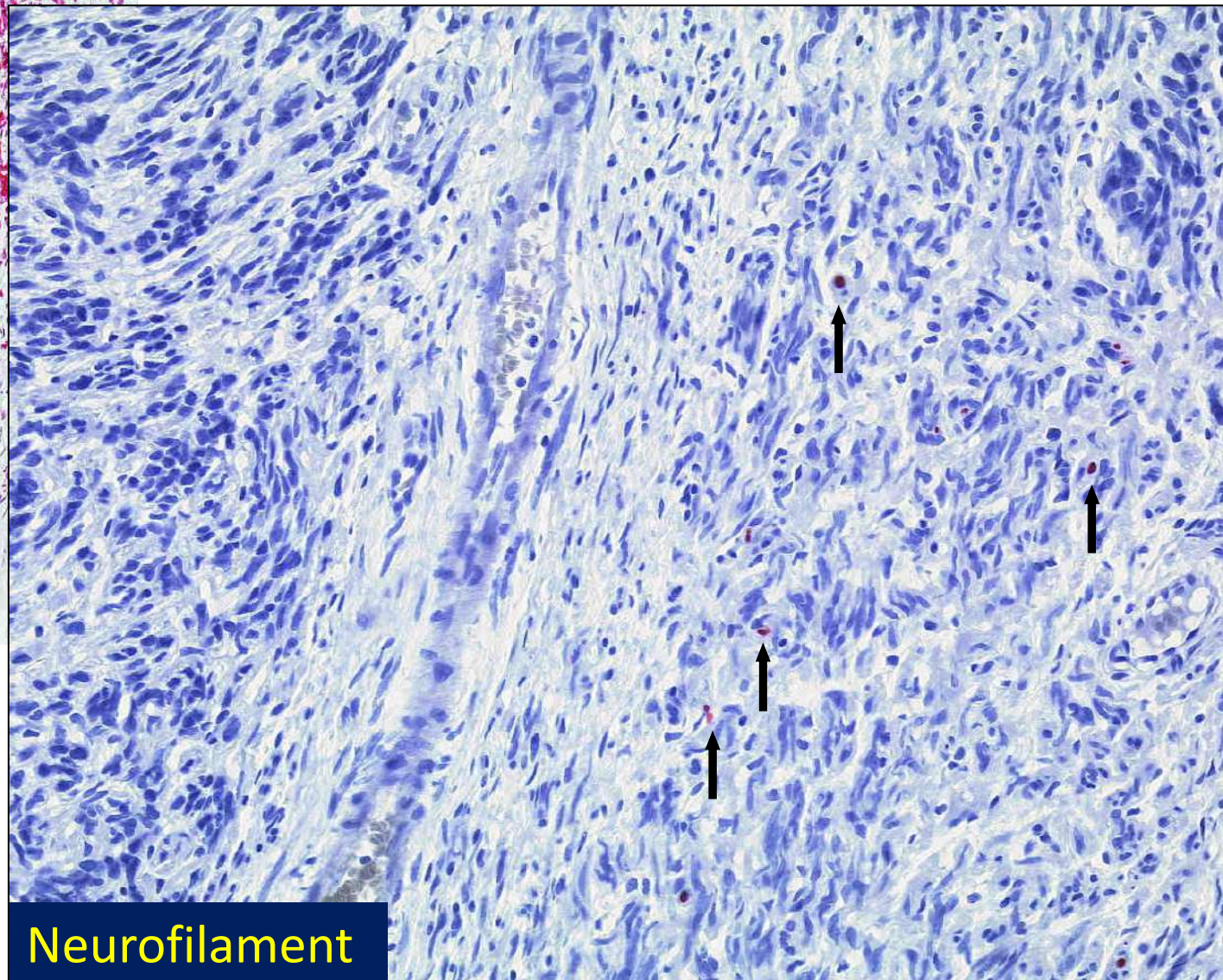
Nerve sheath tumours with hybrid features of neurofibroma and schwannoma (Feany MB et al. Histopathology 1998; 32: 405)

9 cases, 1 F, 8 M, 12 - 66 years
trunk (6), upper (2), lower (1) extremity
dermis (2), subcutis (2), subfascial (5)
plexiform growth (5), neurofibromatosis (1)
well-circumscribed, multinodular
areas of typical neurofibroma
(neurofilment positive axons)
schwannomatous nodules
(degenerative atypia (2), hyalinised vessels)


F, 61 years, back



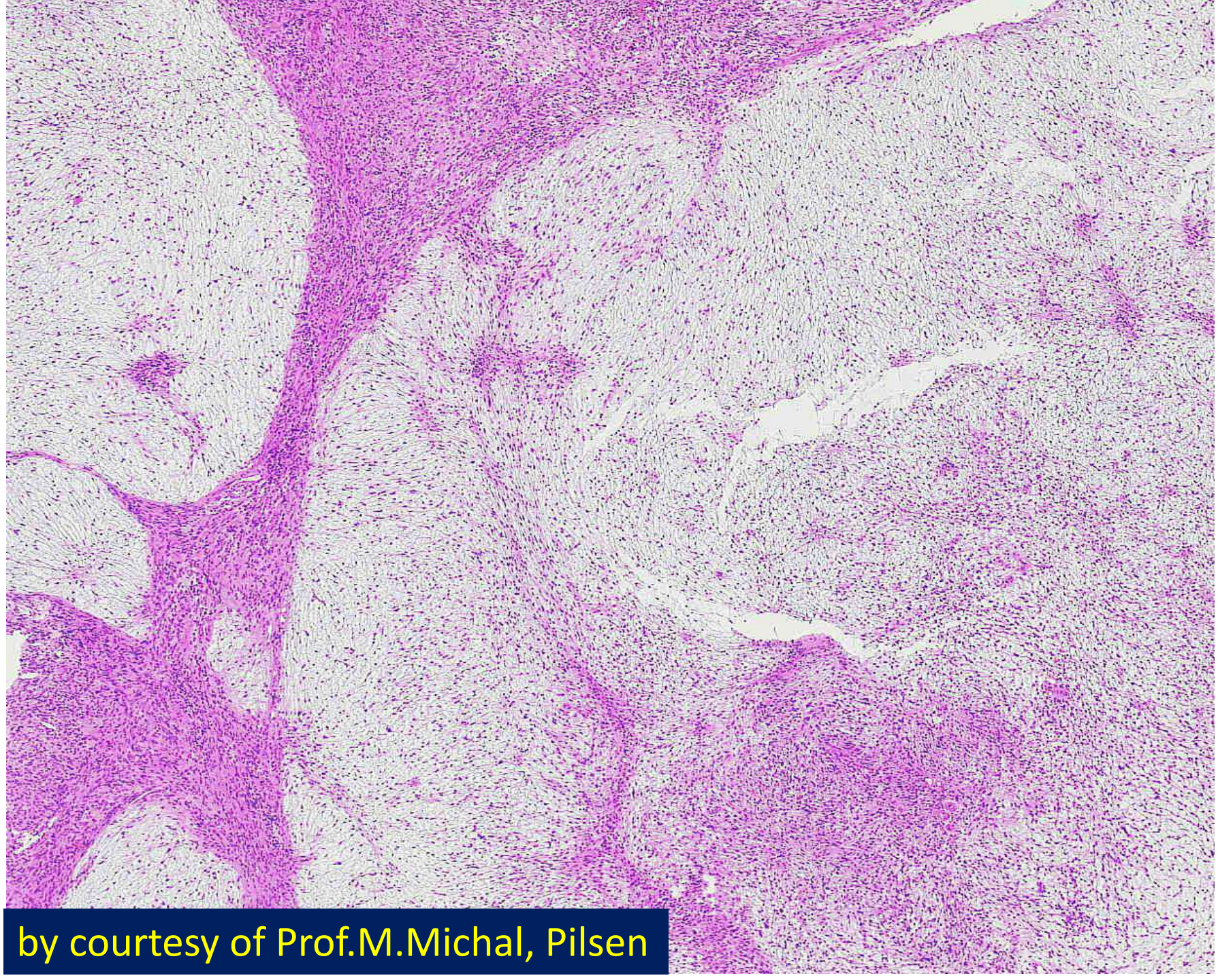

S-100


Neurofilament

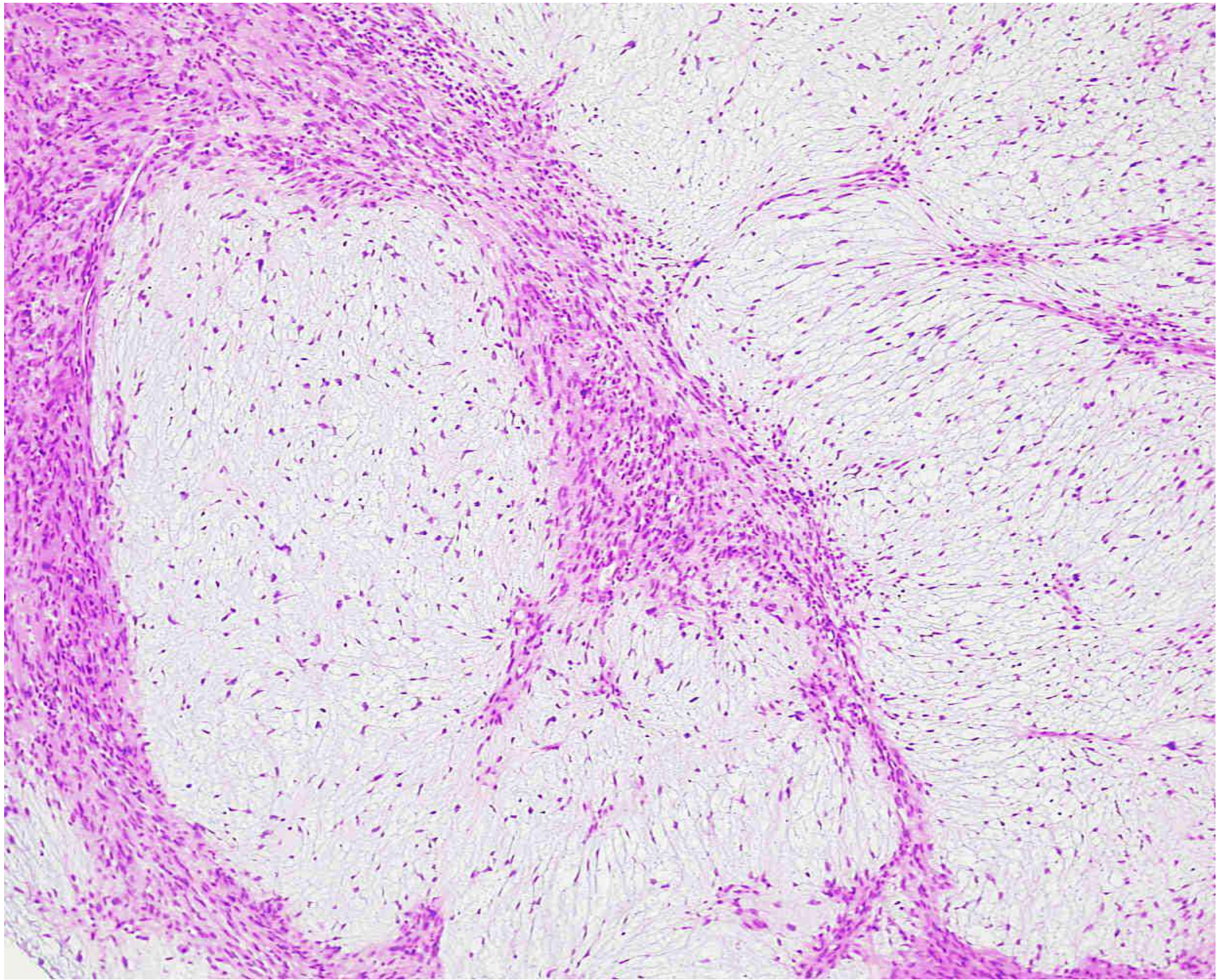
A benign neoplasm with histopathological features of both schwannoma and retiform perineurioma: a report of six cases of a distinctive soft tissue tumor with a predilection for the fingers (Michal M et al. Virchows Arch 2004; 445: 347)

6 cases, 5 F, 1 M, 20 - 52 years
finger (4), thumb (1), thenar (1)
unencapsulated, lobular lesions
myxoid and pseudocystic changes
reticular perineurioma-like areas
- loops of elongated spindled cells, myxoid stroma, EMA +

schwannomatous areas
- compact Antoni A areas, S-100 +

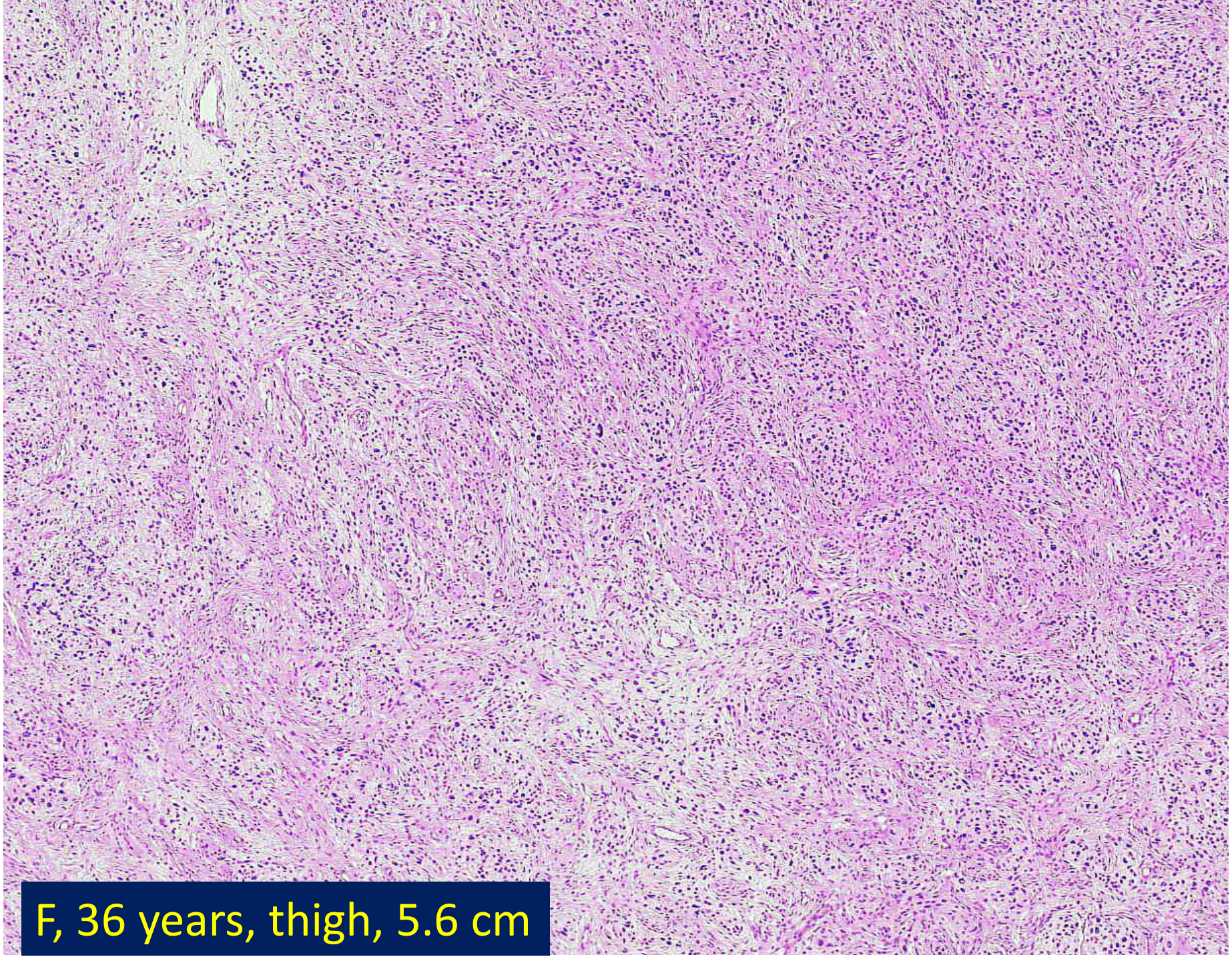


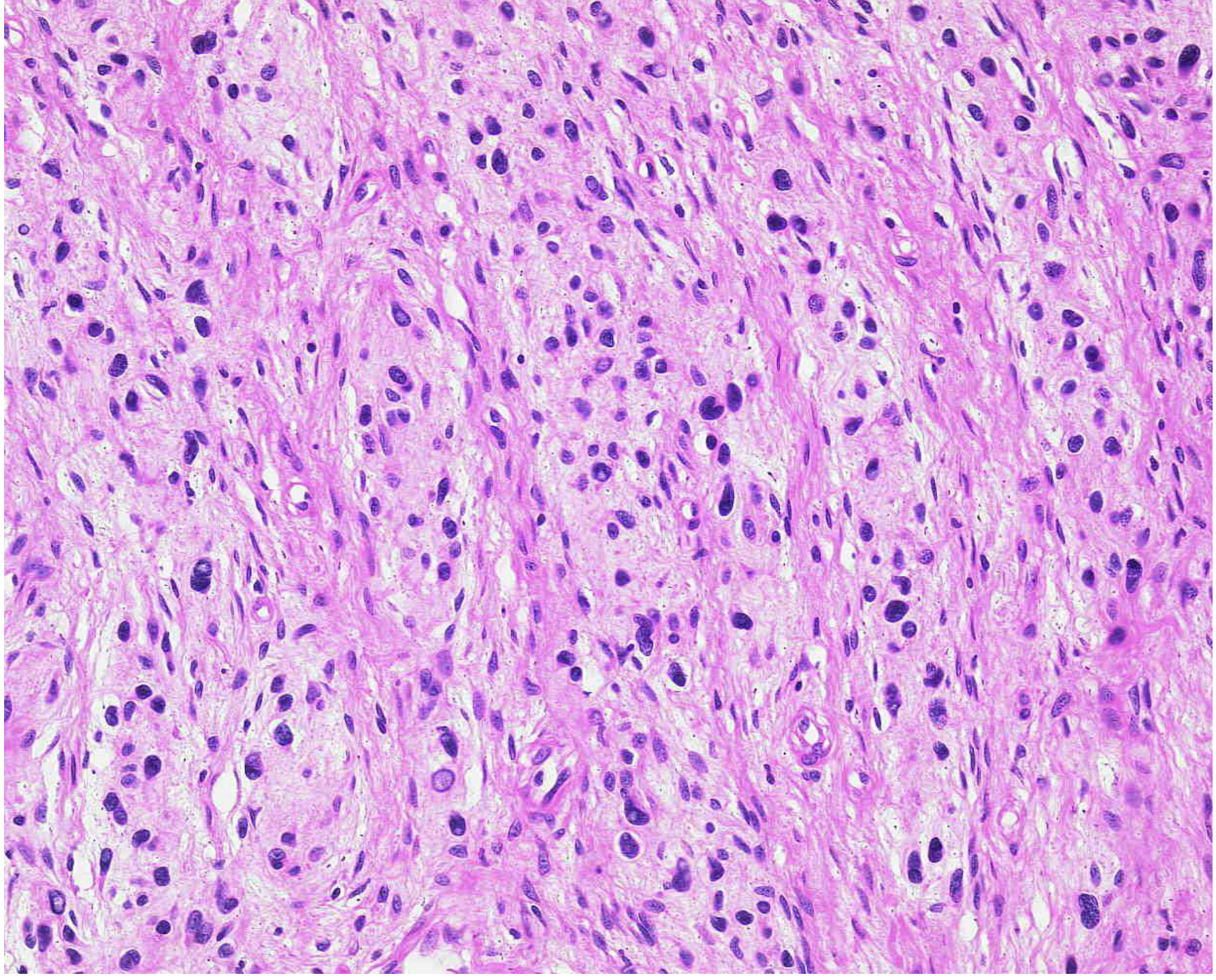
by courtesy of Prof.M.Michal, Pilsen

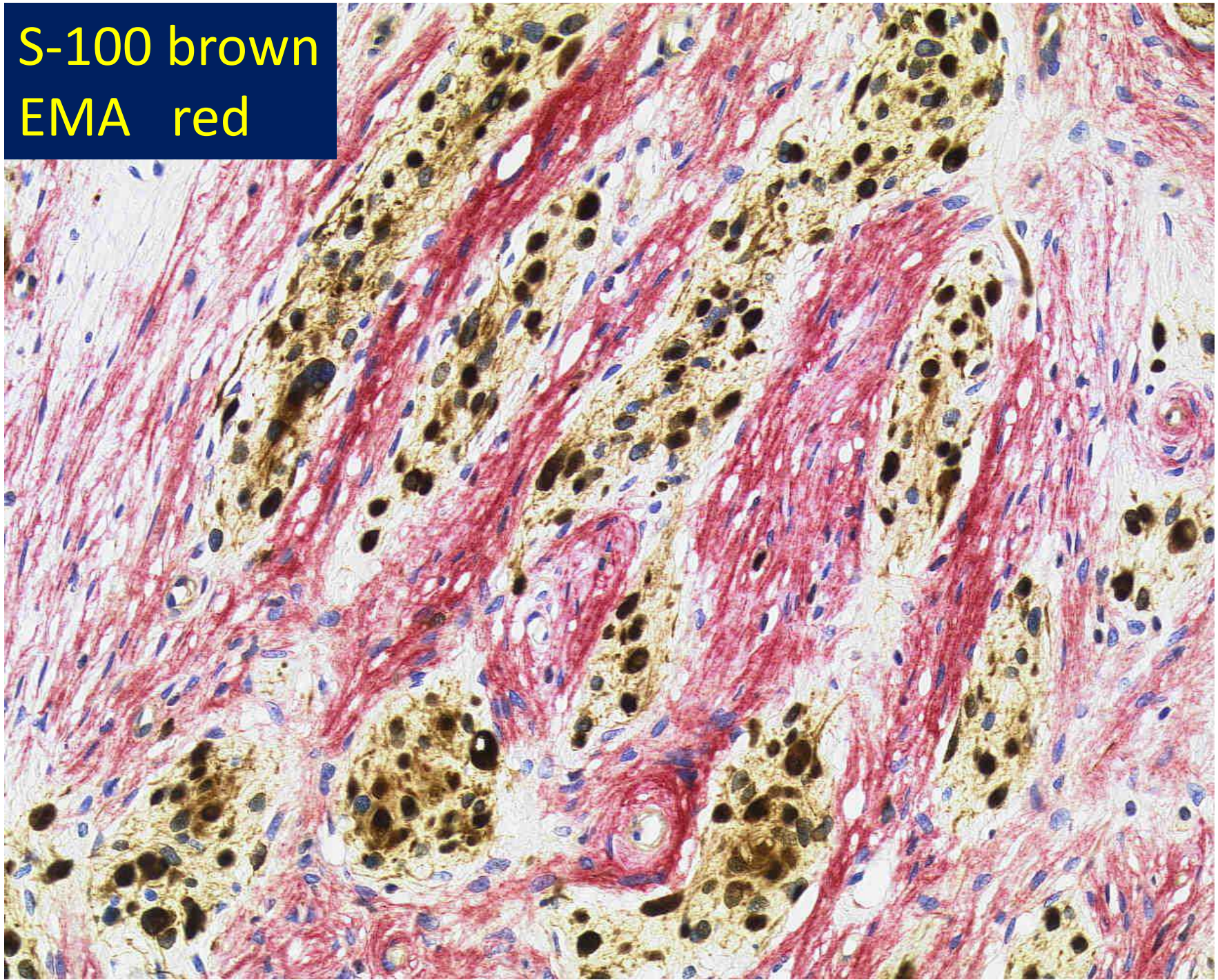


Hybrid Schwannoma / Perineurioma
Clinicopathologic analysis of 42 distinctive benign nerve sheath tumors
(Hornick JL et al. AJSP 2009; 33: 1554)

22 F, 20 M, 2 - 85 years, 1 local recurrence
limbs (31), head / neck (6), trunk (4), colon (1)
tumour size 0.7 – 17.5 cm (mean: 3.0 cm)
skin and subcutaneous tissues (70%)
rarely deep soft tissues or visceral sites
wide age range and anatomic distribution
most often extremities
no association with neurofibromatosis
rarely recurs locally


F, 36 years, thigh, 5.6 cm




S-100 brown
EMA red

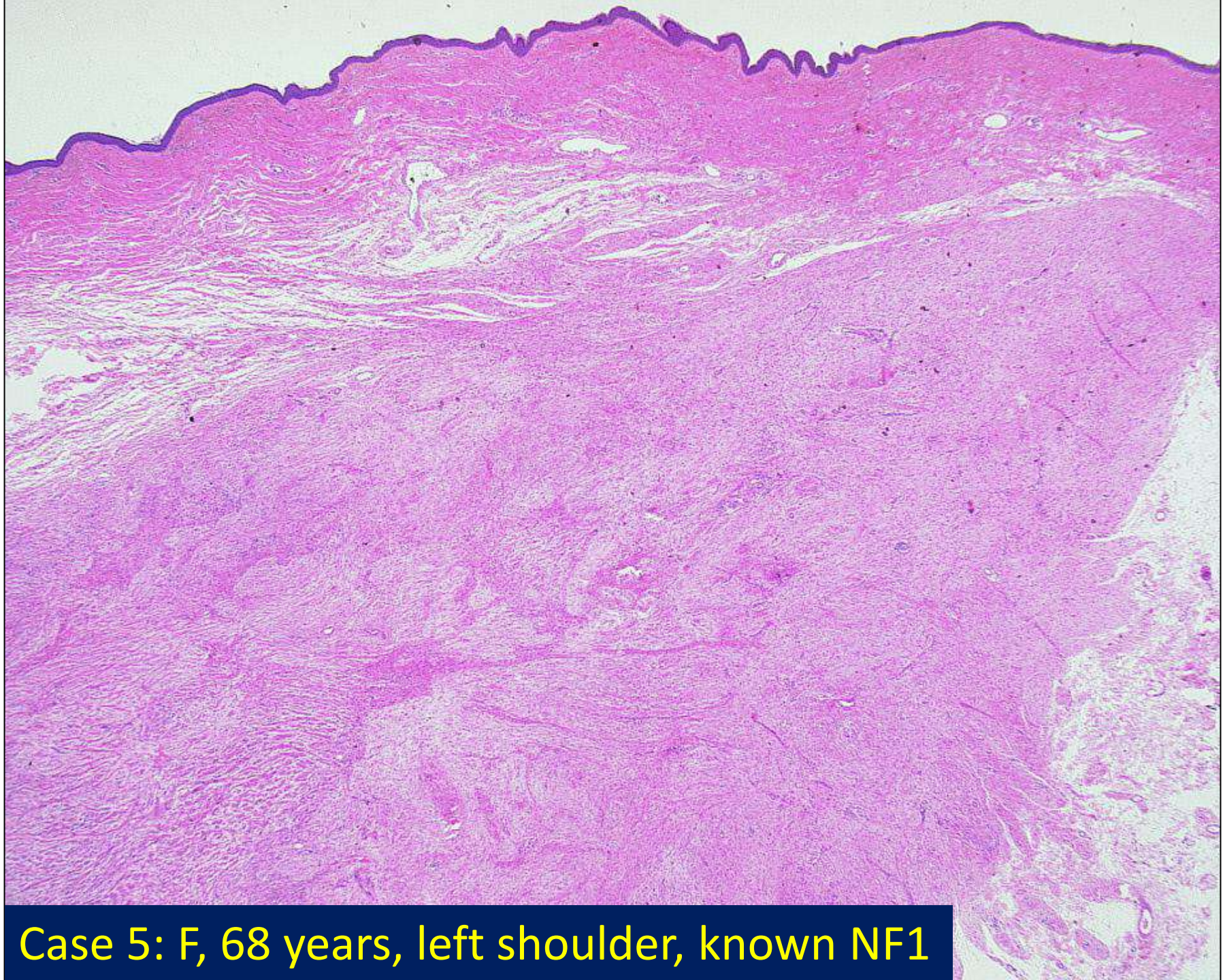
Hybrid schwannoma-perineurioma frequently harbors *VGLL3* rearrangement
Dickson BC et al. Mod Pathol 2021; 34: 1116-1124

CHD7::VGLL3 (56%)
CHD9::VGLL3 (11%)
MAMLD1::VGLL3 (11%)

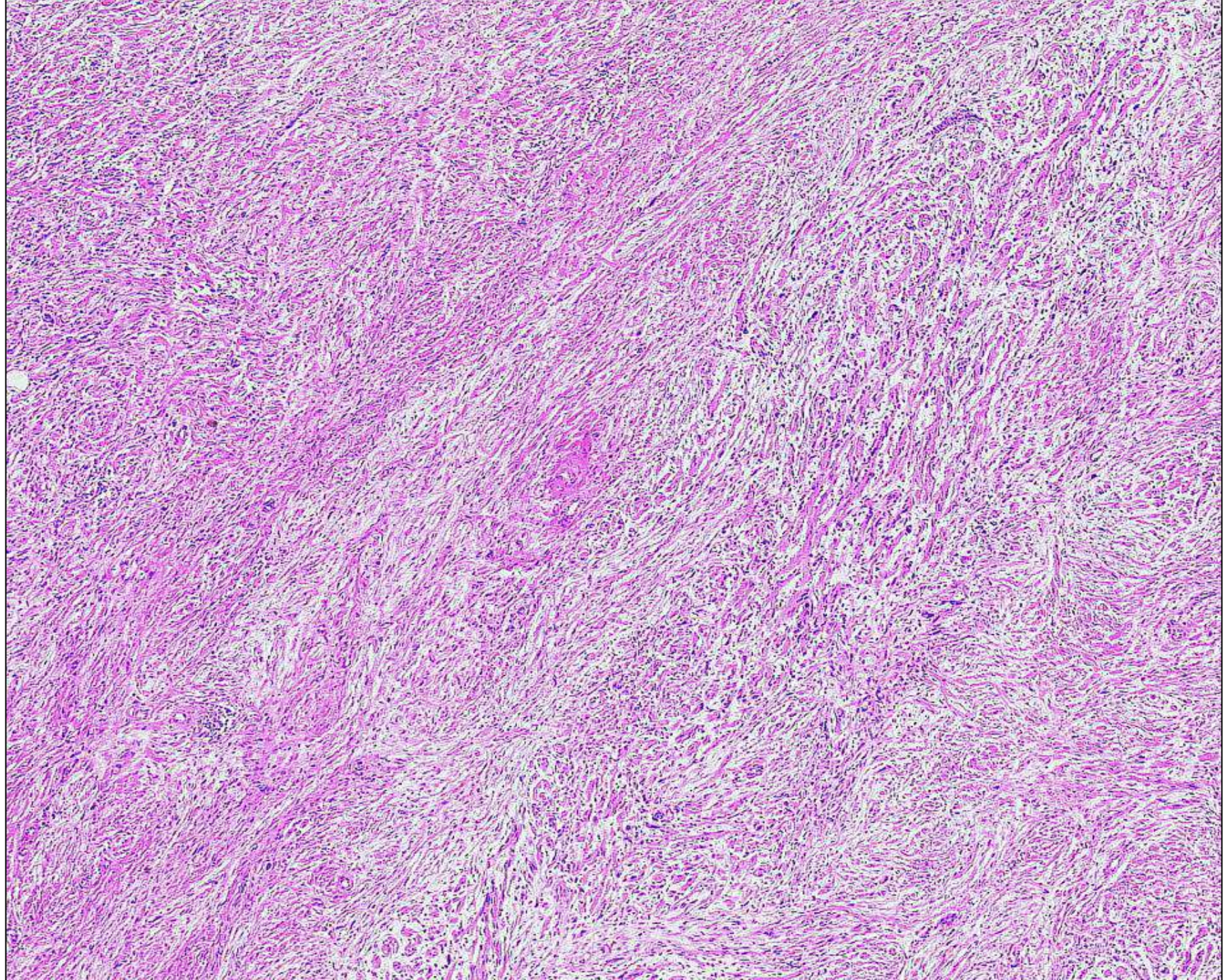
Clinicopathologic and molecular study of hybrid nerve sheath tumors reveals their common association with fusions involving *VGLL3*
Nihous H et al. Am J Surg Pathol 2022; 46: 591-602

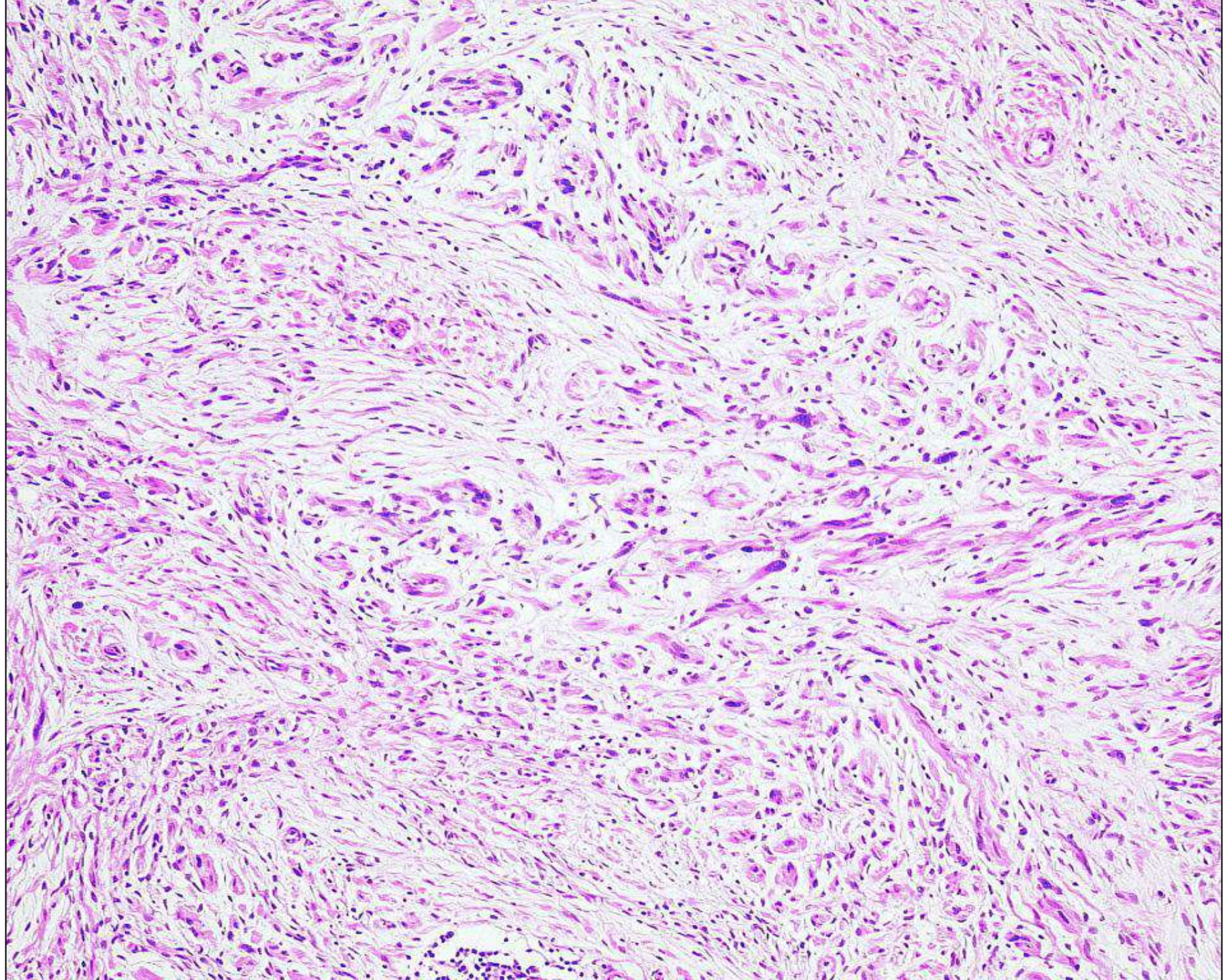
CHD7::VGLL3 (57%)
CHD9::VGLL3 (29%)
CHD9::ZFHX3 (14%)

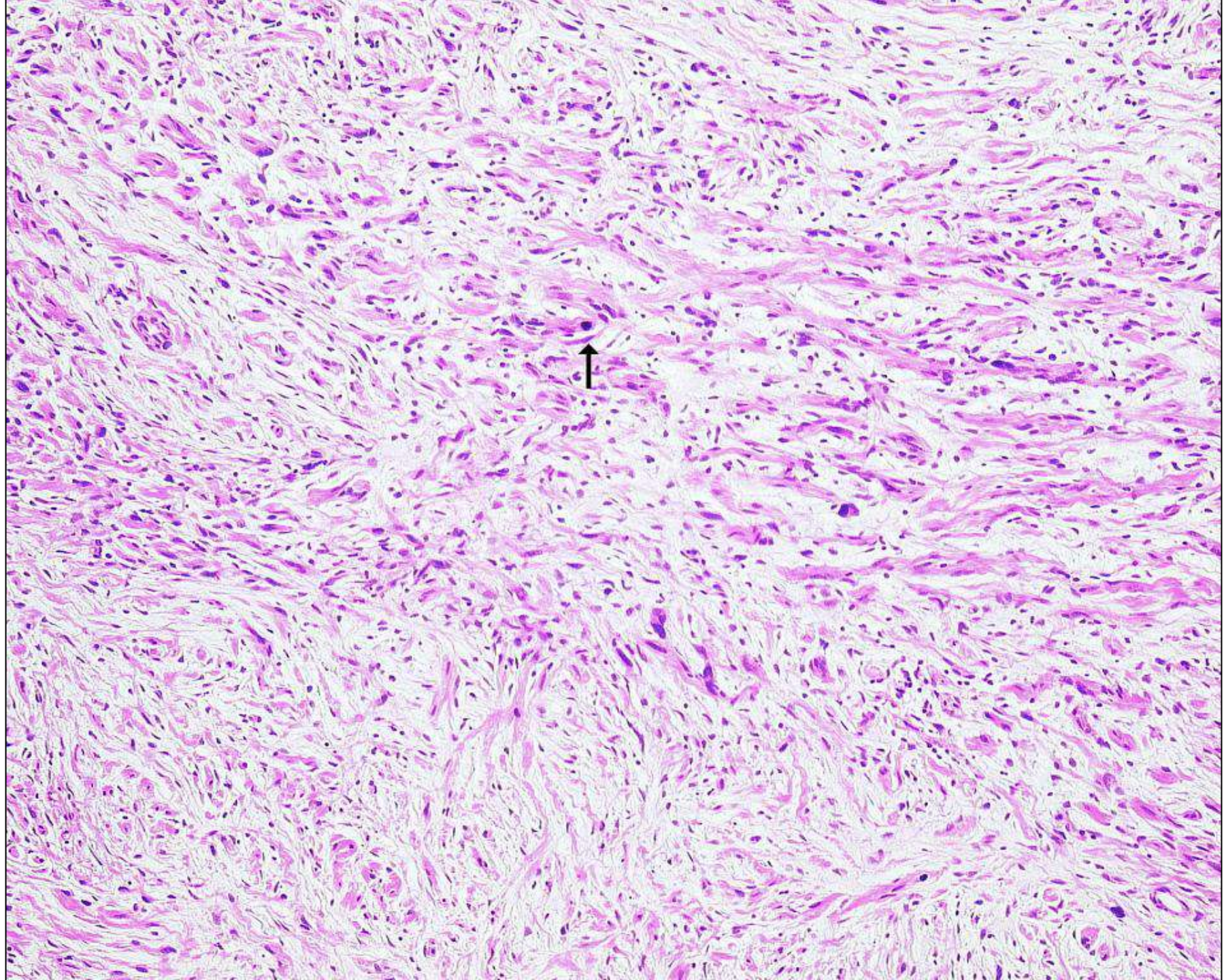
Distinct entity with molecular pathogenesis unrelated to schwannoma or perineurioma

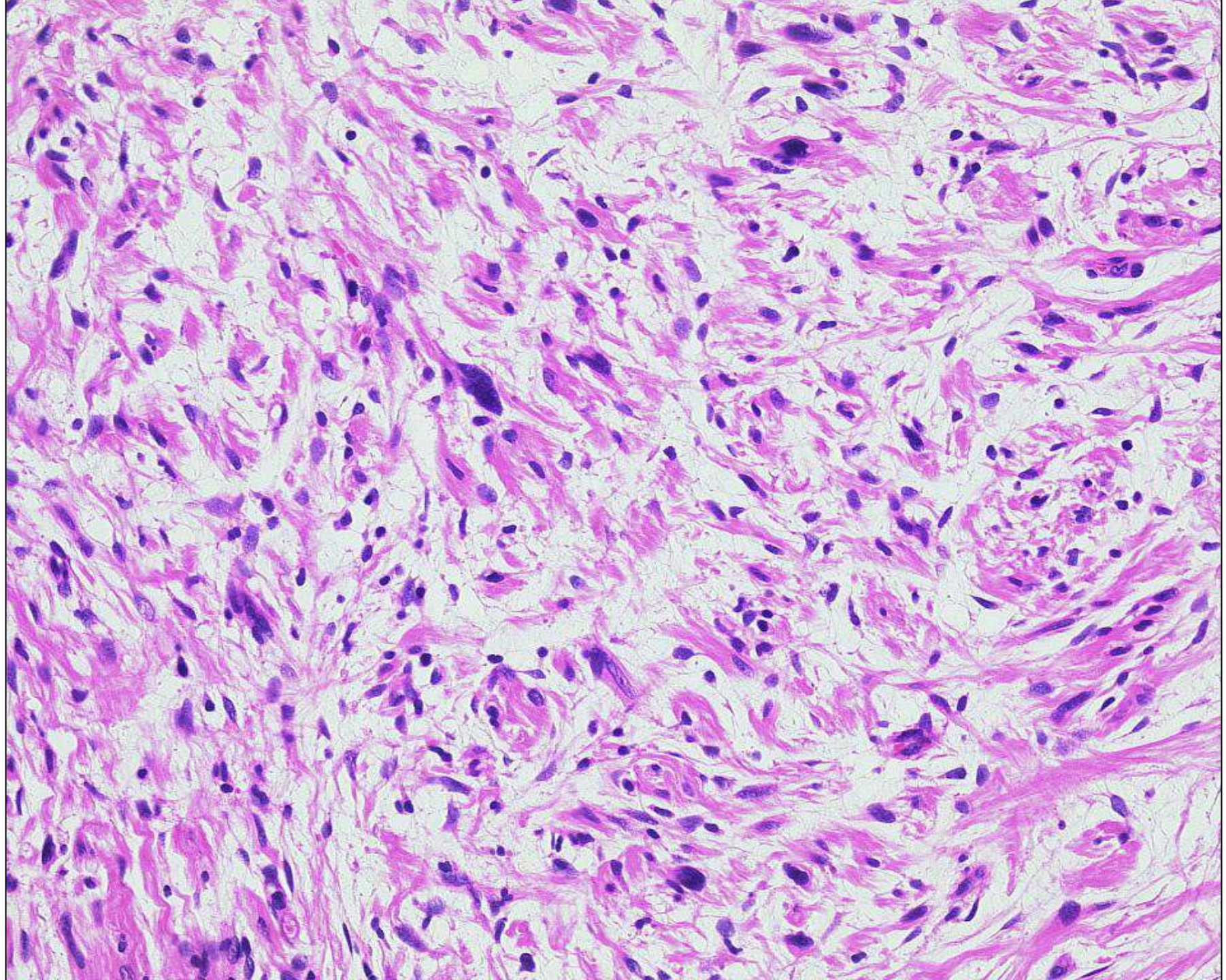


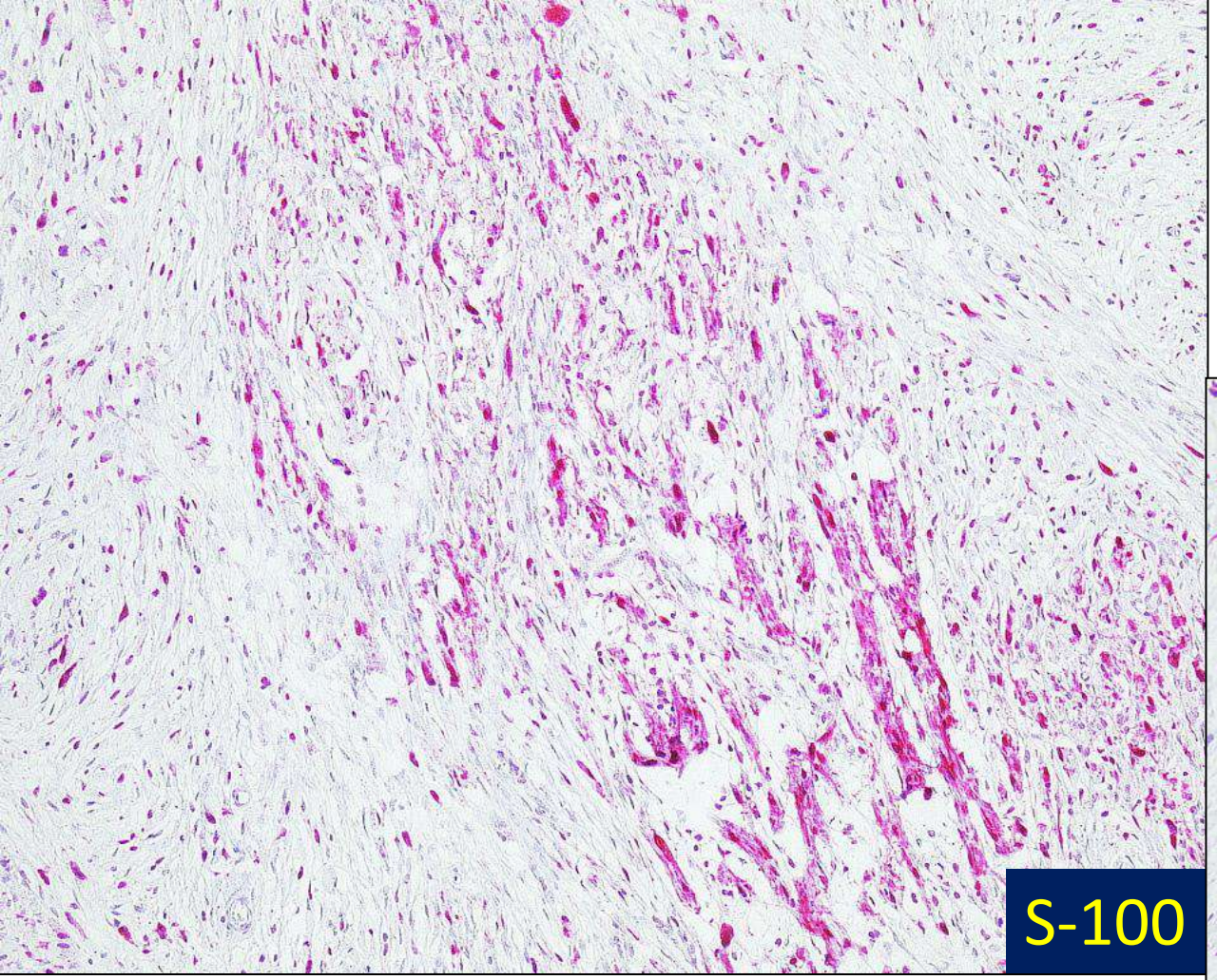
Case 5: F, 68 years, left shoulder, known NF1

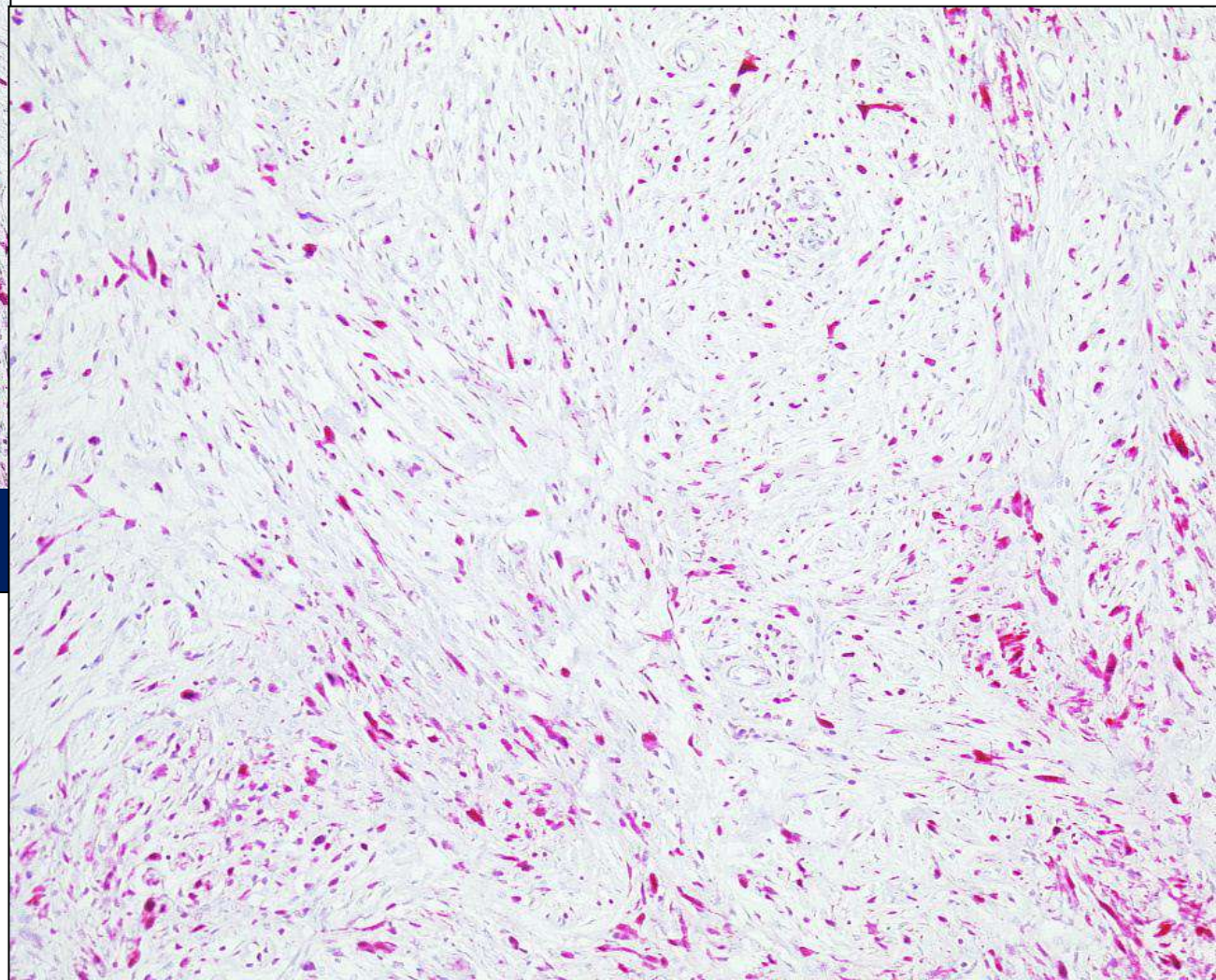


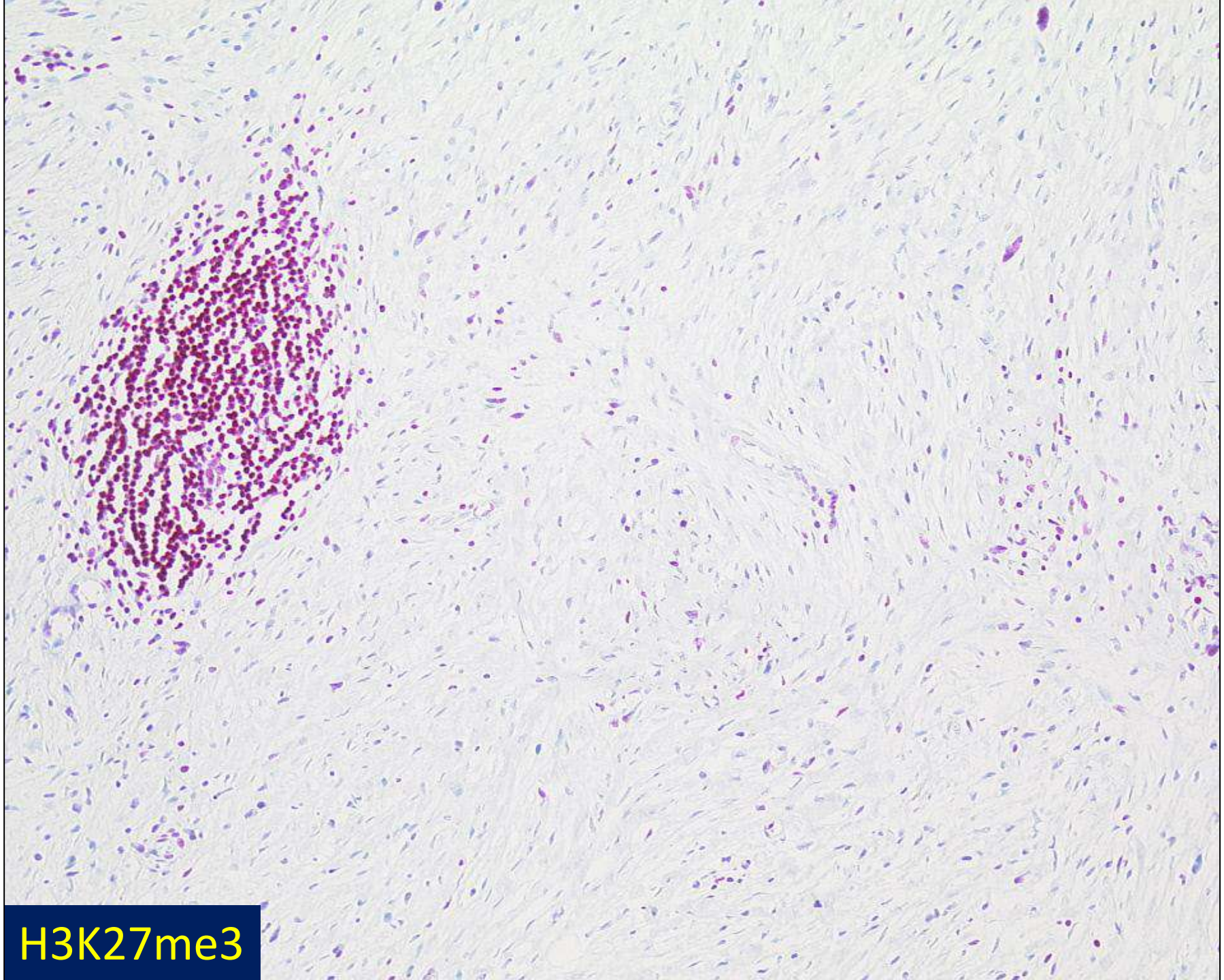


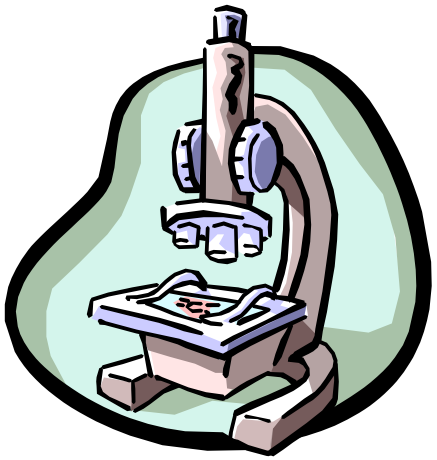





S-100




H3K27me3



Diagnosis Case 5

low-grade malignant peripheral nerve sheath Tumour (MPNST)

Malingnant Peripheral Nerve Sheath Tumour

Arise in patients with NF1, sporadically, or following radiotherapy

Diagnostic criteria:

1. origin from a nerve or a neurofibroma
2. spindle cell sarcoma in a patient with NF1
3. evidence of schwann cell differentiation by IM or EM
   (S-100 protein and SOX10 only 30-50% sensitivity)

Diagnosis in sporadic cases relies on distinctive histology and exclusion of histologic mimics

Polycomb Repressive Complexes (PRC1,2)

PRC2 recruits to chromatin and trimethylates histone H3 at lysine 27
physiologic regulation of cell fate and stem cell differentiation
deregulation – cancer development

PRC2 alterations (*SUZ12* or *EED* mutations) in 85-90% of MPNST

homozygous mutations result in loss of H3K27me3 in > 65% of MPNST

ICH for H3K27me3 is highly specific diagnostic marker

Schaefer IM et al. Loss of H3K27 trimethylation distinguishes malignant peripheral nerve sheath tumors from histologic mimics Mod Pathol 2016; 29: 4-13

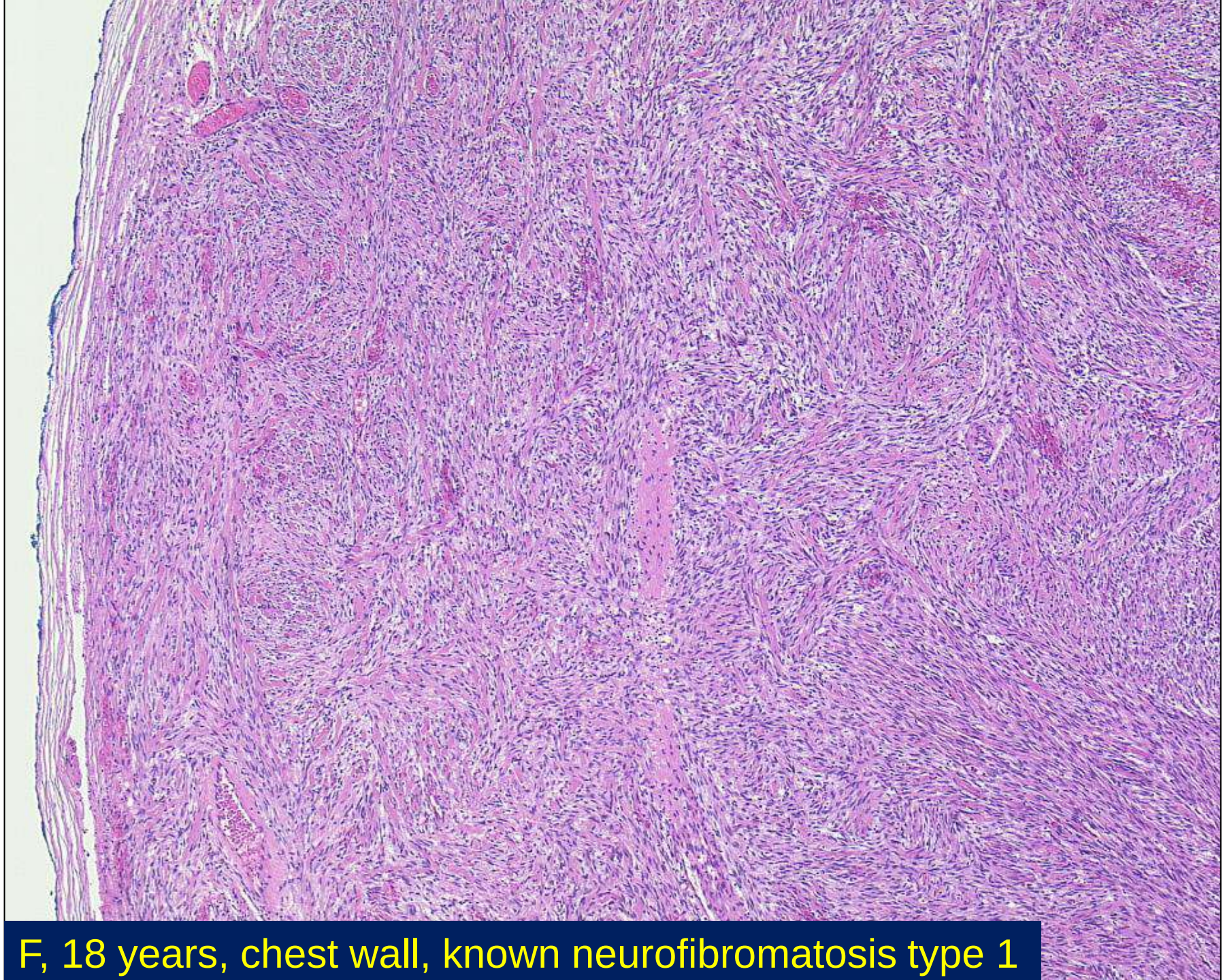
- *NF1* mutations and *CDKN2*A inactivation in MPNST
- *PRC2* inactivation through *EED1* or *SUZ12* loss
- *PRC2* inactivation leads to loss of H3K27me3
- loss of H3K27me3 in MPNST (low-grade 29% - high-grade 83%)

Prieto-Granada CN et al. Loss of H3K27me3 expression is a highly sensitive marker for sporadic and radiation induced MPNST Am J Surg Pathol 2016; 40: 479-489

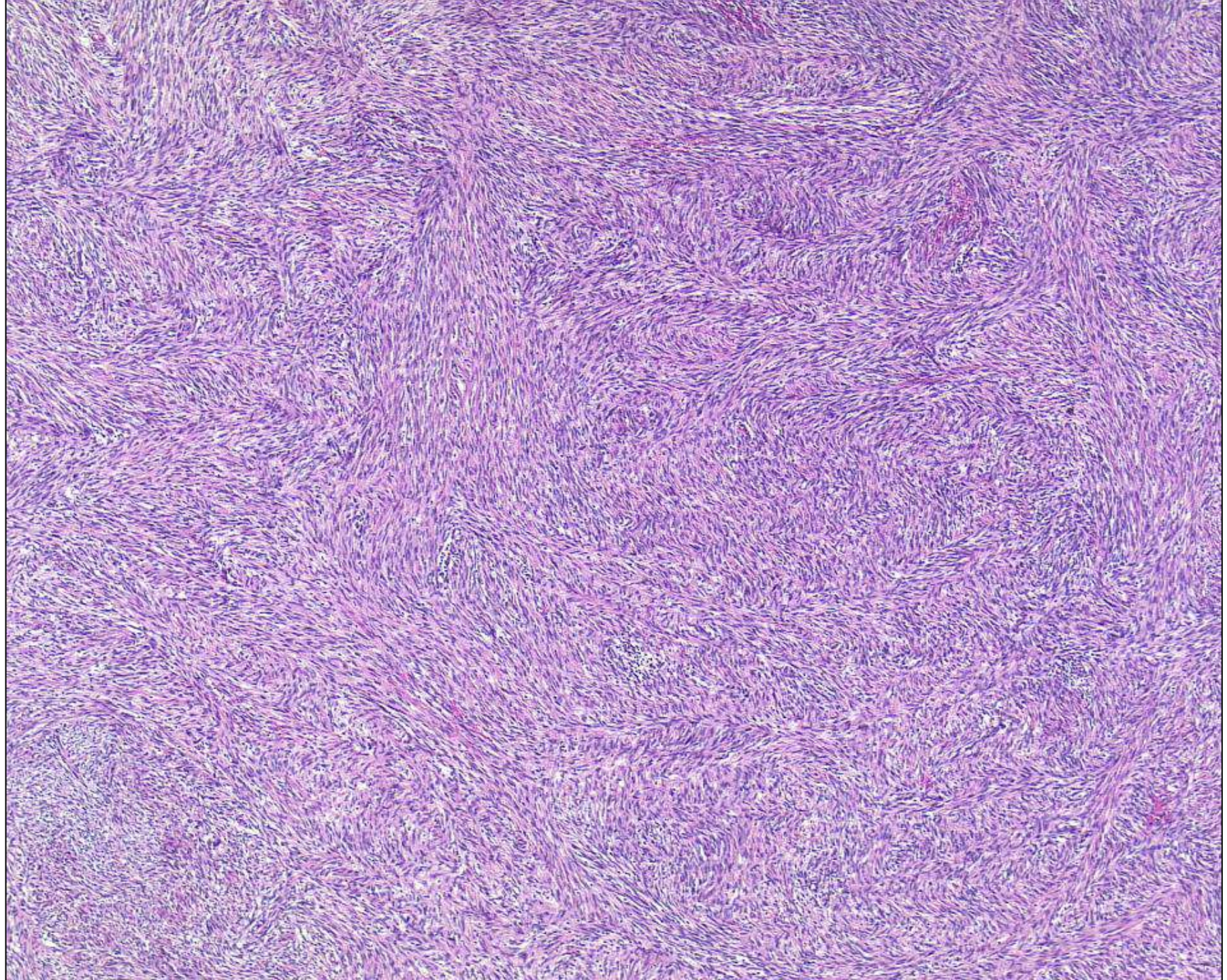
Cleven AH et al. Loss of H3K27 trimethylation is a diagnostic marker for malignant peripheral nerve sheath tumors and an indicator for an inferior survival Mod Pathol 2016; 29: 582-590

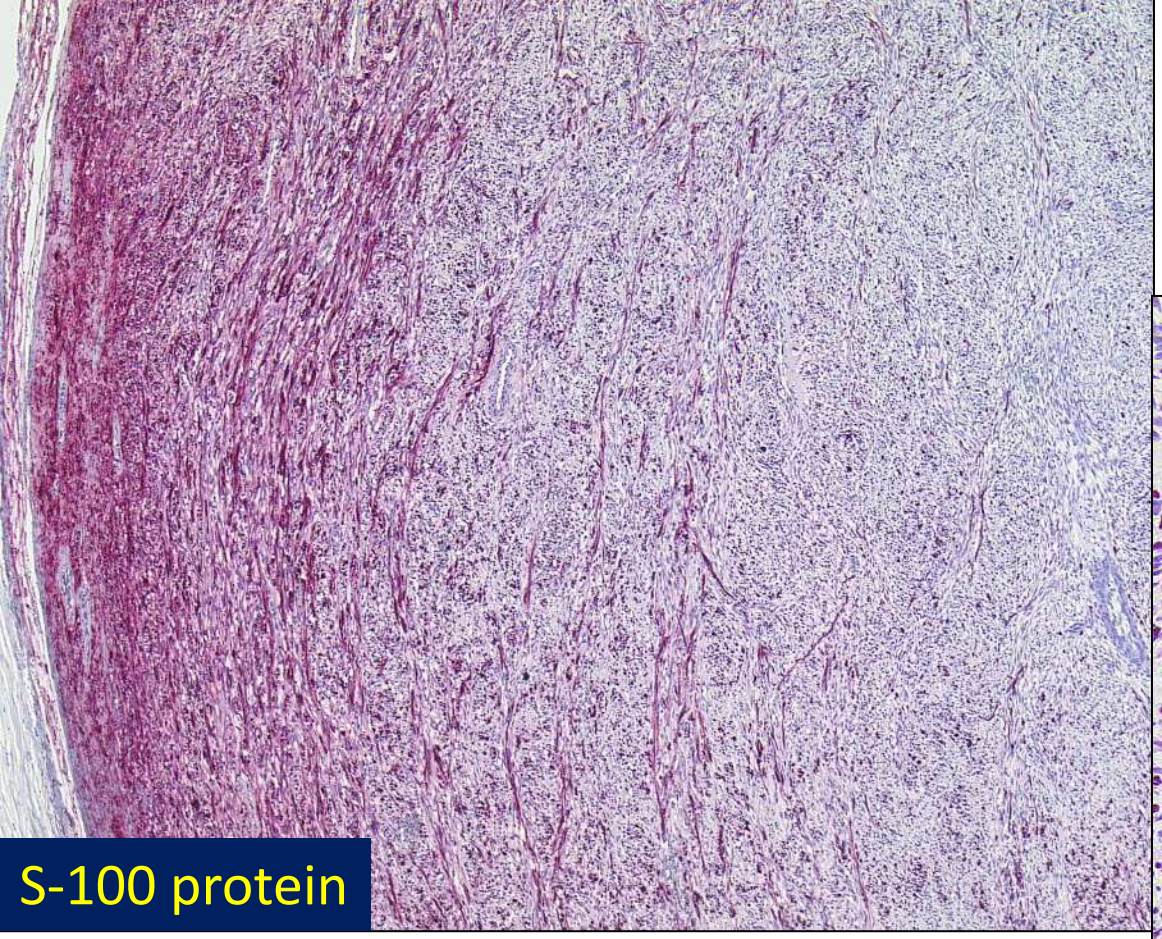
Immunohistochemistry for H3K27me3 in MPNST

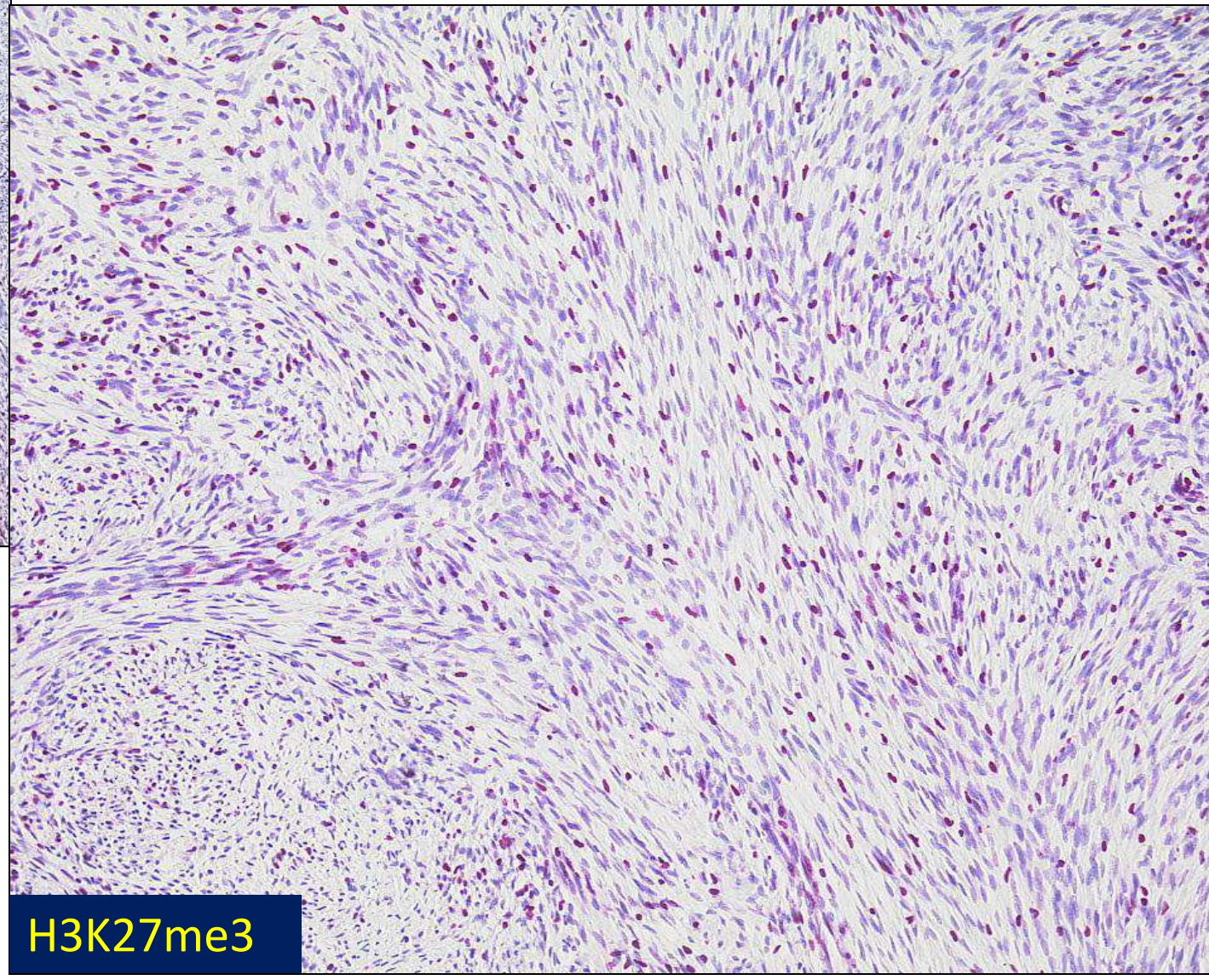
low-grade MPNST	loss in 30%
intermediate grade MPNST	loss in 60%
high-grade MPNST	loss in 80%
radiation induced MPNST	loss in 100%
epithelioid MPNST	loss in 0%

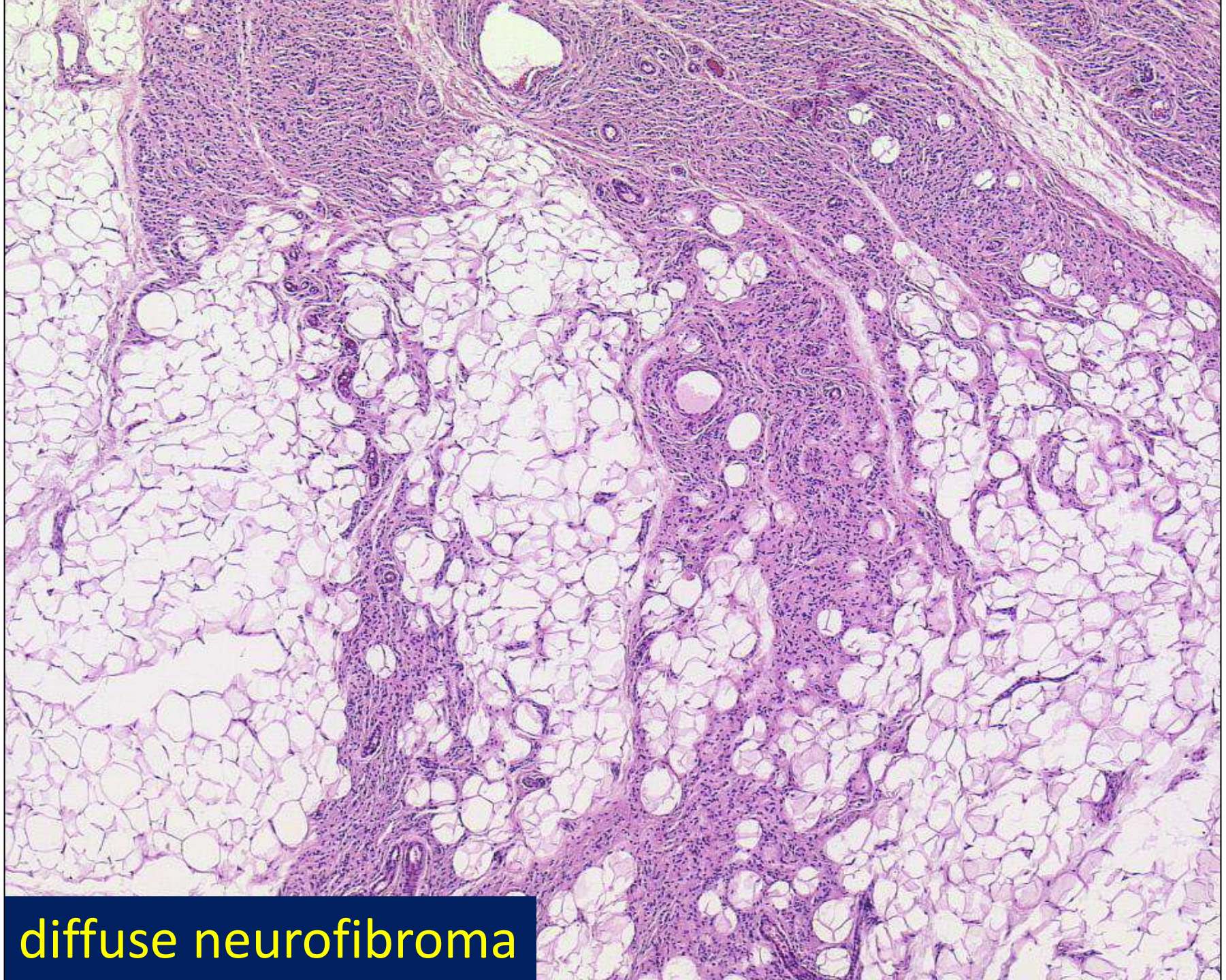


F, 18 years, chest wall, known neurofibromatosis type 1

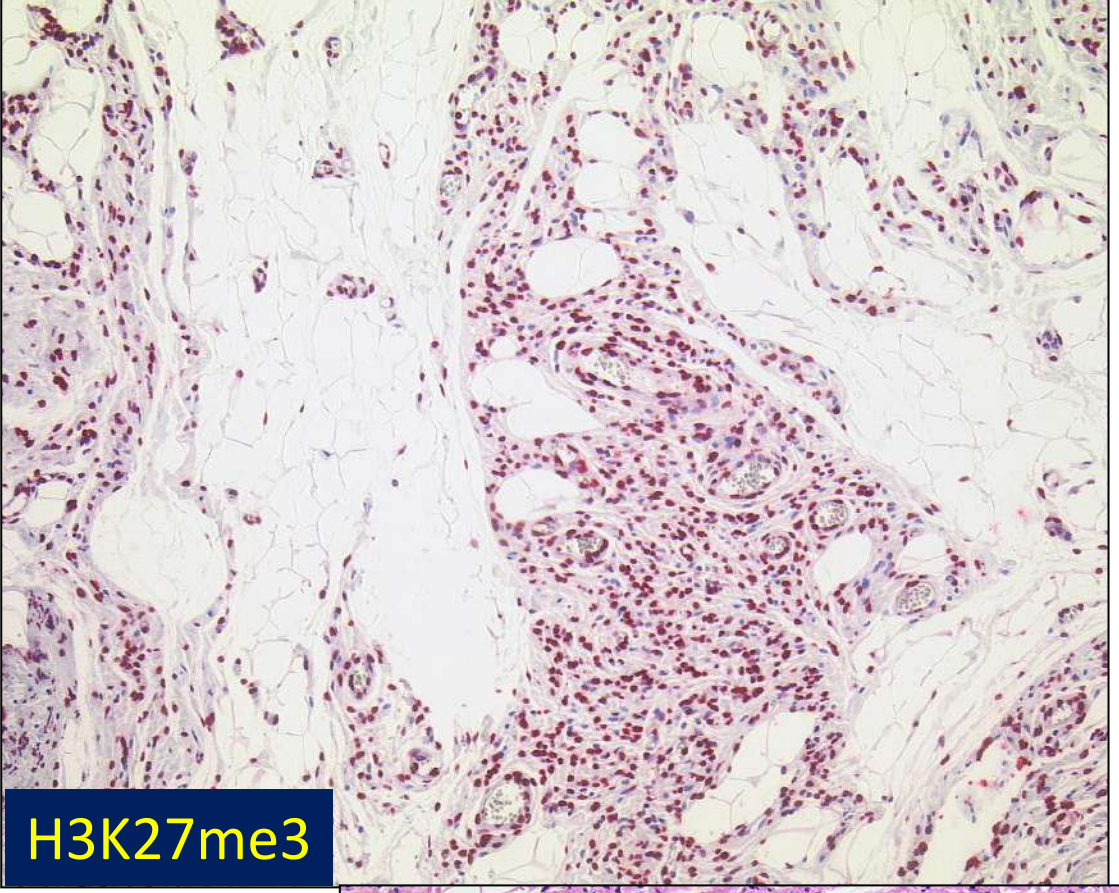



S-100 protein

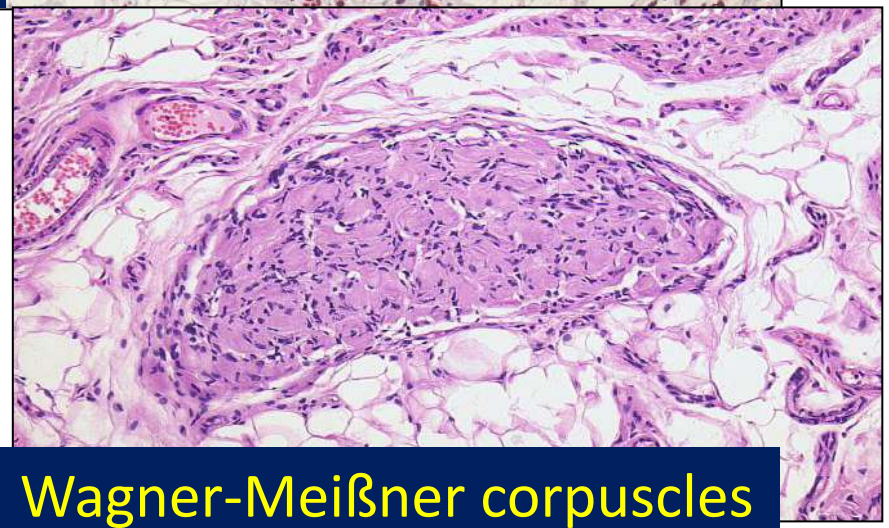

H3K27me3


diffuse neurofibroma

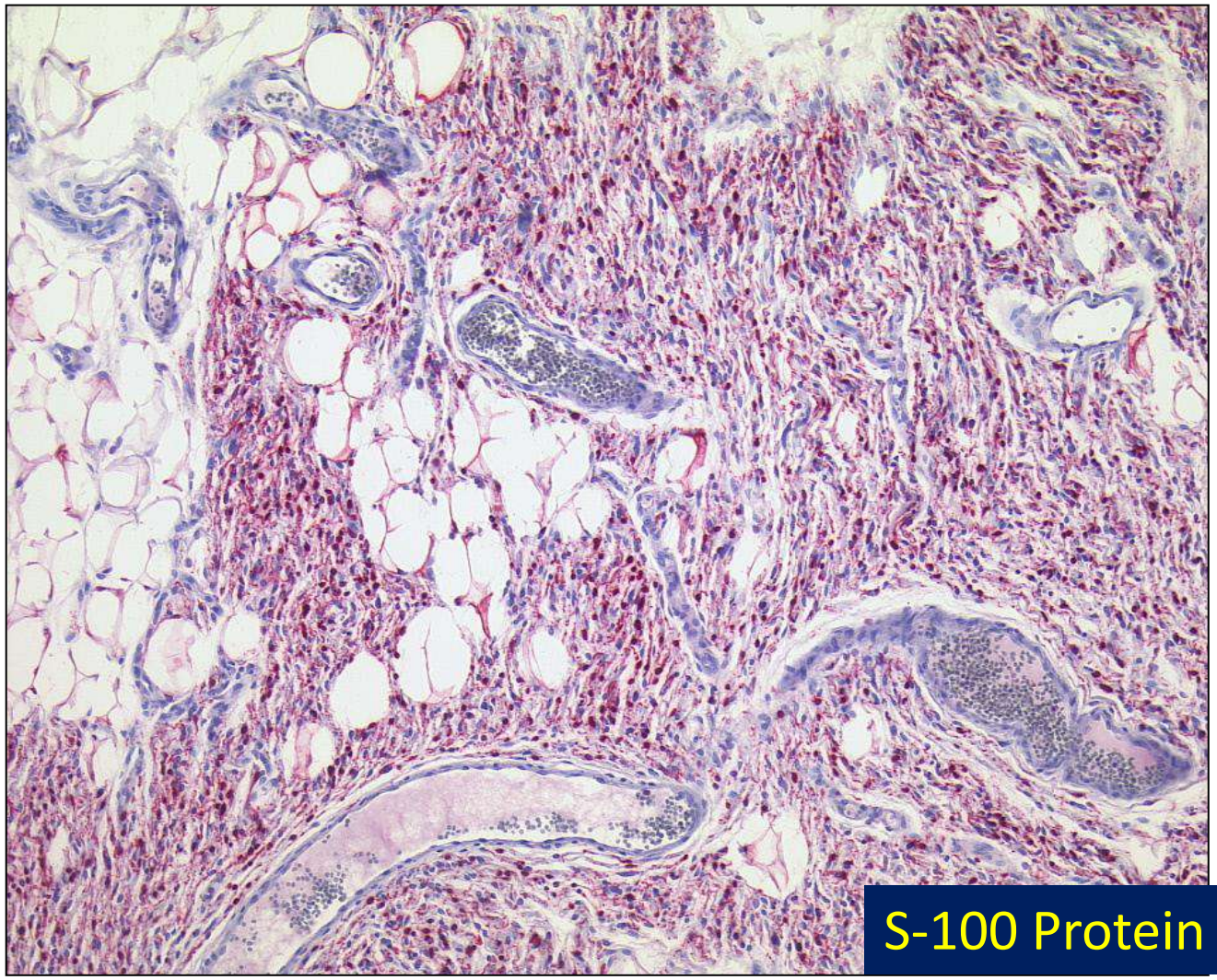
diffuse Neurofibroma



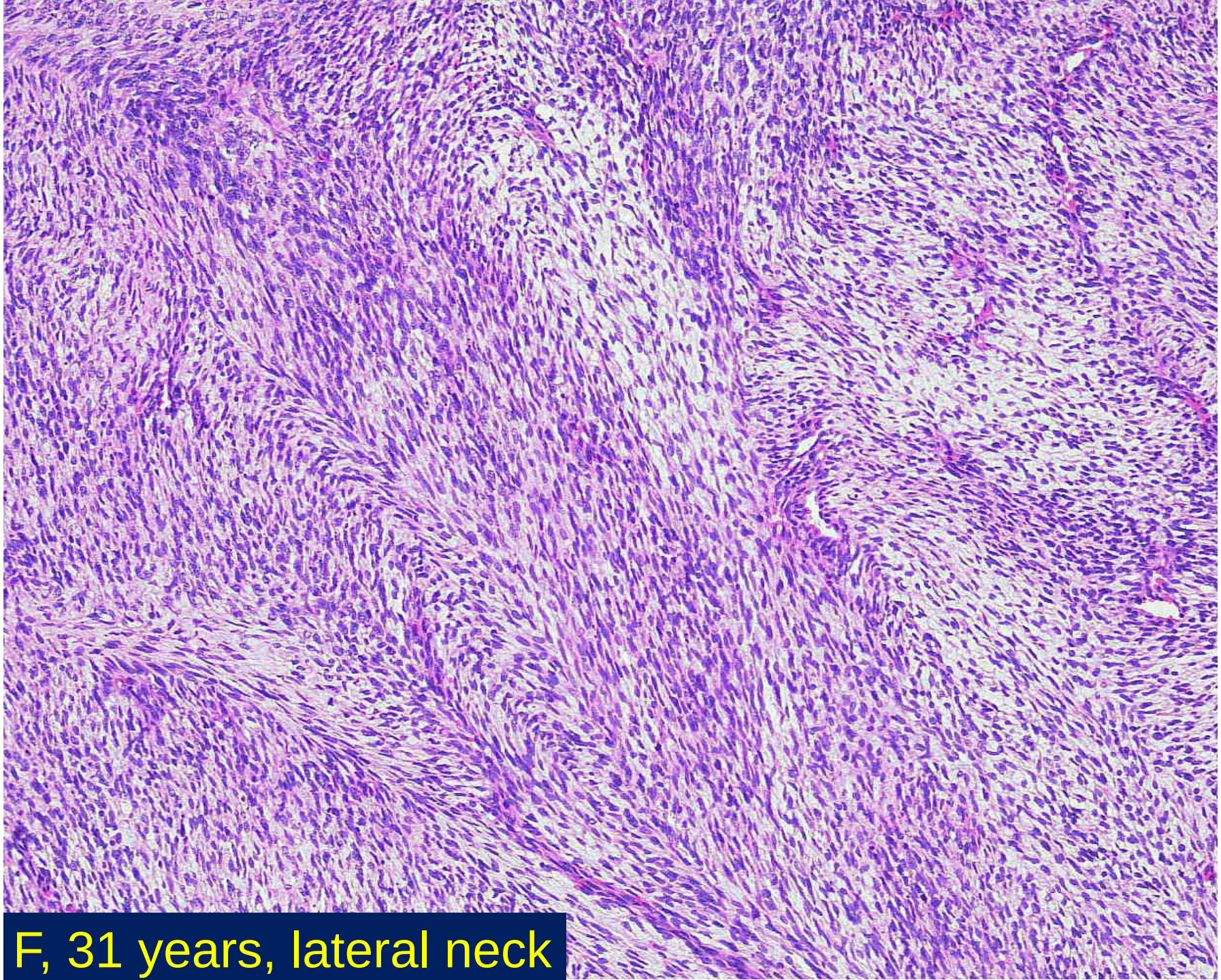
H3K27me3



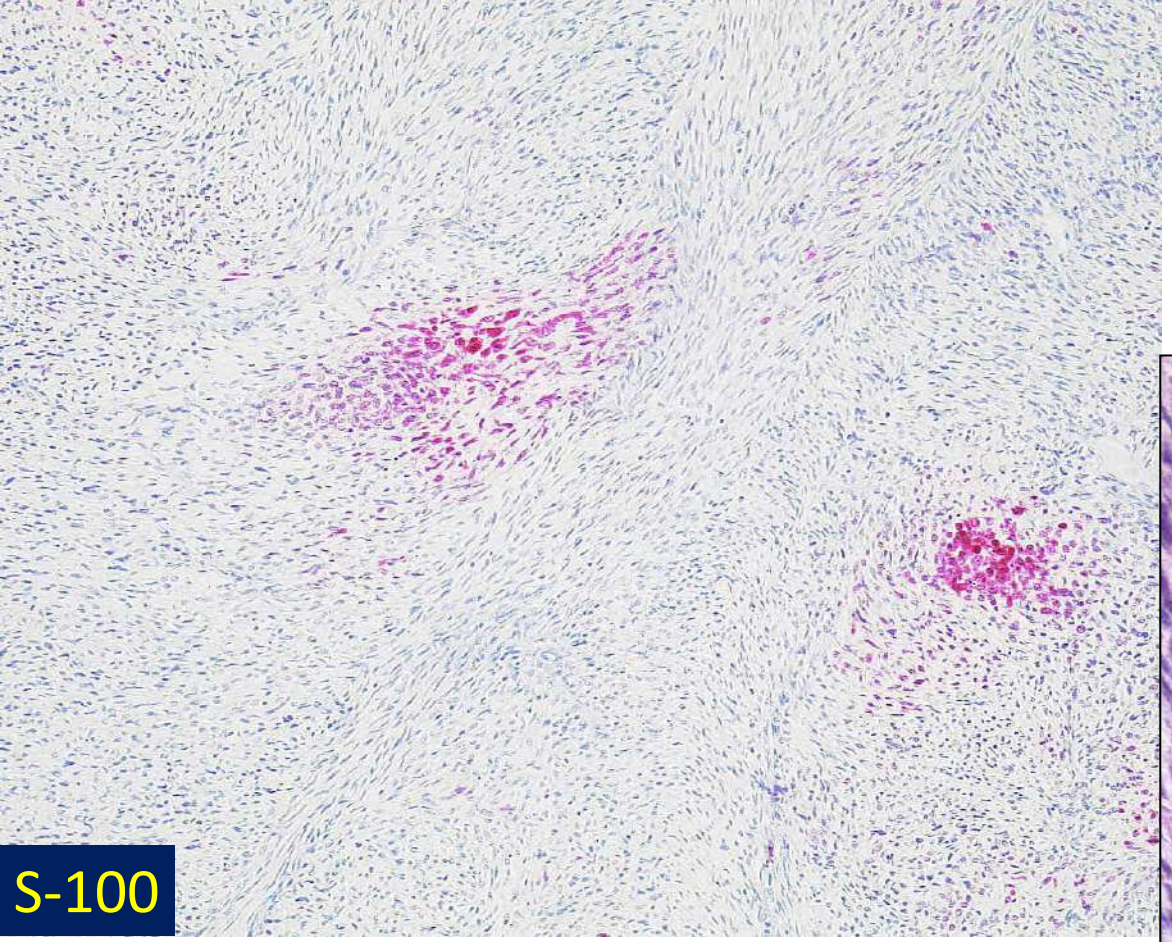
Wagner-Meißner corpuscles

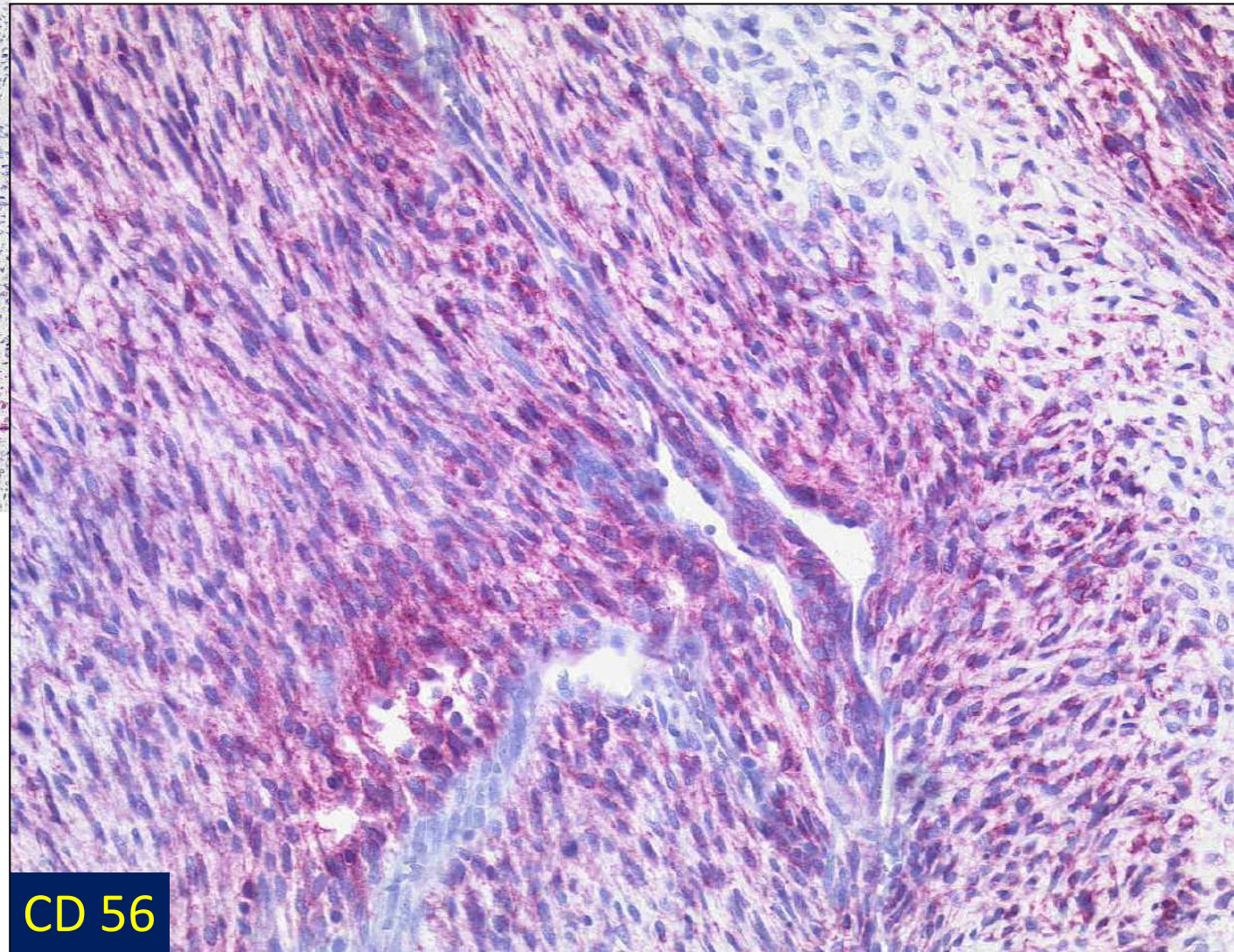


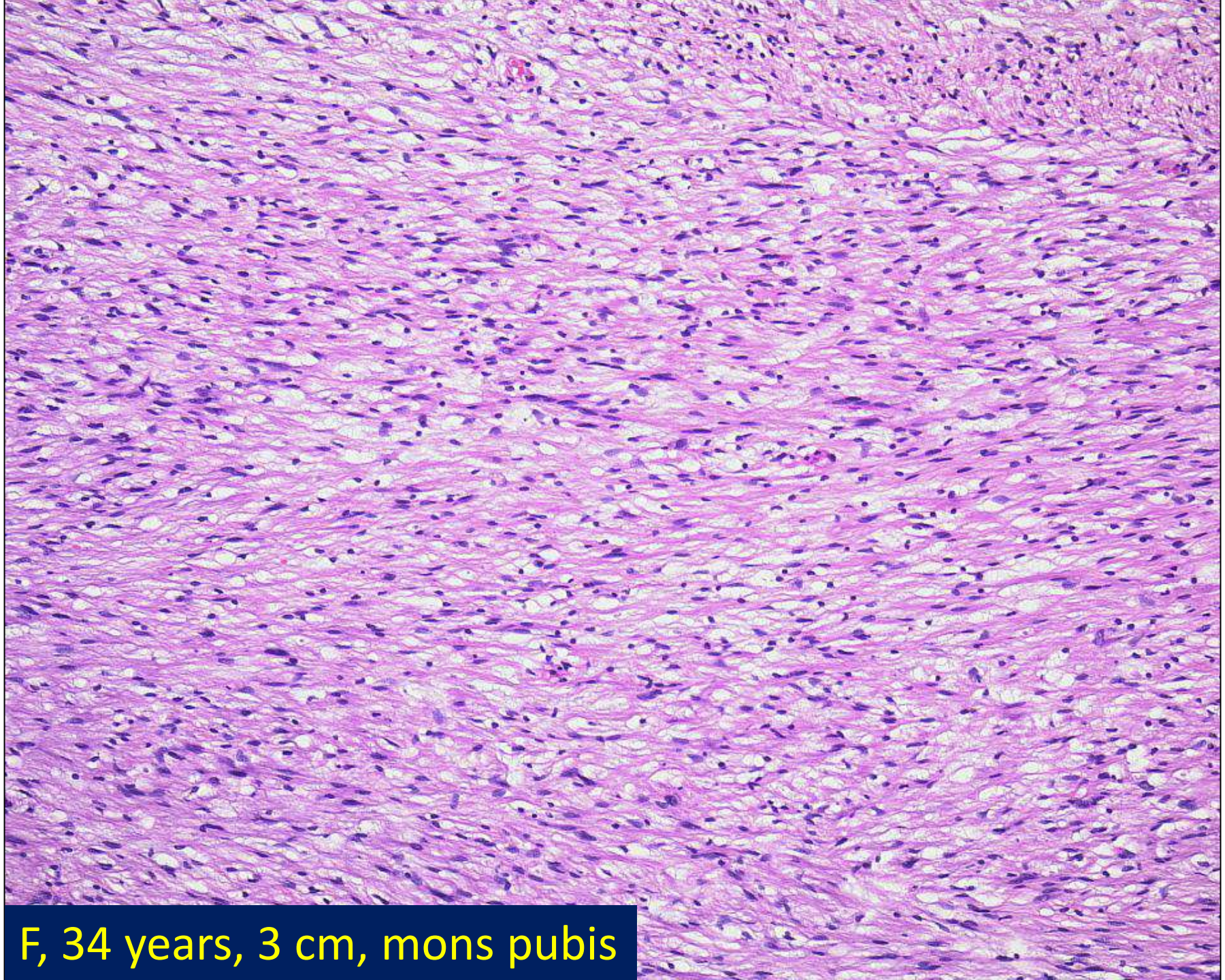
S-100 Protein


F, 31 years, lateral neck

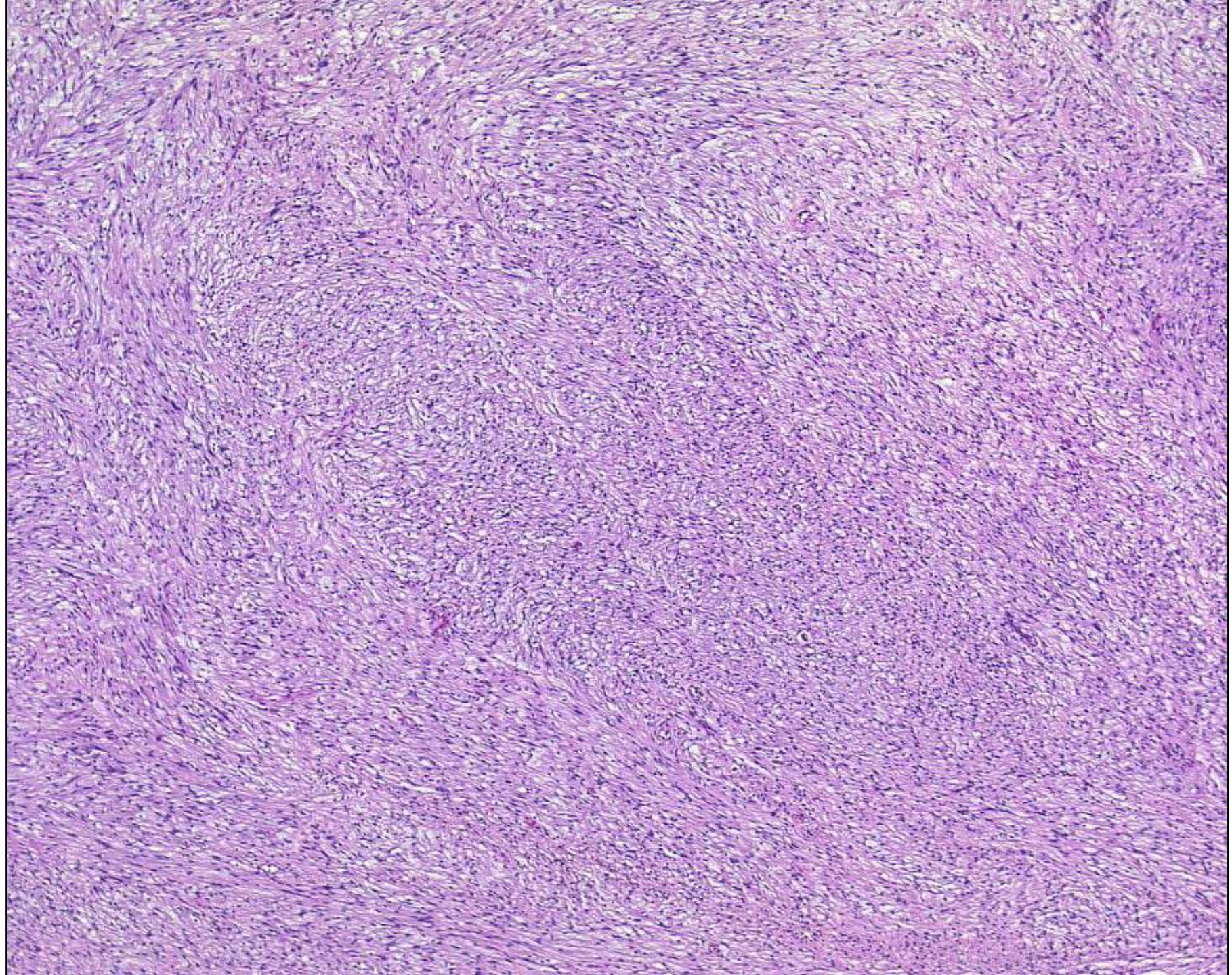
MPNST

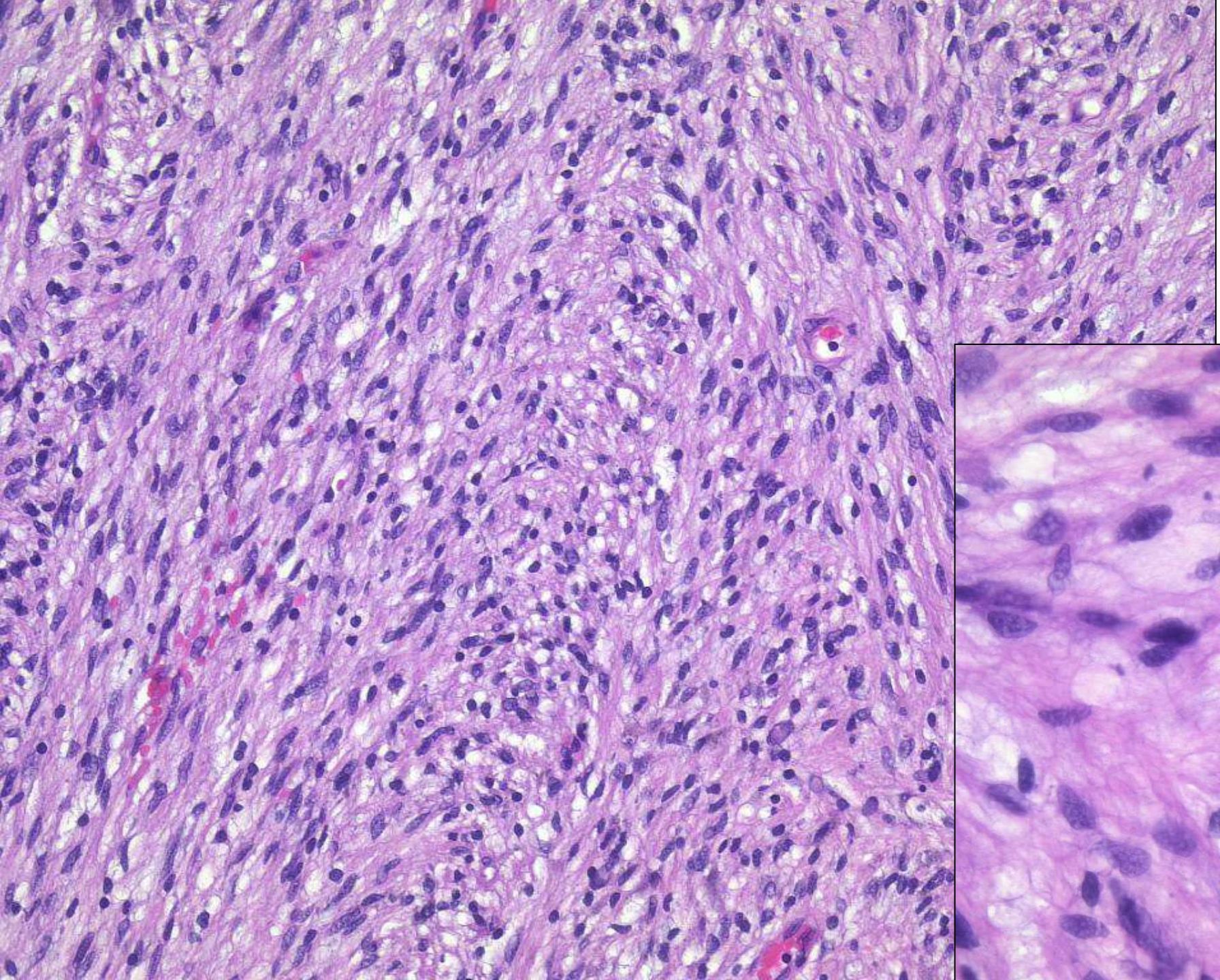
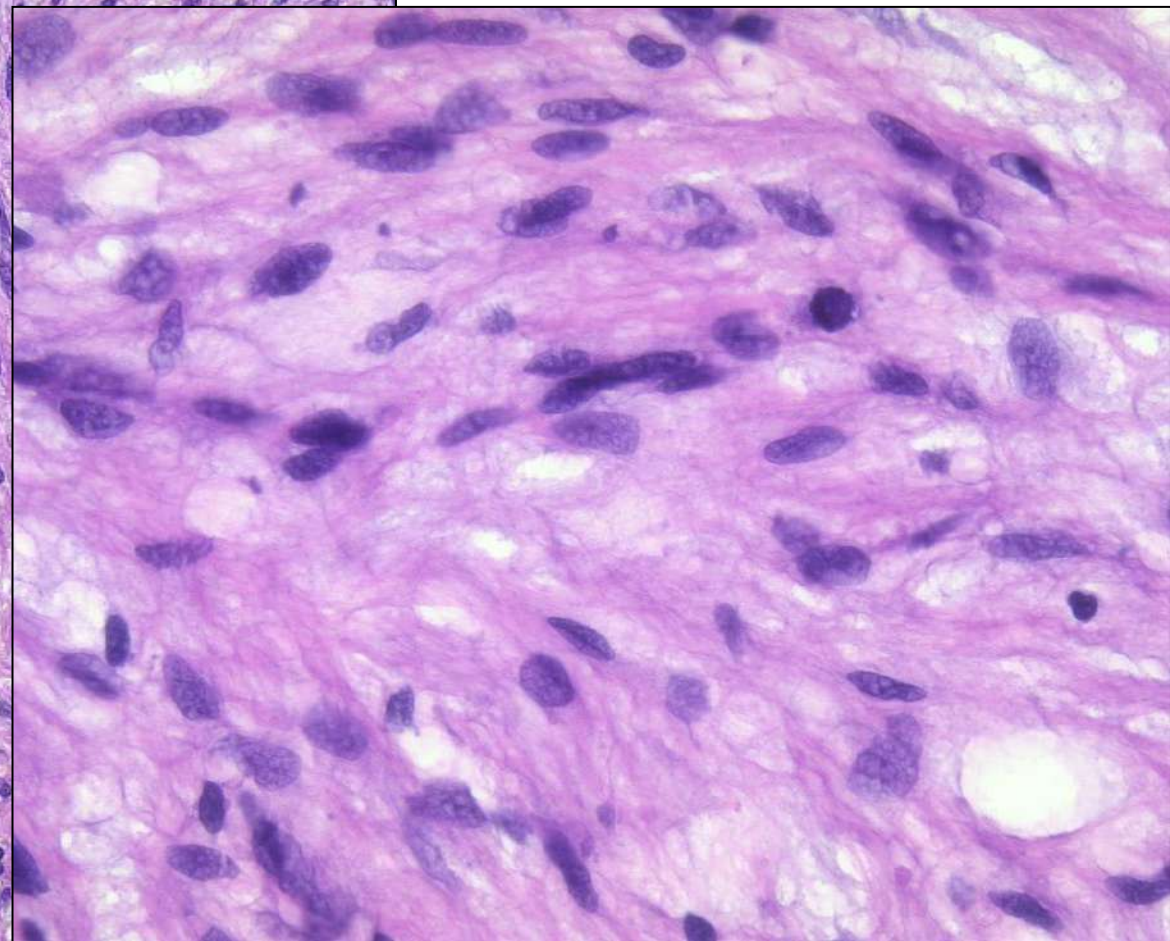






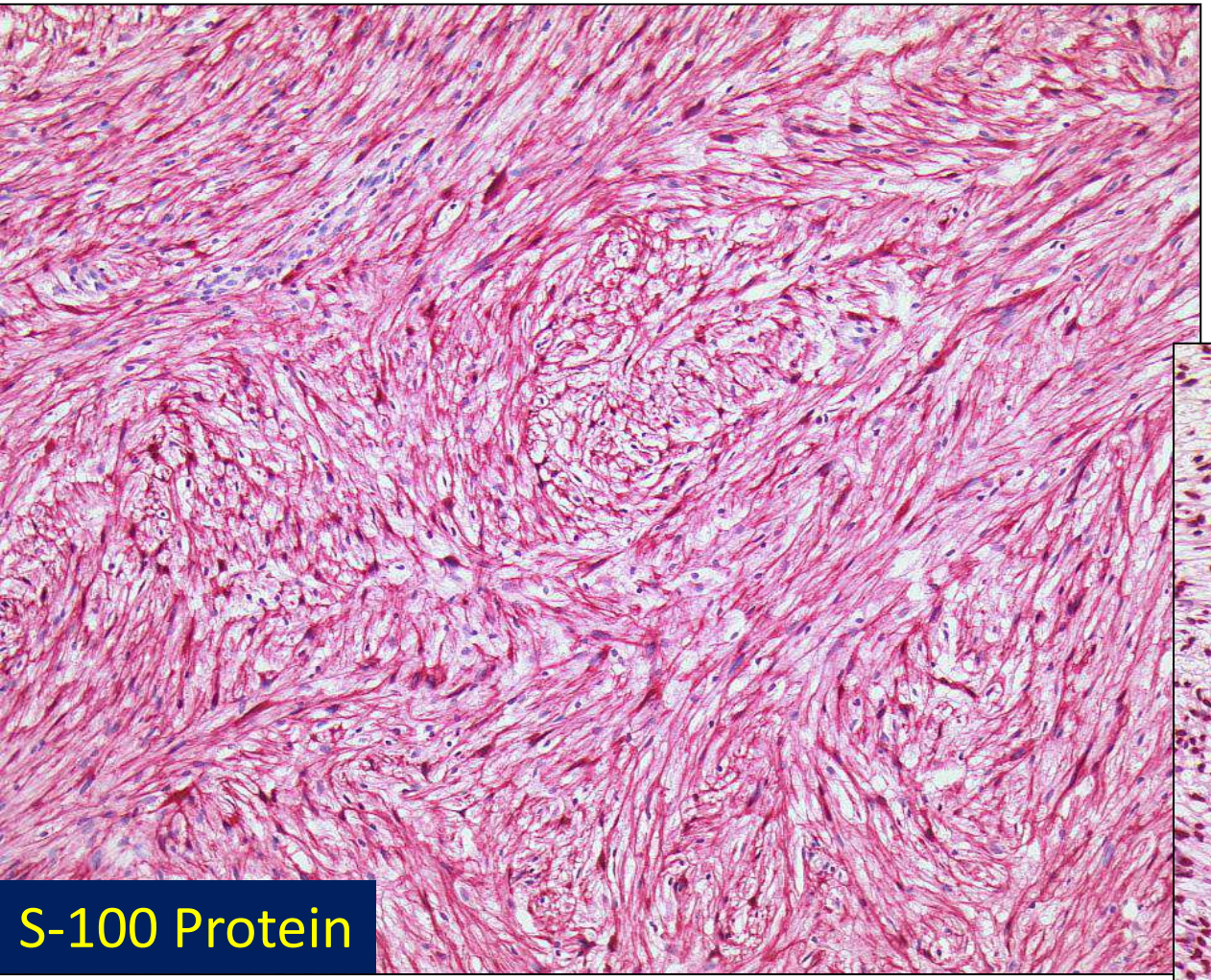
F, 34 years, 3 cm, mons pubis

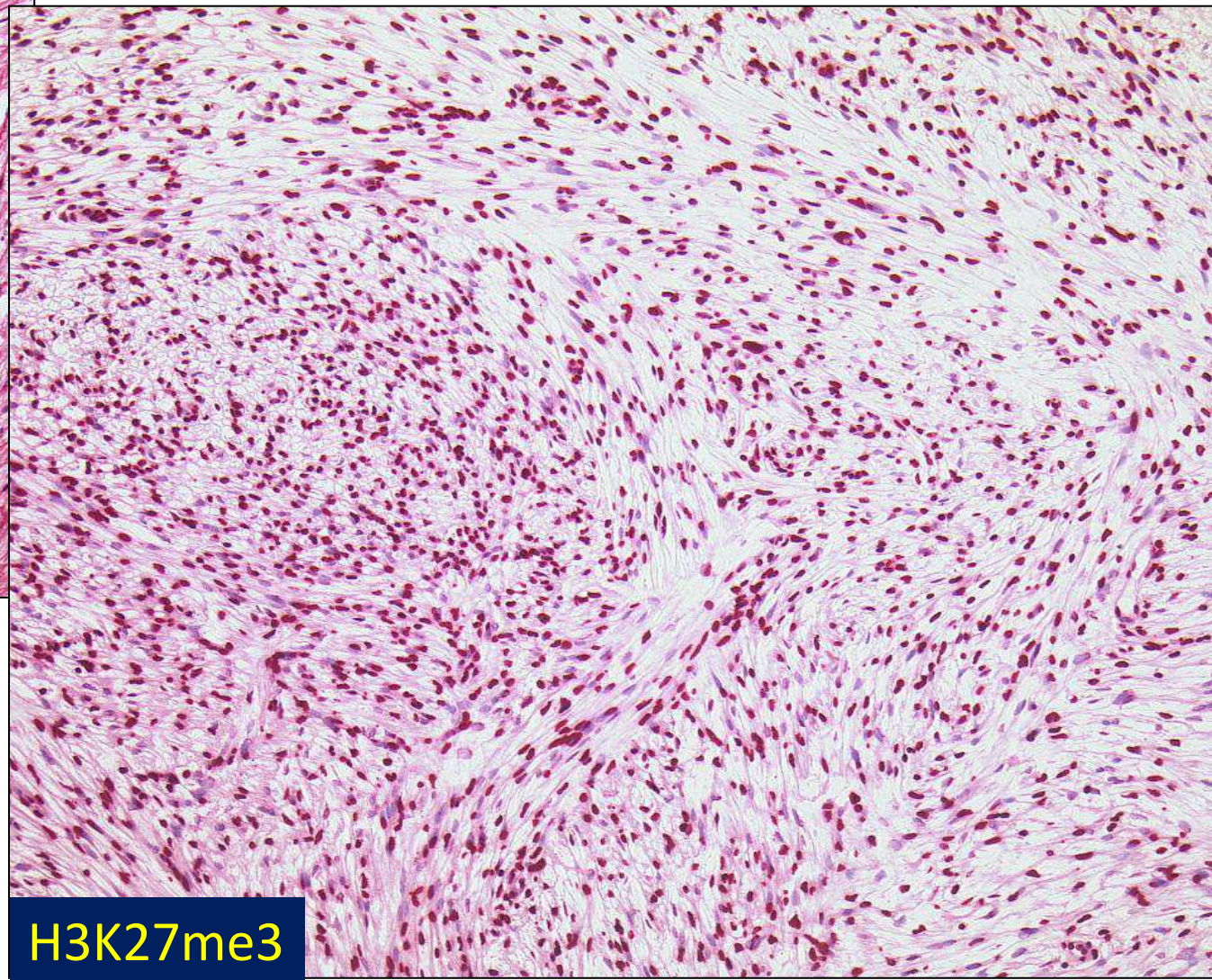


atypical neurofibroma *versus* low-grade MPNST ?

Diagnosis:
atypical neurofibromatous Tumour



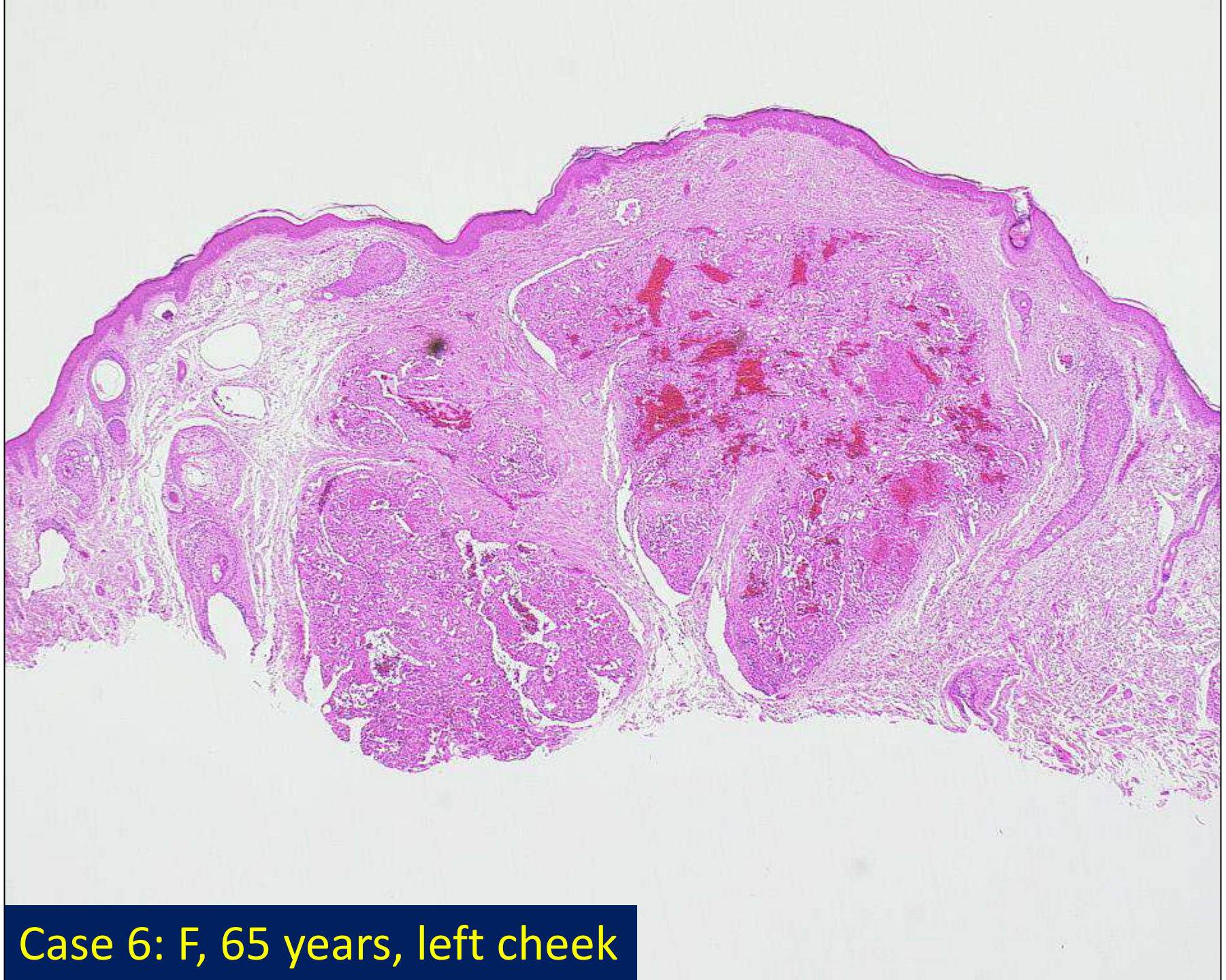


Histopathologic evaluation of atypical neurofibromatous tumors and their transformation into malignant peripheral nerve sheath tumors in patients with neurofibromatosis 1 - a consensus overview

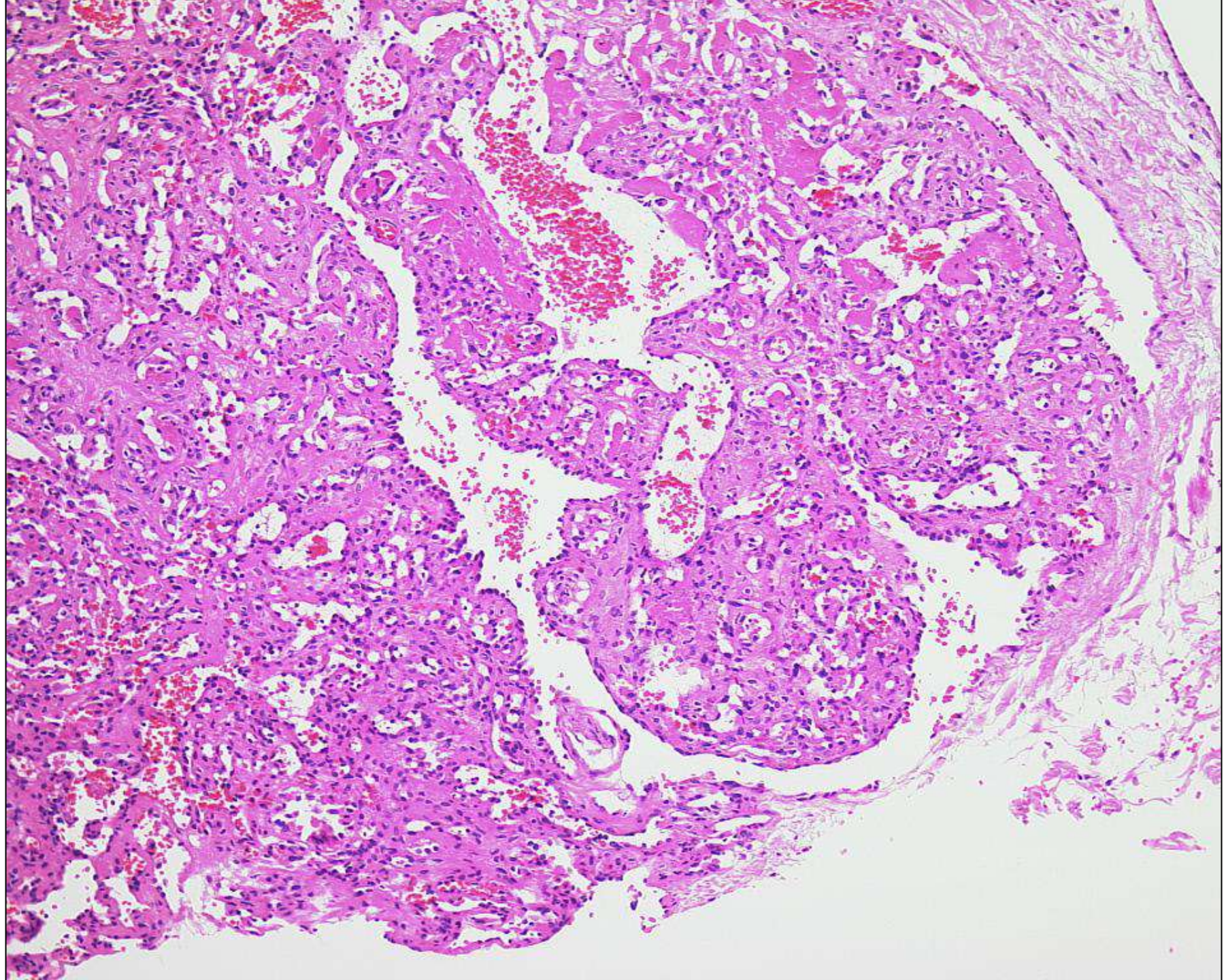
Miettinen M et al. Hum Pathol 2017; 67: 1-10

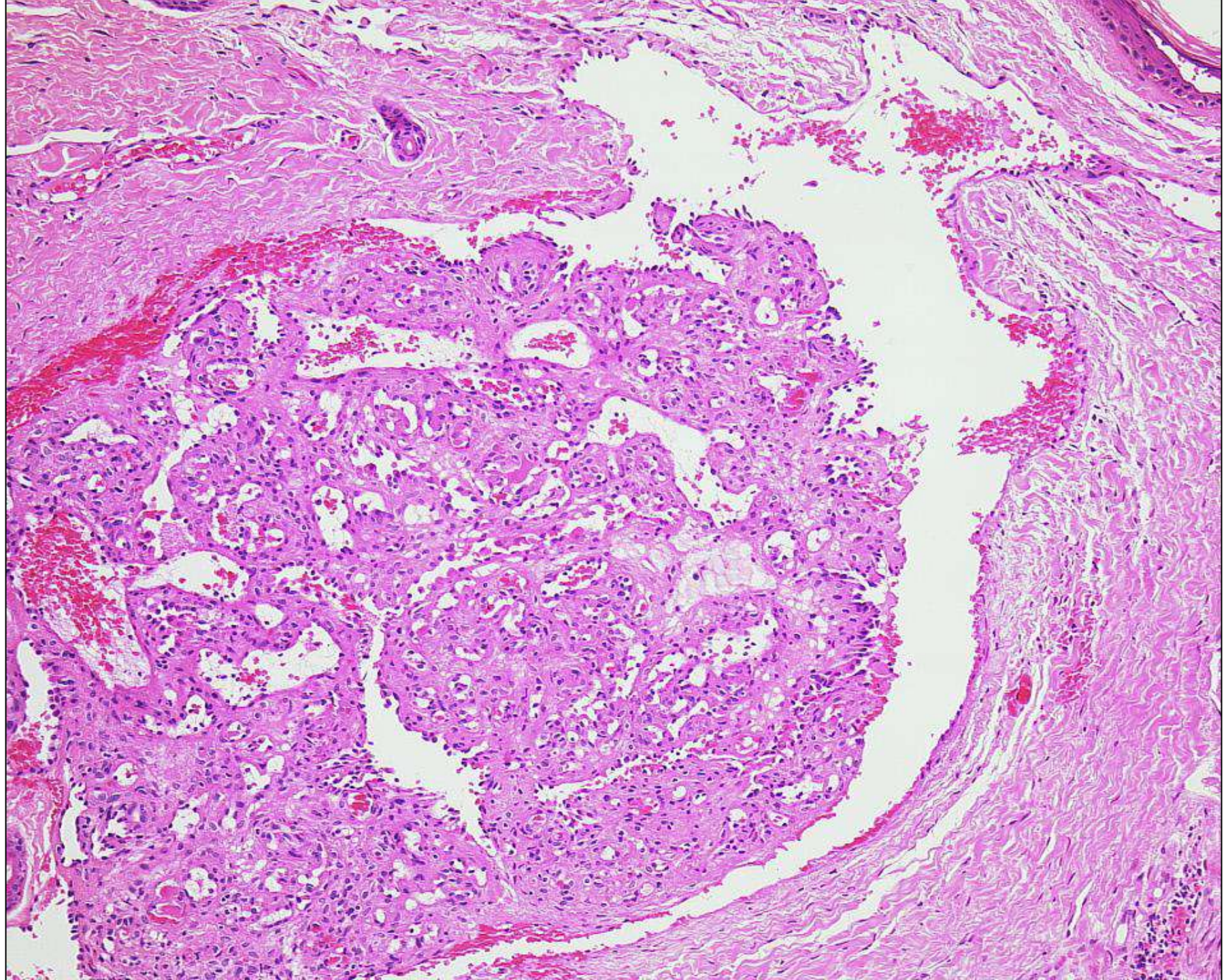
nuclear atypia, loss of neurofibroma architecture (presence of cellular fascicles), high cellularity, mitoses (> 1/50 but <3/10 HPF)

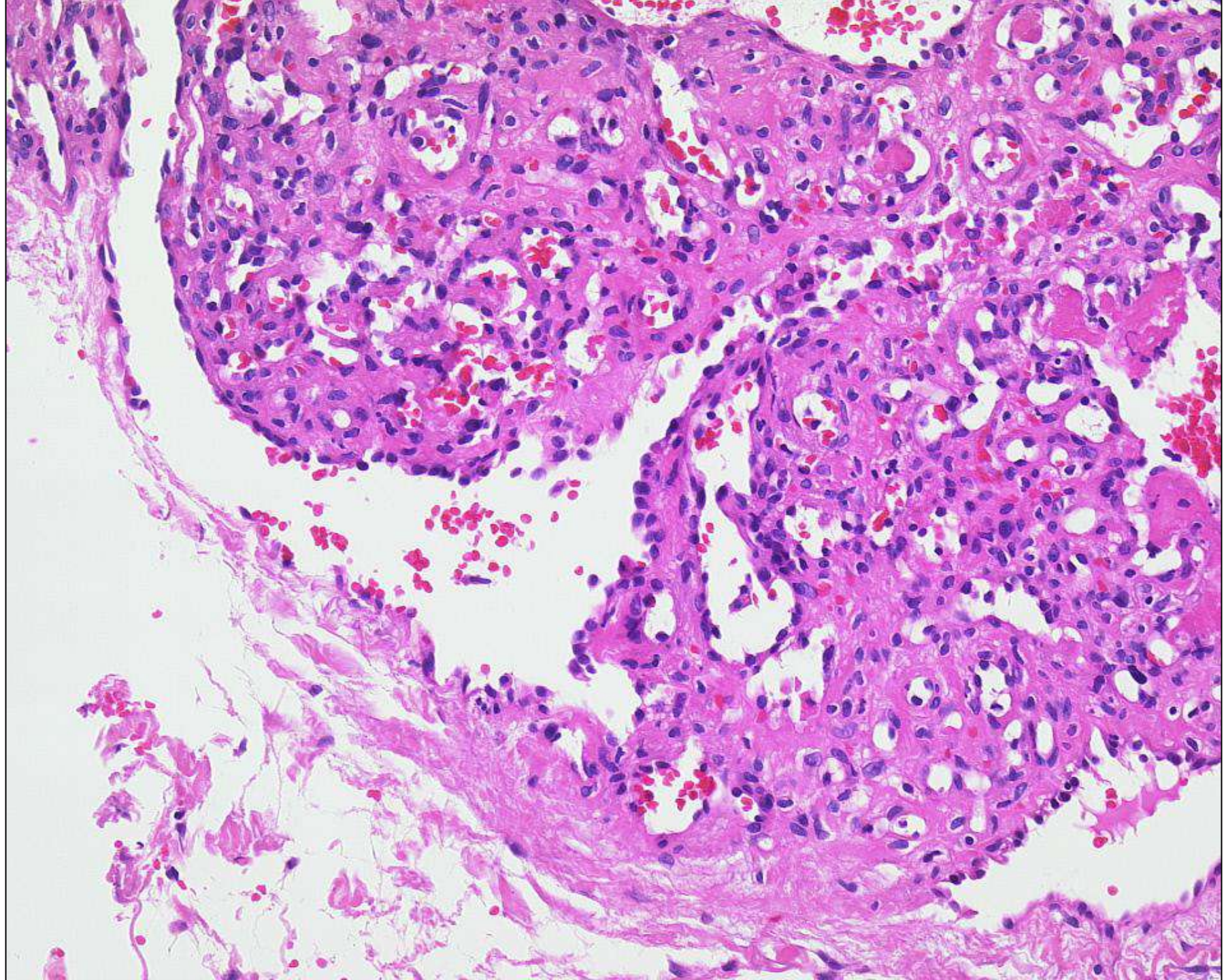
atypical neurofibroma:	only nuclear atypia (enlarged nuclei)
cellular neurofibroma:	hypercellularity, retained NF architecture
atypical NFT:	at least 2 of 4 features
low-grade MPNST:	features of atypical NFT + 3-9 mitoses/10 HPF
high-grade MPNST:	> 10 mitoses/10 HPF or
	3-9 mitoses/10 HPF + tumour necrosis

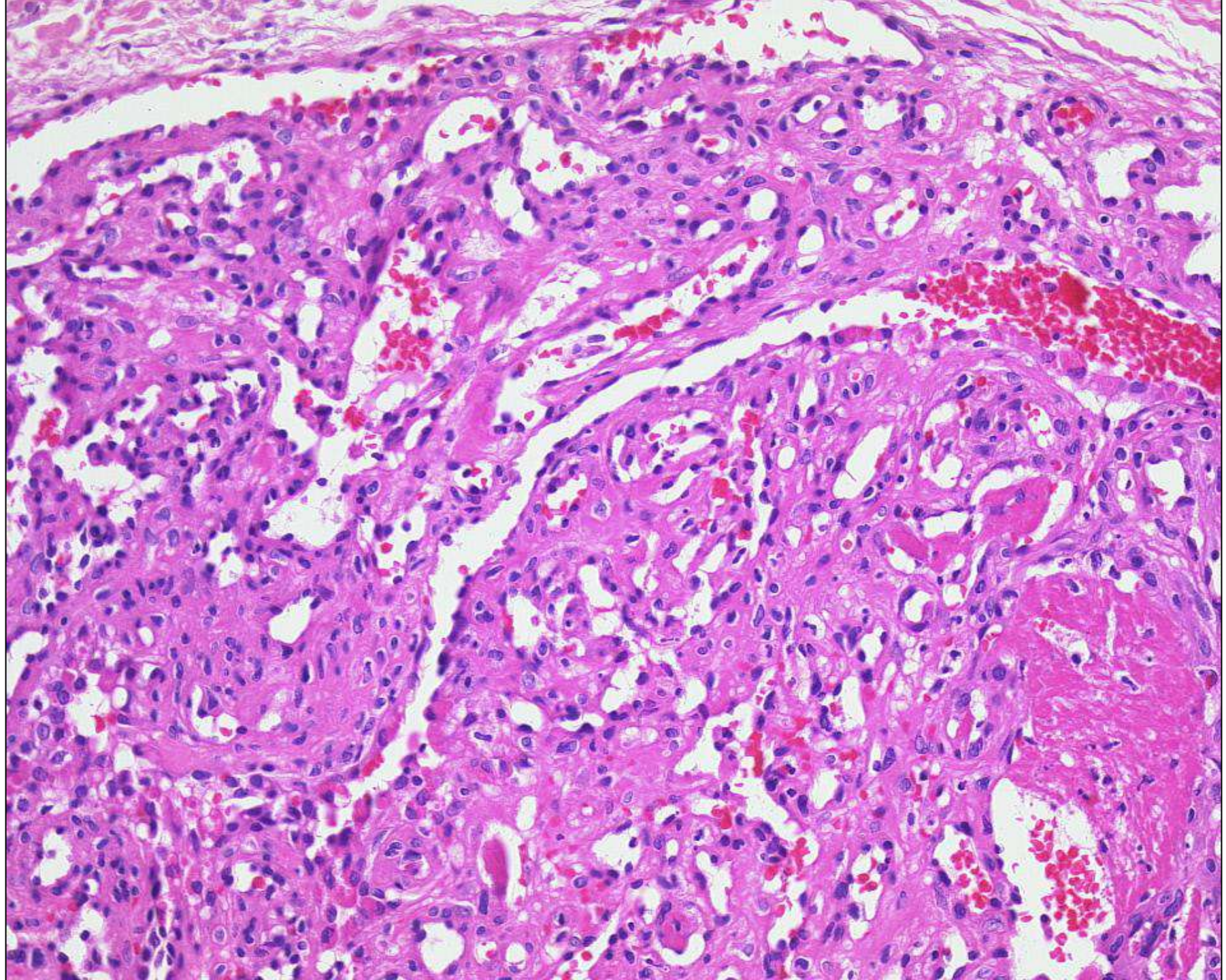


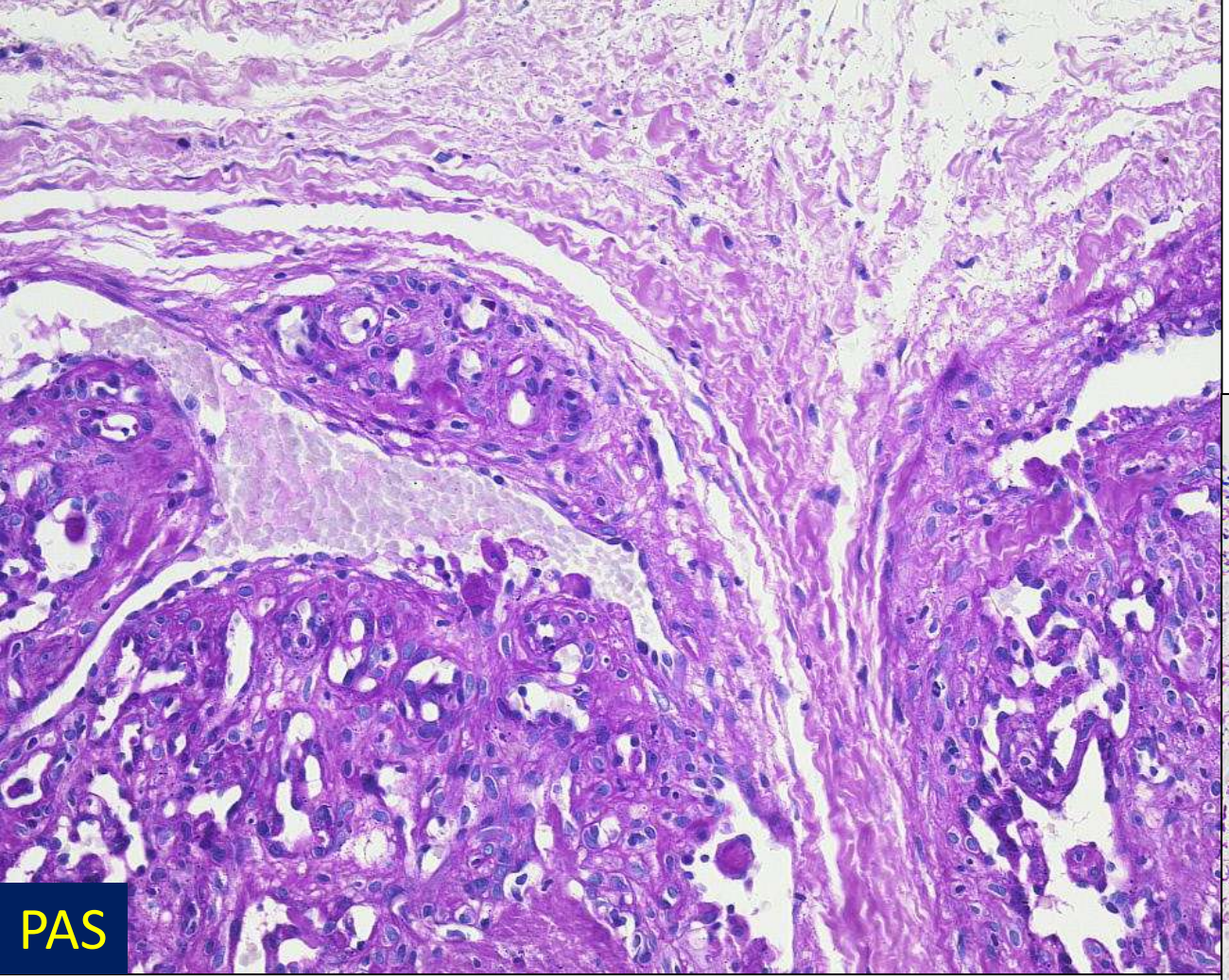
Case 6: F, 65 years, left cheek

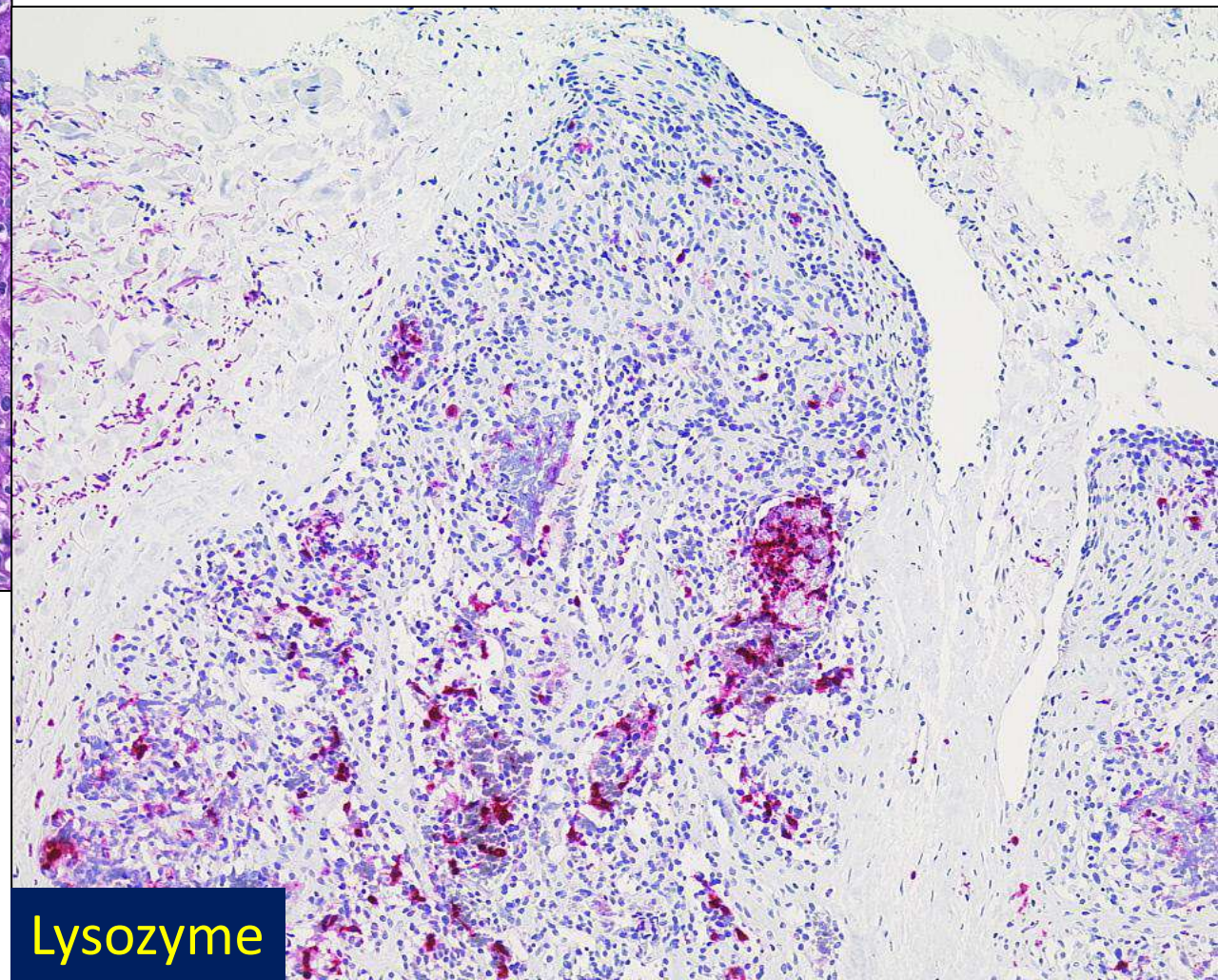


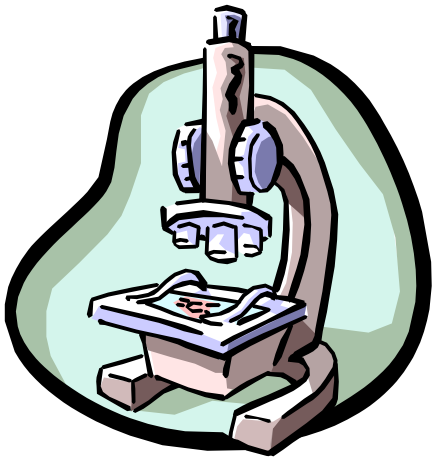







PAS


Lysozyme

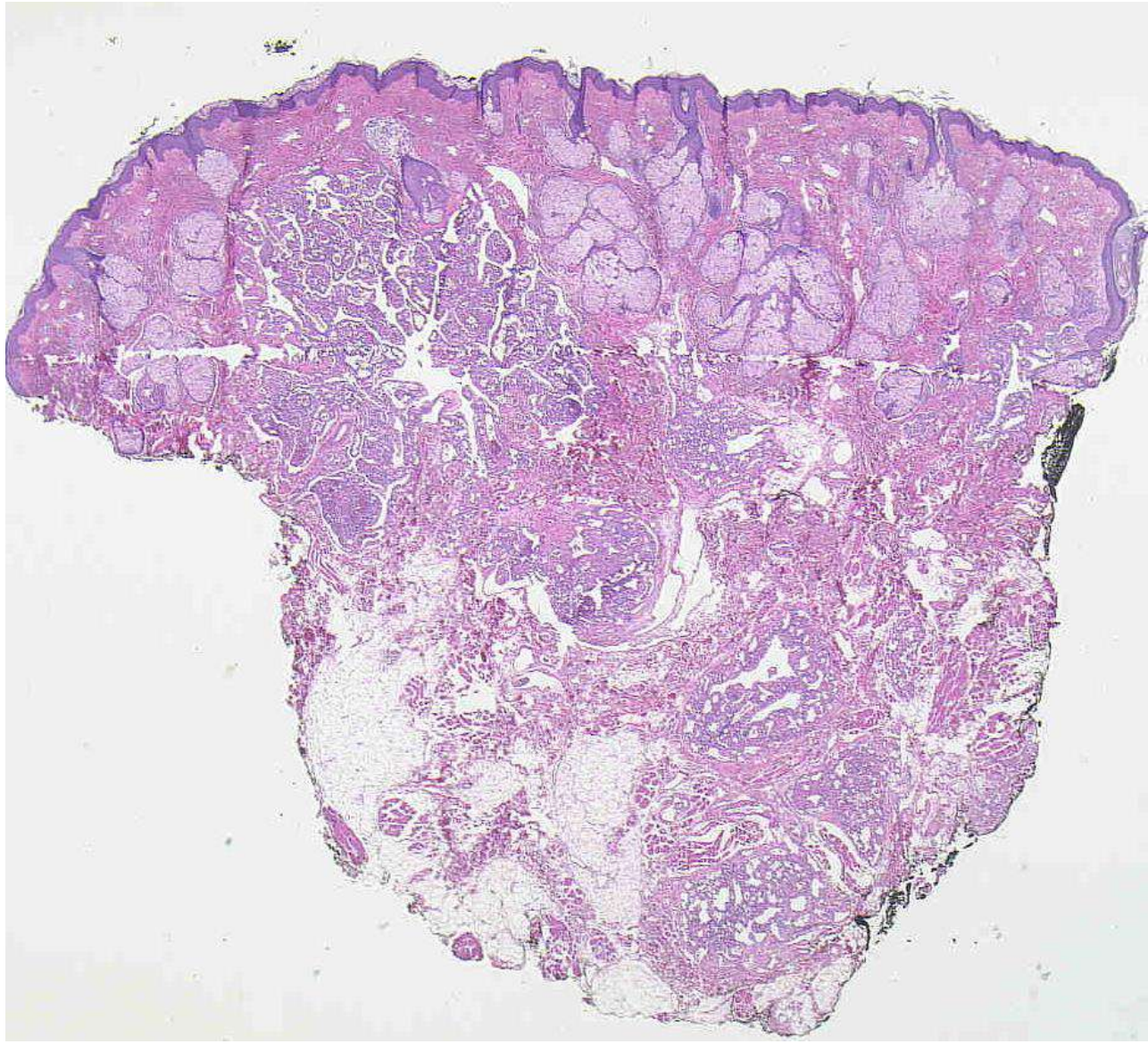


Diagnosis Case 6

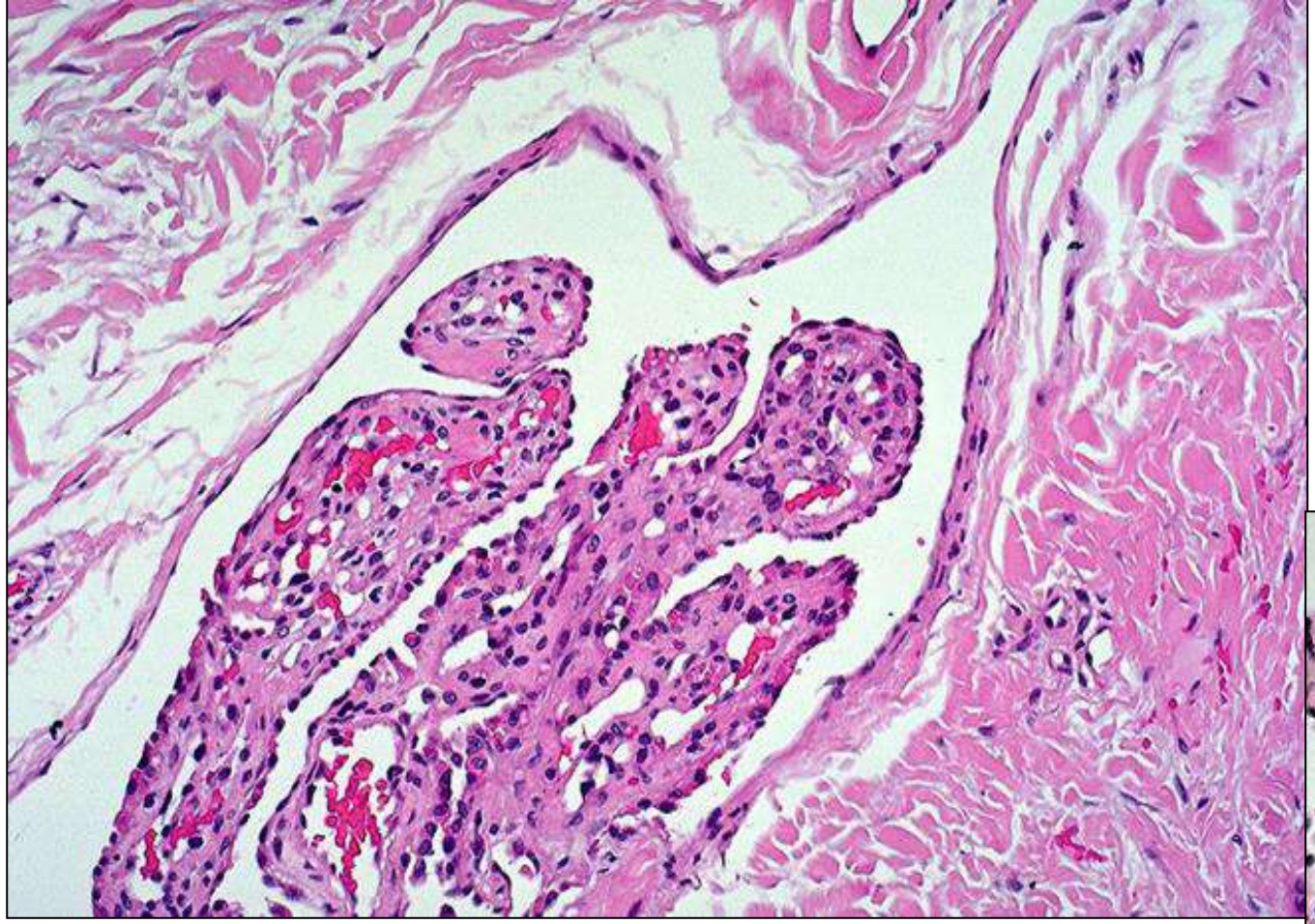
papillary Haemangioma

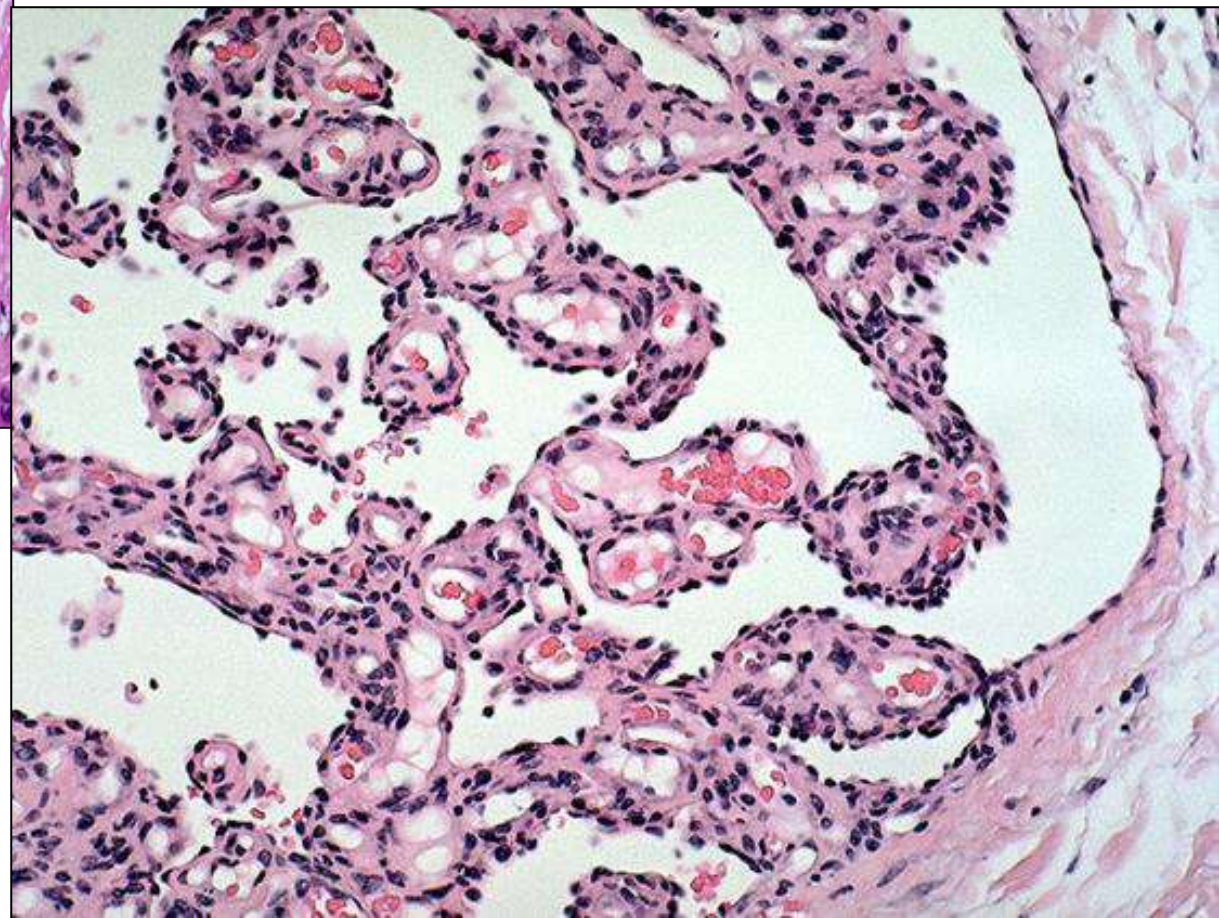
Papillary Haemangioma
(Histopathology 2007; 51: 638)

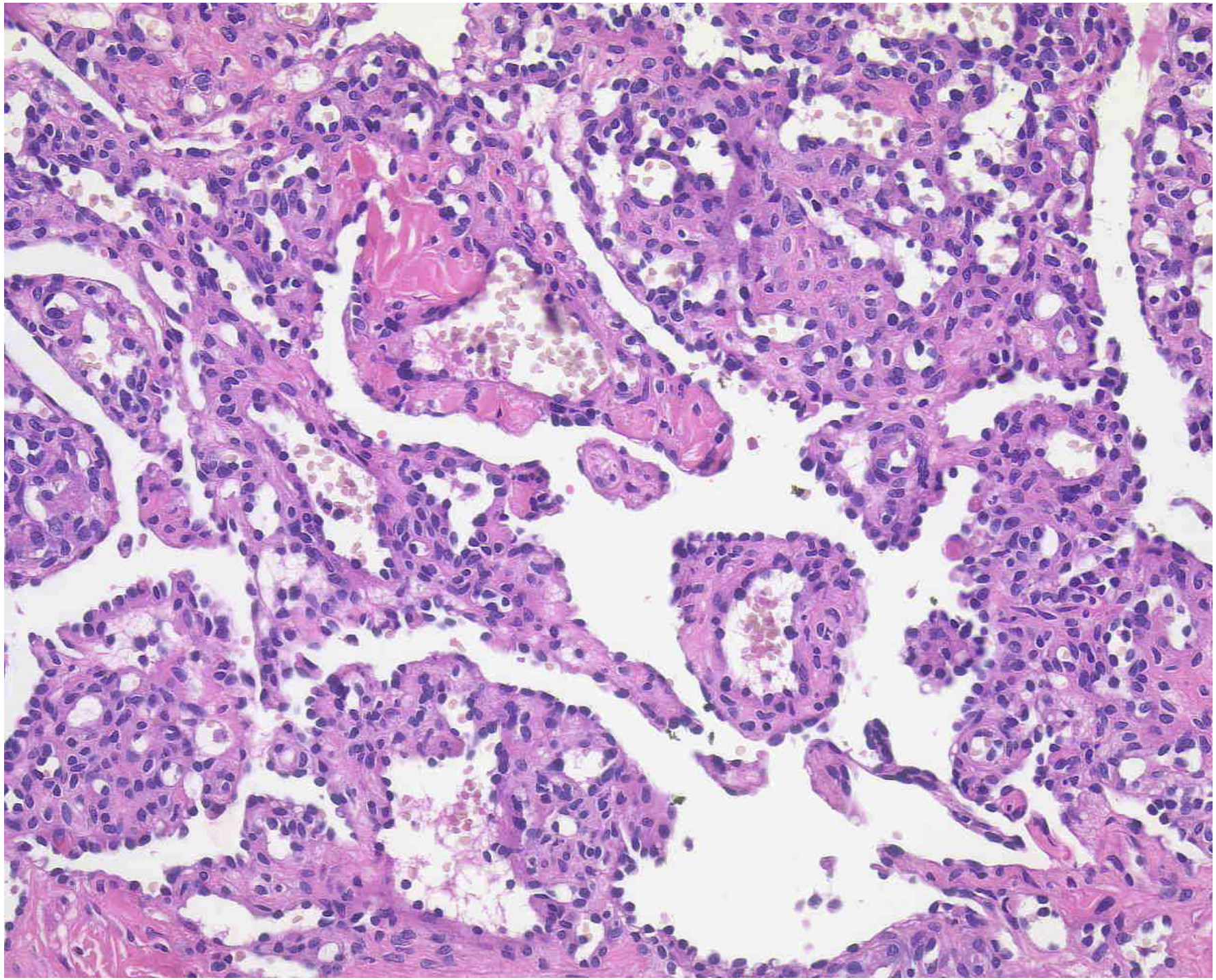
- head / neck region
- solitary lesions, no systemic disease
- ectatic dermal vessels
- intravascular papillae
- papillae with pericytes and stromal cells
- swollen endothelial cells with hyaline globules (giant lysosomes)
- thick mantle of collagen type IV
- papillary hemangioma harbors somatic *GNA11* and *GNAQ* mutations (Gestrich CK et al. AJSP 2024; 48: 106)



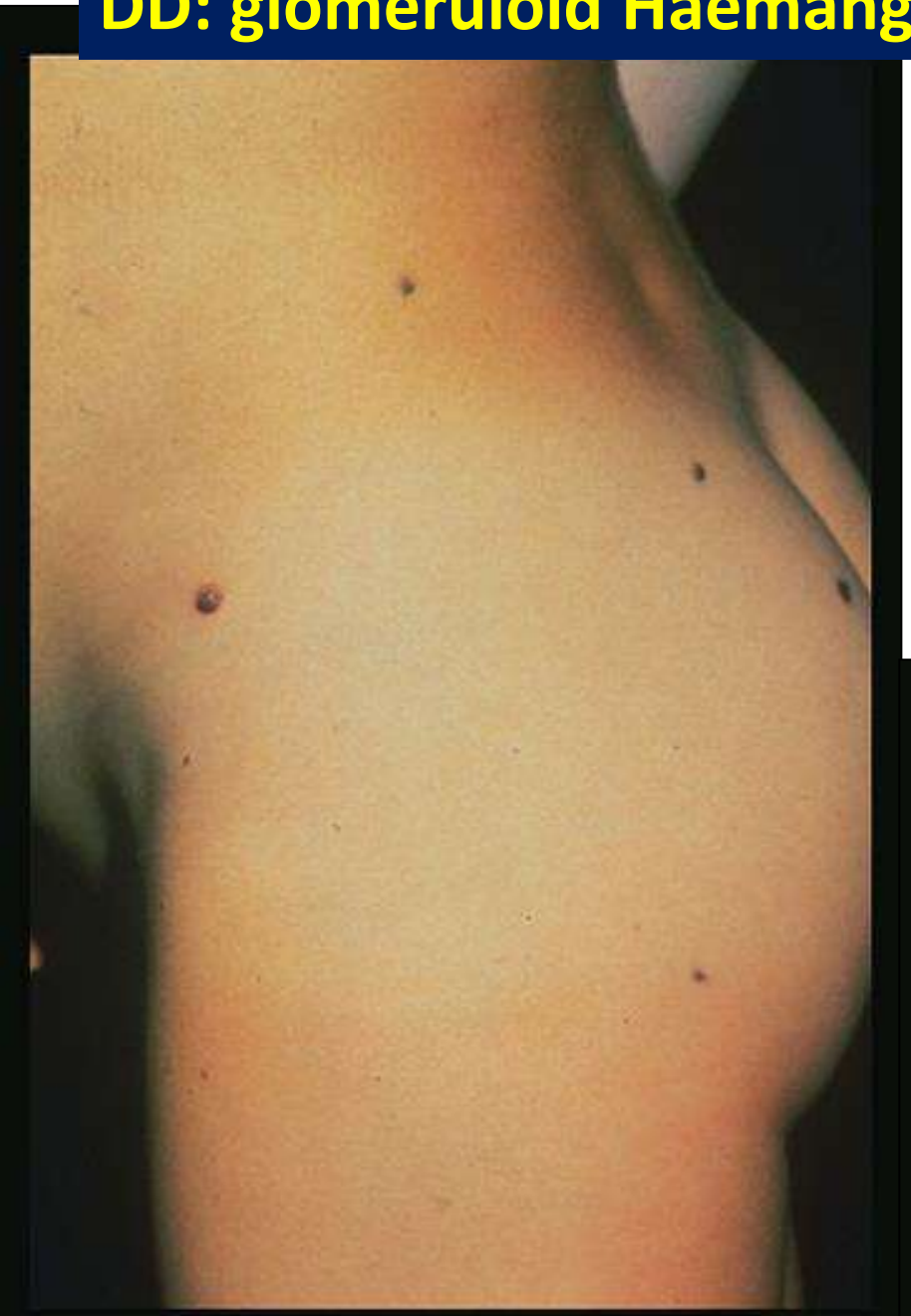
by courtesy of Dr.Suurmeijer, Netherlands

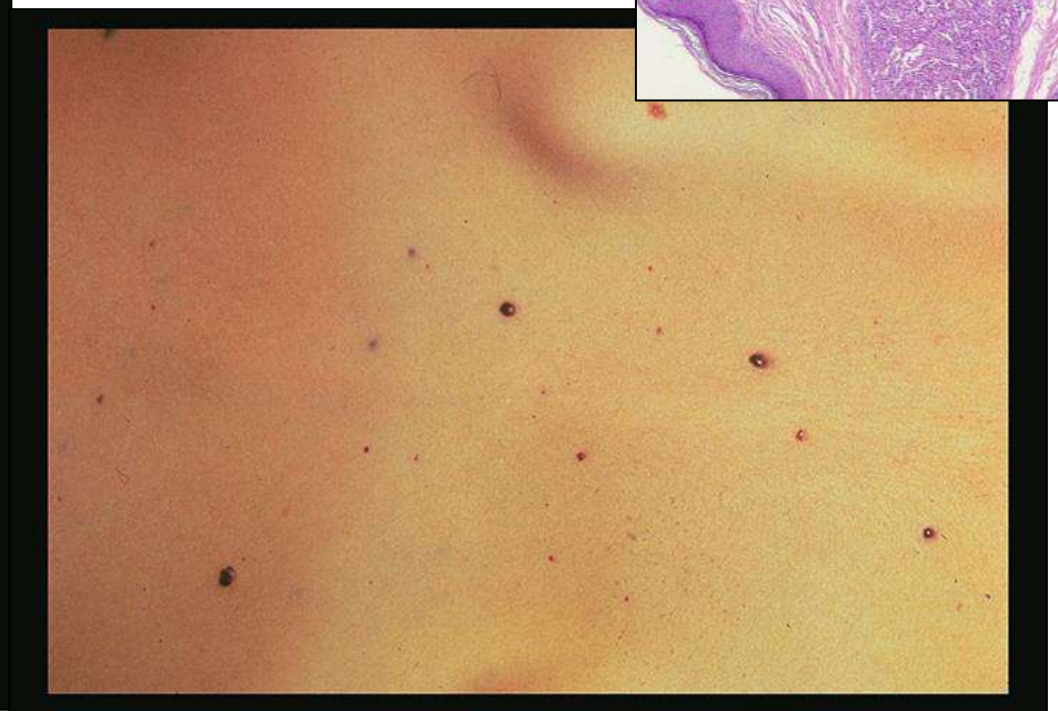


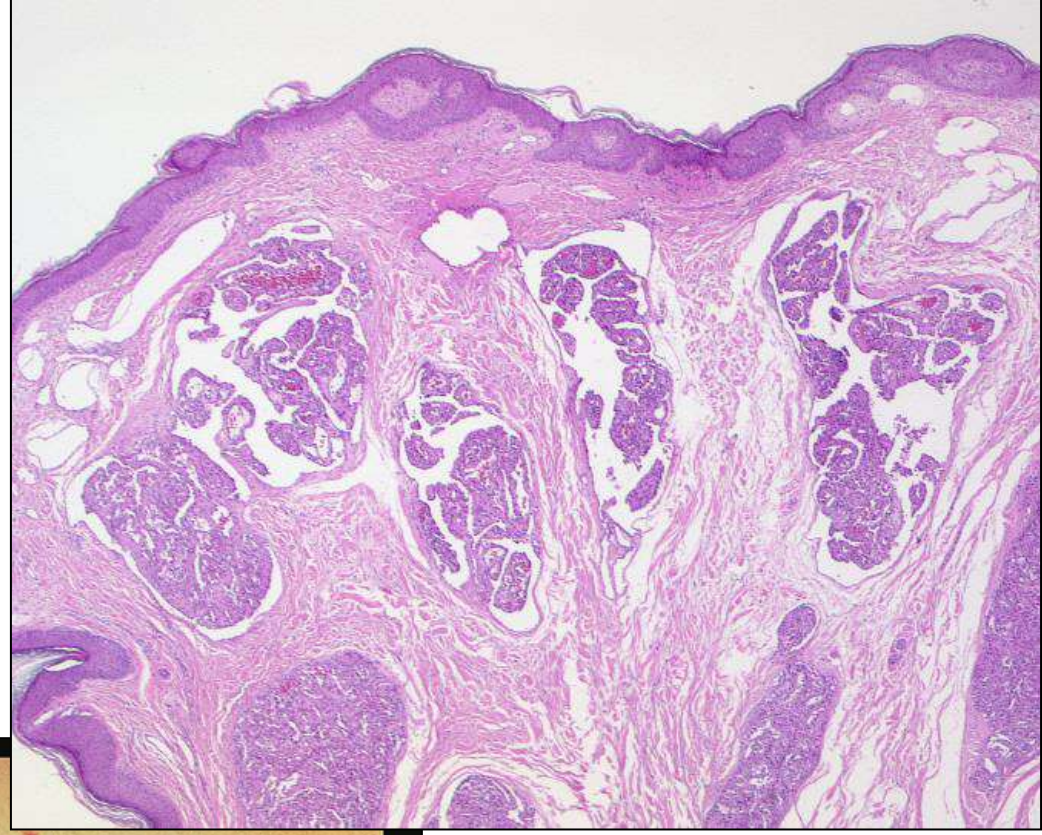




DD: glomeruloid Haemangioma

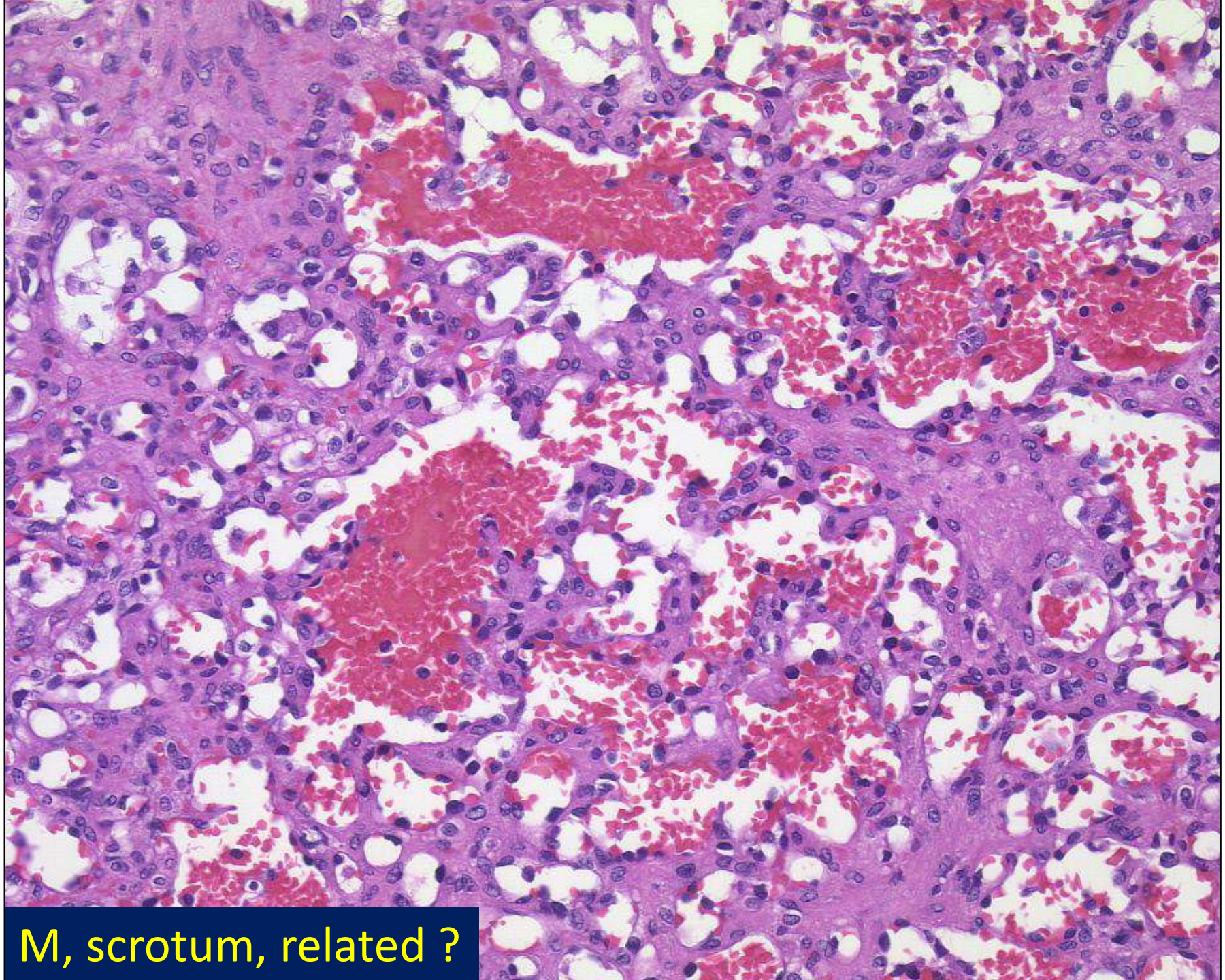






POEMS Syndrome

- Polyneuropathy
- Organomegalie
- Endocrinopathy
- Monoclonal gammopathy (M-protein)
- multiple Skin lesions

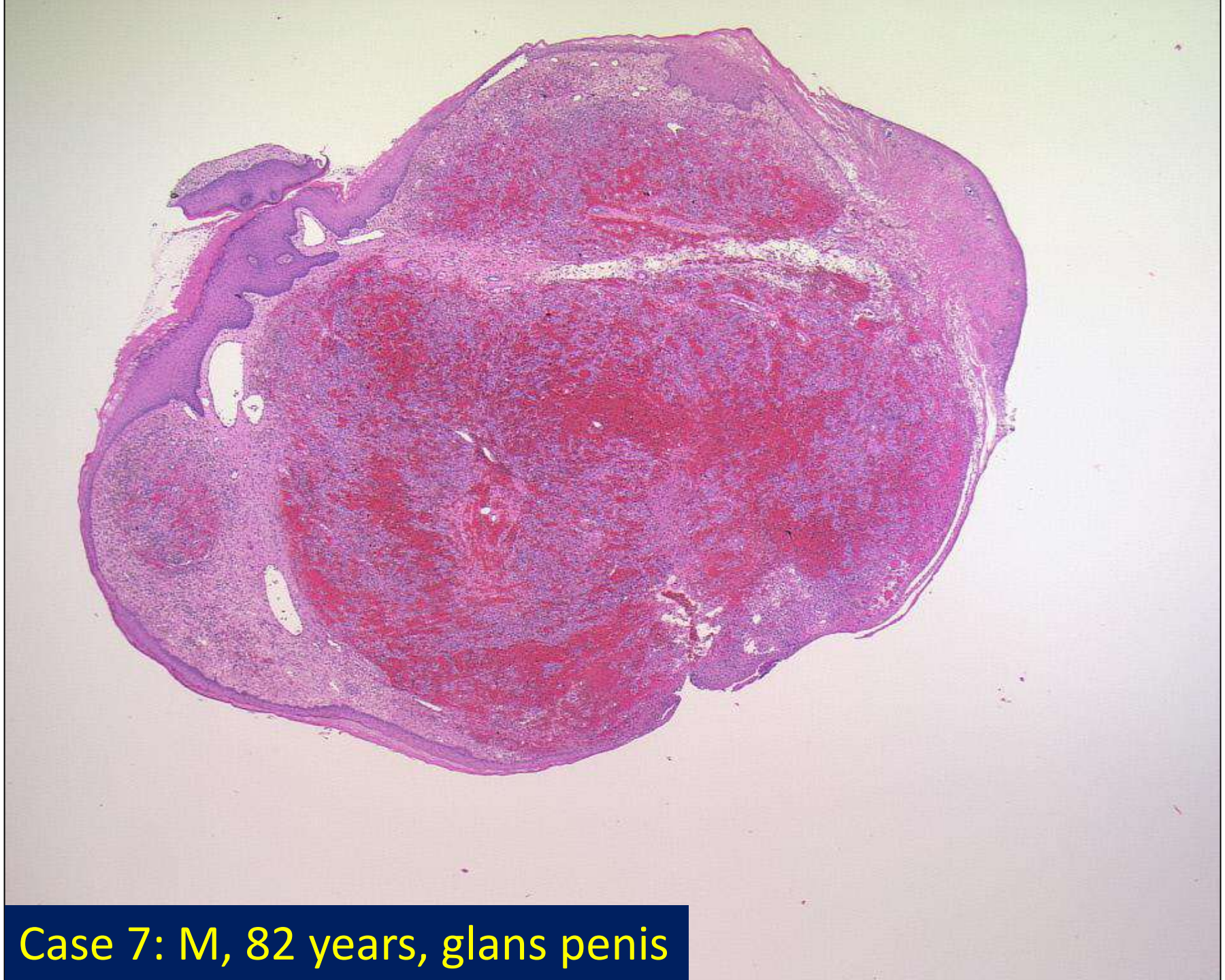

M, scrotum, related ?

anastomosing Haemangioma

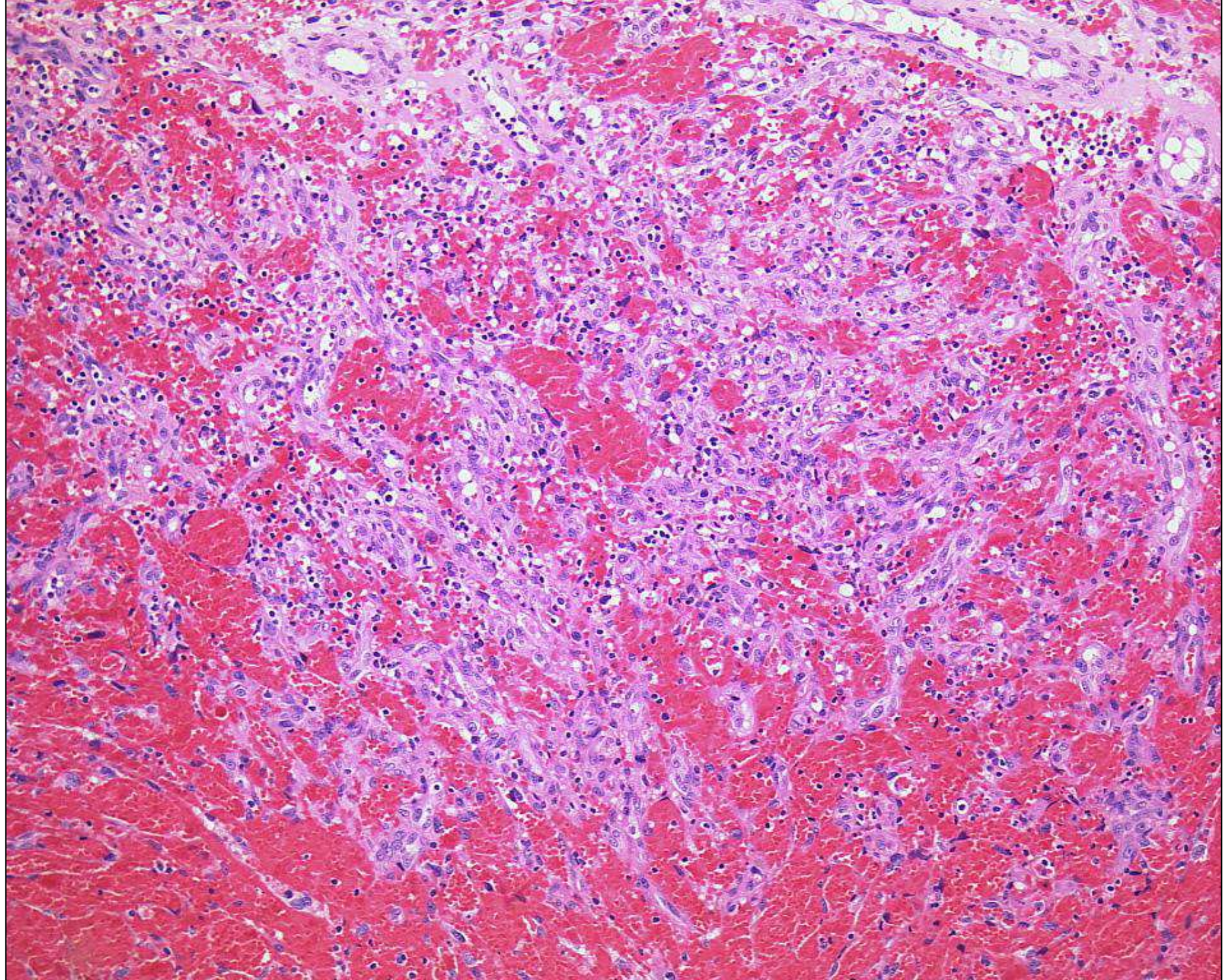
- genital area, visceral organs,skin, soft tissues, children, adults
- solitary, multiple, circumscribed, infiltrative
- dilated, anastomosing vessels,

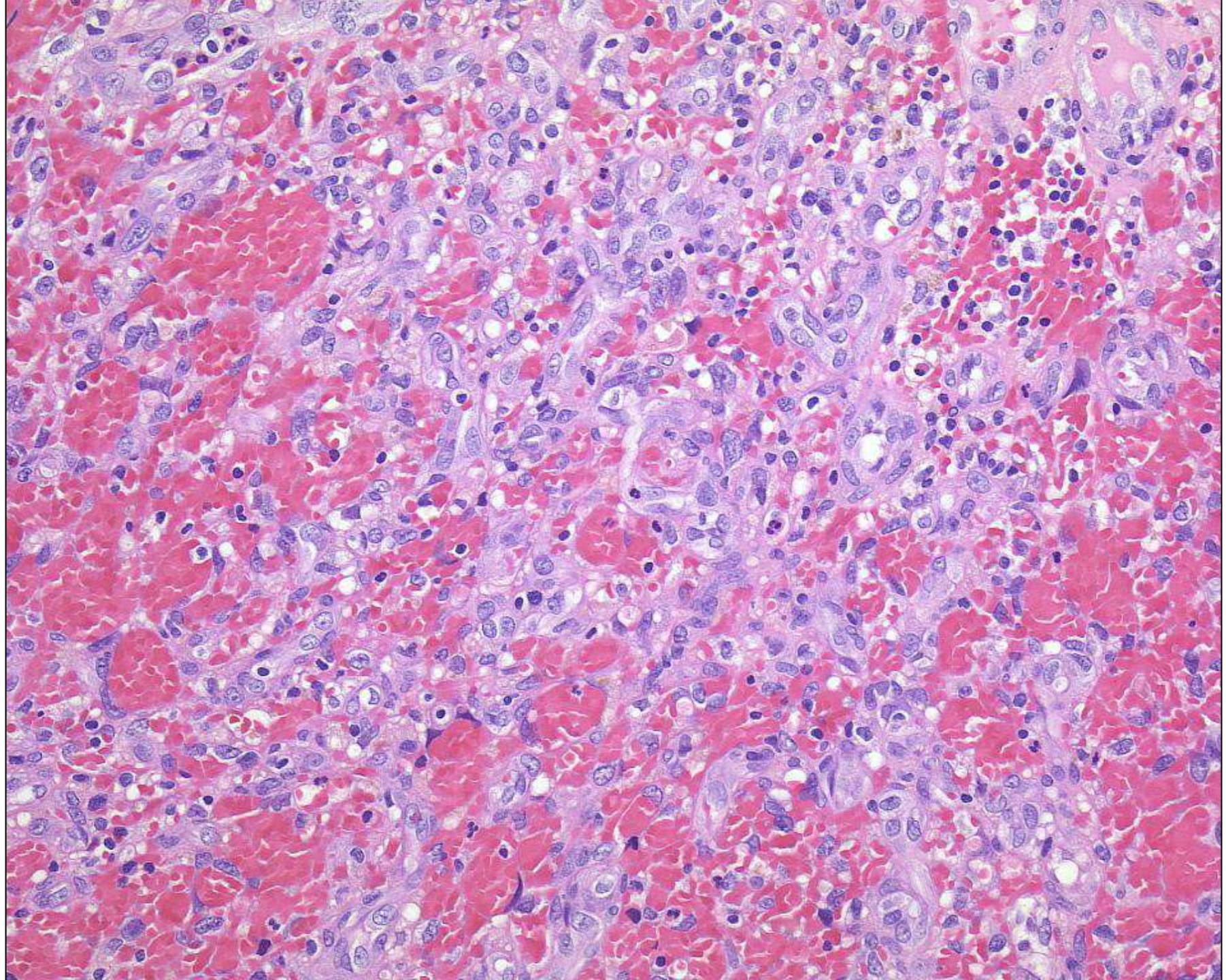
  enlarged, hobnail-like endothelial cells
- hyaline globuli, extramedullary haematopoesis, lipomatous metaplasia,

  few mitoses, no endothelial multilayering
- aktivating *GNAQ* or *GNA14* mutations

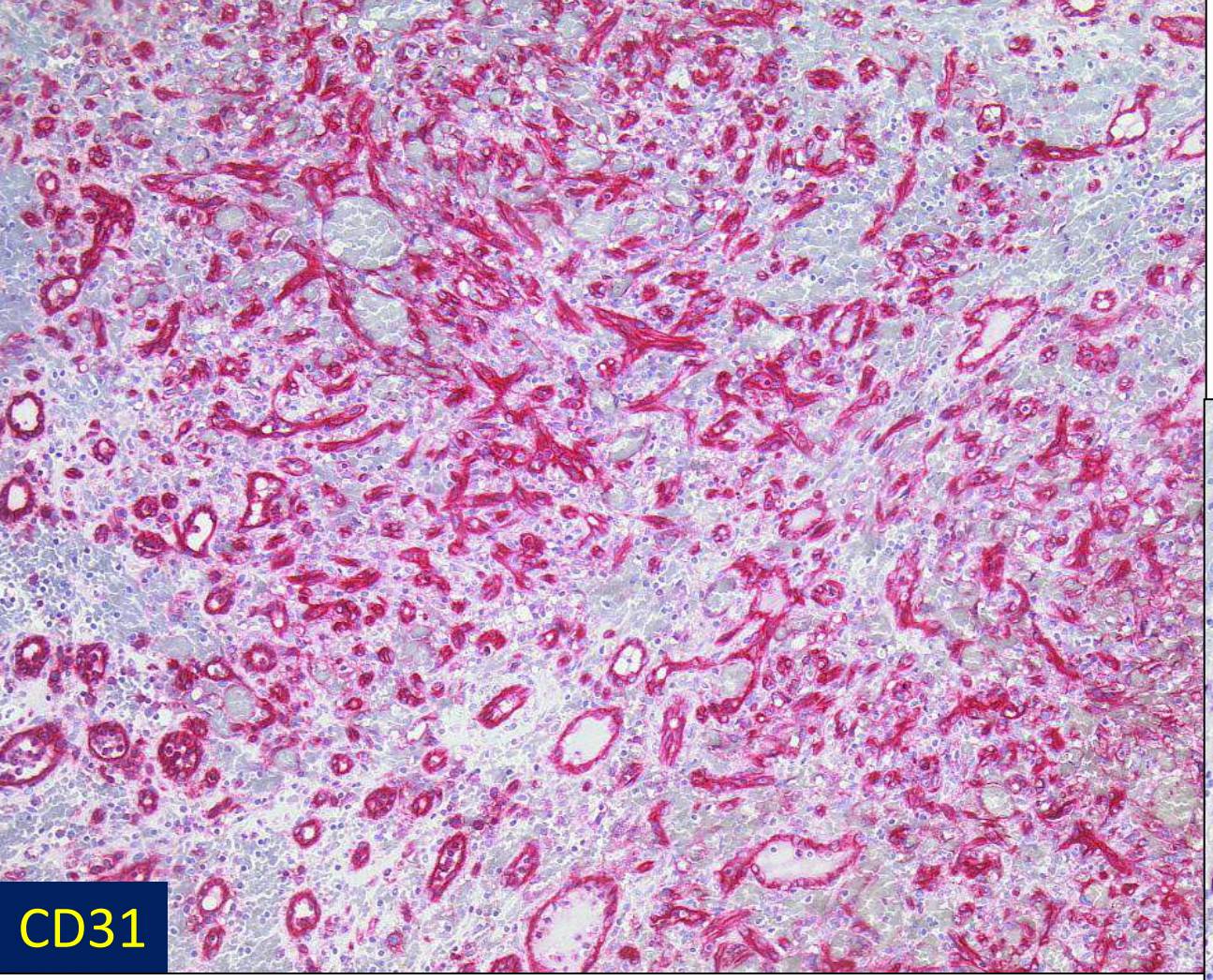


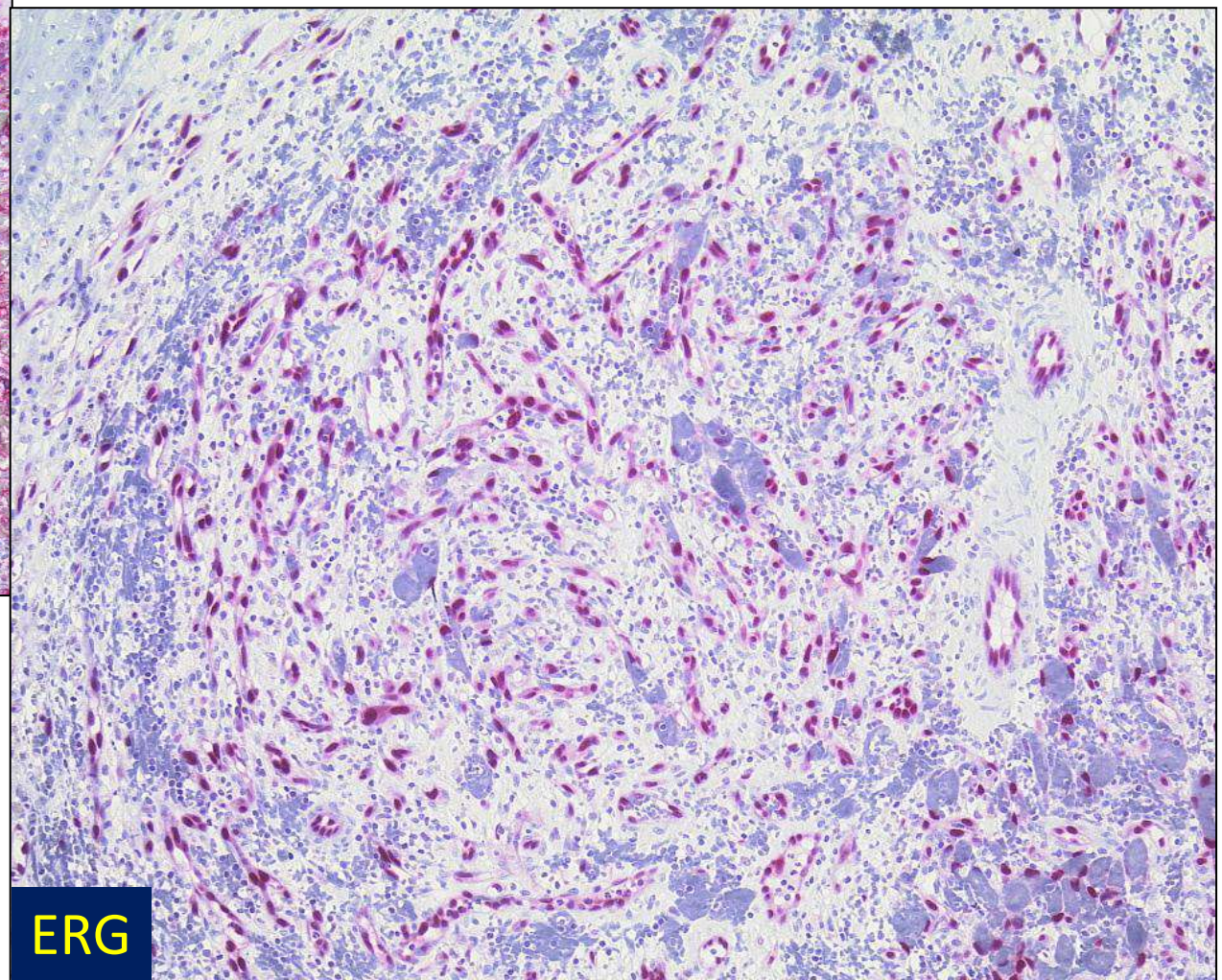
Case 7: M, 82 years, glans penis

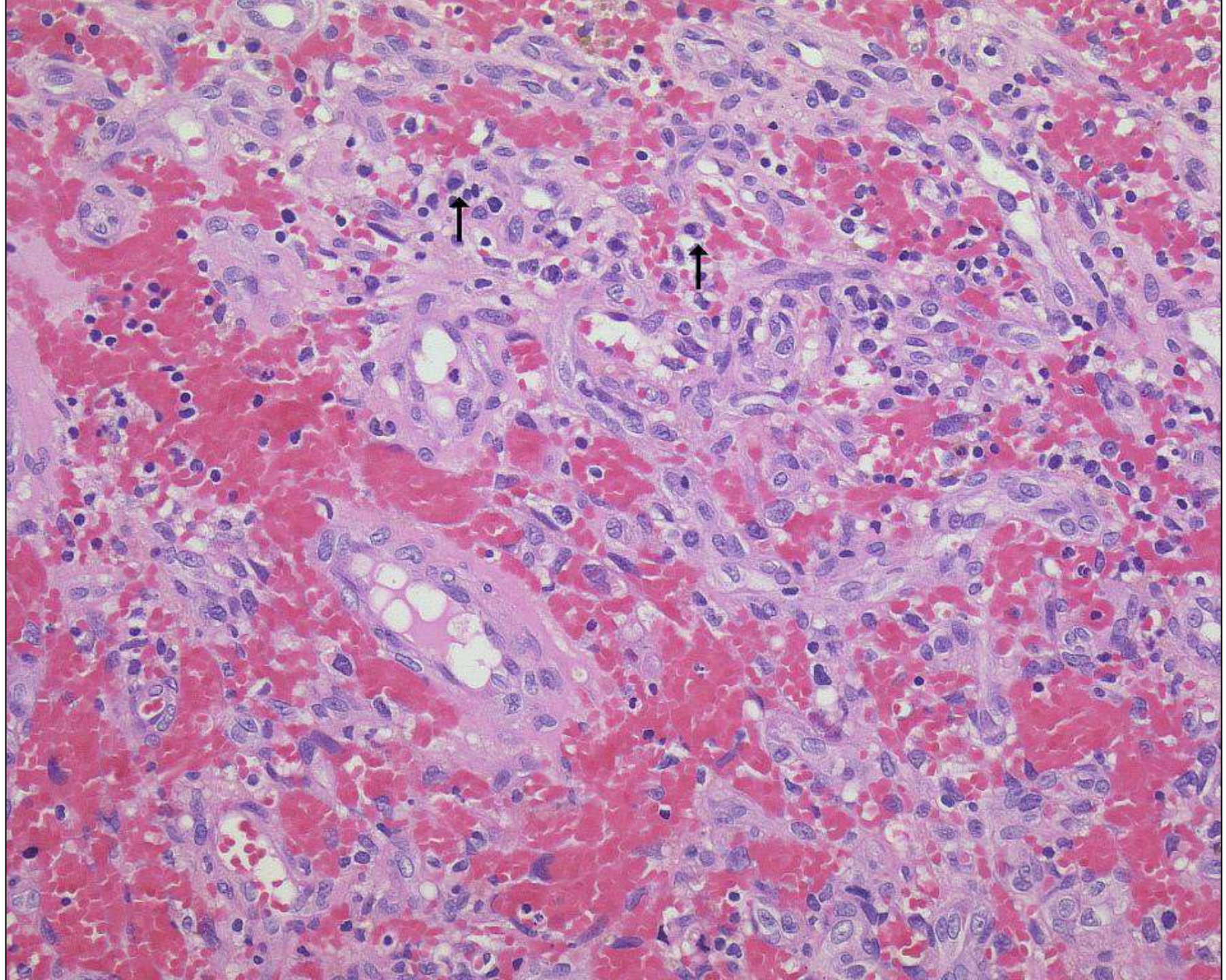


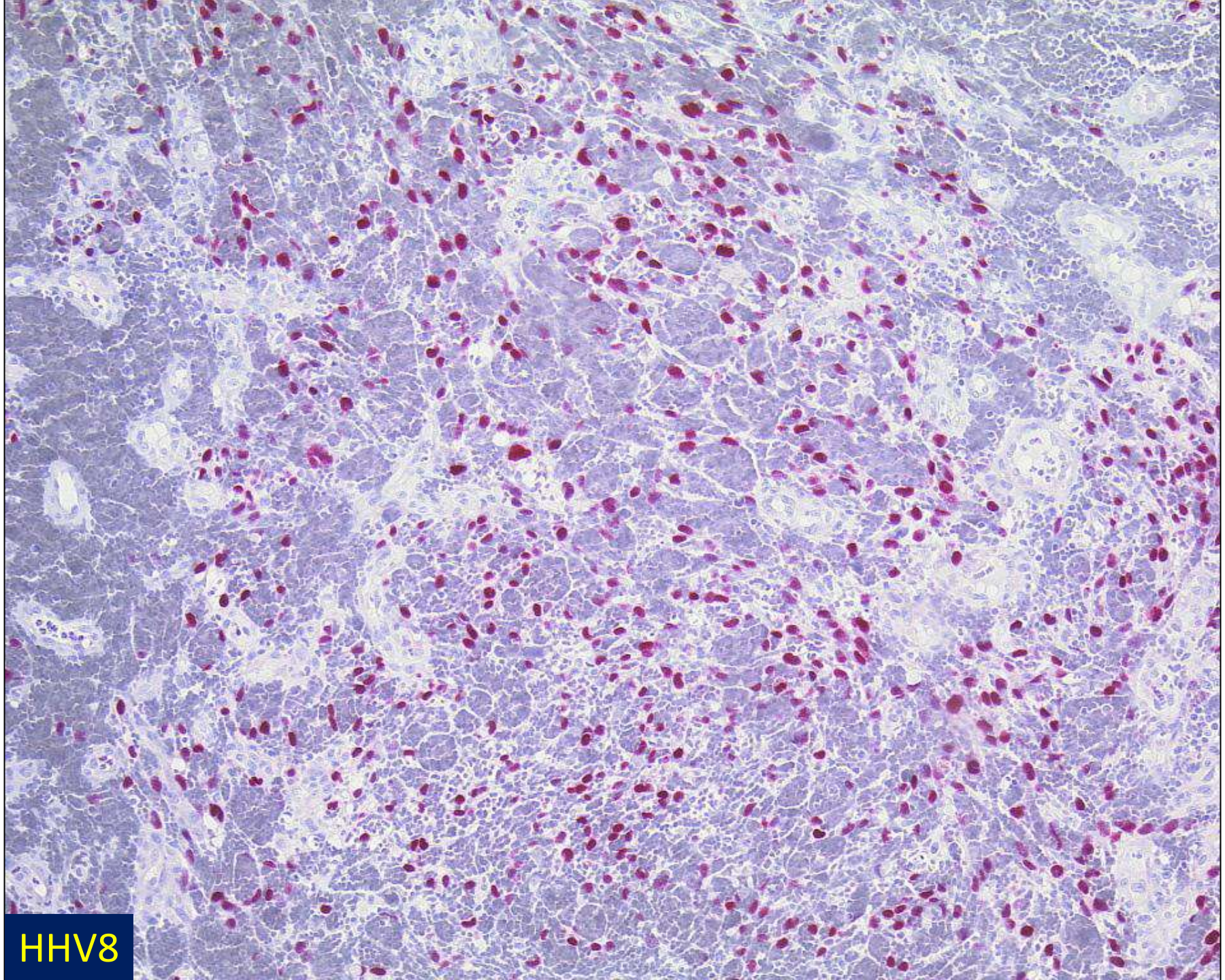


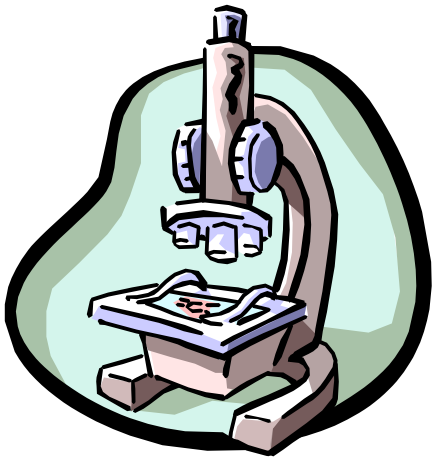
cellular, epithelioid vascular lesion…








HHV8

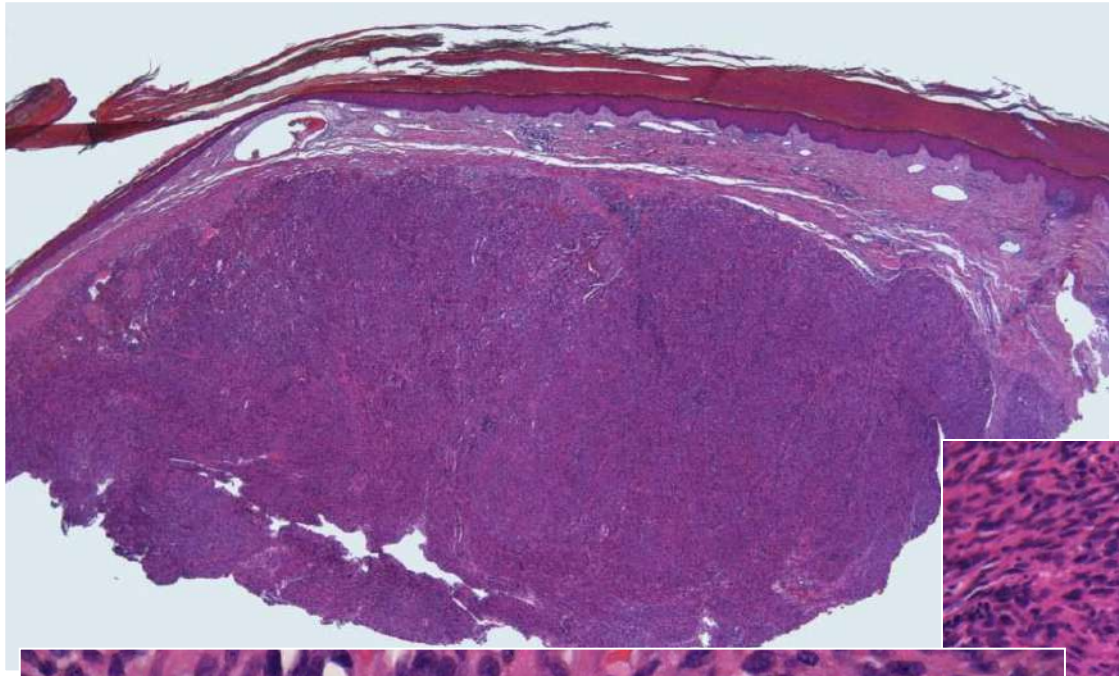


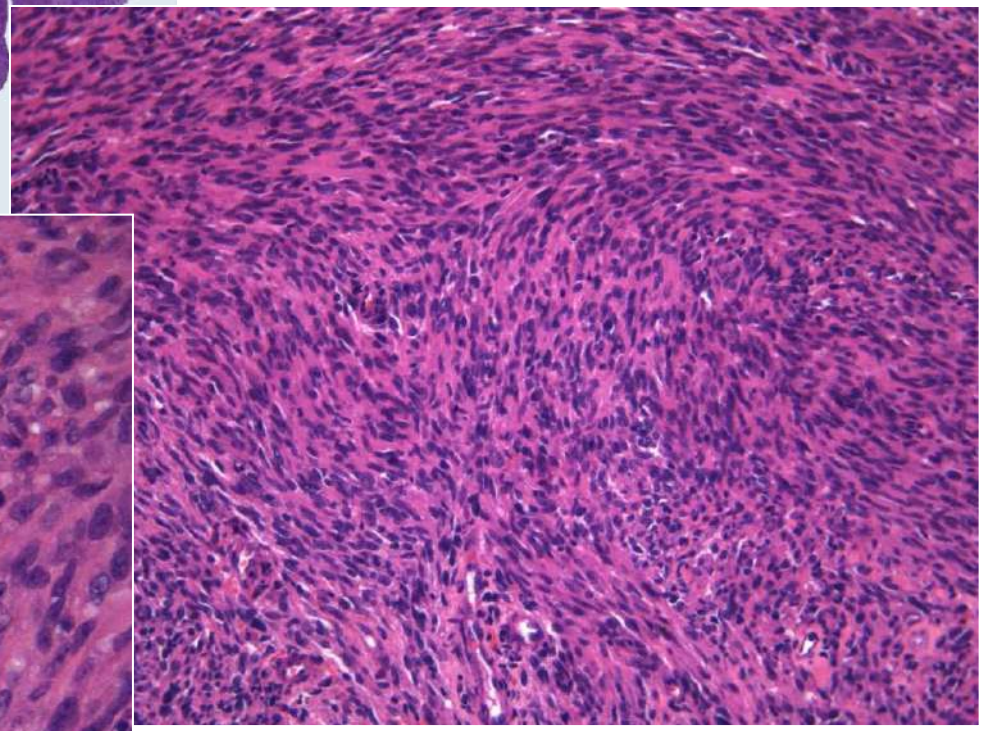
Diagnosis Case 7

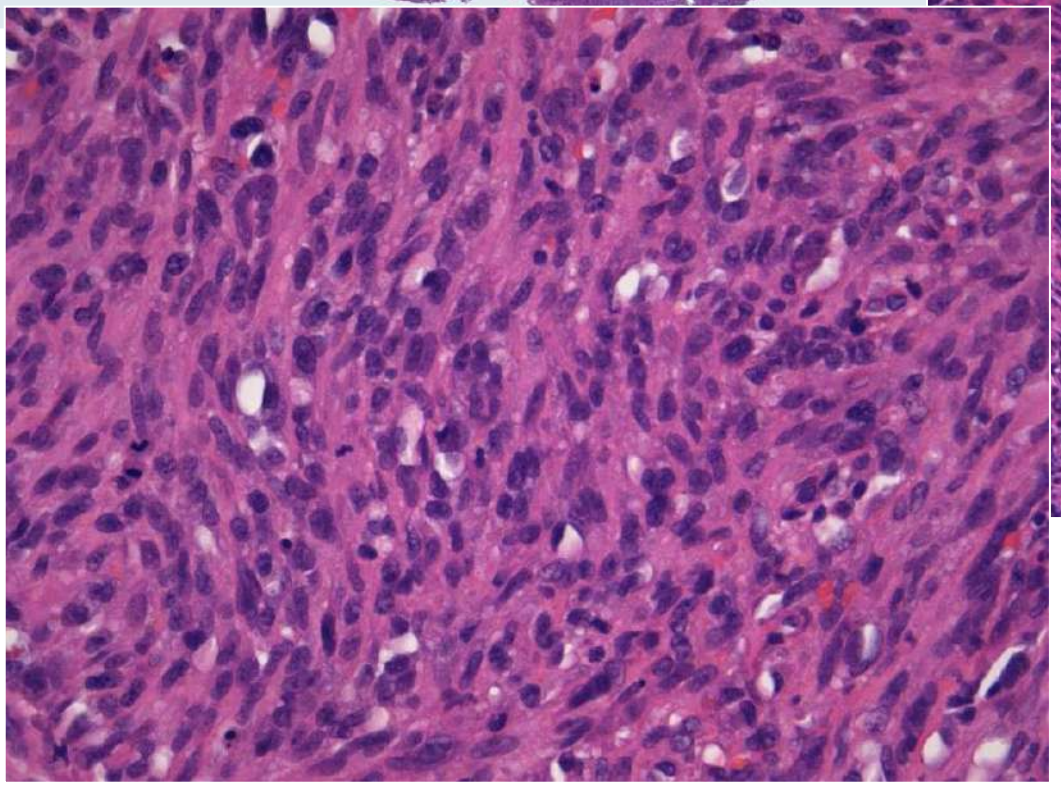
epithelioid Kaposi sarcoma

rare morphological Variants

- anaplastic Kaposi Sarcoma
  (aggressive clinical course, metastases)
- intravascular Kaposi Sarcoma
- lymphangioma-like Kaposi Sarcoma
- micronodular Kaposi Sarcoma
- keloidal Kaposi Sarcoma
- hyperkeratotic Kaposi Sarcoma

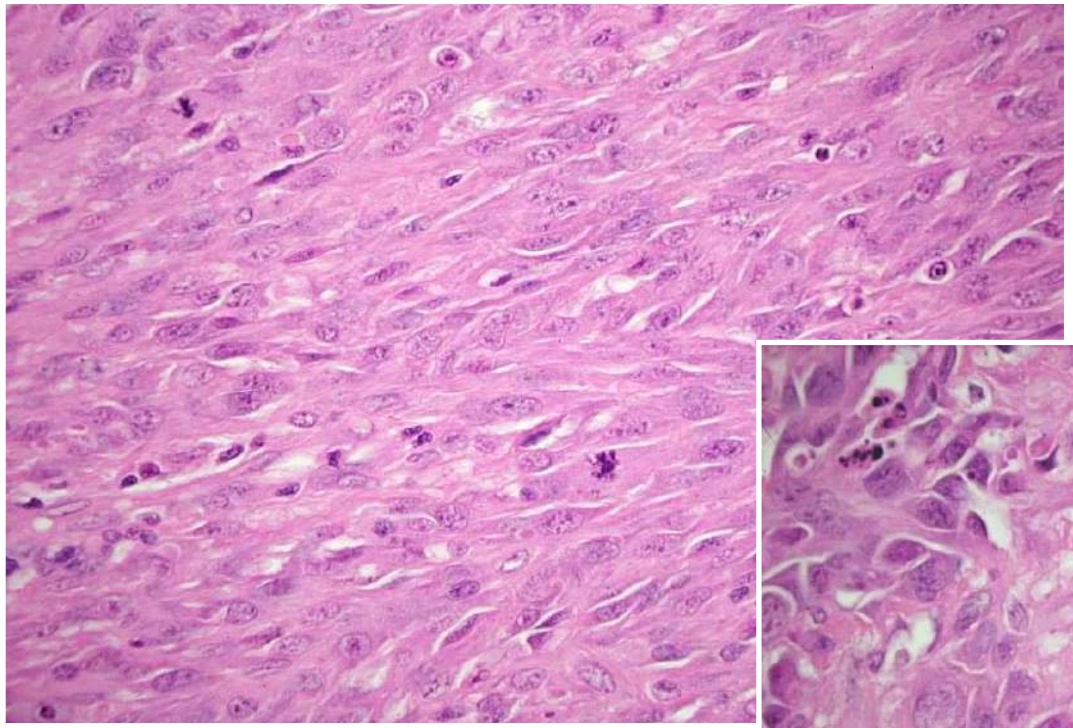


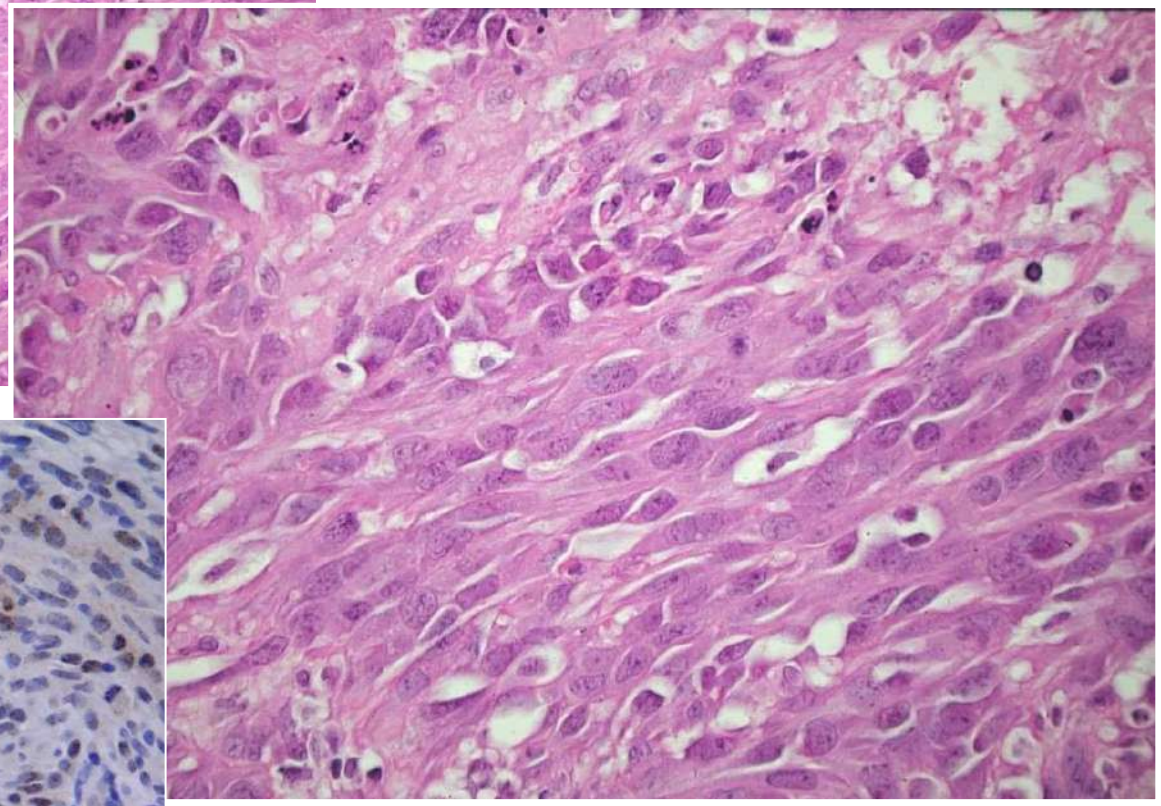


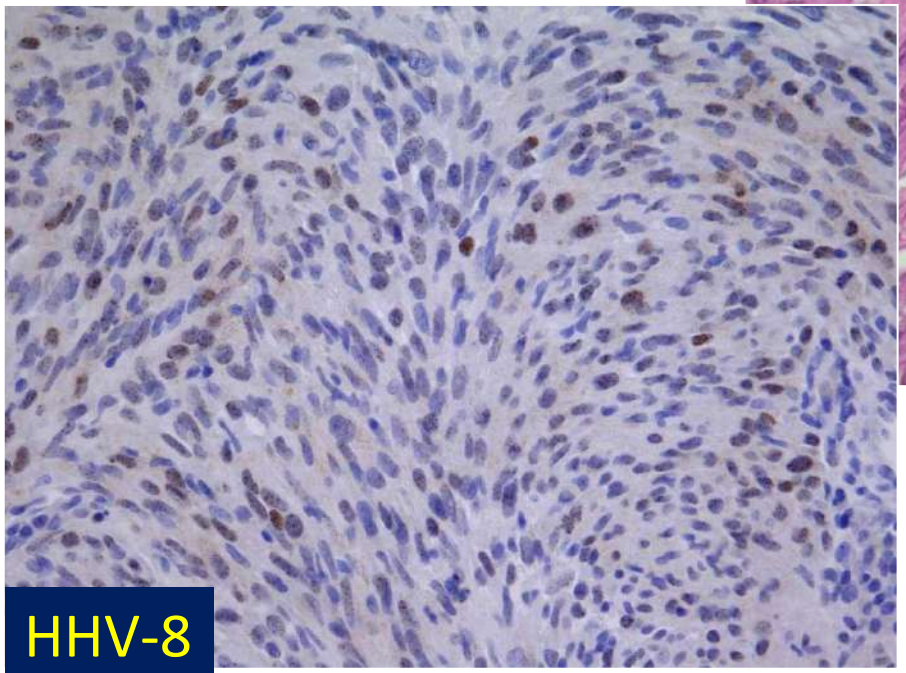


M, 35 years, HIV +

anaplastic Kaposi Sarcoma







Anaplastic Kaposi sarcoma: a clinicopathologic and genetic analysis

Fischer GM et al. Mod Pathol 2023; 36: Epub 2023 Apr 18.

9 anaplastic KS (8 conventional KS),

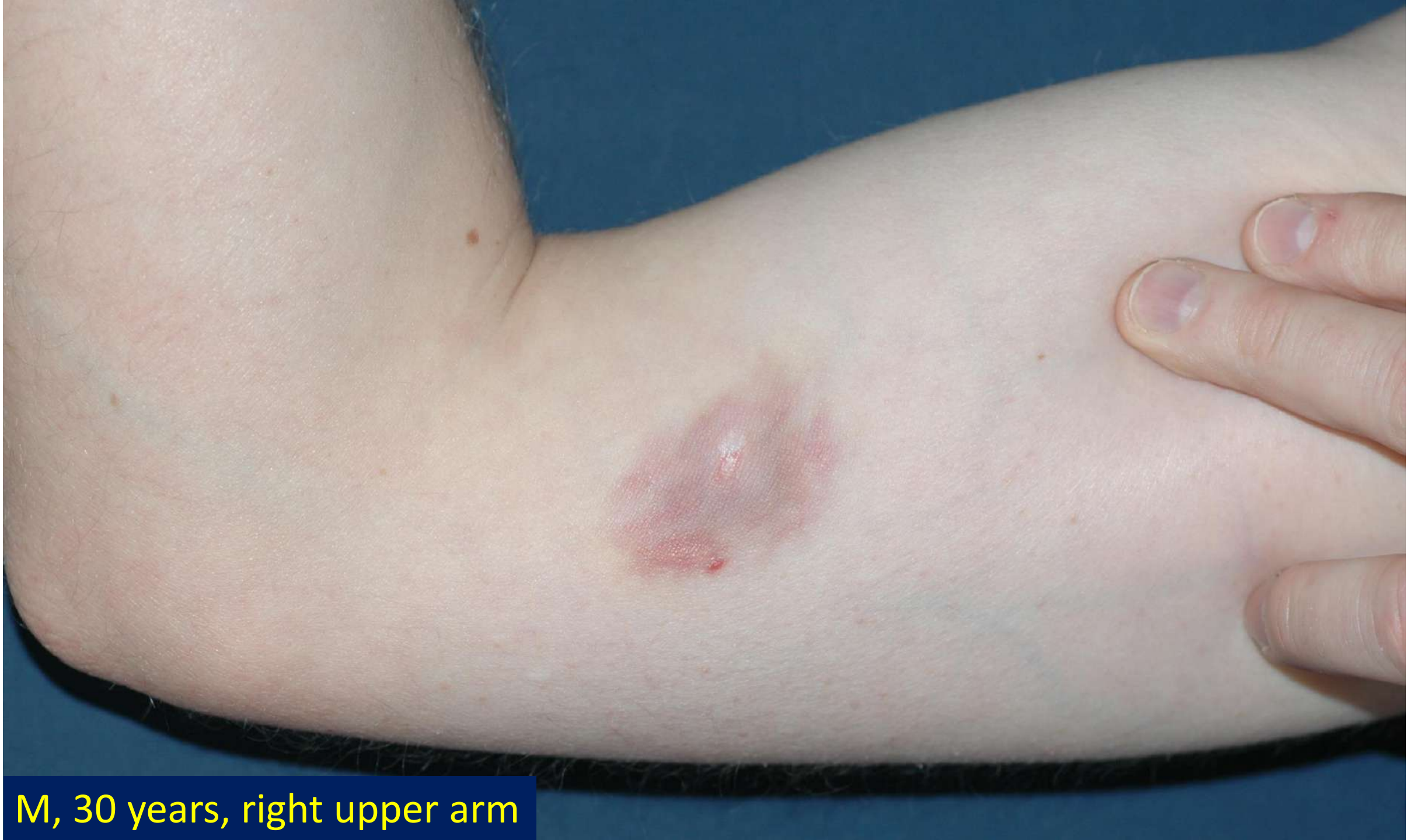
M, 51-82 years, lower extremities

angiosarcoma-like and pleomorphic spindle cell sarcoma morphology

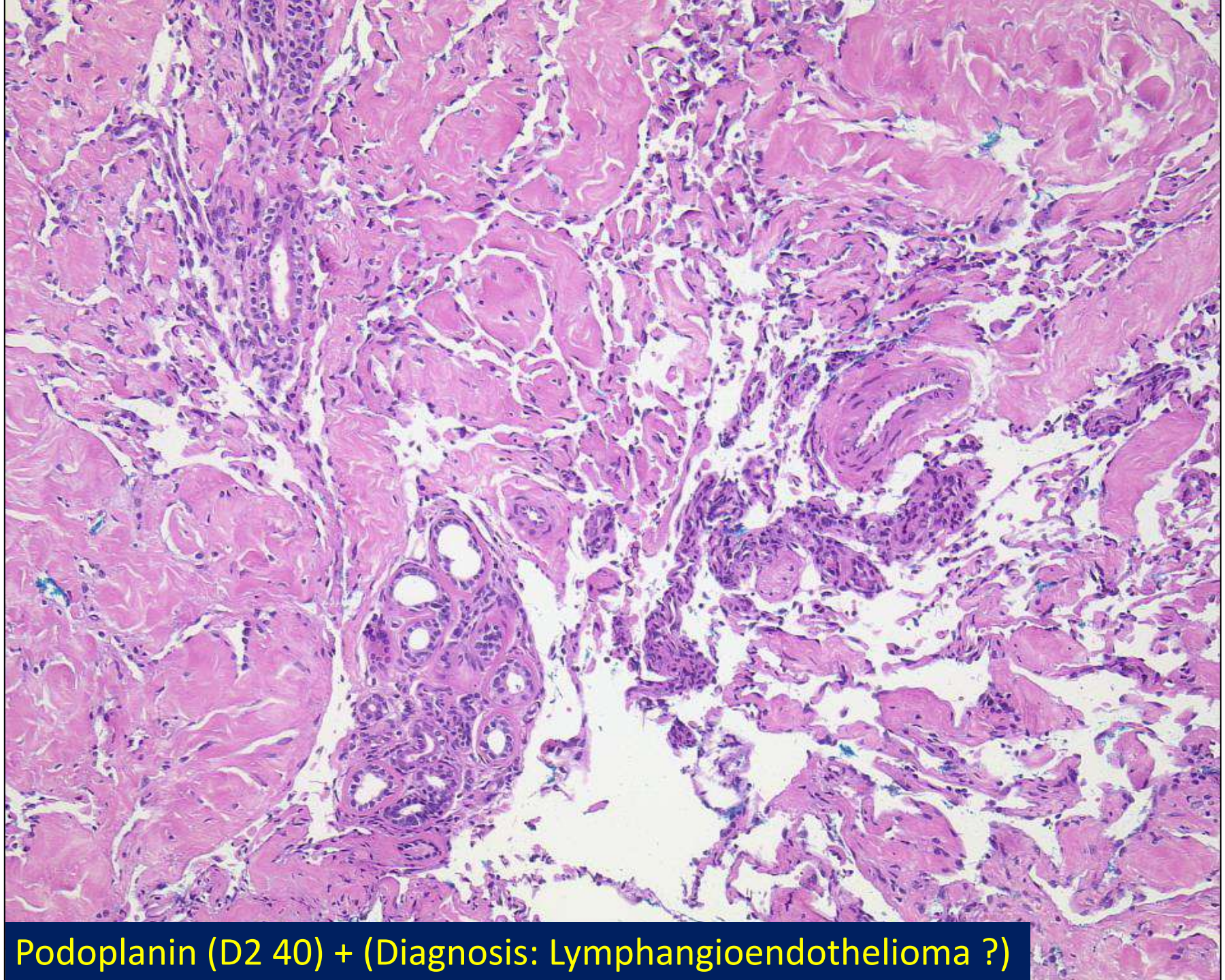
recurrent whole chromosome gains (7,11,19,21)

gains affected genes that facilitate cyclin-dependent cell signaling

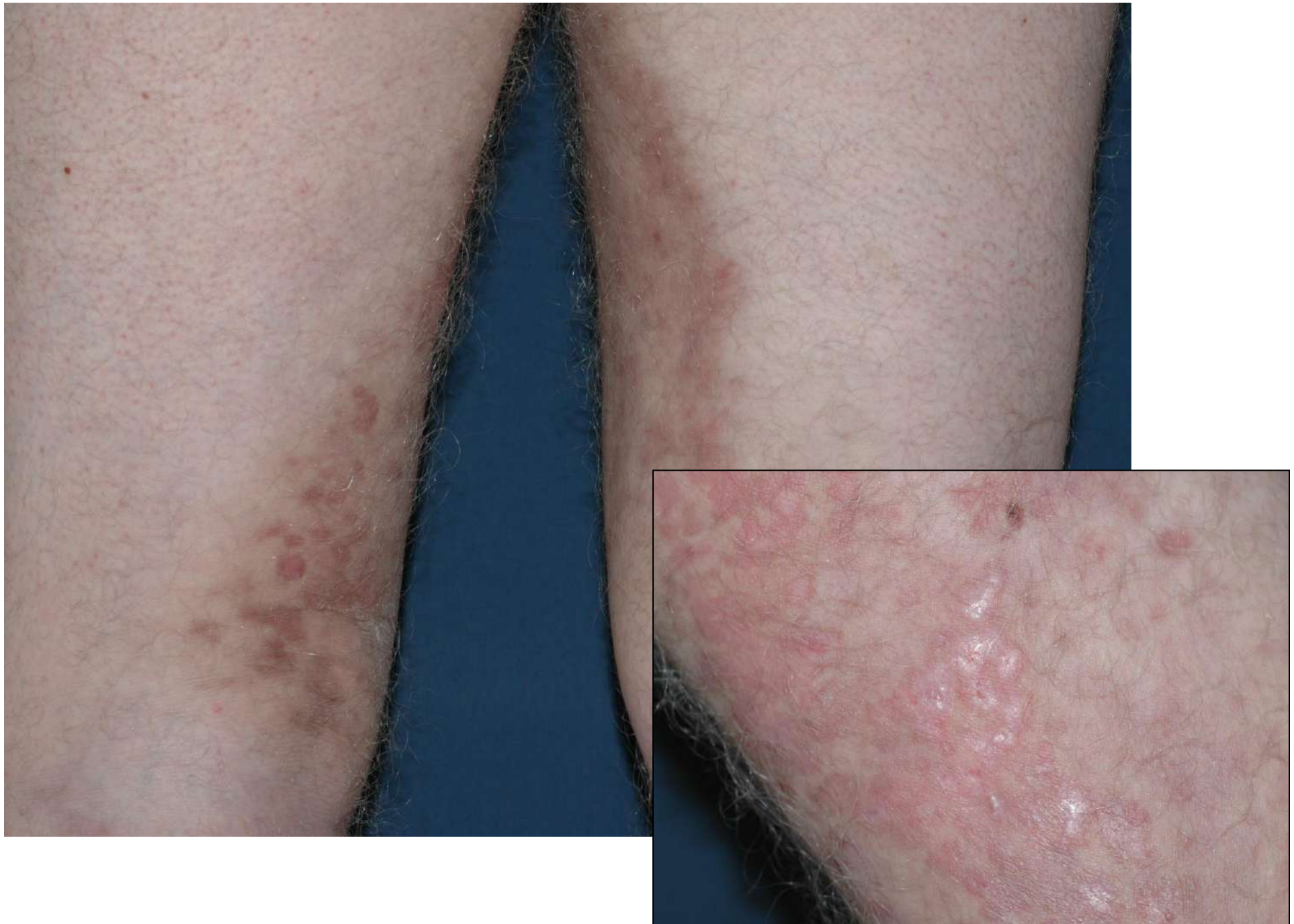
more complex genome and distinct copy number alterations



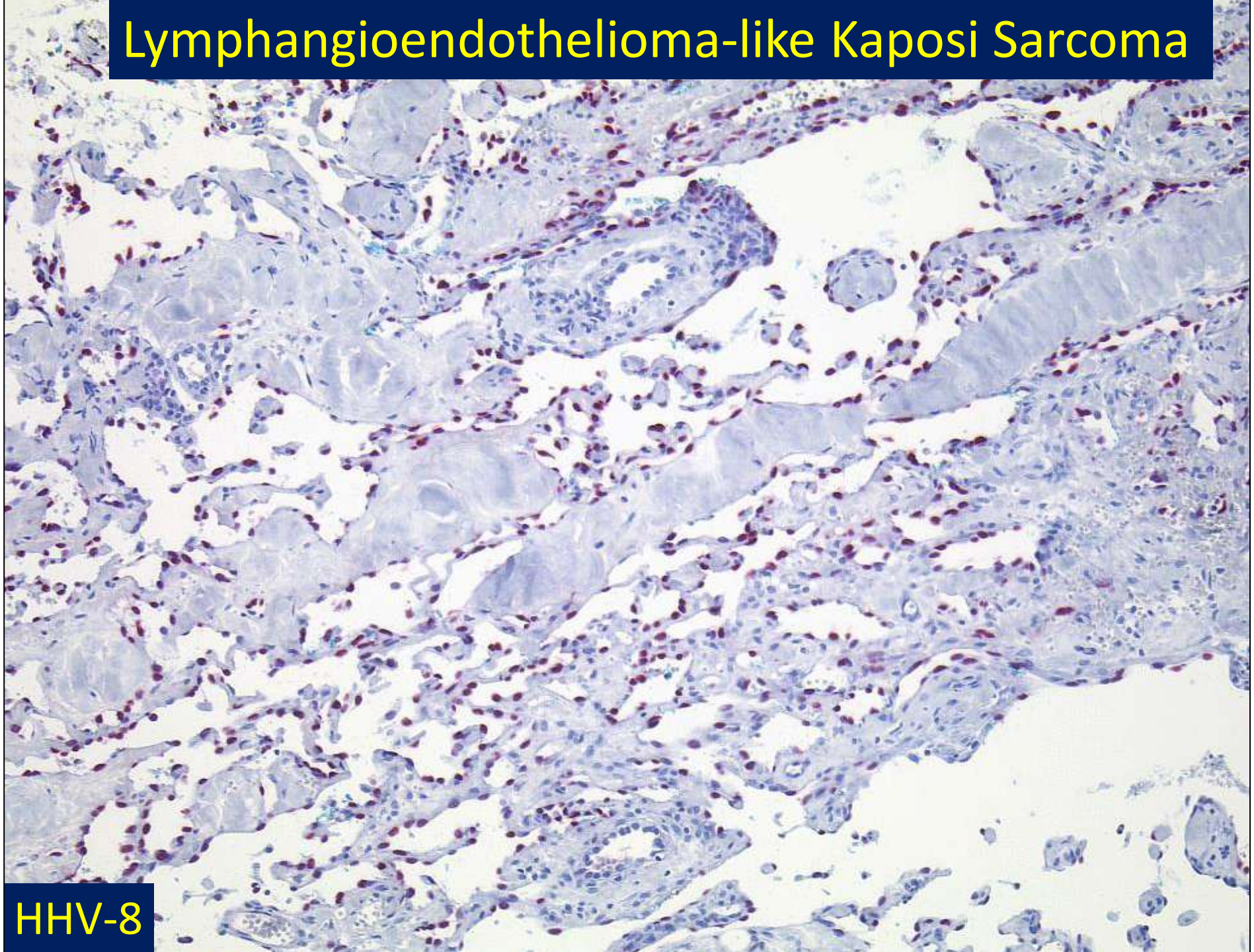
M, 30 years, right upper arm



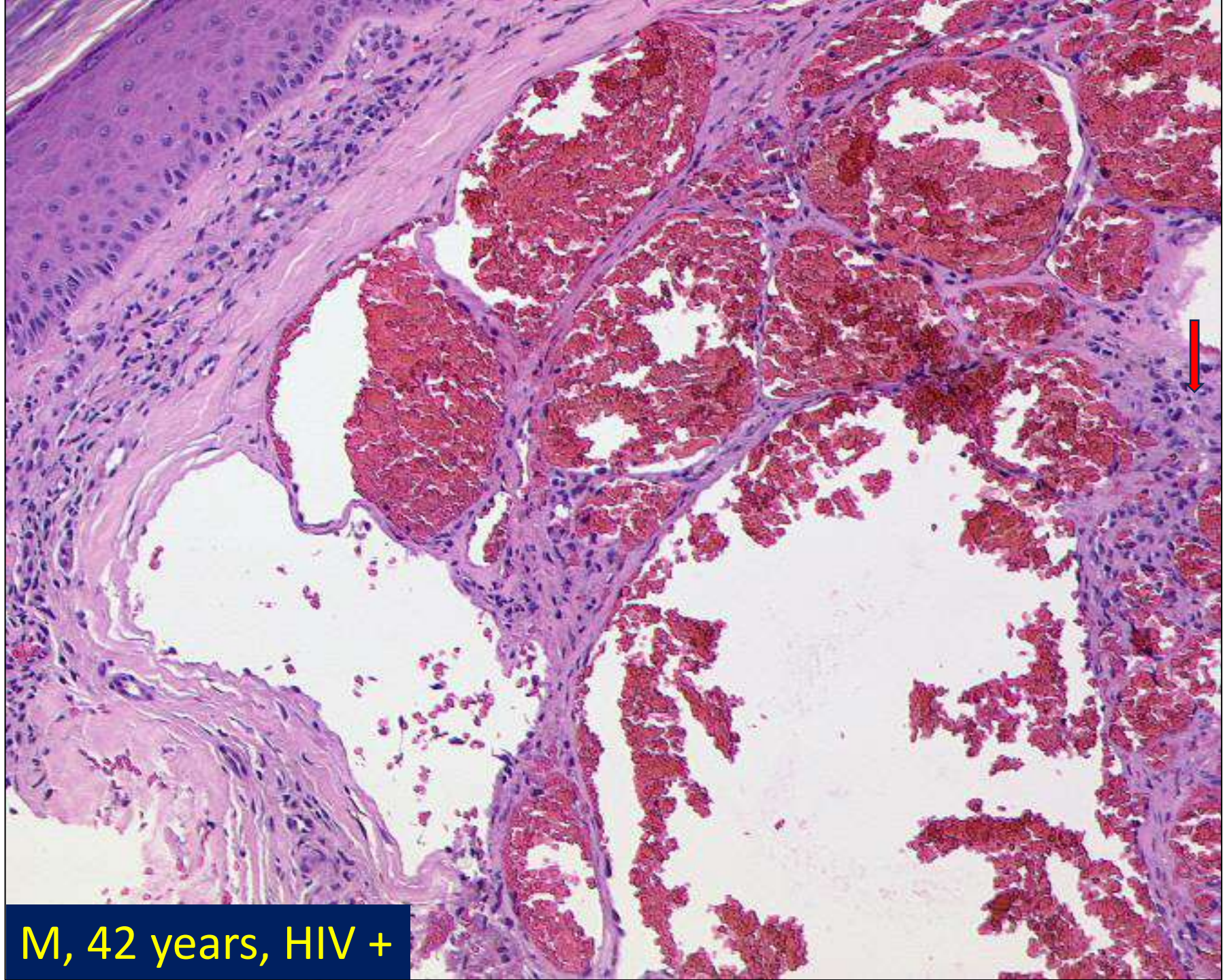
Podoplanin (D2 40) + (Diagnosis: Lymphangioendothelioma ?)

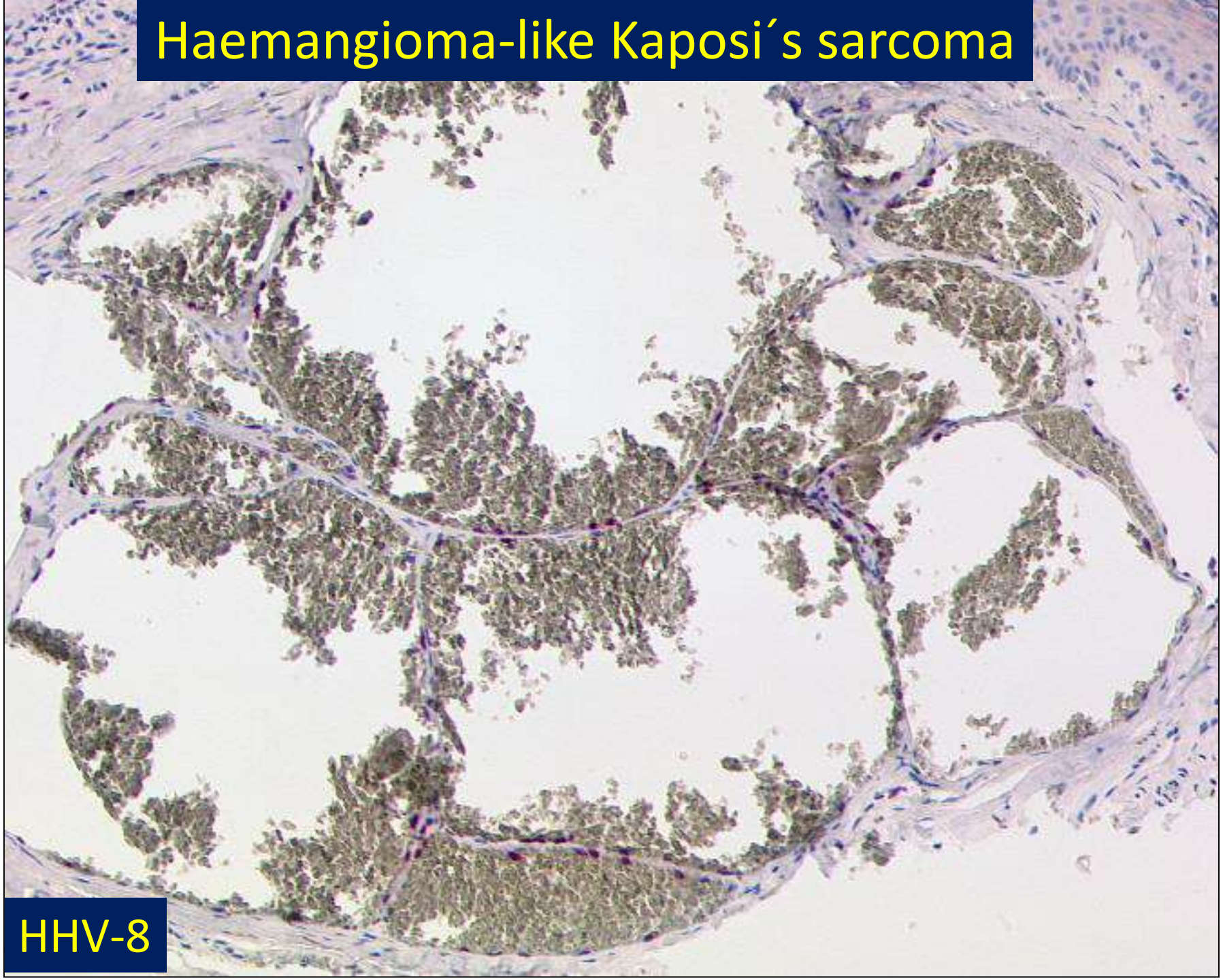


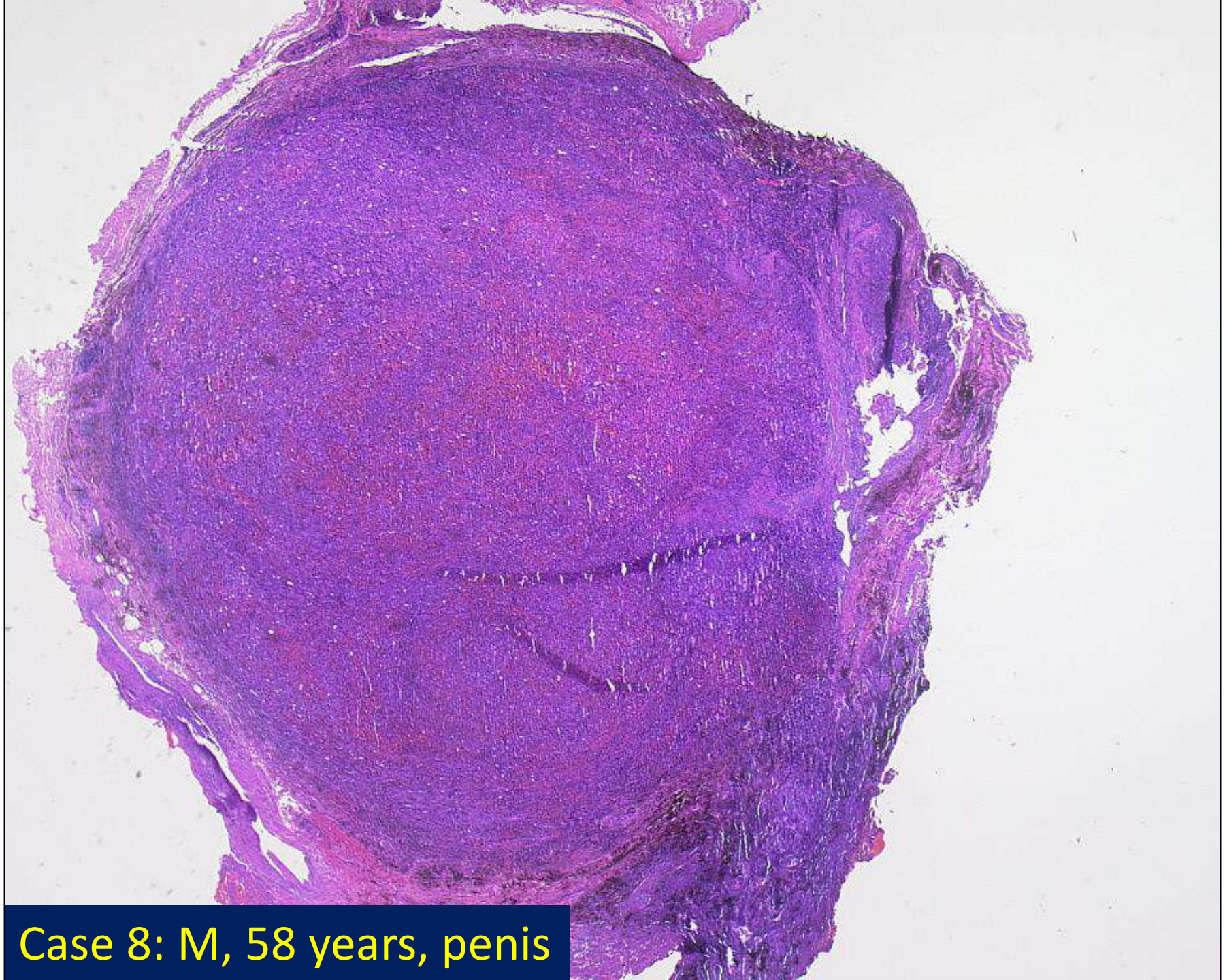
Lymphangioendothelioma-like Kaposi Sarcoma



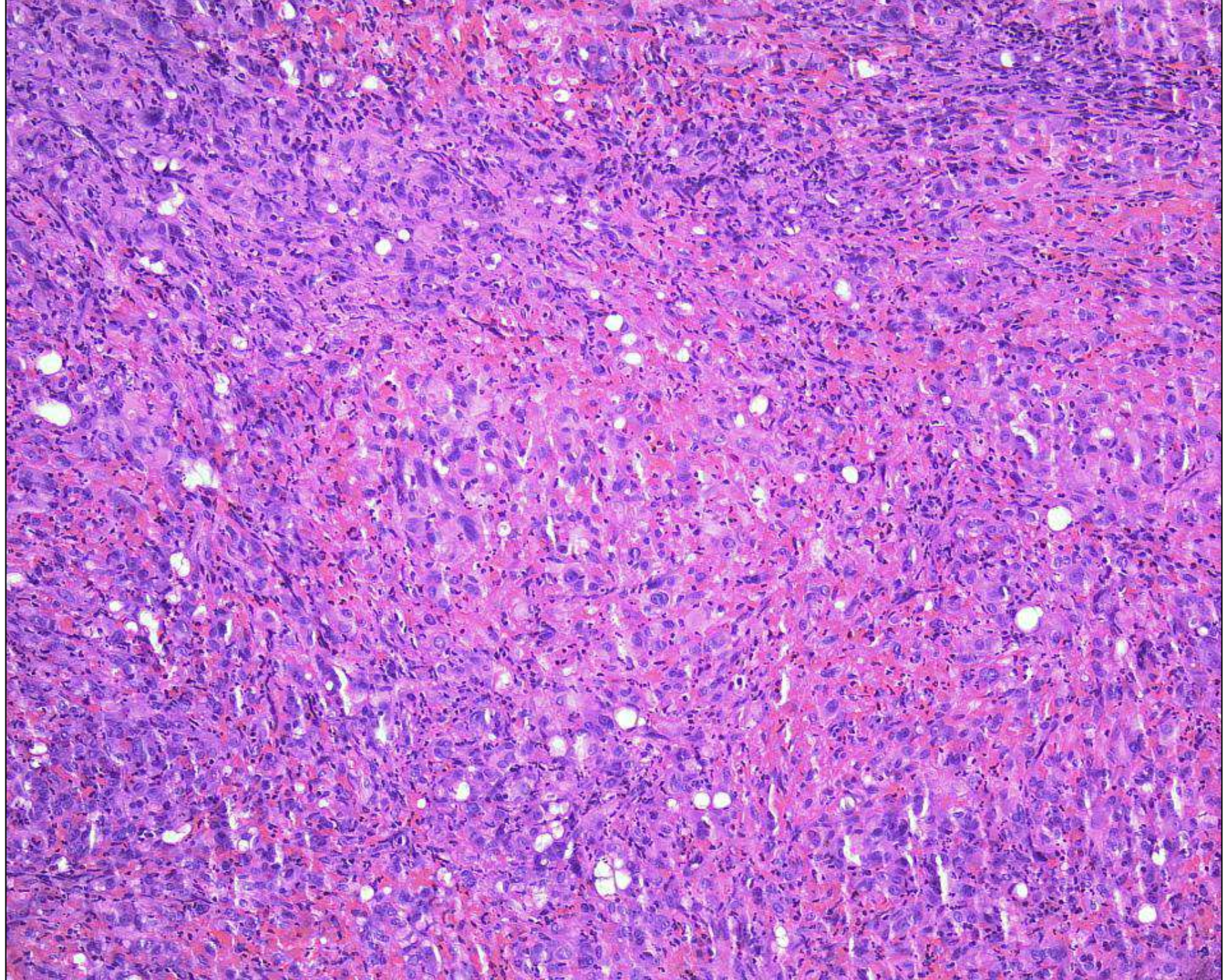
HHV-8

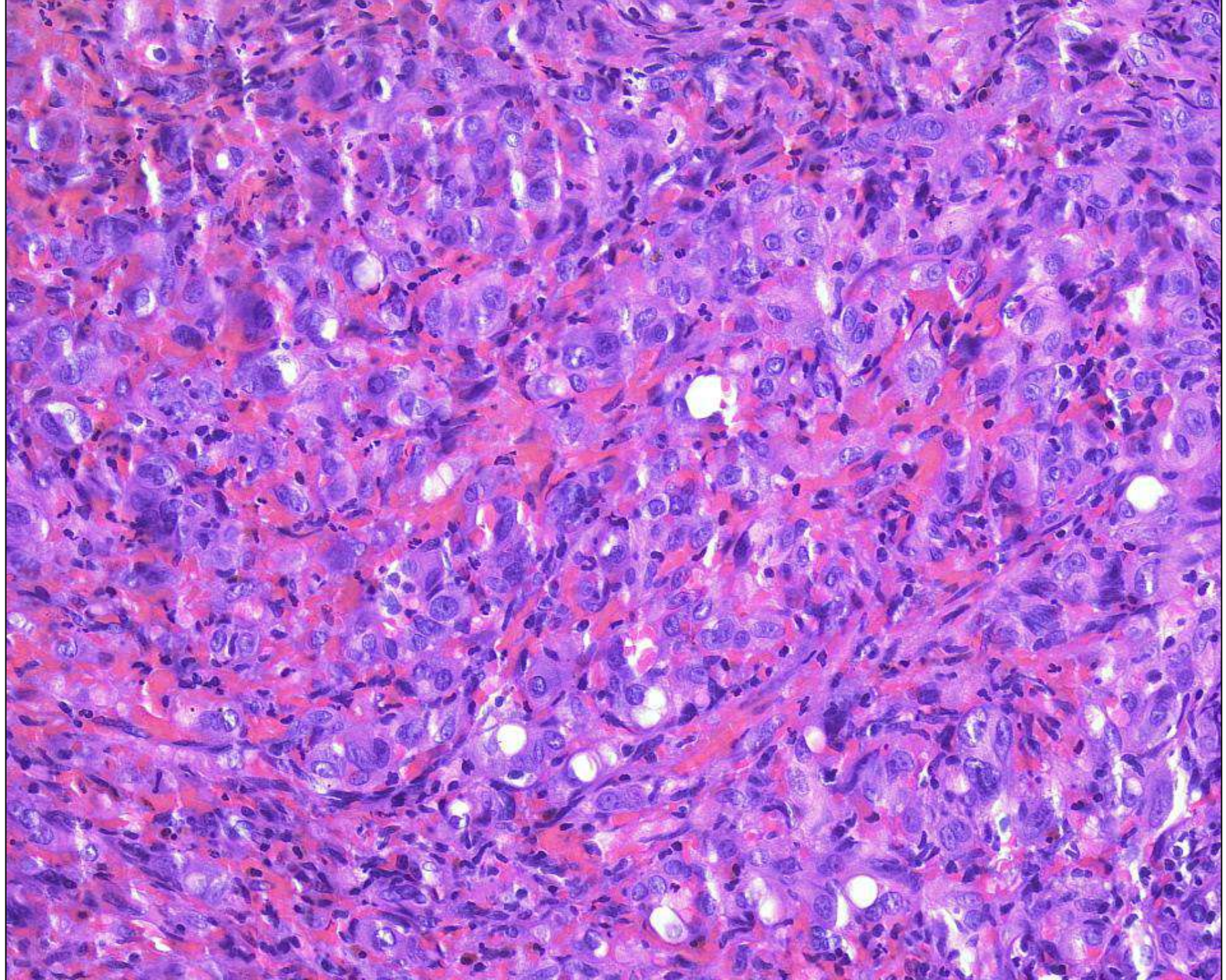

M, 42 years, HIV +


Haemangioma-like Kaposi´s sarcoma
HHV-8

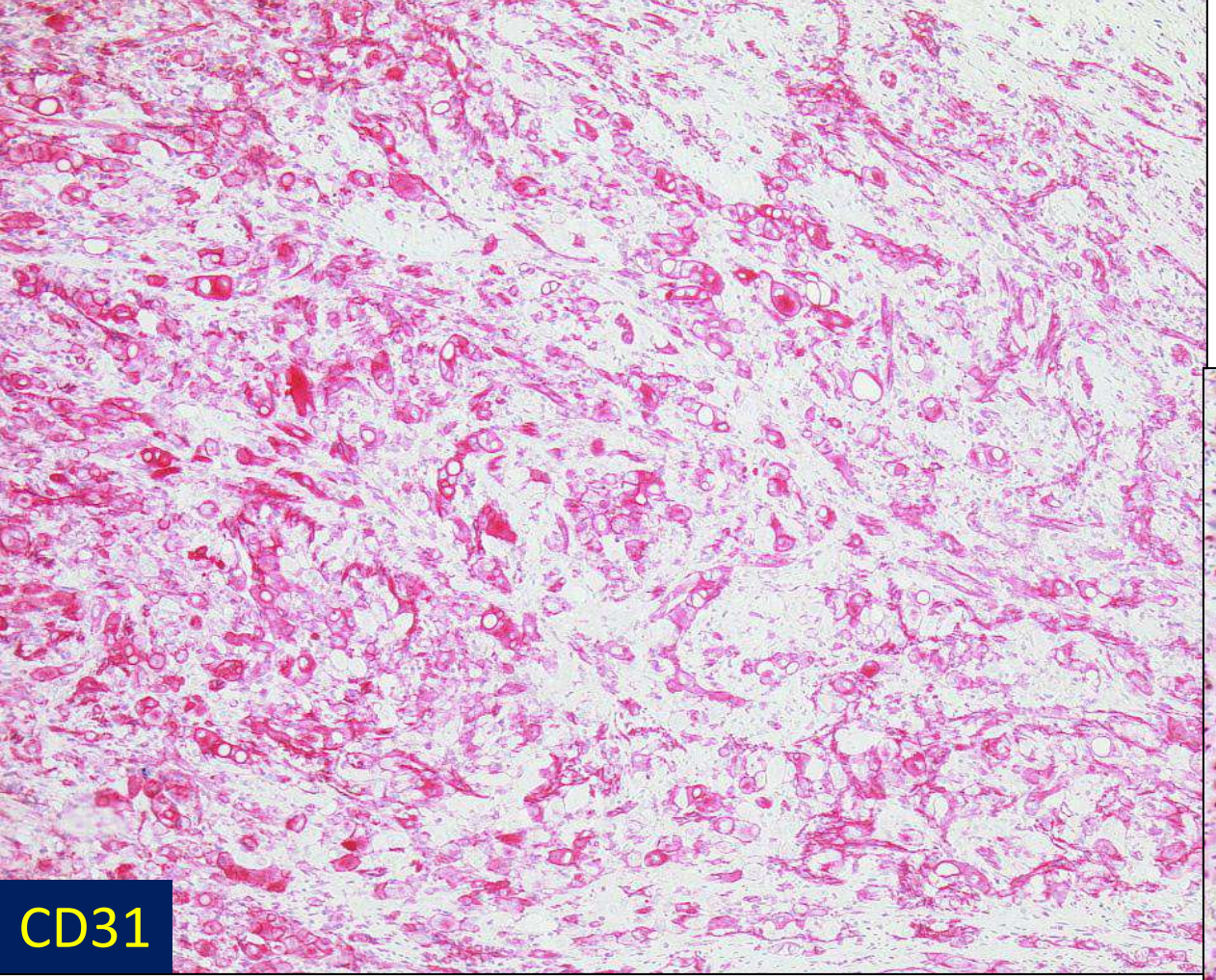


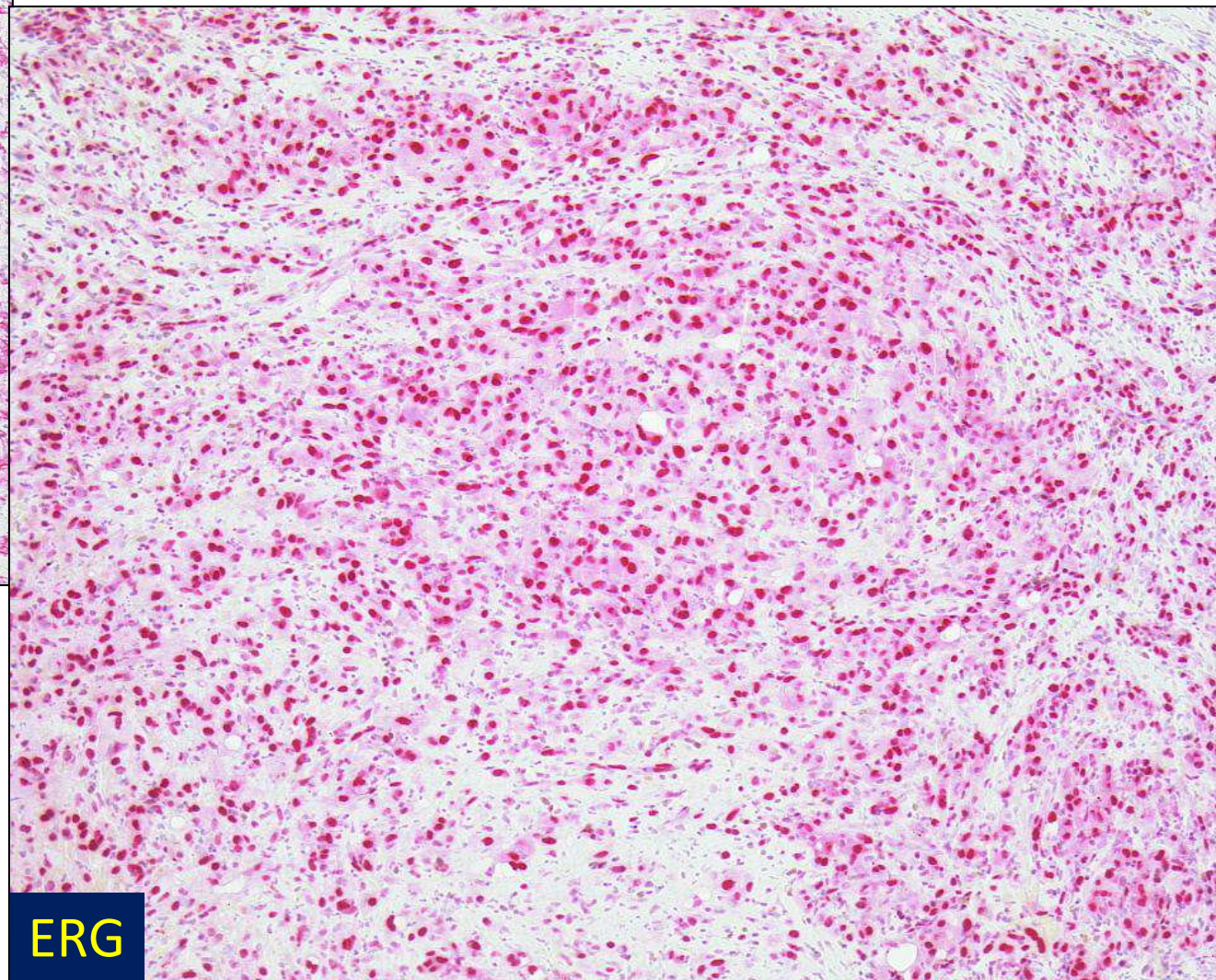
Case 8: M, 58 years, penis

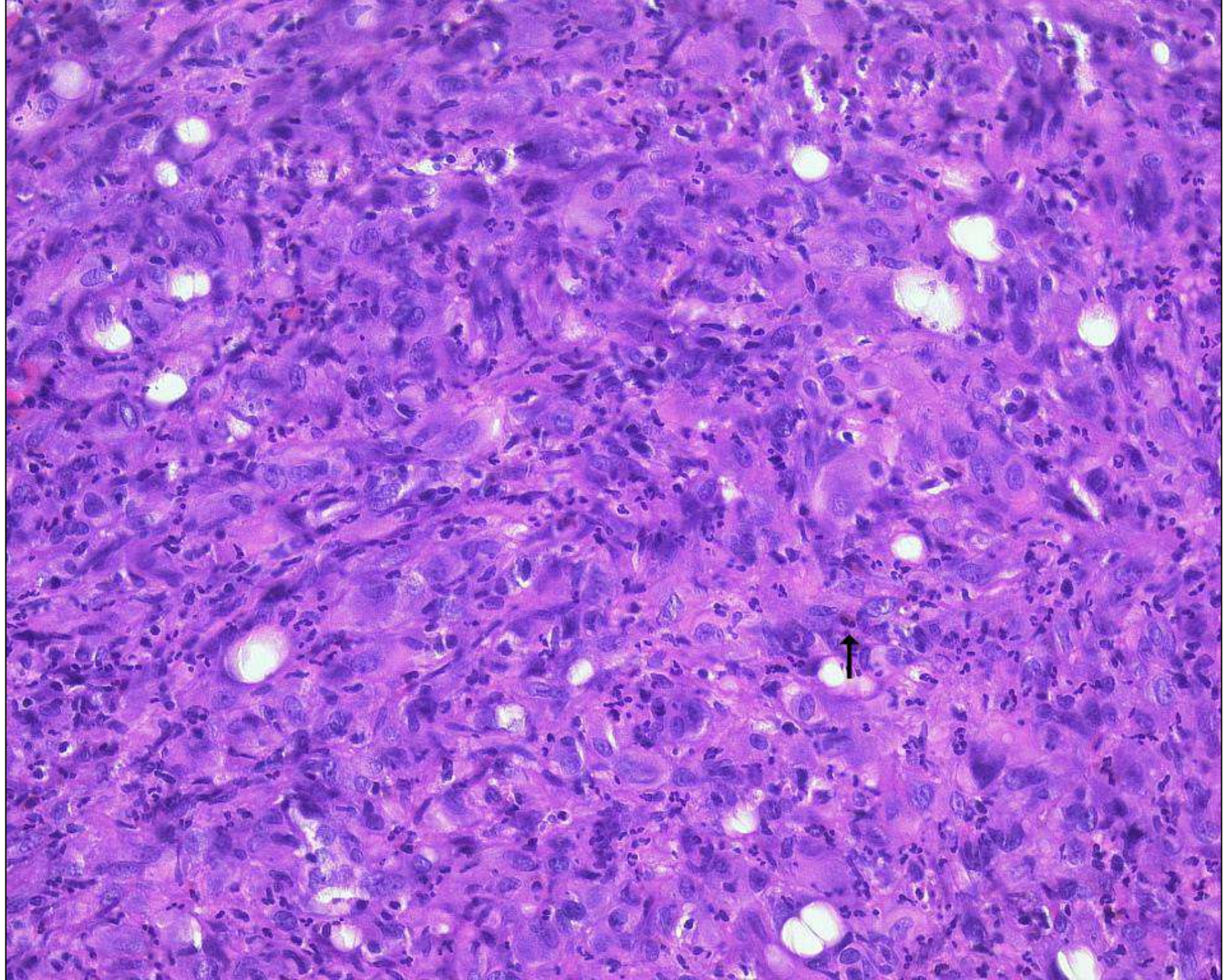


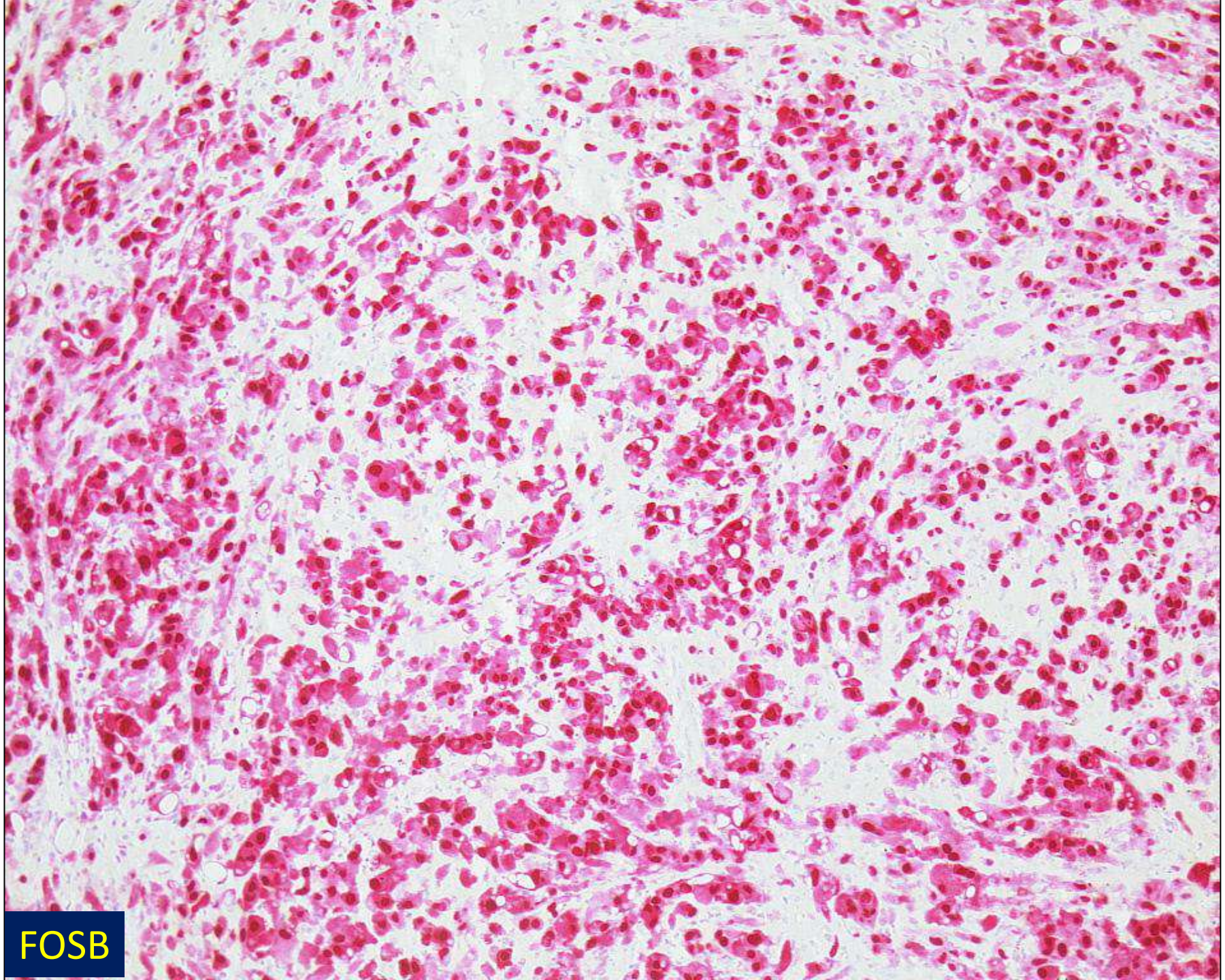


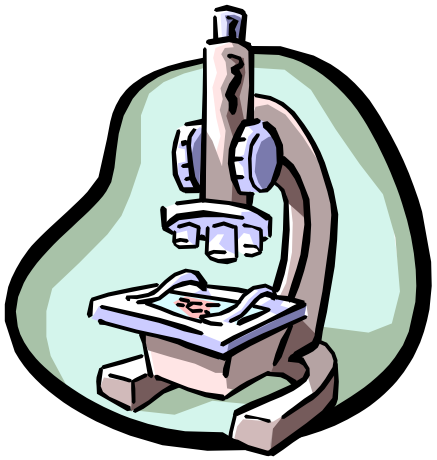
cellular, epithelioid vascular lesion…







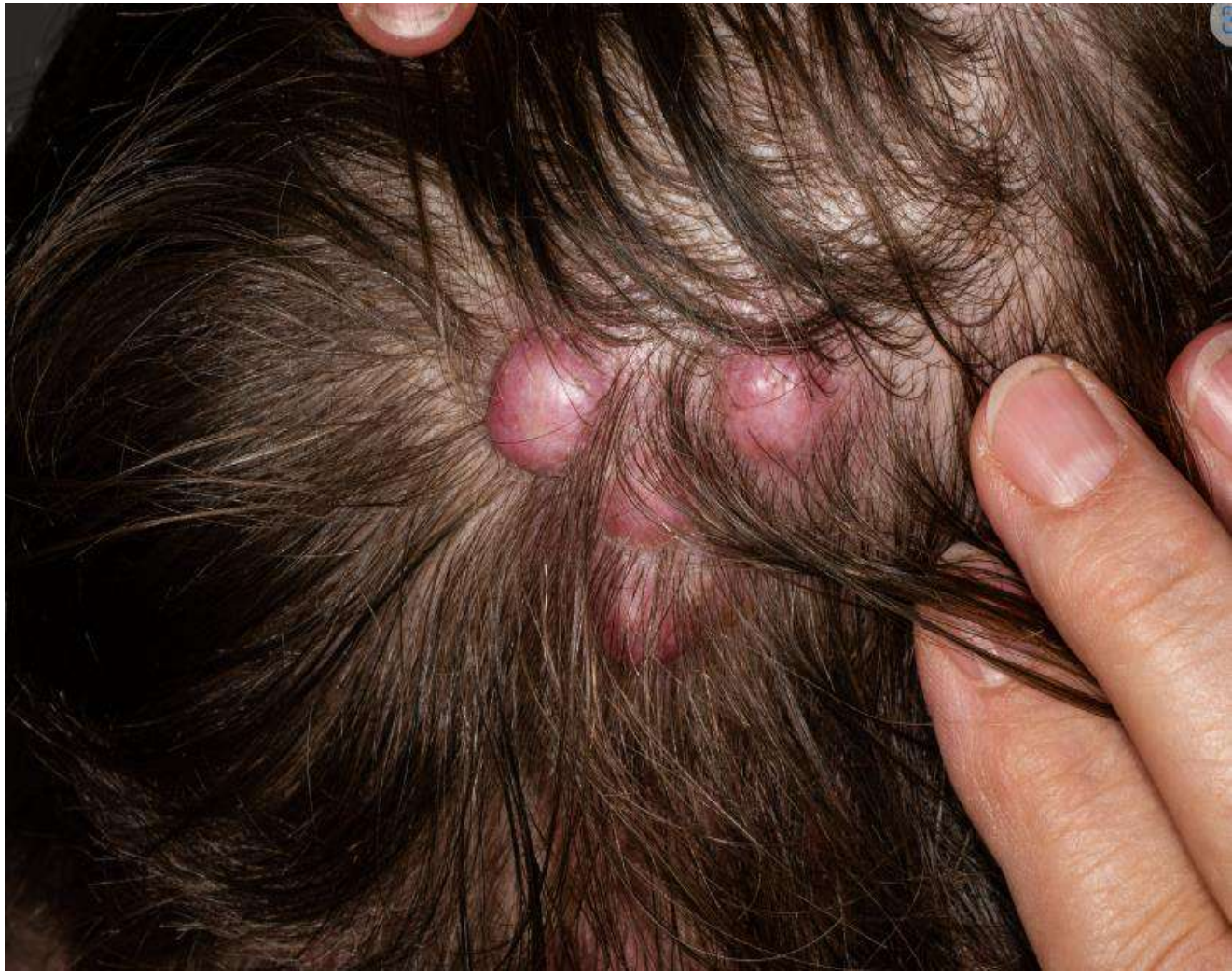

FOSB



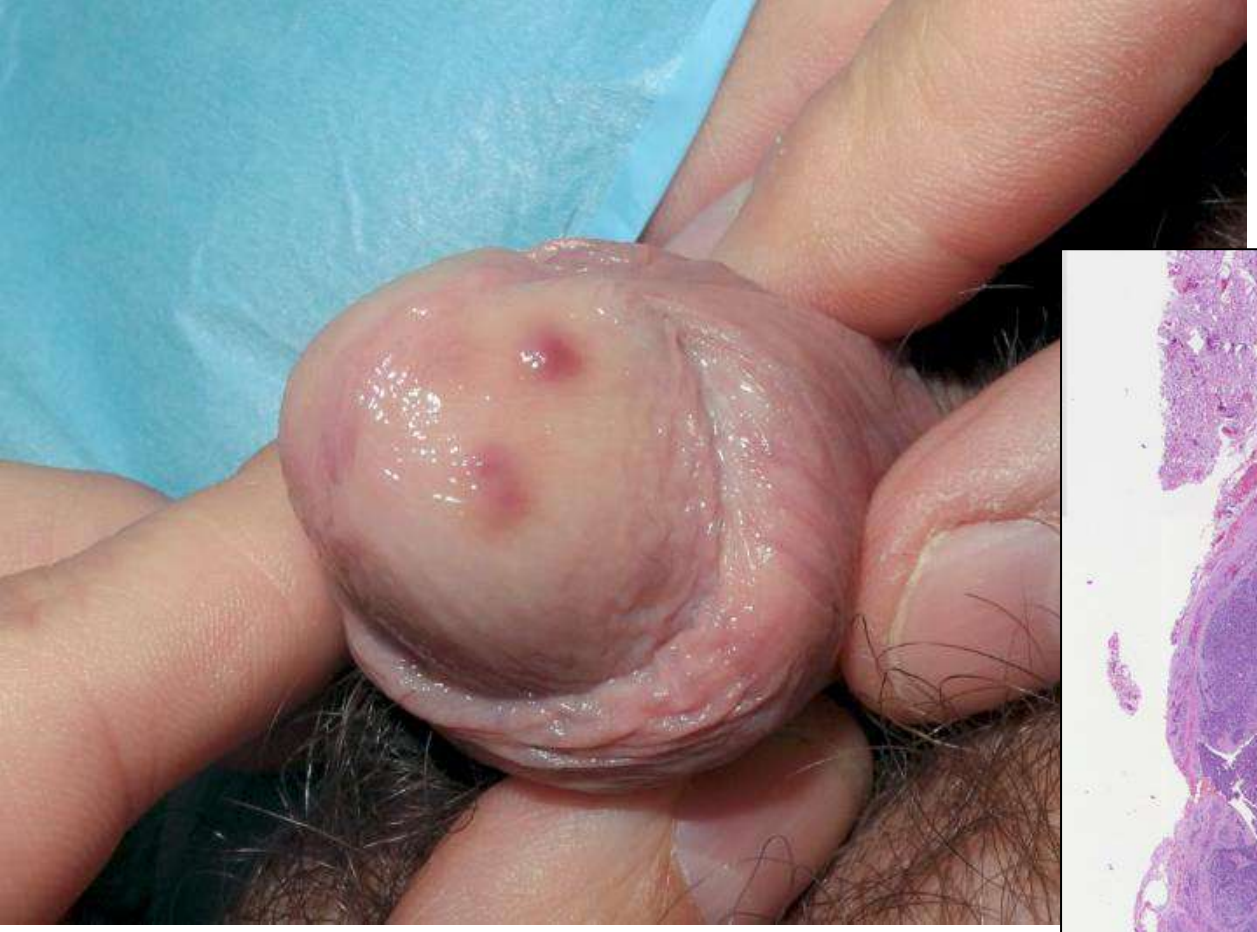
Diagnosis Case 8

cellular, atypical,
epithelioid Haemangioma

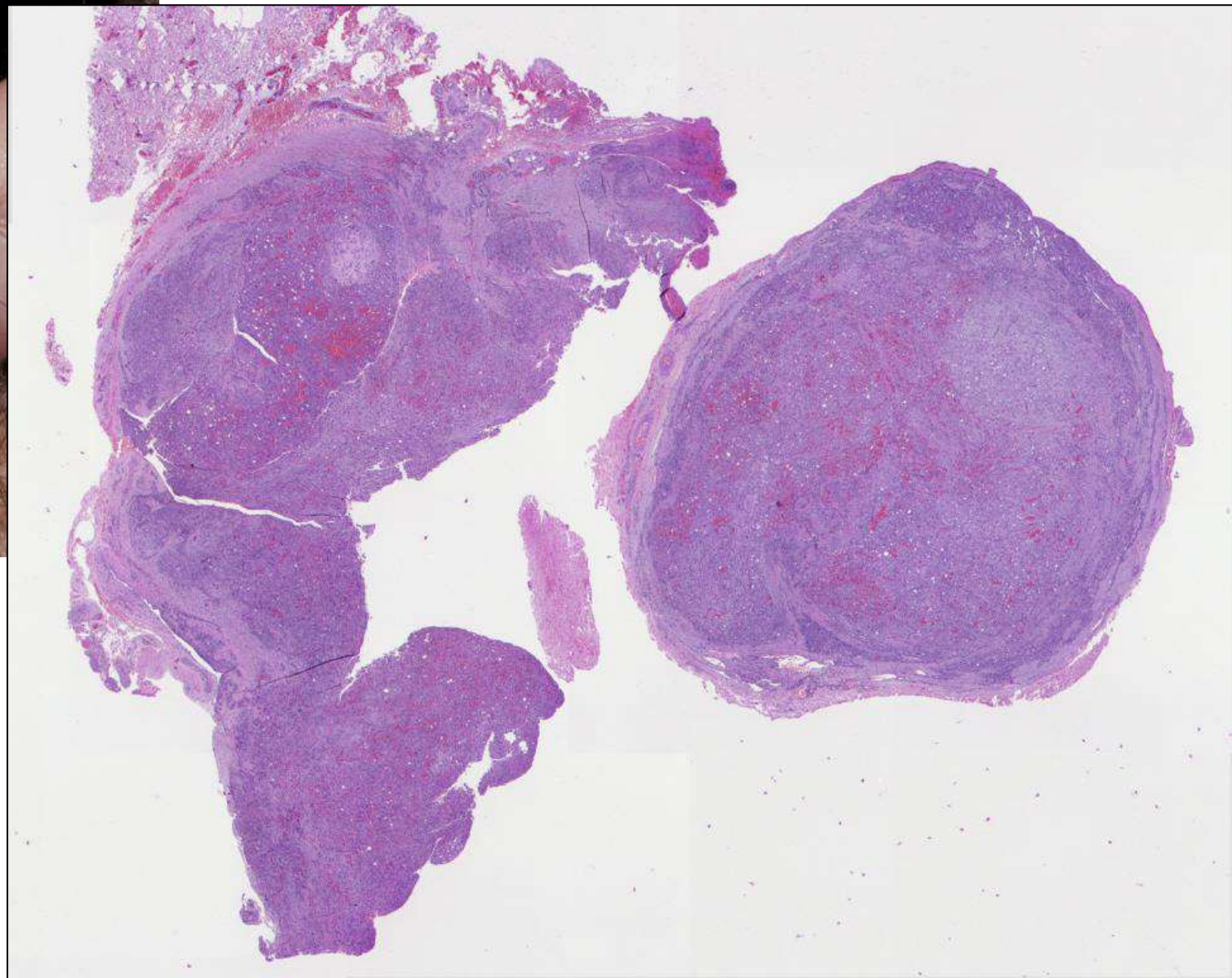
epithelioid Haemangioma

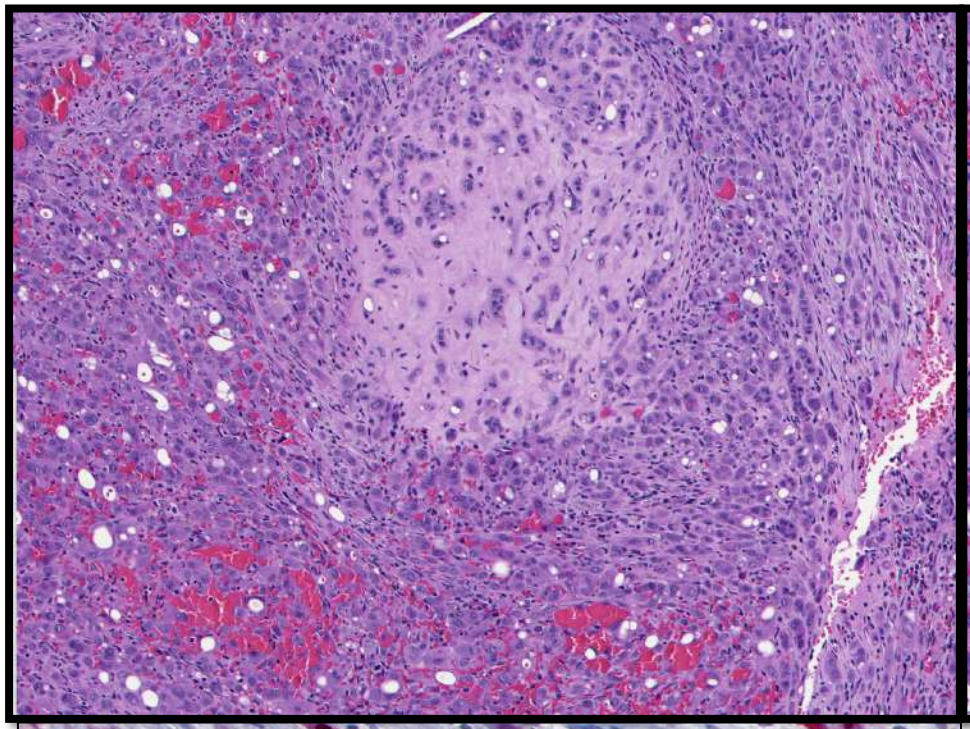


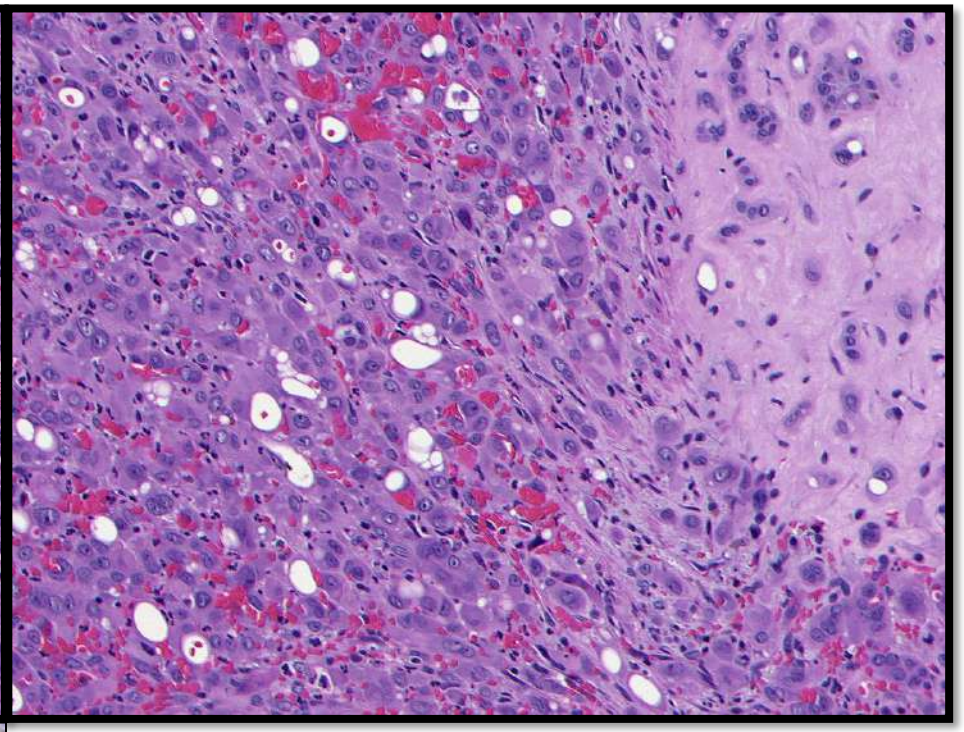
benign vascular neoplasm
head / neck > extremities > penis
10-20% multiple lesions
lobular growth
well-formed vessels
epithelioid endothelial cells
lymphocytes, eosinophils
sometimes *FOSB* gene fusions
intravascular, cellular, multiple eruptive variants

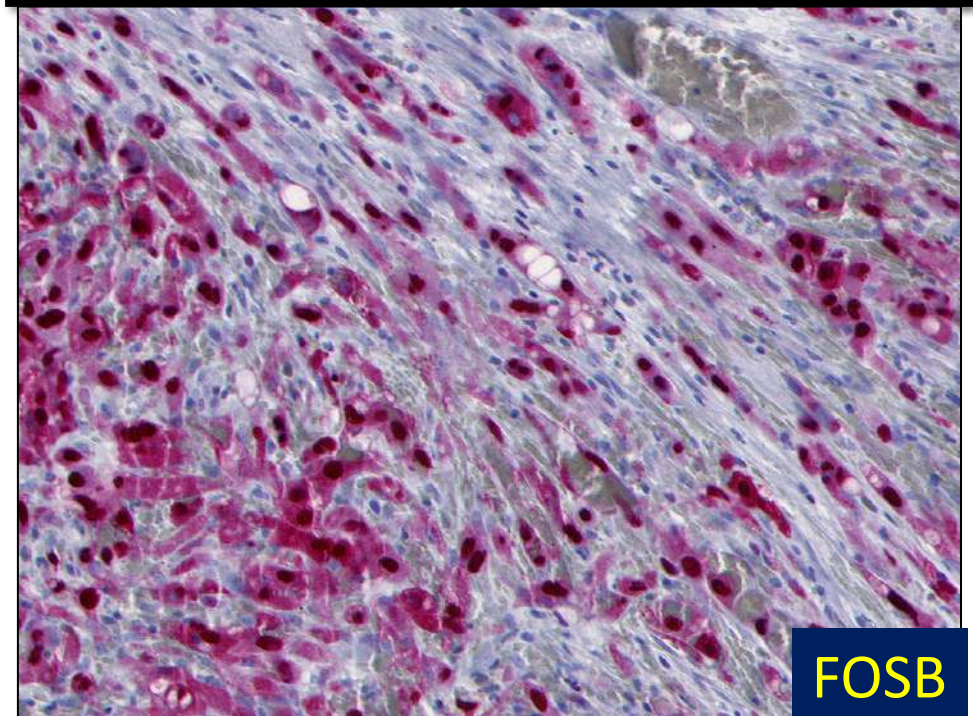


M, 45 years









cellular, atypical,
epithelioid Haemangioma
DD: epithelioid HE
epithelioid AS

FOS-B in vascular neoplasms

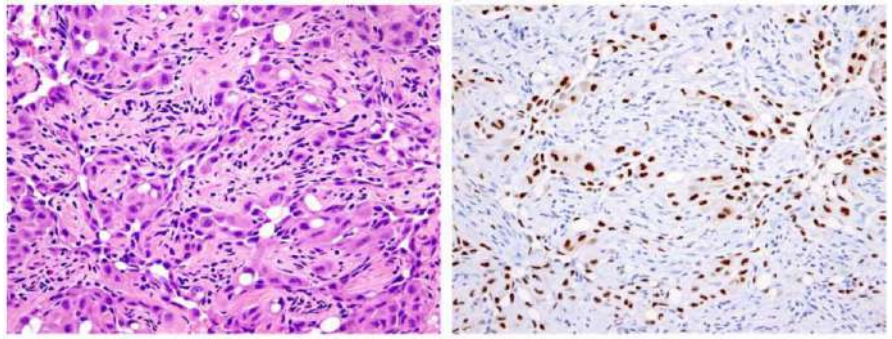
Epithelioid hemangioma (EH)

Molecular studies (FISH)

- *ZFP36-FOSB* fusions (20%)
- *FOS* gene rearrangements (1/3)

Immunohistochemistry

- FOS-B across all subtypes (>50%)

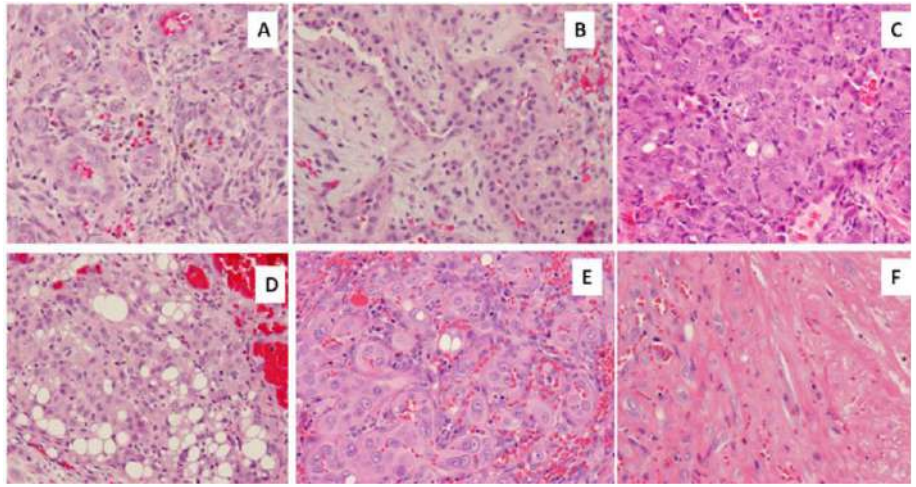


Hung et al, 2017

Genes Chromosomes Cancer. 2014 November ; 53(11): 951–959. doi:10.1002/gcc.22206.

ZFP36-FOSB Fusion Defines a Subset of Epithelioid Hemangioma with Atypical Features

Cristina R Antonescu[1], Hsiao-Wei Chen[1], Lei Zhang[1], Yun-Shao Sung[1], David Panicek[2], Narasimhan P Agaram[1], Brendan C Dickson[3], Thomas Krausz[4], and Christopher D Fletcher[5]



Multiple Eruptive Epithelioid Hemangiomas

A Subset of Cutaneous Cellular Epithelioid Hemangioma With Expression of FOS-B

Mar Llamas-Velasco, MD, Werner Kempf, MD,† Carlo Cota, MD,‡ Maria Teresa Fernández-Figueras, MD,§ Joyce Lee, MD,‖ Gerardo Ferrara, MD,¶ Christian Sander, MD,# Philip E. Shapiro, MD,** Luis Requena, MD,†† and Heinz Kutzner, MD‡‡*

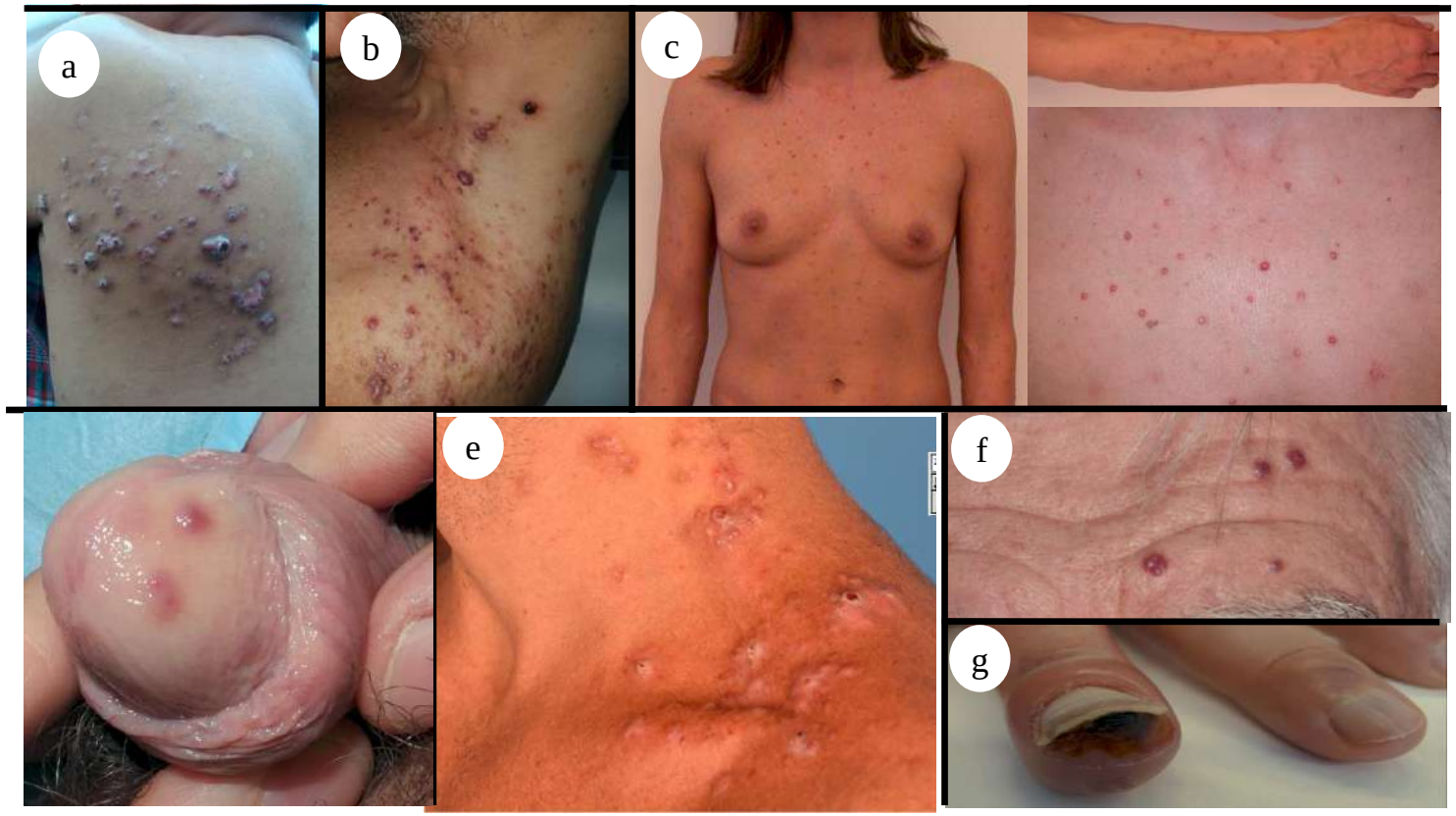
TABLE 1. Our Patients' Lesions' Main Characteristics

No.	Age (y)/ Sex	Location	Clinical	Patt	Coll	NP	Ki67 (%)	IHQ/FISH Myc	IHQ/FISH CAMTA-1	IHQ FOS-B	Treatment
1	85/M	Left-side forehead	Erythematous-violaceous papules. Asymptomatic	U	Y	P	<5	Neg	Neg	Pos	EC, Qx
2	50/M	Left scapular area	Painless nodules scattered with profuse bleeding upon trauma	M	Y	P	<5	Neg	Neg	Pos	EC, Qx, cryotherapy
3	UK/M	Left hand and forearm	Purplish nodules. Le lesion on the fourth digit of the left hand progressively became enlarged and ulcerated	M	N	P	5	Neg	Neg	Pos	EC, imiquimod once a day for 3 wk
4	38/F	Arms, legs, and trunk	Slightly erythematous and skin-colored dome-shaped papules and plaques ranging from 0.4 to 1.2 cm, with symmetrical distribution	M	N	A	<5	Neg	Neg	Pos	Acitretin 0.6 mg/kg for 2 mo
5	73/M	Face	Angiomatous papules in an agminated fashion on the centrofacial region	M	Y	P	5	Neg	Neg	Pos	Qx
5	73/M	Idem	Idem	U	N	P	>15	Neg	Neg	Pos	Qx
6	49/M	Neck	Purple papule slightly pruritic	M	Y	P	20	Neg	Neg	Pos	Qx
6	49/M	Left lateral forehead	Purple papule asymptomatic	U	Y	P		Neg	Neg	Pos	Qx
7	45/M	Penis	Slightly painful purplish papules. No erectile dysfunction	U	N	P	<5	Neg	Neg	Pos	Qx
7	45/M	Idem	Idem	M	N	P	<5	Neg	Neg	Pos	Qx
8	34/M	Left shoulder	Persistent erythematous papules	M	N	P	5-10	Neg	Neg	Pos	Laser, EC
9	38/M	Left Shoulder, neck, and arm	Persistent. The patient developed anemia recently	M	N	A	5	Neg	Neg	Pos	Qx
10	45/F	Face, both shoulders, axilla, and genital area	Persistent	U	Y	P	5	Neg	Neg	Pos	Qx
11	27/M	Penis	Persistent lesions	U	N	P	<5	Neg	Neg	Pos	Qx
12	54/M	Right arm	Asymptomatic nodules	U	N	P	<1	Neg	Neg	Pos	Qx
13	67/M	Trunk and extremities	Asymptomatic nodules	U	N	P	<5	Neg	Neg	Pos	Qx

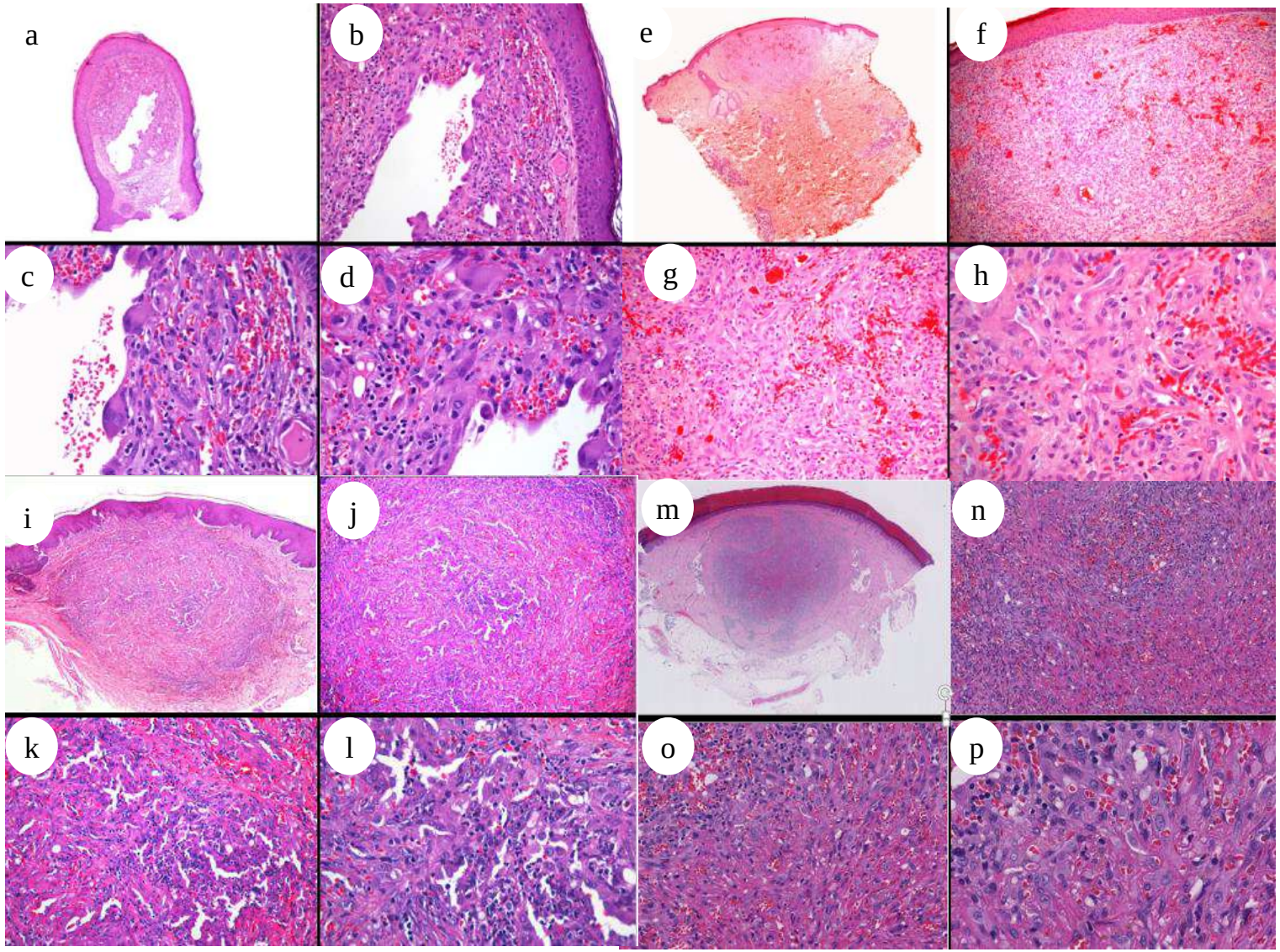
A indicates absent; Coll, collarette; EC, electrocauterization; F, female; M, multilobular; M, male; N, no; Neg, negative; NP, nuclear pleomorphism; P, present; Patt, pattern; Pos, positive; Qx, surgery; U, unilobular; Y, yes.

Am J Surg Pathol. 2019 Jan;43(1):26-34. doi: 10.1097/PAS.0000000000001003.

13 patients, 34-85 years, 3-100 lesions
head/neck (5), trunk (2), extremitites (1), generalised (1)
strong expression of FOSB



(by courtesy of Dr.M. Llamas Velasco, Madrid)


a
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p

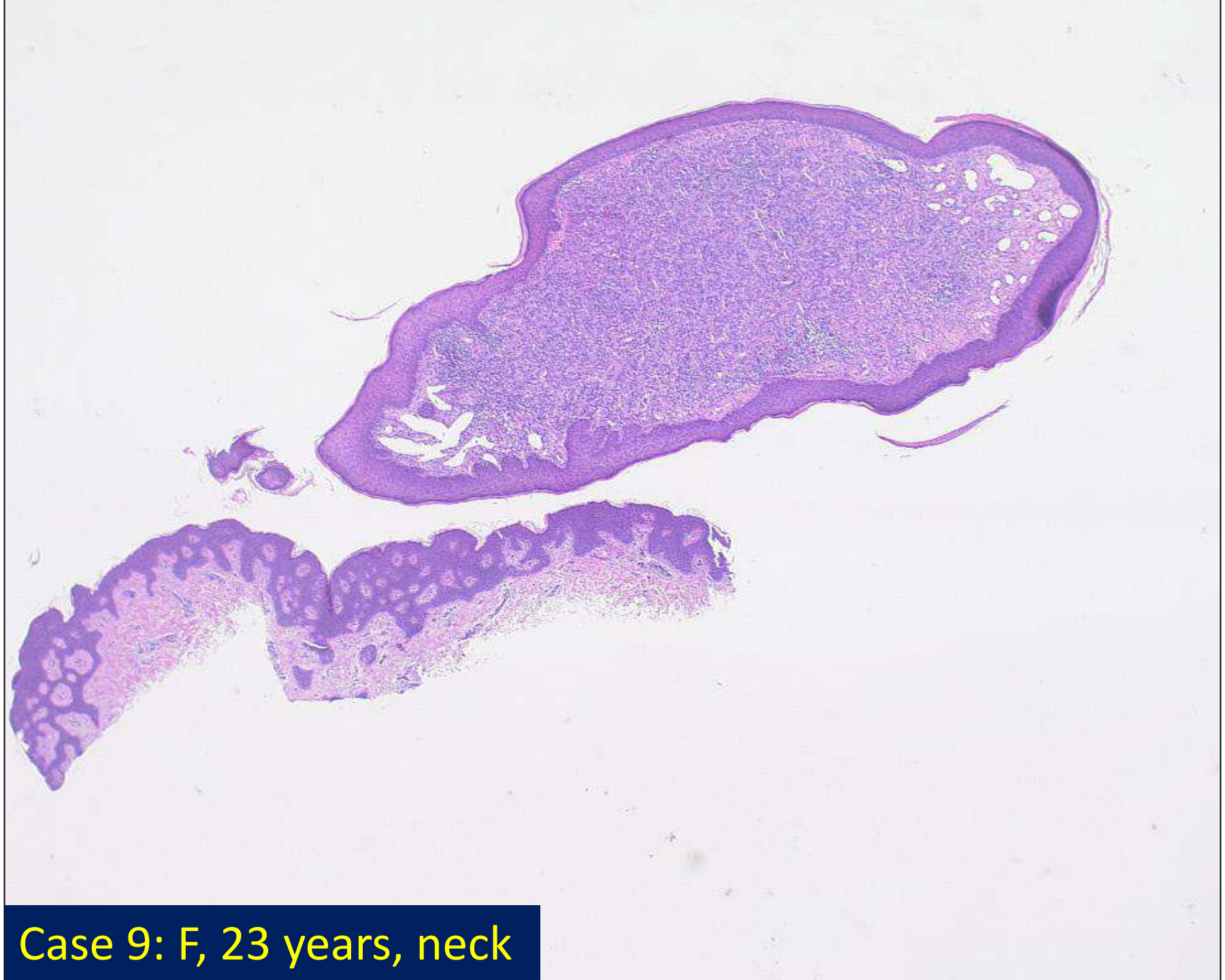
Novel *GATA6-FOXO1* fusions in a subset of epithelioid hemangioma

CR Antonescu et al. Mod Pathol 2021; 34: 934-941

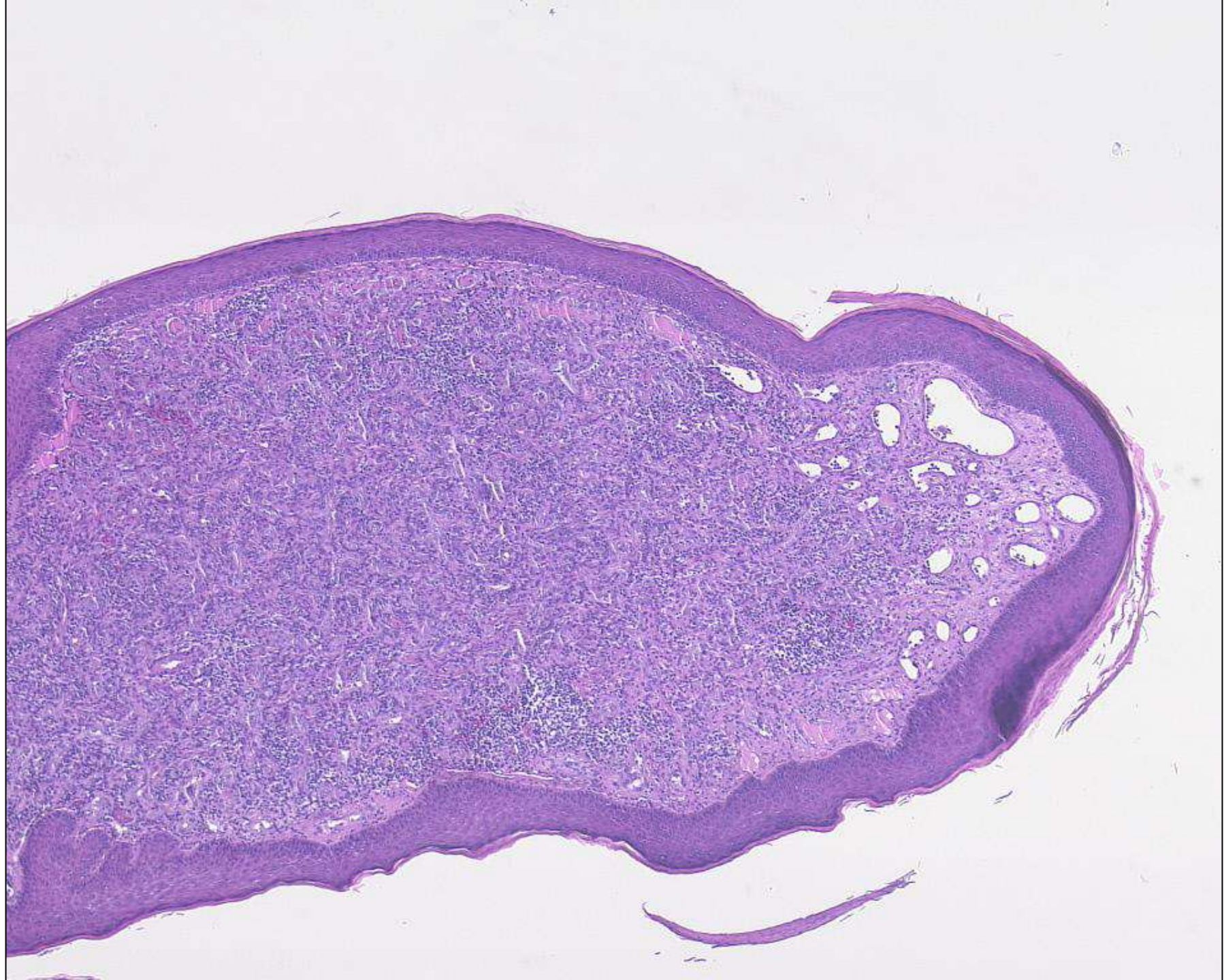
5 cases, 3 F, 2 M
head/neck (3), back 81), leg (1)
2 x skin, 1 intravascular
vasoformative and solid components
mild to moderate cytological atypia
FOS -, FOSB -
GATA::FOXO1 fusions

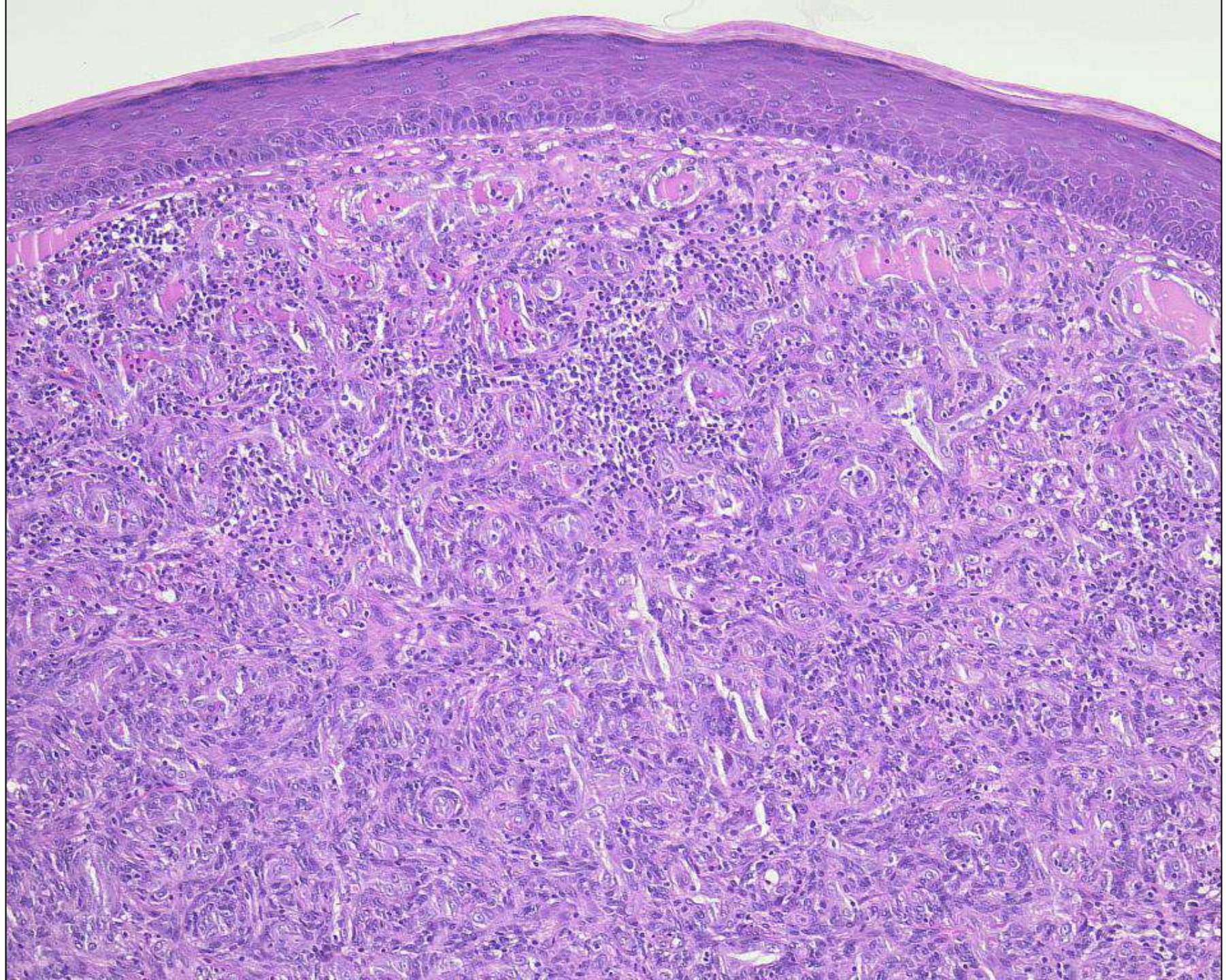
cutaneous epithelioid Haemangioma

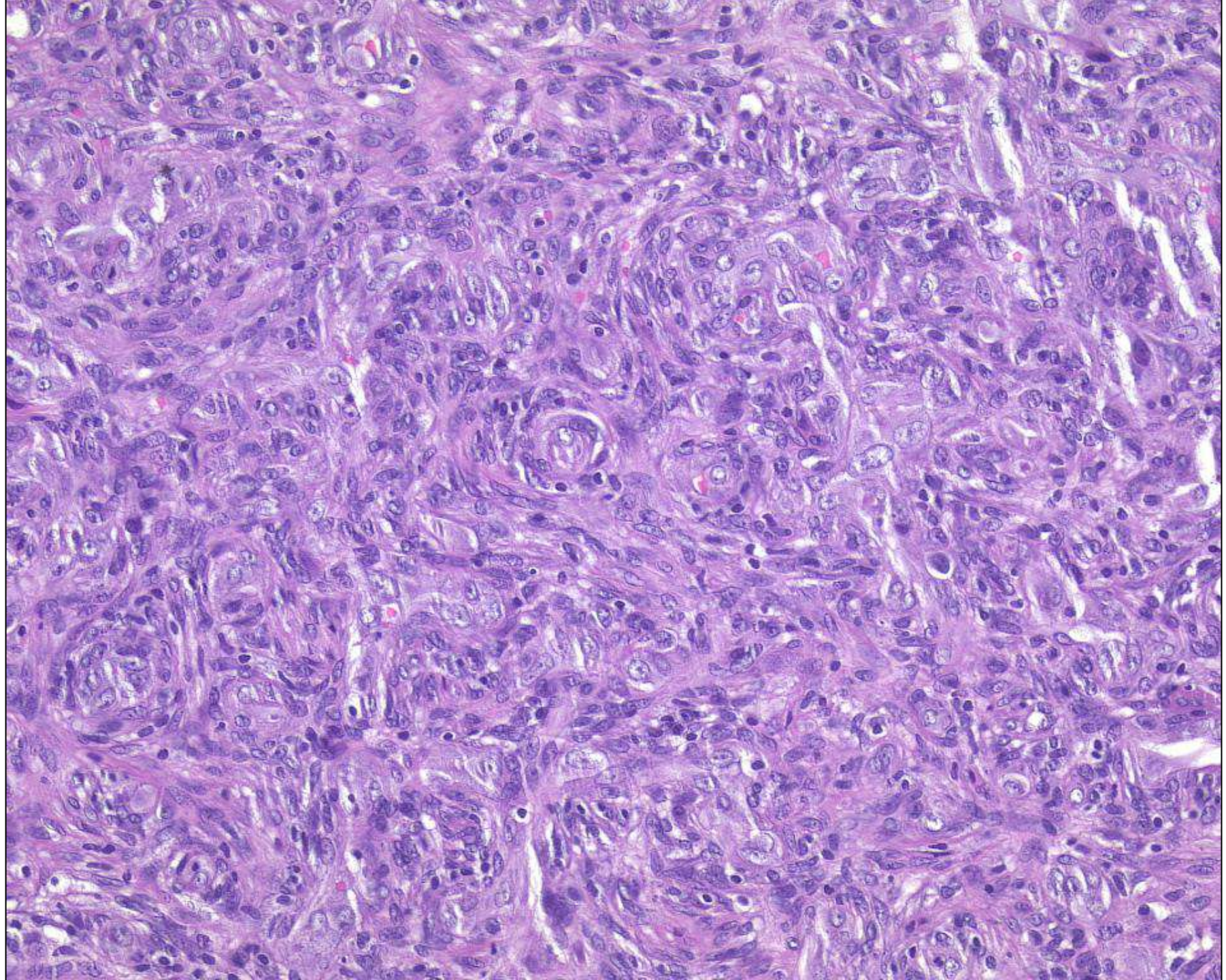
- no / rarely *FOSB* rearrangement
- immunohistochemistry: FOSB +
- translocations-independent phenomenon

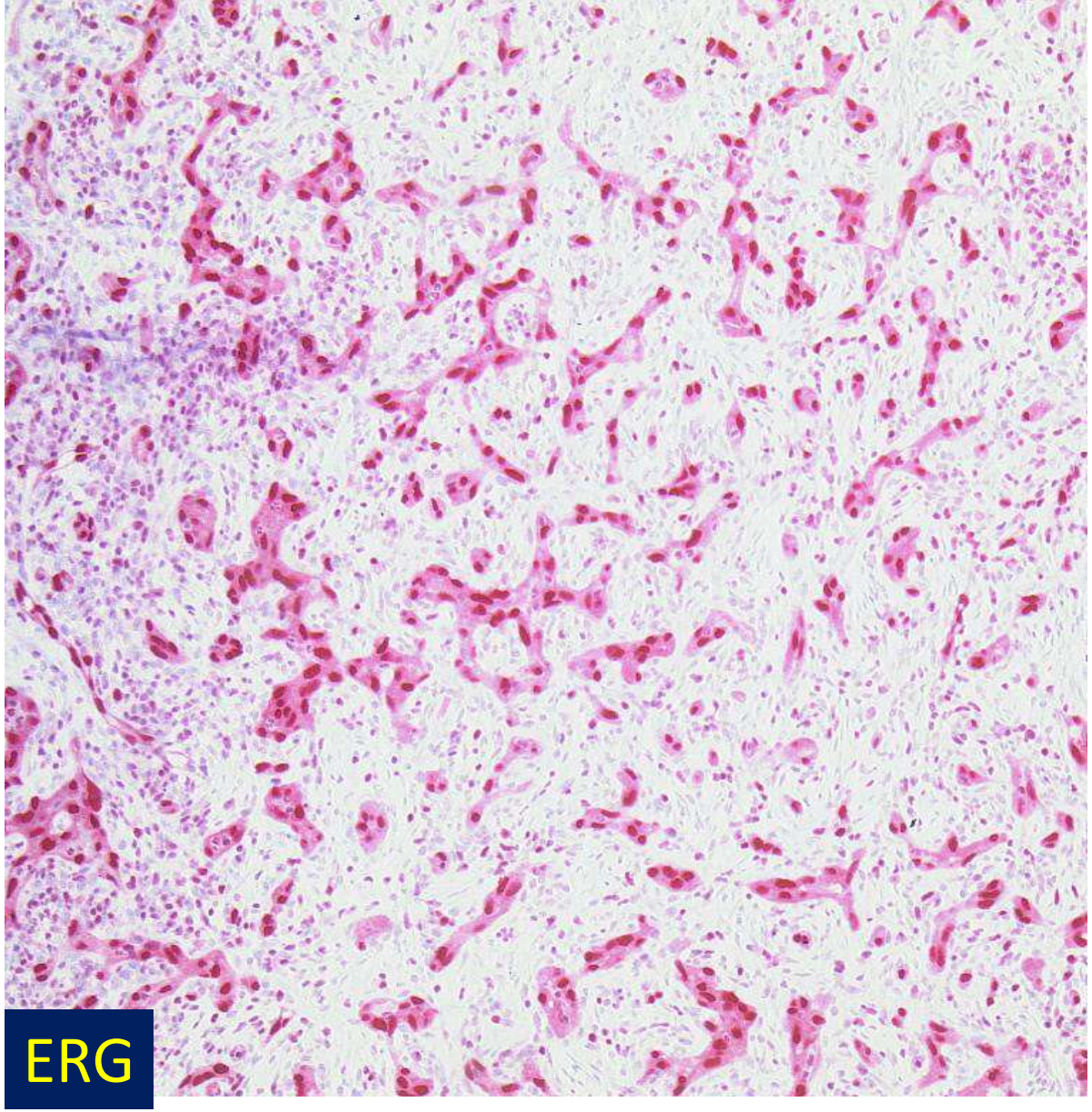


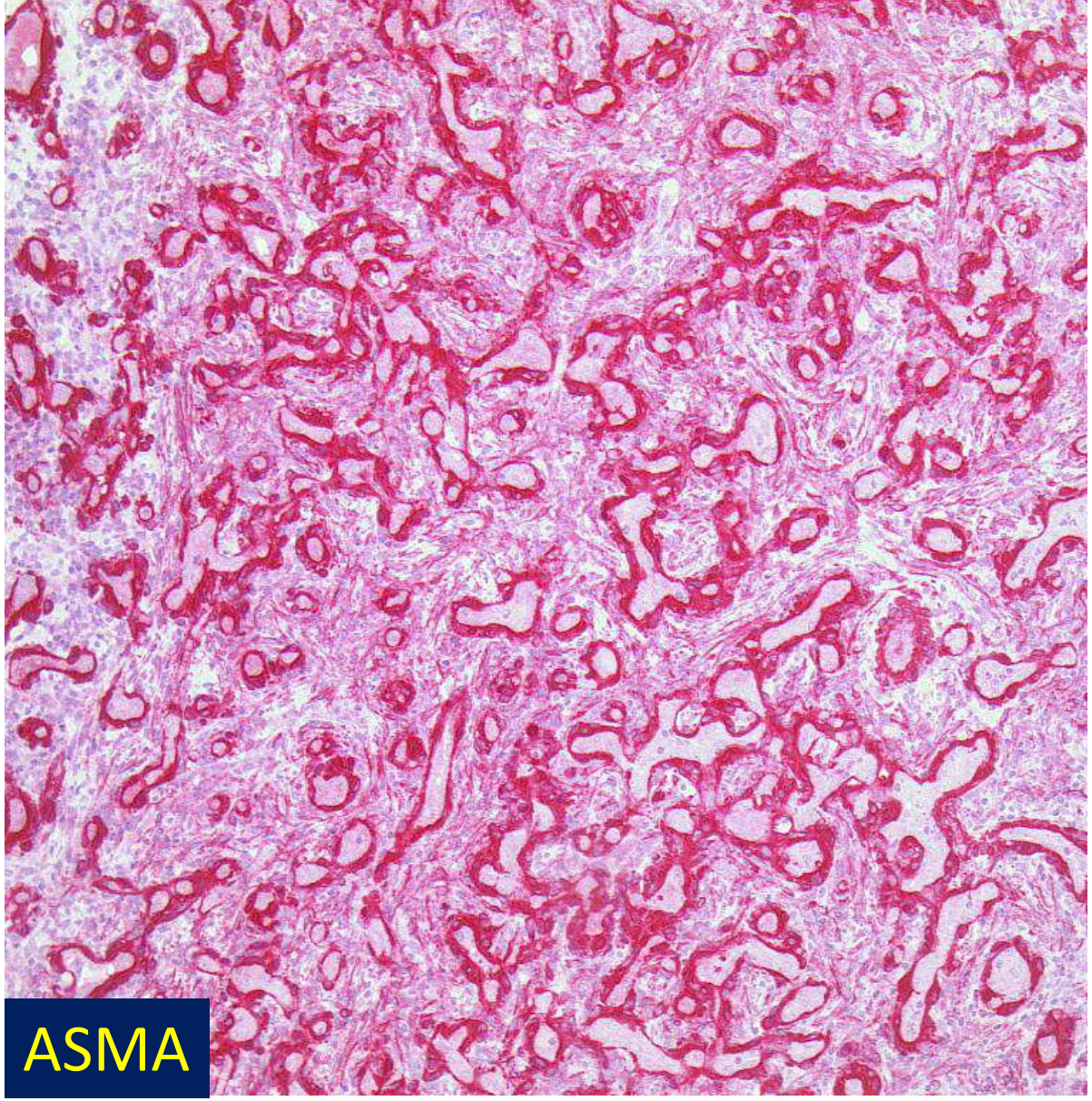
Case 9: F, 23 years, neck



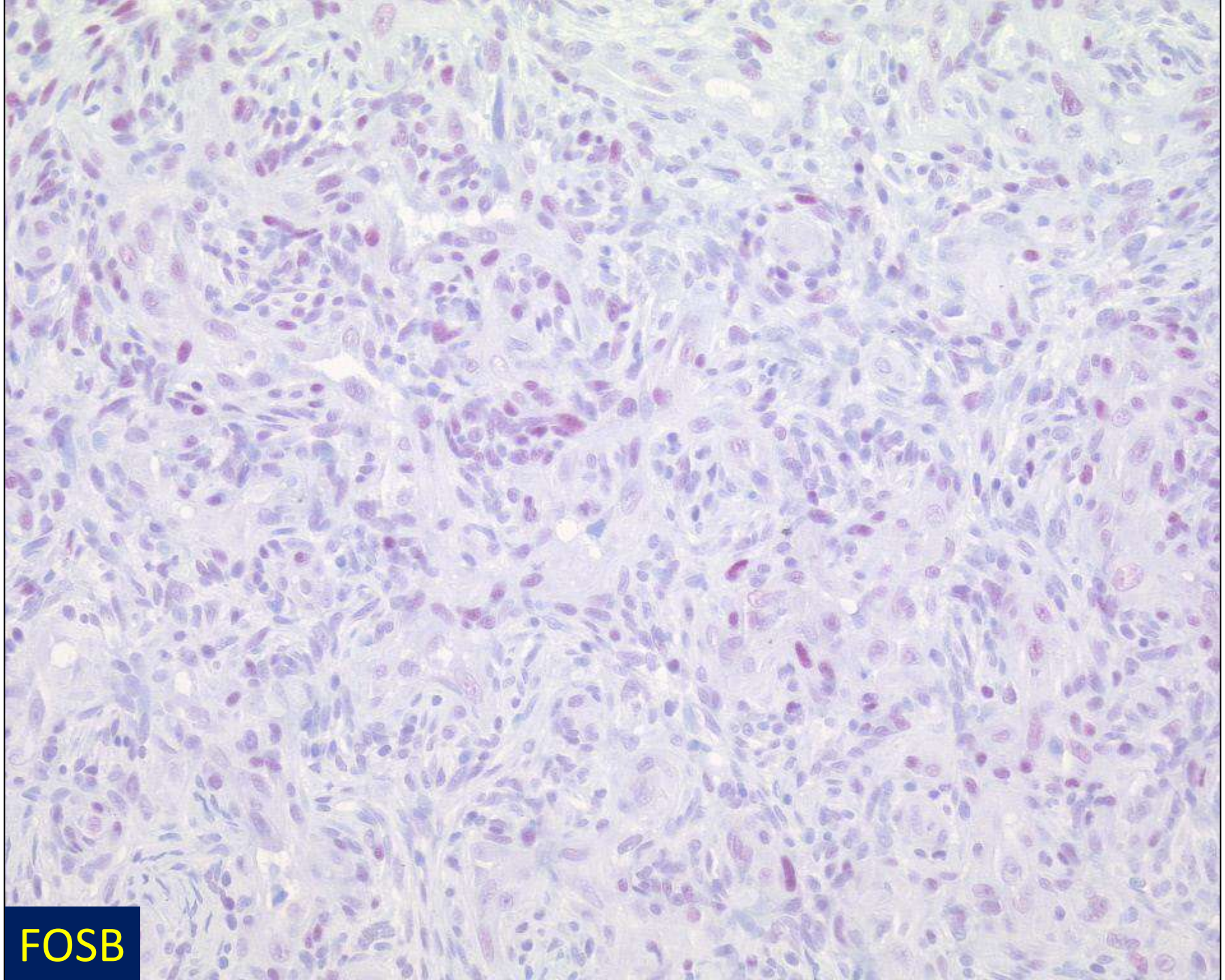


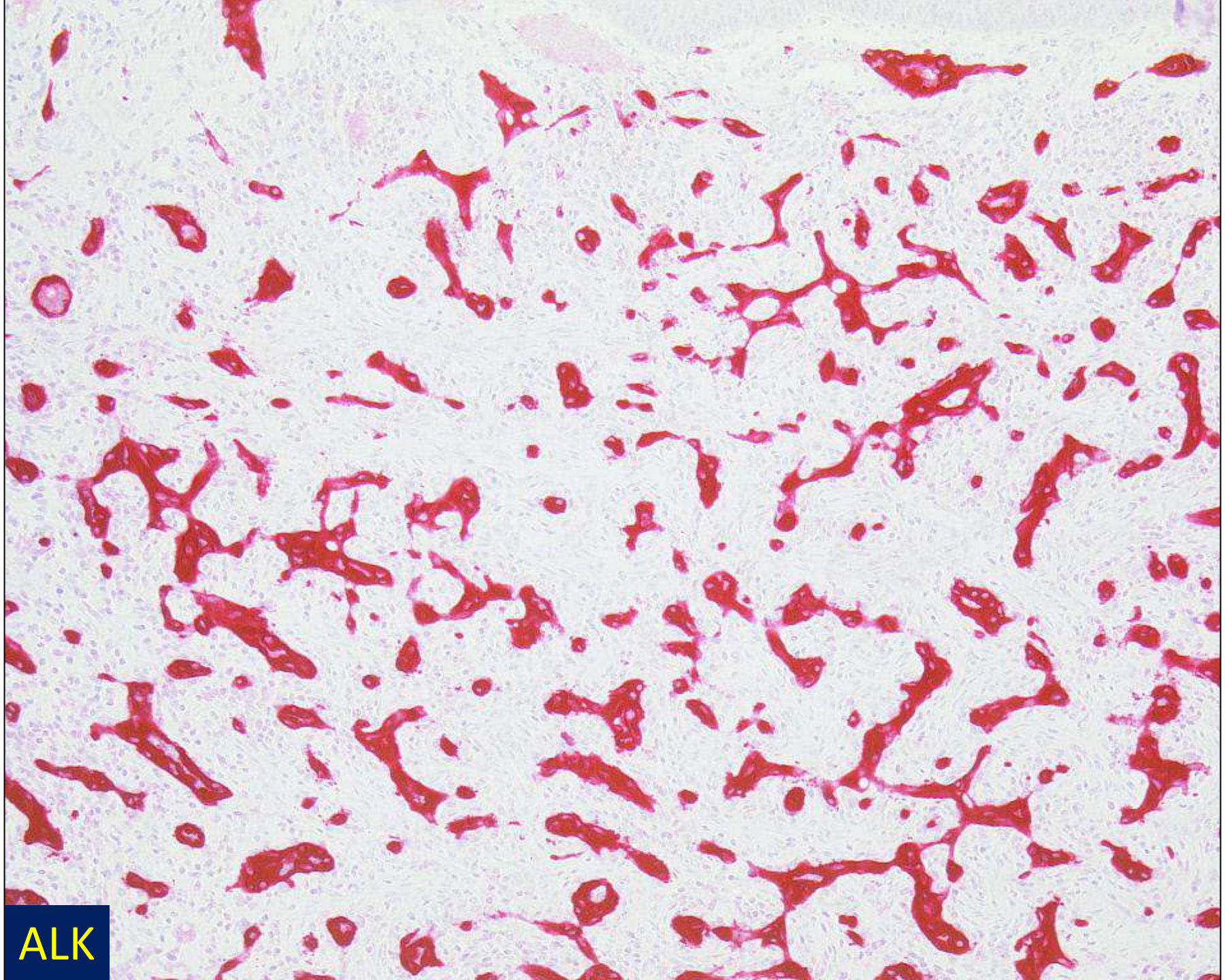






epithelioid vascular neoplasm…


FOSB


ALK

A cutaneous epithelioid vascular tumor harboring a *TPM3::ALK* fusion

Linos K, Chang JC, Busam K Genes Chromosomes Cancer 2024; 63:

M, 18 years, left anterior quadrant
well-circumscribed, intradermal lesion
epithelioid vascular tumour, no high-grade atypia
increased proliferative activity, no necrosis
CD31 +, ERG +, Factor VIII +, ASMA + surrounding myopericytes
in frame fusion between *TPM3* exon 8 and *ALK* exon 20
spectrum of epithelioid haemangioma?

epithelioid cells in vascular lesions

epithelioid Kaposi sarcoma

clinic, plasma cells, HHV8 +

ALK + epithelioid vascular tumour

epithelioid angiomatous nodule

well-circumscribed, CAMTA1 -, FOSB -

epithelioid haemangioma

skin > deep soft tissue > bone

lobular growth, eosinophils, well-formed vessels, FOSB1 +

spindle cell haemangioma

spindled cells, cavernous spaces

scattered epithelioid cells, *IDH1/2* mutations

pseudomyogenic haemangioendothelioma

myogenic spindled and epithelioid cells, AE1/3 +, FOSB1 +

epithelioid haemangioendothelioma

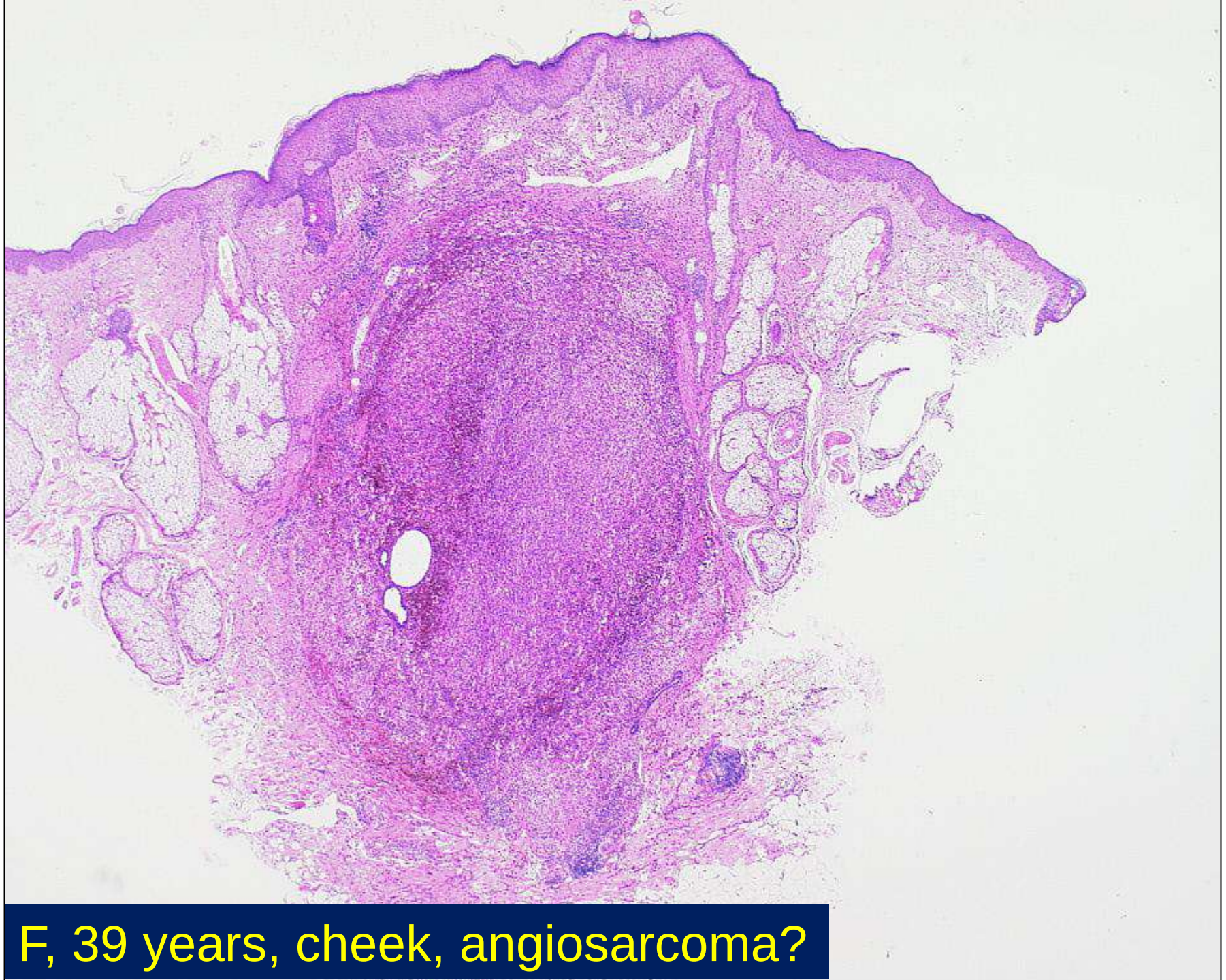
lack of atypia, single cells, cluster and nests

adjacent to preexisting vessels, myxohyaline stroma

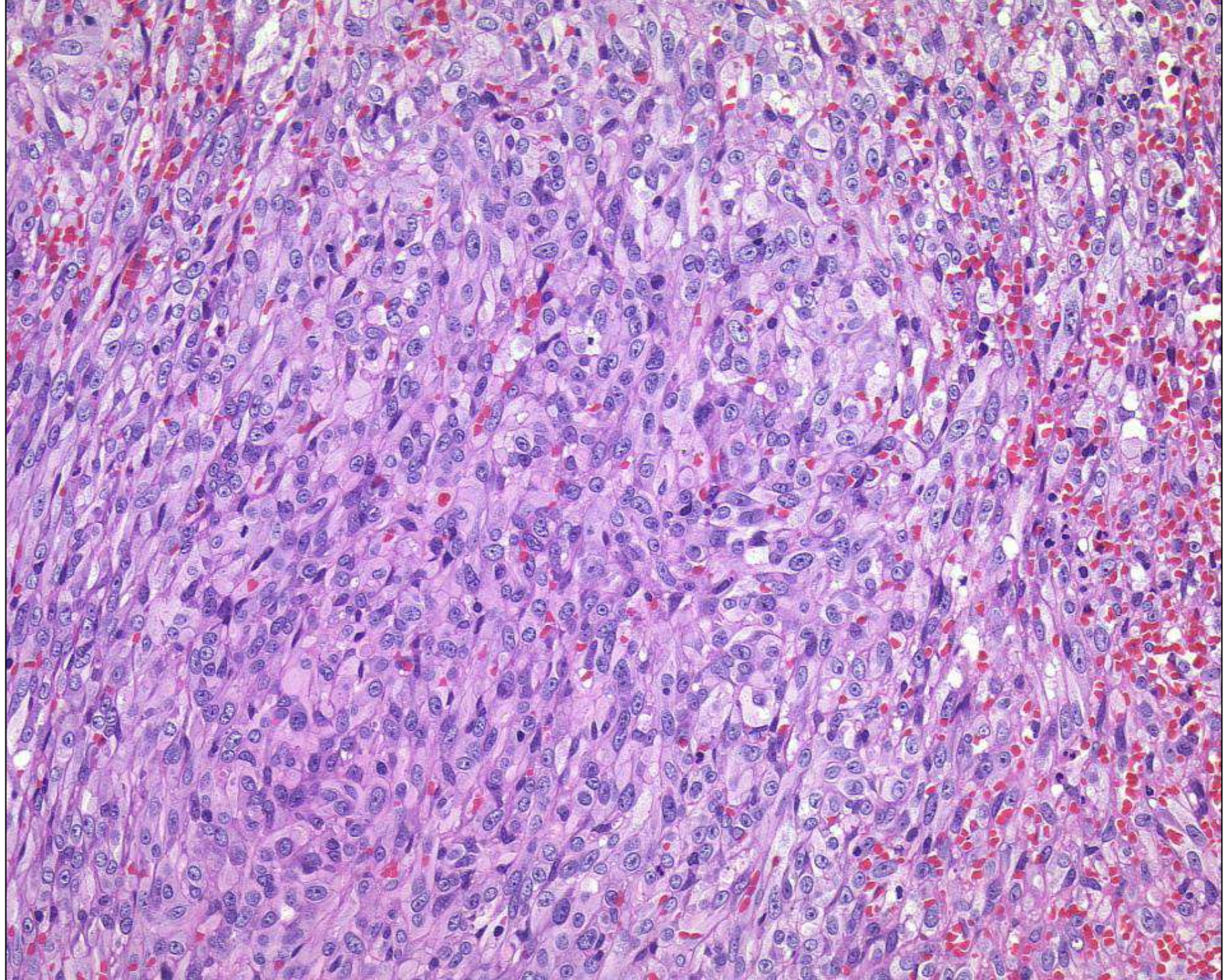
CAMTA + (TFE3 +)

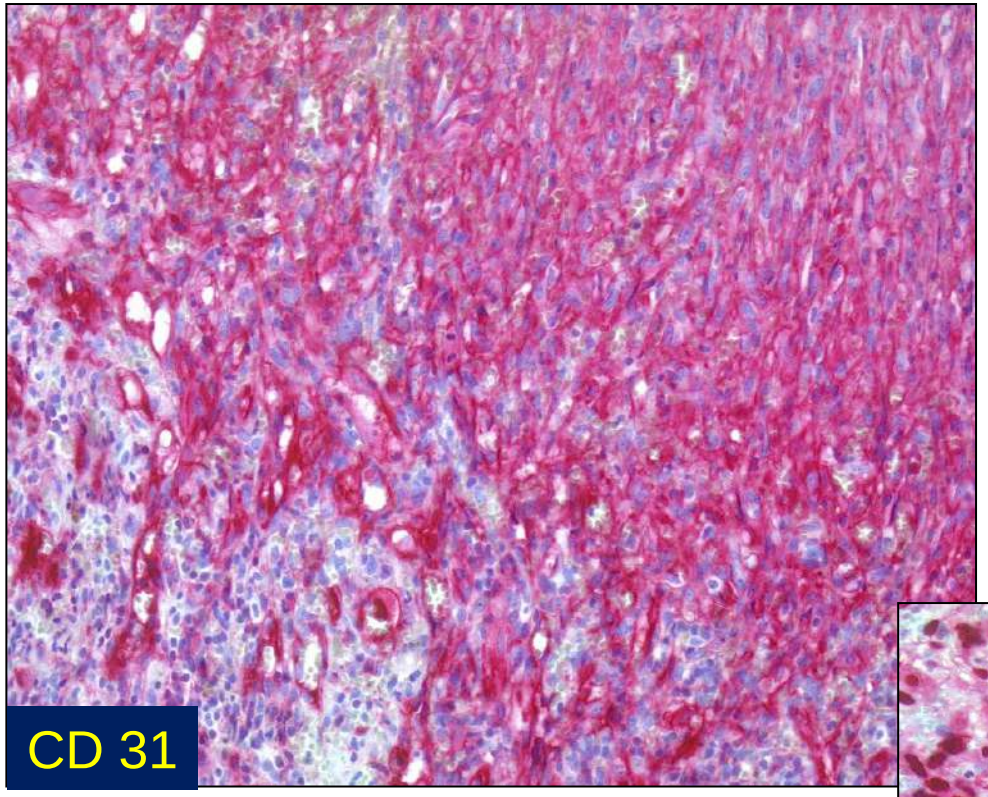
epithelioid angiosarcoma

prominent atypia, numerous mitoses, necrosis

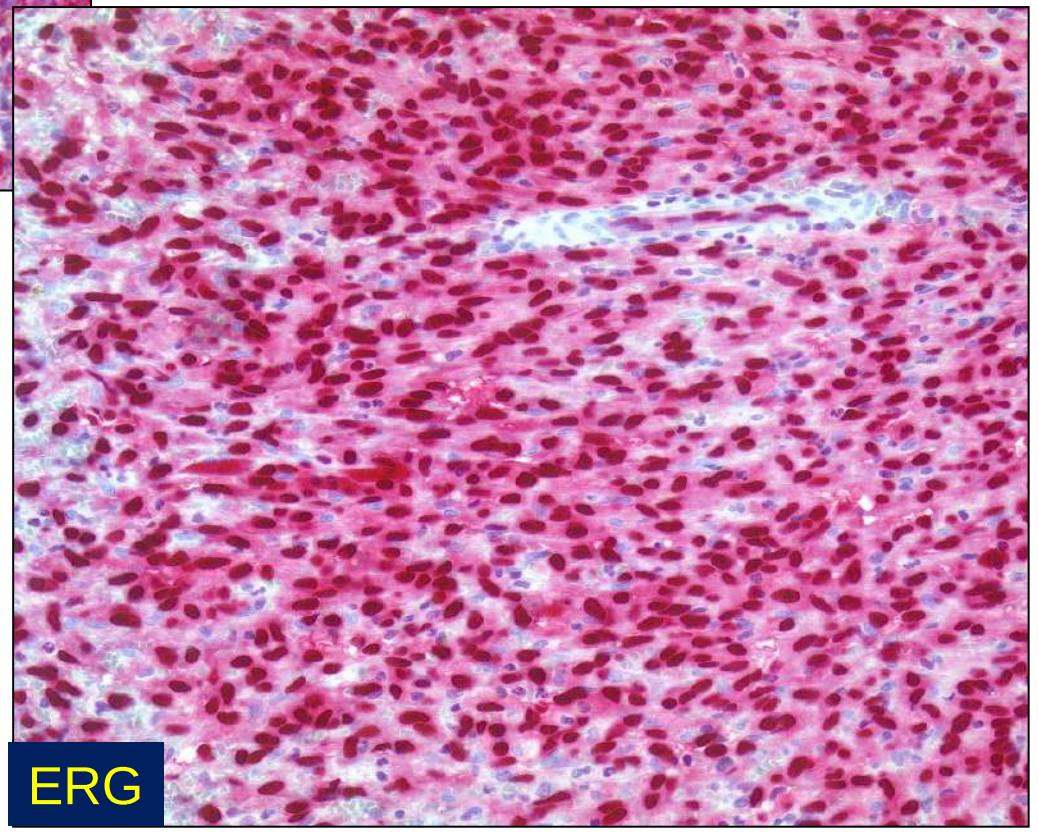


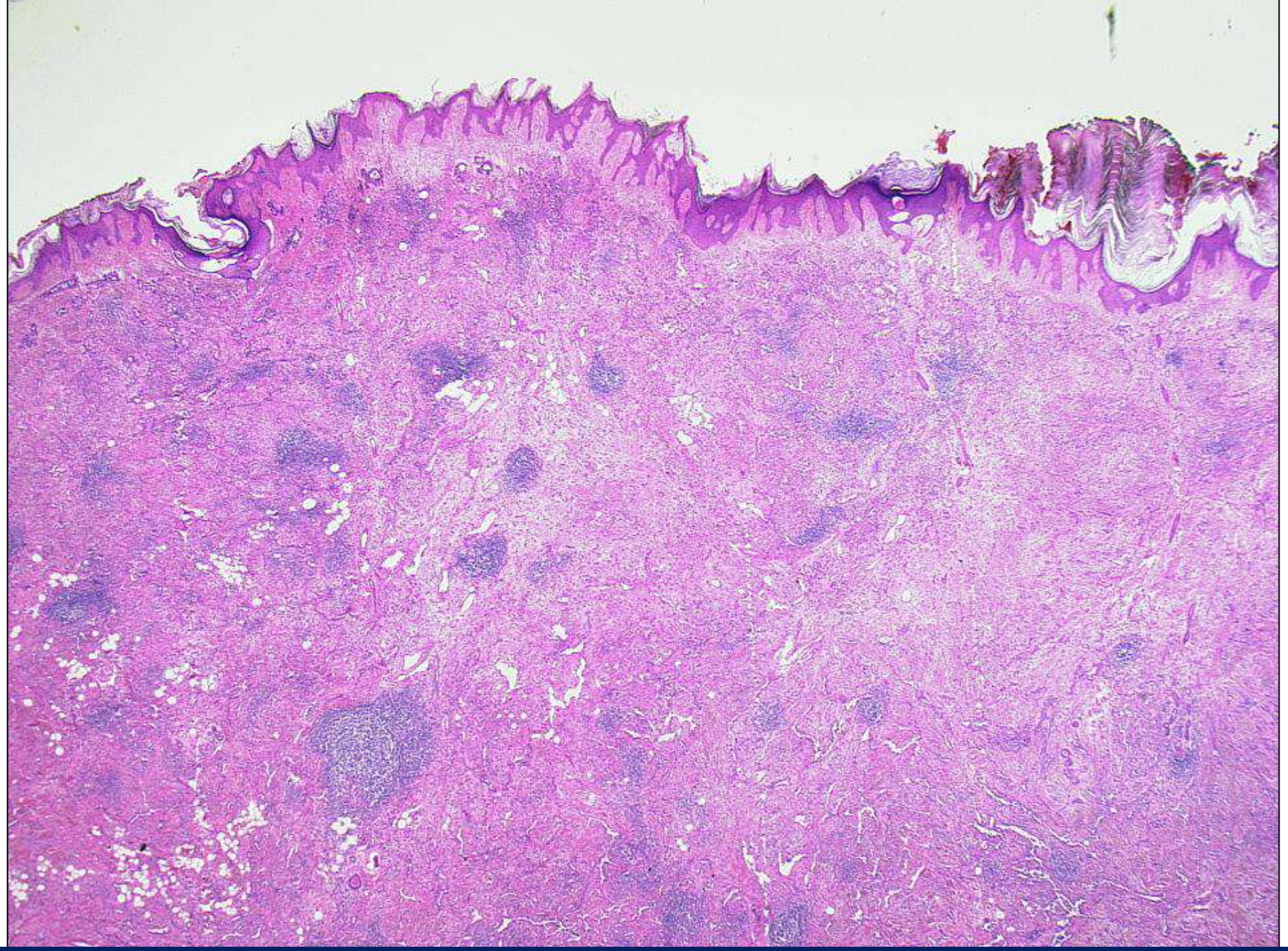
F, 39 years, cheek, angiosarcoma?



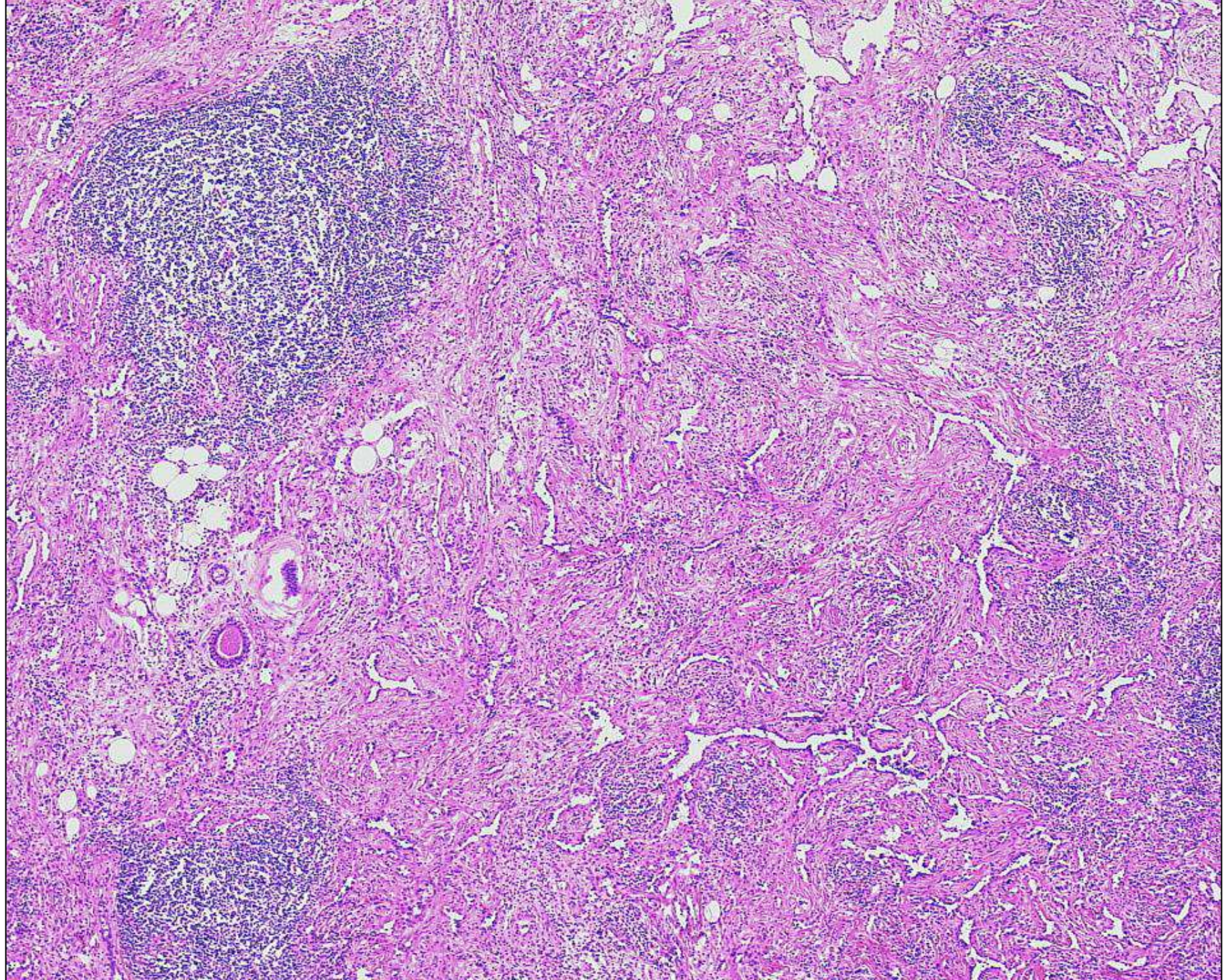


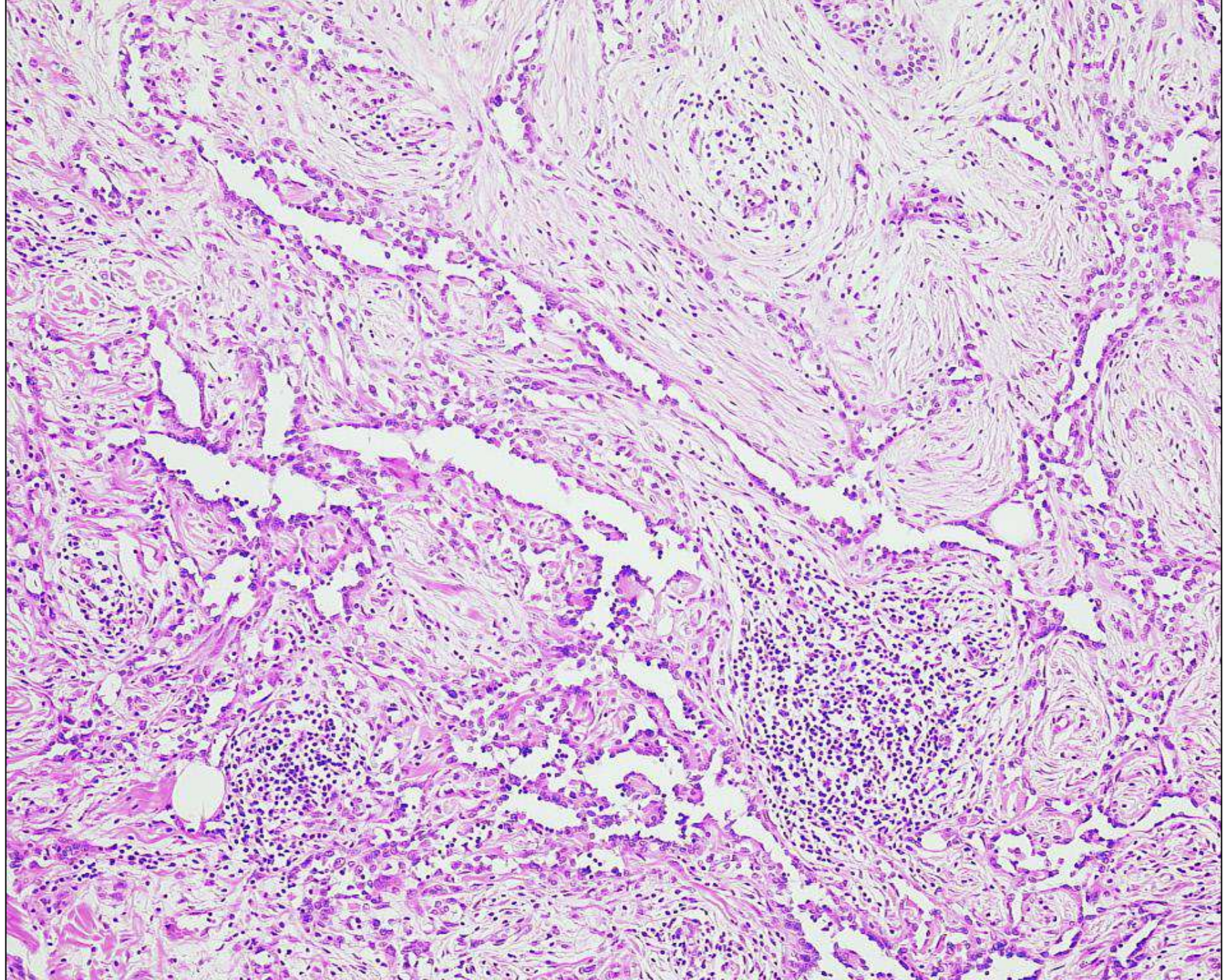
Diagnosis:
cutaneous epithelioid angiomatous nodule

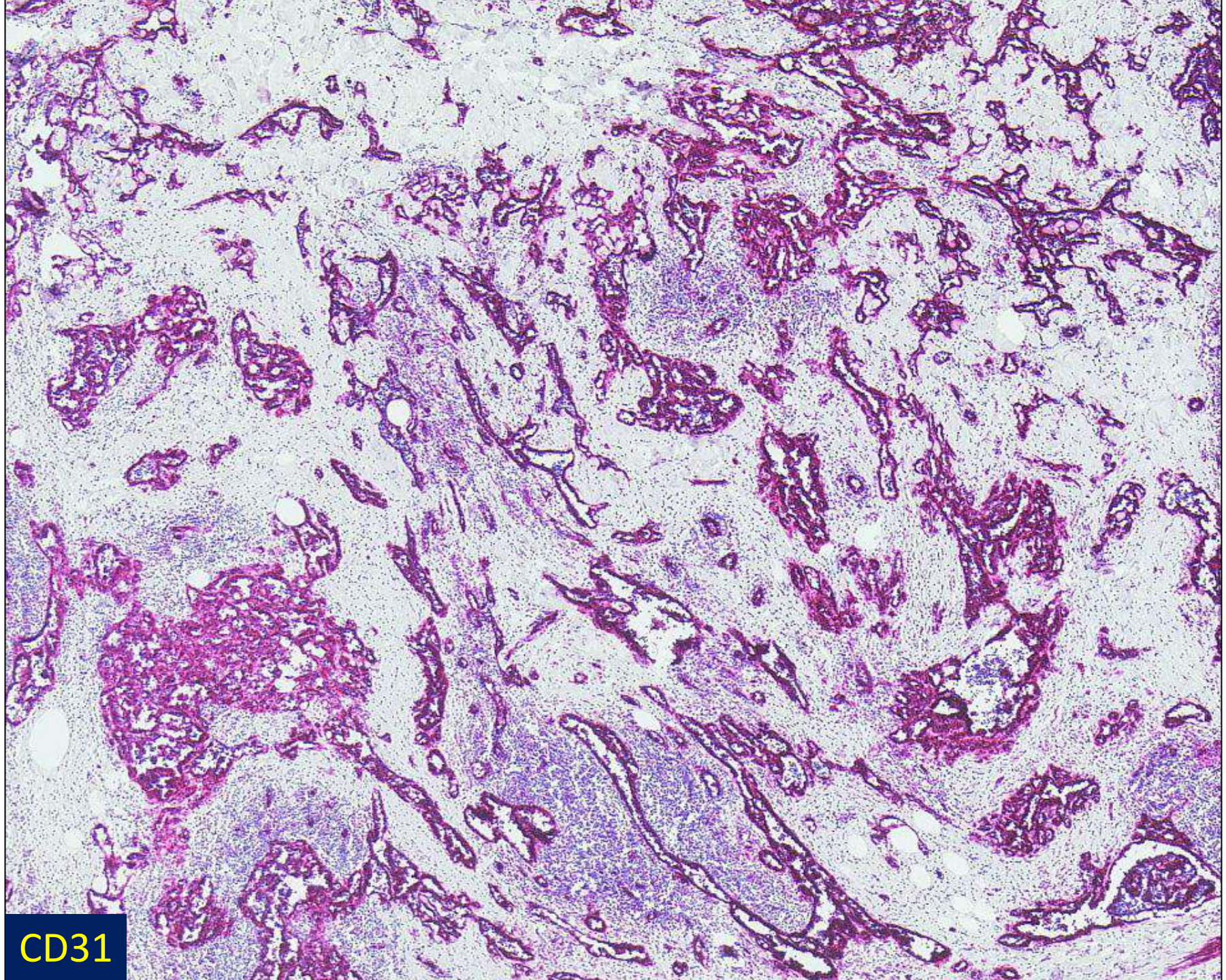


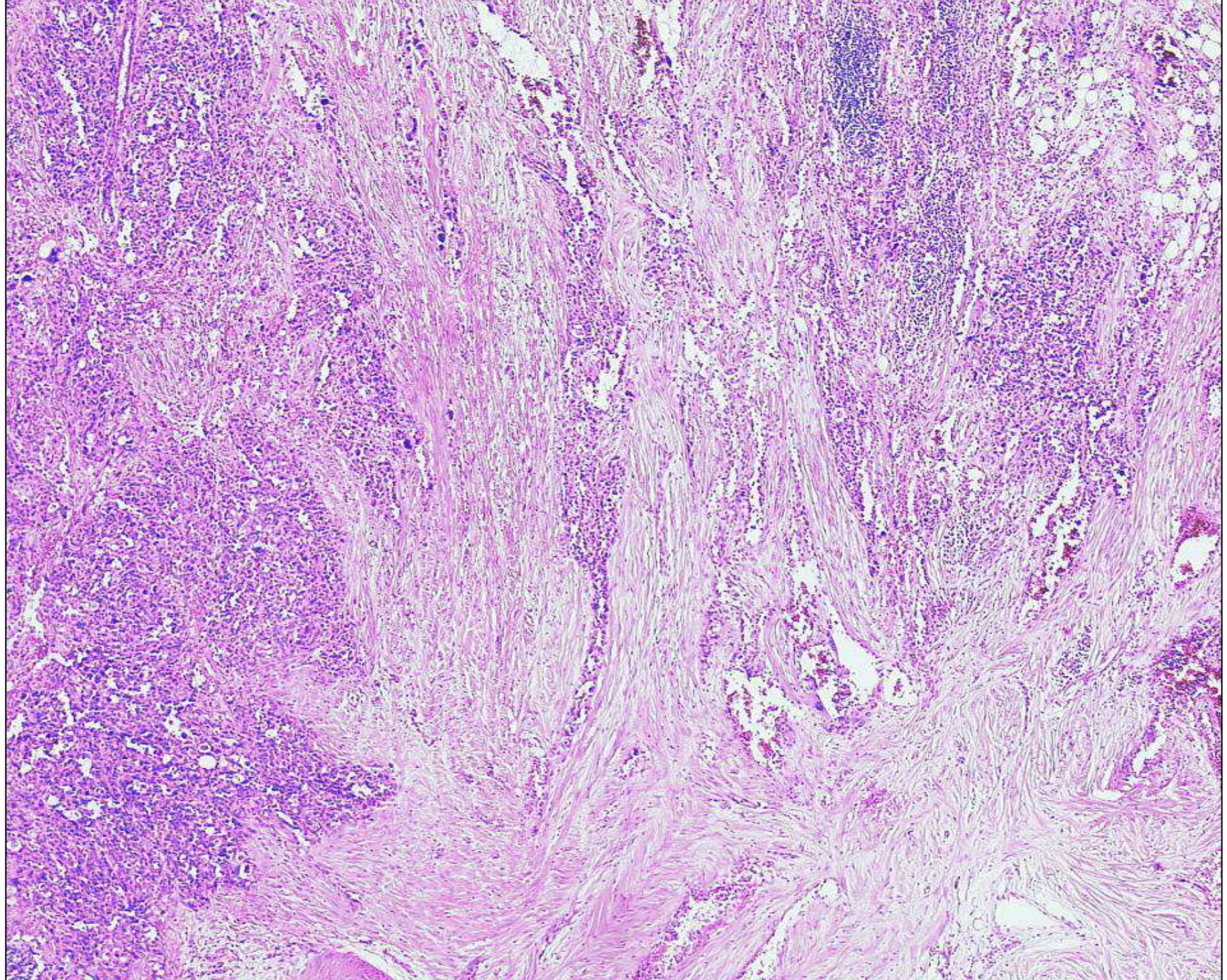


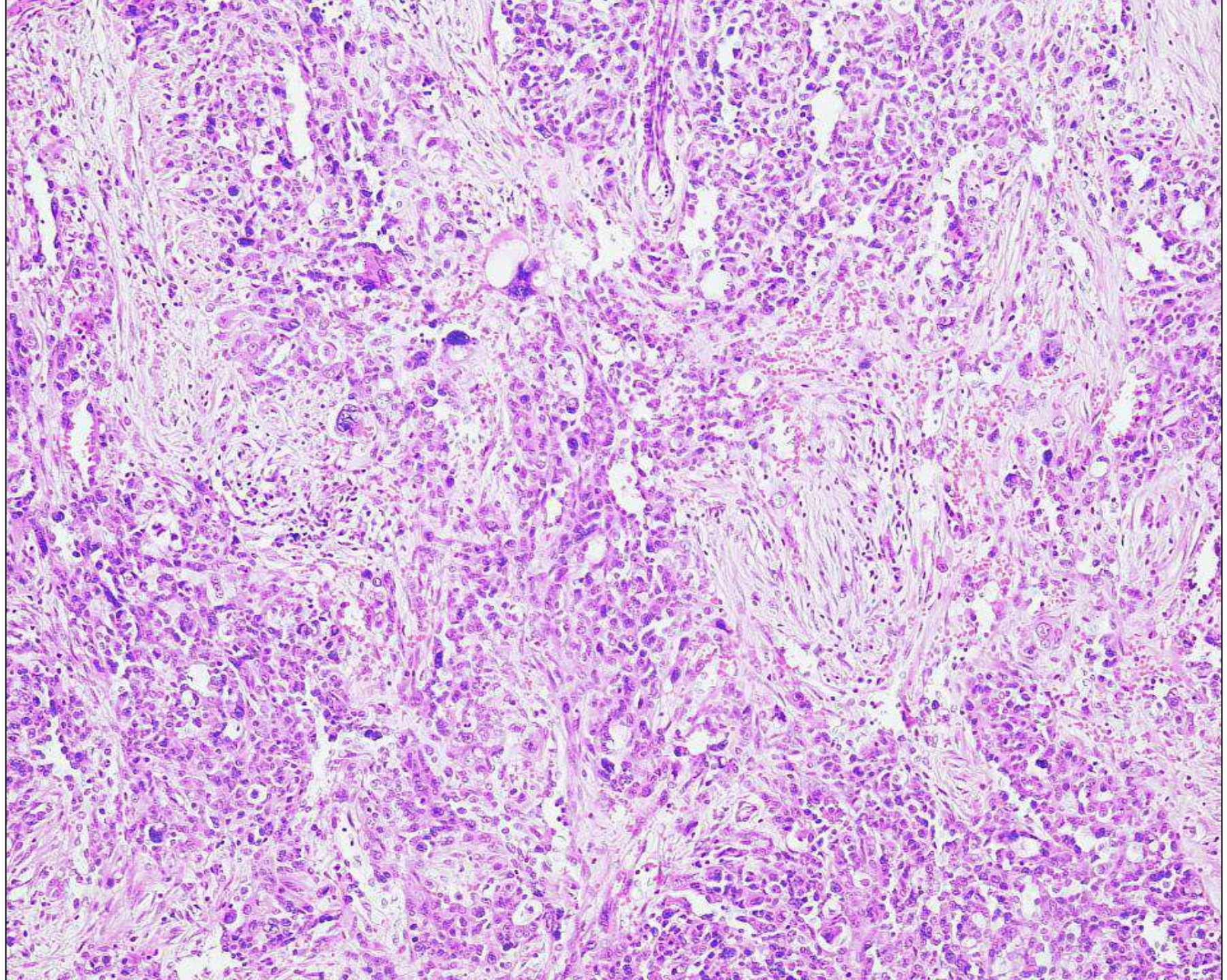
Case 10: F, 54 years, left lower leg, long standing recently enlarged lesion

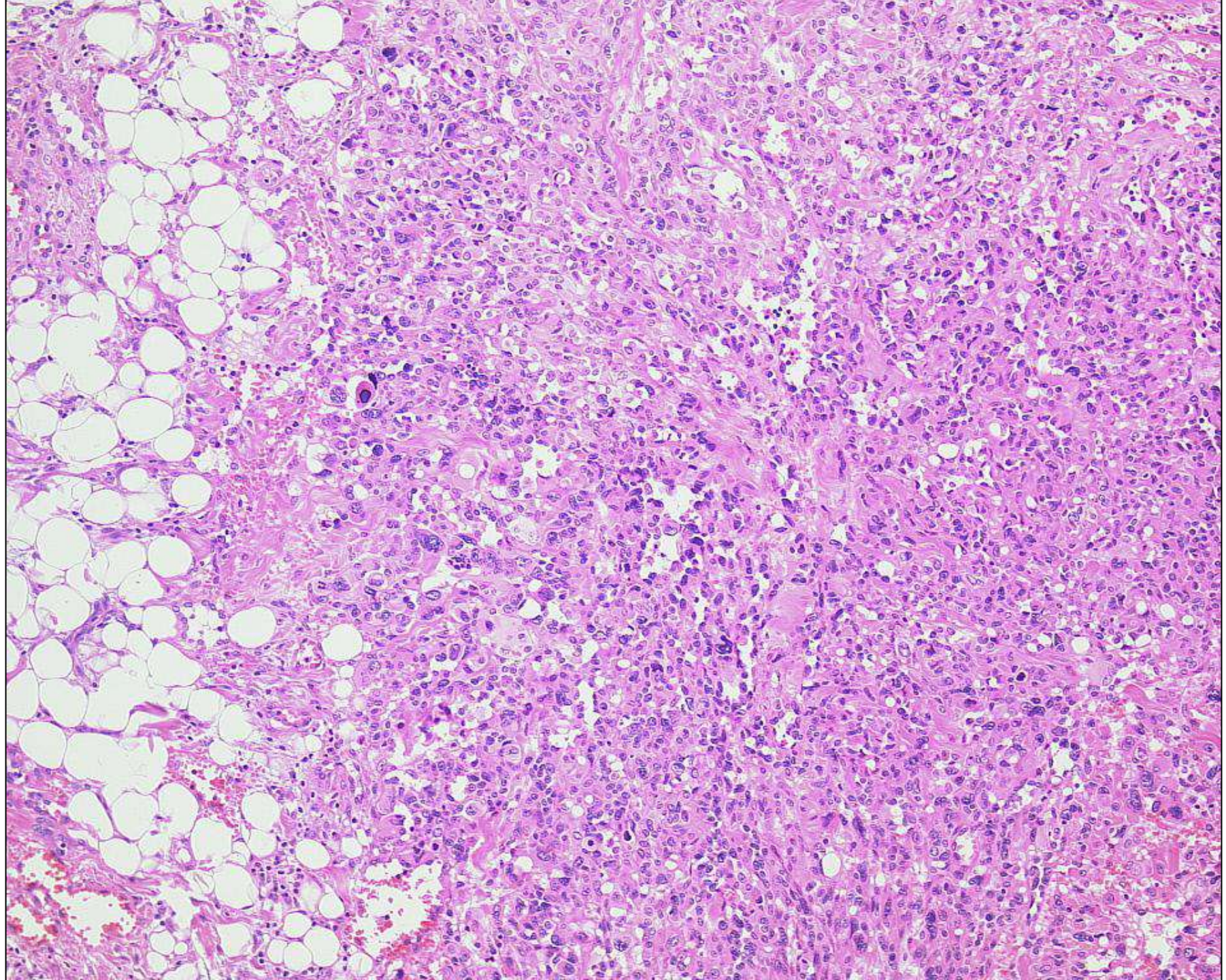


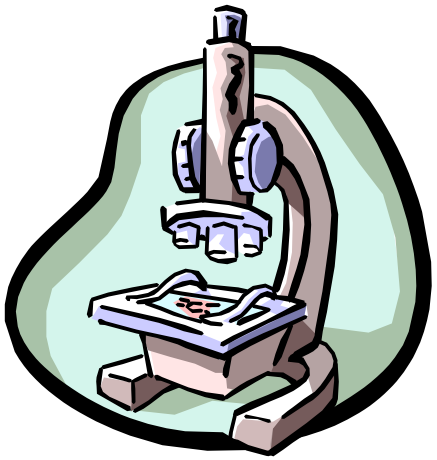



CD31



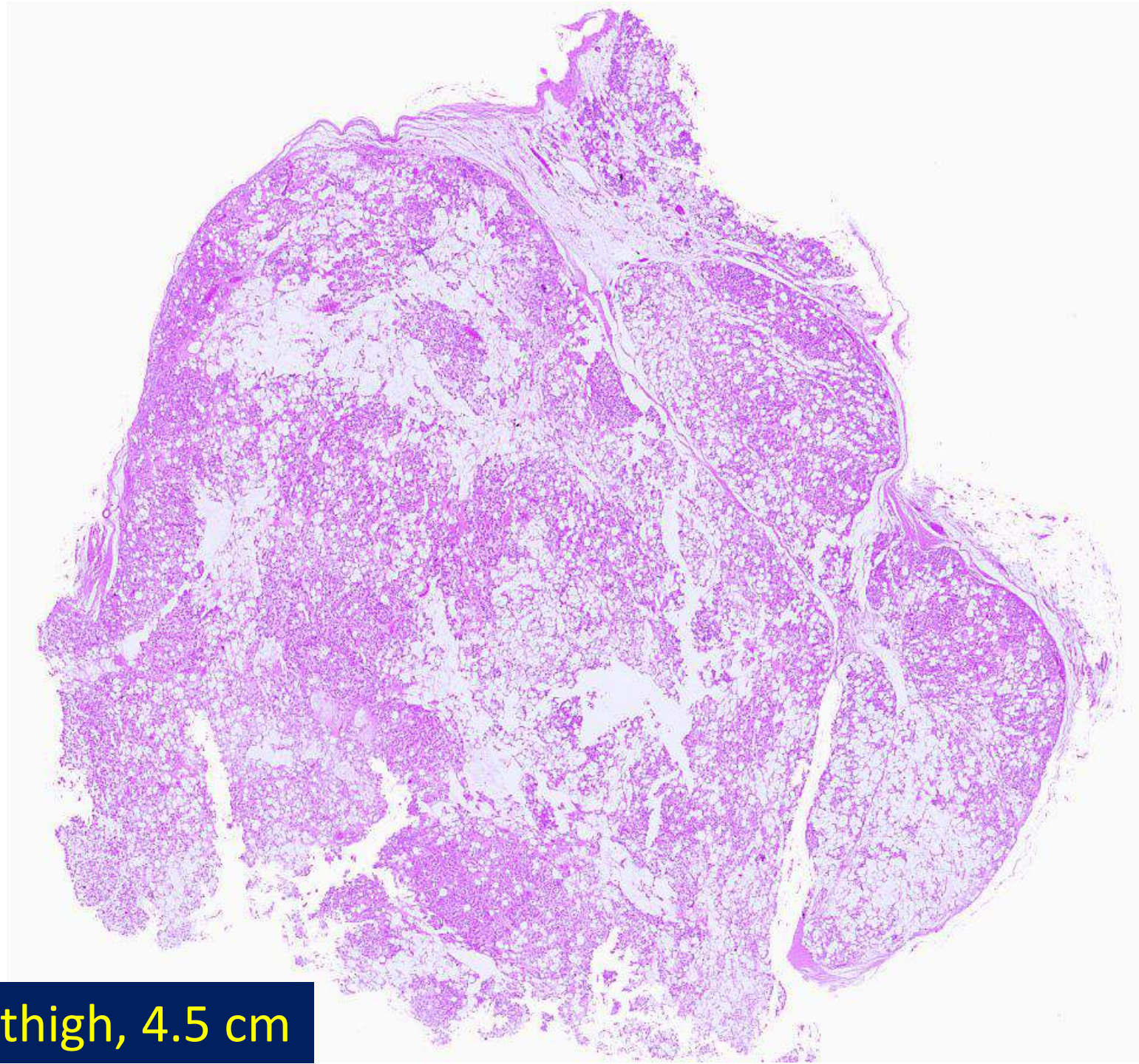




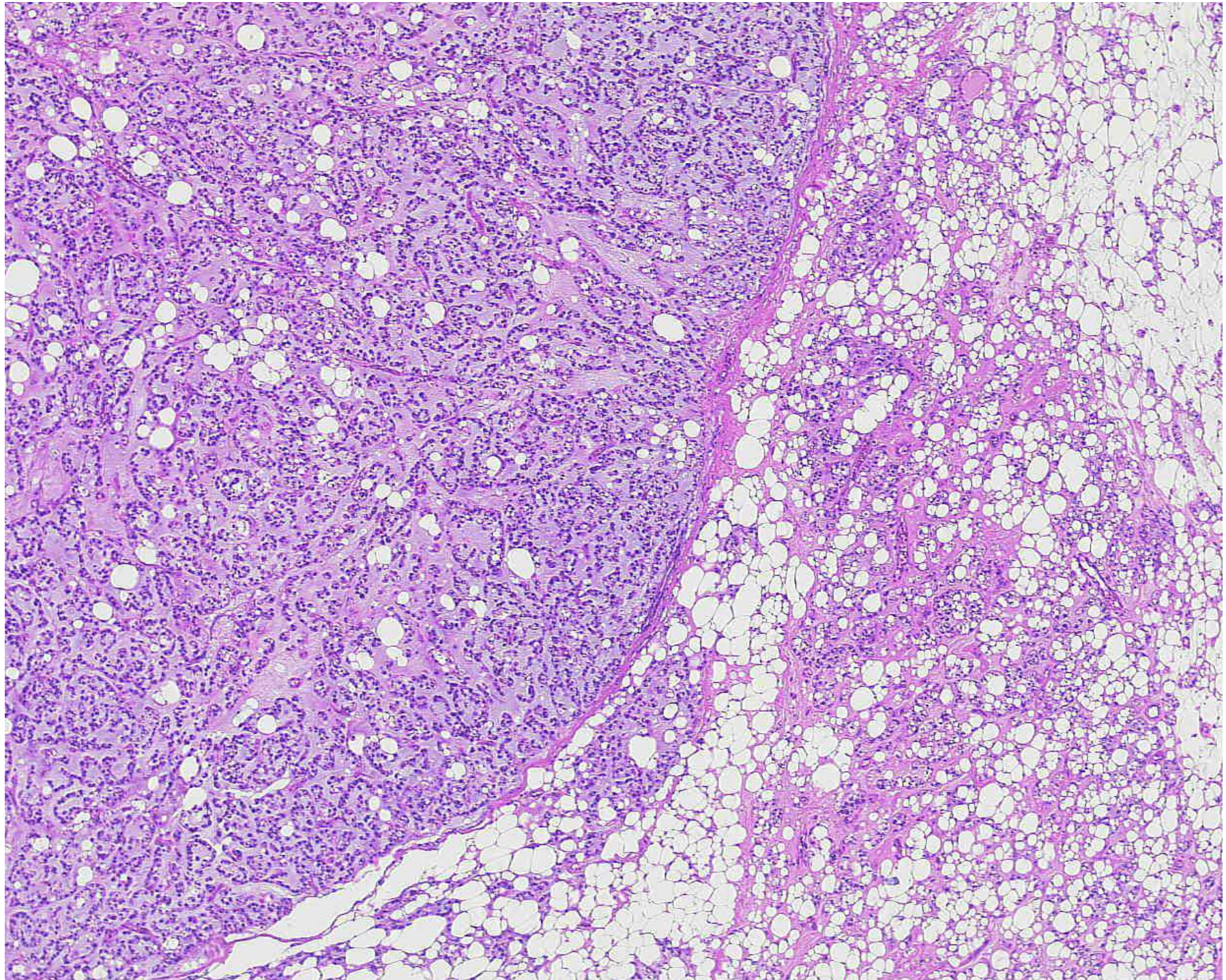


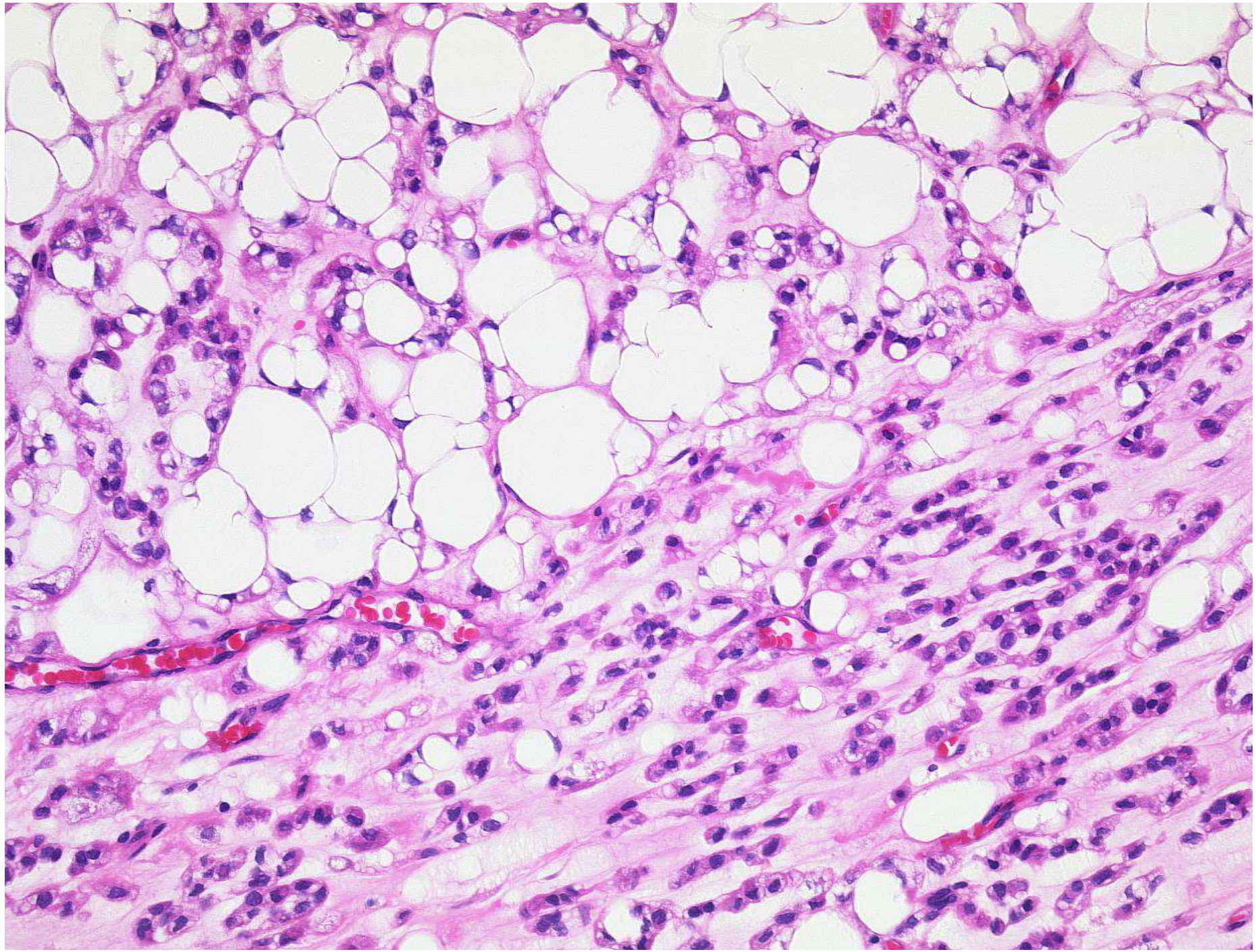
Diagnosis Case 10

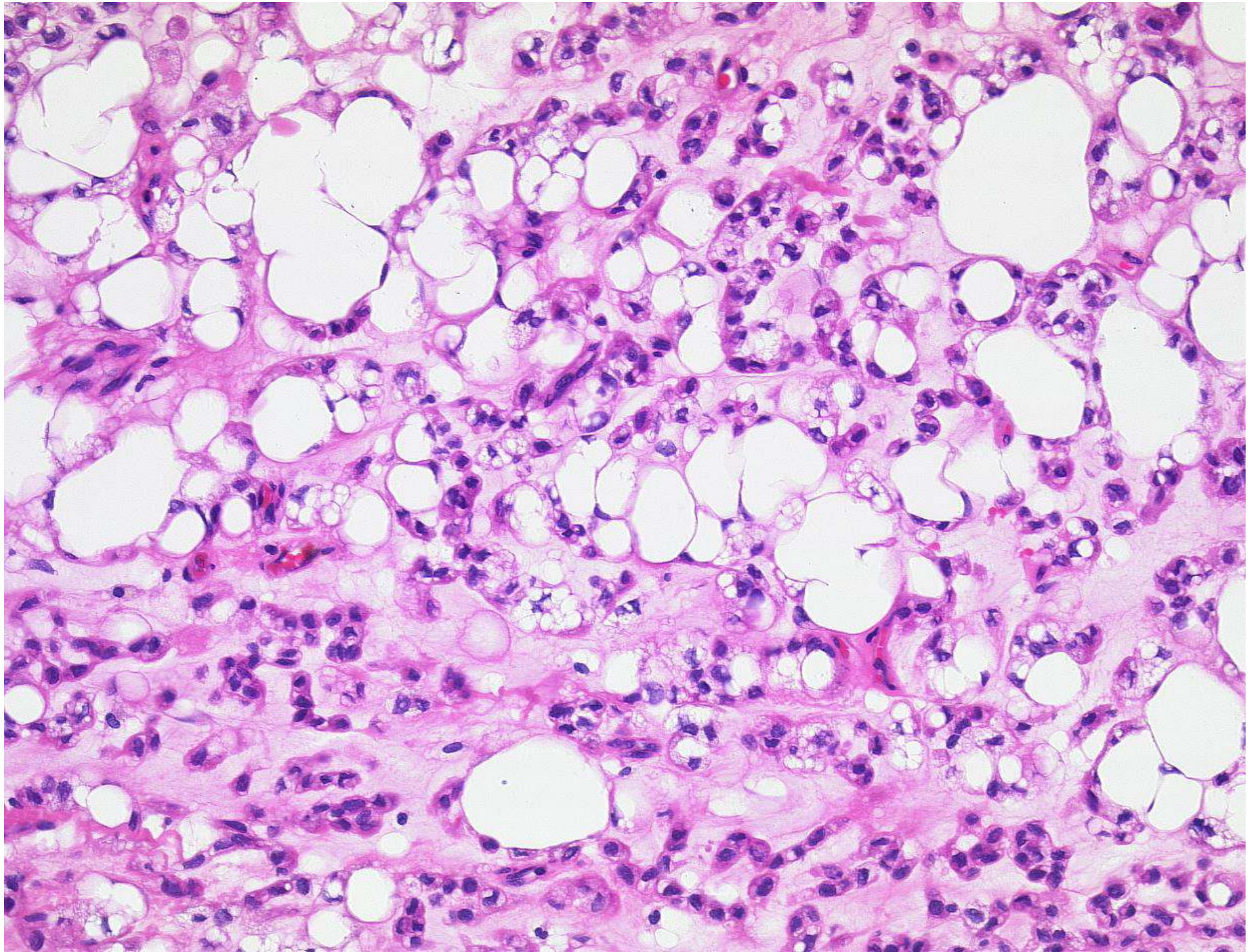
retiform Haemangioendothelioma with malignant transformation

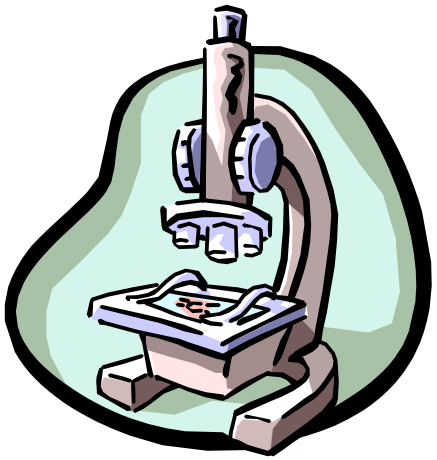


Case 11: F, 75 years, left thigh, 4.5 cm









Diagnosis Case 11

chondroid Lipoma*

* Meis JM, Enzinger F AJSP 1993; 17: 1103

Extraskeletal chondroma with lipoblast-like cells
Chan JK et al. Hum Pathol 1986; 17: 1285-1287

61-year-old woman, wrist
cellular lobular tumour
chondroid cells with mild nuclear atypia
univ- and multivacuolated cells with accumulation
of lipid micking lipoblasts

chondroid Lipoma

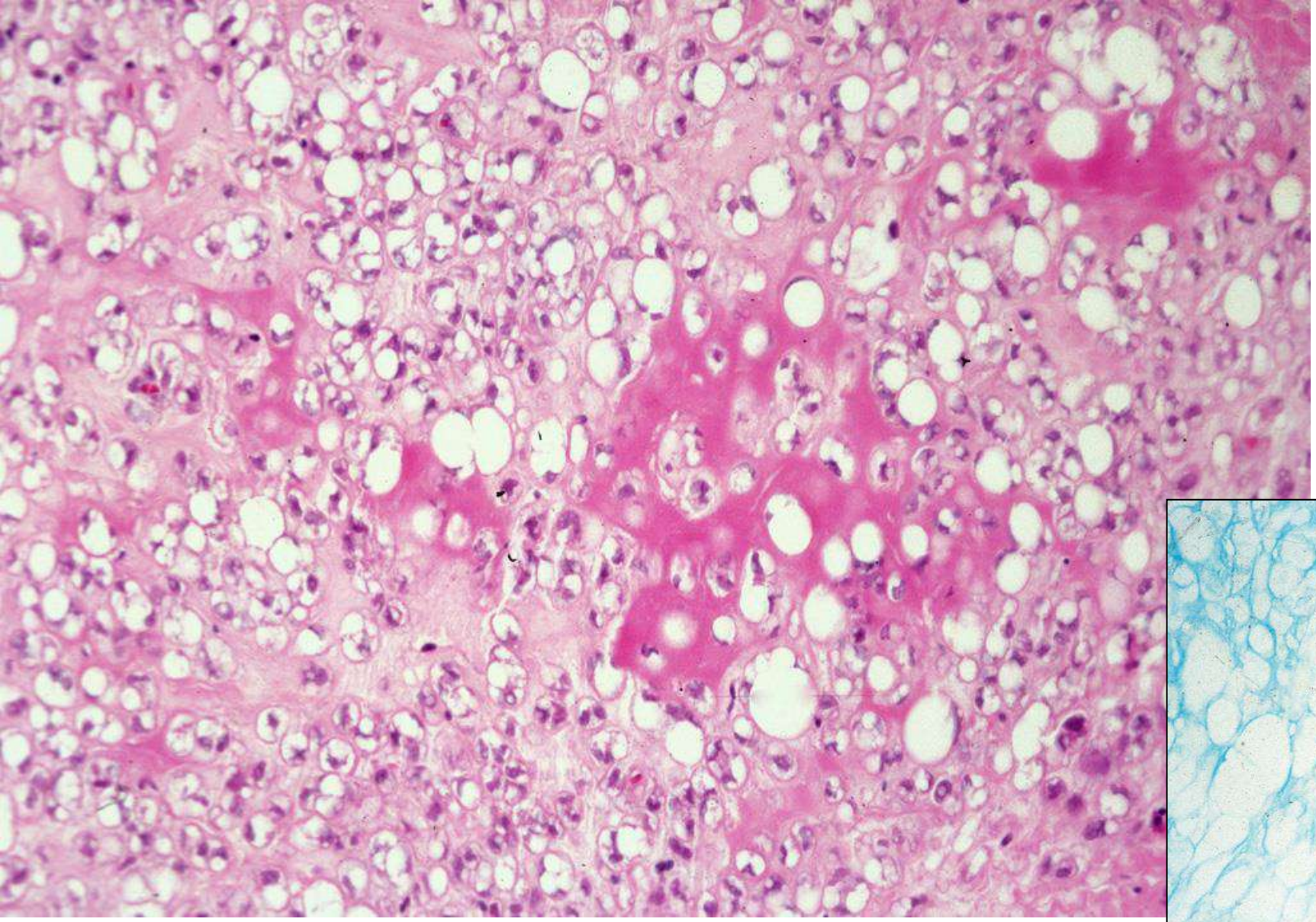
- adult patients, F > M
- slowly growing neoplasms
- subcutis / deep soft tissue
- encapsulated, lobular growth
- adipocytes, lipoblasts, small eosinophilic cells
- myxochondroid stroma
- benign clinical course

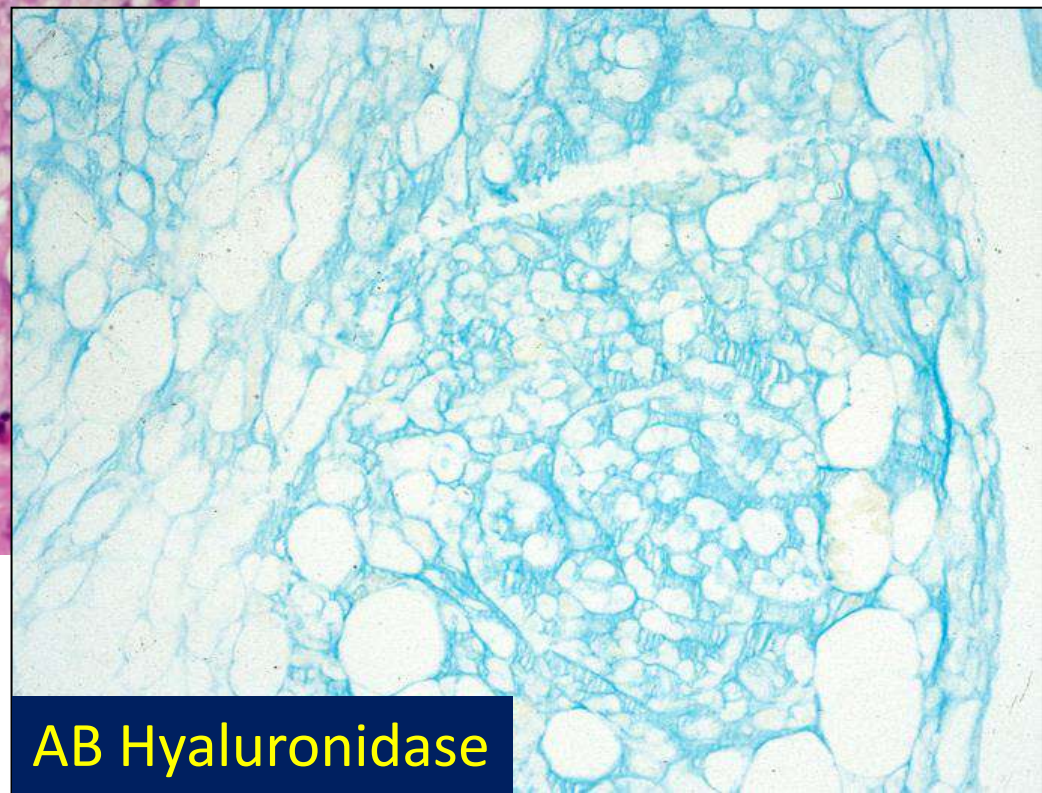
chondroid Lipoma

- vimentin +, S-100 +/-
- CD68 +/-, laminin +/-, collagen type IV +/-
- focal expression of CK in some cases
- EMA -, ASMA -, GFAP -
- t(11;16)(q13;p13) (*MGC3032::MKL2* fusion)

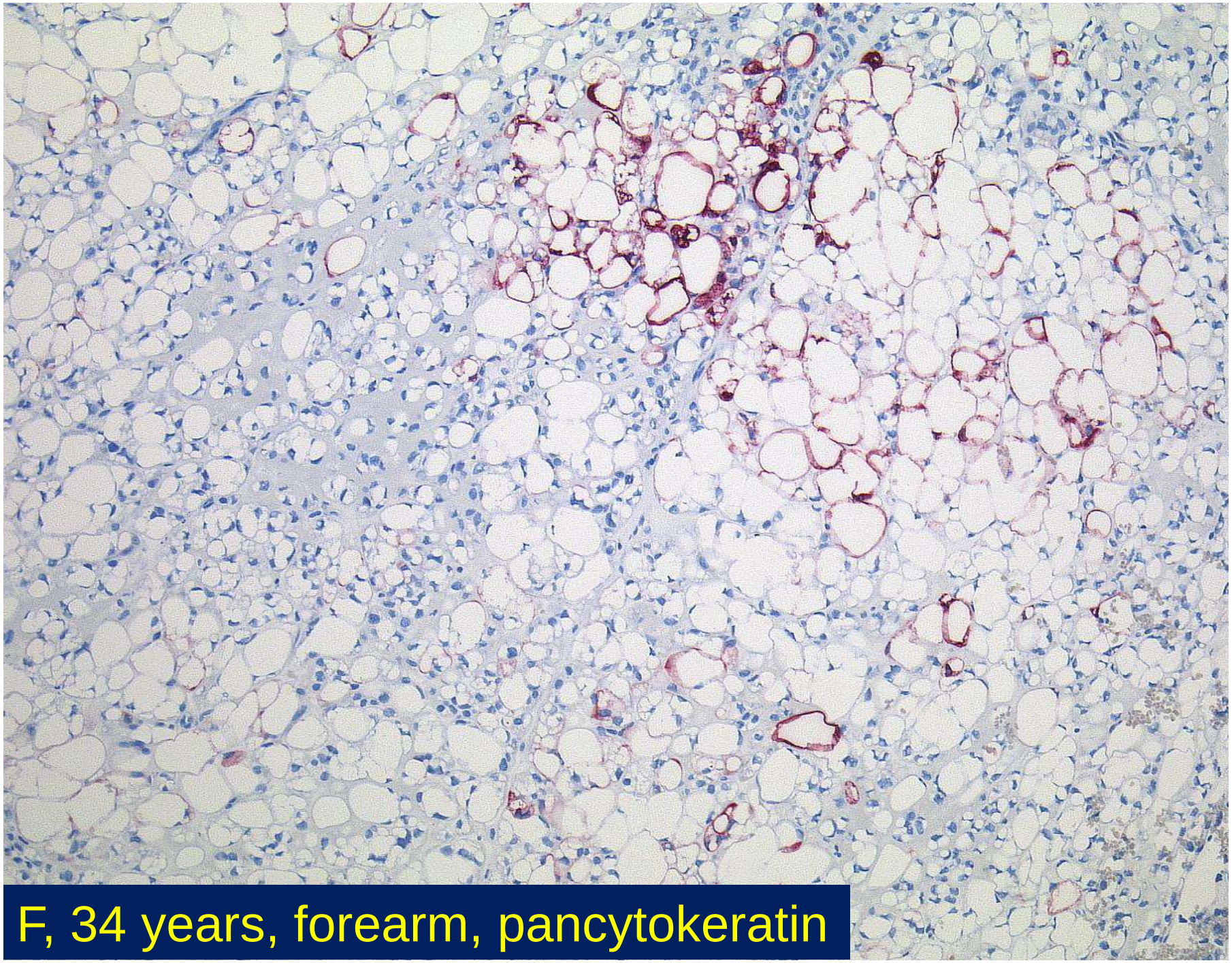
  MKL2: myocardin-related transcription factor

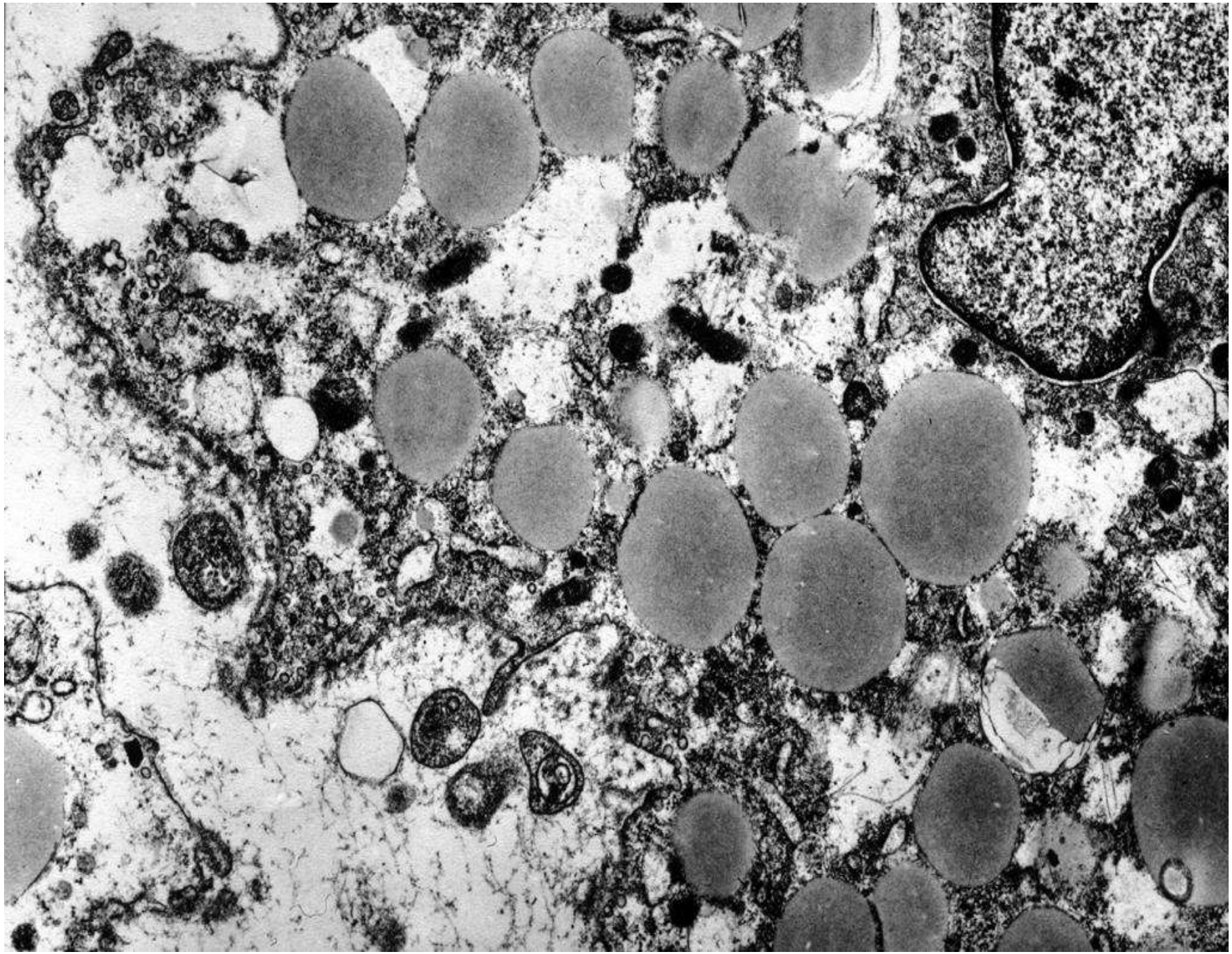
  MGC3032: hypothetical protein
- **ELMI:** clefted nuclei, fat droplets, rough ER, mitochondria, knob-like cell membrane protuberances

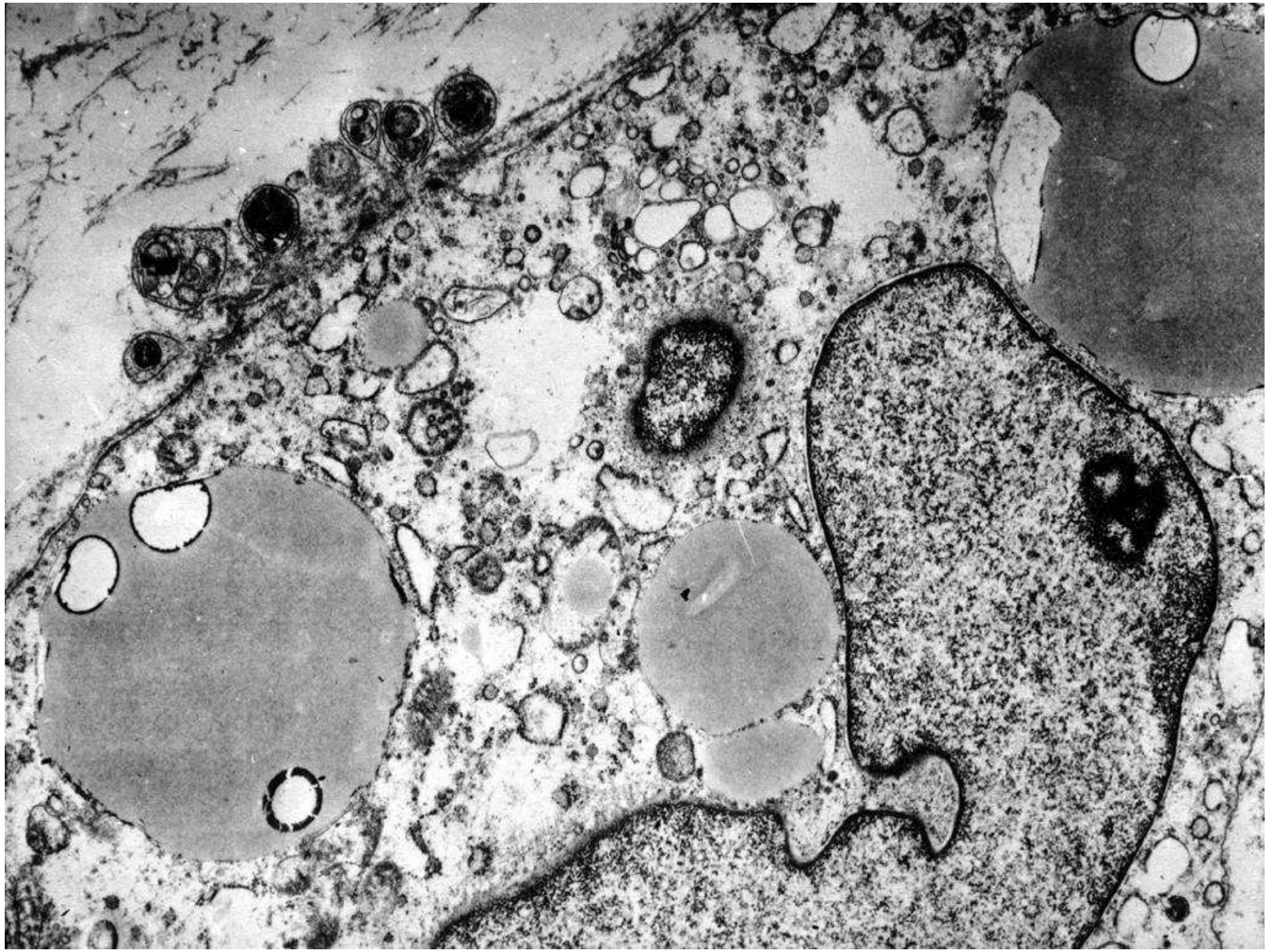




AB Hyaluronidase


F, 34 years, forearm, pancytokeratin





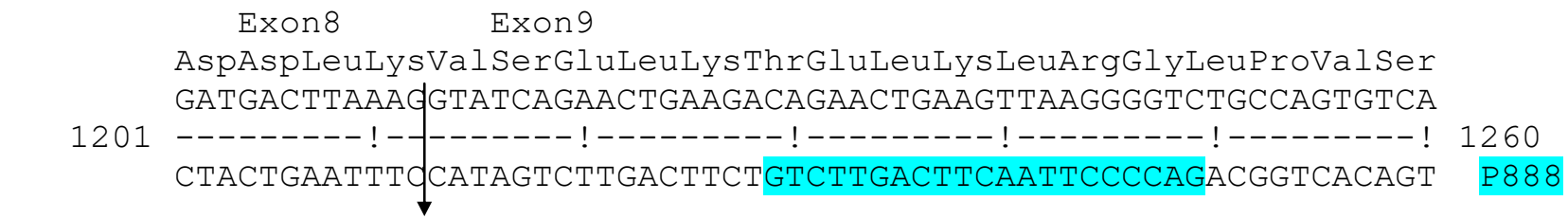
C11orf95-MKL2 is a consistent finding in chondroid lipoma: a study of 8 cases

U.Flucke et al. Histopathology 2013; 62: 925

- 4 F, 4 M, 21-81 years
- forearm (3), lower leg (2), back (1), thigh (1), head (1)
- 1 x local recurrence
- typical morphology
- 7/8 cases with *C11orf95::MKL2* (PCR)

C11orf95-MKL2 ex9-ex5

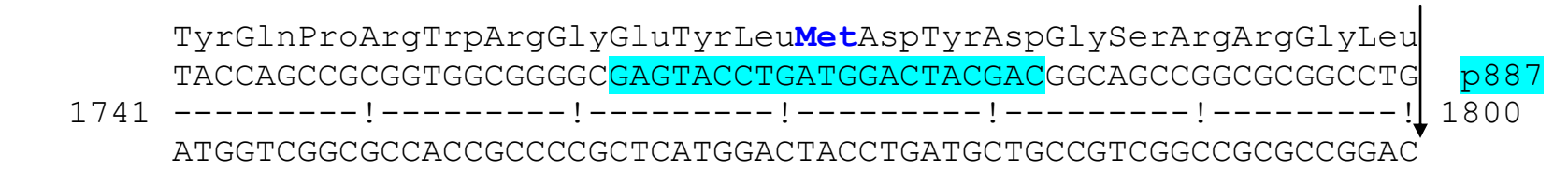
MKL2



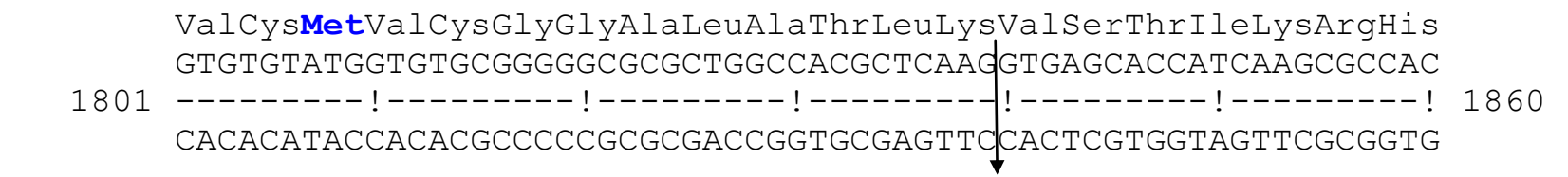
Gen:MKL2/Datum:07-08-2012 /Genomisch: NC_000016.9 /mRNA: NM_014048.3/Eiwit: NP_ 0547676.3

C11orf95 EXON5

1 breakpoint 1159 In exon5 1799-1800



2 breakpoint lit.1839-1840(intron exon5)



Gen: C11orf95 /Datum: 08-08-2012 /Genomisch: NC_000011.9 / mRNA: NM_001144936.1/ Eiwit: NP_ 001138408.1

Lipoblasts in benign lipogenic Neoplasms ?

yes, no problem!

lipoblastoma / lipoblastomatosis

spindle cell lipoma / pleomorphic lipoma

chondroid lipoma

Differential diagnosis: chondroid Lipoma

extraskeletal myxoid Chondrosarcoma

no lipogenic component

uniform, eosinophilic

round / spindled tumour cells

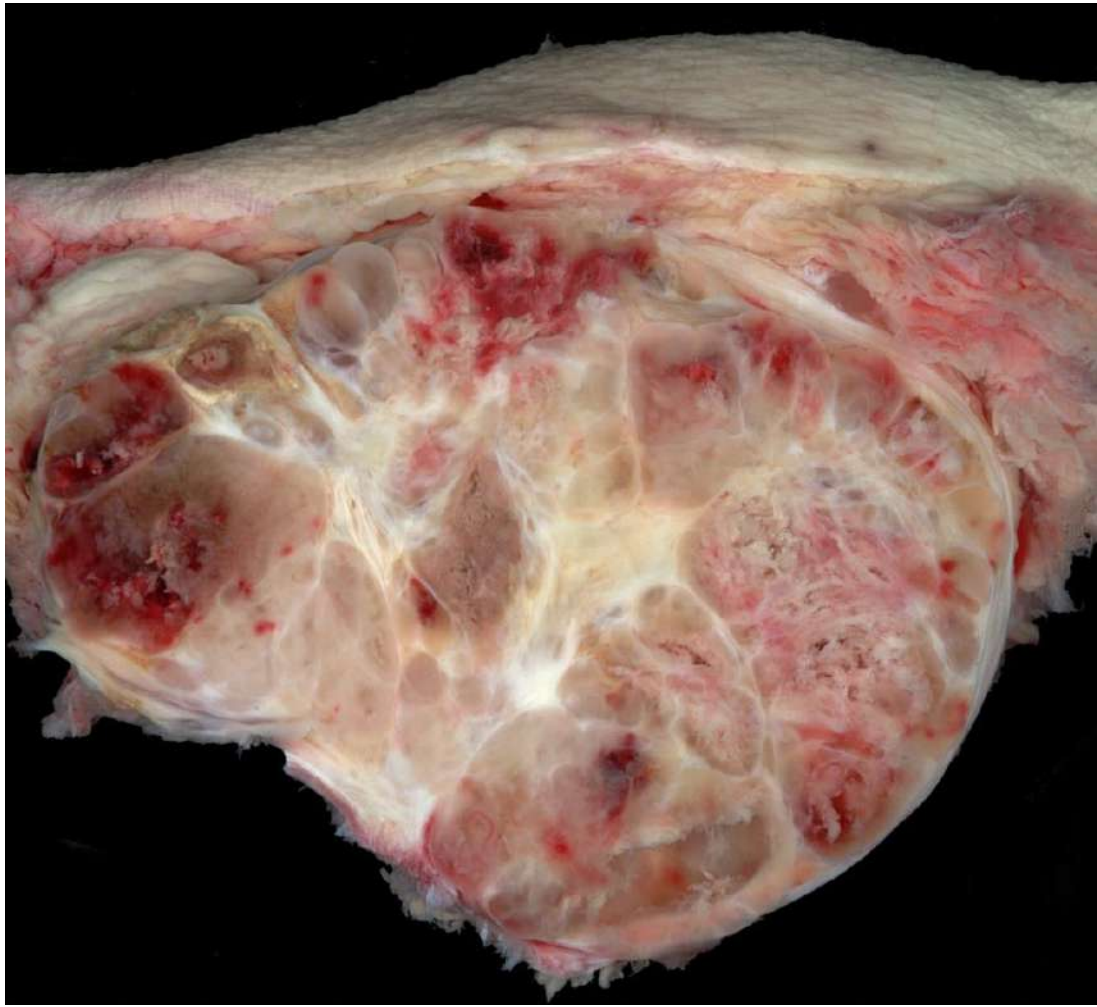
no cytoplasmic vacuoles

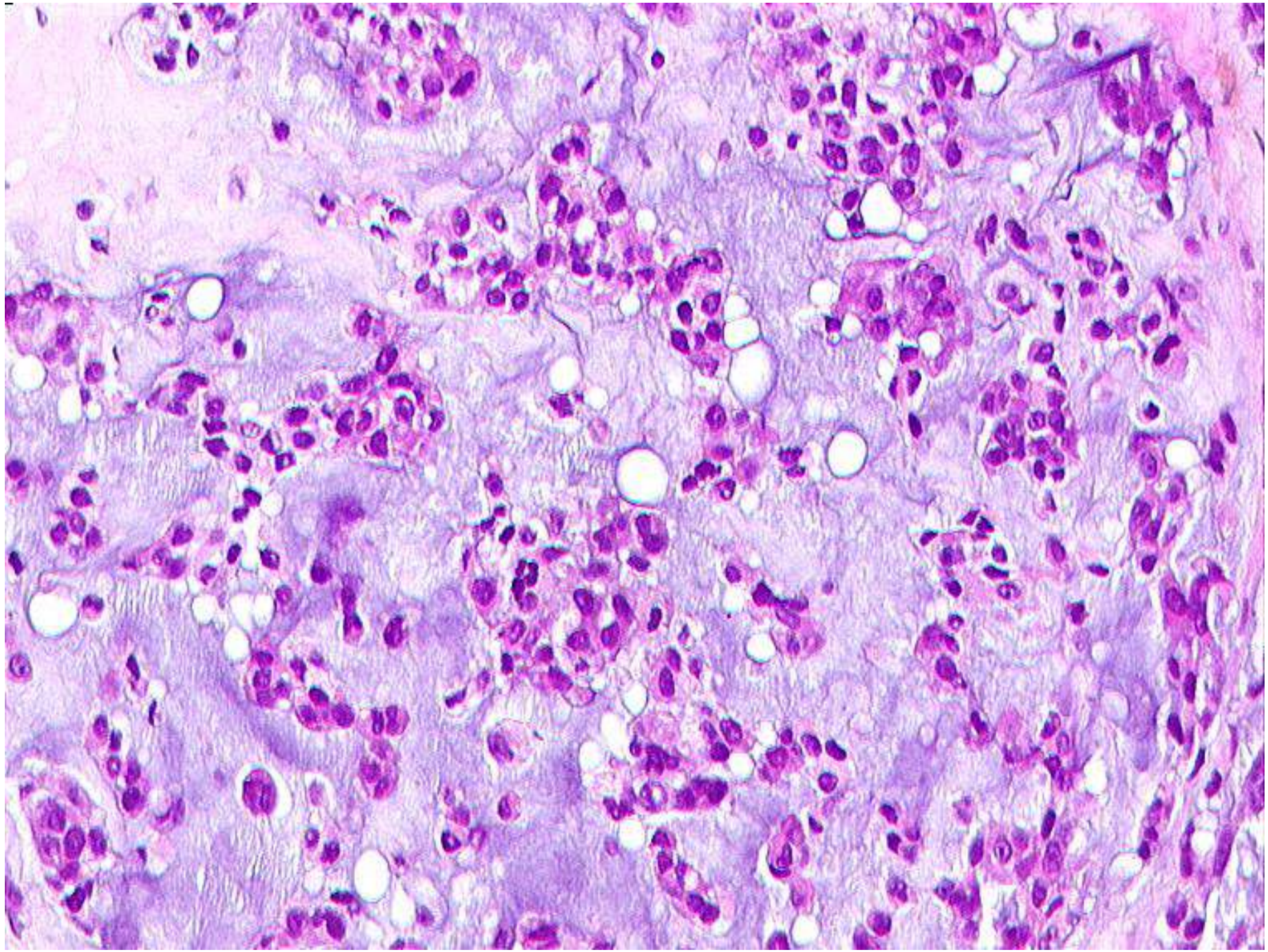
few blood vessels

prominent myxoid stroma

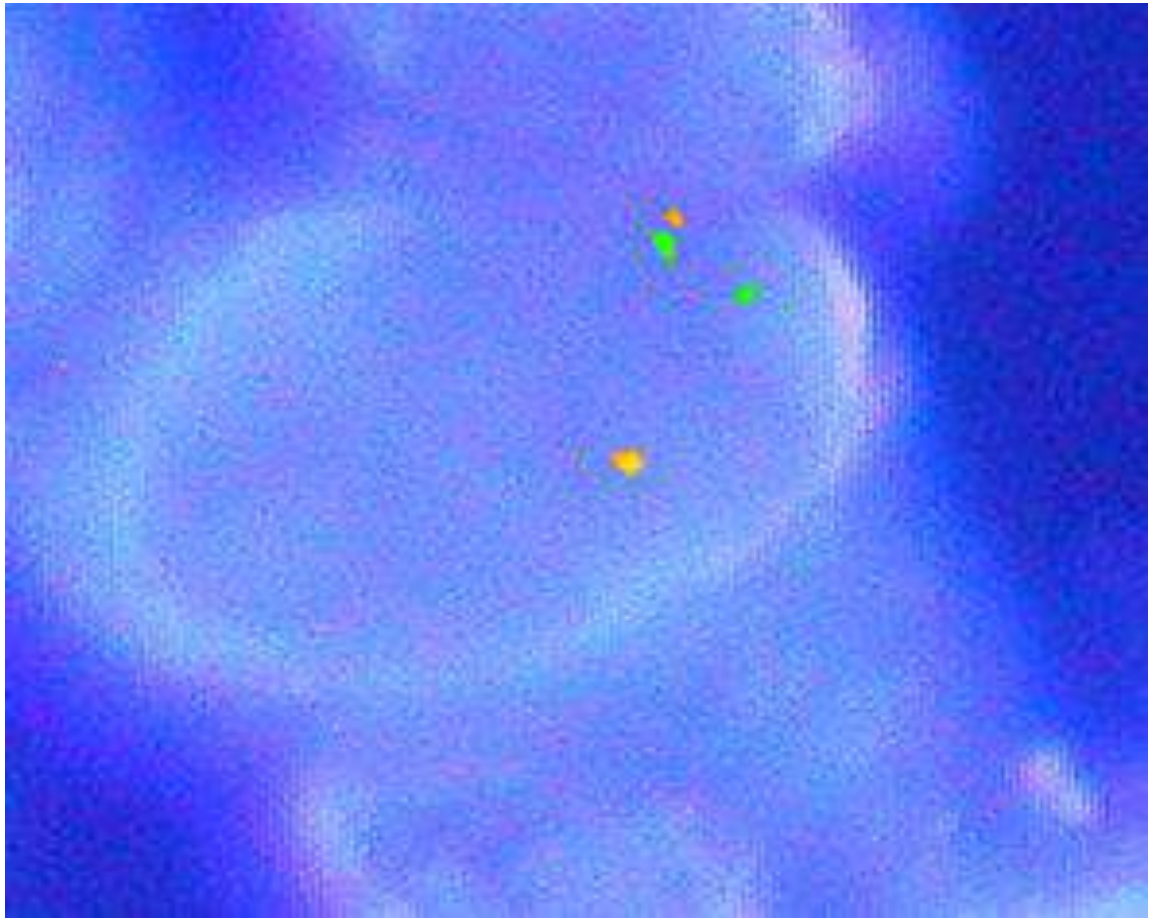
t(9;22)(q22;q12) >

t(9;17)(q22;q12)

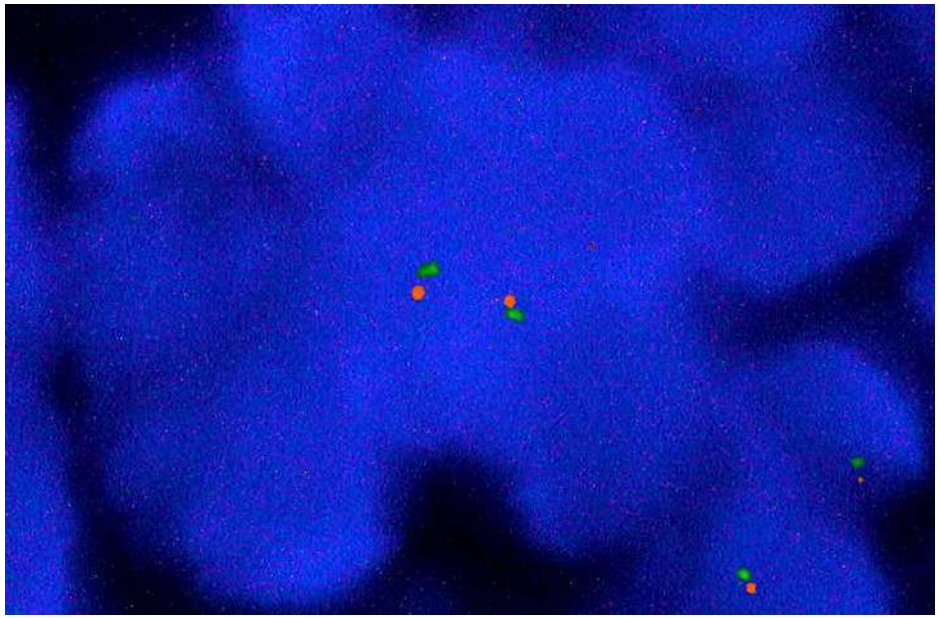




F, 46 years, thigh



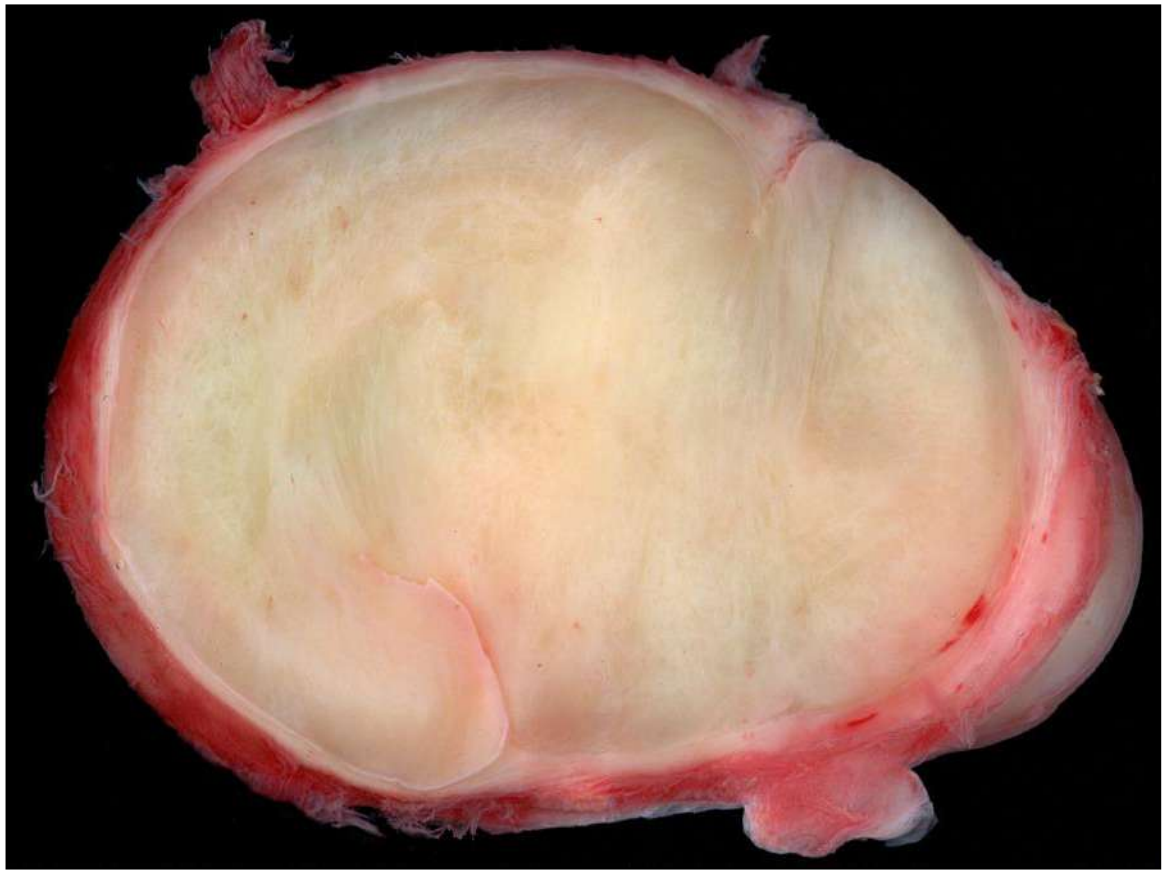
EWS break apart probe
positive in 31 of 50 nuclei

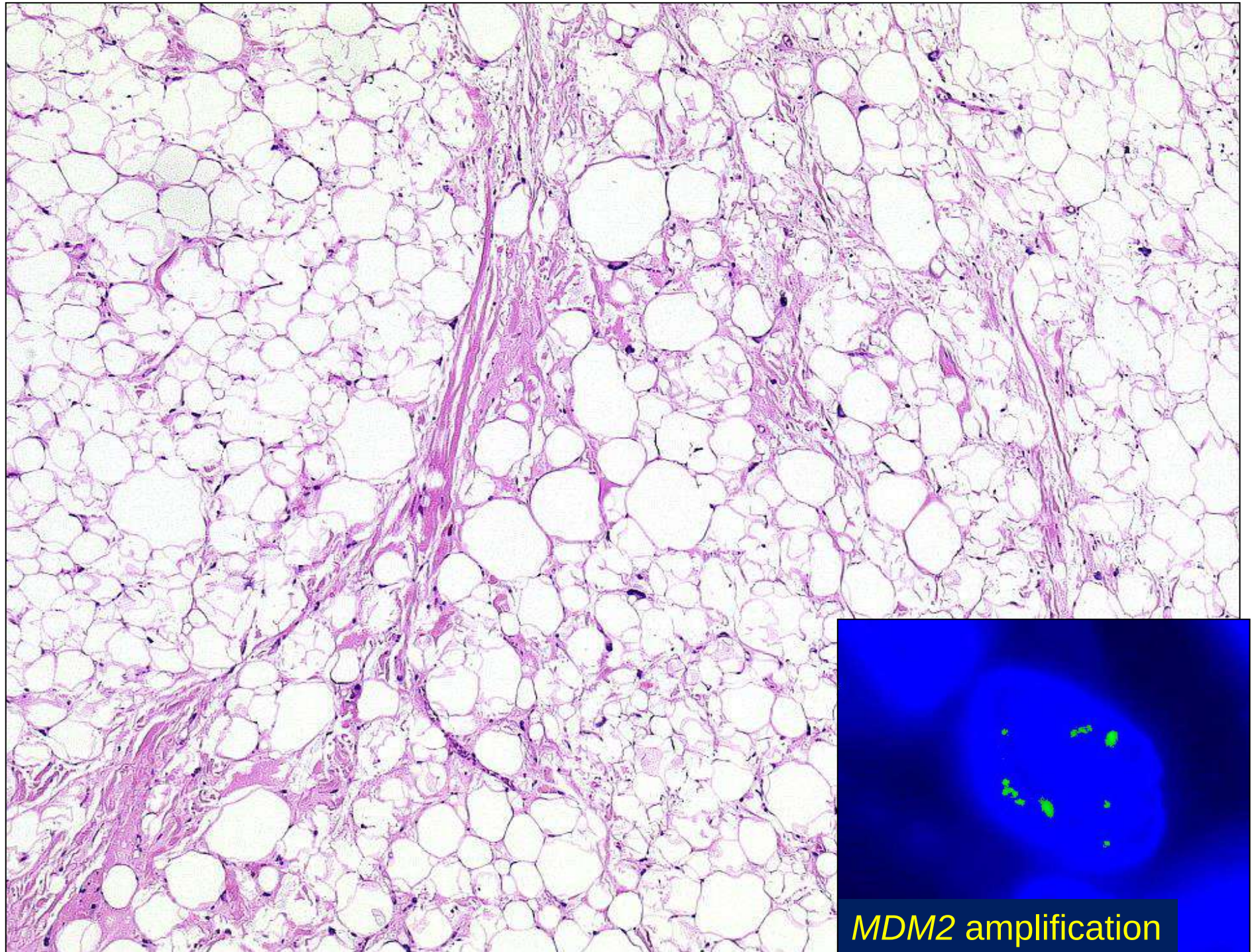


control

Differential diagnosis: chondroid Lipoma

atypical lipomatous Tumour
no lobular growth
no / few lipoblasts
enlarged, hyperchromatic nuclei
fibrous septa with atypical cells
MDM2 + / CDK +
MDM2 / *CDK4 a*mplification

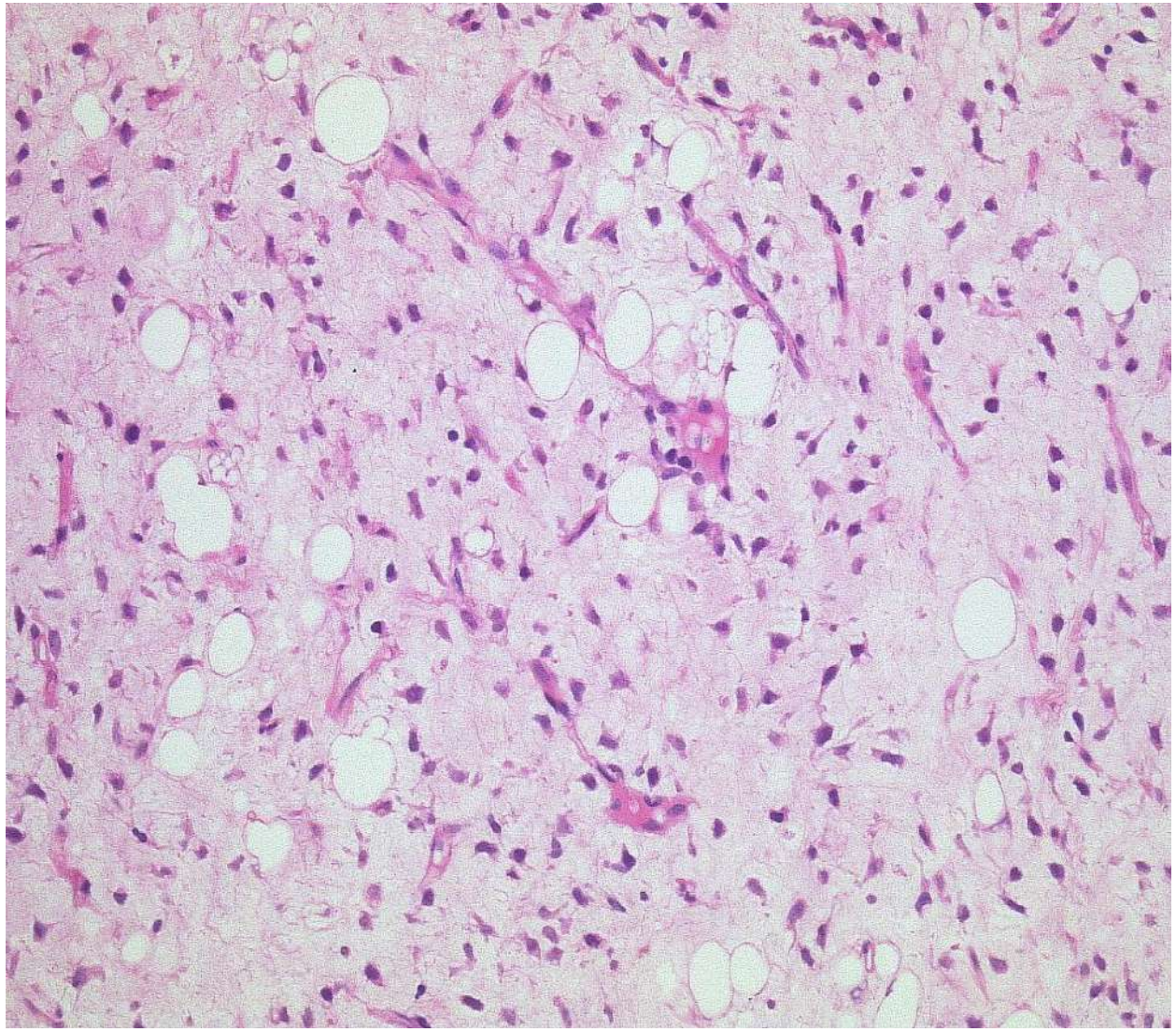



MDM2 amplification

Differential diagnosis: chondroid Lipoma

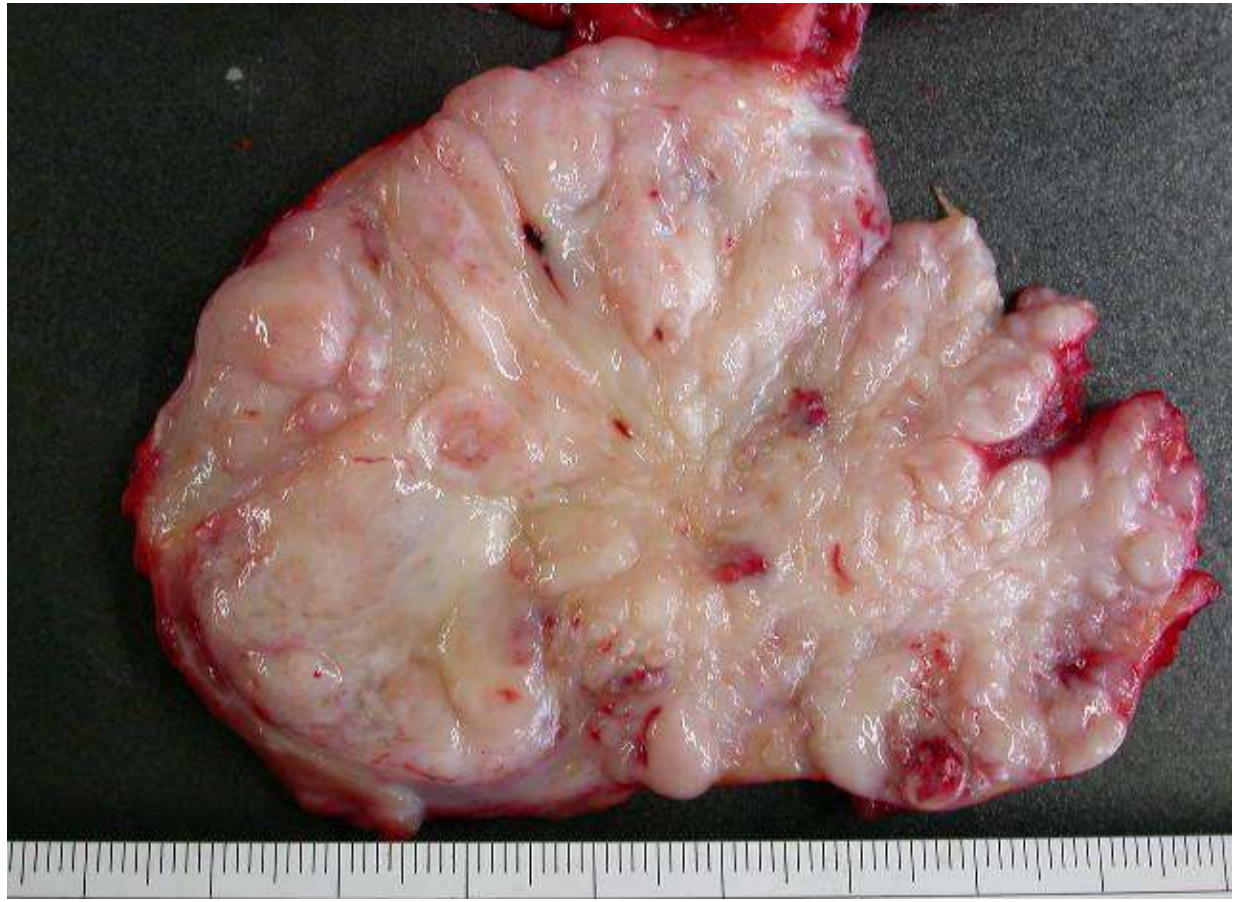
myxoid Liposarcoma

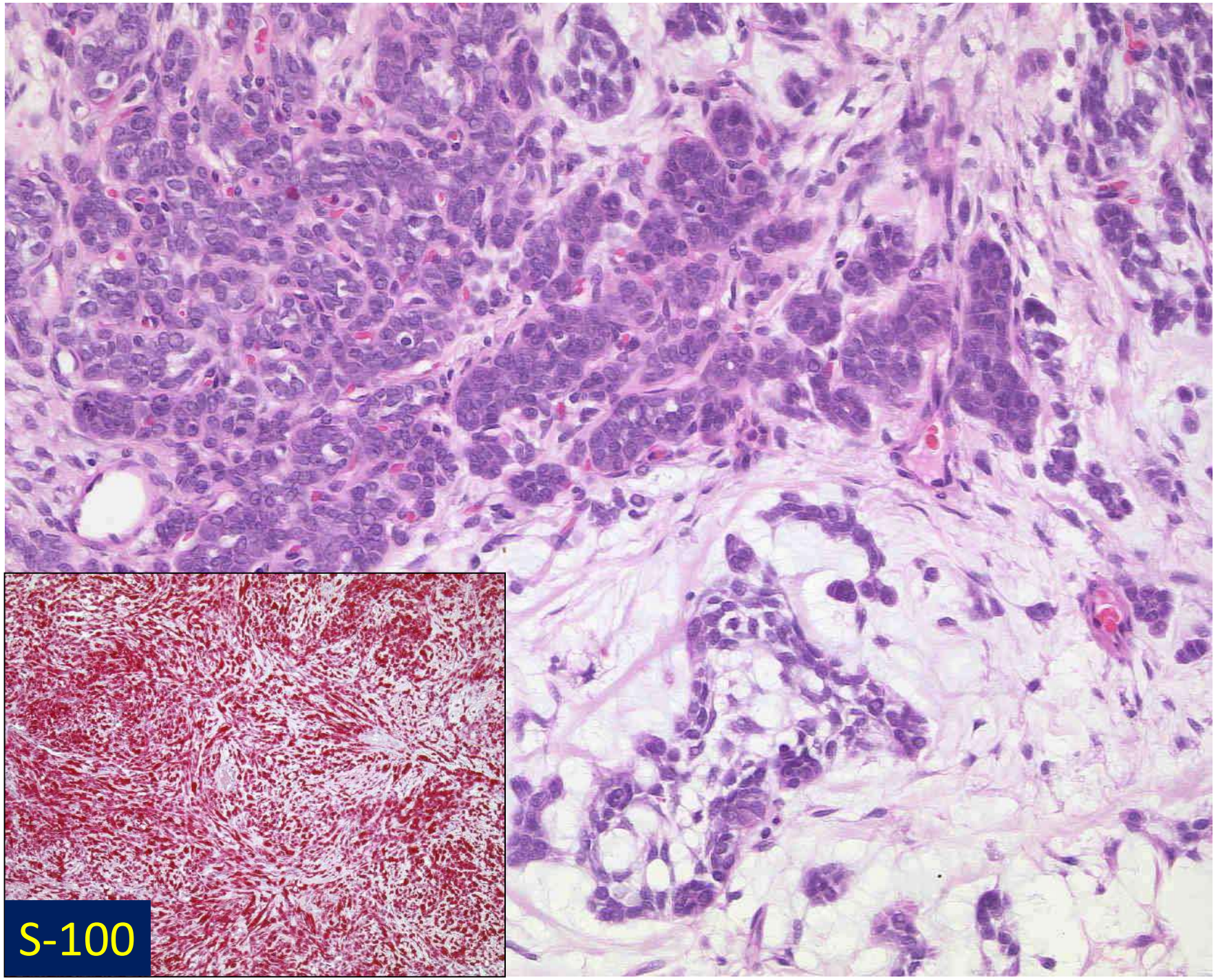
lipoblasts, small, uniform
  immature cells
thin branching vessels
myxoid stroma
  (Hyaluronidase sensitive)
t(12;16)(q13;p11)
  *DDIT3::FUS f*usion
t(12;22)(q13;q12)
  *DDIT3::EWSR1 f*usion



Differential diagnosis: chondroid Lipoma

Myoepithelioma
focal epithelial structures
no lipogenic cells
no eosinophilic, vacuolated cells
S-100 + (80%),
CK +/-, EMA +/-
GFAP +/-, ASMA +/-
Calponin +/-




S-100

Differential diagnosis: chondroid Lipoma

Hibernoma

Macro: yellow-brown

abundant eosinophilic cytoplasm

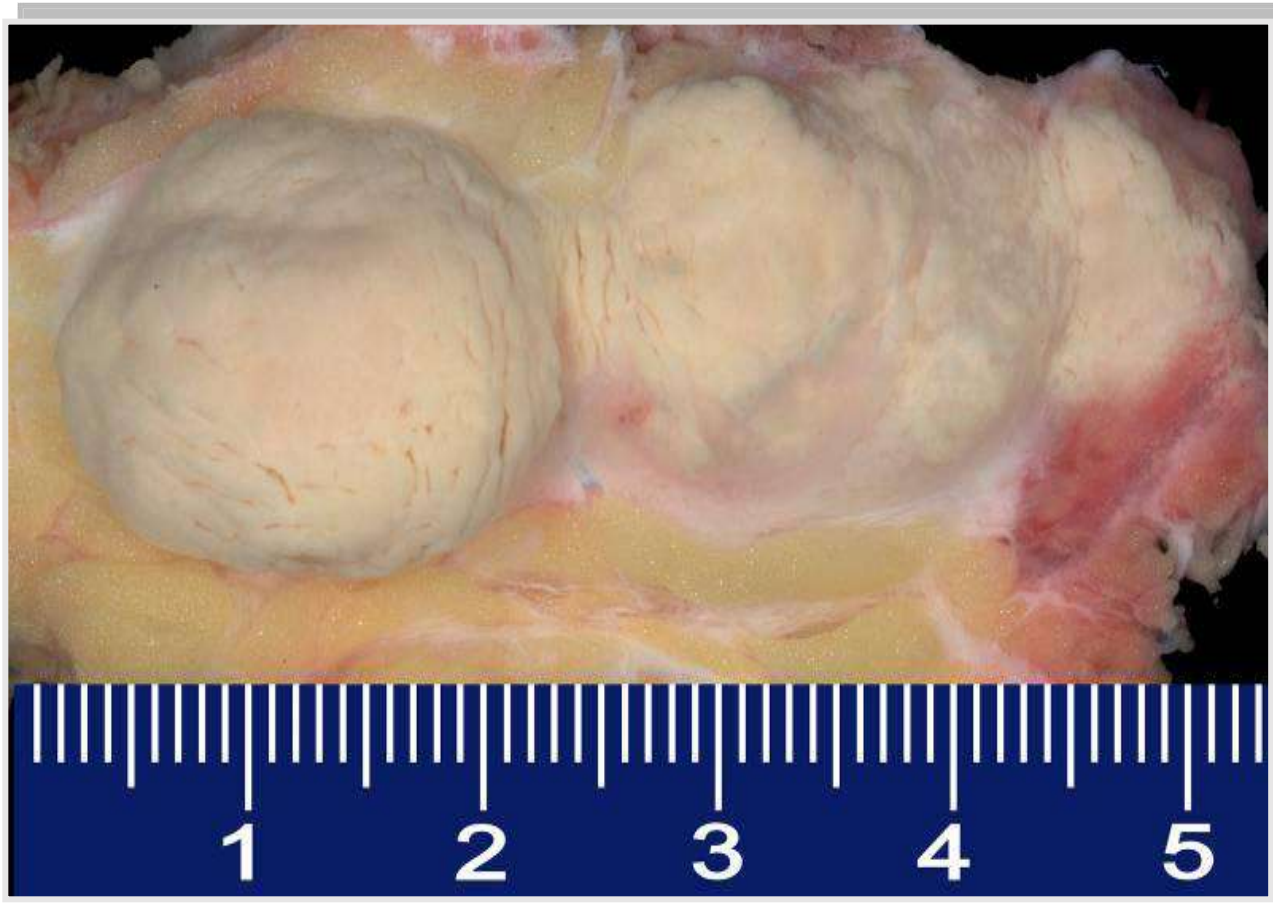
with vacuoles,

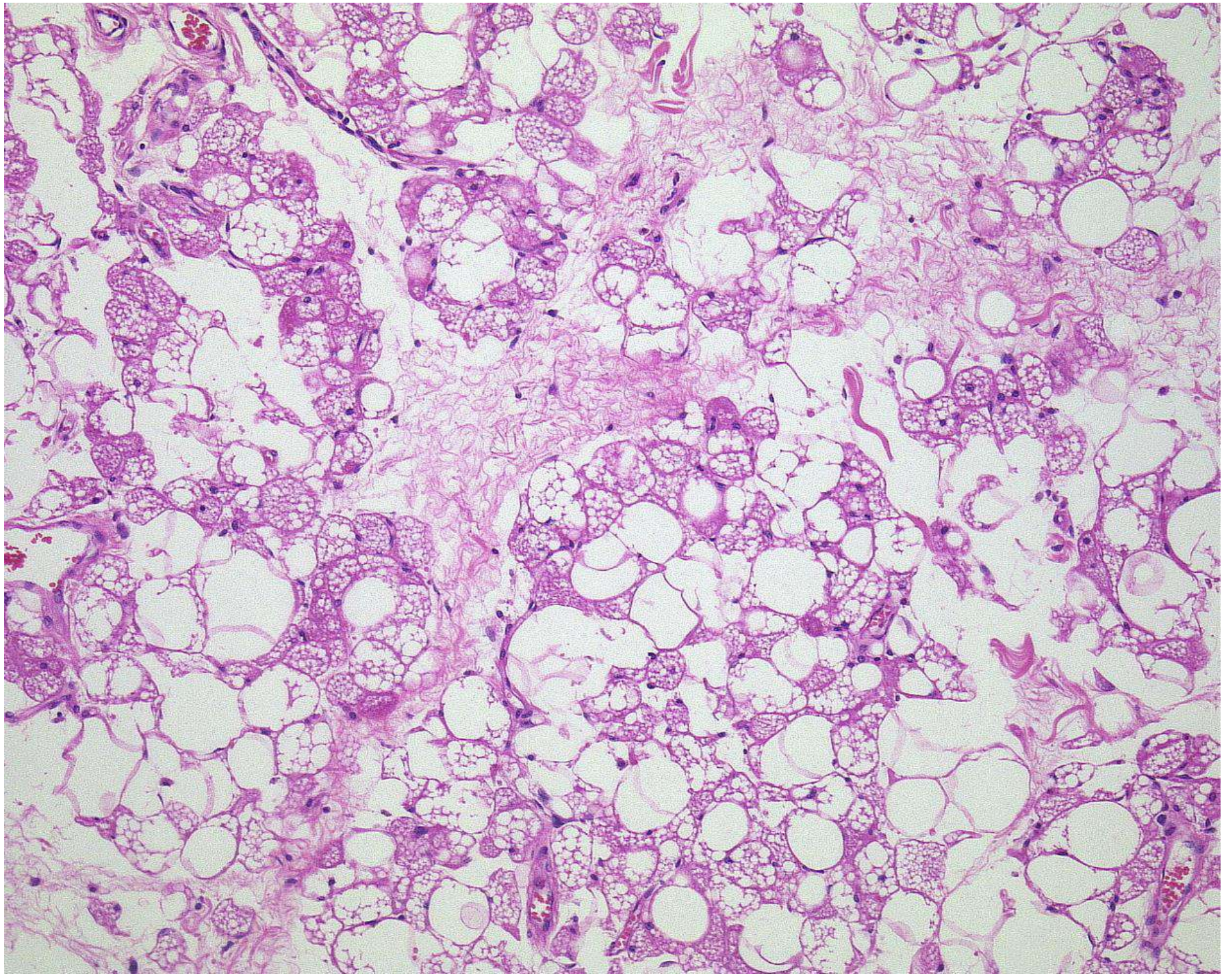
granular cytoplasm

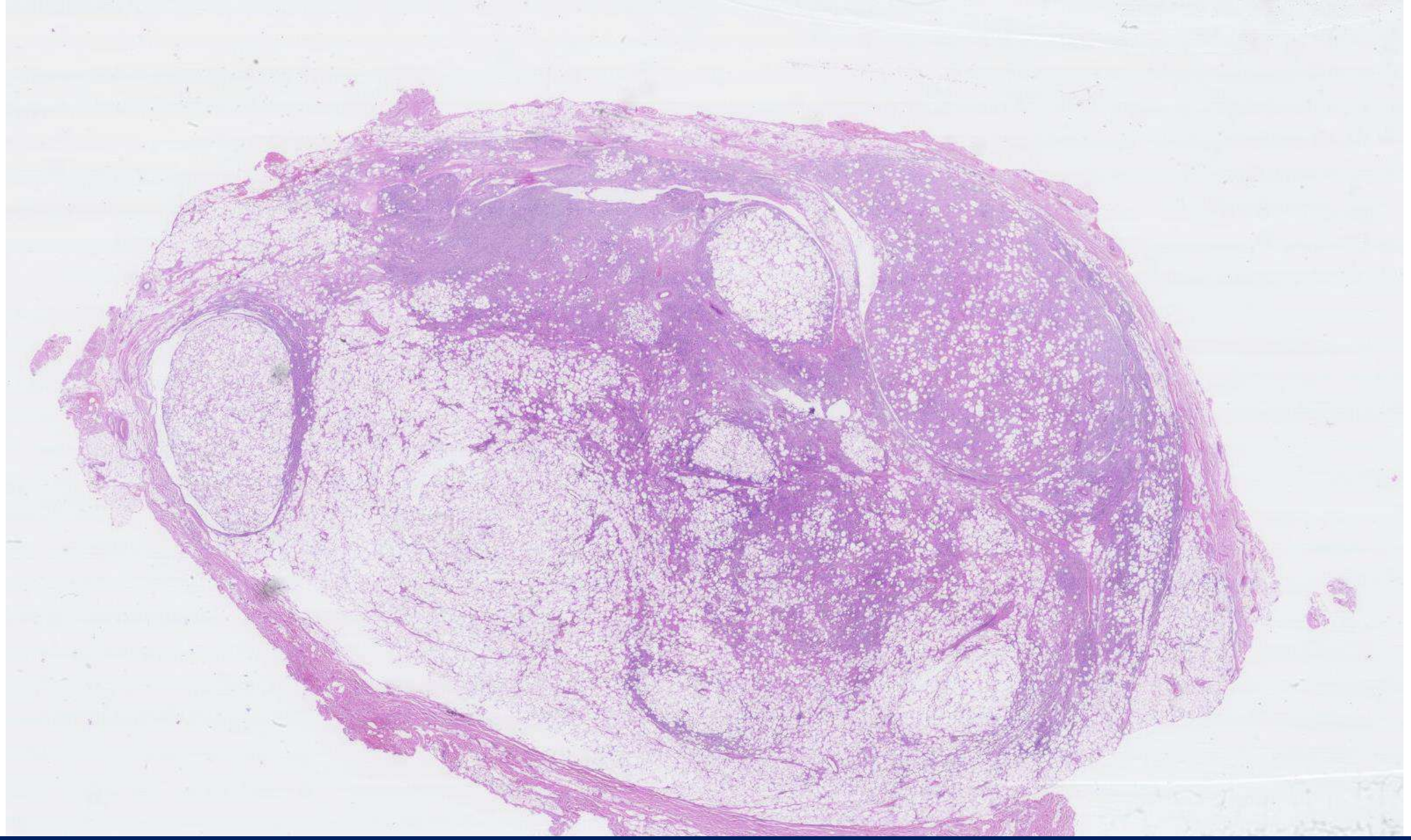
small nuclei

no myxochondroid stroma

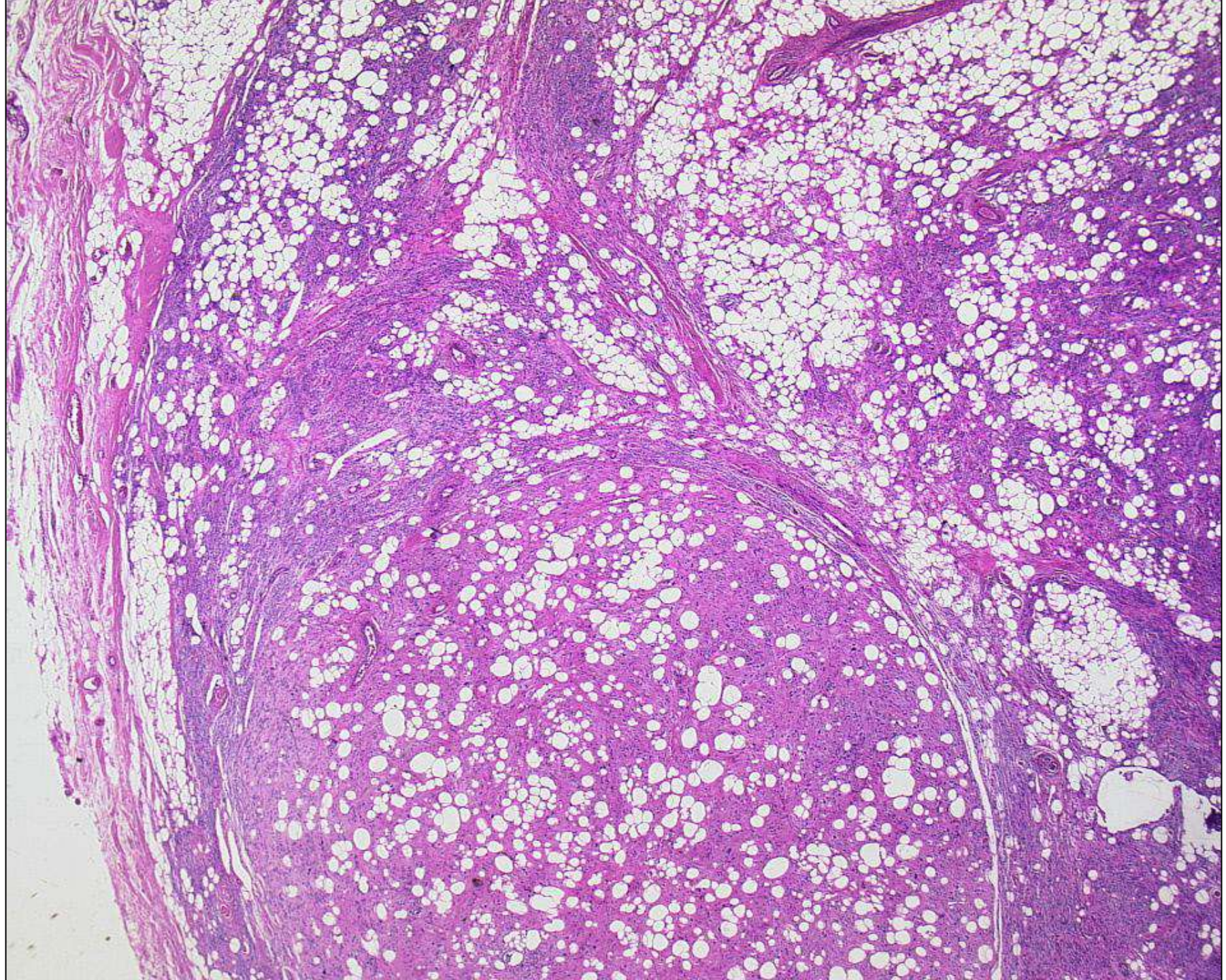
abundant mitochondria

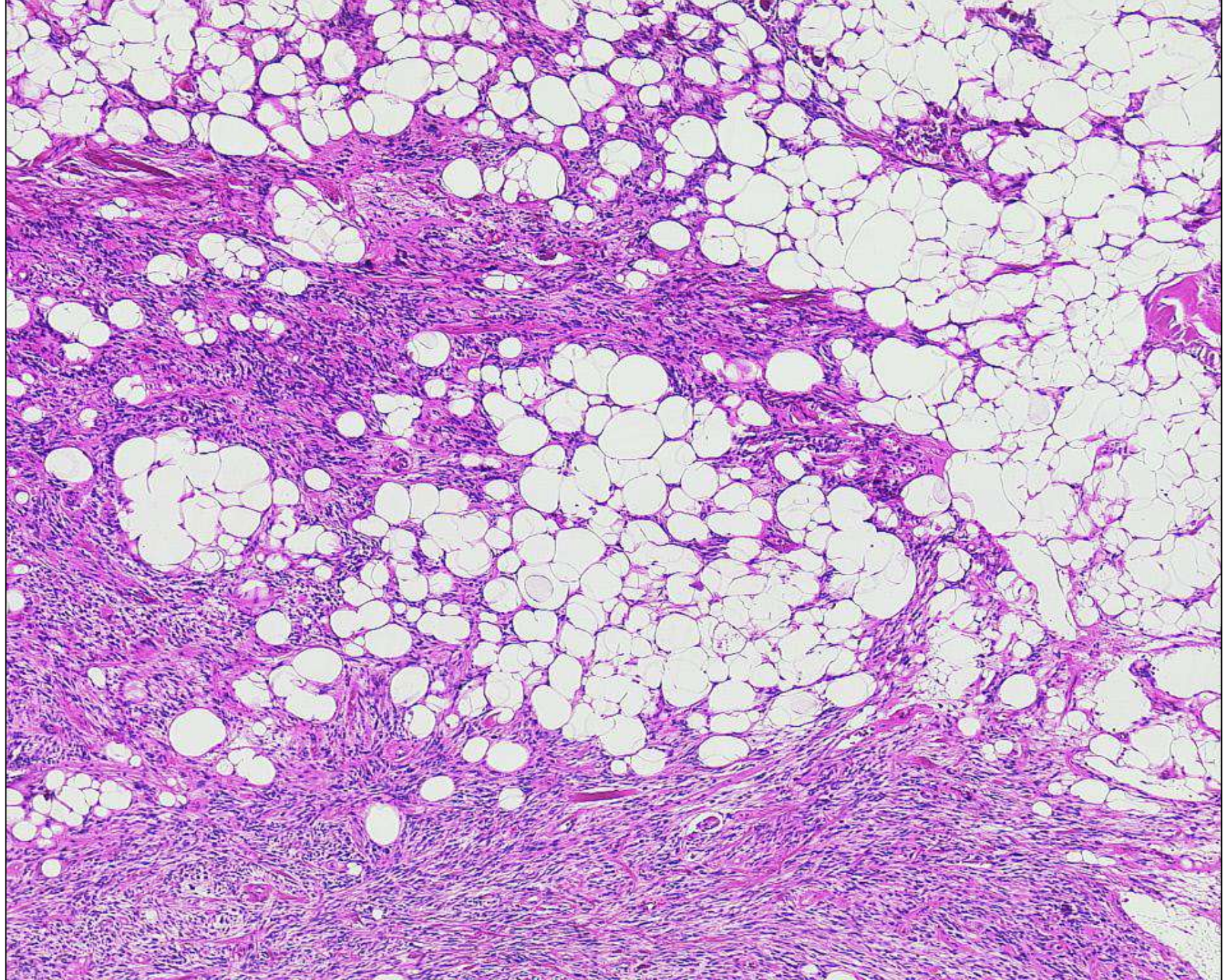


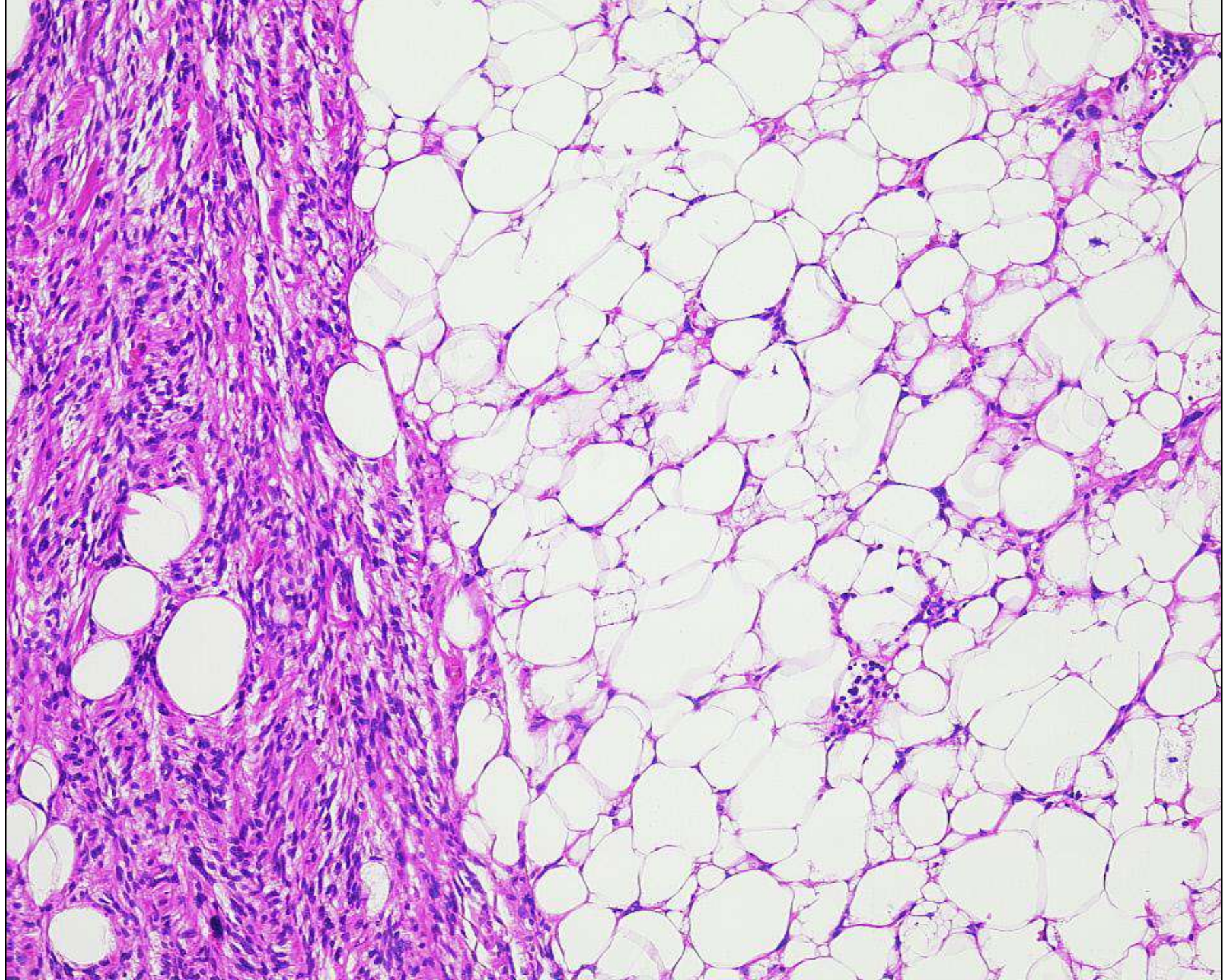


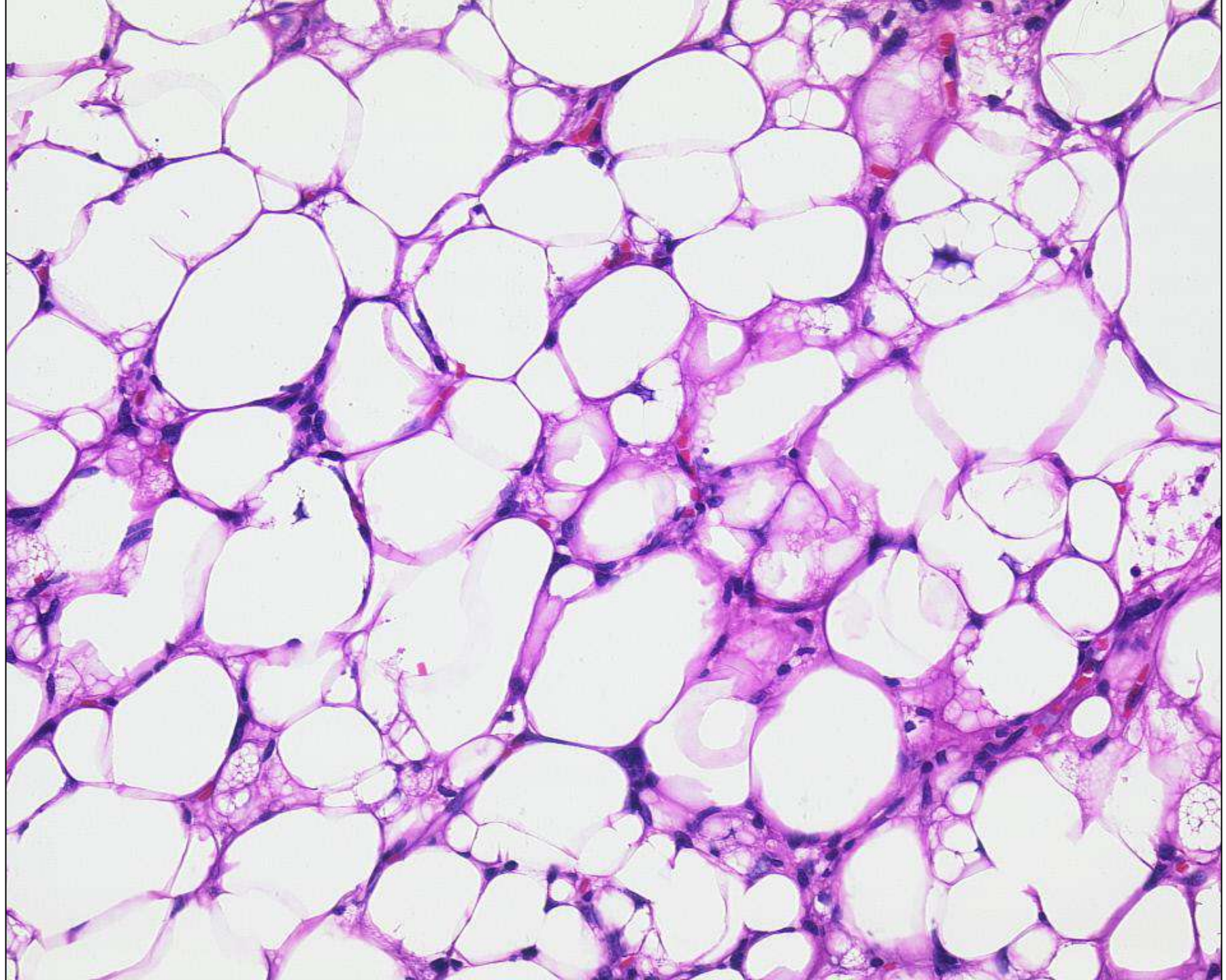


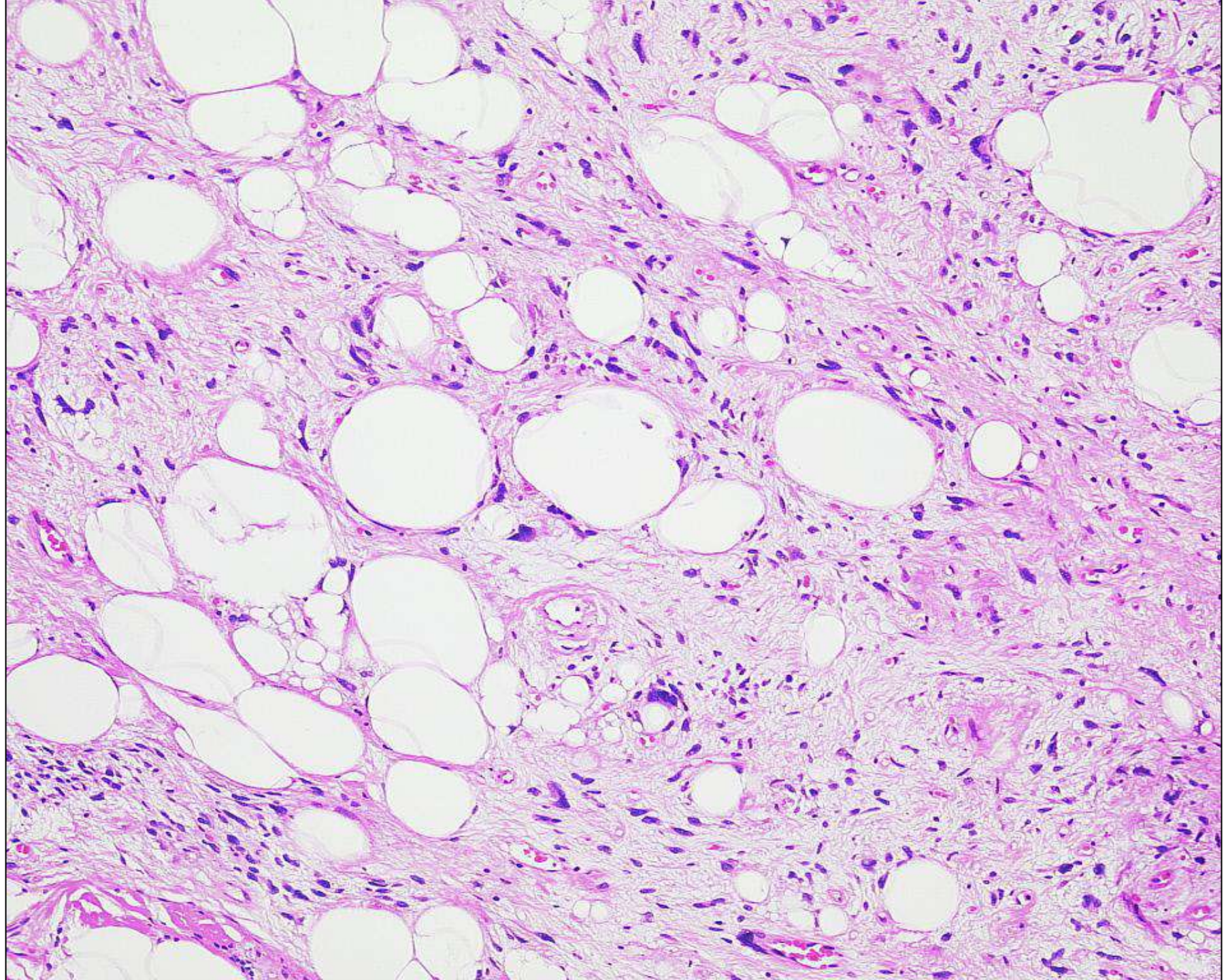
Case 12: M, 73 years, left shoulder, long standing, recently enlarging lesion

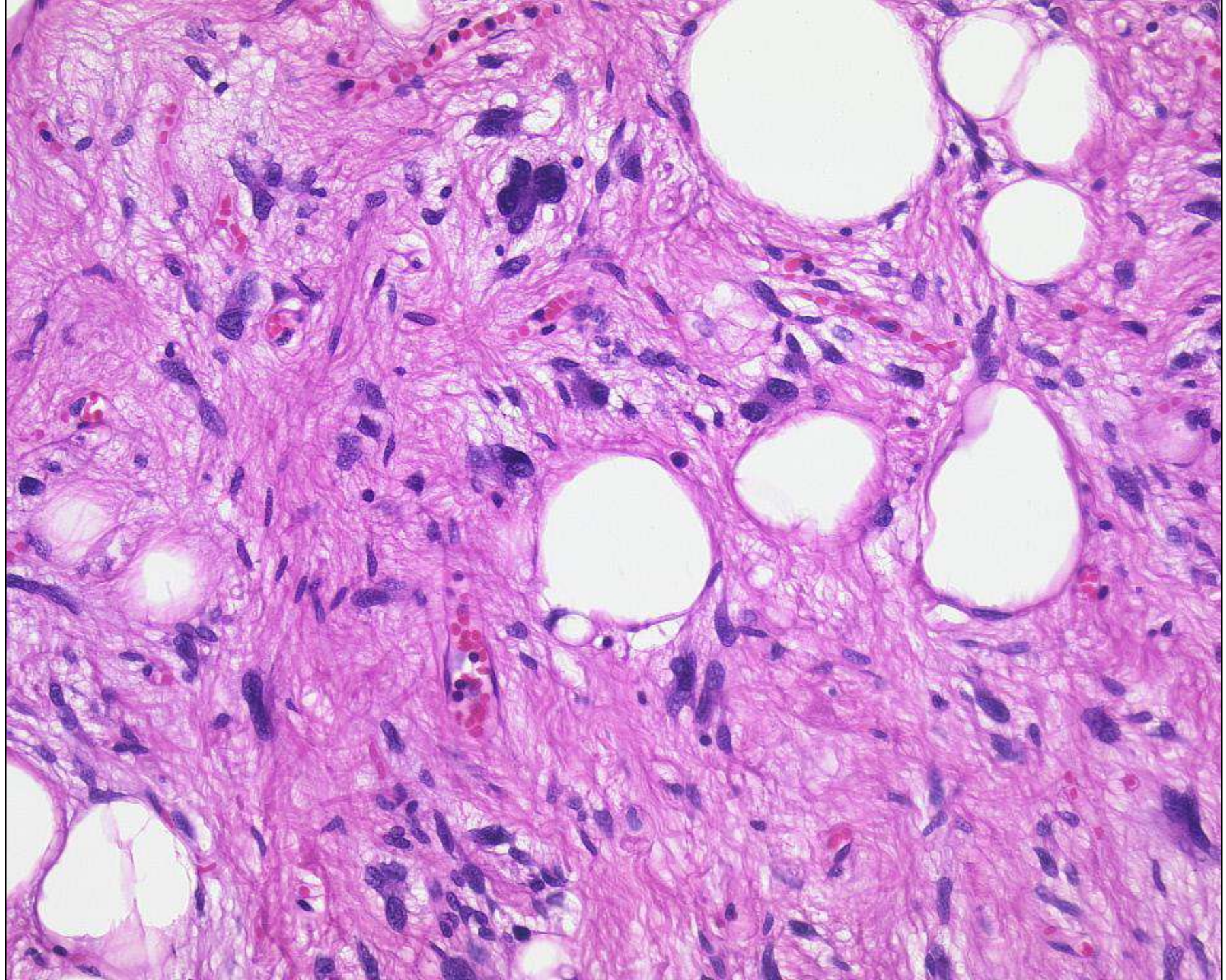


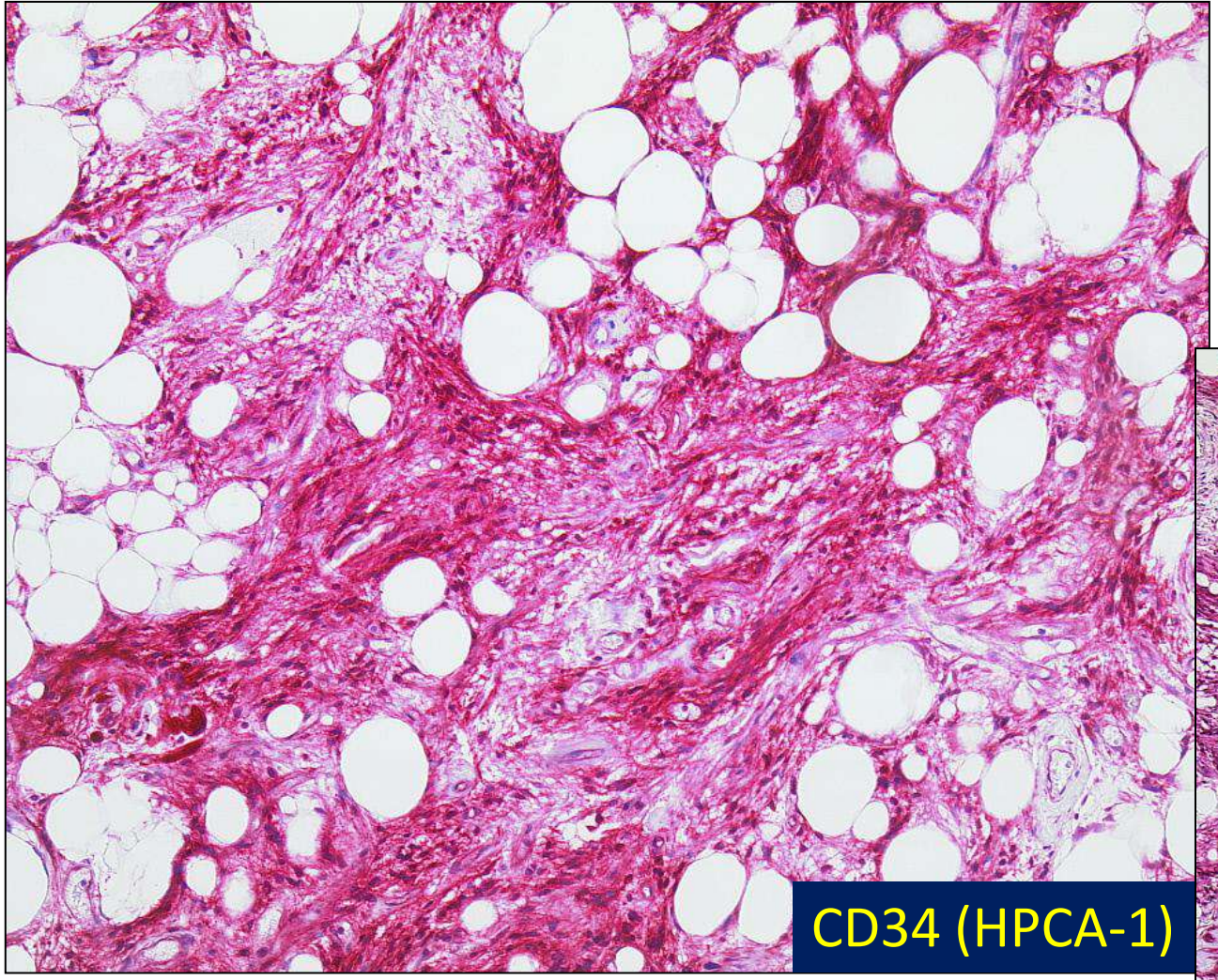


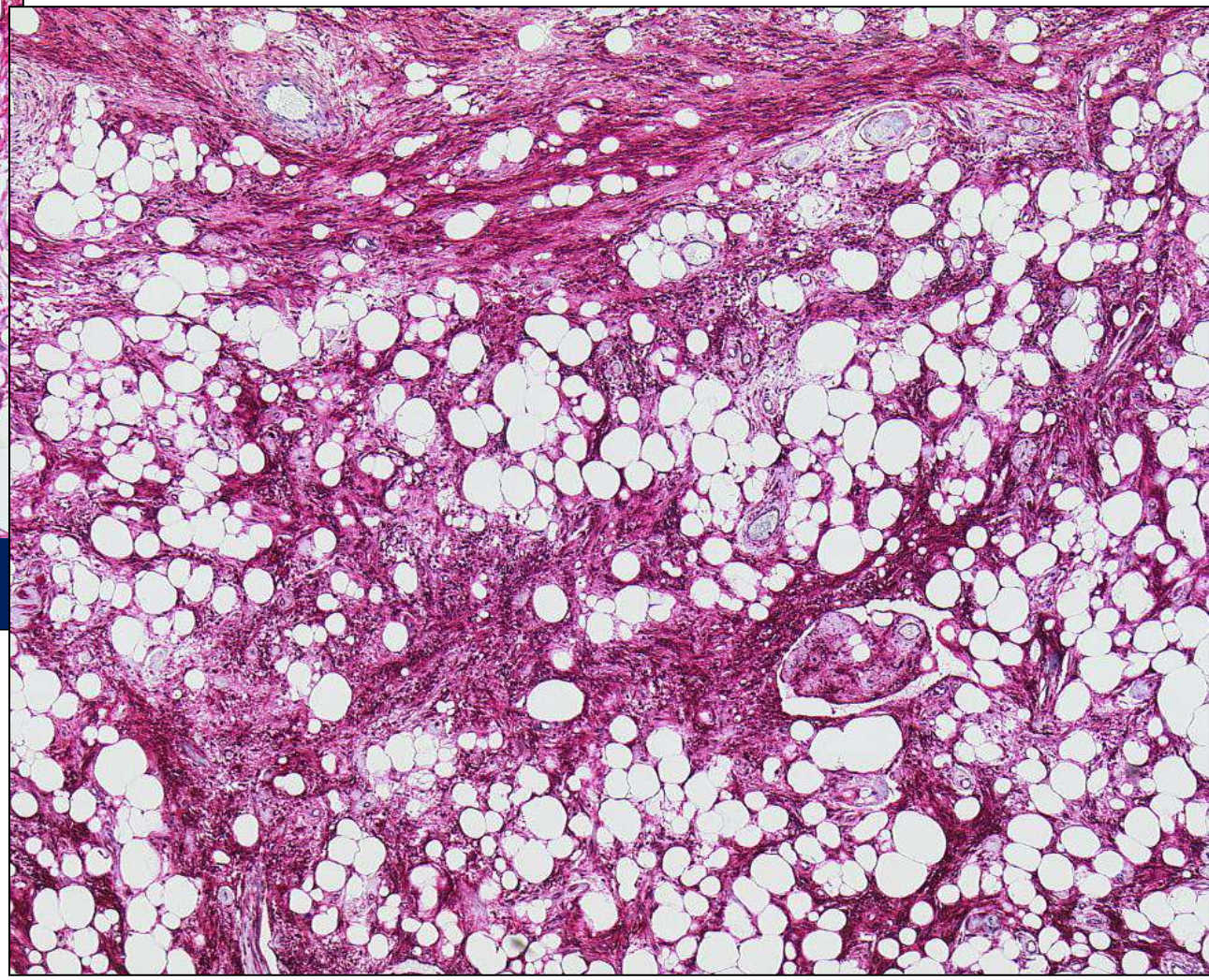


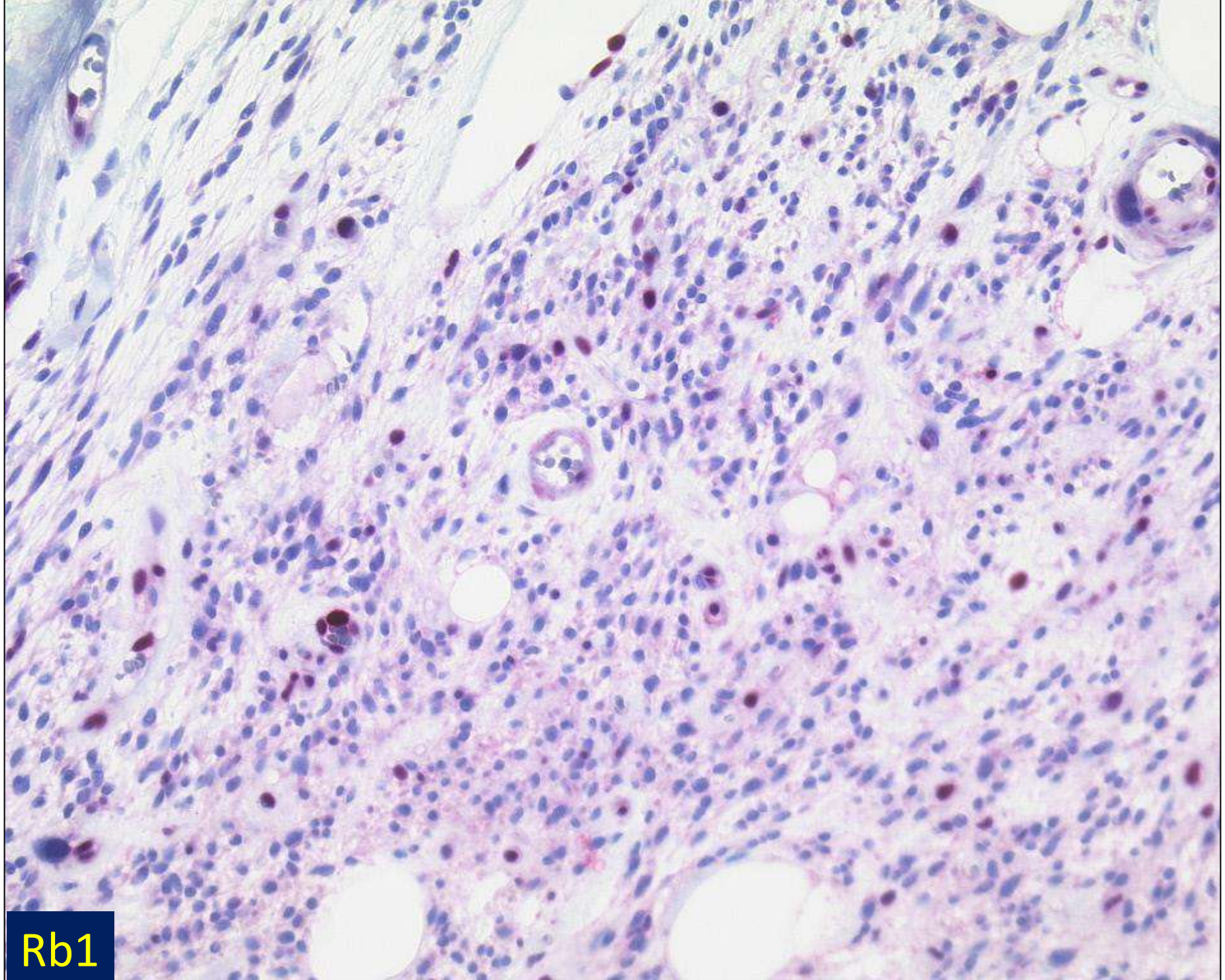


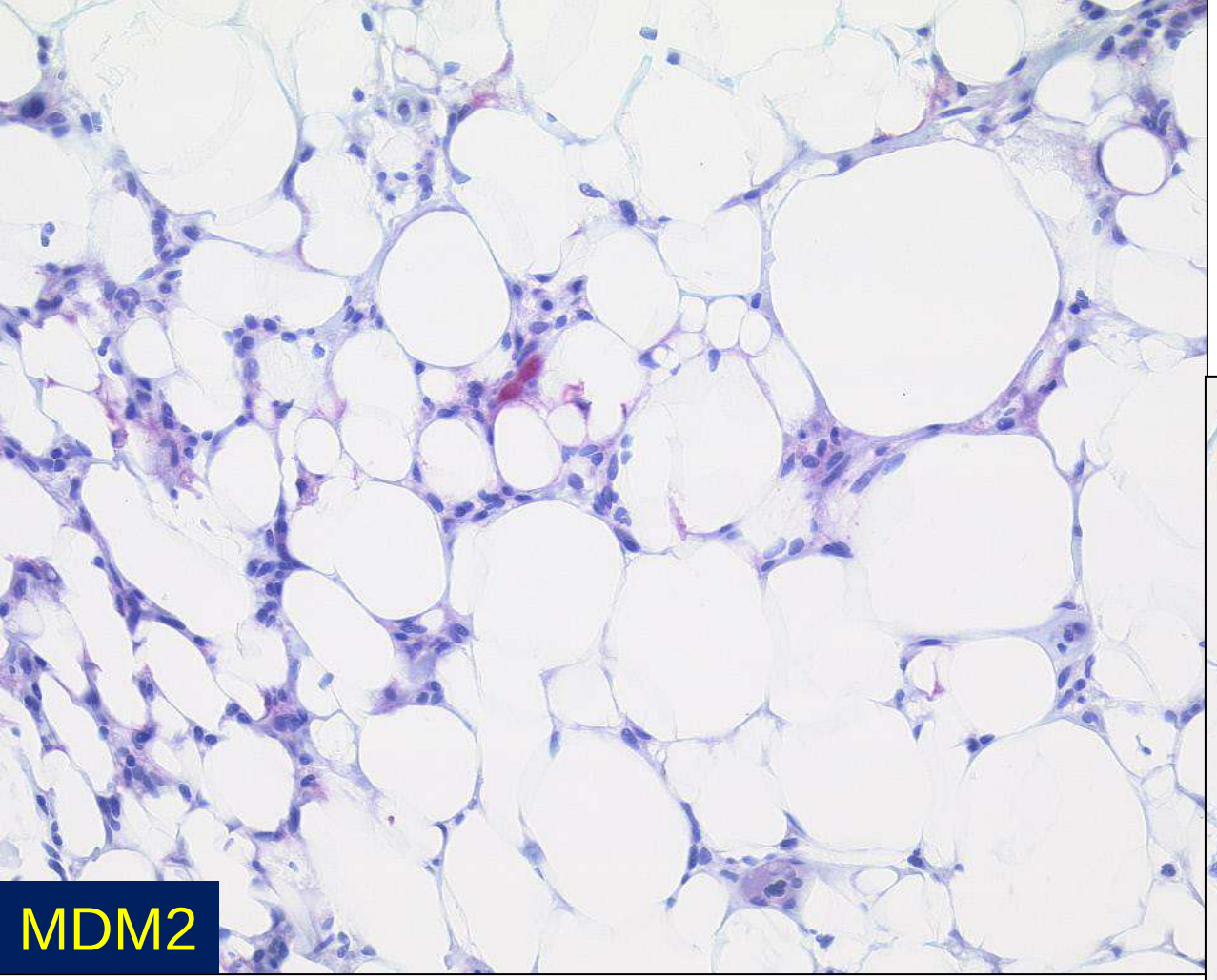


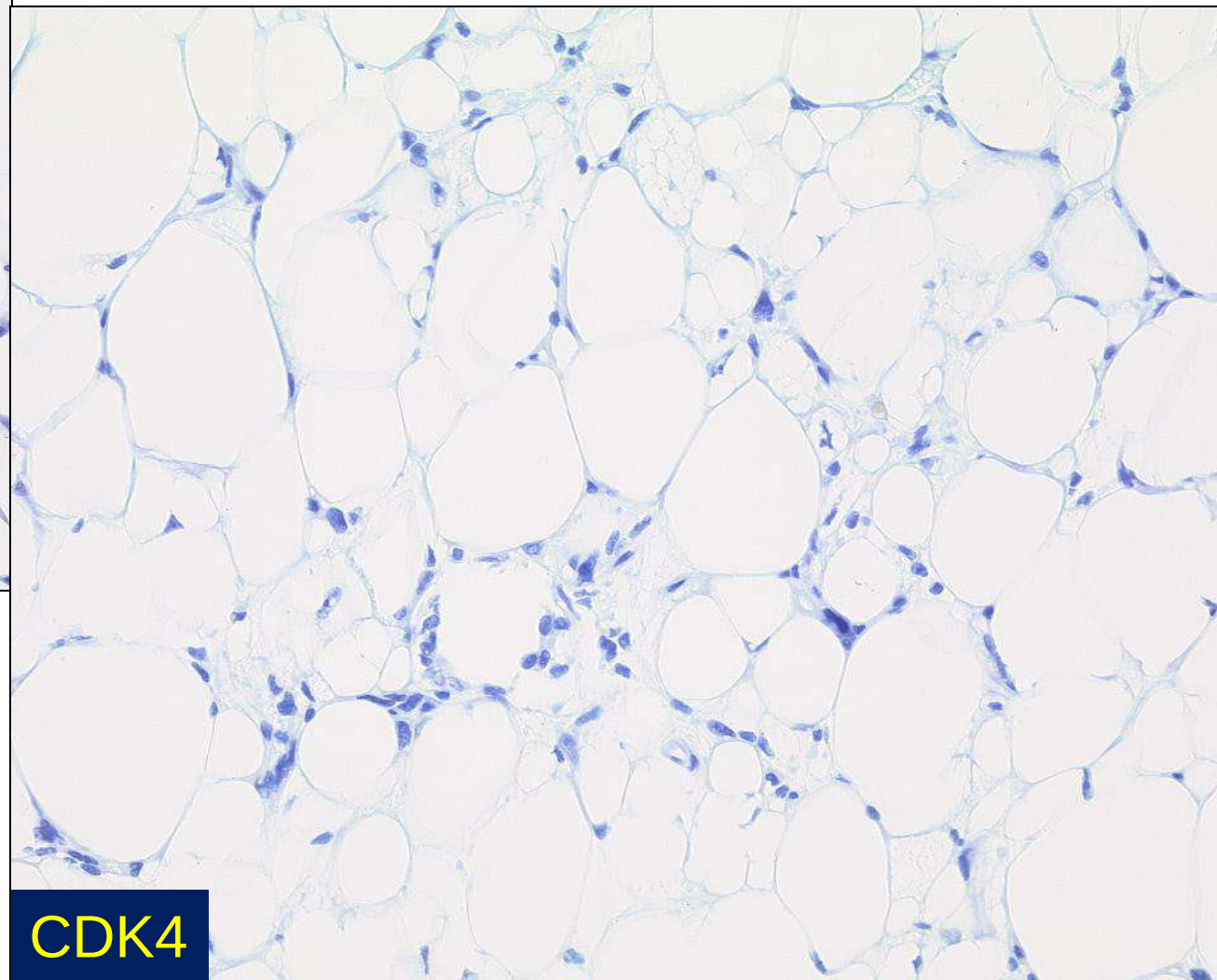


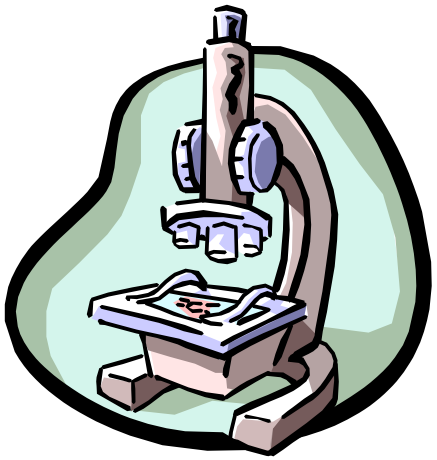

CD34 (HPCA-1)




Rb1


MDM2


CDK4



Diagnosis Case 12

atypical spindle cell lipomatous Tumour

The American Journal of Surgical Pathology 18(9): 913–921, 1994

Spindle Cell Liposarcoma, A Hitherto Unrecognized Variant of Liposarcoma

Analysis of Six Cases

Angelo P. Dei Tos, M.D., Thomas Mentzel, M.D., Paul T. Newman, M.R.C.Path., and Christopher D.M. Fletcher, M.D., M.R.C.Path.

A series of six cases of a previously unrecognized variant of liposarcoma characterized by a prominent spindle cell component is reported herein. Clinically, all of the tumors arose in adults and developed around the shoulder girdle or upper limbs; all but one arose in subcutaneous tissue. Three patients developed multiple local recurrences over a period of 4–20 years. Recurrences in one case were purely lipoma-like. Following dedifferentiation in a recurrence, one patient developed distant metastases and eventually died, 46 months after the primary excision. Grossly, these lesions are characterized by multinodularity, and microscopically they show a relatively bland spindle cell proliferation arranged in fascicles and whorls and set in a variably myxoid stroma. The spindle cell areas are accompanied by an adipocytic component, which exhibits the morphologic features required for inclusion in the well-differentiated liposarcoma–atypical lipoma group, including definite lipoblasts. Main differential diagnoses include benign lesions such as spindle cell lipoma and diffuse neurofibroma, as well as dermatofibrosarcoma protuberans and other malignancies such as sclerosing liposarcoma, low-grade myxofibrosarcoma, low-grade malignant peripheral nerve sheath tumor, and low-grade fibromyxoid sarcoma. In view of their distinctive histologic appearance, and because aggressive clinical behavior was observed despite their superficial location, we propose that these lesions be regarded as spindle cell variants of well-differentiated liposarcoma.

Key Words: Subcutaneous tissue—Spindle cell—Atypical lipoma—Liposarcoma—Sarcoma.

Am J Surg Pathol 18(9): 913–921, 1994.

Classification of lipomatous tumors has been a source of controversy in recent years, particularly with regard to the well-differentiated liposarcoma–atypical lipoma group—i.e., tumors with definite features of well-differentiated liposarcoma arising in surgically amenable soft tissue or adipocytic tumors arising deep to fascia which lack lipoblasts but show atypical stromal cells and variations in adipocyte size (11).

Long-term follow-up studies have shown that location and depth of the primary lesion are key parameters in the prediction of clinical behavior. Differentiated adipocytic neoplasms located in subcutaneous tissue generally do not recur, while those in deep soft tissue of the extremities may recur locally; however, formerly they had been said not to dedifferentiate and thus were believed not to give rise to distant metastases or disease-related deaths (3,7,9). For these reasons, it was suggested that the term *well-differentiated liposarcoma* be dropped and that such lesions in the limbs be called *atypical lipoma*. However, it has been demonstrated (17) that deep-seated differentiated fatty tumors of the extremities are capable of undergoing dedifferentiation and therefore of acquiring life-threatening potential. Weiss and Rao (17) thus preferred retention of the term *well-differentiated liposarcoma* for those lesions arising in the deep soft tissue of an extremity, while the denomination *atypical lipoma* was regarded by those authors as acceptable for histologically identical lesions arising in the subcutaneous fat.

We herein present a series of six cases of a previously unrecognized variant of liposarcoma, characterized histologically by spindled morphology of most of the proliferating cells and clinically by prevalent occurrence in subcutaneous tissue. In view of its distinctive histologic appearance and the clinical behavior observed, we suggest that this is a *spindle cell variant of well-differentiated liposarcoma*.

From the Soft Tissue Tumour Unit (A.P.D.T., C.D.M.F.), Department of Histopathology, St. Thomas's Hospital (U.M.D.S., London, U.K.; Department of Pathology (A.P.D.T.), Ospedale di Conegliano Veneto, Conegliano Veneto, Italy; and Pathology Department (P.T.N.), Memorial Hospital, Darlington, U.K.

Address correspondence and reprint requests to Dr. C.D.M. Fletcher, Soft Tissue Tumour Unit, Department of Histopathology, St. Thomas's Hospital, London SE1 7EH, U.K.

6 cases, 2 F, 4 M
35-82 years, 2-25 cm
shoulder (3), arm (2), back (1)
subcutis (5), intramuscular
multiple recurrences (3)
dedifferentiation, MTS (1)
spindle cells with mild to moderate atypia + atypical lipogenic component
desmin focal + (5)
CD34 focal + (2)

Letters to the Editor (AJSP 1995; 19: 604-607)

„It is obvious that Dei Tos et al. are not aware of Hajdu´s description of fibroblastic liposarcoma … 15 years ago“ (SA Hoda)

„…Steven Hajdu showed us liposarcomas with spindle cell features similar to those depicted in the recent article. In fact, he coined the term „fibroblastic liposarcoma“… I am amazed that Dei Tos et al. ignored the previous description and illustrations of spindle cell liposarcoma“ (WO Russell)

„In 1976 and again in 1979, Hajdu proposed the term fibroblastic liposarcoma… Spindle cell liposarcoma is not a new type of liposarcoma, and the article by Dei Tos et al. should serve as a confirmation and validation of Hajdu´s studies and classification of liposarcoma“ (C Urmacher)

„Such liposarcomas have been previously well illustrated and commented upon in the literature… morphologic spectrum of spindle cell liposarcoma ranging from well-differentiated cases closely resembling spindle cell lipoma … to high-grade fibrosarcoma-like variants“ (LG Kindblom)

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Pathology of Soft Tissue Tumors

LEA & FEBIGER PHILADELPHIA

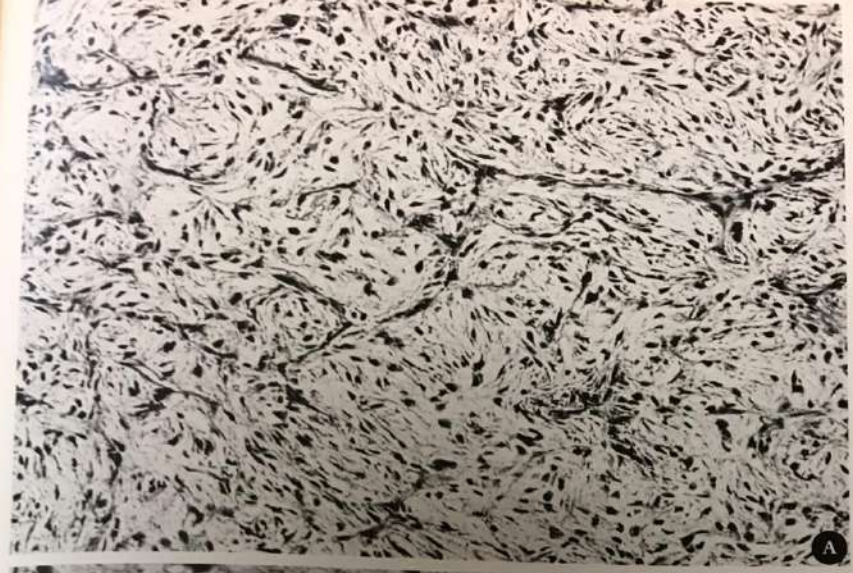

Figure 4-37. Fibroblastic liposarcoma. Note the complete obstruction of the space between capillary vessels by slender fibroblastic cells (prolipoblasts). The arranged pattern of these cells resembles the storiform pattern commonly seen in fibroblastic fibrous histiocytomas (see Figure 2-24) and certain neurogenic tumors (see Figure 7-24). However, the linear or cross-link type of capillary network is distinctly that associated with liposarcomas, e.g., myxoid liposarcoma (see Figures 4-28 and 4-29).

B, The intimate relationship between capillary vessels and individual tumor cells is so unique that one cannot rule out possible histogenetic connection between capillaries and tumor cells (**A**, H & E, ×140; **B**, H & E, ×350).

Author´s Reply

„It was simply for reasons of tact that we did not quote them, since none of Dr.Hajdu´s description provide a clearly illustrated means of diagnosing these lesions. The majority of the illustrations… look remarkably like myxofibrosarcoma (myxoid MFH) of intermediate or high grade. Readers might also like to note that the existence of fibroblastic liposarcoma is not accepted in either the standard textbook of soft tissue tumors or in the recently published WHO-classification.“
(CDM Fletcher)

Nascimento AF, Fletcher CDM
Spindle cell liposarcoma/atypical lipomatous Tumor. A clinicopathologic study of 120 cases.
Mod Pathol 2005; 18: 70A

locally aggressive neoplasm, may recur
no metastases, dedifferentiation very rarely
atypical lipogenic cells +
slightly atypical spindled cells

BUT

no *MDM2/CDK* amplification !

Modern Pathology (2010) 23, 729–738

Well-differentiated spindle cell liposarcoma ('atypical spindle cell lipomatous tumor') does not belong to the spectrum of atypical lipomatous tumor but has a close relationship to spindle cell lipoma: clinicopathologic, immunohistochemical, and molecular analysis of six cases

Thomas Mentzel[1], Gabriele Palmedo[2] and Cornelius Kutzner[2]

[1]Dermatopathologie, Friedrichshafen, Germany and [2]Institute of Pathology, Medical Center, Münster, Germany

Well-differentiated spindle cell liposarcoma represents a rare atypical/low-grade malignant lipogenic neoplasm that has been regarded as a variant of atypical lipomatous tumor. However, well-differentiated spindle cell liposarcoma tends to occur in subcutaneous tissue of the extremities, the trunk, and the head and neck region, contains slightly atypical spindled tumor cells often staining positively for CD34, and lacks an amplification of *MDM2* and/or *CDK4*. In most of the cases analyzed. We studied a series of well-differentiated spindle cell liposarcomas arising in two female and four male patients (age of the patients ranged from 59 to 85 years). The neoplasms arose on the shoulder, the chest wall, the thigh, the lower leg, the back of the hand, and in paratesticular location. The size of the neoplasms ranged from 1.5 to 10 cm (mean: 6.0 cm). All neoplasms were completely excised. The neoplasms were confined to the subcutis in three cases, and in three cases, an infiltration of skeletal muscle was seen. Histologically, the variably cellular neoplasms were composed of atypical lipogenic cells showing variations in size and shape, and spindled tumor cells with slightly enlarged, often hyperchromatic nuclei. Multivacuolated lipoblasts were present in three neoplasms. Focal myxoid stromal changes were seen in three cases. Immunohistochemically, CD34 was at least focally positive in all cases, whereas scattered tumor cells only showed a nuclear expression of MDM2 in two neoplasms. FISH analysis revealed a deletion of the *Rb-1* gene in all six cases, whereas no *MDM2/CDK4* amplification was identified in all cases tested. Follow-up information was available in four cases (range from 4 to 24 months), and revealed a local recurrence in one case. Although well-differentiated spindle cell liposarcoma and atypical lipomatous tumor behave clinically similar, it can be speculated on the basis of clinicopathologic and molecular findings that well-differentiated spindle cell liposarcoma may constitute an independent entity rather than a morphologic variant of atypical lipomatous tumor, and may represent the atypical/low-grade counterpart of spindle cell lipoma.
Modern Pathology (2010) **23**, 729–738; doi:10.1038/modpathol.2010.66; published online 12 March 2010

Keywords: liposarcoma; atypical lipomatous tumor; spindle cell liposarcoma; spindle cell lipoma; immunohistochemistry; cytogenetics

Atypical and malignant lipogenic neoplasms represent the most common soft tissue sarcoma in adults, accounting for approximately 20% of all sarcomas. Liposarcoma is currently subclassified into five main subtypes, including atypical lipomatous tumor/well-differentiated liposarcoma, dedifferentiated liposarcoma, myxoid liposarcoma,

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2 F, 4 M, 59-85 years
shoulder, trunk, thigh,
lower leg, hand, paratesticular
1 out of 4 cases recurred
1.5-10 cm, subcutis (3)
deep soft tissue (3)
CD 34 focally +
Rb-1 deletion (6)
no *MDM2/CDK4*
amplification