Challenging cutaneous spindle cell Neoplasms

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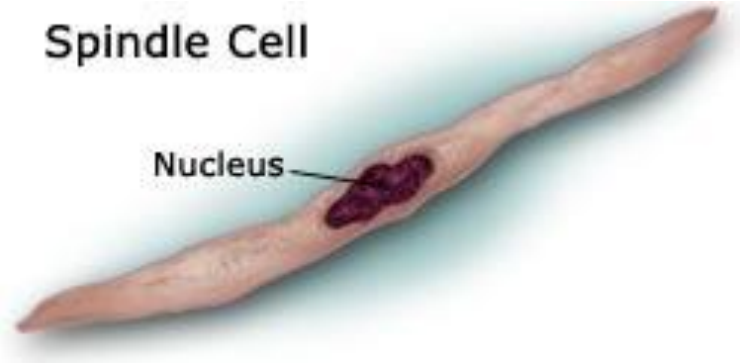
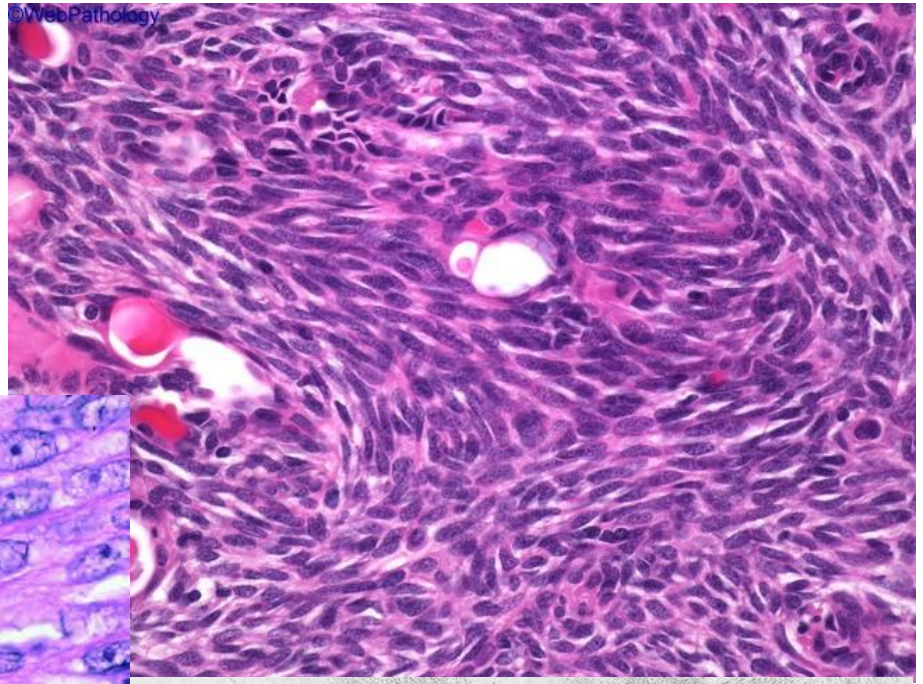

Spindle Cell
Nucleus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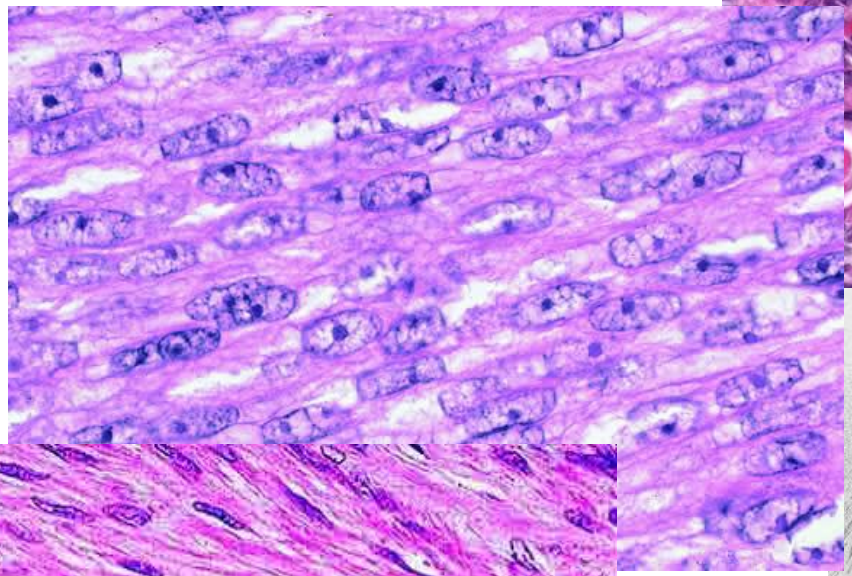
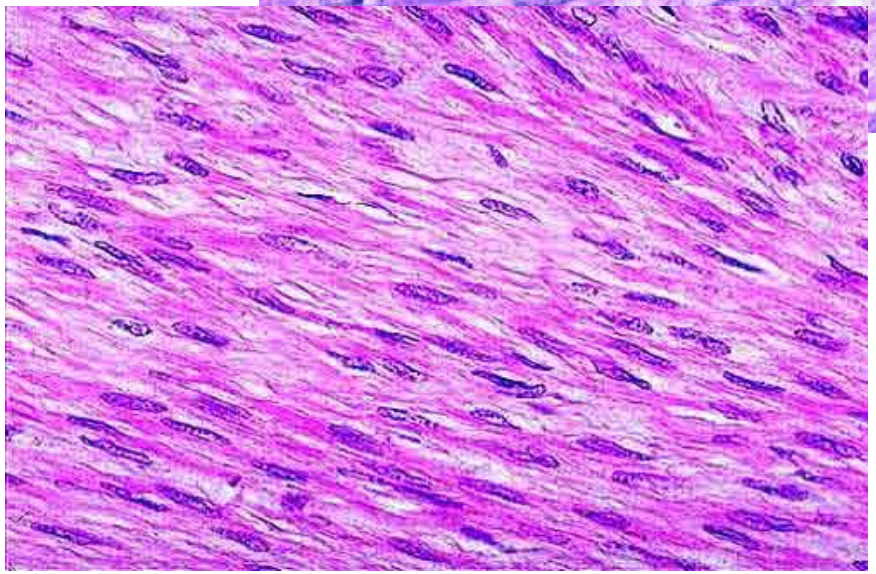
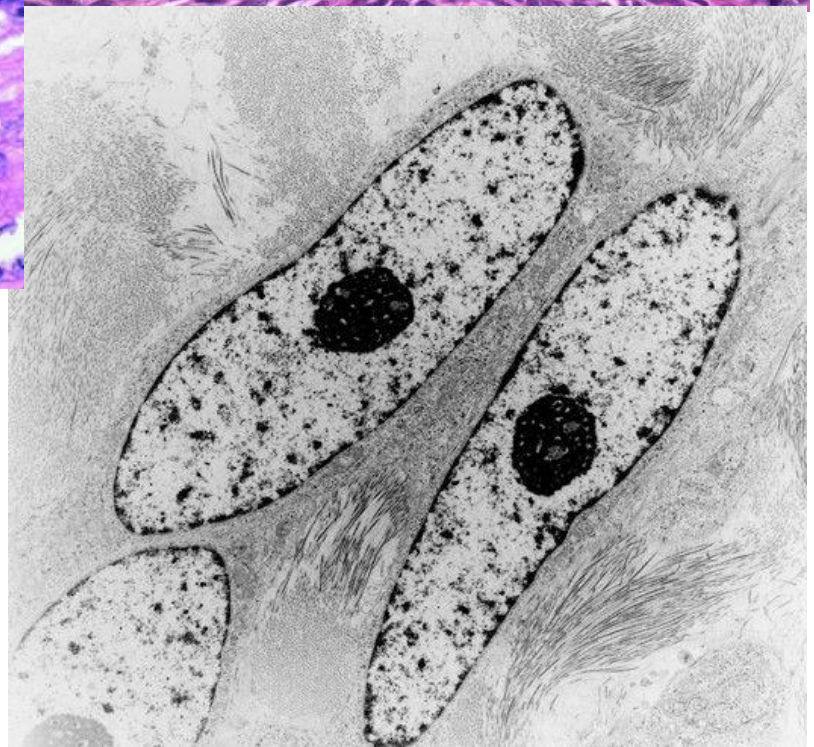
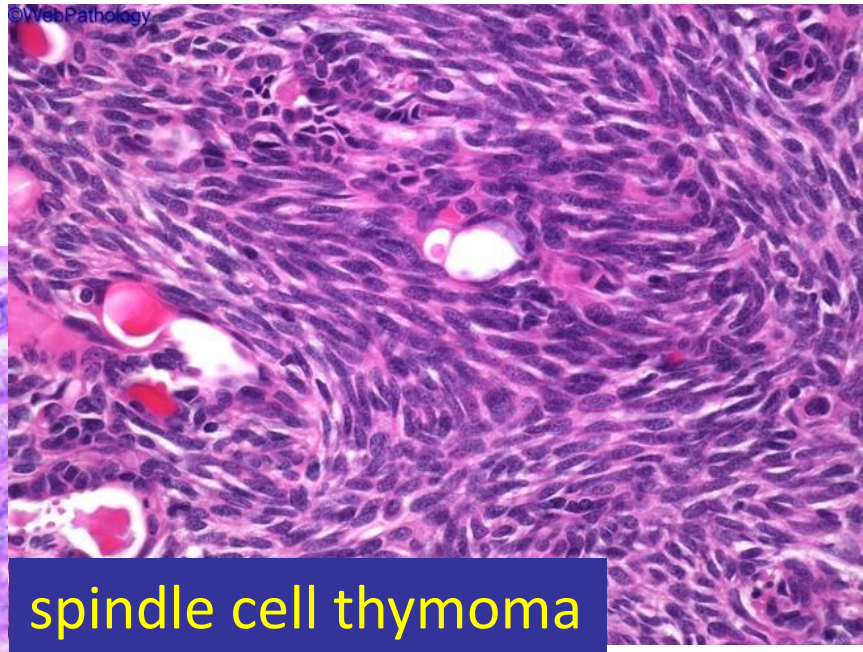
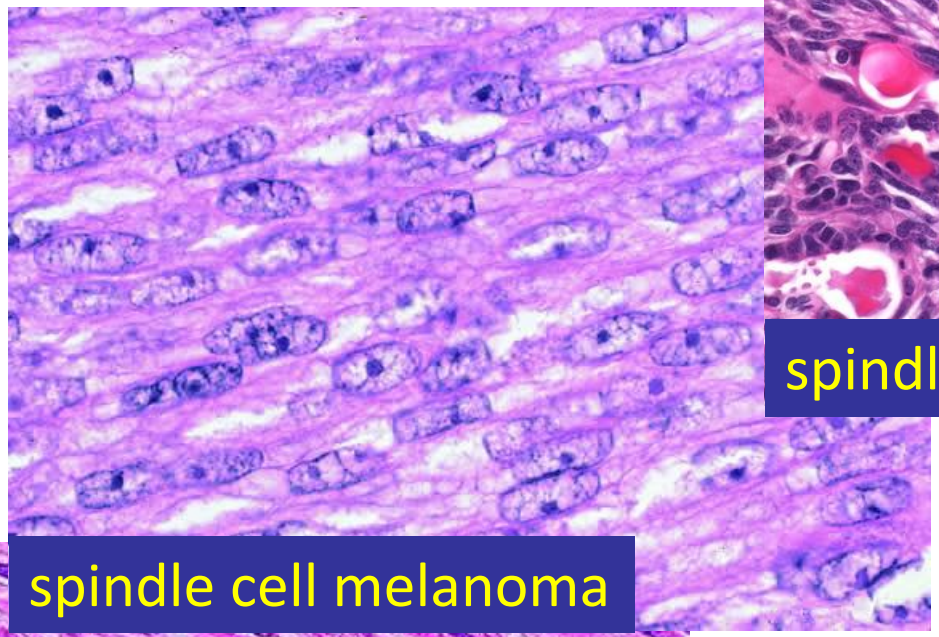








spindle cell thymoma



spindle cell melanoma

low-grade spindle cell sarcoma

Diagnosis of cutaneous spindle cell Tumours

Exclusion of nonmesenchymal spindle cell tumours

(spindle cell carcinoma, spindle cell malignant melanoma)

Determination of the dignity

Characterization of the line of differentiation

Grading in cutaneous sarcomas has limited value

(dermal sarcomas have a good prognosis except

angiosarcoma, epithelioid sarcoma, malignant dermatofibroma)

Tumour margins

Prognosis, treatment

Diagnosis of spindle cell Tumours

Age of patients

lipofibromatosis: children

kaposiform HE: children

Anatomic distribution

spindle cell lipoma: neck, shoulder, upper back

acral fibromyxoma: finger, toe, periungual

Tumour depth

pilar leiomyoma: common

deep leiomyoma: very, very rare

Evaluation of morphological features

Ancillary techniques

immunohistochemistry, molecular techniques

Histological Features

Architecture of cutaneous spindle cell neoplasms

storiform:	dermatofibroma, DFSP
fascicular:	smooth muscle neoplasms
perivascular:	myopericytoma
lamellar:	perineurioma
biphasic:	myofibroma

Interphase tumour and adjacent tissues

ill-defined:	dermatofibroma
diffus infiltrative:	DFSP
well-circumscribed:	perineurioma, low-grade FMS
encapsulated:	schwannoma, lipoma
	spindle cell / pleomorphic lipoma

Tumour stroma

- abundant or scanty stroma
- myxoid stroma
- collagenous stroma
- hyalinised / sclerosing stroma

Vascular pattern

- haemangiopericytoma-like (SFT, MPNST…)
- thin-walled, branching (myx. LS, angiofibroma)
- hyalinised vessel walls (schwannoma)
- abundant vessels (cellular angiofibroma)

Cytomorphology

Proliferative activity, mitoses

- (Cave: neurofibroma, deep seated leiomyoma)

Tumour necrosis

Immunohistochemistry

fibroblastic differentiation:

☹, procollagen type 1 + ?, CD 34 +/-

myofibroblastic differentiation

ASMA +/-, desmin +/-, h-caldesmon -, myf-4 -

smooth-muscle differentiation

ASMA +, desmin +/-, h-caldesmon + (2/3 +)

striated muscle differentiation

ASMA -/+, desmin +, myf-4 +, MyoD1 +

neural differentiation

S-100 +, CD 56 +, Sox10 +, p75 +

perineurial differentiation

EMA +, Claudin-1 +, Glut-1 +, CD34 +/-

endothelial differentiation

ERG +, CD 31 + (histiocytes +), CD 34 +/-

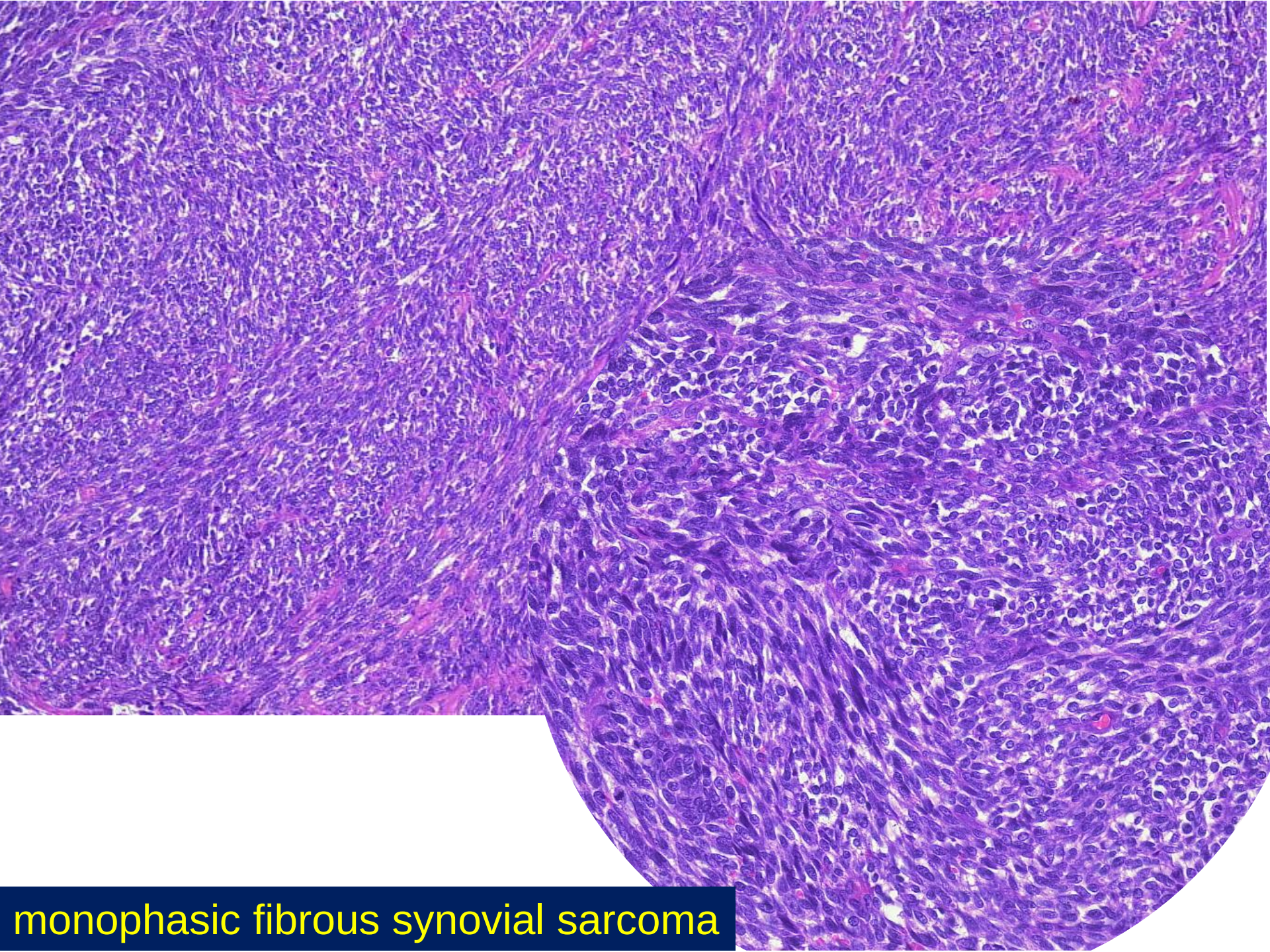
Breakpoint specific Antibodies

A novel SS18-SSX fusion-specific antibody for the diagnosis of synovial sarcoma (E Baranov et al. AJSP 2020; 44: 922-933)

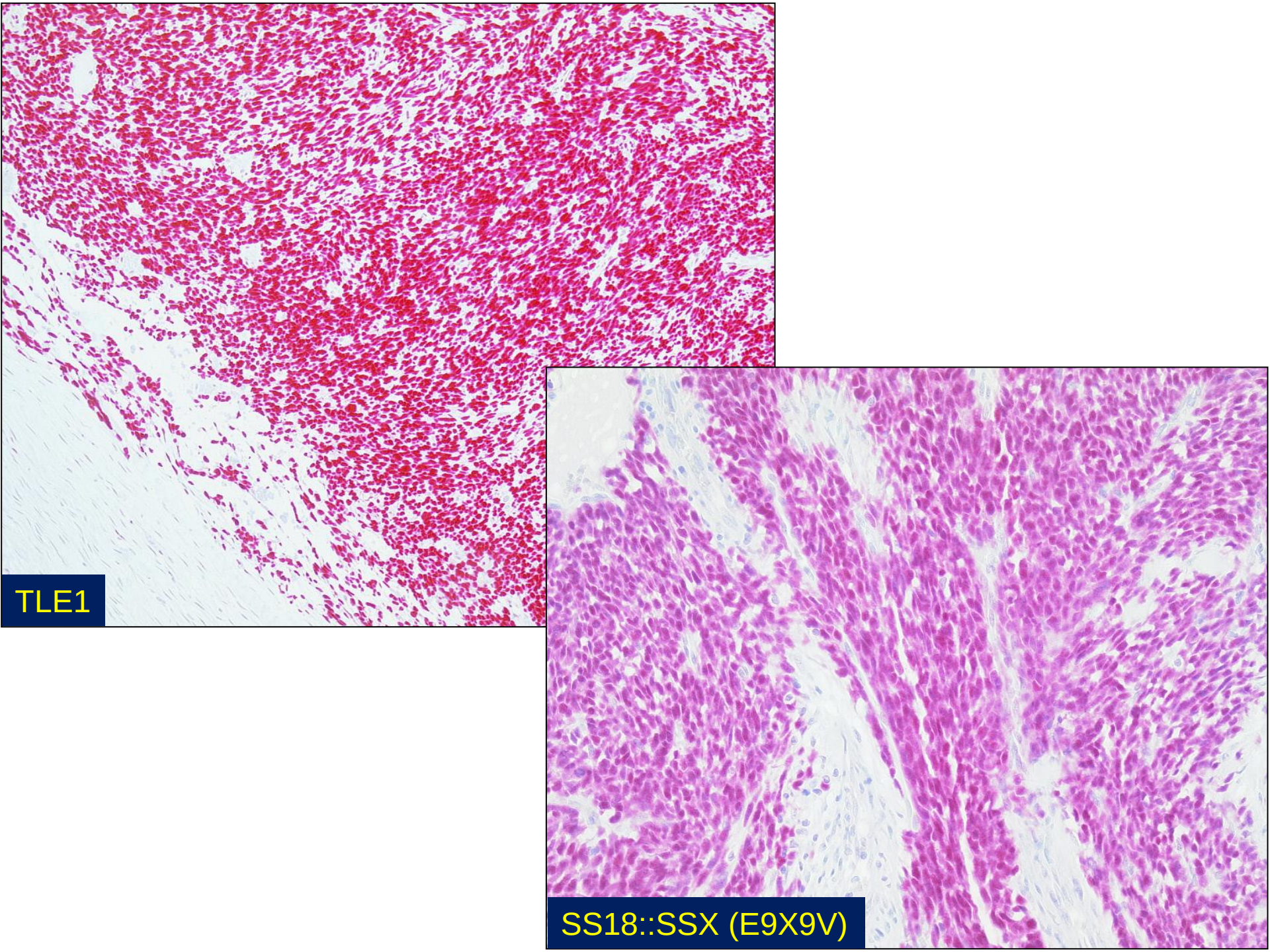
- E9X9V = SS18-SSX fusion antibody
  95% sensitivity, 100% specifity
- E5A2C = SSX-C terminus antibody
  100% sensitivity, 95% specifity

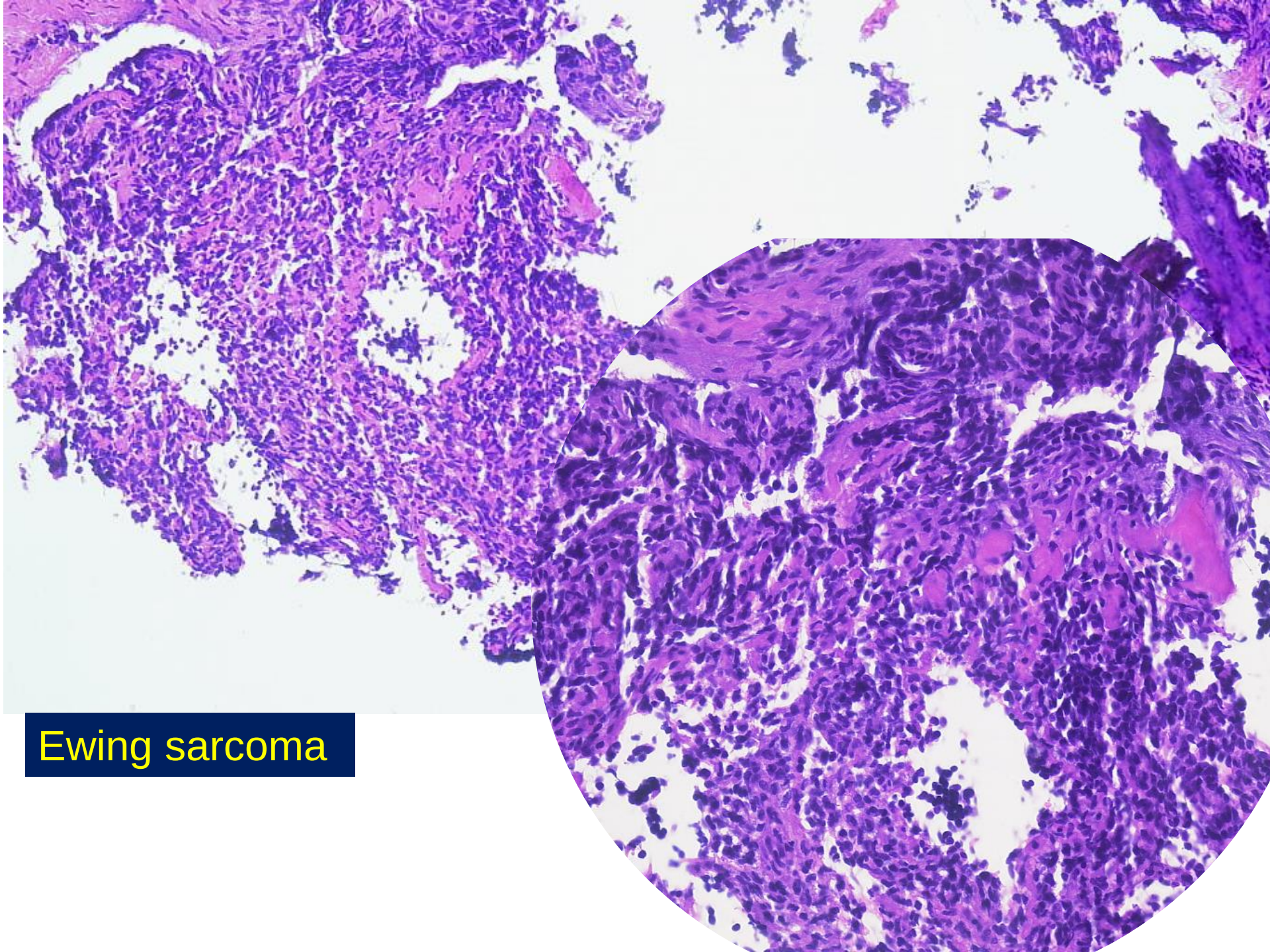
Immunohistochemical detection of PAX-FOXO1 fusion proteins in alveolar rhabdomyosarcoma using breakpoint specific antibodies (DA Azorsa et al. Mod Pathol 2021; 34: 48-57

- PFM.1 und PFM.2
- 91% sensitivity, 100% specifity

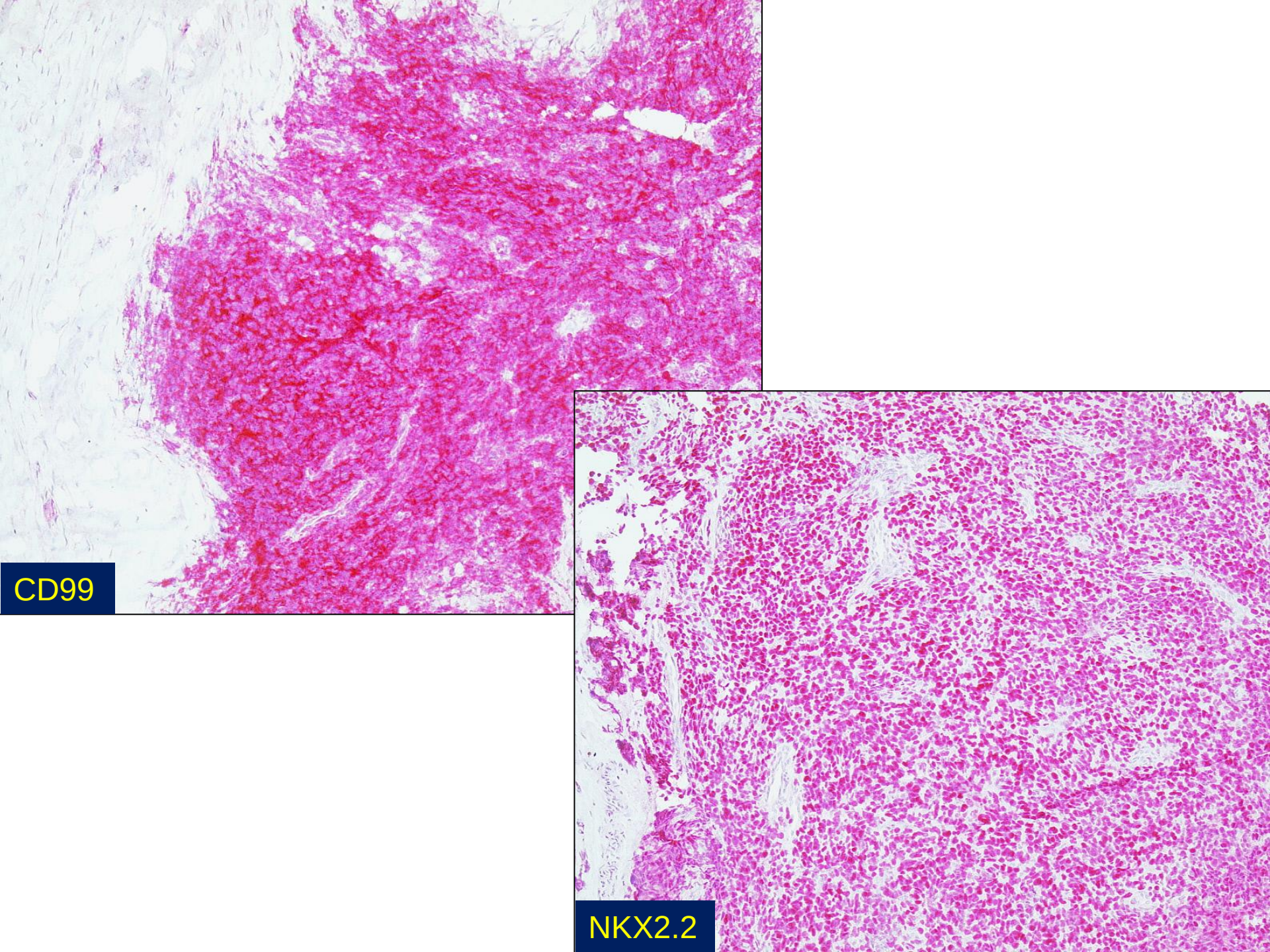


monophasic fibrous synovial sarcoma


TLE1
SS18::SSX (E9X9V)



Ewing sarcoma


CD99
NKX2.2

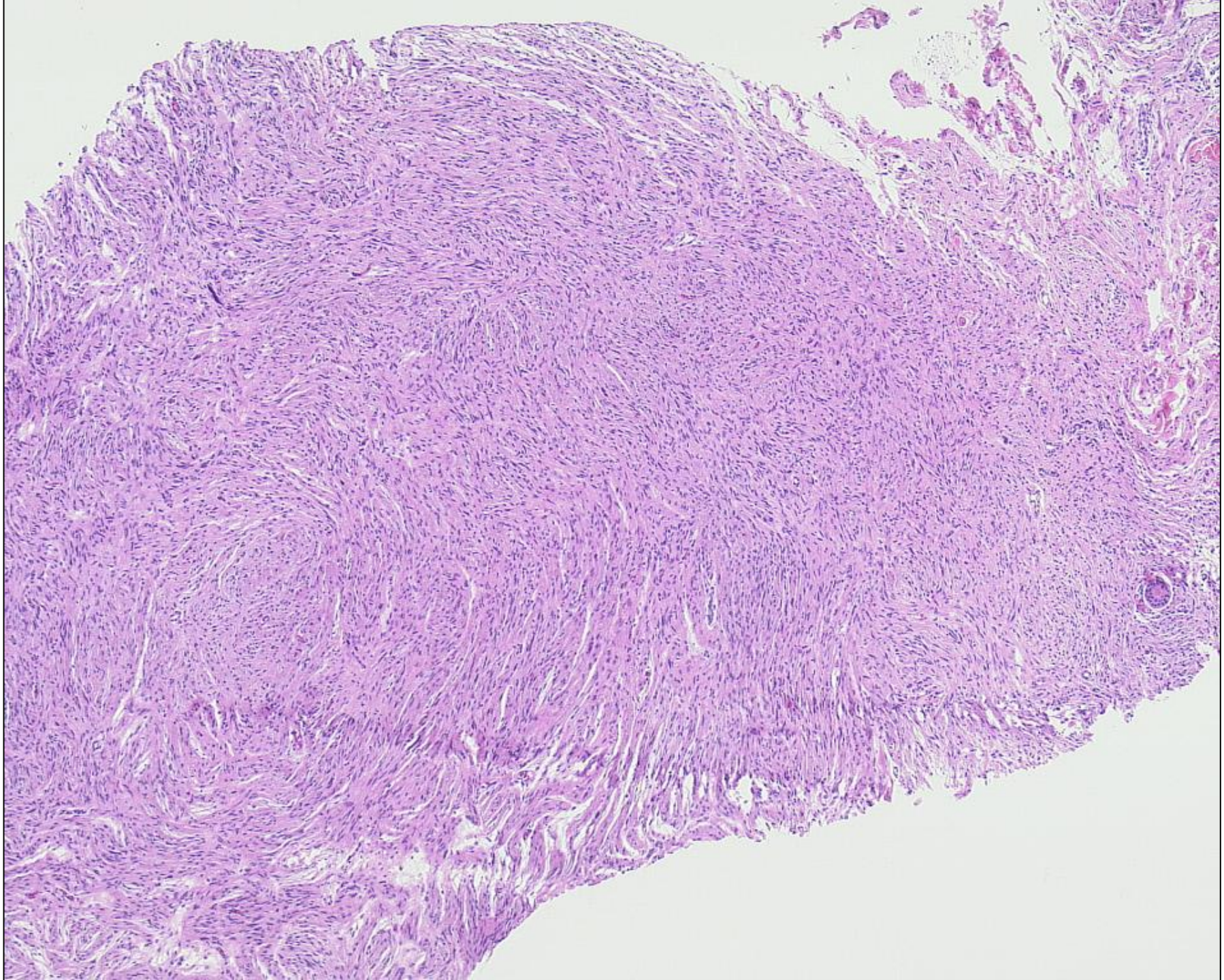
The best specificity and sensitivity has an antibody in the first six months after its description

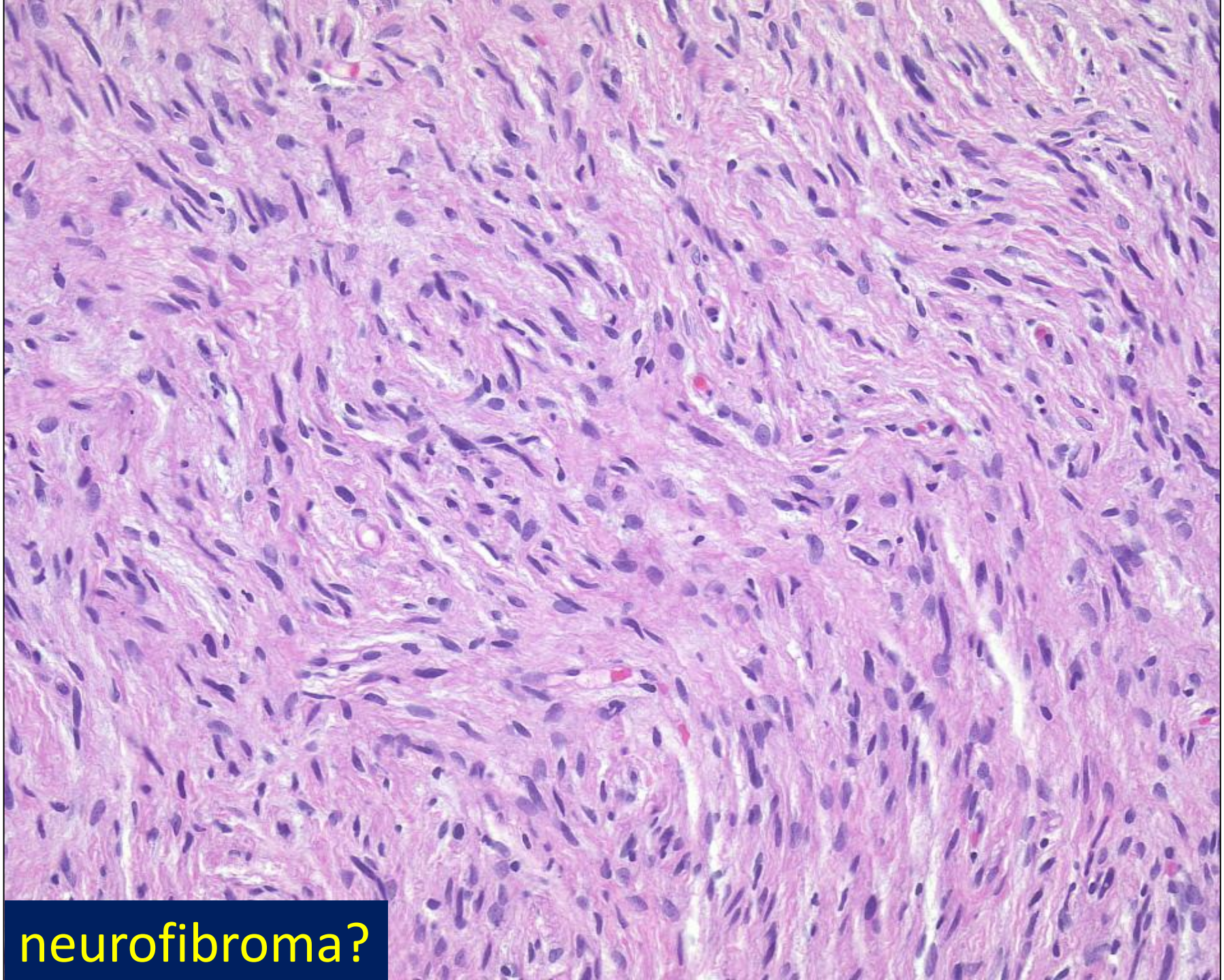
enthusiastic phase
pessimistic phase
realistic phase

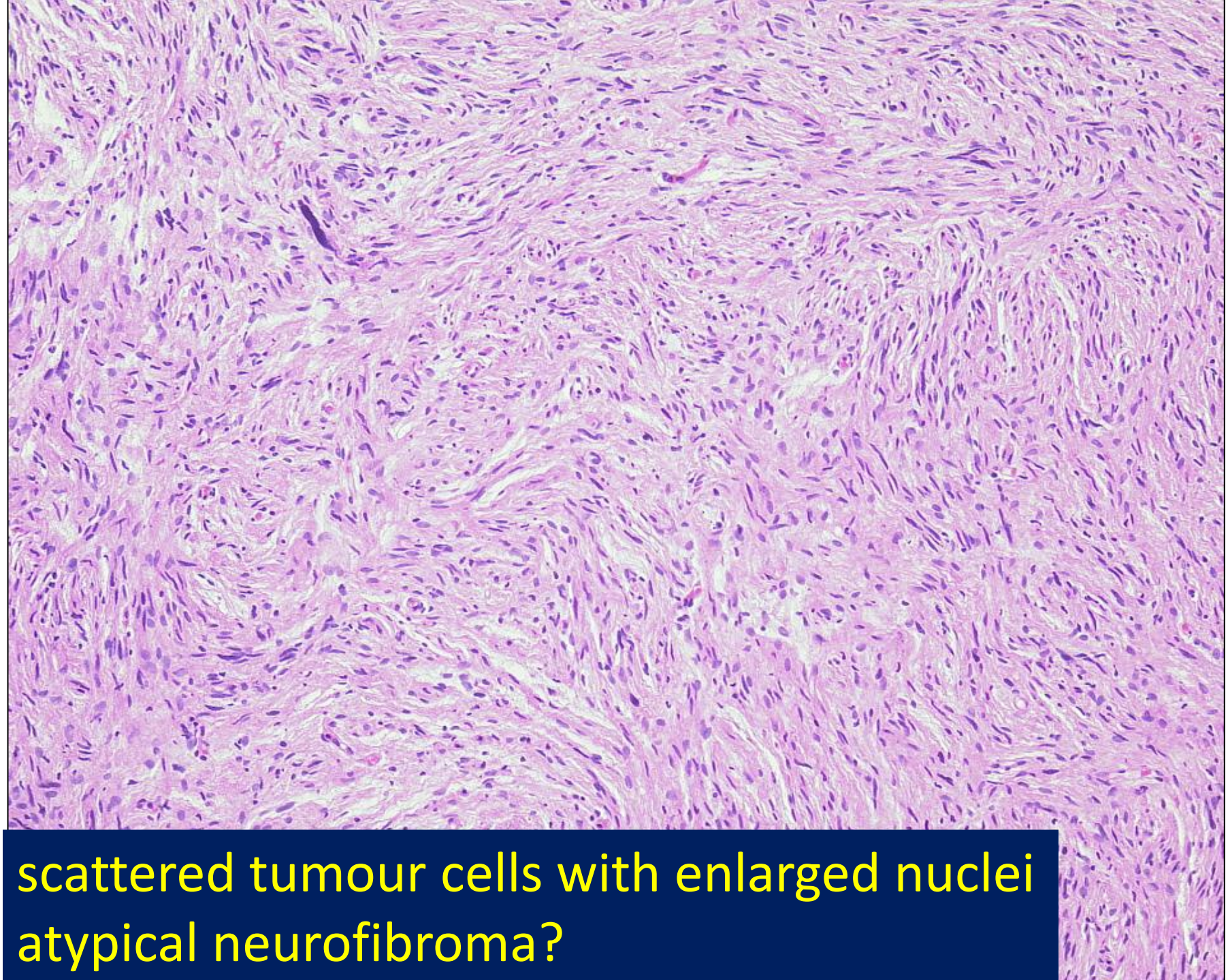
Case 1

M, 33 years, back

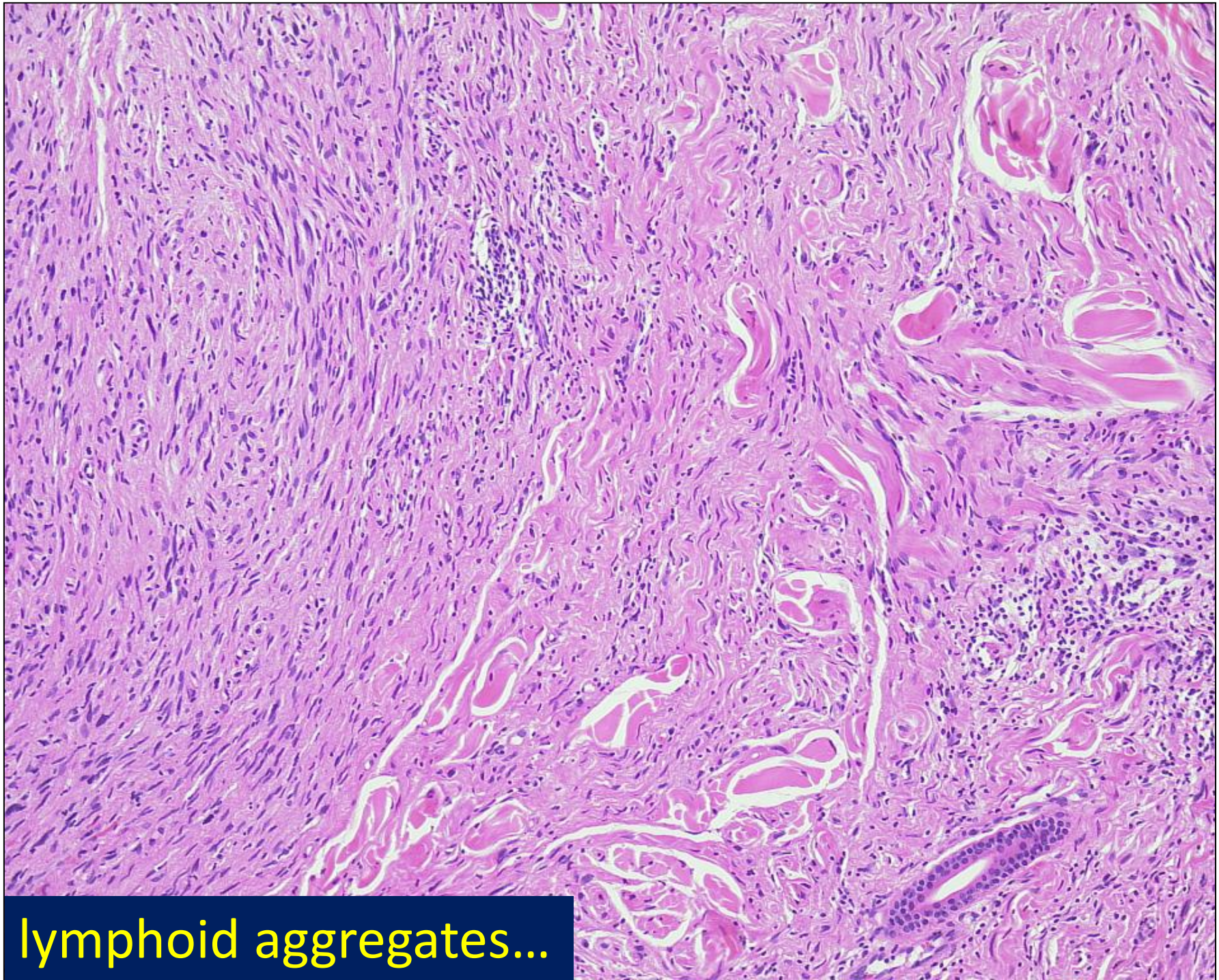
follicular cyst was suspected

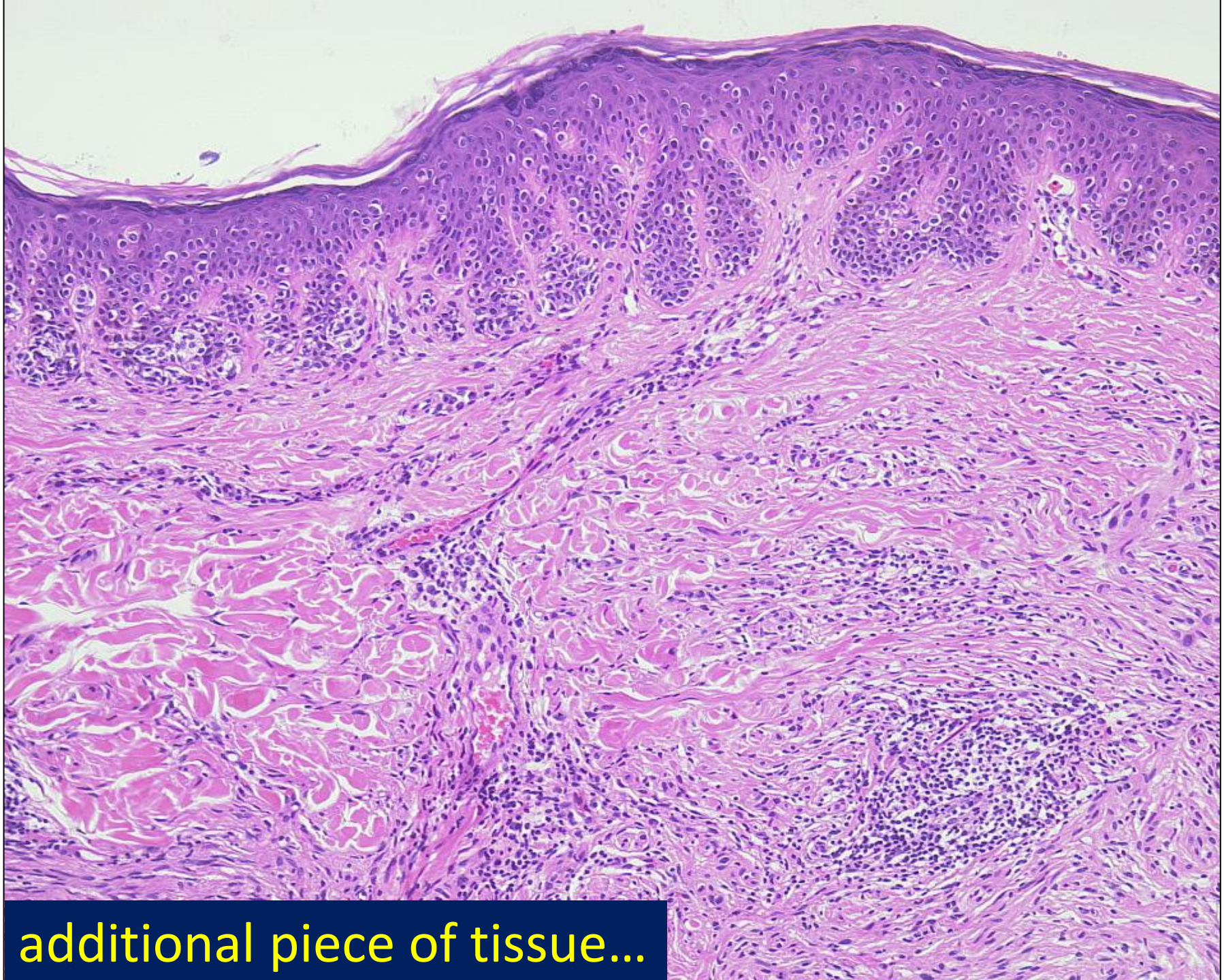


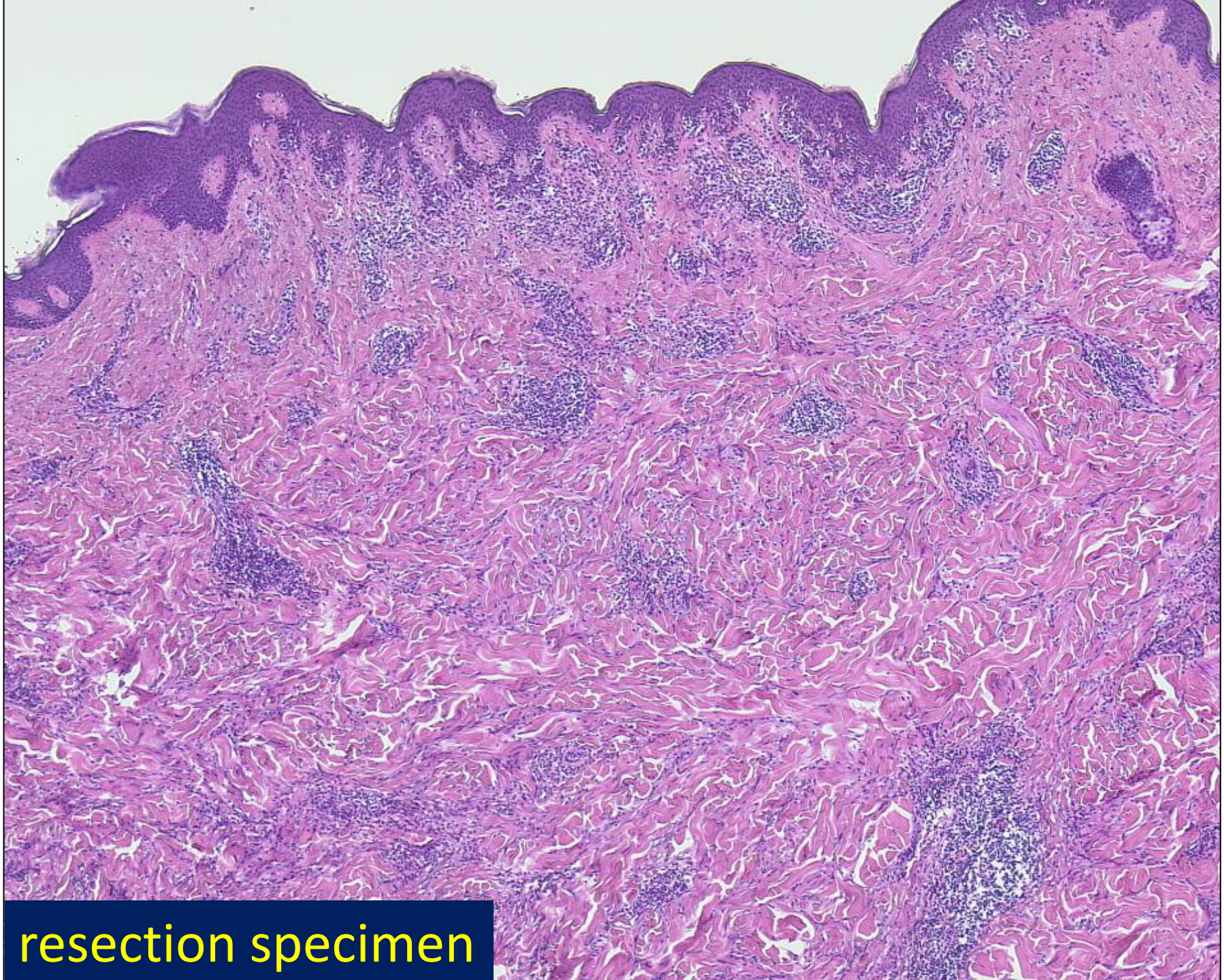

neurofibroma?

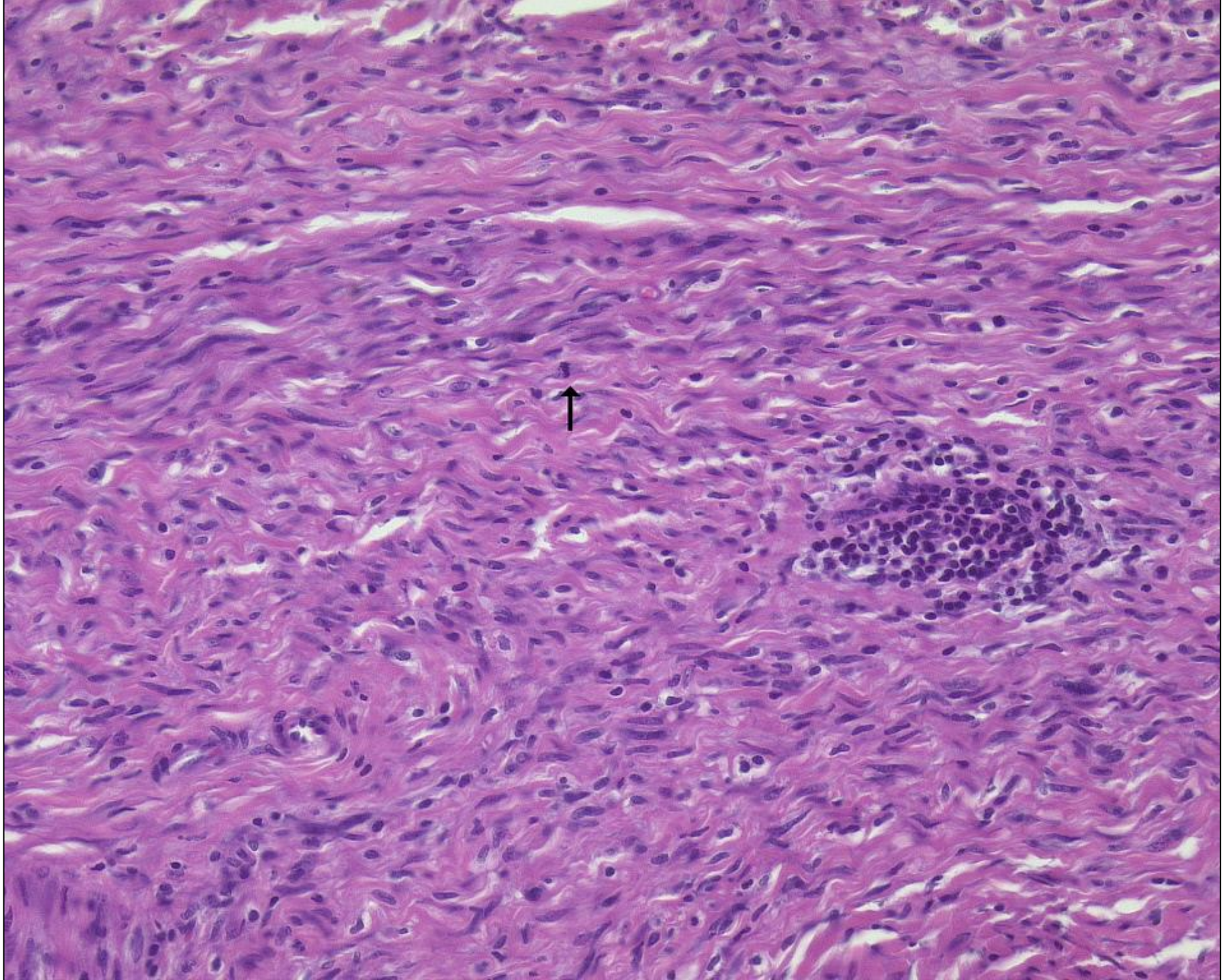


scattered tumour cells with enlarged nuclei
atypical neurofibroma?

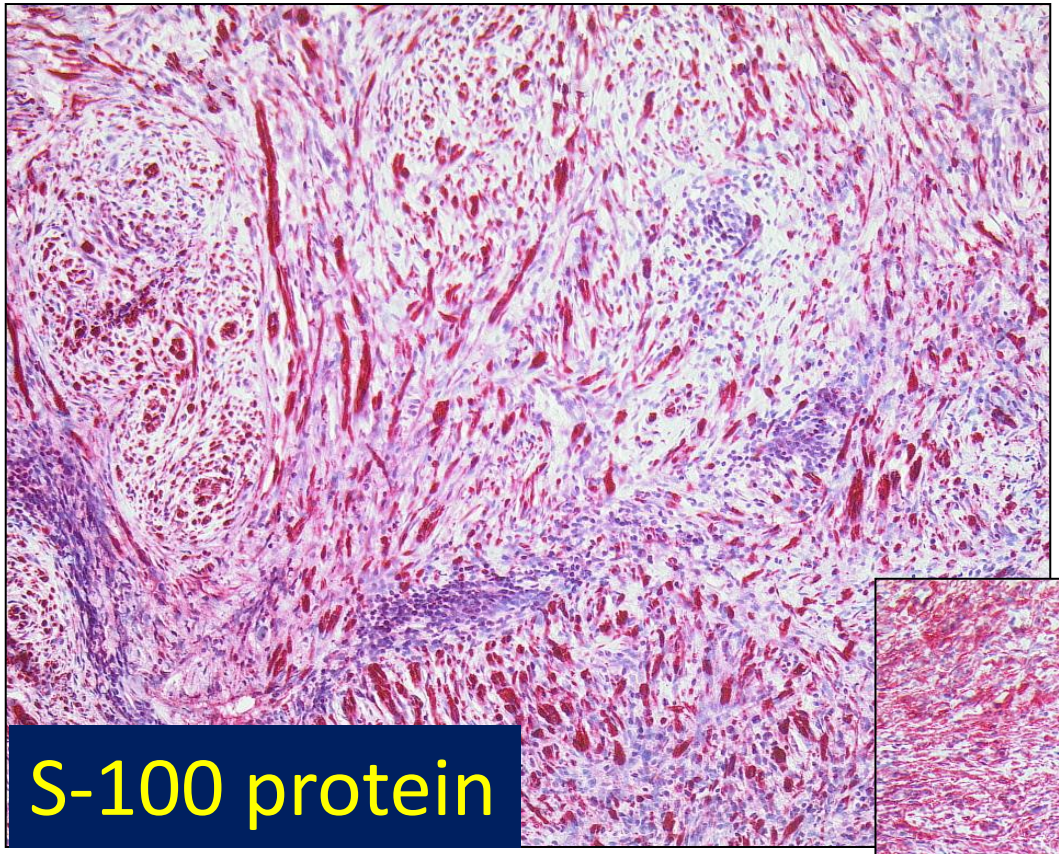

lymphoid aggregates…

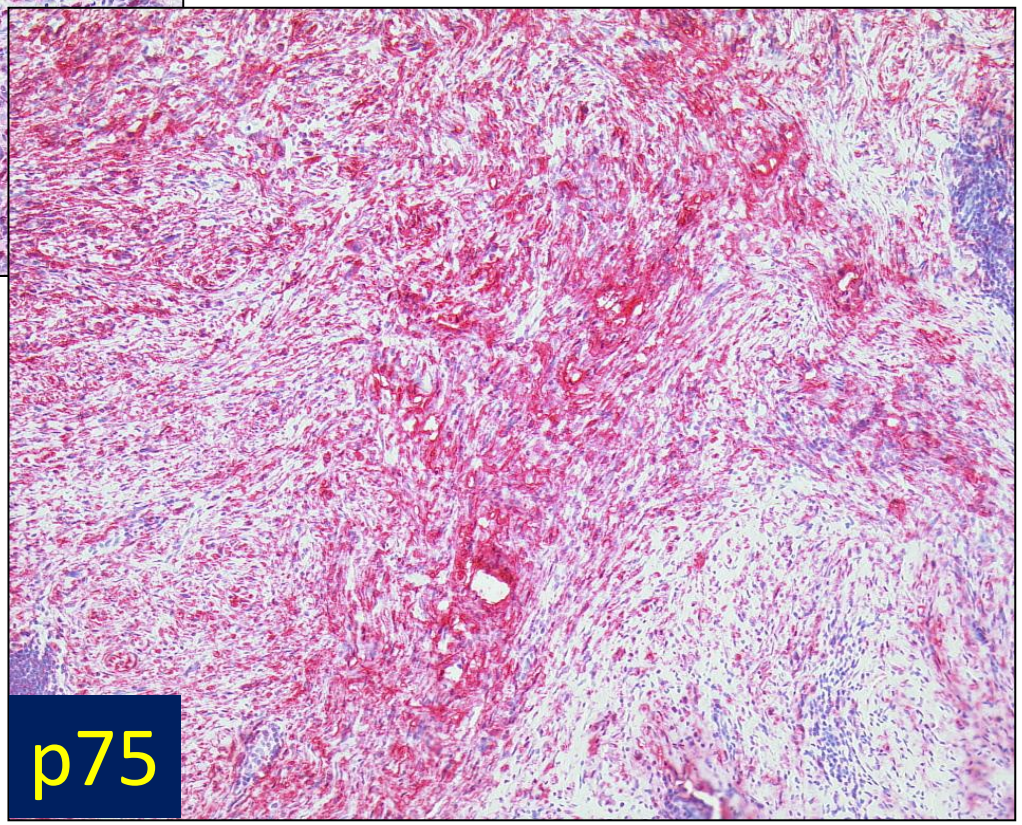

additional piece of tissue…


resection specimen



Diagnosis Case 1: desmoplastic malignant Melanoma





desmoplastic malignant Melanoma

- variant of spindle cell malignant melanoma,
  rare variant of malignant melanoma (< 4%)
- mainly elderly patients (BUT…), head / neck
  > other locations (rarely mucosa, hands, feet)
- indurated, non-pigmented plaques, nodules,
  often delayed diagnosis
- higher rate of local recurrences than classical MM!
  lower metastatic rate than classical MM!

desmoplastic malignant Melanoma

- proliferation of atypical spindled cells,
  slightly enlarged tumour cell nuclei,
  usually few mitoses only
- ill-defined, diffuse infiltration,
  extension into deep dermis / subcutis
- patchy lymphocytic infiltrate,
  scar-like desmoplastic stroma
- associated lentigo maligna (50% of cases),
  neurotropic, myxoid variants
- S-100 +, p75 +, Sox 10 +, WT1 +, Melan-A -, HMB-45 -

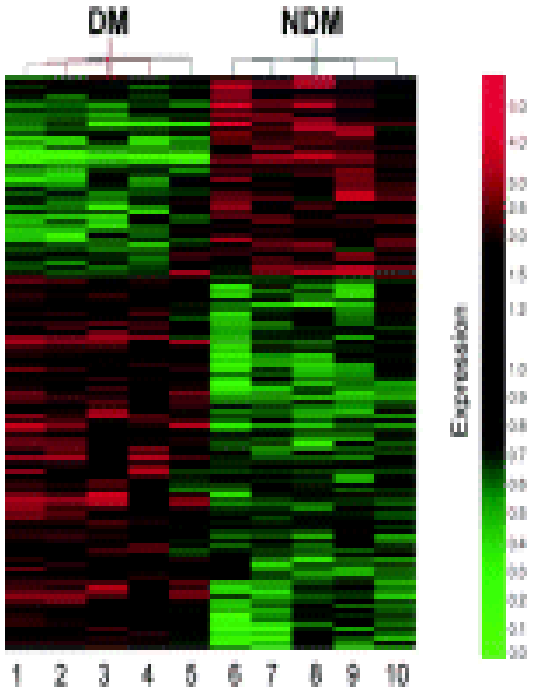
Desmoplastic melanoma: an updated immunohisto-chemical analysis of 40 cases with a proposal for an additional panel of stains for diagnosis
(LA Plaza et al. J Cutan Pathol 2016; 43: 313)
- Sox10, p75, nestin, WT-1 more specific markers

A diagnostic algorithm to distinguish desmoplastic from spindle cell melanoma
(SE Weissinger et al. Mod Pathol 2014; 27: 524)
- laminin, HMB-45, Melan-A, p75, c-kit + in SMM
- collagen IV, trichrome, CD68, MDM2 + in DMM
- *BRAF* mutation in 31% of SMM and 5% of DMM

NF1 mutations are common in desmoplastic melanoma
(T Wiesner et al. Am J Surg Pathol 2015; 39: 1357)

Distinction of desmoplastic melanoma from non-desmoplastic melanoma by gene expression profiling (Busam K et al. J Invest Dermatol 2005; 124: 412)

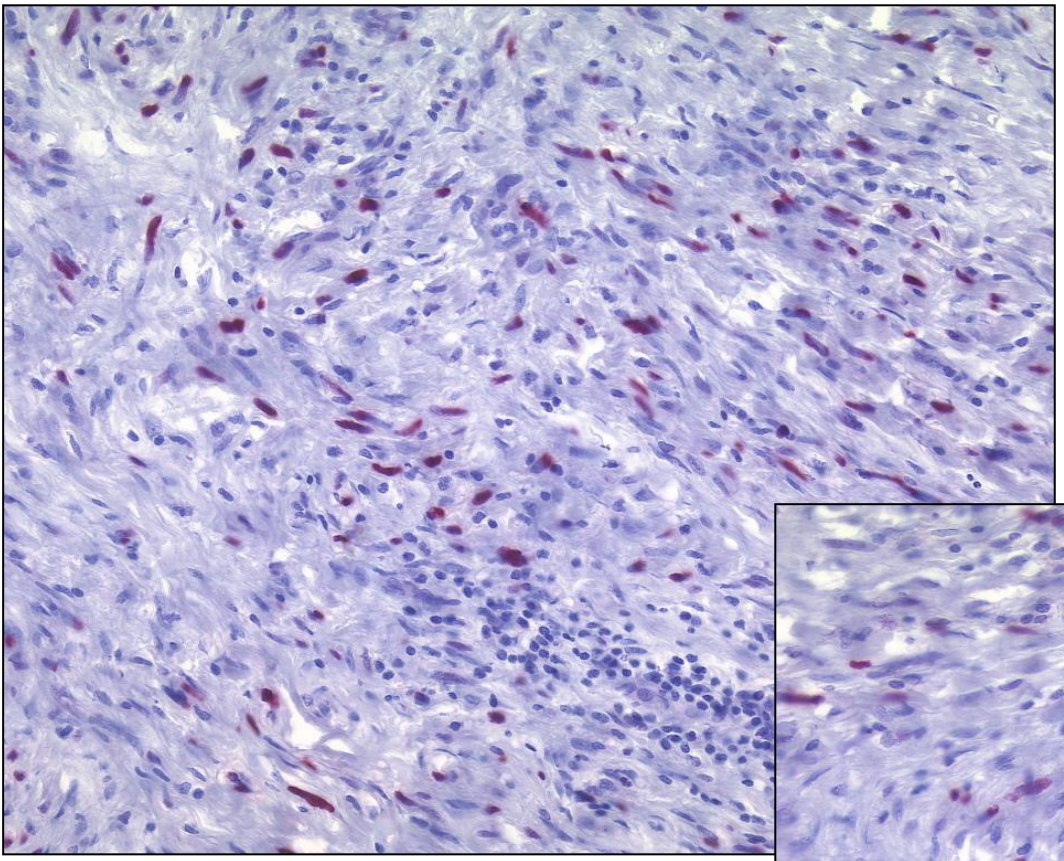
- reduction of the expression of genes for melanocytic differentiation (Melan-A, Mart-1, MiTF, DTC)
- increased expression of genes for neurotropic factors (NGFR) and for extracellular matrix
- high expression of clusterin (involved in cell-stroma interactions)

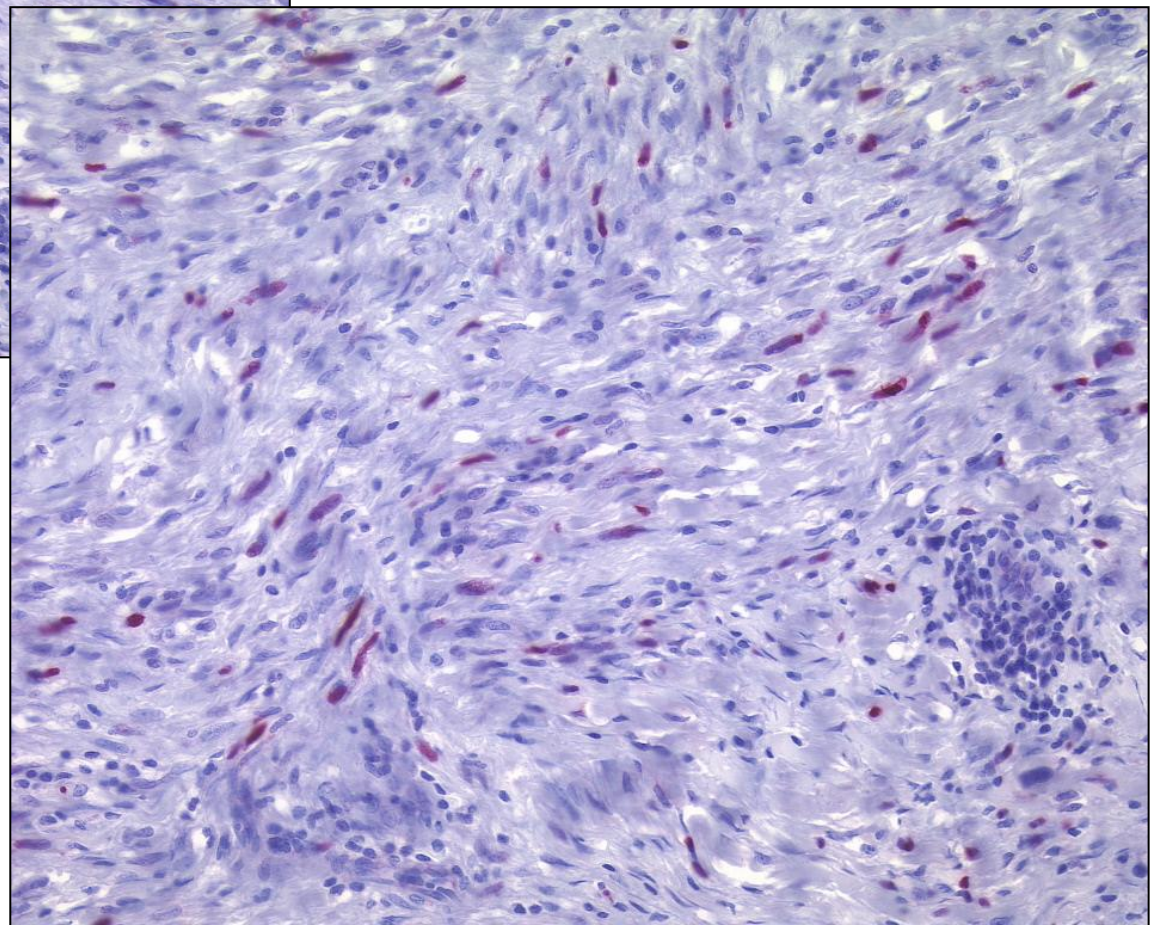


Distinguishing neurofibroma from desmoplastic melanoma: the value of p53

(Elsensohn A et al. AJSP 2018; 42: 372)

- 20 cases of DM (18 M, 2 F)
  20 cases of NF (12 M, 8 F)
- 19/20 of DM p53 positive
  0/20 NF p53 positive
- detection of p53 by immunohistochemistry is helpful in the differential diagnosis

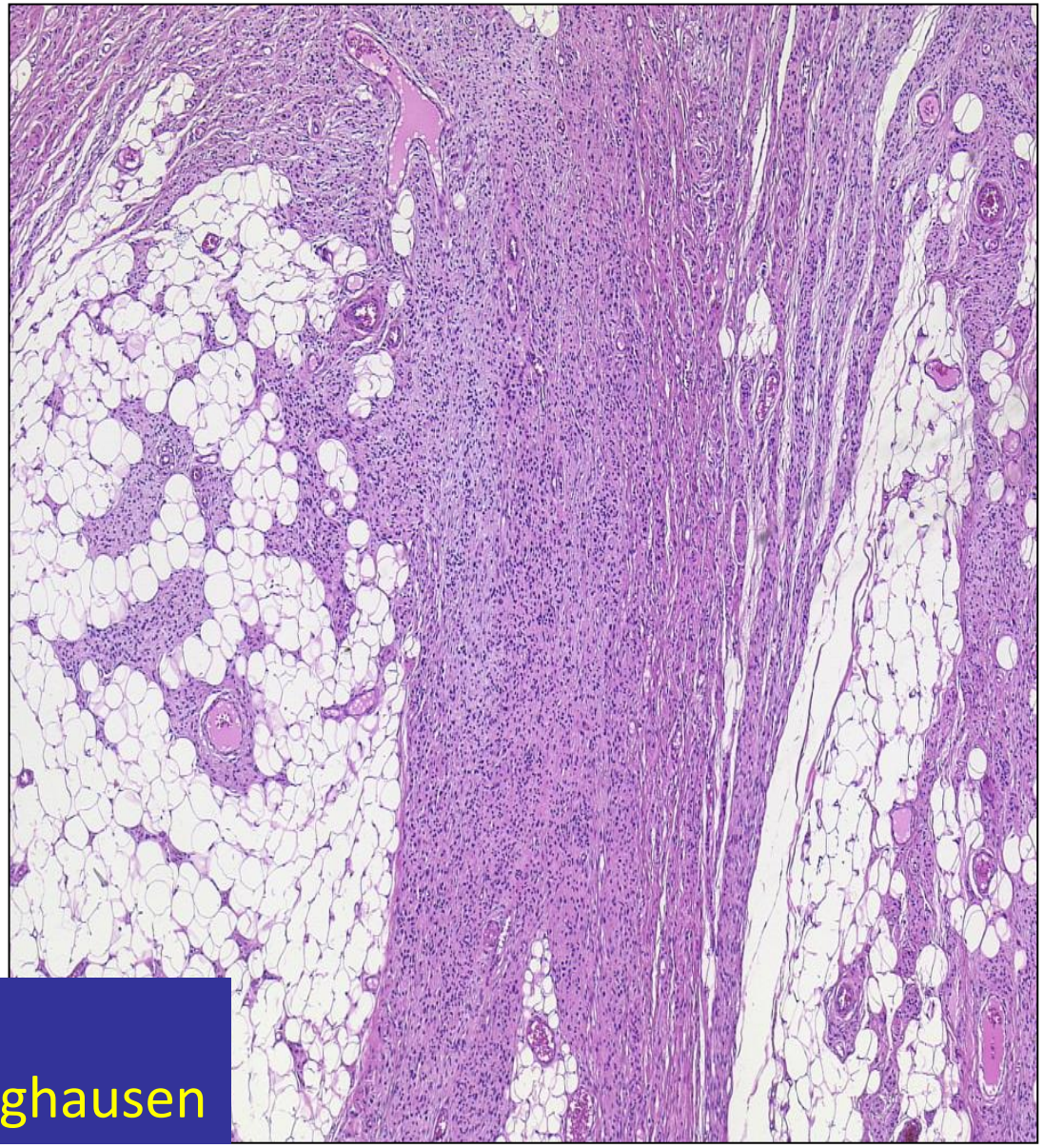




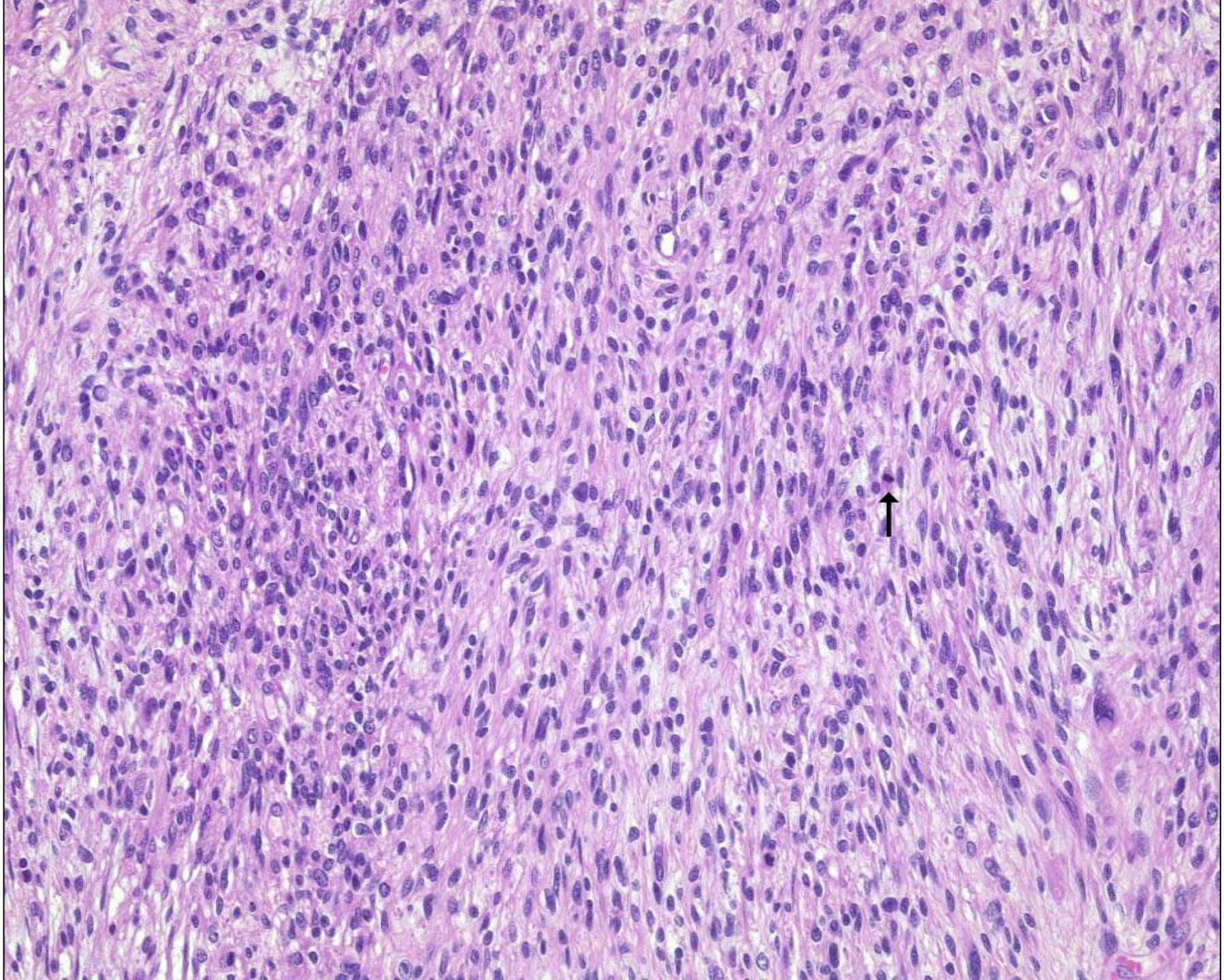
Case 1
p53

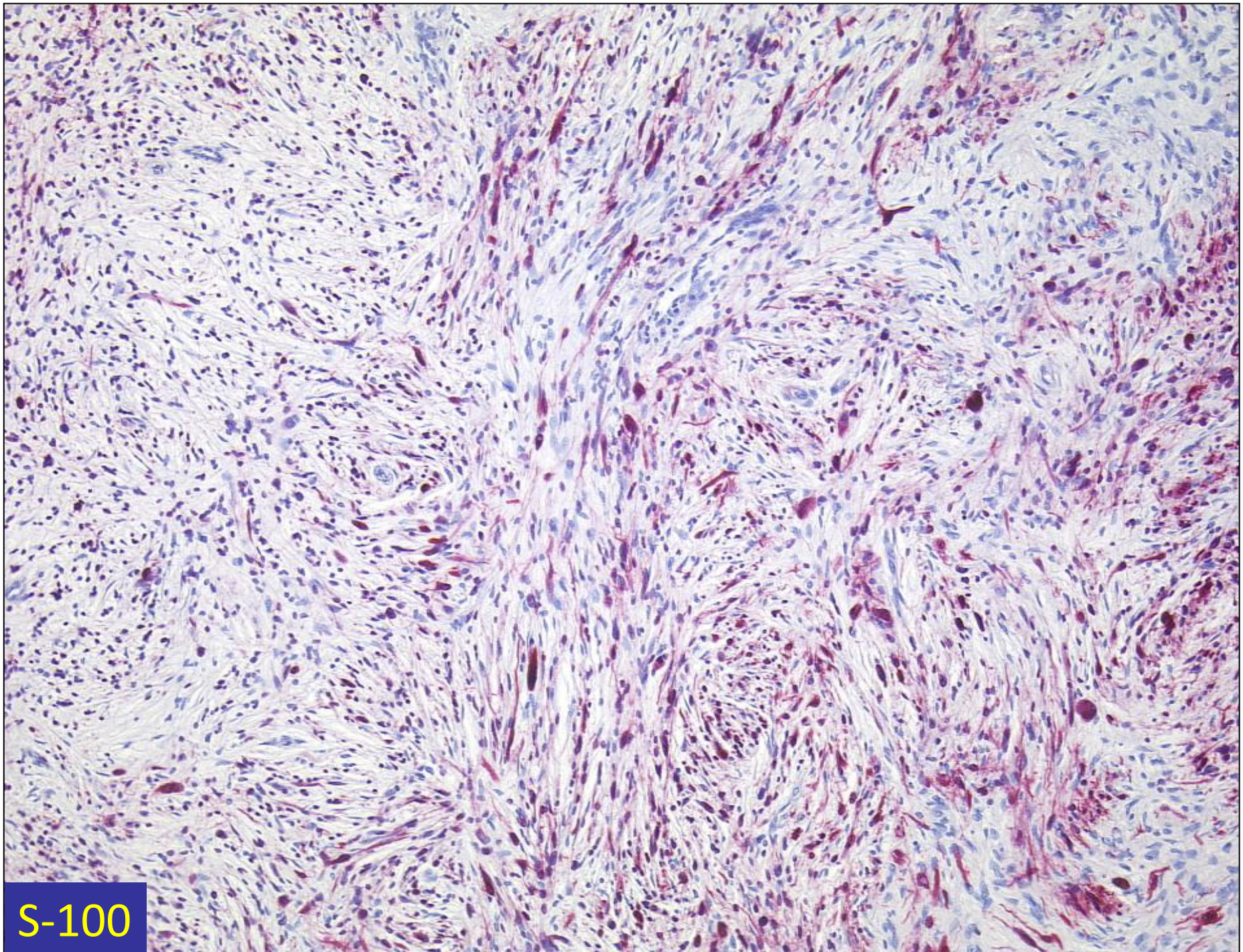
Malignant Peripheral Nerve Sheath Tumour

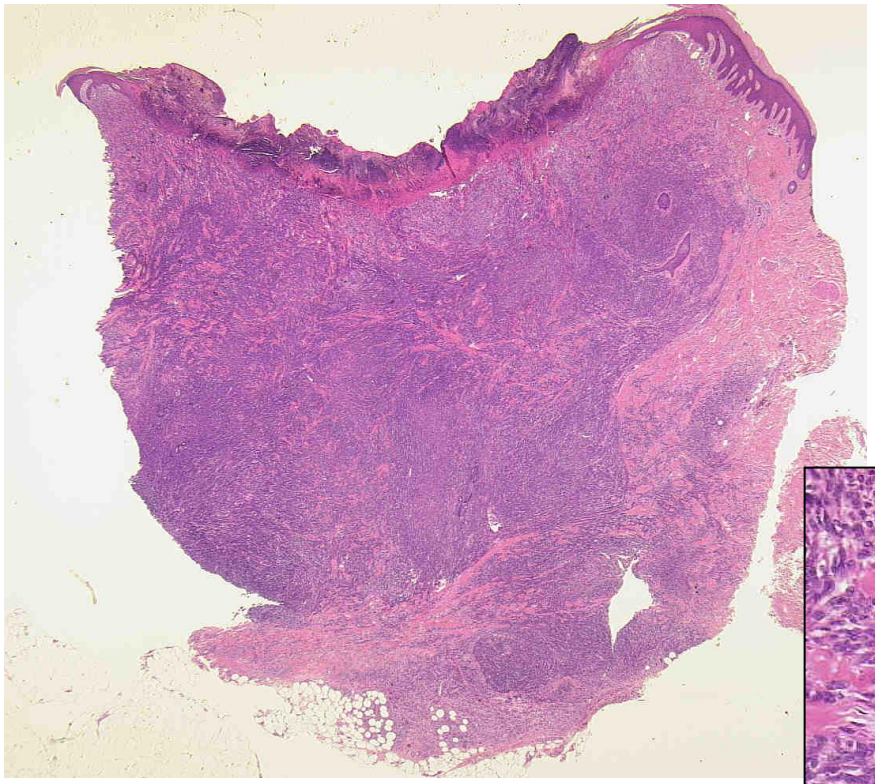
rarely superficial
rarely head / neck
S-100 - / focal +
loss of H3K27me3
(Le Guellec S et al.
Mod Pathol 2017; 30: 1677
- may be seen in desmo-
plastic melanoma as well)



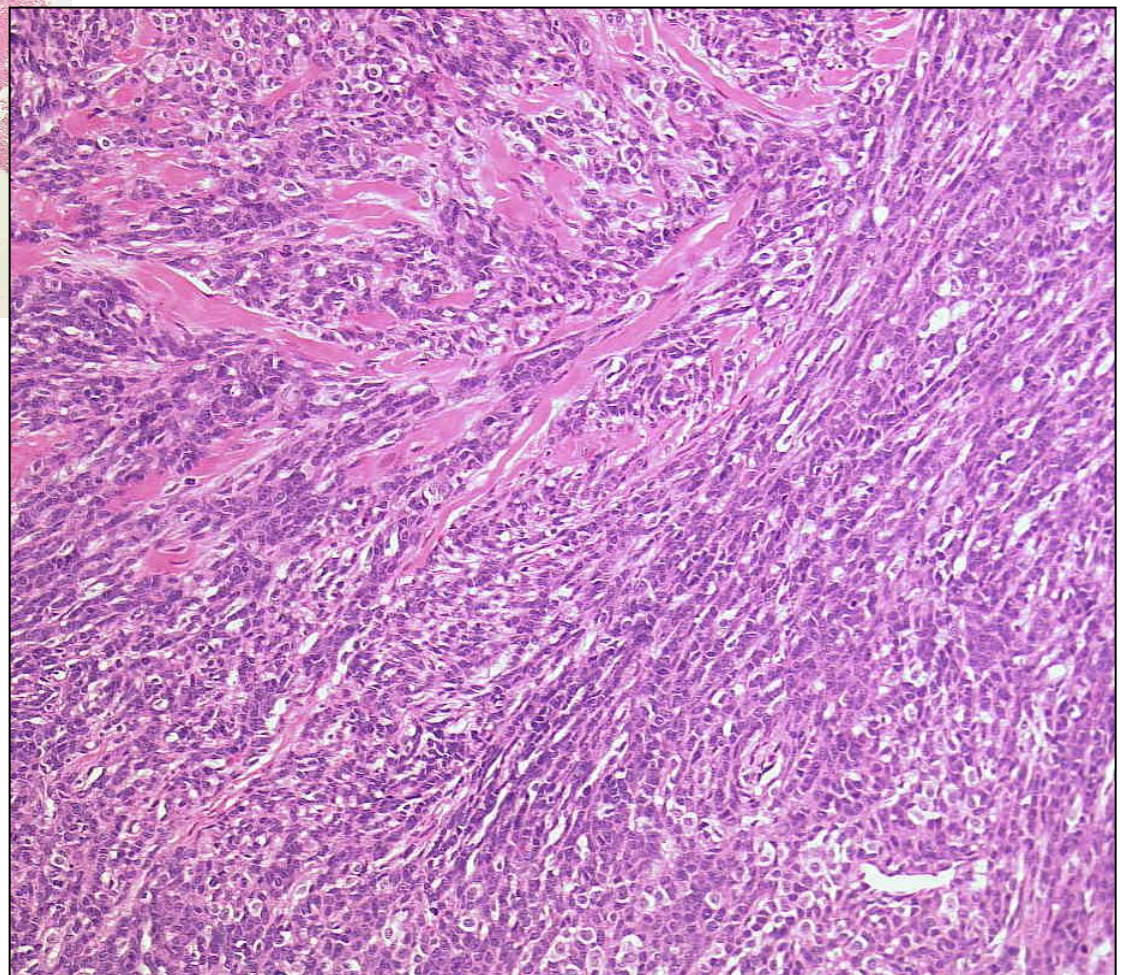
F, 60, back
known M.Recklinghausen

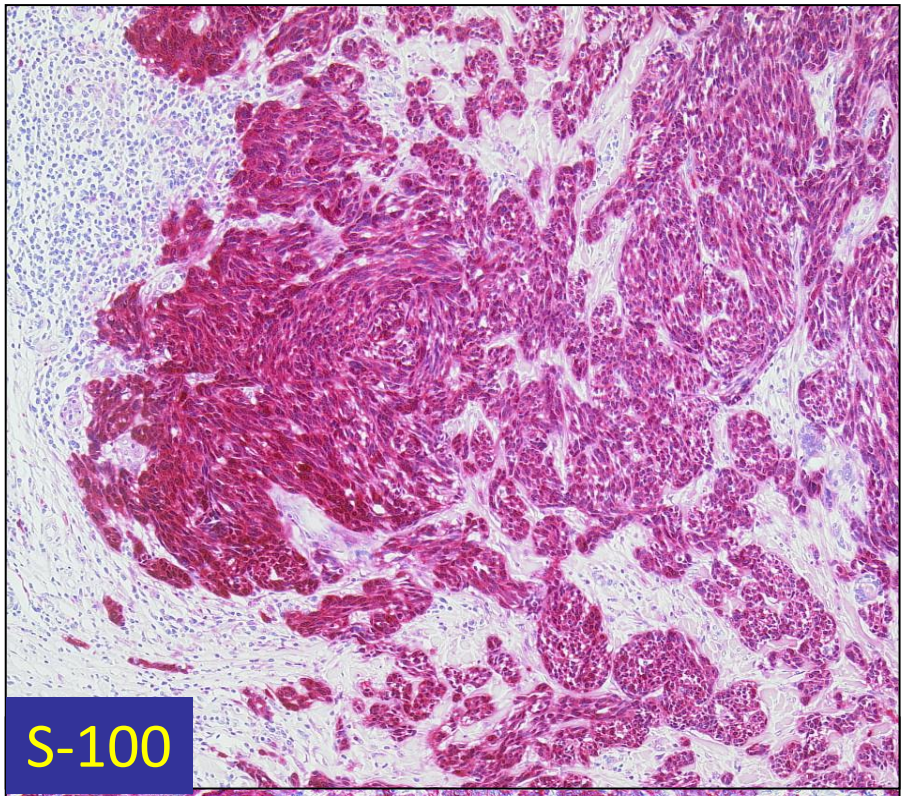


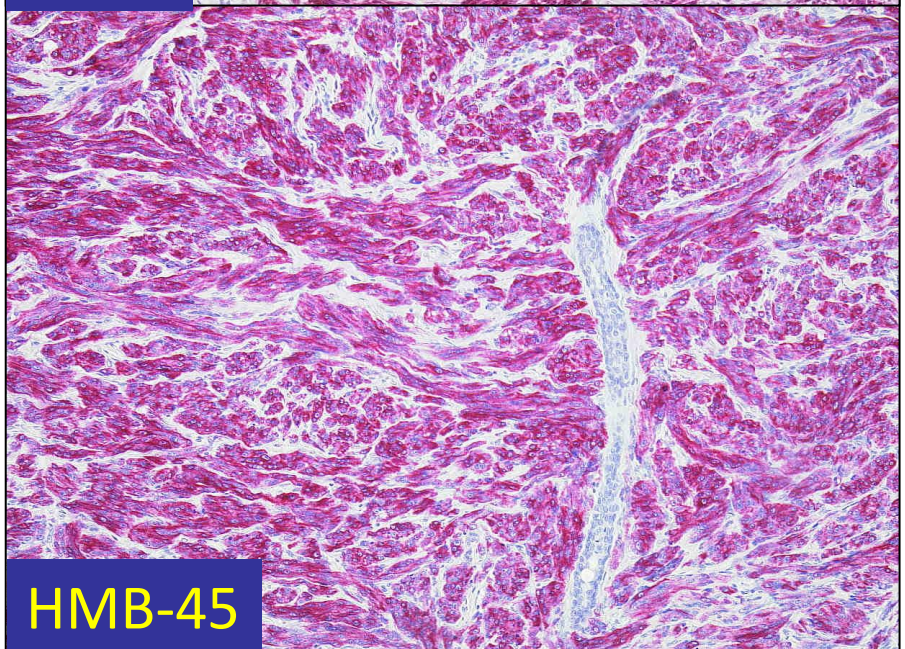

S-100



F, 13 years,
left forearm

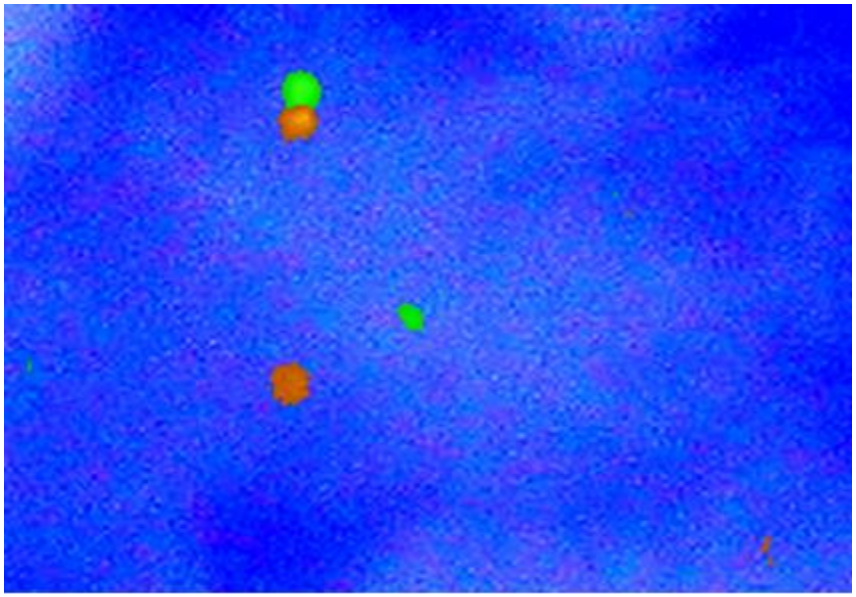






cutaneous clear cell Sarcoma

FISH-Analysis for the detection of *EWS* translocation

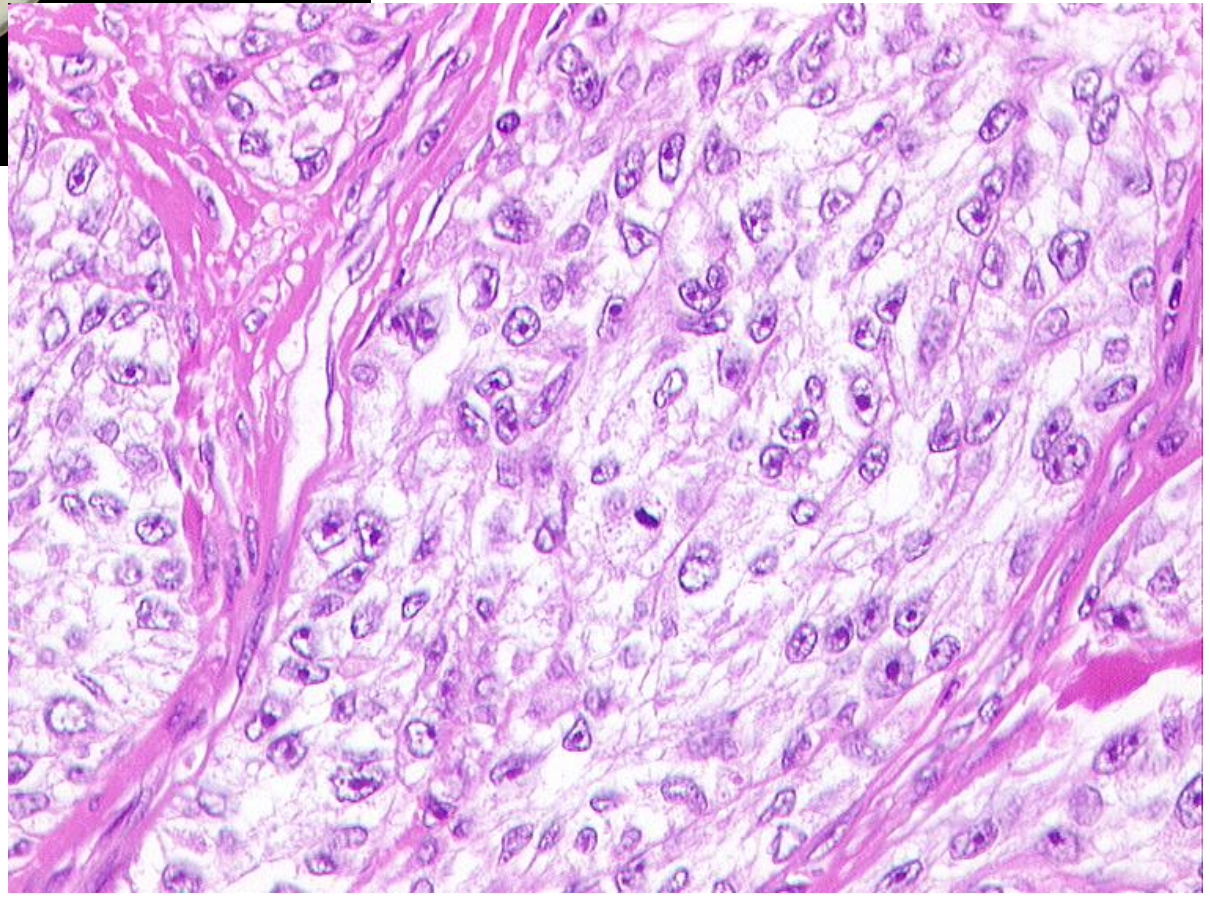


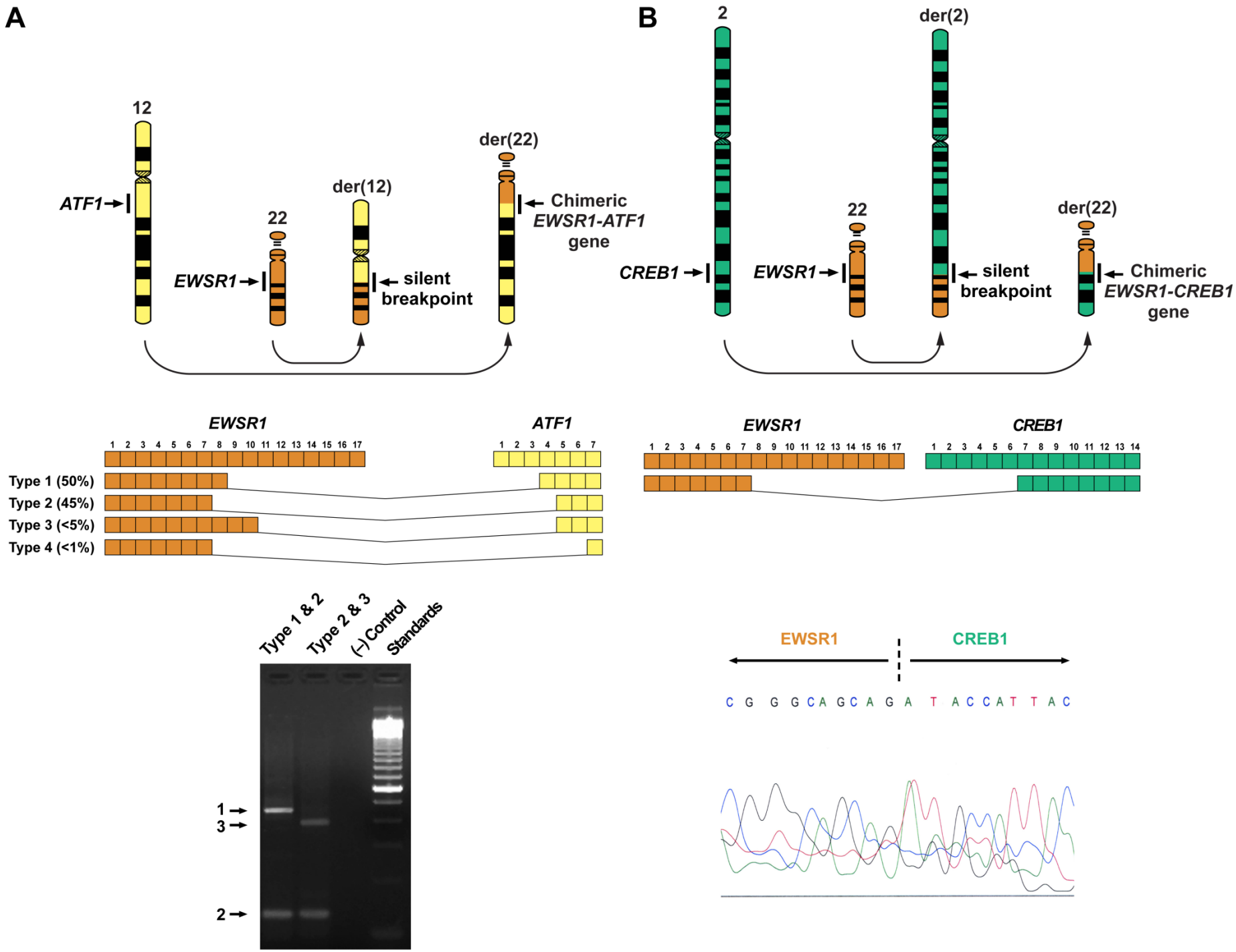
signals are in different areas of the nucleus = positive (16 out of 65 nuclei)

Clear cell sarcoma *versus* malignant Melanoma

- t(12;22)(q13;q12) with *EWSR1-ATF1* fusion
  (4 types of *EWSR1-ATF1* transcripts)
  t(2;22)(q32;q12) with *EWSR1-CREB1* fusion
- additional extra copies of chromosomes 2,7,8
- additional abnormalities of chromosome 22
- no *BRAF* mutations in CCS but common in MM
- MSI is very rare in CCS but common in MM
- no loss of hMLH1, hMSH2 in CCS
- characteristic gene expression profile in CCS

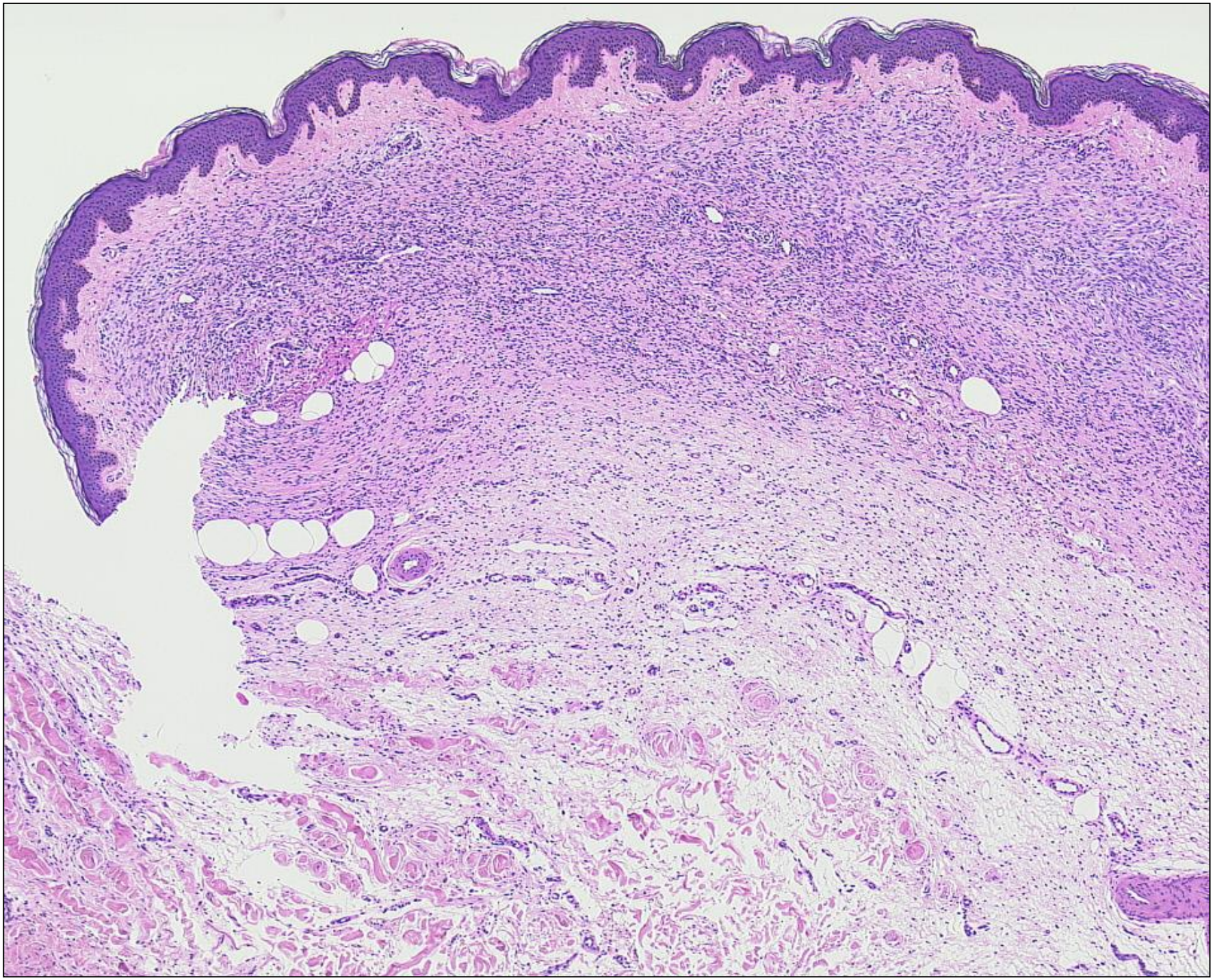
M, 42 years

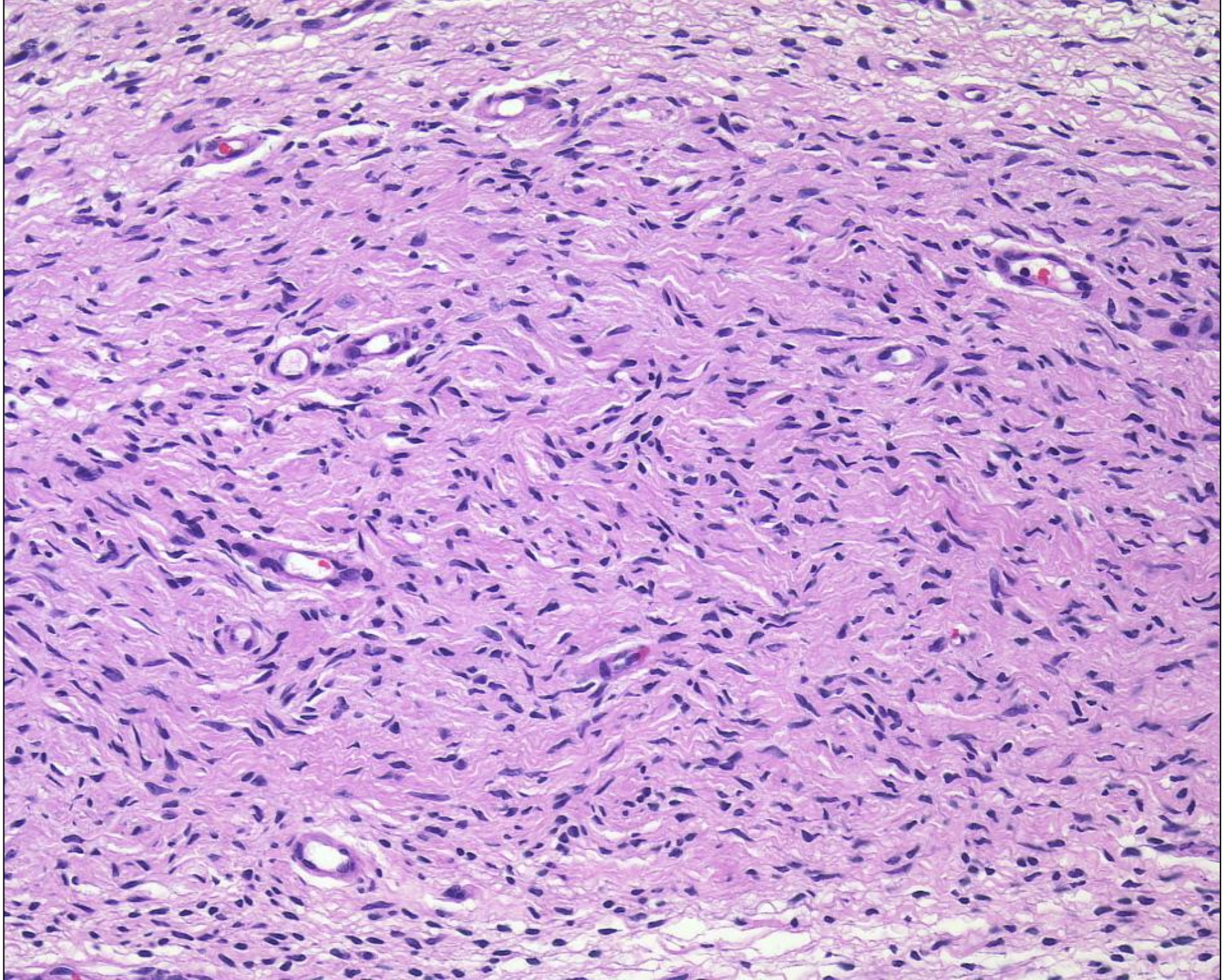



A
12
ATF1
22
EWSR1
der(12)
der(22)
Chimeric
EWSR1-ATF1
gene
silent
breakpoint
B
2
der(2)
22
CREB1
EWSR1
der(22)
silent
breakpoint
Chimeric
EWSR1-CREB1
gene
EWSR1
ATF1
Type 1 (50%)
Type 2 (45%)
Type 3 (<5%)
Type 4 (<1%)
EWSR1
CREB1
Type 1 & 2
Type 2 & 3
(–) Control
Standards
1
3
2
EWSR1
CREB1
C G G G C A G C A G A T A C C A T T A C

Case 2: Clinical Findings

- F, 30 years
- left lateral thigh
- dermatofibroma was suspected





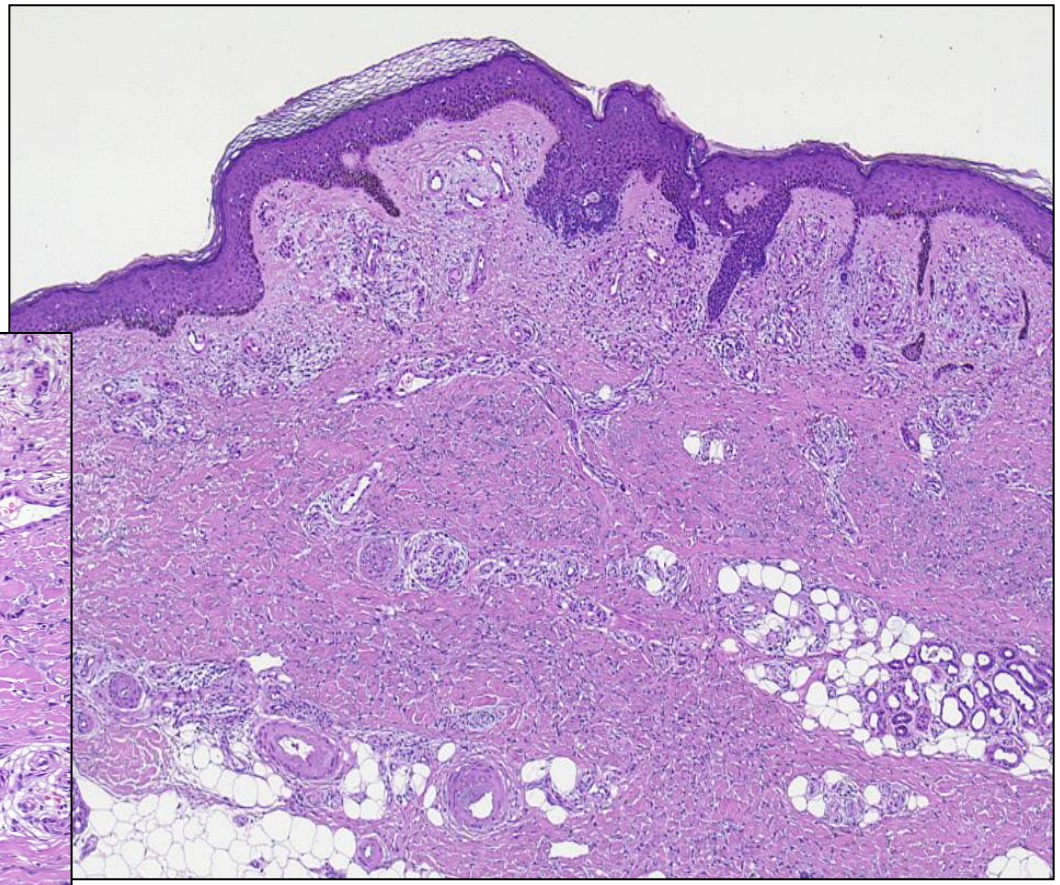
Differential Diagnosis Case 2

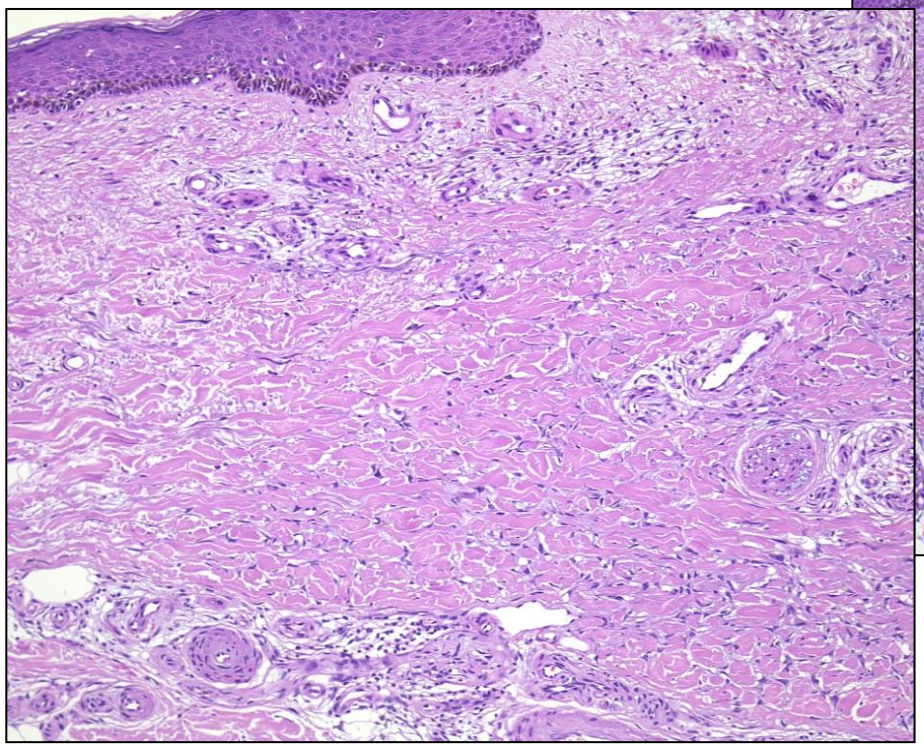
plaque-like, spindle cell, dermal neoplasm (no atypia, no mitoses, no necrosis)

- flat dermatofibroma
- neurofibroma
- dermatomyofibroma
- plaque-like CD34-positive dermal fibroma
- plaque-like DFSP

flat Dermatofibroma

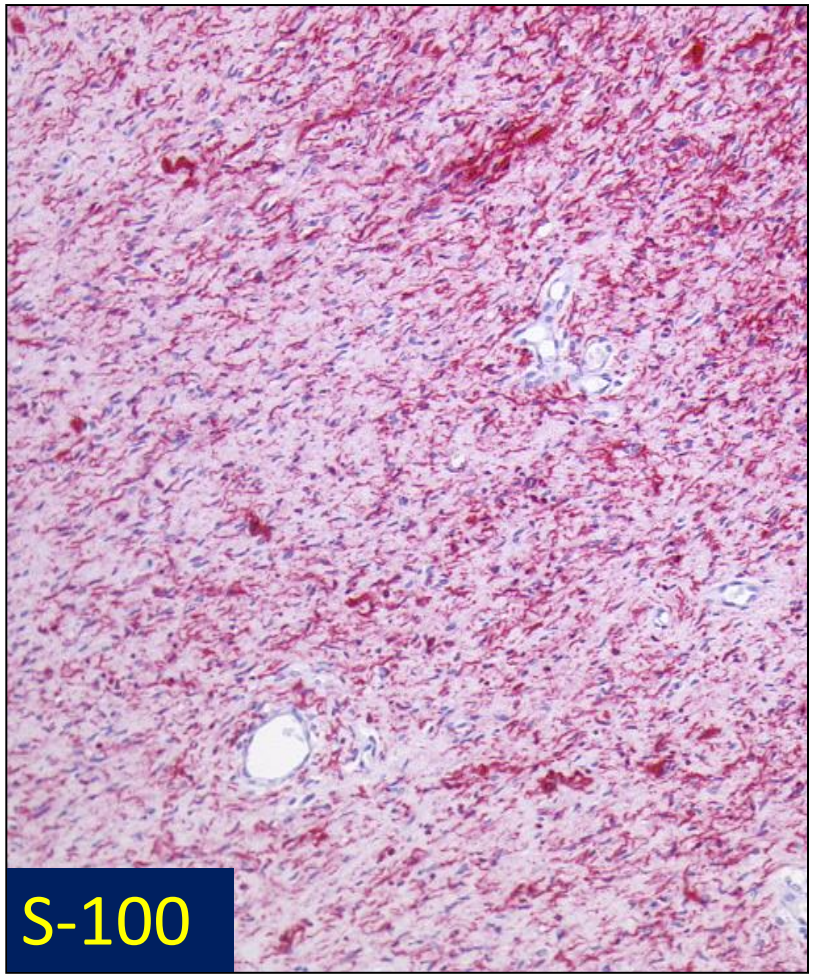
- hyperplasia of the epidermis
- plump spindled tumour cells
- hyalinised collagenous fibres (entrapment)
- CD34 -, CD64 +, HMGA2 +

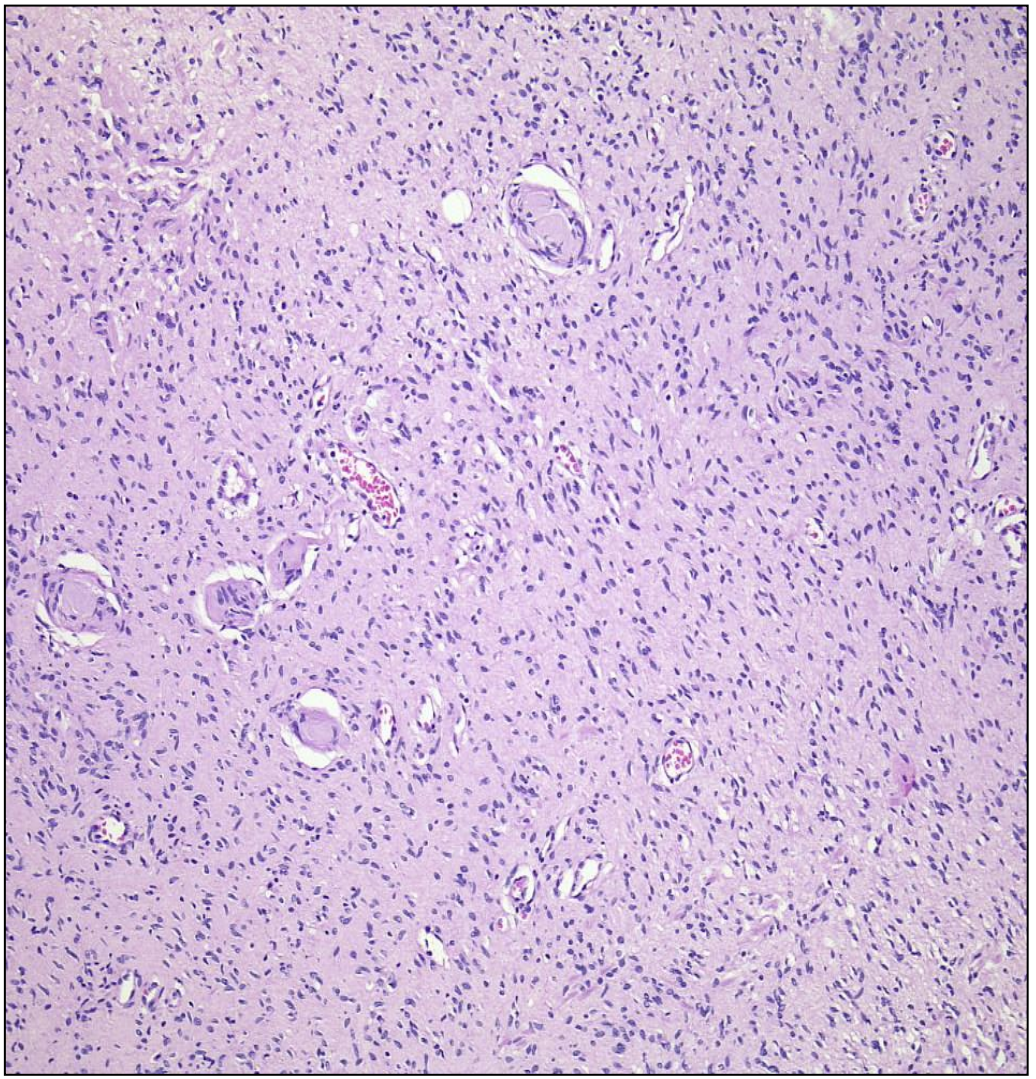




diffuse Neurofibroma

- often myxoid stroma
- scattered mast cells
- S-100 +





Dermatomyofibroma

ORIGINAL ARTICLE

Dermatomyofibroma: Clinicopathologic and Immunohistochemical Analysis of 56 Cases and Reappraisal of a Rare and Distinct Cutaneous Neoplasm

Thomas Mentzel, MD and Heinz Kutzner, MD

Abstract: Dermatomyofibroma represents a rare and distinct benign cutaneous mesenchymal neoplasm of fibroblastic/myofibroblastic differentiation. A series of 56 cases of dermatomyofibroma has been analyzed to further characterize the clinicopathologic spectrum of this entity. Forty patients were female and 8 were male (gender was unknown in 8 cases). Patients' age ranged from 3 to 51 years (mean 30.8 years, median 30 years). Interestingly, 6 patients were younger than 16 years, and in this age group, 3 male and 3 female patients, respectively, were noted. The shoulder (13 cases) was the anatomic site most commonly affected, followed by the upper arm (7 cases), the neck (6 cases), the thigh (6 cases), the chest wall (4 cases), the back (3 cases), the axillary fold (2 cases), the abdominal wall (2 cases), and 1 case each was seen on the forearm, the buttock, and the popliteal fossa (exact anatomic location was unknown in 10 cases). One patient presented with 2 lesions arising simultaneously on both shoulders. Histologically, an ill-defined, plaque-like dermal neoplasm of varying cellularity was seen in all cases, composed of bland spindle-shaped tumor cells often oriented parallel to the overlying epidermis. An infiltration of superficial part of the subcutis was seen in 23 cases, and in 6 cases, deeper parts of the subcutis were involved by often perpendicular growing bands of neoplastic cells. Immunohistochemically, tumor cells in 11 of 48 cases tested stained positively for alpha-smooth muscle actin, and a focal expression of this marker was noted in 20 cases. In addition, a focal expression of CD34 was seen in 10 of 45 cases tested. Follow-up information was available in 38 cases (range from 3 to 156 months, median 34 months), and despite marginal or incomplete excision in 17 cases, none of the cases recurred. Dermatomyofibroma represents a benign fibroblastic/myofibroblastic dermal neoplasm.

Key Words: dermatomyofibroma, mesenchymal neoplasms, plaque-like dermal fibromatosis, skin

(*Am J Dermatopathol* 2009;31:44–49)

INTRODUCTION

The spectrum of fibroblastic/myofibroblastic cutaneous tumors comprises a heterogeneous group of benign, atypical, and malignant neoplasms mainly composed of spindle-shaped tumor cells. Non-neoplastic myofibroblasts resemble fibroblasts; feature immunohistochemically heterogeneous phenotypes with regard to their content of intermediate filaments, muscle actin, and myosin; and are defined ultrastructurally by specialized organelles such as stress fibers and cell to stroma attachment sites (so-called fibronexus). Myofibroblasts are therefore regarded as a functional stage of fibroblasts seen in many physiological and pathological conditions.[1] In addition, with the advent of immunohistochemical markers, an increasing number of benign and more rarely malignant mesenchymal neoplasms showing a myofibroblastic line of differentiation have been reported in the past years. Dermatomyofibroma, first described as a plaque-like dermal fibromatosis,[2] represents a rare but distinct benign dermal proliferation of fibroblasts and myofibroblasts of the skin.[3] We report a series of 56 cases of dermatomyofibroma, discuss histologic and immunohistochemical features, and widen the clinicopathologic spectrum of this entity also in regard to other spindle cell lesions of the dermis and subcutis.

MATERIALS AND METHODS

The tissue in all cases was fixed in 4% buffered formalin, routinely processed, and embedded in paraffin; 4- μm-thick sections were stained with hematoxylin and eosin, and elastic stains were performed in 43 cases. In addition, representative sections in 48 cases were stained immunohistochemically by the labeled streptavidin–biotin technique using commercially available antibodies; antigen retrieval was used for all antibodies. Stainings for alpha-smooth muscle actin (clone: 1A4, dilution: 1:300, source: DAKO, Glostrup, Denmark), muscle actin (HHF35, 1:200; DAKO), h-caldesmon (h-CD, 1:200; DAKO), CD34 (Qbend10, 1:50; DAKO), desmin (D33, 1:200; DAKO), epithelial membrane antigen (Mc5, 1:400; Biogenex, San Ramon, CA), factor XIIIa (AC-1A1, 1:1000; LABVISION, Suffolk, UK), and S-100 protein (polyclonal, 1:4000; DAKO) were available in a varying number of cases. Appropriate positive and negative controls were used in all cases. Clinical information and follow-up were retrieved from the laboratory request forms and contributing clinicians. Cases 51, 52, and 53 have been reported in detail elsewhere.[4]

RESULTS

The clinical findings are summarized in Table 1. Briefly, the analyzed neoplasms arose in 40 female and 8 male patients (gender was unknown in 8 cases), and patients' age ranged

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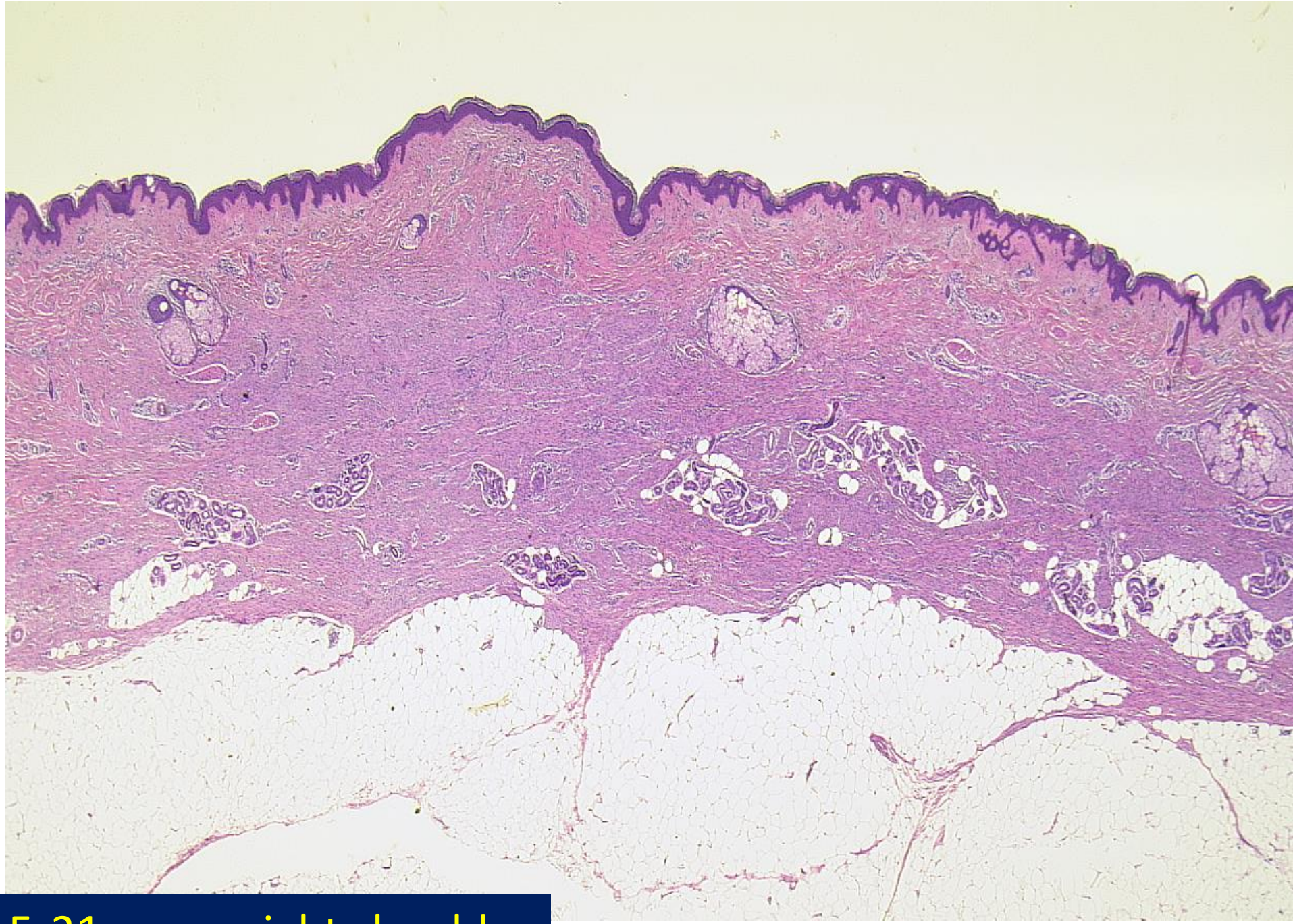
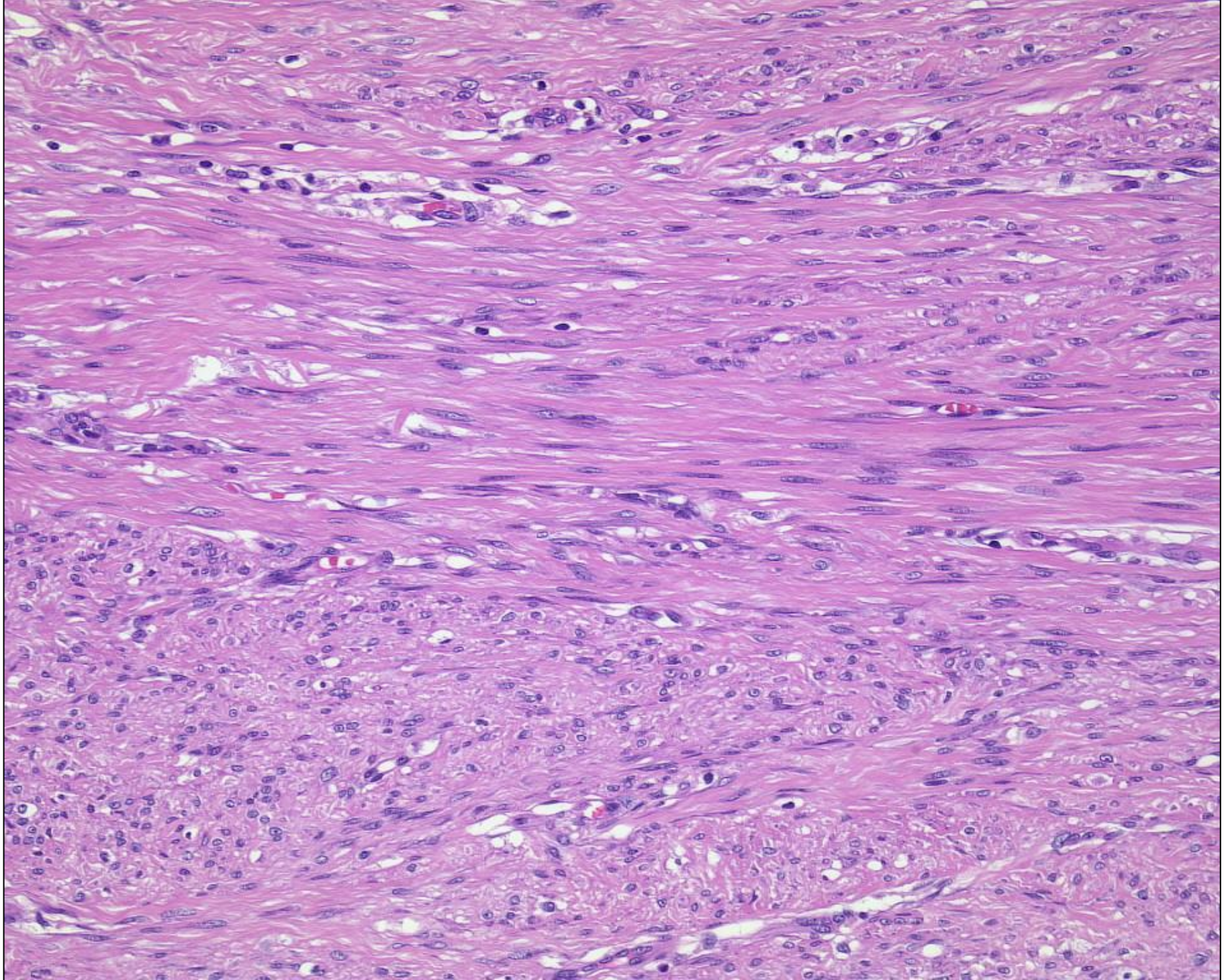
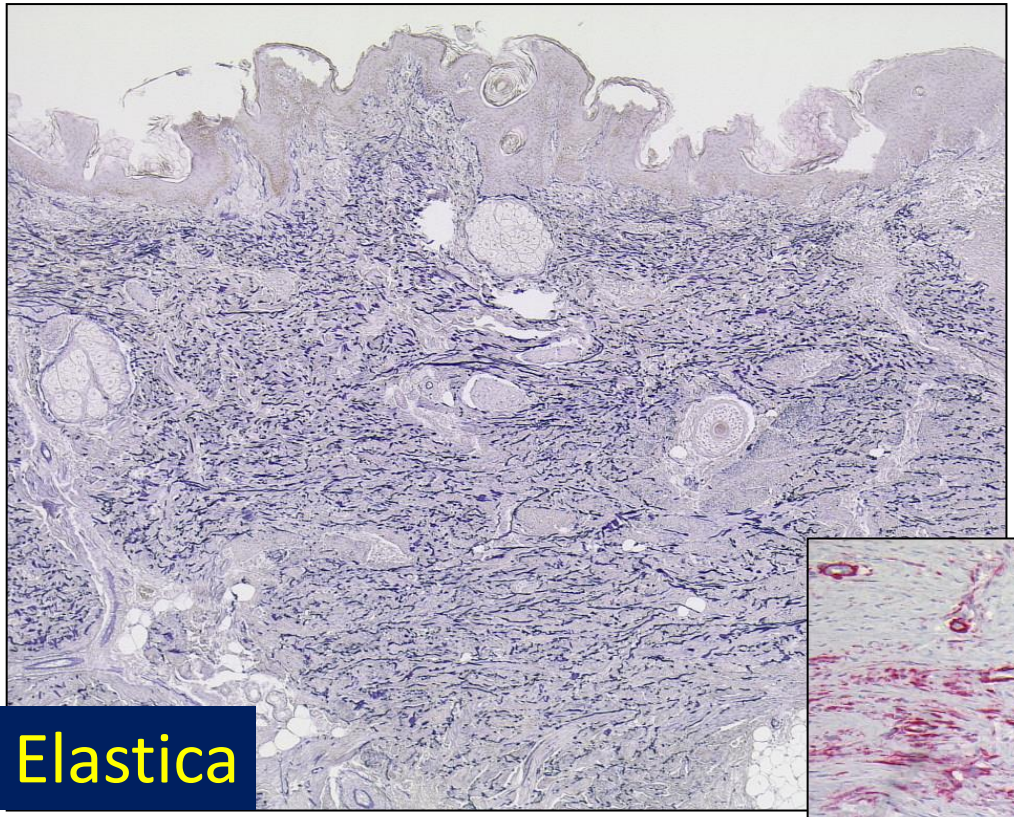
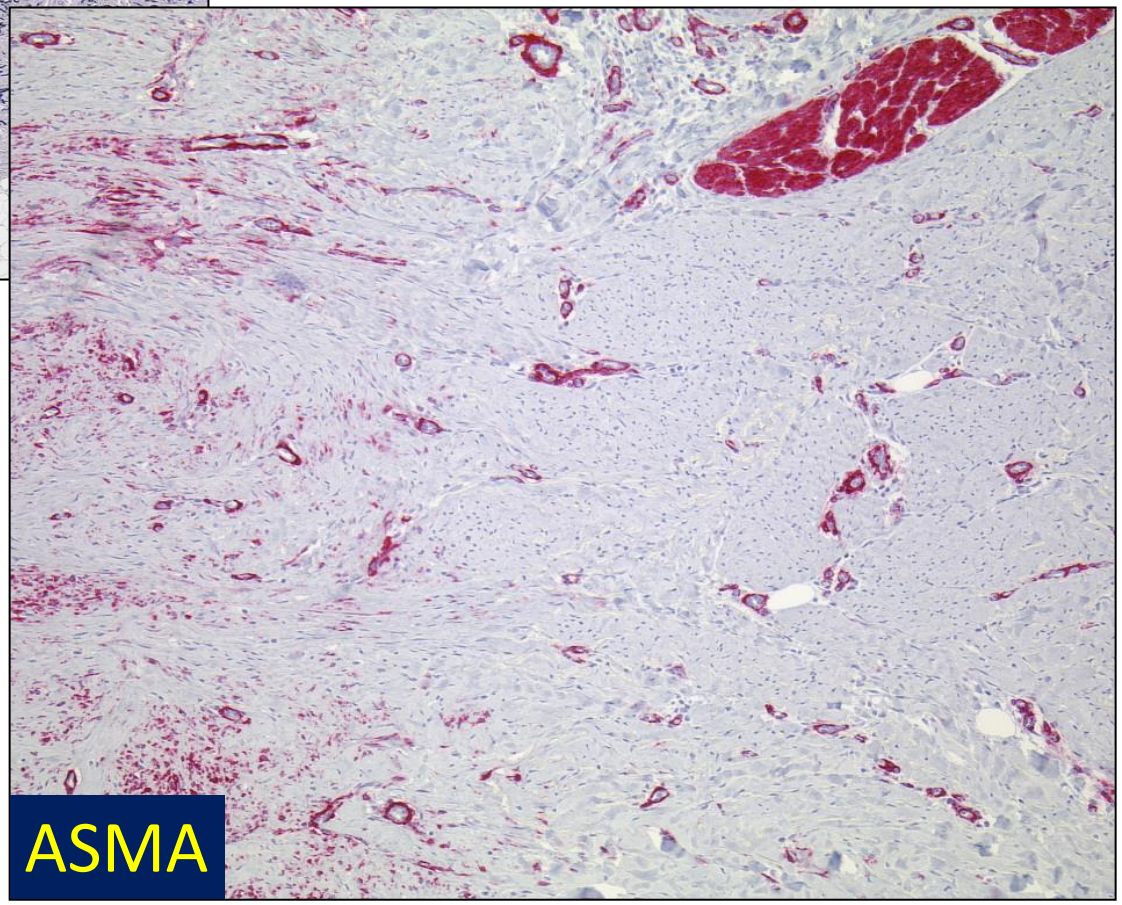


F, 31 years, right shoulder




Elastica


ASMA

Plaque-like CD34 positive dermal Fibroma („Medallion-like Dermal Dendrocyte Hamartoma“)

Plaque-like CD34-positive Dermal Fibroma (''Medallion-like Dermal Dendrocyte Hamartoma'')

Clinicopathologic, Immunohistochemical, and Molecular Analysis of 5 Cases Emphasizing its Distinction From Superficial, Plaque-like Dermatofibrosarcoma Protuberans

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Abstract: Medallion-like dermal dendrocyte hamartoma (DH) and superficial (plaque-like) dermatofibrosarcoma protuberans (DFSP) are CD34-positive dermal neoplasms with overlapping clinicopathologic features. We analyzed the clinical, histomorphologic, and molecular criteria of 5 DH and 7 DFSP to delineate diagnostically relevant differences between incipient dermal DFSP and its benign look-alike, DH. We expand the clinical and histologic spectrum of DH. As medallion-like dermal DH is neither of dermal dendrocyte lineage nor a genuine hamartoma, we propose instead the descriptive term of plaque-like CD34-positive dermal fibroma (PDF). Both PDF/DH and DFSP presented as slightly pigmented and indurated plaques on neck, trunk, and extremities. Histologically, DFSP was characterized either by horizontally oriented spindle cell fascicles or by diffusely arranged fibroblasts within a slightly myxoid stroma in the upper two-thirds of the dermis, whereas PDF/DH presented with a cellular band-like fibroblastic proliferation mostly in the papillary and adjacent upper reticular dermis. Only one congenital PDF/DH in a 9-year-old boy extended into the septa of the subcutaneous fat. Formalin-fixed paraffin-embedded archival tissue was used for detection of the *COL1A1-PDGFB* gene rearrangement by multiplex reverse transcription-polymerase chain reaction (RT-PCR) and by dual color fusion fluorescence in-situ hybridization (FISH). Archival blocs older than 4 years did not yield amplifiable RNA because of RNA degradation, whereas FISH analysis was feasible in all investigated cases. FISH analysis revealed *COL1A1-PDGFB* gene rearrangement in all DFSP cases (n = 7), whereas RT-PCR could detect the *COL1A1-PDGFB* fusion transcript only in 1 DFSP. Two cases were negative. In 4 archival cases with st between 4.5 and 12 years, RNA had been degraded m these cases unsuitable for RT-PCR. In PDF/DH, both RT- and FISH analysis did not reveal any evidence of *COL PDGFB* gene rearrangement. We show that PDF/DH superficial (plaque-like) DFSP, subtle clinicopathologic c ences notwithstanding, are morphologic look-alikes that c kept apart by molecular studies of the *COL1A1-PDGFB* fusion. For the detection of the *COL1A1-PDGFB* gene rearr ment in diagnostically difficult cases, RT-PCR and FISH lysis are reliable and helpful diagnostic tools. In arc formalin-fixed paraffin-embedded tissue, however, FISH ysis is more robust and exhibits a higher clinical sensitivity RT-PCR.

Key Words: medallion-like dermal dendrocyte hamart plaque-like CD34+ dermal fibroma, superficial (plaque dermatofibrosarcoma protuberans, CD34, *COL1A1-PL* fusion gene

(*Am J Surg Pathol* 2010;34:190–201)

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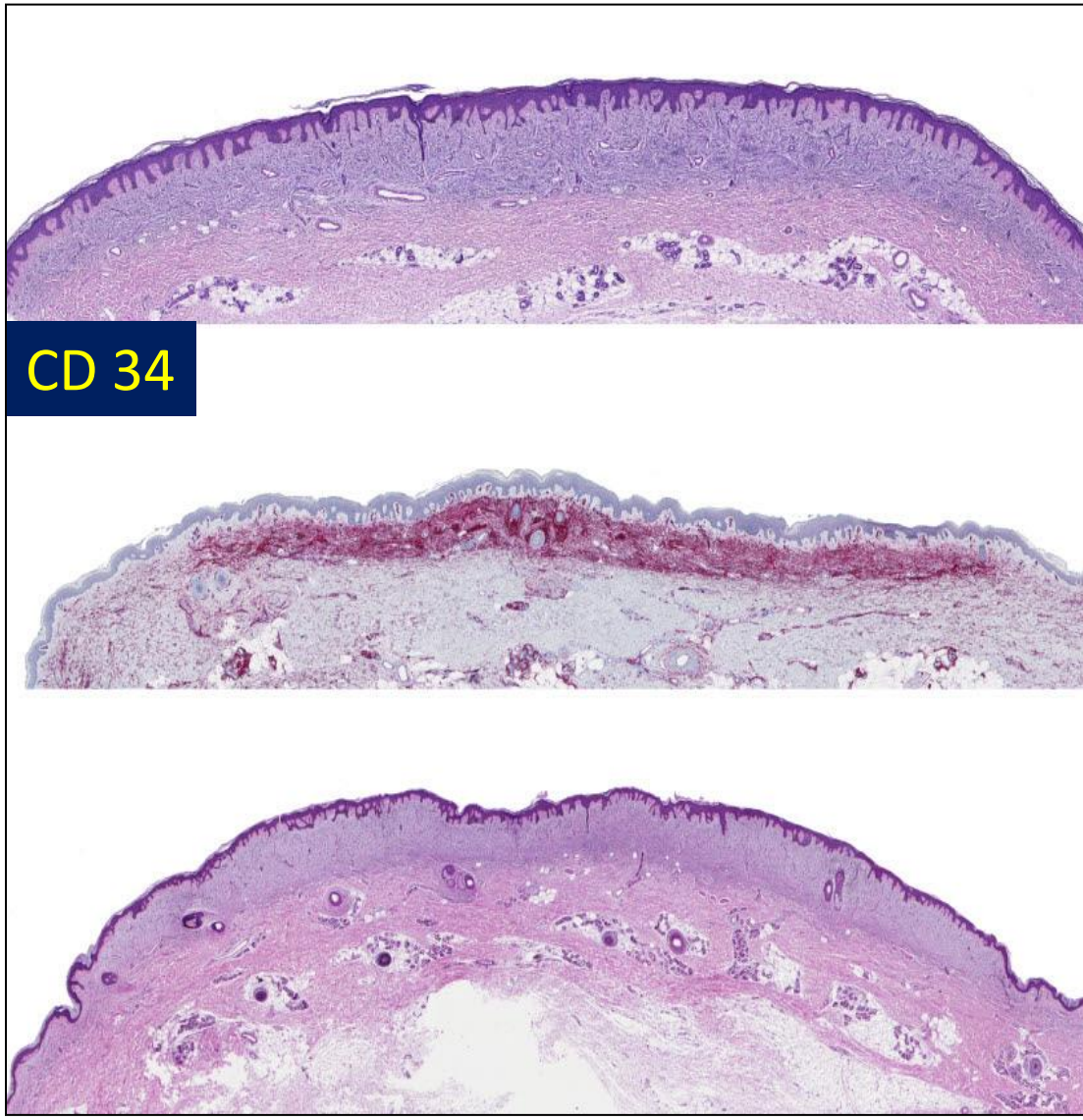
The spectrum of CD34-positive (CD34+) tumo the skin comprises a heterogeneous family of senchymal neoplasms with multiple lines of differe tion, ranging from the fibroblastic to the hematop lineage.[43] Among these, most diagnostic difficulties encountered within the group of dermal fibrocytic sp cell proliferations, some of which are poorly de and present with a wide clinical and histomorpho spectrum.[8,11,13,25,31,37]

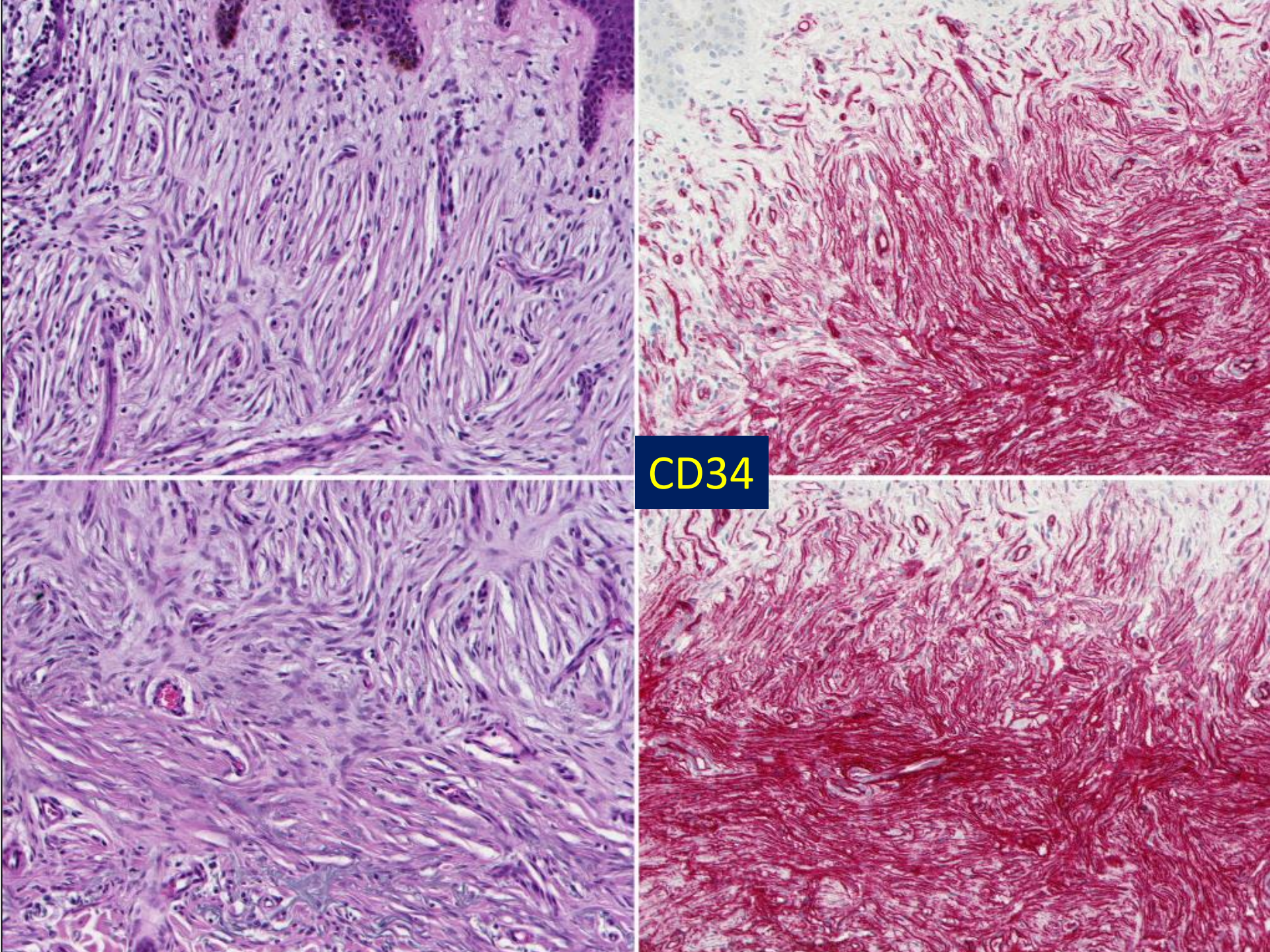
Medallion-like dermal dendrocyte hamart (DH) is a recently described presumably hamartom neoplasm[34] showing morphologic overlap with conge atrophic dermatofibrosarcoma protuberans (DFSP).

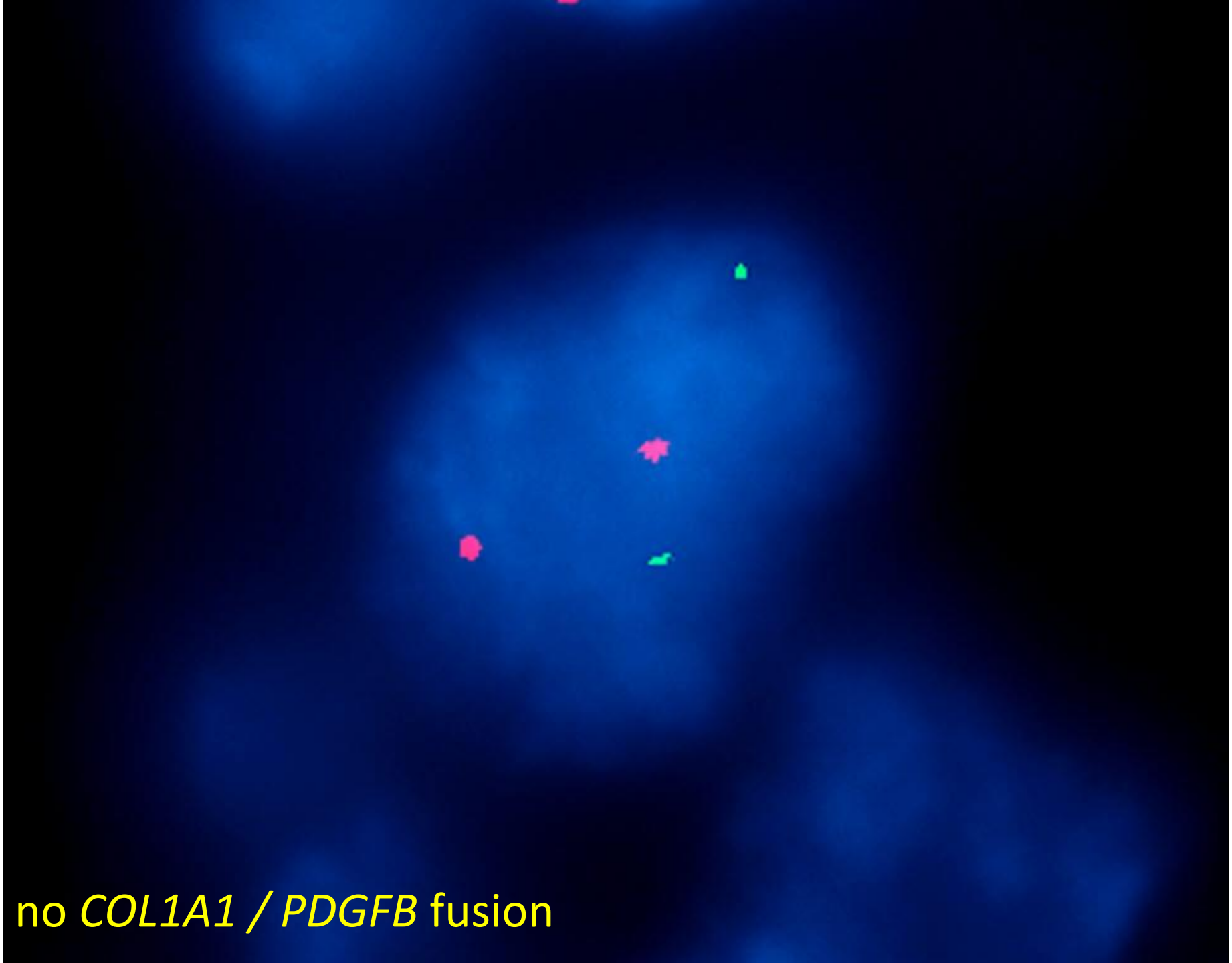
We report a series of 5 cases of DH and 7 cas superficial (plaque-like) DFSP, expand the clinicop logic spectrum of these neoplasms, and discuss mole methods for differential diagnosis. We will show multiplex reverse transcription-polymerase chain rea

Plaque-like CD34-positive dermal Fibroma

- children, adults
- bandlike fibroblastic proliferation
- upper half of the dermis
- no involvement of stratum papillare
- adnexal structures are spared
- many vessels
- biphasic growth

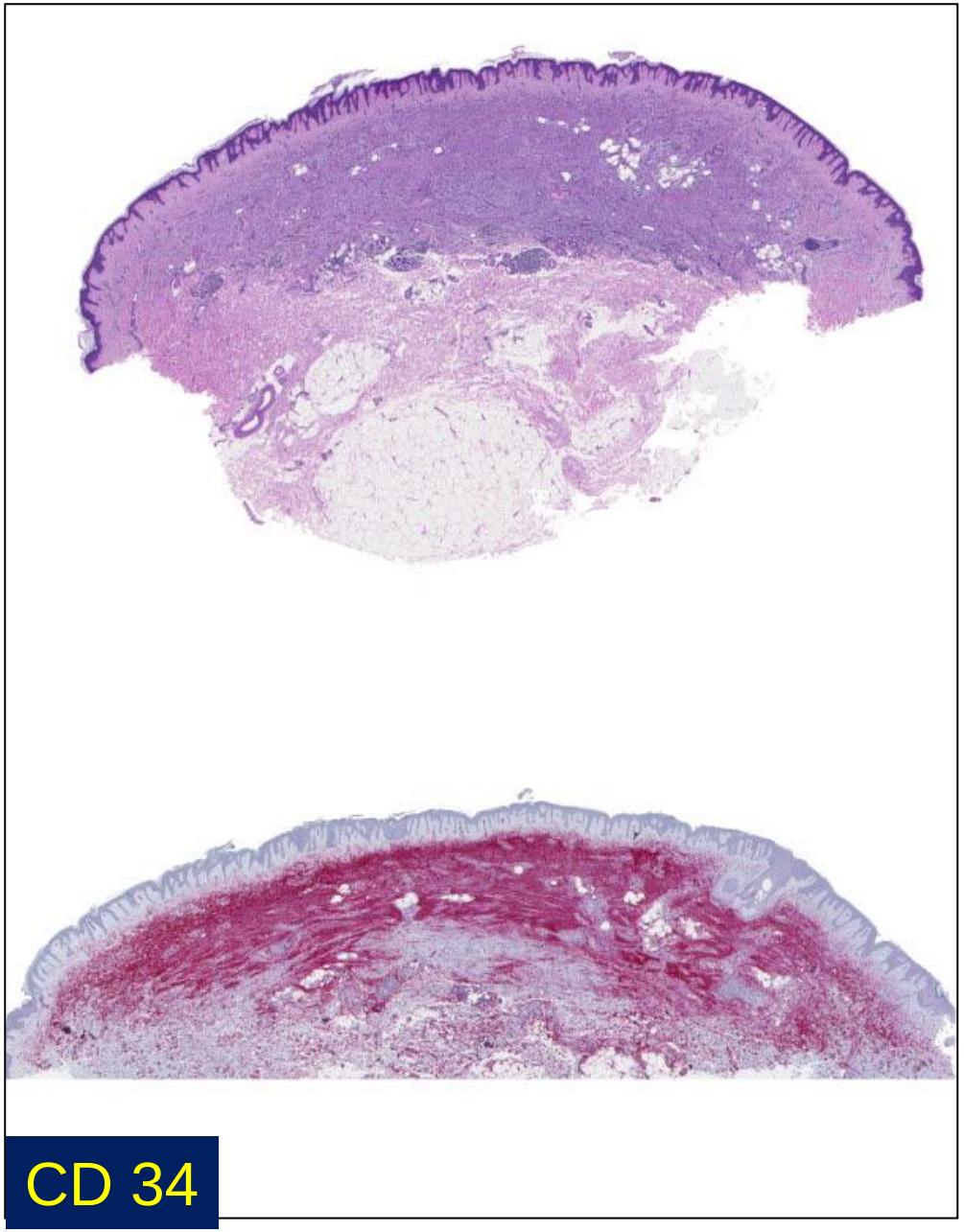


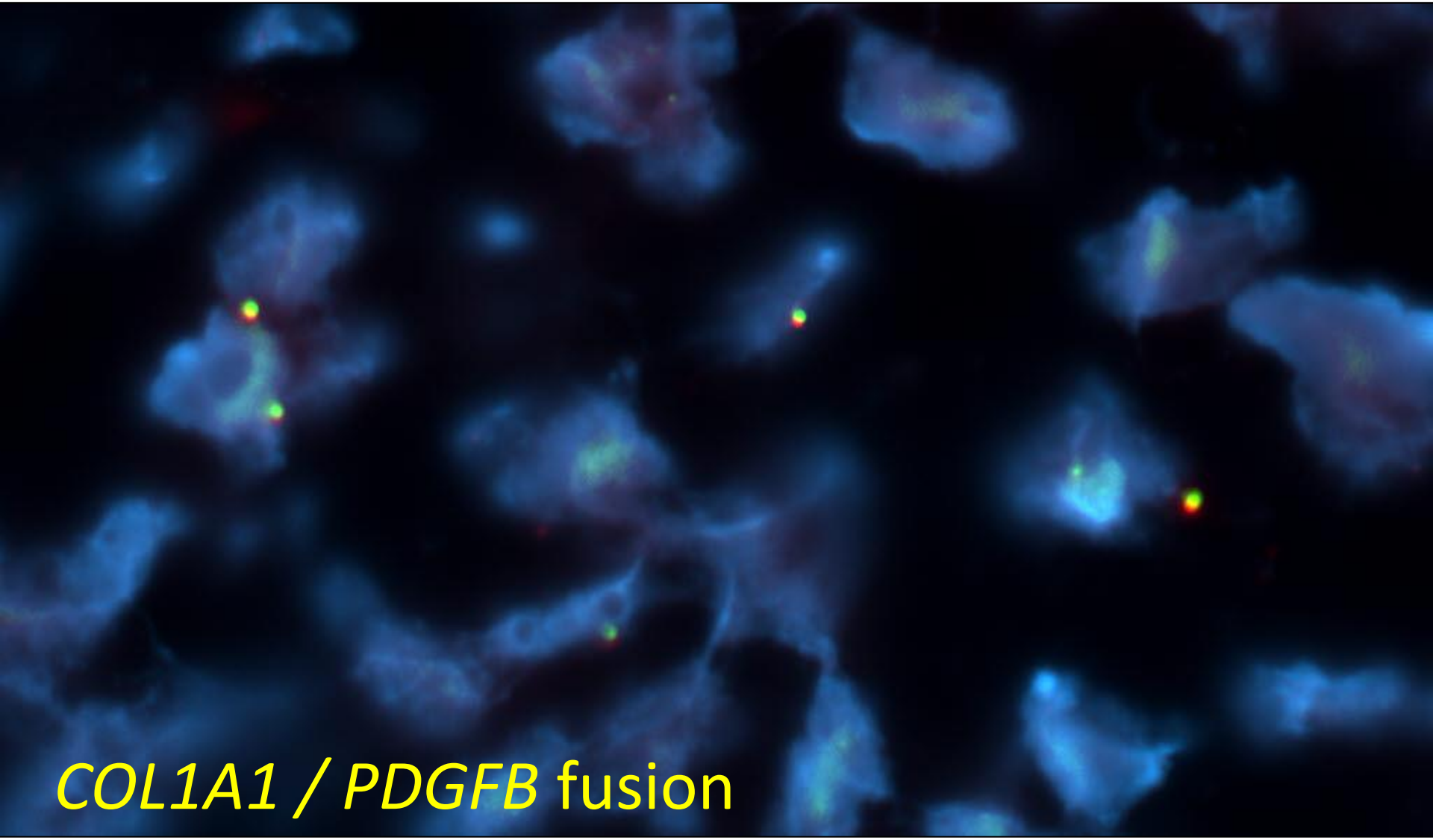

CD34

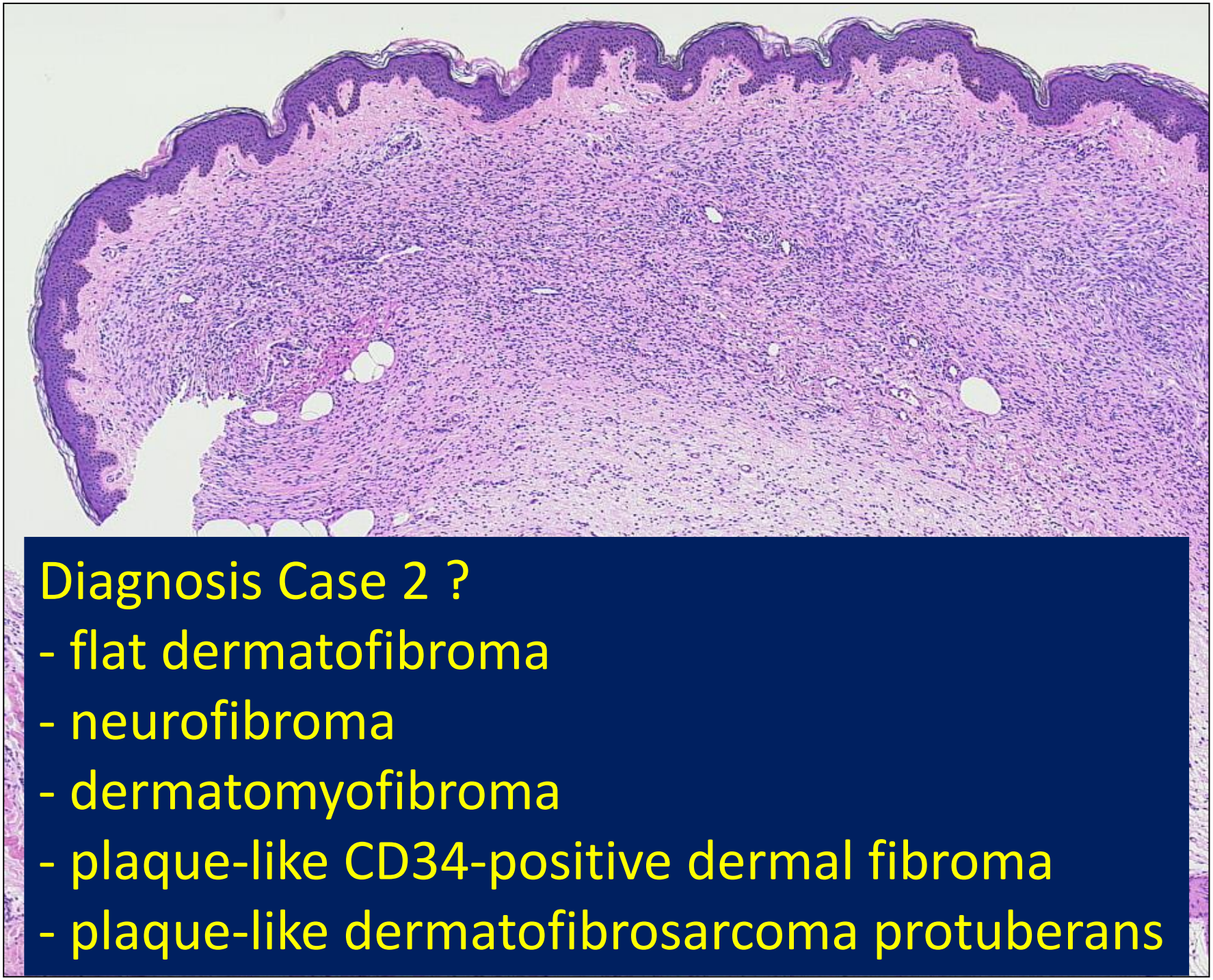

no *COL1A1 / PDGFB* fusion

plaque-like DFSP

- horizontal growth
- also in deeper parts of the dermis
- myxoid stroma
- adnexal structures are not spared
- *COL1A1 / PDGFB* fusion

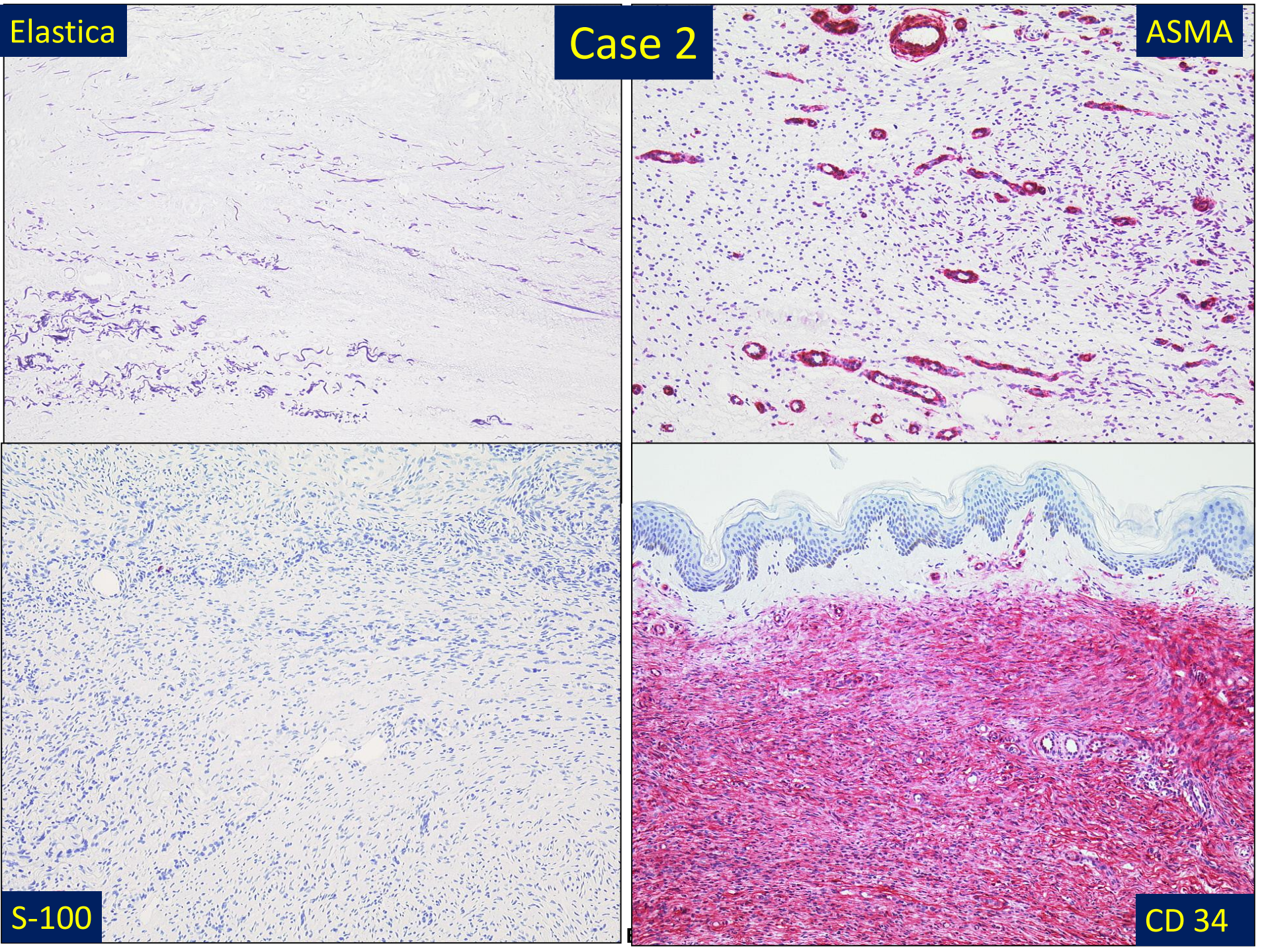



COL1A1 / PDGFB fusion



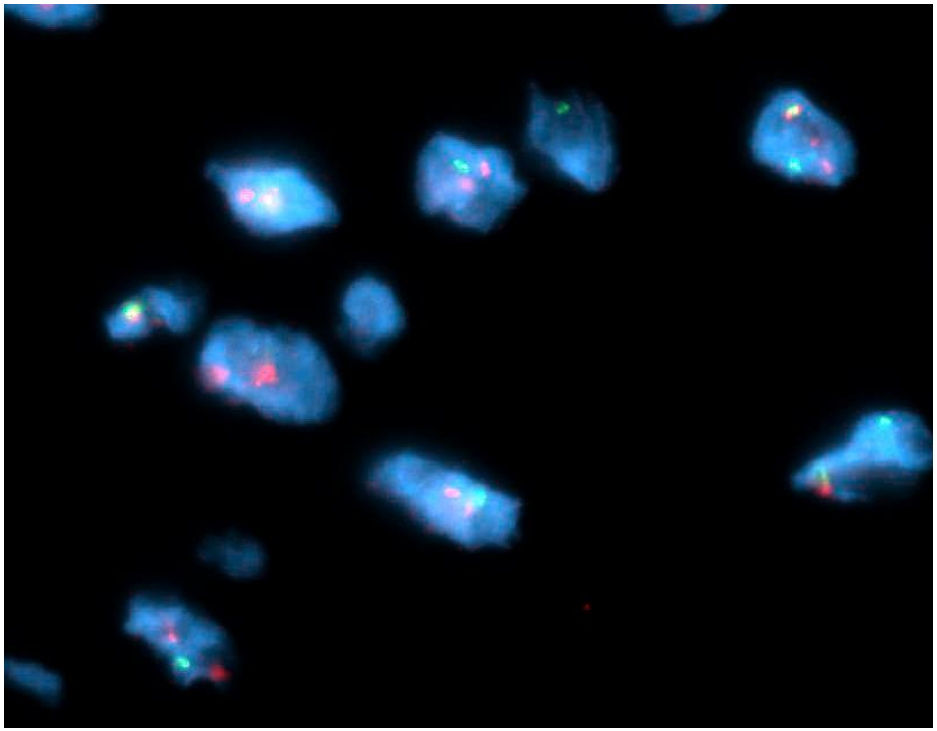
Diagnosis Case 2 ?

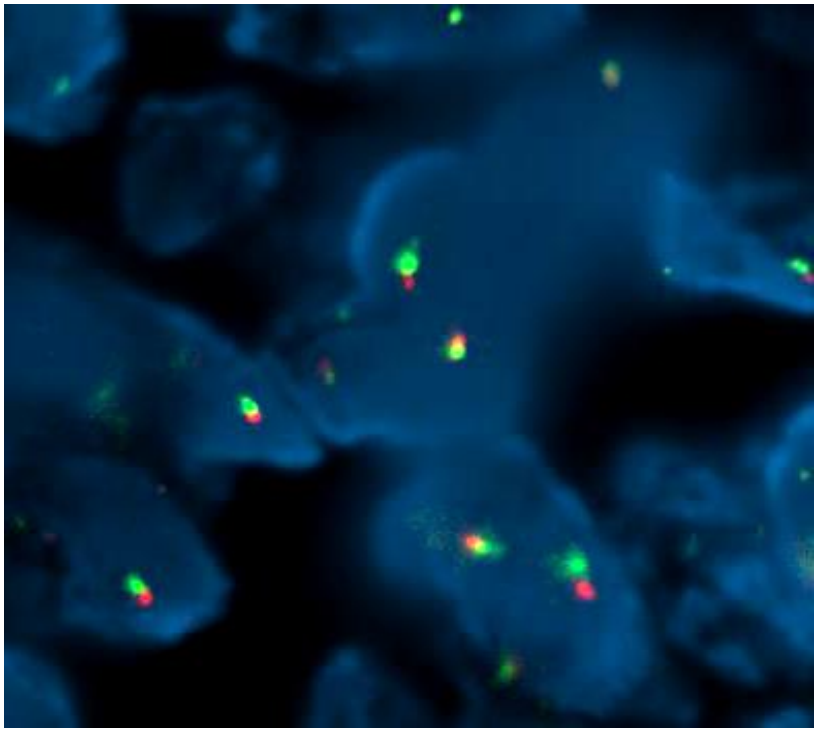
- flat dermatofibroma
- neurofibroma
- dermatomyofibroma
- plaque-like CD34-positive dermal fibroma
- plaque-like dermatofibrosarcoma protuberans


Elastica
Case 2
ASMA
S-100
CD 34

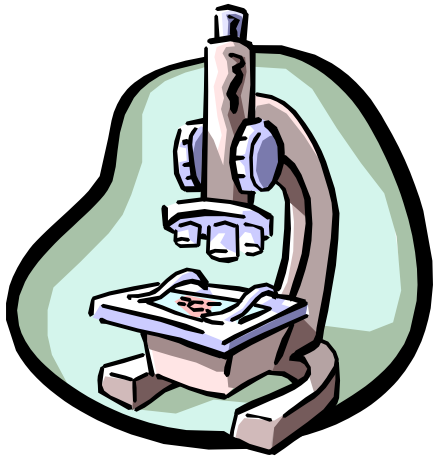
COL1A1 break apart probe

negative control



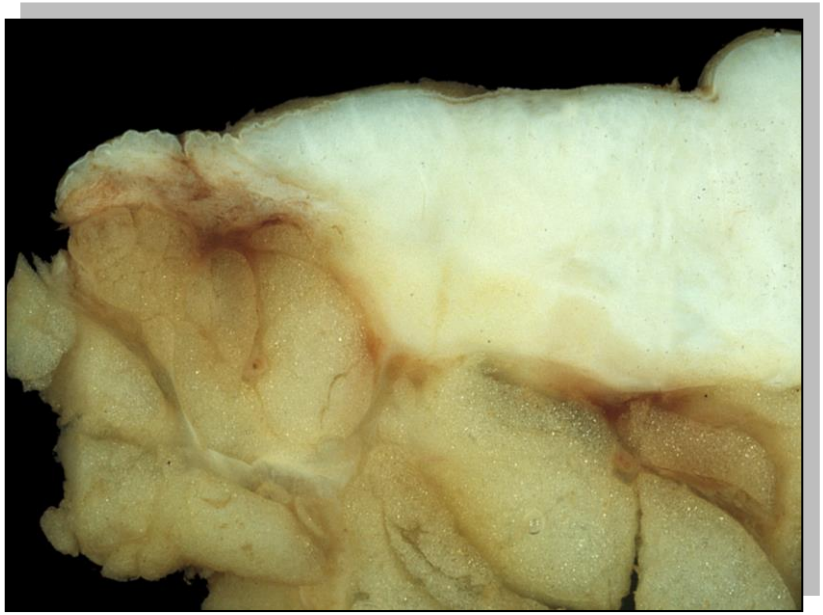


Case 2:
separated signals are present in
42 out of 50 nuclei counted

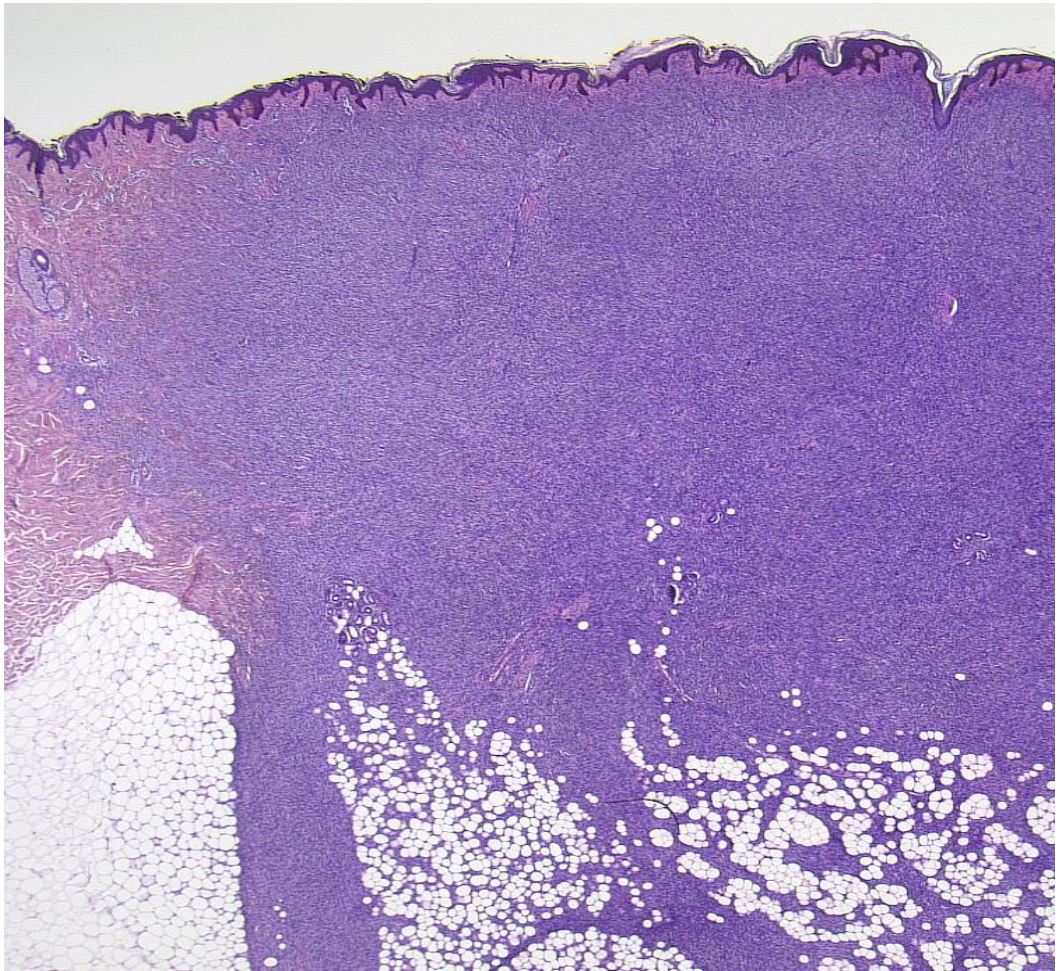


Diagnosis Case 2

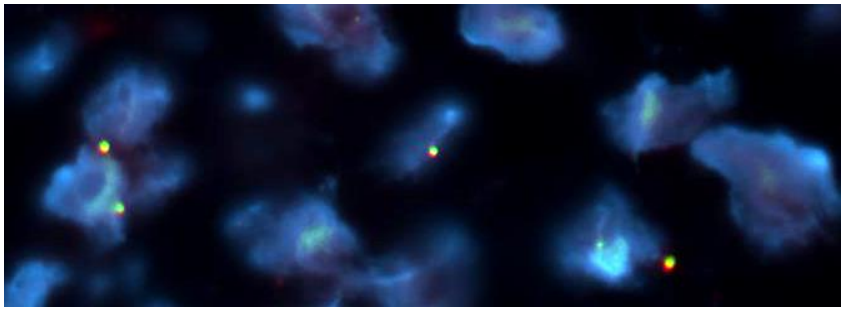
plaque-like DFSP



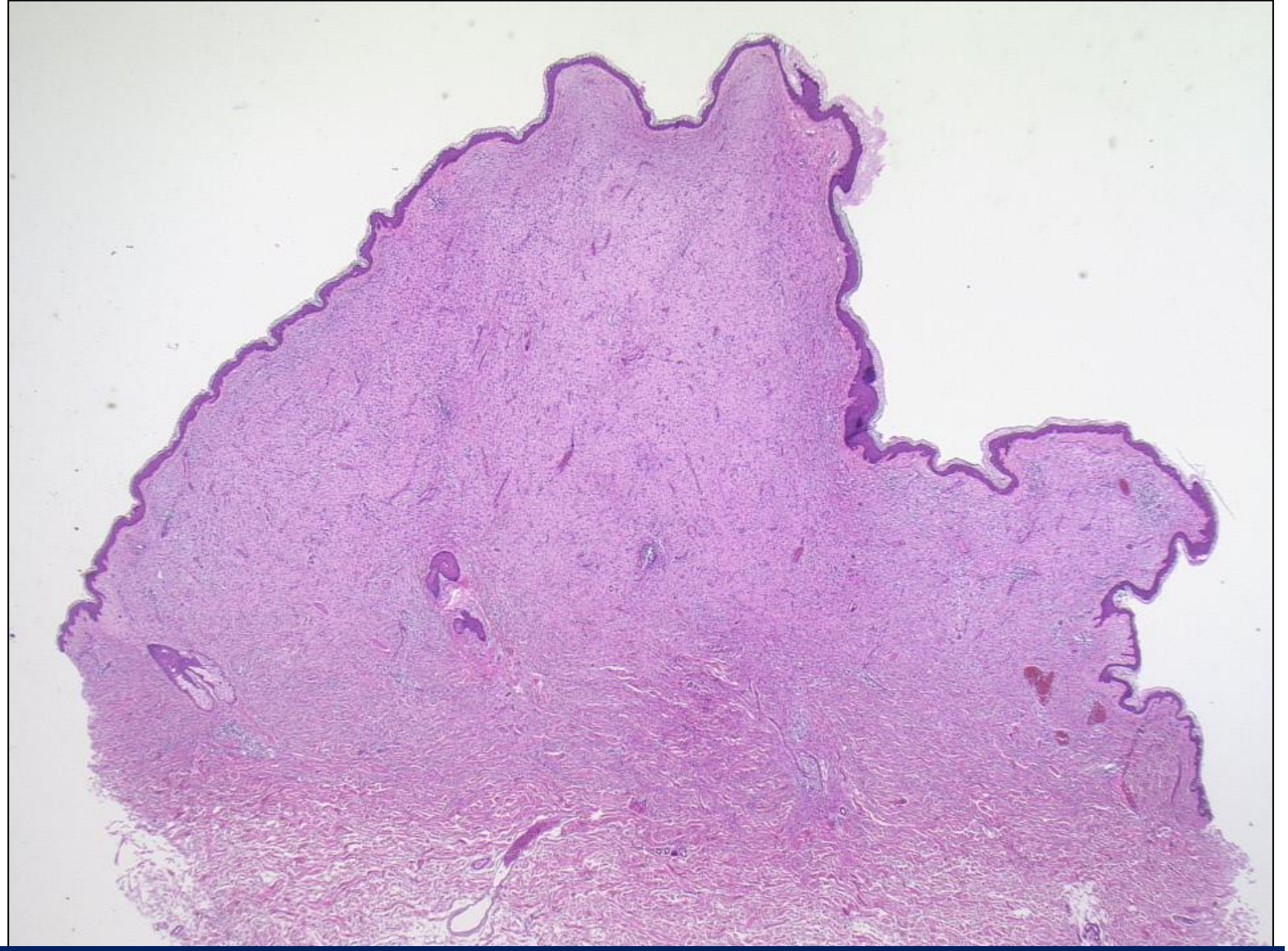
Dermatofibrosarcoma protuberans (DFSP)



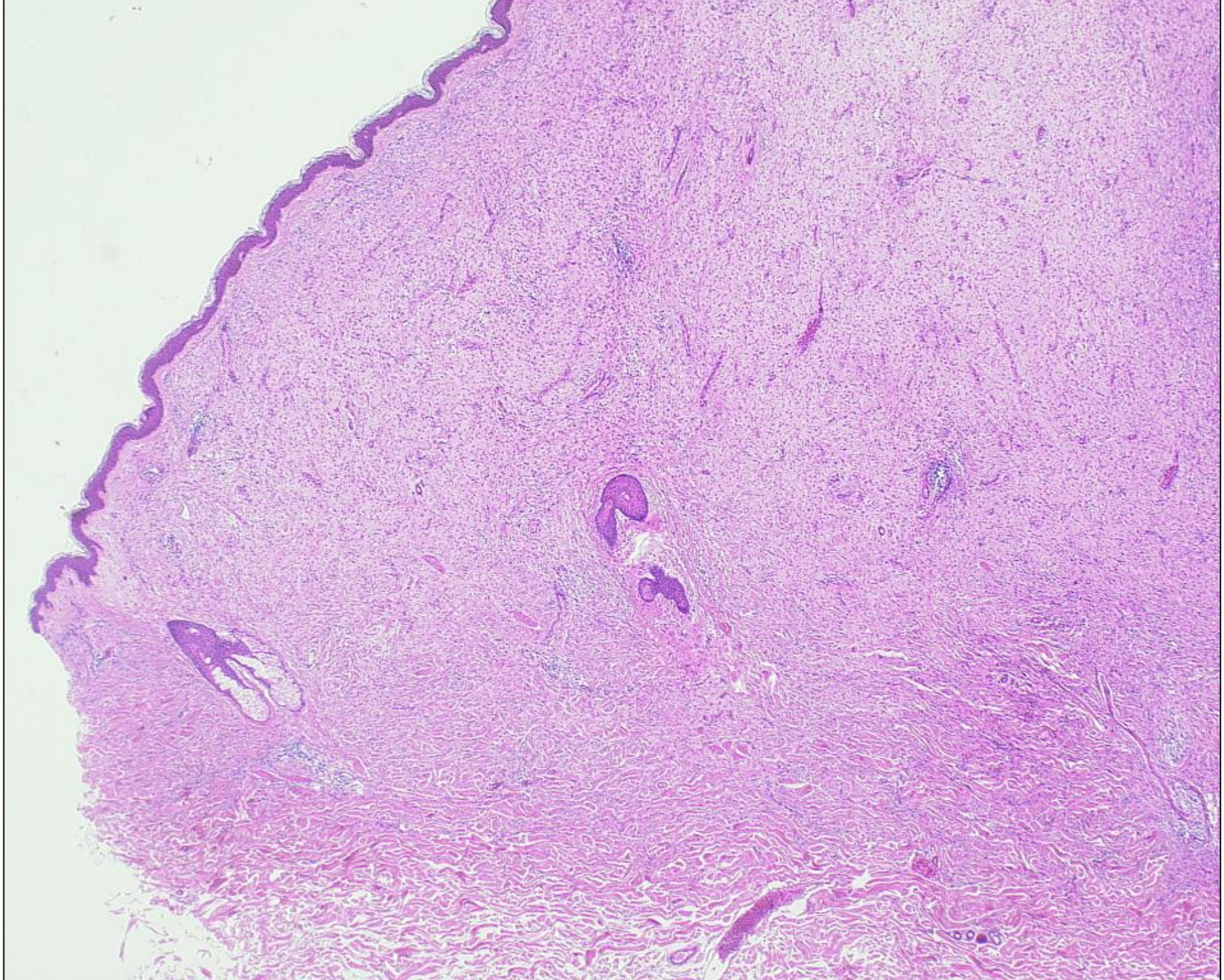
COL1A1::PDGFB
(classic or cryptic)

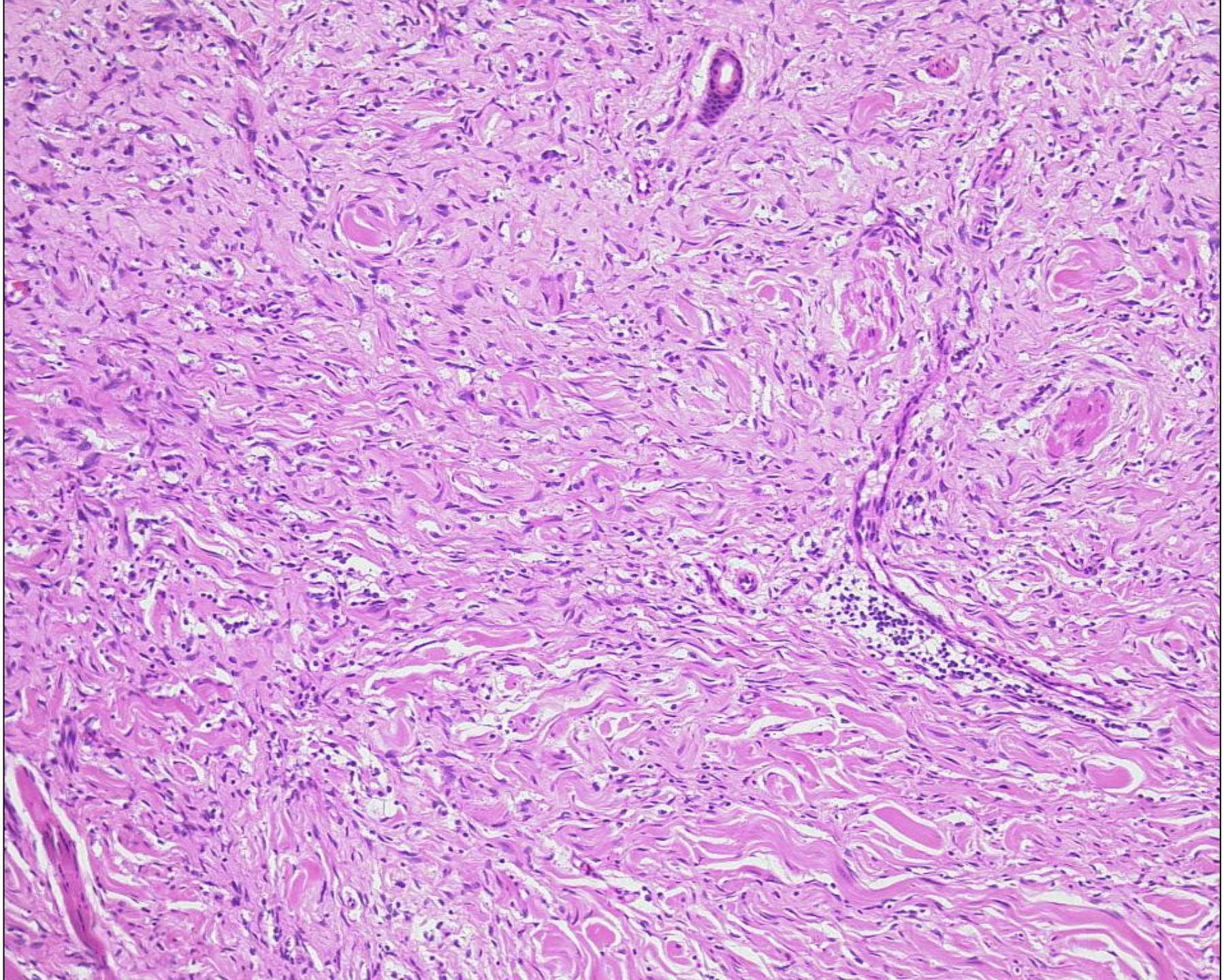


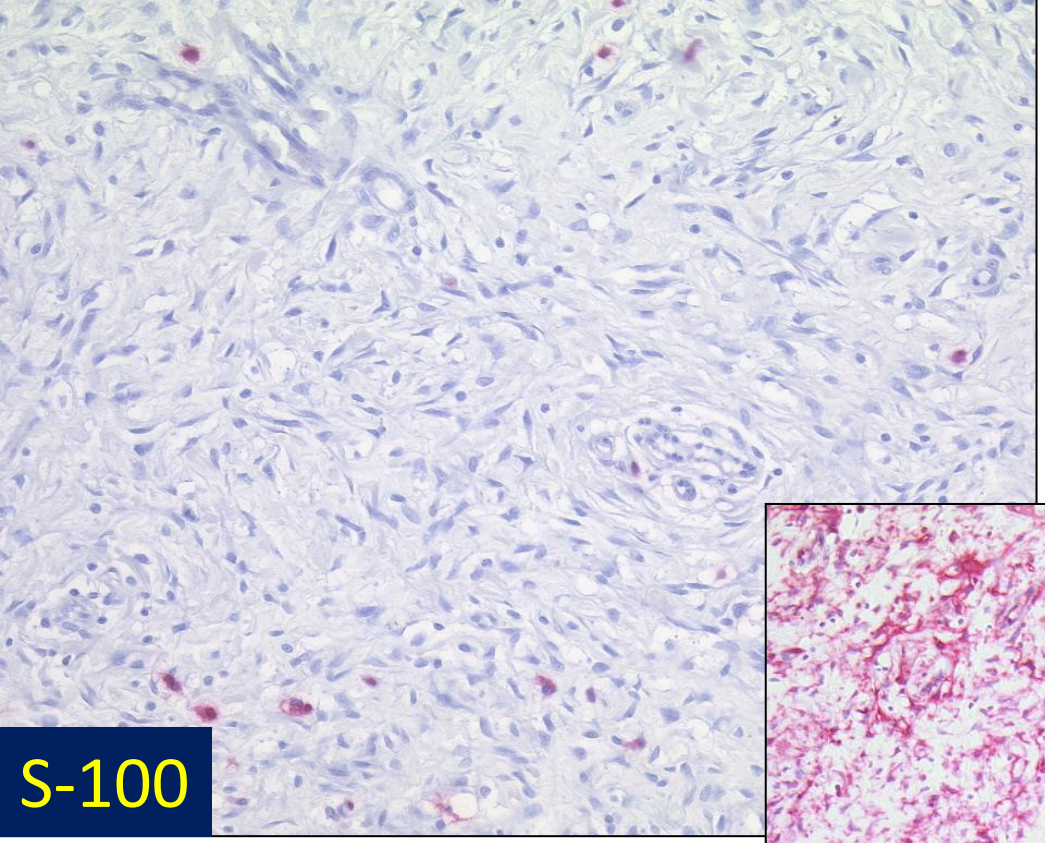
FISH-probes for t (17;22)
green BAC 93L18 (chromosome 22)
red BAC 506F07 (chromosome 17)

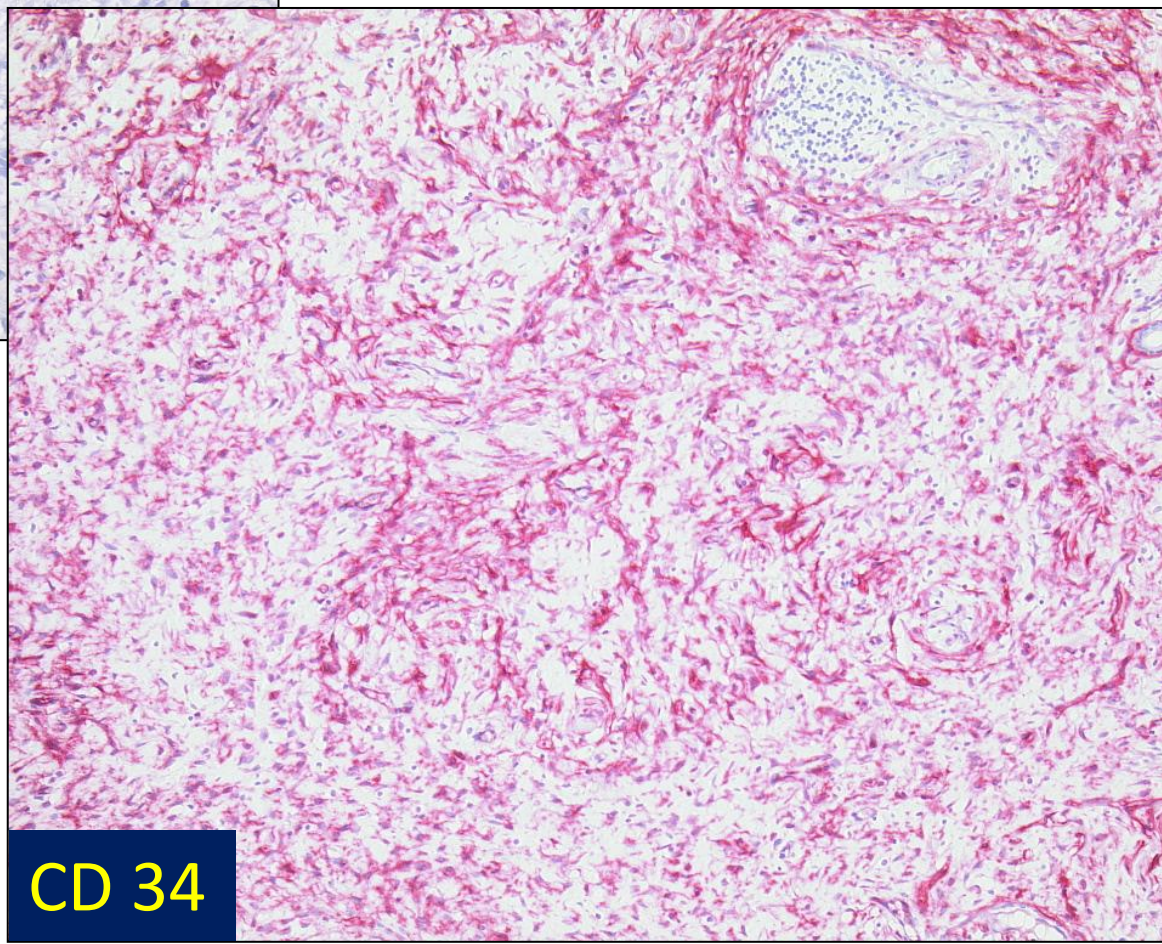


M, 47 years, right shoulder 1982
(history: recurring neurofibroma, neurofibromatosis ?
multiple lesions between 1962-1981, no histology!





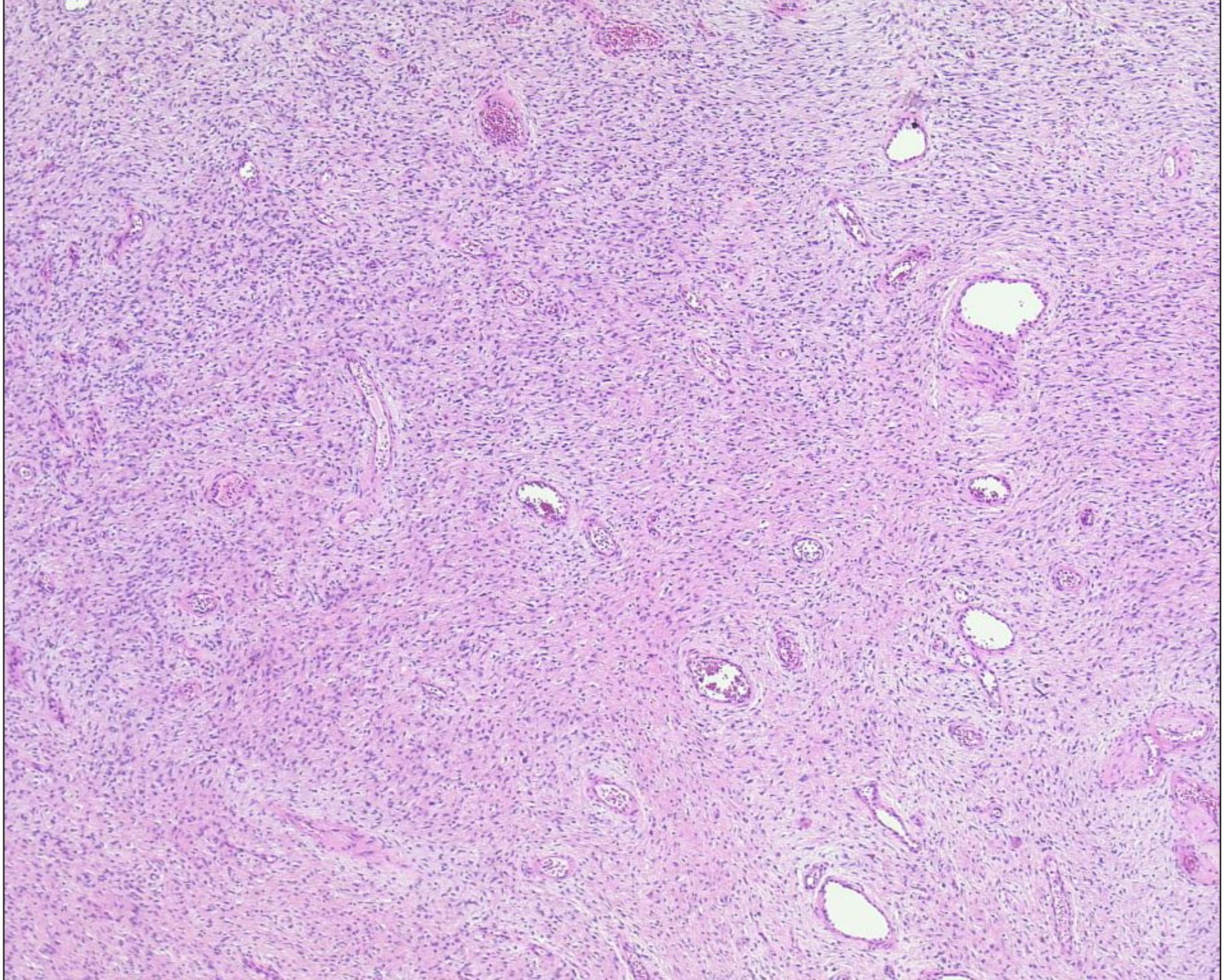

S-100

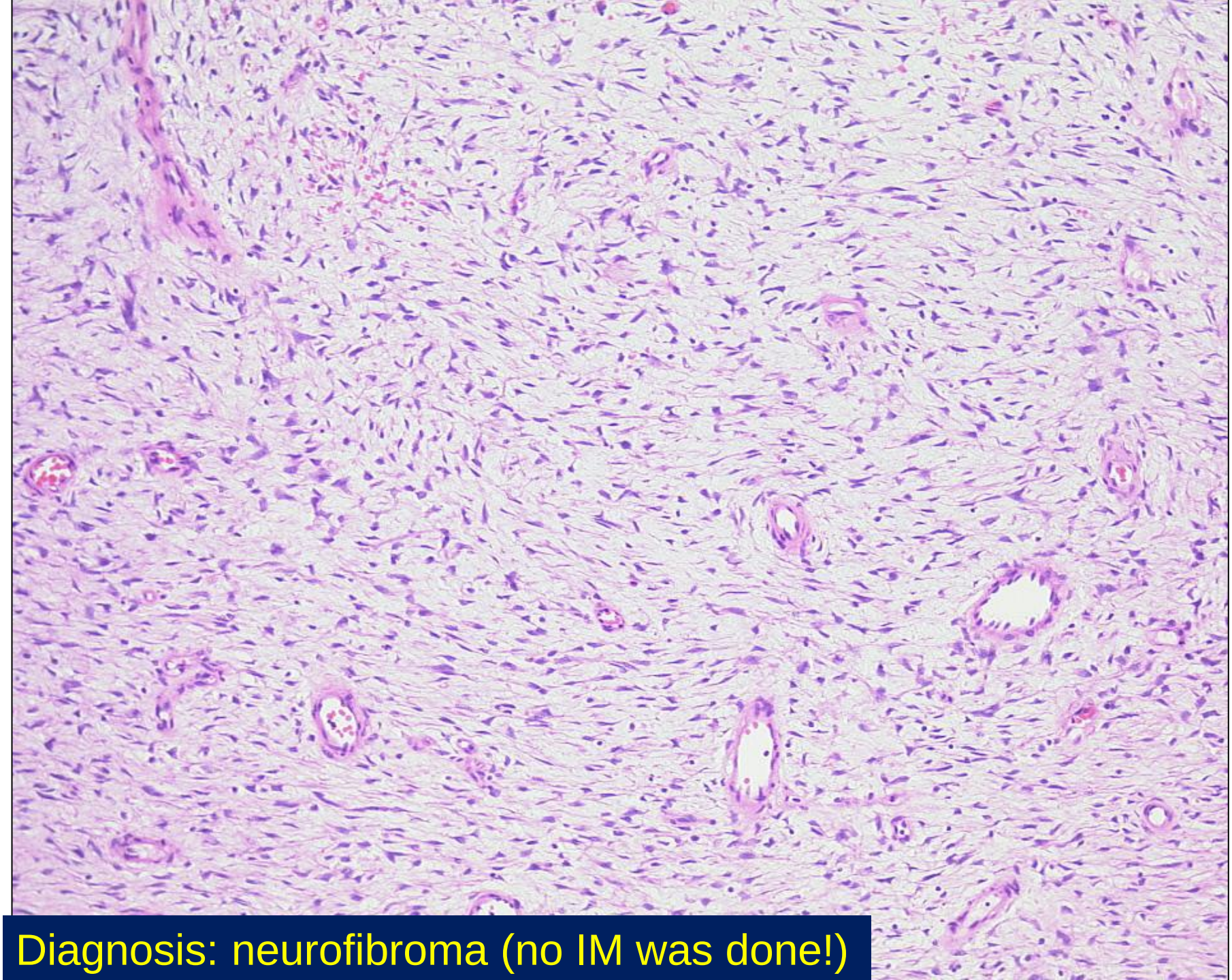

CD 34

Fibrosarcomatous DFSP

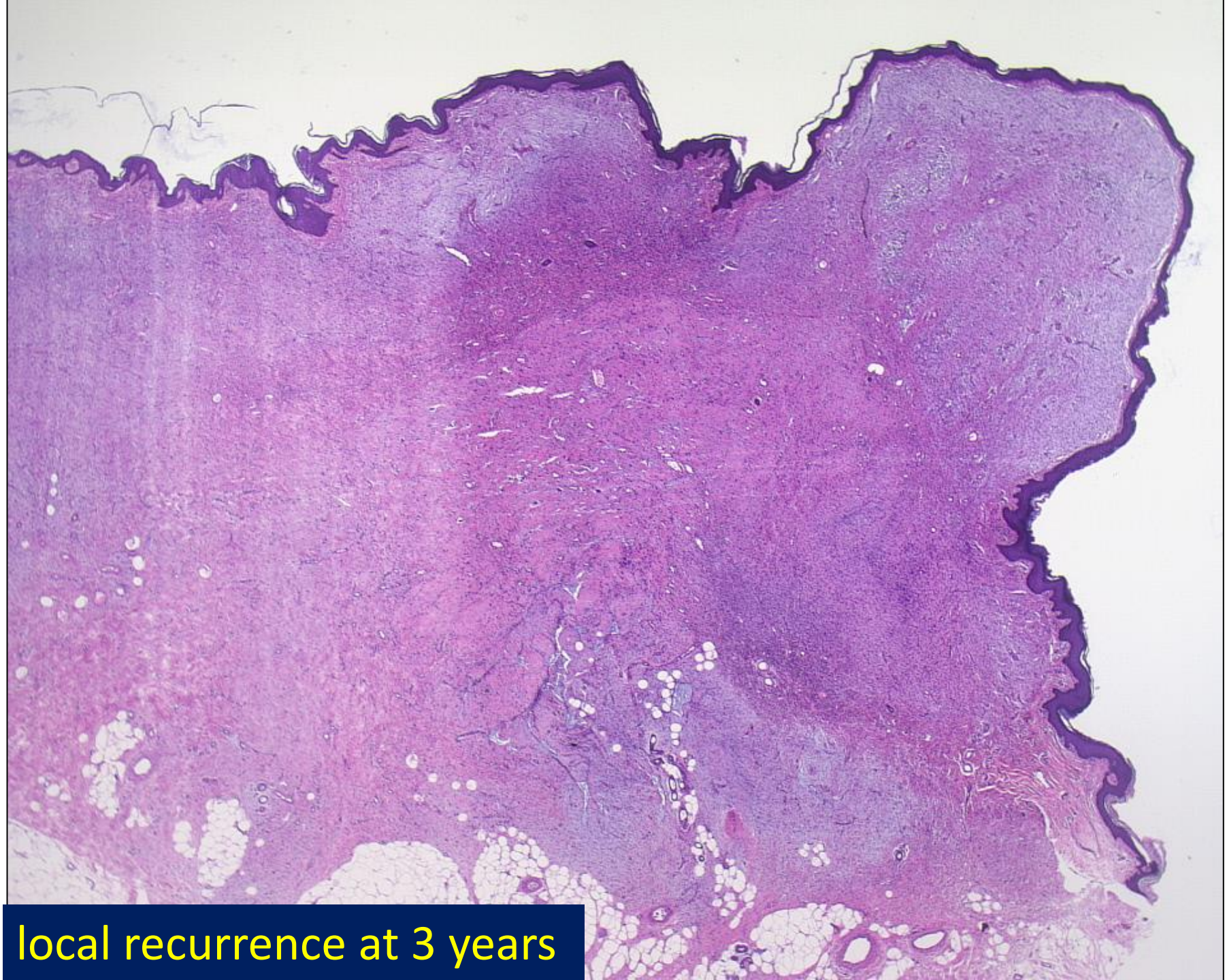
M, 47 years
multiple lesions
FS-transformation in R
liver MTS, DOD

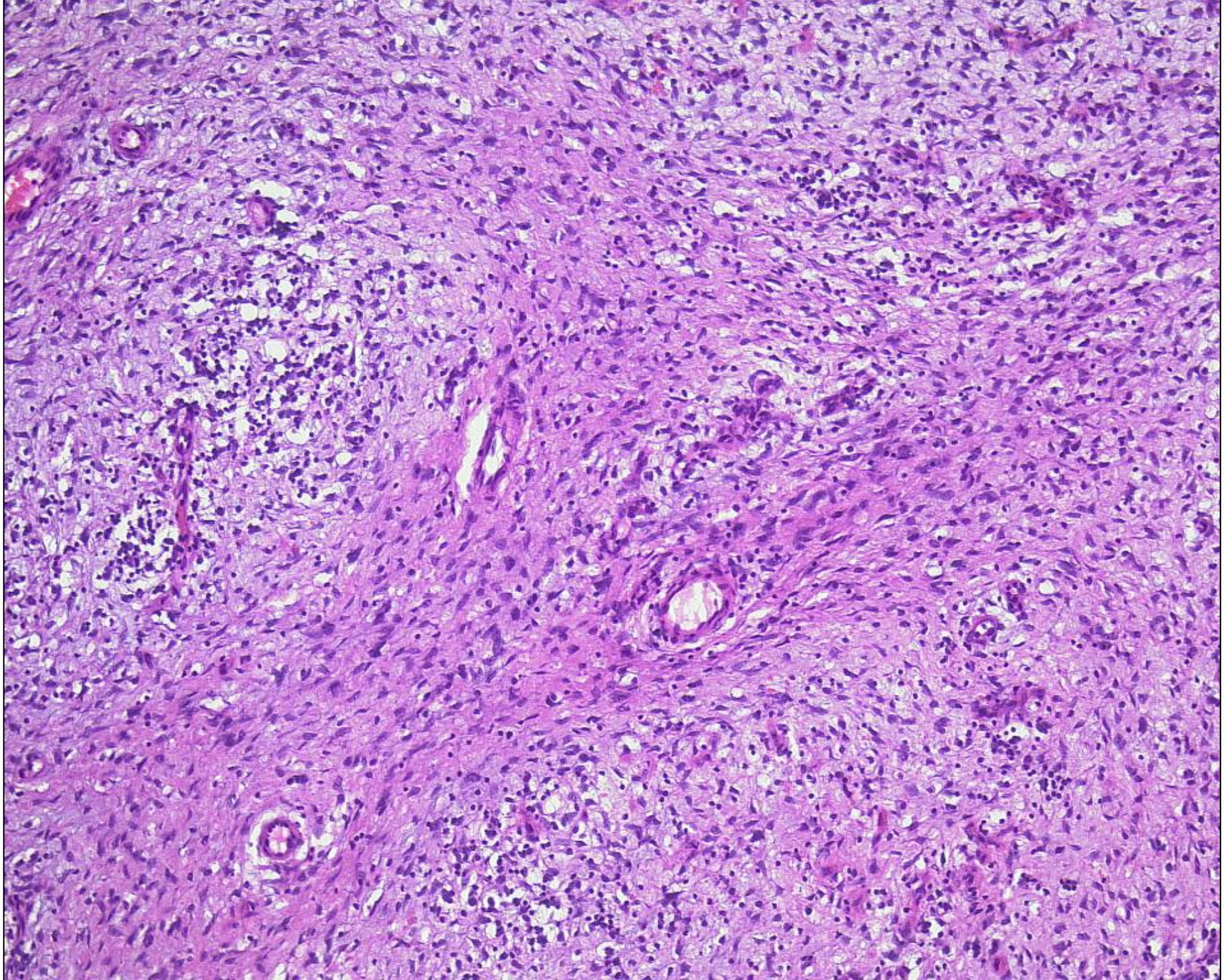
M, 52 years, left groin

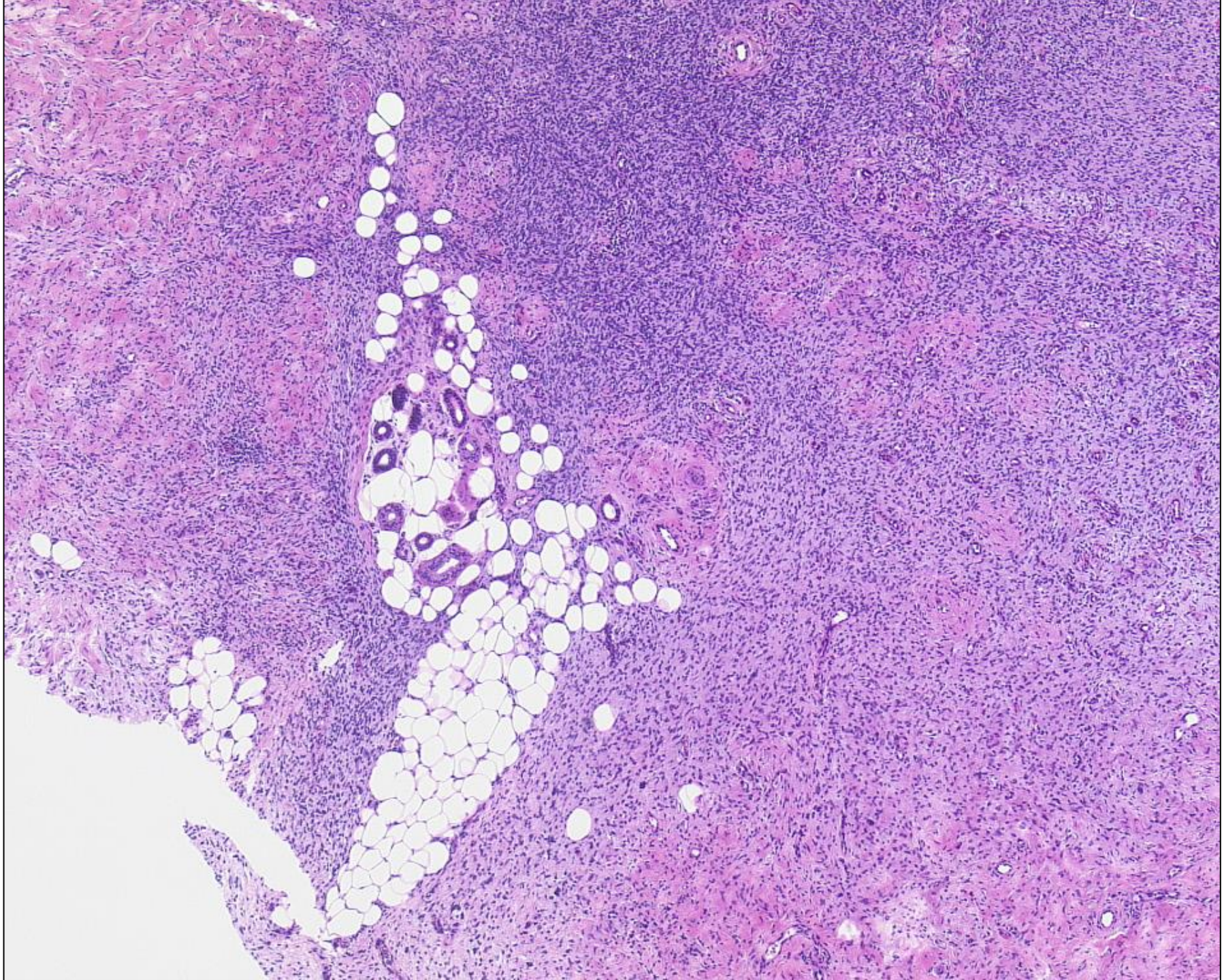


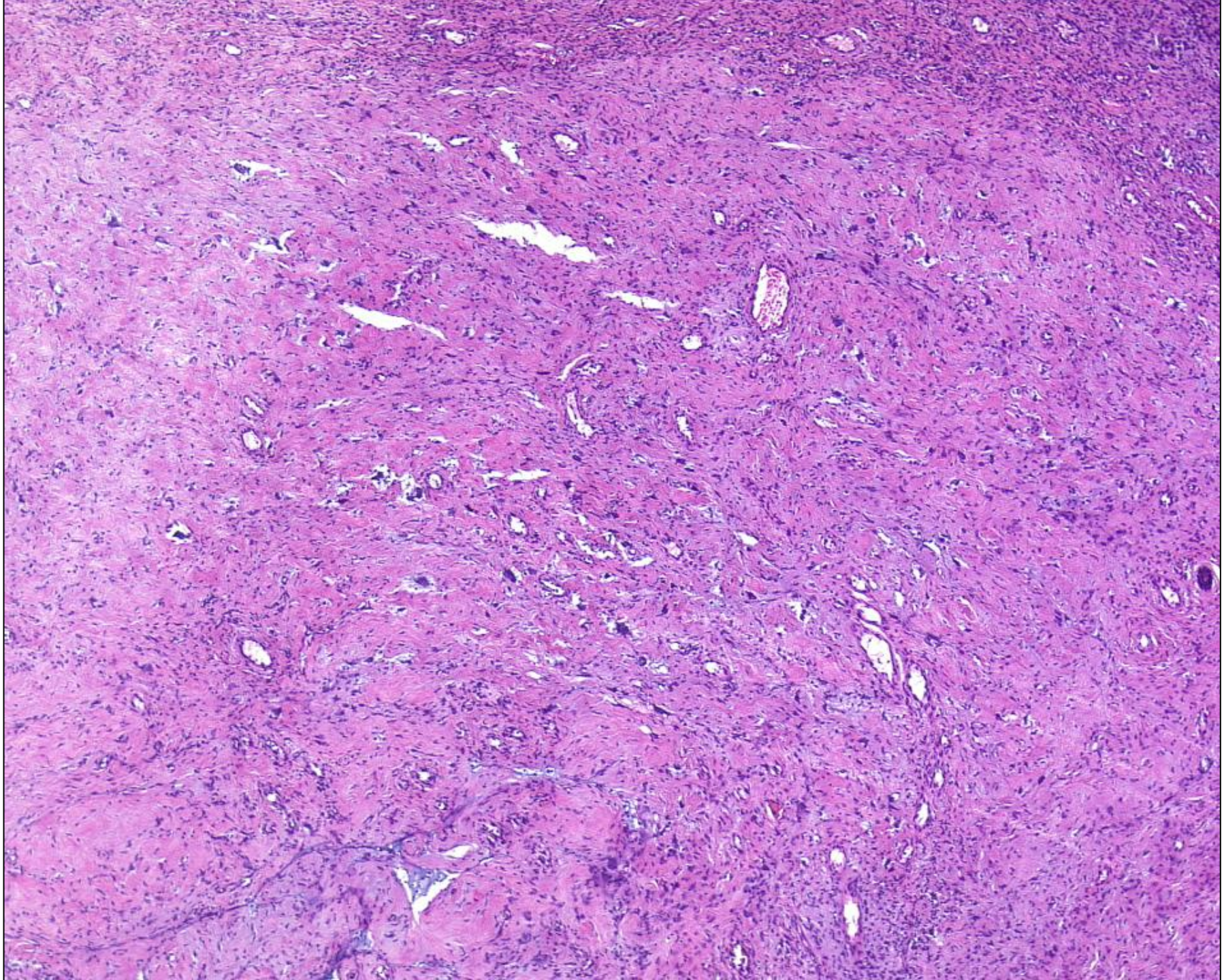


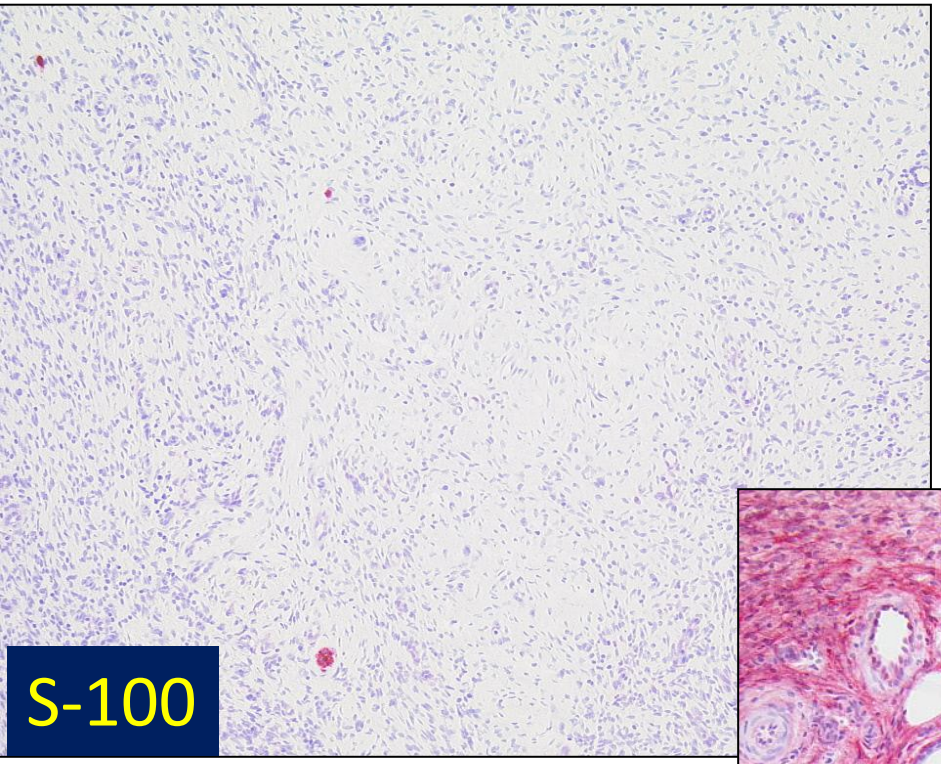
Diagnosis: neurofibroma (no IM was done!)


local recurrence at 3 years

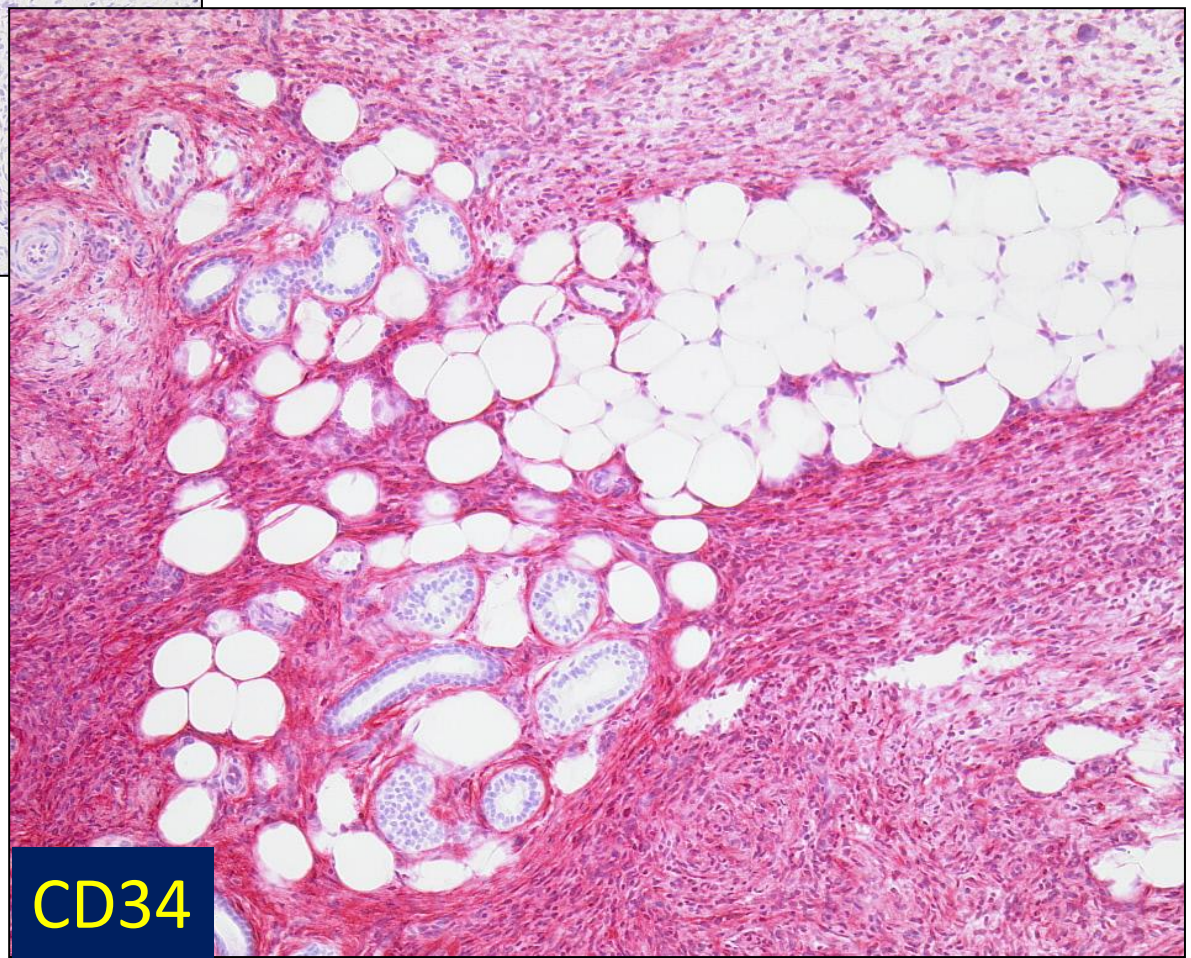








Diagnosis:
DFSP with giant cell fibroblastoma-like areas

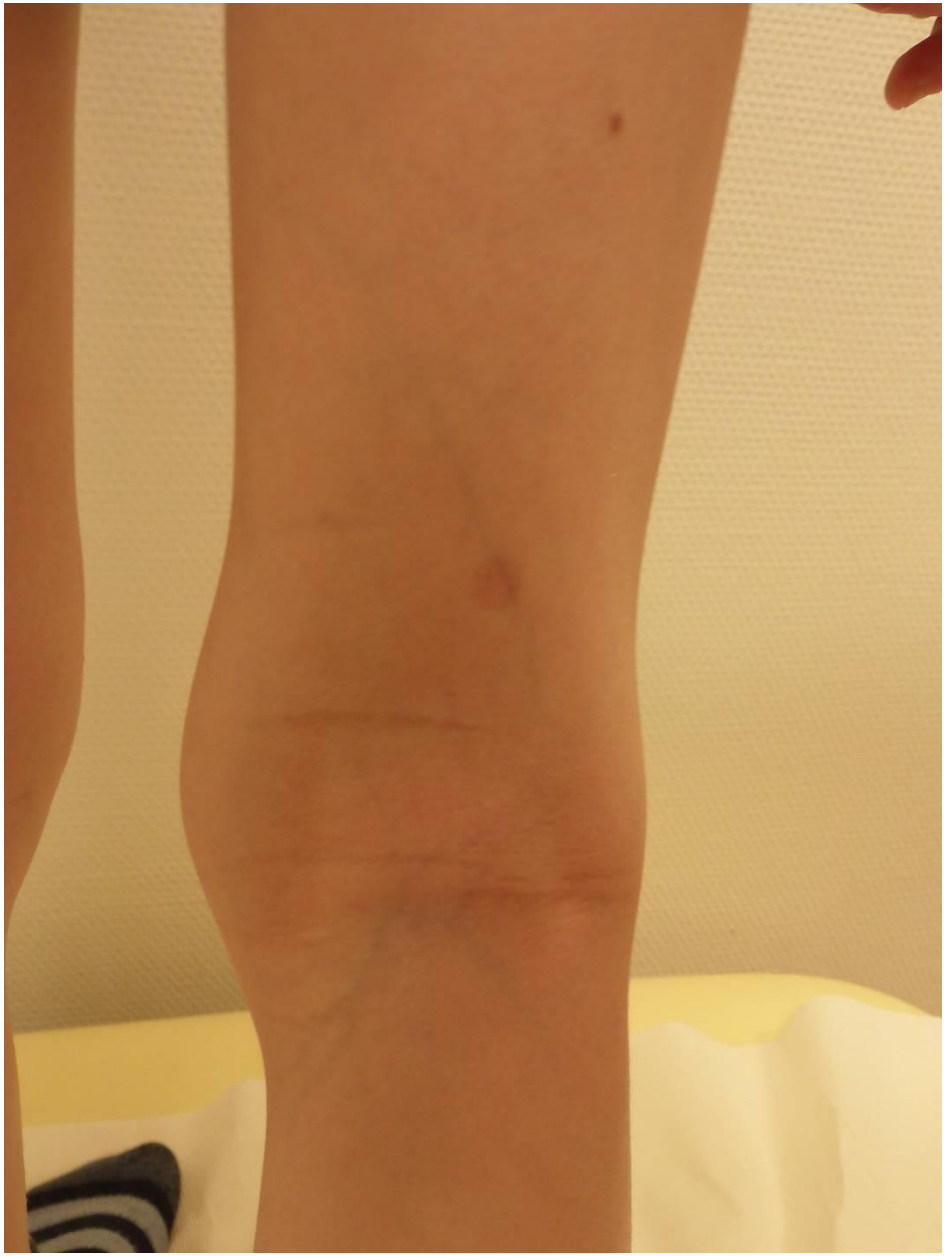


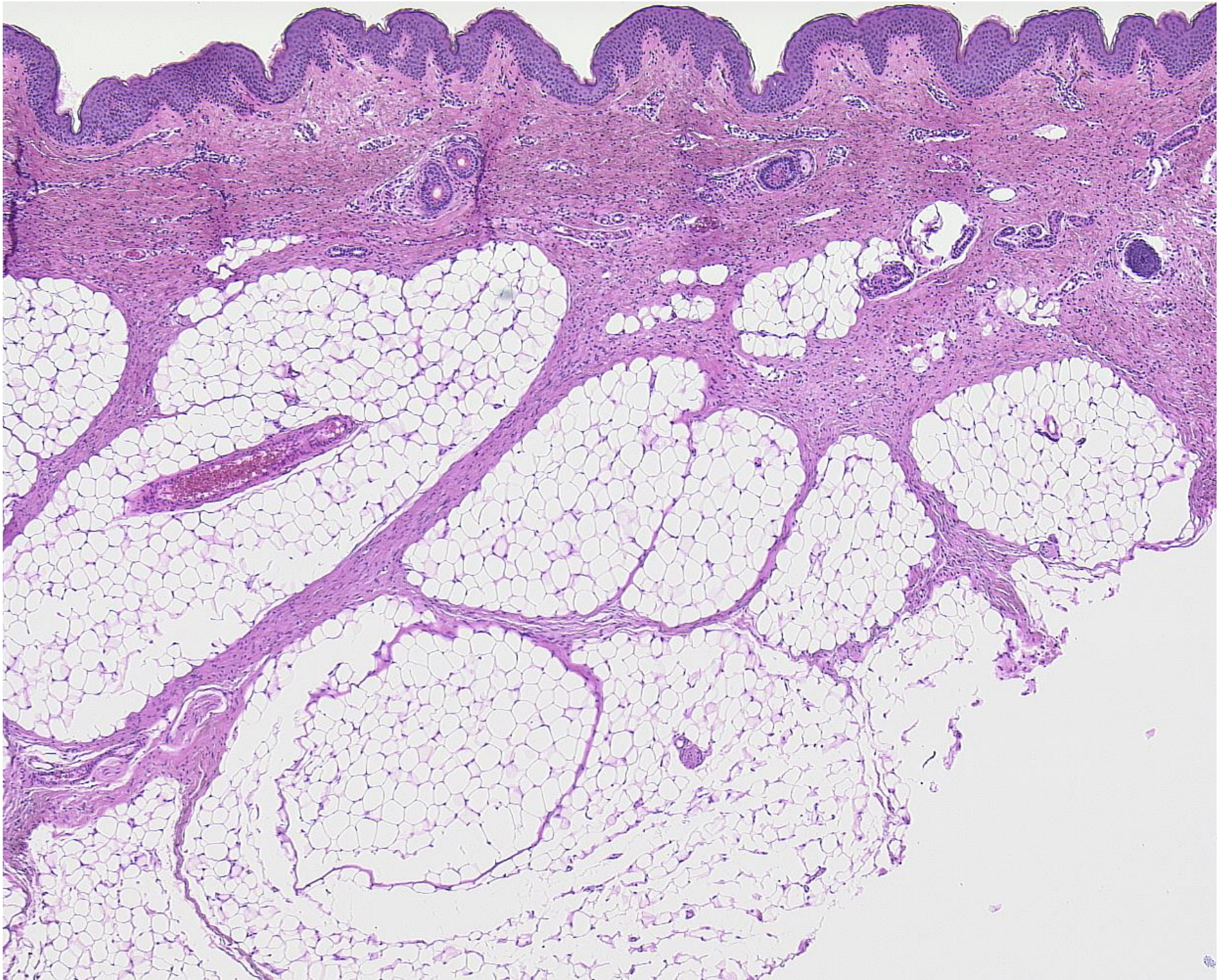
Neurofibromatous changes in dermatofibrosarcoma protuberans: a potential pitfall in the diagnosis of a serious cutaneous soft tissue neoplasm

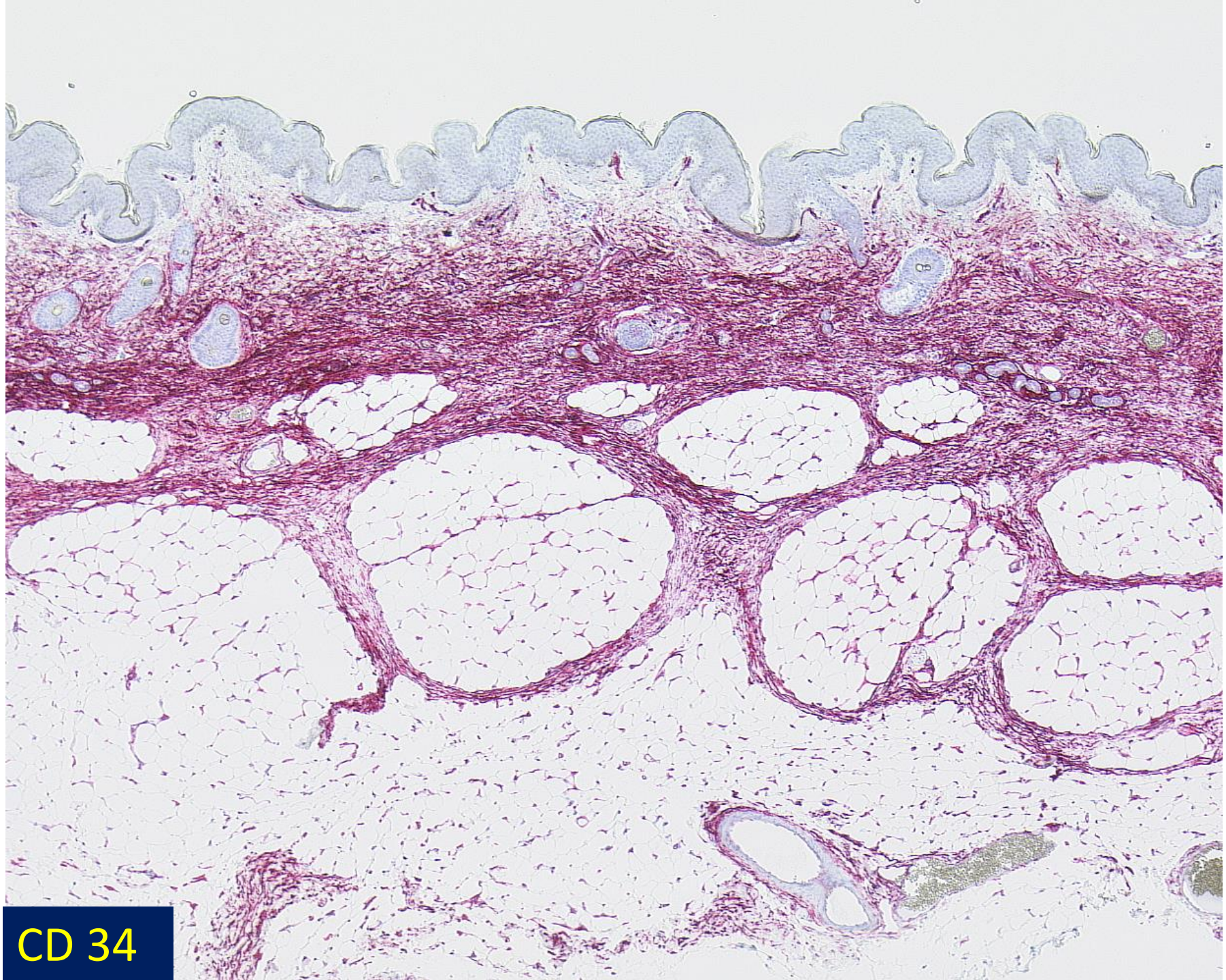
CL Kovarik et al.
J Cutan Pathol 2004; 31: 492-496

6 cases, 3 M, 3 F, 21-80 years
spindled cells with wavy nuclei in a loose mucinous stroma suggesting neural differentiation
3 cases: S-100 +, CD 34 +
3 cases: S-100 -, CD 34 +

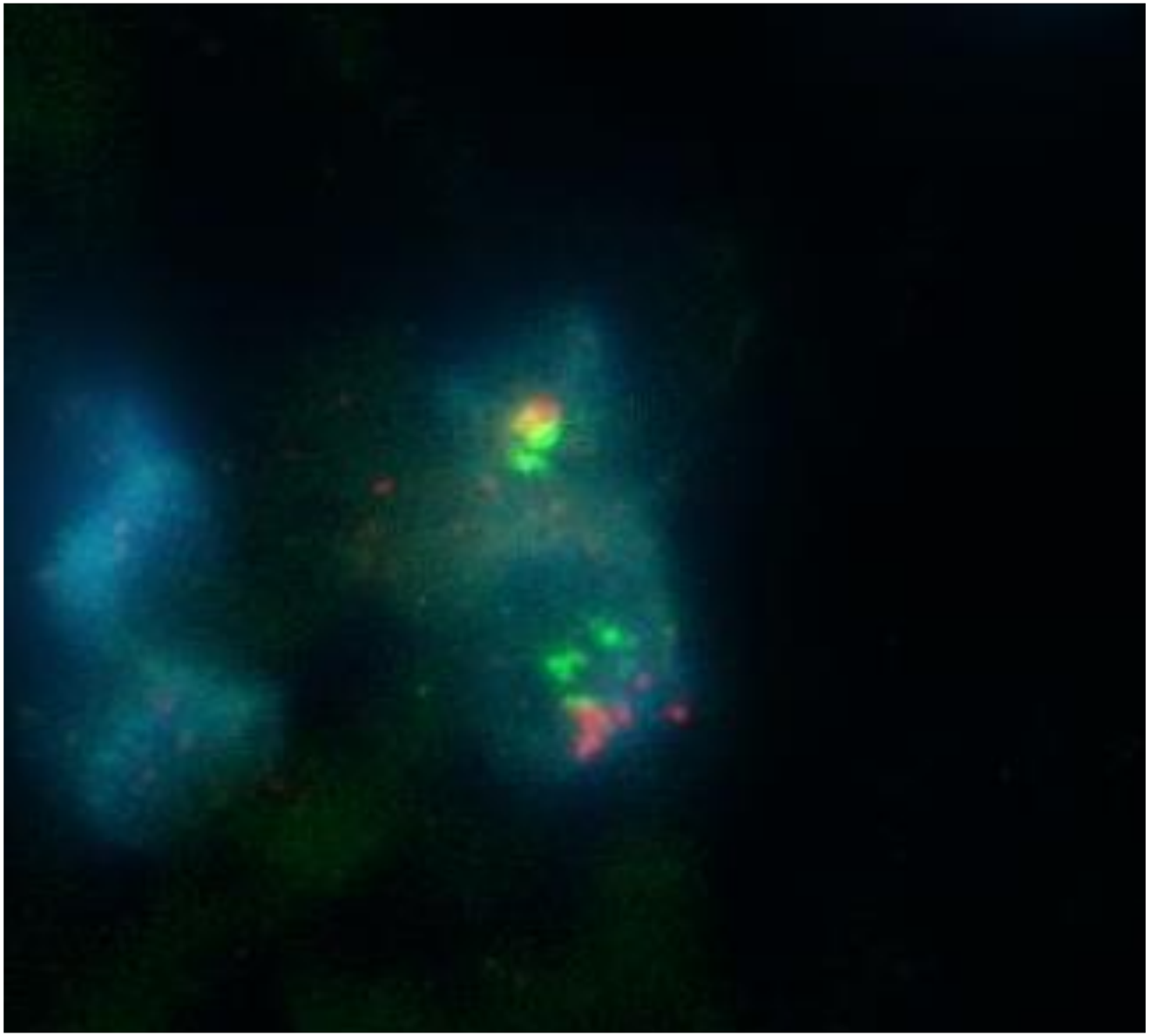
M, 4 years






CD 34

COL1A1 dual color break-apart probe,16 of 50 nuclei positive



Diagnosis:

multicentric, flat DFSP in a young patient with ADA-SCID syndrome (adenosine desaminase-deficient severe combined immunodeficiency)

ADA-SCID:
- rare genetic disorder
- humoral and cellular immunity are affected
- increased risk for life-threatening infections

Multicentric dermatofibrosarcoma protuberans in patients with adenosine desaminase-deficient severe combined immune deficiency
(C Kesserwan et al.
J Allergy Clin Immunol 2012; 129: 762-769)

- 12 patients with ADA-SCID were evaluated
- 8 patients had DFSP
- 7 patients had multiple lesions (4-15 lesions)
- most lesions presented as round, atrophic plaques
- 3 lesions were nodular
- CD34 + in all cases
- t(17;22)(q22;q13) in 6 patients
- FISH: *COL1A1-PDGFB* fusion in 7 patients
- RT-PCR: *COL1A1-PDGFB* fusion transcript in 6 patients

Genetics of DFSP

COL1A1::PDGFB fusion: majority of cases

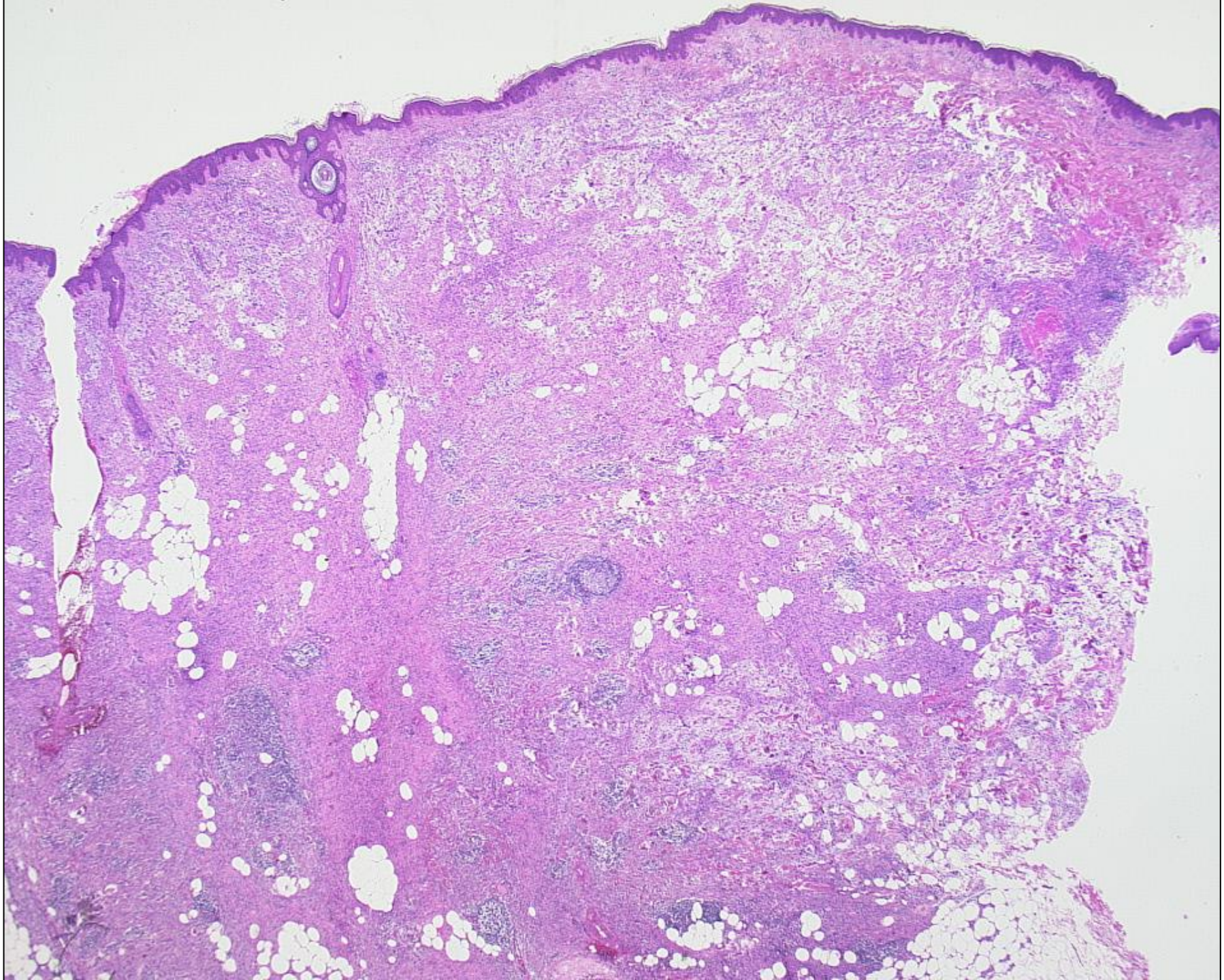
COL6A3::PDGFD fusion: F, breast
(Dickson BC et al. Genes Chromosomes Cancer 2018; 57: 437)

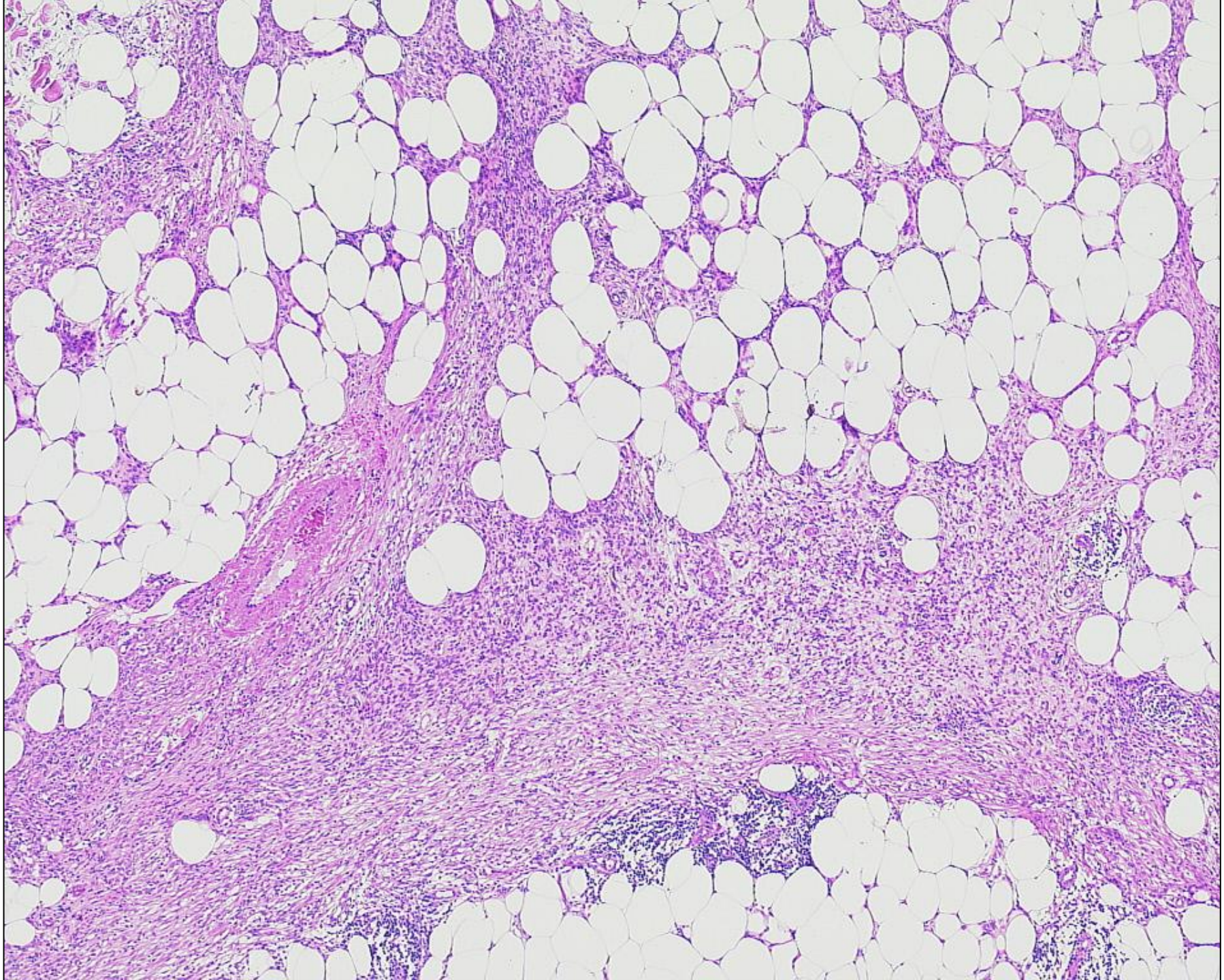
EMILIN2::PDGFD fusion: subcutaneous growth
(Lee PH et al. AJSP 2022; 46: 942)

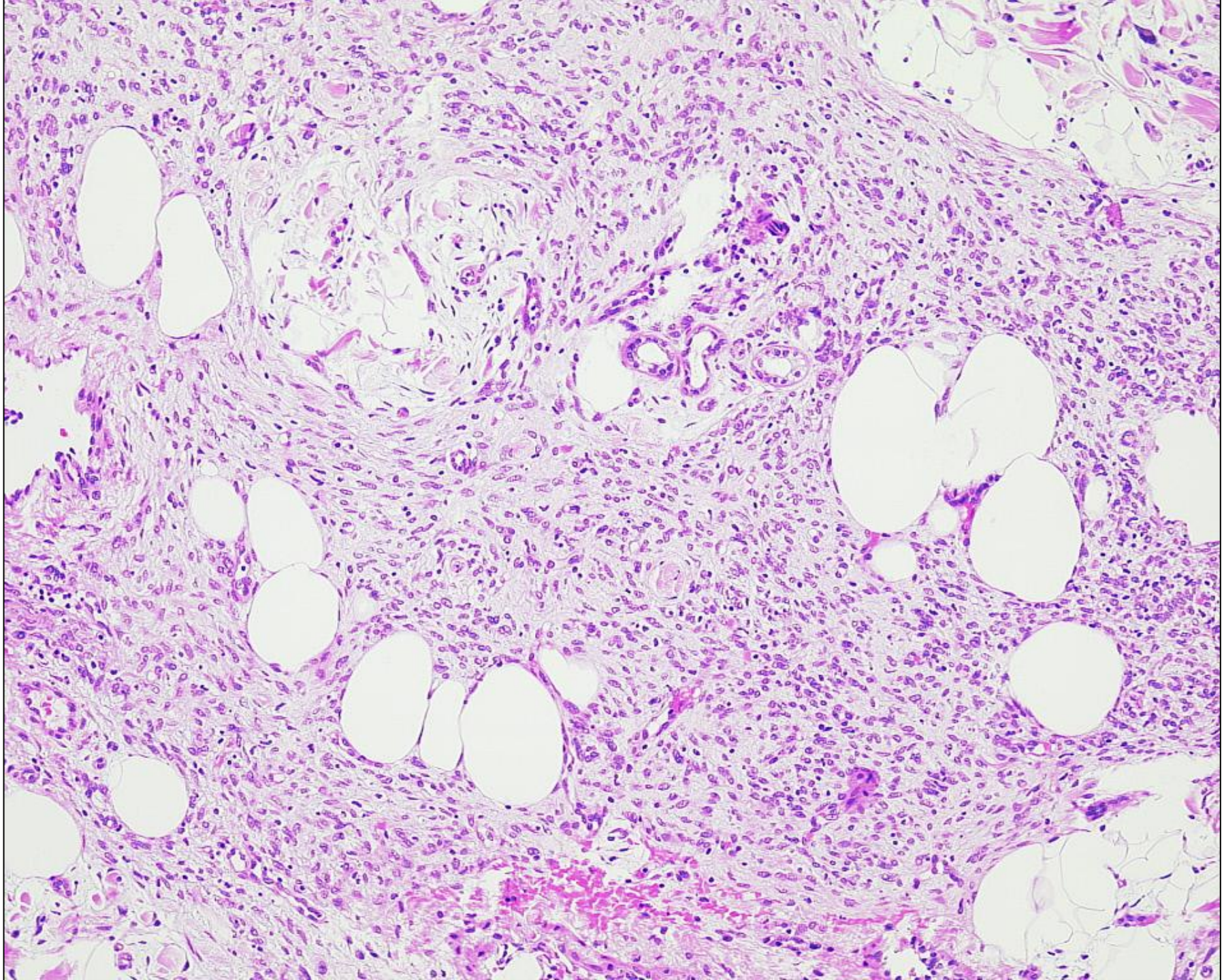
PDGFB/D negative cases with ALK expression/rearrangement
(Agrawal S et al. Mod Pathol 2023; 35: 213A)

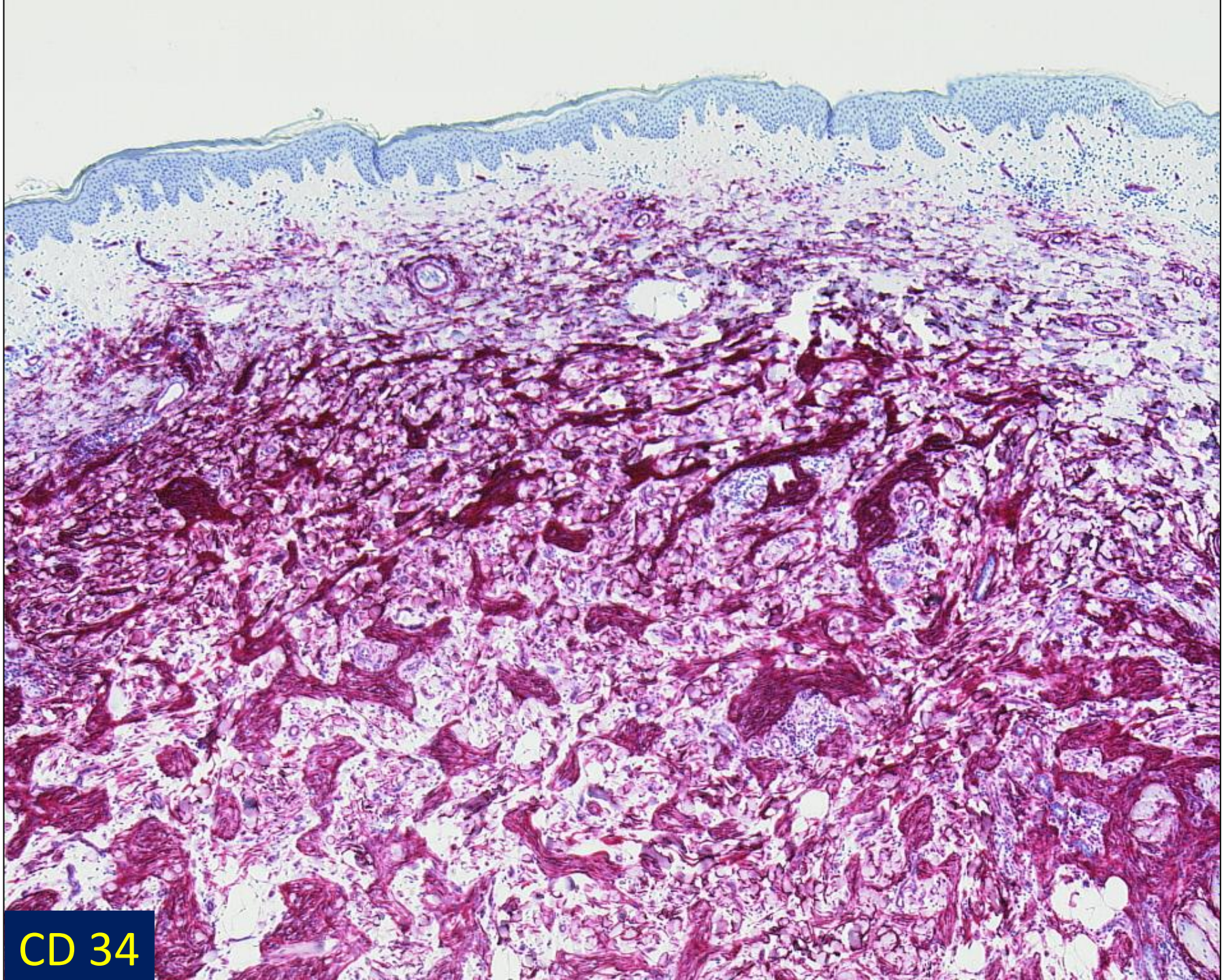
Case 3: Clinical Findings

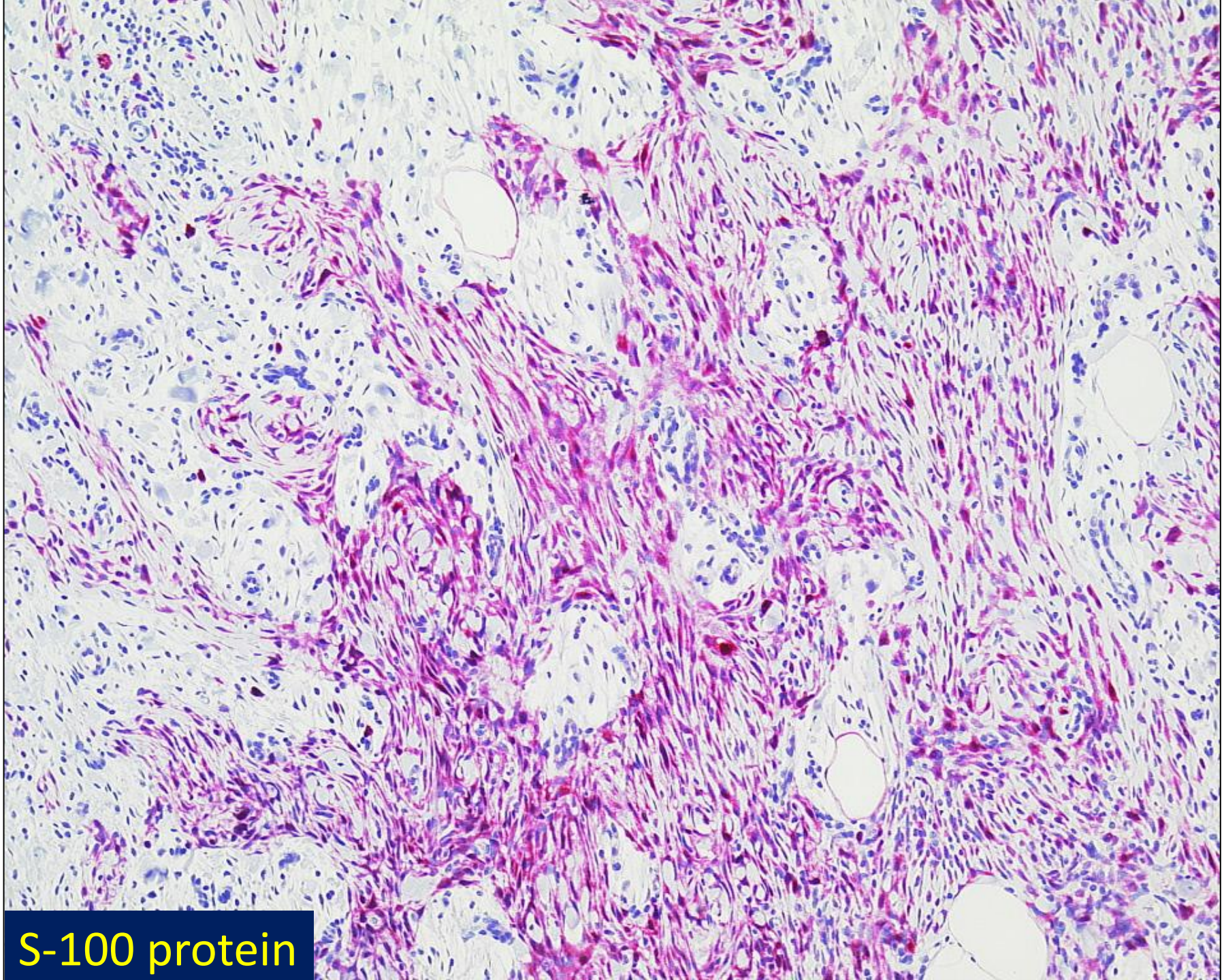
- F, 67 years
- buttock
- DFSP was suspected

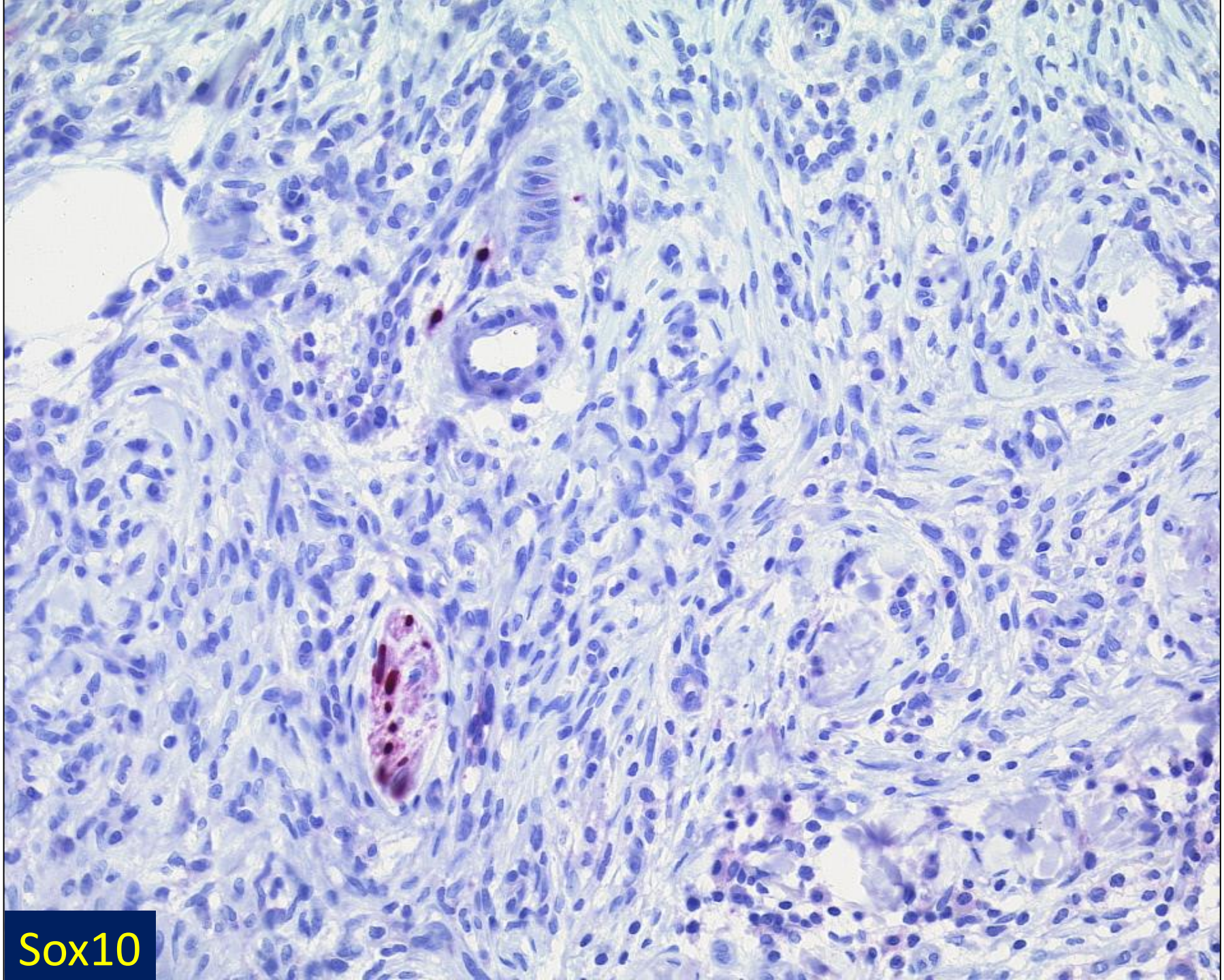


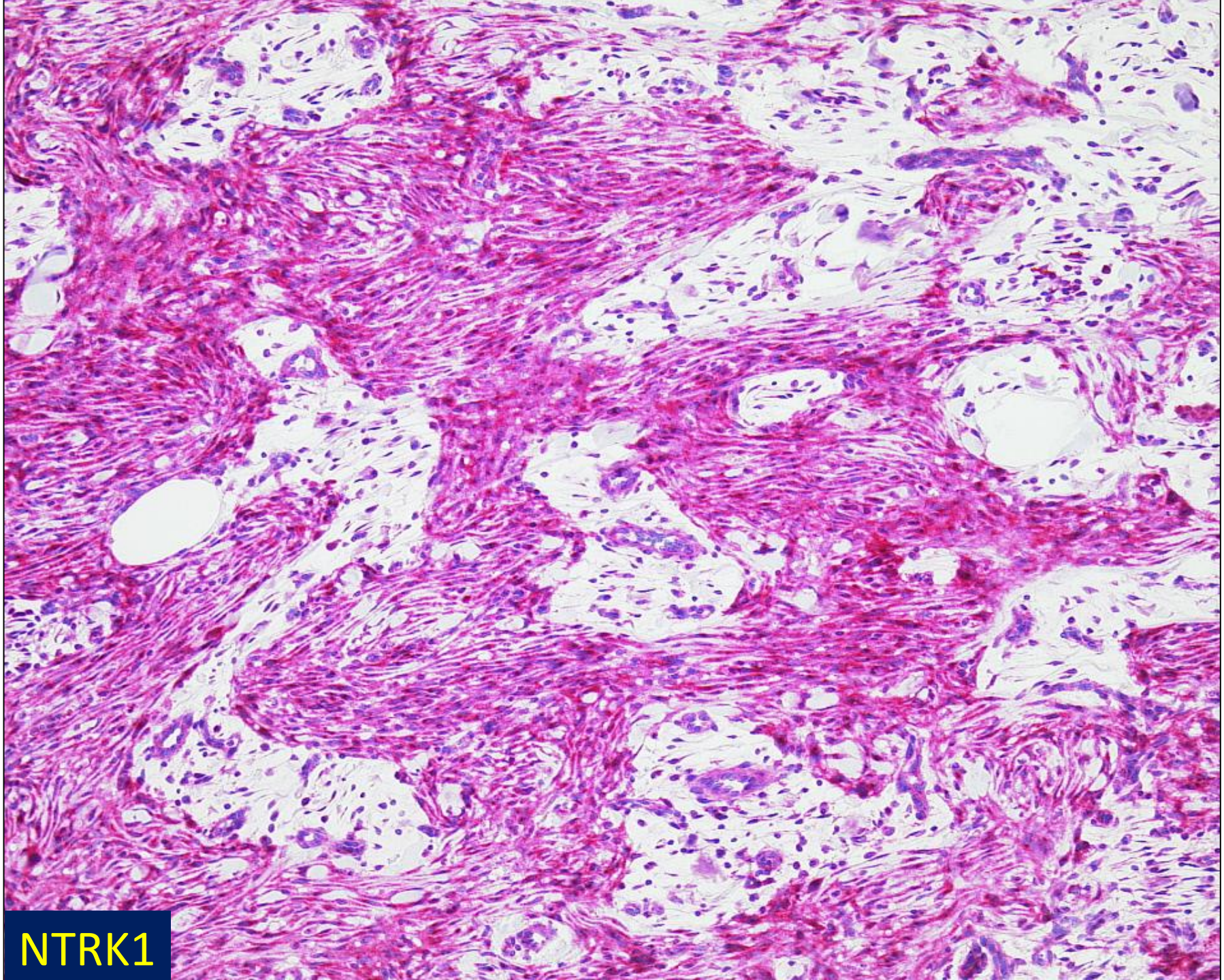





CD 34


S-100 protein


Sox10


NTRK1

Recurrent NTRK1 gene fusions define a novel subset of locally aggressive lipofibromatosis-like neural tumors

(NP Agaram et al. Am J Surg Pathol 2016; 40: 1407)

8 F, 6 M, 4-38 years, local recurrence in 5/12 cases

upper (6), lower extremity (5), head (2), flank (1)

1.3 - 5.4 cm, subcutaneous lesions

infiltrative spindle cell neoplasms

mild nuclear atypia, no / few mitoses

S-100 +, CD34 + (10/11), ASMA + (3/8), desmin -,

Sox-10 -, HMB-45 -, Melan-A -, STAT6 -, H3K27me3 +

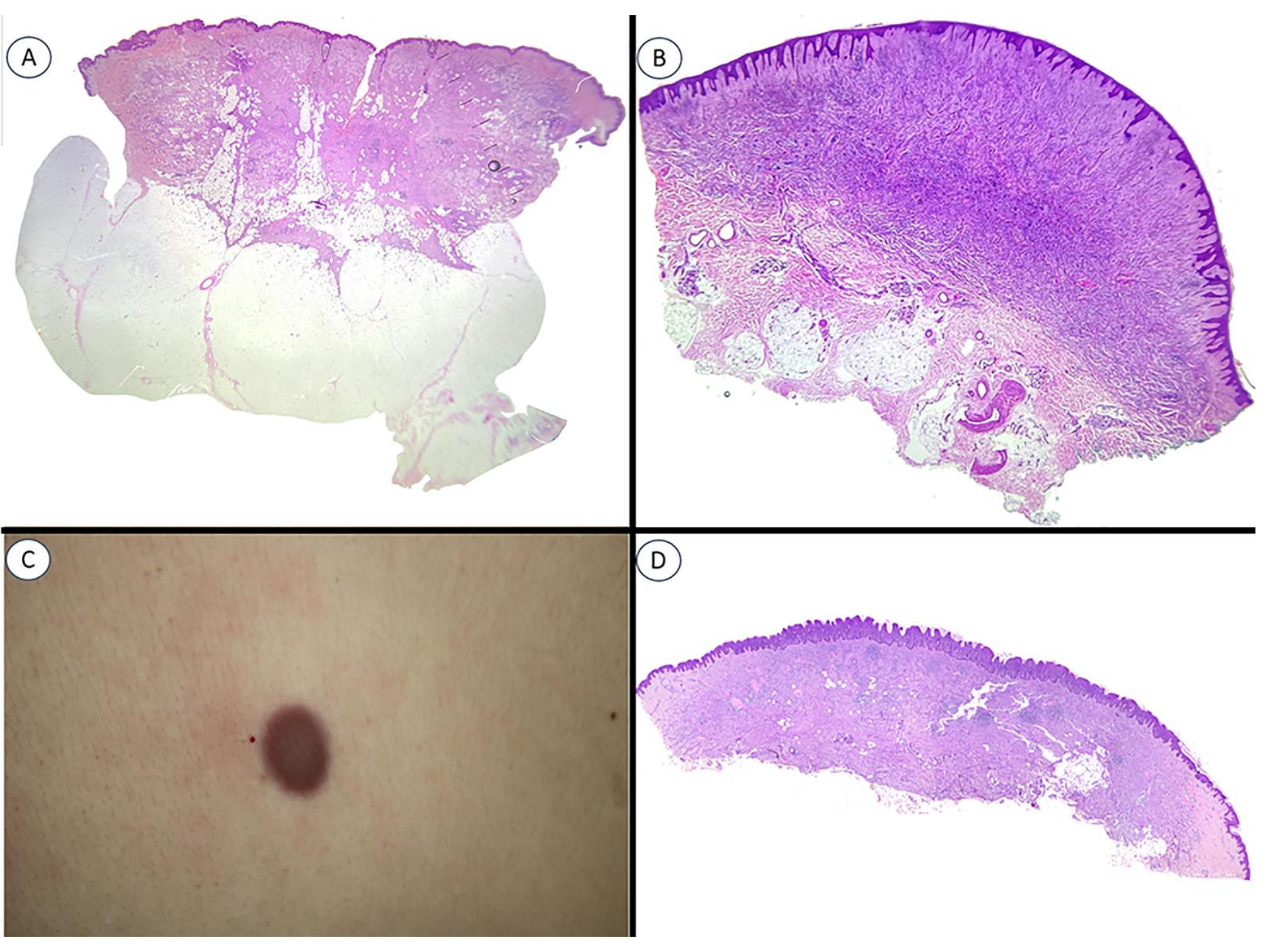
NTRK1 gene rearrangements with **NTRK1 staining**

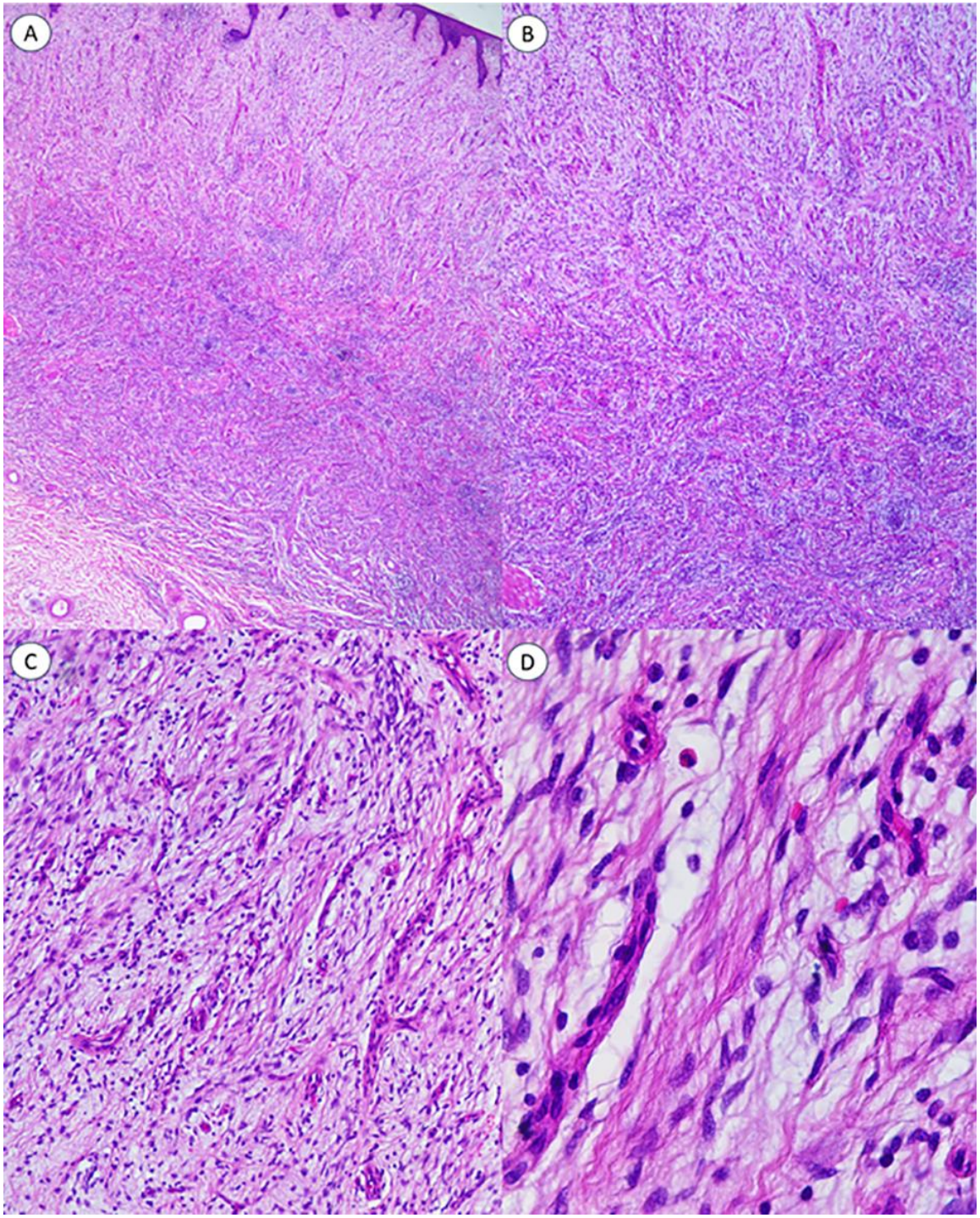
Dermal lipofibromatosis-like neural Tumor

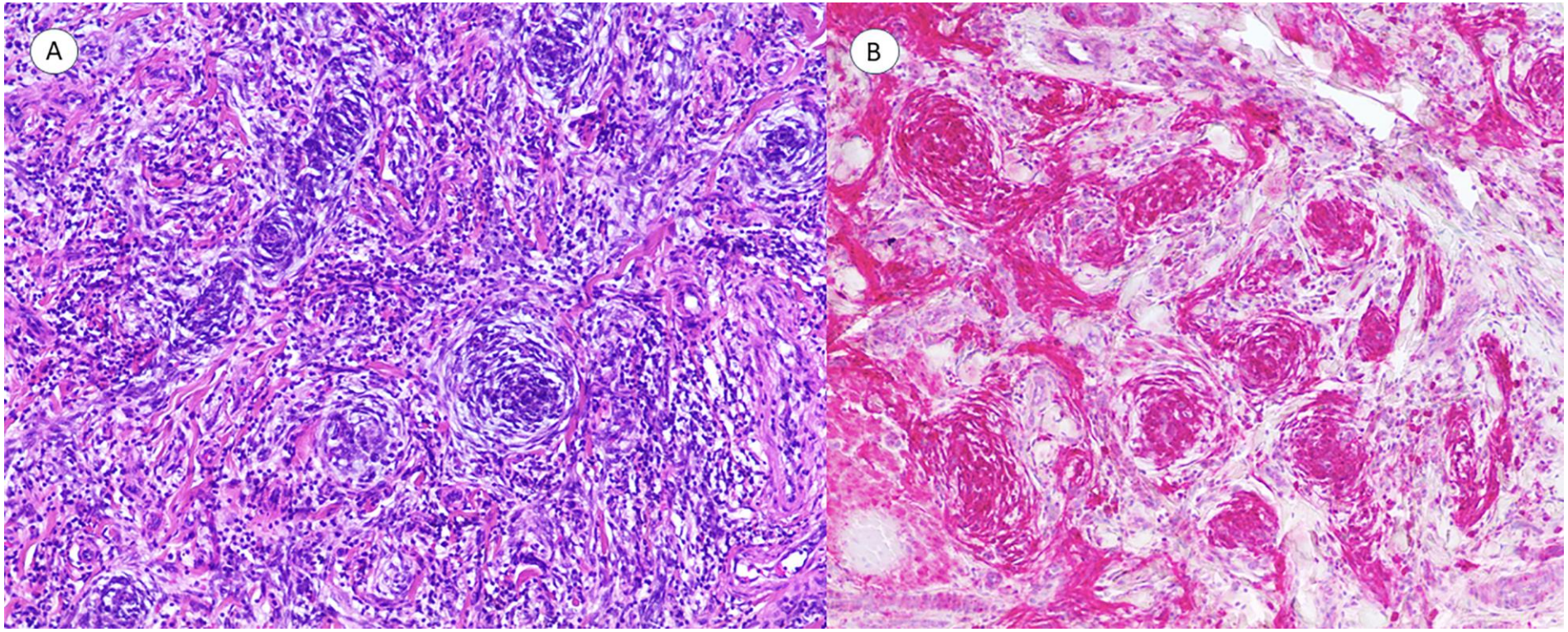
(M Llamas-Velasco et al. J Cutan Pathol 2022; 6: 525)

- 5 cases, 3 M, 2 F, 14-68 years
- lower limbs (4), back (1)
- poorly circumscribed dermal neoplasms
- monomorphous spindle-shaped tumour cells
- CD 34 +, S-100 +, NTRK1 +,
  ALK -, EMA -, NKIC3 -, MNF116 -, ASMA -

DD: dermatofibrosarcoma protuberans
fibrous hamartoma of infancy
lipofibromatosis
infantile fibrosarcoma
low-grade MPNST

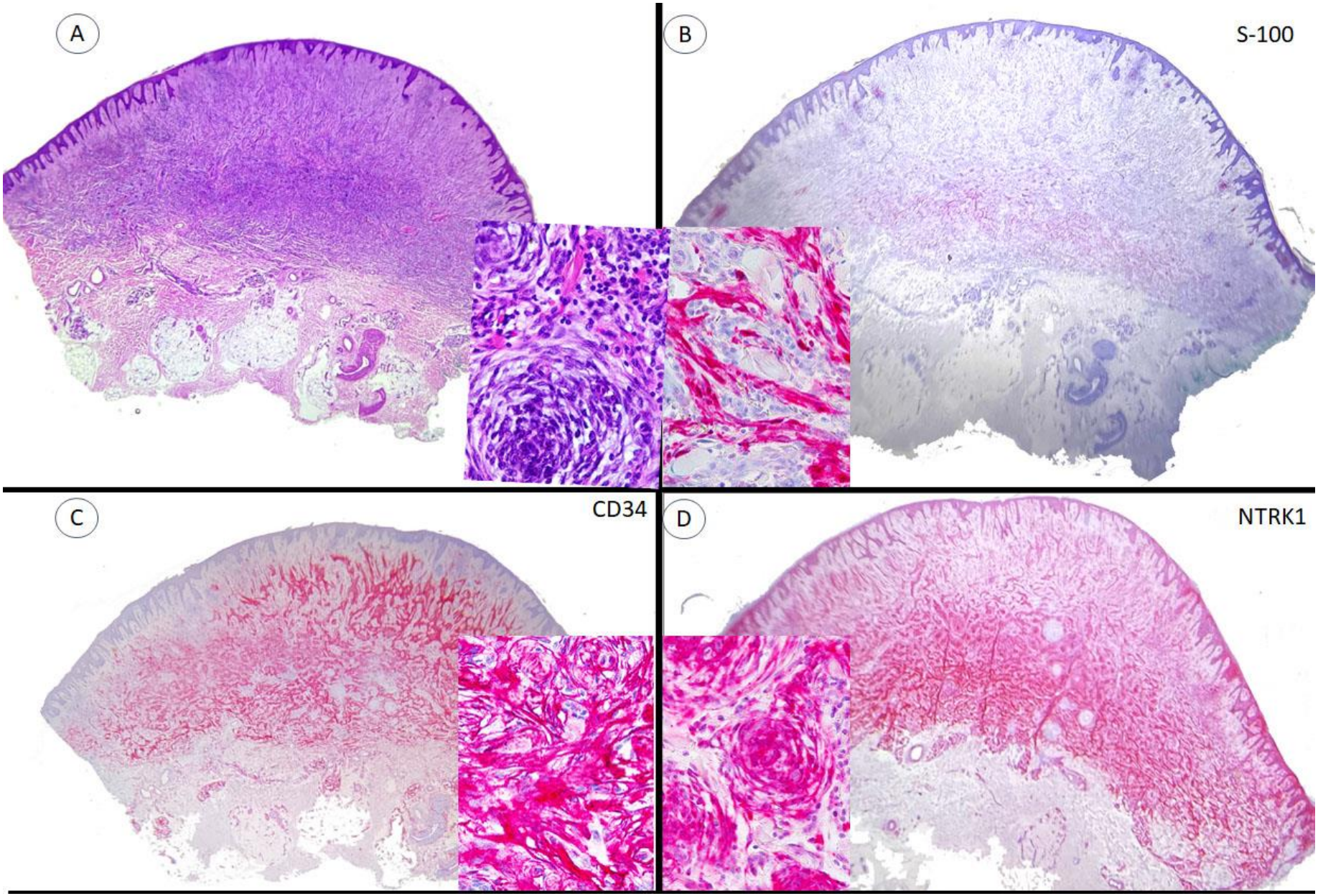

A
B
C
D


A
B
C
D



Foci of myxoid areas

NTRK1 +


A
B
S-100
C
CD34
D
NTRK1

Superficial ALK-rearranged myxoid spindle cell neoplasm: a cutaneous soft tissue tumor with distinctive morphology and immunophenotype

(JK Dermawan et al. Mod Pathol 2021; 34: 1710)

6 cases (2 F, 4 M), 18-84 years, back (3), leg (3)

concentric whorls and cords of spindled tumor cells + cellular aggregates of ovoid to epithelioid tumor cells

myxoid to myxohyaline stroma

peripheral lipofibromatosis-like areas in two cases!

ALK +, CD34 +, S100 5/6 +, Sox10 -, CK -, EMA -

ALK-FLNA fusion (3)

ALK-MYH10 fusion (2)

ALK-HMBOX1 fusion (1)

NTRK-rearranged spindle cell Neoplasms

Definition:

Emerging family of rare spindle cell neoplasms with a wide morphological spectrum, from lipofibromatosis-like neural tumour to infantile fibrosarcoma-like lesions; harboring *NTRK1/2/3* gene rearrangements or other gene alterations (i.e. *RAF1, BRAF, RET*) implicated in receptor kinase pathway activation.

NTRK-fused mesenchymal Neoplasms

heterogeneous group of mesenchymal tumours with fibroblastic or neural differentiation

lipofibromatosis-like neural tumour

infantile fibrosarcoma (*ETV6::NTRK3*)

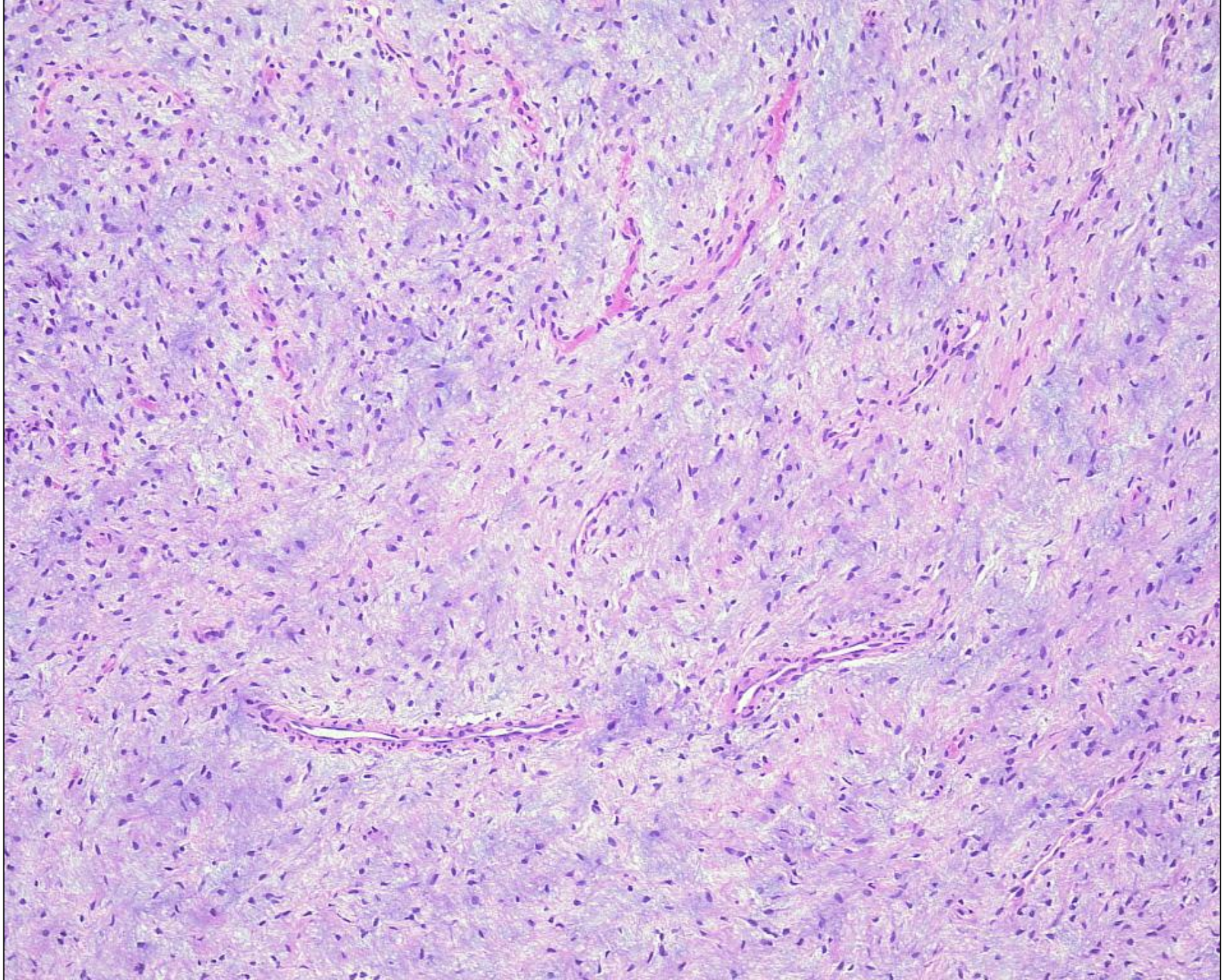
MPNST-like tumours (h3K27me3 +)

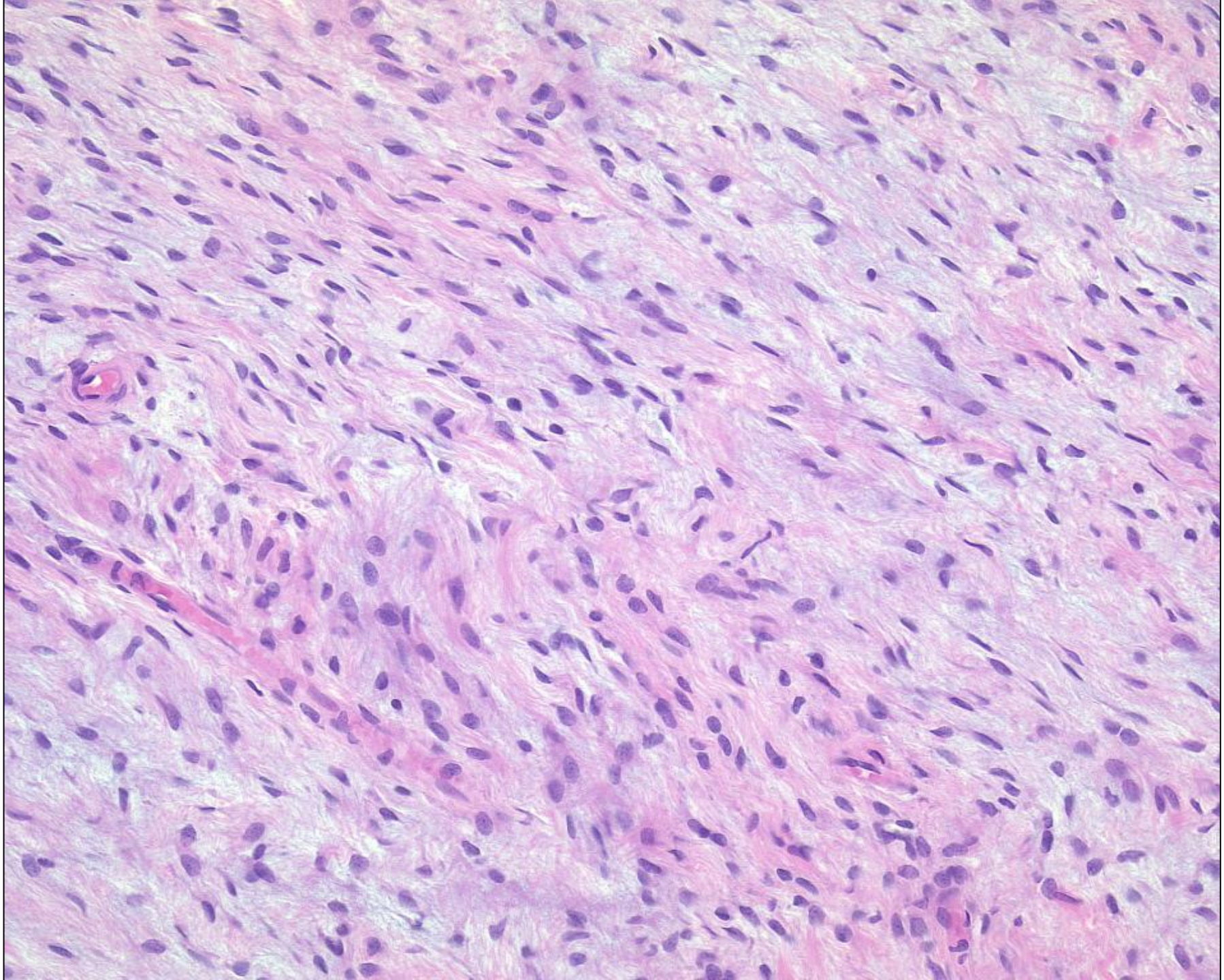
LMNA::NTRK1 spindle cell sarcoma

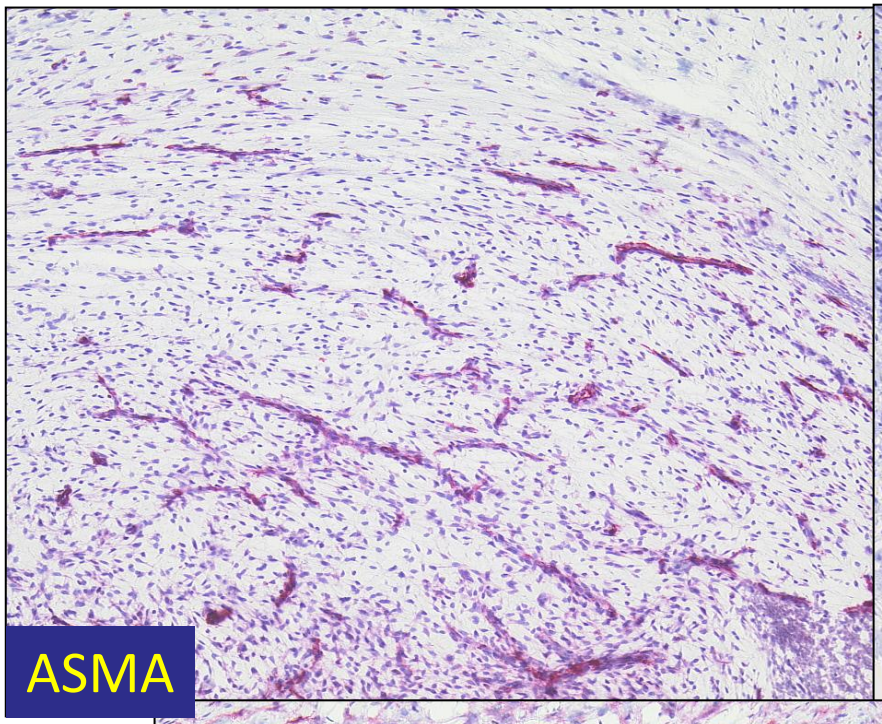
S-100 +, CD 34 +, NTRK +, Sox10 -

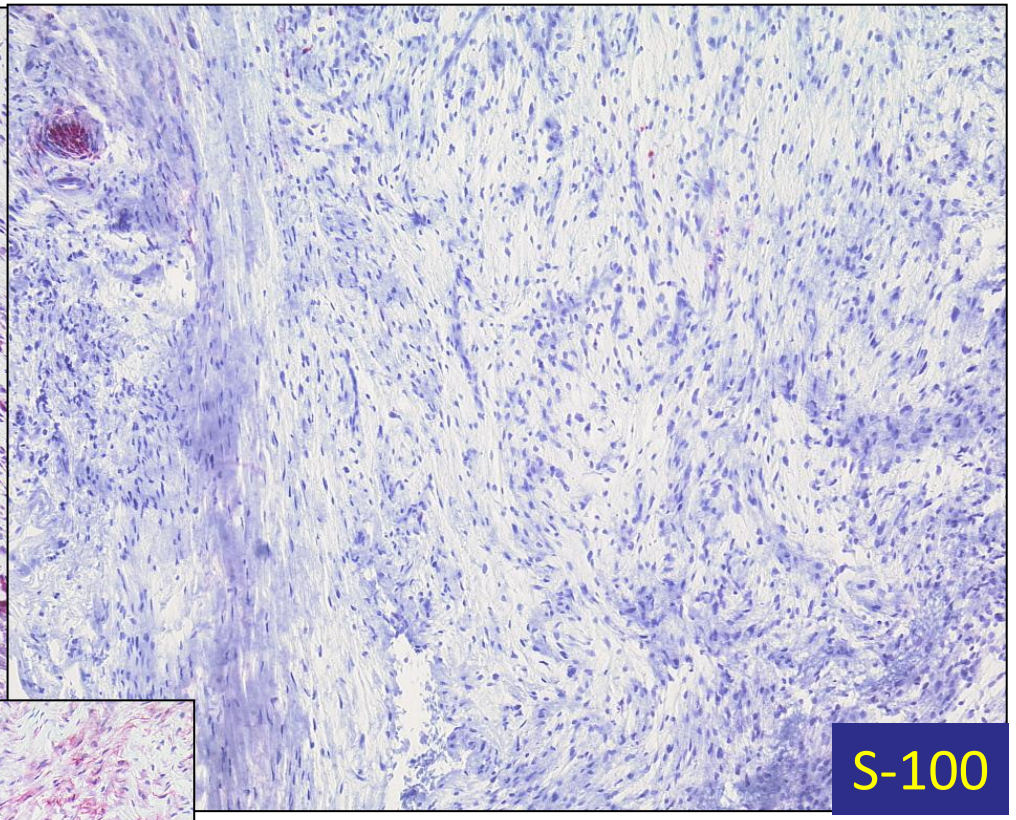
treatment with NTRK inhibitors in aggressive neoplasms

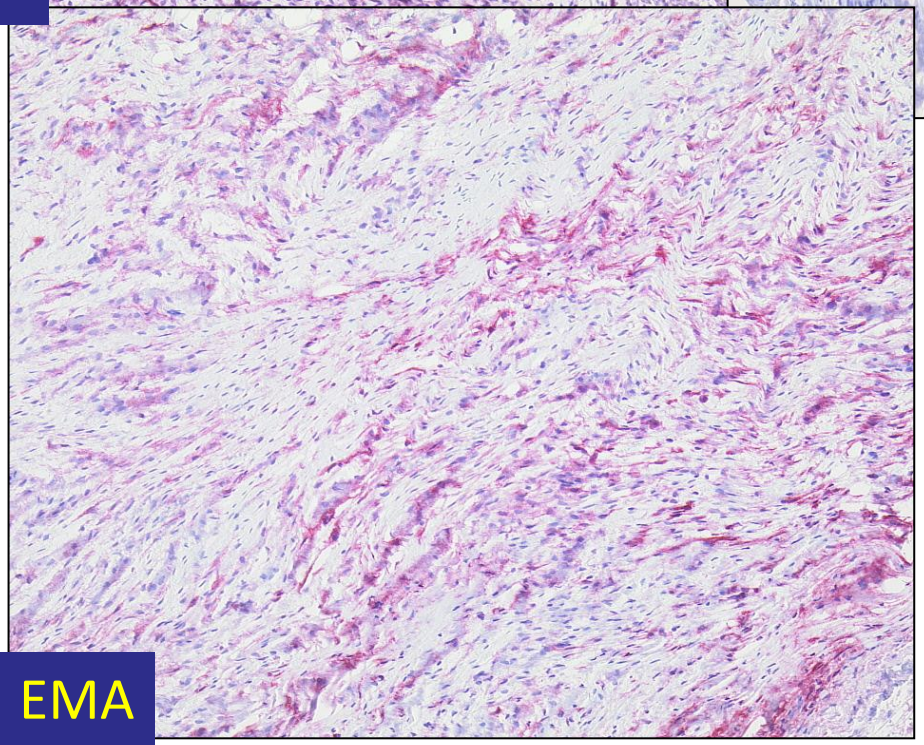
Case 4







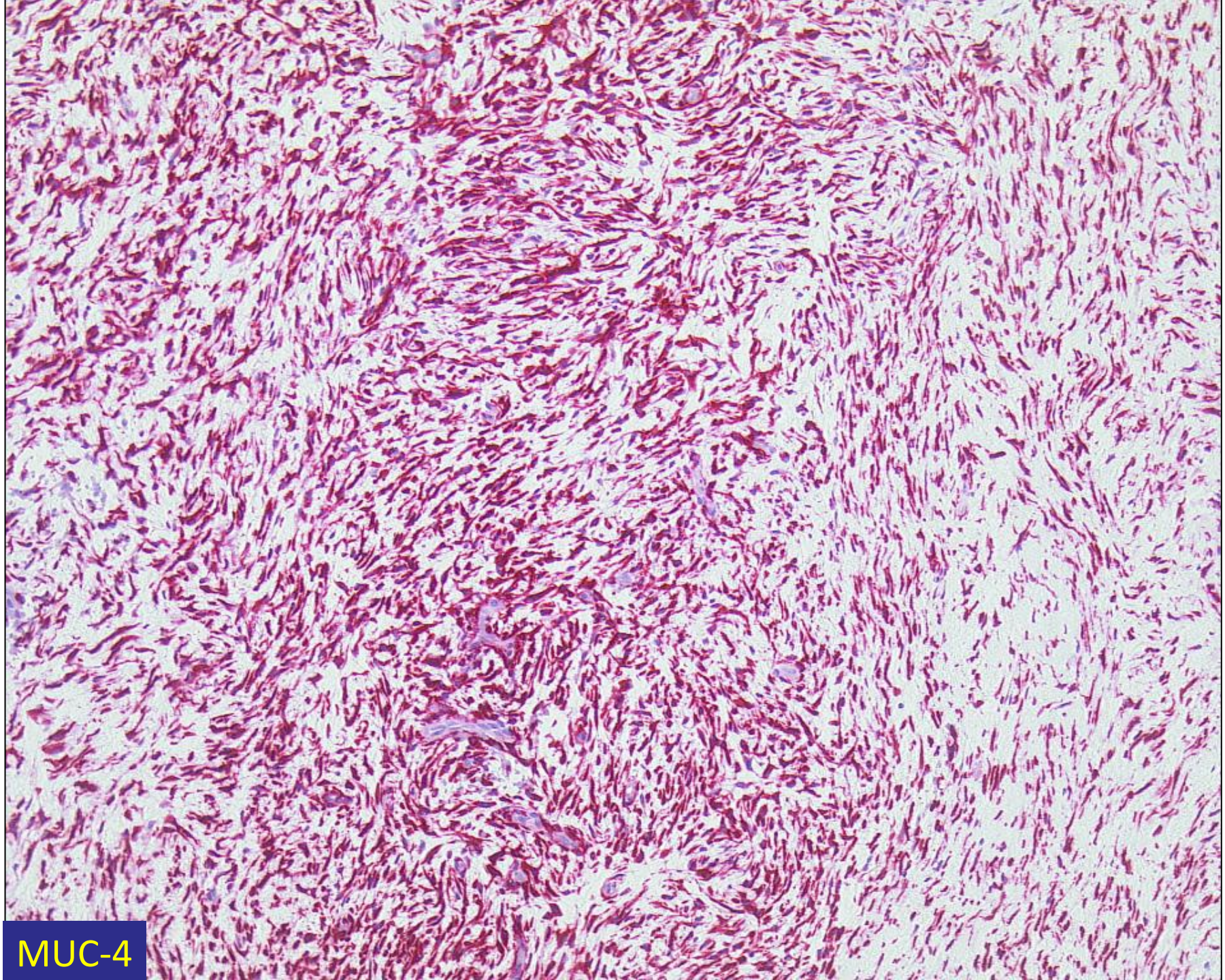




Claudin-1 -

Desmin -

Pancytokeratin -


MUC-4

Diagnosis Case 4

Low-grade fibromyxoid Sarcoma

- Evans HL. Low-grade fibromyxoid sarcoma: A report of metastasizing neoplasms having a deceptively benign appearance. Am J Clin Pathol 1987; 88: 615-619
- Evans HL. Low-grade fibromyxoid sarcoma: A report of 12 cases. Am J Surg Pathol 1993; 17: 595-600
- Evans HL. Low-grade fibromyxoid sarcoma: a clinico-pathologic study of 33 cases with long-term follow-up. Am J Surg Pathol 2011; 35: 1450-1462

    21 out of 33 patients had local recurrence

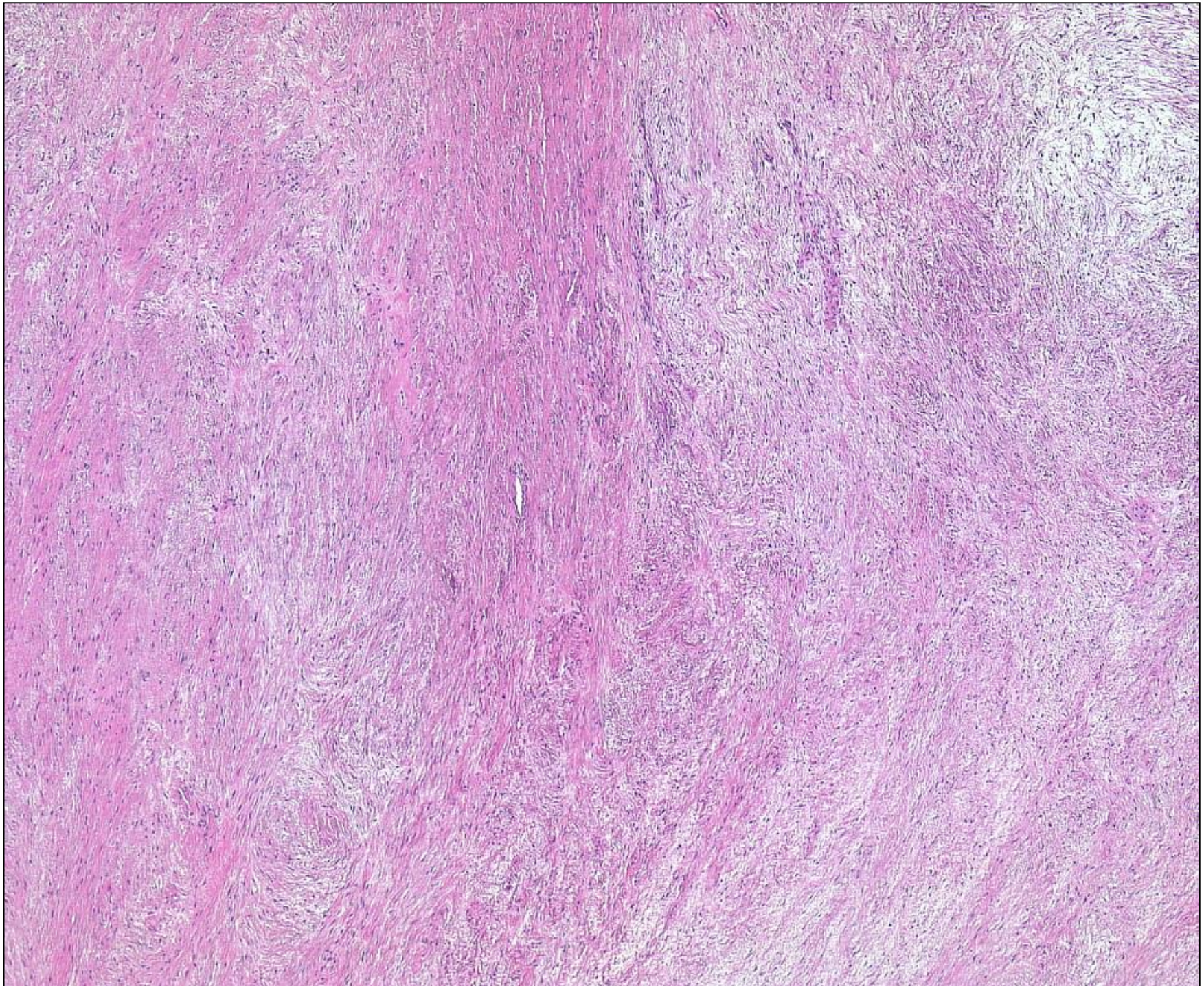
    15 out of 33 patients developed metastases

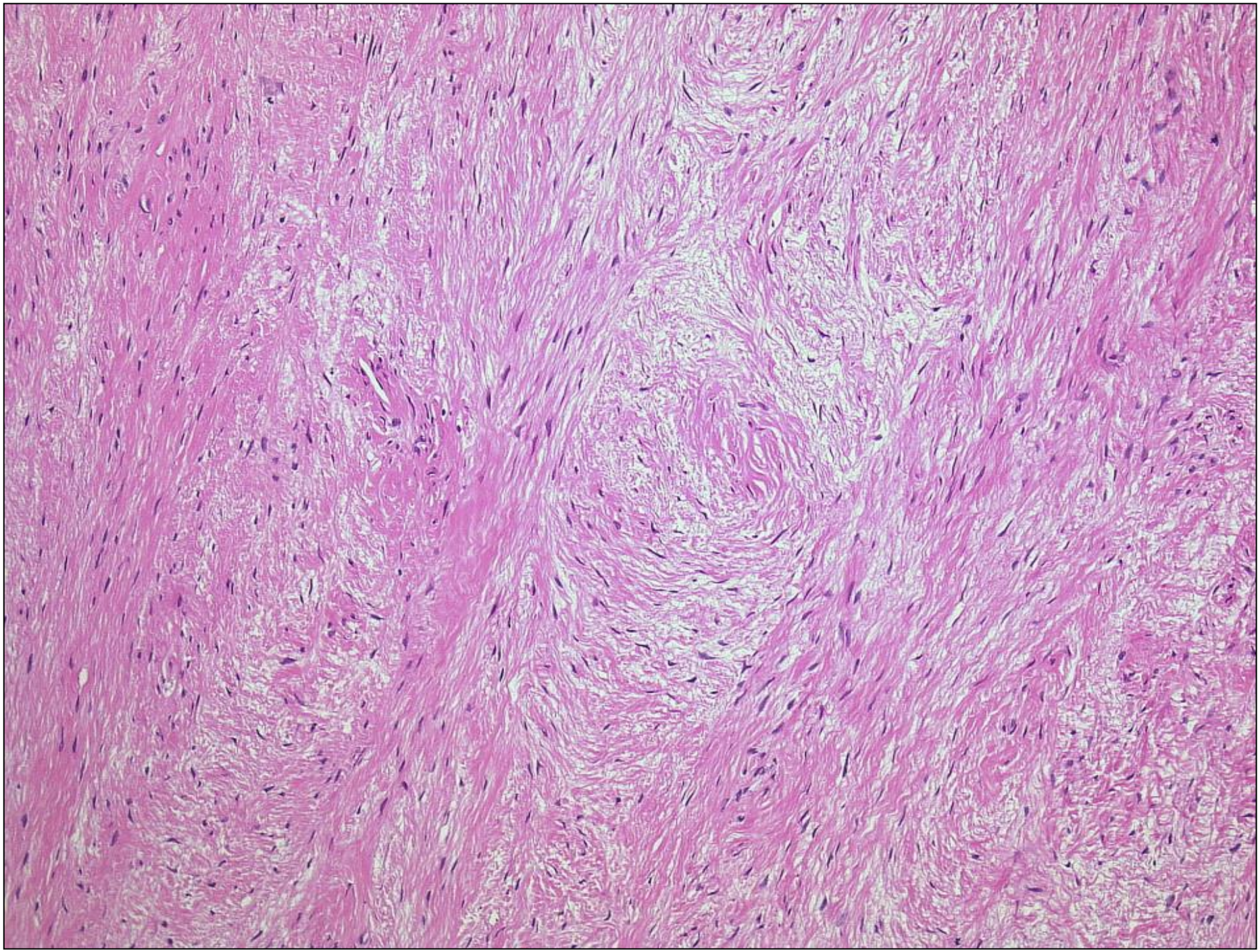
    14 out of 33 patients died of tumour (3-42 years)

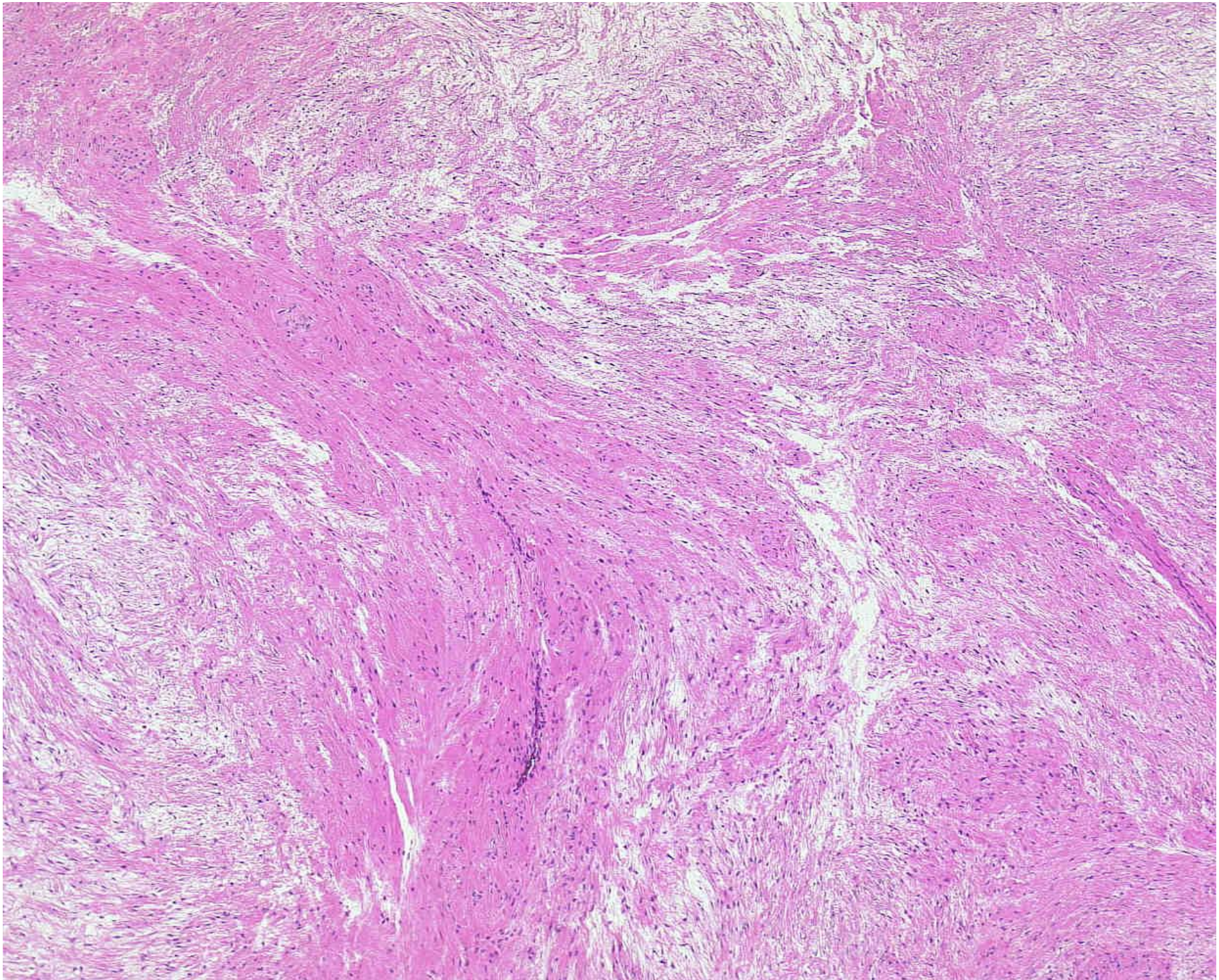
Low-grade fibromyxoid Sarcoma

- young adults >> children, soft tissue >> dermis,
  proximal extremities > trunk > retroperitoneum
- collagenous / myxoid stroma,
  short fascicles, whorling and swirling,
  bland, spindled, fibroblastic tumour cells,
  arcades of blood vessels
- MUC4 +, EMA + (75%), ASMA rarely focal +,
  CD34 rarely focal +, S-100 -
- translocation associated sarcoma
  t(7;16) with *FUS-CREB3L2 (*in most cases)
  rarely *FUS-CREB3L1* or *EWS-CREB3L1*)

F, 36 years, pelvis
by courtesy of Prof. Fletcher, USA



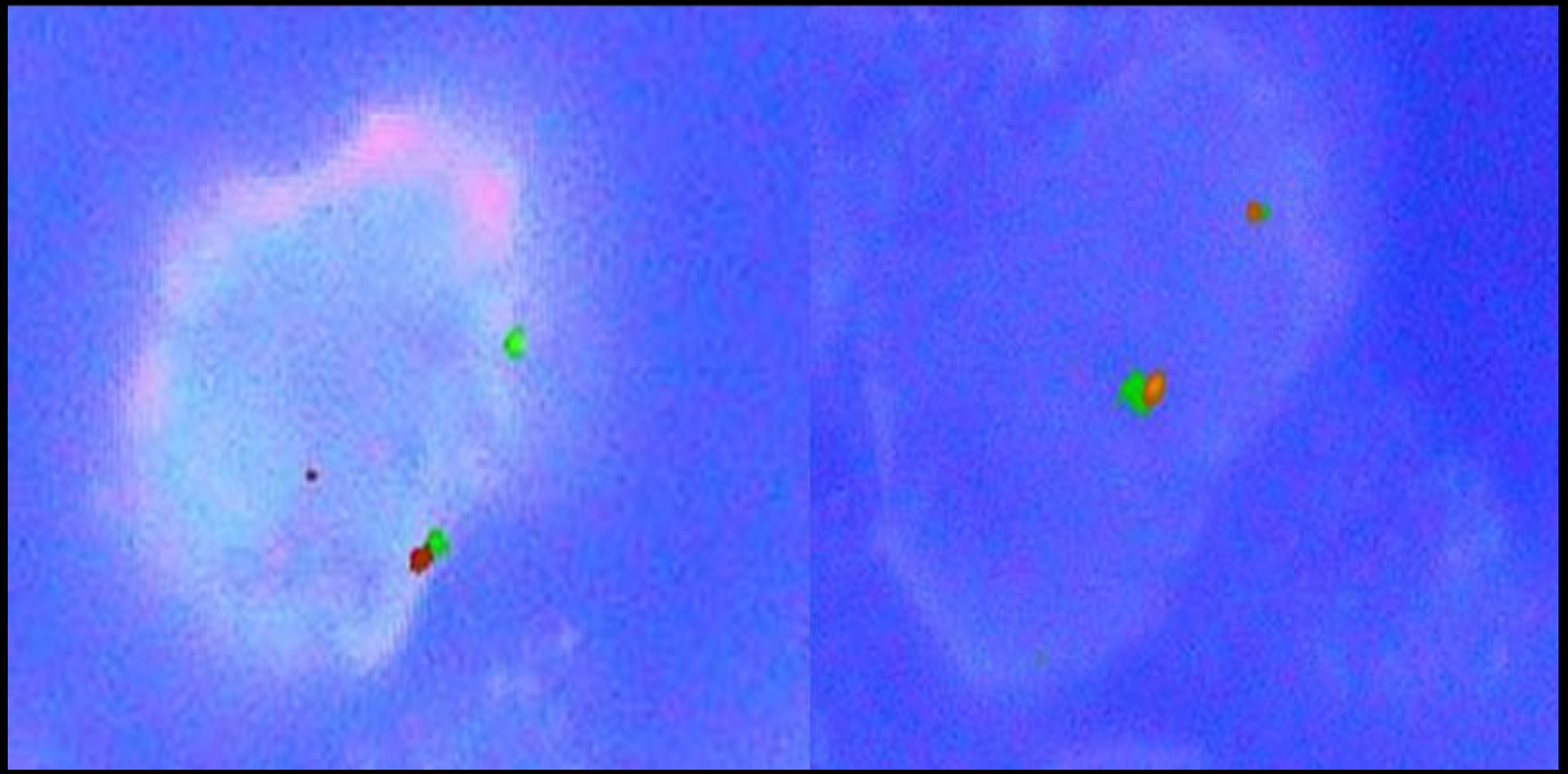




FISH-analysis for *FUS* Translocation

WT 689/06

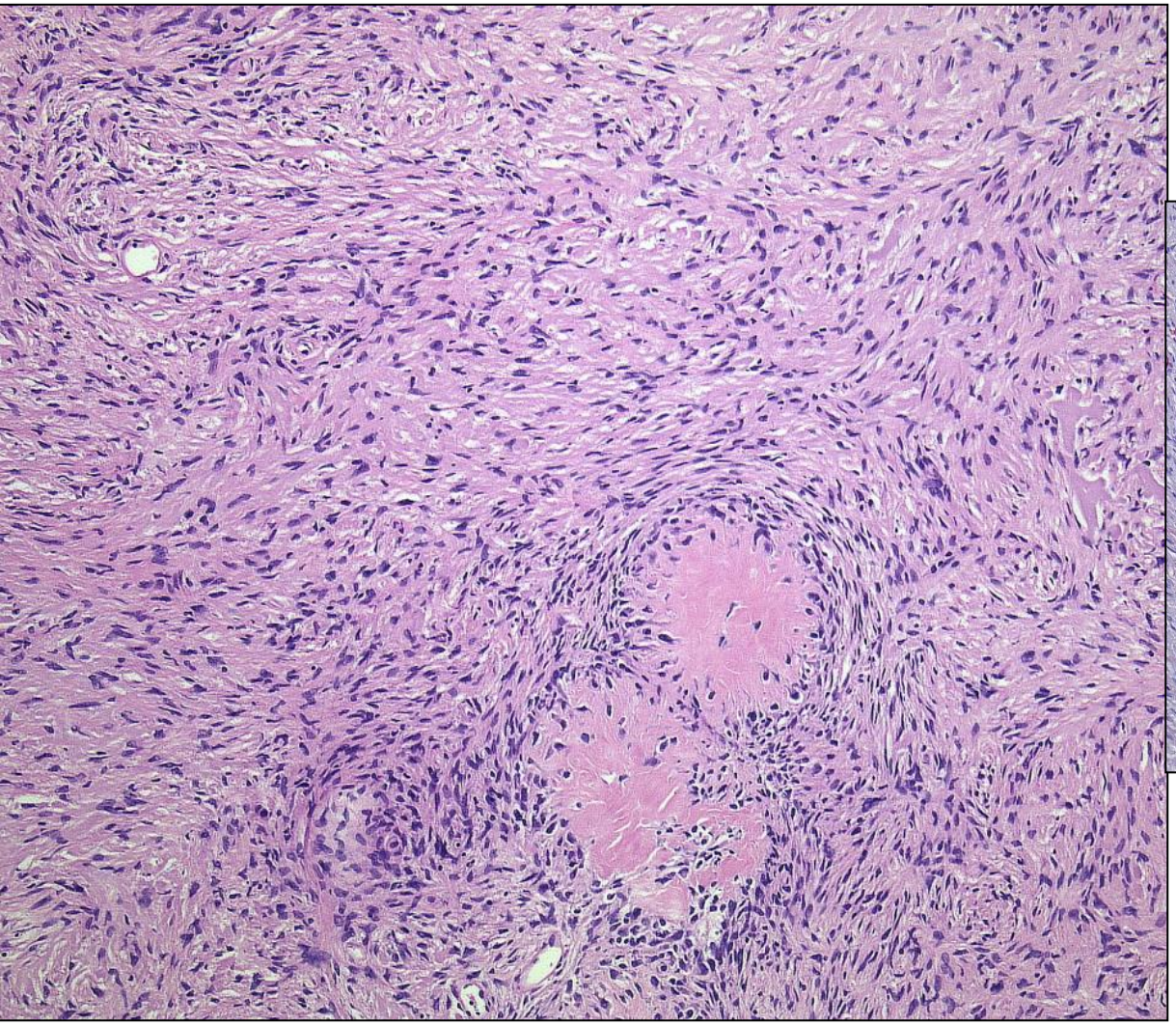
negative control

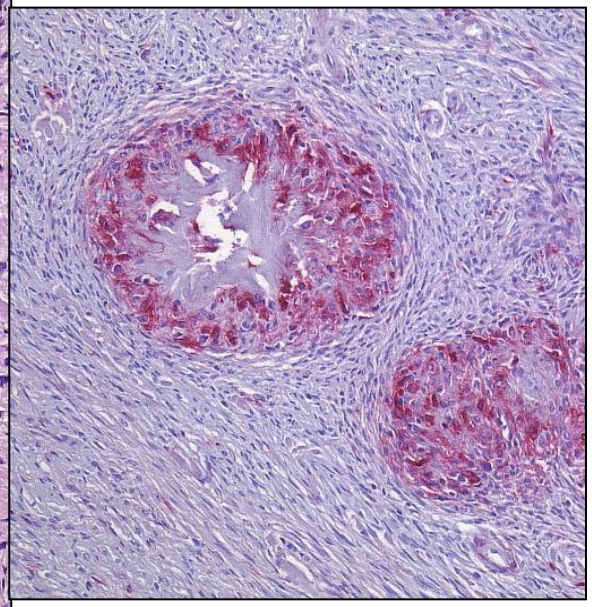


Signals are in different parts of the nucleus = positive

Signals are close together = negative

Low-grade fibromyxoid Sarcoma with giant rosettes (Lane KL et al. AJSP 1997; 21: 1481)





CD56 +

Histological mimics of low-grade fibromyxoid sarcoma are MUC4 negative

angiofibroma of soft tissue:	variable EMA, CD34 expression, *AHRR::NCOA2*
acral fibromyxoma:	fascicular growth, EMA +, CD34 +, nestin +
superficial angiomyxoma:	lobular growth, perivascular neutrophils
perineurioma:	EMA +, claudin-1 +
neurofibroma:	tapering nuclei, S-100 +
cellular intramuscular myxoma:	no arcades of vessels, CD34 +/-
myxoid SFT:	CD34 +, STAT6 +, HPC-like vessels
desmoidfibromatosis:	long fascicles, ASMA +, ß-catenin +, LEF 1 +
low-grade MPNST:	cytological atypia, S100 / GFAP focal +
low-grade myxofibrosarcoma:	cytological atypia, curvilinear vessels

Conclusions Case 4

low-grade fibromyxoid sarcoma may occur in children

low-grade fibromyxoid sarcoma may occur superficially

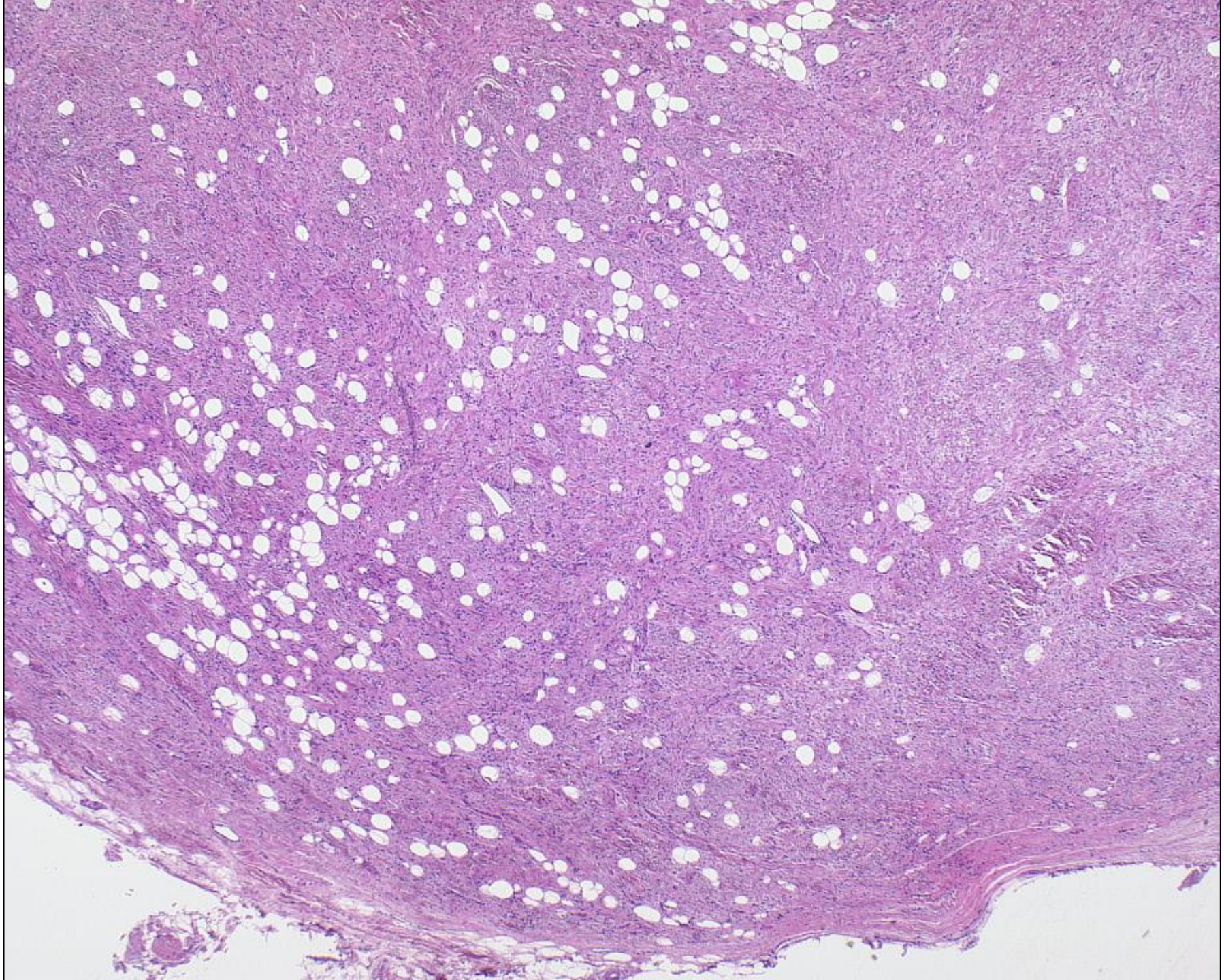
low-grade fibromyxoid sarcoma is mimicking

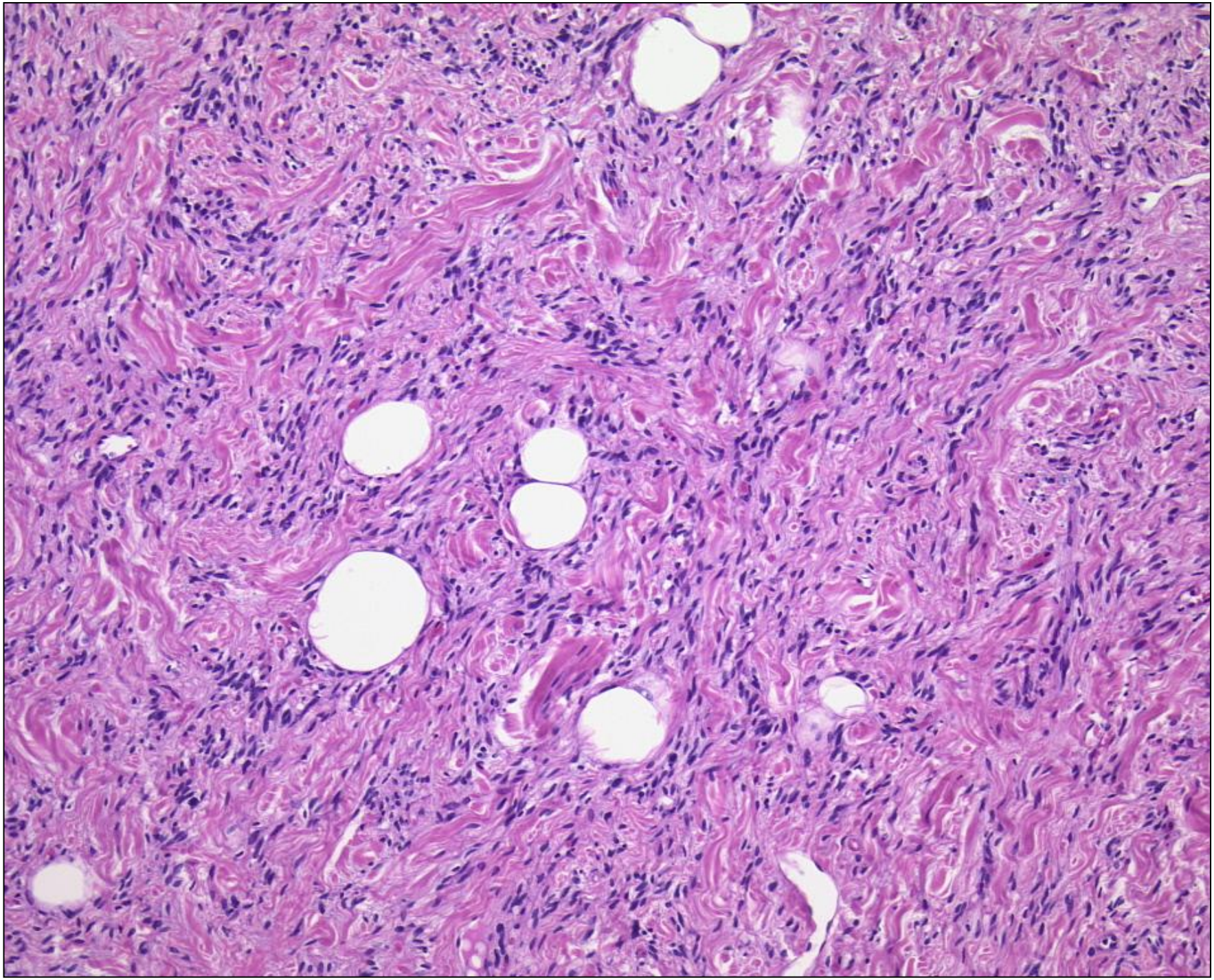
benign neoplasms

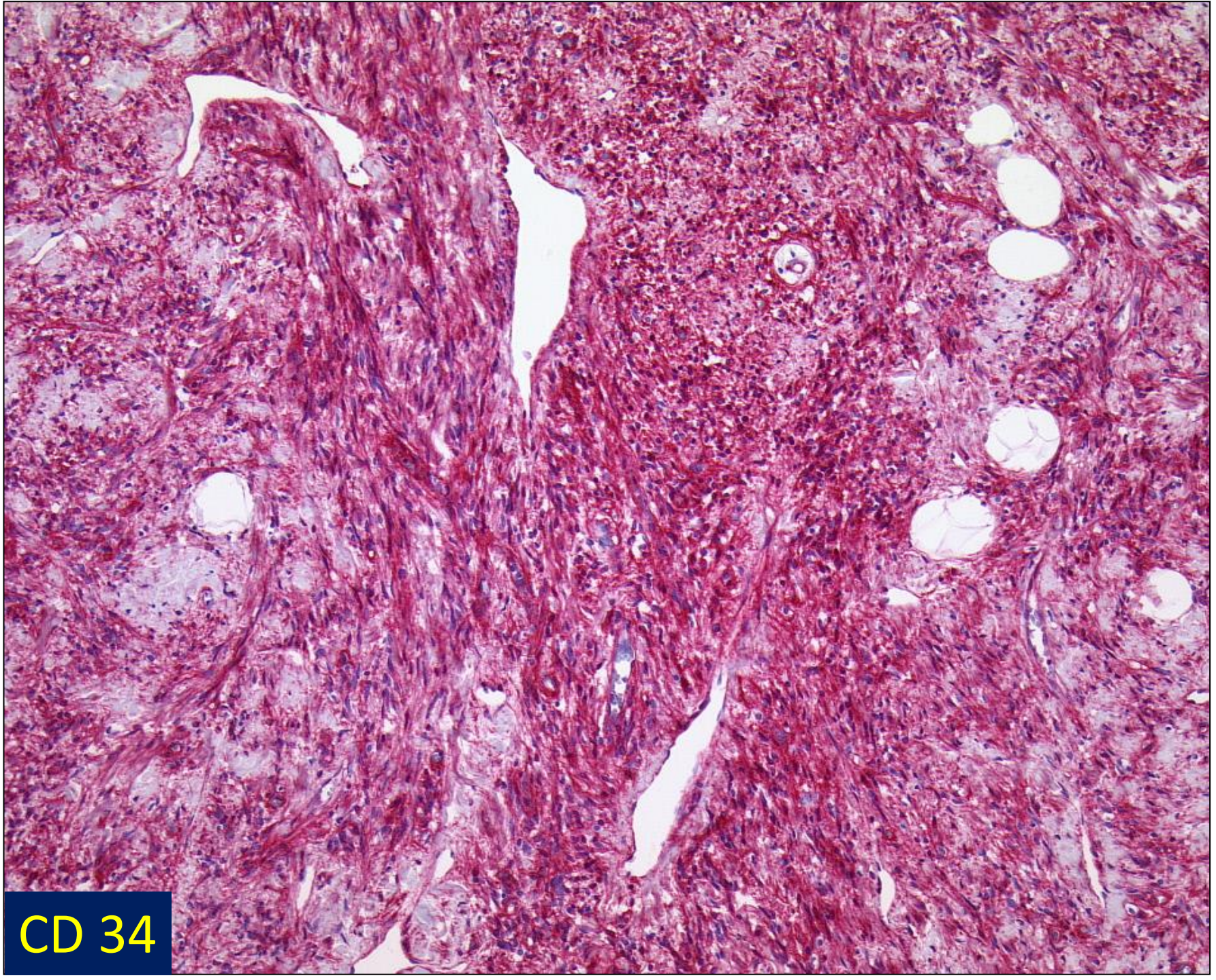
MUC4 represents the most sensitive marker

Case 5

- M, 77 years
- upper back
- subcutaneous lesion
- encapsulated lesion



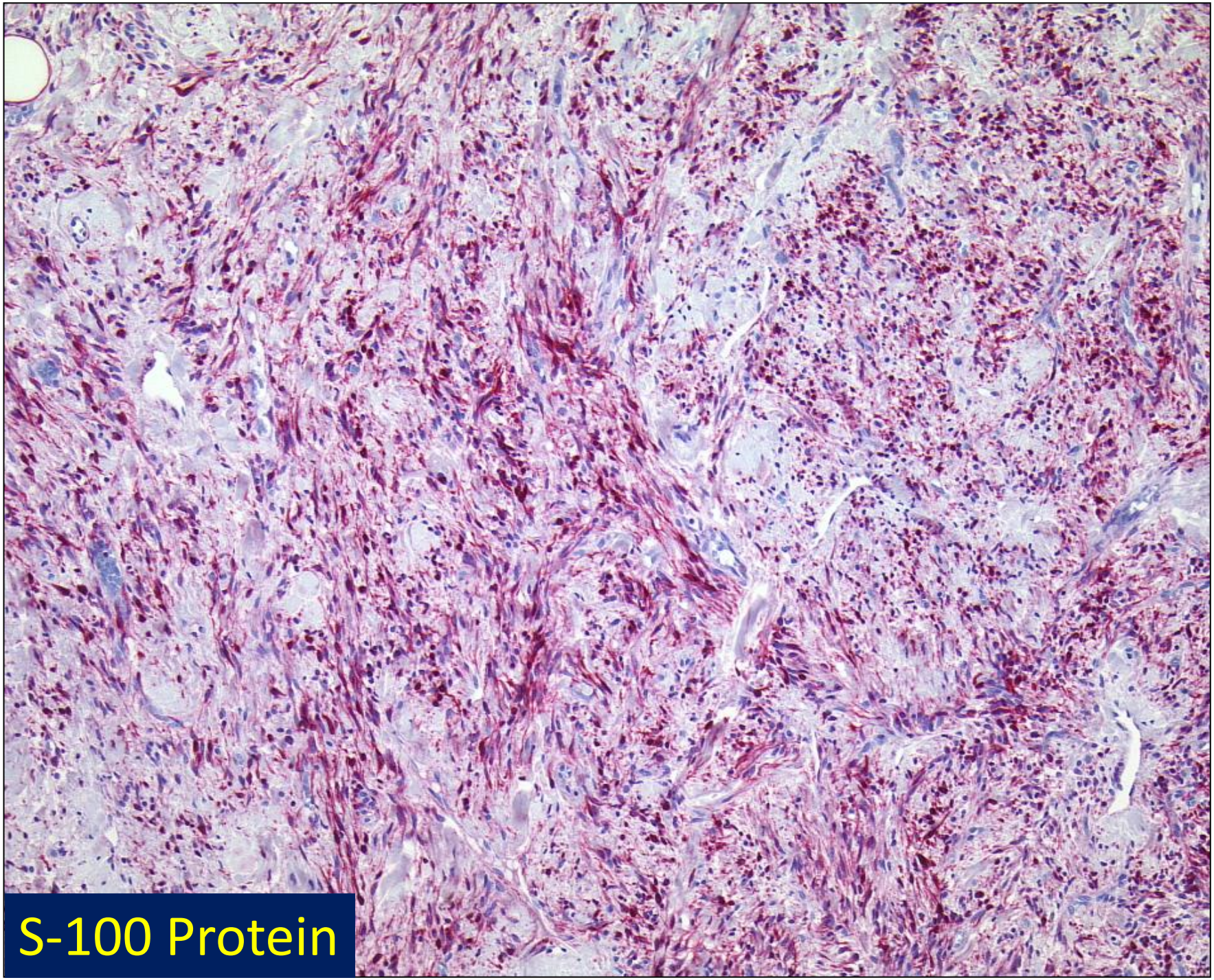



CD 34

Diagnosis Case 5

spindle cell Lipoma

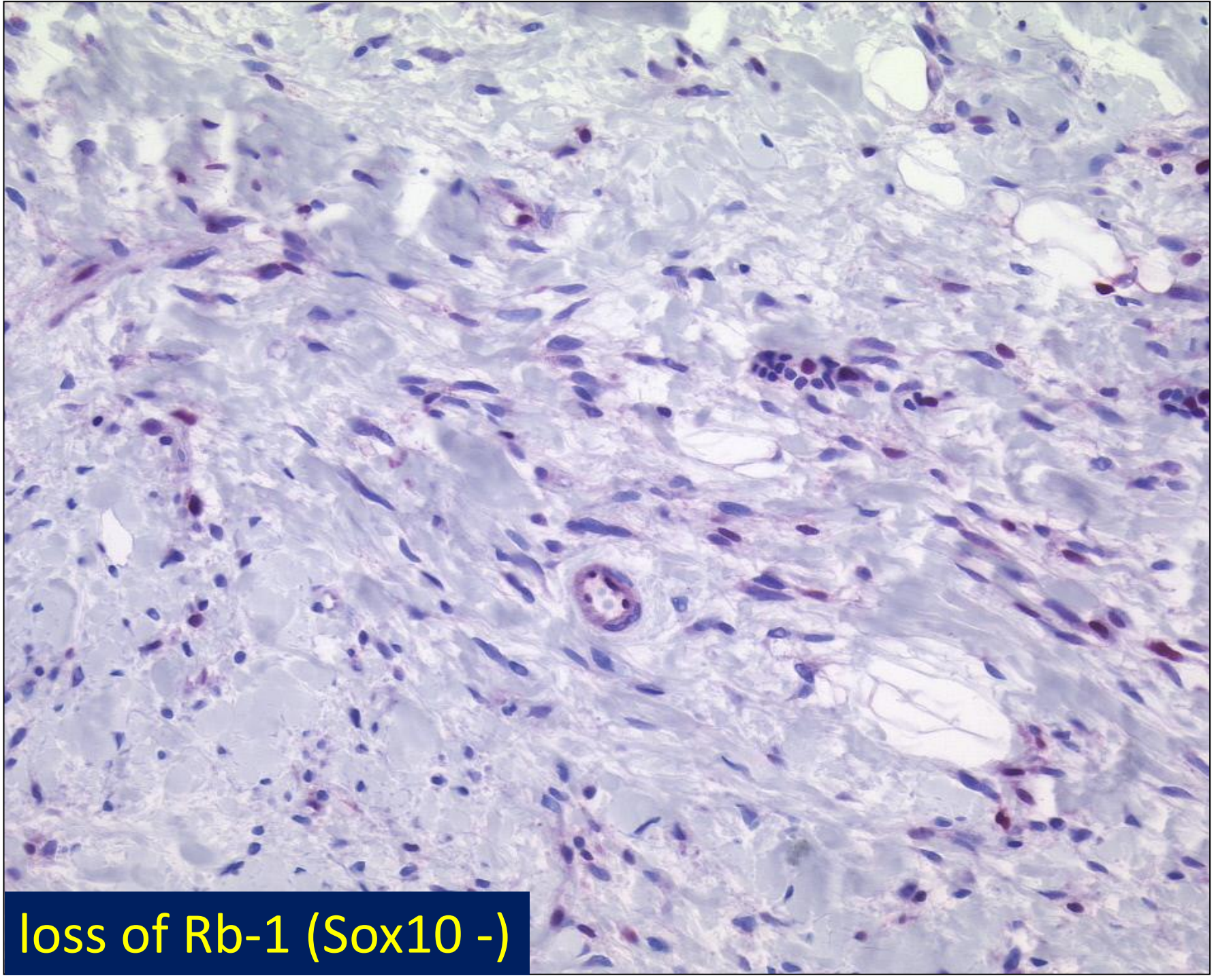
BUT


S-100 Protein

Diagnosis Case 5

encapsulated Neurofibroma

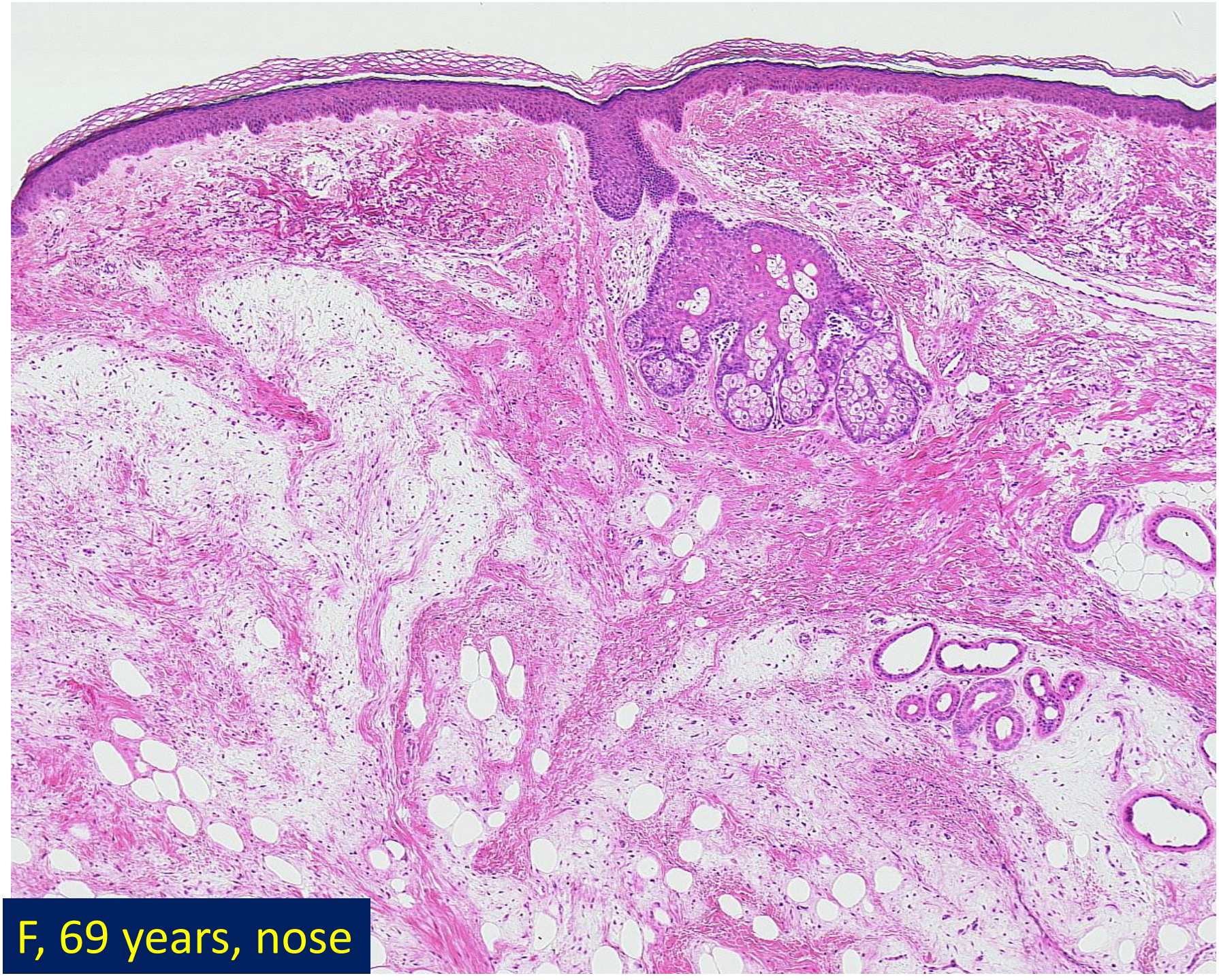
BUT

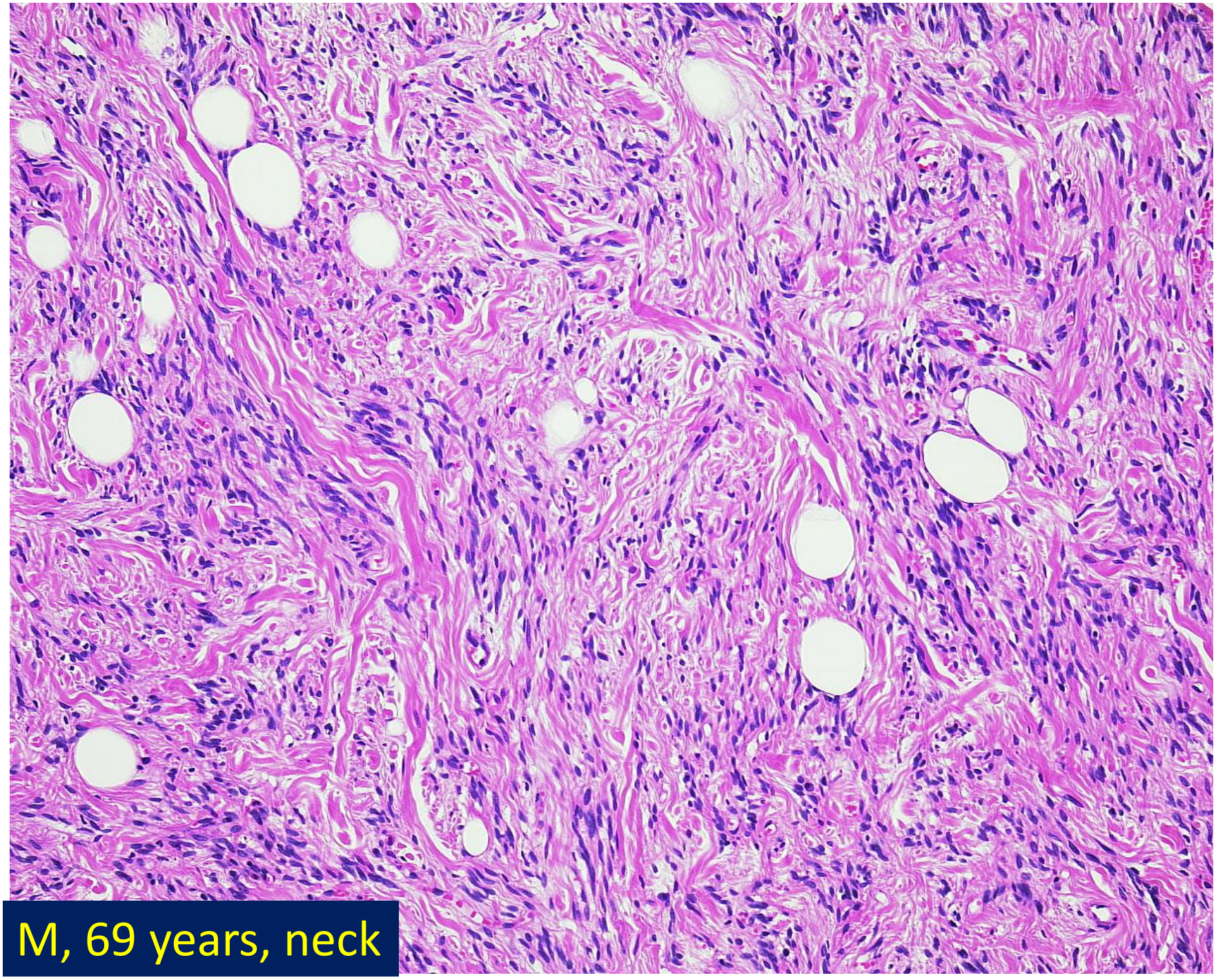

loss of Rb-1 (Sox10 -)

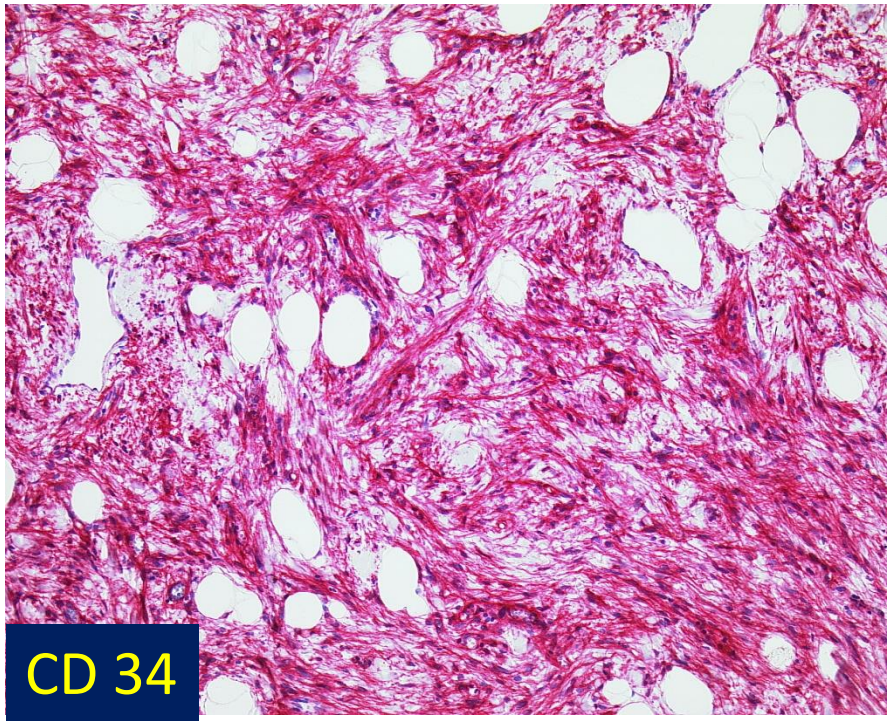
S-100 protein expression of spindle cells in spindle cell lipoma: a diagnostic pitfall

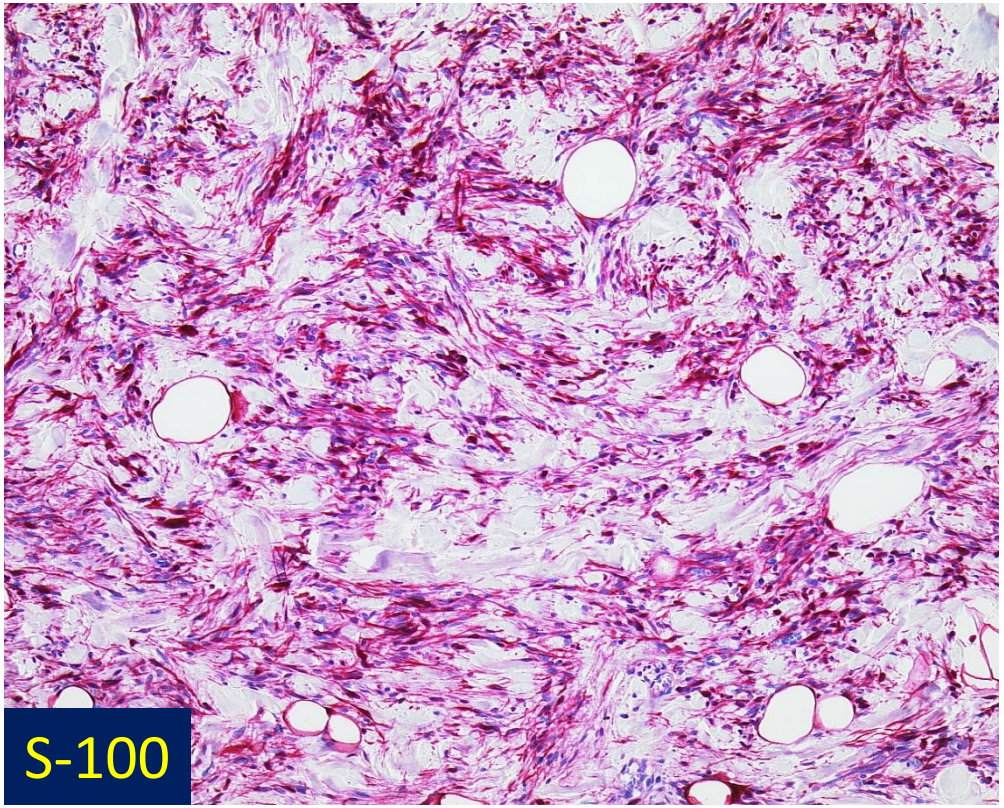
Mentzel T et al. Virchows Archiv 2016; 469: 435

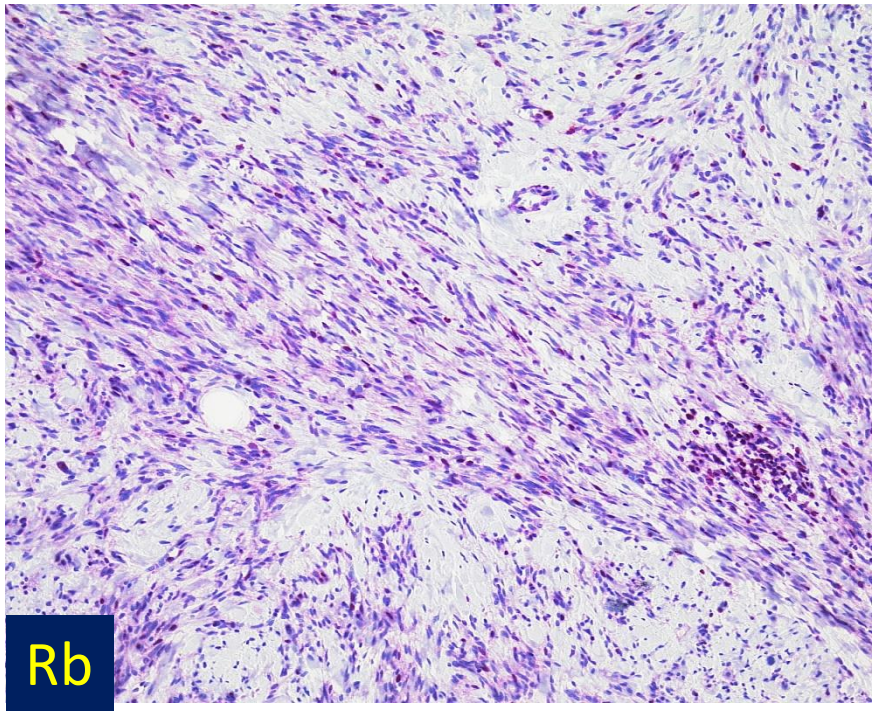
5 cases (1 F, 4 M, 55-89 years, 0.6 - 2.5 cm)
nose, chin, neck, forehead, retroauricular
dermis (1), subcutis (4)
ill-defined (1), encapsulated (4)
CD 34 +, S-100 +, Rb -, Sox 10 -
DD: Neurofibroma (Sox 10 +, Rb +, unencapsulated)
desmoplastic MM (Sox 10 +, cytological atypia, lymphoid aggregates, ass. lentigo maligna)
Schwannoma (no fat, hyalinised vessel walls, Rb1 +)

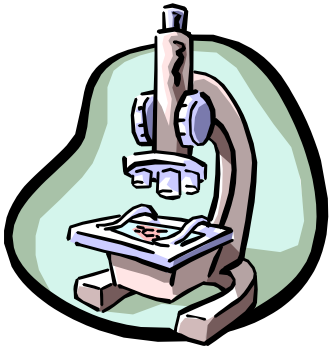

F, 69 years, nose


M, 69 years, neck


CD 34


S-100


Rb

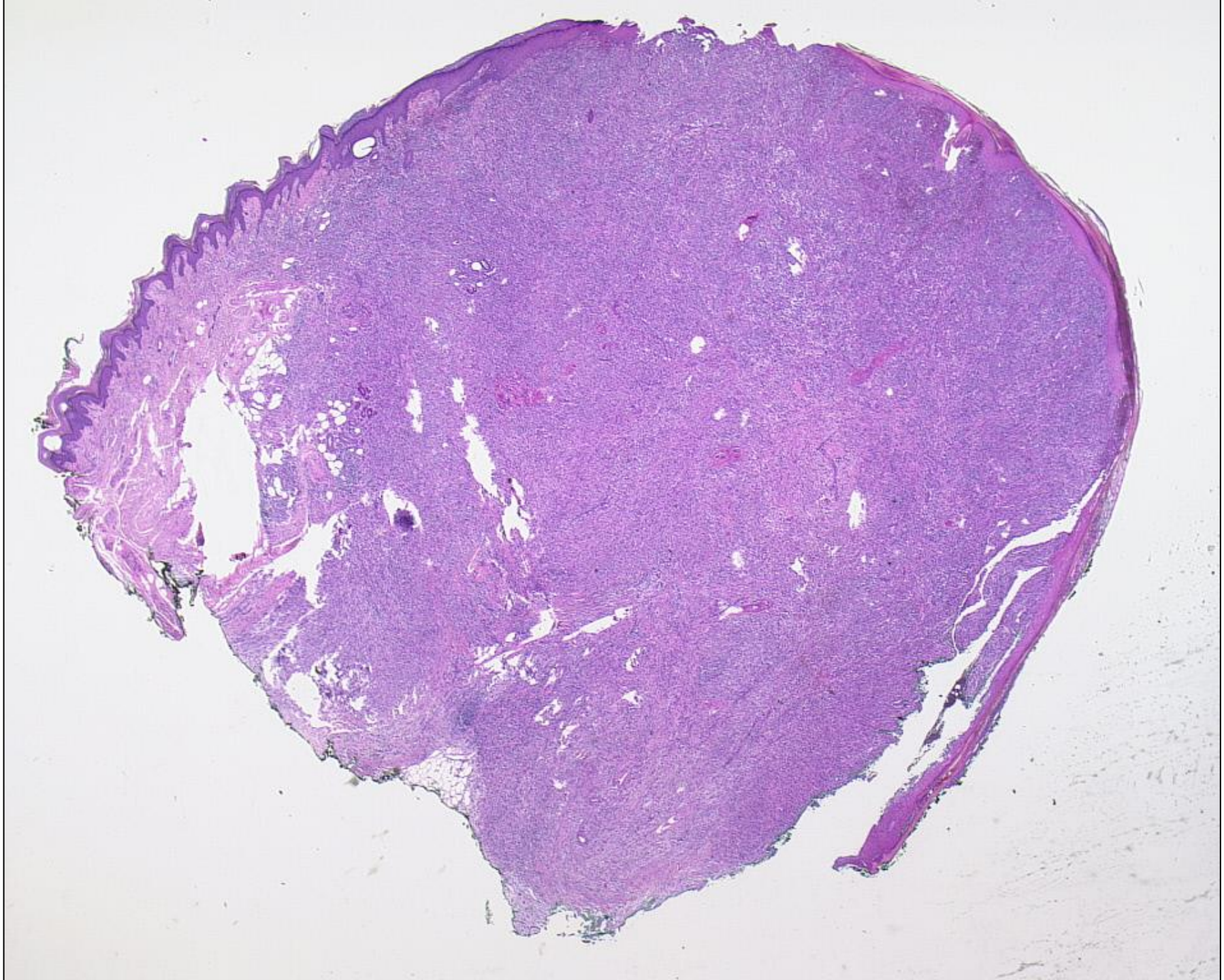


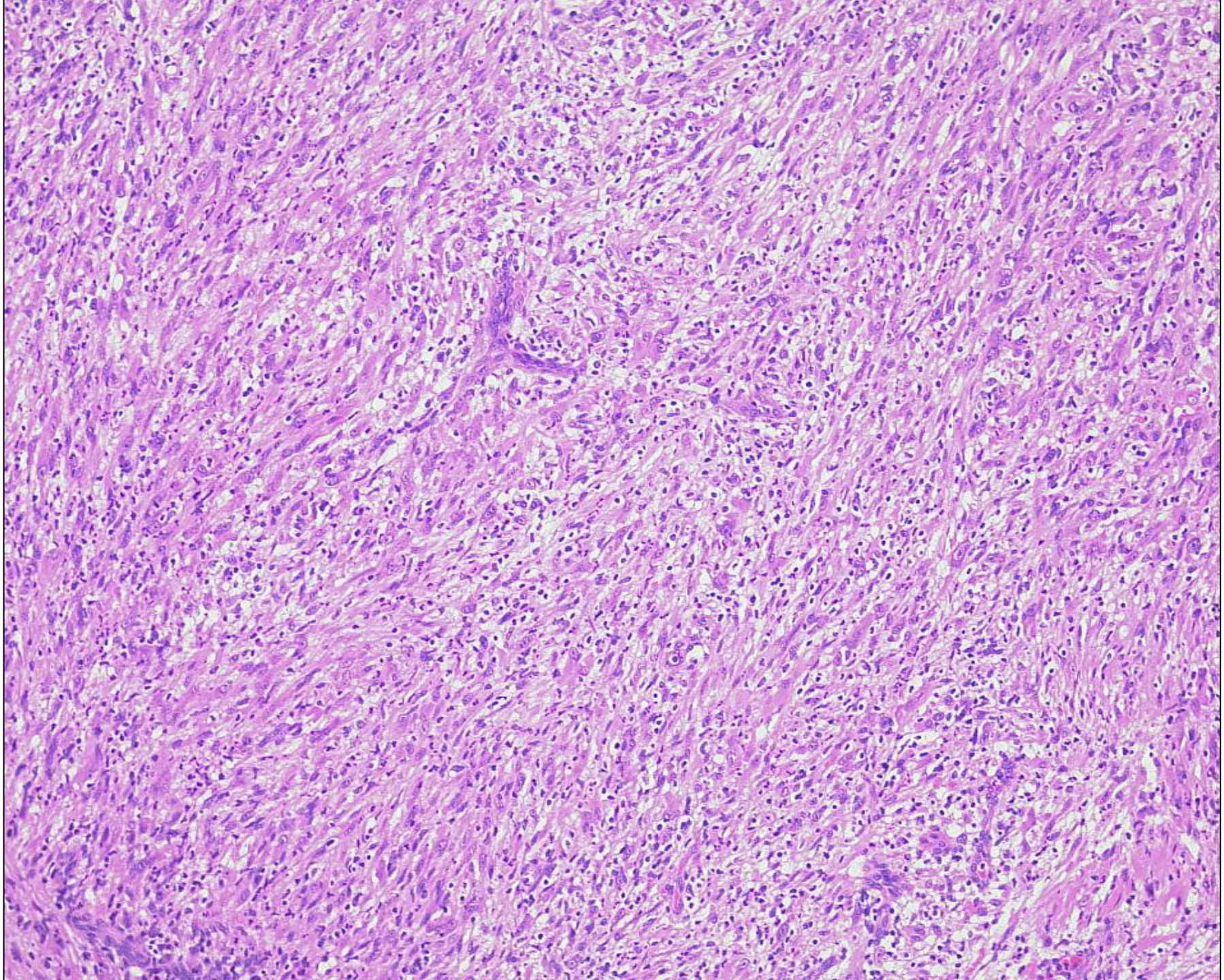
Diagnosis Case 5:

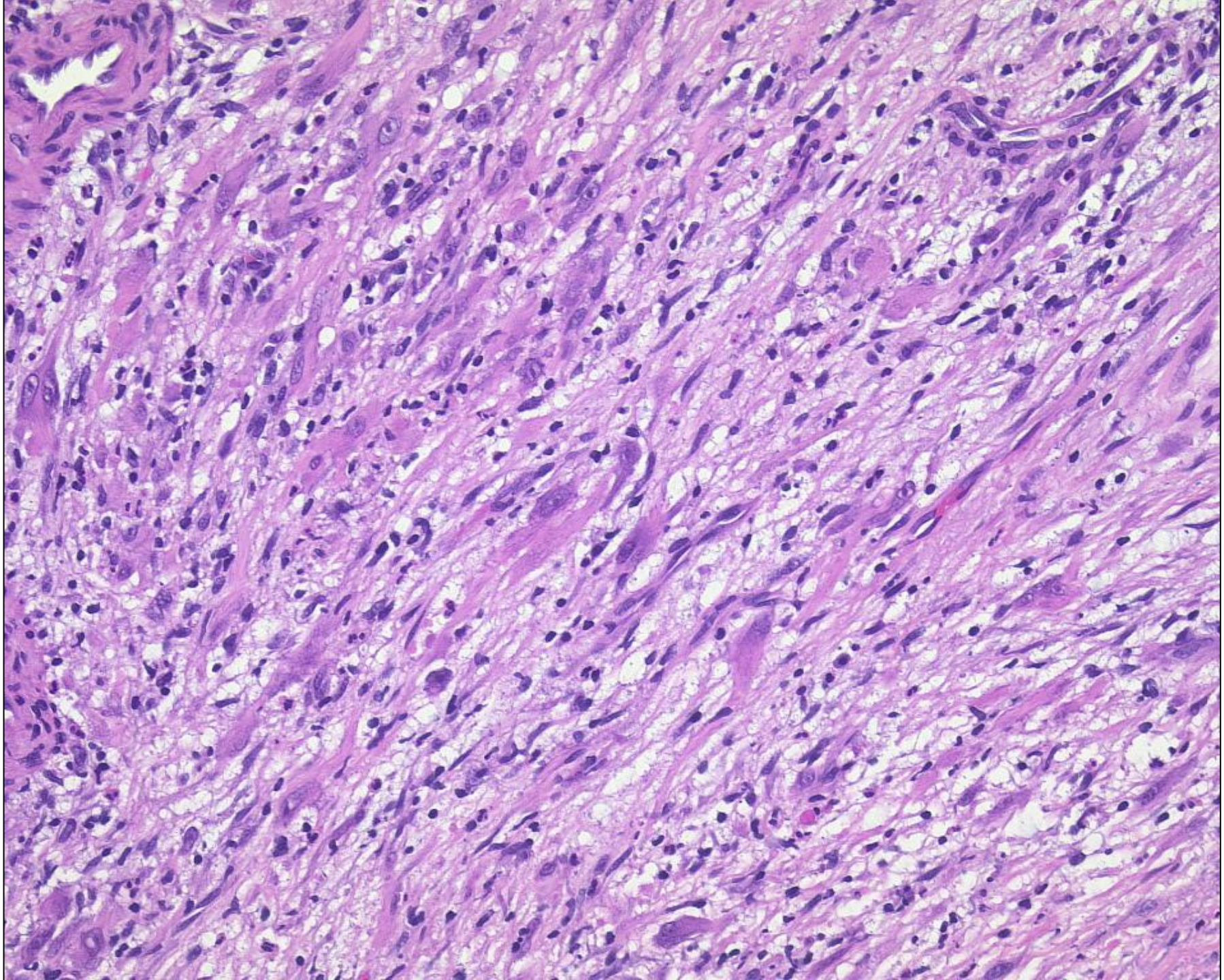
S-100 positive Spindle cell Lipoma

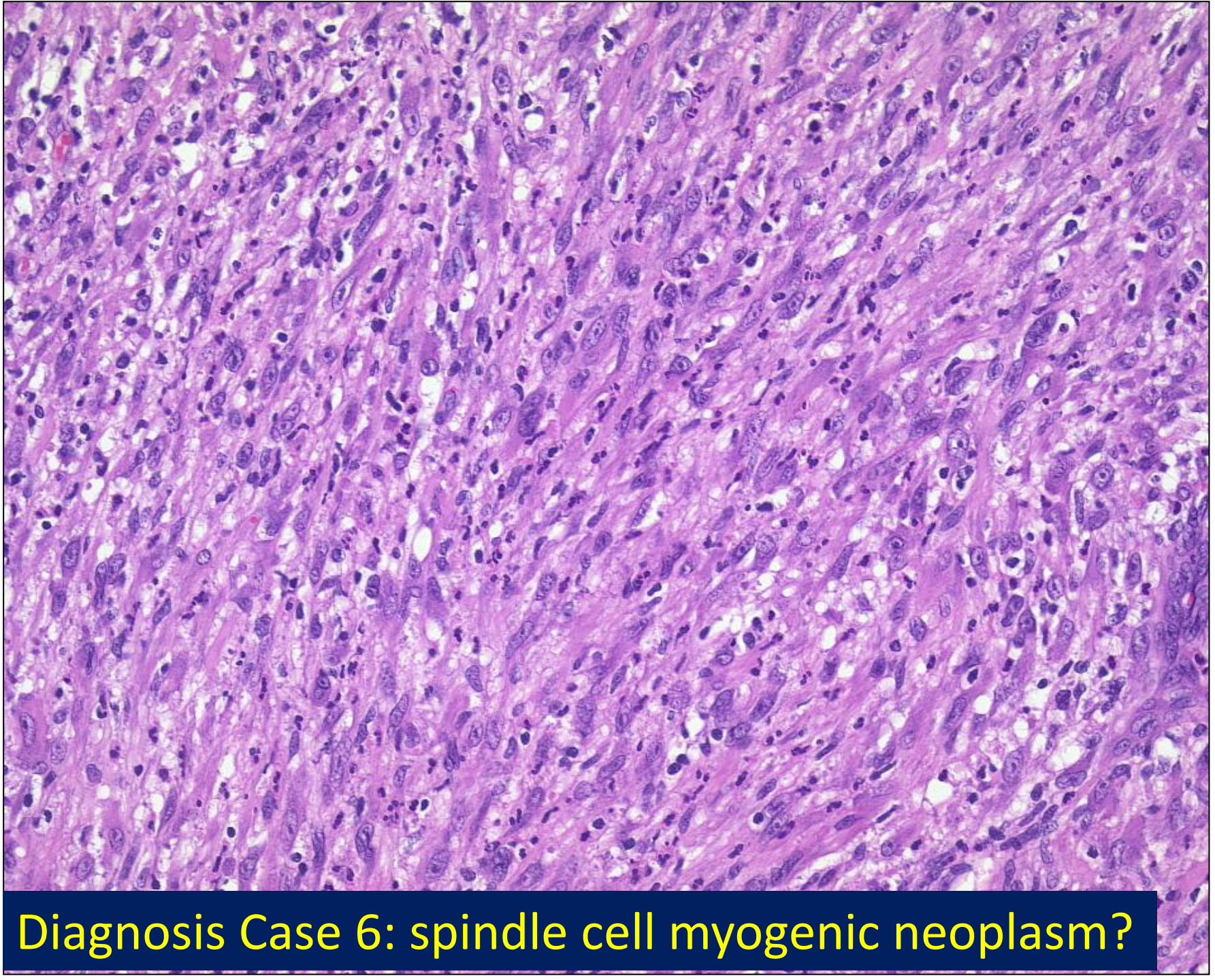
spindle cells in cases of spindle cell lipoma may show an unusual immunophenotype
(Desmin expression in spindle cell lipomas:
a potential diagnostic pitfall
Tardio JC et al. Virchows Archiv 2004; 445: 354)

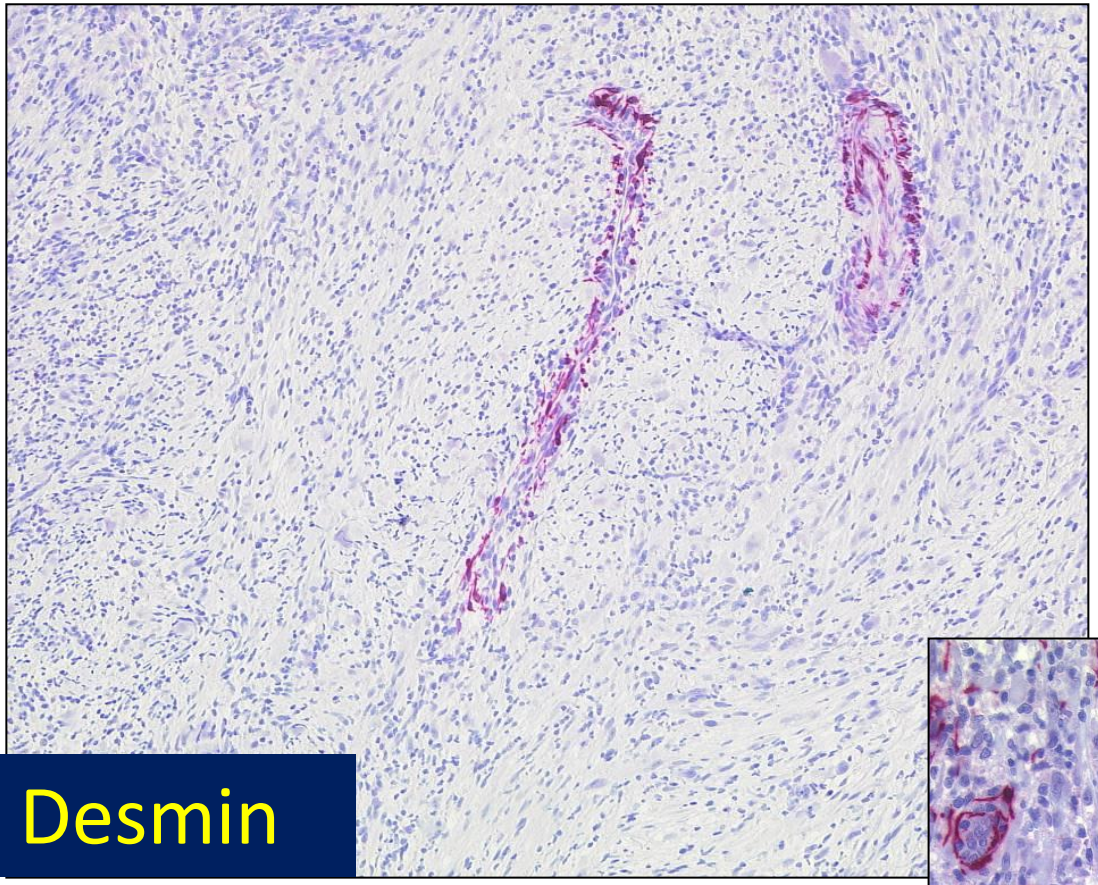
Case 6 (by courtesy of Prof. G.Massi, Rome)
M, 17 years, painful lesions, biopsy

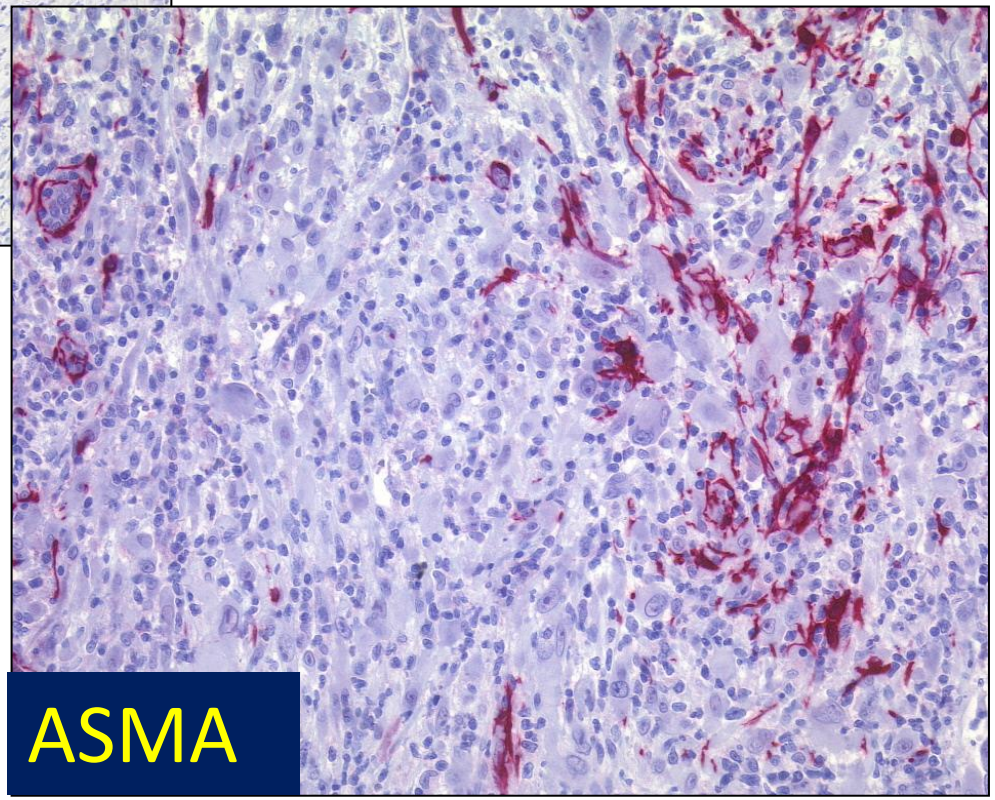


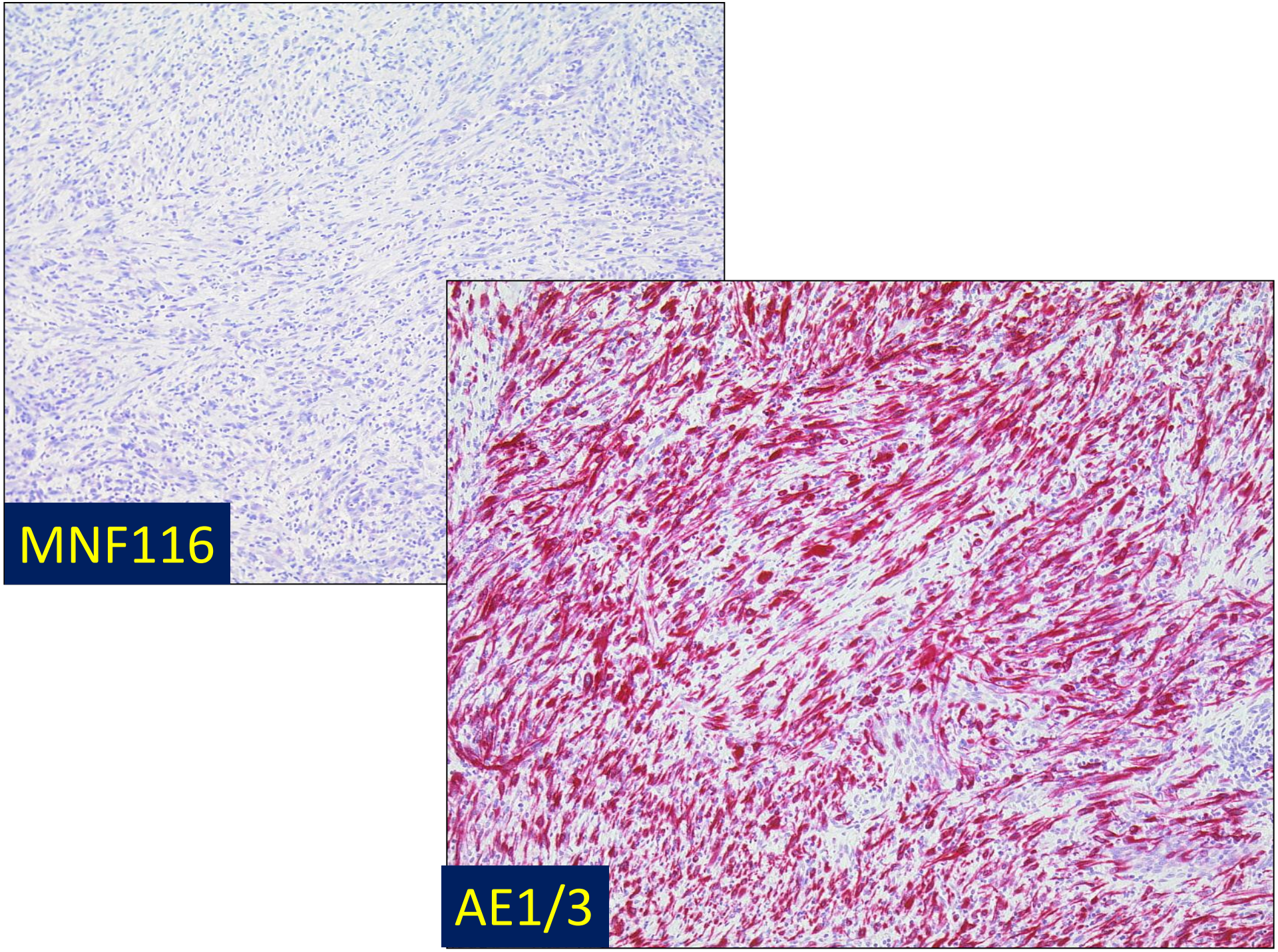


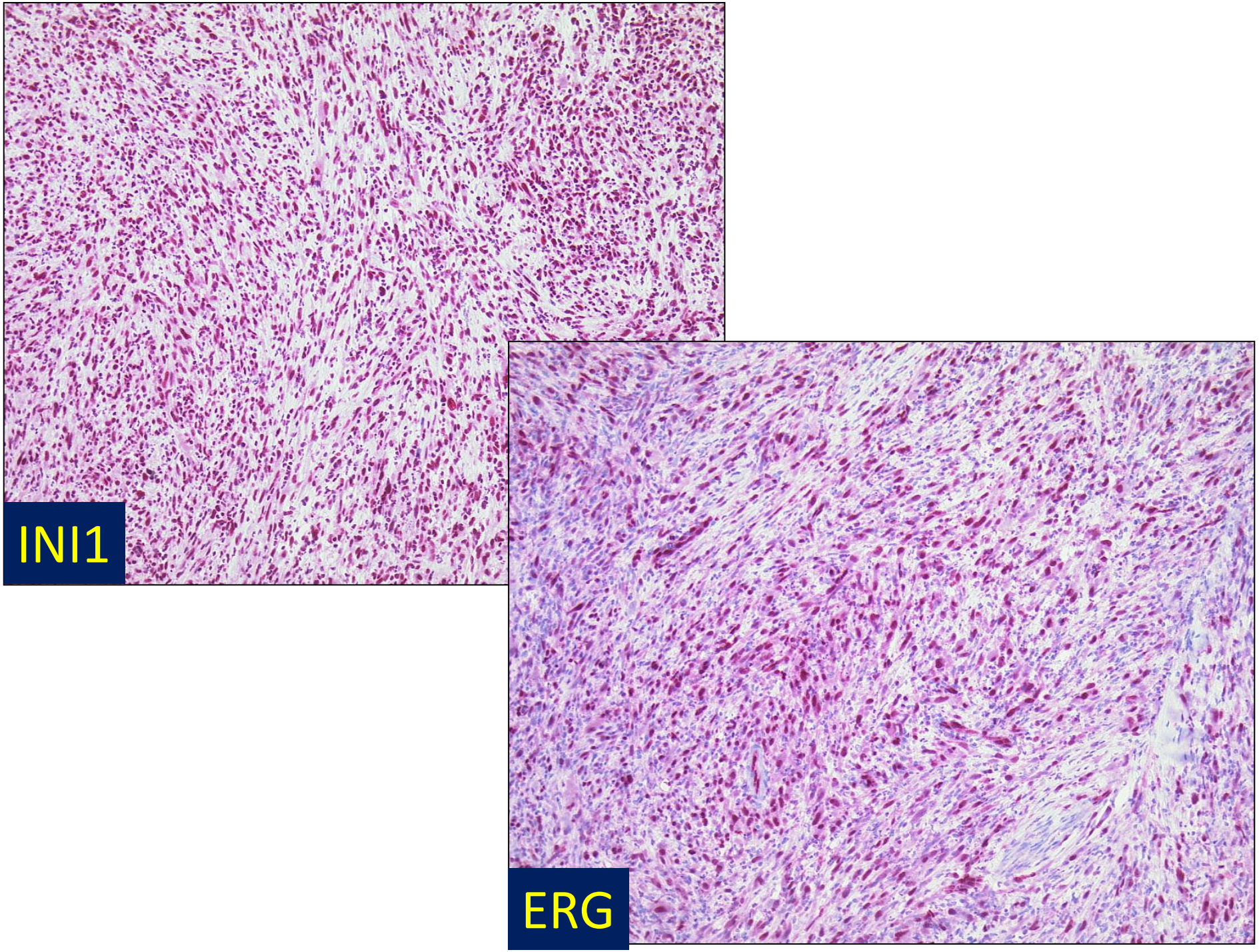



Diagnosis Case 6: spindle cell myogenic neoplasm?

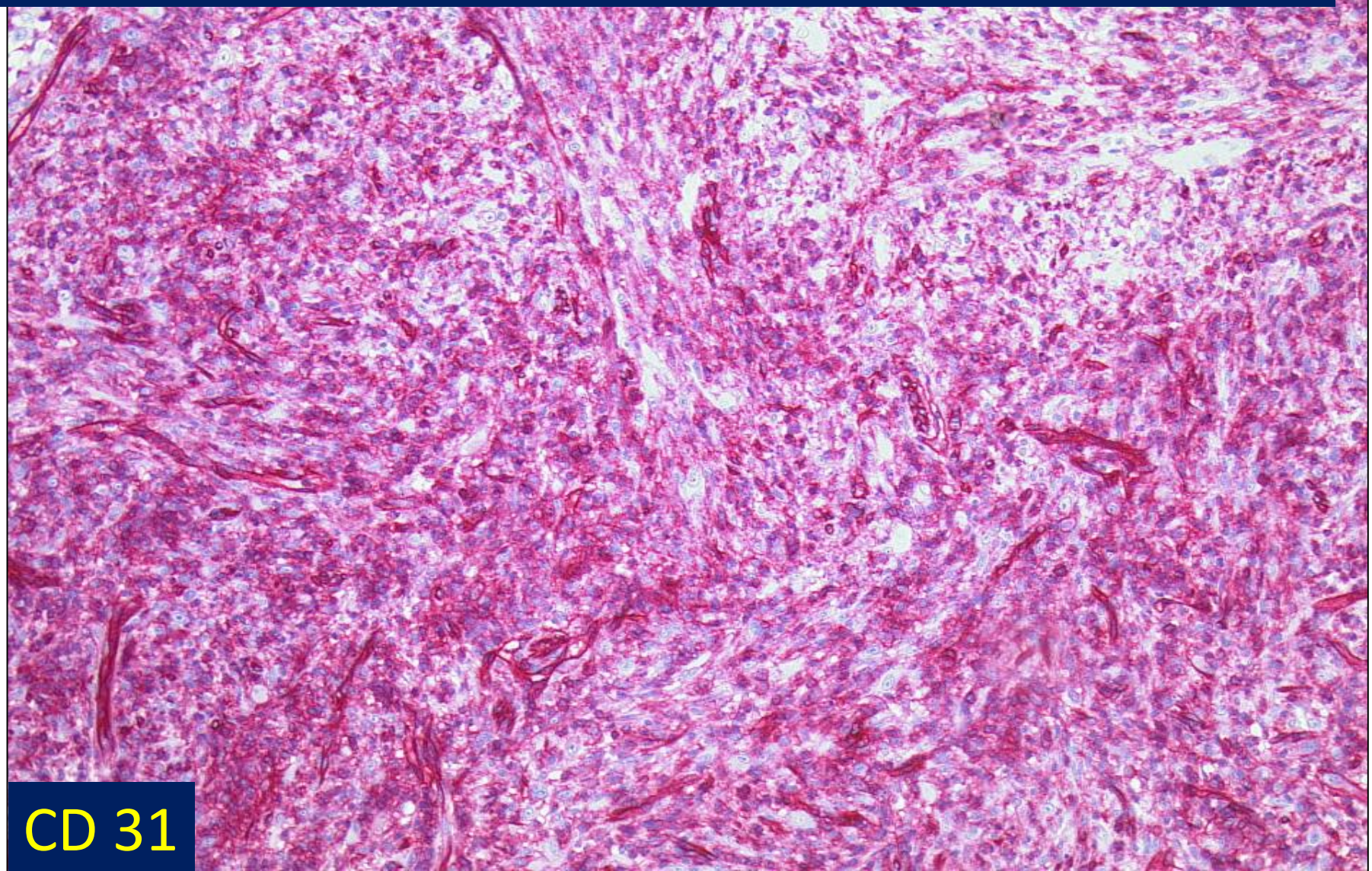

Desmin


ASMA


MNF116
AE1/3


INI1
ERG

Diagnosis Case 6:
pseudomyogenic Haemangioendothelioma („epithelioid sarcoma-like Haemangioendothelioma“)



CD 31

Pseudomyogenic Hemangioendothelioma: A distinctive, often multicentric tumor with indolent behavior

(Hornick JL, Fletcher CDM AJSP 2011; 35: 190)

- 50 cases, 41 M, 9 F, 14 - 80 years
- lower (54%), upper (24%) extremities, trunk (18%), head / neck region (4%)
- multifocal neoplasms (2-15 neoplasms) (66%)
- fascicles, sheets of plump spindled cells
- few epithelioid cells
- AE1/3 +, Fli-1 +, 22/47 CD 31 +, 7/49 EMA + CD 34 -, INI1 +, S-100 -
- local recurrence (58%), MTS (2 x)

Differential diagnosis: pseudomyogenic Haemangioendothelioma

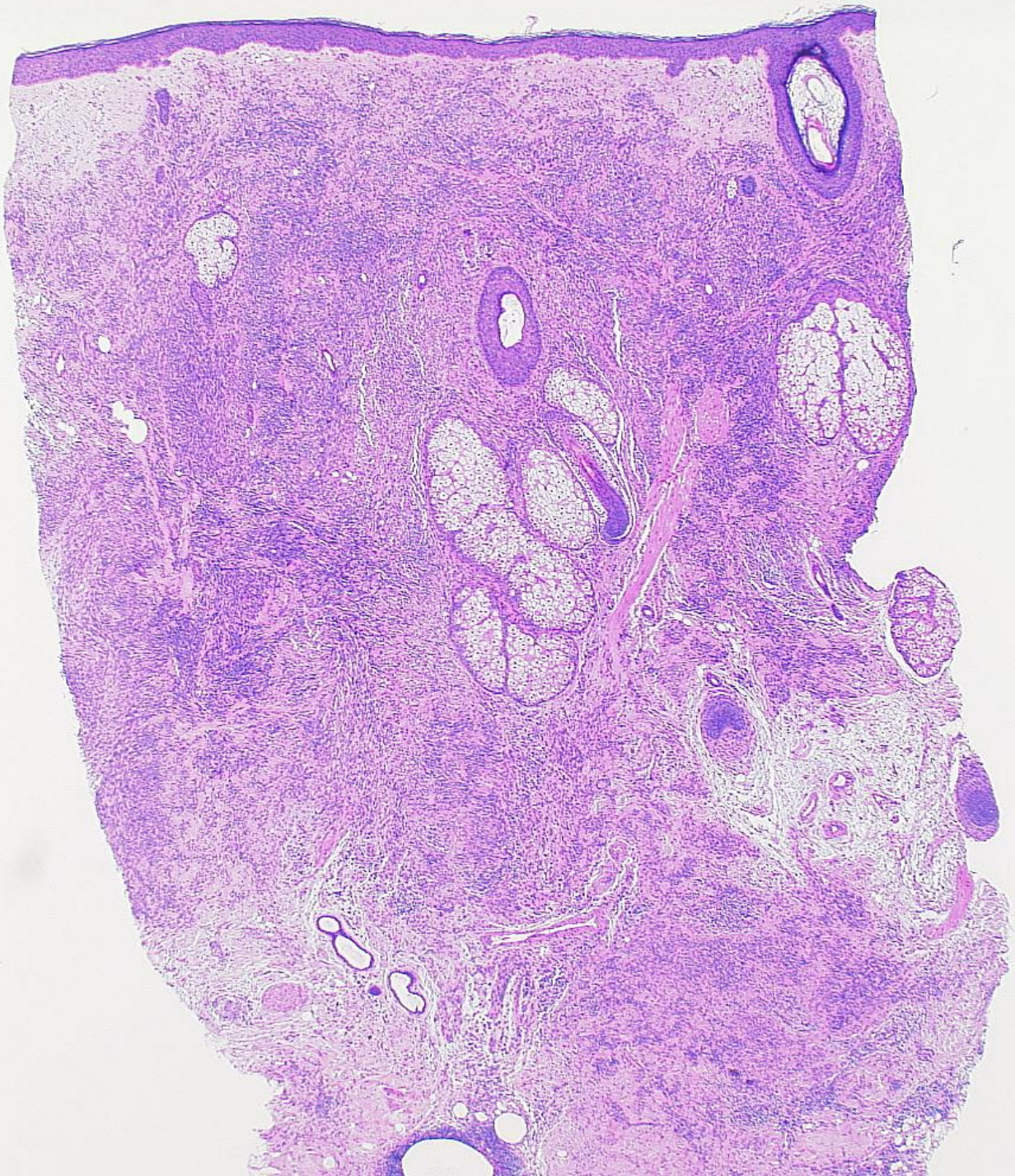
Cutaneous tumours: dermatofibroma, leiomyoma myofibroma, epithelioid sarcoma (INI1 -), spindle cell squamous carcinoma

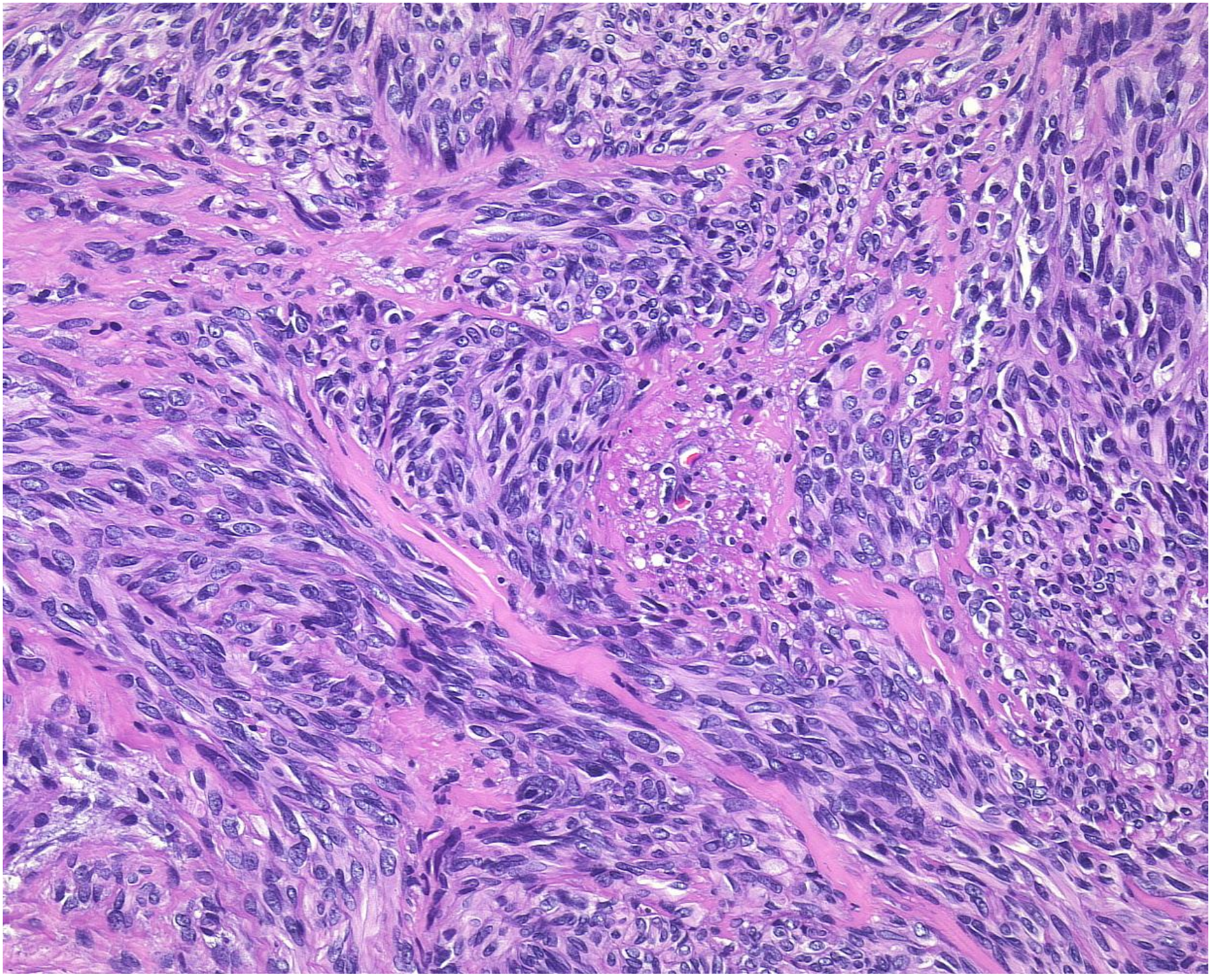
Deep seated tumours: epithelioid sarcoma, epithelioid haemangioendothelioma, angiosarcoma nodular/proliferative fasciitis

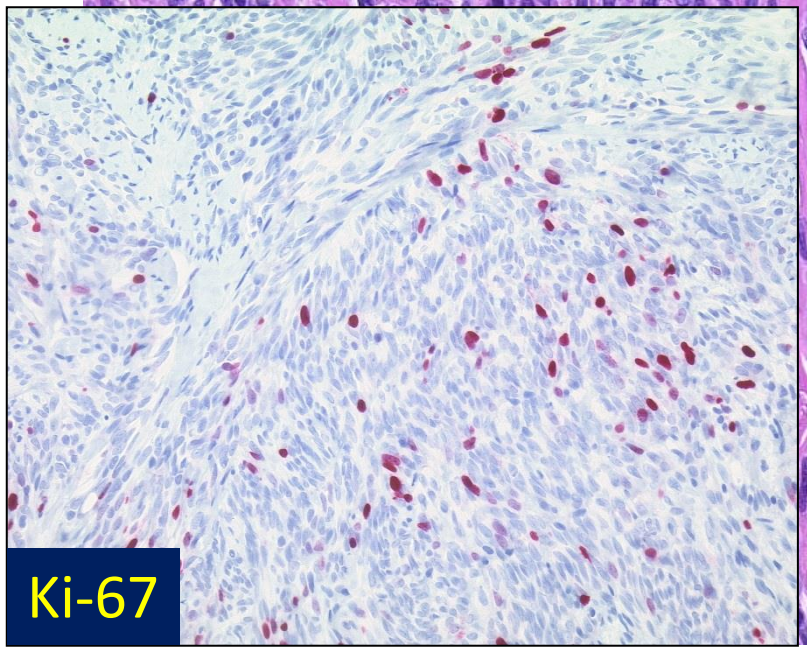
Bone tumours: epithelioid haemangioma, giant cell tumour, osteoblastoma, fibroma

Case 7

- 71-year-old male patient
- indurated dermal lesion
- forehead
- biopsy
- subsequent R0 resection

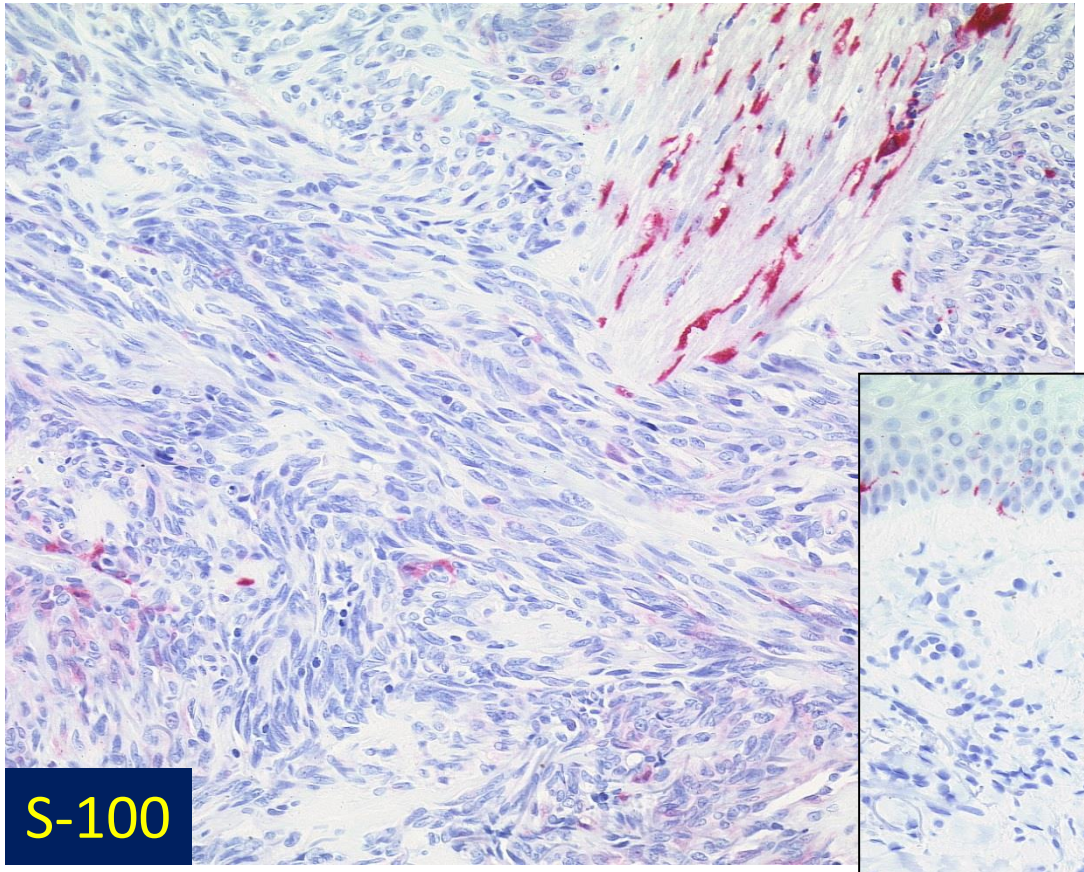


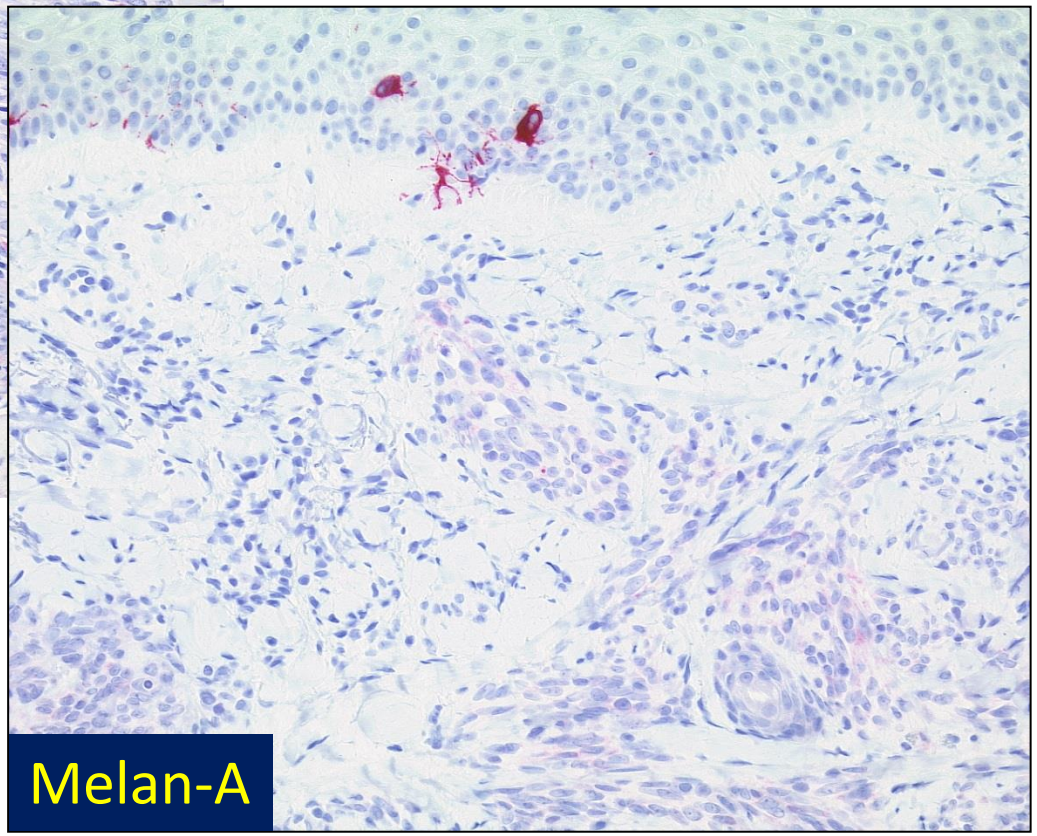



Ki-67

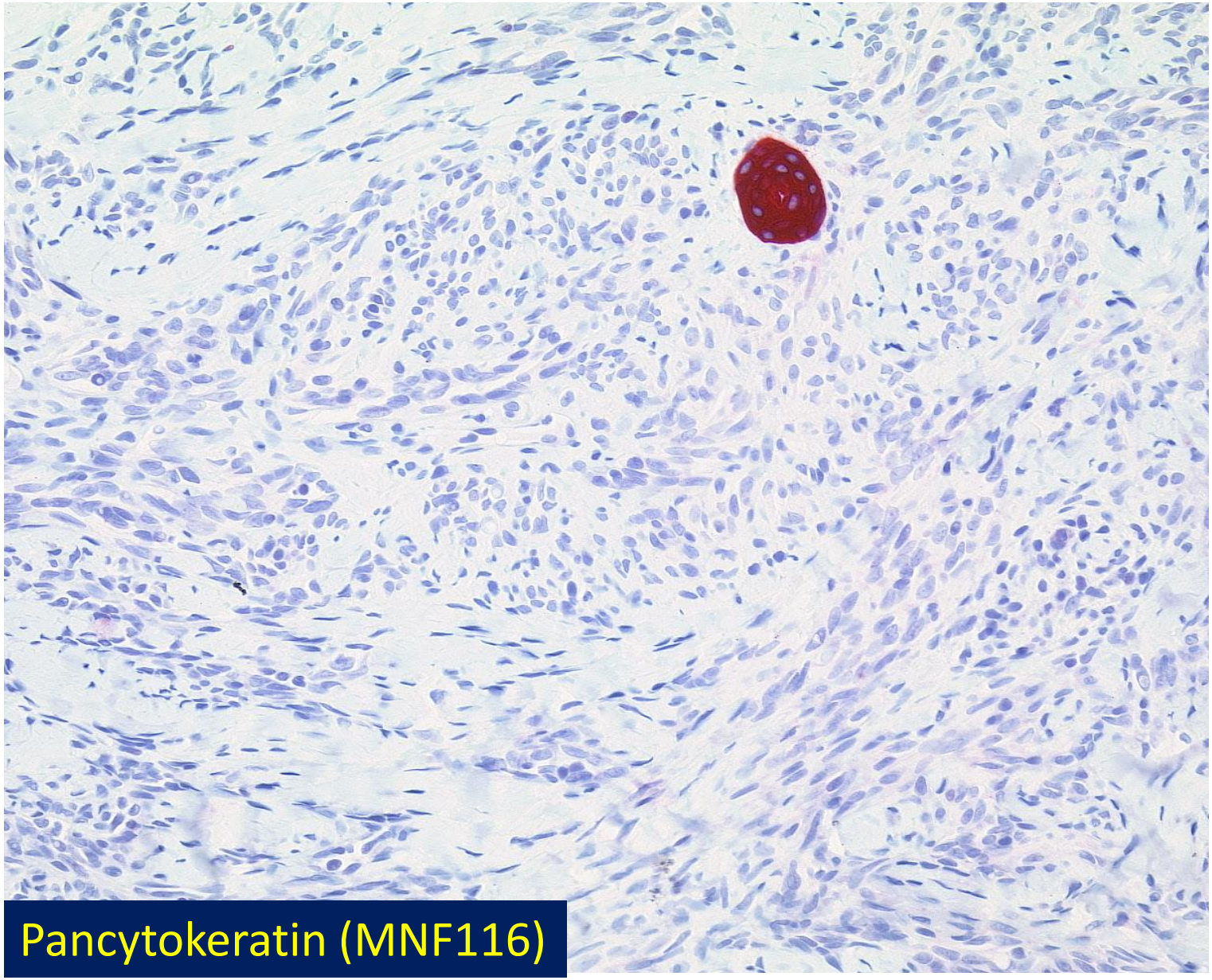
malignant cutaneous spindle cell tumour in an elderly patient arising on the head

spindle cell malignant Melanoma ?

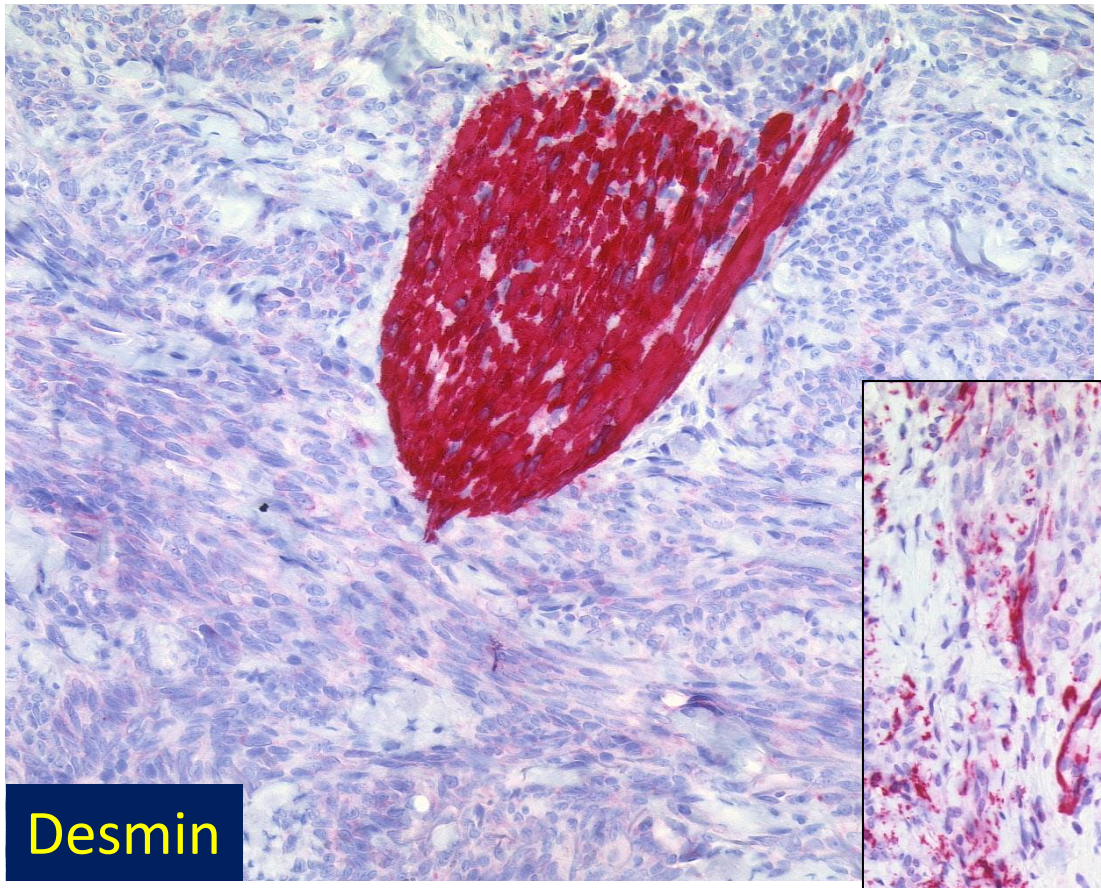


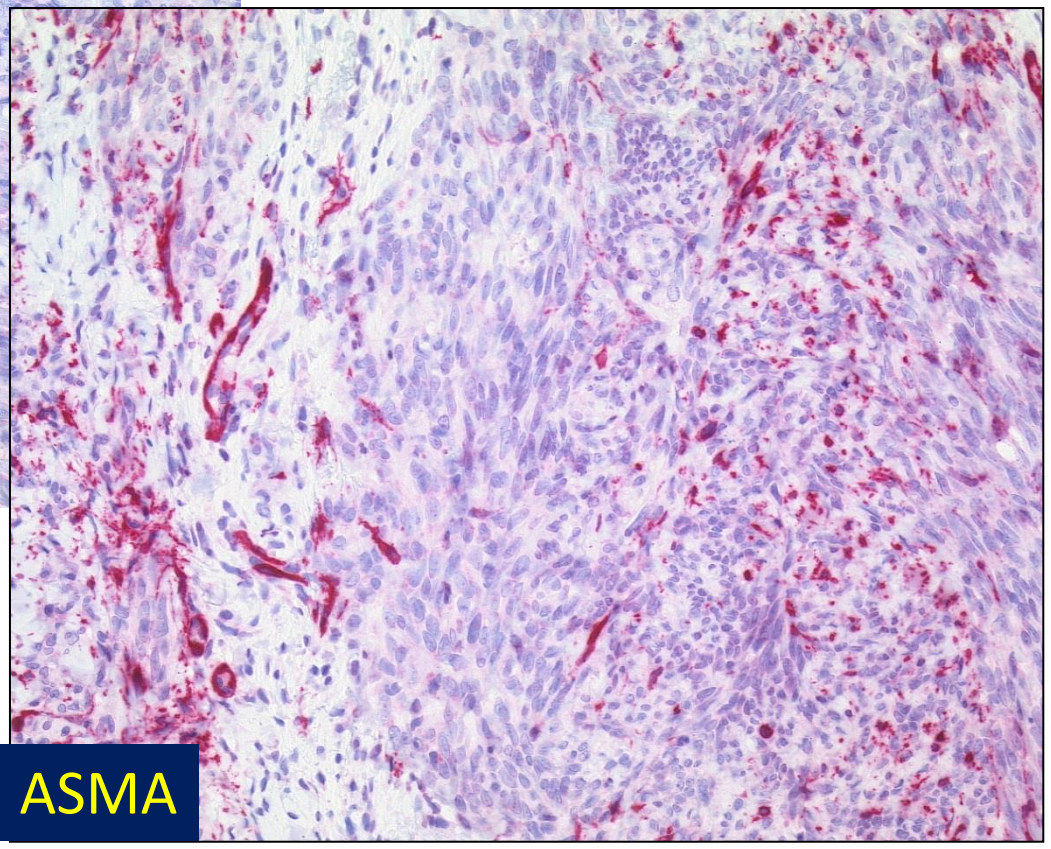


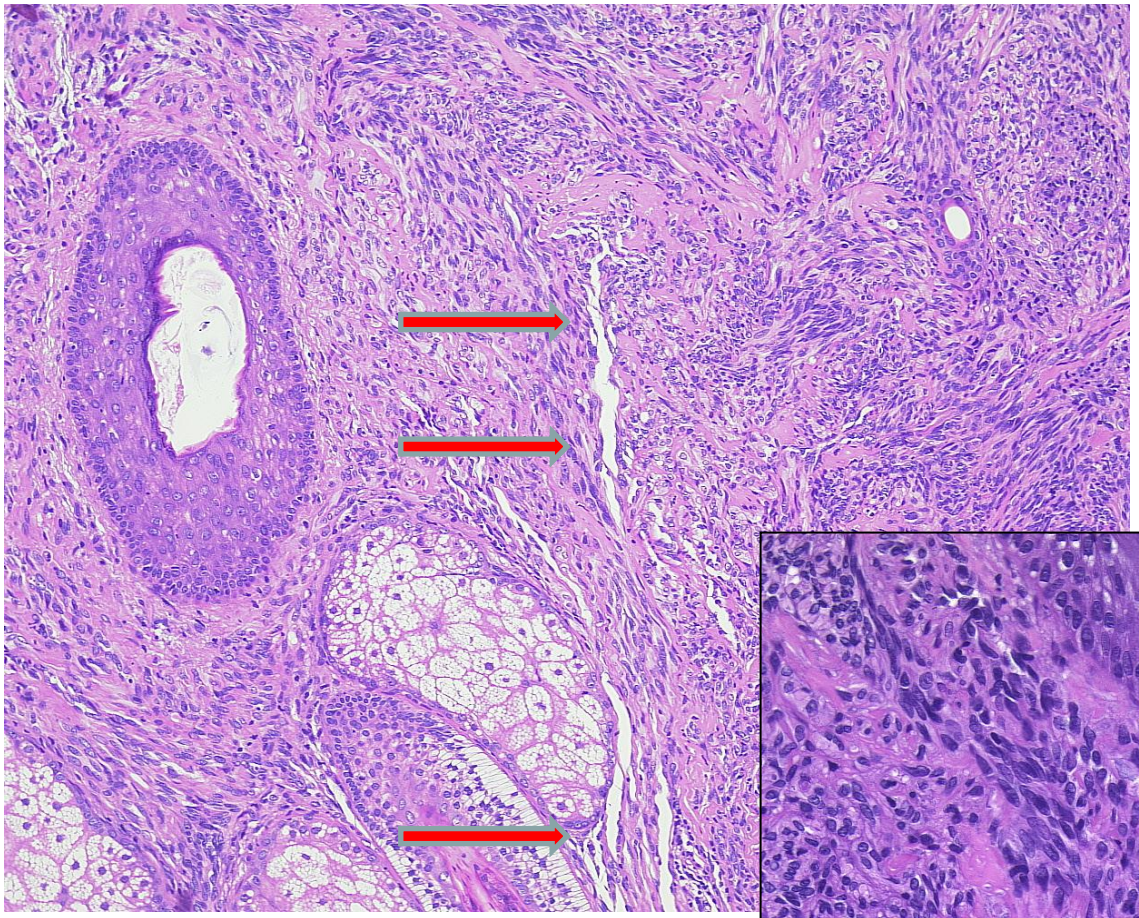
spindle cell sarcomatoid Carcinoma ?

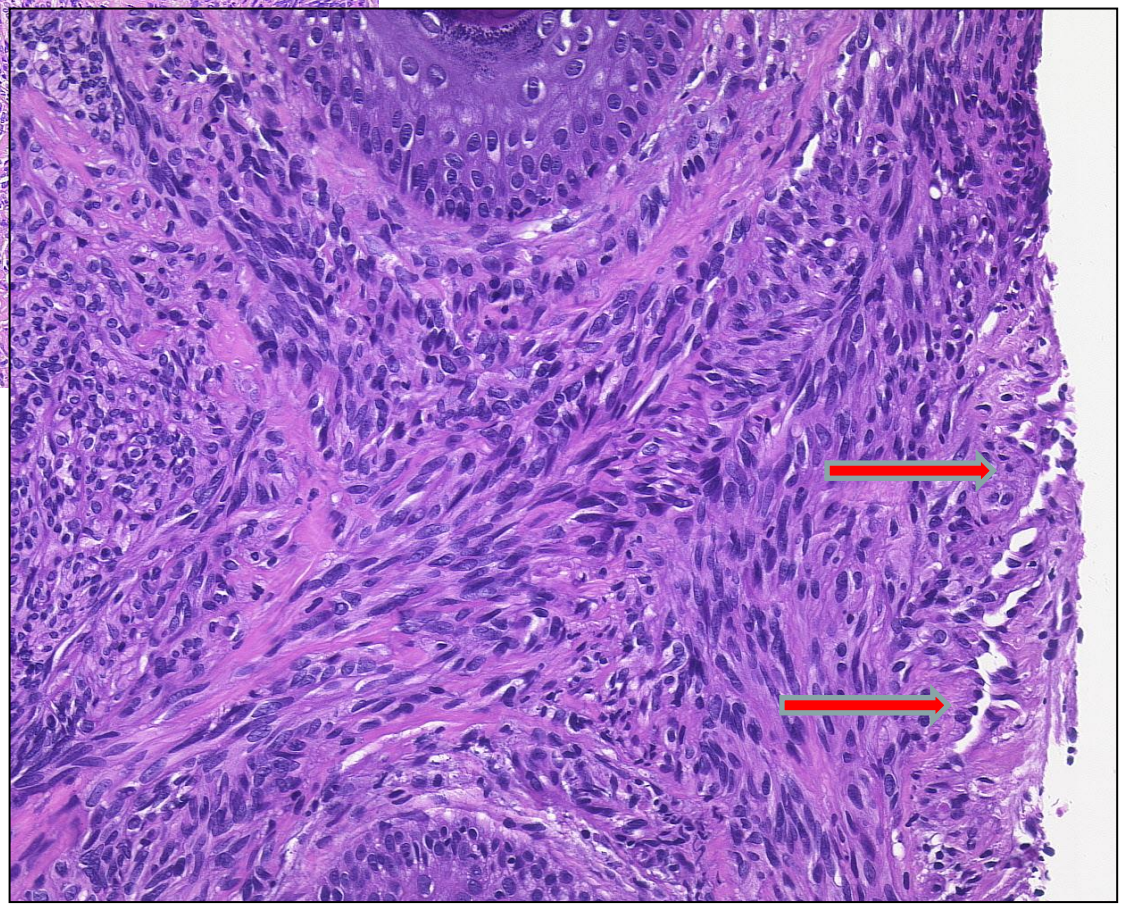


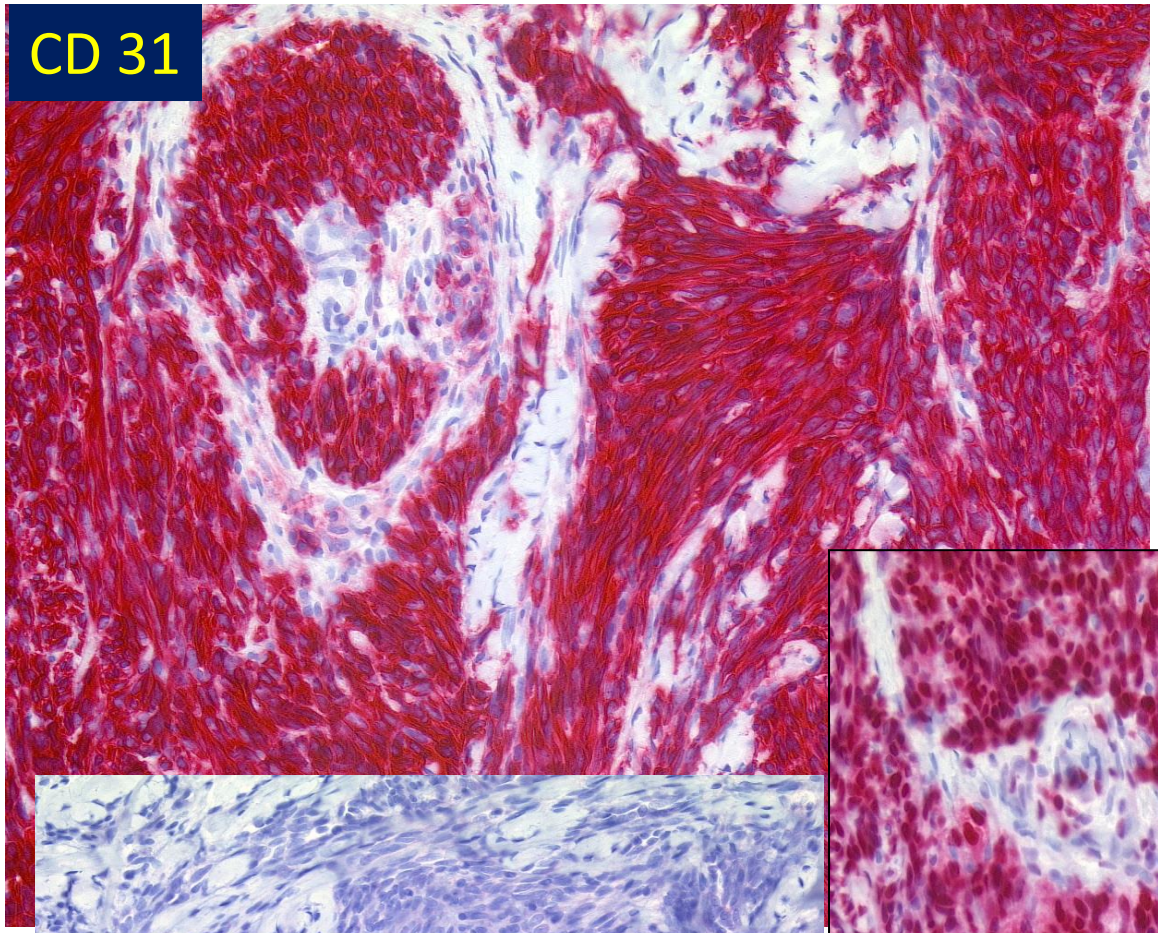
myogenic Sarcoma?



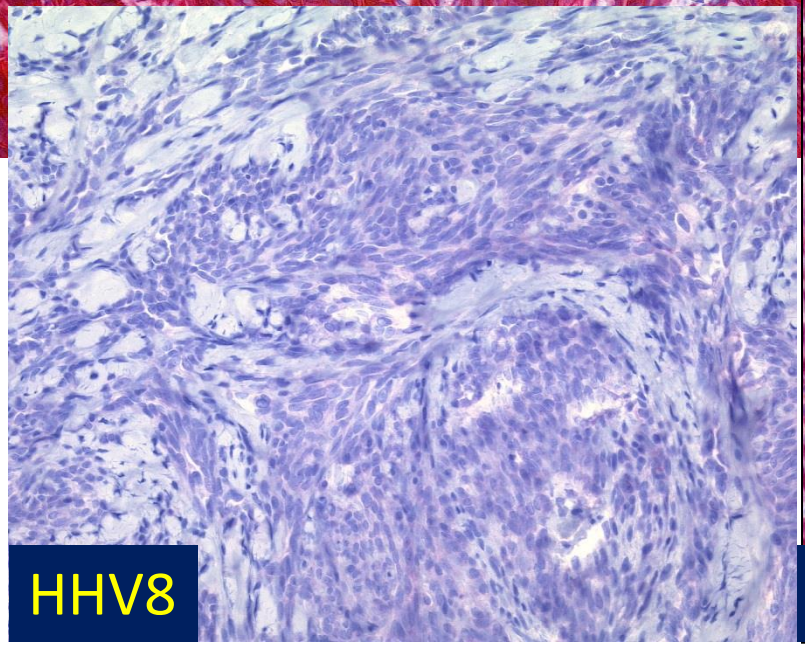


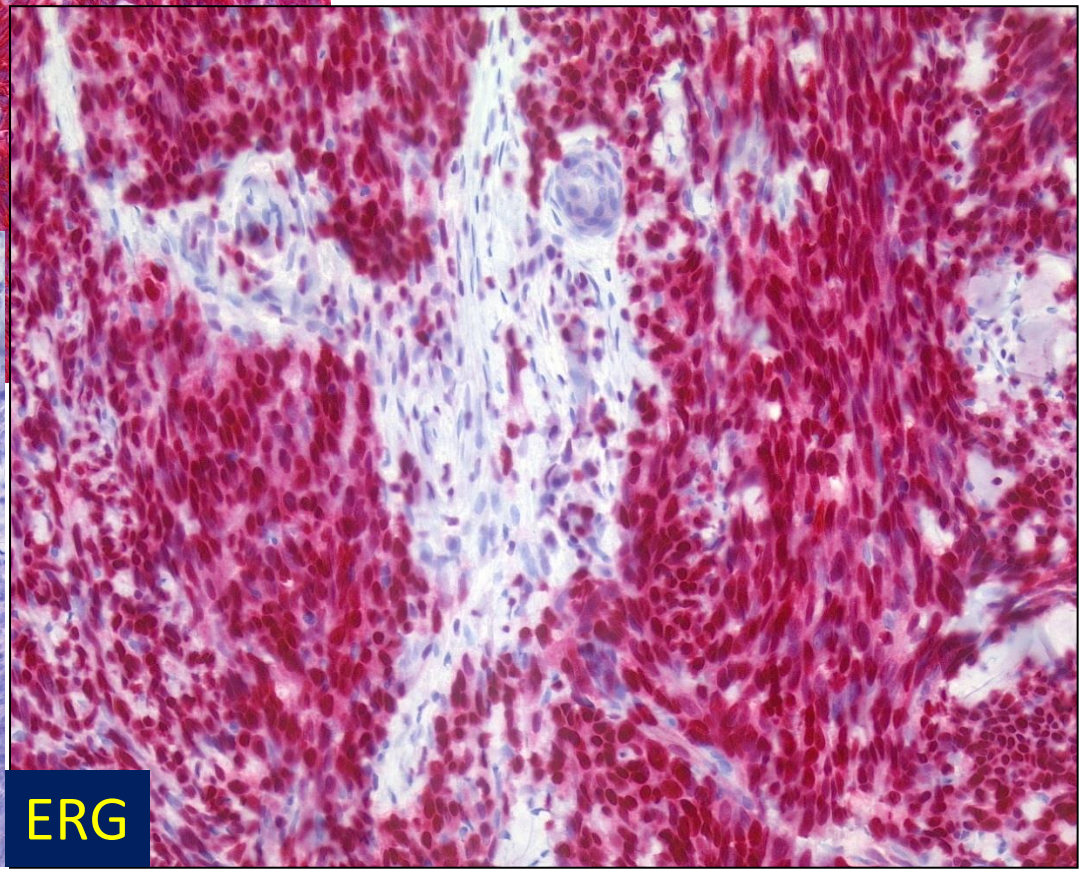






Diagnosis Case 7:
spindle cell
cutaneous
Angiosarcoma



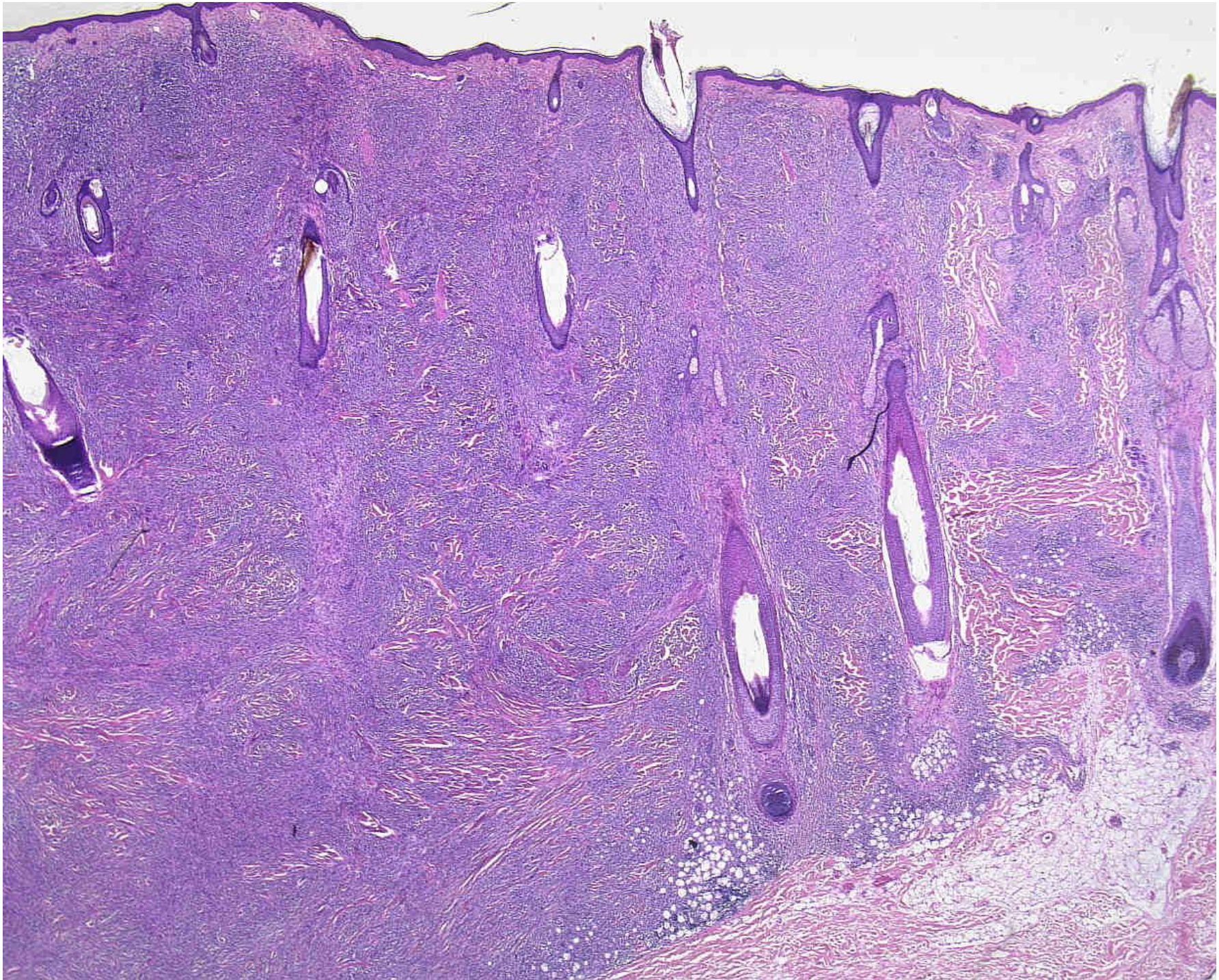


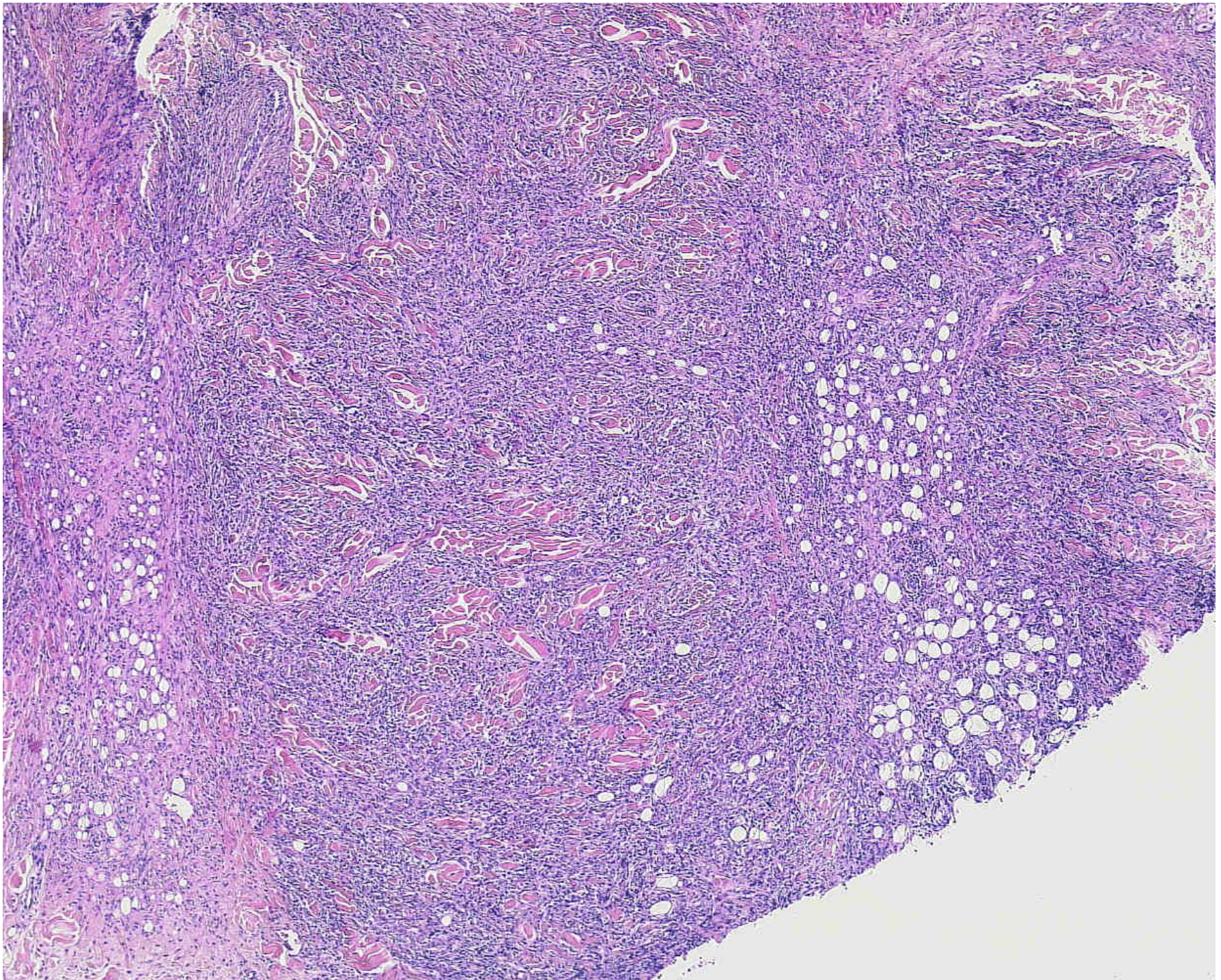
Case 8

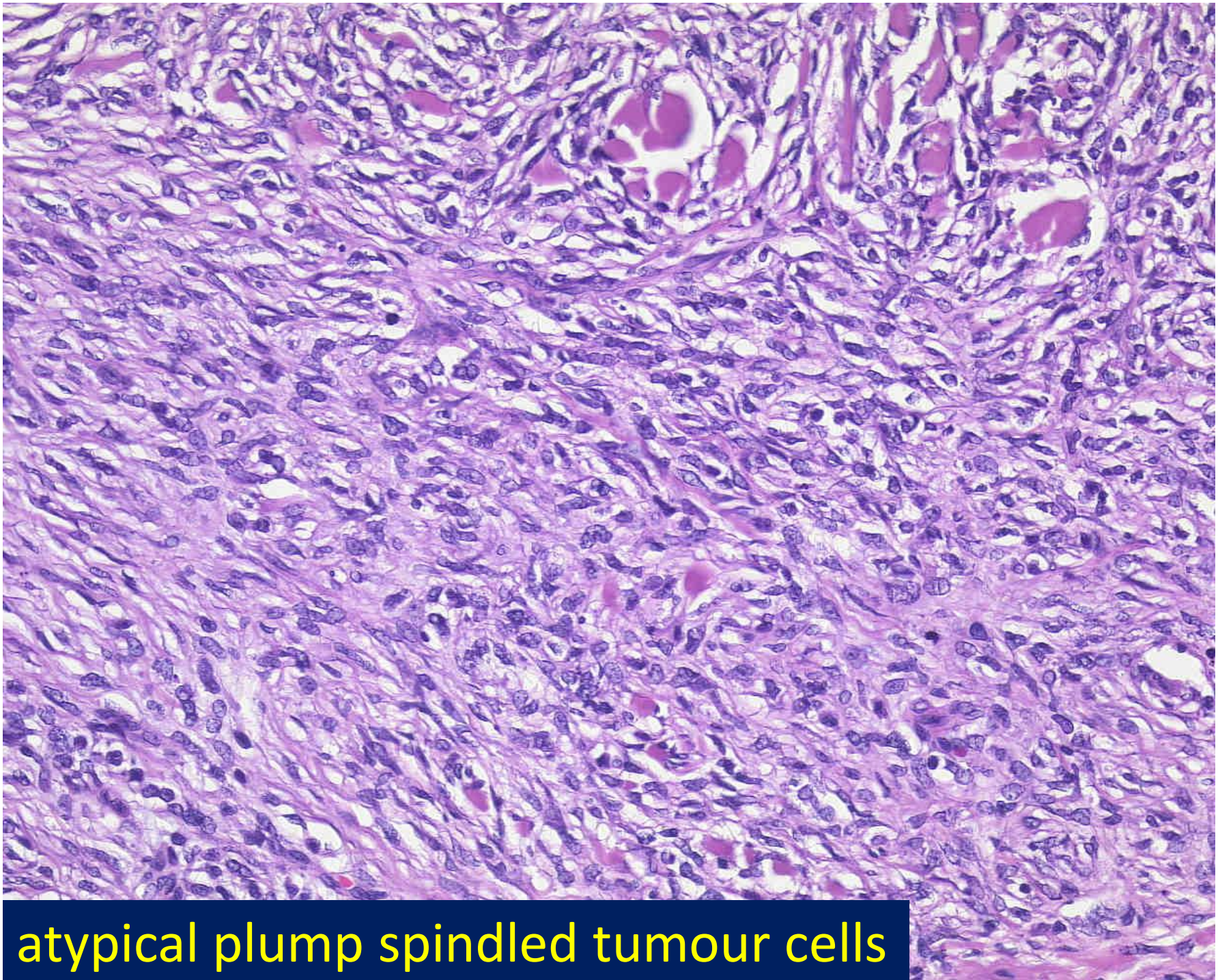
M, 56 years

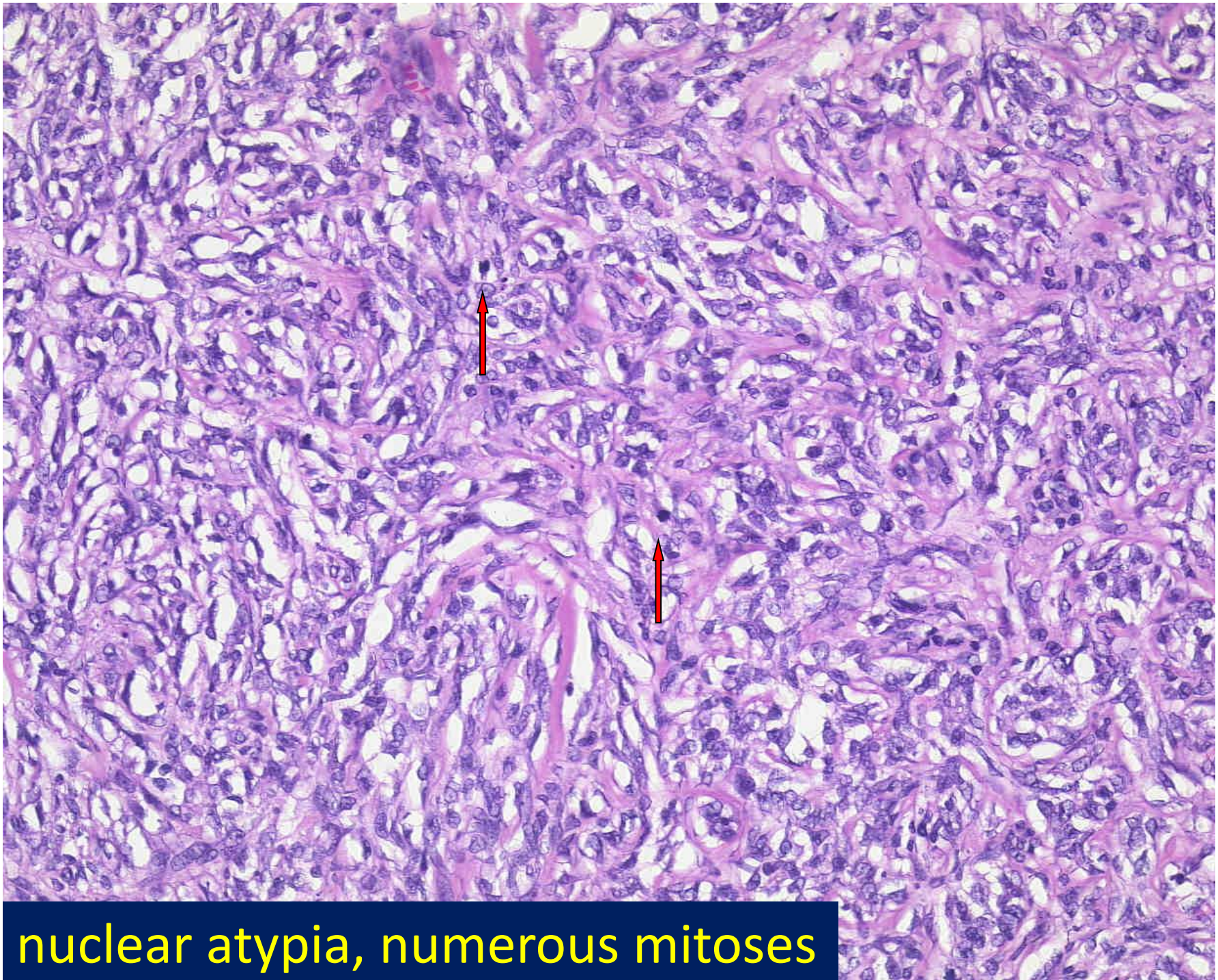
biopsy, excision

NSR at 15 months





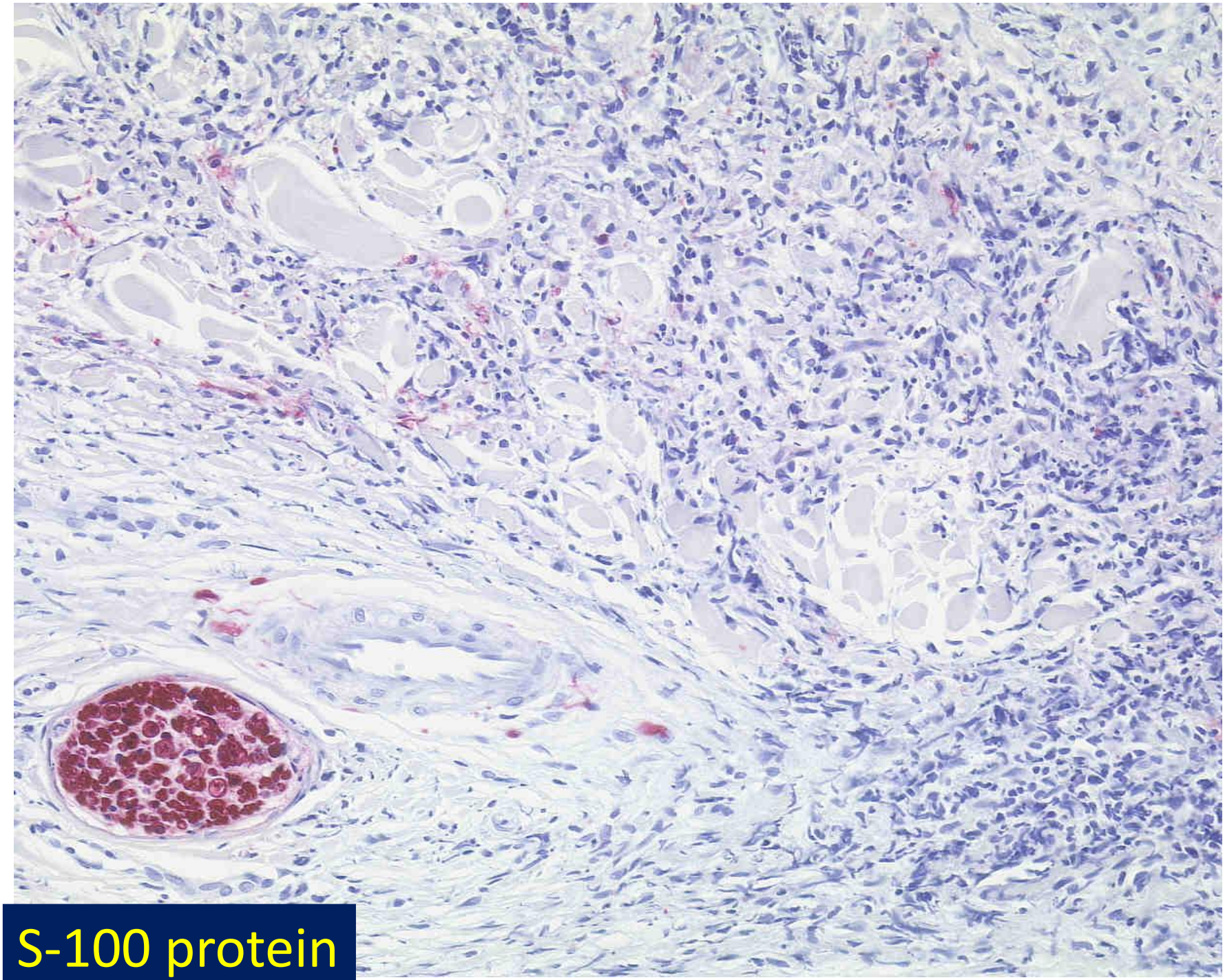

atypical plump spindled tumour cells


nuclear atypia, numerous mitoses

Diagnosis Case 8:

malignant spindle cell neoplasm of the dermis in a middle-aged male patient …

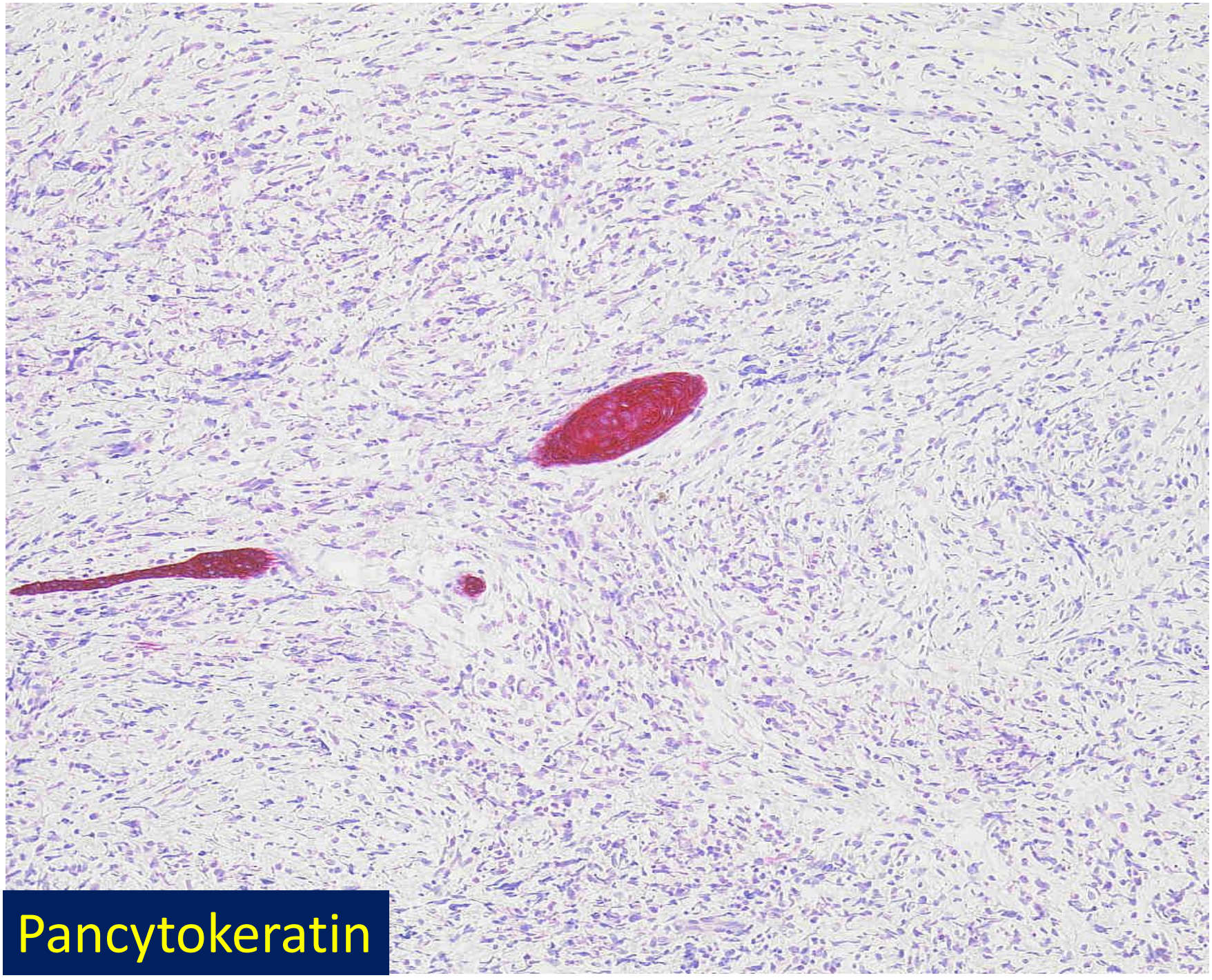
? spindle cell melanoma ?


S-100 protein

Diagnosis Case 8:

malignant spindle cell
neoplasm of the dermis in a
middle-aged male patient …

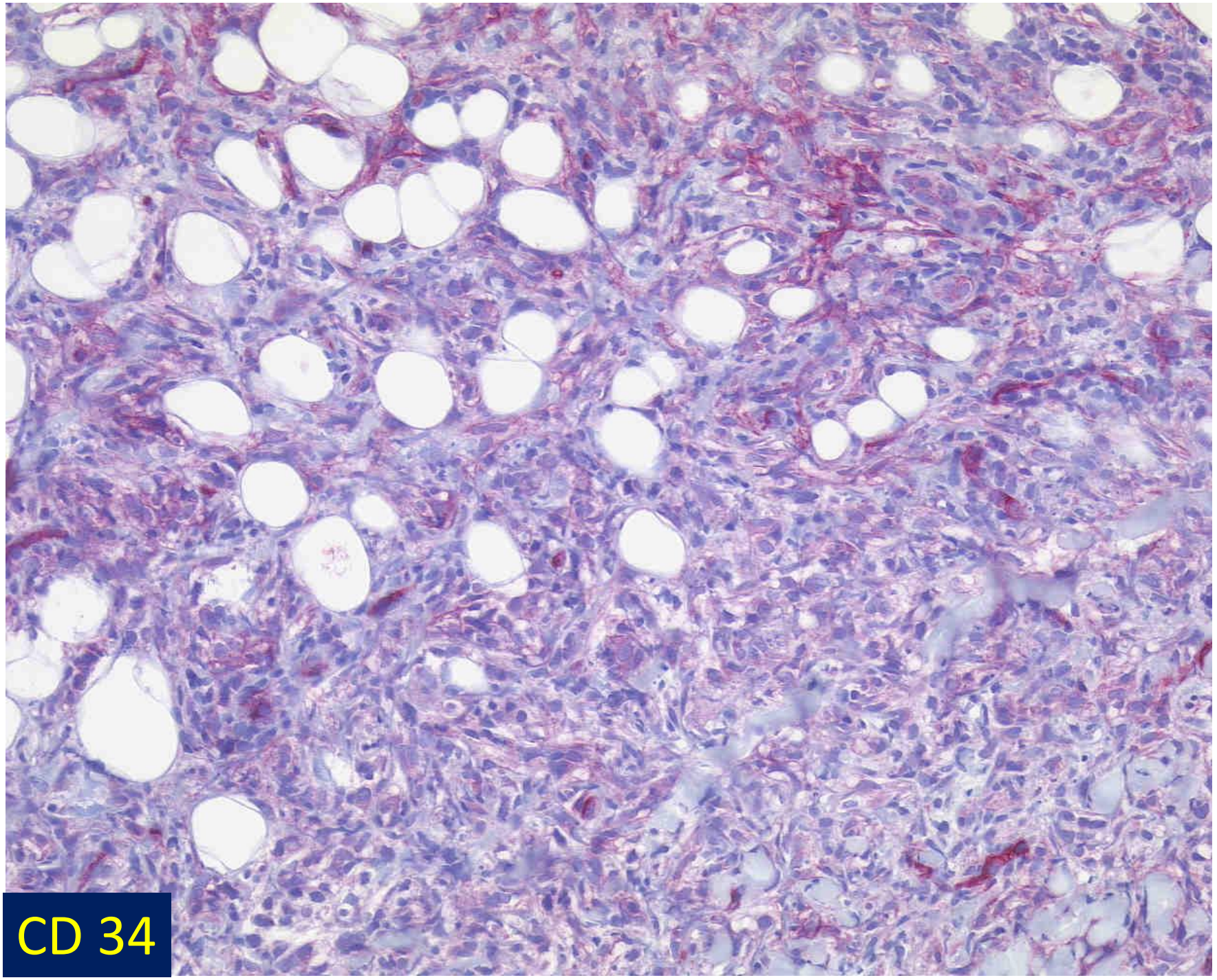
? spindle cell sarcomatous carcinoma ?

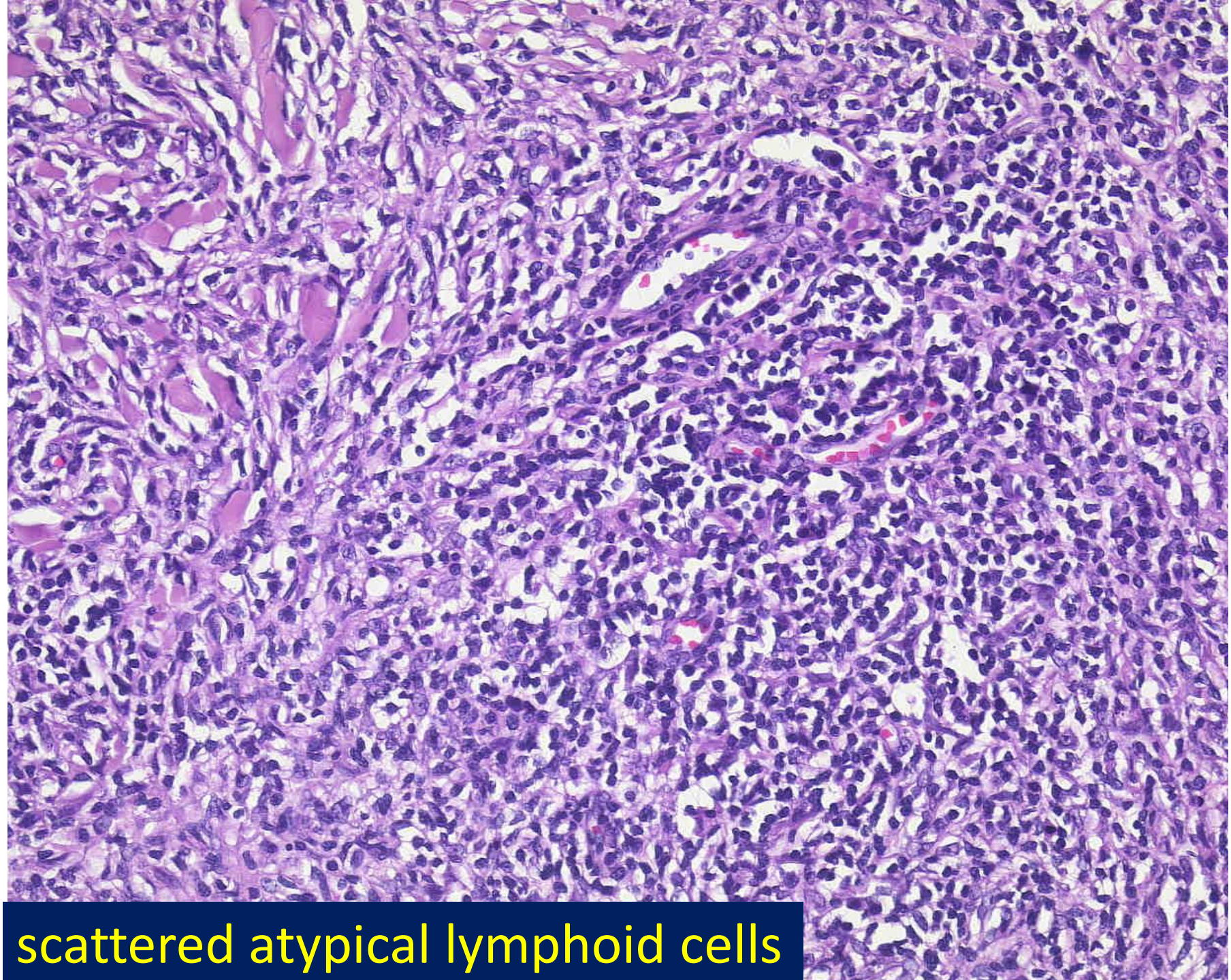

Pancytokeratin

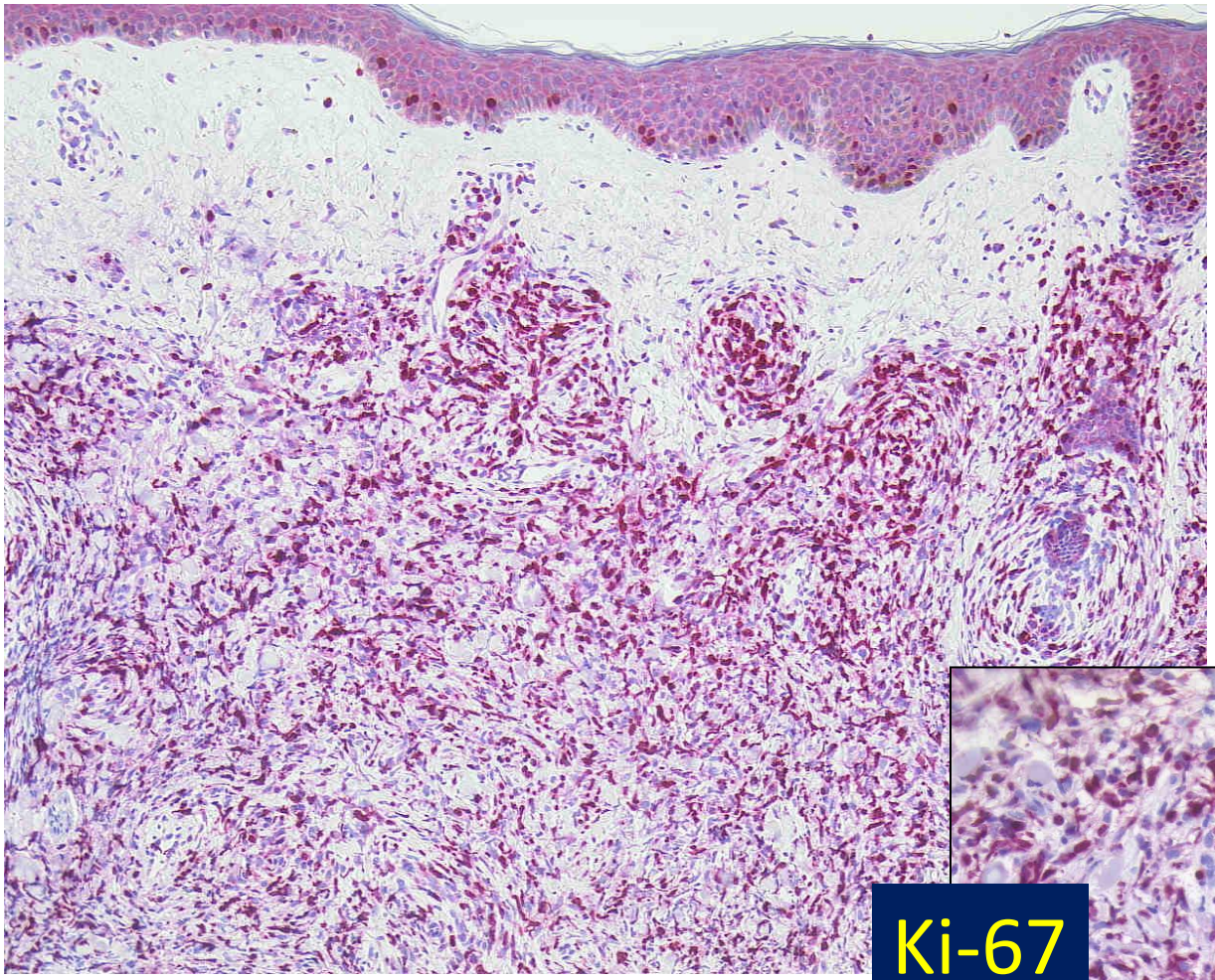
Diagnosis Case 8:

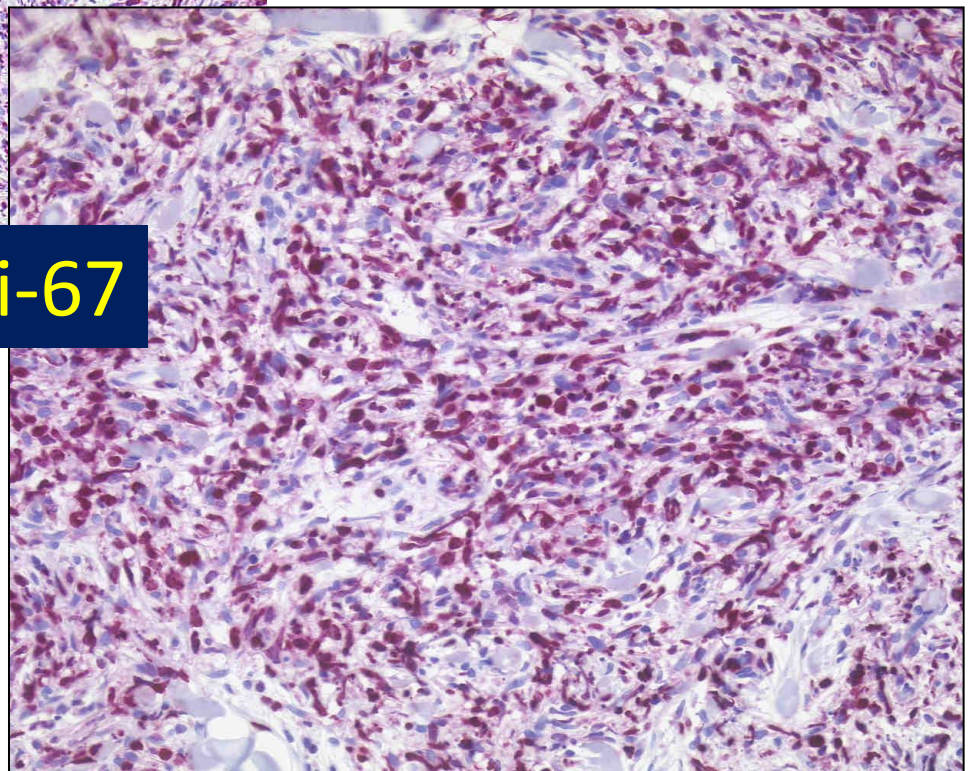
malignant spindle cell neoplasm of the dermis in a middle-aged male patient …

? high-grade DFSP ?

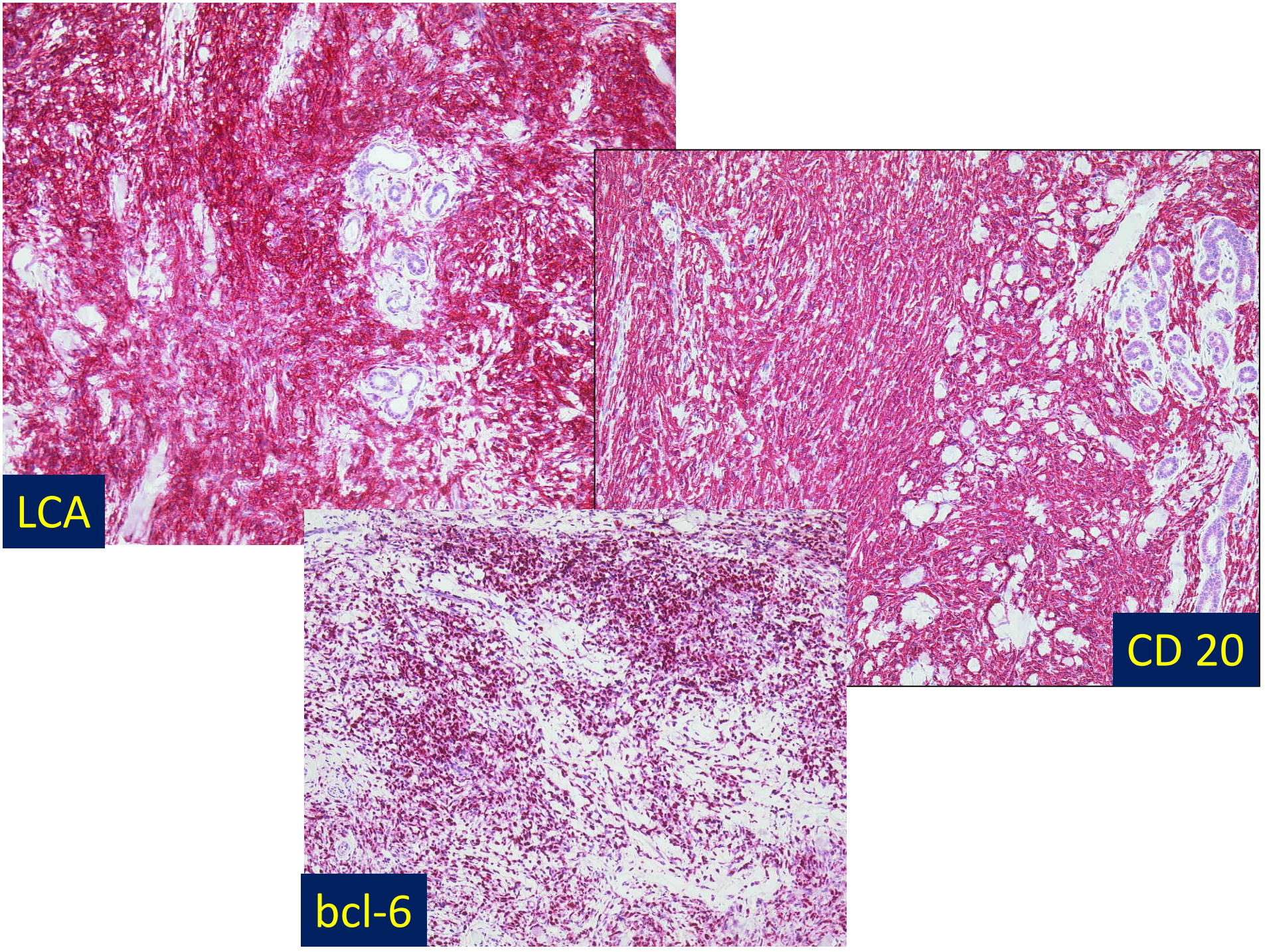

CD 34

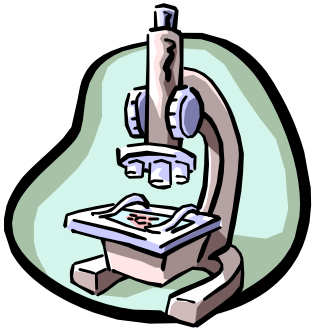

scattered atypical lymphoid cells





Ki-67


LCA
CD 20
bcl-6



Diagnosis Case 8

cutaneous spindle cell B-cell lymphoma

Cutaneous spindle cell B-cell lymphoma: a morphologic variant of cutaneous large B-cell lymphoma

Cerroni L et al. AJDP 2000; 22: 299

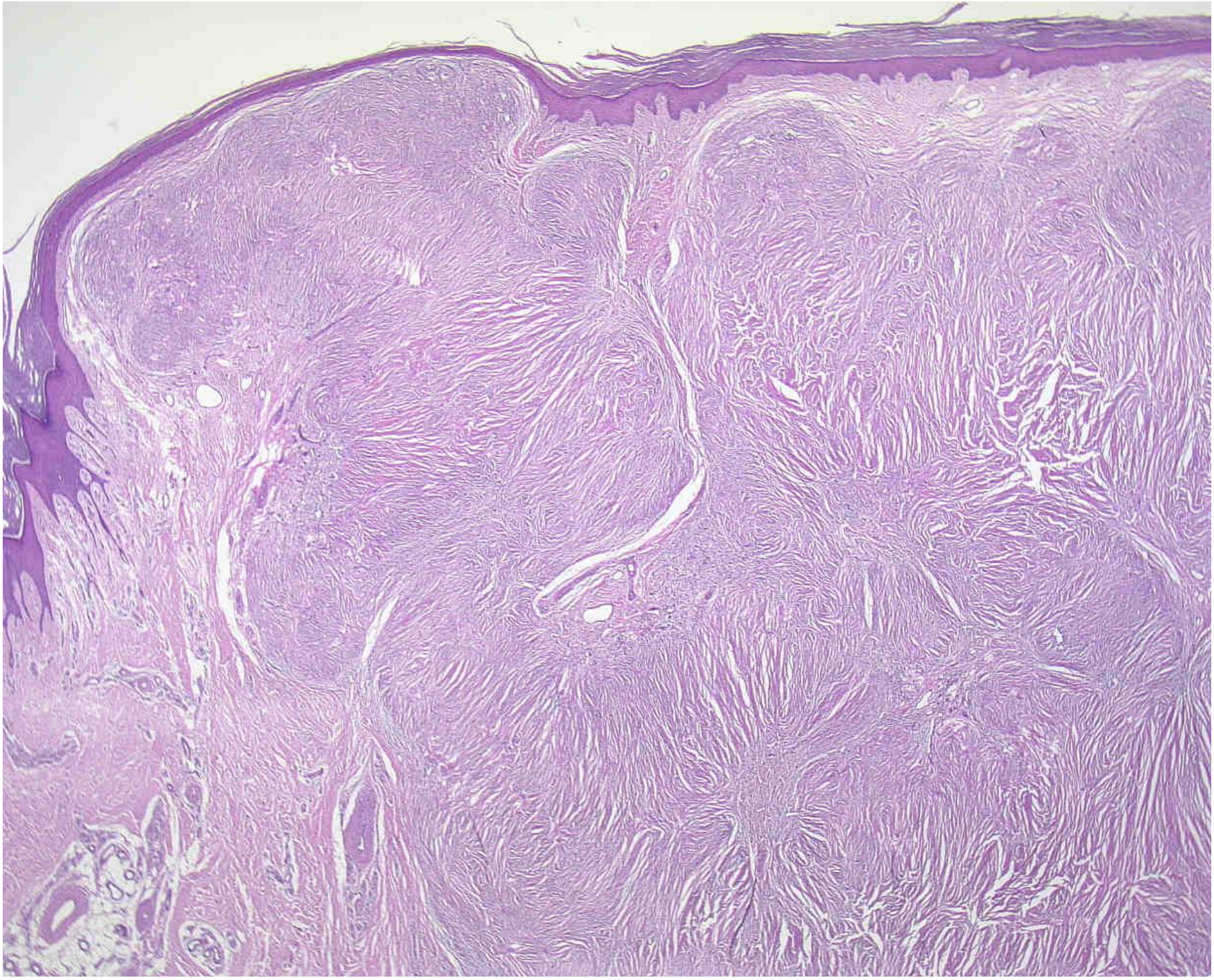
Cutaneous spindle cell B-cell lymphomas: most are neoplasms of follicular center cell origin

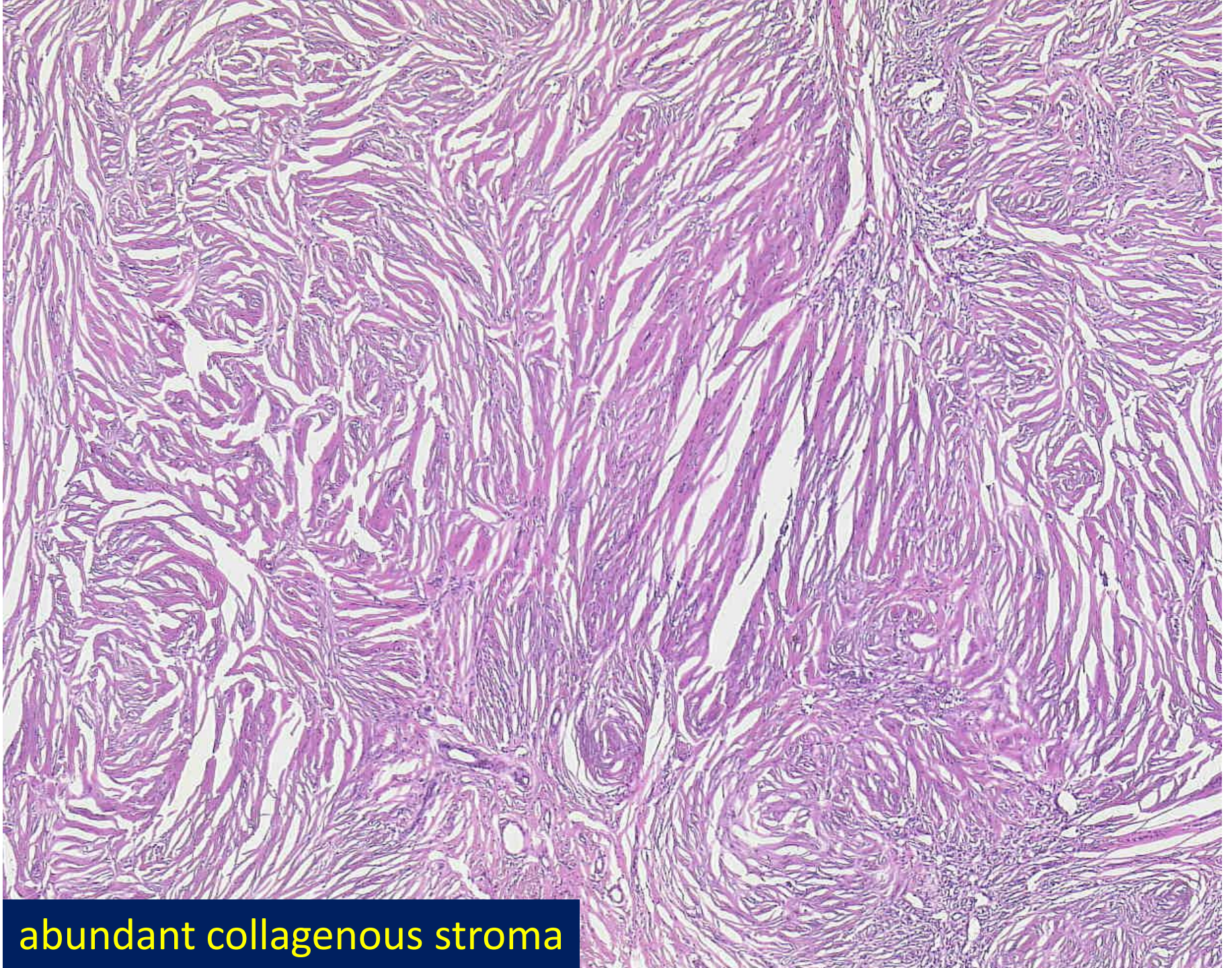
Charli-Joseph Y et al. AJSP 2015; 39: 737

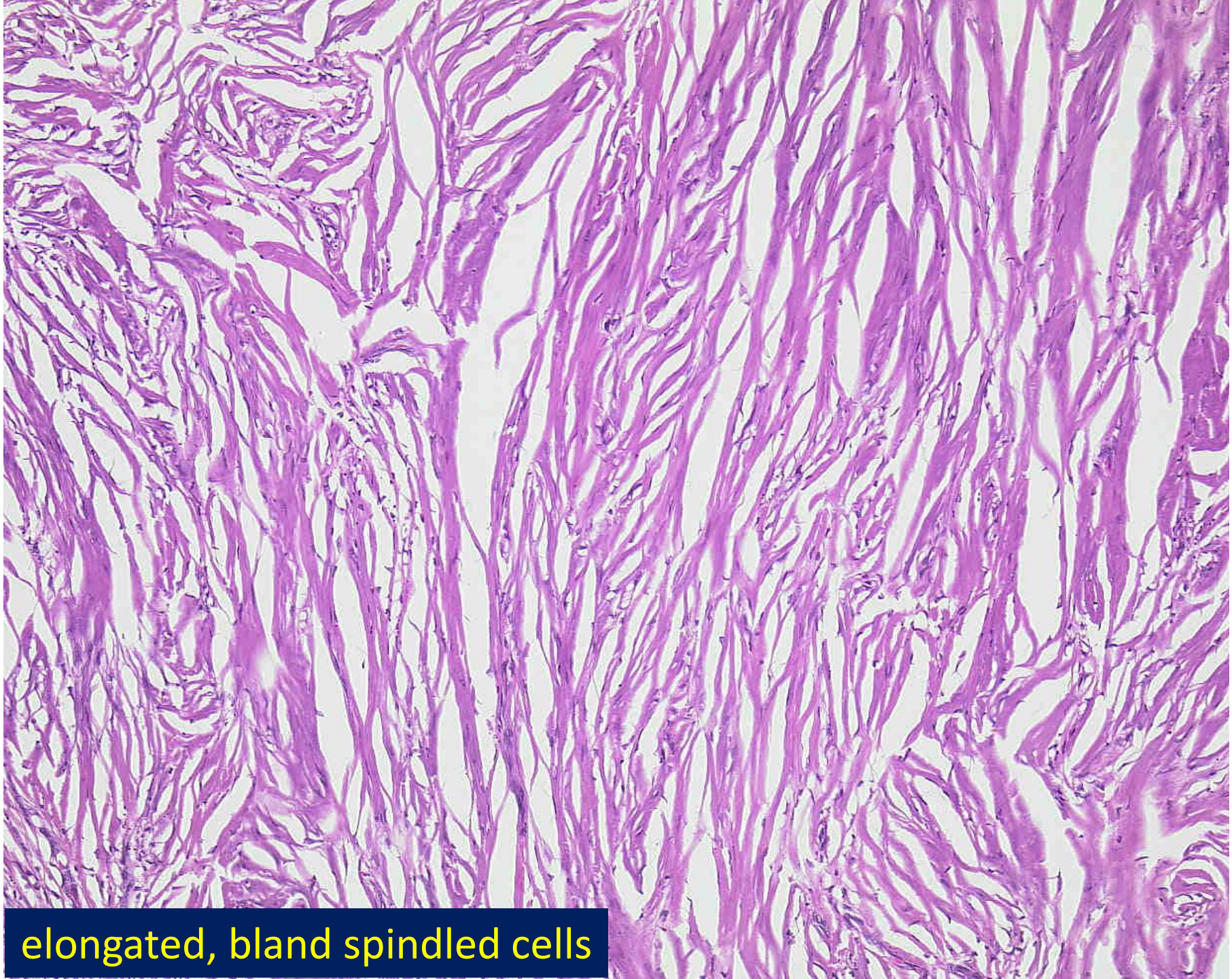
- very rare neoplasms (< 30 cases described)
- high-grade cutaneous lymphomas???
- atypical spindled tumour cells
- expression of LCA, B-cell markers
- nuclear expression of bcl-6
- bcl-6 mutations
- no MUM1 expression
- features of germinal center B-cell origin

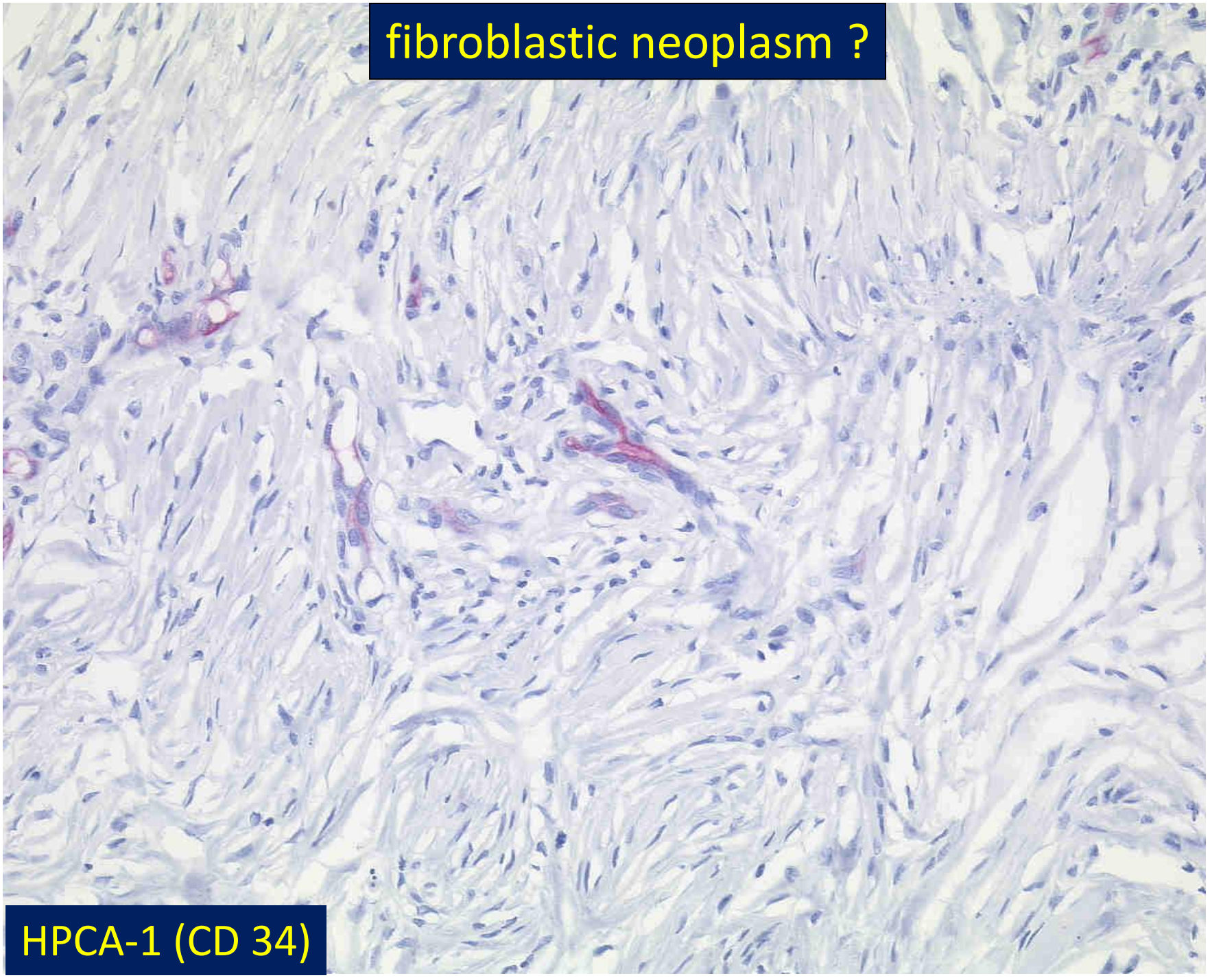
Case 9: Clinical Findings

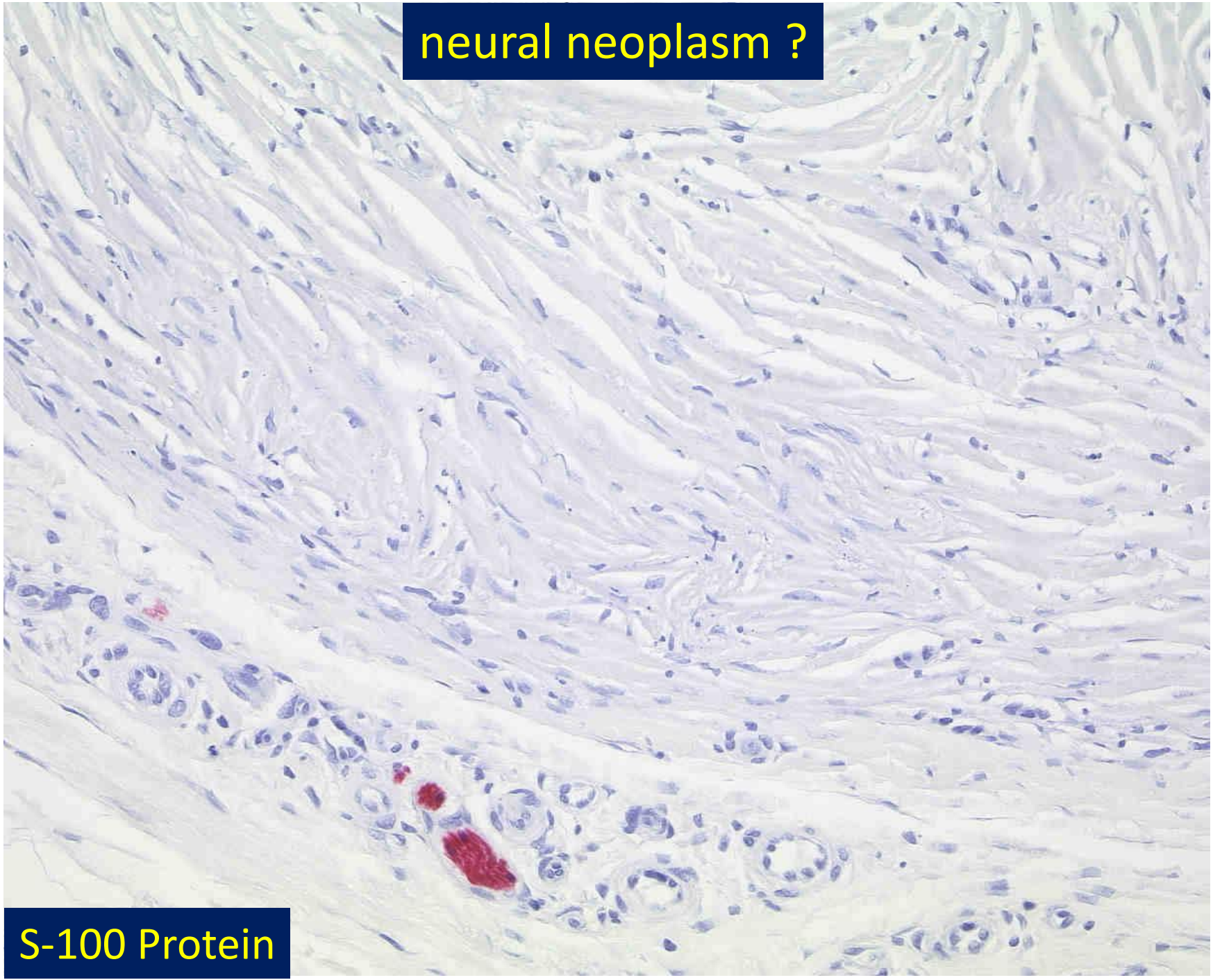
- 57-year-old female patient
- multiple lesions on both feet
- exophytic, nodular dermal lesions
- previously blisters have been reported
- fibromatosis has been suspected
- biopsy

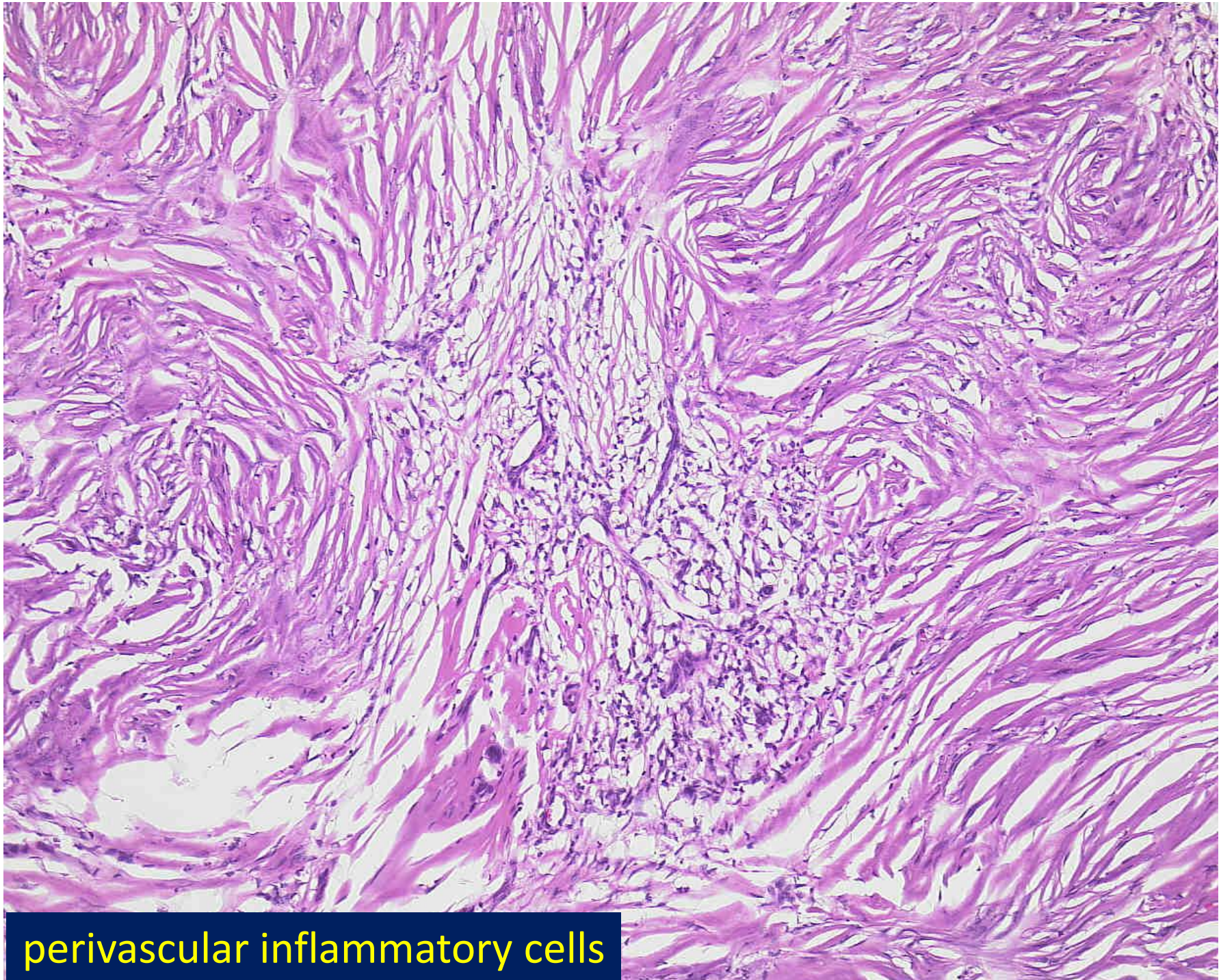


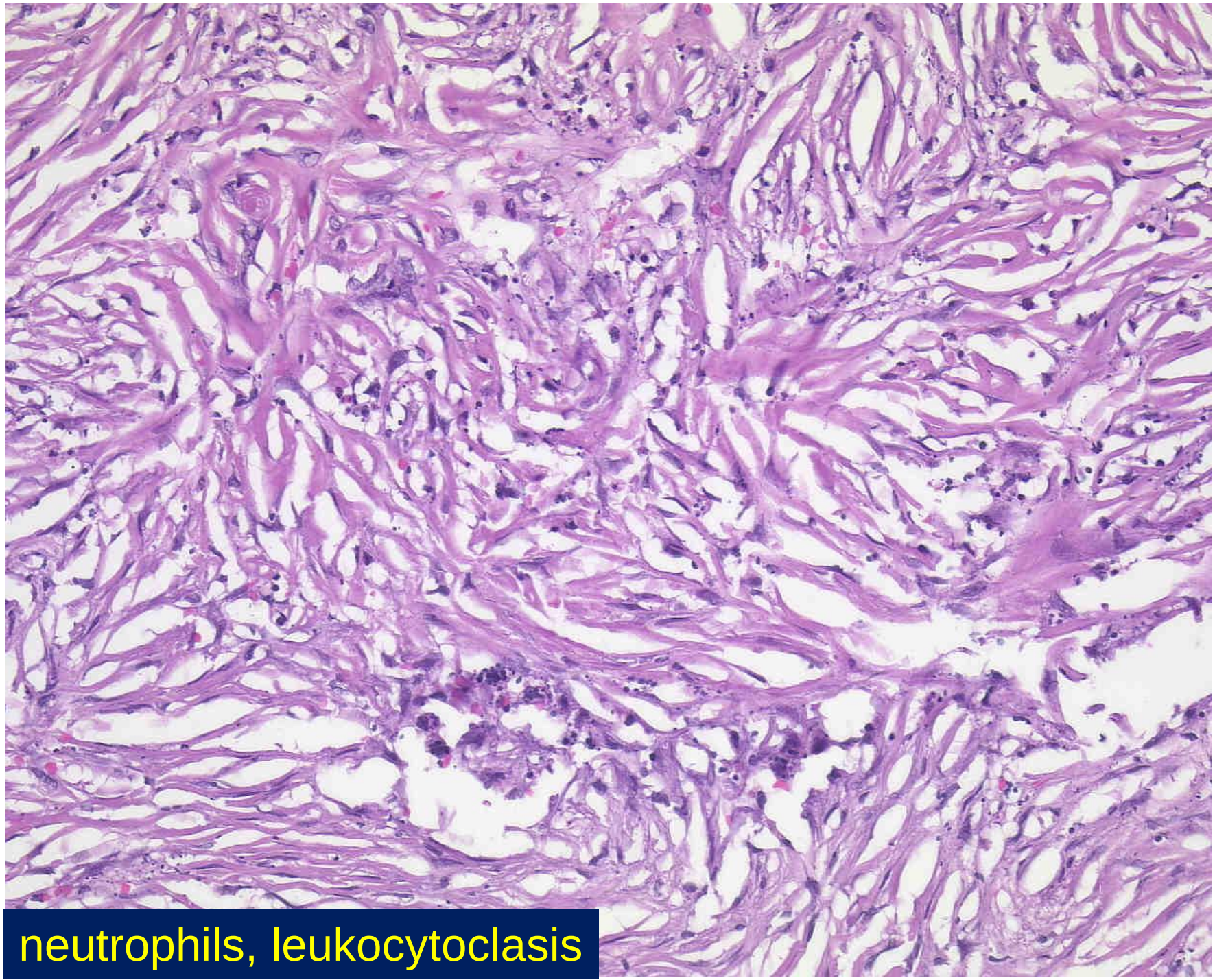

abundant collagenous stroma

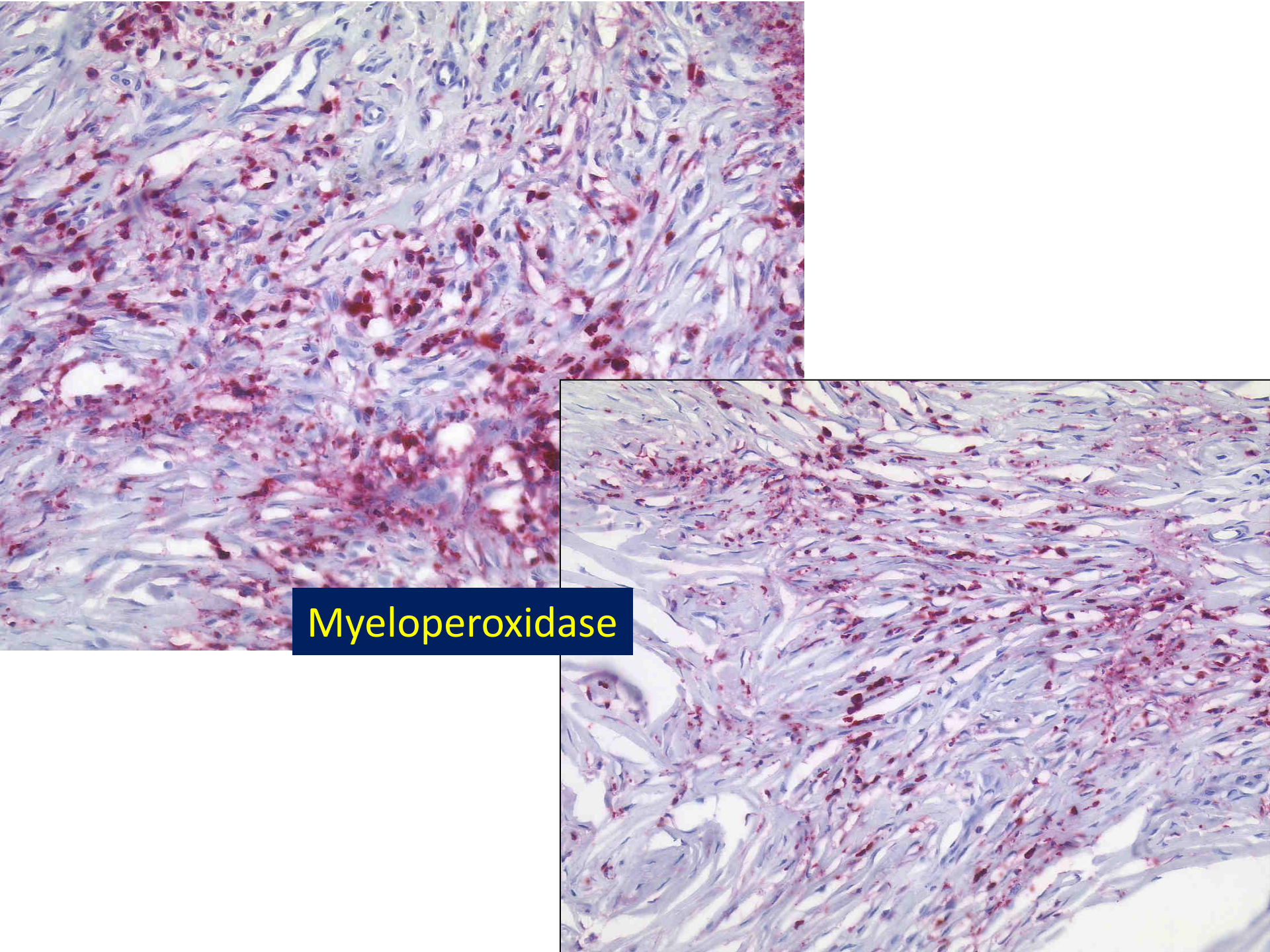

elongated, bland spindled cells

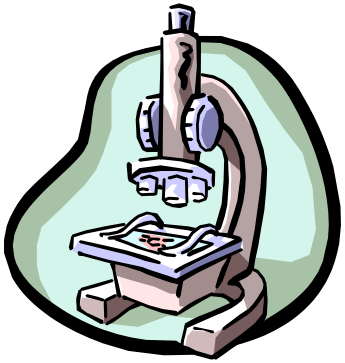

fibroblastic neoplasm ?
HPCA-1 (CD 34)


neural neoplasm ?
S-100 Protein


perivascular inflammatory cells


neutrophils, leukocytoclasis


Myeloperoxidase



Diagnosis Case 9

Erythema elevatum et diutinum (tumour stage)

Erythema elevatum et diutinum

- variant of chronic vasculitis
- long duration
- persistent papules, plaques and nodules
- multiple, symmetrical lesions
- distal extremities
- associated systemic diseases
  (MDS, lymphoma, IgA gammopathy…)
- different stages of disease

Erythema elevatum et diutinum

early lesions:

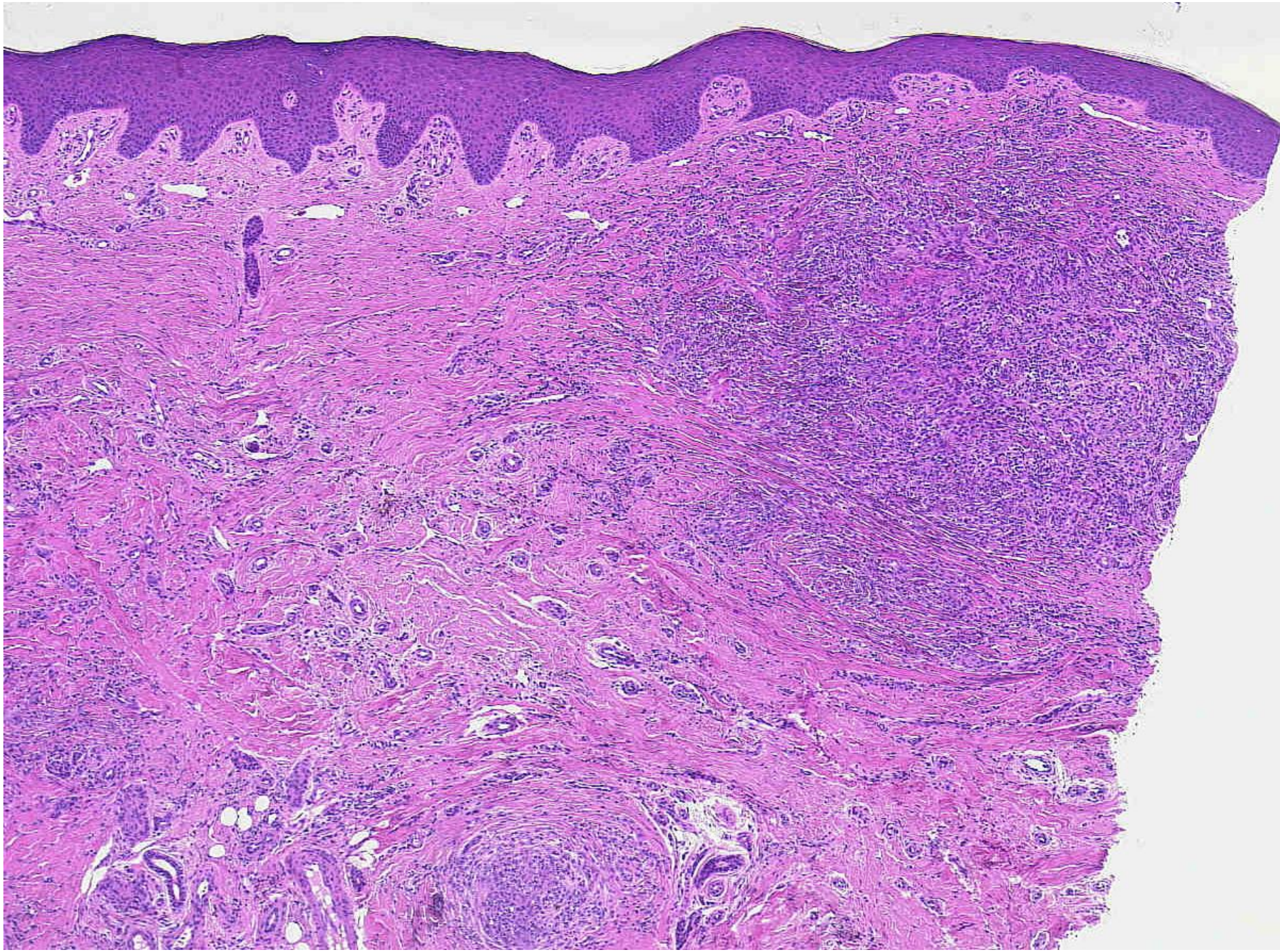
- perivascular infiltrate of neutrophils
- leukocytoclasis, fibrin deposition

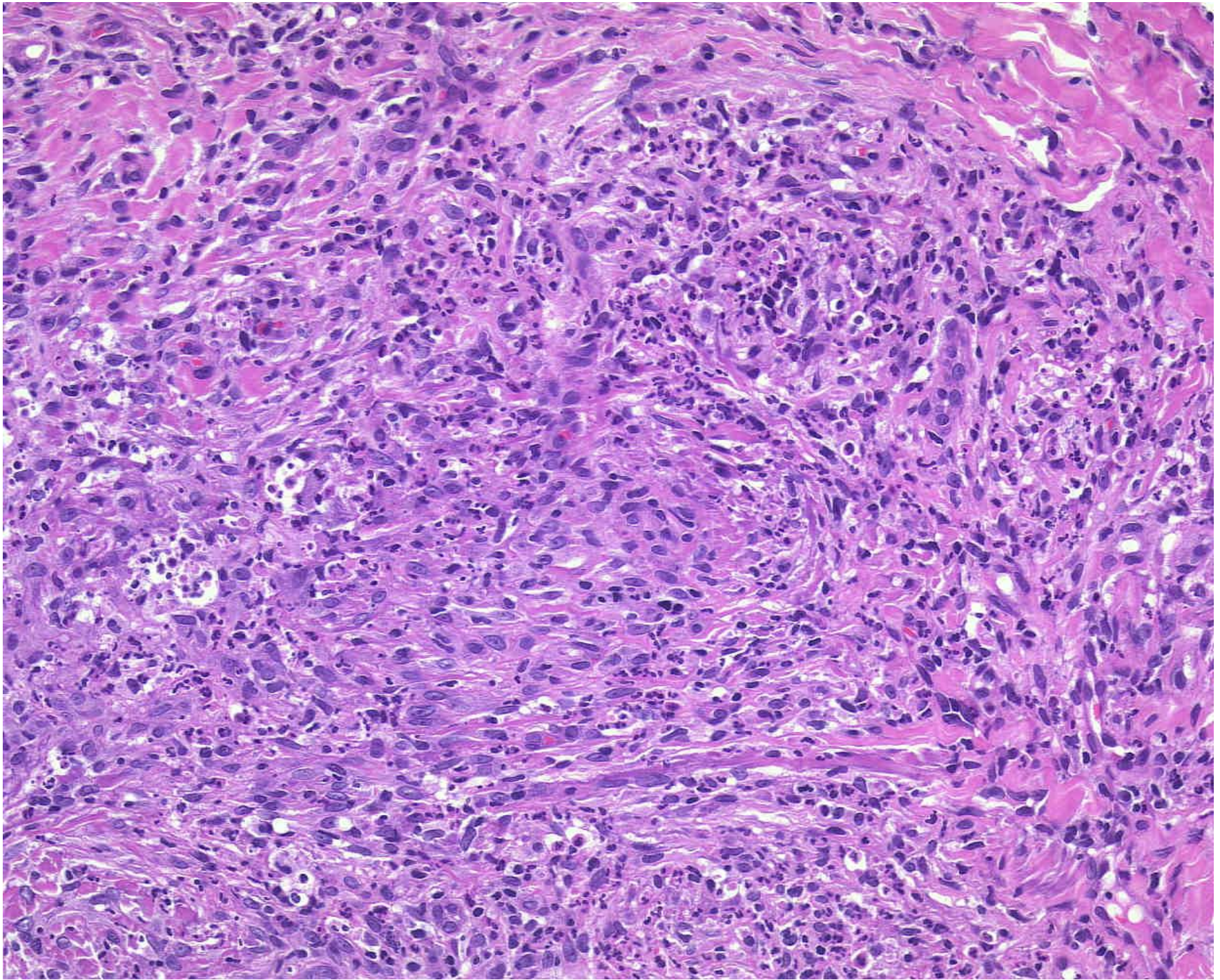
established lesions:

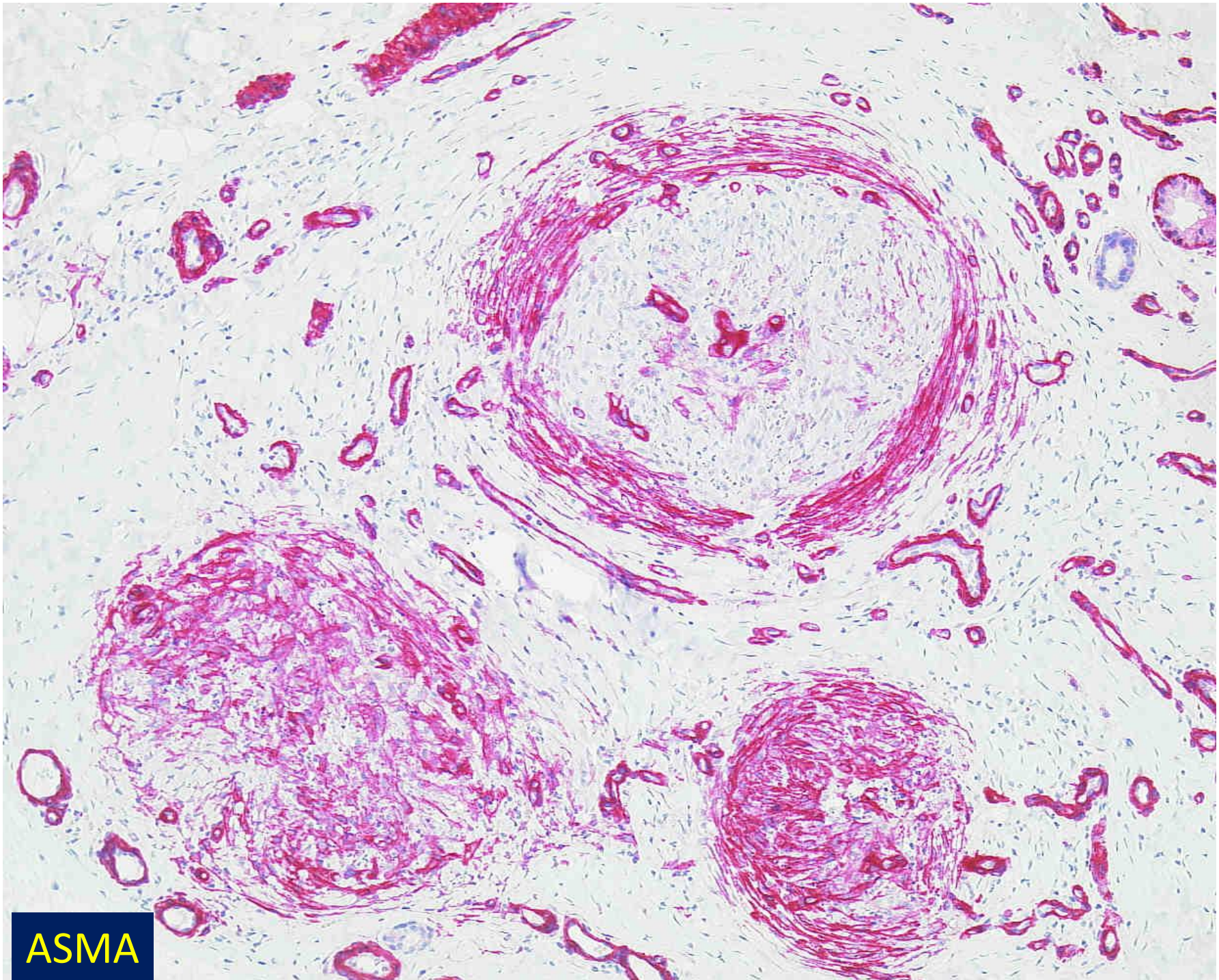
- neutrophilic infiltrate of the entire dermis
- sometimes spongiosis, blister, necrosis

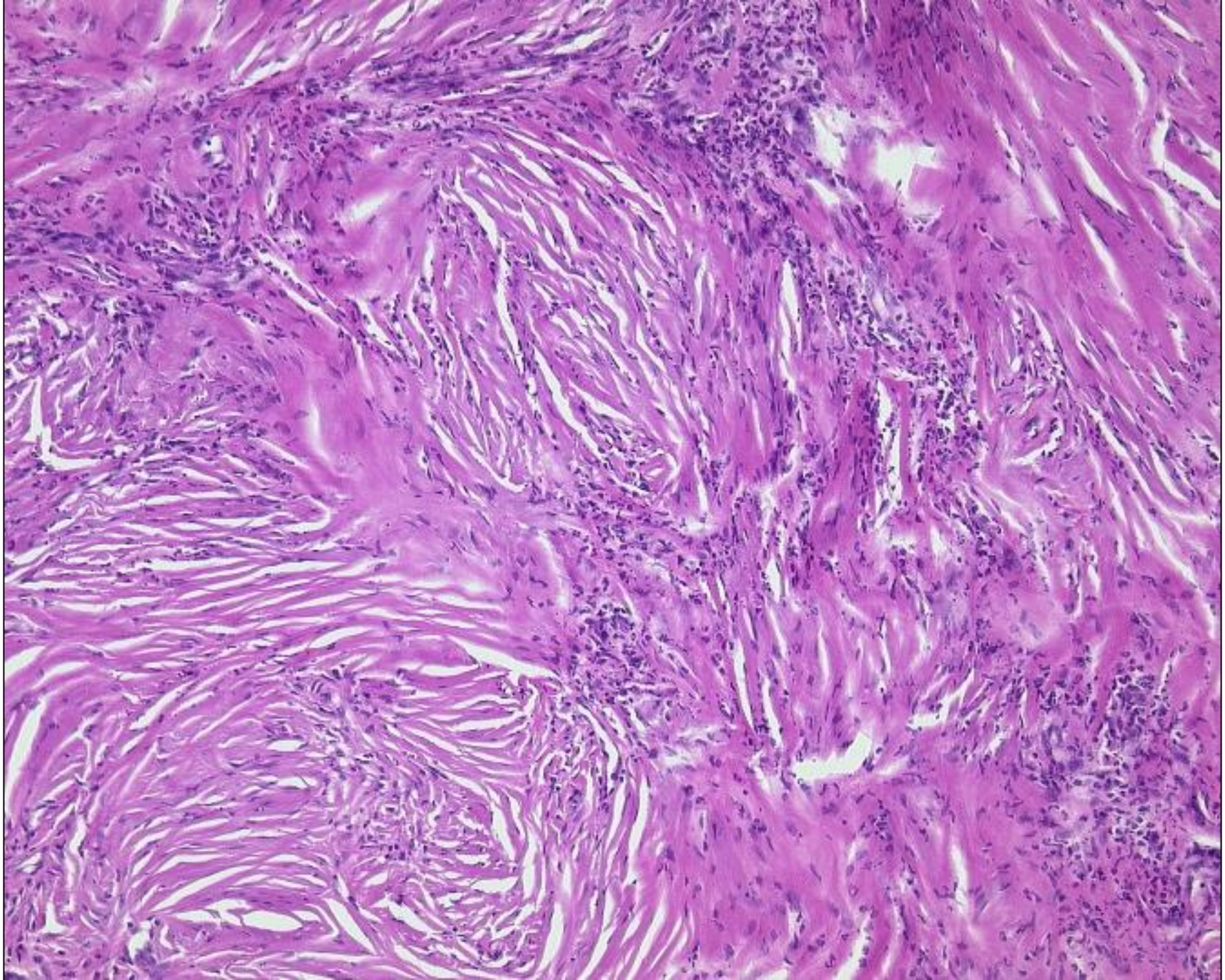
late lesions:

- variable fibrosis, capillary proliferation
- tumour-like fibroblastic proliferation
- scattered neutrophils






ASMA



Conclusions

- intradermal spindle cell proliferations represent a heterogeneous group of neoplasms / lesions
- spindle cell mesenchymal neoplasms of the skin include all lines of differentiation
- be aware of mimics
- immunohistochemical stainings are very helpful in establishing the diagnosis
- be aware of aberrant expression !
- molecular studies are helpful in selected cases

Thank you very much for your attention !