THE EVOLVING CLASSIFICATION OF SOFT TISSUE TUMORS

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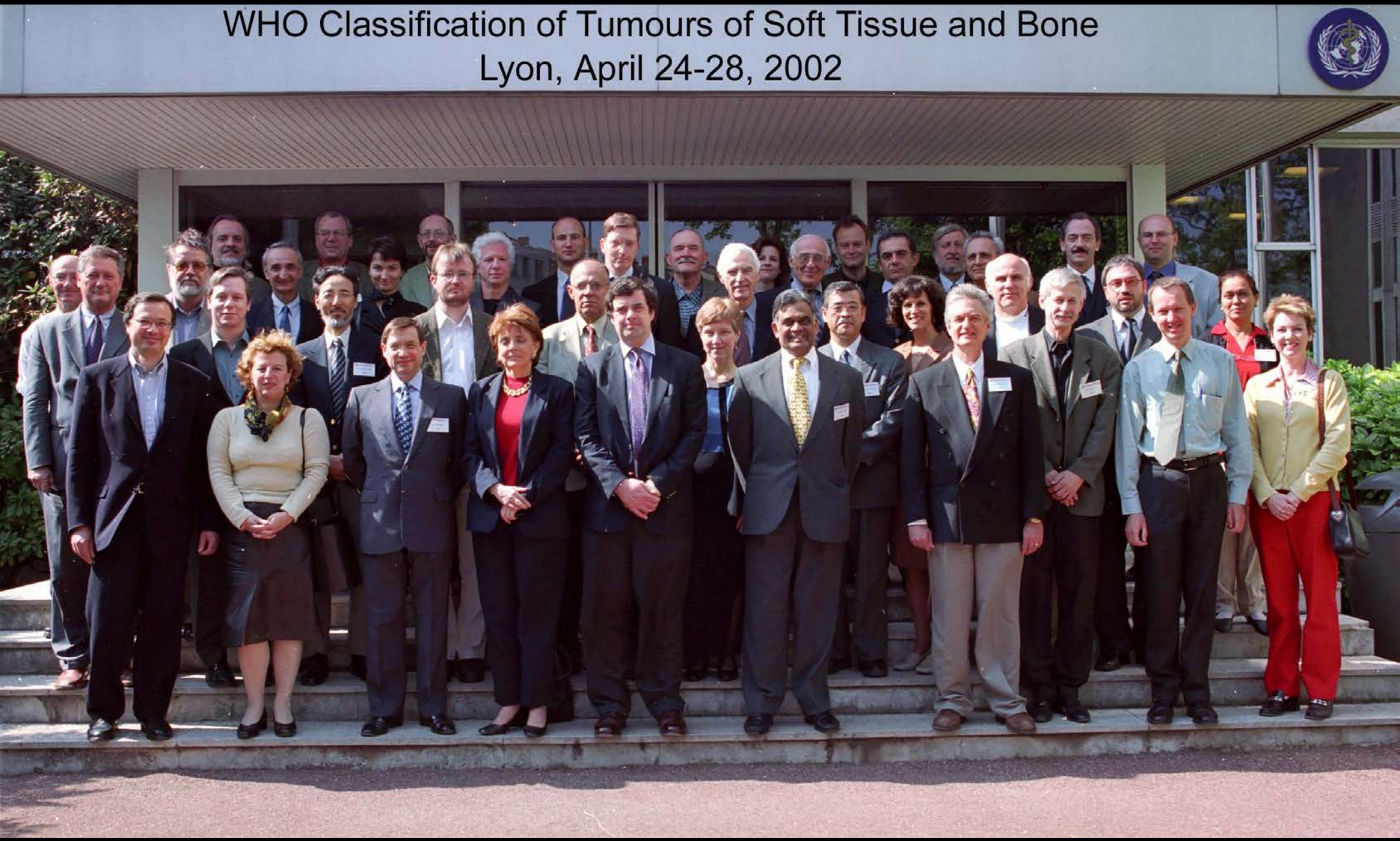

WHO Classification of Tumours of Soft Tissue and Bone
Lyon, April 24-28, 2002

MAJOR STRENGTHS

Broad concensus view

New approach to authorship

More extensive text / illustrations

Inclusion of genetics

Timeliness

World Health Organization (2002) Classification of Tumours of Soft Tissue

SIGNIFICANT CHANGES FROM 1994 CLASSIFICATION

Approach to biologic potential

Approach to fibrohistiocytic tumours

Approach to haemangiopericytoma

Recategorisation of 'intermediate' vascular tumours

Numerous 'new' entities

More tumours of 'uncertain differentiation'

World Health Organization (2002) Classification of Tumours of Soft Tissue

BENIGN CATEGORY

Most benign soft tissue tumours do not recur locally. Those that do recur do so in a non-destructive fashion and are almost always readily cured by complete local excision. Exceedingly rarely (almost certainly <1/50,000 cases, and probably even less than that), a morphologically benign lesion may give rise to distant metastases. This is entirely unpredictable on the basis of conventional histological examination and, to date, has been best documented in cutaneous benign fibrous histiocytoma.

World Health Organization (2002) Classification of Tumours of Soft Tissue

INTERMEDIATE CATEGORY

(Locally aggressive)

Soft tissue tumours in this category often recur locally and are associated with an infiltrative and locally destructive growth pattern. Lesions in this category do not have any evident potential to metastasise but typically require wide excision with a margin of normal tissue in order to ensure local control. The prototypical lesion in this category is desmoid fibromatosis.

World Health Organization (2002) Classification of Tumours of Soft Tissue

INTERMEDIATE CATEGORY

(Rarely metastasising)

Soft tissue tumours in this category are often locally aggressive but, in addition, show the well documented ability to give rise to distant metastases in occasional cases. The risk of such metastases appears to be <2% and is not reliably predictable on the basis of histomorphology. Metastasis in such lesions is usually to lymph node or lung. Prototypical examples in this category include plexiform fibrohistiocytic tumour and so-called angiomatoid fibrous histiocytoma.

World Health Organization (2002) Classification of Tumours of Soft Tissue

MALIGNANT CATEGORY

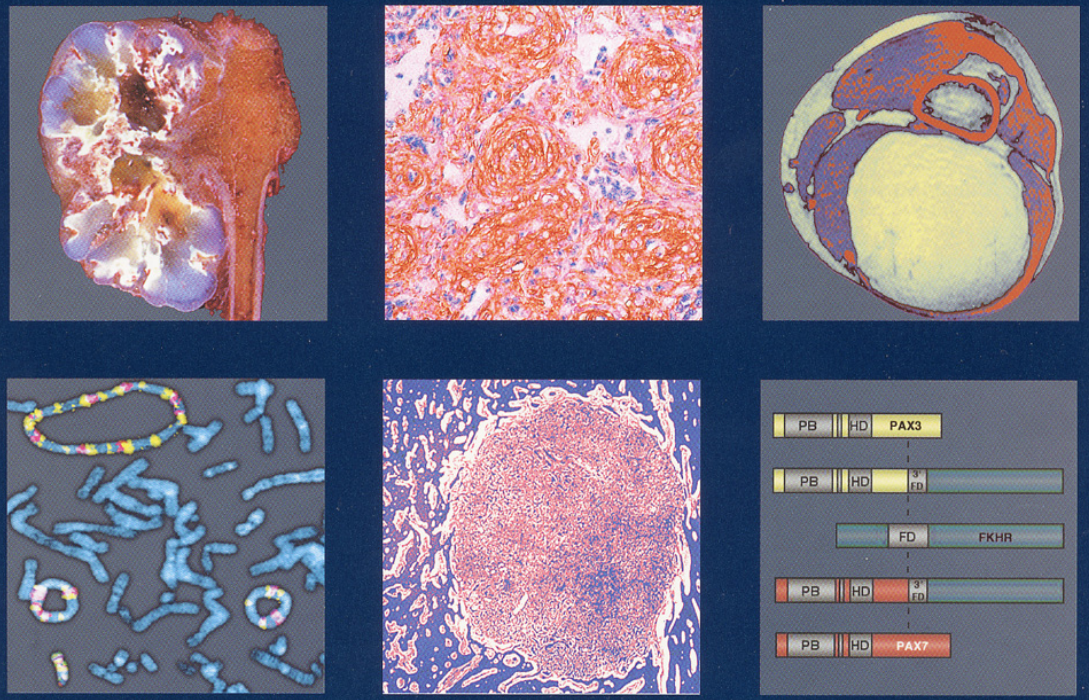
In addition to the potential for locally destructive growth and recurrence, malignant soft tissue tumours (known as soft tissue sarcomas) have significant risk of distant metastasis, ranging in most instances from 20% to almost 100%, depending upon histological type and grade. Some (but not all) histologically low grade sarcomas have a metastatic risk of only 2-10%, but such lesions may advance in grade in a local recurrence, and thereby acquire a higher risk of distant spread (e.g., myxofibrosarcoma and leiomyosarcoma).

World Health Organization Classification of Tumours

Pathology & Genetics

Tumours of Soft Tissue and Bone

Edited by Christopher D.M. Fletcher, K. Krishnan Unni, Fredrik Mertens



CONTEMPORARY CONCENSUS CLASSIFICATION

- NOT A TEXTBOOK

REASONS TO HAVE CLASSIFICATIONS

- Reproducible diagnostic criteria
- Better determine biologic potential
- Better understand intrinsic biology
- Reflect conceptual evolution

WHO Classification of Soft Tissue and Bone, Consensus and Editorial meeting
University Hospital Zurich, Switzerland, 18-20 April 2012

SIGNIFICANT CHANGES FROM 2002 CLASSIFICATION

- ‘MFH’ is gone
- ‘Haemangiopericytoma’ is gone
- Pericytic (perivascular) tumours better defined
- GIST and nerve sheath tumours now allocated to this volume
- Category of undifferentiated sarcomas introduced
- Some “new entities” added
- More genetic data added

World Health Organization (2013) Classification of Tumours of Soft Tissue

"NEW ENTITIES"

Pseudomyogenic (ES-like) haemangioendothelioma

Hybrid nerve sheath tumours

Acral (digital) fibromyxoma

Haemosiderotic fibrolipomatous tumour

Phosphaturic mesenchymal tumour

World Health Organization (2013)
Classification of Tumours of Soft Tissue

ADIPOCYTIC TUMOURS
Benign

Lipoma
Lipomatosis
Lipomatosis of nerve
Lipoblastoma(tosis)
Angiolipoma
Myolipoma
Chondroid lipoma
Extrarenal angiomyolipoma
Extra-adrenal myelolipoma
Spindle cell/pleomorphic lipoma
Hibernoma

World Health Organization (2013) Classification of Tumours of Soft Tissue

ADIPOCYTIC TUMOURS

Intermediate (locally aggressive)

Atypical lipomatous tumour / well differentiated liposarcoma

Malignant

Dedifferentiated liposarcoma

Myxoid liposarcoma

Pleomorphic liposarcoma

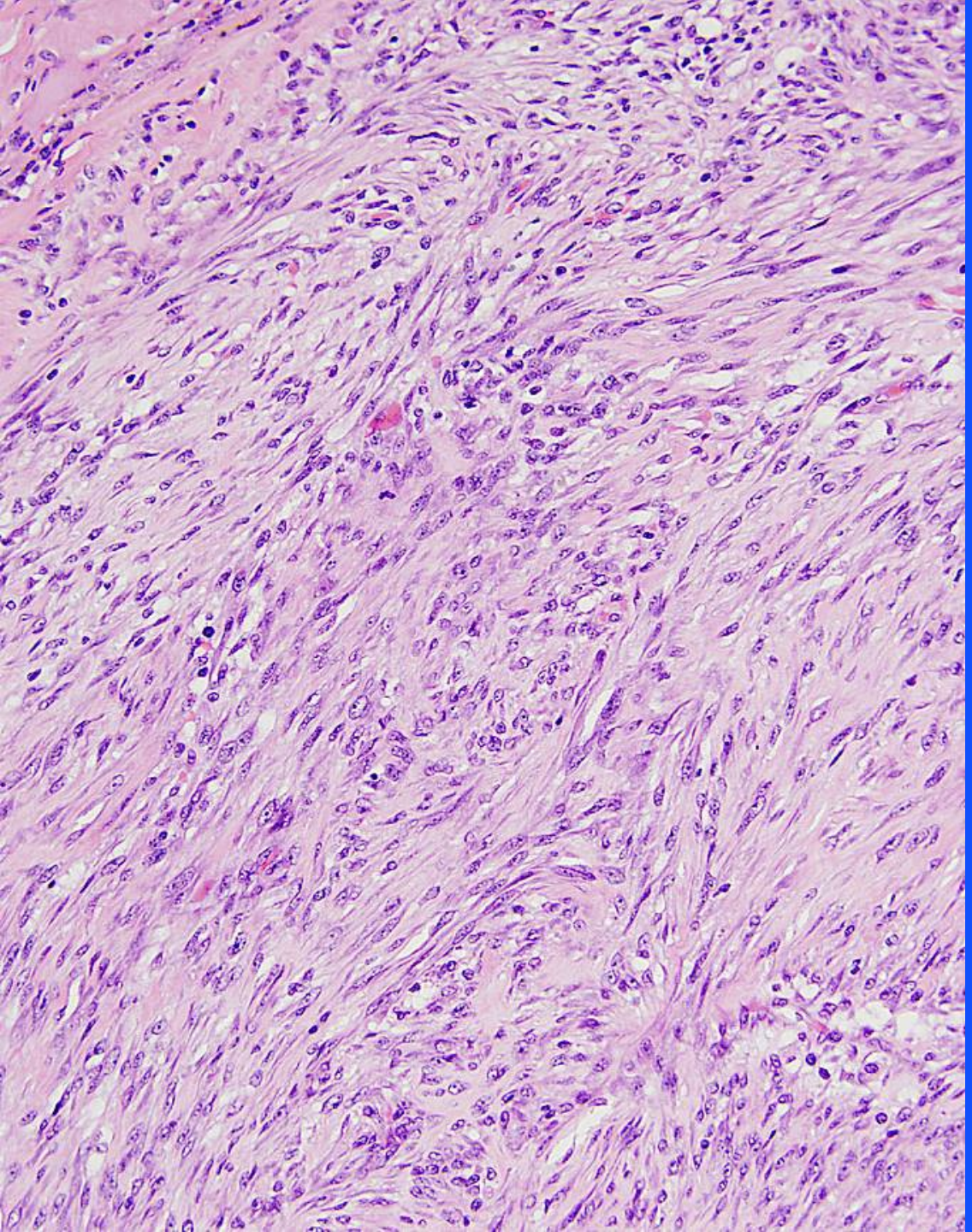
Liposarcoma, not otherwise specified

World Health Organization (2013)
Classification of Tumours of Soft Tissue

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Benign (1)

Nodular fasciitis
Proliferative fasciitis (?)
Proliferative myositis (?)
Myositis ossificans and fibro-osseous pseudotumour of digits
Ischaemic fasciitis
Elastofibroma
Fibrous hamartoma of infancy
Fibromatosis colli
Juvenile hyaline fibromatosis
Inclusion body fibromatosis



NODULAR FASCIITIS

t(17;22)(p13;q12.3)
(cryptic)

USP6-MYH9

ICD-0: 8828/0
Never had a
code before !

World Health Organization (2013) Classification of Tumours of Soft Tissue

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Benign (2)

Fibroma of tendon sheath
Desmoplastic fibroblastoma
Mammary-type myofibroblastoma
Calcifying aponeurotic fibroma
Angiomyofibroblastoma
Cellular angiofibroma
Nuchal-type fibroma
Gardner fibroma
Calcifying fibrous tumour

World Health Organization (2013) Classification of Tumours of Soft Tissue

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Intermediate category

Locally aggressive

Superficial fibromatoses
Desmoid-type fibromatoses
Lipofibromatosis
Giant cell fibroblastoma

Rarely metastasising

Dermatofibrosarcoma protuberans
Solitary fibrous tumour
Inflammatory myofibroblastic tumour
Low grade myofibroblastic sarcoma
Myxoinflammatory fibroblastic sarcoma/atypical myxoinflammatory fibroblastic tumour
Infantile fibrosarcoma

World Health Organization (2013) Classification of Tumours of Soft Tissue

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

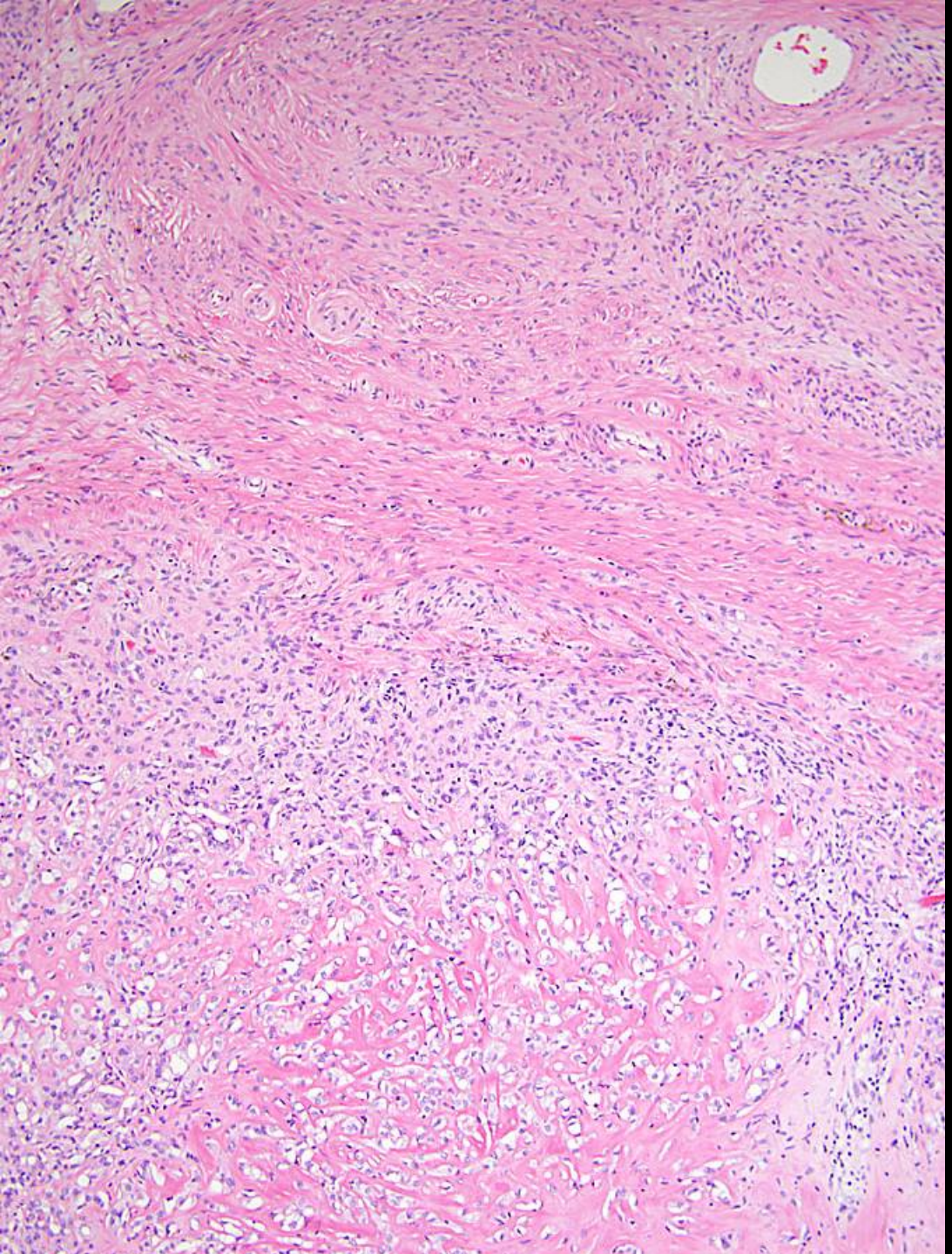
Malignant

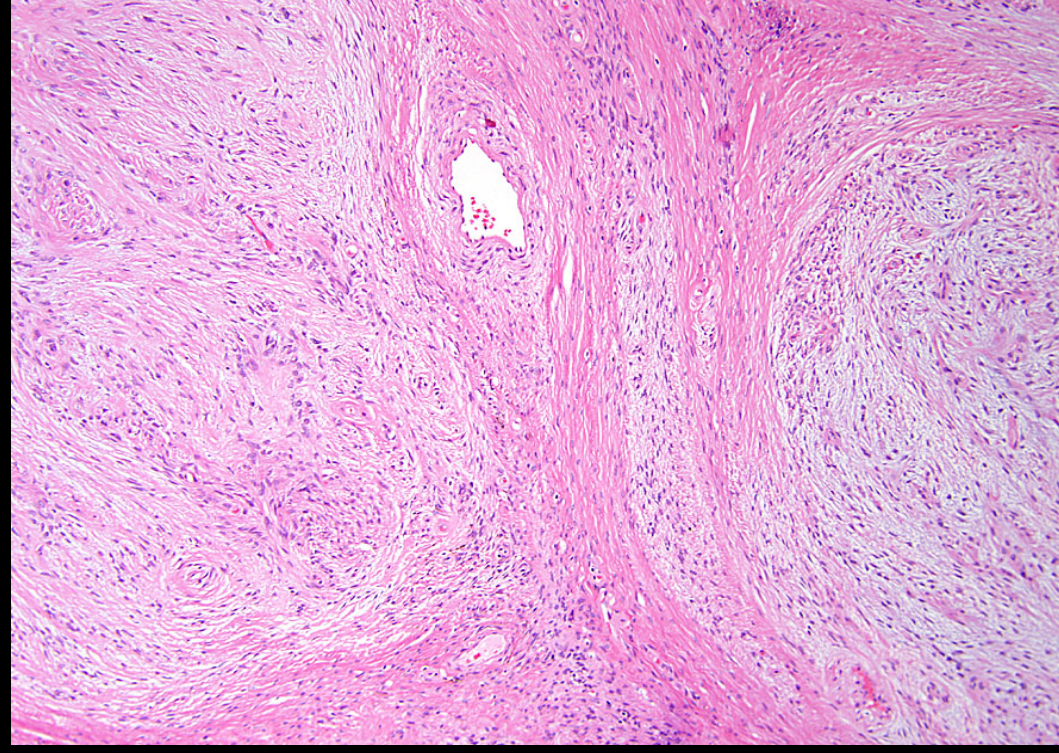
Adult fibrosarcoma

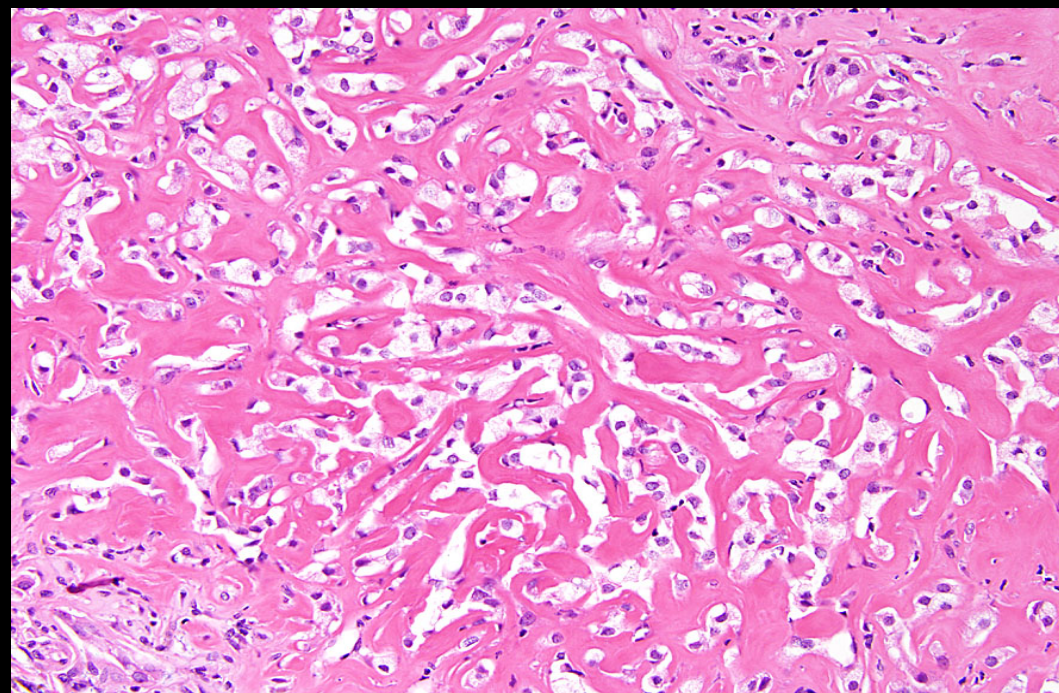
Myxofibrosarcoma

Low grade fibromyxoid sarcoma

Sclerosing epithelioid fibrosarcoma







LGFMS/SEF
MOLECULAR GENETICS

PURE LGFMS — Most have t(11;16)(q33;p11) *FUS-CREB3L2*
Few have t(11;16)(p11;p11) *FUS-CREB3L1*
Basically all are MUC4 immunopositive

PURE SEF

If MUC4 +ve (70%) – ? Up to 90% have *EWSR1-CREB3L1*

? 30-40% have *FUS* rearrangement (some with *CREB3L1* or *CREB3L2*)

MUC4 -ve – *FUS* negative, otherwise unknown

HYBRID LGFMS/SEF

All are MUC4 +ve – Most have either *FUS* or *EWSR1* rearrangement (usually with *CREB3L2*)

World Health Organization (2013) Classification of Tumours of Soft Tissue

SO-CALLED FIBROHISTIOCYTIC TUMOURS

Benign

Tenosynovial giant cell tumour
- **localised**
- **diffuse**

Deep benign fibrous histiocytoma

Intermediate (rarely metastasising)

Plexiform fibrohistiocytic tumour
Giant cell tumour of soft tissues

World Health Organization (2013) Classification of Tumours of Soft Tissue

SMOOTH MUSCLE TUMOURS

Deep leiomyoma

Leiomyosarcoma (excluding skin)

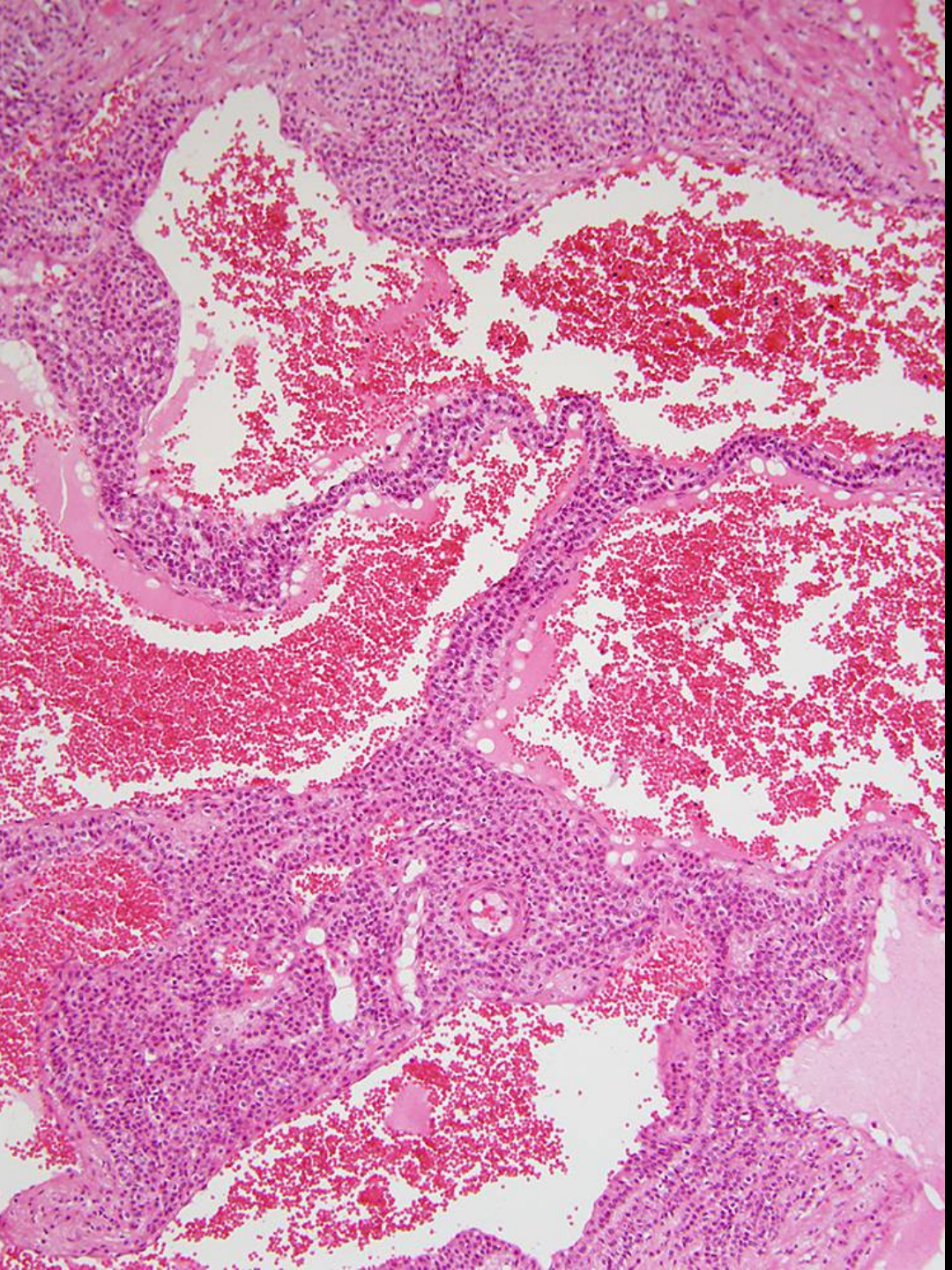
World Health Organization (2013) Classification of Tumours of Soft Tissue

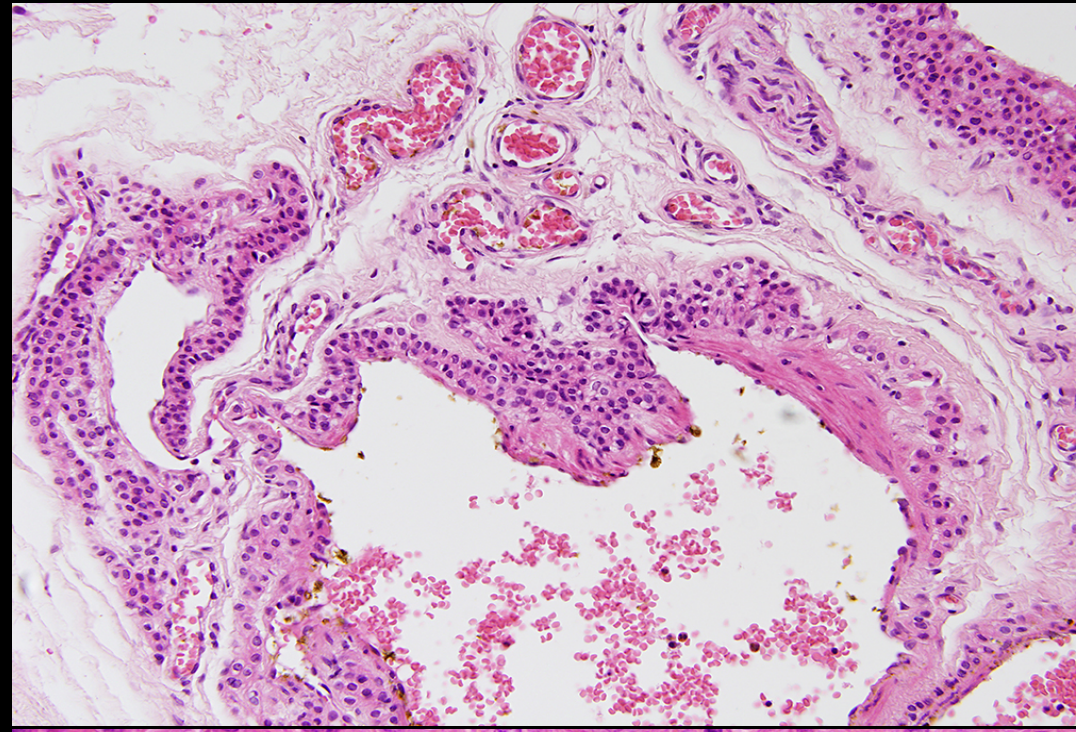
PERICYTIC (PERIVASCULAR) TUMOURS

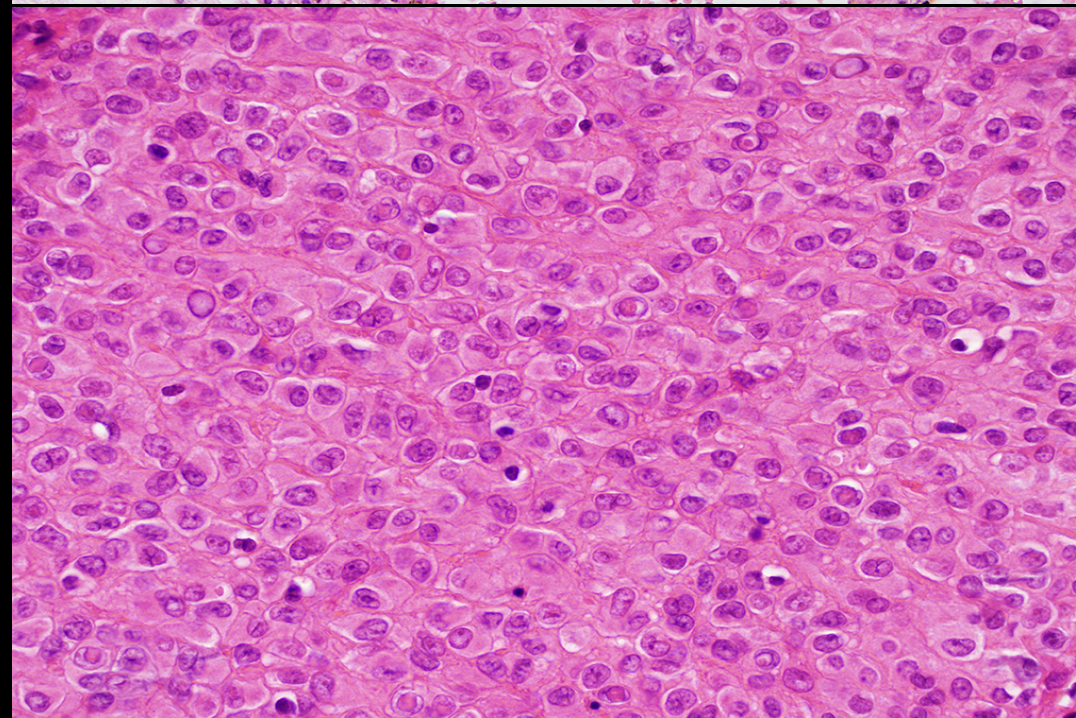
Glomus tumour (and variants)
- **Glomangiomatosis**
- **Malignant glomus tumour**

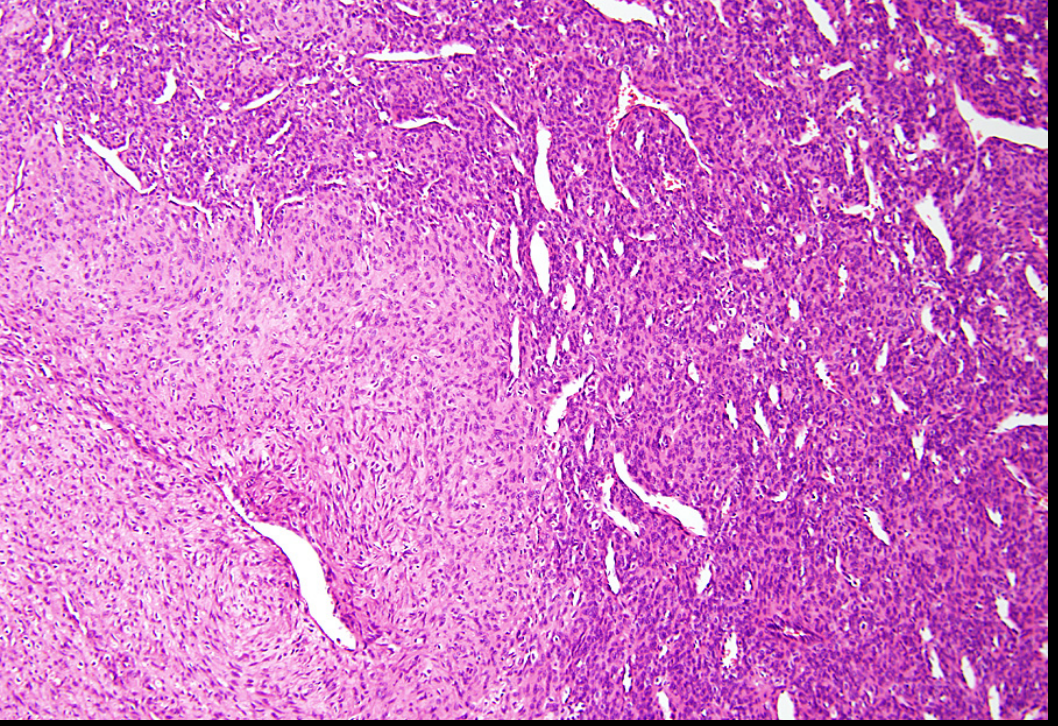
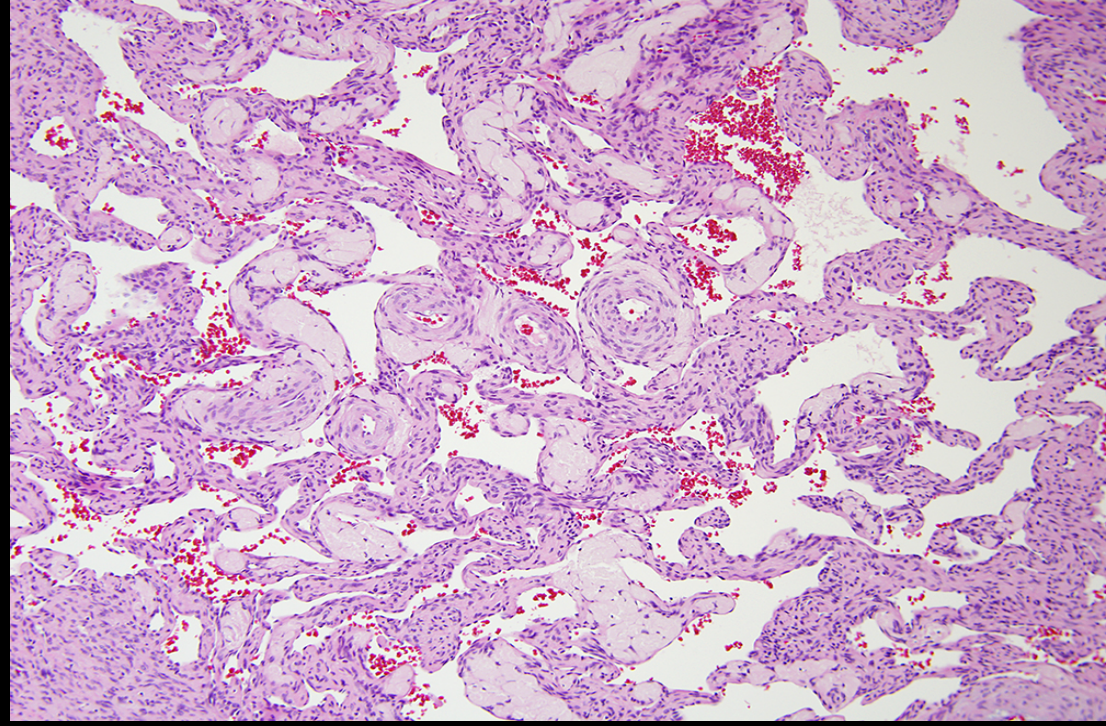
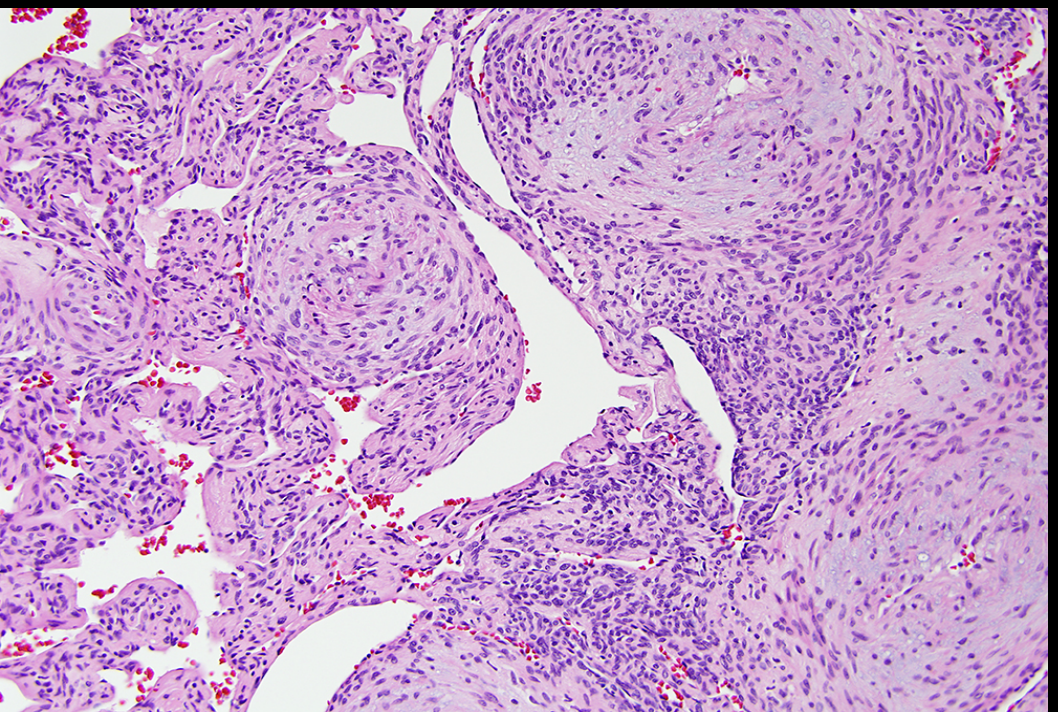
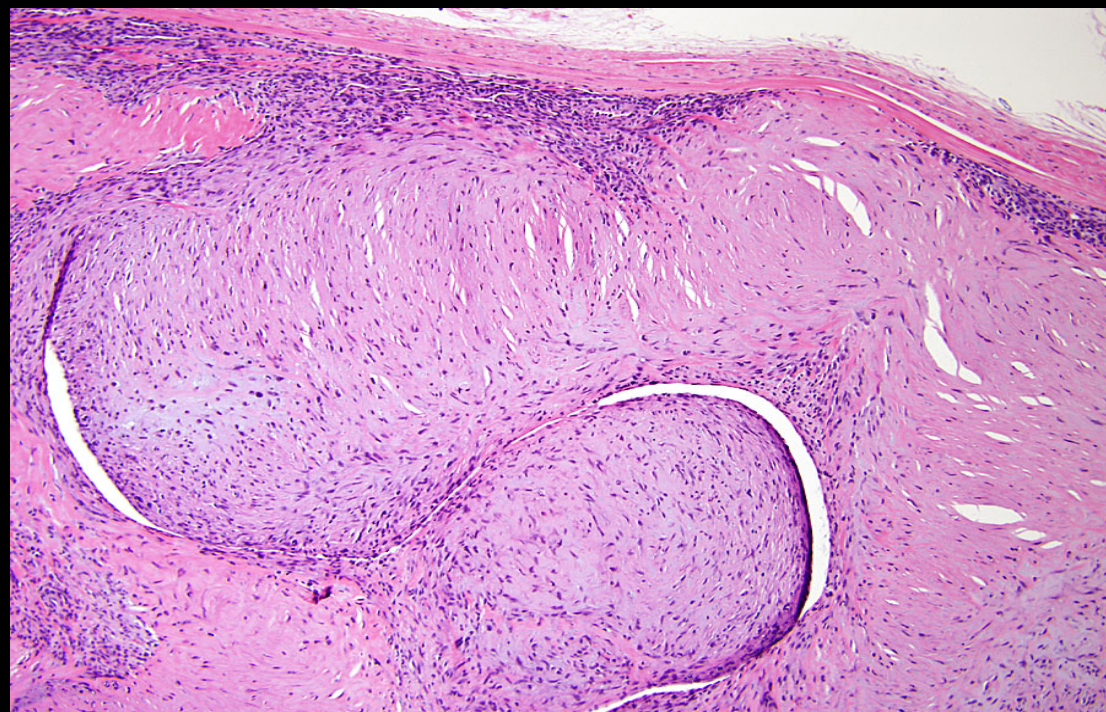
Myopericytoma
- **Myofibroma**
- **Myofibromatosis**

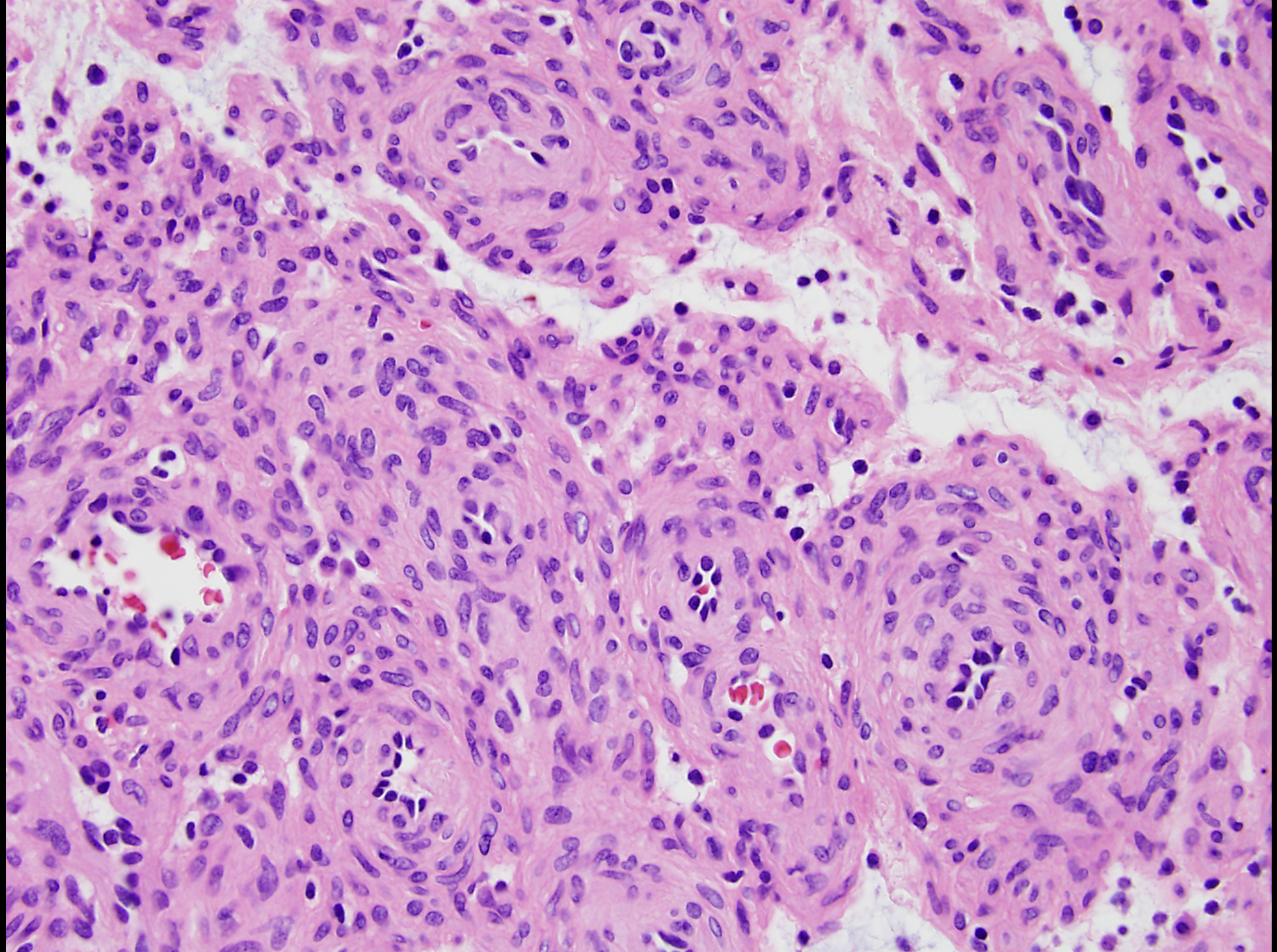
Angioleiomyoma

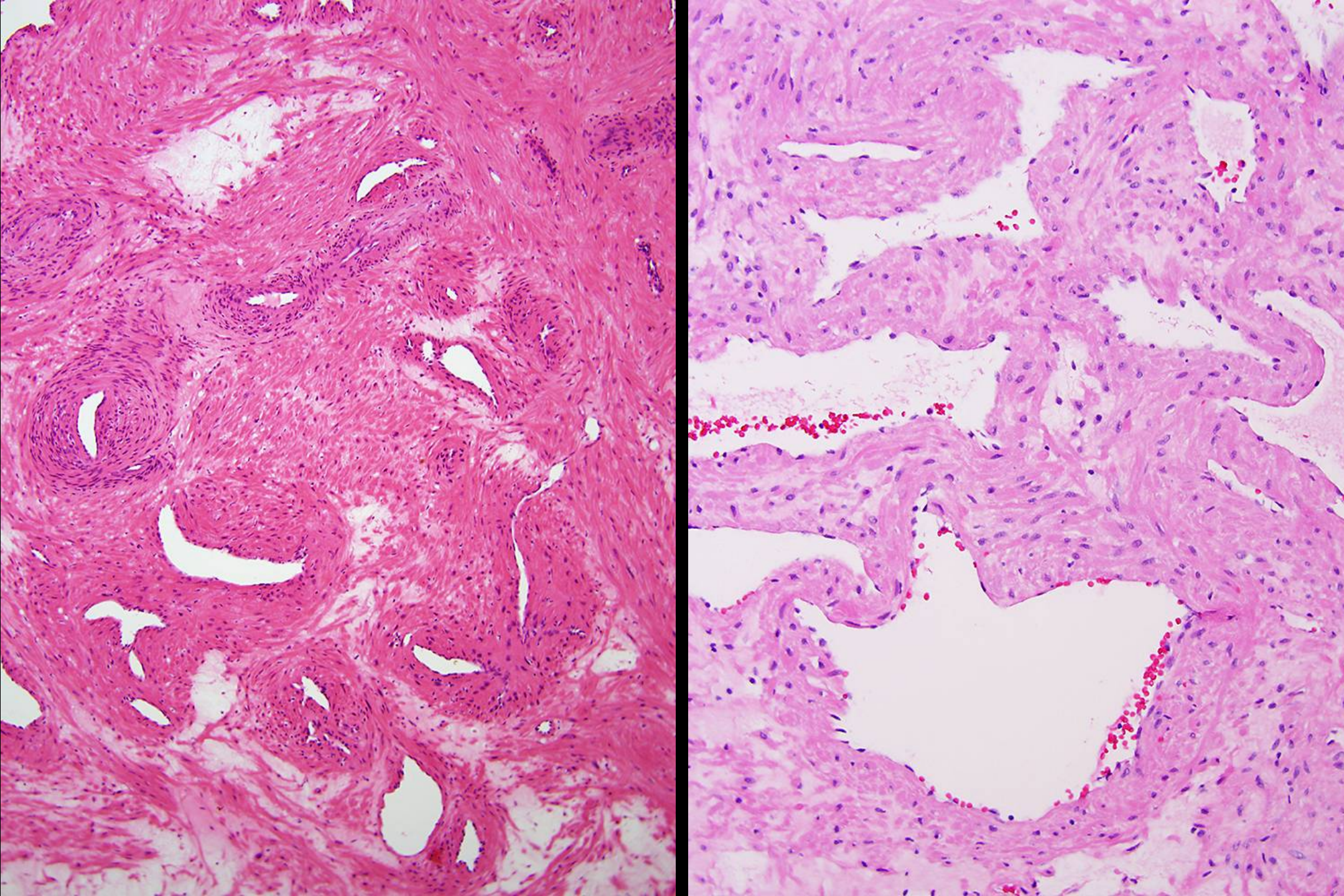










PERICYTIC (PERIVASCULAR) TUMOURS
NEW GENETIC DATA

- **Multiple familial glomus tumours result from germline *GLMN* mutation**
- **NF-1 may be associated with multiple digital glomus tumours (which show *NF-1* inactivation)**
- ***NOTCH2* or *NOTCH3* rearrangement identified in 60% of sporadic soft tissue glomus tumours**
- ***BRAF* (10%) and *KRAS* (rare) mutations identified in sporadic glomus tumours**

PERICYTIC (PERIVASCULAR) TUMOURS
KEY POINTS

- **Morphologic continuum, includes myofibroma**
- **Angioleiomyoma fits better here**
- **Could ultimately be renamed as haemangiopericytoma !**

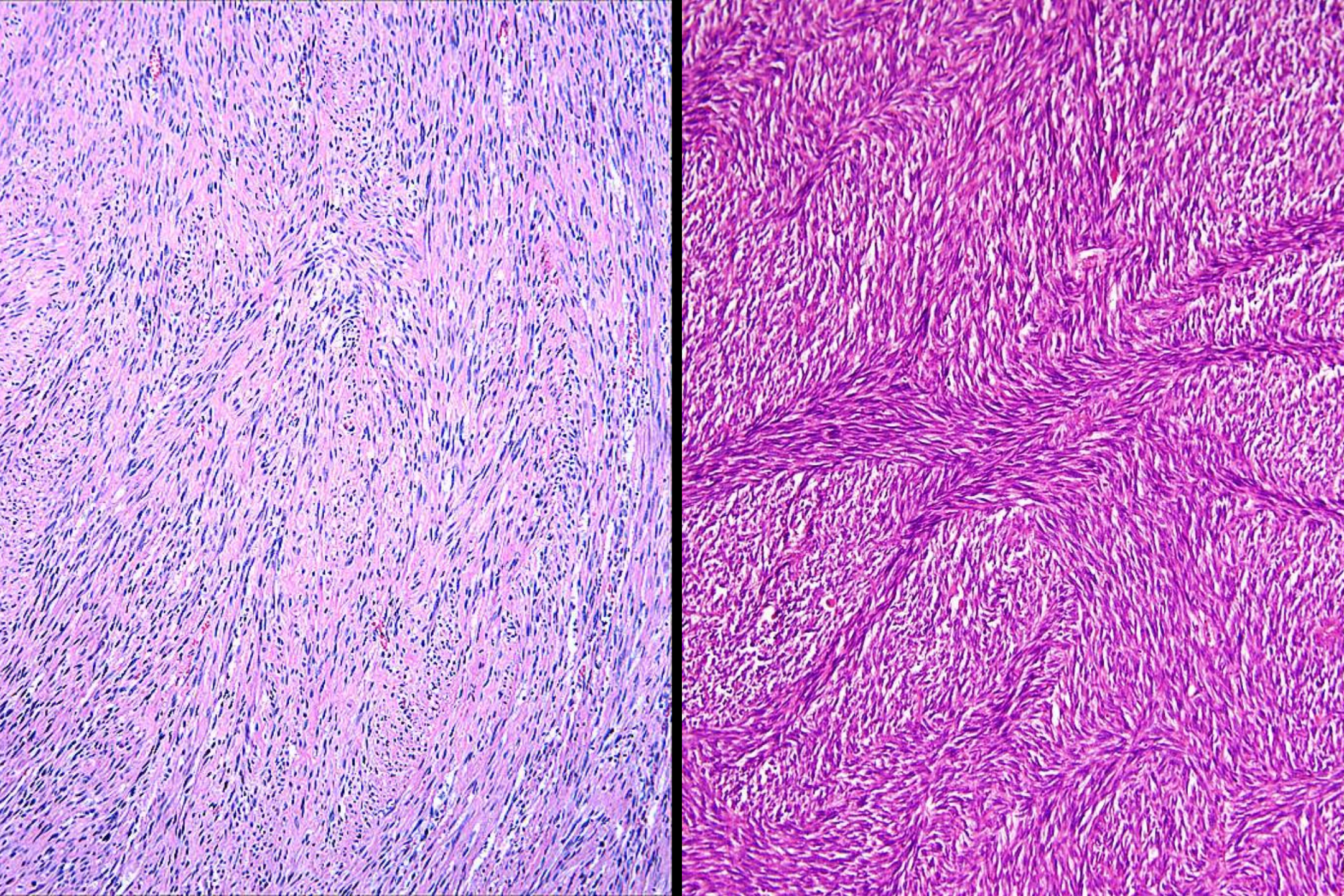
World Health Organization (2013) Classification of Tumours of Soft Tissue

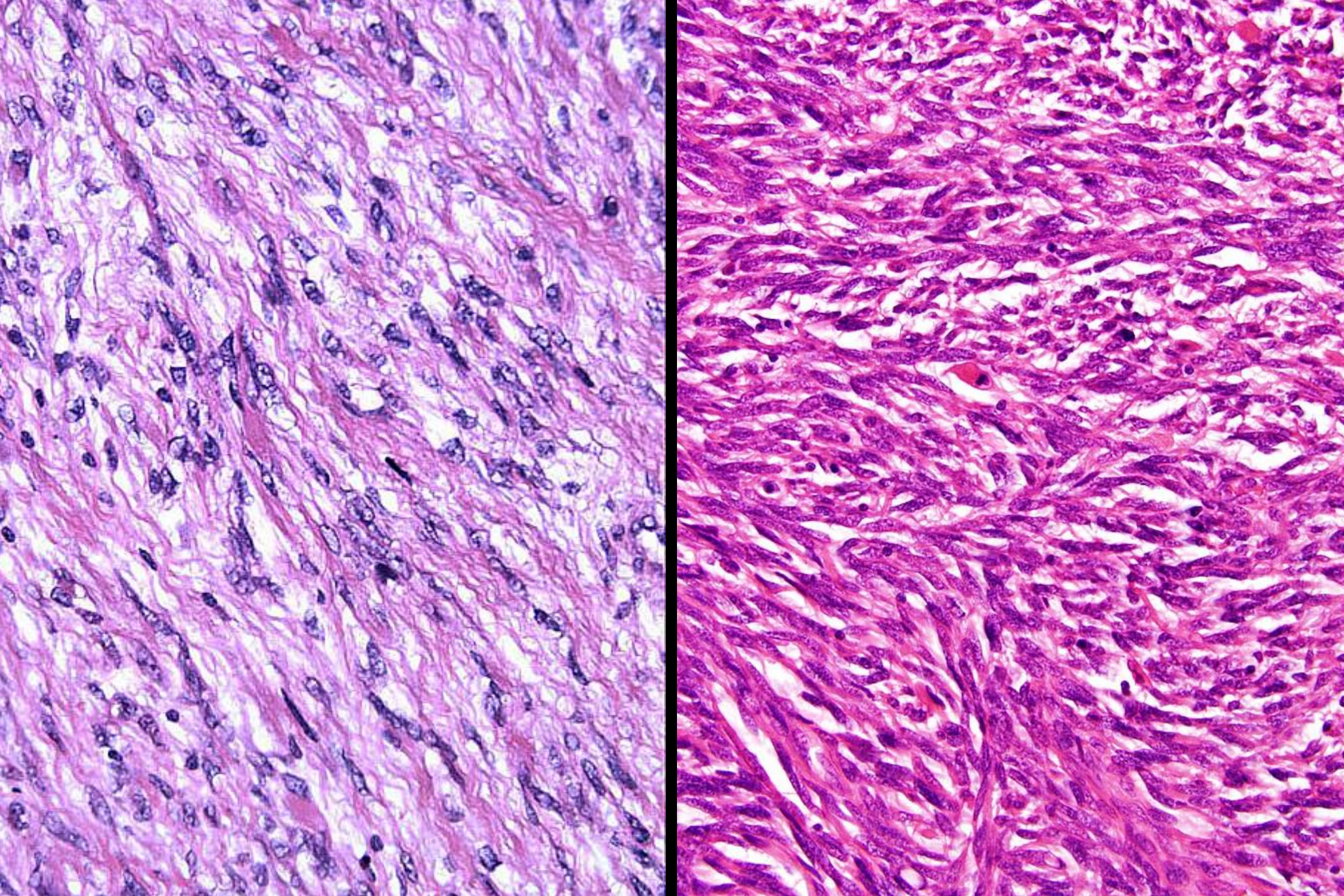
SKELETAL MUSCLE TUMOURS

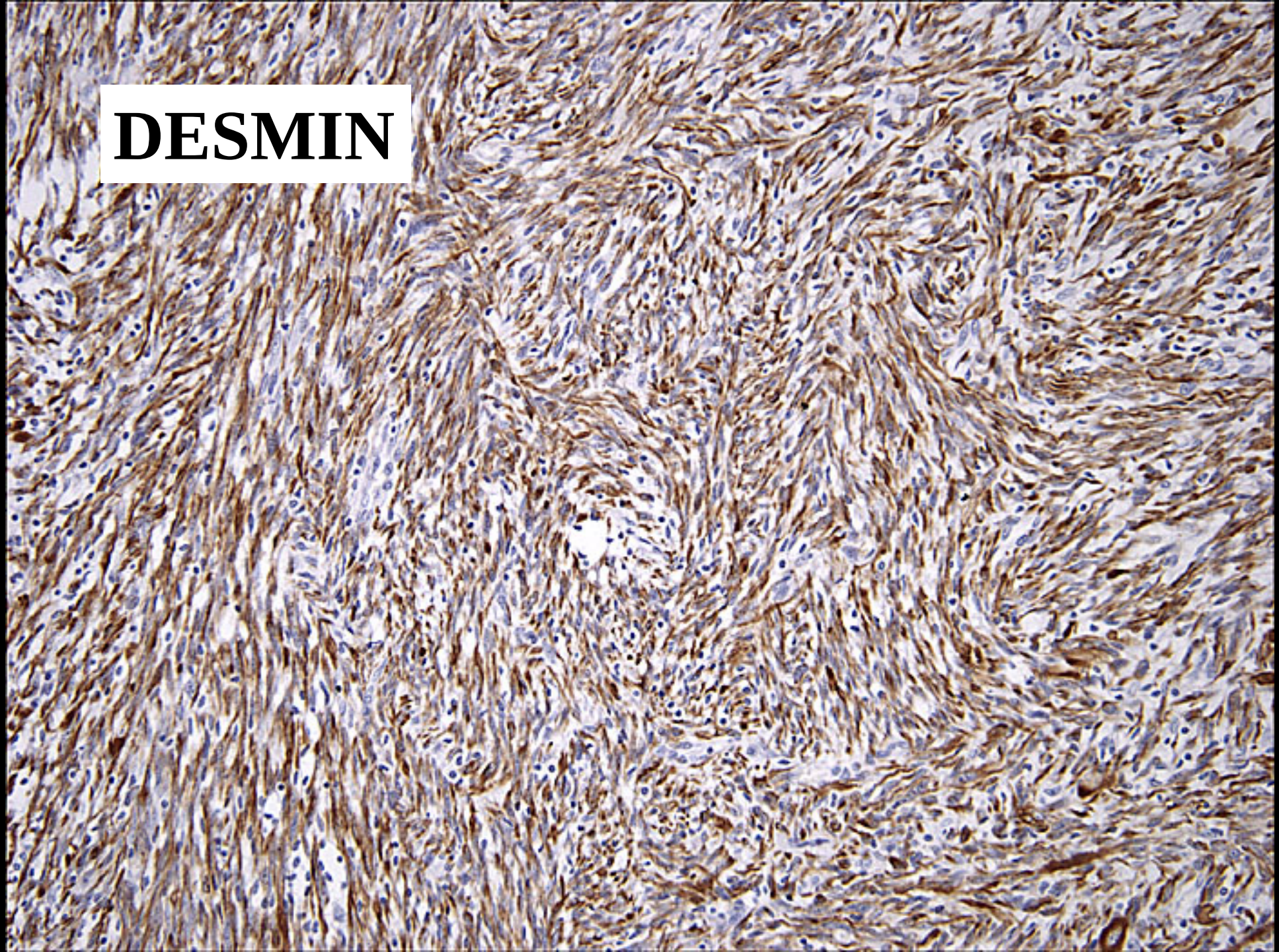
Benign	*Malignant*
Rhabdomyoma	Embryonal rhabdomyosarcoma
adult type	(incl. botryoid, anaplastic)
fetal type	Alveolar rhabdomyosarcoma
genital type	(incl. solid, anaplastic)
	Pleomorphic rhabdomyosarcoma
	Spindle cell/sclerosing rhabdomyosarcoma

SPINDLE CELL RHABDOMYOSARCOMA

- 1st described 1992 / 1993
  Long regarded as variant of embryonal
- Commonest in children / adolescents
- Mainly paratesticular
- 5 year survival > 90% in children
- Easily confused with other spindle cell sarcomas



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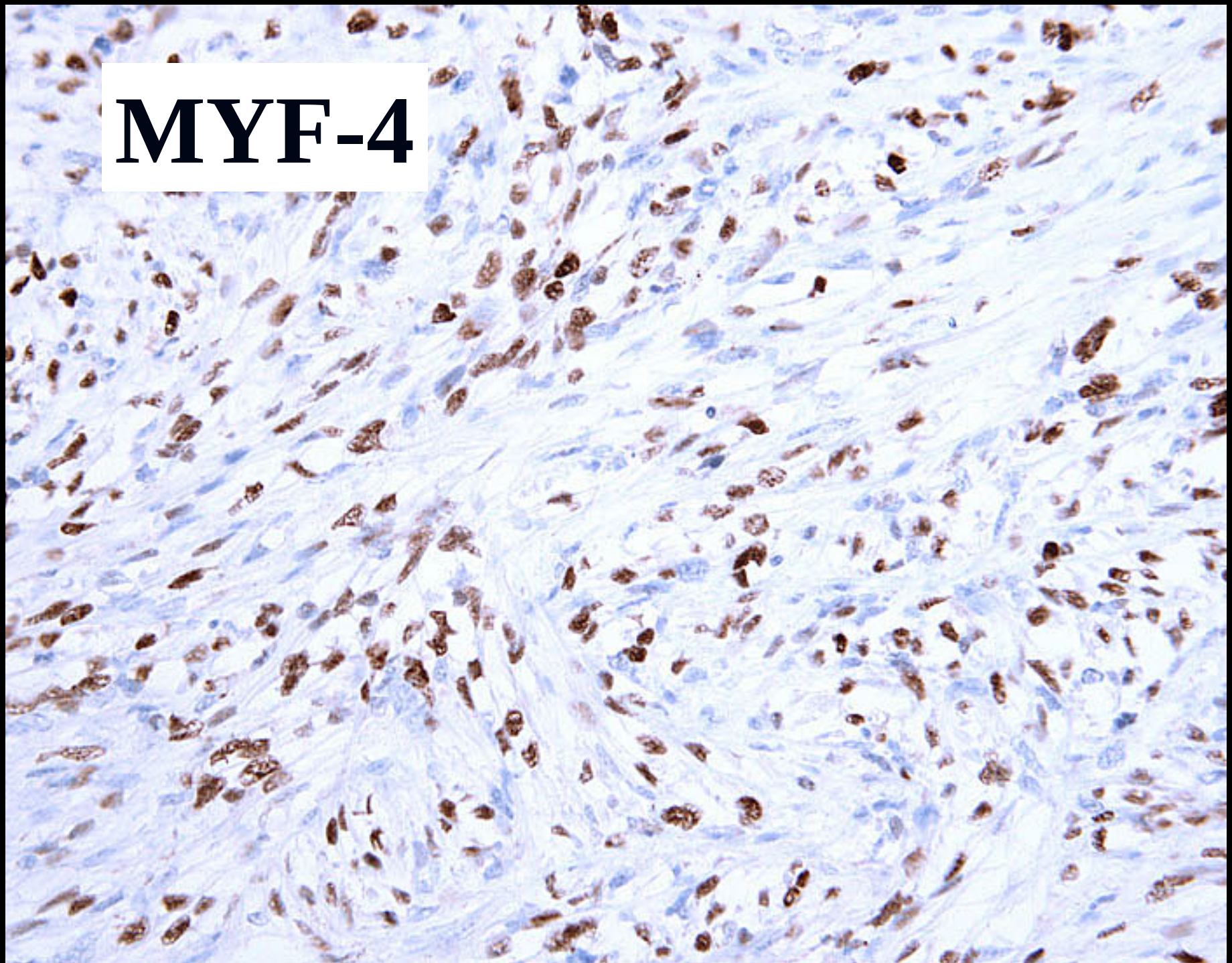
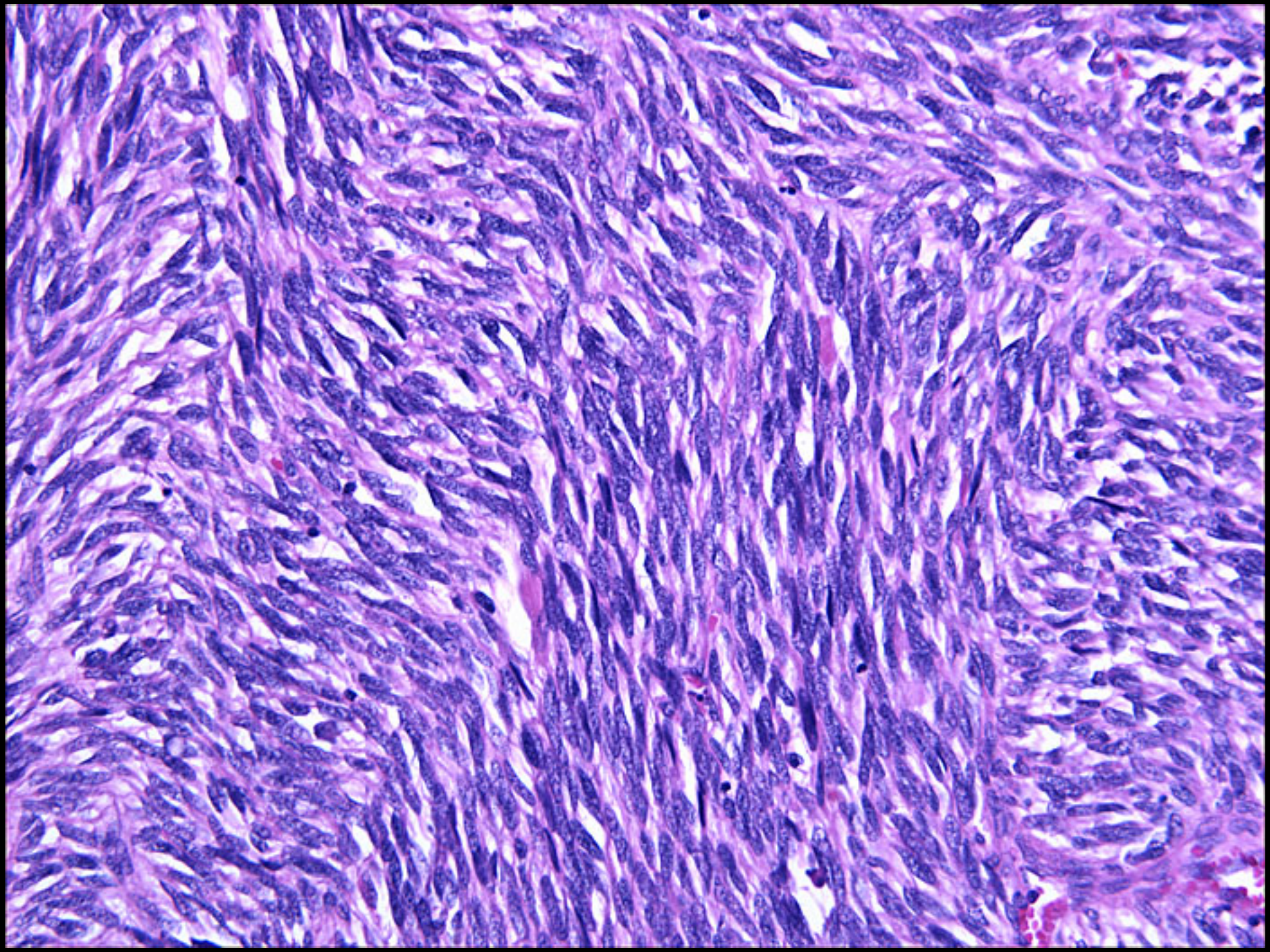

MYF-4

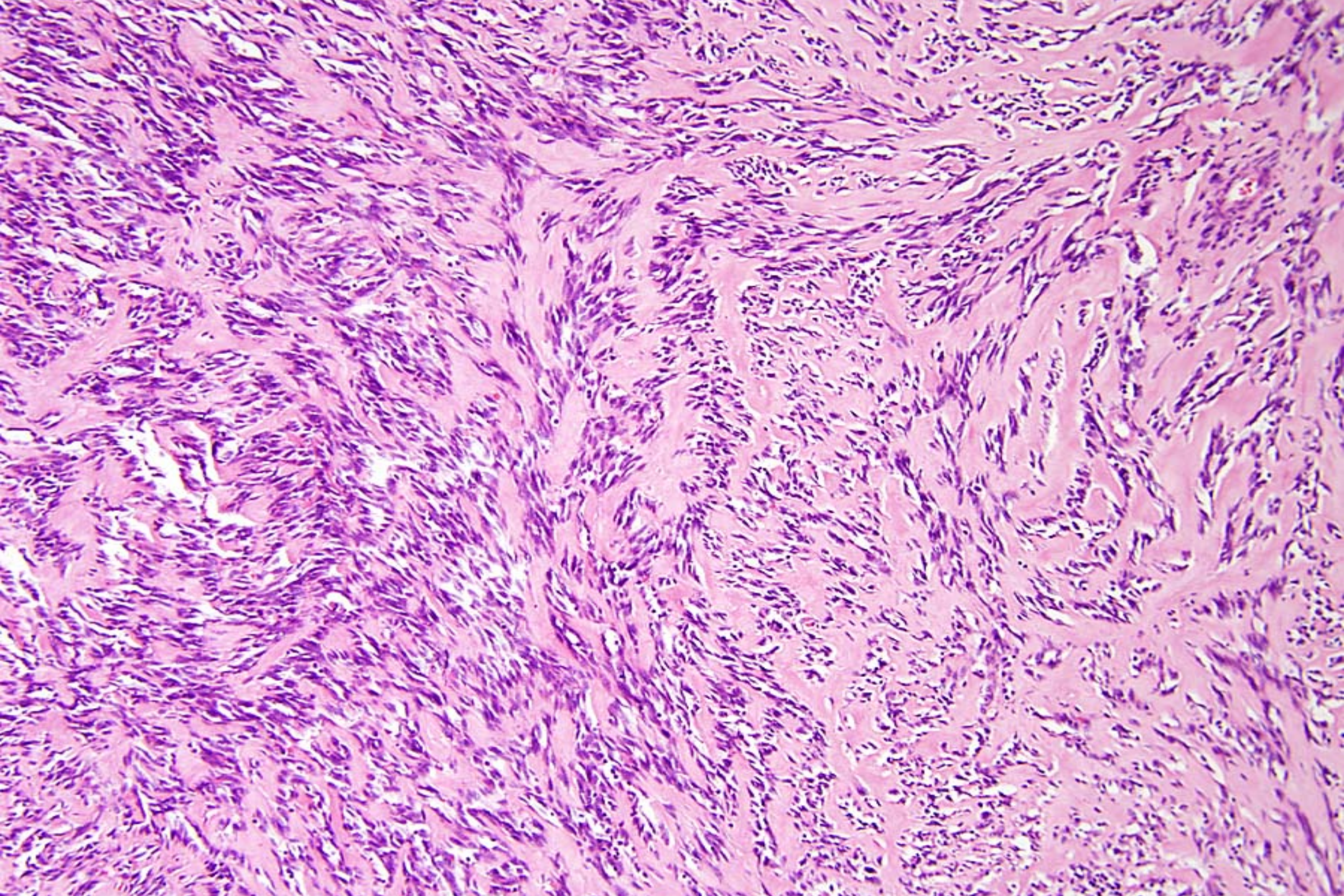
SPINDLE CELL RHABDOMYOSARCOMA IN ADULTS

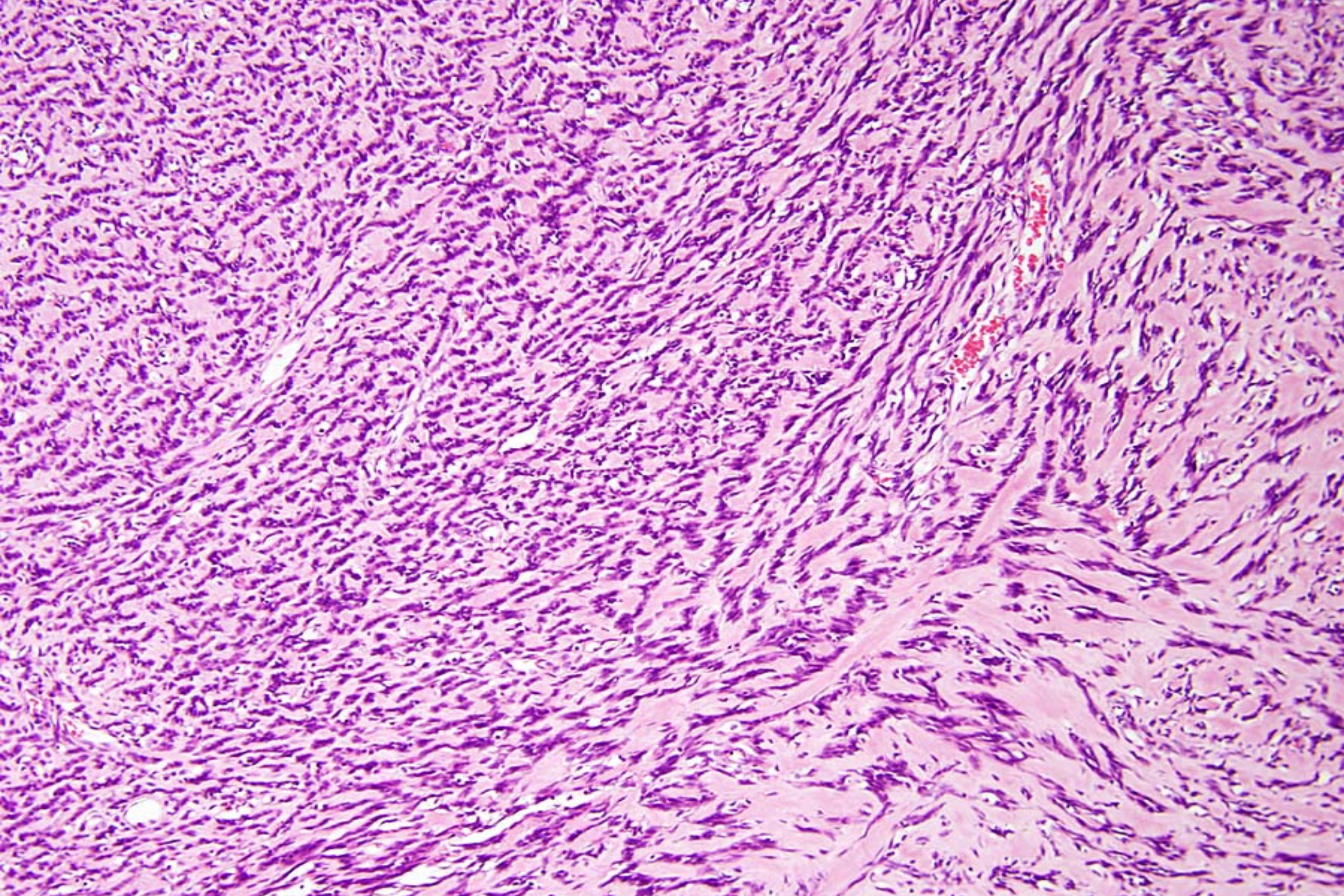
- Mainly 3rd / 4th decades
- Males > females
- Head and neck commonest (50%)
  - but wide range of sites
- More aggressive than in children

? Relationship to sclerosing rhabdo

Morphologic overlap in 15-20% of cases

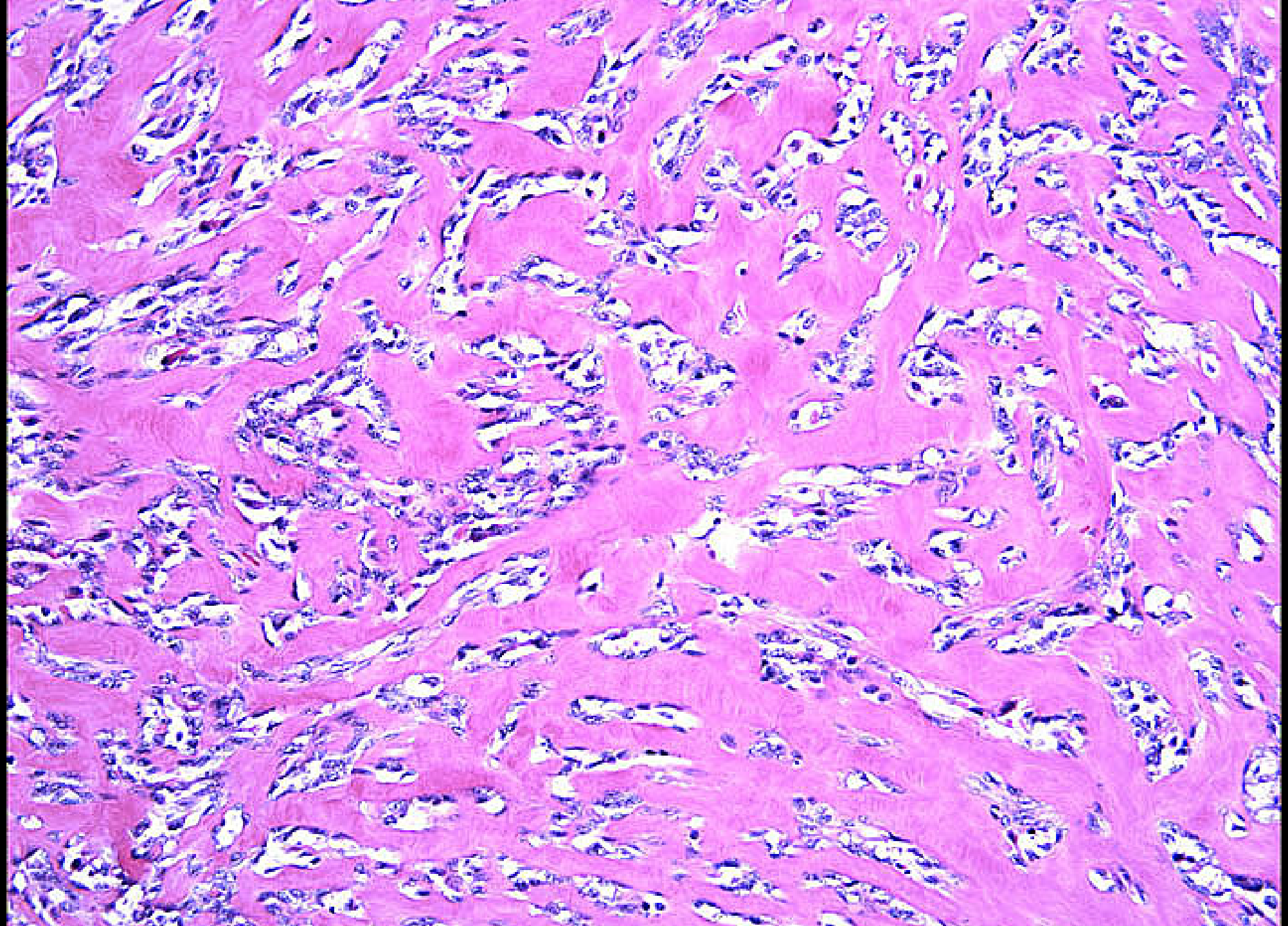


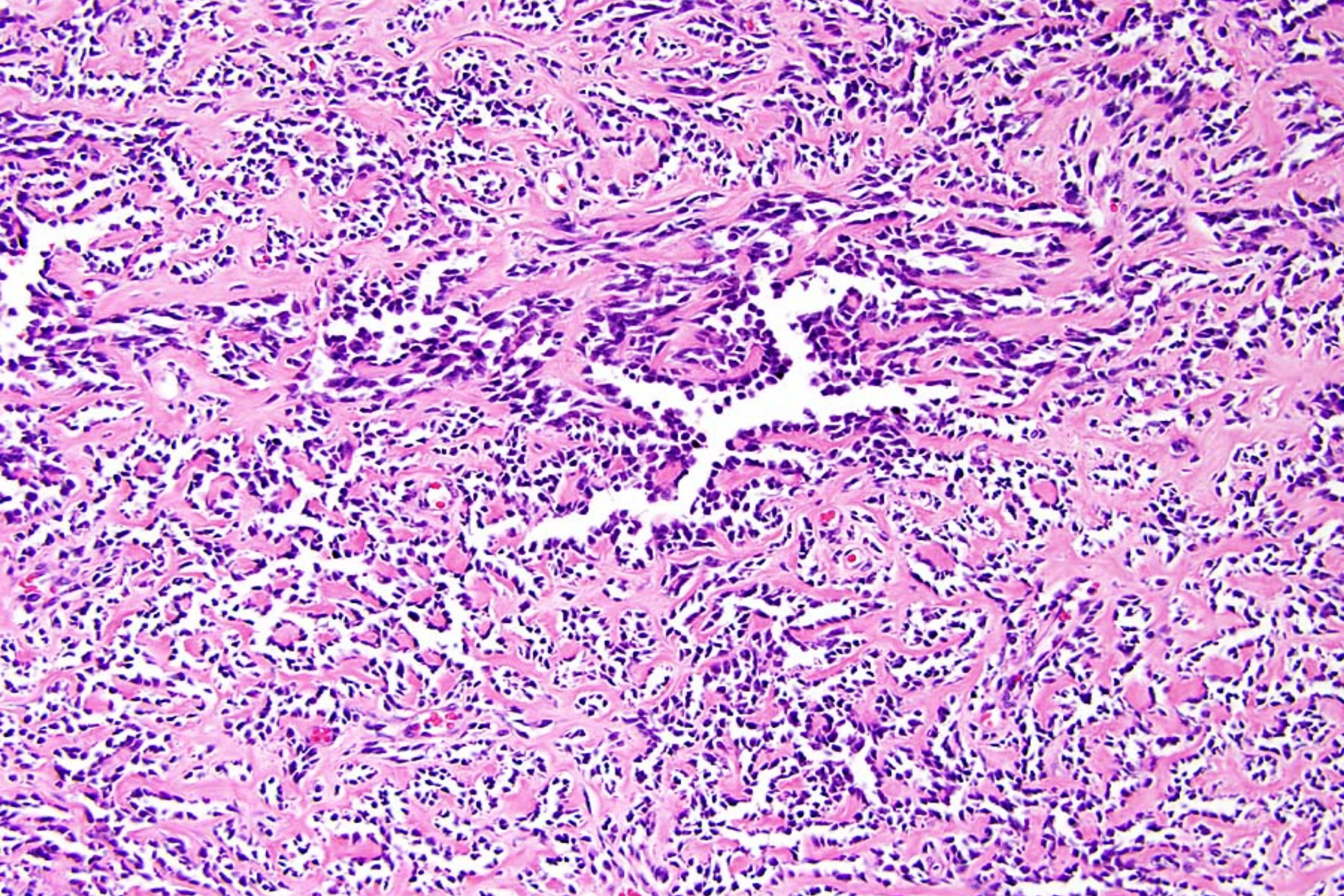


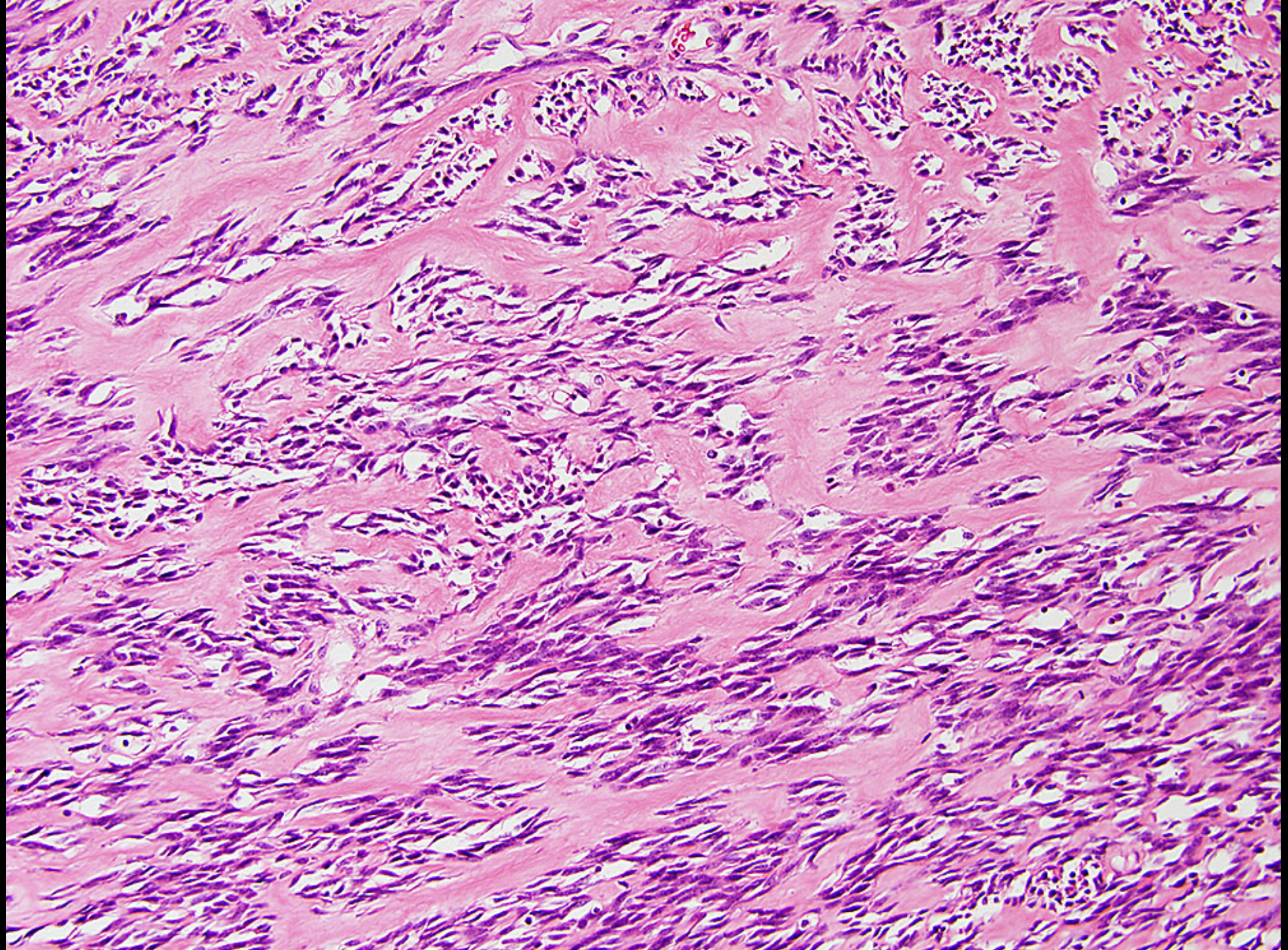


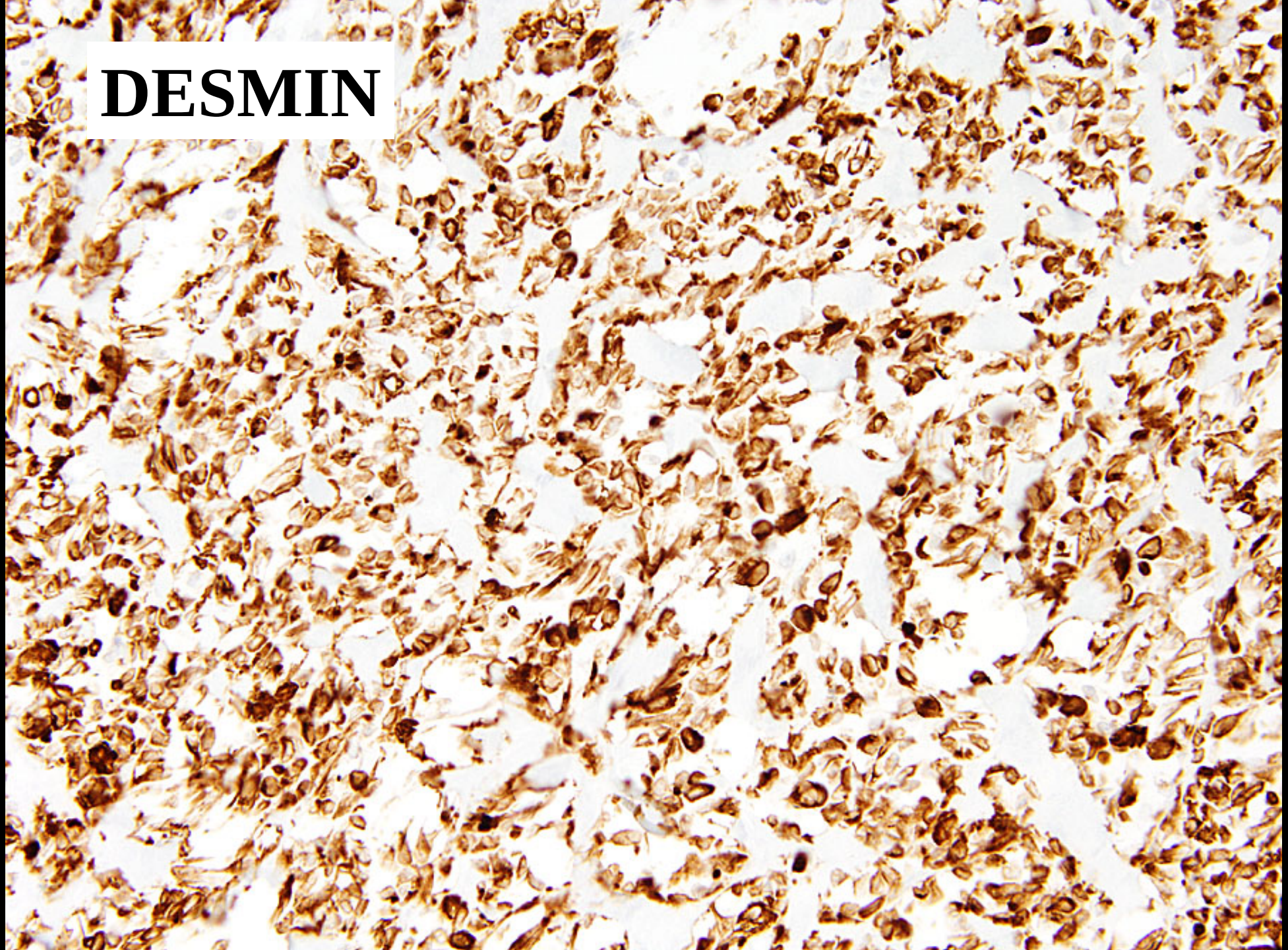
SCLEROSING RHABDOMYOSARCOMA

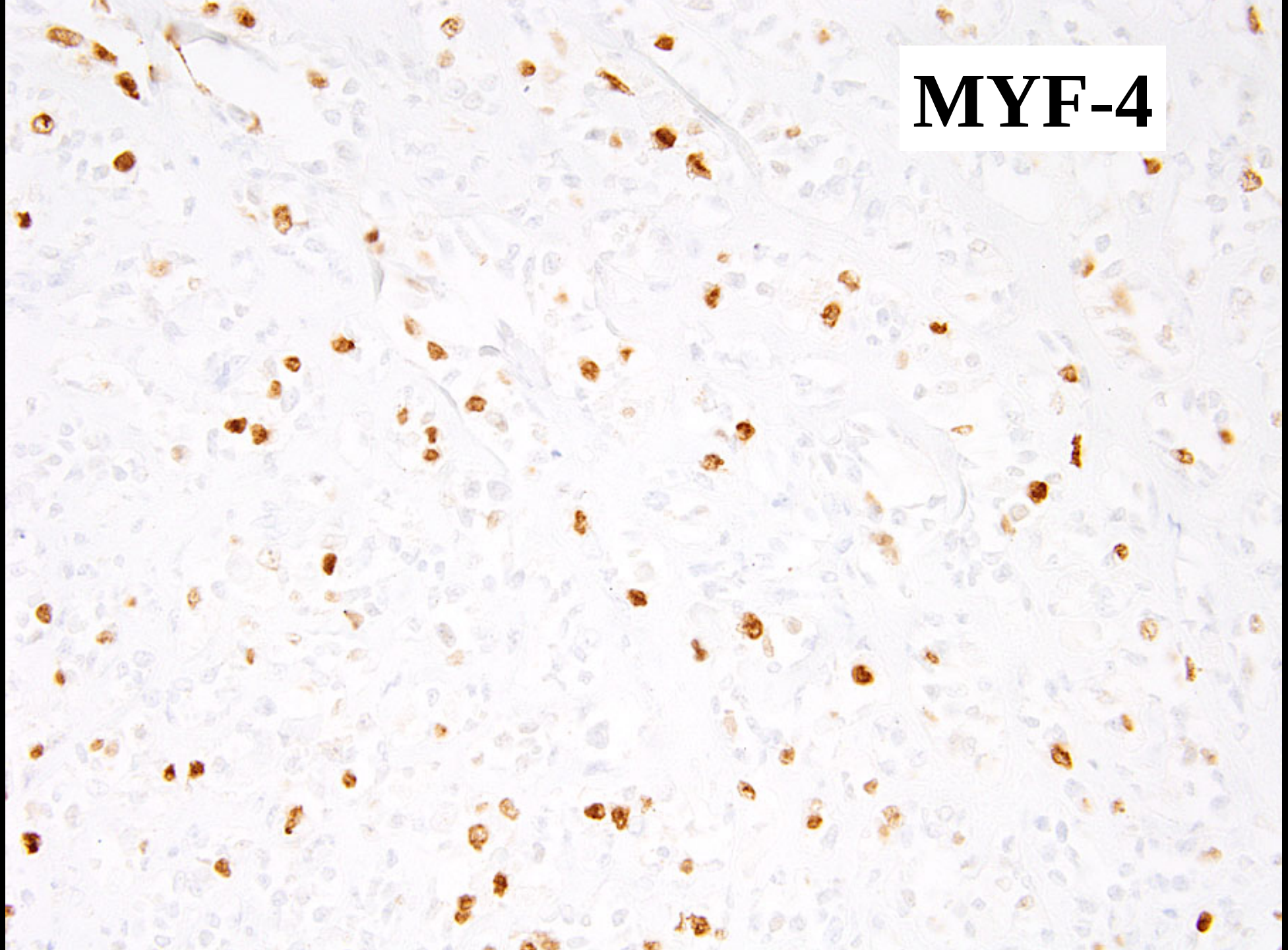
- 1st described 2000 / 2002 (Mentzel et al; Folpe et al)
- Affects adults & children / adolescents
- Head & neck = Limbs
- Prognosis still somewhat uncertain
- No clear genetic data until recently
- Easily confused with angiosarcoma or perhaps even osteosarcoma





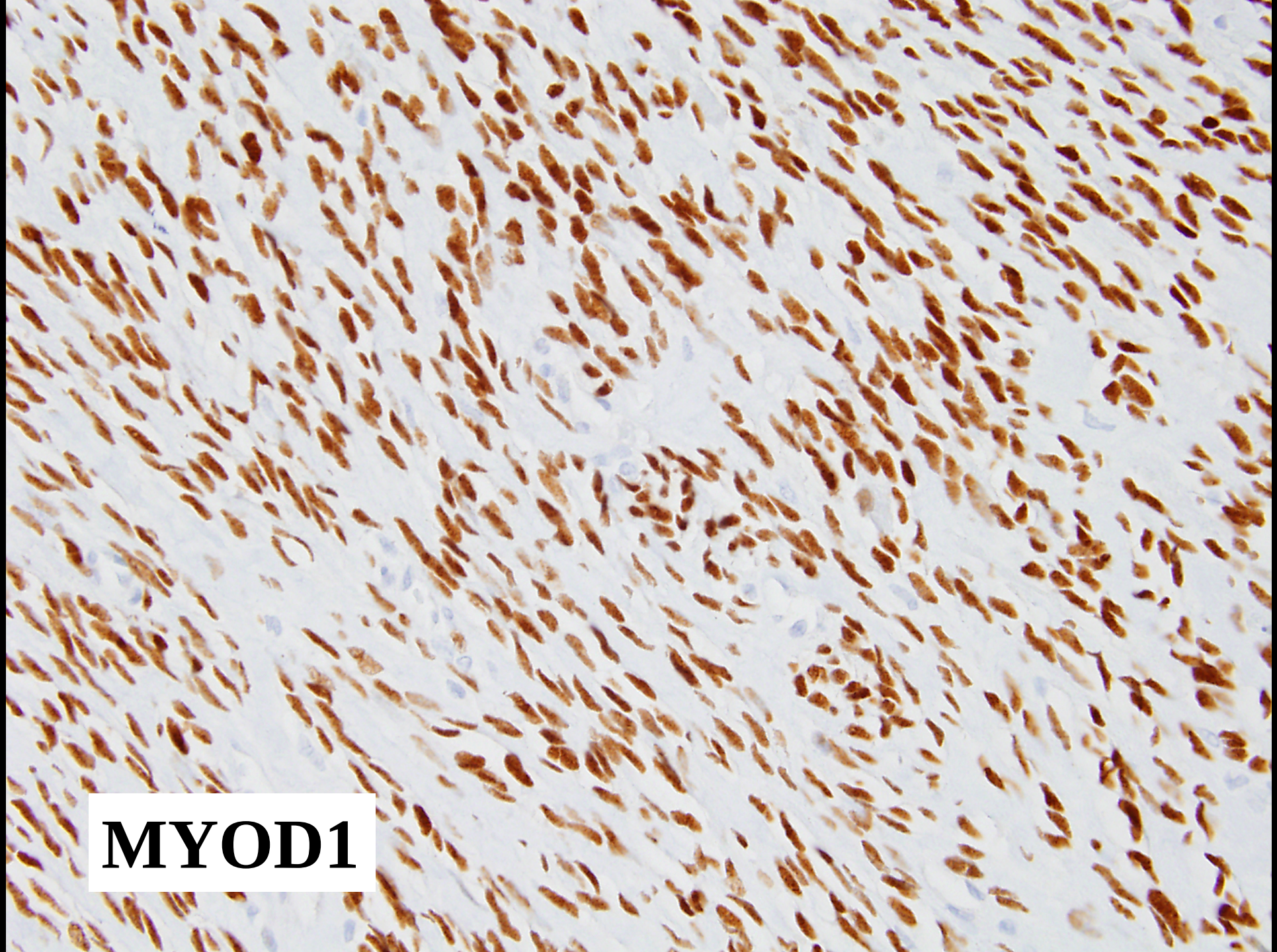



DESMIN


MYF-4

SPINDLE CELL / SCLEROSING RHABDOMYOSARCOMA
POST-WHO GENETIC FINDINGS

- ***NCOA2*** **gene rearrangements in congenital/ infantile spindle cell rhabdo (Mosquera et al)**
- ***MYOD1*** **mutations in spindle cell rhabdo in adults (Szuhai et al)**
- ***MYOD1*** **(+*PI3K*) mutations in BOTH spindle cell and sclerosing rhabdos in children and adults (distinct from *NCOA2* group) (Agaram et al)**
- ***MYOD1*** **(+ *PI3K*) mutations in "aggressive embryonal" rhabdos (Kohsaka et al)**


MYOD1

SPINDLE CELL / SCLEROSING RHABDOMYOSARCOMA

KEY POINTS

- No clear relationship to embryonal rhabdo
- Form a morphologic continuum
- Affect both children (paratesticular ++) and adults (head/neck > limbs)
- Worse prognosis in adults
- Treatment uncertain
- Recent genetic data very informative and support separate classification

World Health Organization (2013) Classification of Tumours of Soft Tissue

VASCULAR TUMOURS

Benign

Haemangiomas
- **synovial**
- **venous**
- **arteriovenous (malformation)**
- **intramuscular**

Epithelioid haemangioma

Angiomatosis

Lymphangioma

World Health Organization (2013) Classification of Tumours of Soft Tissue

VASCULAR TUMOURS

Intermediate (locally aggressive)

Kaposiform haemangioendothelioma

Intermediate (rarely metastasising)

Retiform haemangioendothelioma

Papillary intralymphatic angioendothelioma

Composite haemangioendothelioma

Pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma

Kaposi sarcoma

Malignant

Epithelioid haemangioendothelioma

Angiosarcoma of soft tissue

NB NEW GENETIC DATA

PSEUDOMYOGENIC ('EPITHELIOID SARCOMA-LIKE') HAEMANGIOENDOTHELIOMA

CLINICAL FEATURES

Young adults

Males > females ++

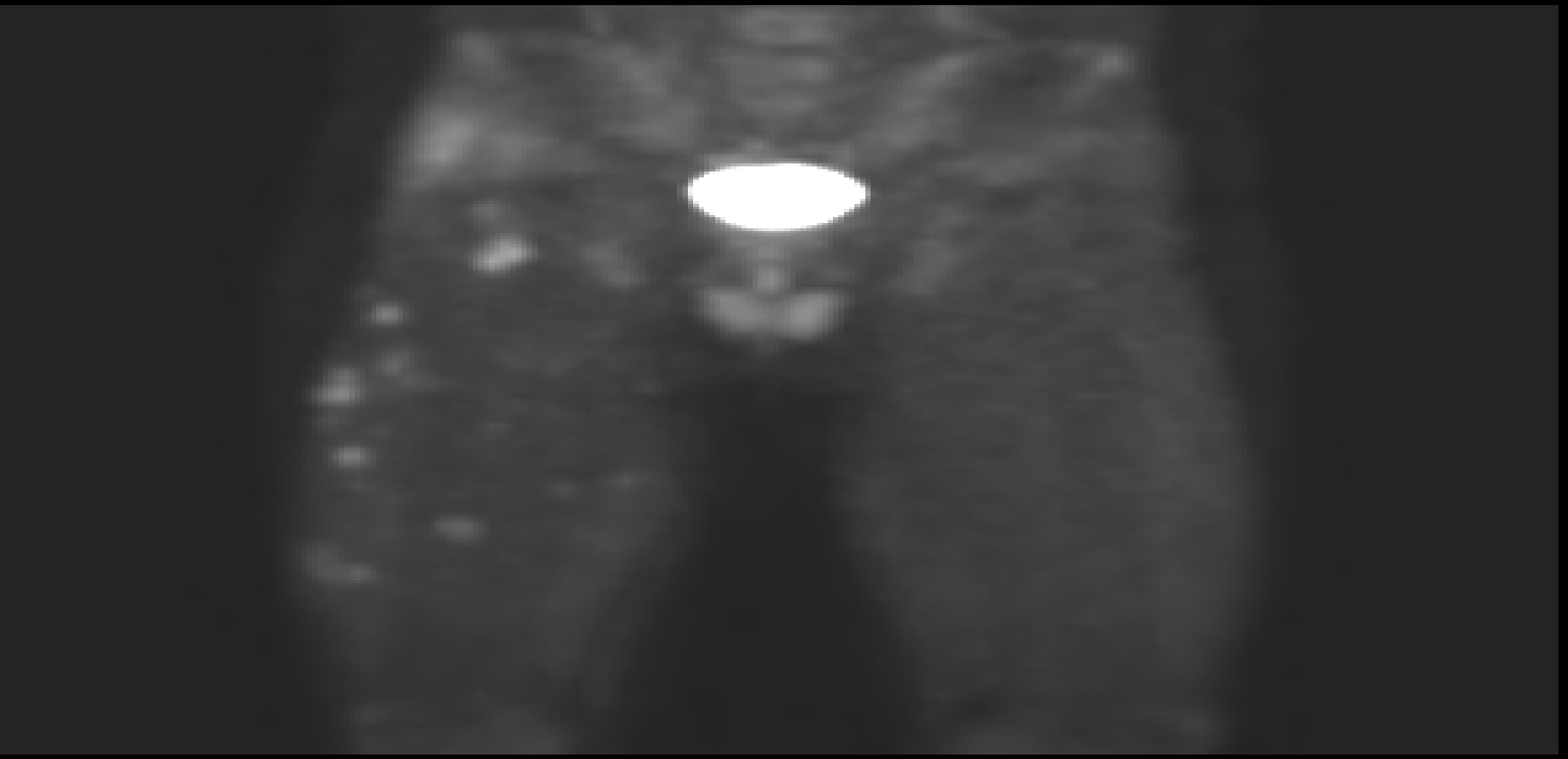
80% limbs – leg > arm

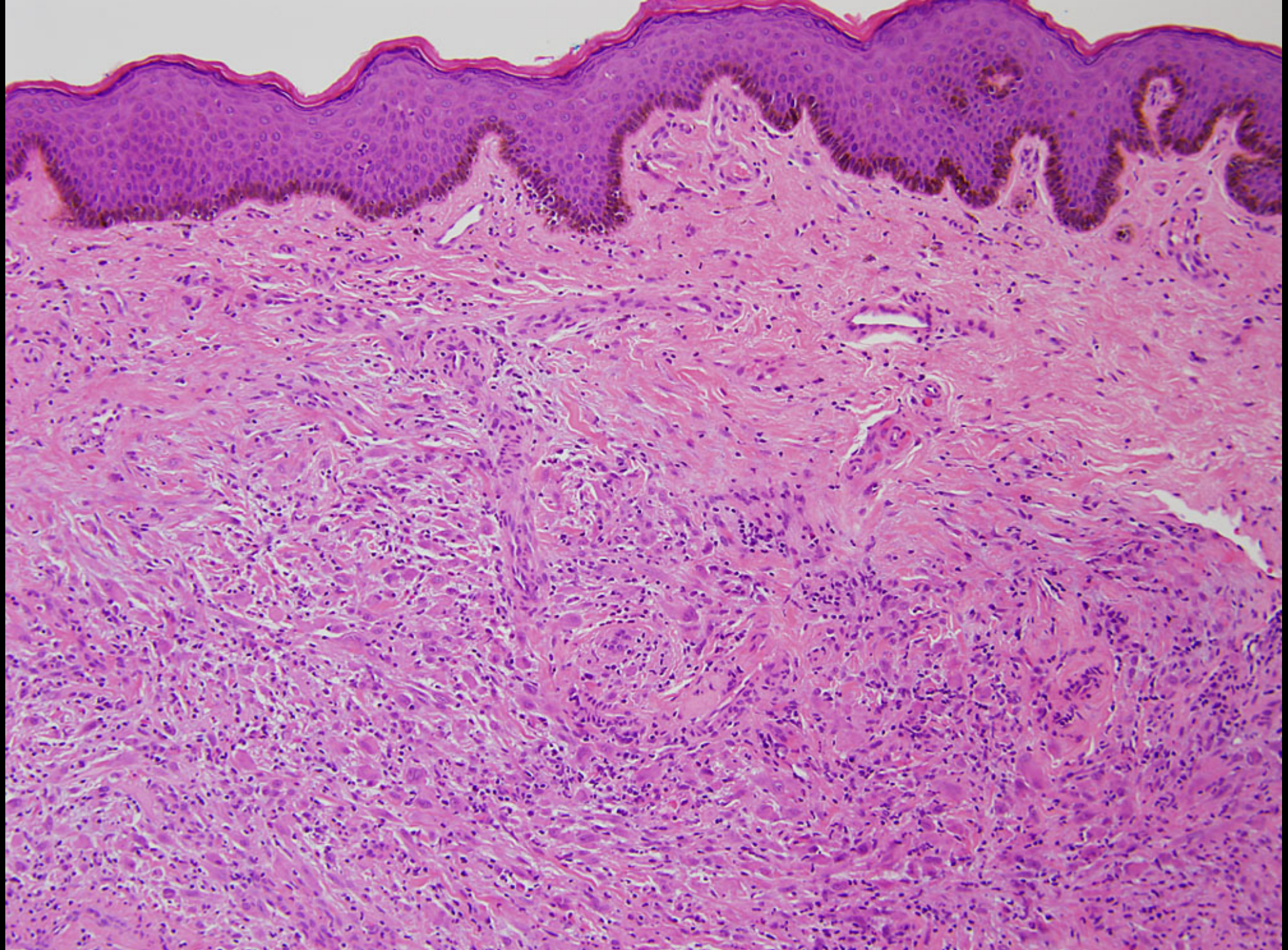
Multiple nodules – usually < 3 cm

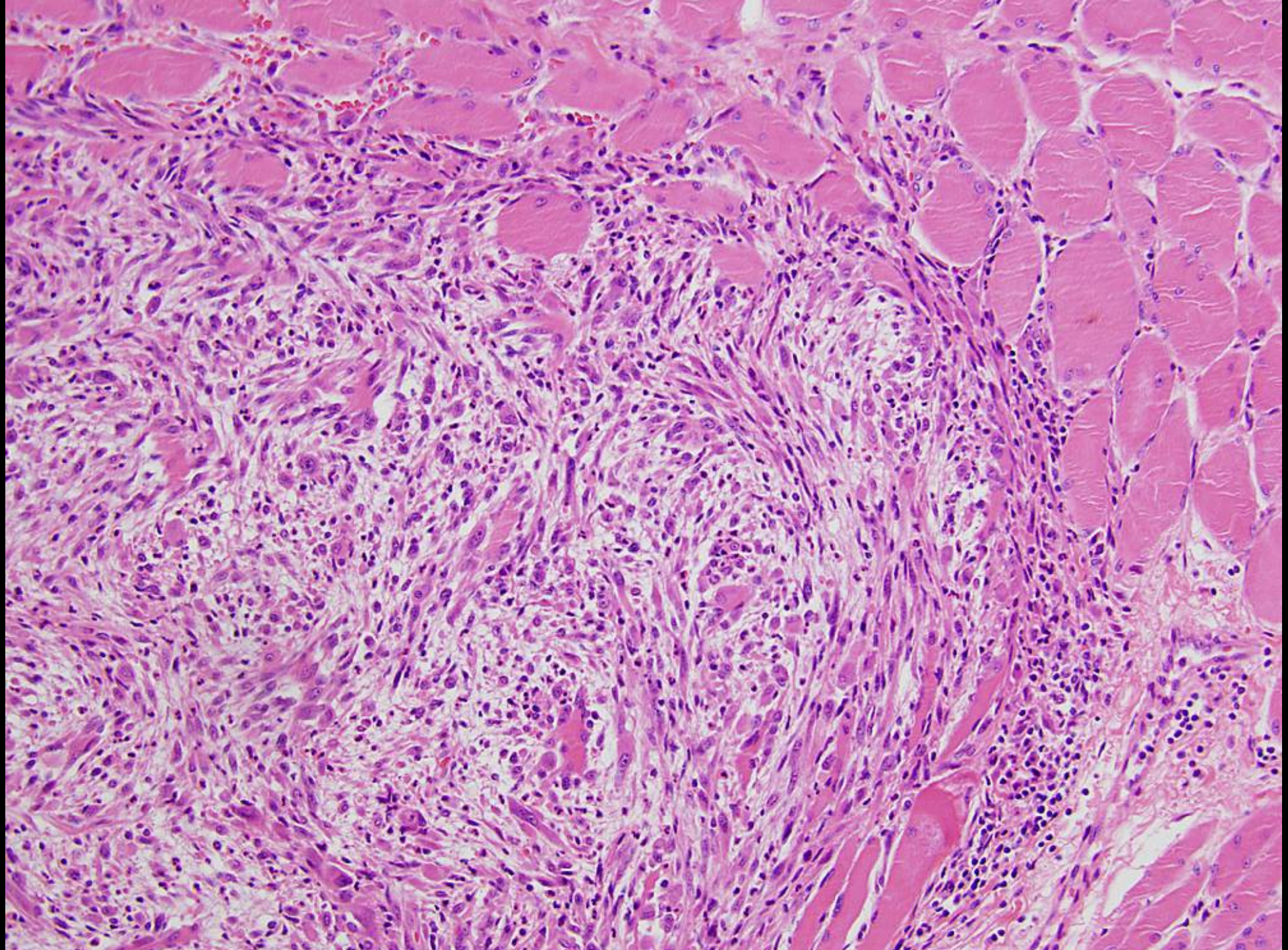
Multiple planes – skin > subcutis > muscle > bone

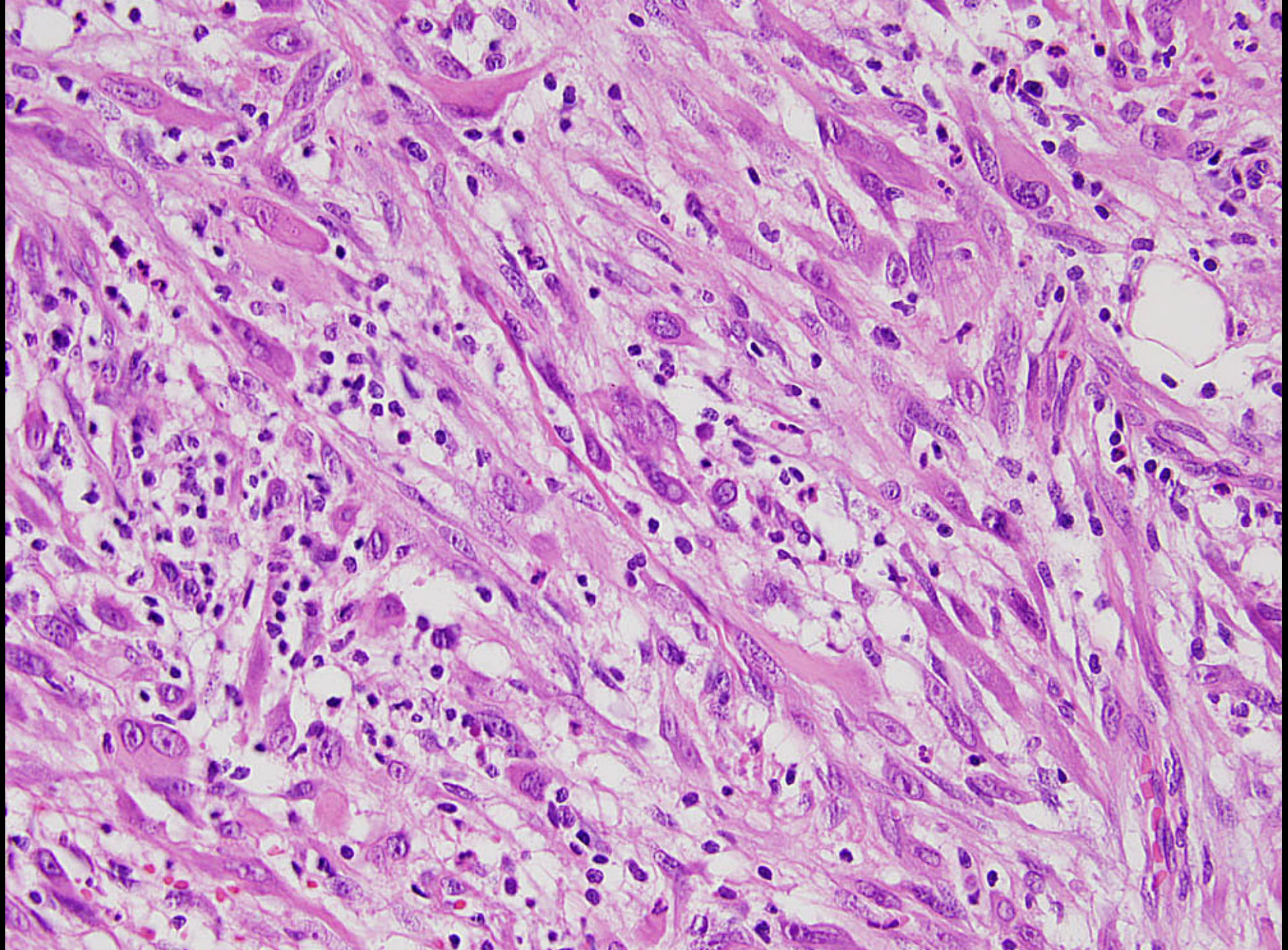
Often painful

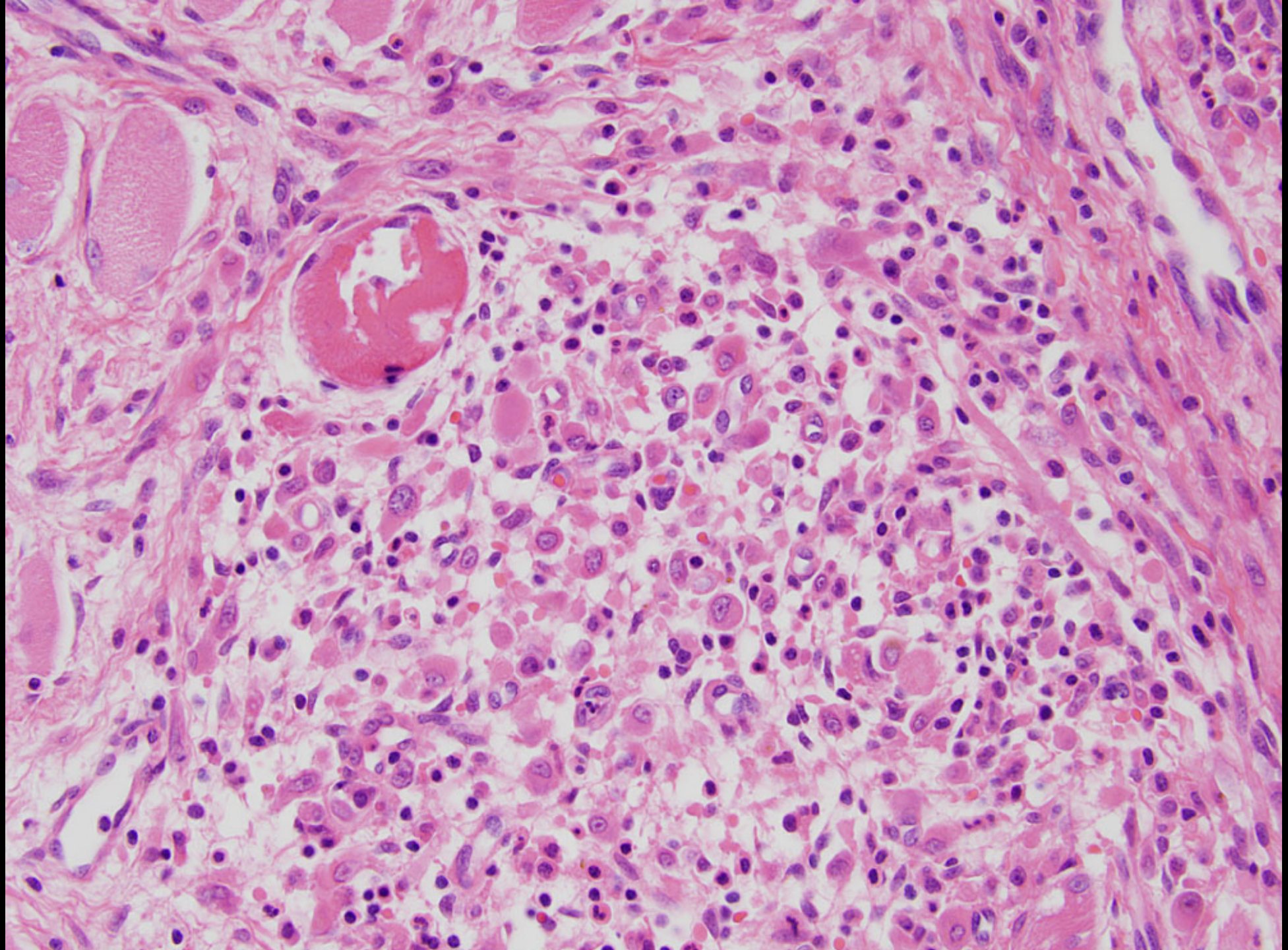
Metastasis infrequent - ? Indolent / delayed

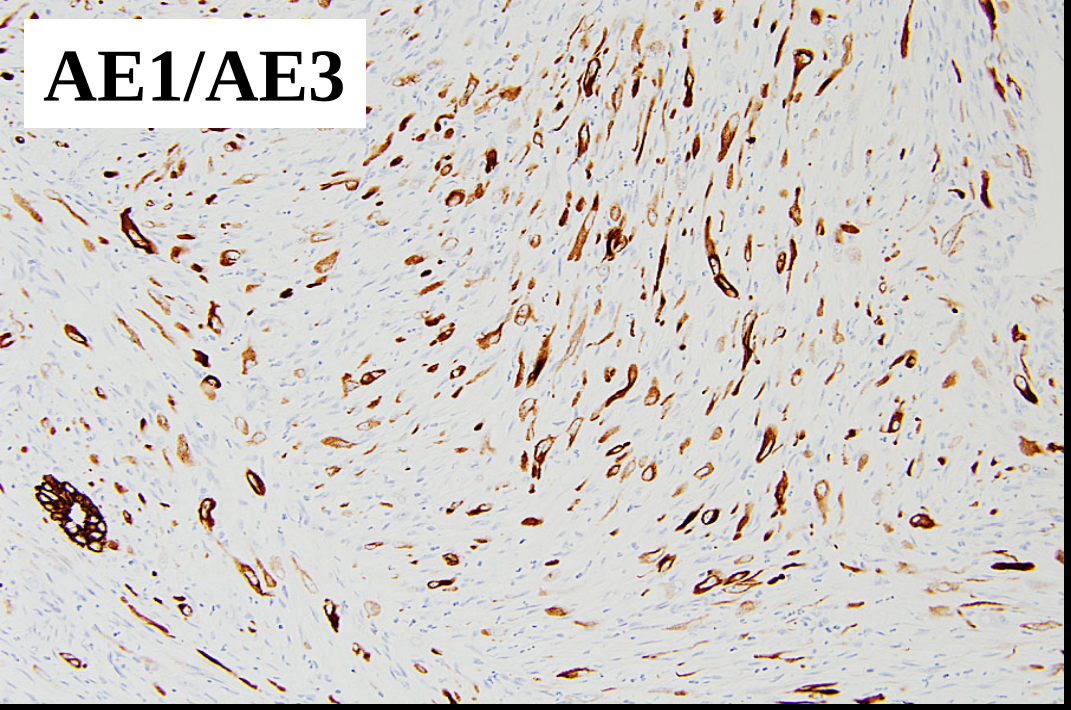


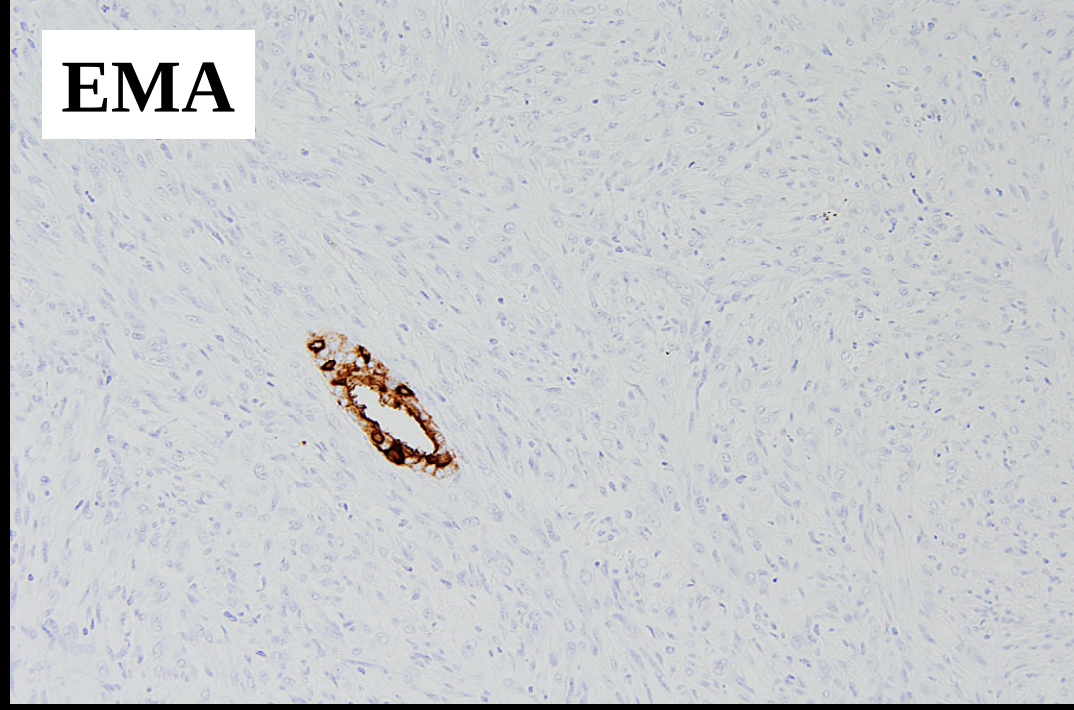









AE1/AE3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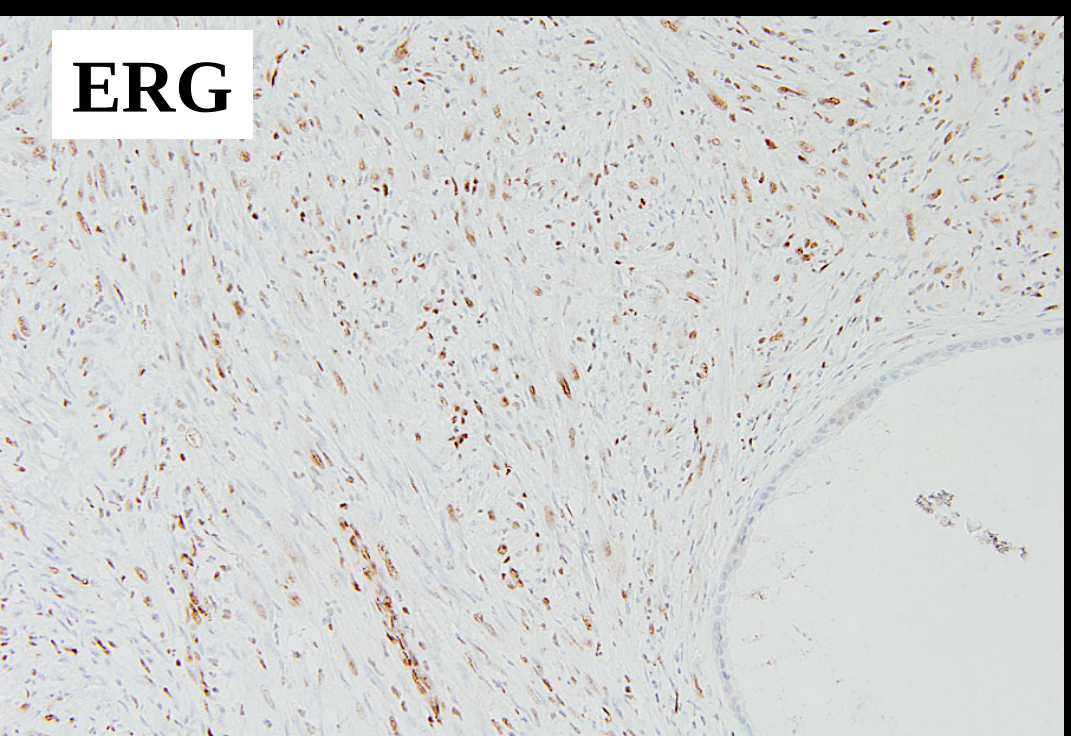
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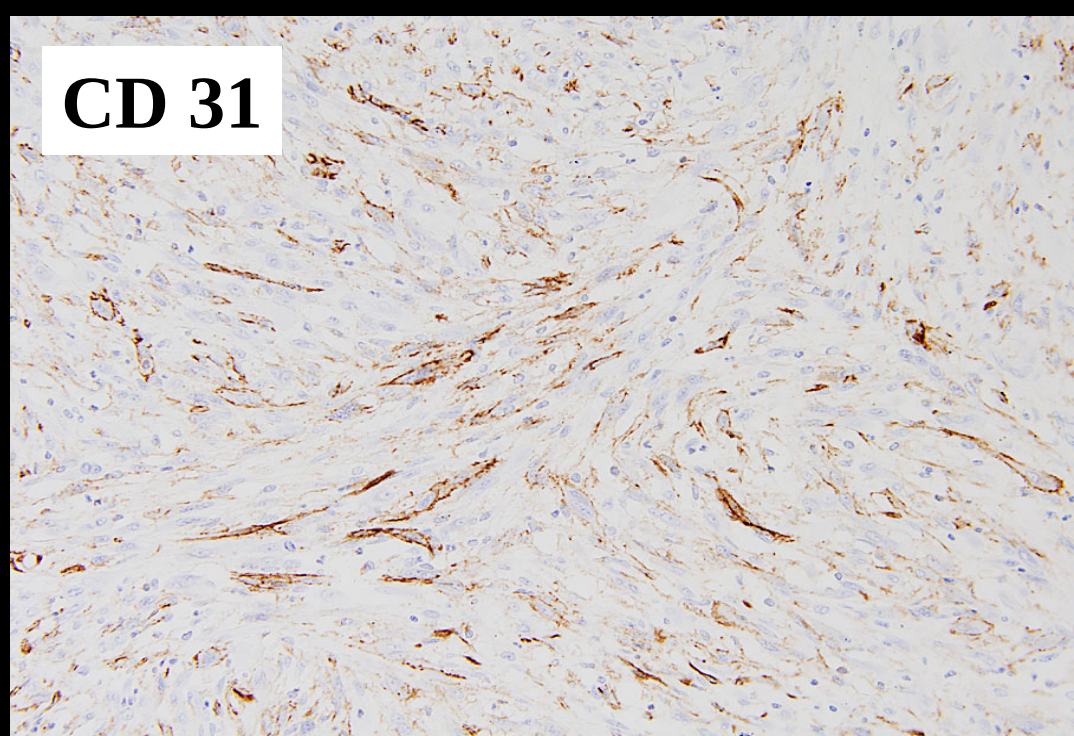

CD 31

World Health Organization (2013)
Classification of Tumours of Soft Tissue

CHONDRO-OSSEOUS TUMOURS

Soft tissue chondroma

Extraskeletal mesenchymal chondrosarcoma

Extraskeletal osteosarcoma

World Health Organization (2013)
Classification of Tumours of Soft Tissue

GASTROINTESTINAL STROMAL TUMOURS

GIST, benign

GIST, uncertain malignant potential

GIST, malignant

PROPOSED GUIDELINES FOR DEFINING RISK OF AGGRESSIVE BEHAVIOUR IN GISTs (NCI 2002)

	Size	Mitotic Count
Very low risk	< 2 cm	< 5 per 50 HPF
Low risk	2-5 cm	≤ 5 per 50 HPF
Intermediate risk	≤ 5 cm	6-10 per 50 HPF
	5-10 cm	≤ 5 per 50 HPF
High risk	> 5 cm	> 5 per 50 HPF
	> 10 cm	Any mitotic rate
	> Any size	> 10 per 50 HPF

Table 1 Risk Stratification of Primary GIST by Mitotic Index, Size, and Site

Tumor Parameters		Risk for Progressive Disease*(%), Based on Site of Origin			
Mitotic Rate	Size	Stomach	Jejunum/Ileum	Duodenum	Rectum
≤ 5 per 50 HPF	≤ 2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	> 2, ≤ 5 cm	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
	> 5, ≤ 10 cm	Low (3.6%)	Moderate (24%)	Insufficient data	Insufficient data
	> 10 cm	Moderate (10%)	High (52%)	High (34%)	High (57%)
> 5 per 50 HPF	≤ 2 cm	None†	High†	Insufficient data	High (54%)
	> 2, ≤ 5 cm	Moderate (16%)	High (73%)	High (50%)	High (52%)
	> 5, ≤ 10 cm	High (55%)	High (85%)	Insufficient data	Insufficient data
	> 10 cm	High (86%)	High (90%)	High (86%)	High (71%)

Data are based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs.
Abbreviations: GIST, gastrointestinal stromal tumor; HPF, high-power field.
*Defined as metastasis or tumor-related death.
†Denotes small numbers of cases.
Adapted from Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Sem Diagn Pathol 2006;23:70–83.

Zoom out (Ctrl+Minus)

Table 10.1 Prognosis for patients with g[illegible]omal tumours (GIST), based on long-term follow-up

Tumour parameters			Progressive disease during follow-up (% of patients)[a]	
Prognostic group	Size	Mitotic rate per 50 HPFs	Gastric GISTs	Small-intestinal GISTs
1	≤ 2	≤ 5	0	0
2	> 2 ≤ 5	≤ 5	1.9	4.3
3a	> 5 ≤ 10	≤ 5	3.6	24
3b	> 10	≤ 5	12	52
4	≤ 2	> 5	0[b]	50[b]
5	> 2 ≤ 5	> 5	16	73
6a	> 5 ≤ 10	> 5	55	85
6b	> 10	> 5	86	90

HPF, high-power field

[a] Based on observation of 1784 patients in studies carried out by the Armed Force Institute of Pathology (AFIP). Intestinal GISTs generally follow the behaviour of small-intestinal GISTs.

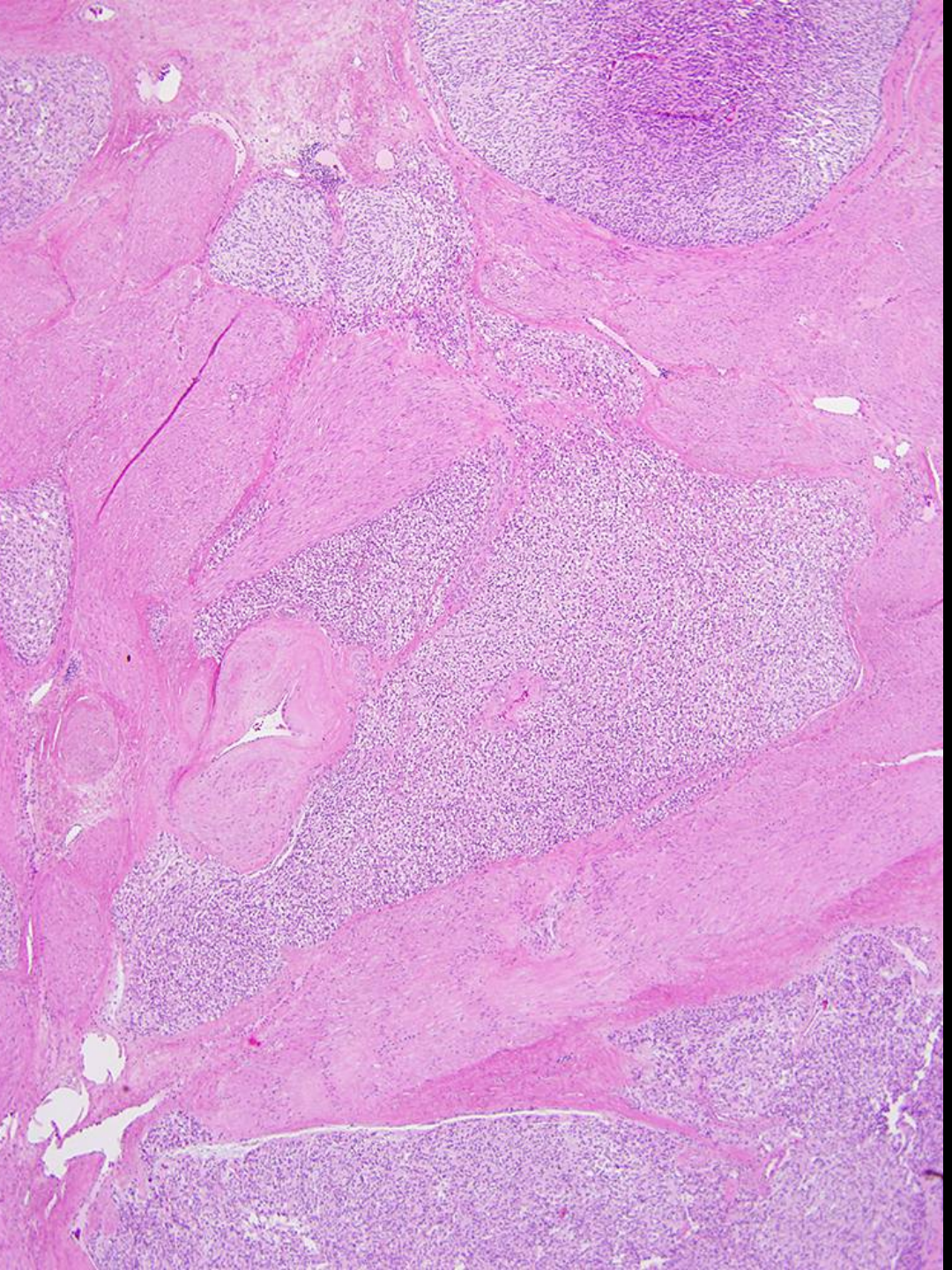
[b] Denotes tumour categories with very small numbers of cases. Data based on reference {1885}

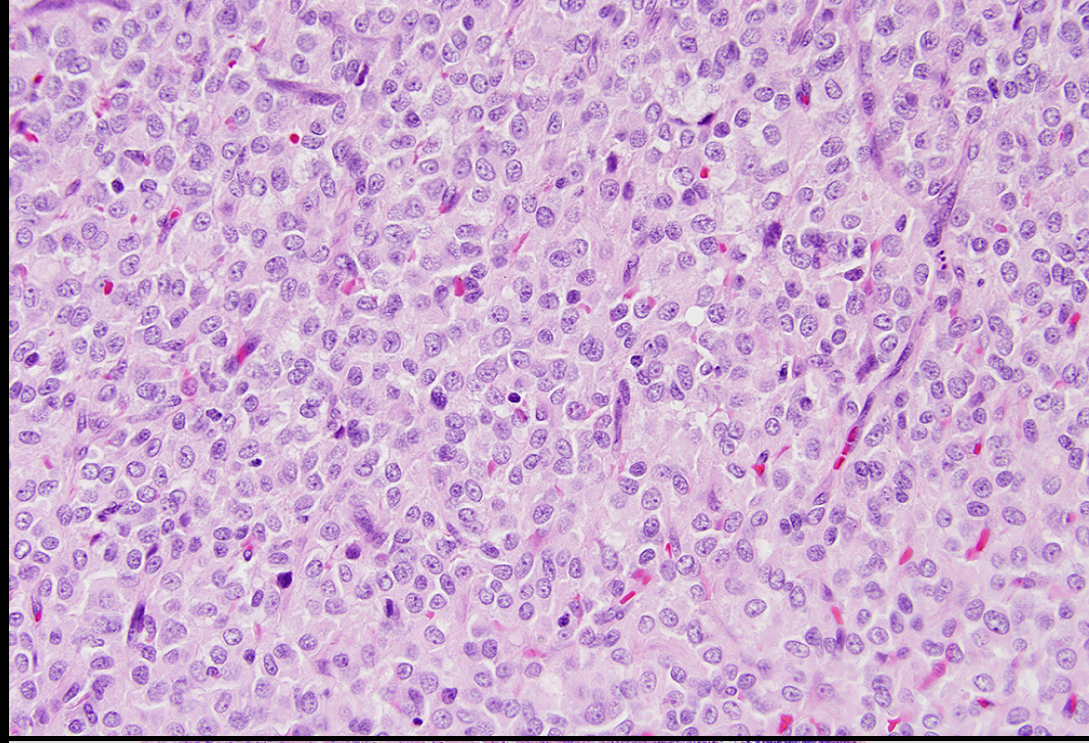
WHO 2013

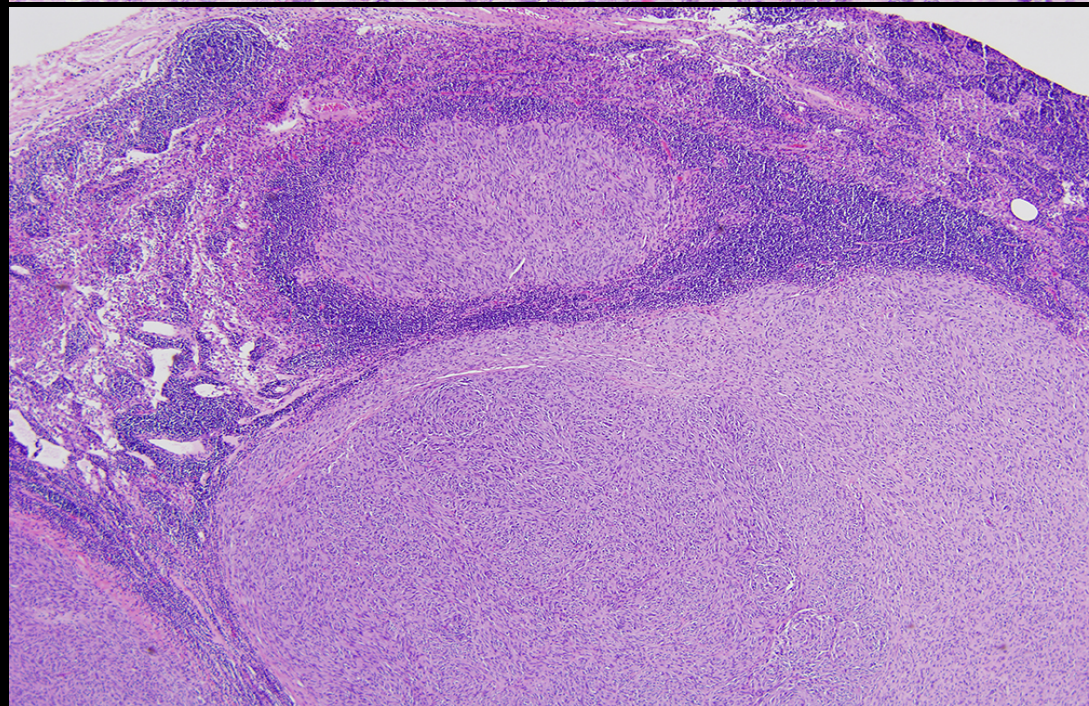
SDH-DEFICIENT GISTS

KEY POINTS REGARDING A NEW GROUP

- **Approx. 5-7% of gastric GISTs**
- **Wild-type *KIT* and *PDGFRA***
- **Distinct subsets of GIST – pediatric-type, Carney-Stratakis syndrome, Carney triad**
- **Epithelioid, multinodular, show LVI**
- **Frequent nodal mets – but v. indolent**
- **All SDHB-neg by IHC – but few mutations**
- **25% also SDHA-neg – predicts mutation**







World Health Organization (2013) Classification of Tumours of Soft Tissue

NERVE SHEATH TUMOURS

Benign (1)

Schwannoma (including variants)

Melanotic schwannoma

Neurofibroma (including variants)

Plexiform neurofibroma

Perineurioma

Granular cell tumour

World Health Organization (2013) Classification of Tumours of Soft Tissue

NERVE SHEATH TUMOURS

Benign (2)

Dermal nerve sheath myxoma

Solitary circumscribed neuroma

Ectopic meningioma

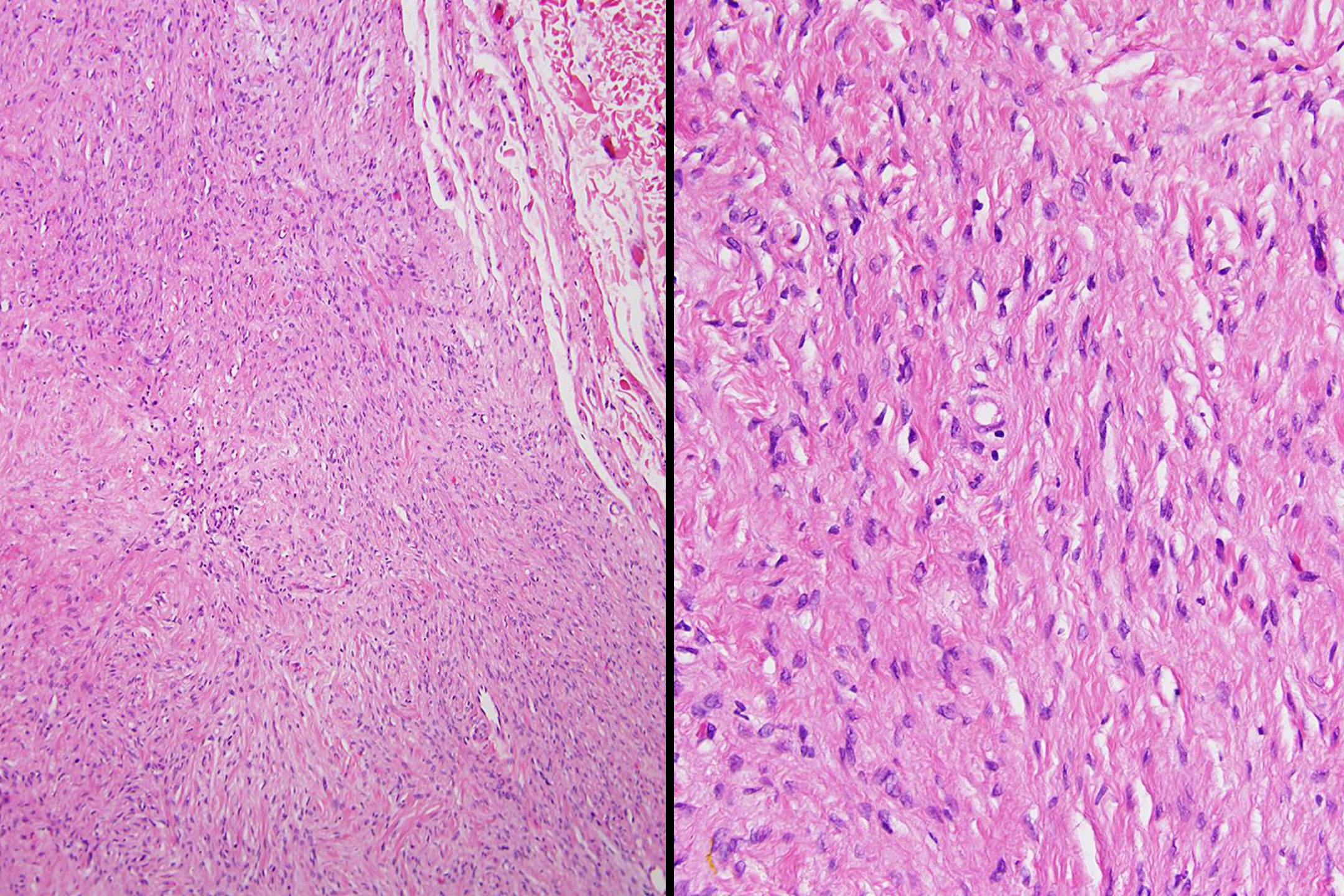
Nasal glial heterotopia

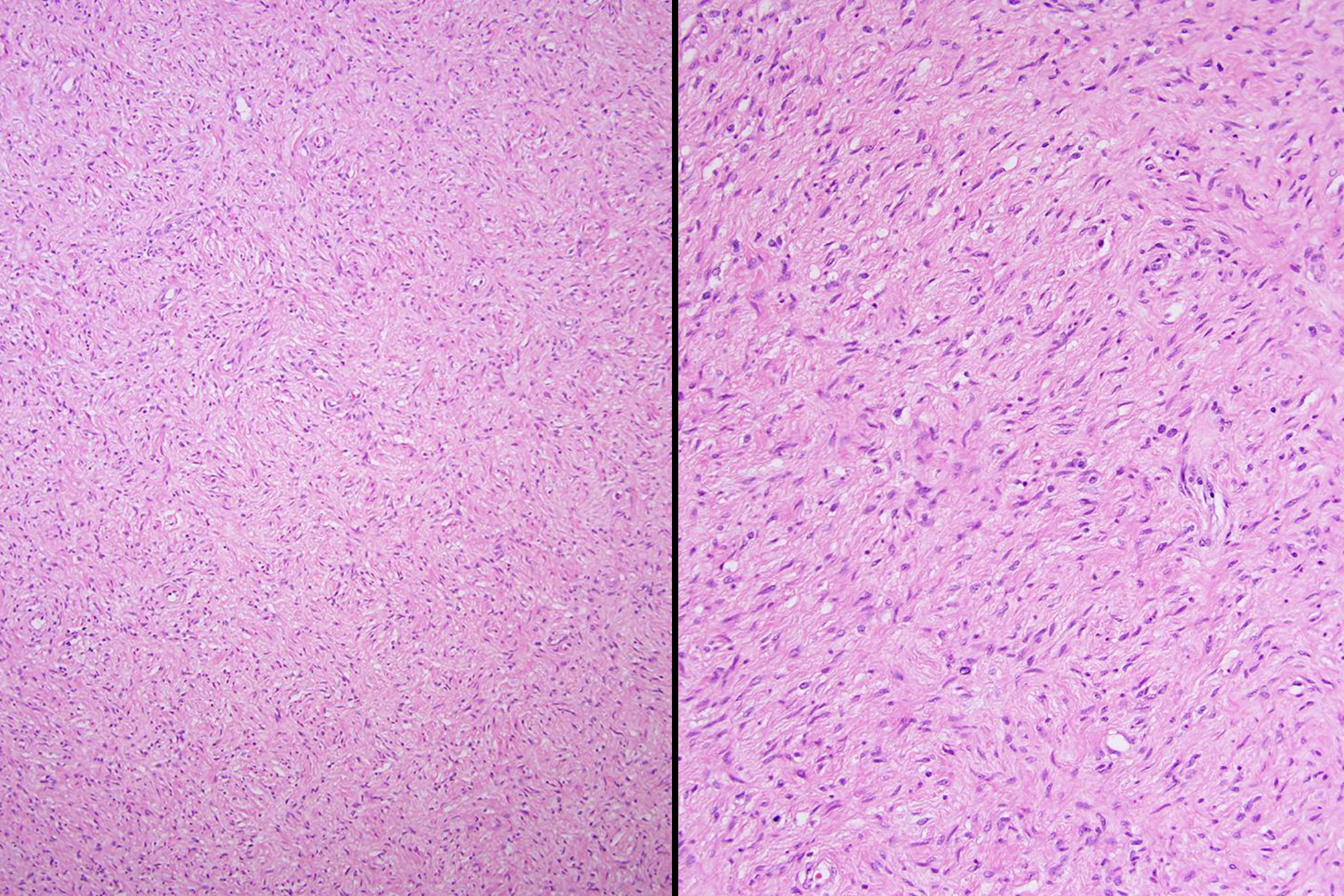
Benign Triton tumour

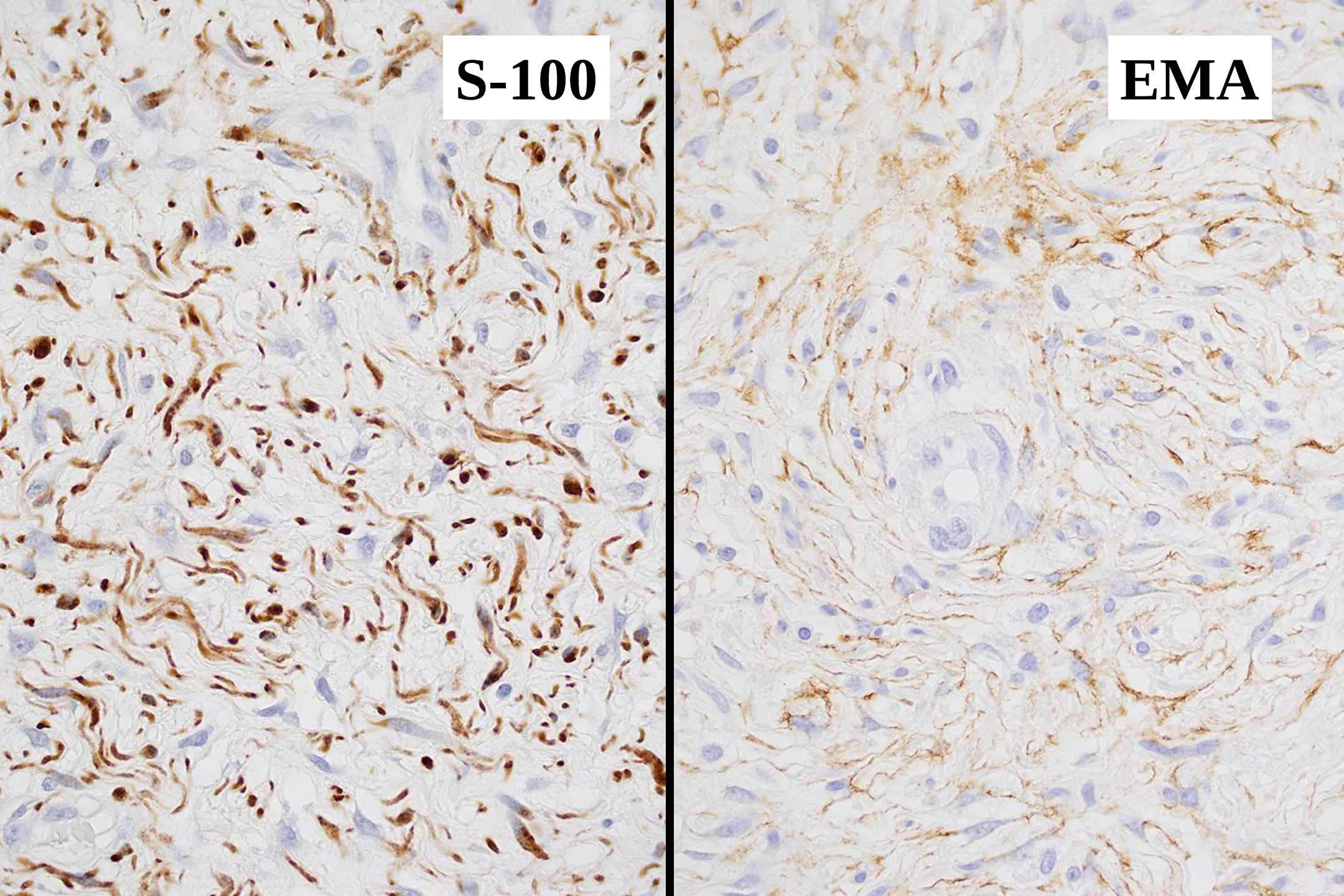
Hybrid nerve sheath tumours

HYBRID NERVE SHEATH TUMOURS

Hybrid schwannoma / perineurioma
Hybrid neurofibroma / schwannoma
Hybrid granular cell tumour / perineurioma
Hybrid neurofibroma / perineurioma (?)



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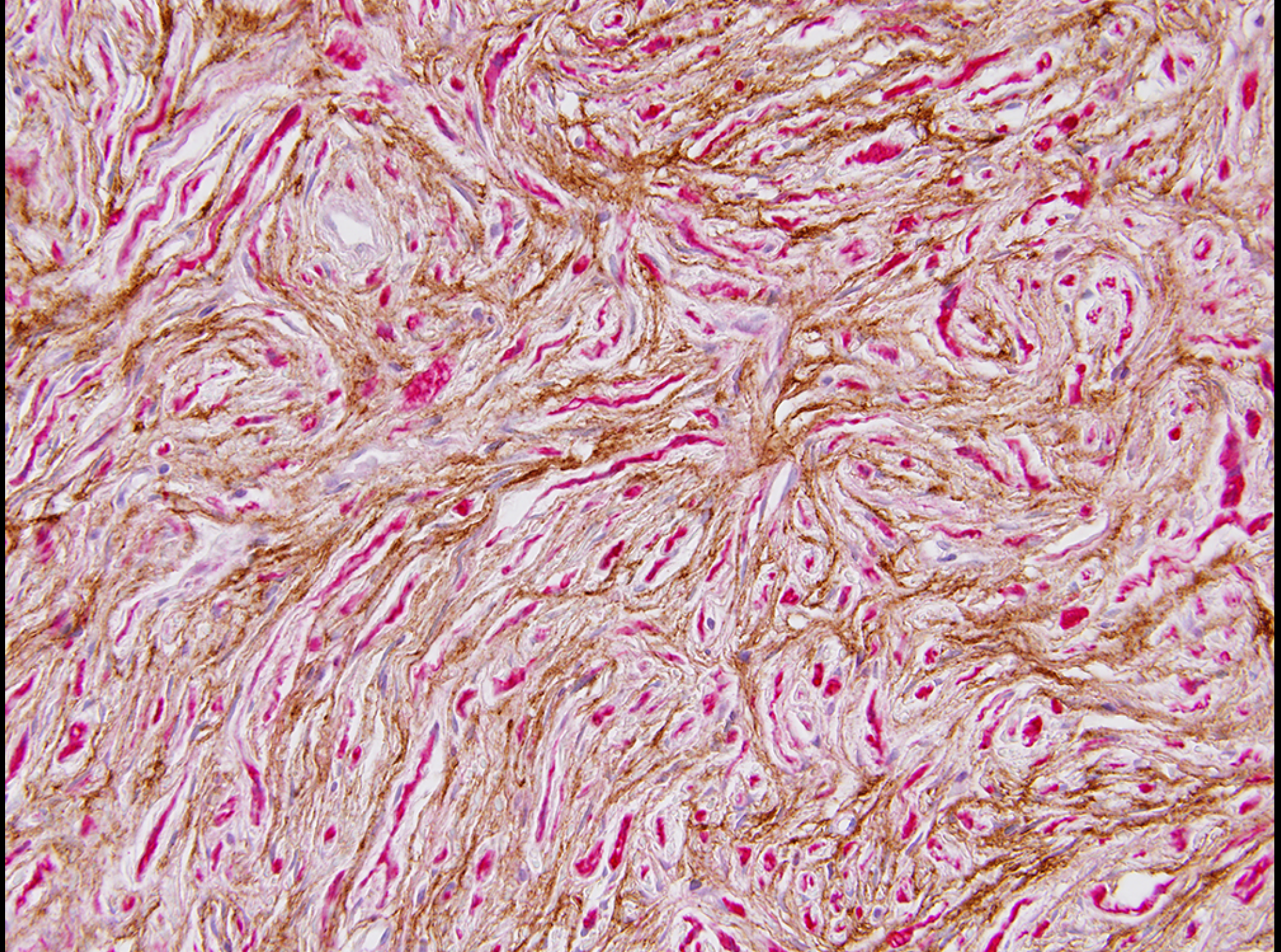
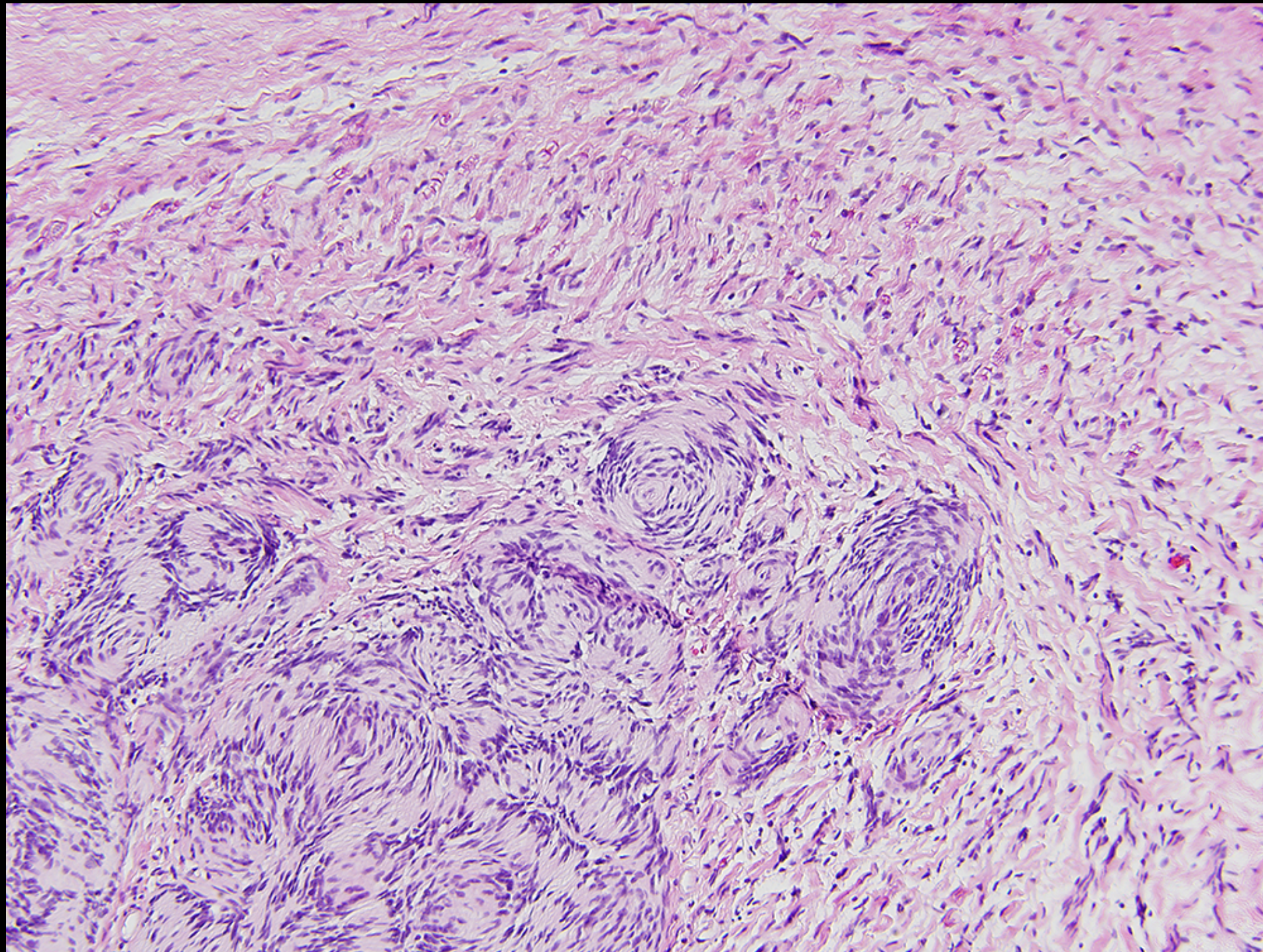




World Health Organization (2013) Classification of Tumours of Soft Tissue

NERVE SHEATH TUMOURS

Malignant

Malignant peripheral nerve sheath tumour

Epithelioid malignant peripheral nerve sheath tumour

Malignant Triton tumour

Malignant granular cell tumour

Ectomesenchymoma

World Health Organization (2013)
Classification of Tumours of Soft Tissue

TUMOURS OF UNCERTAIN DIFFERENTIATION

Benign

Acral fibromyxoma
Intramuscular myxoma
(incl. cellular variant)
Juxta-articular myxoma
Deep 'aggressive' angiomyxoma
Pleomorphic hyalinizing angiectatic tumour
Ectopic hamartomatous thymoma

ACRAL (DIGITAL) FIBROMYXOMA
CLINICAL FEATURES

Adults; M > F

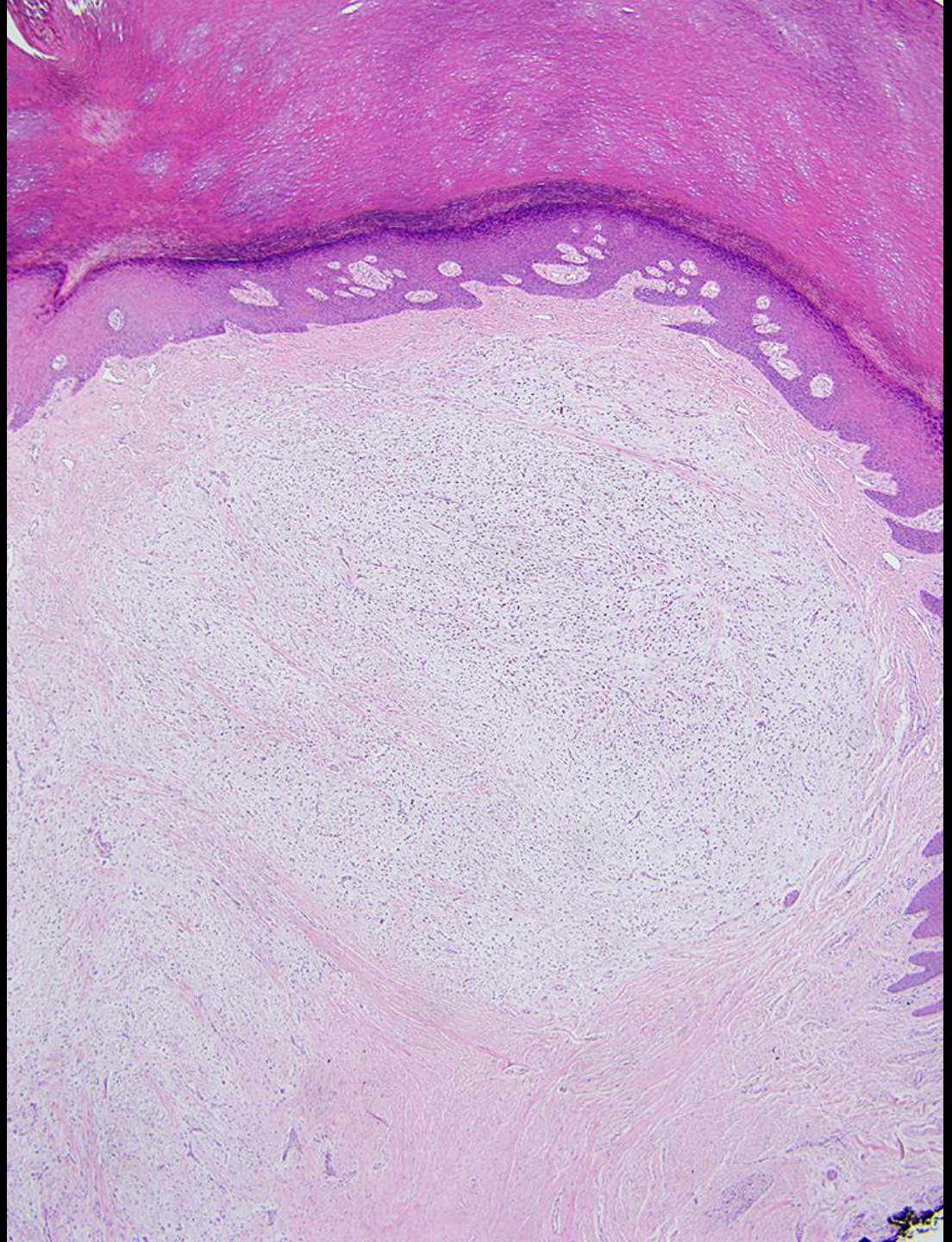
Toes / fingers ++

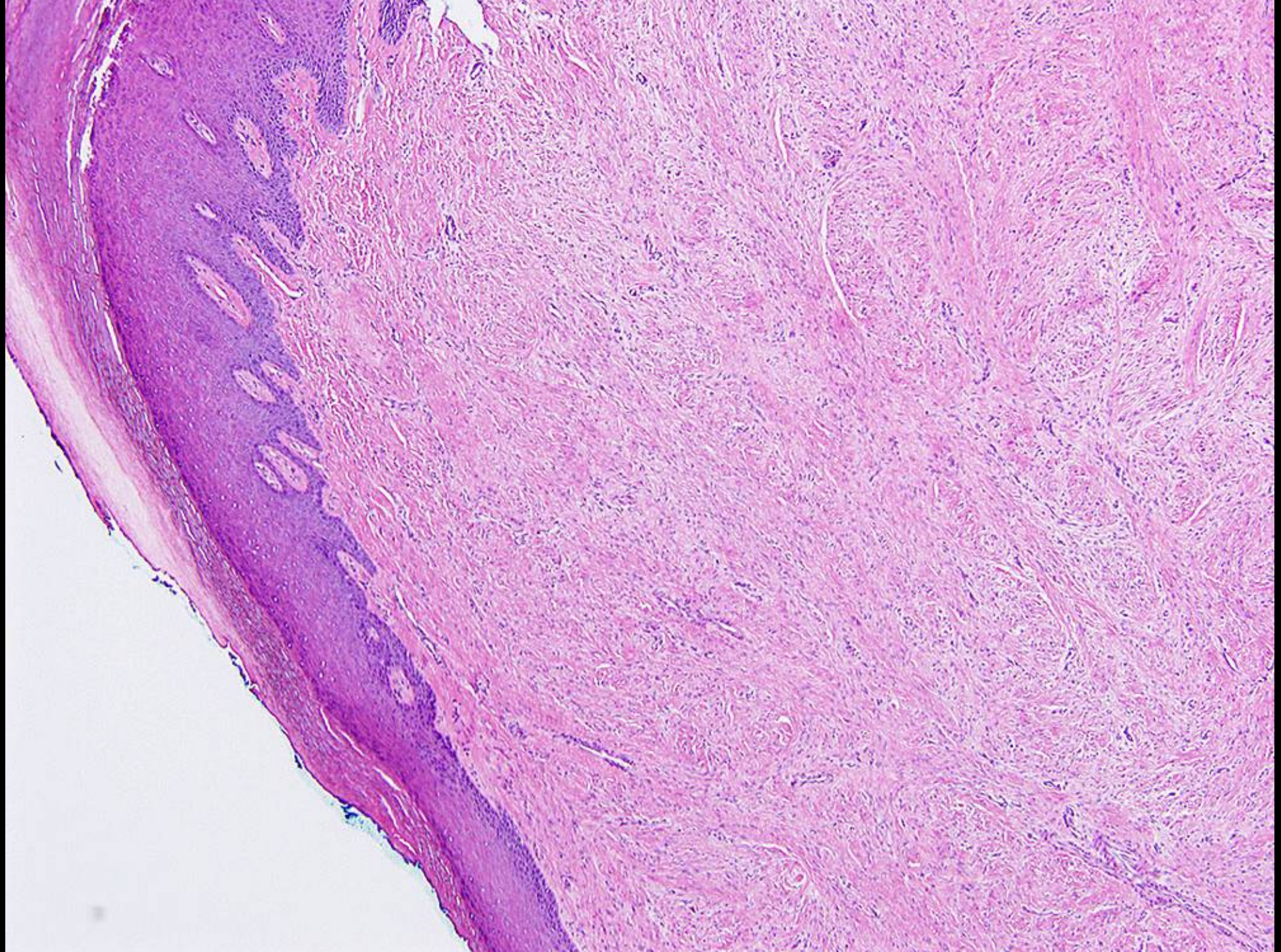
Often adjacent to nail bed

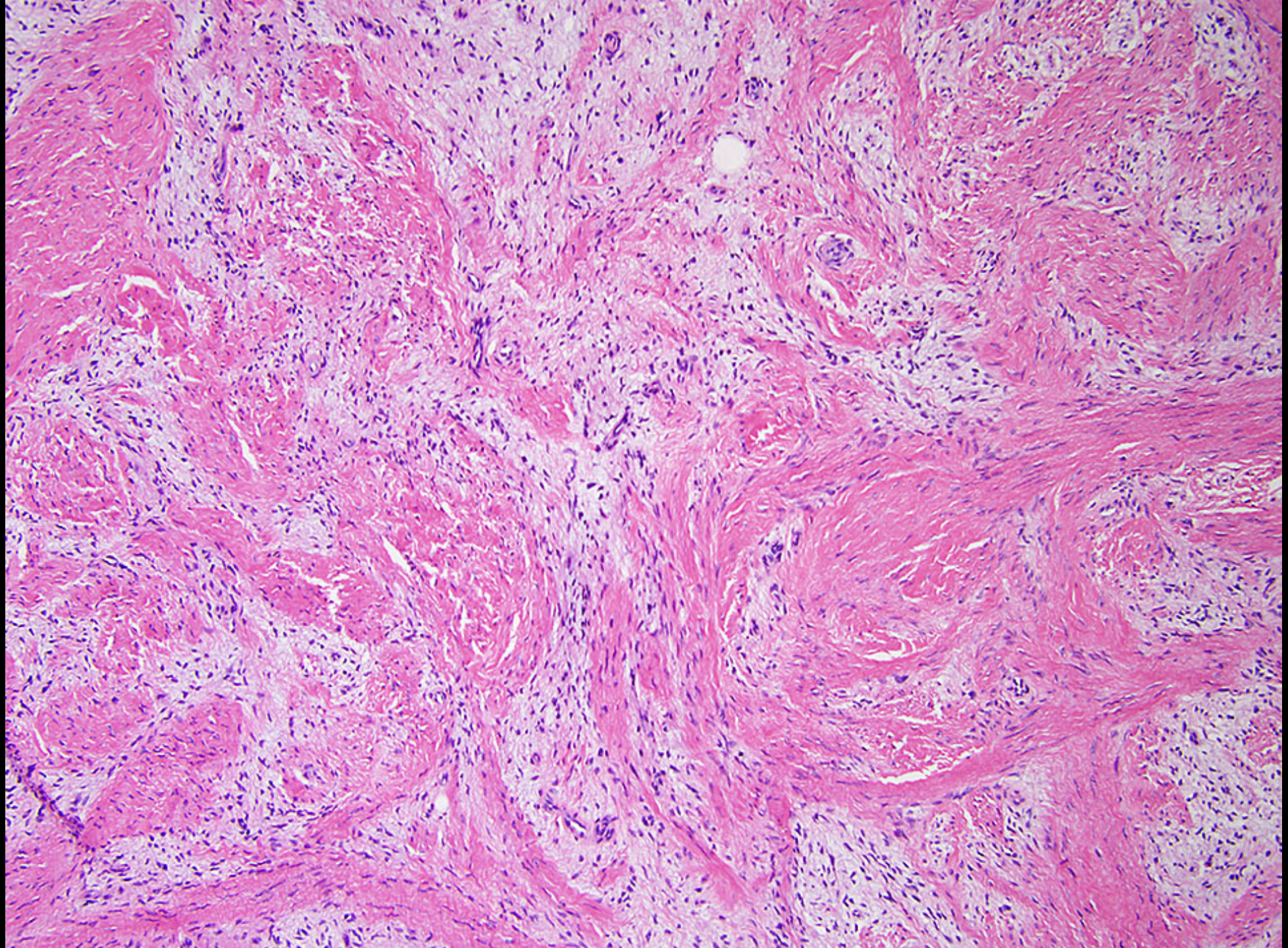
Dermal / subcutaneous nodule

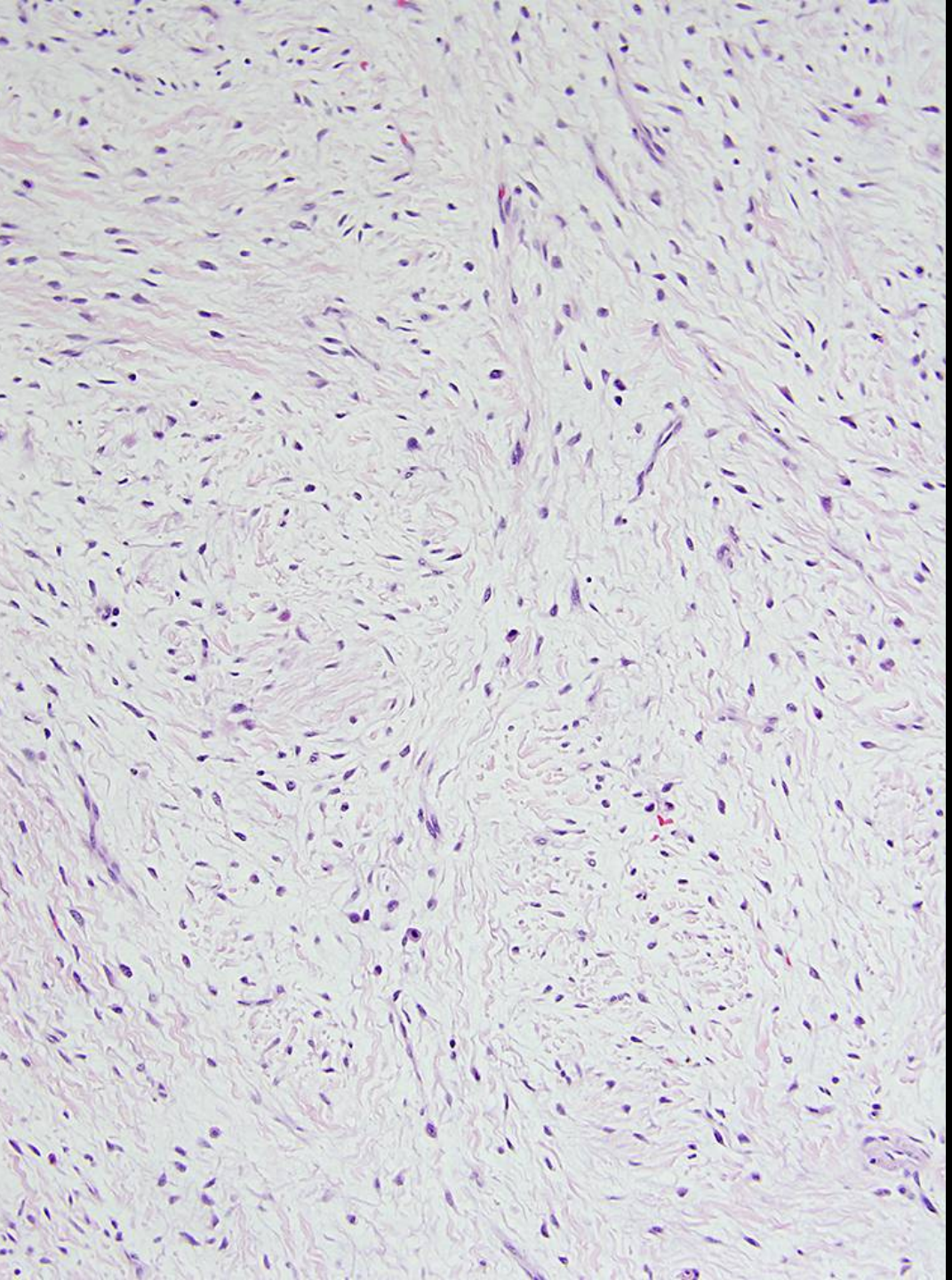
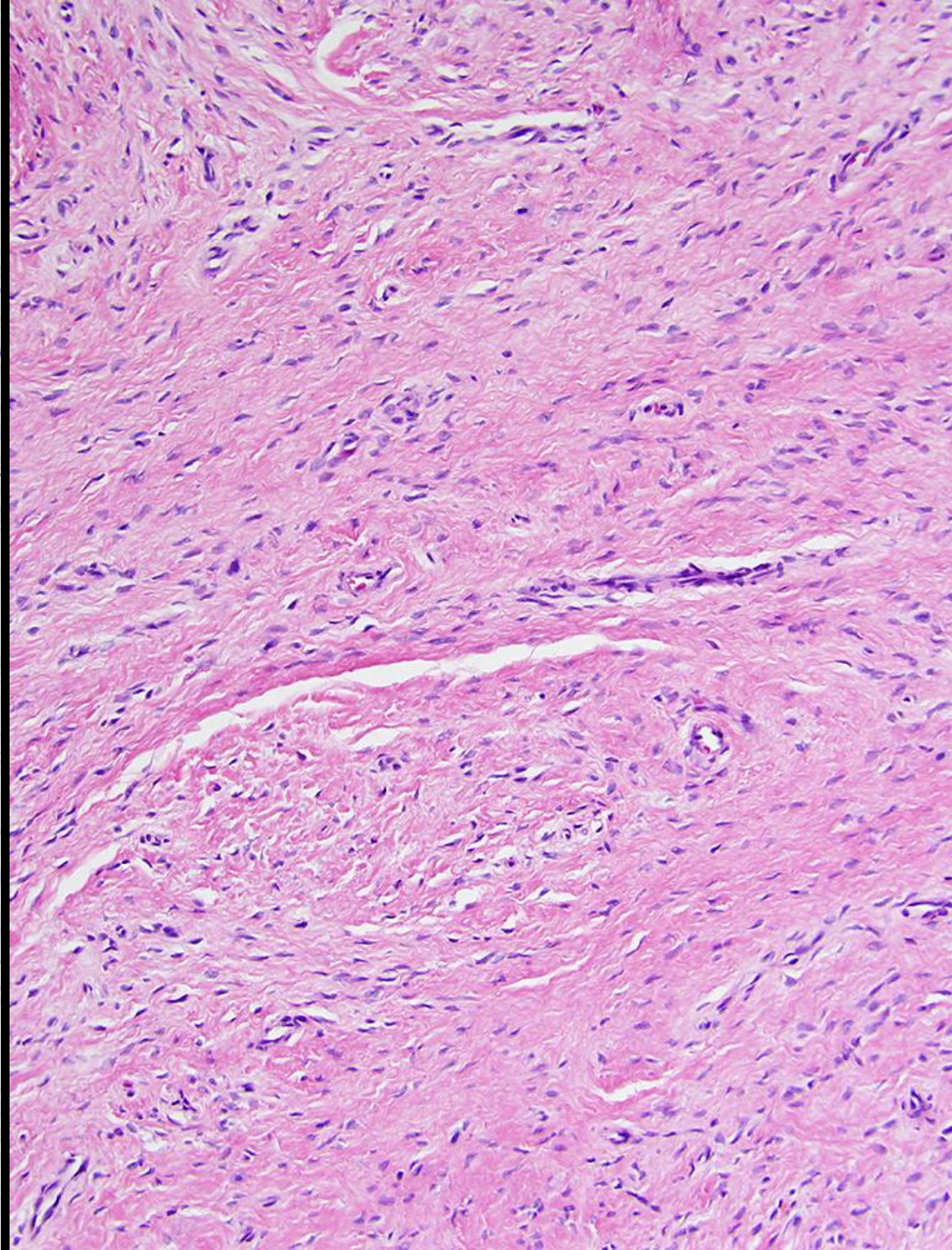
Most < 2 cm

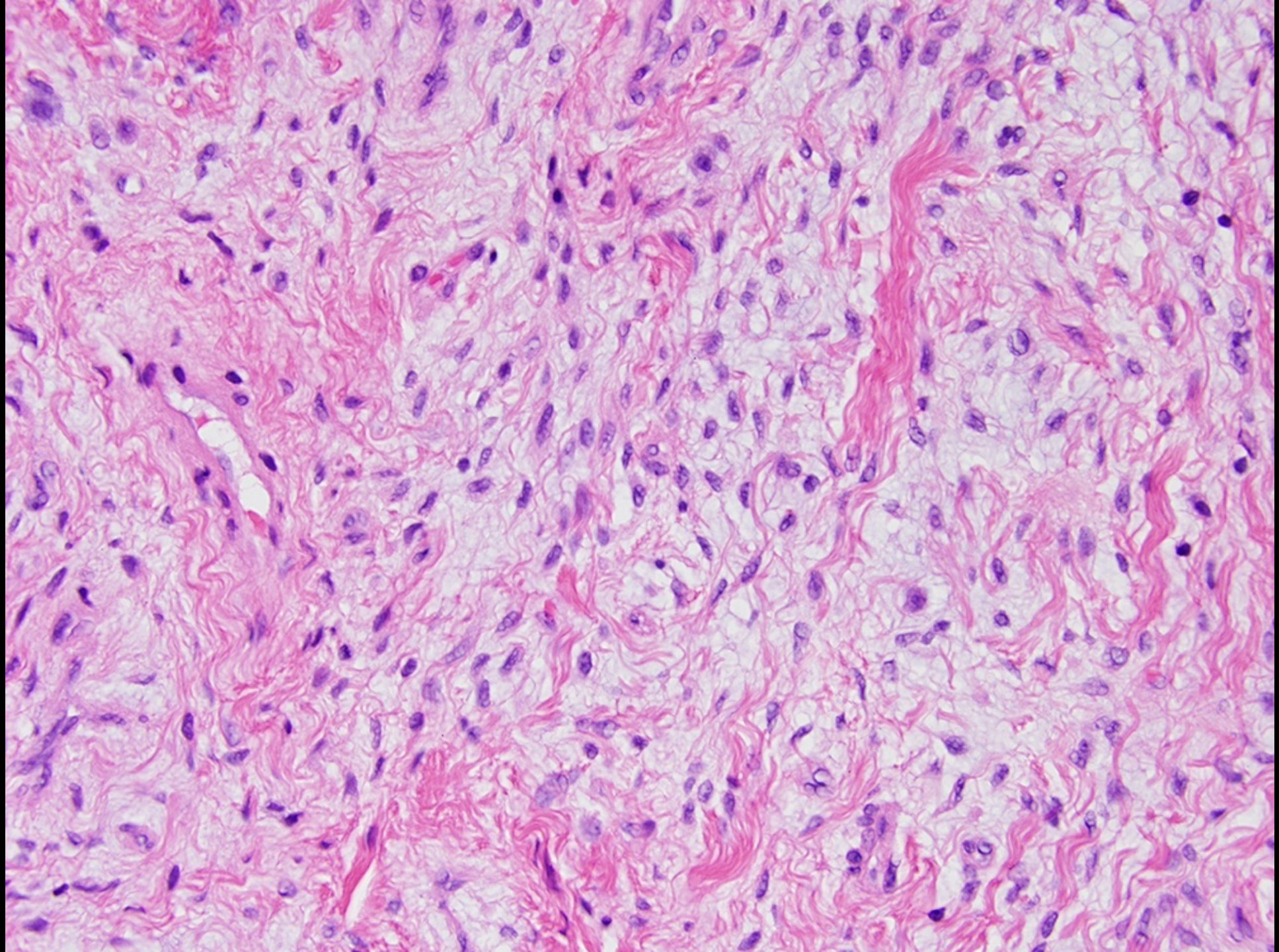
Local recurrence ~ 10%

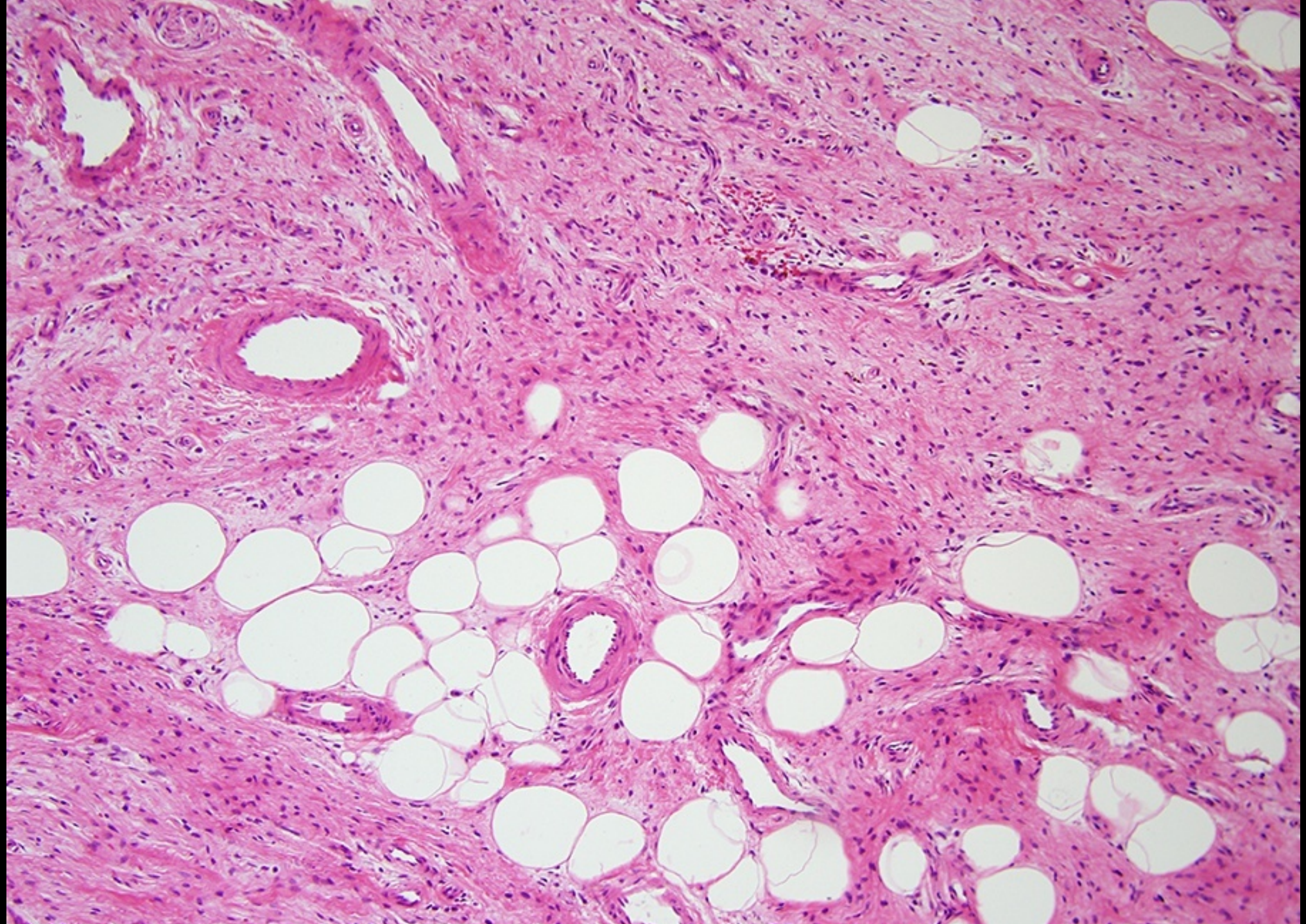


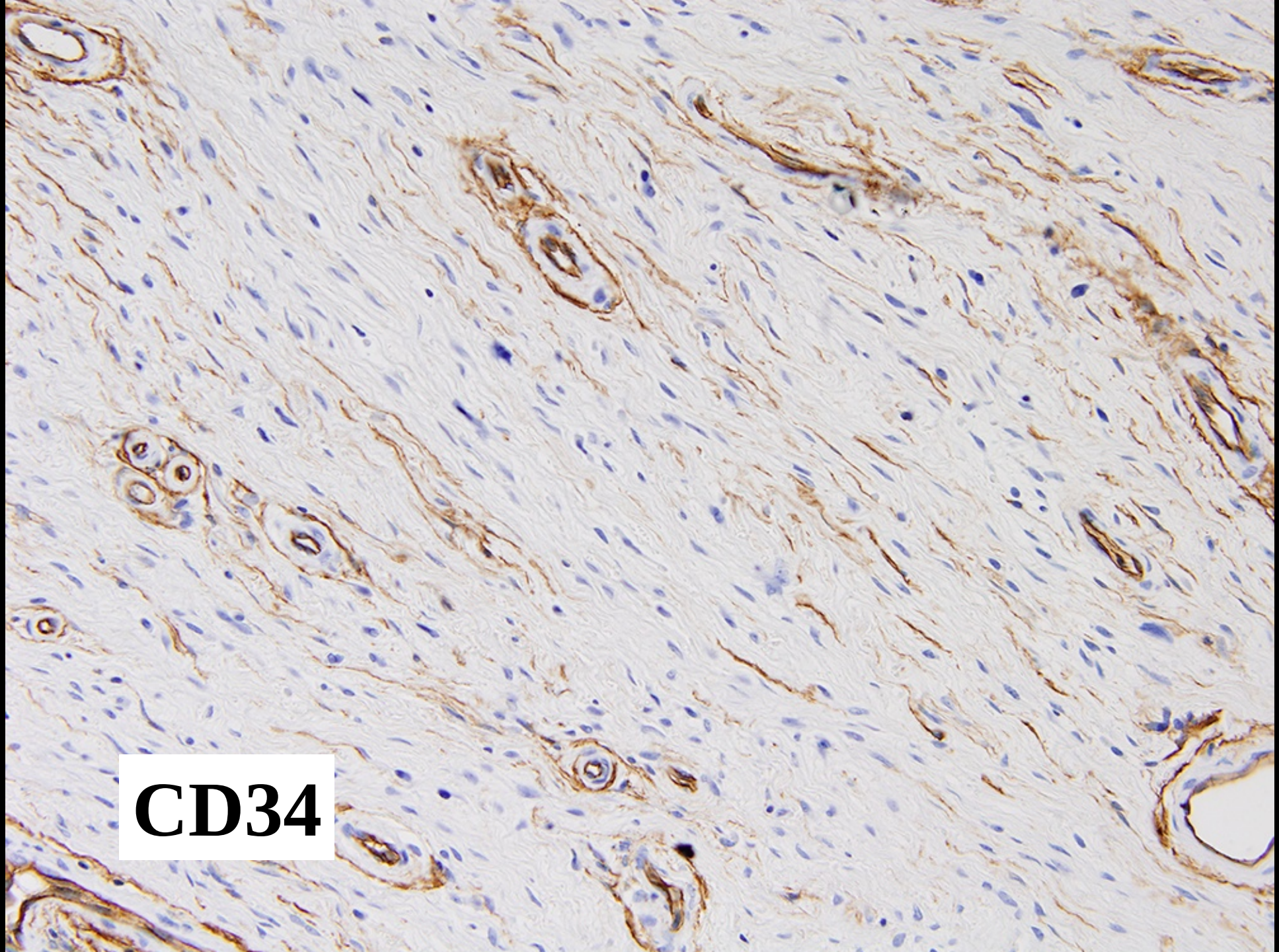









CD34

World Health Organization (2013)
Classification of Tumours of Soft Tissue

TUMOURS OF UNCERTAIN DIFFERENTIATION

Intermediate (locally aggressive)

Haemosiderotic fibrolipomatous tumour

Intermediate (rarely metastasising)

Atypical fibroxanthoma

Angiomatoid fibrous histiocytoma

Ossifying fibromyxoid tumour
(incl. atypical / malignant)

Mixed tumour / Myoepithelioma / Myoep. Carcinoma

Phosphaturic mesenchymal tumour

HAEMOSIDEROTIC FIBROLIPOMATOUS TUMOUR
(aka "haemosiderotic fibrohistiocytic lipomatous lesion")

CLINICAL FEATURES

Adults > children
Females slightly > males
Ankle / foot ++
Subcutaneous / poorly marginated
Usually < 5 cm

Local recurrence 30%
Possible potential to progress (?)

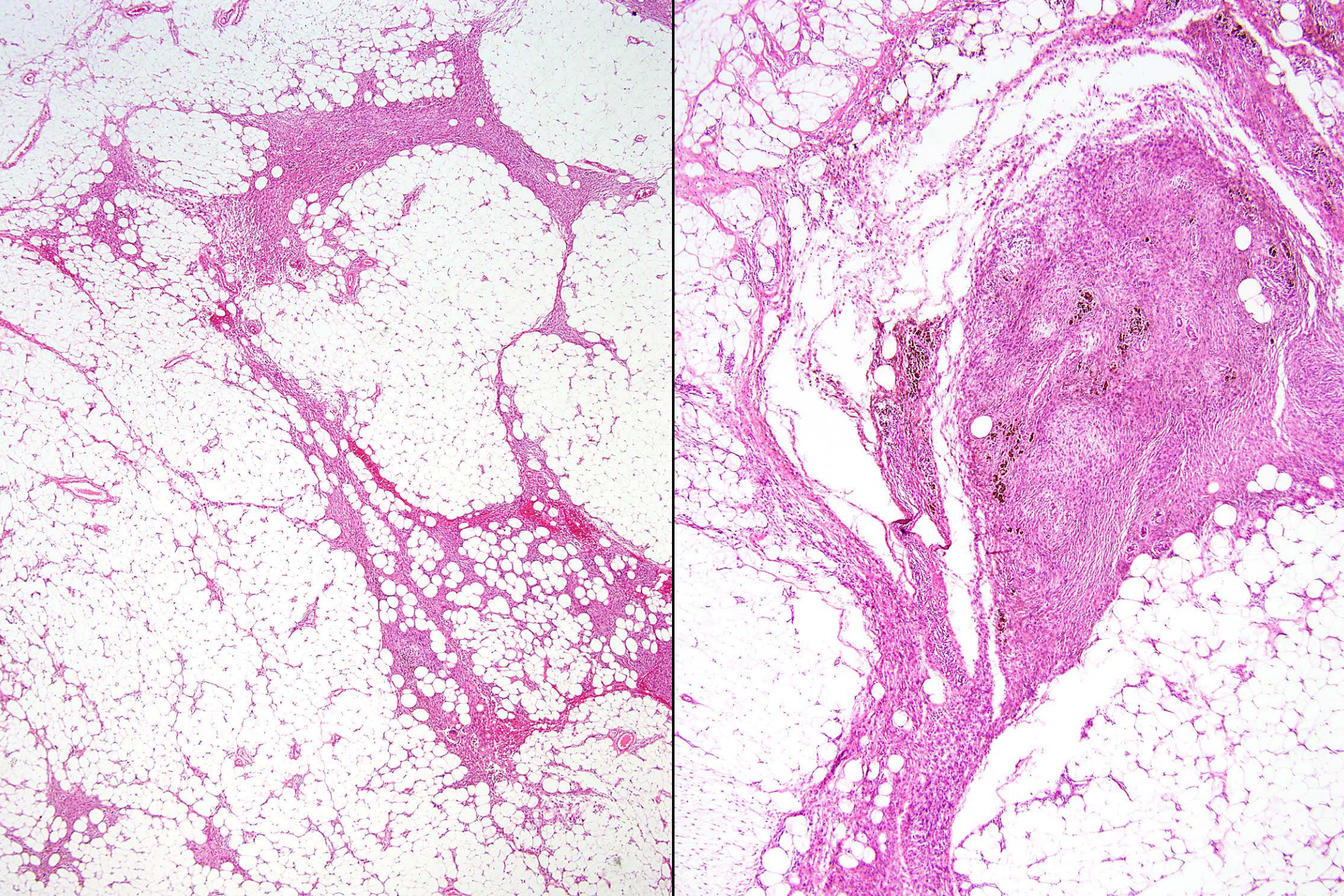
HAEMOSIDEROTIC FIBROLIPOMATOUS TUMOUR
(aka "haemosiderotic fibrohistiocytic lipomatous lesion")

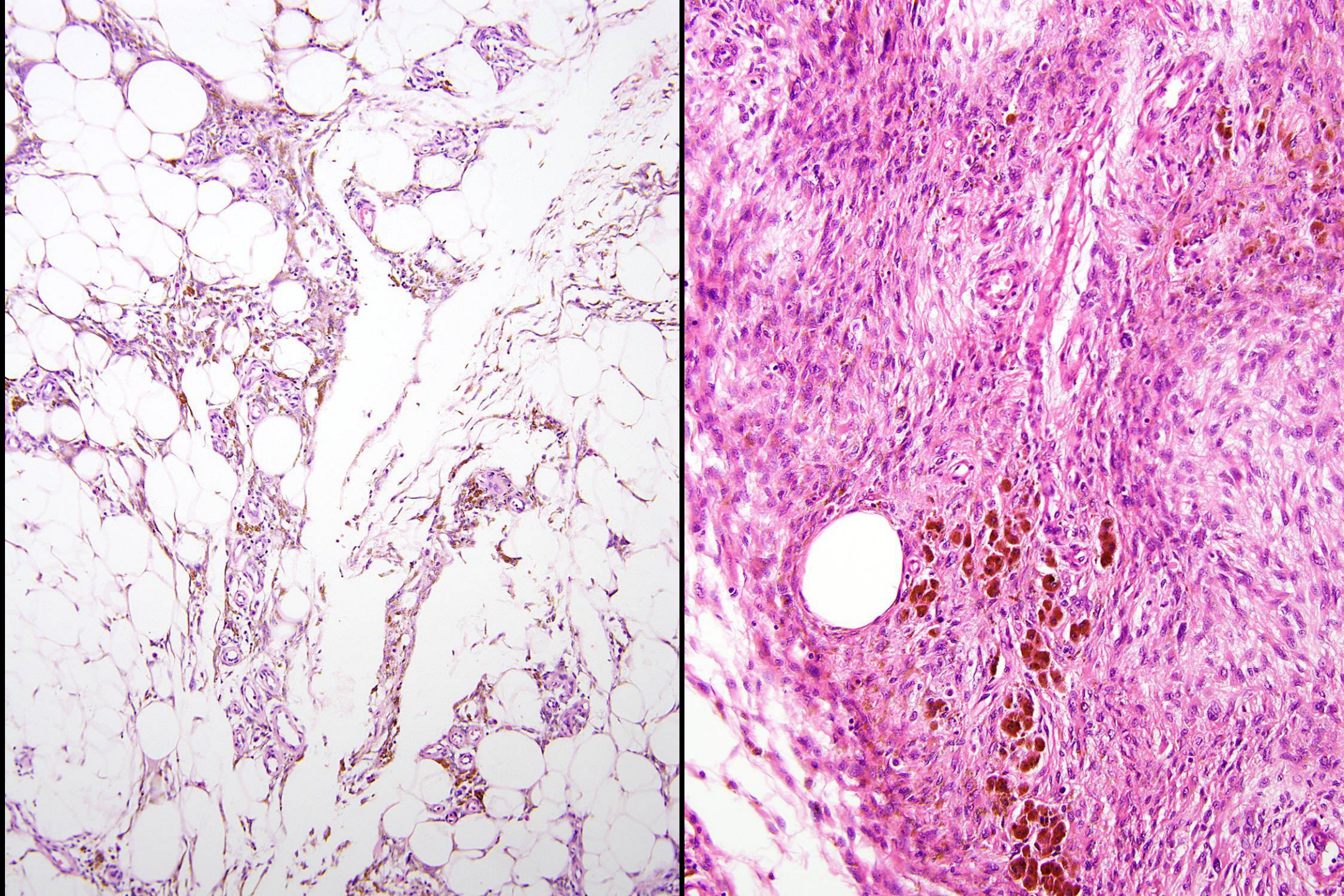
PATHOLOGIC FEATURES

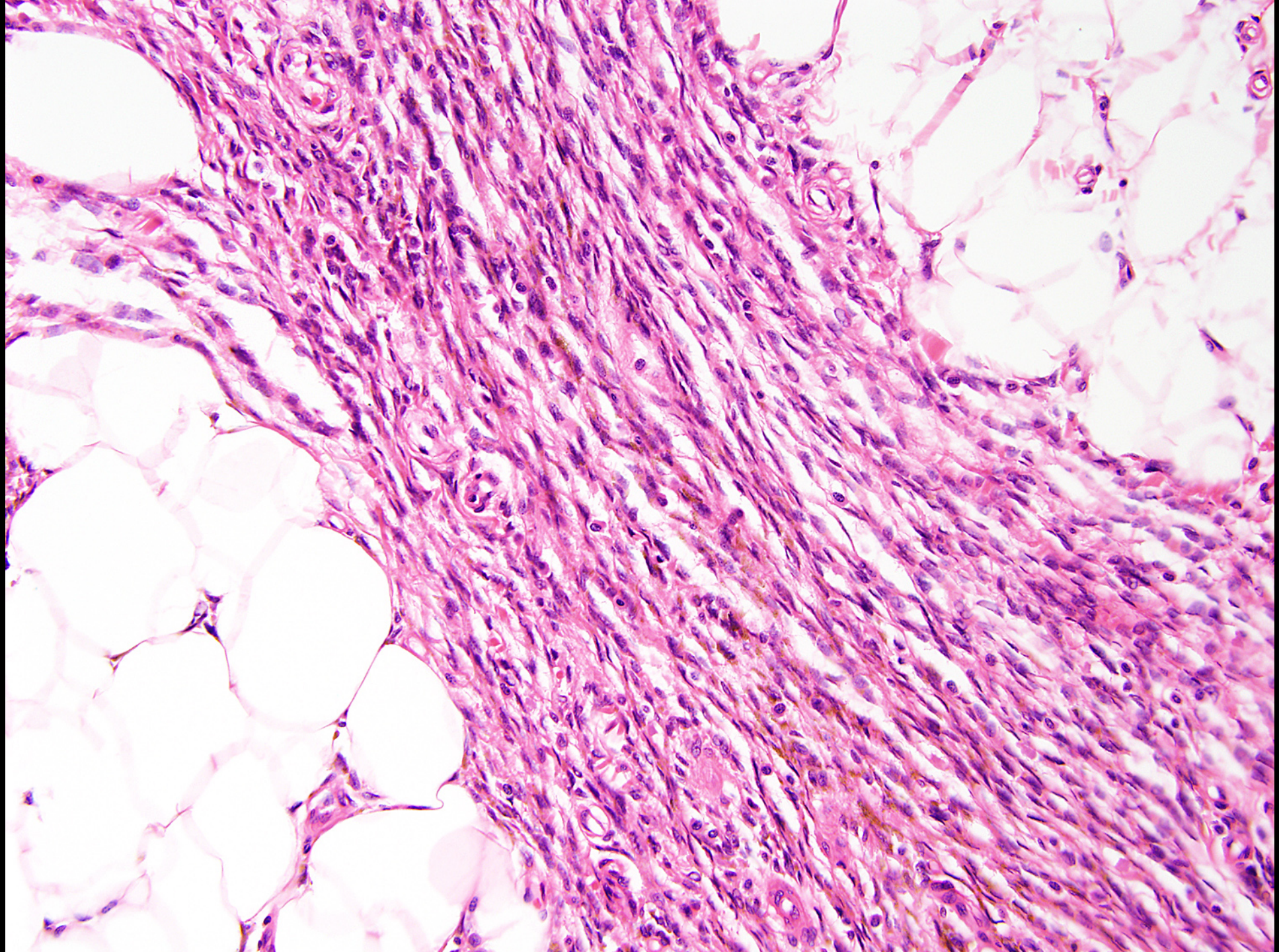
Admixture, in variable proportions, of:
- **Fibroblastic spindle cells**
- **Mature adipocytes**

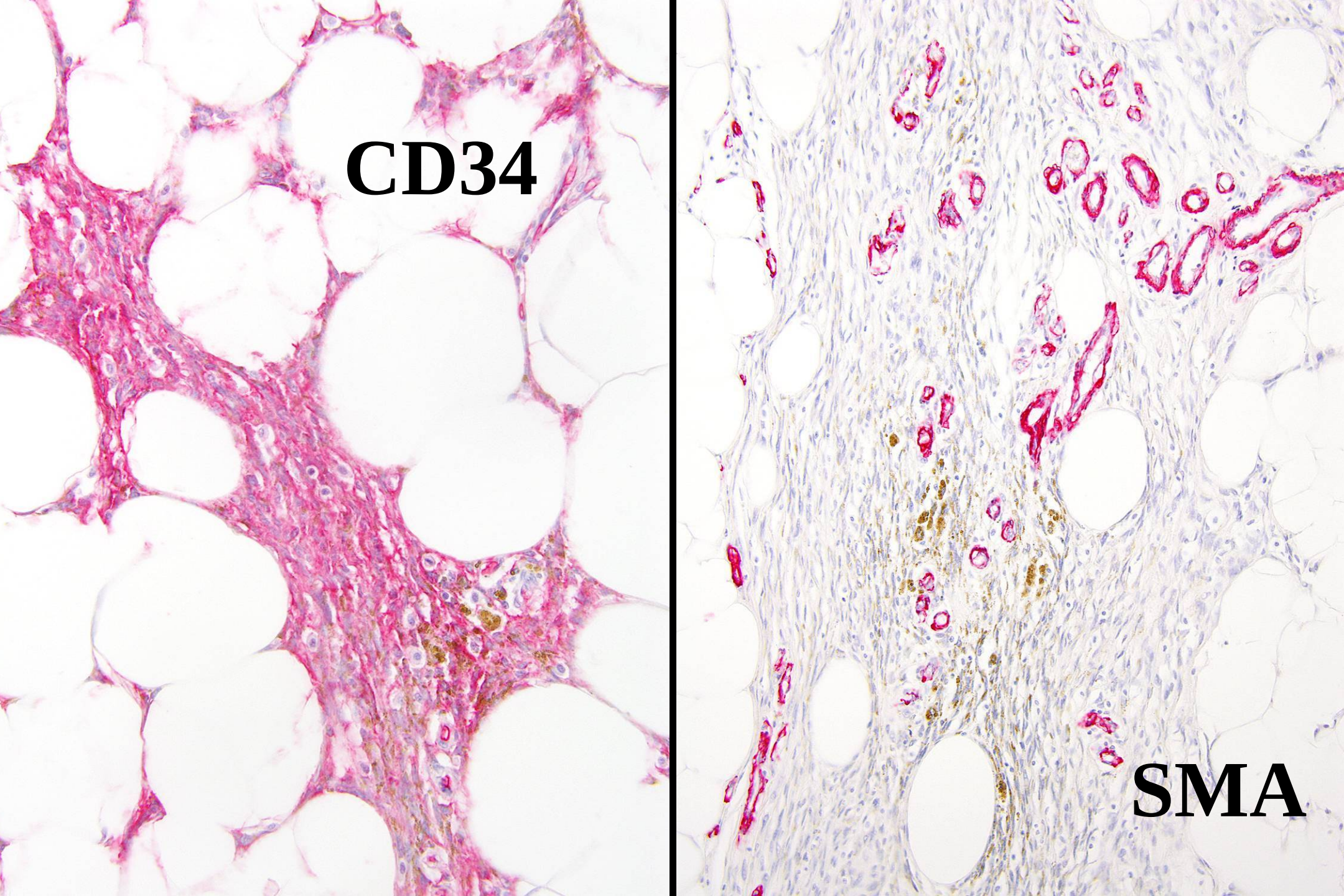
Fascicular or whorled pattern
Usually prominent haemosiderin
Scattered osteoclastic giant cells
Mitoses scarce

Occasional atypia / pleomorphism





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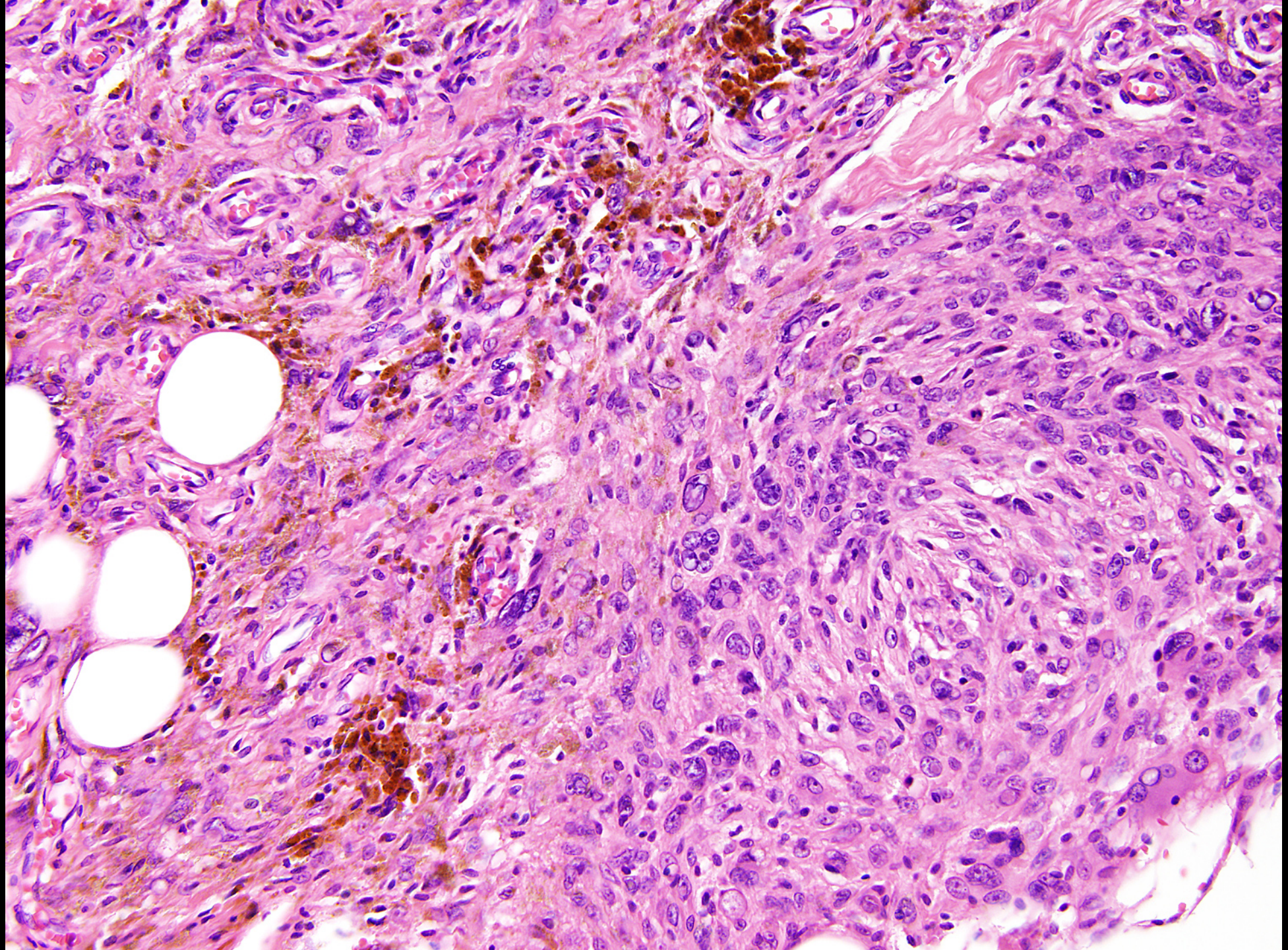
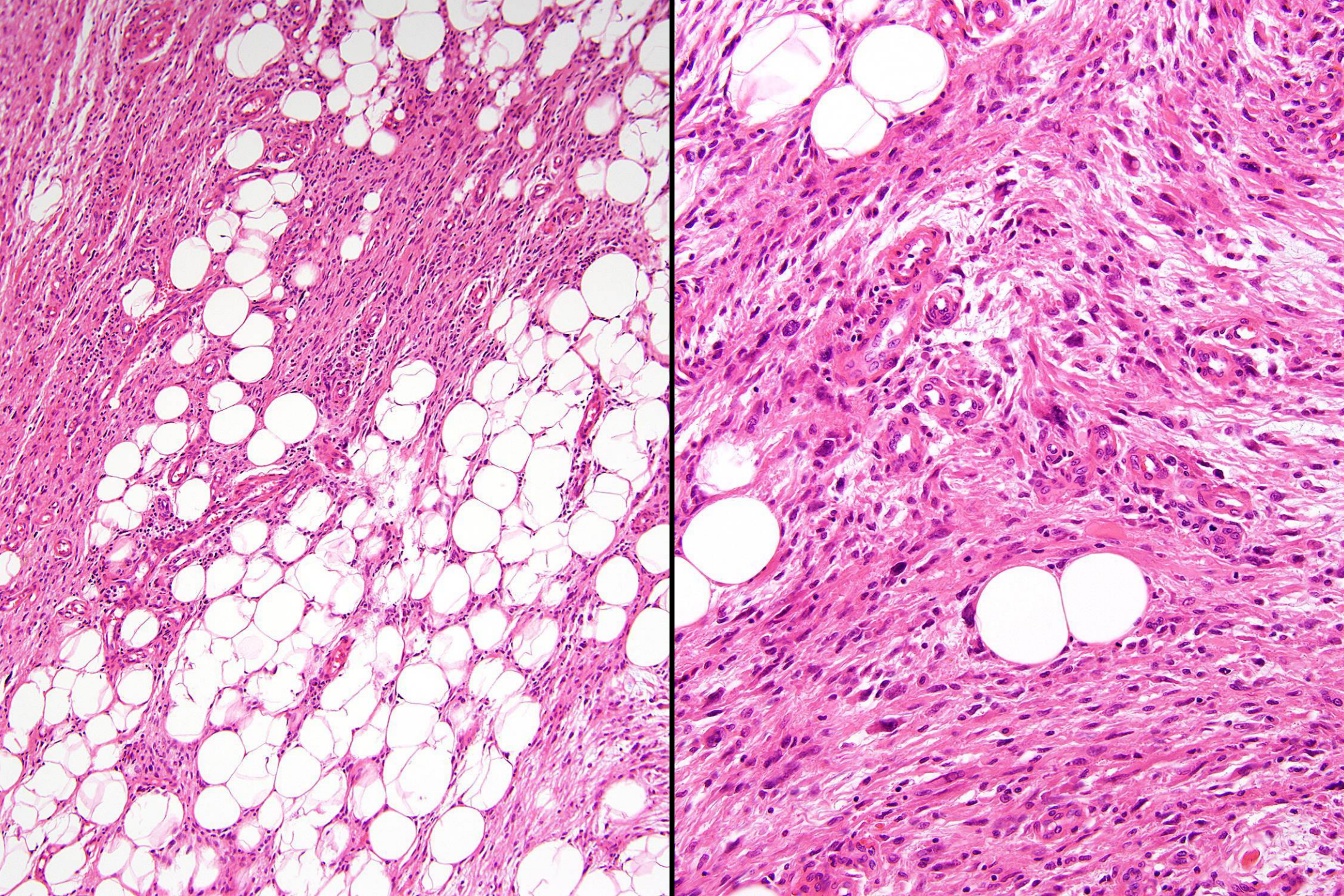
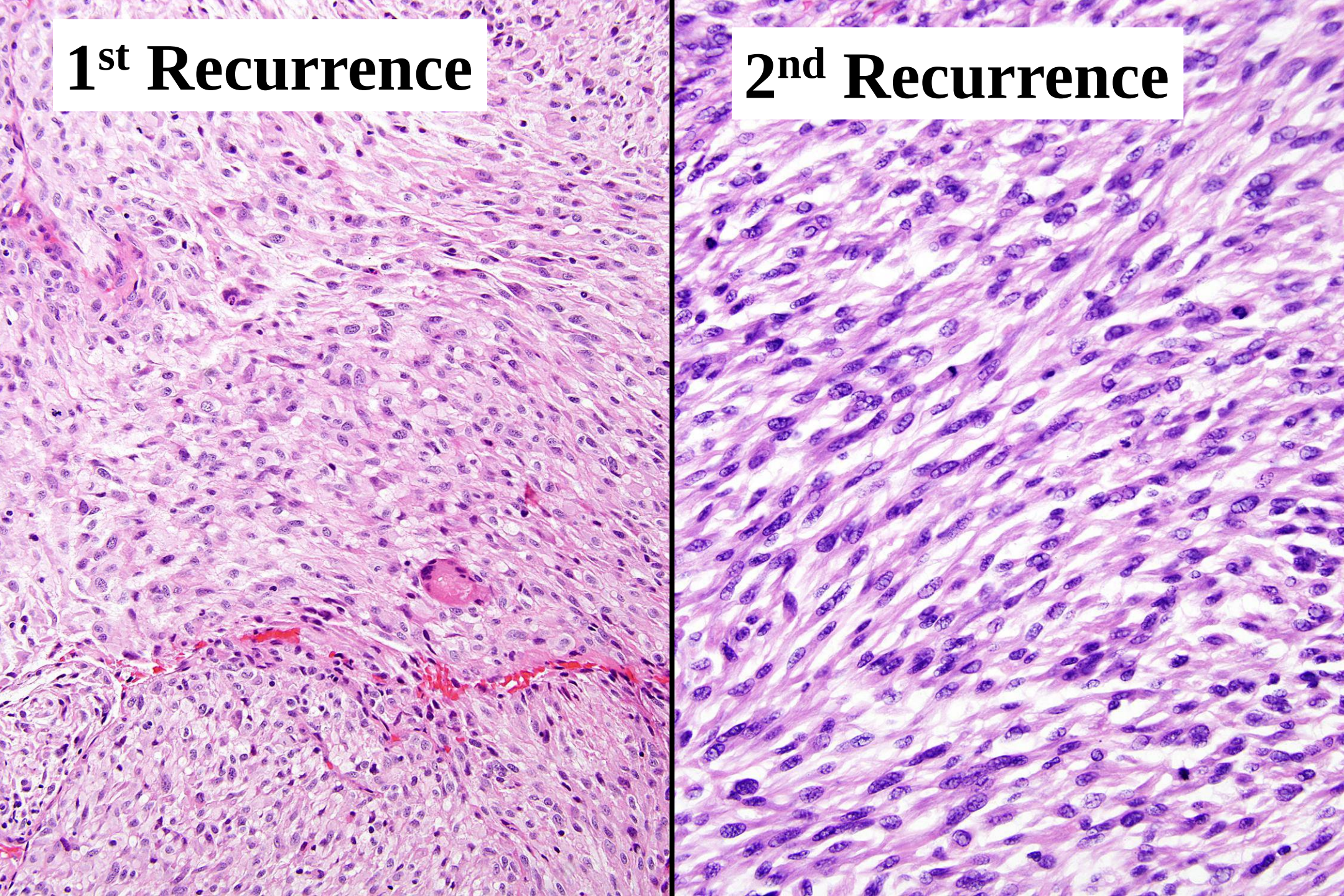
HAEMOSIDEROTIC FIBROLIPOMATOUS TUMOUR
(aka "haemosiderotic fibrohistiocytic lipomatous lesion")

ISSUES OF INTEREST

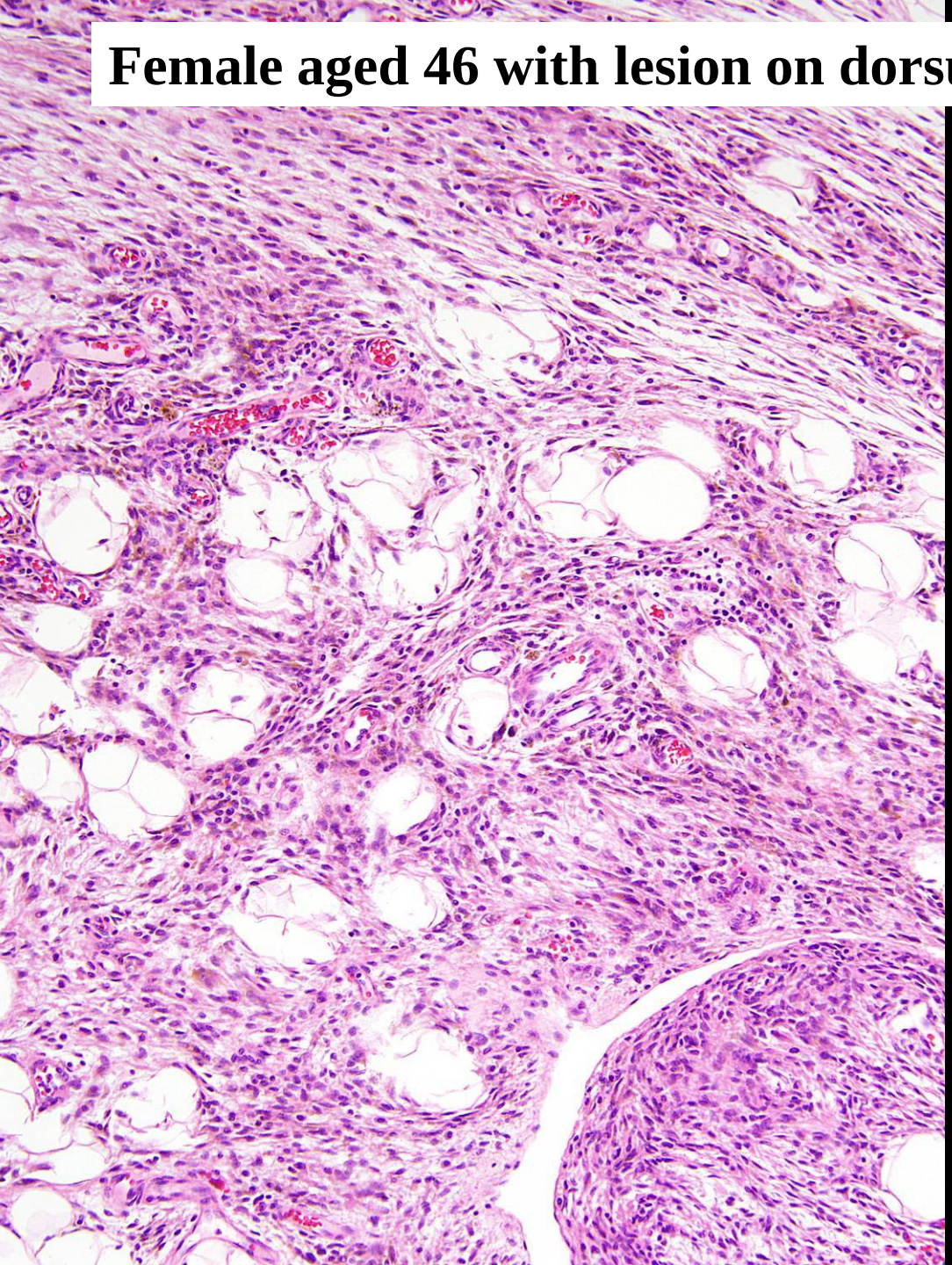
Reactive (??) vs. neoplastic
Significance of atypia
Biologic potential
Relationship to other entities ??

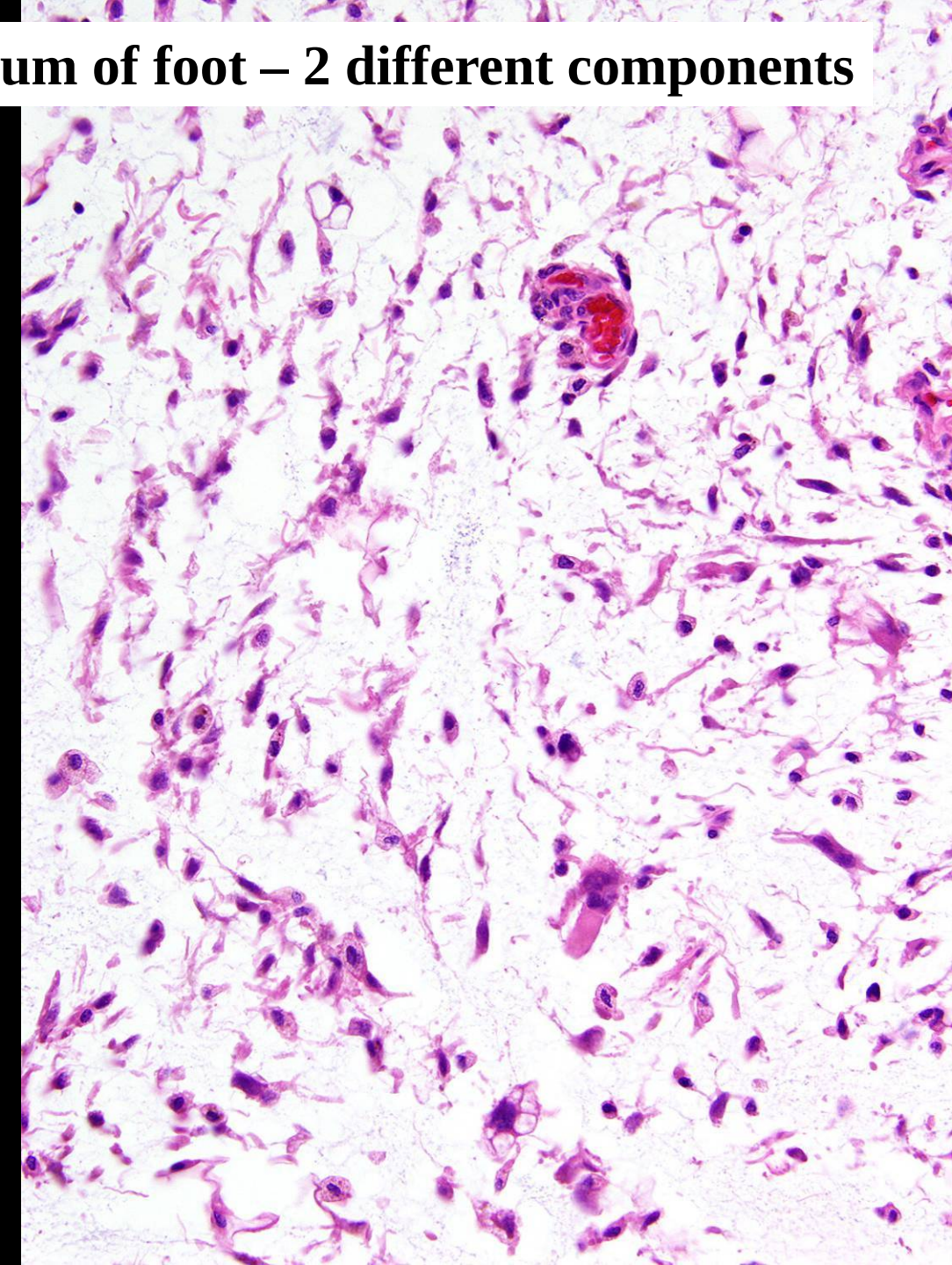





1st Recurrence
2nd Recurrence

Female aged 46 with lesion on dorsum of foot – 2 different components





MYXOINFLAMMATORY FIBROBLASTIC SARCOMA

CLINICAL FEATURES

Adults, wide age range

Equal sex distribution

Slowly growing, ill-defined mass

Distal extremities

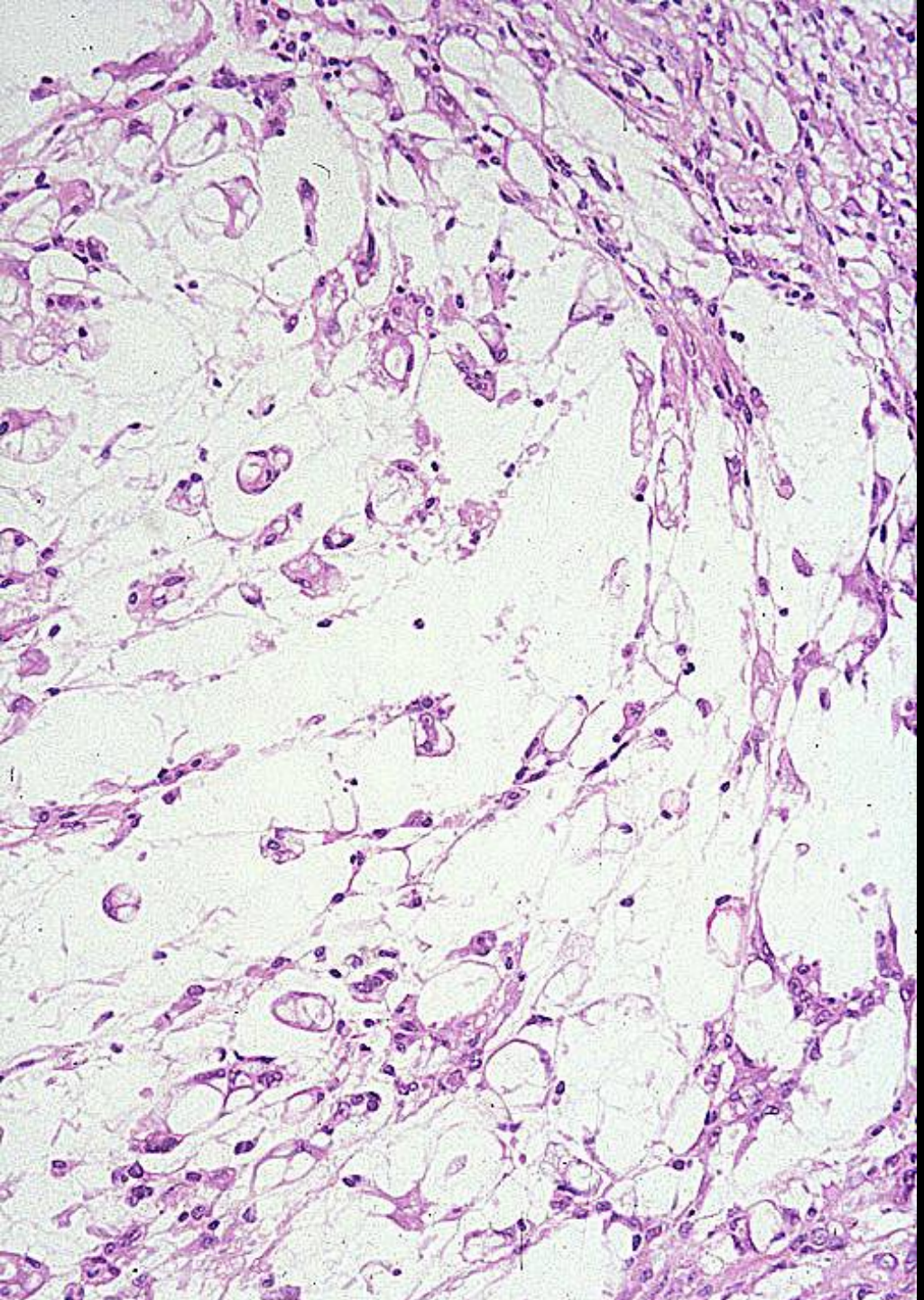
- especially hands and feet

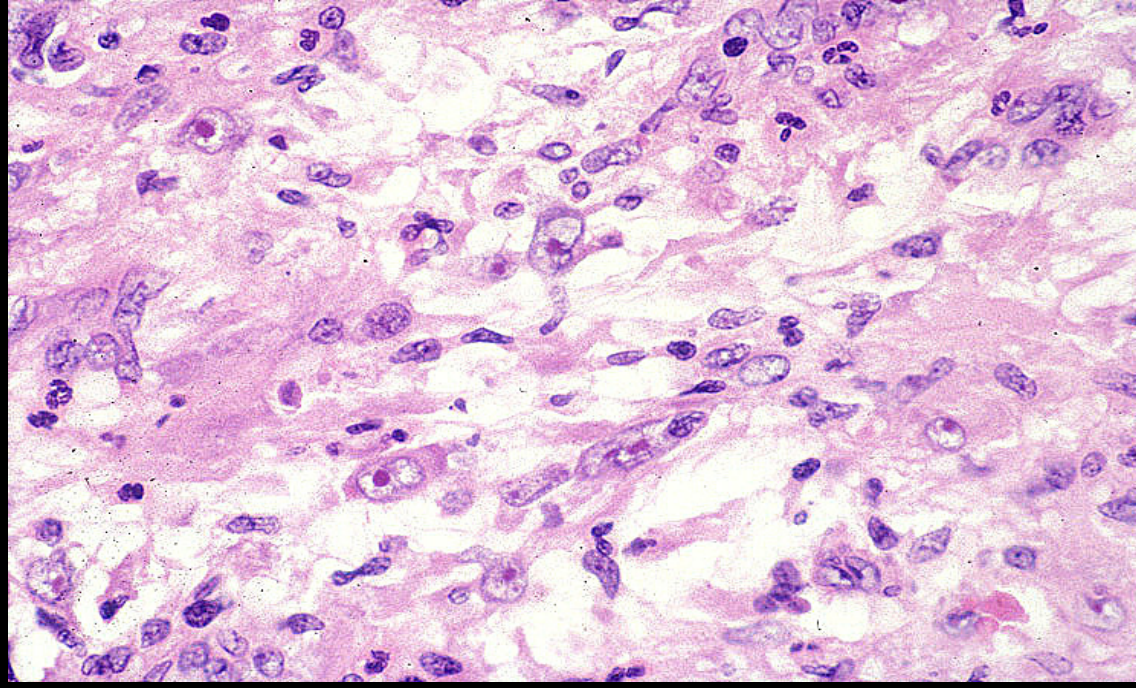
Subcutaneous / tenosynovial

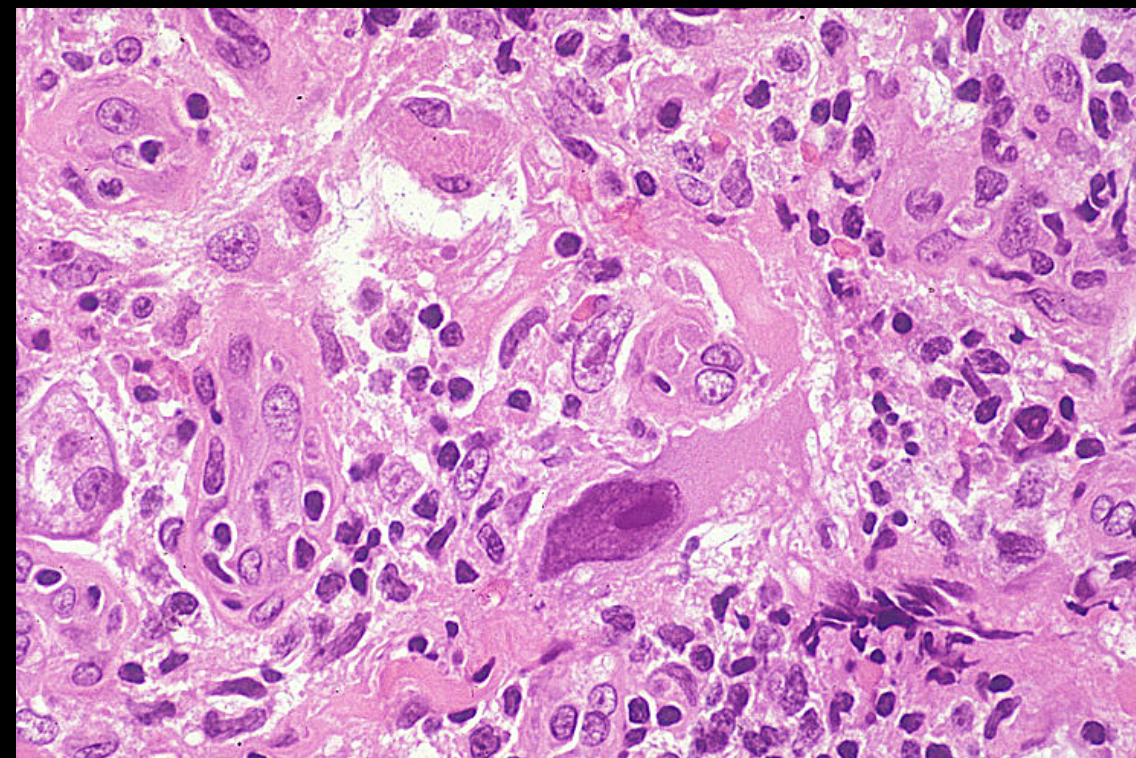
Usually < 5 cm

Local recurrence common

Metastasis very rare







MYXOINFLAMMATORY FIBROBLASTIC SARCOMA AND HEMOSIDEROTIC FIBROLIPOMATOUS TUMOR

SHARED CLINICOPATHOLOGIC & GENETIC FEATURES

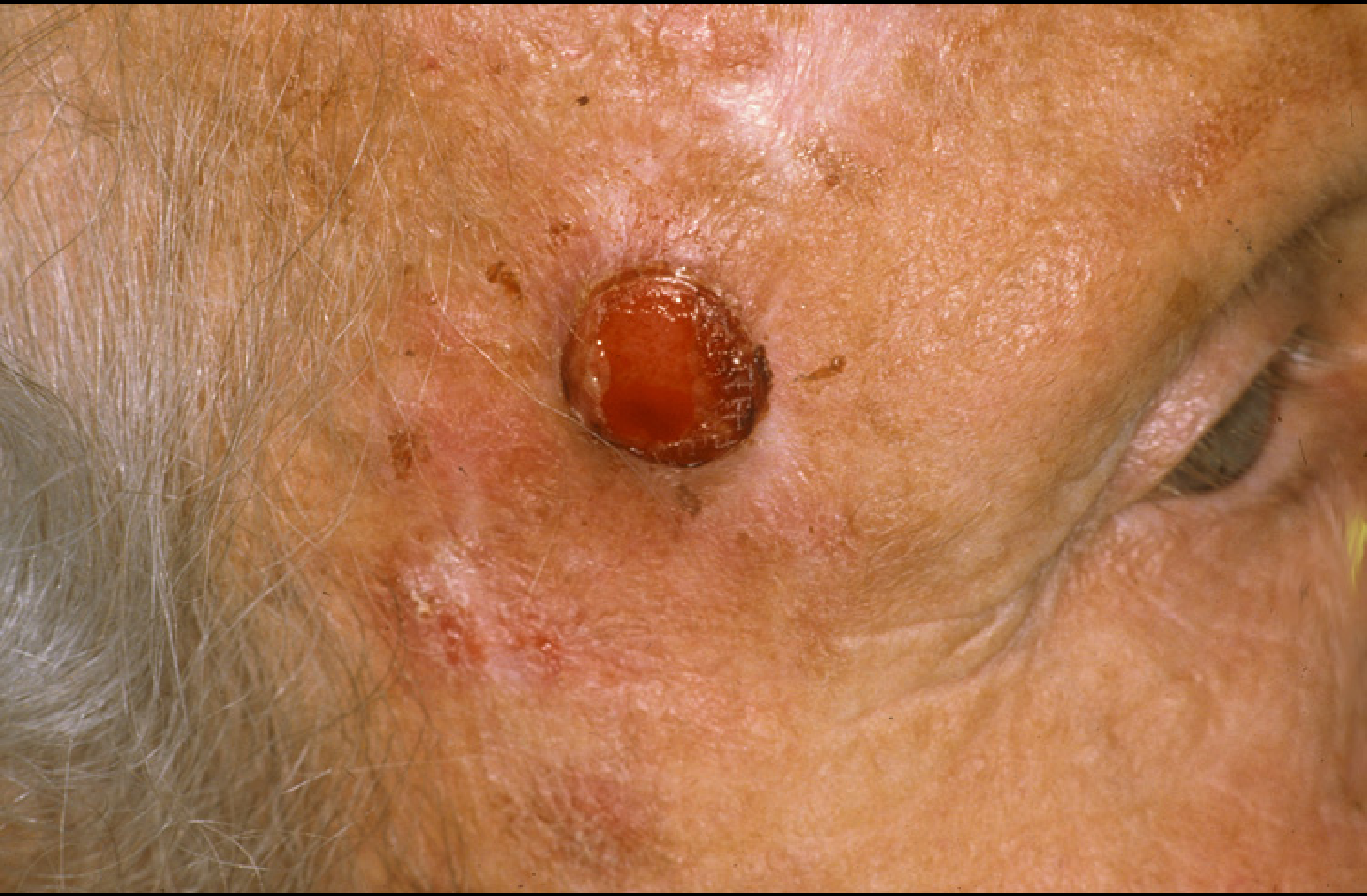
Predilection for distal extremities, esp. feet
Recur ++ - but ? almost never metastasise
Isolated cases show hybrid morphologic features
Both show reciprocal t(1;10)(p22;q24)
Gene fusion *TGFBR3 – MGEA5*
Leads to up-regulation of *FGF8*
Also amplified 3p in ring chromosomes

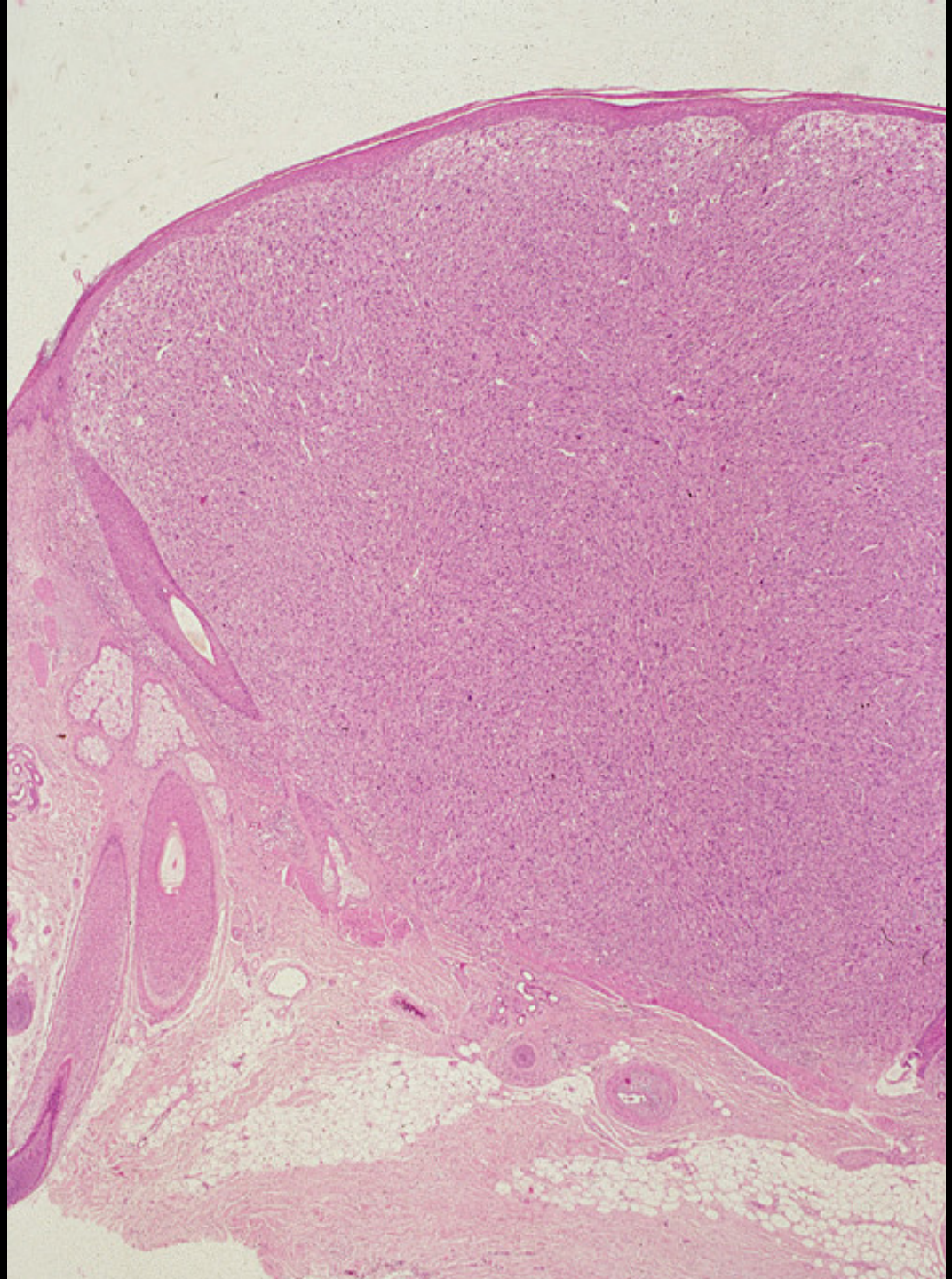
Lambert et al, *Virchows Arch* 2001; 438:509-512
Wettach et al, *Cancer Genet Cytogenet* 2008; 182:140-143
Hallor et al, *J Pathol* 2009; 217:716-727
Antonescu et al, *Genes Chromosomes & Cancer* 2011; 50:757-764

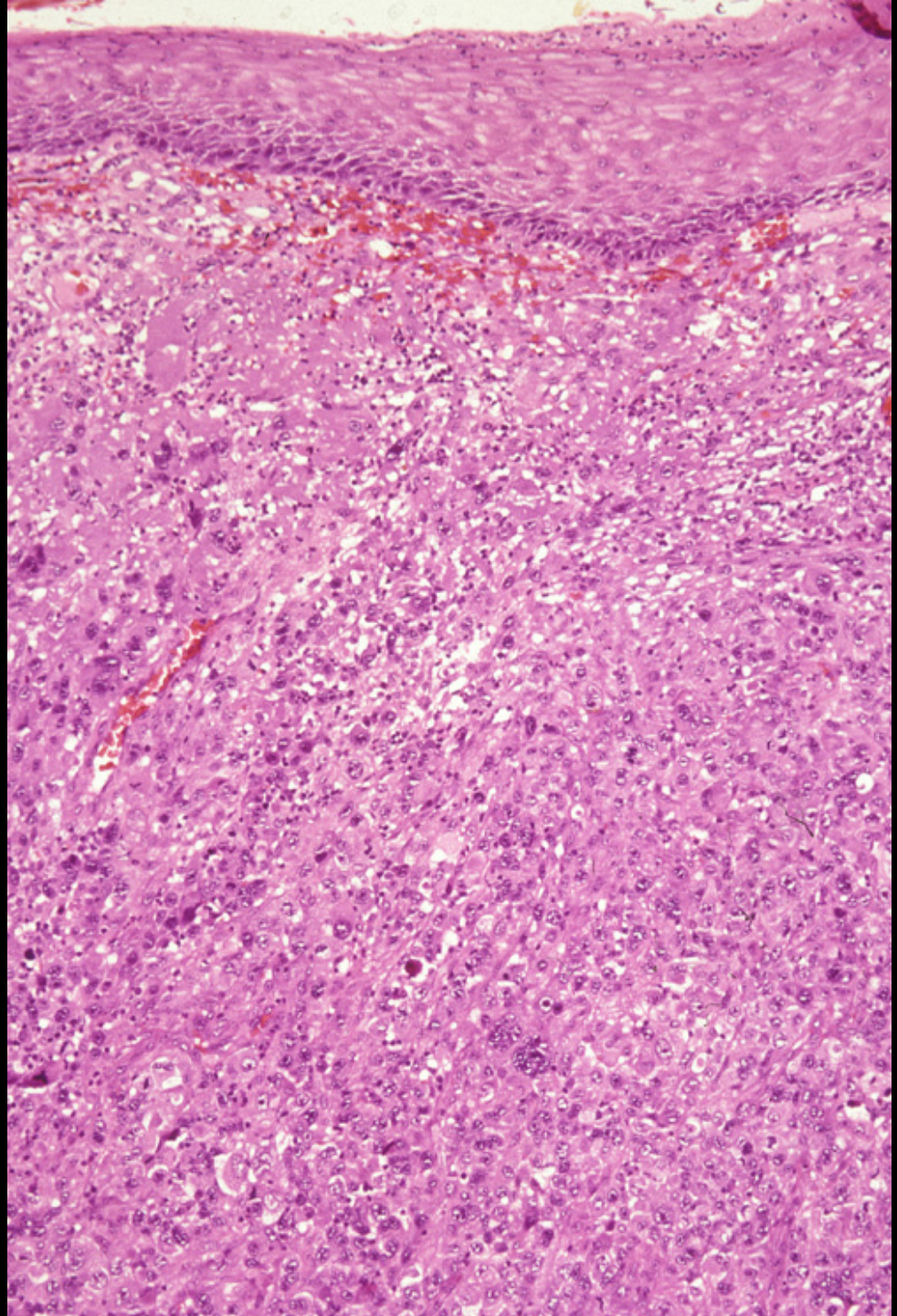
ATYPICAL FIBROXANTHOMA
CLINICAL FEATURES

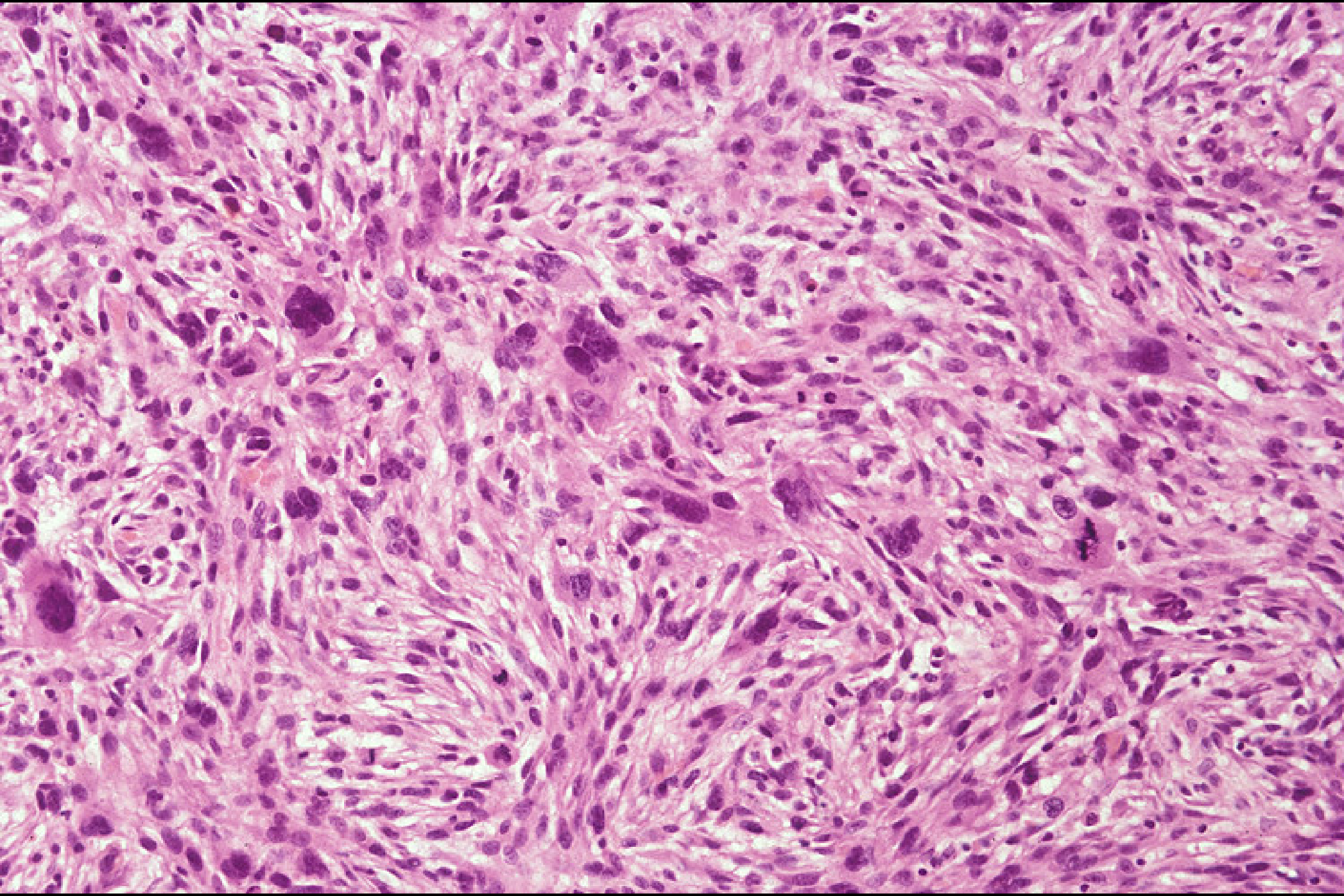
Mainly elderly patients
Males > females
Head and neck++ / limbs rare
Rapidly enlarging exophytic
Sometimes multiple / asynchronous

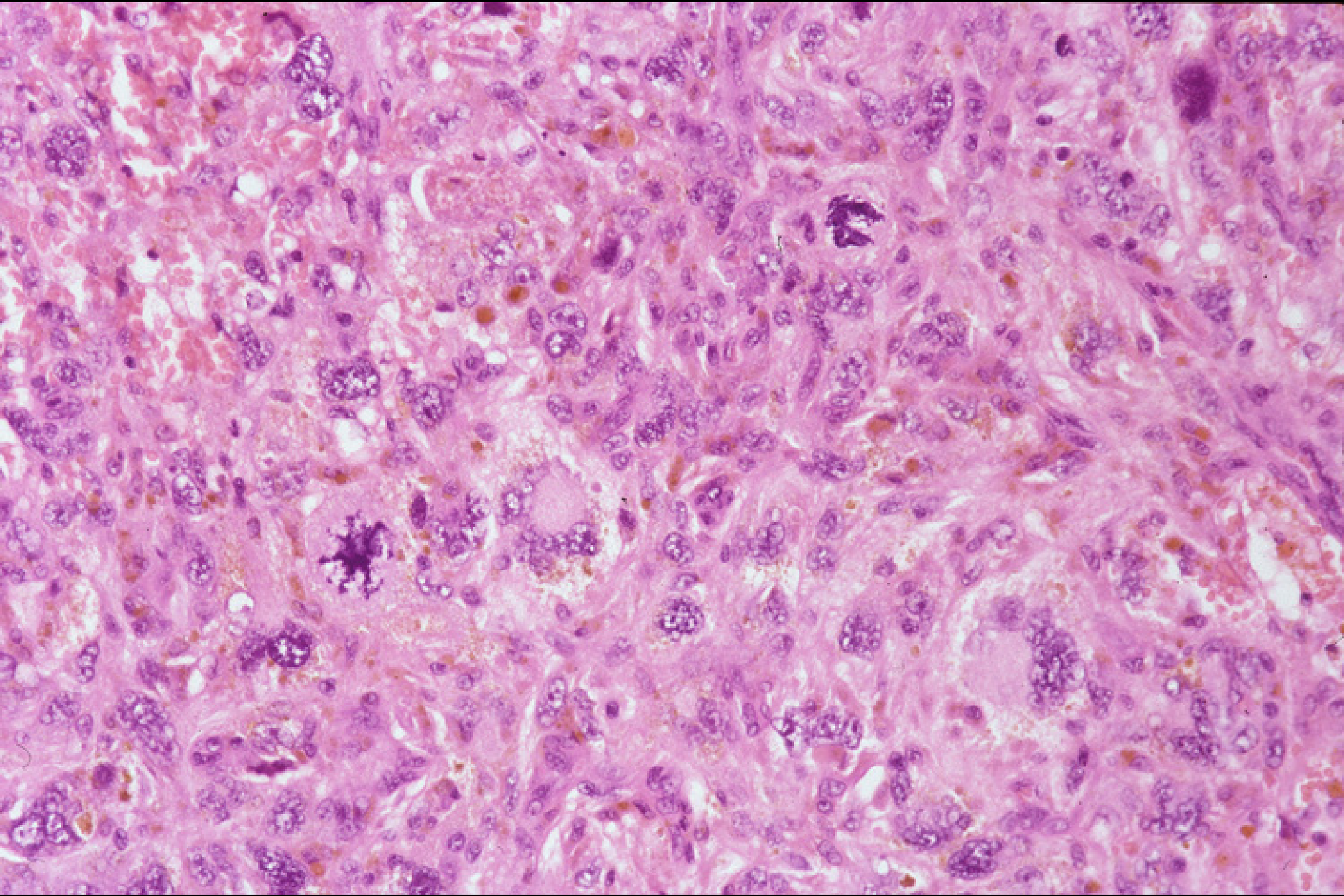
Recurrence infrequent
No metastasis if carefully diagnosed

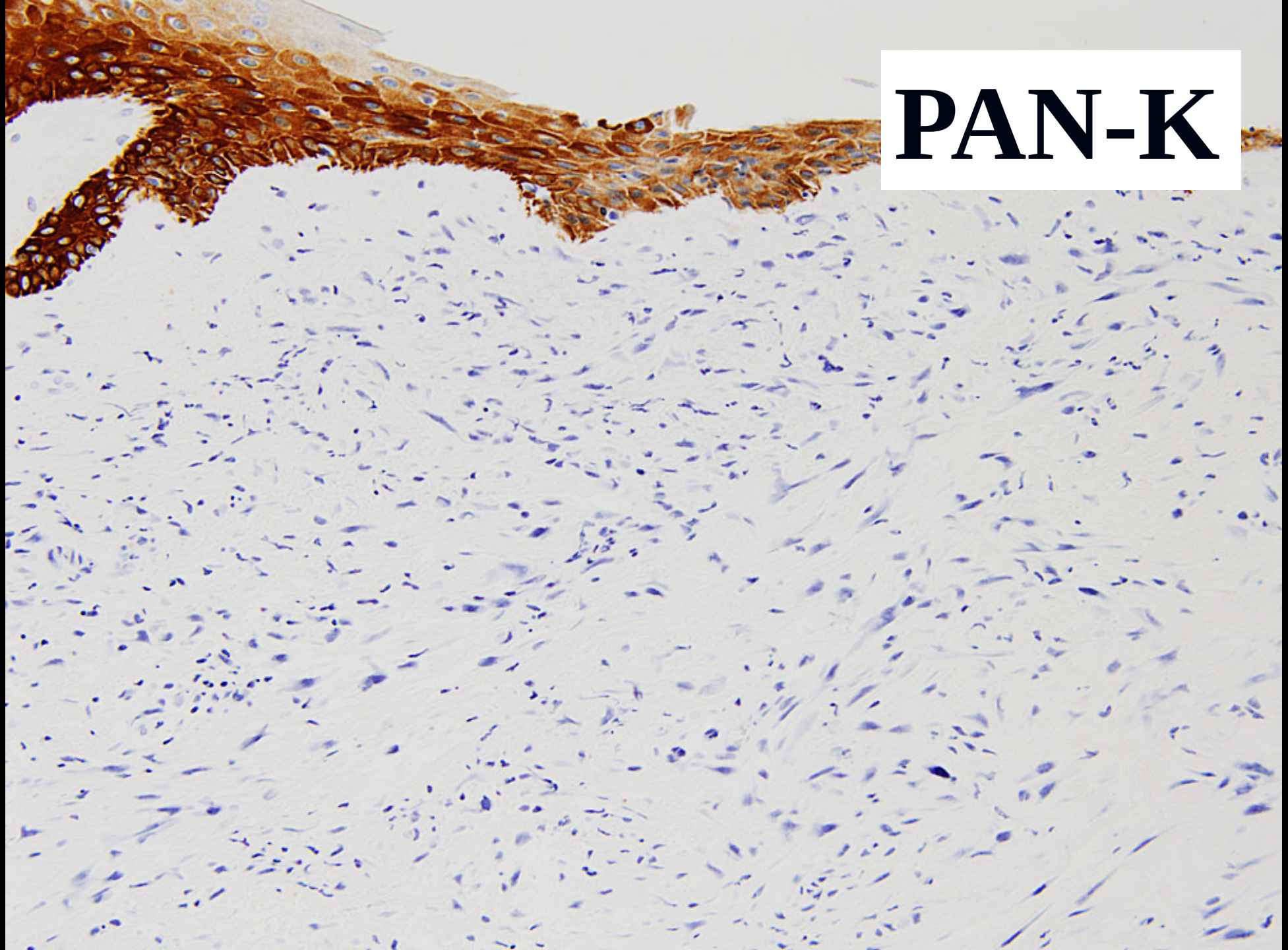








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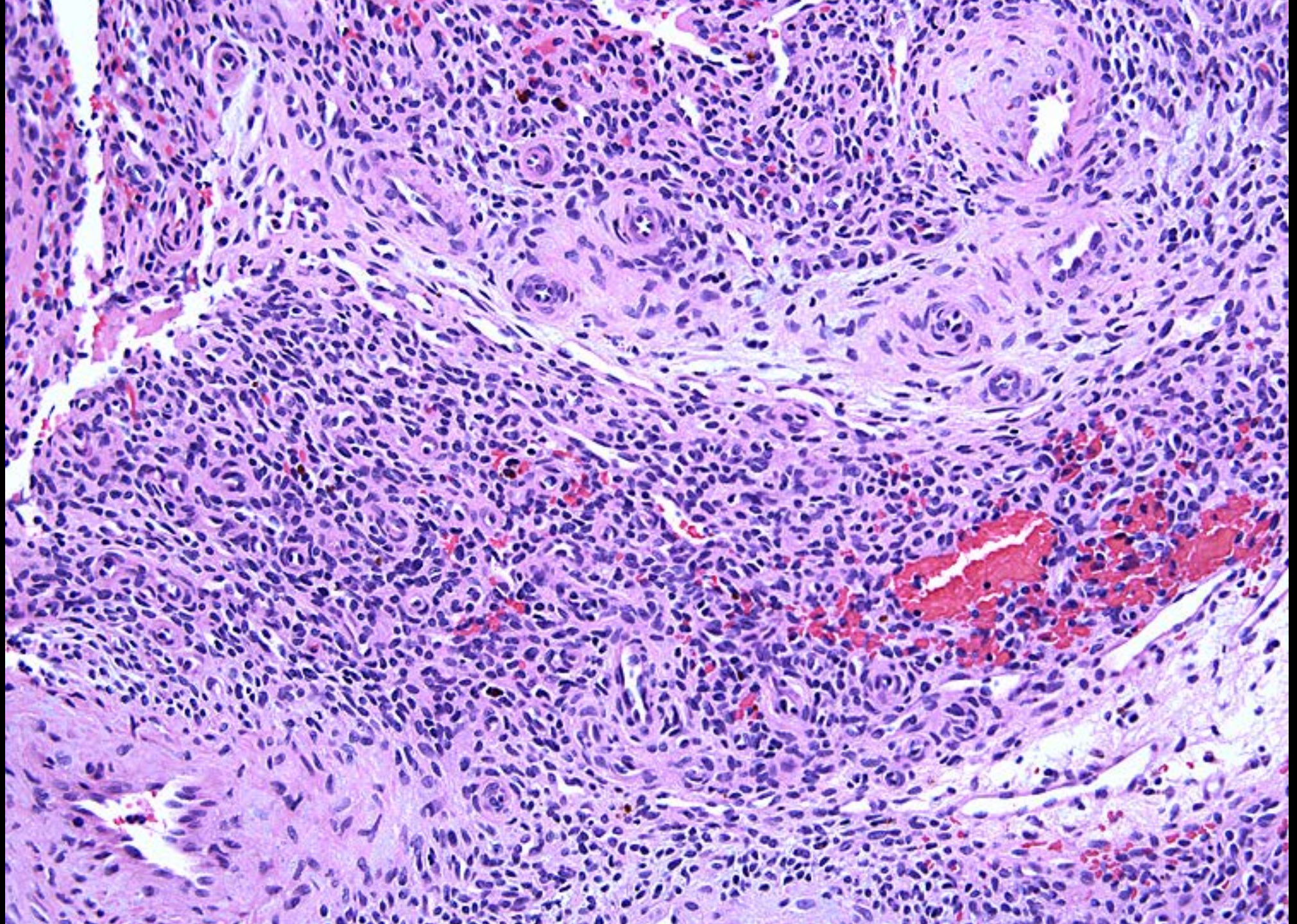
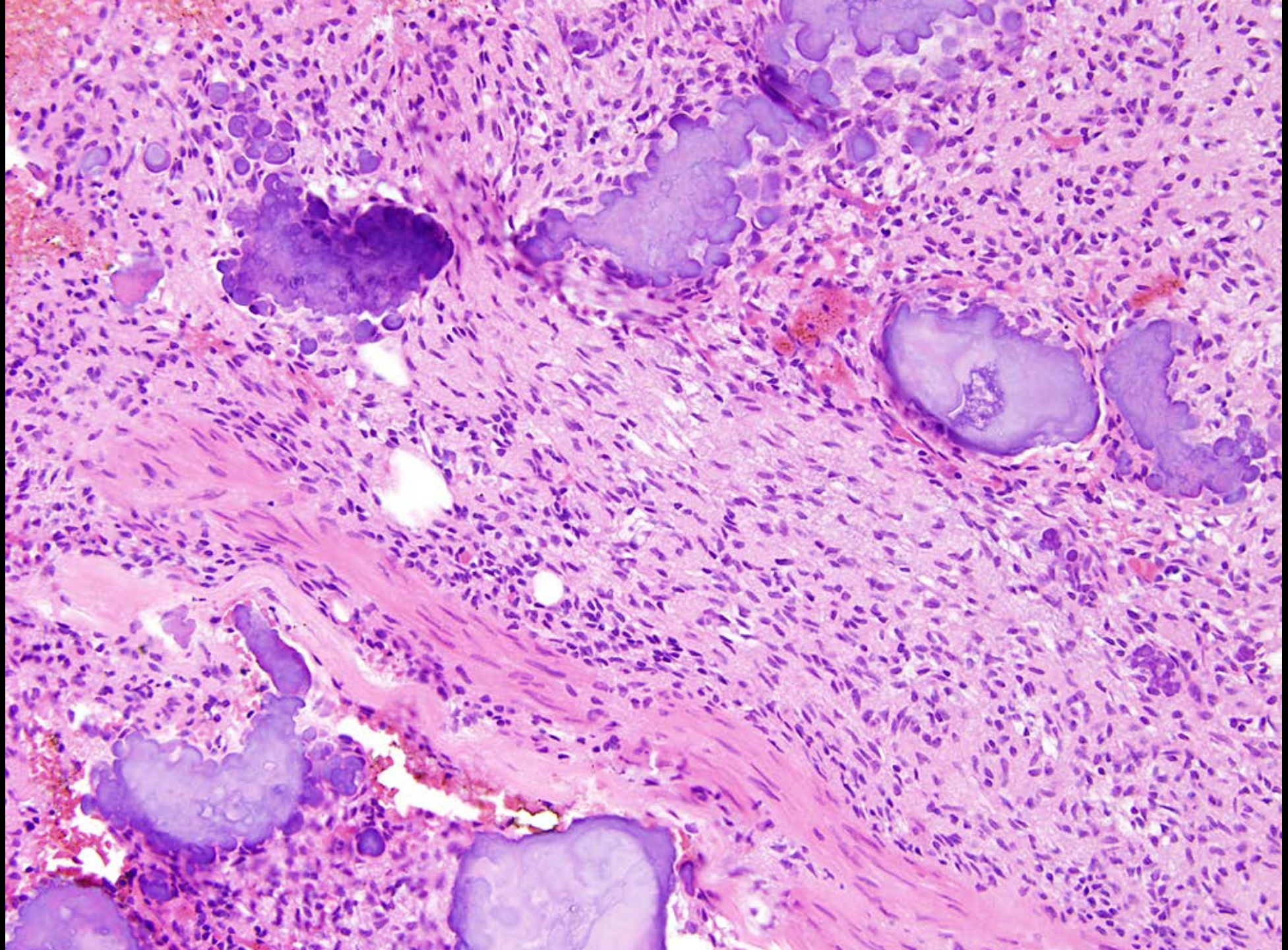
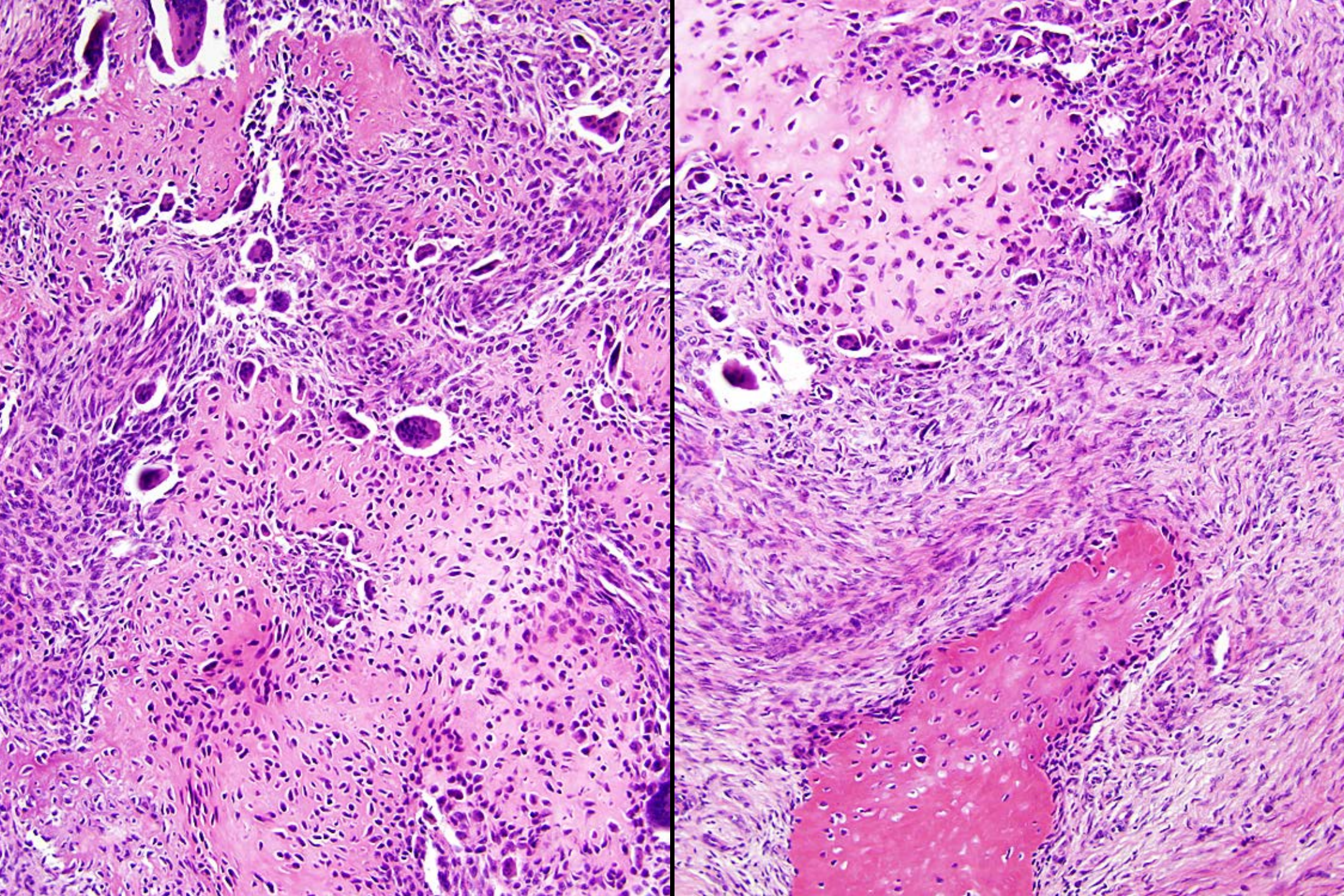
PHOSPHATURIC MESENCHYMAL TUMOUR

KEY POINTS

- Mostly middle-aged adults – almost any site
- Most assoc. with tumour-induced osteomalacia due to FGF23 production
- Varied morphology but most are myoid or myopericytoma-like with blueish matrix and granular calcification
- Vast majority are benign







World Health Organization (2013) Classification of Tumours of Soft Tissue

TUMOURS OF UNCERTAIN DIFFERENTIATION

Malignant

Synovial sarcoma
Epithelioid sarcoma
Alveolar soft part sarcoma
Clear cell sarcoma of soft tissue
Extraskeletal myxoid chondrosarcoma
Extraskeletal Ewing sarcoma
Desmoplastic small round cell tumour
Extra-renal rhabdoid tumour
PEComa
Intimal sarcoma

World Health Organization (2013) Classification of Tumours of Soft Tissue

UNDIFFERENTIATED / UNCLASSIFIED SARCOMAS

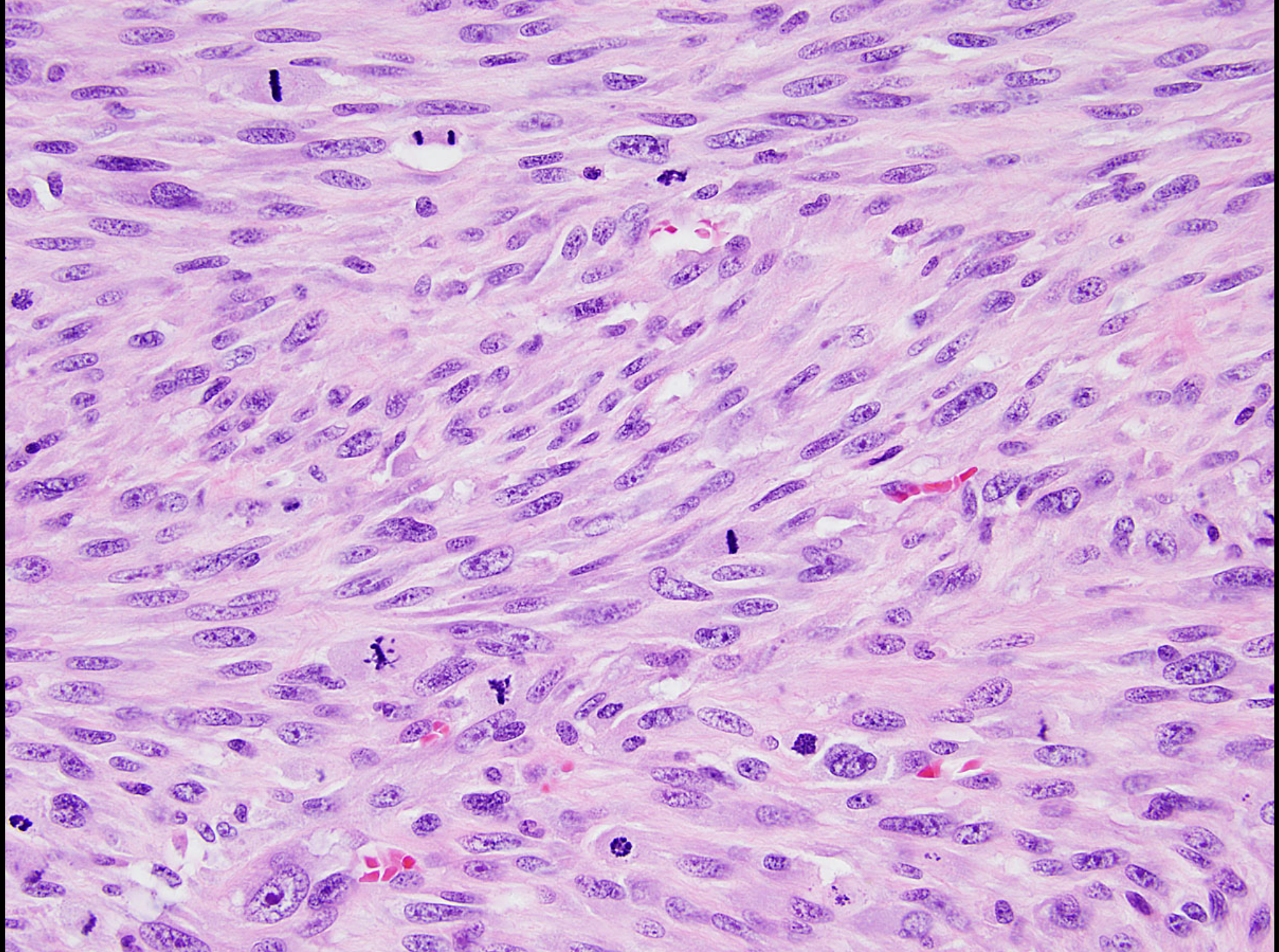
Undifferentiated spindle cell sarcoma

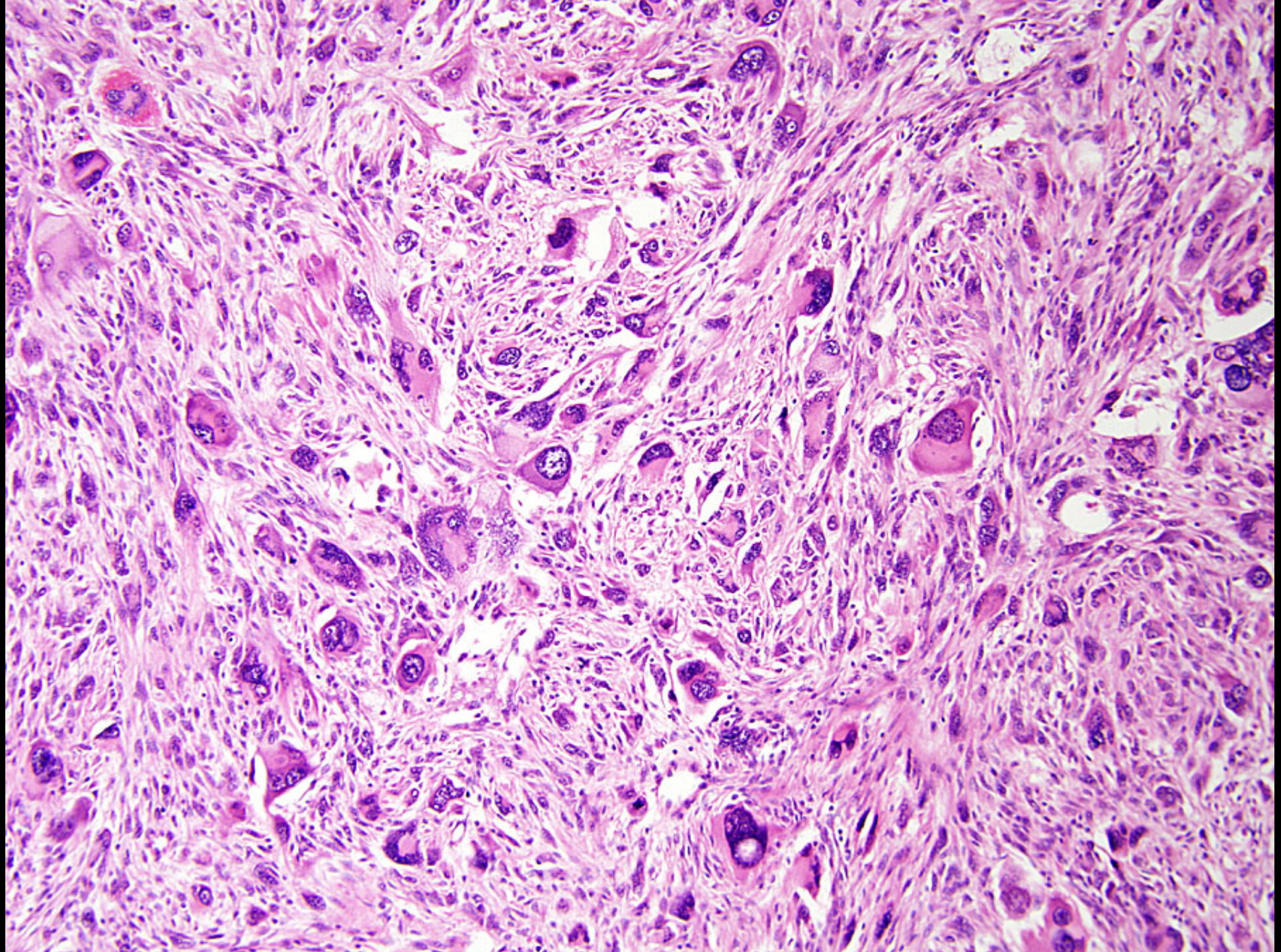
Undifferentiated pleomorphic sarcoma

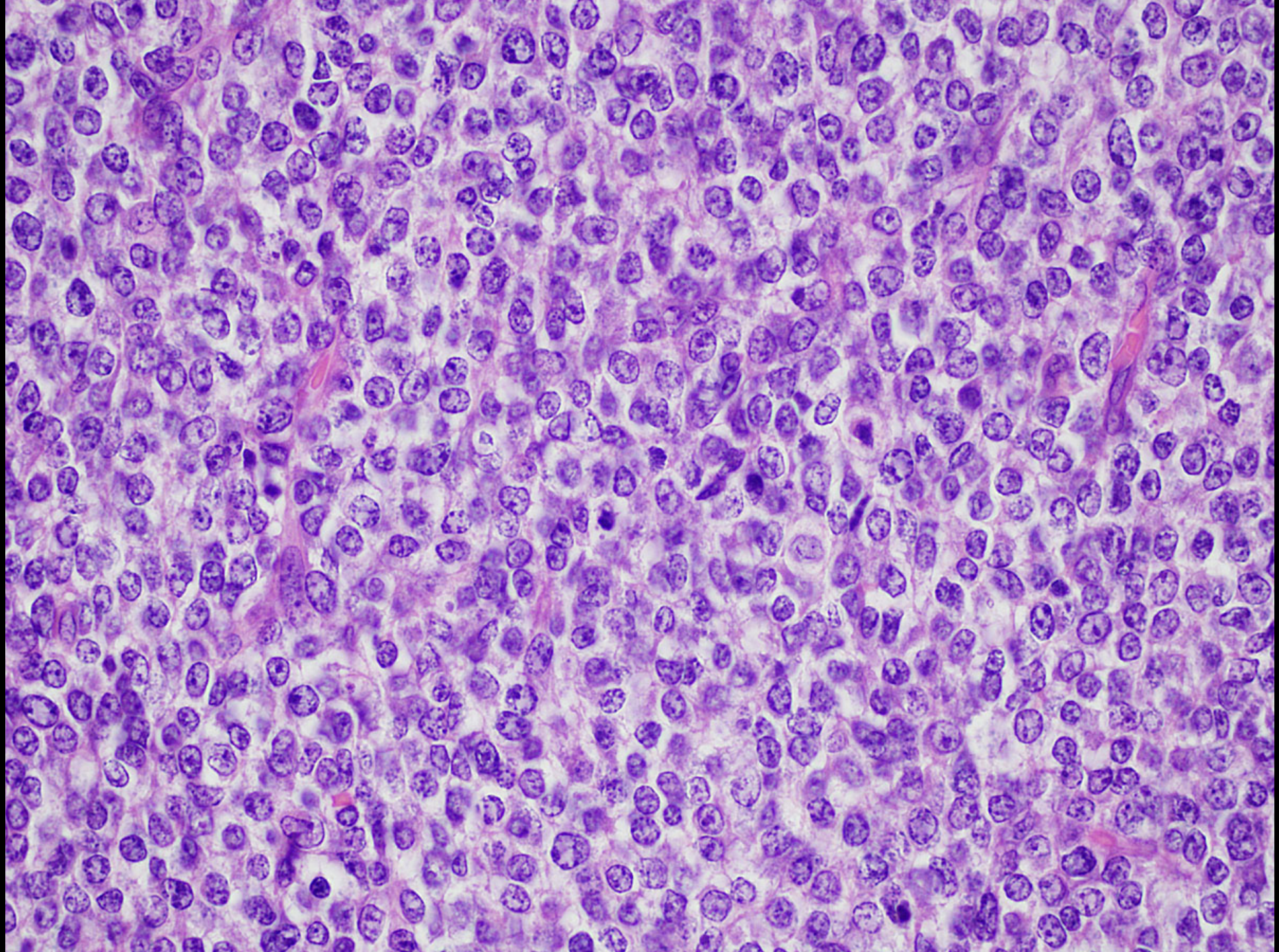
Undifferentiated round cell sarcoma

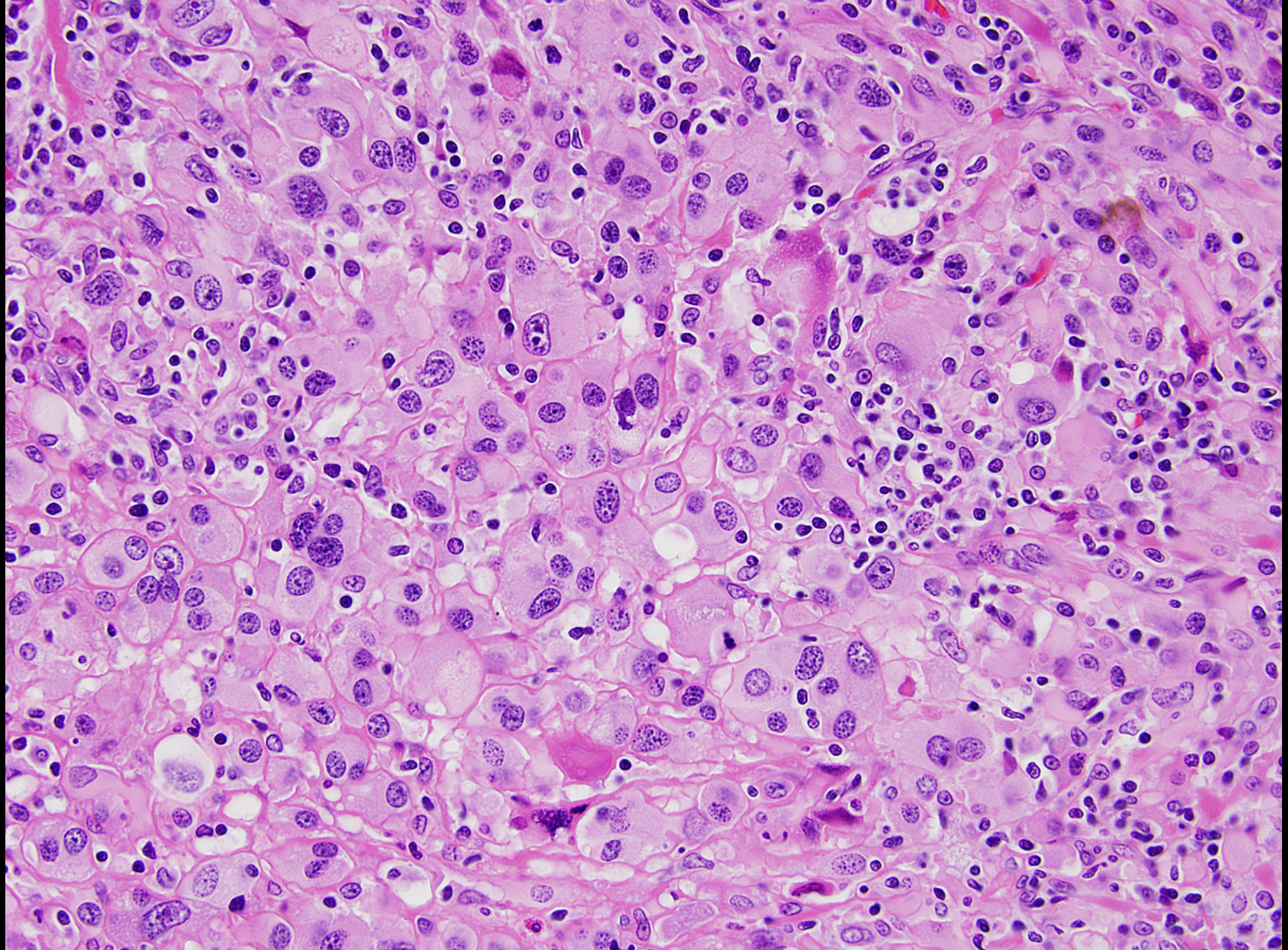
Undifferentiated epithelioid sarcoma

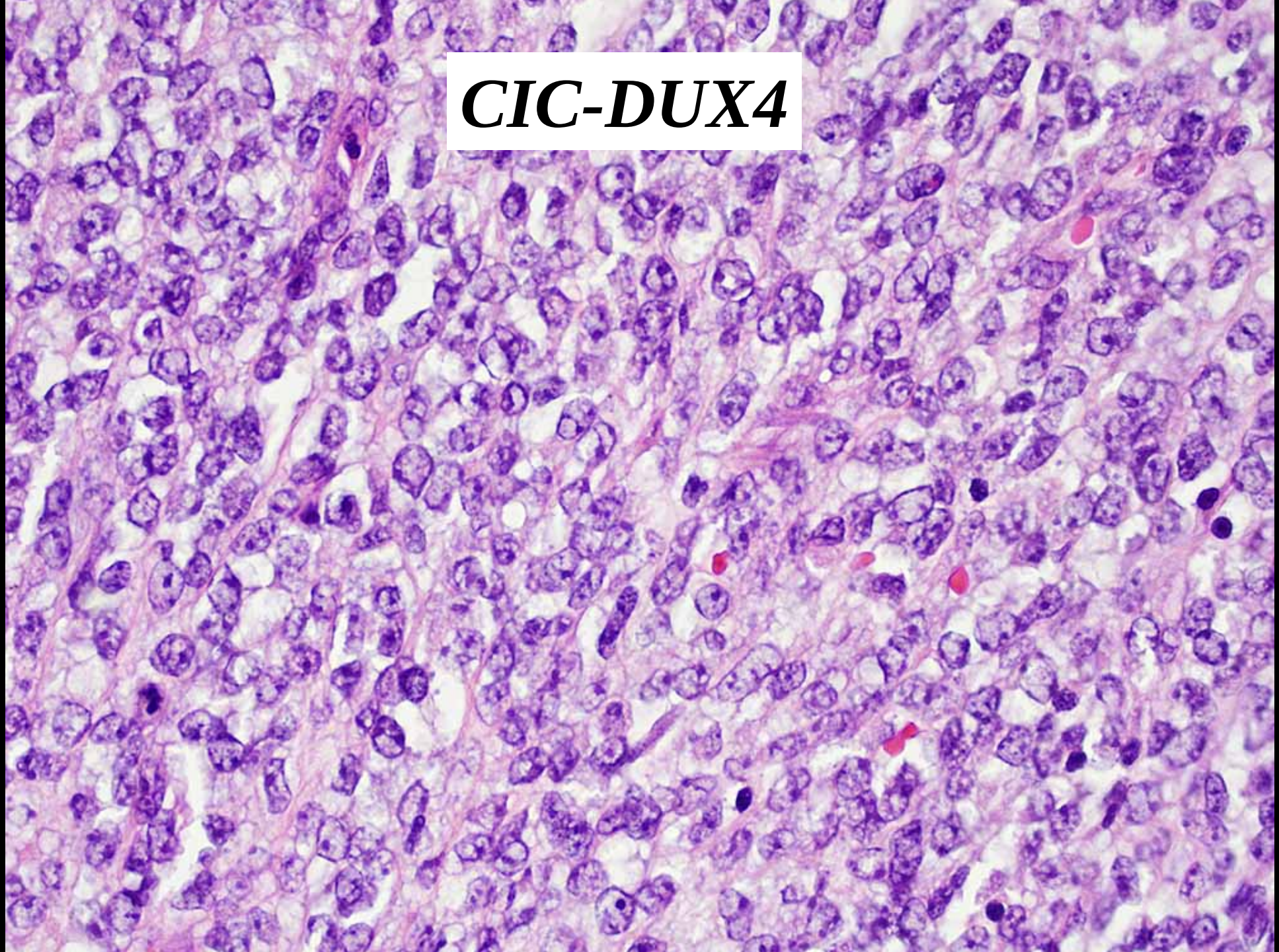
Undifferentiated sarcoma NOS

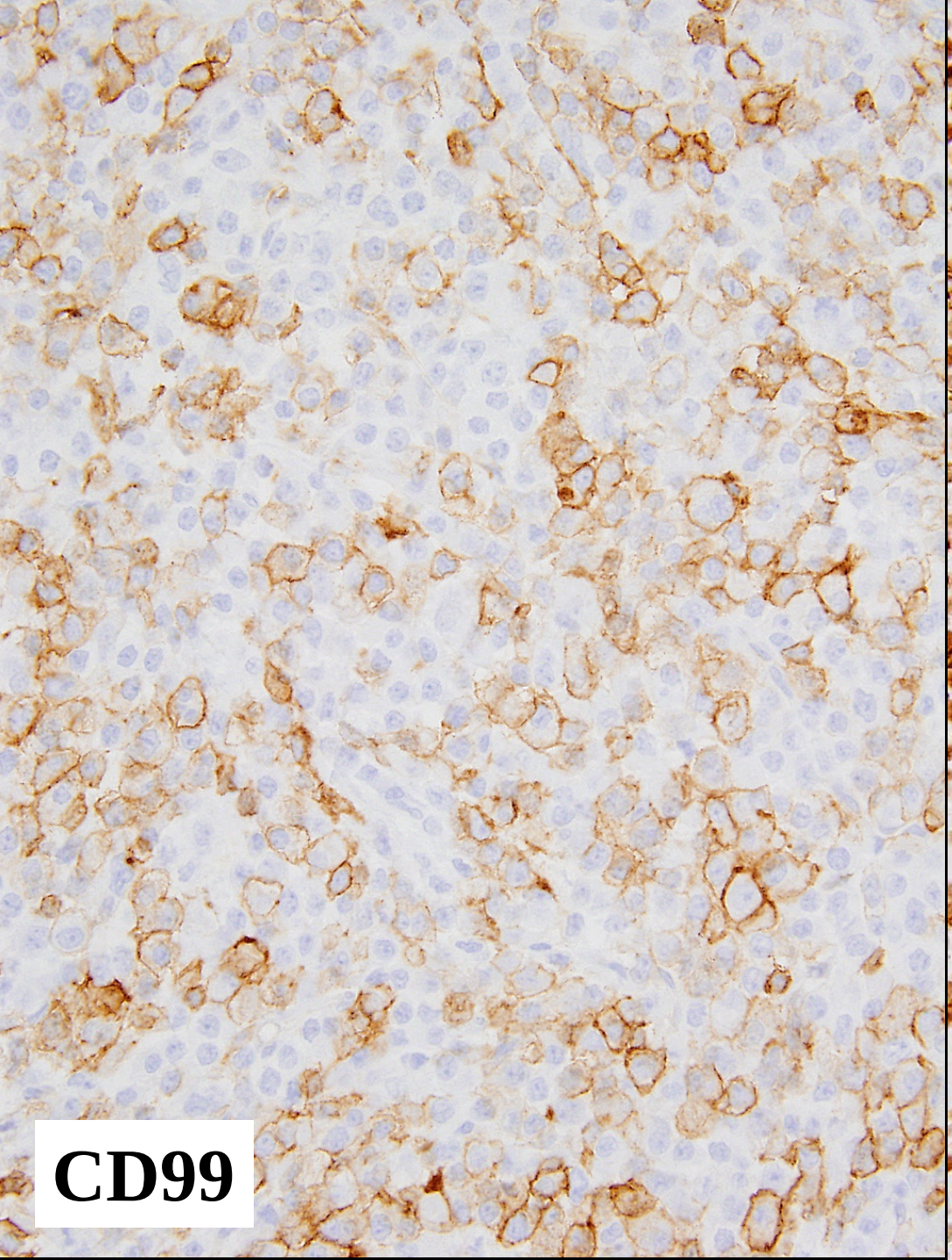


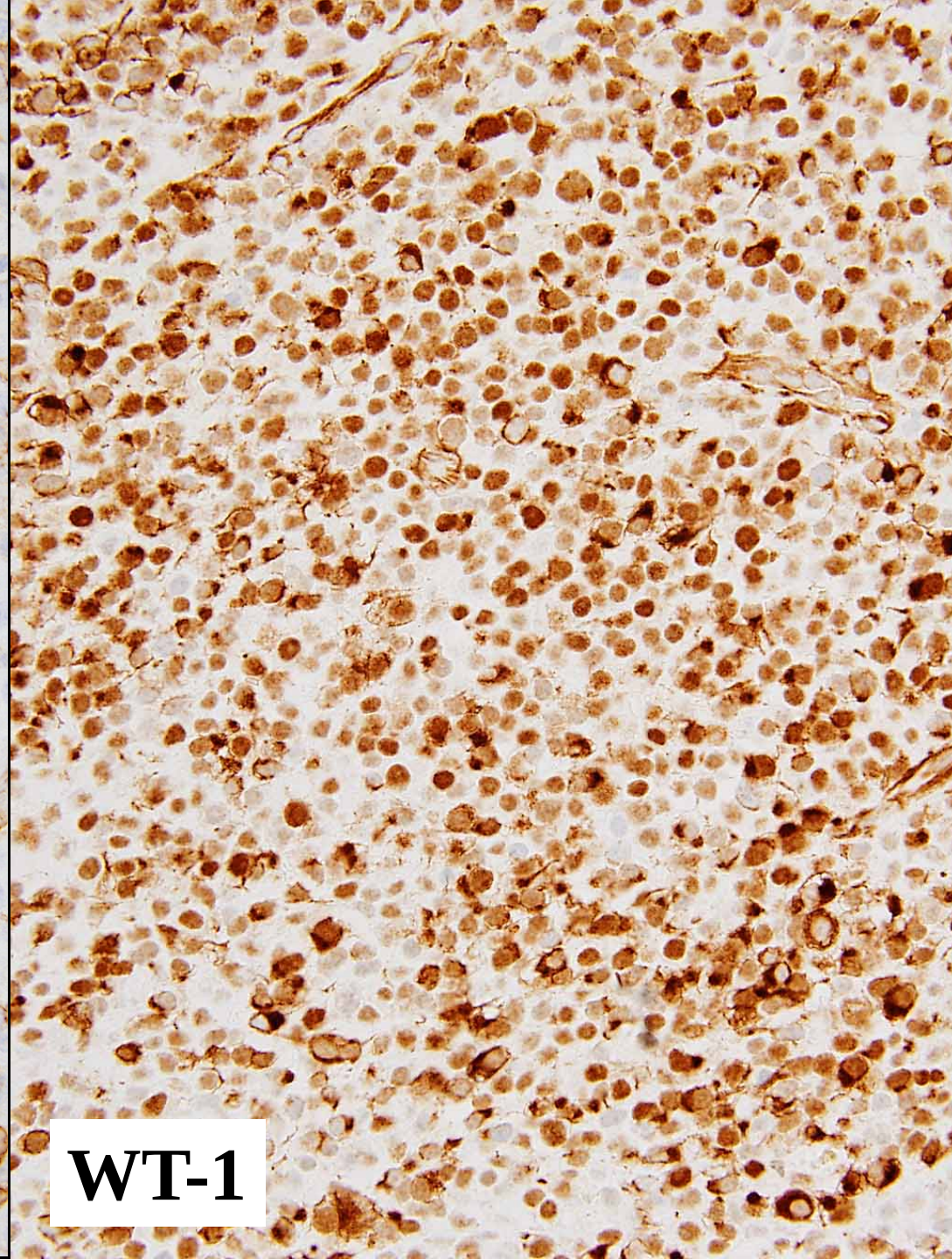







CIC-DUX4


CD99


WT-1

World Health Organization (2013) Classification of Tumours of Soft Tissue

NEW GENETICS (1)

Fibroblastic / Myofibroblastic tumours

Nodular fasciitis	**t(17;22)(p13;q12.3)**	***USP6-MYH9***
Myxoinflammatory fibroblastic sarcoma	**t(1;10)(p22;q24)**	***TGFBR3-MGEA5***

- **also seen in HFLT and hybrid lesions**

Low grade fibromyxoid sarcoma	**t(7;16)(q33;p11)**	***FUS-CREB3L2***
	t(11;16)(p13;p11)	***FUS-CREB3L1***

- **also seen in a subset of SEF and hybrid lesions**

(Post-WHO – Solitary fibrous tumor inv12(q13q13) *NAB2-STAT6*)

World Health Organization (2013) Classification of Tumours of Soft Tissue

NEW GENETICS (2)

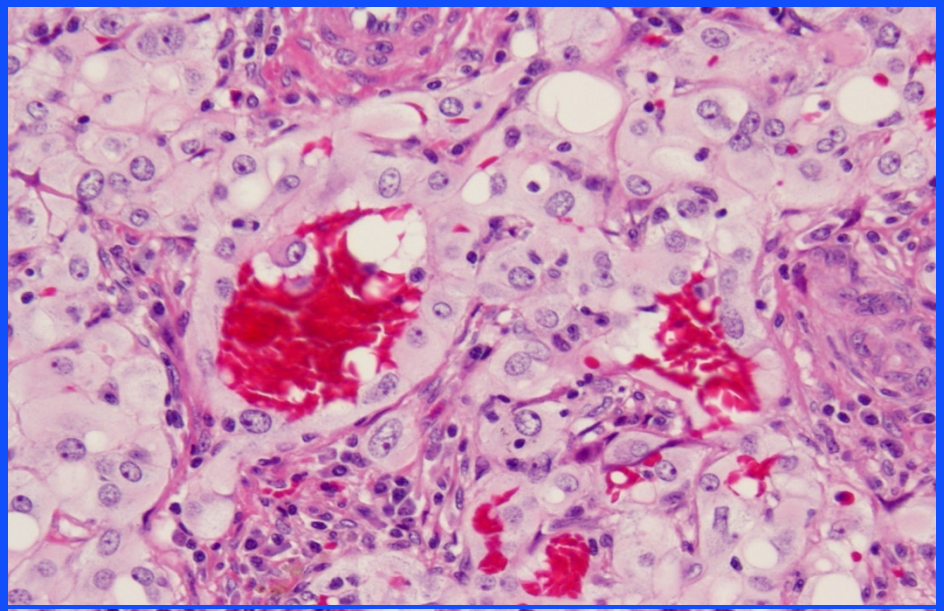
Vascular tumours

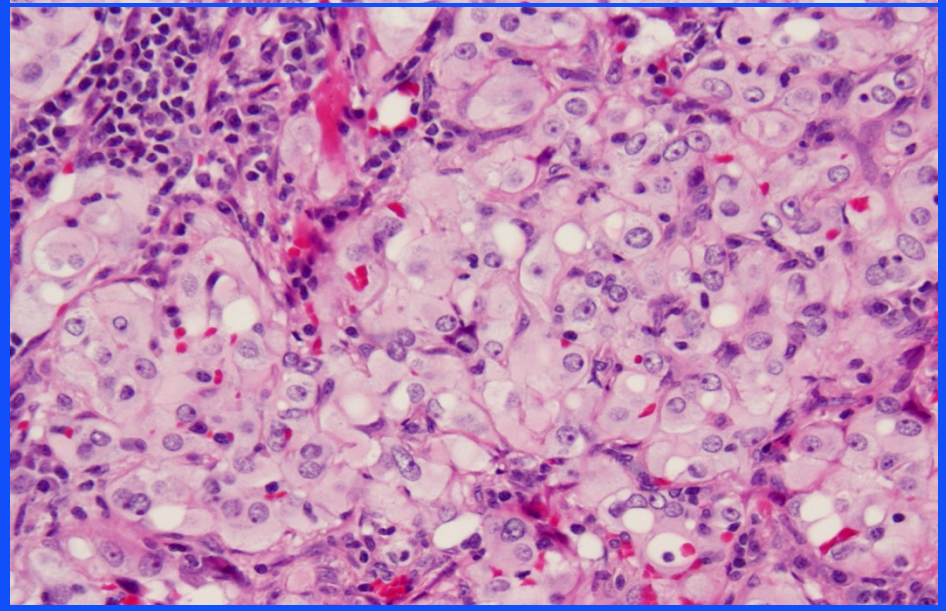
Pseudomyogenic haemangioendothelioma	**t(7;19)(q22;q13)**	***SERPINE1-FOSB***
Epithelioid haemangioendothelioma	**t(1;13)(p36.3;q25)**	***WWTR1-CAMTA1***

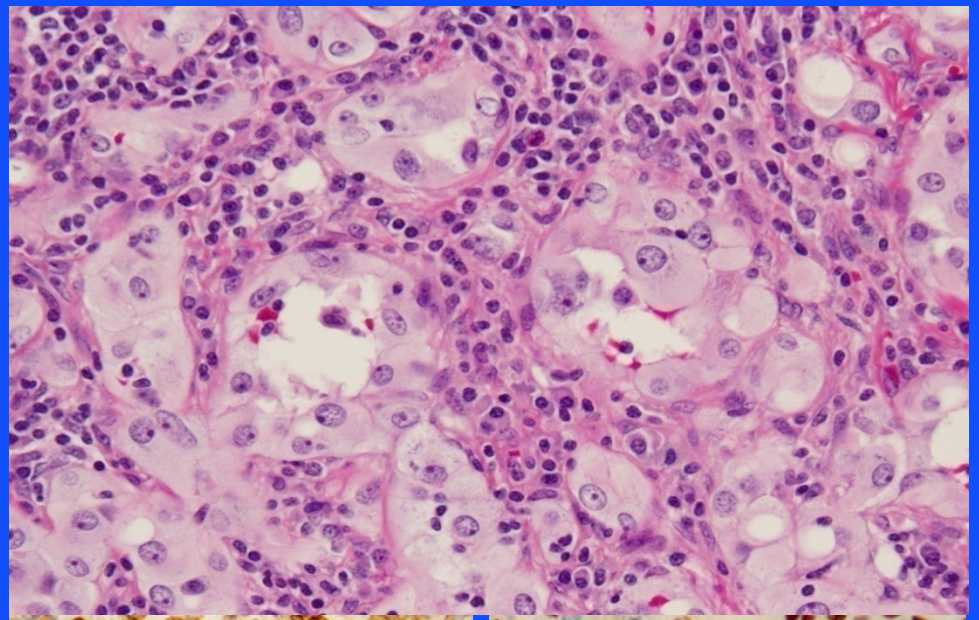
Angiosarcoma (breast)	***KDR* mutation**	**(25%)**
Angiosarcoma (secondary)	***MYC* amplification**	**(100%)**
	***FLT4* coamplification**	**(25%)**

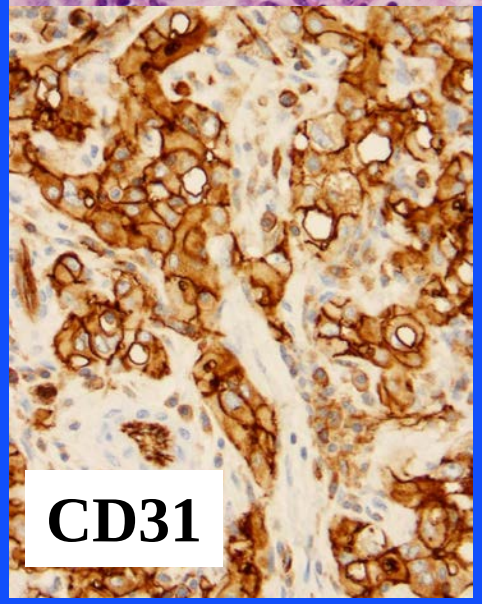
(Post-WHO – EHE – new subset with *YAP1-TFE3* gene fusion)

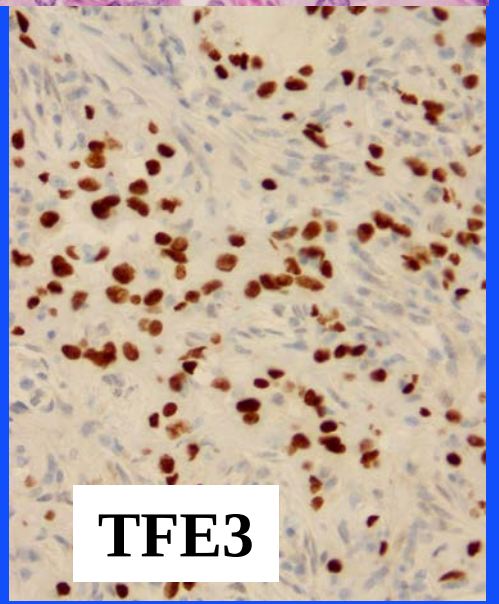
EHE Subset with *TFE3* gene overexpression











World Health Organization (2013) Classification of Tumours of Soft Tissue

NEW GENETICS (3)

Tumours of Uncertain Differentiation

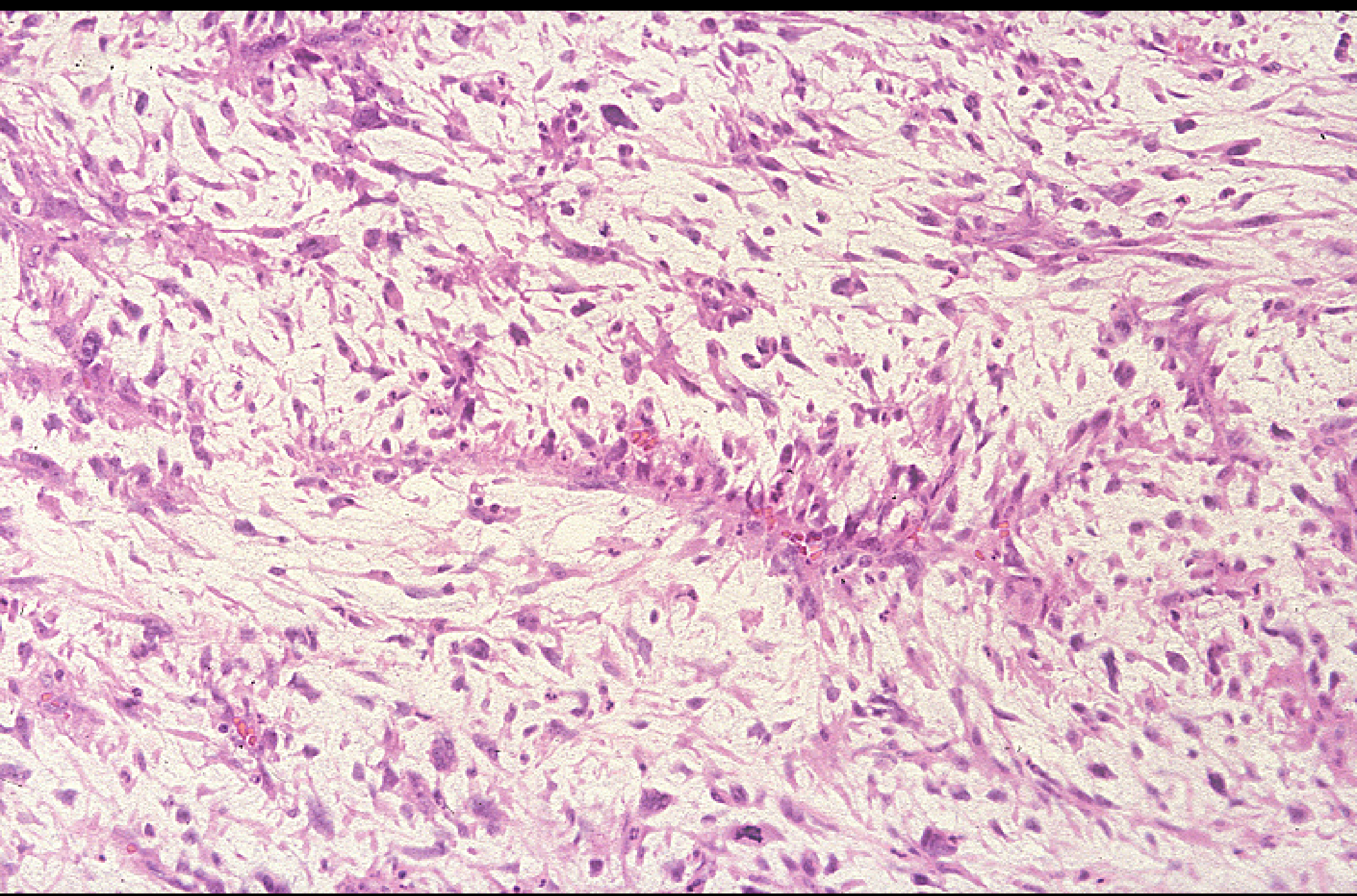
Angiomatoid 'FH'	**t(2;22)(q33;q12)**	***EWSR1-CREB1***	**> 90%**
	t(12;22)(q13;q12)	***EWSR1-ATF1***	**(rare)**
	t(12;16)(q13;p11)	***FUS-ATF1***	**(rare)**
OFMT	***PHF1* rearrangement**	**(on 6p21)**	**(80%)**
	- fused with *EP400* (55%) or *EPC1*		
Myoepithelial tumours (mainly malignant)	***EWSR1* rearrangement with various partners**		**(45% of cases)**
PEComa	***TSC2* deletion /rearrangement**		
	***TFE3* rearrangement (rare, distinct subset)**		
Undifferentiated round cell sarcoma	**t(4;19)(q35;q13.1)**	***CIC-DUX4***	
	t(10;19)(q35;q26)	***CIC-DUX4***	

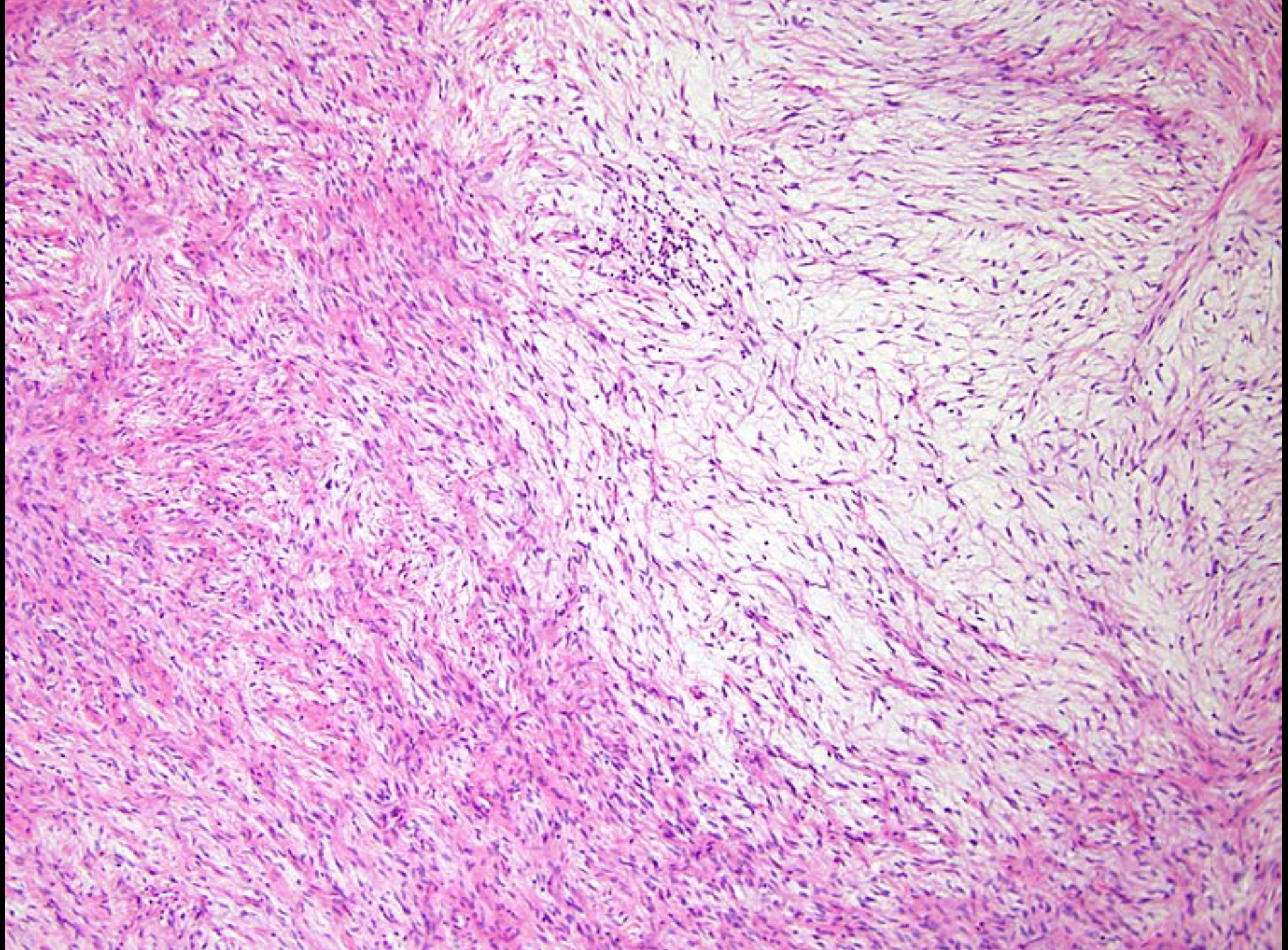
ISSUES STILL TO ADDRESS

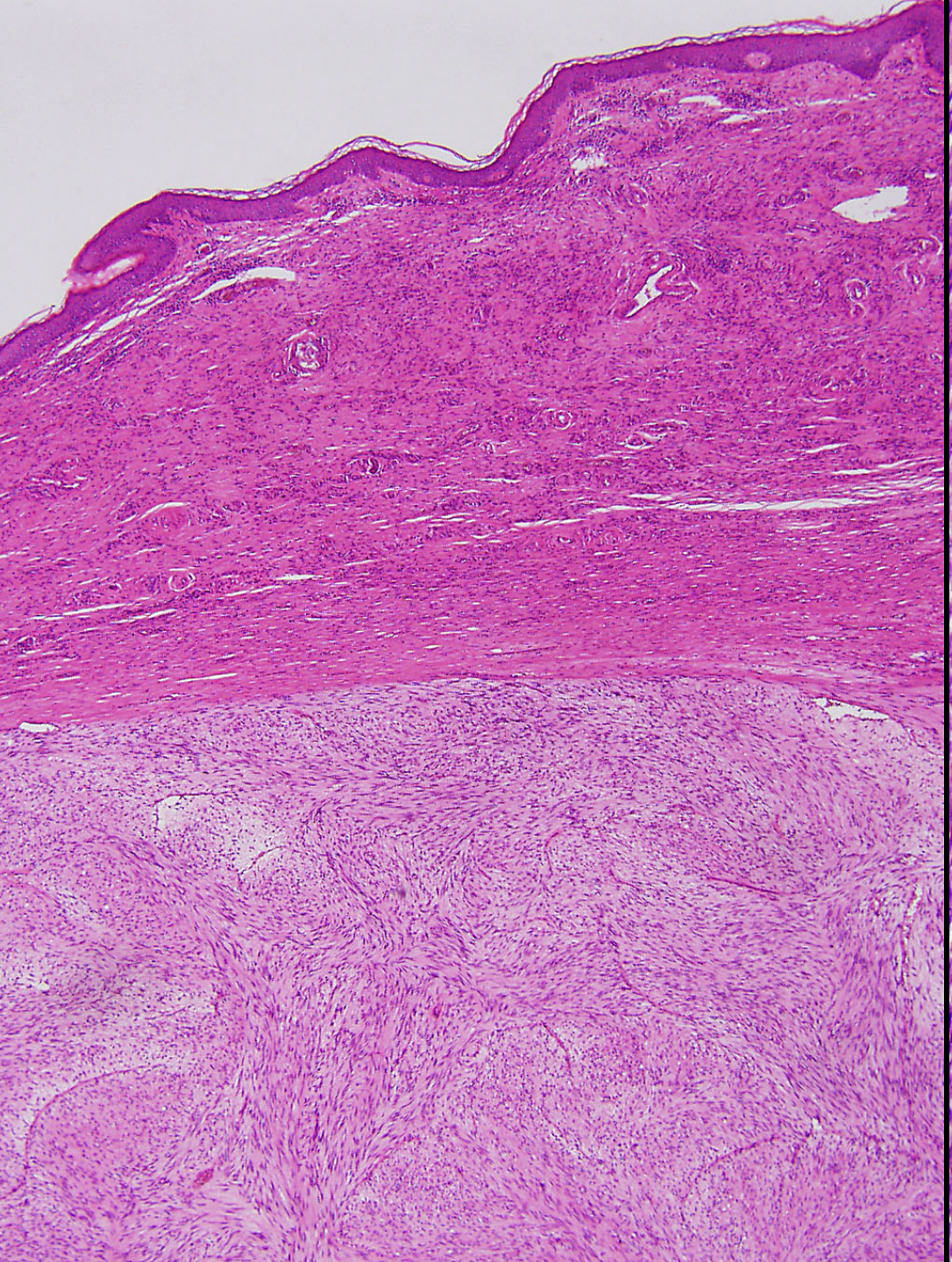
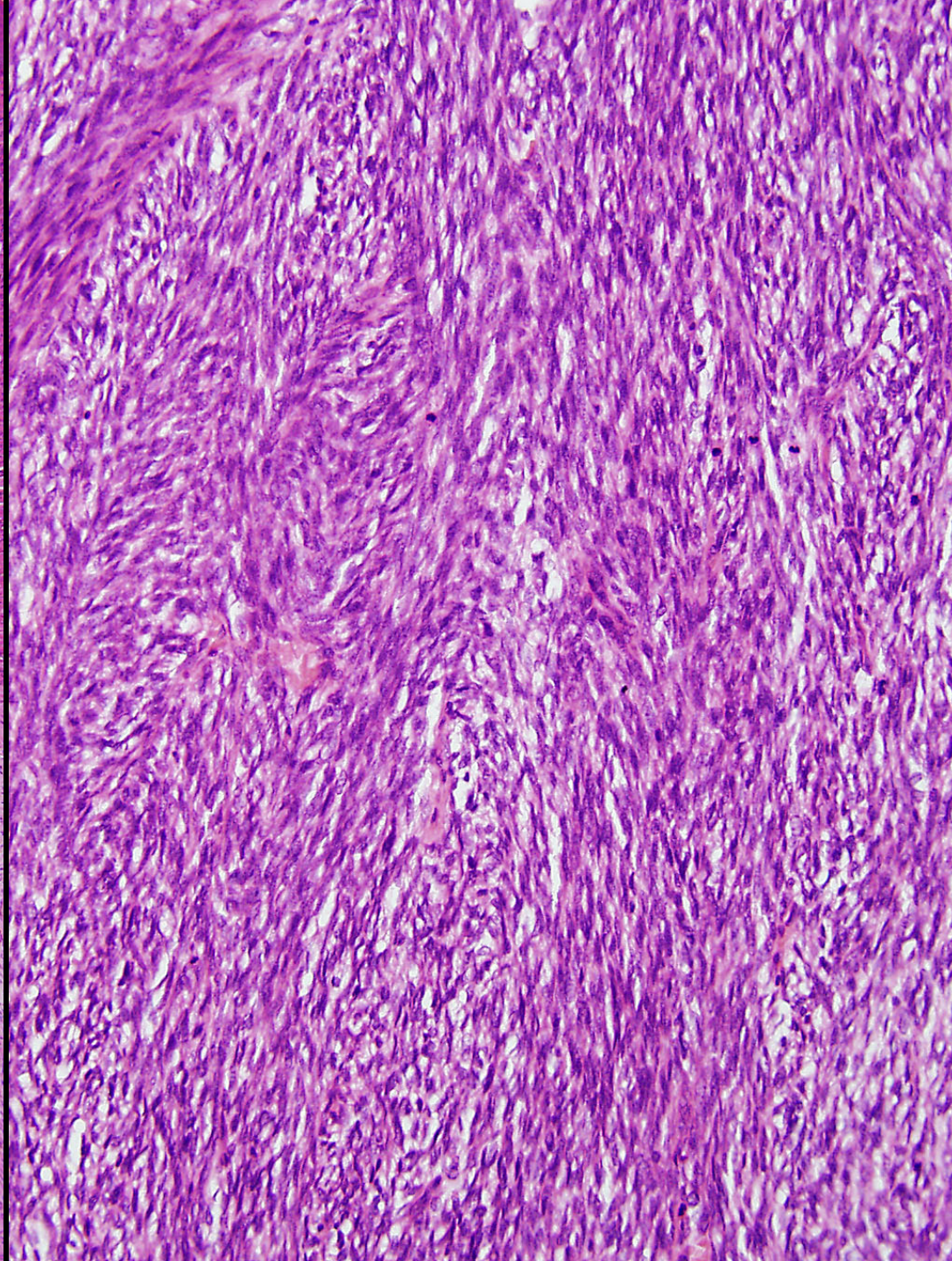
- Outdated diagnostic concepts
- Nomenclatural anomalies
- Lack of biologic understanding in some broad areas
- Genetic uncertainties

ADULT FIBROSARCOMA
CURRENT STATUS

- Most lesions so classified in the past would nowadays be relabelled synovial sarcoma or MPNST
- Malignant fibroblastic tumors in adults do exist – eg myxofibrosarcoma, LGFMS, fibrosarcomatous DFSP
- Other less well-defined tumors may well belong in this category, but fibrosarcoma NOS is not currently a useful concept
- Our ability to define fibroblasts/fibroblastic neoplasms is still very limited
- The fact that some but not all fibroblastic tumors form a continuum with myofibroblastic tumors adds another level of complexity





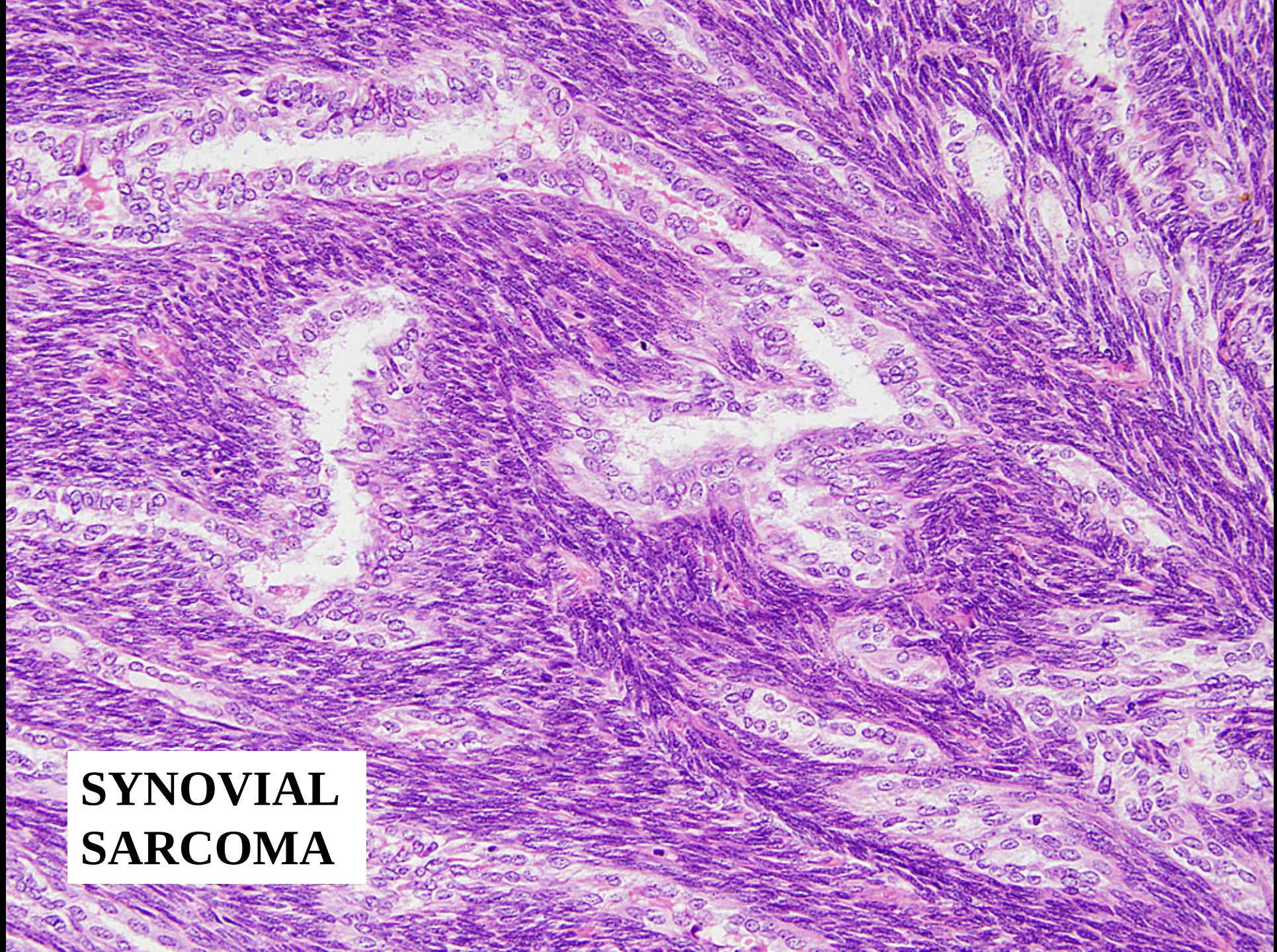
FIBROBLASTIC SARCOMAS
PROBLEMS TO CONSIDER

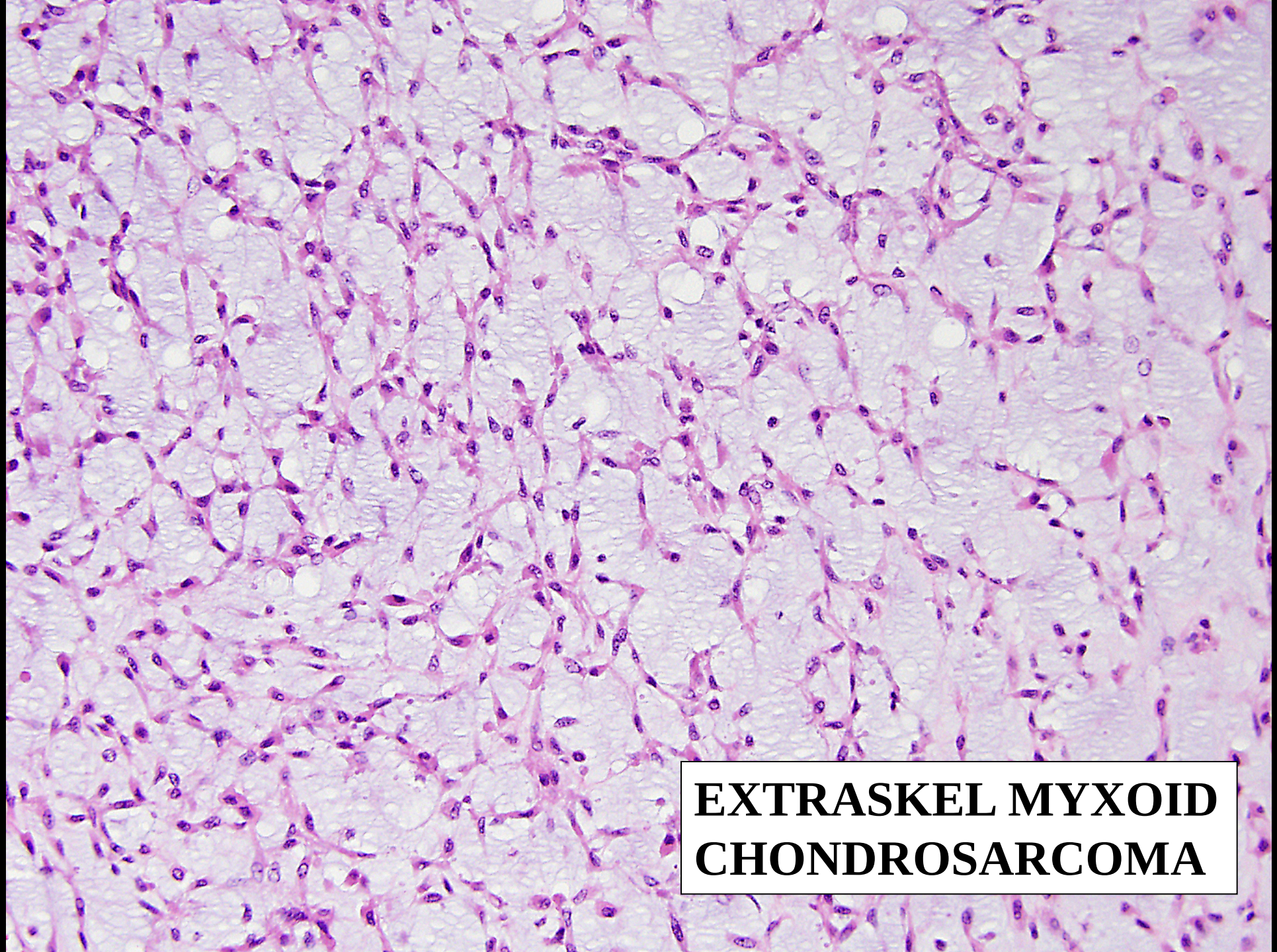
- **Virtual non-existence of adult-type fibrosarcoma as presently defined**
- **Difficulties in reproducibly defining fibroblastic differentiation**
- **Undoubted existence of fibroblastic sarcomas, some with reproducible features, some without**

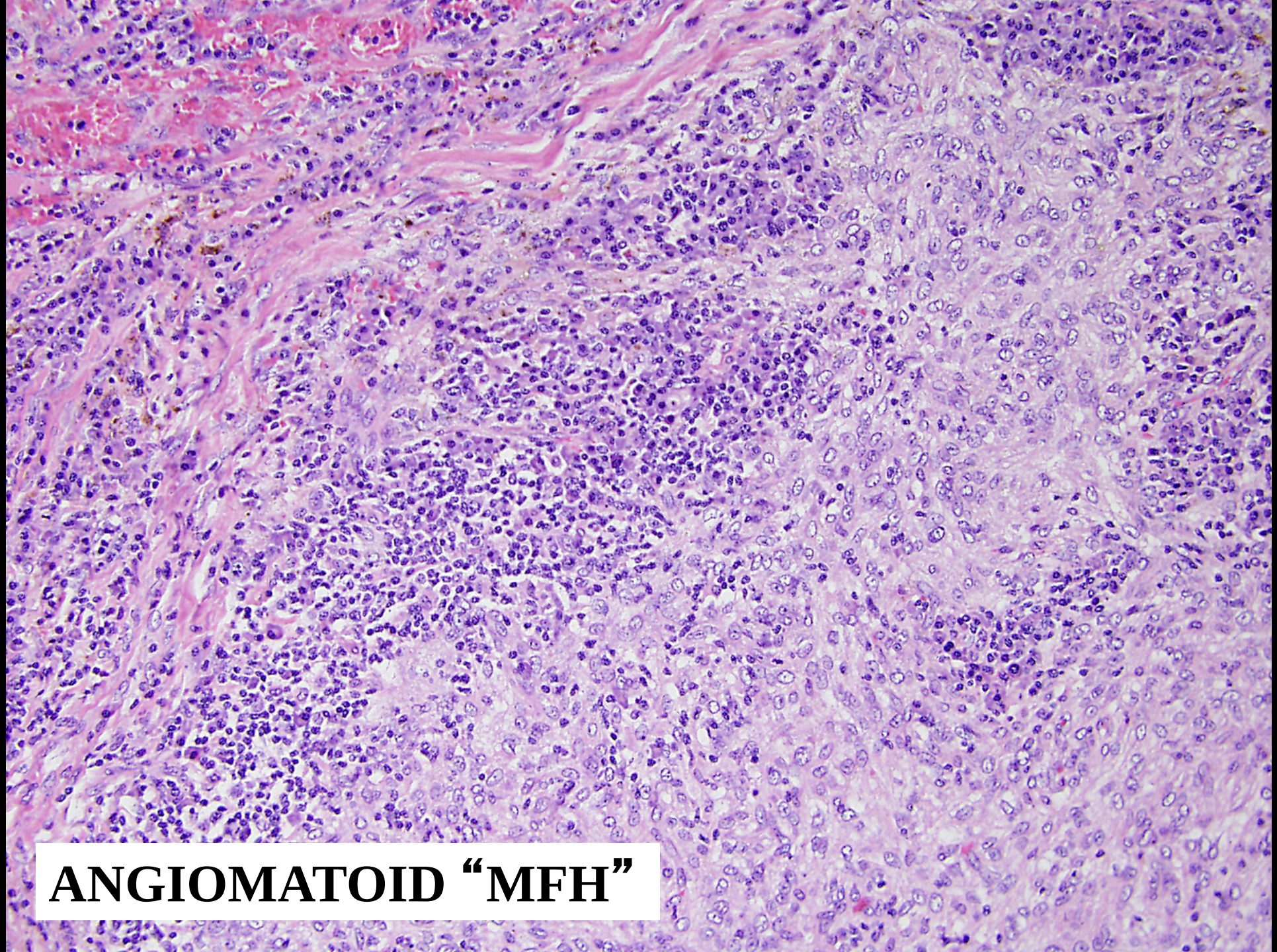
NOMENCLATURAL ANOMALIES

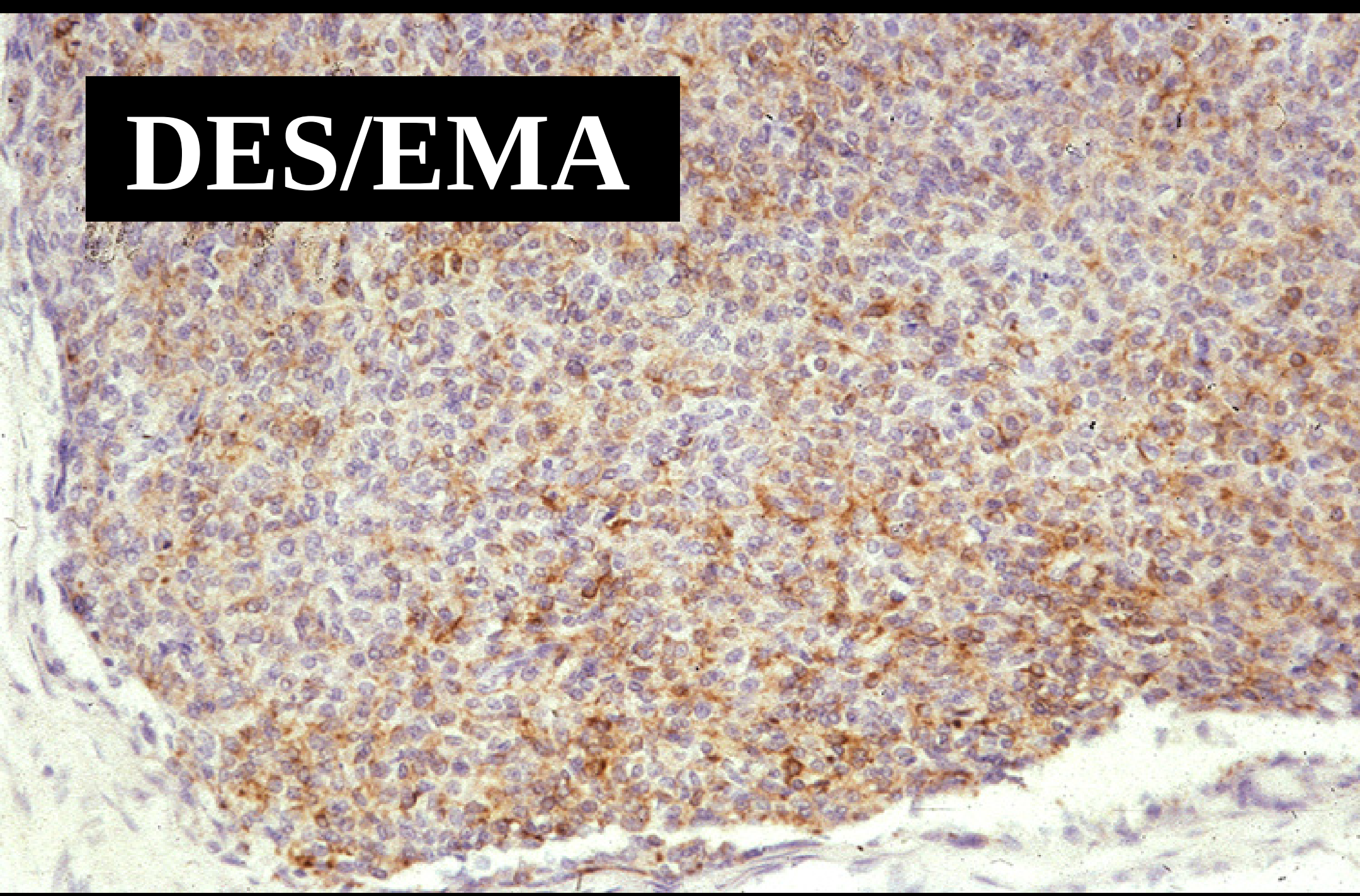
Practical considerations vs scientific accuracy
How best to define nomenclature ?
Historical precedent vs line of differentiation (which may be unknown) vs genetics
Potential consequences for patient care
(Isn't it our job to re-educate clinicians ?)
Fossilising sociologic issues …..

Is there another branch of science that is quite so slow to change ?

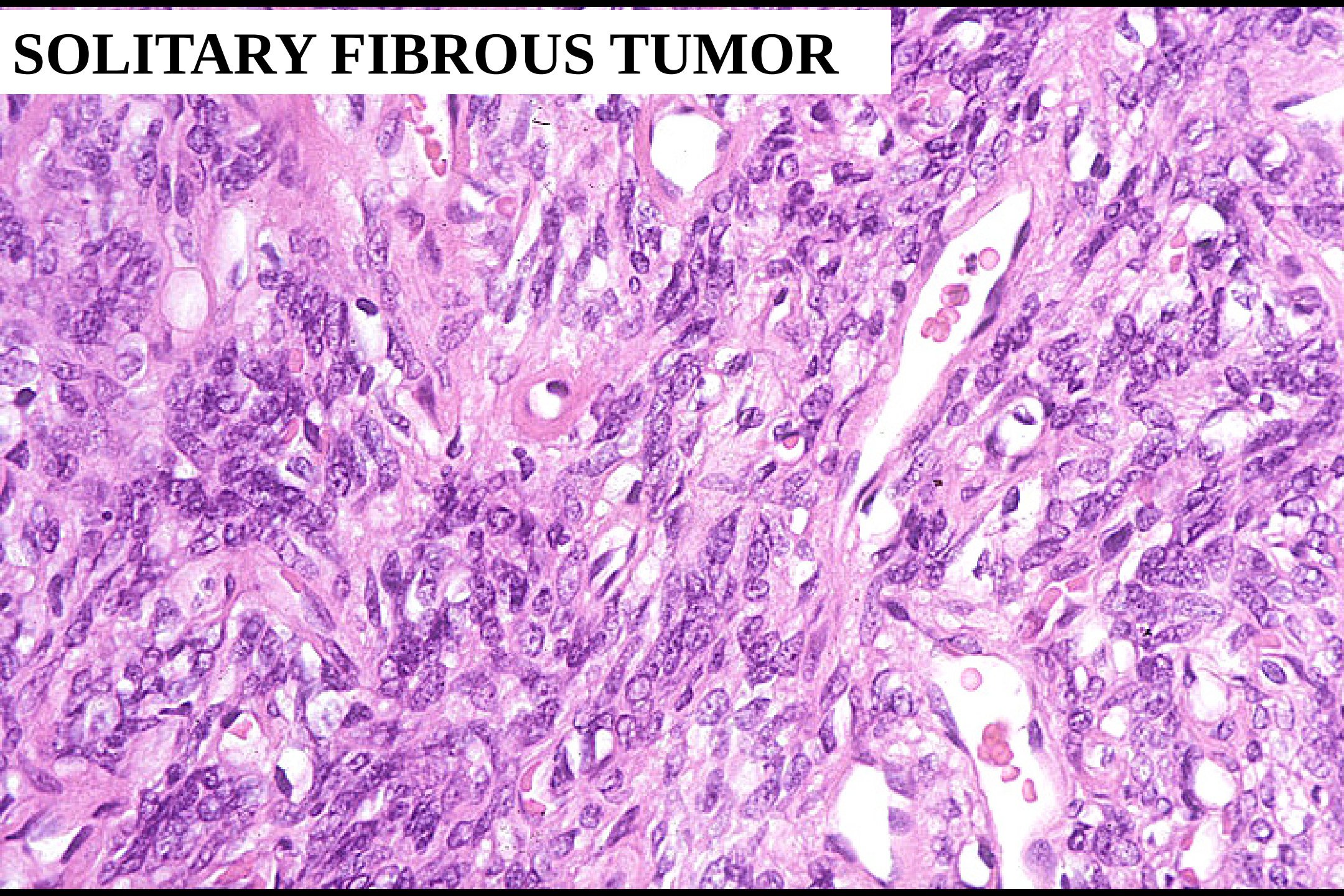

SYNOVIAL
SARCOMA

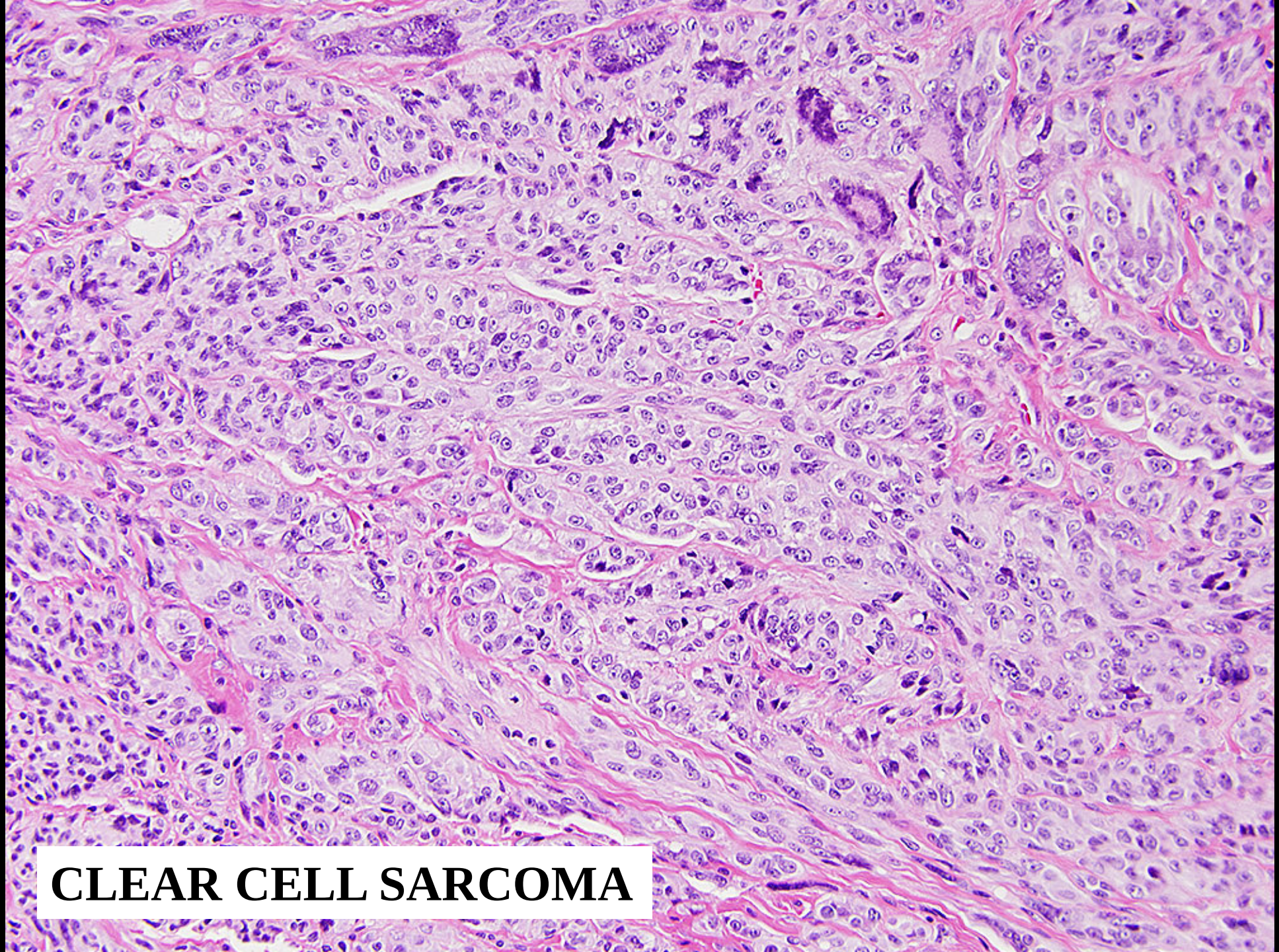

EXTRASKEL MYXOID
CHONDROSARCOMA


ANGIOMATOID “MFH”


DES/EMA

SOLITARY FIBROUS TUMOR



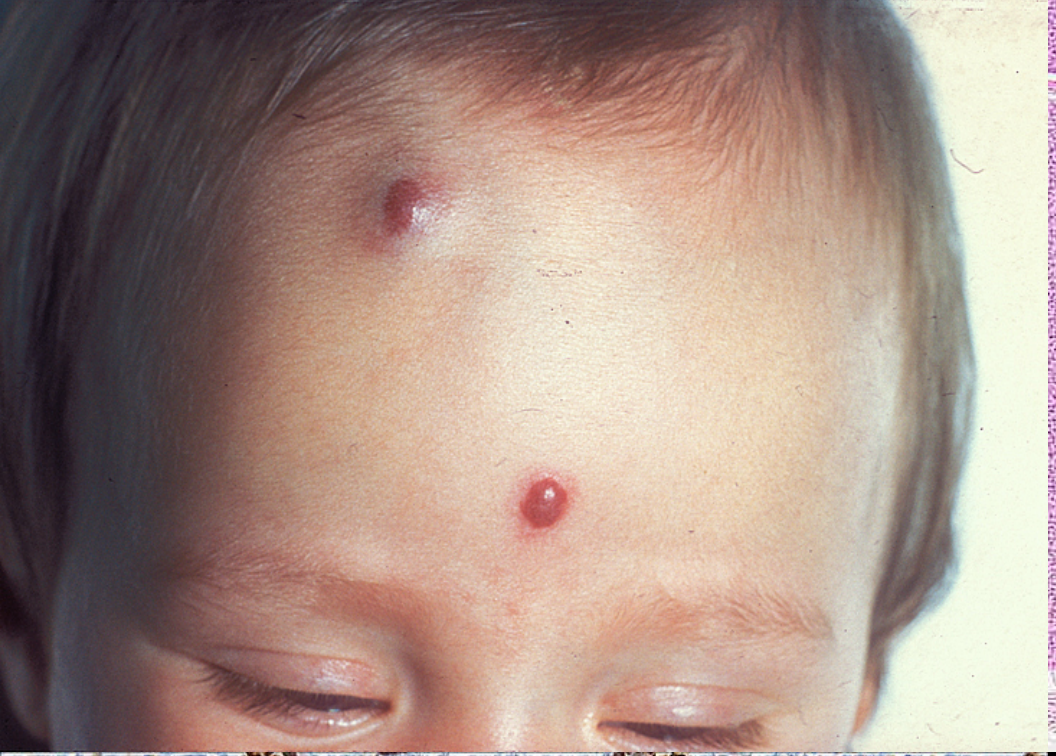

CLEAR CELL SARCOMA

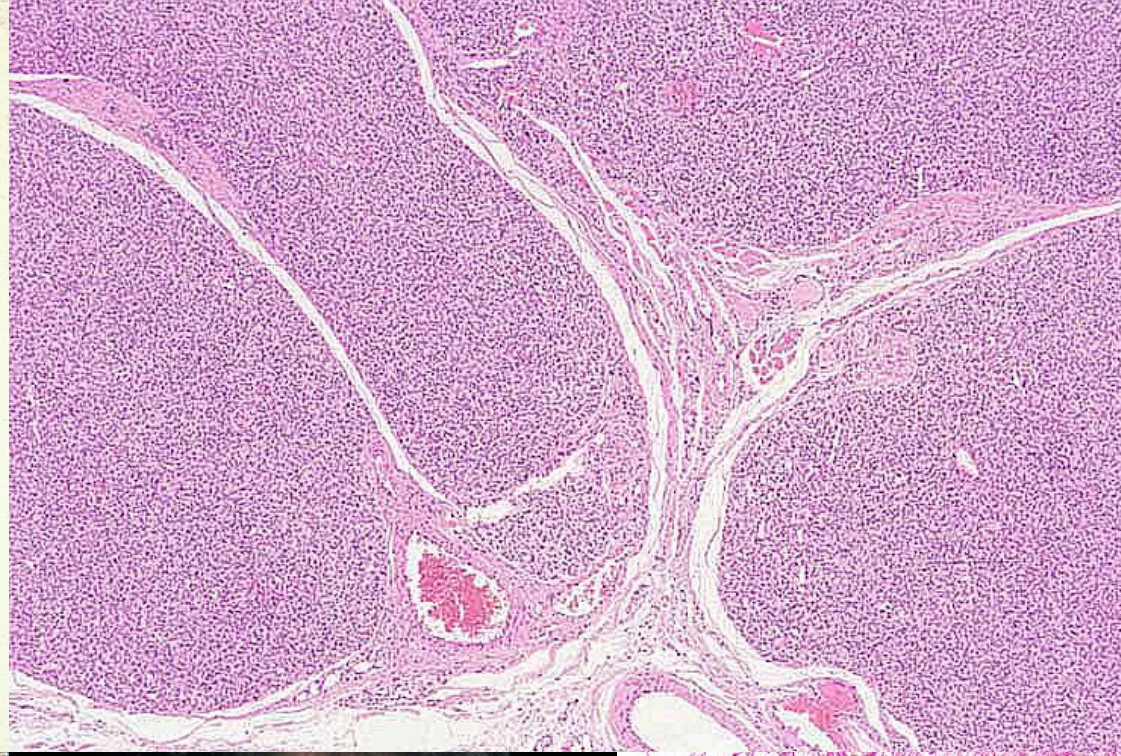
NOMENCLATURAL ANOMALIES
POSSIBLE WAYS FORWARD

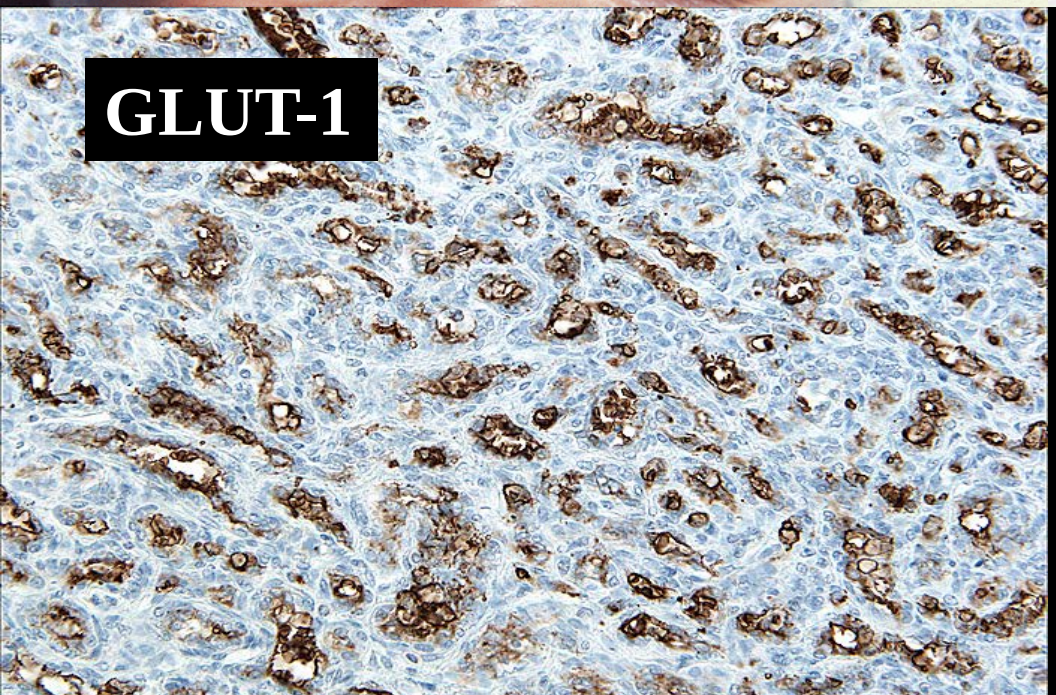
- **Openness to gradual revision on the basis of good/rational evidence**
- **Willingness to accept genetic definitions (as with leukemias)**
- **Committment to bringing clinicians along with us (perhaps thro' concensus conferences)**
- **? 'Radical' approaches, dismissing time-honored terminology - ? Less likely to succeed**
- **? WHO Working Groups should formally validate terminology**

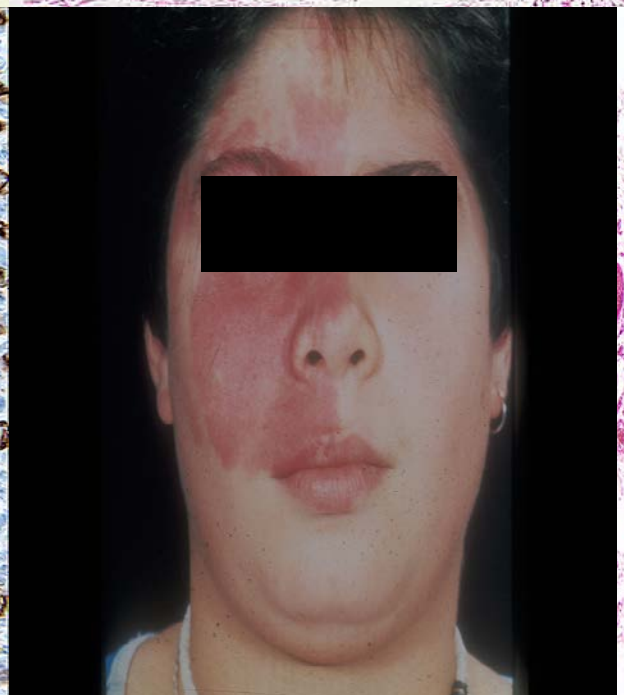
LACK OF BIOLOGIC UNDERSTANDING

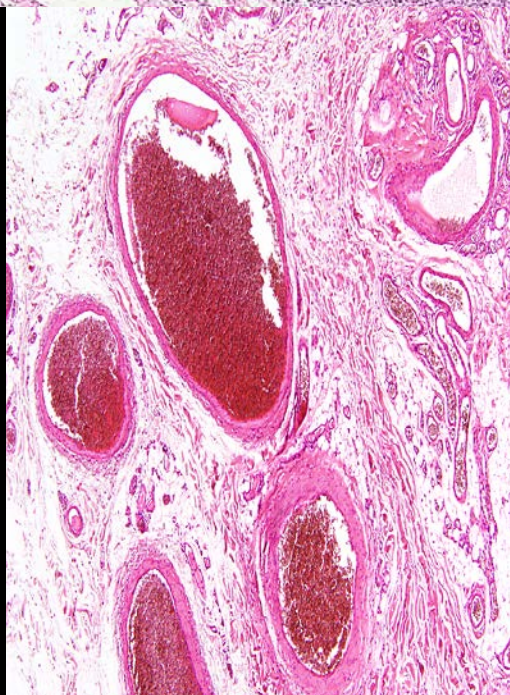
Vascular tumours – par excellence !
Neoplasm vs malformation / hamartoma
How to define a neoplasm ?
Relevance of clonality / mixed cell types
Limited genetic data
Blood vascular vs lymphovascular
Potential to be overtaken by clinicoradiologic classification

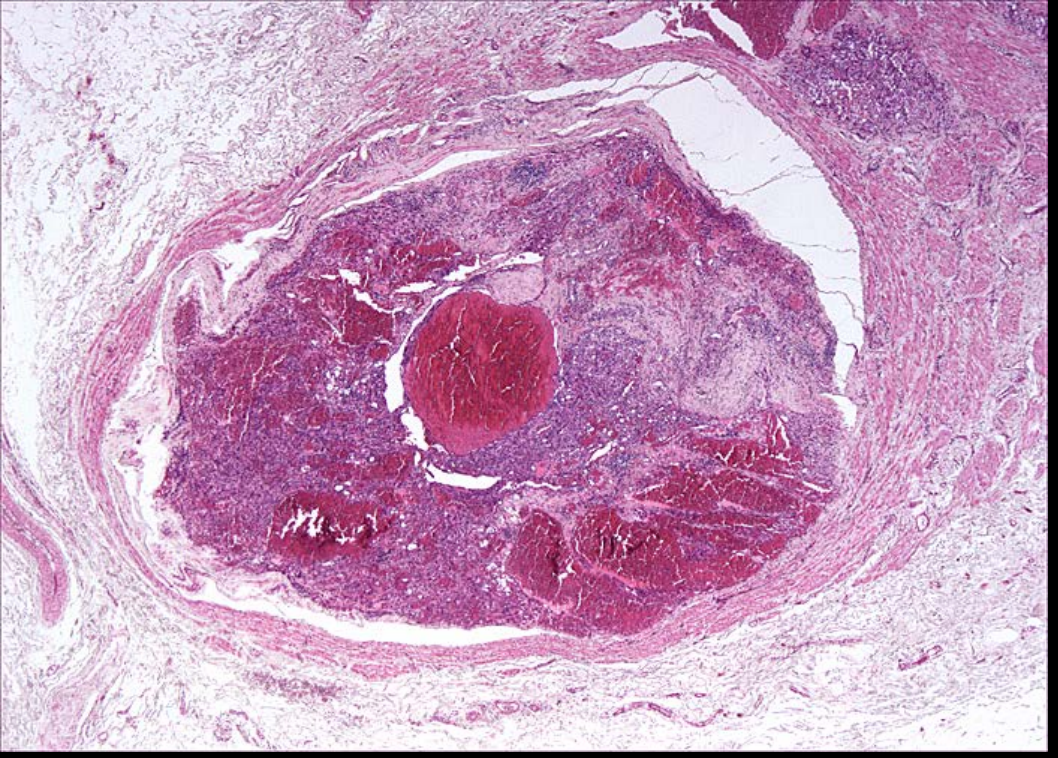


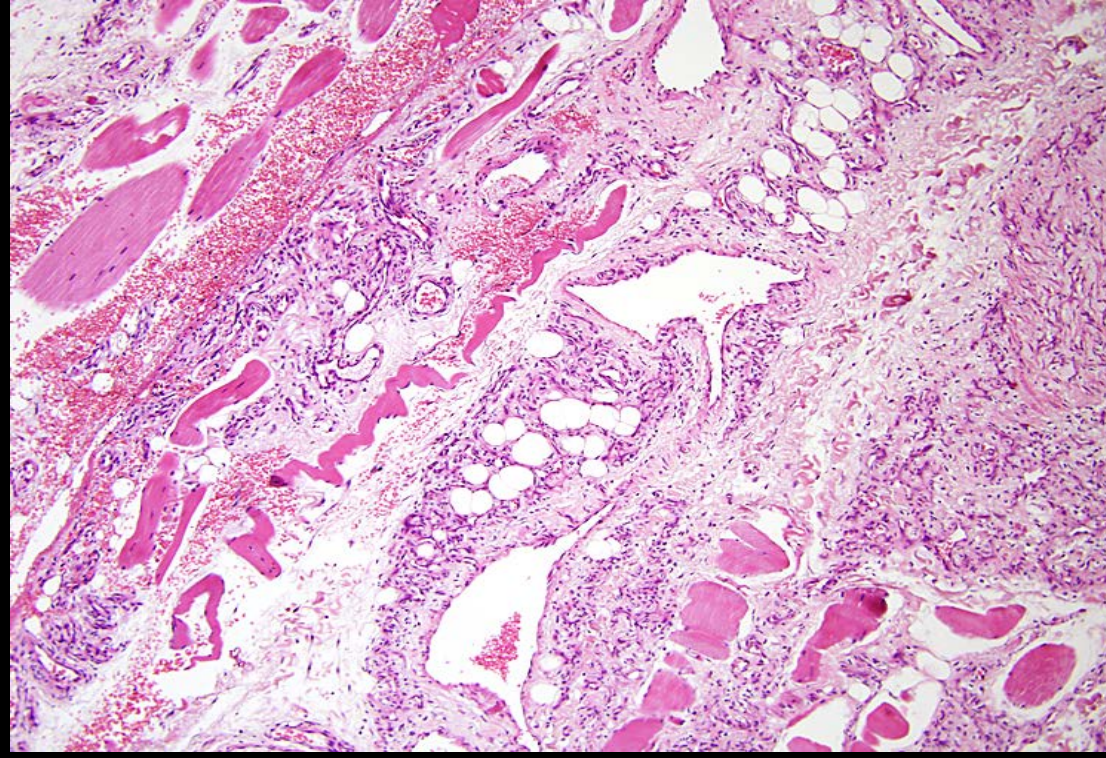


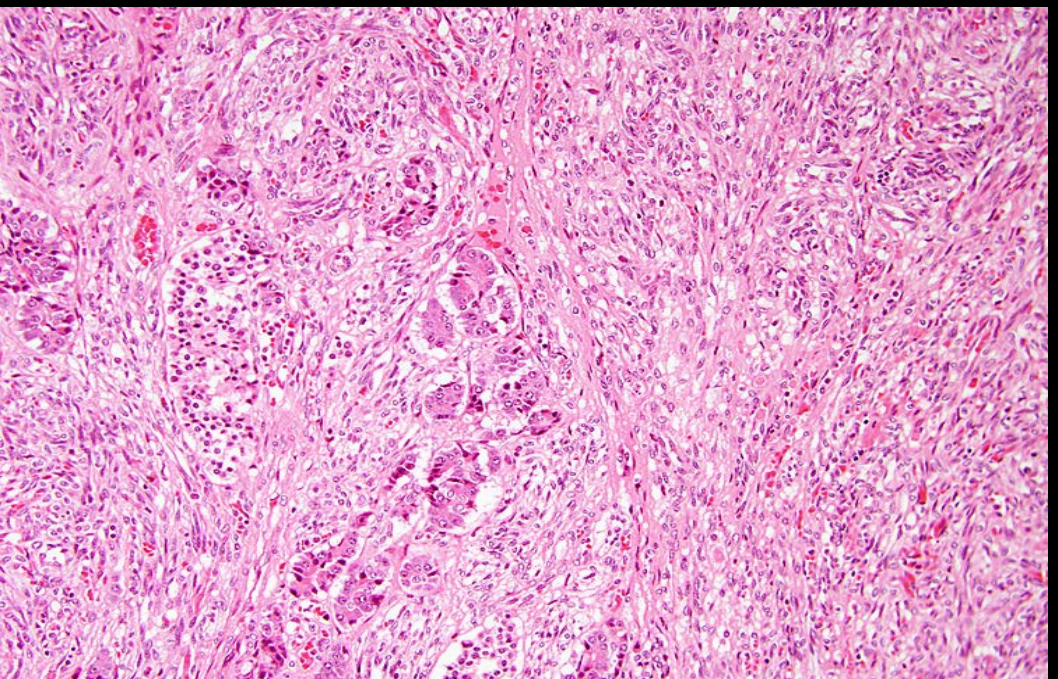

GLUT-1

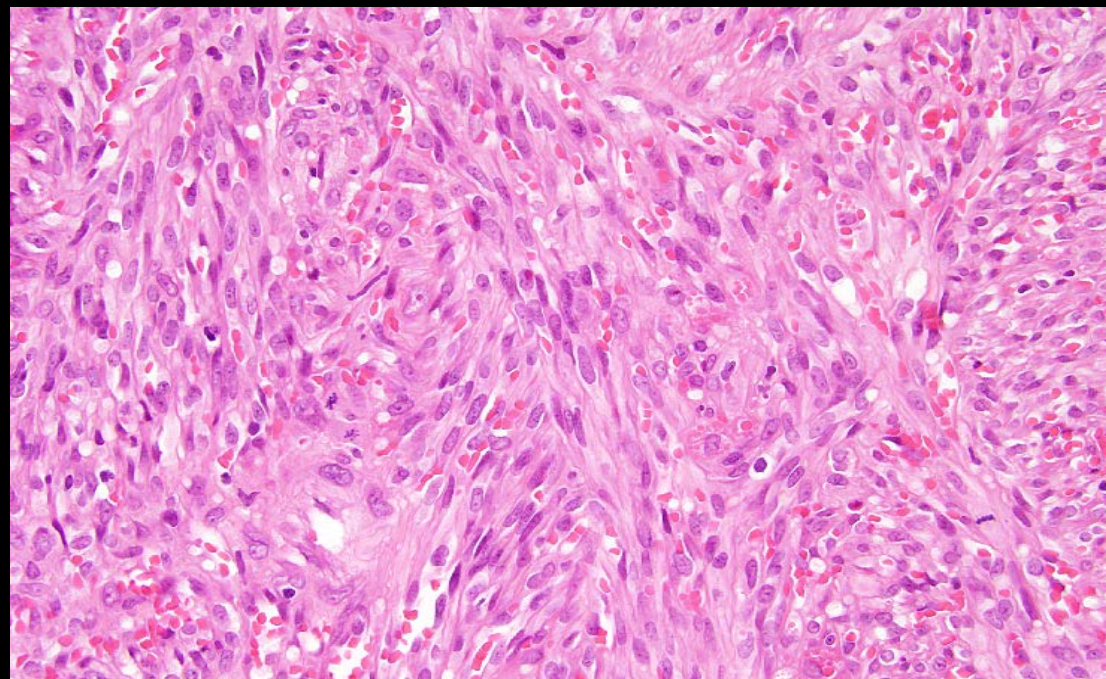










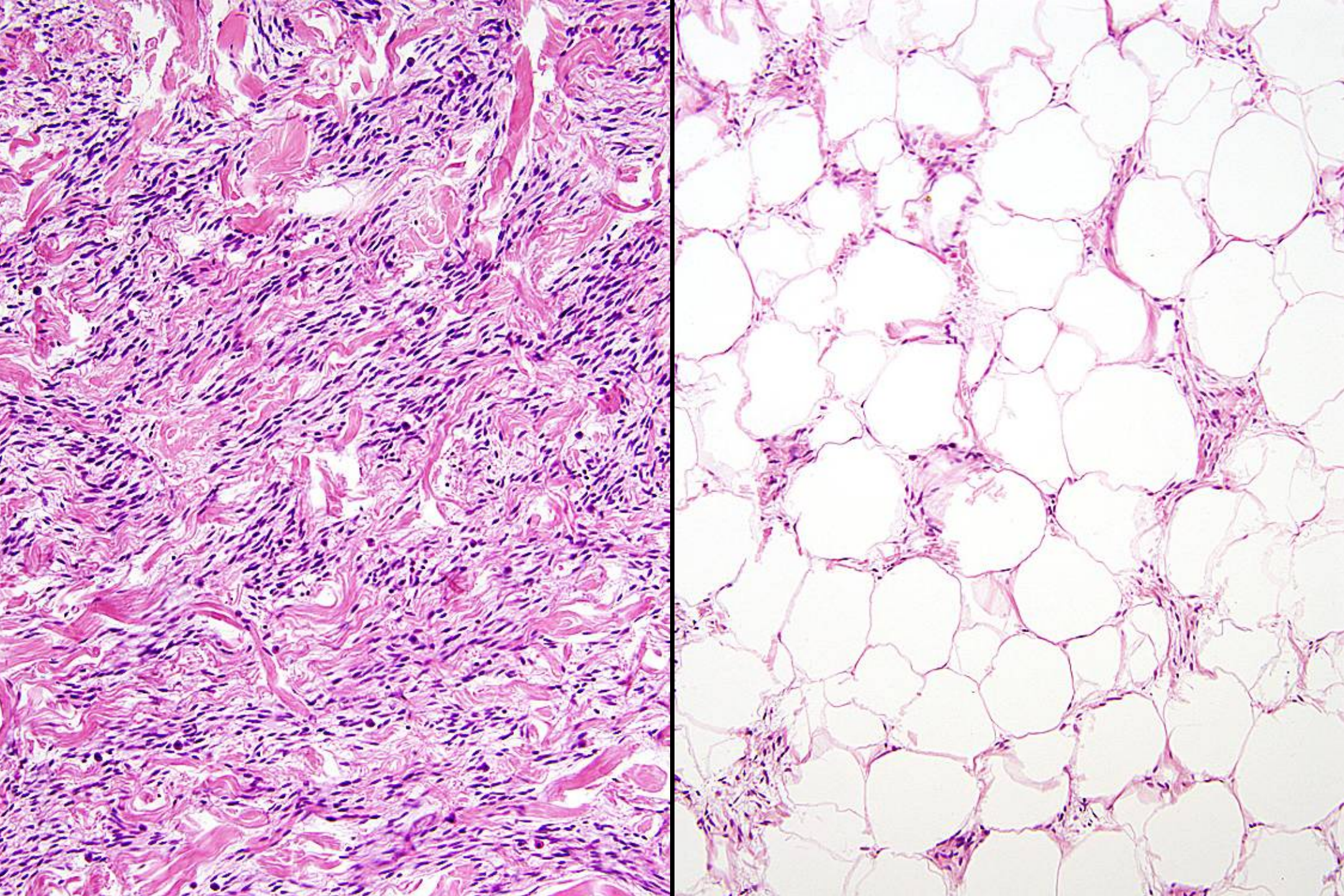


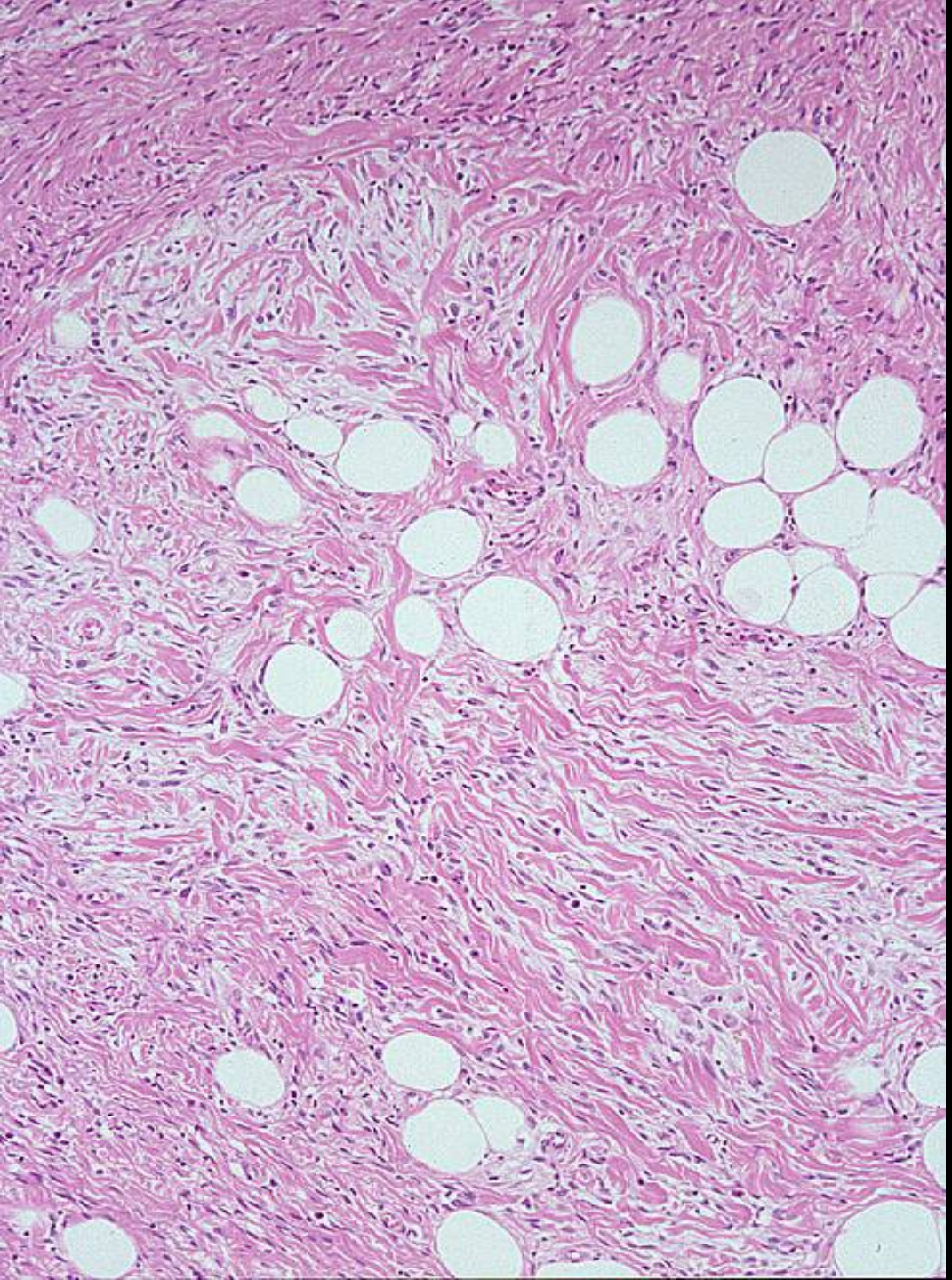
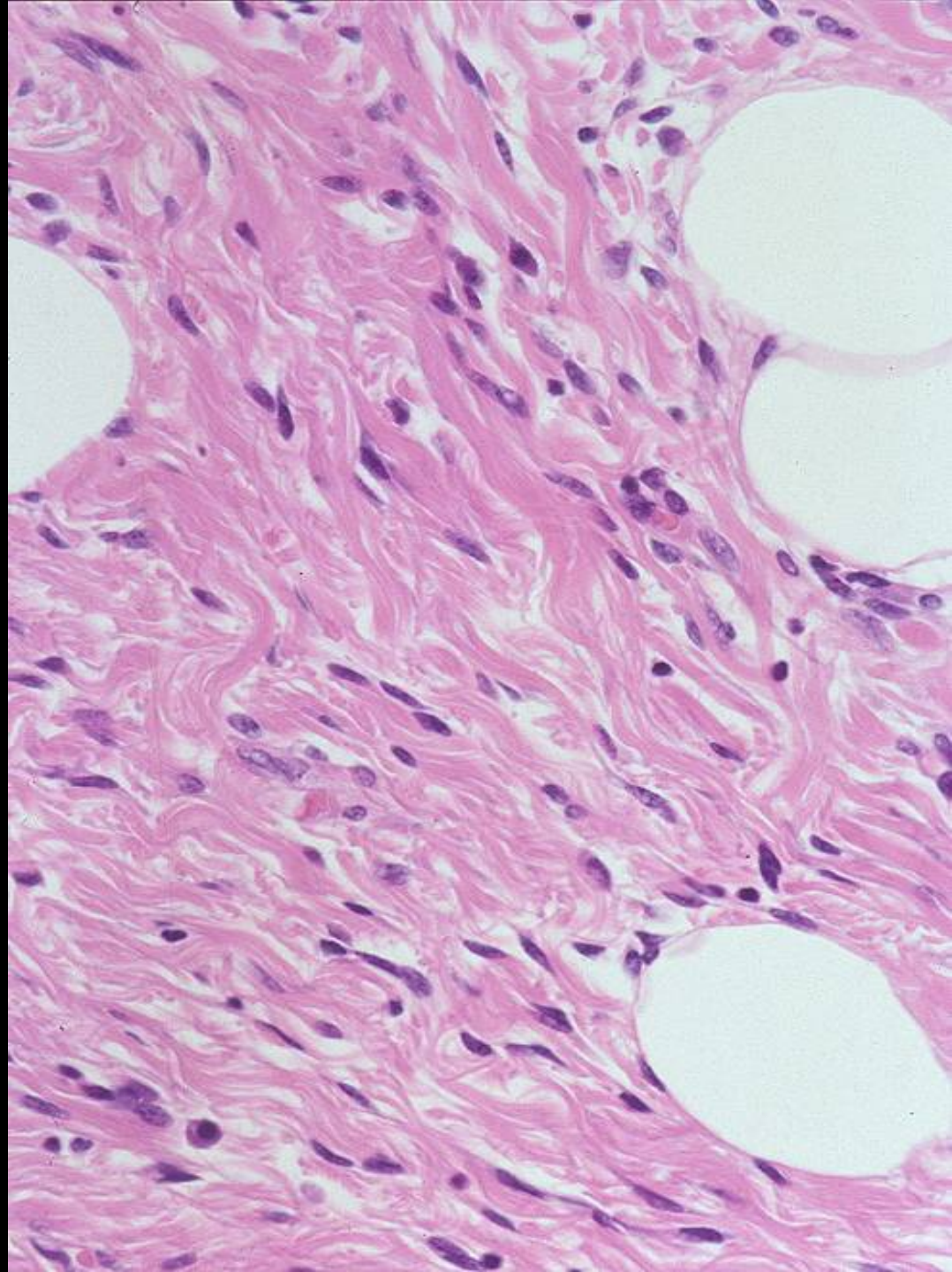
SOFT TISSUE TUMORS
EXAMPLES OF GENETIC OVERLAP

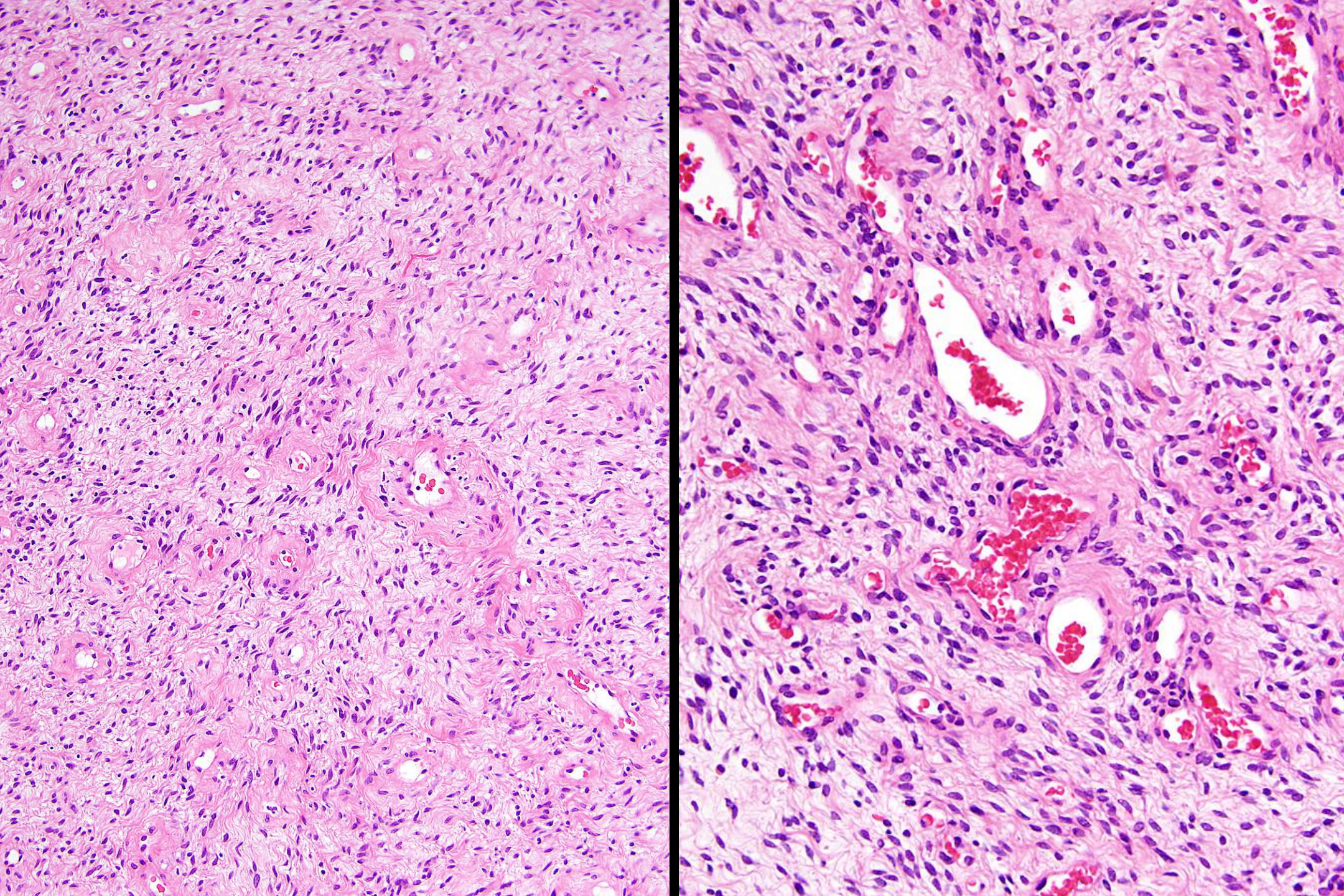
- Tumors with similar morphology
- Tumors that may show hybrid morphology
- Seemingly totally unrelated tumors
- Tumors of different lineages

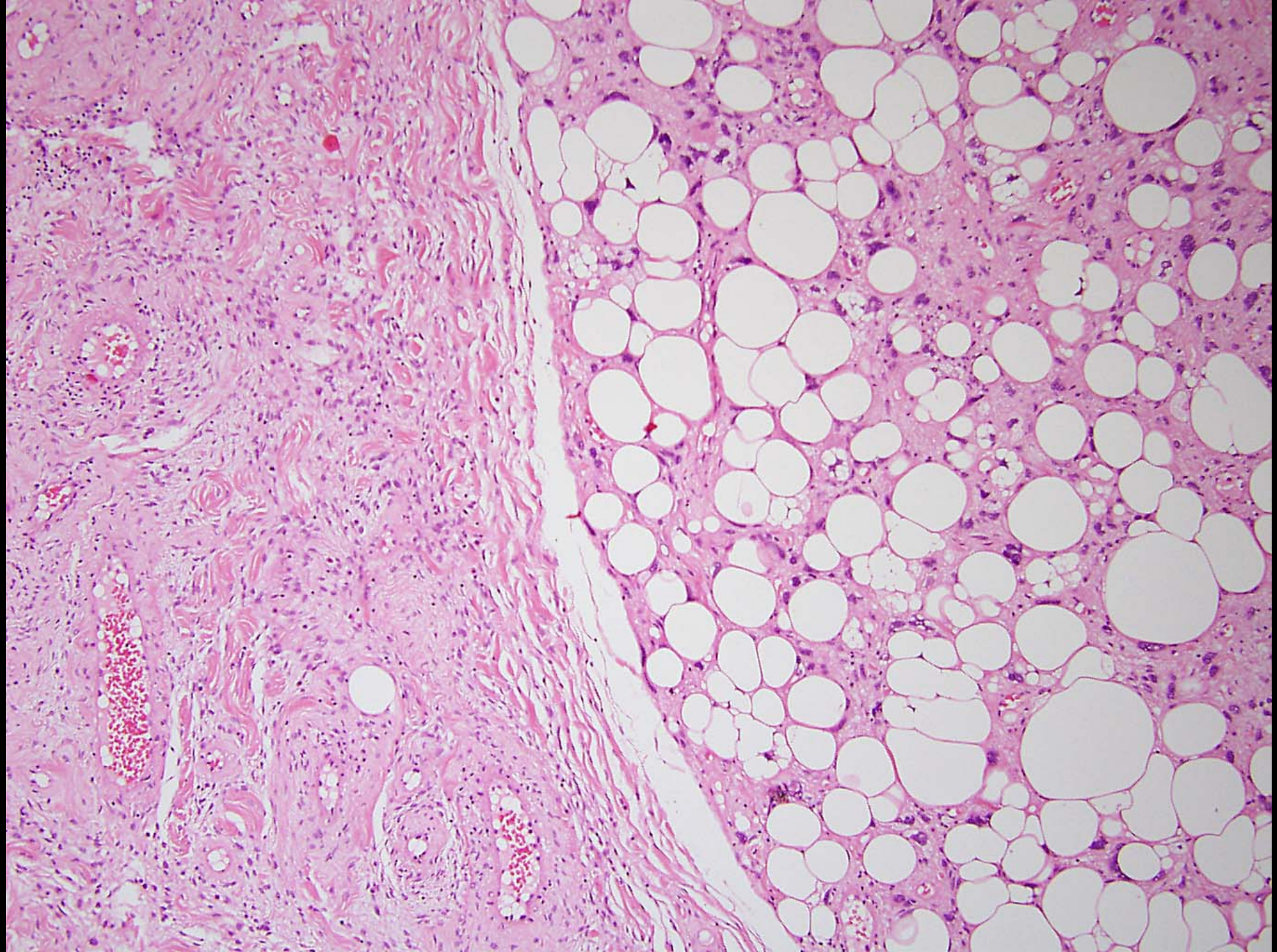
EXAMPLES OF GENETIC OVERLAP

- **Tumors with similar morphology**
  e.g. spindle cell lipoma, cellular angiofibroma, mammary-type myofibroblastoma
- **Tumors that may show hybrid morphology**
  e.g. DFSP and giant cell fibroblastoma
- **Seemingly totally unrelated tumors**
  e.g. clear cell sarcoma and angiomatoid "MFH"
- **Tumors of different lineages**
  e.g. infantile fibrosarcoma and secretory carcinoma







RELATIONSHIP BETWEEN SPINDLE CELL LIPOMA, MAMMARY-TYPE MYOFIBROBLASTOMA & CELLULAR ANGIOFIBROMA

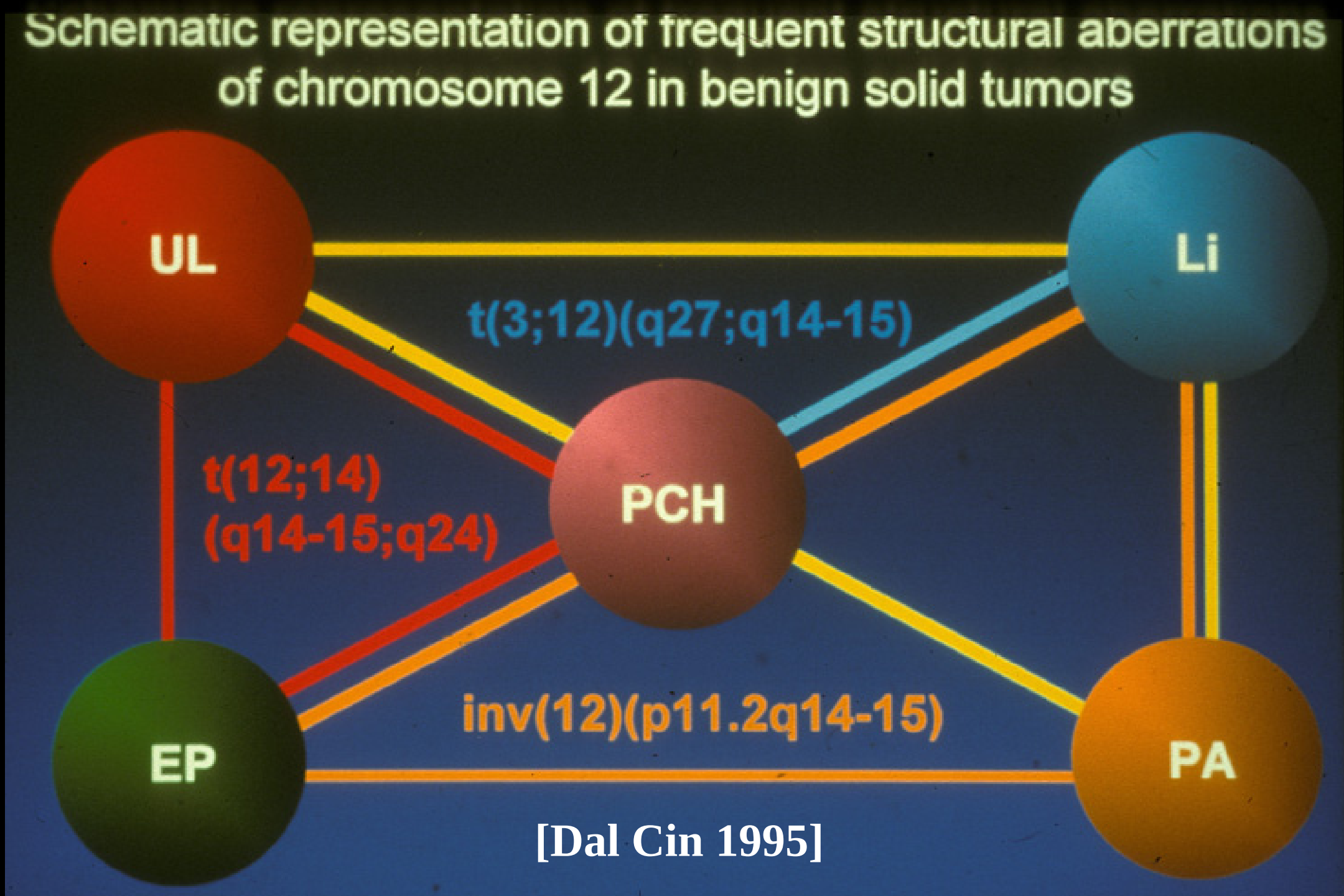
- Generally different anatomic sites - does this influence the phenotype ?
- Morphologic overlap with subtle differences
- Immunophenotypic differences
- Same rearrangement/loss of 13q14 (Rb)
- All benign/rarely recur
- Cellular angiofibroma may perhaps have potential for progression

SOFT TISSUE TUMORS
TYPES OF GENETIC OVERLAP

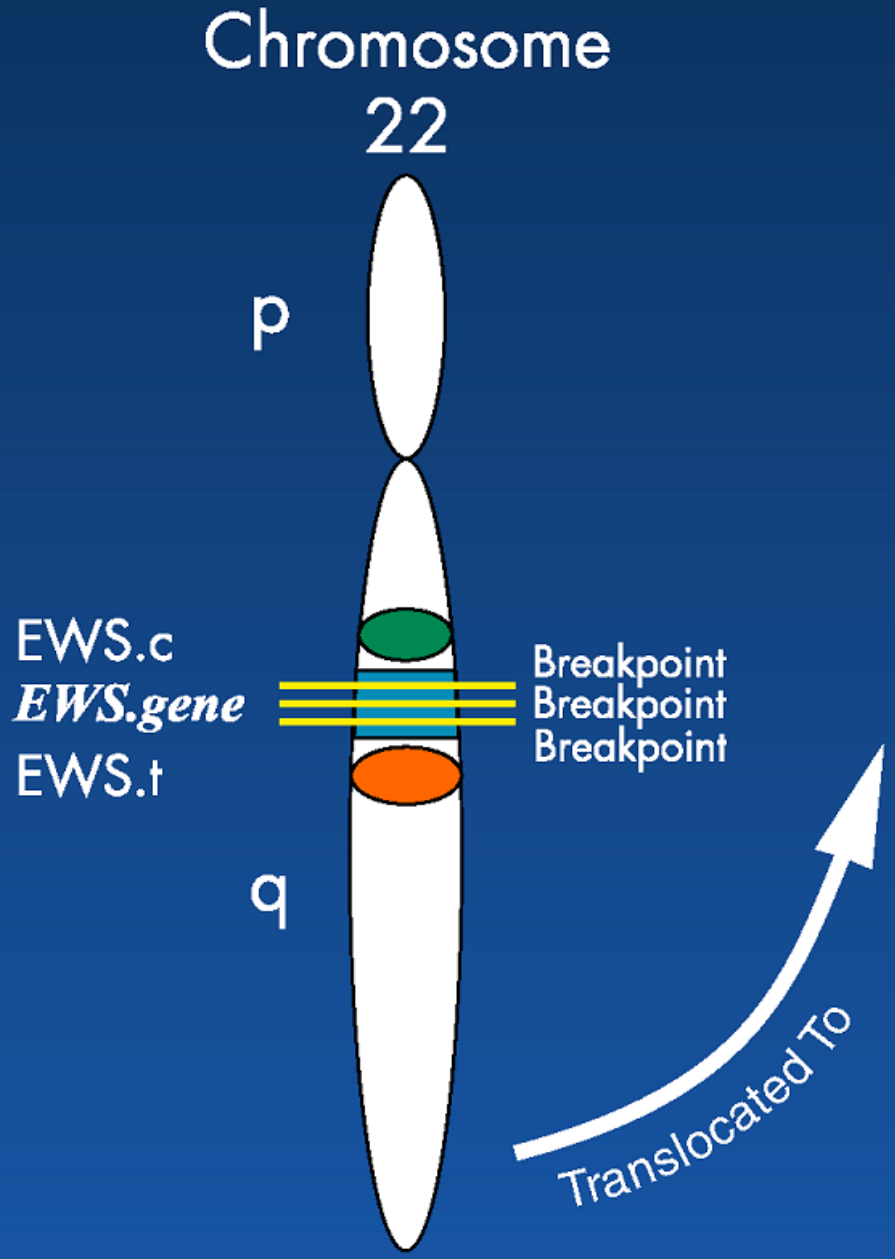
- **Frequently involved genes in multiple different tumor types, e.g. *EWSR1*, *HMGA2***
- **Interchangeable genes in multiple distinct tumor types, e.g. *EWSR1* and *FUS***
- **Shared fusion genes in tumors thought to be distinct entities, e.g. *TGFBR3-MGEA5***
- **Shared fusion genes in tumors which appear totally unrelated, e.g. *EWSR1-ATF1***

IMPACT OF GENETICS
SHARED GENE REARRANGEMENTS

- ***EWSR1***
- ***FUS***
- ***CREB1***
- ***ATF1***
- ***HMGA-2***


Schematic representation of frequent structural aberrations of chromosome 12 in benign solid tumors
UL
Li
t(3;12)(q27;q14-15)
t(12;14)
(q14-15;q24)
PCH
inv(12)(p11.2q14-15)
EP
PA

[Dal Cin 1995]



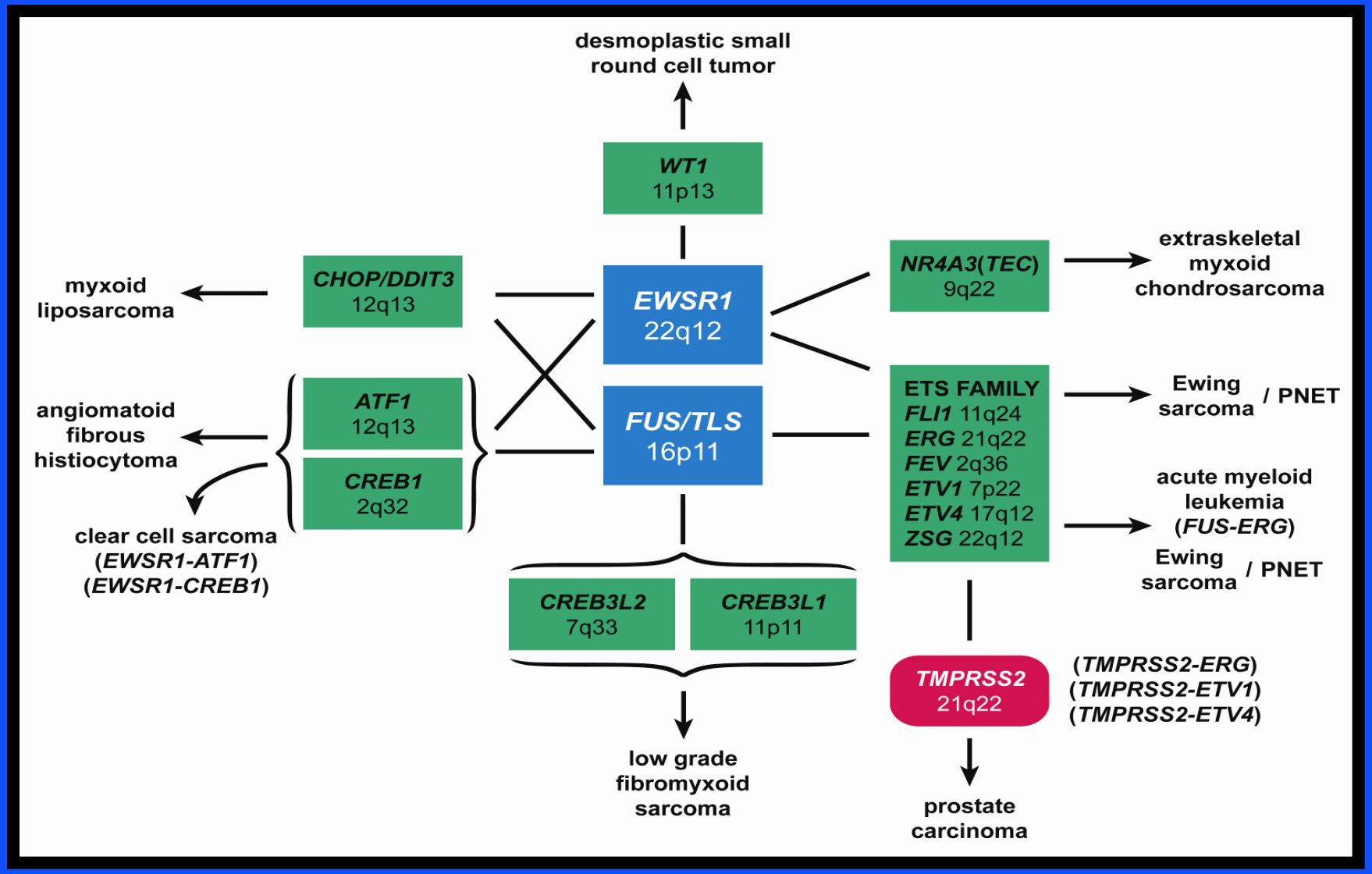
Ewing's sarcoma
FLI1 >80%
ERG 10-15%
ETV1 (<5%)
E1AF (<5%)
FEV (<5%)

DSRCT
WT1

Clear cell sarcoma
ATF1

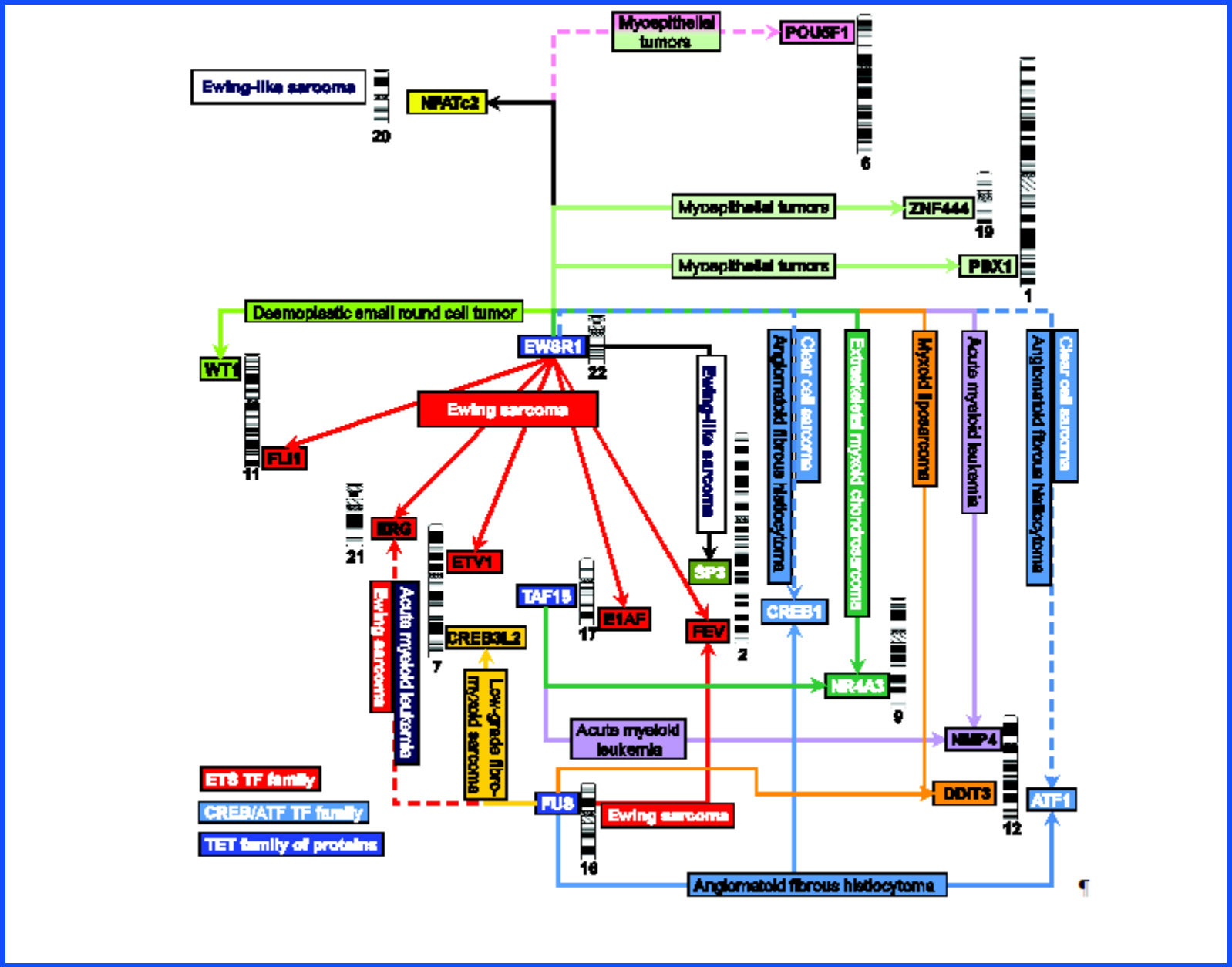
Extraskel myxoid chondrosarc
CHN & others

[2001]



Courtesy of Dr. Alex Lazar, MDACC (2008)

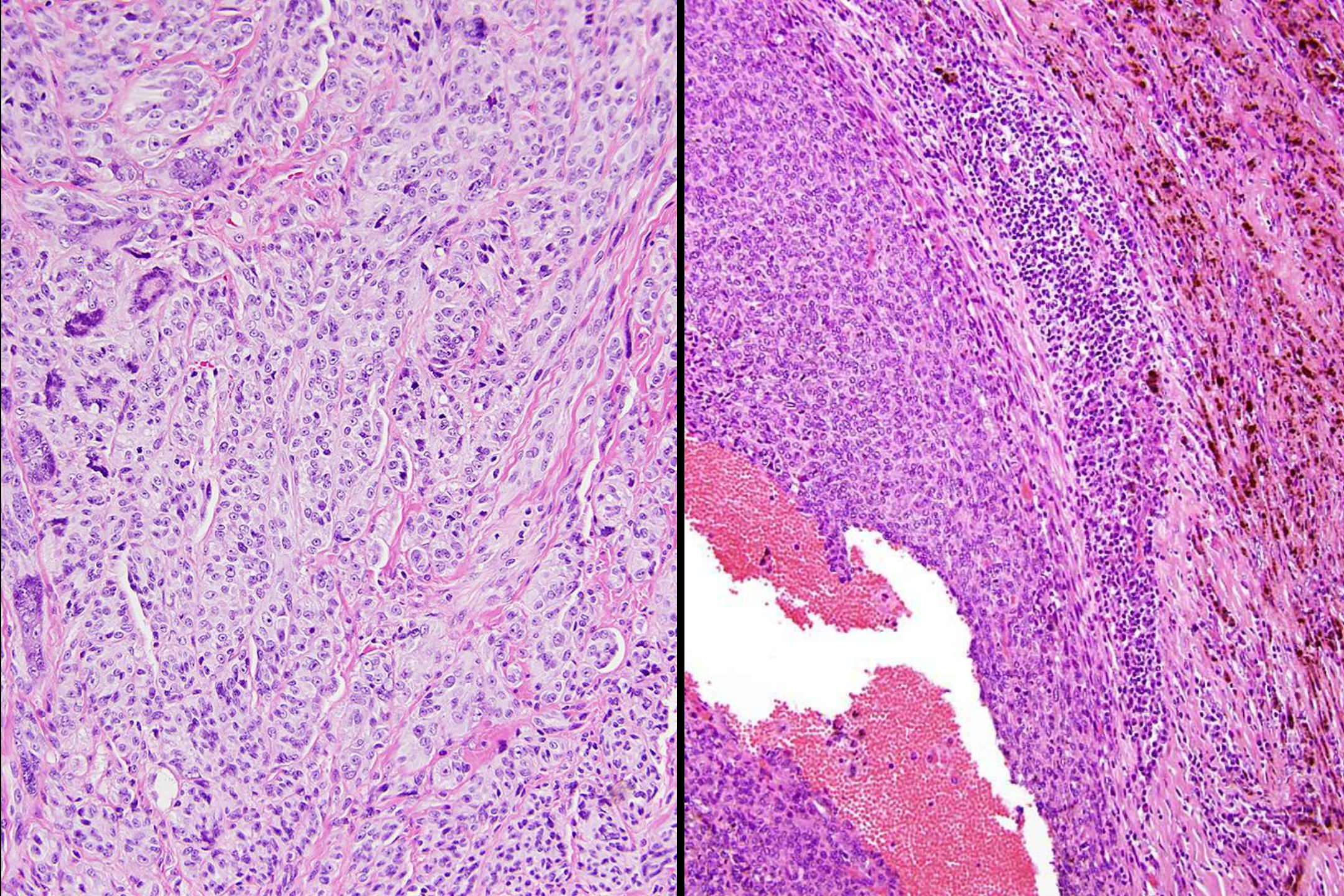
SHARED FUSION GENES IN SOFT TISSUE SARCOMAS



Szuhai & Bovee, 2012

ETV6-NTRK3

- **Infantile fibrosarcoma**
- **Cellular mesoblastic nephroma**
- **Secretory carcinoma of breast (and salivary gland)**
- **Rare cases of AML, CML &ALL**
- **Radiation-assoc^{d} thyroid carcinomas**



EWSR1-ATF1
EWSR1-CREB1

- **Clear cell sarcoma**

- **Melanocytic**
- **Deep soft tissue/GI**
- **Adults (mainly young)**
- **> 50% metastasise**

- **Angiomatoid "MFH"**

- **Lineage unknown ?? dendritic cell**
- **Mostly subcutaneous**
- **Commonest < 20 years**
- **< 2% metastasise**

- **Evidence of relationship?**
- **Biologic / mechanistic significance ?**
- **Impact on classification schemes?**
- **Variants of a single ‘molecular’ entity?**
- **Potential impact on diagnosis**

IMPACT OF GENETICS
WHERE NEXT ?

- **Need to more sharply define diagnostic role**
- **Need to reassess role in classification – how best to reconcile/prioritise genotype with phenotype ?**
- **Need to determine significance (pathogenetic and ?? clinical) of such prominently shared fusion genes – are the downstream signaling events the same ?**
- **Need to keep up this work !**

OTHER UNANSWERED QUESTIONS WHICH MIGHT IMPACT TAXONOMY

- Cell of origin in many/most tumor types ?
- Line of differentiation in many tumor types ?
- Nature of multistep process in mesenchymal tumorigenesis ?

WHO CLASSIFICATION OF SOFT TISSUE TUMOURS 2013

WEAKNESSES

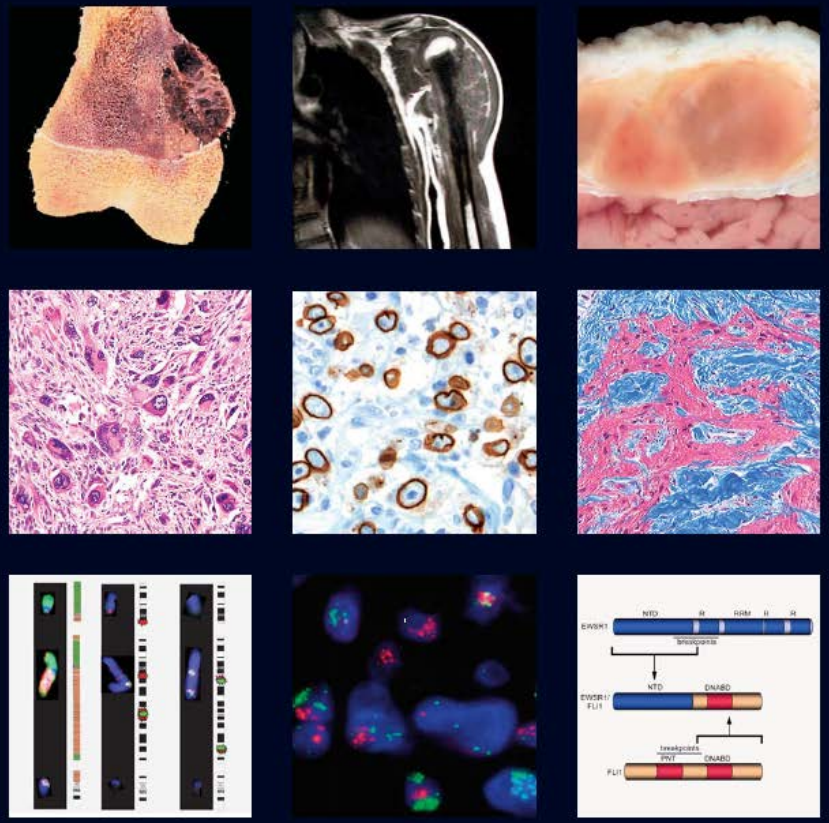
- Some ‘newer’ entities or genetic findings left out
- Continued nomenclatural anomalies
- Rigidity of ICD-0 coding system
- Increasing problem/challenge of genetic overlap

CONCLUSIONS

- There remain important opportunities to improve the classification of soft tissue tumours
- Objectivity and diagnostic reproducibility are both the goals as well as the validation of any classification scheme
- Cytogenetics / molecular genetics have been invaluable thus far, but their impact has become more complex and confusing
- Old habits die hard …….. Need to maintain open-mindedness to allow ongoing evolution

WHO Classification of Tumours of Soft Tissue and Bone

Edited by Christopher D.M. Fletcher, Julia A. Bridge, Pancras C.W. Hogendoorn, Fredrik Mertens



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