Spanish Society of Pathology
Zaragoza, May 2011
ARTHUR PURDY STOUT SYMPOSIUM

HOW MAY THE CLASSIFICATION OF SOFT TISSUE TUMORS EVOLVE ?

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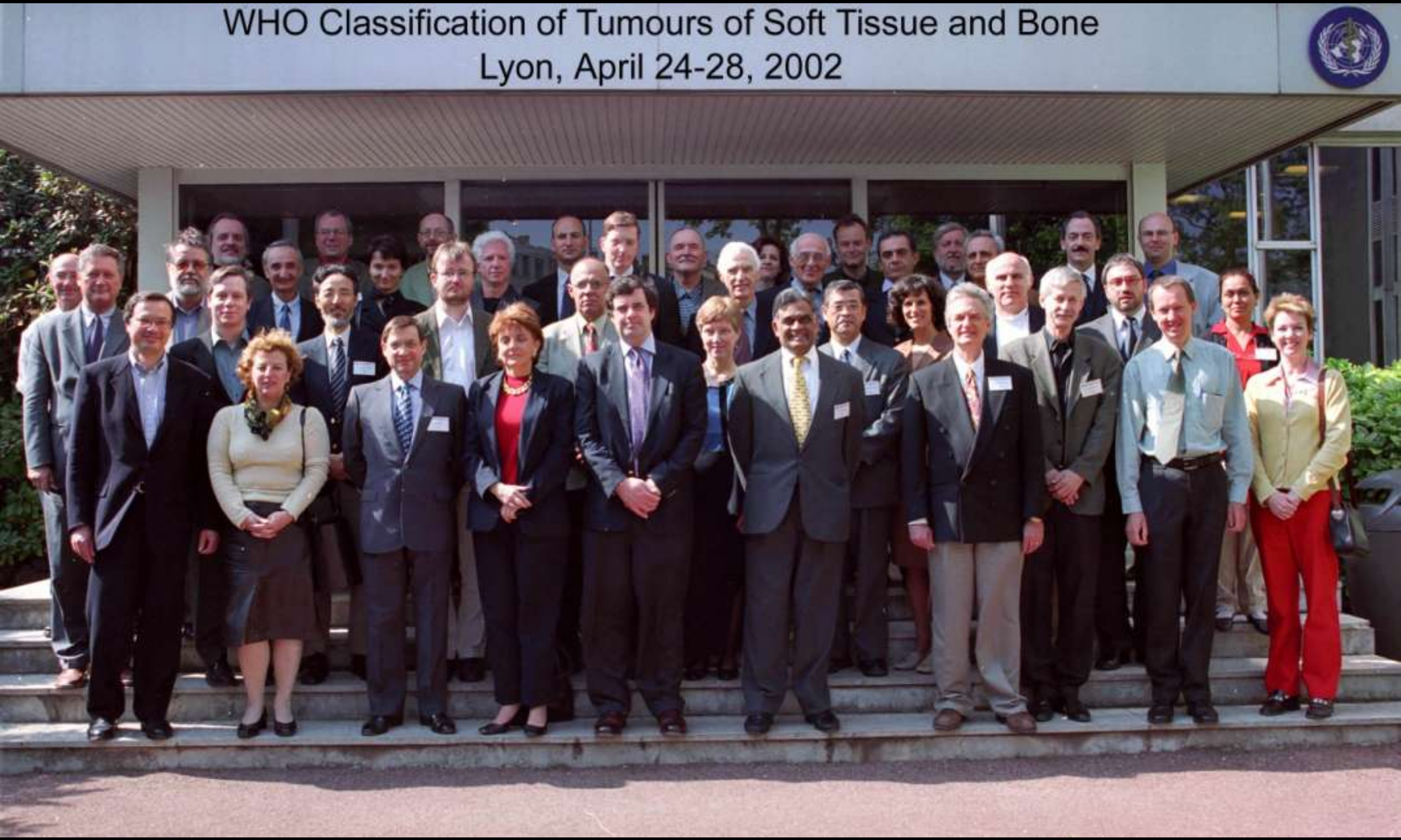
CURRENT STATUS

- Huge steps towards consensus classification schemes and more rational / reproducible diagnoses over the past 20-25 years
- Cytogenetic / molecular genetic data have facilitated objectivity and reproducibility – but have begun to pose new questions
- Better-defined concepts regarding biologic potential have emerged
- Classification now based on line of differentiation (not ‘histogenesis’, which is largely unknown)


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

WHO CLASSIFICATION 2002
MAJOR CHANGES

- Clearer definitions of biologic potential
- Acknowledgement of problems with "MFH" terminology ("undiff^{d} pleomorphic sarcoma")
- Acknowledgement that h'pericytoma was formerly a wastebasket with most tumors being unrelated to pericytes (SFT)
- Major restructuring of intermediate vascular tumors
- More lesions classified as 'Tumors of Uncertain Differentiation'

ISSUES STILL TO ADDRESS

- Outdated diagnostic concepts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

OUTDATED DIAGNOSTIC CONCEPTS

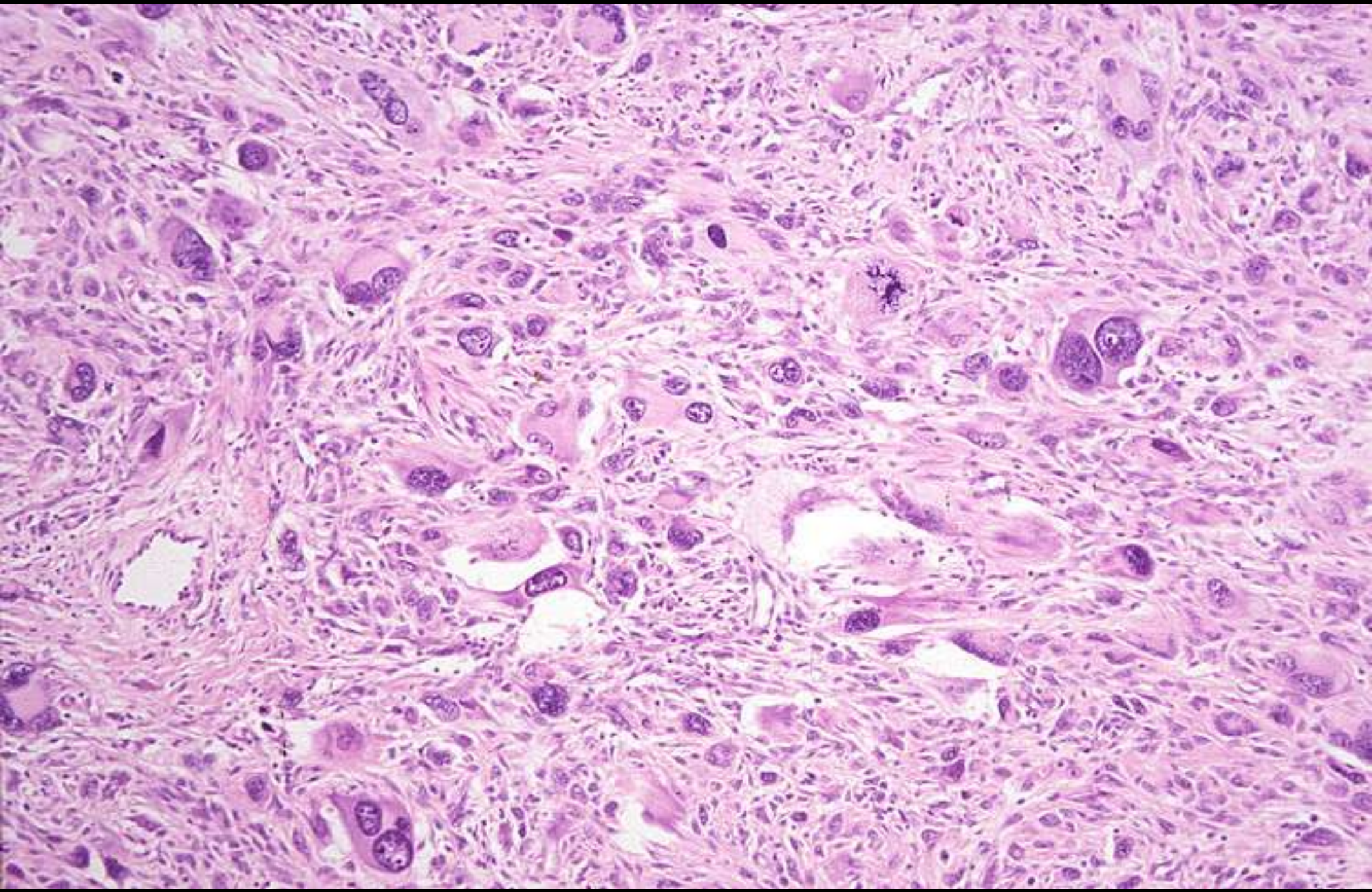
- **“Malignant fibrous histiocytoma”**
- **“Haemangiopericytoma”**
- **“Fibrosarcoma” (at least in adults)**

Challenges posed by major change

Power of existing literature across multiple disciplines

"MALIGNANT FIBROUS HISTIOCYTOMA"

- **Myxofibrosarcoma and angiomatoid "MFH" have been reallocated (WHO 2002)**
- **Pleomorphic, giant cell and inflammatory "subtypes" are unrelated**
- **"Undifferentiated pleomorphic sarcoma" facilitates transition but is neither a specific nor a common diagnosis**



PLEOMORPHIC SARCOMAS
APPROX RISK OF METASTASIS AT 5 YRS

Dedifferentiated liposarcoma	15-20%
High grade myxofibrosarcoma	30-35%
Pleomorphic liposarcoma	40-50%
Pleomorphic leiomyosarcoma	60-70%
Pleomorphic rhabdomyosarcoma	80-90%

PLEOMORPHIC 'MFH'

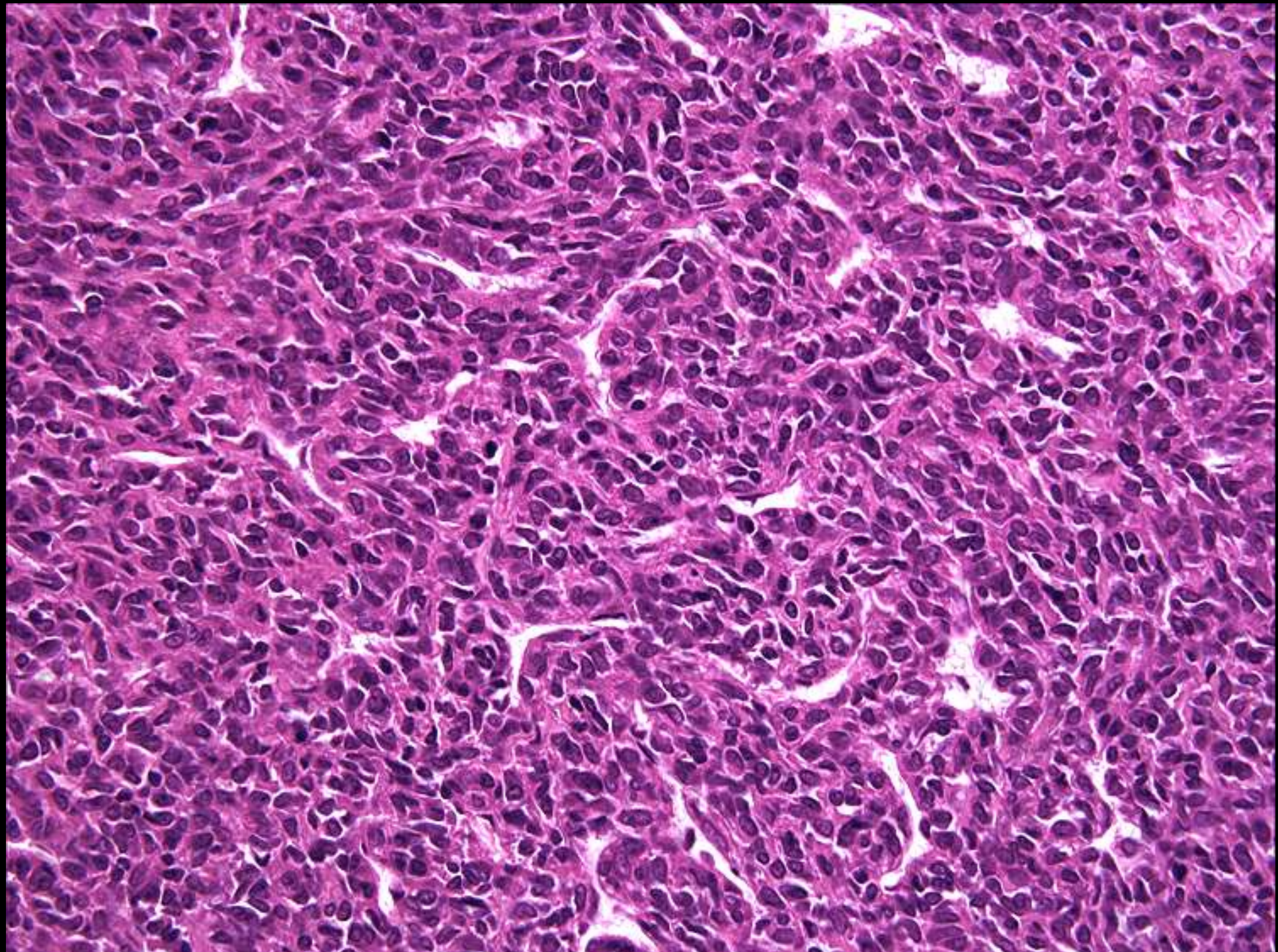
KEY POINTS

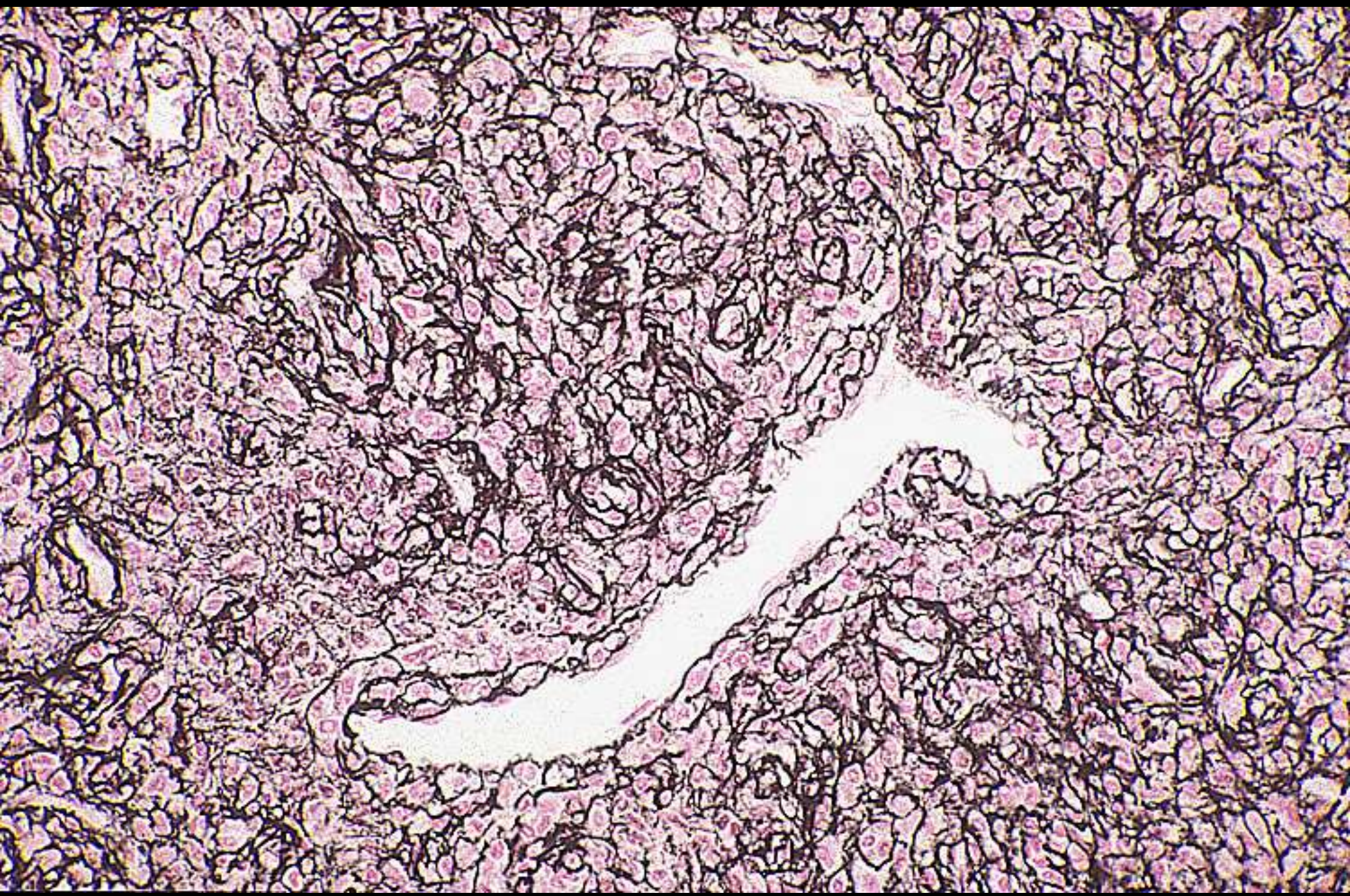
- Not an 'entity' – but synonymous with undifferentiated pleomorphic sarcoma
- Diagnosis of exclusion
- Accounts for no more than 5% of adult sarcomas
- Subclassification of pleomorphic sarcomas has clinical relevance (myogenic is bad…)
- MFH terminology should ideally disappear, but clinicians need to understand why

‘MALIGNANT FIBROUS HISTIOCYTOMA’

WHAT TO DO NEXT ?

- No continuing rationale for maintaining the term, other than “clinical convenience”
- No good definition for fibrohistiocytic differentiation
- Need to begin to acknowledge existence of undifferentiated or unclassified sarcomas as a routine clinical problem
- ?? Create category of undifferentiated sarcomas with criteria for inclusion/exclusion





HEMANGIOPERICYTOMA CONCERNS RAISED (early 1990s)

- No convincing immuno or EM evidence of true pericytic differentiation
- Branching thin-walled vessels notably non-specific among mesenchymal tumors
- Striking morphologic overlap with certain specific tumors, including solitary fibrous tumor (increasingly recognised at that time)
- Uncertain relationship (if any) between the originally defined subsets

CURRENT DIAGNOSTIC PATHOLOGY

Mini-symposium

Haemangiopericytoma – A dying breed? Reappraisal of an 'entity' and its variants: a hypothesis

Curr Diagn Pathol 1994; 1: 19-23

C. D. M. Fletcher

Semin Diagn Pathol 1995; 12: 221-232

Hemangiopericytoma: Histopathological Pattern or Clinicopathologic Entity?

Oscar Nappi, MD,*† Jon H. Ritter, MD,‡ Guido Pettinato, MD,† and Mark R. Wick, MD‡

● The tumor designated by Stout and Murray as "hemangiopericytoma" (HPC) more than 50 years ago continues to represent a source of uncertainty and disagreement among pathologists. In particular, questions exist regarding the synonymity of a hemangiopericytomatous growth pattern—defined by a monomorphic population of compact polygonal or bluntly fusiform cells and a branching stromal vascular pattern with a "staghorn" configuration—and the presence of a reproducible biological entity. It has been shown repeatedly that these same histologic features may be observed at least focally in a diversity of neoplasms, including "true" hemangiopericytomas, synovial sarcomas, mesenchymal chondrosarcomas, infantile fibrosarcomas, malignant fibrous histiocytomas, malignant peripheral nerve sheath tumors, leiomyosarcomas, endometrial stromal sarcomas, solitary fibrous tumors, myofibromas, malignant mesotheliomas, thymomas, sarcomatoid carcinomas, malignant melanomas, and "phosphaturic mesenchymal tumors." Despite their potential sharing of the microscopic attributes in question, such neoplasms have individualistic clinical features and can also be distinguished from one another by specialized pathologic analyses. HPC is "defined" in that context by reactivity for vimentin, with or without CD34 and CD57, but it lacks other immunodeterminants of epithelial, neural, and myogenous differentiation. Paradoxically, this phenotype is indeed associated with the presence of myogenous-type cytoplasmic filaments in ultrastructural evaluations of HPC. Other lesions that may resemble "true" HPC—but which possess dissimilar subcellular and clinical characteristics—include solitary fibrous tumors, hemangiopericytomalike tumors of the sinonasal tract, and "infantile (congenital) hemangiopericytomas." Such observations suggest that the hemangiopericytoma is both a pathologic entity and a morphological pattern, and they emphasize the utility

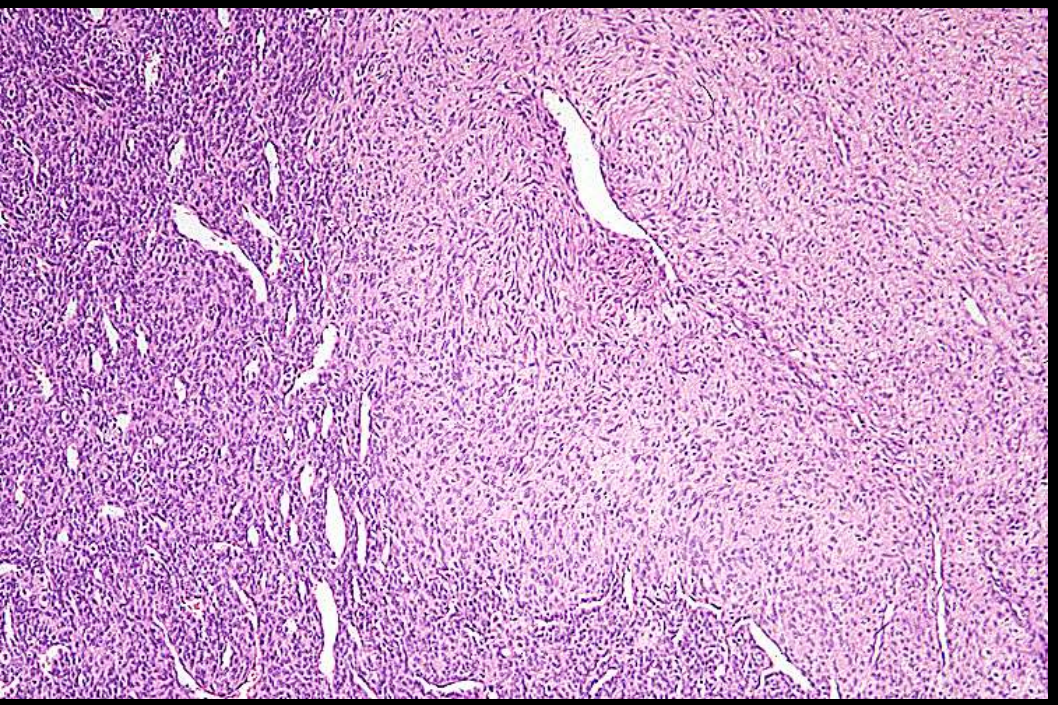
HEMANGIOPERICYTOMA
REVISED DEFINITION

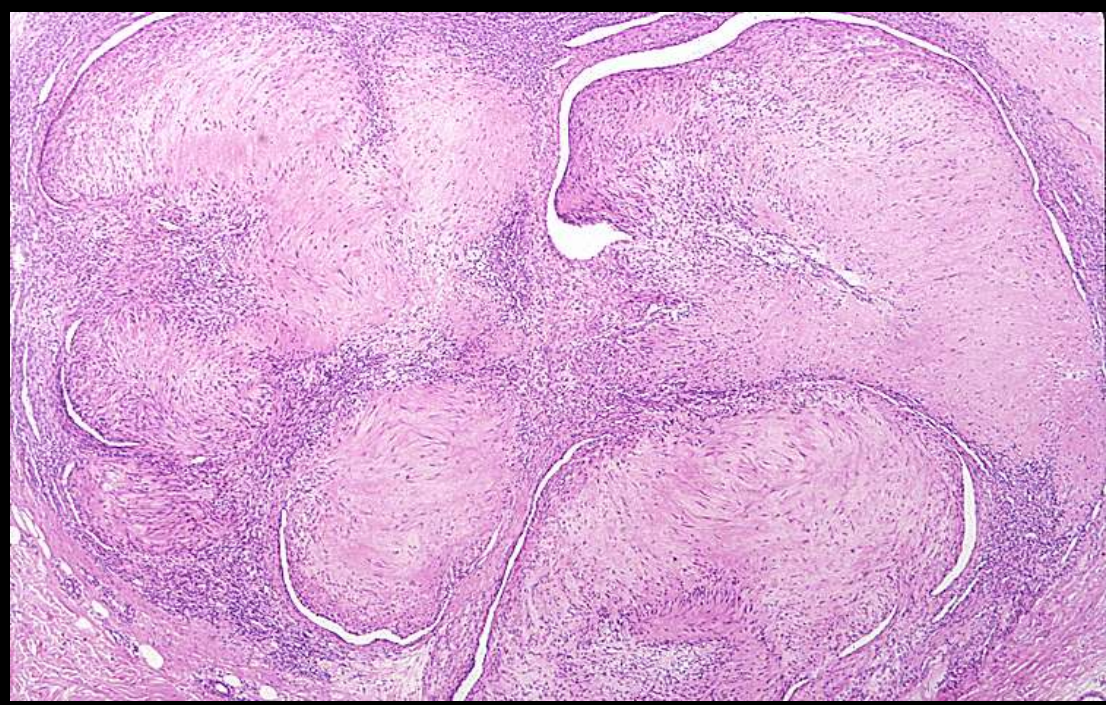
"The… group of lesions, previously combined under the term hemangiopericytoma, which closely resemble cellular areas of solitary fibrous tumor (SFT) and which appear fibroblastic in type. It has a range of clinical behavior and is closely related to, if not synonymous with, SFT."

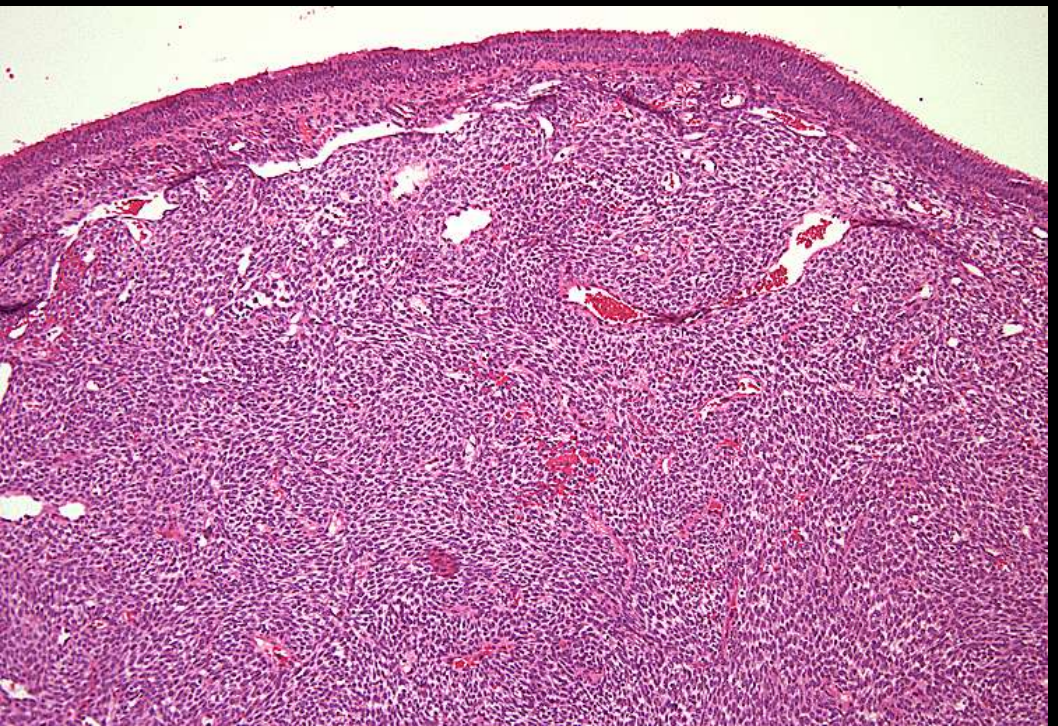
WHO Classification 2002

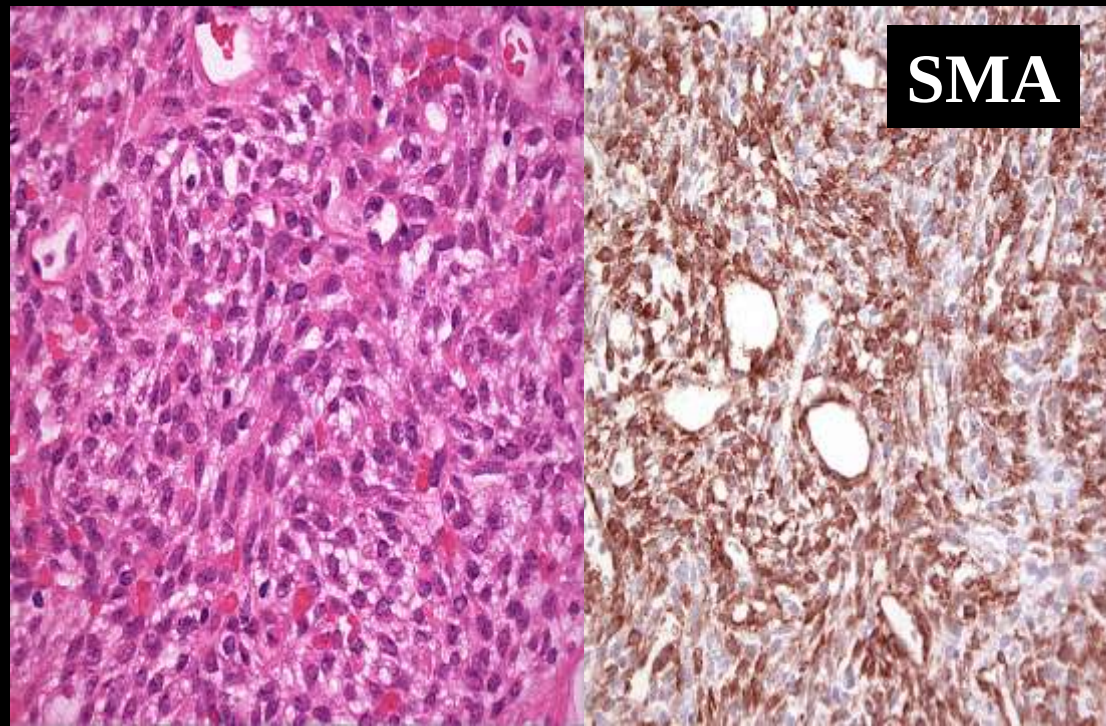
"HEMANGIOPERICYTOMA"

- Diagnosis was formerly based largely on thin-walled branching vascular pattern – which is shared by multiple tumour types
- Most tumours formerly labelled as "hemangiopericytoma" are fibroblastic – specifically solitary fibrous tumours
- Pericytic neoplasms undoubtedly exist (e.g. myopericytoma spectrum, sinonasal HPC) – but need to be separated clearly from the old concept of HPC








SMA

HEMANGIOPERICYTOMA
'MODERN PERSPECTIVE'

Adult hemangiopericytoma
- most are solitary fibrous tumors

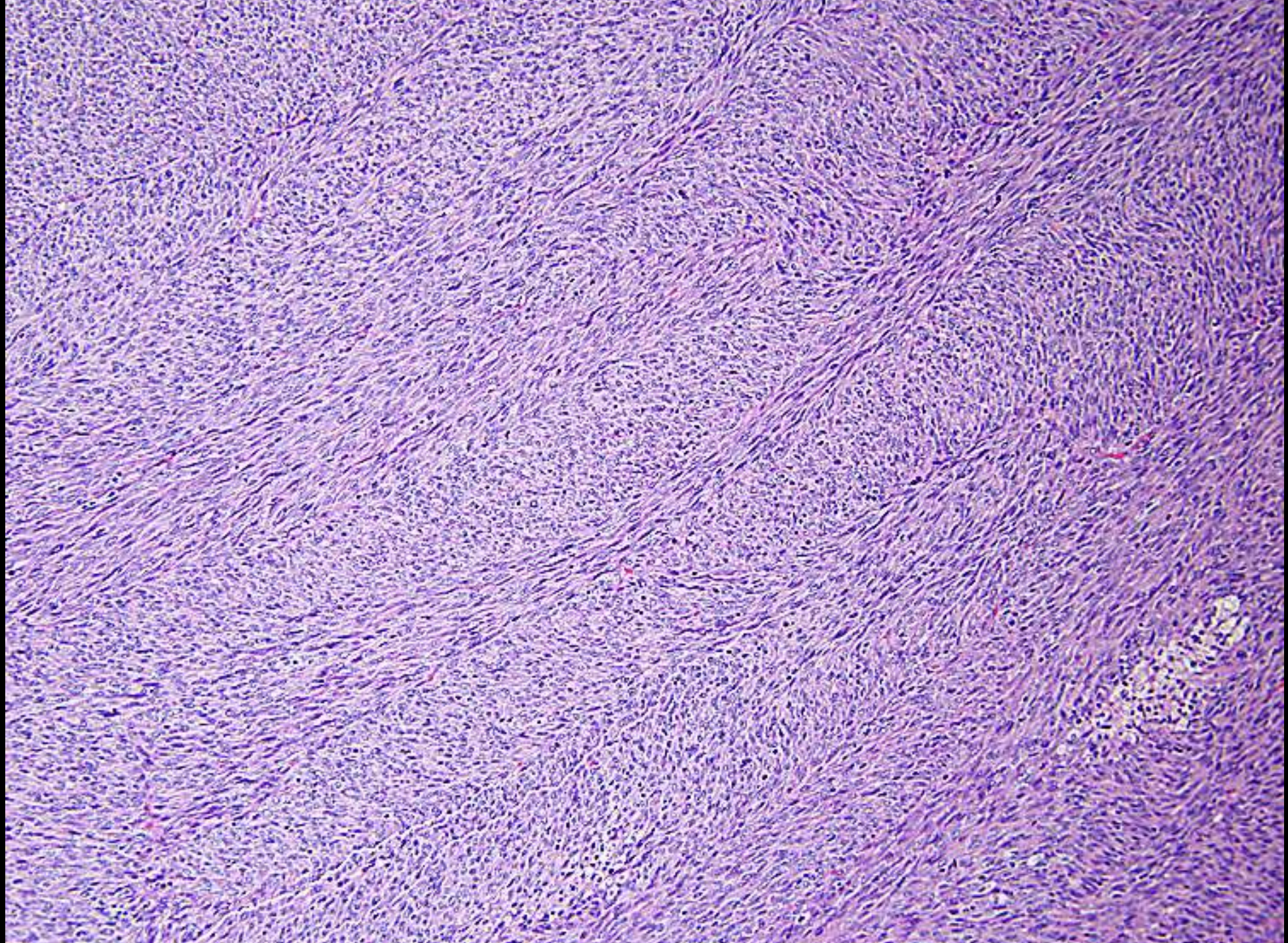
Infantile hemangiopericytoma
- is part of the myopericytoma spectrum

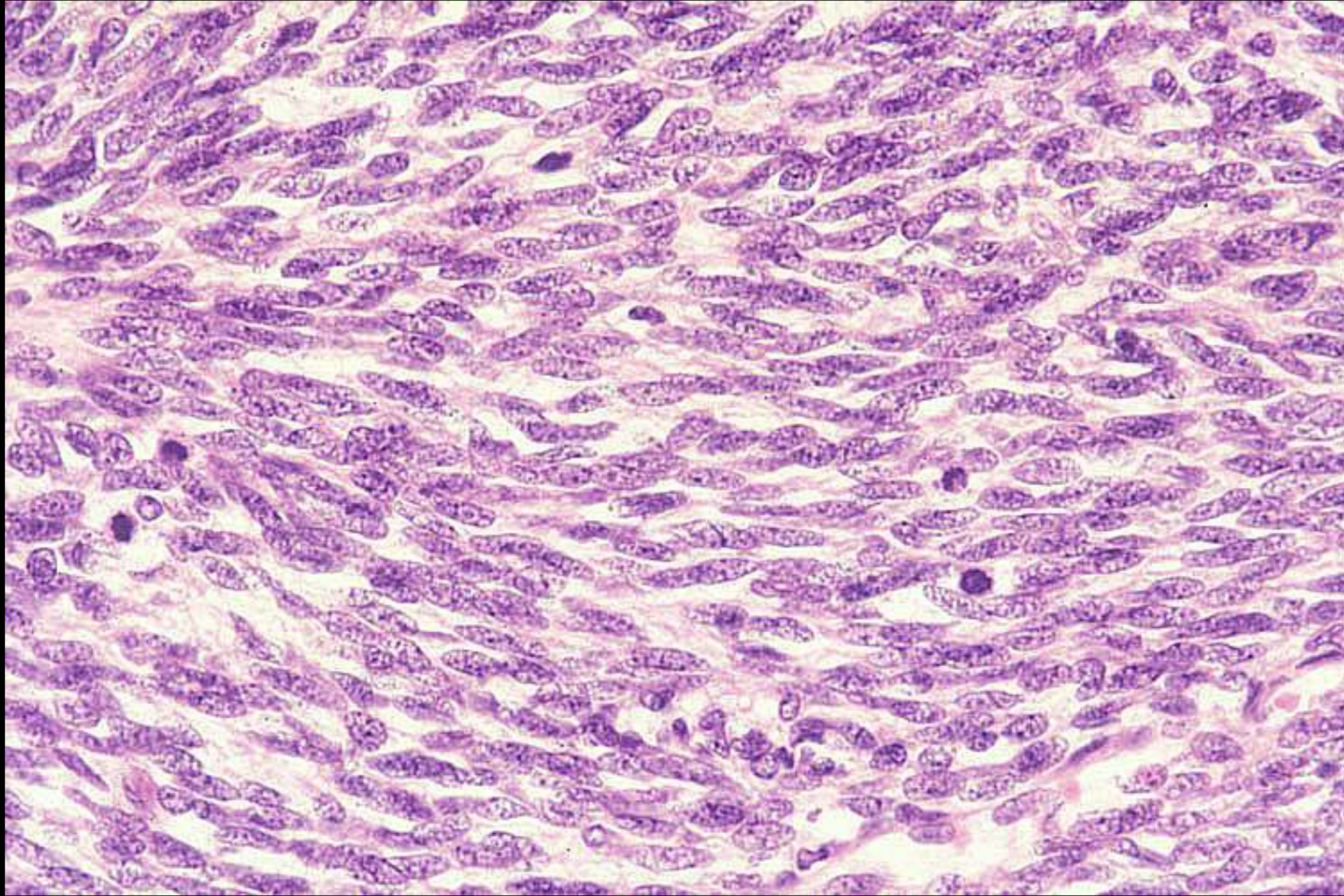
Meningeal hemangiopericytoma
- is indistinguishable from cellular / malignant SFT

Sinonasal hemangiopericytoma
- is a myopericytic neoplasm

‘HEMANGIOPERICYTOMA’
WHAT TO DO NEXT ?

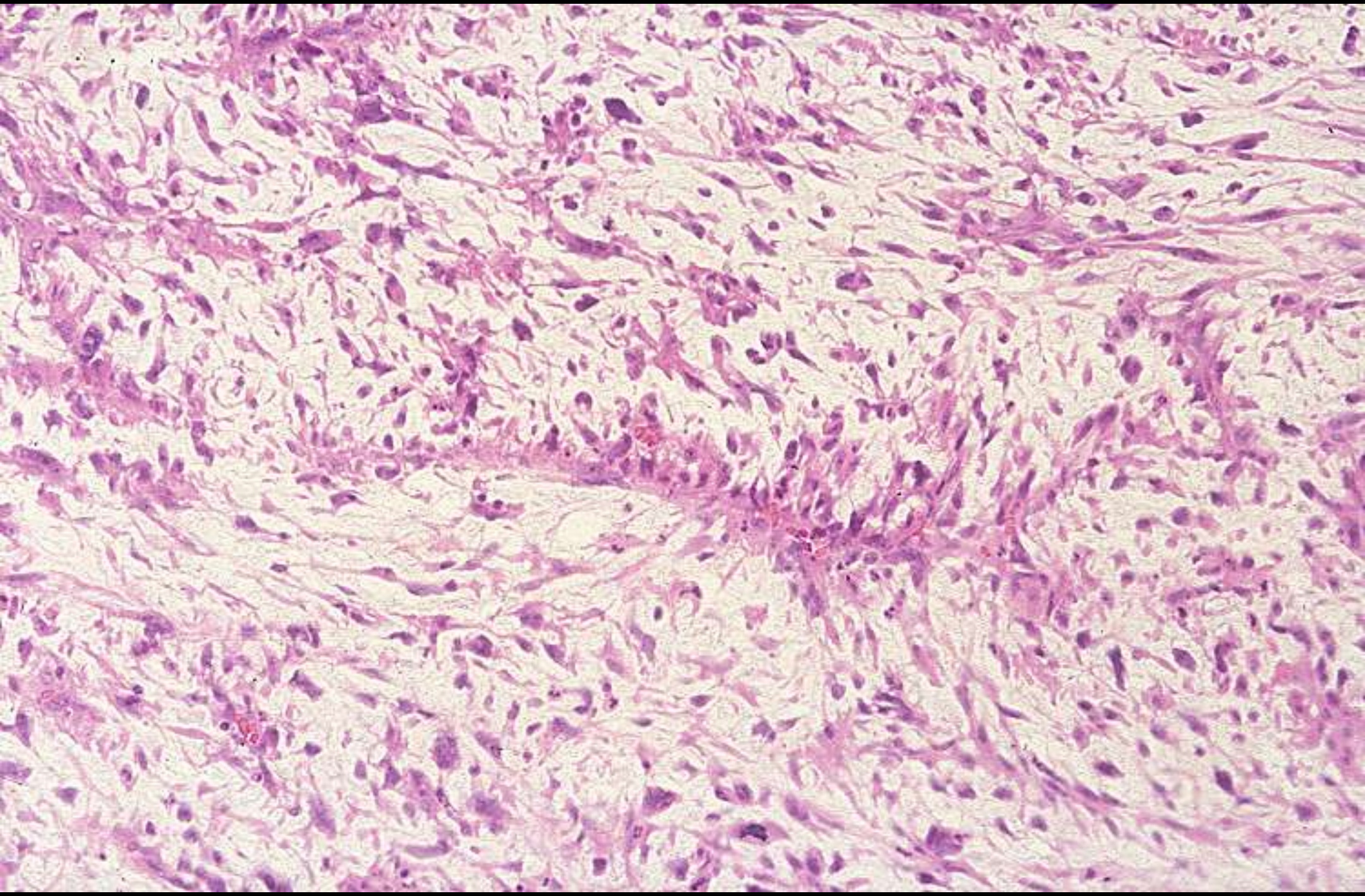
- **? Remove as synonym for SFT**
- **? Reintroduce as synonym for myopericytoma**
- **? Redefine as preferred term for myopericytoma**
- **Nothing….**

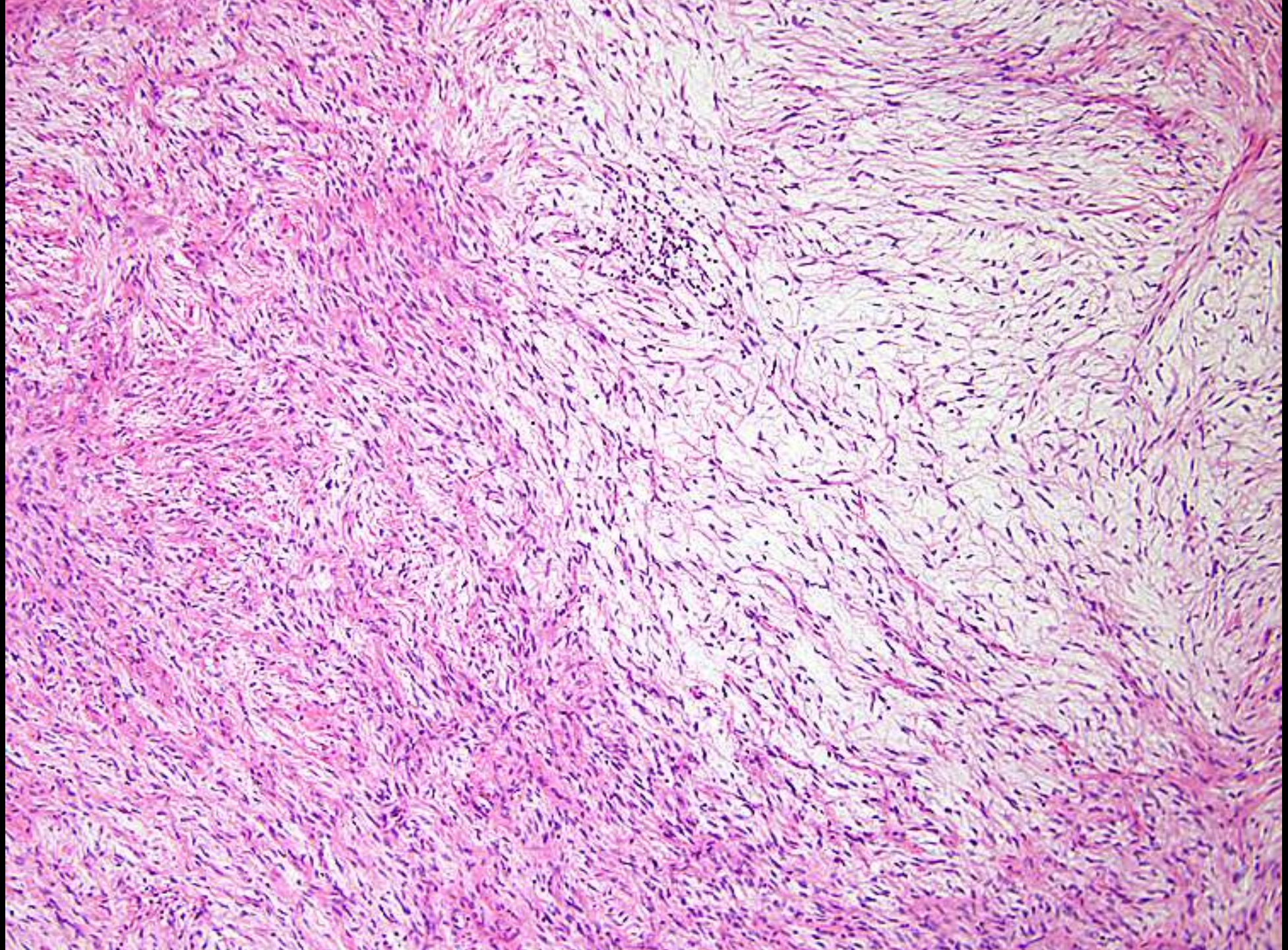


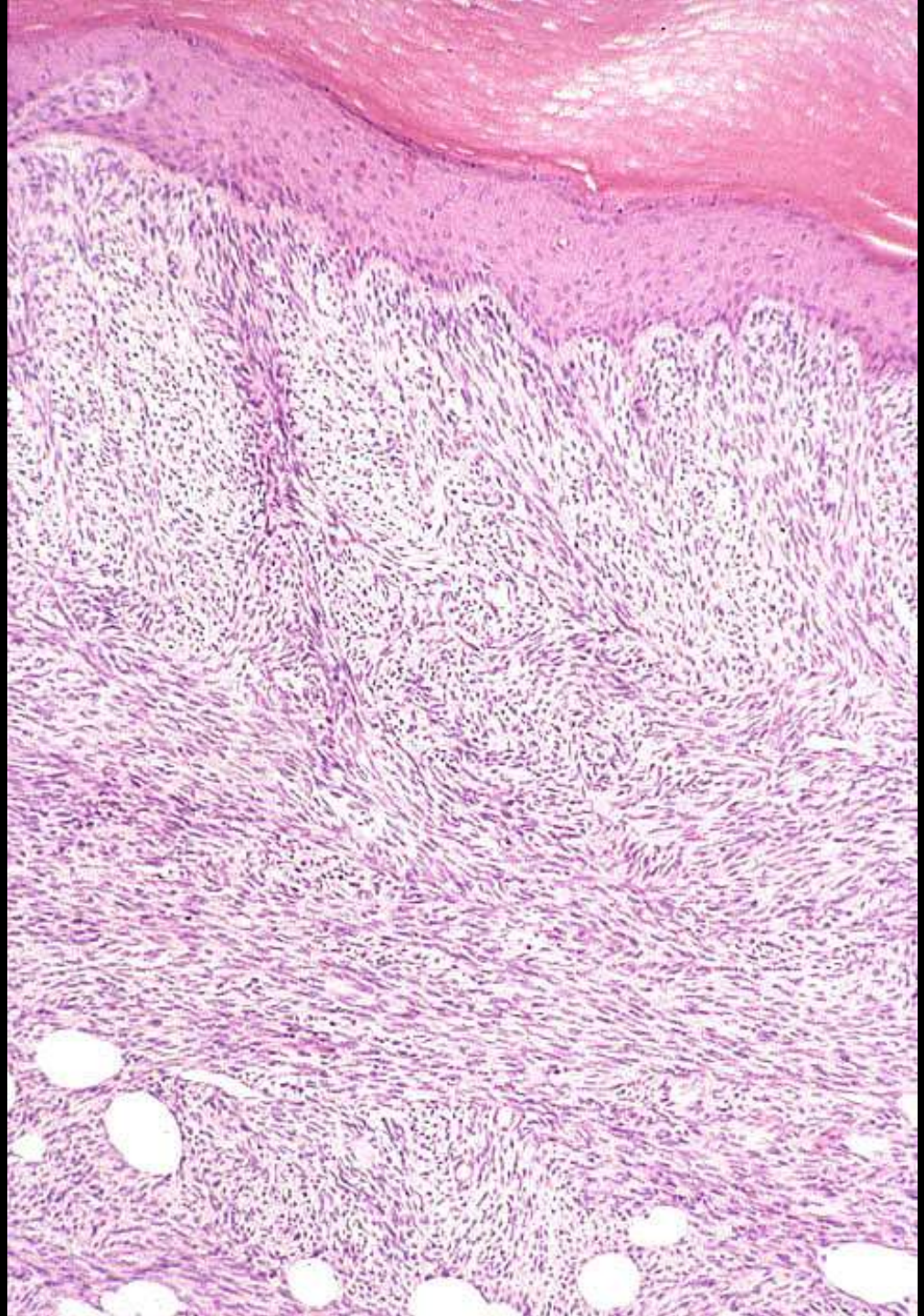


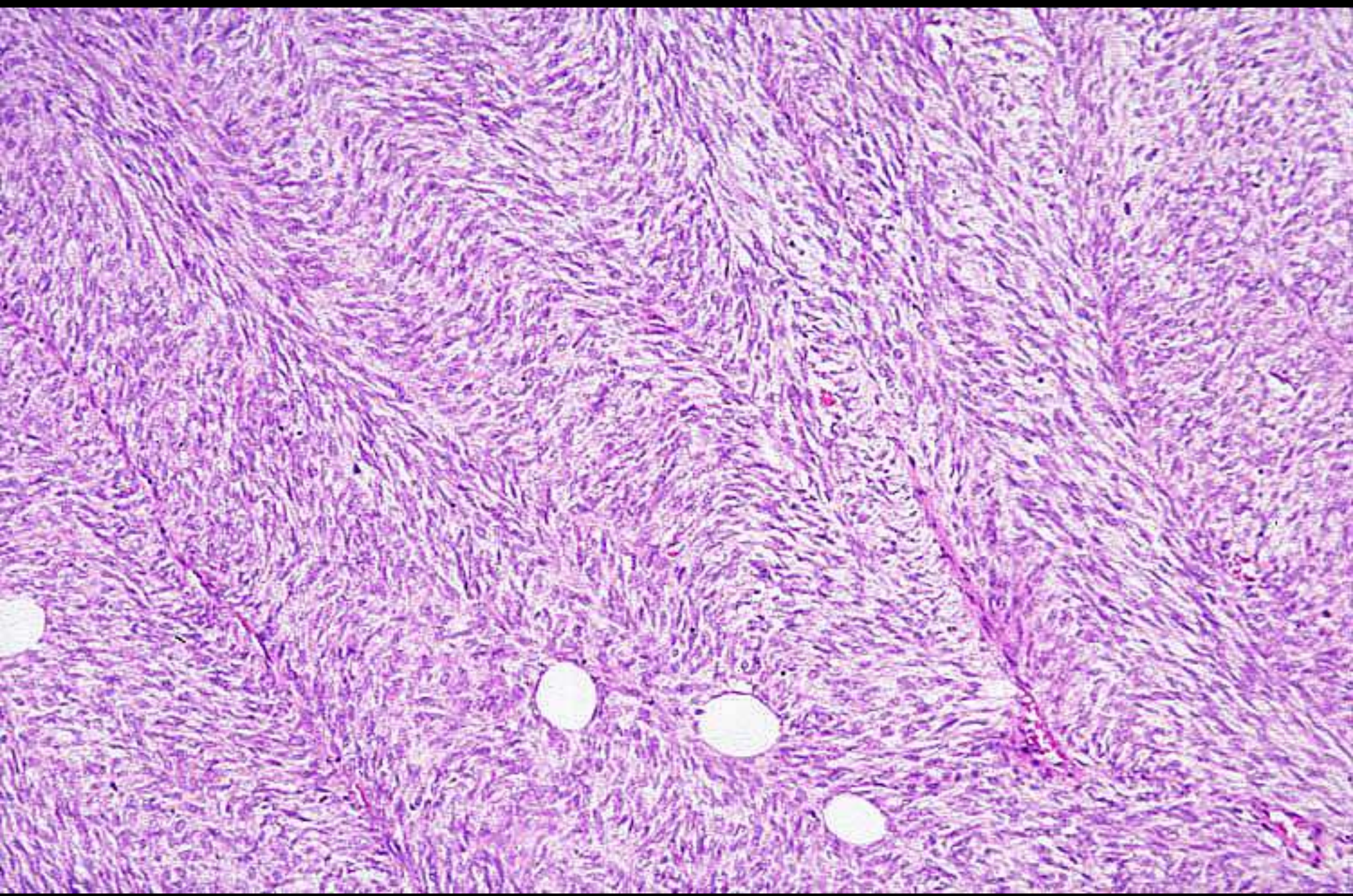
ADULT FIBROSARCOMA
CURRENT STATUS

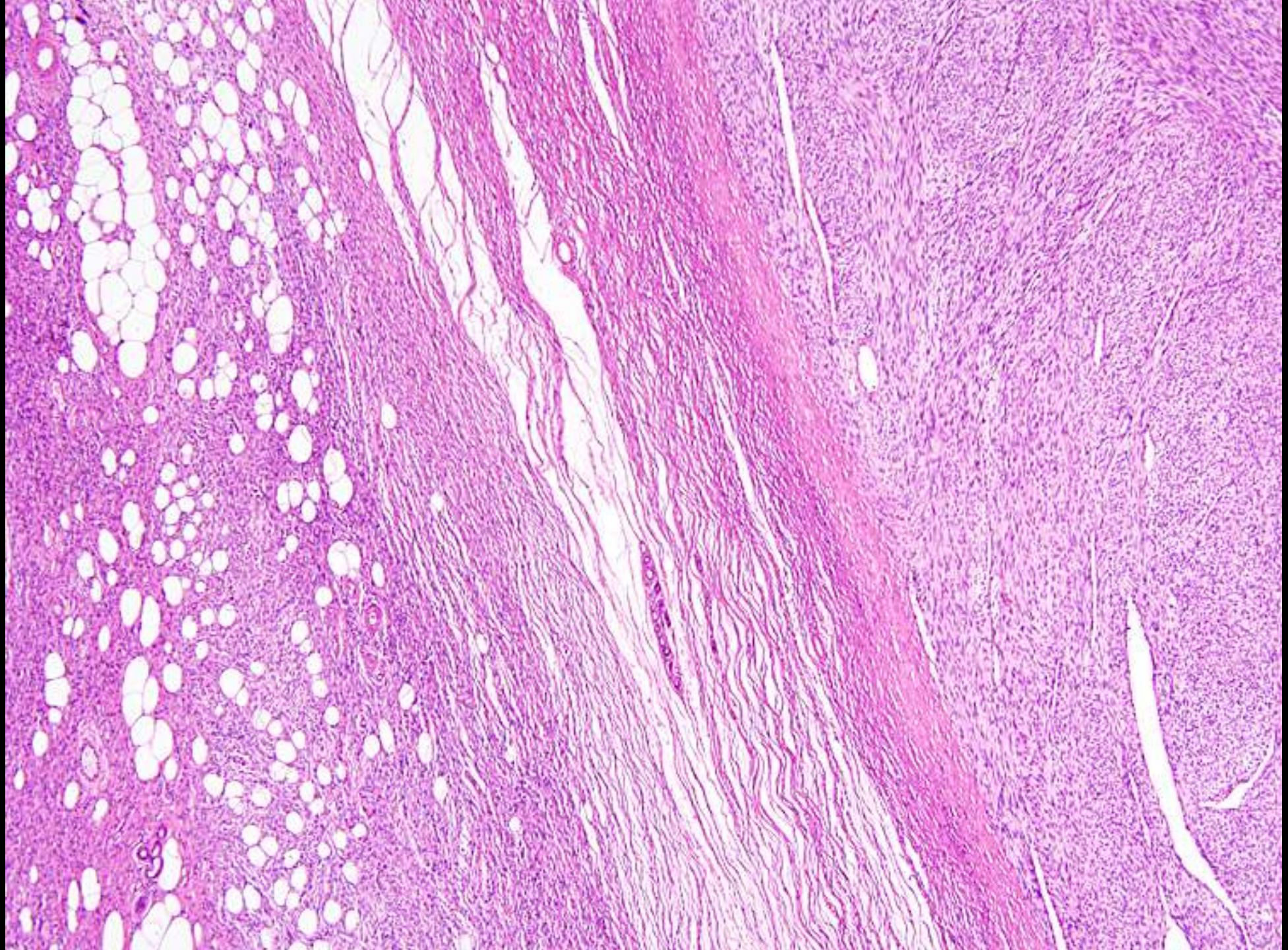
- Most lesions so classified in the past would nowadays be relabelled synovial sarcoma or MPNST
- Malignant fibroblastic tumors in adults do exist – eg myxofibrosarcoma, LGFMS, fibrosarcomatous DFSP
- Other less well-defined tumors may well belong in this category, but fibrosarcoma NOS is not currently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











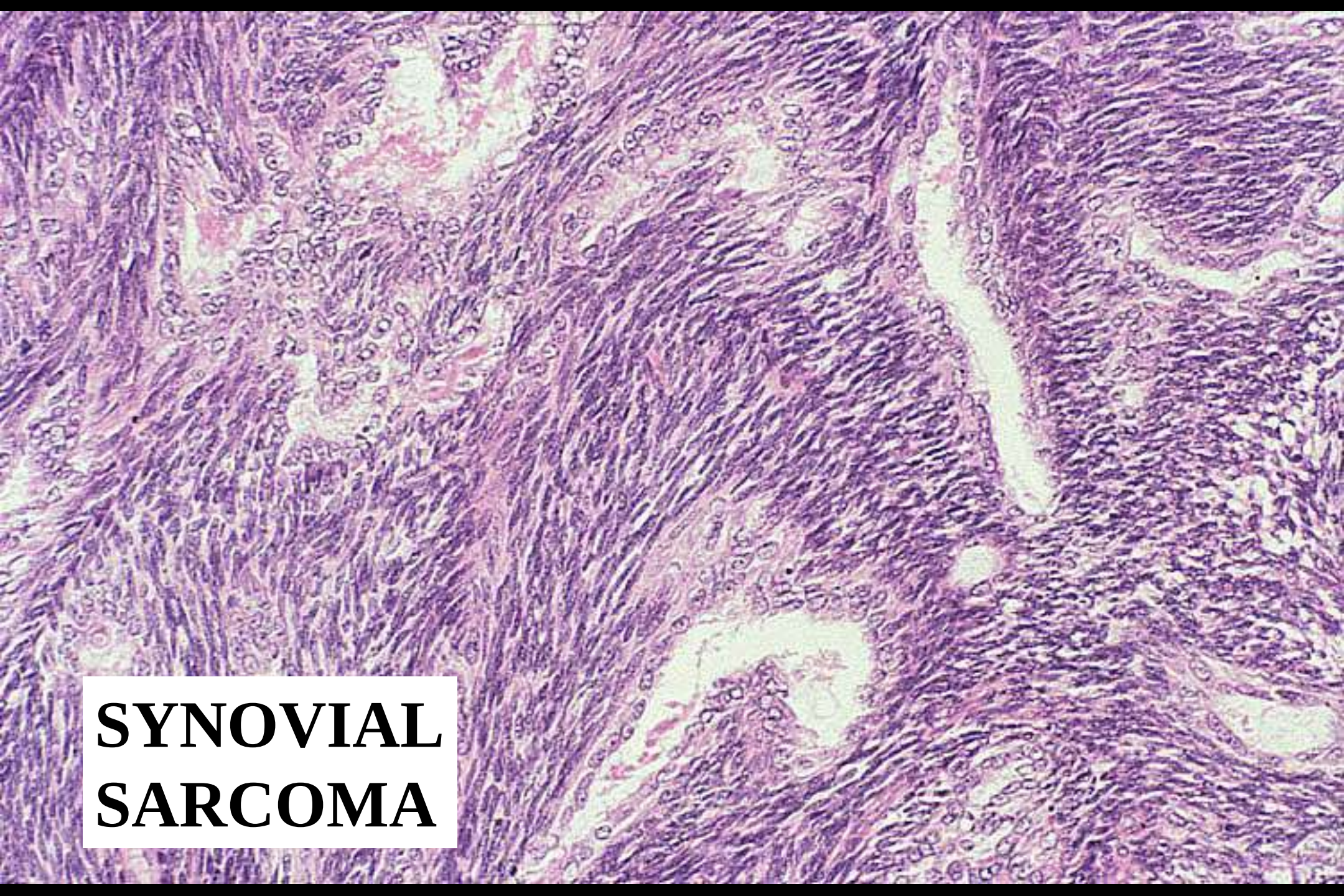
FIBROBLASTIC SARCOMAS
PROBLEMS TO CONSIDER

- **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**

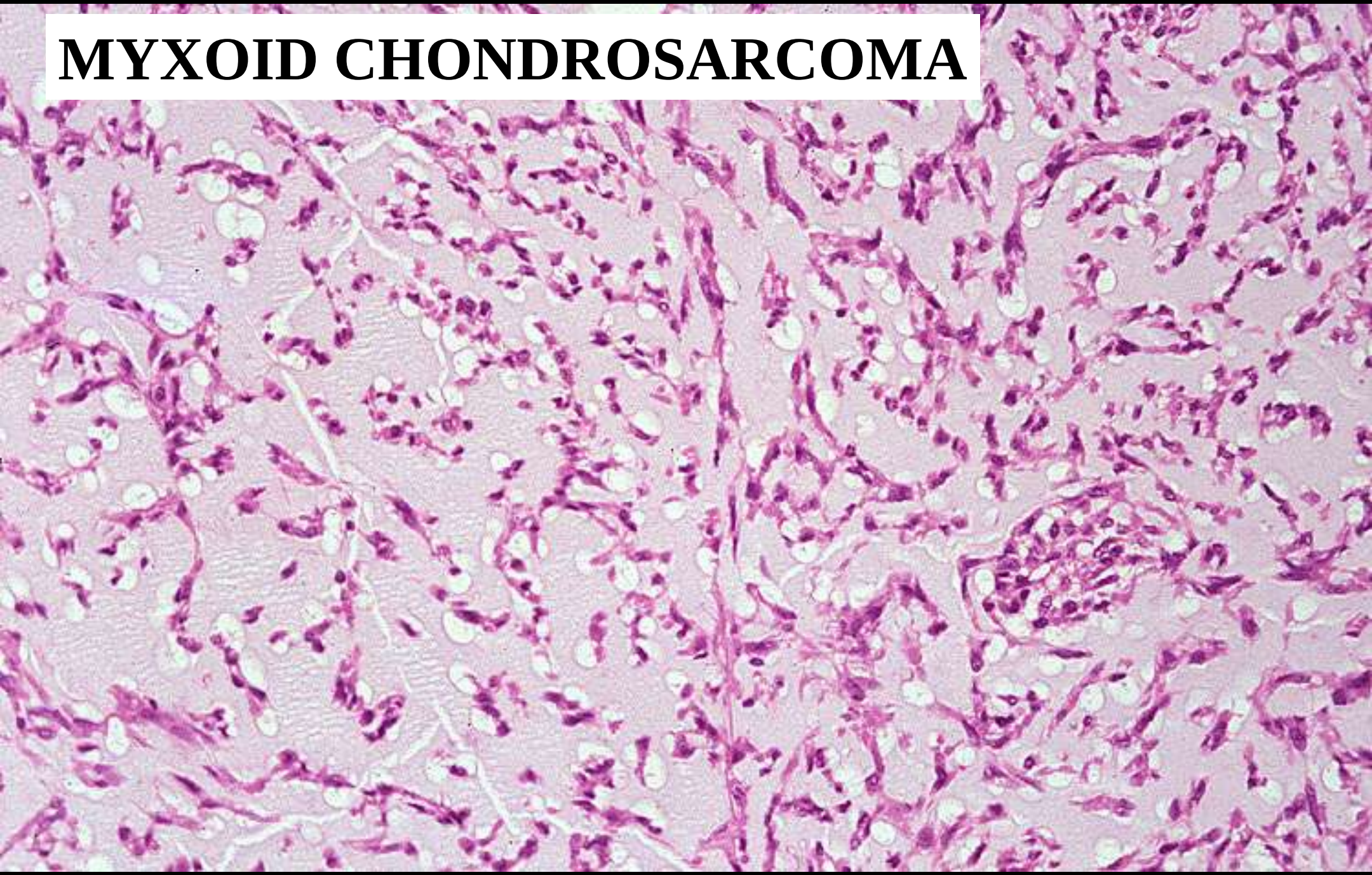
NOMENCLATURAL ANOMALIES

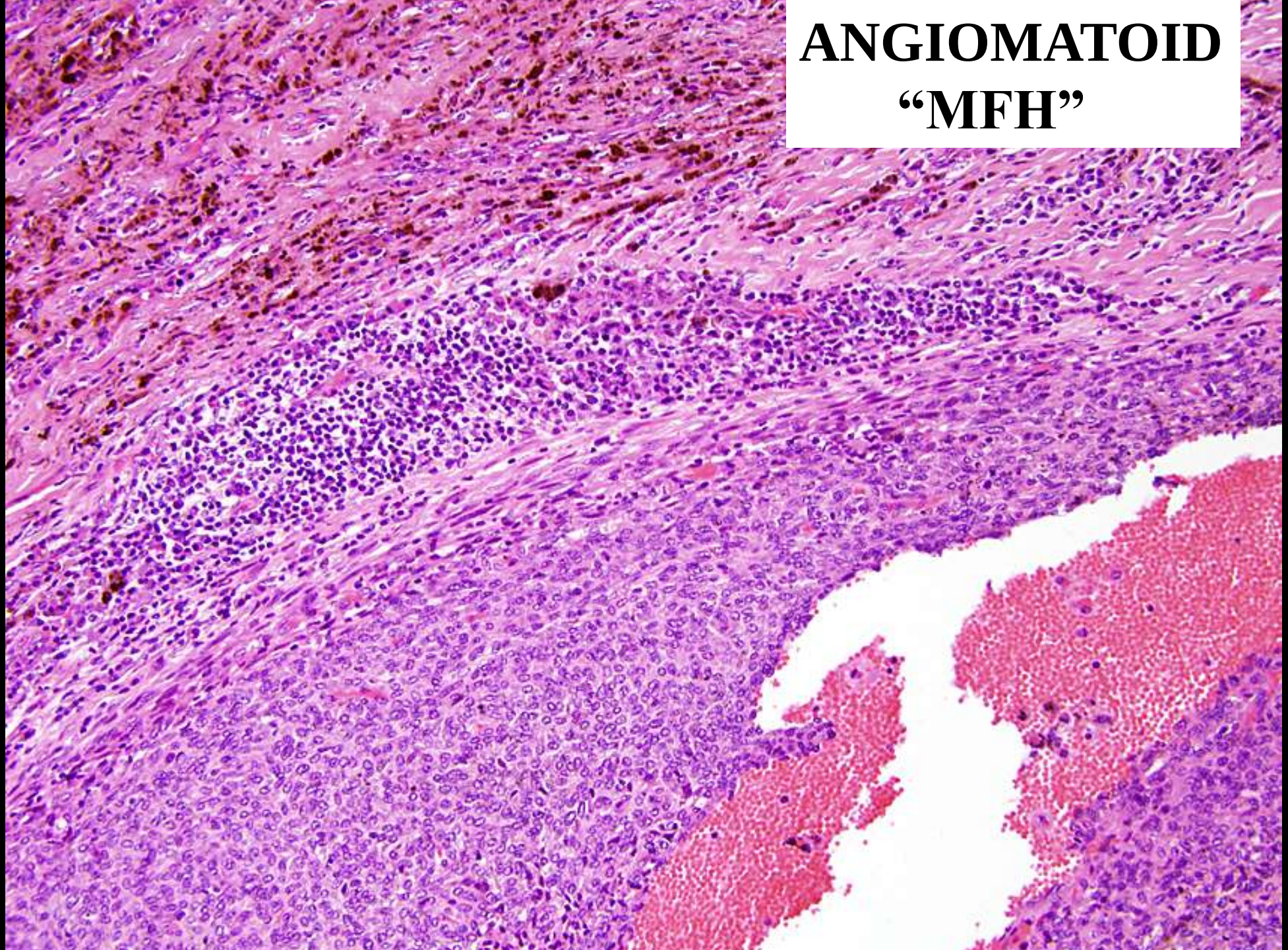
Practical considerations vs scientific accuracy
How best to determine nomenclature ?
Historical precedent vs line of differentiation (which may be unknown) vs genetics
Potential consequences for patient care
(Isn't it our job to re-educate clinicians ?)
Fossilising sociologic issues …..

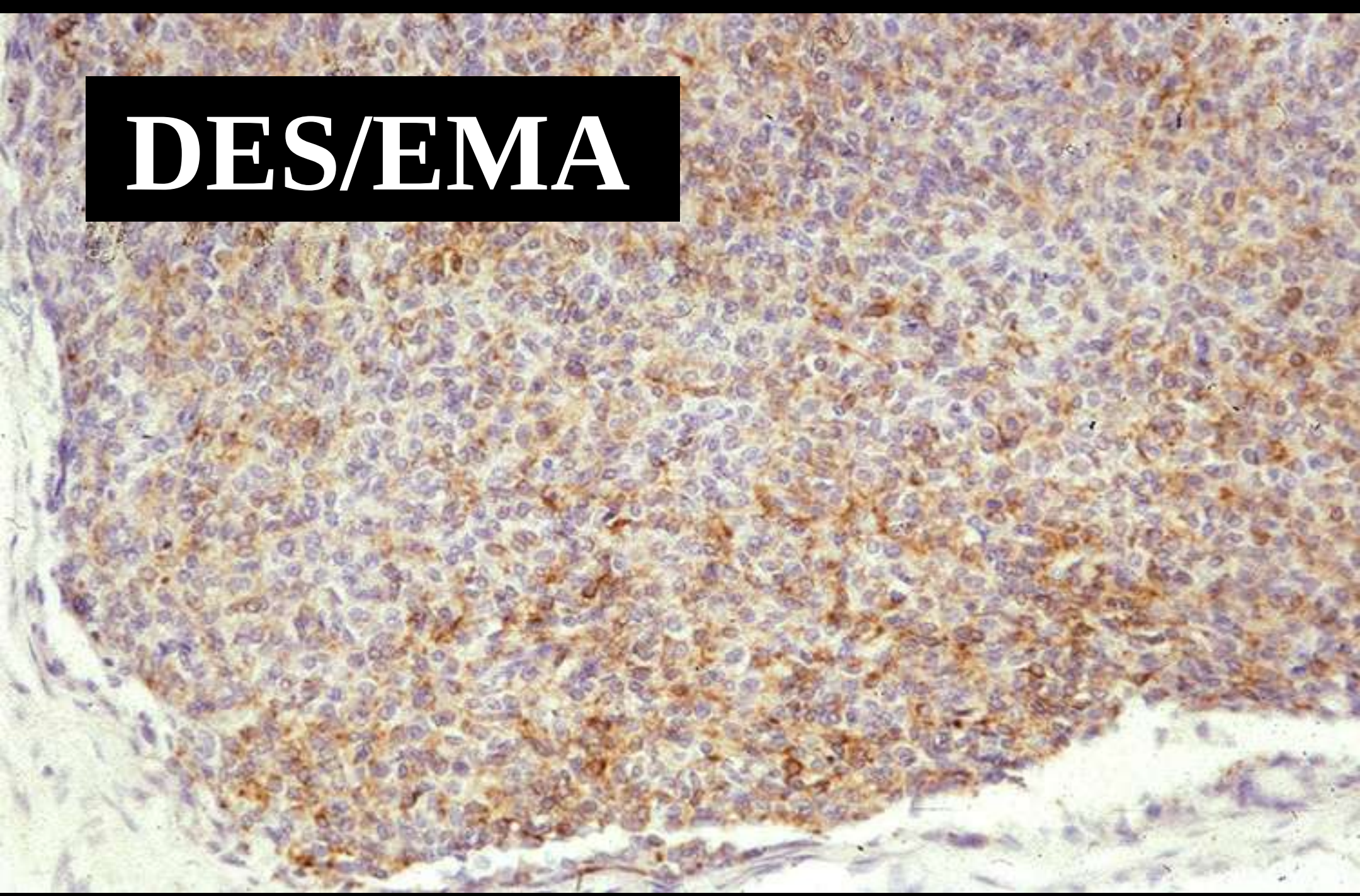
Are there other branches of science that are quite so slow to evolve or correct themselves ?


SYNOVIAL
SARCOMA

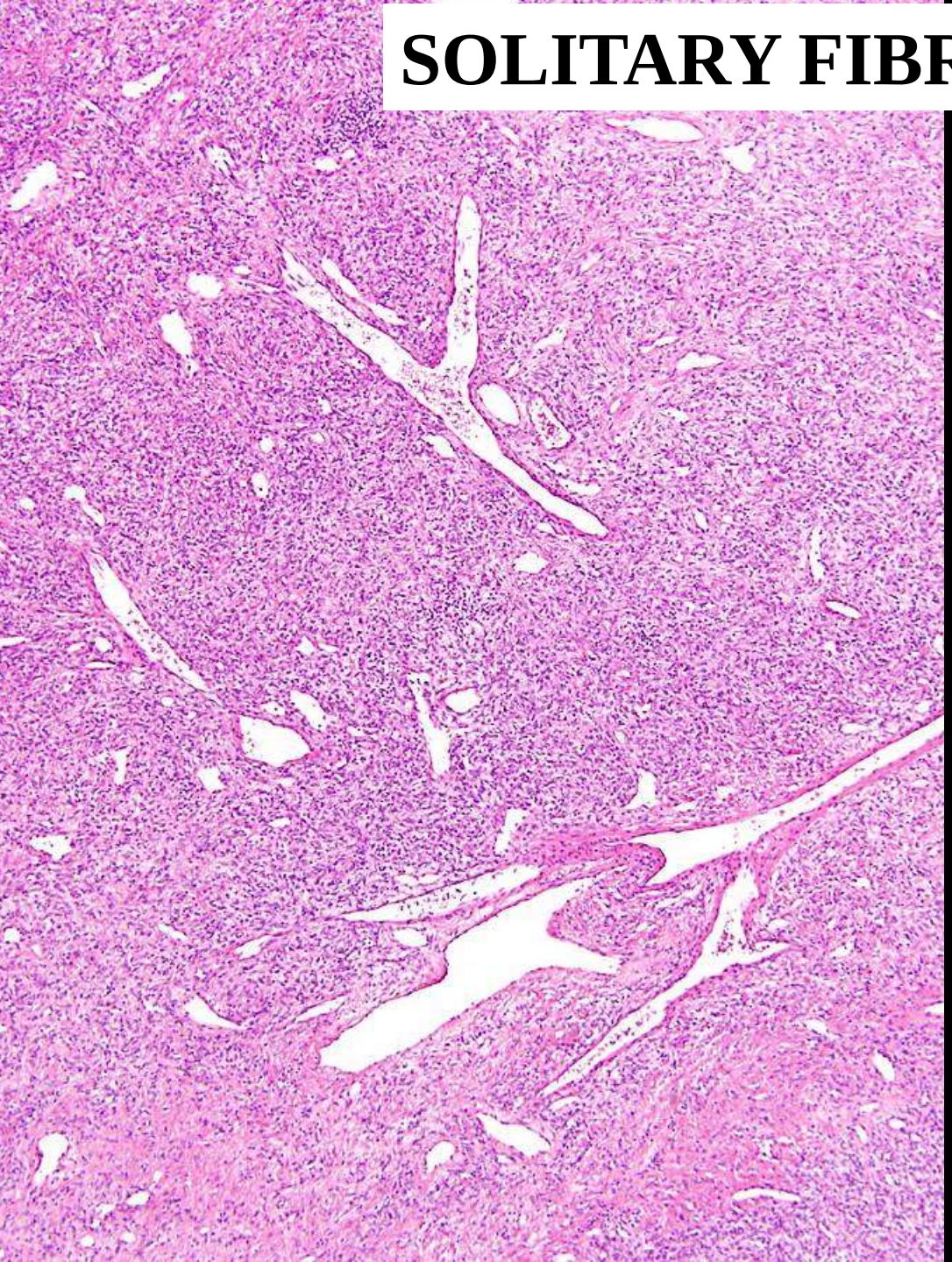
MYXOID CHONDROSARCOMA

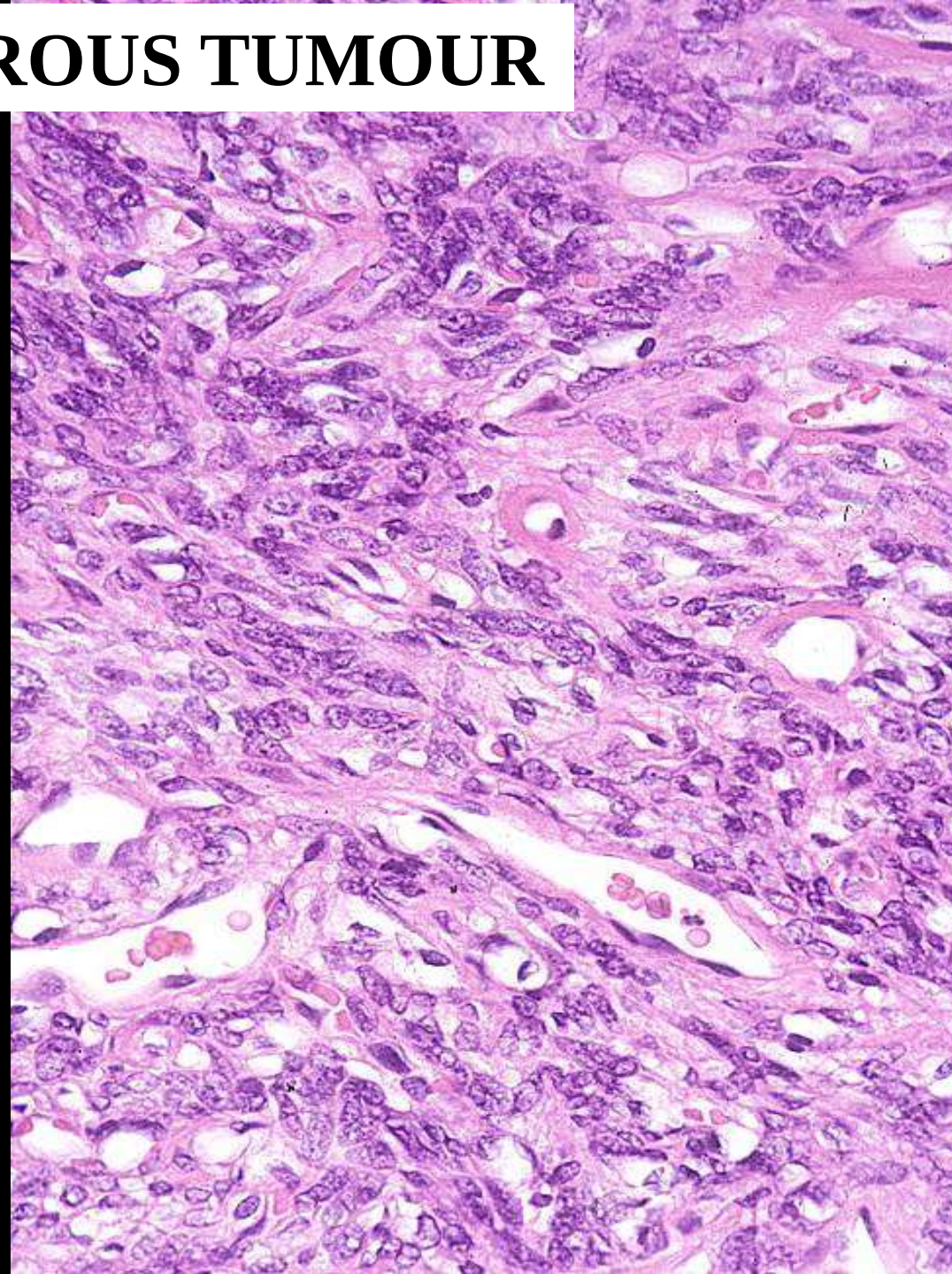


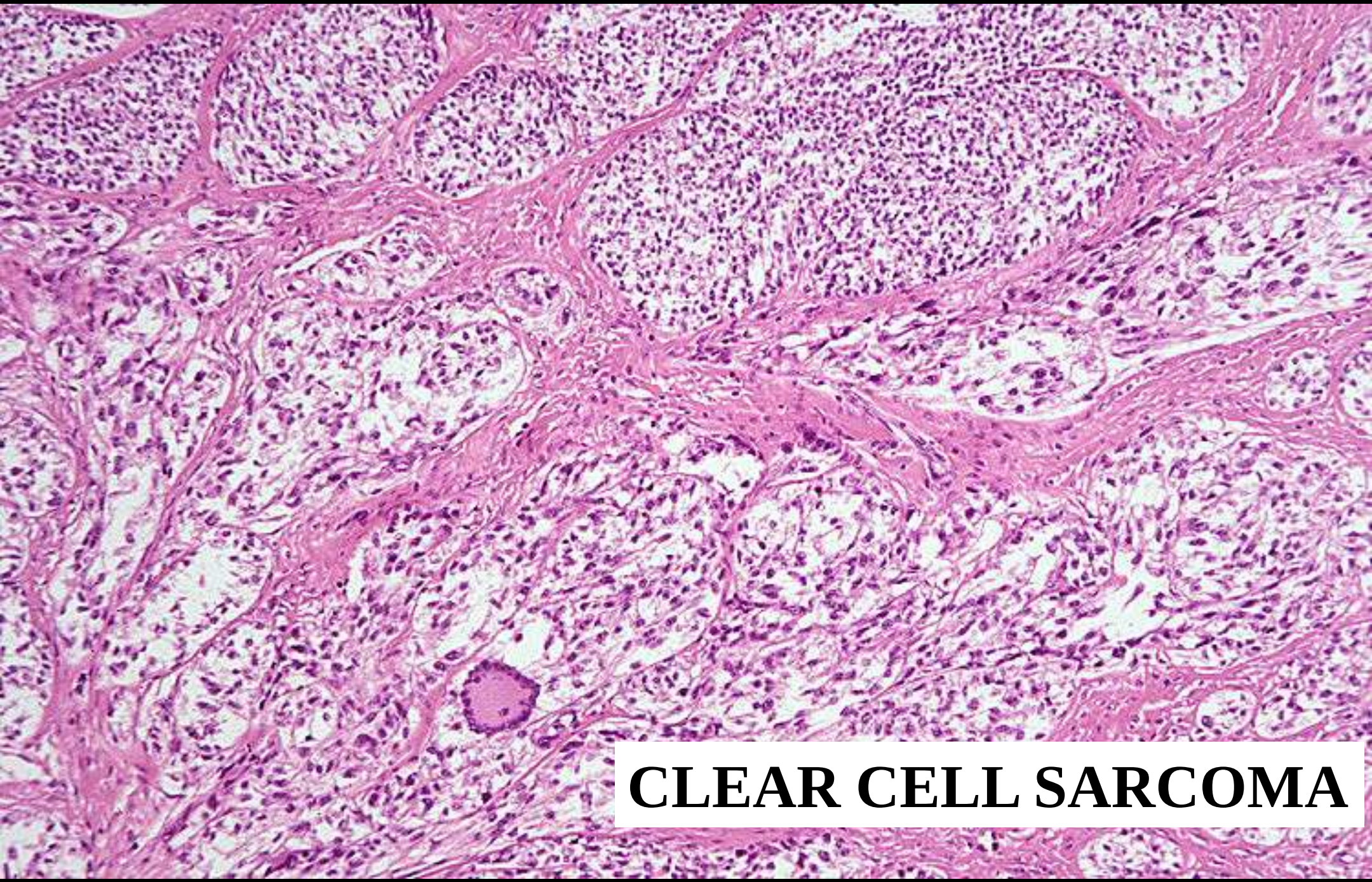

ANGIOMATOID
“MFH”

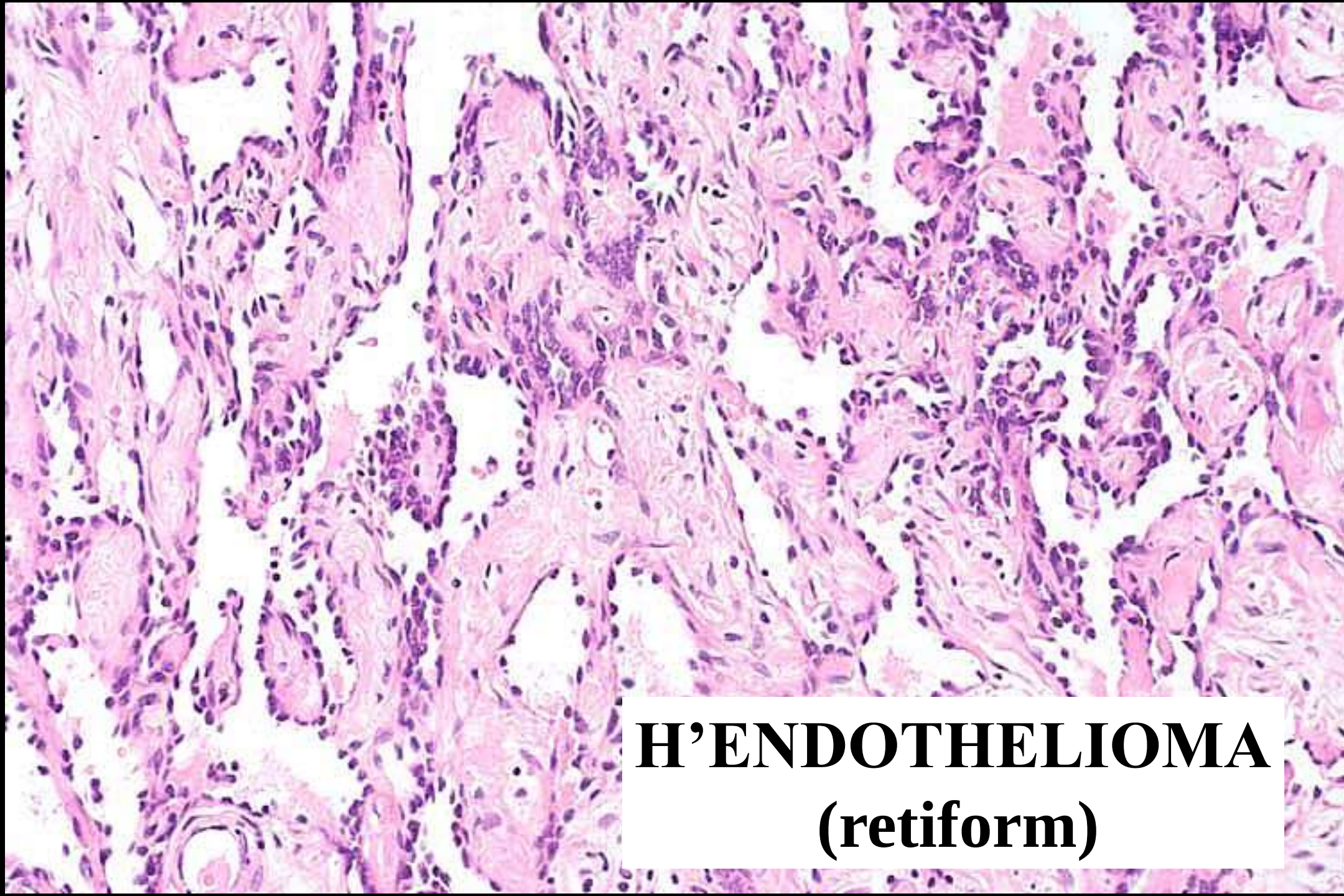

DES/EMA

SOLITARY FIBROUS TUMOUR






CLEAR CELL SARCOMA

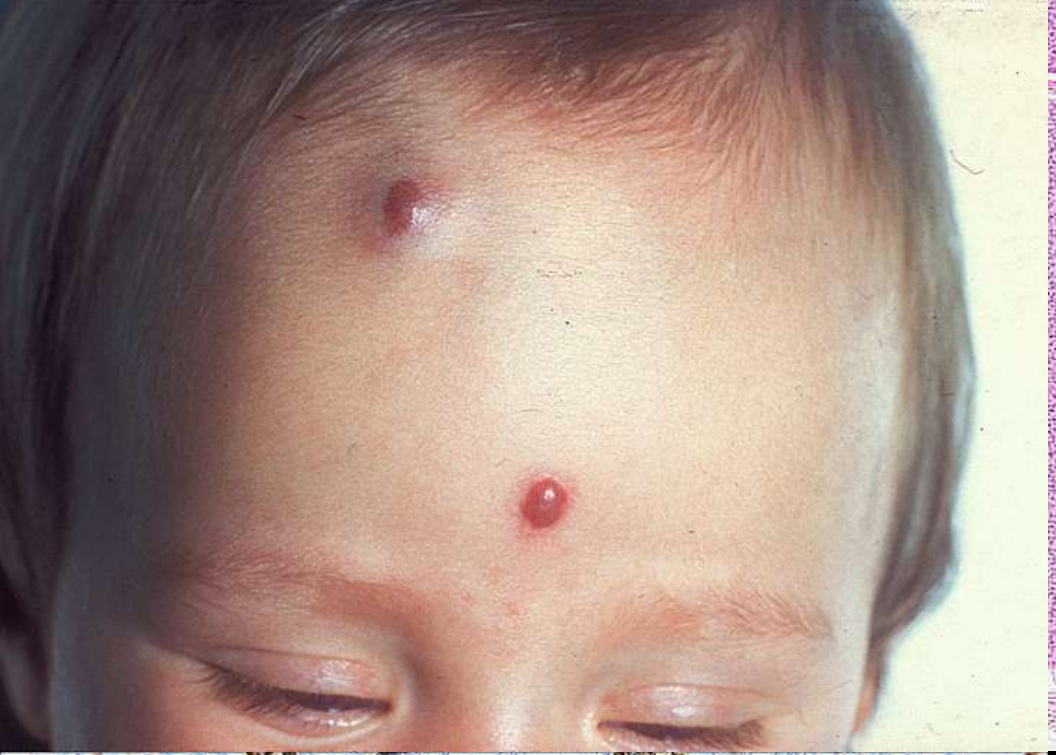

H'ENDOTHELIOMA
(retiform)

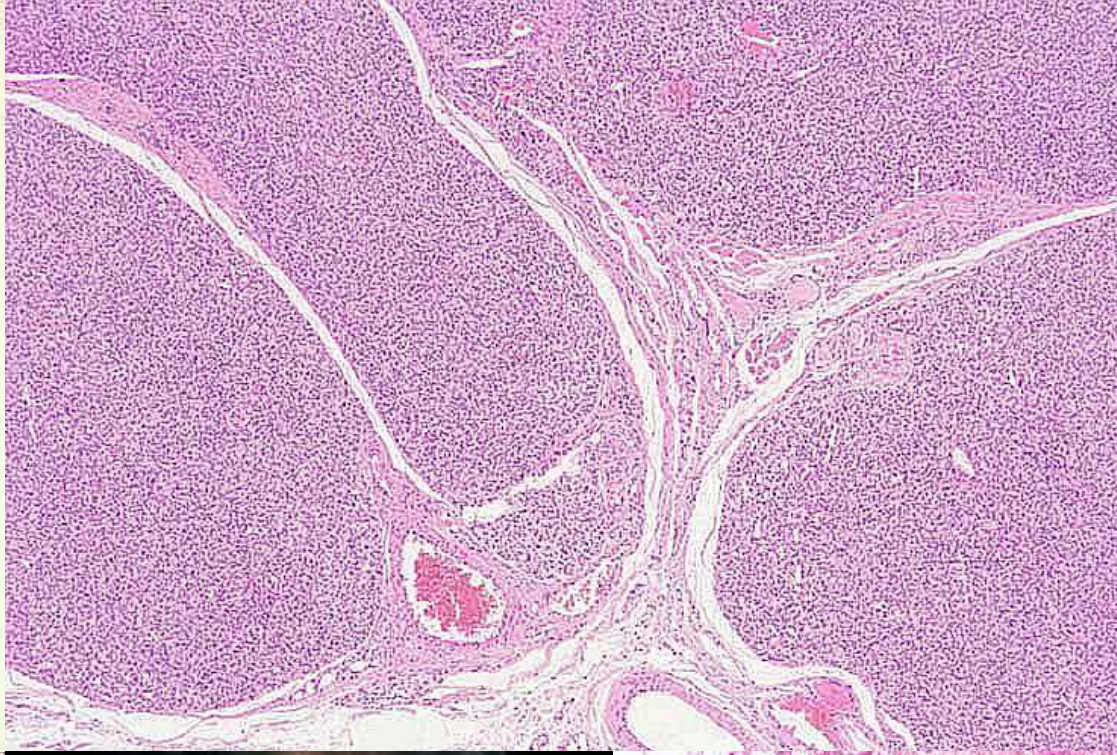
NOMENCLATURAL ANOMALIES
POSSIBLE WAYS FORWARD

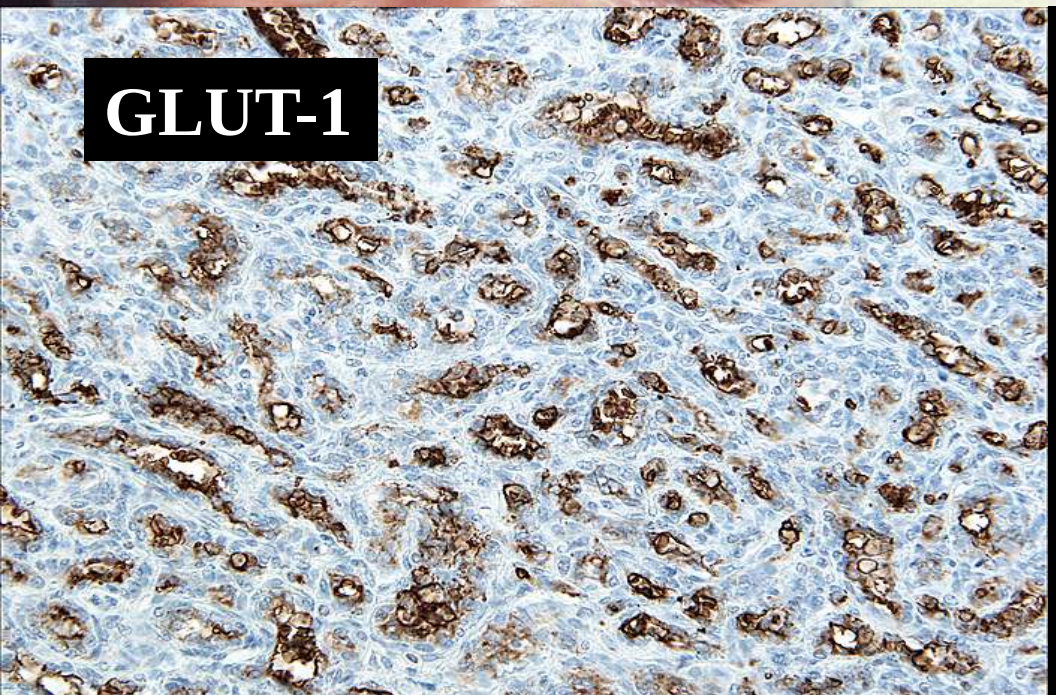
- **Openness to gradual revision on the basis of good/rational evidence**
- **Willingness to accept genetic definitions (as with leukemias)**
- **Committment to bringing clinicians along with us (perhaps thro' concensus conferences)**
- **? 'Radical' approaches, dismissing time-honored terminology -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

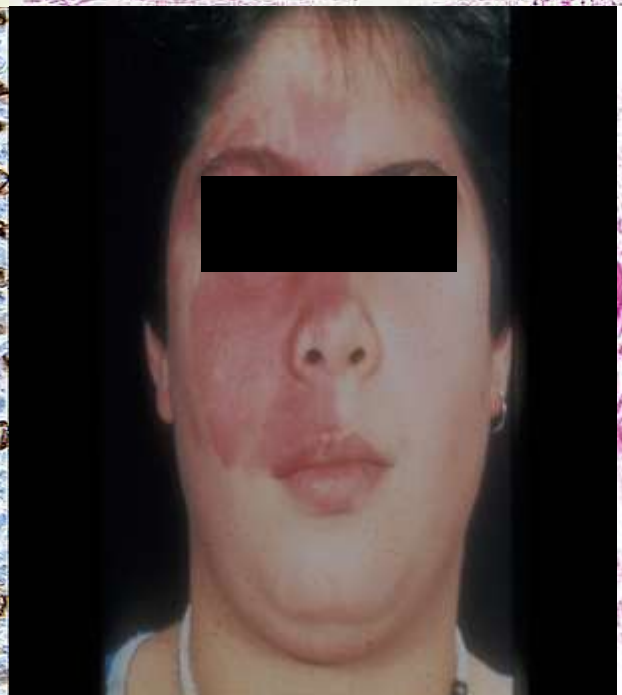
LACK OF BIOLOGIC UNDERSTANDING

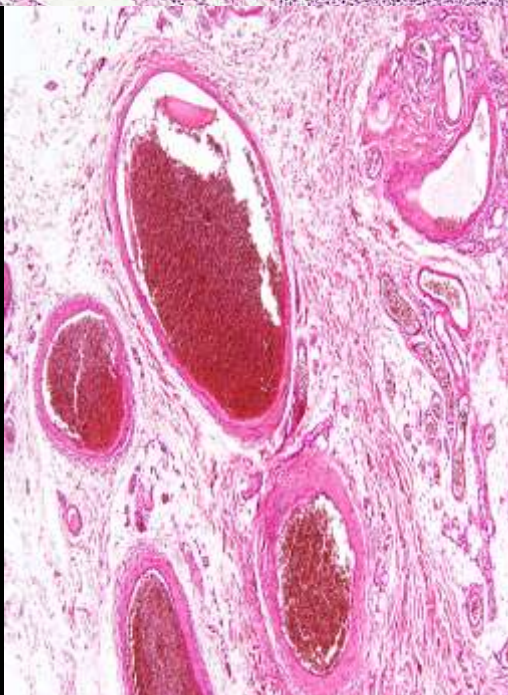
Vascular tumours – par excellence !
Neoplasm vs malformation / hamartoma
How to define a neoplasm ?
Relevance of clonality / mixed cell types
Limited genetic data
Blood vascular vs lymphovascular
Problem of “intermediate” lesions
Potential to be overtaken by clinicoradiologic classification

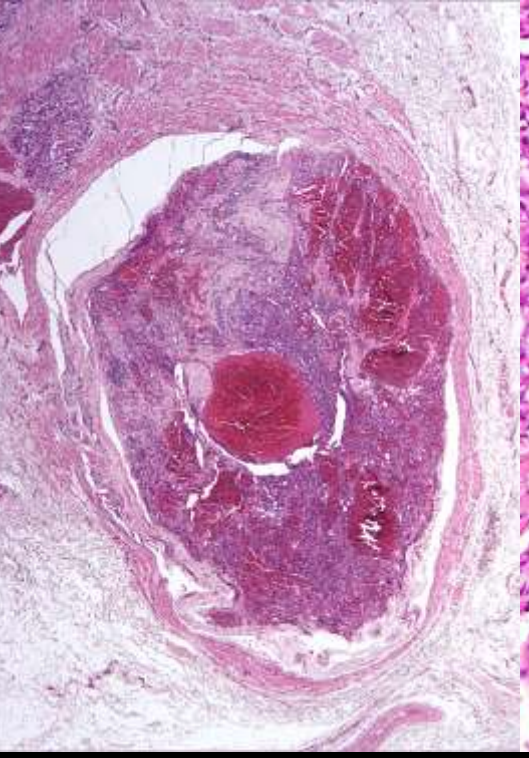
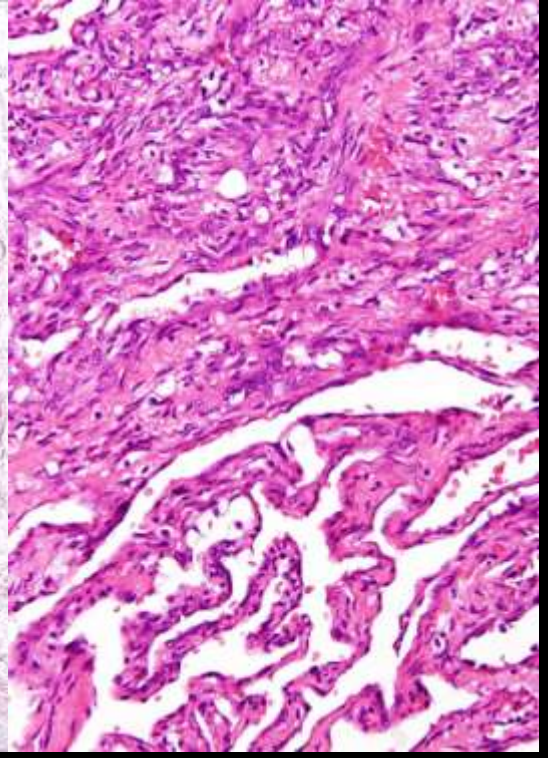
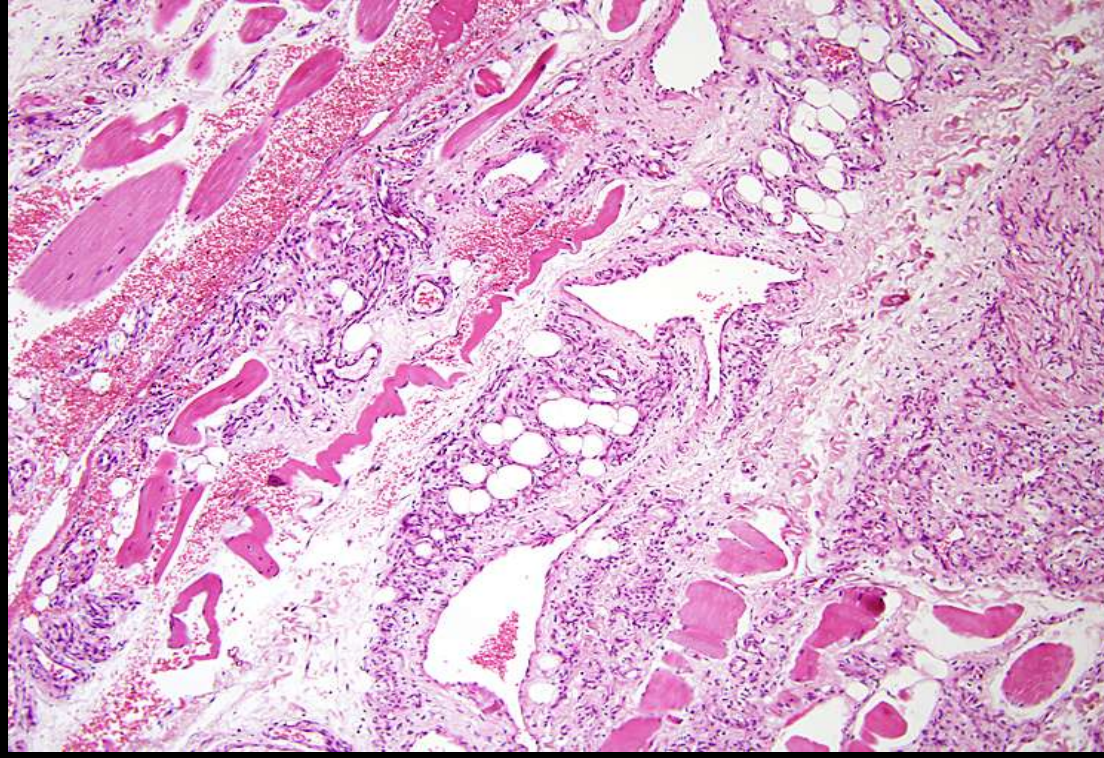
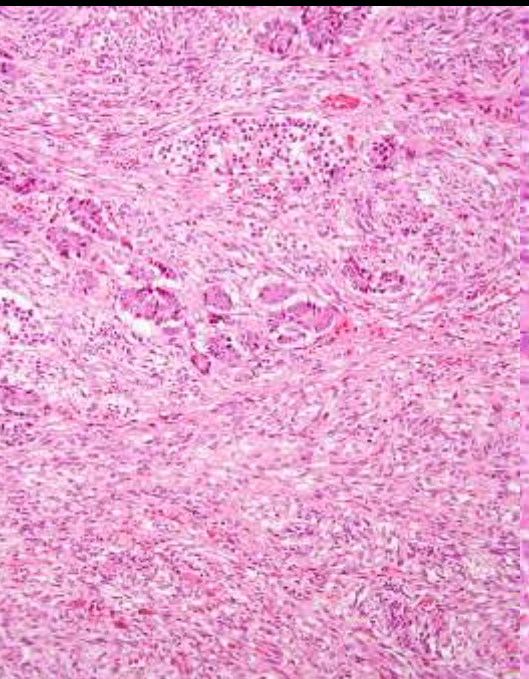
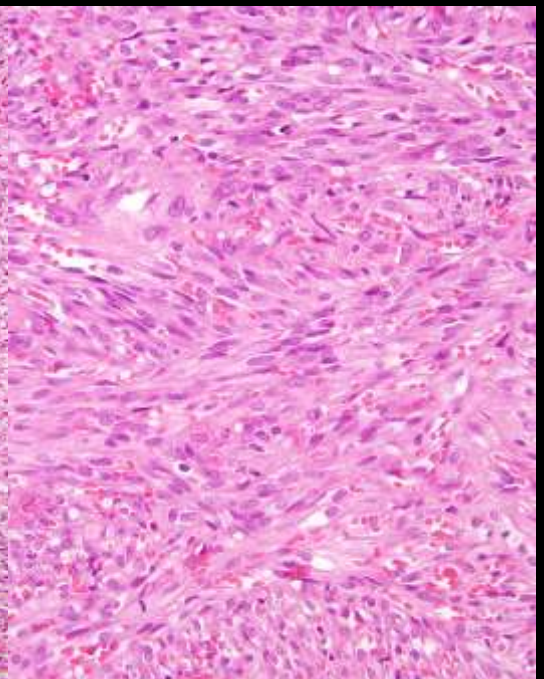
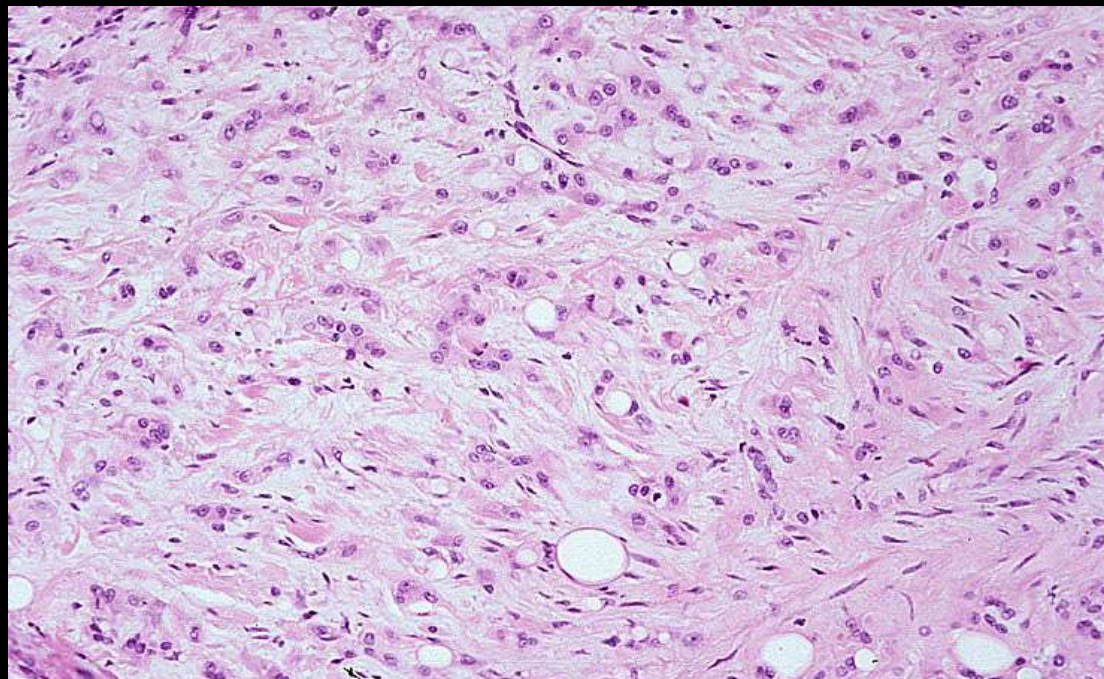





GLUT-1





IMPACT OF GENETICS
CURRENT STATUS

- Important impact on classification
- Valuable diagnostic adjunct in selected tumor types
- Uncertain prognostic value
- Limited but increasing impact on understanding pathogenesis

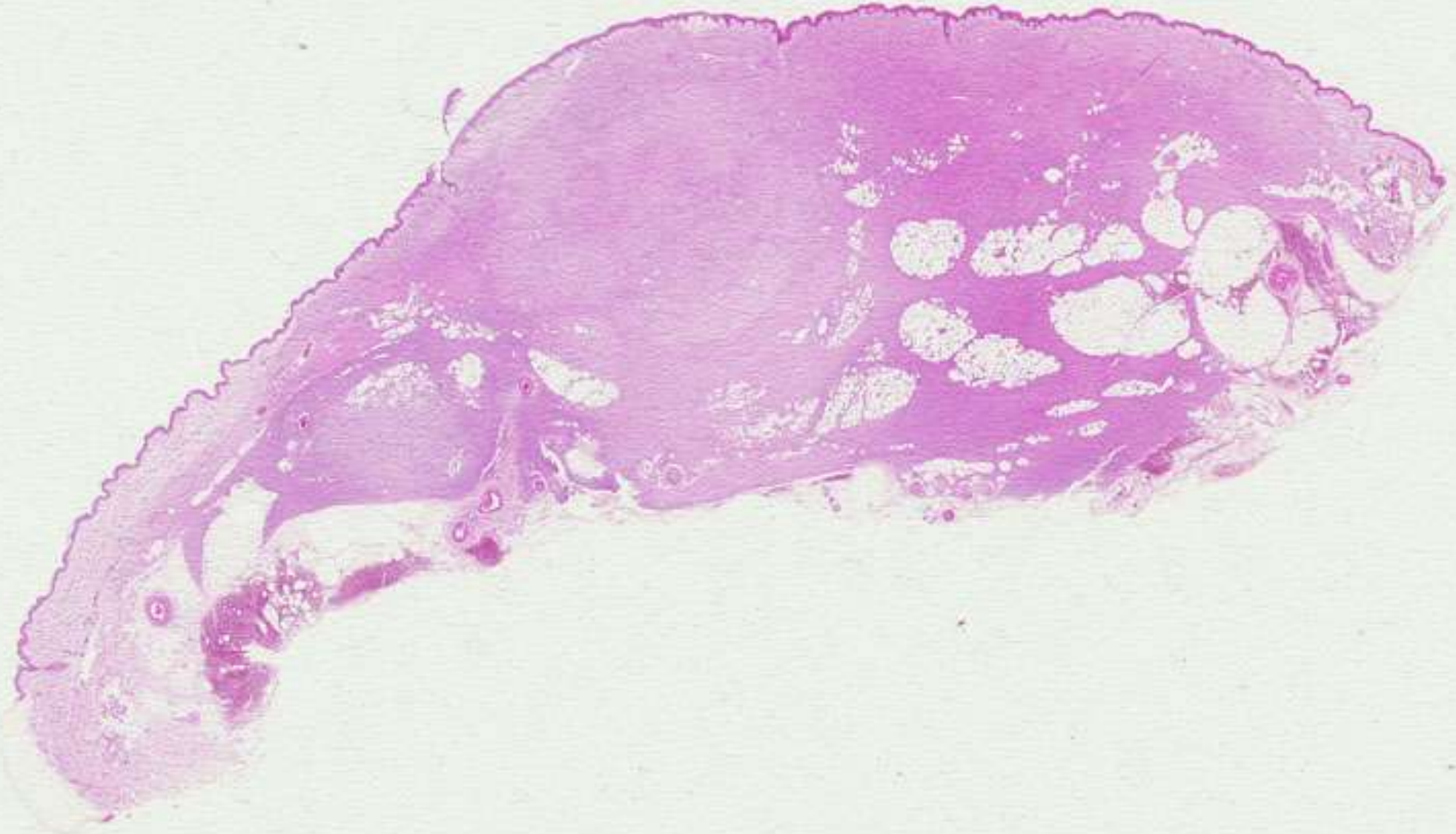
CYTOGENETIC ABERRATIONS IN SOFT TISSUE SARCOMAS

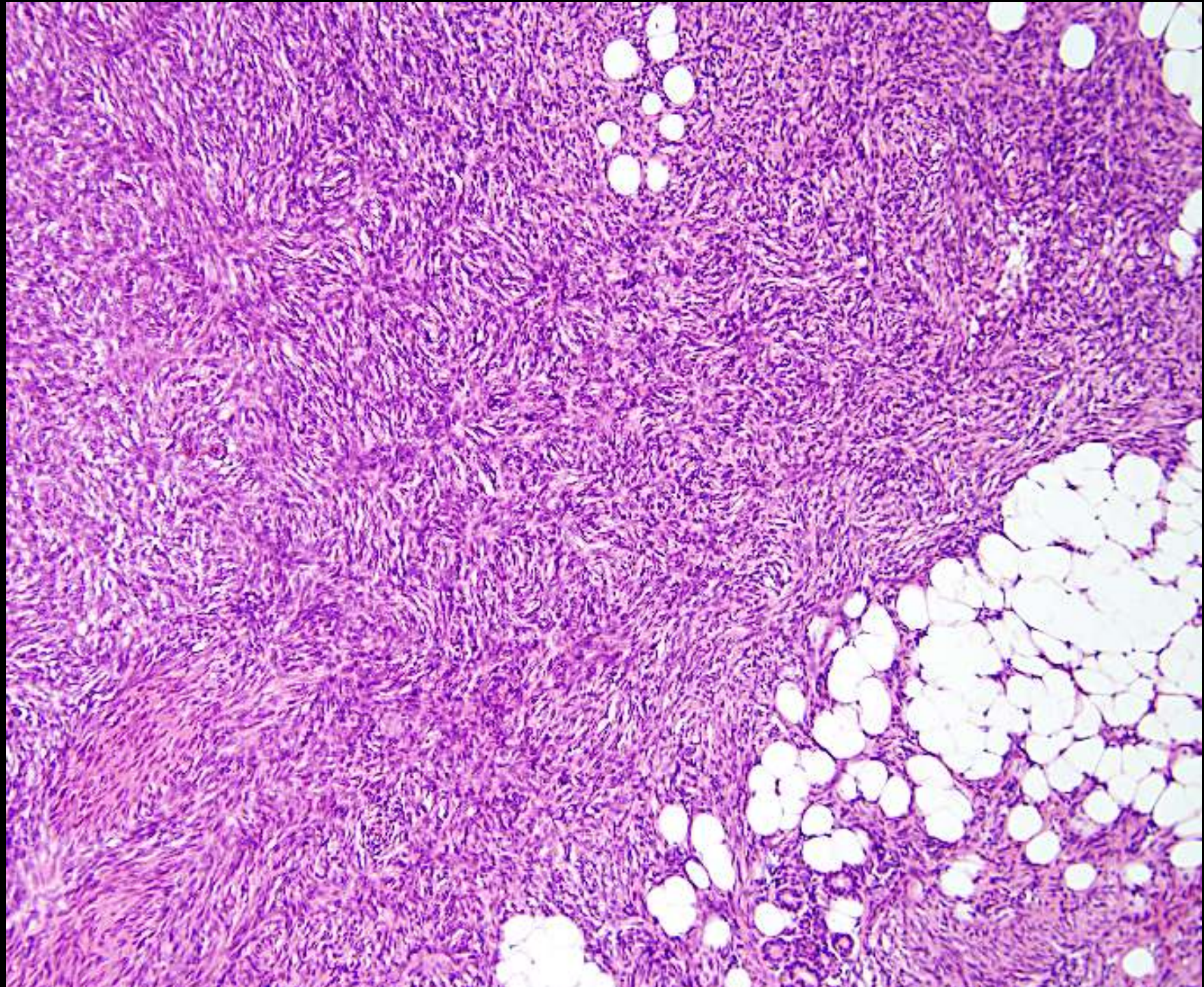
Tumor type	Cytogenetic changes	Gene fusion
Ewing's sarcoma/primitive neuroectodermal tumor	t(11;22)(q24;q12)	*FLI-1-EWSR1*
	t(21;22)(q22;q12)	*ERG-EWSR1*
	t(7;22)(p22;q12)	*ETV1-EWSR1*
	t(17;22)(q12;q12)	*EIAF-EWSR1*
	t(2;22)(q33;q12)	*FEV-EWSR1*
	t(16;21)(p11;q22)	*FUS-ERG*
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3-FOXO1A*
	t(1;13)(p36;q14)	*PAX7-FOXO1A*
Myxoid/round cell liposarcoma	t(12:16)(q13;q11)	*DDIT3-FUS*
	t(12;22)(q13;q11-12)	*DDIT3-EWSR1*
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*WT1-EWSR1*
Synovial sarcoma	t(X;18)(p11.2;q11.2)	*SSX1-SYT*
		SSX2-SYT
Clear cell sarcoma/ so-called angiomatoid 'MFH'	t(12;22)(q13;q12)	*ATF-1-EWSR1*
	t(2;22)(q33;q12)	*CREB1-EWSR1*
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	*NR4A3-EWSR1*
	t(9;17)(q22;q11)	*NR4A3-TAF15*
Dermatofibrosarcoma protuberans/ giant cell fibroblastoma	t(17;22)(q22;q13)	*PDGFB-COL1A1*
Infantile fibrosarcoma	t(12;15)(p13;q25)	*ETV6-NTRK3*
Alveolar soft part sarcoma	t(X;17)(p11;q25)	*ASPL-TFE3*
Low grade fibromyxoid sarcoma	t(7;16)(q33;p11)	*FUS-CREB3L2*
	t(11;16)(p13;p11)	*FUS-CREB3L1*
Myxoinflammatory fibrobl. sarcoma	t(1;10)(p22;q24)	*TGFBR3-MGEA5*

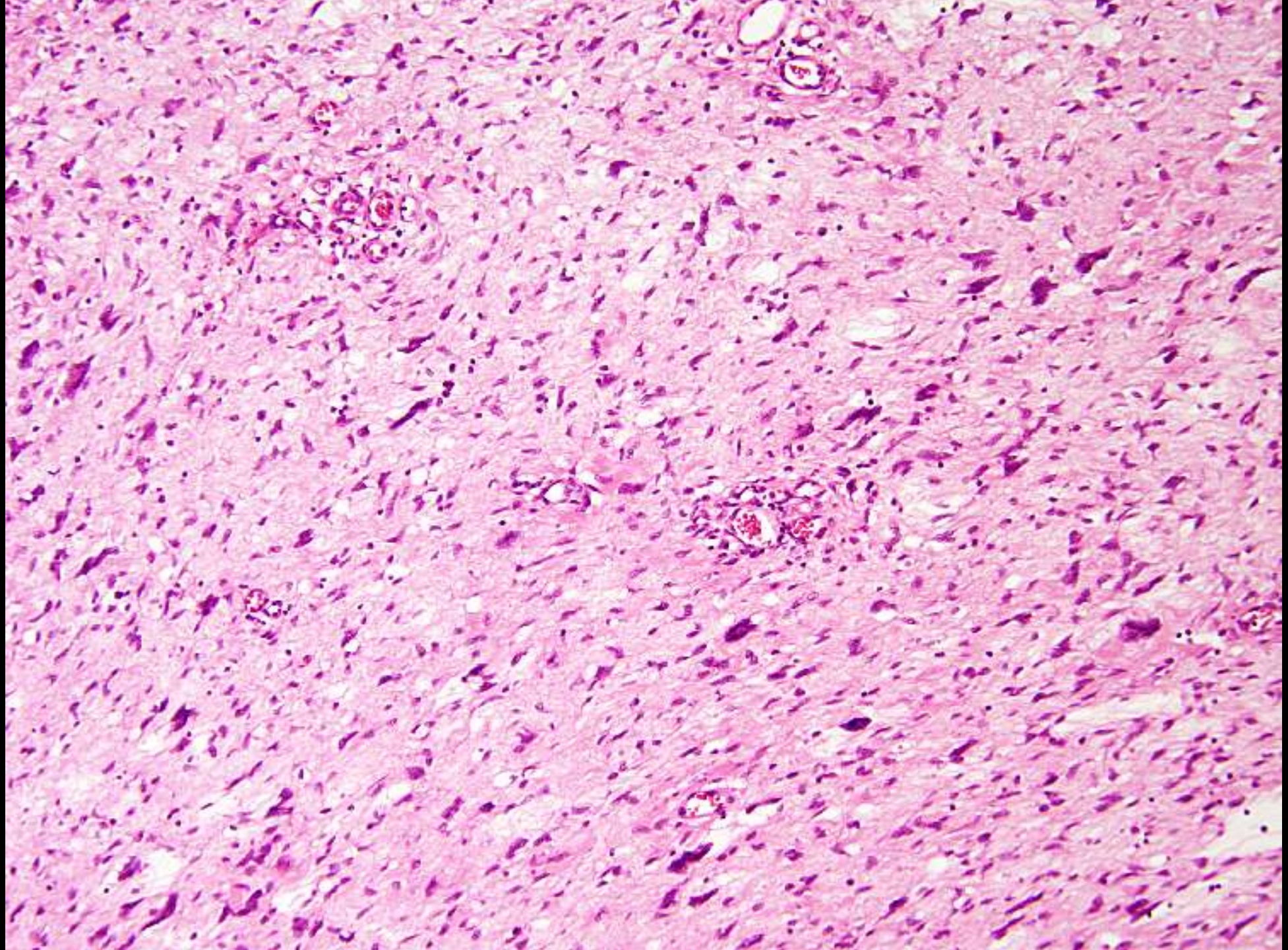
IMPACT OF GENETICS
POSSIBLE INFLUENCE ON NOMENCLATURE AND / OR CLASSIFICATION ?

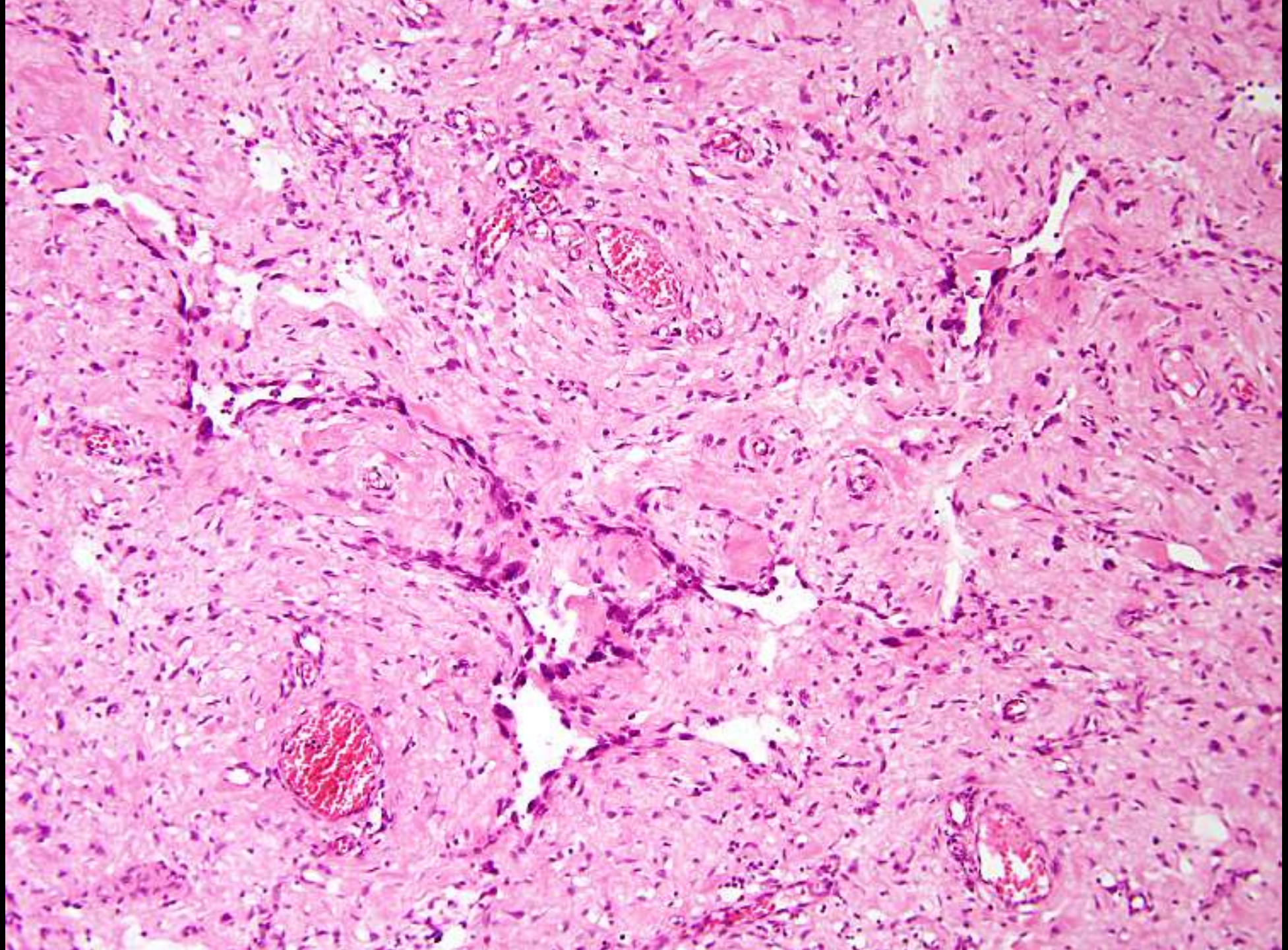
- **DFSP**
  Giant cell fibroblastoma
- **Spindle cell lipoma**
  Mammary-type myofibroblastoma
  Cellular angiofibroma

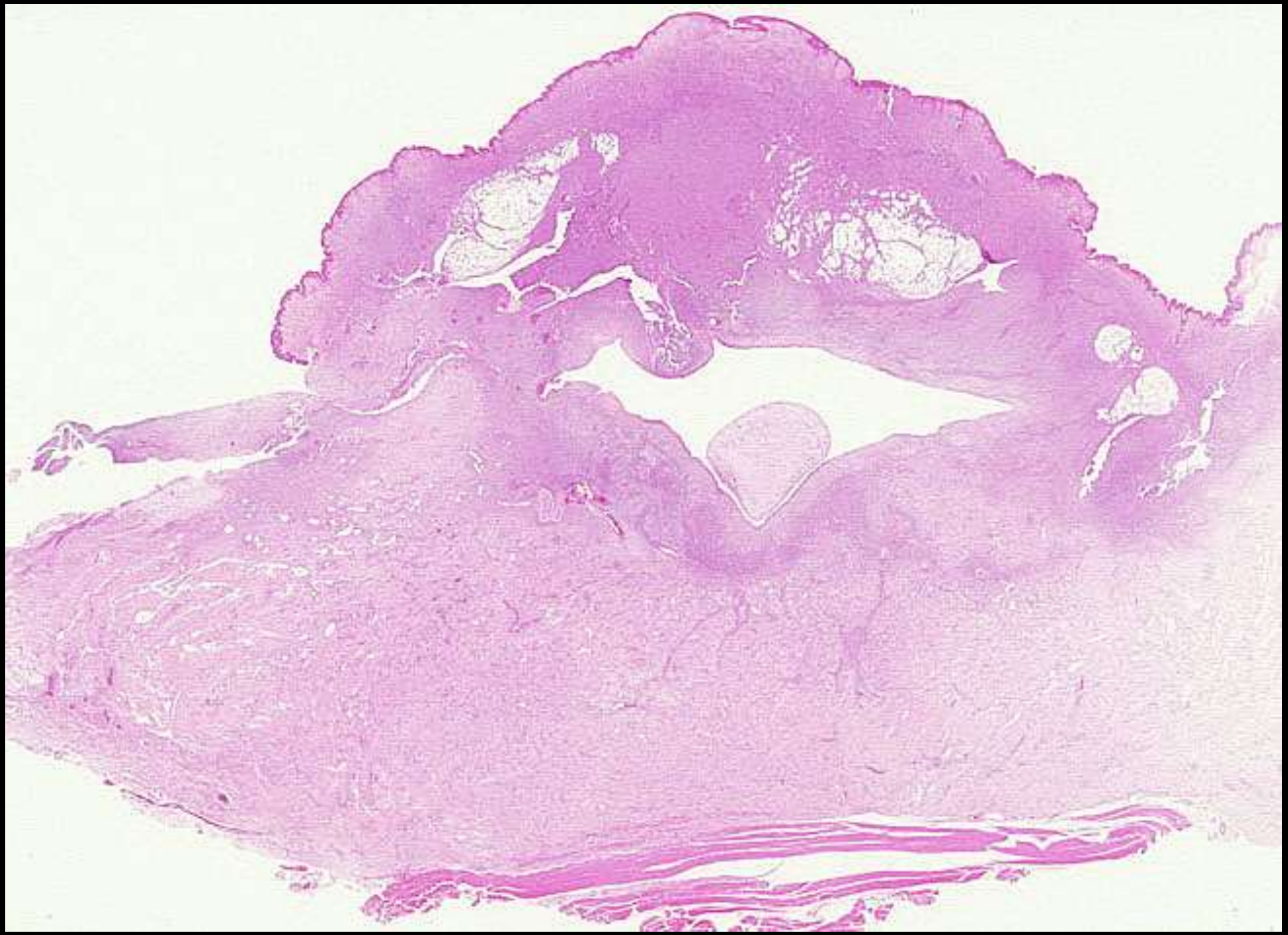
Just ‘related’ ? Or variants of a single ‘entity’ ?

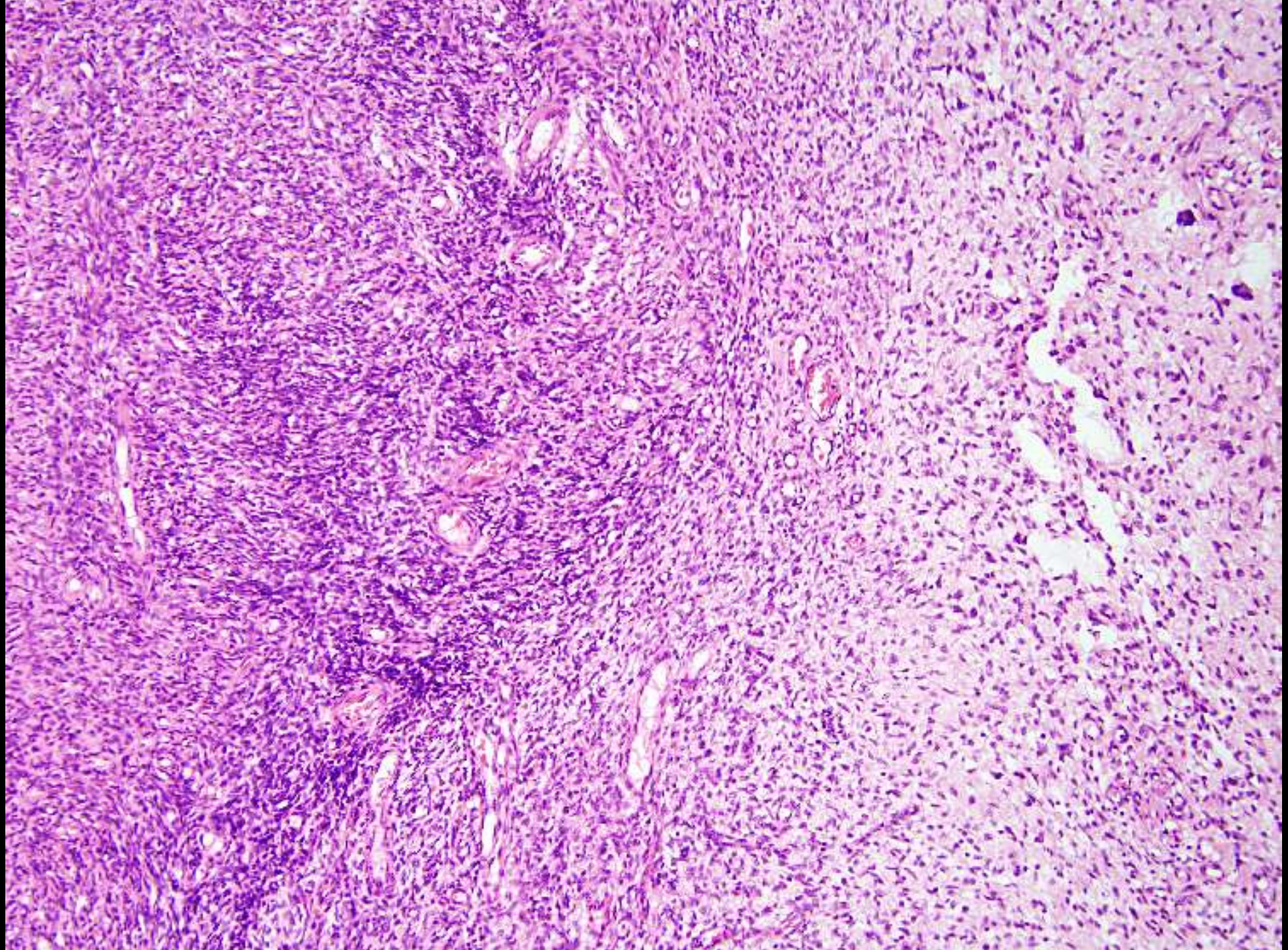












DERMATOFIBROSARCOMA PROTUBERANS AND GIANT CELL FIBROBLASTOMA CYTOGENETIC FEATURES

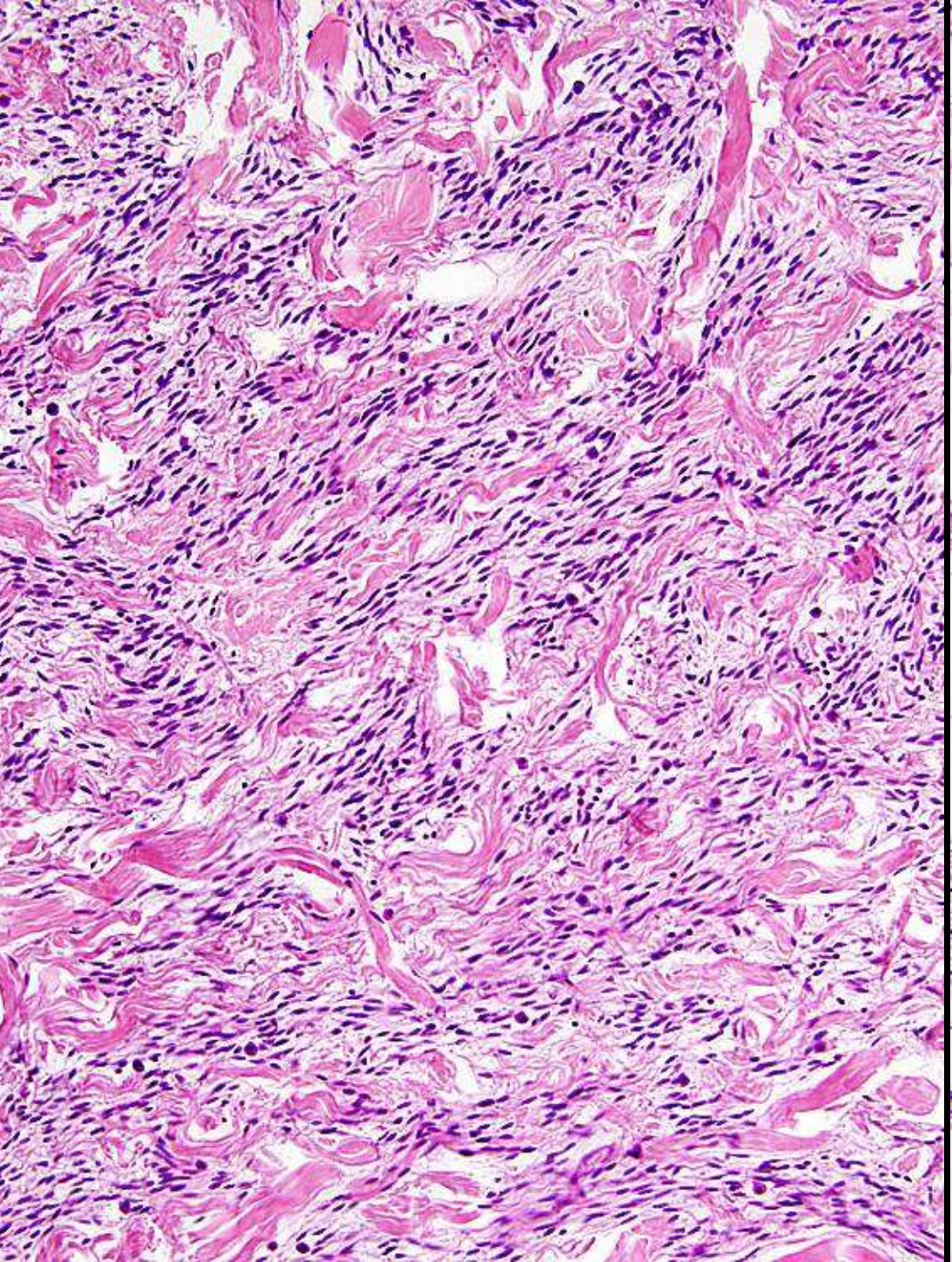
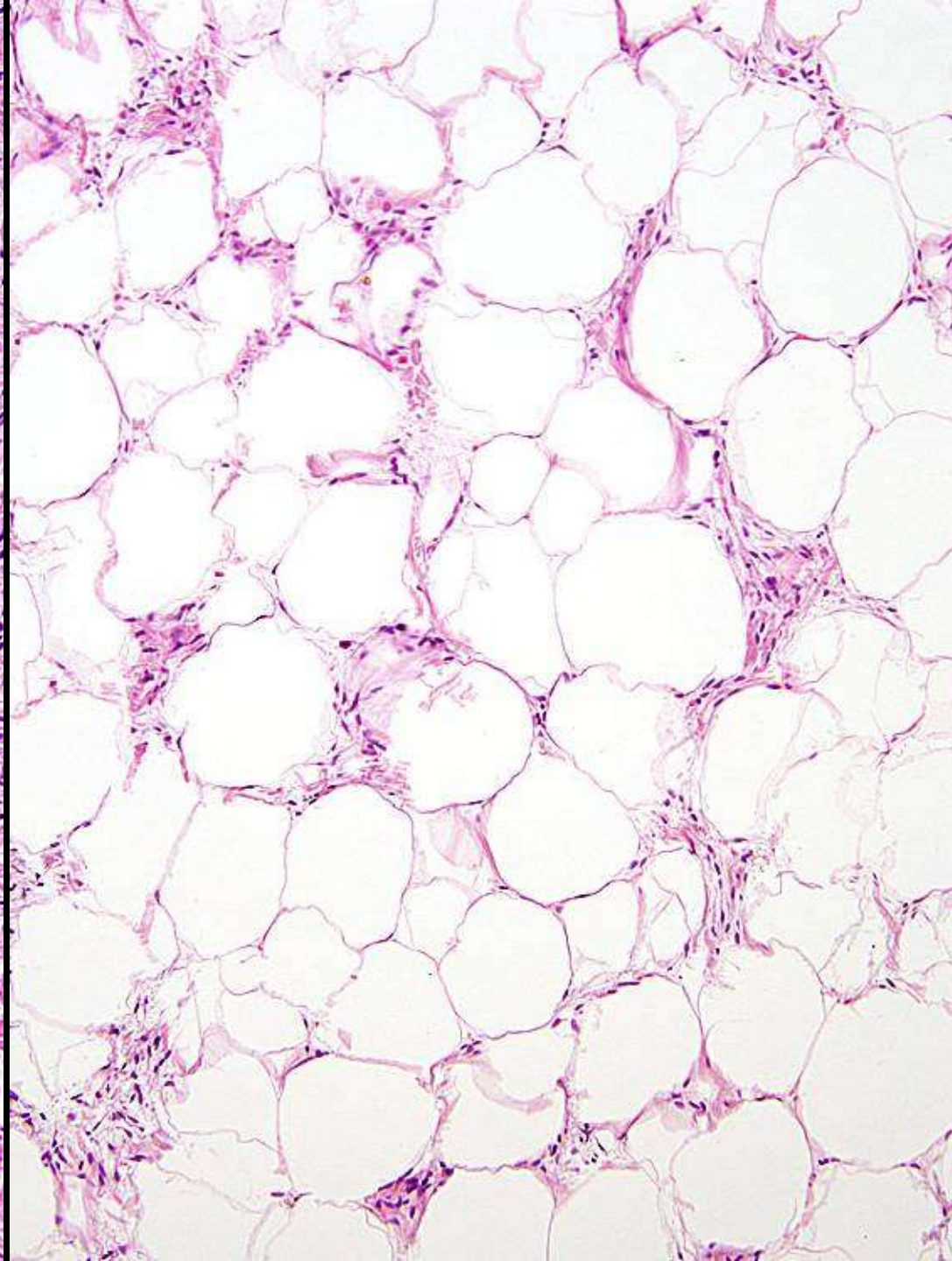
t(17;22)(q22;q13)
Leading to *PDGFB-COL1A1* fusion

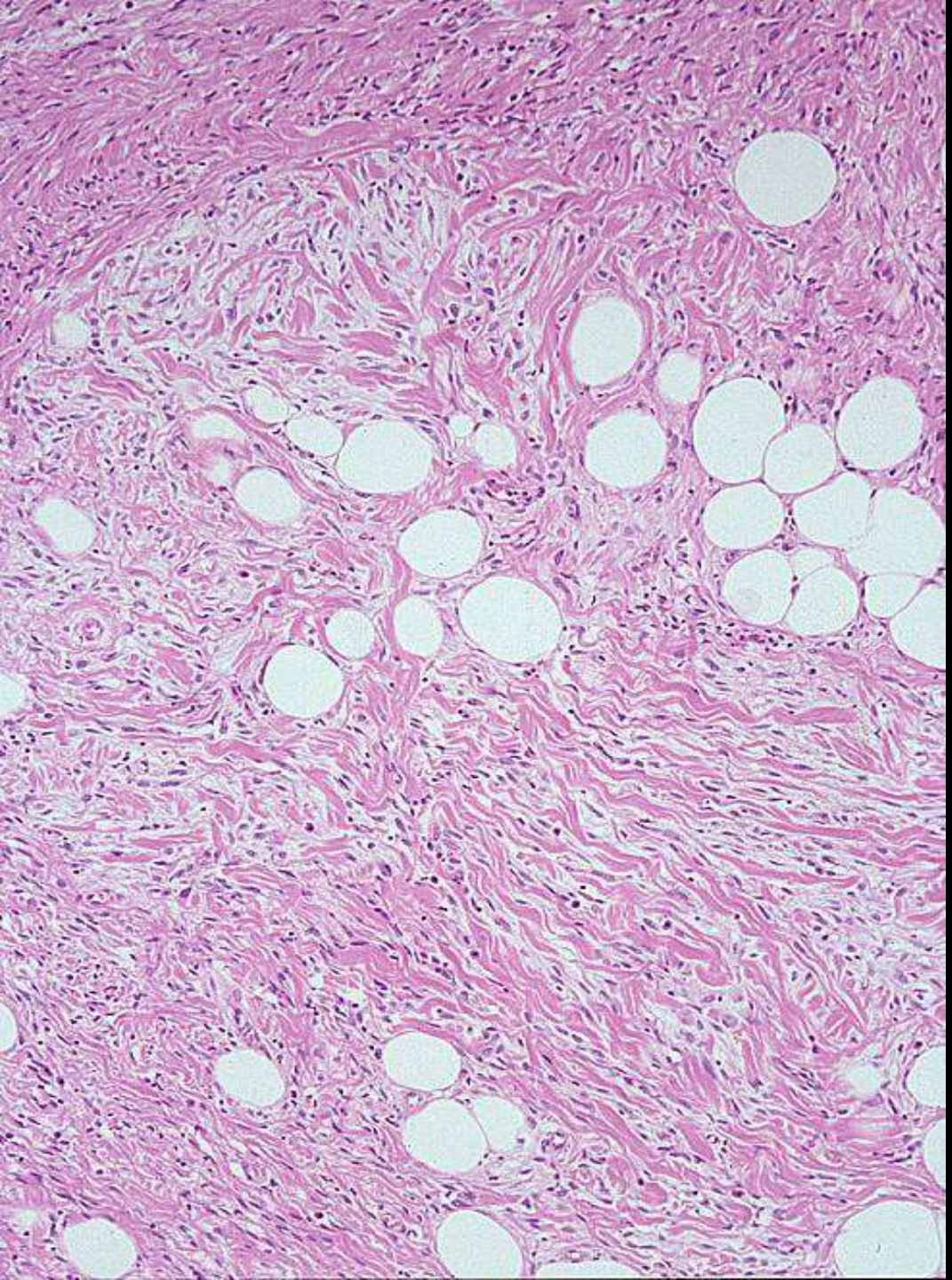
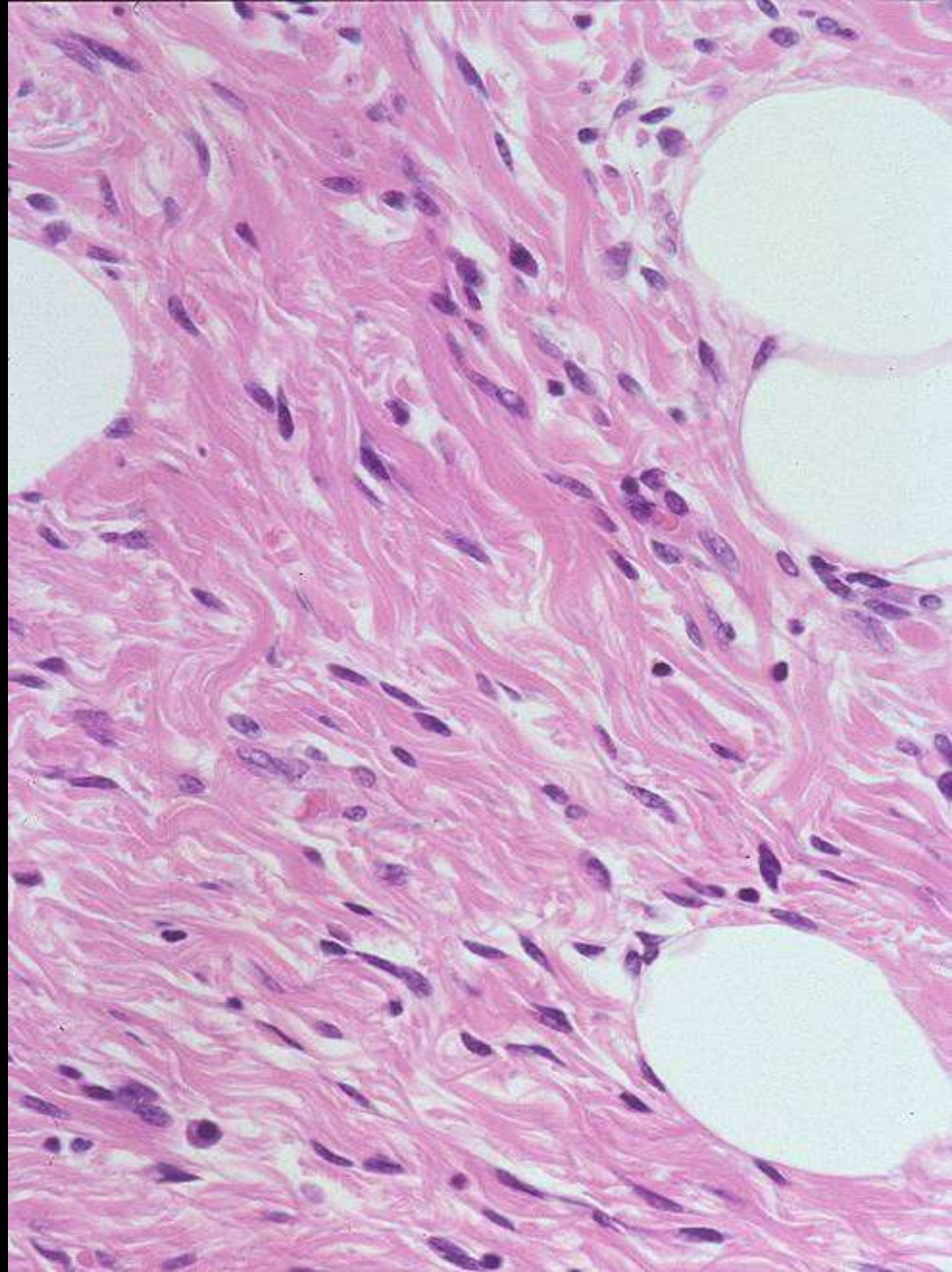
Ring chromosomes in DFSP – composed of amplified elements of same regions of 17 and 22

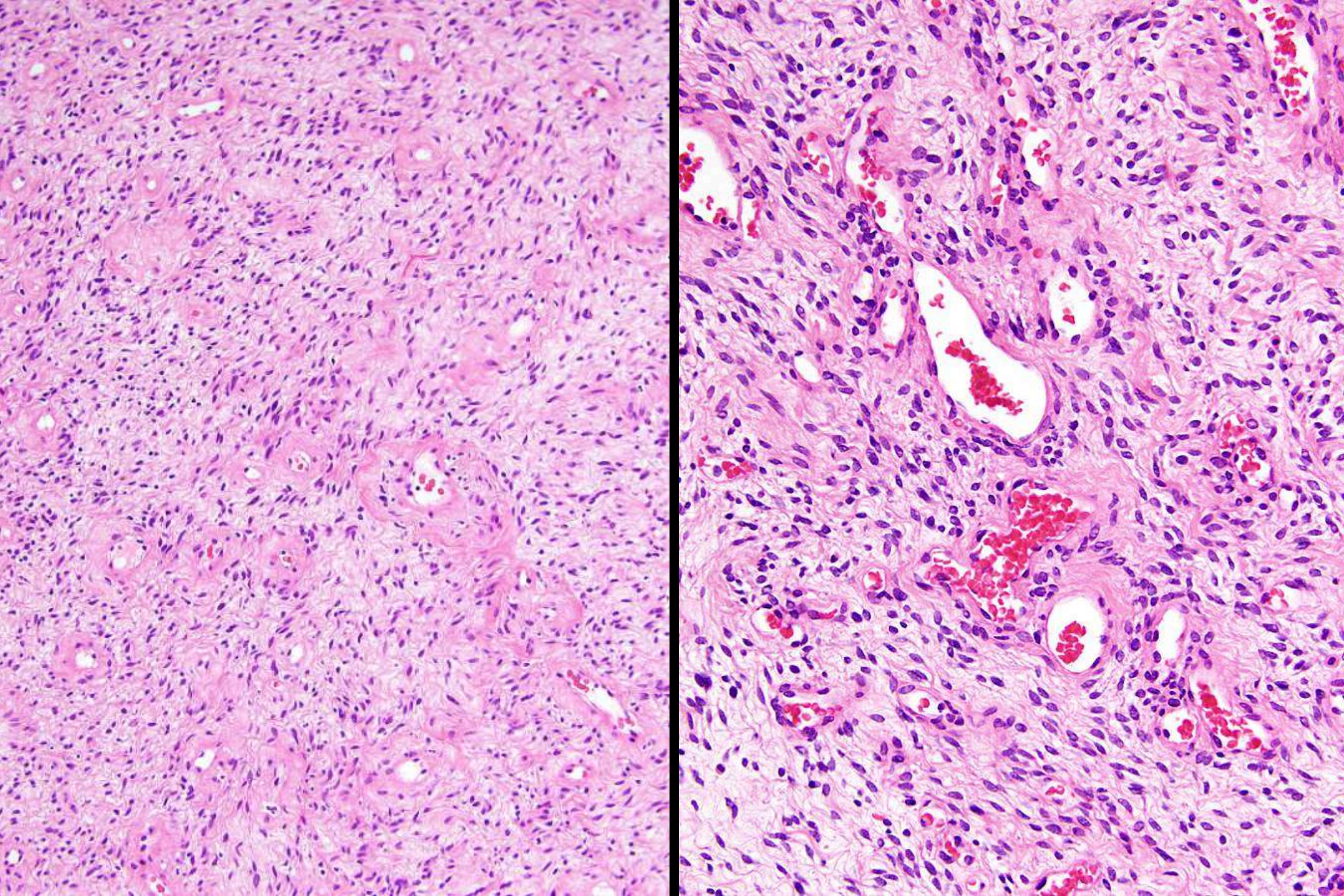
Same also (with additional genomic gains) in fibrosarcomatous DFSP

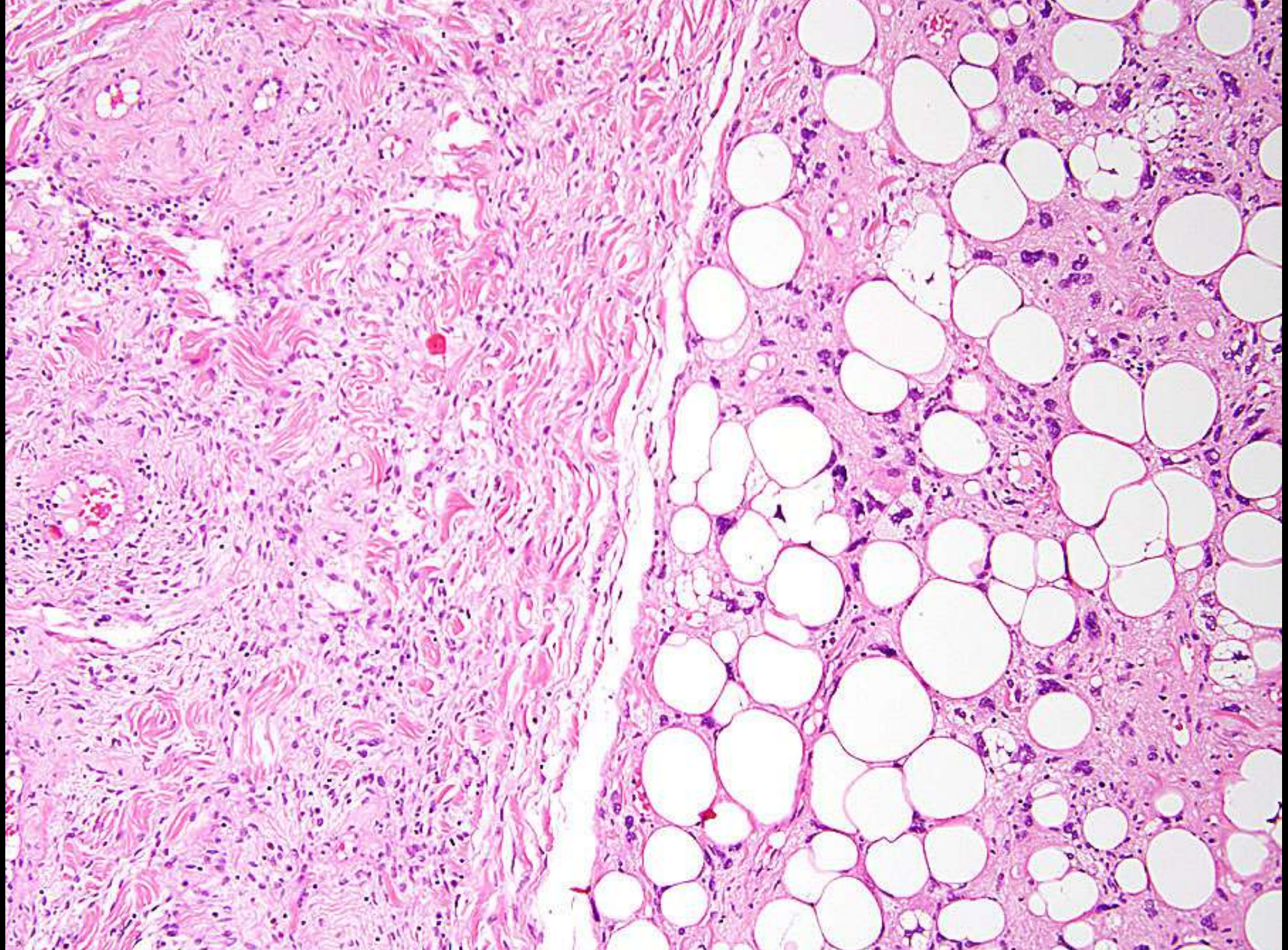
RELATIONSHIP BETWEEN DFSP AND GIANT CELL FIBROBLASTOMA

- Similar anatomic sites – but usually different ages at presentation
- Similar infiltrative pattern / recurrence
- Morphologic hybrids
- GCF may recur as DFSP (and vice versa)
- ? Neither metastasises without progression to “fibrosarcoma”
- Same translocation / fusion gene - but ? role of different copy numbers

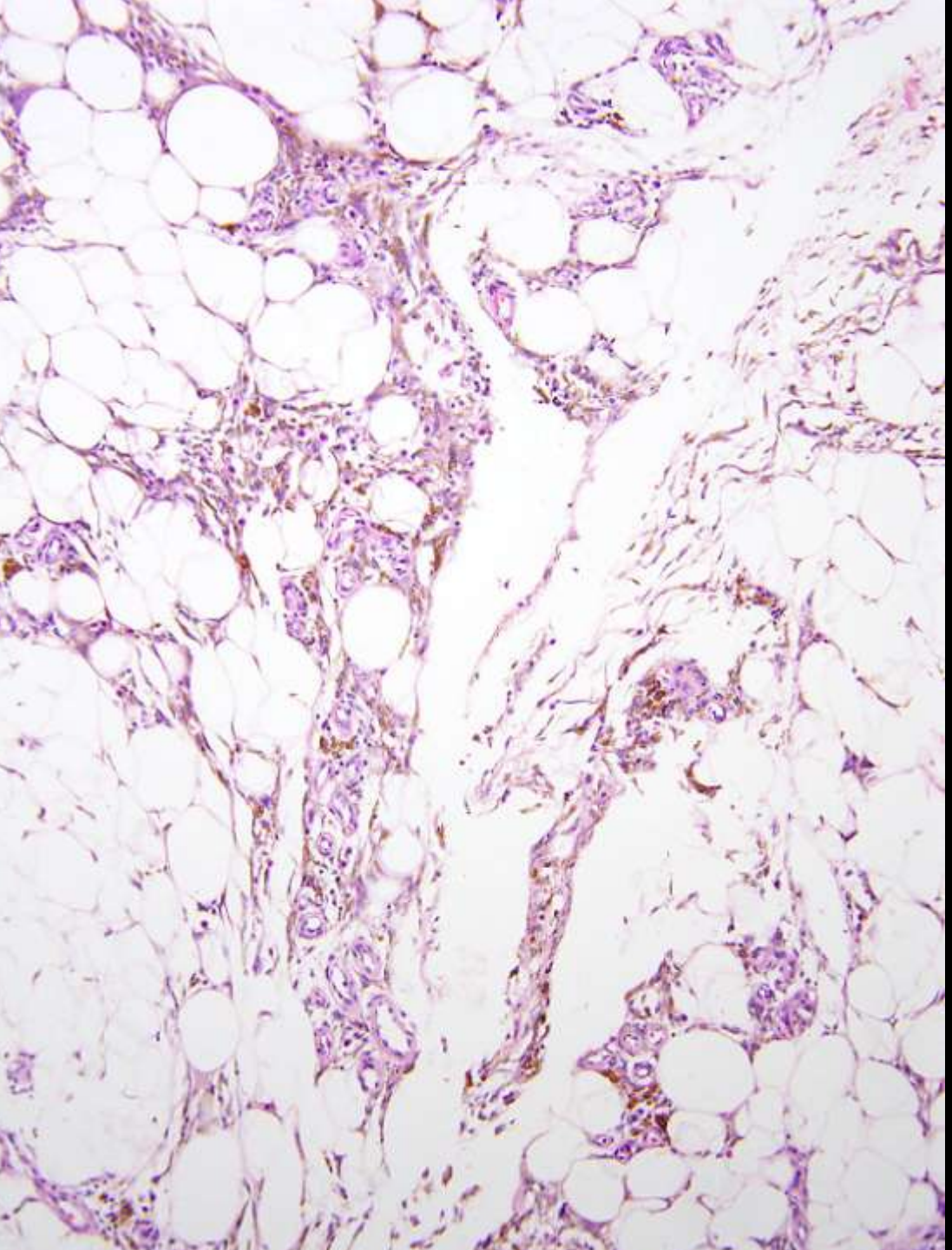



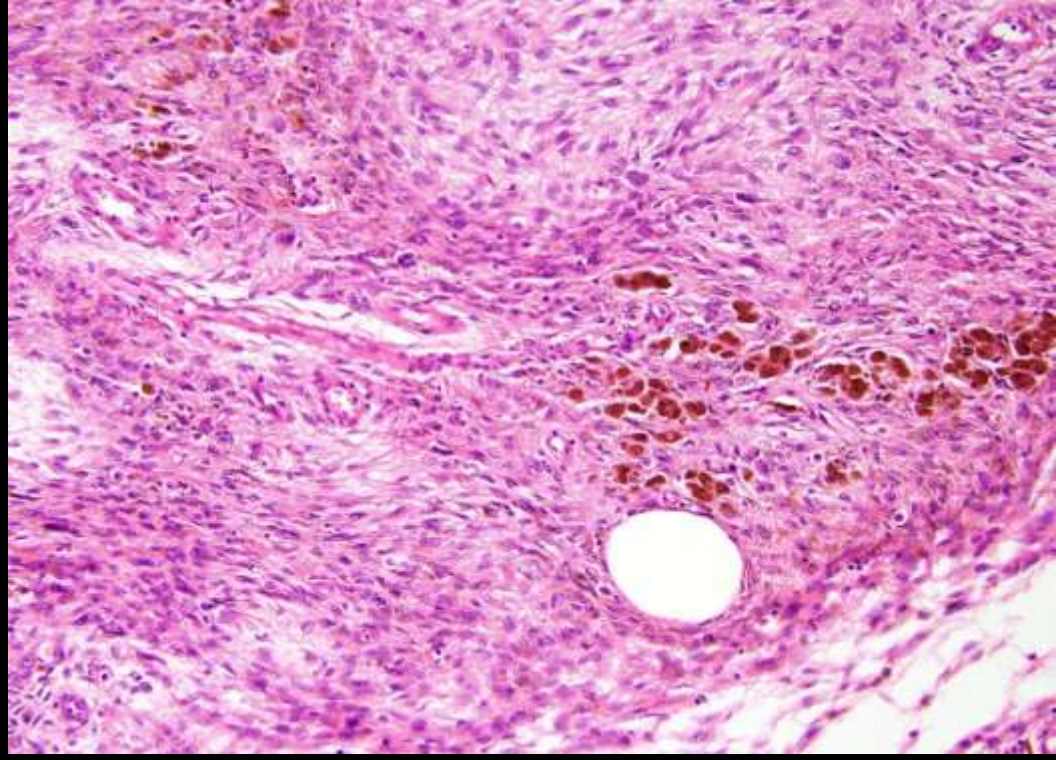


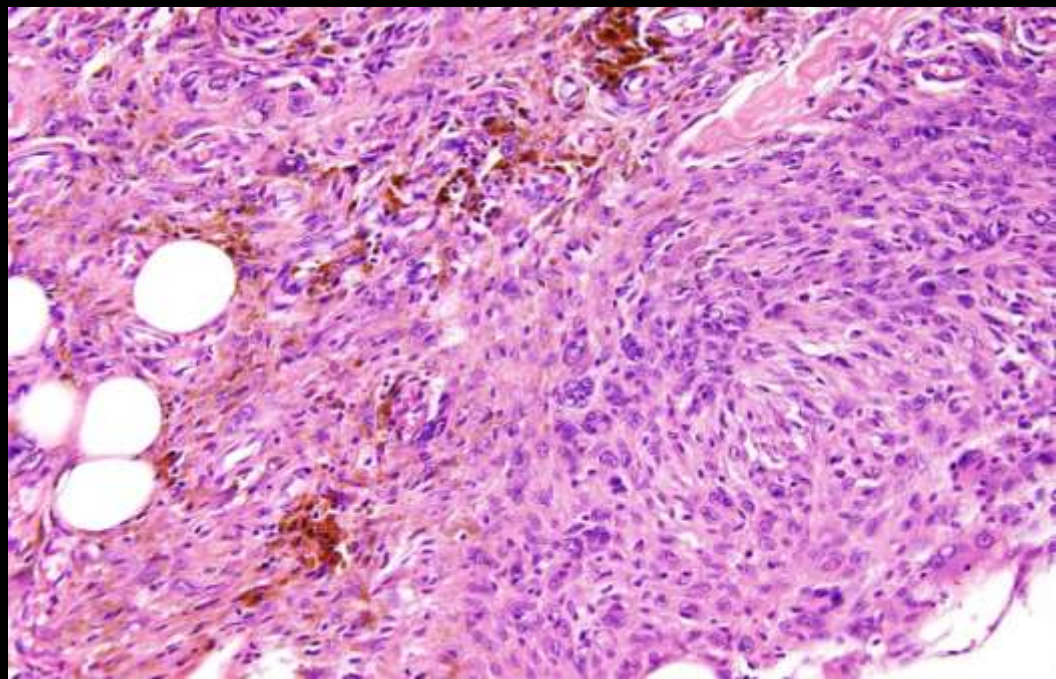


RELATIONSHIP BETWEEN SPINDLE CELL LIPOMA, MAMMARY-TYPE MYOFIBROBLASTOMA & CELLULAR ANGIOFIBROMA

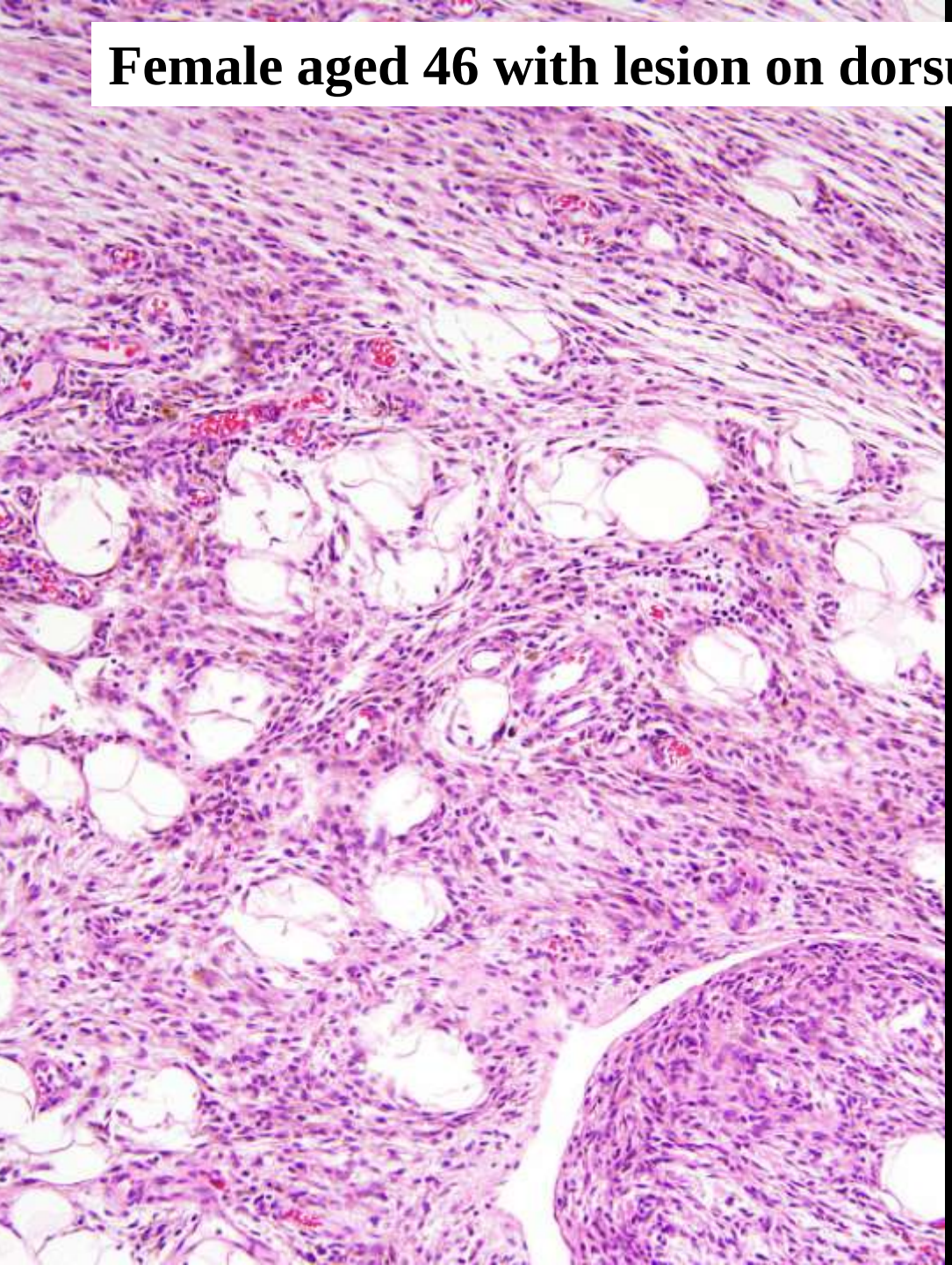
- Generally different anatomic sites - does this influence the phenotype ?
- Morphologic overlap with subtle differences
- Immunophenotypic differences
- Same rearrangement/loss of 13q14
- All benign/rarely recur
- Cellular angiofibroma may perhaps have potential for progression

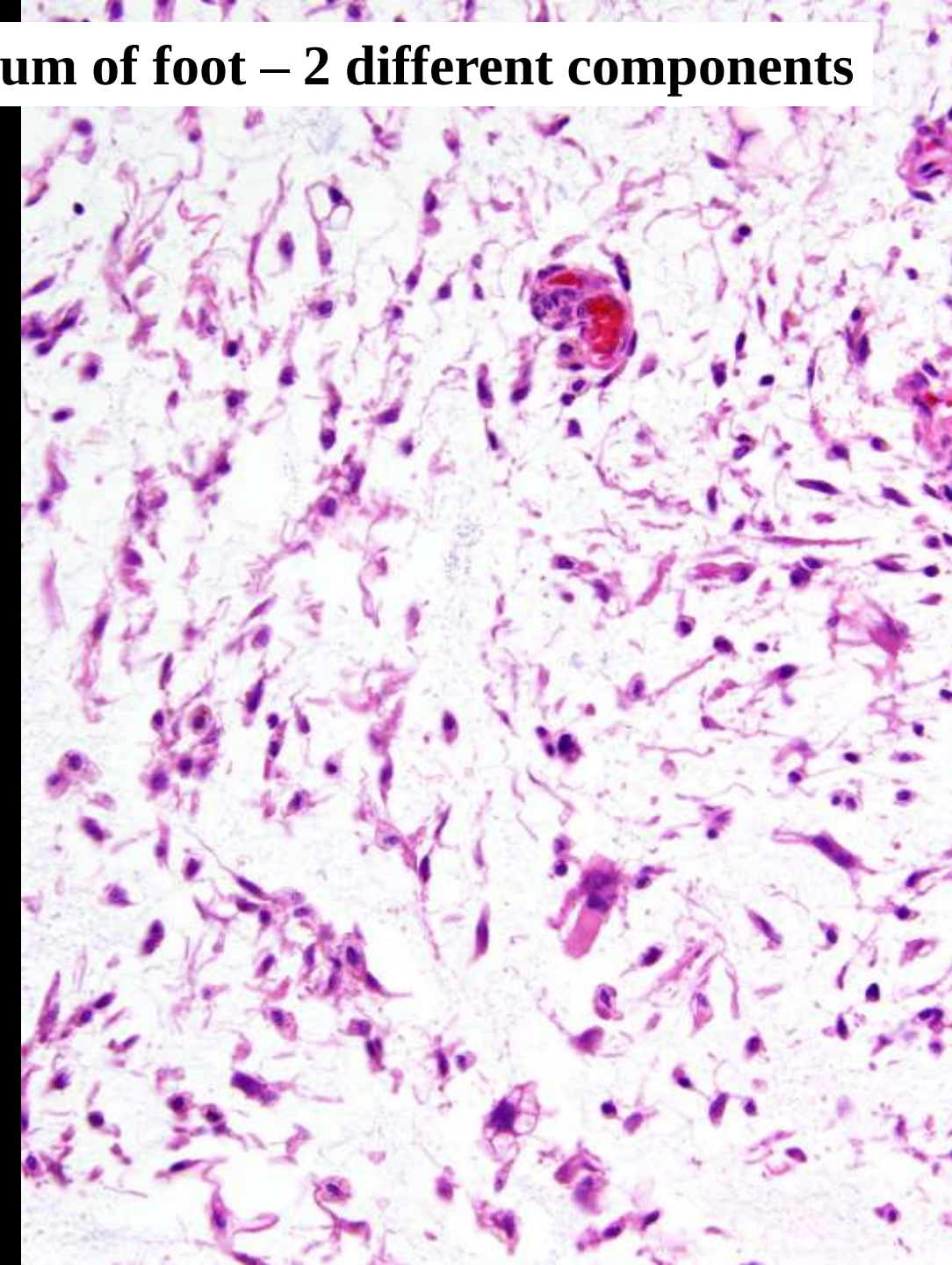


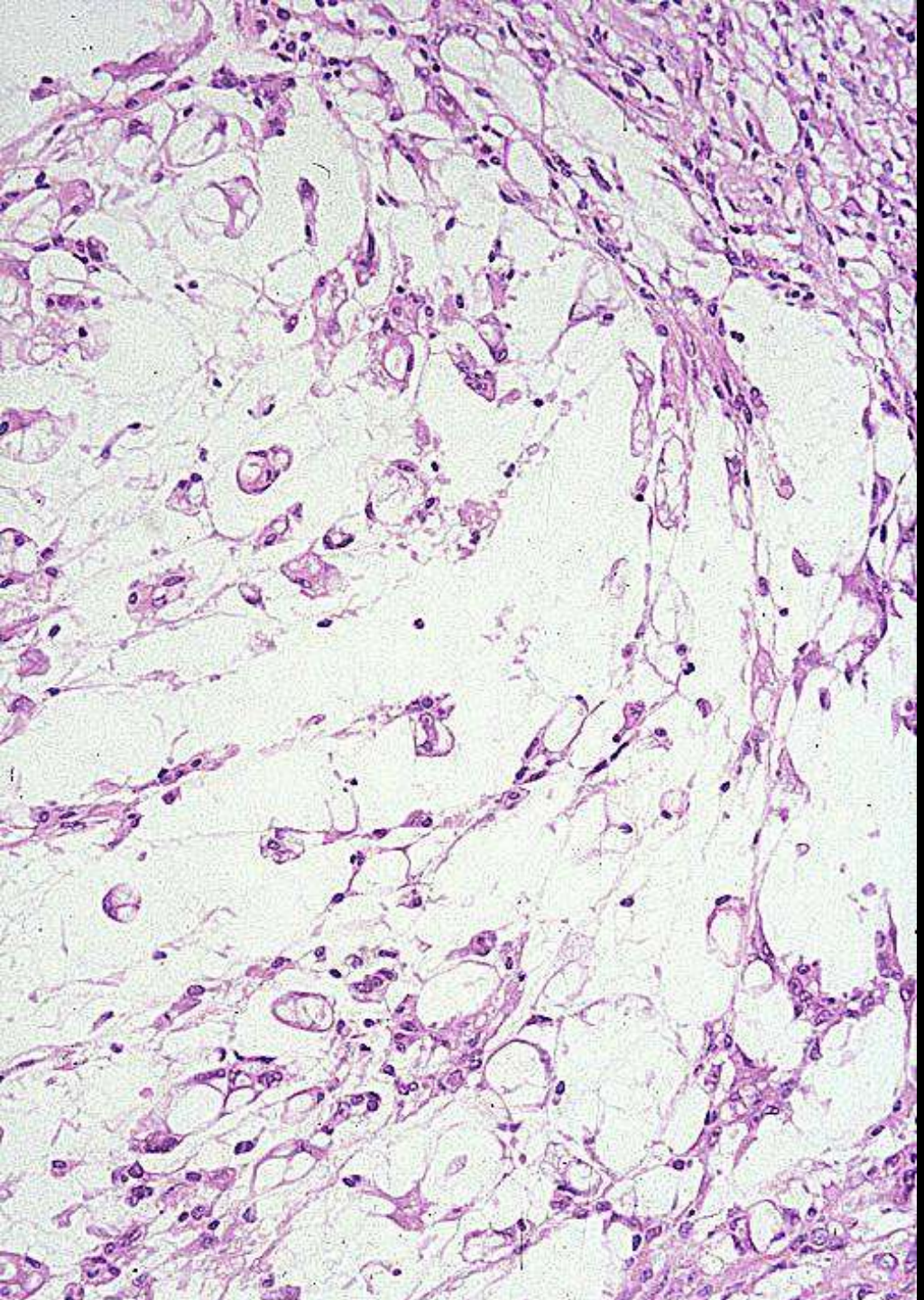


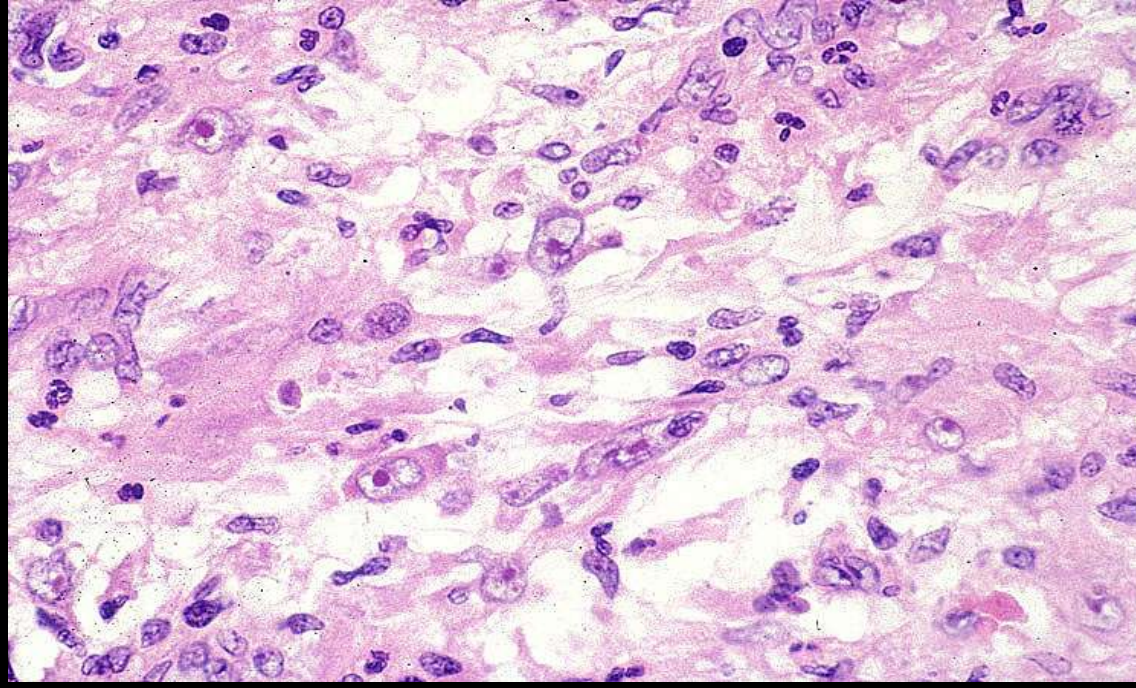


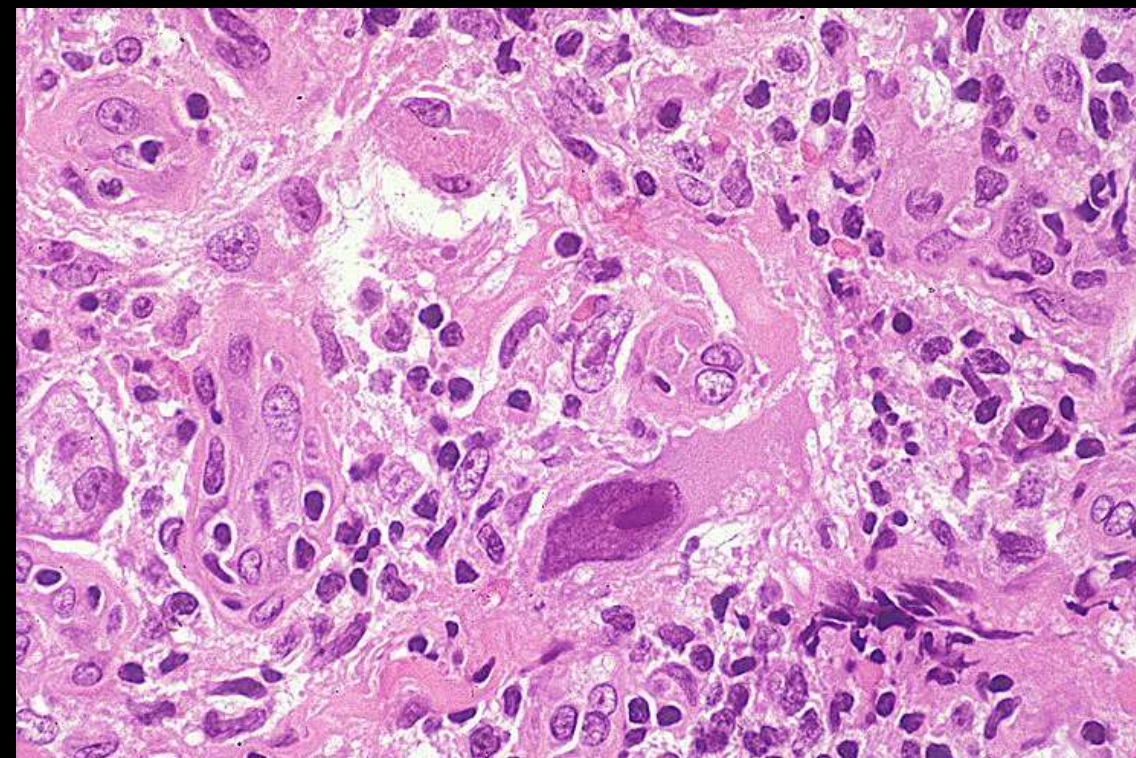
Female aged 46 with lesion on dorsum of foot – 2 different components











MYXOINFLAMMATORY FIBROBLASTIC SARCOMA AND HEMOSIDEROTIC FIBROLIPOMATOUS TUMOR

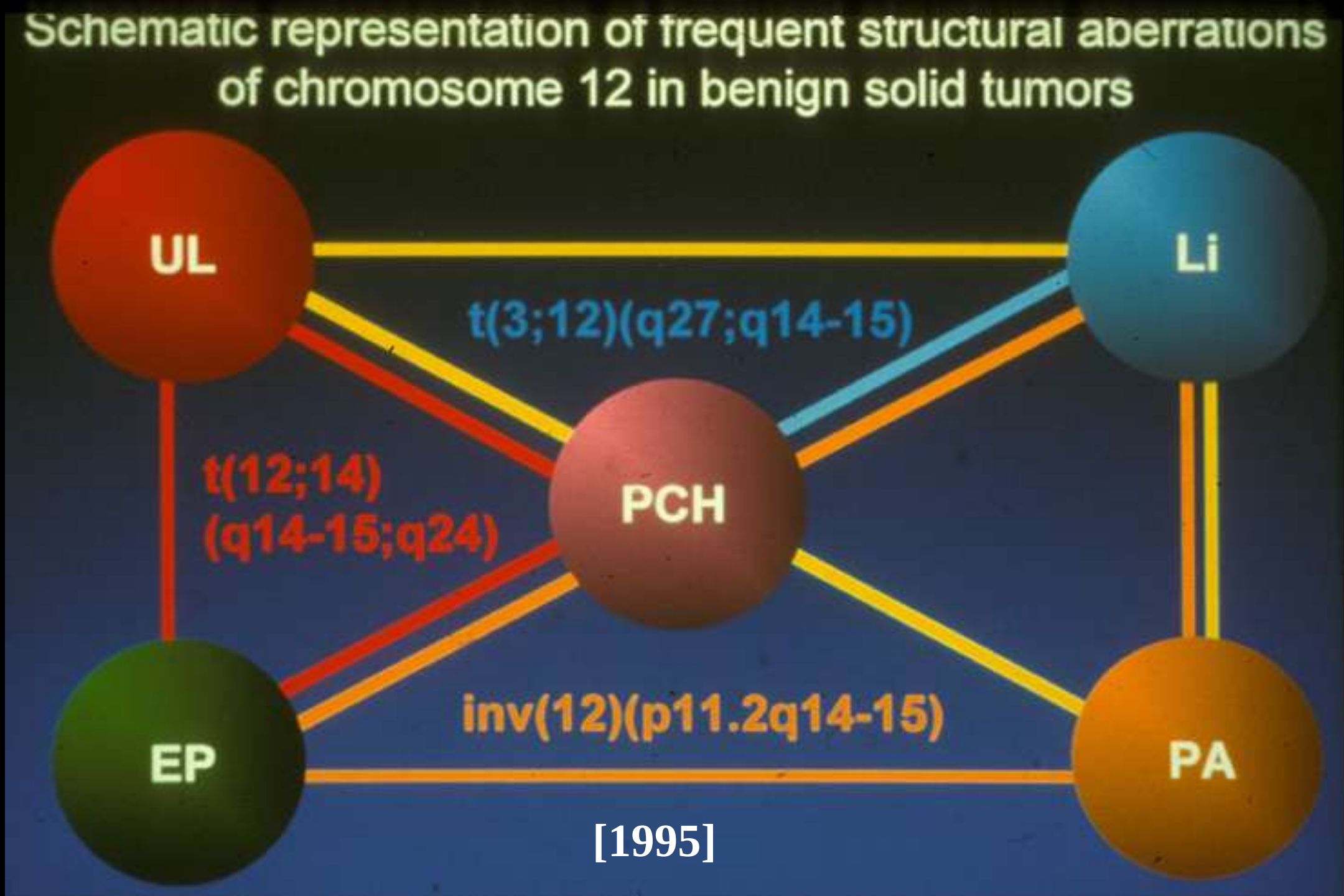
SHARED CLINICOPATHOLOGIC & GENETIC FEATURES

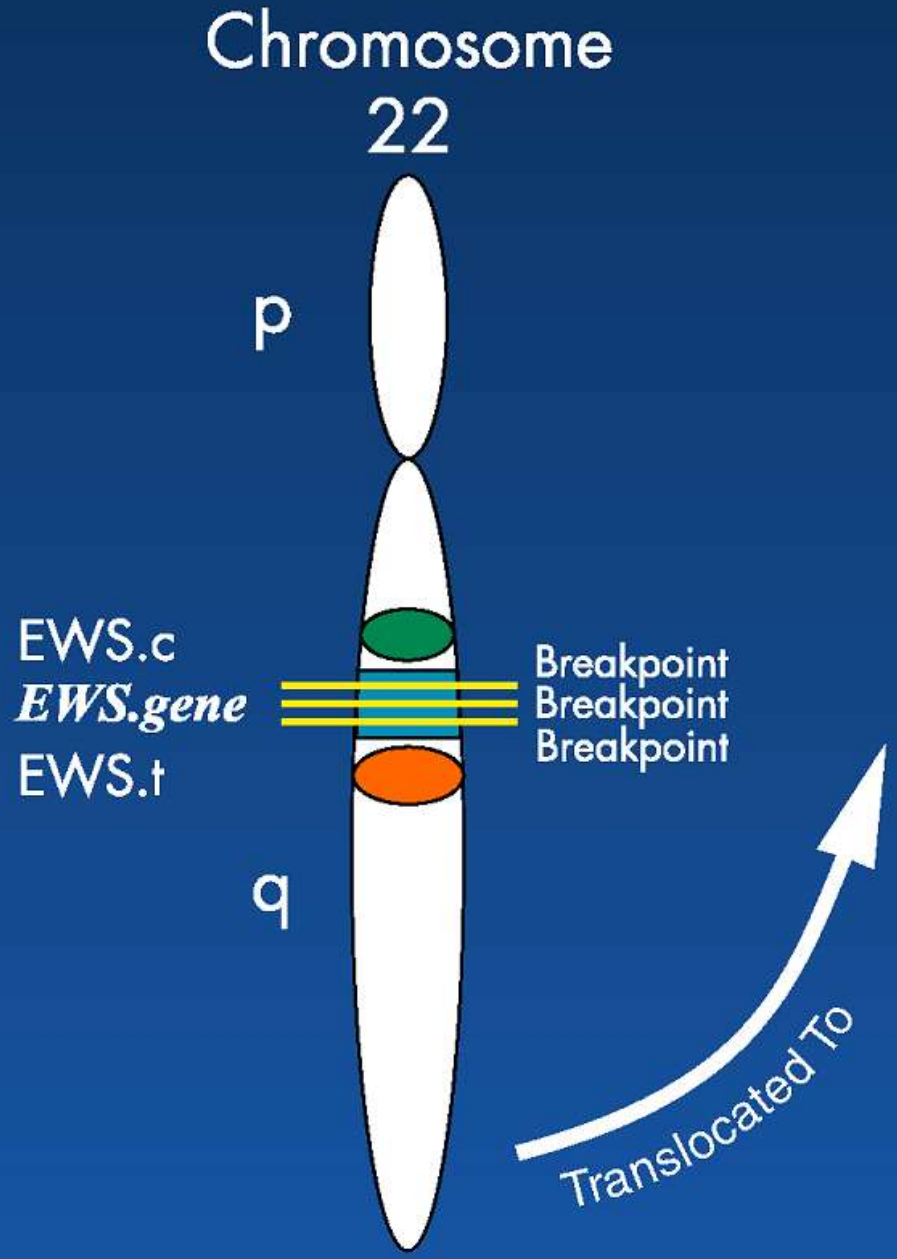
Predilection for distal extremities, esp. feet
Recur ++ - but ? almost never metastasise
Isolated cases show hybrid morphologic features
Both show reciprocal t(1;10)(p22;q24)
Gene fusion *TGFBR3 – MGEA5*
Leads to up-regulation of *FGF8*
Also amplified 3p in ring chromosomes

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 – in press

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
EP
inv(12)(p11.2q14-15)
PA
[1995]



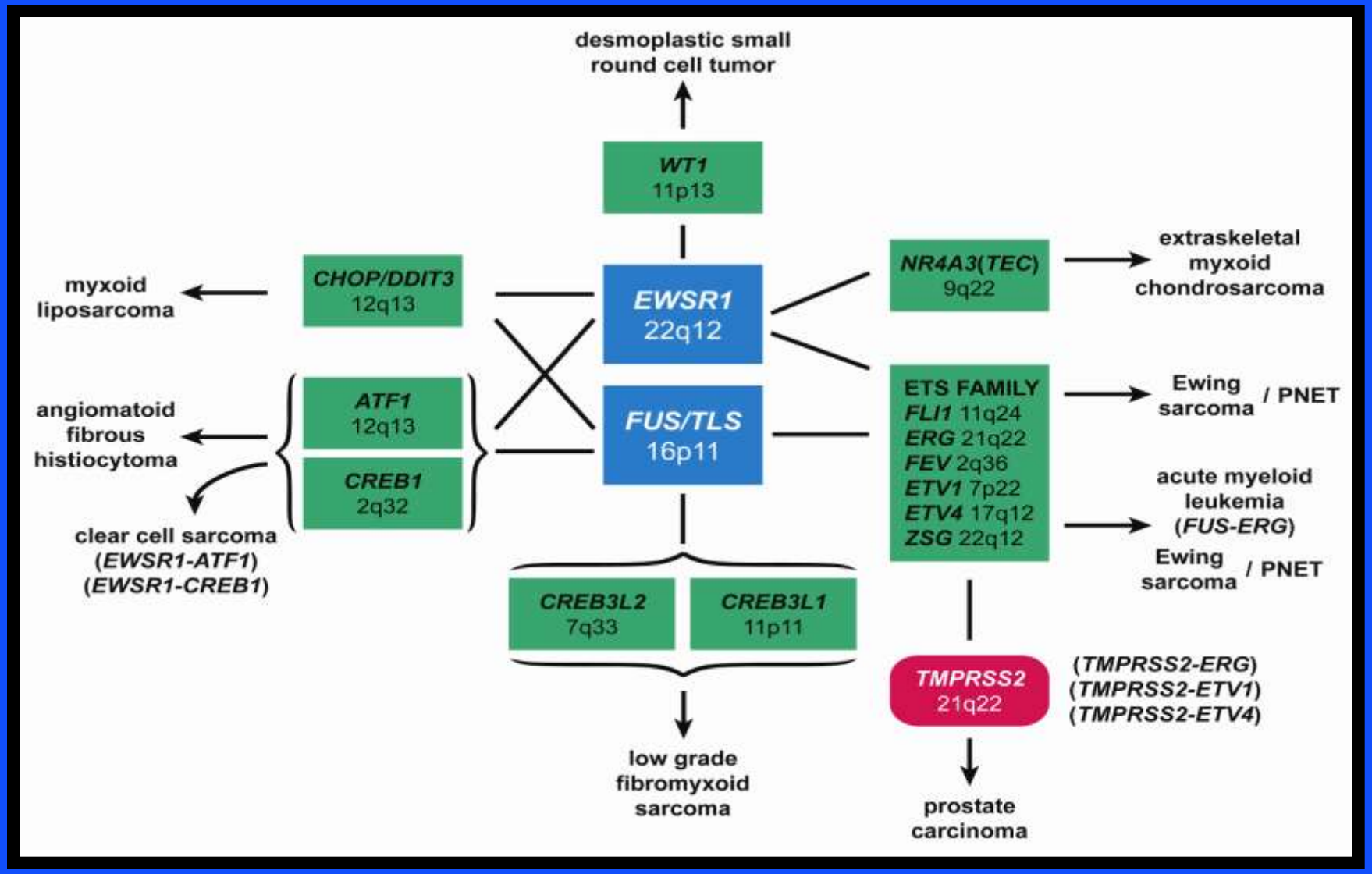
Ewing's sarcoma
FLI1 >80%
ERG 10-15%
ETV1 (<5%)
E1AF (<5%)
FEV (<5%)

DSRCT
WT1

Clear cell sarcoma
ATF1

Extraskel myxoid chondrosarc
CHN & others

[2001]



Courtesy of Dr. Alex Lazar, MDACC (2008)

ETV6-NTRK3

- Infantile fibrosarcoma
- Cellular mesoblastic nephroma
- Secretory carcinoma of breast (and now salivary gland)
- Rare cases of AML (M2) & CML

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**

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 perhaps clinical) of such prominently shared fusion genes**
- **Need to actively maintain this work since valuable and remarkable new data continue to emerge**

IMPACT OF GENETICS
THE STORY CONTINUES…
MYOEPITHELIAL TUMORS OF SOFT TISSUE

- **45% have *EWSR1* gene rearrangement**
- **New fusion gene partners - *POU5F1*, *PBX1*, *ZNF444* – with apparent morphologic correlates**
- **Skin lesions seem different/usually lack *EWSR1* involvement**
- **In contrast to salivary gland counterparts, no involvement of *PLAG1* or *HMGA2* in soft tissue**

Antonescu et al, *Genes, Chromosomes & Cancer* 2010; 49: 1114-1124

OTHER UNANSWERED QUESTIONS WHICH MIGHT IMPACT TAXONOMY

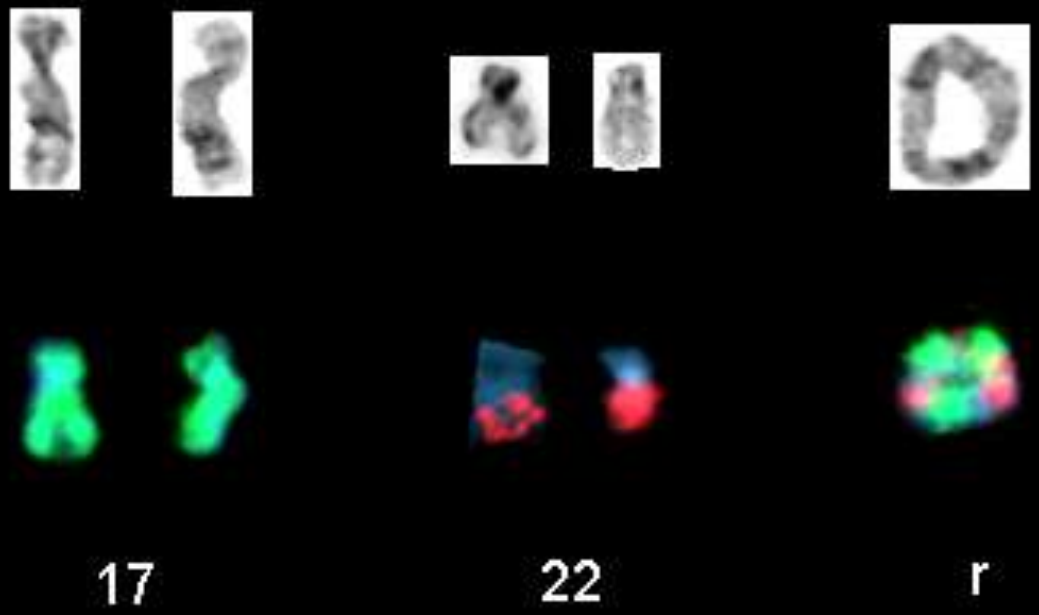
- Cell of origin in many/most tumor types ?
- Line of differentiation in many tumor types ?
- Nature of multistep process in mesenchymal tumorigenesis ?
- Relevance of “mesenchymal stem cell” ?

For these questions, what insights can we gain from molecular genetic data ?

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 ……..

RING CHROMOSOME IN DERMATOFIBROSARCOMA



IMPACT OF GENETICS
SHARED FUSION GENES

- ***ETV6-NTRK3***

  Infantile fibrosarcoma, mesoblastic nephroma, secretory carcinoma of breast, AML (rarely)

- ***ALK-1 fusions***

  Inflammatory myofibroblastic tumour, anaplastic large cell lymphoma, NSCLC

- ***EWSR1-CREB1 / EWSR1-ATF1***

  Clear cell sarcoma, angiomatoid 'MFH'