Slide Seminar
Spanish Society of Pathology

John R. Goldblum, M.D.

Chairman, Department of Anatomic Pathology
Cleveland Clinic
Professor of Pathology
Cleveland Clinic Lerner College of Medicine

1921 – Original Clinic Building

(still in use today)

Patients First

90 Years

Born in War.

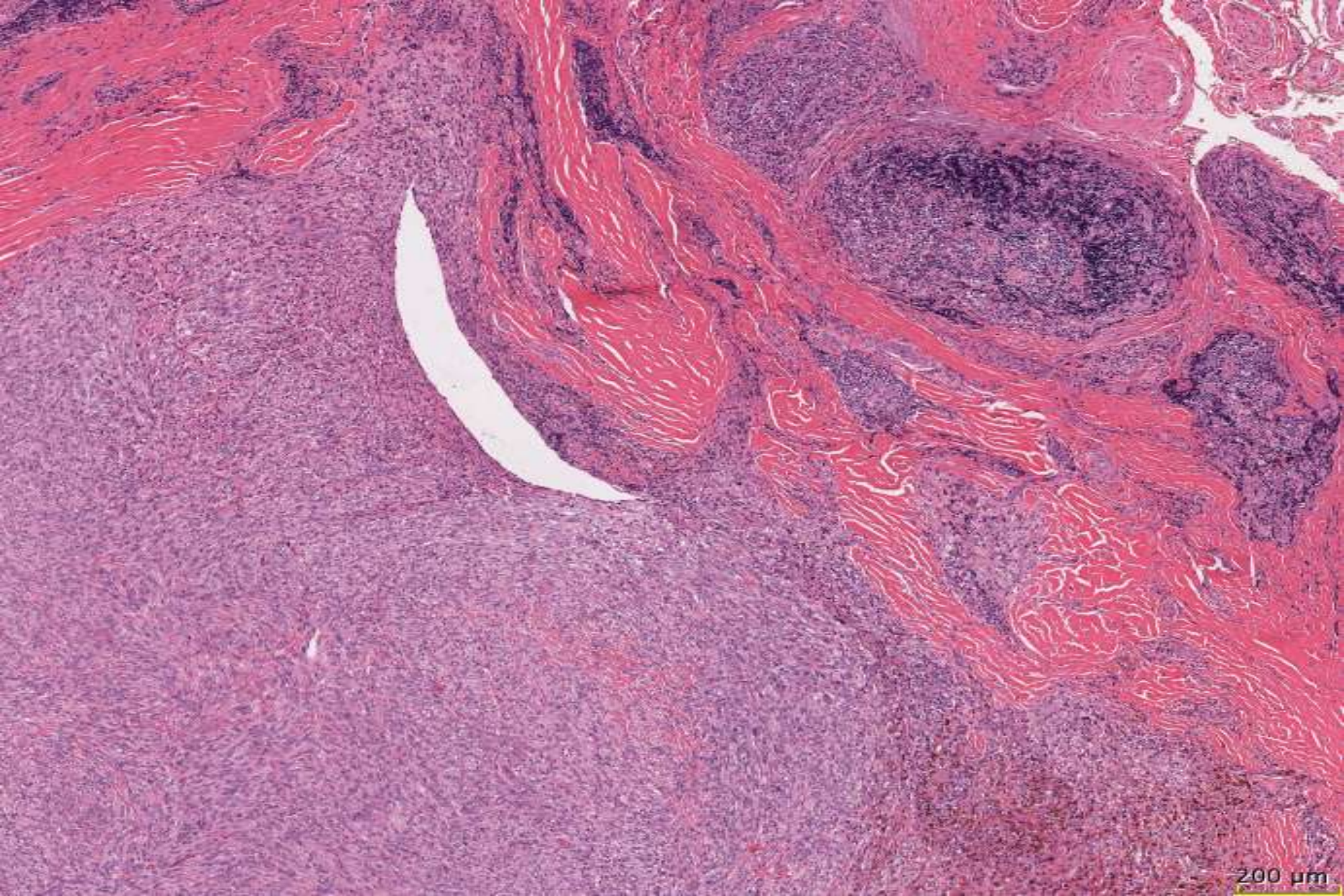
Tested in Peace.

2011 - Lou Ruvo Center

for Brain Health - Nevada

Case History

12-year-old male with a 3.5-cm soft tissue mass of the left forearm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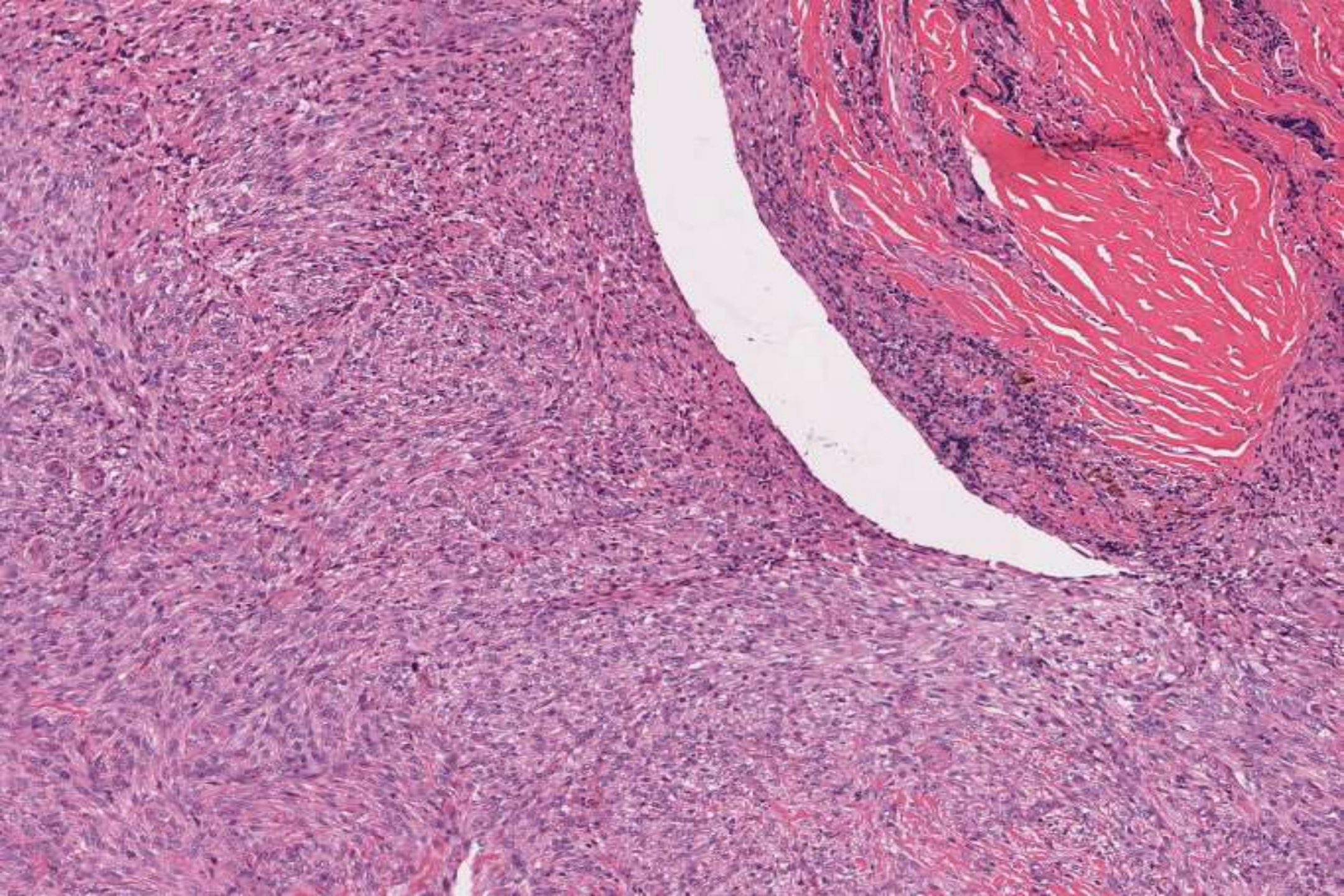

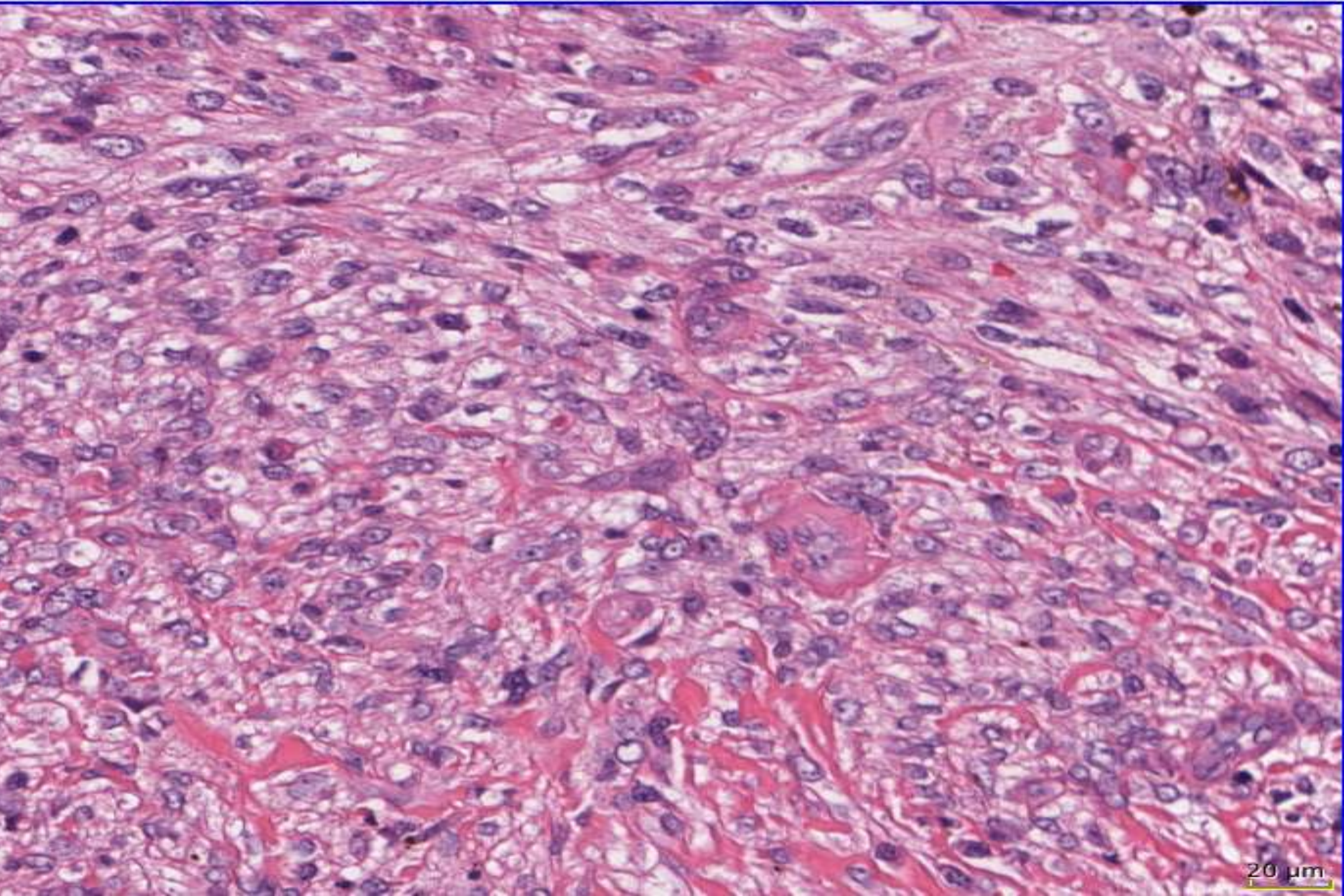
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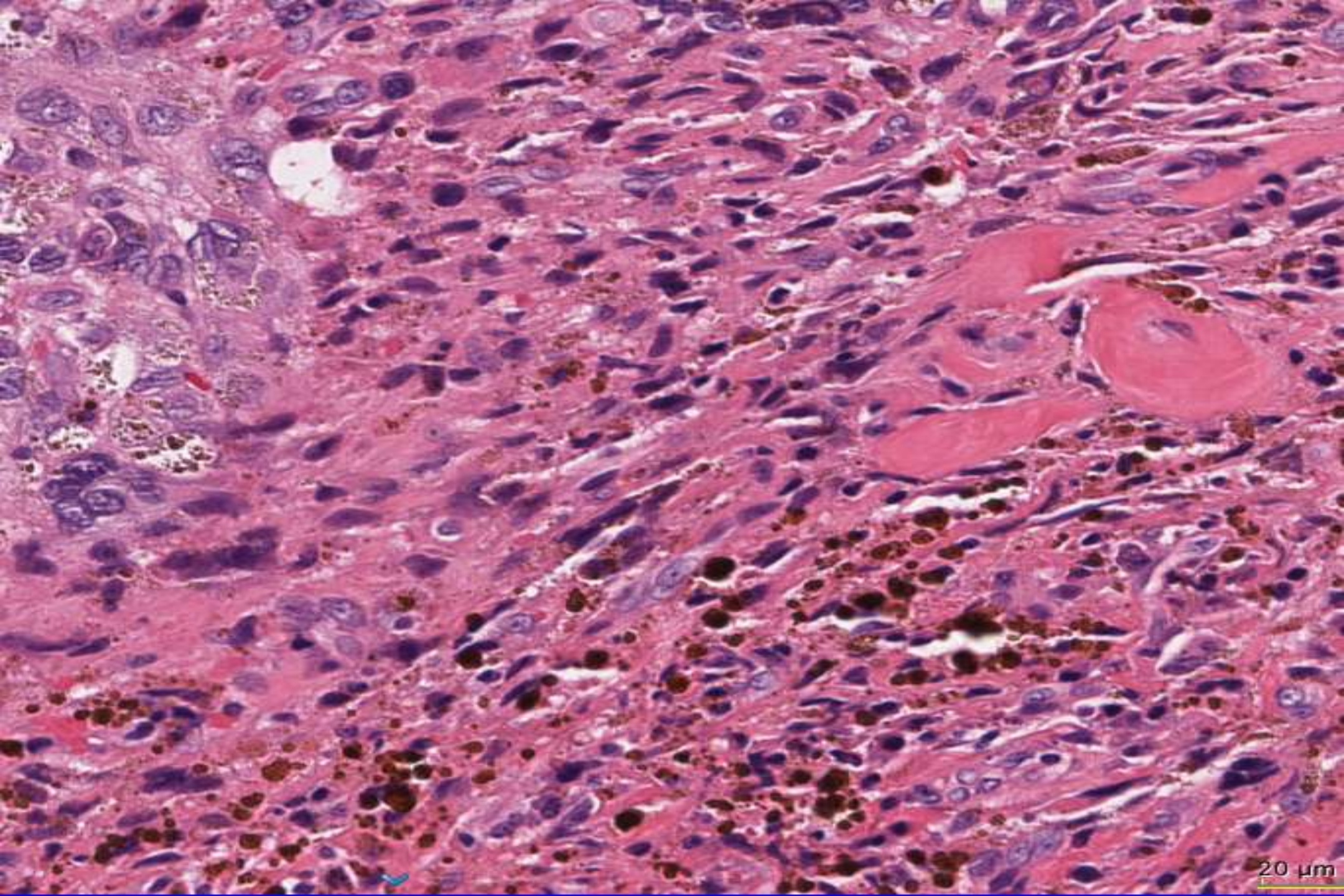
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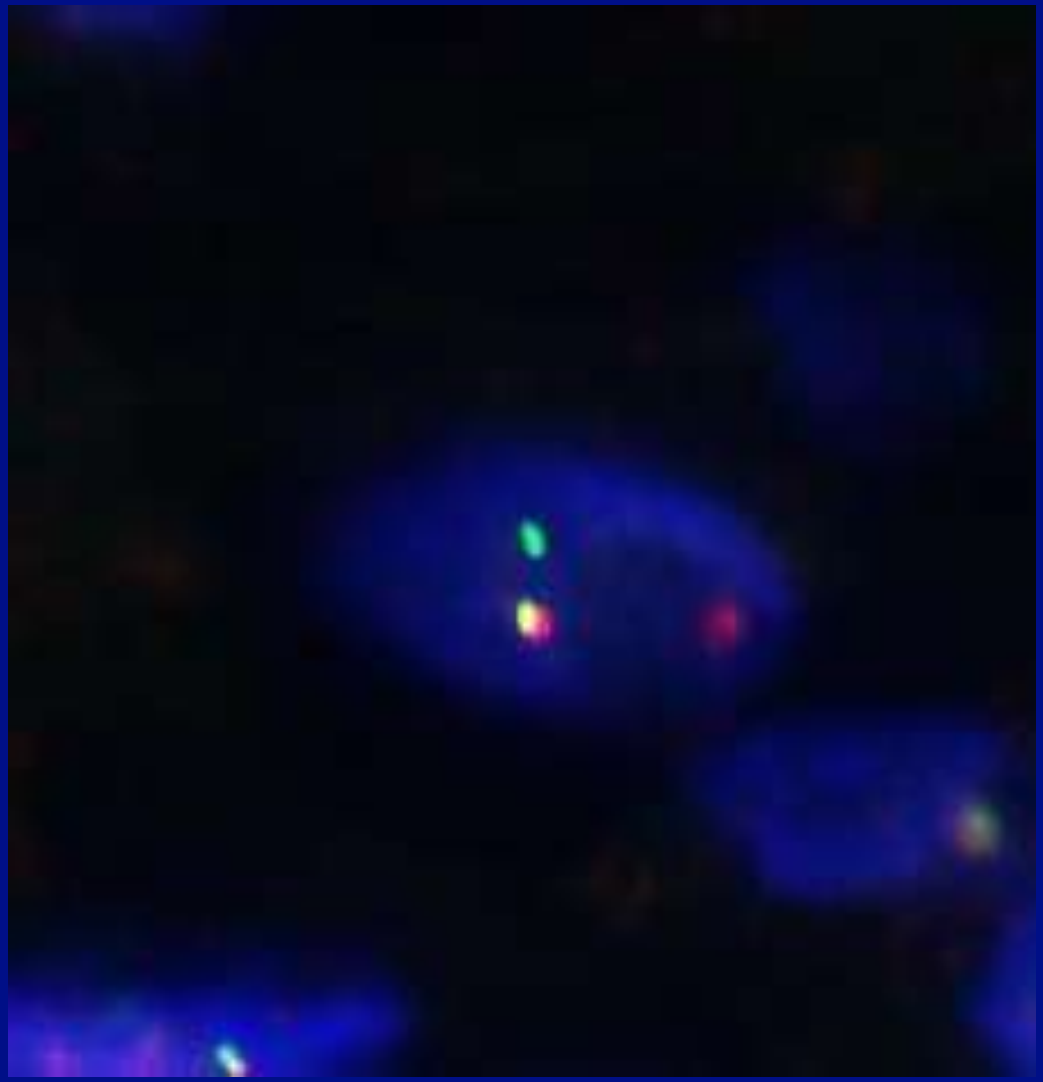
Ancillary Studies



EWSR1

AE1/AE3	-
Desmin	+ (focal)
CD99	+ (focal)
EMA	-
S100 protein	-
SMA	-
EWS FISH	+

Case Diagnosis

Angiomatoid (malignant) Fibrous Histiocytoma

Fibrohistiocytic Tumors

"best used as a descriptive term with no histogenetic implications, to encompass a heterogeneous group of tumors that share histologic similarities."

Calonje E, Fletcher CDM. Adv Anat Pathol, 1994

Fibrohistiocytic Tumors
Benign

- Benign fibrous histiocytoma
- Juvenile xanthogranuloma
- Reticulohistiocytoma
- Xanthoma

Fibrohistiocytic Tumors
Malignant

- Storiform-pleomorphic
- Myxoid
- Giant cell
-
- Inflammatory

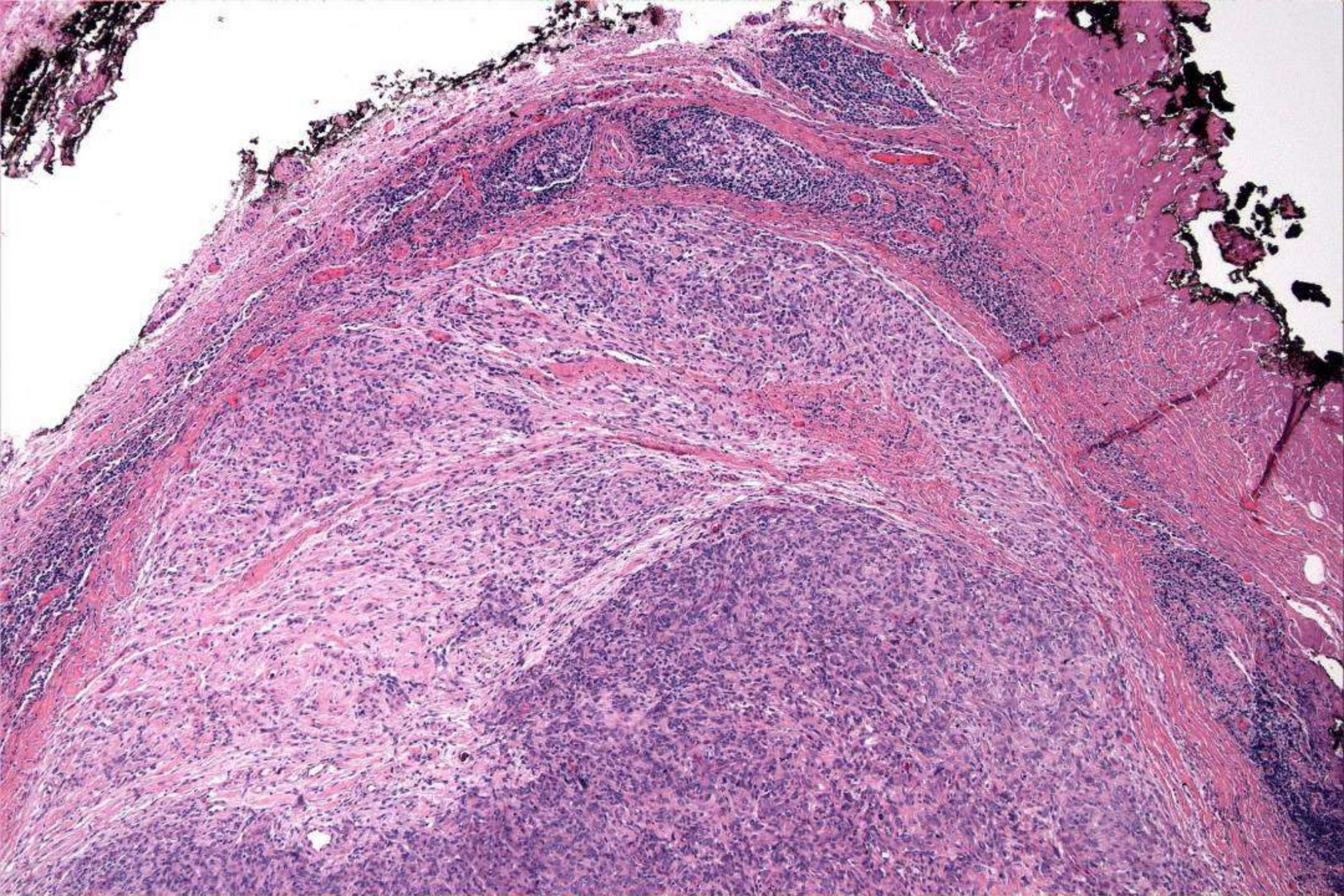
Undifferentiated pleomorphic sarcoma

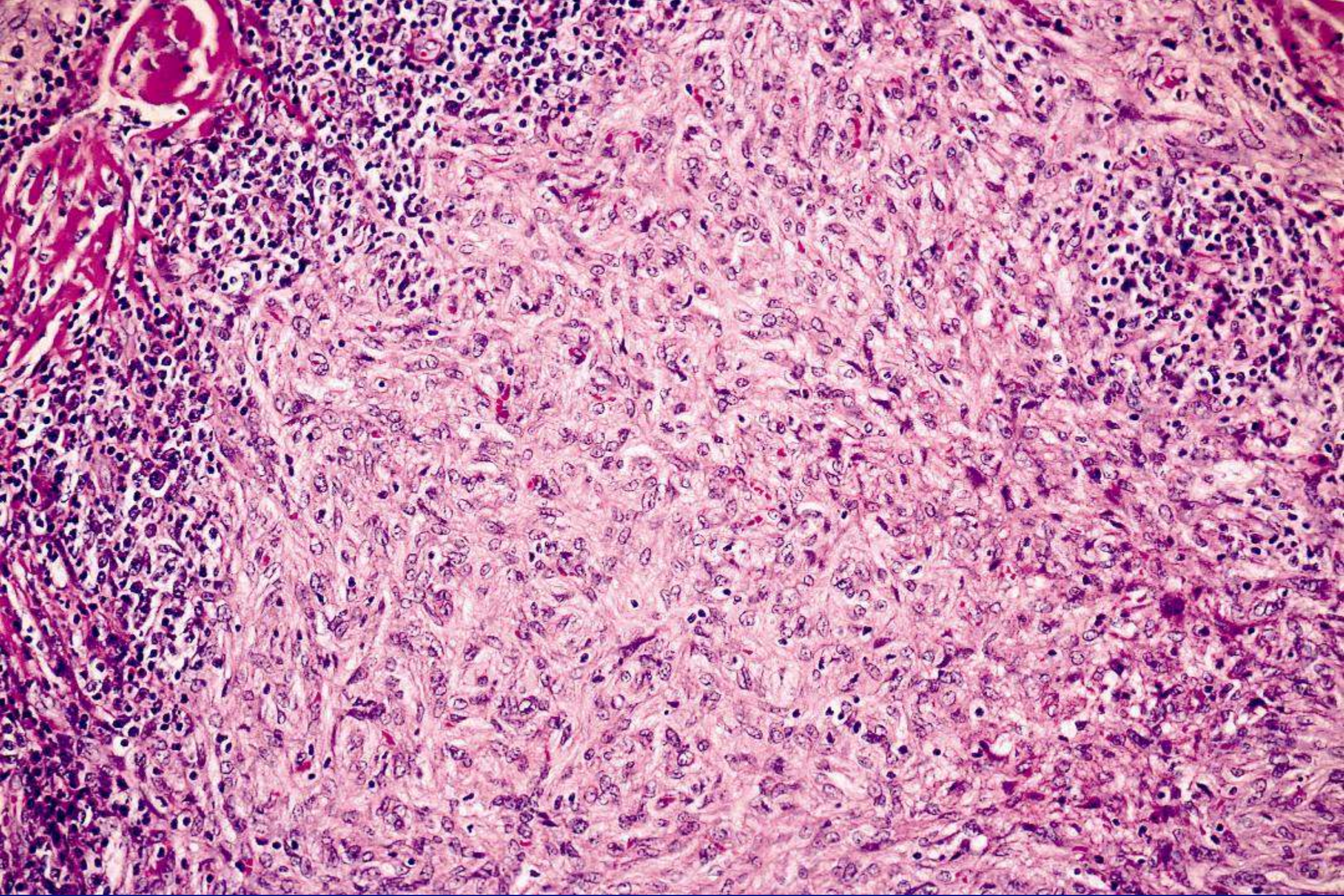
Fibrohistiocytic Tumors
Low Malignant Potential

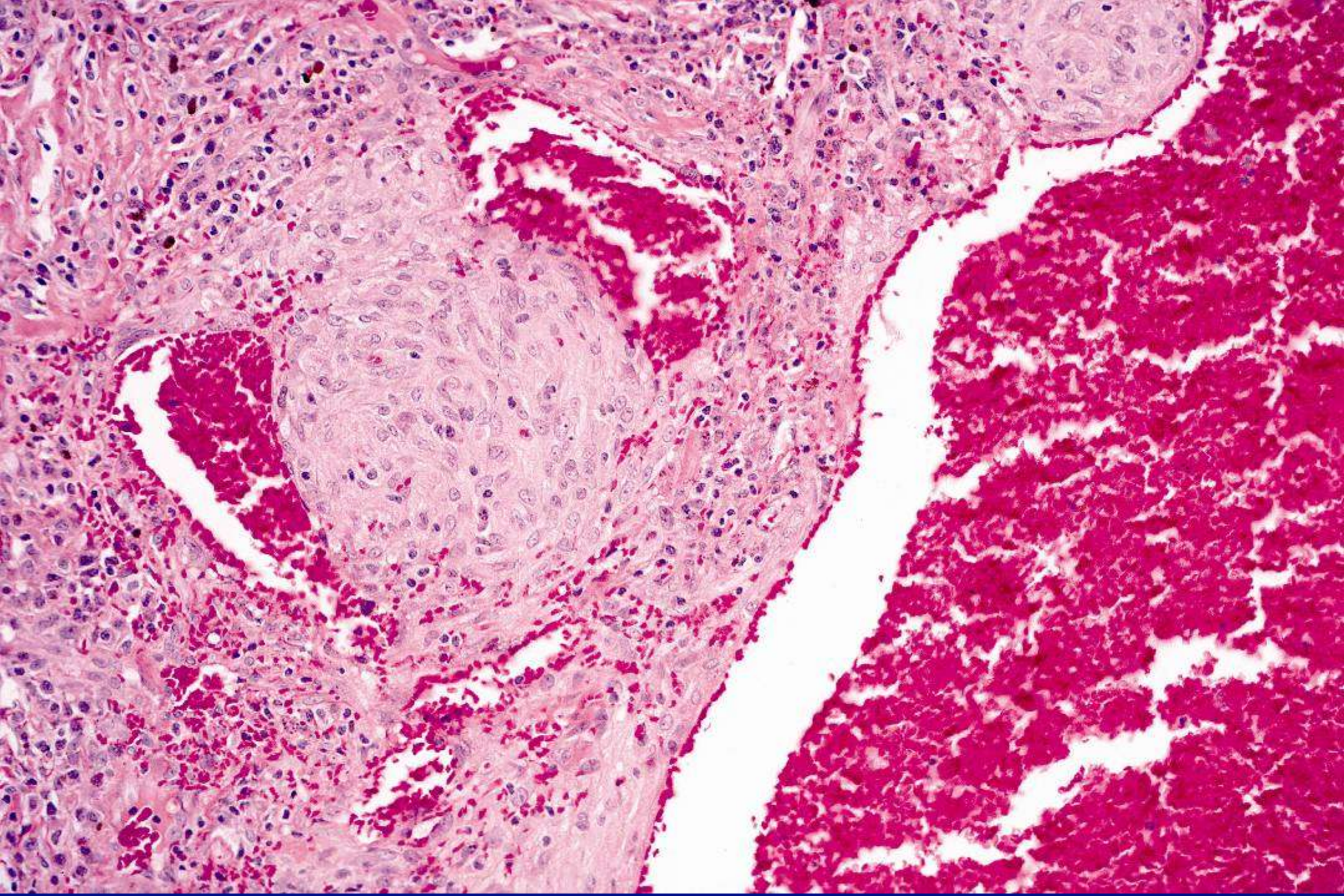
- Atypical fibroxanthoma
- DFSP / Bednar tumor
- Giant cell fibroblastoma
- Plexiform fibrohistiocytic tumor
- Angiomatoid fibrous histiocytoma
- Giant cell tumor of soft tissue

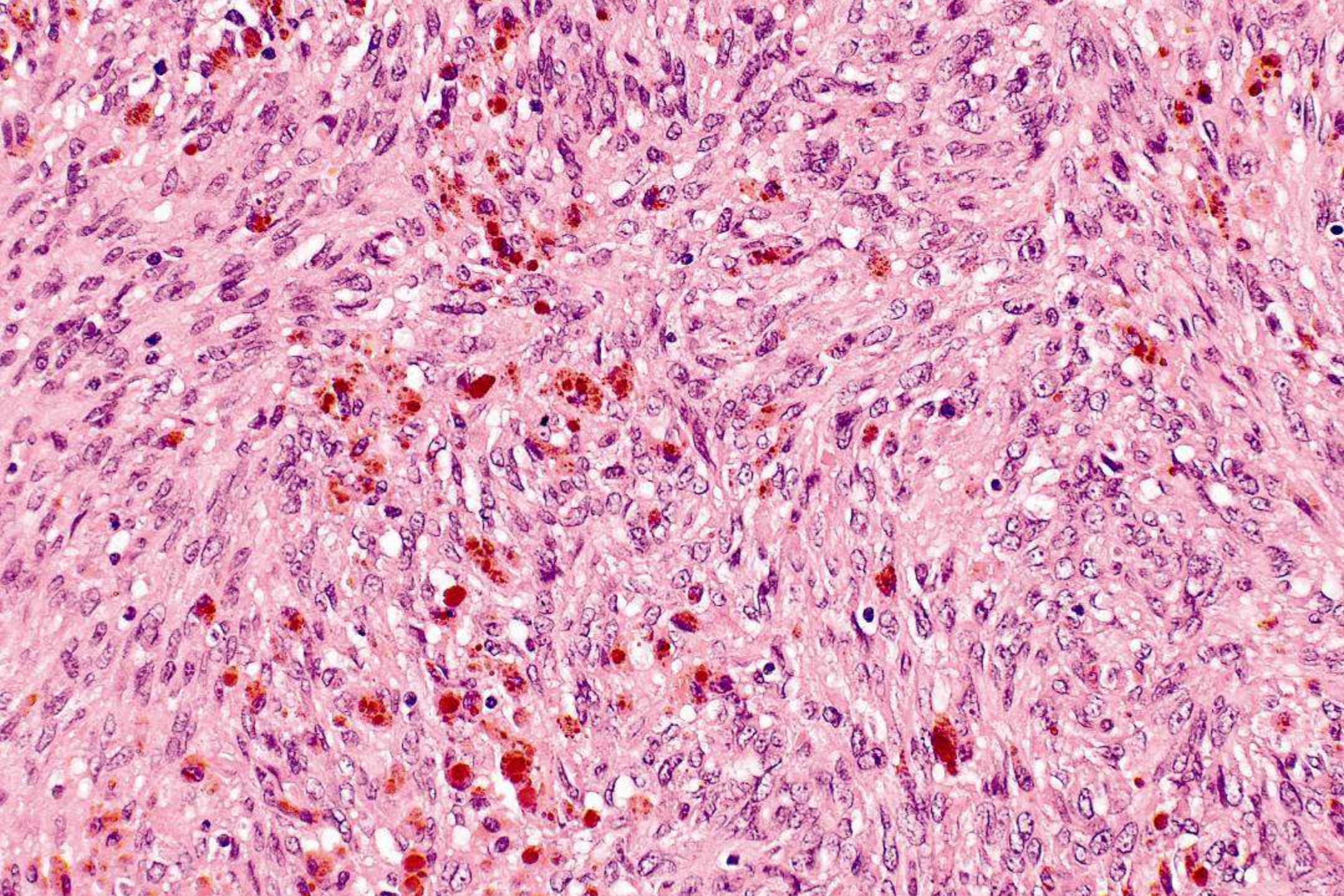
Angiomatoid Fibrous Histiocytoma

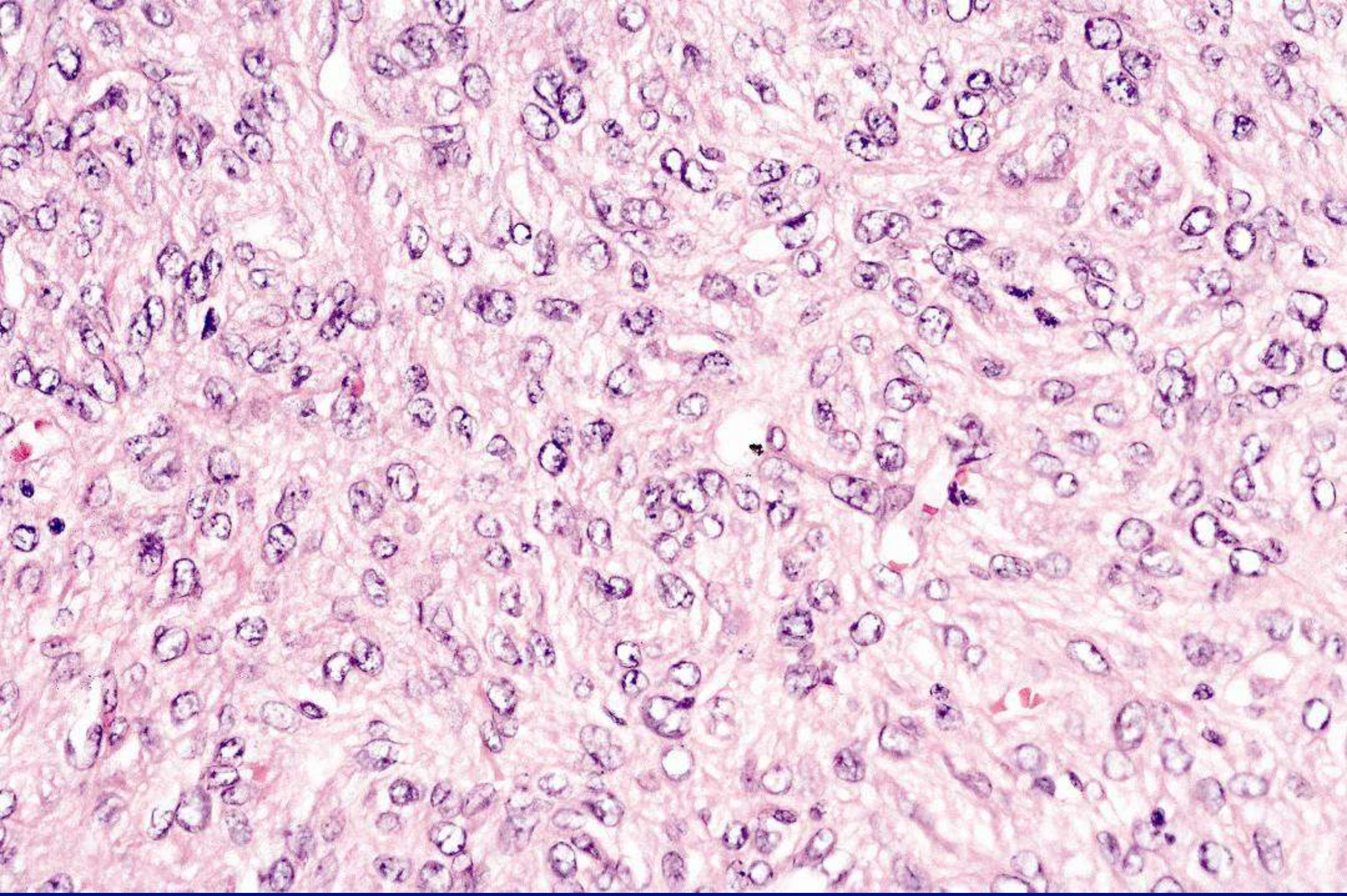
- Majority of patients < 20 years
- Majority located on extremities
- Slow-growing subcutaneous mass
- Fever, weight loss, anemia

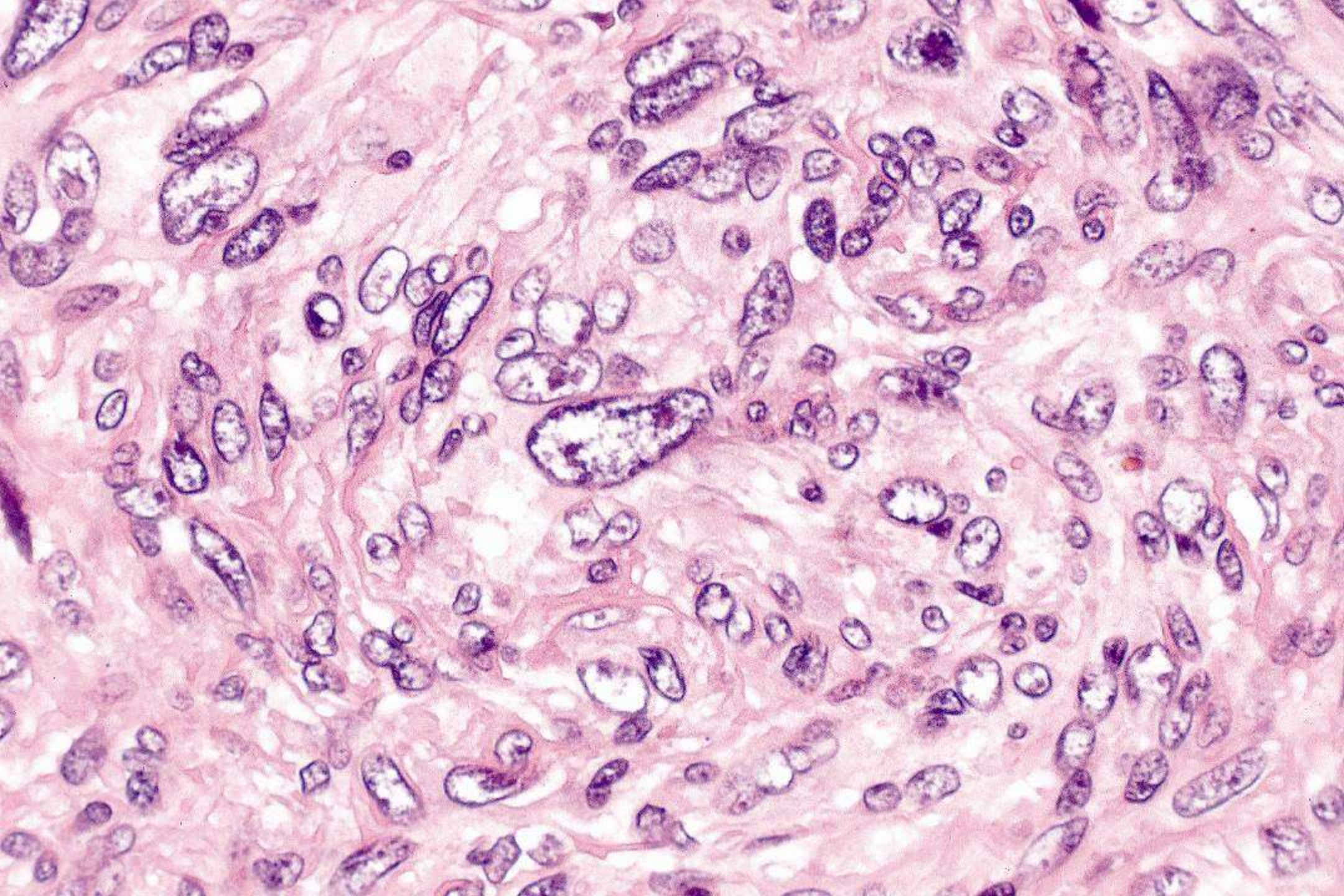












AFH: Immunophenotype

• Desmin	50%
• EMA	50%
• CD99	45%
• CD68	30%
• MSA/SMA	<15%
• S100 protein	-
• AE1/AE3	-

AFH: Genetics

Genetic Characterization of Angiomatoid Fibrous Histiocytoma Identifies Fusion of the *FUS* and *ATF-1* Genes Induced by a Chromosomal Translocation Involving Bands 12q13 and 16p11

Brenda L. Waters, Ioannis Panagopoulos, and Elizabeth F. Allen

ABSTRACT: *This case report documents the first karyotypic, fluorescence in situ hybridization, and genetic analysis of an angiomatoid fibrous histiocytoma that arose and recurred in the arm of a 5.5-year-old girl. Complex rearrangements between chromosomes 2, 12, 16, and 17 were noted, as well as deletion in the long arm of chromosome 11. Flow cytometry revealed a normal cell population. The t(12;16) site was further investigated using reverse transcriptase-polymerase chain reaction. We found that the* FUS *(also known as* TLS*) gene from 16p11 combined with the* ATF-1 *gene from 12q13 to generate a chimeric* FUS/ATF-1*. The* FUS *gene is rearranged in the t(12;16)(q13;p11) that characterizes myxoid liposarcoma and in acute myeloid leukemia with t(16;21)(p11;q22), while the* ATF-1 *gene is rearranged in the t(12;22)(q13;q12) found recurrently in clear cell sarcomas (malignant melanoma of soft parts). Thus, the* FUS/ATF-1 *gene in angiomatoid fibrous histiocytoma is predicted to code for a protein that is very similar to the chimeric EWS/ATF-1 found in clear cell sarcoma.* *© 2000 Elsevier Science Inc. All rights reserved.*

Waters et al. Cancer Genet Cytogenet 2000

AFH: Genetics

GENES, CHROMOSOMES & CANCER 44:97–102 (2005)

BRIEF COMMUNICATION

Fusion of the *EWSR1* and *ATF1* Genes Without Expression of the *MITF-M* Transcript in Angiomatoid Fibrous Histiocytoma

Karolin Hansén Hallor,[1]* Fredrik Mertens,[1] Yuesheng Jin,[1] Jeanne M. Meis-Kindblom,[2] Lars-Gunnar Kindblom,[2] Mikael Behrendtz,[3] Anders Kalén,[4] Nils Mandahl,[1] and Ioannis Panagopoulos[1]

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Hallor KH et al. Genes Chromosome Cancer 2005

AFH: Genetics

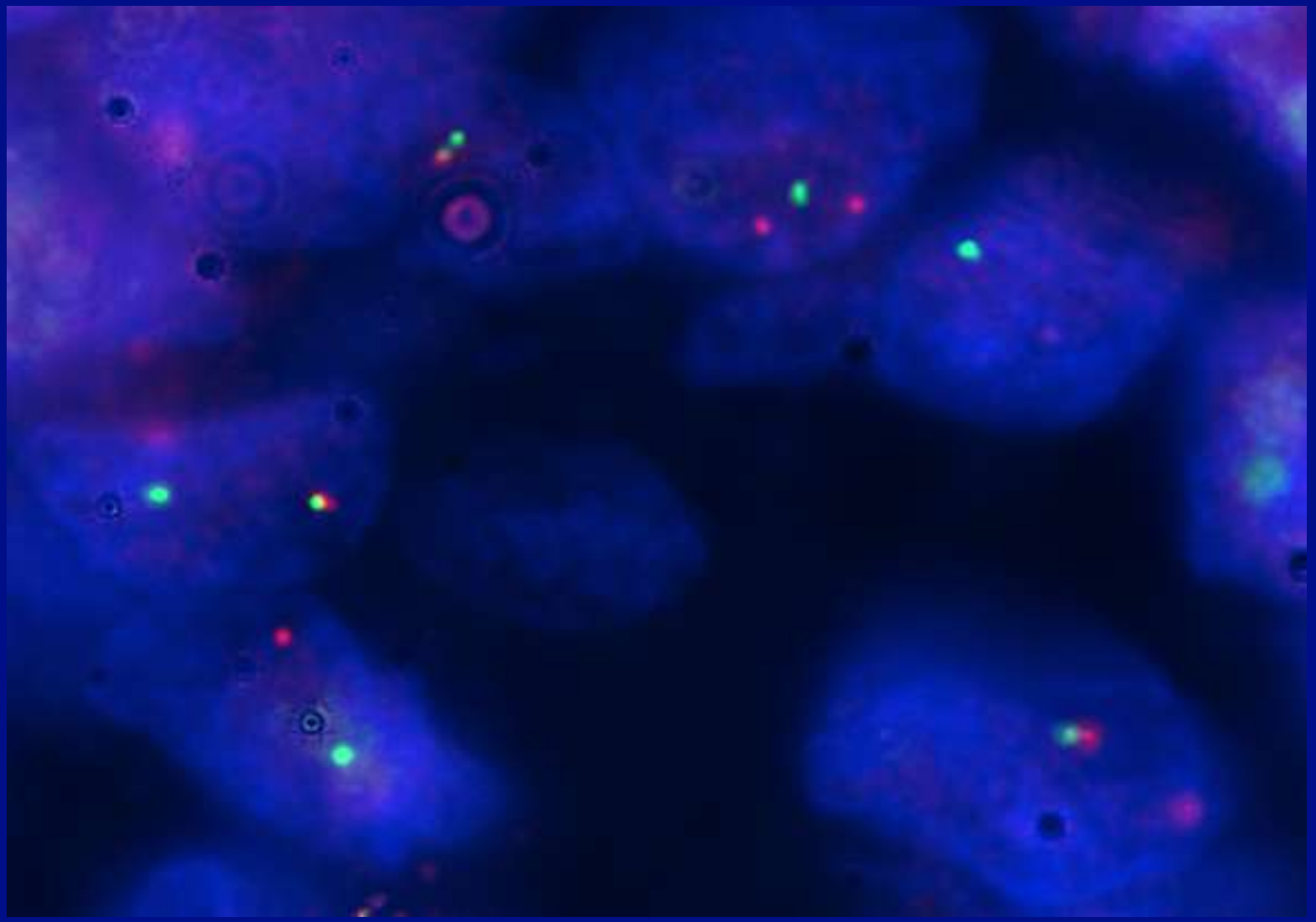
EWSR1 rearrangement

Oliveira **12/24 (50%)**

- ***EWSR1-CREB1*** **7**
- ***EWSR1-ATF1*** **3**
- ***EWSR1*-alternate** **2**
- ***FUS-ATF1*** **1**

Tanas **13/17 (86%)**

EWS (22q12) - Break Apart Probe

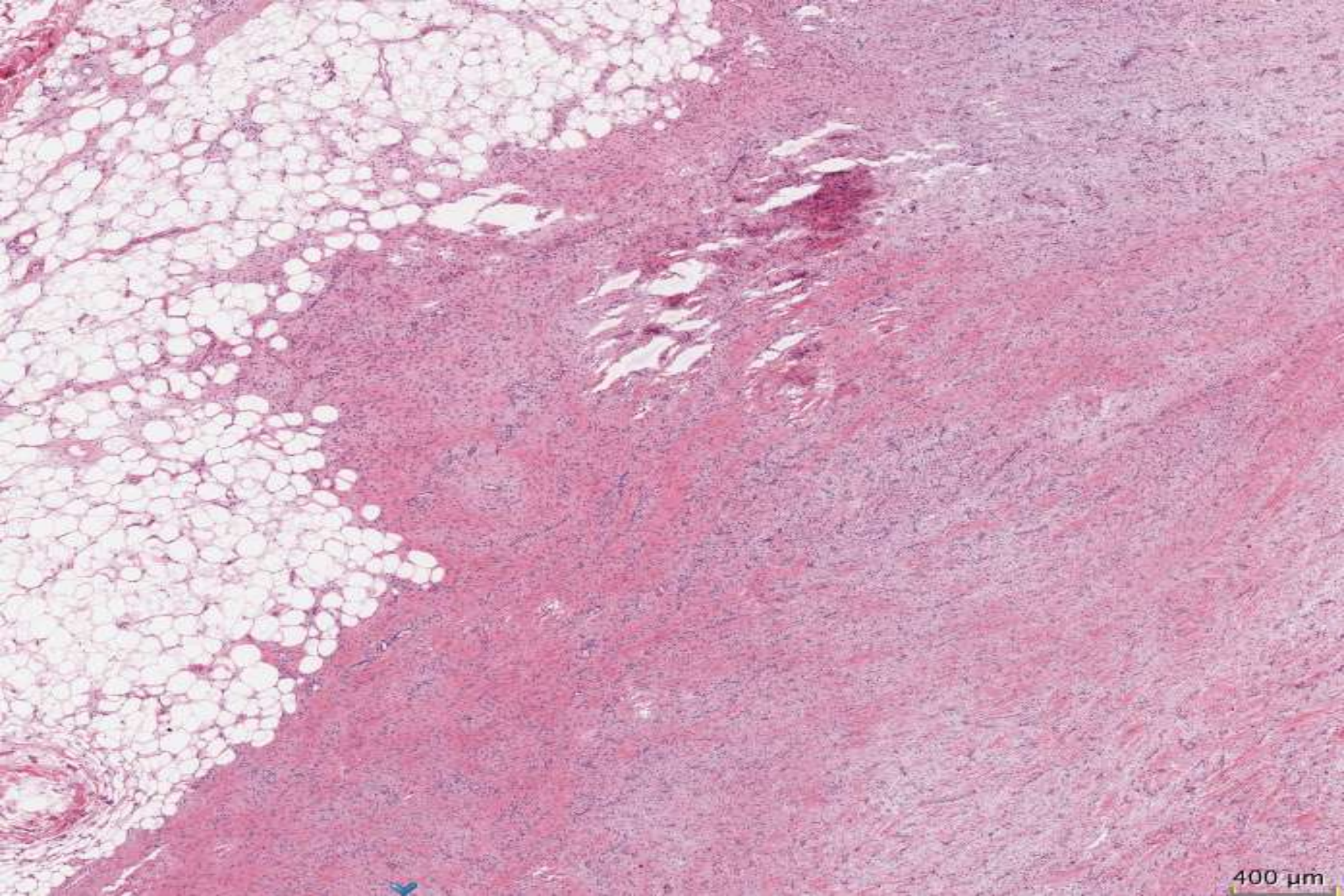


Angiomatoid Fibrous Histiocytoma

Author	Recurrence	Metastasis	Death
Enzinger (1979)	46%	21%	13%
Costa (1990)	12%	5%	1%
Fanburg-Smith (1999)	2%	1%	0%

Case History

- 15-year-old boy with a deeply situated 4.6 cm mass of the calf region
- Present for at least four years and slowly growing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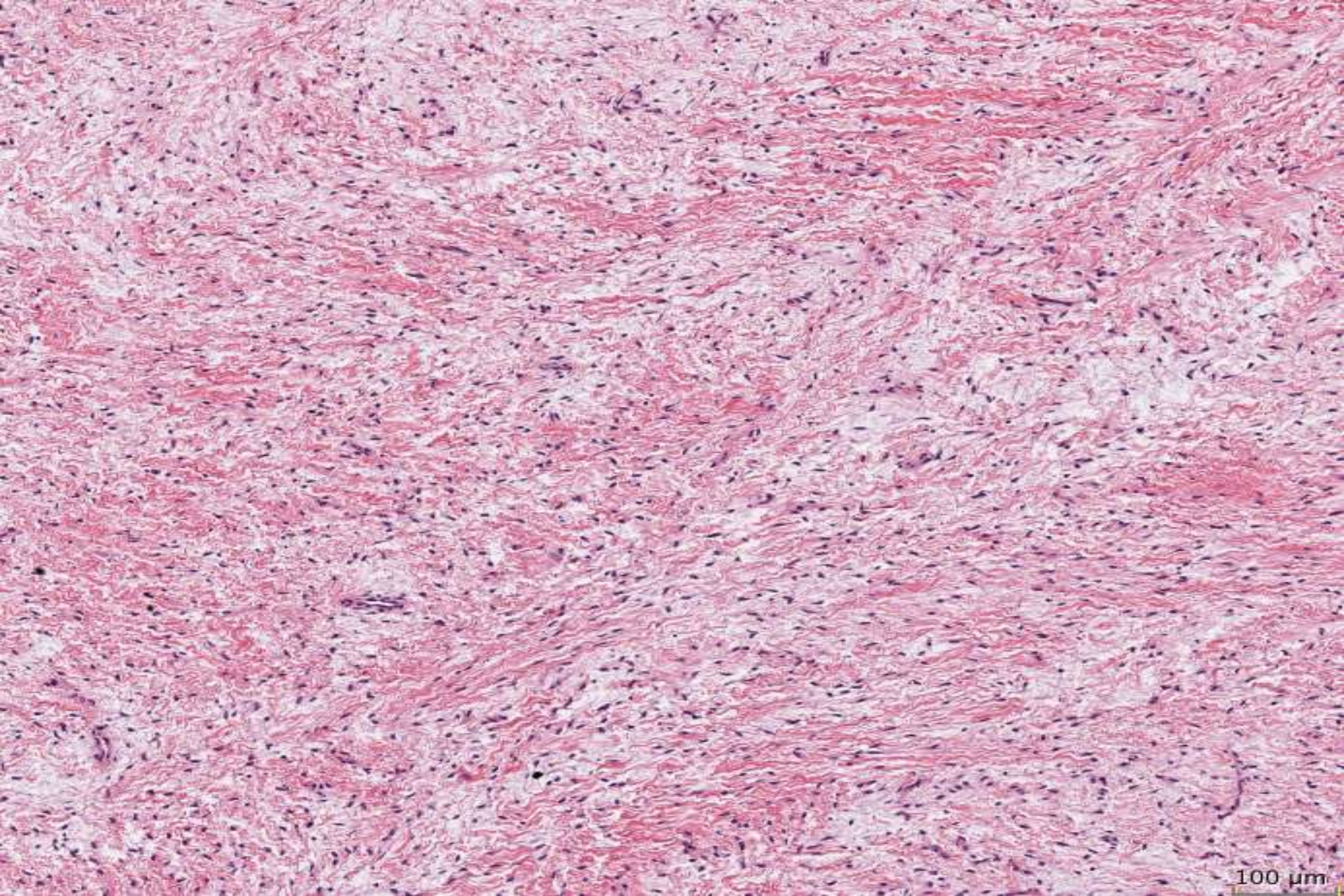
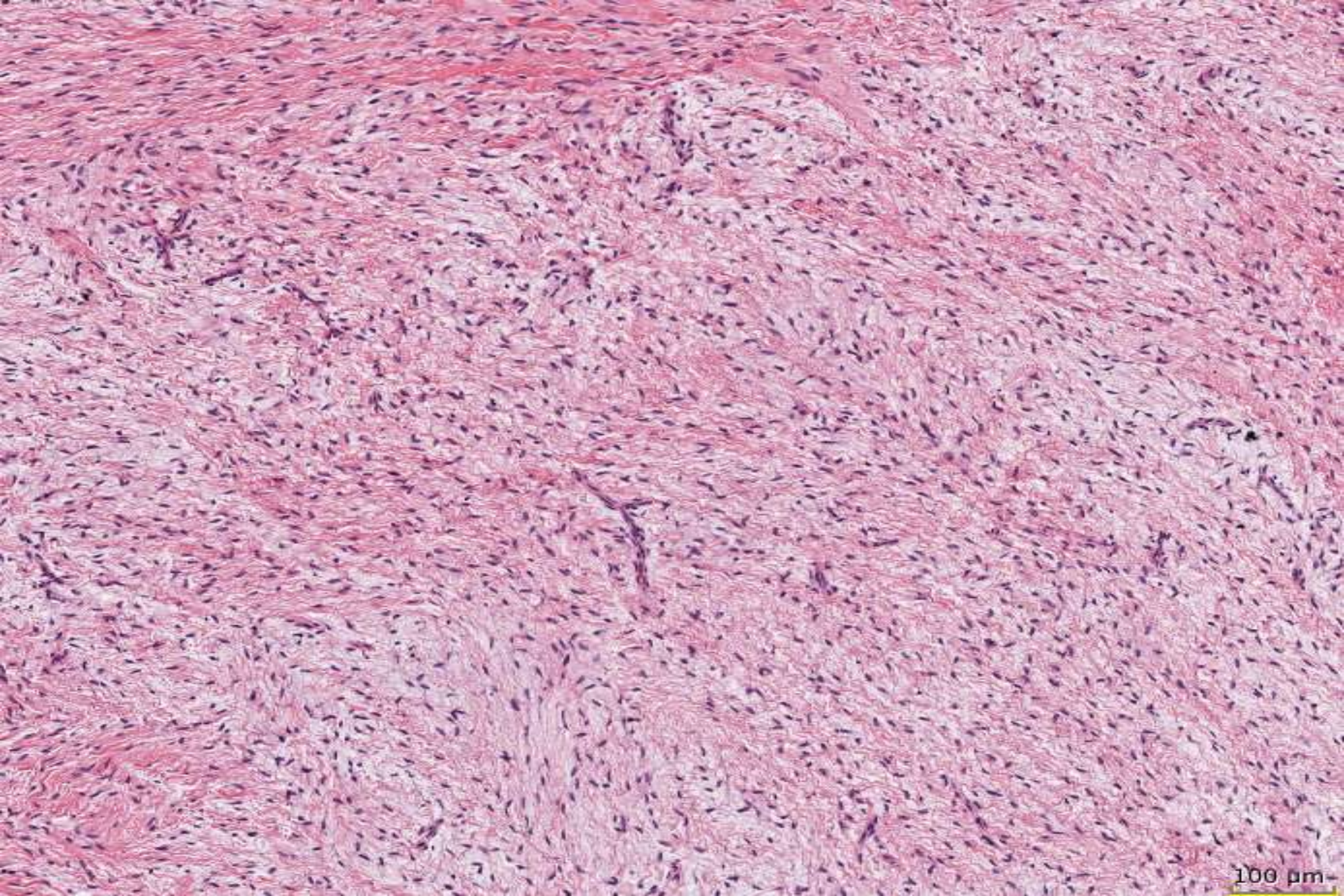

100 µm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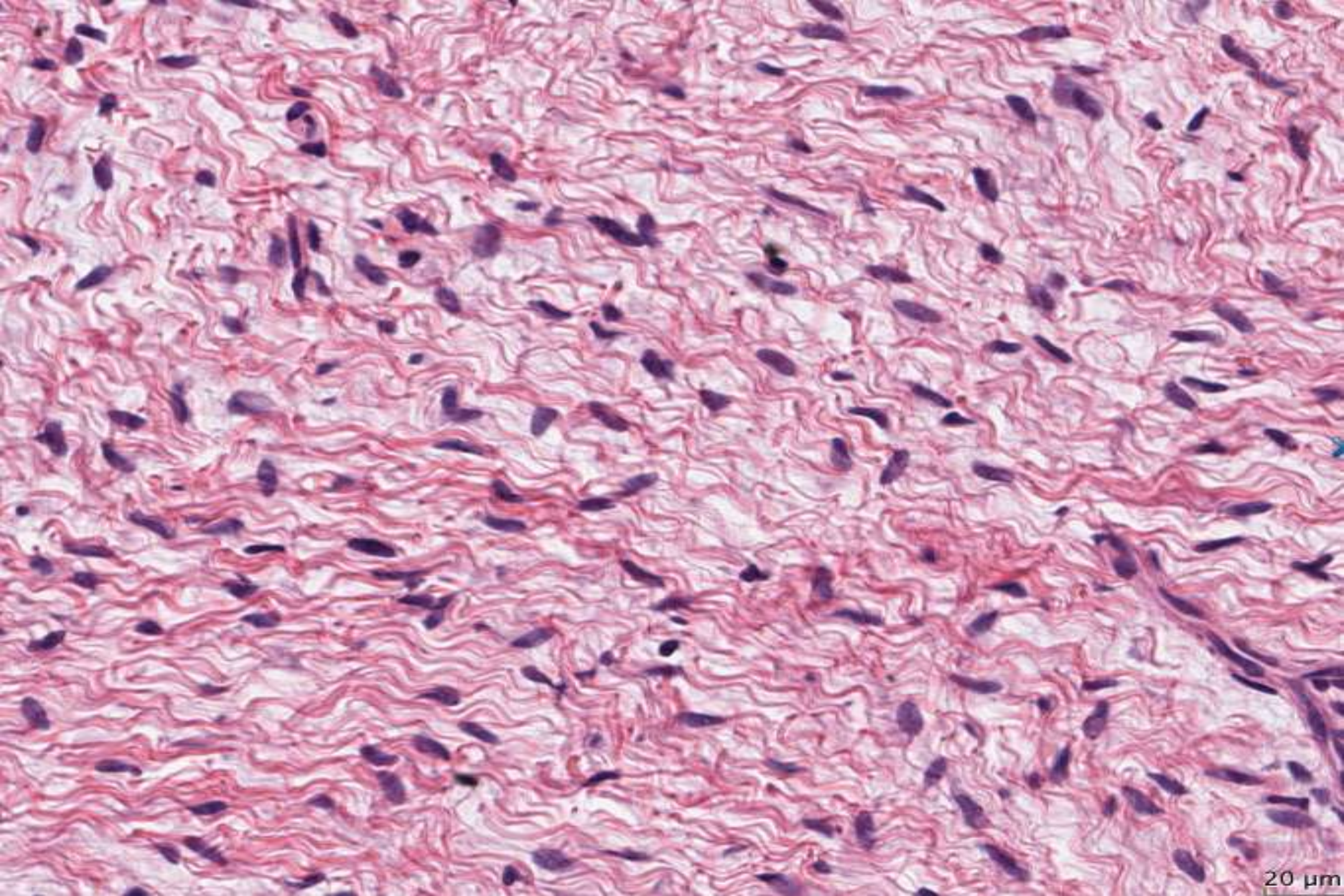
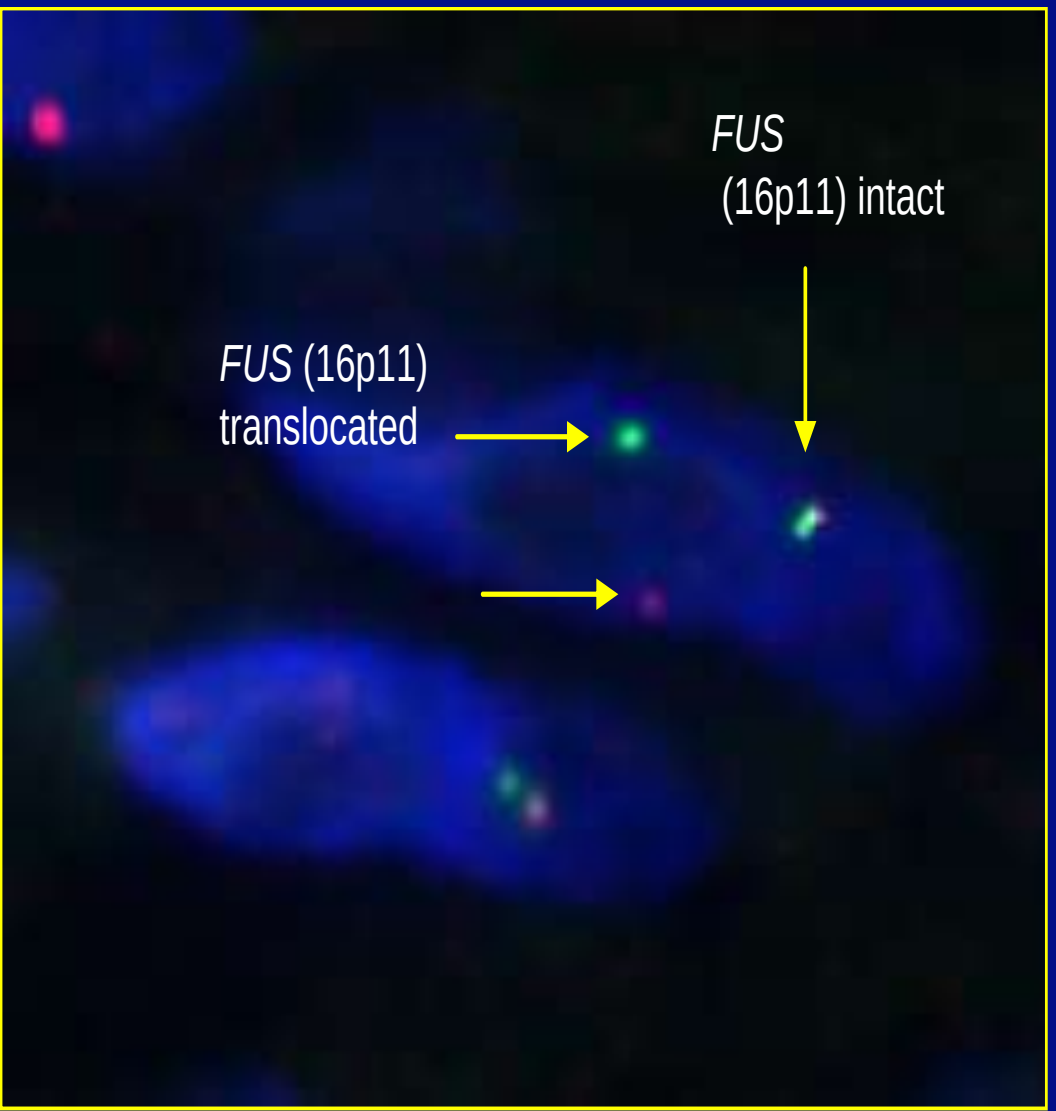

20 µm

Ancillary Studies



- **S100 protein -**
- **SMA -**
- **Desmin -**
- **AE1/AE3 -**
- **CD34 -**
- **FUS (FISH) +**

Diagnosis

Low-Grade Fibromyxoid Sarcoma (Evans' tumor)

Myxoid Soft Tissue Lesions

Benign

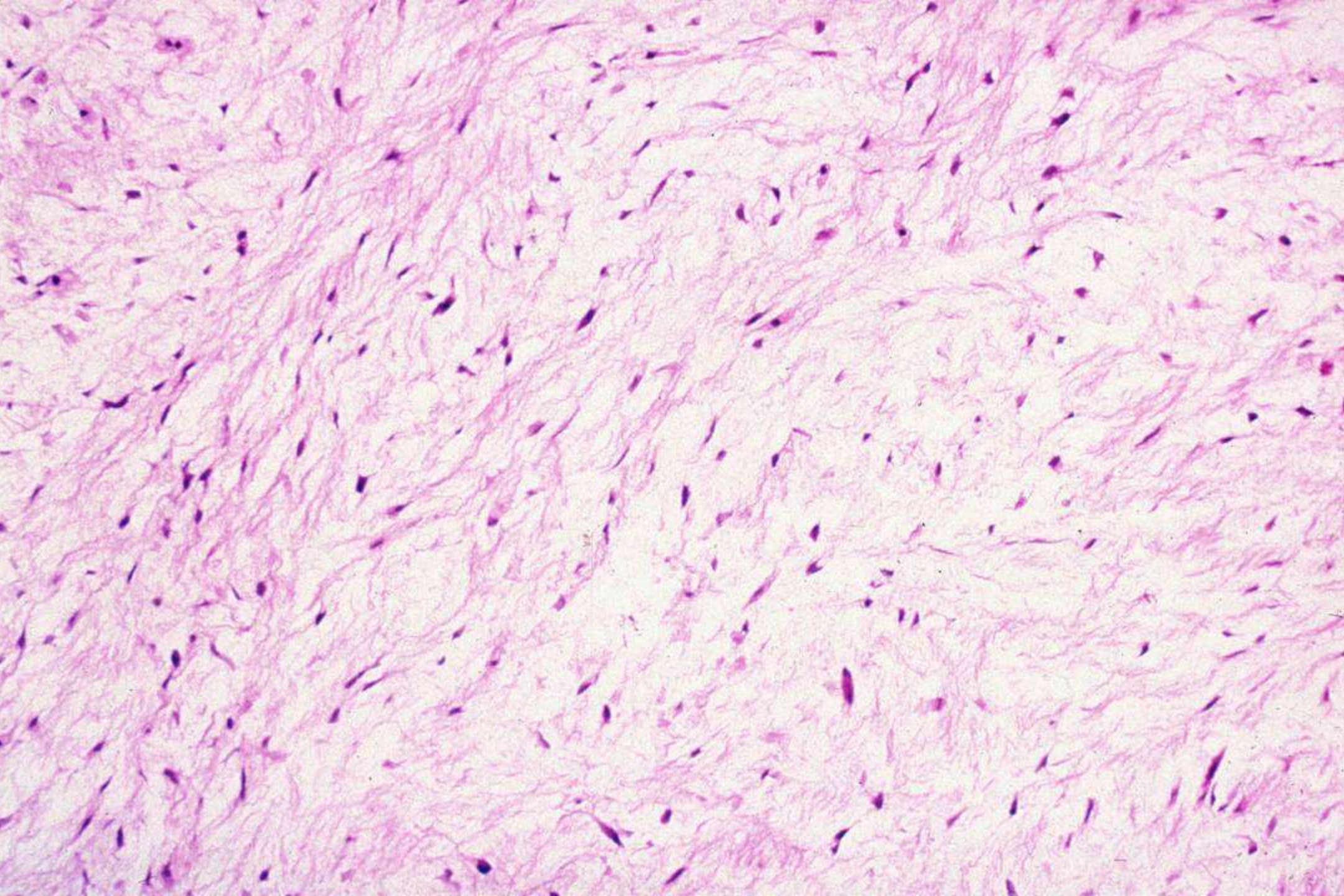
- Nodular fasciitis
- Myxoma
  - intramuscular
  - juxta-articular
  - cutaneous
- Nerve sheath tumors
  - neurofibroma
  - neurothekeoma
  - schwannoma

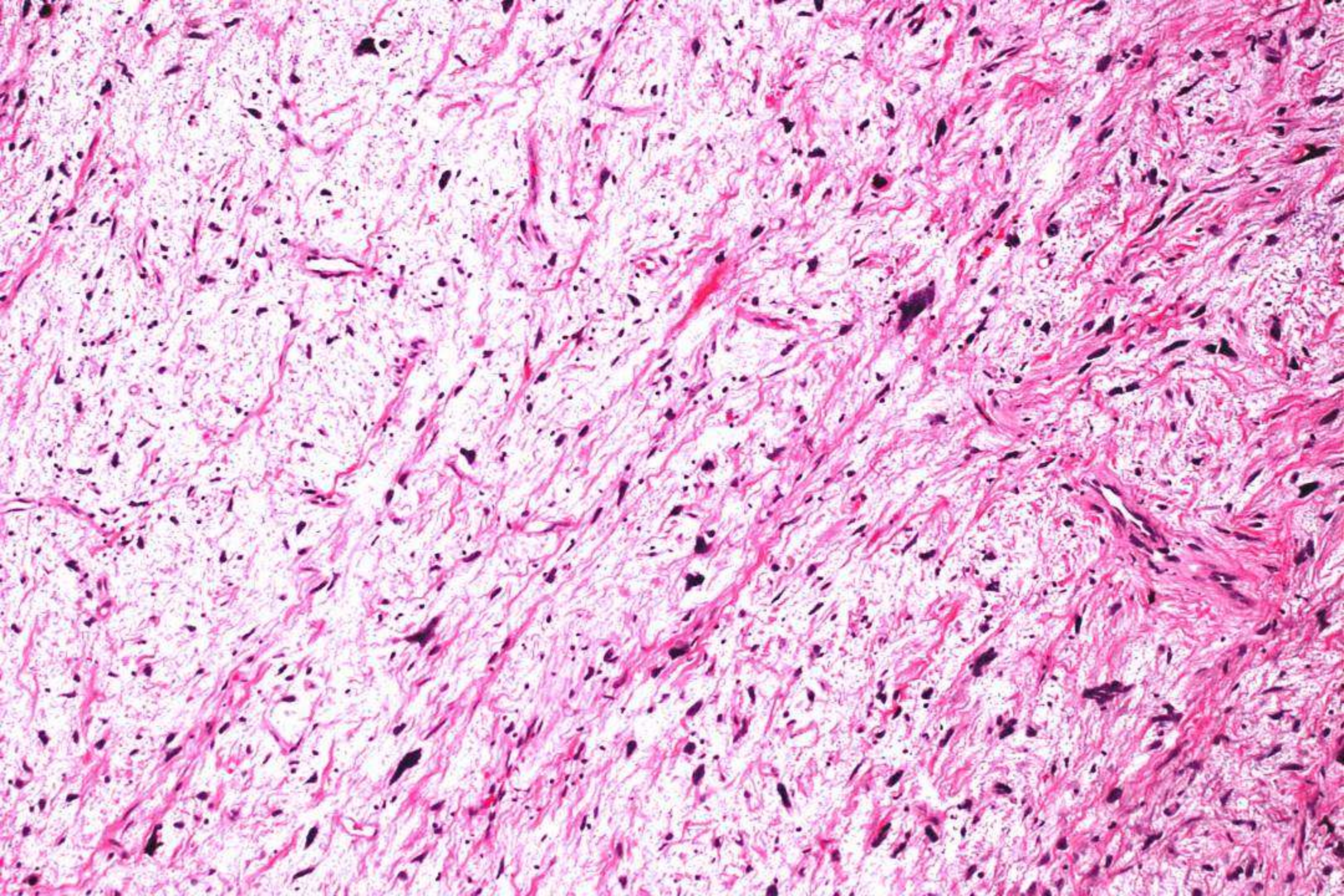
Malignant

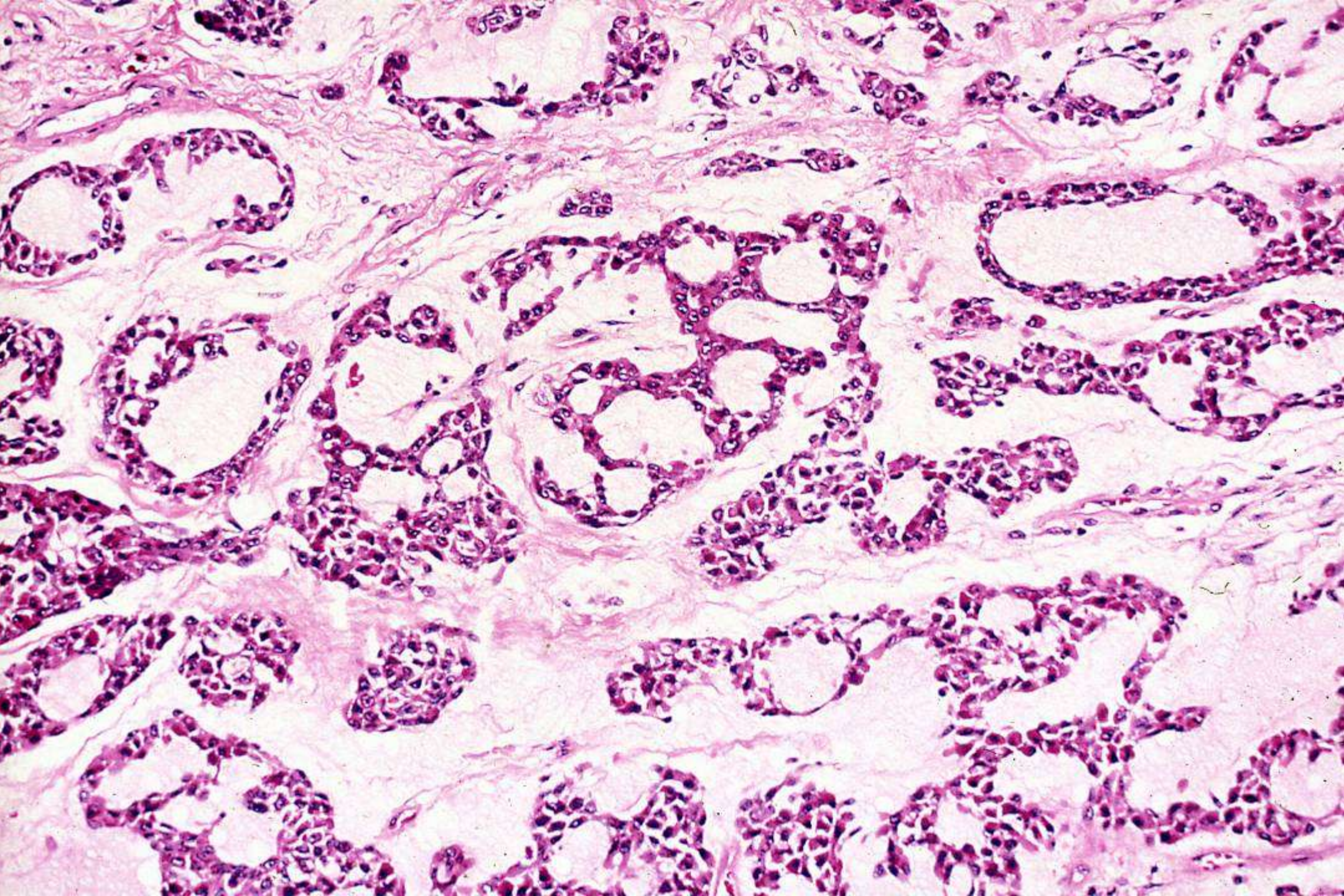
- Myxoid liposarcoma
- Myxofibrosarcoma (myxoid MFH)
- Myxoid chondrosarcoma
- Low-grade fibromyxoid sarcoma
- All other sarcomas

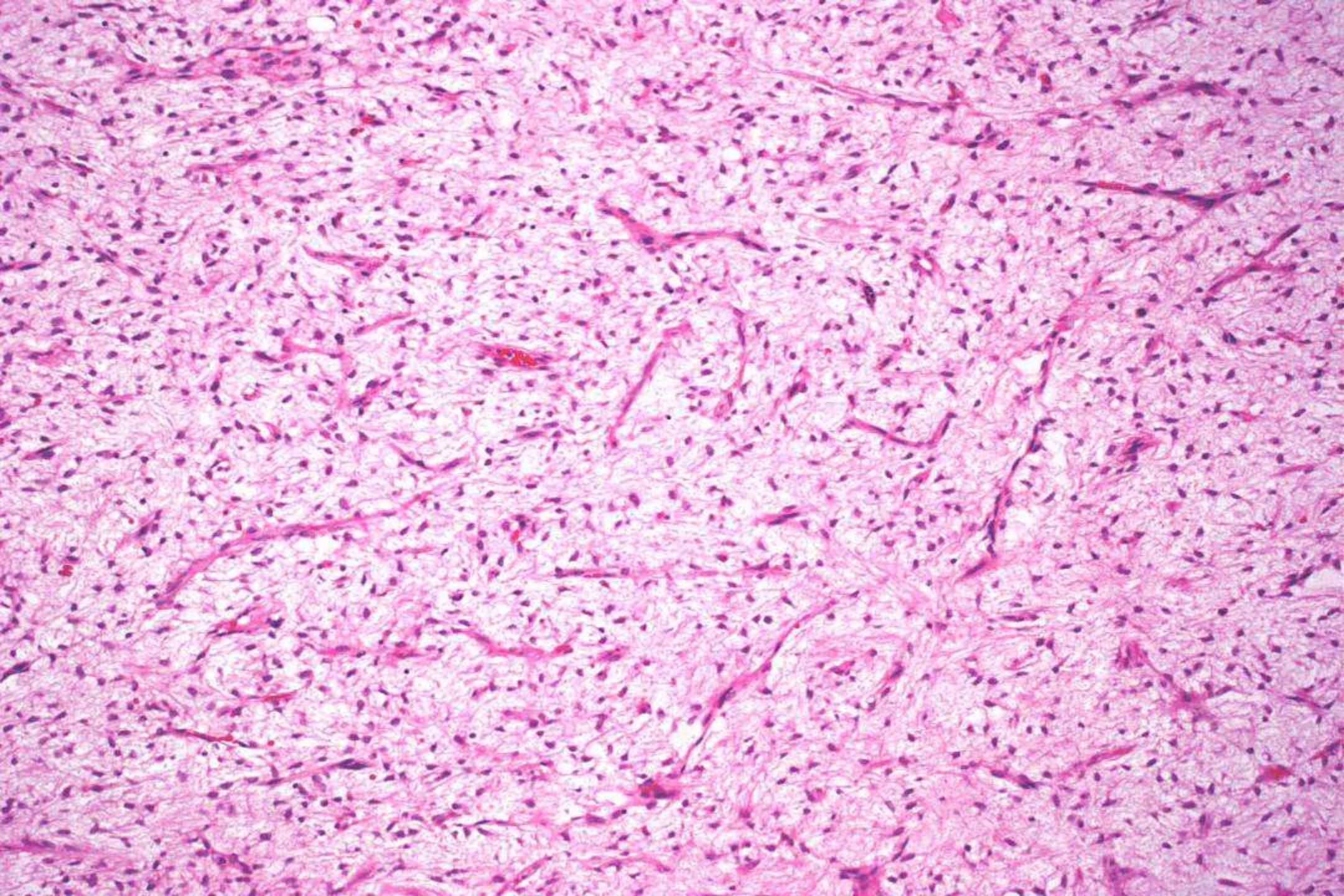
Myxoid Soft Tissue Tumors

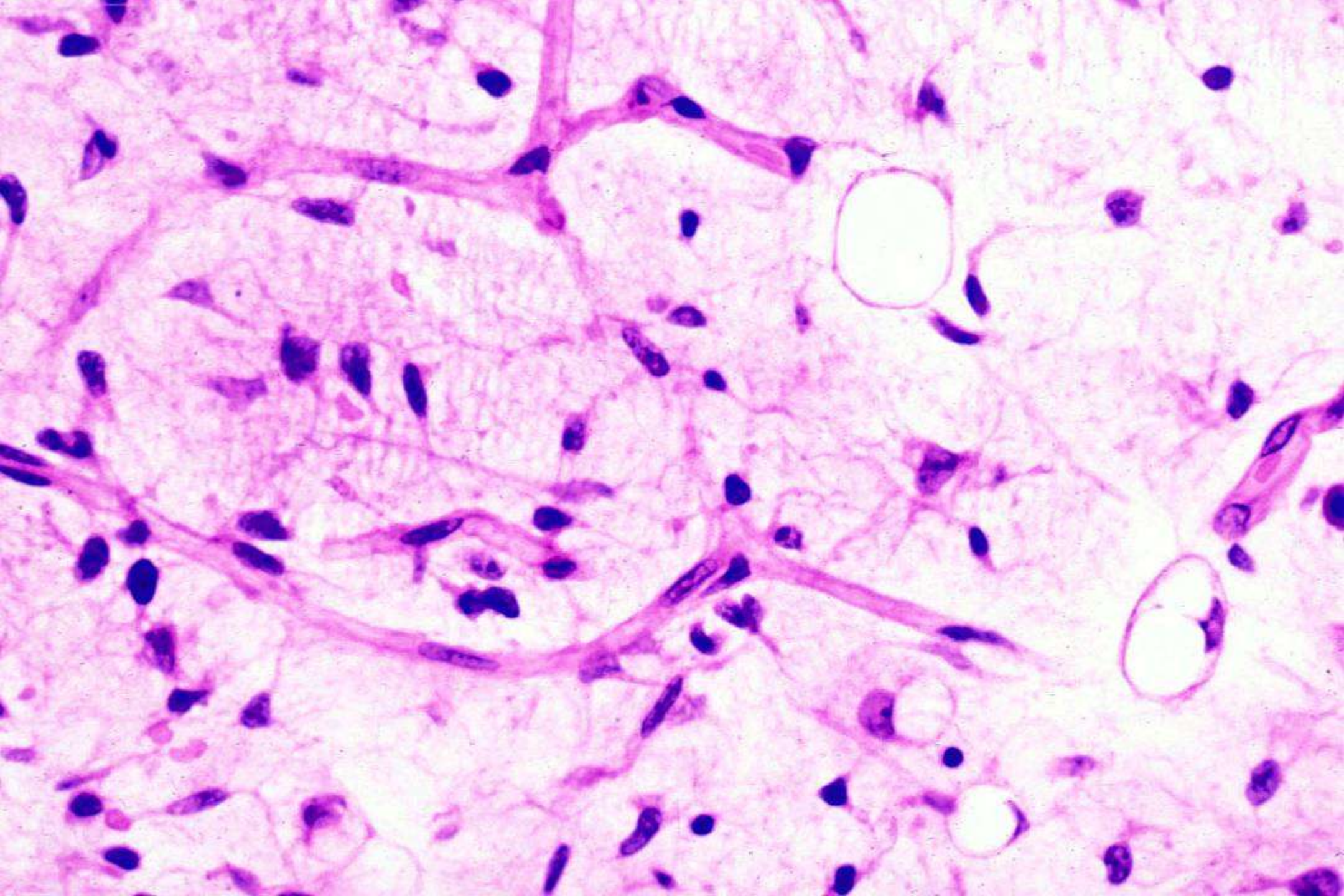
- Morphology is most useful
  - Cellularity and cellular arrangement
  - Atypia
  - Vascular pattern
- Limited use of IHC (S100)
- FISH extremely useful

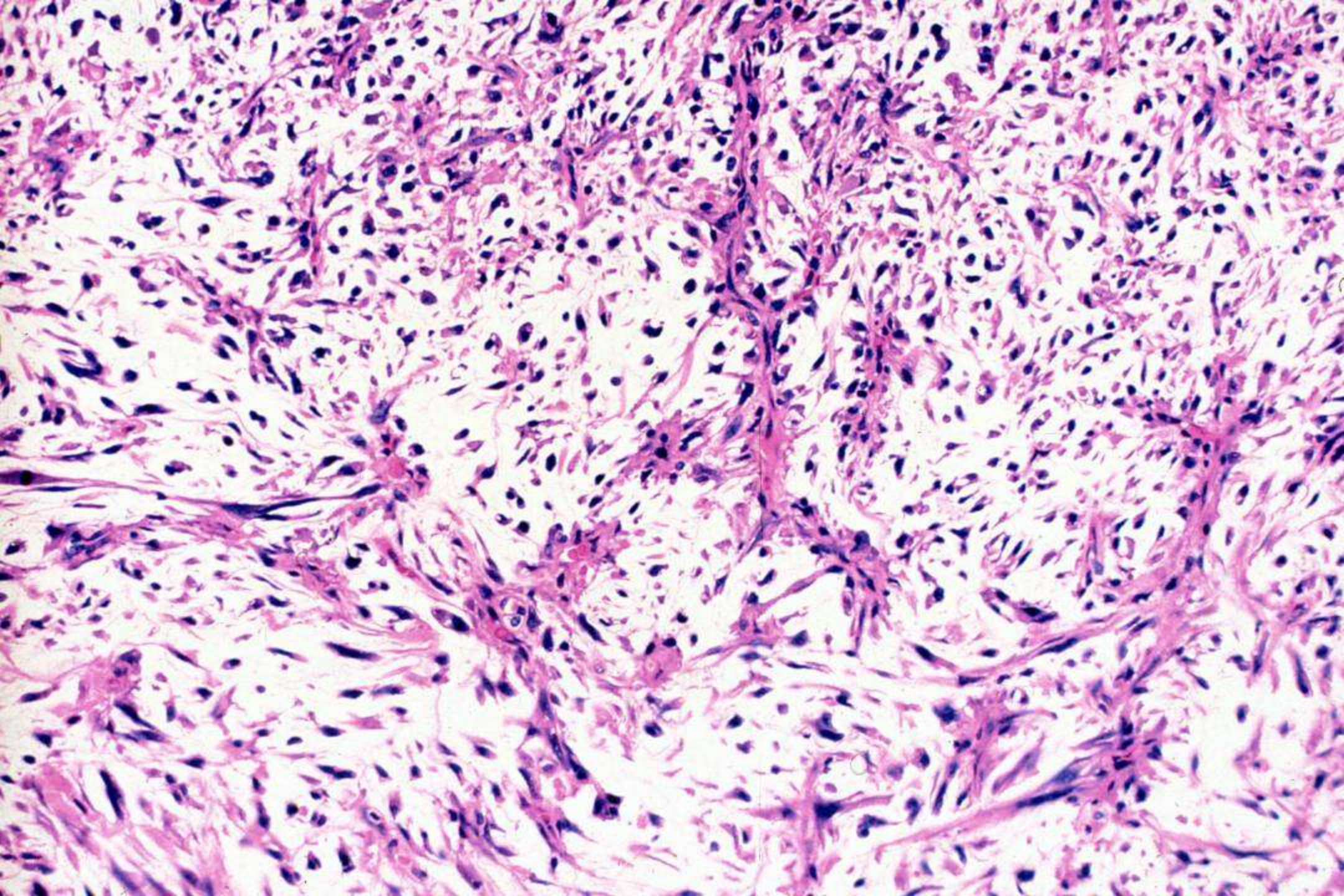












LGFMS

- Originally described by Harry Evans in 1987 (n=2)
  - Both originally diagnosed as benign
  - Both locally recurred and eventually metastasized
  - One patient died from disease
- Follow-up study by Evans in 1993 (n=10)
  - 10 new cases
  - 8/10 diagnosed retrospectively after recurrence / metastasis
    - 7/10 recurred
    - 5/10 metastasized (some late)
    - 4/10 died of disease

LGFMS: 1987 - 2000

- Characteristic bland histology, frequently misdiagnosed as benign
- Paradoxically aggressive behavior
  - 68% local recurrence
  - 41% metastases
  - 18% died of disease

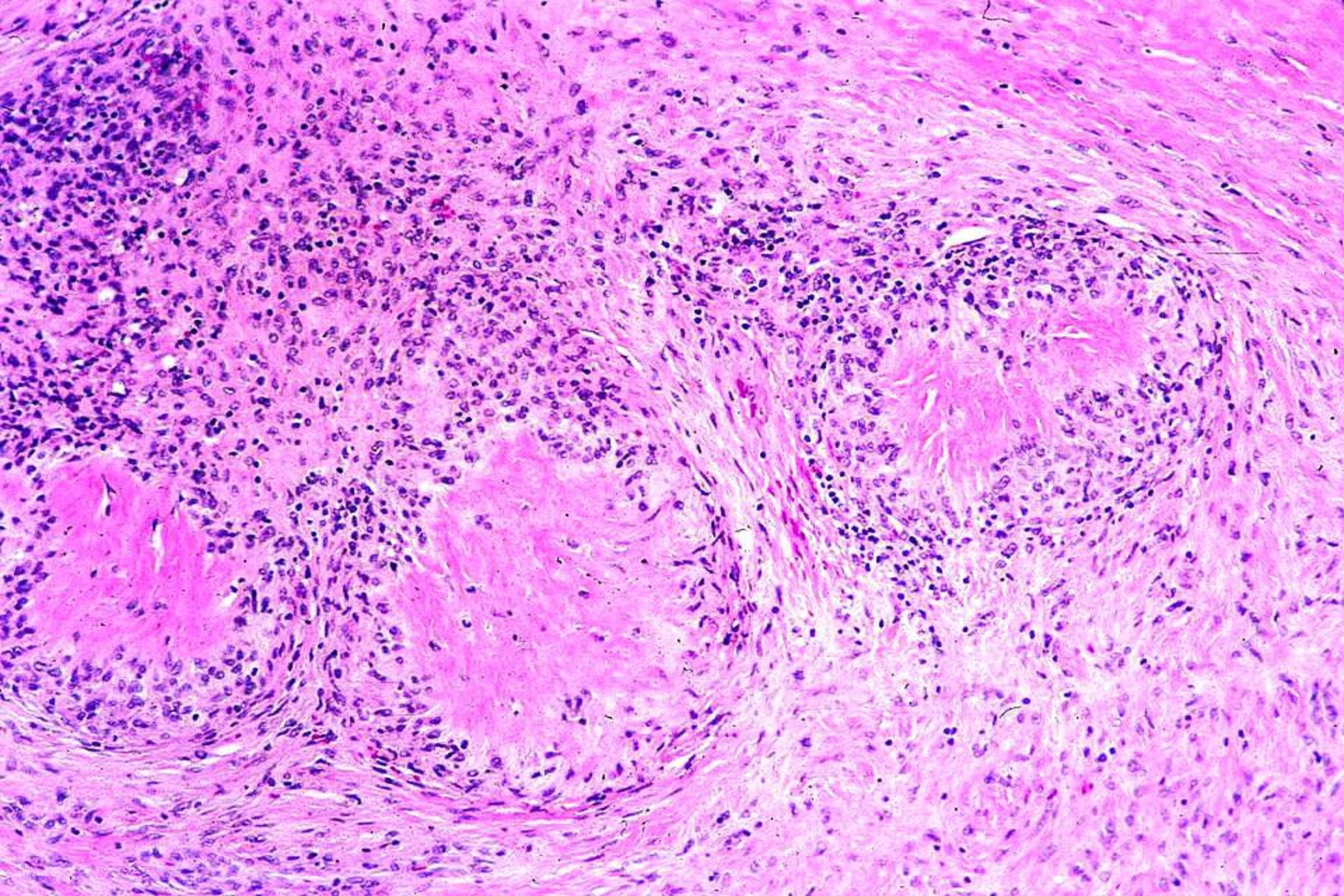
- Some cases with increased cellularity and atypia

- “The important feature of this neoplasm is that, despite its banal morphology, as many as 50% of cases eventually metastasize and pursue a fatal clinical course over a period of 10-30 years.” (CDM Fletcher, 2000)

Hyalinizing Spindle Cell Tumor with Giant Rosettes (HSCT)

- Described by Lane et al in 1997 (19 cases)
  - Giant collagen rosettes with surrounding epithelioid cells
  - Focal areas resembling LGFMS
  - Benign behavior (1 recurrence; no mets)

    - Very few cases subsequently reported, including metastatic cases



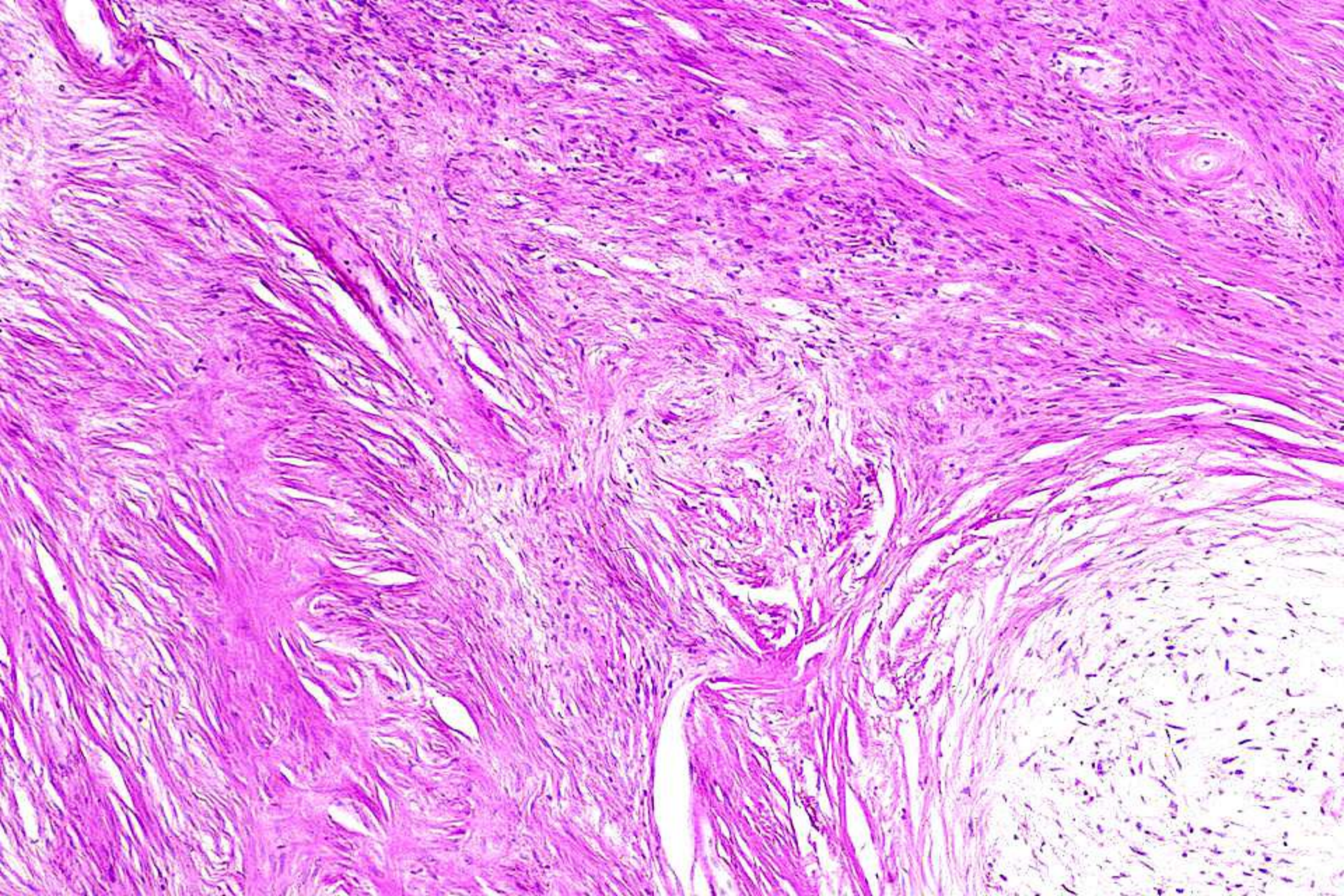
LGFMS / HSCT
Folpe et al (2000)

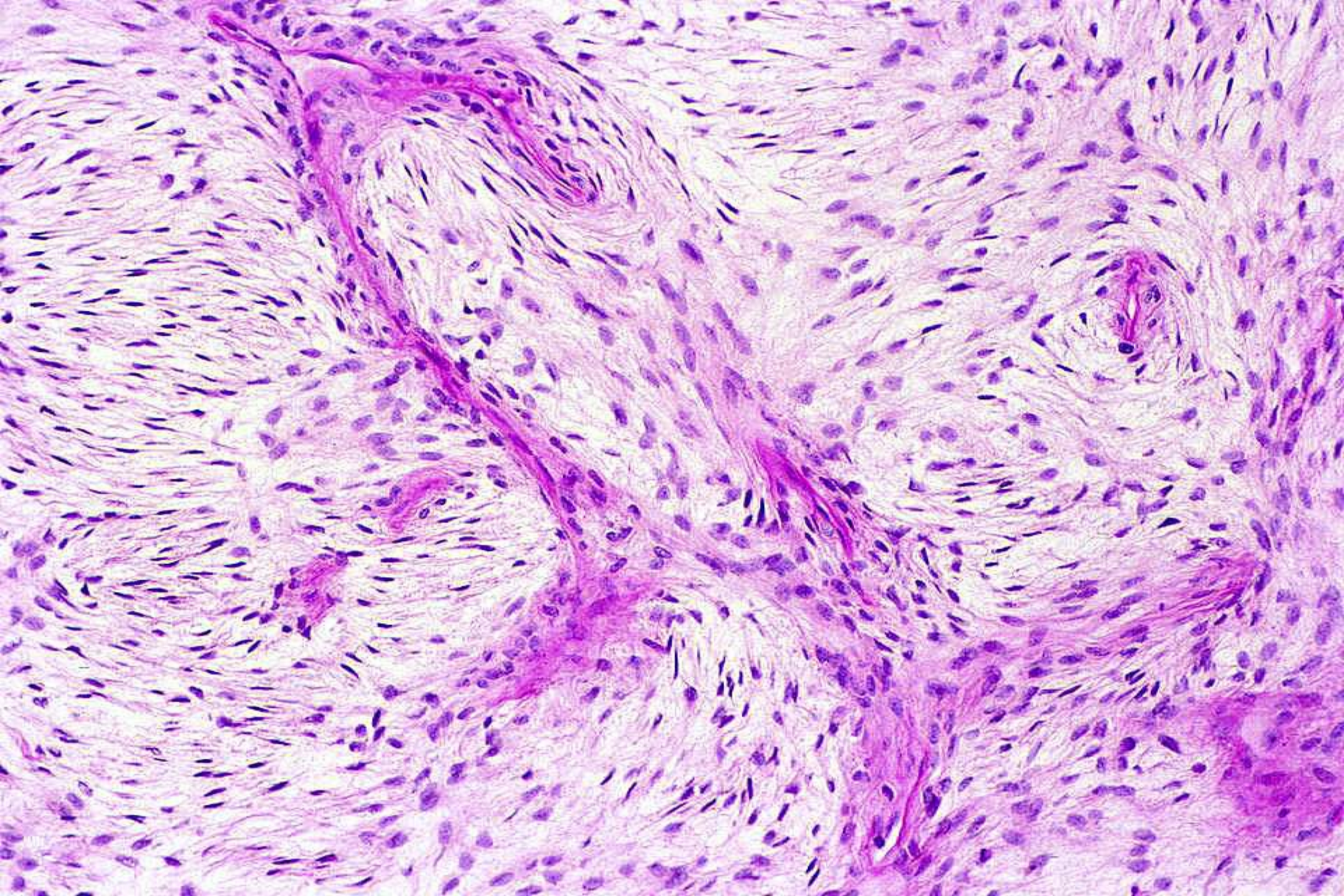
- N = 73 cases
- 70/73 initially diagnosed correctly
- 3/73 with metastasis, previously diagnosed with “benign” tumors

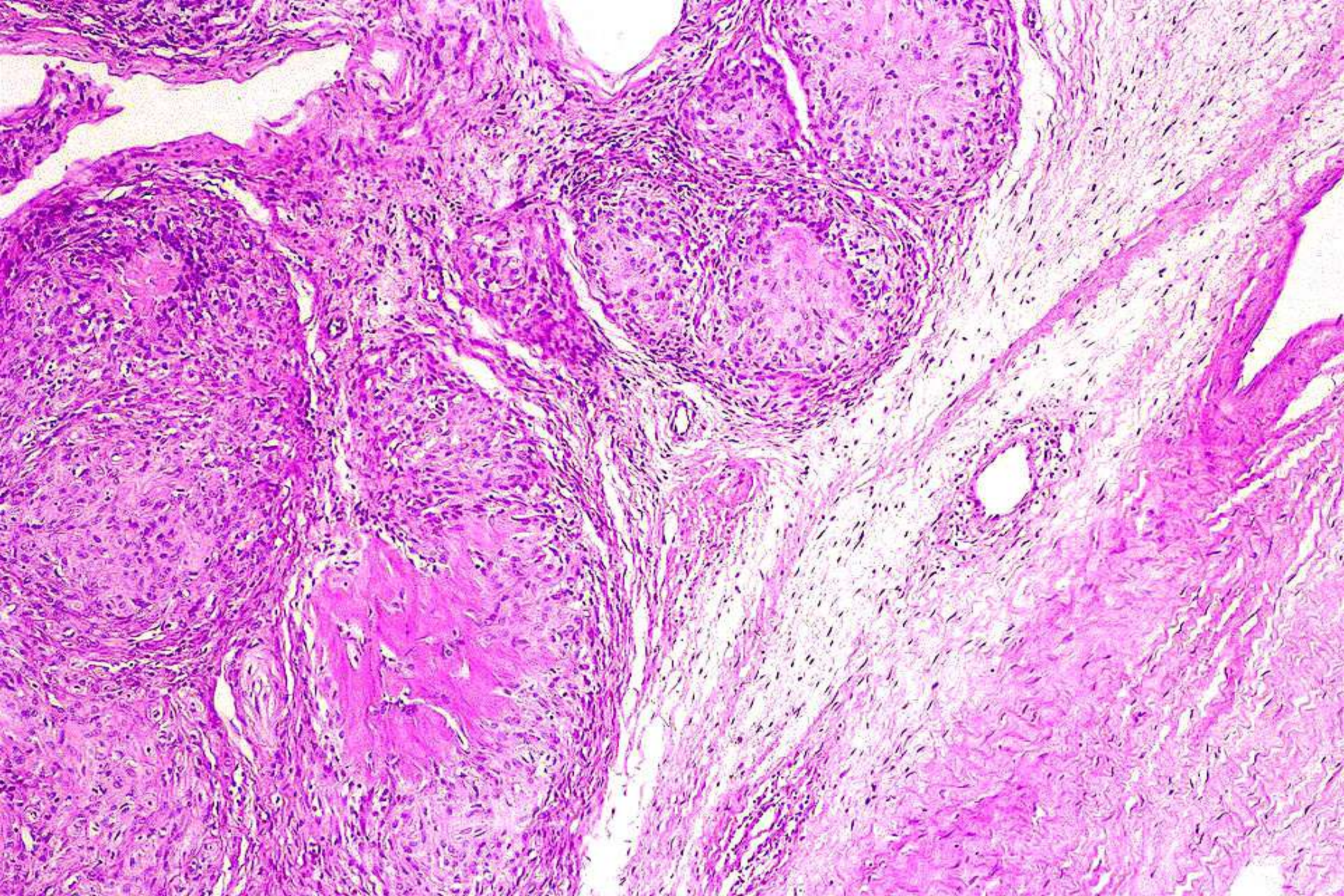
LGFMS / HSCT

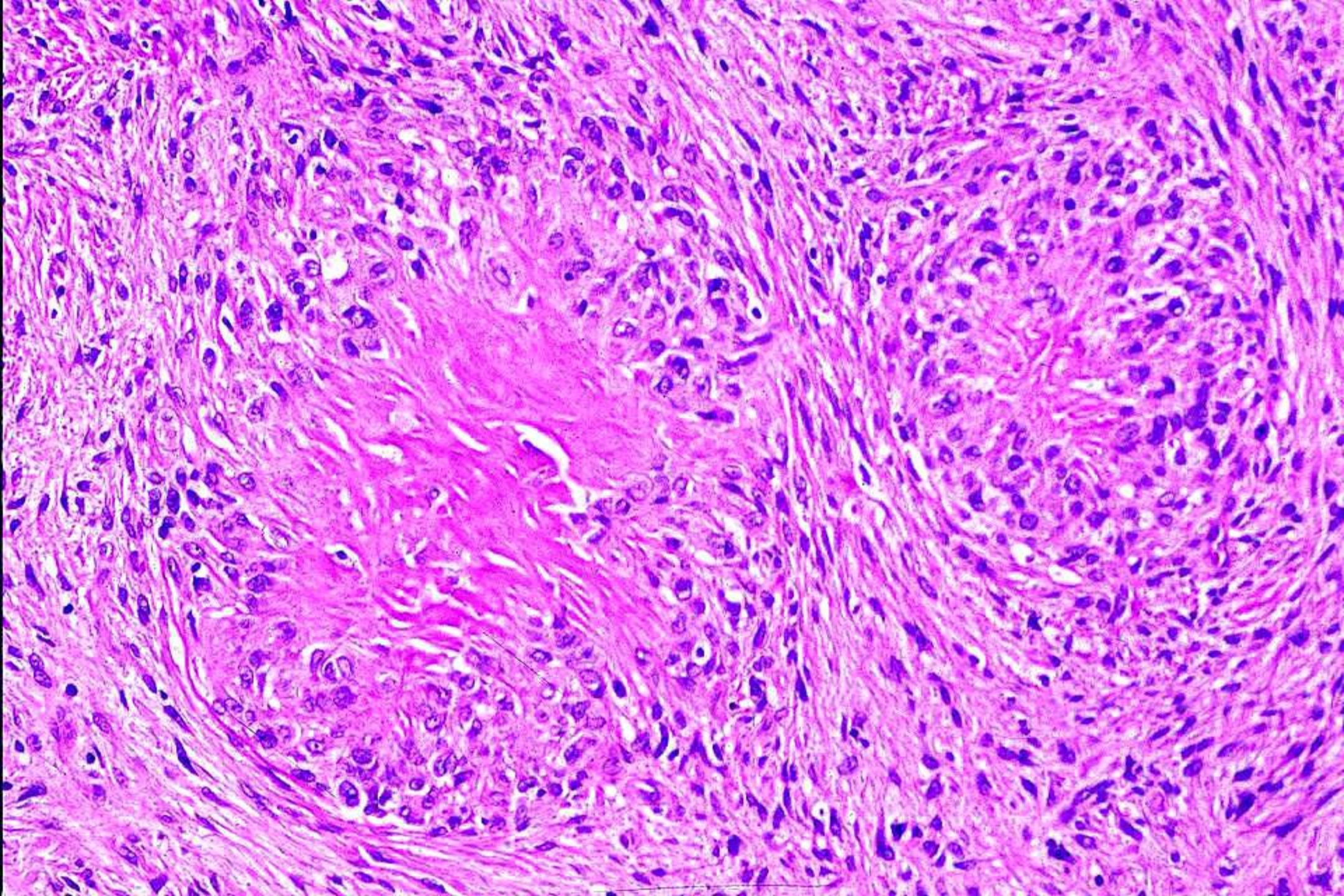
- No sex predilection
- Occur at any age but usually in young adults
- Most common in deep soft tissues of proximal extremities and trunk
- Often large, slowly growing
- May have long pre-biopsy duration

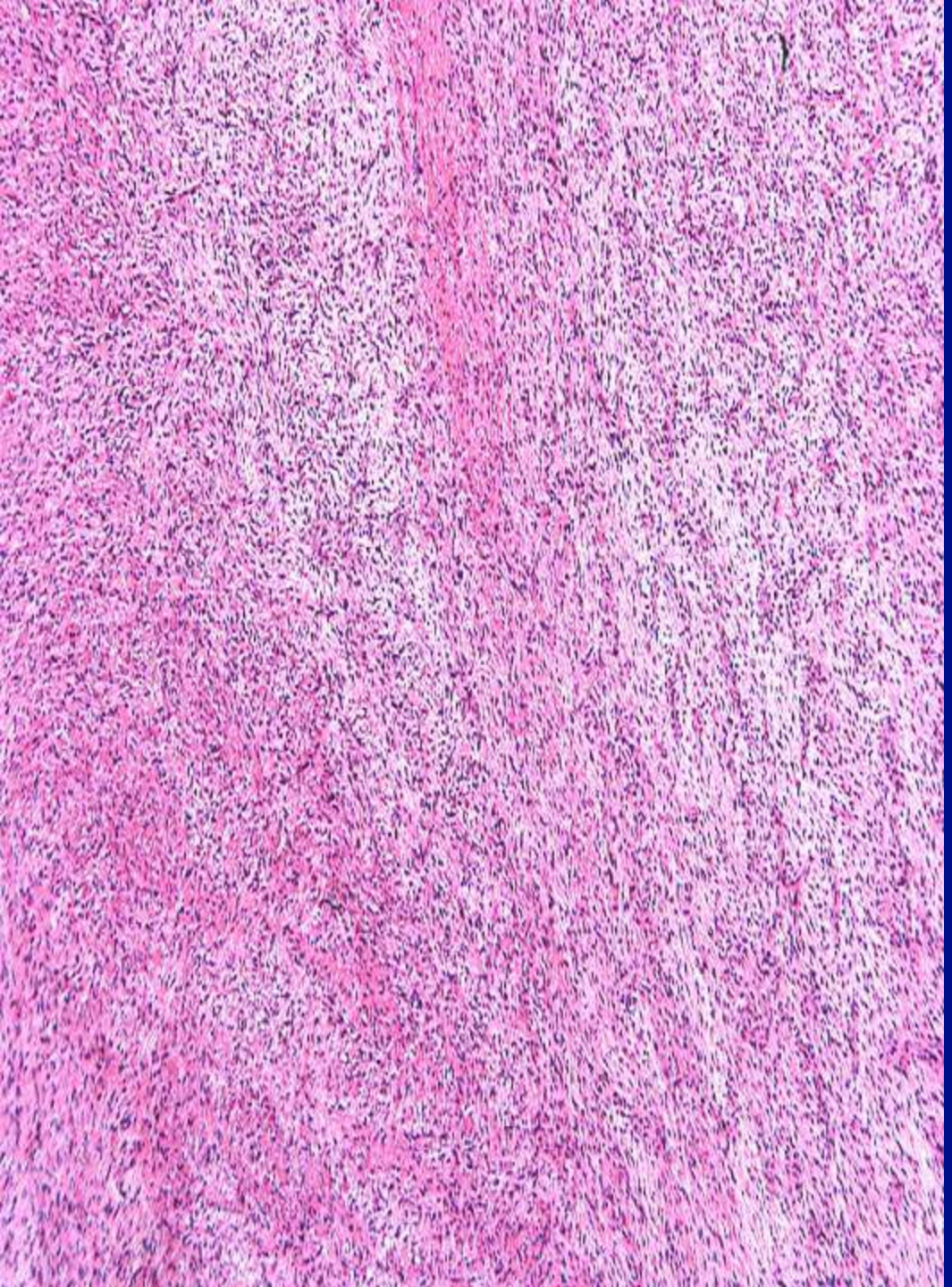
Folpe et al, AJSP 2000











LGFMS / HSCT

S100	-
CD34	-
Bcl-2	-
CD99	-
SMA	-
EMA	+/-

MUC4 in LGFMS

LGFMS (all FUS+)	**49/49 (100%)**
• Marked hypercellularity	7/7
• Giant collagen rosettes	3/3
• HPC-like vessels	4/4
• Focal epithelioid morphology	3/3
• Focal marked pleomorphism	2/2

Doyle LA et al. AJSP 2011; 35:733-41

MUC4 in LGFMS

Tumor	MUC4^{+}
Cellular myxoma	0/20
Desmoid fibromatosis	0/20
DFSP	0/20
Low-grade MPNST	0/20
Myxofibrosarcoma	0/40
SFT	0/20
Soft tissue perineurioma	0/40
Monophasic synovial sarcoma	6/20 (30%)

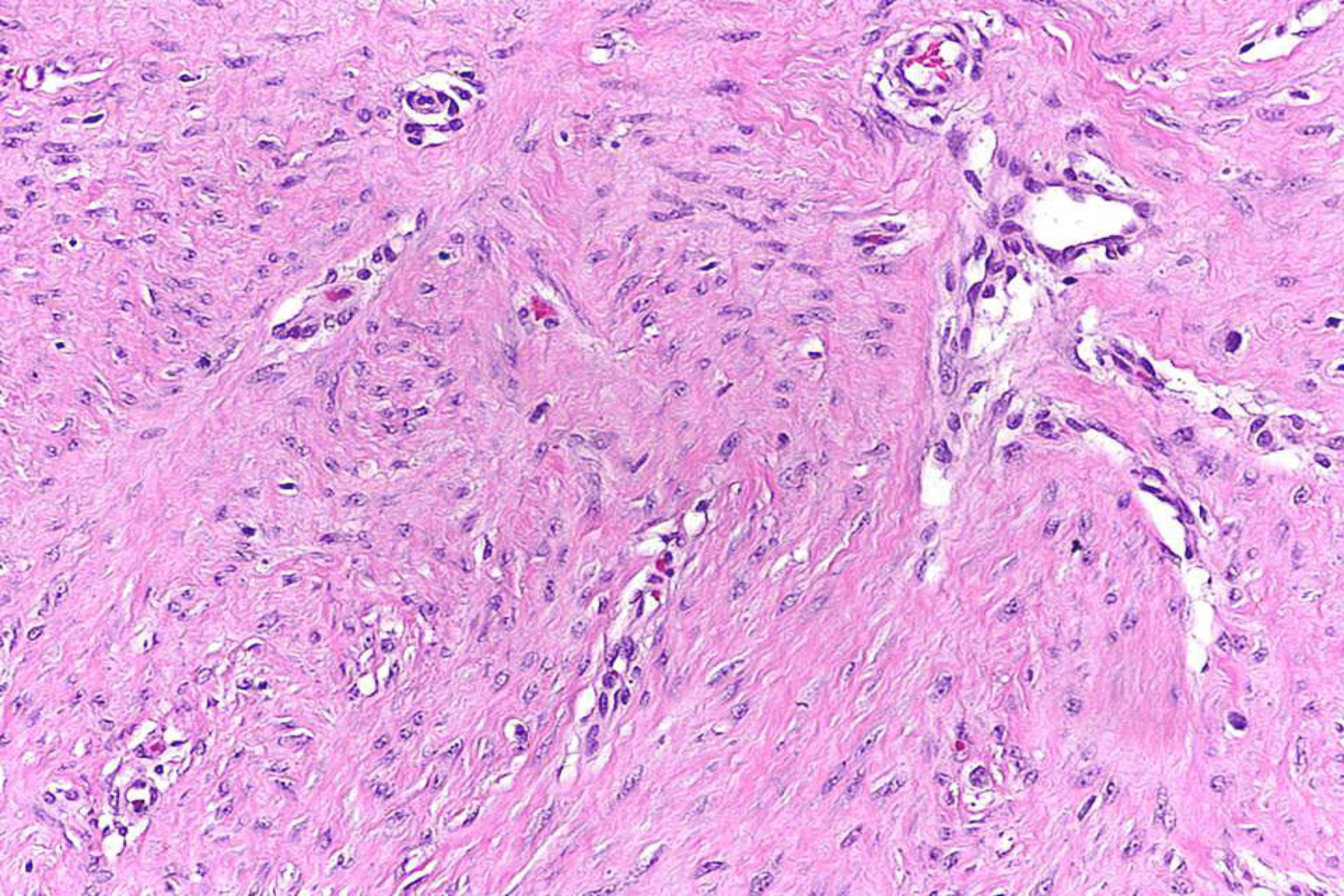
LGFMS / HSCT
Clinical Behavior

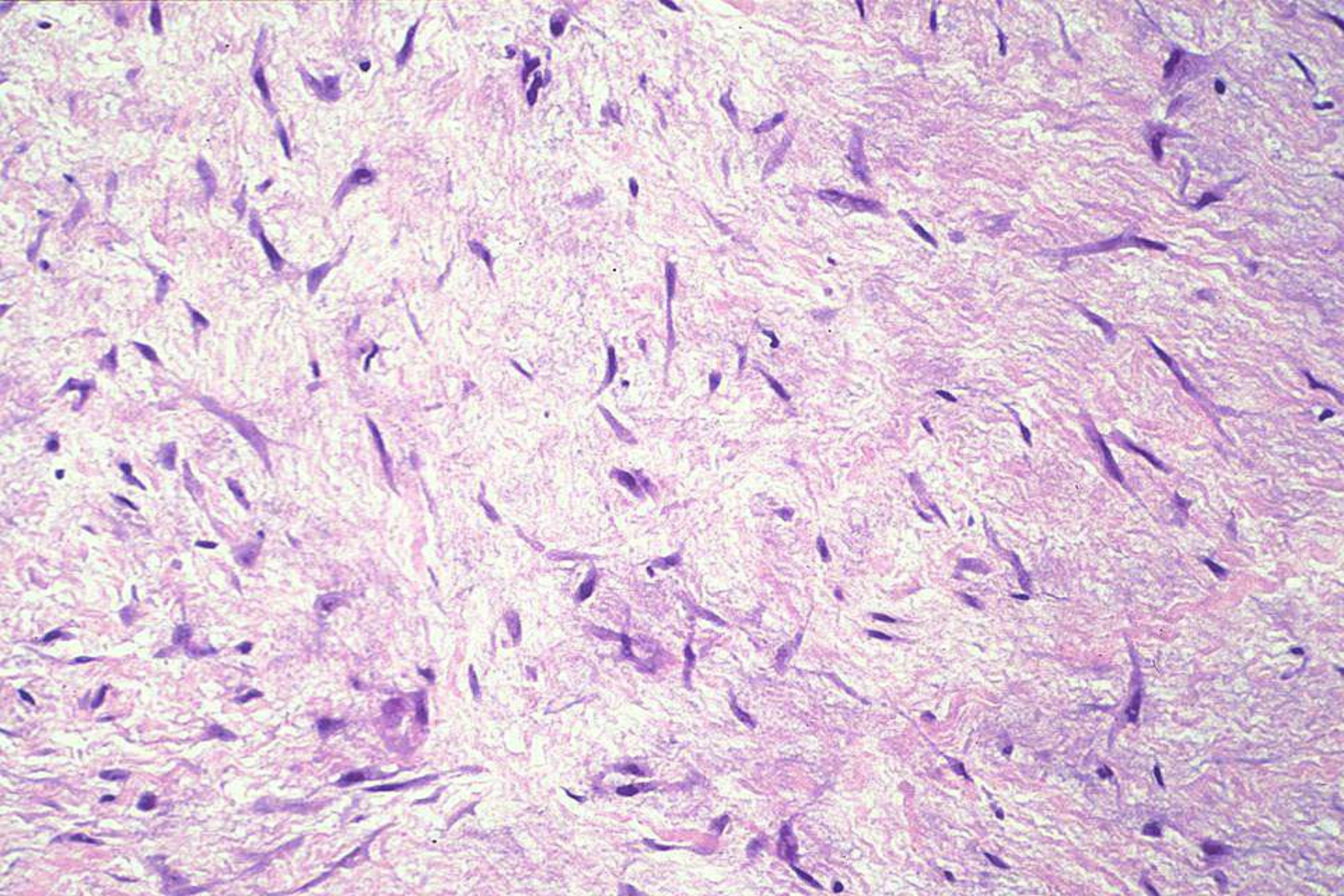
- Follow-up: 2-192 mos (mean: 38 mos)
  - Local recurrence: 5/54 (9%)
  - Metastasis: 3/54 (6%)
  - Died of disease: 1/54 (2%)

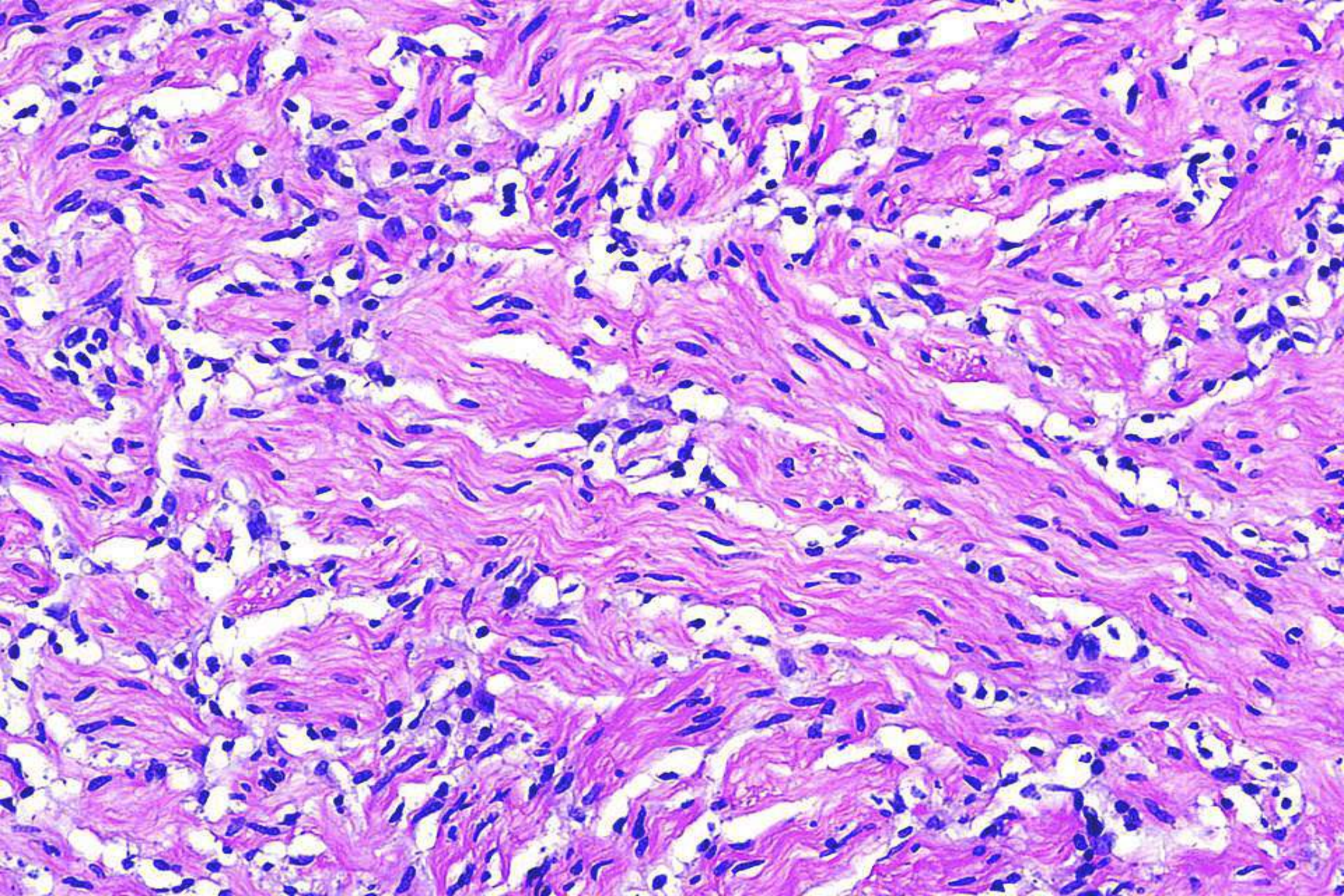
Folpe et al. AJSP, 2000

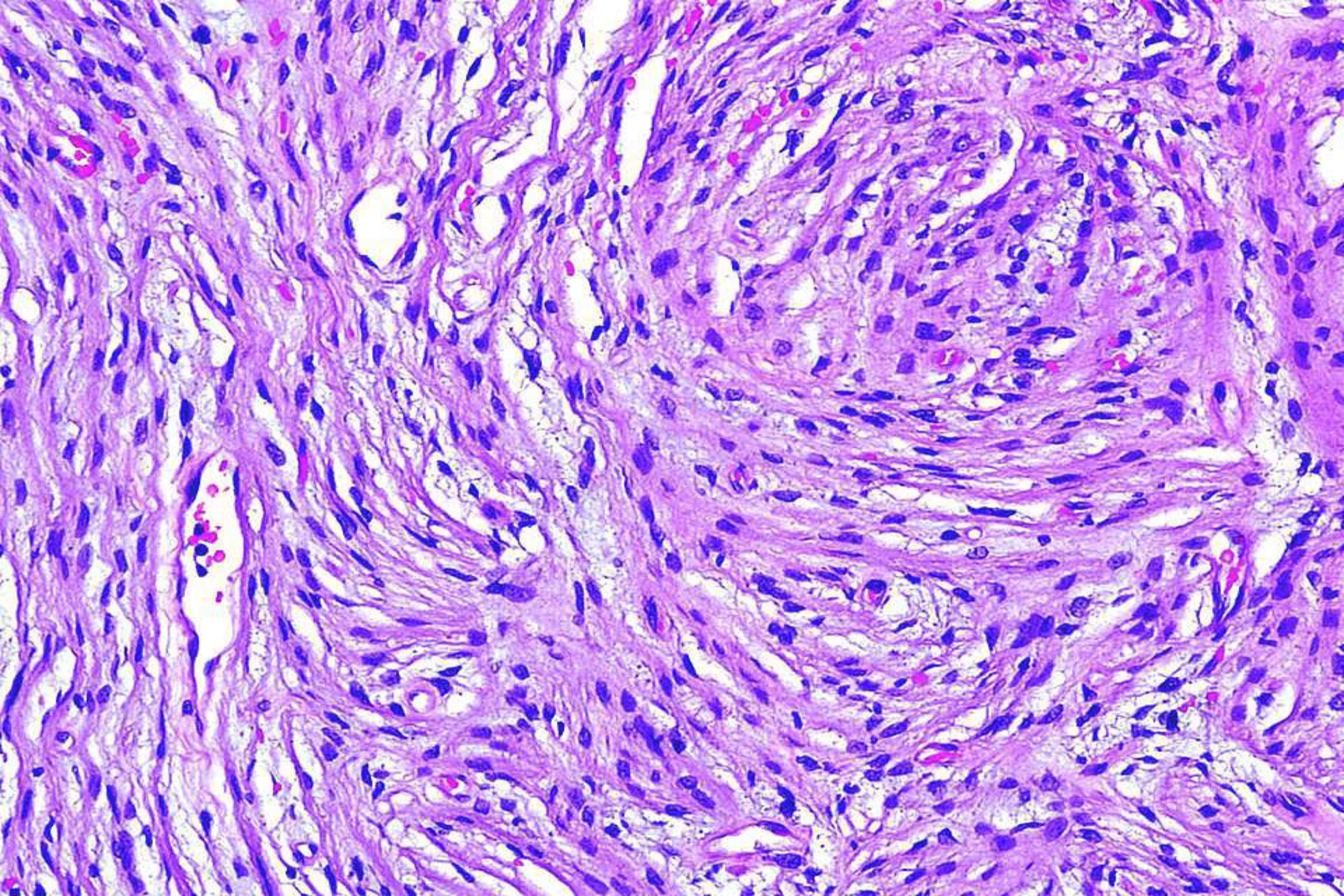
Differential Diagnosis Collagenous Tumors

- Fibromatosis
- Desmoplastic fibroblastoma (collagenous fibroma)
- Neurofibroma
- Perineurioma







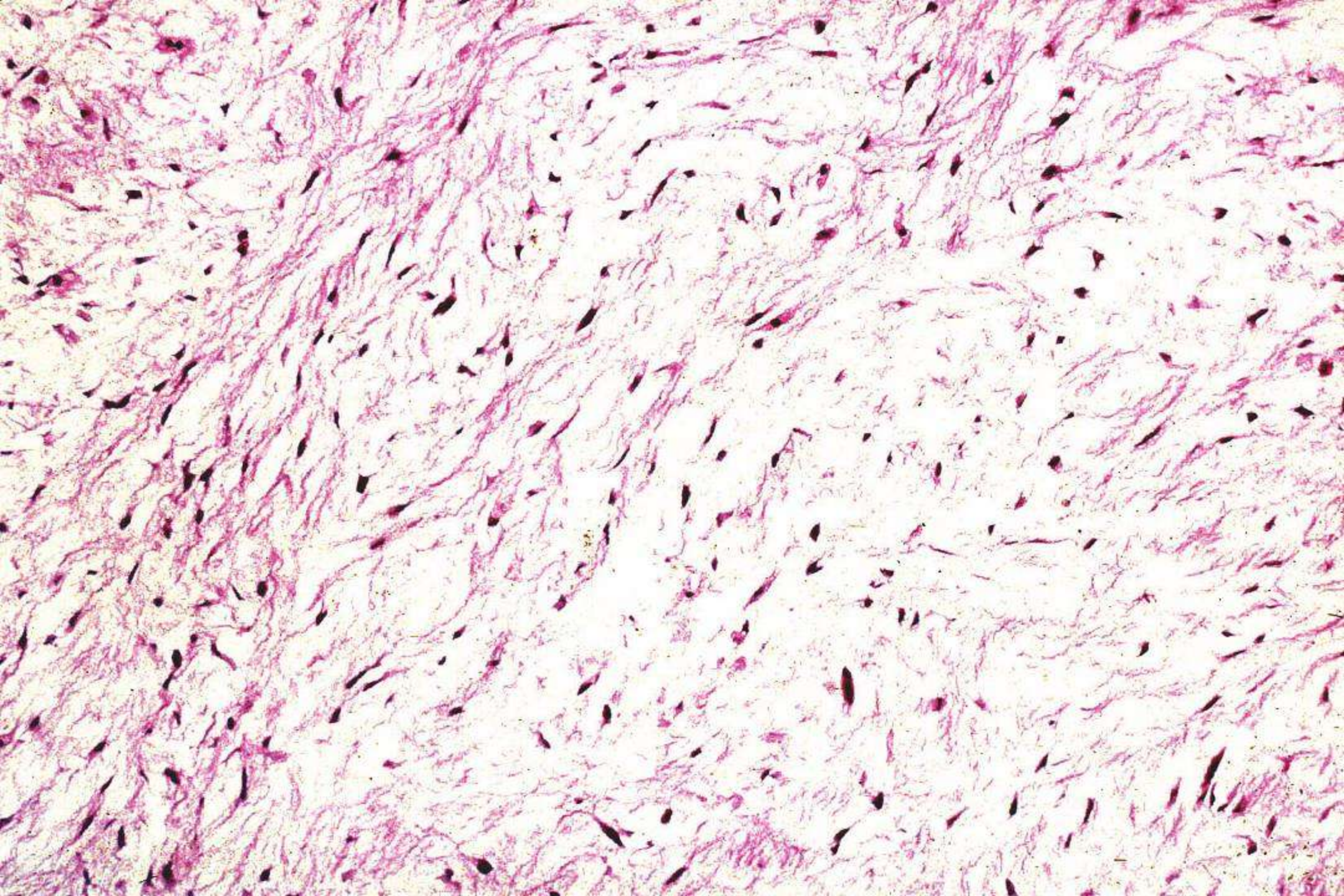


Differential Diagnosis Myxoid Tumors

- Intramuscular myxoma
- Myxofibrosarcoma ("myxoid MFH")

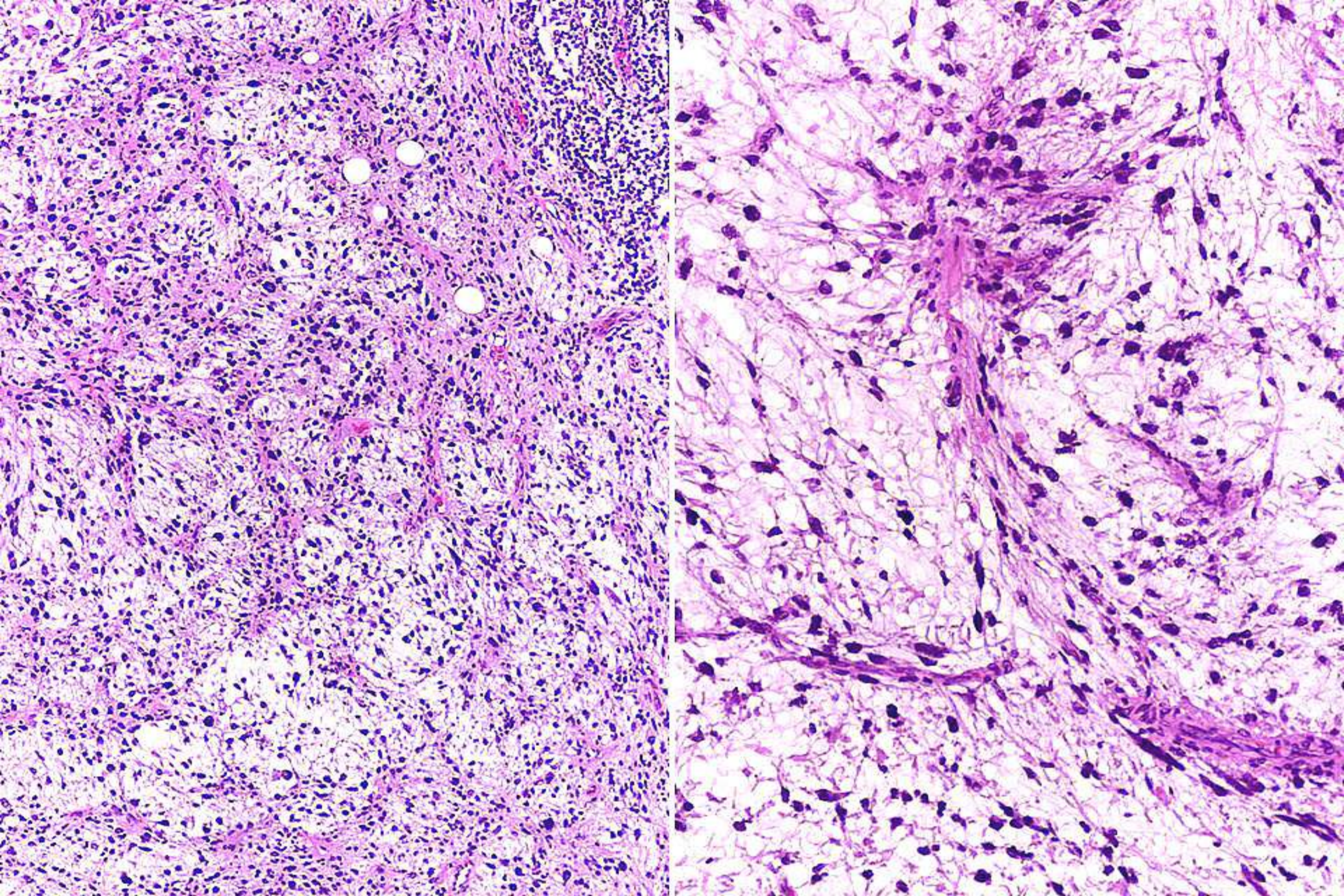
Intramuscular Myxoma

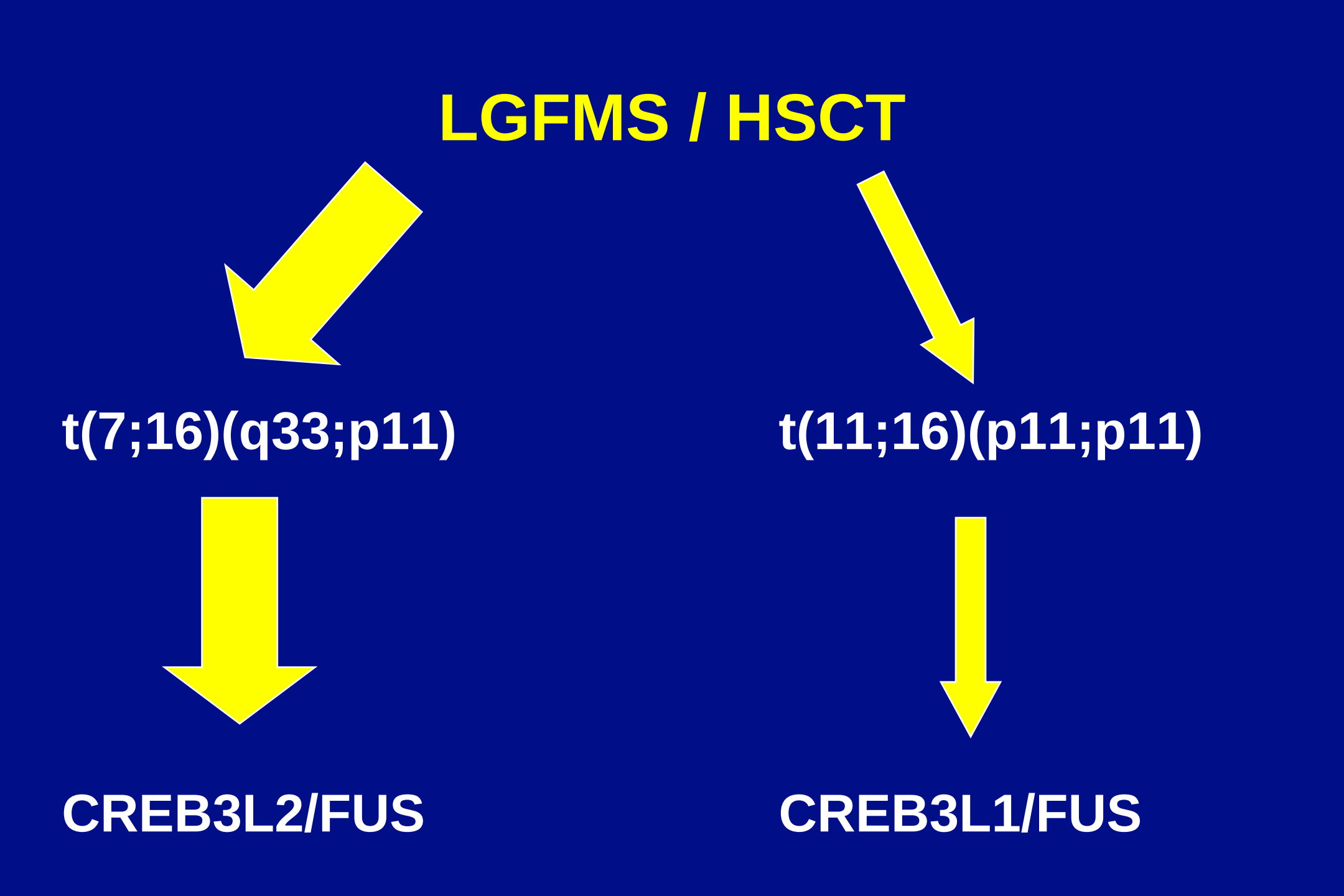
- Uniformly myxoid
- Hypocellular, bland spindled cells with pyknotic nuclei
- Hypovascular
- Splays apart surrounding skeletal muscle



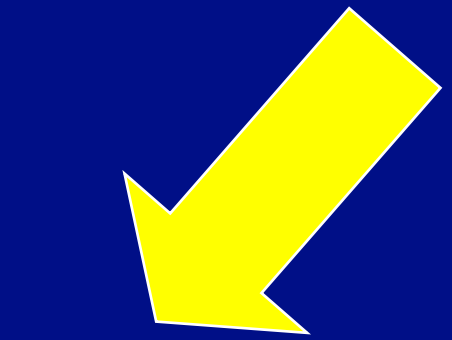
Myxofibrosarcoma ("Myxoid MFH")

- Multinodular, subcutis, older patients
- More atypical spindled / stellate cells
- Curvilinear thick-walled vessels with perivascular hypercellularity
- Less cellular bland areas; more cellular pleomorphic areas

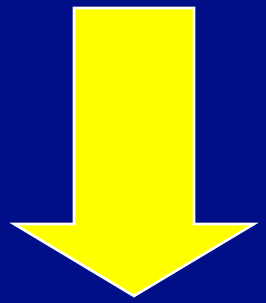



LGFMS / HSCT
t(7;16)(q33;p11)
t(11;16)(p11;p11)
CREB3L2/FUS
CREB3L1/FUS

Myxoid/Round Cell Liposarcoma
Cytogenetics



t(12;16)(q13;p11)

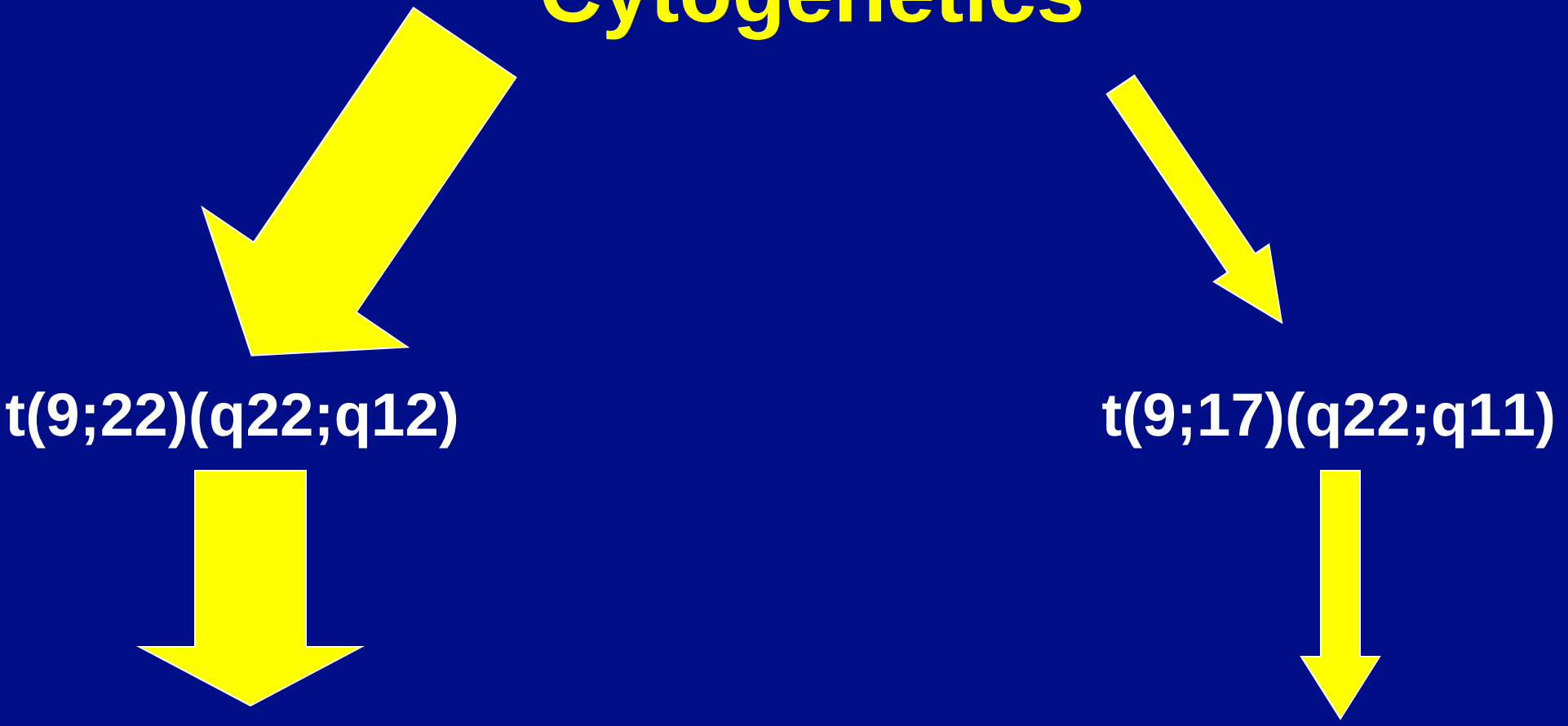


DDIT3 (CHOP)/FUS

t(12;22)(q13;q12)

DDIT3 (CHOP)/EWSR1

Extraskeletal Myxoid Chondrosarcoma Cytogenetics



Myxoid Soft Tissue Tumors

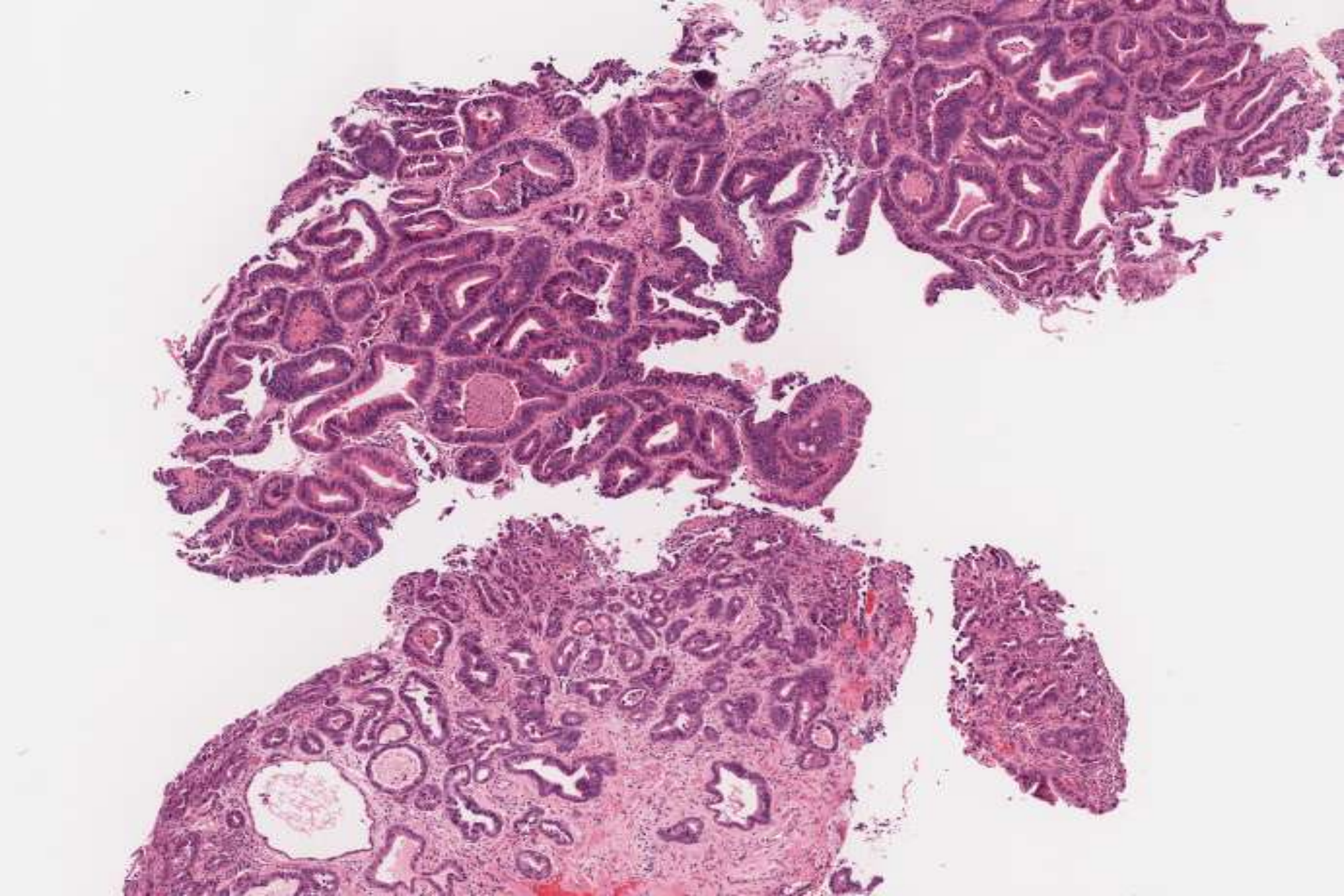
Tumor	Defect	Genes
Myxoma	activating GNAS mutations	
LGFMS/HSCT	t(7;16)(q33;p11)	CREB3L2/FUS
	t(11;16)(p11;p11)	CREB3L1/FUS
MLS/RCLS	t(12;16)(q13;p11)	DDIT3/FUS
	t(12;22)(q13;q12)	DDIT3/EWSR1
ESMCS	t(9;22)(q22;q12)	NR4A3/EWSR1
	t(9;17)(q22;q11)	NR4A3/TAF2N
MyxoFS	None characteristic	

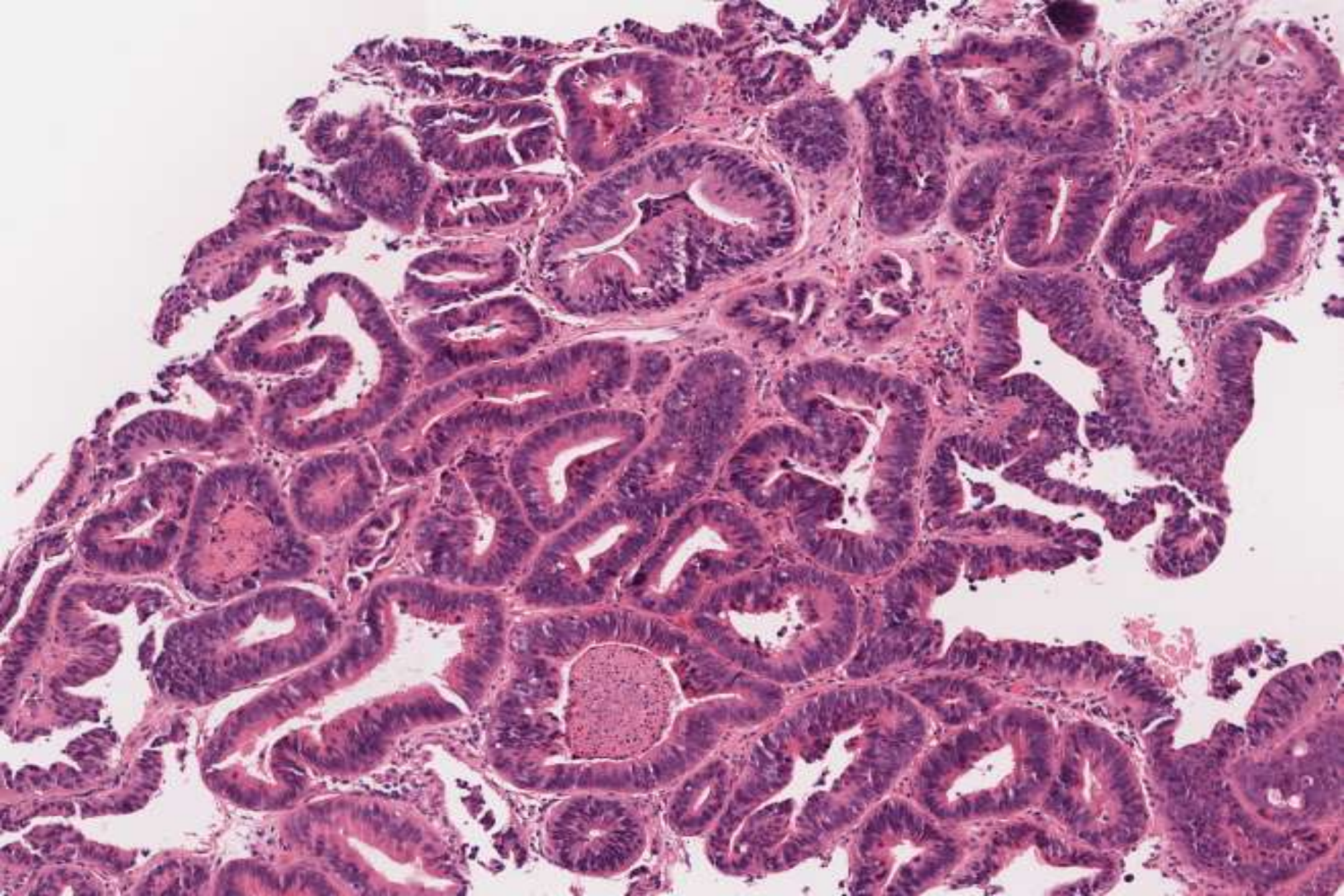
LGFMS / HSCT: Summary

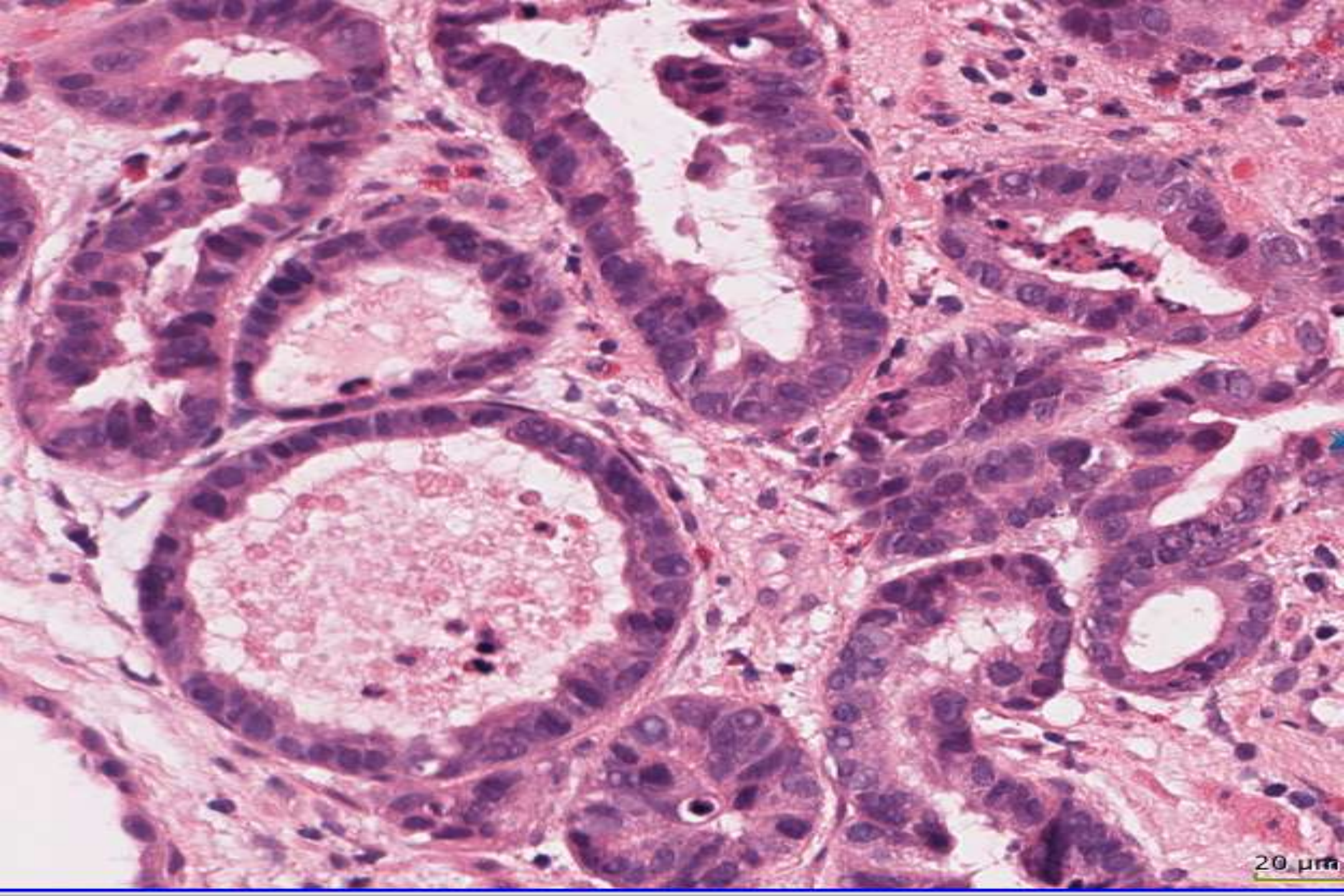
- Sarcoma of children and young adults
- Deep soft tissues of proximal extremities
- Deceptively bland histologic features
- Overlapping features between LGFMS/HSCT
- Characteristic molecular alteration t(7;16)
- Treatment: complete excision with tumor-free margins
- Outcome: low rate of recurrence and rare late metastases

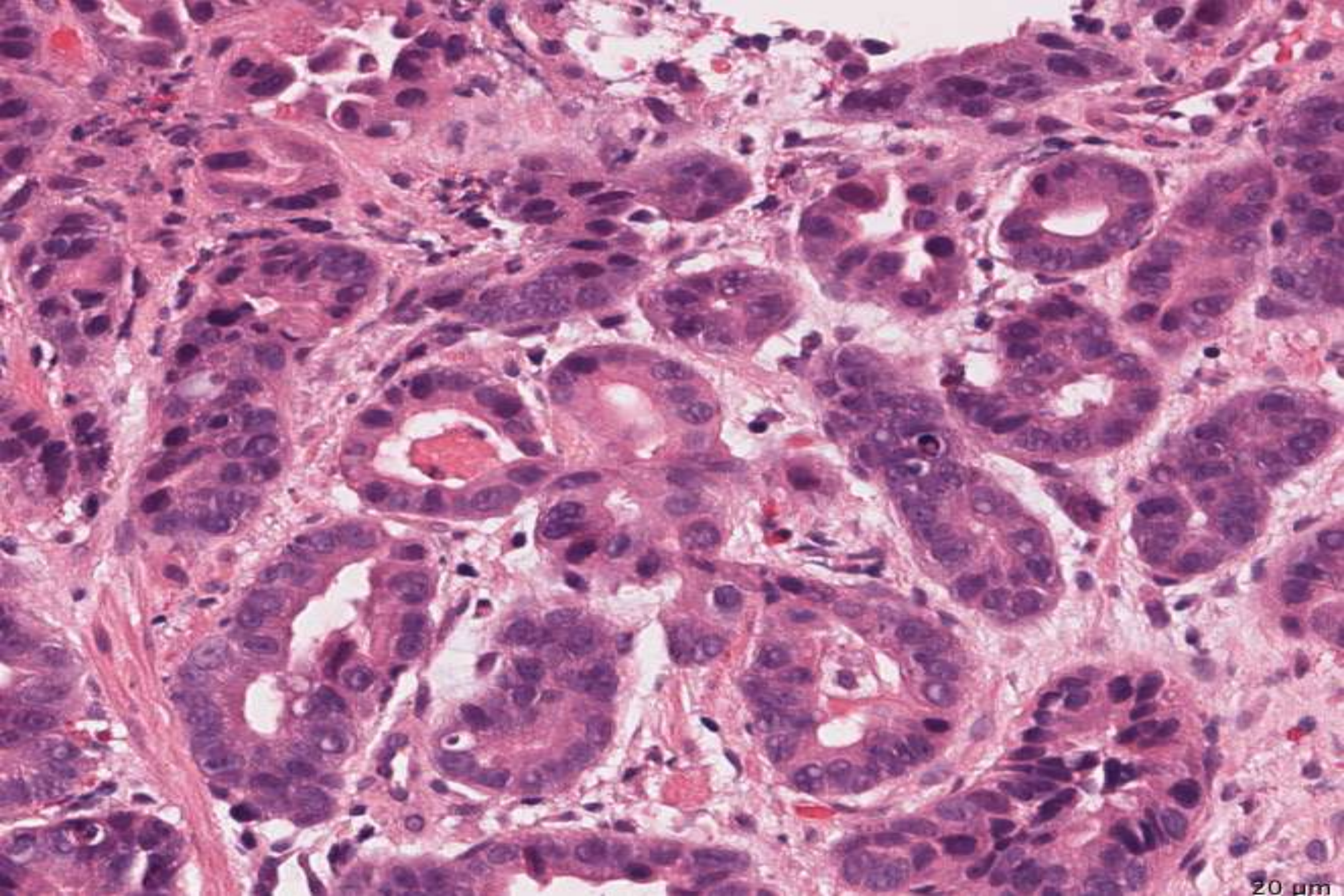
Case History

76-year-old male with a history of Barrett's esophagus






20 µm


20 µm

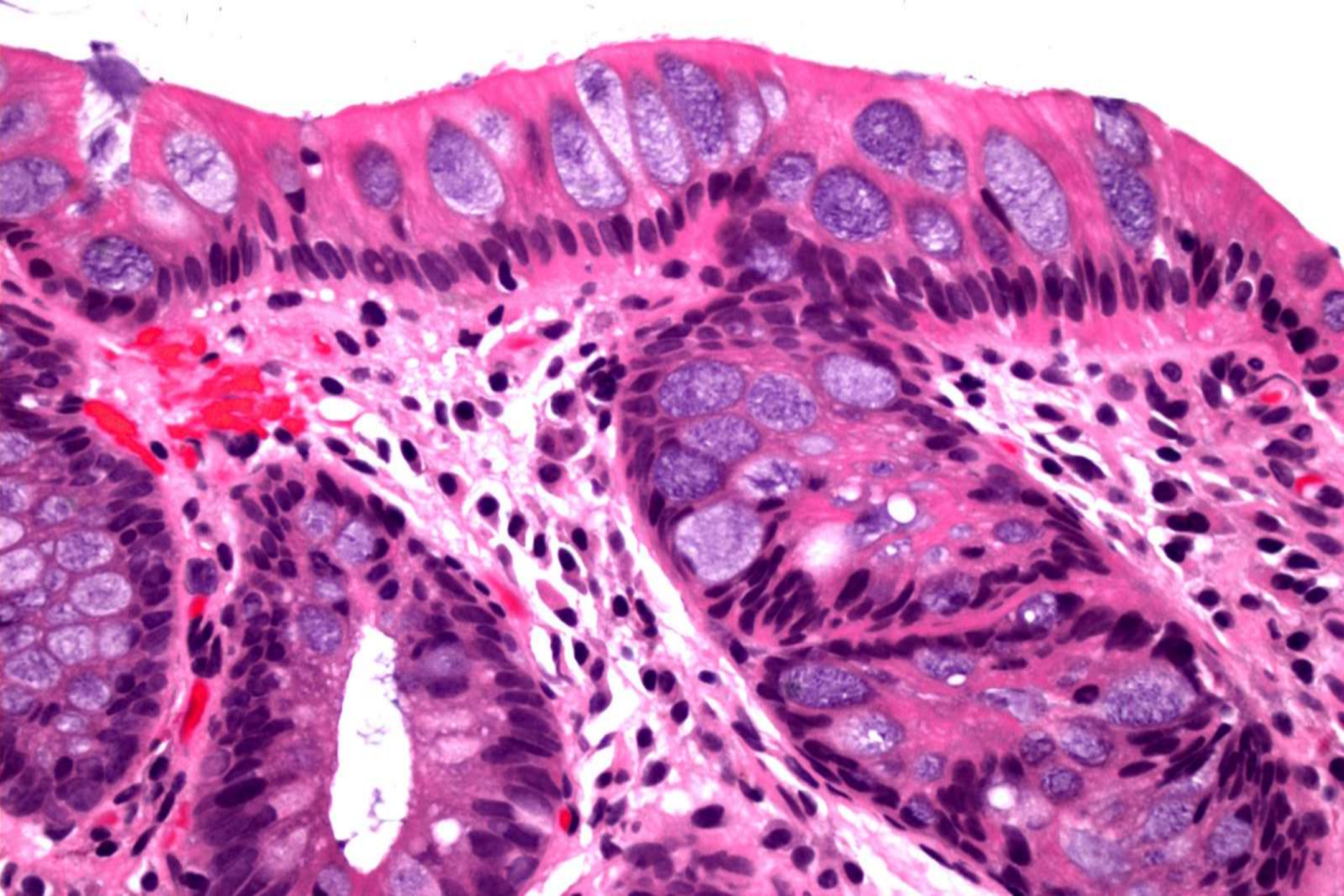
Diagnosis

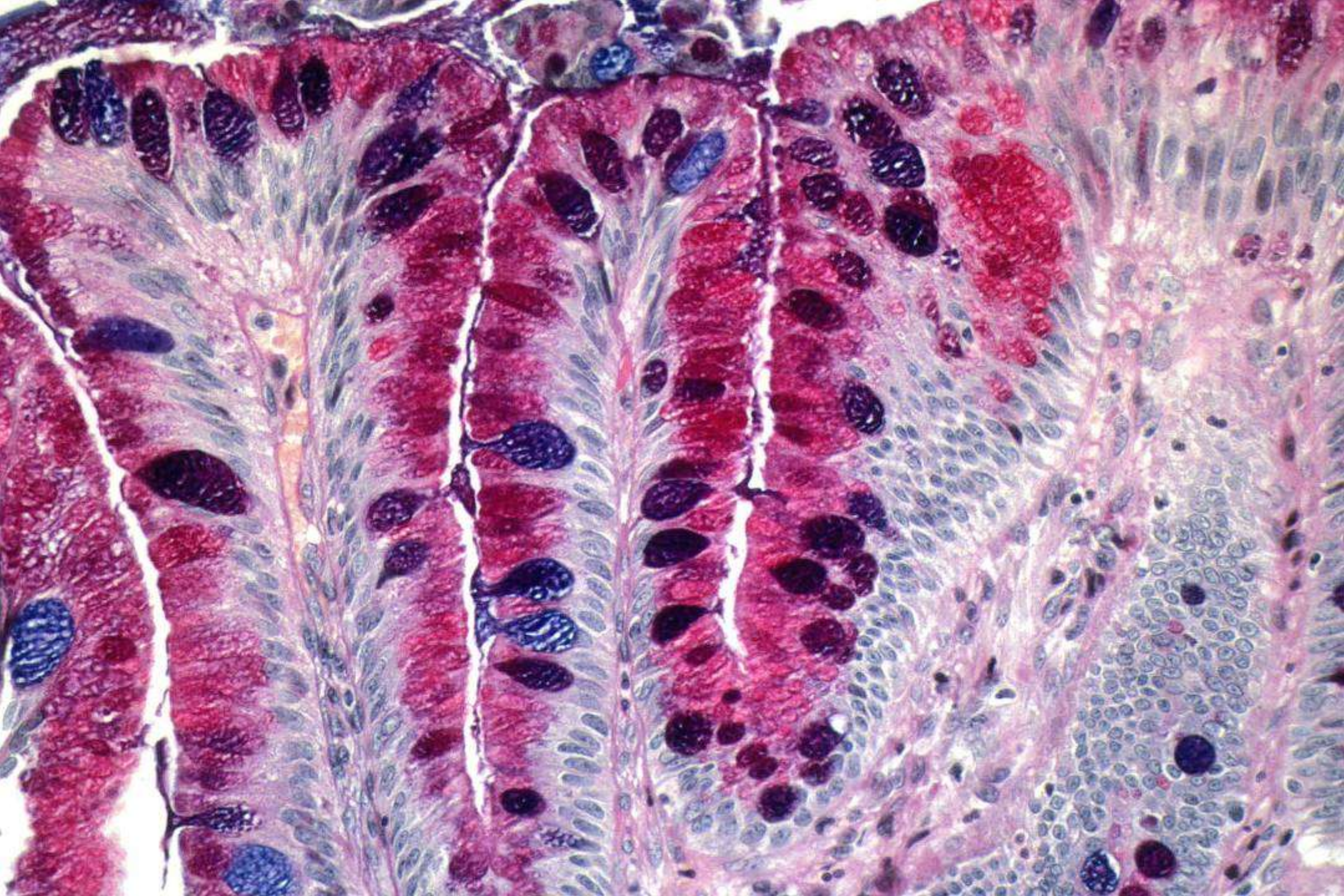
High-grade dysplasia with marked architectural distortion, cannot exclude intramucosal adenocarcinoma, arising in the setting of Barrett's esophagus

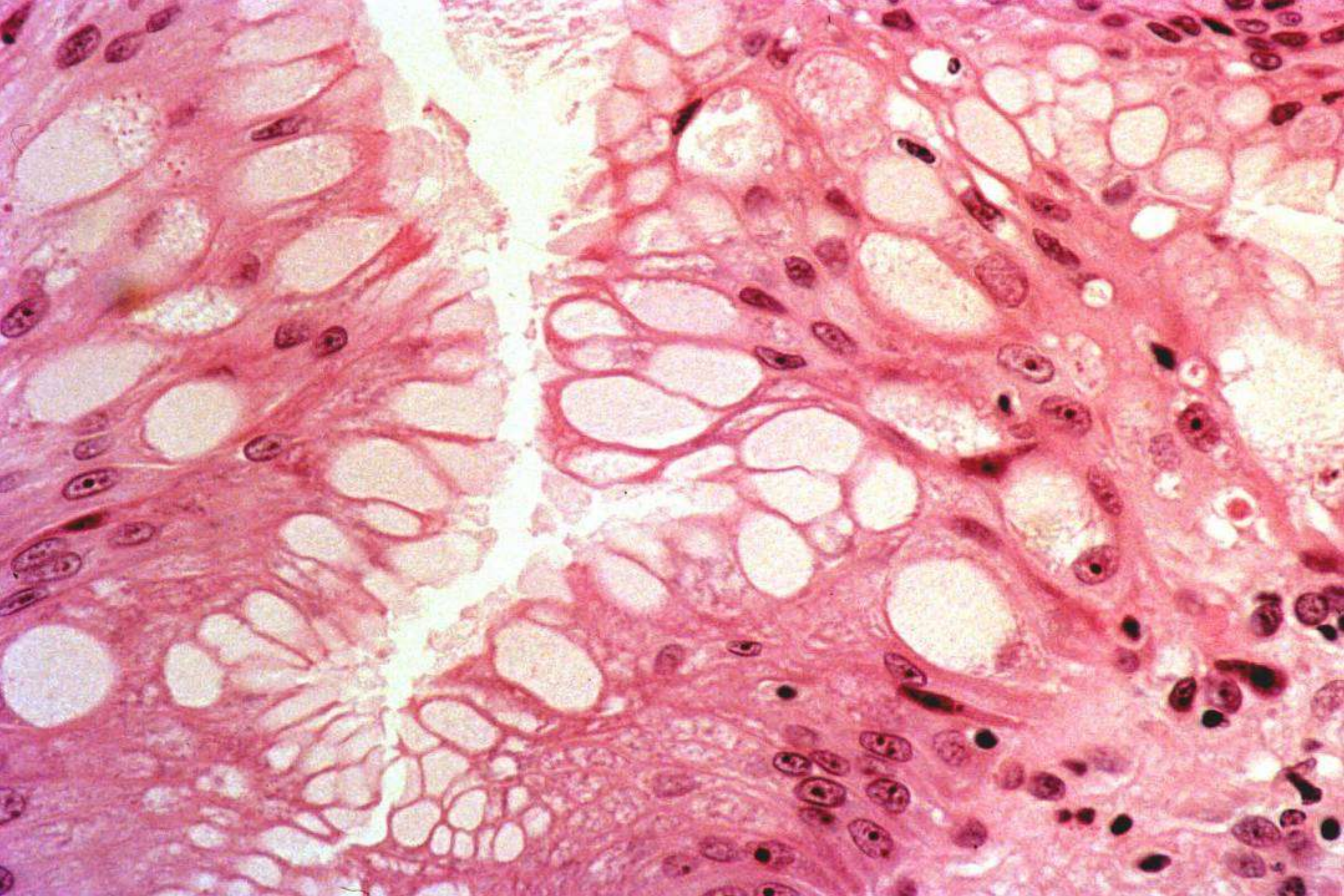
Barrett's Esophagus ACG Definition

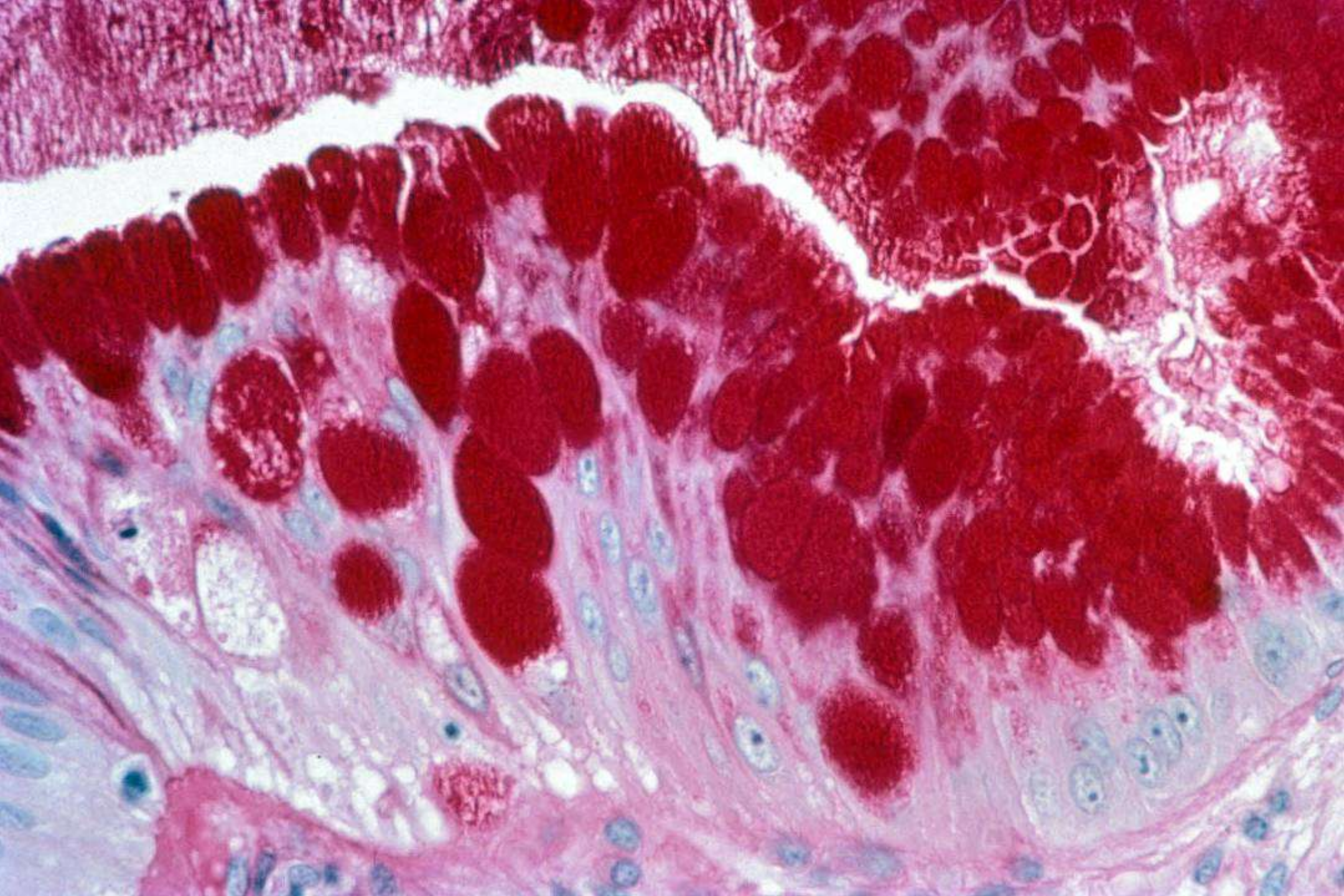
- A change in the esophageal epithelium of any length that can be
  - recognized at endoscopy
  - confirmed to have intestinal metaplasia by biopsy

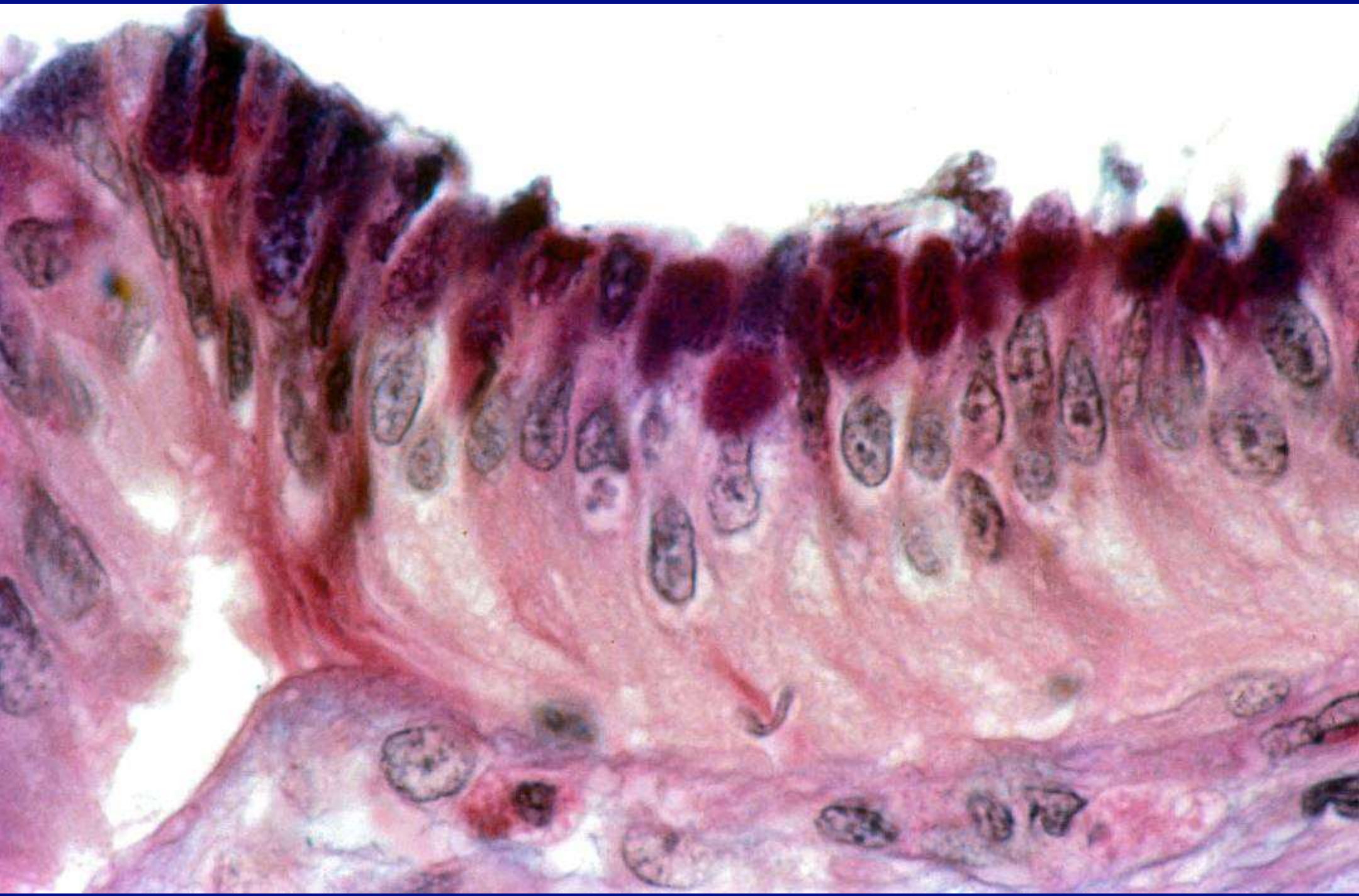
Sampliner RE et al. Am J Gastroenterol 2008











Barrett's Esophagus
Cancer: Risk Factors

Age (elderly)

Sex (males)

Race (Caucasians)

Epithelium type (IM)

Dysplasia

Length

Barrett's Esophagus
Dysplasia: Definition

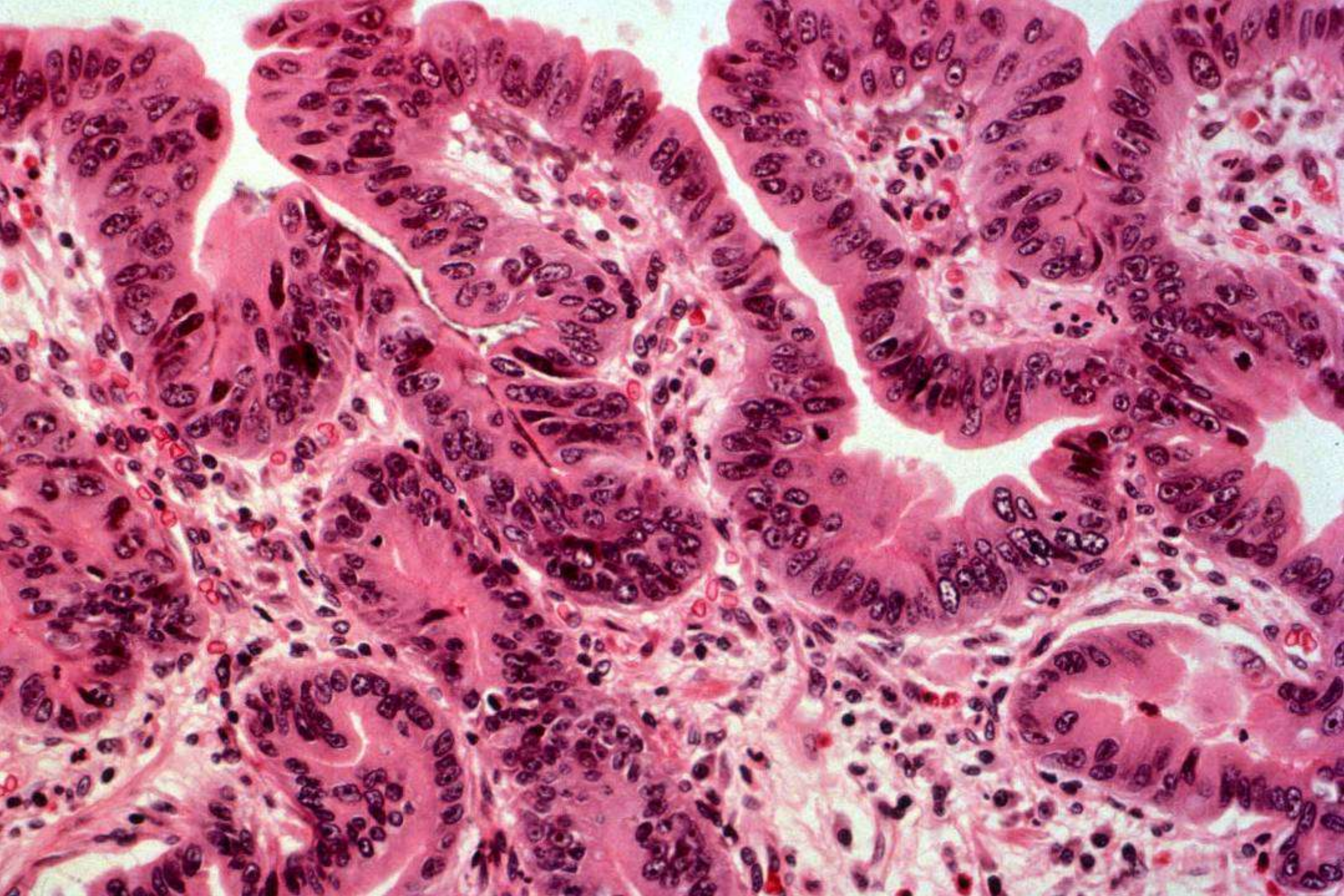
- "Neoplastic epithelium that remains confined within the basement membrane"
    - not synonymous with "atypical"
    - unlikely to spontaneously regress
- Both a marker and the precursor of adenocarcinoma

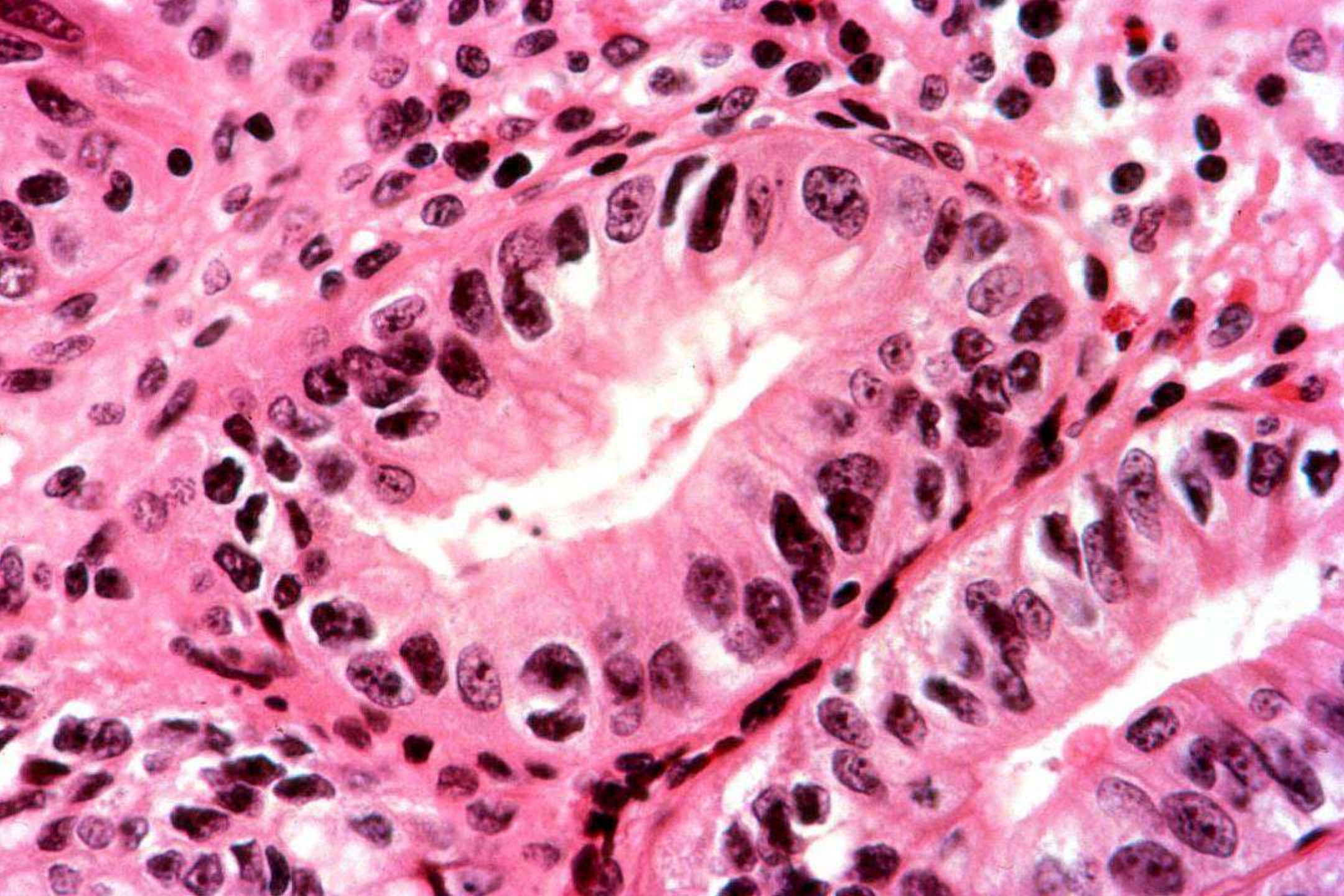
Barrett's Esophagus
Dysplasia

- Negative for dysplasia
- Positive for dysplasia
  - Low-grade
  - High-grade
- Indefinite for dysplasia

Barrett's Esophagus
The Problem With Dysplasia

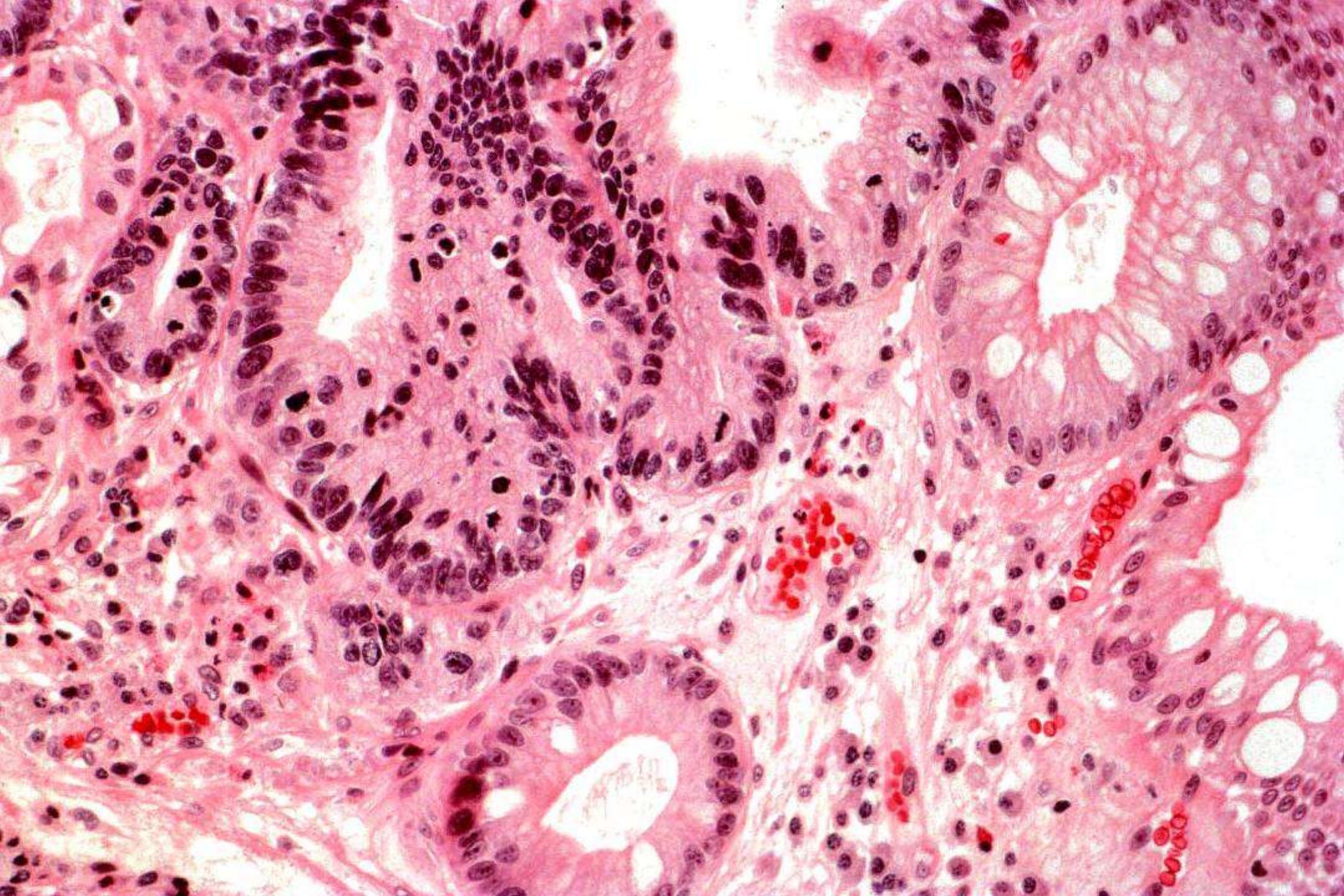
- Sampling error
- Diagnostic interpretation
  - reactive vs dysplastic
  - low-grade vs high-grade
  - high-grade vs intramucosal cancer





Barrett's Esophagus & Dysplasia Rules To Live By

- ***Dysplasia is recognizable at low magnification (hyperchromatic)***
- **"Baseline atypia" of Barrett's mucosa (regenerative zone)**
- **Hold out for cytologic atypia on surface epithelium**
- **Be wary of active inflammation**
- **Don't use "indefinite for dysplasia" as a crutch**



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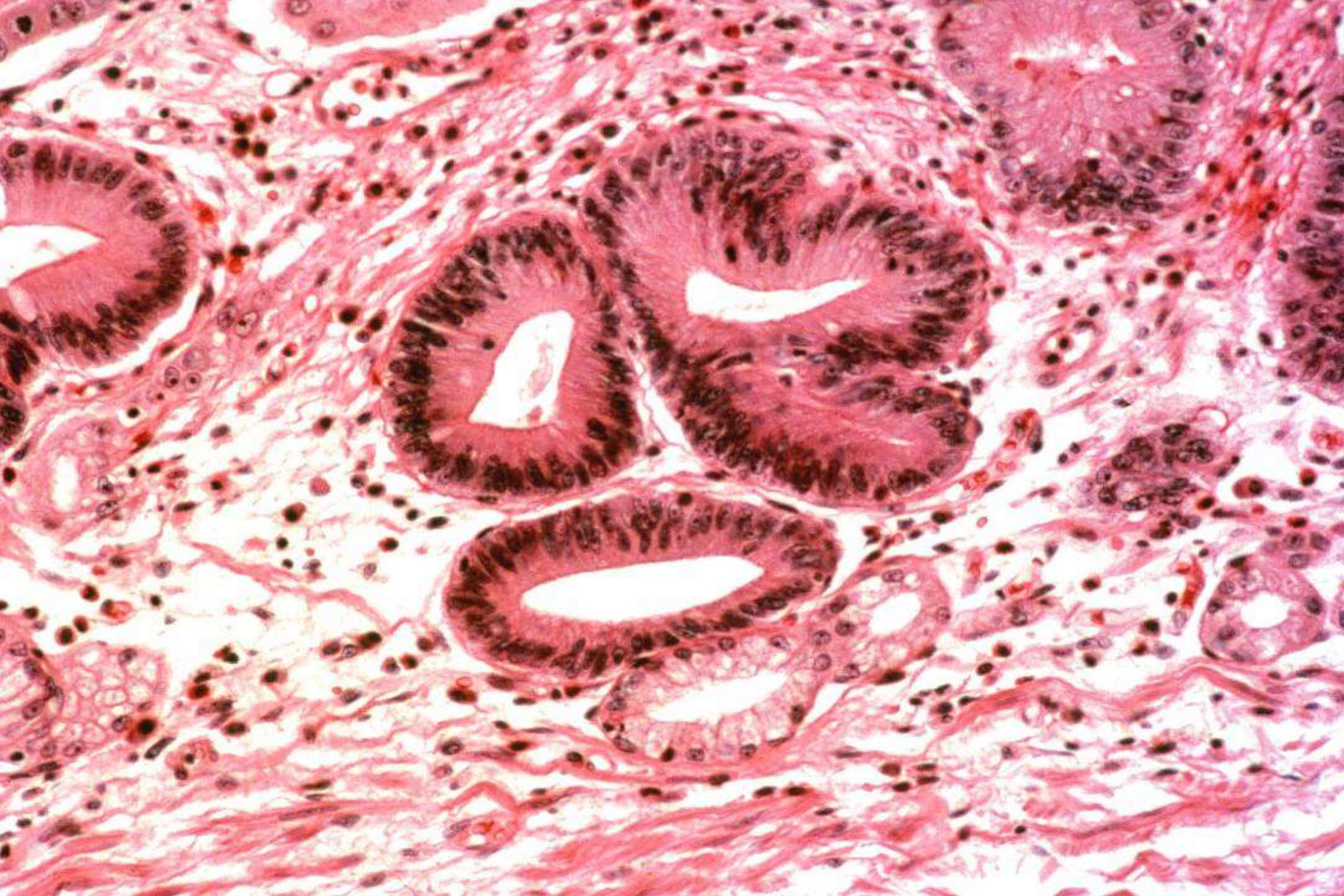

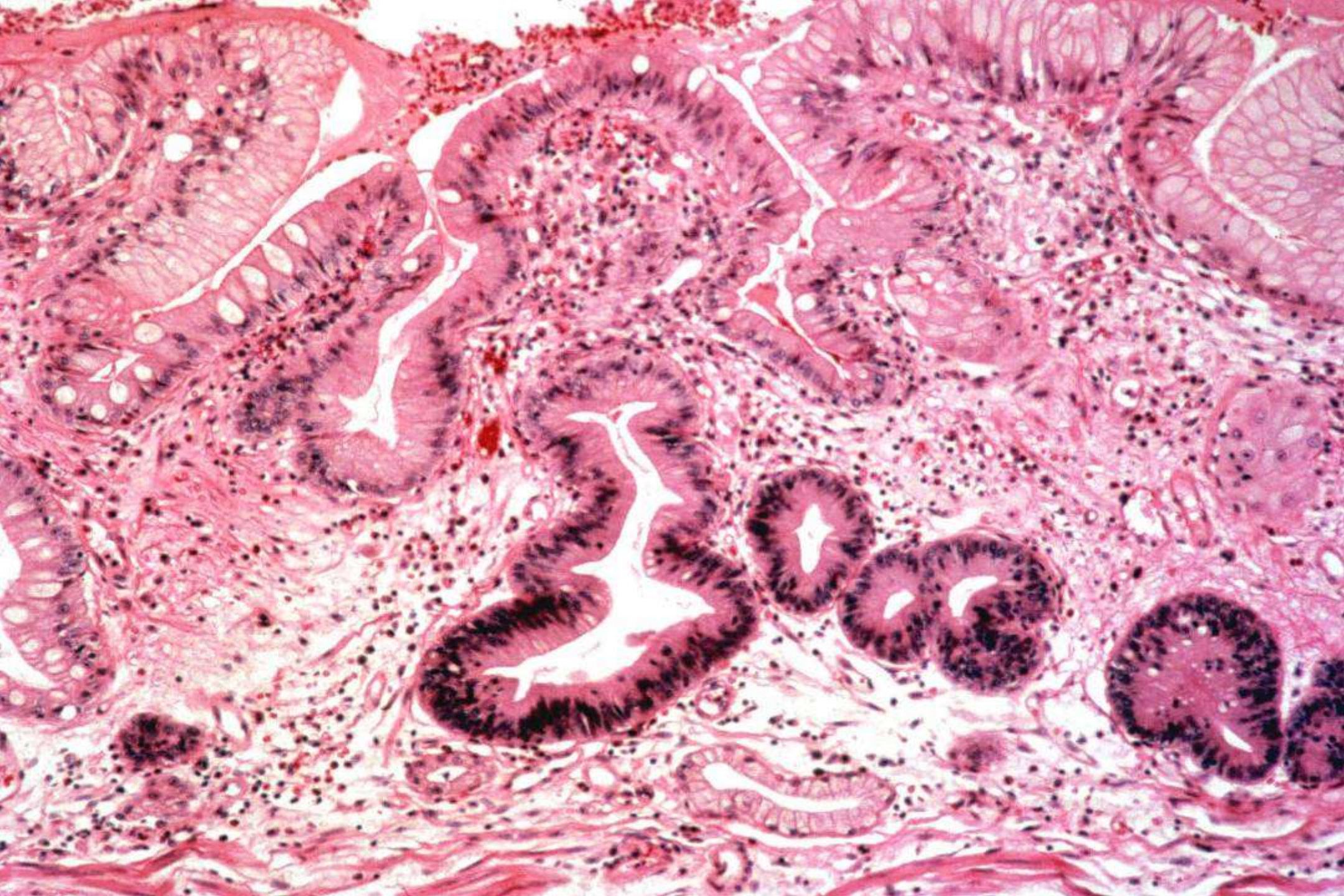

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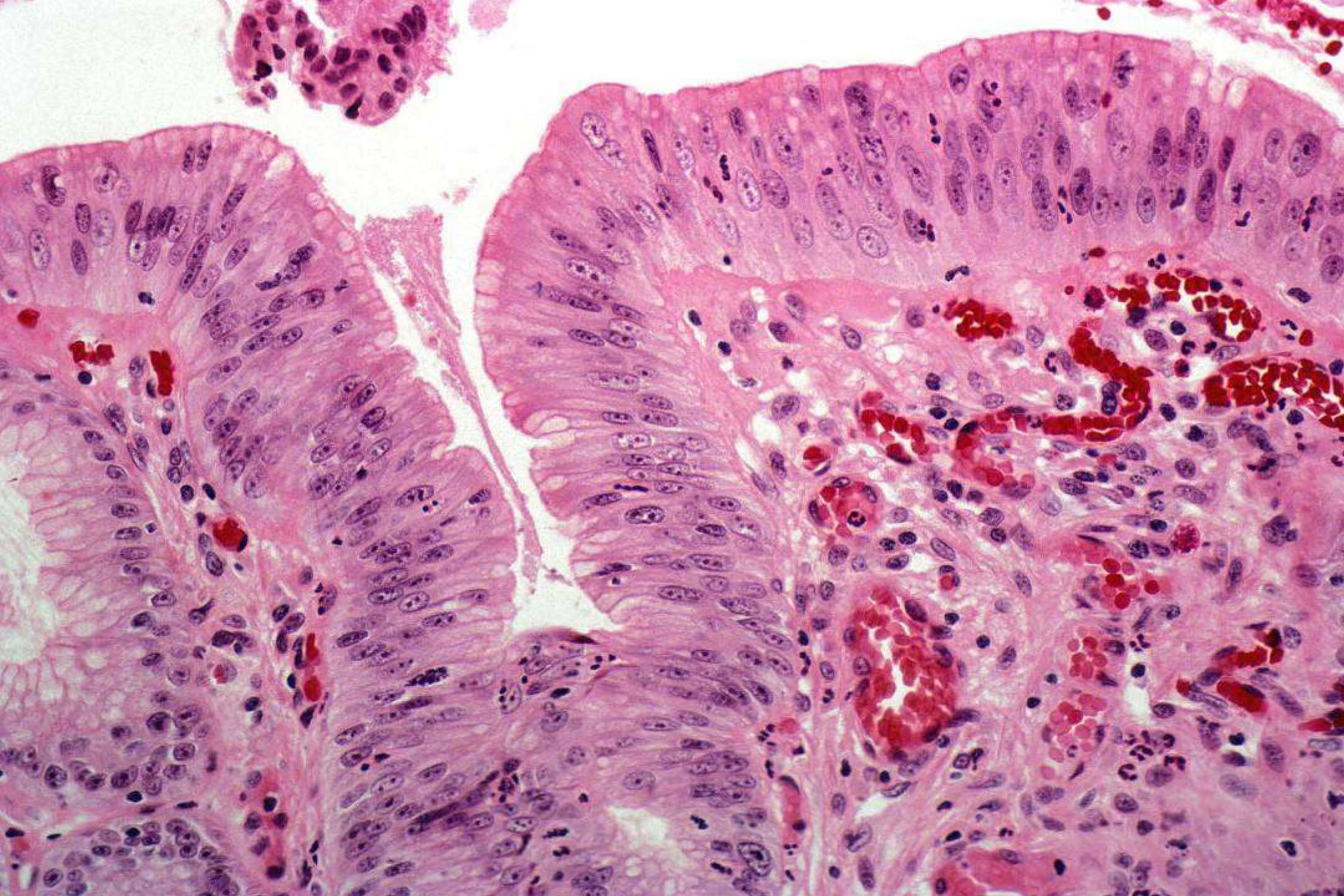
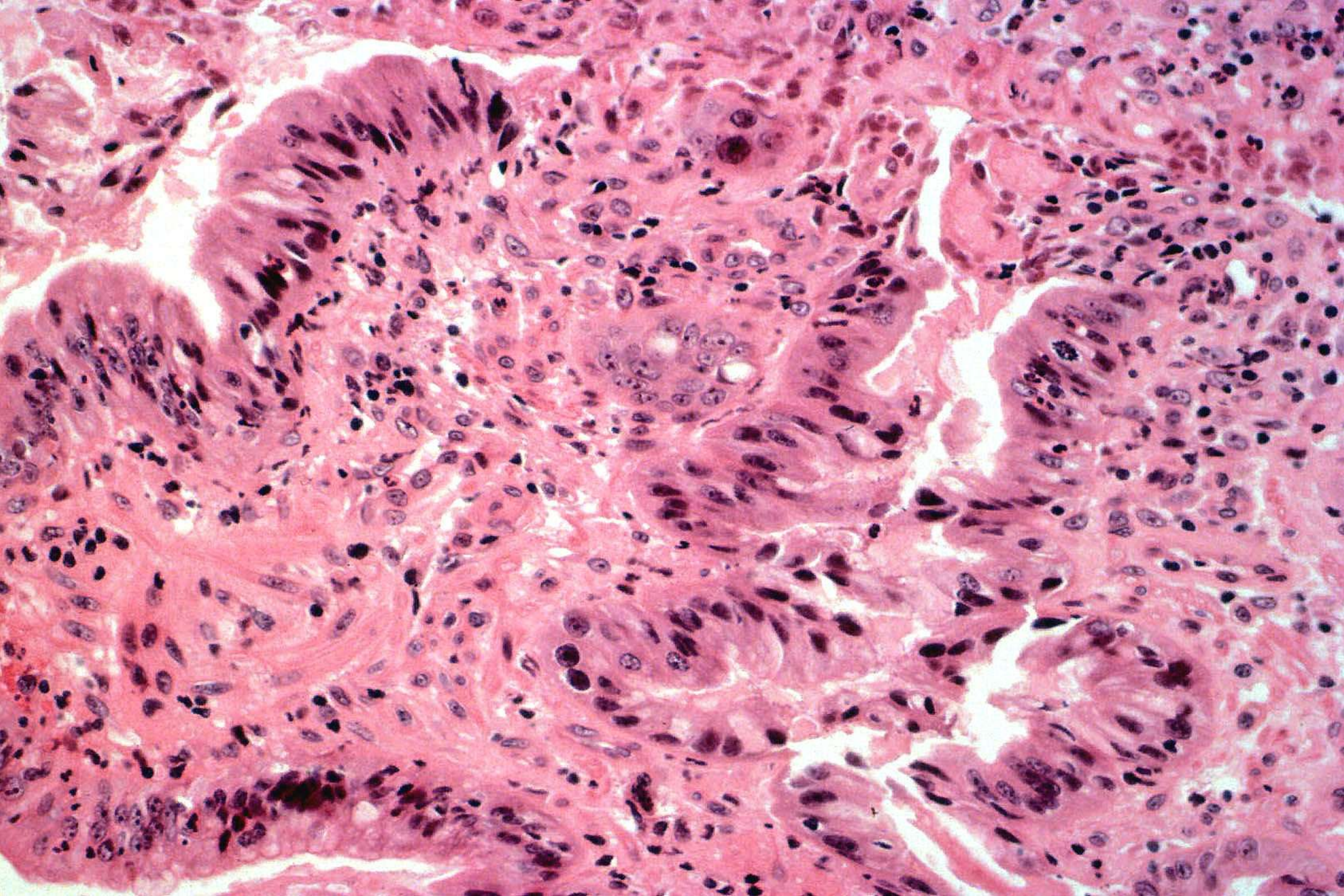
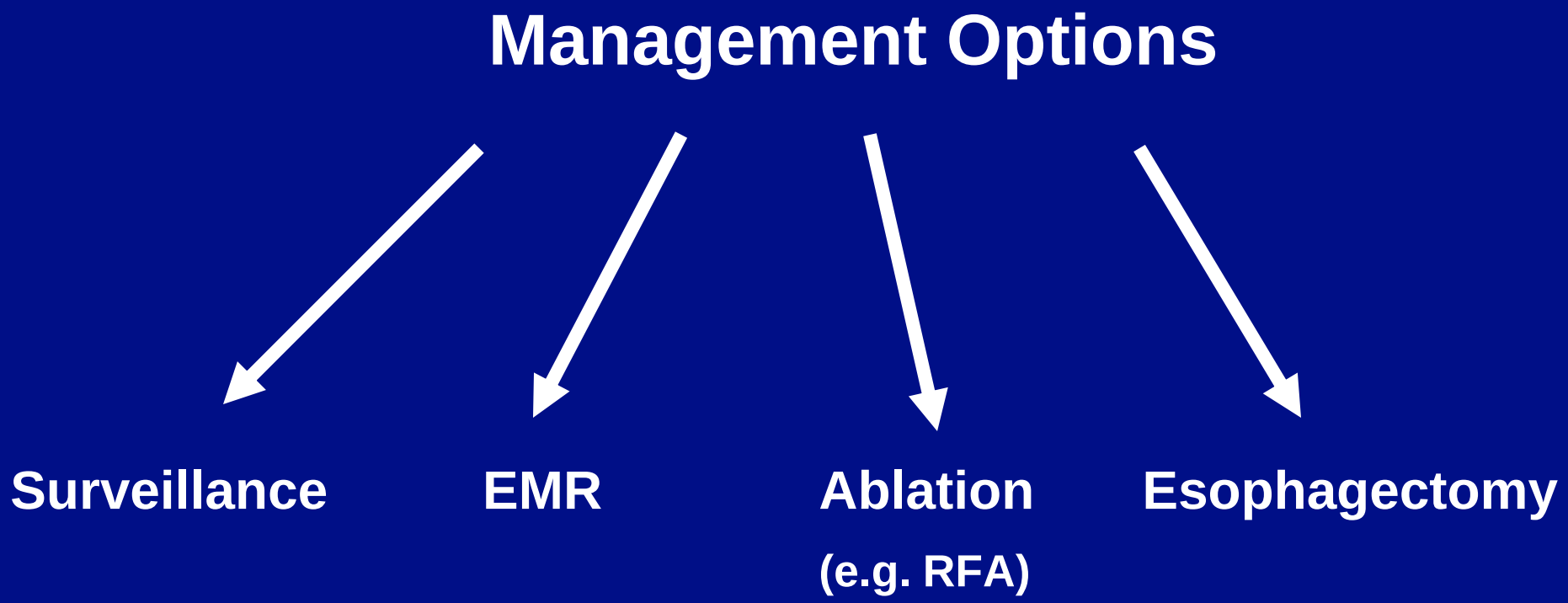
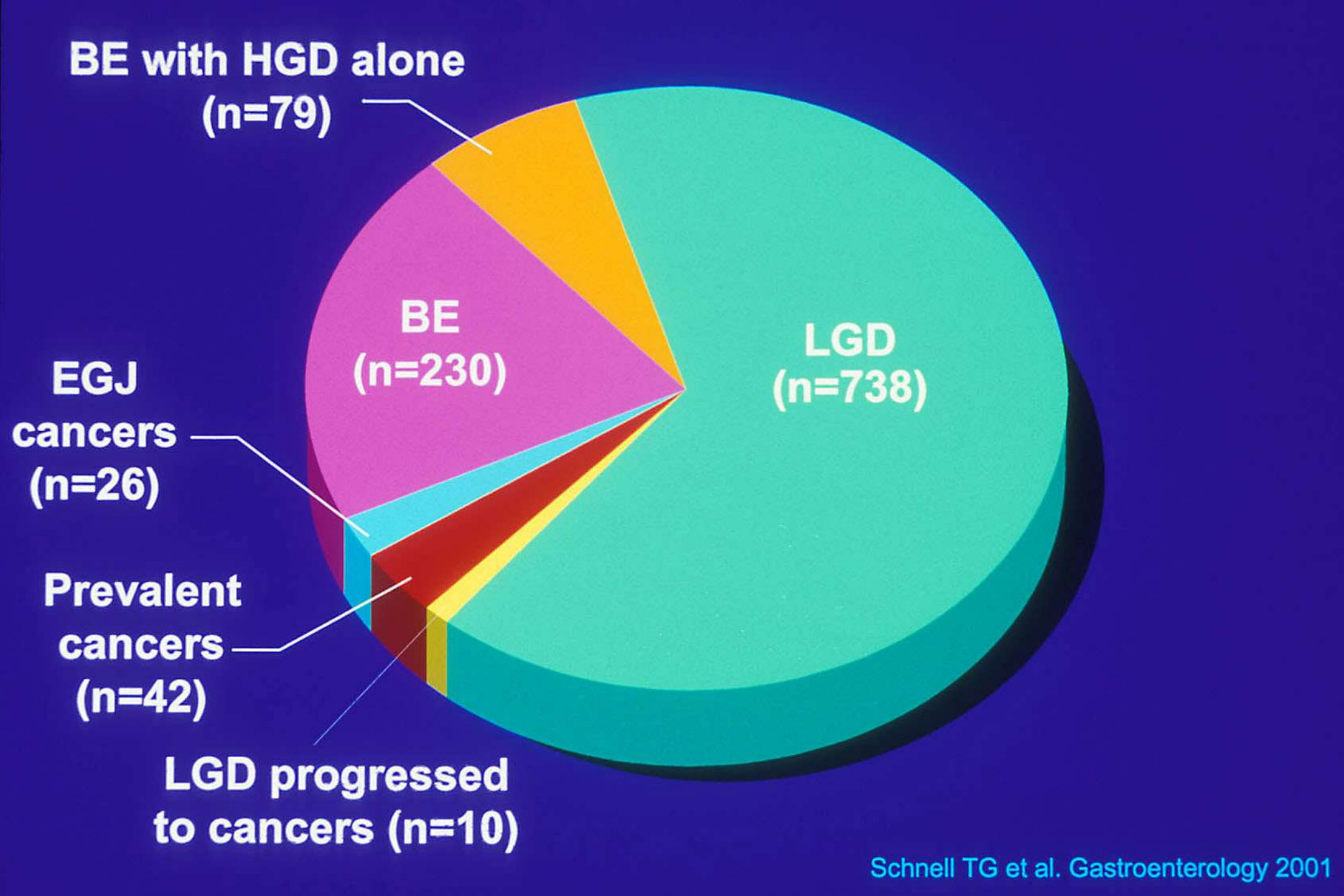




High-Grade Dysplasia





Schnell TG et al. Gastroenterology 2001

High-Grade Dysplasia Natural History

1099 patients

79 with HGD without evidence of cancer
(34 prevalent/45 incident)

4 with cancer found within one year

75 without detectable cancer within one year

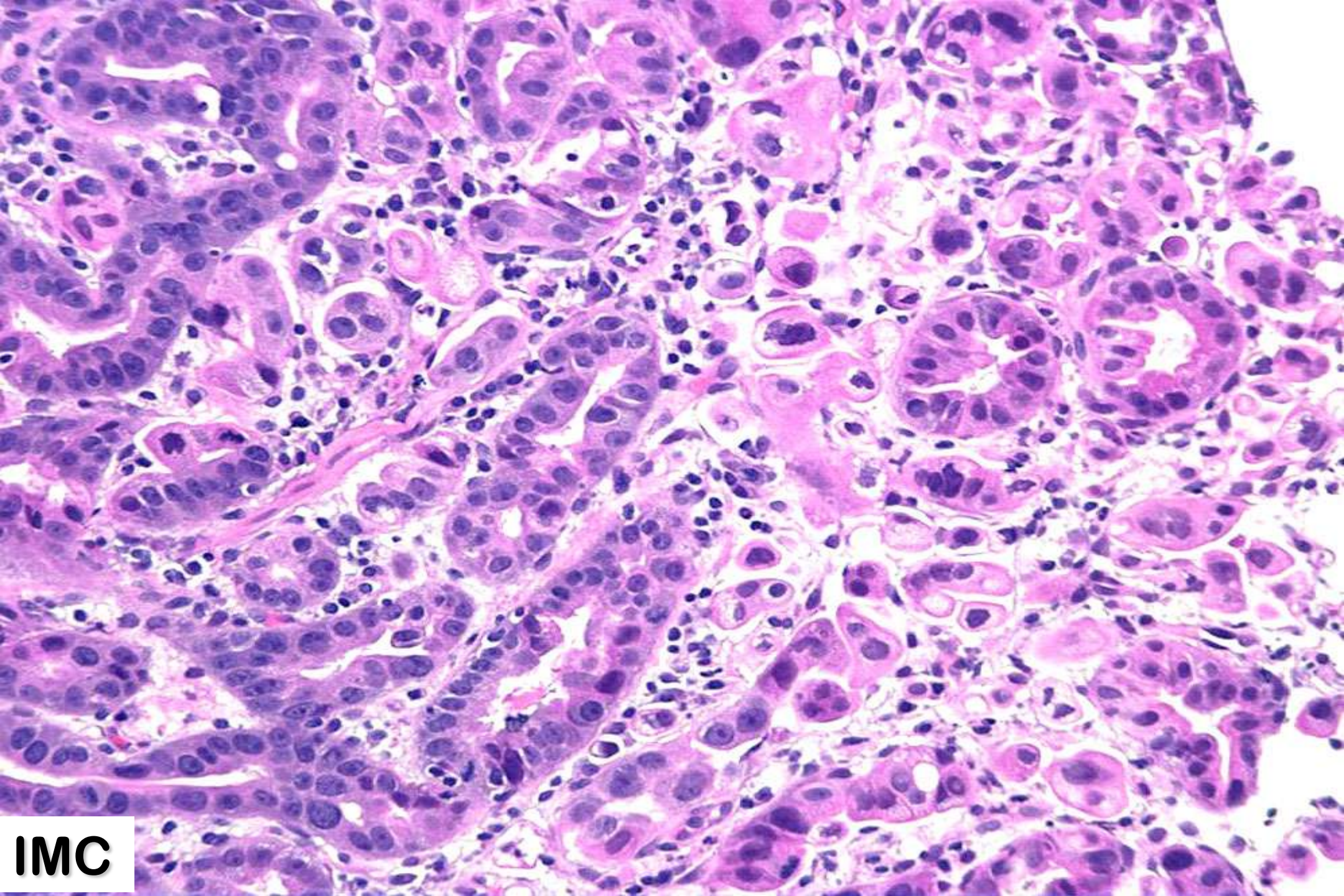
12/75 (16%) developed cancer
(mean surveillance: 7.3 yrs)

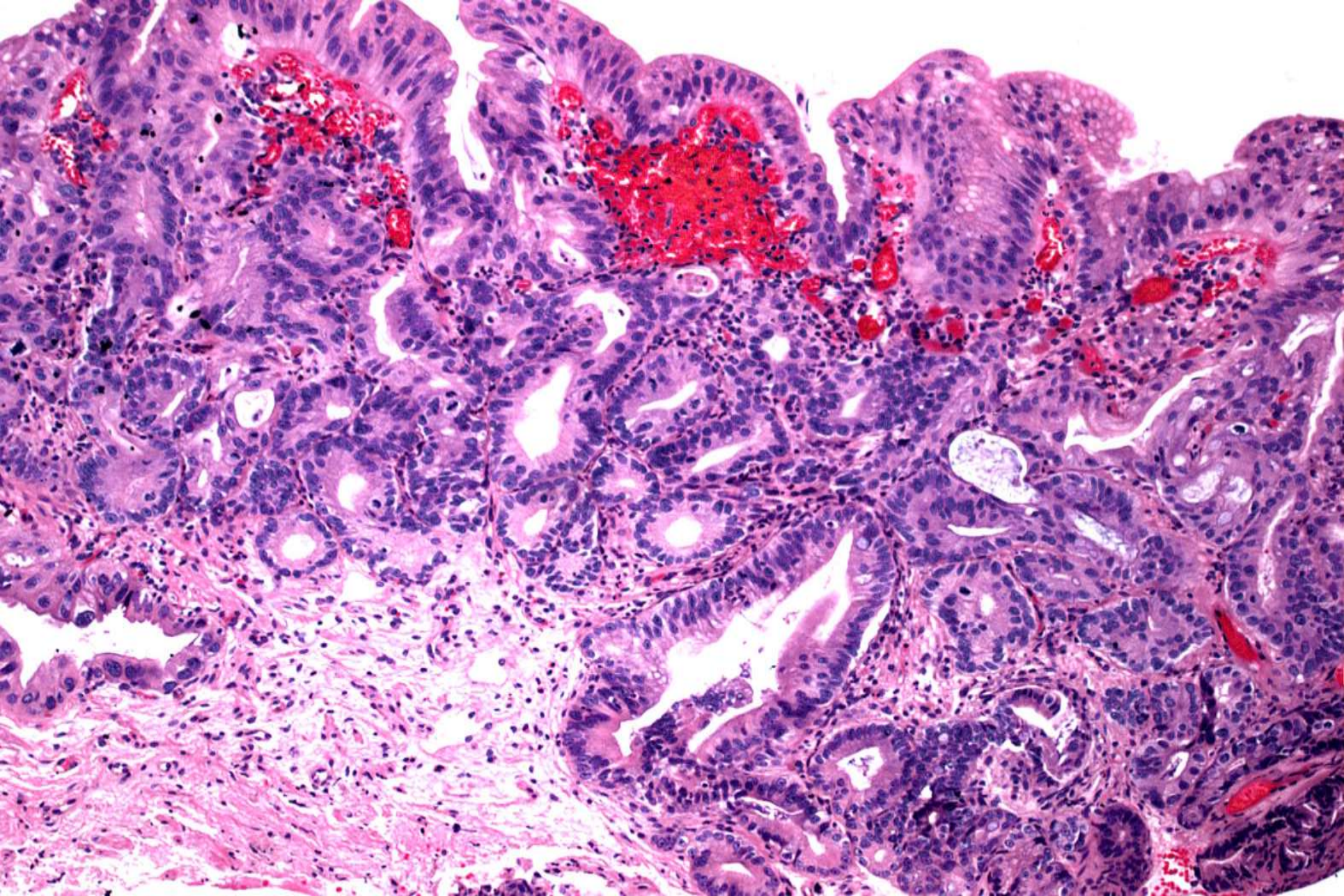
Schnell TG et al. Gastroenterology 2001

High-Grade Dysplasia Conclusions

- Patients with HGD without apparent cancer can be safely followed with frequent endoscopic surveillance with biopsies
    - Provided that 1 year of intensive endoscopic searching (“the hunt”) fails to detect cancer
- Reserve esophagectomy for those patients with documented cancer

Schnell TG et al. Gastroenterology 2001


IMC



Results

Diagnosis	Kappa	P-value	95% CI	Interobserver agreement
HGD	0.47	<0.001	0.42 – 0.50	Moderate
HGD/MAD	0.21	<0.001	0.17 – 0.25	Fair
IMC	0.30	<0.001	0.27 – 0.35	Fair
SMC	0.14	<0.001	0.10 – 0.18	Poor

Downs-Kelly E et al. AJG 2008

Cleveland Clinic

Every life deserves world class care.