

Deceptive Soft Tissue Tumors

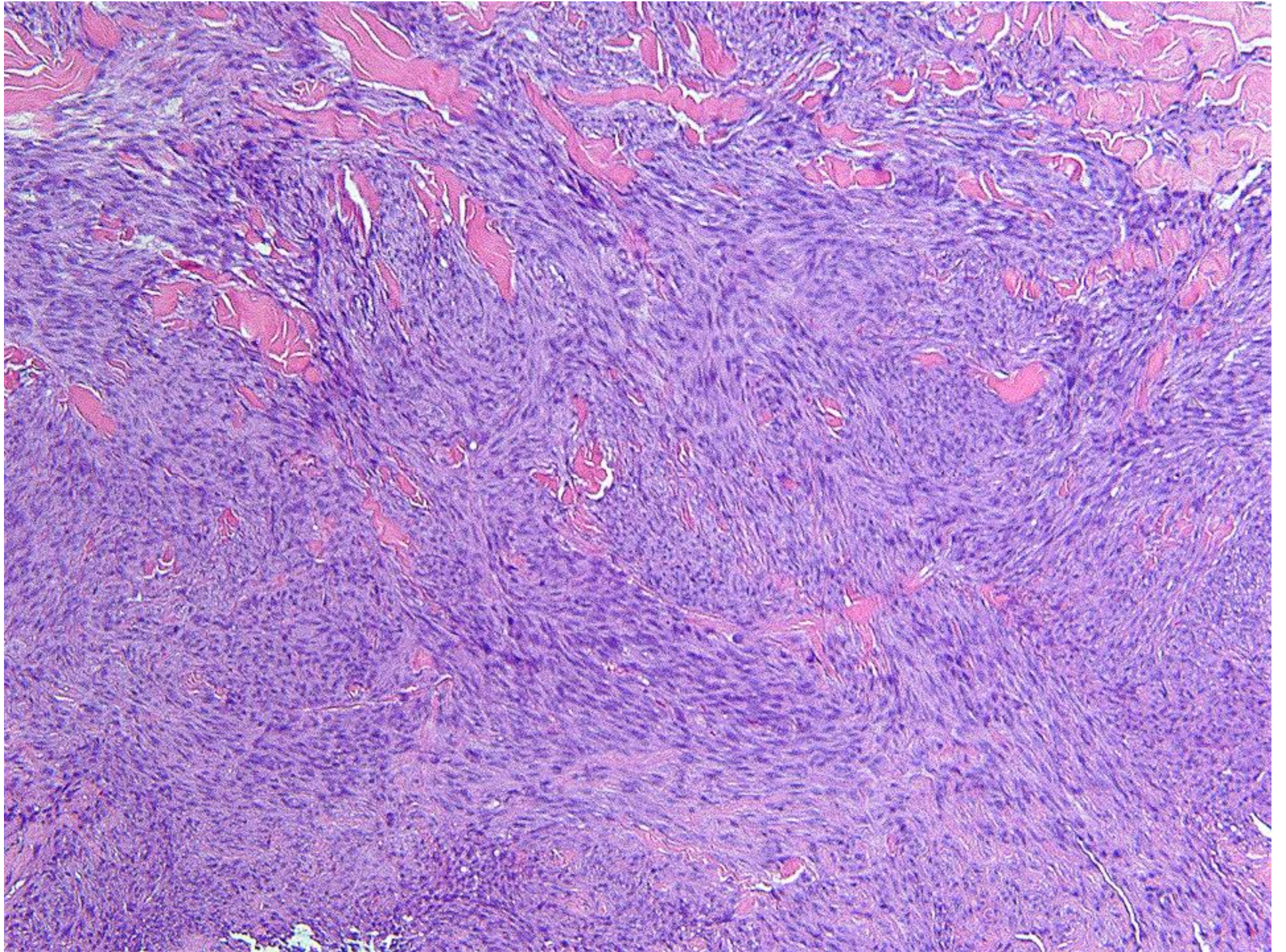
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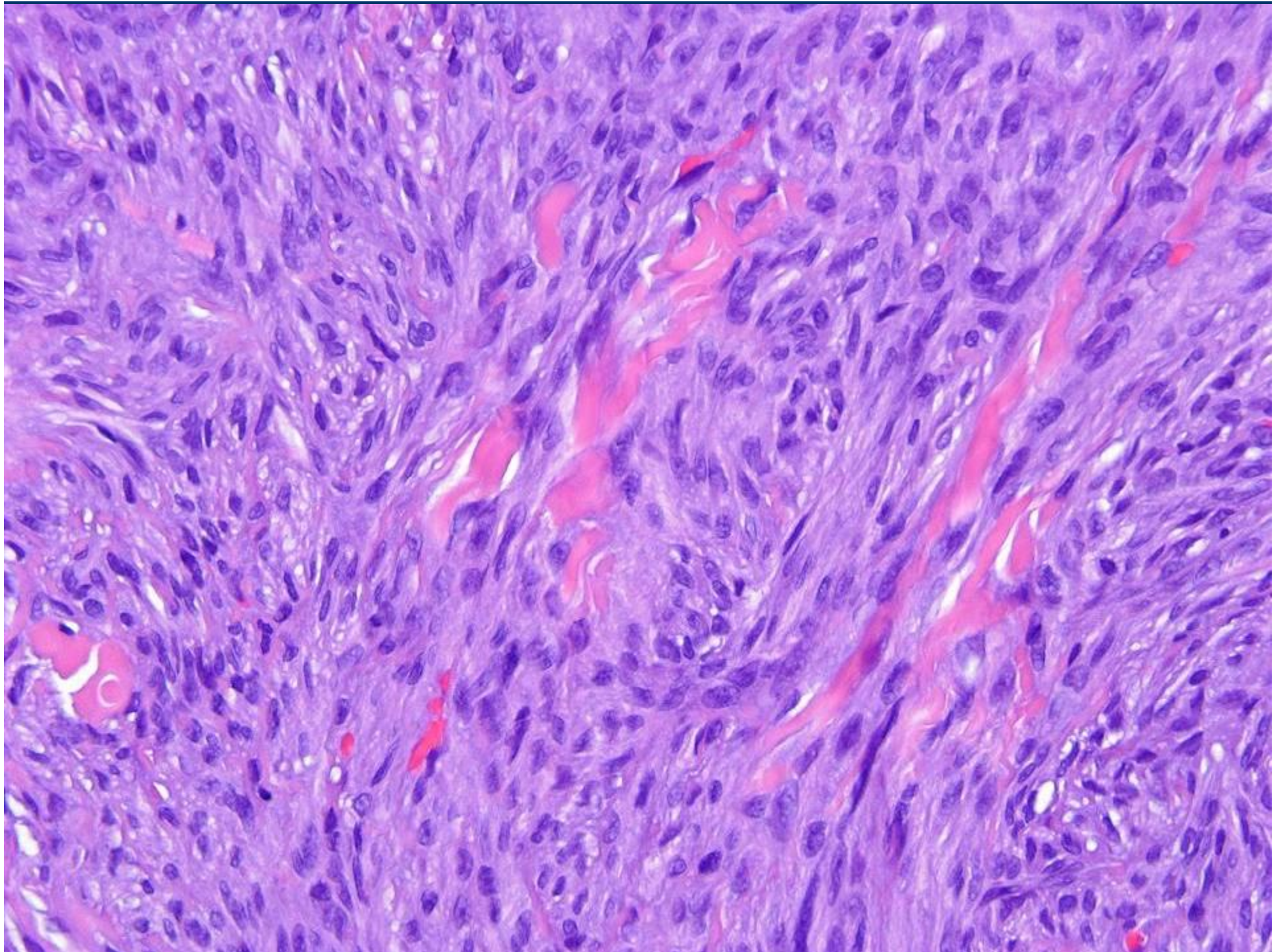


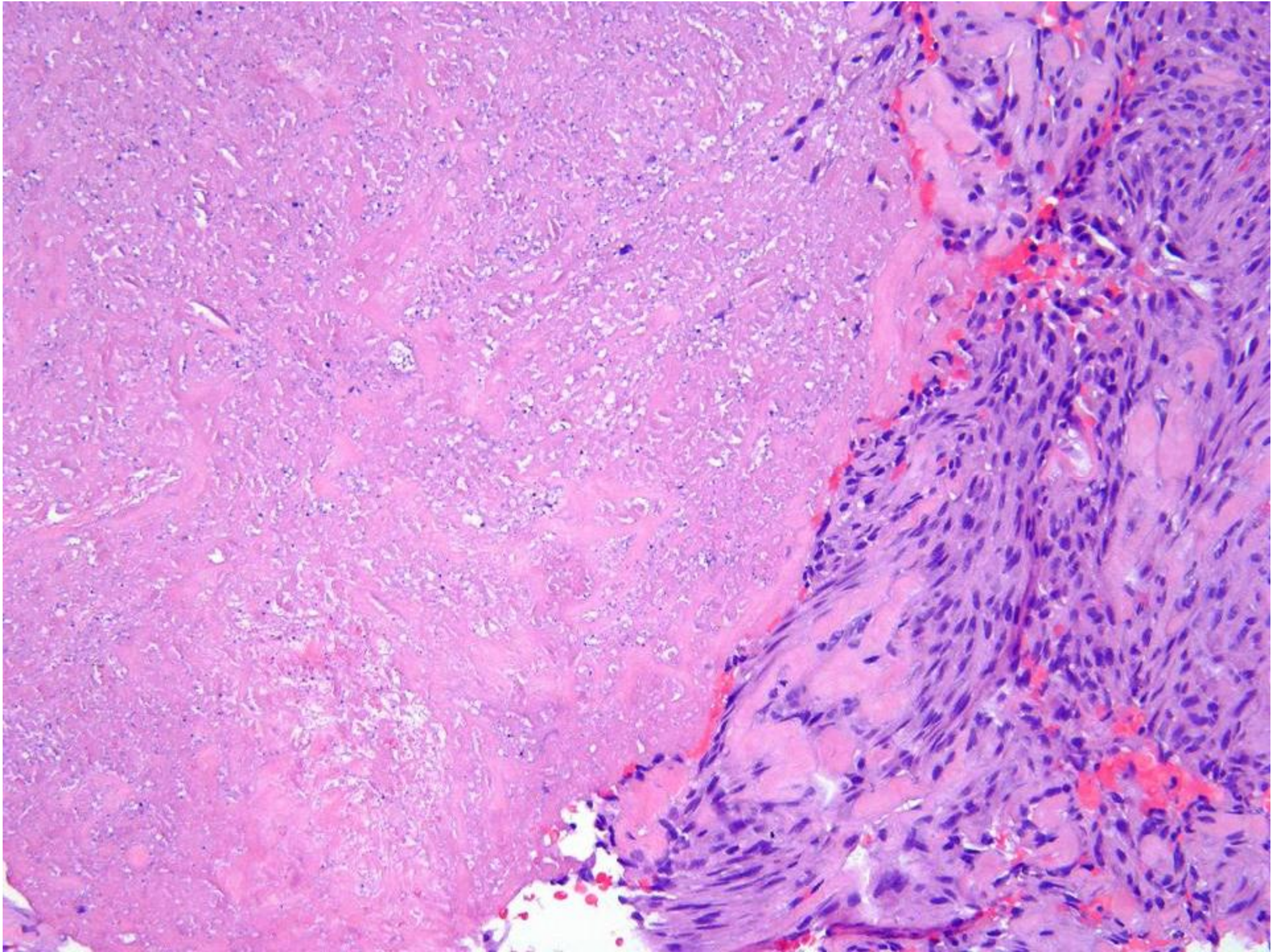
The Good, the Bad and the Ugly of Cutaneous Soft Tissue Tumors

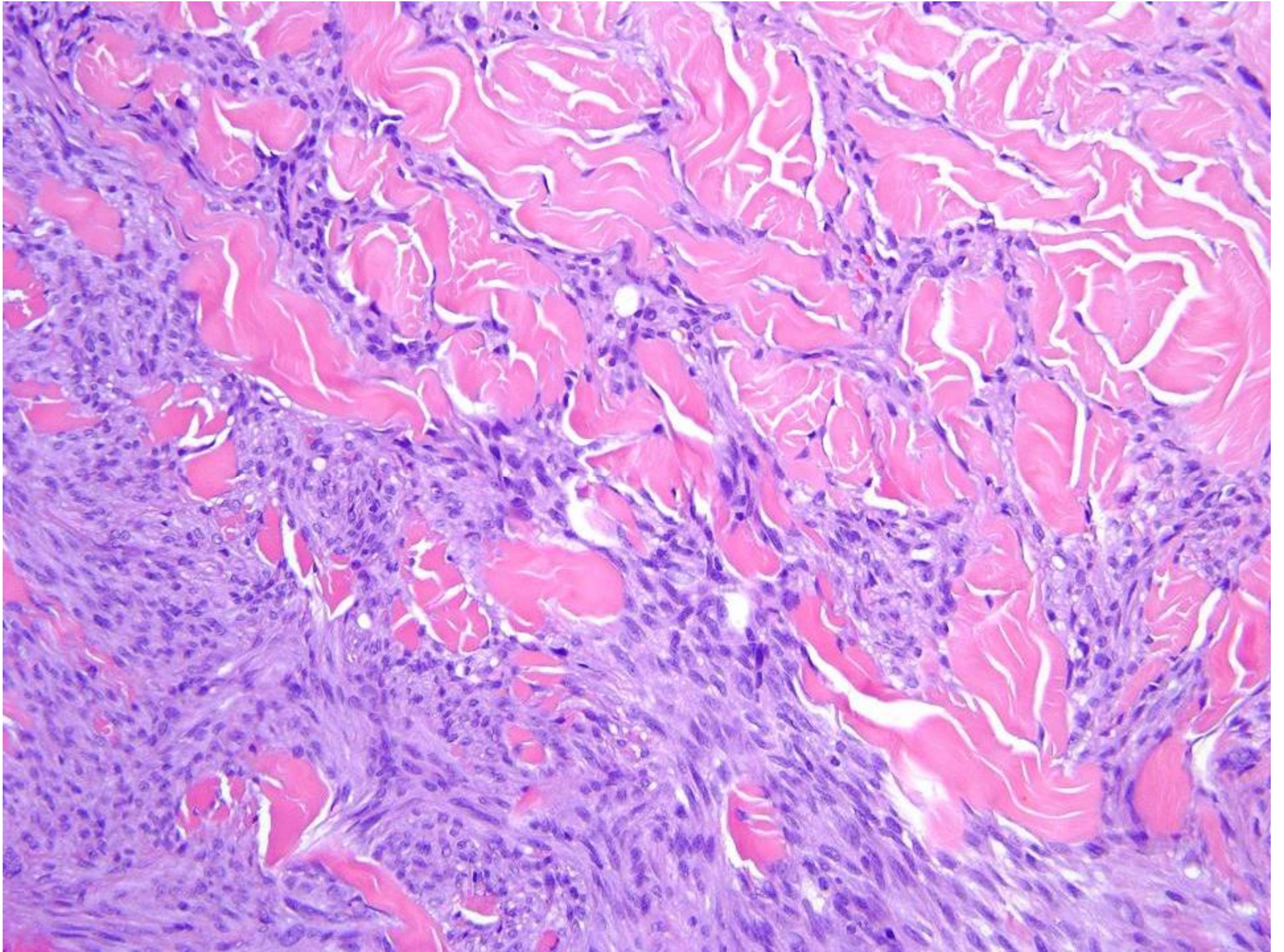
A 25-year-old man presented with a non-pigmented, small nodule on the posterior neck











Diagnosis?

Cellular Fibrous Histiocytoma

Variant of Dermatofibroma

The Good



Things that look bad but aren't

Cellular Fibrous Histiocytoma

- Variant of benign fibrous histiocytoma (dermatofibroma family)
- Clinical features
 - Most frequently presents on proximal extremities and head and neck area
 - Clinical differential diagnosis: basal cell carcinoma, epidermoid cyst, pyogenic granuloma, dermatofibroma

Cellular Fibrous Histiocytoma

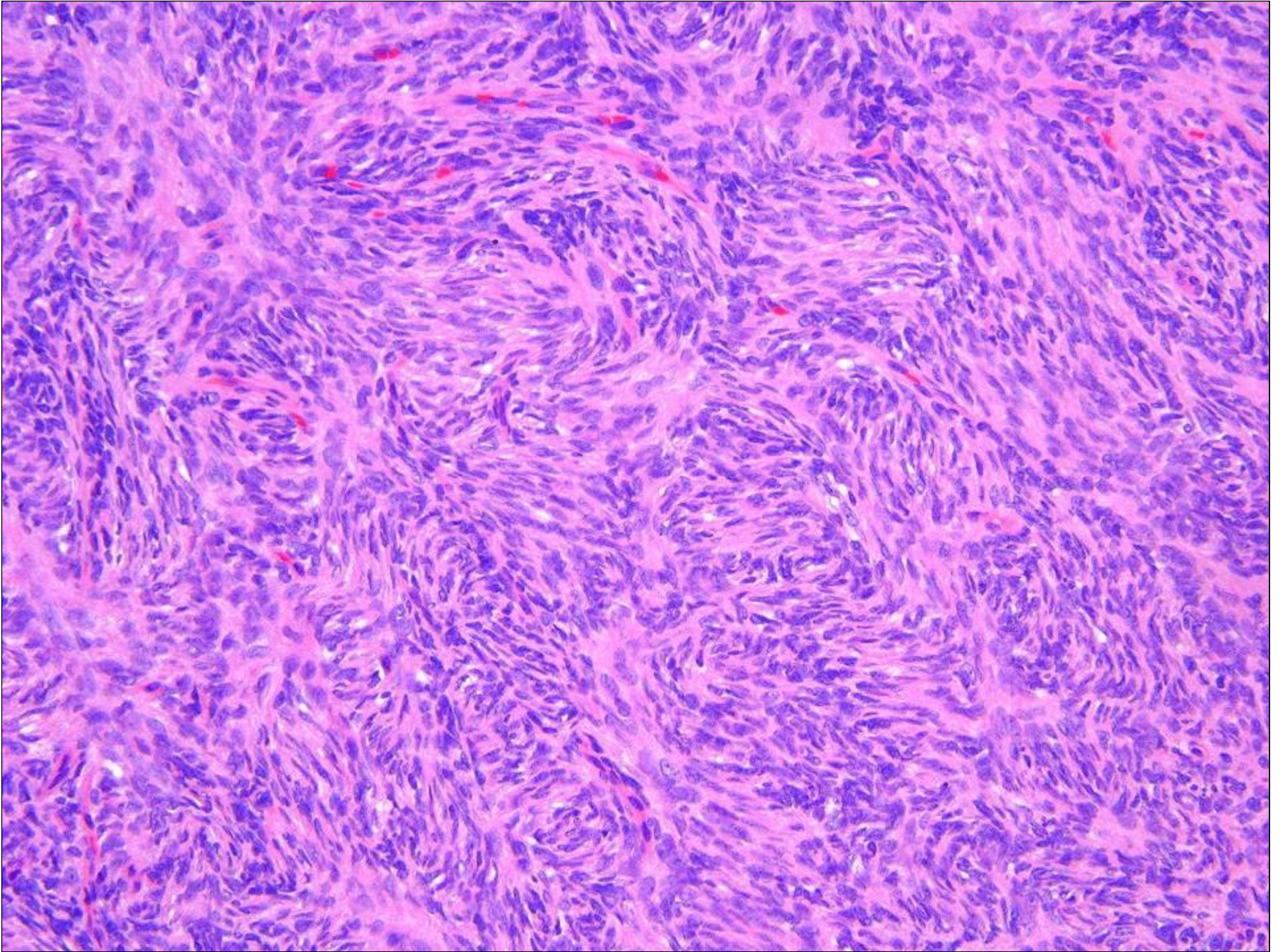
- Composed of lightly eosinophilic to amphophilic spindled cells with fascicular to storiform pattern
- Monomorphous, without siderophages and foam cells seen in ordinary BFH
- Few admixed inflammatory cells
- Necrosis in 10%

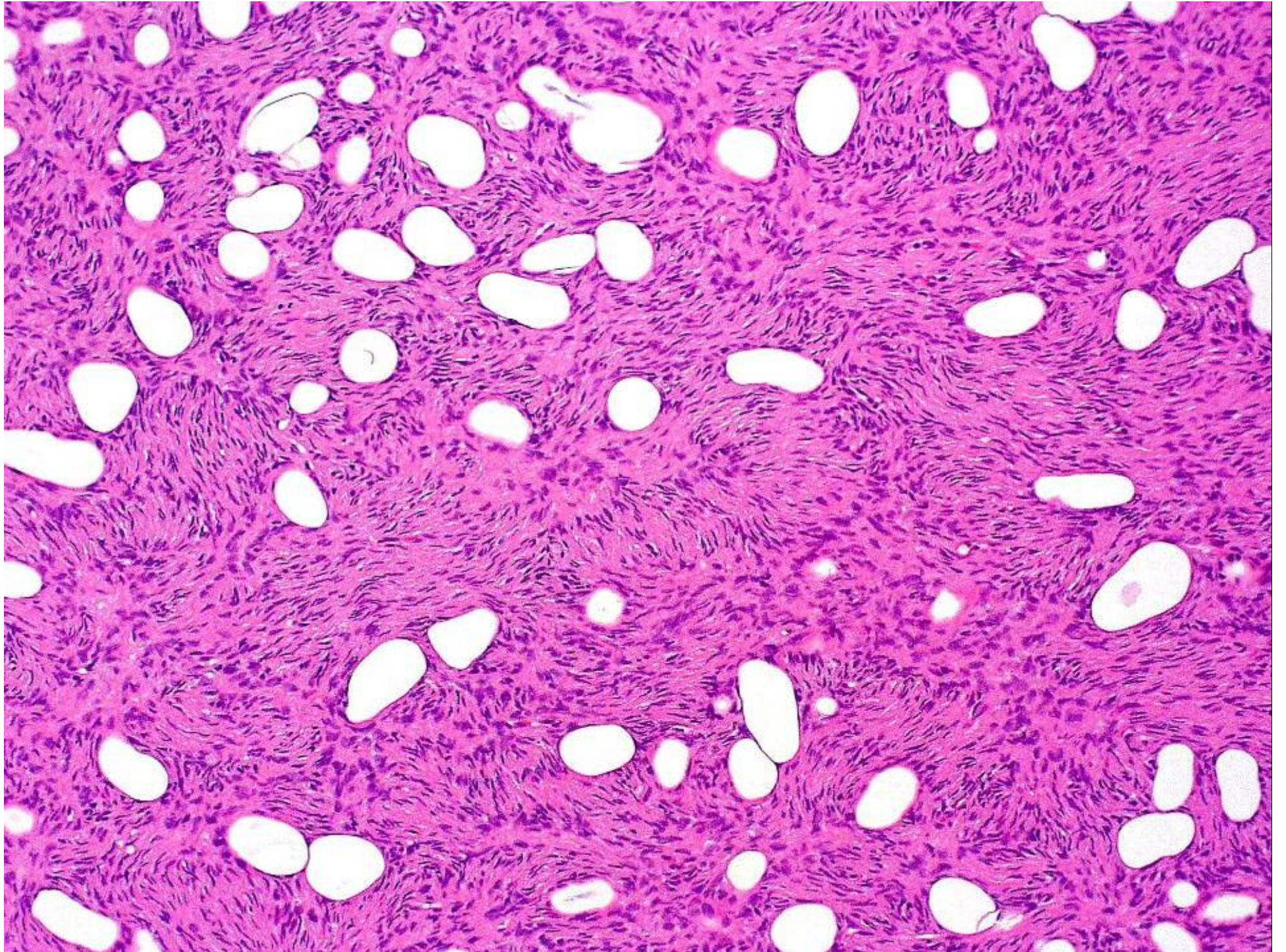
Cellular Fibrous Histiocytoma

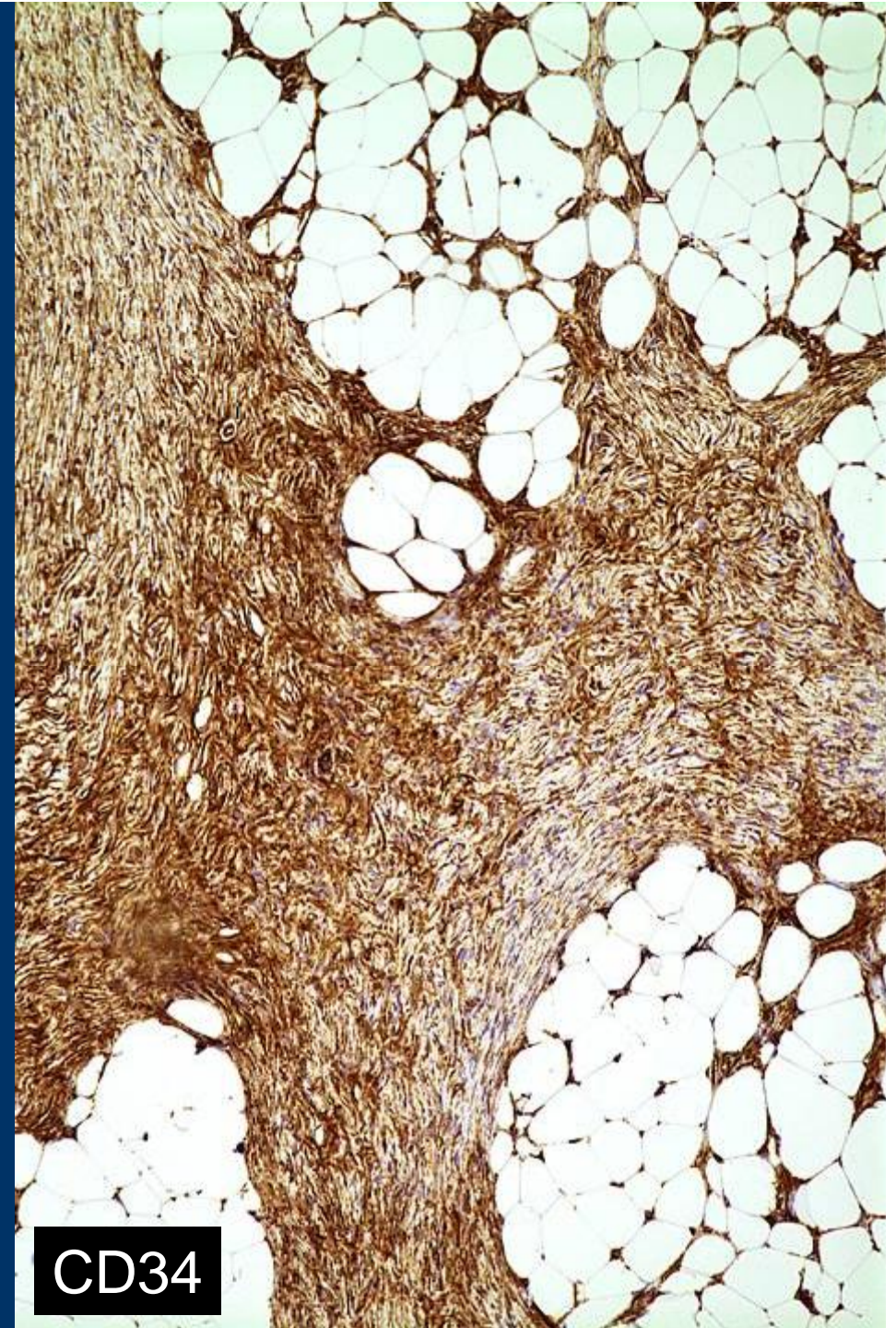
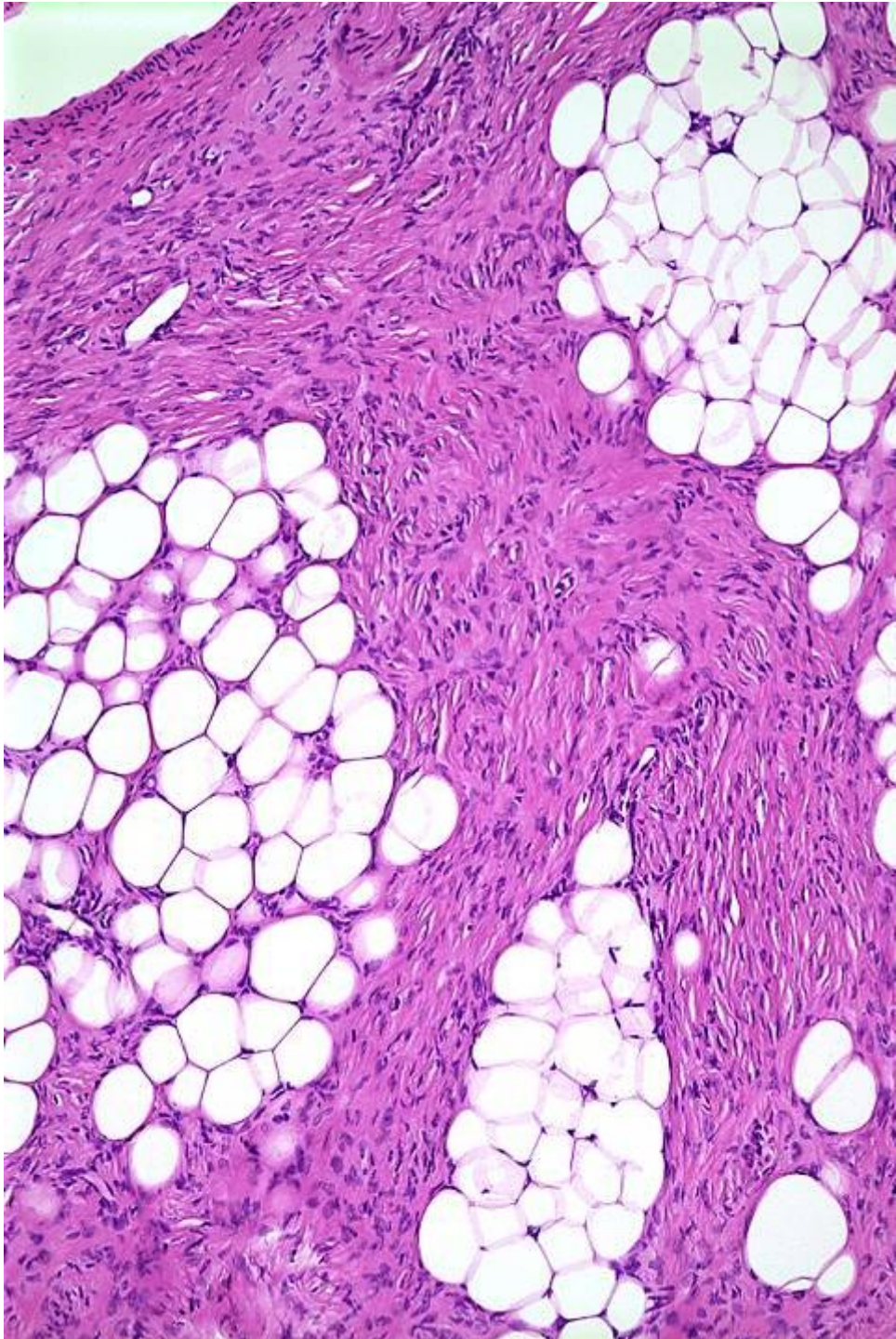
- Mitotic figures frequent
- May show limited involvement of subcutaneous fat
- Recognition of features of ordinary BFH essential
 - Overall low-power circumscription
 - Variable epidermal hyperplasia
 - Peripheral “collagen trapping”

Differential Diagnosis

- **Dermatofibrosarcoma protuberans**
- Nodular fasciitis
- Spindled variant of epithelioid sarcoma
- Leiomyosarcoma

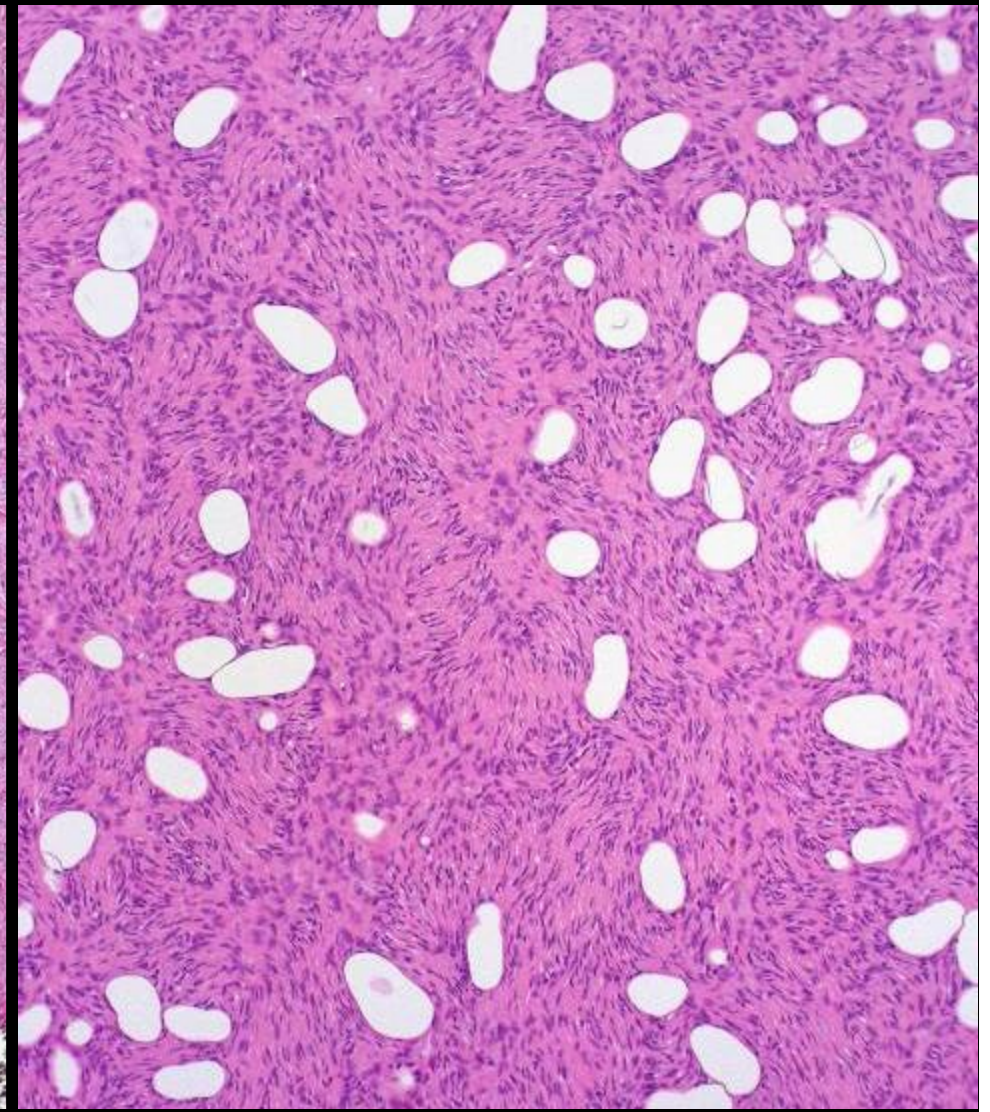
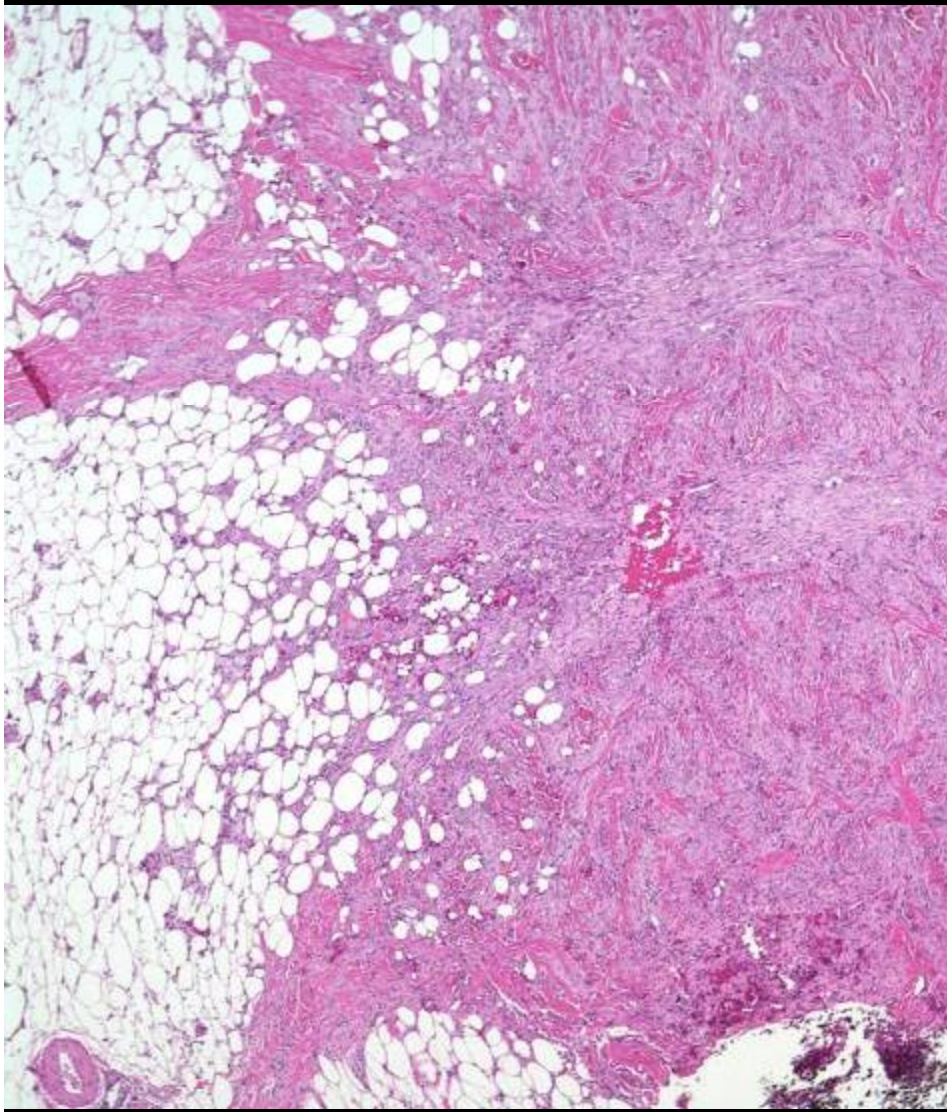


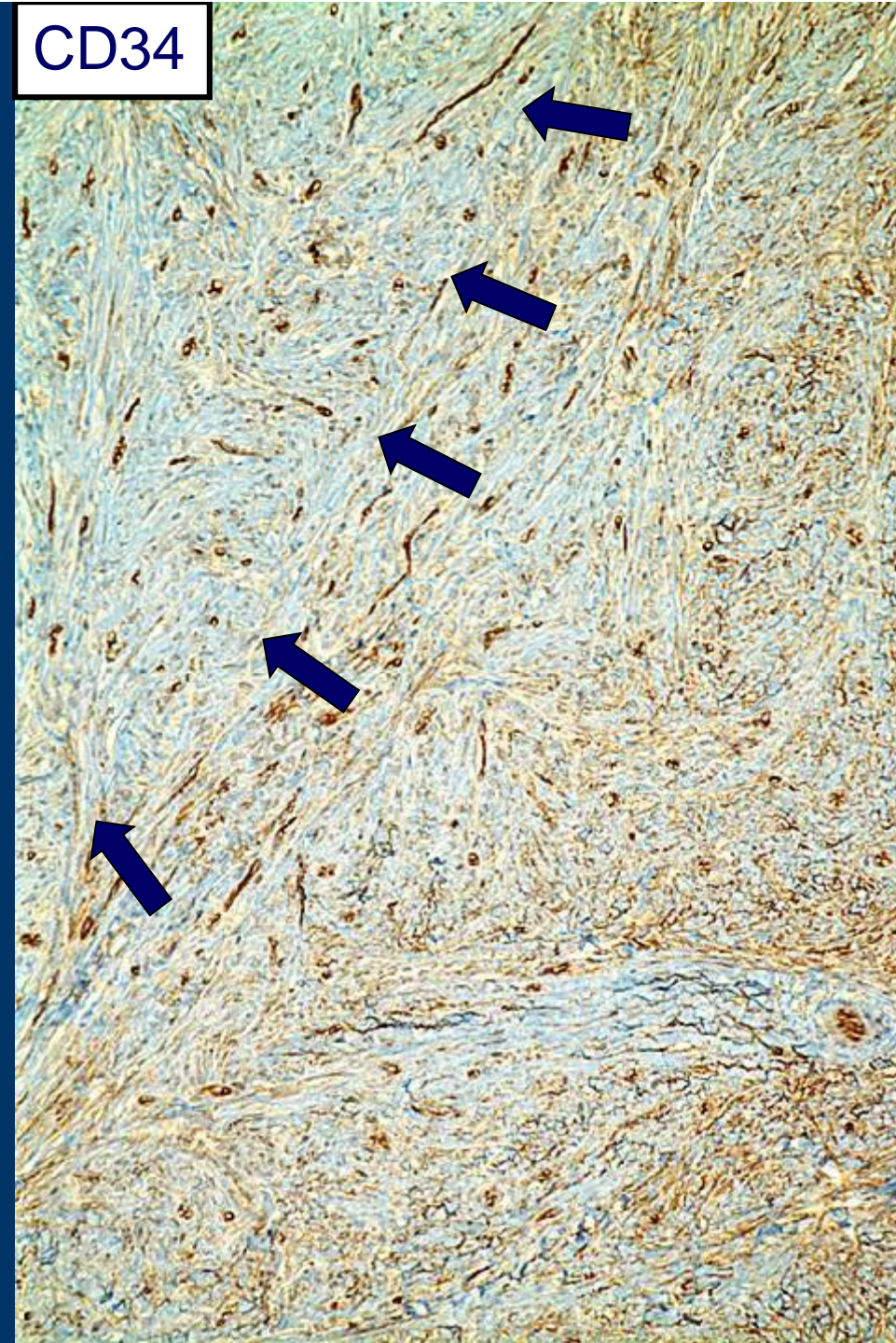
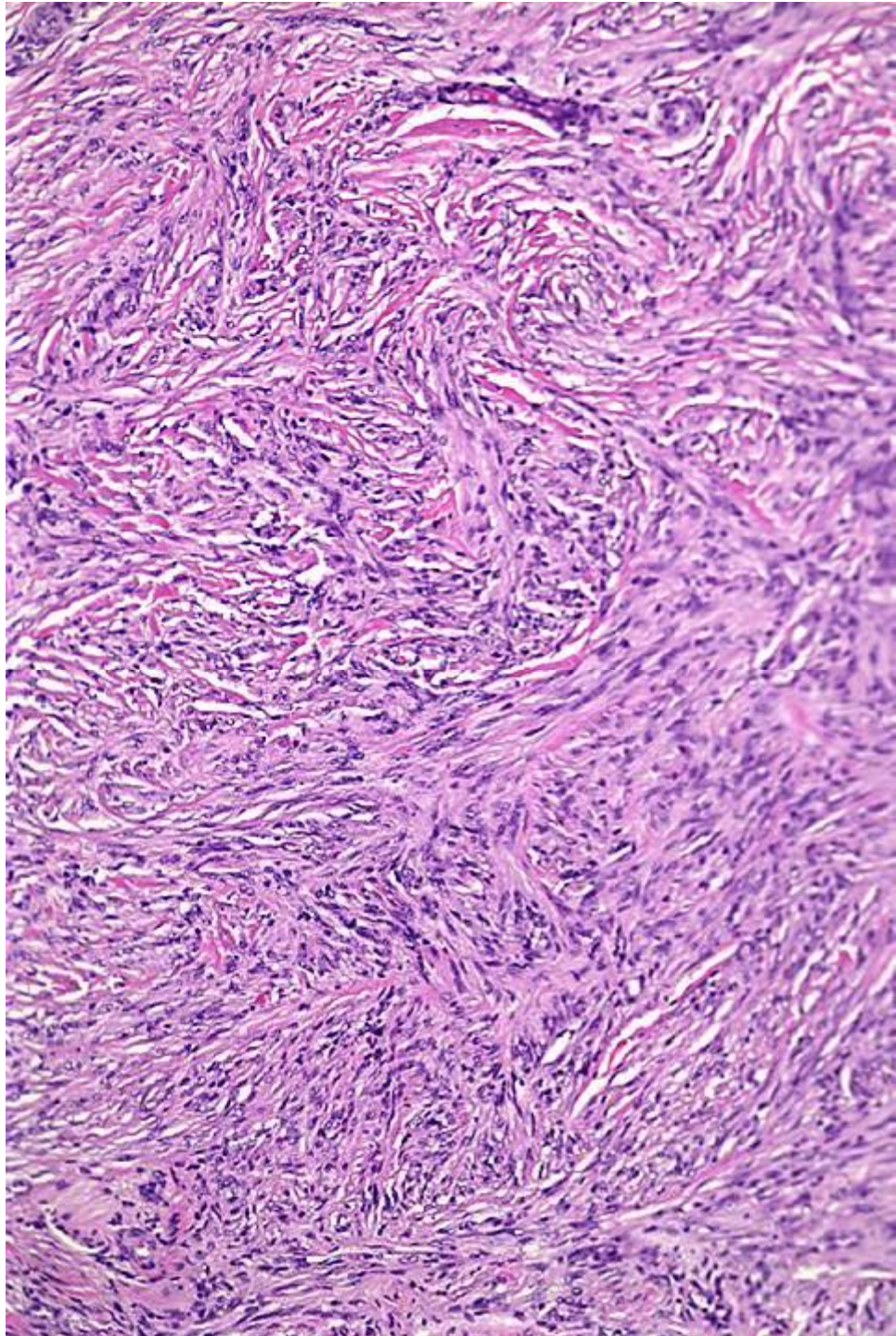




CD34

CFH vs. DFSP

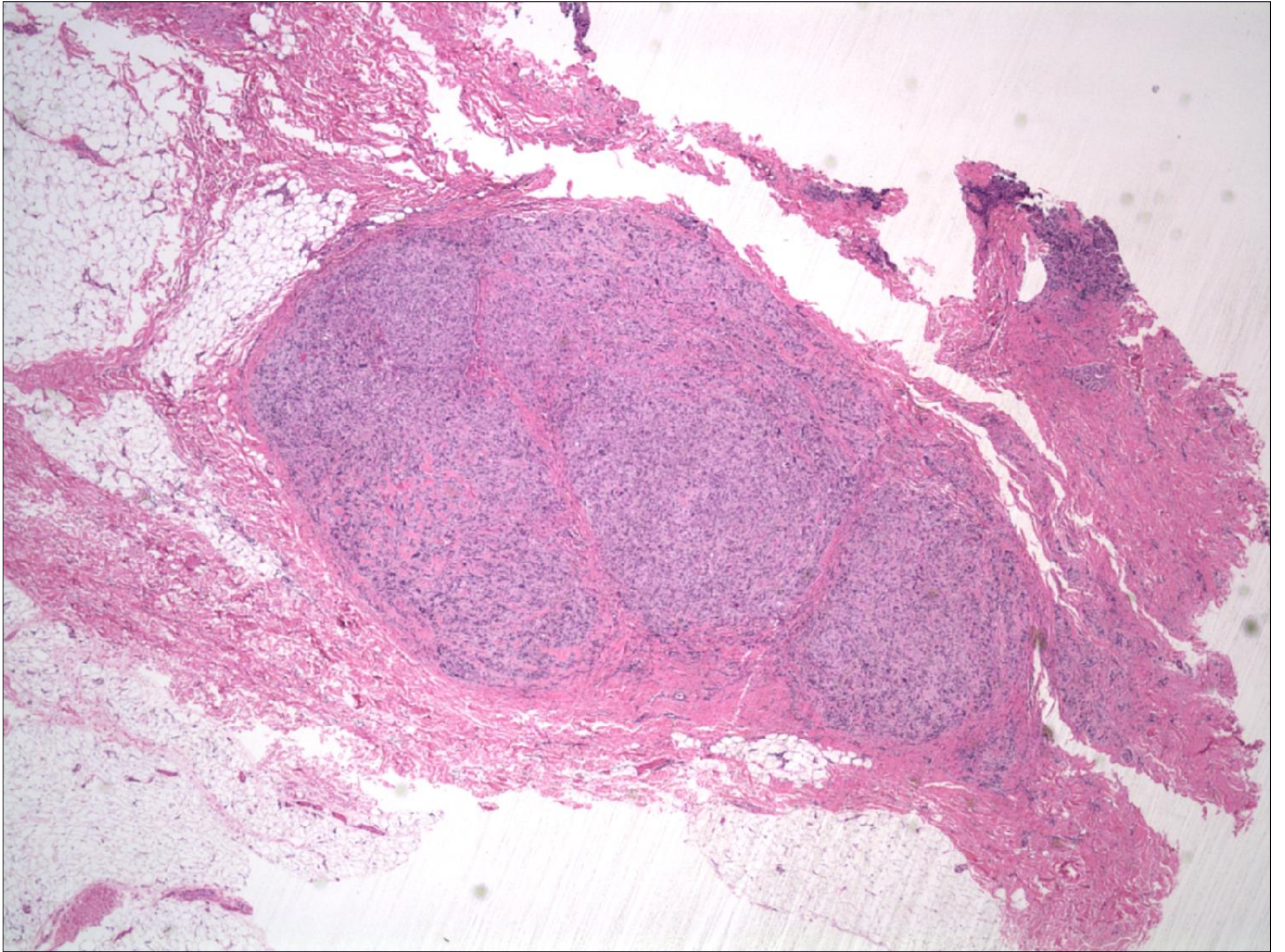


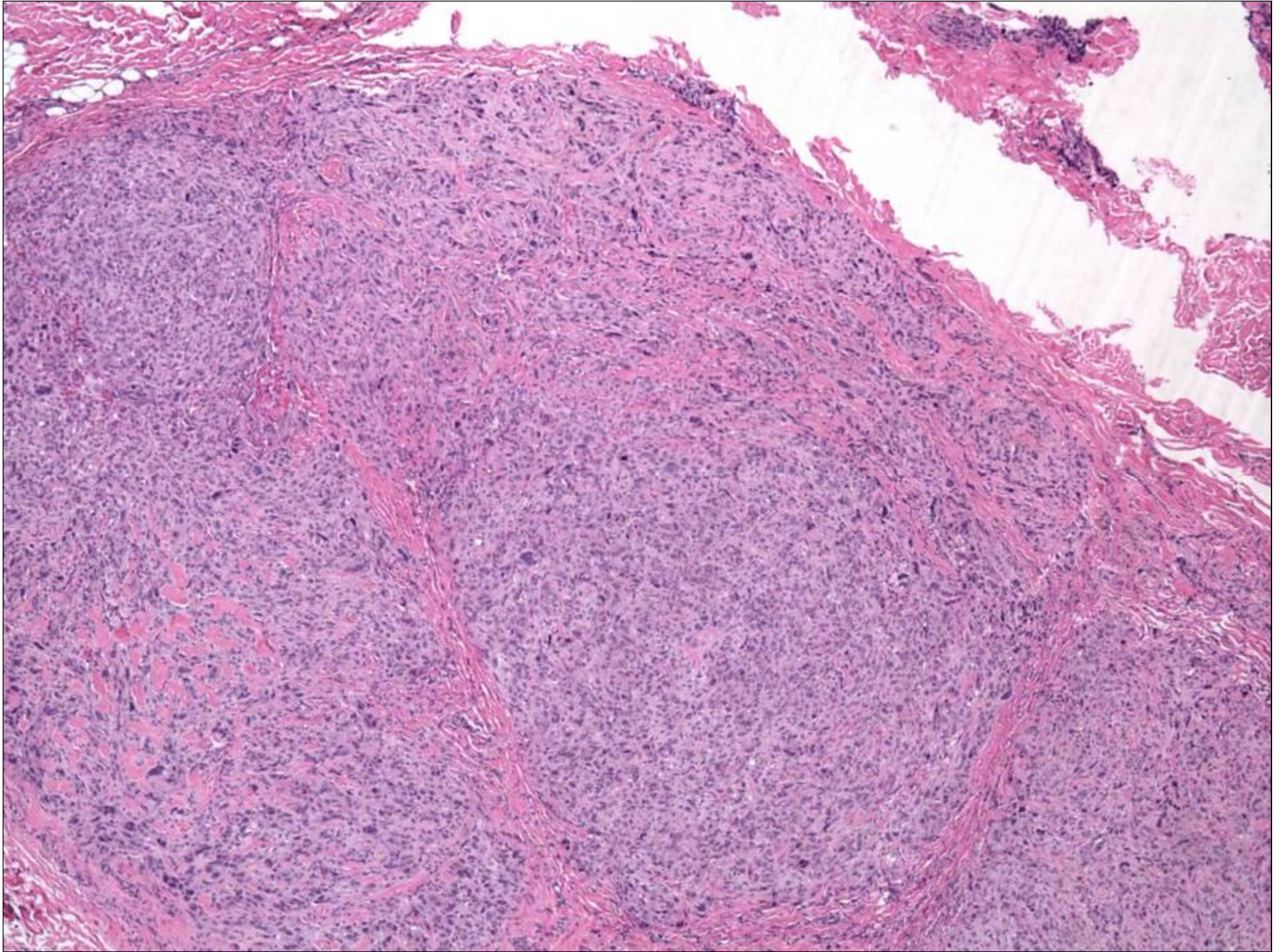


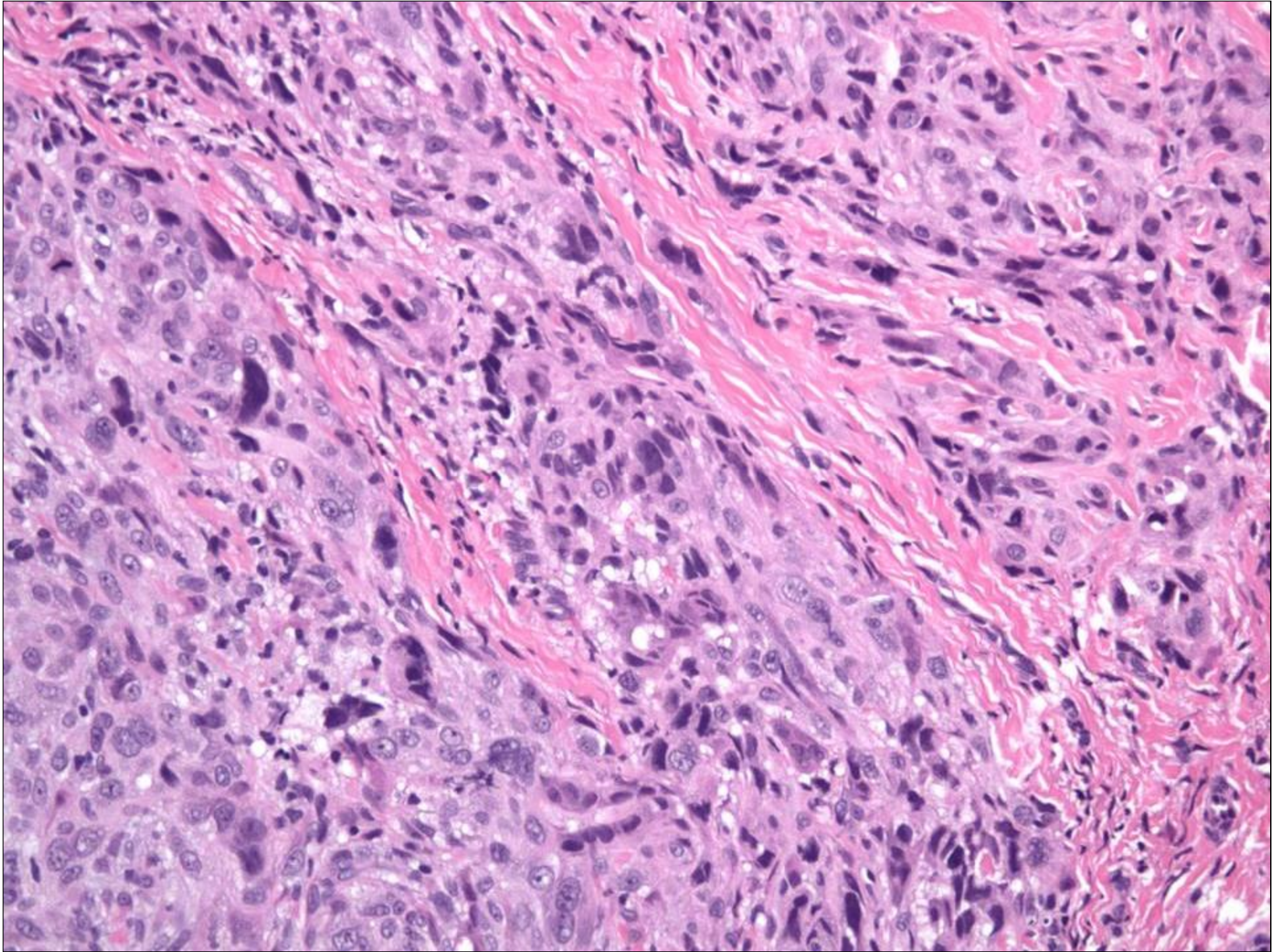
CFH vs. DFSP

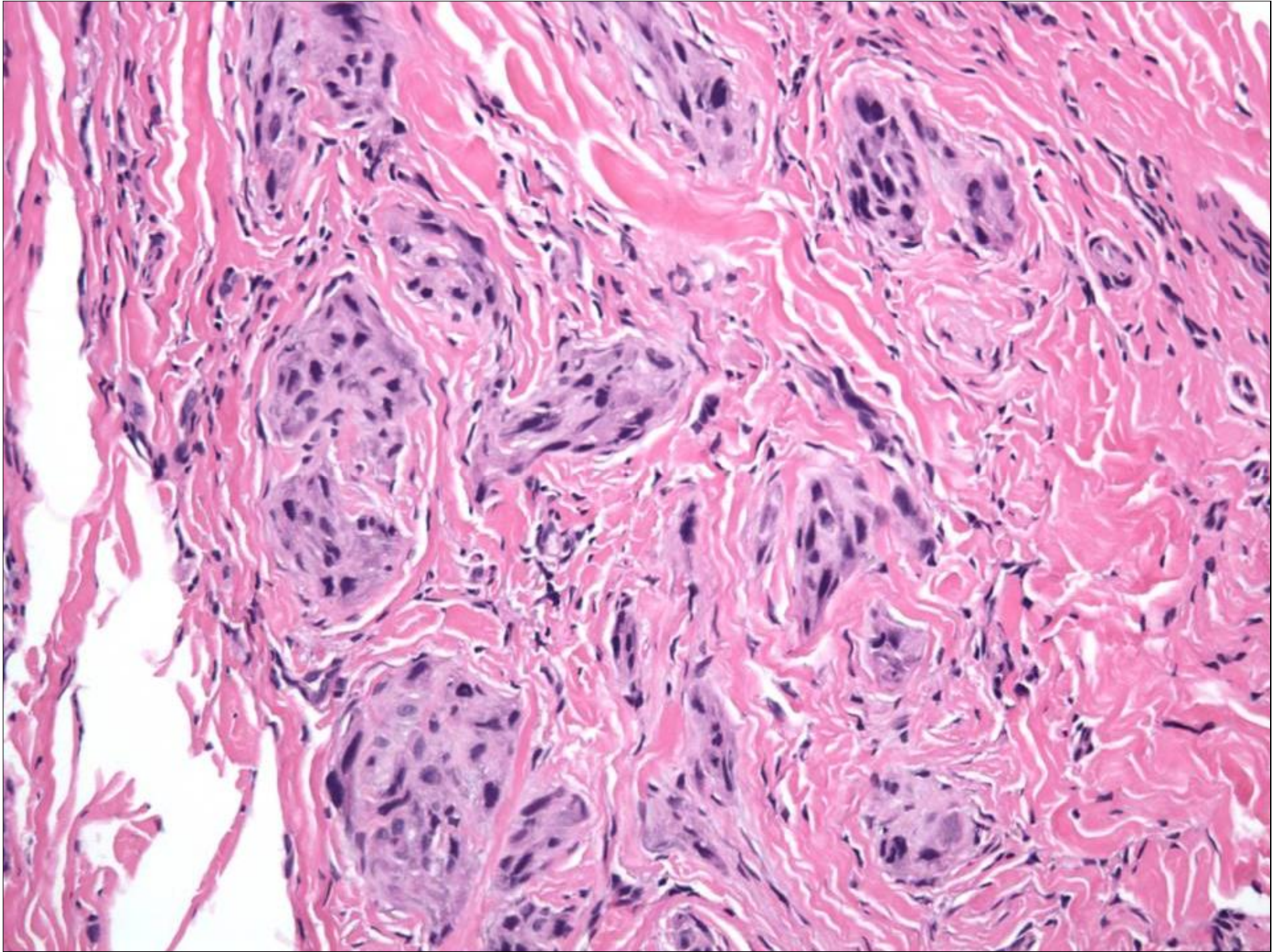
	CFH	DFSP
Circumscription	+	-
Epidermal hyperplasia	+/-	-
Collagen trapping	+	-
Secondary elements	Focal	-
Pattern of fat infiltration	Limited, lace-like	Diffuse
Immunostains	Factor XIIIa -/+; CD34 -	Factor XIIIa-; CD34+

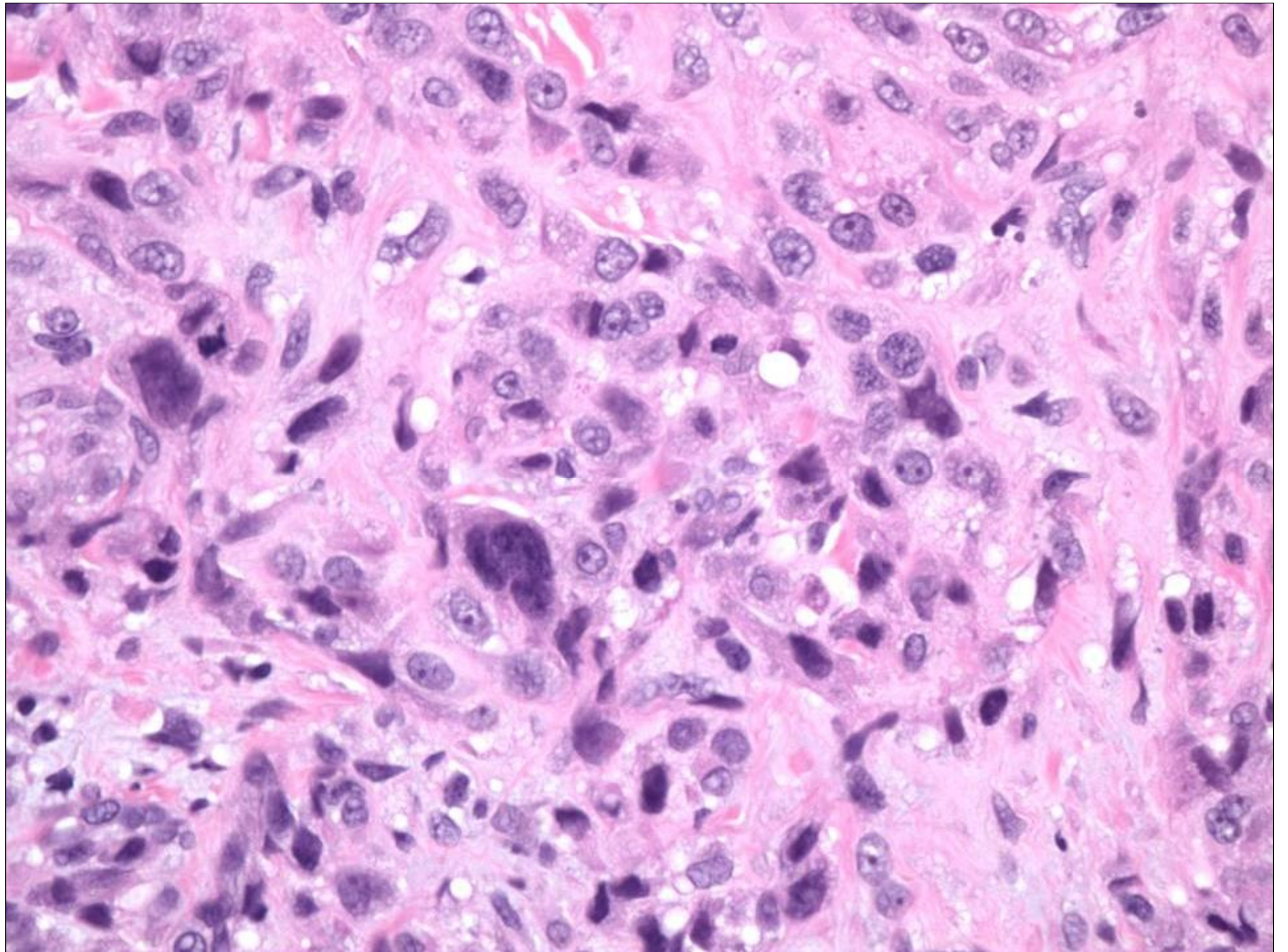
12-year-old boy with lesion on
hand





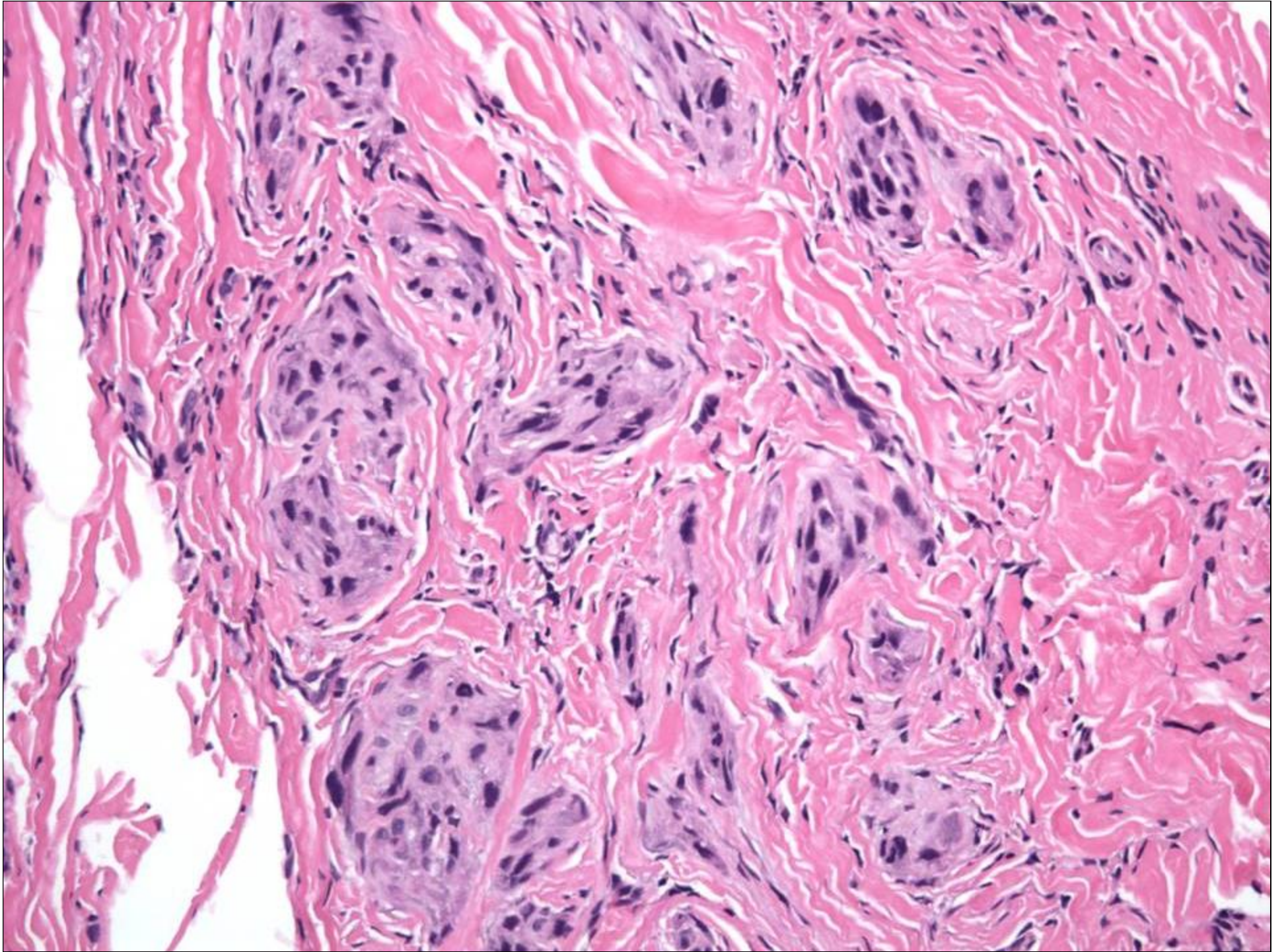




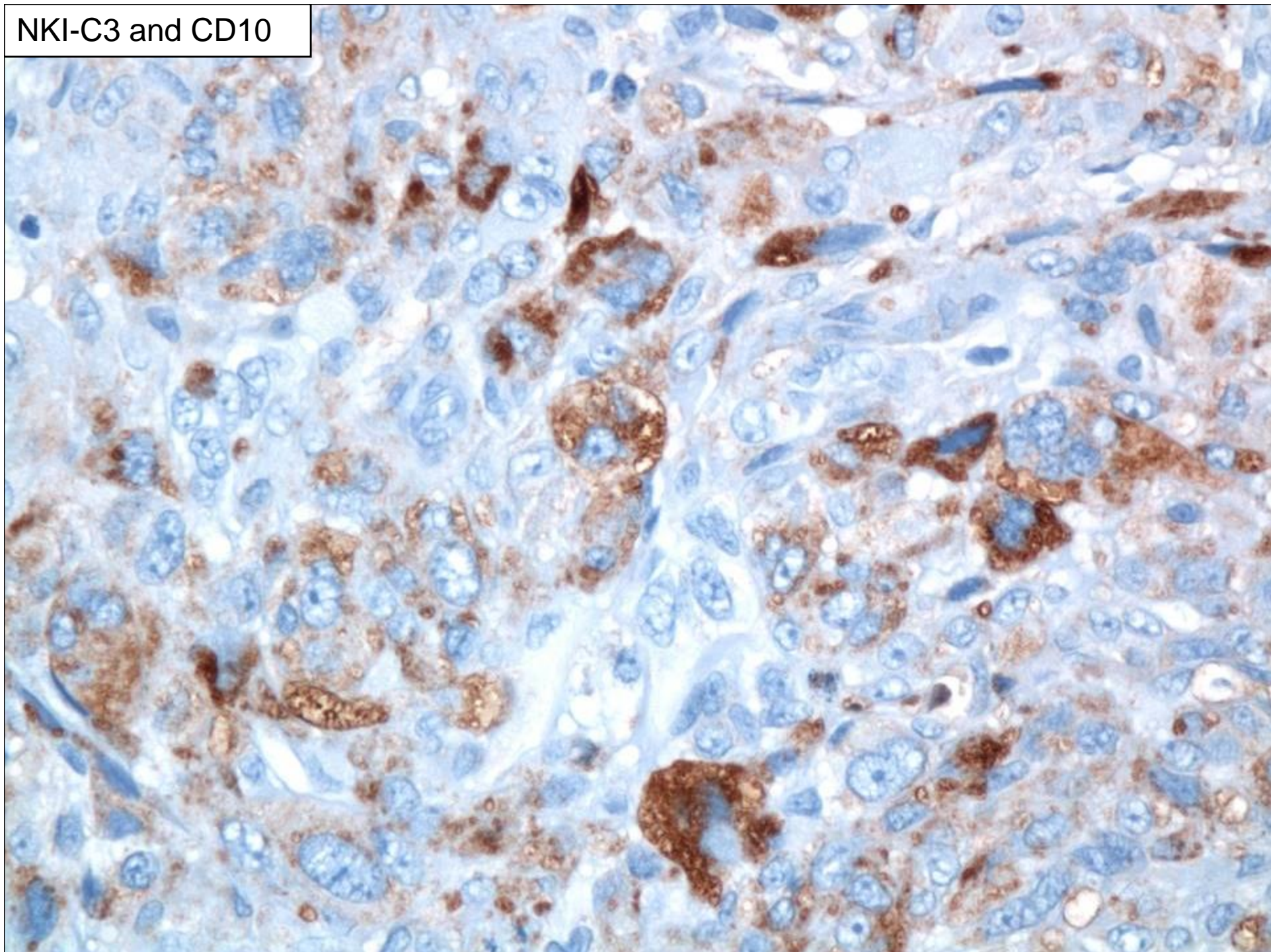


Diagnosis?

Negative for cytokeratin, S100,
and INI-1 expression retained



NKI-C3 and CD10

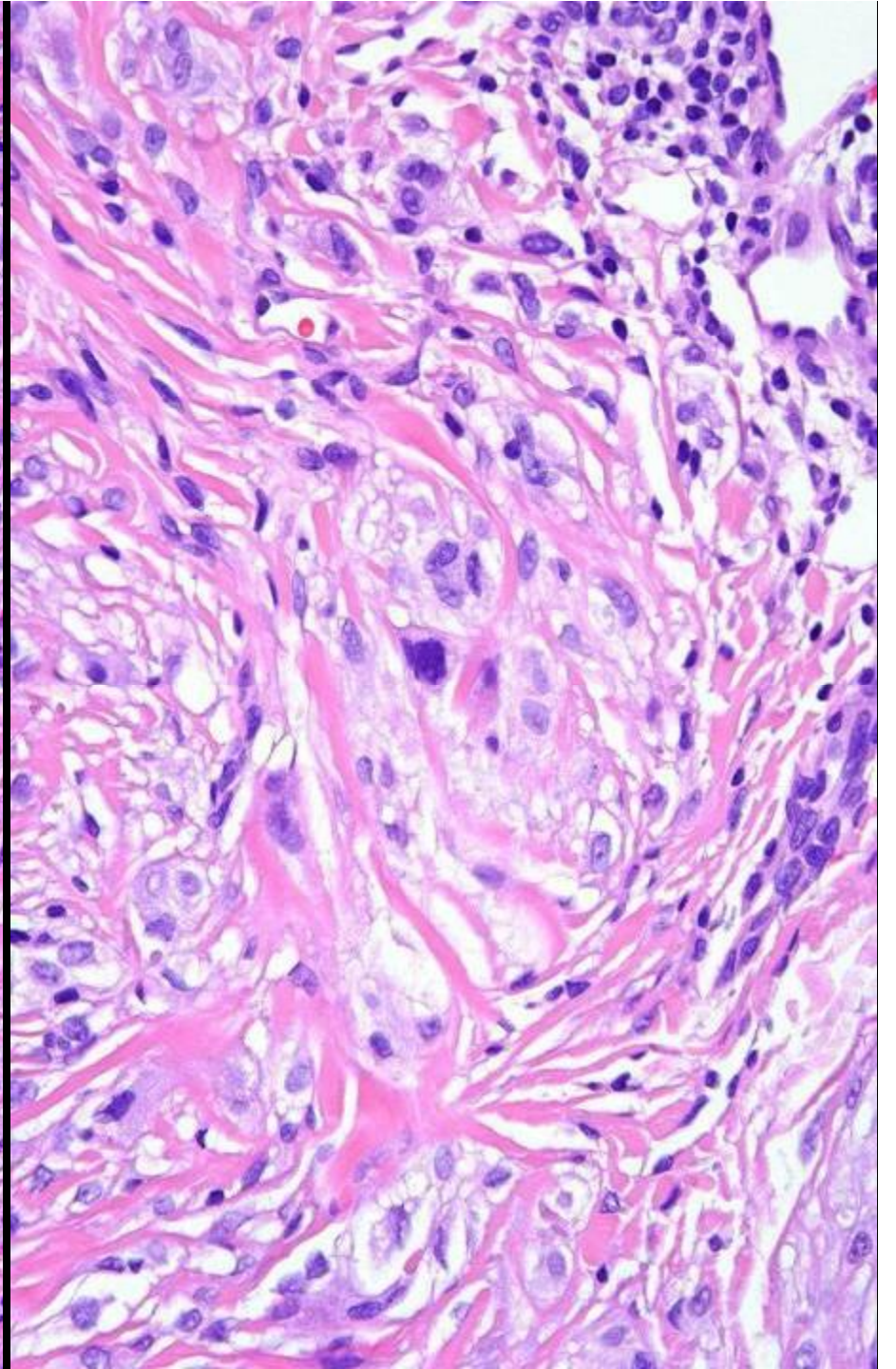
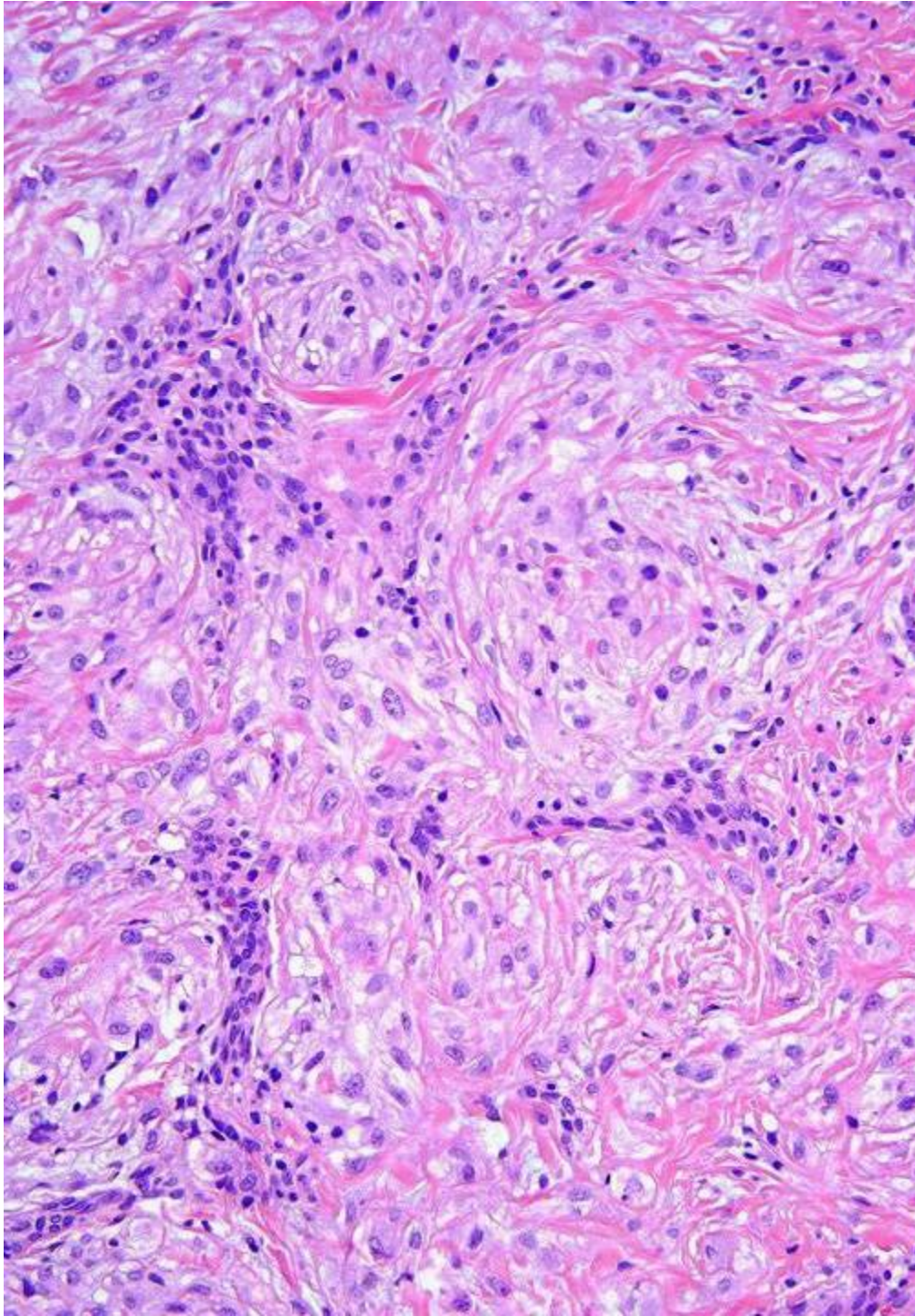


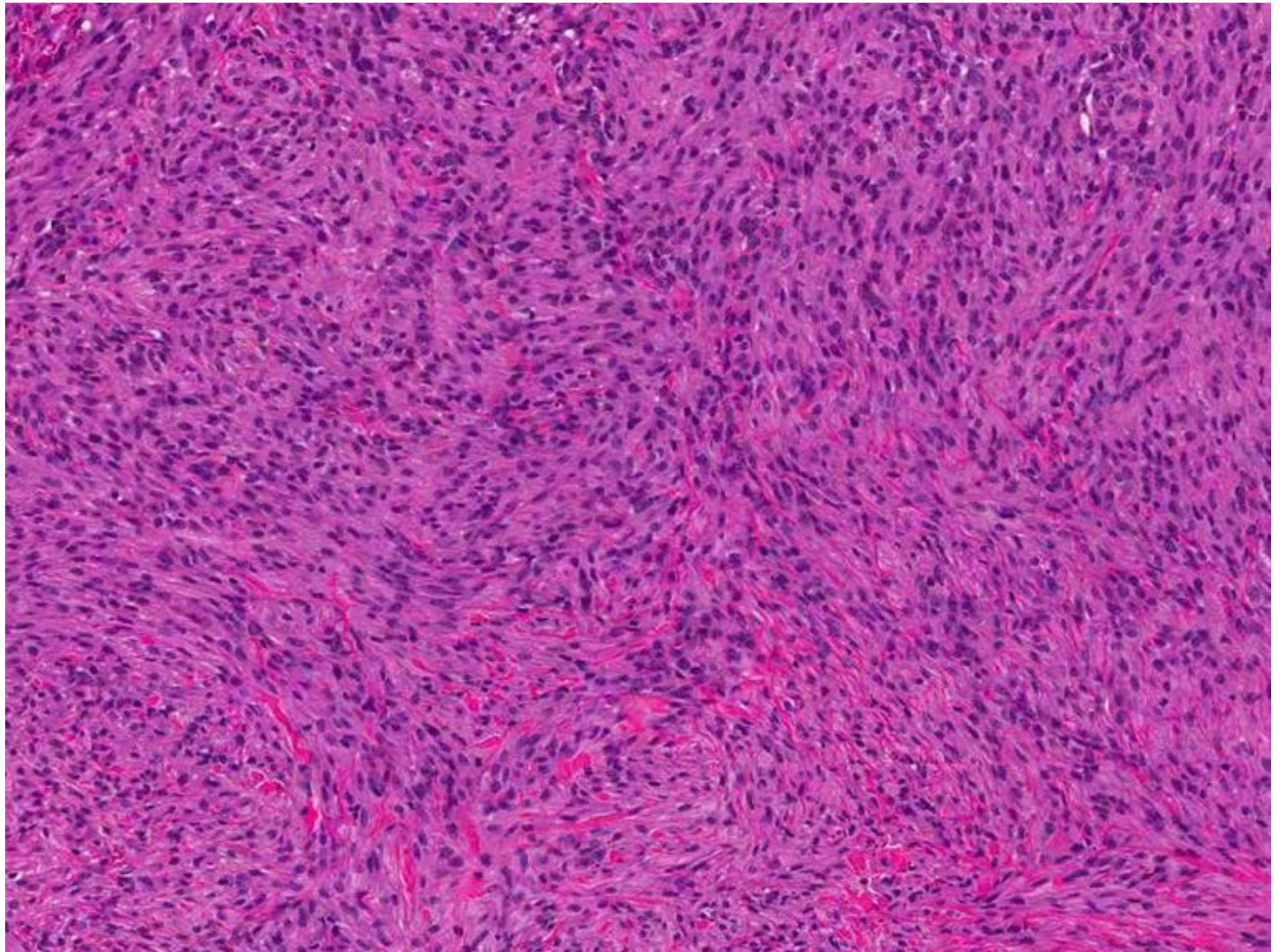
Cellular Neurothekeoma

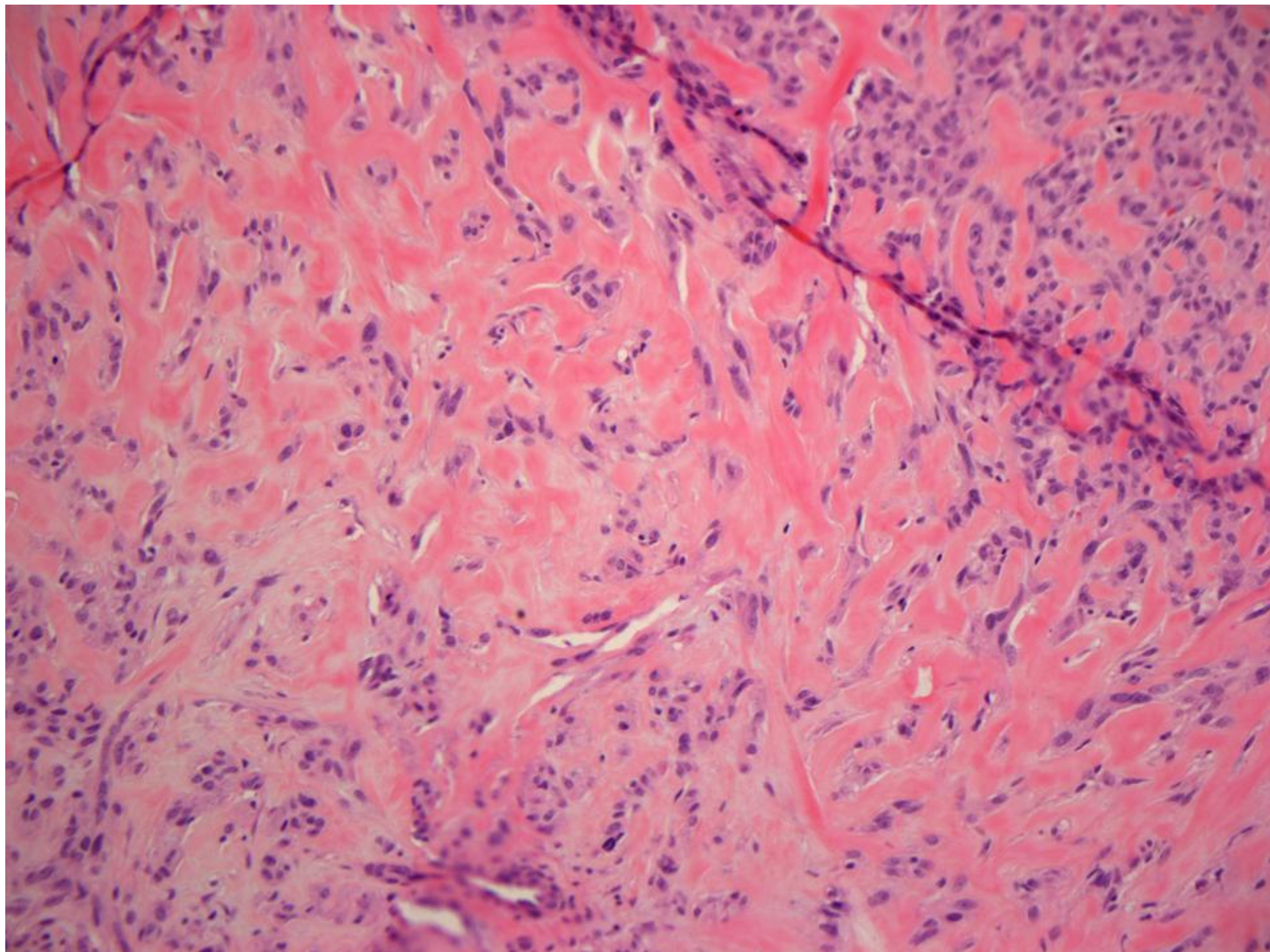
- Benign tumor (rare local recurrence)
- Head and neck and proximal upper extremity of young adults
- Present as painless flesh colored papules or nodules
- Originally considered a nerve sheath tumor; now considered a fibrohistiocytic tumor

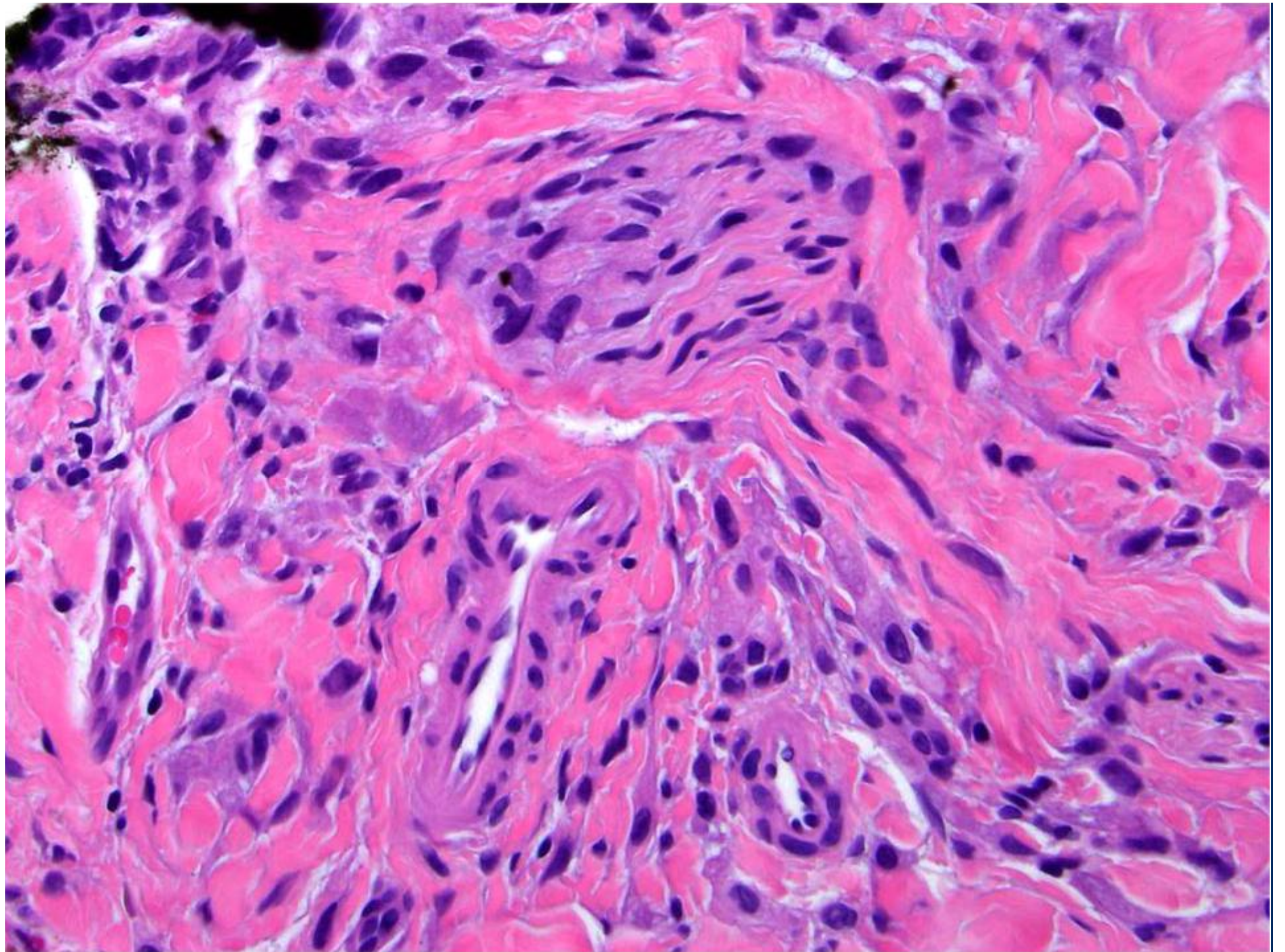
Histopathology

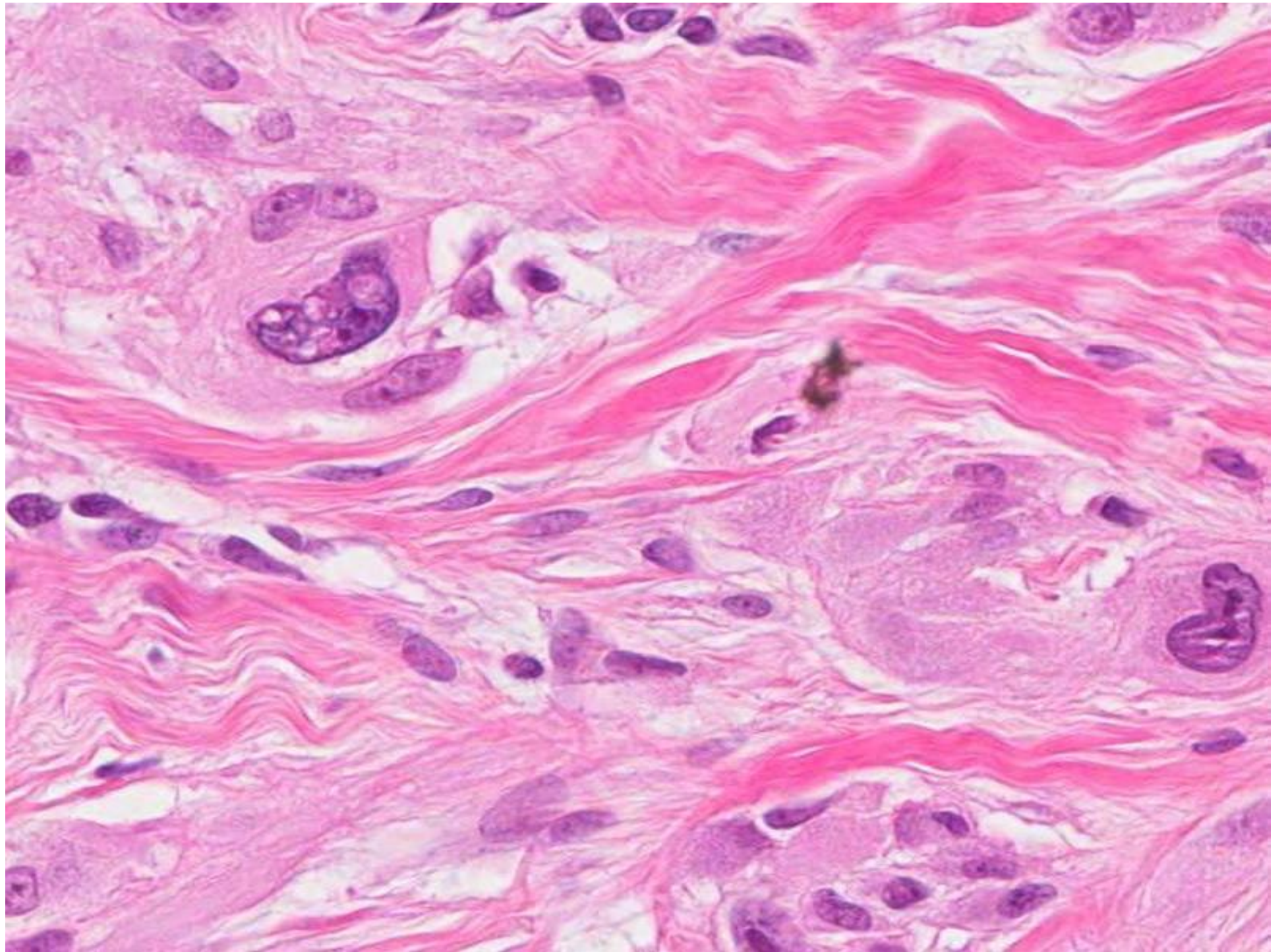
- Distinctly nested to fascicular growth pattern
- Subtle whorling arrangement of tumor cells in tumor nests
- Hyalinized stroma
- Myxoid stroma less prominent
- Neoplastic cells have abundant eosinophilic cytoplasm and round to oval nuclei
- Focal nuclear atypia common
- Mitotic figures may be present (<5/10 HPF)





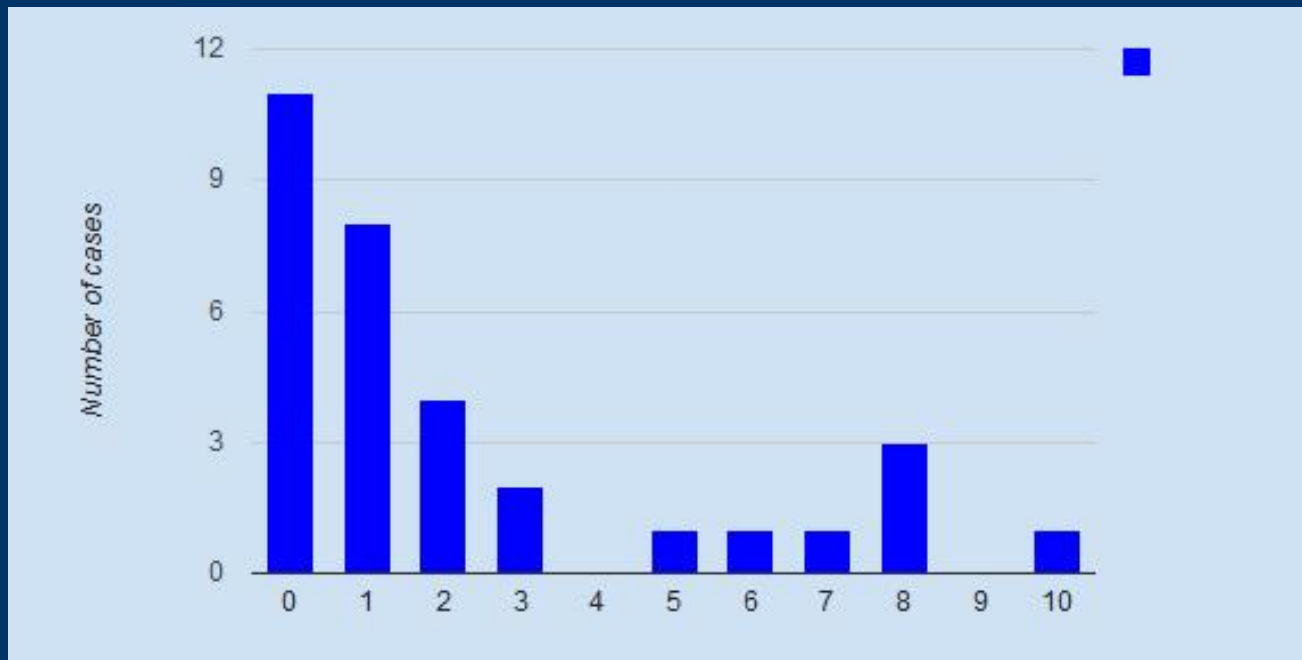






Mitotic Rate

- Counted using the hot-spot method per mm^2
- Cases varied from 0-10 mitoses/ mm^2 Mean (2.35)



Atypical Cellular Neurothekeoma

- Increased atypia
- Mitotic activity
- Perineural invasion
- Vascular invasion
- Does not impact behavior
 - Very rare local recurrence
 - No metastasis

Cellular Neurothekeoma

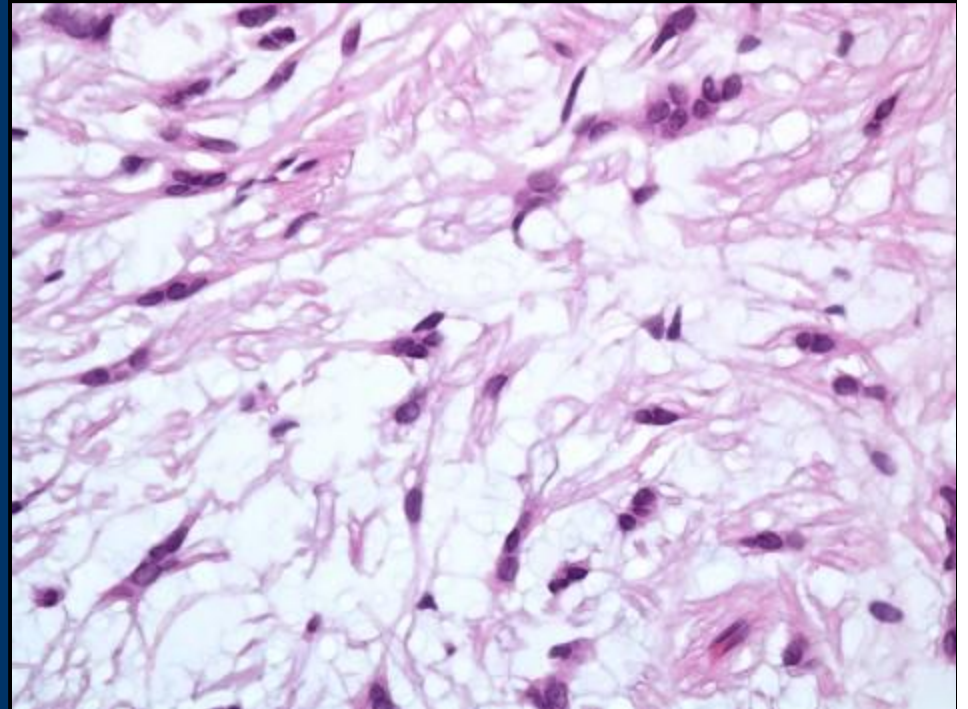
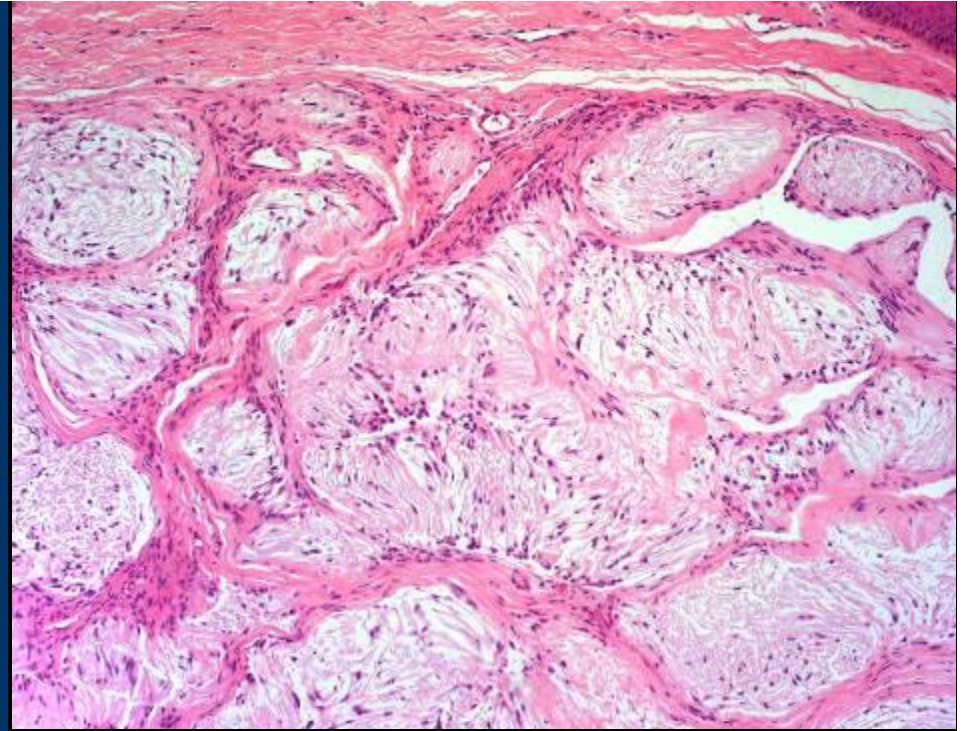
- Immunophenotype variable
 - Useful positives: NKIC3 and CD10, S100A6, MiTF
 - Sometimes positive: SMA
 - Positive but not all that helpful: vimentin, PGP9.5
 - Negative: cytokeratin, S100

Cellular Neurothekeoma

- Differential Diagnosis
 - Myxoid neurothekeoma/dermal nerve sheath myxoma
 - Plexiform fibrohistiocytic tumor
 - Epithelioid sarcoma

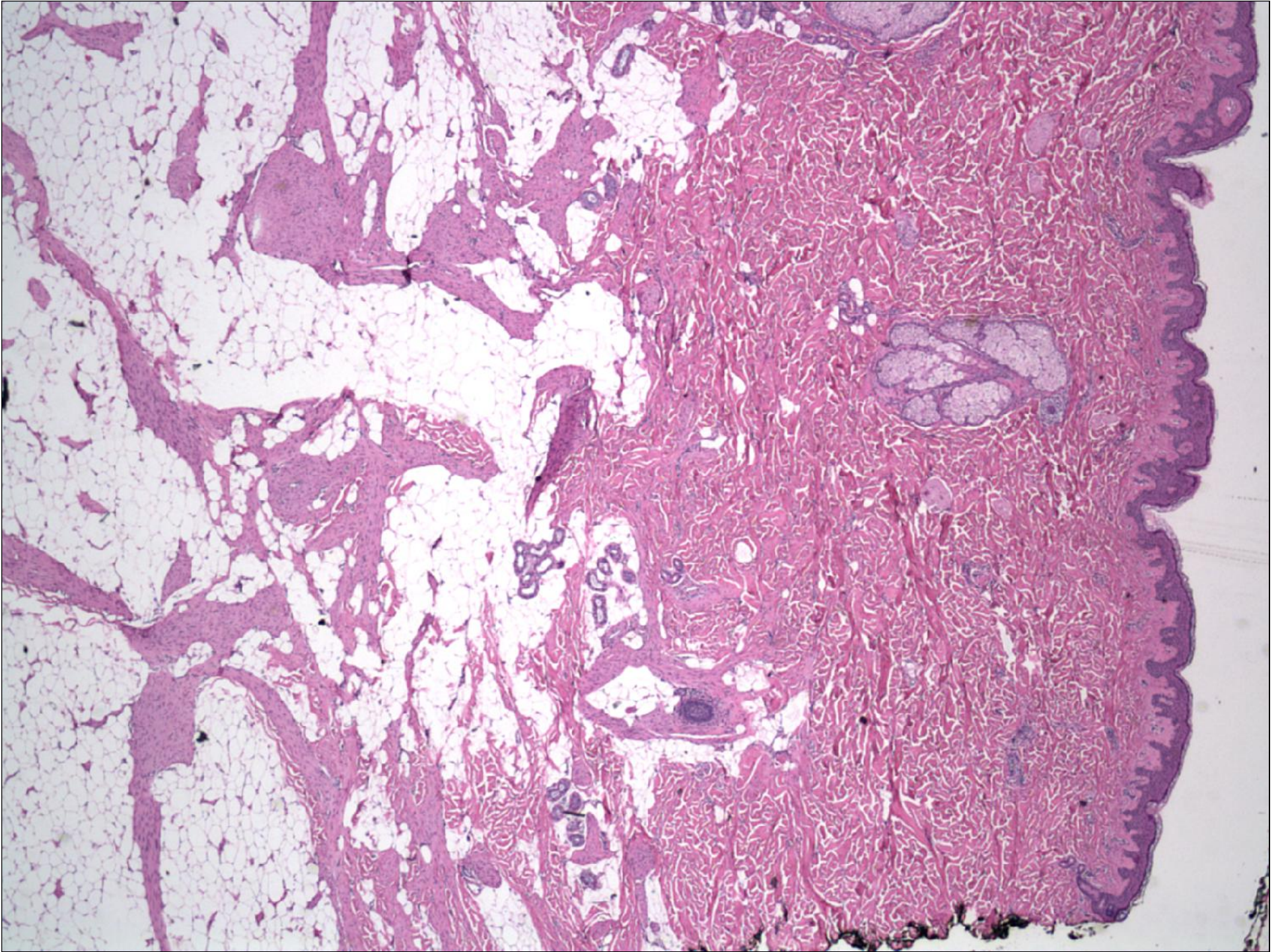
Dermal Nerve Sheath Myxoma

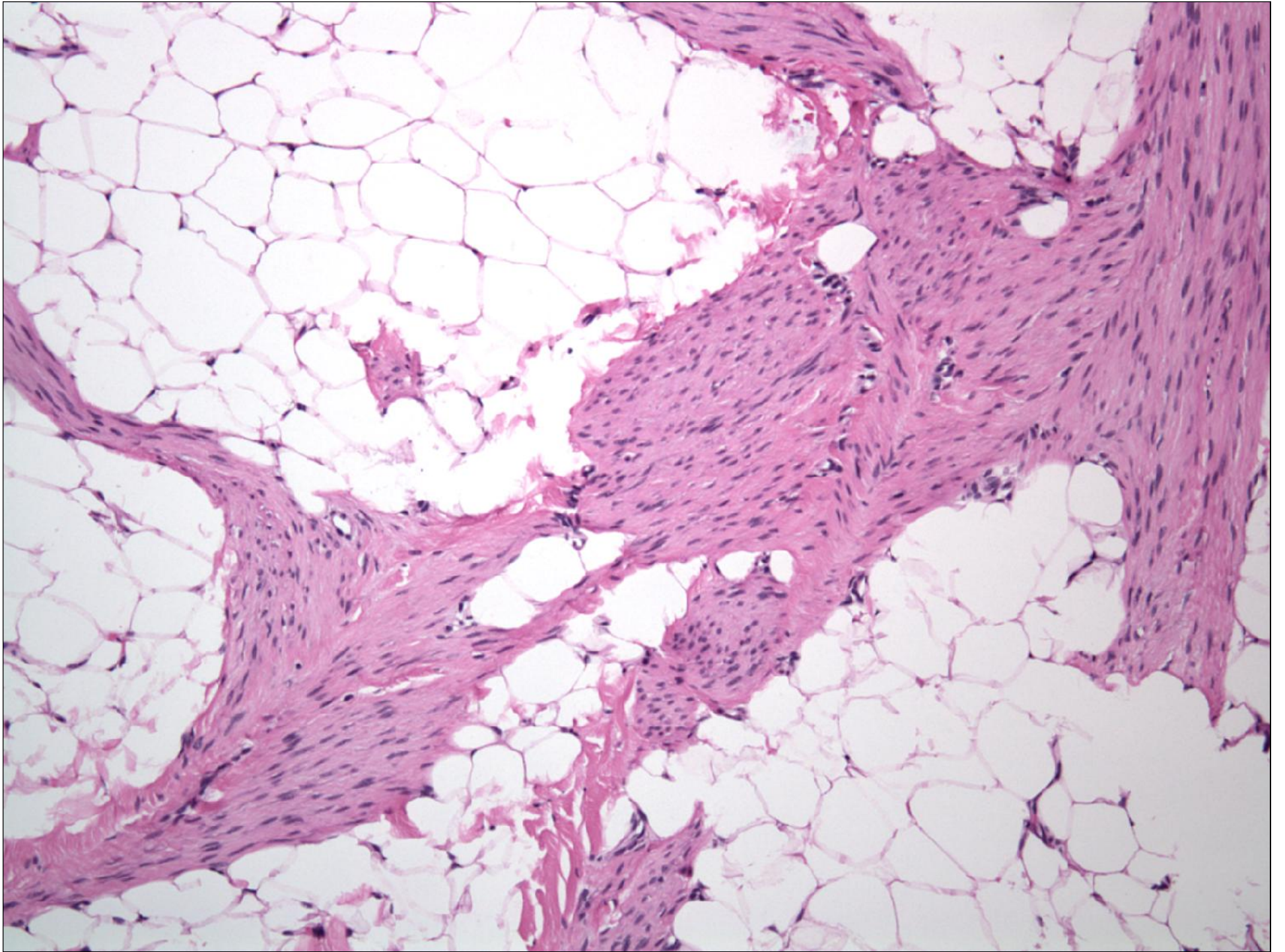
- True nerve sheath tumor
- Distinct nodules of spindled cells in myxoid stroma
- Nodules separated by fibrous septae
- S100+

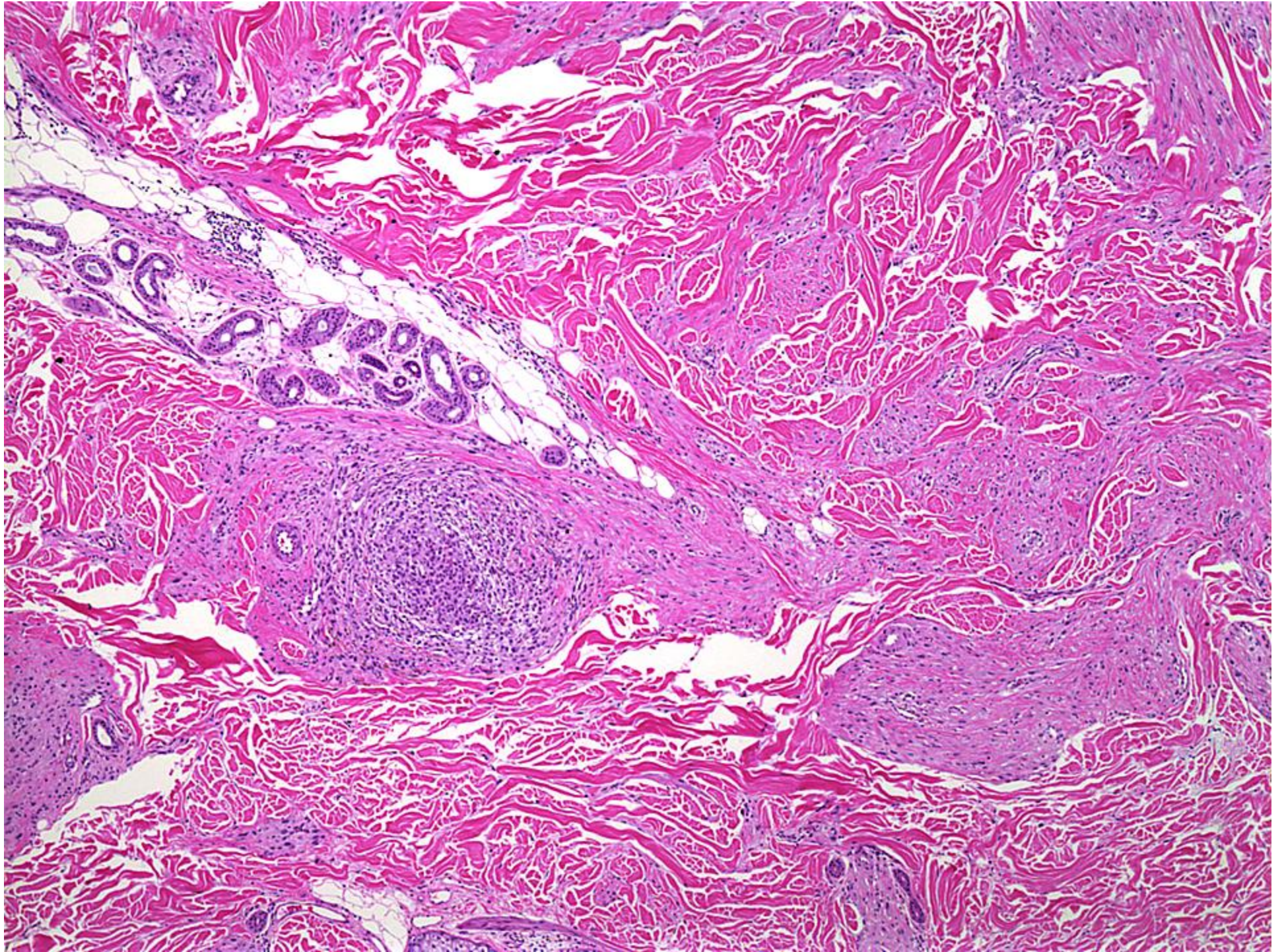


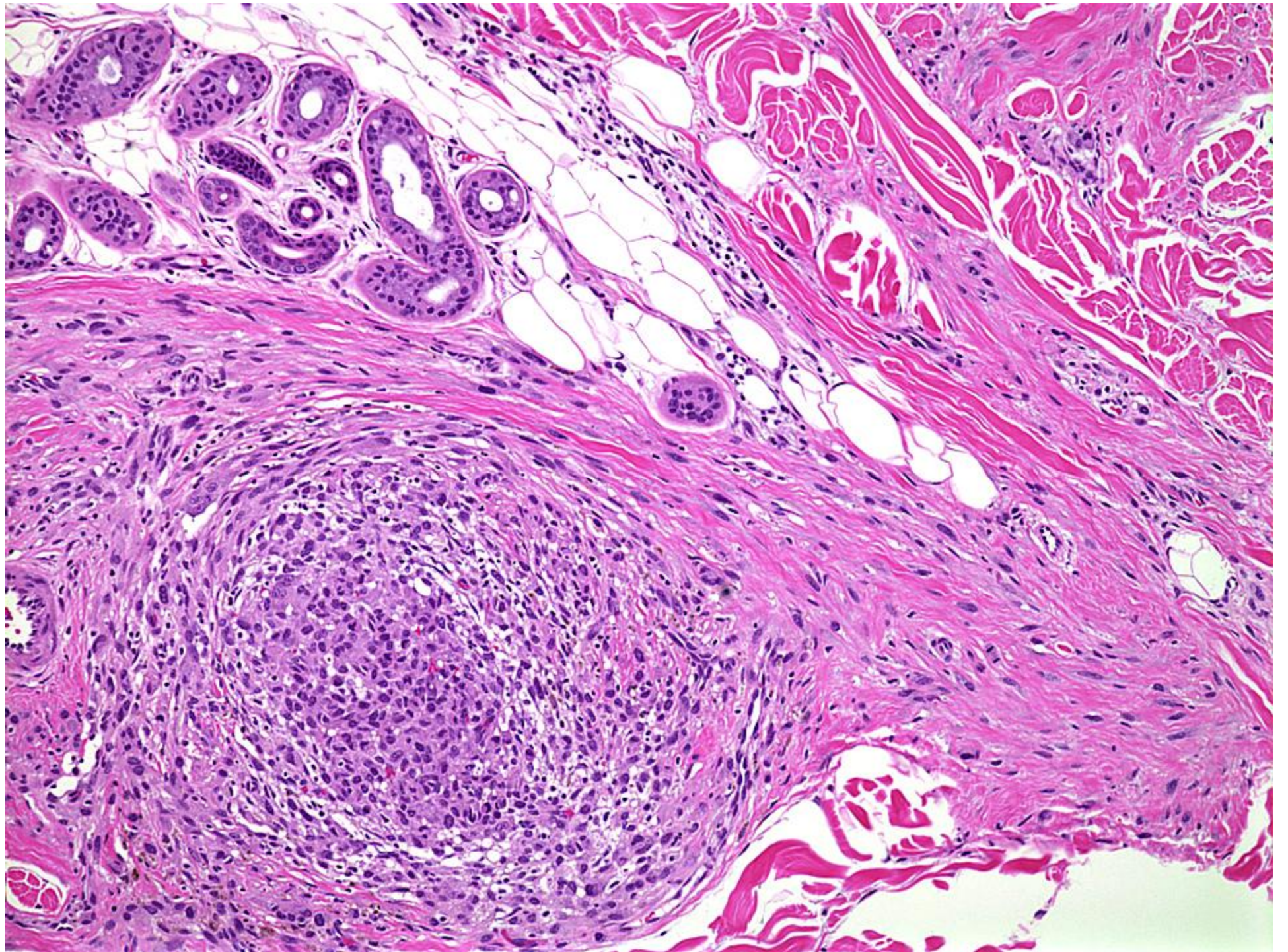
Plexiform Fibrohistiocytic Tumor

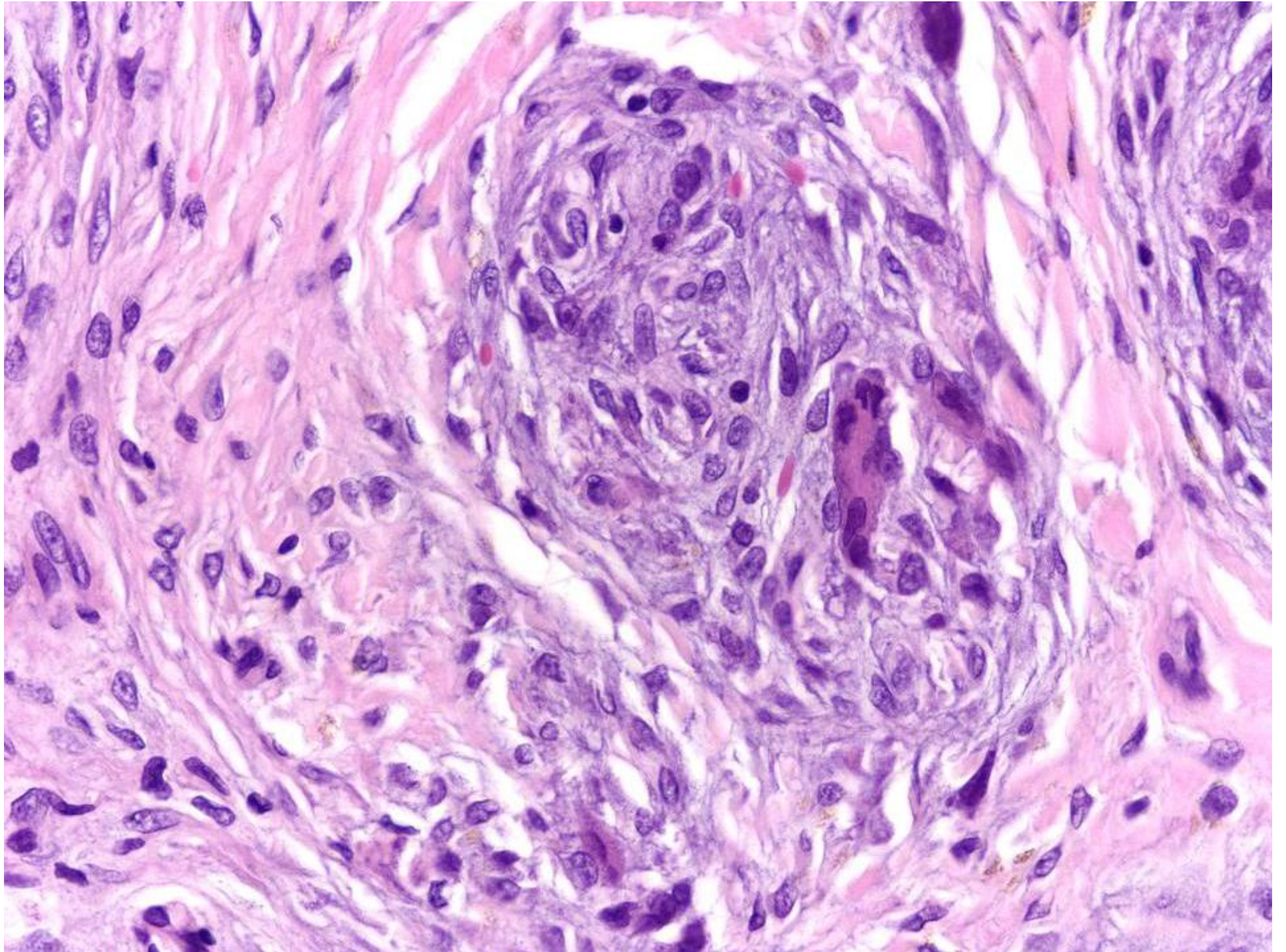
- Children or young adults
- Extremities
- Cutaneous or subcutaneous
- Distinctly plexiform growth pattern
- Minute nodules of round cells and interspersed osteoclasts surrounded by fascicles of myofibroblasts
- May be primarily rounded or spindle
- Immunophenotype: Overlap with CNT but MiTF negative

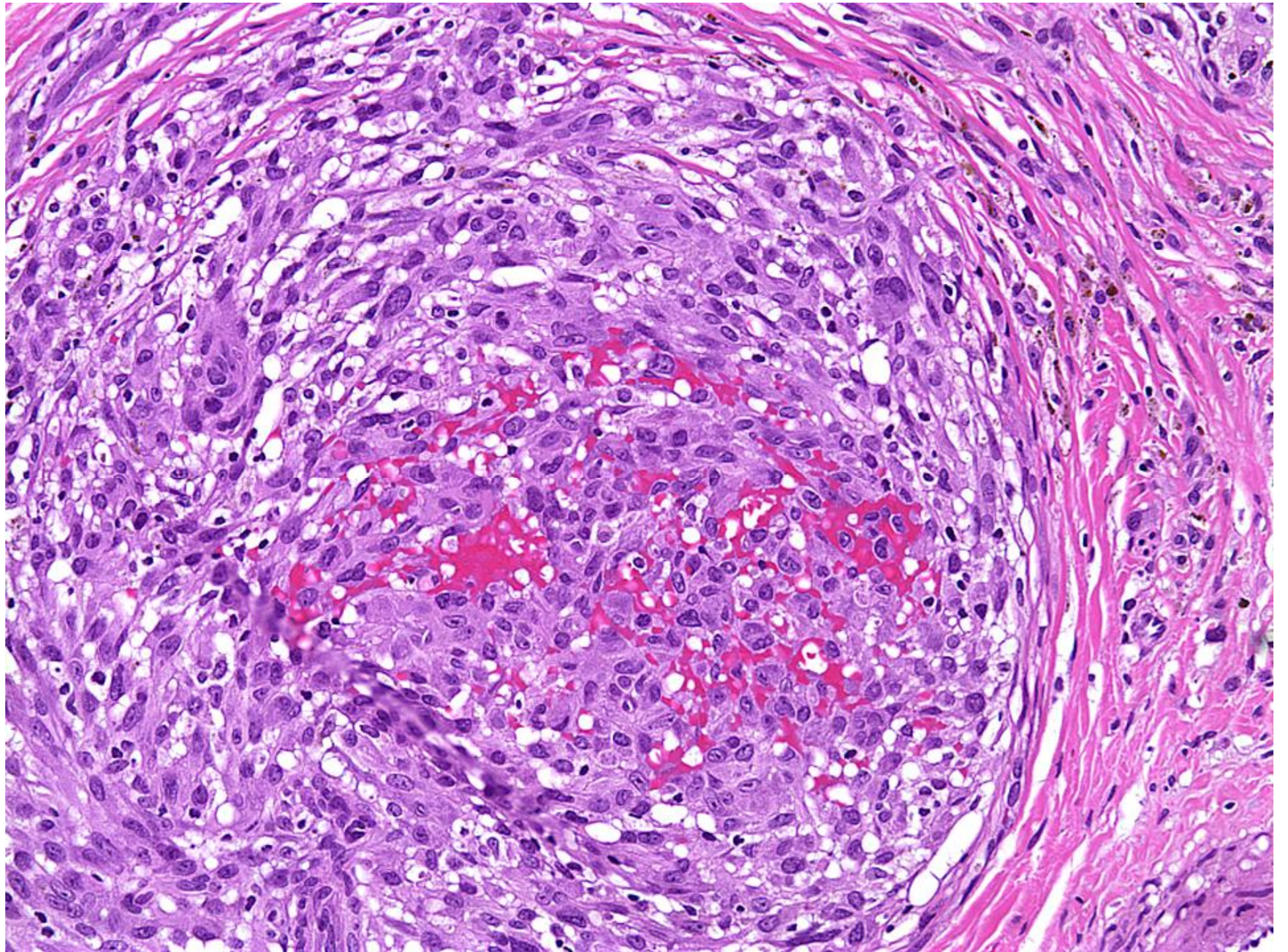








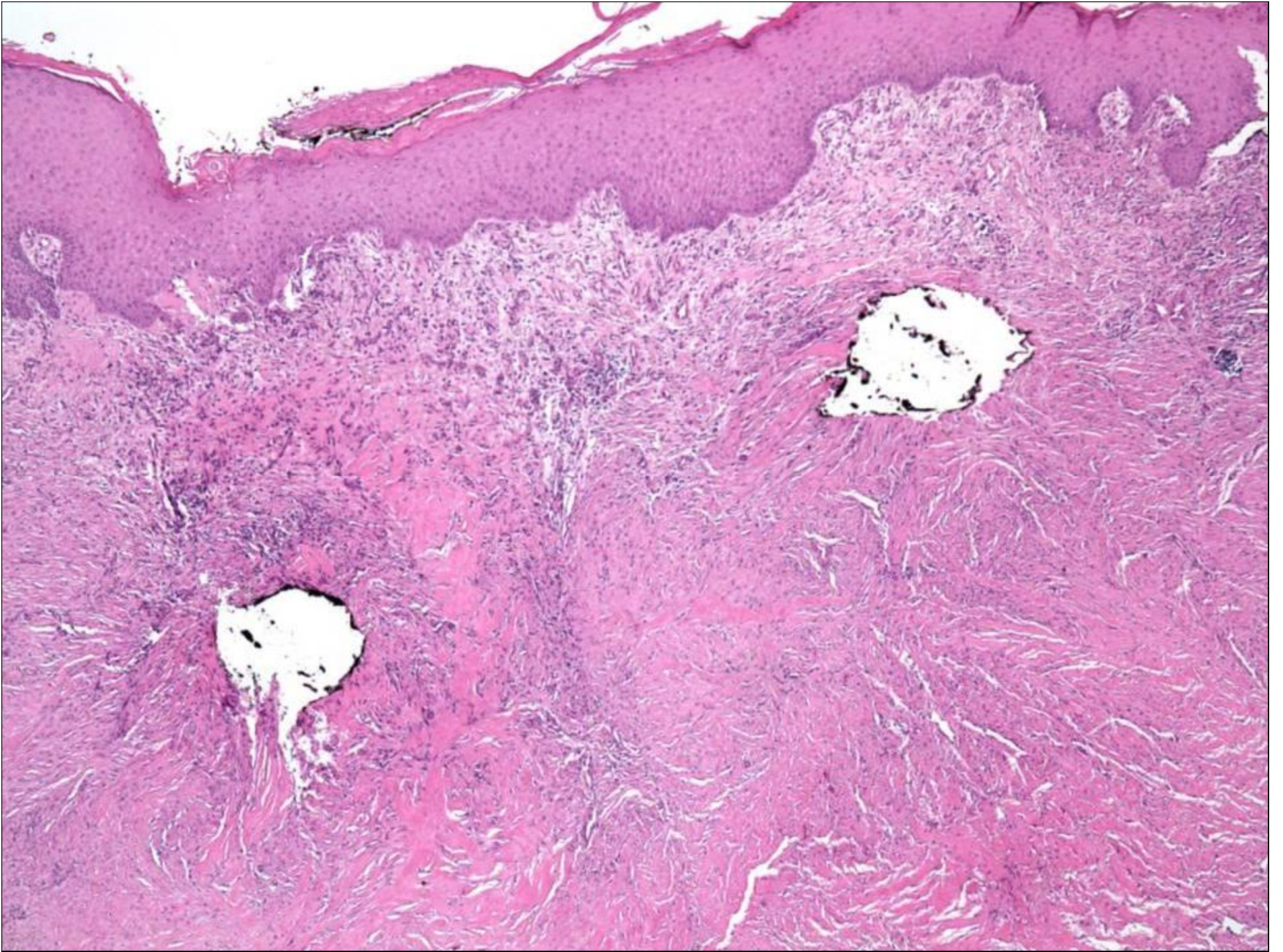


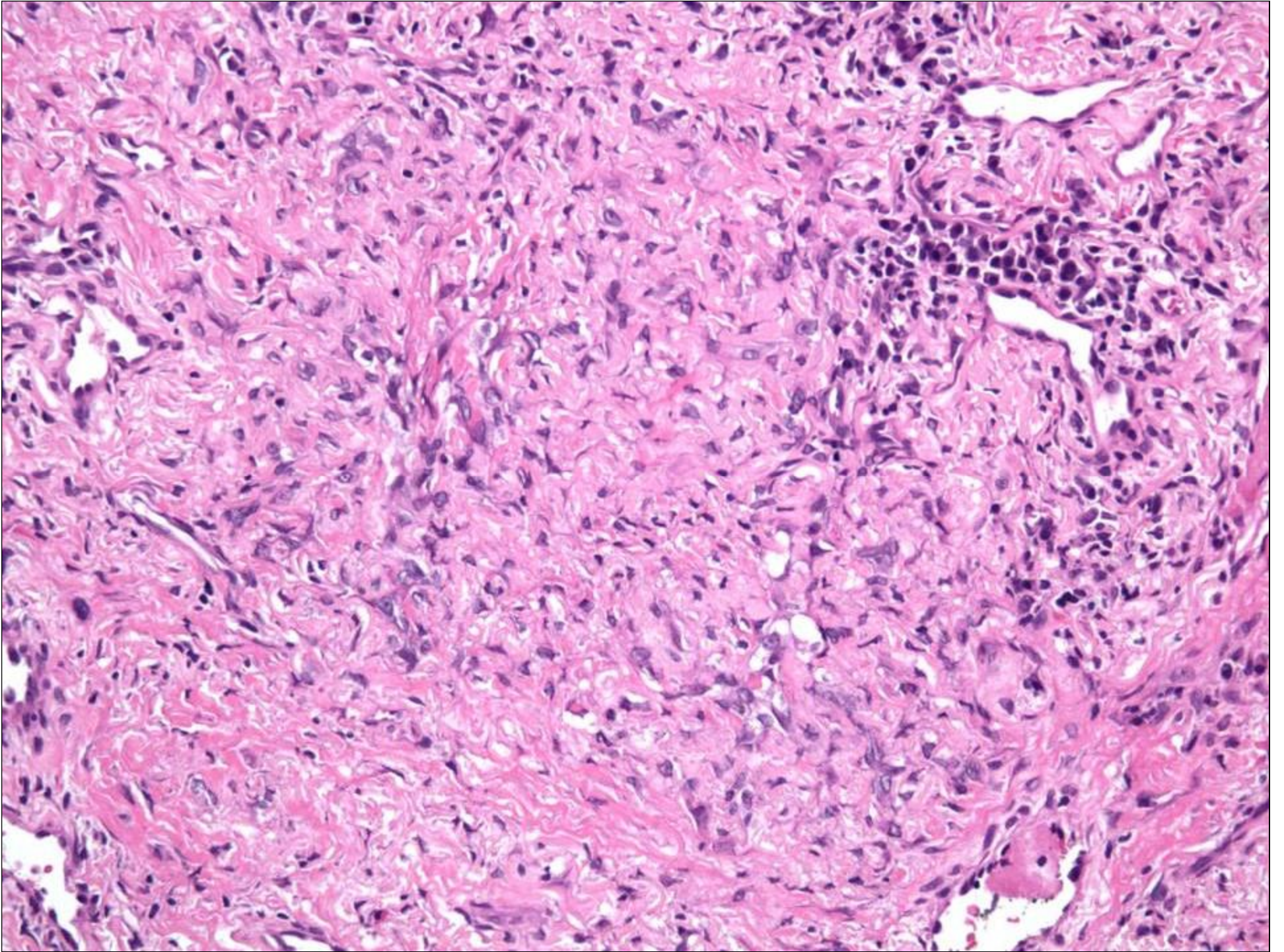


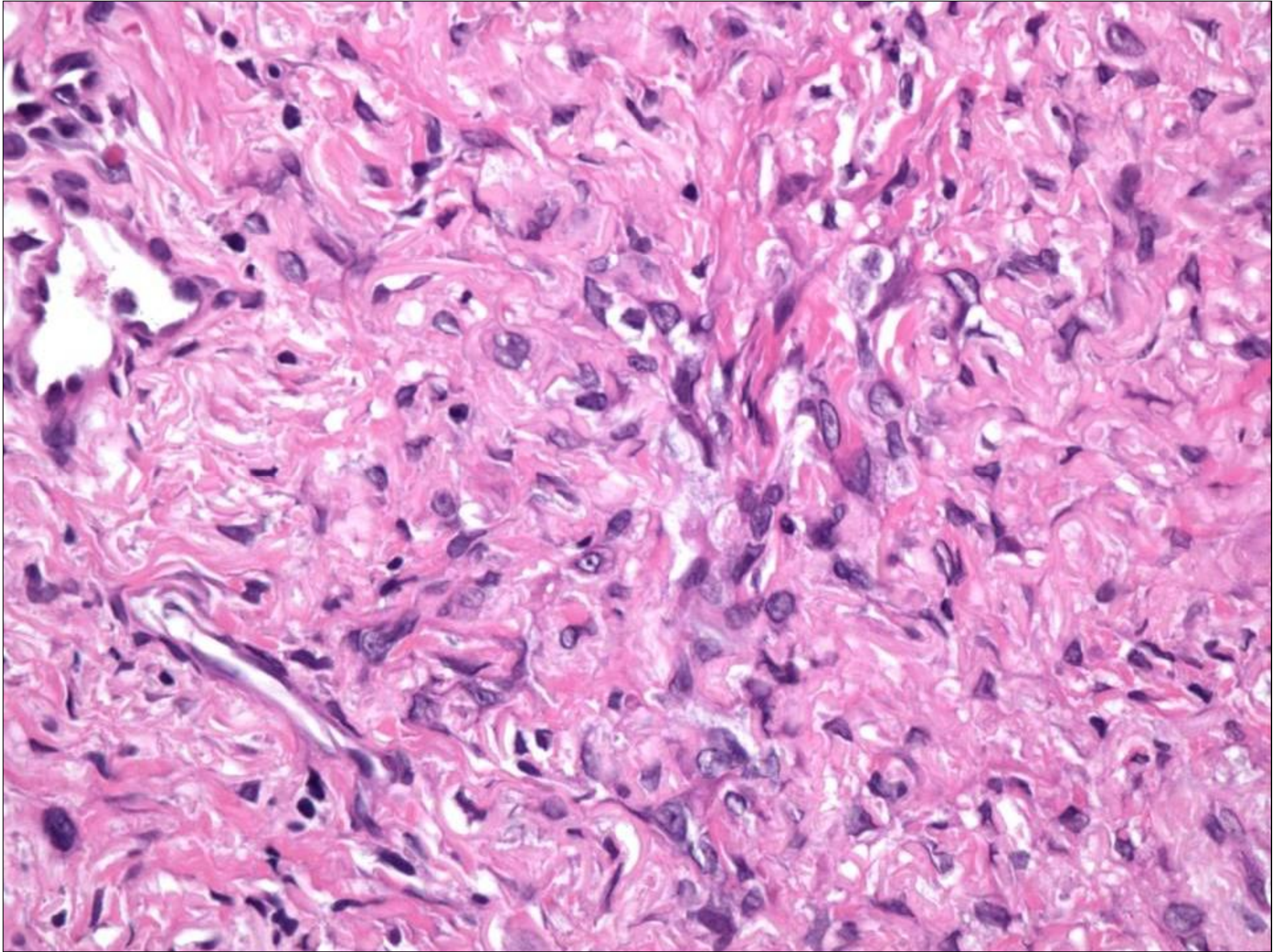
Behavior

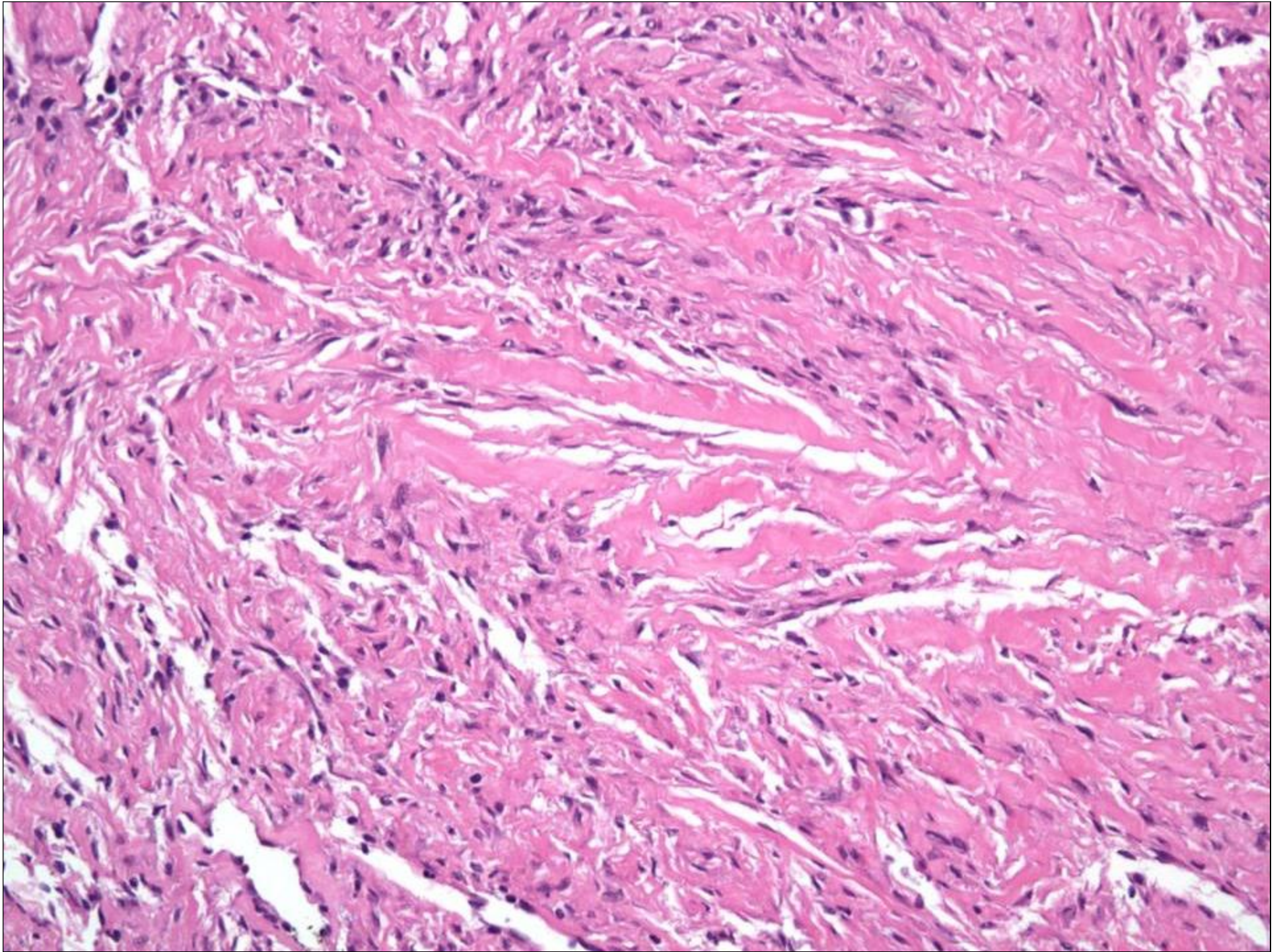
- Tumor of intermediate malignancy
- Local recurrences in 12-40% of cases
- Recommend wide excision
- Metastatic disease very uncommon
 - Several reported lymph node metastases
 - Three reported pulmonary metastases
- Single report of t (4;15) (q21; q15)

54-year-old diabetic woman presented with depressed plaque with focal ulceration. Patient reports burning sensation in arm.







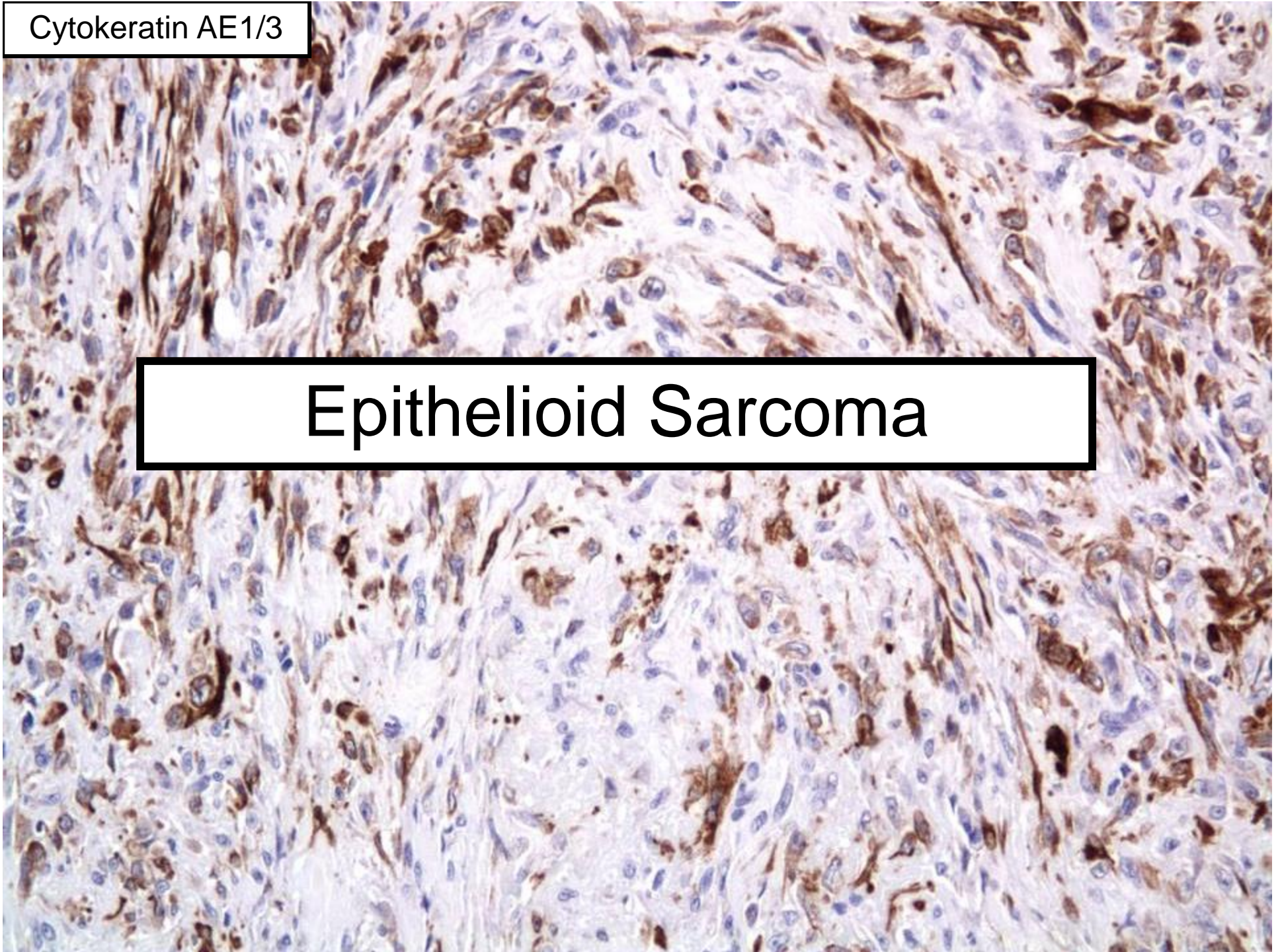


Diagnosis

- Granuloma annulare?
- Necrobiosis lipoidica?
- Rheumatoid nodule?
- Dermatofibroma?
- Scar?
- Something else?

Cytokeratin AE1/3

Epithelioid Sarcoma



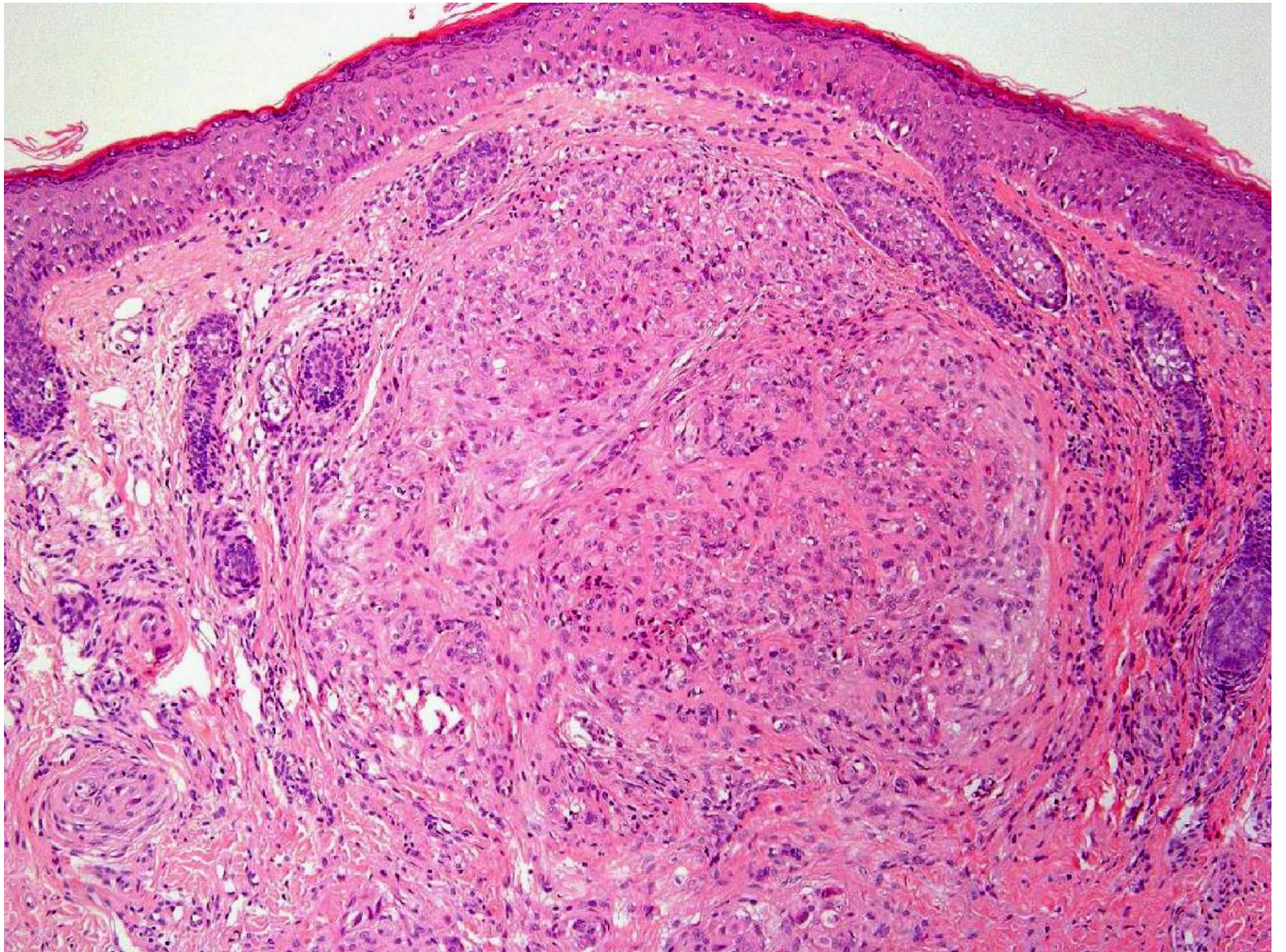
The Bad

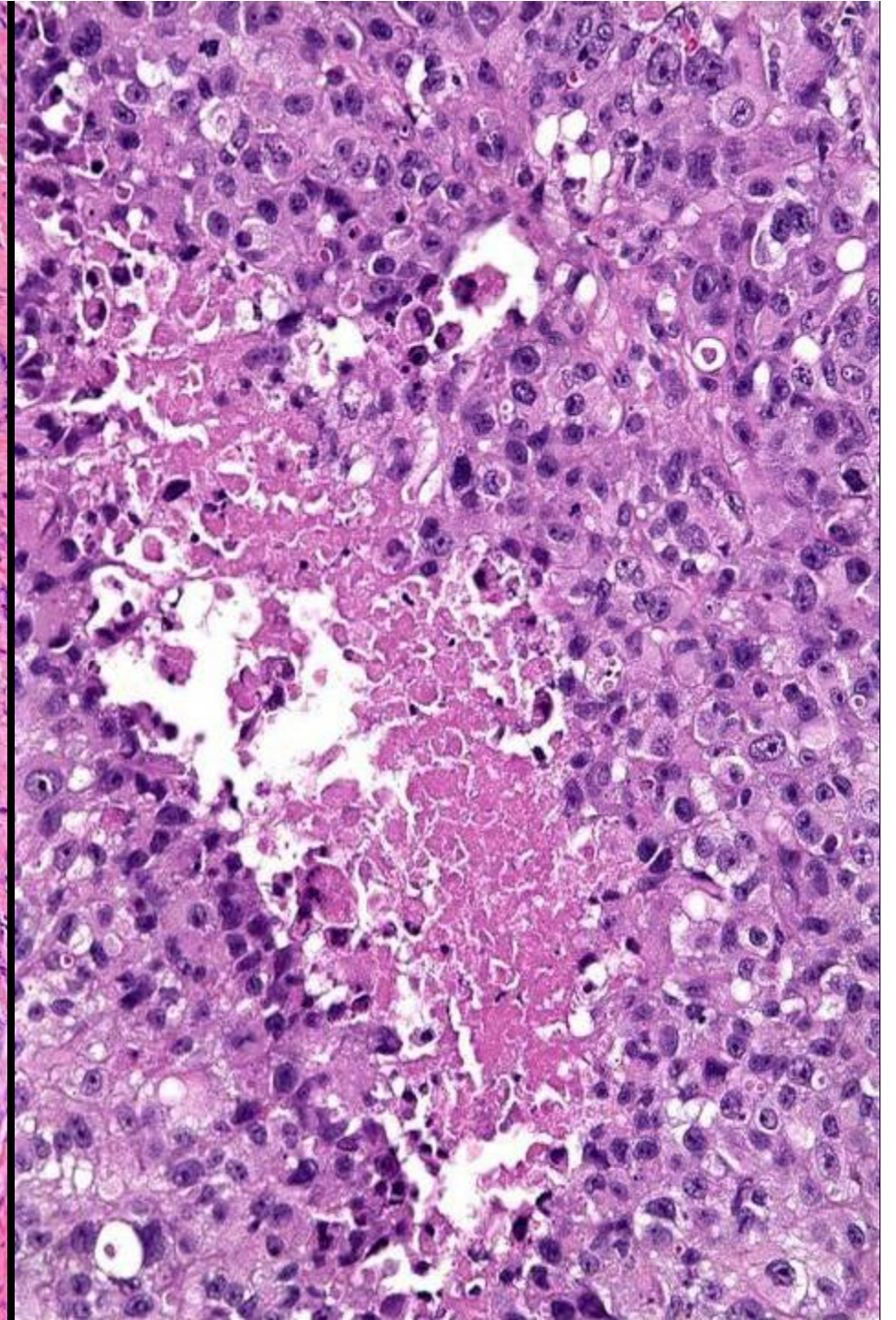
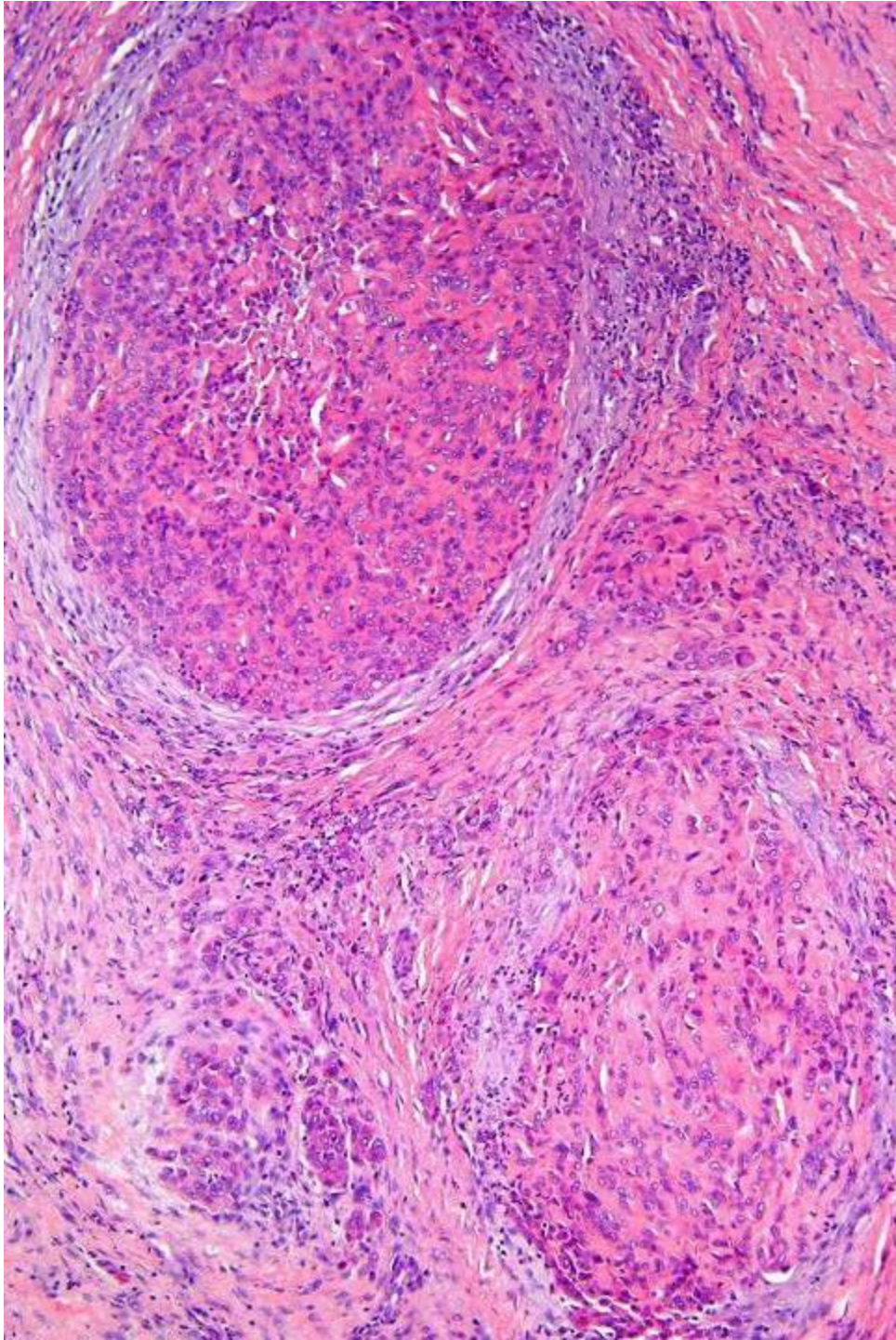


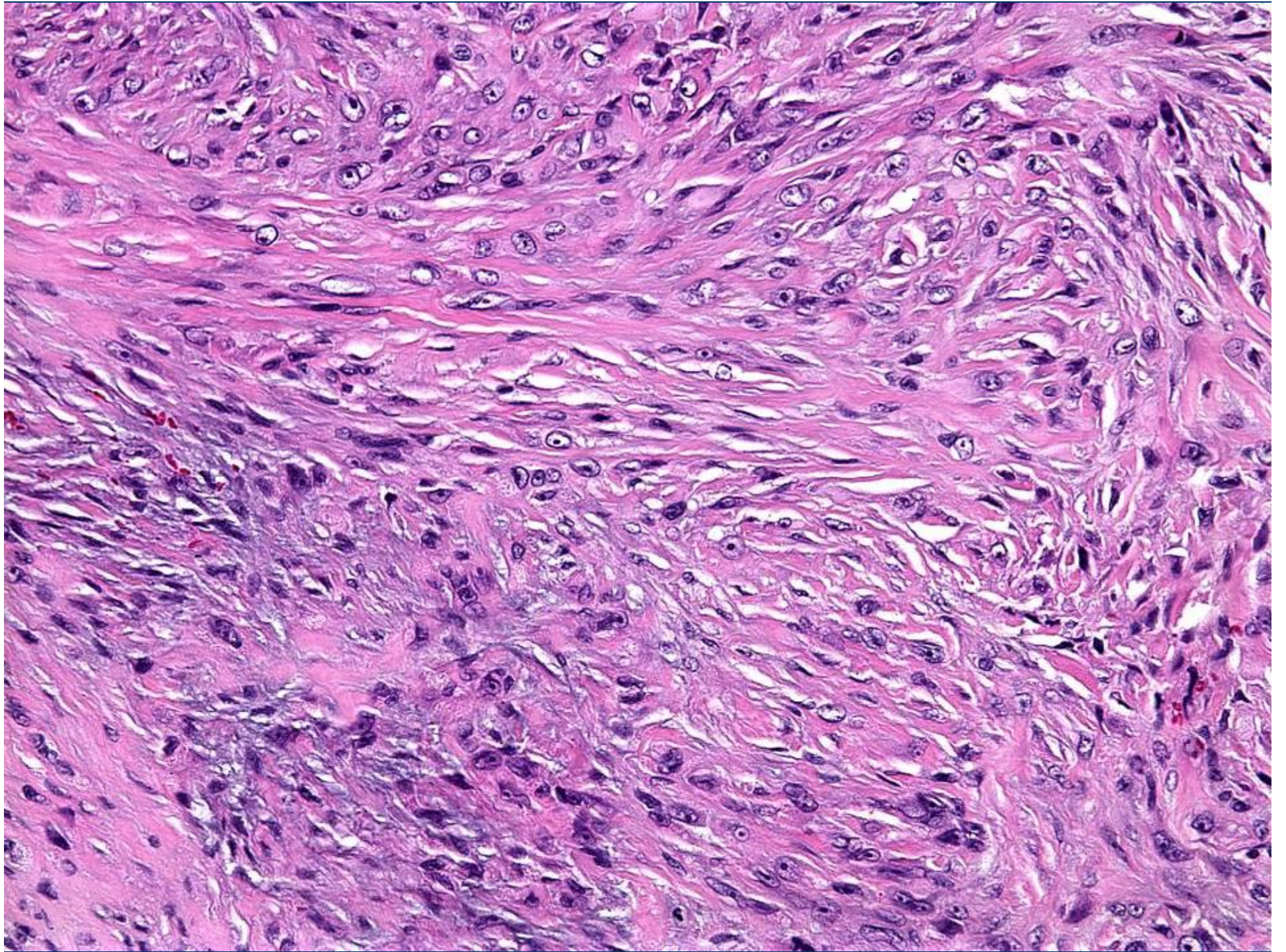
Things that are bad even though they don't look bad

Epithelioid Sarcoma

- Clinical Features
 - Children and young adults (wide age range)
 - Most common on distal extremities
 - Subcutaneous nodule, often ulcerated
- Microscopic features
 - Nodules of relatively bland epithelioid cells, often with central necrosis
 - May be predominantly spindled
- Immunophenotype
 - Positive for cytokeratin, EMA, and CD34 (50%)
 - Negative for INI-1
 - May be Factor XIIIa-positive







Behavior

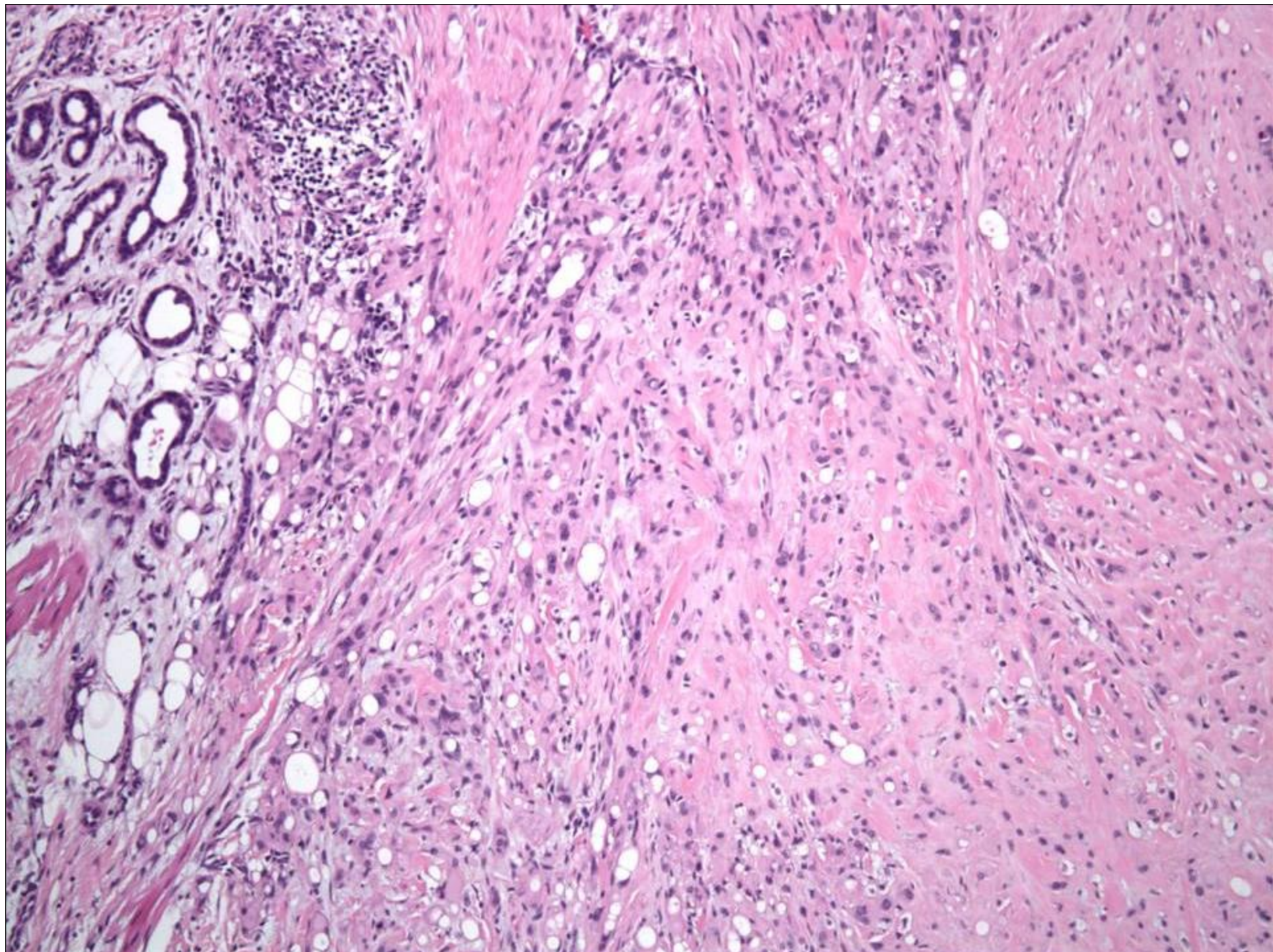
- Frequent local recurrence and metastasis
- 5 year survival 50-85%
- 10 year survival 42-55%
- Treatment
 - Wide local excision
 - Amputation
 - Lymph node dissection

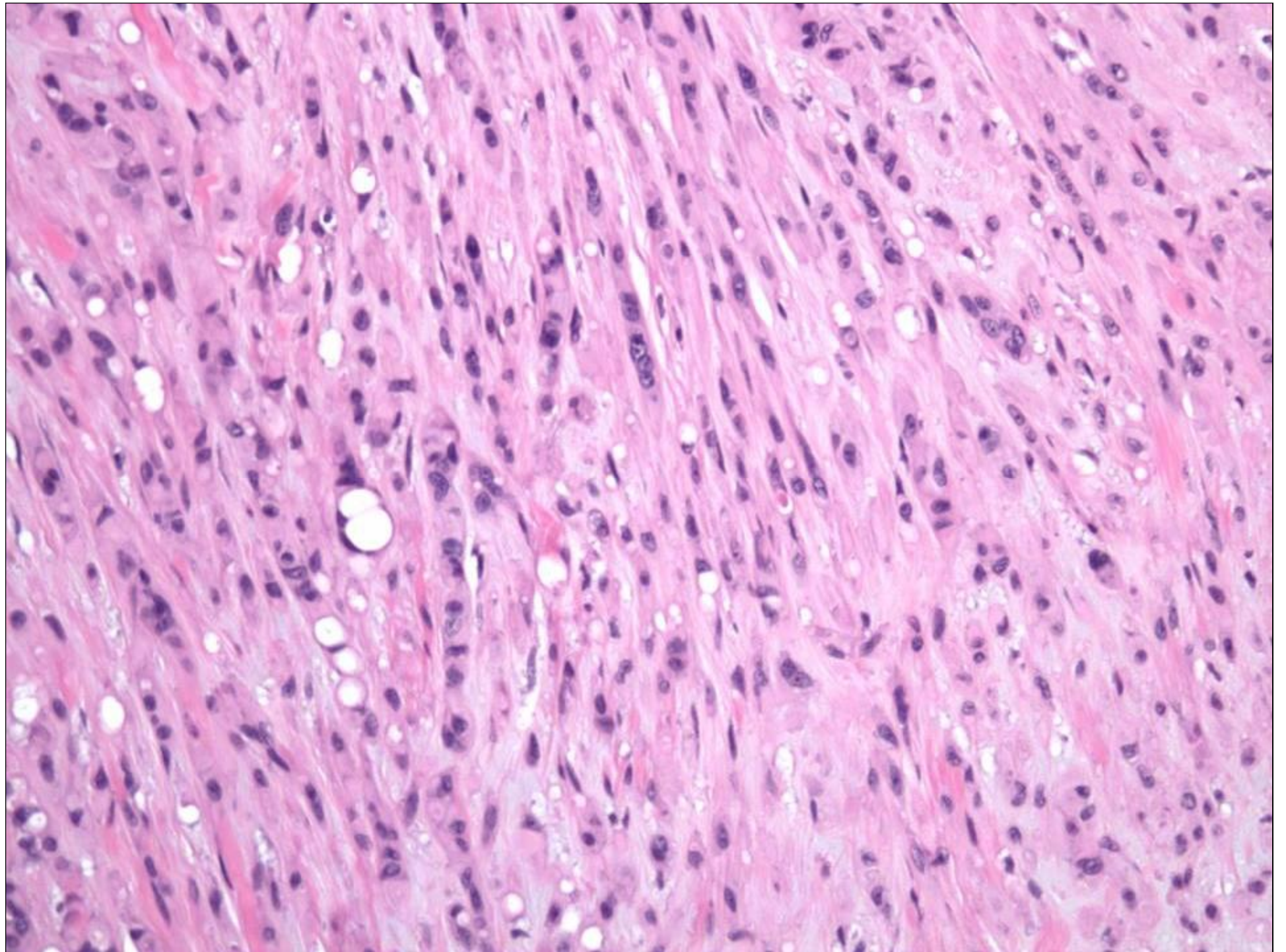
Differential Diagnosis

- Granulomatous processes
 - Infection, sarcoidosis, granuloma annulare, necrobiosis lipoidica, rheumatoid nodule
- Cellular fibrous histiocytoma
 - Rule of thumb: Consider ES when contemplating CFH of distal extremity
- Cellular neurothekeoma
- Plexiform fibrohistiocytic tumor
- Epithelioid hemangioendothelioma
- Epithelioid sarcoma-like hemangioendothelioma

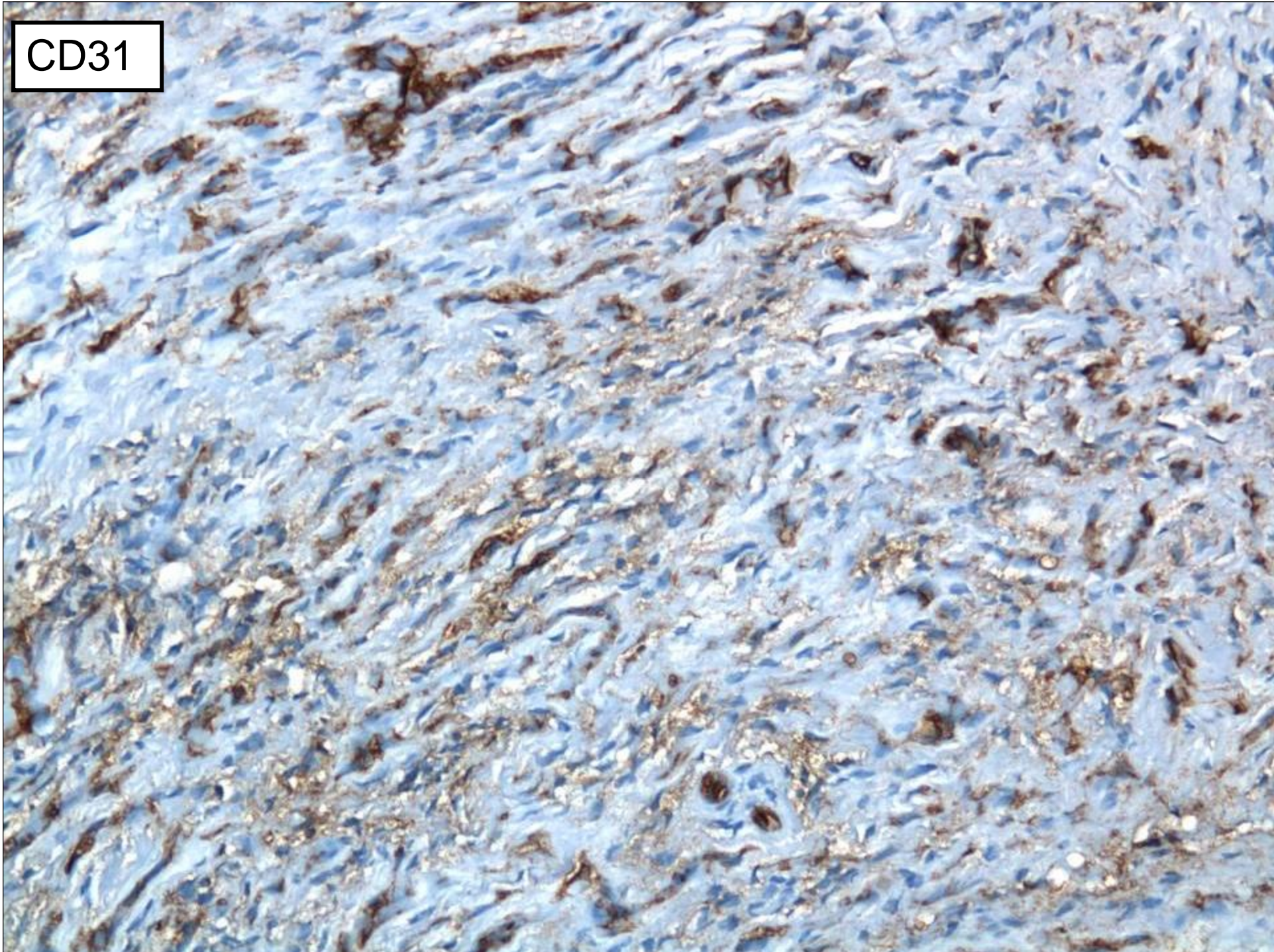
Epithelioid Hemangioendothelioma

- Clinical Features
 - Usually adults
 - Usually nondescript appearance
 - Usually not violaceous
- Microscopic features
 - 50% associated with vessel (less commonly seen in cutaneous tumors)
 - Cords to nests of epithelioid cells
 - Bland nuclei with intracytoplasmic lumens
 - 25% significant atypia
 - Myxohyaline stroma
 - CD31 and CD34+; 25% Keratin+





CD31



Epithelioid Hemangioendothelioma: New insights into pathogenesis

- Cytogenetics

- >90% Epithelioid hemangioendotheliomas have $t(1;3)(p36;q25)$
- Fusion of *WWTR1* and *CAMTA1*
- *WWTR1*: transcriptional coactivator highly expressed in endothelial cells
- *CAMTA1*: DNA binding transcriptional regulatory protein usually expressed in brain
- Possible therapeutic target

MR Tanas et al. Sci Transl Med. 2011;3:98ra82.

Epithelioid Hemangioendothelioma

- Behavior
 - Considered tumor of intermediate malignancy
 - Frequent recurrence (10-15%)
 - Lymph node and pulmonary metastasis (up to 30%)
 - Overall mortality: 10-20%

Epithelioid Sarcoma-like Hemangioendothelioma

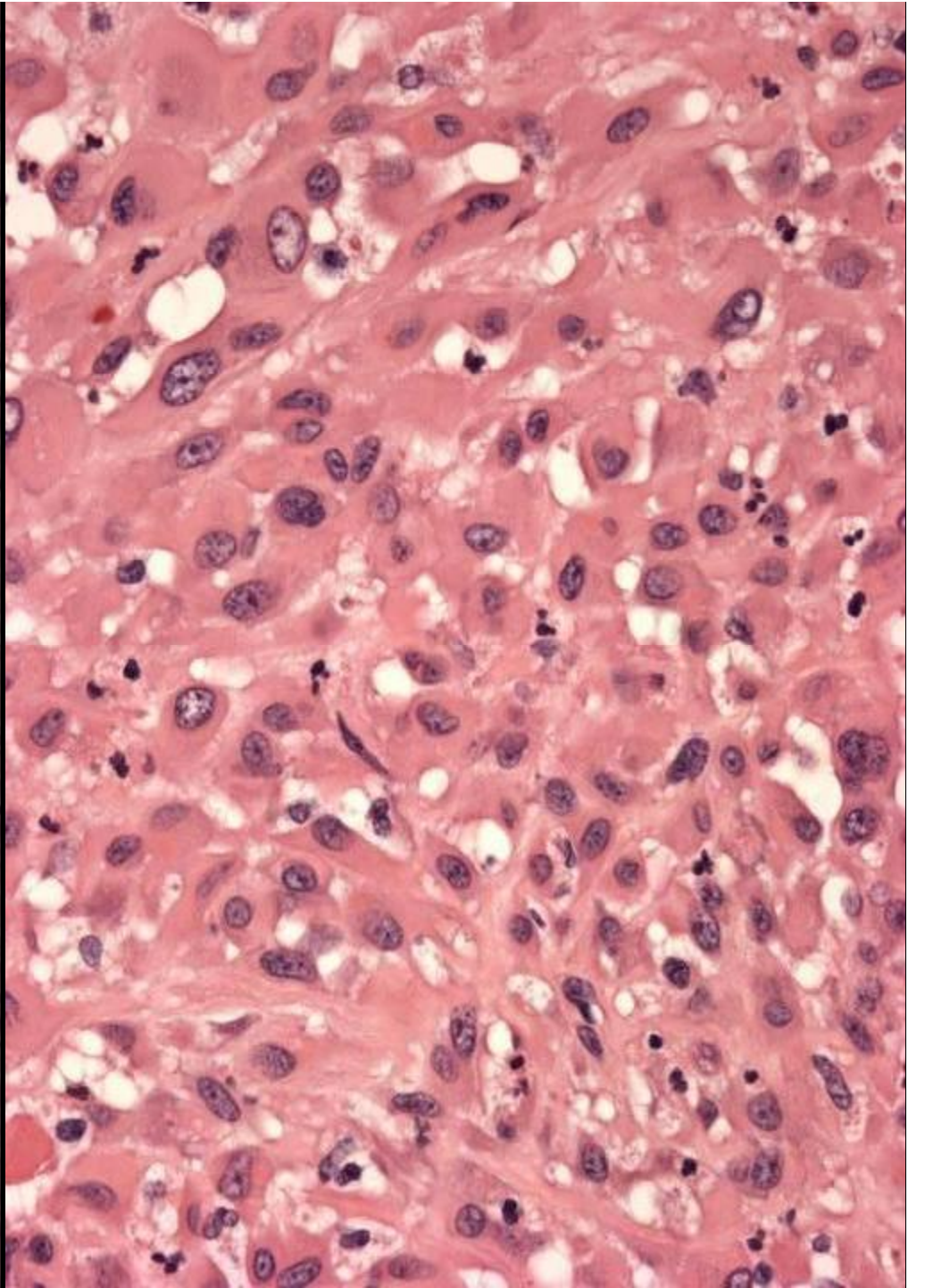
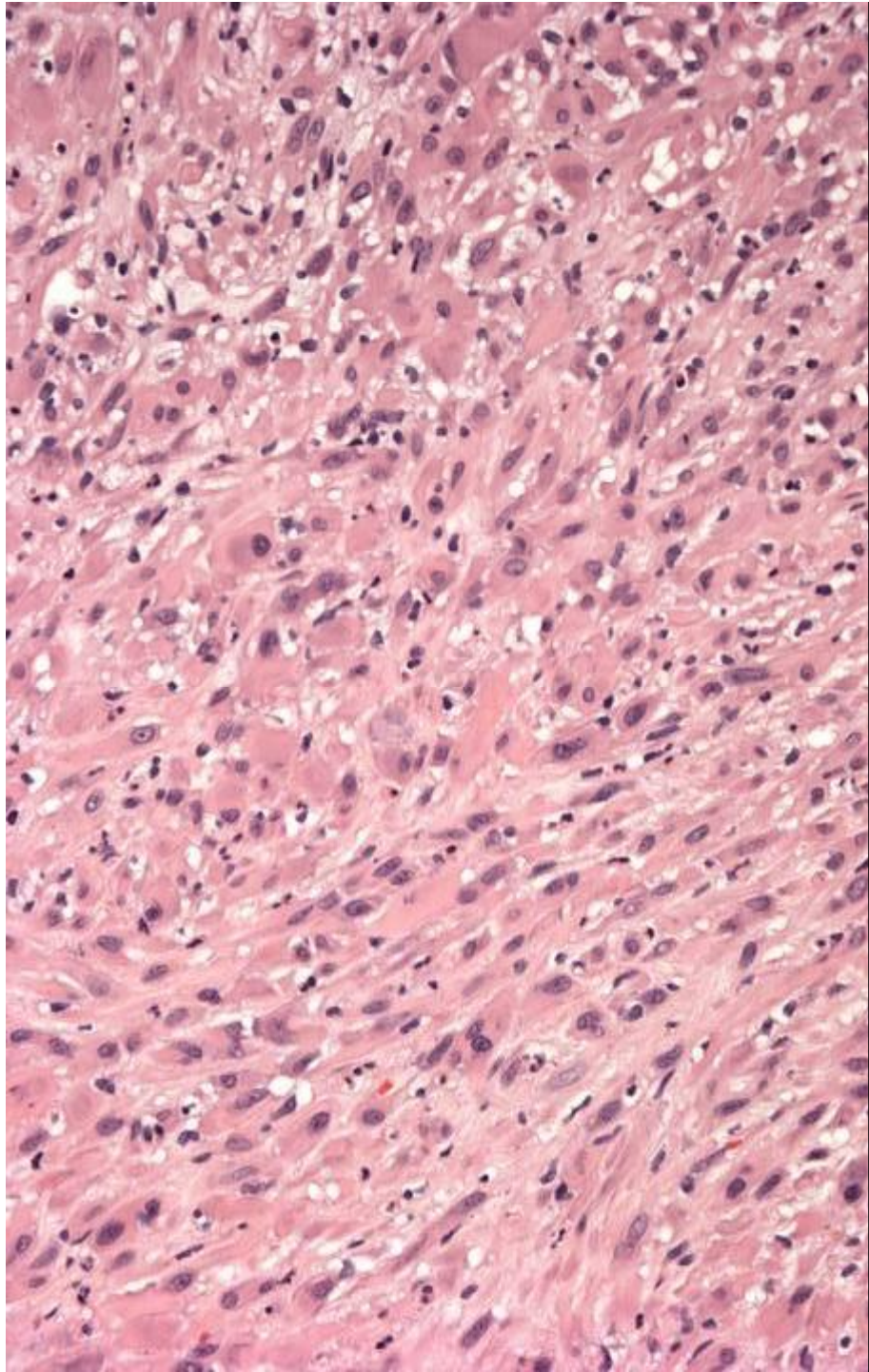
- Rare entity originally described in 2003
- Equally involves superficial or deep soft tissue
- Can present as ulcerated lesion



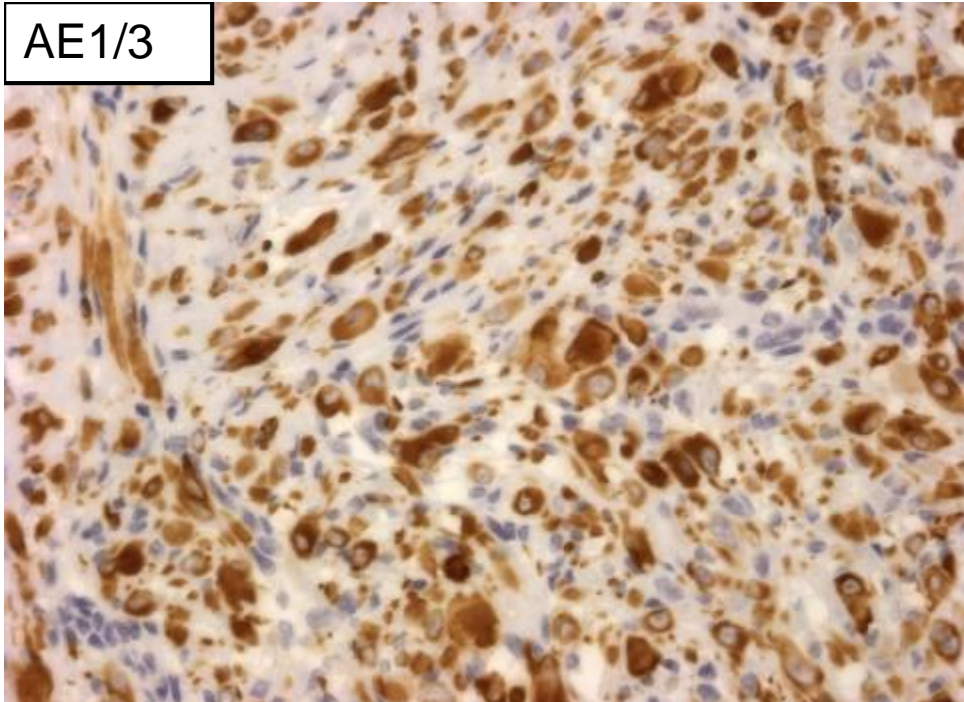
(Am J Surg Pathol 27:48-57, 2003.)

Epithelioid Sarcoma-like Hemangioendothelioma

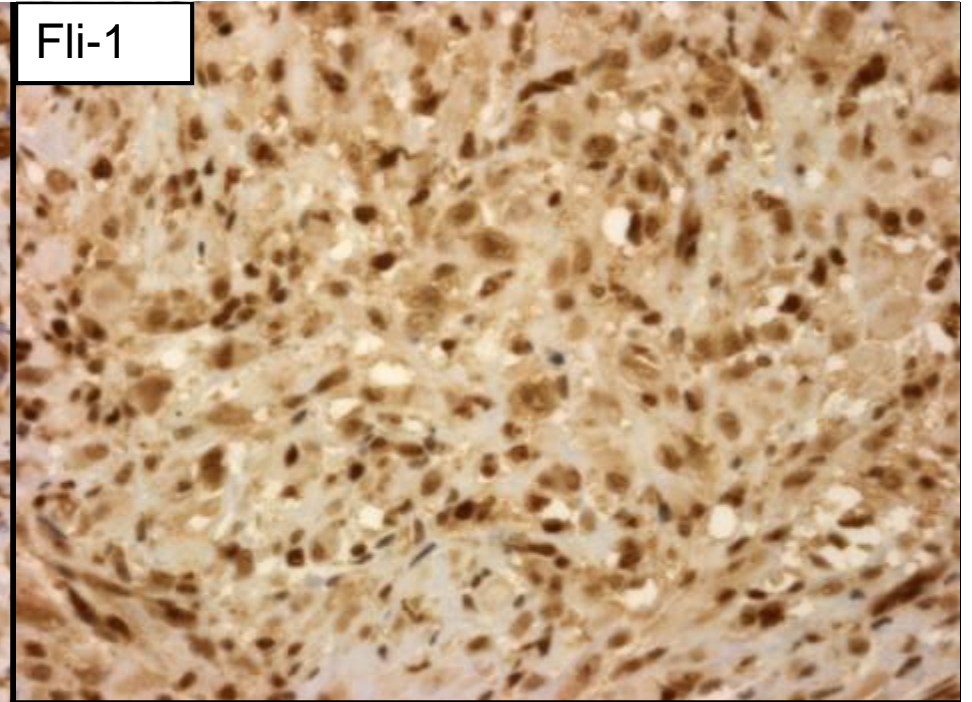
- Ill-defined nodules, sheets or fascicles
- Epithelioid to spindled tumor cells
- Abundant eosinophilic cytoplasm
- No overt vascular channels
- Subtle evidence of vascular differentiation consisting of focal intracytoplasmic lumen
- Unique immunophenotype
 - AE1/3+, CD31+, Fli-1+
 - CD34-



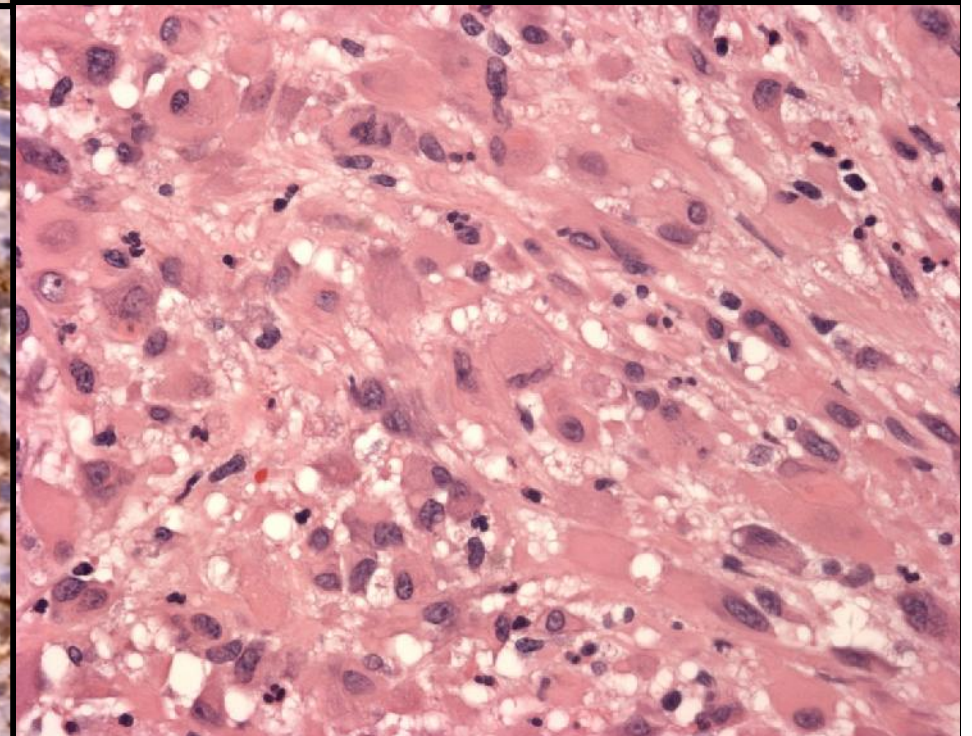
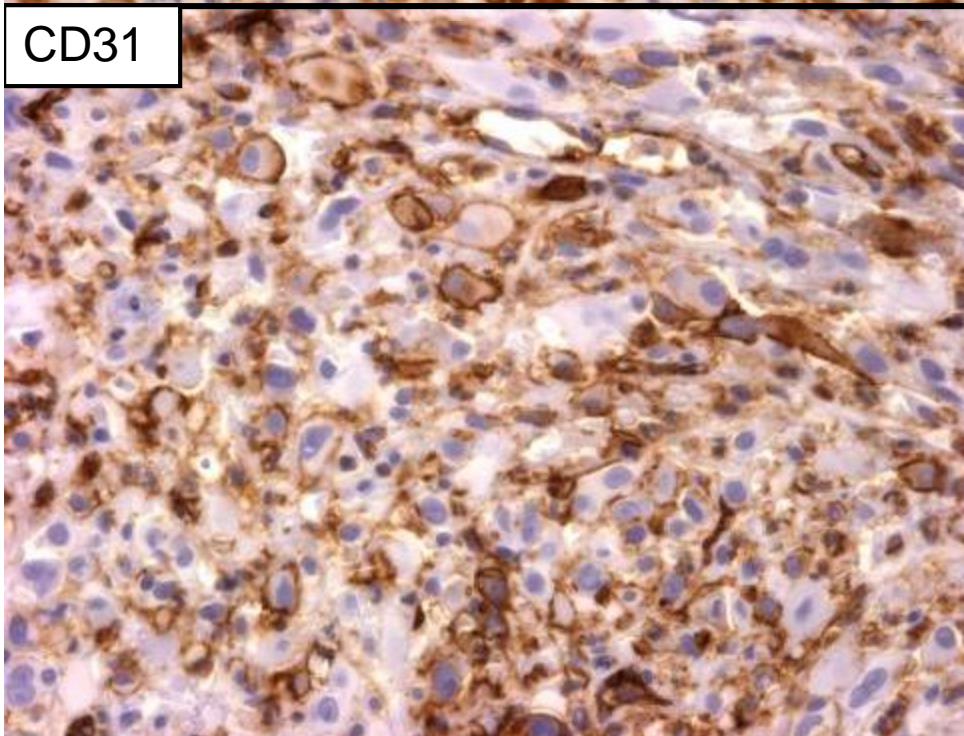
AE1/3



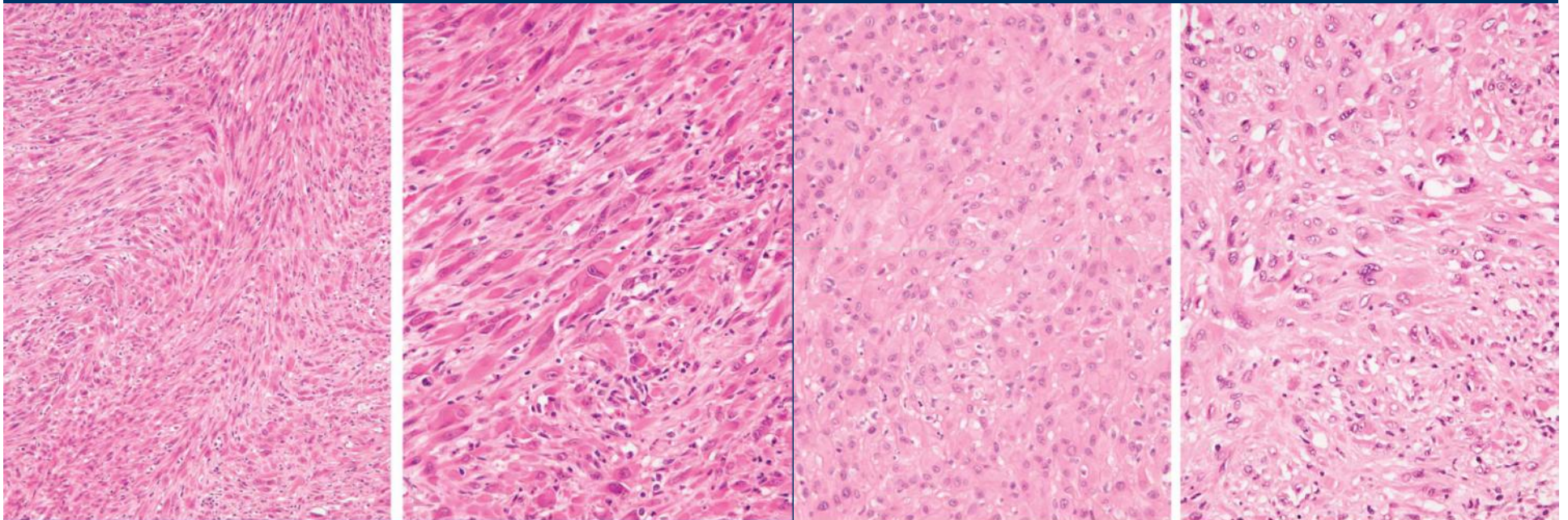
Fli-1



CD31

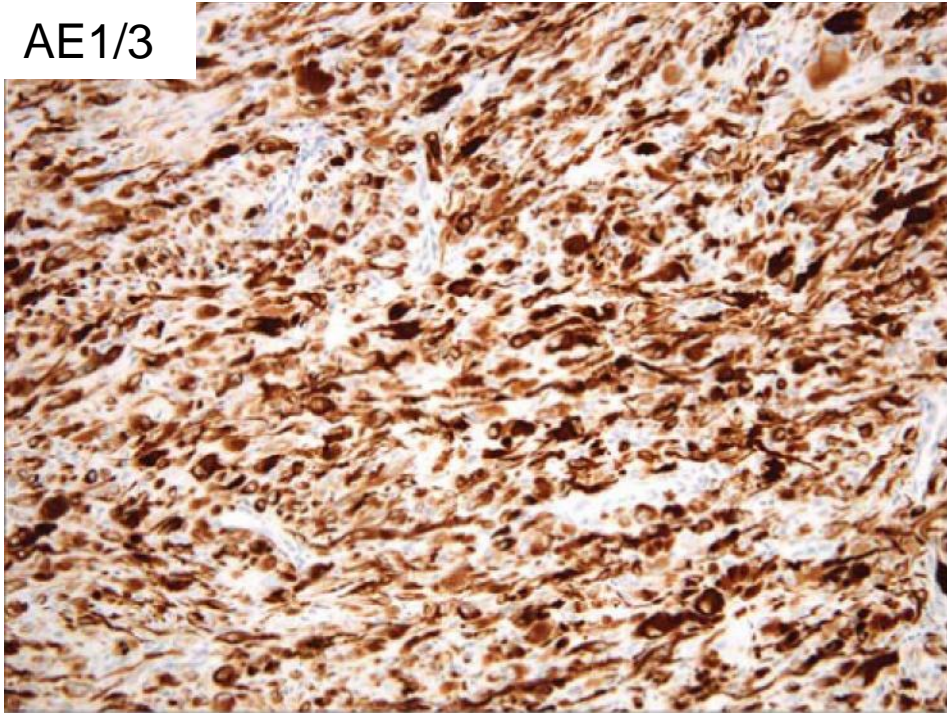


“Pseudomyogenic Hemangioendothelioma”

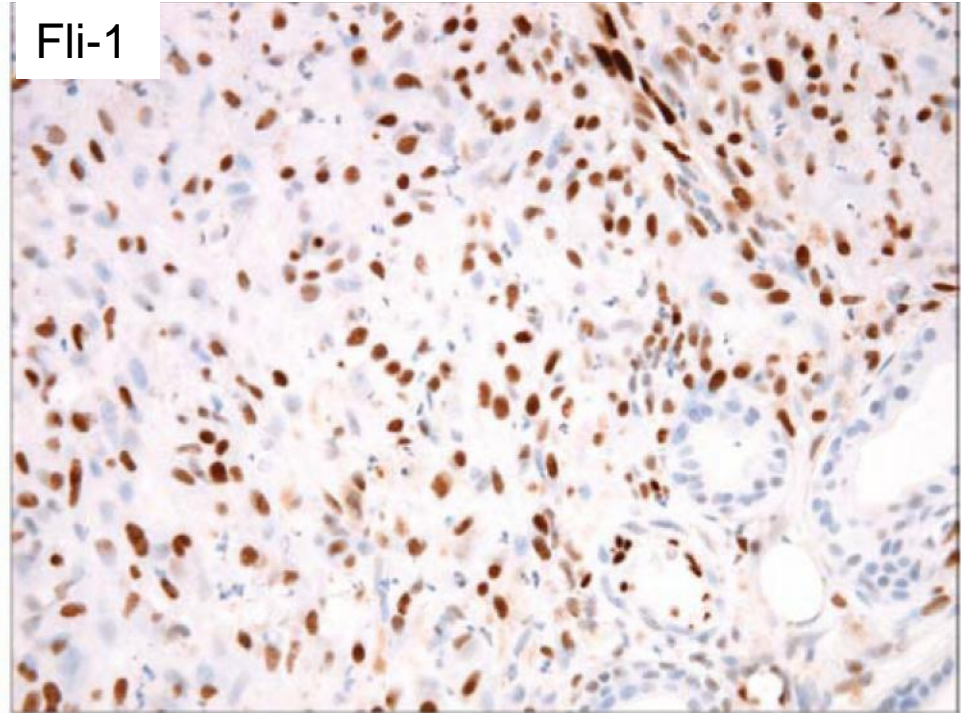


Hornick and Fletcher Am J Surg
Pathol 35:190-201, 2011

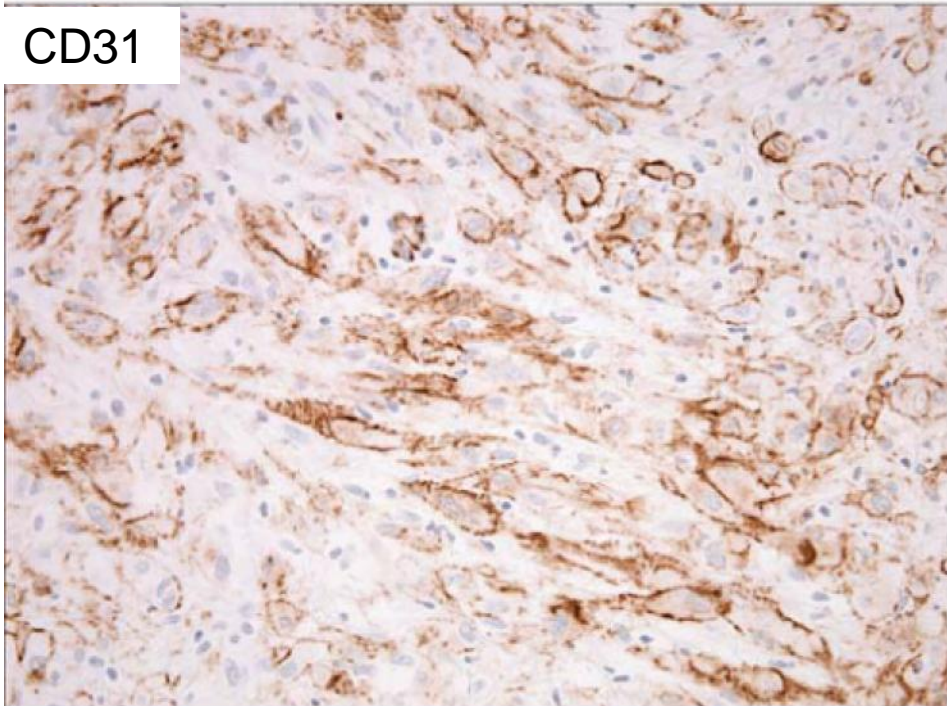
AE1/3



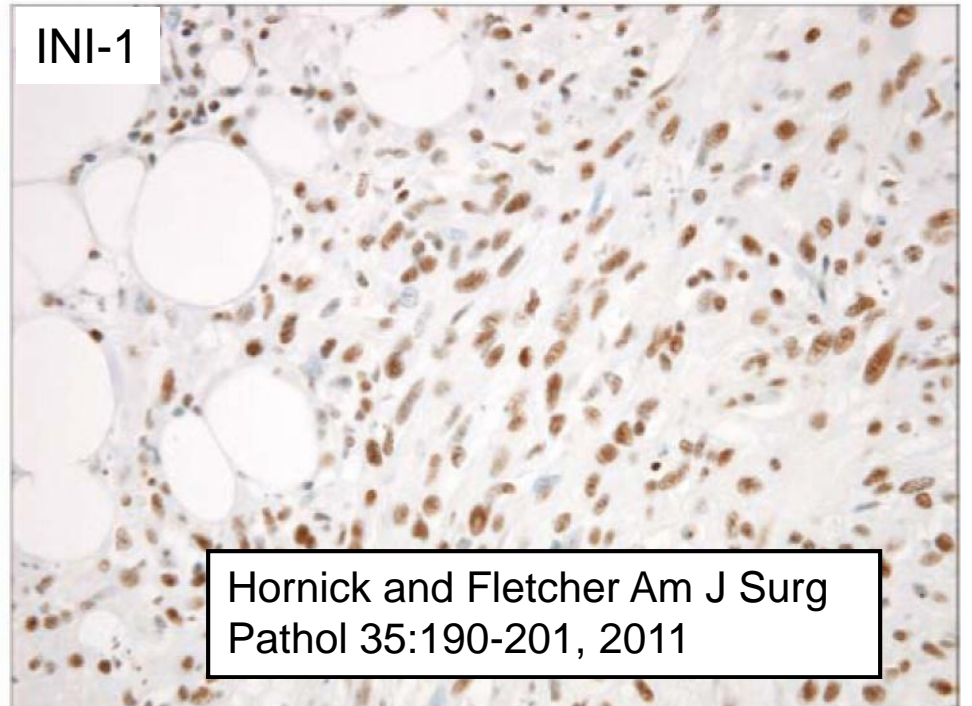
Fli-1



CD31



INI-1



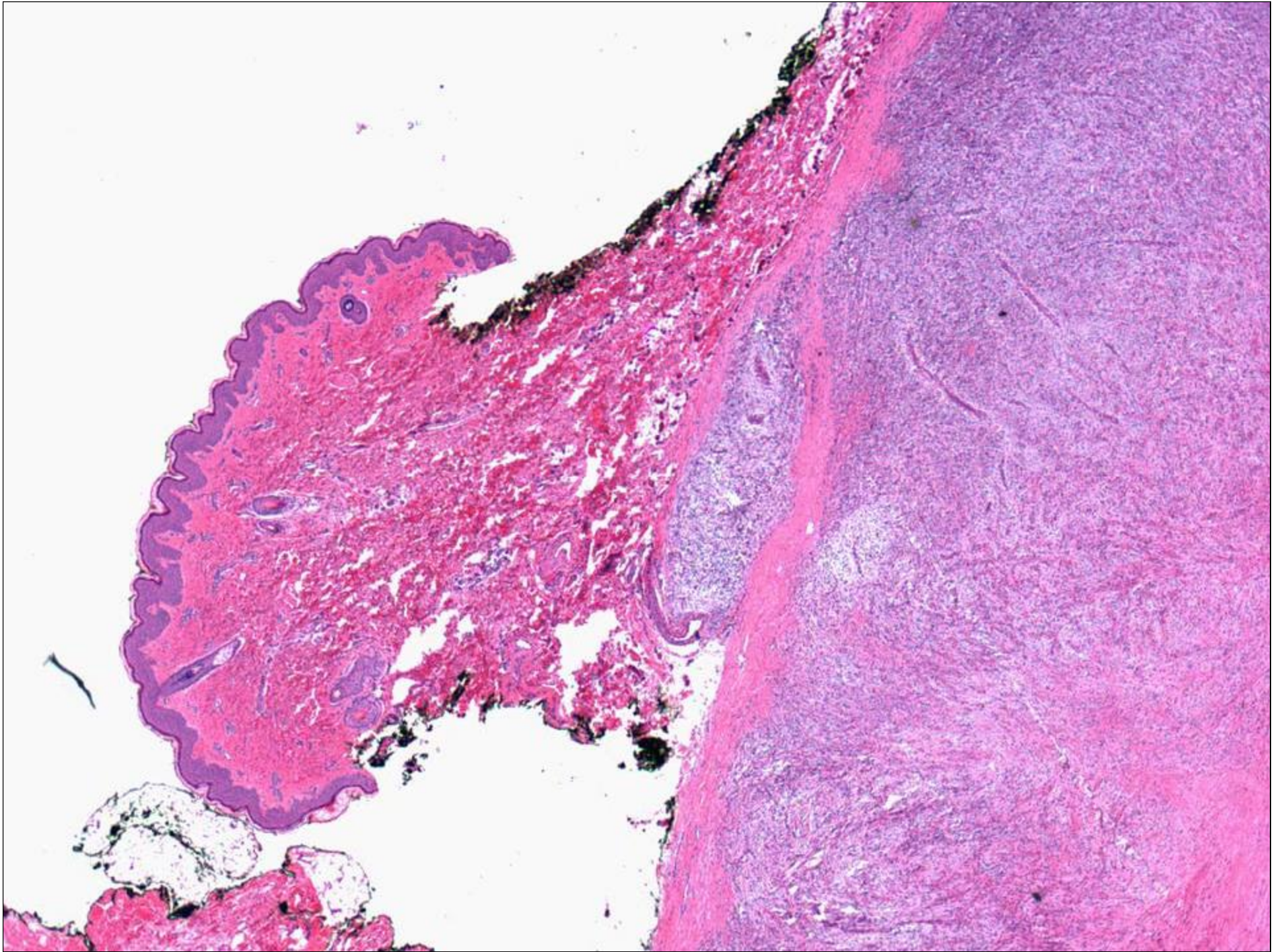
Hornick and Fletcher Am J Surg Pathol 35:190-201, 2011

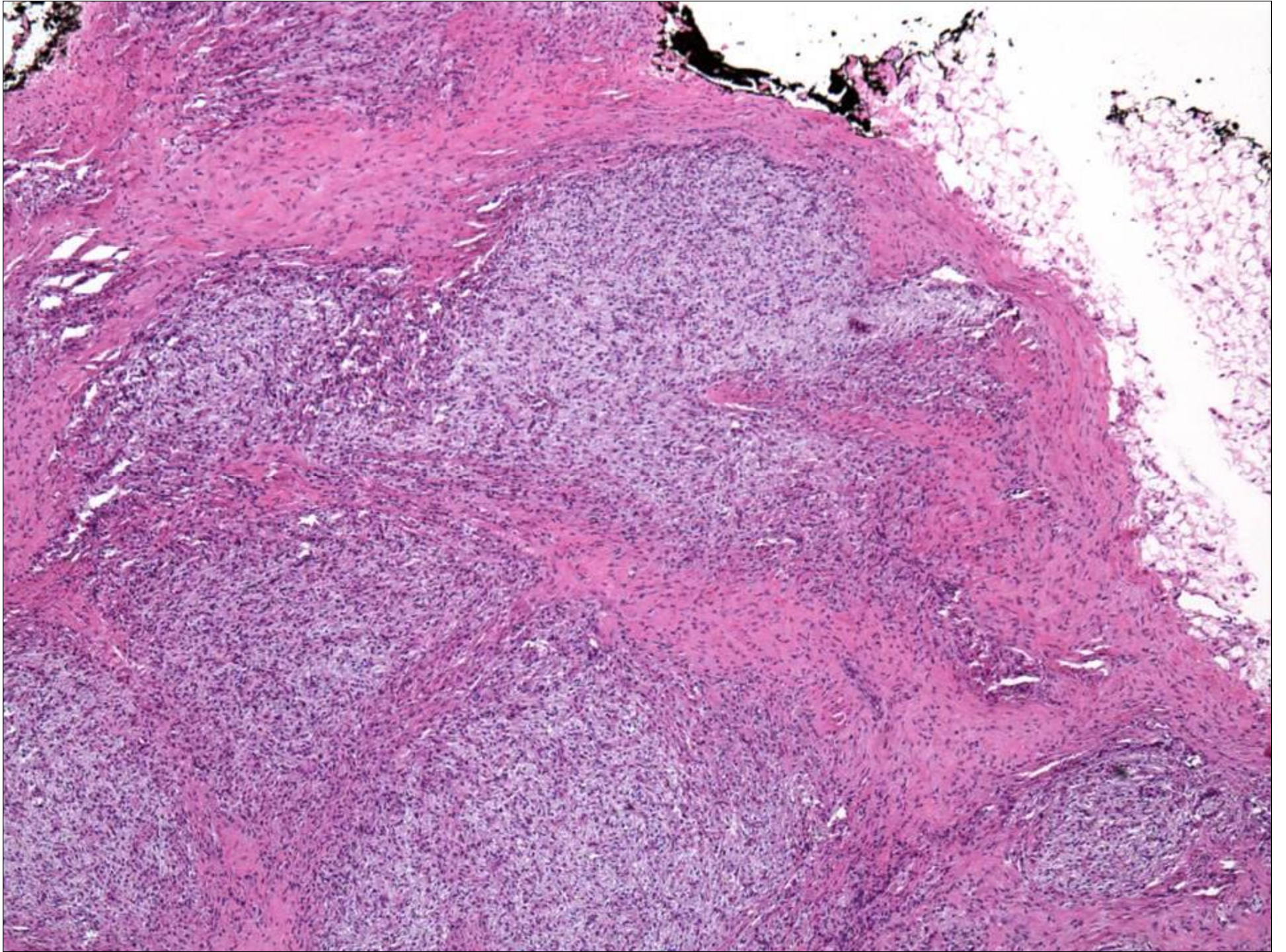
Epithelioid Sarcoma-like/Pseudomyogenic Hemangioendothelioma

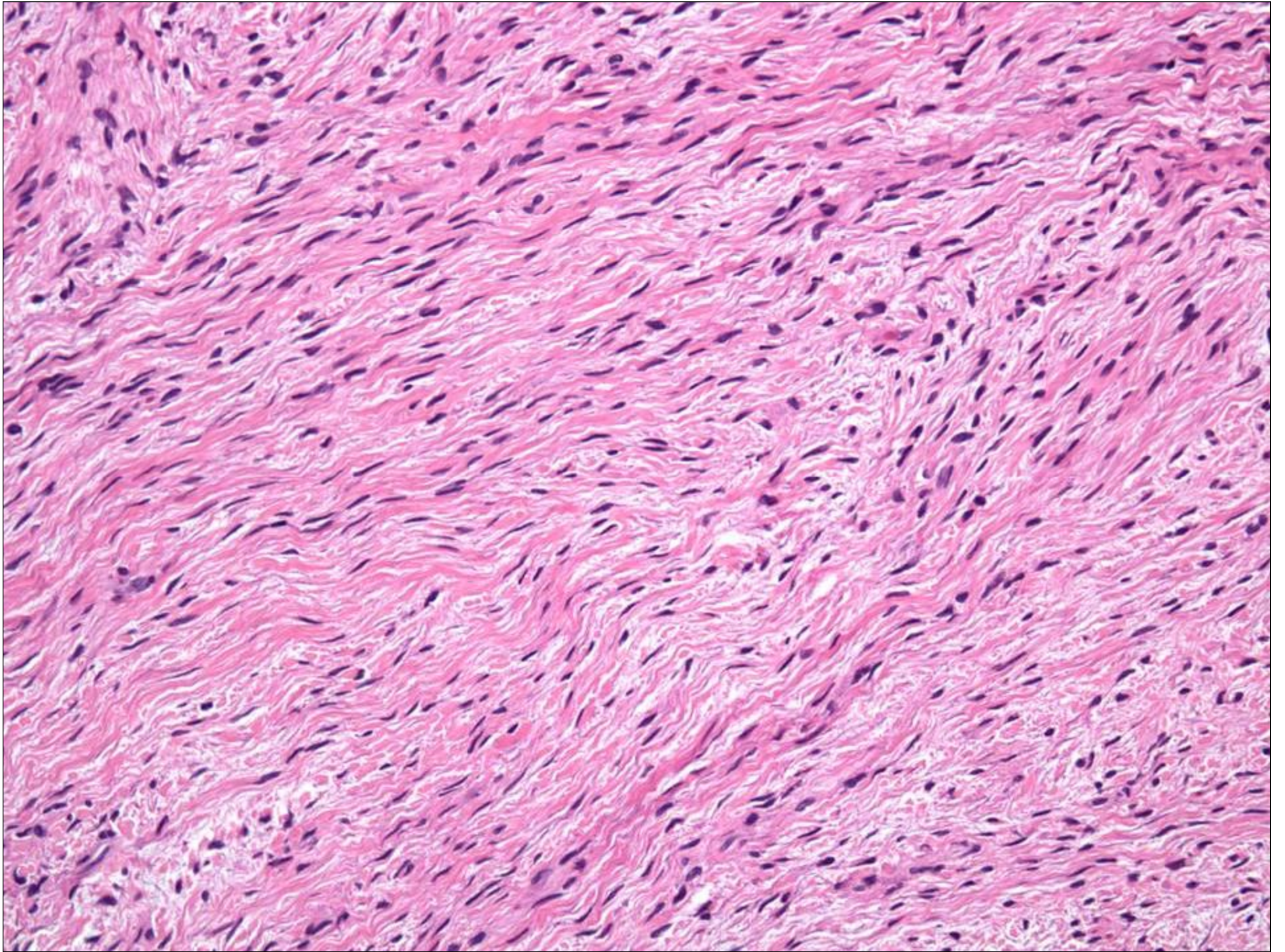
- Behavior
 - Relatively indolent
 - Risk of local recurrence
 - Multifocal disease ~2/3 of patients
 - Rare lymph node and distant metastasis

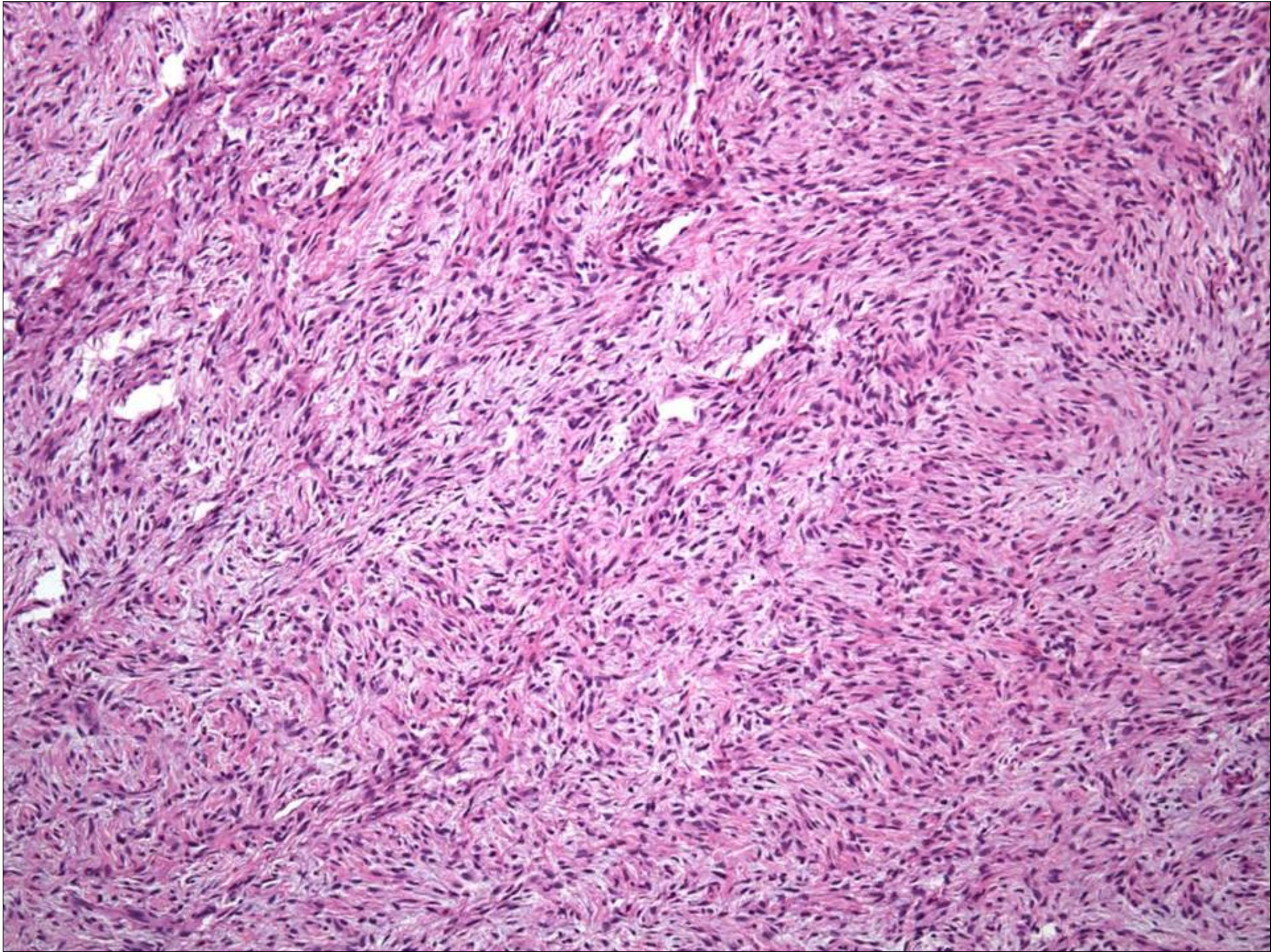
Case

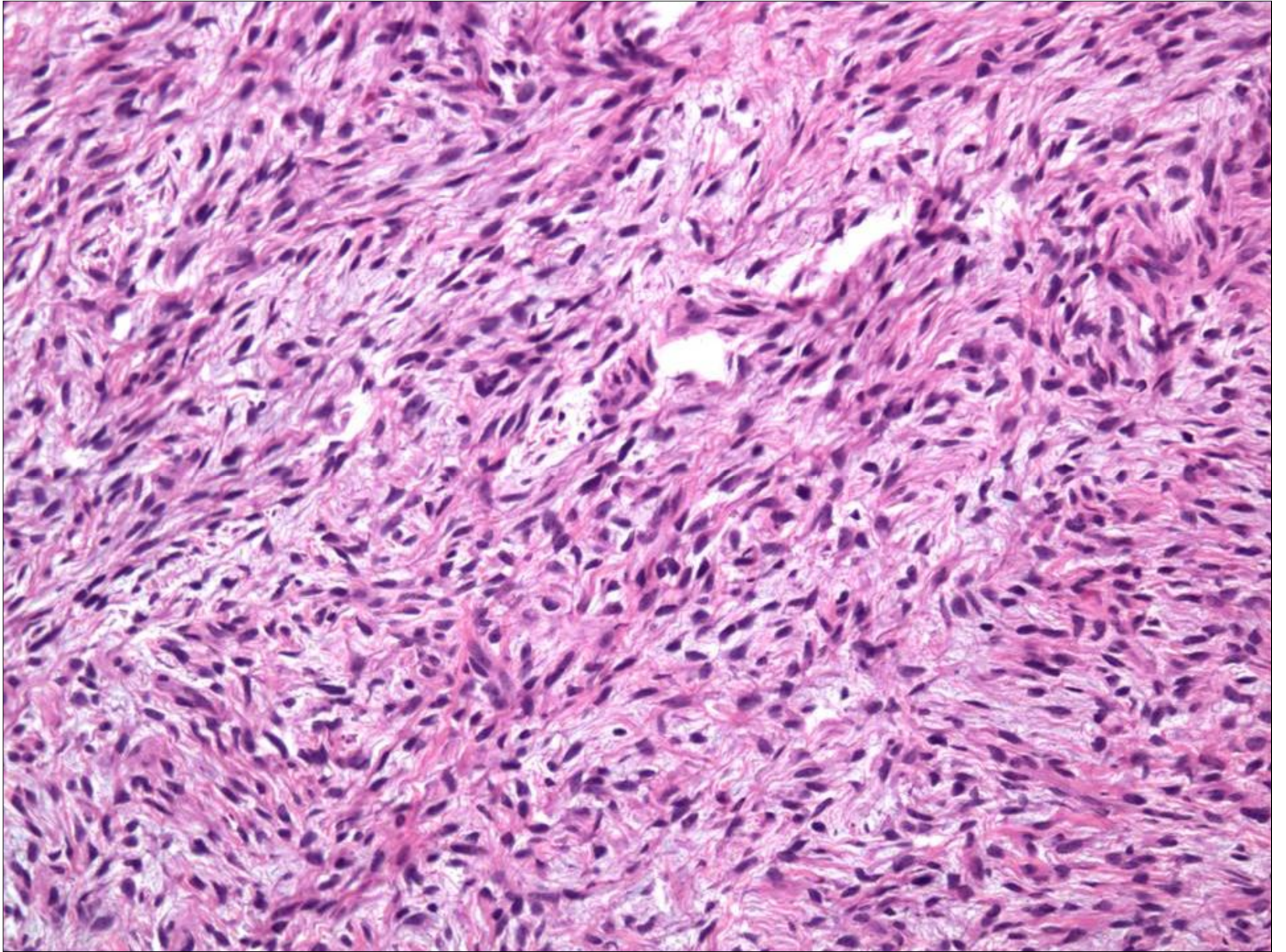
A 4-year-old girl presented with a
flank mass







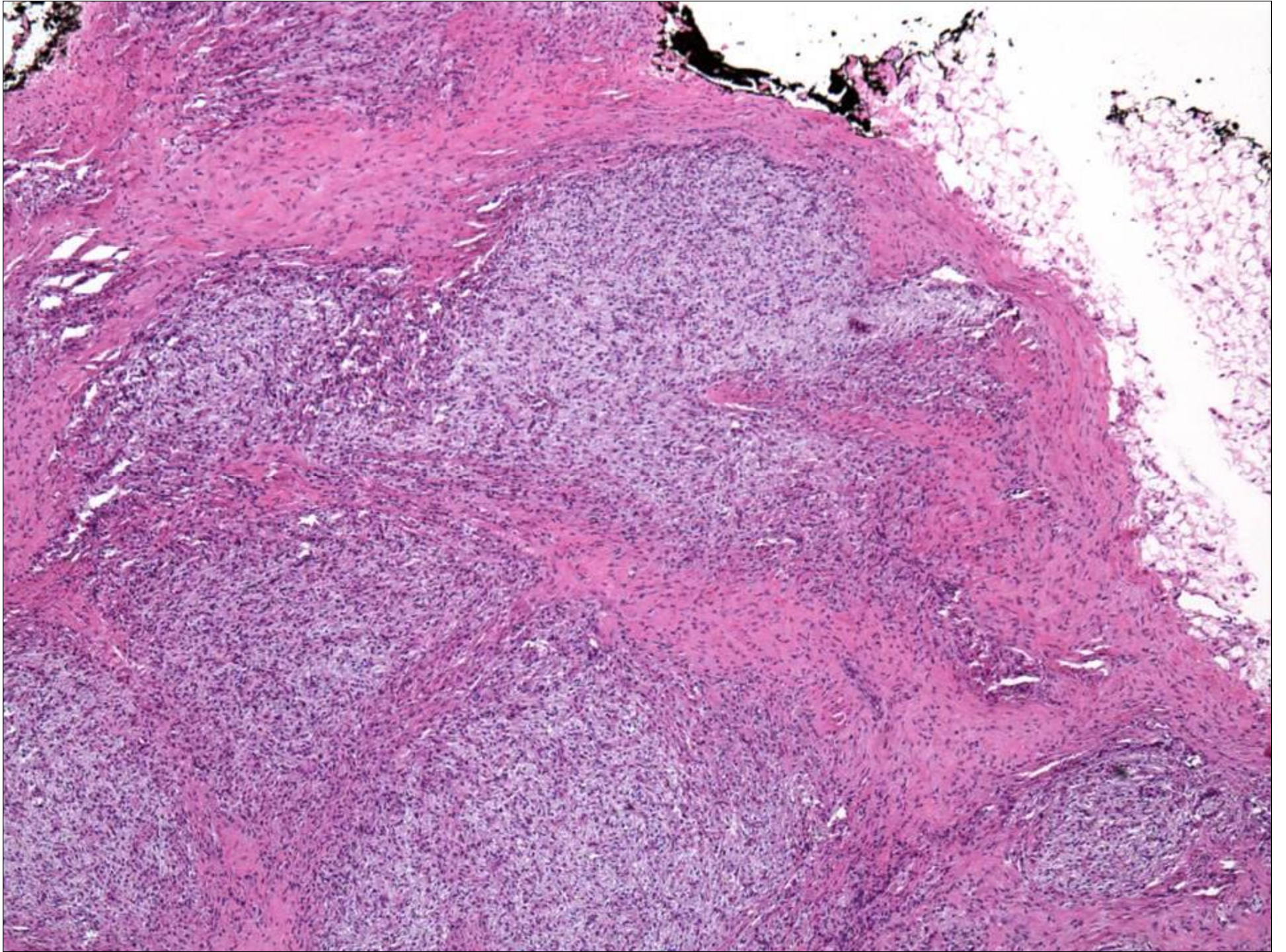




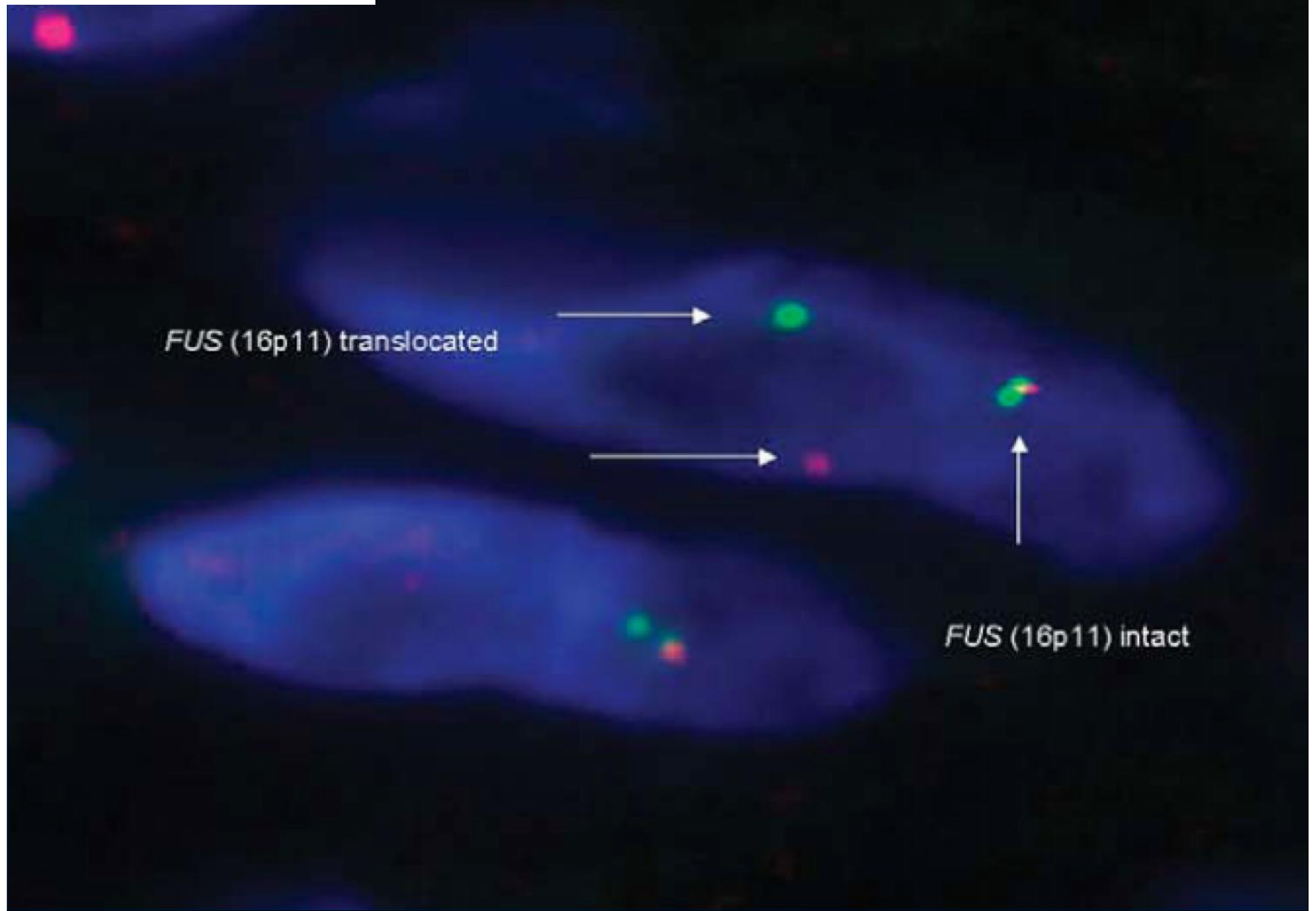
Diagnosis?

Immunostains

- S100 protein negative
- CD34 negative
- EMA negative
- Cytokeratin negative



FSH for *FUS*



Low Grade Fibromyxoid Sarcoma

- 1986: First described by Evans
 - 2 cases of deceptively bland sarcomas with paradoxically aggressive behavior
- 1993: 12 additional cases
 - Similarly bland features
 - Aggressive behavior:
 - Metastasis in 7/12
 - 4 DOD
 - 3 AWD

Hyalinizing Spindle Cell Tumor with Giant Collagen Rosettes (HSTGR)

- Described in 1997 (Lane et al, AJSP 1997)
- Clinical and histologic similarities to LGFMS
- Possibly a variant of LGFMS
- Relationship with LGFMS supported by presence of focal rosettes and small collagen rosettes in cases of LGFMS (Folpe et al, AJSP 2000)

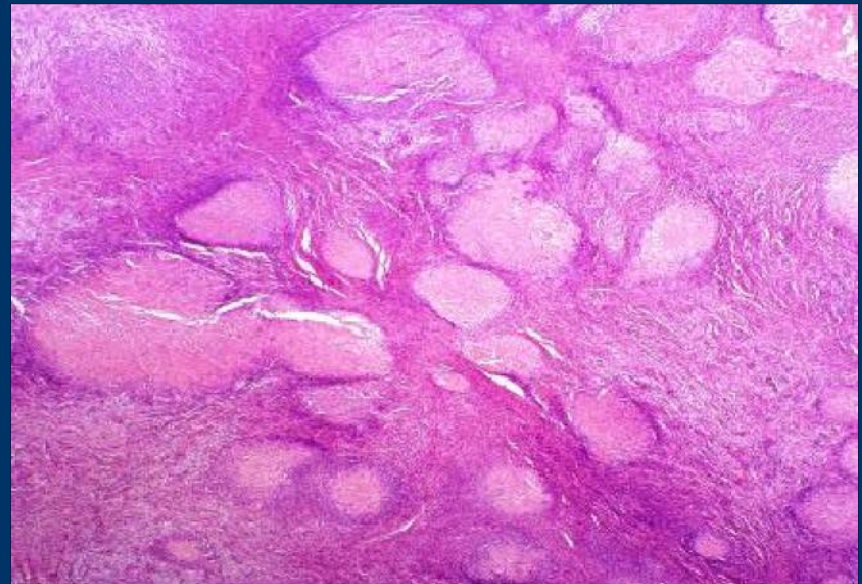
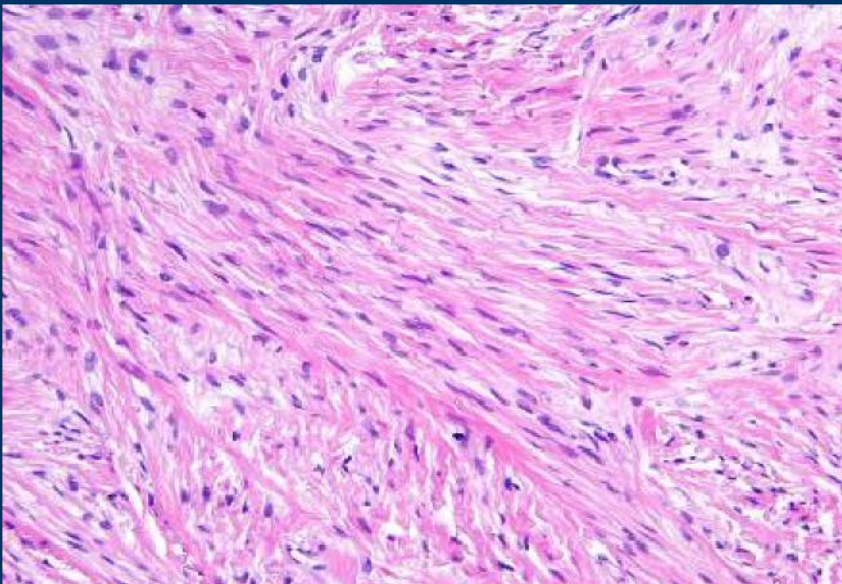
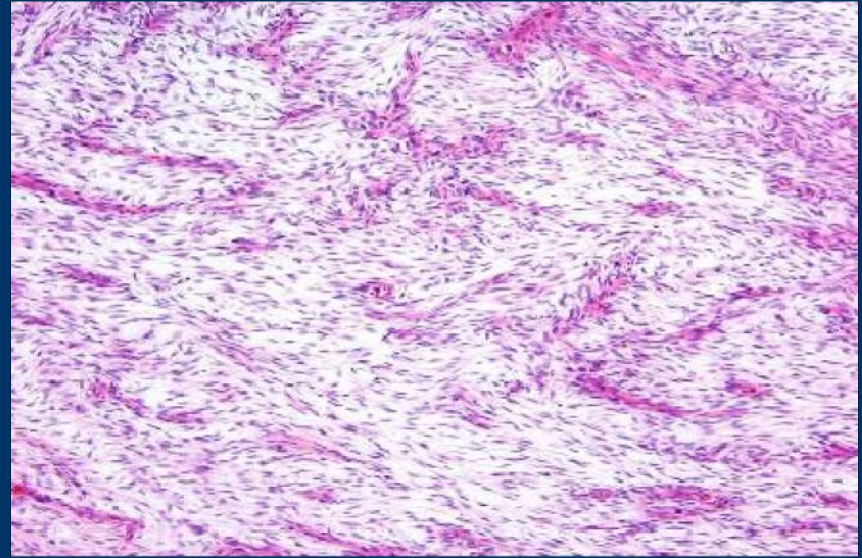
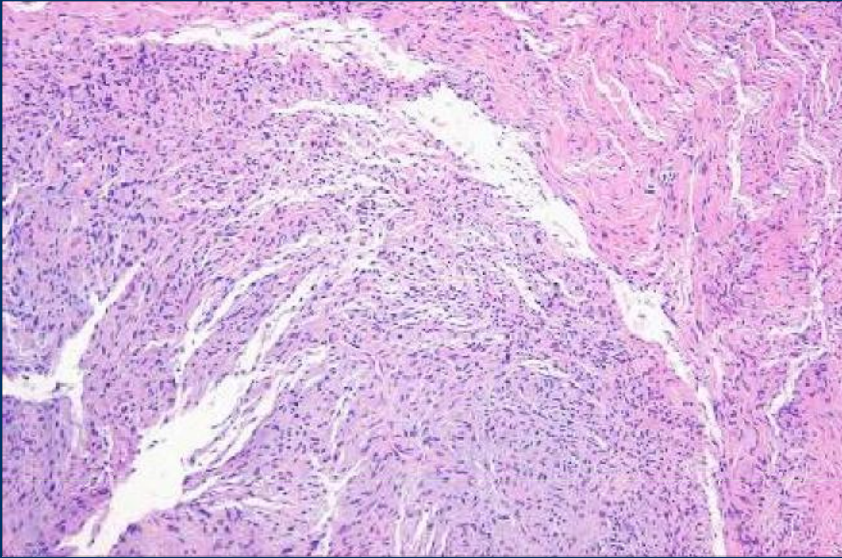
Cytogenetics

- Both HSTGR and LGFMS share common cytogenetic abnormality
 - t(7;16)(q34;p11)
 - Fusion of *FUS/CREB3L2*
 - *FUS*: RNA-binding protein
 - *CREB3L2*: member of OASIS B-ZIP family of transcription factors

Clinical Features

- Primarily affects young to middle-aged adults
 - 10-20% of cases present in children
- Predominantly present as deep soft tissue mass
 - 20% present as superficial tumors of dermis or subcutis (Billings, et al AJSP 2005)
 - Superficial tumors relatively common in children (~40% of superficial tumors)

Histologic features



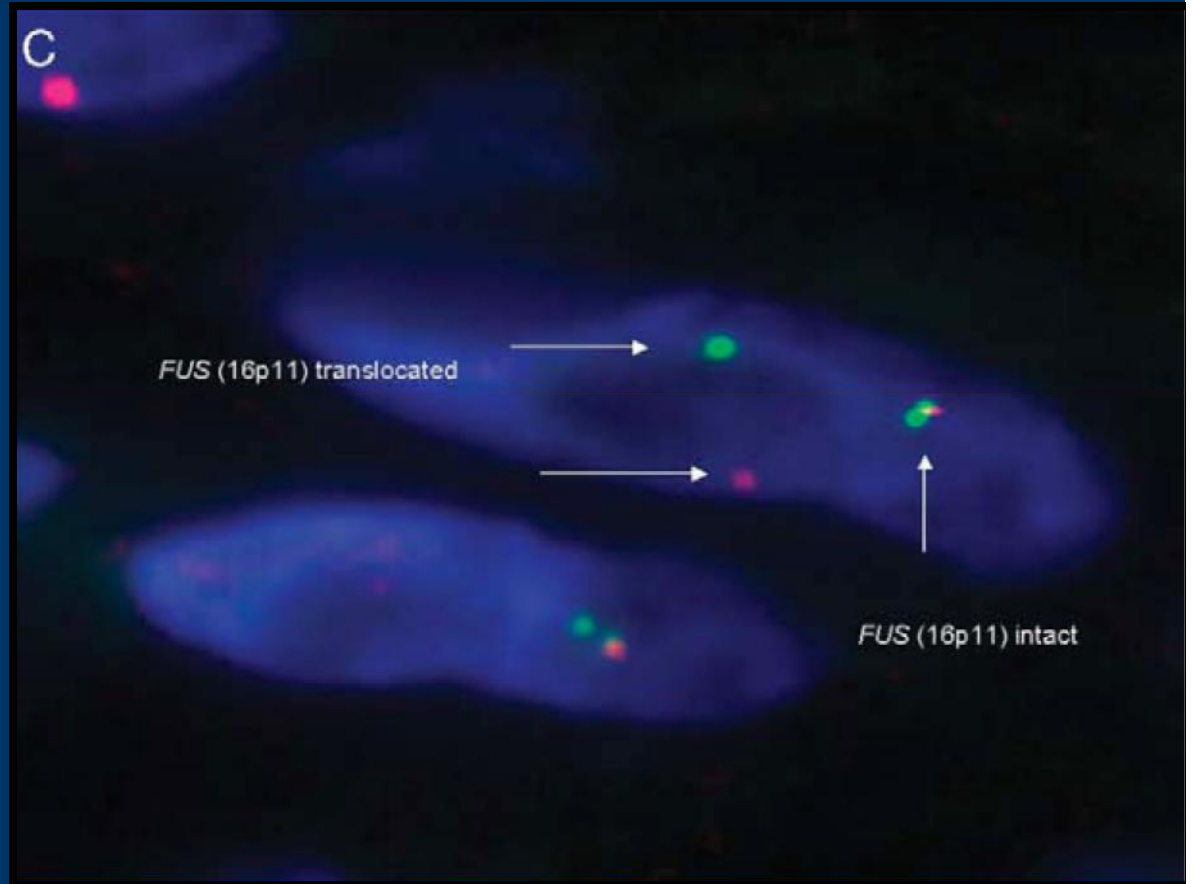
Immunohistochemistry

Previously a tool of exclusion

- Vimentin +
- Actins +/-
- EMA -/+ (30%)
- S100 -/+
- CD34 – (rare focal positivity)
- Desmin –
- Exception: MUC-4 positive >90%

FISH

- Dual color break apart probes for FUS
- Positive in 70-90%



Downs-Kelly et al Am J Surg
Pathol 2008;32:8-13

Low-Grade Fibromyxoid Sarcoma and Hyalinizing Spindle Cell Tumor With Giant Rosettes

A Clinicopathologic Study of 73 Cases Supporting Their Identity and Assessing the Impact of High-Grade Areas

Andrew L. Folpe, M.D., Kathryn L. Lane, M.D., Gerson Paull, M.D., and Sharon W. Weiss, M.D.

- 51 prospectively diagnosed as LGFMS
- 0 metastases
- 0 DOD
- LGFMS clinically behaves as low-grade sarcoma if accurately diagnosed and treated like a sarcoma
- Caveat: short follow-up

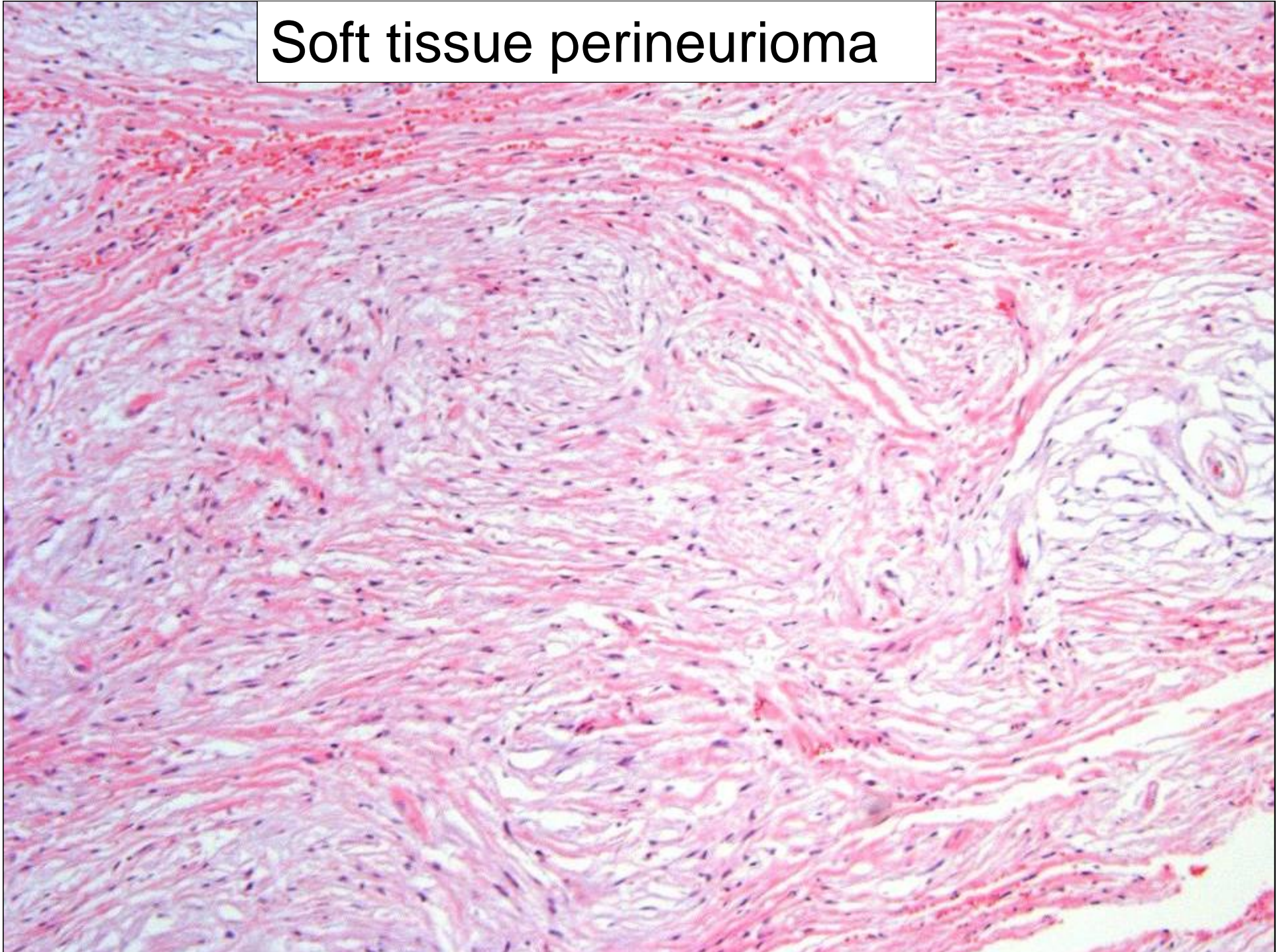
Low-Grade Fibromyxoid Sarcoma: A Clinicopathologic Study of 33 Cases With Long-Term Follow-Up

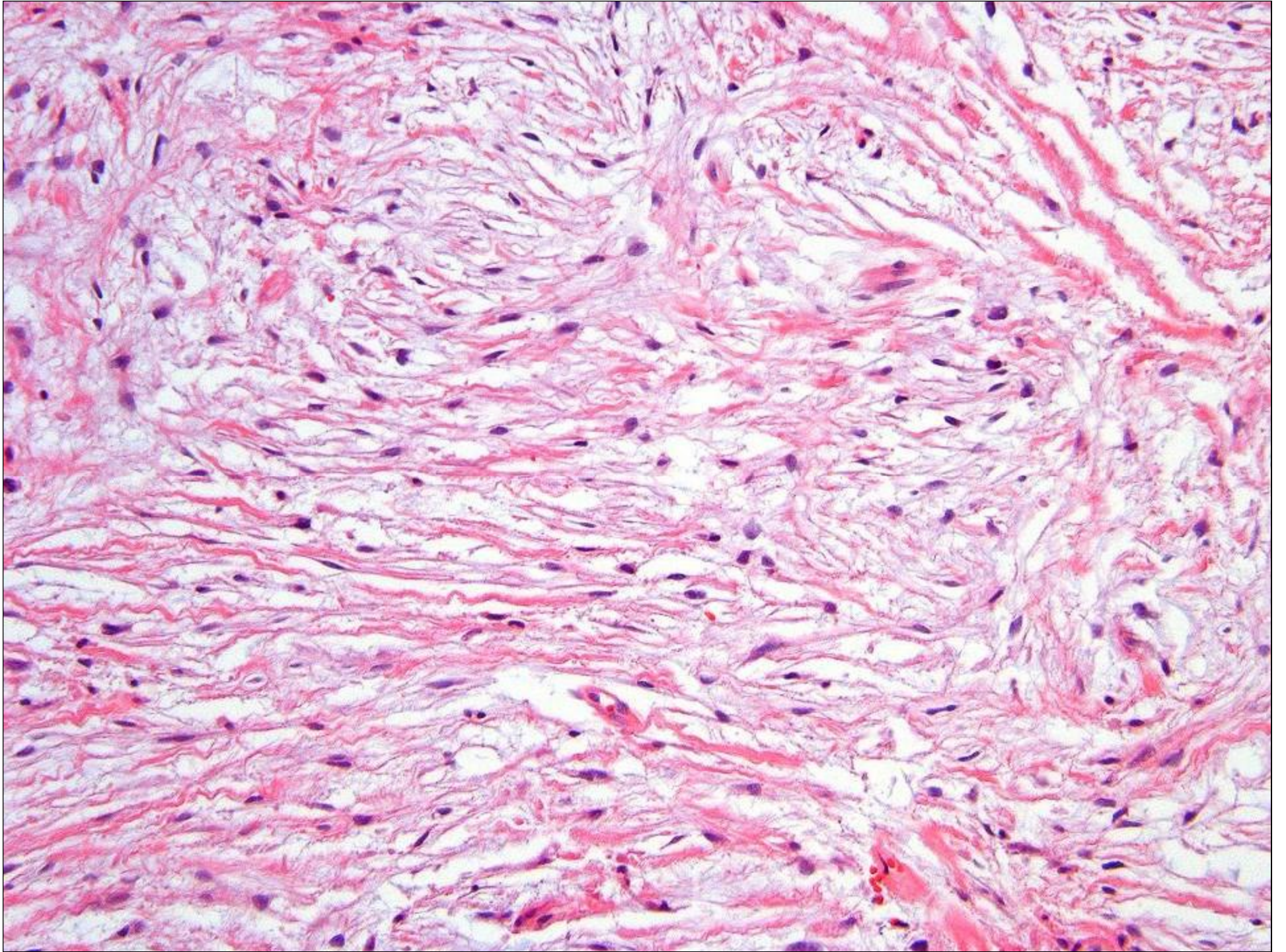
Harry L. Evans, MD

- 21 patients recurrences after intervals up to 15 years (median 3.5 yrs)
- 15 with metastasis after periods up to 45 years (median 5 yrs)
- Still aggressive
- Patients need lifelong follow-up

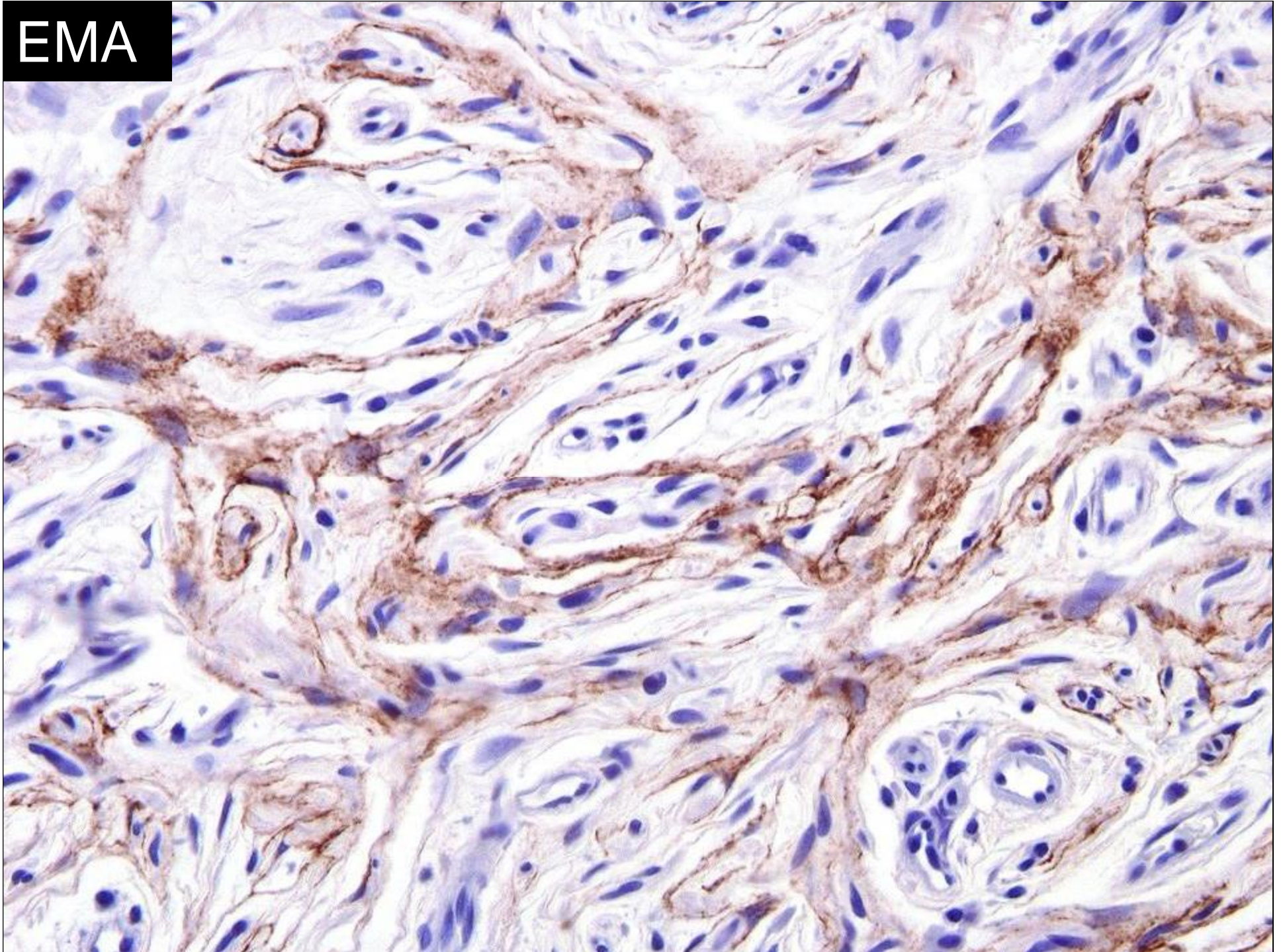
Differential Diagnosis

Soft tissue perineurioma





EMA

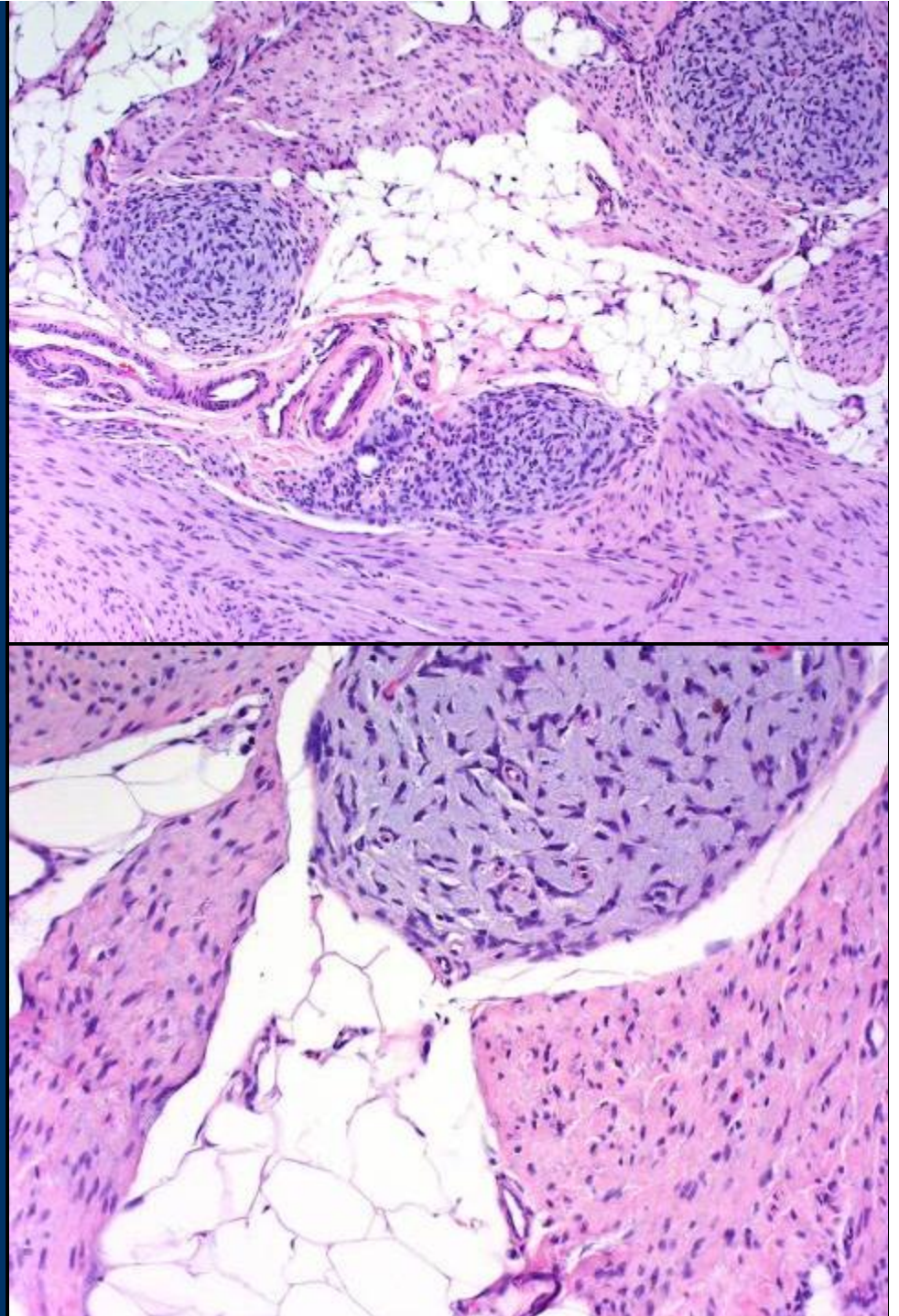


Fibrous Hamartoma of Infancy

- Clinical features
 - First two years of life, ~20% at birth
 - Dermal or subcutaneous mass
 - Present on upper half of body, especially around axilla

Fibrous hamartoma of infancy

- Triphasic tumor
 - Fibromatosis like fascicles
 - Myxoid nodules with bland spindled to stellate cells
 - Mature fat



LGFMS vs. Fibrous hamartoma

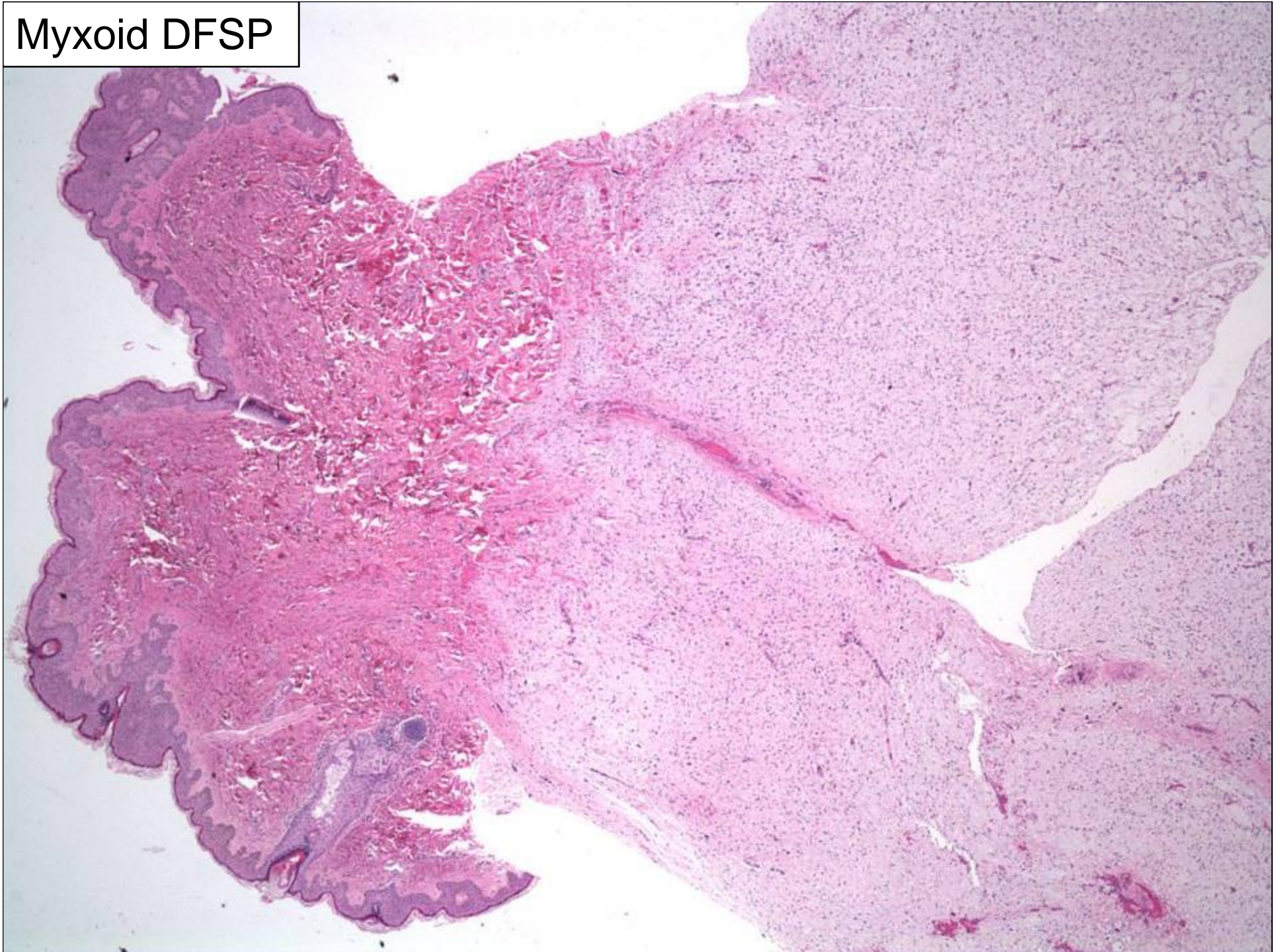
LGFMS

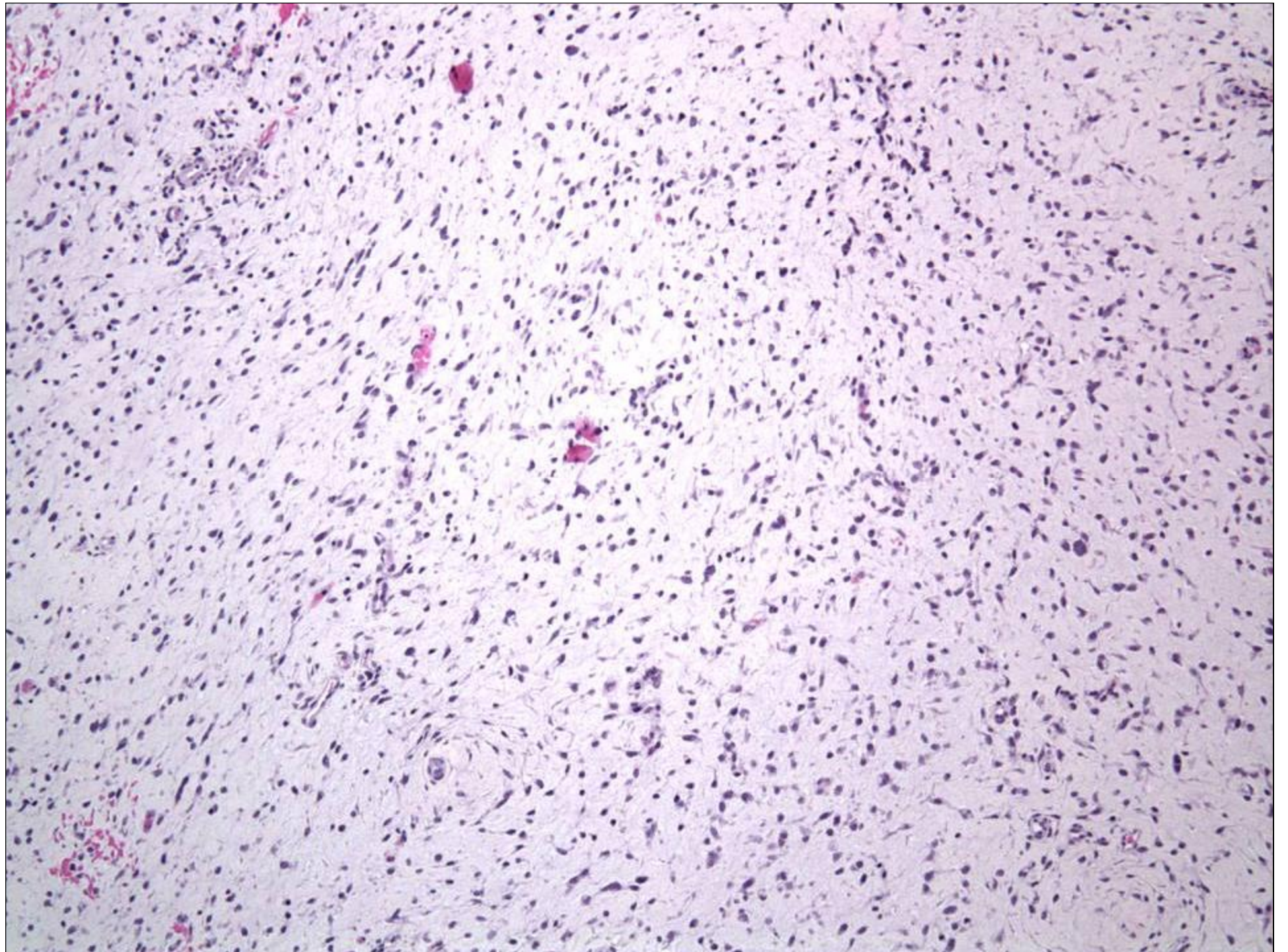
- Older patients
- Biphasic (lacks fat)
- Myxoid areas with prominent vasculature
- More atypia
- t(7;16)

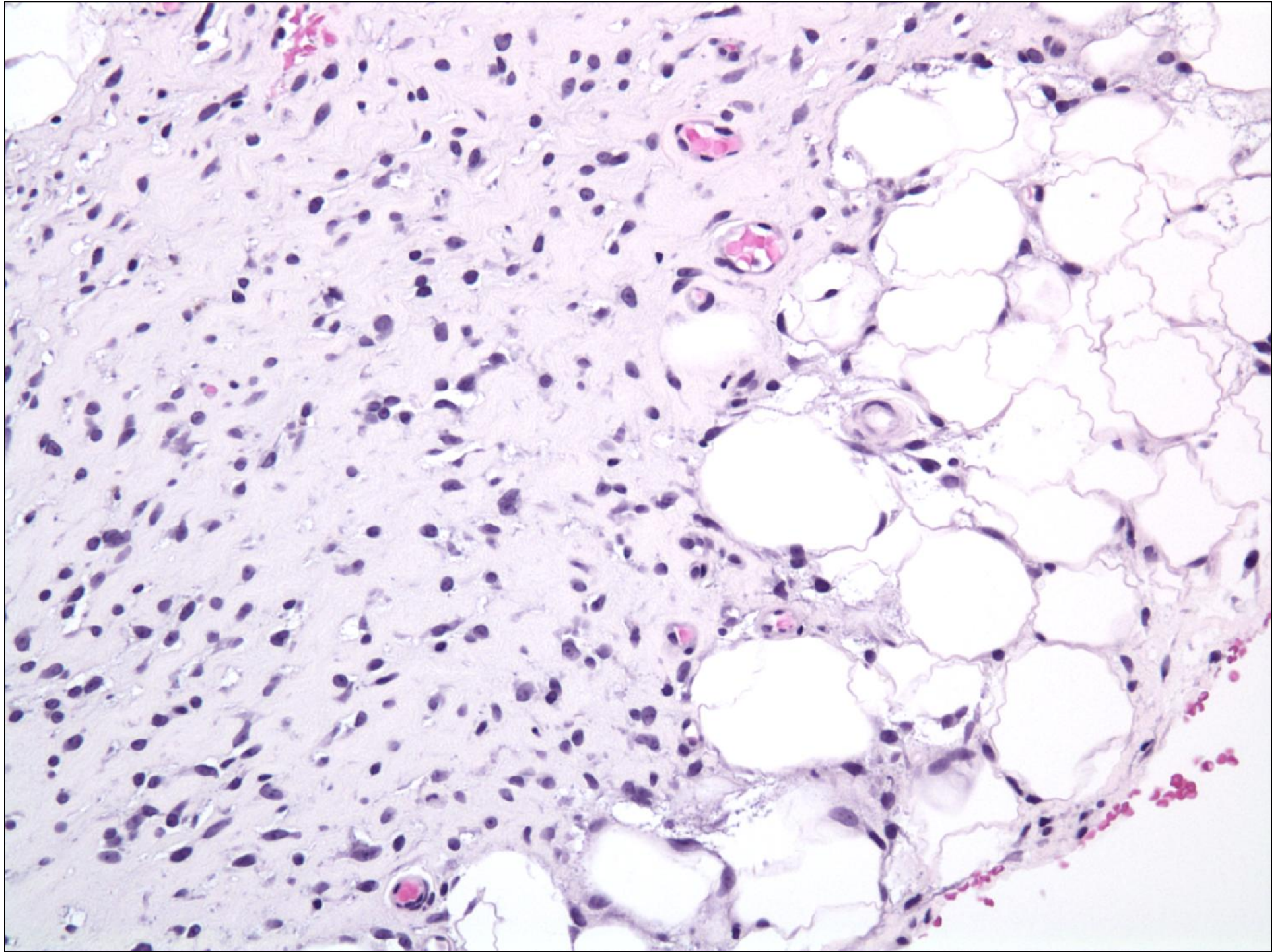
Fibrous hamartoma

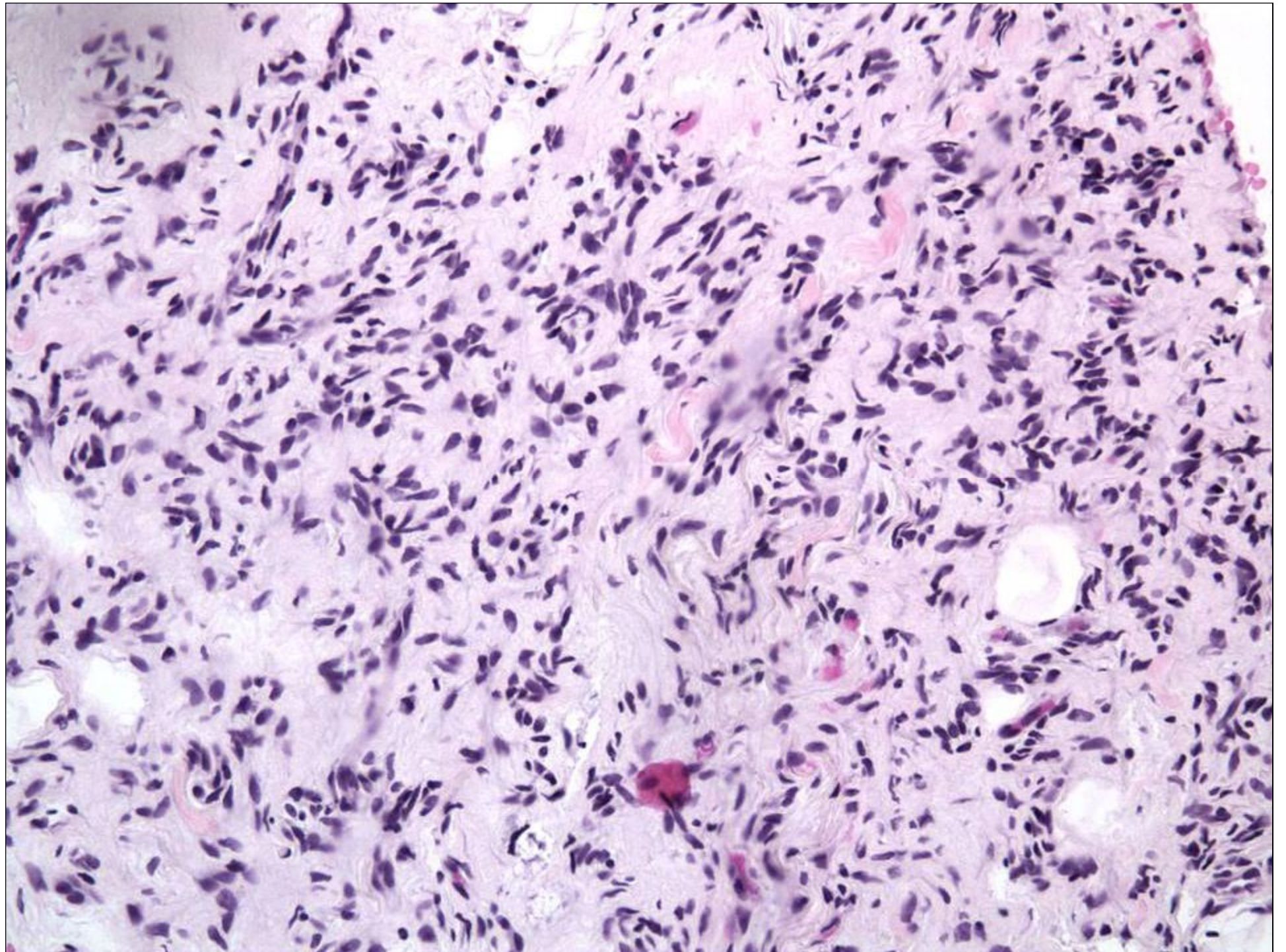
- Infants
- Triphasic with fat
- Myxoid areas without prominent vasculature
- No atypia
- No characteristic genetic findings

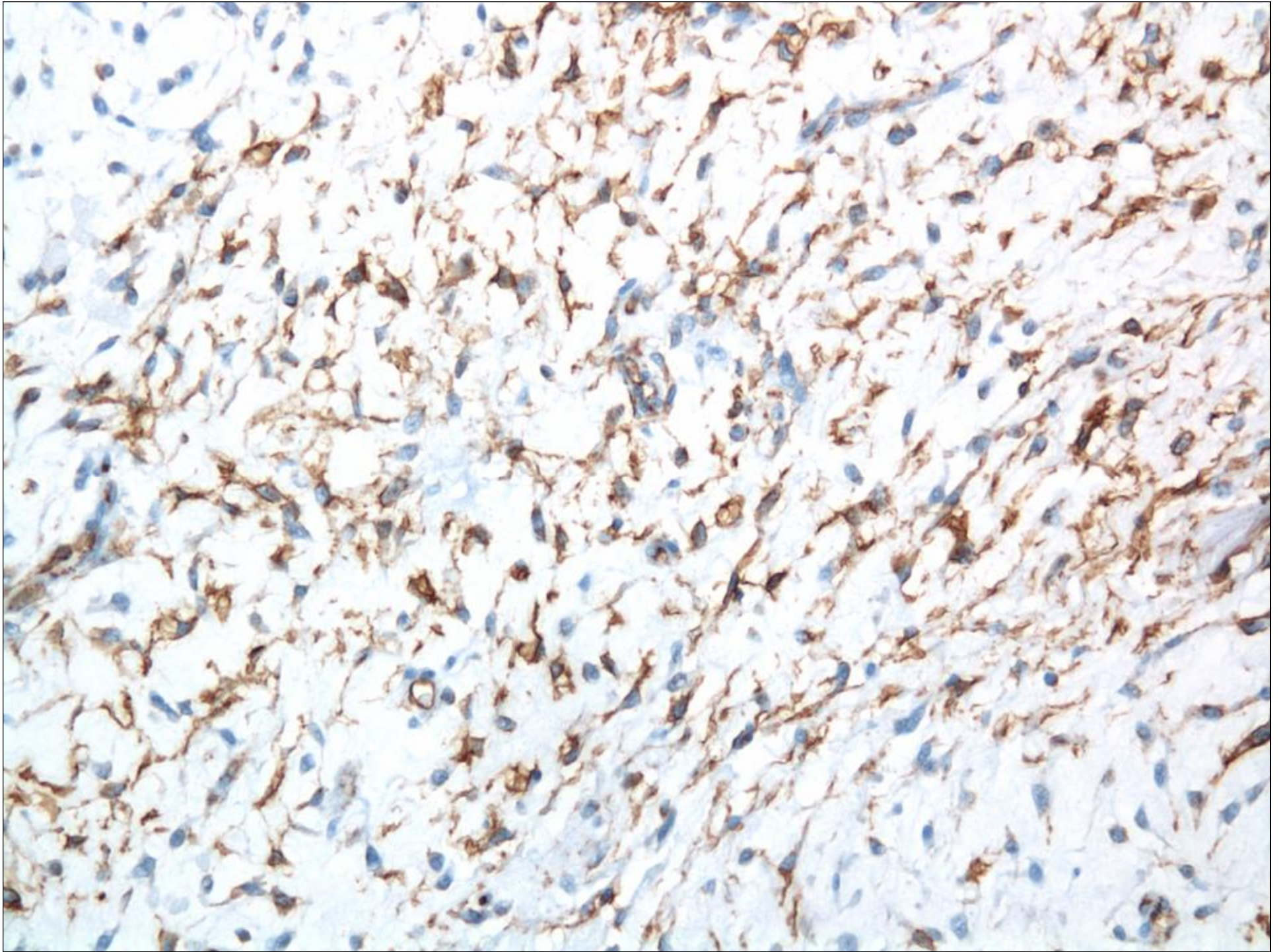
Myxoid DFSP











LGFMS vs. Myxoid DFSP

LGFMS

- Whorled to fascicular
- Pushing border
- Myxoid/collagenous
- Rosettes (sometimes)
- CD34 -
- t(7;16)

Myxoid DFSP

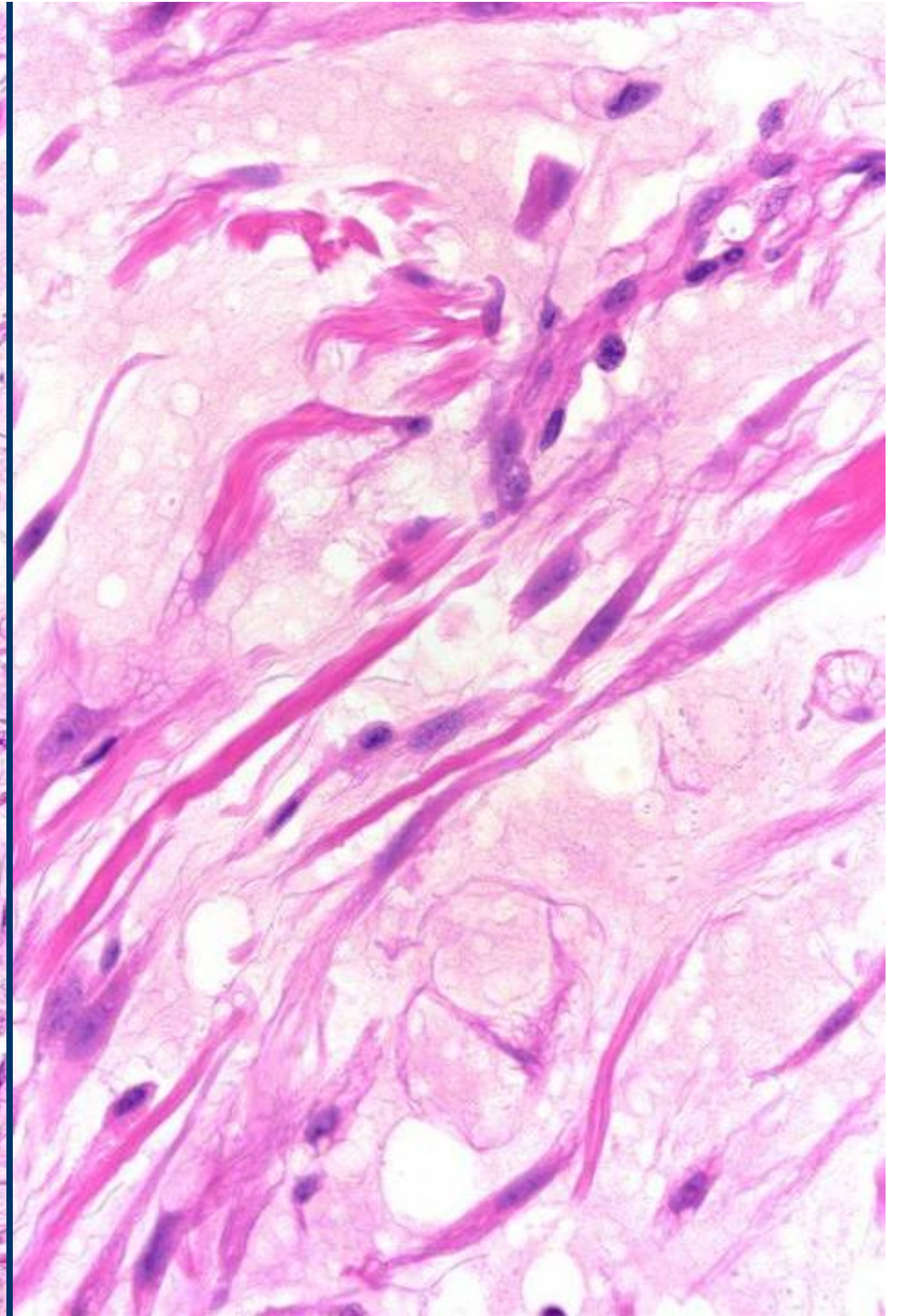
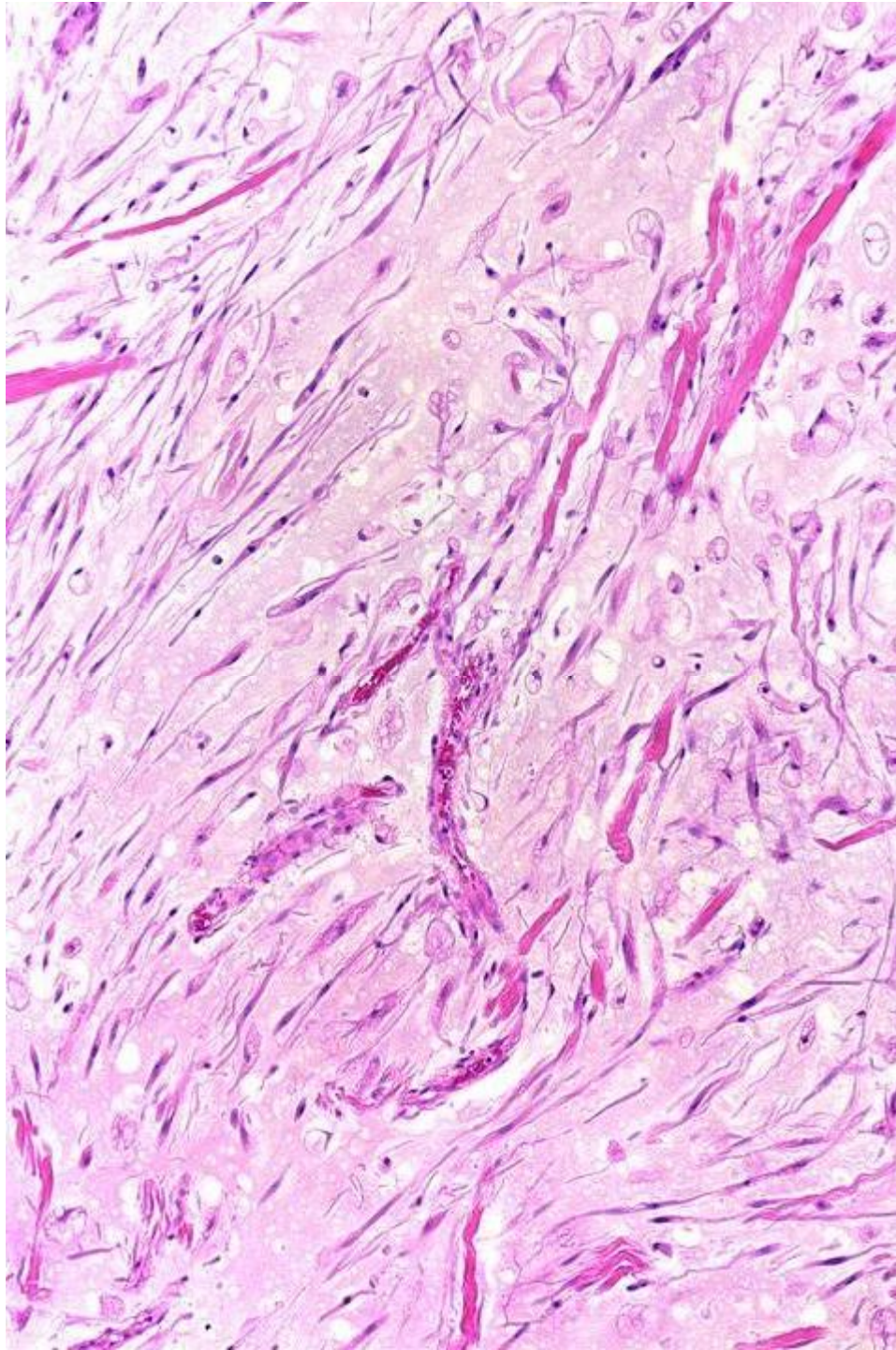
- Random
- Infiltrative
- Purely myxoid
- No rosettes
- CD34+
- t(17;22)

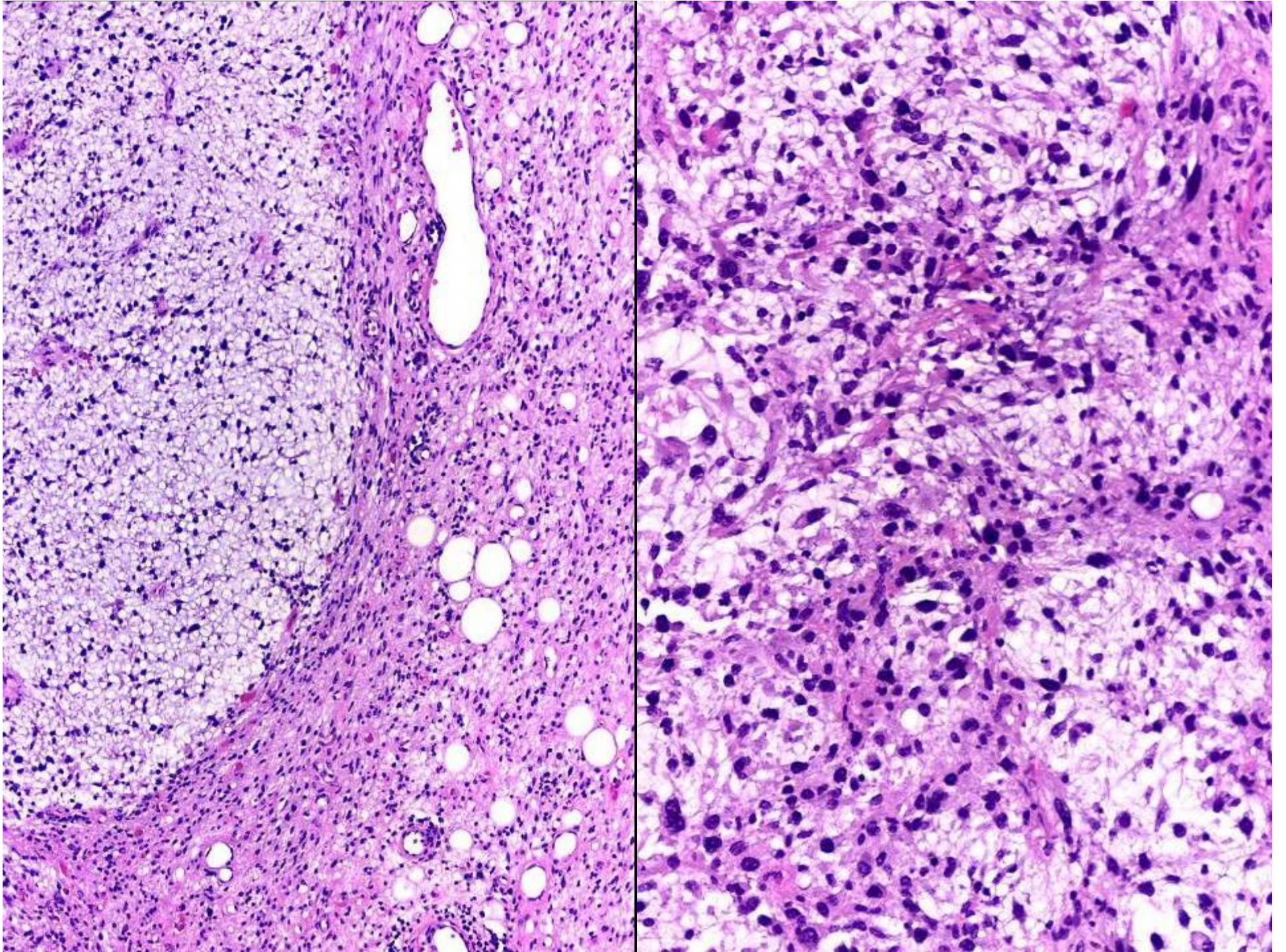
Myxofibrosarcoma (myxoid MFH)

- Clinical features
 - Older patients
 - Extremities (esp. thigh) rarely involves head and neck
 - Often a subcutaneous mass
 - Larger tumor

Myxofibrosarcoma (myxoid MFH)

- Microscopic features
 - Infiltrative tumors extending along subcutaneous septae
 - Spectrum from low to high-grade tumors
 - Low-grade tumors are purely myxoid with low cellularity and often subtle atypia
 - Intermediate and high-grade tumors have increasing solid areas, greater nuclear pleomorphism, mitoses and necrosis
 - Neoplastic cells proliferate off arborizing thick-walled vessels





LGFMS vs. Myxofibrosarcoma

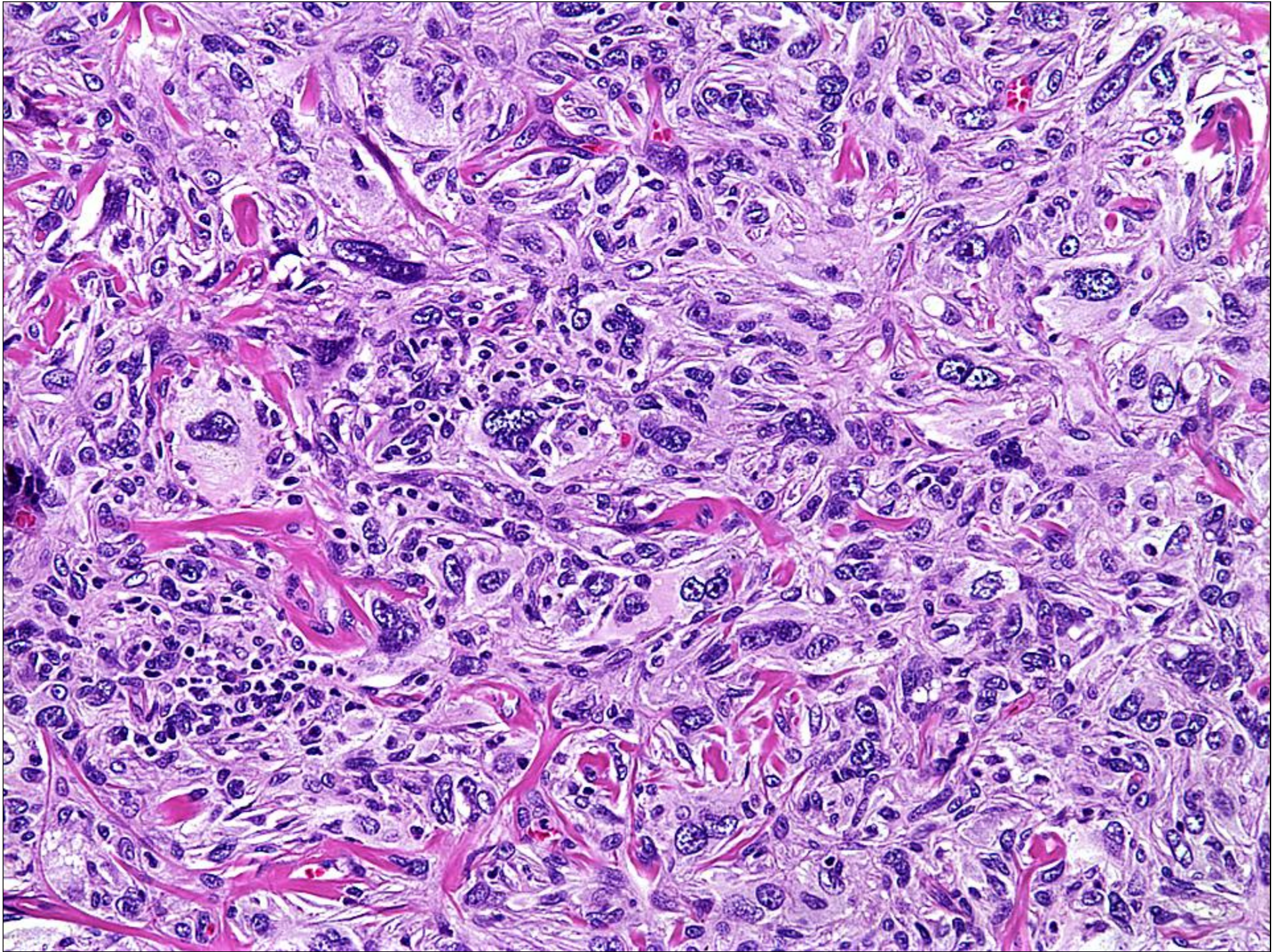
LGFMS

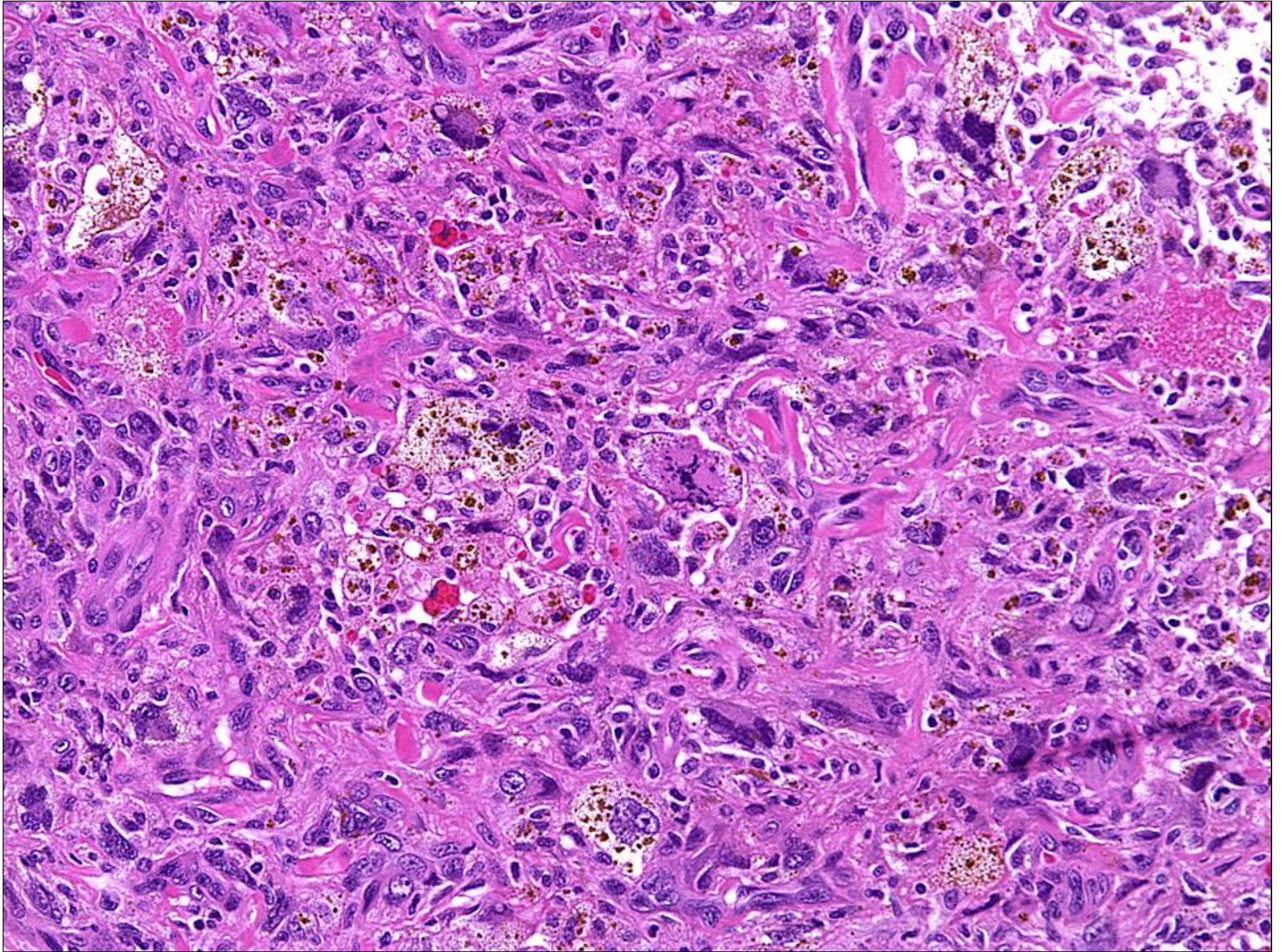
- Less atypia
- Pushing border (superficial)
- Myxoid/collagenous
- Rosettes (sometimes)
- MUC4 positive
- t(7;16)

Myxofibrosarcoma

- More atypia
- Infiltrative
- Purely myxoid (low grade)
- No rosettes
- MUC4 negative
- No characteristic genetic findings

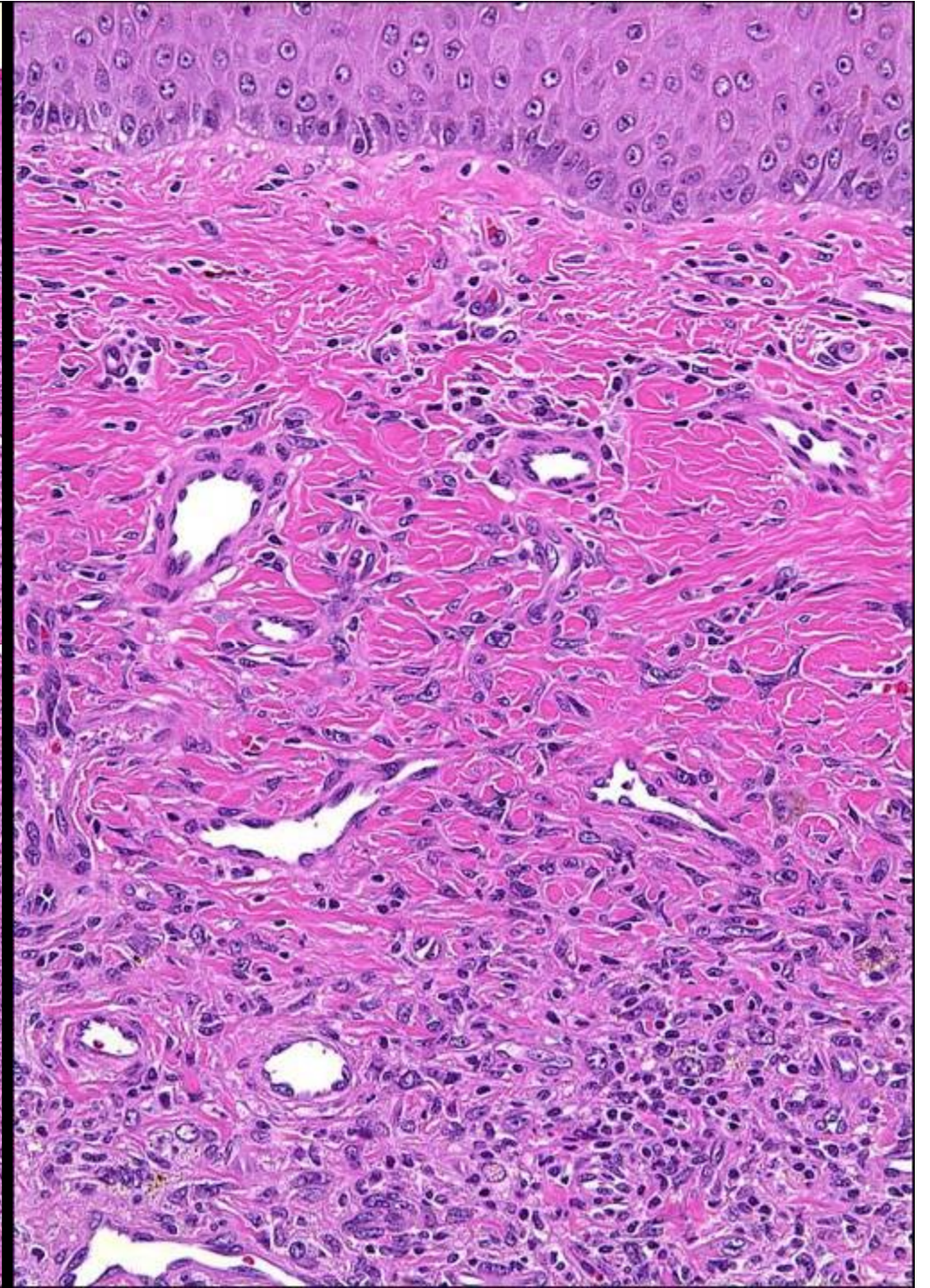
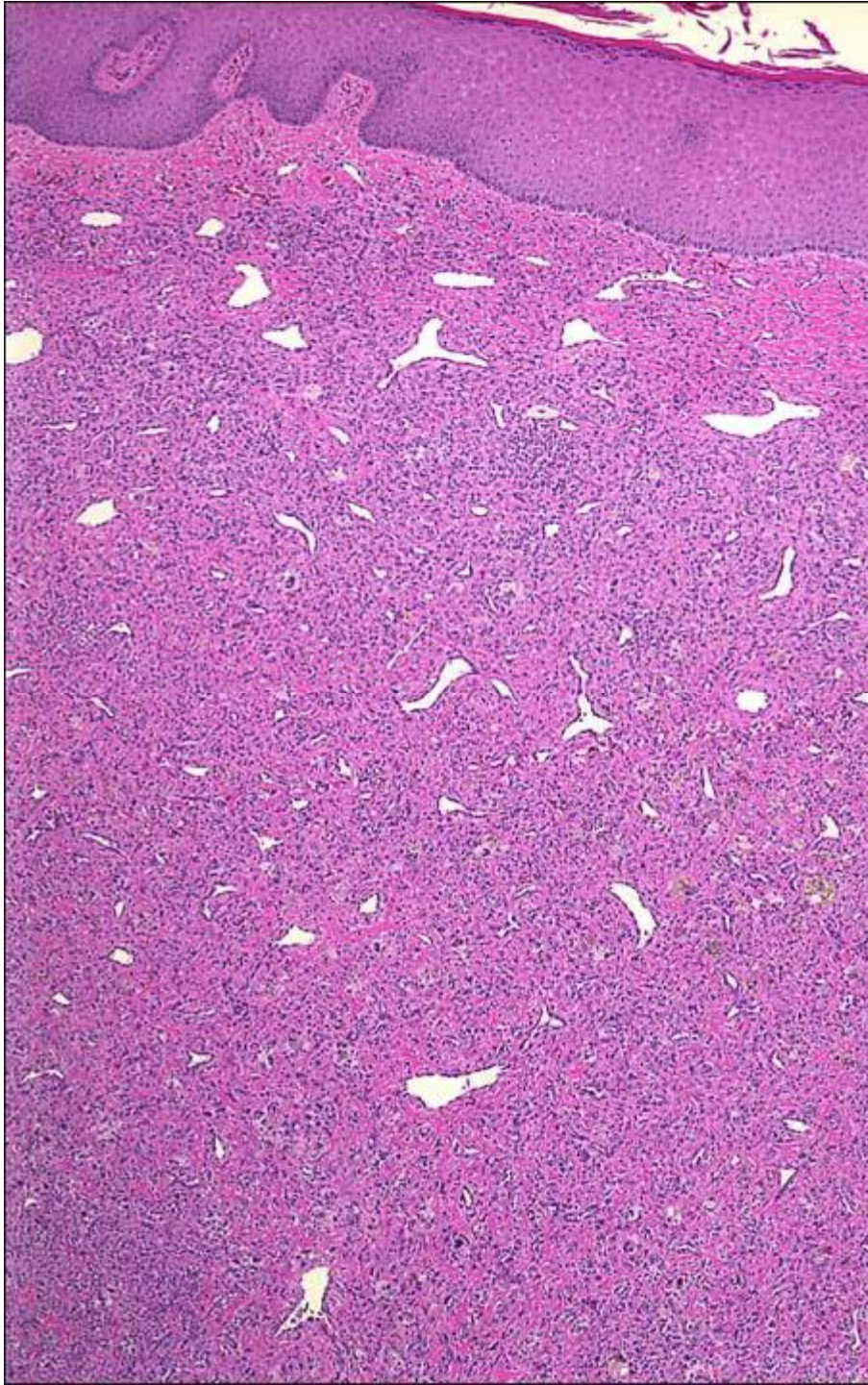
35-year-old woman presented with nodule on the leg. Rule-out dermatofibroma.

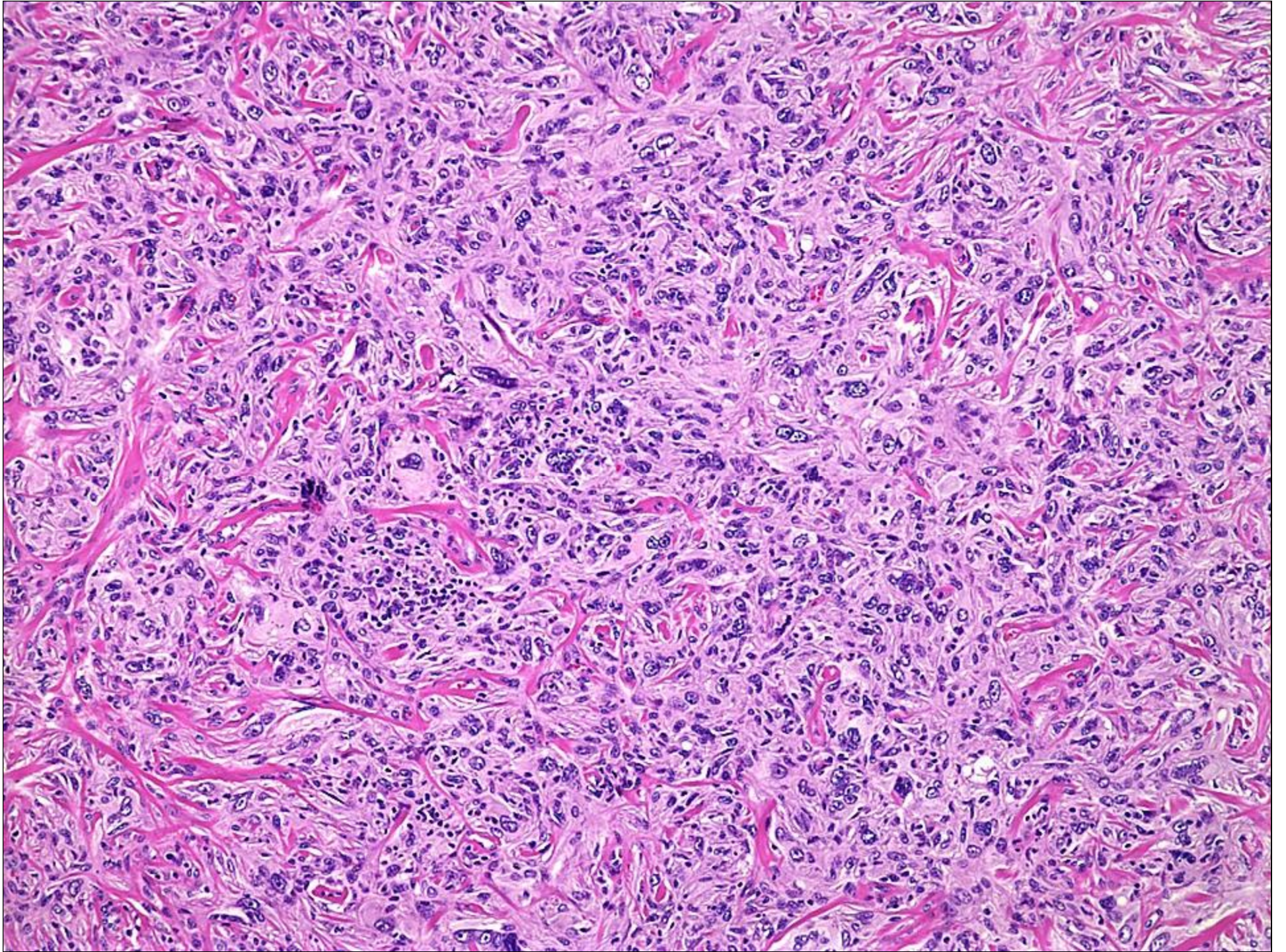




How worried are you?

- Dermatofibroma?
- Undifferentiated pleomorphic sarcoma (MFH)?
- Atypical fibroxanthoma?





Atypical Fibrous Histiocytoma (DF with Monster Cells)

The Ugly



Things that are not as bad as they look...

Atypical Fibrous Histiocytoma

Clinical features

- Similar to conventional dermatofibroma
- Extremities of young patients
- Non-sun damaged skin

Microscopic features

- Low power resemblance to ordinary DF
 - Epidermal hyperplasia
 - Circumscribed
 - Peripheral collagen trapping
- High power:
 - Markedly atypical, sometimes multinucleated cells admixed with bland spindle cells
 - Mitotic figures (including atypical forms)



Behavior

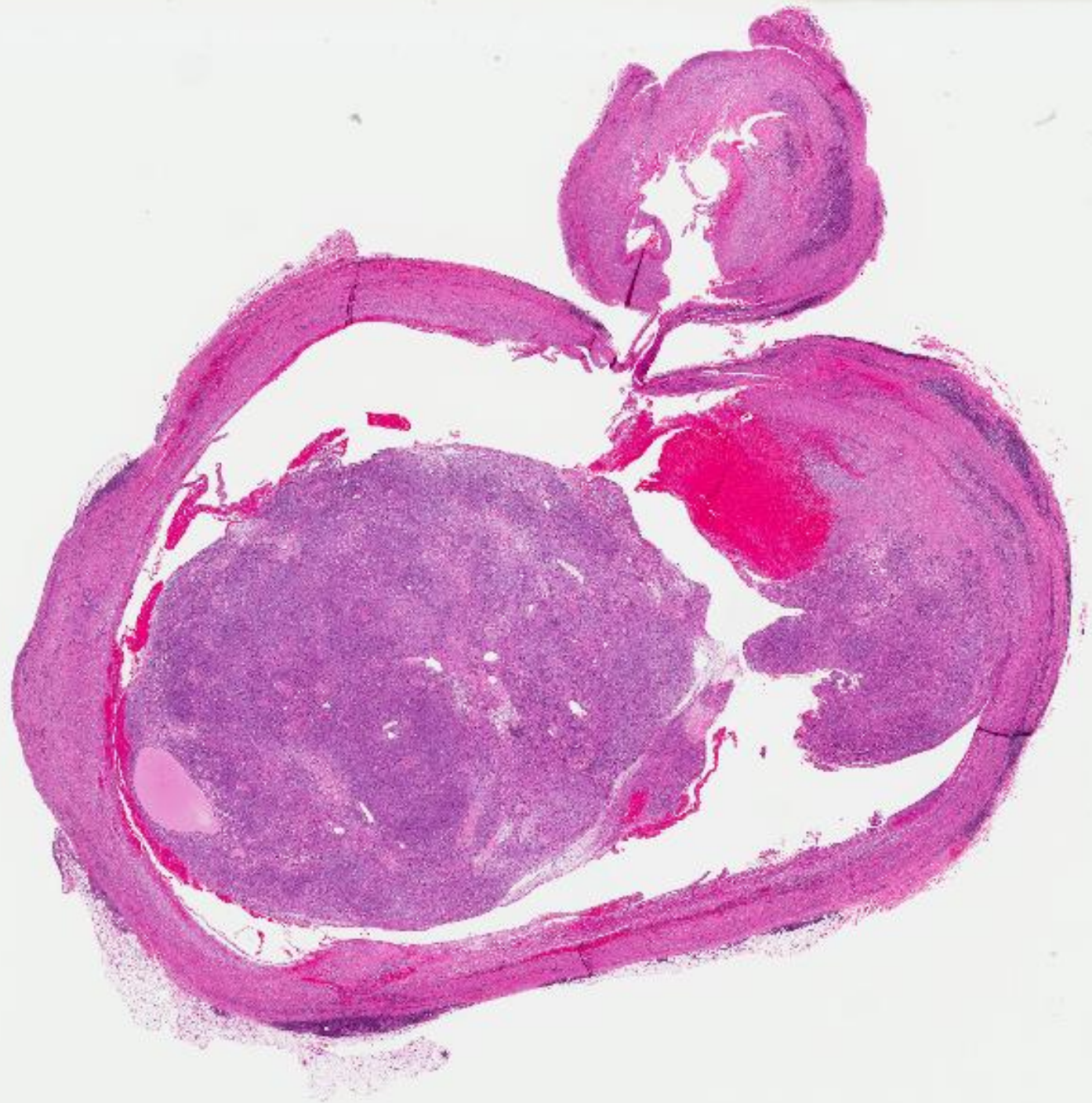
- Fundamentally benign
- Frequent local recurrence (~20%)
- Rare metastasis (one patient DOD)
- Conservative but complete excision and follow-up

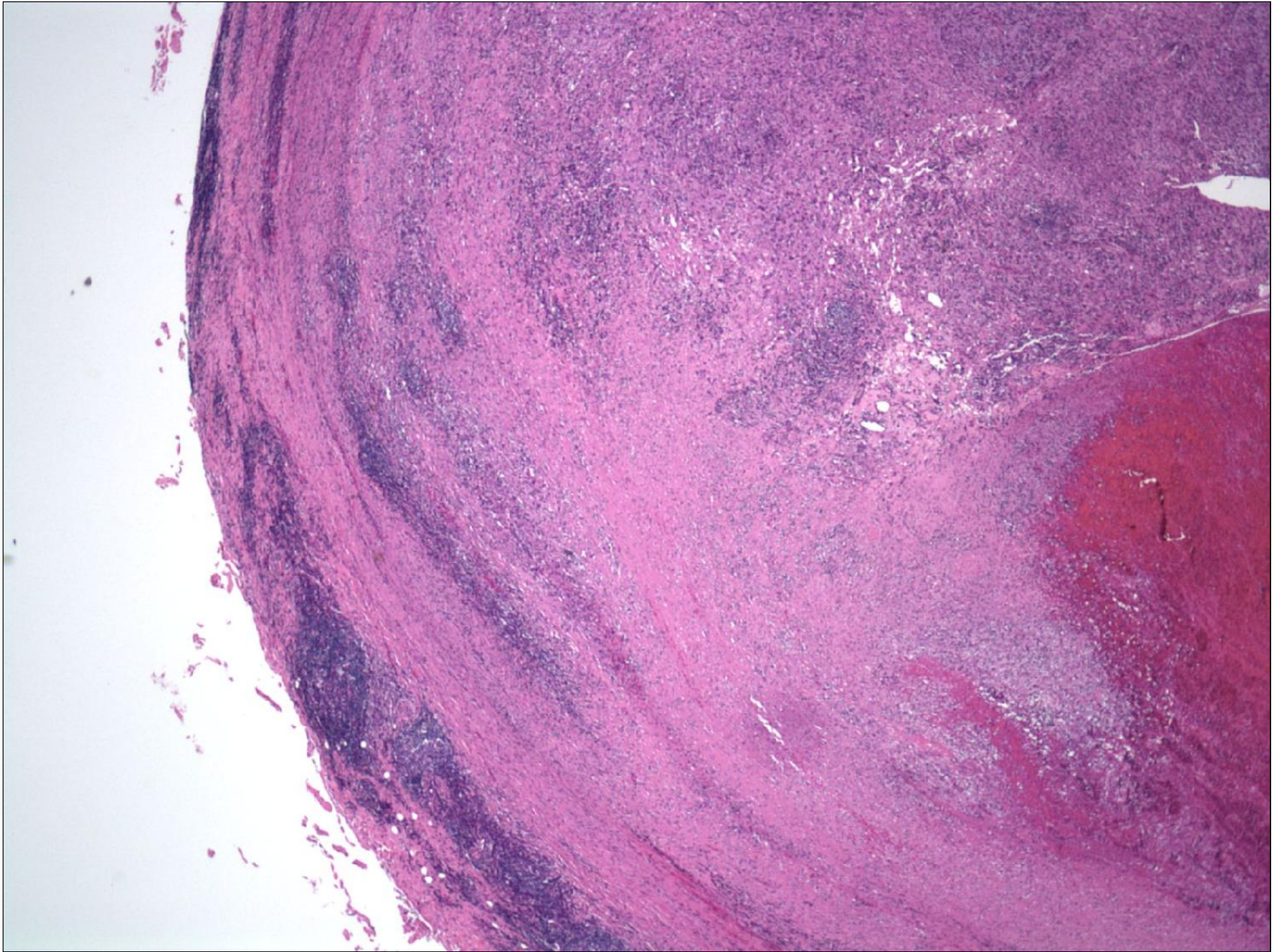
DDx: Atypical Fibrous Histiocytoma

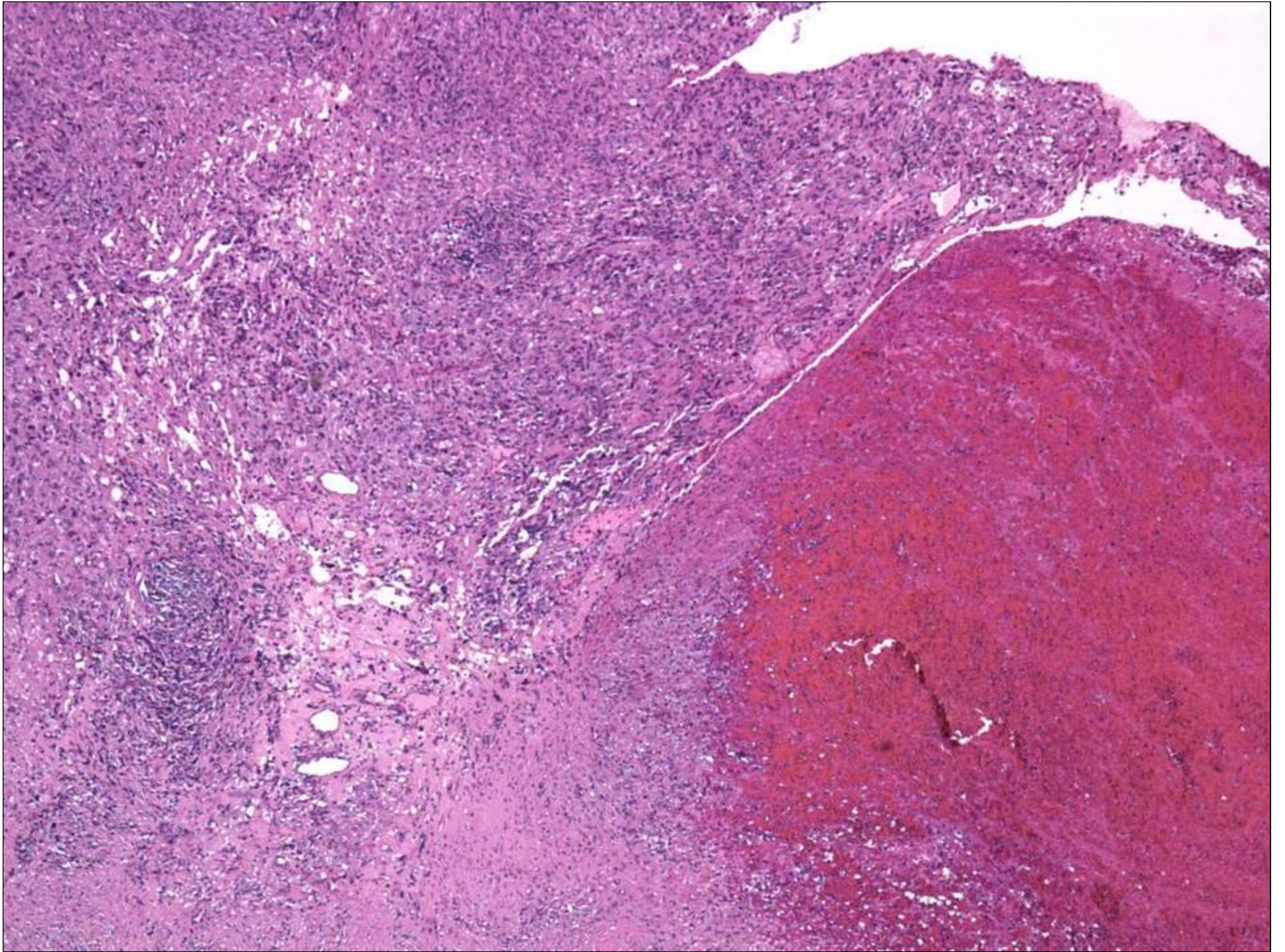
- Atypical fibroxanthoma
 - Usually much older patients
 - Sun damaged skin
 - Absence of areas of typical dermatofibroma
- Pleomorphic sarcoma (MFH)
 - Infiltrative, deep soft tissue

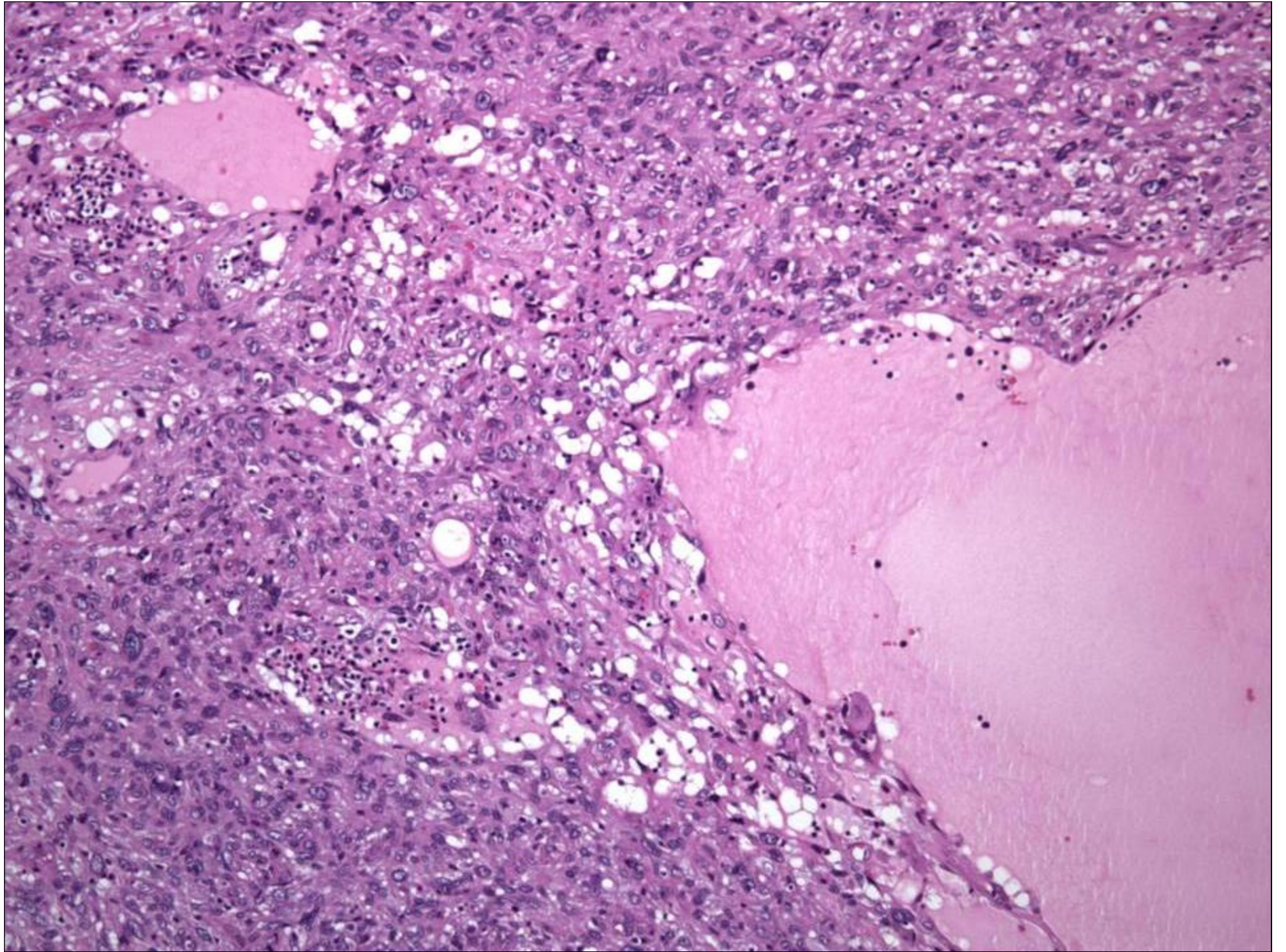
43-year-old man with mass on
upper extremity

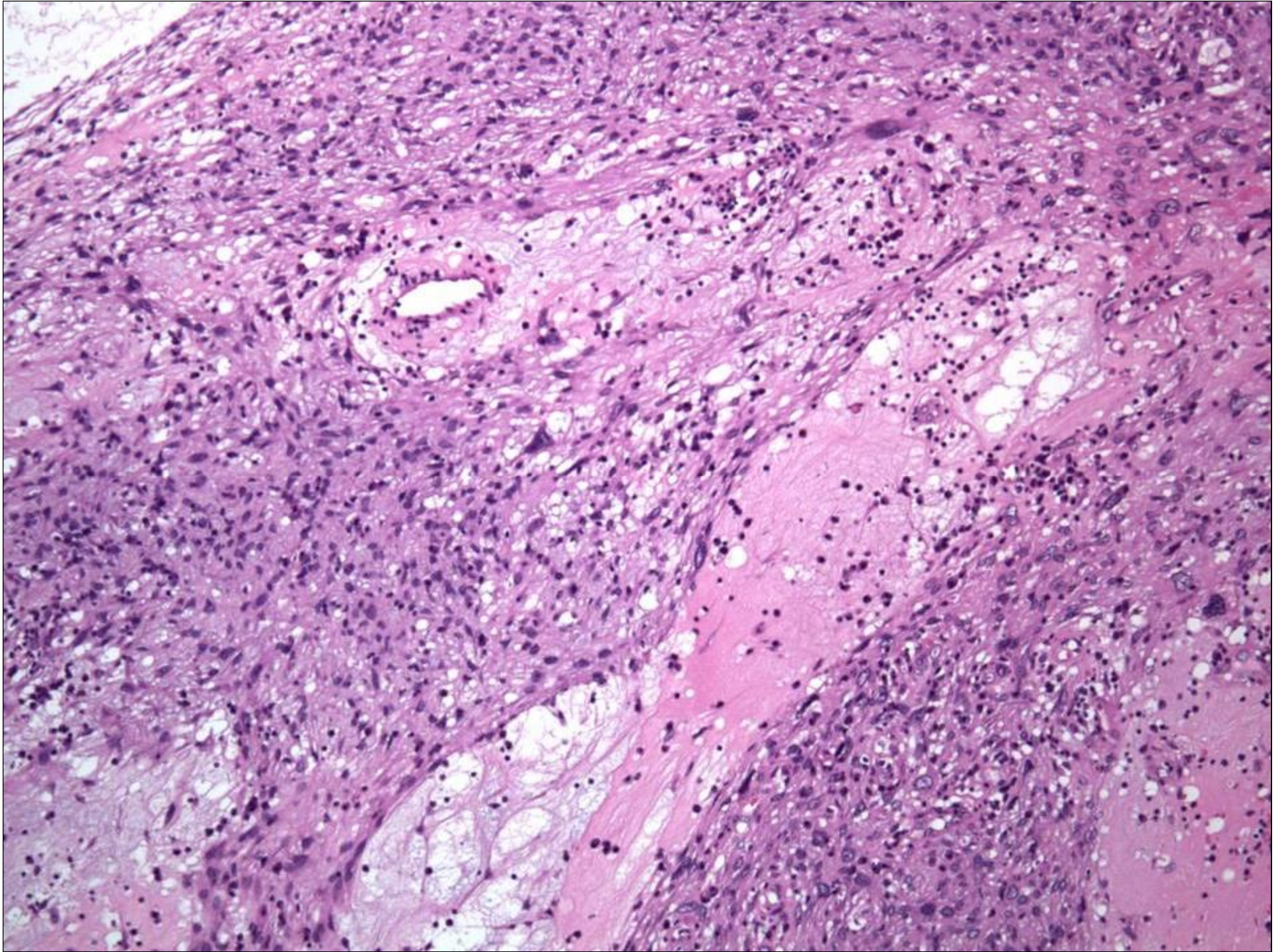
43-year-old man with mass on
upper extremity

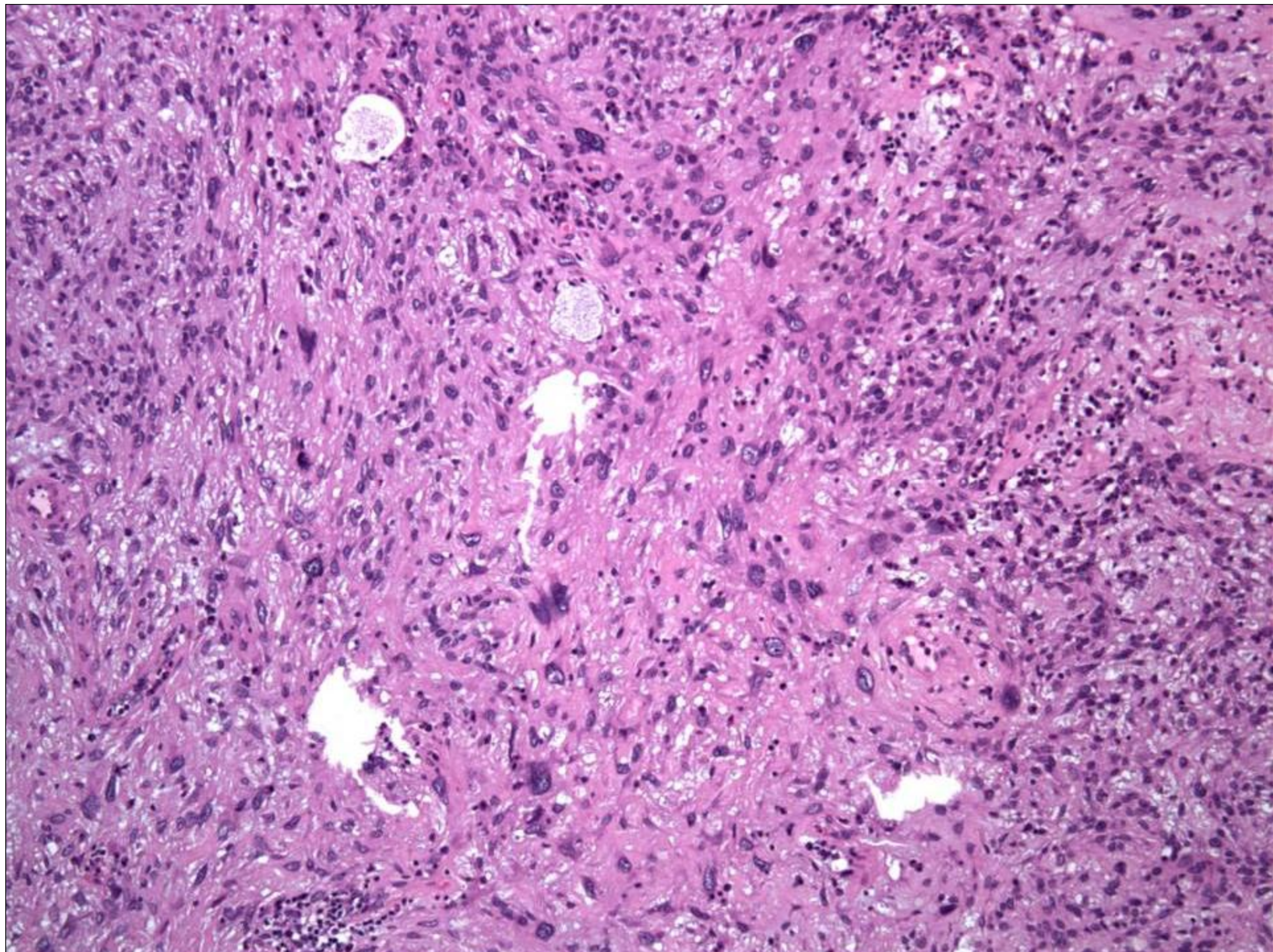


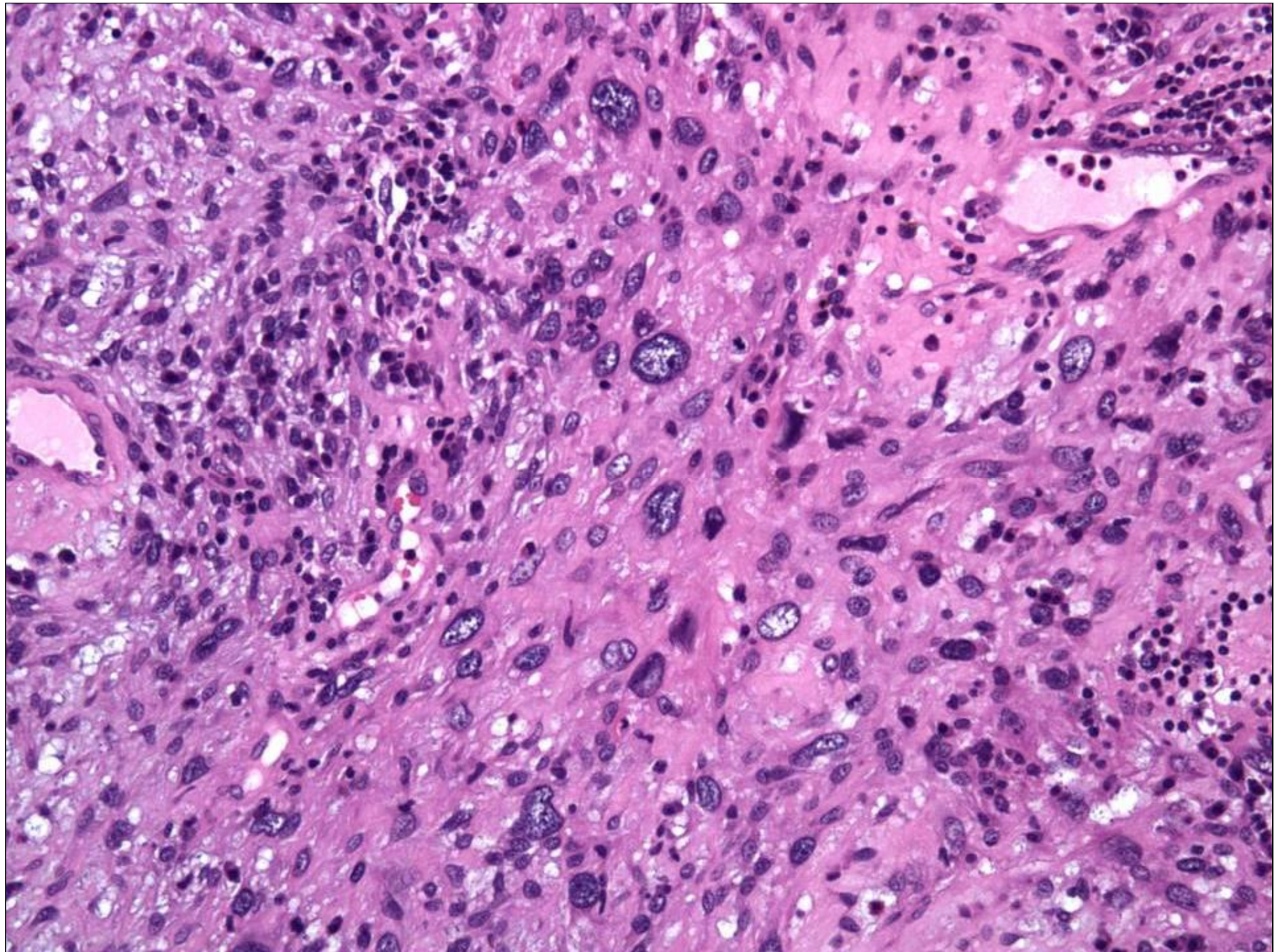


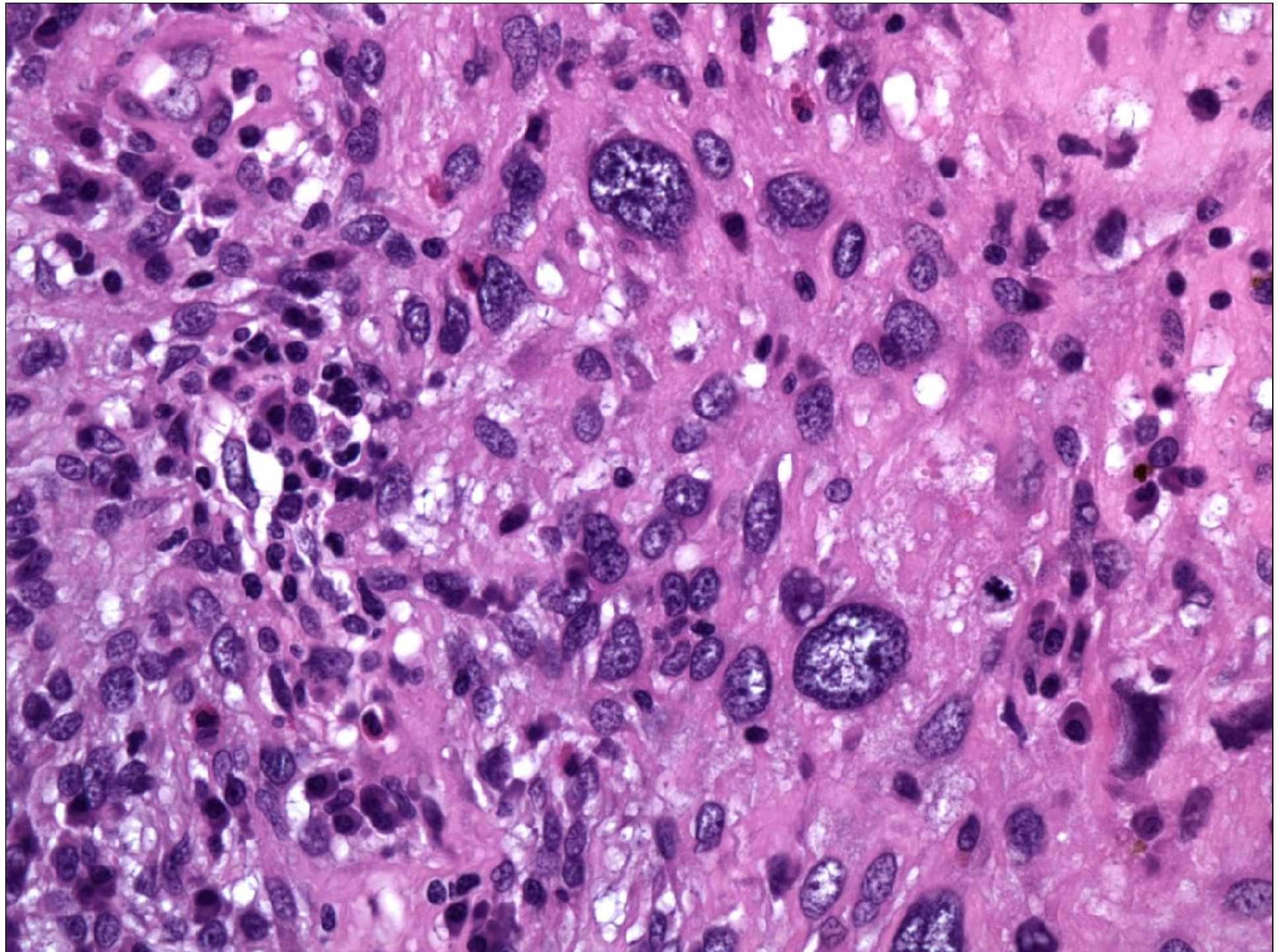




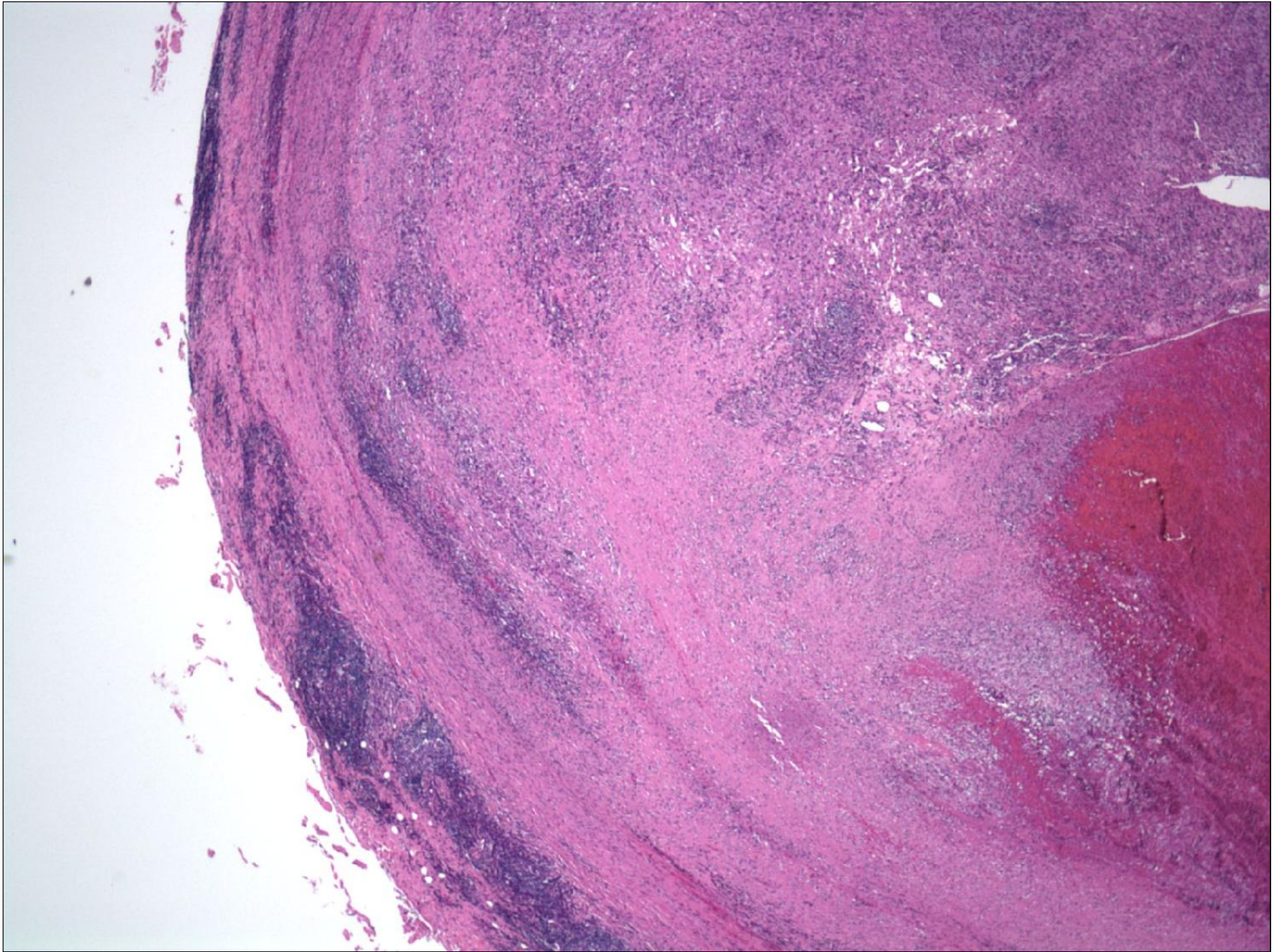


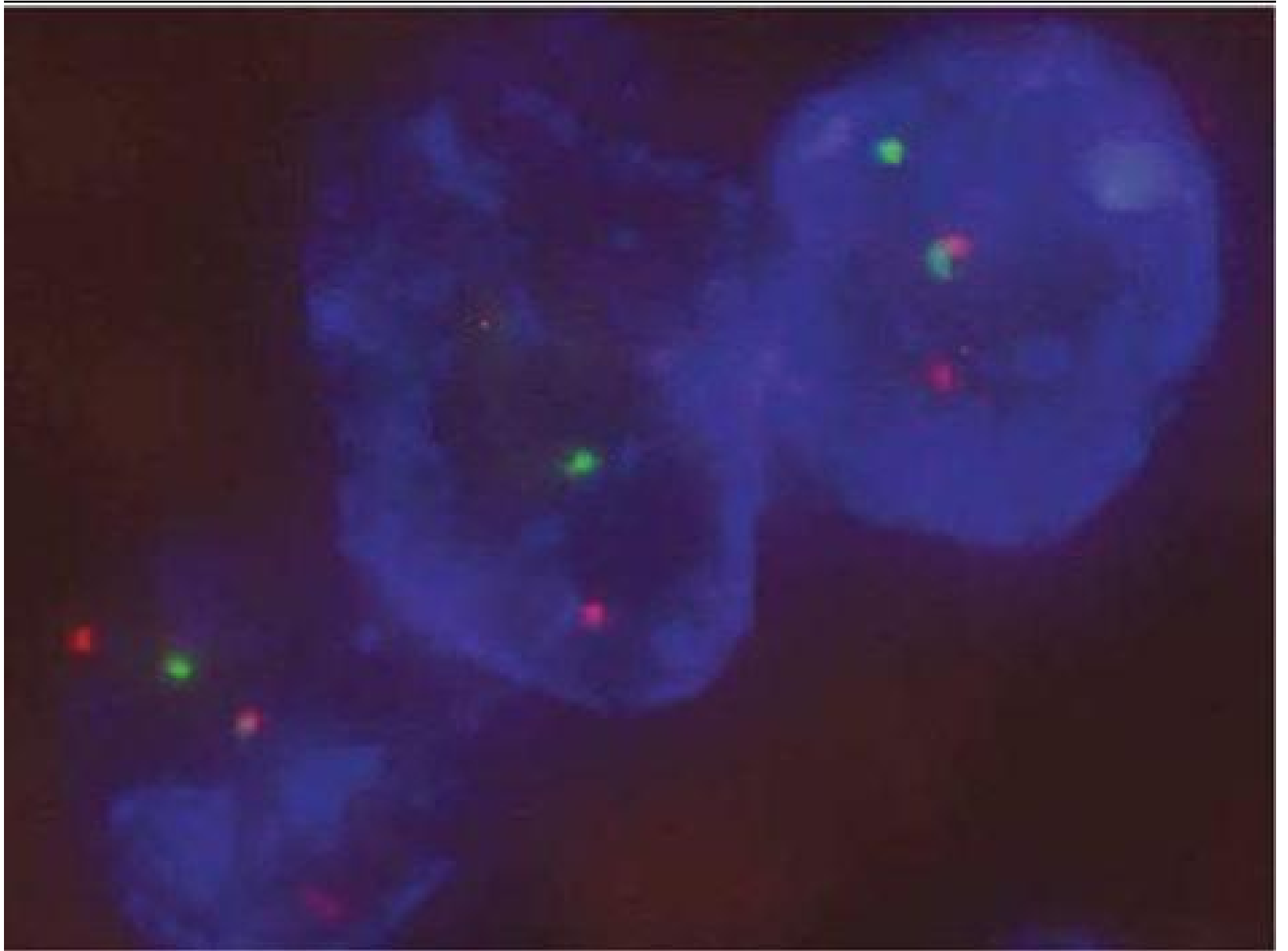






Diagnosis?





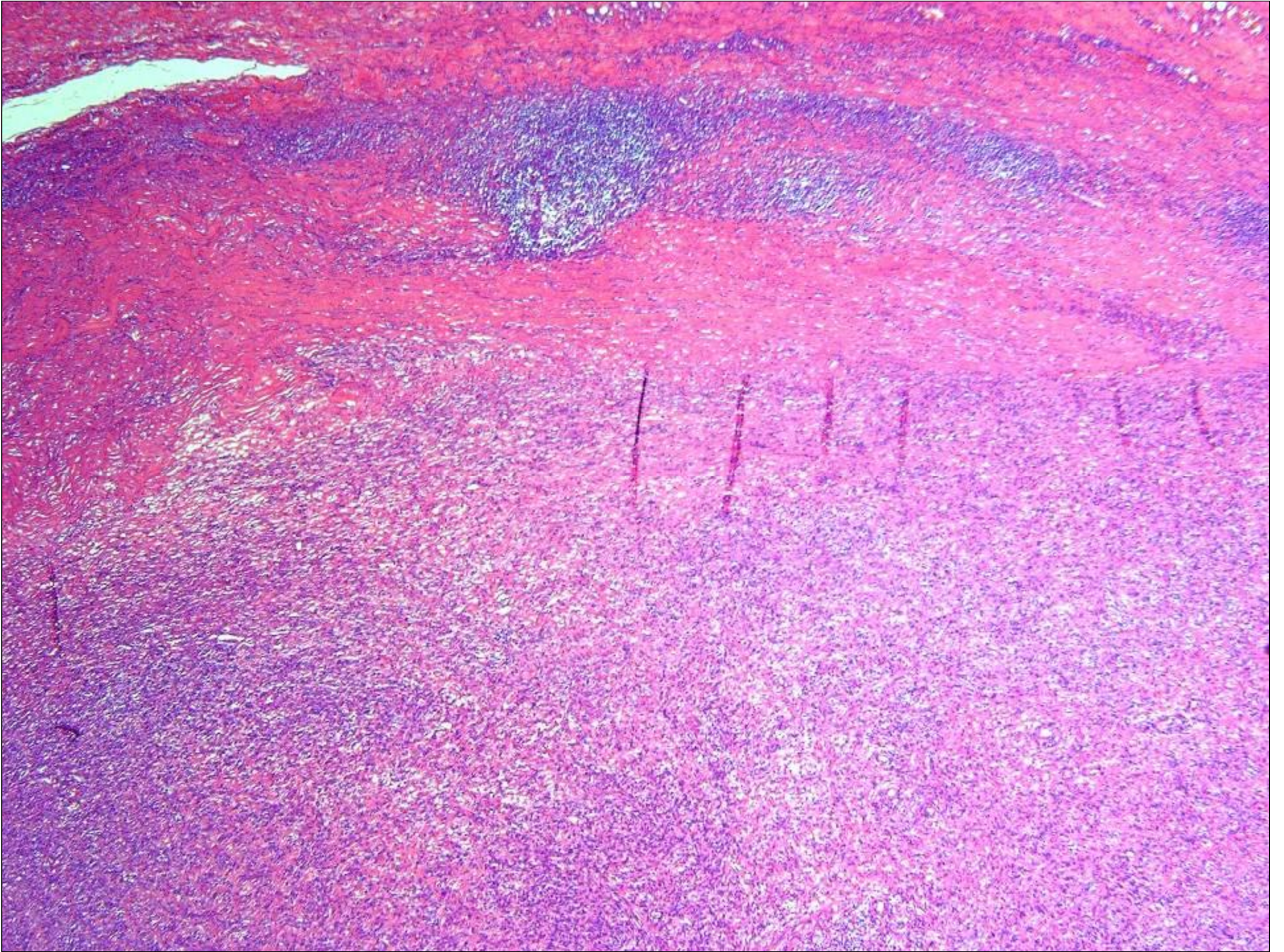
Angiomatoid Fibrous Histiocytoma (AFH)

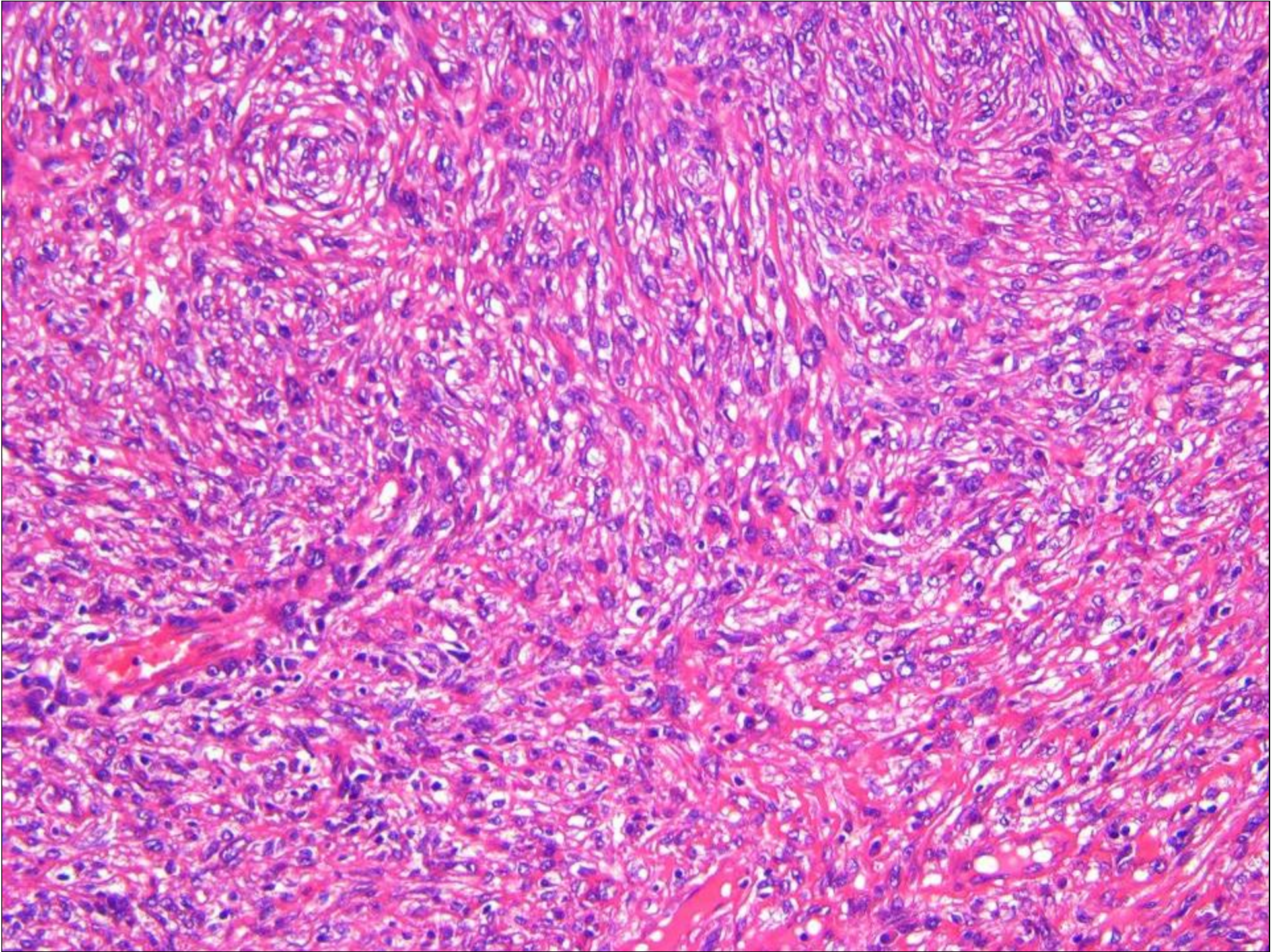
- Occurs in children and young adults
- Nodular dermal or subcutaneous mass
- May have systemic symptoms
 - Anemia
 - Pyrexia
 - Weight loss
- Frequently recur (20-40%)
- Low risk of metastasis (<5%)
 - Regional lymph nodes or lungs

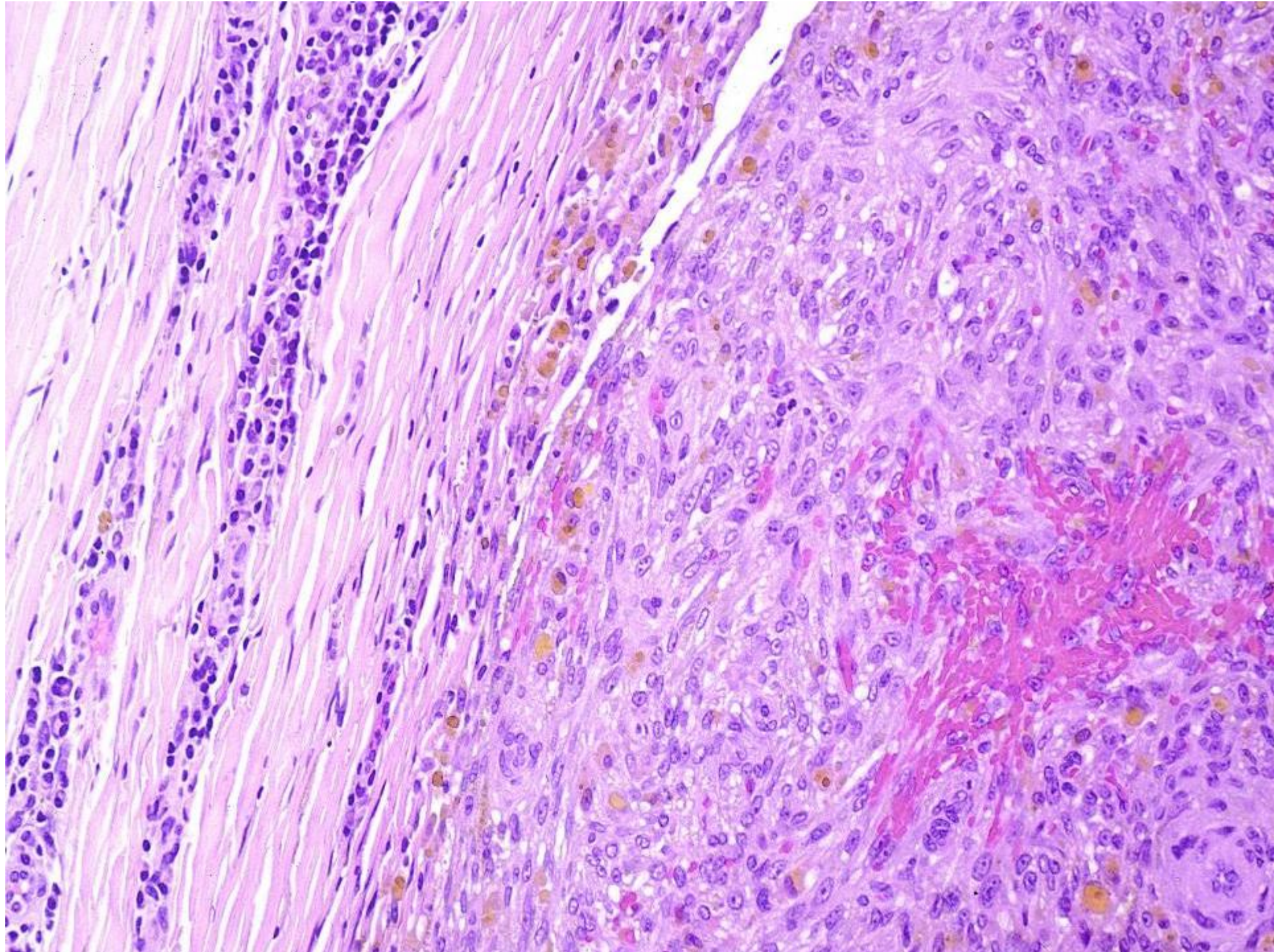
AFH

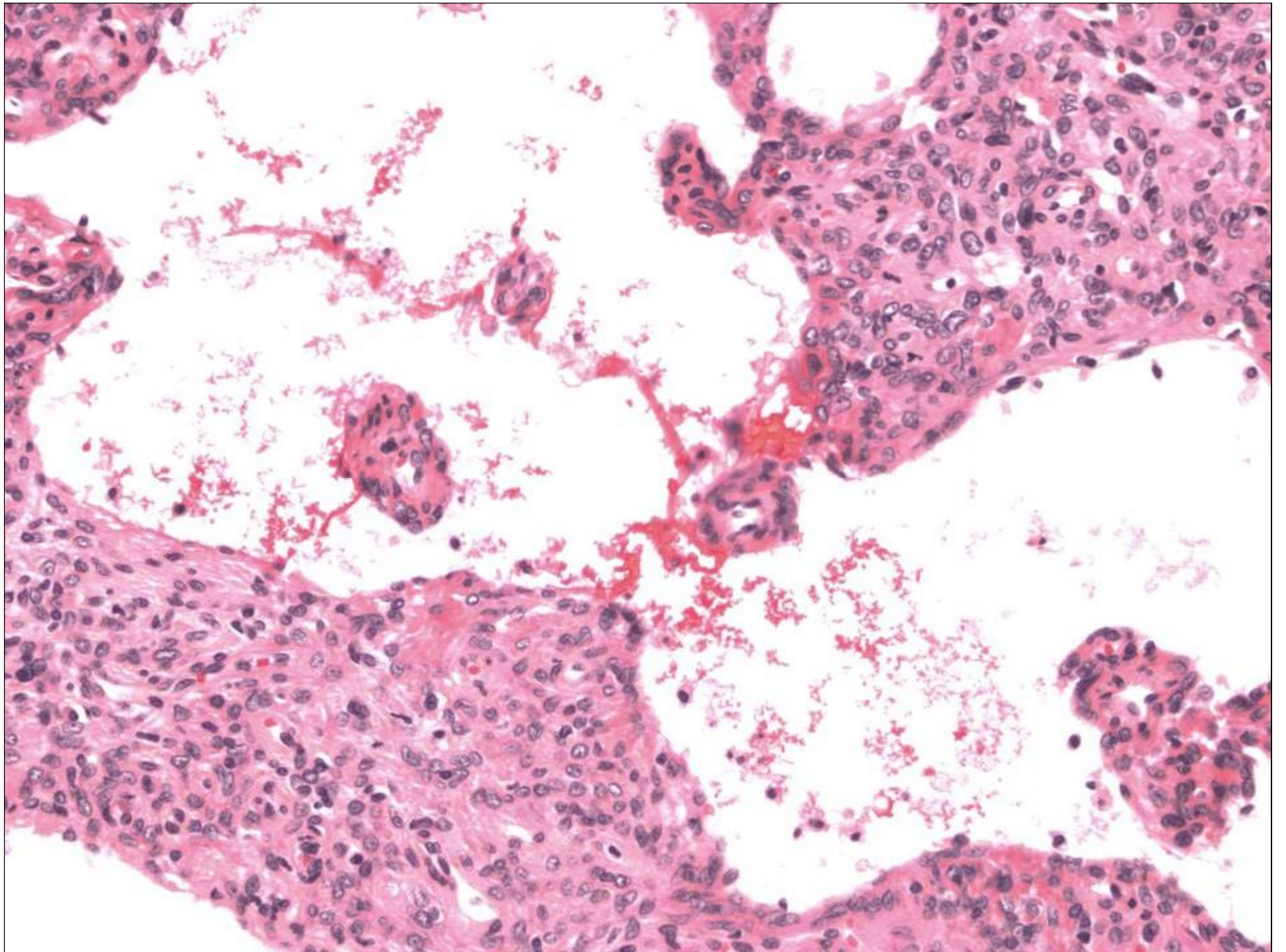
Histologic Features

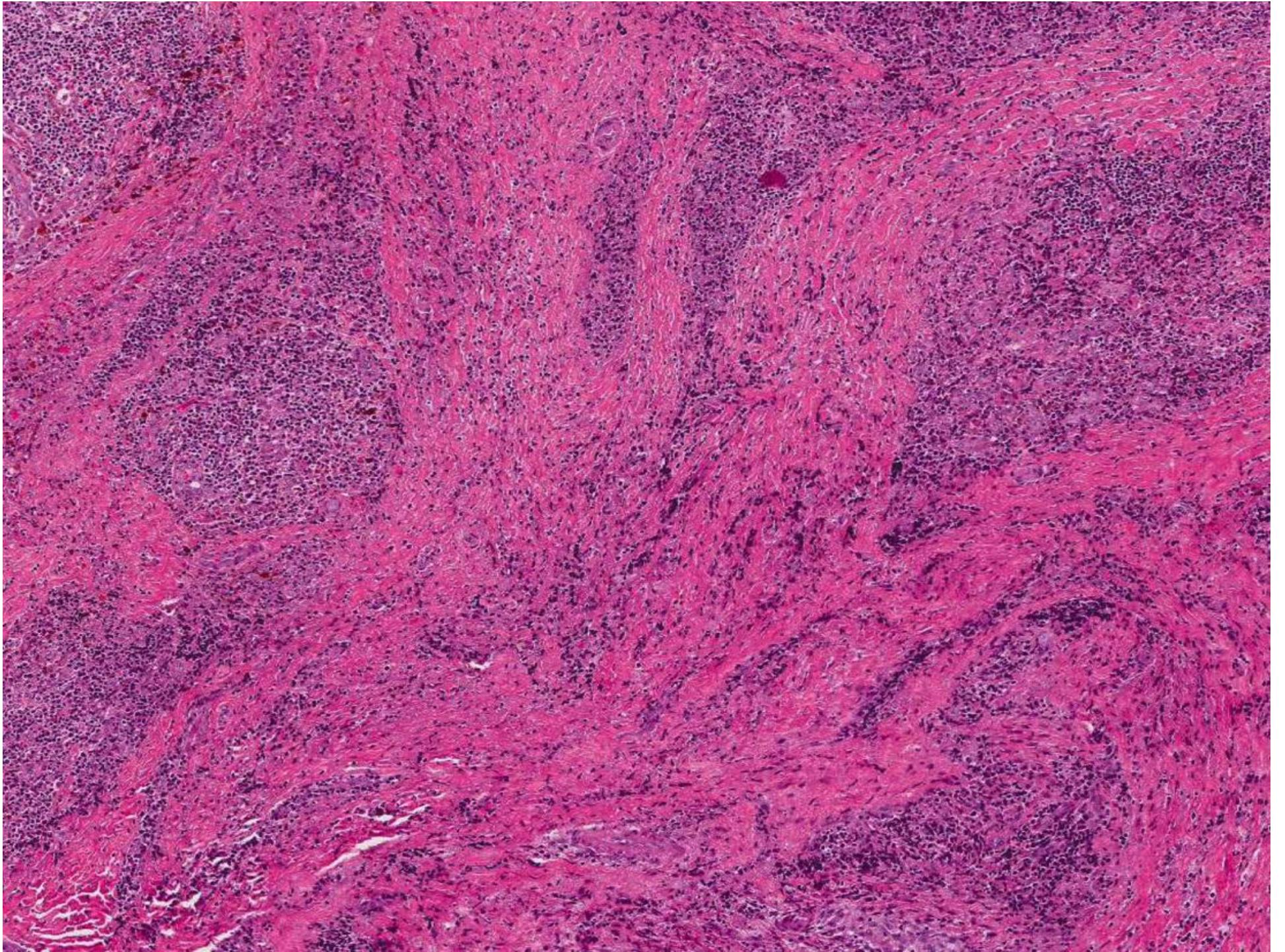
- Circumscribed
- Fibrous pseudocapsule
- Chronic inflammation with lymphoid aggregates
- Solid proliferation of histiocyte-like cells
- Hemorrhage
- Pseudovascular spaces
- May have significant pleomorphism (no impact on behavior)

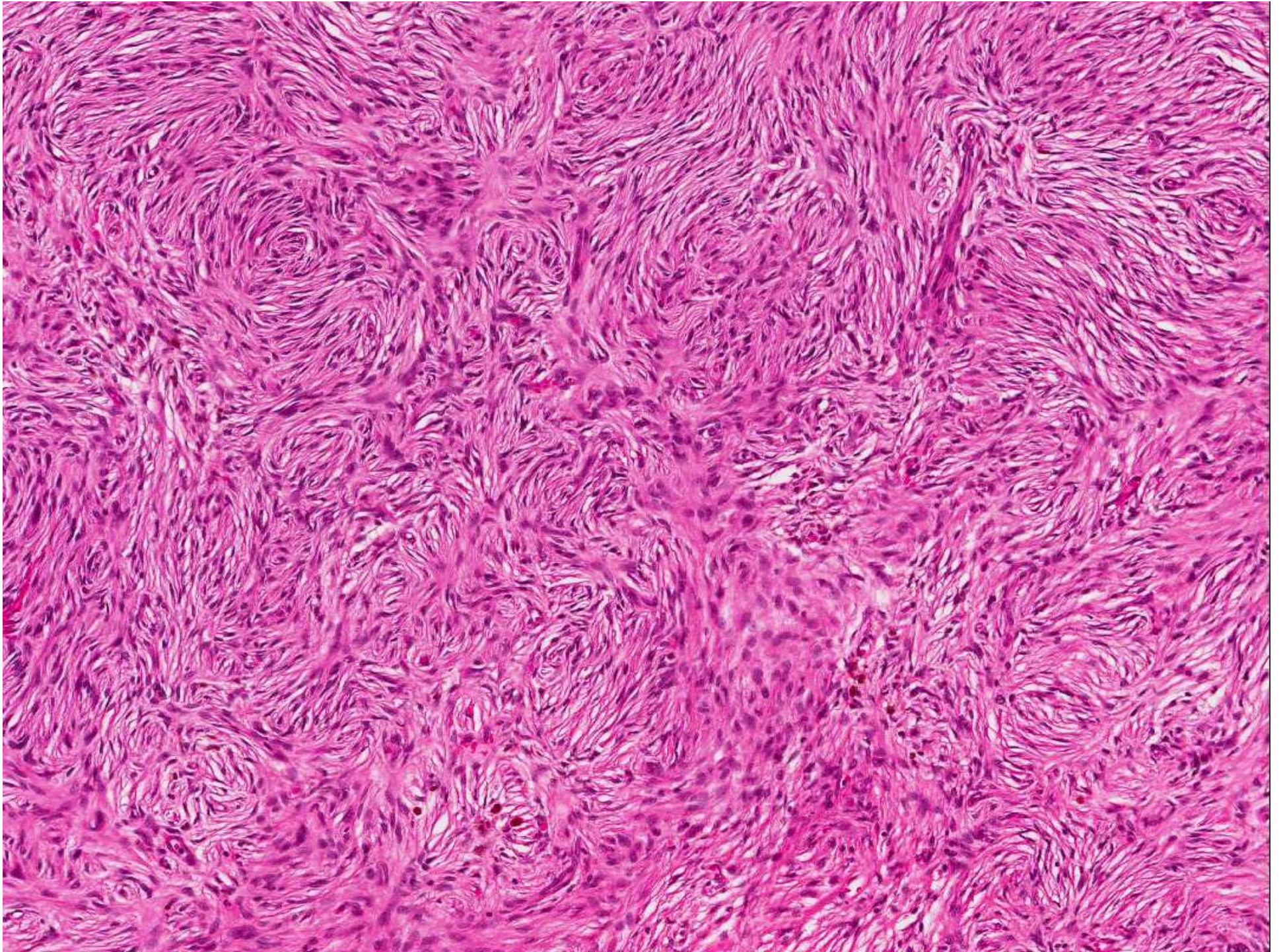


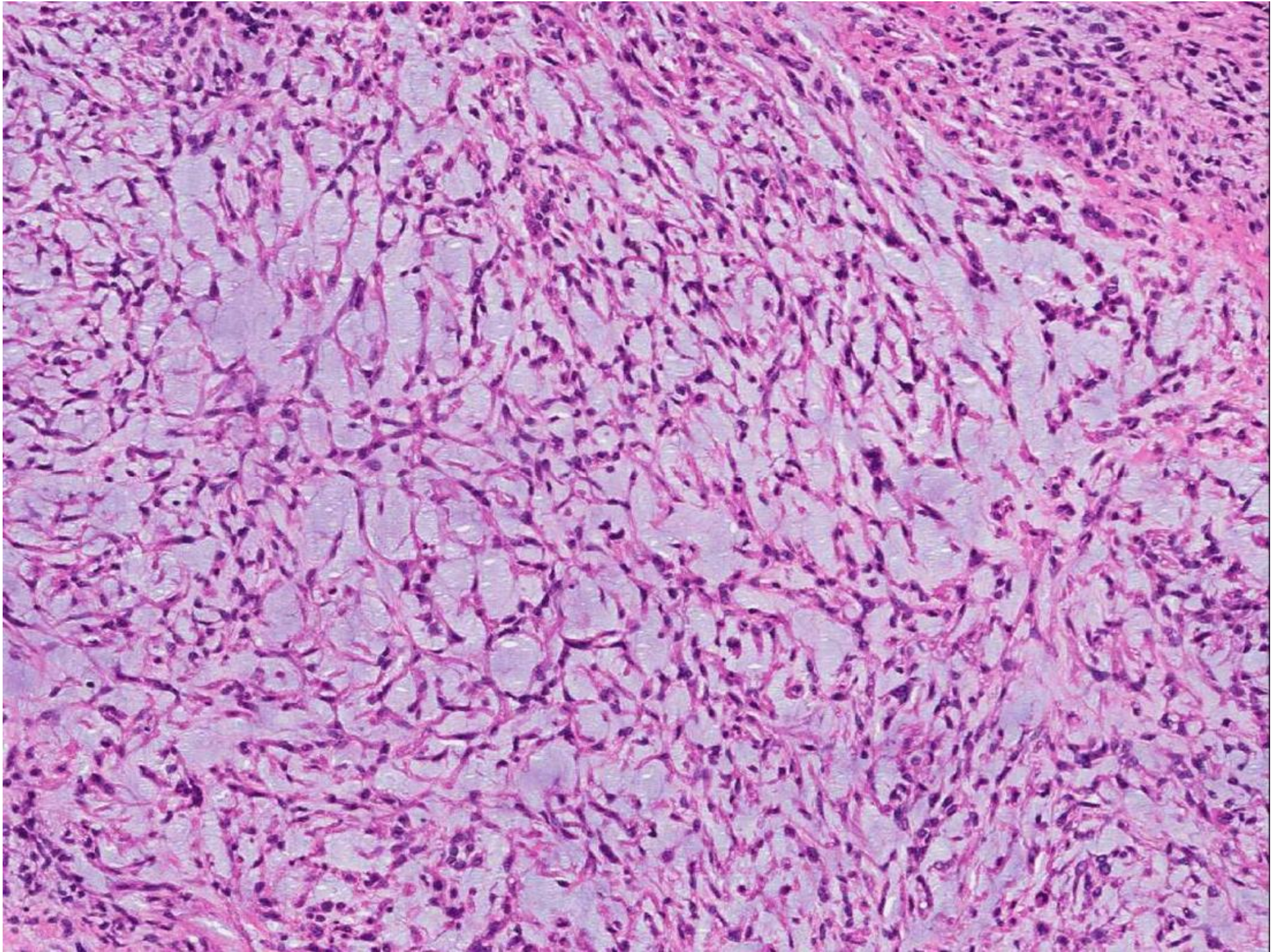


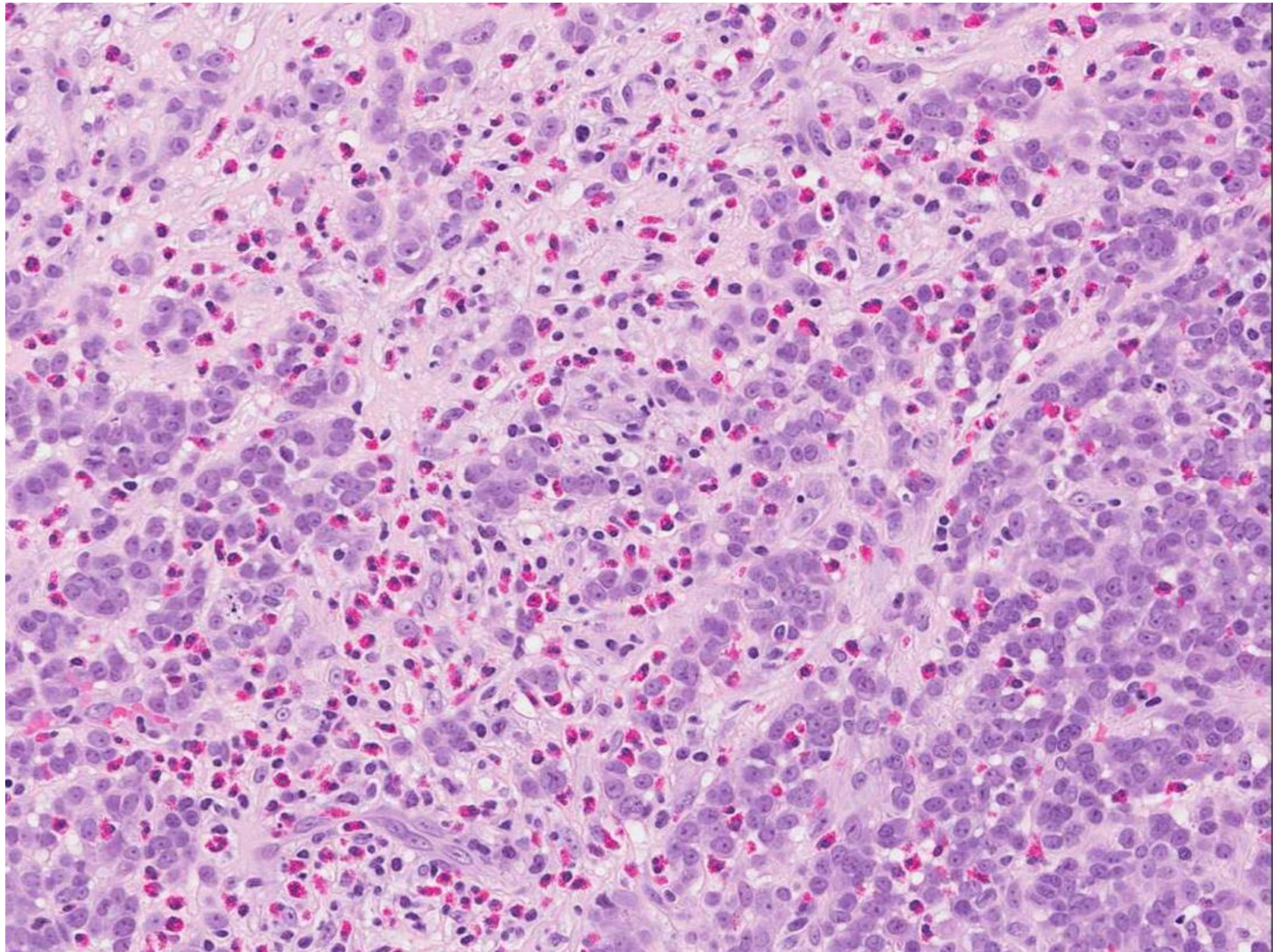


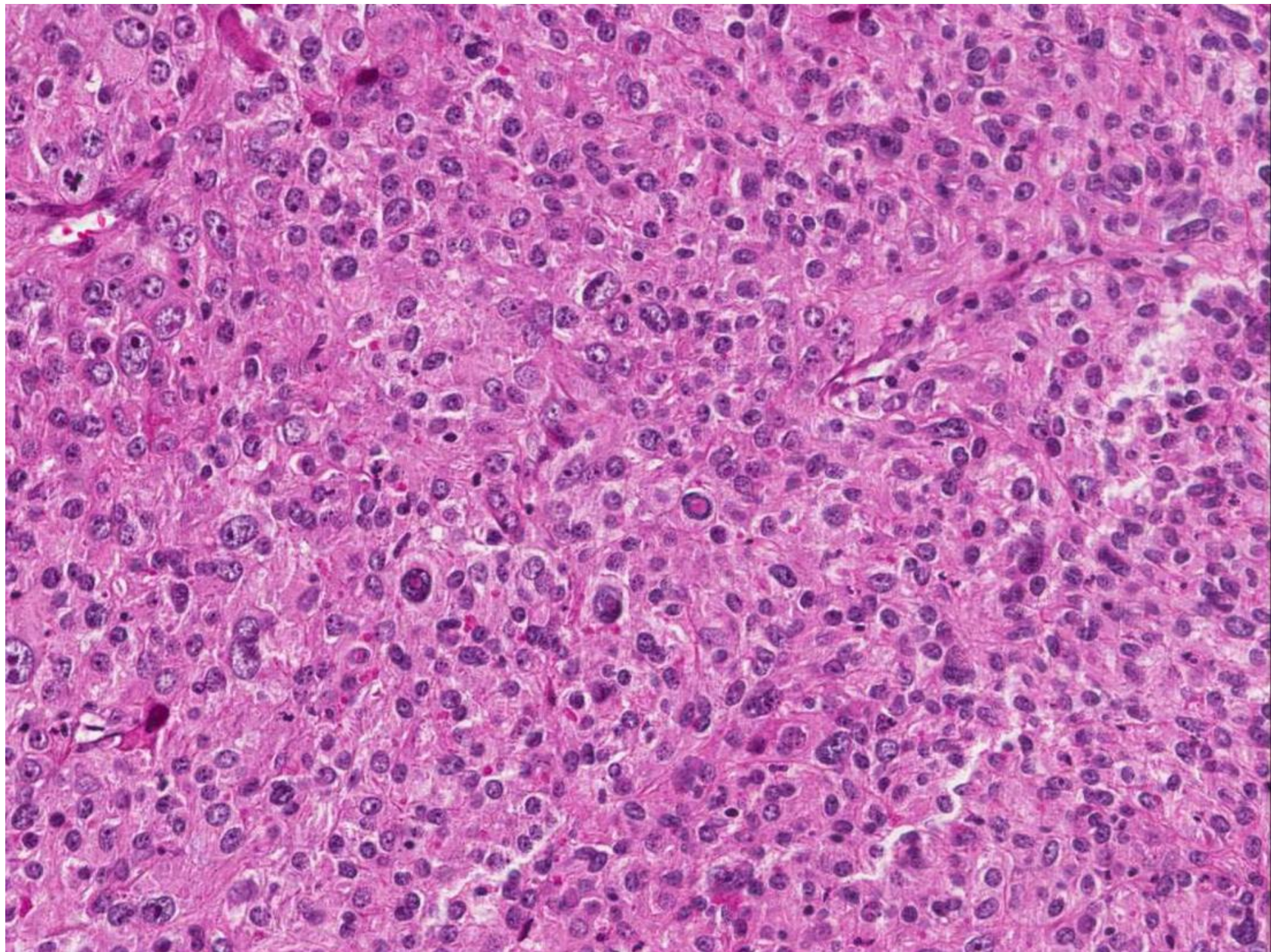


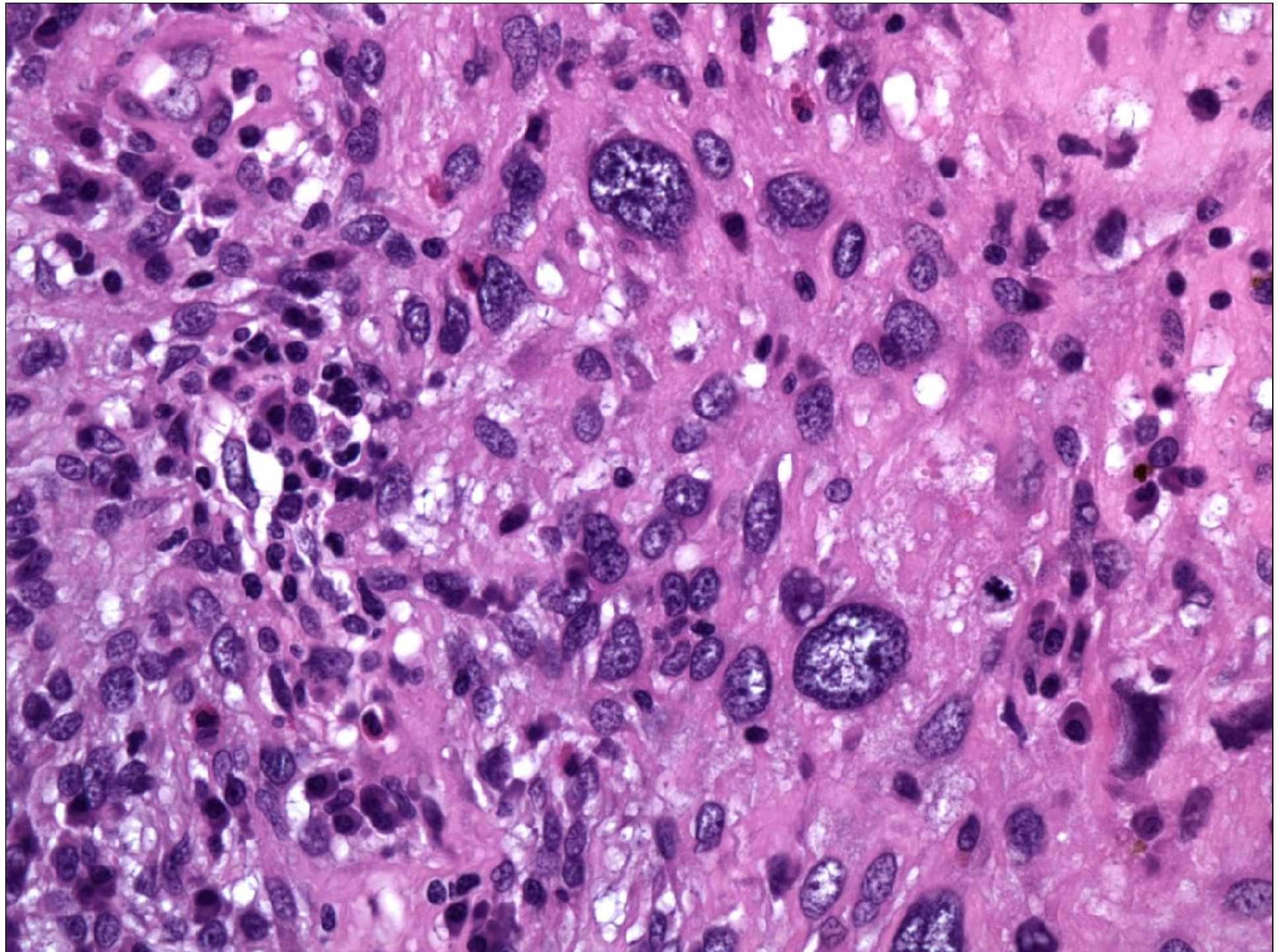


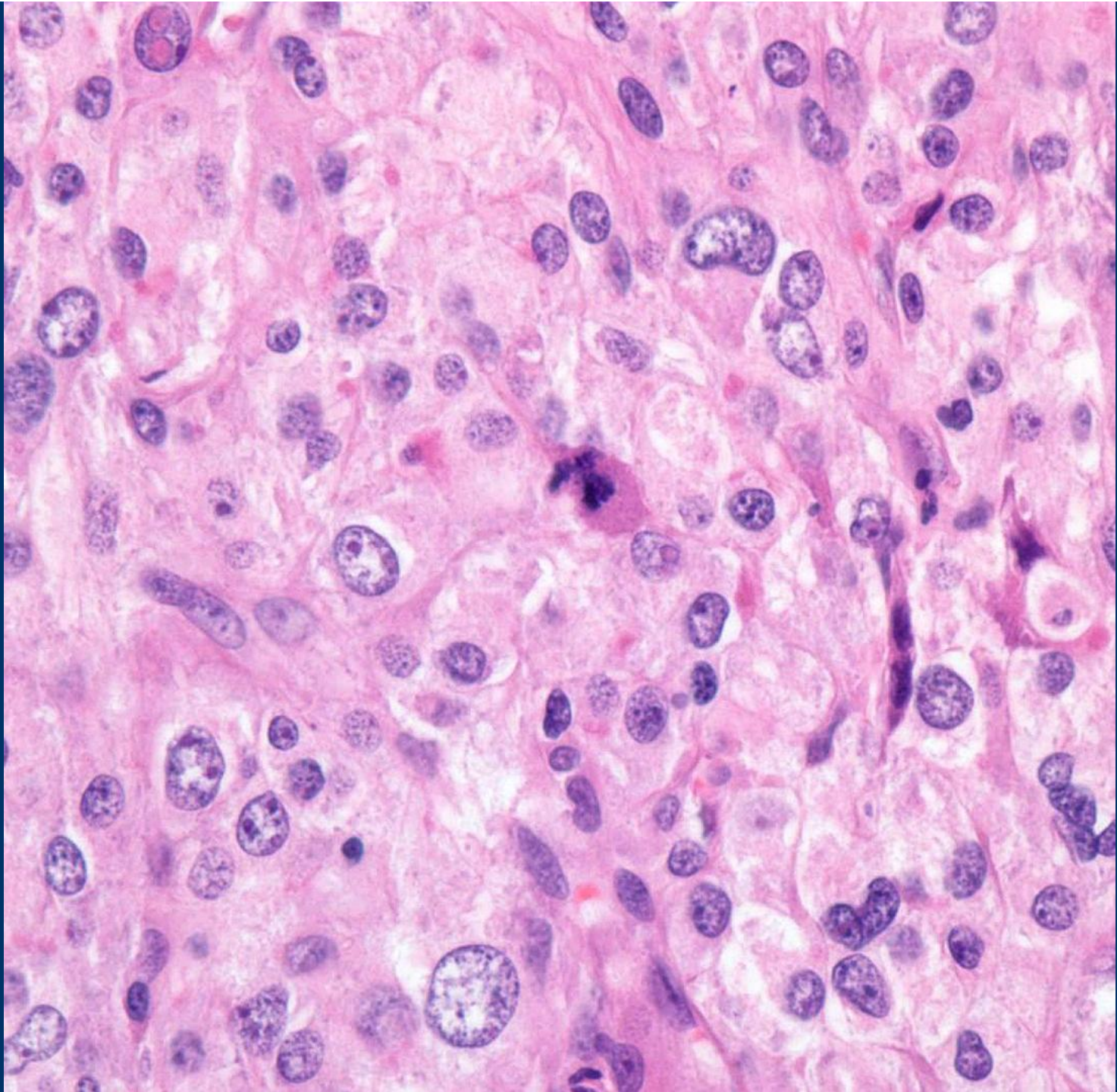






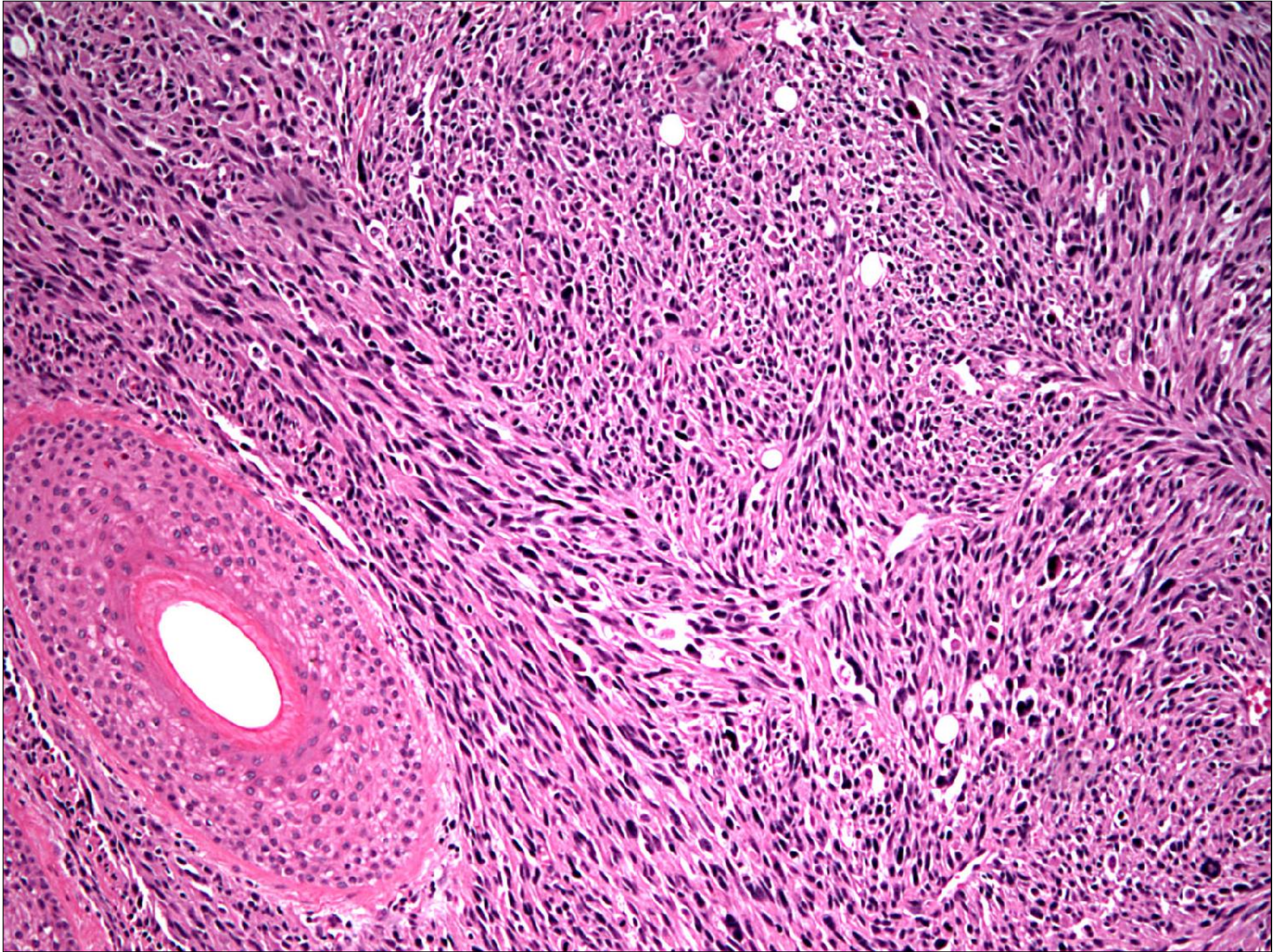


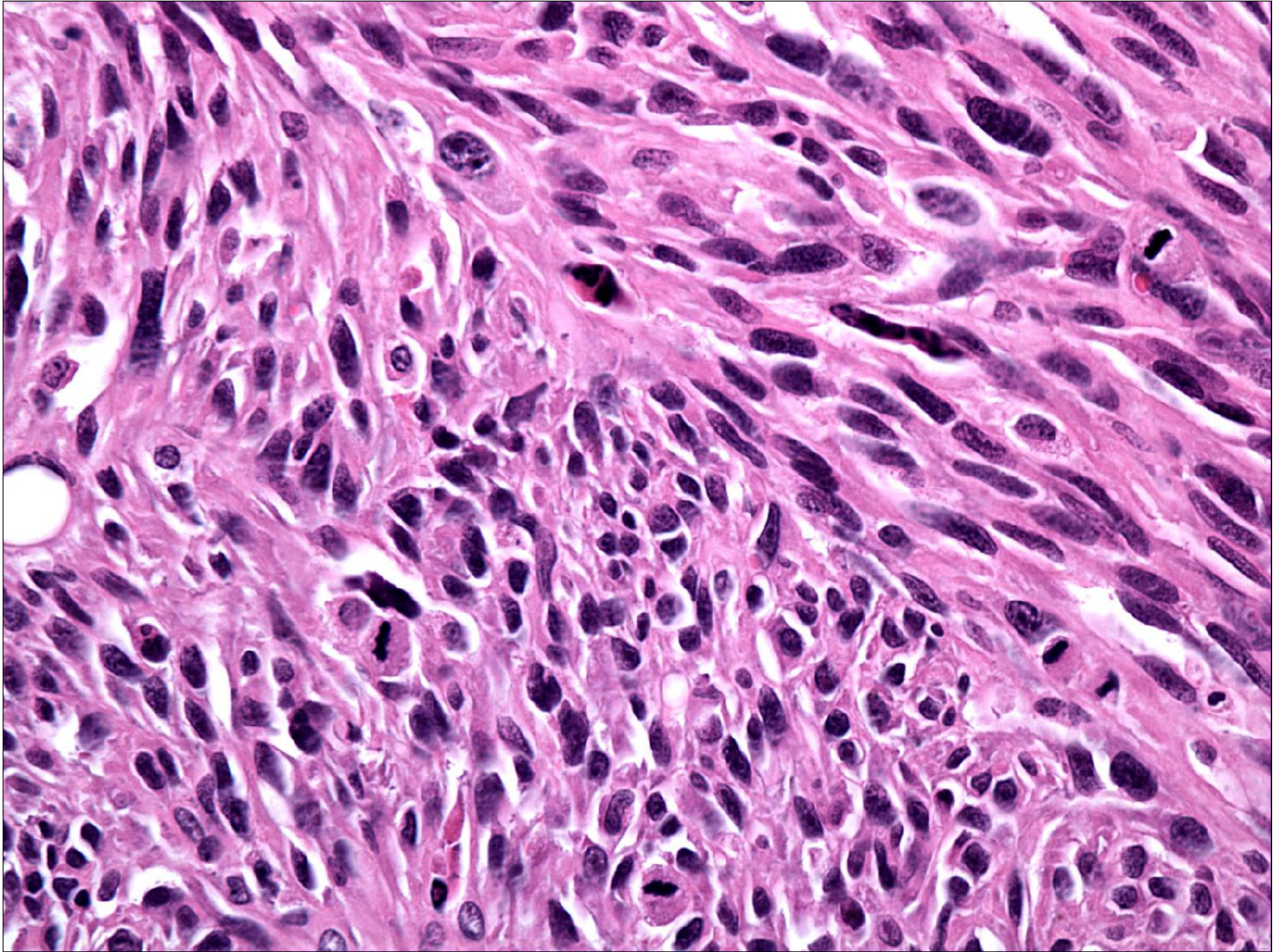




Life is a long lesson in
humility. (James M. Barrie,
1860-1937)

77-year-old woman with scalp
lesion



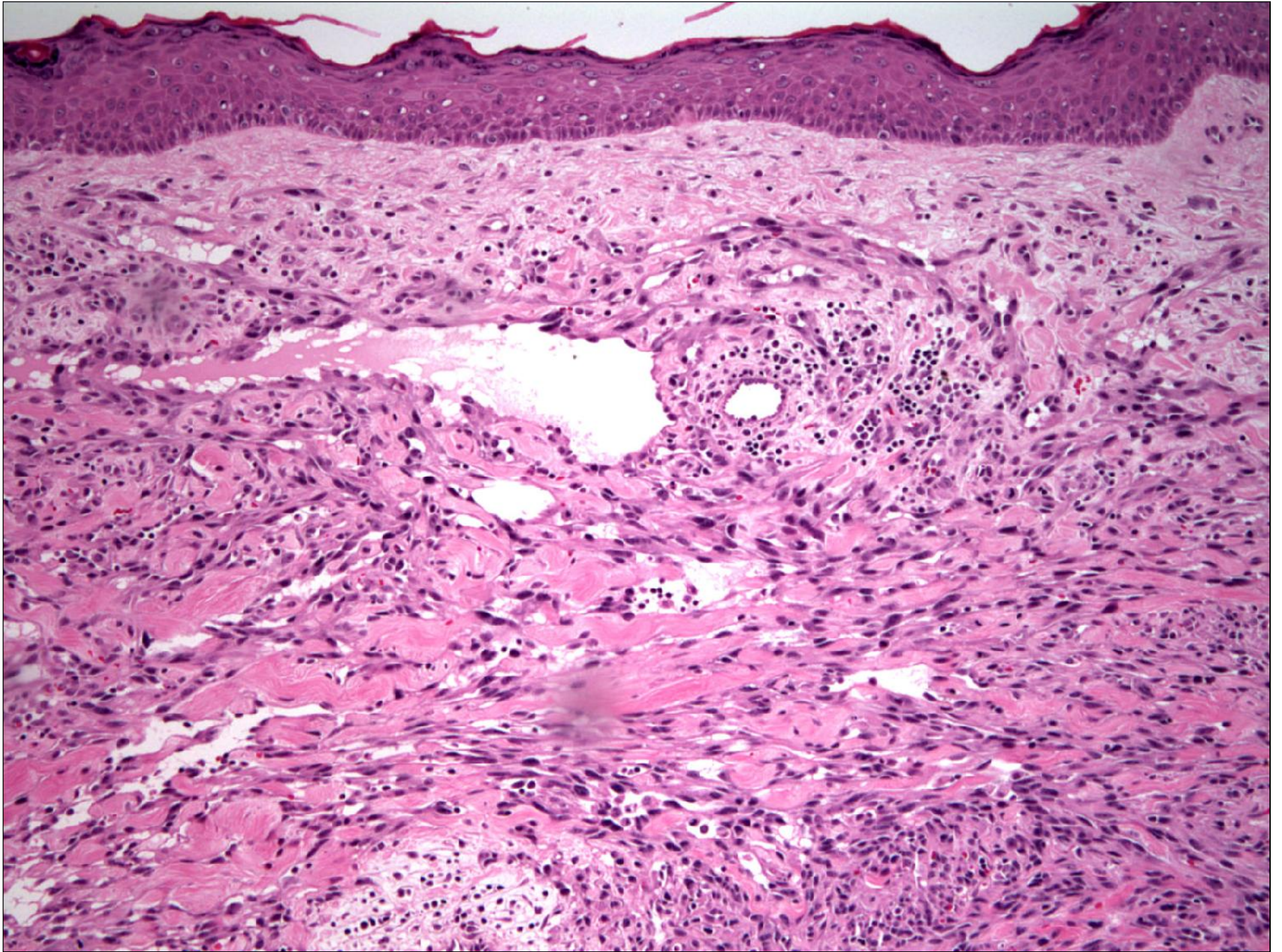


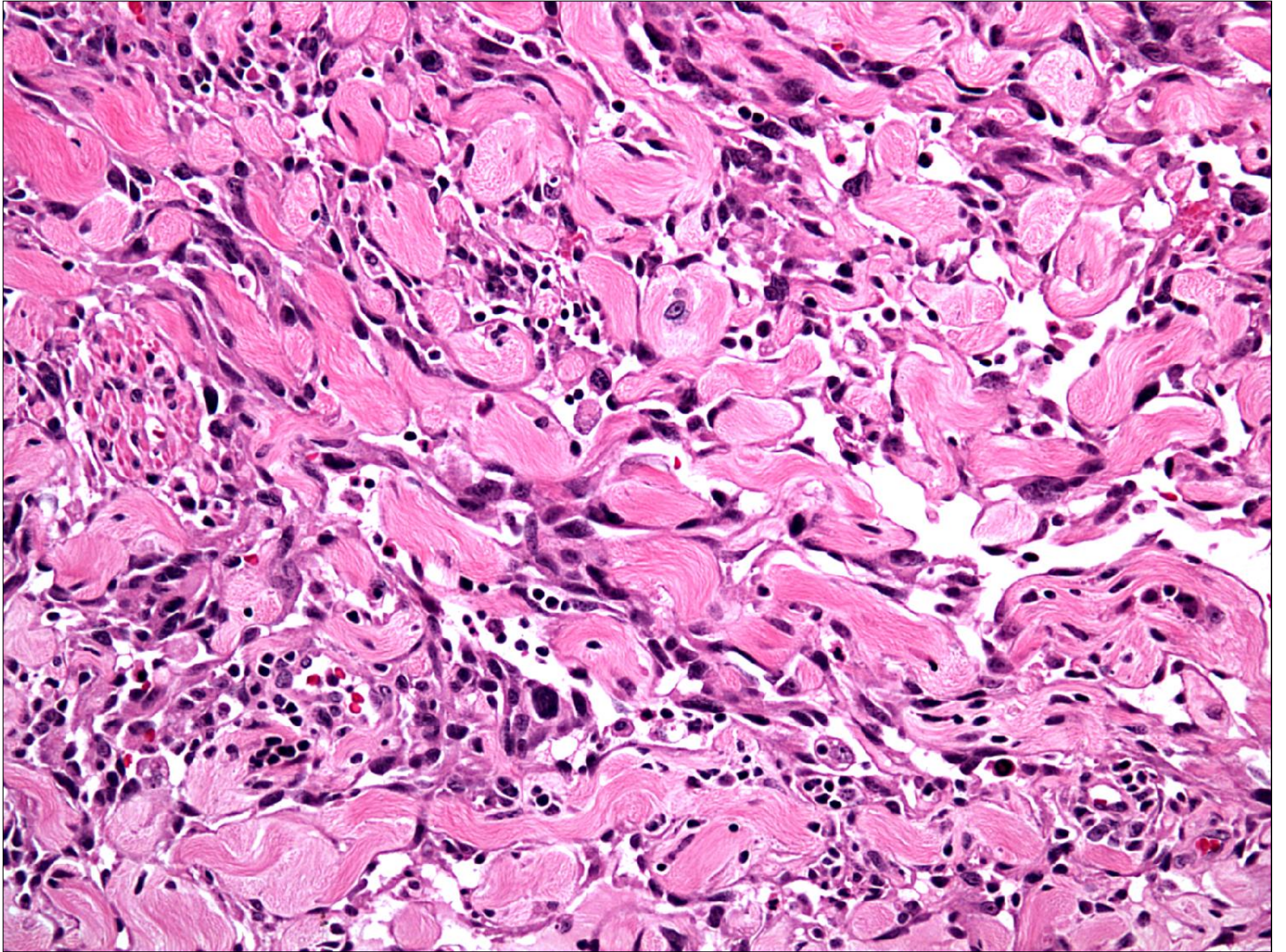
Dx: Malignant spindle cell neoplasm, see comment

- Comment: Sections demonstrate pleomorphic, hyperchromatic spindled cells arranged in irregular fascicles. By immunohistochemistry, the tumor cells are negative for cytokeratin 5/6, p63 and S100 protein. The histologic features and immunophenotype are consistent with atypical fibroxanthoma (AFX). If this is a larger lesion, it could represent a superficial pleomorphic sarcoma (MFH). A re-excision and clinical correlation is recommended.

Two weeks later.....

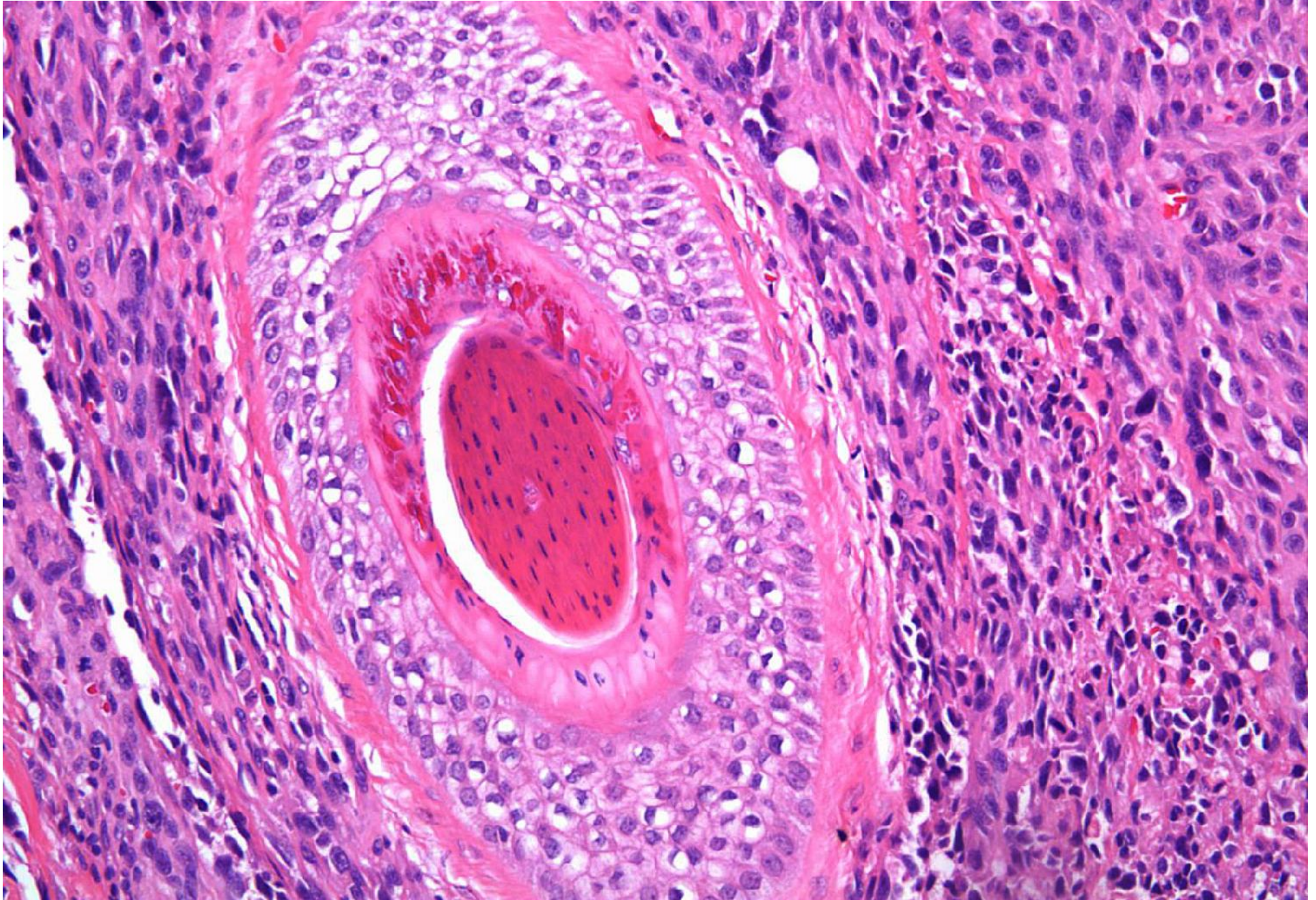
- My colleague comes into my office and says the words that no pathologist wants to hear:
- “Remember that case I showed you? I have the slides from the resection specimen....”



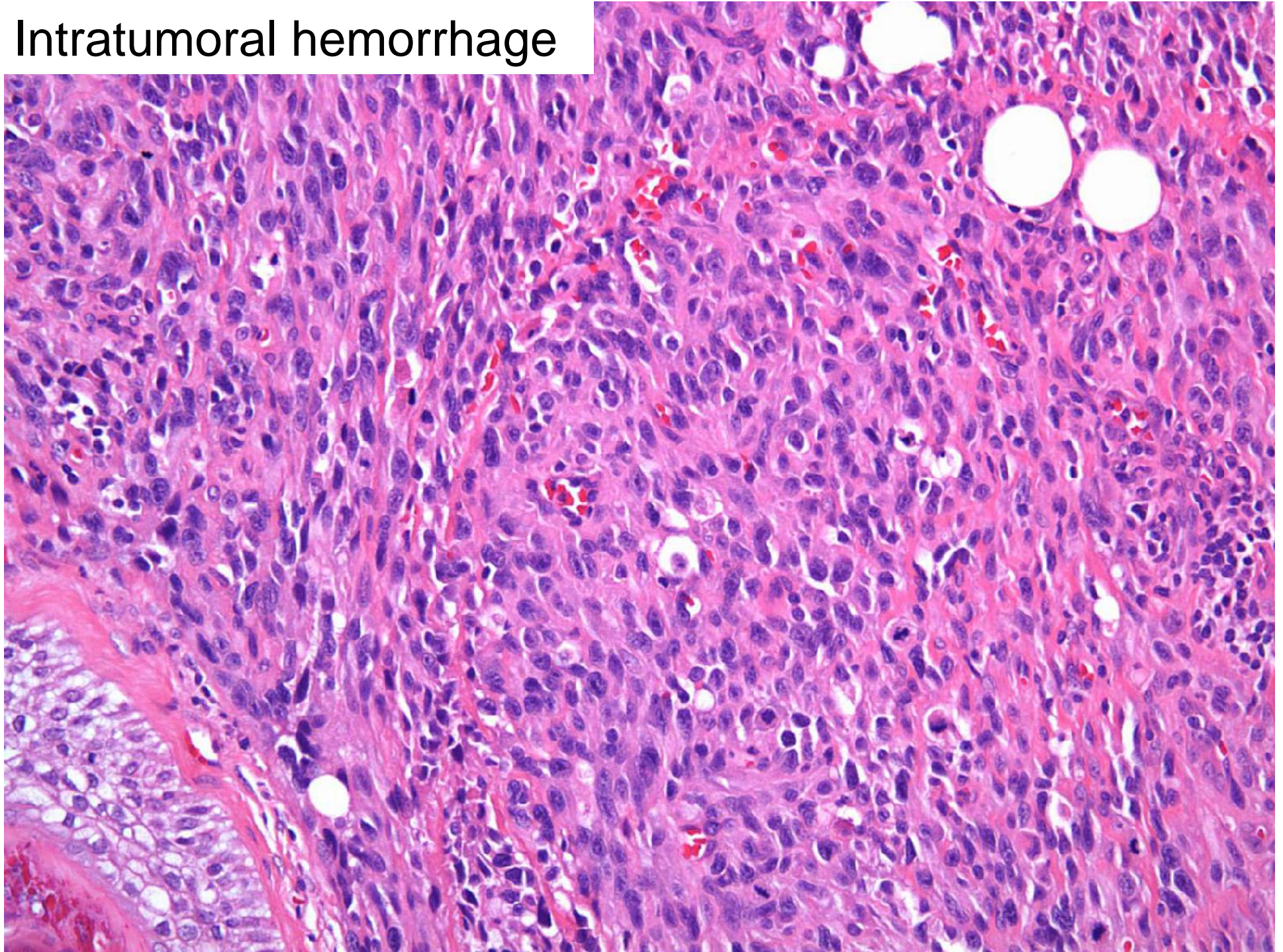


What did I miss?

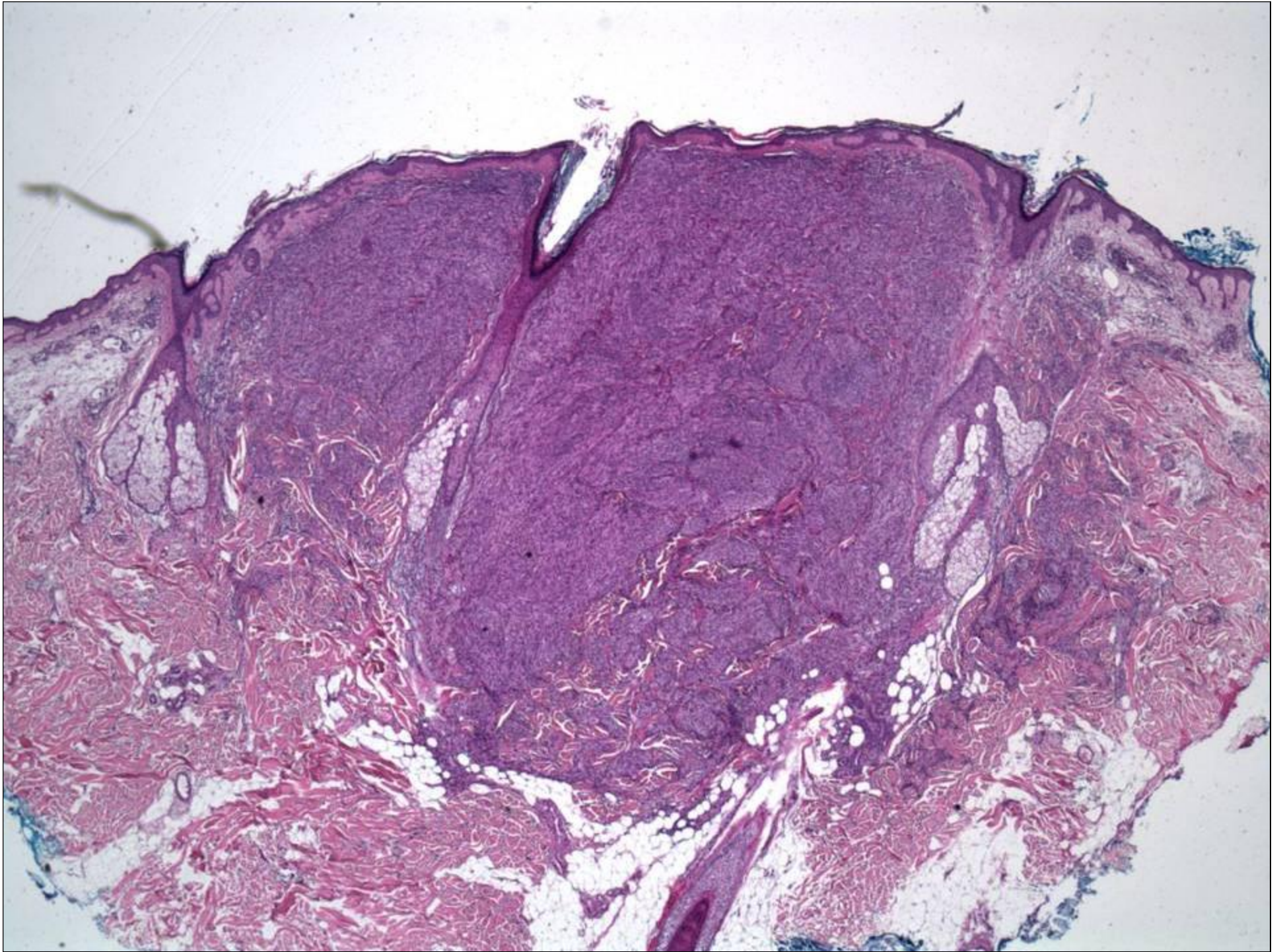
Tumor is infiltrating around adnexal structures

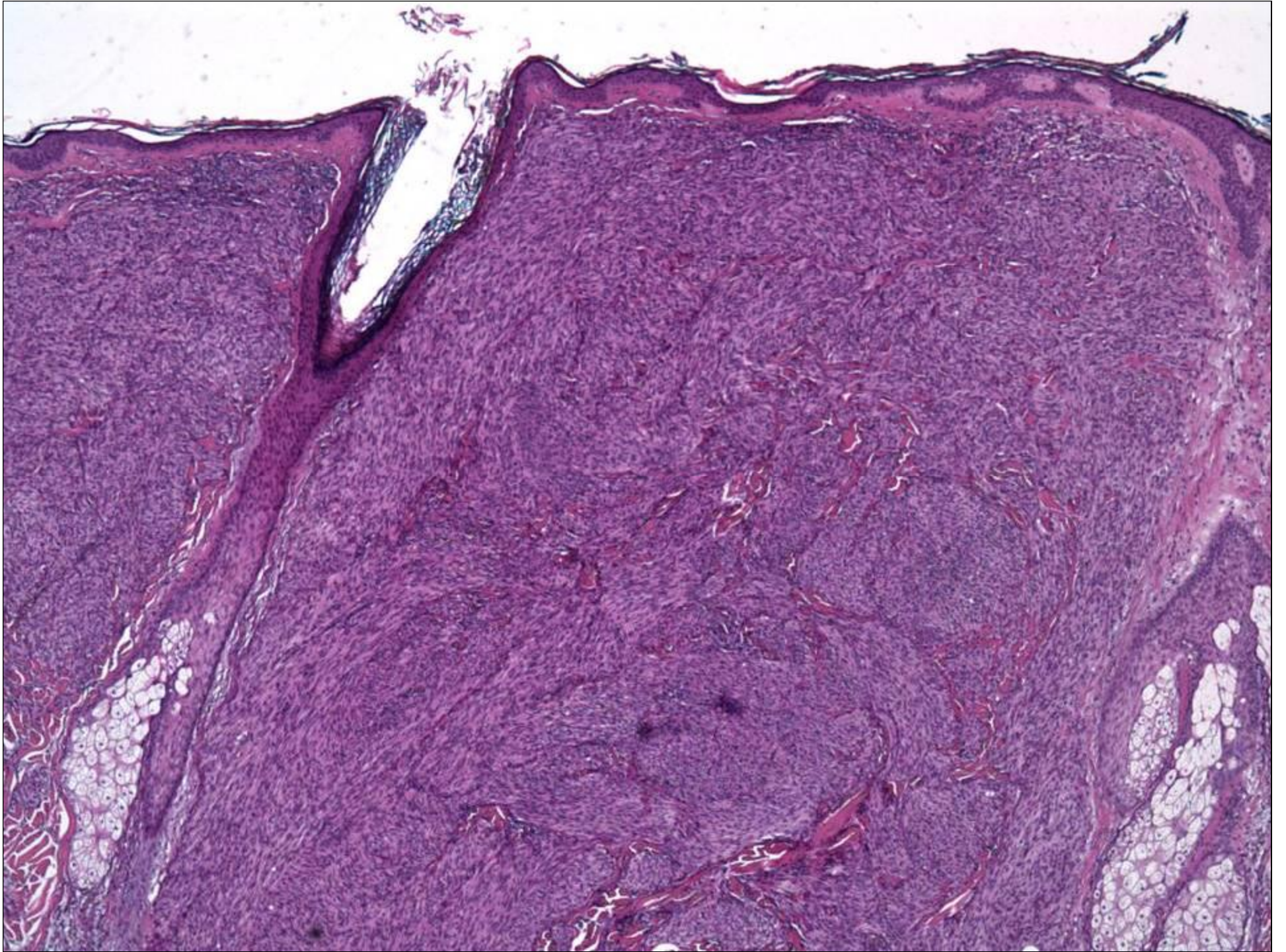


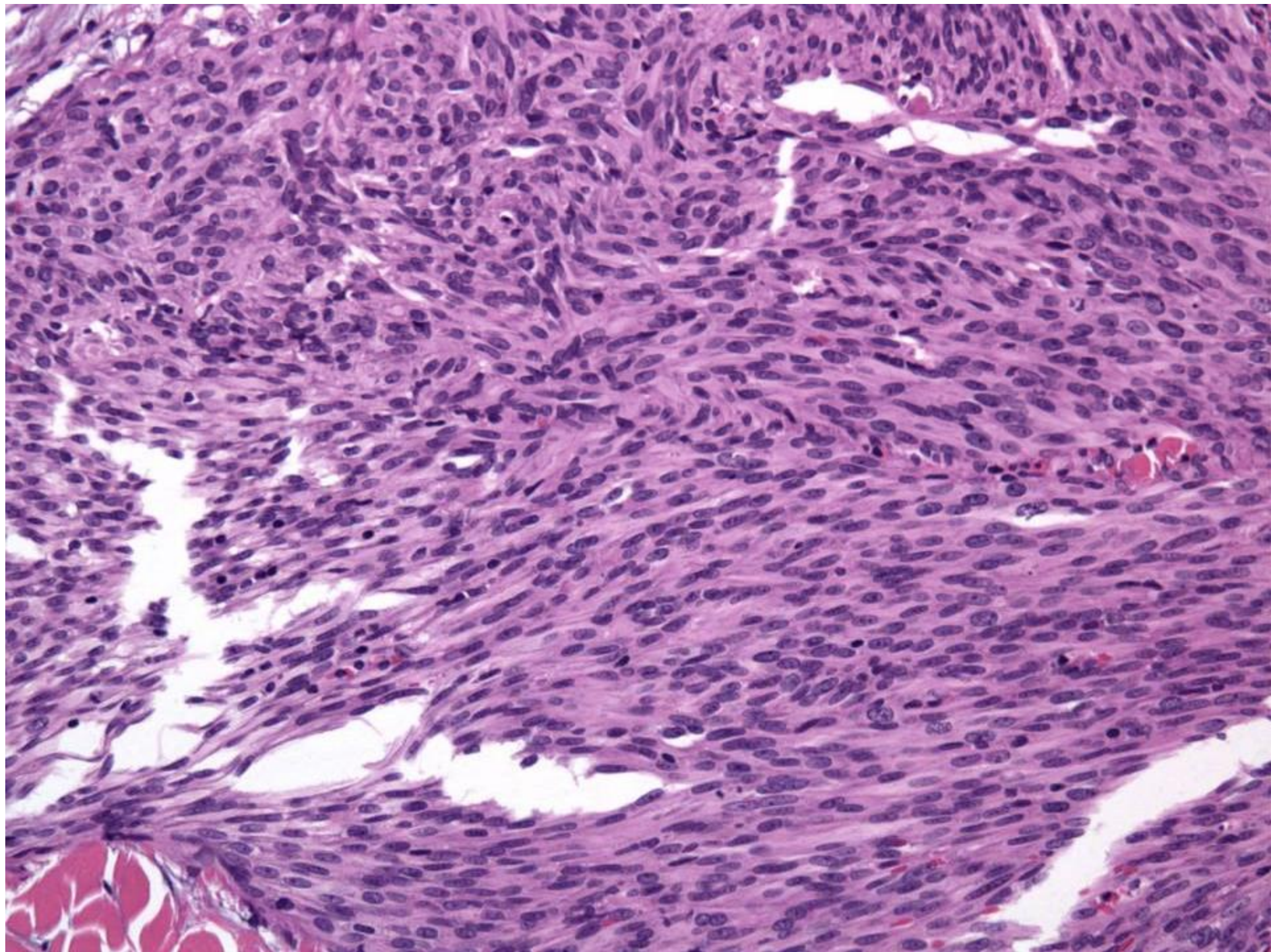
Intratumoral hemorrhage

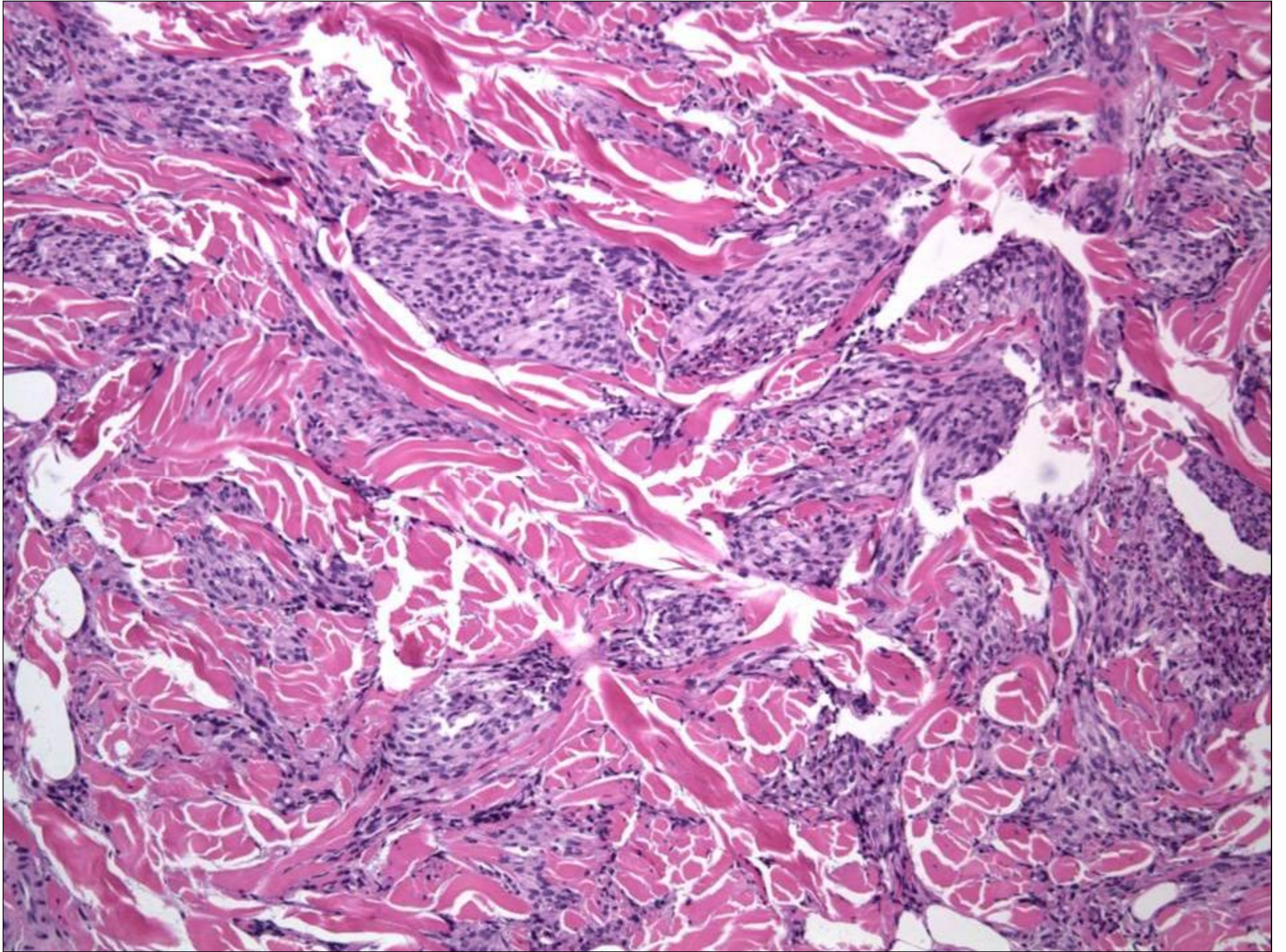


90-year-old man with lesion
on face; rule out basal cell
carcinoma



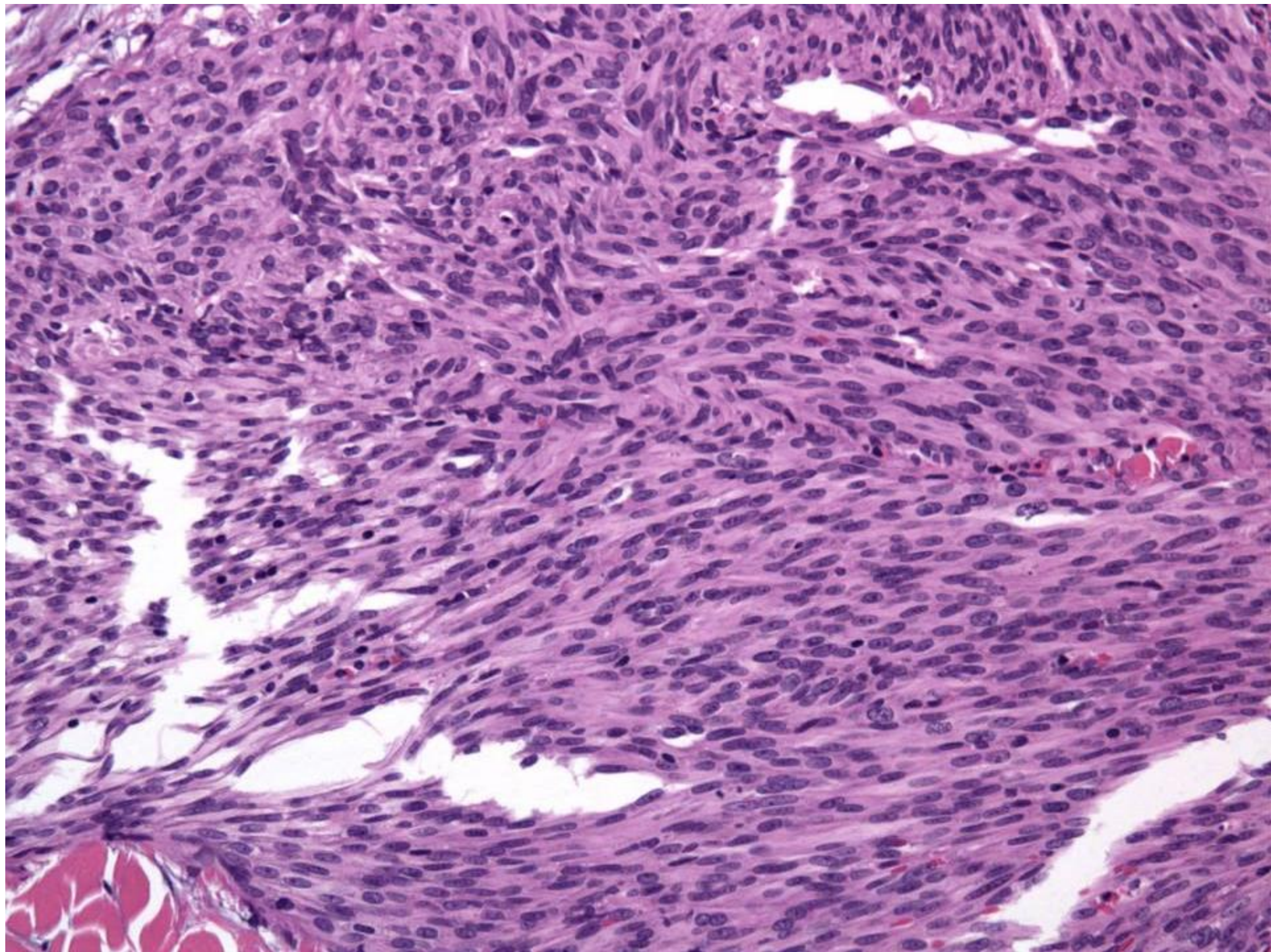


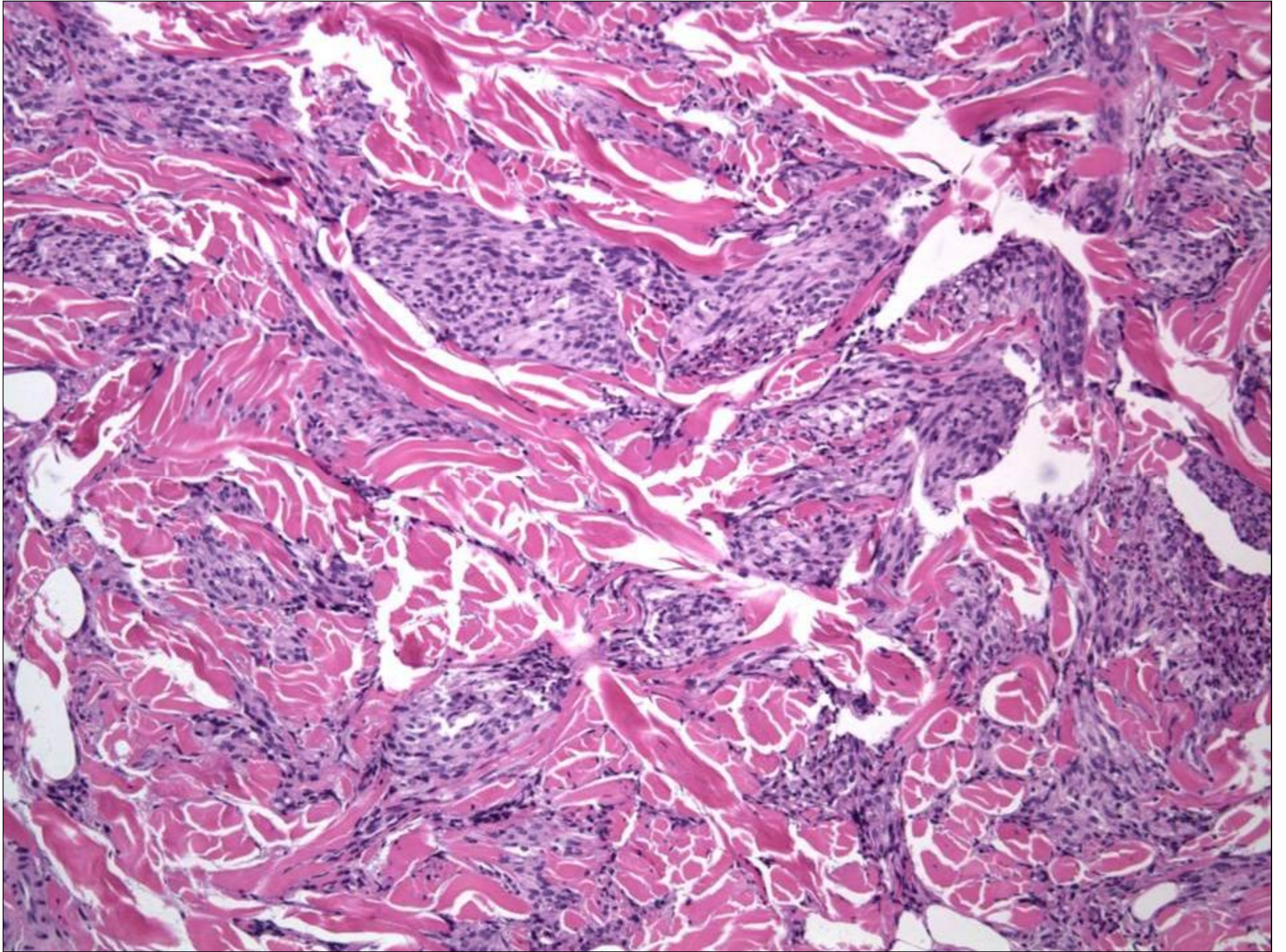


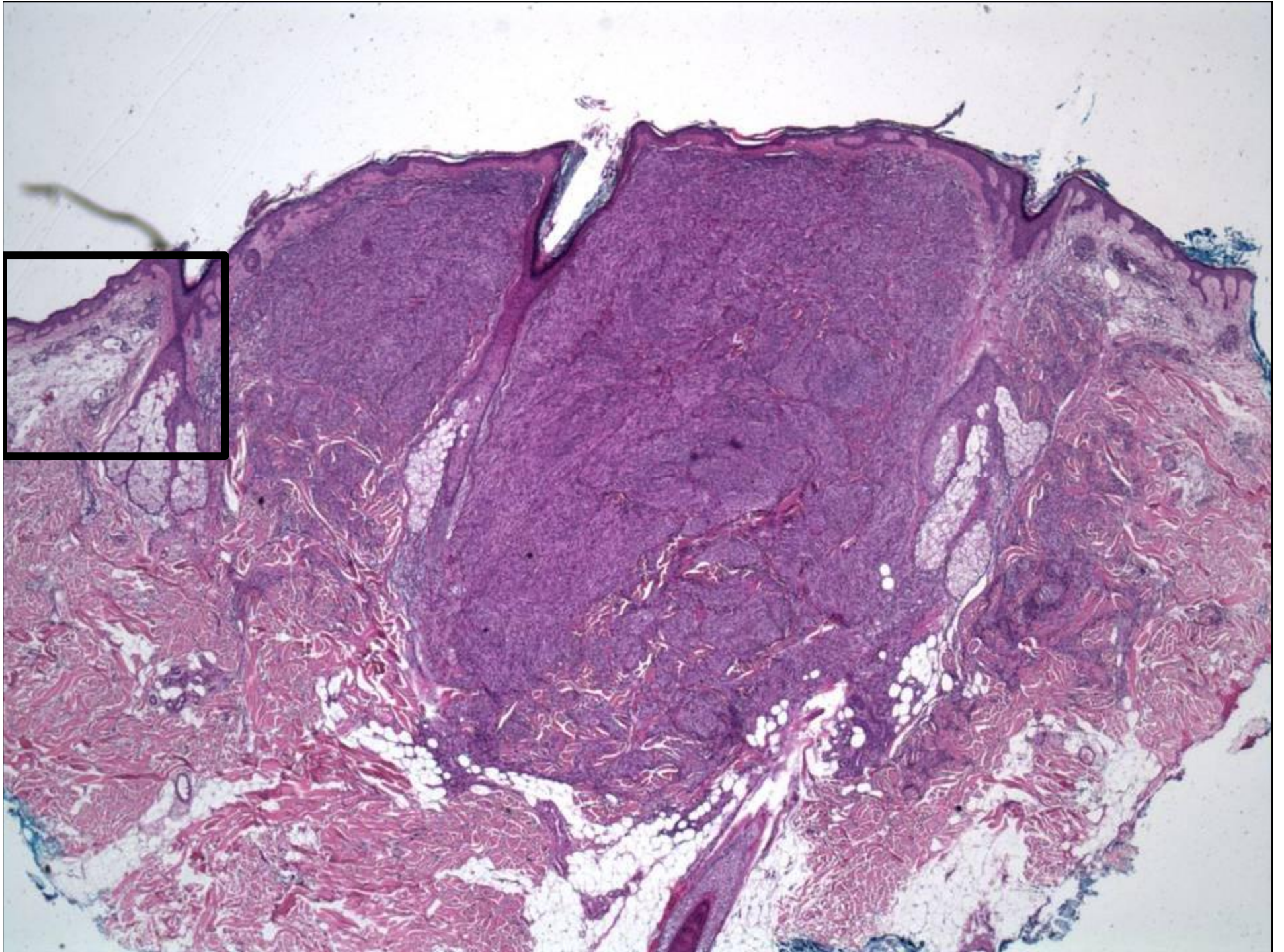


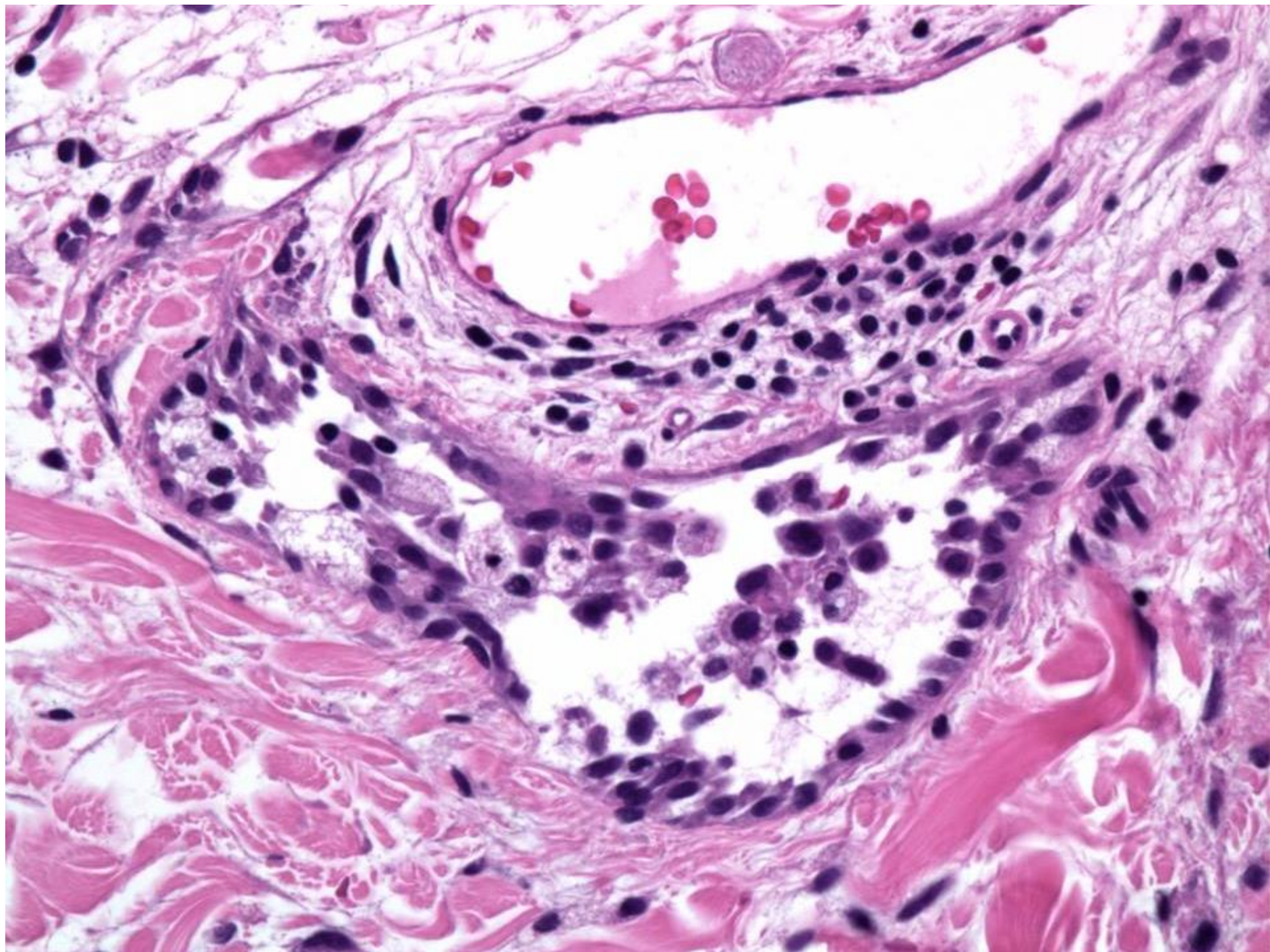
90 year-old man; rule out BCC

- Malignant spindle cell neoplasm
- Negative for CK5/6, p63, S100 protein

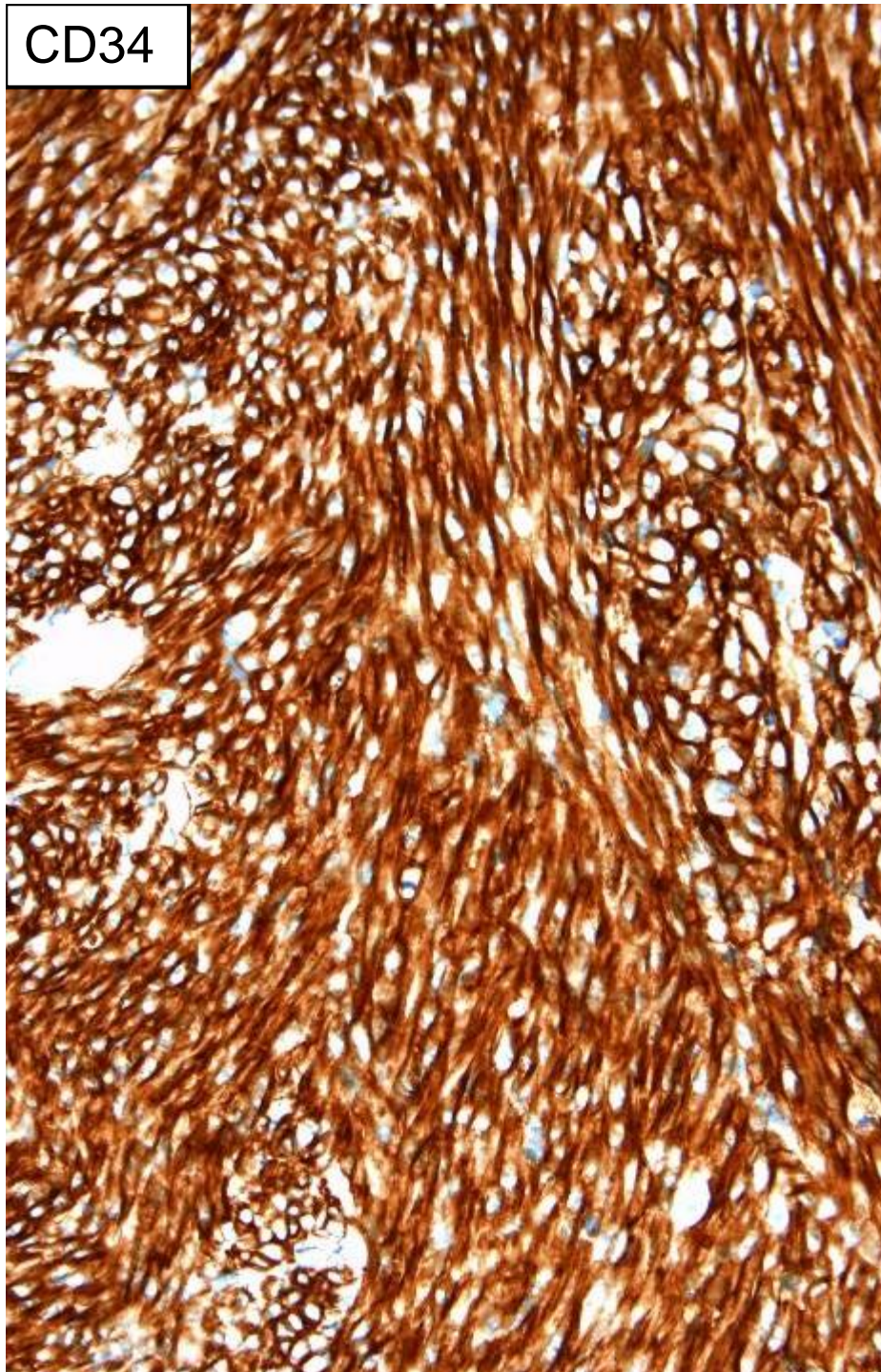




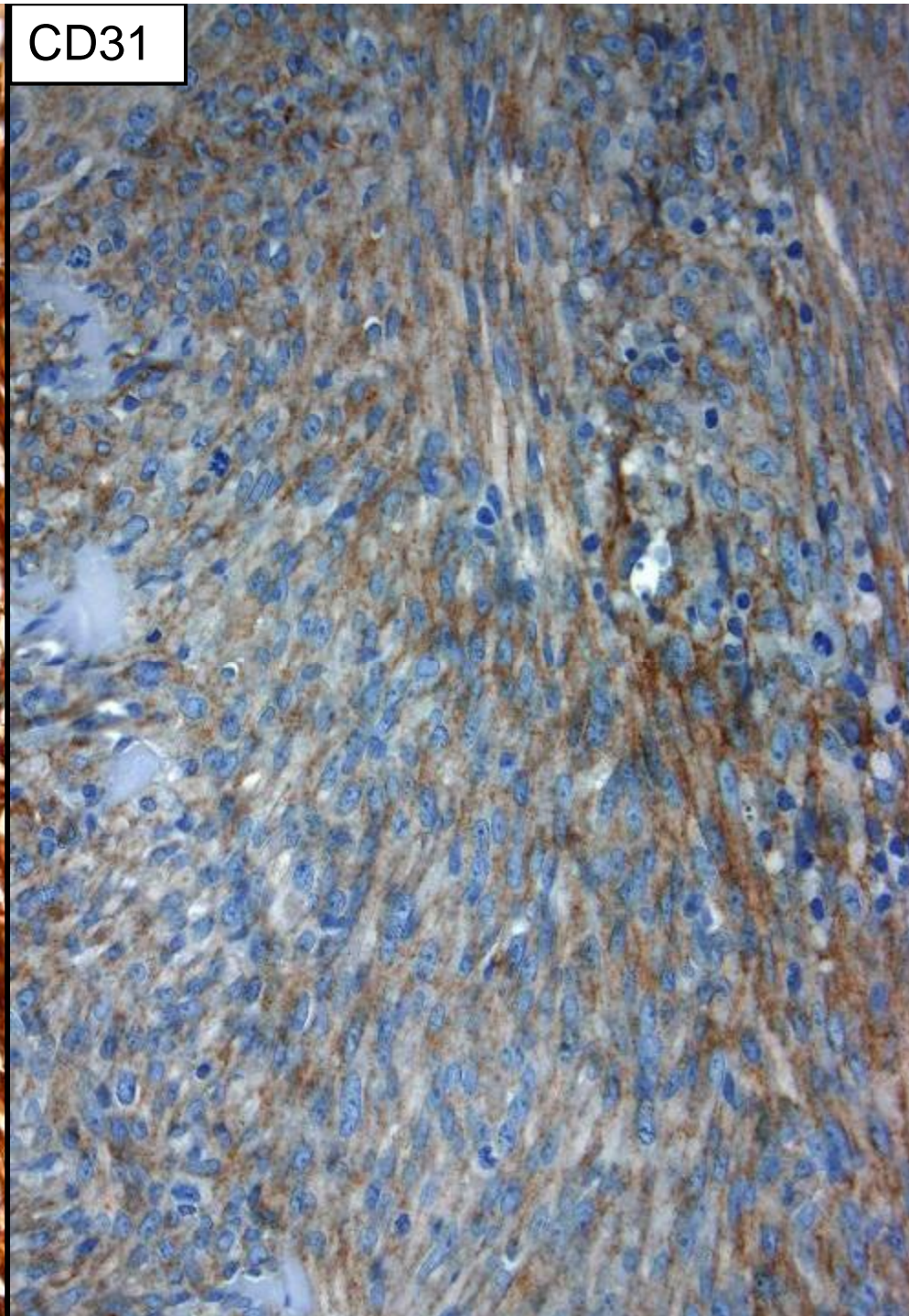




CD34



CD31



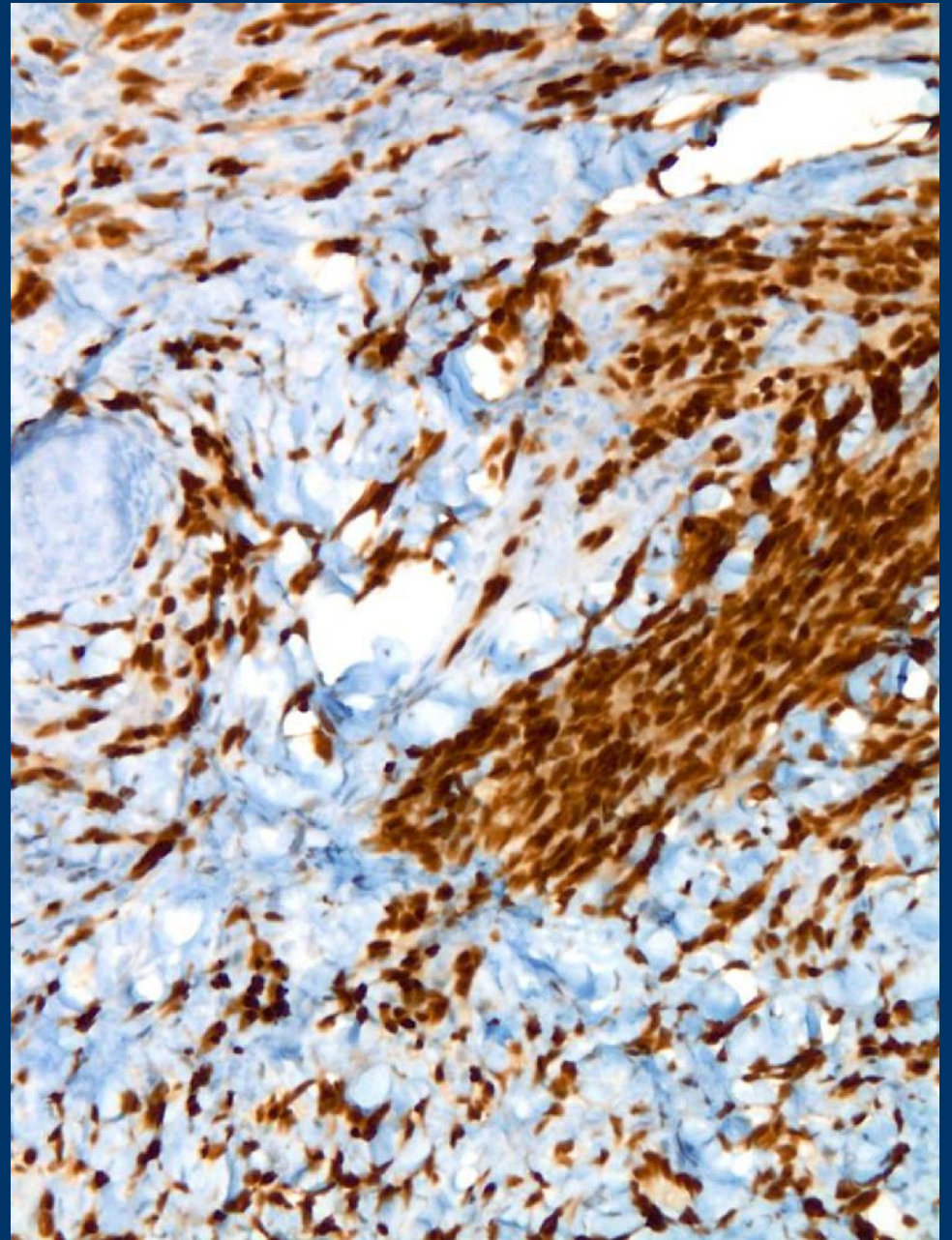
Angiosarcoma

- Can have solid spindle cell areas
- Keep a high index of suspicion for this diagnosis in tumors from the head and neck of older patients
- Infiltrative growth and hemorrhage are clues to the diagnosis
- Look at periphery of tumor: vasoformative areas often present at periphery
- Immunostains for ERG and CD34 are best stains to confirm diagnosis

ERG

- ETS family of transcription factors
- Sensitive and specific marker for vascular tumors
- Nuclear stain
 - Positive in all hemangiomas and lymphangiomas
 - 96/100 angiosarcomas
 - 42/43 epithelioid hemangioendotheliomas
 - 26/26 Kaposi sarcoma

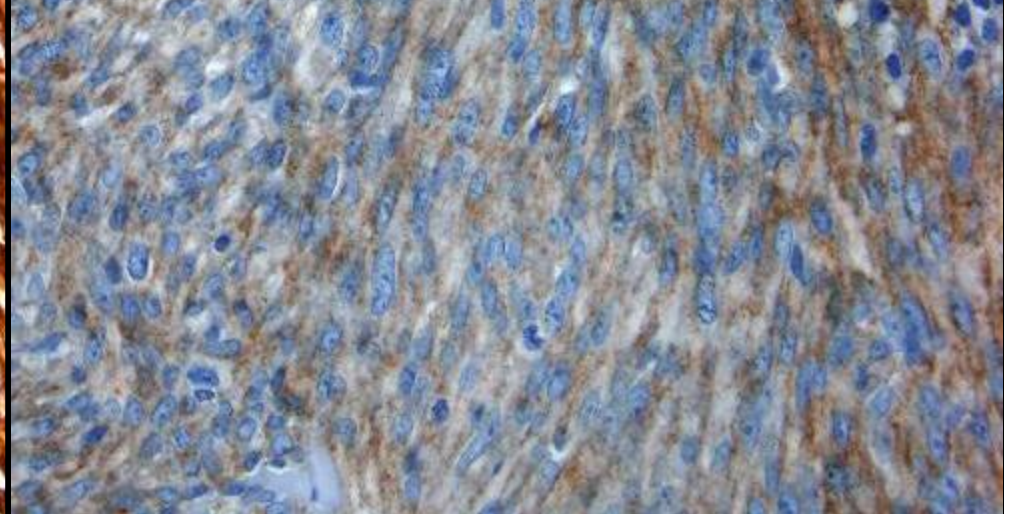
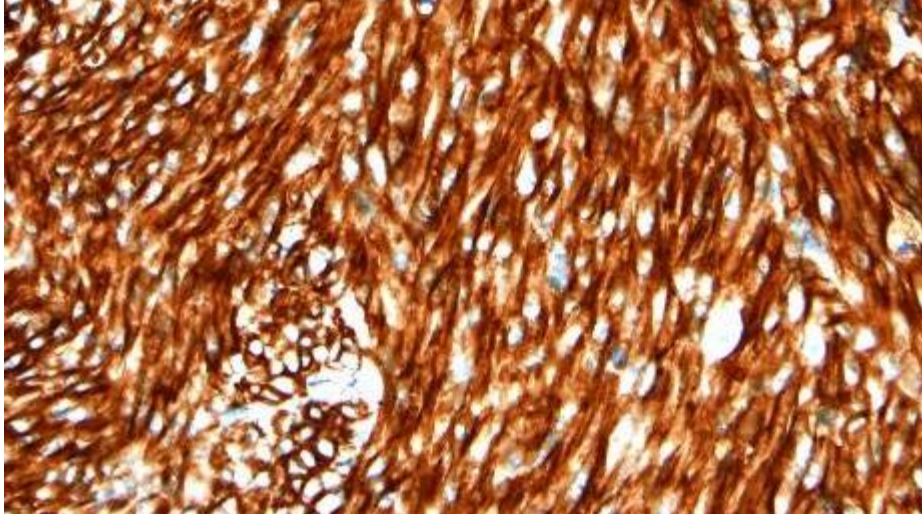
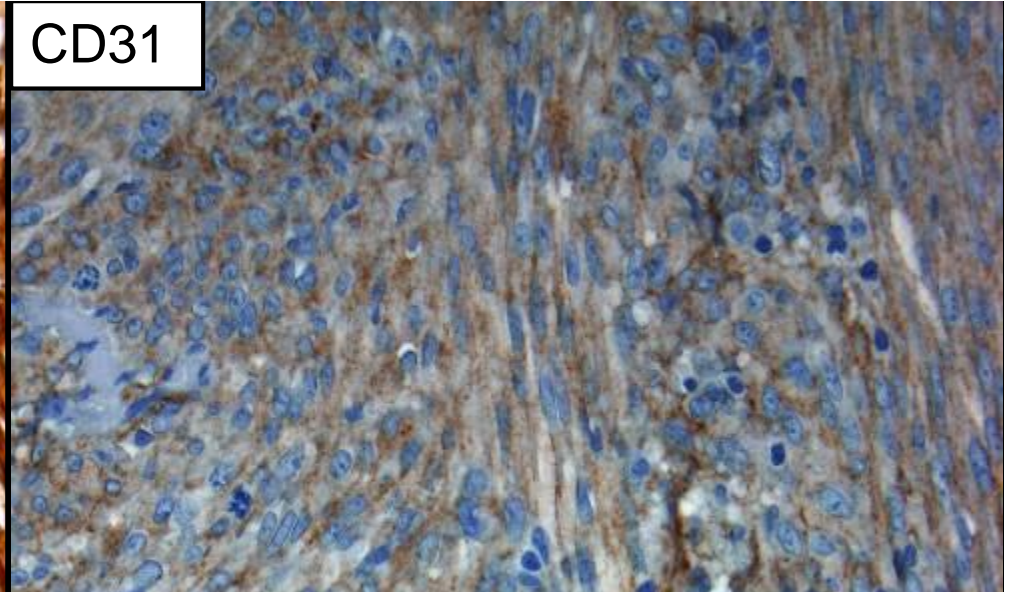
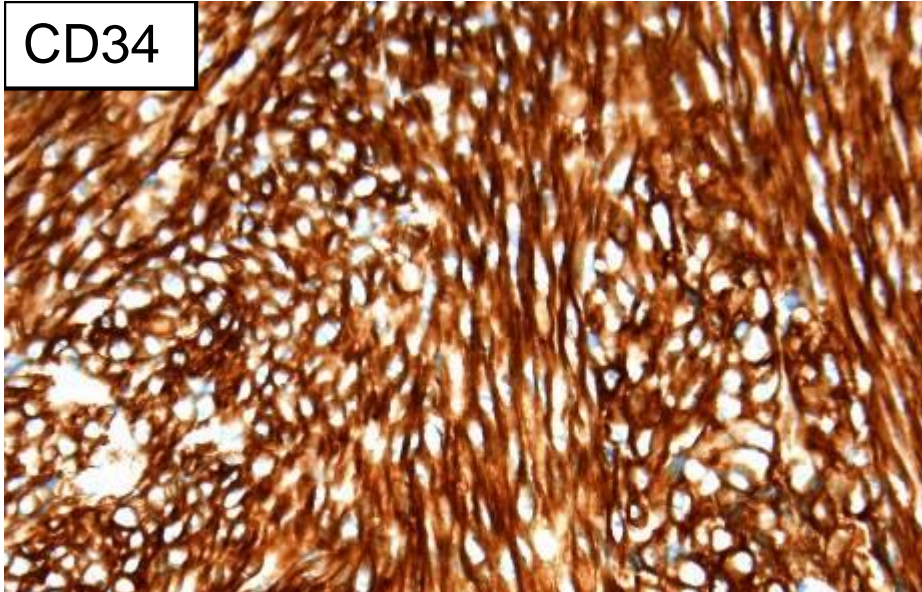
M Miettinen et al. Am J Surg Pathol 2011;35:432-441.



CD34

CD31

Spindle cell angiosarcomas
may be negative or only
weakly positive for CD31



*The Good,
The Bad,
and The Ugly*



*The Good,
The Bad,
and The Ugly*

