

Spindle Cell Lesions of the Breast

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Disclosures

- Zip, Zero, Zilch

Objectives

- Describe the histomorphology of benign and malignant spindle cell lesions of the breast
- Discuss the role of immunohistochemistry in this diagnosis
- Develop a diagnostic algorithm for spindle cell lesions of the breast
- Point out the limitations sometimes posed on core needle biopsy

Spindle cell lesions of the breast

- Broad differential diagnosis that includes reactive processes, primary benign or malignant lesions, and metastatic lesions
 - Overlap clinically and histomorphologically
 - Uncommon
- Any spindle cell lesion of the breast raises the possibility of a metaplastic carcinoma
 - Focal and weak immunoreactivity
 - Panel of cytokeratin AE1/3, 34 β E12, Cam5.2, cytokeratins 7 and 14, MNF116
 - p63
- Many of the primary benign lesions arise from fibroblasts and myofibroblasts
 - Variable expression of CD34, smooth muscle actin, desmin, and hormone receptors

Features to consider

- Composition
 - Pure spindle cell
 - Mixed spindle cell and epithelioid populations
 - Adenomyoepithelioma, low grade adenosquamous carcinoma, syringomatous adenoma, radial sclerosing lesion, metaplastic carcinoma
- Tumor border with adjacent breast parenchyma
- Mitotic activity
- Presence or absence of atypia
 - Absence of atypia does not always equate to benign
- Clinical and radiologic features

Spindle Cell Lesions: Fairly Inclusive List

- Low grade or bland cytology
 - Reactive spindle cell nodule
 - Fibromatosis
 - Low-grade fibromatosis-like metaplastic carcinoma
 - Angiosarcoma
 - Atypical vascular lesion
 - Hemangioma
 - Angiolipoma
 - Pseudoangiomatous stromal hyperplasia (PASH) and fascicular PASH
 - Myofibroblastoma
 - Leiomyoma
- Atypical cytology
 - Nodular fasciitis
 - Spindle cell metaplastic carcinoma
 - Mammary sarcoma
 - Angiosarcoma
 - Stromal component of a borderline or malignant phyllodes tumor
 - Metastases with a spindled appearance
 - Melanoma
 - Sarcoma
 - Poorly differentiated carcinoma

Bland spindle cell lesions of the breast with benign behavior

- Reactive spindle cell nodule
- Pseudoangiomatous stromal hyperplasia (PASH)
- Myofibroblastoma
- Fibromatosis
- Vascular lesions
 - Atypical vascular lesion
 - Hemangioma
- Angiolipoma
- Leiomyoma

Reactive spindle cell nodule

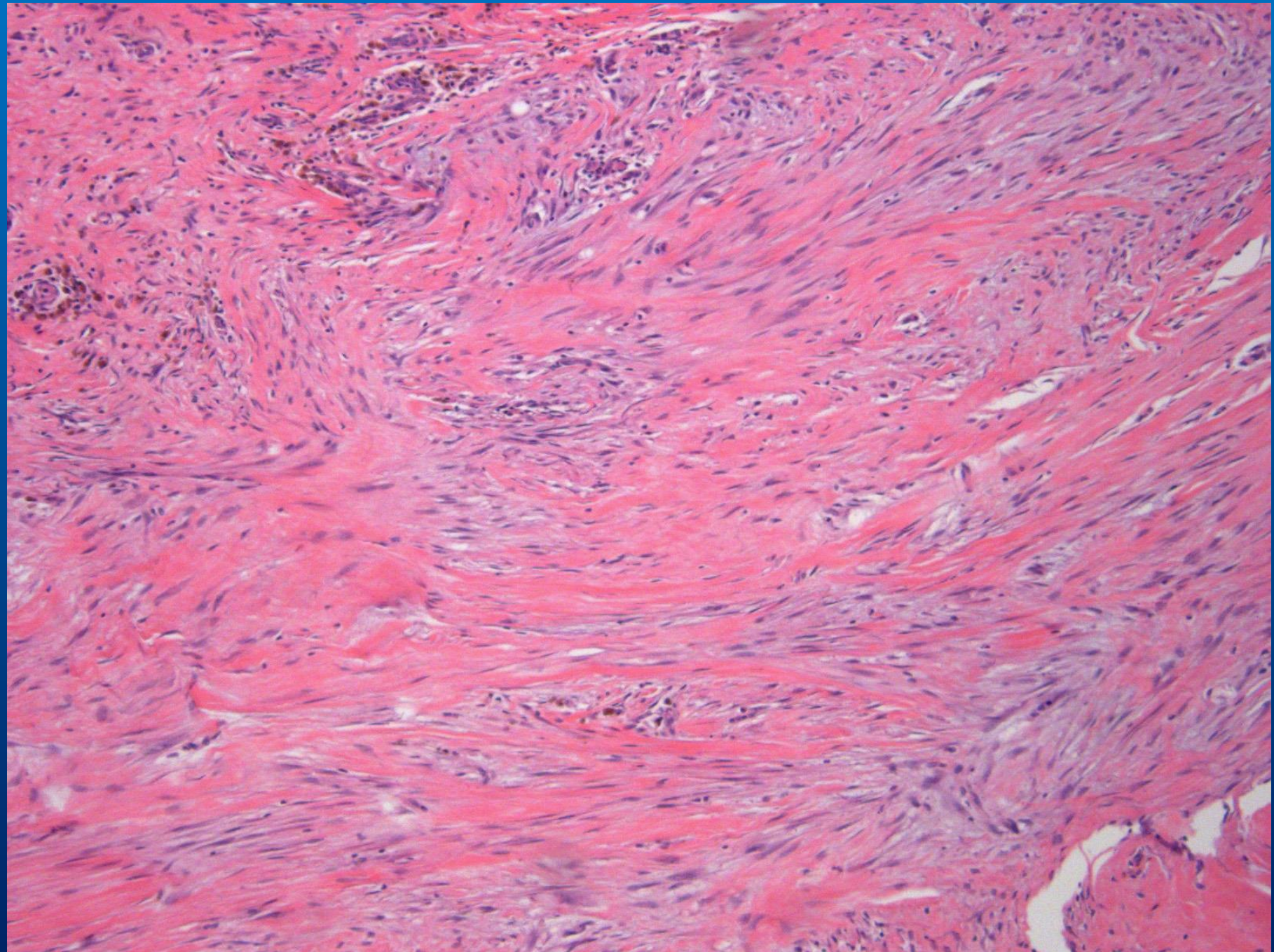
- Clinical Features
 - Associated with previous FNA or core needle biopsy
 - Distinct nodule, ranging from 1 mm up to 9 mm
 - Most commonly seen after biopsy of a papillary lesion
- Microscopic features
 - Intersecting fascicles of plump spindle cells with a vague storiform architecture
 - Numerous intermixed thin walled vessels and inflammatory cells
 - Hemosiderin laden macrophages, rare giant cells, lymphocytes and plasma cells
 - Mild nuclear pleomorphism with rare mitotic figures (0-1 per 10 hpf) and no atypical mitotic figures
 - Metaplastic squamous epithelium

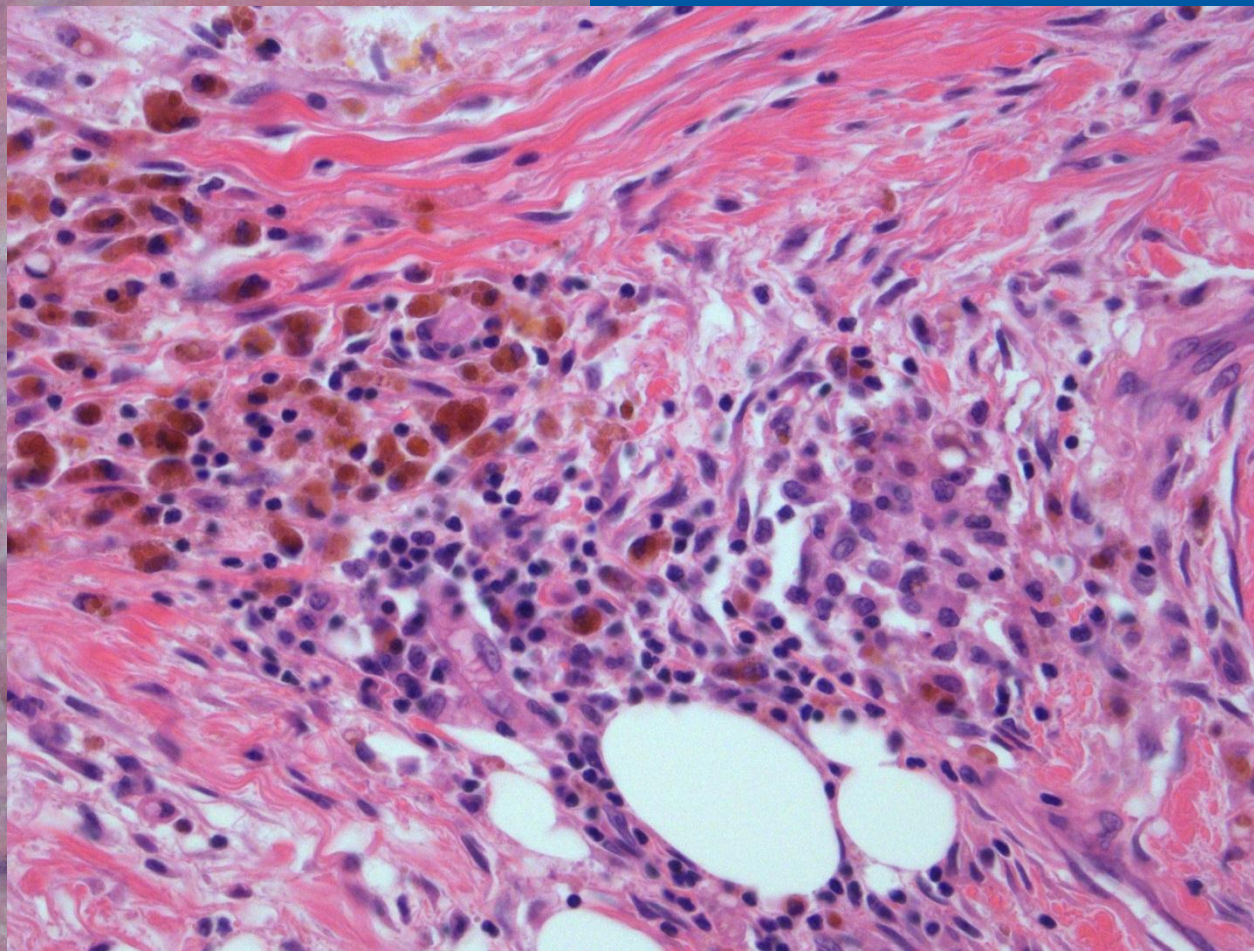
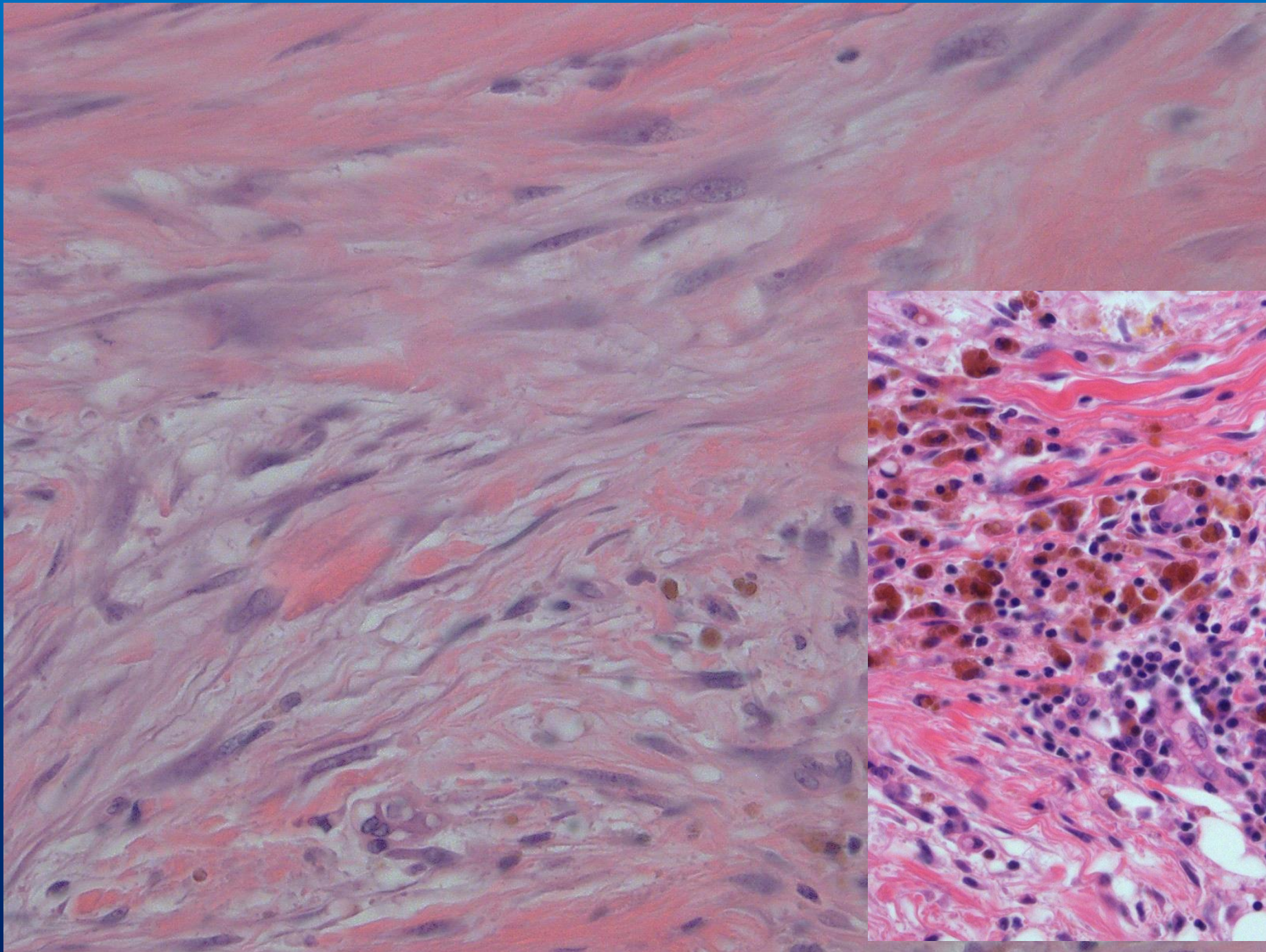
Reactive spindle cell nodule

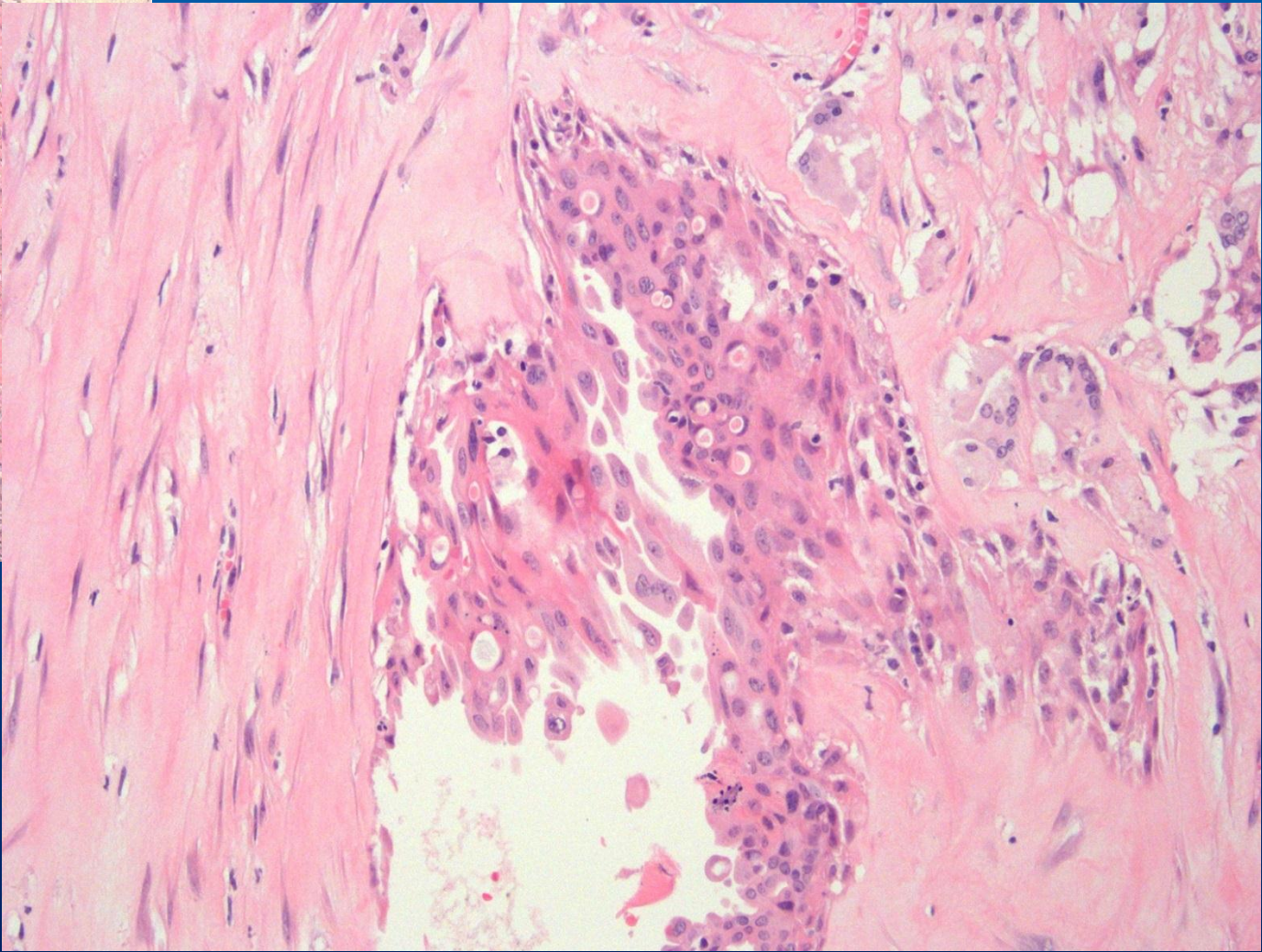
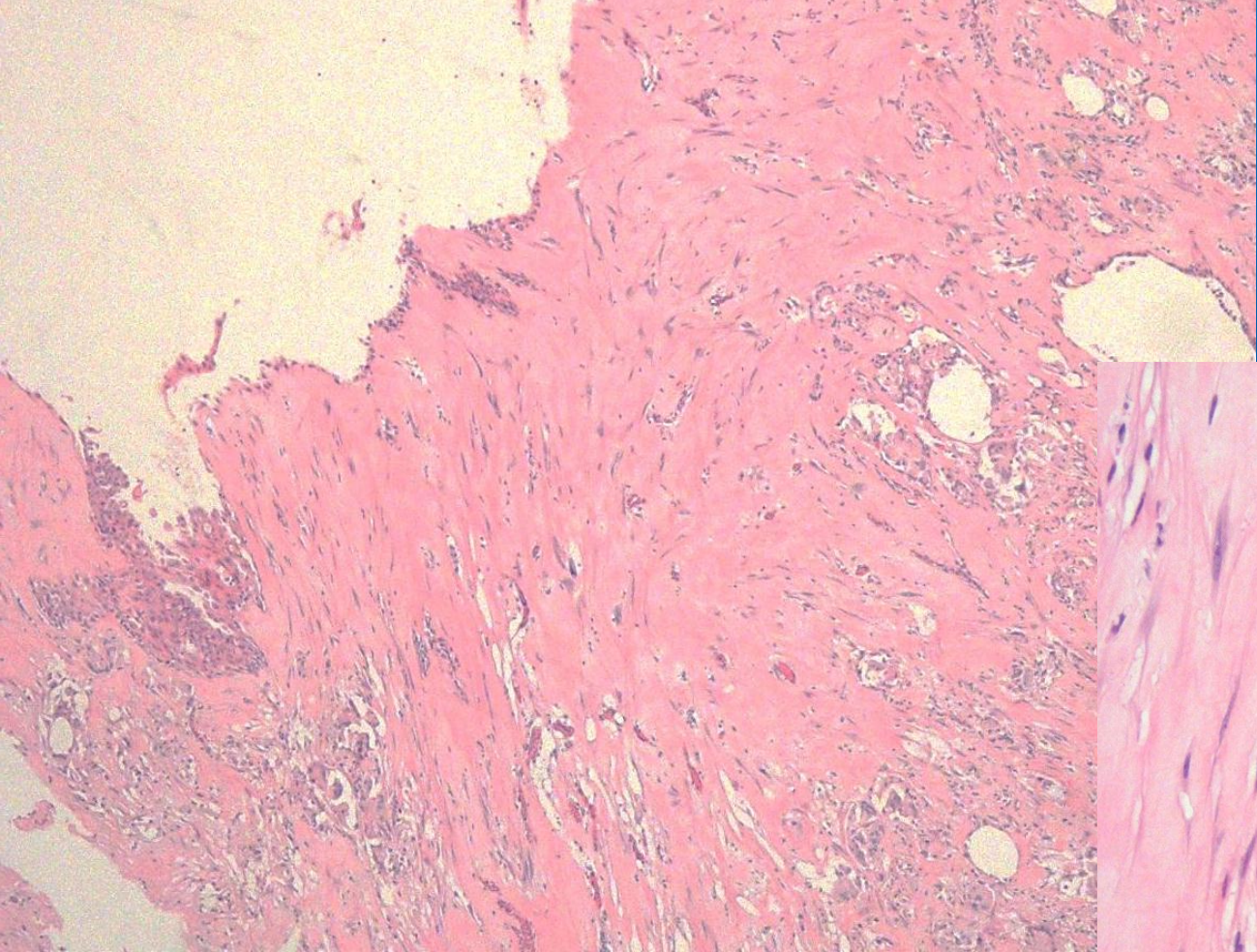
- Immunohistochemical findings
 - Smooth muscle actin and muscle specific actin: positive
 - Cytokeratin AE1/AE3 and high-molecular weight keratins: negative

Reactive spindle cell nodule

- Vague storiform arrangement of spindle cells with admixed small vessels







Pseudoangiomatous stromal hyperplasia (PASH)

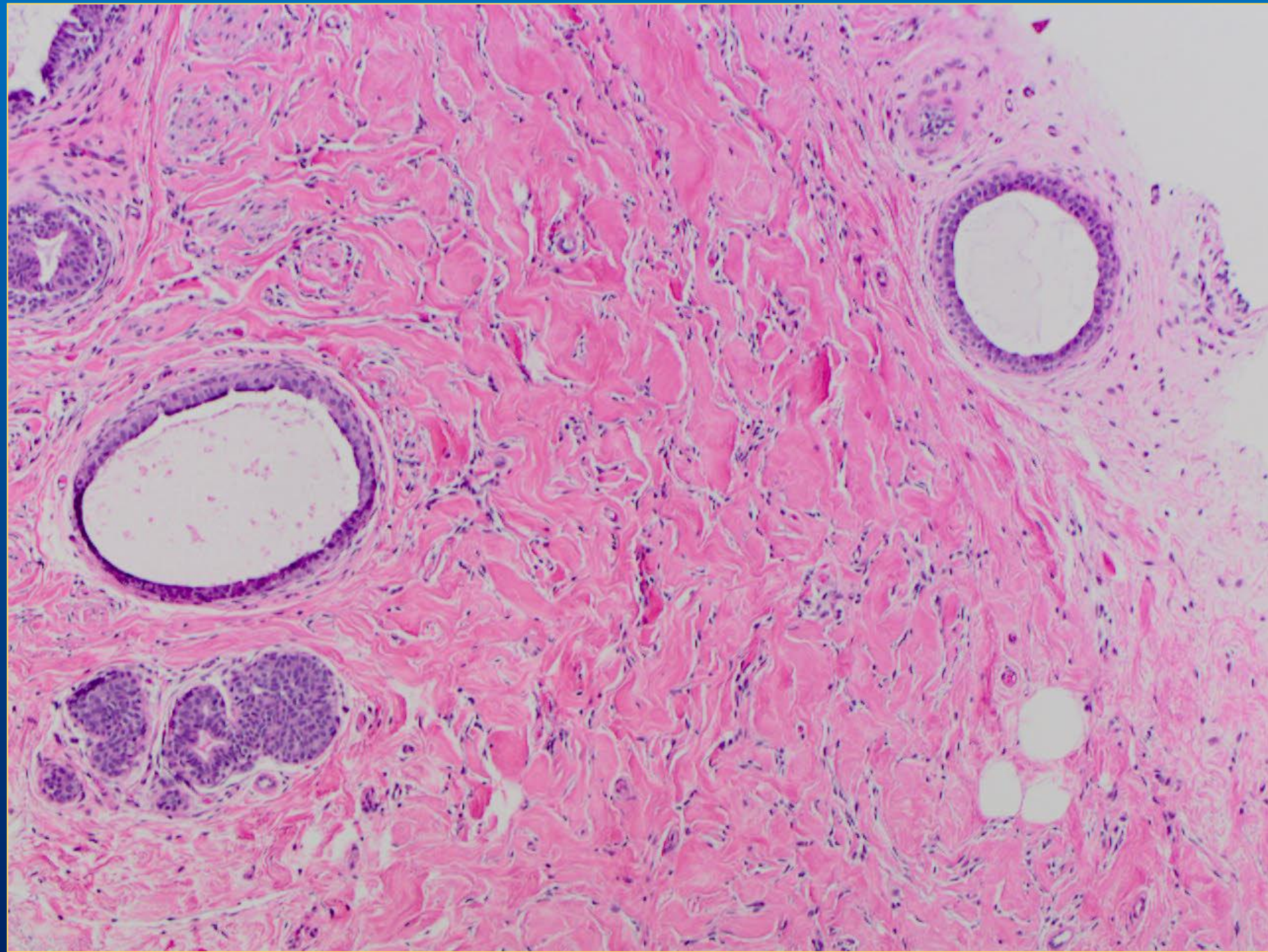
- Clinical features
 - Incidental finding in 23% of breast biopsies
 - Scattered foci in association with other lesions
 - Fibroadenoma, gynecomastia, phyllodes tumor
 - Palpable/radiographic mass (PASH tumor), well circumscribed
 - Firm, non-tender unilateral mass
 - Commonly identified in premenopausal women

PASH

- Microscopic features
 - Complex anastomosing slit-like spaces lined by spindled myofibroblasts
 - Spaces are usually empty, may contain erythrocytes
 - Eosinophilic and hyalinized keloid-like stroma
- Immunophenotype
 - CD34+, PgR+, ER-, CD31-, ERG-, smooth muscle actin+/-, desmin+/-

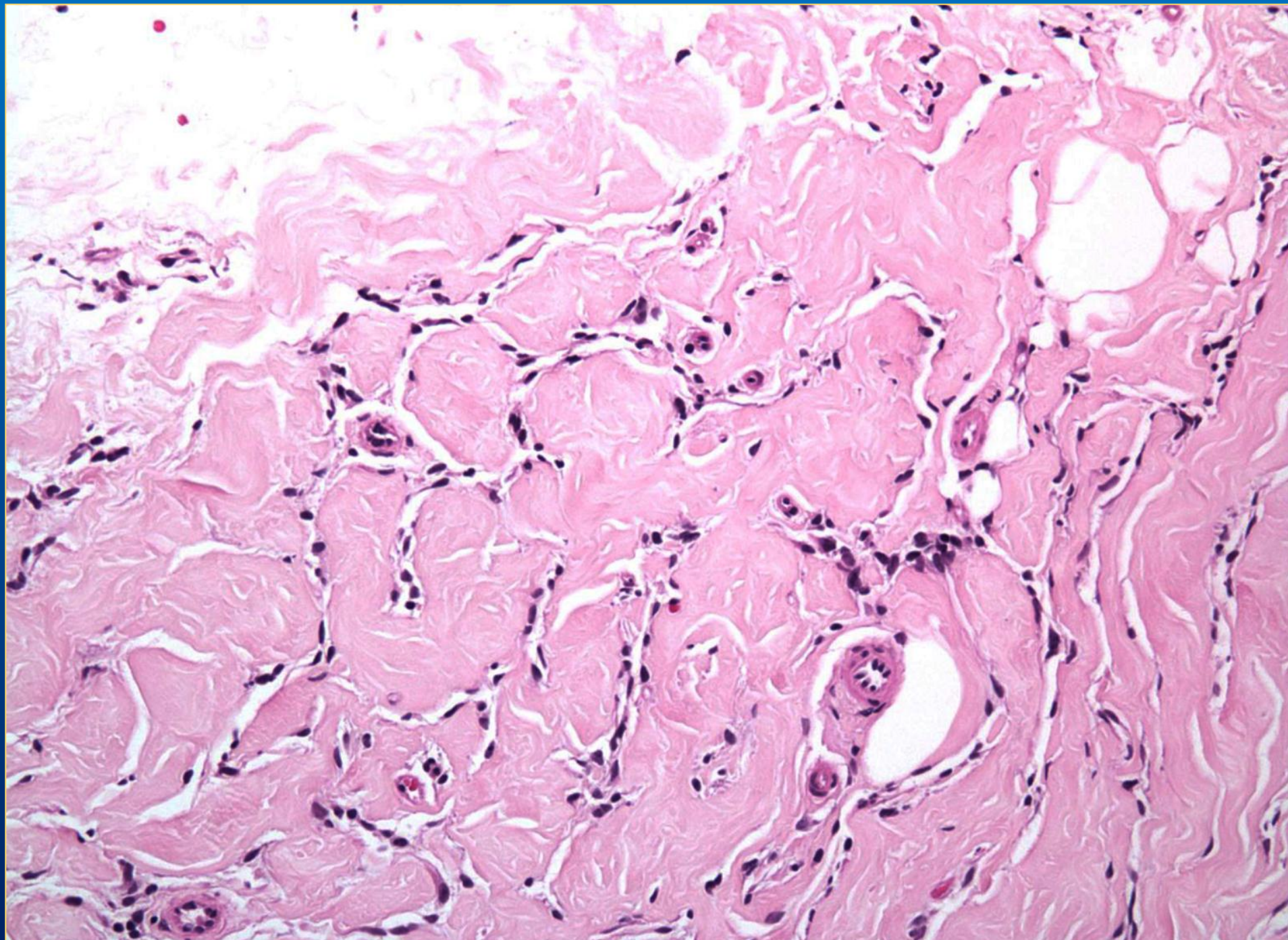
PASH

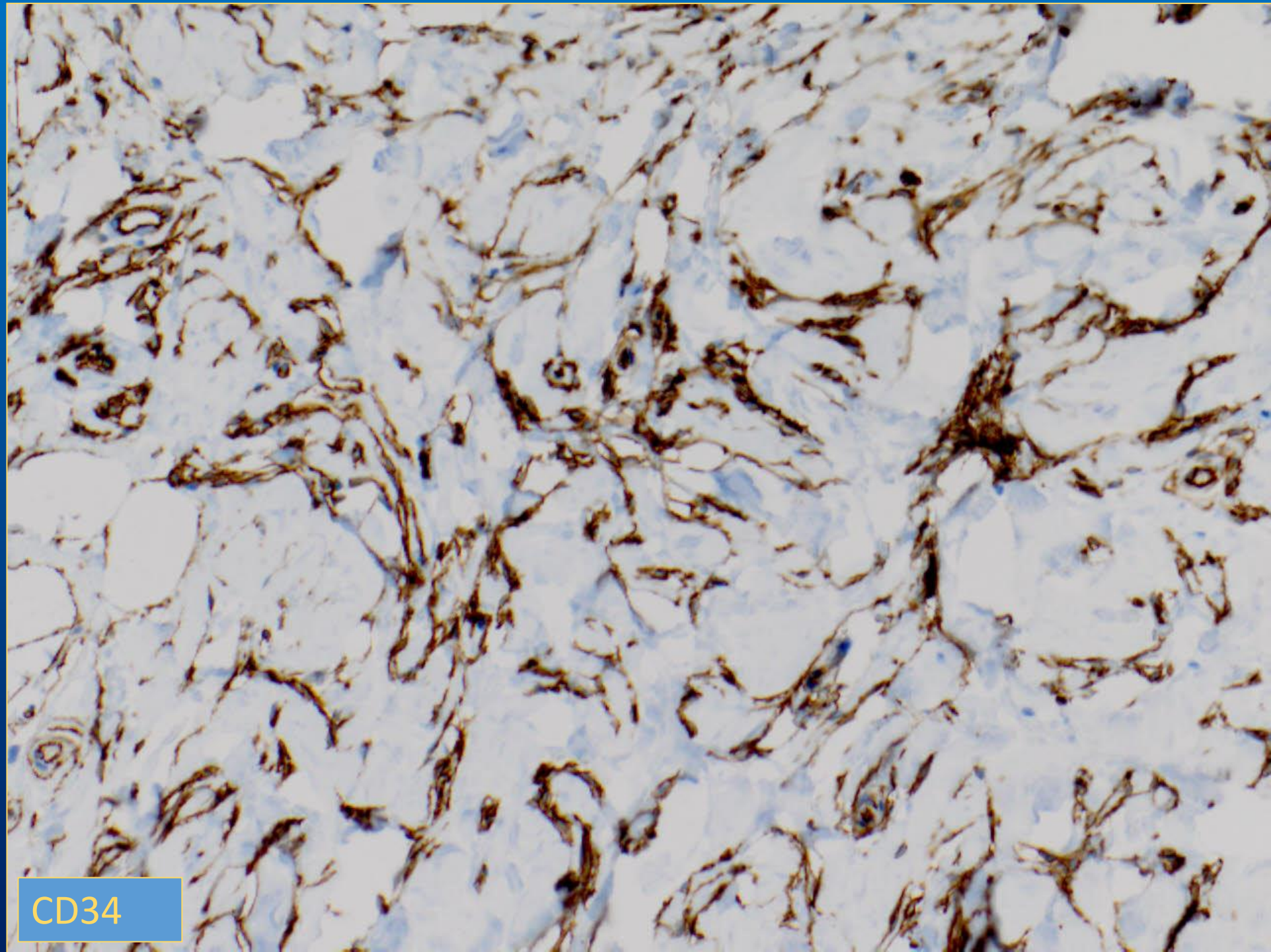
- Anastomosing, slit like spaces in a dense hyalinized stroma
- Involves both the perilobular and intralobular areas



PASH

- Bland spindle cells line the periphery of the slit like spaces
- No atypia or mitotic figures identified





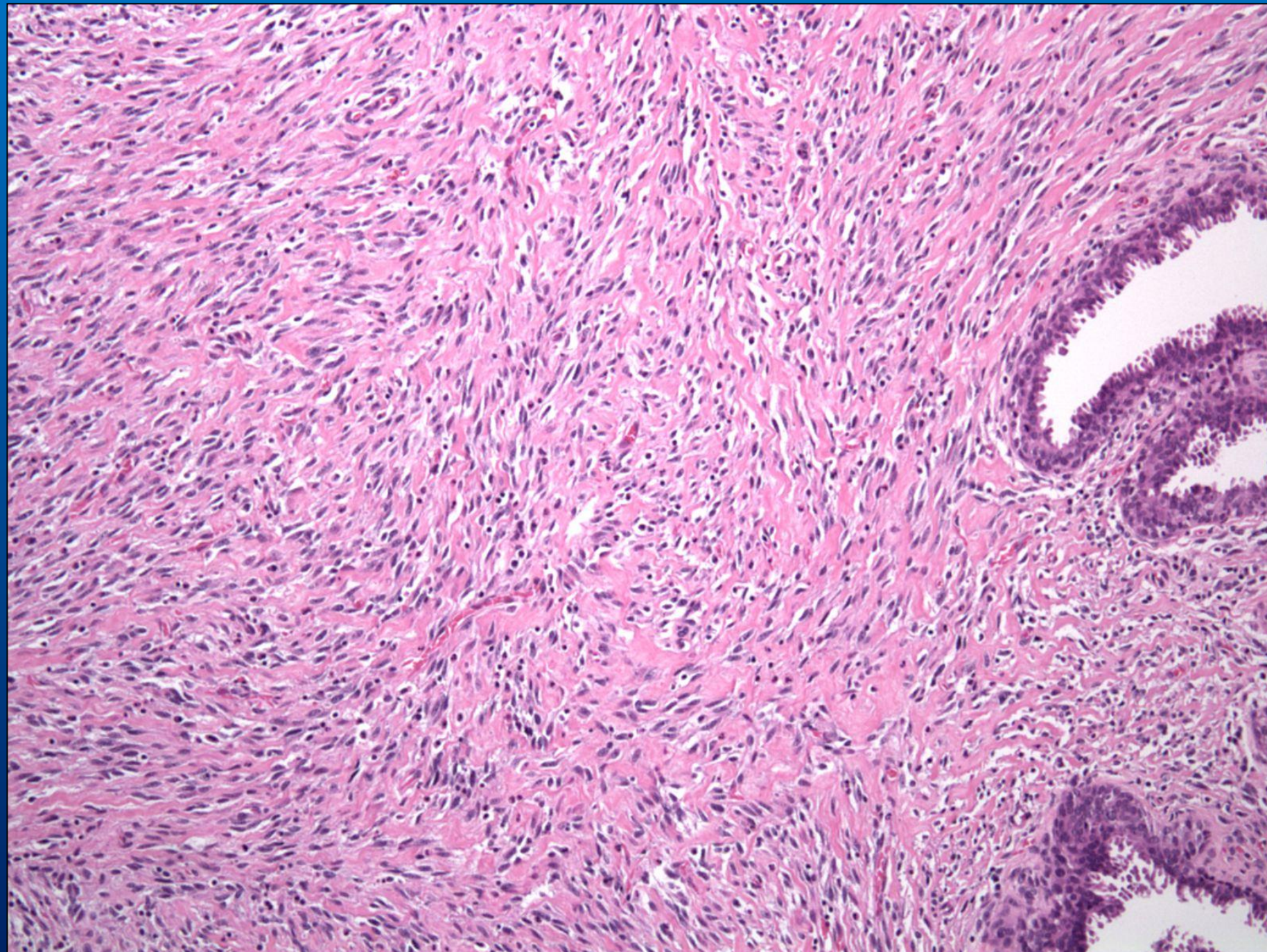
CD34

Fascicular PASH

- Myofibroblasts aggregate into compact sheets with only rare pseudovascular spaces and scant hyalinized stroma
 - Differential diagnosis: myofibroblastoma
 - Both myofibroblastoma and PASH arise from myofibroblasts, some have proposed they are related and represent opposite ends of a spectrum

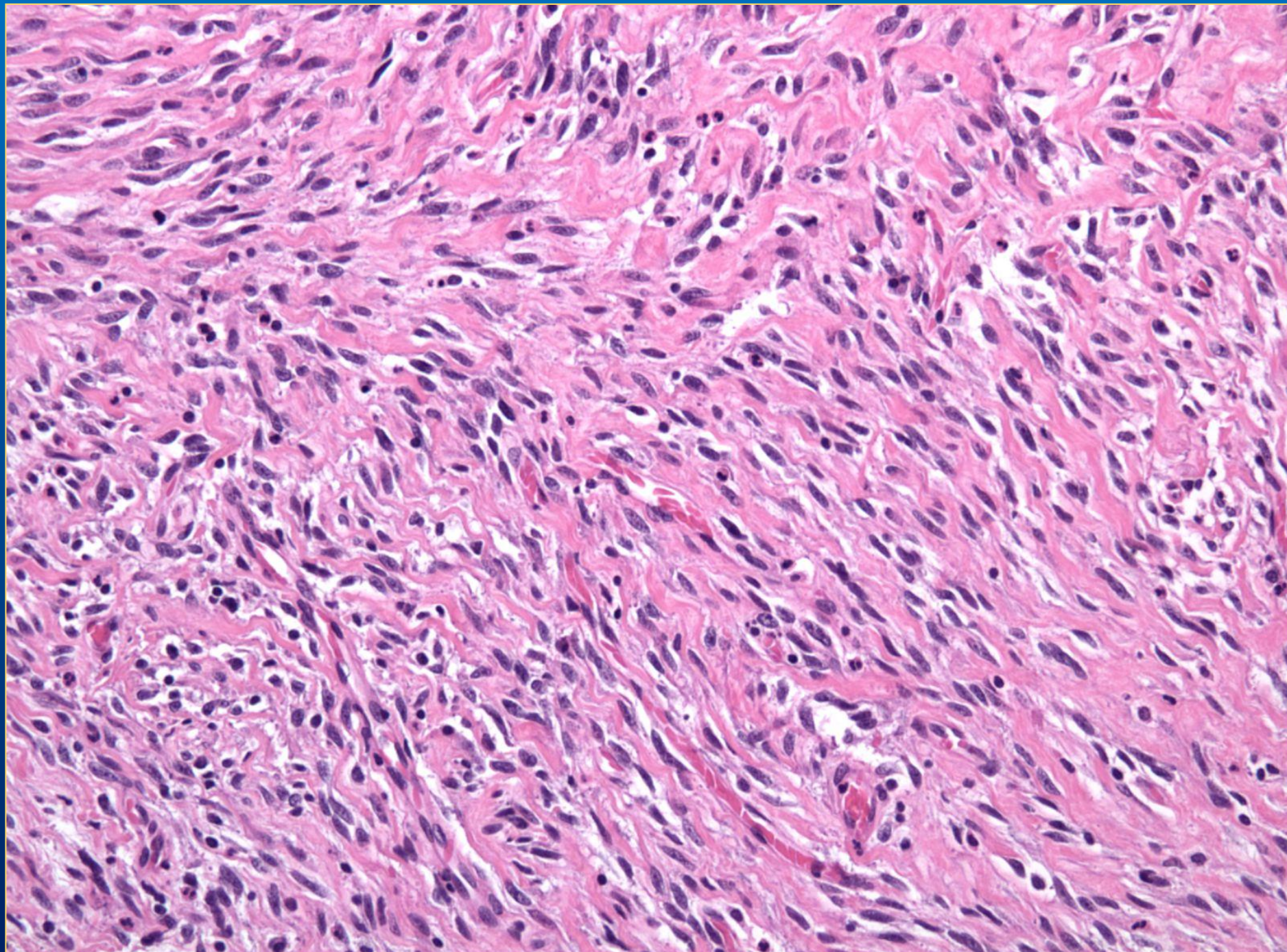
Fascicular PASH

- Fascicles of bland spindle cells expand the stroma with only a suggestion of slit like spaces
- Again with a perilobular and intralobular distribution



Fascicular PASH

- Uniform population of spindle cells, lacking significant atypia or mitotic activity



PASH tumors: Management

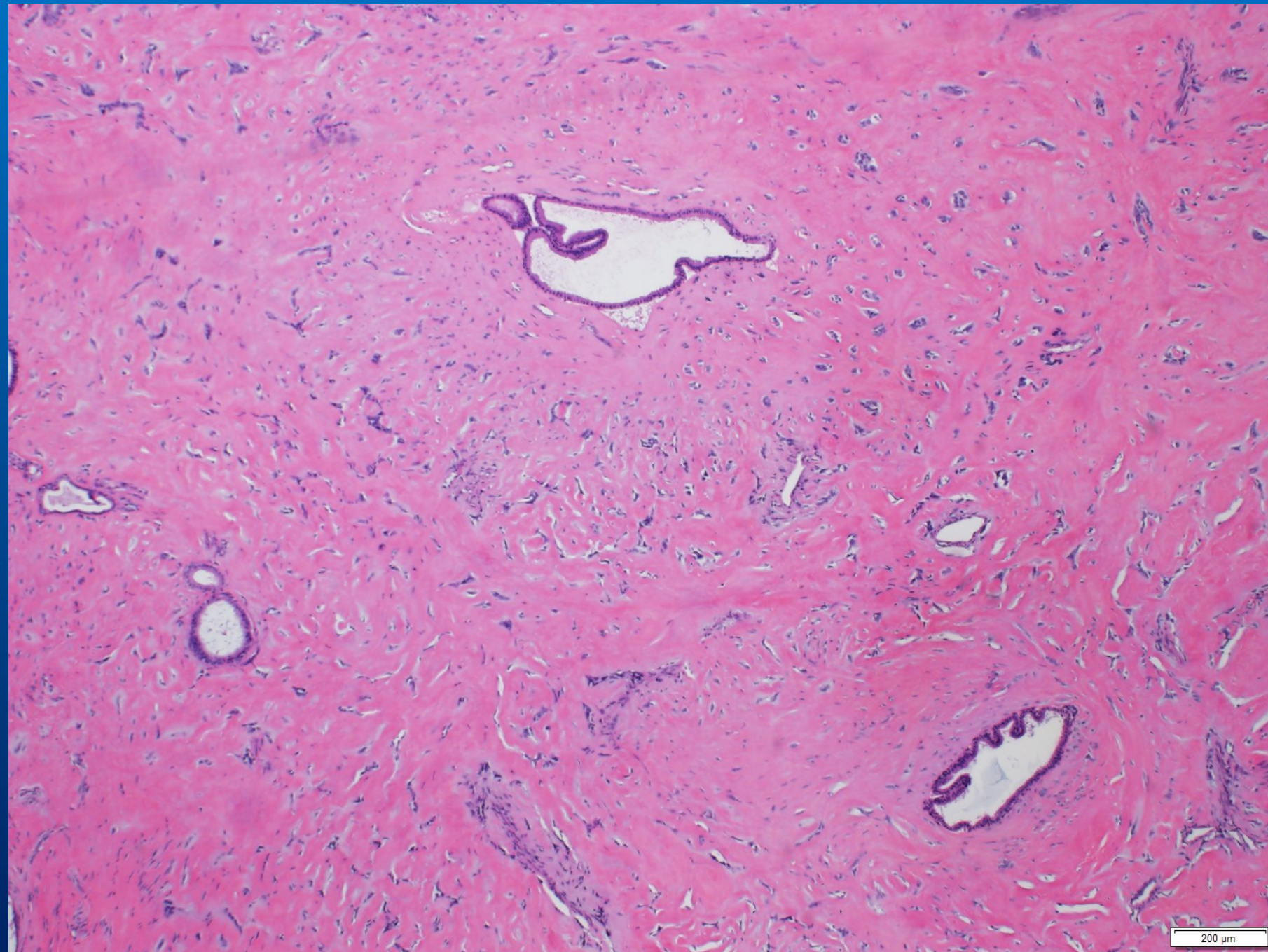
- Most PASH tumors mimic fibroadenomas on imaging
 - Mammography: well defined mass
 - US: well circumscribed hypoechoic lesion
- For PASH tumors, pervasive thought has been excise
- Ferreira et al suggests that close clinical surveillance may be acceptable
 - Cohort who remained clinically and radiologically stable without excision
 - Rebiopsy or excise if subsequent imaging identified changes

Atypical PASH

- Extremely rare, described in two teen age females with tumor forming PASH
- Conventional areas of PASH admixed with cytologically atypical myofibroblasts with mitotic activity and atypical multinucleated stromal cells
- Thought to represent myofibroblastic sarcoma arising in PASH

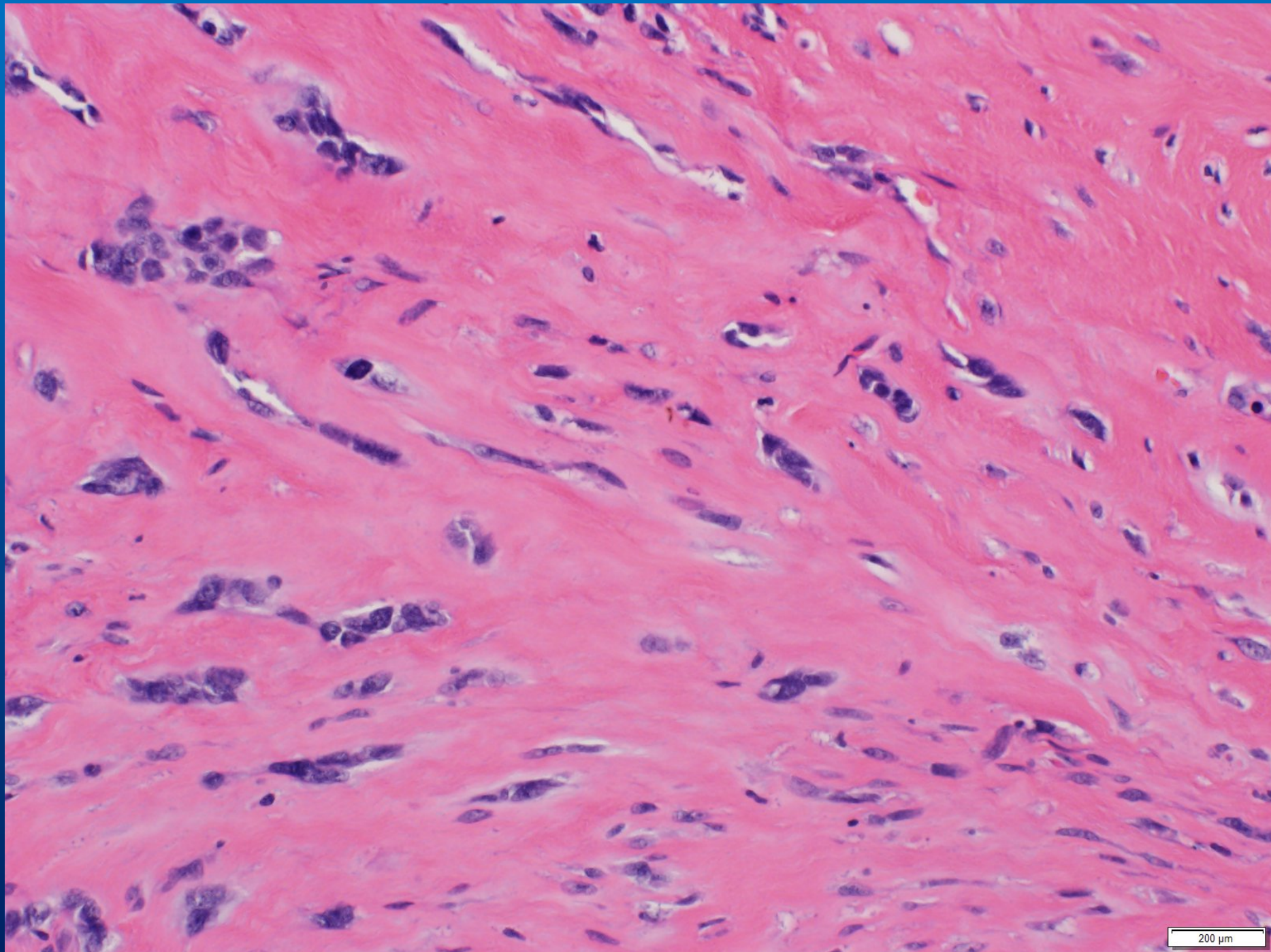
Atypical PASH

- Conventional architecture of PASH with slit like spaces with hyperchromatic appearing nuclei



Atypical PASH

- Nuclei which are enlarged and hyperchromatic, a single mitotic figure and occasional giant cells

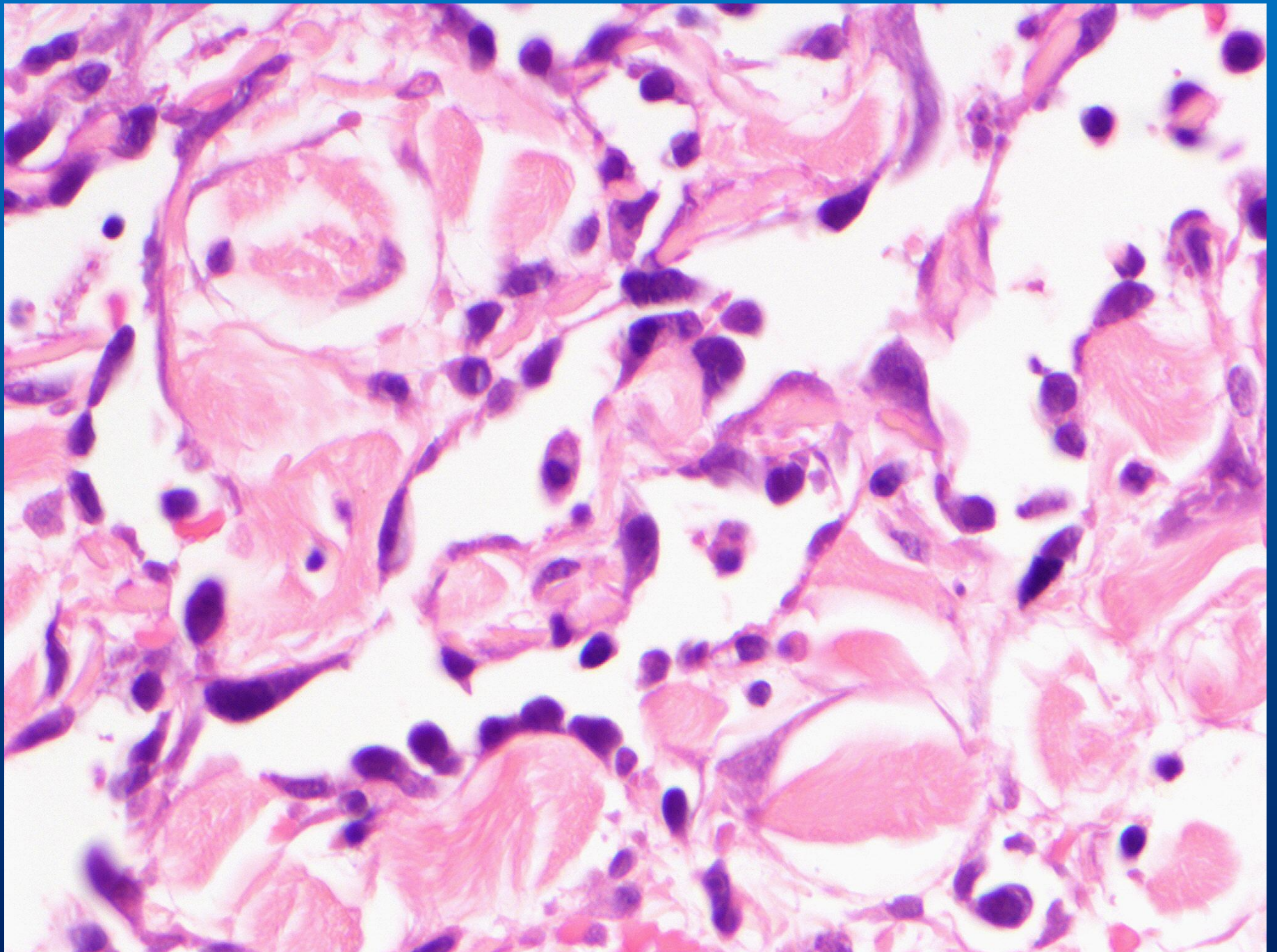


PASH

- Differential diagnosis for PASH: Angiosarcoma (histologically low grade)
 - PASH lacks multilayering, mitotic activity, or atypia
 - Slit-like spaces surrounded by dense collagen; no dissection through normal tissue
 - CD31 negative, ERG negative
 - Pitfall: CD34+
- Differential diagnosis for fascicular PASH: Myofibroblastoma
 - Fascicular PASH lacks the ropey collagen of myofibroblastoma

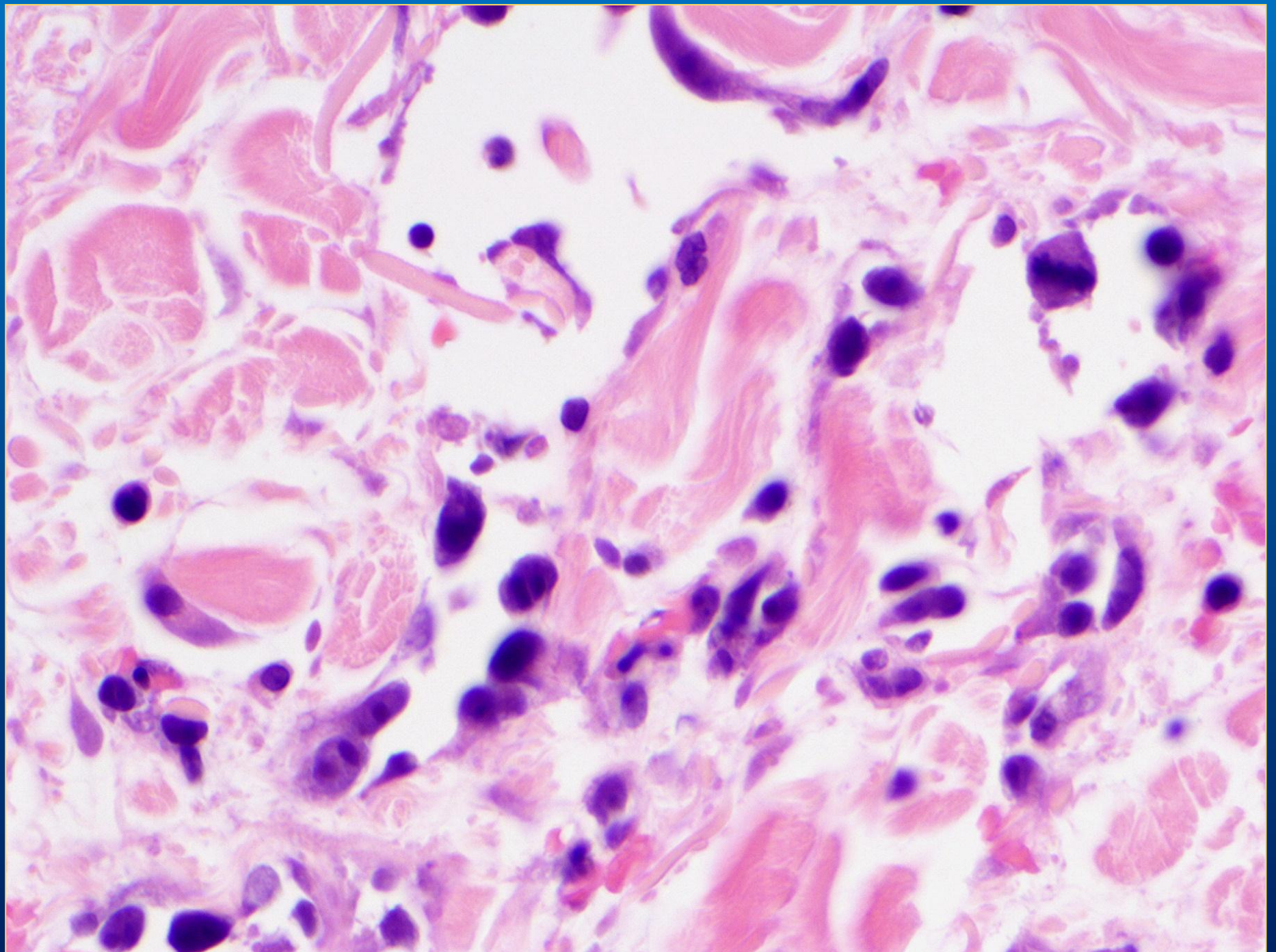
Angiosarcoma

- Vasoformative proliferation dissecting through the stroma
- Endothelial cell atypia with hyperchromatic nuclei and high nuclear to cytoplasmic ratios



Angiosarcoma

- Endothelial cell atypia and a rare mitotic figure



Myofibroblastoma

- Clinical features
 - Traditionally more common in men (~70%)
 - Increasingly seen in women
 - Seen after the 5th decade
 - Solitary, painless, unilateral nodule
 - Typically slow growing over months to years
 - Ultrasound shows a circumscribed and homogeneous mass
 - Suggestive of fibroadenoma

Myofibroblastoma

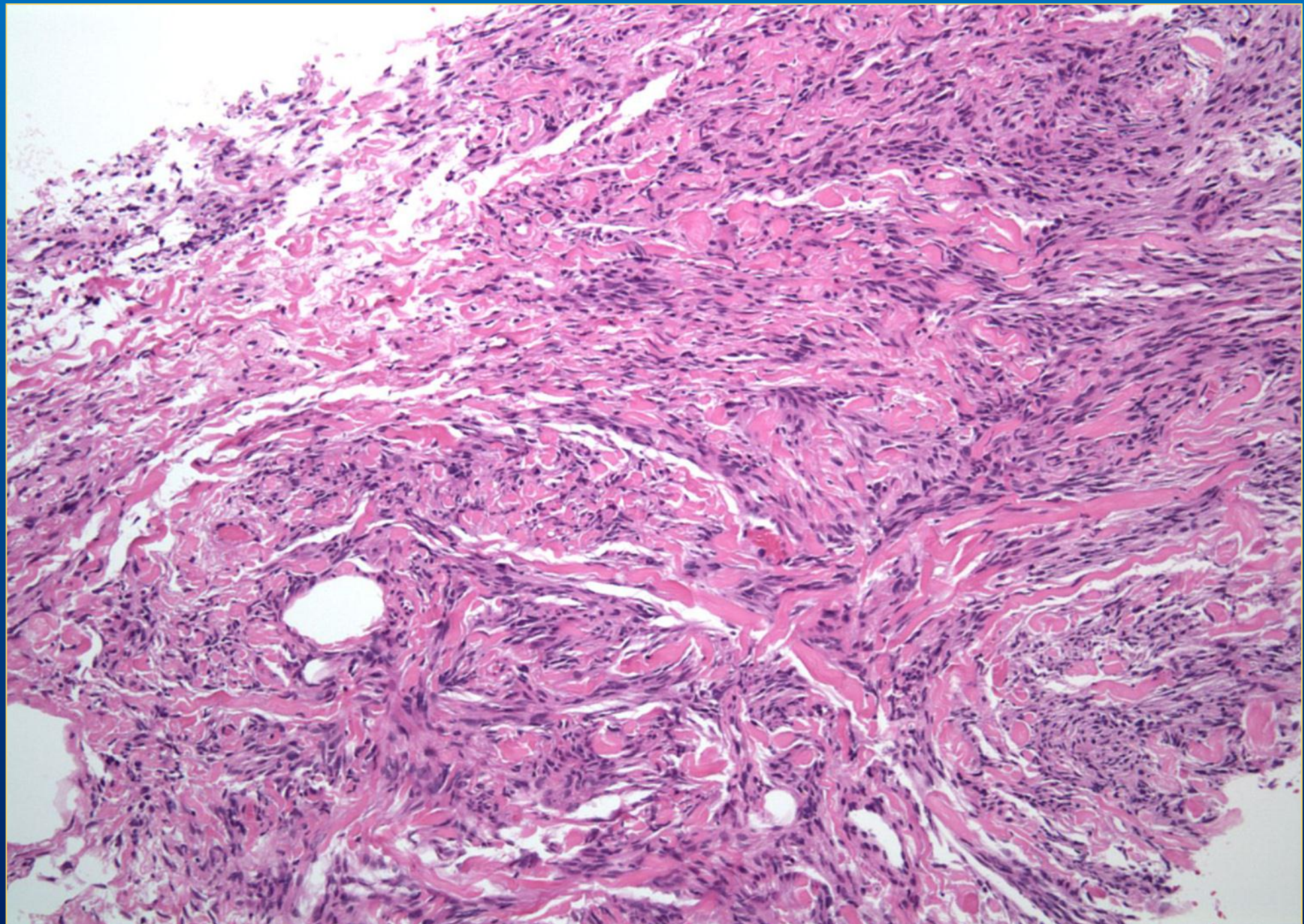
- Wide variety of morphologies described
 - Classic, cellular, infiltrating, epithelioid, deciduoid-like, lipomatous, collagenized/fibrous, myxoid and mixed (two or more variants within the same lesion)
- Microscopic features
 - Circumscribed
 - Myofibroblasts that may be either spindled or epithelioid
 - Short, intersecting fascicles with admixed thick, eosinophilic collagen
 - Rare mitotic figures (0-2 per 10 high-power fields)
 - No atypical mitotic figures
 - Typically pushes normal breast parenchyma aside
 - Common features despite varied morphologies include
 - Thick hyalinized collagen bundles
 - Low mitotic count, absence of atypical mitotic figures
 - No necrosis

Myofibroblastoma

- Immunohistochemistry
 - CD34+, desmin+
 - Variable expression of BCL2, CD99 and smooth muscle actin
 - Roughly 70-90% express ER and/or PgR
 - Negative for cytokeratins, EMA and S100

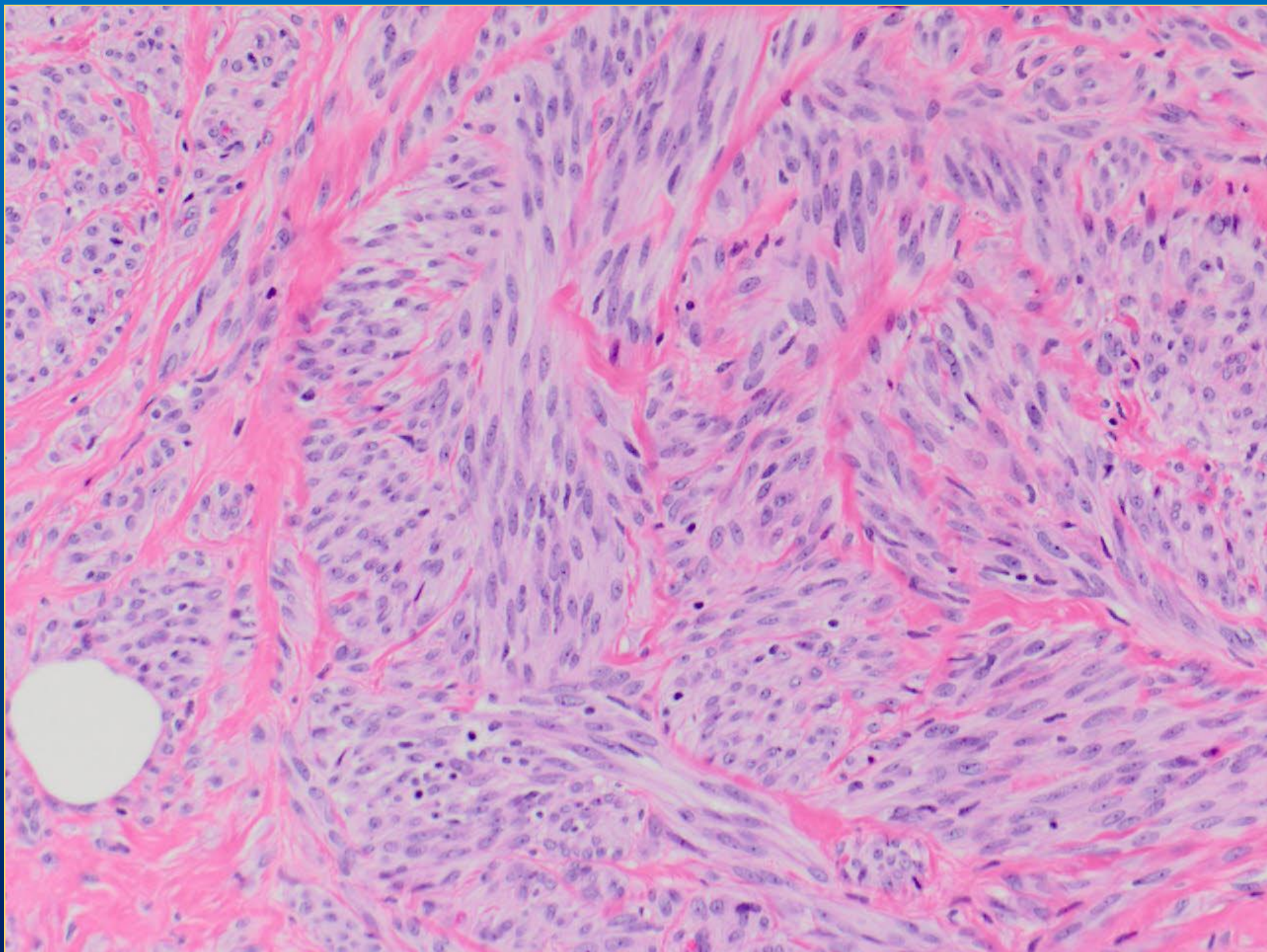
Myofibroblastoma: Classic

- Fascicles of bland spindle cells arranged in intersecting fascicles with admixed thick keloidal-type collagen bundles



Myofibroblastoma: Classic

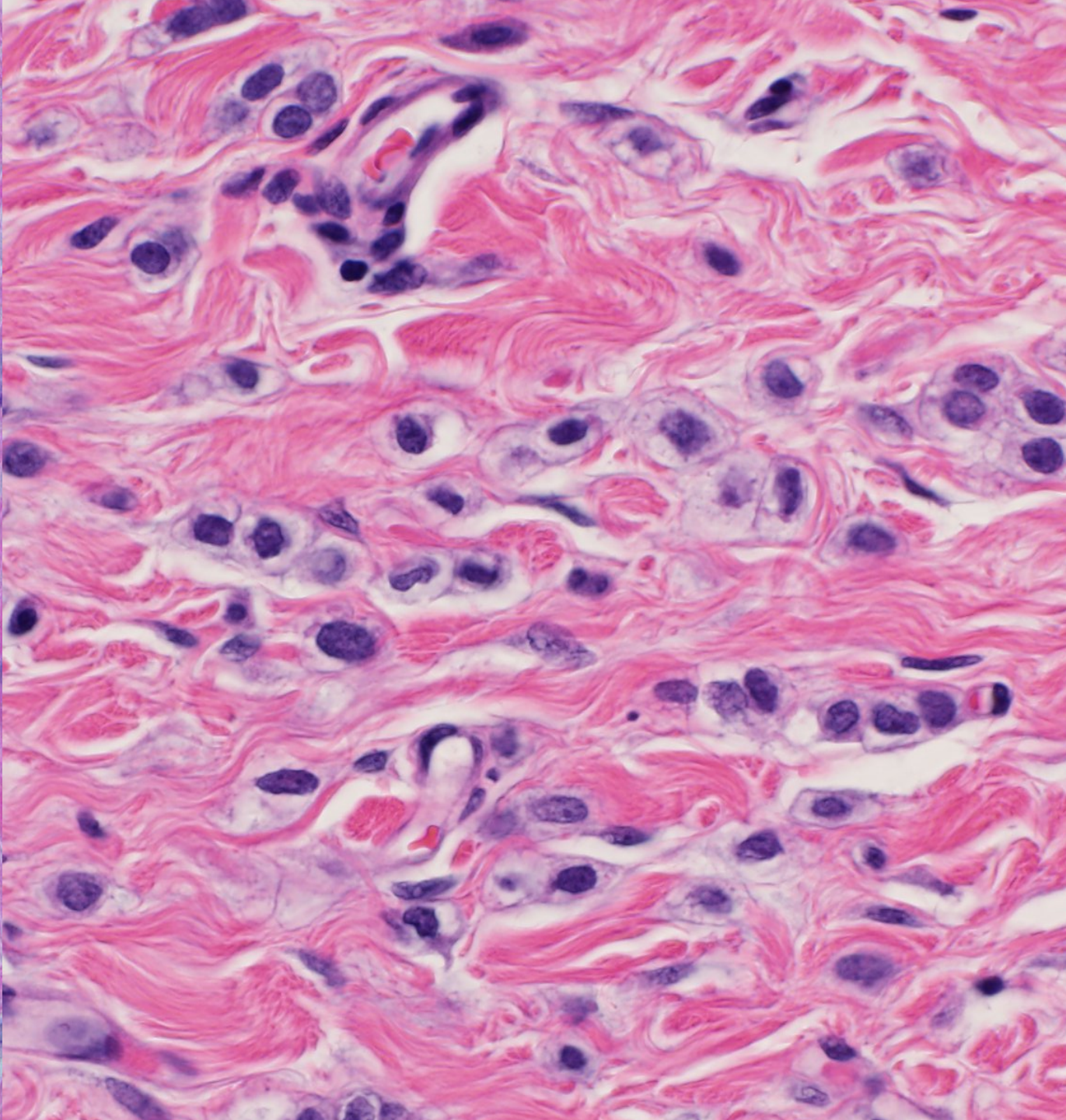
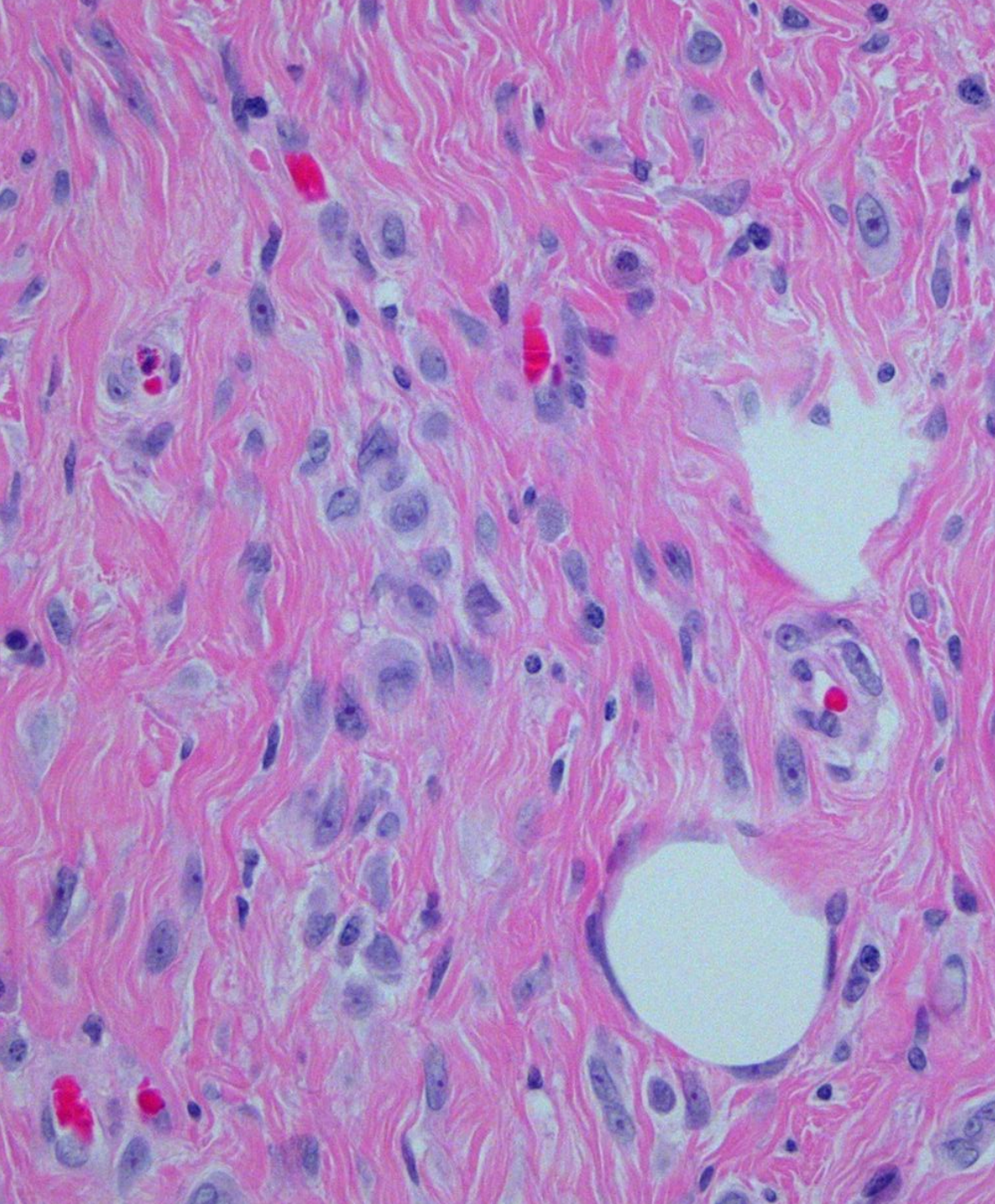
- Lesional cells are bland with elongate nuclei, small nucleoli and eosinophilic cytoplasm
- Rare nuclear grooves or intracytoplasmic inclusions may be seen
- Admixed mast cells are typically identified



Epithelioid Myofibroblastoma

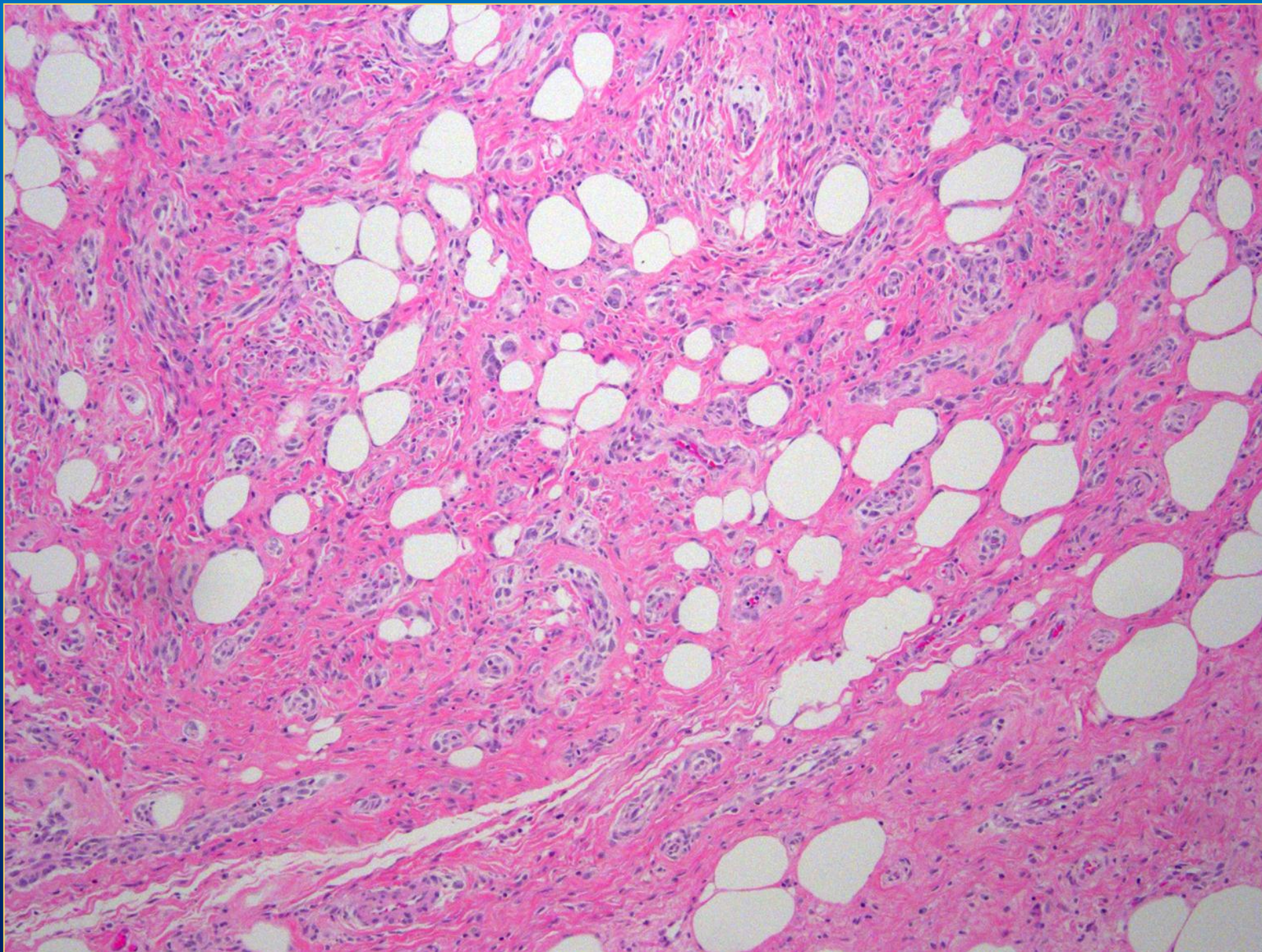
- Microscopic features
 - Cord-like arrangement
 - Tumor cells with round nuclei
 - Hyalinized stroma
 - CD34+, ER+, PgR+
 - Negative for cytokeratins
- Differential diagnosis: Invasive lobular carcinoma

Which of the following panels is the epithelioid myofibroblastoma and which is the invasive lobular carcinoma?



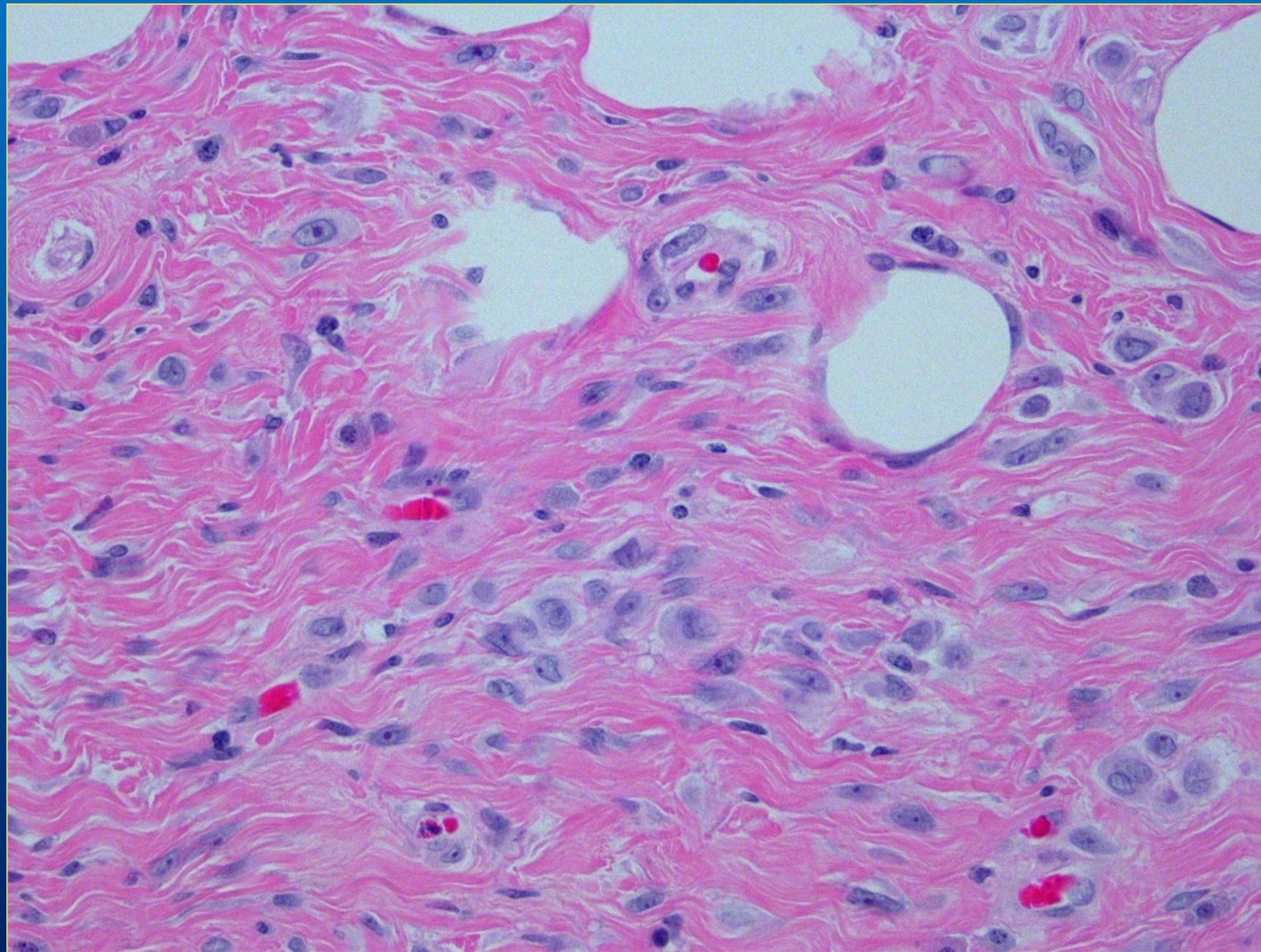
Myofibroblastoma: Epithelioid Type

- Small clusters and nests of epithelioid cells with an infiltrative pattern present admixed with dense collagen

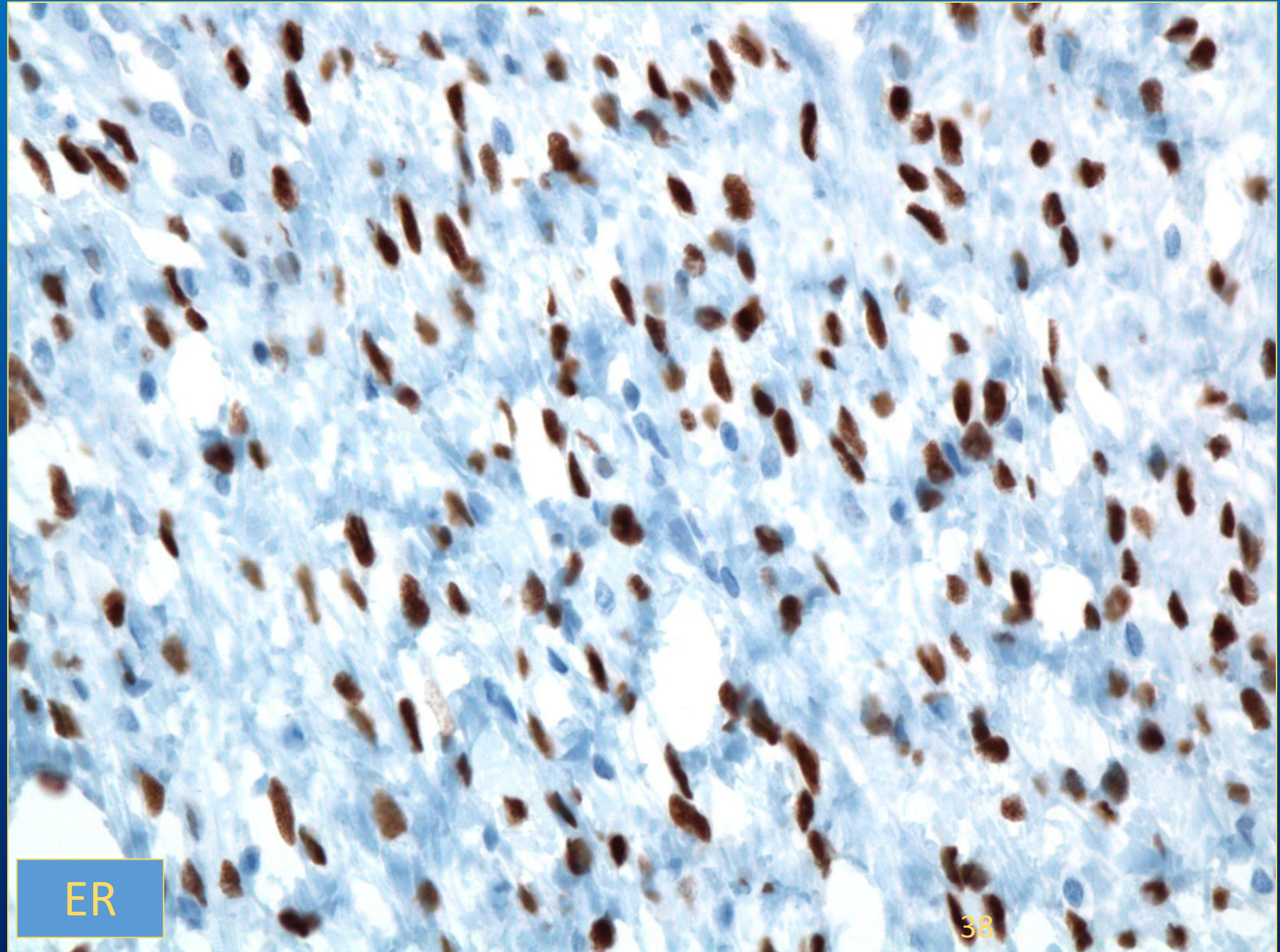


Myofibroblastoma: Epithelioid Type

- Single epithelioid appearing cells within the stroma
- Lesional cells are monomorphic with a somewhat eccentrically placed nucleus and pinpoint nucleoli

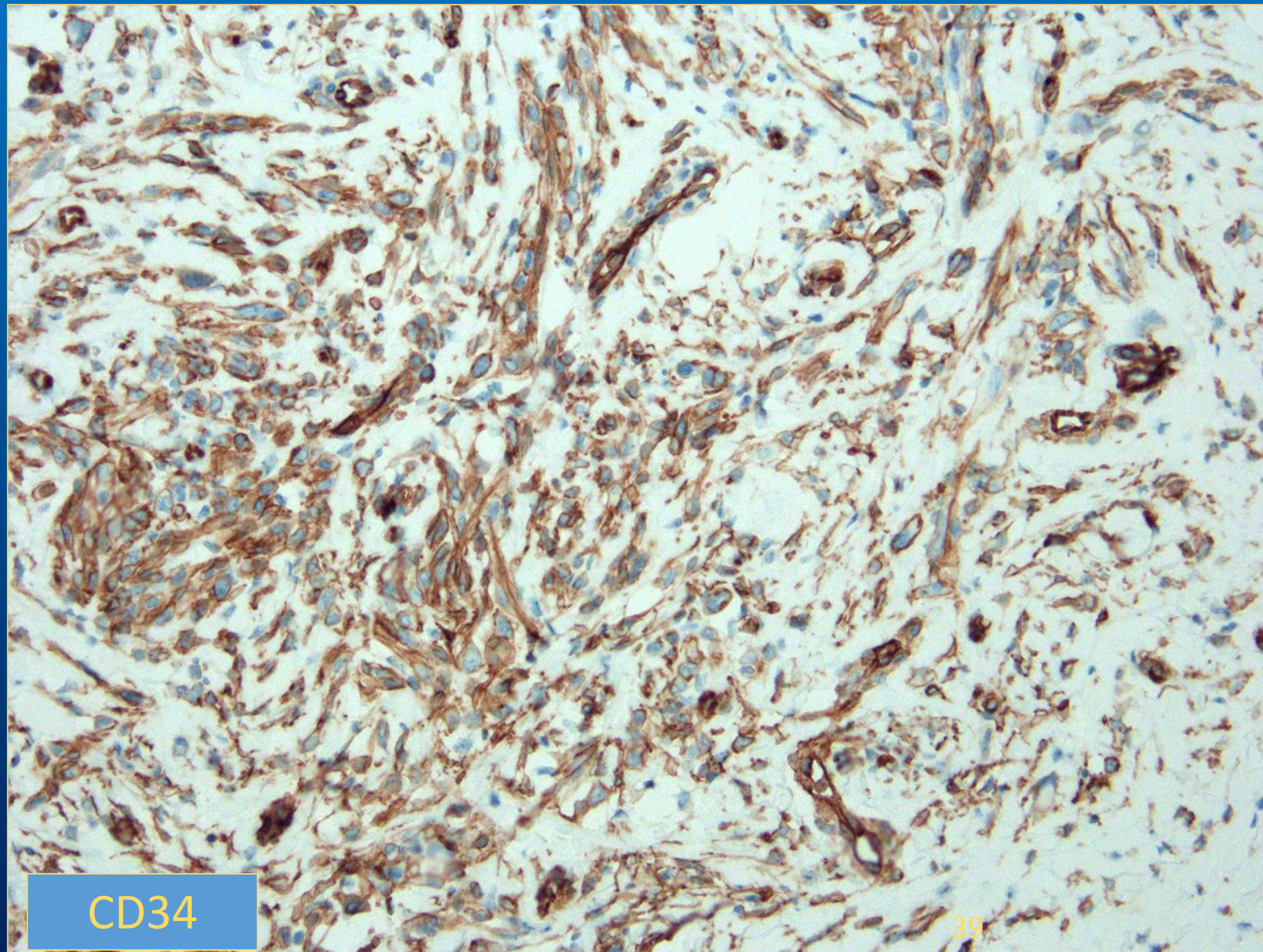


Myofibroblastoma: Epithelioid
Type



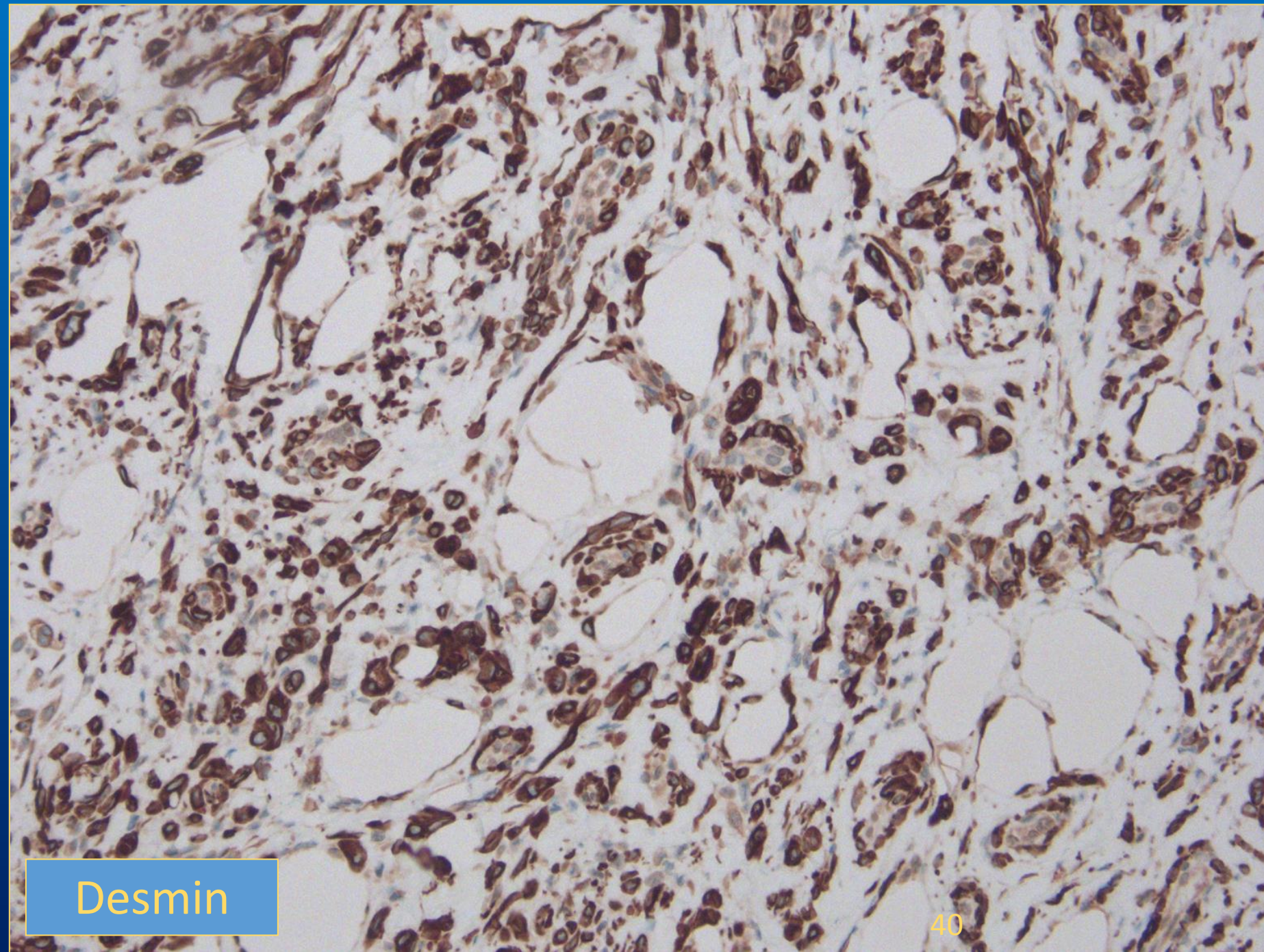
ER

Myofibroblastoma: Epithelioid
Type



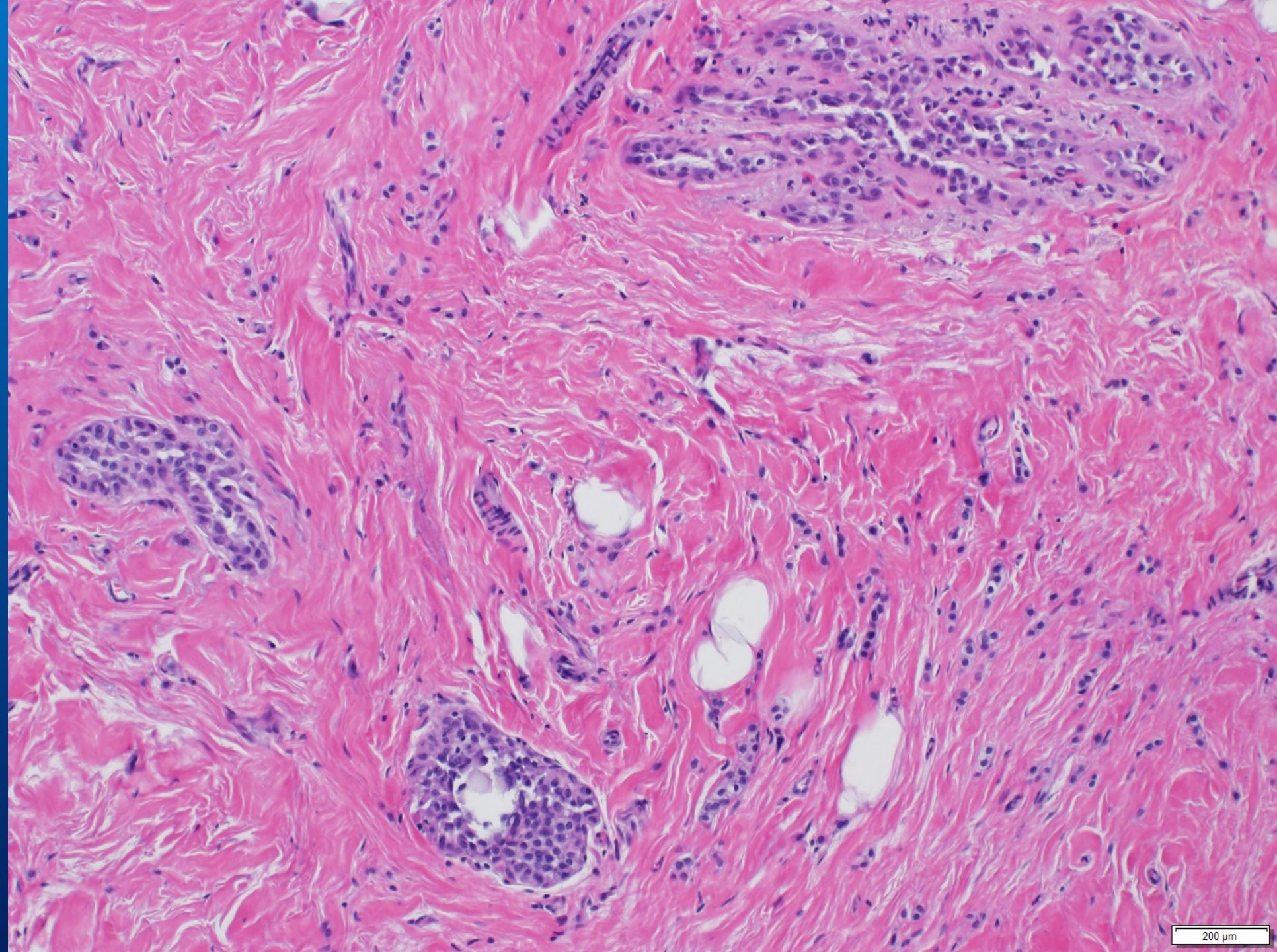
CD34

Myofibroblastoma: Epithelioid
Type



Desmin

- The picture becomes more clear when there is additional tissue to evaluate
- Other helpful features:
 - Exclusion of breast epithelium from the lesion
 - Thick ropey collagen
 - Myofibroblastoma forms a well delineated nodule
 - Invasive lobular is frequently an architectural distortion
- When in doubt, use of a cytokeratin stain can be very helpful especially on a core needle biopsy



Myofibroblastoma

- Behavior/treatment
 - Benign, treated by local excision
 - Studies have shown no evidence of recurrence or metastasis after years of follow up
- Differential diagnosis
 - Fibromatosis
 - Nodular fasciitis
 - Fascicular PASH
 - Invasive lobular carcinoma (epithelioid variant)
 - Spindle cell carcinoma (Metaplastic carcinoma)

Fibromatosis

- Infiltrative proliferation of fibroblasts and myofibroblasts that can be locally aggressive
- Primary mammary fibromatosis or spread from the chest wall (musculo-aponeurotic fibromatosis)
- Clinical features
 - Most frequently seen in women between 20 - 40 years
 - Rare reports in men
 - Typically present with a painless palpable mass this is clinically suspicious for carcinoma
 - Mammography usually shows a spiculated and stellate mass with infiltrative borders
 - Most sporadic, but may be seen in familial adenomatous polyposis
 - Anecdotal reports arising after previous breast surgery

Fibromatosis

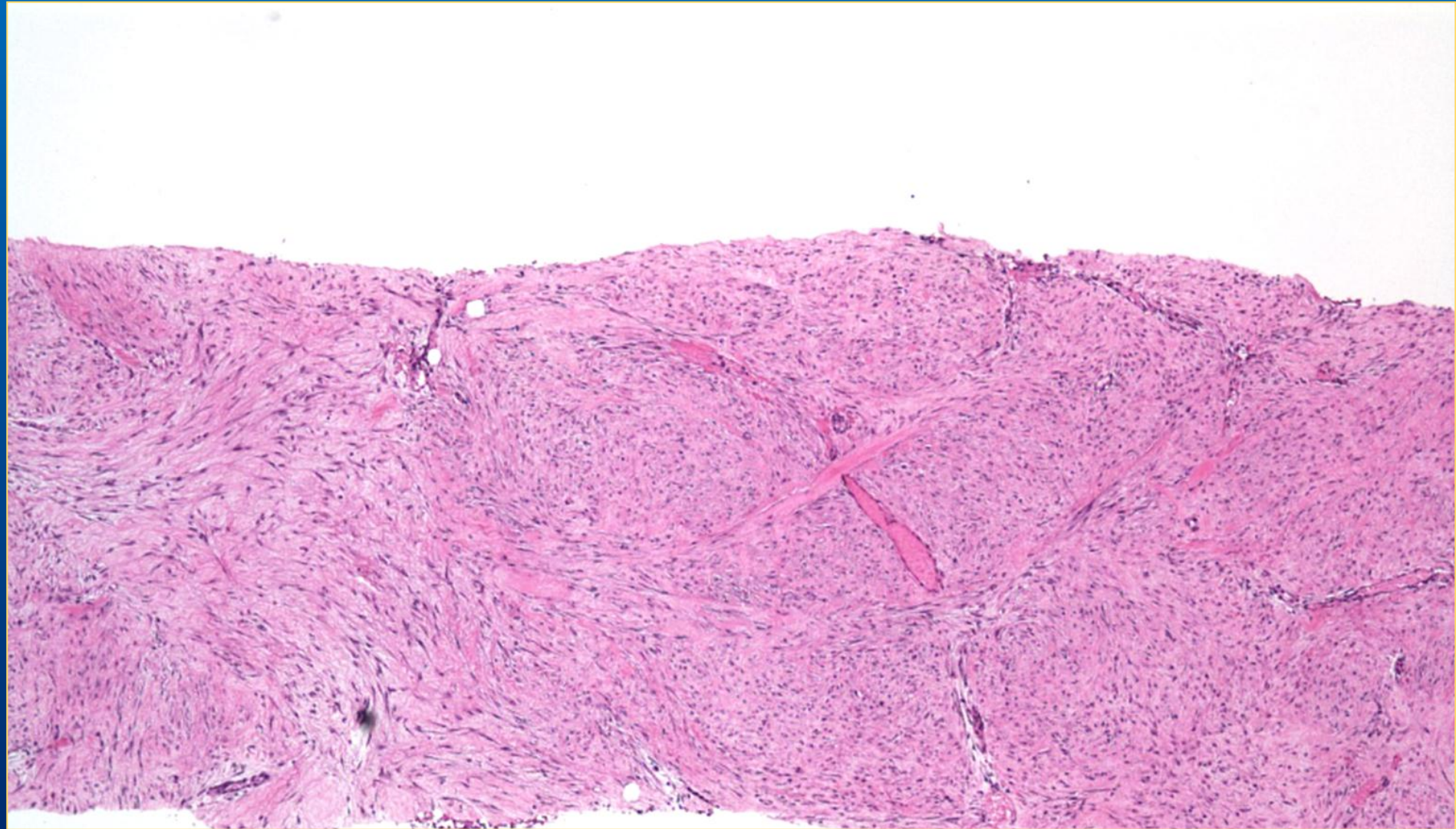
- Microscopic features
 - Entrapment of fat and epithelium at the periphery while the center of the lesion is typically devoid of epithelium
 - Bland spindle cells arranged in long sweeping fascicles that infiltrate into breast parenchyma
 - May have prominent ropey collagen
 - Low to moderate cellularity that increases at the periphery
 - Uniform spindled cells with elongate nuclei, tapered ends and open chromatin
 - Absent or rare mitotic figures (0-1/10 HPF)

Fibromatosis

- Immunohistochemical findings
 - Lesional cells are usually positive for smooth muscle actin and muscle specific actin
 - Desmin may be focally positive
 - Nuclear β -catenin has been described in roughly 75% of cases
 - Mutation of *CTNNB1*
 - Negative for CD34, cytokeratins, ER and PgR

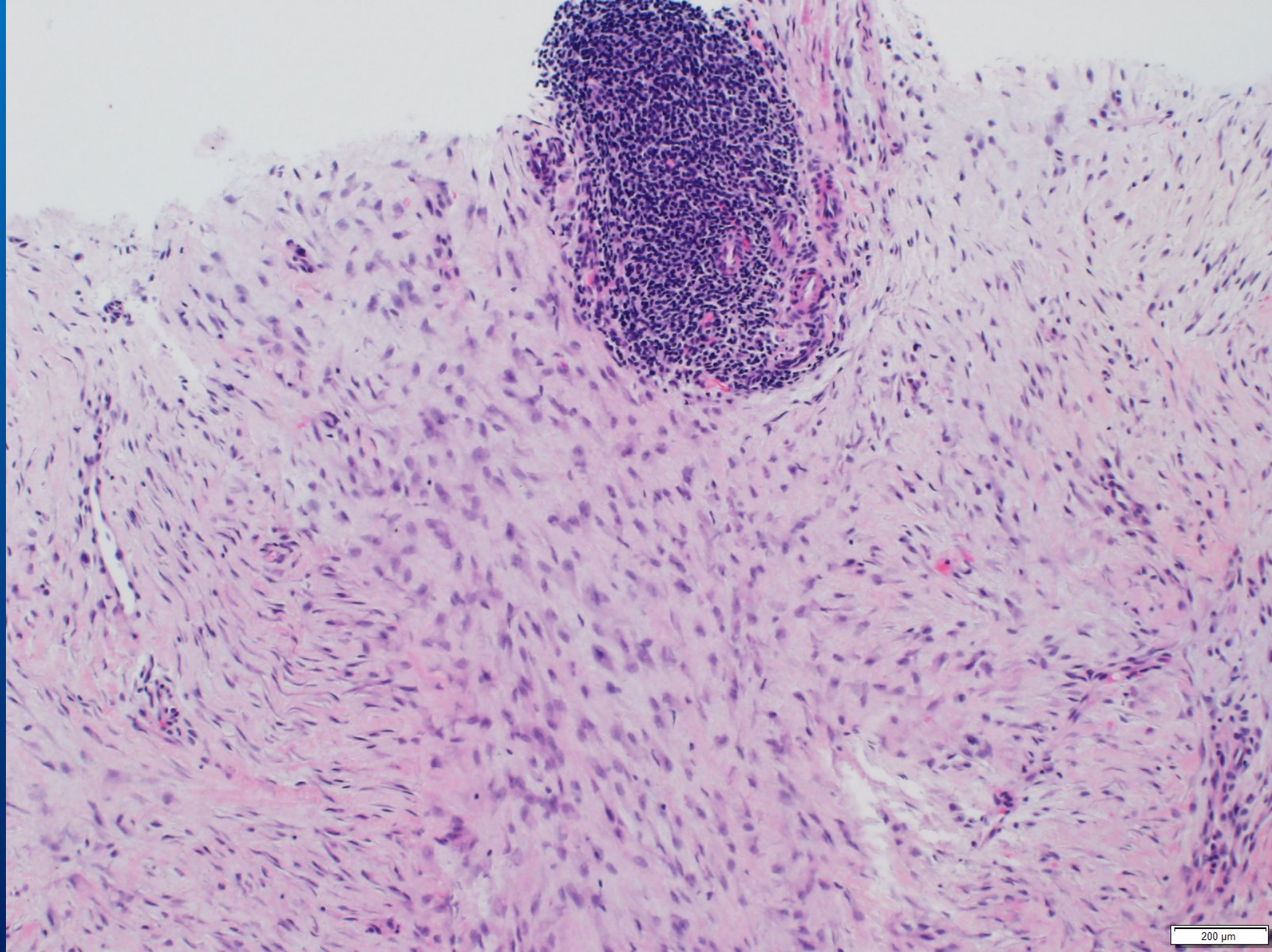
Fibromatosis

- Relatively hypocellular spindle cell lesion with a fascicular architecture
- May have admixed dense collagen



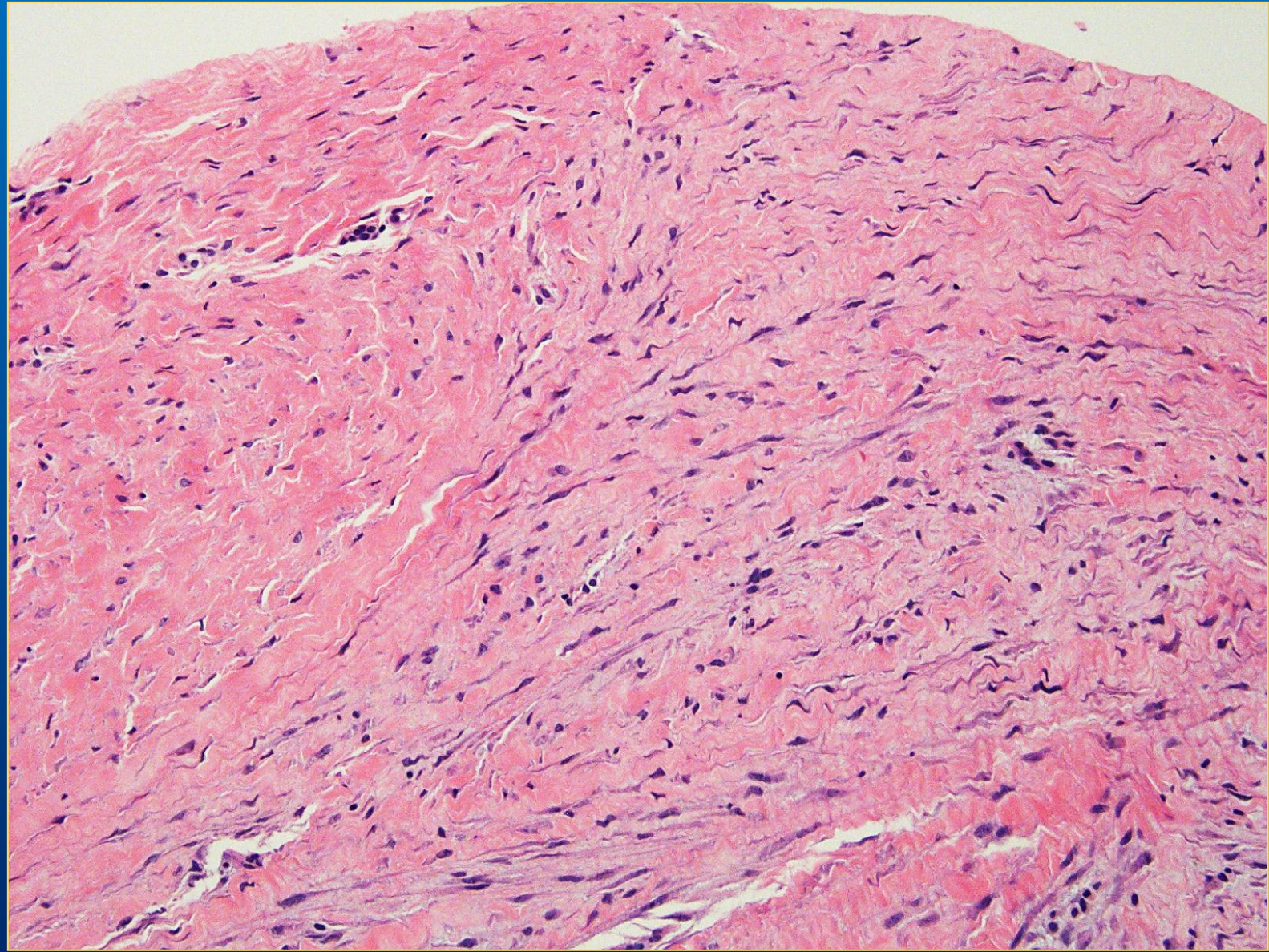
Fibromatosis

- Roughly 50% will have lymphoid aggregates at the periphery



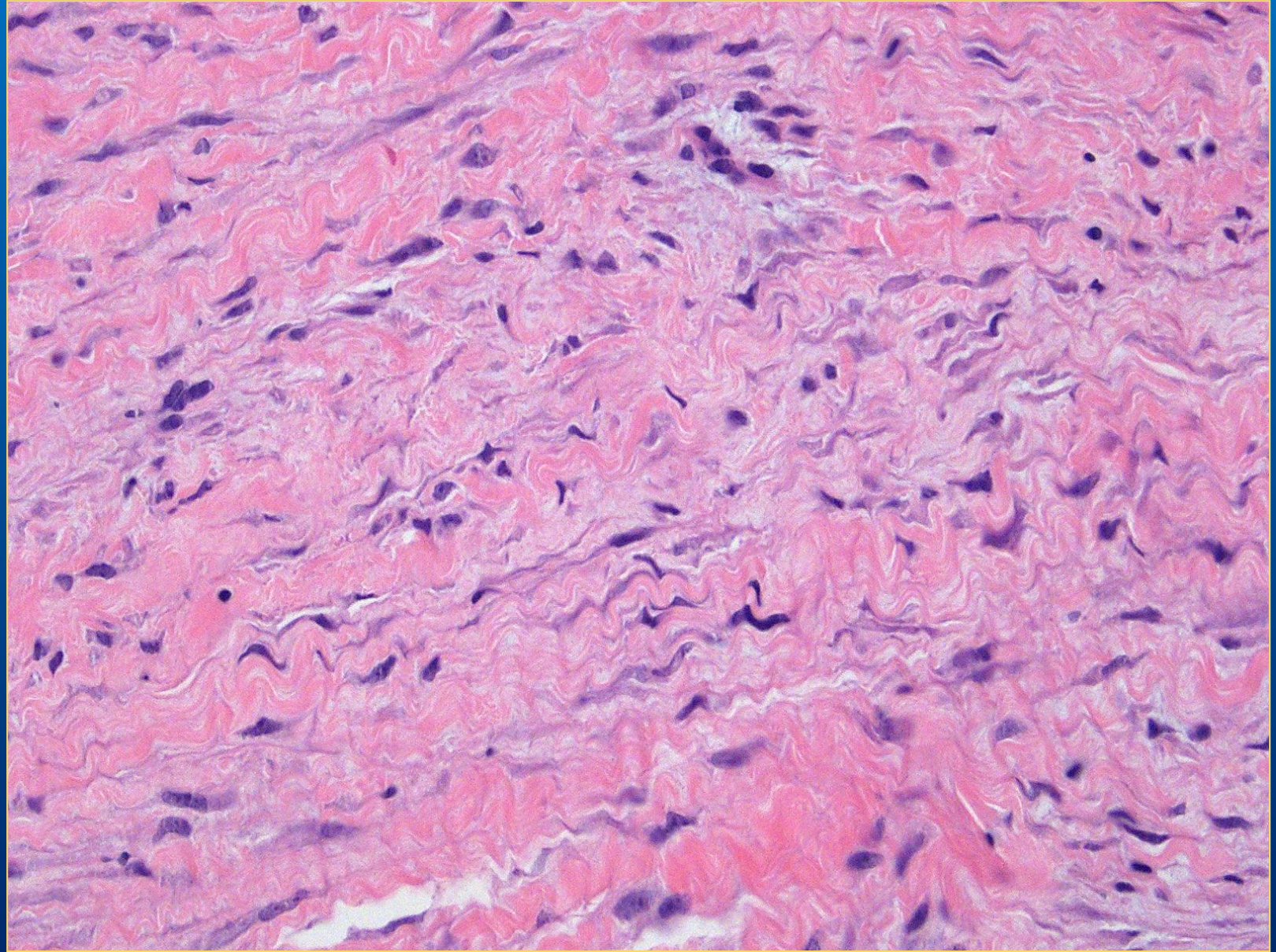
Fibromatosis

- Typical cytologic features with bland spindled nuclei with tapered ends



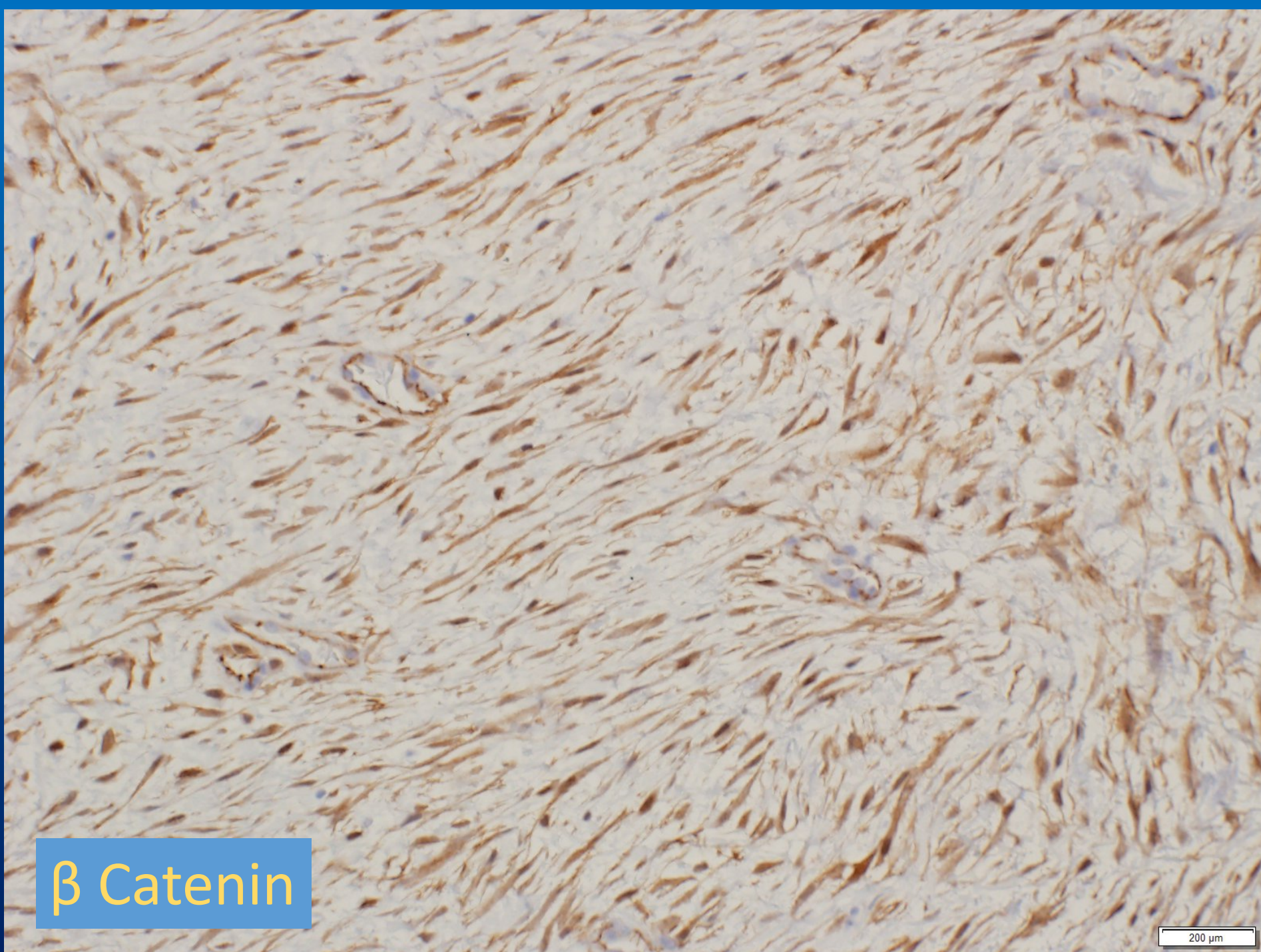
Fibromatosis

- Lesional cells lacking either significant atypia or mitotic figures



Fibromatosis

- Lesional cells with nuclear β catenin expression



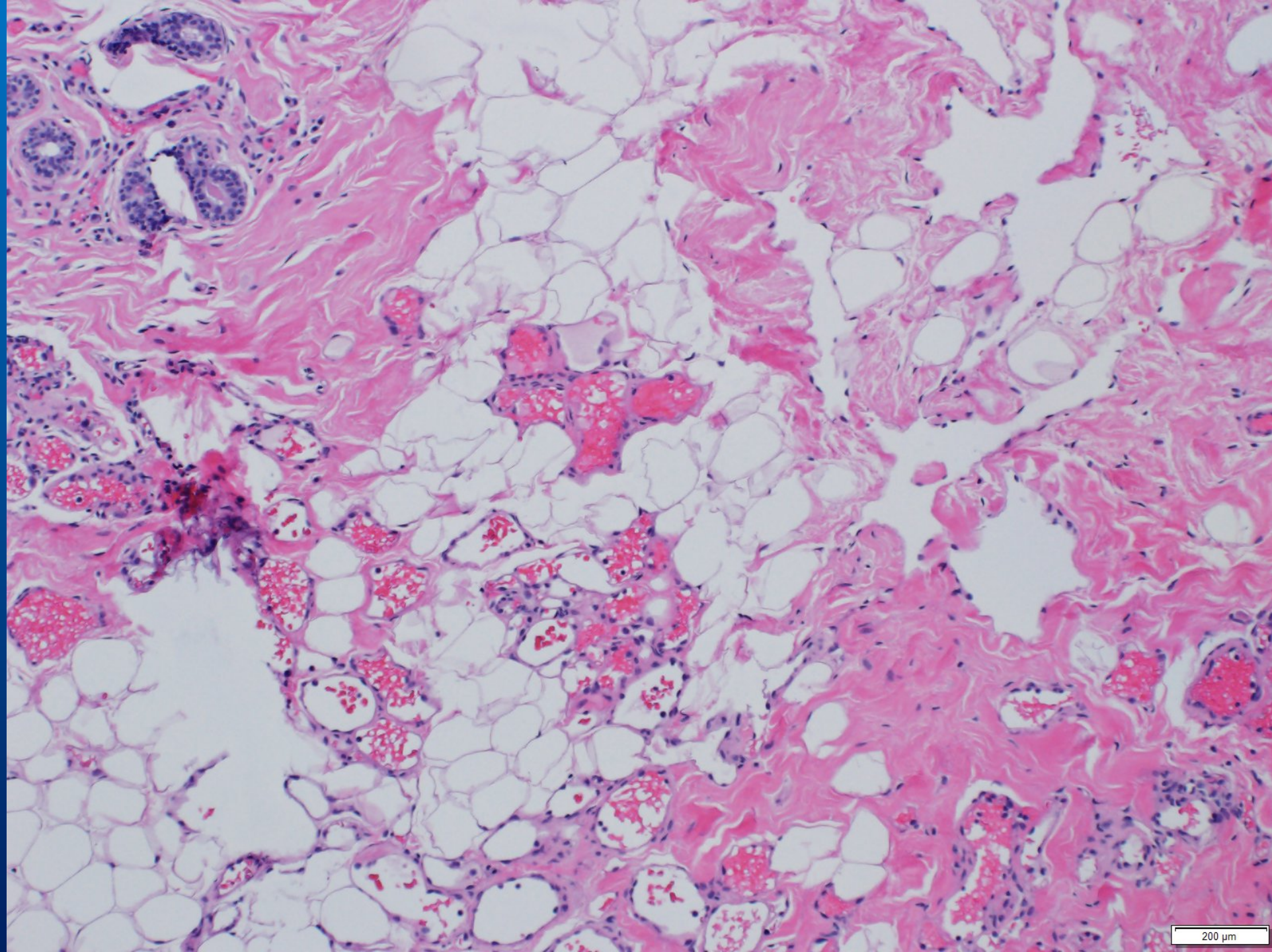
Fibromatosis

- Mammary fibromatosis can be locally aggressive
 - Wide excision with negative margins has been the recommended treatment
- Recurrence rates are quoted around 30%
 - 57% for a chest wall fibromatosis secondarily involving the breast
- Some response to Tamoxifen
- Differential:
 - Low grade fibromatosis like spindle cell carcinoma and scar

Benign vascular lesions: Perilobular hemangioma

- Microscopic benign vascular lesions identified incidentally
 - None have been identified mammographically
 - Seen in 4.5% of breast biopsies and in 11% of women with breast tissue sampled at autopsy
- Microscopic features
 - Despite name, not limited to perilobular region
 - Well defined collection of small, distinct vascular channels with variable caliber
 - Endothelial cells are bland and surrounded by thin supporting stroma without a muscle coat

Perilobular
hemangioma



Perilobular hemangioma

- Rare examples of “atypical perilobular hemangioma” have been described due to endothelial cell atypia
 - Hyperchromatic endothelial cells
 - No mitotic figures
 - No extensive vascular anastomoses
- No examples of progression of these lesions

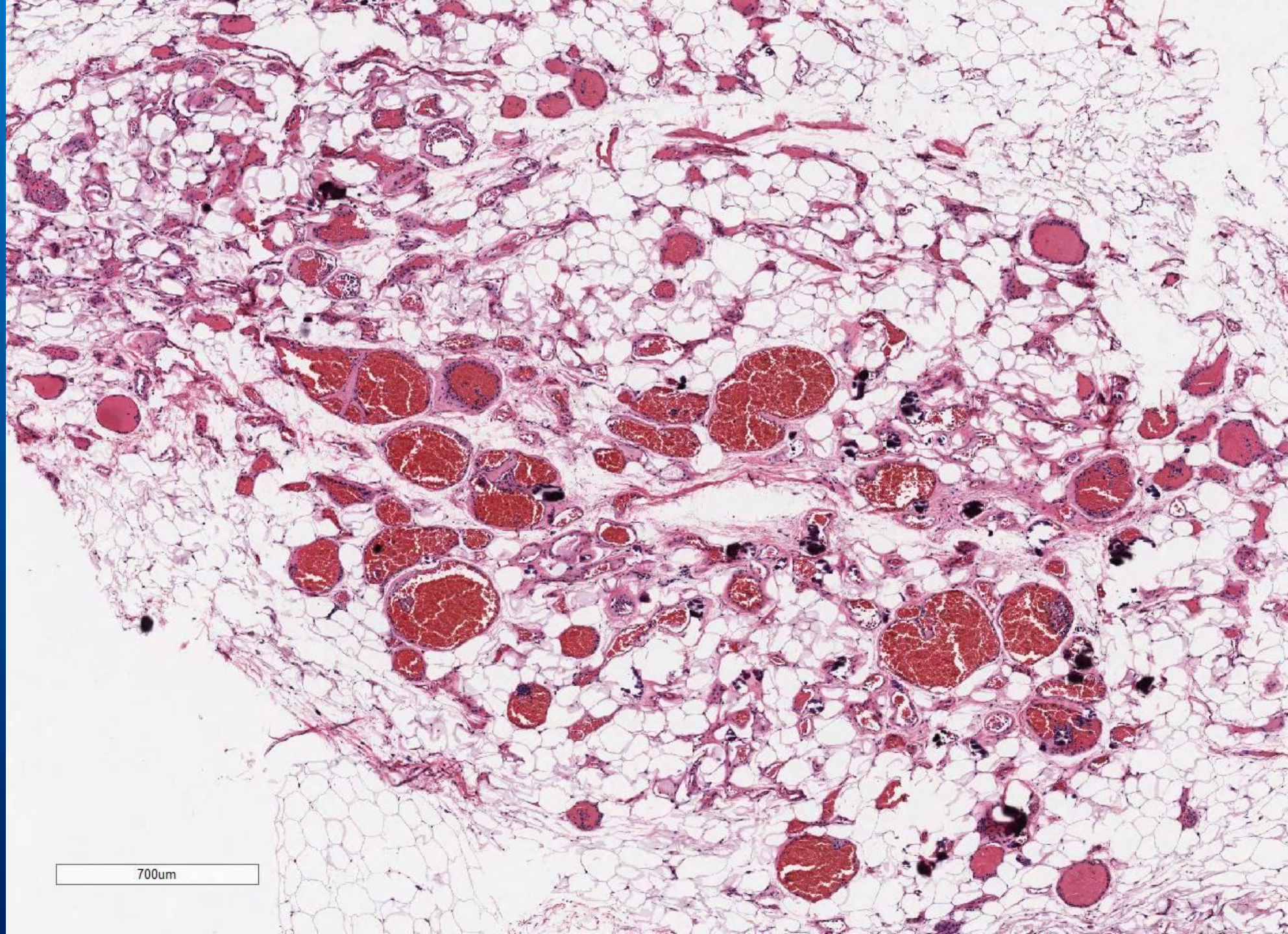
Benign vascular lesions: Hemangioma

- Hemangioma: cavernous, capillary or complex
- Large enough to be palpable or detected by imaging
 - Mammographically is typically a well defined lobulated mass which may have associated calcifications
- Size range is 0.4 to 2 cm
- Differential: Angiosarcoma
- Microscopic features:
 - Well defined grossly, microscopically the vascular channels frequently blend with the adjacent parenchyma
 - Papillary endothelial hyperplasia is common
 - Extramedullary hematopoiesis has been described

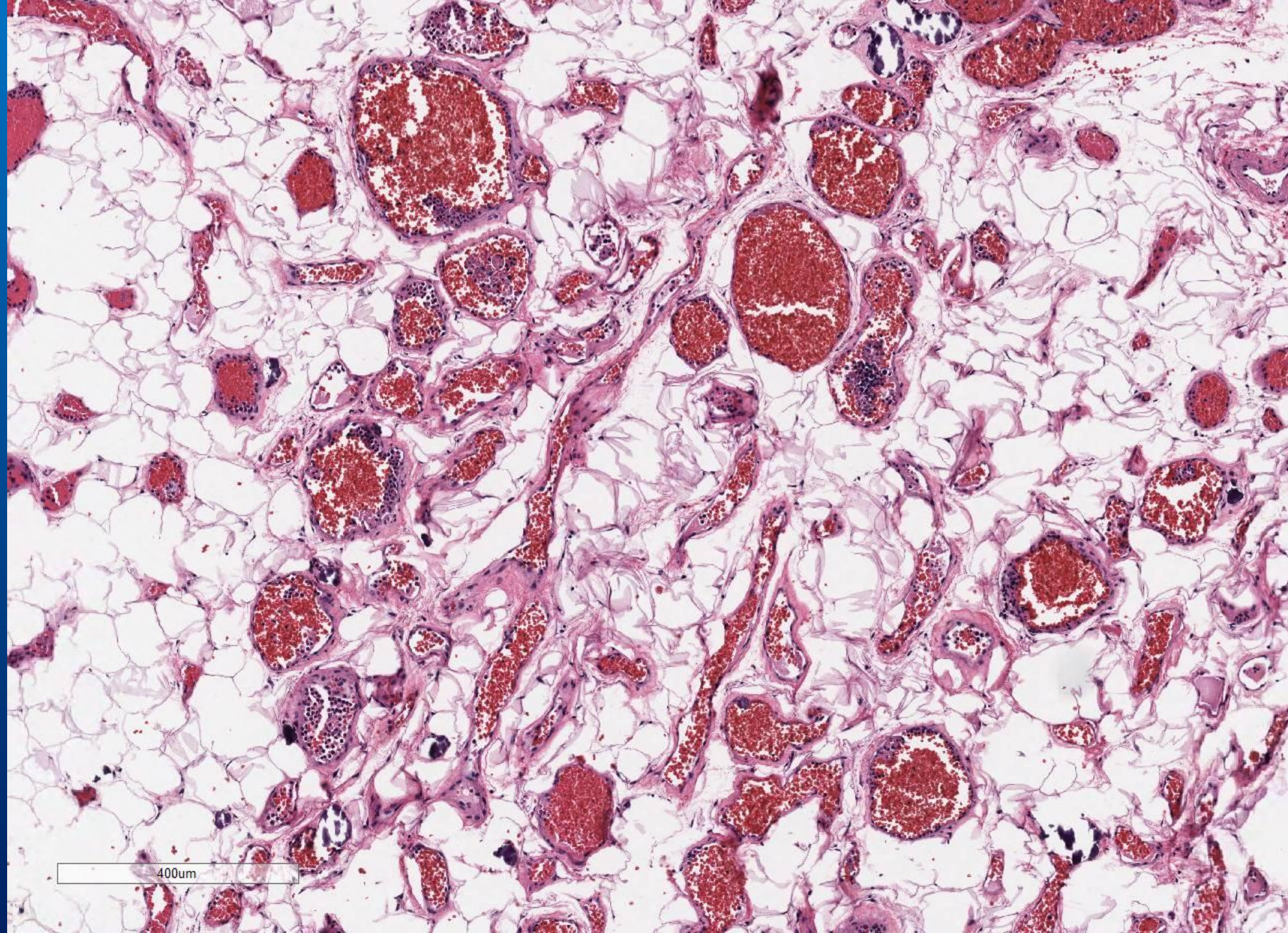
Cavernous Hemangioma

- Dilated vessels with congestion
- Only rare anastomosing channels, most are individual channels
- Endothelial cells are inconspicuous and compressed
- Minimal fibrous stroma supporting the vessels
- Organizing thrombus not uncommon

Cavernous Hemangioma



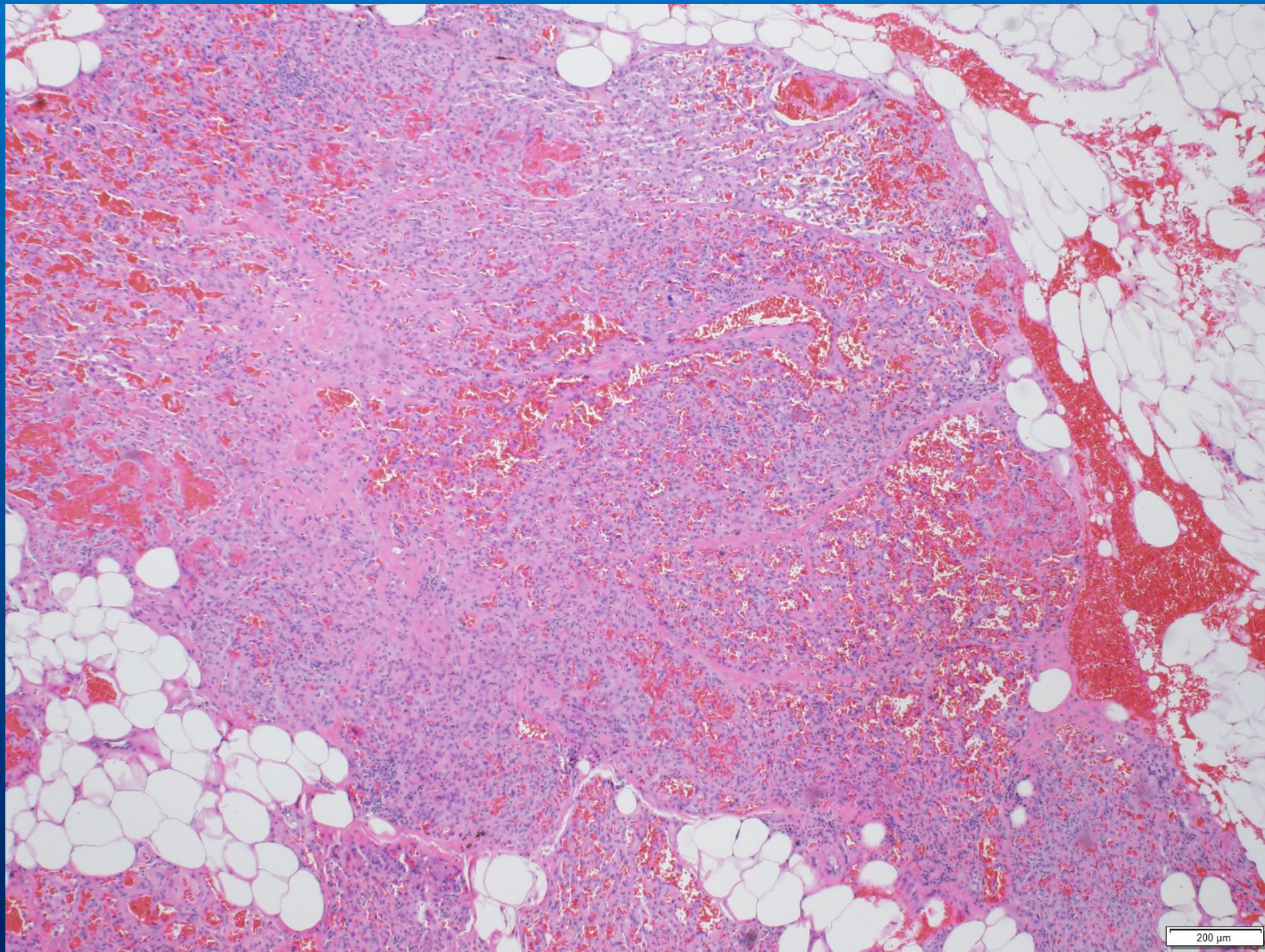
Cavernous Hemangioma



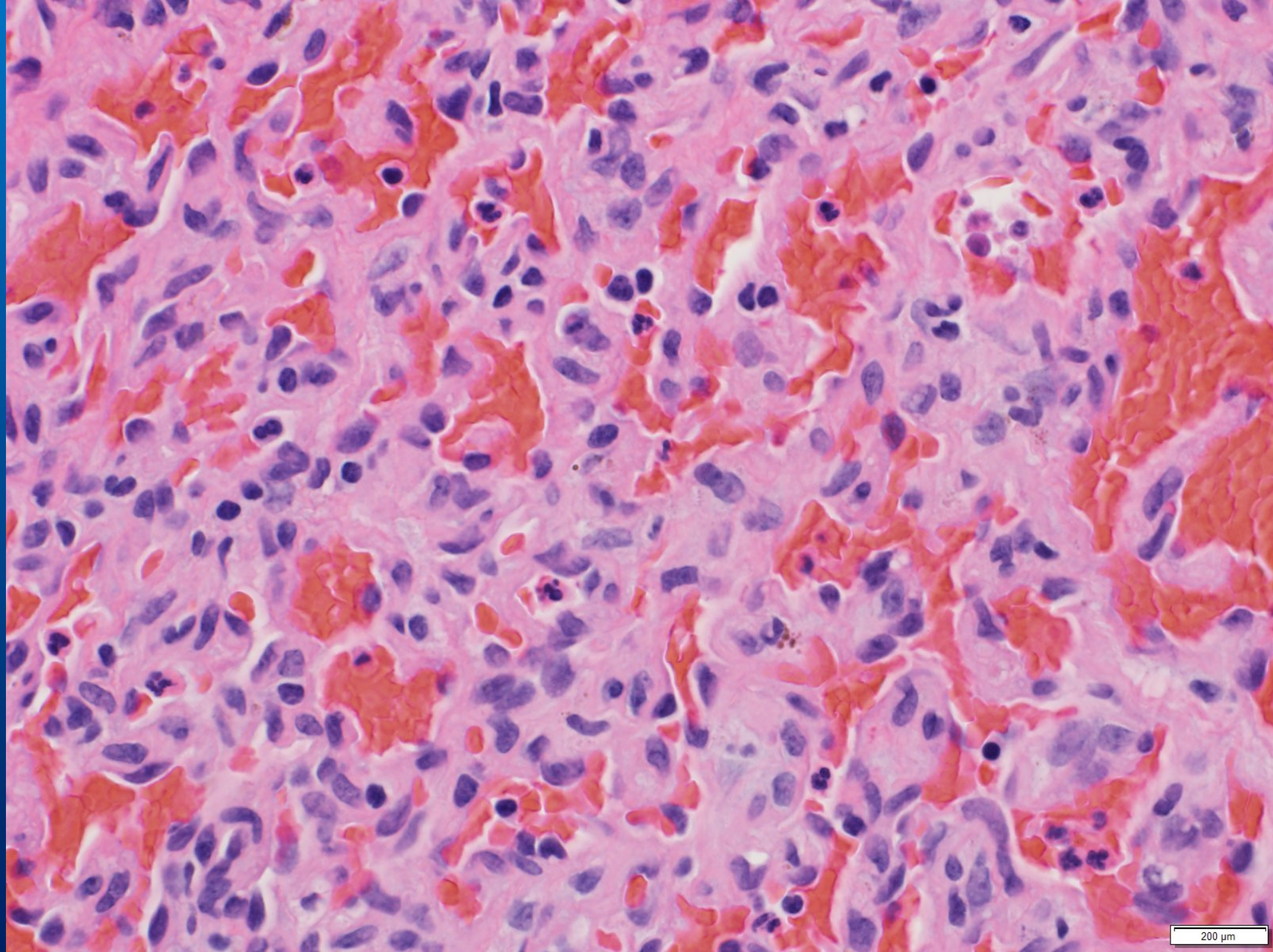
Capillary Hemangioma

- Well circumscribed, lobulated structure due to fibrous septa dividing the lesion into segments
- Quite cellular and are composed of small vascular channels containing endothelial cells that tend to be hyperchromatic but overall uniform
- Muscular vessels often present at periphery

Capillary Hemangioma



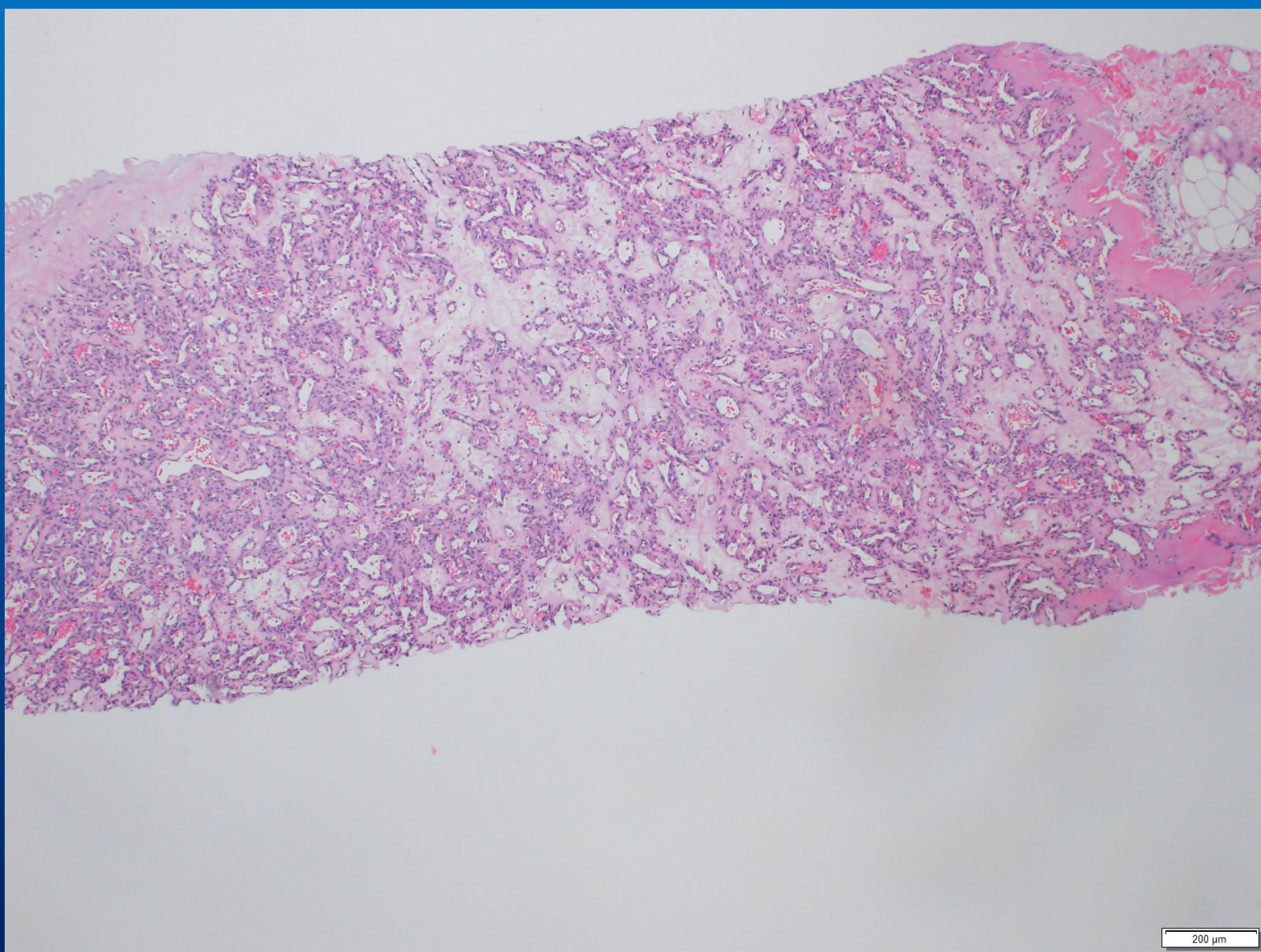
Capillary Hemangioma



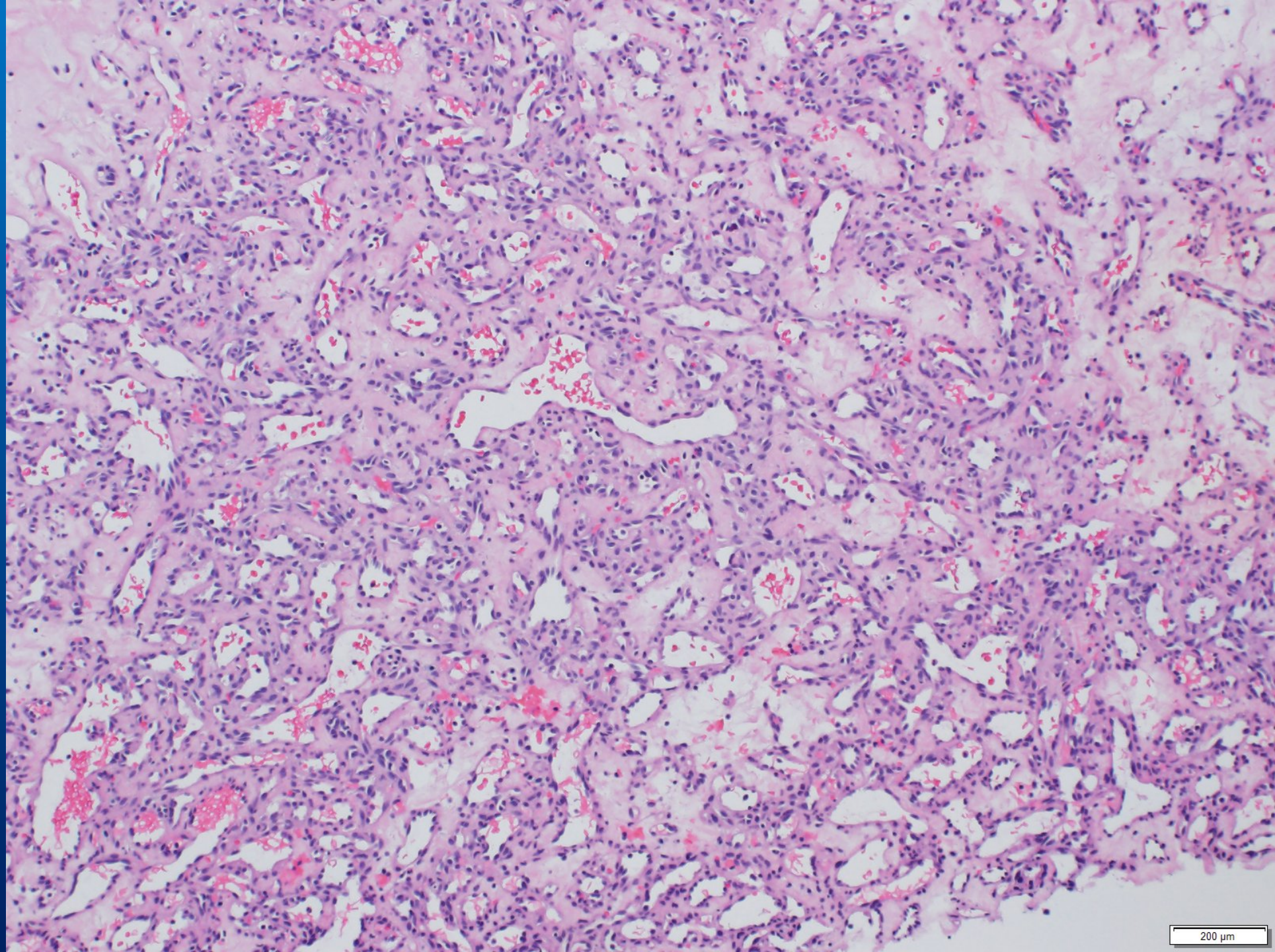
Complex Hemangioma

- Well circumscribed lesion composed of dilated vascular channels of variable size with admixed dense aggregates of capillary structures
- Feeder vessel may be identified at the periphery

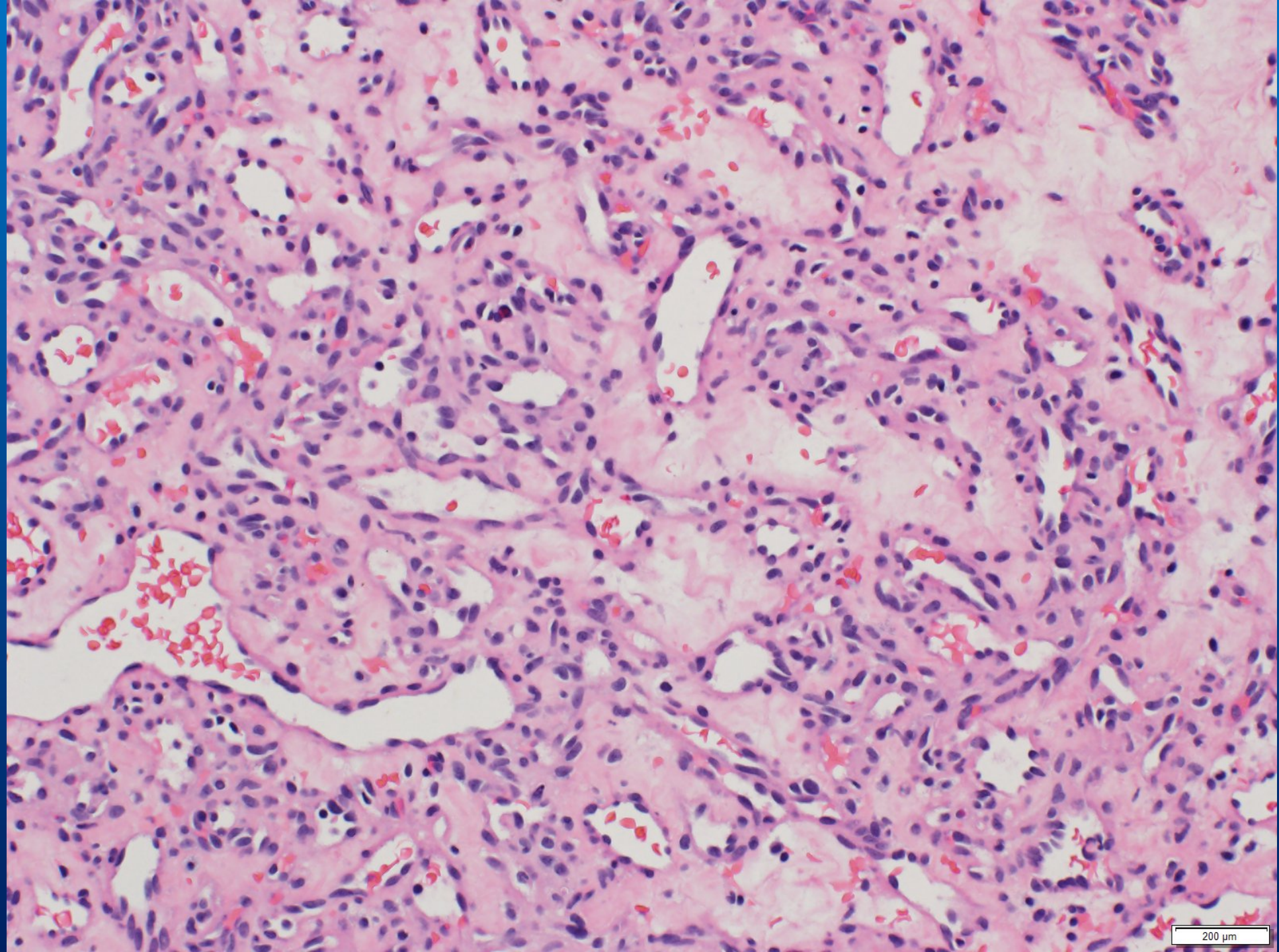
Complex Hemangioma



Complex Hemangioma



Complex Hemangioma



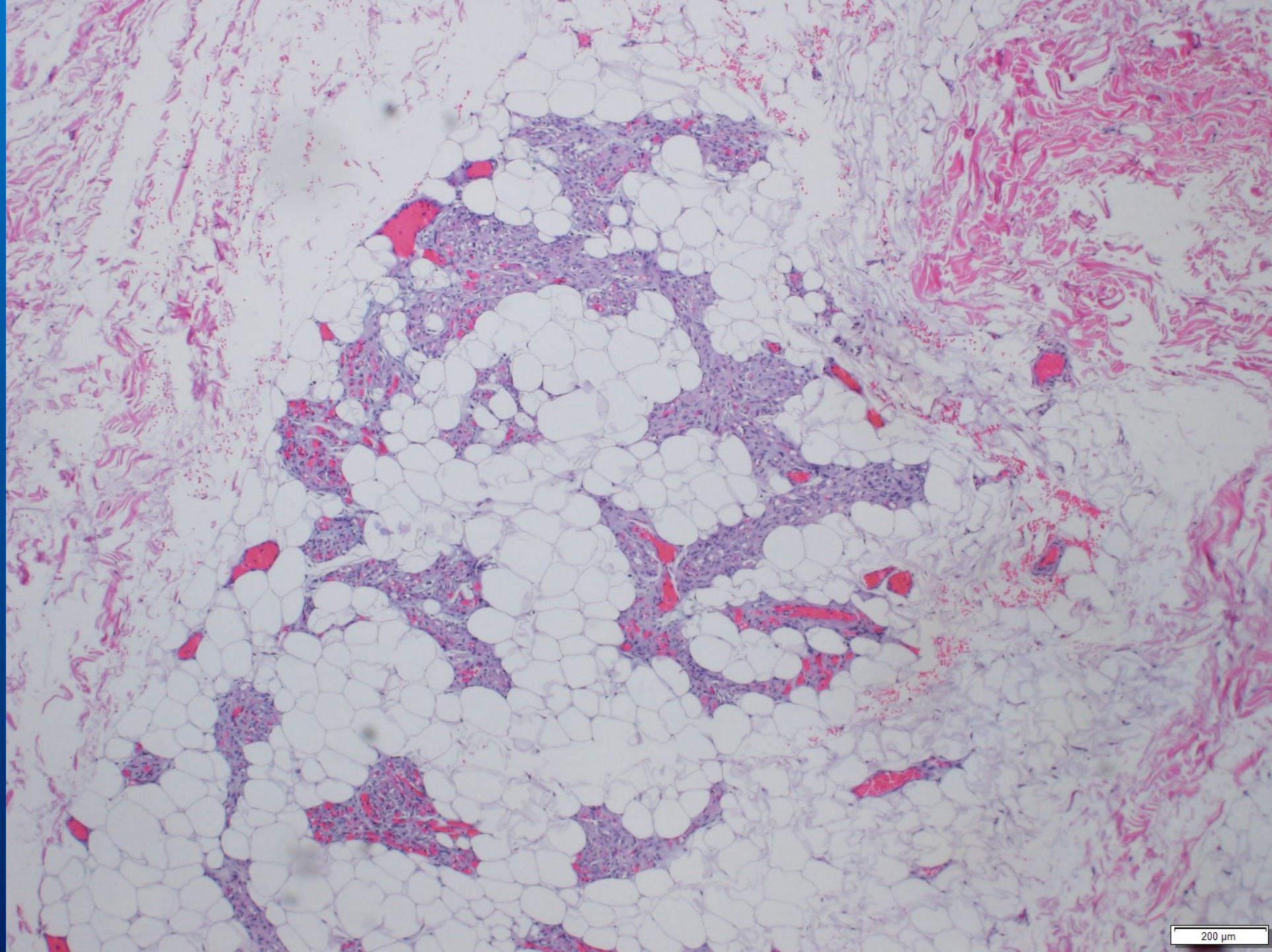
Hemangioma

- If diagnosed on core needle biopsy, excision has typically been recommended to exclude the possibility of angiosarcoma
 - Hemangiomas rarely exceed 2 cm, angiosarcomas are typically greater than 3 cm
 - Ki67 is typically 5% or less in hemangiomas while usually 20% or greater in angiosarcomas
- If post core needle biopsy imaging shows that most or all of the lesion has been removed and a clip was placed at the site, follow-up mammography may be acceptable

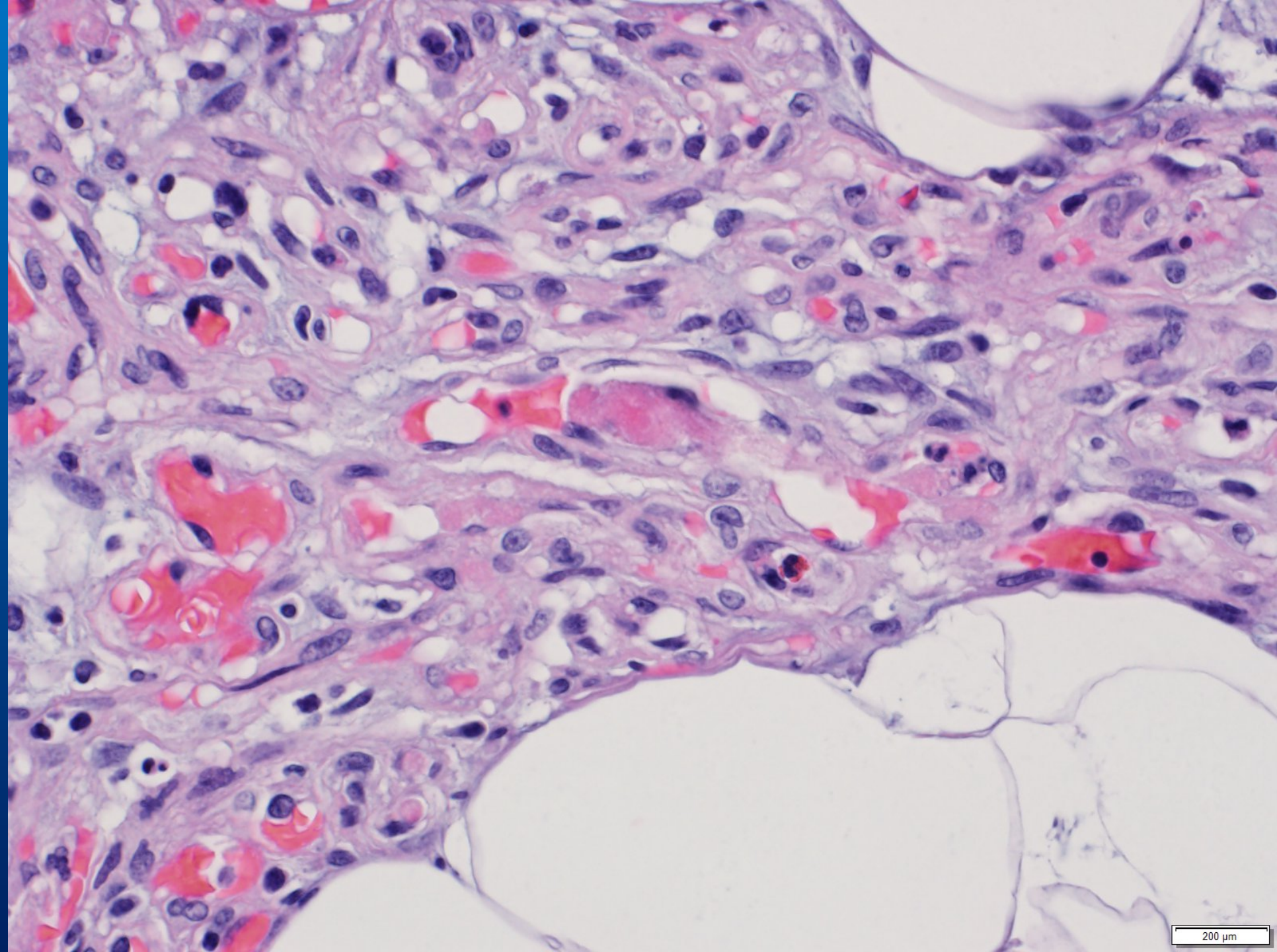
Angiolipoma

- Frequently identified in the subcutaneous tissue of the breast rather than the breast parenchyma itself
- Present as a mass; US can be helpful in determining location
- Microscopic features
 - Capillary proliferation with admixed fat
 - Delicate fibrous stroma
 - Presence of fibrin thrombi

Angiolipoma



Angiolipoma



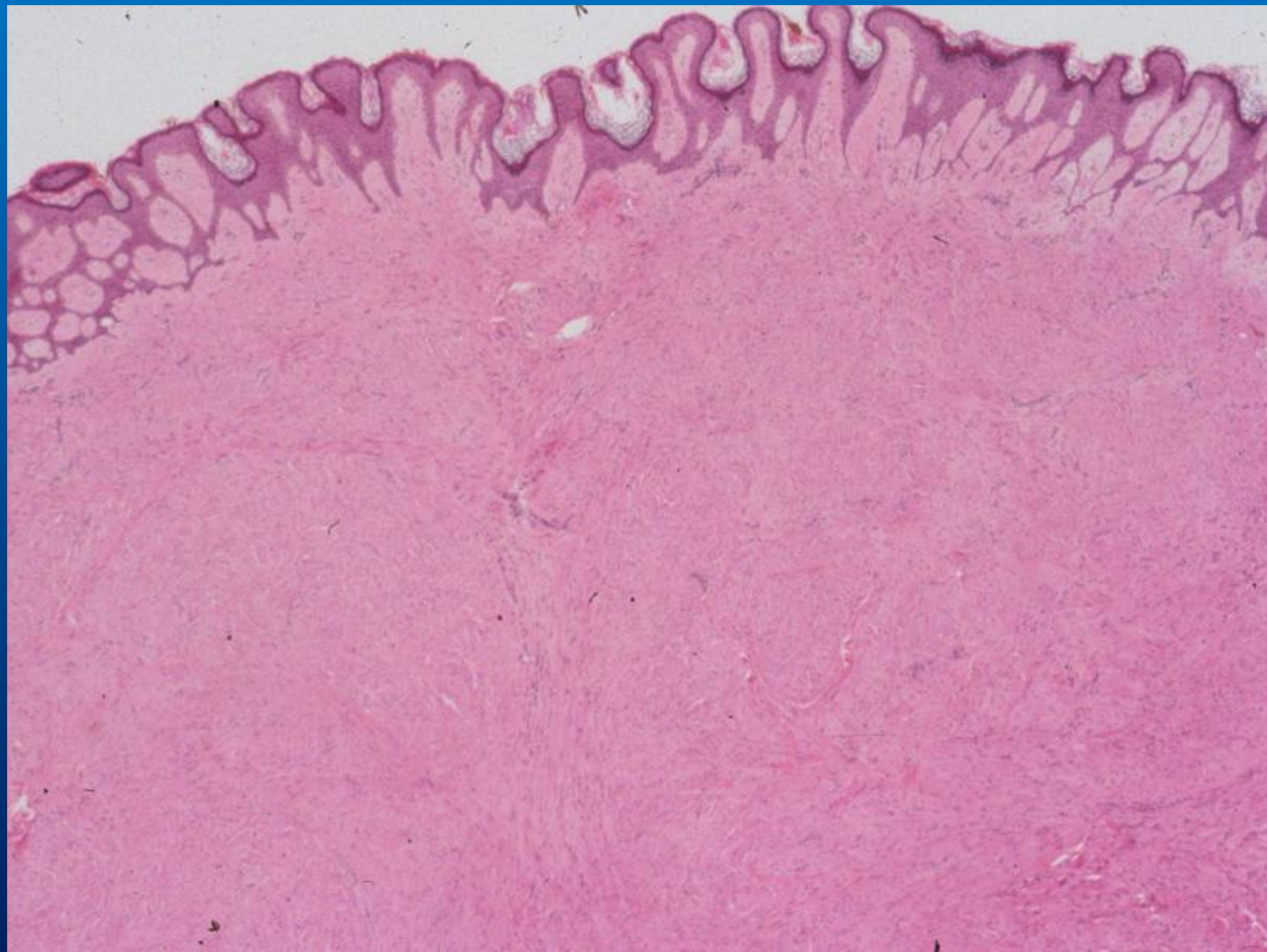
Angiolipoma

- If diagnosed on core needle biopsy, excision has typically been recommended to exclude the possibility of angiosarcoma

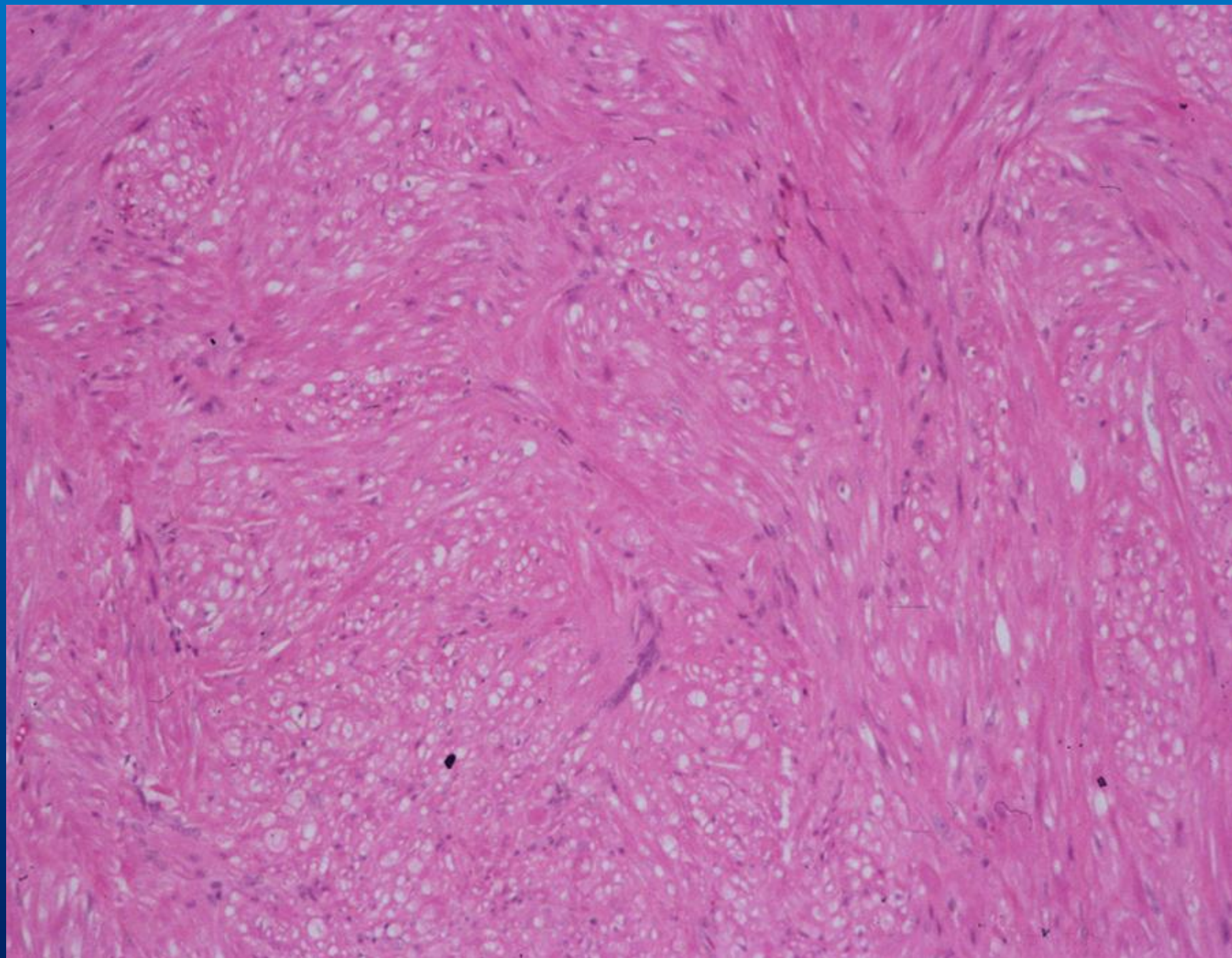
Leiomyoma

- Typically arise from the smooth muscle present within the nipple areolar complex
- Parenchymal lesions thought to arise from blood vessel wall or represent smooth muscle metaplasia of myoepithelial cells or myofibroblasts
- Usually present as a solitary palpable mass; those arising in the nipple may cause nipple alteration
- Microscopic features
 - Fascicles of spindle cells with eosinophilic cytoplasm
 - No necrosis, atypia or mitotic activity should be appreciated

Nipple leiomyoma



Nipple leiomyoma



Leiomyoma

- Complete excision has been suggested
 - Removal of nipple
- Recurrences have been documented including recurrence as a leiomyosarcoma

Bland spindle cell lesions of the breast with malignant behavior

- Low-grade fibromatosis-like spindle cell carcinoma

Low-grade fibromatosis-like spindle cell carcinoma

- Subtype of metaplastic carcinoma
- Arises de novo or within benign papillary or sclerosing lesions
- Typically well circumscribed and palpable masses
- True of any metaplastic carcinoma, imaging can be suggestive of a benign process
 - Yang et al compared metaplastic carcinomas and invasive ductal carcinomas via mammography and US
 - Malignant imaging features such as irregular shape, spiculated margins, and posterior acoustic shadowing are uncommon in metaplastic carcinoma
 - Tended to show more benign imaging features like round or oval shape with circumscribed margins
- Patient's usually report rapid growth in a short time span

Low-grade fibromatosis-like spindle cell carcinoma

- Microscopic features
 - Significant overlap with fibromatosis and scar
 - Variable cellularity, usually lack significant hypercellularity
 - Composed of spindle or stellate cells with bland nuclei with tapered ends
 - Cells arranged in intersecting fascicles or dispersed with admixed collagen
 - Foci of squamous differentiation may be seen

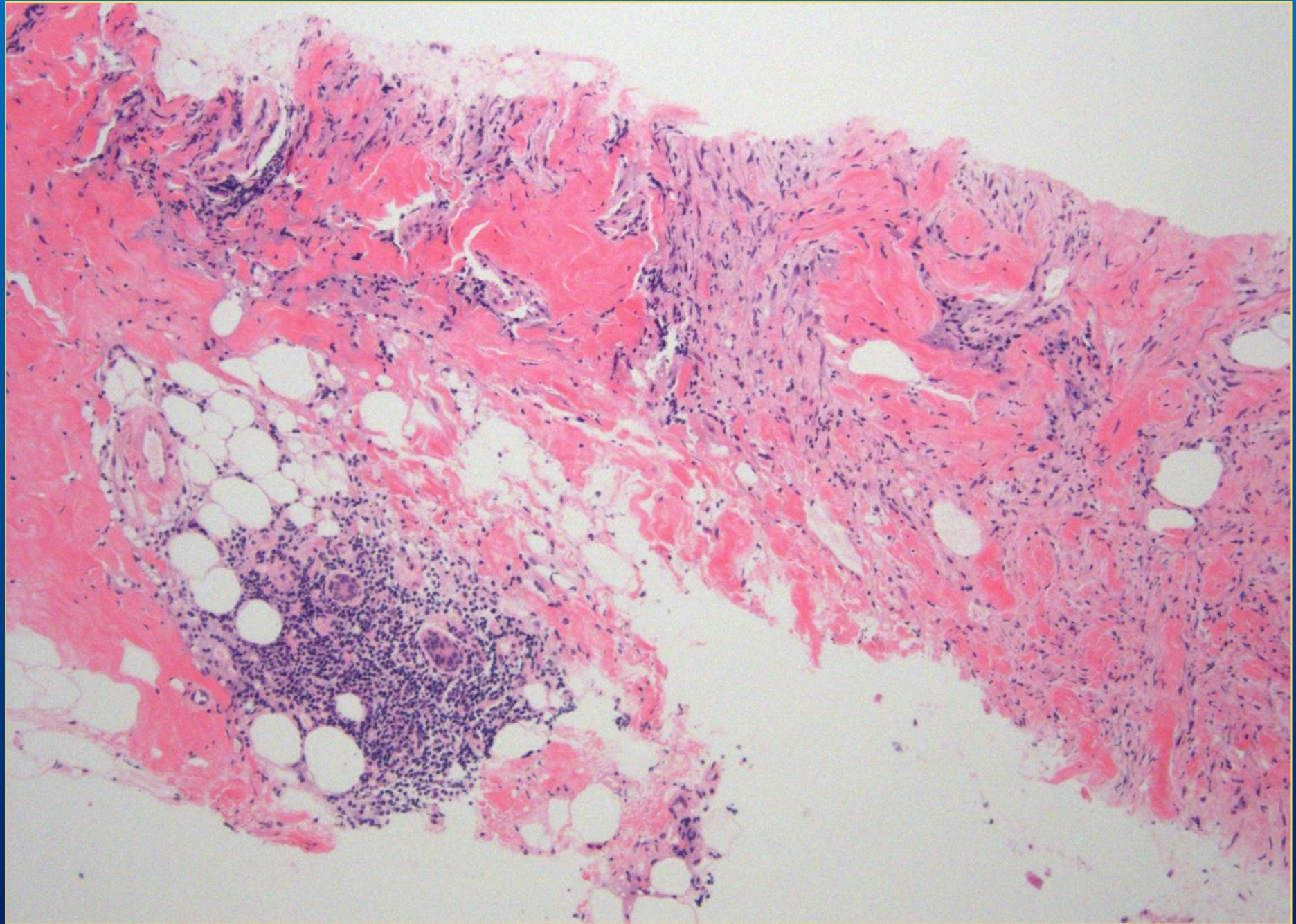
Low-grade fibromatosis-like spindle cell carcinoma

- Immunohistochemical findings
 - Cytokeratin positive
 - Panel should be used
 - p63 positive
 - Nuclear β catenin+/-
 - Typically negative for ER, PgR, and HER2

Low-grade
fibromatosis-like
spindle cell carcinoma

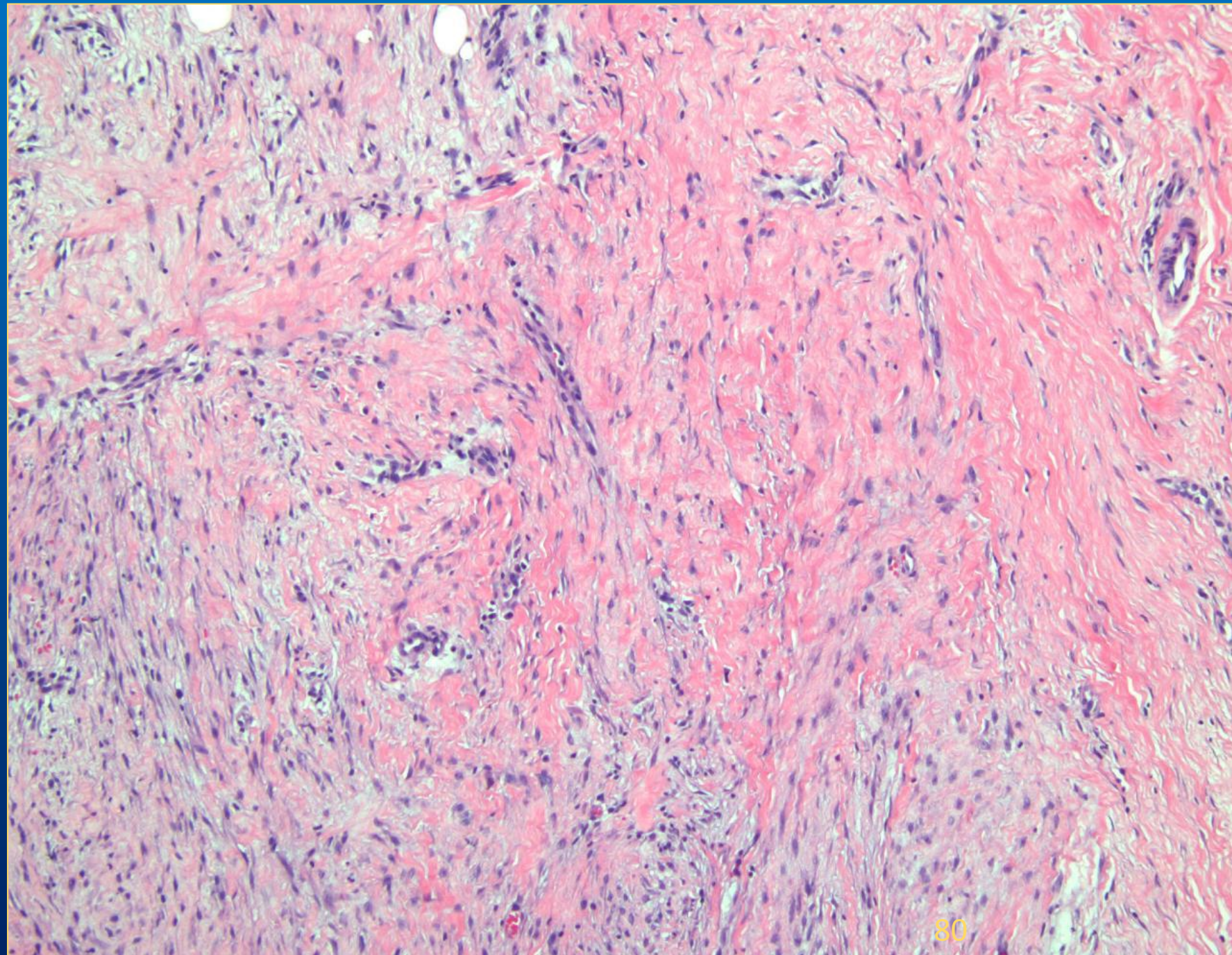
Hypocellular spindle
cell lesion with short
fascicles and admixed
dense collagen
bundles

Adjacent lymphoid
aggregate



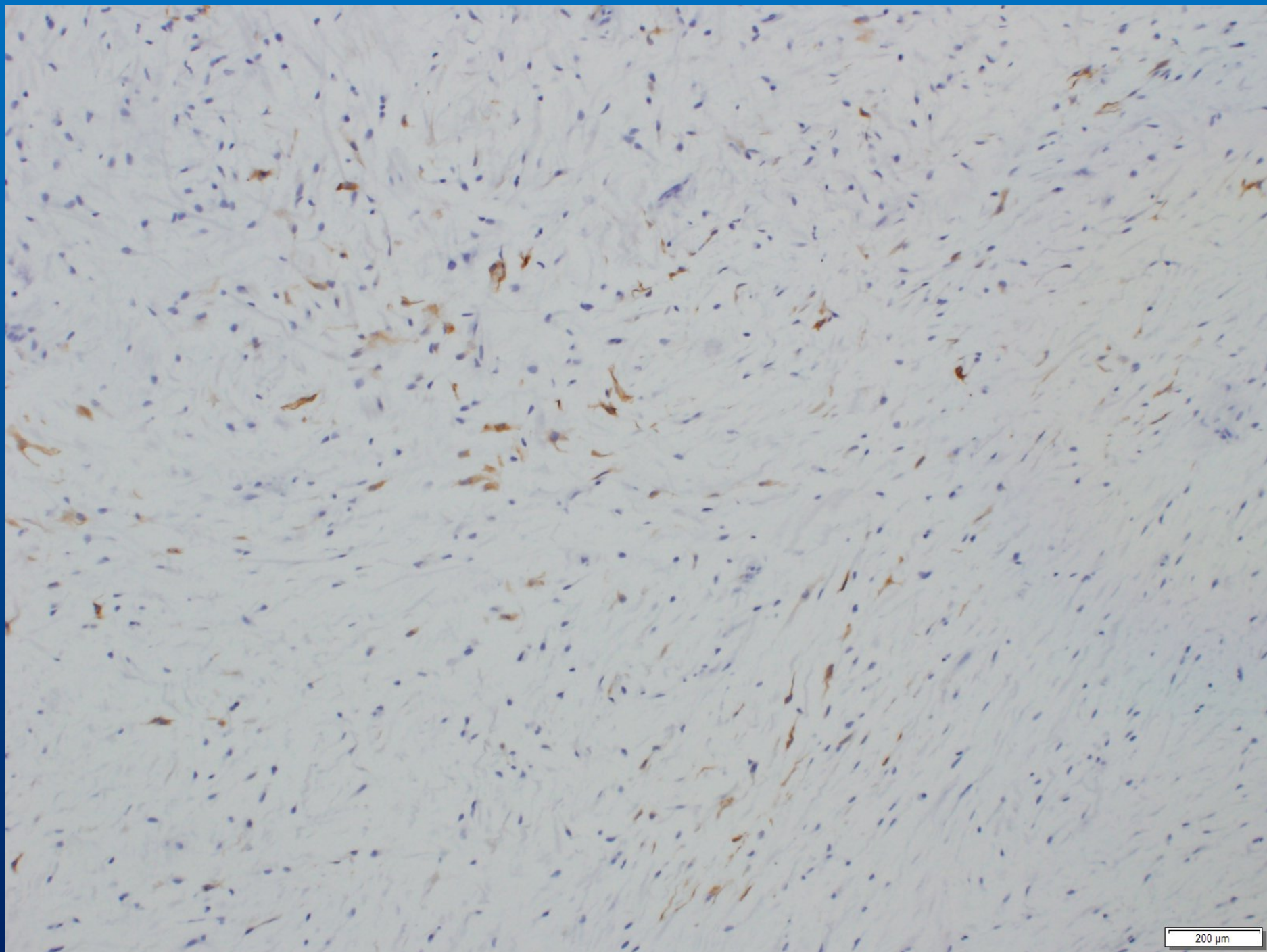
Low-grade
fibromatosis-like
spindle cell carcinoma

Hypocellular, bland
spindle cell lesions
with a vague fascicular
architecture



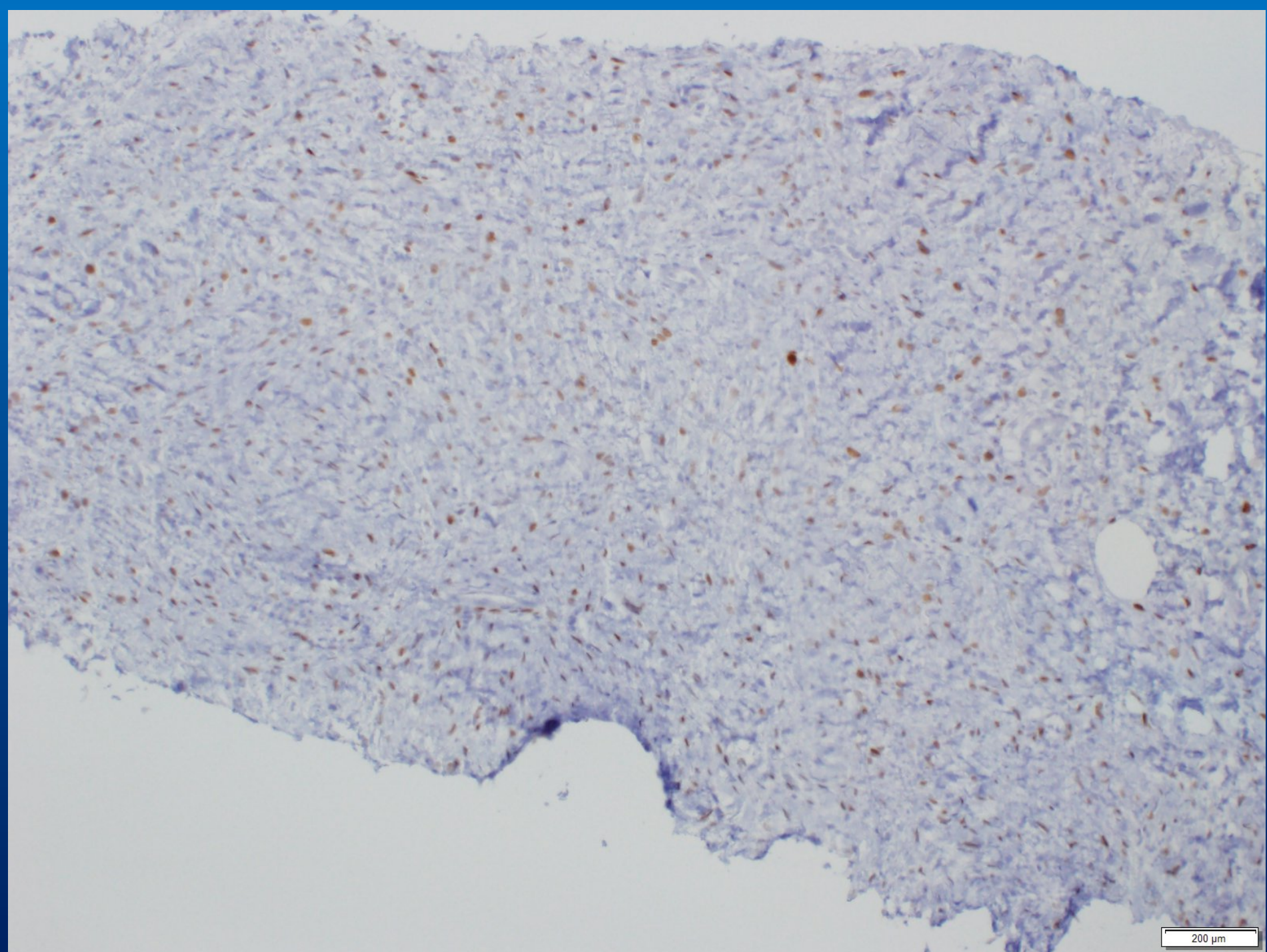
Low-grade
fibromatosis-like
spindle cell carcinoma

Cytokeratin AE1/AE3



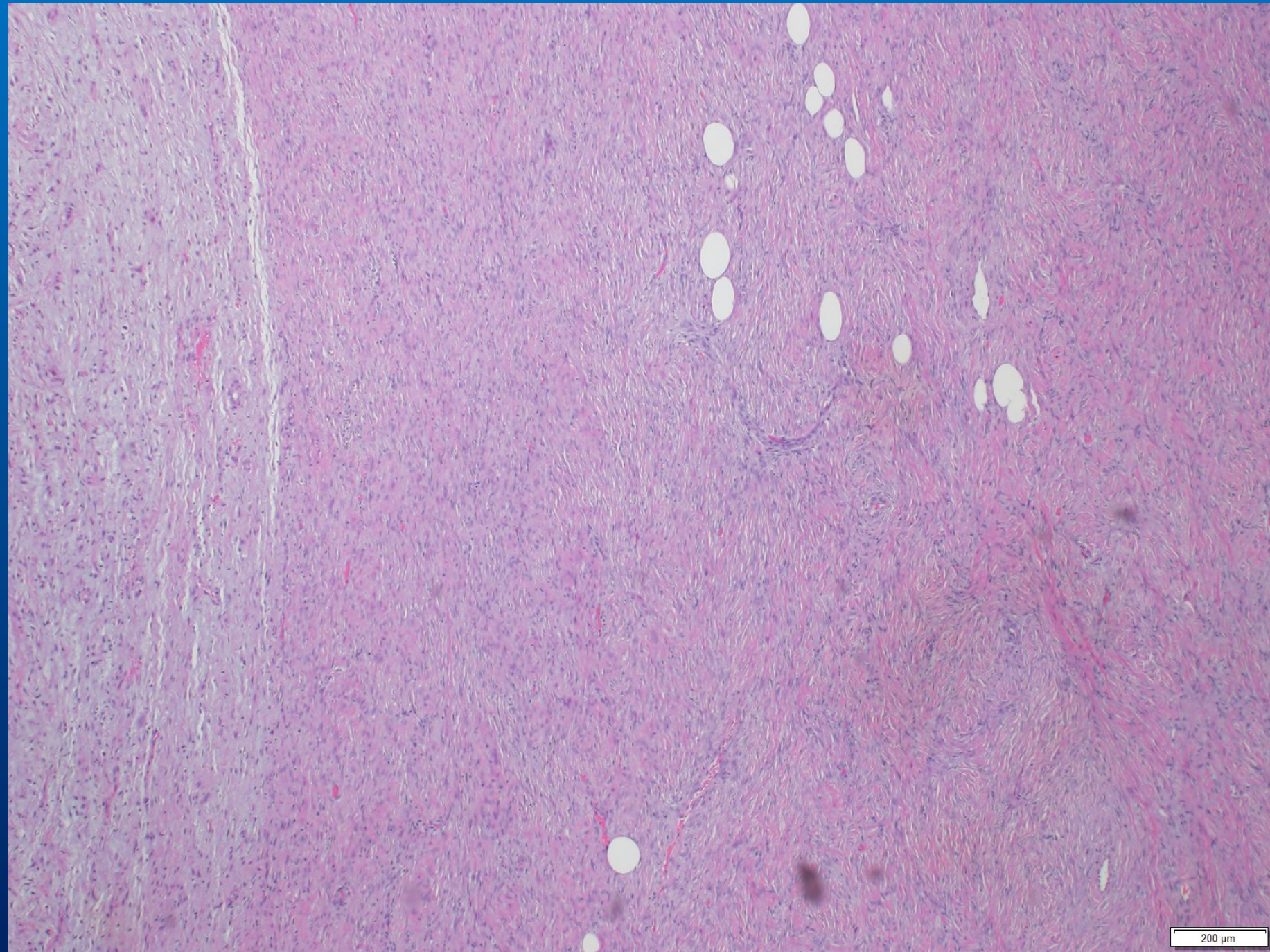
Low-grade
fibromatosis-like
spindle cell carcinoma

p63



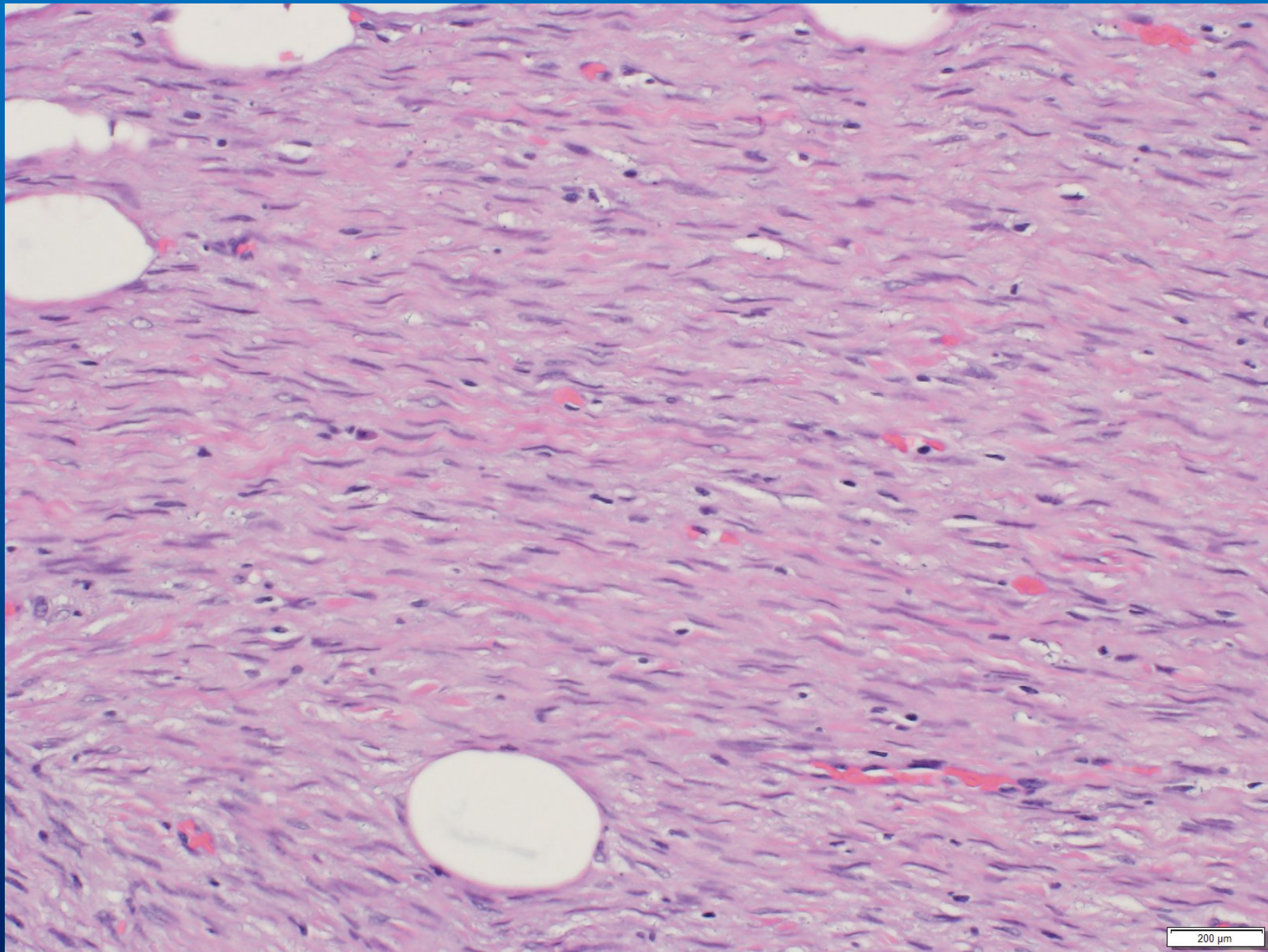
Mastectomy specimen:
Low-grade
fibromatosis-like
spindle cell carcinoma

Overall bland cytology
of the spindle cells
without mitotic activity



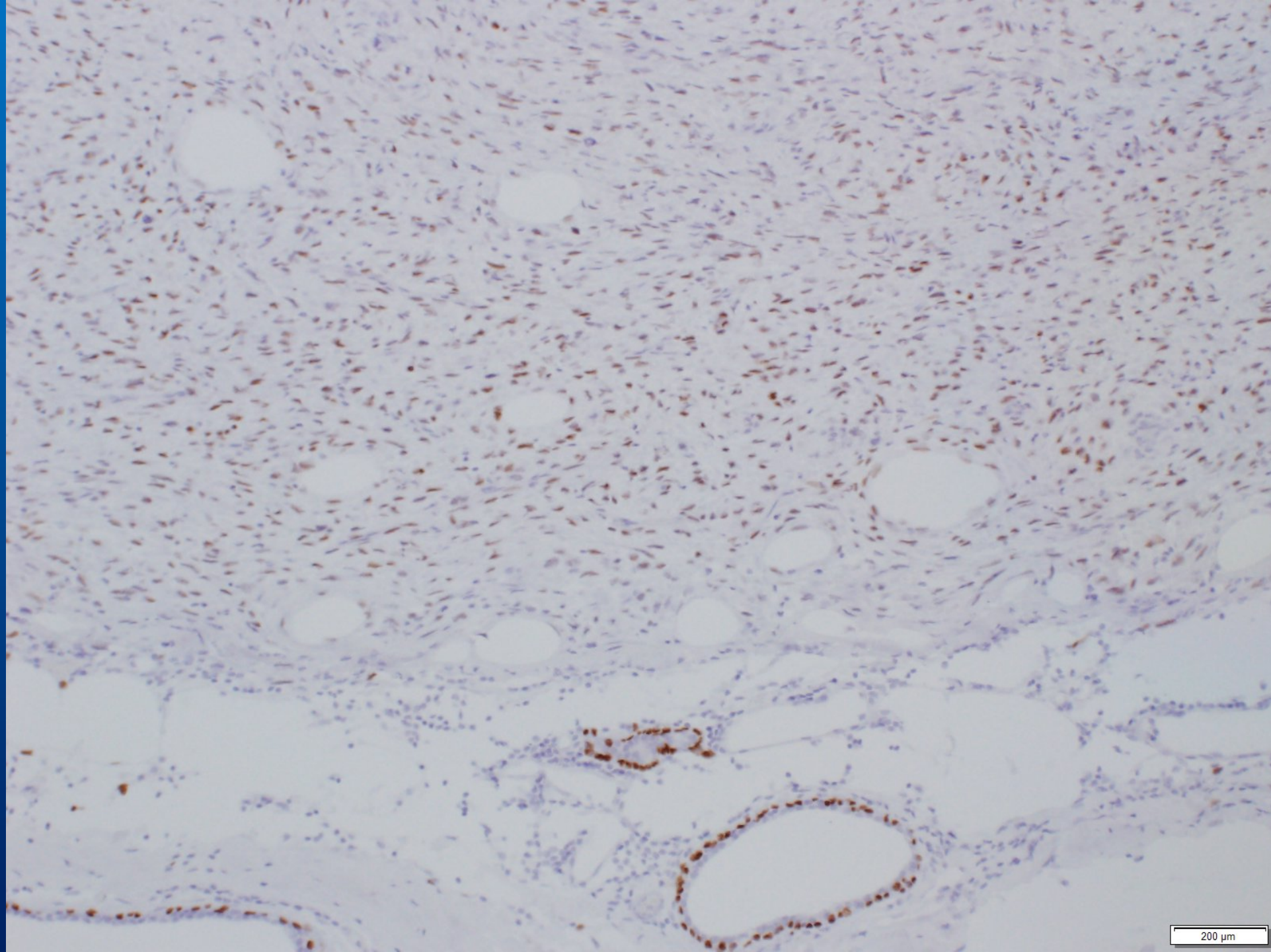
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Mastectomy
specimen: Low-
grade fibromatosis-
like spindle cell
carcinoma

p63



Low-grade
fibromatosis-like
spindle cell
carcinoma

β catenin on
mastectomy
specimen



Low-grade fibromatosis-like spindle cell carcinoma of the breast: IHC pitfall

- Immunohistochemistry pitfall:
 - Lacroix-Triki et al described finding nuclear β catenin in 22% of spindle cell carcinomas of the breast (using 2 different antibody clones)
 - Variable intensity with <33% of cells staining
 - Fibromatosis have diffuse staining

Low-grade fibromatosis-like spindle cell carcinoma

- High rates of local recurrence
- Rare reports of metastatic disease to lung
- Axillary lymph node metastases have not been identified

Gobbi H, et al. Cancer 1999;85:2170-2182

Sneige N, et al. Am J Surg Pathol. 2001;25:1009-1016

Spindle Cell Lesions of the Breast: Key Findings

Diagnosis	Pattern of growth	Nuclear features	IHC
Fascicular PASH	Variable fascicles	Uniform, spindled	CD34+, SMA+/-, β -catenin-, CK-, p63 -
Myofibroblastoma	Short intersecting fascicles	Uniform, spindled or epithelioid	CD34+, SMA+, β -catenin-, CK-, p63 -
Nodular fasciitis	Short fascicles	Plump, uniform spindled	CD34-, SMA+, β -catenin-, CK-, p63 -
Fibromatosis	Long sweeping fascicles	Spindled with tapered ends	CD34-, SMA+, β -catenin+, CK-, p63-
Low-grade fibromatosis-like spindle cell carcinoma	Variable	Spindled with tapered ends, atypia may be present	CD34-, SMA+/- β -catenin+/-, CK+, p63 +

Atypical spindle cell lesions of the breast

Atypical spindle cell lesions of the breast with benign behavior

- Nodular fasciitis
 - Mitotic activity and variable nuclear features with prominent nucleoli

Nodular Fasciitis

- Uncommon in the breast; may be either in the parenchyma or the subcutaneous tissue
- Clinical features
 - Painful and rapidly enlarging
 - Previous history of trauma rarely
 - May radiographically resemble a fibroadenoma or have imaging characteristics worrisome for malignancy

Nodular Fasciitis

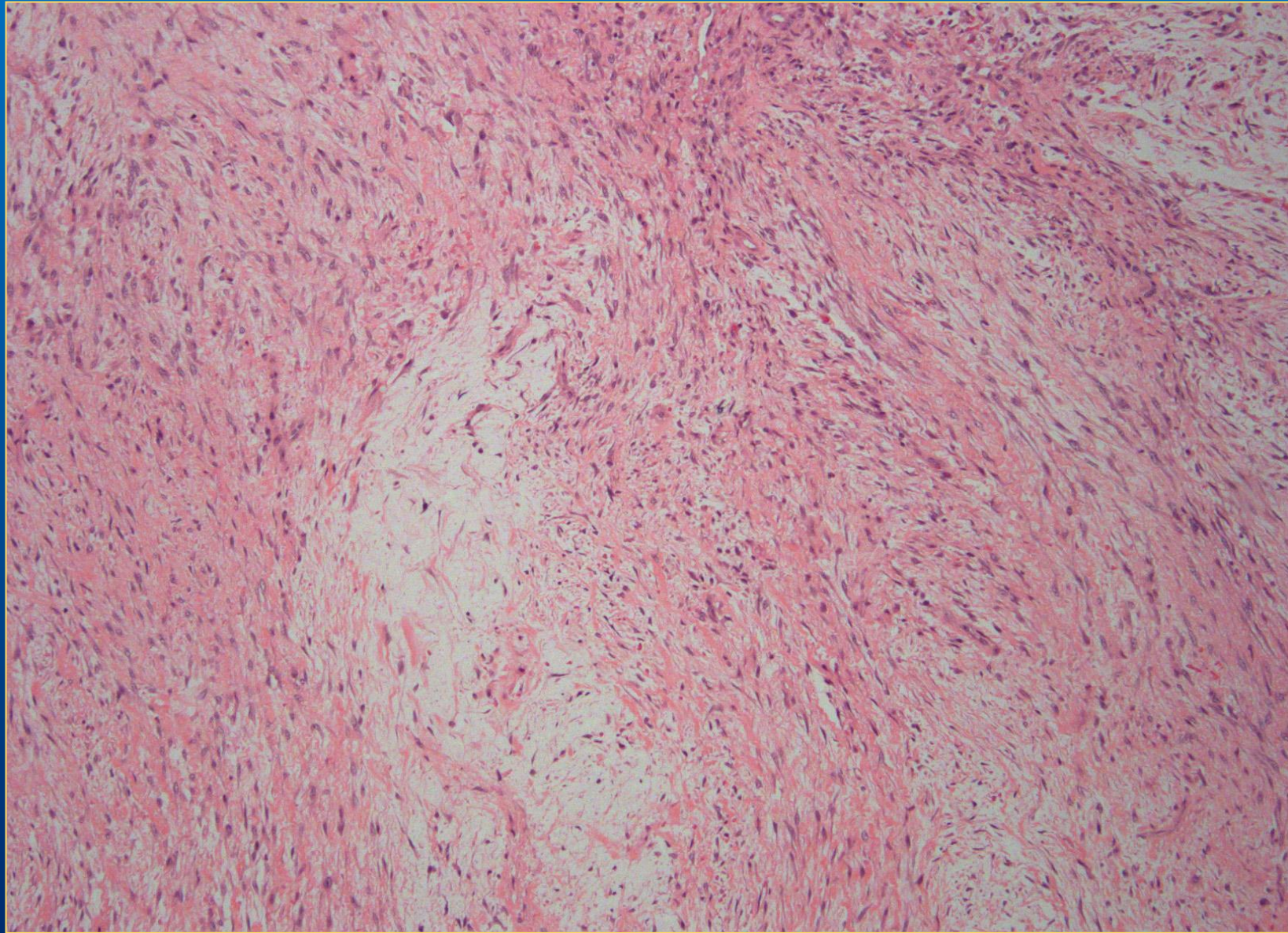
- Microscopic Features
 - Unencapsulated mass that may be circumscribed or infiltrative with expansile growth and displacement of mammary epithelium
 - Irregular loose fascicles (tissue-culture pattern)
 - Variable spindle cells with prominent nucleoli with wispy cytoplasm in a myxoid background
 - Cystic breakdown and extravasated red blood cells in a mixed inflammatory infiltrate
 - Frequent mitotic figures, no atypical forms
 - Cellularity and stroma vary depending on the age of the lesion

Nodular Fasciitis

- Immunohistochemical findings
 - Lesional cells will express smooth muscle actin, desmin expression is rare
 - Negative for nuclear β -catenin and cytokeratins

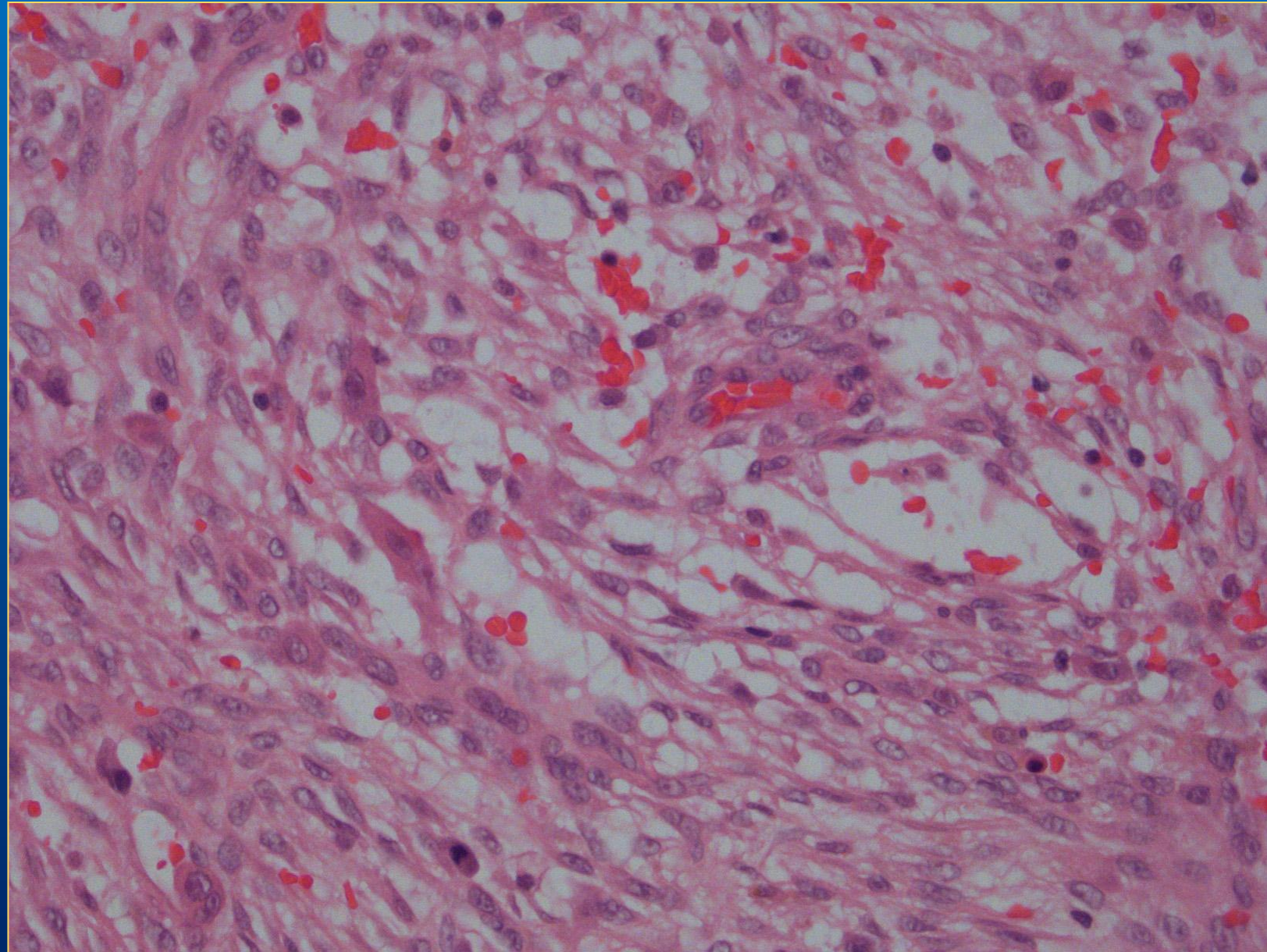
Nodular fasciitis

- Early lesion with variable morphology spindle cells with wispy cytoplasm arranged in short fascicles
- Areas of myxoid stroma



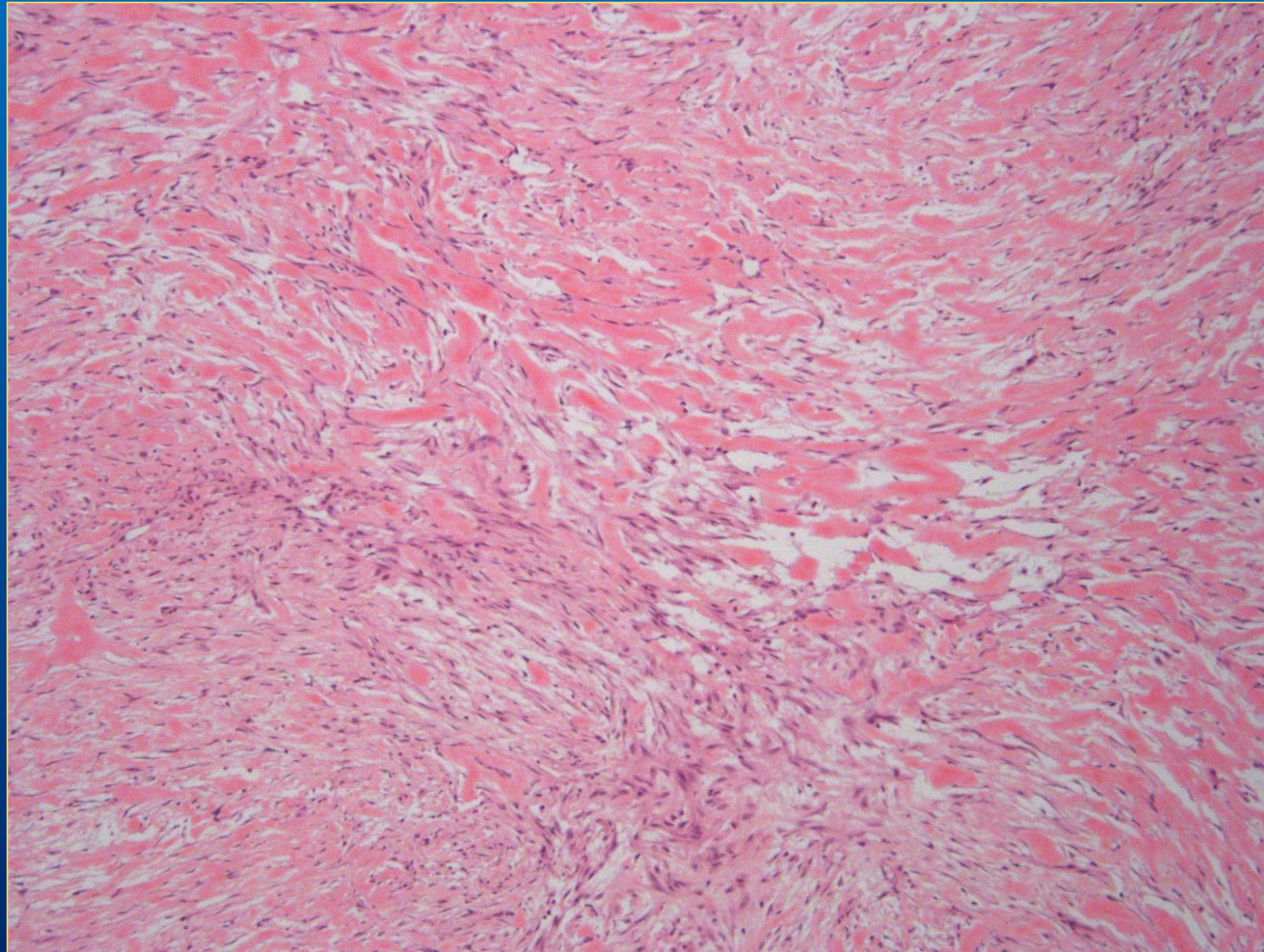
Nodular fasciitis

- Spindle cells with discernable nucleoli
- Occasional mitotic figures
- Extravasated red blood cells



Nodular fasciitis

- Older lesion with increased stromal collagen and only a focal area of loose stroma



Nodular Fasciitis

- Even though NF spontaneously regresses, excision has typically been recommended
 - Largely due to discordant imaging findings
- Differential diagnosis:
 - Fibromatosis
 - Low grade fibromatosis like spindle cell carcinoma
 - Myofibroblastoma

Atypical spindle cell lesions of the breast with malignant behavior

- Metaplastic carcinoma
 - Spindle cell type (sarcomatoid carcinoma)
 - Myoepithelial carcinoma
- Primary sarcomas of the breast
- Stromal component of a malignant phyllodes tumor
- Metastatic lesions
 - Malignant melanoma
 - Sarcomas
 - Poorly differentiated carcinoma

Metaplastic carcinoma

- 2012 WHO Classification of Tumours of the Breast
- Characterized by differentiation of neoplastic epithelium into squamous cells and/or mesenchymal appearing components
 - Spindle, chondroid, osseous and rhabdomyoid
 - Purely composed of metaplastic elements or admixture of identifiable carcinomatous component and metaplastic elements
- Low-grade (fibromatosis-like) spindle cell carcinoma
- Spindle cell carcinoma (sarcomatoid carcinoma)
- Metaplastic carcinoma with osteoclastic giant cells
- Squamous cell carcinoma
- Low grade adenosquamous carcinoma
- Carcinoma with mesenchymal differentiation
 - Chondroid
 - Osseous
 - Other mesenchymal differentiation
- Myoepithelial carcinoma

Metaplastic carcinoma

- Clinical features
 - Account for <5% of invasive breast malignancies
 - Purely mesenchymal metaplastic tumors account for 1% of invasive breast cancers
 - Same age distribution as invasive ductal carcinoma, NOS
 - Well circumscribed, palpable
 - Rapid growth
- As a group, appear to have a lower response rate to conventional adjuvant chemotherapy and a worse clinical outcome than those of other triple negative tumors

Spindle cell carcinoma (Sarcomatoid carcinoma)

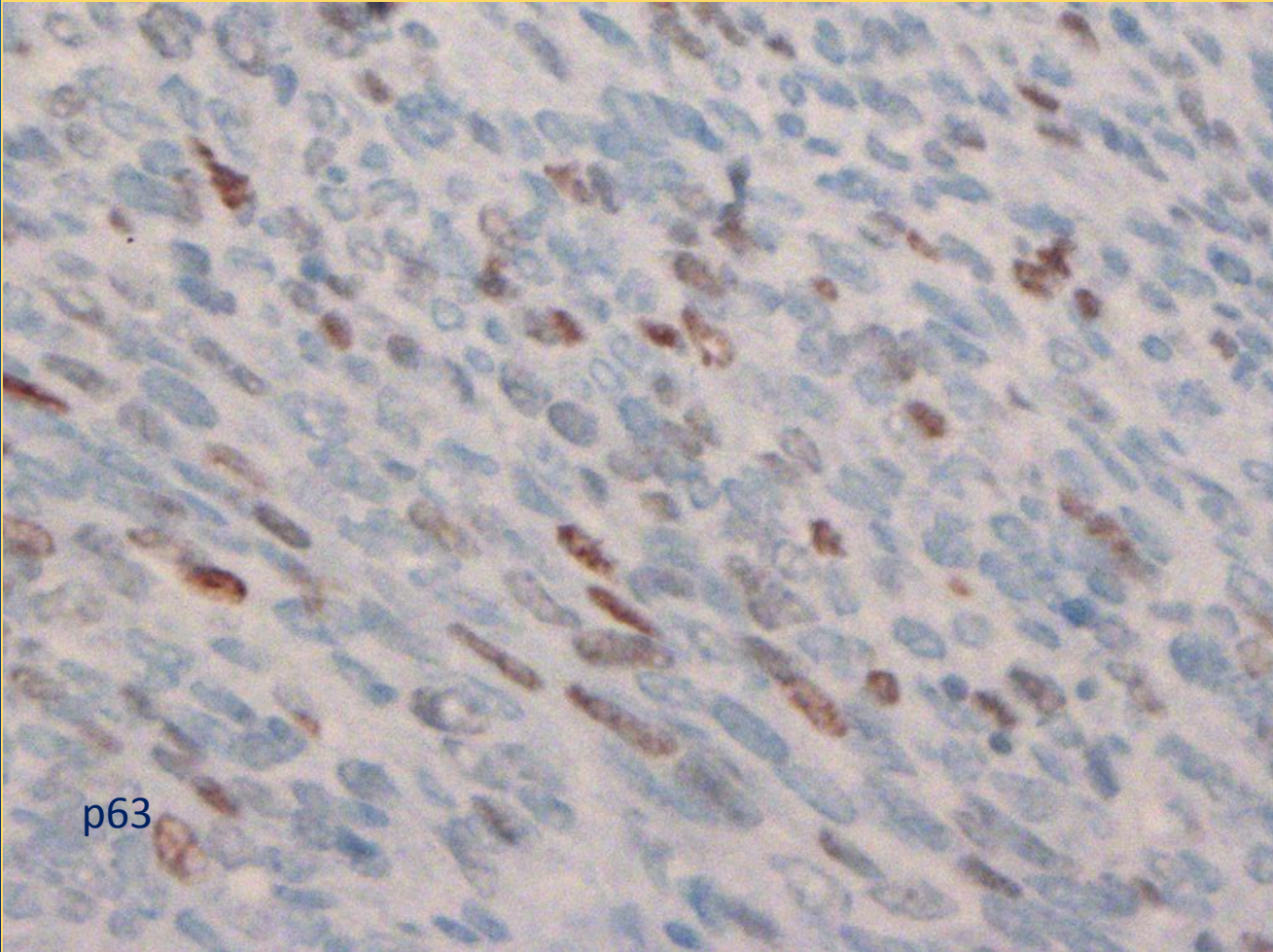
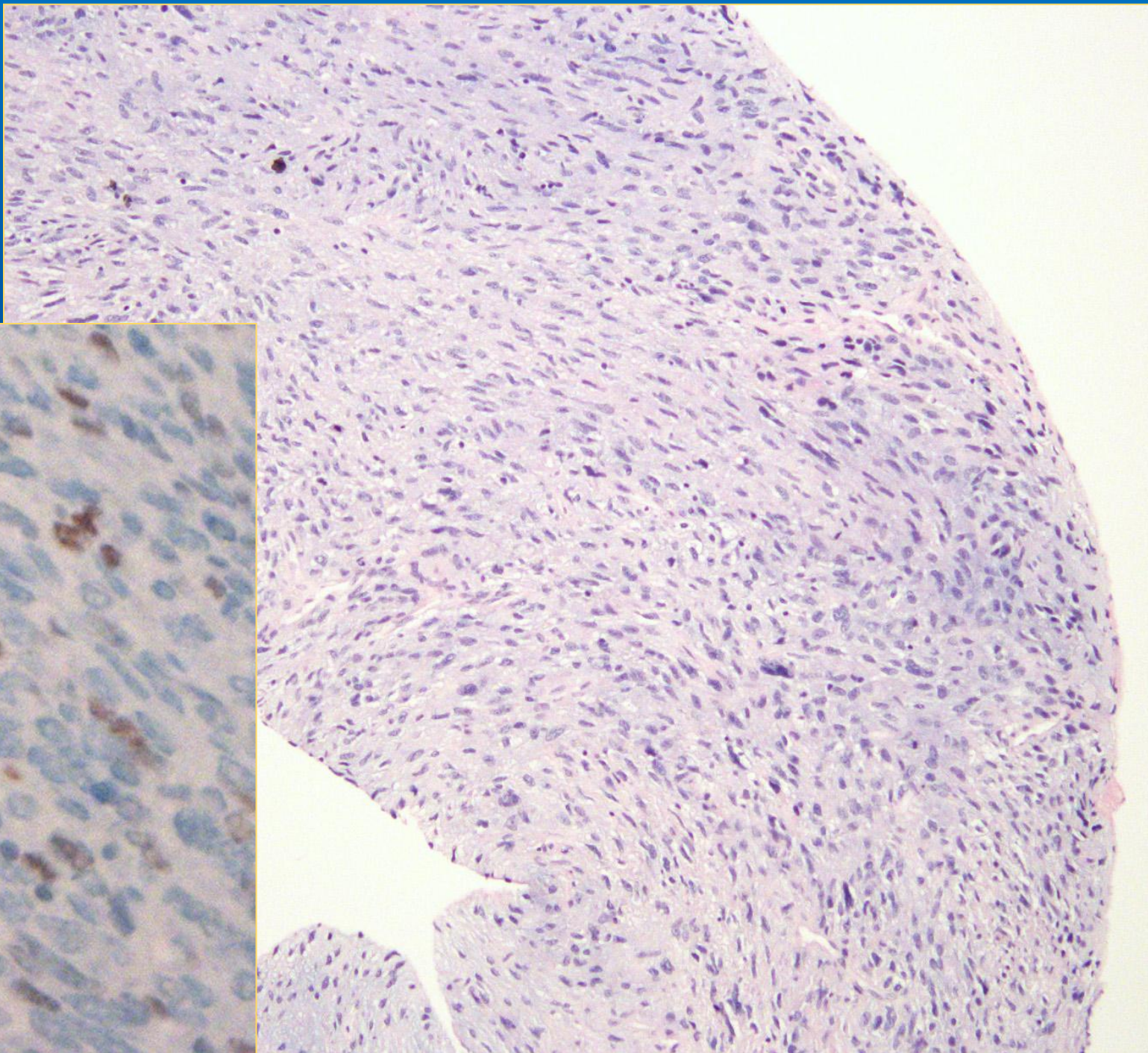
- Rarely have axillary nodal metastases
- More commonly metastasize to lungs
- Microscopic findings
 - Atypical spindle cells arranged in varied patterns
 - Fascicles with a herringbone appearance or storiform
 - Nuclear pleomorphism is usually moderate to high
 - Frequent mitotic figures
 - May entrap breast epithelium at the leading edge

Spindle cell carcinoma (Sarcomatoid carcinoma)

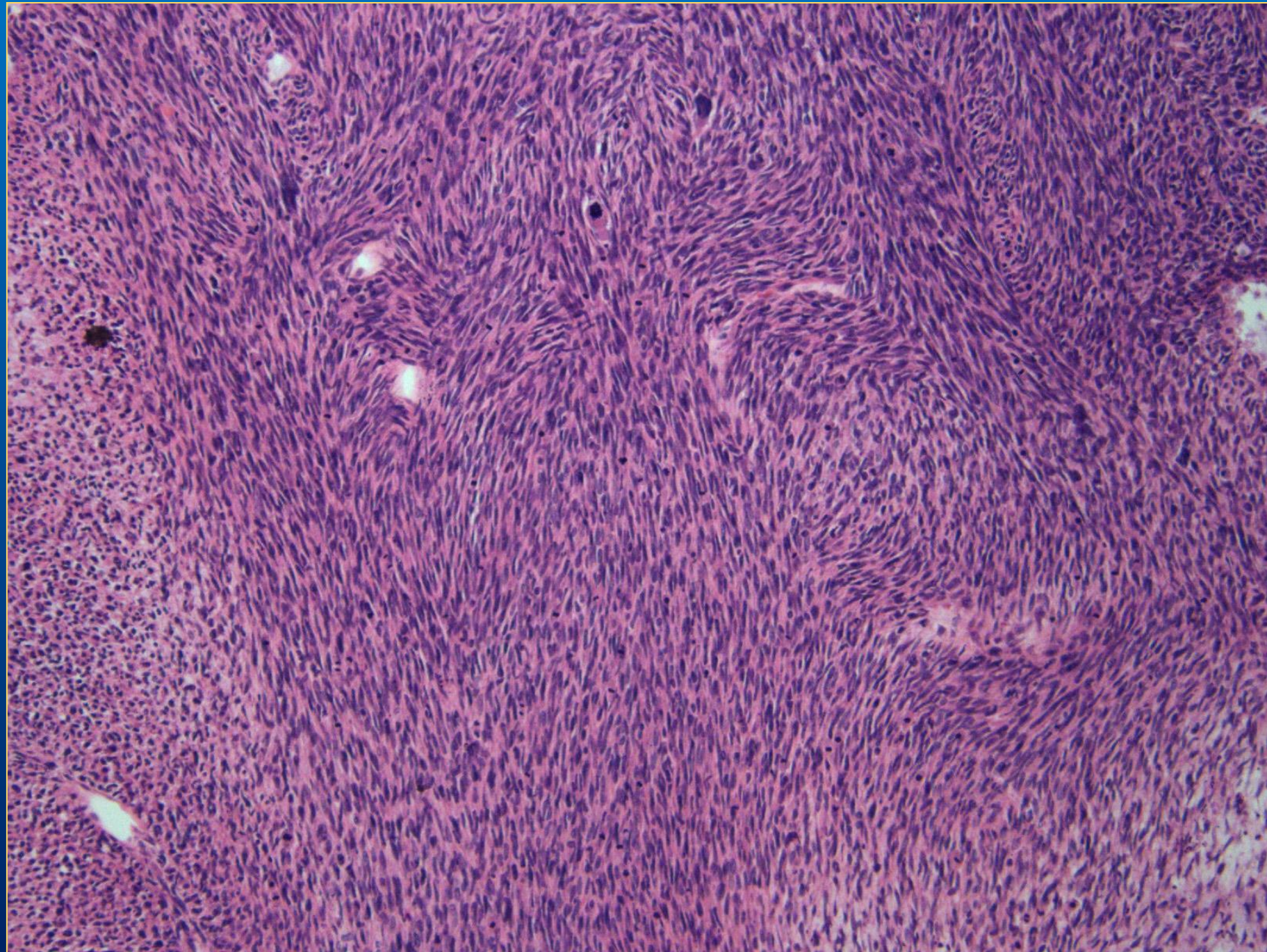
- No marker is expressed by all spindle cell carcinomas so it is important to use a panel of antibodies to both basal and luminal cytokeratins
 - Cytokeratin 14, cytokeratin 5/6, 34 β E12, Cam5.2, cytokeratin 7, MNF116 and AE1/AE3
 - p63
 - SMA+/-
 - Typically negative for ER, PgR, and HER2

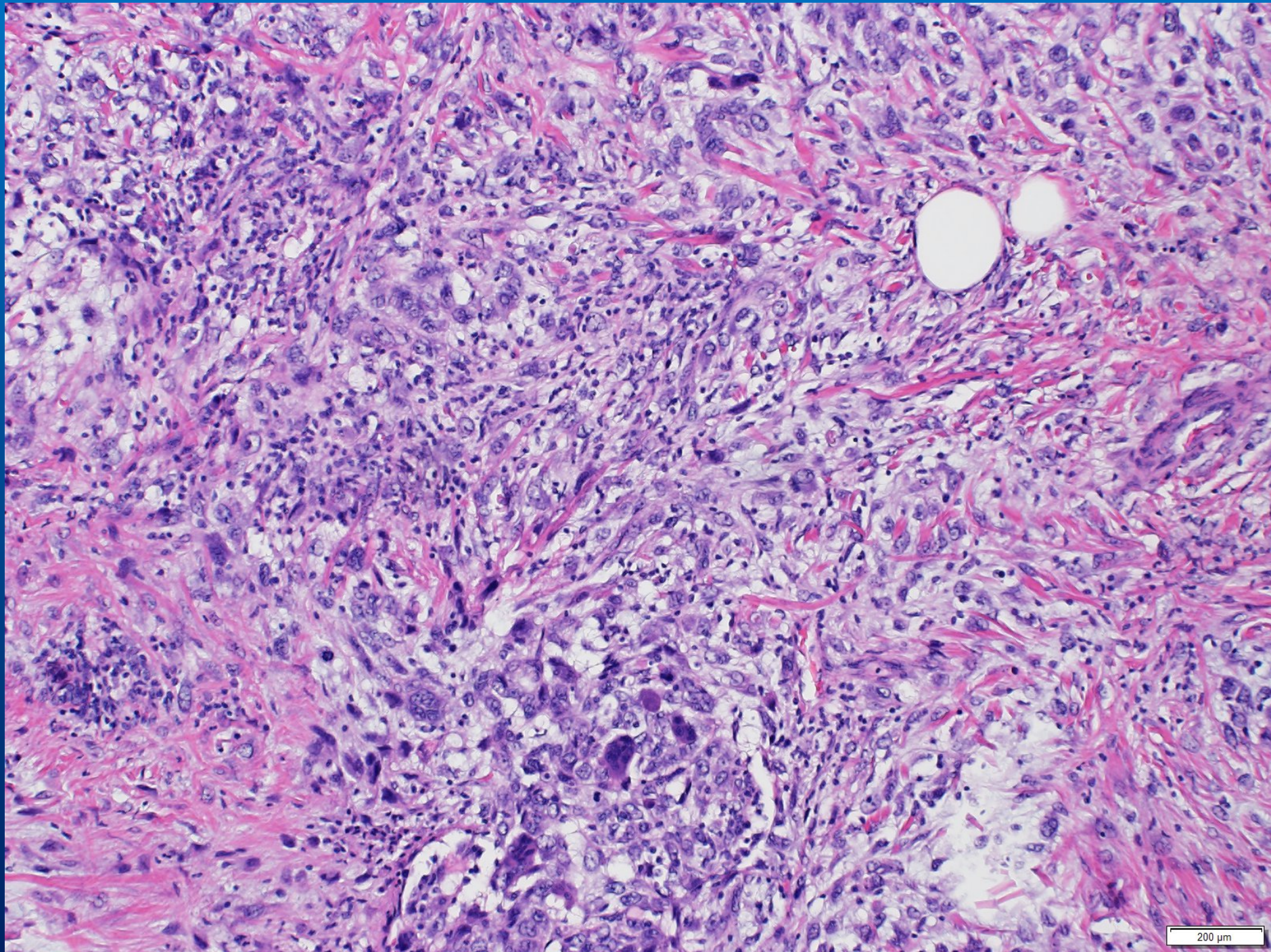
Metaplastic carcinoma: IHC pitfall

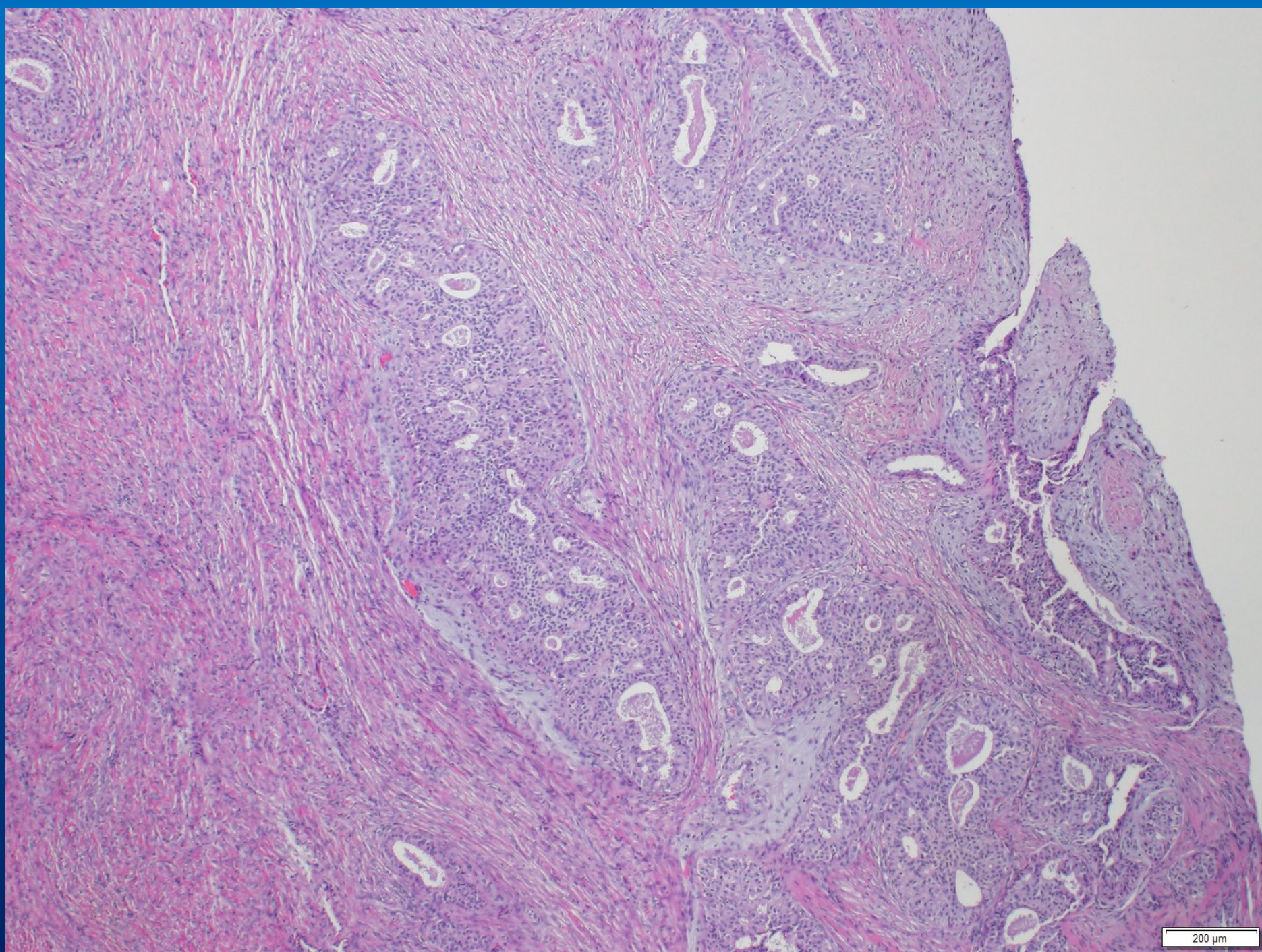
- When first evaluated in metaplastic carcinoma and phyllodes, p63 appeared sensitive and highly specific for metaplastic carcinoma
 - Koker et al: 189 invasive breast carcinomas (15 metaplastic carcinomas, 10 phyllodes tumors and 5 pure sarcomas of the breast)
 - p63 was strongly expressed in 13 of 15 metaplastic carcinomas (86.7%); phyllodes tumors and sarcomas were negative for p63 expression
 - Sensitivity and specificity of 86.7% and 99.4%, respectively
- More recently, Cimino-Mathews et al identified expression of focal p63, p40, and cytokeratin (AE1/AE3, Cam5.2, 34 β E12) in malignant PT but not in borderline or benign PT



p63

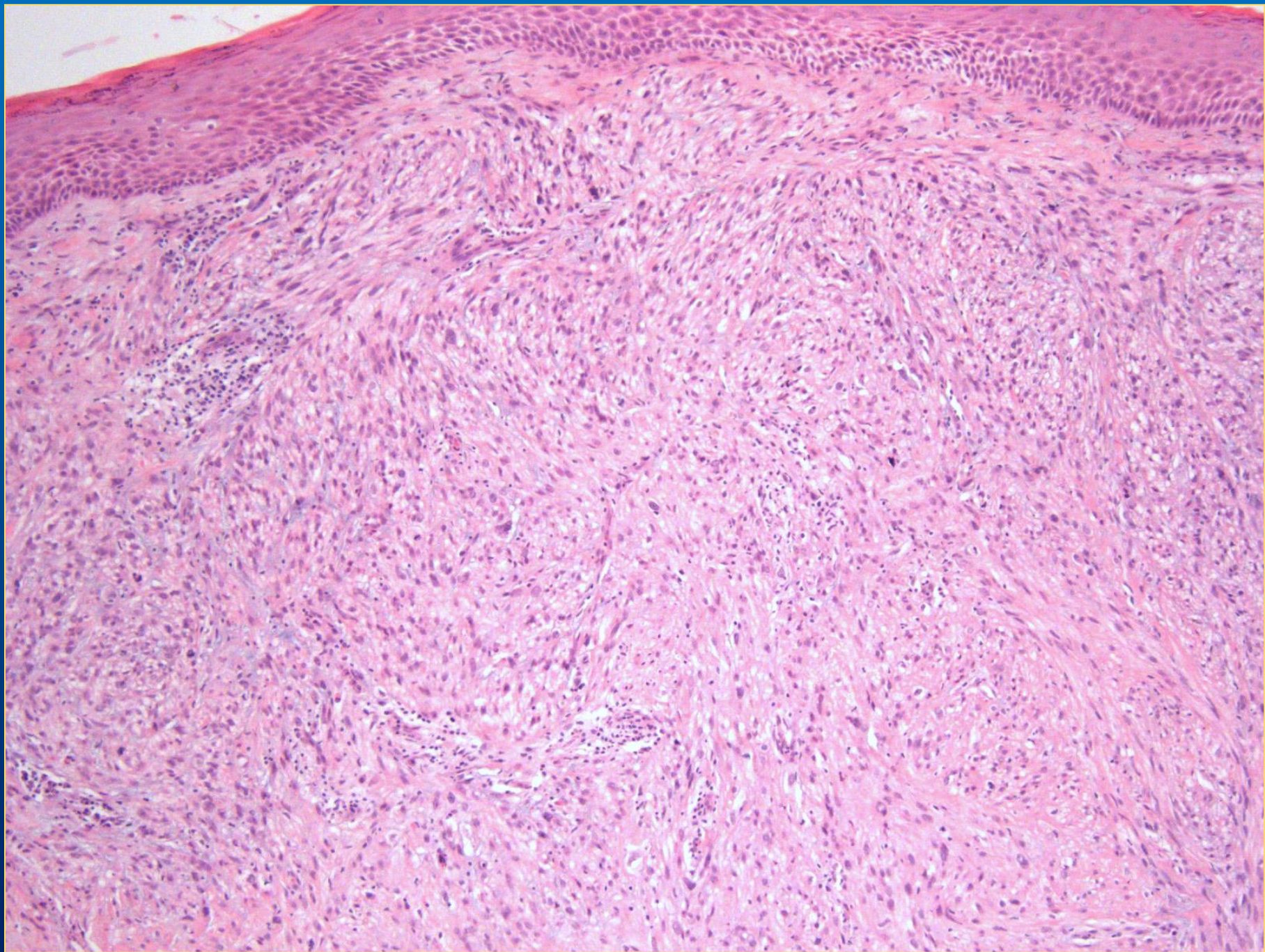


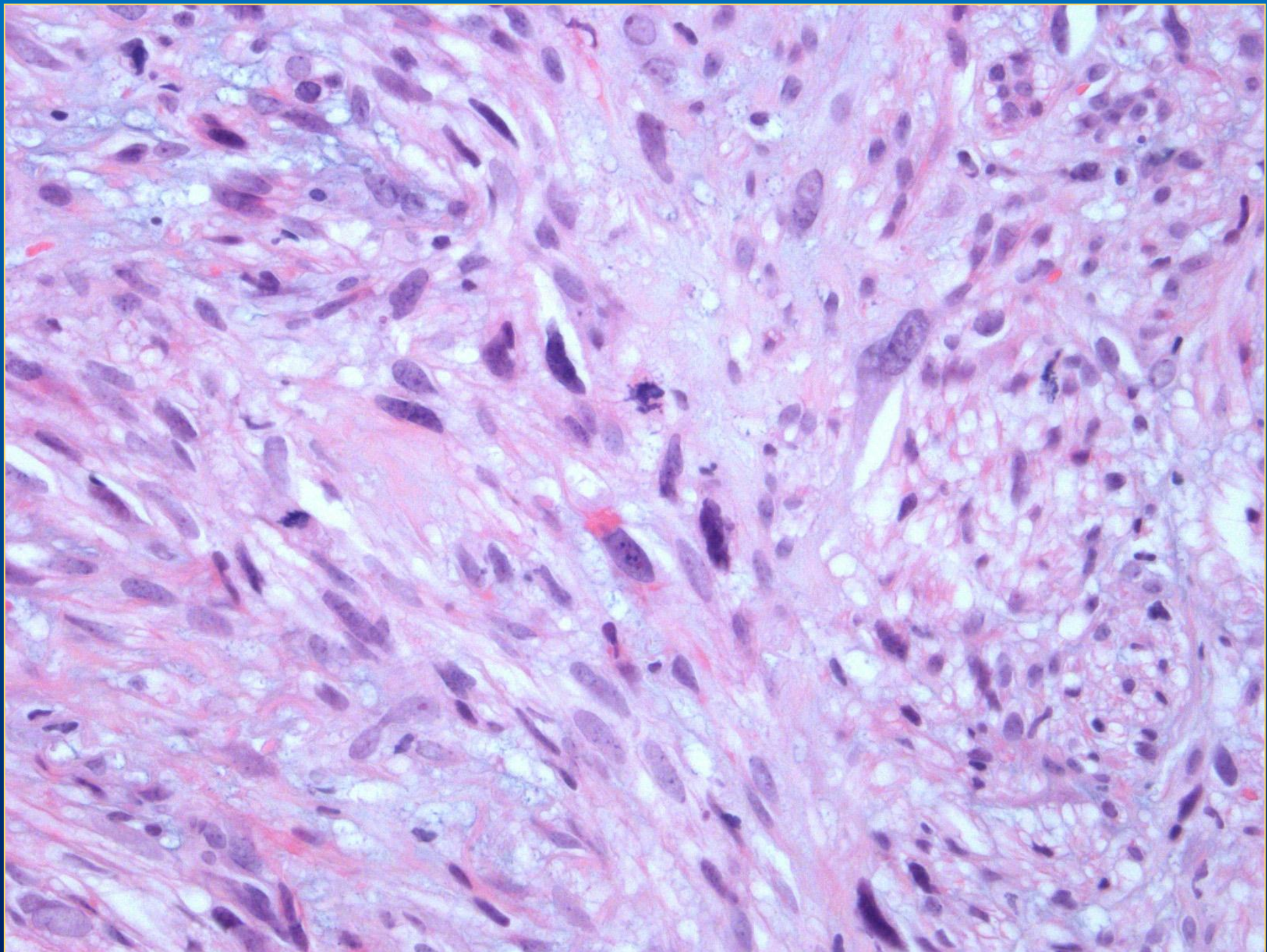


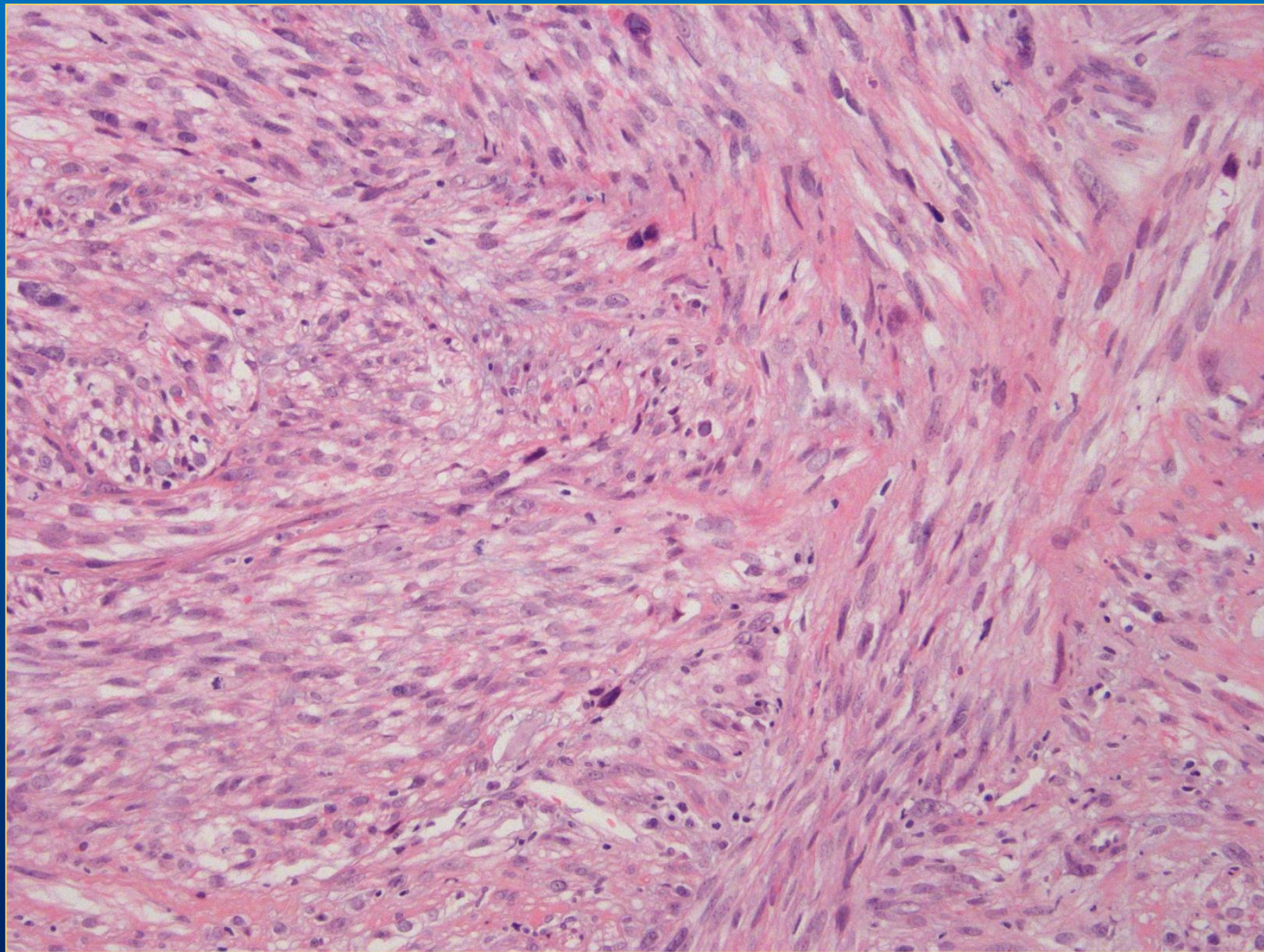


Case in Point

- A 55 year old women presented with a right breast palpable 3 cm mass and overlying skin changes. Given the location of the mass, a punch biopsy was performed.







Immunoprofile of this lesion on biopsy

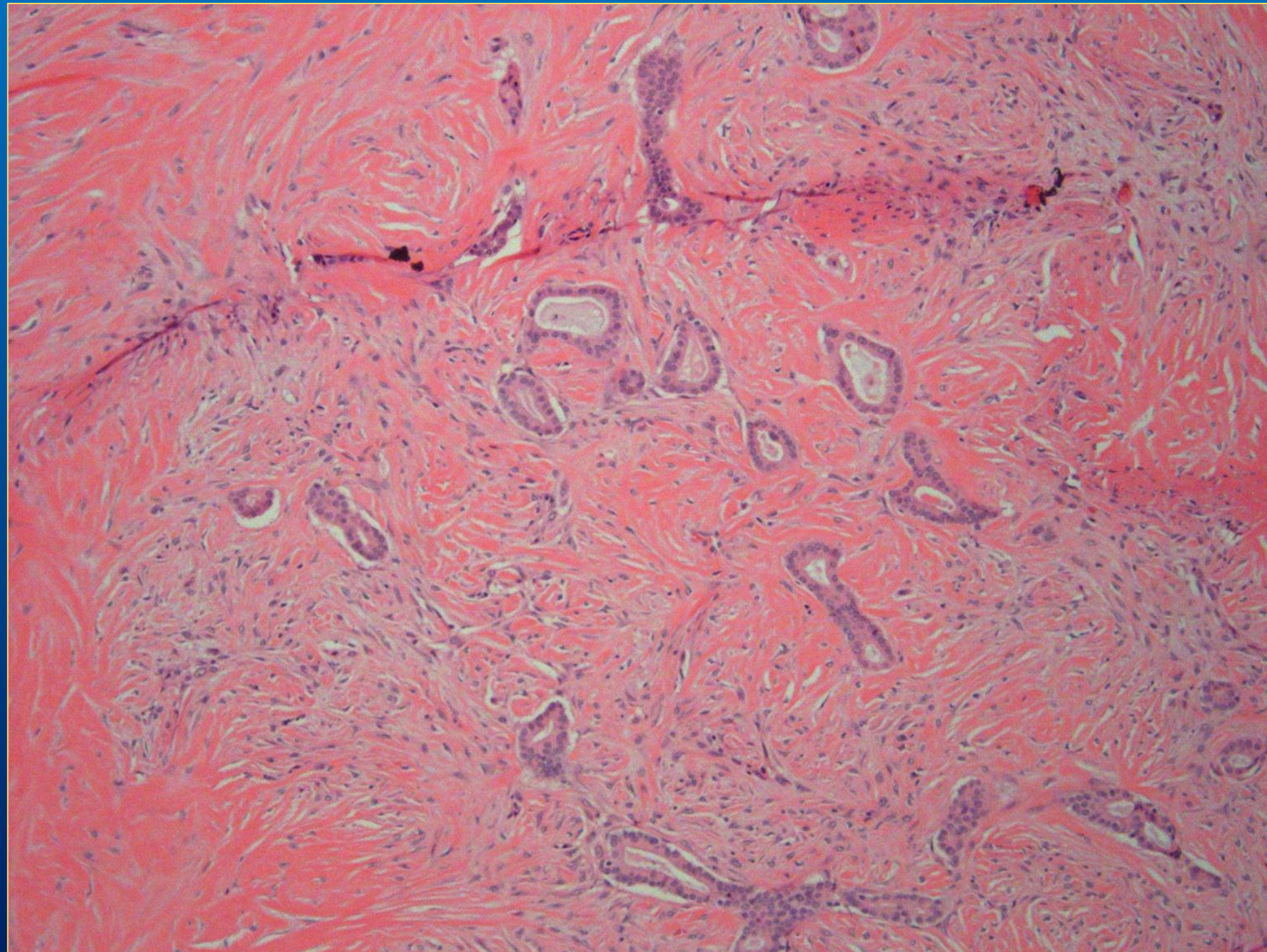
- Cytokeratin AE1/AE3, cytokeratin 5/6 and p63 negative
- SMA focally positive

Based on the punch biopsy.....

- Malignant spindle cell neoplasm, favor leiomyosarcoma

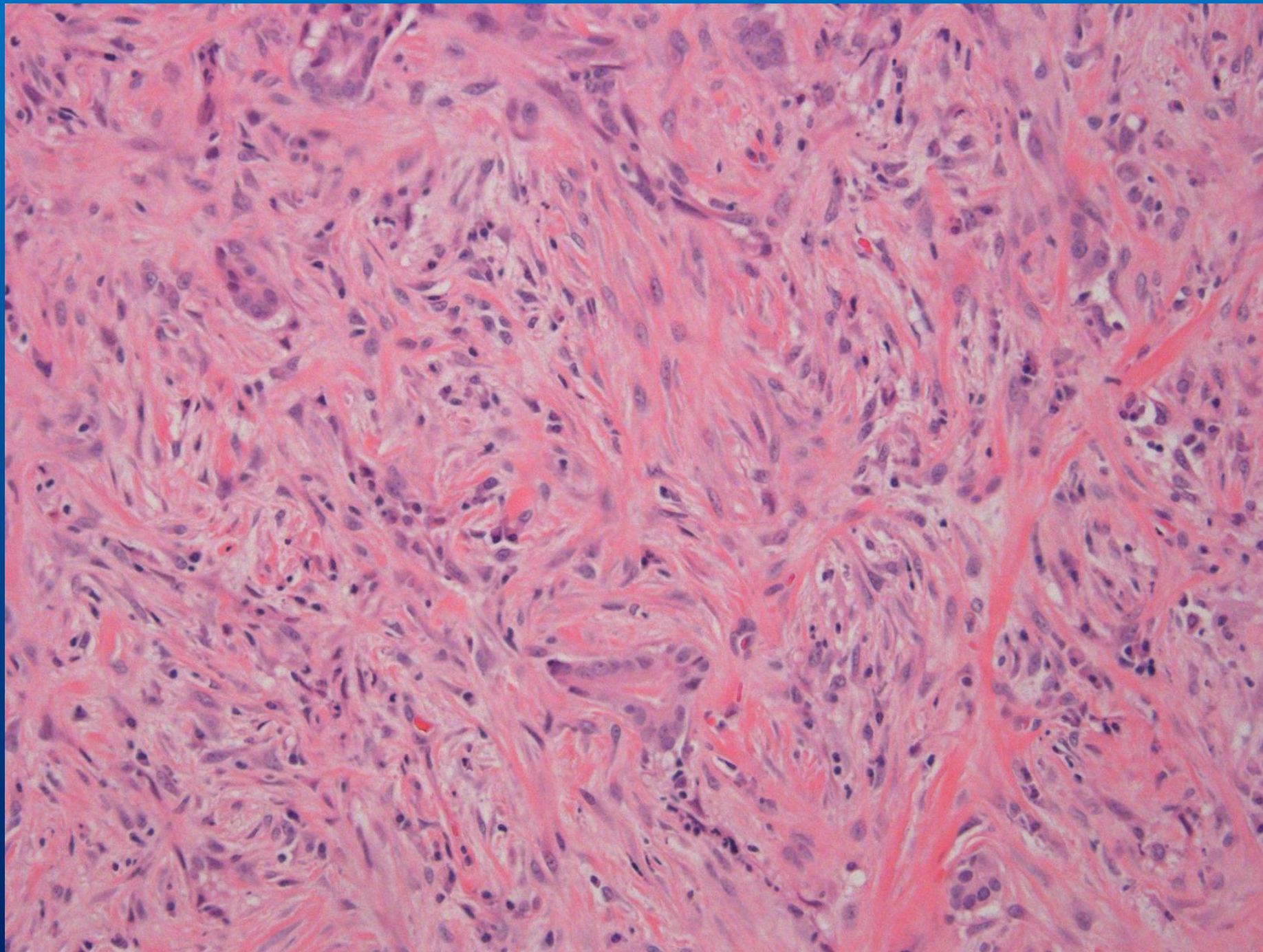
Follow up resection:

- After extensive sampling, the majority of the lesion was spindled, however a few foci of glandular differentiation were found



Final diagnosis:

Metaplastic carcinoma



Primary Sarcoma

- Before diagnosing a primary sarcoma of the breast, consider and exclude
 - Metaplastic carcinoma: IHC and extensive tumor sampling to exclude in situ or invasive carcinoma
 - Heterologous sarcomatous elements in phyllodes tumor (PT) can be prominent and the epithelial components can be relatively inconspicuous
 - Metastasis?
- Primary sarcomas
 - Arise from interlobular mesenchymal elements
 - Subclassified according to their growth patterns and histogenesis
 - Most common primary sarcoma of the breast is angiosarcoma, followed by liposarcoma, leiomyosarcoma, pleomorphic undifferentiated sarcoma

Primary sarcoma

- Very rare, SEER data reports the annual incidence as 4.6 cases per 1,000,000 women
- Previous history of radiation increases the risk for development of angiosarcoma and pleomorphic undifferentiated sarcoma
- Complete excision is crucial for treatment
 - Presence of residual disease after initial treatment had a 10 year probability of local control and of disease free survival of 0%

Angiosarcoma of the Breast

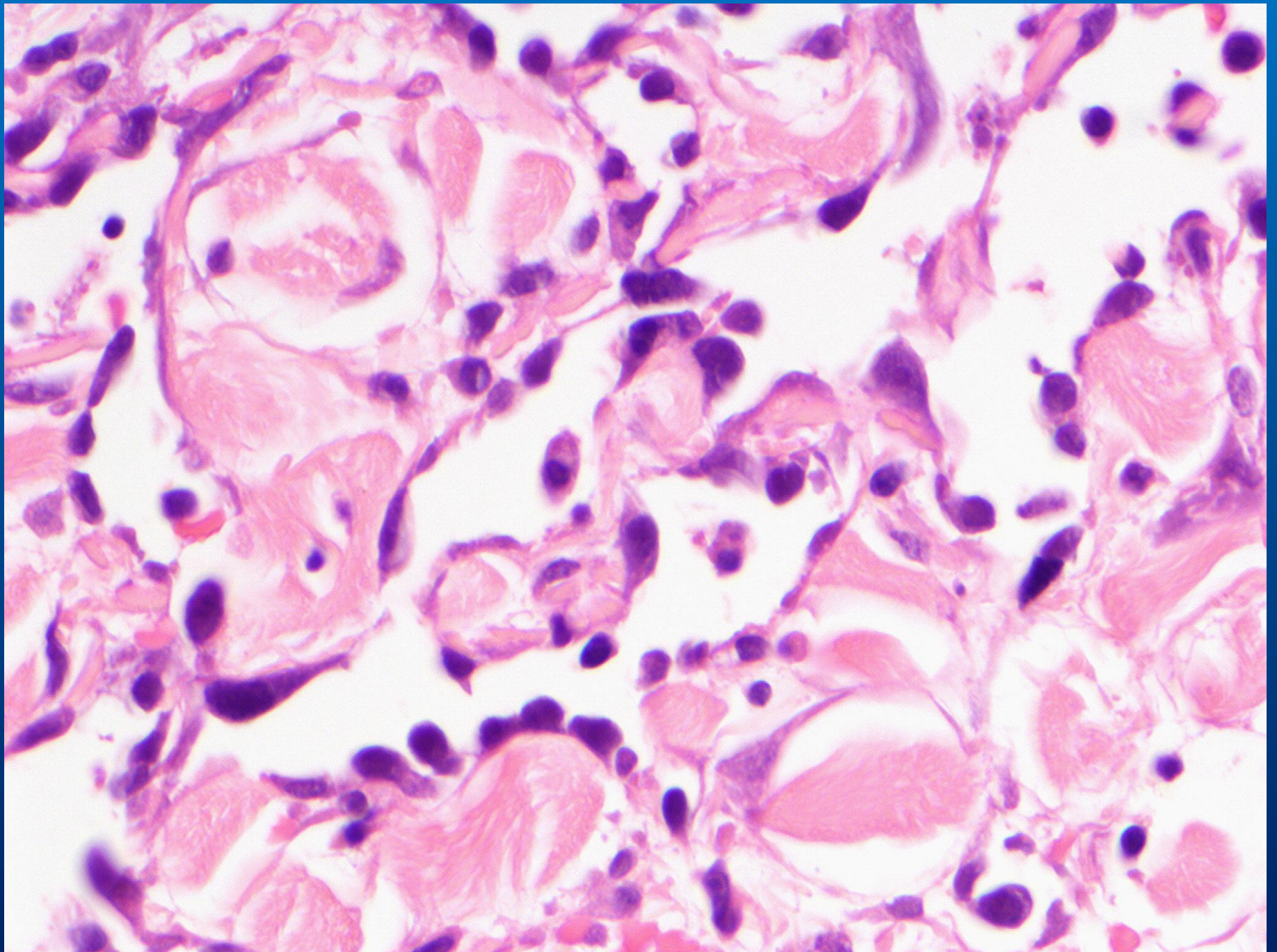
- Primary angiosarcoma
 - Mean age, 34 years
 - No identified pre-disposing factors
 - Involves breast parenchyma and presents as a painless mass
 - Concurrent bilateral angiosarcoma is very uncommon and involvement of the contralateral breast usually represents metastatic spread
- Secondary (iatrogenic) angiosarcoma
 - Older patients in setting of breast cancer
 - Stewart-Treves syndrome
 - Post-radiation cutaneous angiosarcoma

Primary Angiosarcoma

- Histologic features
 - Low grade: open anastomosing vascular channels that infiltrate into lobules, endothelial cells are hyperchromatic with small nucleoli, mitotic figures are scarce, no significant layering of endothelial cells, no necrosis or blood lakes
 - Intermediate grade: anastomosing vascular channels that infiltrate into lobules, endothelial cells are hyperchromatic with small nucleoli, mitotic figures are scarce, foci of multilayering of endothelial cells, mitotic activity noted within multilayered endothelium, no necrosis or blood lakes
 - High grade: anastomosing vascular channels that infiltrate the breast parenchyma, markedly atypical endothelial cells with areas of solid growth, prominent endothelial cell layering, numerous mitoses with necrosis and blood lakes

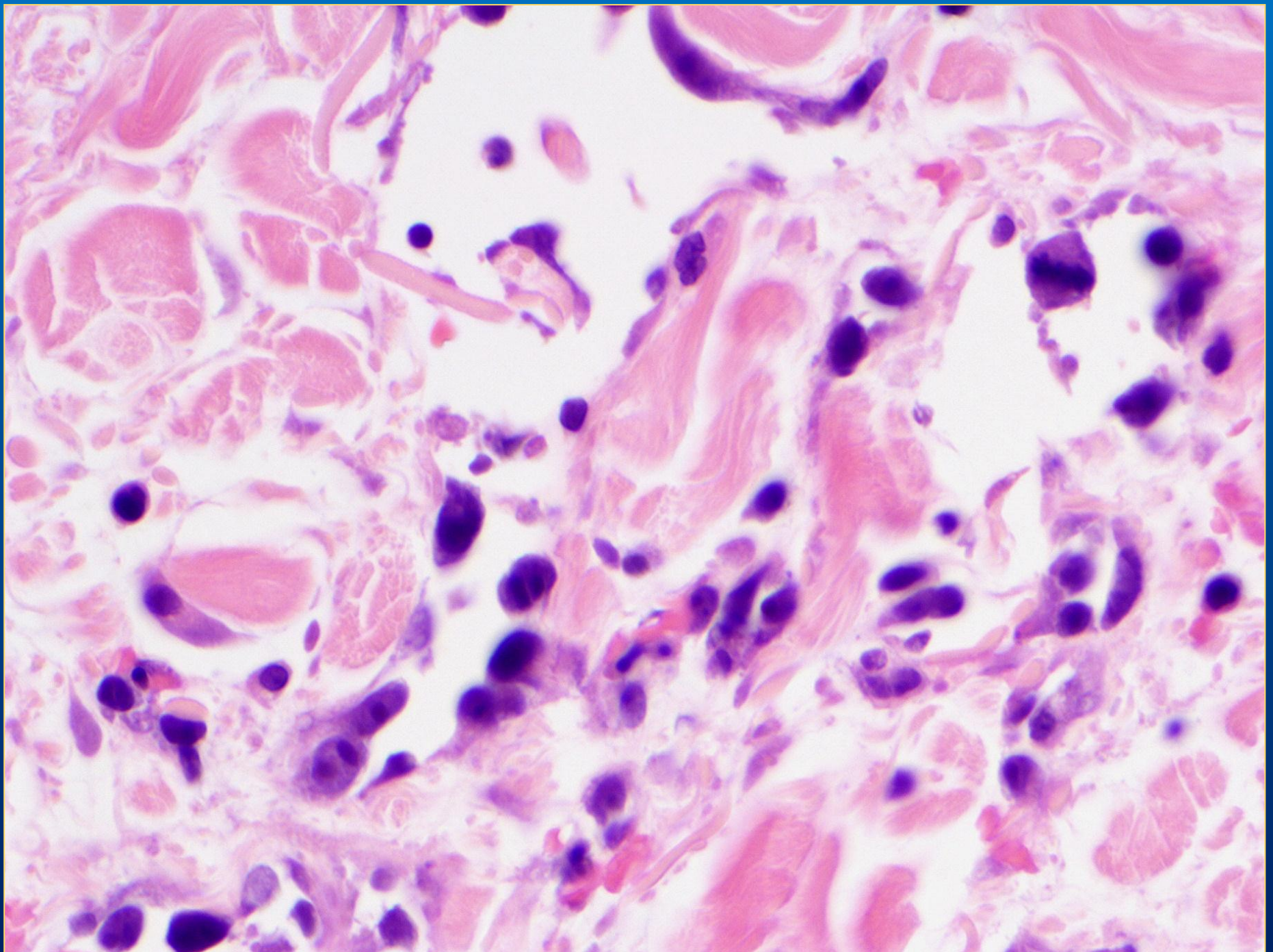
Angiosarcoma: Low grade

- Vasoformative proliferation dissecting through the stroma
- Endothelial cell atypia with hyperchromatic nuclei and high nuclear to cytoplasmic ratios

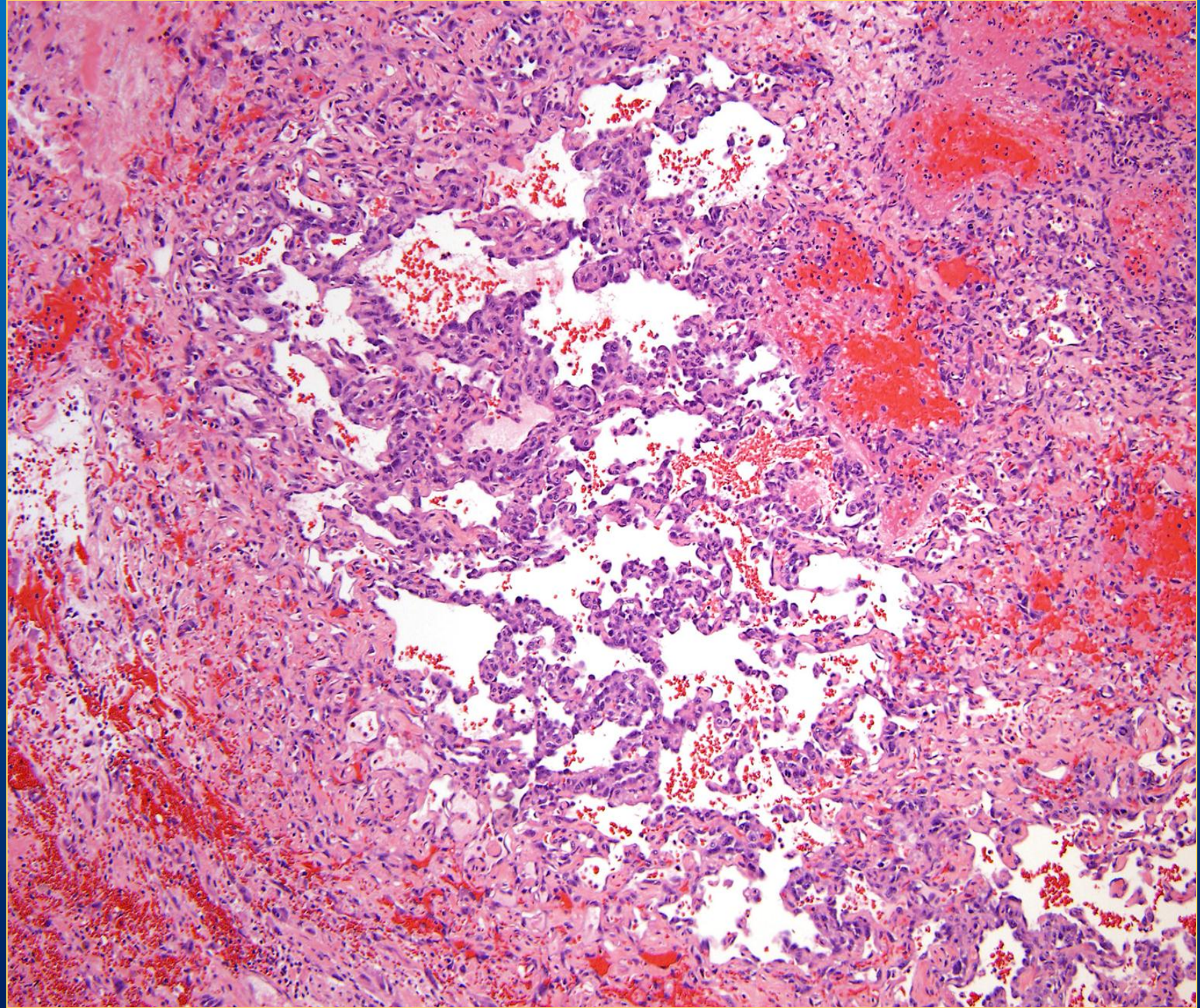


Angiosarcoma: Low grade

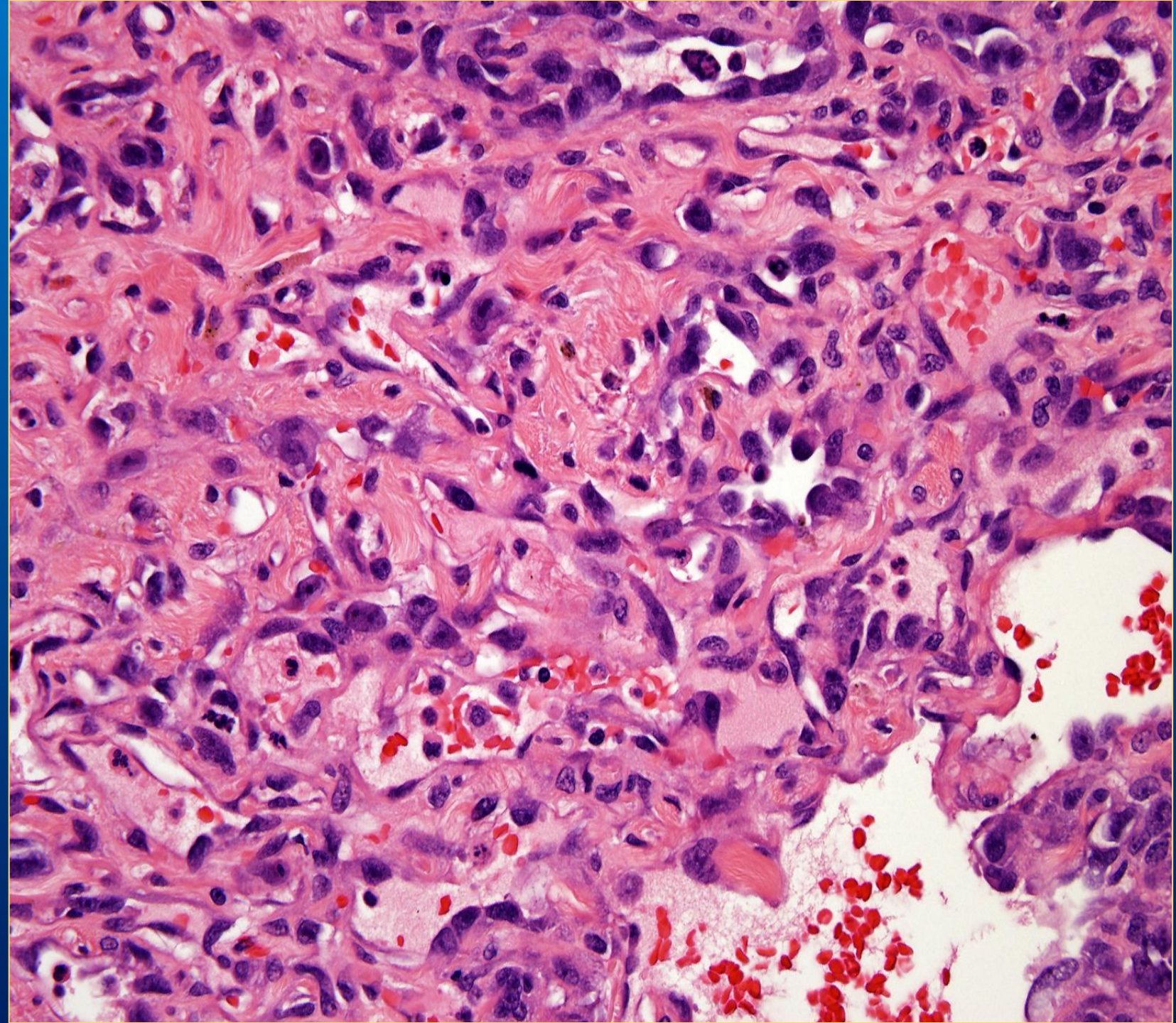
- Rare endothelial cell mitotic figure



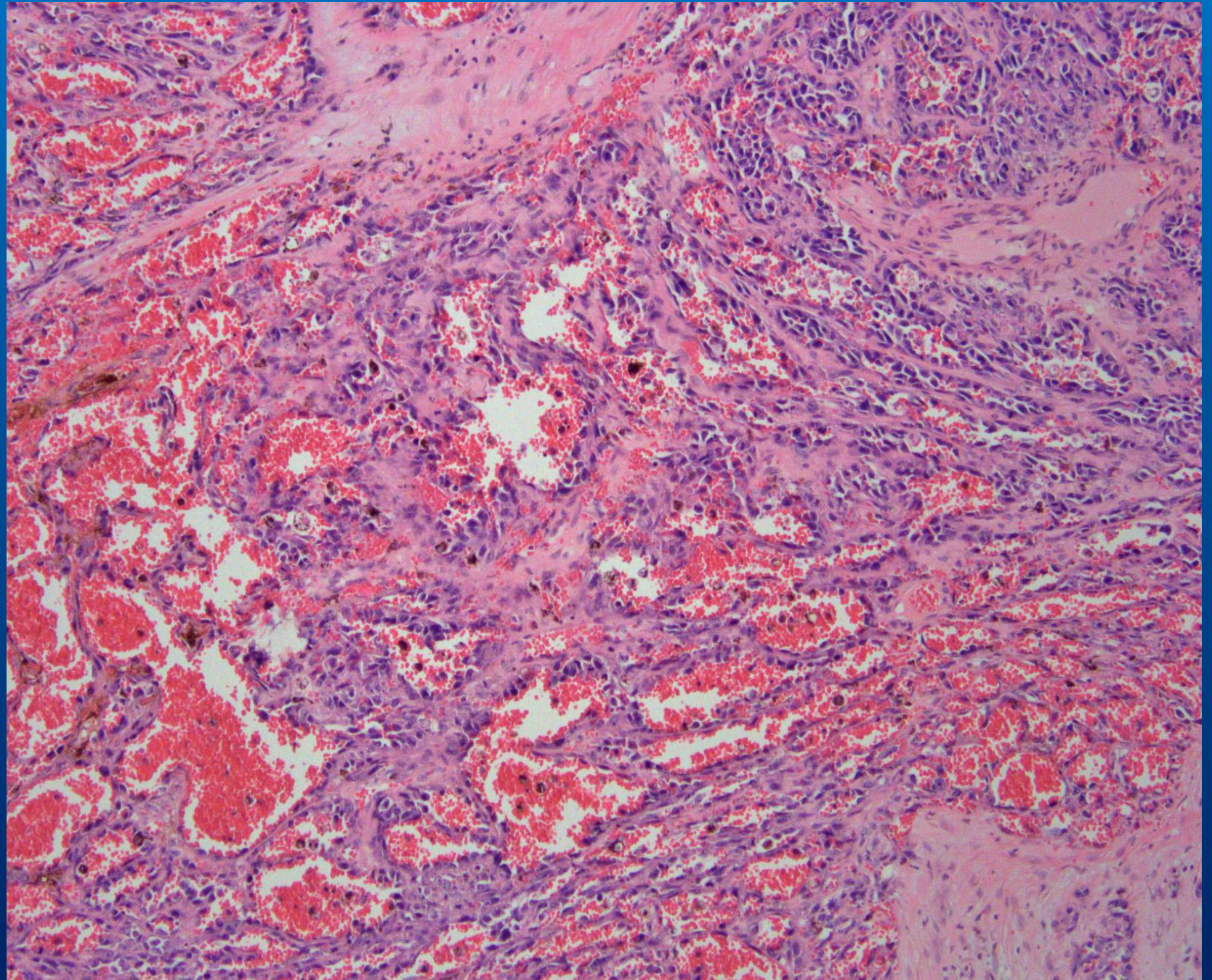
Angiosarcoma: Intermediate
grade



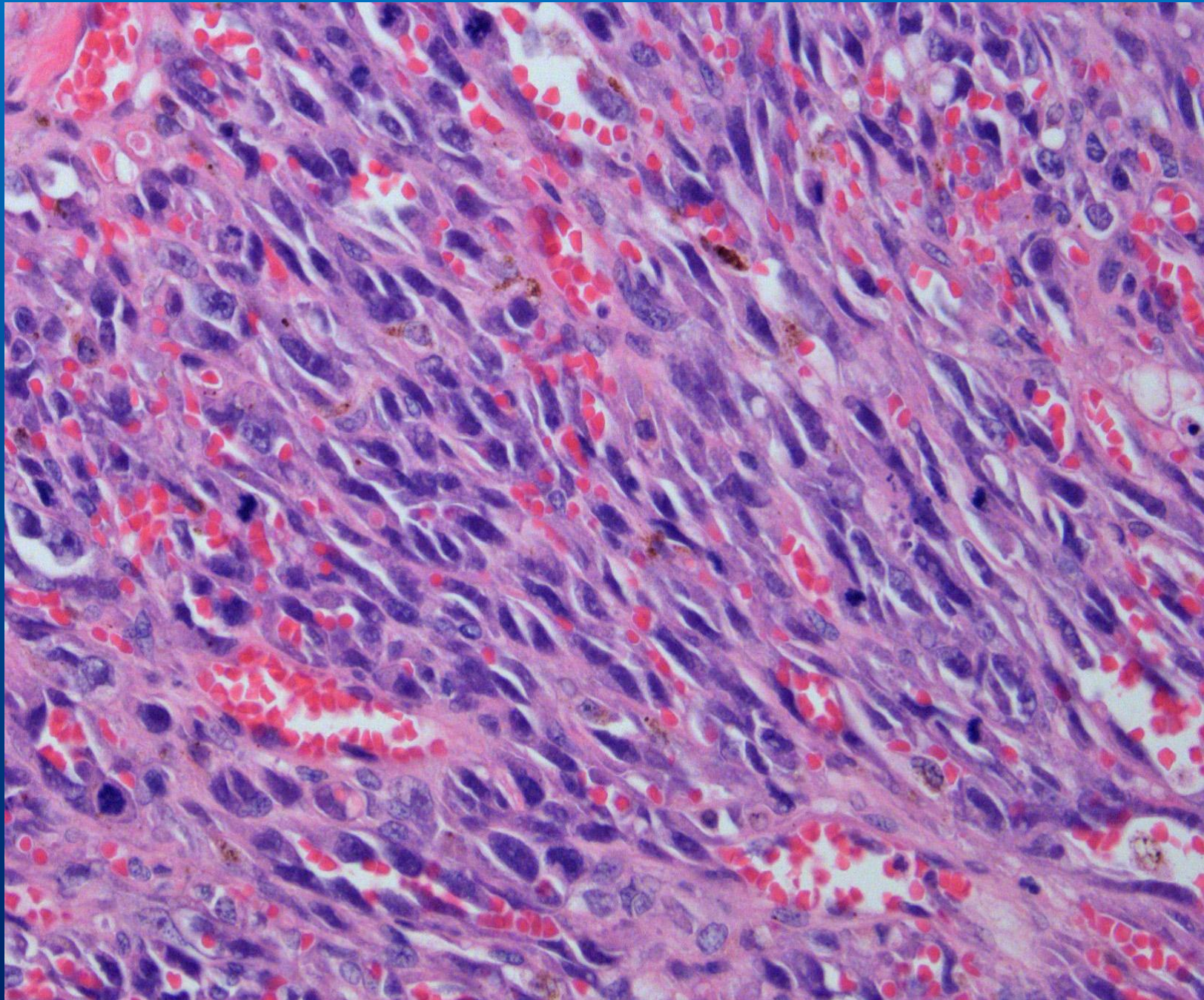
Angiosarcoma: Intermediate
grade



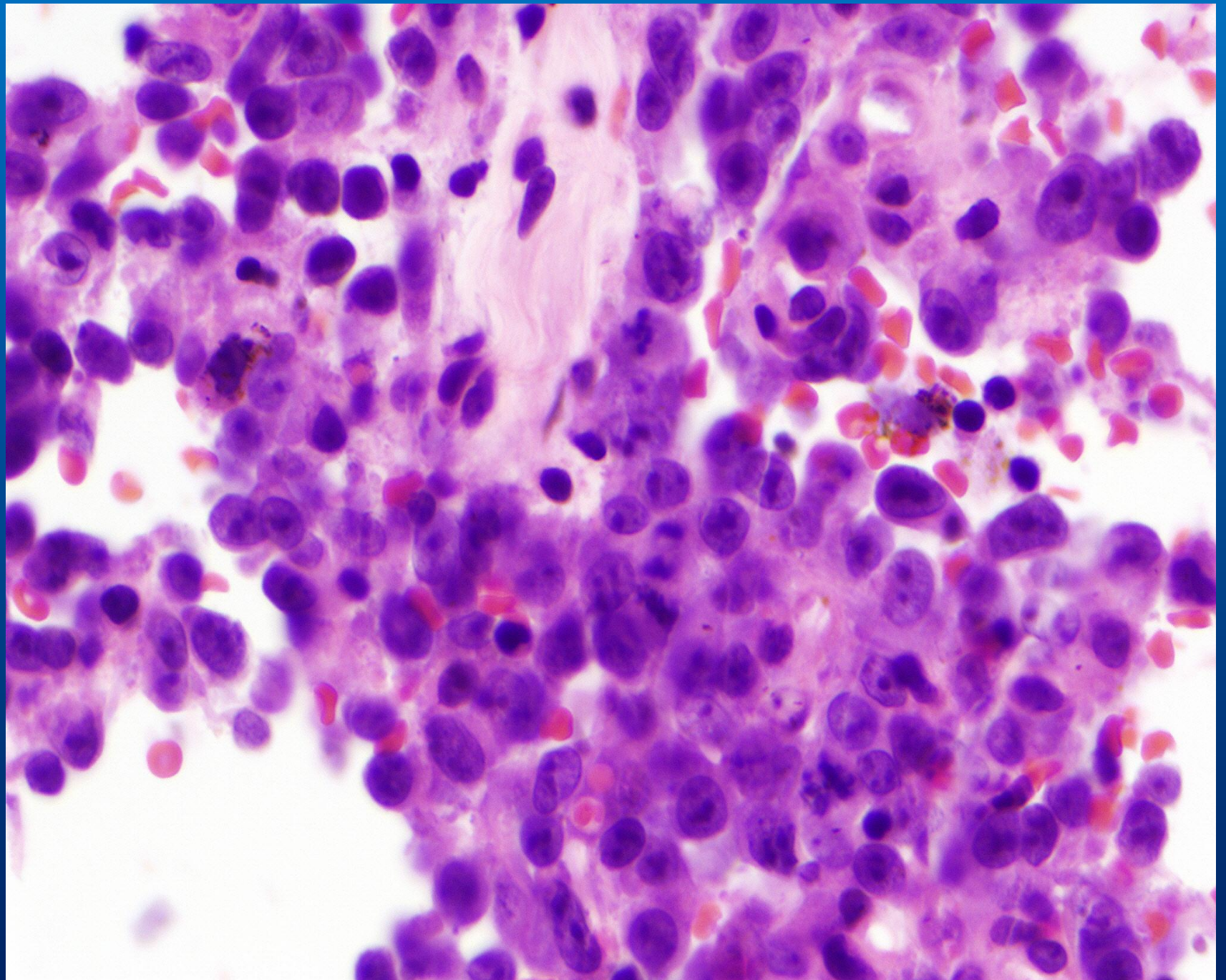
Angiosarcoma: High grade



Angiosarcoma: High grade



Angiosarcoma: High grade



Angiosarcoma: To grade or not to grade?

- Rosen text talks at length about grade and the correlation with different outcomes
 - Median duration of DFS correlated with tumor grade
 - Low grade >15 years, intermediate >12 years, high grade 15 months
- Nascimento et al suggest that grade in primary mammary angiosarcoma, similar to soft tissue and skin, shows no correlation with the likelihood of local recurrence, distant metastasis, and death

Rosen et al. Cancer 1988;62:2145-2151

Nascimento A, et al. Am J Surg Pathol 2008;32:1896–1904

Angiosarcoma

- Total mastectomy is recommended
- Axillary nodal dissection is not indicated unless clinically apparent; lymph node mets identified in fewer than 10% of cases
- Role of XRT and systemic chemotherapy?

Phyllodes tumor, borderline and malignant

- In the differential diagnosis of spindle cell lesions of the breast, especially on core needle biopsy with limited sampling
 - Sarcomatous overgrowth
- Represent <1% of primary breast tumors
- Most common in middle aged females
 - Average age at presentation is 40-50
- Present as a solitary, painless lobulated mass
- Believed to be derived from periductal stroma
- On imaging, PT is typically rounded and well demarcated

WHO 2012 Histologic Features of PT

	Benign 60-75%	Borderline 15-20%	Malignant 10-20%
Tumor border	Well defined	Well defined, focally permeative	Permeative
Stromal overgrowth	Absent	Absent, very focal	Often present
Stromal cellularity	Mild, non uniform	Moderate, non uniform or diffuse	Marked and diffuse
Stromal atypia	Mild or none	Mild or moderate	Marked
Mitotic Figures (per 10 HPF)	Few, <5 per 10 HPF	Usually frequent, 5-9 per 10 HPF	Numerous, ≥ 10 per 10 HPF
Malignant heterologous elements	Absent	Absent	May be present

Tan, PH et al. WHO Classification of Tumours of the Breast. 2012 While these features are often observed in combination, they may not always be present simultaneously. Presence of malignant heterologous element qualifies designation as a malignant phyllodes tumor, without requirement for other histological criteria.

Stanford

- Adverse features
 - Stromal overgrowth
 - High mitotic index (>10 /10 hpf)
 - Sarcomatous stroma
 - stromal nuclear pleomorphism
 - atypia
 - Infiltrative margin

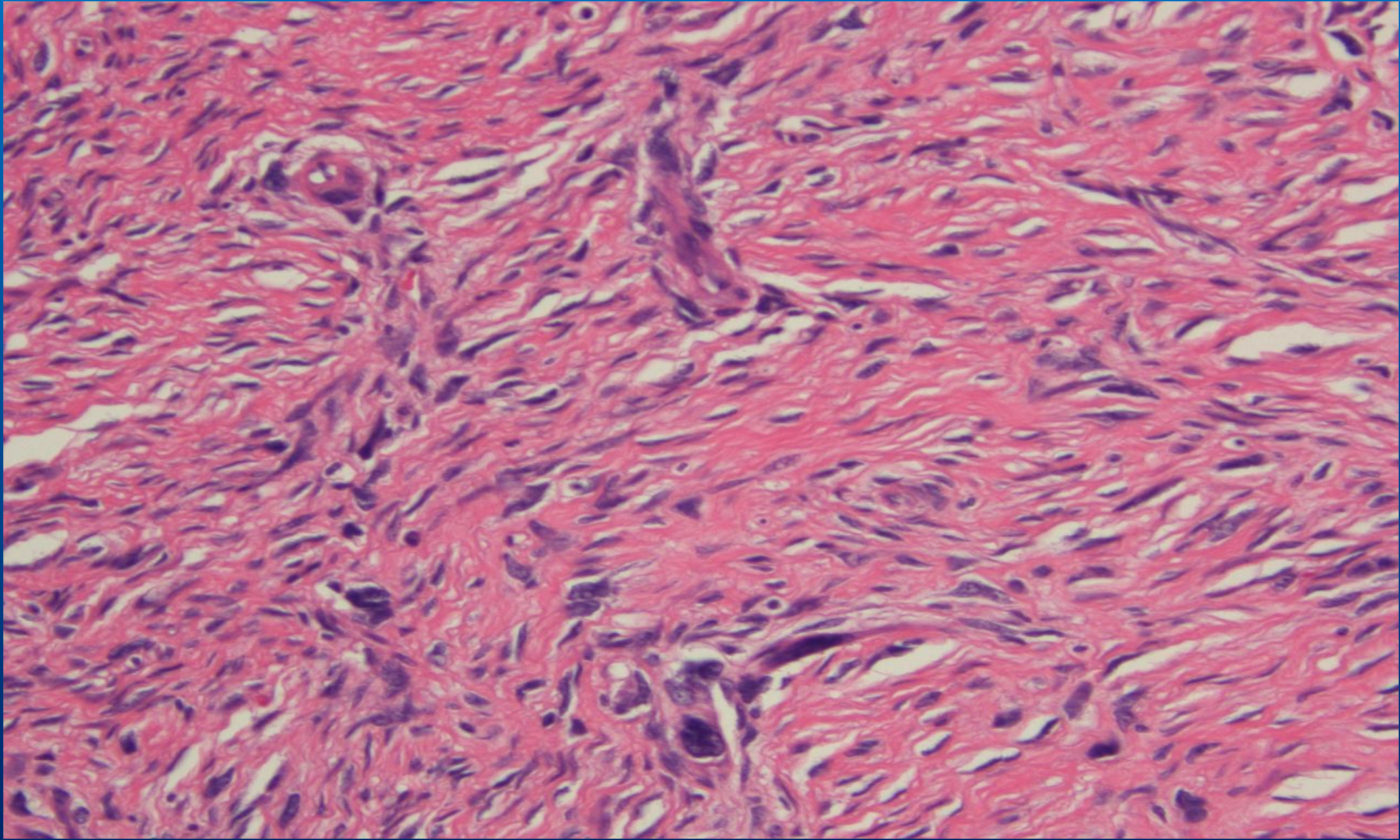
Stanford

- Benign
 - No adverse features
- Borderline
 - One or more adverse features but does not meet criteria for malignant
- Malignant
 - High mitotic index and sarcomatous stroma OR
 - Stromal overgrowth plus one of the above

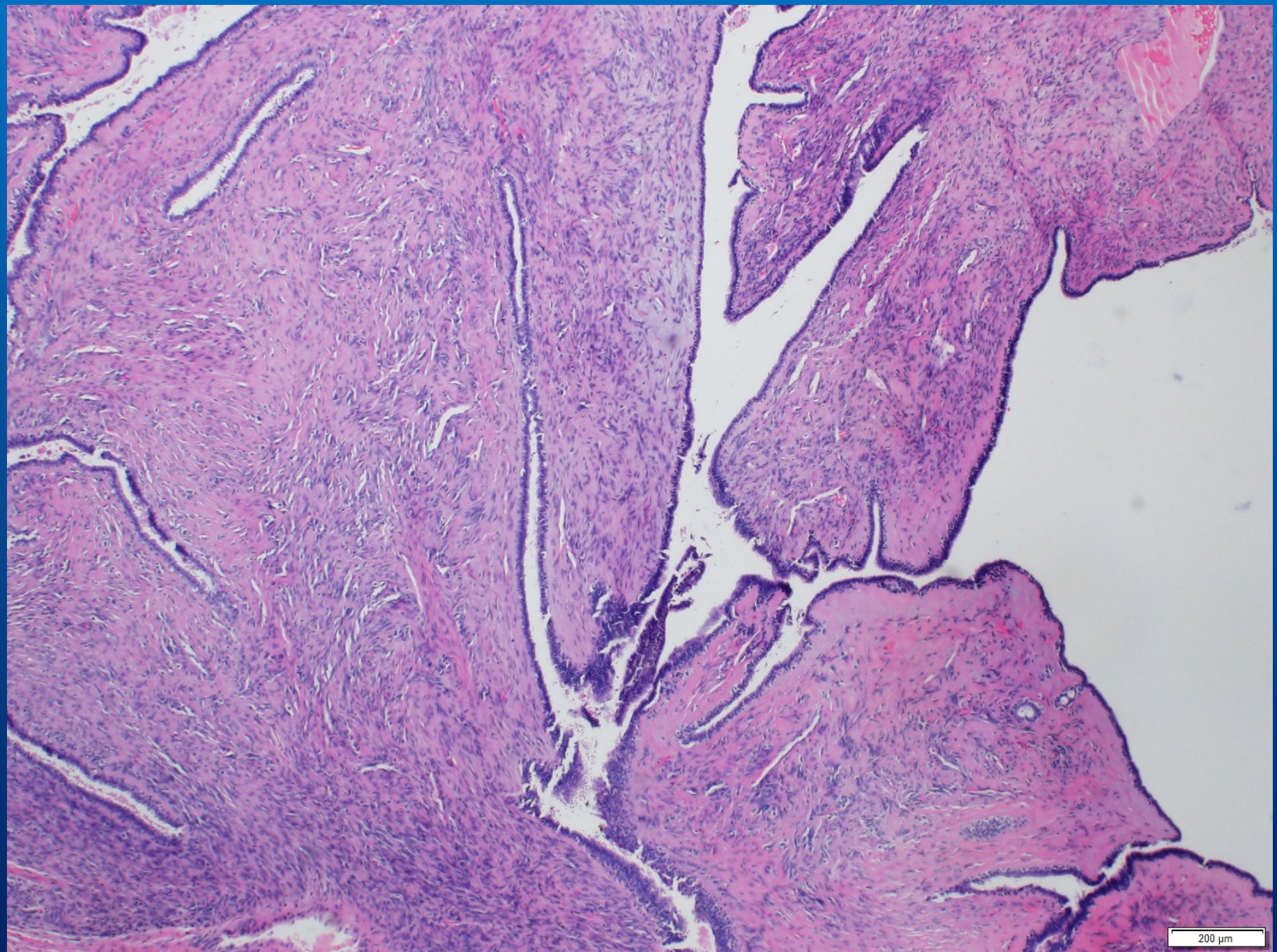
Benign PT



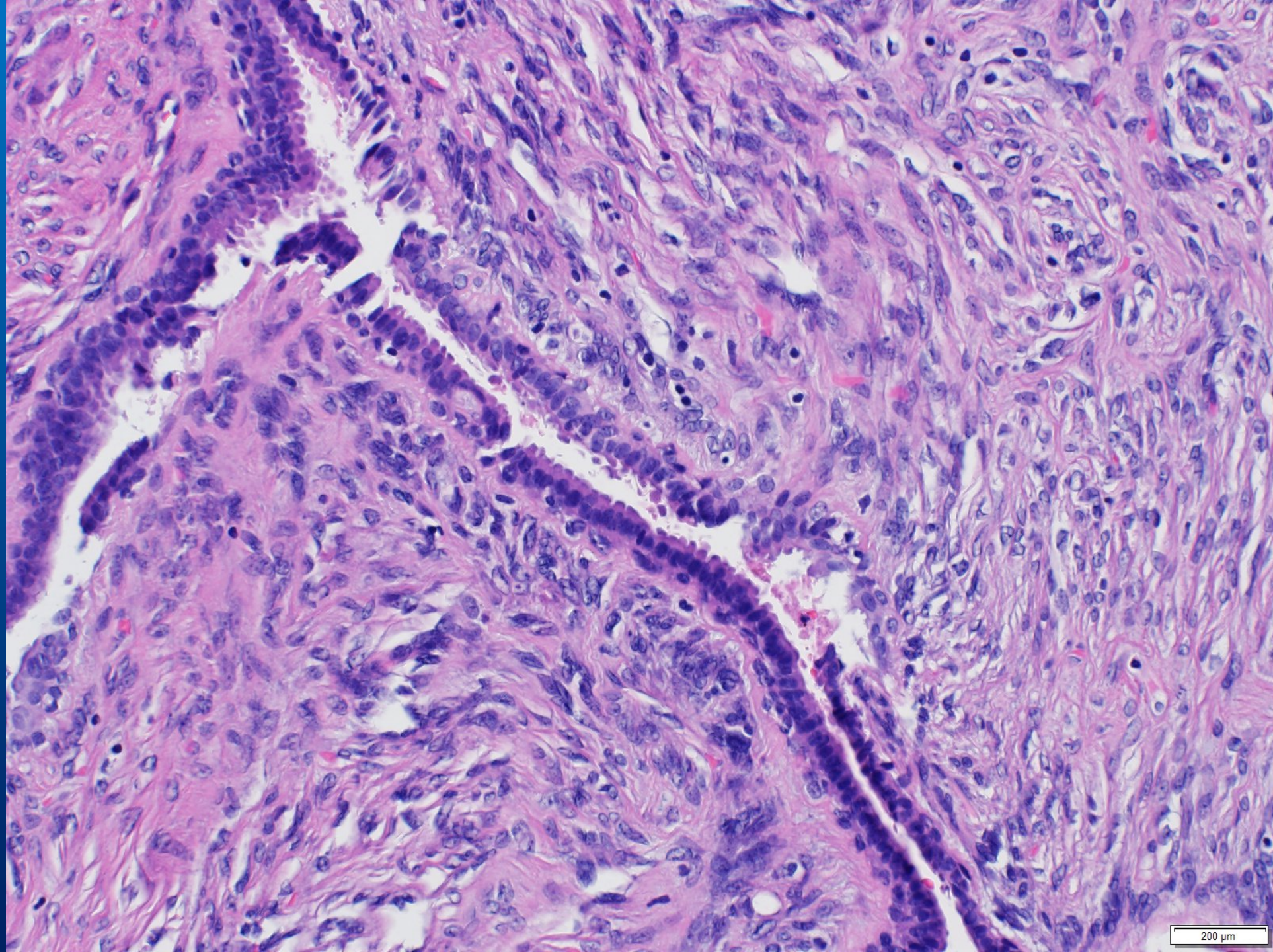
Benign PT



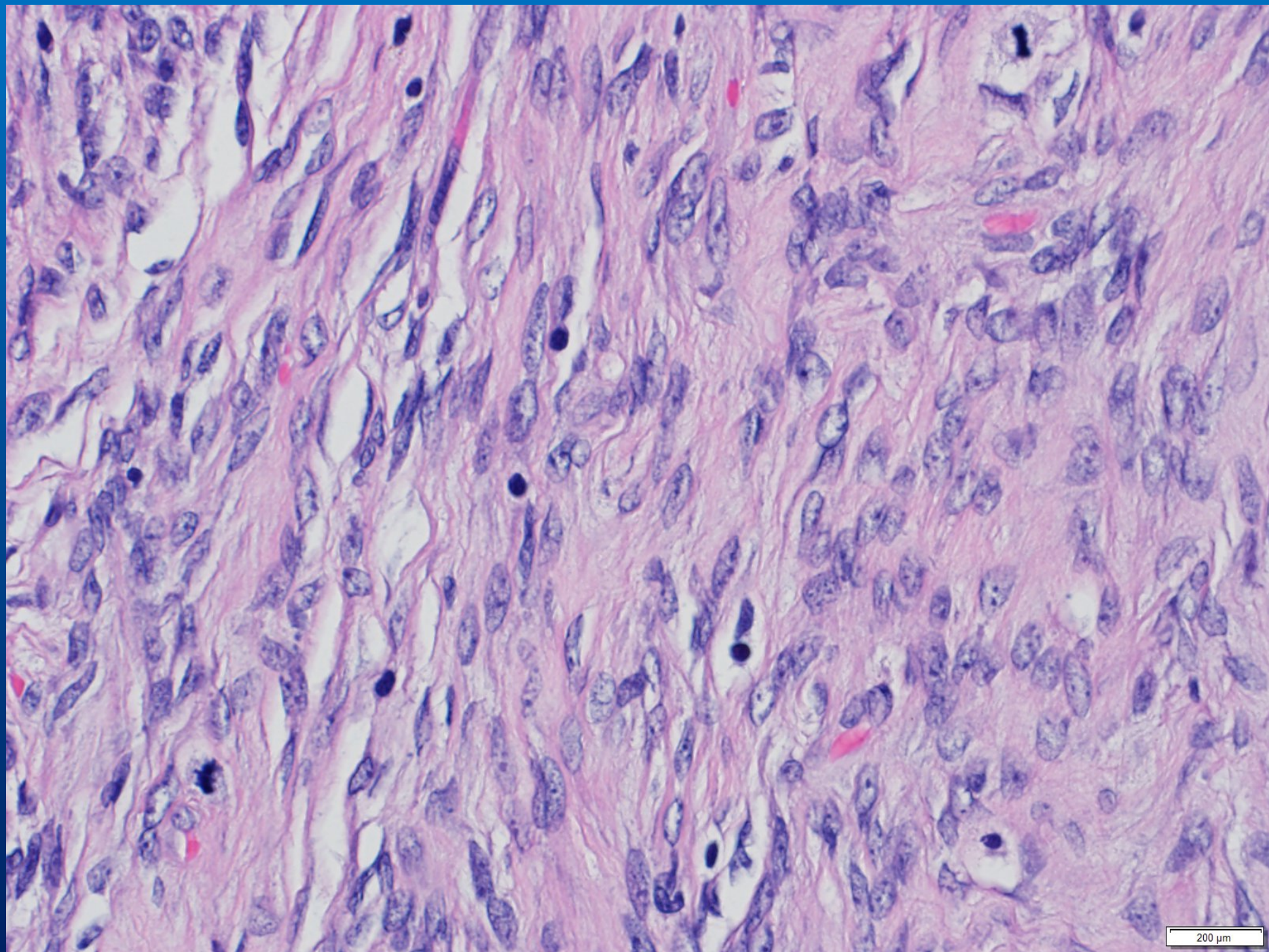
PT: Best category?



PT: Best category?

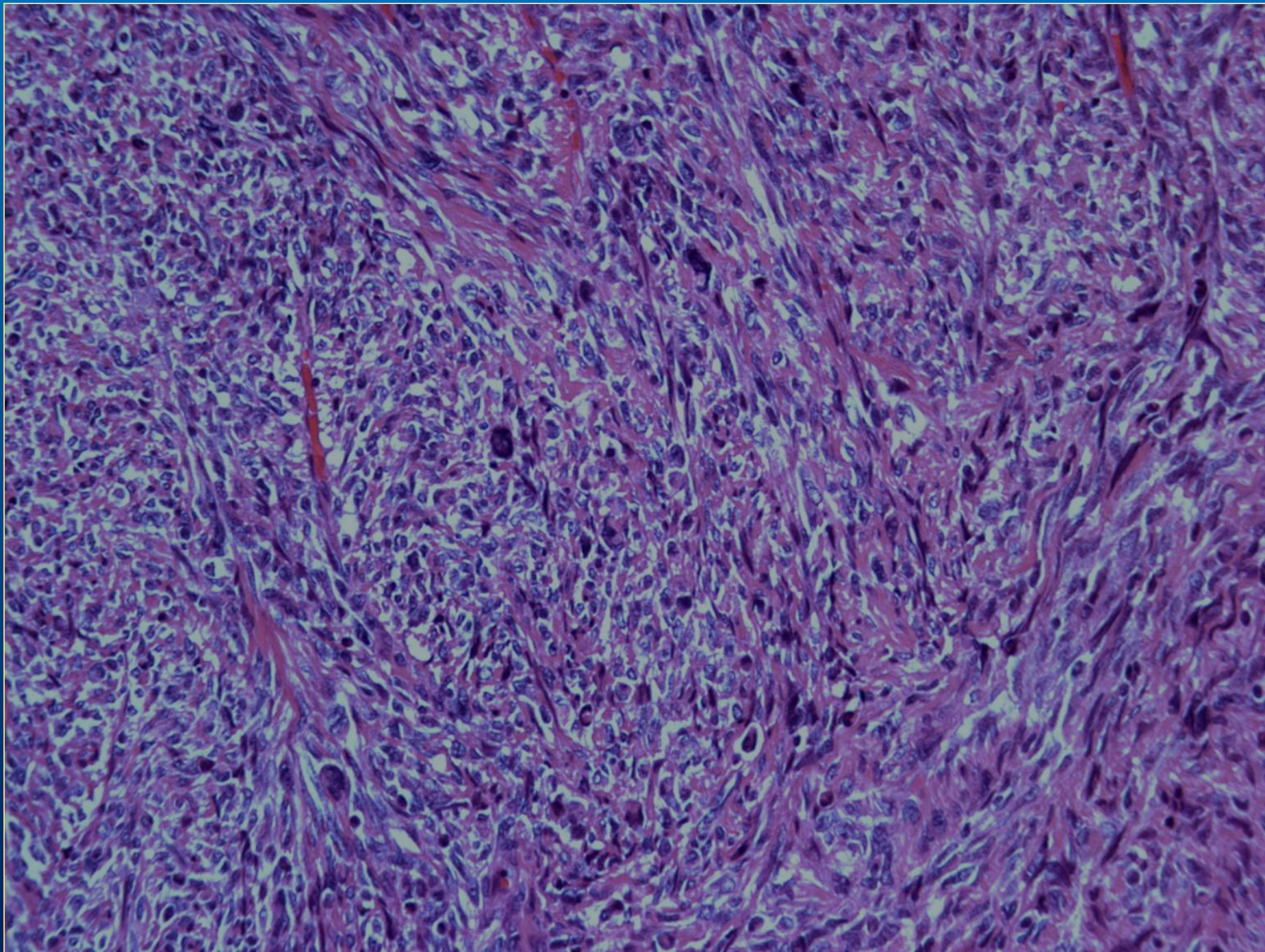


PT: Best category?



PT: Malignant

- Sarcomatous overgrowth
 - 4x field devoid of epithelium



Treatment

- Complete excision with breast conservation
- Mastectomy
 - Large tumors
 - Malignant PT
 - Recurrent tumors
- Benign / Borderline
 - Conservative surgery or simple mastectomy
- Axillary lymph node dissection
 - Only for clinically positive lymph nodes

Metastasis

- Frequent sites
 - Lungs and skeleton
 - Axilla, rare
- Malignant PTs
 - Rate of 3-10%
 - Sarcomatous features
 - Stromal overgrowth

Factors in recurrence and metastatic potential

- Local recurrence
 - Predictive value for local recurrence: Positive margin, stromal overgrowth, atypia and mitotic activity
 - 10-17% for benign
 - 14-25% for borderline
 - 23-30% for malignant
- Metastatic potential
 - Histologic classification as malignant
 - Lungs and skeleton are most common sites of spread
 - Very rare axillary nodal mets have been described
- Malignant heterologous elements impart a worse prognosis

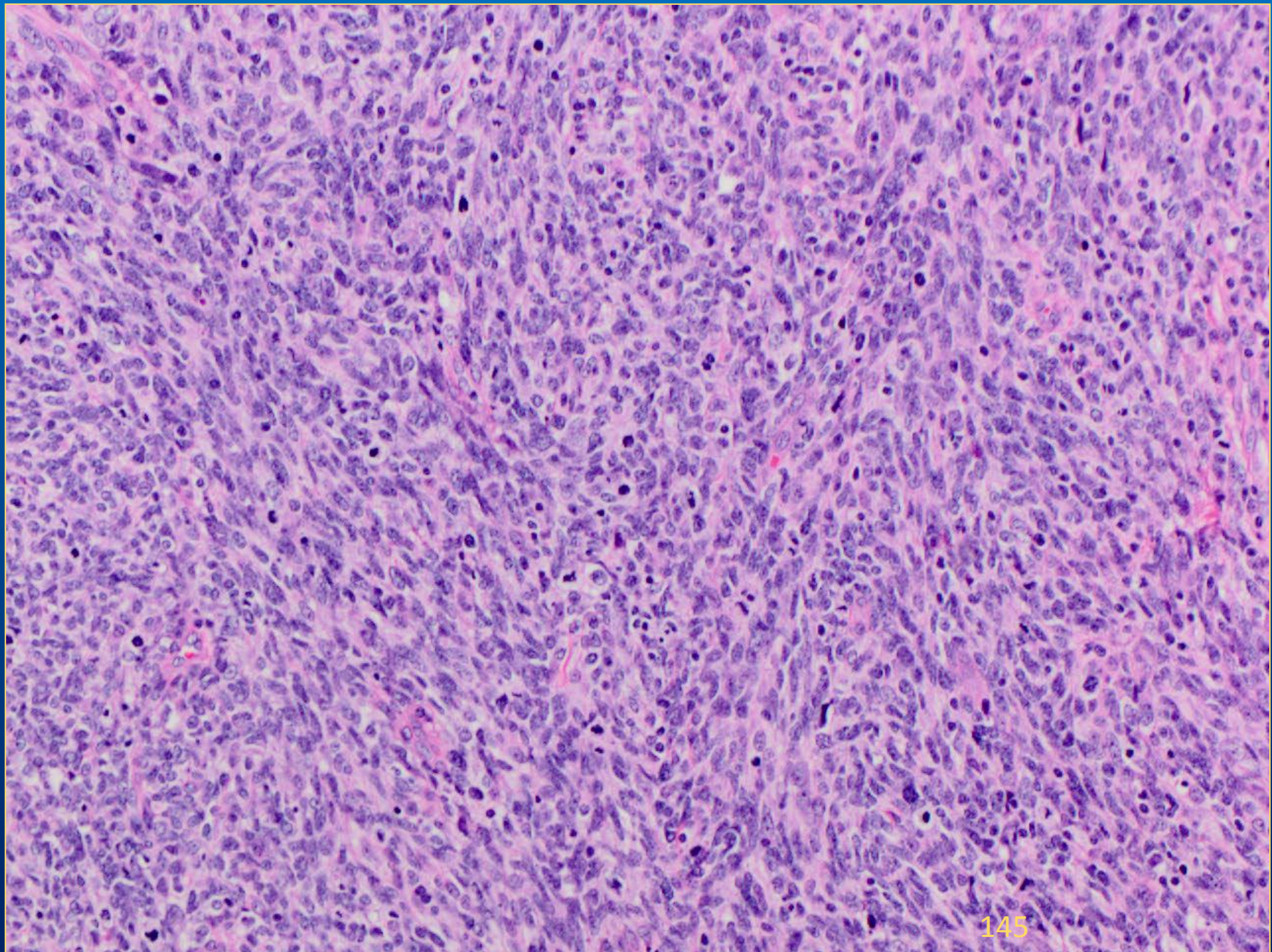
Treatment

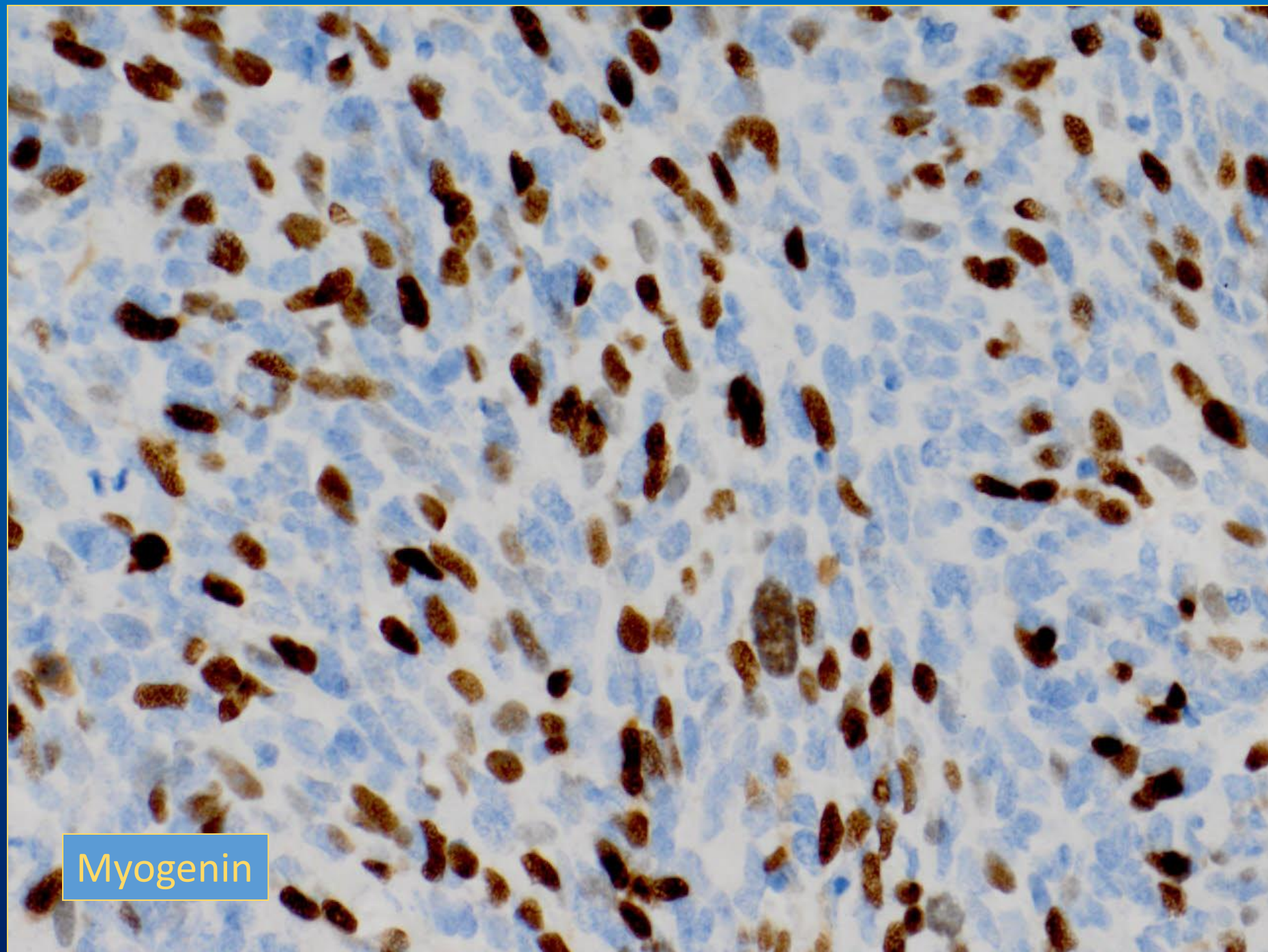
- Surgery is mainstay, NCCN suggests a 1 cm margin
- Positive margins after the initial resection
 - Surgery
- No prospective randomized data supporting radiation therapy in PT; may be considered in the setting where additional recurrence would create significant morbidity
- Hormonal treatment and chemotherapy
 - Have failed to show an effect
 - Considered in the treatment of metastatic disease

Metastases

- Clinical history is key
- Most common entities to metastasize to the breast:
 - Malignant melanoma
 - Lung and ovary
- Breast metastasis is first sign of malignancy in roughly 30% of cases
- Propensity for rhabdomyosarcoma, in adolescents, to metastasize to breast

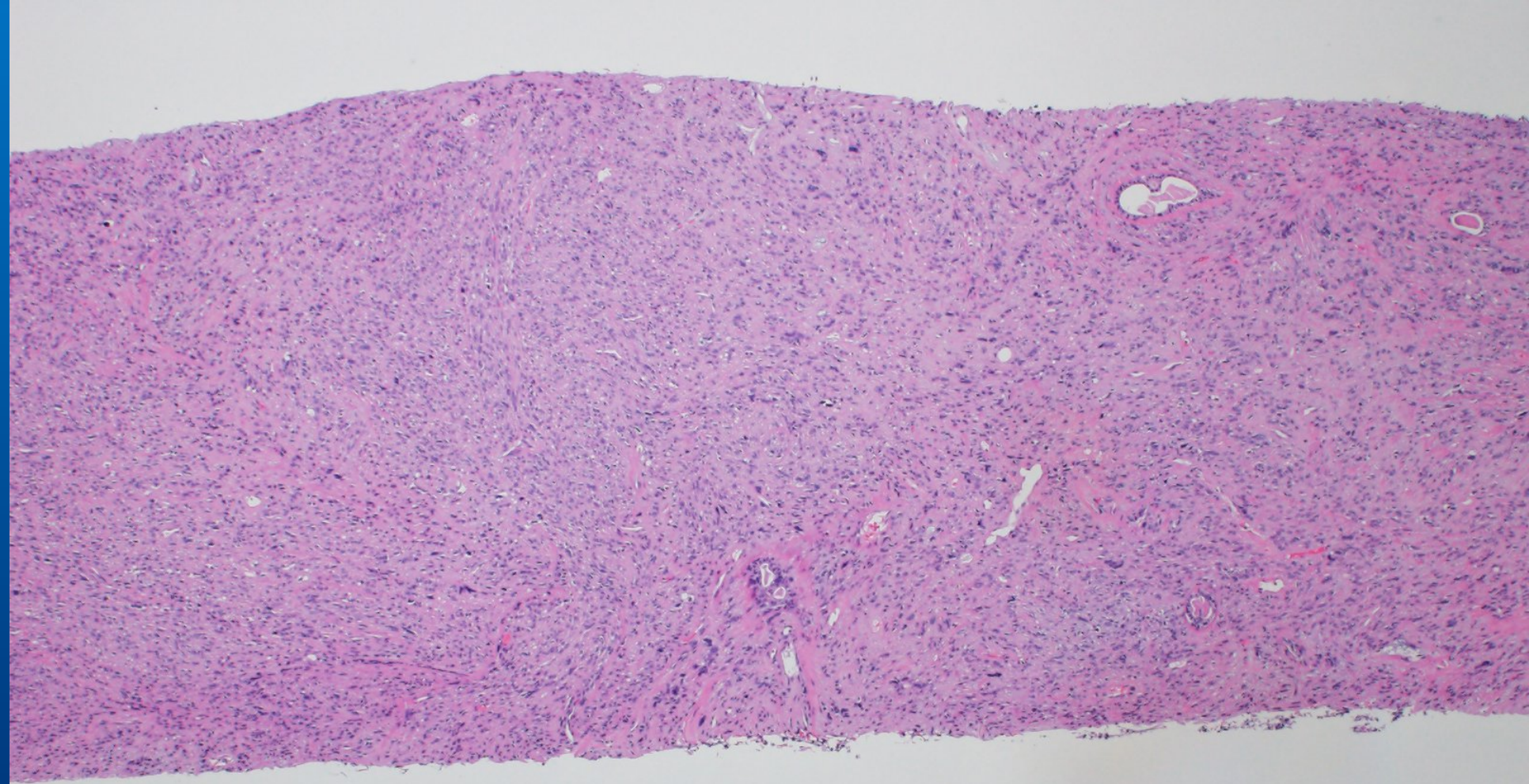
2.5 cm breast mass in 15
year old female with no
previous history



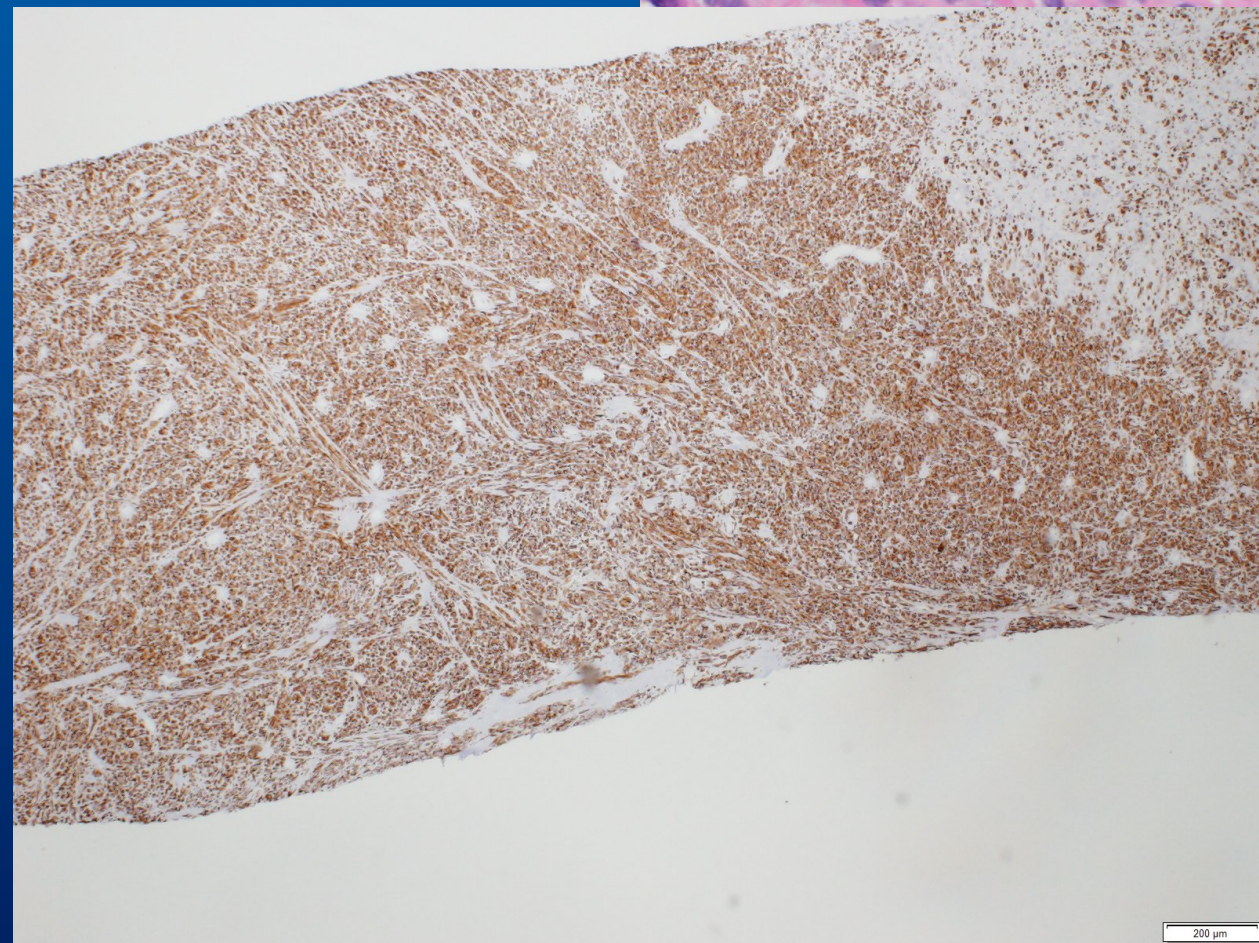
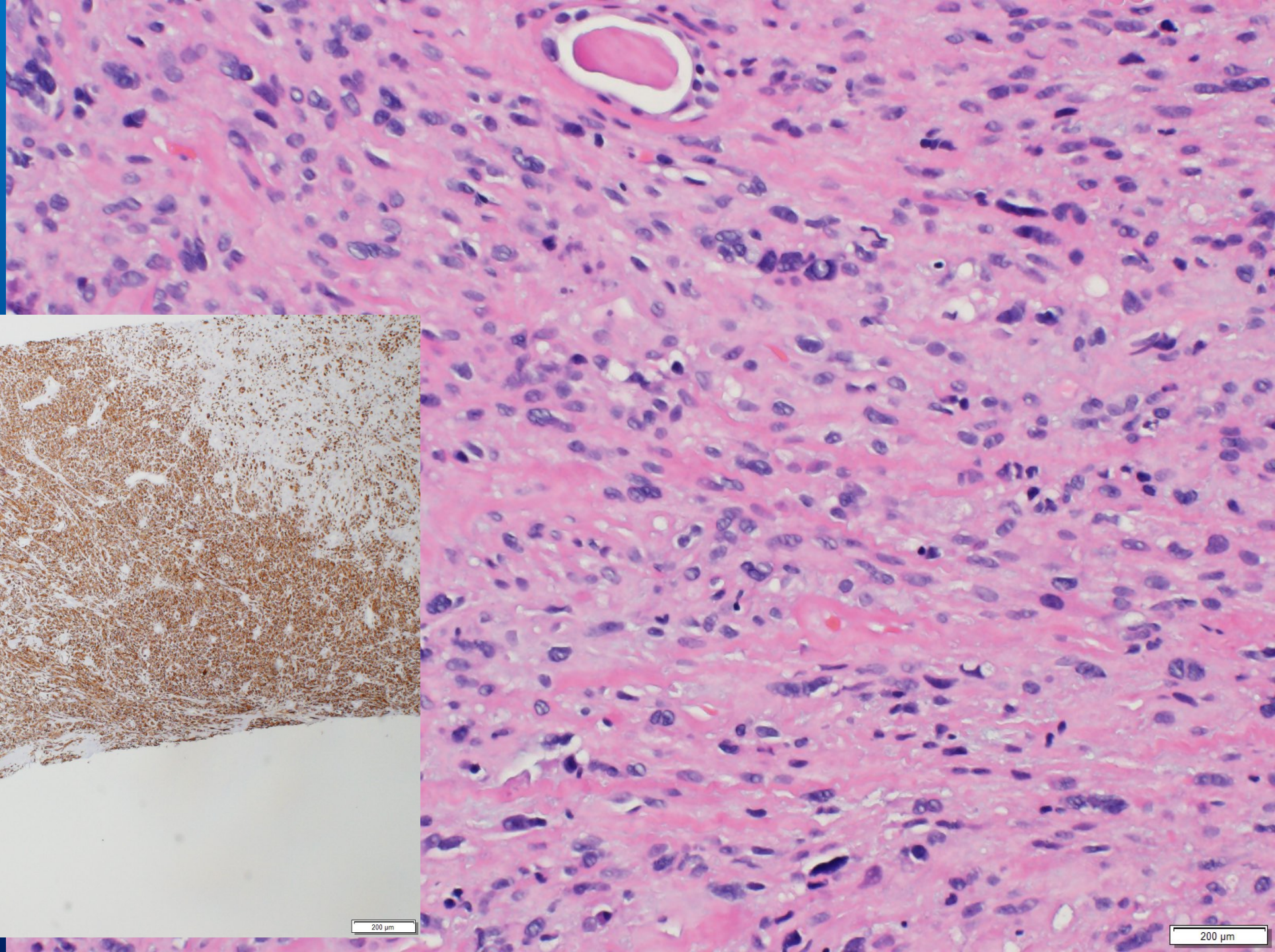


Myogenin

3 cm breast mass in a patient
with known metastatic
leiomyosarcoma to the lung



Strong and diffuse H-
caldesmon



200 μm

Summary

- Most benign spindle cell lesions of the breast arise from myofibroblasts
 - Can be challenging on core needle biopsy as many of these lesions have overlapping histomorphologies
- Metaplastic carcinoma should be excluded when faced with an atypical spindle cell lesion in the breast or when considering a fibromatosis
 - Cytokeratin and p63 stains can be helpful if positive, however if negative does not exclude a metaplastic carcinoma

Summary

- Core needle biopsies can undersample key elements which would allow for a definitive diagnosis
- Cytokeratins can be capricious in metaplastic carcinoma, especially in a limited core needle biopsy
- On occasion, it may be prudent to sign the core out as spindle cell neoplasm either low or high grade and admit that thorough sampling of the resection specimen is needed to accurately classify the lesion