Topics in Cytopathology: Case Presentation and Review of Diagnostic Entities

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Learning Objectives

- Generation of differential diagnosis based on morphology in conjunction with clinical work-up
- Review of diagnostic considerations: Immunohistochemical and/or molecular work-up
- Considerations for Rapid On-Site Evaluation (ROSE) of Spindle Cell Lesions

Outline

- Case Presentation
- ROSE considerations
- Review of pertinent diagnostic considerations
- Case Conclusion

Our patient

- The patient is a 55 year old woman initially seen at an outside hospital (OSH) in March 2022 for chest pain and shortness of breath. Pertinent work-up included CT chest which was normal at the time and the patient was treated for pleurisy with symptom resolution.

- May 2023: the patient again presented to OSH with progressive shortness of breath with any exertion along with progressive mid sternal pain. Overall symptoms felt similar to prior episode a year ago. Further work-up with chest X-ray demonstrated a mass.

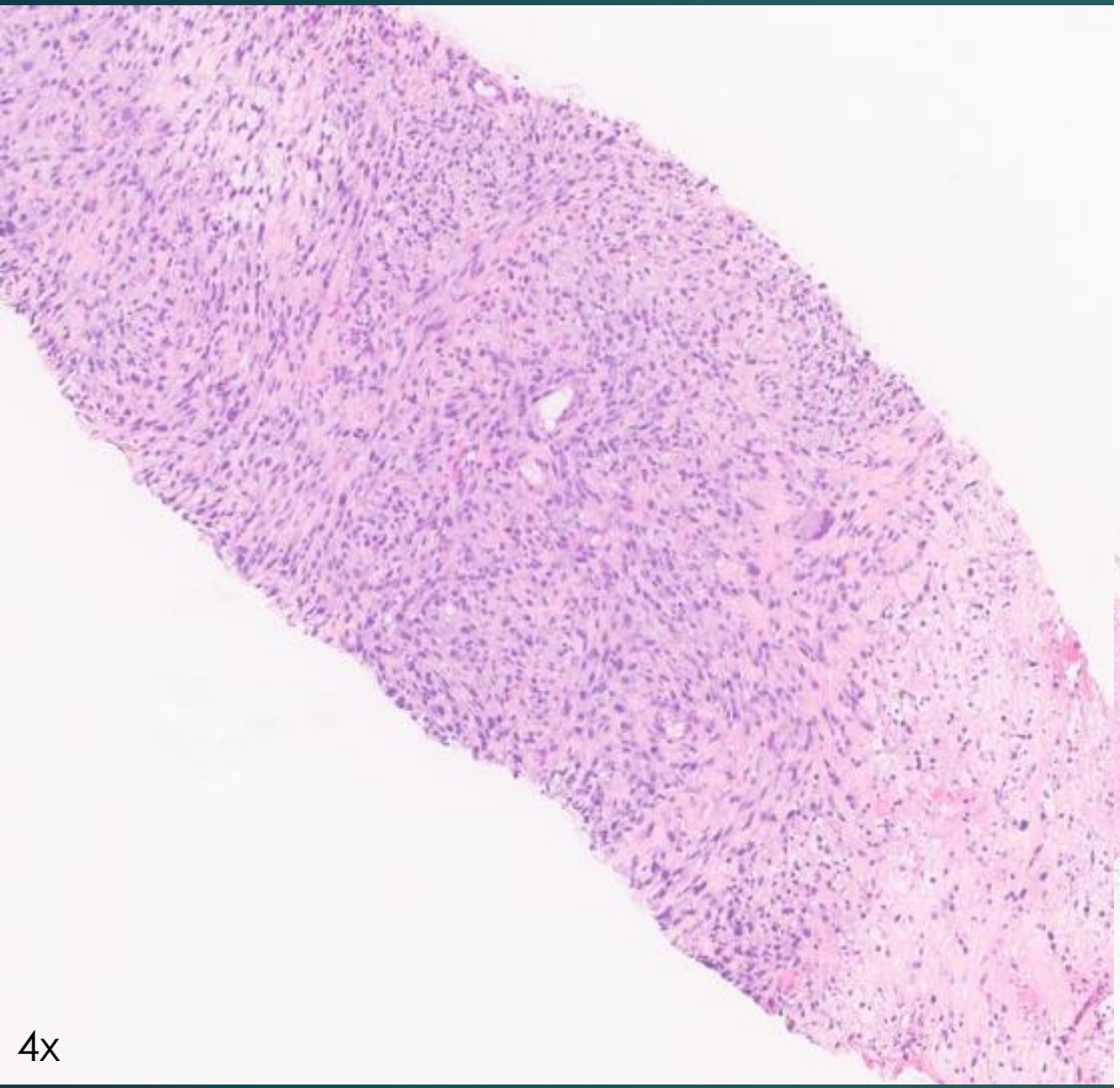
Further imaging:

- Chest CT: 9 x 8 x 8 cm pleural based mass in antero-medial left upper lobe with extension in the anterior mediastinum

- PET CT Whole Body:
  - Heterogenous predominantly cystic left lung mass with FDG avid thickened nodular pleural wall, left lower lobe subpleural mass paraspinal mass with adjacent left lower lobe atelectasis
  - Heterogenous uterine mass, likely uterine fibroid with possible malignant transformation

- CT Abdomen Pelvis:
  - Multilobulated, heterogeneously enhancing, central necrotic uterine mass, 10 x 9 x 7 cm with mass effect on right posterior bladder dome, vagina, and sigmoid colon

Our patient undergoes image-guided biopsy of the left thorax/mediastinum mass and the pathology is reviewed at the University of Utah



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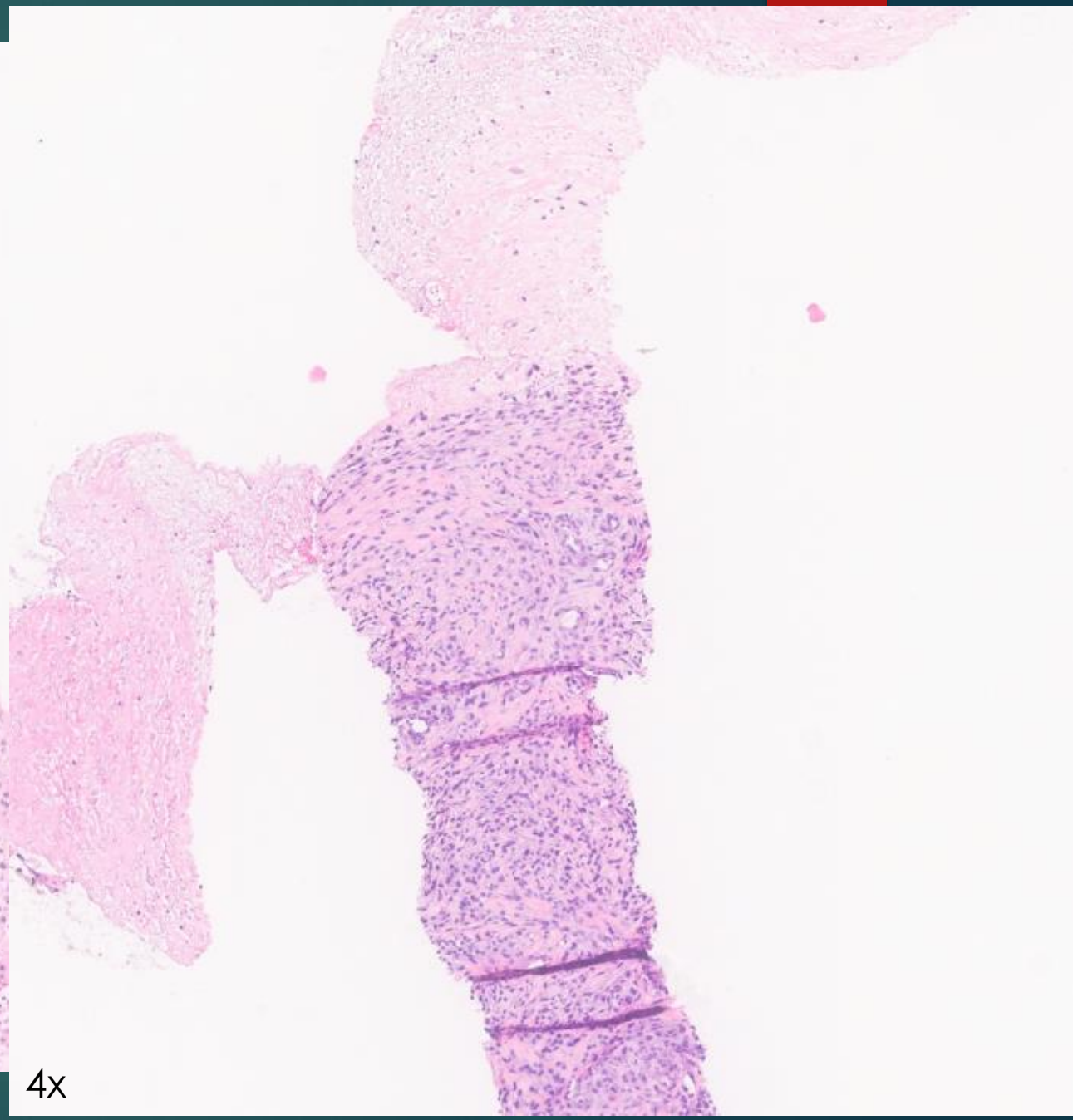

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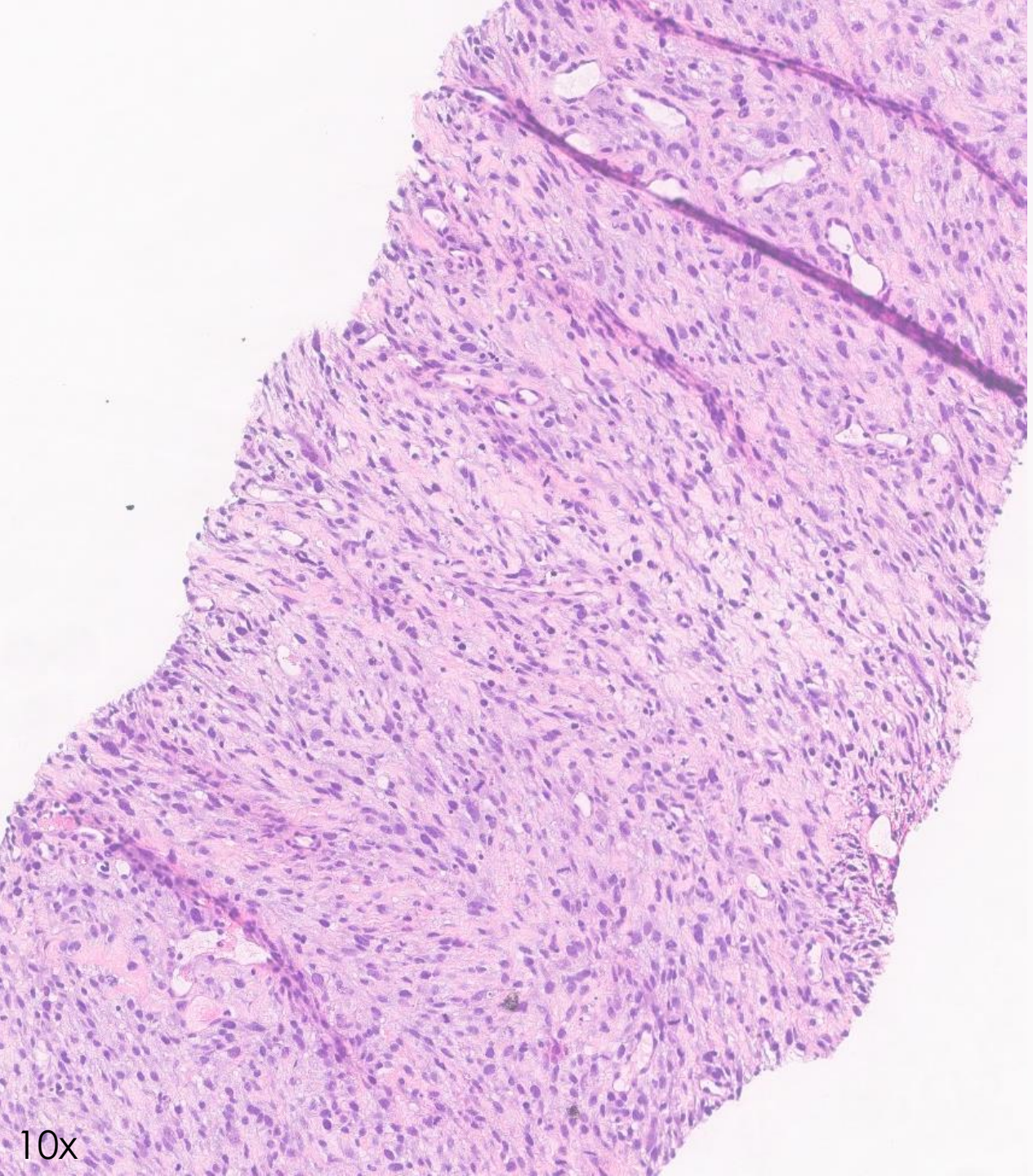
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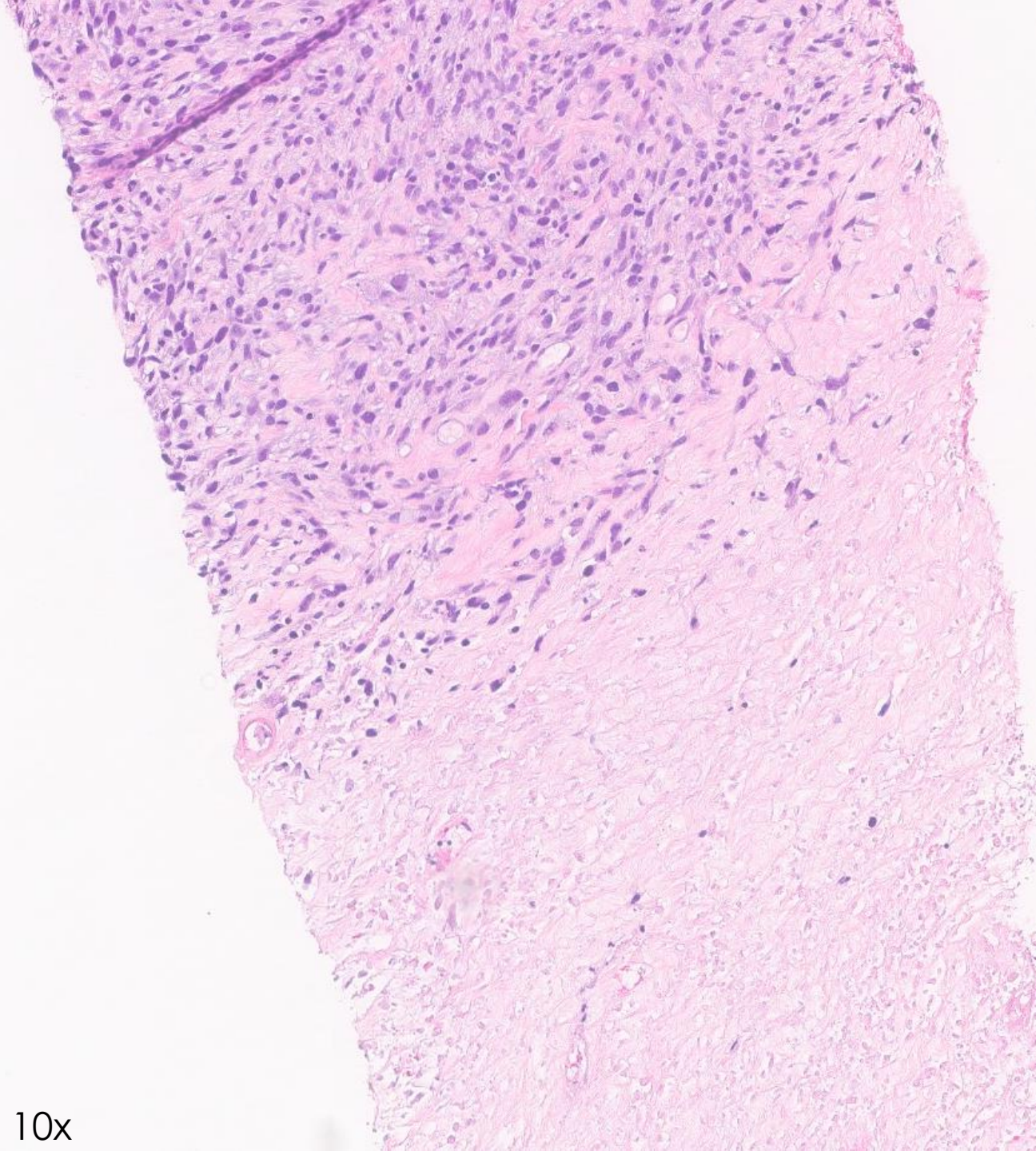
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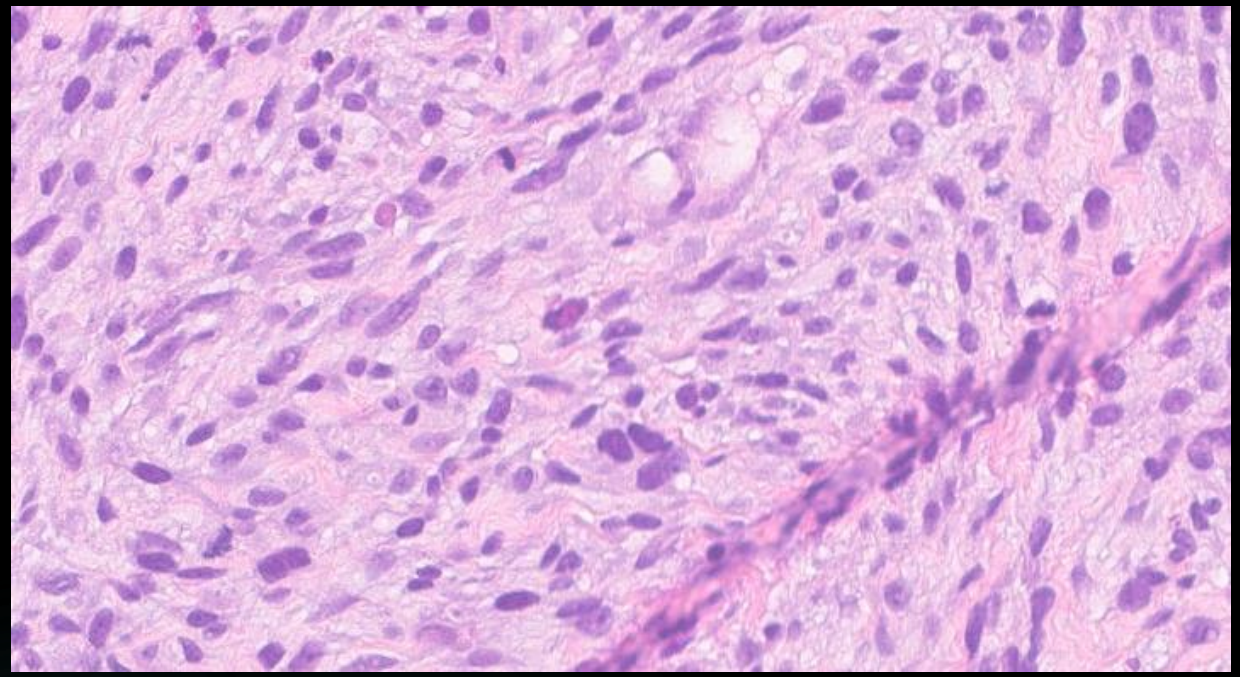
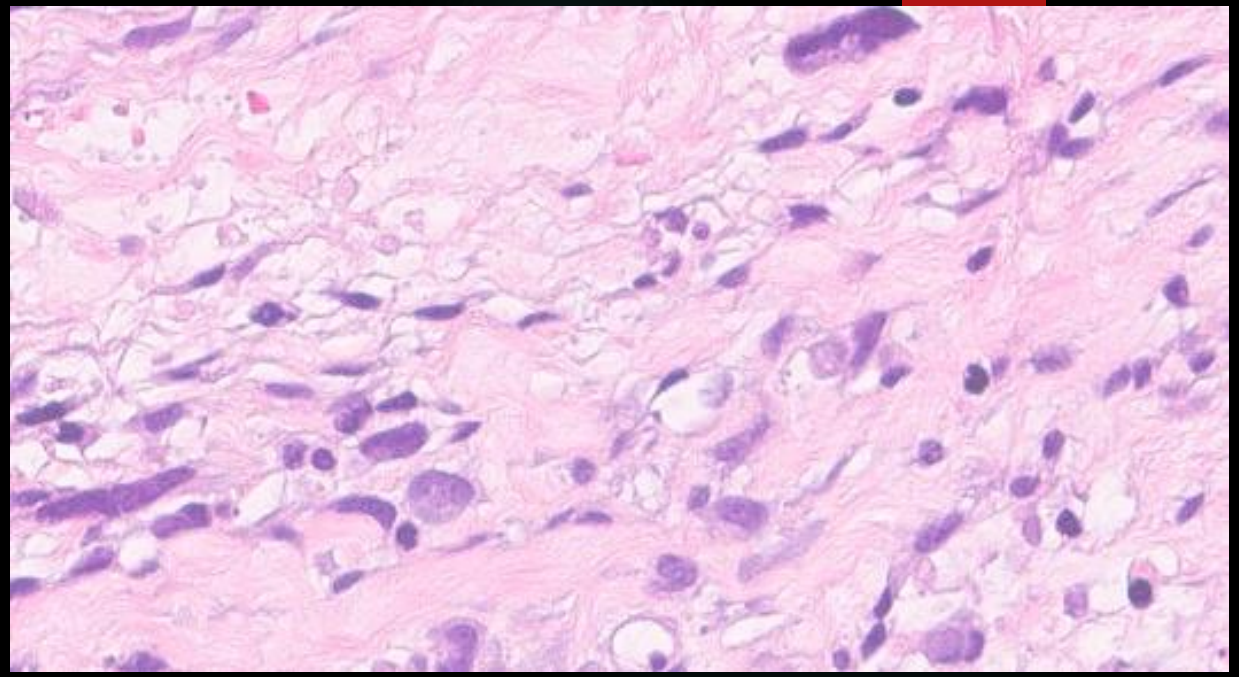
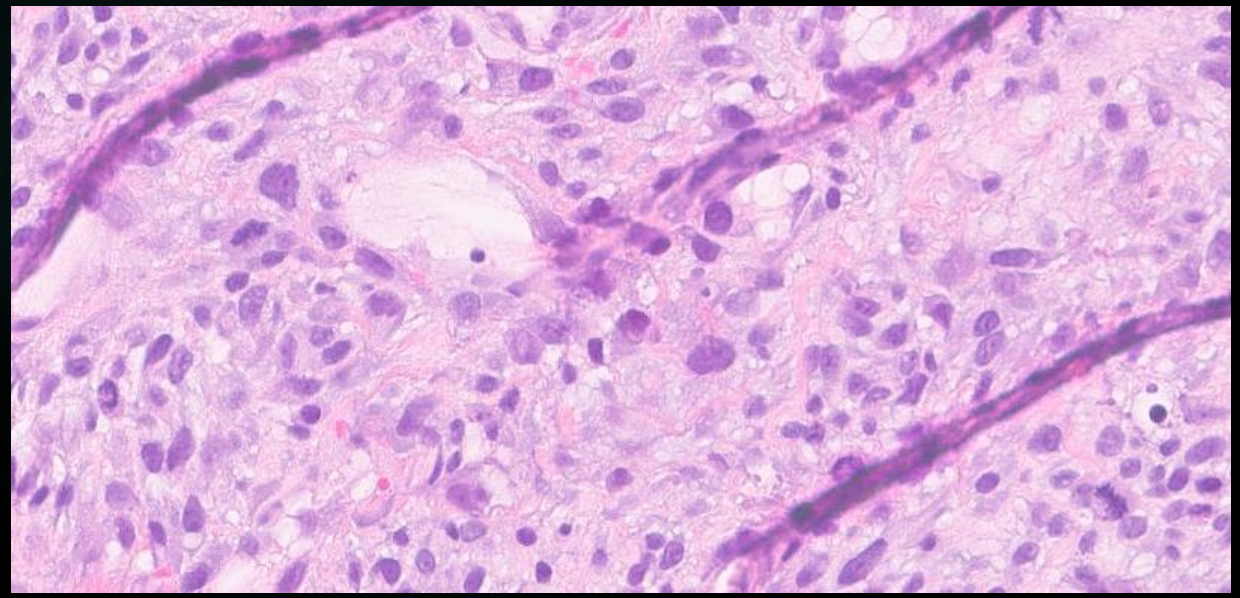
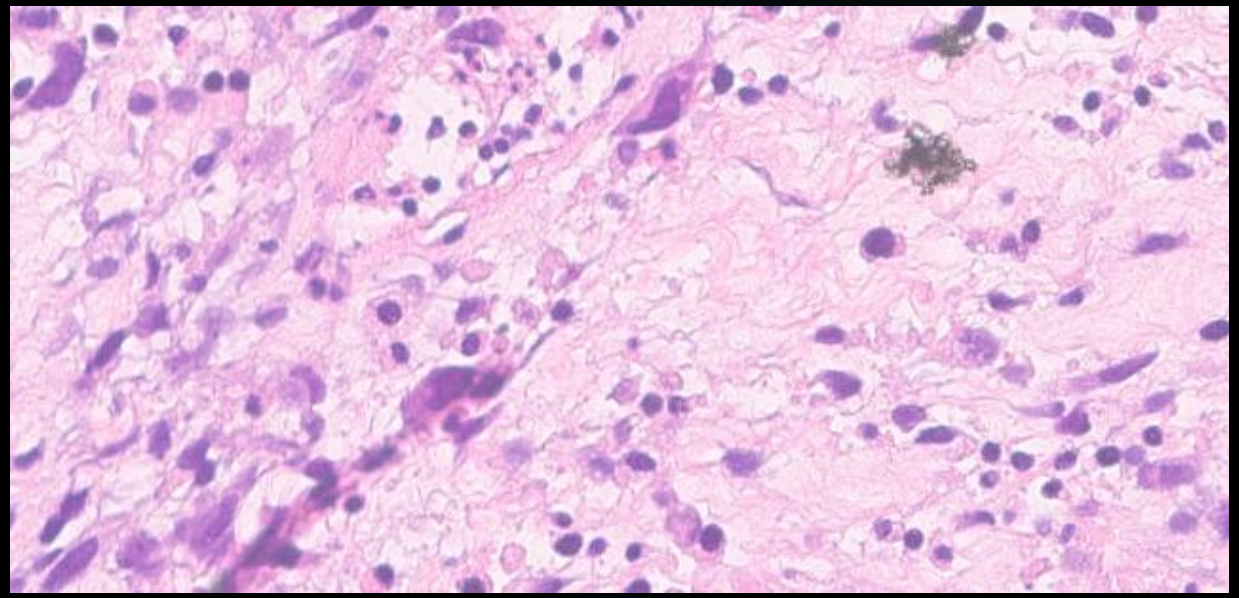

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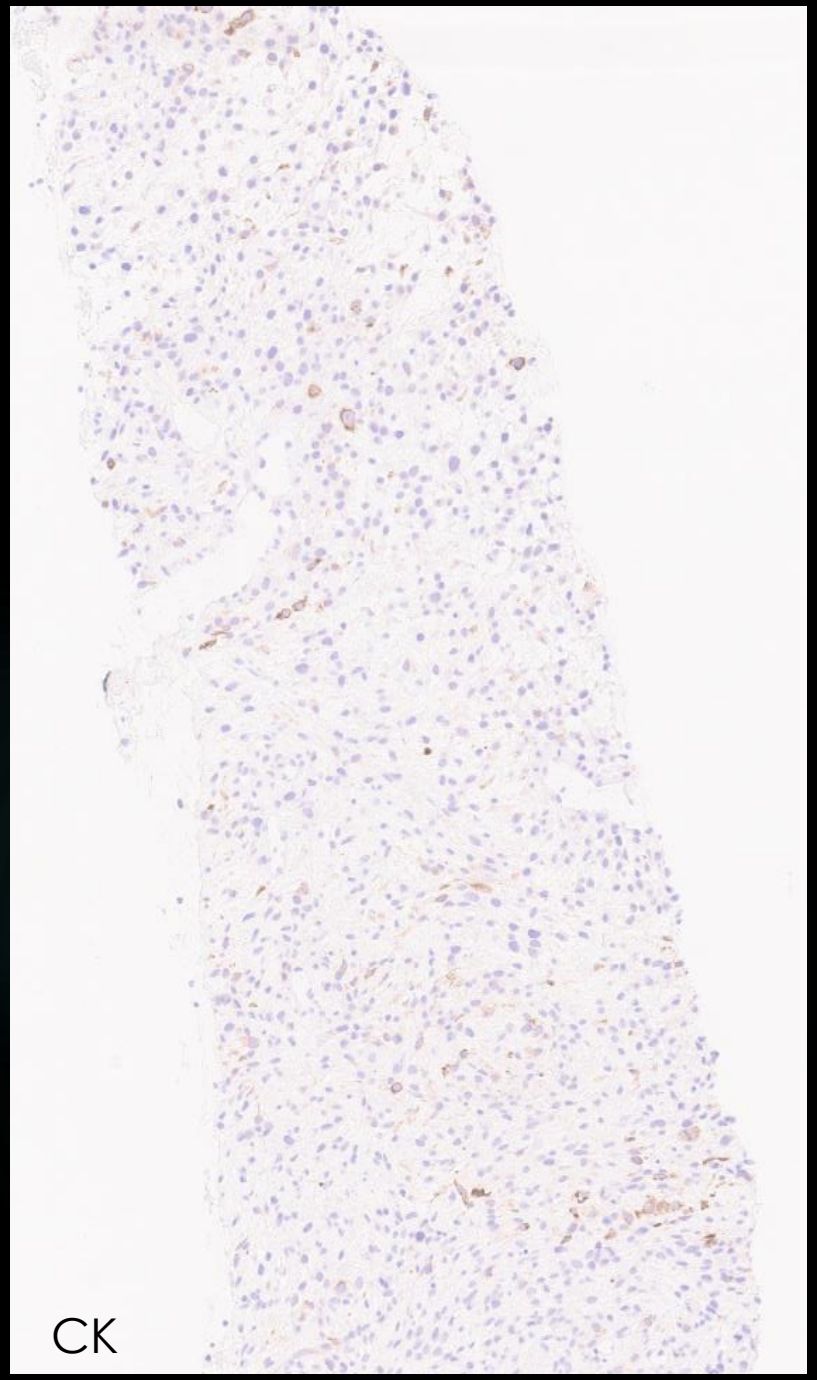
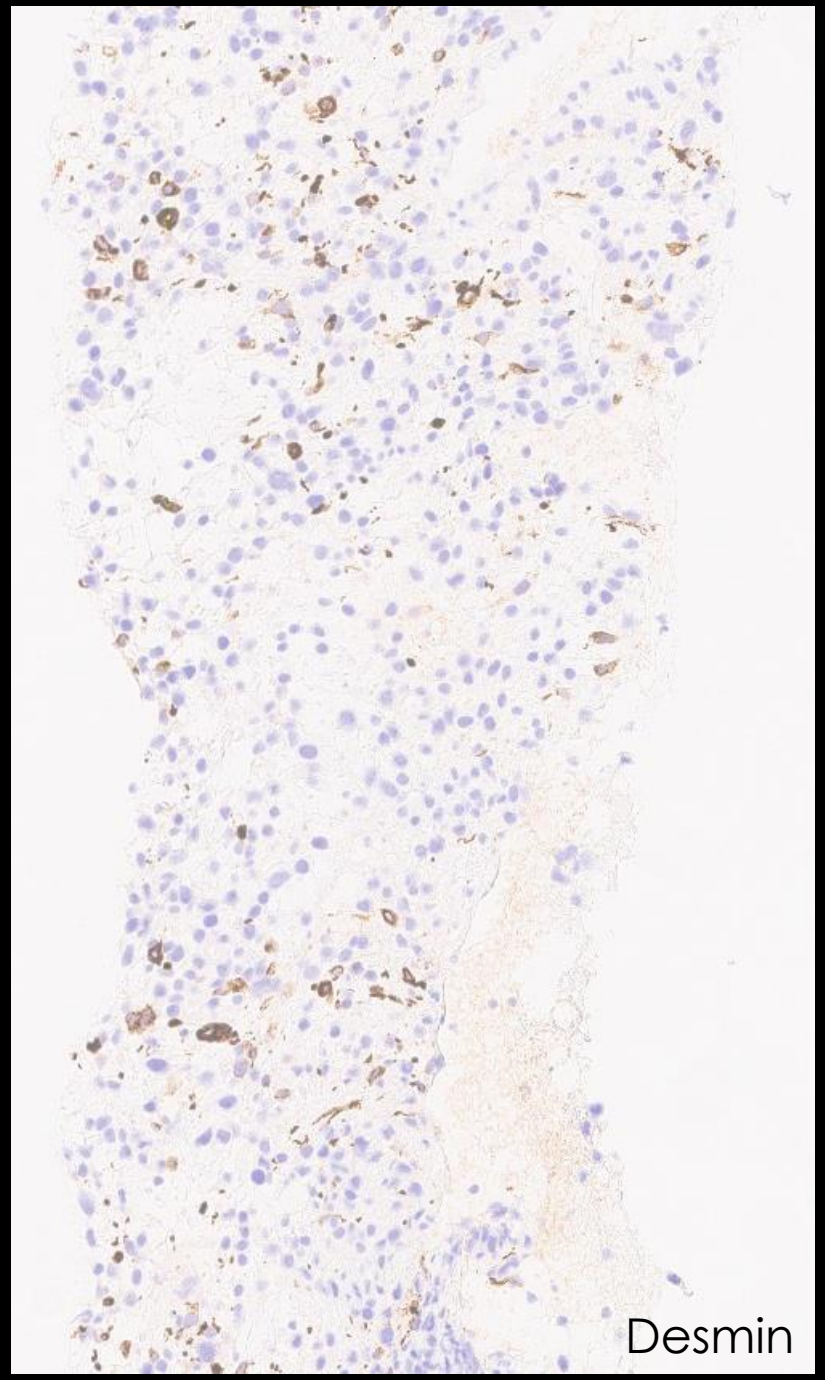
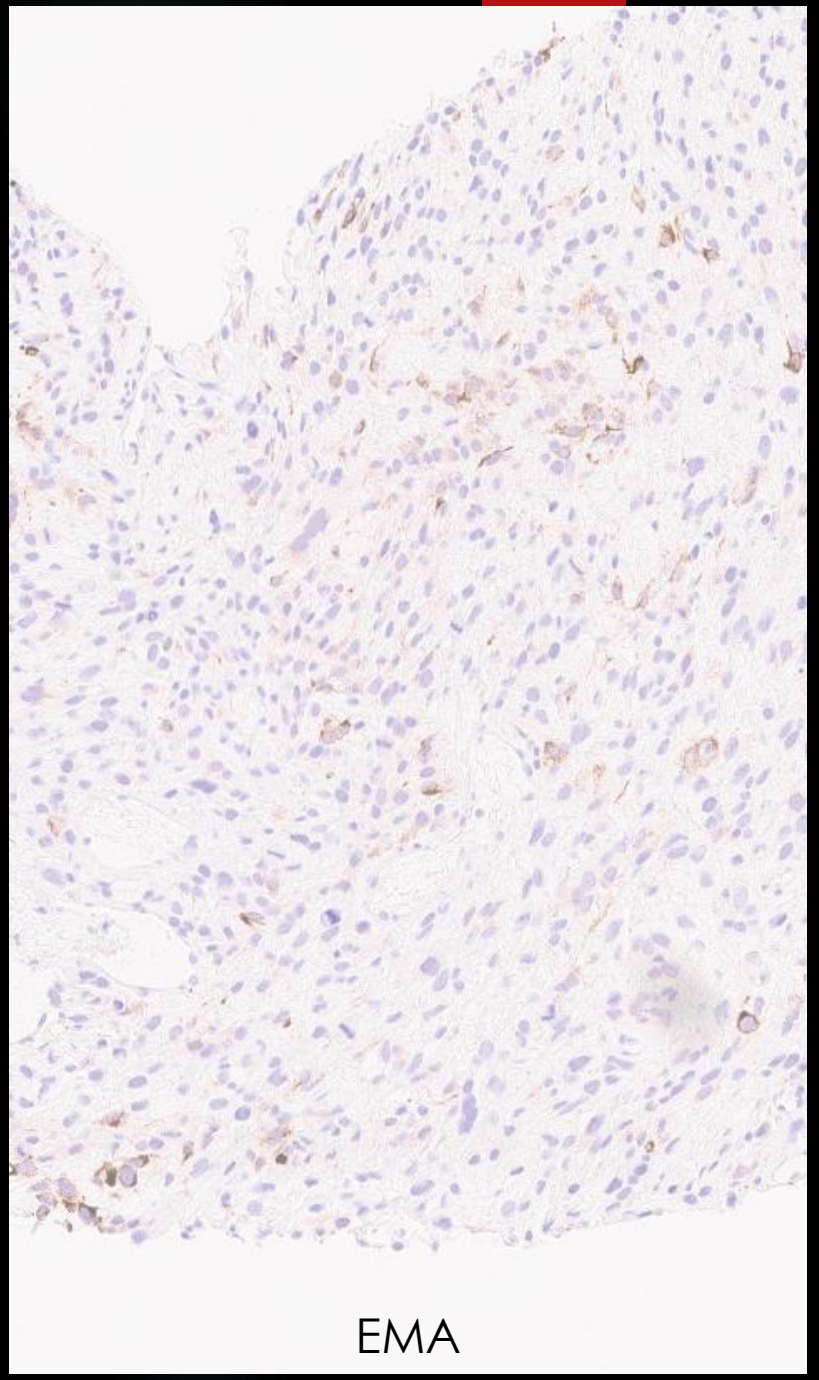
Microscopic Examination:

- Highly cellular spindled and ovoid cell tumor with mild to moderate pleomorphism; rare, possible rhabdomyosarcomatous morphology
- Numerous atypical mitotic figures
- Necrosis


CK


Desmin


EMA

Negative stains

- SOX10
- MDM2
- MUC4
- STAT6
- TLE-1
- TTF-1
- ALK-1
- CD34
- CD45
- CK7
- CK20
- H2K27Me3 (retained)

What do you think this could be?

Primitive, high grade malignancy with limited rhabdomyosarcomatous differentiation

- Combination of epithelial staining with lack of diffuse Desmin positivity does not support primary rhabdomyosarcoma
- Given the patient's pelvic mass, this thoracic lesion is suspicious for metastatic carcinosarcoma
- Recommend biopsy of the pelvic mass

Next steps

- Our patient is seen by medical oncologists of the Sarcoma Division at Hunstman Cancer Hospital. Given worsening symptoms and progression of disease, discussion of treating for likely carcinoma with carboplatin/taxol versus waiting for pelvic mass biopsy
- Ordered image-guided biopsy of pelvic mass with on-site evaluation
- Initiated Cycle 1 of carboplatin/taxol regimen due to worsening symptoms

Rapid On-Site Evaluation (ROSE)

CONSIDERATIONS

Rapid On-Site Evaluation

- Fine Needle Aspiration or Touch Preparation
- Confirm good site for core biopsy
- Confirm viable material
- Obtain as much tissue as possible for diagnosis and ancillary work-up

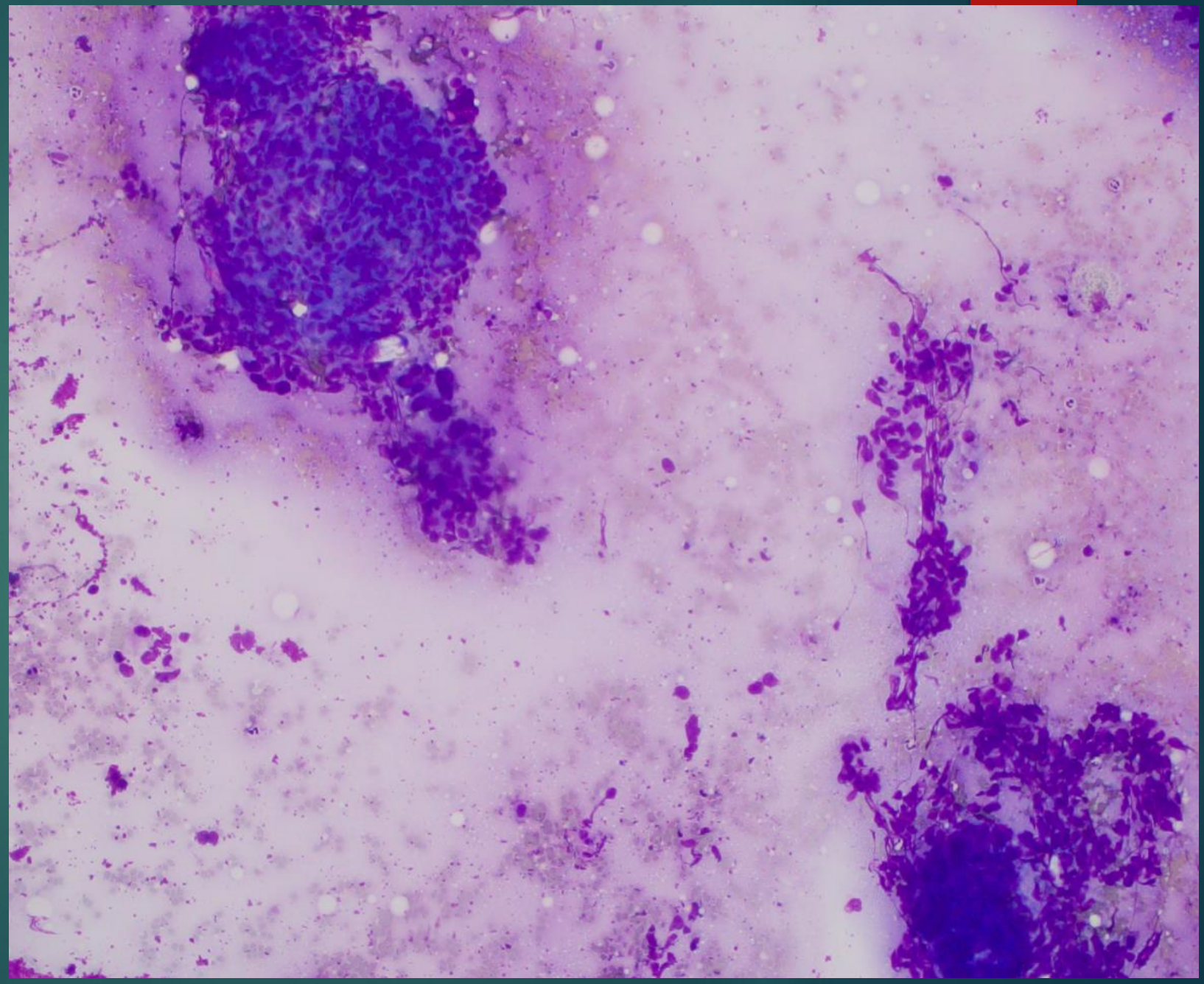
ROSE on Spindle Cell Lesions

- Soft tissue lesions (especially fibrous or vascular lesions) tend not to release many cells on FNA or touch prep
- Consider "squash" preparation to confirm site/viability
  - Sacrifice whole core
  - Sacrifice small piece of core
- Consider placing multiple cores in separate containers
  - Avoid depletion (container for IHC; container for molecular testing)
  - Triage soft tissue fragments to containers that don't need decalcification
    - Decalcification using EDTA takes a long time (decalcification in strong acids will preclude molecular testing)

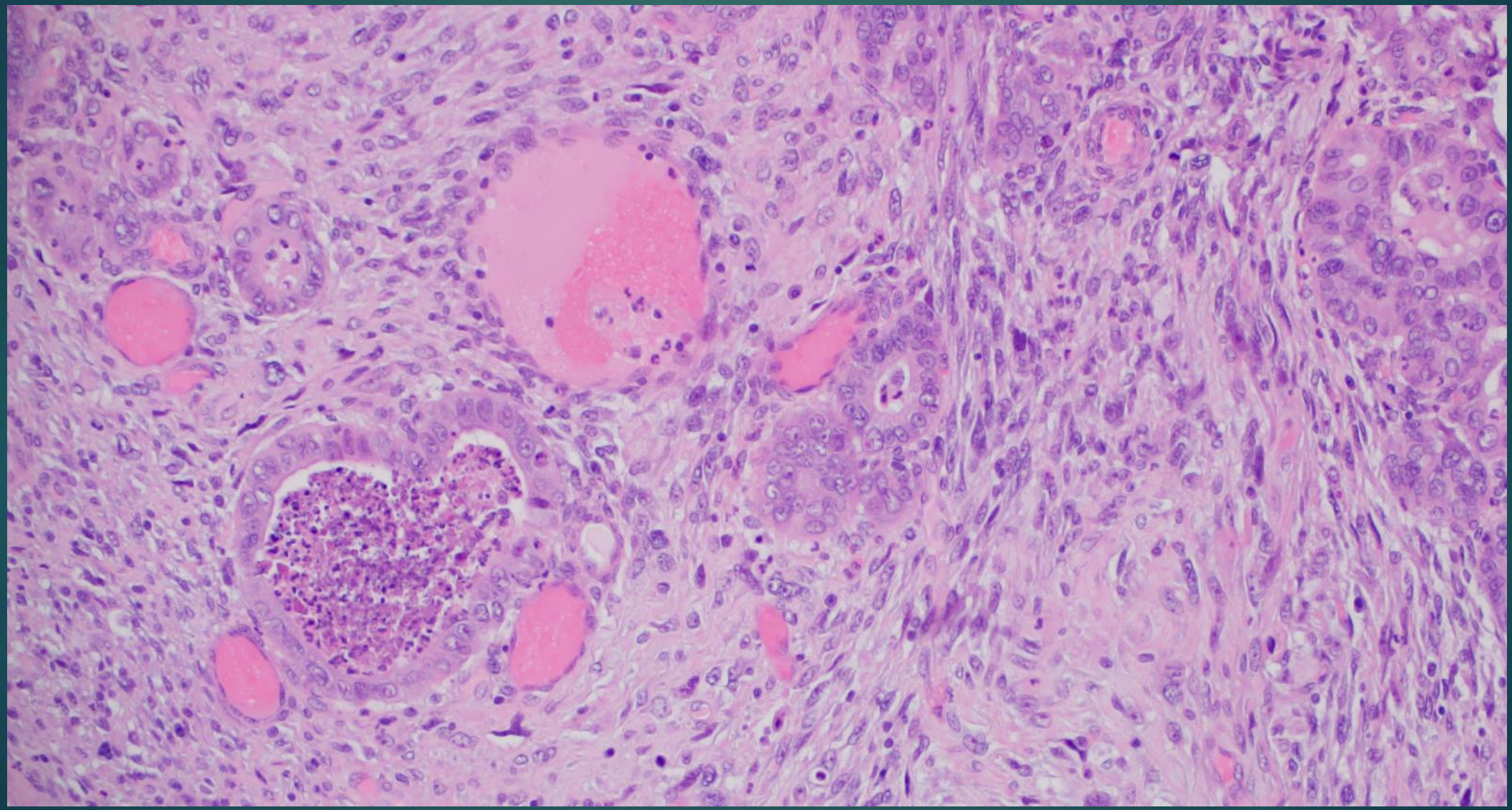
Diagnostic Considerations

REVIEW OF 5 CASES SEEN BY OUR CYTO- AND SURGICAL PATHOLOGY SERVICES OF THORACIC SPINDLE CELL LESIONS SEEN IN FEMALE PATIENTS WHO ALSO HAD A PELVIC MASS

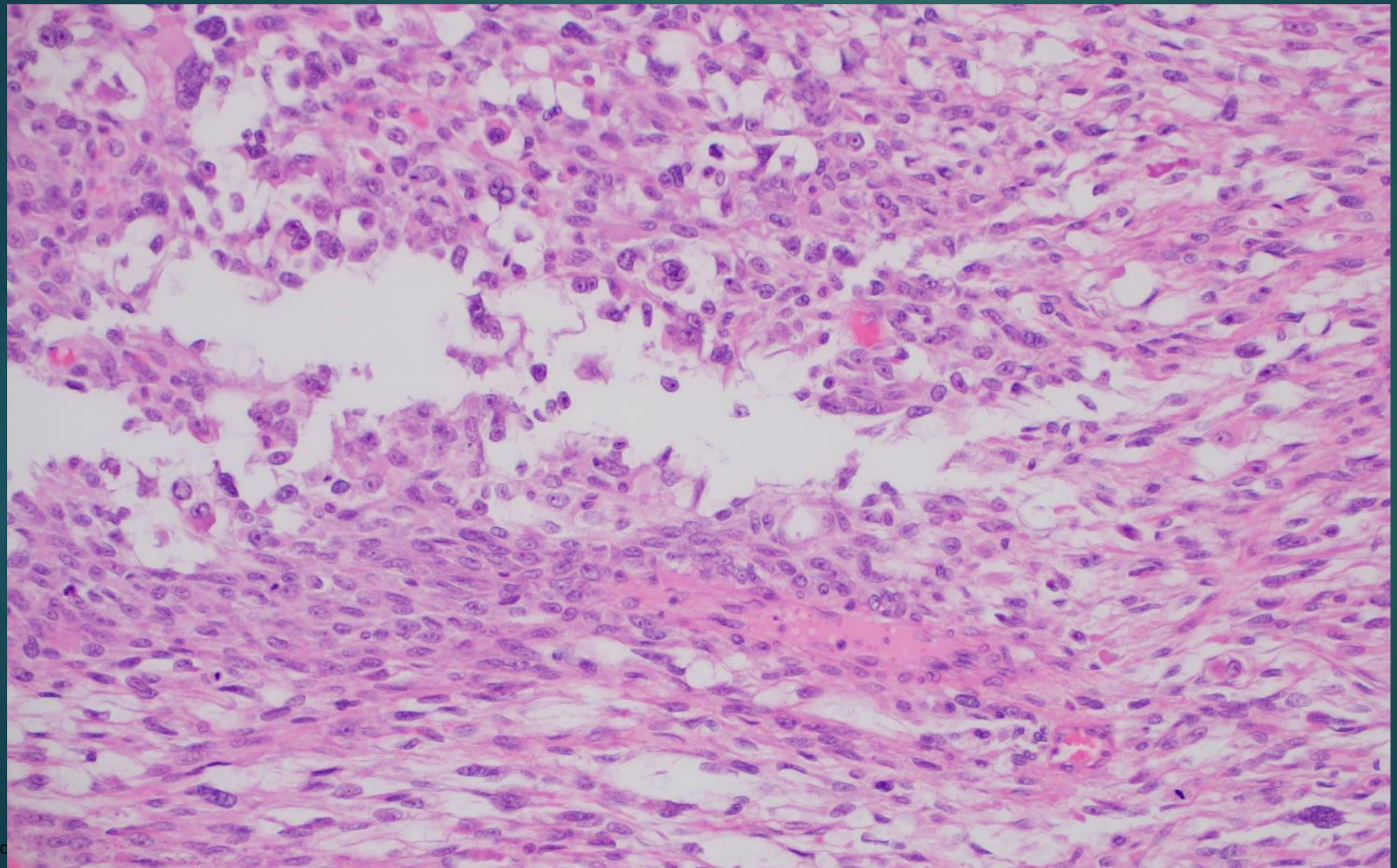
Case 1:
60 yo F with Hilar Mass/Lymph Node:
ROSE, DQ 10x



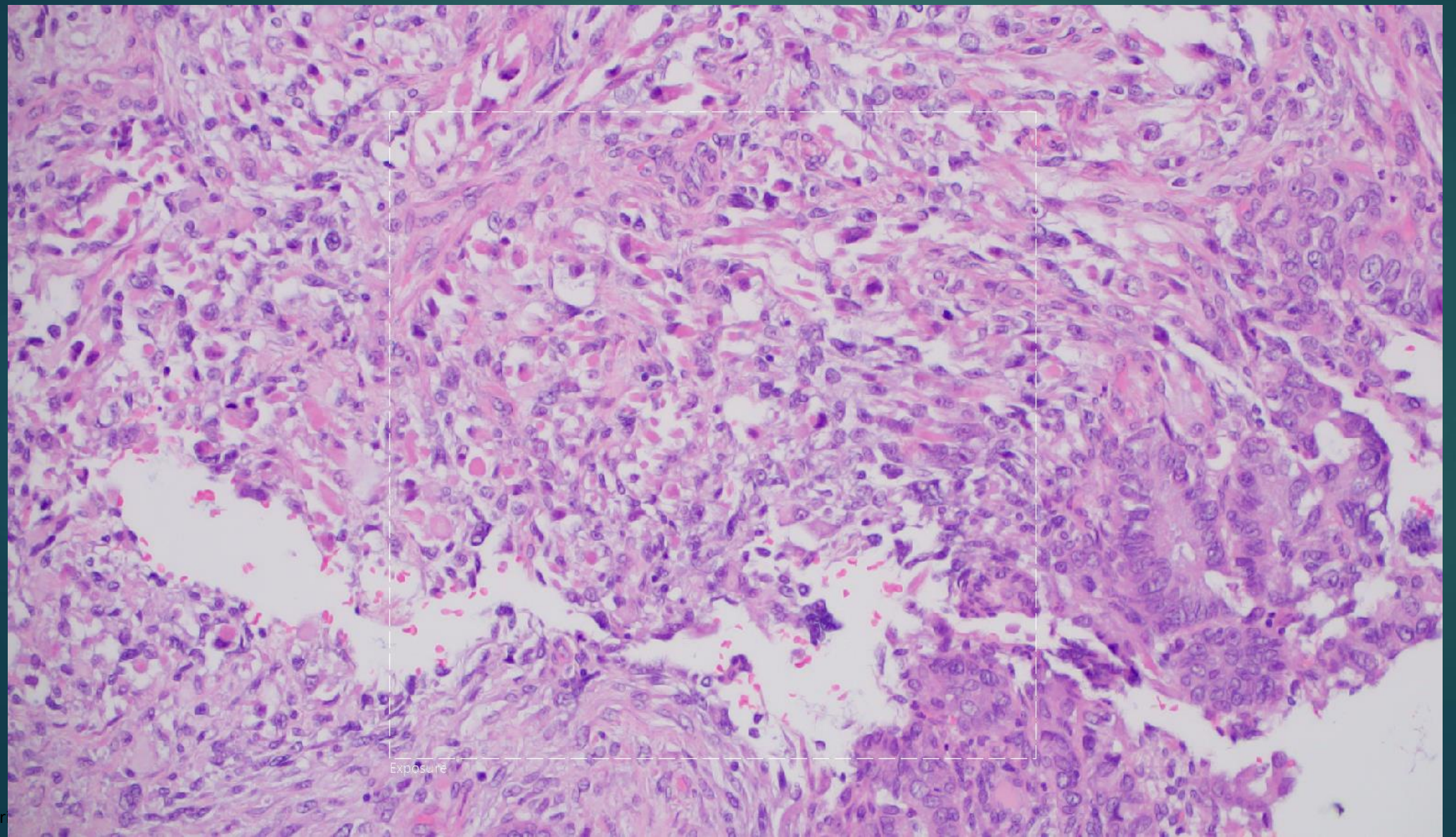
Core biopsy, 20x



Core biopsy, 20x



Core biopsy, 20x



Stains

- PAX8: Positive
- AE1/3: Positive in epithelial and spindled component (stronger in epithelial component)
- Desmin: Positive in rhabdomyoblastic elements
- Estrogen Receptor: Positive (weak, 5%)
- Progesterone Receptor: Positive (weak, 60%)

Malignant cells present, consistent with involvement by the patient's uterine carcinosarcoma

Uterine Carcinosarcoma

- Biphasic neoplasm composed of high-grade carcinomatous and sarcomatous elements
- Less than 5% of all uterine malignant tumors
- Typically postmenopausal women, mean age 65 years

Uterine Carcinosarcoma, Microscopic

- Carcinomatous component: usually predominates; high-grade endometrioid, serous, clear cell, squamous, mixed

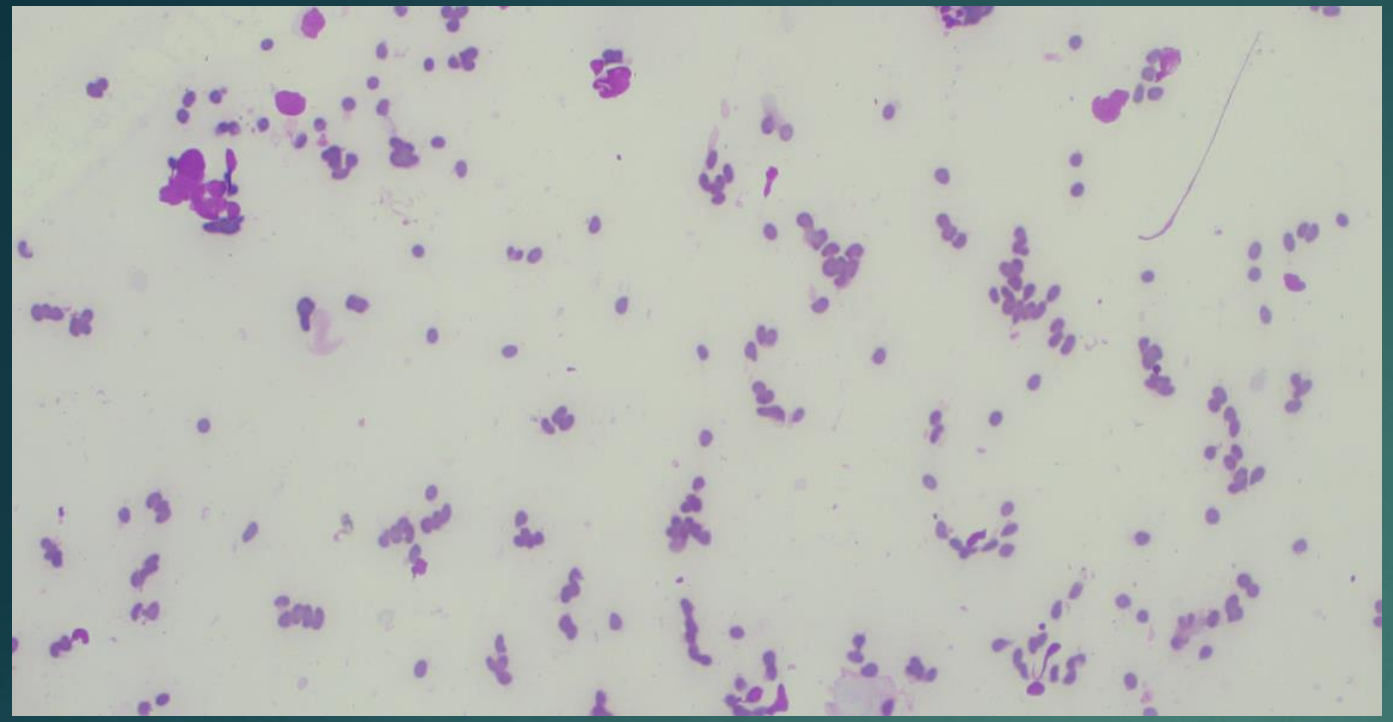
- Sarcomatous component:
  - Homologous (undifferentiated, fibrosarcoma, leiomyosarcoma)
  - Heterologous (rhabdomyosarcoma and chondrosarcoma most common)

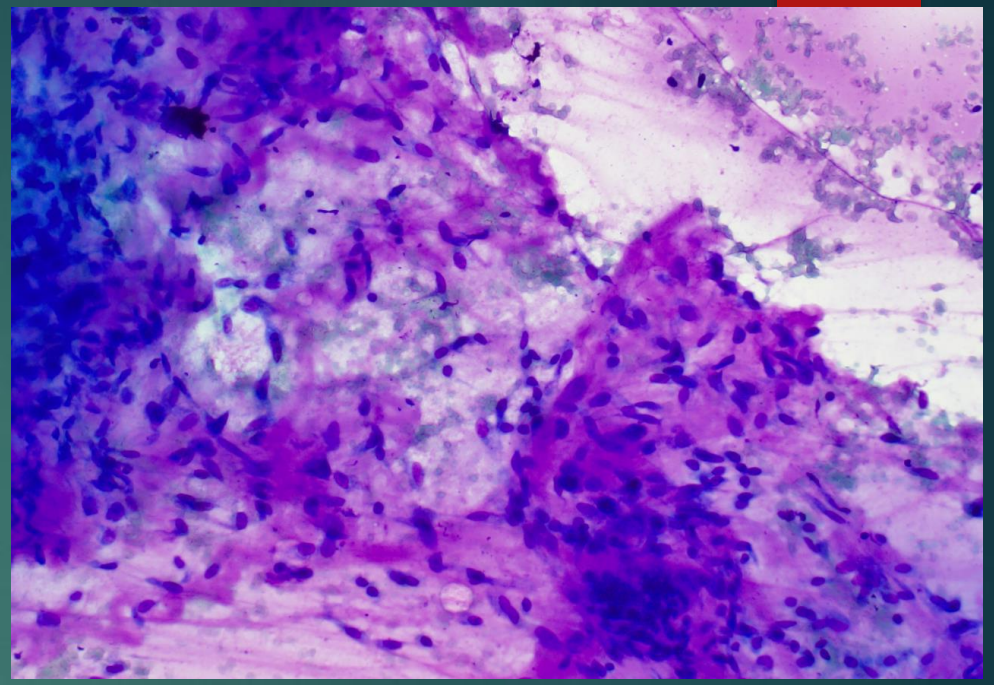
Uterine Carcinosarcoma, IHC

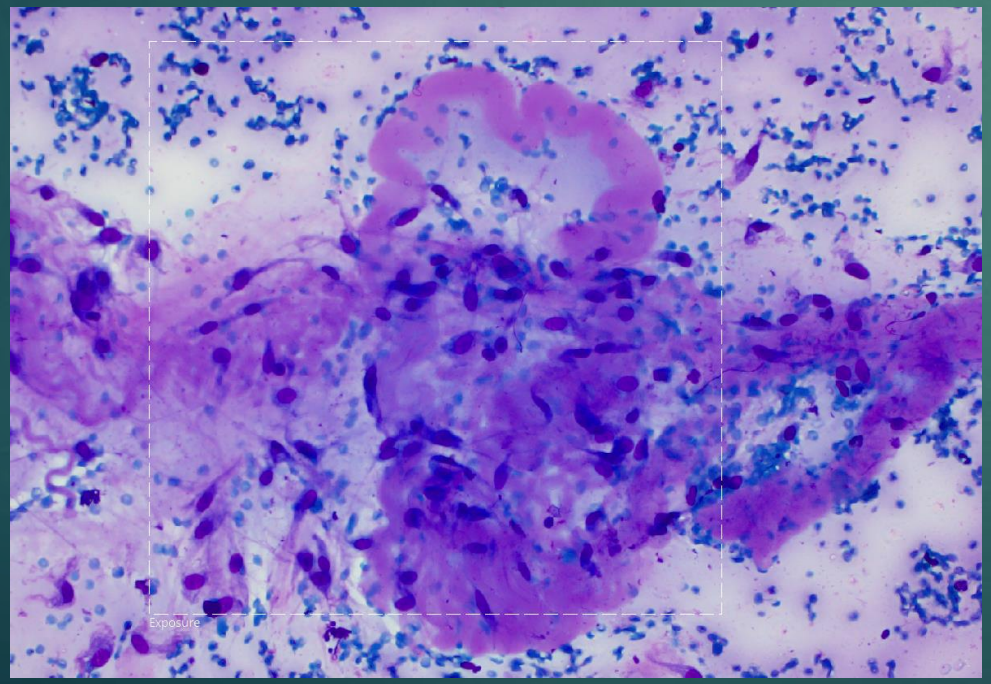
- Carcinomatous Component
  - Cytokeratins and EMA variably positive
  - Estrogen Receptor/Progesterone Receptor positive (endometrioid); ER/PR negative/positive (serous)
- Sarcomatous Component
  - CD10, CD34, Desmin, skeletal markers may be positive
  - Cytokeratins frequently positive
- Frequent aberrant p53 staining and strong p16 positivity in both

Uterine Carcinosarcoma, Genetics

- Similar molecular genetic alterations in carcinomatous and sarcomatous components
  - Loss of MMR proteins may occur
  - Copy-number high profile (60-78%)
  - *TP53, PIK3CA, FBXW7, PIK3R1, PIK3R2, PTEN, KRAS*

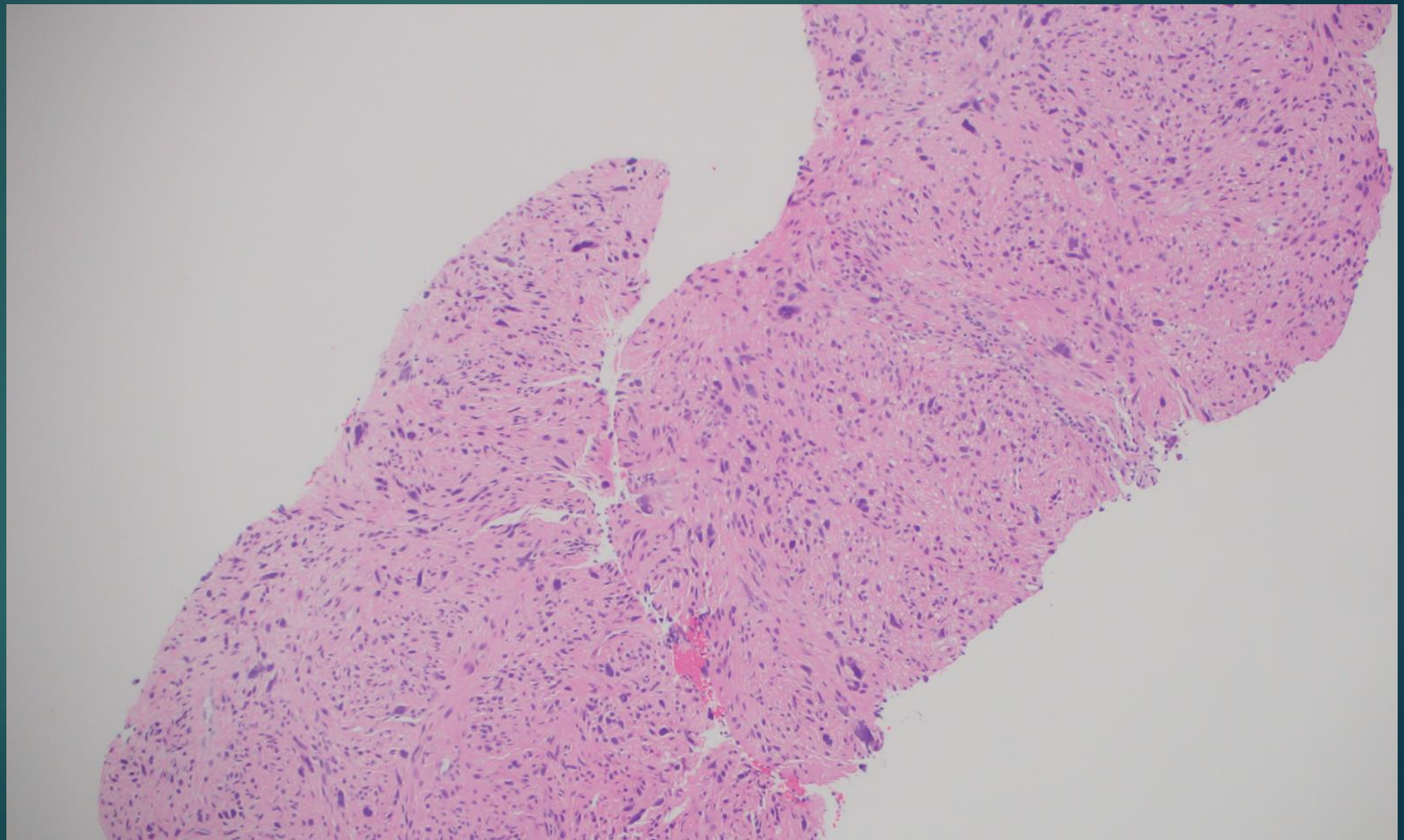




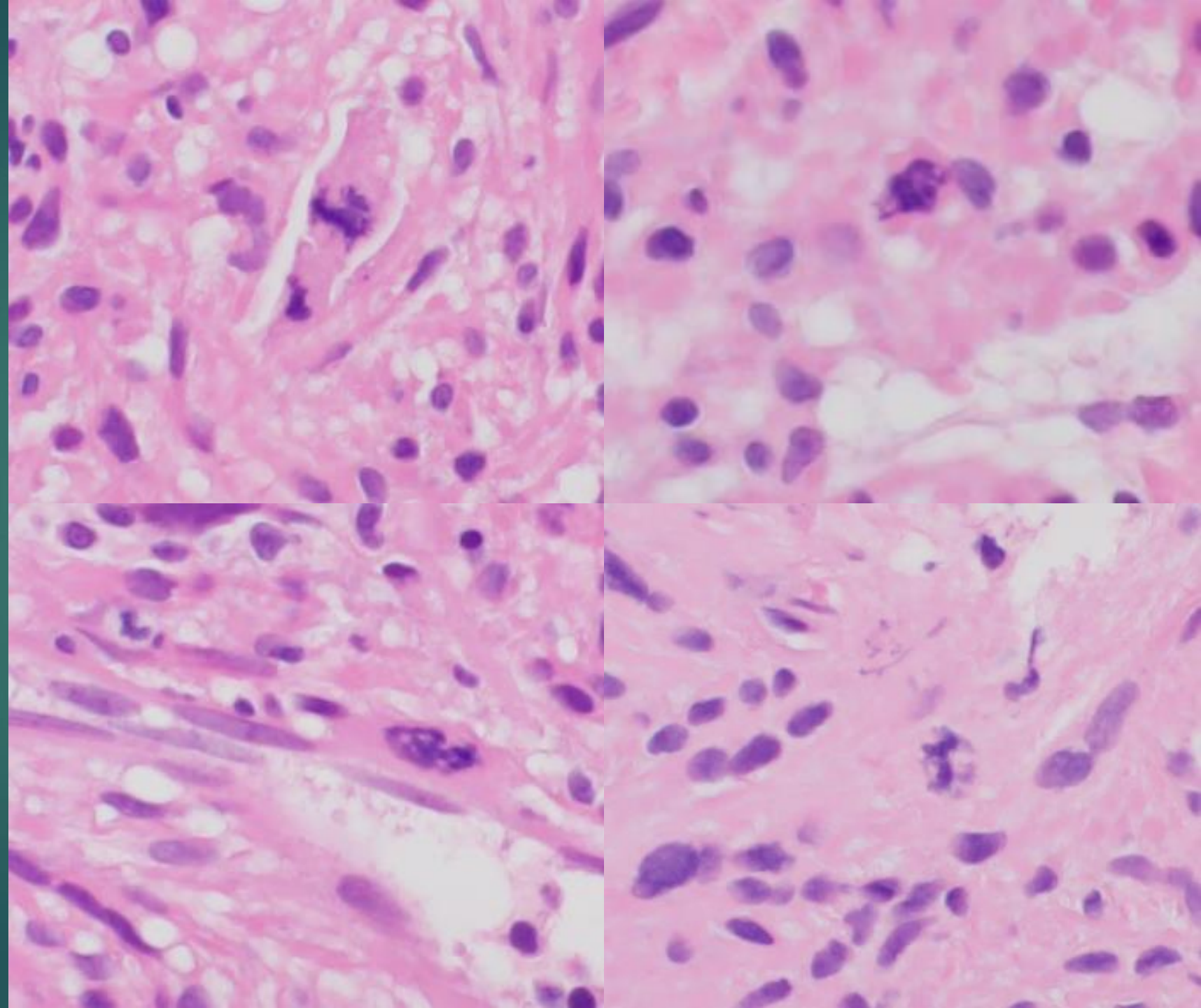


Case 2:
54 yo F, lung mass, ROSE, DQ
20x

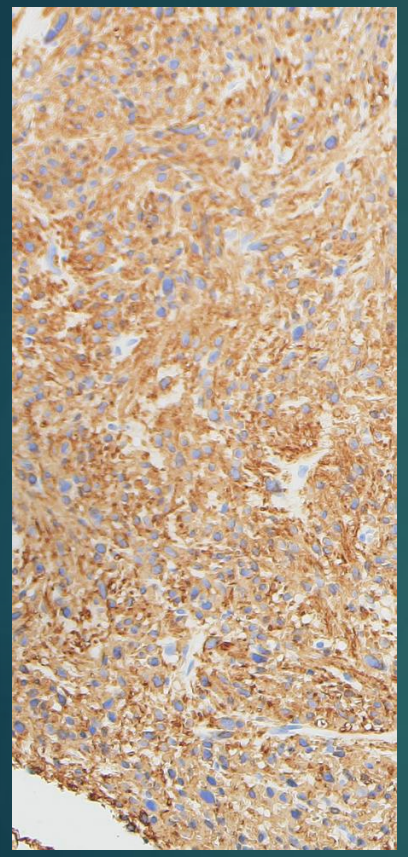
Core biopsy, 10x



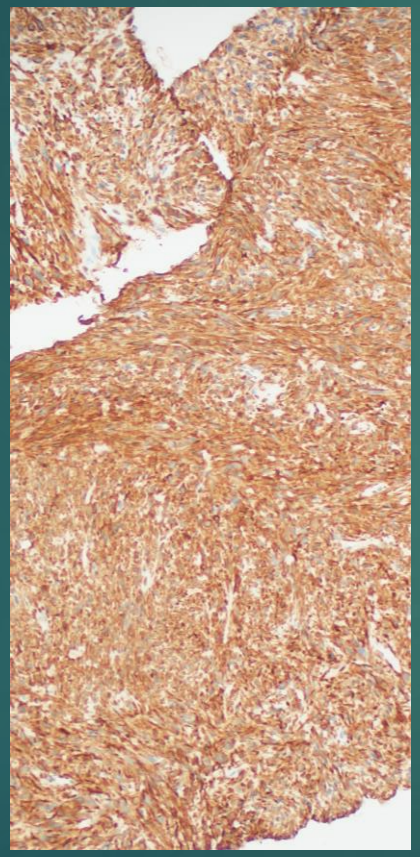
Core Biopsy, 40x



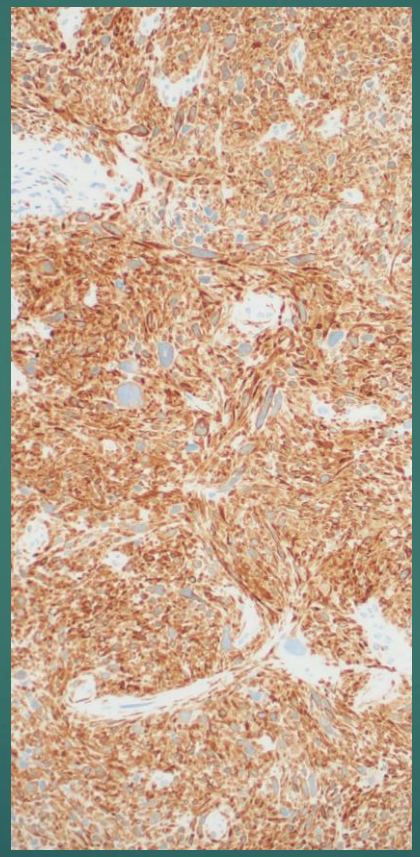
Stains, 20x



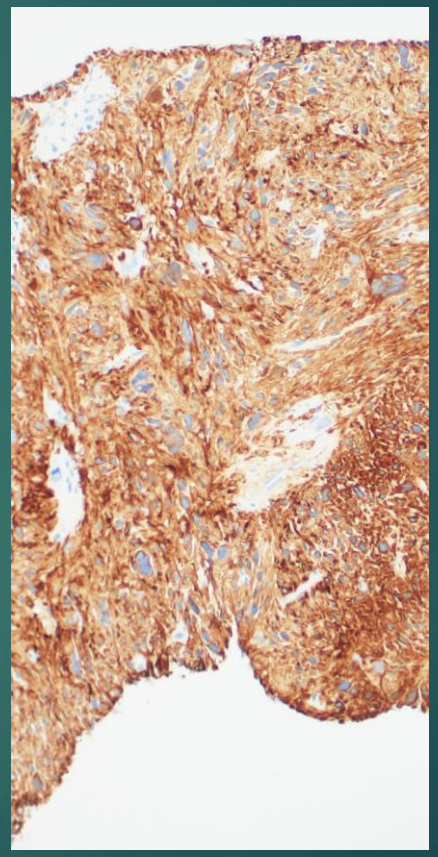
SMA



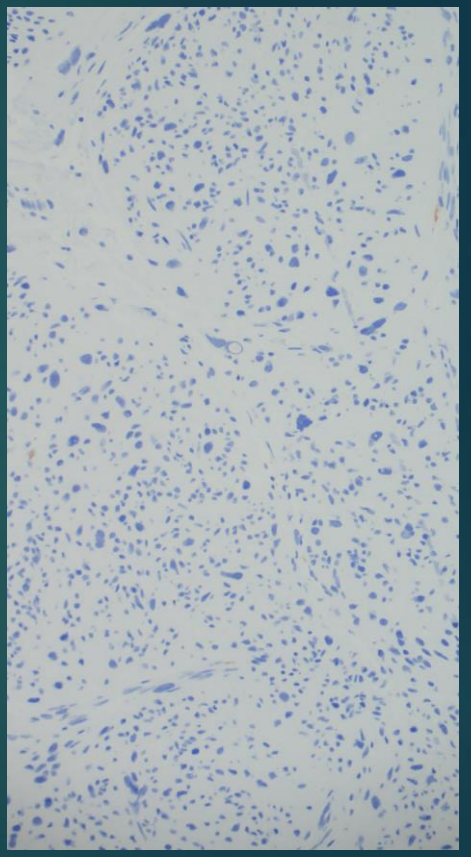
Desmin



Calponin



Caldesmon



S100

Malignant cells present, consistent with involvement by the patient's known uterine leiomyosarcoma

Uterine leiomyosarcoma

- Malignant mesenchymal tumor of smooth muscle lineage
- ~45% of uterine sarcomas
- Typically > 40 years old, peak at 50 years

Uterine leiomyosarcoma, Microscopic

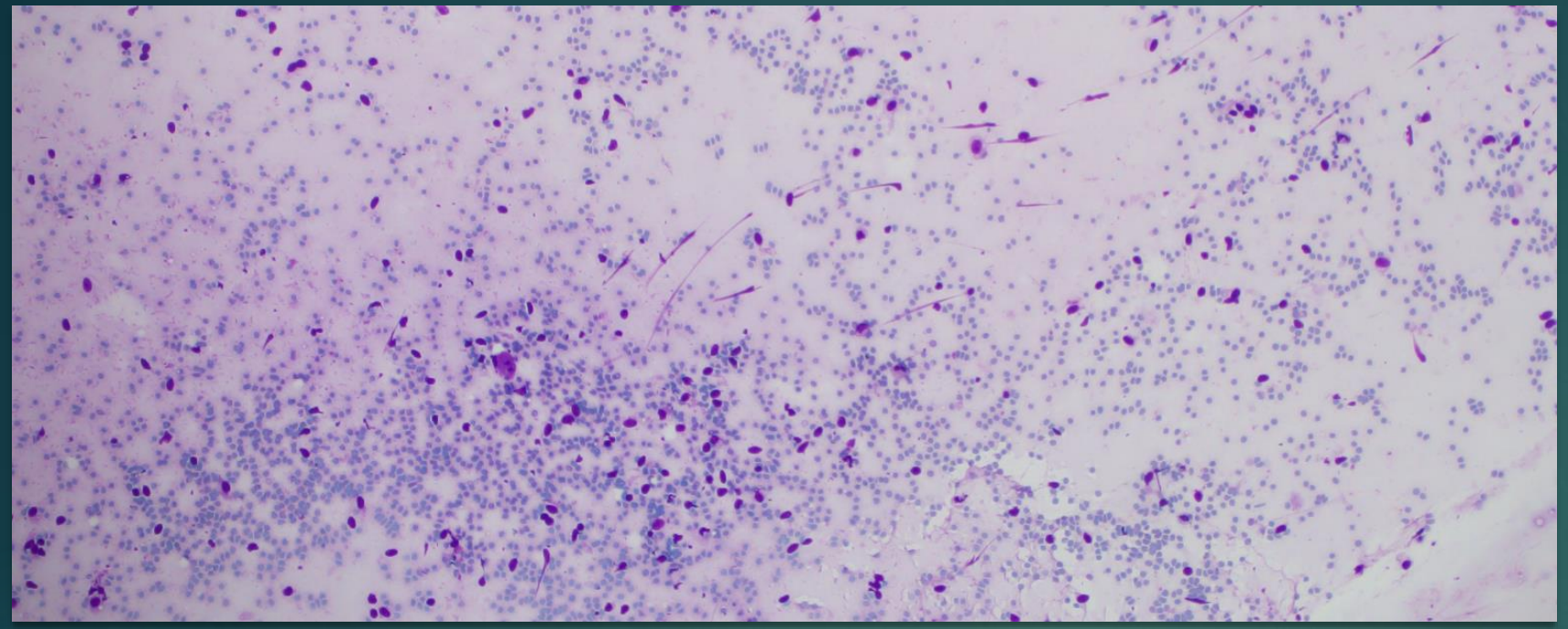
- Destructive infiltrative margin
- Spindle
  - Spindle (cigar-shaped nuclei) cells in long intersecting fascicles, sometimes with bizarre cytology
- Epithelioid
  - Polygonal cells in diffuse, nested, corded, or plexiform growth
- Myxoid
  - Spindle to stellate cells (nuclei not cigar-shaped) in diffuse or fascicular growth, possible cyst formation; myxoid background
- Tumor cell necrosis (abrupt transition from viable to necrotic tumor with no intervening areas of granulation tissue; atypical cells within areas of necrosis)
- Mitotic activity
  - Spindled: ≥ 10/10 HPF
  - Epithelioid: ≥ 4/10 HPF
  - Myxoid: > 1-2/10 HPF

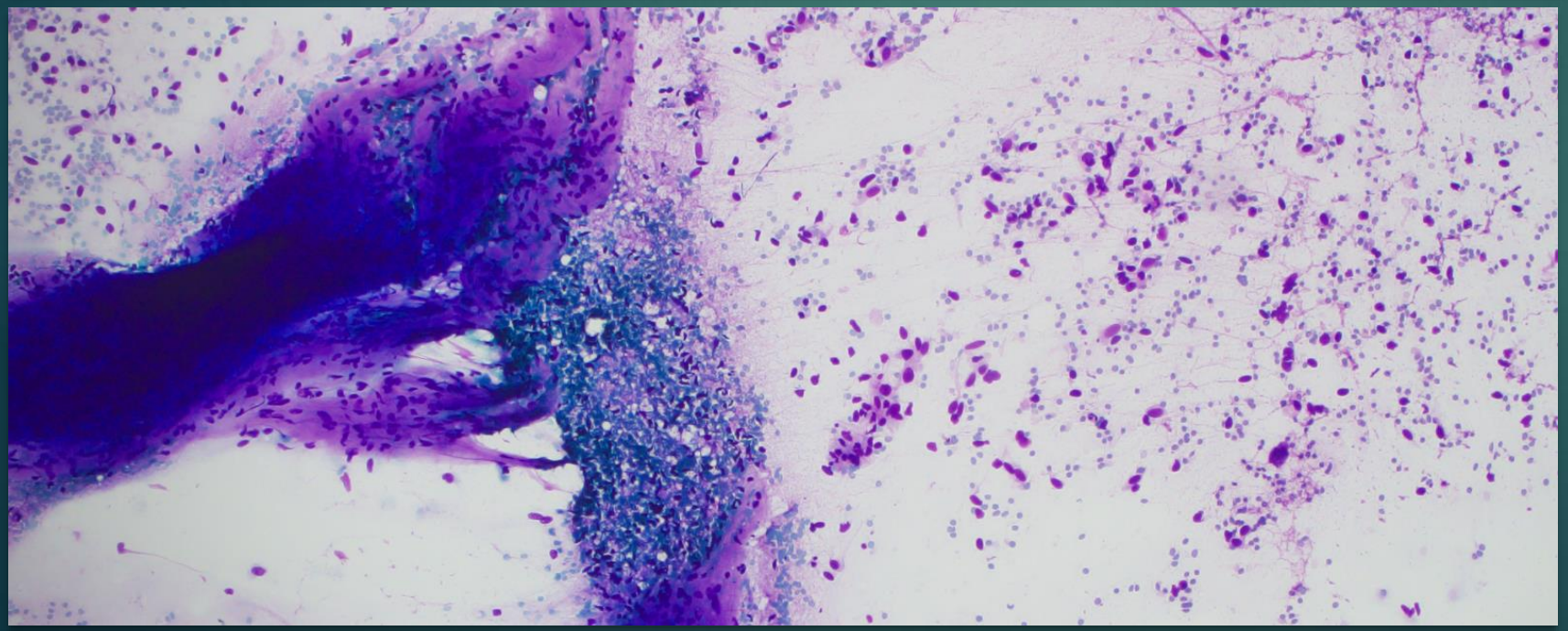
Uterine leiomyosarcoma, IHC

- SMA, Desmin, Caldesmon, Calponin positive
- Estrogen Receptor/Progesterone Receptor positive
- Cytokeratin may be positive in epithelioid
- S100 negative

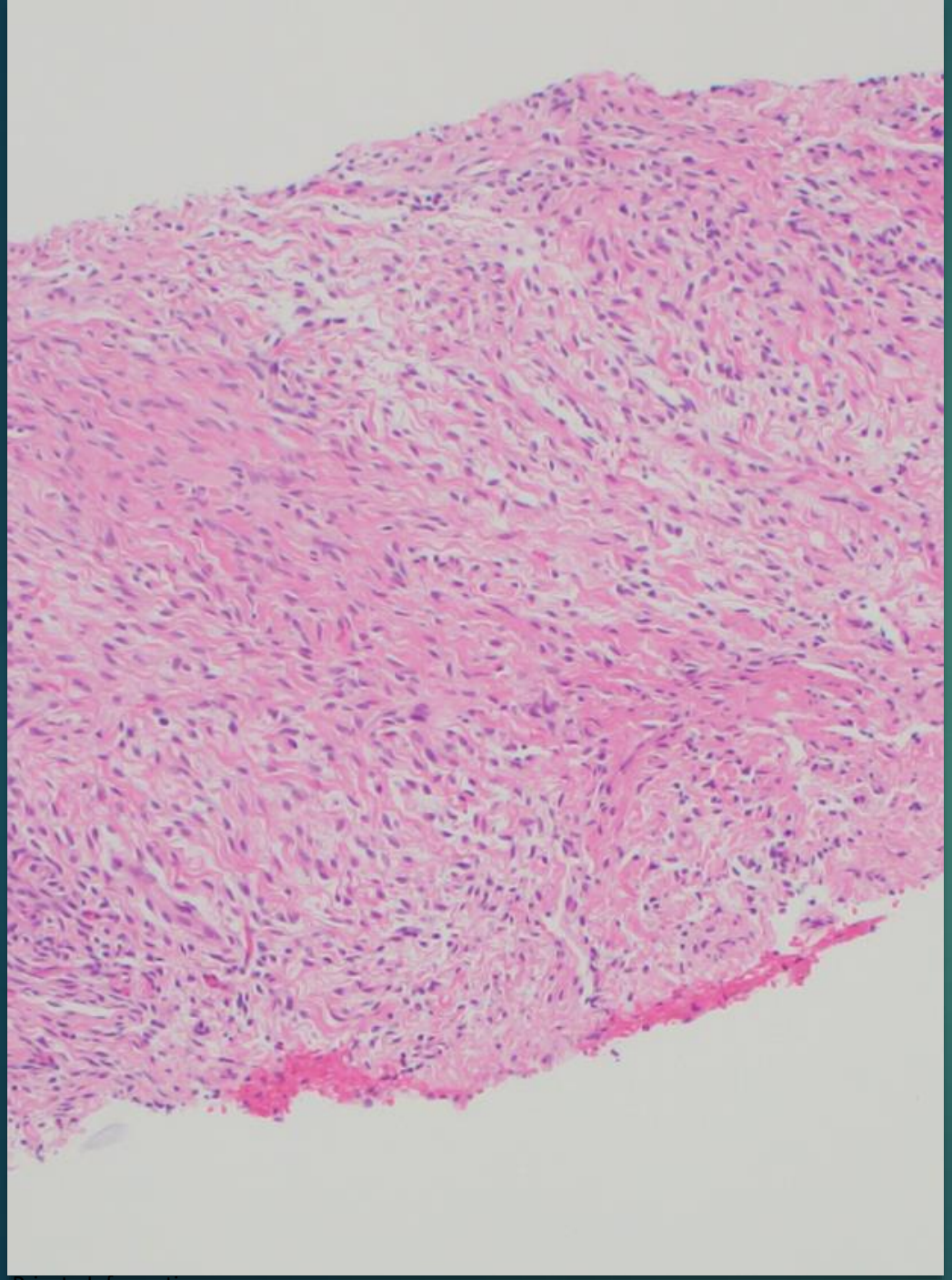
Uterine leiomyosarcoma, Genetics

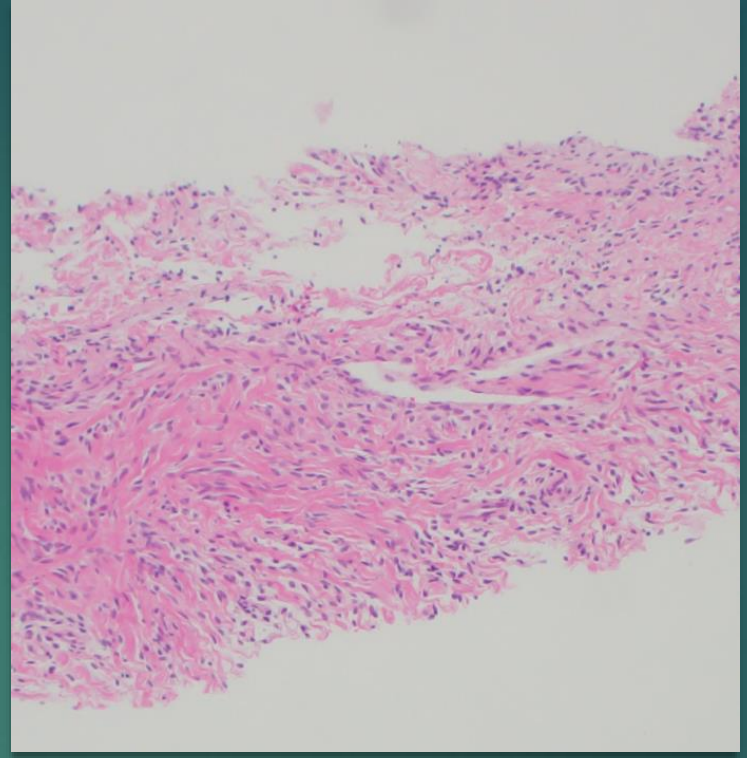
- Frequent *TP53* (~40%), *ATRX* (25%), *RB1, HMGA2* mutations



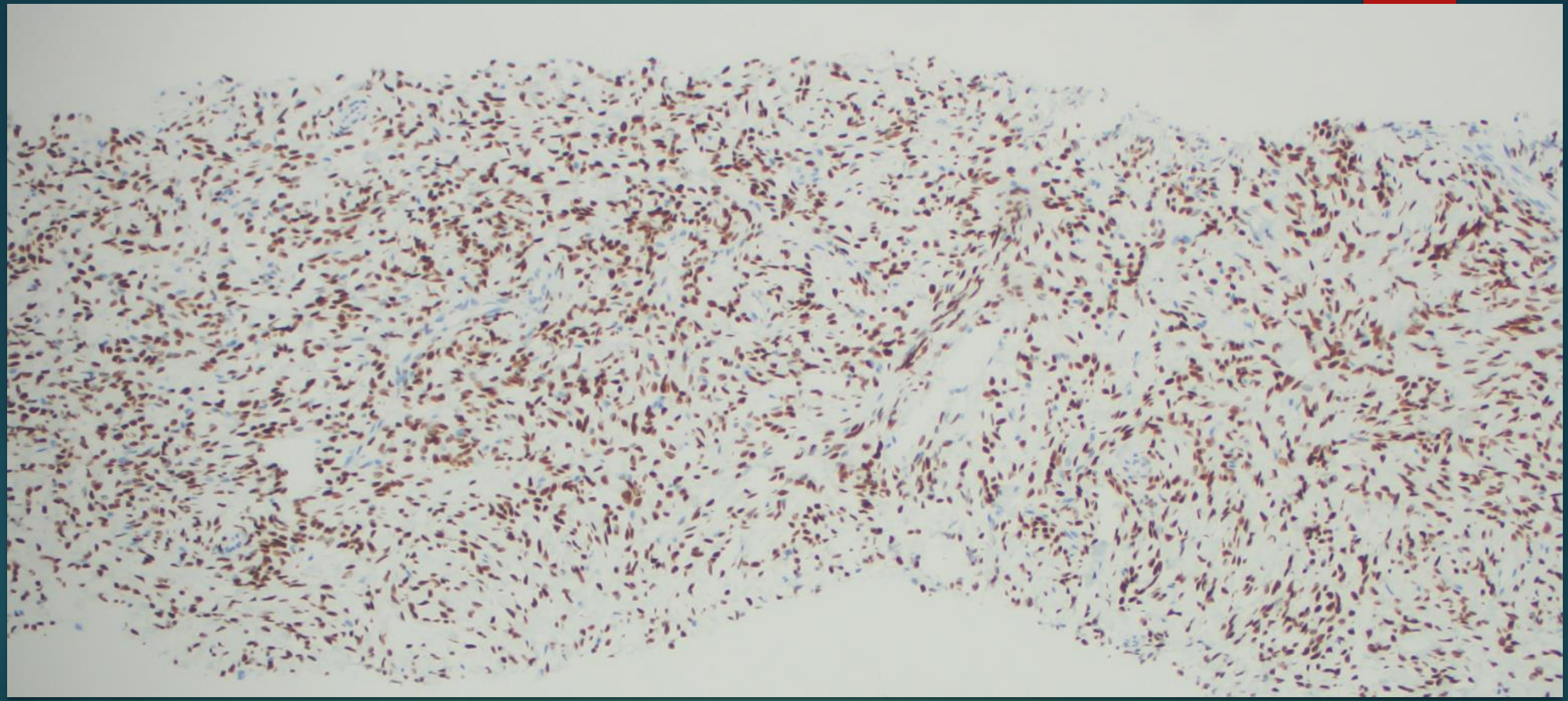


Case 3: 31 yo F, Left pleural mass, ROSE, DQ 10x



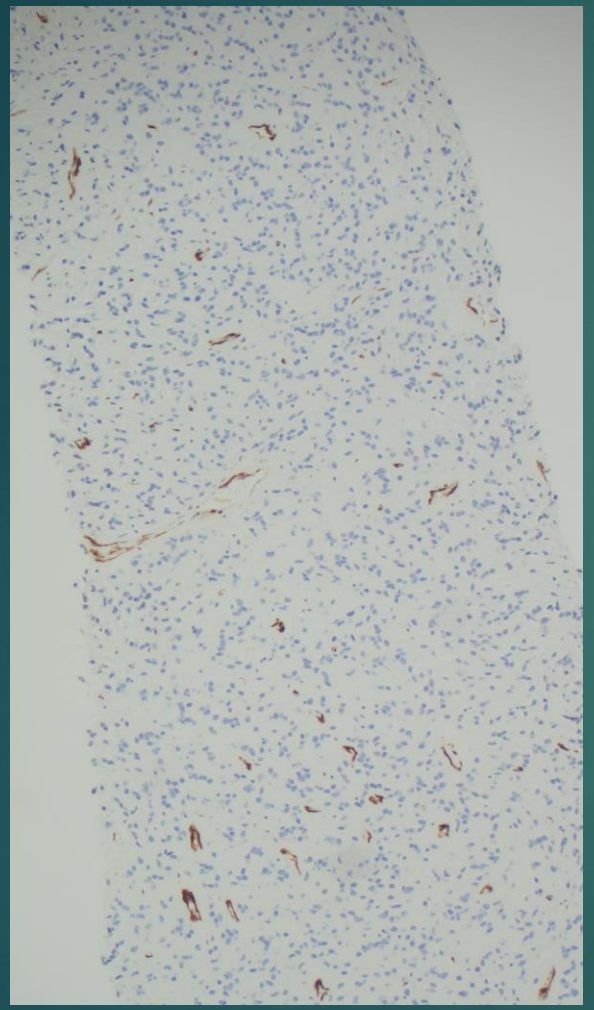


Core biopsy, 10x

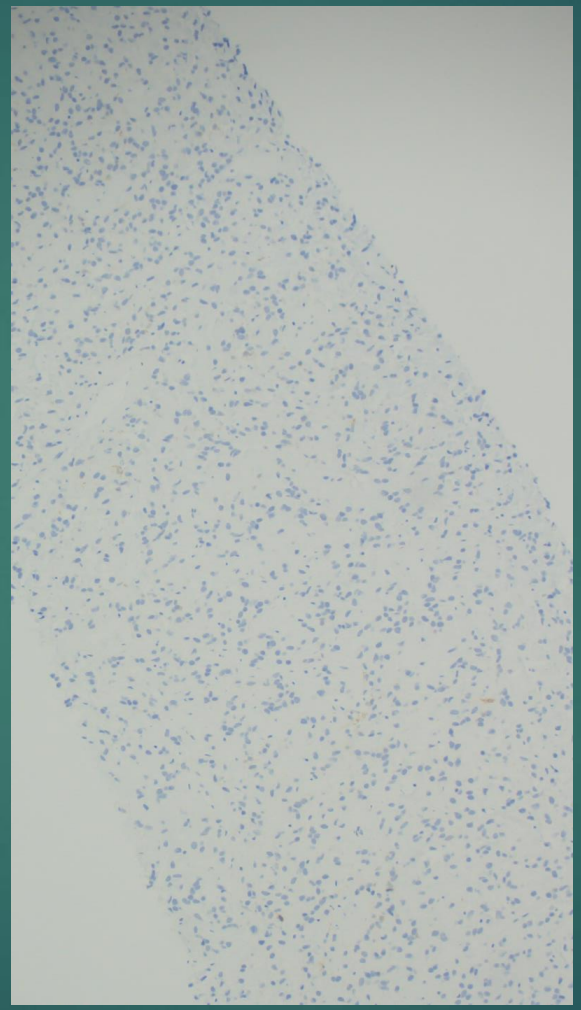


STAT6, 10x

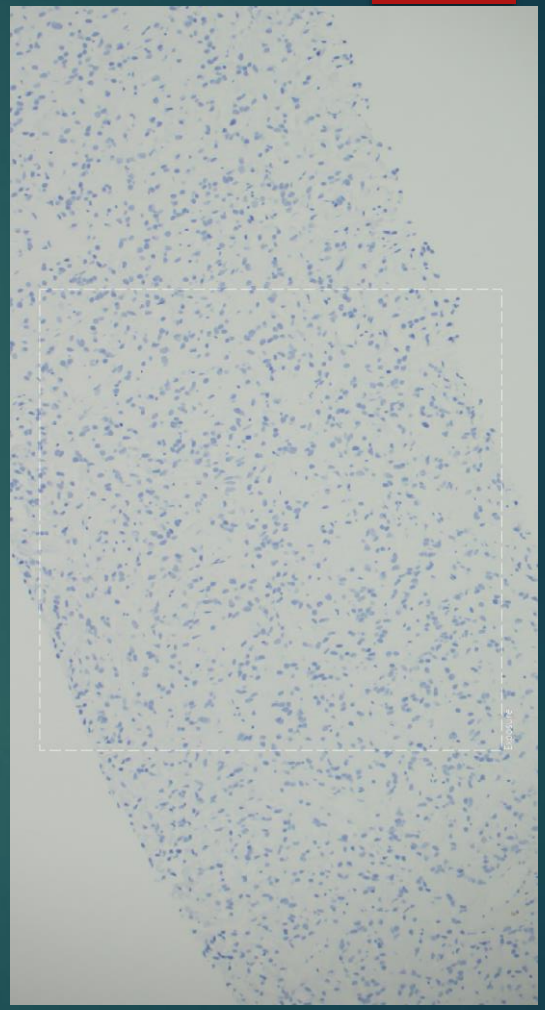
Other stains, 10x



SMA



Desmin



S100

Solitary fibrous tumor

Solitary Fibrous Tumor

- Fibroblastic mesenchymal neoplasm often characterized by prominent branching staghorn vascular pattern and *NAB2::STAT6* fusion
- 20-70 years of age
- Can arise virtually anywhere
- Most are benign (85-90%)
  - Risk stratification should be performed

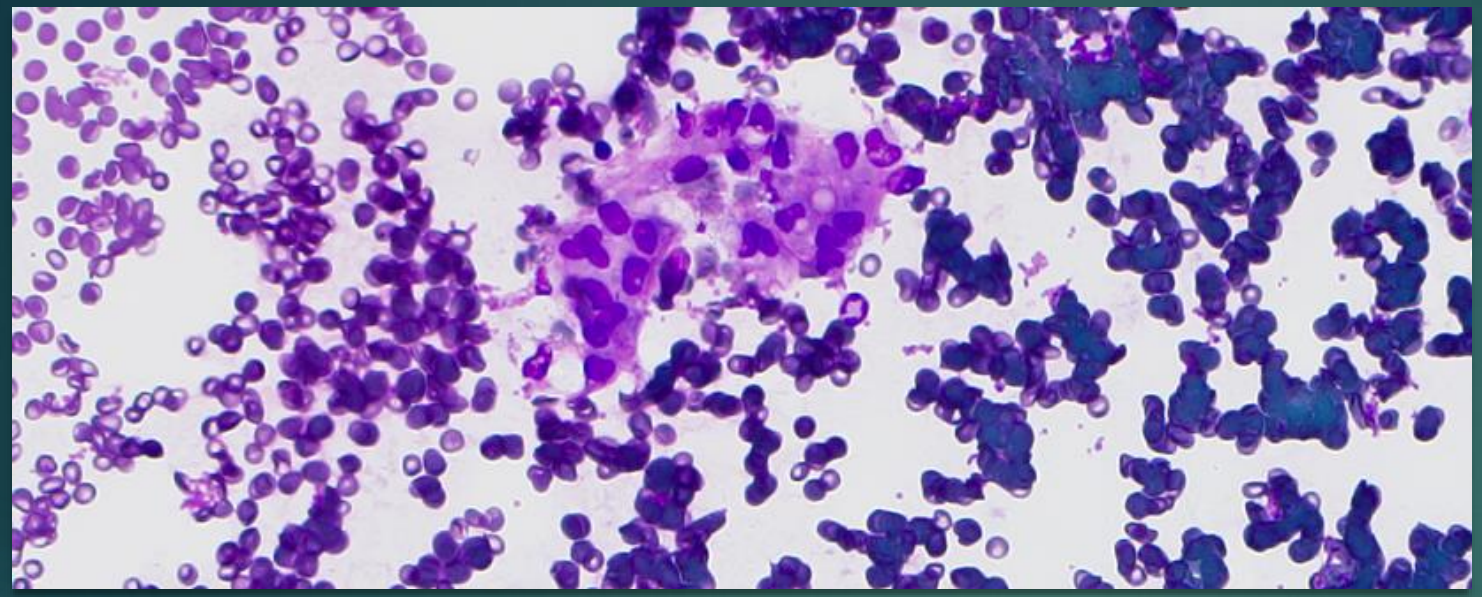
Solitary Fibrous Tumor, Microscopic & IHC

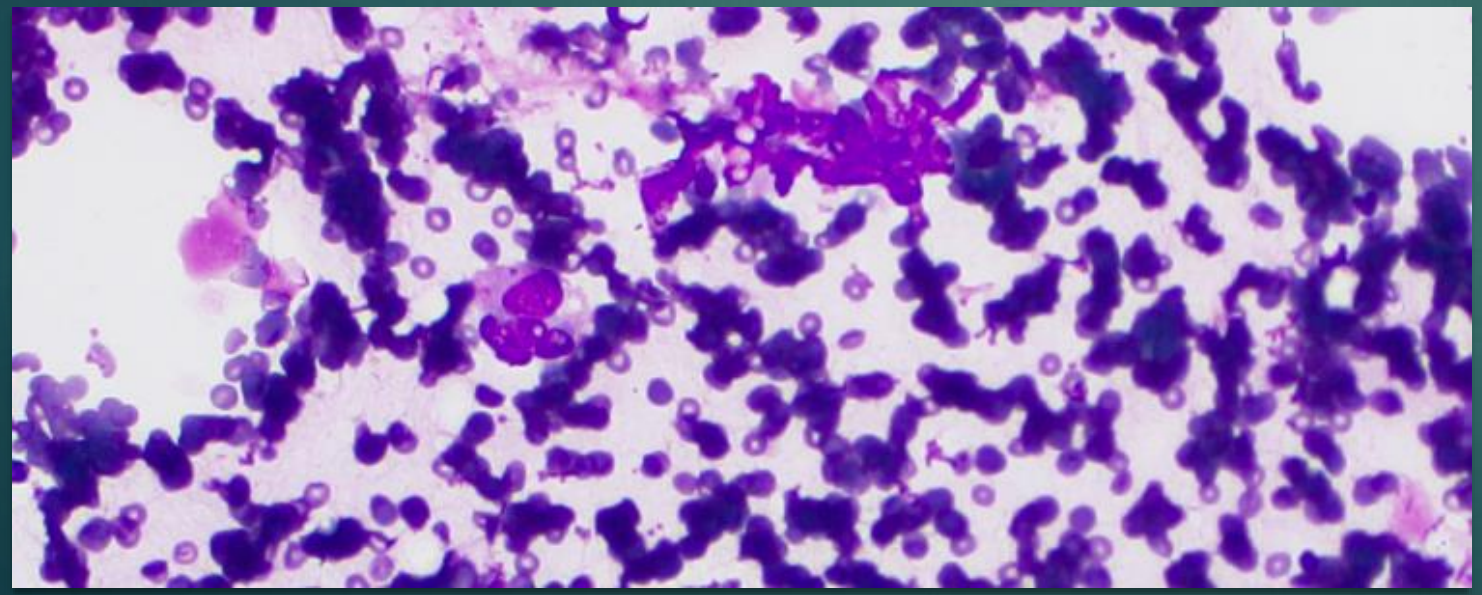
- Classic "patternless" pattern showing field-to-field variations in cellularity and general absence of defined architecture
  - Tumors can show areas of more defined storiform, trabecular, or fascicular growth
- Cells are spindled to ovoid with scant cytoplasm and small, uniform, vesicular nuclei
- Characteristic prominent vascular pattern: branching or "staghorn-shaped" vessels commonly with perivascular hyalinization
- IHC: STAT6 diffusely positive, often diffuse, strong CD34 positivity but can be patchy
  - Generally keratin, S100, SOX10, Desmin, CD117, DOG1, CD31, and ERG negative

Solitary Fibrous Tumor, Risk Stratification: Demicco, et al

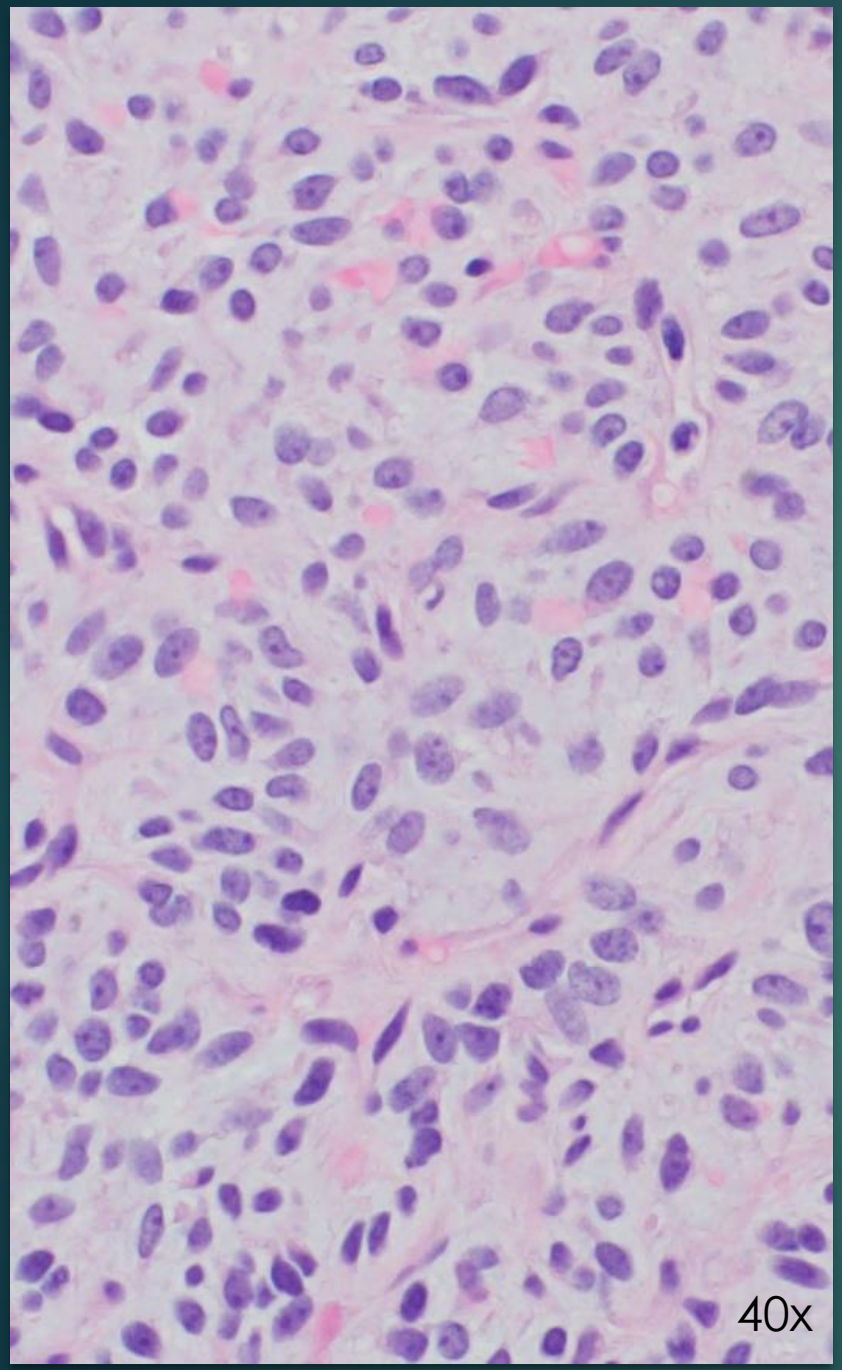
Risk Factor	Cut-off	Points assigned (3 variable model)	Points assigned (4 variable model)
Patient age (years)	<55	0	0
	≥55	1	1
Mitoses per 10 HPFs	0	0	0
	1-3	1	1
	≥4	2	2
Tumor size (cm)	0-4.9	0	0
	5-9.9	1	1
	10-14.9	2	2
	≥15	3	3
Tumor necrosis	<10%	n/a	0
	≥10%	n/a	1
Risk	Low	0-2 points	0-3 points
	Intermediate	3-4 points	4-5 points
	High	5-6 points	6-7 points

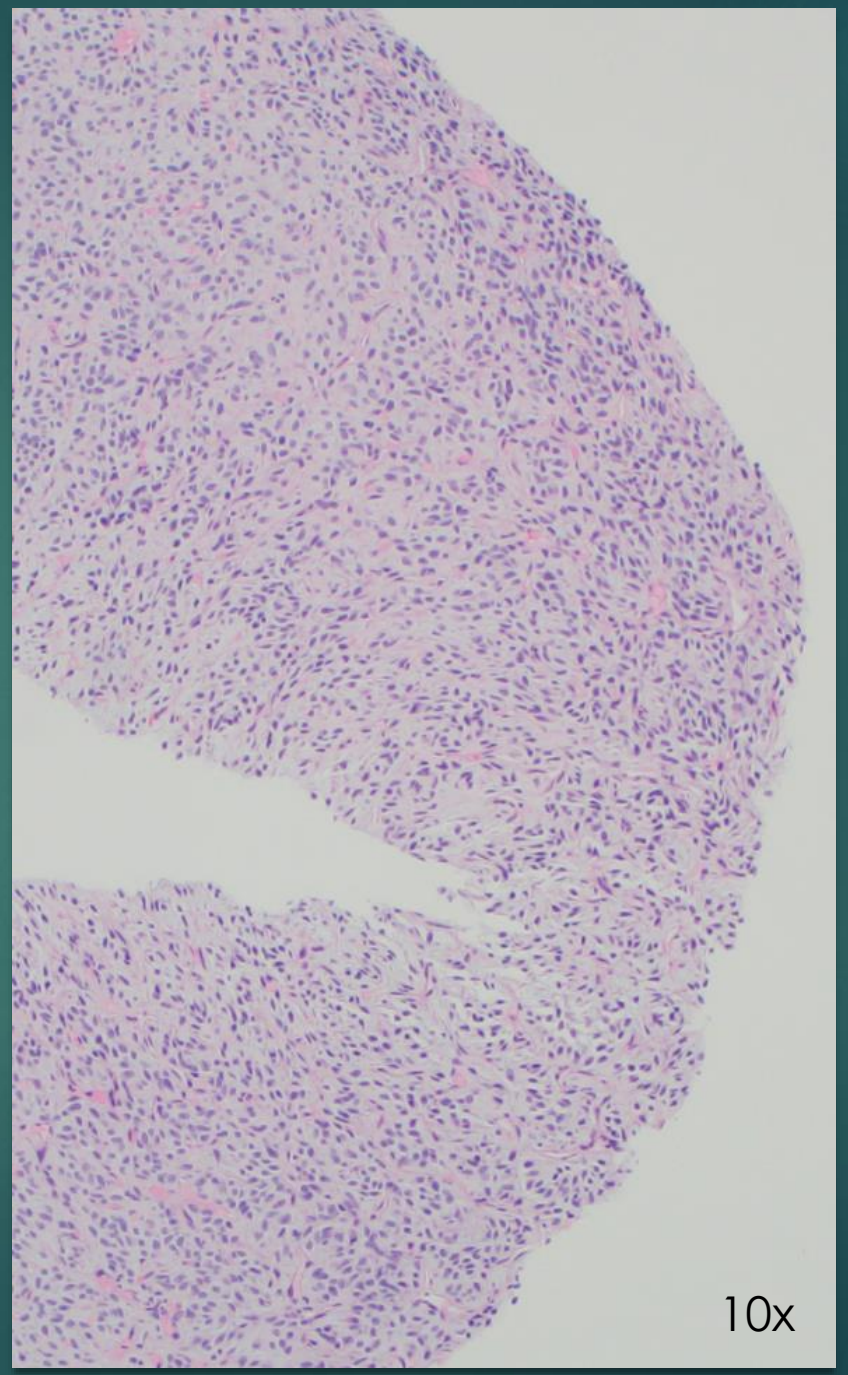
Adapted from WHO:
Demicco, EG, Fritchie, KJ, Han A. Solitary fibrous tumour. In: WHO Classification of Tumours Editorial Board. Soft tissue and bone tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2020 [cited 2024 Jan 16]. (WHO classification of tumours series, 5th ed.; vol. 3). Available from: https://https://tumourclassification.iarc.who.int/chaptercontent/33/37.



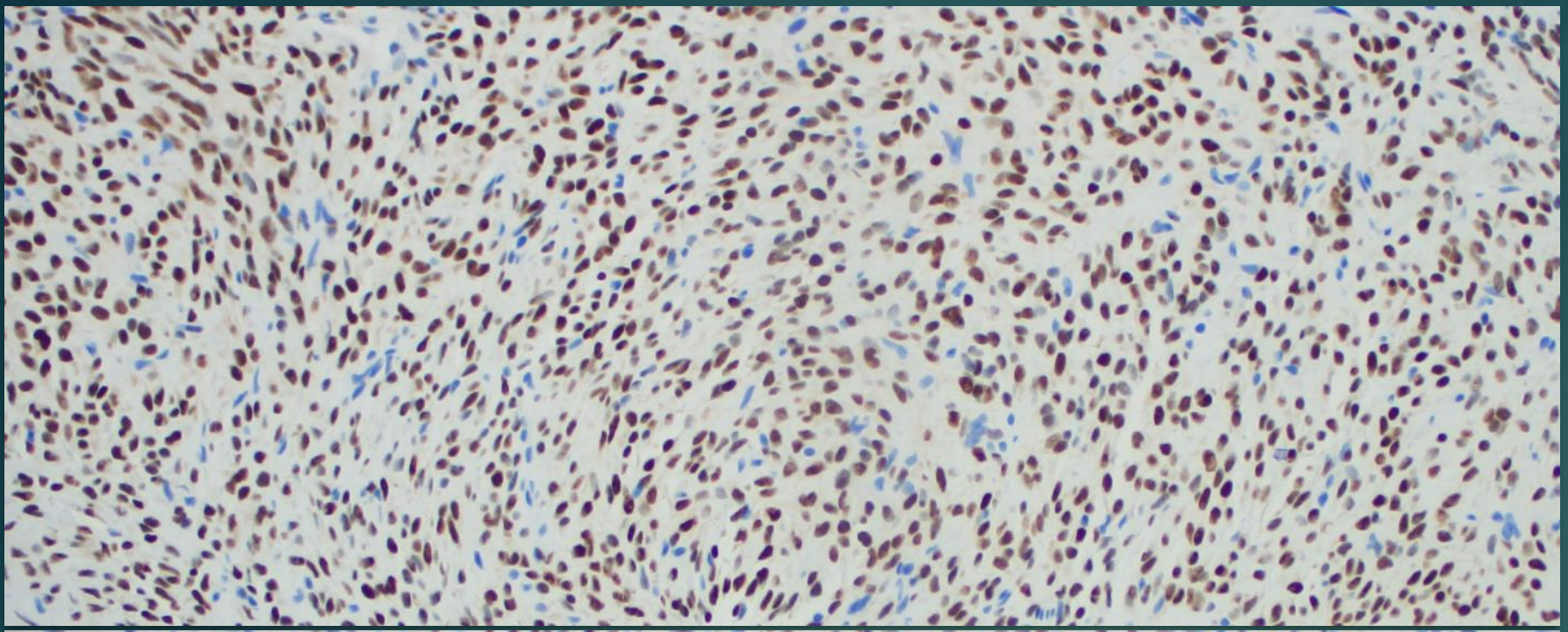


Case: 4
50 yo F, Lung mass, ROSE, DQ 20x

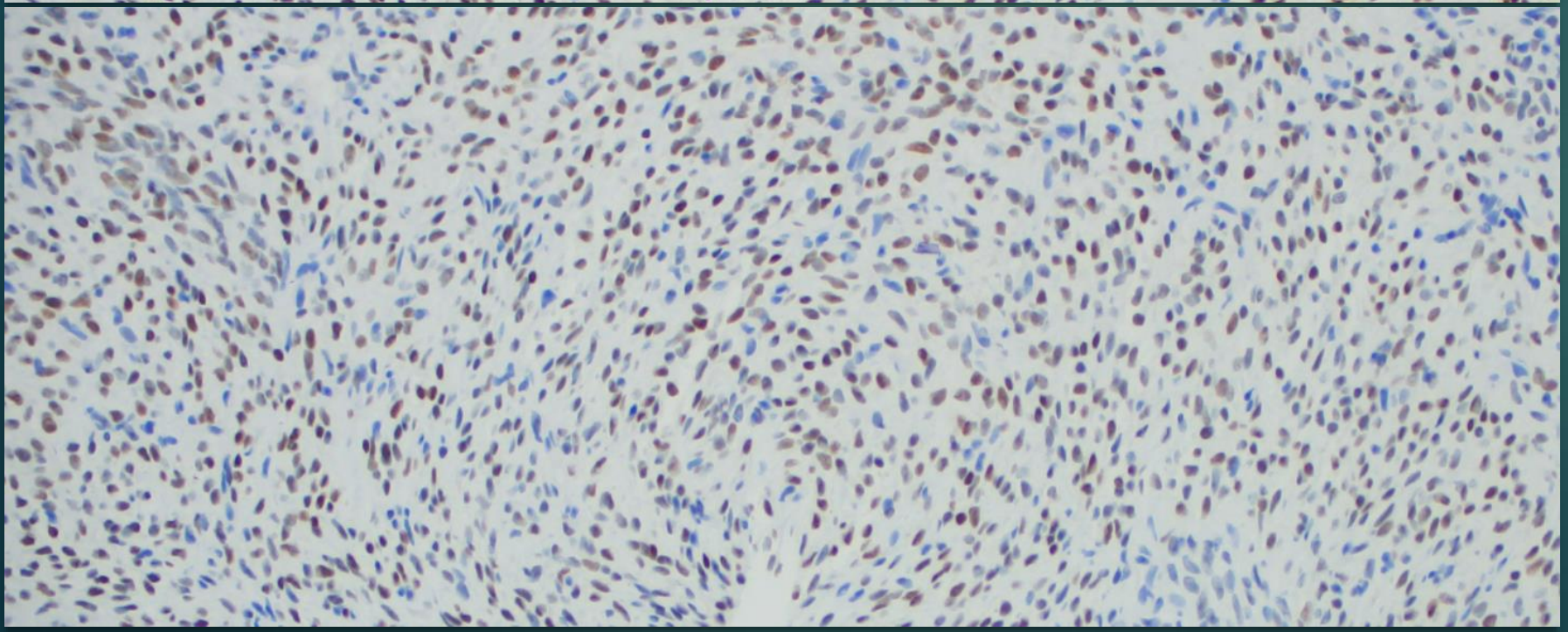




Core Biopsy



Progesterone



Estrogen

Negative stains:
Caldesmon,
CD117,
STAT-6,
DOG-1

Pertinent history: Patient previously diagnosed with uterine neoplasm that has a JAZF1-PHF1 mutation

Consistent with involvement by the patient's known endometrial stromal sarcoma

Patient previously diagnosed with Low-Grade Endometrial Sarcoma

Low-Grade ESS

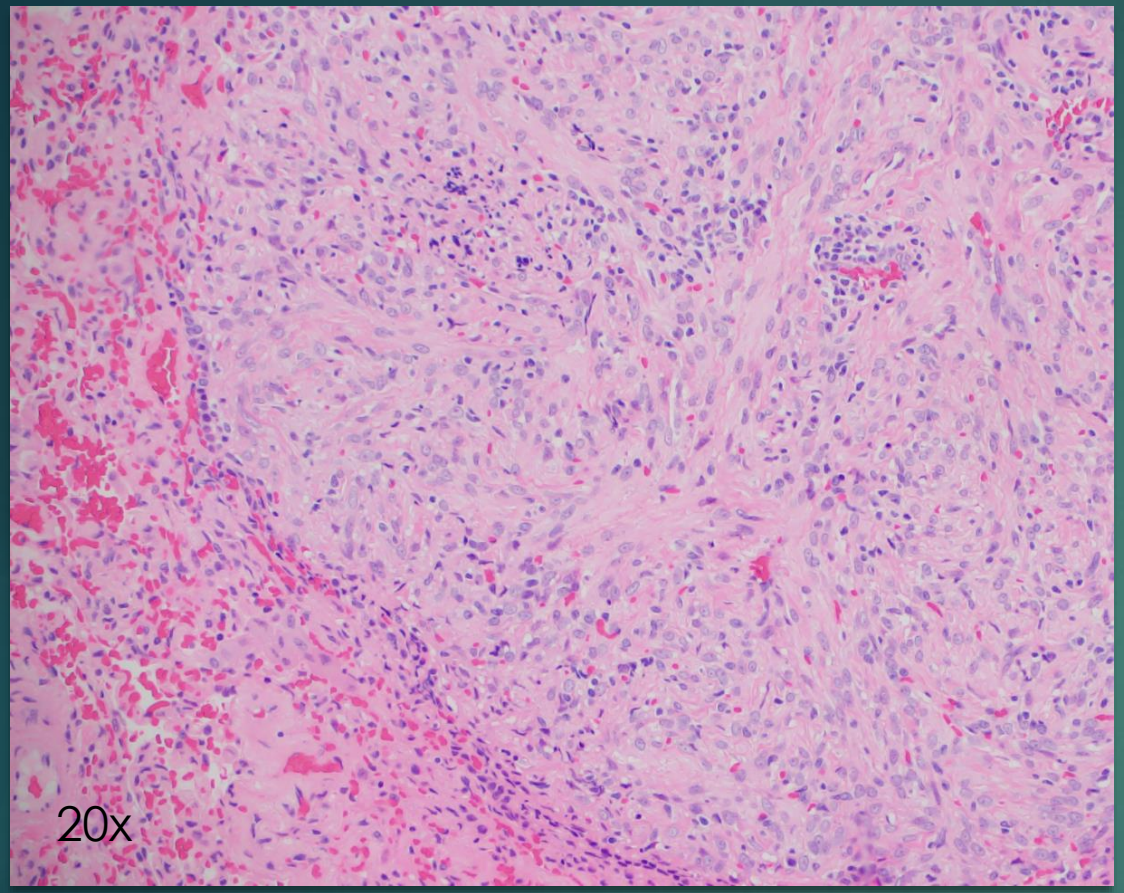
- 6-20% of all uterine sarcomas; 0.1-1.0% of all uterine malignancies
- Mean age 55 years old (17-96)
- Microscopic
  - Small, oval cells with high N:C ratio, evenly distributed chromatin, small nucleoli
  - Typically low mitotic activity (<5/10 HPF) but may be high (up to 15-20/10 HPF
- IHC
  - CD10 (+/focally+/-), ER/PR + (typically), rare Desmin, Caldesmon staining unless smooth muscle differentiation, Inhibin + if sex cord-like differentiation
  - Cyclin-D1, BCOR, DOG1 typically negative
- Genetics
  - t(7;17) most common (*JAZF1*::*SUZ12* fusion)
  - *PHF1* gene arrangements (sex cord areas)

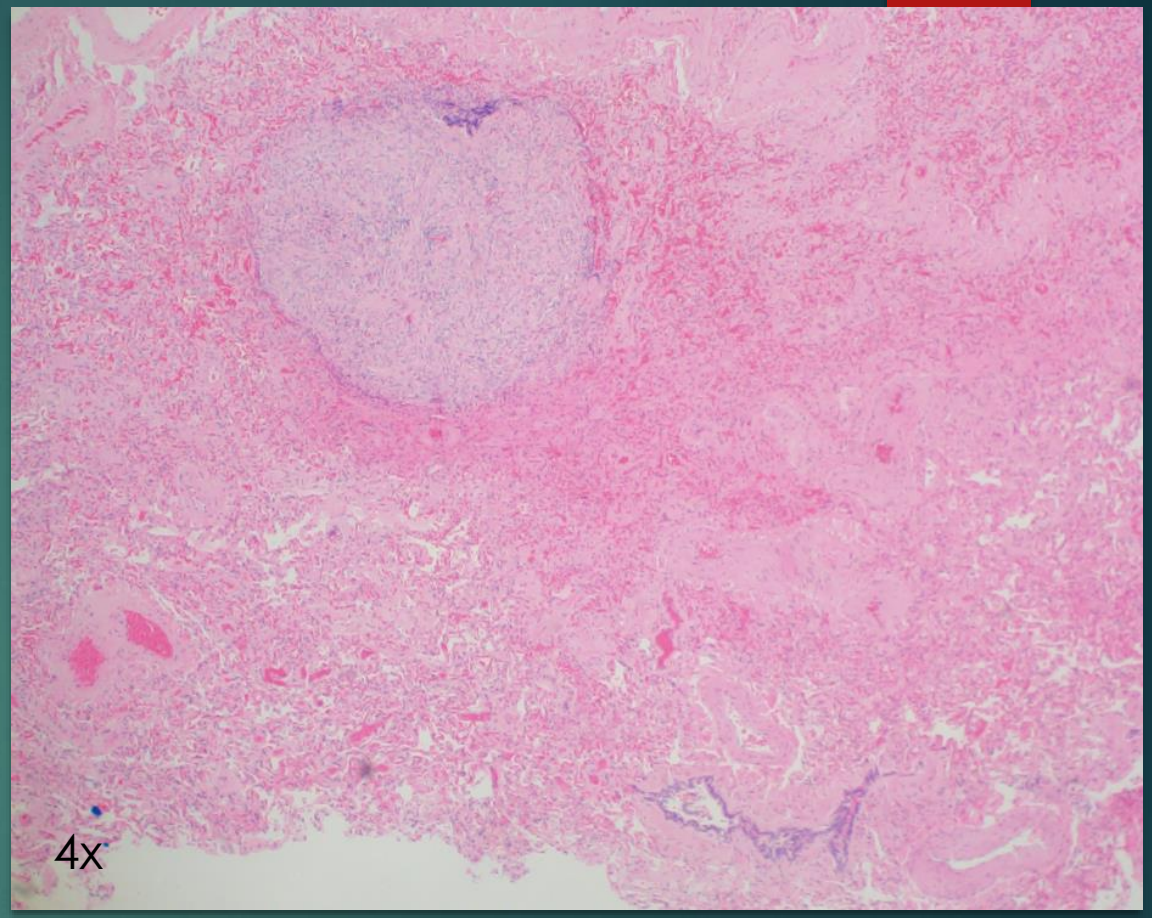
Some notes on High-Grade ESS

- Incidence is rare; mean 50 years (20-67), though young age (mean ~44 years) if *BCOR* ITD

- High grade endometrial stromal neoplasm with variable morphologies and staining profiles depending on molecular type
  - *YWHAE::NUTM2A/NUTM2B* HG-ESS
  - *ZC3H7B::BCOR* HG-ESS
  - *BCOR* ITD HG-ESS
  - *BCORL1* HG-ESS
  - High-grade sarcoma NOS, associated with conventional low-grade ESS

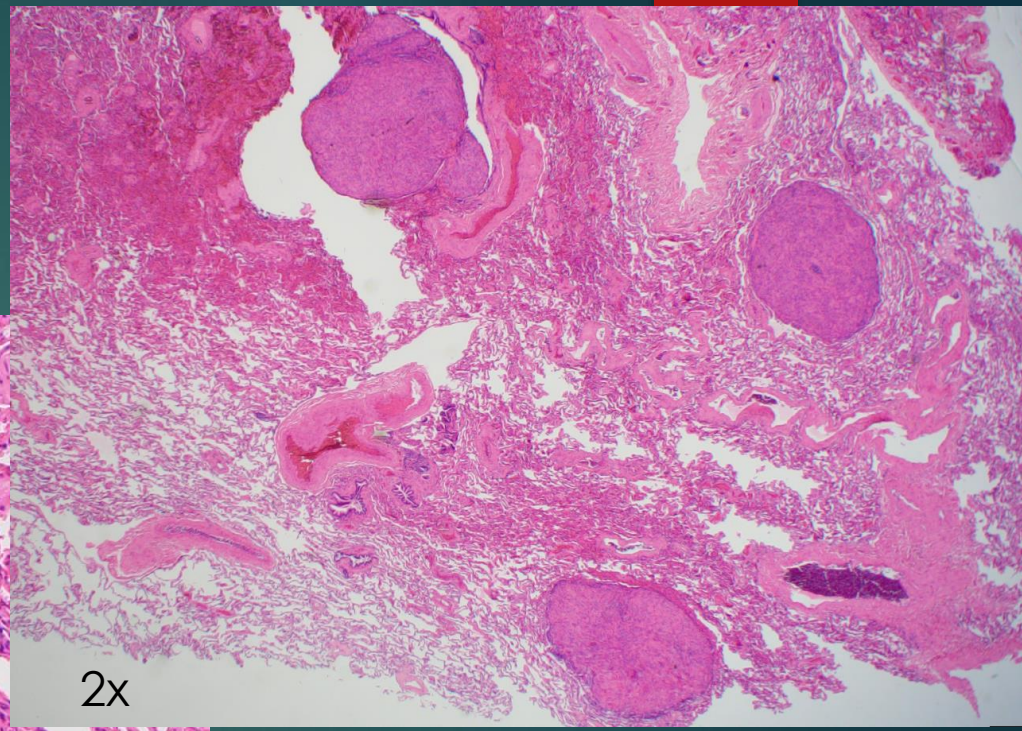
Case 5:
46 yo F with multiple left-sided pulmonary nodules. History of melanoma. Undergoes VATS procedure with multiple wedge resections

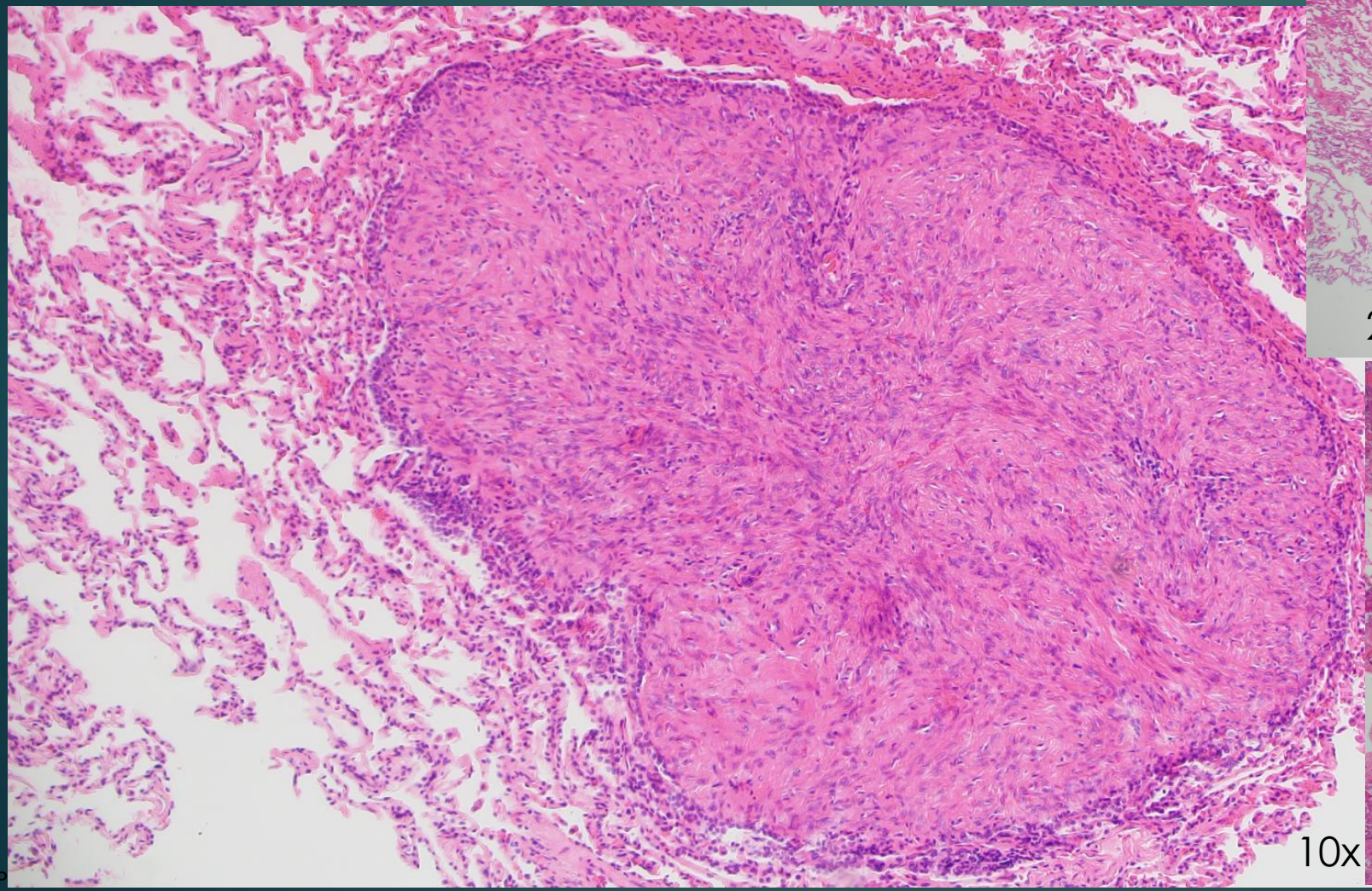


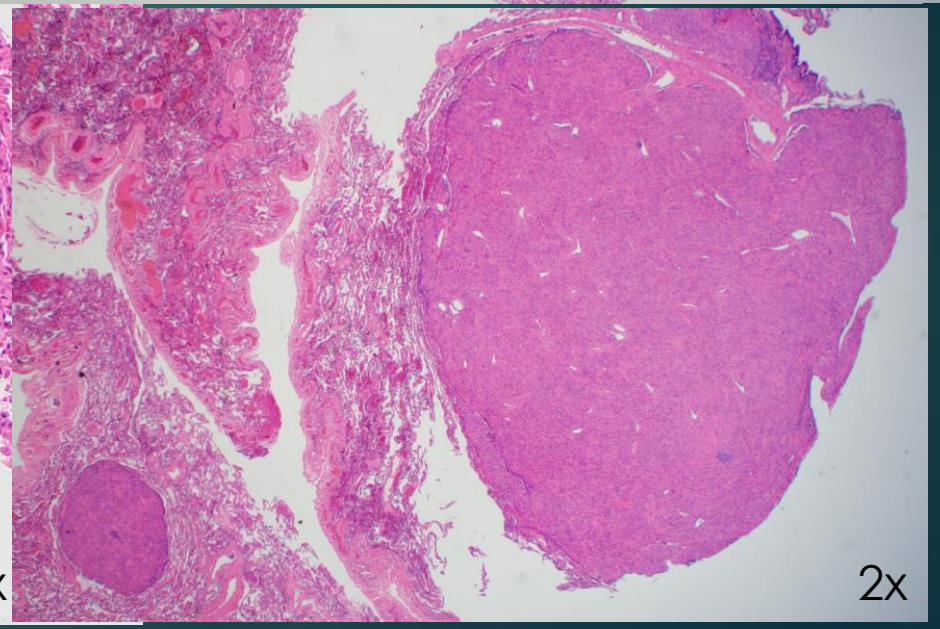


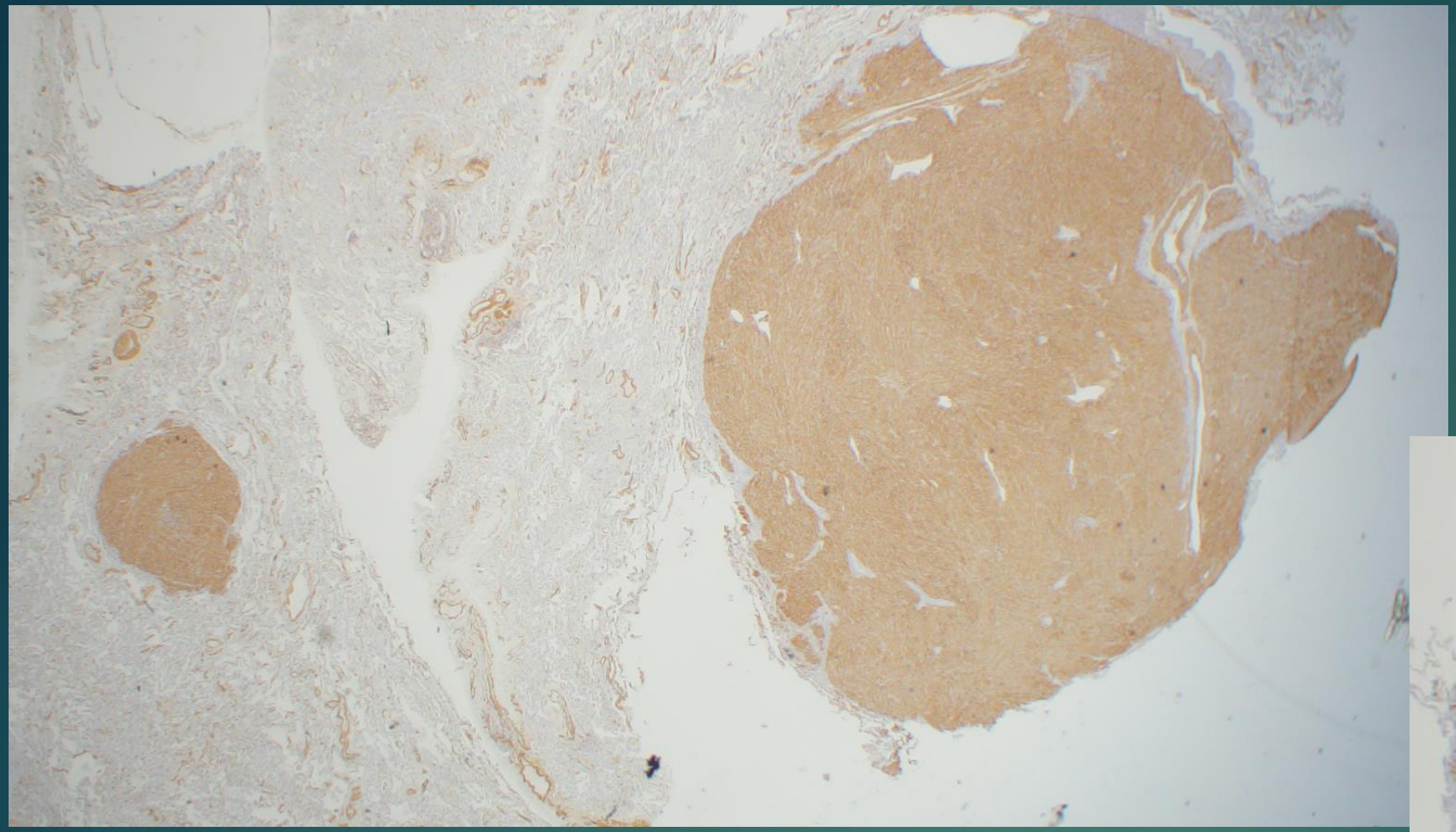
Multiple wedge resection specimens

Wedge resections



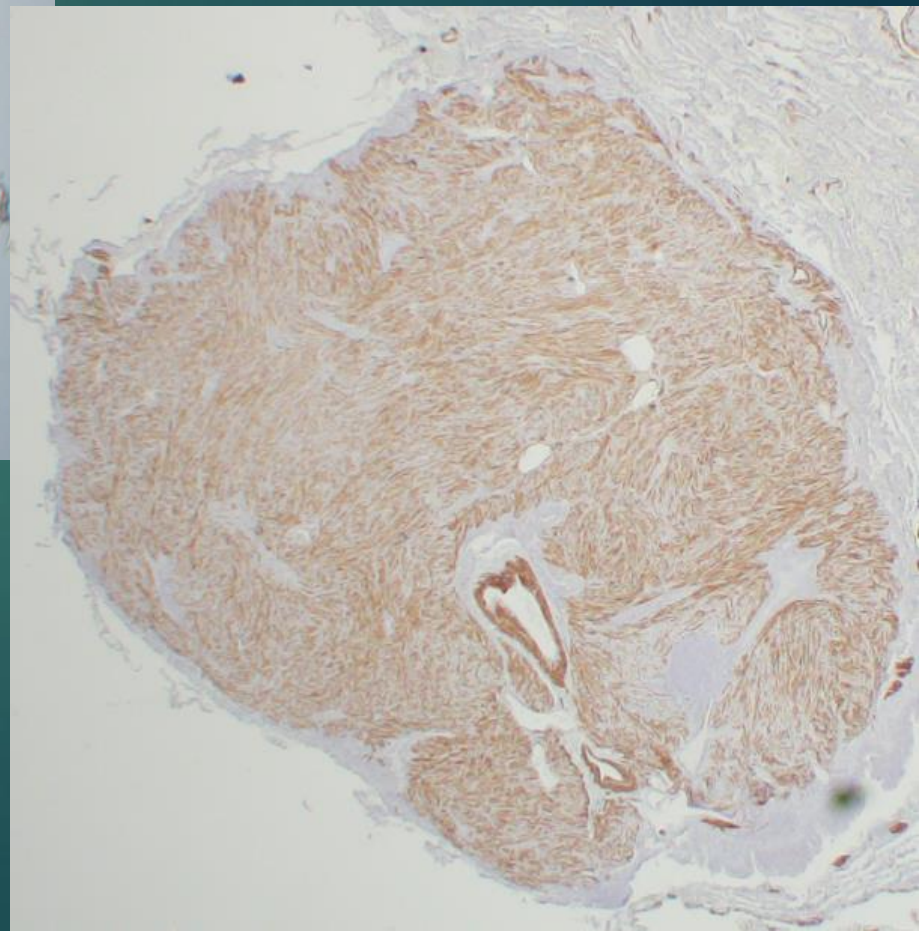


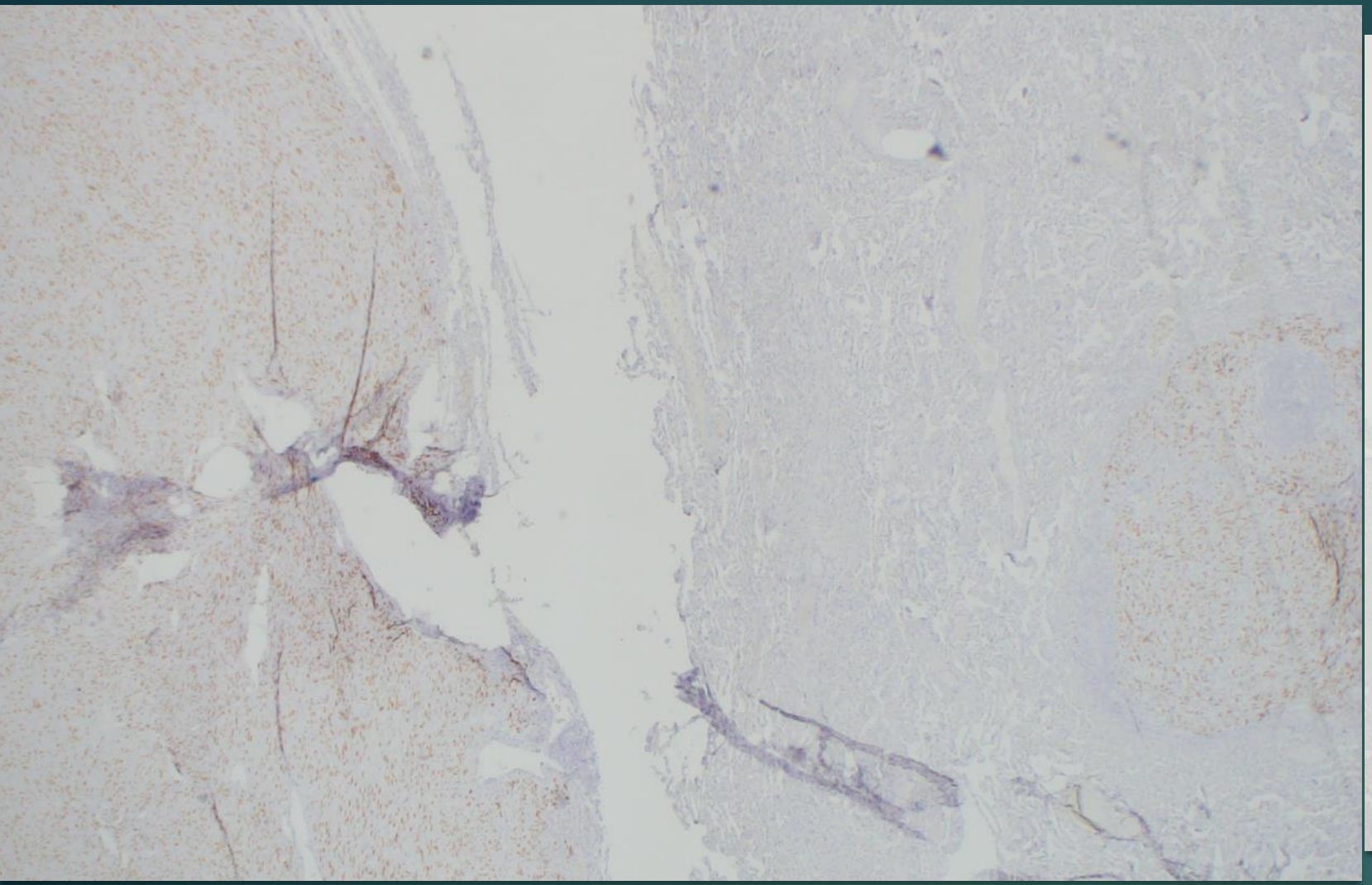




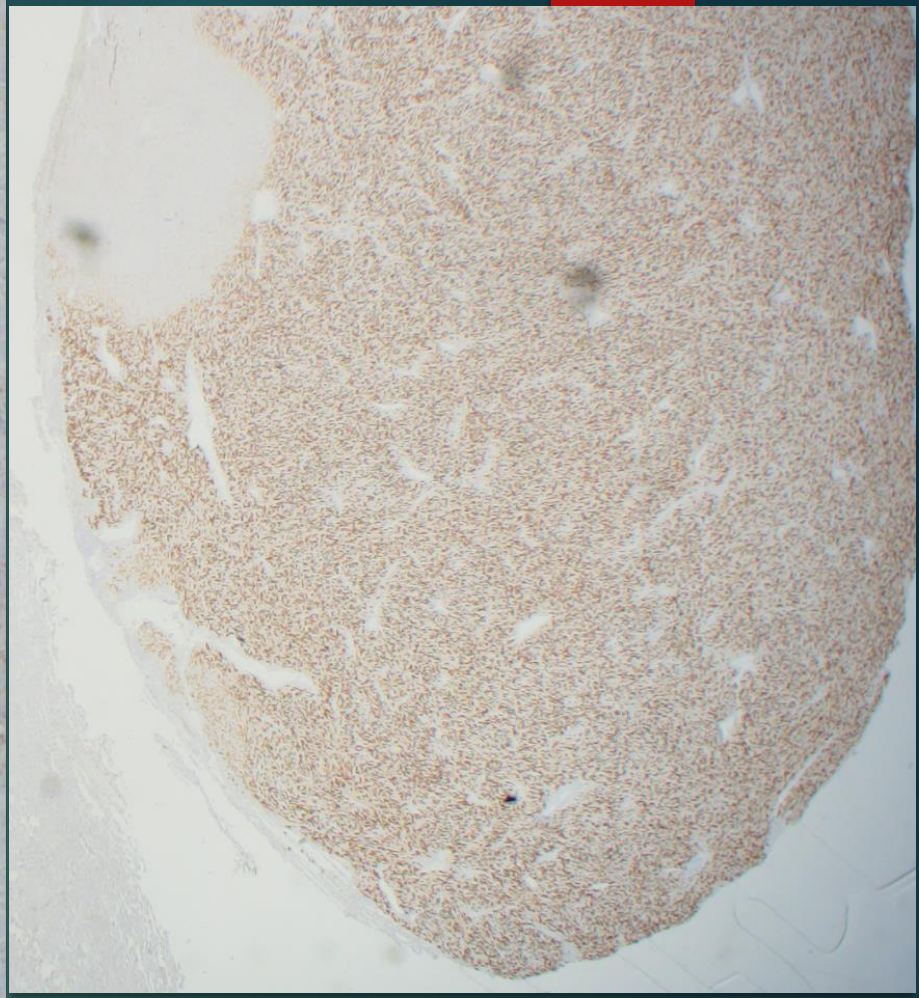
SMA, 2x

Caldesmon, 2x





Estrogen Receptor, 2x



Progesterone Receptor, 2x

Negative stains: HMB45, CD10

Multiple benign smooth muscle tumors of the lung

The exact origin of these smooth muscle tumors is difficult to know for sure on histologic grounds. Given that this patient is a female, consideration should be given to whether or not these represent the rather controversial entity of so-called "benign metastasizing leiomyoma" vs merely pulmonary hamartomas. If this patient does have known uterine leiomyomas, then this might lend further support to "benign metastasizing leiomyoma".

Further pathologic historical review…

- A year prior to lung wedge resections, patient underwent total hysterectomy and bilateral salpingo-oophorectomy with pertinent findings of multiple intramural leiomyomata

Benign metastasizing leiomyoma

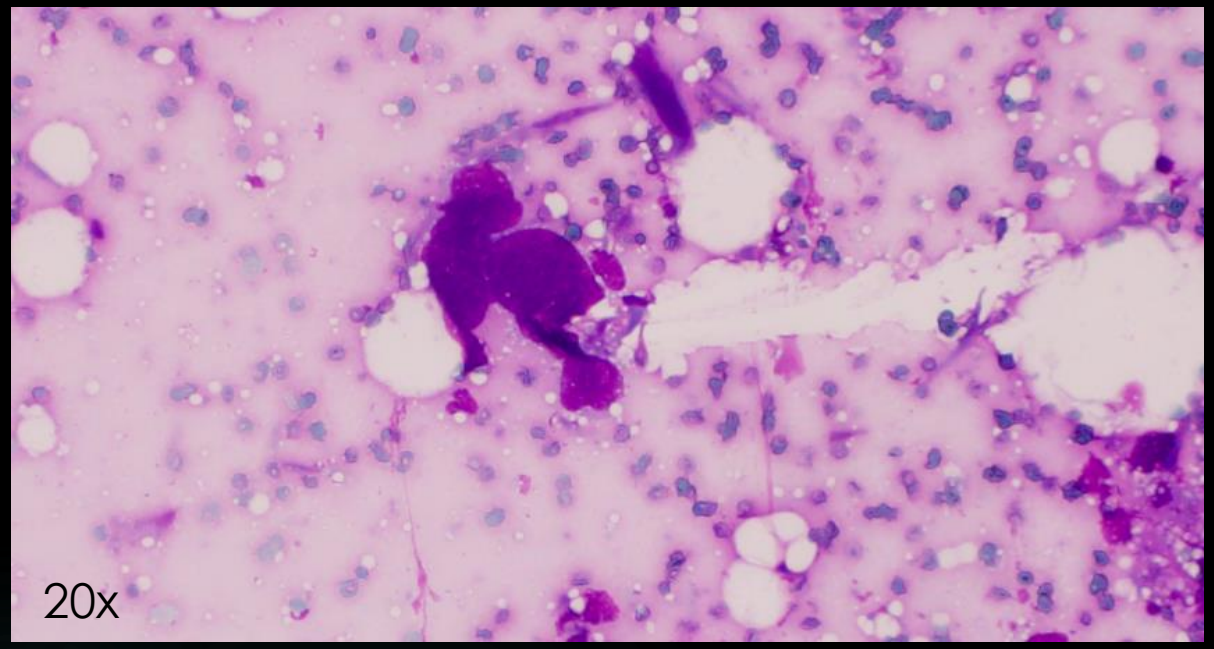
- Incidence is very rare, 30-50 years of age, exclusively observed in women
- Microscopic
  - Fascicles of monotonous, bland-appearing spindle cells that are sharply separated from surrounding lung parenchyma
  - May entrap normal respiratory mucosa and airspaces in vicinity of lesion
  - Blunt-ended nuclei showing dispersed chromatin and small or inconspicuous nucleoli
  - No nuclear pleomorphism, mitoses, or tumor cell necrosis
- IHC
  - Positive: SMA, Desmin, Calponin, H-caldesmon, may show ER/PR expression
- Pathogenesis: hypothesized to result from remote implantation of benign cells released into circulation during surgery

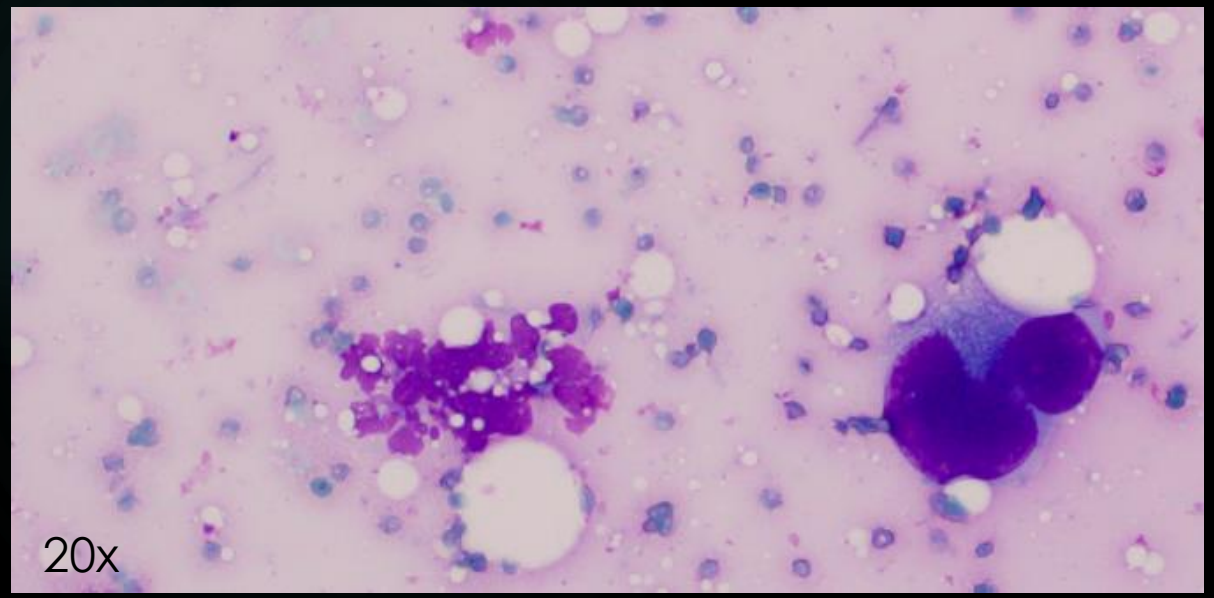
Back to our initial patient

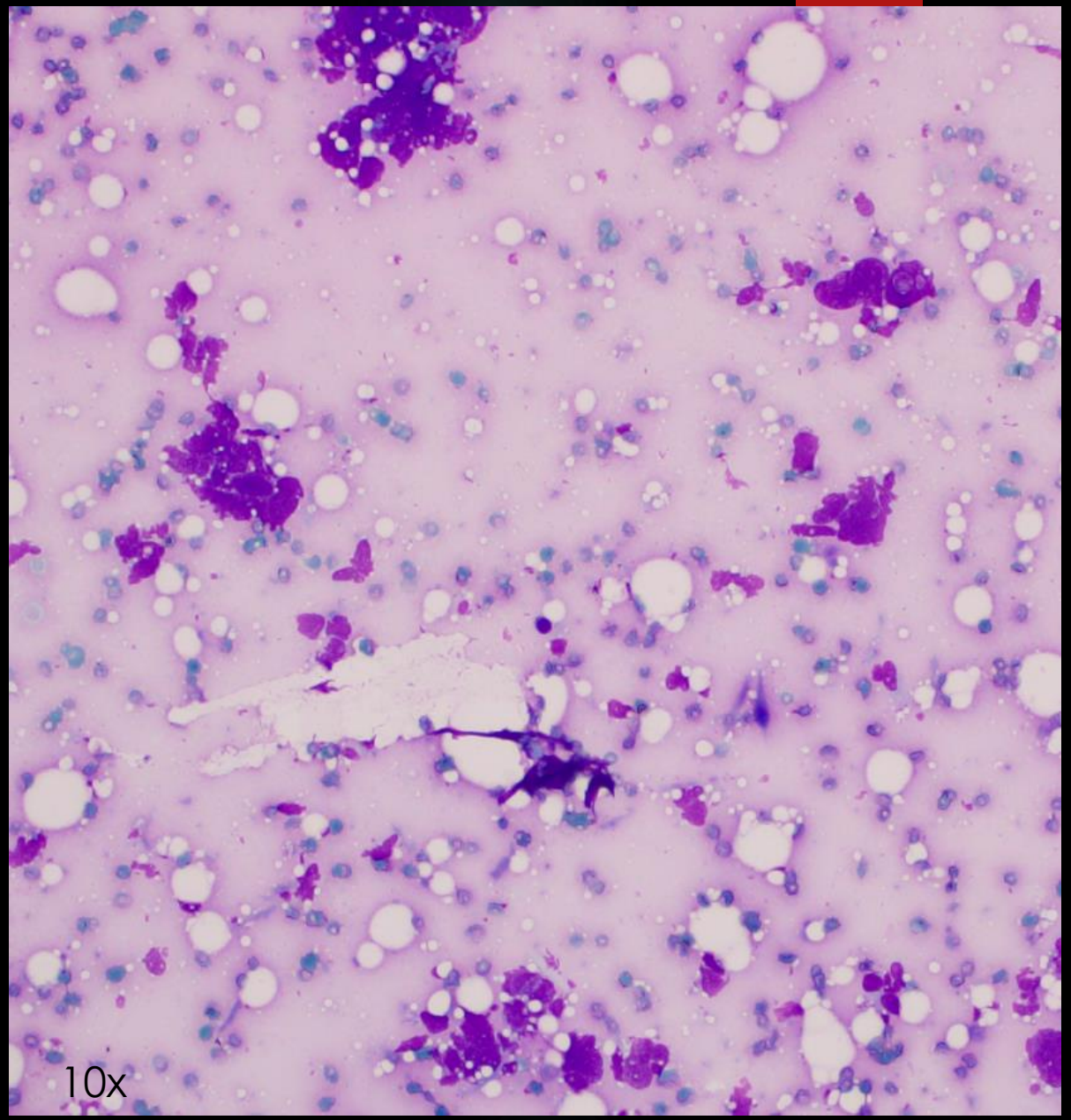
CT-GUIDED CORE BIOPSY WITH TOUCH PREPARATIONS ON RIGHT PELVIC MASS

Primitive, high grade malignancy with limited rhabdomyosarcomatous differentiation

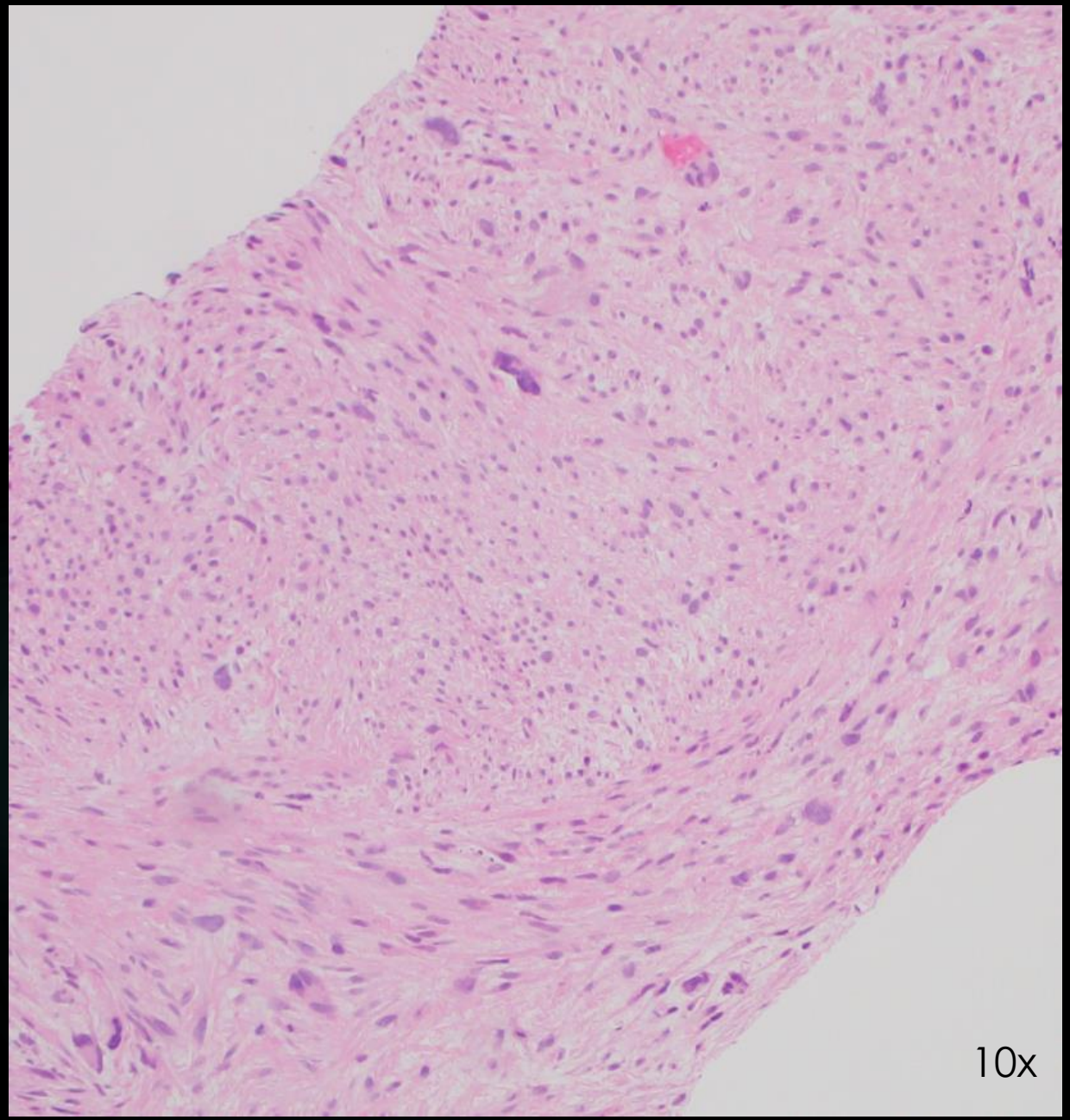
- Combination of epithelial staining with lack of diffuse Desmin positivity does not support primary rhabdomyosarcoma
- Given the patient's pelvic mass, this thoracic lesion is suspicious for metastatic carcinosarcoma
- Recommend biopsy of the pelvic mass







ROSE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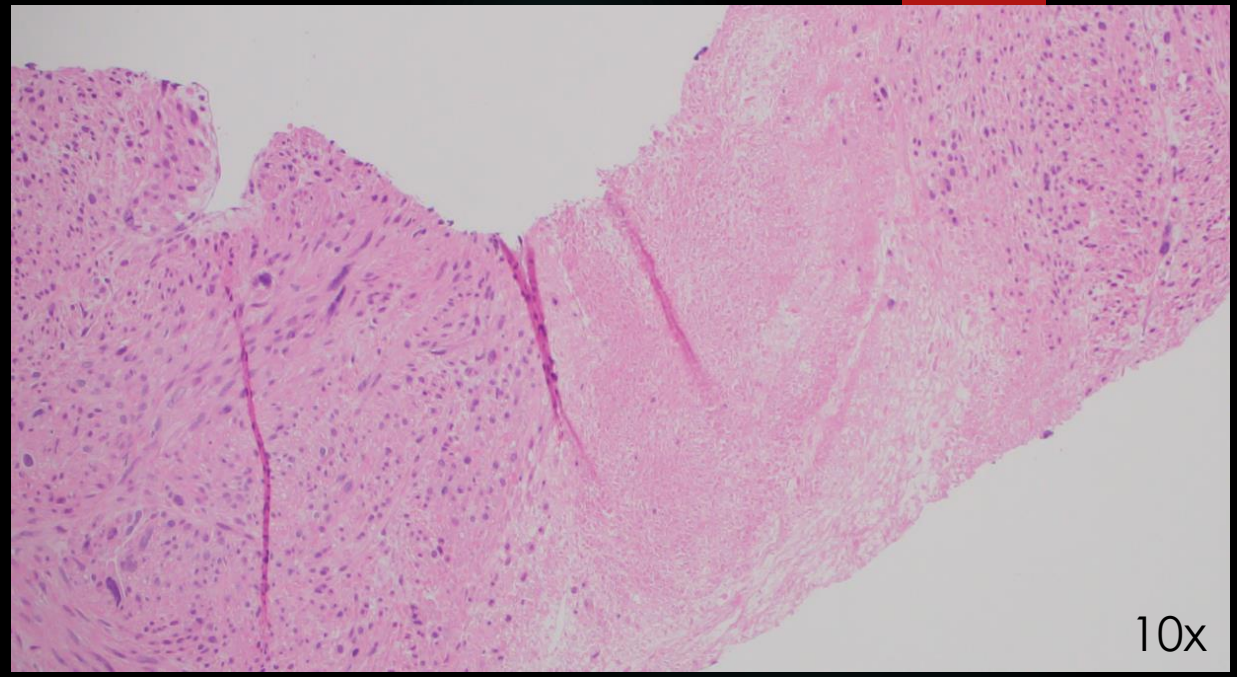
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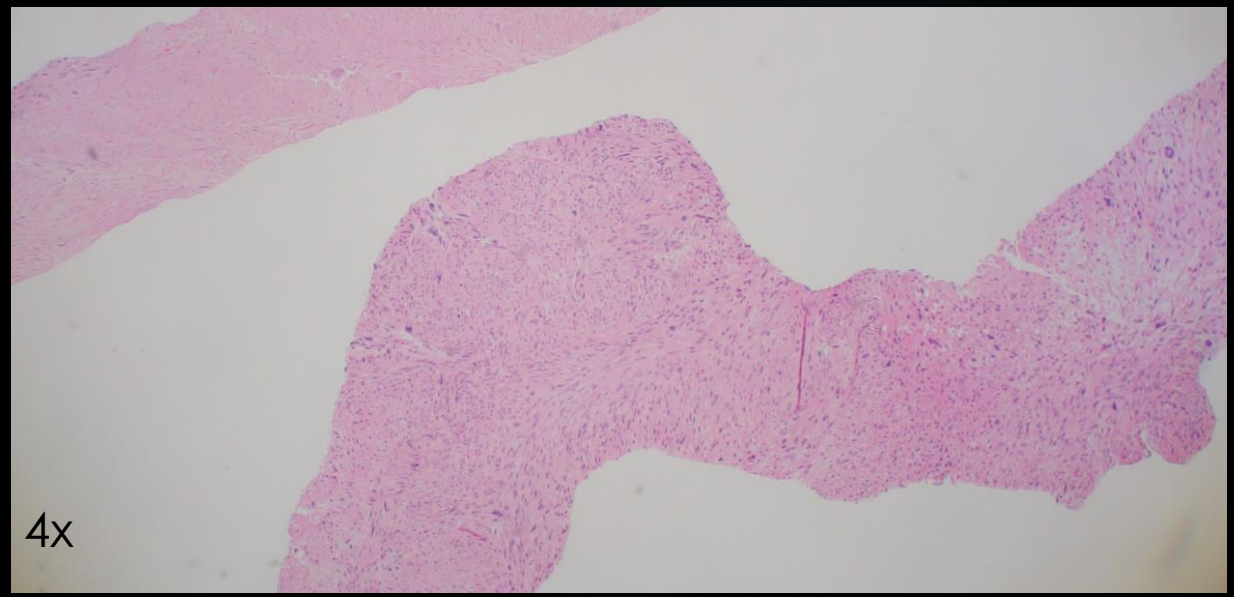
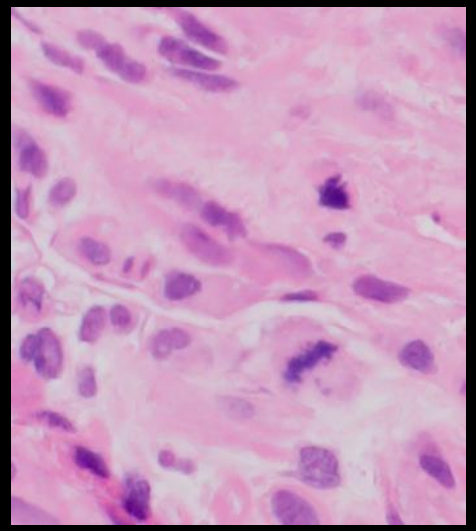
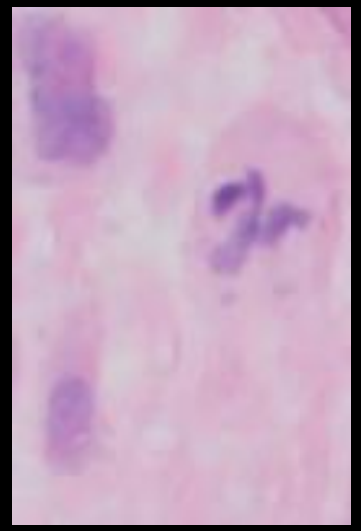
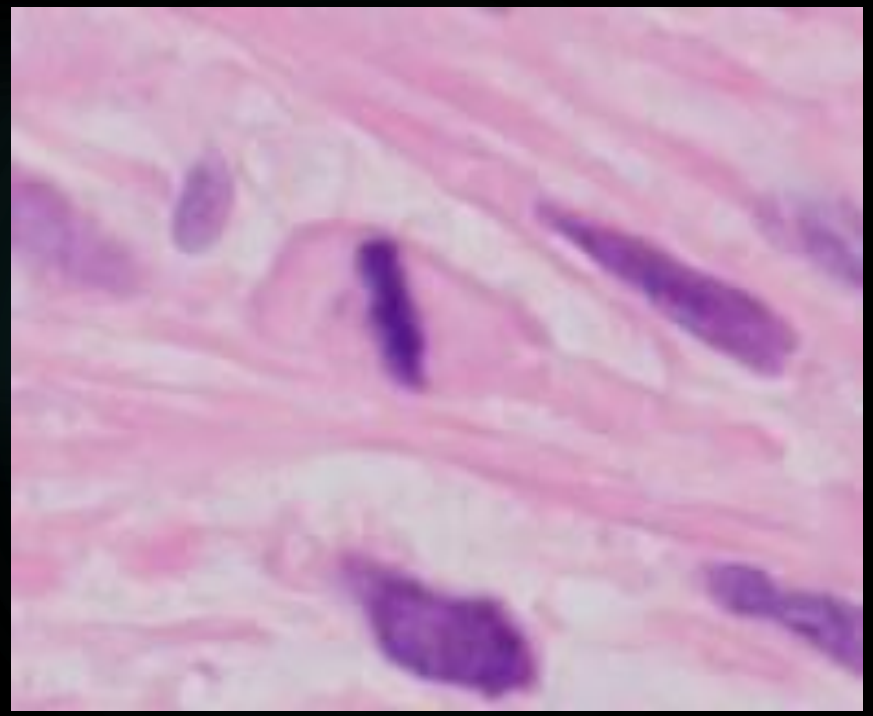
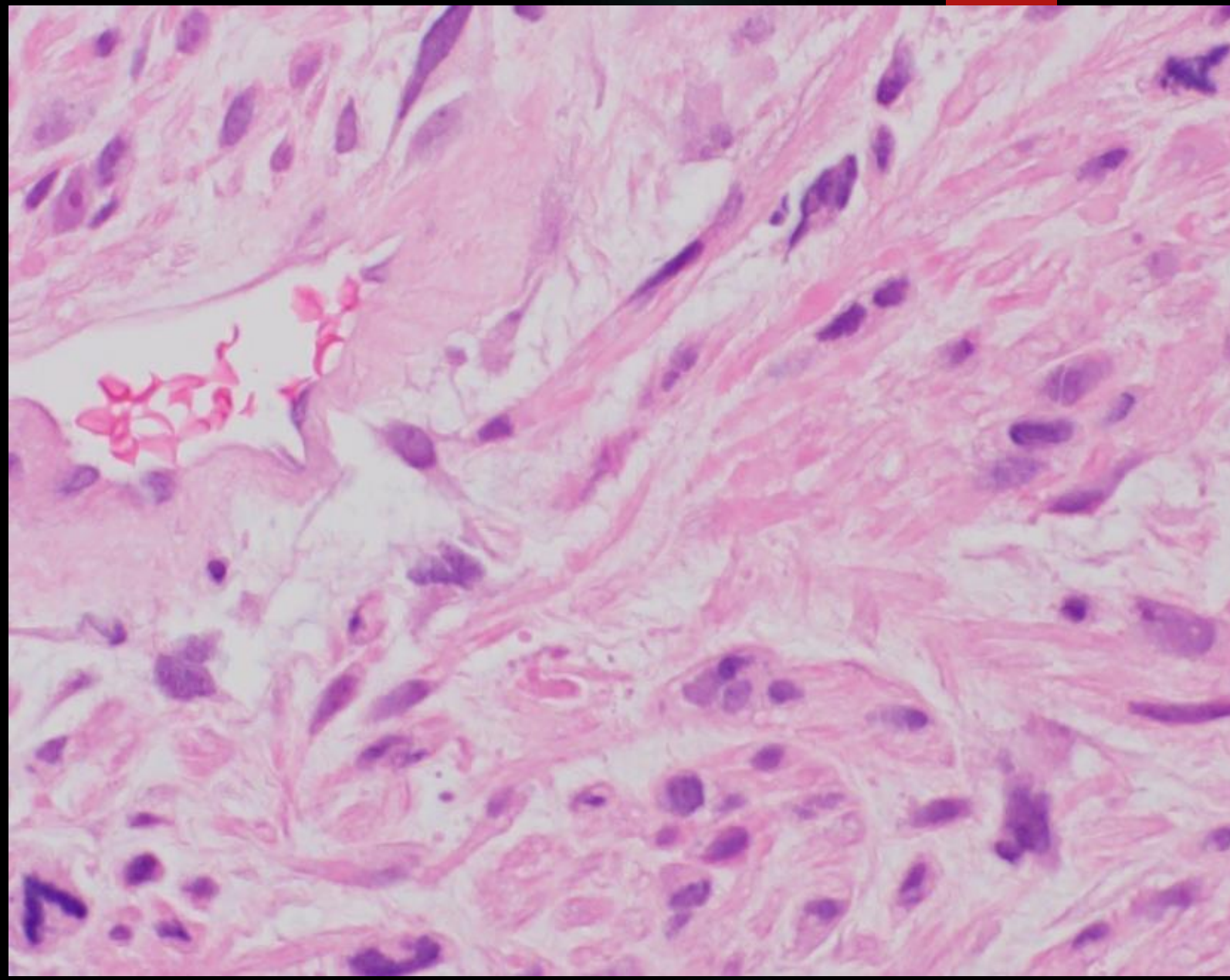
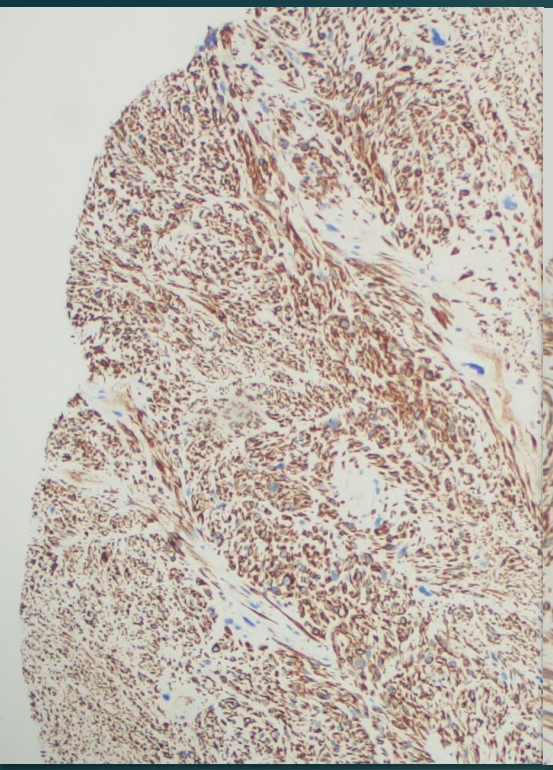

4x



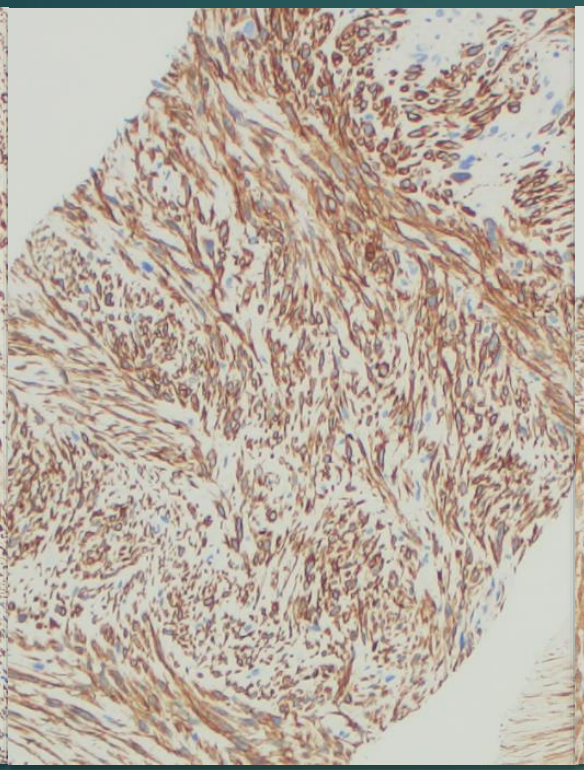




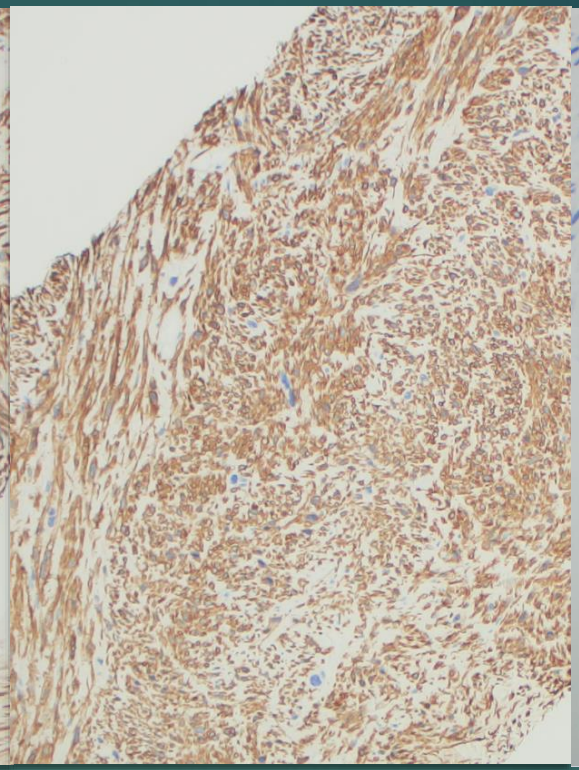




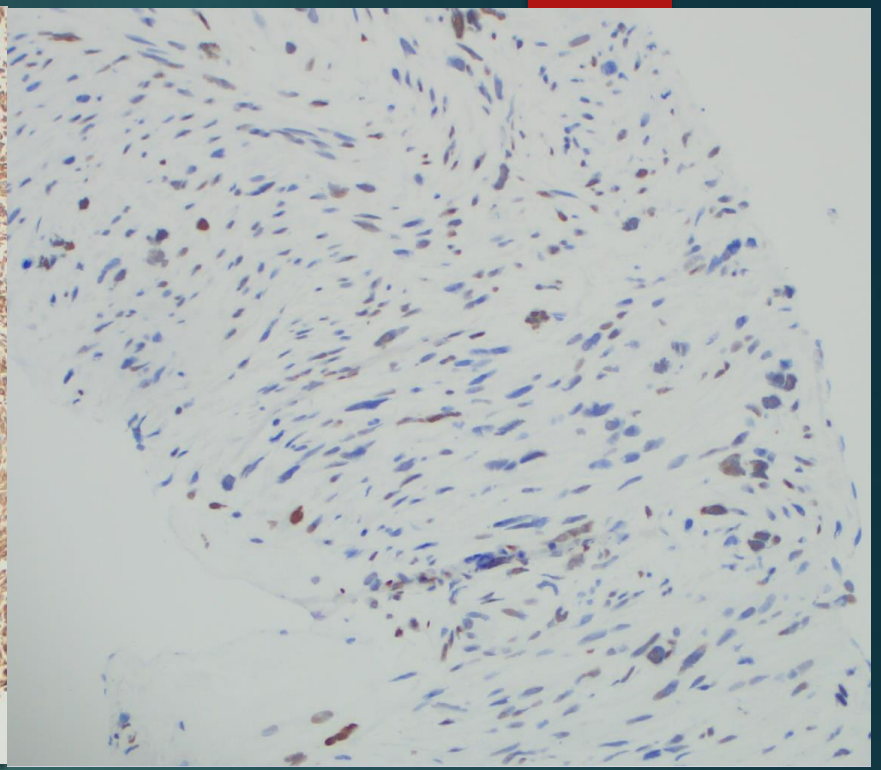
Desmin



SMA



Caldesmon



Estrogen Receptor

Negative stains: Myogenin, AE1/3, Progesterone

Malignant spindle cell neoplasm consistent with leiomyosarcoma

The staining pattern supports smooth muscle differentiation and an overall classification of leiomyosarcoma in this sample.

Given the partial morphologic overlap with biopsy of a left thoracic/mediastinal mass, additional stains were performed on the thoracic/mediastinal mass showing the tumor to be only focally positive for Desmin and negative for Estrogen Receptor and Caldesmon.

Overall, given the absence of complete morphologic overlap, it is possible that the thoracic/mediastinal mass could represent metastatic involvement by a dedifferentiated component of the pelvic mass but could also represent two distinct synchronous lesions. Next generation sequencing performed on both biopsies is therefore recommended to clarify this question.

Conclusion

- Patient switched to Doxorubicin/Dacarbazine for leiomyosarcoma
- NGS sent on both pelvic mass and lung/mediastinal mass
  - Lung/mediastinal Mass mutations: *PTEN, TP53, RB1*
  - Pelvic Mass mutations: *PTEN, TP53, RB1*
- Patient passes away

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Thank you!