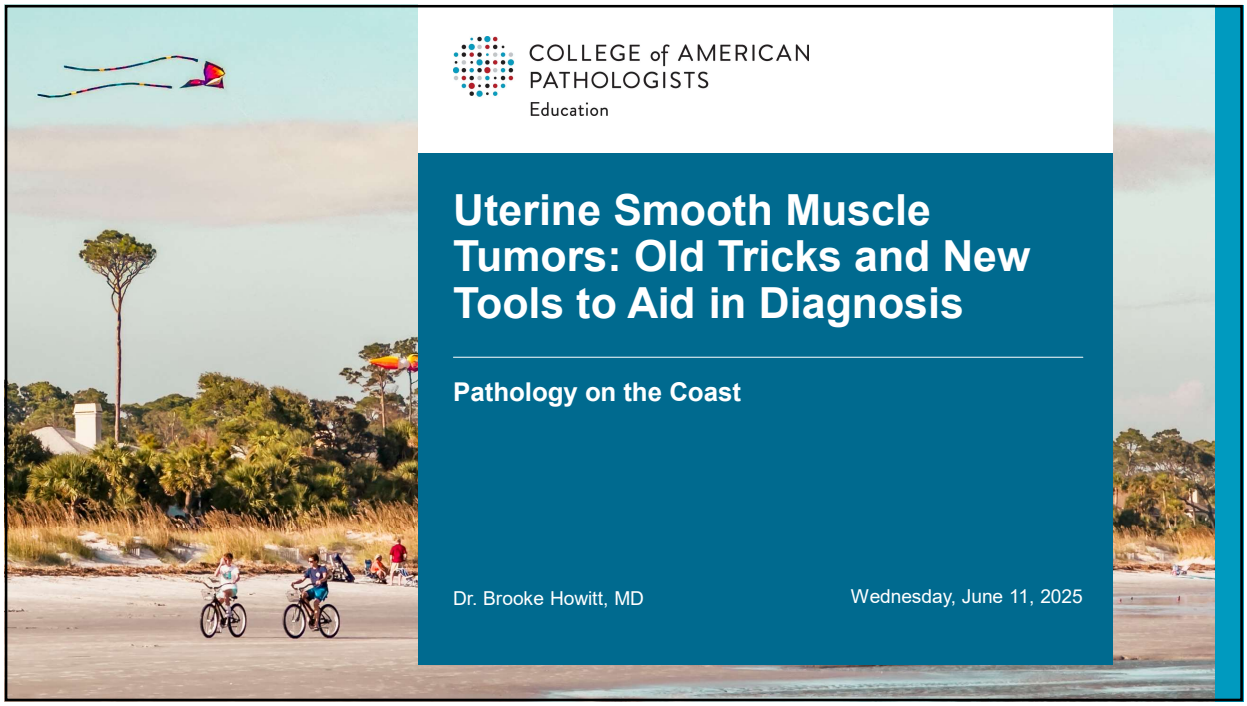

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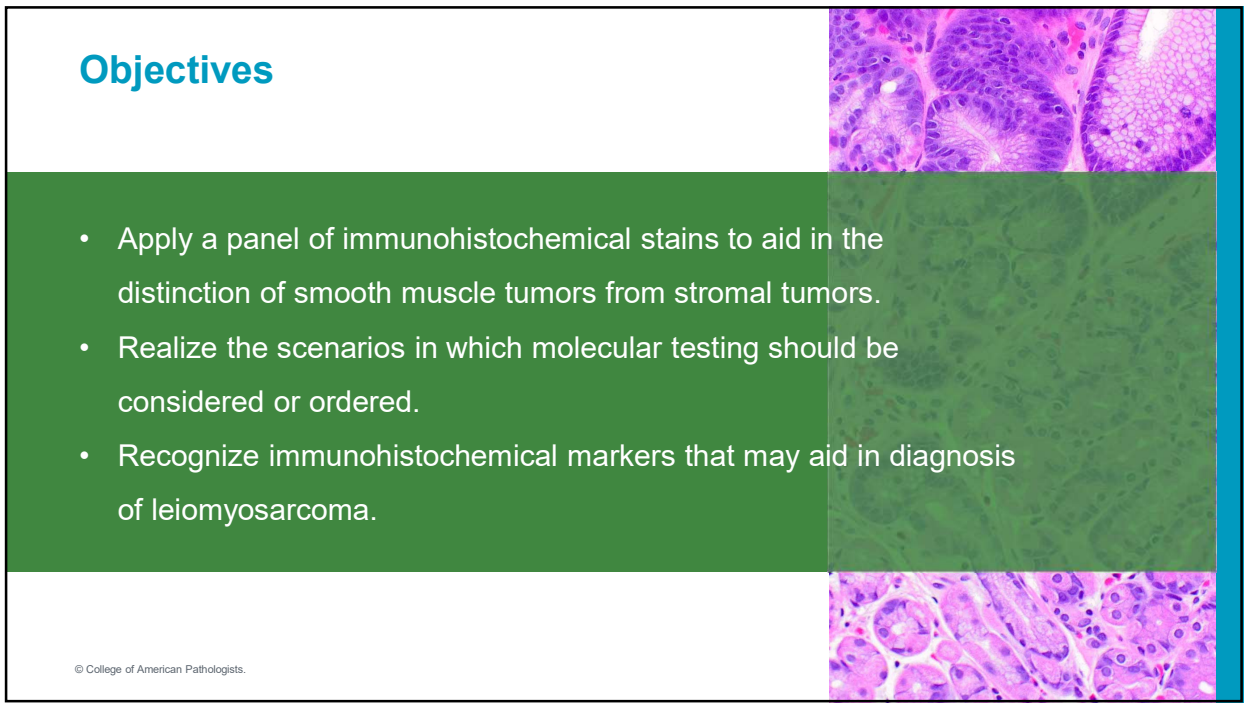

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Outline

1. **Smooth muscle tumor classification**
    1. Cellular leiomyoma, intravenous leiomyomatosis (IVL)
    2. Mitotically active
    3. Apoplectic
    4. Leiomyoma with bizarre nuclei (LBN)/Atypical leiomyoma
    5. STUMP
    6. LMS and variants
    7. "Molecular IHC" panel for aid in distinction of STUMP from LMS
2. **Distinguishing smooth muscle tumors from mimics**
    A. Stromal tumors
    B. Inflammatory myofibroblastic tumor (IMT)
    C. PEComa

3

1. Smooth muscle tumor classification

4

Leiomyoma—Many variants!

- Epithelioid
- Myxoid
- Hydropic (edematous)
- Cellular/Highly cellular
- Intravenous leiomyomatosis
- Mitotically active
- Apoplectic
- Lipoleiomyoma

5

Leiomyoma—Many variants!

- Epithelioid
- Myxoid

→ Very rare- usually not the "right" diagnosis

- Hydropic (edematous)
- Cellular/Highly cellular
- Intravenous leiomyomatosis
- Mitotically active
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6

Leiomyoma—Many variants!

- Epithelioid
- Myxoid
- Hydropic (edematous)
- Cellular/Highly cellular
- Intravenous leiomyomatosis
- Mitotically active
- Apoplectic
- Lipoleiomyoma → Uncommon but generally recognized with few diagnostic dilemmas

7

Leiomyoma—Many variants!

- Epithelioid
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- Hydropic (edematous)
- Cellular/Highly cellular
- Intravenous leiomyomatosis
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- Apoplectic
- Lipoleiomyoma

→ Focus for today

8

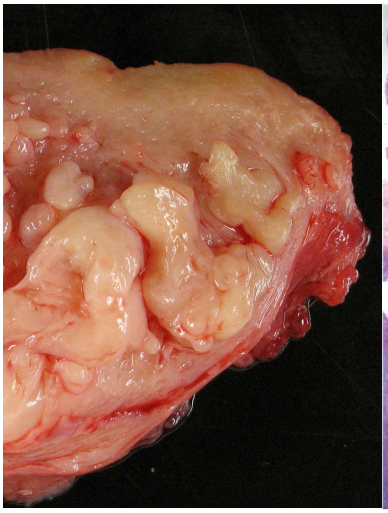
Cellular leiomyoma

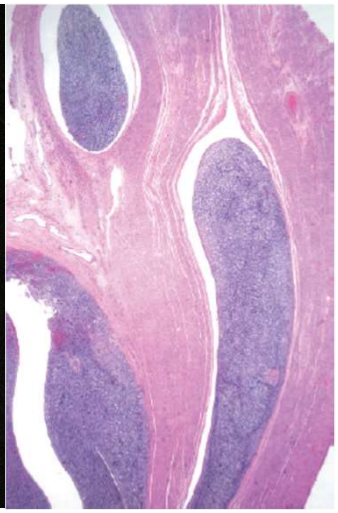
- **Appear "blue" from low power and significantly more cellular than surrounding myometrium**
- **Grossly may have softer, less rubbery cut surface and yellow to tan color**
- **By gross and microscopic assessment, more likely to be confused with non-smooth muscle neoplasms**
- **BLAND cytologic features and inconspicuous mitoses**
- **May have irregular (but "gentle") borders and "satellite" nodules**

9

Intravenous leiomyomatosis (IVL)

- **Intravascular proliferation of benign (often cellular) smooth muscle neoplasm**
- **Prognosis directly related to completeness of resection**
  - **Importance of pathologic gross examination**
  - **Relaying this information in the pathology report is critical**





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Mitotically active leiomyoma

- **In short… it's a leiomyoma with mitoses**
- **I only make this diagnosis in consult cases**

11

Mitotically active leiomyoma

- **In short… it's a leiomyoma with mitoses**
- **I only make this diagnosis in consult cases**
- **Pearl: if it is pink from low power, no cytologic atypia at high power, and no necrosis…. Don't count mitoses!!**

12

Apoplectic leiomyoma

- **Risk of mistaking for malignancy due to frequent hemorrhage and necrosis**
- **Necrosis is multifocal and stellate, usually with associated hemorrhage**
- **May be focally hypercellular**
- **Atypia and mitoses (mean 3 per 10, range 0-14) present mostly in the apoplectic zone**
- **Edema/cystic change, myxoid change, hyalinization helpful clues**
- **History of progestin therapy or pregnancy in vast majority**

Bennett JA, Lamb C, Young RH. Apoplectic Leiomyomas: A Morphologic Analysis of 100 Cases Highlighting Unusual Features. Am J Surg Pathol. 2016 Apr;40(4):563-8. PMID: 26685083.

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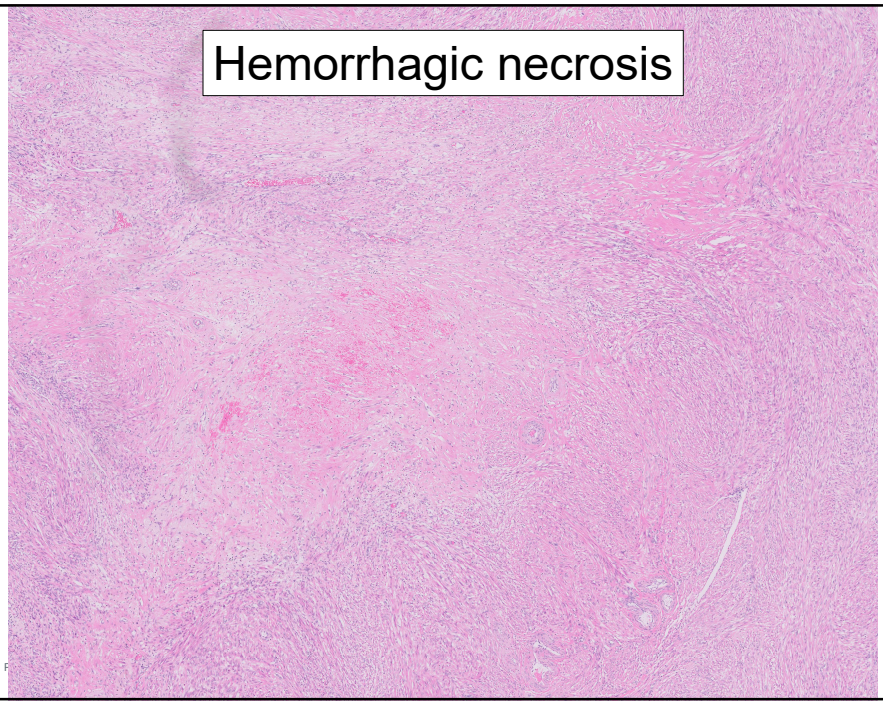

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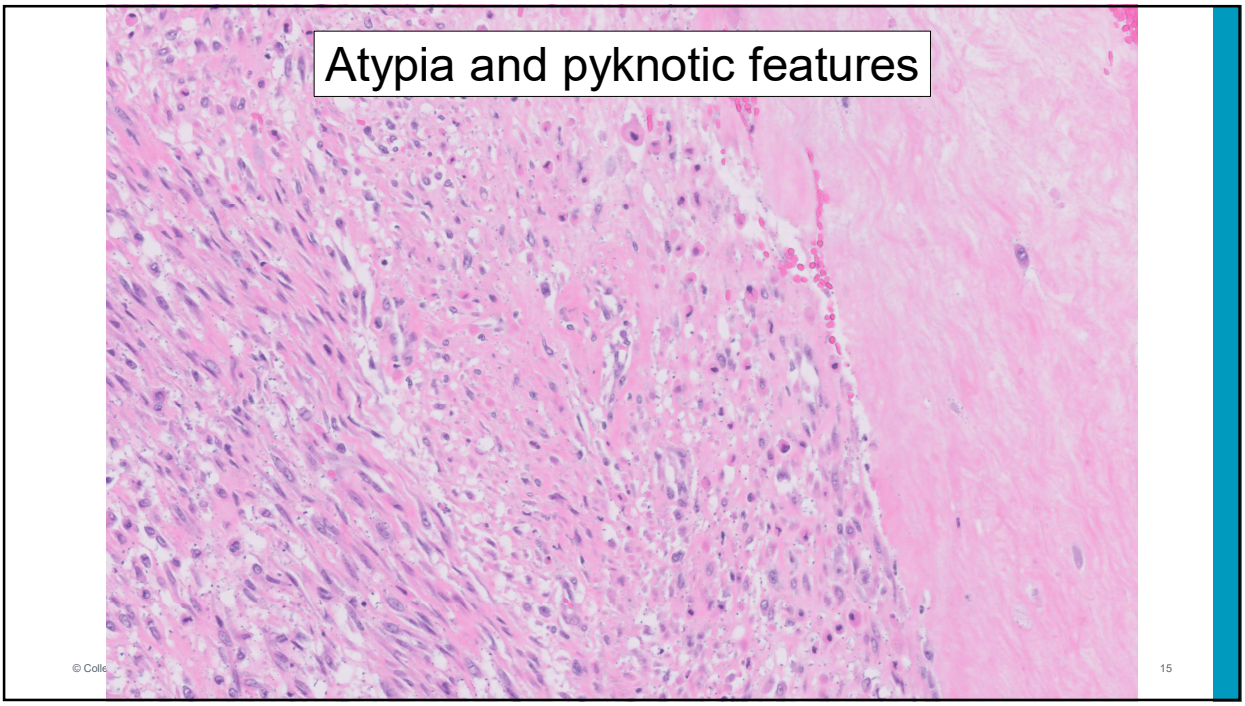

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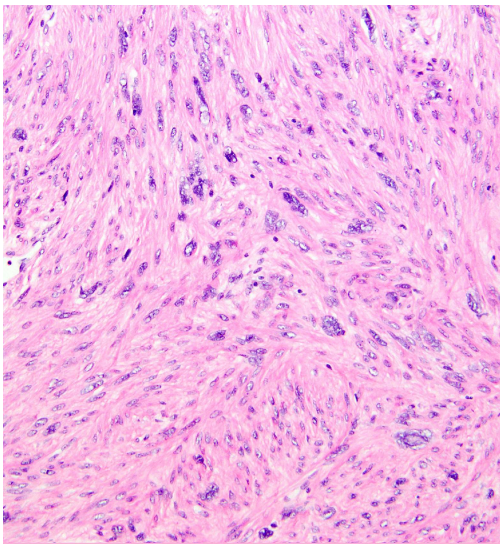
Leiomyoma with bizarre nuclei ("atypical")

- **++ Moderate-severe nuclear atypia**
- **NO necrosis**
- **Low mitotic activity**
- **Subset associated with *FH* alteration (germline or somatic) and resultant loss of expression of FH IHC and expression of 2SC IHC**



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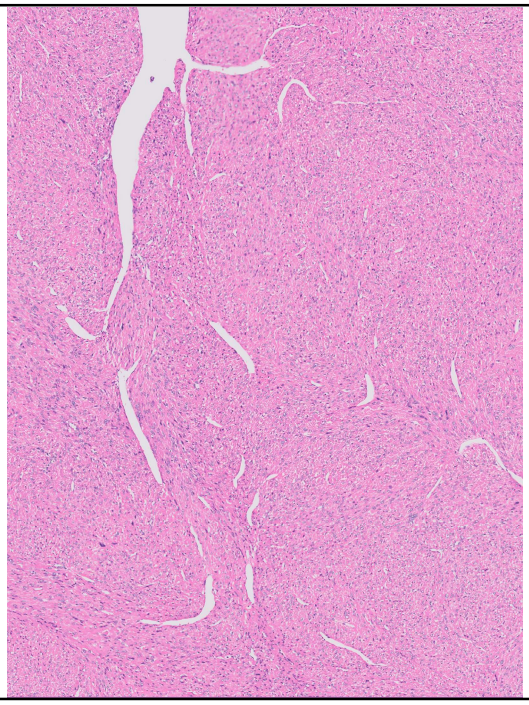
FH-deficient leiomyoma

- **May indicate germline FH mutation (HLRCC)**
- **Staghorn-shaped vasculature**
- **Alveolar-type edema**
- **Fibrillary growth**
- **Eosinophilic globules**
- **Macronucleoli with perinucleolar clearing**



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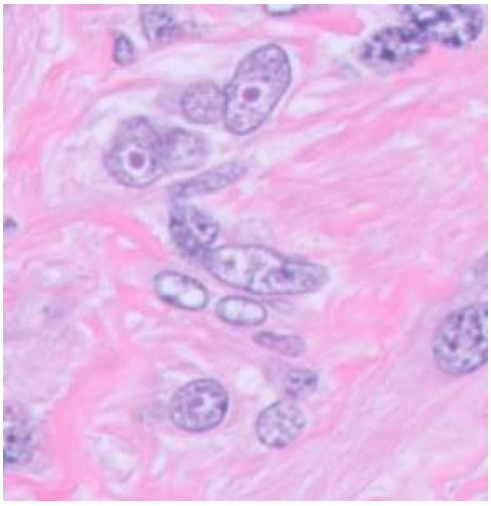

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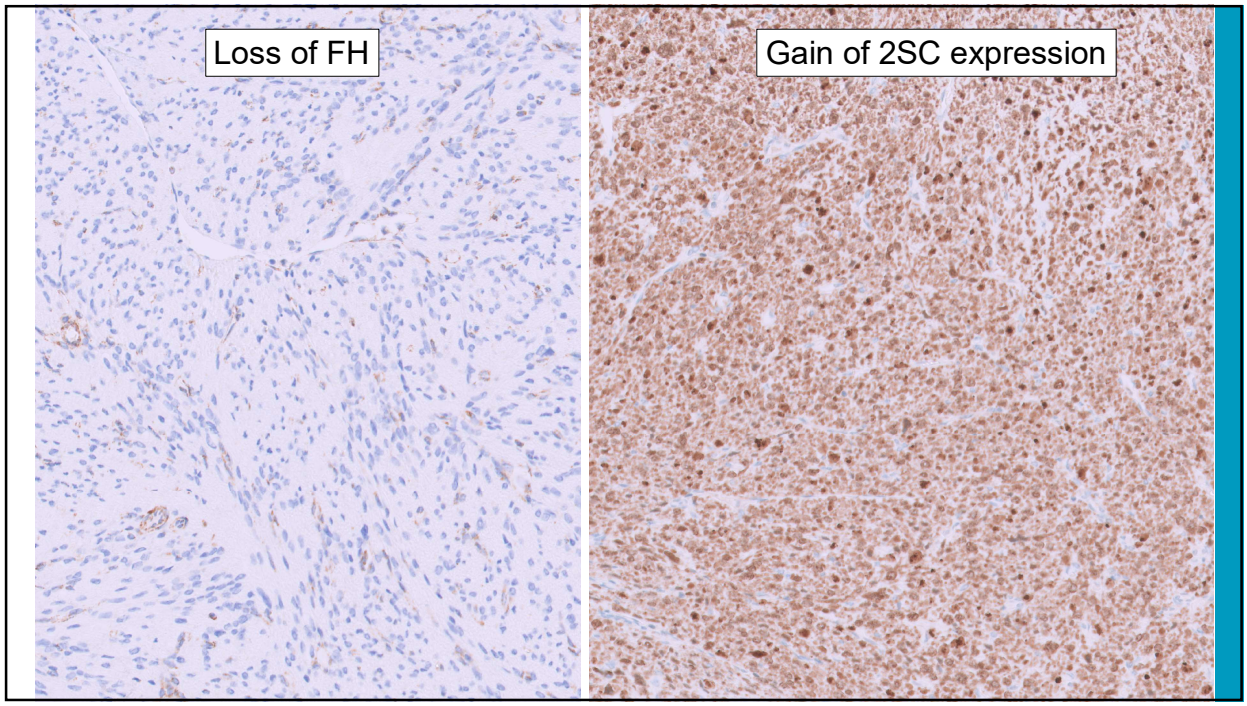

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Microscopic Features of Malignancy in Uterine Smooth Muscle Tumors (Leiomyosarcoma)

- **Geographic tumor necrosis**
- **Mitotic activity**
- **Nuclear atypia (severe)**
  - **Infiltrative/destructive borders**
  - **Atypical mitotic figures**

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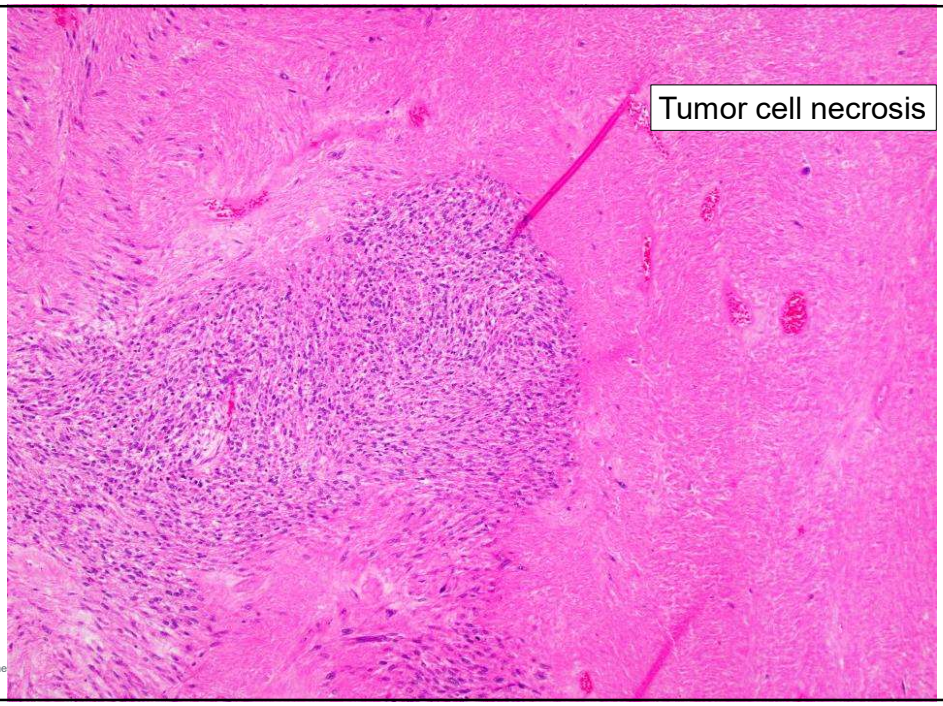

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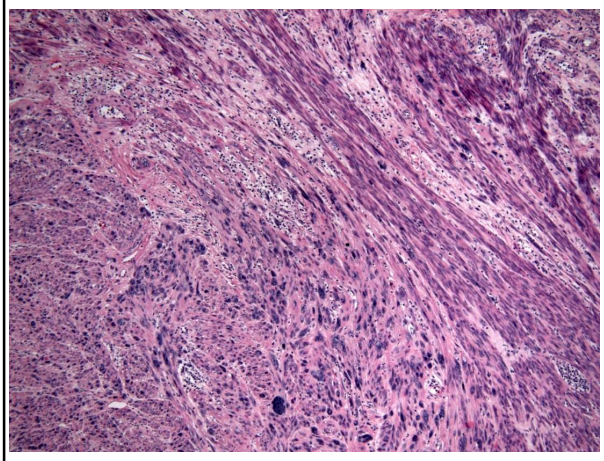
STUMP (smooth muscle tumor of uncertain malignant potential)



- **Has worrisome features, but subdiagnostic for LMS**
  - **Moderate-severe atypia**
  - **Mitoses**
  - **Indeterminate necrosis**
- **Does not fit into one of the leiomyoma variants**
- **Uncommon**

22

Leiomyosarcoma (LMS)- conventional

- **Most common malignant mesenchymal tumor of the uterus**
- **Typically large (mean 10 cm) with or without grossly apparent necrosis**
- **Majority are spindle cell (conventional) type**
- **Fascicular growth; eosinophilic cytoplasm**
- **Other morphologic variants:**
  - **Epithelioid**
  - **Myxoid**

23

LMS- Myxoid

- **Generally hypocellular**
- **Abundant myxoid stroma**
- **DIFFERENT criteria for malignancy compared to conventional/spindle cell:**
  - **One or more of the following**
    1. **Moderate to severe cytologic atypia**
    2. **Tumor cell necrosis**
    3. **≥2 mitoses per 10 HPFs**
    4. **Infiltrative/irregular border**

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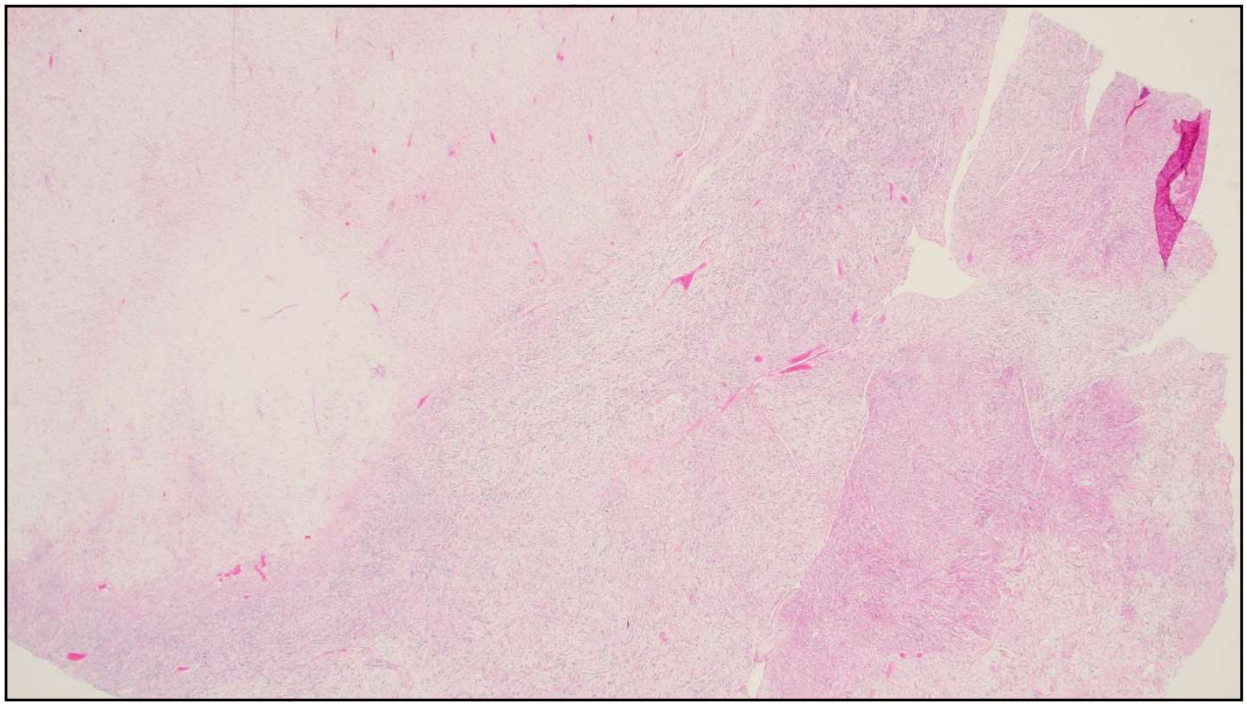

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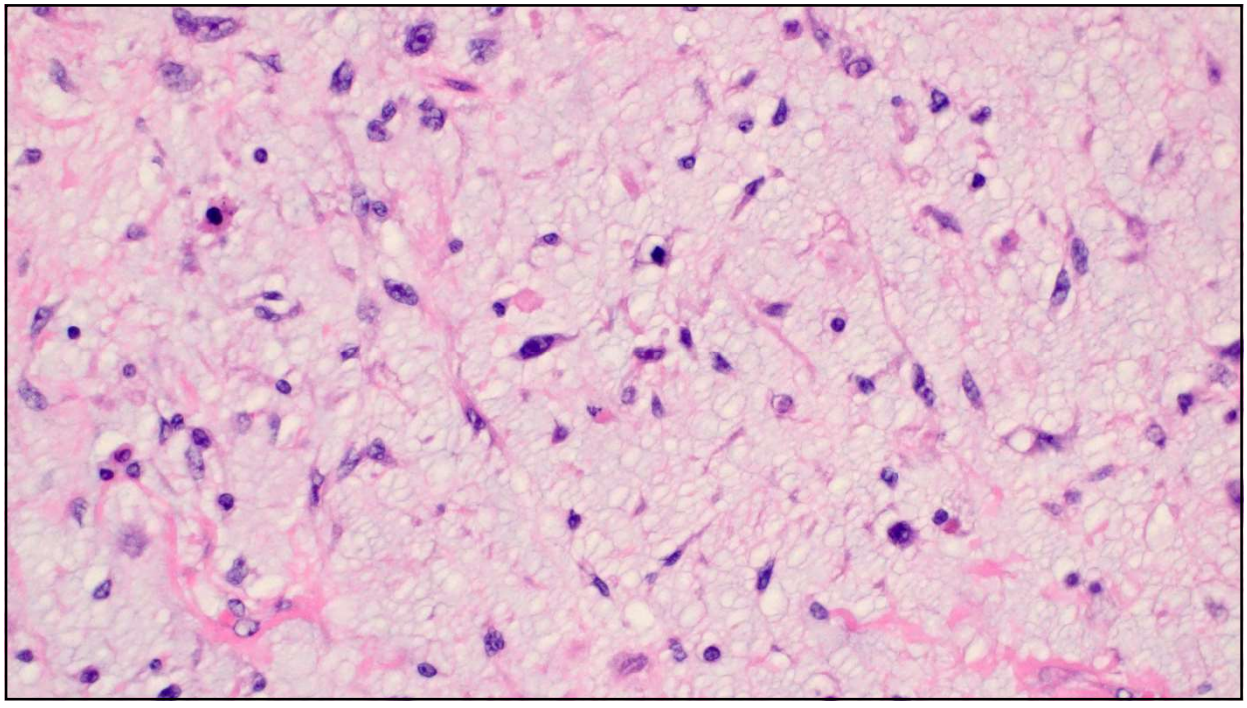

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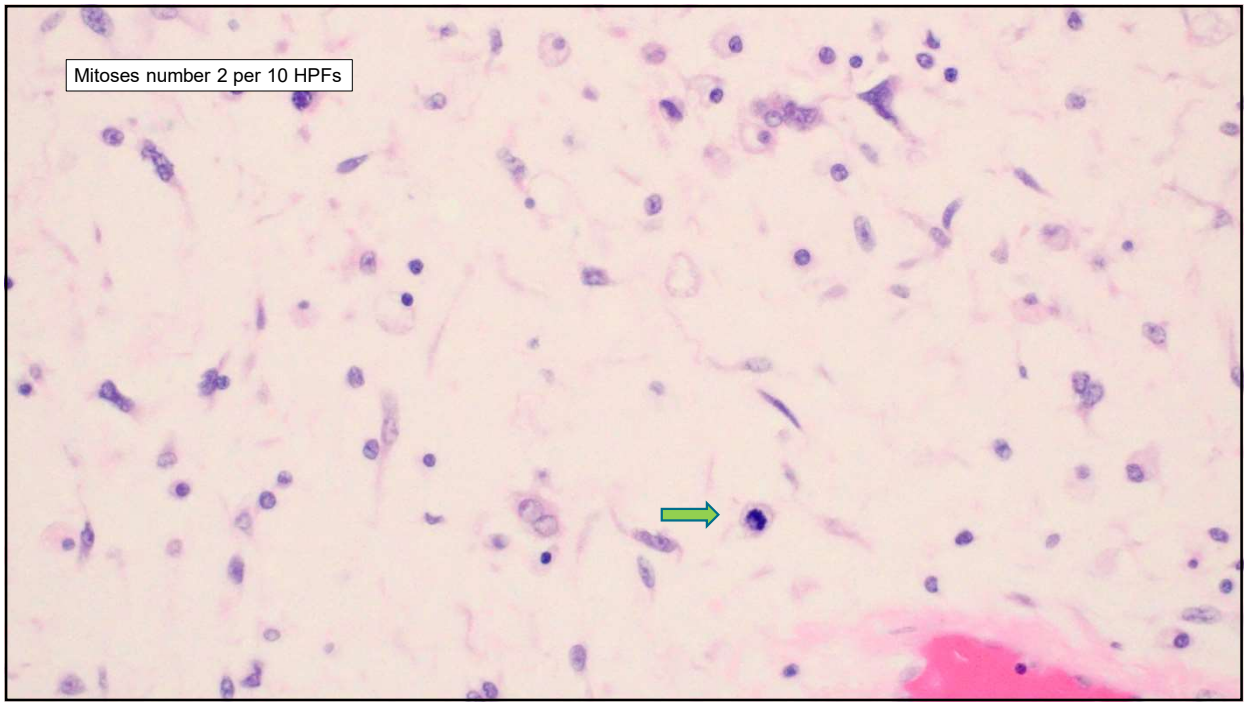

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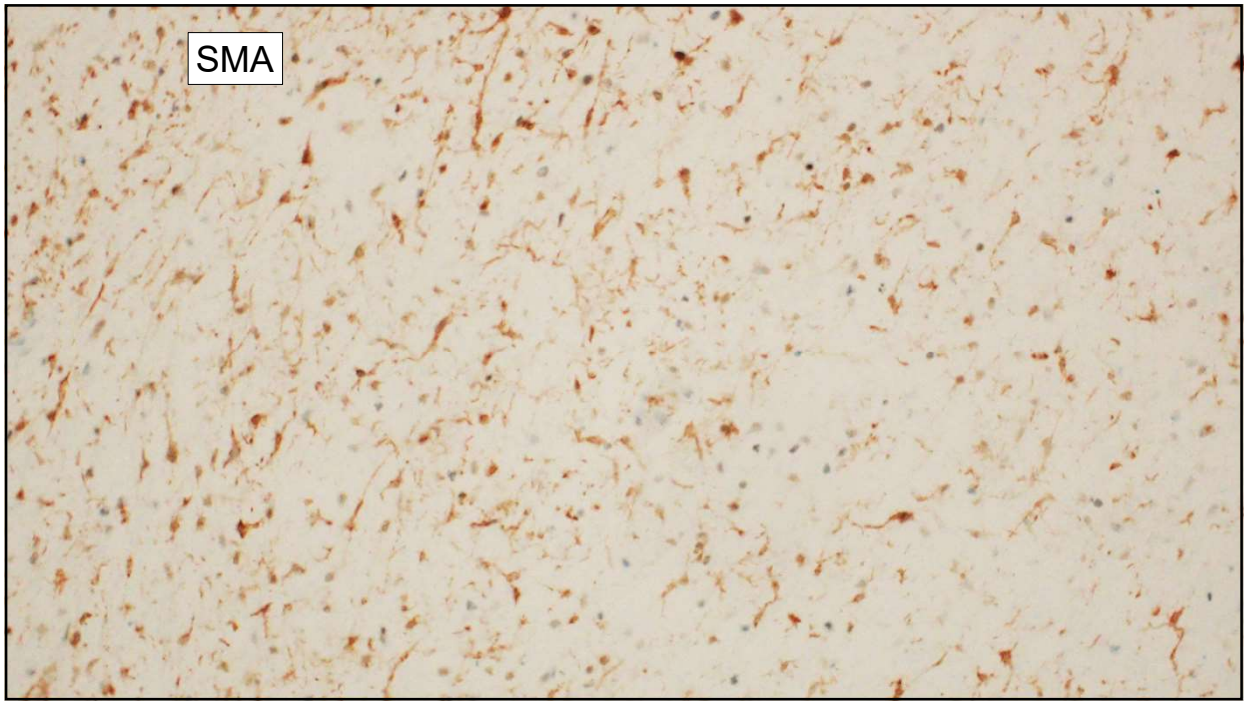

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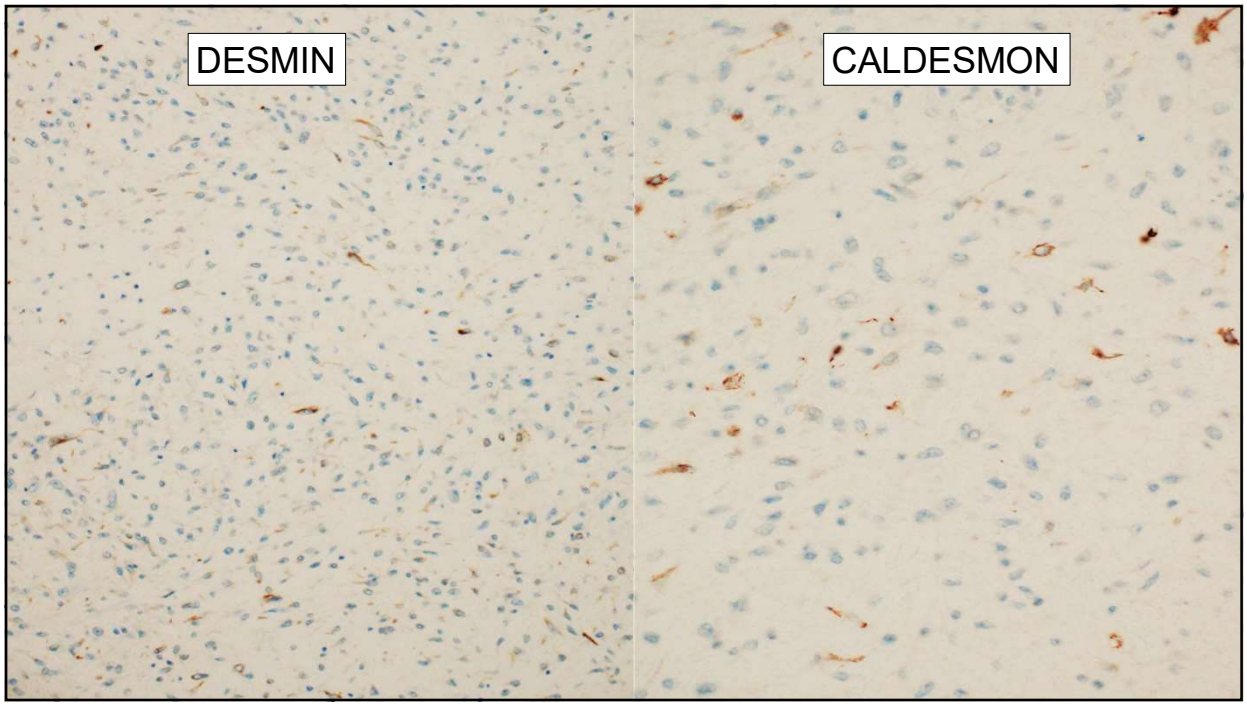

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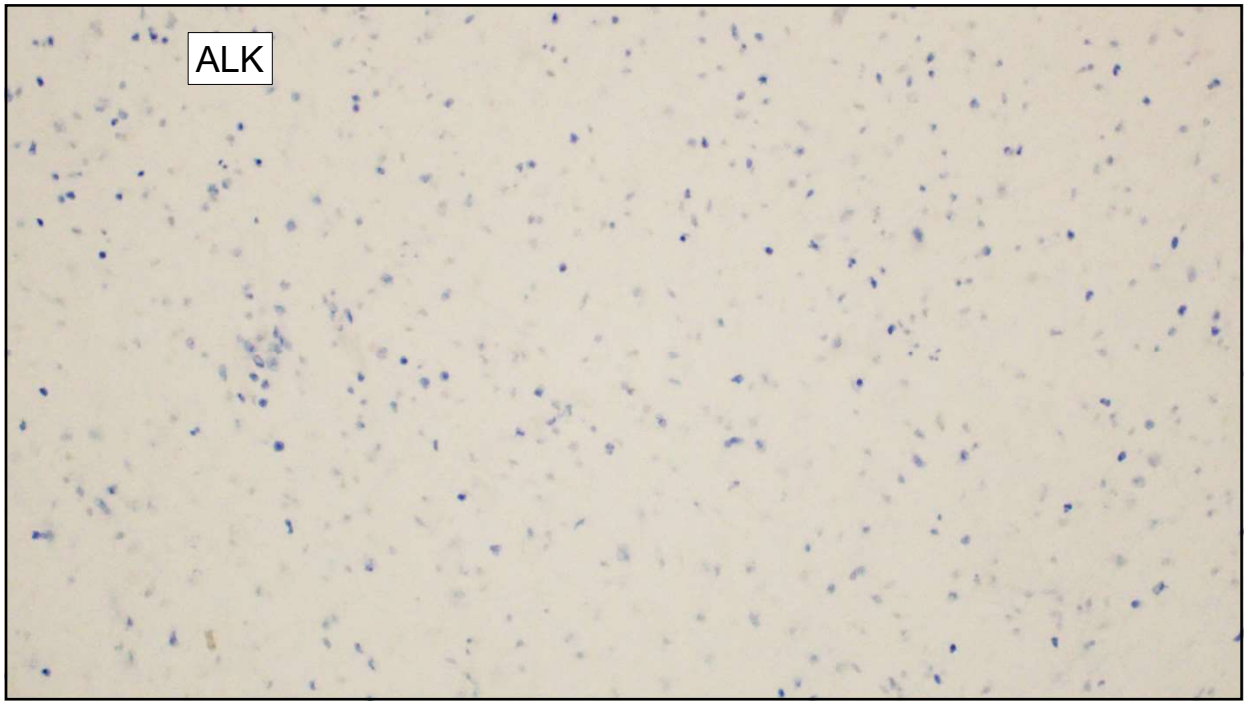

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Diagnosis: Myxoid LMS

- **May have limited smooth muscle marker IHC positivity**
- **Consider additional sampling if overt features of malignancy not seen**
- **Always do Alk IHC ! (will re-visit later)**

31

2. Distinguishing smooth muscle tumors from mimics

32

- **Cellular leiomyoma vs stromal tumors**
  - **Morphologic features (H&E)**
  - **Immunohistochemistry pitfalls**

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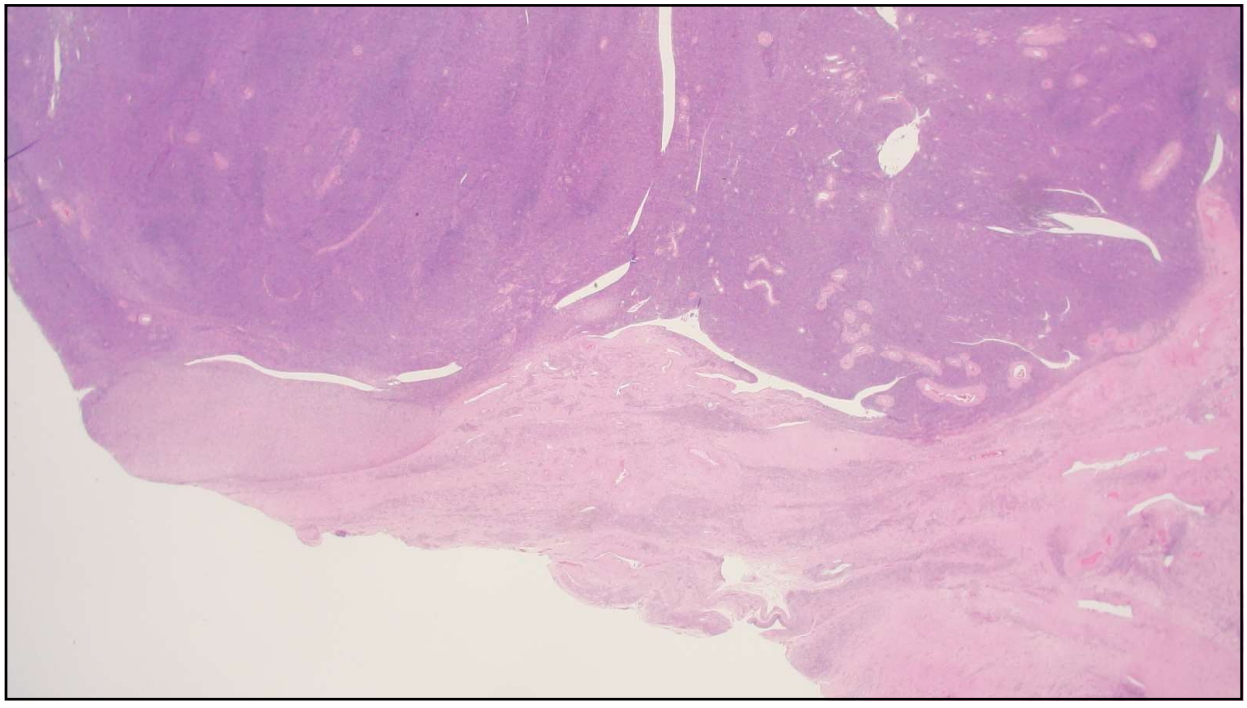

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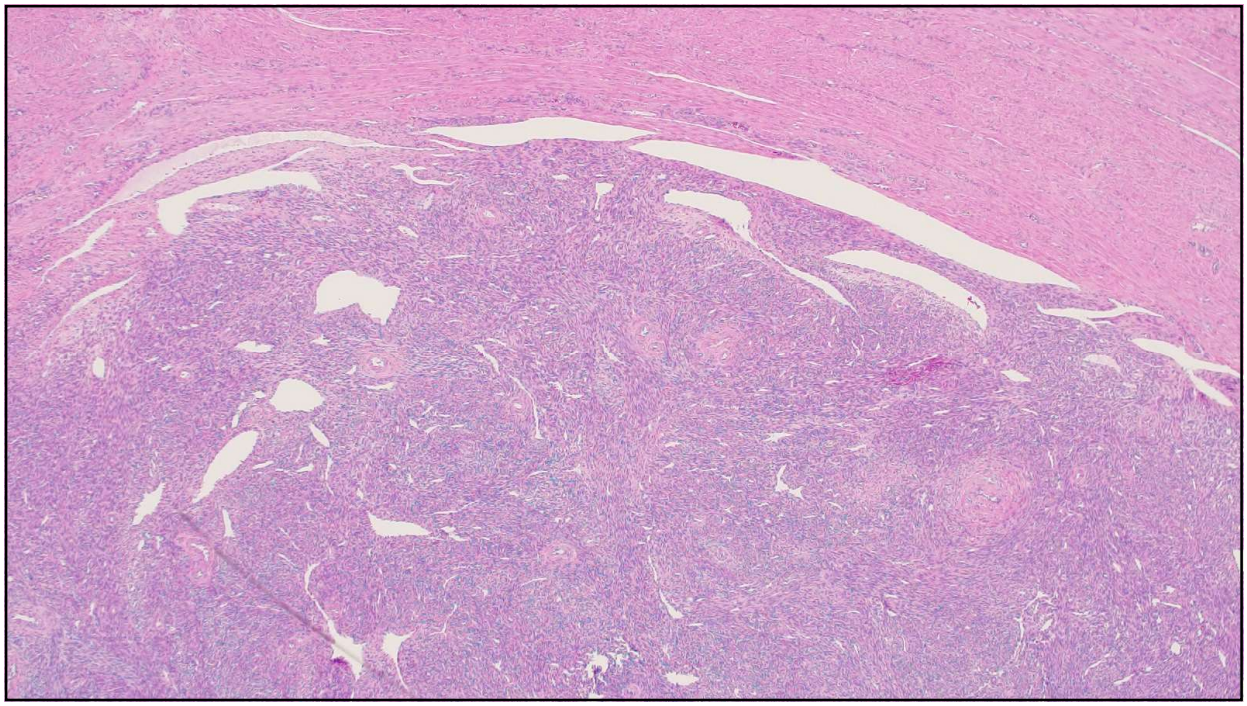

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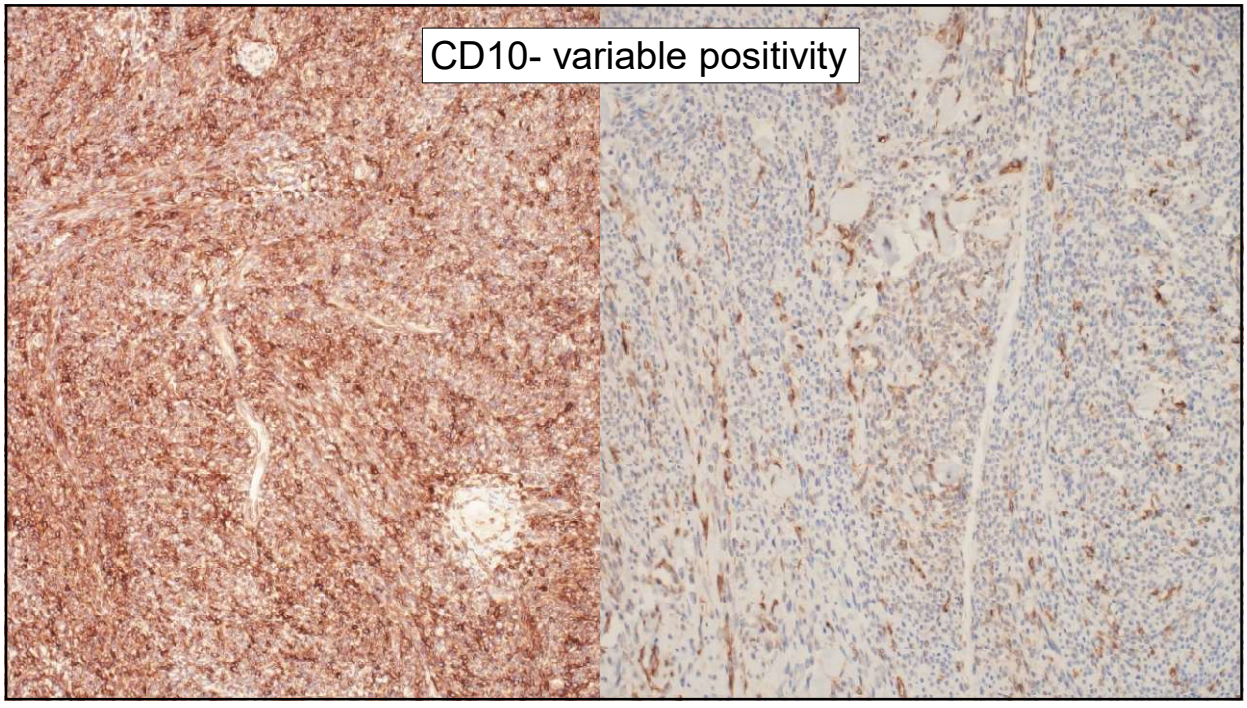

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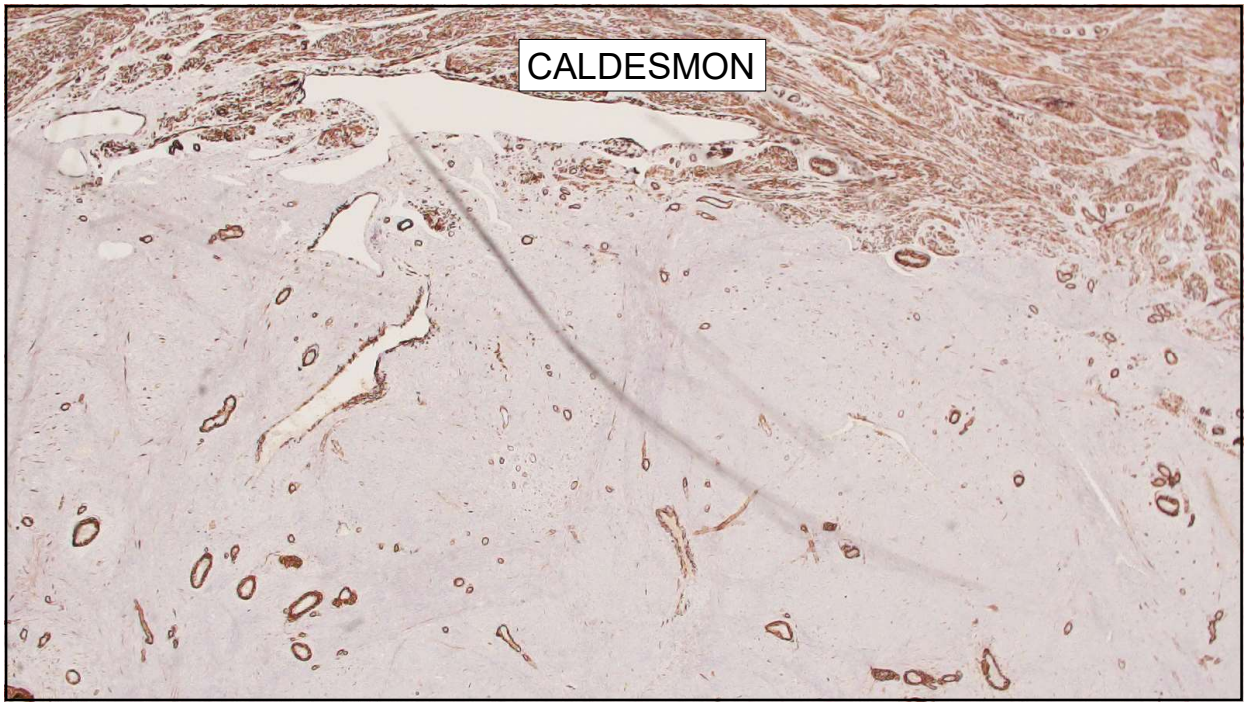

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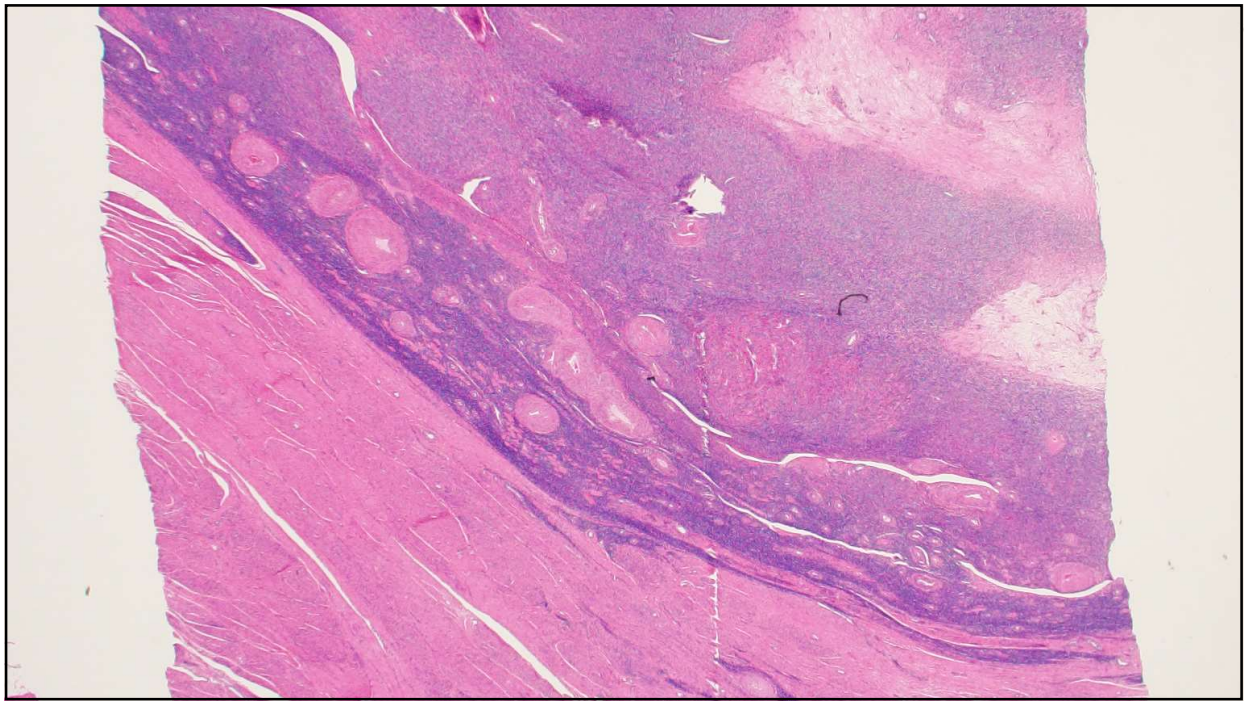

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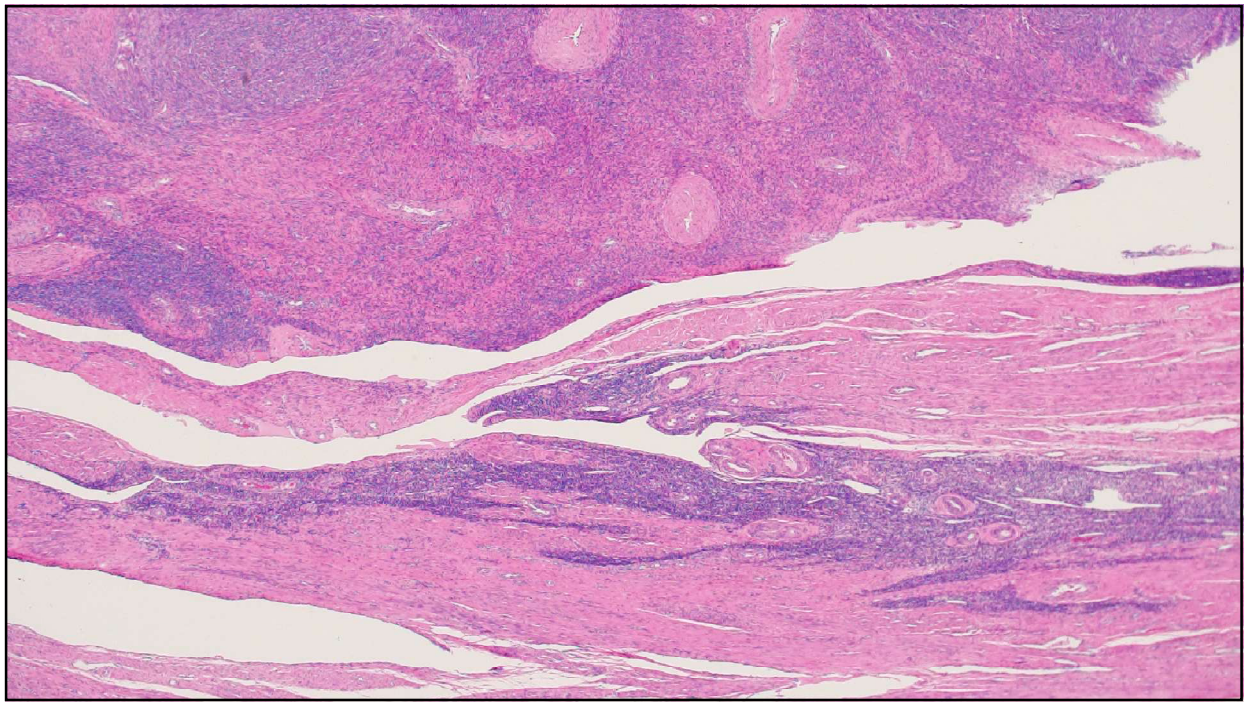

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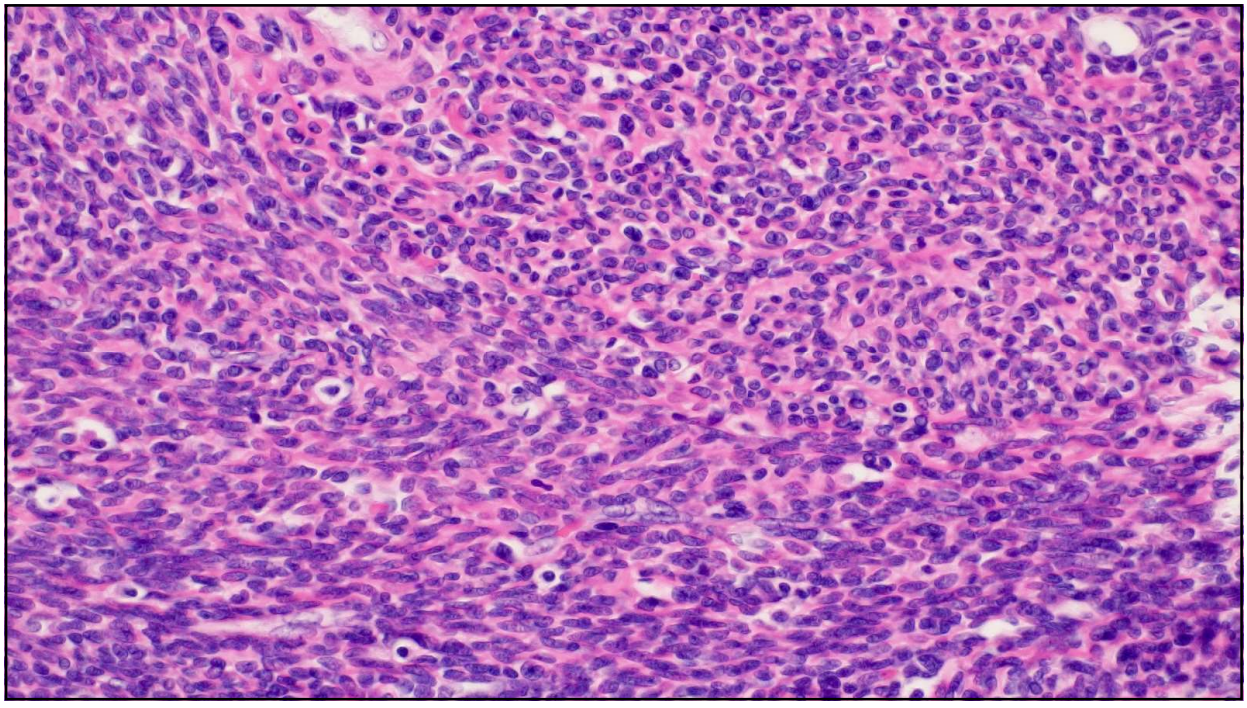

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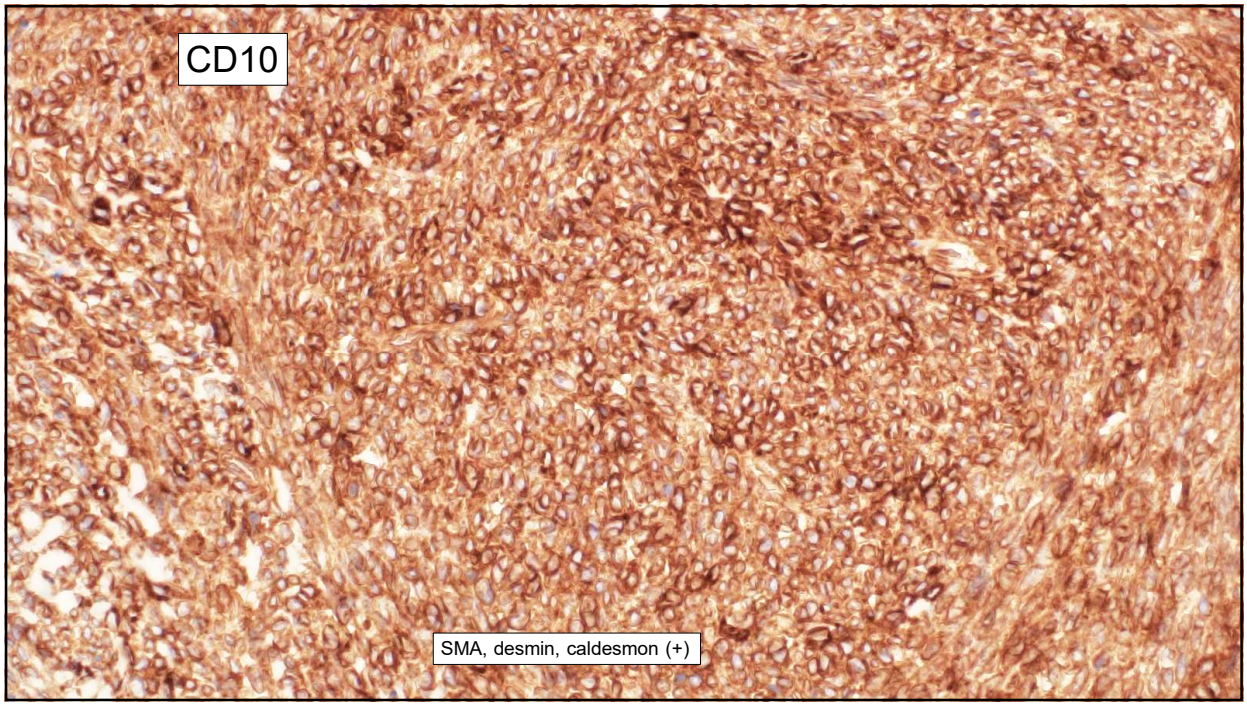

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Cellular leiomyoma

CD10 positivity ≠ LGESS/ESN

Morphologic context critical

Molecular testing (FISH) in questionable cases

42

Practical pearls

- **Cellular leiomyomas and intravascular leiomyomatosis:**
  - **Clefting, large caliber vessels**
  - **May demonstrate wandery edges at periphery**
  - **May have diminished smooth muscle marker expression**
  - **May be positive for CD10**
- **Watch out for:**
  - **Destructive infiltration of myometrium**
  - **Cytologic atypia and increased mitotic activity**
  - **Lack of clefting and large caliber vessels**

43

Pitfall

- **Some LGESS/ESN have patchy CD10 expression (non-diffuse), so this stain is rarely helpful**

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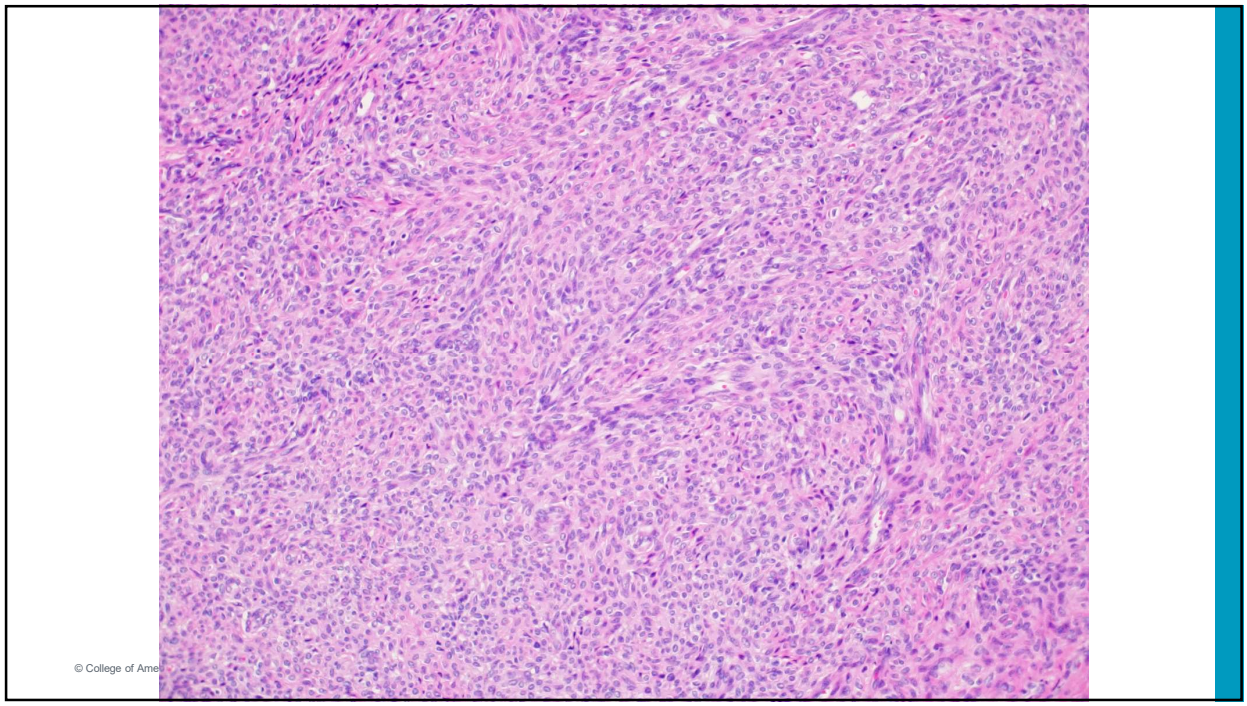

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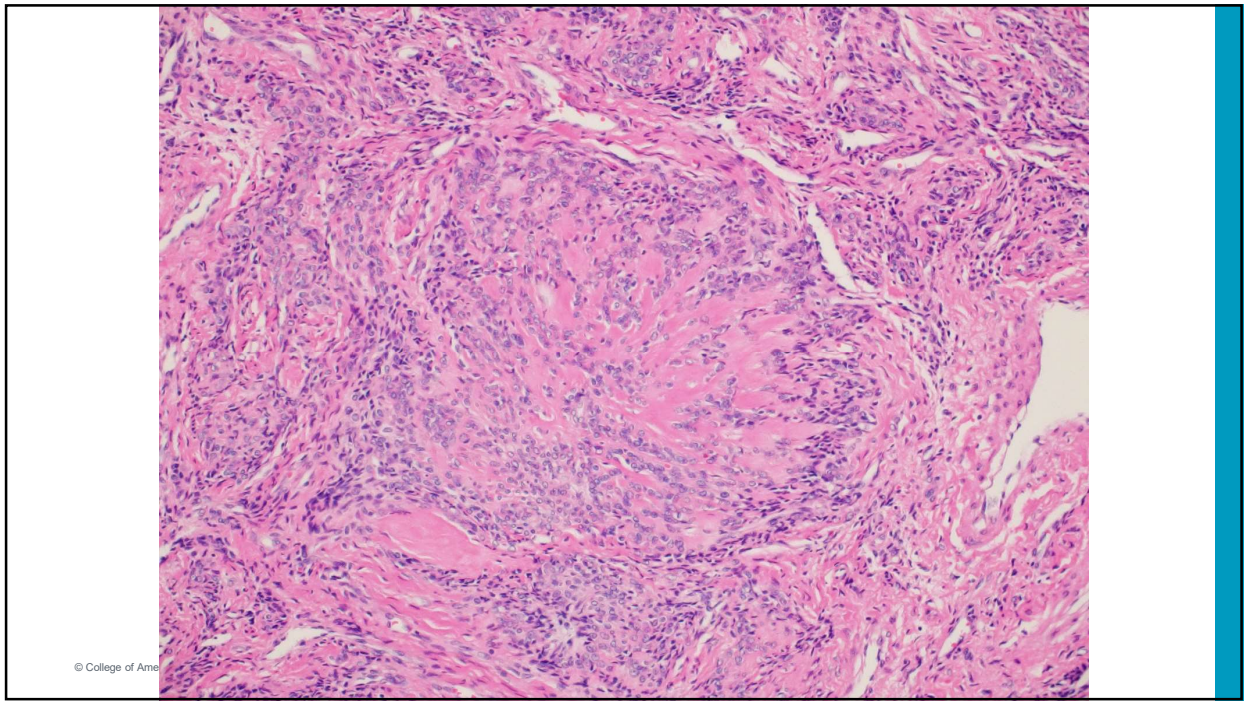

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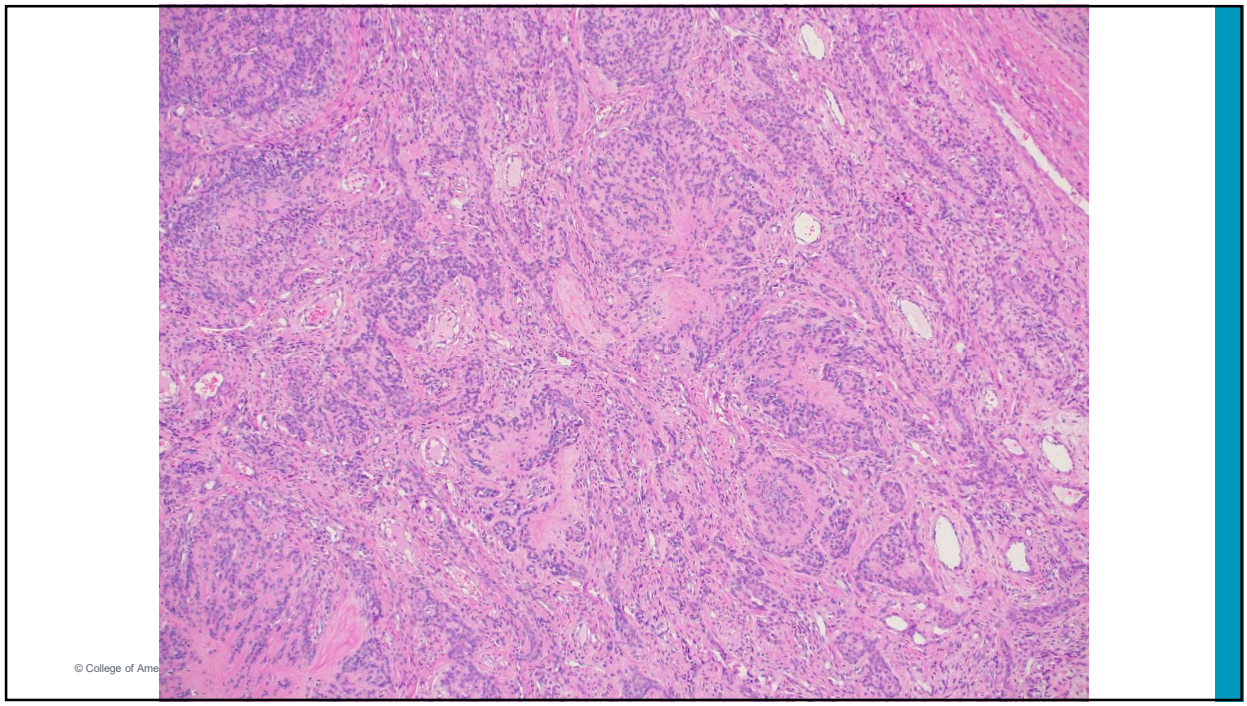

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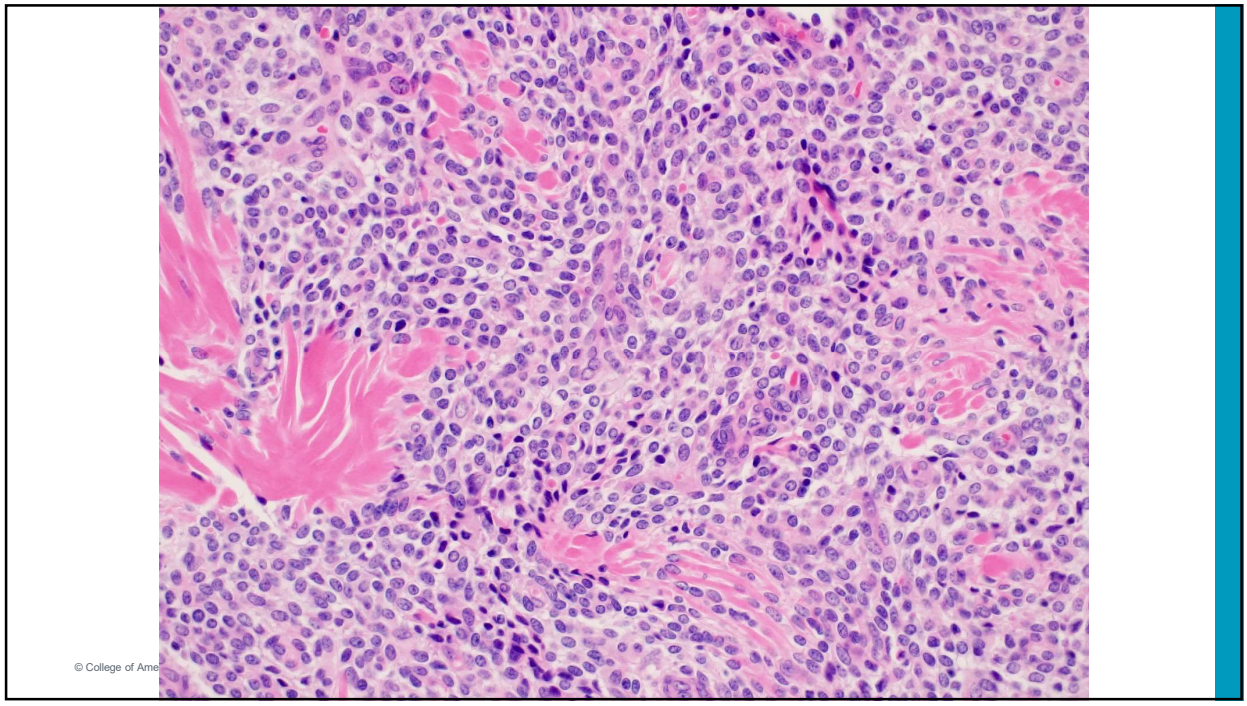

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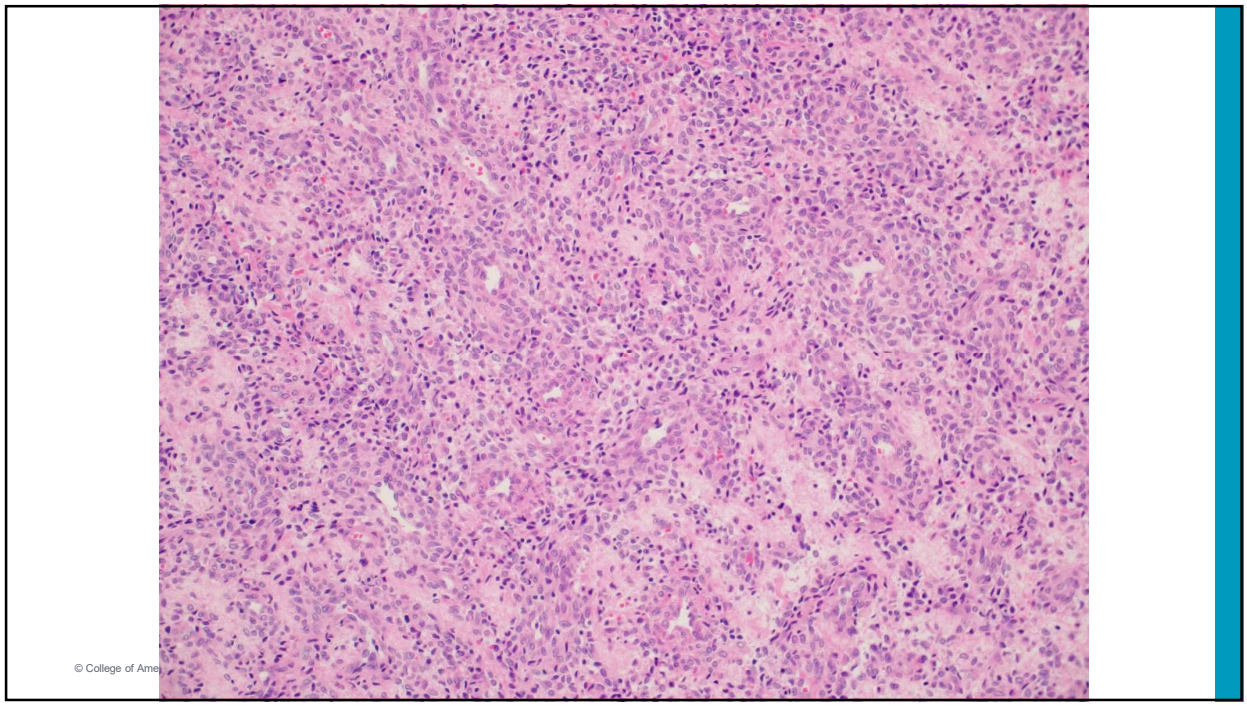

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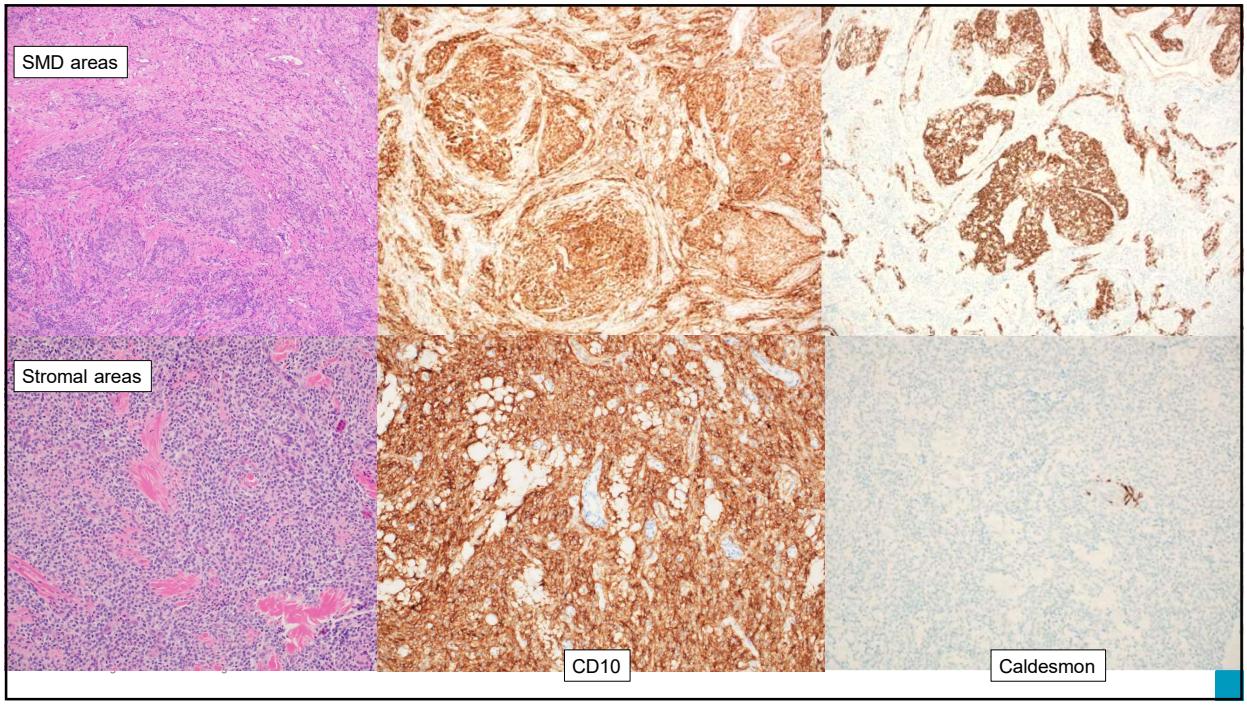

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LGESS with smooth muscle differentiation (SMD)

- ***JAZF1*+ by FISH**
- **Careful selection of blocks to stain with IHC panel based on morphologic findings**

51

IVL/cellular SMTs vs endometrial stromal

	SMTs	Endometrial stromal neoplasms (LG)
Morphology: vessels	Thick-walled, present throughout tumor	Small caliber thin walled spiral arteriole-like vasculature; may have thicker vessels at periphery
Morphology: tumor cells	Elongated, blunt nuclei, abundant eosinophilic cytoplasm	Fusiform ovoid, inconspicuous cytoplasm
Morphology: other	Clefting, may have plexiform patterns Slightly irregular borders acceptable	
IHC	SMA, desmin, caldesmon (+) May be CD10(+)	CD10 (+) ER/PR (+) May be (+) for smooth muscle markers in areas of SMD
Molecular	Negative for ESS-associated rearrangements	JAZF1, PHF1, etc

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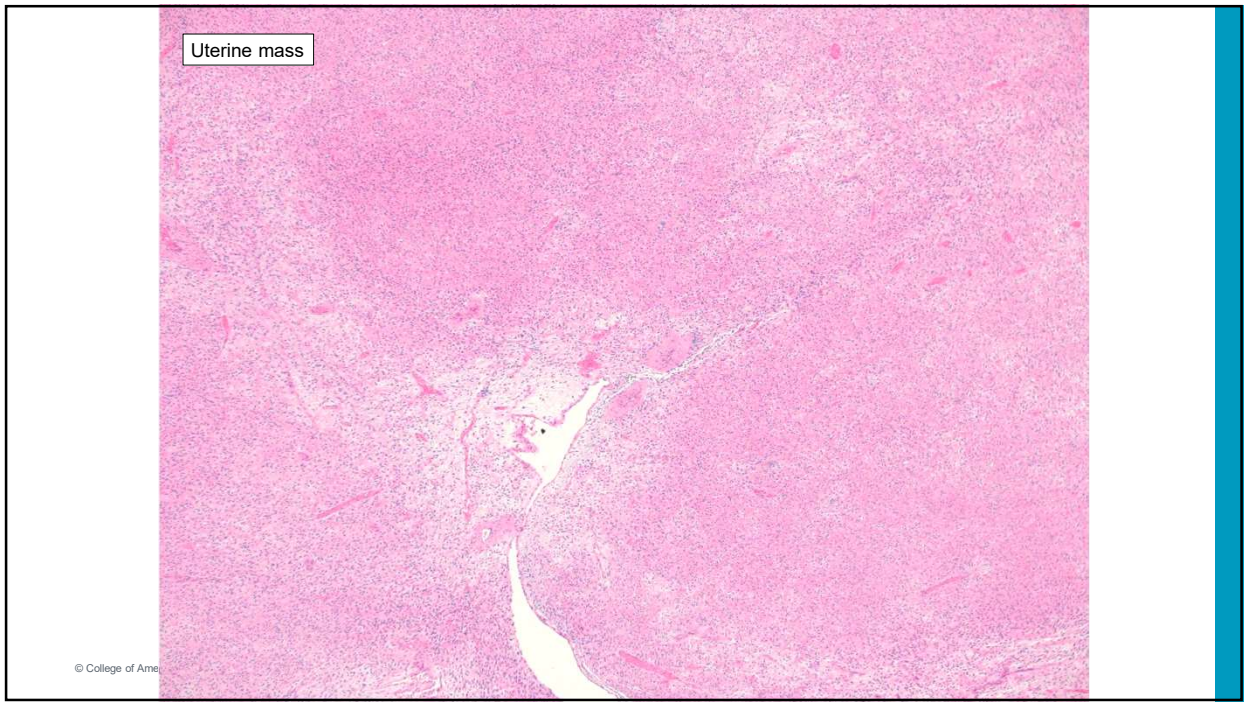

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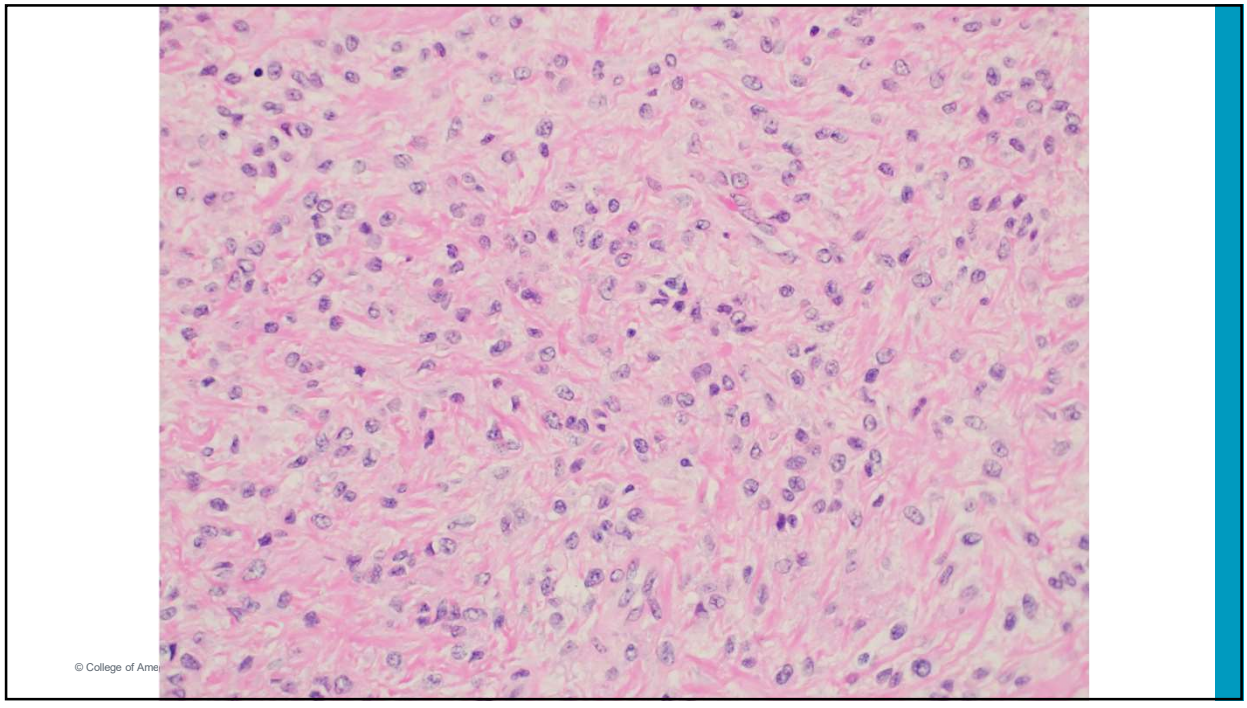

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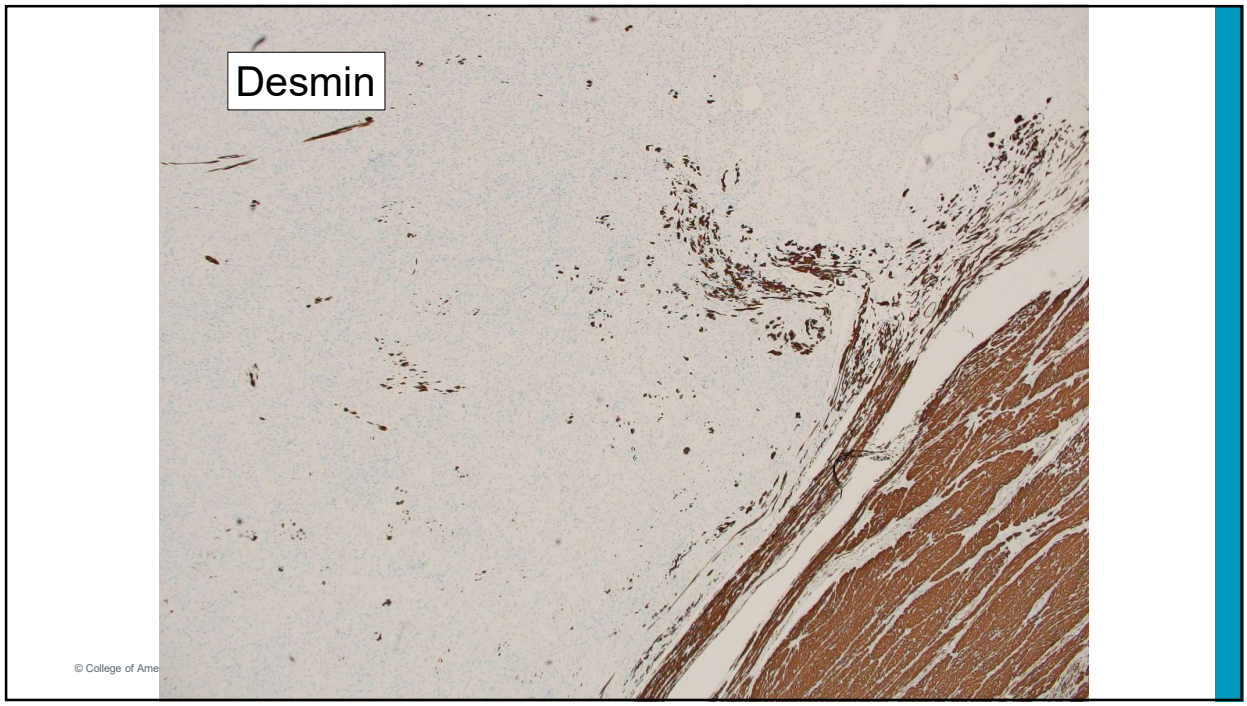

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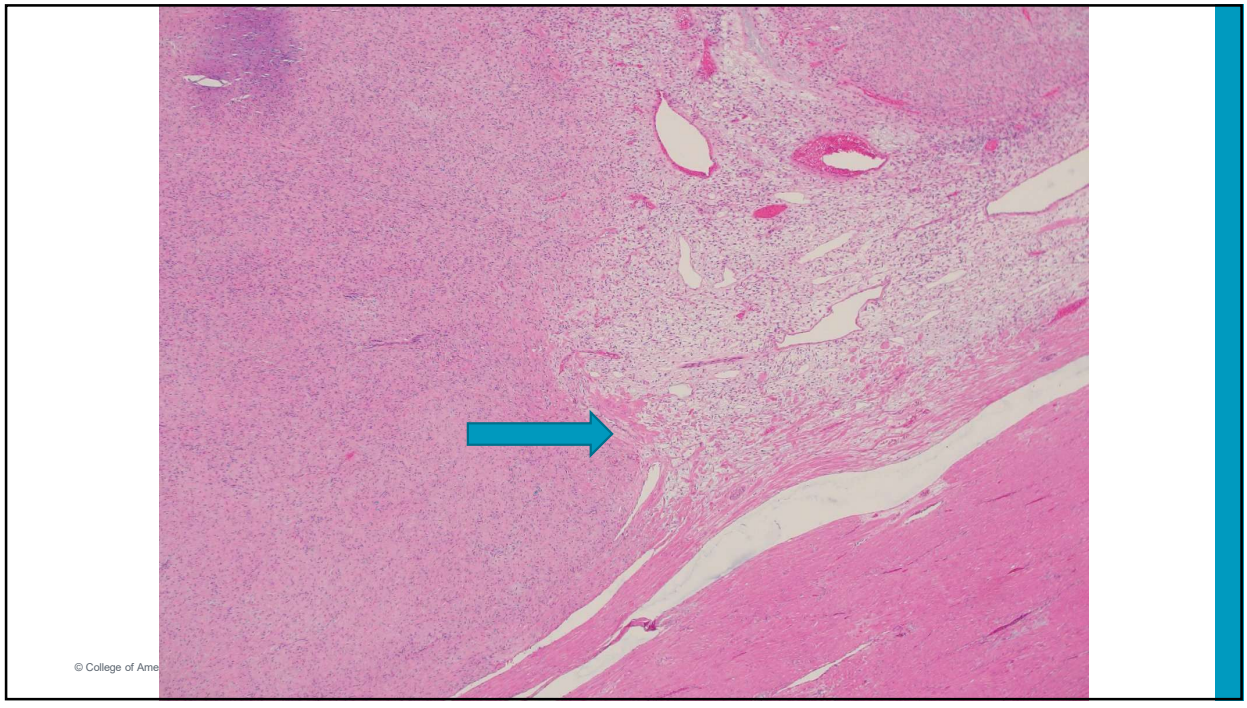

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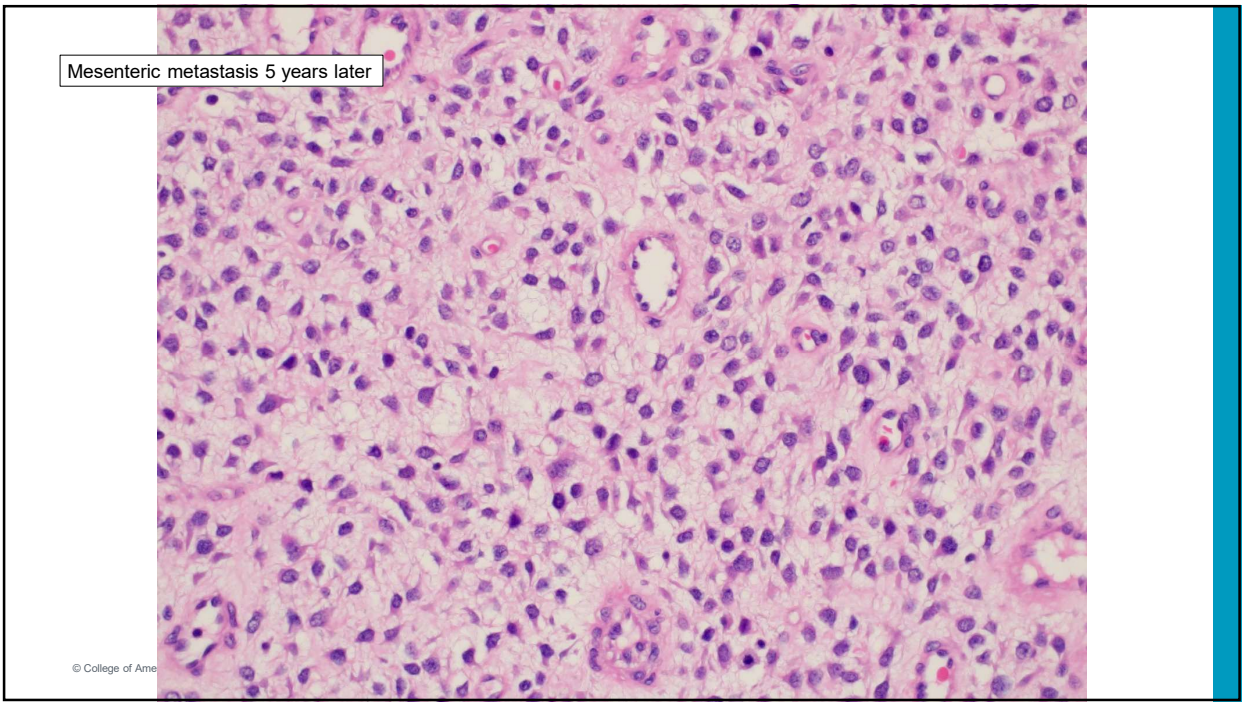


57

Diagnosis: LGESS

Positive for *JAZF1* and *PHF1* breakapart FISH

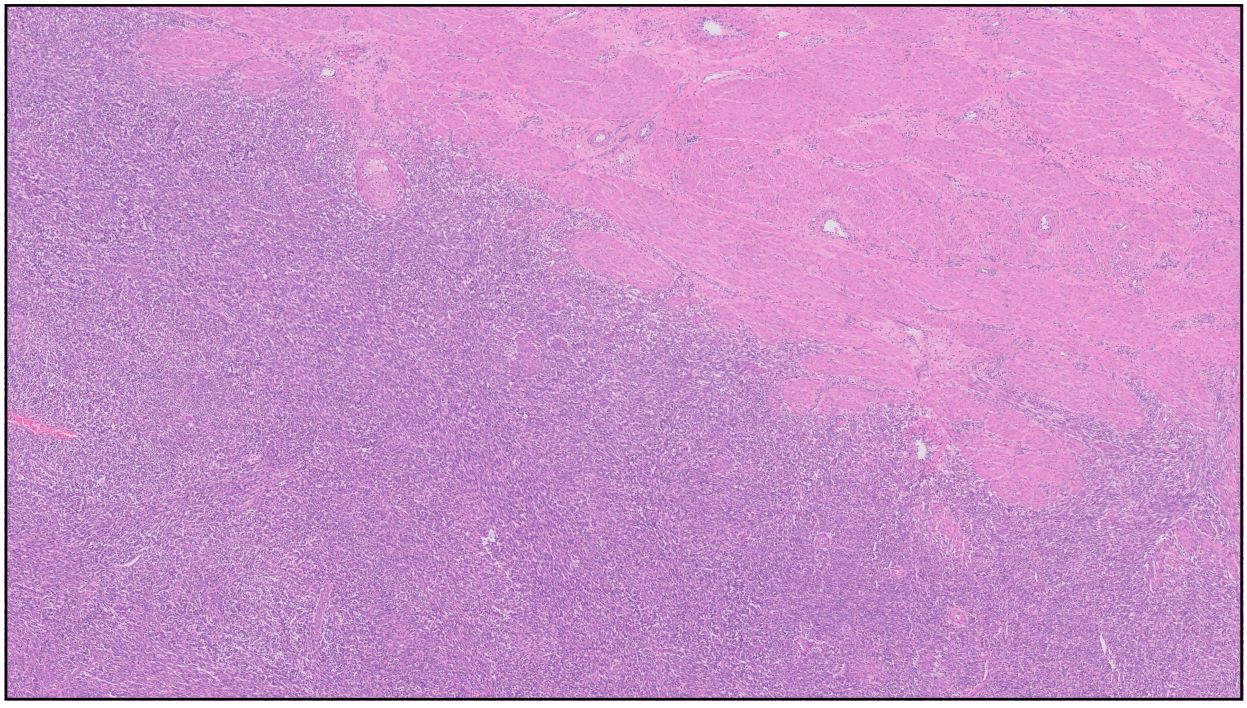
Originally misdiagnosed as leiomyoma until recurrence

58

Practical Pearls

- **When interpreting smooth muscle markers in uterine tumors, consider possibility of entrapped myometrium and ensure the staining is convincingly in tumor cells**
- **Panel of IHC needed with careful morphologic guidance for block(s) to stain**

59



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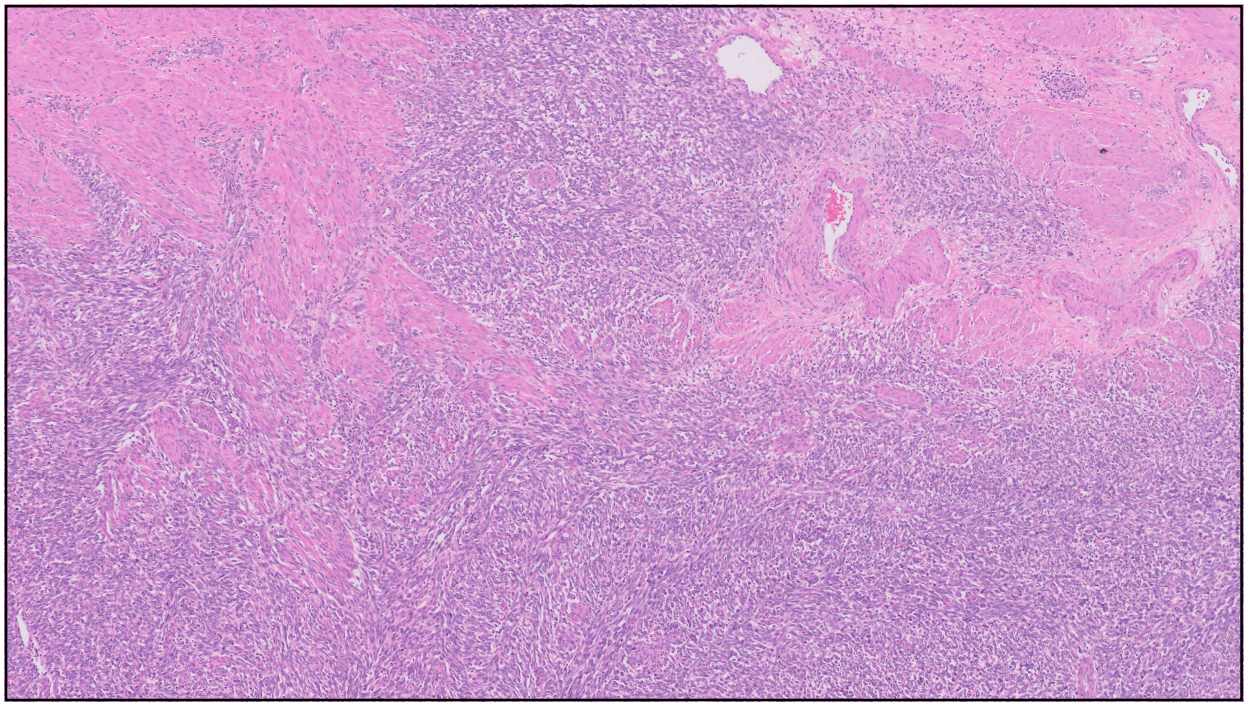

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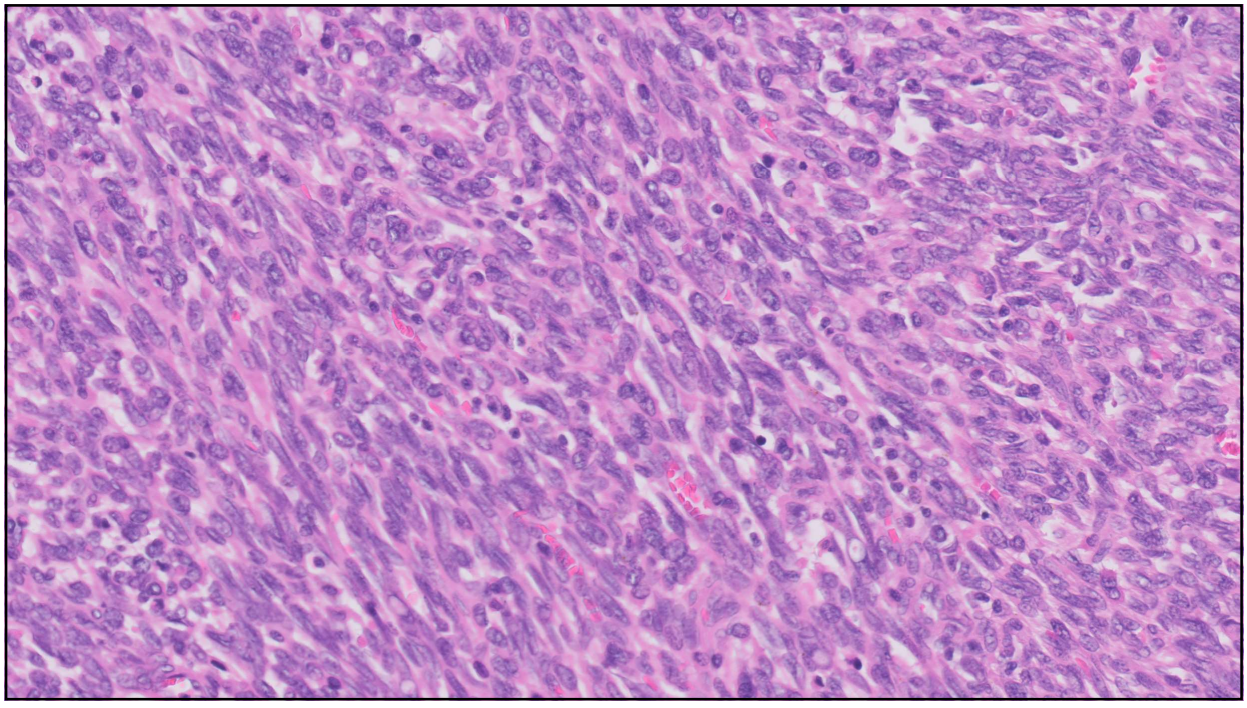

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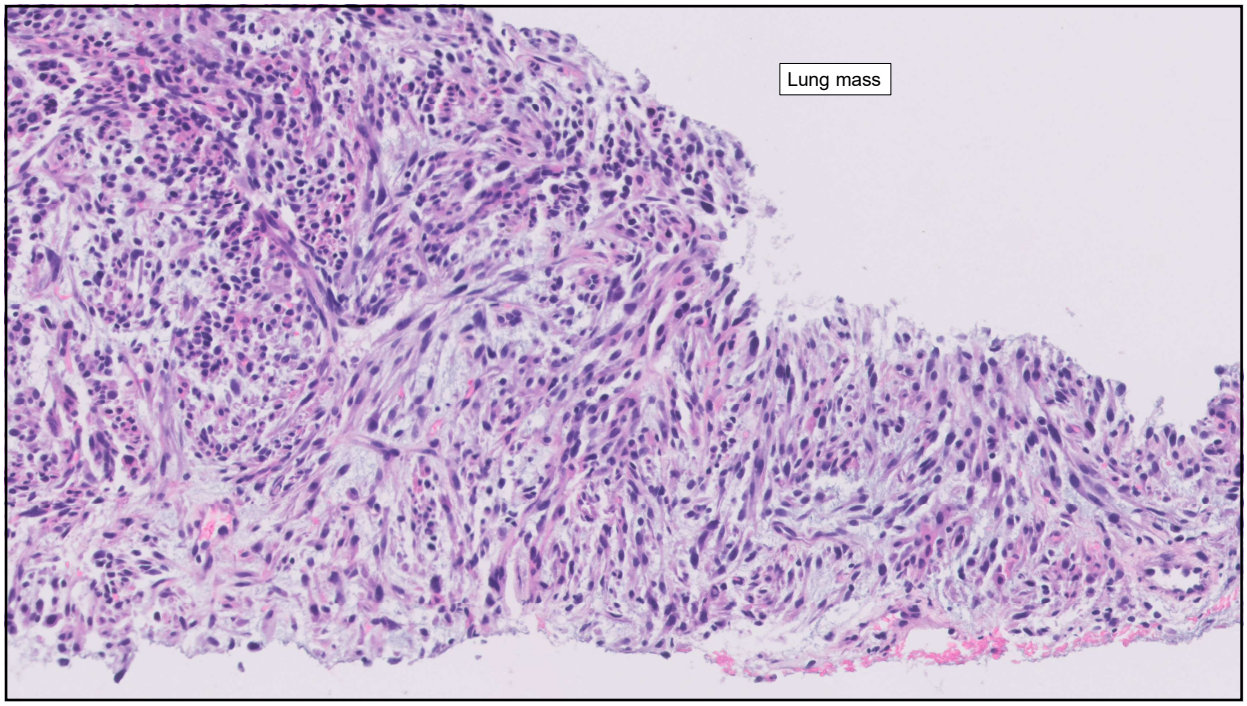

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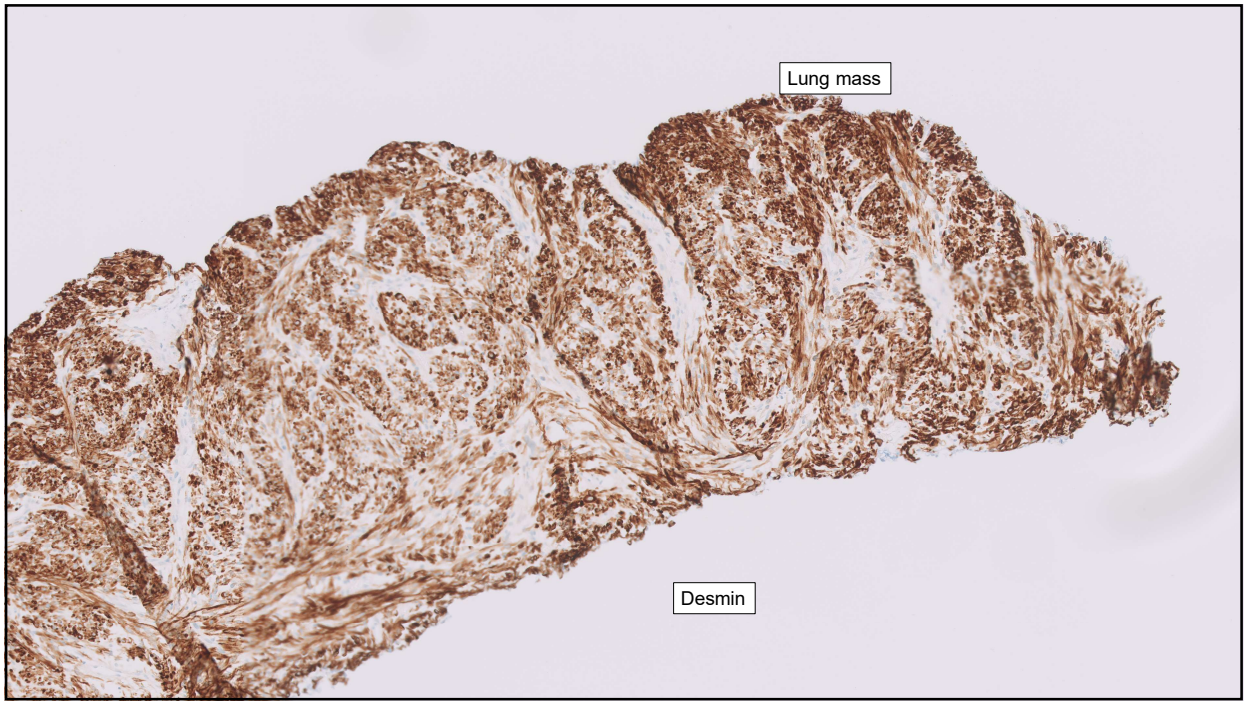

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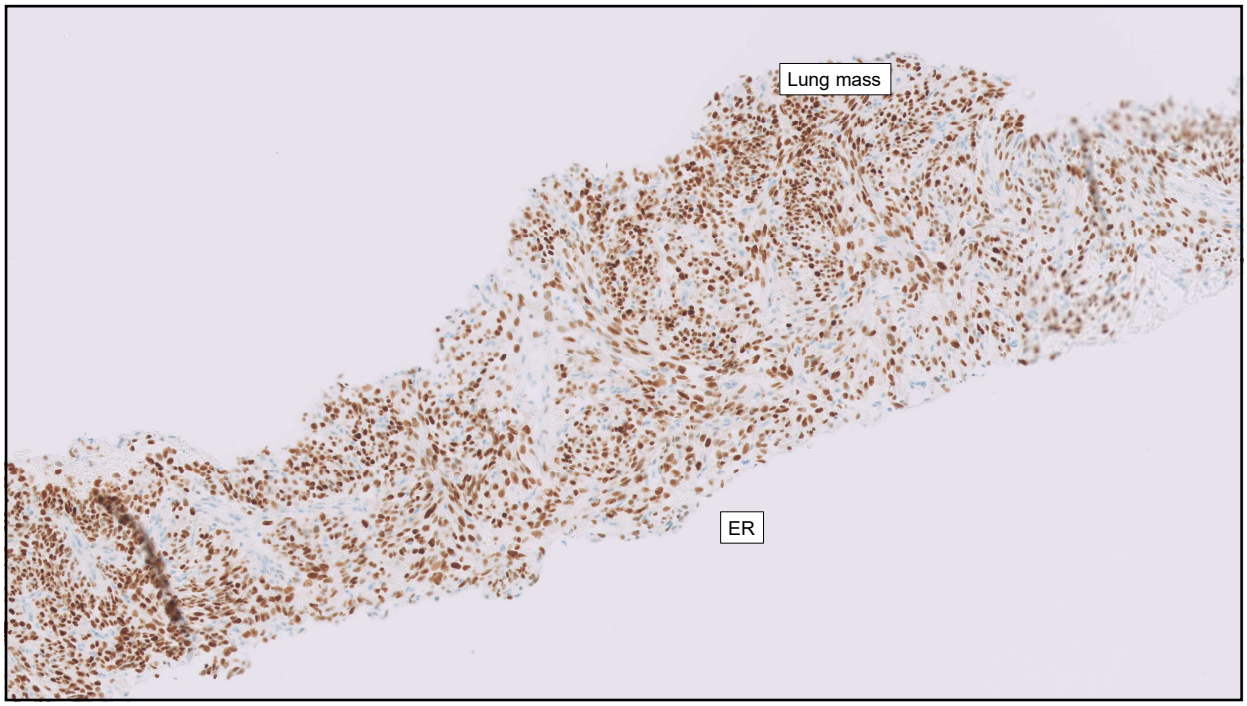

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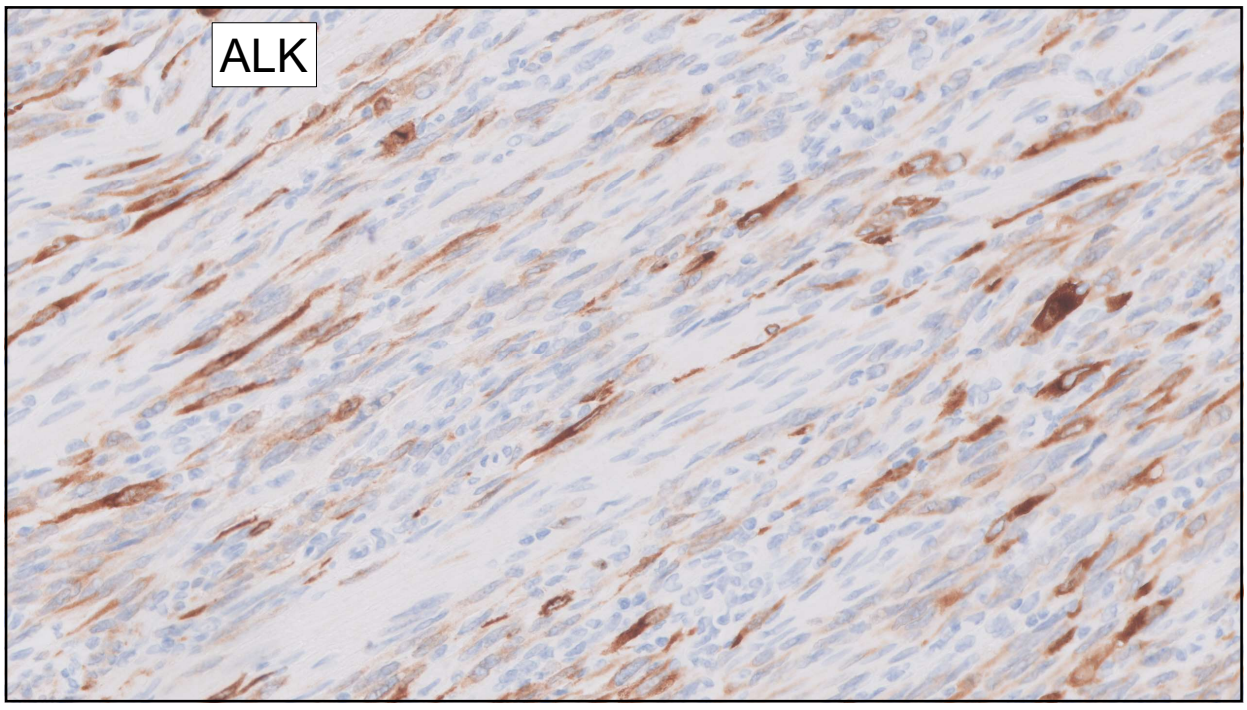


66

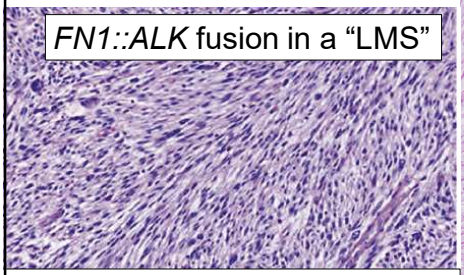
Practical pearls

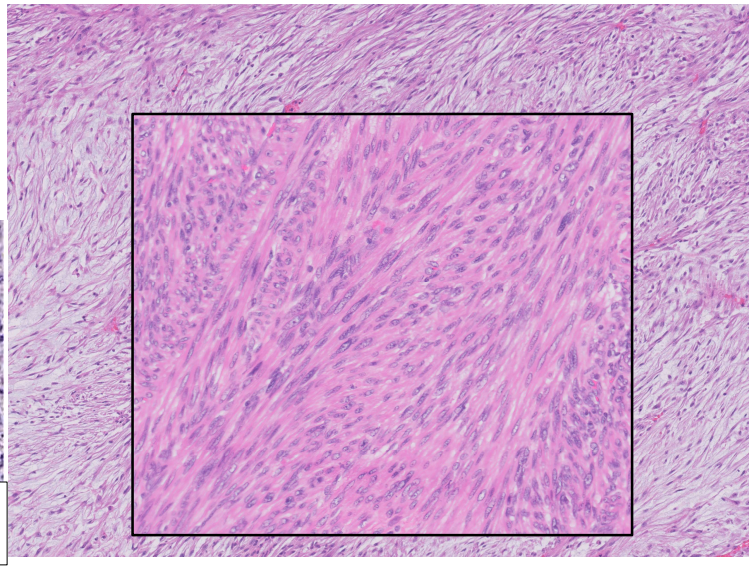
- **Low threshold for ordering ALK in smooth muscle tumors, particularly those with any amount of myxoid stroma or unusual morphology**
  - **Destructive infiltration of surrounding myometrium**
- **ALK IHC may correlate with degree of myxoid stroma so care should be taken in selecting block to test**
  - **In contrast, molecular testing can be performed on any block**
- **ALK IHC positivity does not always indicate Alk fusion; followup molecular testing is advised (Alk amplification in some cases)**
- **A tumor with classic IMT morphology but negative Alk IHC can still be tested via FISH/sequencing**

67

Inflammatory Myofibroblastic Tumor (IMT)

- *ALK* fusions
- *TIMP3::RET*
- *TIMP3::ROS1*
- *FN1::ROS1*





Testa S, et al. Uterine Leiomyosarcoma with FN1-Anaplastic Lymphoma Kinase Fusion Responsive to Alectinib and Lorlatinib. Case Rep Oncol. 2021

68

Utility of mutation (DNA) profiling in gynecologic mesenchymal tumors

Common problems:

- **LMS vs STUMP**
- **LMS vs PEComa**

69

LMS vs STUMP

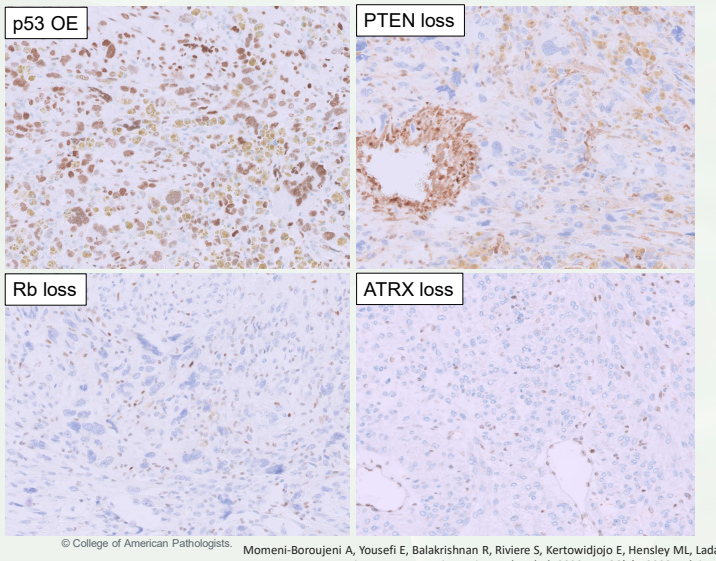
- **Morphologic distinction**
  - **Atypia**
  - **Mitoses**
  - **Necrosis**

➢ **Highly subjective→ poor reproducibility**

➢ **Poor reproducibility leads to less clinical relevance**

70

IHC as molecular surrogates in uterine smooth muscle tumors



Immunohistochemical markers that can be used as molecular surrogates:

p53/MDM2/MTAP

PTEN

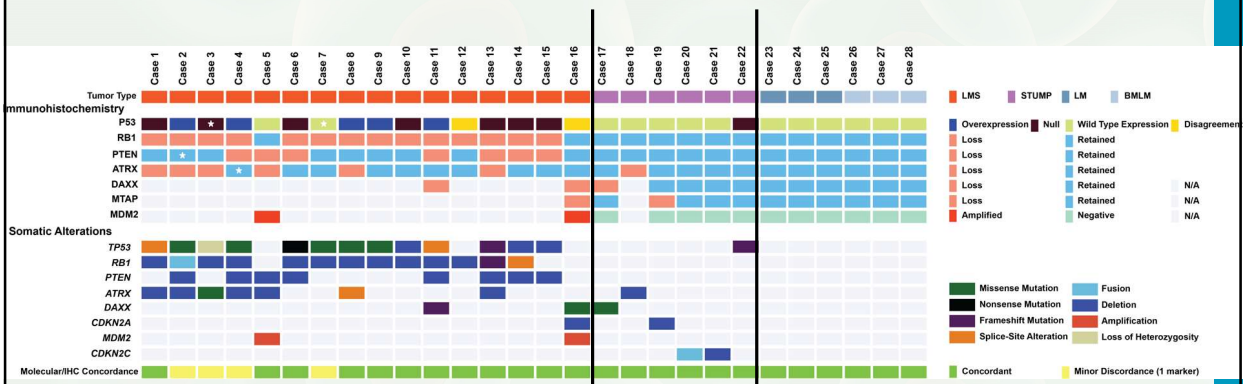
ATRX/DAXX

Rb

Momeni-Boroujeni A, Yousefi E, Balakrishnan R, Riviere S, Kertowidjojo E, Hensley ML, Ladanyi M, Ellenson LH, Chiang S. Molecular-Based Immunohistochemical Algorithm for Uterine Leiomyosarcoma Diagnosis. Mod Pathol. 2023 Apr;36(4):100084. doi: 10.1016/j.modpat.2022.100084. Epub 2023 Jan 10. PMID: 36788080; PMCID: PMC10191186.

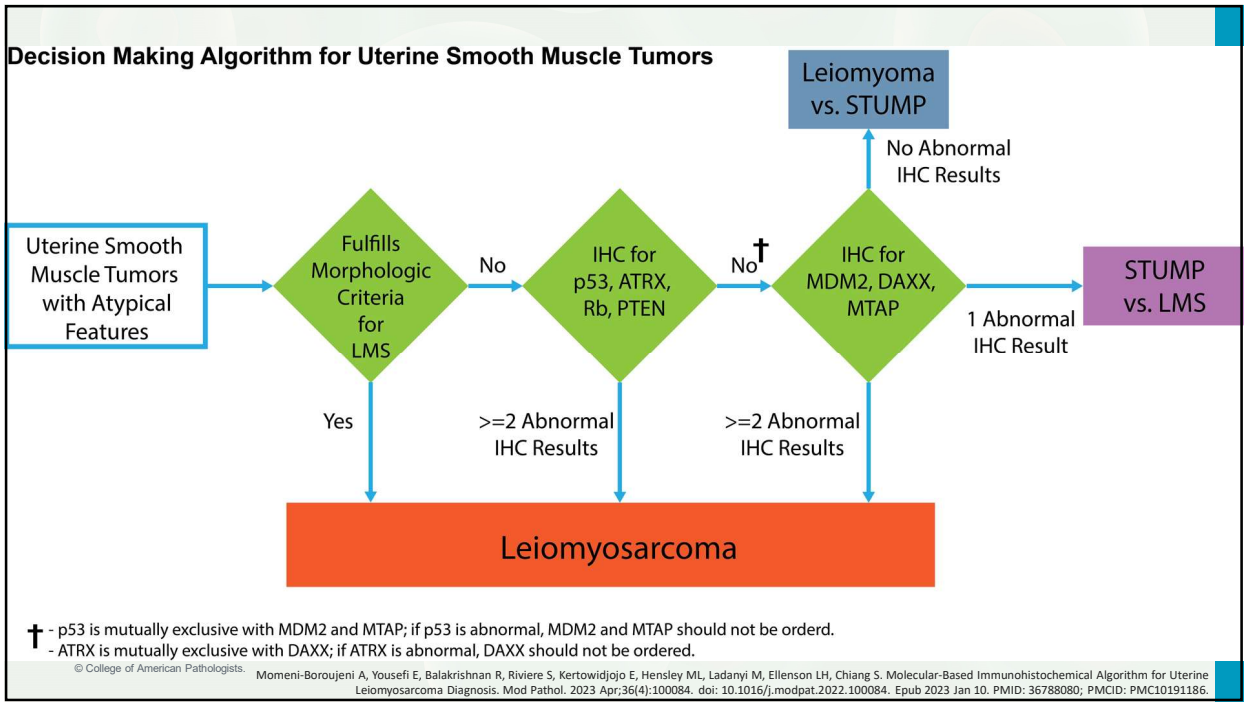
71

IHC as molecular surrogates in uterine smooth muscle tumors



Momeni-Boroujeni A, Yousefi E, Balakrishnan R, Riviere S, Kertowidjojo E, Hensley ML, Ladanyi M, Ellenson LH, Chiang S. Molecular-Based Immunohistochemical Algorithm for Uterine Leiomyosarcoma Diagnosis. Mod Pathol. 2023 Apr;36(4):100084. doi: 10.1016/j.modpat.2022.100084. Epub 2023 Jan 10. PMID: 36788080; PMCID: PMC10191186.

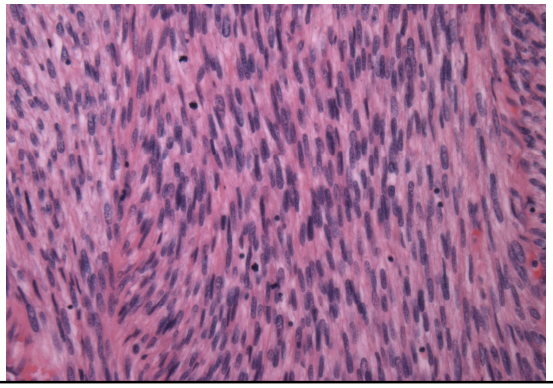
72



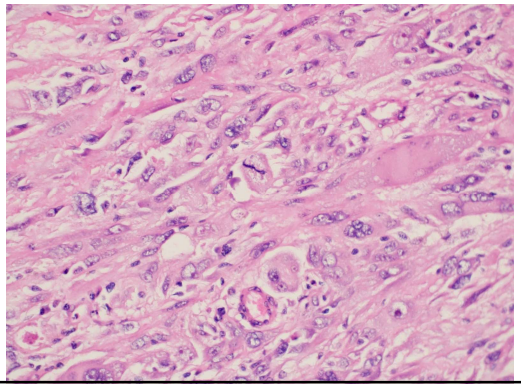
73

Leiomyosarcoma vs PEComa: Morphology

- **Spindled cells**
- **Fascicular growth**
- **Elongated nuclei**



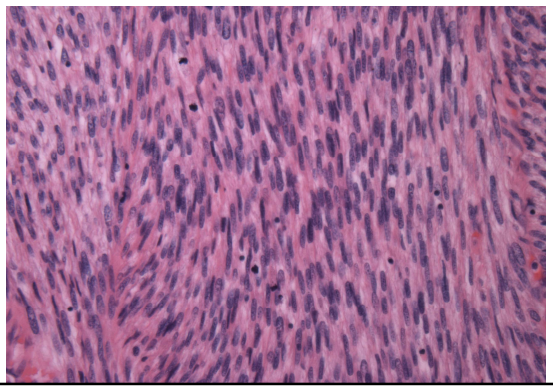
- **Epithelioid cells, abundant esosinophilic cytoplasm**
- **Spider cells**
- **Sclerosis may be present**



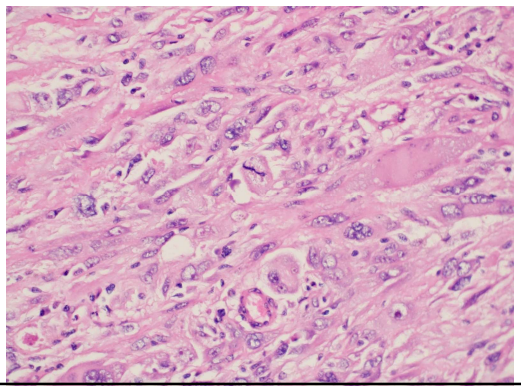
74

Leiomyosarcoma vs PEComa: IHC

- SMA/desmin/caldesmon variably(+)
- HMB45, CathepsinK (-) or focal
- MelanA (-)



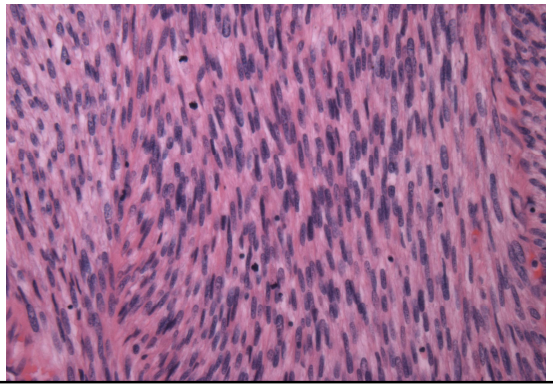
- SMA/desmin/caldesmon variably (+)
- HMB45, CathepsinK (+)
- MelanA ideally (+) but often (-)



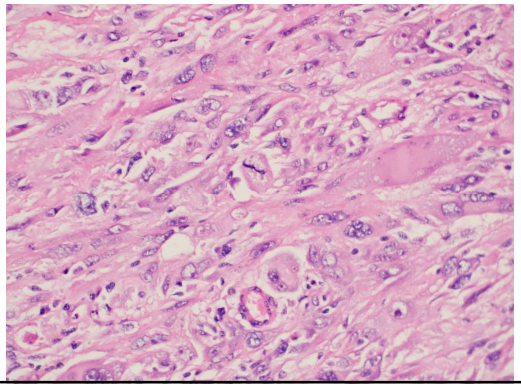
75

Leiomyosarcoma vs PEComa: Molecular

- Alterations including gene truncating fusion events involving tumor suppressor genes ***RB1***, ***TP53***, ***ATRX***, others (LMS)



- Alterations in TSC1/2 (PEComa)
- ***TFE3*** (PEComa)

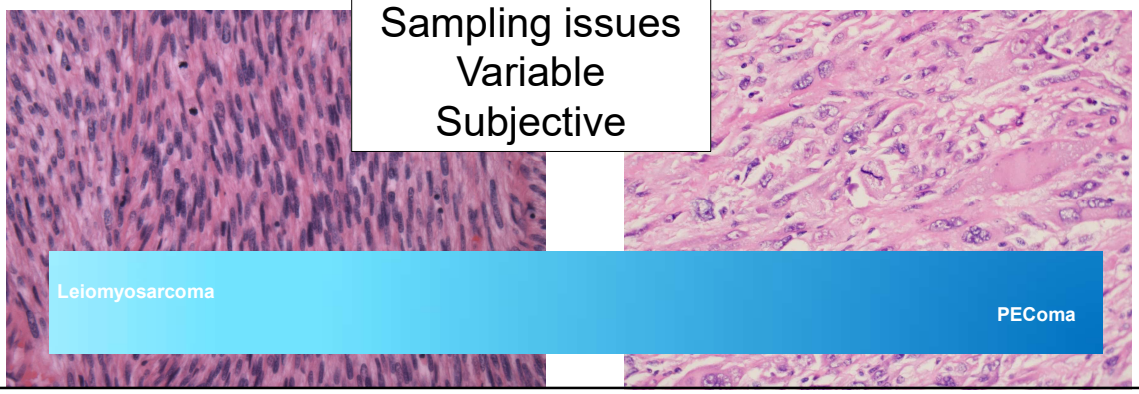


76

Where do we draw the line?

- **Alterations including gene truncating fusion events involving tumor suppressor genes *RB1*, *TP53*, *ATRX*, others (L**
- **Alterations in TSC1/2 (PEComa)**
- ***TFE3* (PEComa)**

Morphology
Sampling issues
Variable
Subjective

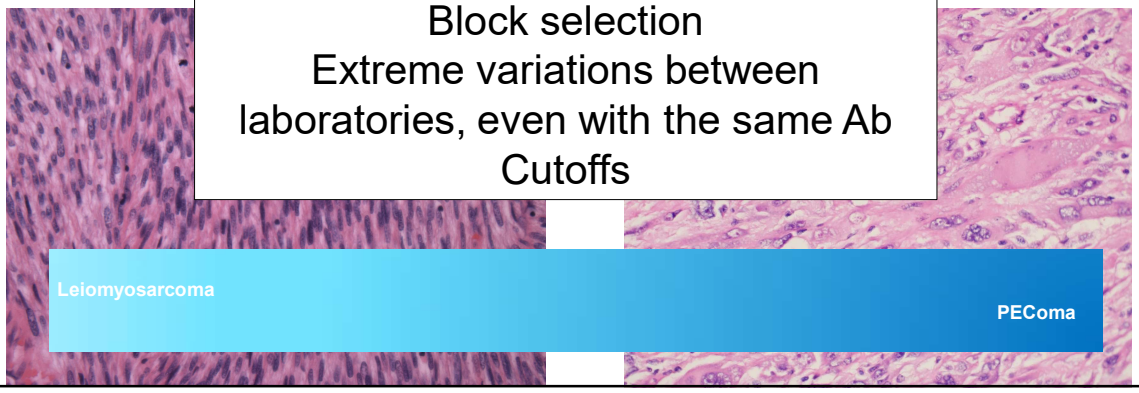


77

Where do we draw the line?

- **Alterations including gene truncating fusion events involving tumor suppressor genes *RB1*, *TP53*, *ATR***
- **Alterations in TSC1/2 (PEComa)**
- ***TFE3* (PEComa)**

Immunohistochemistry
Block selection
Extreme variations between laboratories, even with the same Ab
Cutoffs

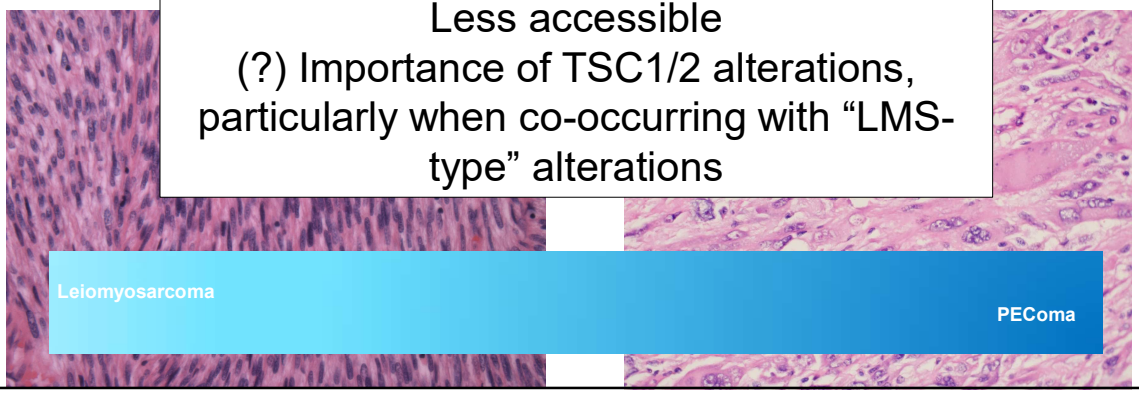


78

Where do we draw the line?

- **Alterations including gene truncating fusion events involving tumor su**
  TP53, AT
- **Alterations in TSC1/2 (PEComa)**

Molecular Profiling
Expensive, time
Less accessible
(?) Importance of TSC1/2 alterations, particularly when co-occurring with "LMS-type" alterations



79

Summary

- **CD10 positivity ≠ LGESS!**
  - **Other uterine mesenchymal tumors that can be positive for CD10:**
    - **Smooth muscle tumors (Cellular leiomyoma, IVL)**
    - **HGESS (BCOR>YWHAE)**
    - **Inflammatory myofibroblastic tumor (IMT)**
    - **NTRK-rearranged sarcoma**
    - **Undifferentiated carcinoma (not mesenchymal, but in the DDX!)**
- **Consider Alk on tumors with myxoid features or infiltrative growth**
- **Cellular leiomyomas and intravascular leiomyomatosis, particularly cellular variants, may lose smooth muscle marker positivity**
- **Careful morphologic examination is crucial**

80

Questions?

81

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82