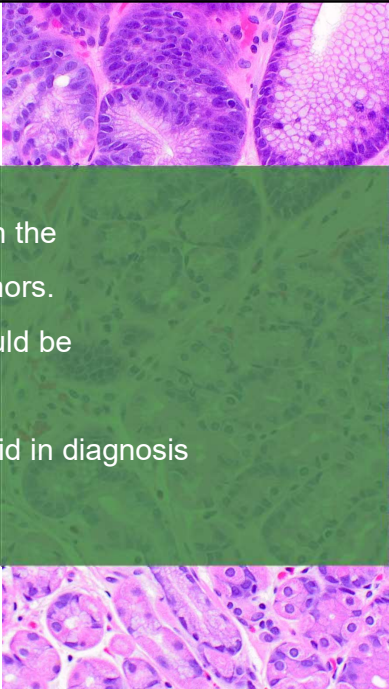


1

Objectives

- Apply a panel of immunohistochemical stains to aid in the distinction of smooth muscle tumors from stromal tumors.
- Realize the scenarios in which molecular testing should be considered or ordered.
- Recognize immunohistochemical markers that may aid in diagnosis of leiomyosarcoma.

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This slide contains three histological images of uterine smooth muscle tumors. The top image shows a cross-section of a tumor with a central area of necrosis, characterized by a pale, eosinophilic center surrounded by a ring of viable tumor cells. The middle image is a high-magnification view of a tumor section, showing a dense population of cells with prominent, hyperchromatic nuclei and a high nuclear-to-cytoplasmic ratio. The bottom image shows another high-magnification view of a tumor section, featuring a cluster of cells with large, pleomorphic nuclei and prominent nucleoli, suggesting a high-grade malignancy.

2

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

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1. Smooth muscle tumor classification

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4

Leiomyoma—Many variants!

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

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5

Leiomyoma—Many variants!

- Epithelioid
 - Myxoid
- ➔ Very rare- usually not the "right" diagnosis
- Hydropic (edematous)
 - Cellular/Highly cellular
 - Intravenous leiomyomatosis
 - Mitotically active
 - Apoplectic
 - Lipoleiomyoma

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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

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7

Leiomyoma—Many variants!

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



Focus for today

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8

Cellular leiomyoma

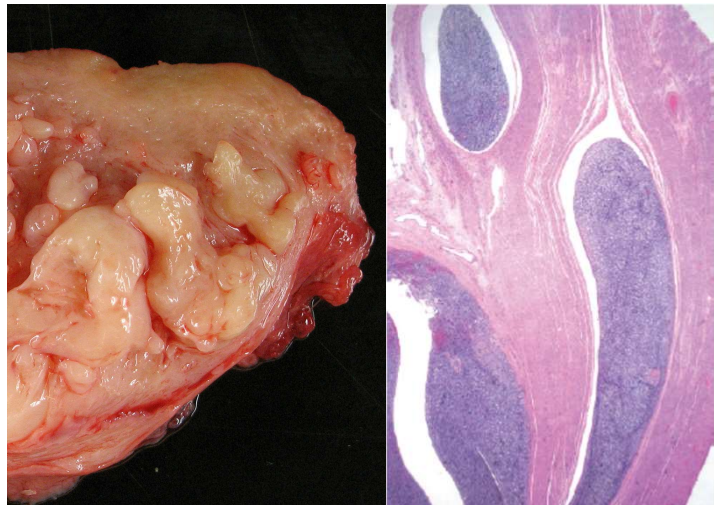
- Appear “blue” from low power and significantly more cellular than surrounding myometrium
- Grossly may have softer, less rubbery cut surface and yellow to tan color
- By gross and microscopic assessment, more likely to be confused with non-smooth muscle neoplasms
- BLAND cytologic features and inconspicuous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

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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

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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!!

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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

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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

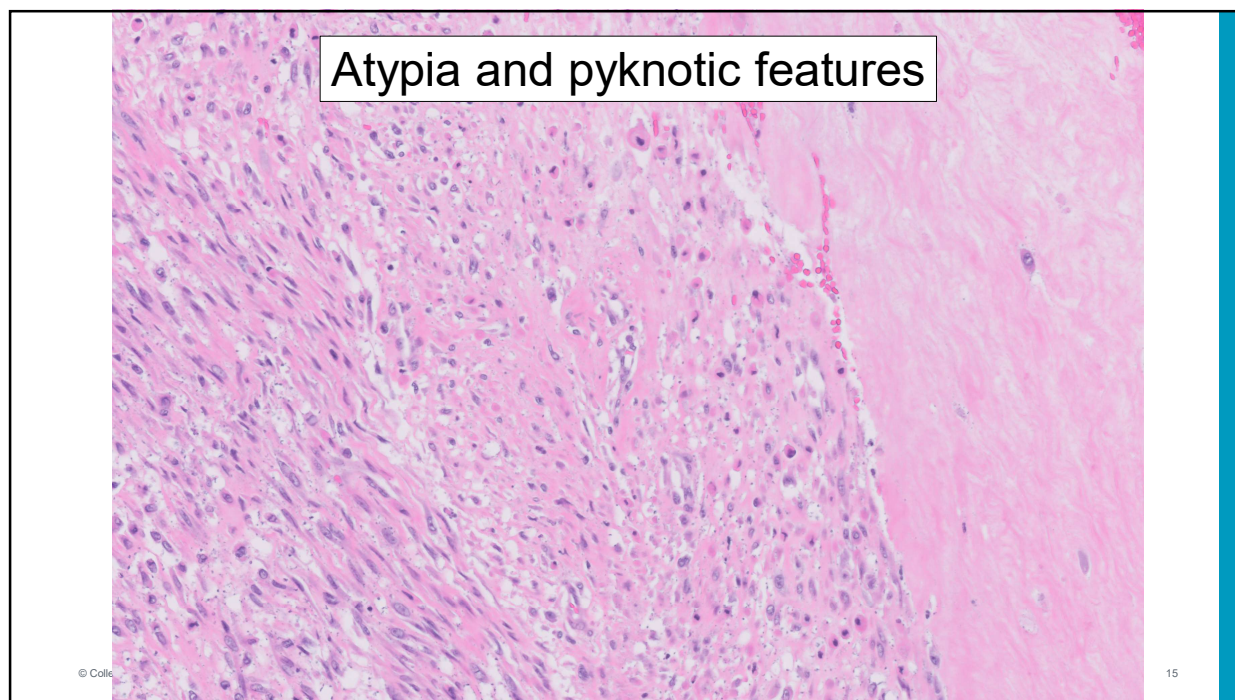
13

Hemorrhagic necrosis

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14



15

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**

A histological micrograph showing a leiomyoma with atypical nuclei. The tissue is stained with H&E, showing spindle-shaped cells with elongated, hyperchromatic nuclei. Some nuclei are notably larger and more irregular than others, consistent with the "bizarre nuclei" mentioned in the text.

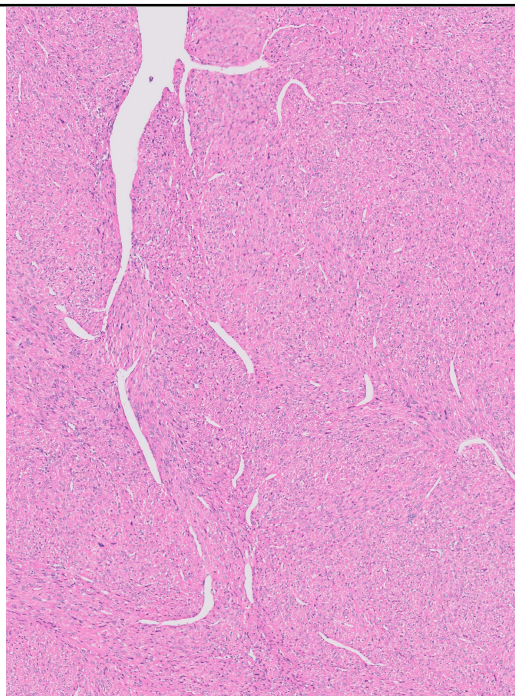
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FH-deficient leiomyoma

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

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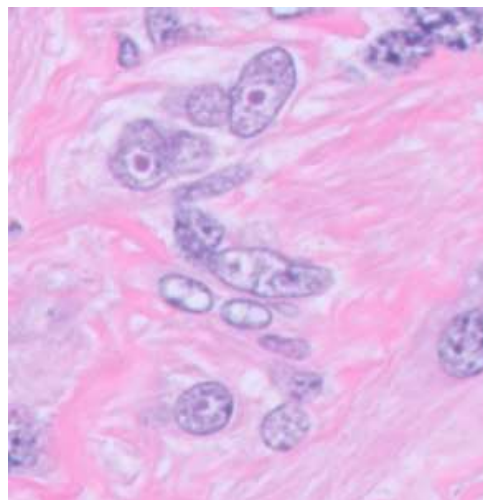


17

FH-deficient leiomyoma

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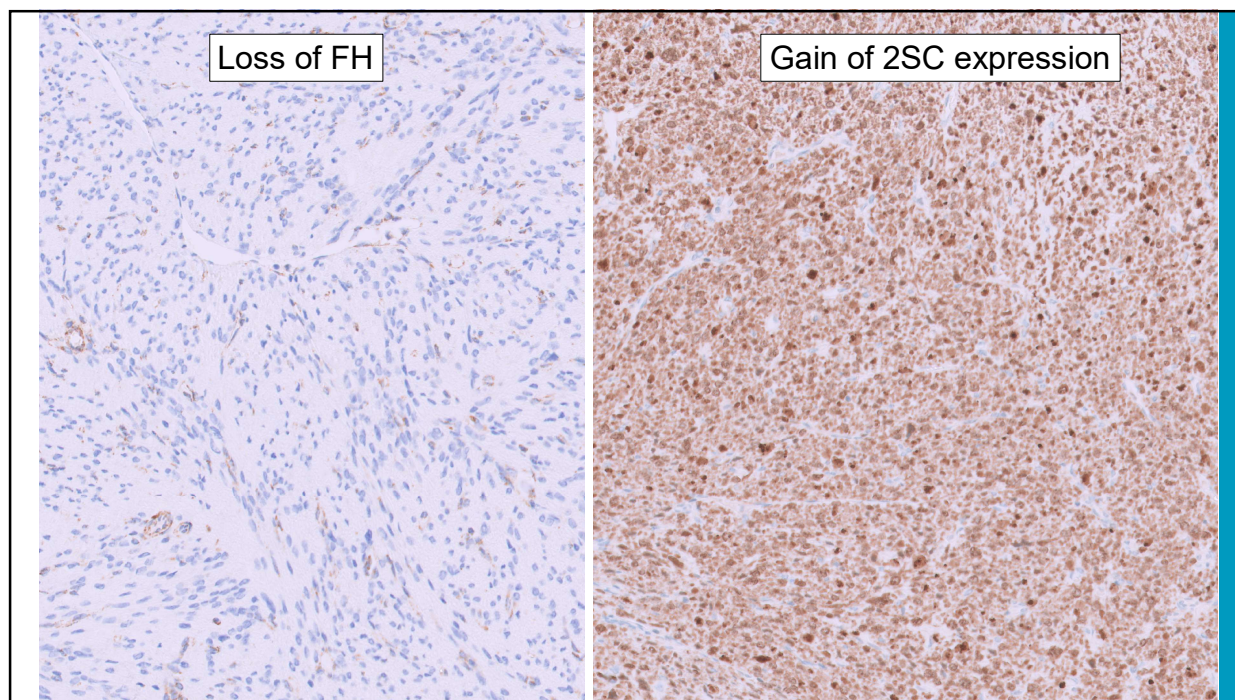
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18



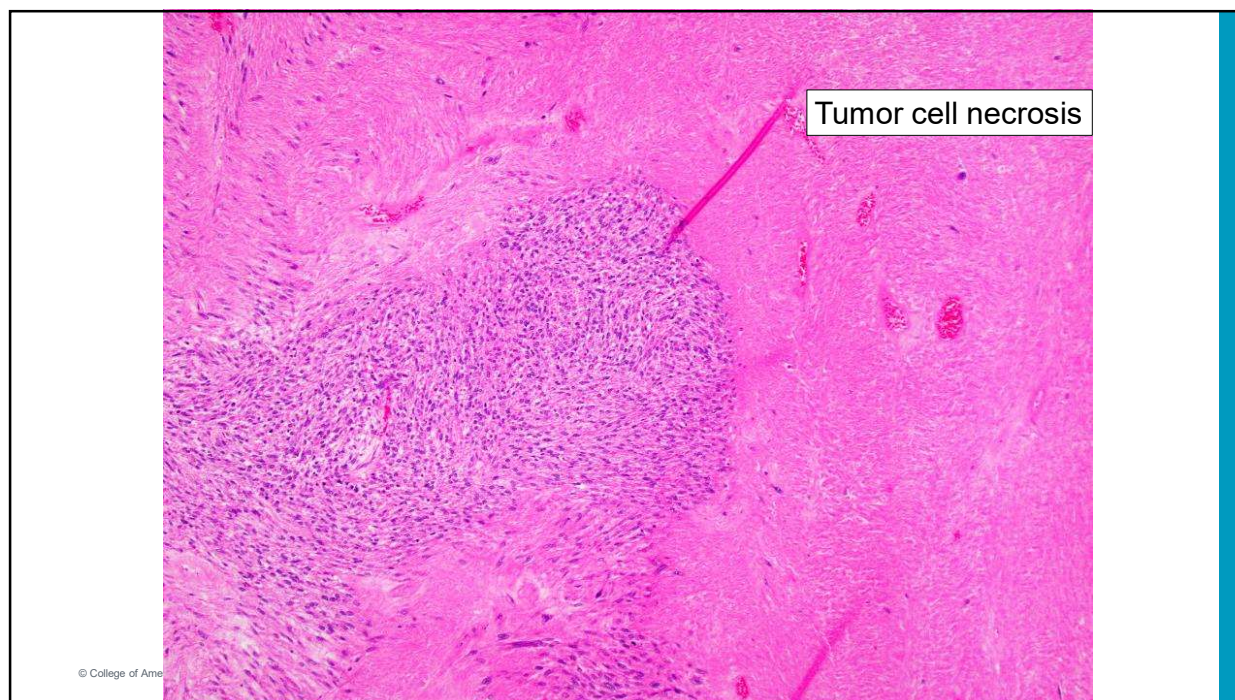
19

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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STUMP (smooth muscle tumor of uncertain malignant potential)

A histological micrograph of a STUMP (smooth muscle tumor of uncertain malignant potential) stained with H&E. The image shows a dense proliferation of spindle-shaped cells with elongated nuclei, similar to leiomyoma but with more pronounced atypia and mitotic activity. The tissue architecture is disorganized, with areas of necrosis and increased cellularity.

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

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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

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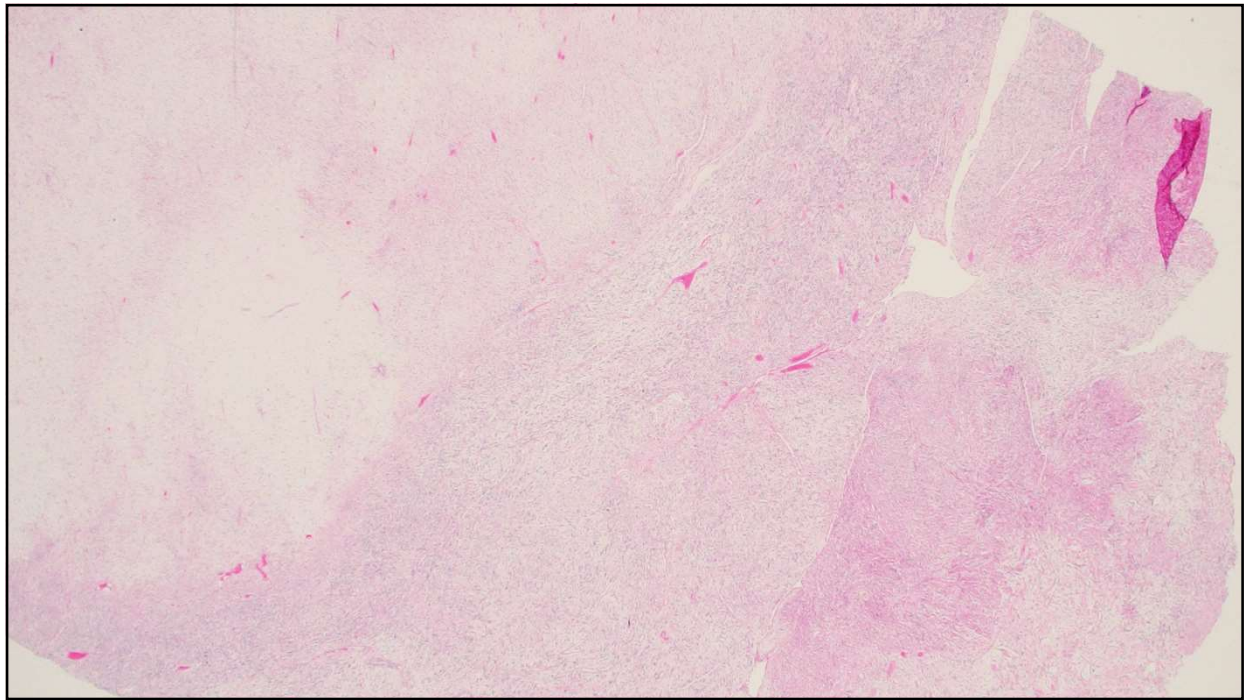
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LMS- Myxoid

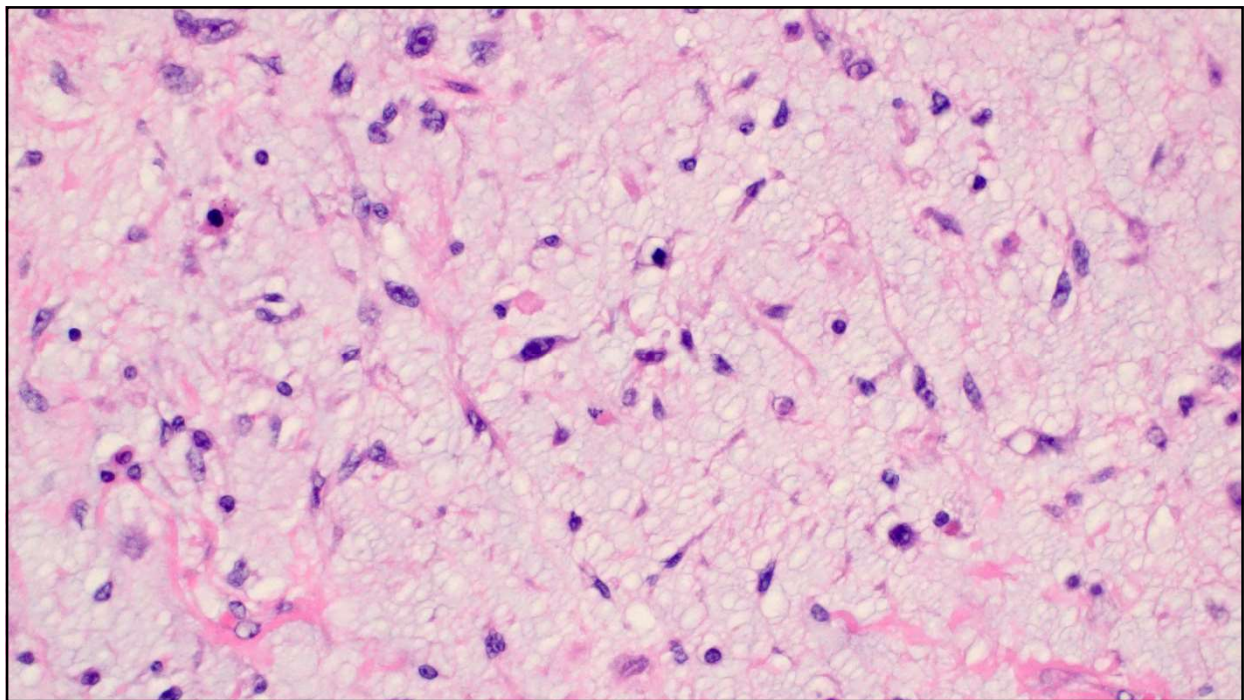
- **Generally hypocellular**
- **Abundant myxoid stroma**
- **DIFFERENT criteria for malignancy compared to conventional/spindle cell:**
 - One or more of the following
 1. Moderate to severe cytologic atypia
 2. Tumor cell necrosis
 3. ≥ 2 mitoses per 10 HPFs
 4. Infiltrative/irregular border

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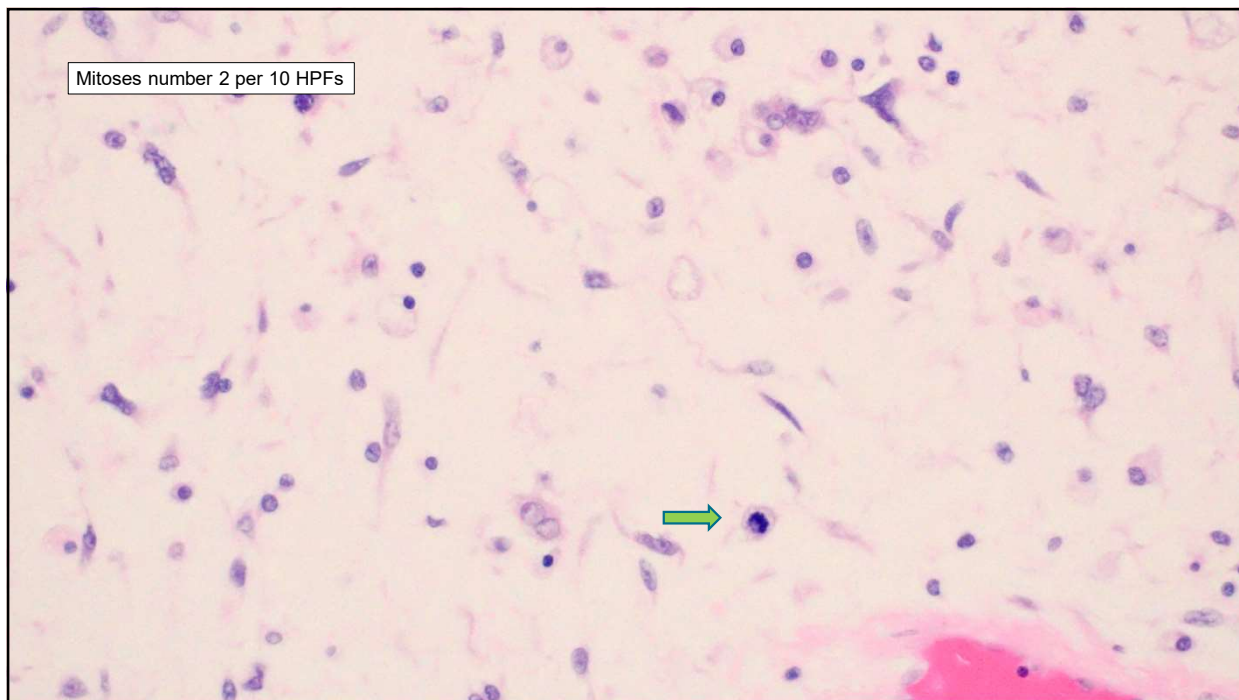
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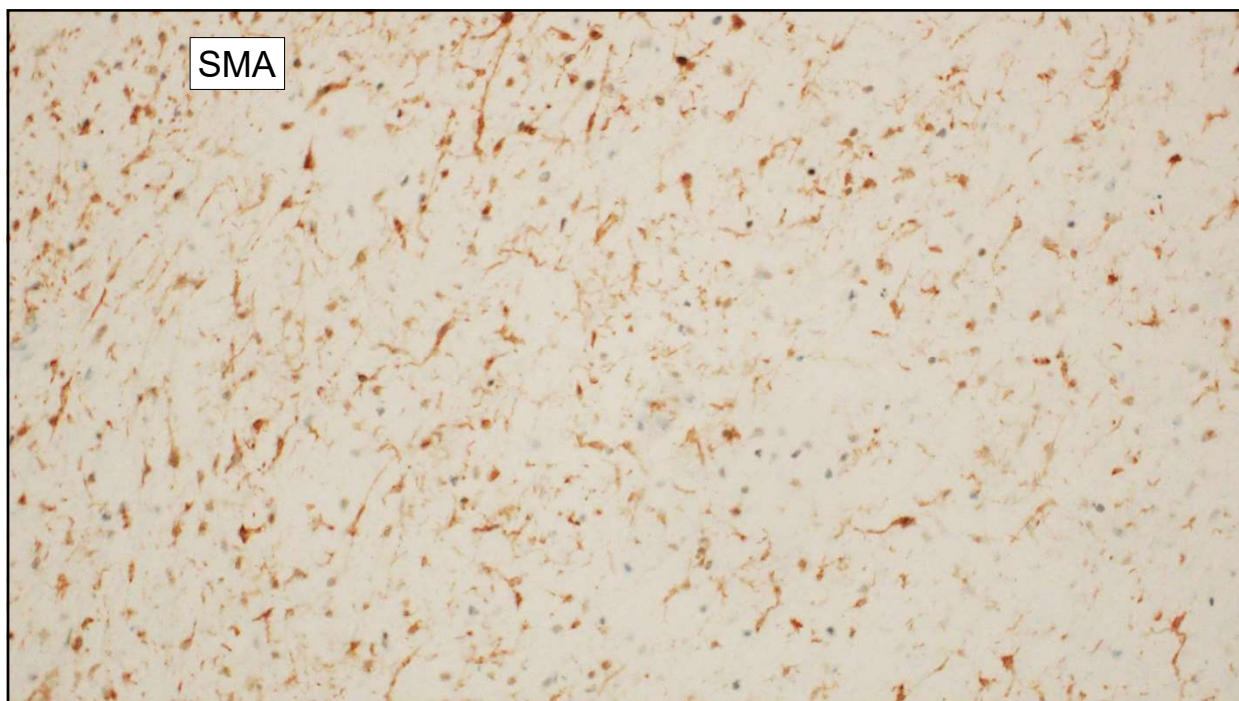
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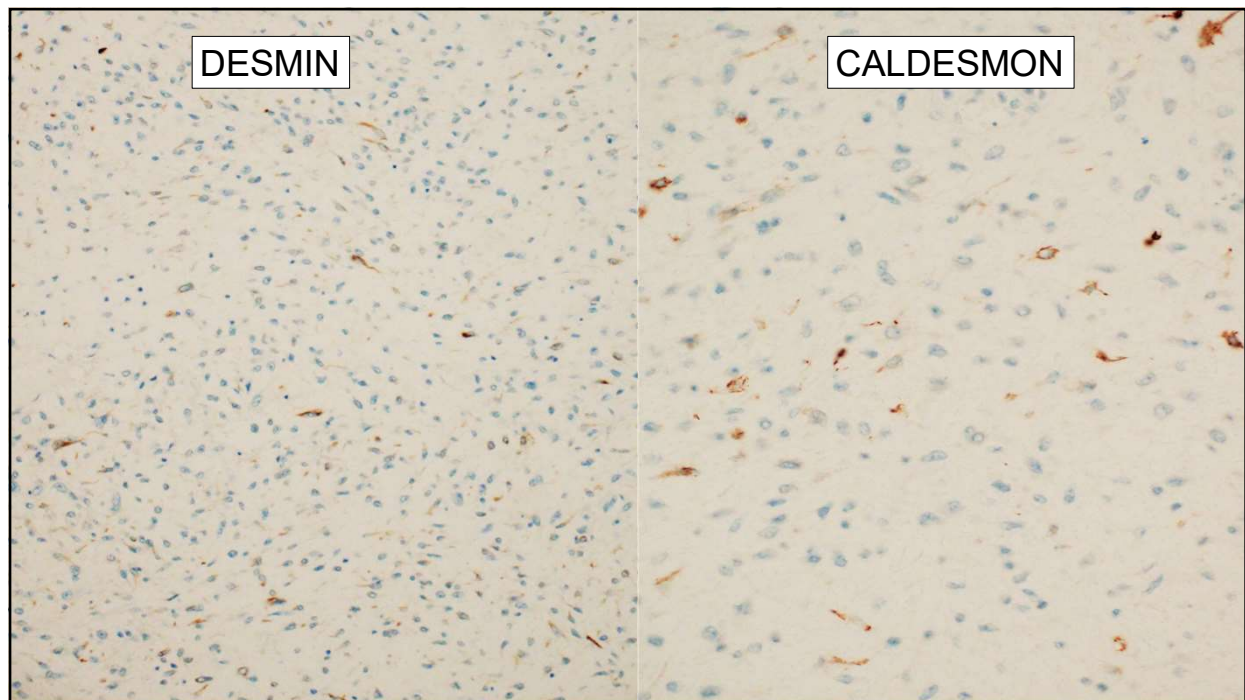
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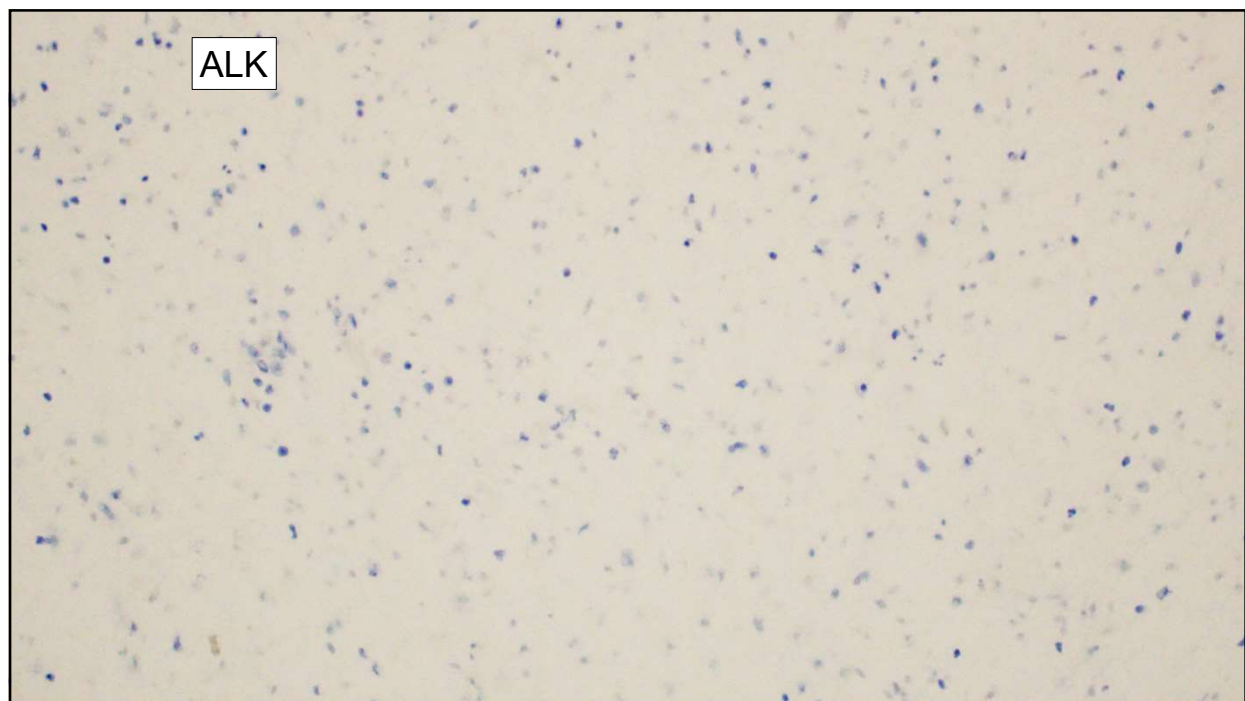
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28



29



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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)**

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2. Distinguishing smooth muscle tumors from mimics

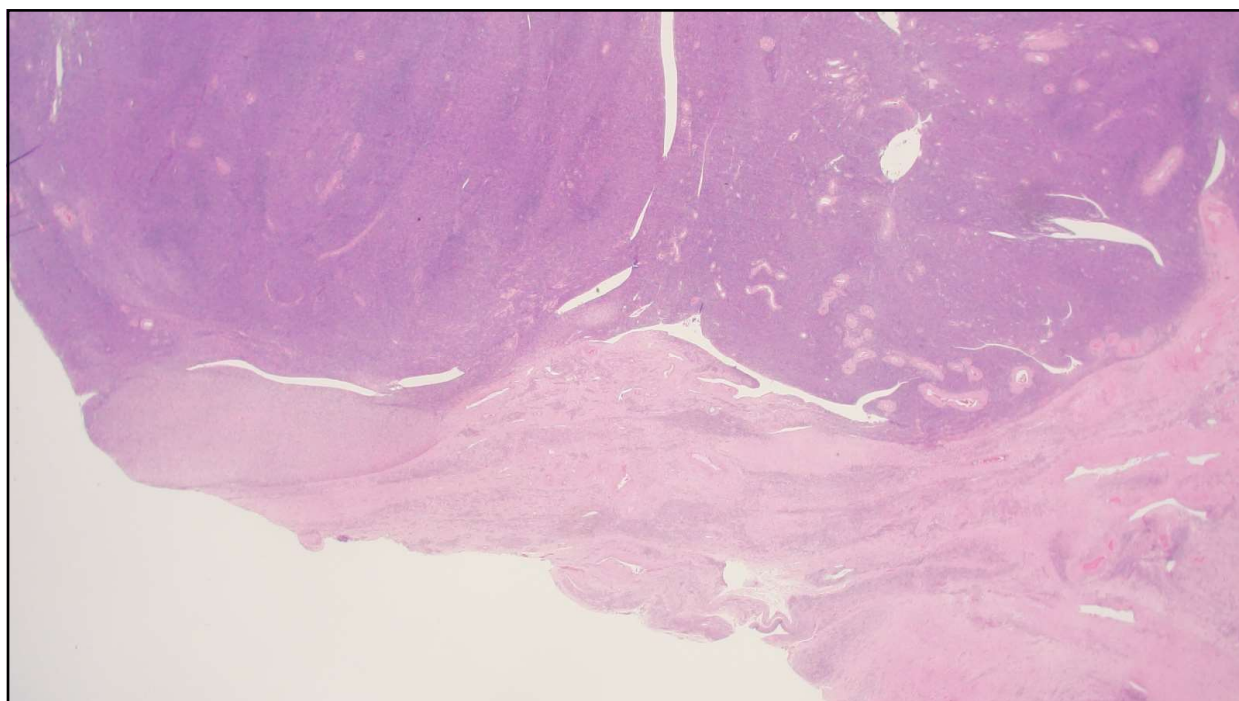
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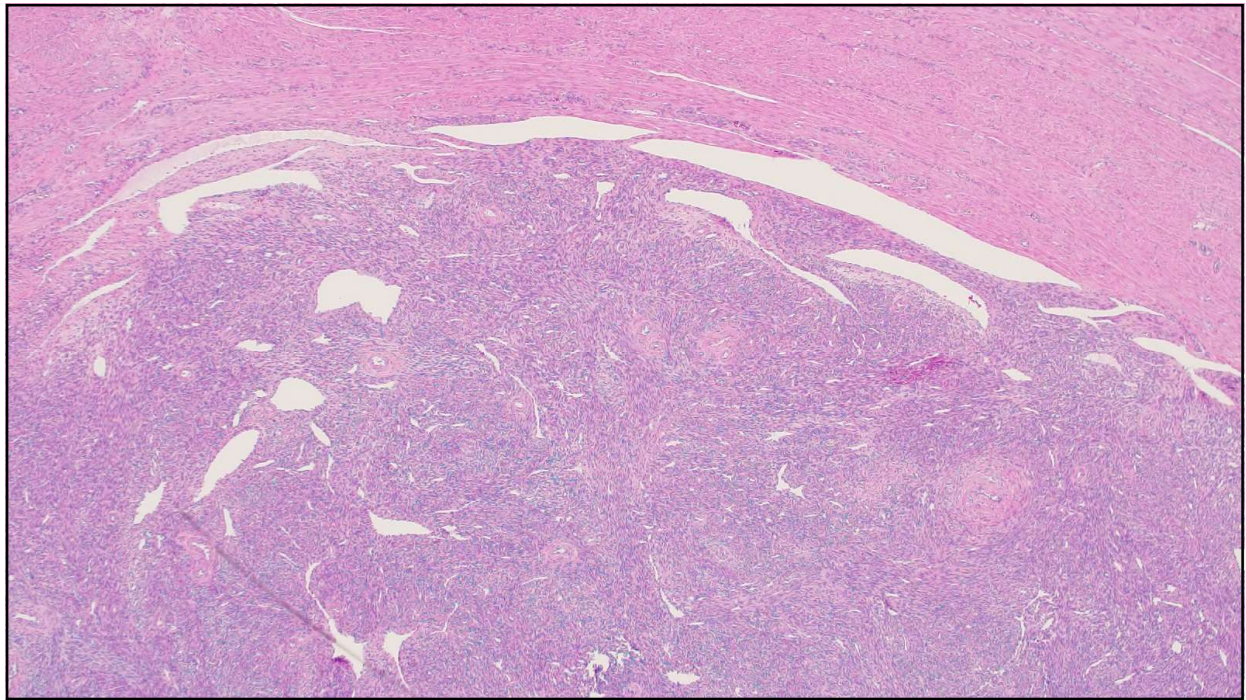
- **Cellular leiomyoma vs stromal tumors**
 - **Morphologic features (H&E)**
 - **Immunohistochemistry pitfalls**

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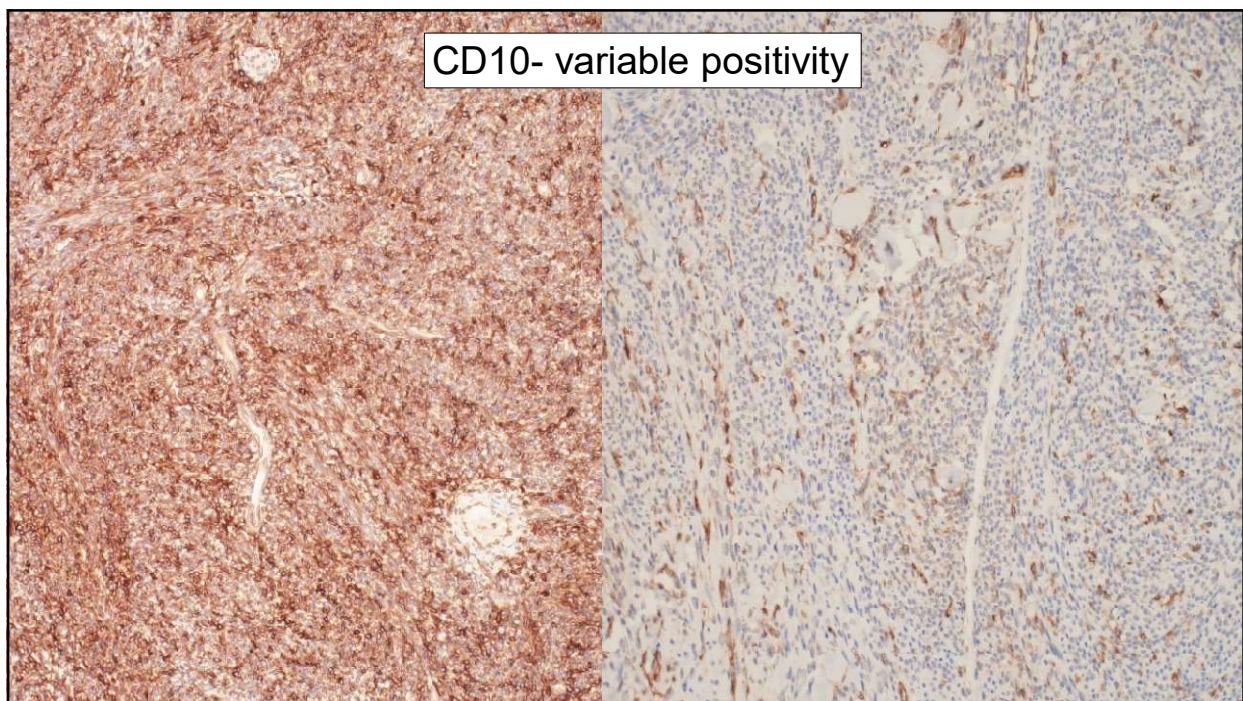
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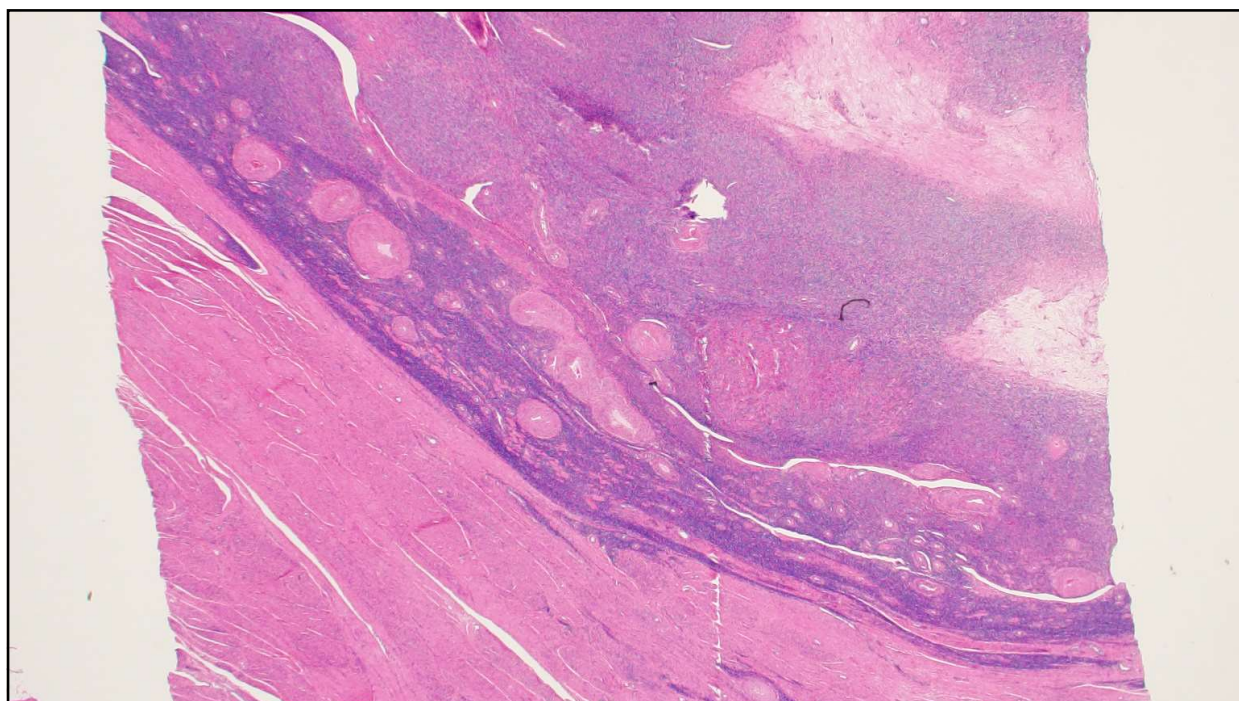
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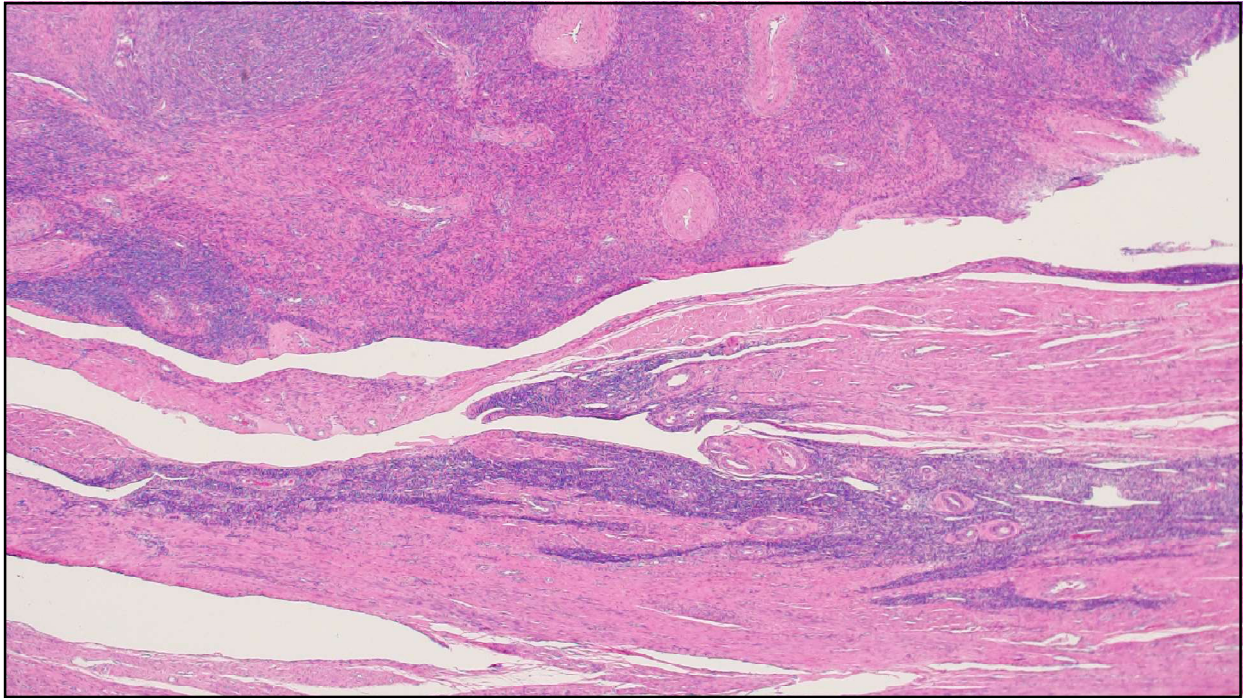
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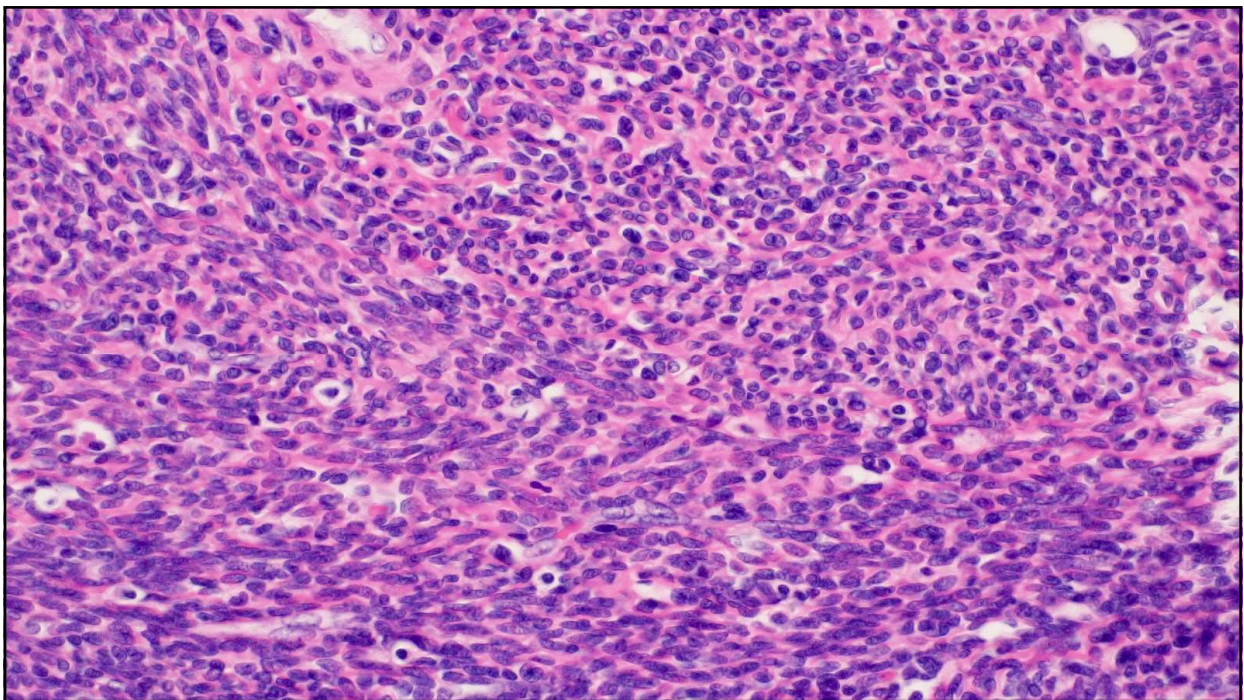
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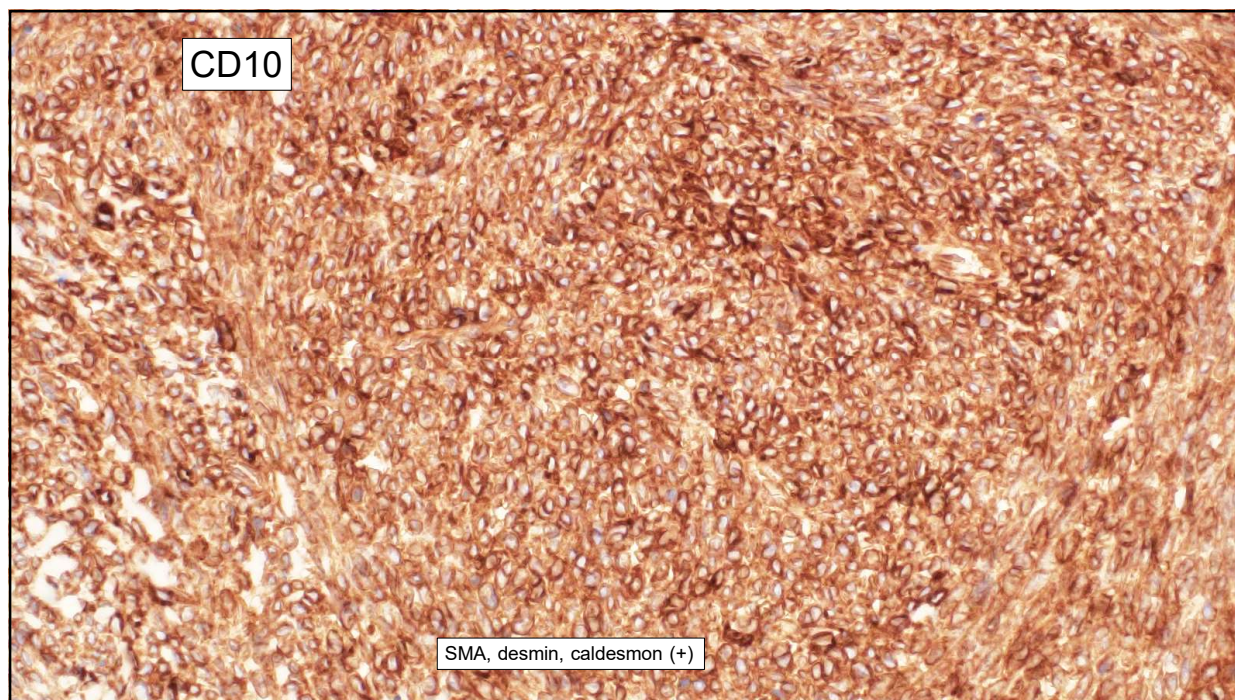
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Cellular leiomyoma

CD10 positivity \neq LGESS/ESN

Morphologic context critical

Molecular testing (FISH) in
questionable cases

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Practical pearls

- **Cellular leiomyomas and intravascular leiomyomatosis:**

- Cleaving, large caliber vessels
- May demonstrate waxy 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 cleaving and large caliber vessels

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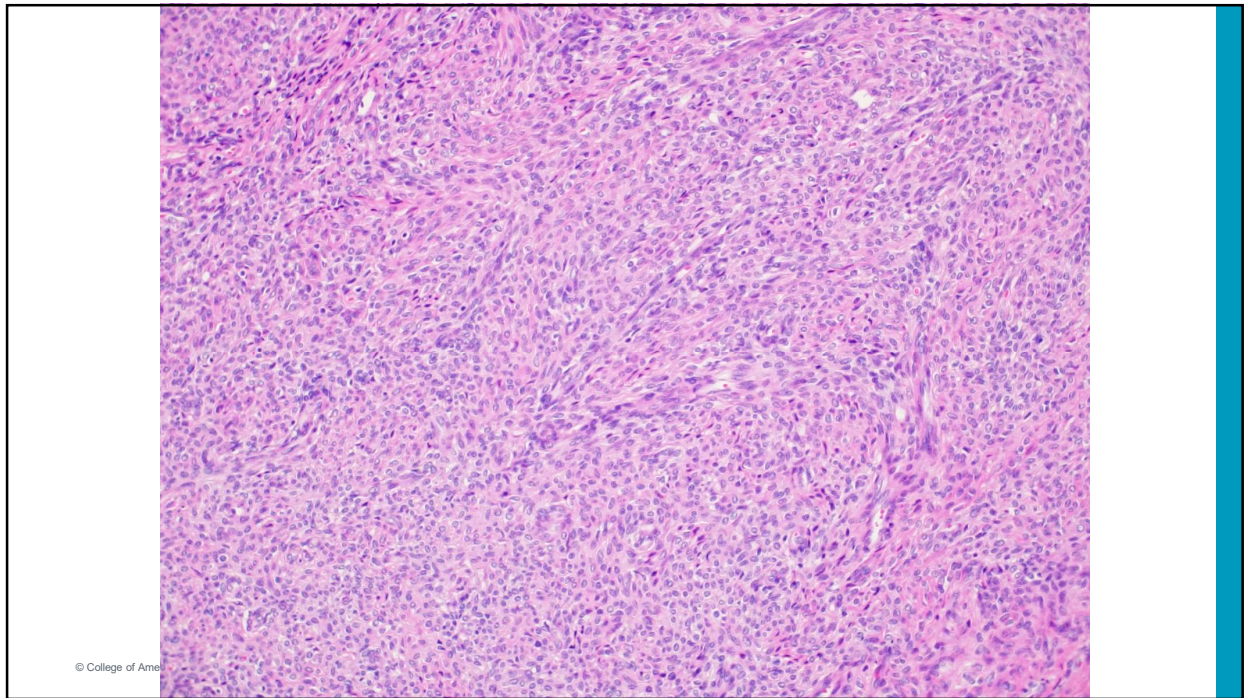
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Pitfall

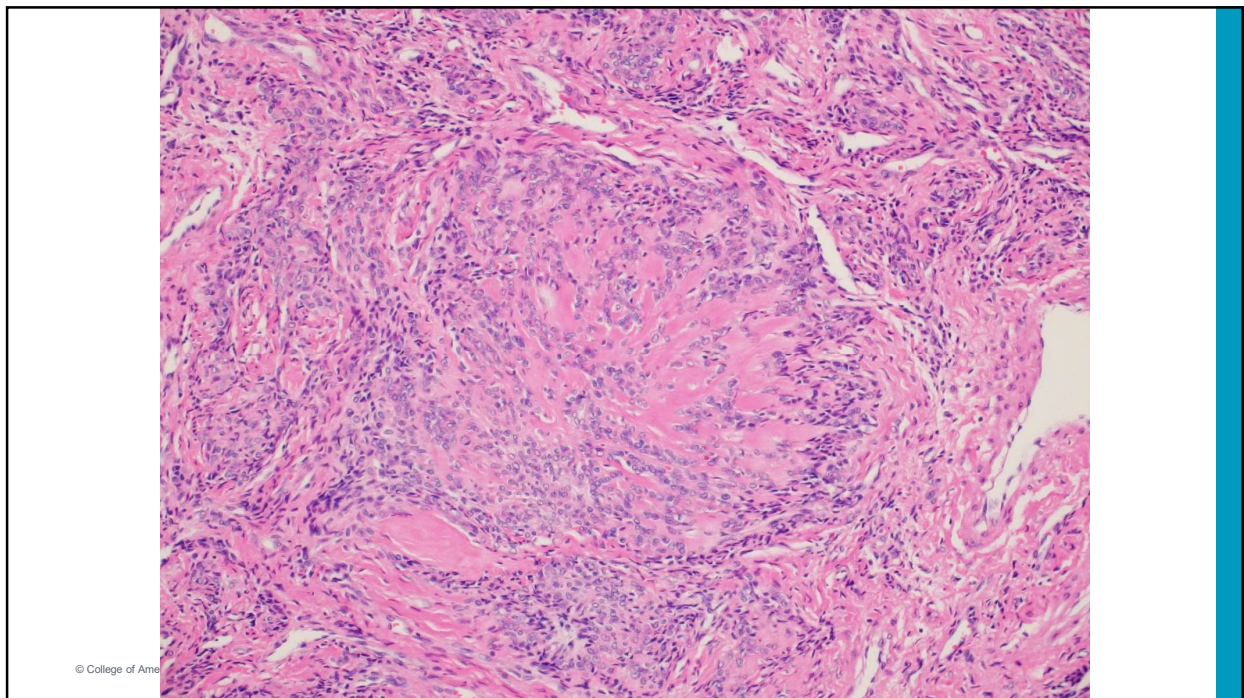
- **Some LGEES/ESN have patchy CD10 expression (non-diffuse), so this stain is rarely helpful**

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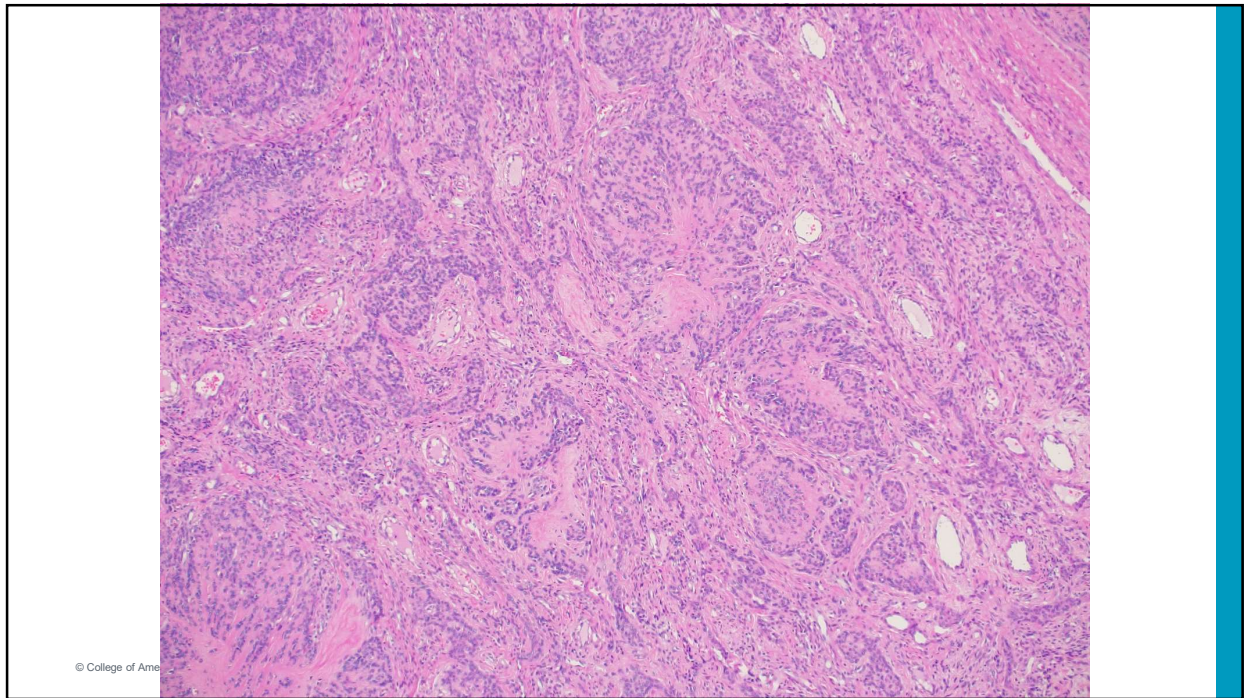
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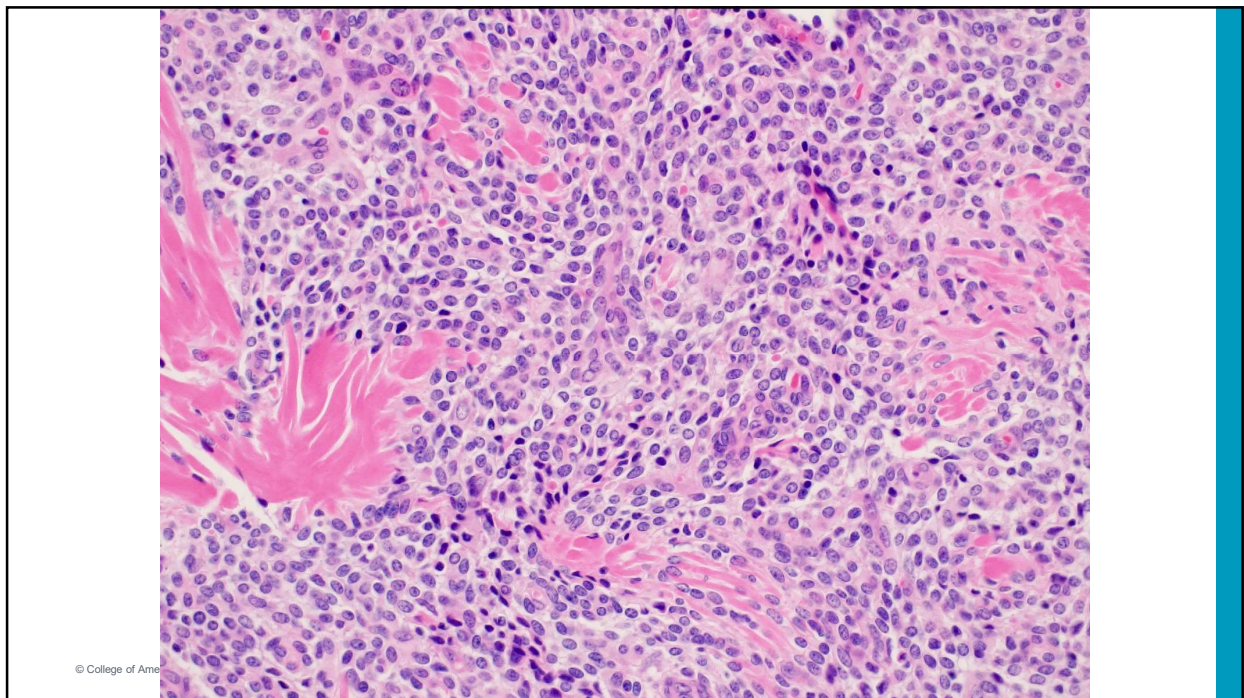
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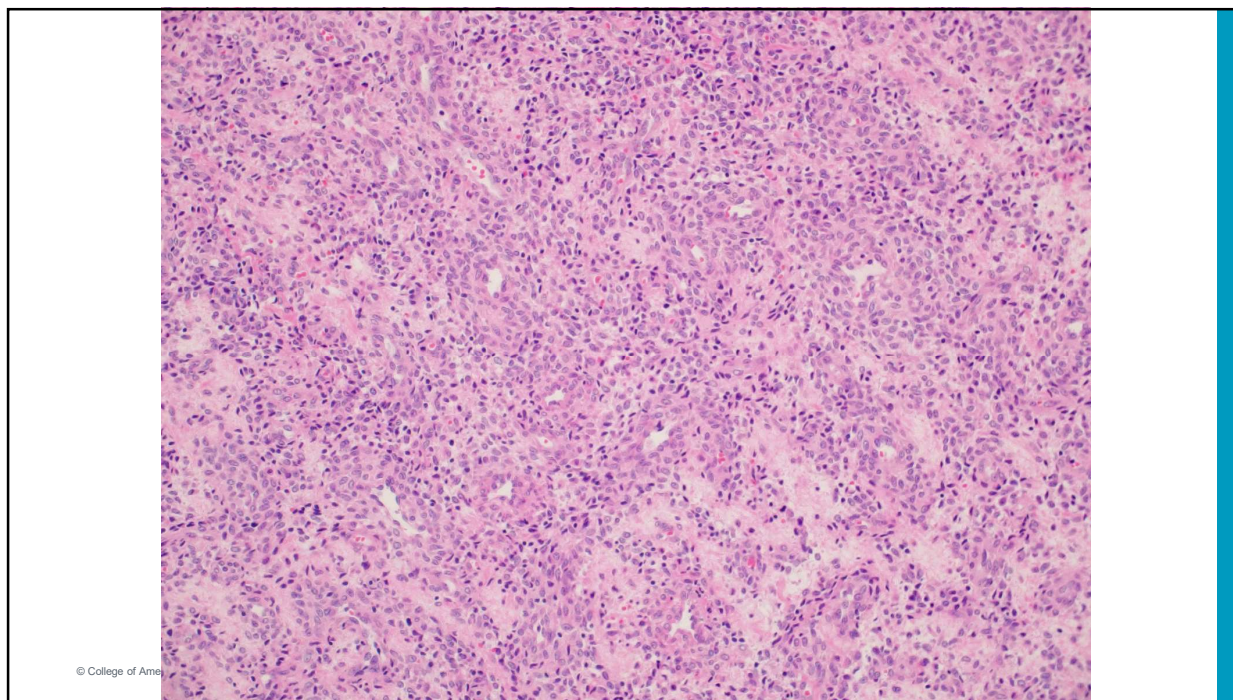
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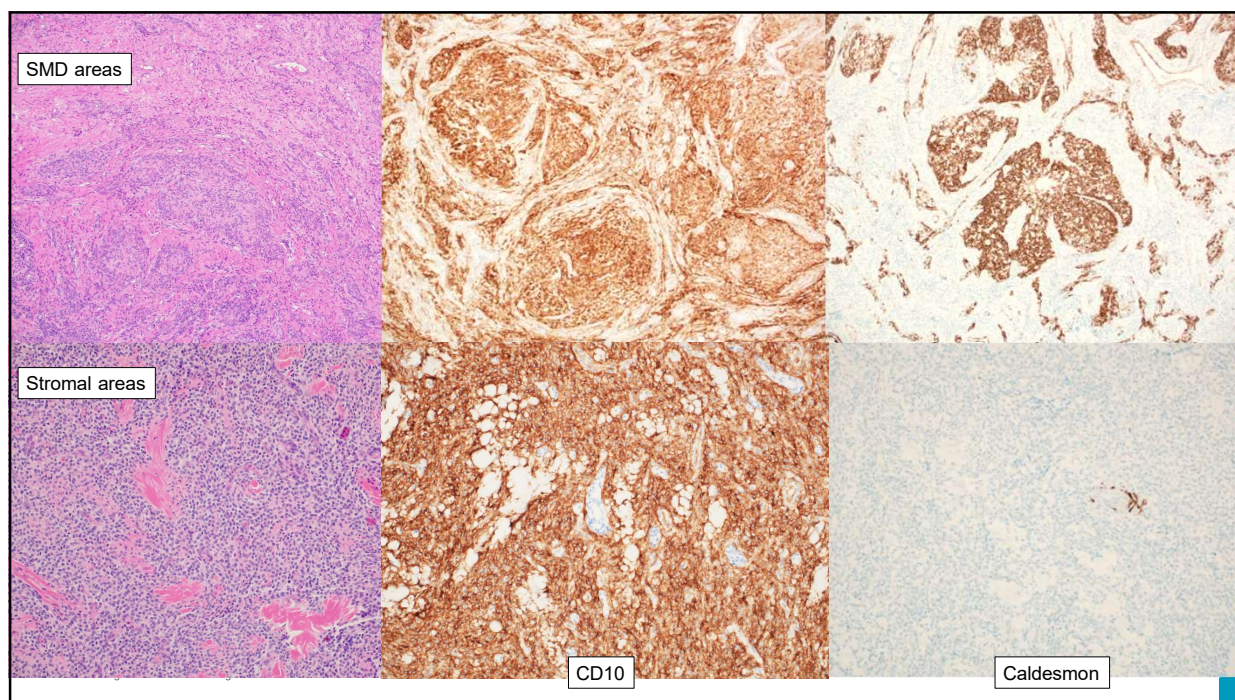
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LGESS with smooth muscle differentiation (SMD)

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

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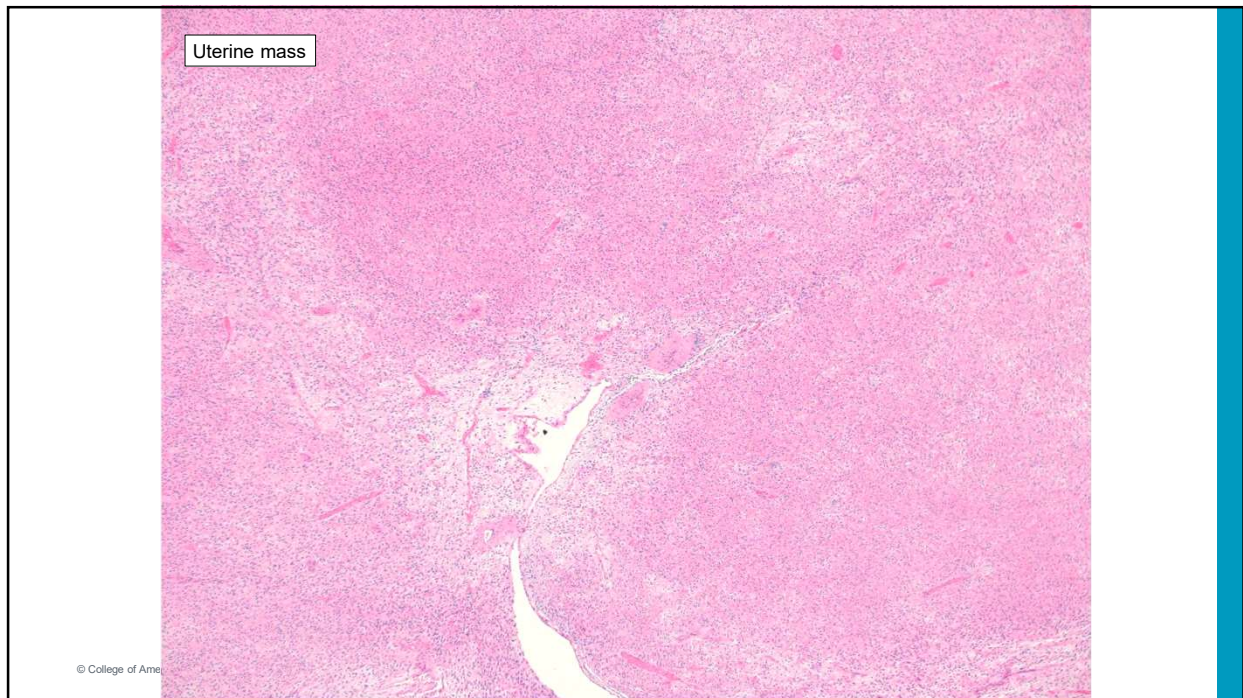
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IVL/cellular SMTs vs endometrial stromal

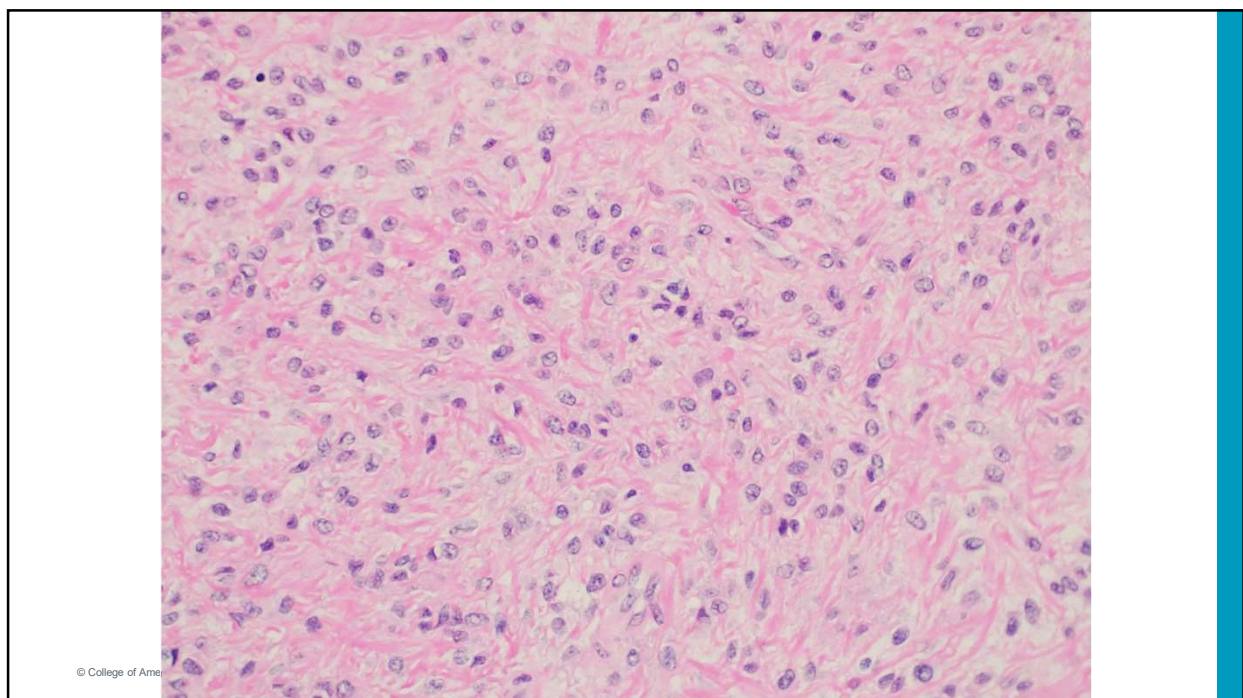
	SMTs	Endometrial stromal neoplasms (LG)
Morphology: vessels	Thick-walled, present throughout tumor	Small caliber thin walled spiral arteriole-like vasculature; may have thicker vessels at periphery
Morphology: tumor cells	Elongated, blunt nuclei, abundant eosinophilic cytoplasm	Fusiform ovoid, inconspicuous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

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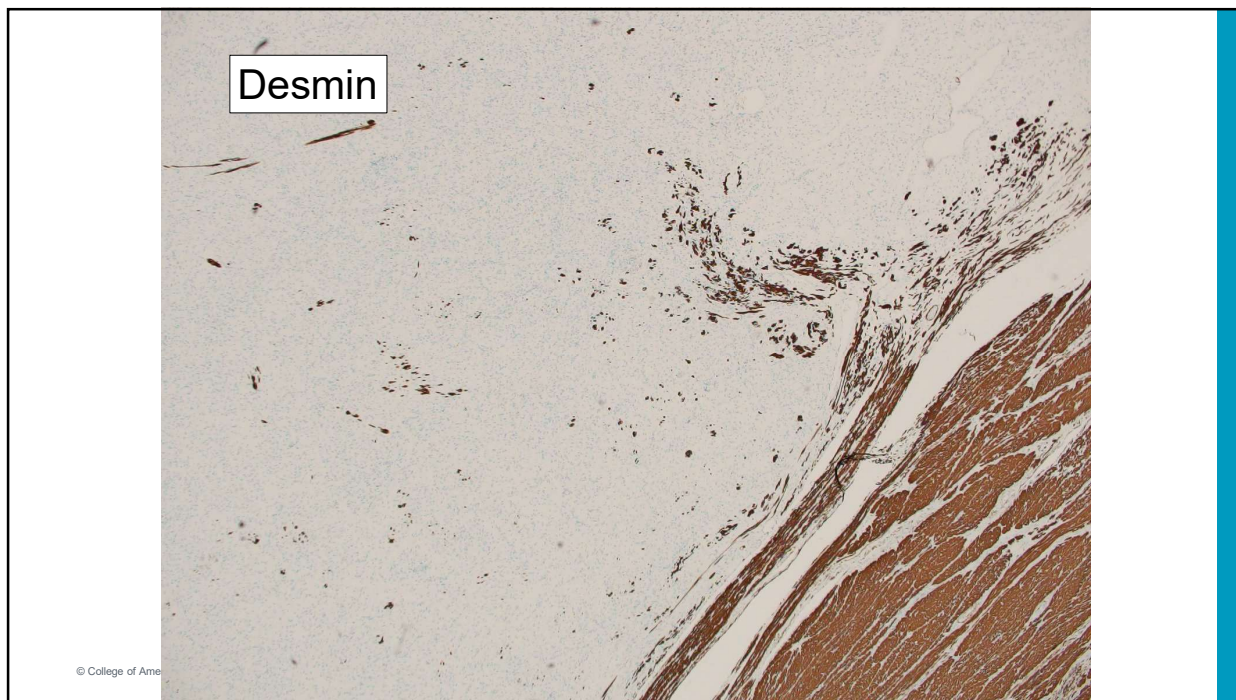
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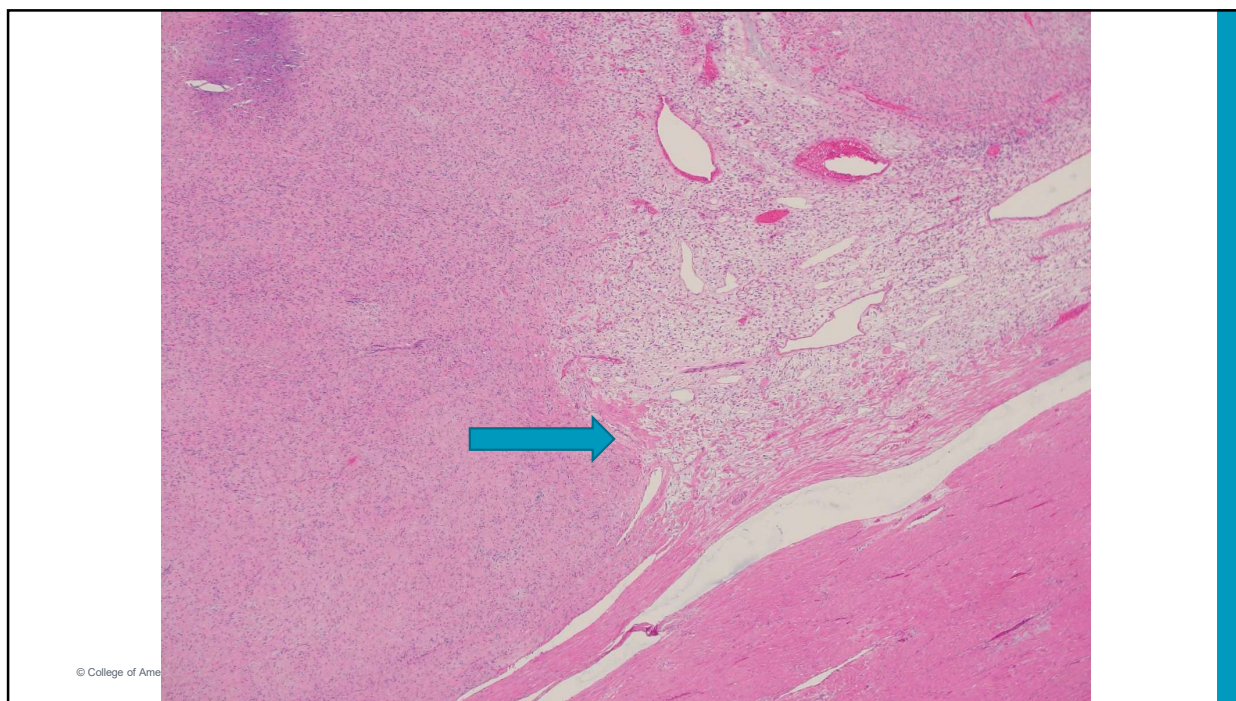
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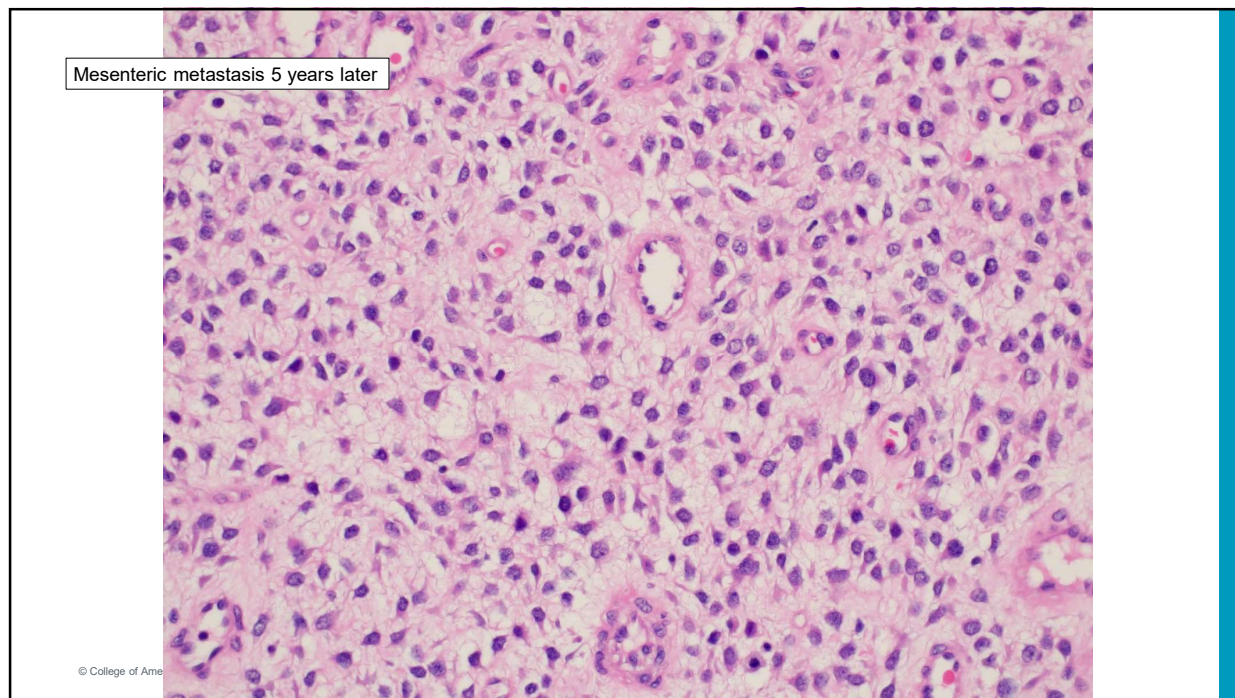
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Diagnosis: LGESS

Positive for *JAZF1* and *PHF1* breakapart FISH

Originally misdiagnosed as leiomyoma until recurrence

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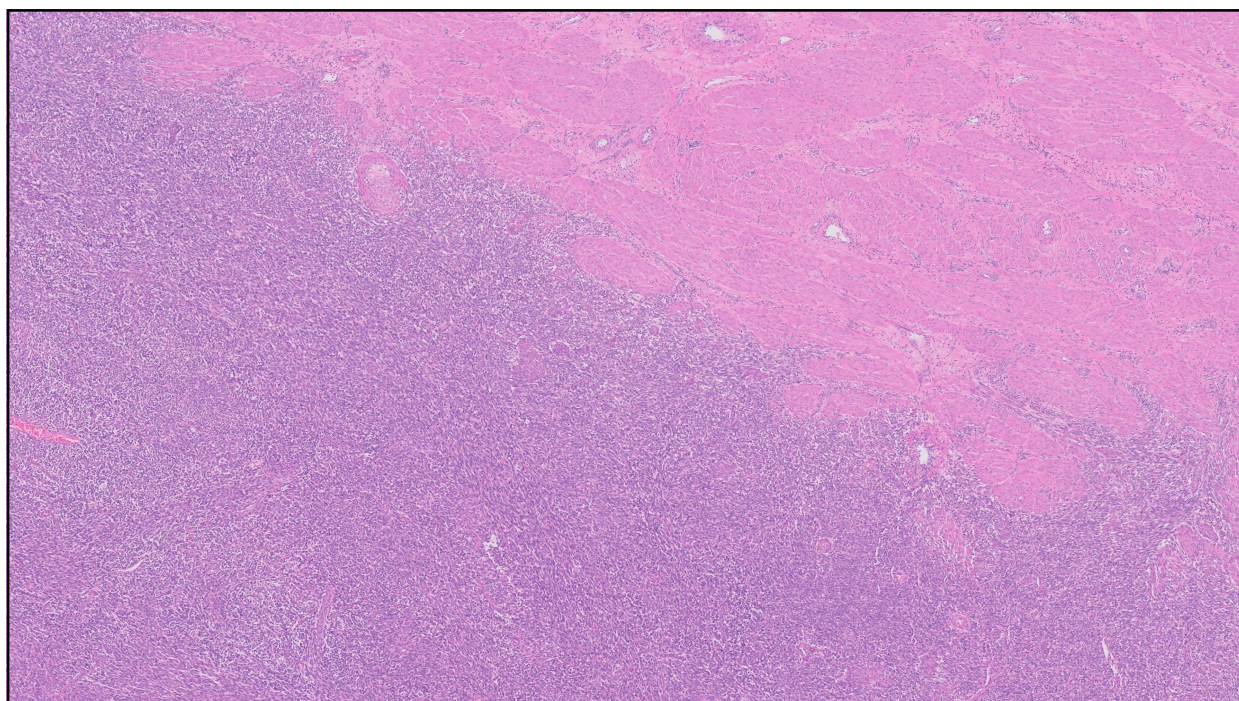
58

Practical Pearls

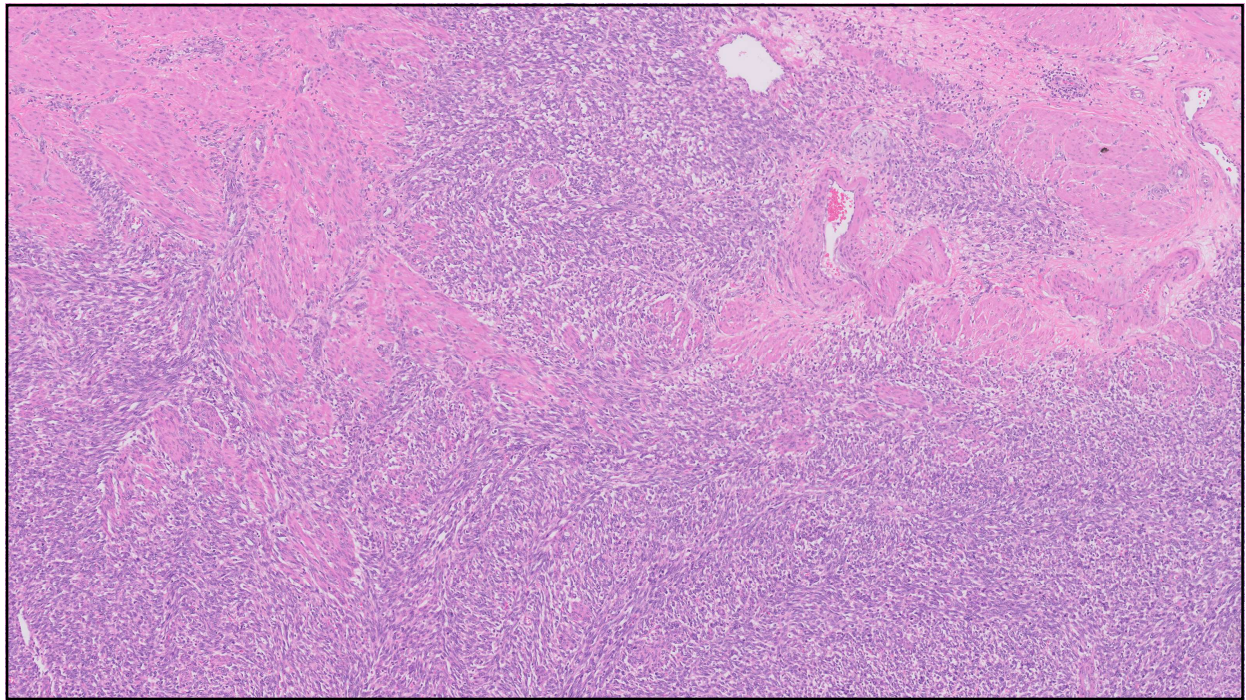
- **When interpreting smooth muscle markers in uterine tumors, consider possibility of entrapped myometrium and ensure the staining is convincingly in tumor cells**
- **Panel of IHC needed with careful morphologic guidance for block(s) to stain**

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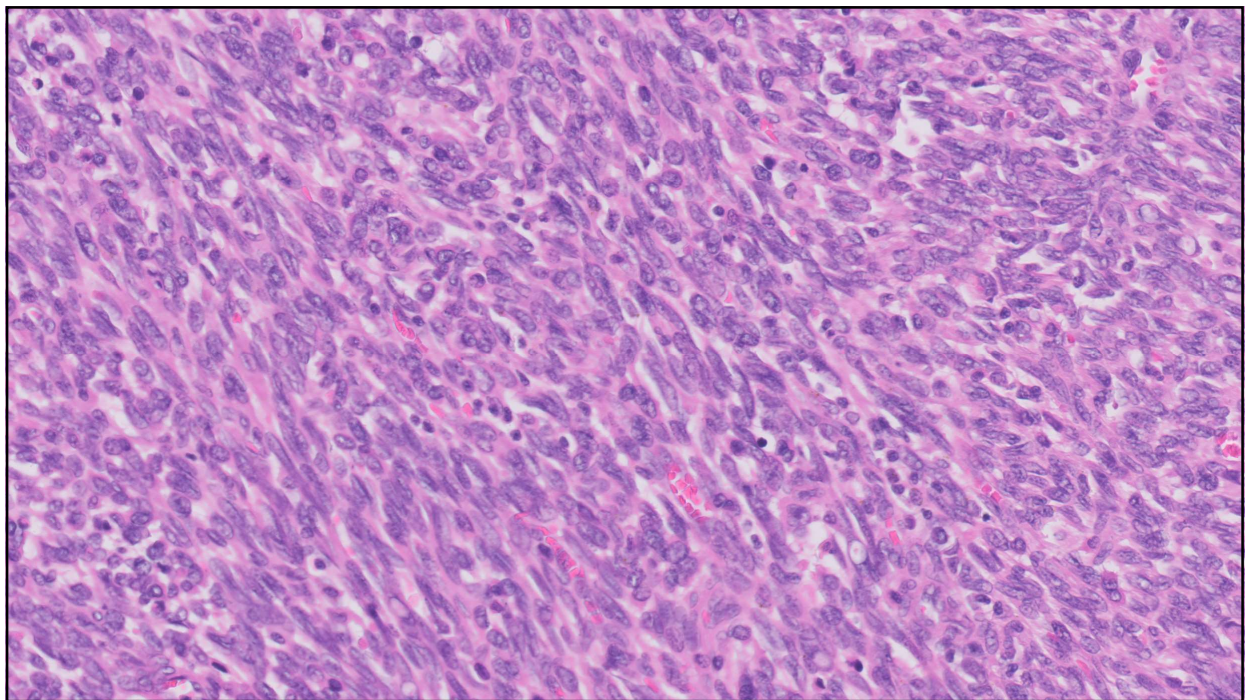
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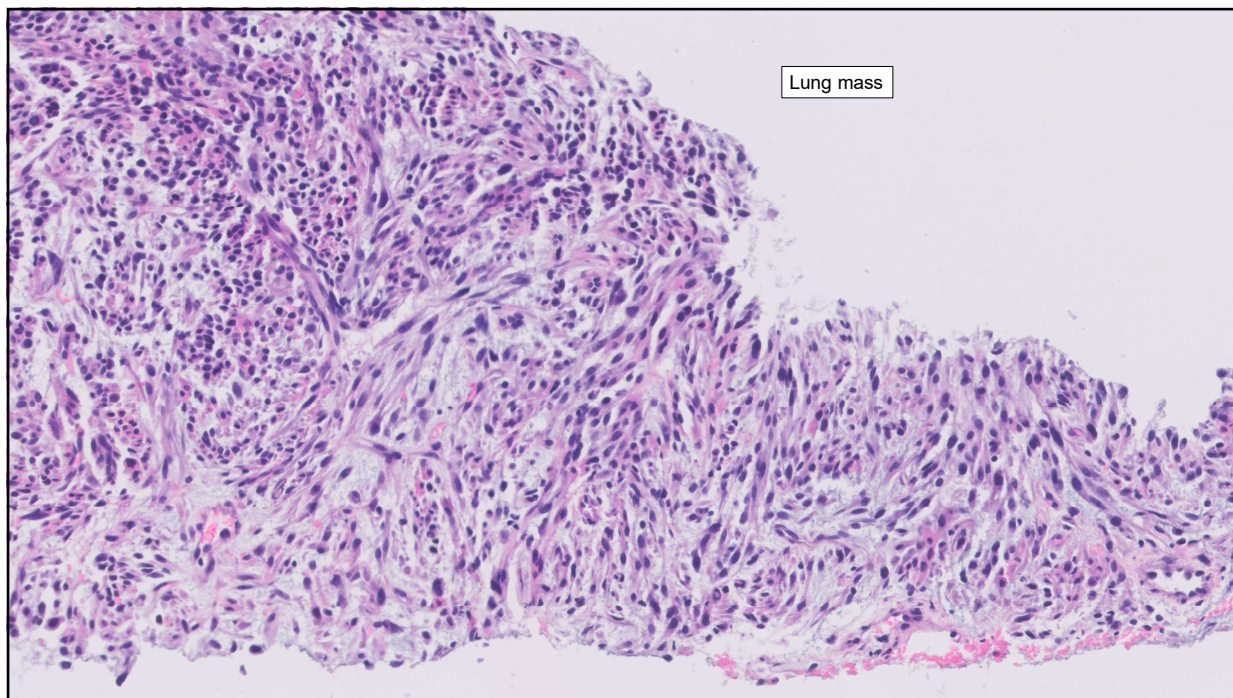
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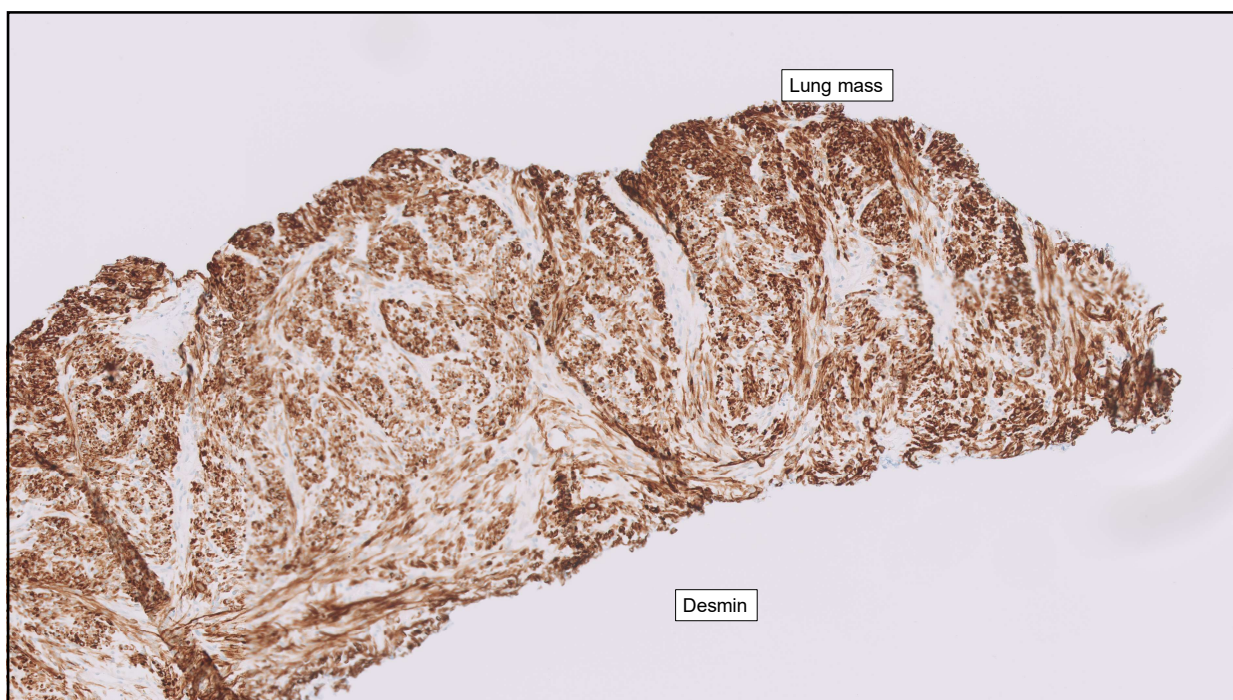
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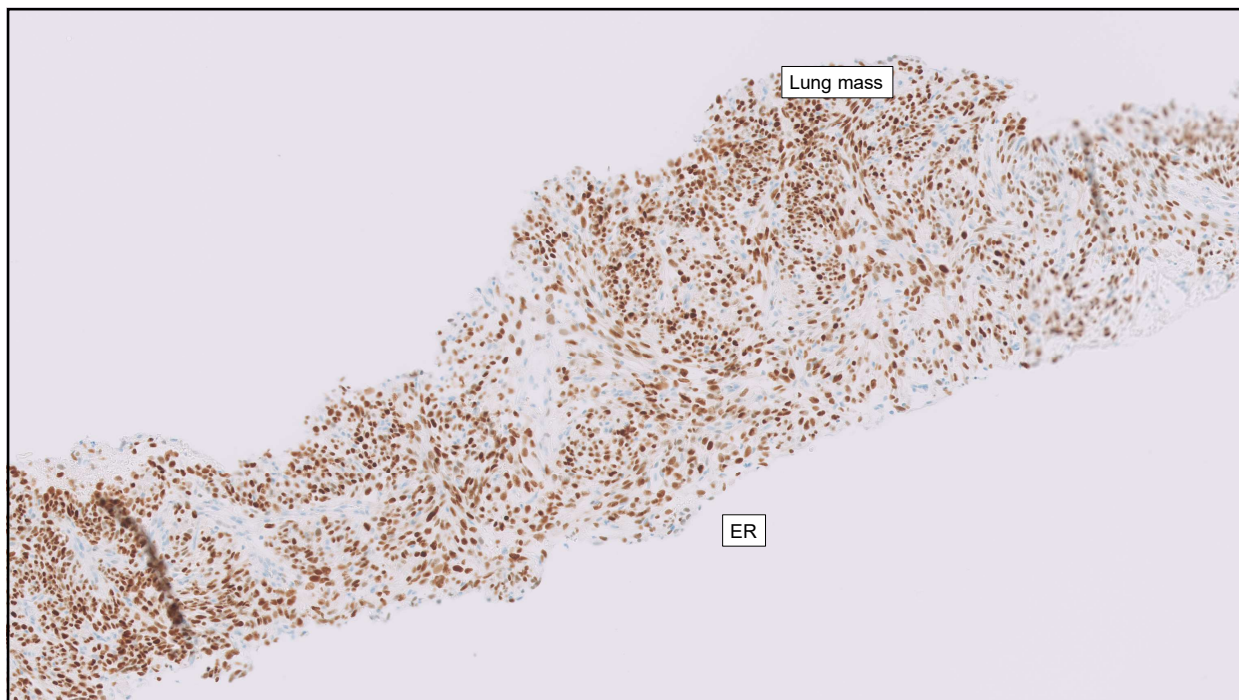
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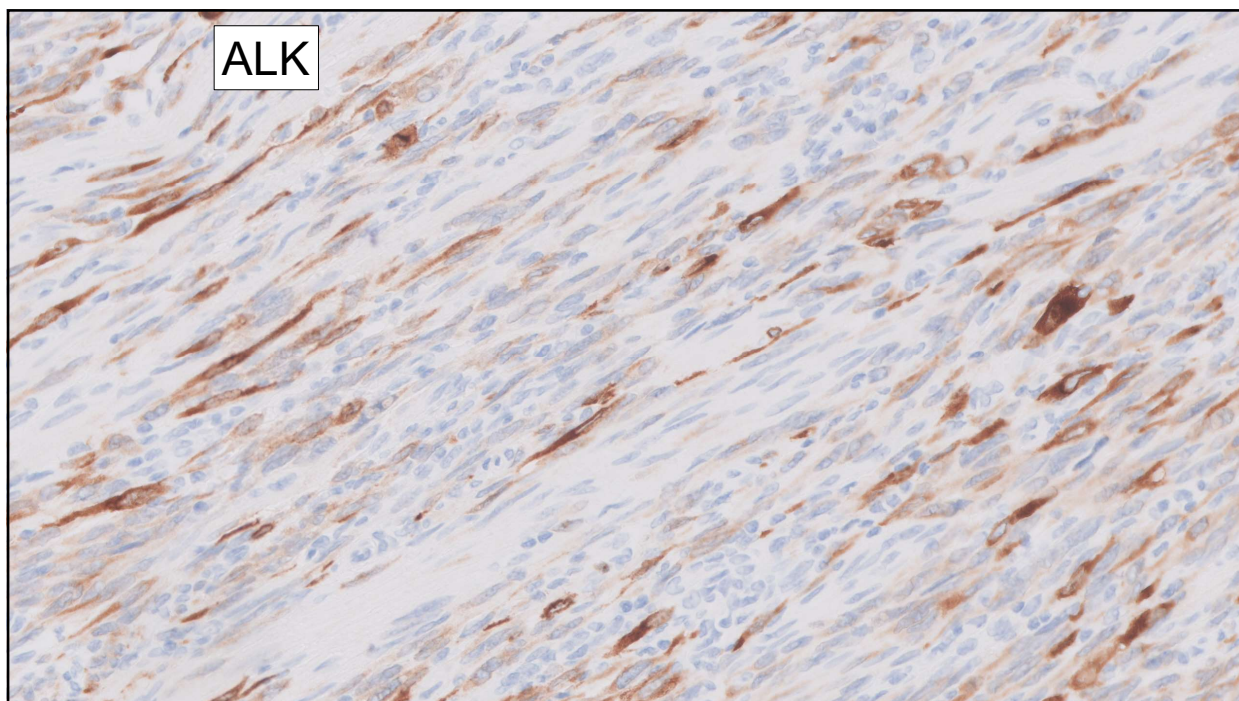
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66

Practical pearls

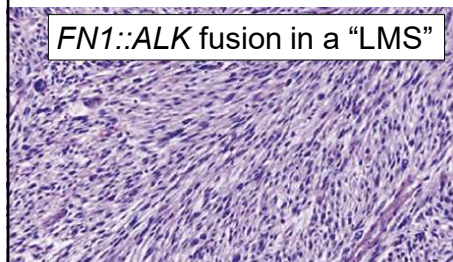
- **Low threshold for ordering ALK in smooth muscle tumors, particularly those with any amount of myxoid stroma or unusual morphology**
 - Destructive infiltration of surrounding myometrium
- **ALK IHC may correlate with degree of myxoid stroma so care should be taken in selecting block to test**
 - 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**

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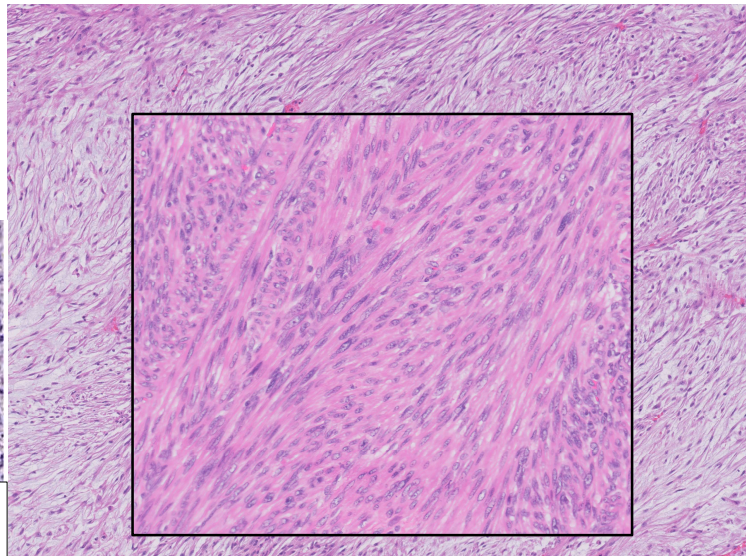
67

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**

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LMS vs STUMP

- **Morphologic distinction**
 - **Atypia**
 - **Mitoses**
 - **Necrosis**
- **Highly subjective → poor reproducibility**
- **Poor reproducibility leads to less clinical relevance**

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IHC as molecular surrogates in uterine smooth muscle tumors

p53 OE

PTEN loss

Rb loss

ATRX loss

Immunohistochemical markers that can be used as molecular surrogates:

p53/MDM2/MTAP

PTEN

ATRX/DAXX

Rb

71

IHC as molecular surrogates in uterine smooth muscle tumors

Immunohistochemistry

Somatic Alterations

Molecular/IHC Concordance

Legend:

- Overexpression (Red)
- Loss (Orange)
- Null (Black)
- Wild Type Expression (Green)
- Disagreement (Yellow)
- Retained (Blue)
- Retained (Light Blue)
- Retained (Dark Blue)
- Retained (Light Green)
- Retained (Dark Green)
- N/A (Grey)
- Amplified (Red)
- Negative (Green)
- Missense Mutation (Dark Green)
- Nonsense Mutation (Black)
- Frameshift Mutation (Purple)
- Splice-Site Alteration (Orange)
- Fusion (Light Blue)
- Deletion (Dark Blue)
- Amplification (Red)
- Loss of Heterozygosity (Light Green)
- Concordant (Green)
- Minor Discordance (1 marker) (Yellow)

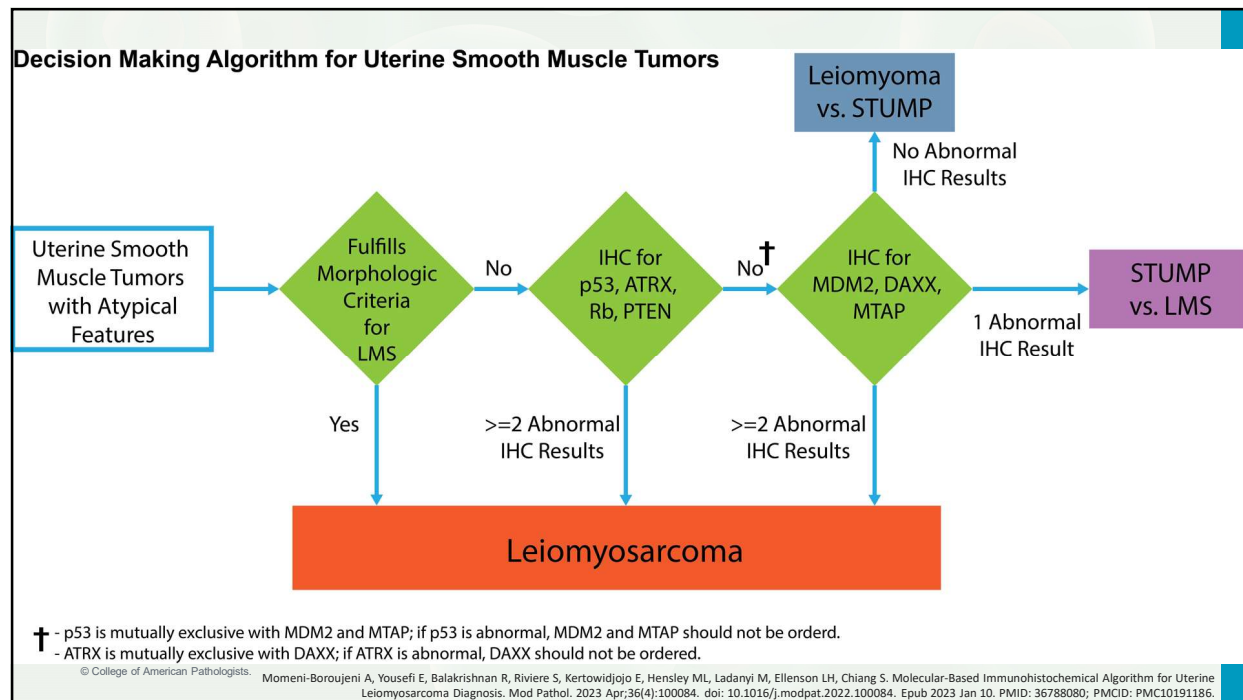
Tumor Type

Case

LMS **STUMP** **Benign**

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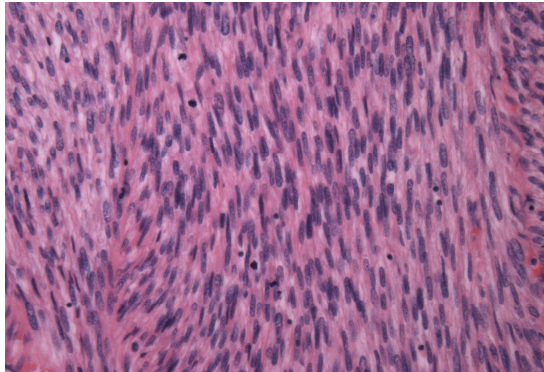
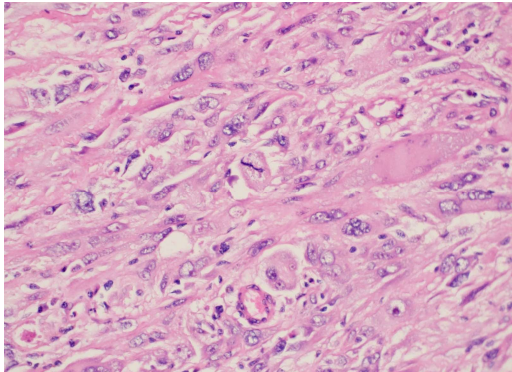


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Leiomyosarcoma vs PEComa: Morphology

- Spindled cells
- Fascicular growth
- Elongated nuclei

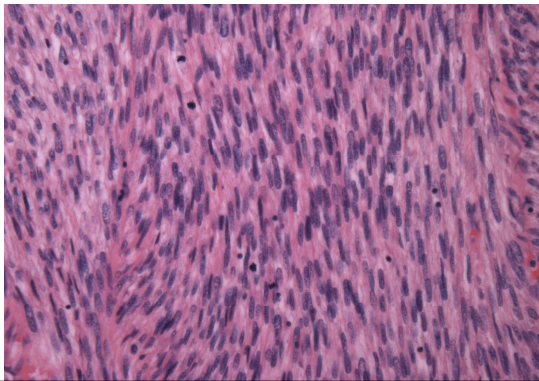
- Epithelioid cells, abundant eosinophilic cytoplasm
- Spider cells
- Sclerosis may be present

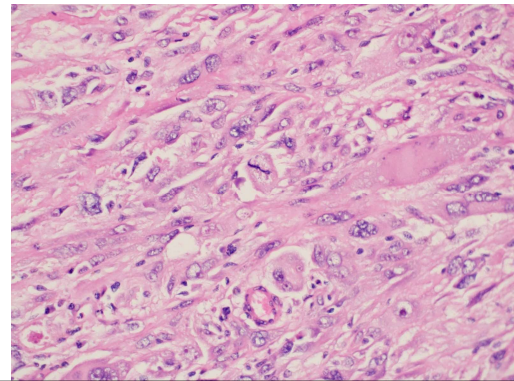
74

Leiomyosarcoma vs PEComa: IHC

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



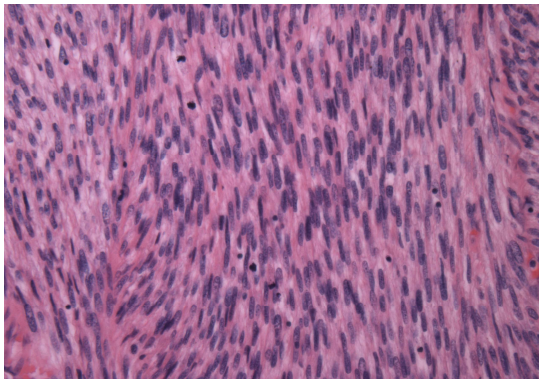
- SMA/desmin/caldesmon variably (+)
- HMB45, CathepsinK (+)
- MelanA ideally (+) but often (-)



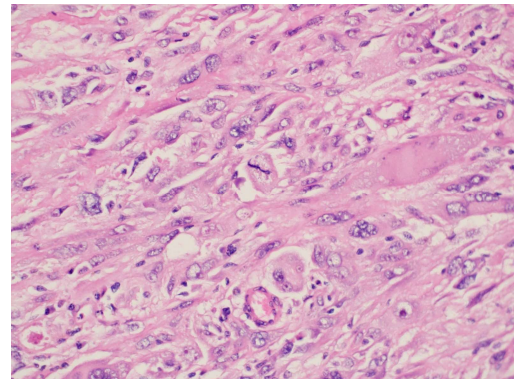
75

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)



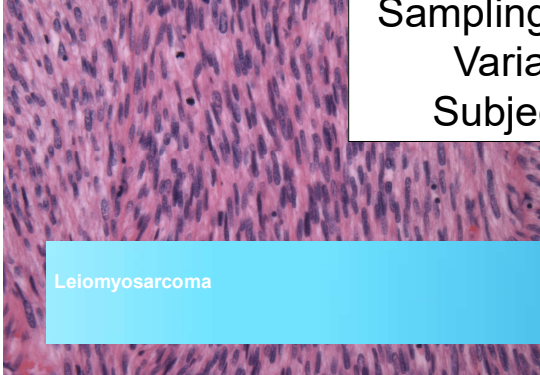
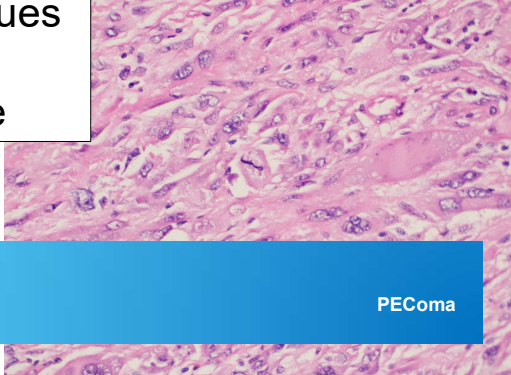
76

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

Leiomyosarcoma

PEComa


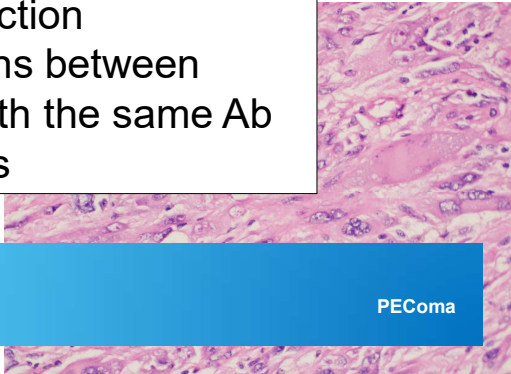
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Where do we draw the line?

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

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

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

Leiomyosarcoma

PEComa

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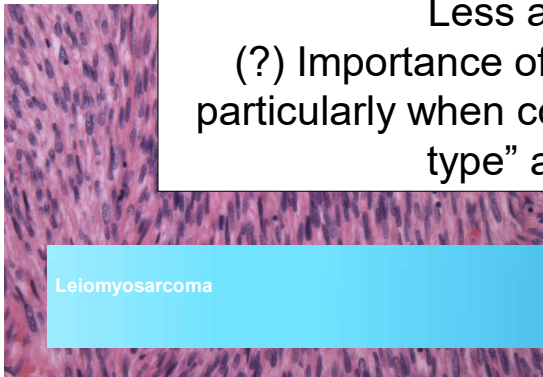
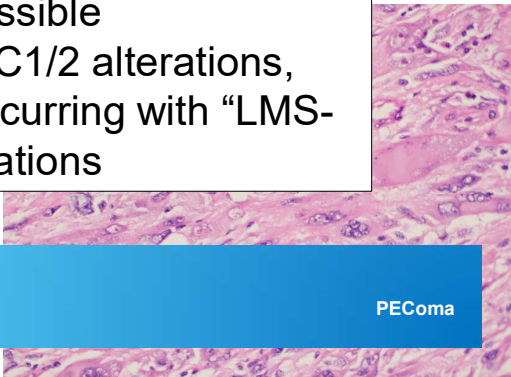
Where do we draw the line?

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

Molecular Profiling

Expensive, time
Less accessible

(?) Importance of *TSC1/2* alterations, particularly when co-occurring with “LMS-type” alterations

Leiomyosarcoma

PEComa

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Summary

- **CD10 positivity ≠ LGESS!**
 - Other uterine mesenchymal tumors that can be positive for CD10:
 - Smooth muscle tumors (Cellular leiomyoma, IVL)
 - HGESS (BCOR>YWHAЕ)
 - 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**

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Questions?

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