

Uterine Mesenchymal Tumors in the Laparoscopic Era: When Does Molecular Analysis Help?

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Notice of Faculty Disclosure

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Historical Perspective

- Smooth muscle
 - Leiomyoma
 - Leiomyosarcoma
- Endometrial stromal
 - Benign stromal nodule
 - Low-grade endometrial stromal sarcoma
 - High-grade endometrial stromal sarcoma
- Other
 - Undifferentiated sarcoma
 - Differentiated sarcoma (e.g., angiosarcoma)

Historical Perspective

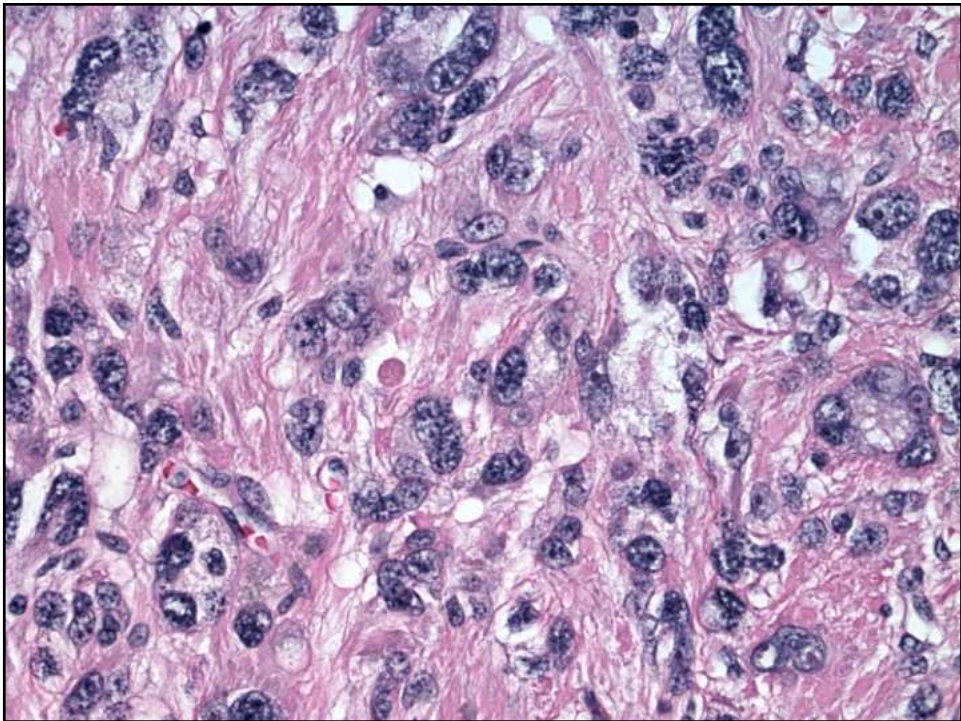
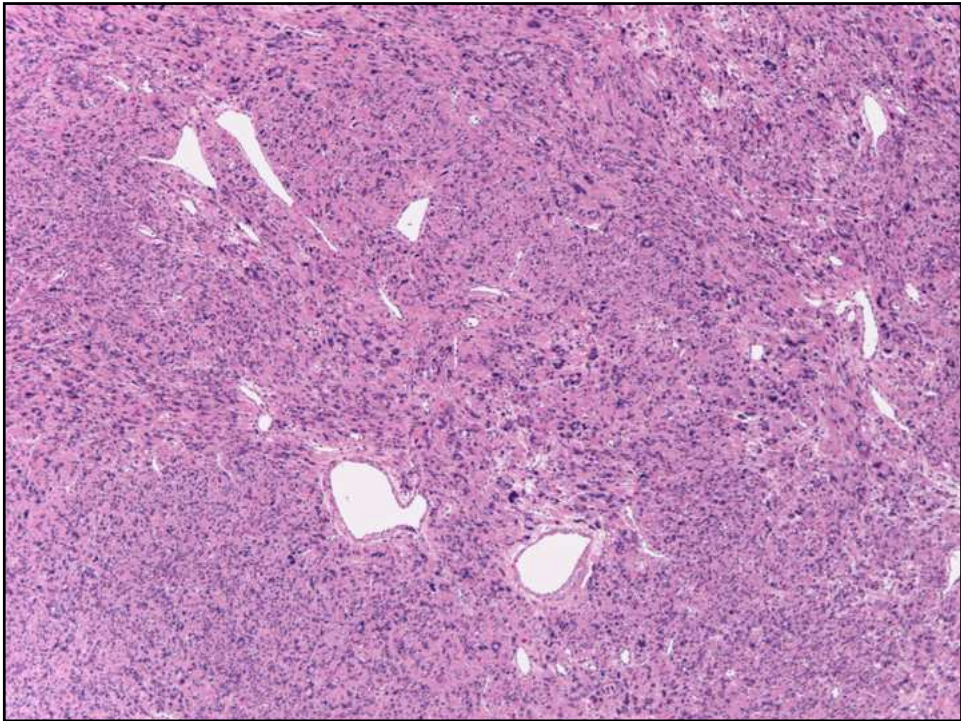
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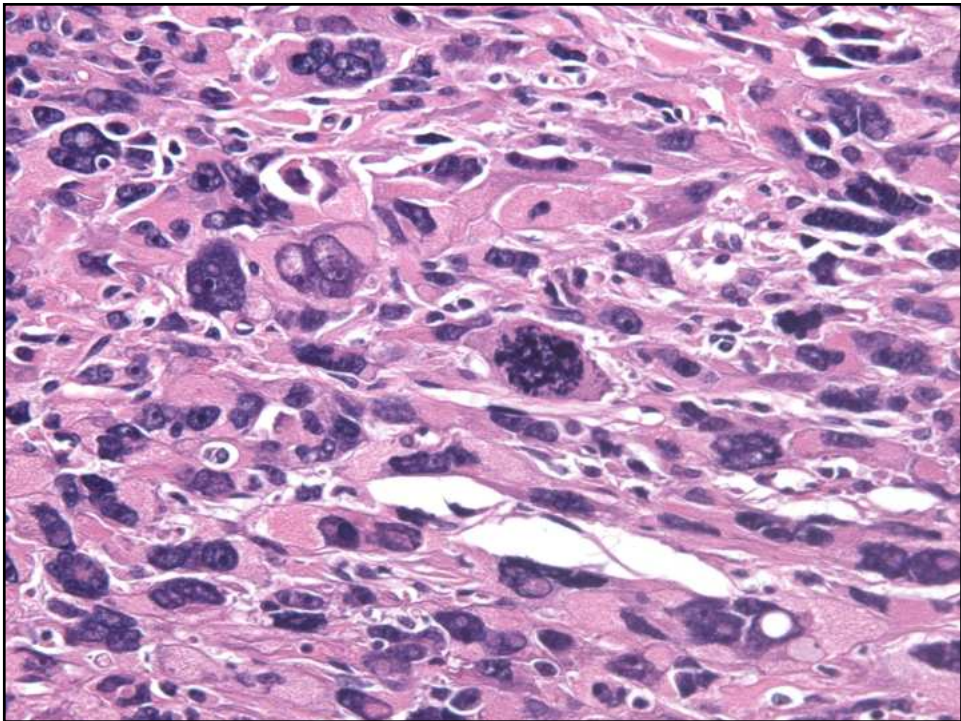
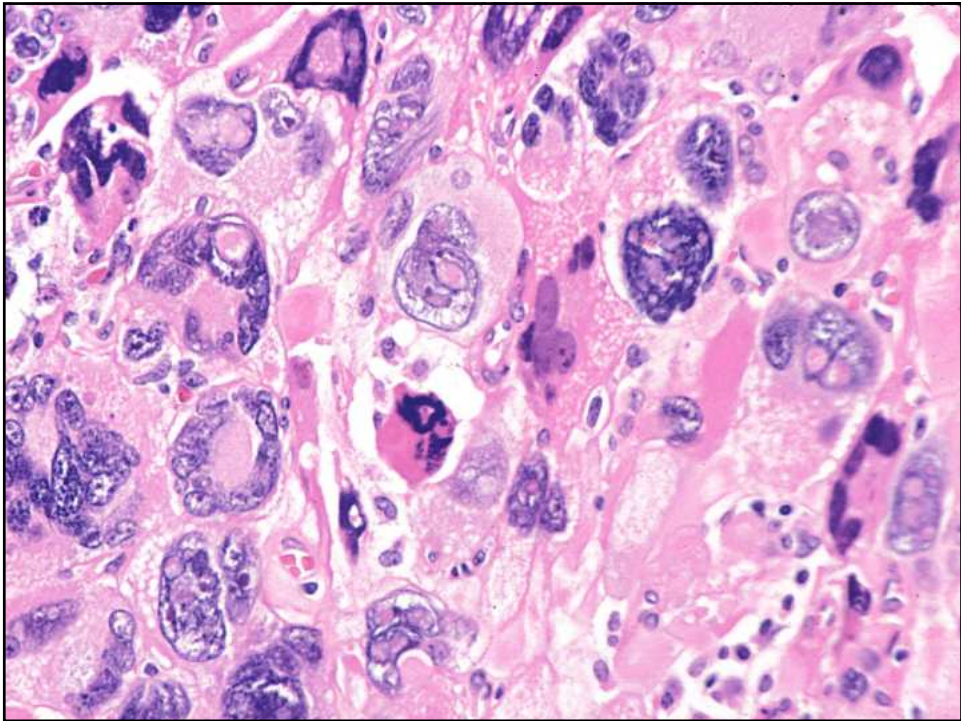
Approach To Diagnosis of Uterine Mesenchymal Tumors

- Determine smooth muscle vs stromal vs other
 - Histologic cues
 - Immunohistochemical cues
 - Molecular cues
- Determine type: standard, epithelioid, myxoid
- Determine distribution of disease
- Determine benign vs malignant

Case Presentation

35-year-old with uterine mass and vaginal bleeding





Diagnosis?

- Leiomyosarcoma
- Leiomyoma with bizarre nuclei
- Hereditary leiomyomatosis
- STUMP
- Sarcomatous component of carcinosarcoma

Approach To Diagnosis of Uterine Smooth Muscle Tumors

- Confirm smooth muscle – exclude stromal
- Determine type: standard, epithelioid, myxoid
- Determine distribution of disease
- Determine benign vs malignant

Immunohistochemistry

- Desmin – may be lost in myxoid & epithelioid
- H-caldesmon
- SMA
- CD10 – typically less than muscle markers, but can be quite strong
- ER/PR
- HMB-45 - PEComa
- Cytokeratin – may be extensive

Atypical Leiomyoma With Low Recurring Potential

(“Leiomyoma with bizarre nuclei”)

- Diffuse *or focal* moderate to severe atypia
- No tumor cell necrosis
- Mitotic index ≤ 10 MF/10 HPF
- Very low risk of recurrence

Atypical Leiomyoma (Leiomyoma with Bizarre Nuclei): Stanford Update (n=76)

- Mean follow up: 37 mos.
- Very low risk of local recurrent disease (2.6%)
- Compatible with successful pregnancy
- Can be managed with myomectomy

Am J Surg Pathol 1994;18:535-558
Am J Surg Pathol 2013;37:643-691

Atypical Leiomyoma (Leiomyoma with Bizarre Nuclei) (n=59)

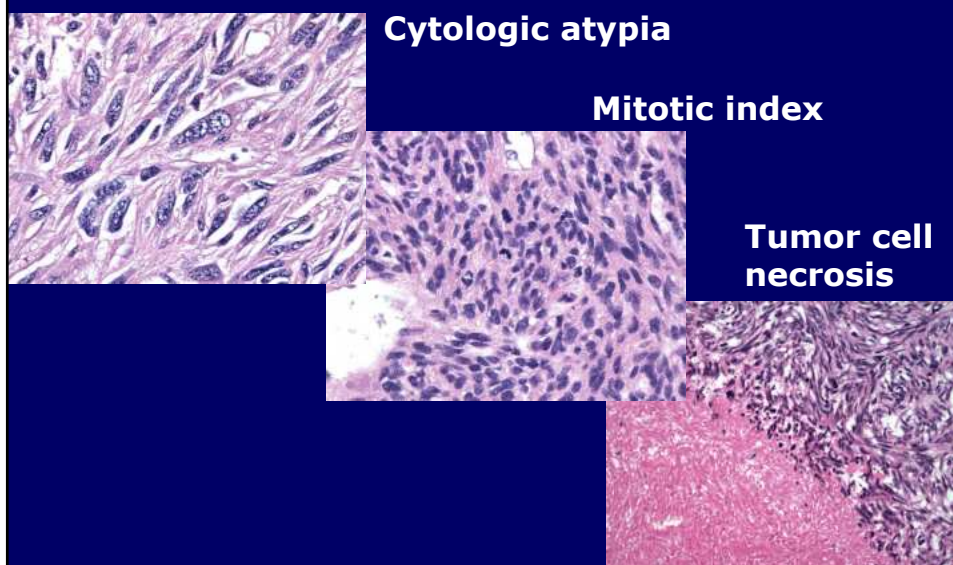
- Mean follow up: 6 years (1-13)
- No recurrences

Am J Surg Pathol 2014;38:1330-9

Differential Diagnosis

- Leiomyosarcoma
- Hereditary leiomyomatosis
- STUMP
- Undifferentiated sarcoma
- Sarcomatous component of carcinosarcoma

Morphologic Criteria for Malignancy in Uterine Smooth Muscle Tumors



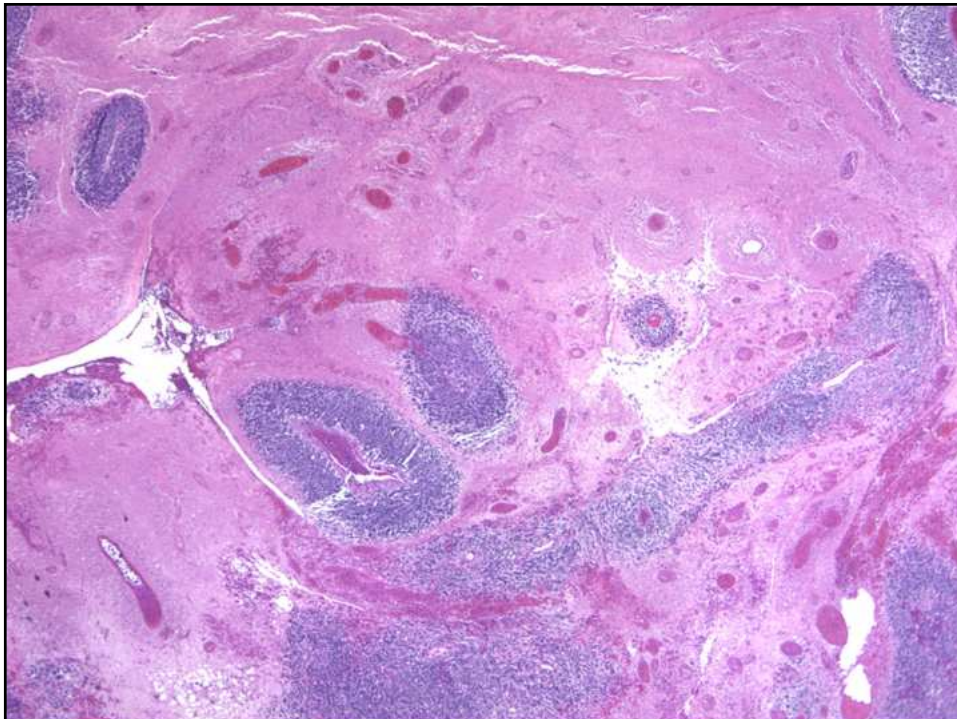
Patterns of Necrosis

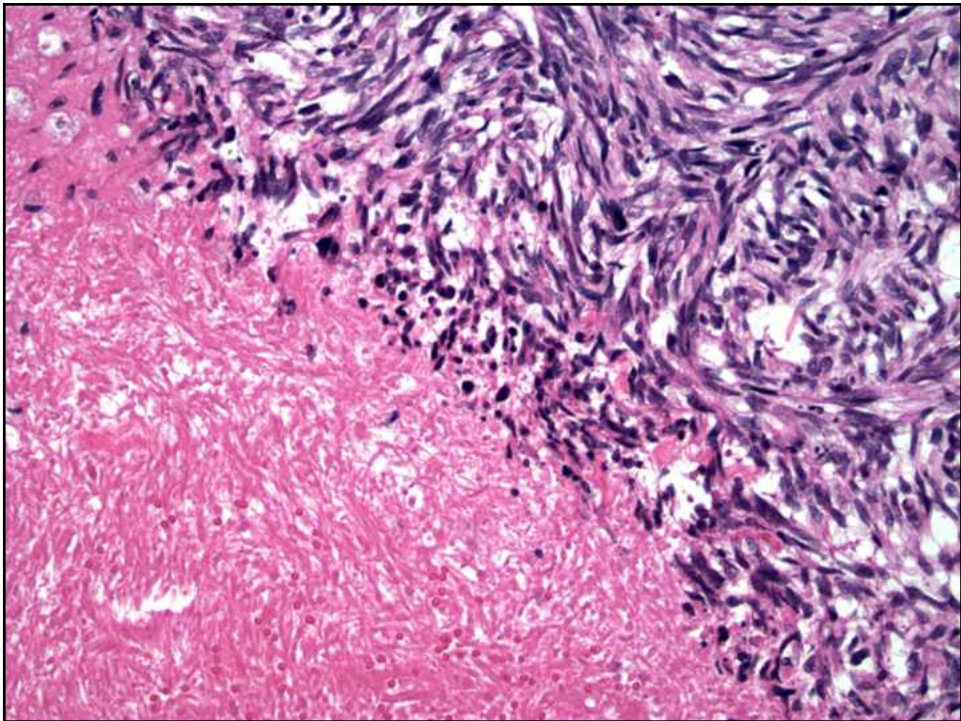
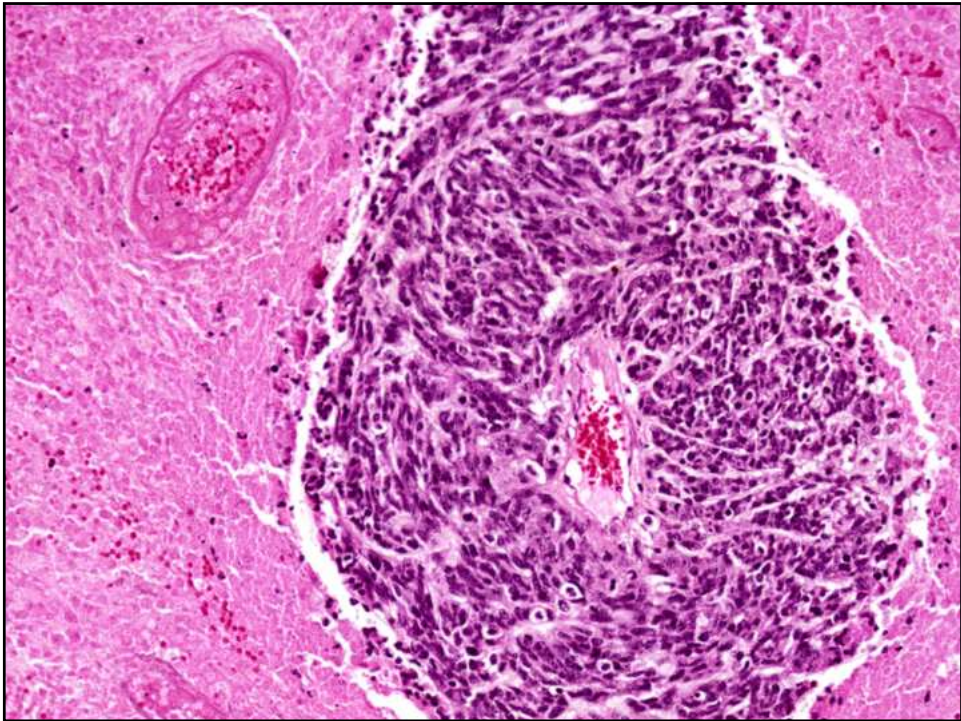
- Coagulative tumor cell necrosis
- Hyaline (infarction) necrosis

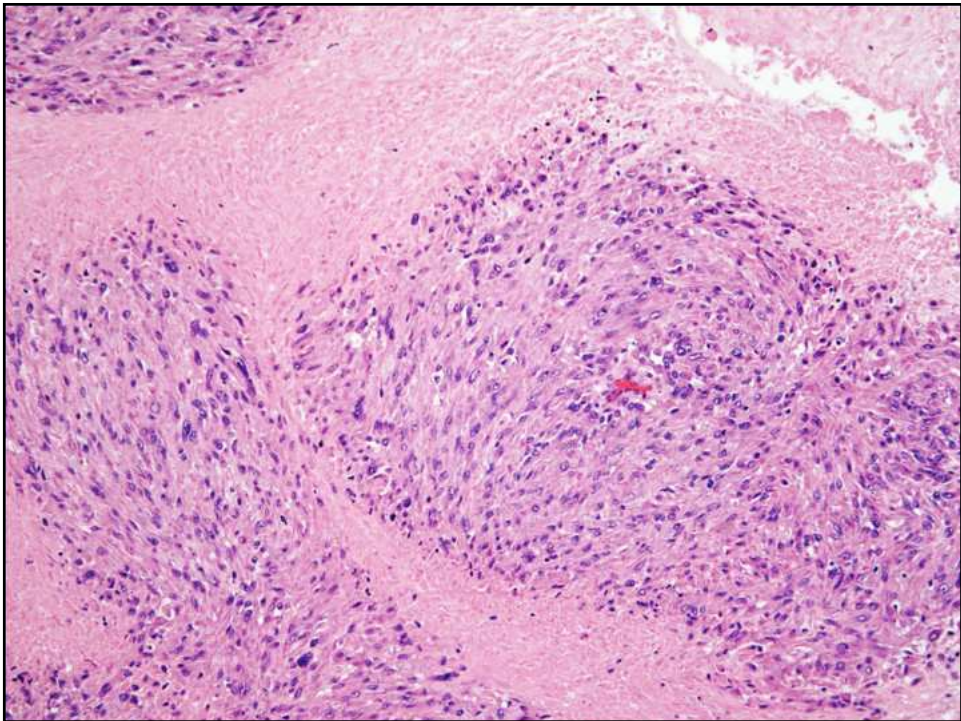
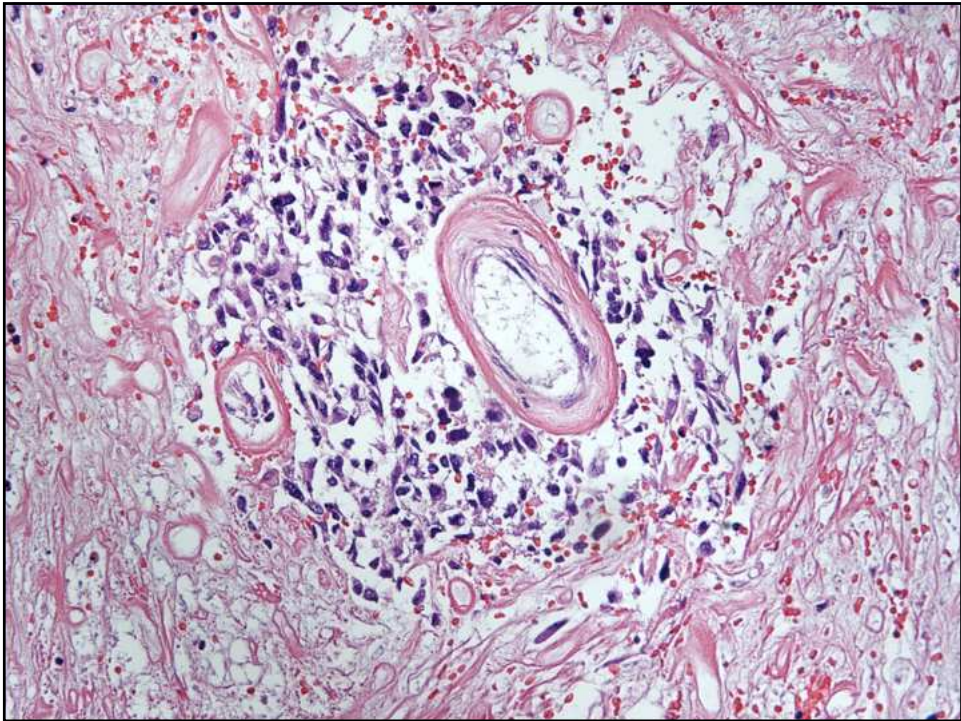


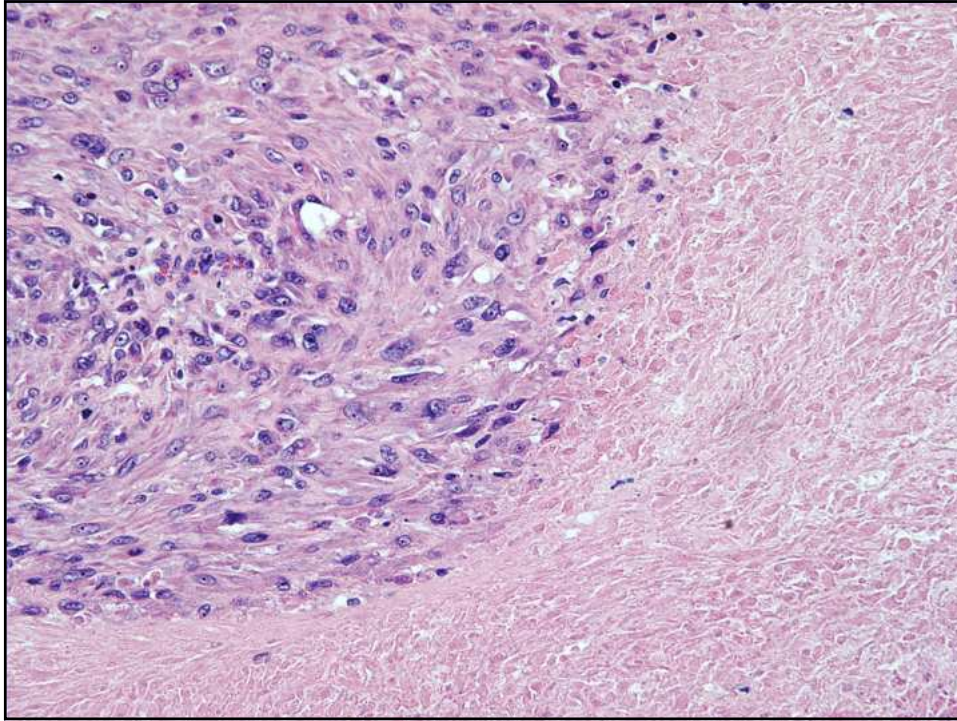
Tumor Cell Necrosis

- Abrupt transition from live cells to necrotic cells
- More than single cells
- Often see cuffs of viable tumor cells surrounding blood vessels surrounded by zone of necrosis





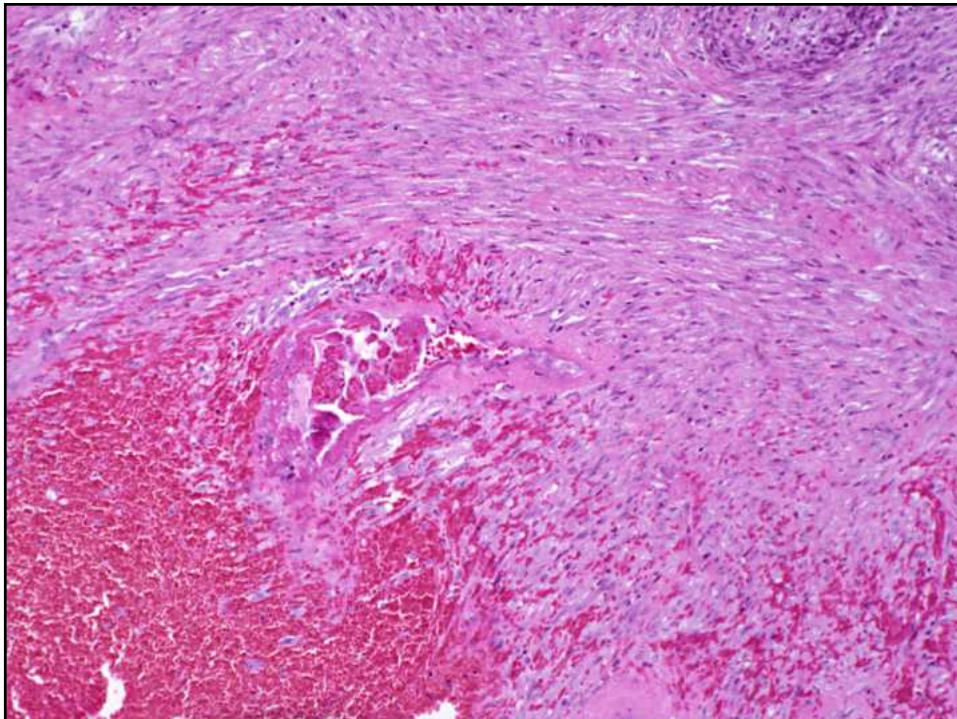


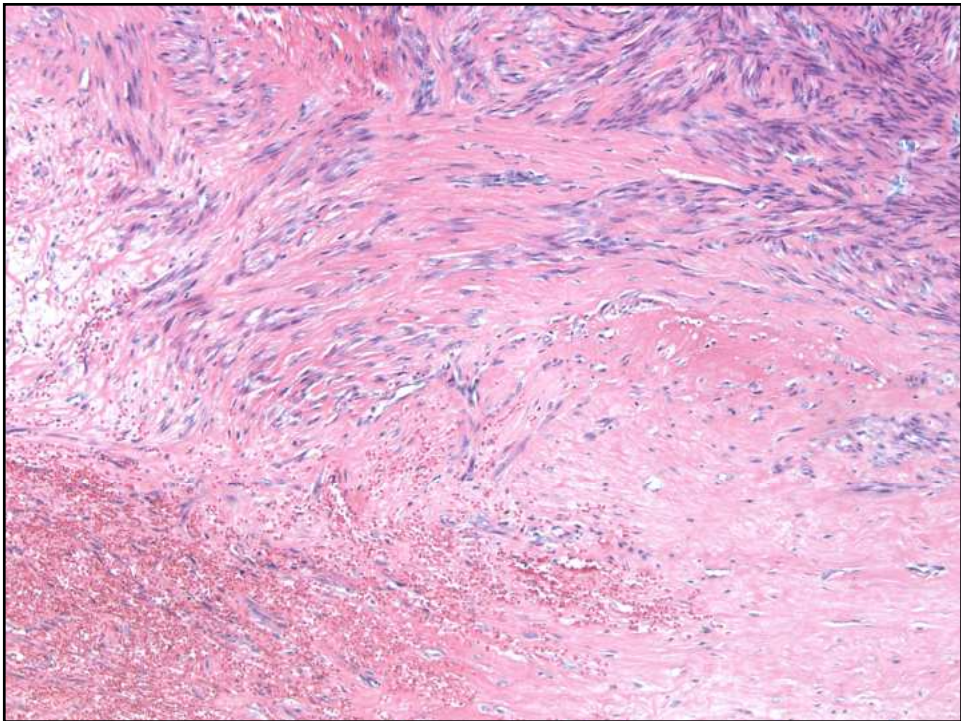
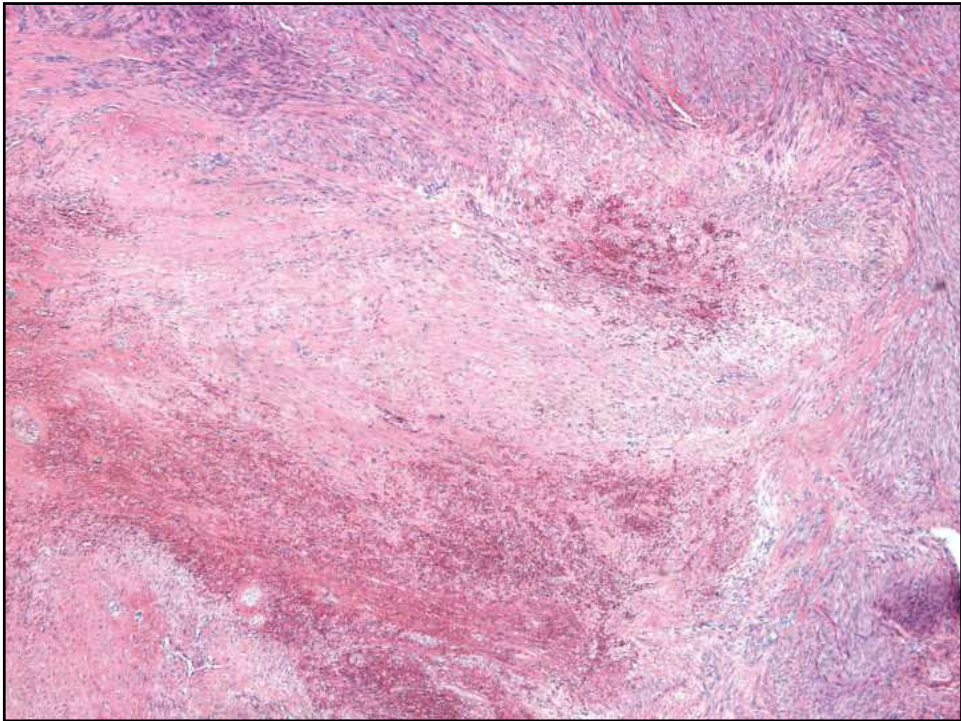


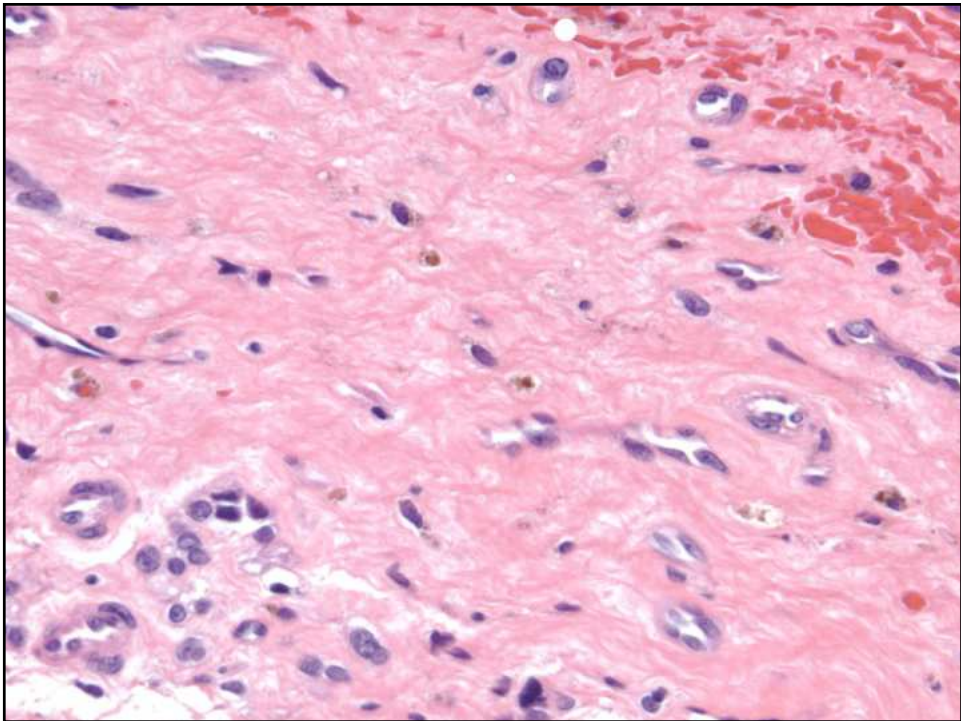
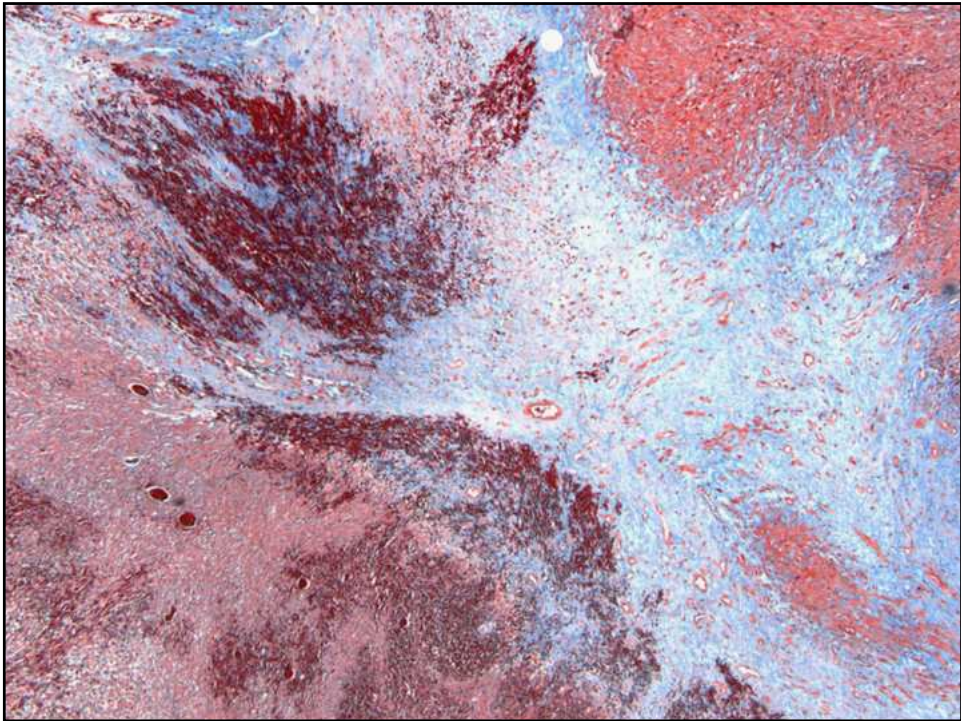
Hyaline (Infarction) Necrosis

Hyaline (Infarct) Necrosis

- Analogous to development and healing of an infarction (e.g., heart)







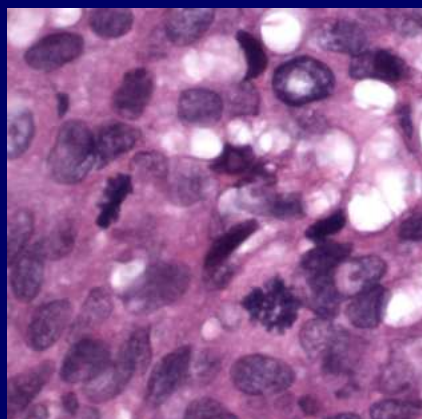
Reproducibility of Tumor Cell Necrosis

- Overall, moderate at best ($\kappa=0.436$)
- If tumors with “indeterminate” necrosis removed, agreement between 6 GYN pathologists was 86%

) Am J Surg Pathol. 2013;37:650-8

Mitotic Figures

- ✓ Be assiduous
- ✓ Exclude lymphocytes, nuclear fragments, bits of hematoxylin, etc.
- ✓ Mitotic figures may be difficult to discern in areas of severe atypia
- ✓ Abnormal mitotic figures vs. dying cells



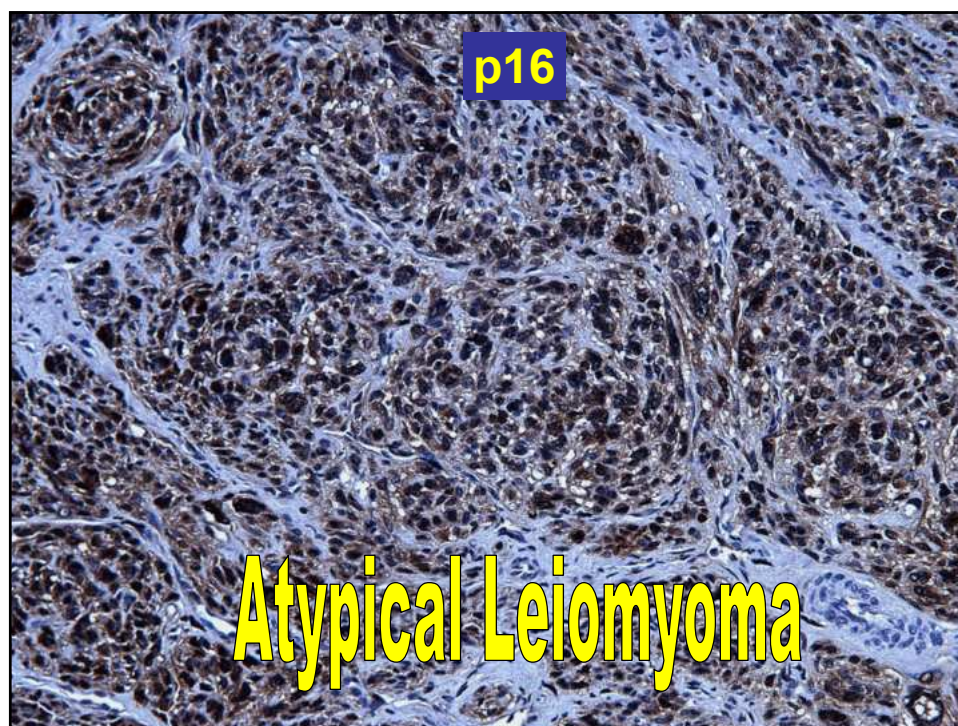


Atypical Leiomyoma vs Leiomyosarcoma

	<u>Atypical Leio</u>	<u>LeioSarc</u>
Mitotic index (MF/10HPF)	≤10	>10
Tumor cell necrosis	Absent	Present
Ki-67 (MIB-1)	Low	High
p16	Low	High
p53	Negative	Positive

Use With Caution

Am J Surg Pathol 2013;37:634-42

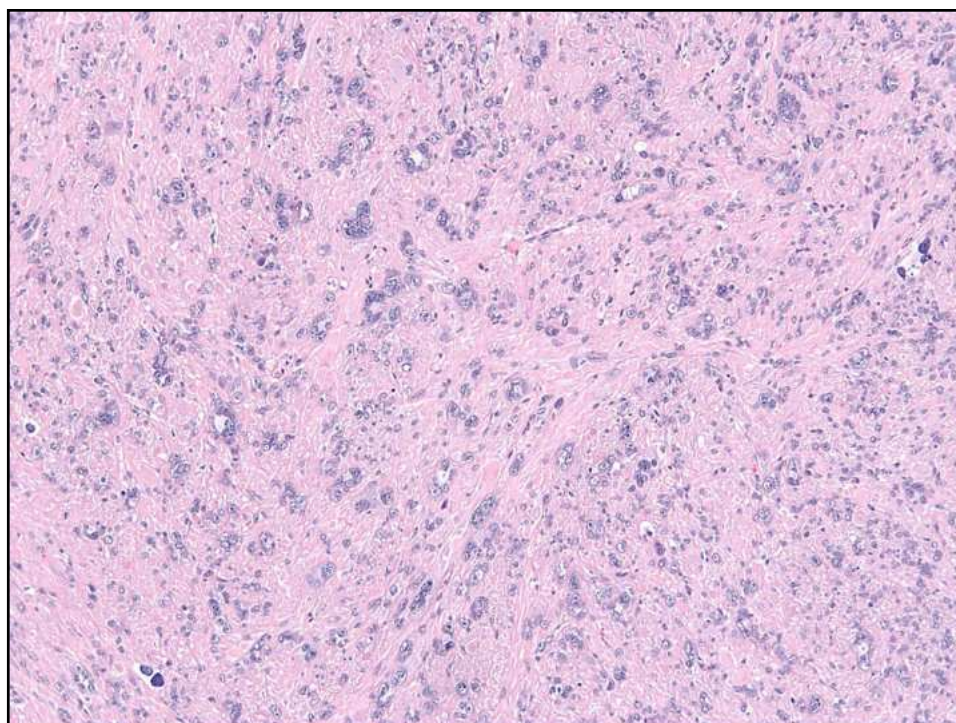


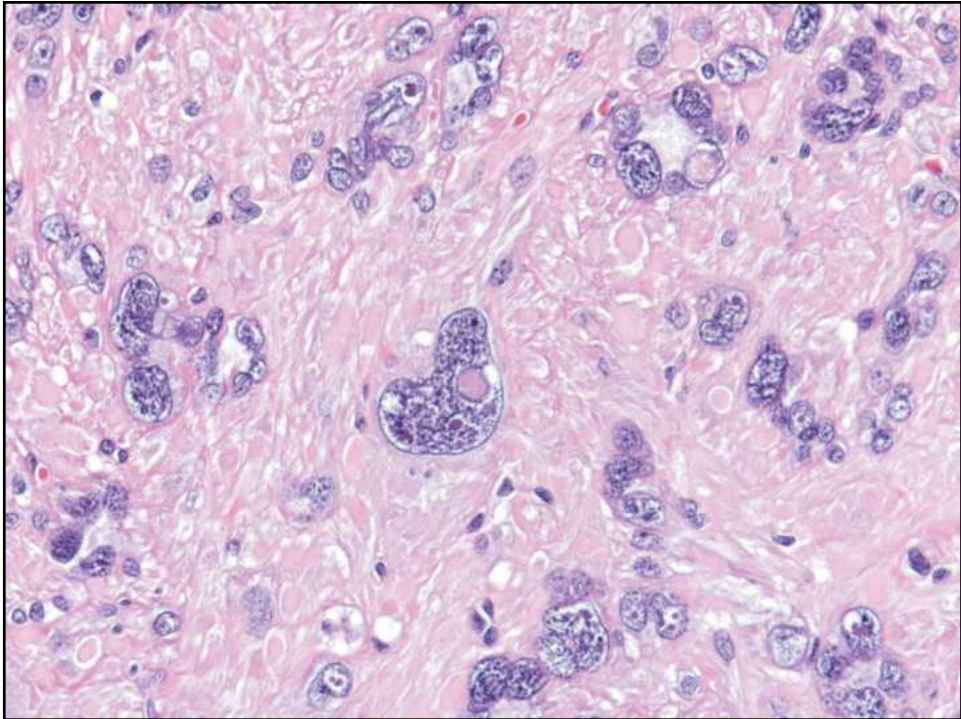
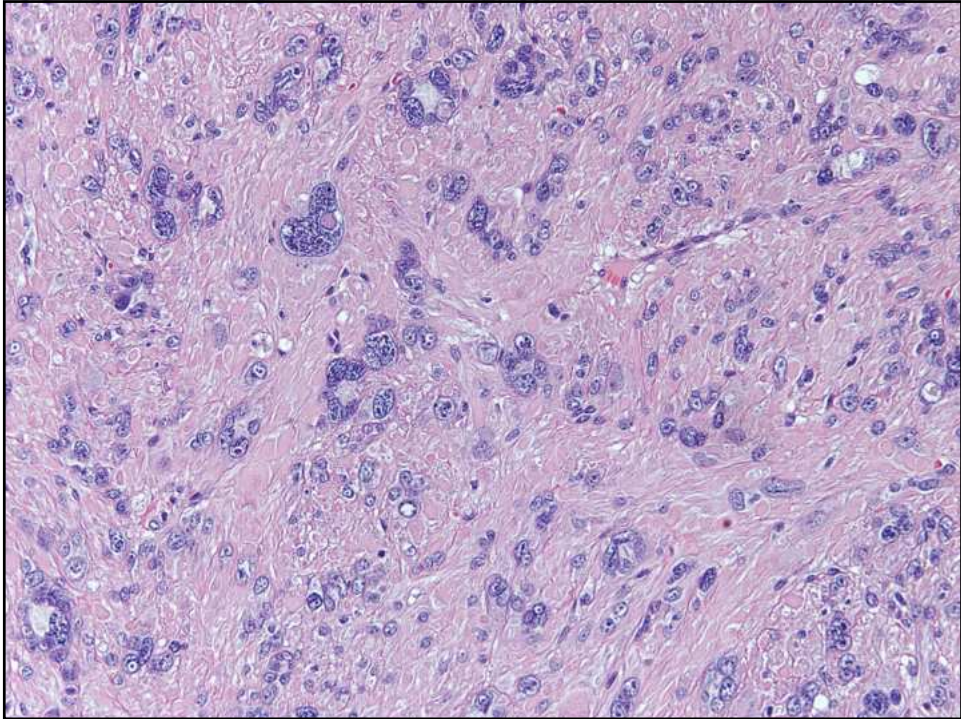
Final Diagnosis

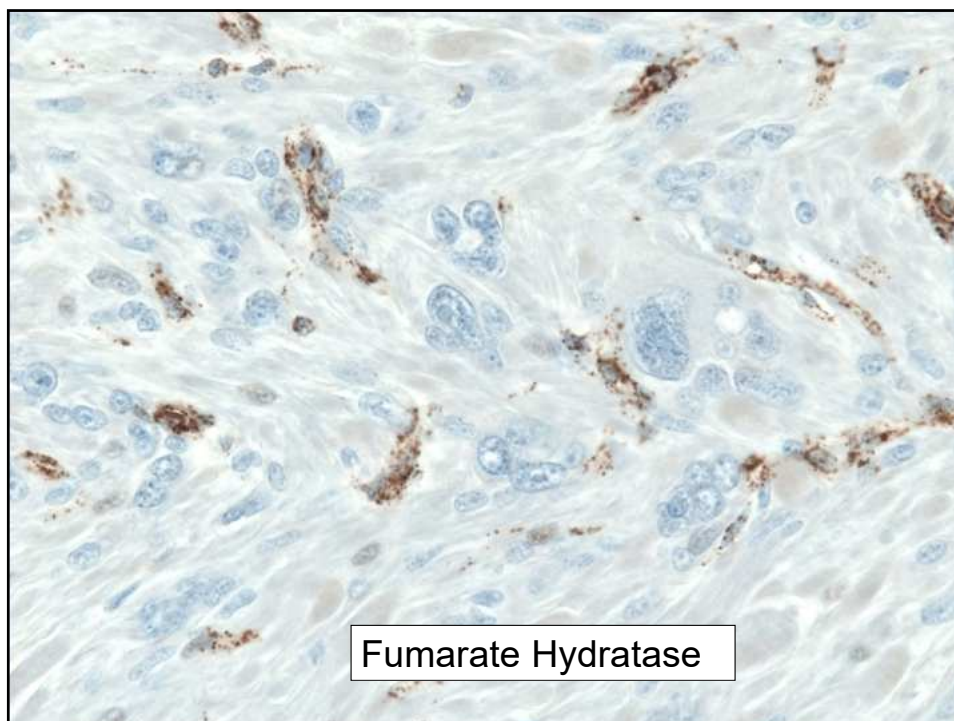
Atypical leiomyoma (leiomyoma with bizarre nuclei)

Case Presentation

29-year-old with uterine mass and vaginal bleeding







Hereditary Leiomyomatosis & Renal Cell Carcinoma Syndrome (HLRCC)

- Autosomal dominant inheritance
- Mutations in fumarate hydratase gene on chromosome 1q42.3
- FH acts a suppressor gene – loss imparts protection from apoptosis in renal and fibroblast cells

Nat Genet 2002;30:406-410

Hereditary Leiomyomatosis & Renal Cell Carcinoma Syndrome (HLRCC)

- Multiple leiomyomas of skin and uterus
- Subset of patients develop type II renal cell papillary carcinoma
- Rare: 1/10,000 – to 1/50,000

Tumors in HLRCC

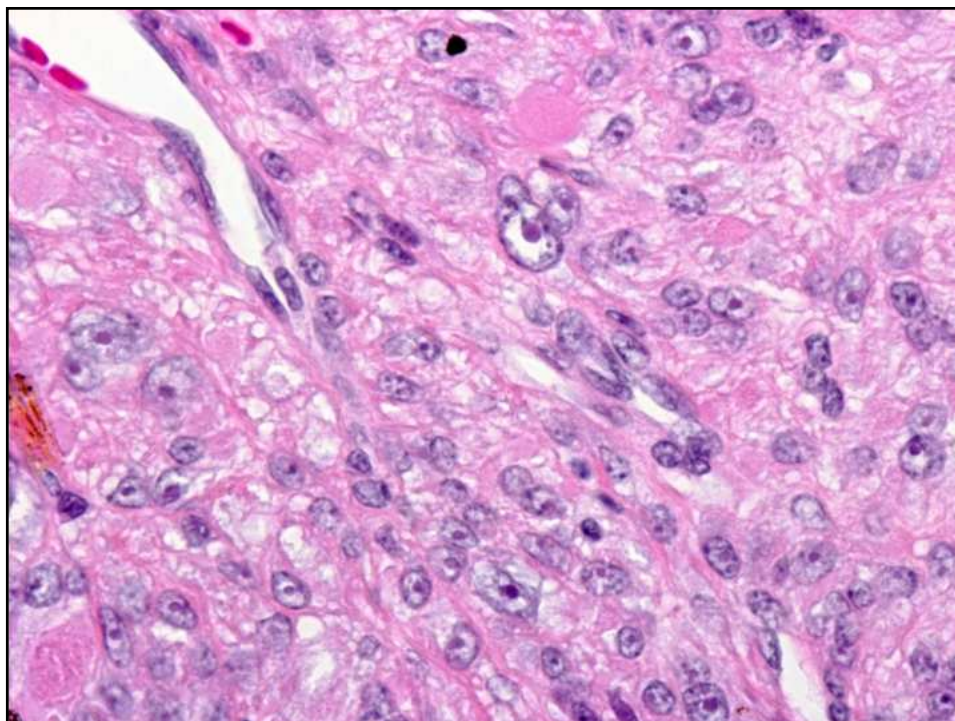
Tumor	Mean Age at Presentation (years)
Cutaneous leiomyomas	25
Uterine leiomyomas	30
Renal cell carcinomas*	46

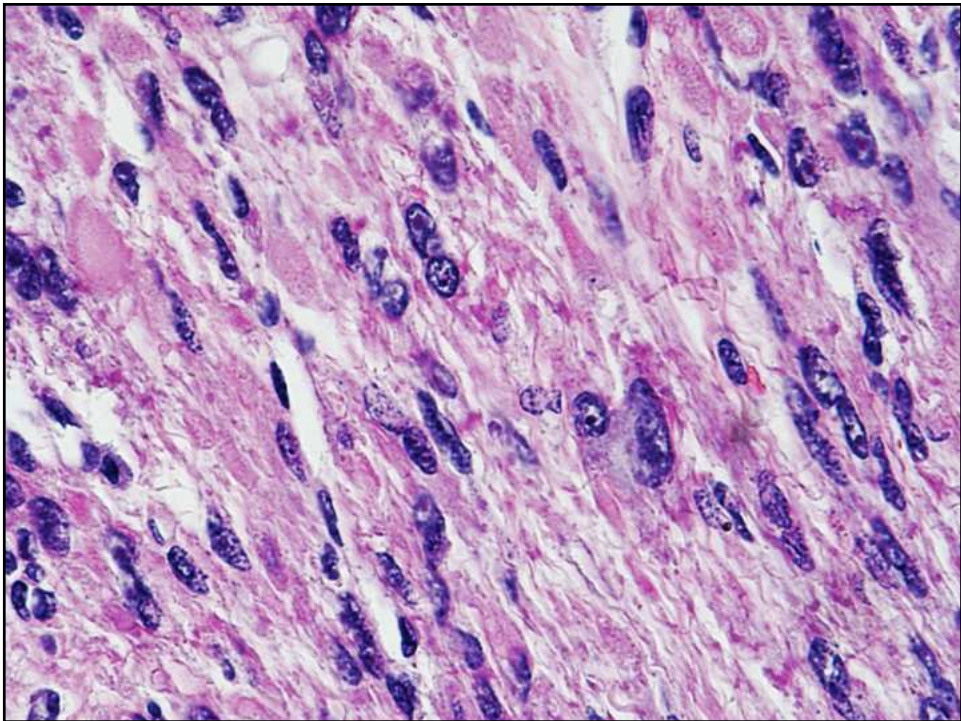
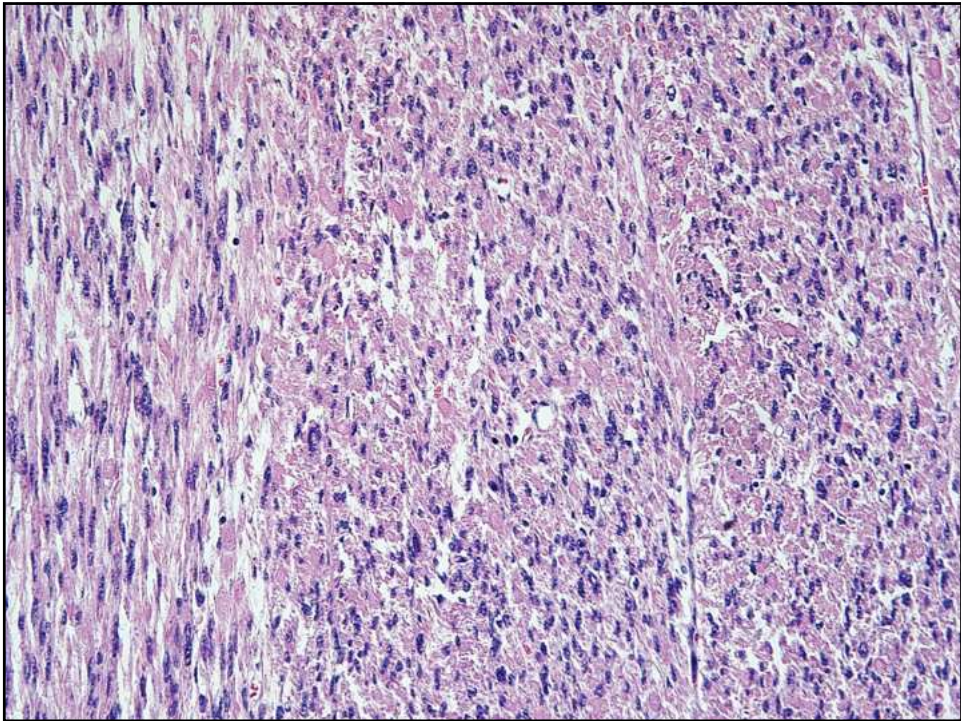
Renal cell carcinomas are unilateral, high stage, poor prognosis
– 20-30% penetrance

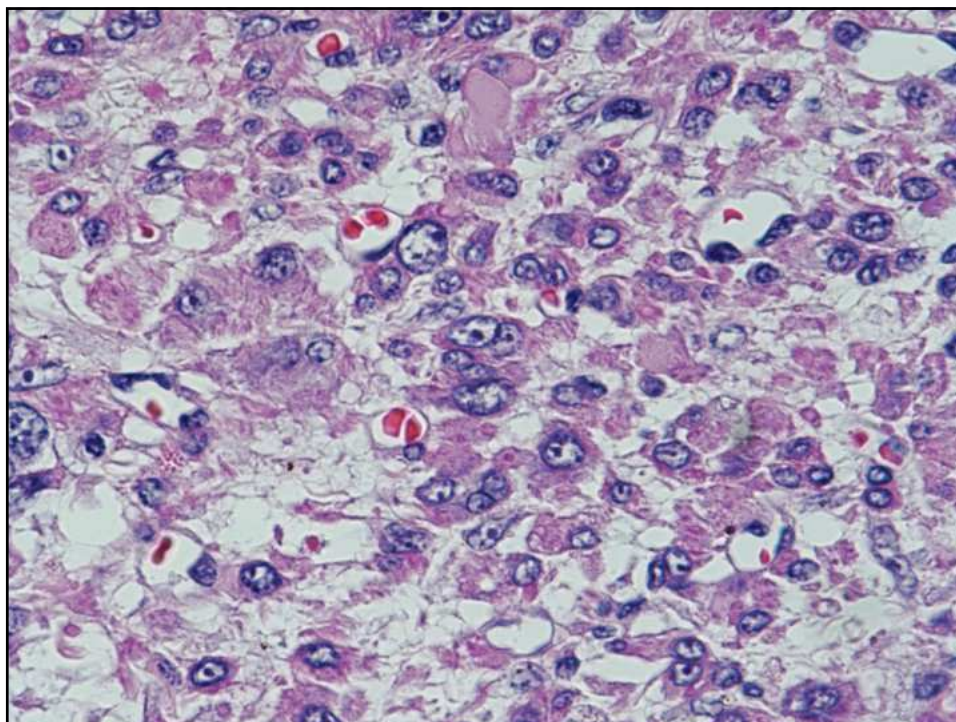
Histology of Uterine Leiomyomas in HLRCC

- Increased cellularity, multinucleation & atypia
- Hemangiopericytomatous blood vessels
- Large orangeophilic nucleoli surrounded by perinuclear halo
- Eosinophilic cytoplasmic inclusions
- Complete loss of fumarate hydratase on IHC*
1% of all uterine leiomyomas are deficient due to somatic mutation

Am J Surg Pathol. 2015;39:1529-39; Am J Surg Pathol 2016;40:599-607



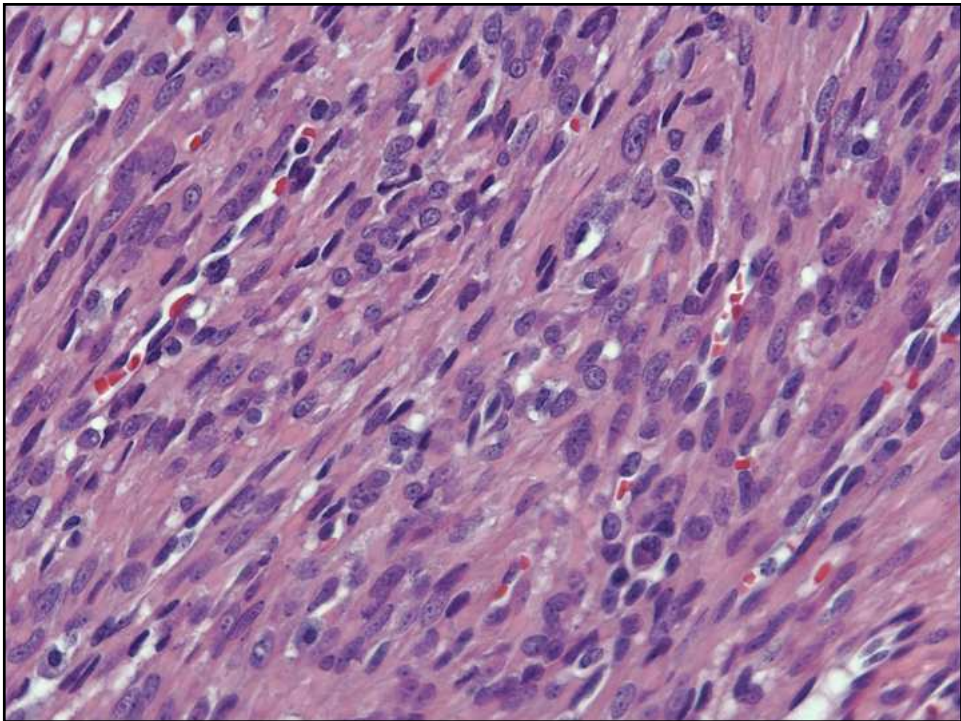
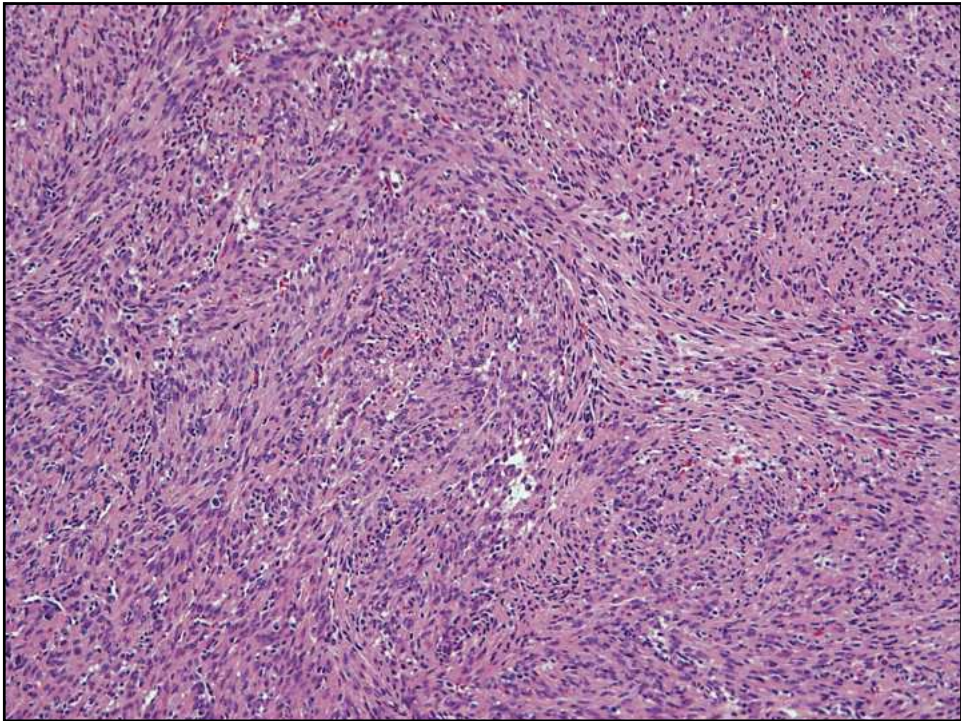


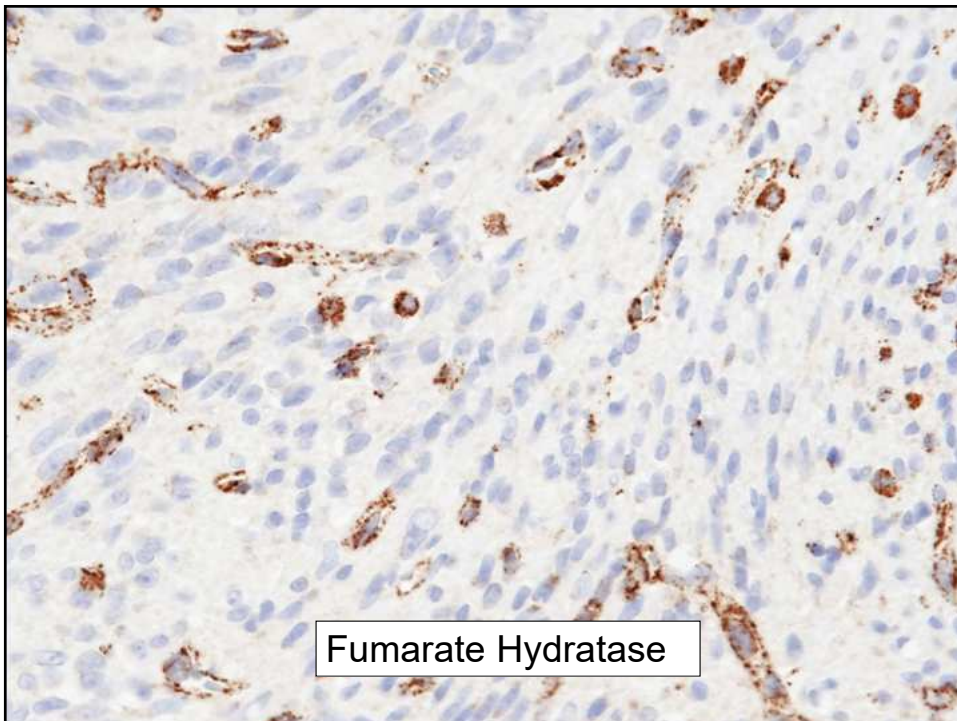
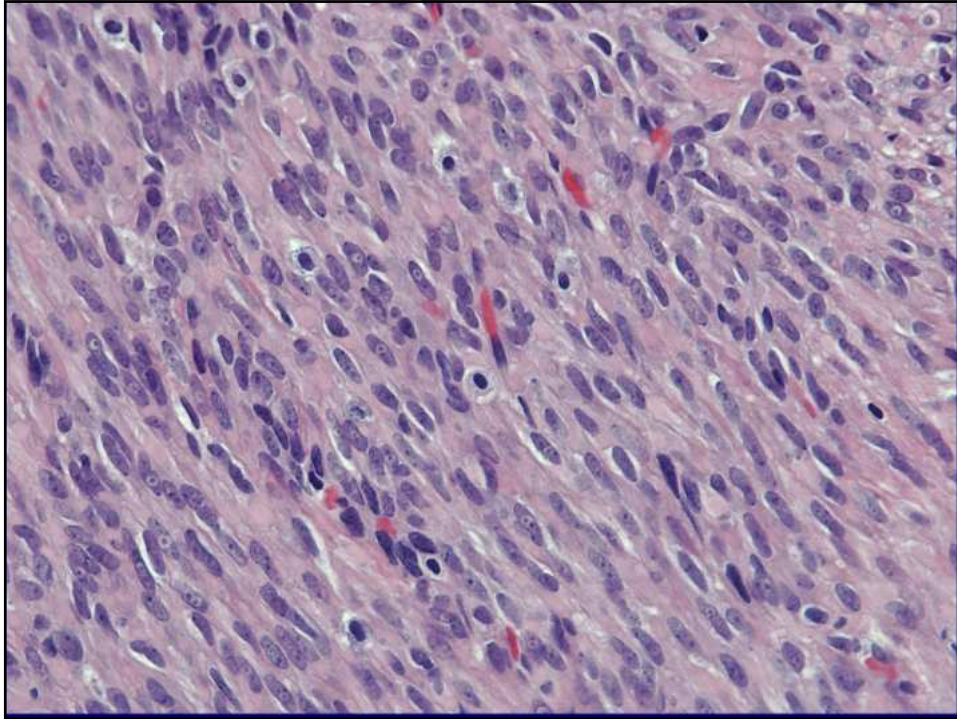


FH-Deficient Leiomyoma

- No cellular packeting
- Chain-like or palisading nuclear arrangements
- Prominent staghorn-shaped blood vessels
- Oval nuclei with no or at most mild atypia
- Small eosinophilic nucleoli
- Low mitotic rate (0 to 1/10 HPF)

Am J Surg Pathol 2016;40:1661-1669





Are There 2 Types of Atypical Leiomyoma?

Type I

- Round or oval nuclei
- Distinct smooth nuclear membranes
- Prominent nucleoli with perinucleolar halos
- Open coarse chromatin
- Patchy atypia

Type II

- Elongated or spindled nuclei
- Irregular nuclear membranes
- Pinpoint or no nucleoli
- Dark smudgy chromatin
- Diffuse atypia

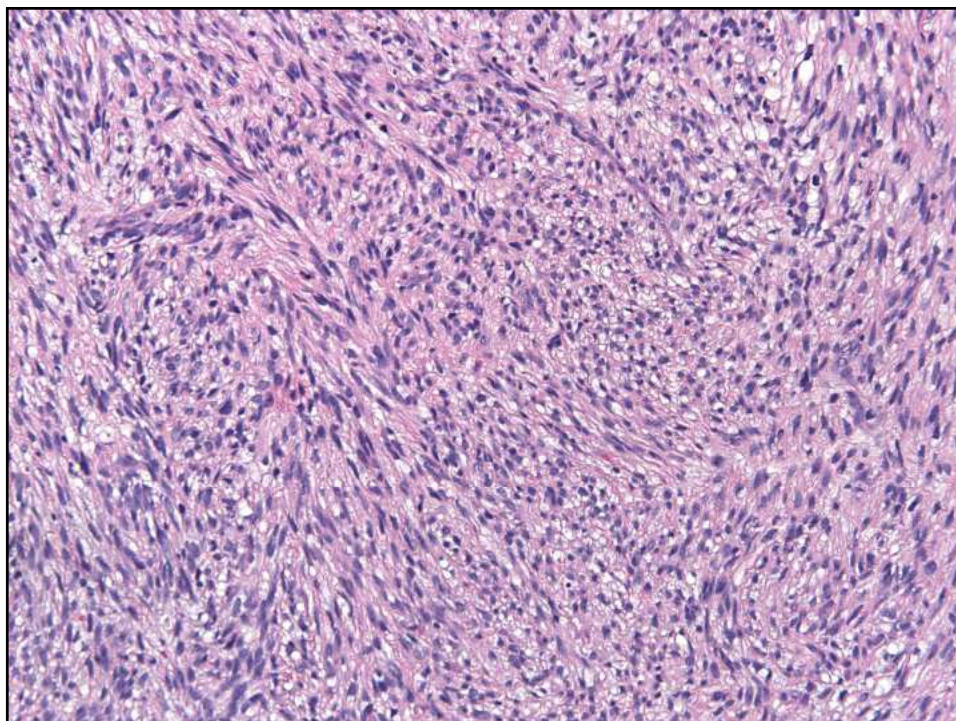
Am J Surg Pathol 2016;40:923-33

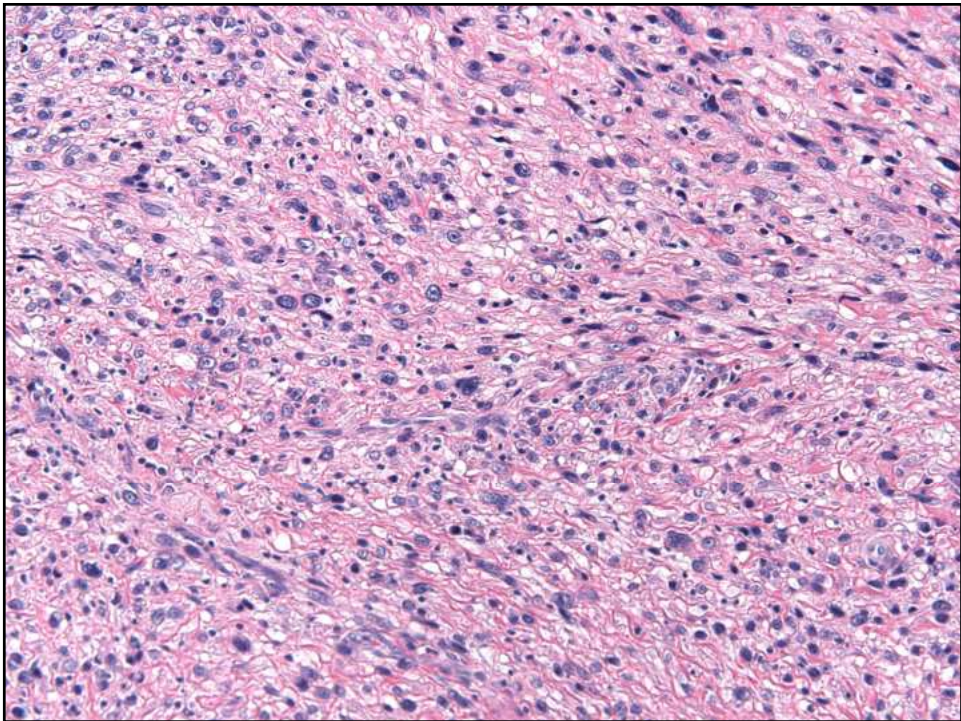
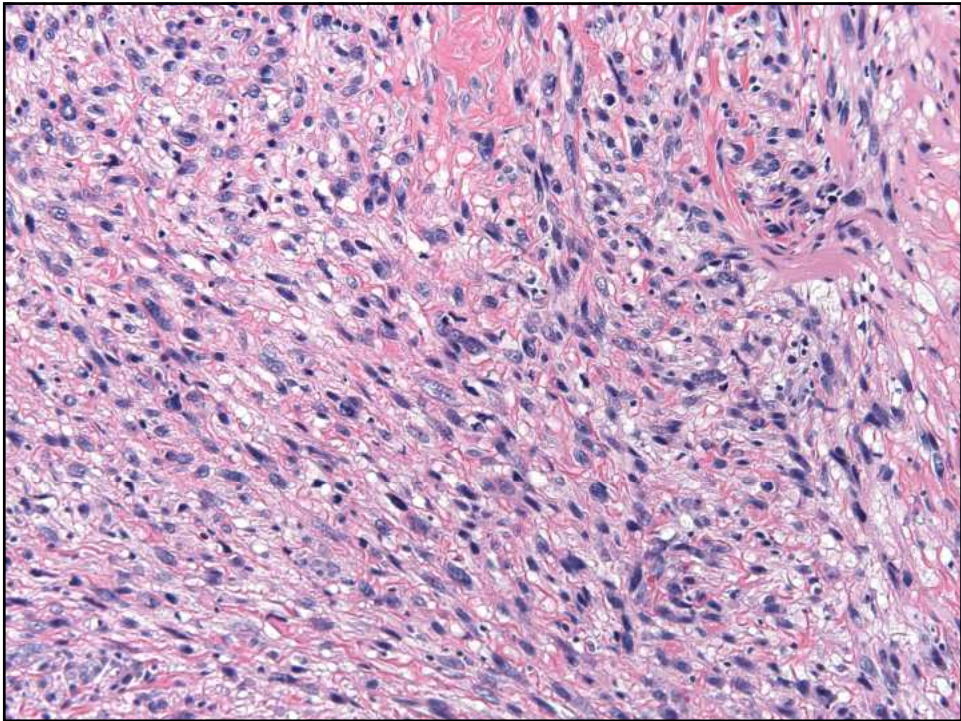
Final Diagnosis

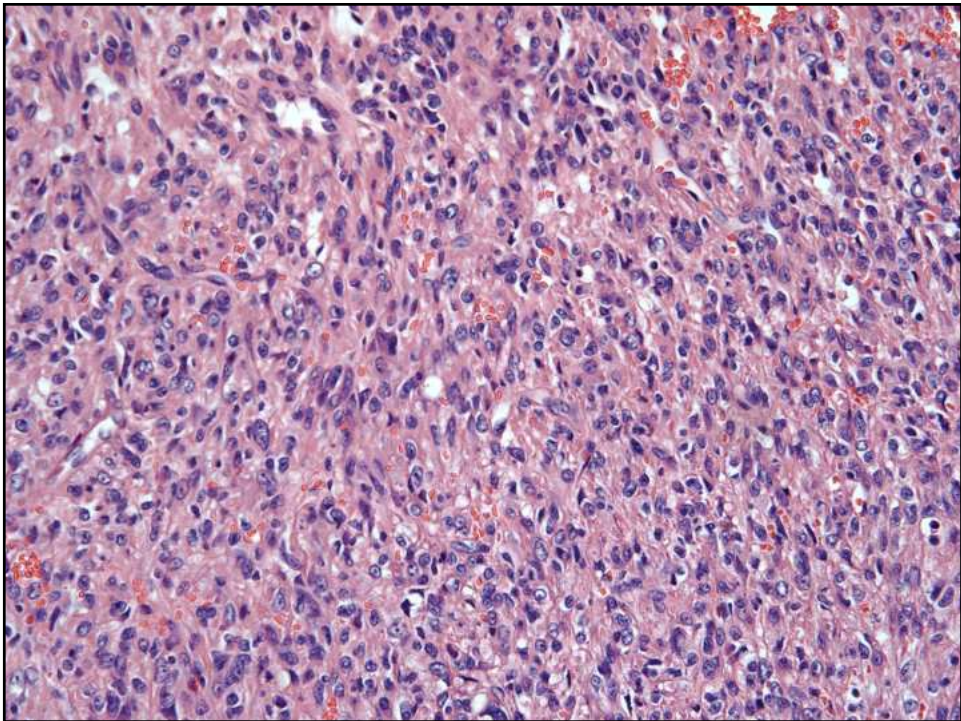
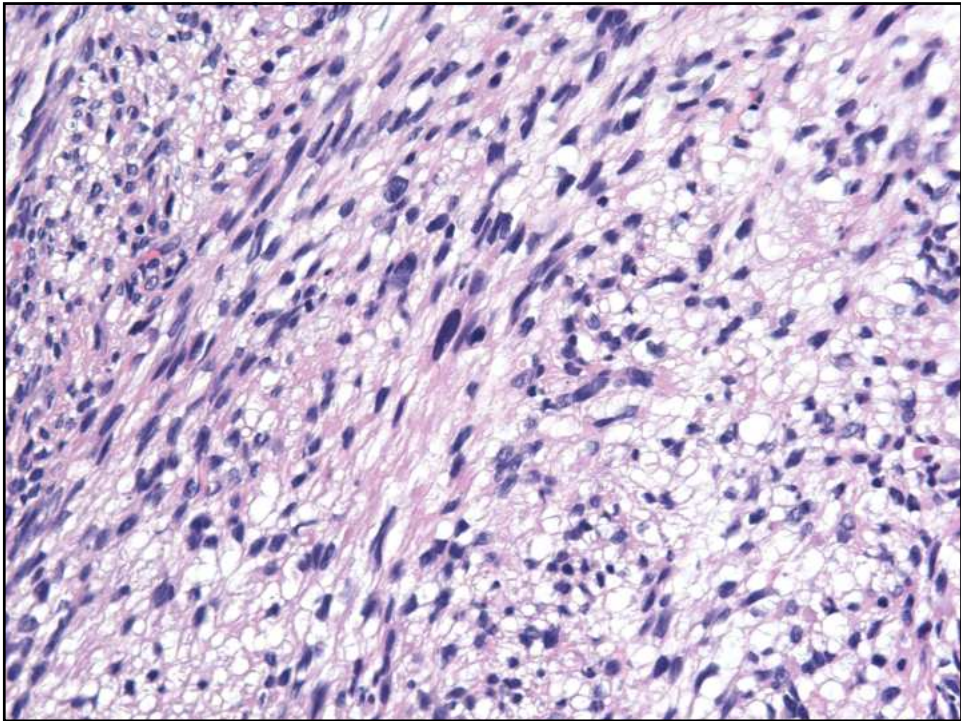
Fumarate hydratase-deficient atypical leiomyoma

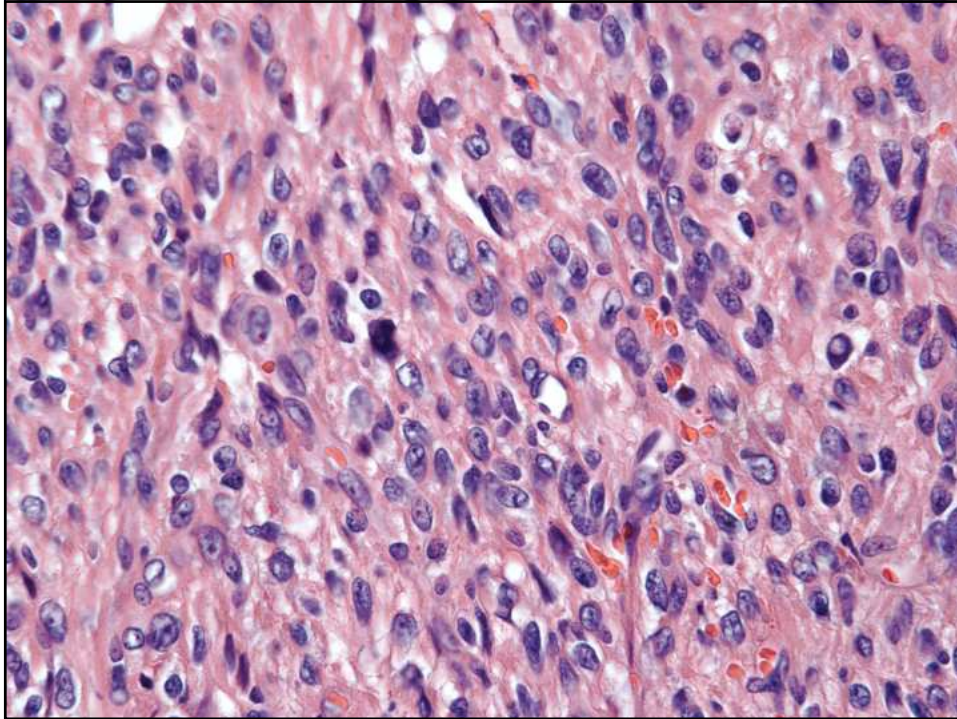
Case Presentation

43 year old with uterine leiomyomas and
“atypical” pelvic leiomyoma









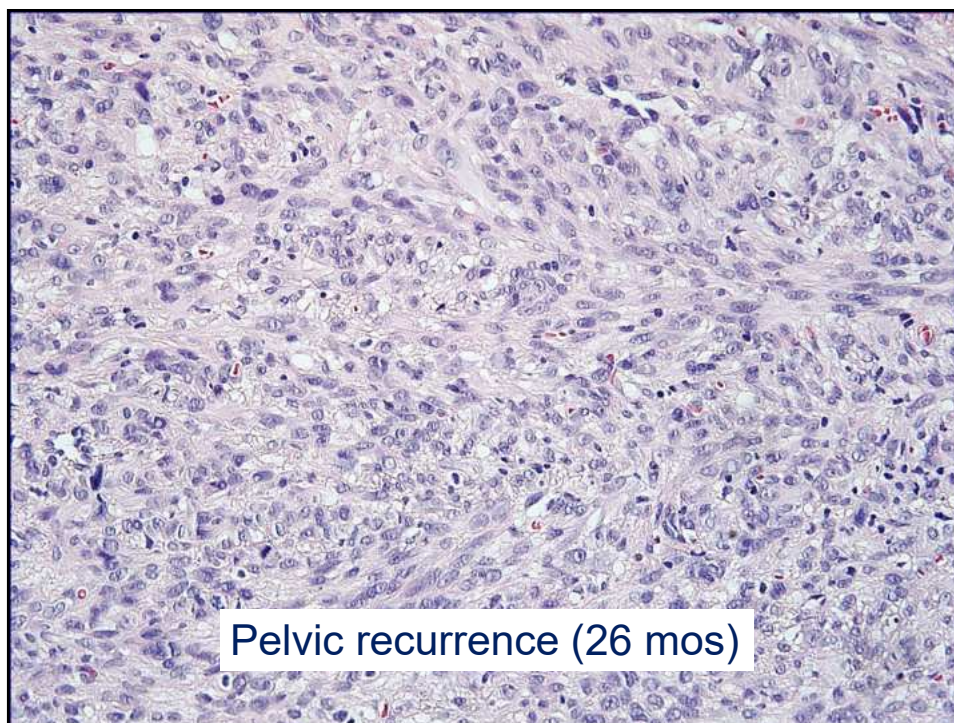
Diagnosis?

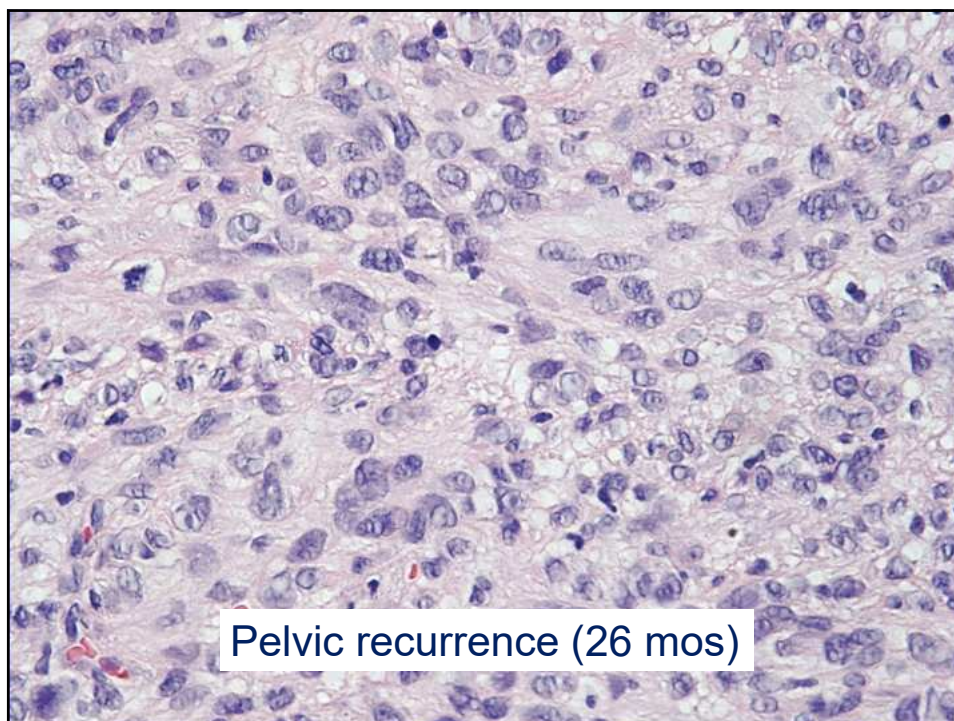
- Leiomyosarcoma
- Leiomyoma with (focal) bizarre nuclei
- Hereditary leiomyomatosis
- STUMP
- Sarcomatous component of carcinosarcoma

Final Diagnosis

Smooth muscle tumor of uncertain malignant potential (STUMP)

No further treatment. Close clinical follow up





'Iatrogenic' Pelvic Smooth Muscle Tumors

- Laparoscopic hysterectomy with morcellation of the uterus
- Vaginal hysterectomy
- Limited follow up suggests recurrence in this setting is indolent, but few cases studied

STUMP: Stanford Experience

- 9 patients (20%) developed recurrent disease at 12 to 90 months (mean 38)
- 8 had morcellation or myomectomy procedure

Management

- Management of STUMP on myomectomy?
- Management of STUMP on hysterectomy?
- Management of STUMP in pelvis/abdomen?
- What about single vs multiple tumors?
- How do you factor in “expert” disagreement: LMS vs STUMP?

Management

- Management of STUMP on local (pelvic vs abdominal) recurrence?
- Does time to recurrence influence management?
- Does prior laparoscopic procedure (esp. morcellation) play a role in management decision?

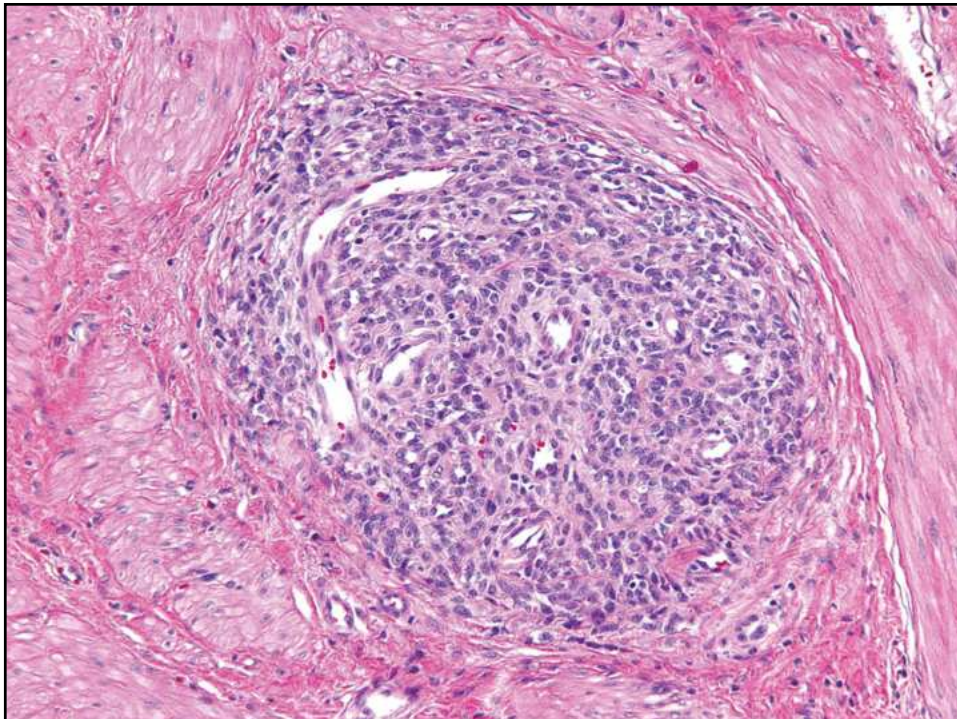
Final Diagnosis

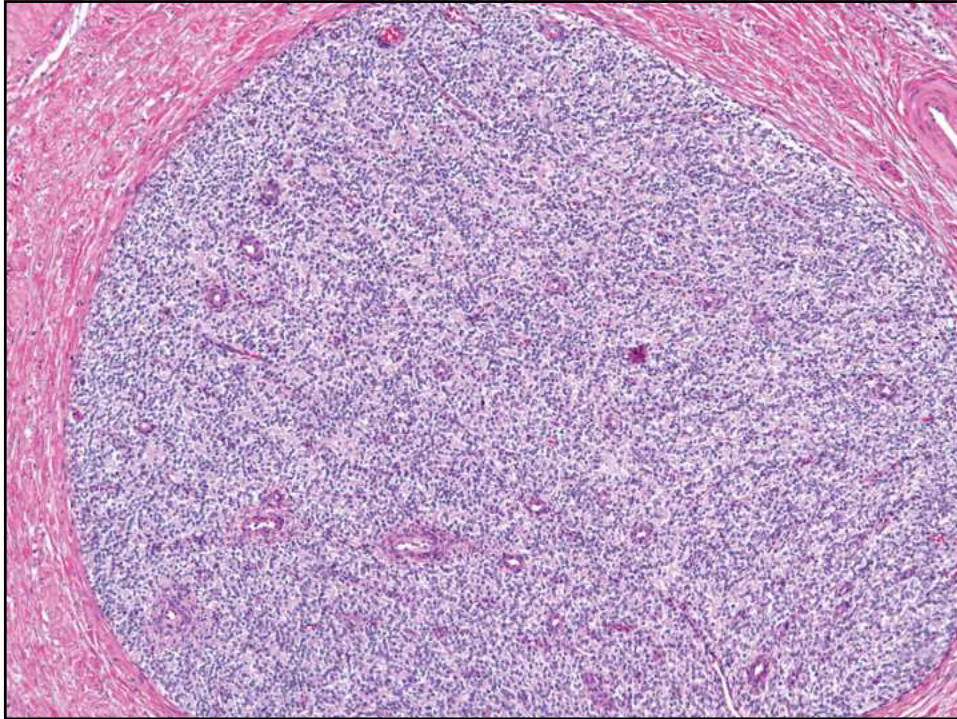
Smooth muscle tumor of uncertain malignant potential (STUMP)

Follow up: benign clinical course

Case Presentation

45-year-old with uterine mass undergoes myomectomy





Diagnosis?

- Endometrial stromal nodule
- Cellular leiomyoma
- Low-grade endometrial stromal sarcoma
- Gland-poor adenomyosis

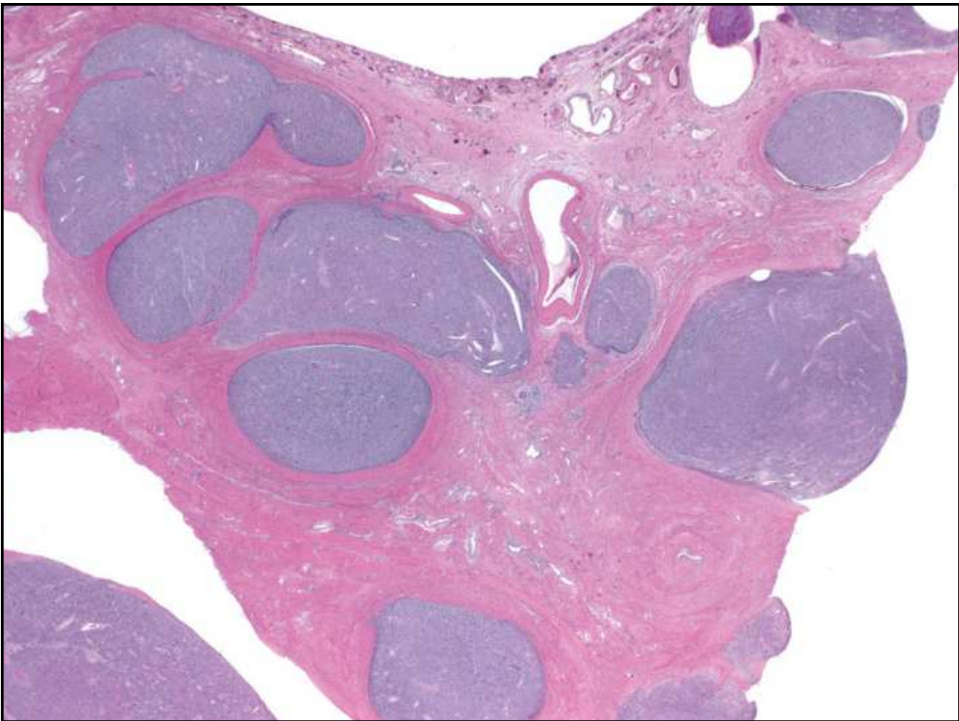
Endometrial Stromal Nodule

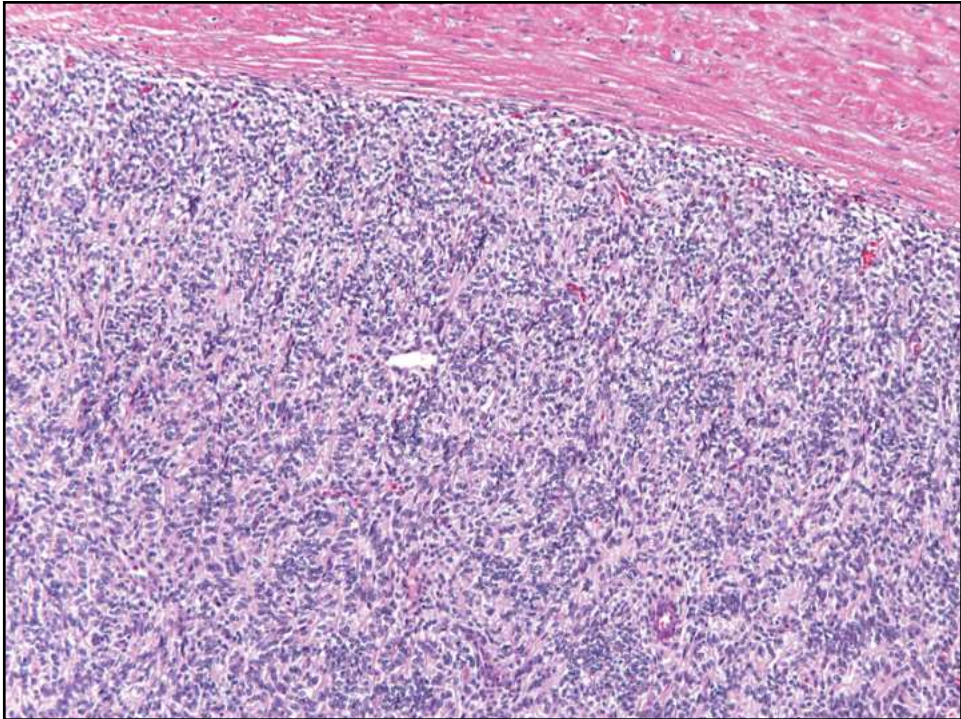
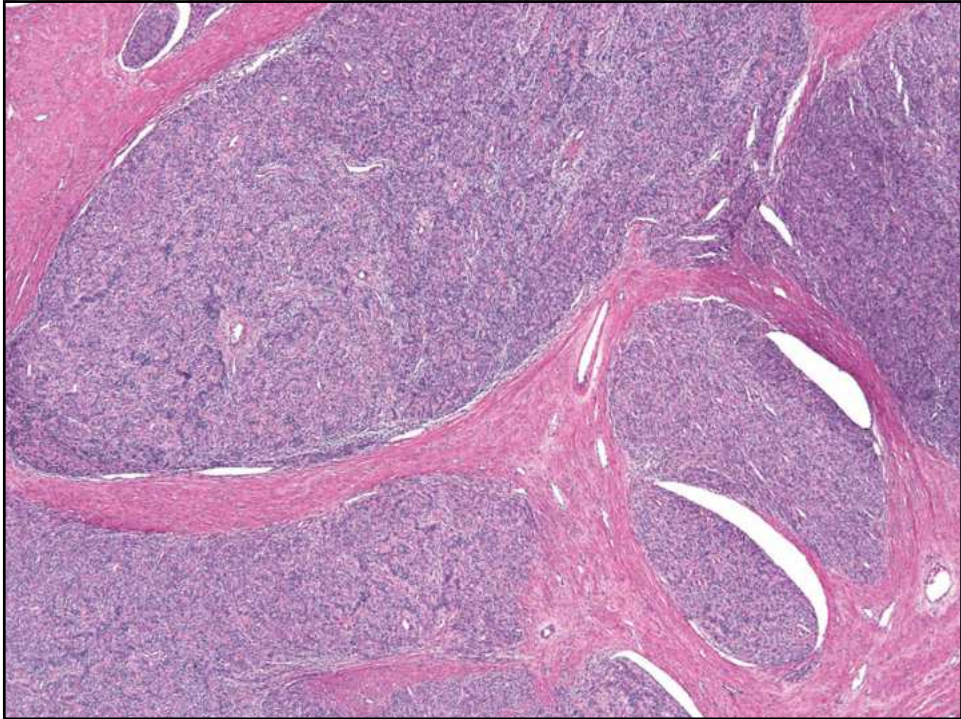
- Circumscribed, expansile nodule - usually small (< 5 cm), but large nodules have been reported*
- No lymphatic-vascular intrusion or invasion
- Focal irregular margin is allowed in the form of lobulated or finger-like projections (< 3) into the adjacent myometrium that do not exceed 3 mm*

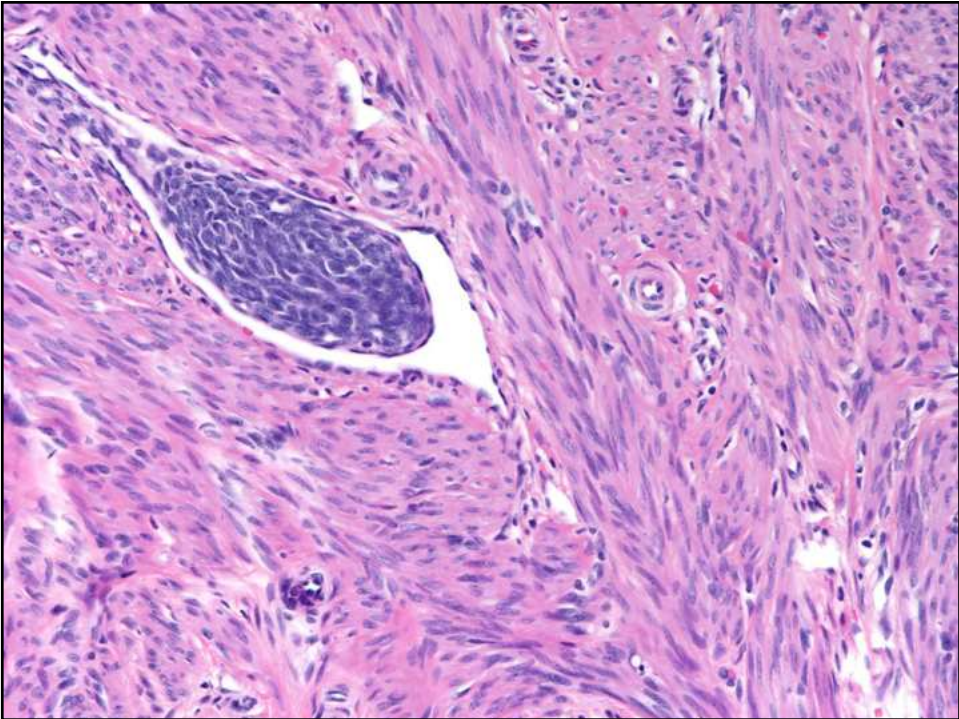
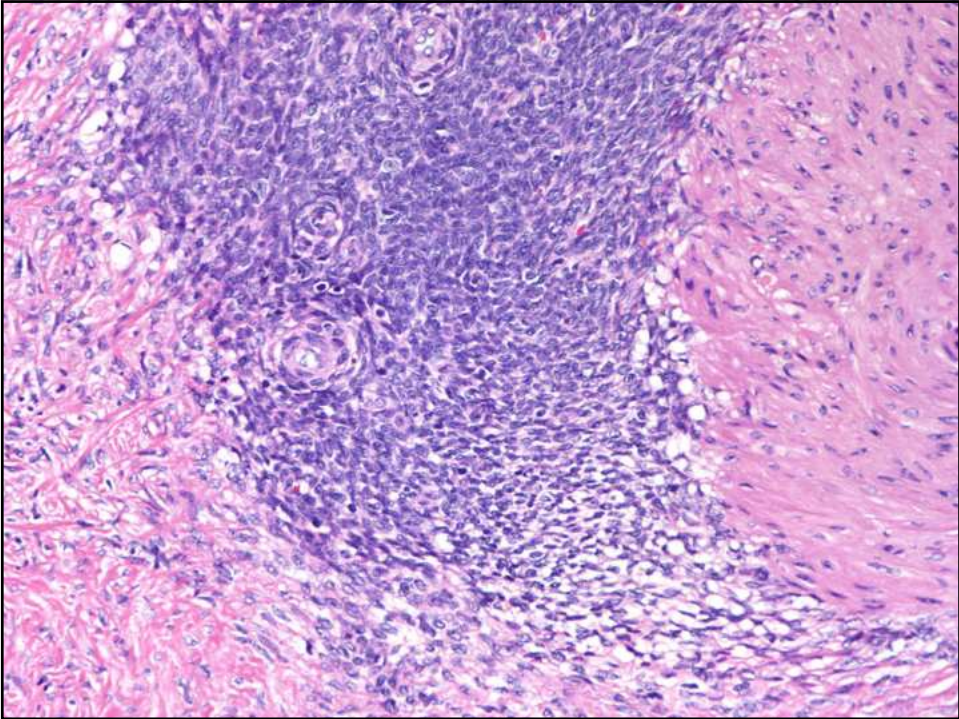
*Requires extensive sectioning & evaluation of entire nodule

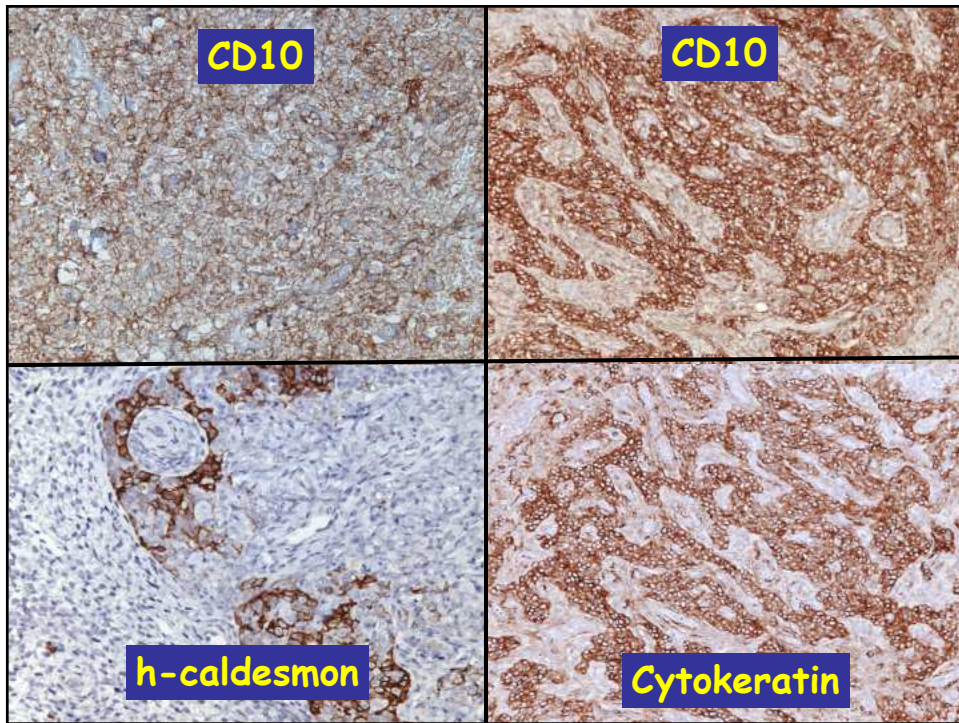
Stromal Sarcoma vs Stromal Nodule

- Requires assessment of full tumor interface & presence of vascular invasion
- Distinction not possible in uterine sampling unless lesion is small and completely excised
- What to do in reproductive aged woman? Imaging, ultrasound, hysteroscopy and curettage – all carry risk









Endometrial Stromal Sarcoma

- Low grade malignancy – one-third present with extra-uterine extension
- Middle aged women
- 10-15% uterine mesenchymal malignancies
- Assoc with estrogen, tamoxifen, pelvic radiation (rare)
- Mitotic index does not stratify patients in this group
- Responsive to hormonal therapy
- Immunoprofile: ER+, PR+, CD10+

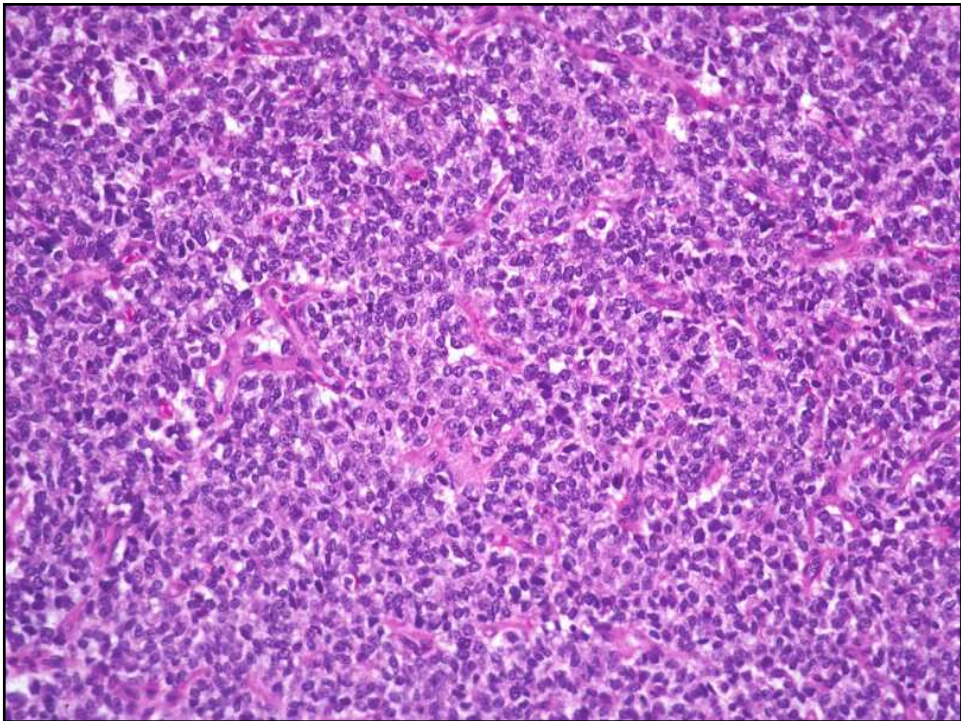
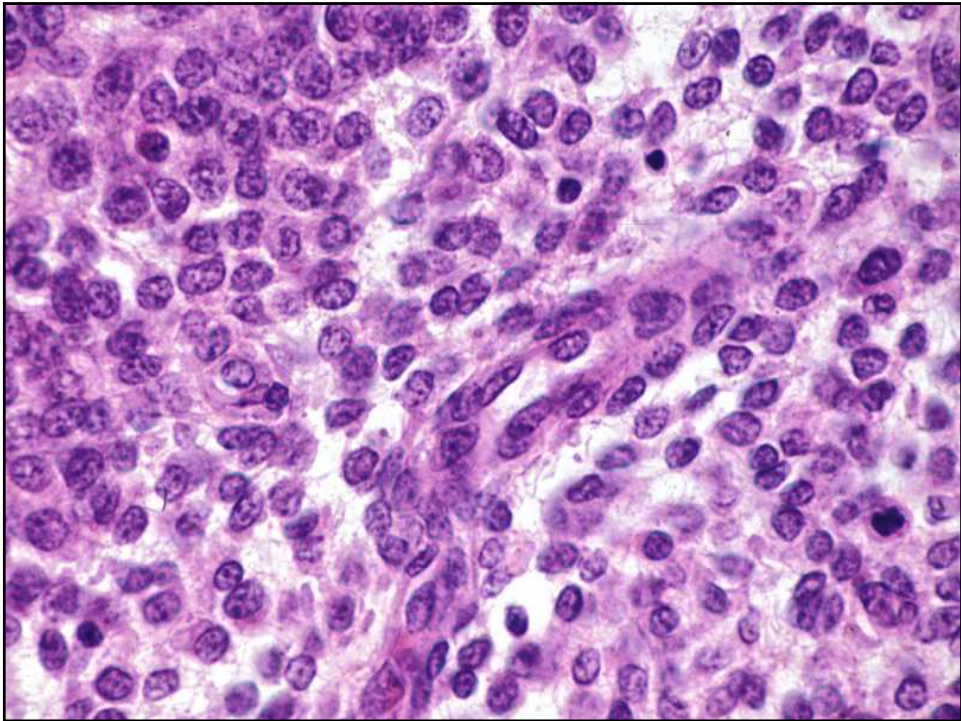
Immunohistochemical Markers

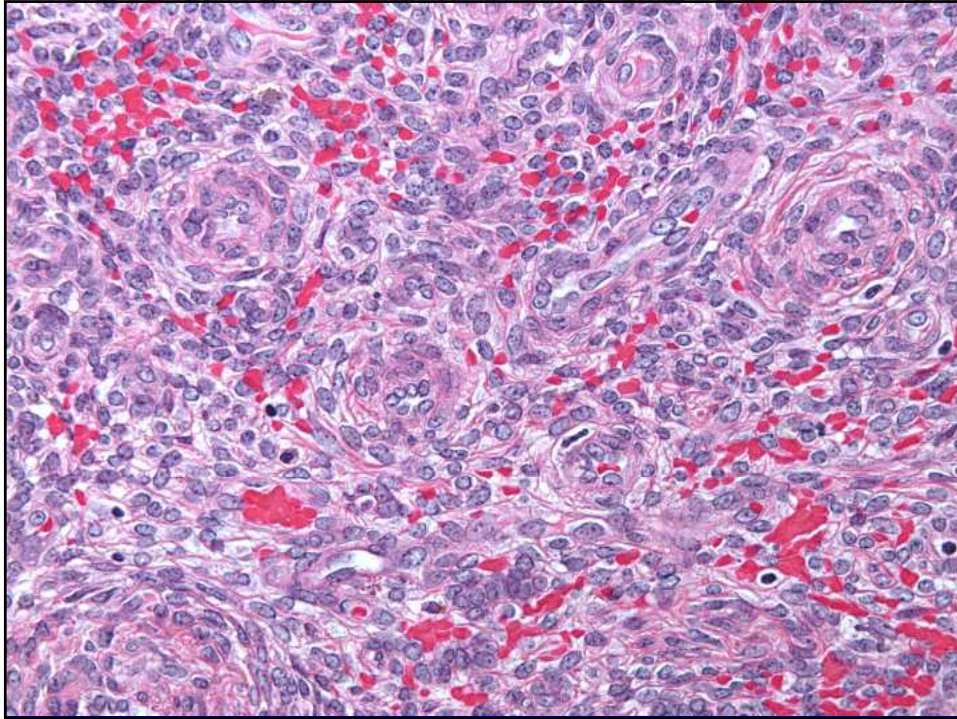
CD10

Desmin

Caldesmon

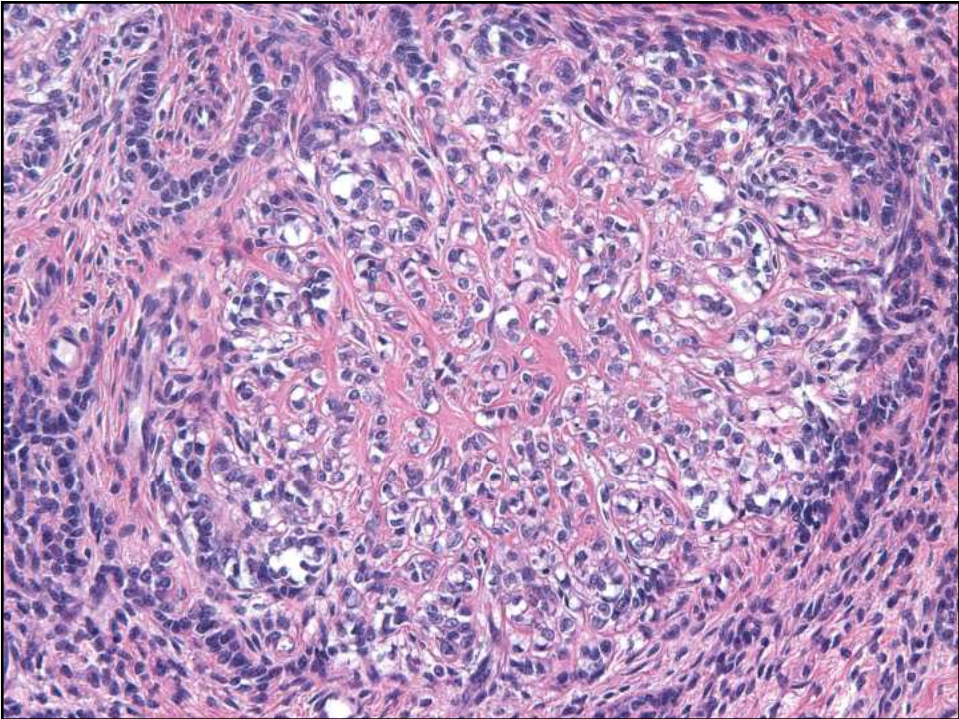
Smooth Muscle Actin

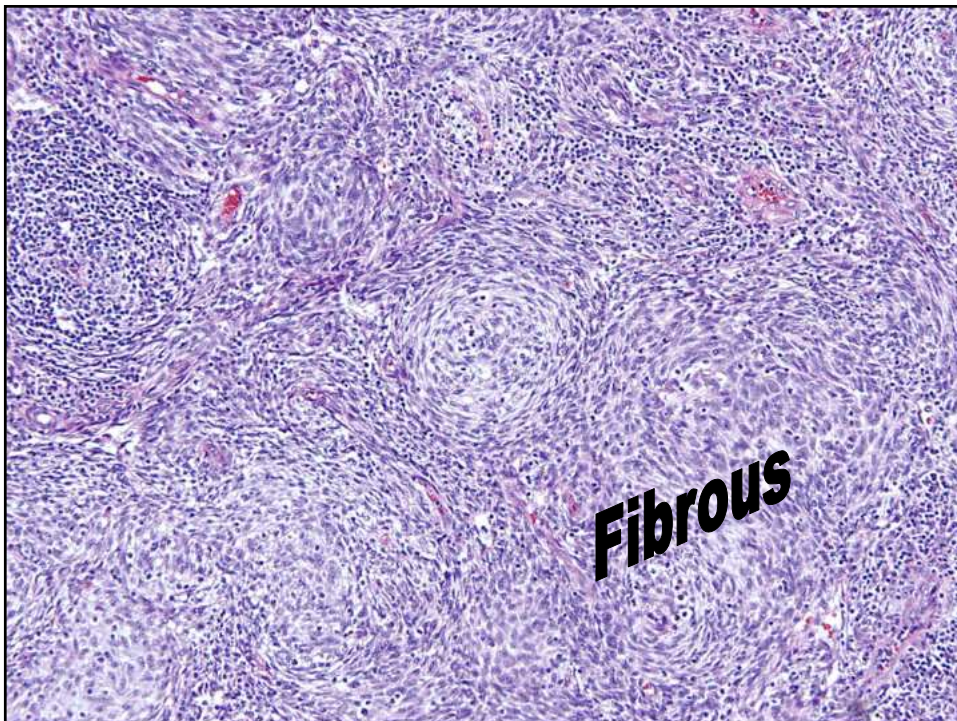
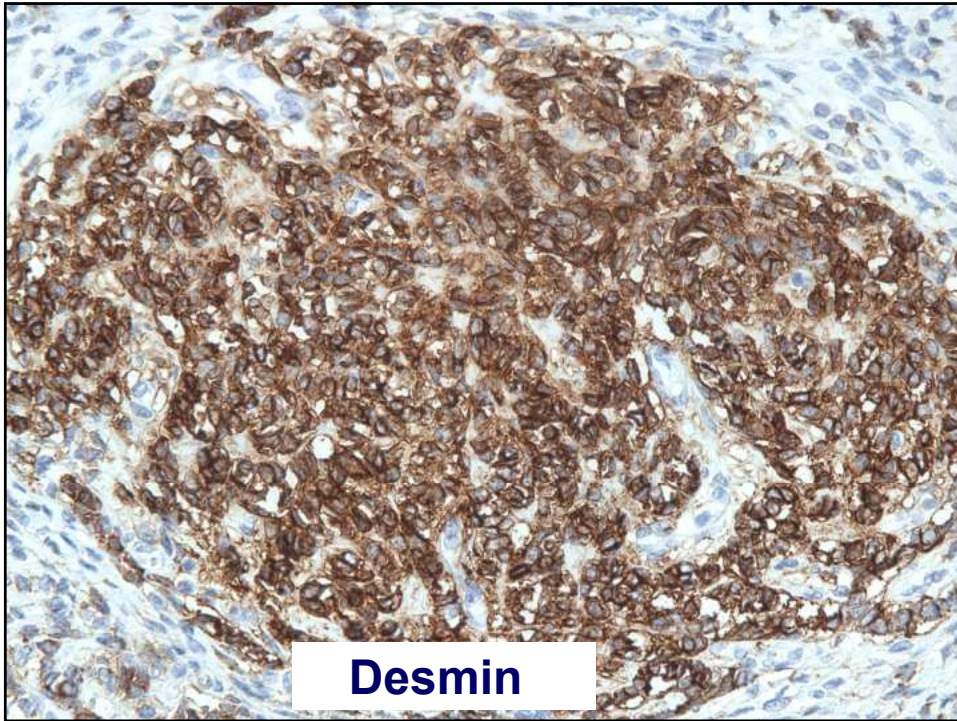


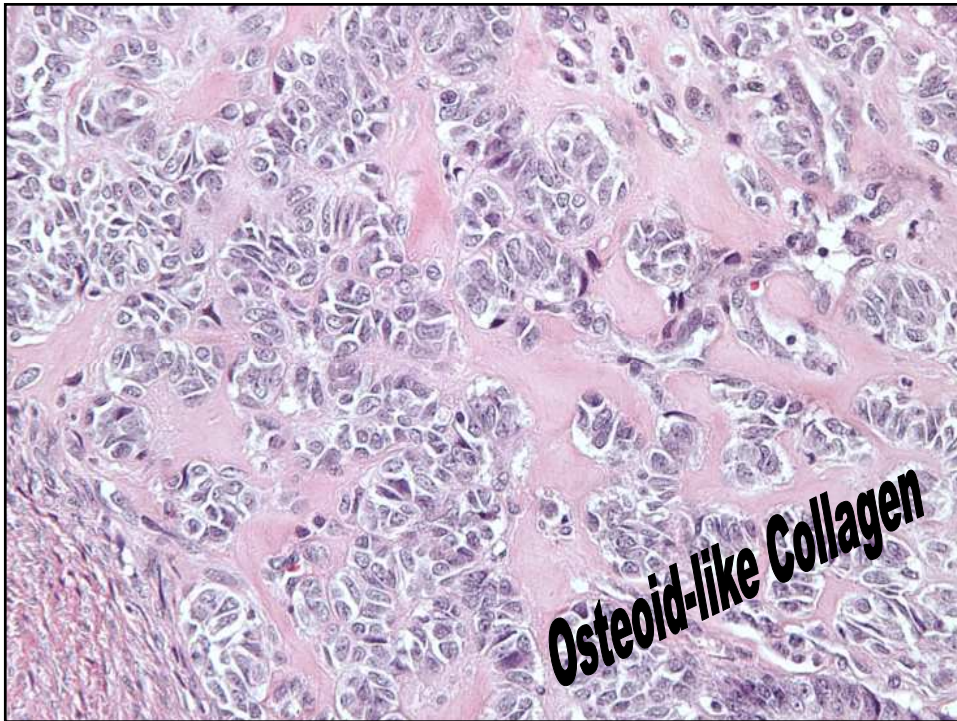
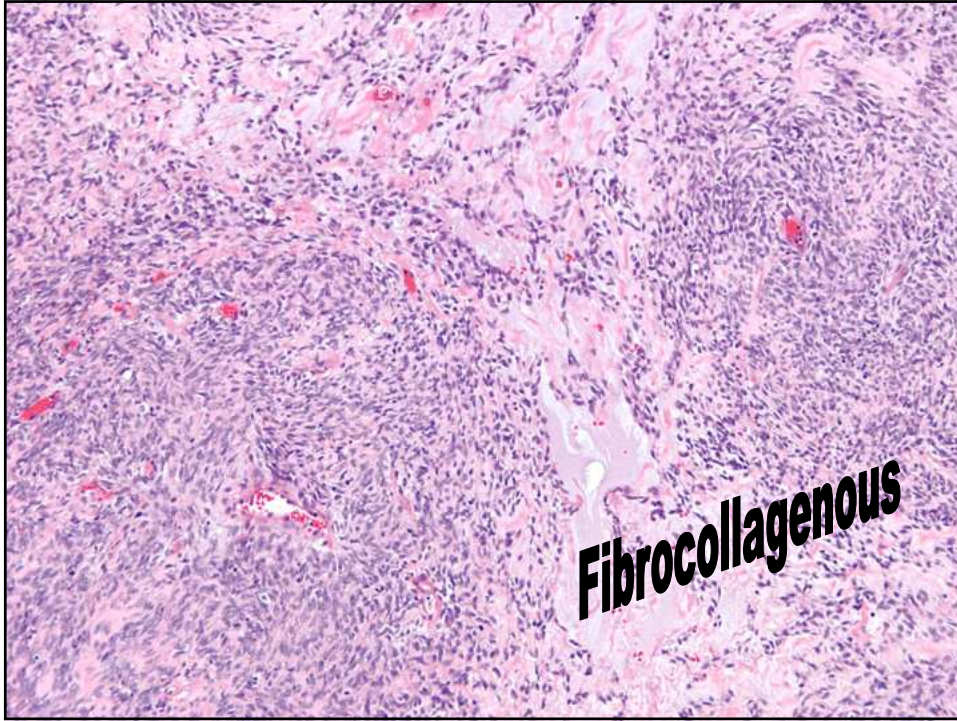


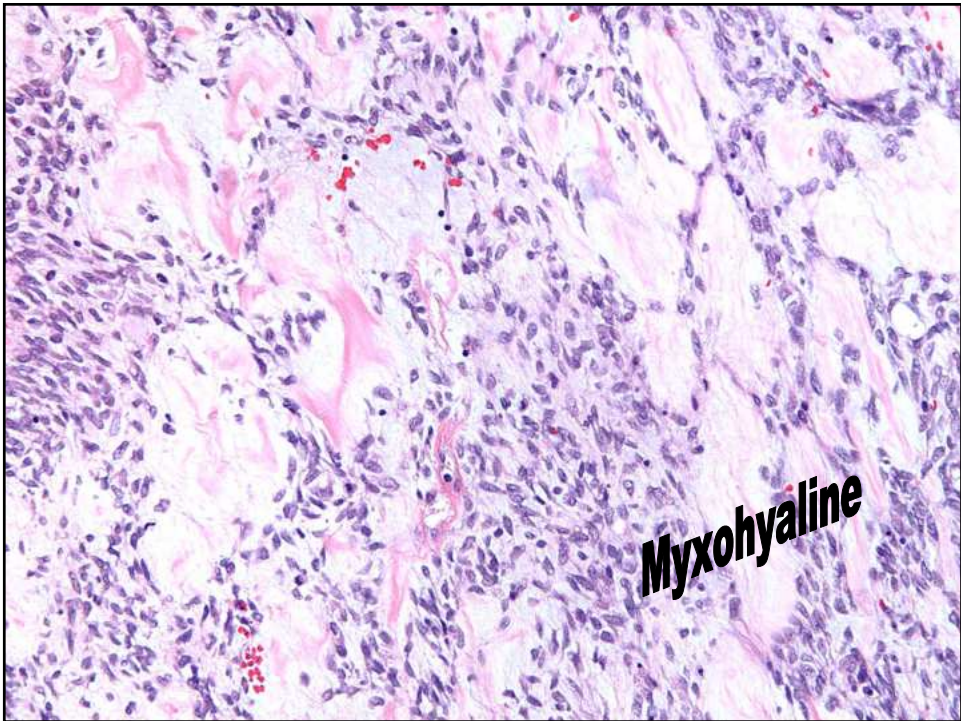
Alternate Differentiation In Endometrial Stromal Tumors

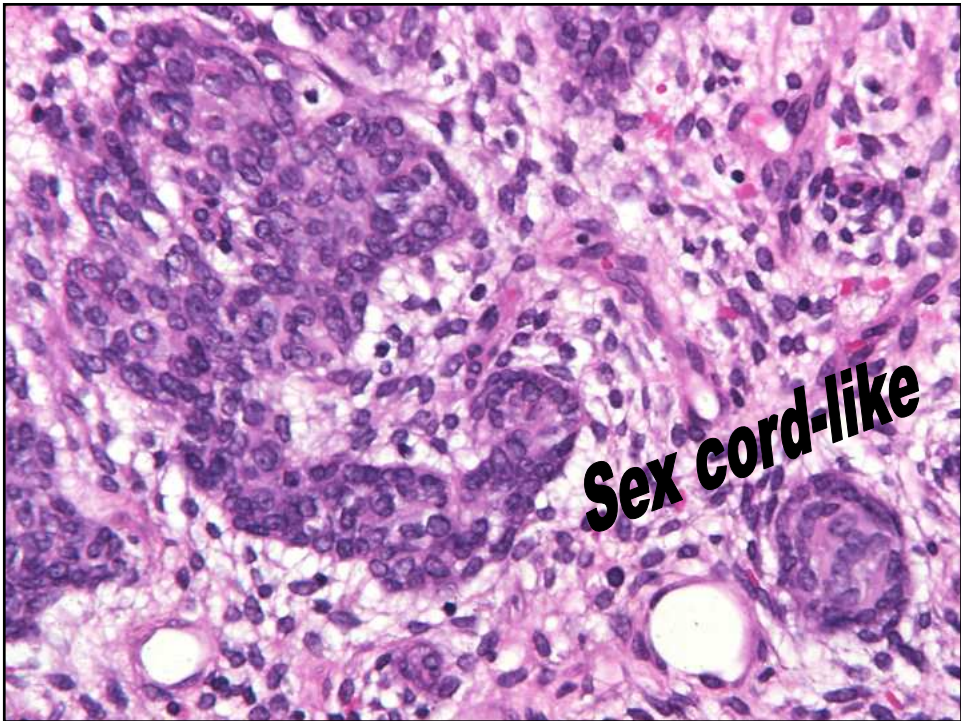
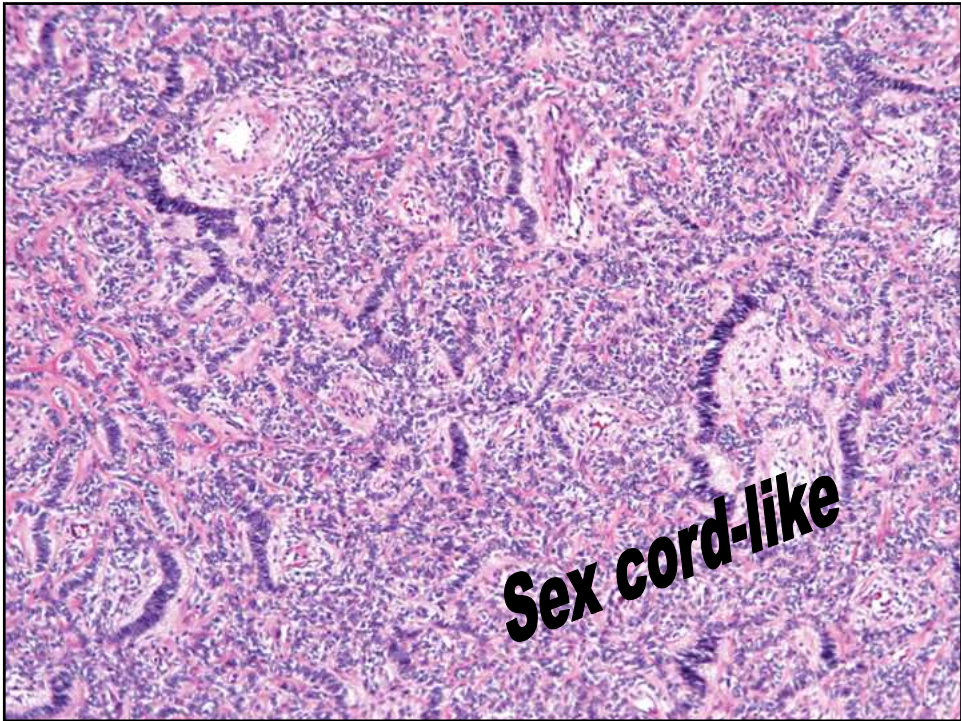
- Smooth muscle
- Fibrous
- Myxoid
- Sex cord-like
- Epithelioid
- Glandular elements

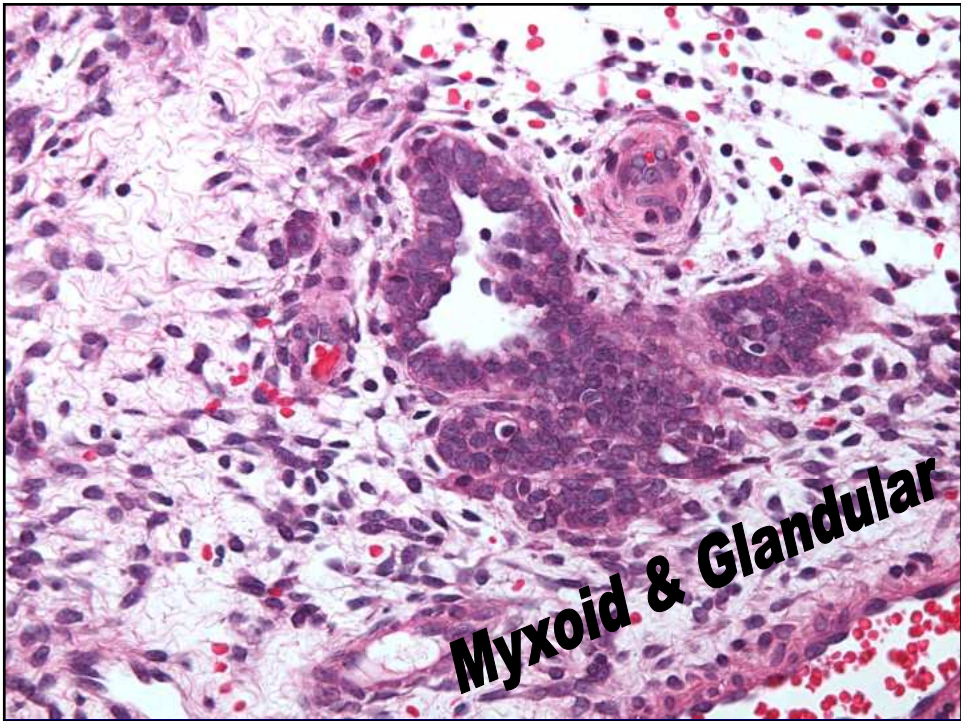
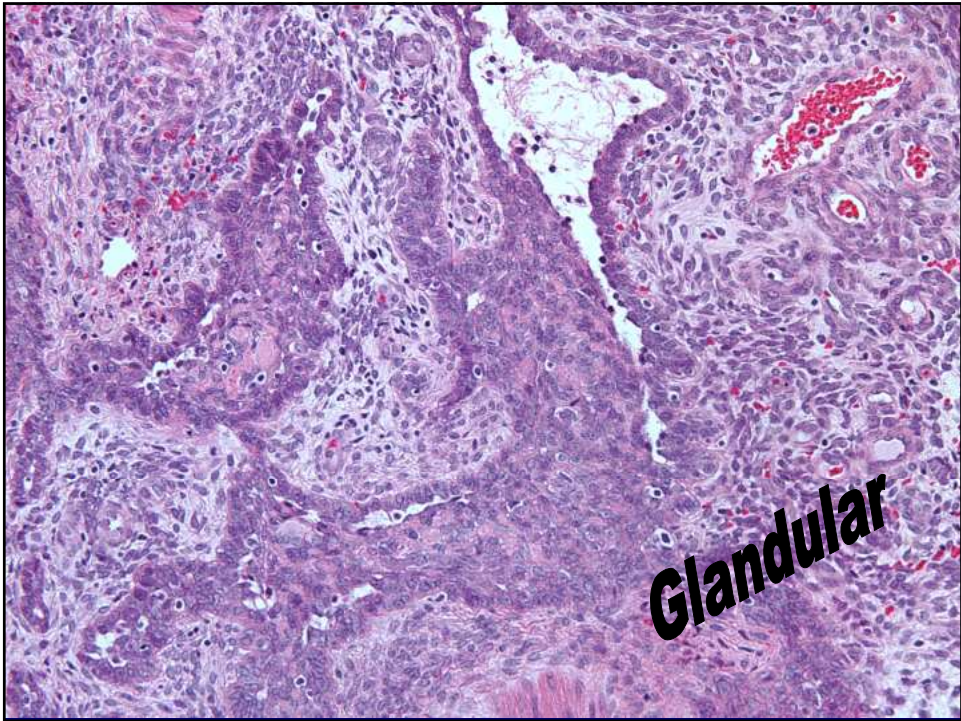


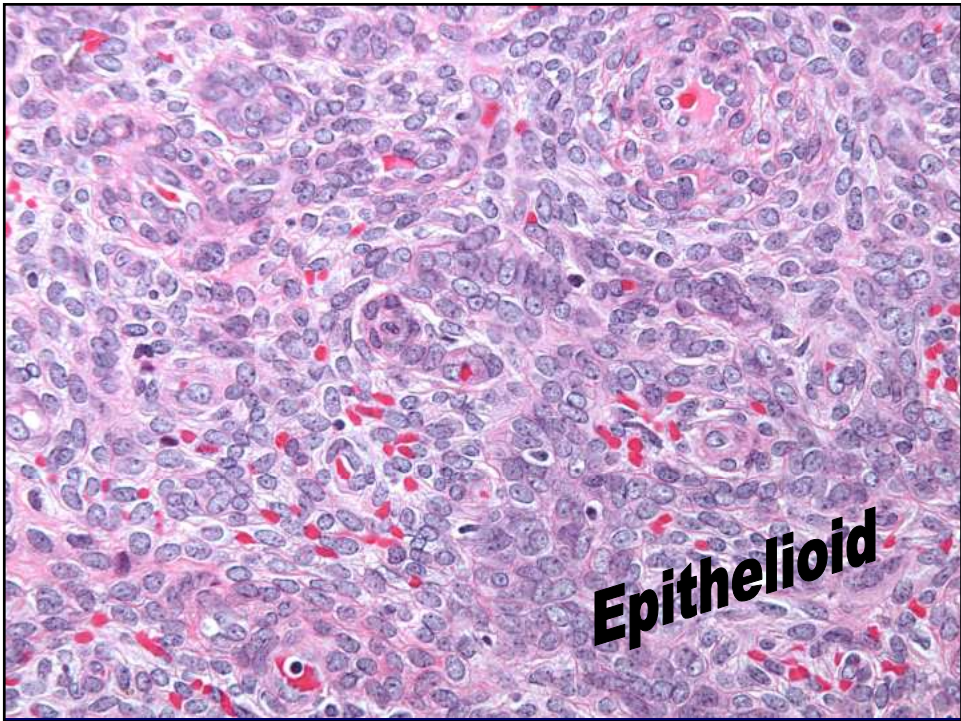
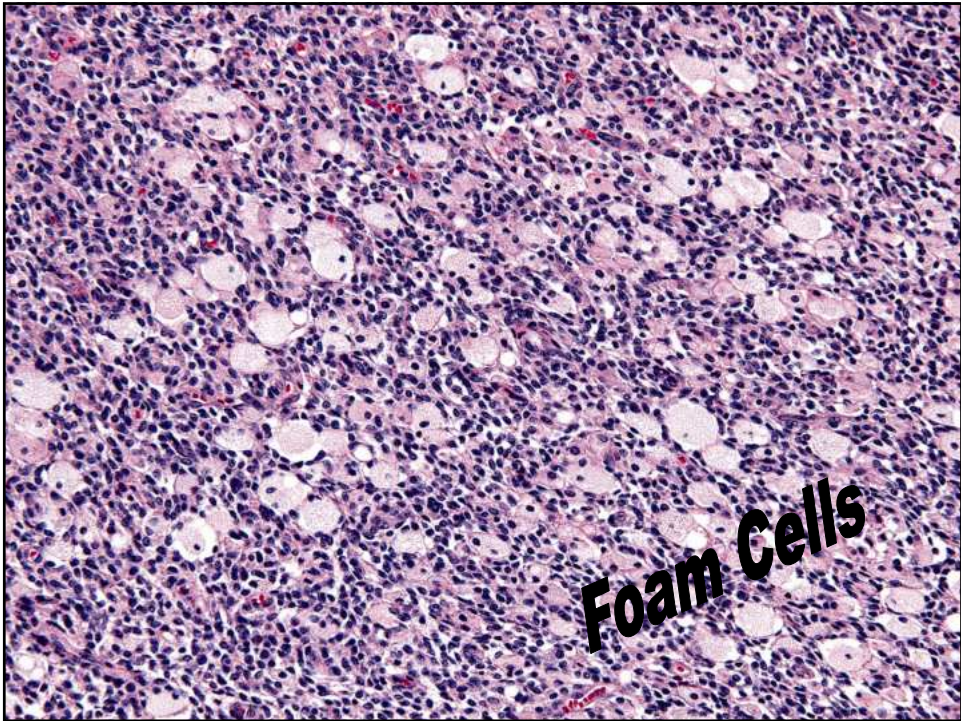


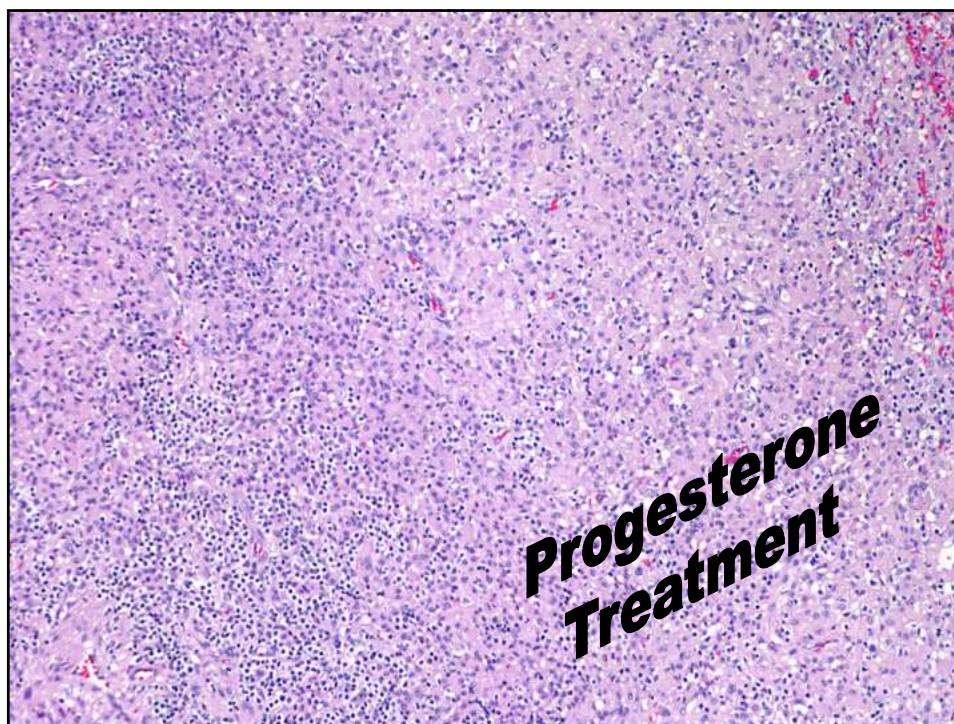












JAZF1/SUZ12 Gene Fusion

- 75% of stromal nodule
- 50% of LG-ESS (classic type)
- 15% of HG-ESS
- Seen less frequently in variants

Orphanet J Rare Dis. 2016 Feb 16;11:15

Final Diagnosis

Low-grade endometrial stromal sarcoma

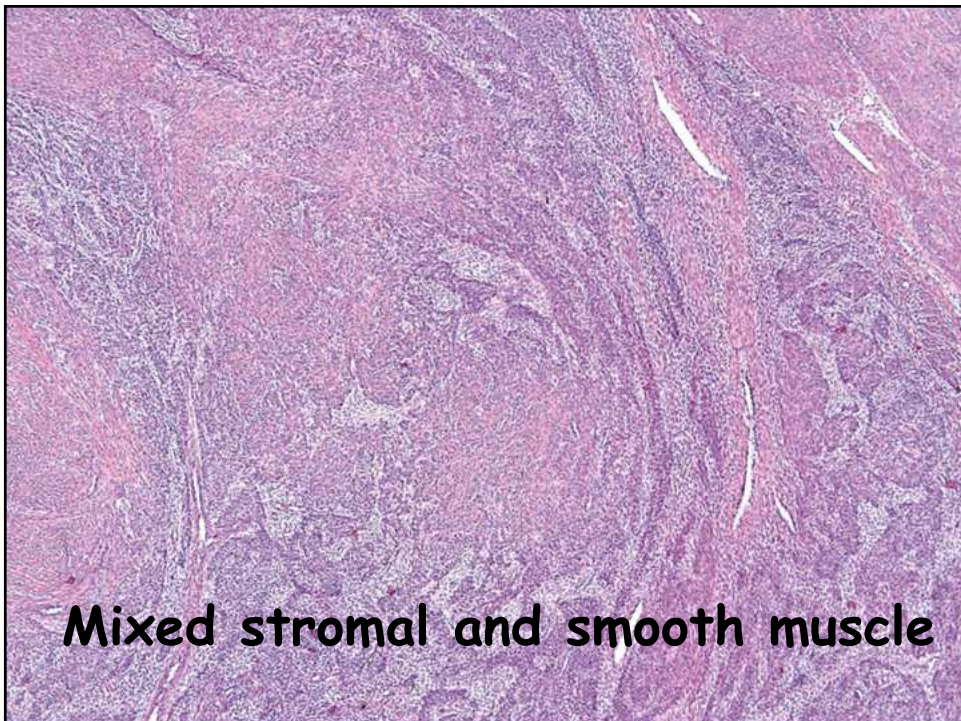
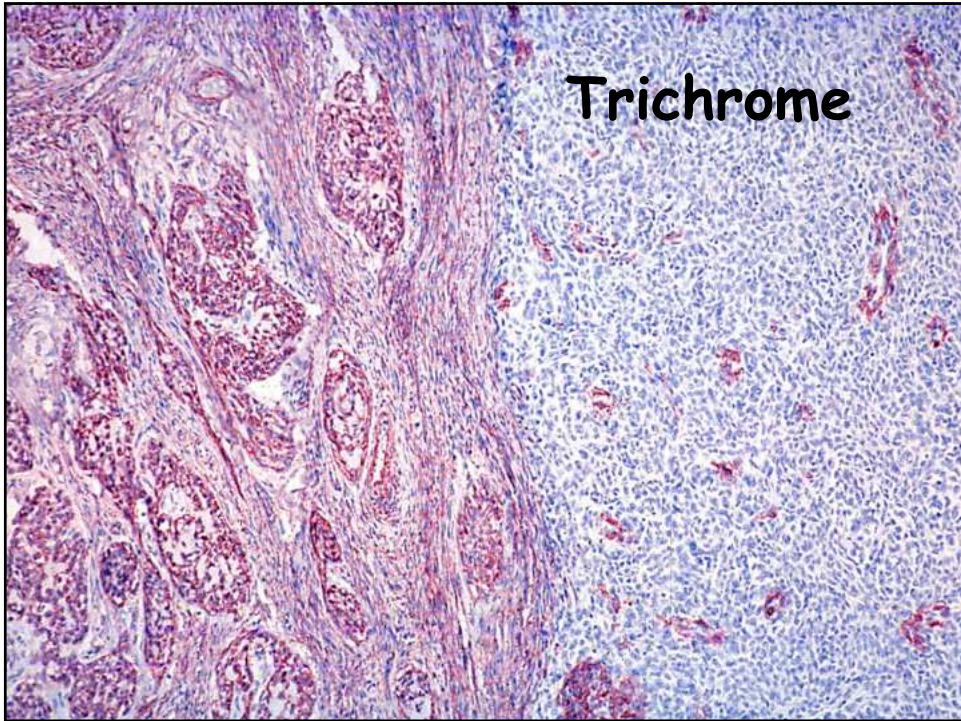
Stromal Tumor With Smooth Muscle Differentiation vs Stromomyoma

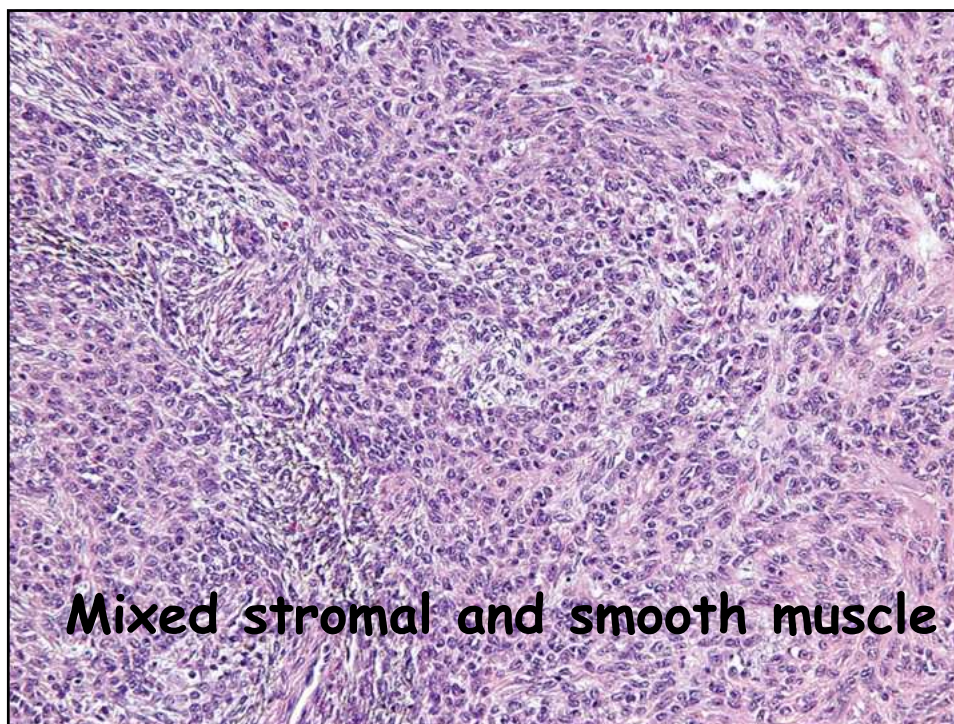
- Tough enough when entire lesion is present for evaluation
- Does it matter?
 - Stromal nodule vs leiomyoma → NO
 - Stromal sarcoma vs IVL (or leiomyoma) → YES
- Conventional light microscopy
- Immuno: CD10, desmin, caldesmon
- If ambiguous →
Act as if endometrial stromal differentiation

Mixed Endometrial Stromal Smooth Muscle Tumors: The Evidence

- Definition: >30% smooth muscle component
- Smooth muscle component is typically benign in appearance → These can recur!
- If recurrent, one or both components may be present
- Therefore, best to diagnose & treat the endometrial stromal component – i.e., stromal nodule vs sarcoma

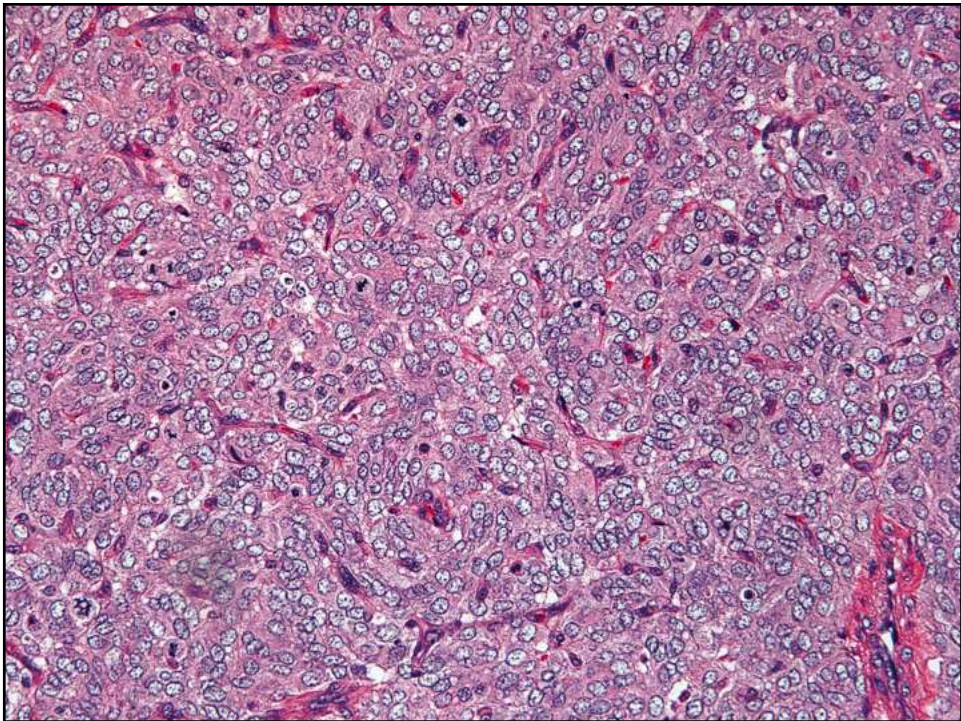
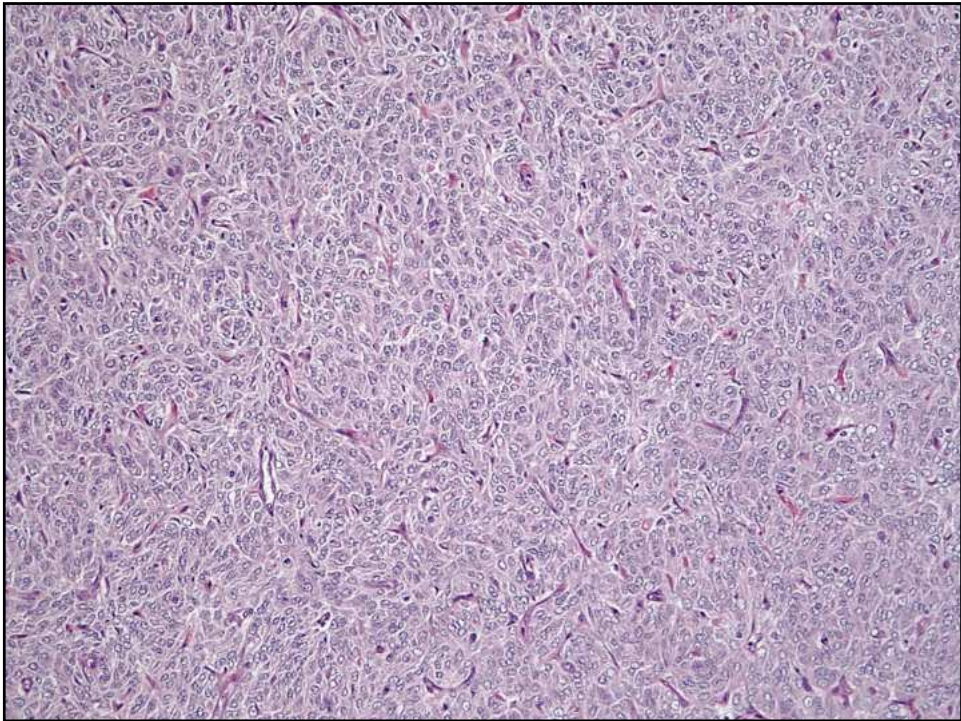


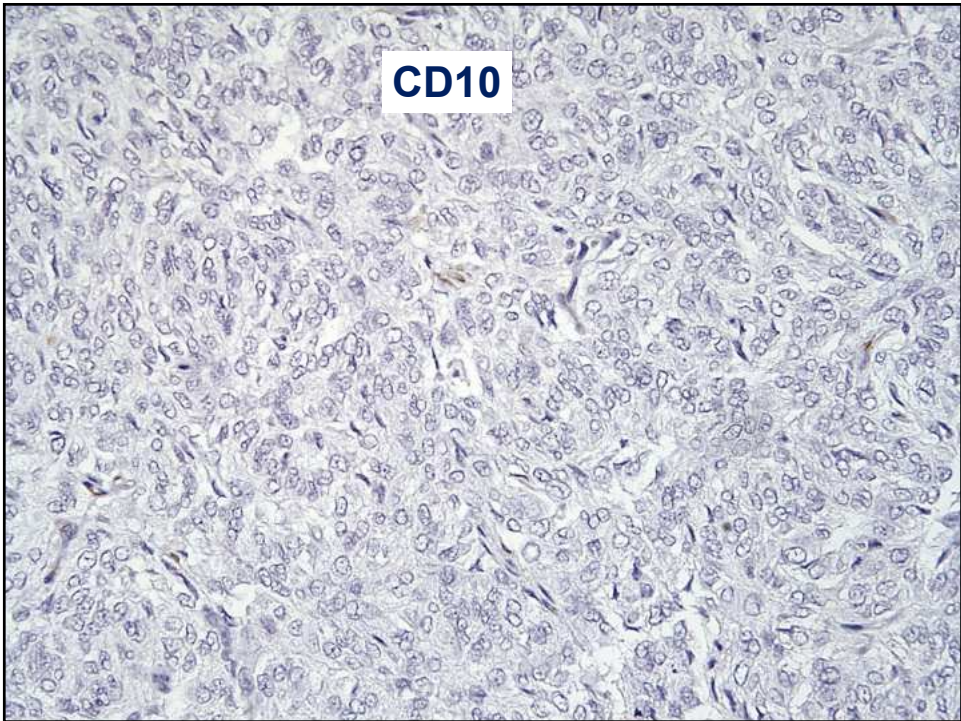
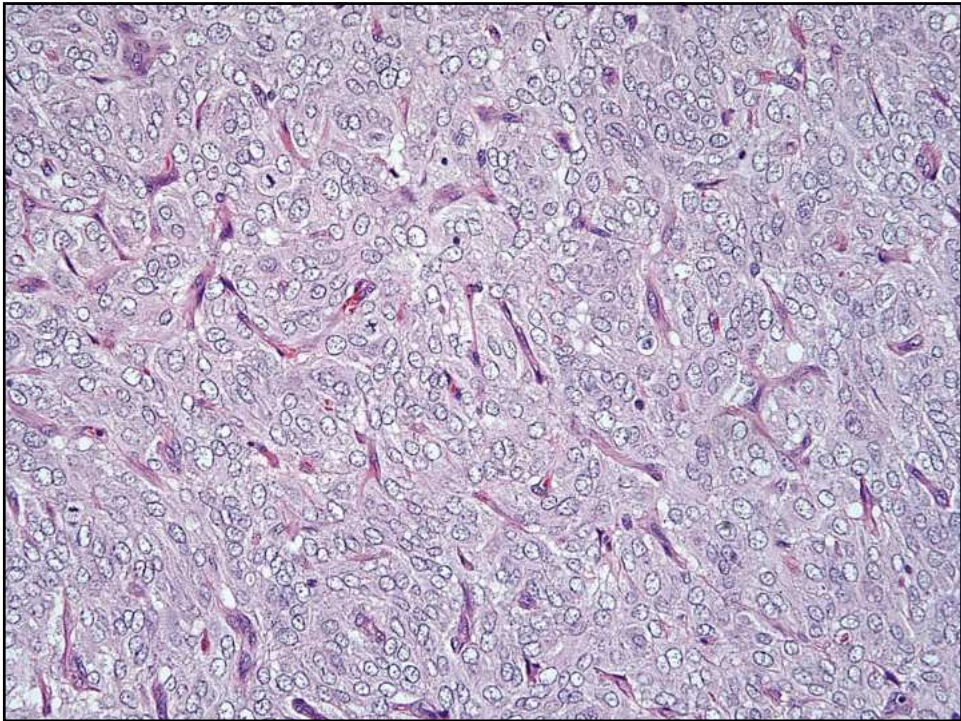


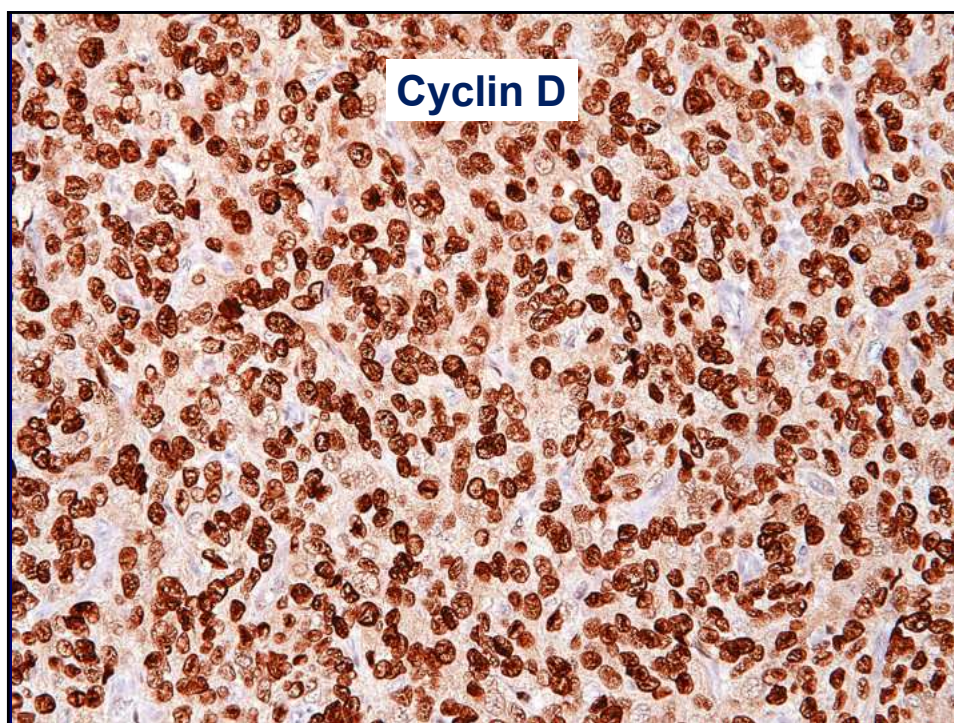


Case Presentation

53-year-old with uterine mass undergoes myomectomy







High-Grade Endometrial Stromal Sarcoma

- Round cell morphology but high-grade
- May have low-grade fibromyxoid spindle cell component
- Mitotic index usually >10 per 10 HPFs

High-Grade Endometrial Stromal Sarcoma

- Cyclin D in high-grade component
- CD10, ER, & PR in low-grade component
- *YWHAE/NUTM2* fusion
- Intermediate prognosis

Final Diagnosis

High-grade endometrial stromal sarcoma
with *YWHAE/NUTM2* fusion

High-Grade Endometrial Stromal Sarcoma: Take 2

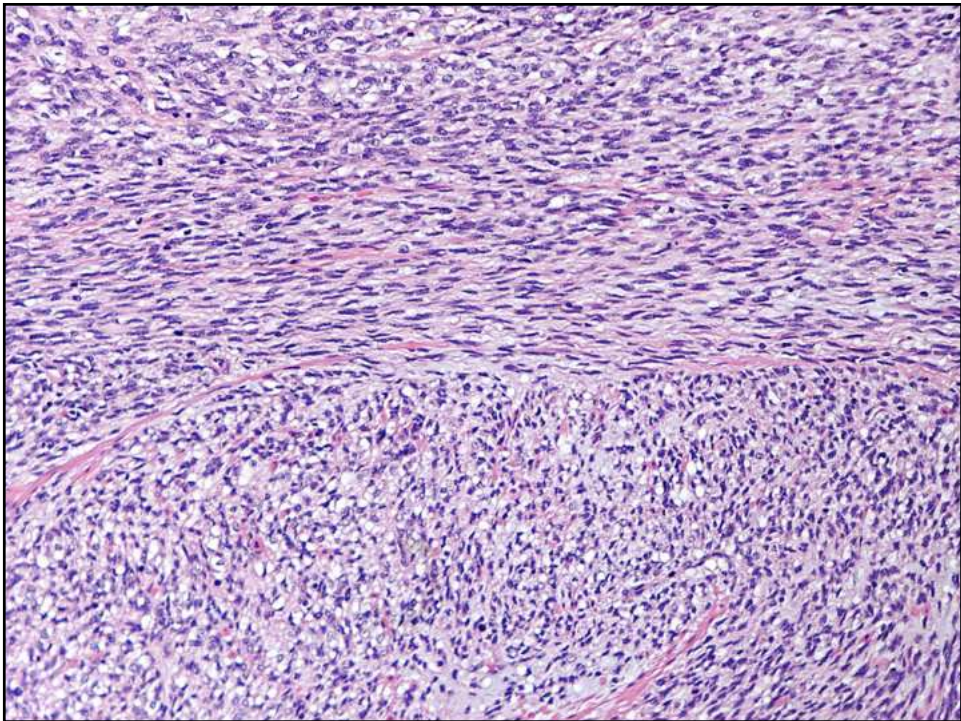
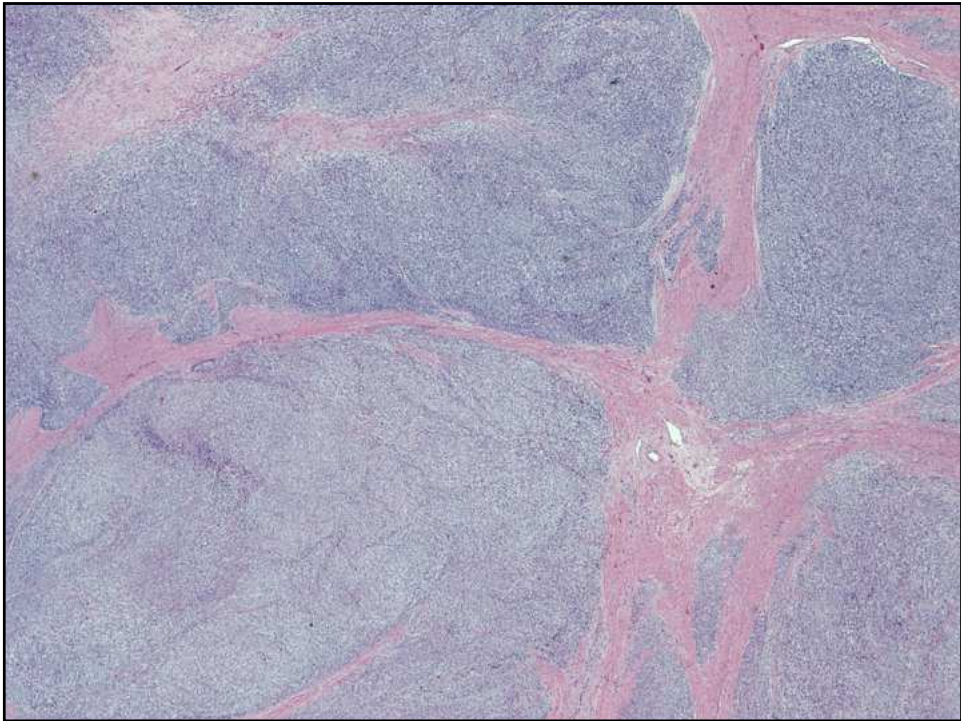
- Uniformly cellular fascicles of spindle cells
- Mild to moderate nuclear atypia
- Myxoid matrix (82%) & collagen plaques (47%).
- Mitotic index $\geq 10/10$ high-power fields

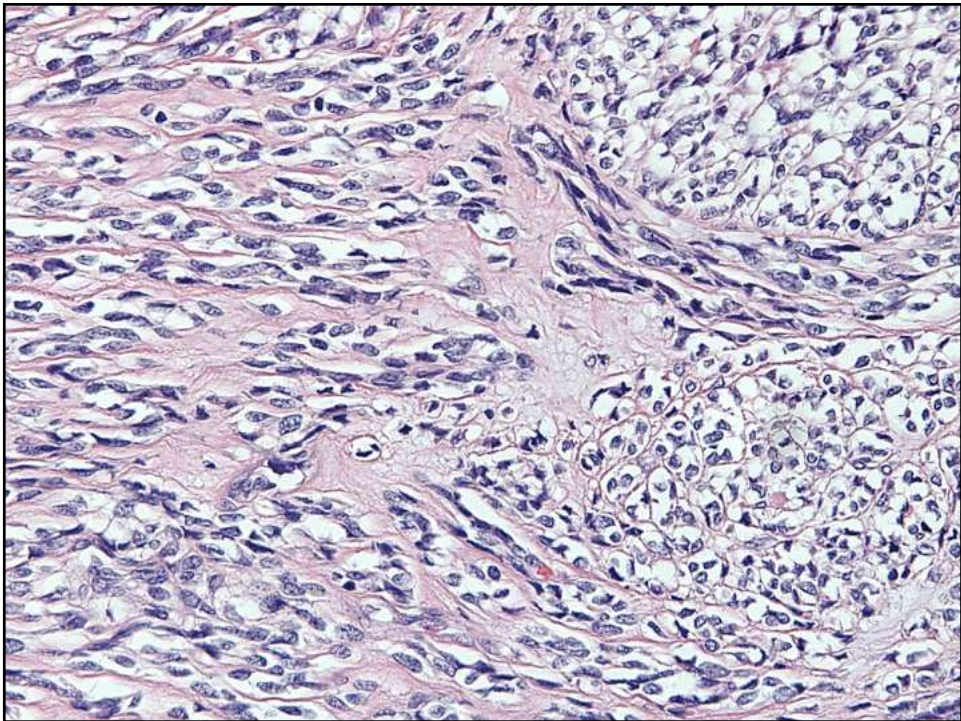
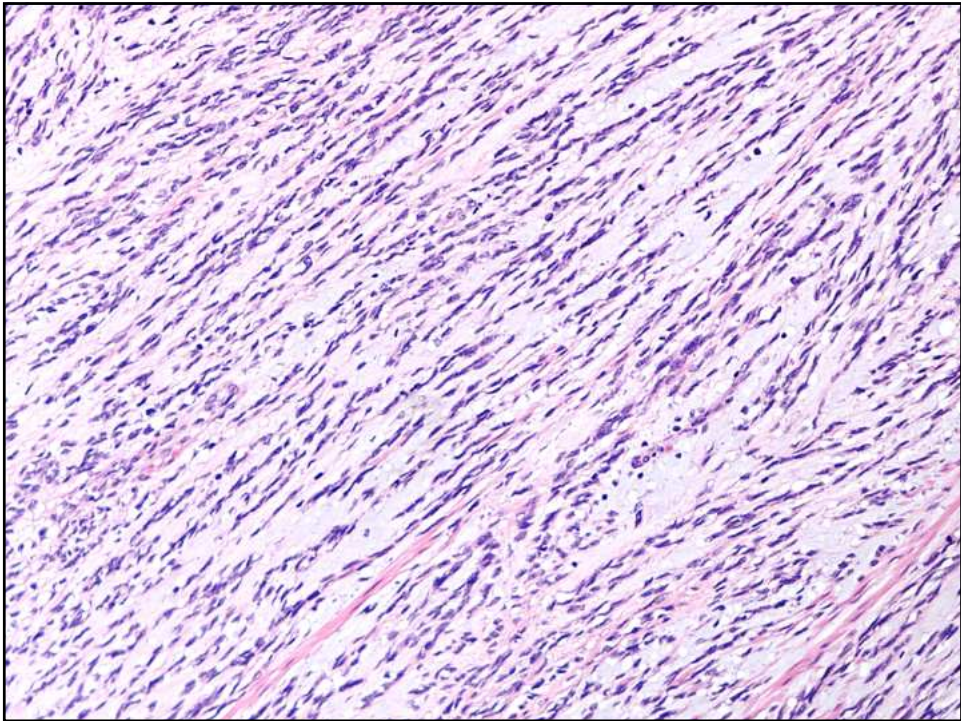
Am J Surg Pathol 2017;41:12-24

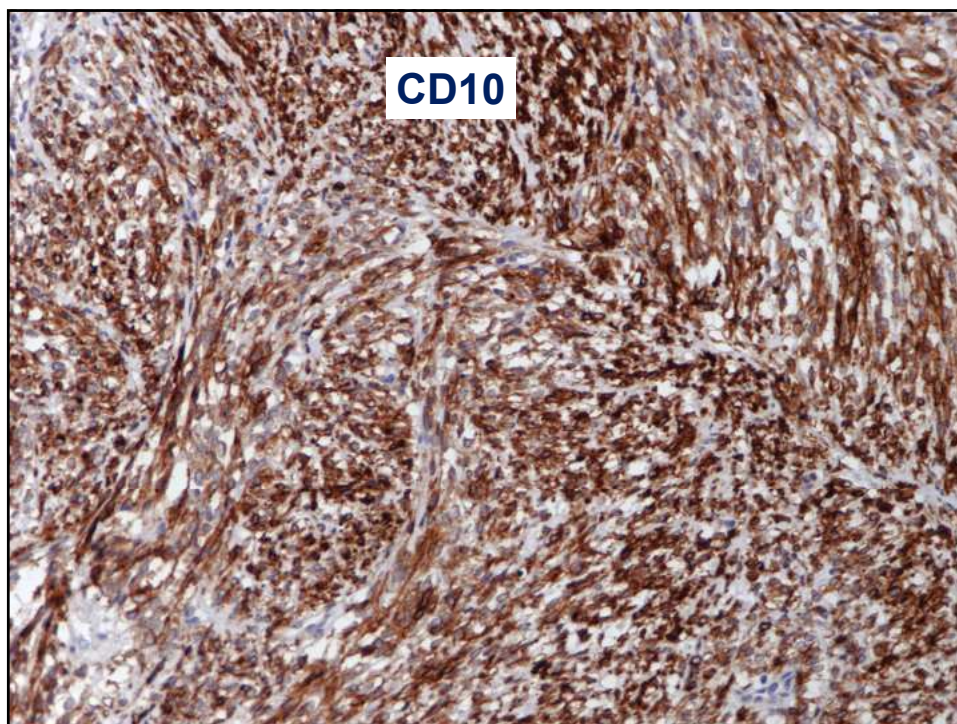
High-Grade Endometrial Stromal Sarcoma: Take 2

- CD10, cyclin D1, BCOR
- *ZC3H7B-BCOR* gene fusion
- Aggressive clinical course (?)

Am J Surg Pathol 2017;41:12-24





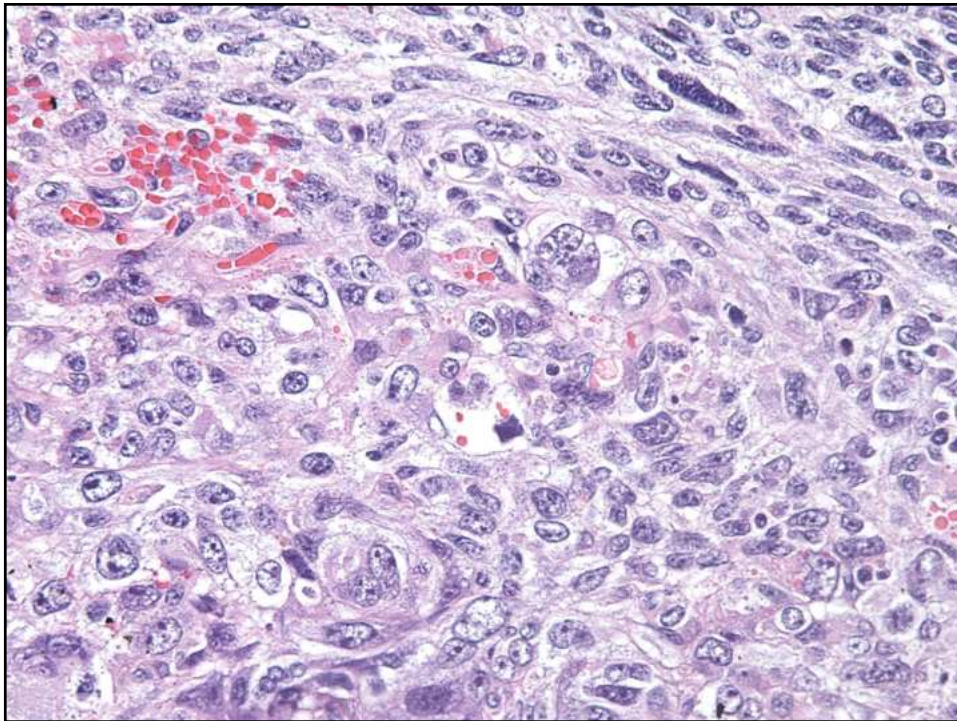


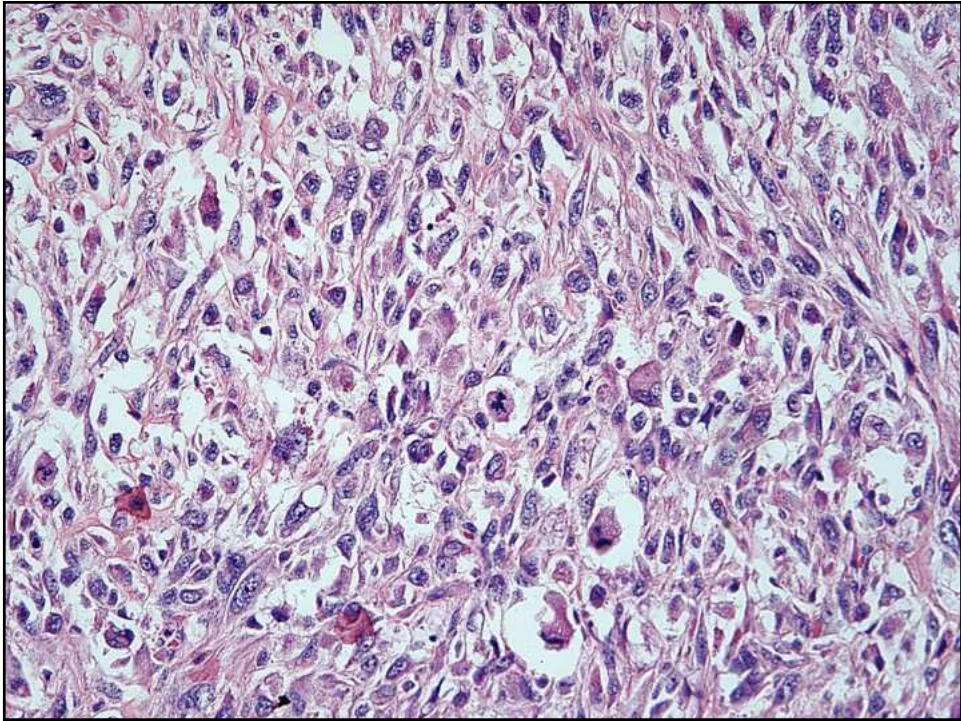
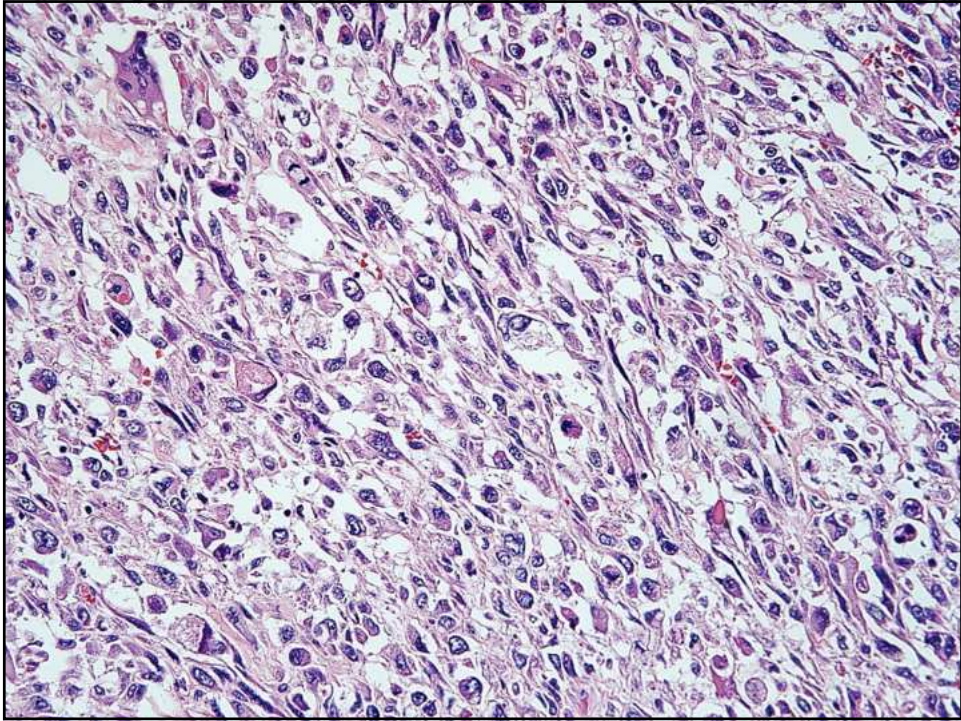
Undifferentiated Uterine Sarcoma

- No histologic evidence of smooth muscle, endometrial stromal or epithelial differentiation
- High grade
- High mitotic index
- Subset may express CD10, but this does not warrant classification as endometrial stromal sarcoma
- Highly aggressive

Undifferentiated (High Grade) Uterine Sarcoma

- A subtype of endometrial stromal sarcoma (?)
- Diagnosis of exclusion: MMMT, adenosarcoma, undifferentiated carcinoma, sarcomas exhibiting specific differentiation (e.g., leiomyosarcoma, osteosarcoma, rhabdomyosarcoma), lymphoma, leukemia, etc





Undifferentiated (High Grade) Uterine Sarcoma

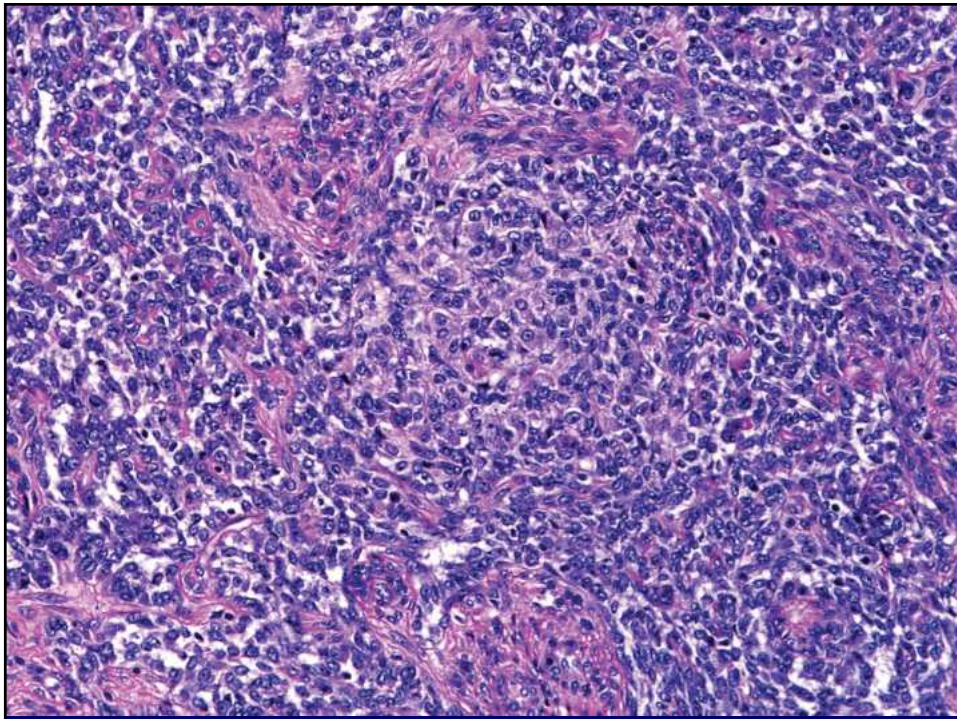
- Typically postmenopausal – vaginal bleeding
- Large, fleshy polyps/masses with necrosis & extensive invasion into myometrium
- Clinically aggressive – poor prognosis
- Not amenable to hormonal therapy

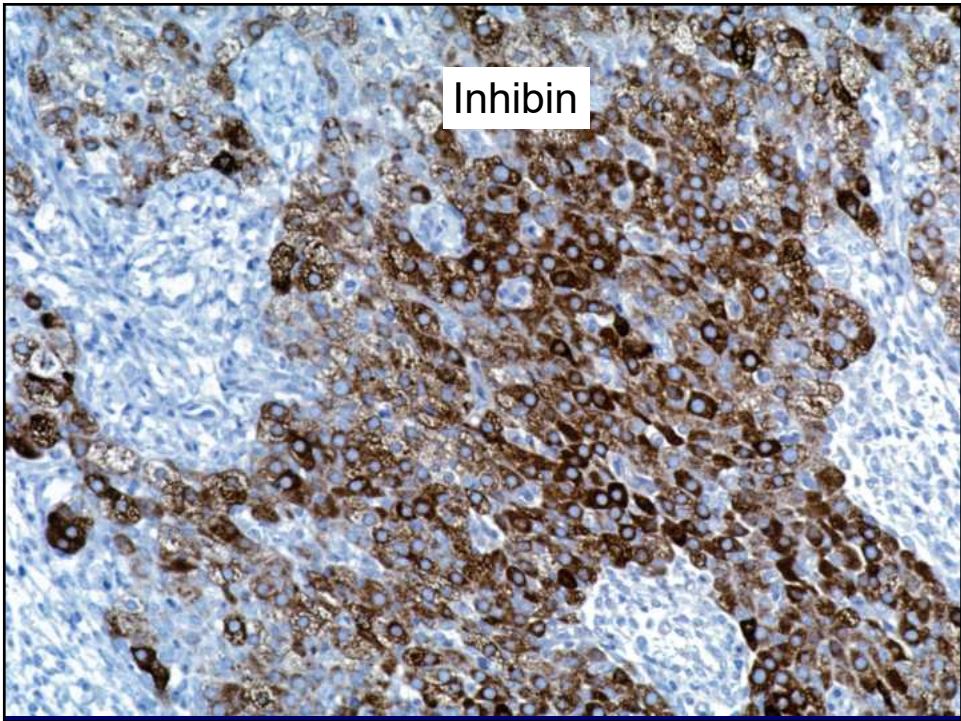
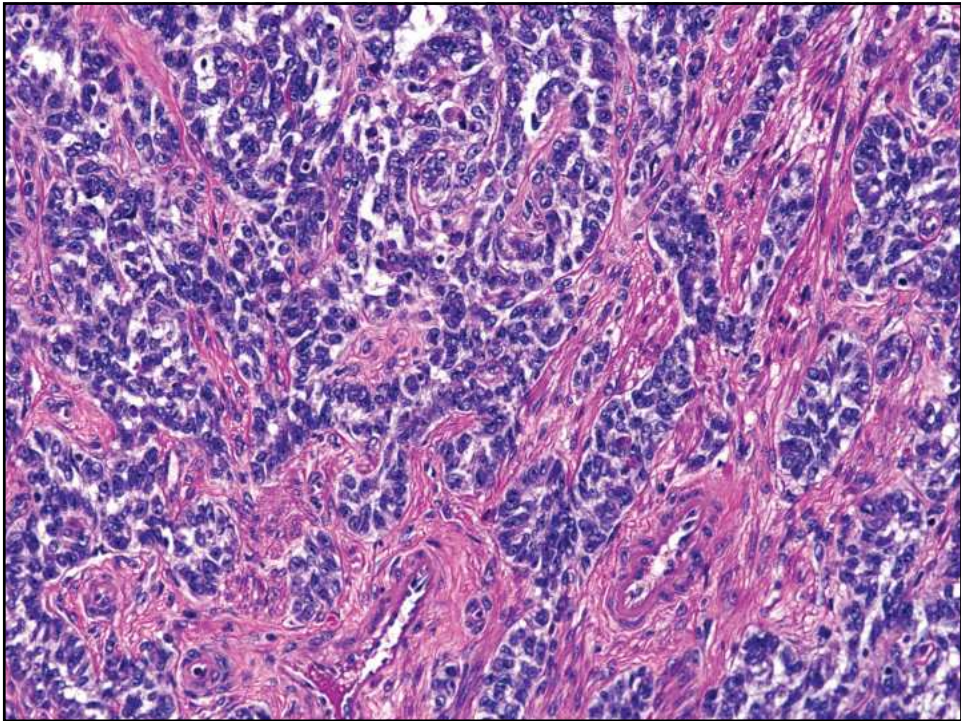
Undifferentiated (High Grade) Sarcoma: Caveats

- On occasion, a low-grade ESS may 'transform' into high-grade sarcoma with undifferentiated areas
- Although this technically qualifies as an endometrial stromal sarcoma, the high-grade undifferentiated element drives prognosis

Case Presentation

- 48-year-old with uterine mass



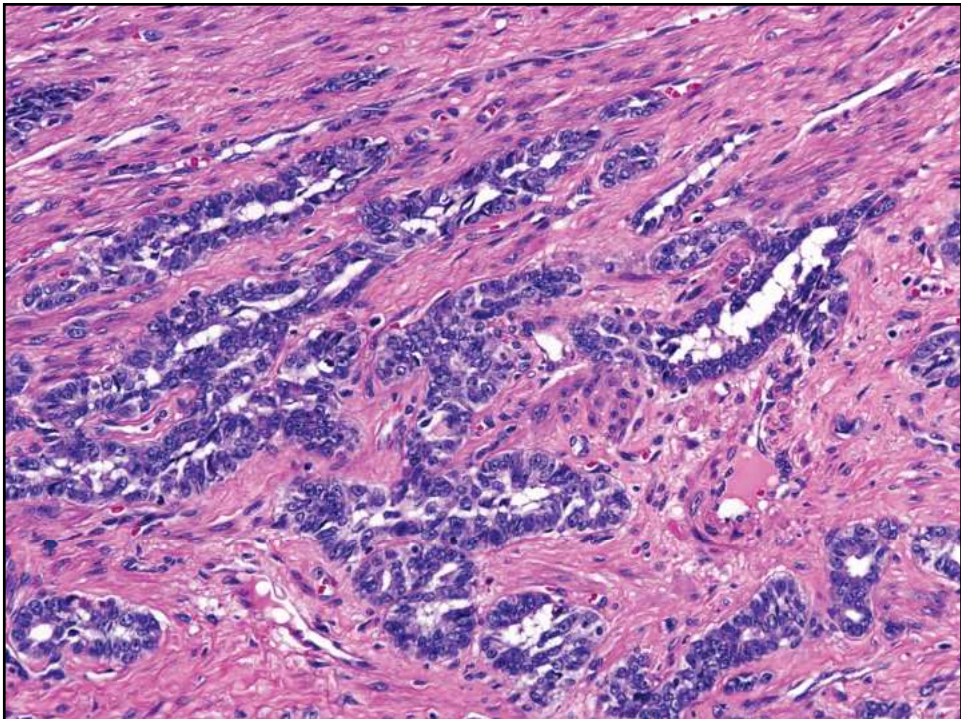
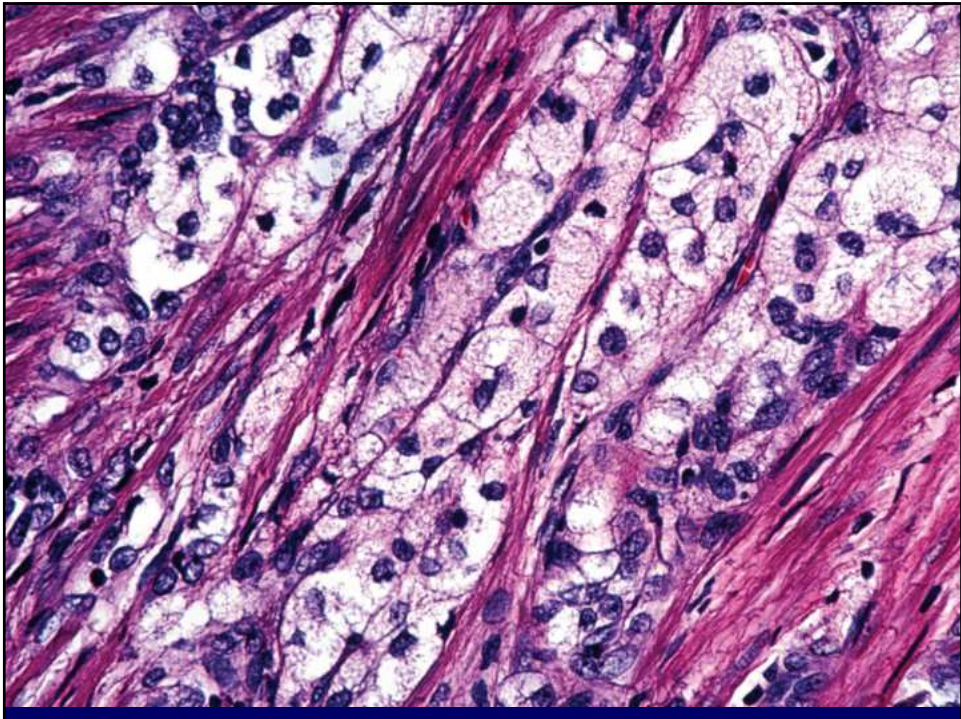


Diagnosis?

- Endometrial stromal nodule
- Cellular leiomyoma
- Low-grade endometrial stromal sarcoma
- Other?

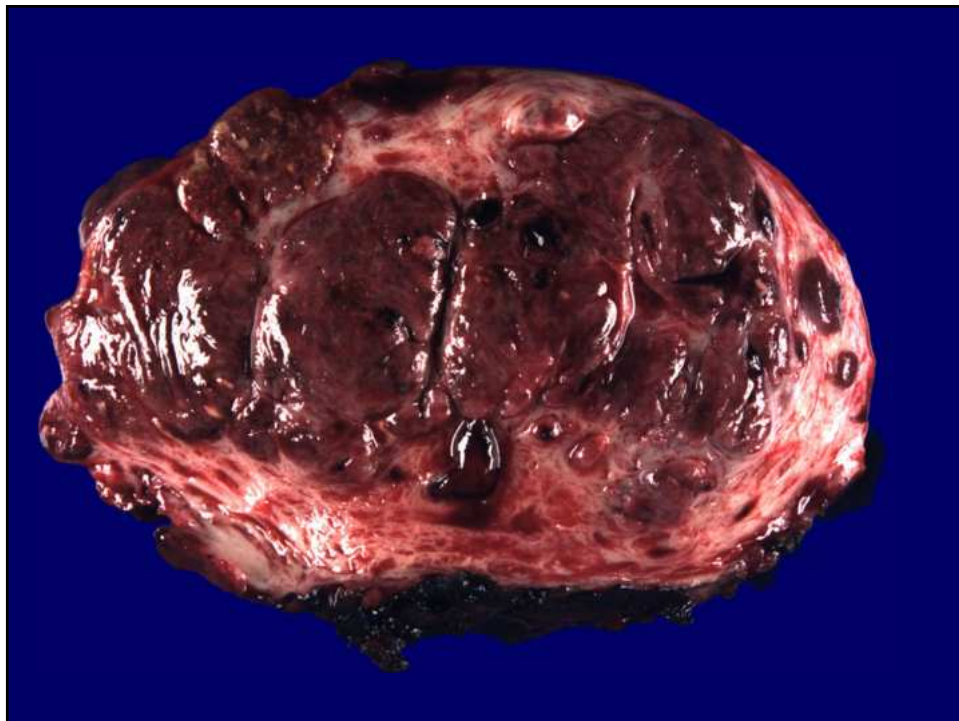
Uterine Tumor Resembling Ovarian Sex Cord-Stromal Tumor

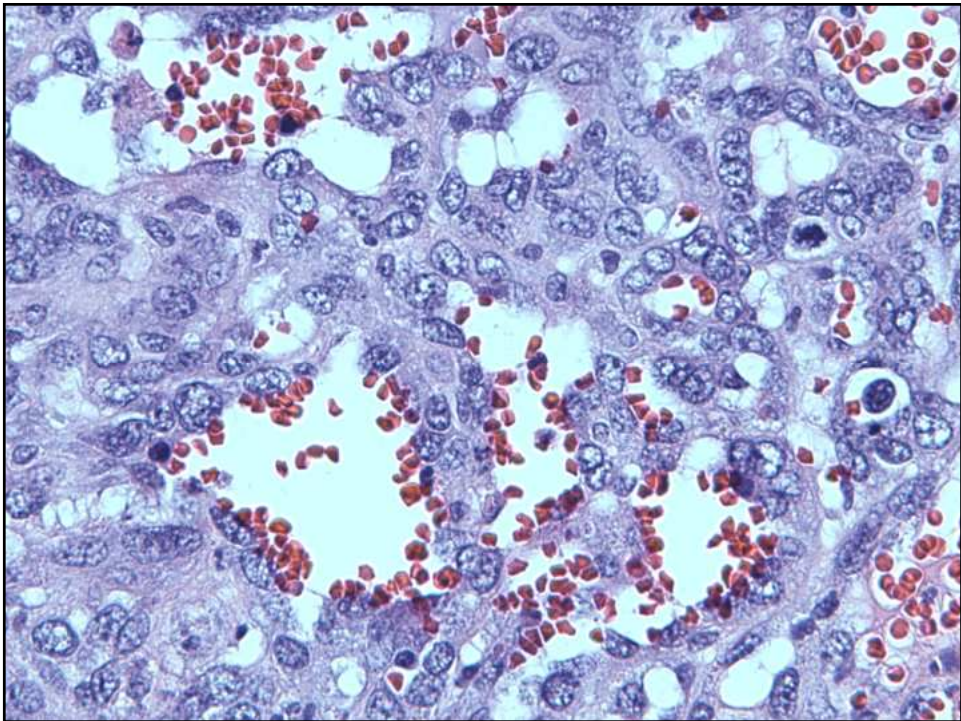
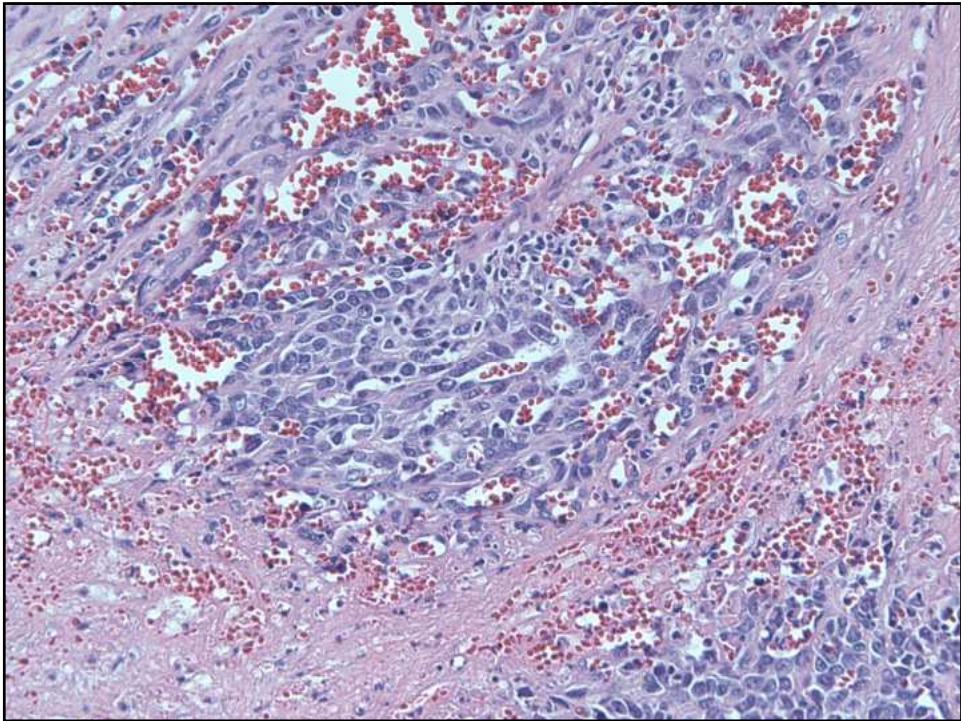
- May express inhibin, calretinin, desmin, actin, cytokeratin – polyphenotypic
- No endometrial stromal component – should be CD10 negative
- Uncertain clinical behavior – most, but not all are clinically benign

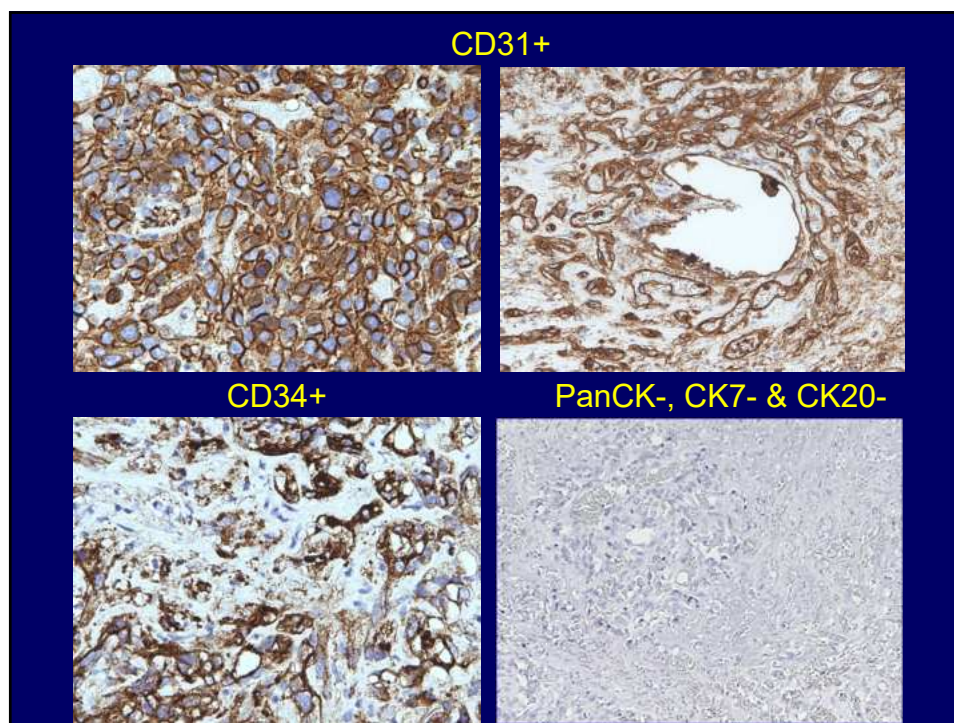


Case Presentation

- 43-year-old with large uterine mass concerning for leiomyosarcoma







Uterine Angiosarcoma

- Less than 25 reported cases in the literature – considered one of the rare non-muscle homologous sarcomas to arise in uterus
- Age range: 17 to 81 years, but most in perimenopausal or postmenopausal women
- Extrauterine spread to ovarian and other pelvic sites (but not lymph nodes) is common at diagnosis
- Poor prognosis

Am J Surg Pathol 1998; 22:246-250.

Uterine Angiosarcoma

- Associated with ovarian and tubal angiomatosis in one patient
- Prior exposure to radiation for cervical squamous cell carcinoma in one patient
- Associated with leiomyoma in ? patients

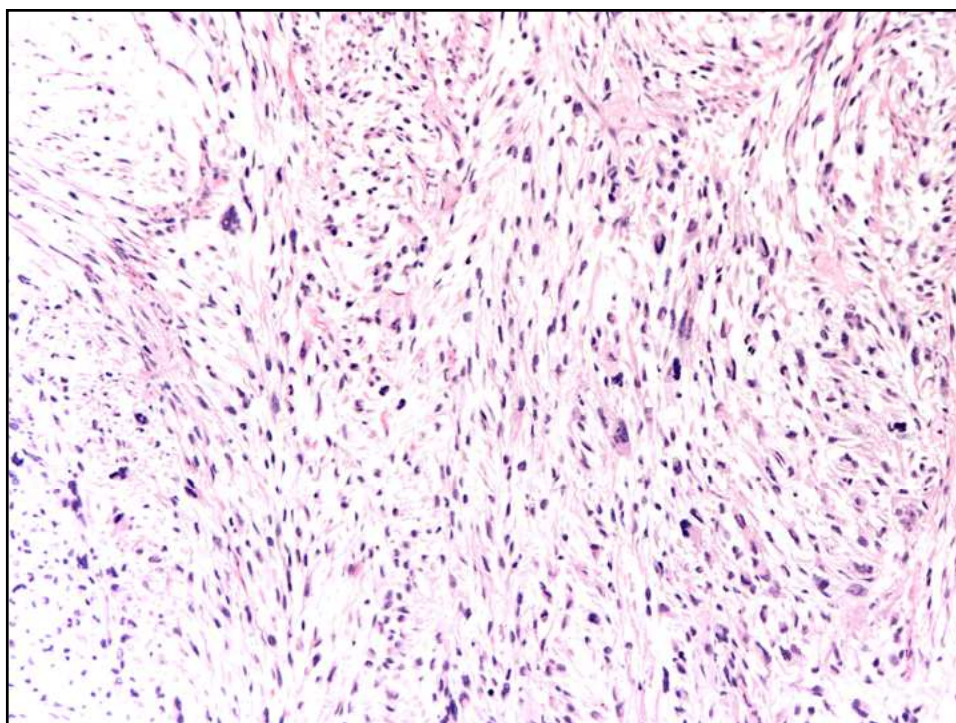
Am J Surg Path 1998; 22:246-250.

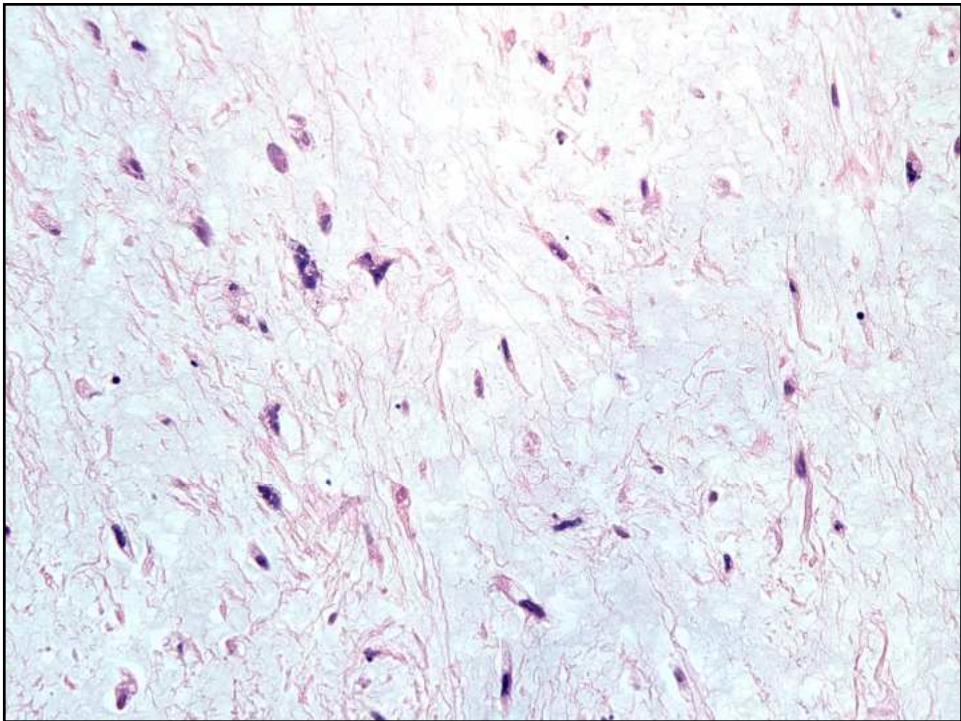
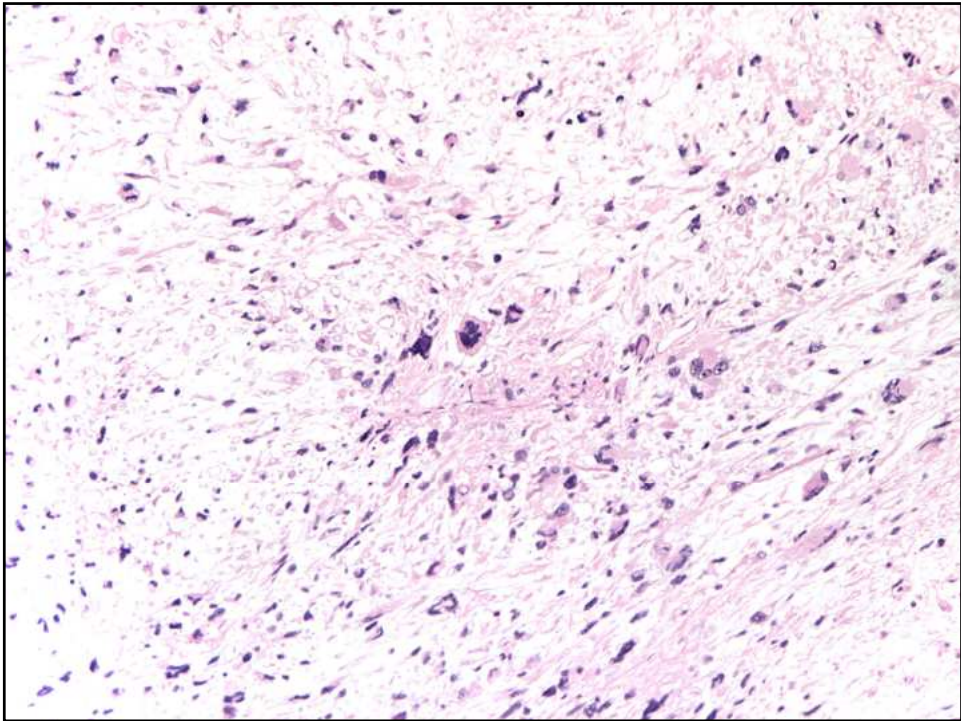
Final Diagnosis

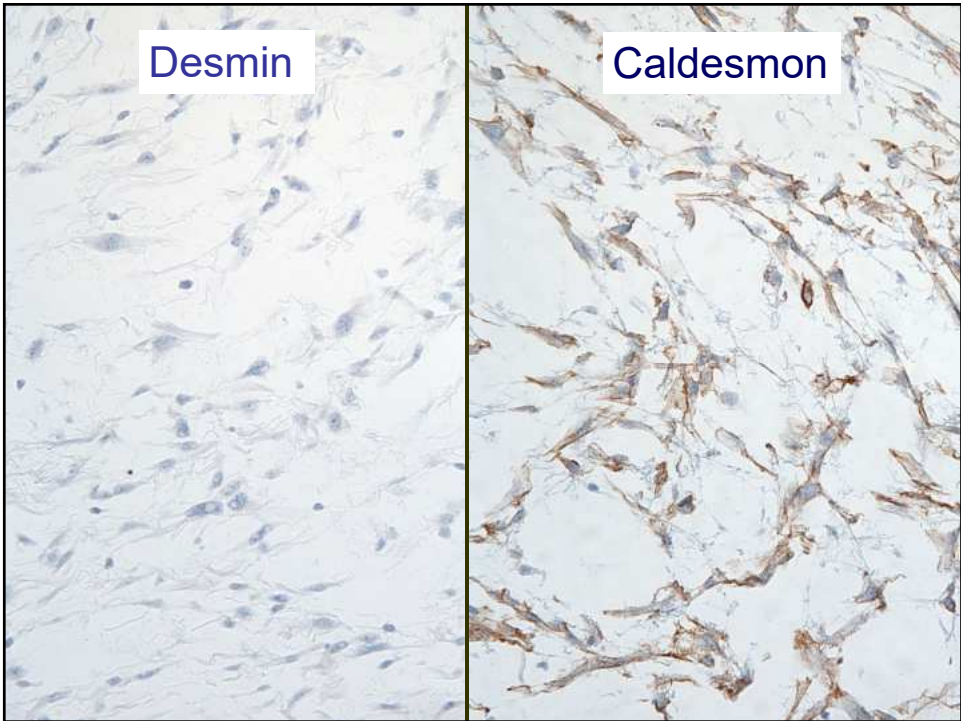
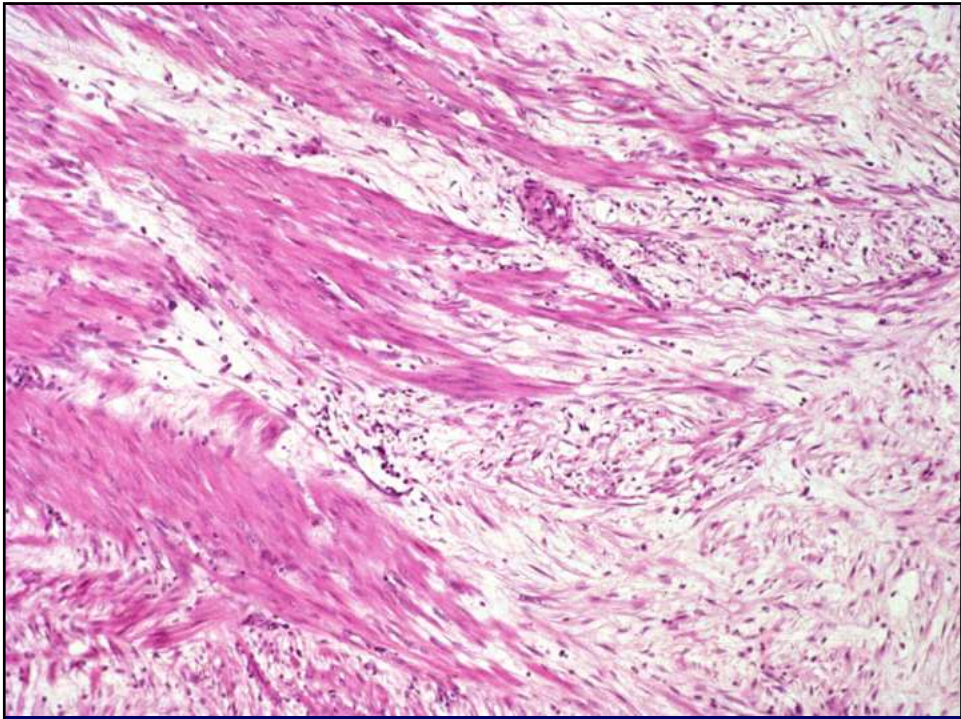
Uterine high-grade angiosarcoma

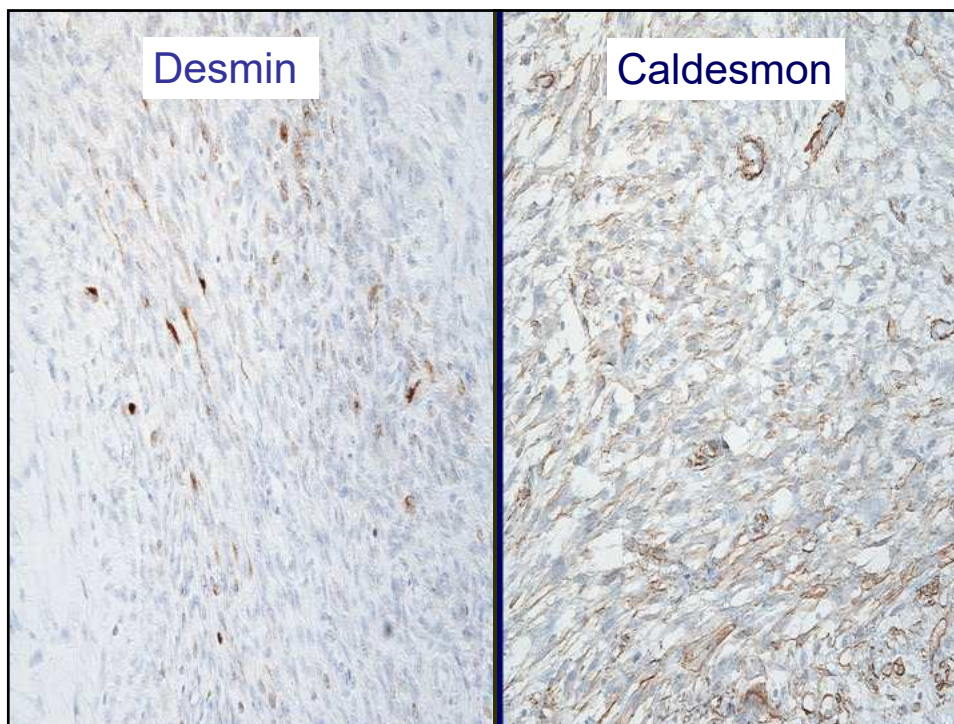
Case Presentation

32-year-old with 3.5 x 3.0 x 2.9 mucinous, "necrotic" polyp protruding through cervix









Diagnosis?

- Myxoid leiomyosarcoma
- Myxoid leiomyoma
- Leiomyoma with myxoid degeneration
- Inflammatory myofibroblastic tumor
- STUMP
- Sarcomatous component of adenosarcoma or carcinosarcoma

The Background Issues

- Reproductive age
- Low-grade or high-grade process?
- Can we STUMP or equivocate?

Myxoid Smooth Muscle Tumors: Criteria For Leiomyosarcoma

- Tumor cell necrosis
or
- Moderate to severe cytologic atypia *or*
- Mitotic index ≥ 2 MF/10 HPF

Myxoid Smooth Muscle Neoplasms of the Uterus

		Y ₄	Y ₁₀	Y ₃₀
Severe				
Moderate	■	Y _{1.6}	■ 2.6	✕ 6.6 Y ₁₀
	■ ■ ■ ■		✕ 4	
Mild	■ ■ ■ ■			
None	■ ■ ■ ■		✕ 2.2	Y ₁₀

2

Y = TCN Mitotic index: mf/10 hpf

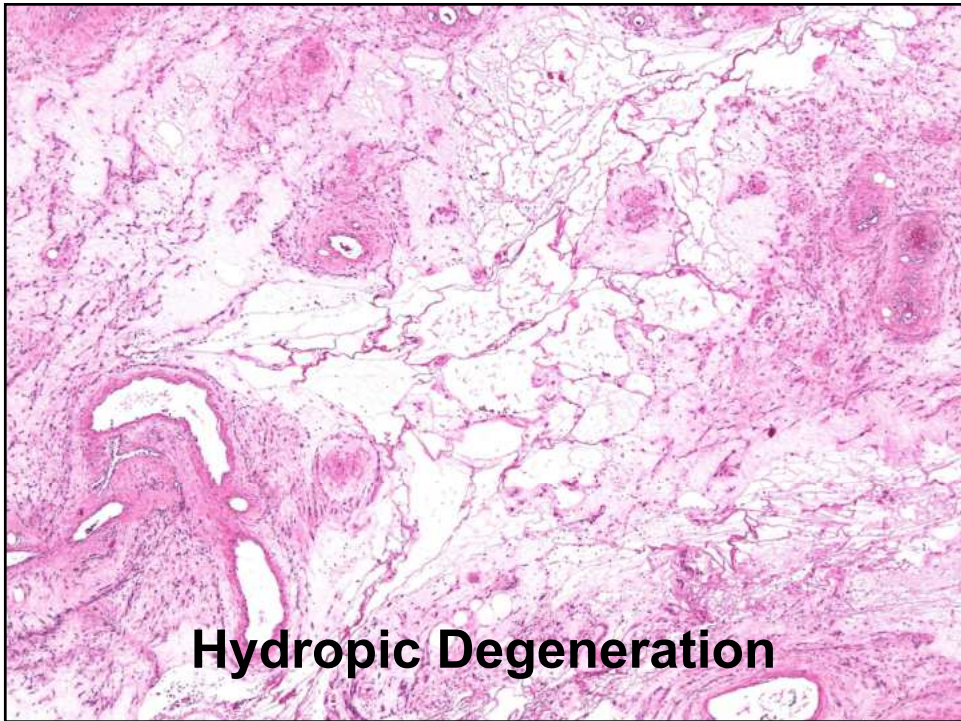
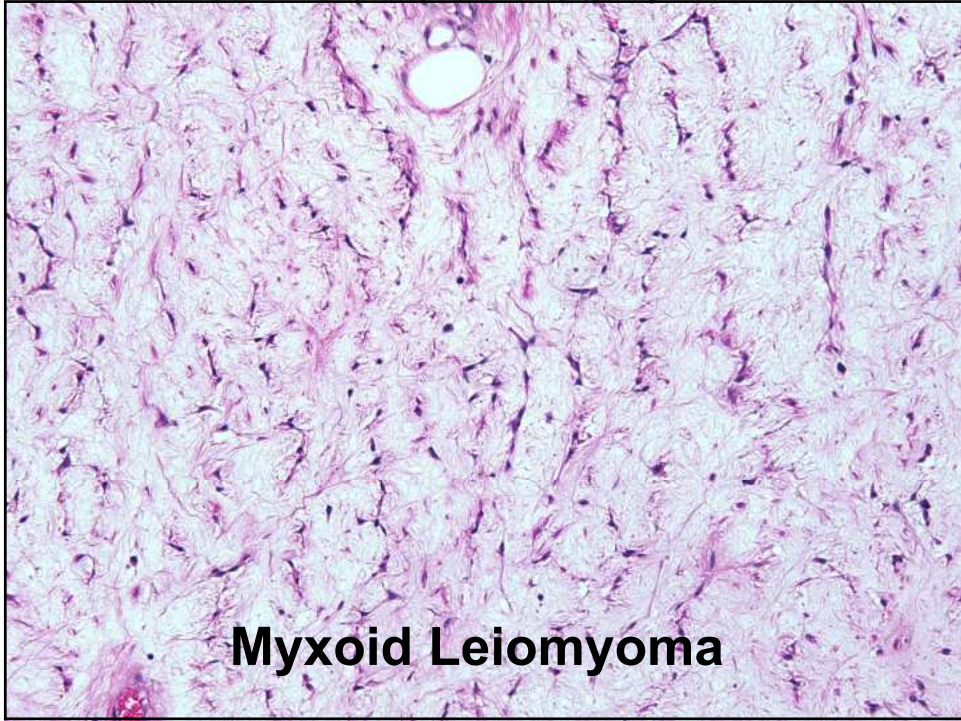
Atkins et al, Manuscript In Preparation

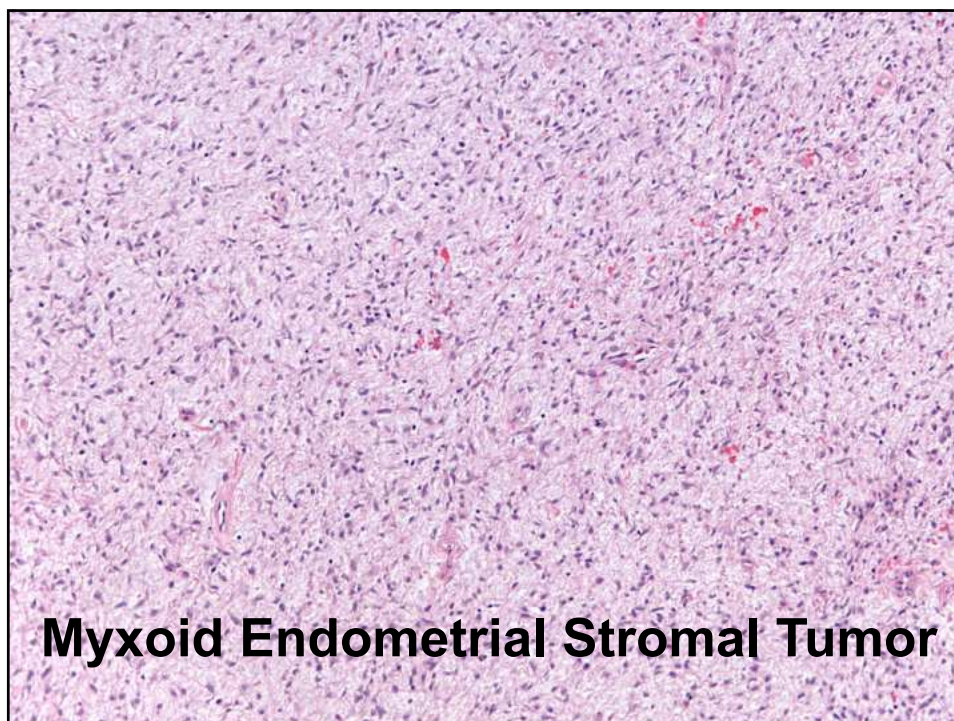
Final Diagnosis

Myxoid leiomyosarcoma

Myxoid LMS: Differential Diagnosis

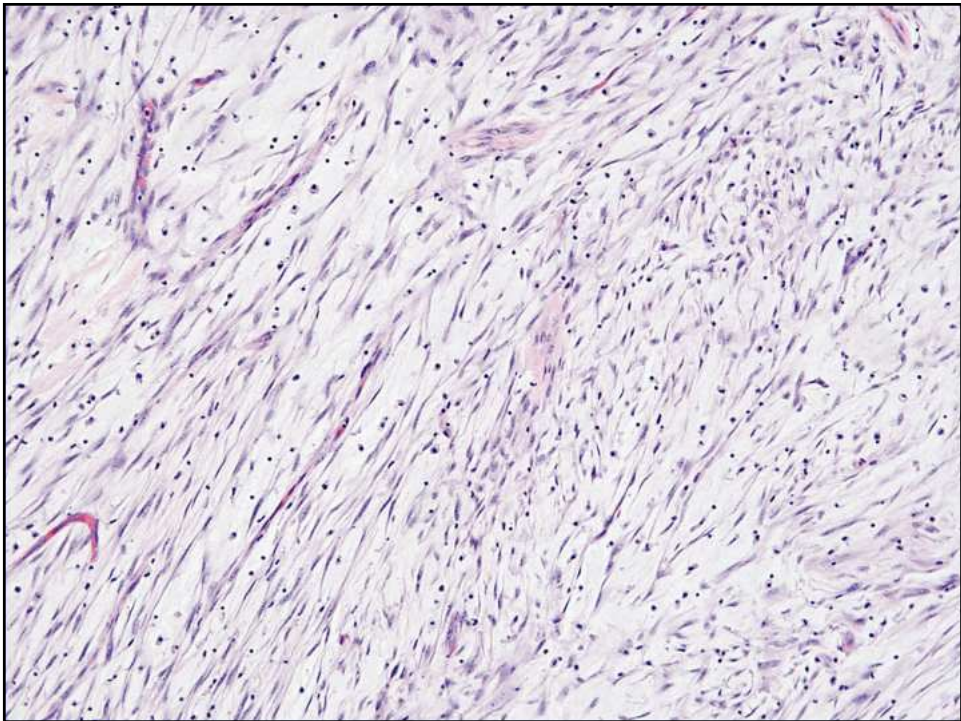
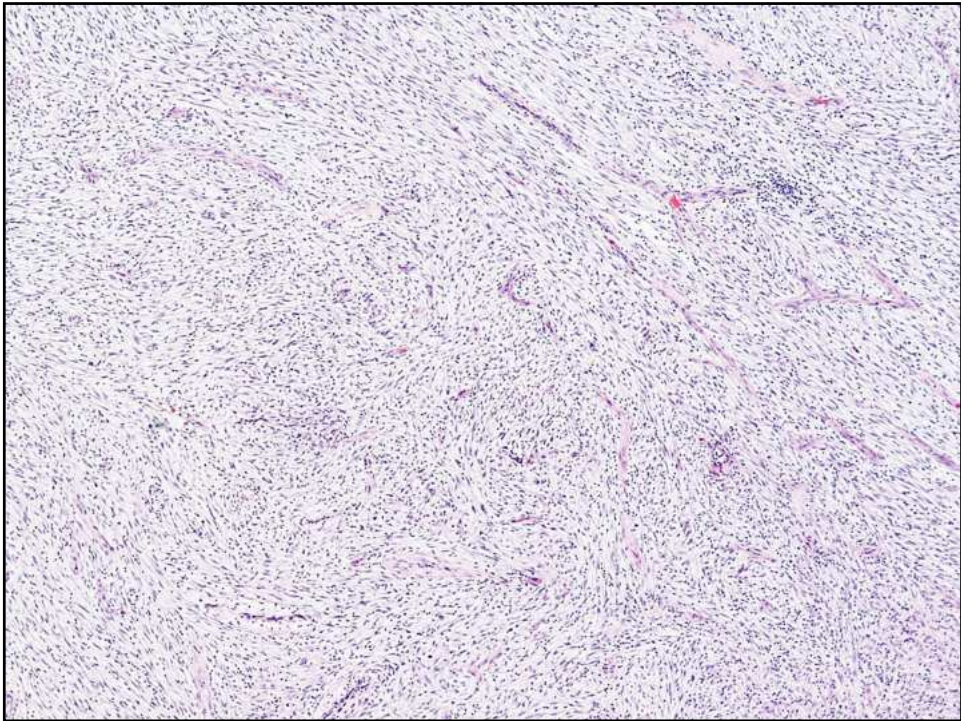
- Myxoid leiomyoma
- Hydropic degeneration in a leiomyoma
- Myxoid endometrial stromal tumor

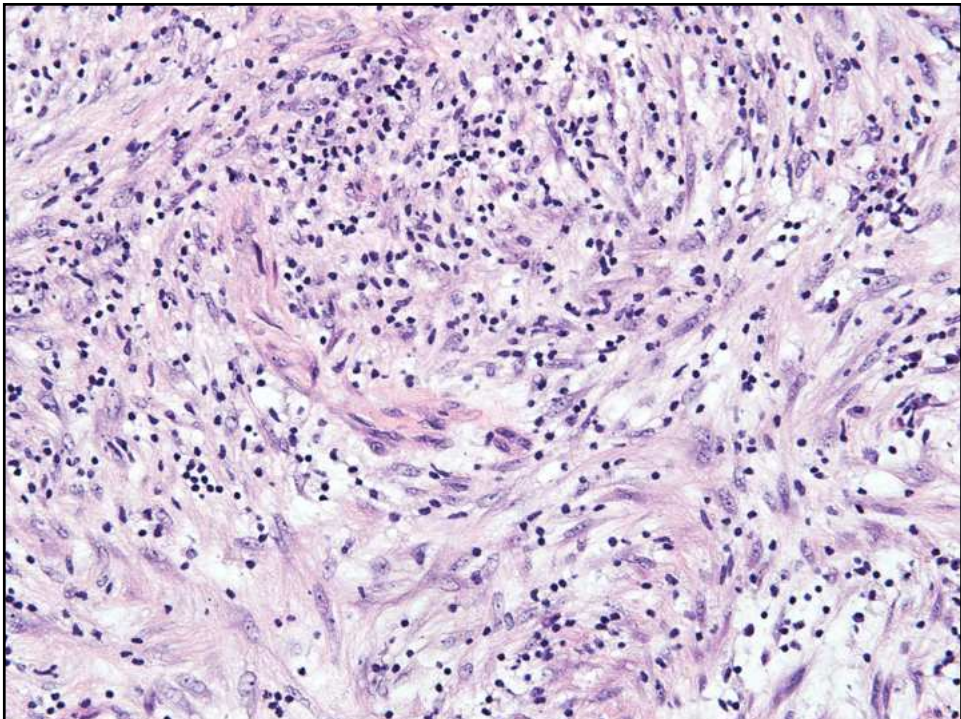
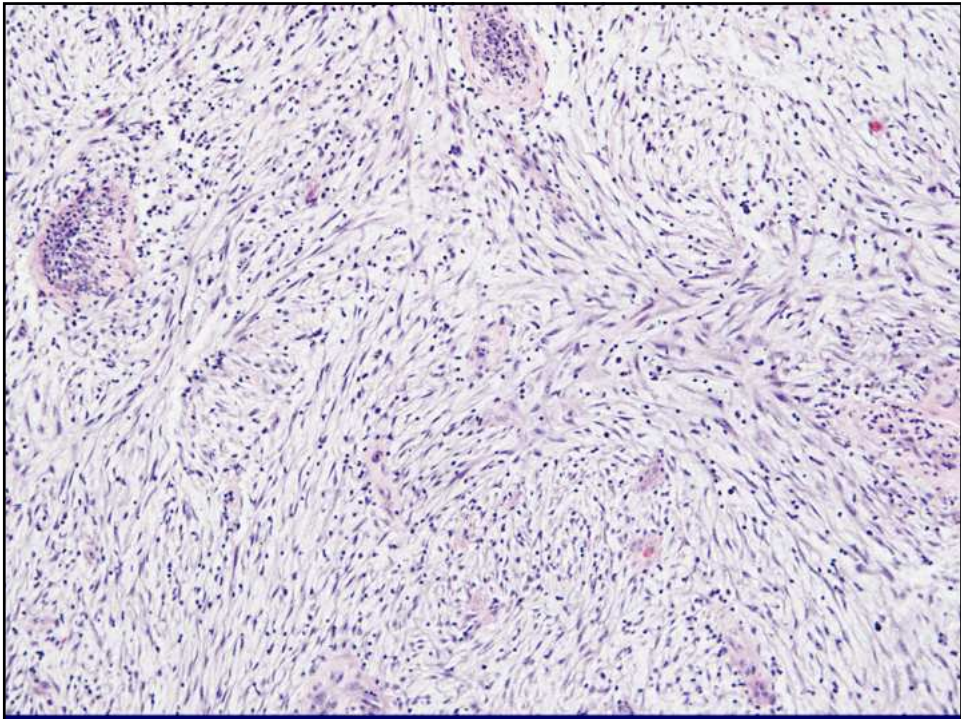


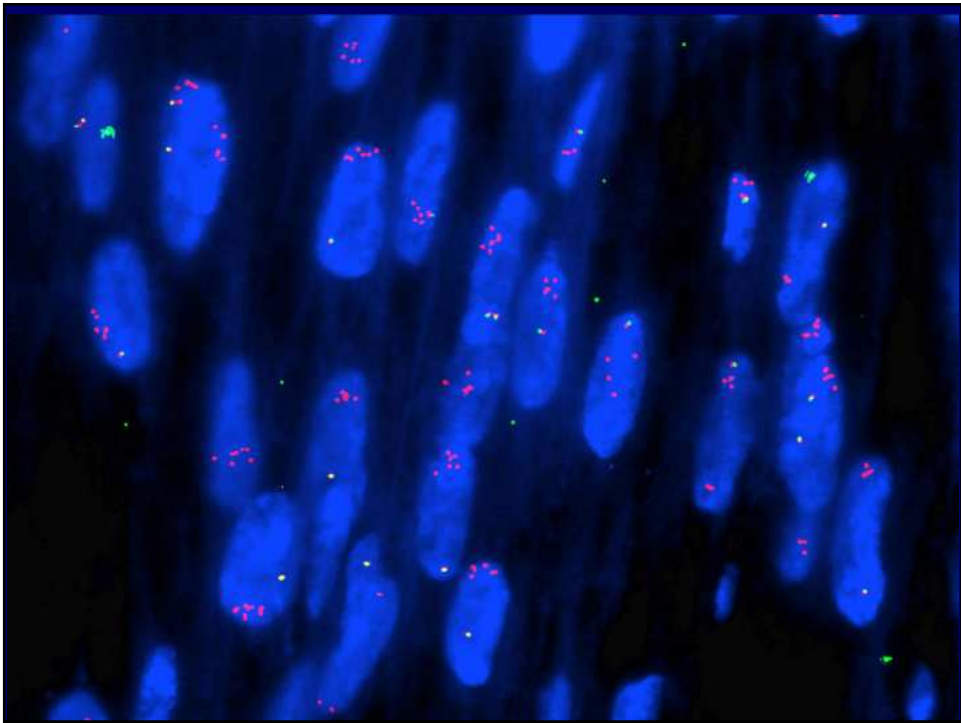
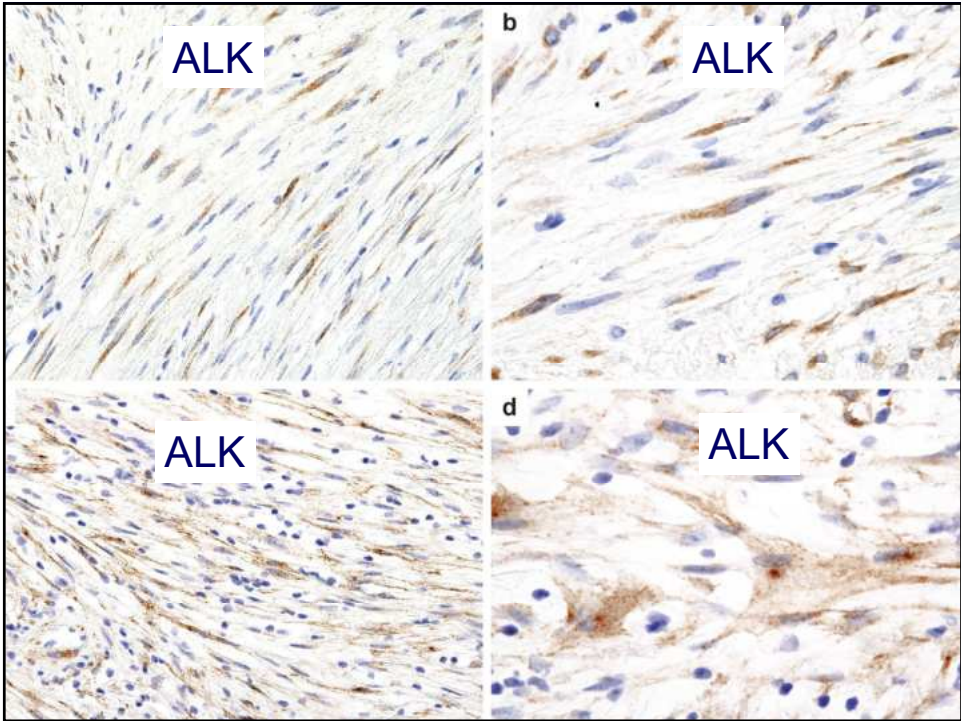


Case Presentation

22-year-old status post term delivery with persistent vaginal bleeding and 4.5 cm submucosal uterine mass







What About Inflammatory Myofibroblastic Tumor?

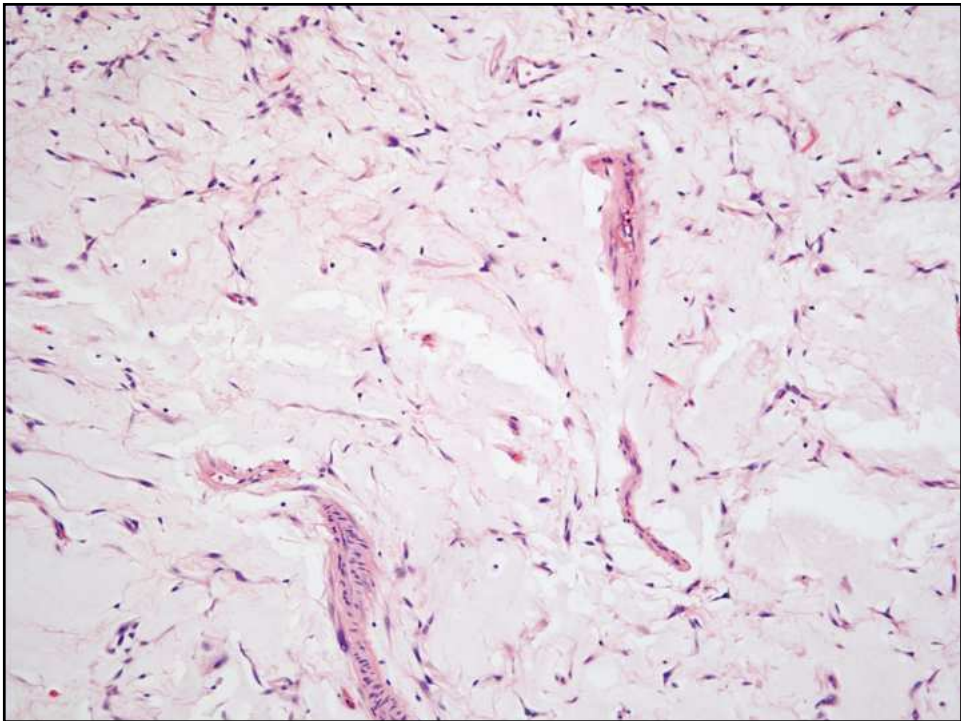
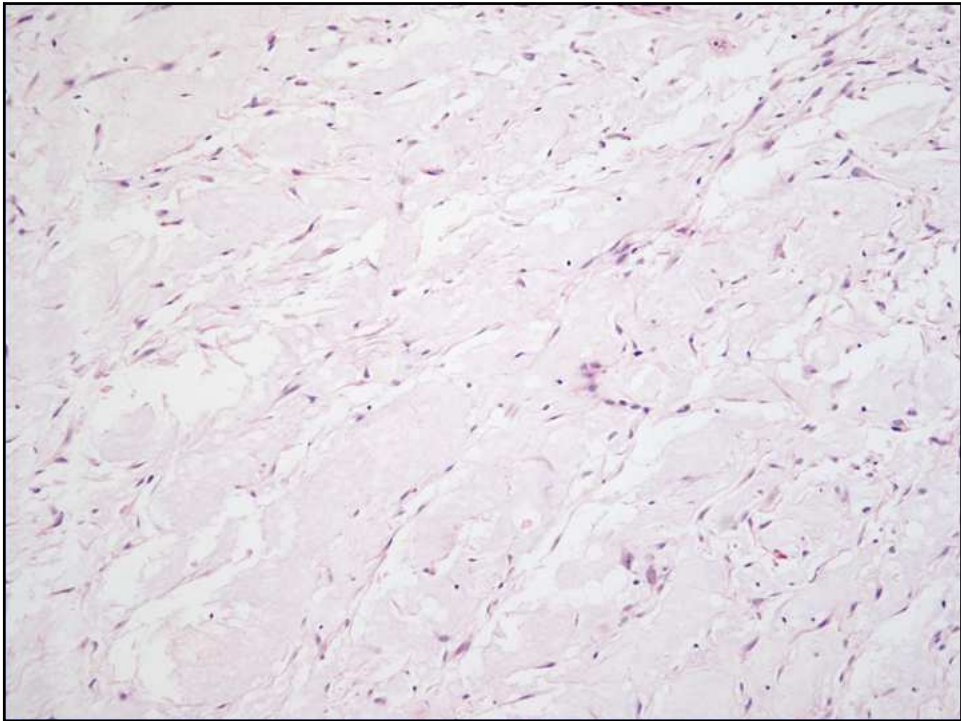
- Uterine IMT contains ALK fusions that are enriched in novel 50 ALK fusion partners: IGFBP5 and THBS1
- Not seen in myxoid LM or myxoid LMS (to date)
- ALK IHC may be helpful
- *ALK* translocation on chromosome 2p23

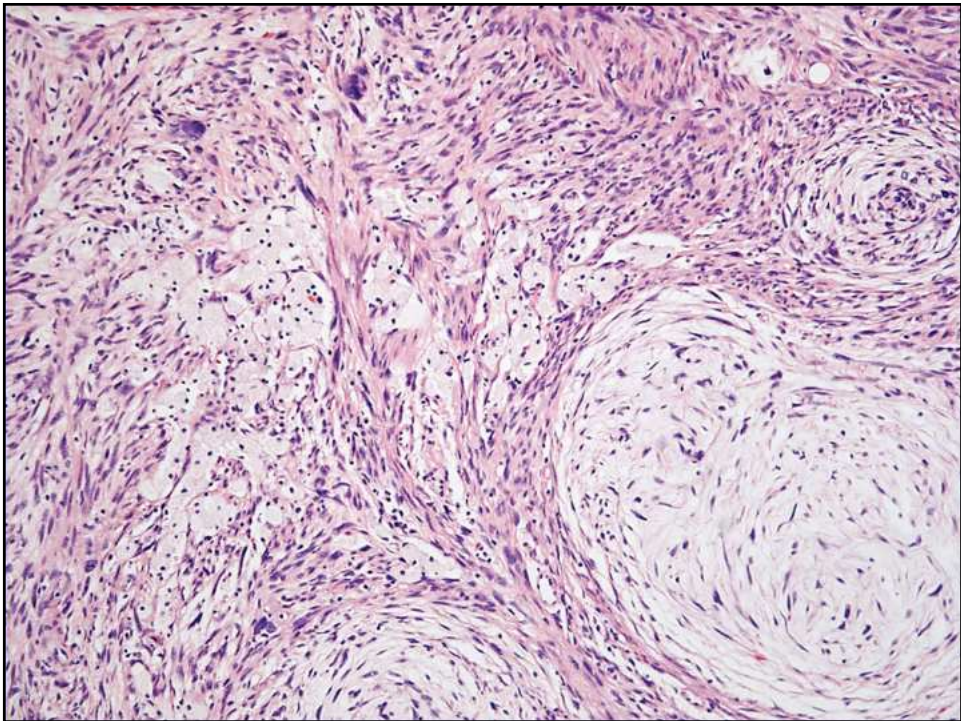
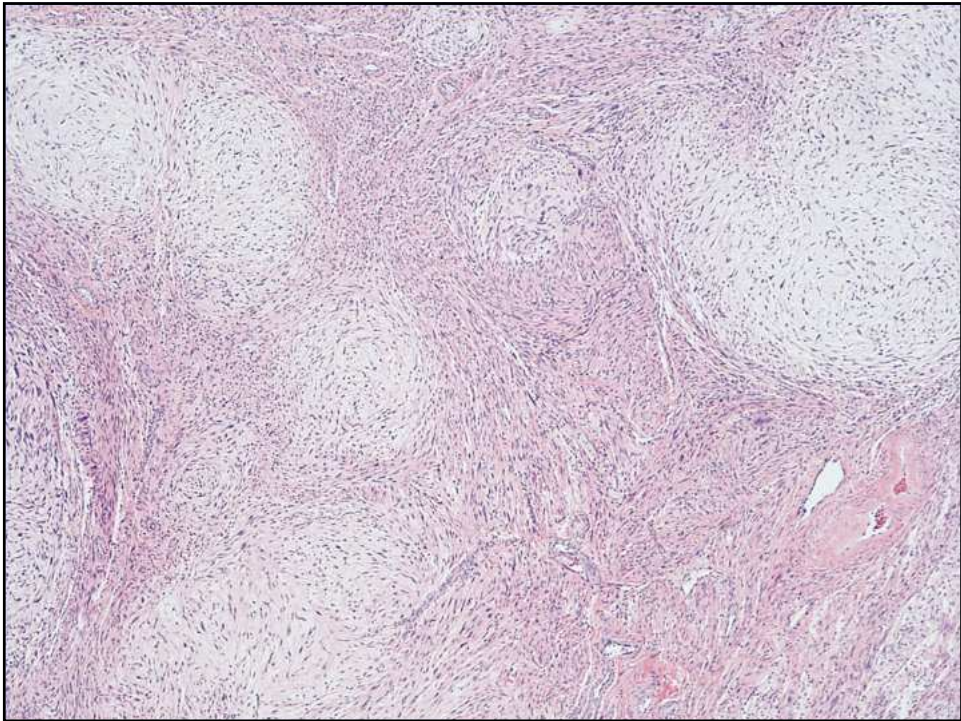
Uterine *ALK*-rearrangements

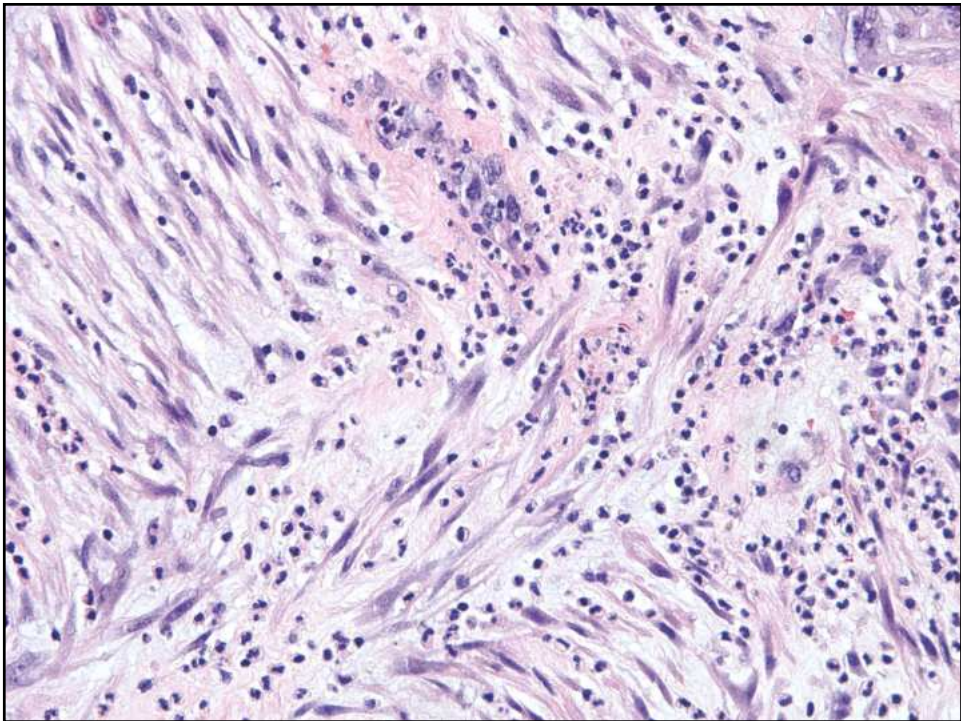
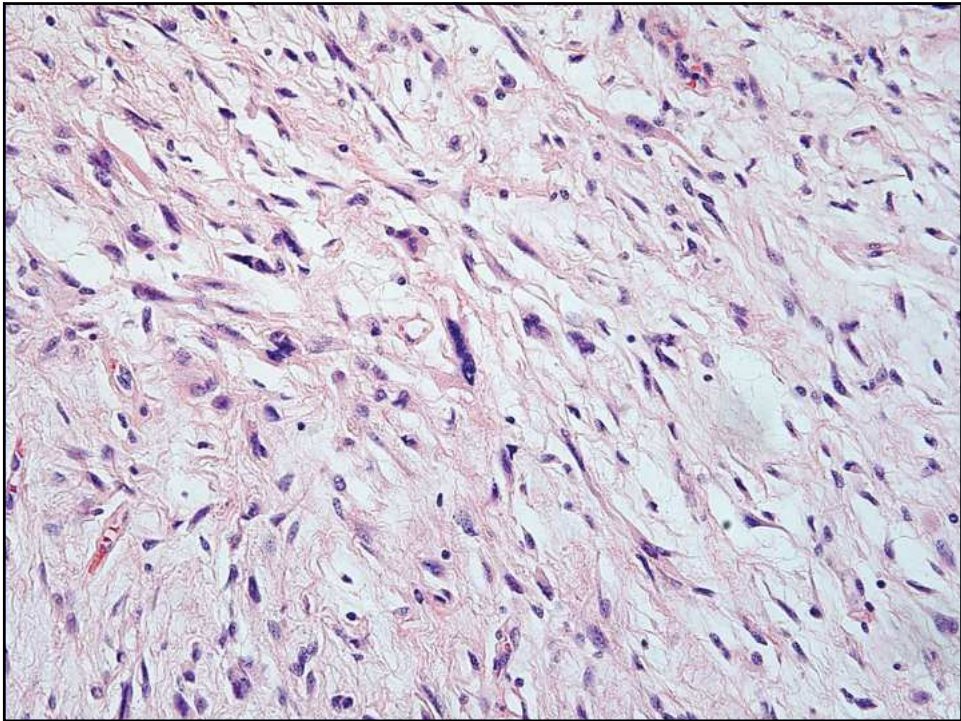
- 6 of 1752 (0.34%) leiomyomas
- 1 of 44 (2.3%) leiomyosarcomas
- 2 of 30 (6.7%) myxoid leiomyosarcomas

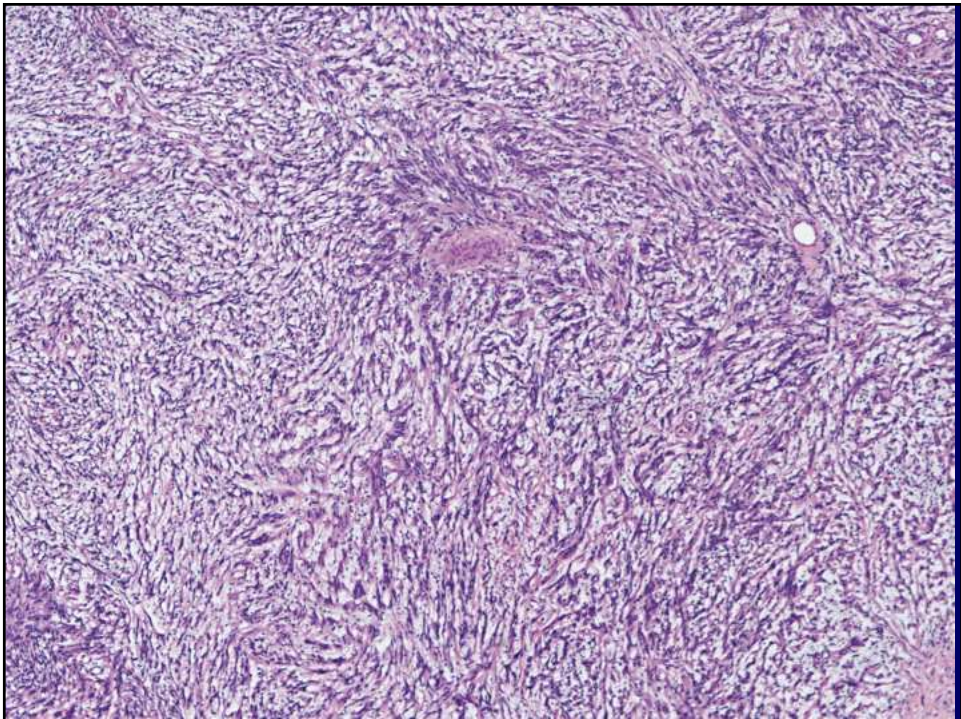
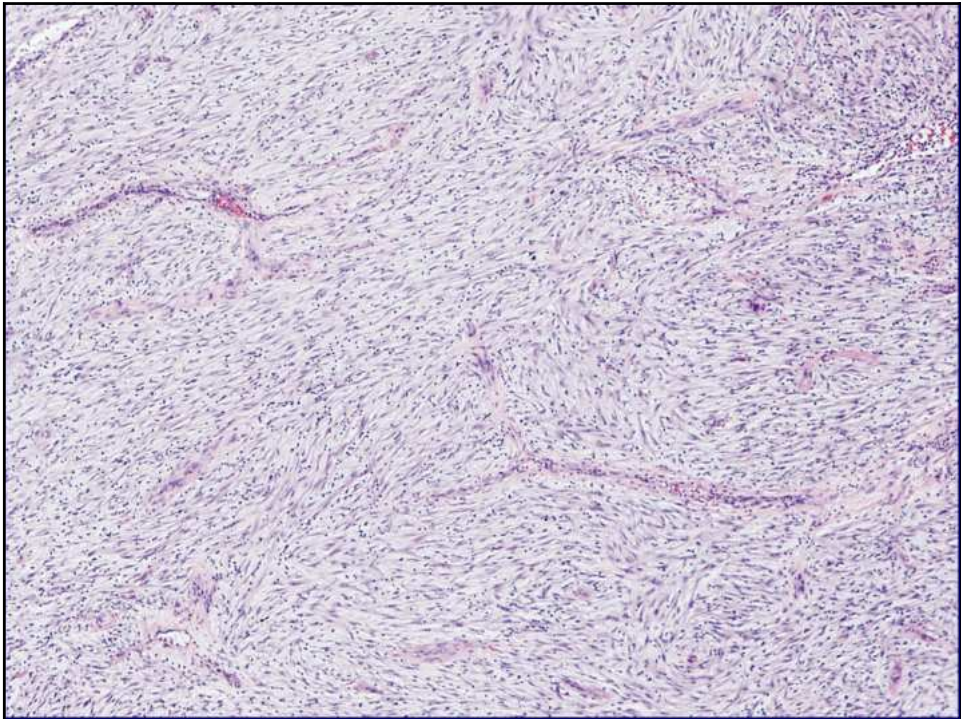
- 6 of the 43 (14%) STUMPs*
- 6 of 17 (35%) myxoid STUMPs*

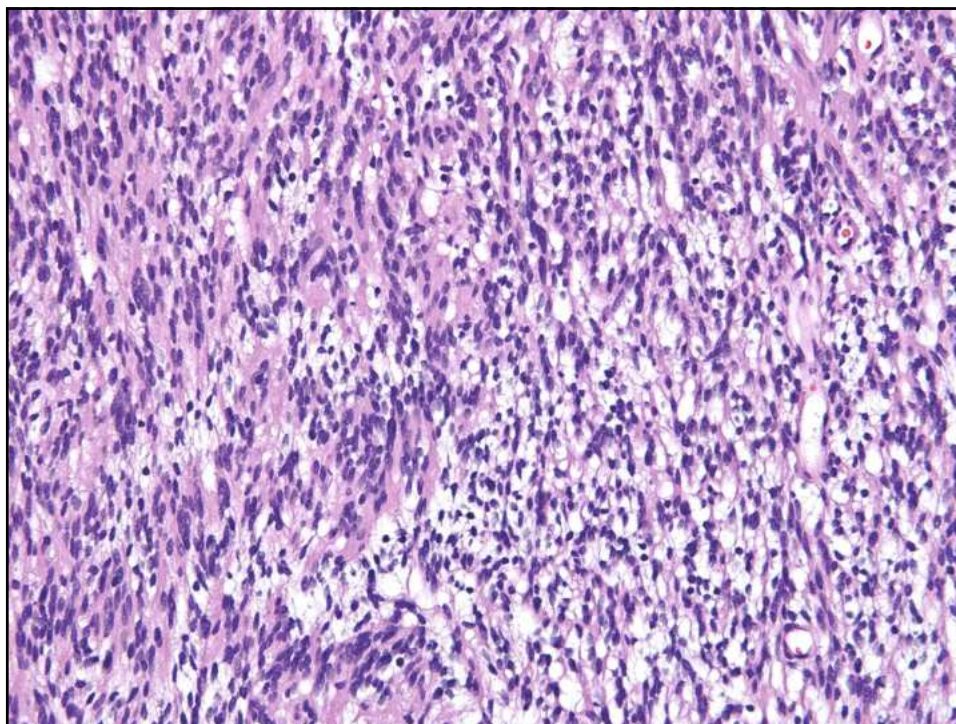
J Hematol Oncol 2015;8:66; Am J Surg Pathol 2016;40:285-301; Am J Surg Pathol 2017;41:773-80; Am J Surg Pathol 2017;41:1433-42











If IMT, What Does it Mean?

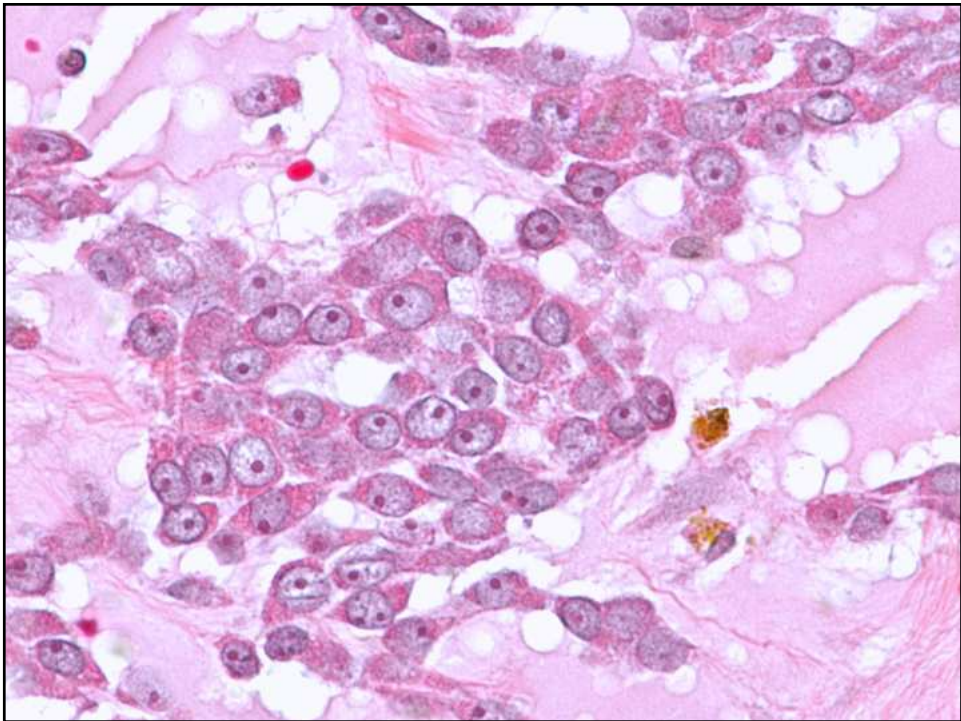
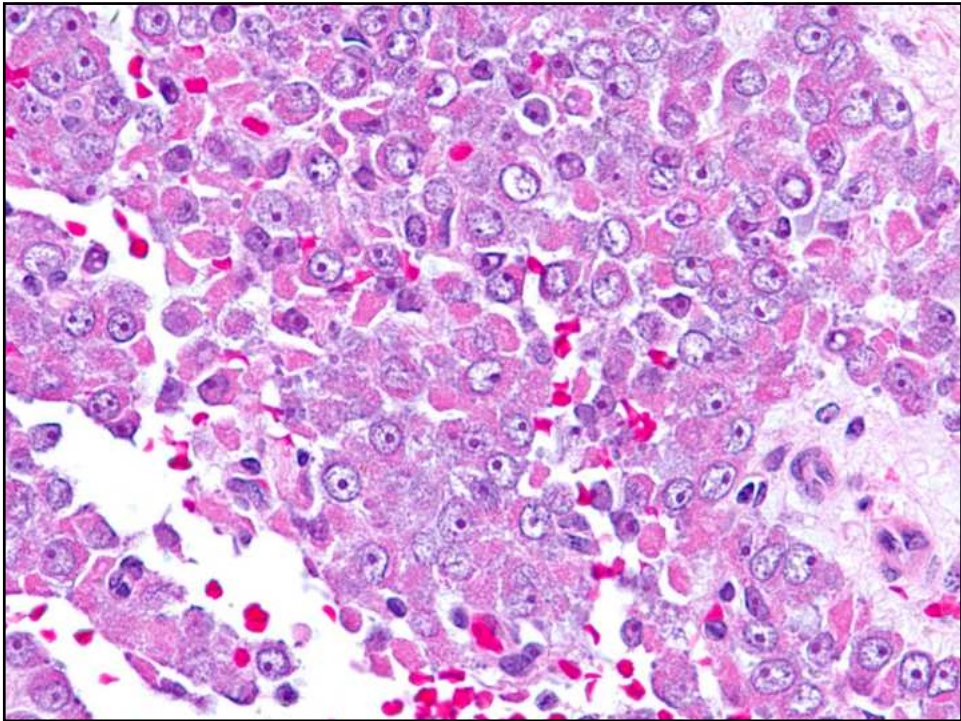
- First & foremost, confirm the diagnosis
- Morphology + IHC + FISH should all point to the diagnosis
- No clear data, but some behave aggressively
- Potential benefit from targeted therapy

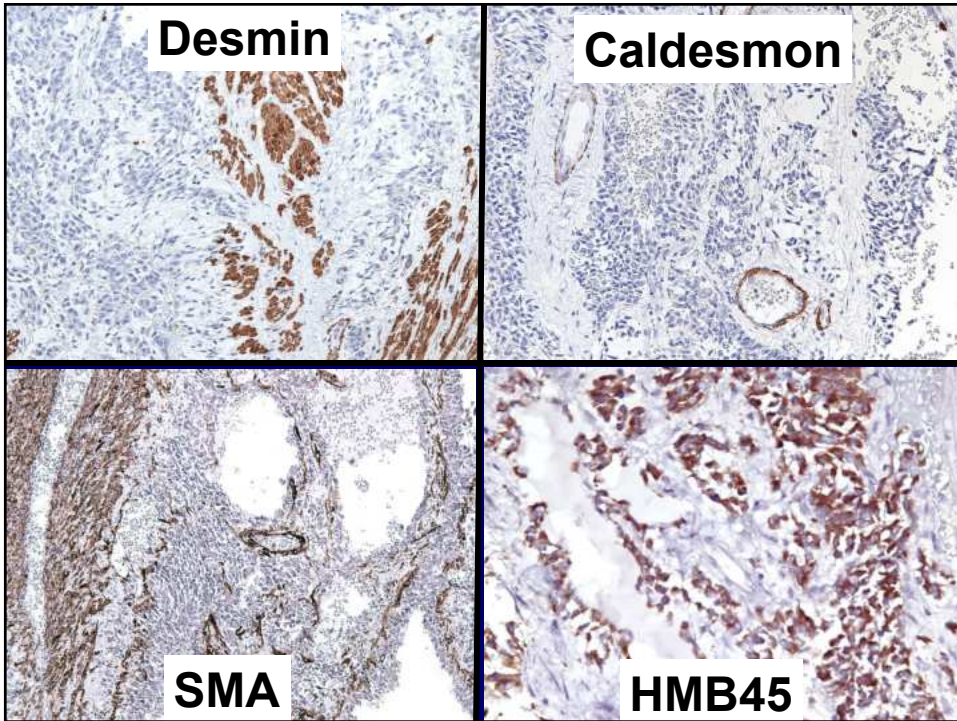
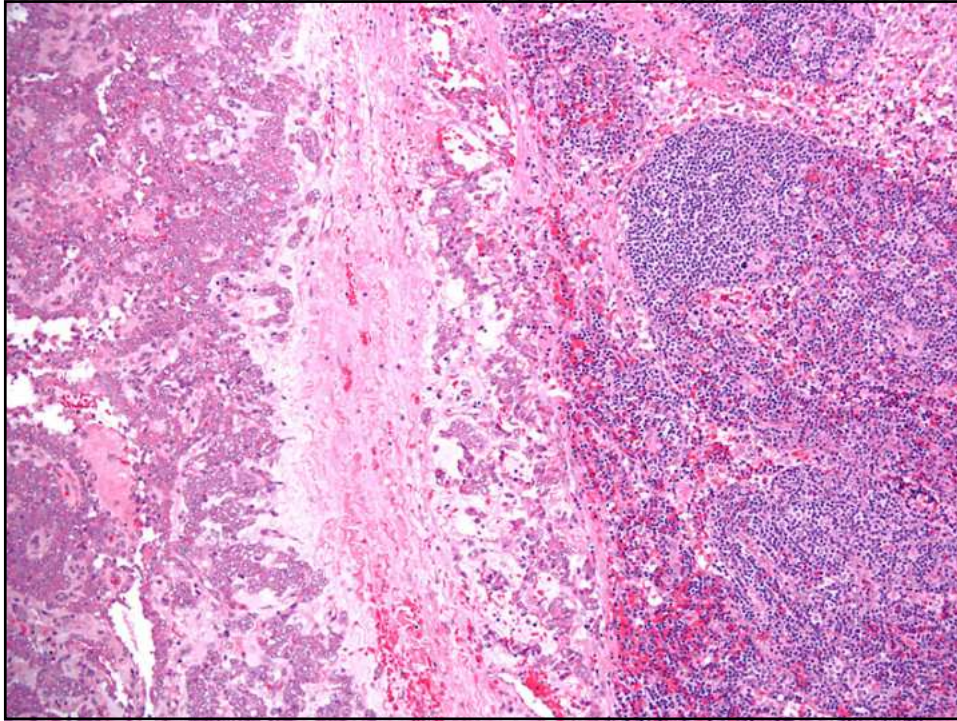
Final Diagnosis

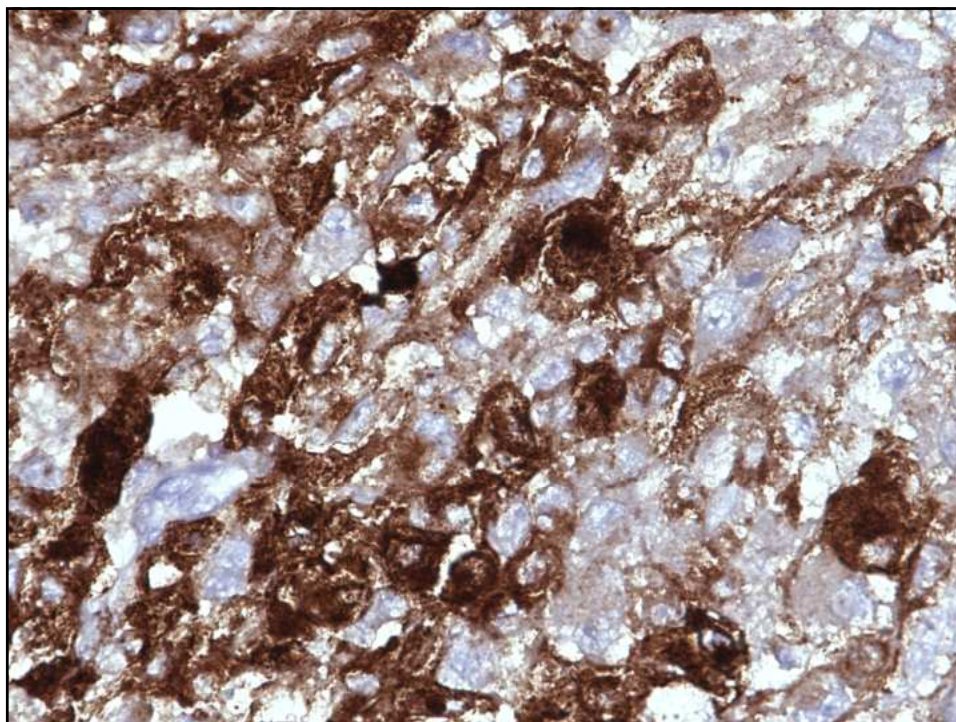
Inflammatory myofibroblastic tumor

Case Presentation

45-year-old with uterine mass undergoes myomectomy



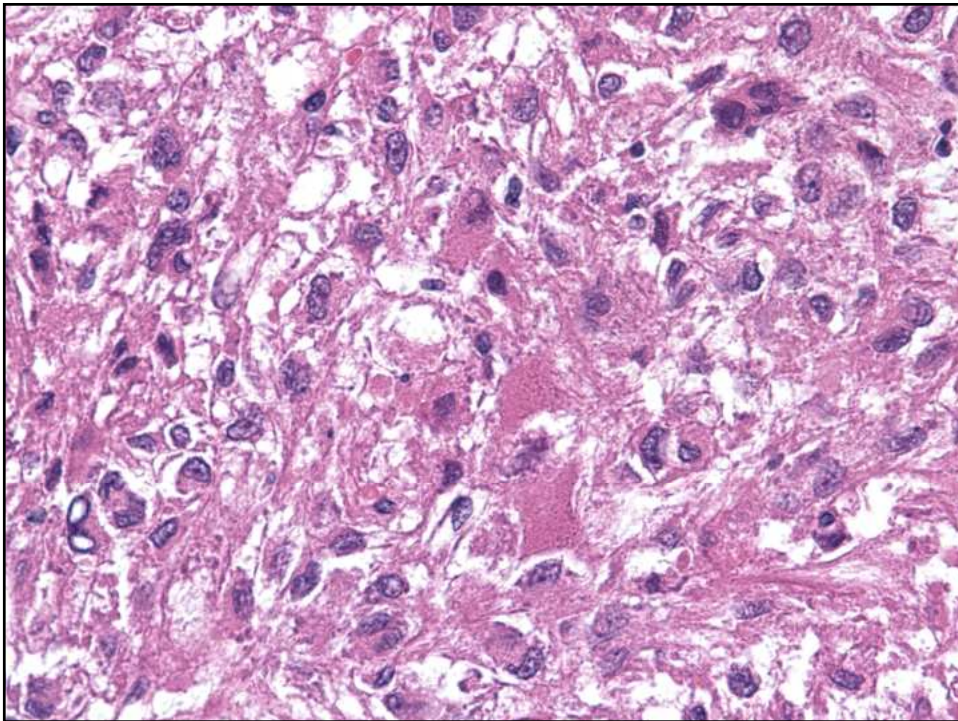
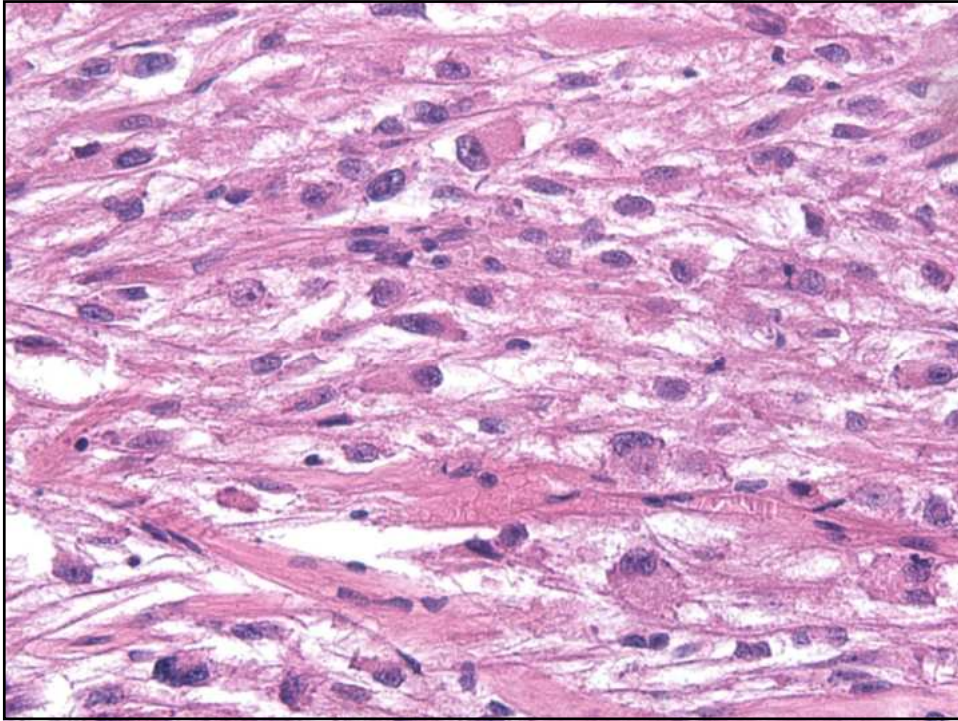




Uterine PEComa: Histology

- Spindled – epithelioid cells in short fascicles or cell nests
- Prominent intrinsic vasculature ranging from capillary network to thick-walled, large caliber vessels
- Stroma may be hyalinized
- Clear to eosinophilic cells with granular cytoplasm

,Am J Surg Pathol 2002;26:1-13



Uterine PEComa: Melanocytic Markers*

- HMB-45 92%
- Melan-A 72%
- MiTF 50%
- S100 protein 1-20% (focal, <5%)

***Most PEComa coexpress SMA and melanocytic markers**

Folpe et al, Am J Surg Pathol 2005;29:1558-1575

PEComa: Criteria for Malignancy (2 or more)

- Size \geq 5 cm
- Infiltrative growth pattern
- High nuclear grade cellularity
- Mitotic rate $>$ 1/50 high power fields
- Necrosis
- Vascular invasion

Am J Surg Pathol 2005;29:1558-1575

PEComa Uncertain Malignant Potential (only 1)

- Nuclear pleomorphism
- Multinucleated giant cell
- Size \geq 5 cm

Am J Surg Pathol 2005;29:1558–1575

HMB-45 Expression in Uterine Mesenchymal Tissue

- Normal myometrium
- Leiomyoma - 1/9
- Epithelioid smooth muscle tumor - 5/9
- Leiomyosarcoma, usual 21/67
- Leiomyosarcoma, epithelioid - 4/5
- Mixed smooth muscle – stromal tumors

Mod Pathol 2006;86:191A

PEComa: Revised Criteria for Malignancy

- Size \geq 5 cm
- Mitotic rate $>$ 1/50 high power fields

Sarcoma 2012;54:1626. Epub 2012 Apr 26.

Uterine PEComa: Spectrum

- Frequent co-expression of muscle markers
- HMB-45 expression in other tumors
- No normal perivascular epithelioid cell

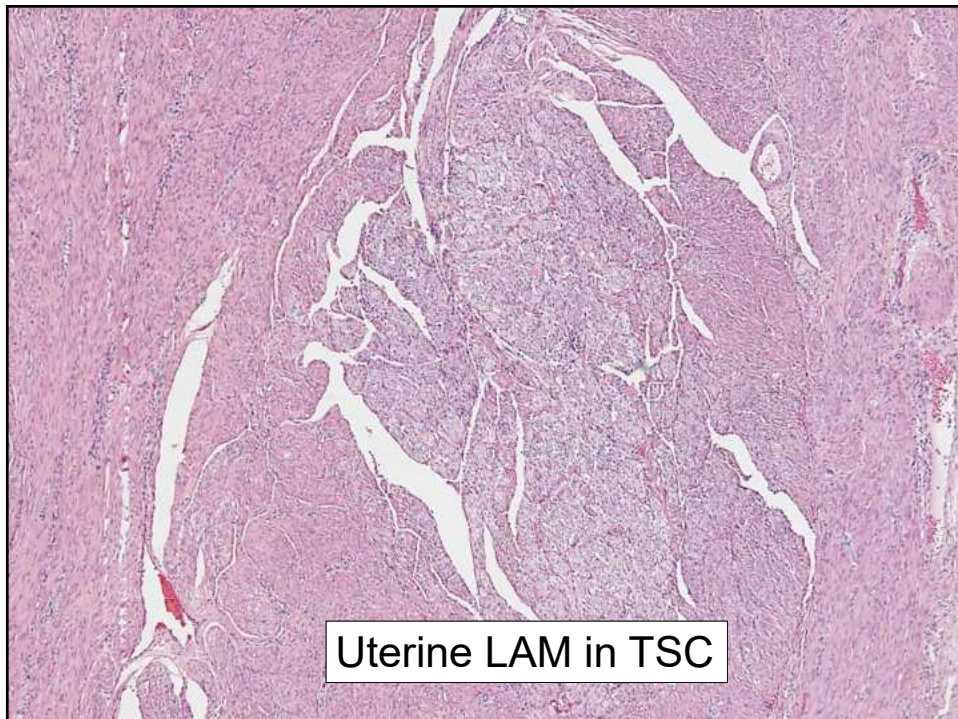
Uterine PEComa: Distinct Entity

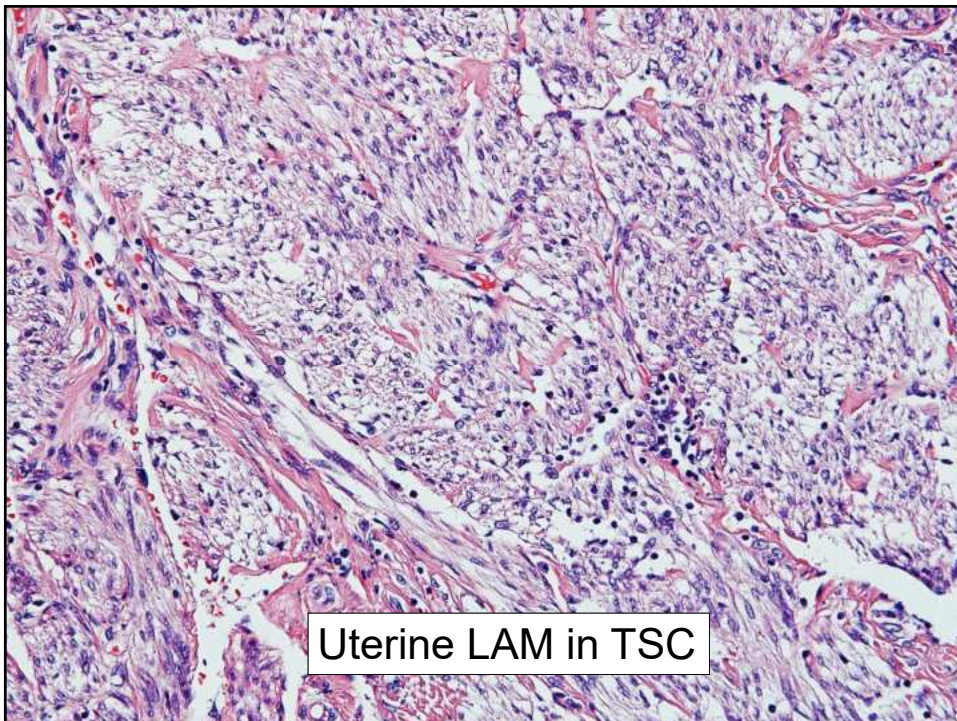
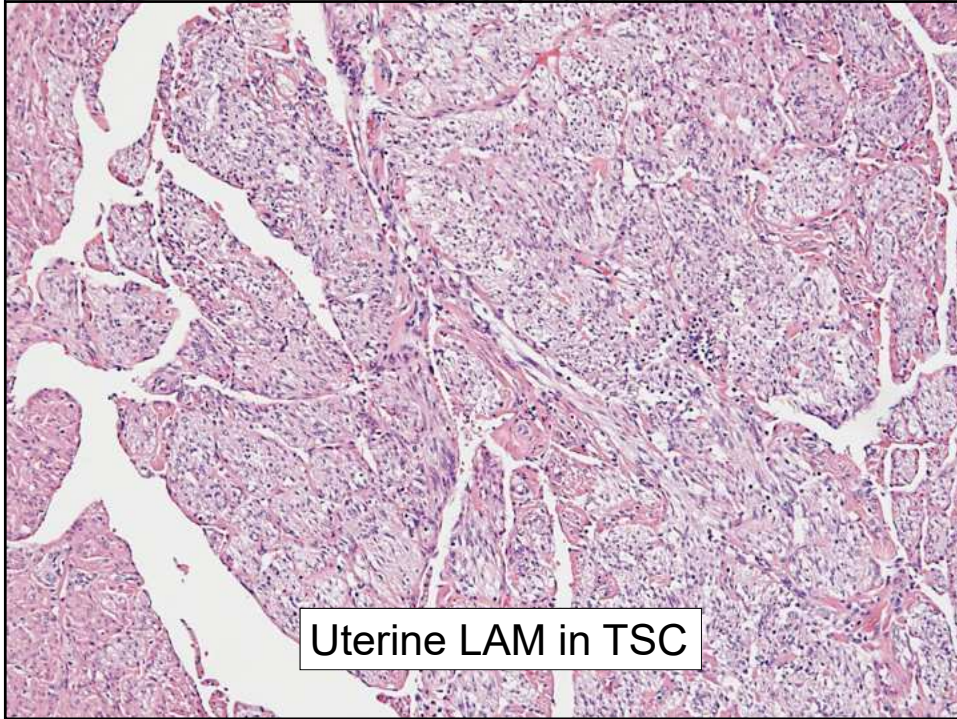
- Absence of smooth muscle markers in some cases
- CGH profiles different from uterine leiomyosarcoma
- Association with LAM, tuberous sclerosis complex

Silva et al, Am J Surg Pathol 2004;28:244-249
Simpson et al, Am J Surg Pathol 2007;31:95-98

PEComa Family

- PEComa
- Angiomyolipoma
- Clear cell “sugar” tumor of the lung
- Lymphangiomyomatosis





Final Diagnosis

Malignant PEComa

Follow up: Hysterectomy. Consider mTOR inhibitor.

Current Perspective

- Smooth muscle
 - Leiomyoma
 - Leiomyoma with bizarre nuclei (atypical leiomyoma)
 - Fumarate hydratase deficient leiomyoma
 - Leiomyosarcoma
 - STUMP
 - Uterine tumor resembling ovarian sex cord tumor (UTROSCT)

Current Perspective

- Endometrial stromal
 - Benign stromal nodule
 - Low-grade endometrial stromal sarcoma
 - High-grade endometrial stromal sarcoma
 - *YWHAE/NUTM2*
 - *ZC3H7B-BCOR*
 - Stromomyoma (mixed stromal/smooth muscle)

Current Perspective

- Other
 - Inflammatory myofibroblastic tumor
 - PEComa
 - High-grade undifferentiated sarcoma
 - Differentiated sarcoma (e.g., angiosarcoma)

