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

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Notice of Faculty Disclosure

US Pathology Biomarker Advisory Board, Merck

Teri Ann Longacre, MD
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)
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

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

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

Differential Diagnosis

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

Morphologic Criteria for Malignancy in Uterine Smooth Muscle Tumors

- Cytologic atypia
- Mitotic index
- Tumor cell necrosis
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 (κ=0.436)
- If tumors with “indeterminate” necrosis removed, agreement between 6 GYN pathologists was 86%


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

<table>
<thead>
<tr>
<th></th>
<th>Atypical Leio</th>
<th>LeioSarc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitotic index (MF/10HPF)</td>
<td>≤10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Tumor cell necrosis</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Ki-67 (MIB-1)</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>p16</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>p53</td>
<td>Negative</td>
<td>Positive</td>
</tr>
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</table>

Use With Caution

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

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Mean Age at Presentation (years)</th>
</tr>
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<tbody>
<tr>
<td>Cutaneous leiomyomas</td>
<td>25</td>
</tr>
<tr>
<td>Uterine leiomyomas</td>
<td>30</td>
</tr>
<tr>
<td>Renal cell carcinomas*</td>
<td>46</td>
</tr>
</tbody>
</table>

*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

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)

Fumarate Hydratase
### Are There 2 Types of Atypical Leiomyoma?

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Round or oval nuclei</td>
<td>Elongated or spindled nuclei</td>
</tr>
<tr>
<td>Distinct smooth nuclear membranes</td>
<td>Irregular nuclear membranes</td>
</tr>
<tr>
<td>Prominent nucleoli with perinucleolar halos</td>
<td>Pinpoint or no nucleoli</td>
</tr>
<tr>
<td>Open coarse chromatin</td>
<td>Dark smudgy chromatin</td>
</tr>
<tr>
<td>Patchy atypia</td>
<td>Diffuse atypia</td>
</tr>
</tbody>
</table>


### 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

Pelvic recurrence (26 mos)
‘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

Mixed stromal and smooth muscle
Mixed stromal and smooth muscle

Trichrome
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 ≥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 (?)
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

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


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

*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%) STUMP*s
- 6 of 17 (35%) myxoid STUMP*s

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

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


PEComa: Criteria for Malignancy (2 or more)

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

**PEComa Uncertain Malignant Potential (only 1)**

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


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**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 ≥ 5 cm
- Mitotic rate > 1/50 high power fields


<table>
<thead>
<tr>
<th>Uterine PEComa: Spectrum</th>
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<tbody>
<tr>
<td>• Frequent co-expression of muscle markers</td>
</tr>
<tr>
<td>• HMB-45 expression in other tumors</td>
</tr>
<tr>
<td>• No normal perivascular epithelioid cell</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Uterine PEComa: Distinct Entity</th>
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<tbody>
<tr>
<td>• Absence of smooth muscle markers in some cases</td>
</tr>
<tr>
<td>• CGH profiles different from uterine leiomyosarcoma</td>
</tr>
<tr>
<td>• Association with LAM, tuberous sclerosis complex</td>
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</table>

PEComa Family

- PEComa
- Angiomyolipoma
- Clear cell “sugar” tumor of the lung
- Lymphangioleiomyomatosis
Uterine LAM in TSC

Uterine LAM in TSC
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)
Thank you