Uterine Mesenchymal Tumors: When Does Molecular Analysis Help?

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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

• Smooth muscle
  – Leiomyoma
  – Leiomyosarcoma

• Endometrial stromal
  – Benign stromal nodule
  – Low-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
Marked atypia
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

- 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>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Mean Age at Presentation (years)</th>
</tr>
</thead>
<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

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

Pelvic recurrence (26 mos)

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

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

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
- 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
Final Diagnosis

High-grade endometrial stromal sarcoma with YWHAE/NUTM2 fusion

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
Myxoid LMS: Differential Diagnosis

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

Myxoid Leiomyoma
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*

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 if translocation present

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 Uncertan Malignant
Potential (only 1)

- Nuclear pleomorphism
- Multinucleated giant cell
- Size ≥ 5 cm


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


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


PEComa Family

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

• Endometrial stromal
  – Benign stromal nodule
  – Low-grade endometrial stromal sarcoma
  – High-grade endometrial stromal sarcoma
  – Stromomyoma (mixed stromal/smooth muscle)
Current Perspective

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