Recent Developments in the Diagnosis of Uterine Sarcomas

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Disclosure

- I have nothing to disclose
Entities to Discuss

• Endometrial Stromal Sarcoma
  – Low and High Grade Subtypes
• Undifferentiated Uterine Sarcoma
• Perivascular Epithelioid Cell Tumor
Endometrial Stromal Tumors

“Old” Terminology: Norris and Taylor

• Endometrial Stromal Nodule

• Endometrial Stromal Sarcoma
  – Low grade (< 10 mits/10 hpf)
  – High grade (>10 mits/10 hpf)

• Undifferentiated Uterine Sarcoma
93/109 (85%) patients had follow-up information

- 73/85 stage I with followup

- 36% of stage I relapsed (23% DOD)

- Mitotic rate does not predict recurrence in stage I patients

• Endometrial Stromal Nodule

• Endometrial Stromal Sarcoma (“low grade”)

• Undifferentiated Uterine Sarcoma
Endometrial Stromal Sarcoma

Clinical Features

Most patients < 50 years old

Dysfunctional uterine bleeding/enlargement

Variable size (polypoid, bulky)

Indolent, protracted course
Endometrial Stromal Sarcoma
Finger-like myometrial permeation
Lymphovascular invasion – “worm-like”
Resembles proliferative phase stroma
Foam cells
Hyaline bands
Fibrous Variant
Sex-cord differentiation
Endometrial Stromal Sarcoma

CD 10
Desmin Staining in Endometrial Stromal Neoplasms

Dot-like and perinuclear staining pattern
Desmin and h-Caldesmon Staining in Endometrial Stromal Tumors
CD 10 Pitfall!
Positive in Leiomyosarcoma
Differential Diagnosis of Endometrial Stromal Sarcoma

- Endometrial Stromal Nodule
  - Highly Cellular Leiomyoma
  - Intravascular Leiomyomatosi
Well defined border
Endometrial stromal nodules and endometrial stromal tumors with limited infiltration: A clinicopathologic analysis of 50 cases.


- 3 cases, 4-6 irregularities extending up to 9 mm
- No F/U in two including those with greatest infiltration
Differential Diagnosis of Endometrial Stromal Sarcoma

• Endometrial Stromal Nodule
  ➢ Highly Cellular Leiomyoma

• Intravascular Leiomyomatosis
Highly Cellular Leiomyoma
Highly Cellular Leiomyoma

Distinguish from Stromal Neoplasia by:

- Fascicular architecture
- Large thick-walled vessels
- Cleft-like spaces
- “Merging” of cells at periphery
- Biomarkers (h-caldesmon, desmin)
Differential Diagnosis of Endometrial Stromal Sarcoma

- Endometrial Stromal Nodule
- Highly Cellular Leiomyoma
  - Intravascular Leiomyomatosis
Intravenous Leiomyomatosis
Intravenous Leiomyomatosis
Intravenous Leiomyomatosis
Intravenous Leiomyomatosis

Distinguish from Stromal Neoplasia by:

- Fascicular architecture
- Large thick-walled vessels
- Cleft-like spaces
- Hydropic change
- Multilobulated contours
- Biomarkers (h-caldesmon, desmin)
How Molecular Genetics Helped “Re-Define” High Grade ESS
Molecular Genetics of ESS

- t(7;17) (most common)
  - JAZF1-SUZ12
- 6p21 rearrangements
  - t(6;7) PHF1-JAZF1
  - t(6;10) EPC1-PHF1
  - t(1;6) MEAF6-PHF1
- der22t(X;22) ZC3H7-BCOR
- t(X;17)(p11.2;q21.33) MBTD1-CXorf67
- t(10;17)(q22;p13) YWHAE-FAM22A/B
- Some cases lack demonstrable genetic rearrangements
The clinicopathologic features of *YWHAE-FAM22* endometrial stromal sarcomas – a histologically high-grade and clinically aggressive tumor

Clinical Features

- Age at presentation: 28 to 67 years (median 50)
- Presenting symptom: Abnormal vaginal bleeding (menorrhagia or peri/post-menopausal bleeding)

<table>
<thead>
<tr>
<th></th>
<th>YWHAE rearranged ESS</th>
<th>JAZF1 rearranged ESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of cases</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>FIGO staging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (18%)</td>
<td>11 (69%)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>3</td>
<td>7 (64%)</td>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>4</td>
<td>2 (18%)</td>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>Clinical follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(time period)</td>
<td>Average 3.5 years</td>
<td>Average 10 years</td>
</tr>
<tr>
<td>No evidence of disease</td>
<td>1 (10%)</td>
<td>13 (76%)</td>
</tr>
<tr>
<td>Alive with disease</td>
<td>7 (70%)</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Died of disease</td>
<td>2 (20%)</td>
<td>2 (12%)</td>
</tr>
</tbody>
</table>
High grade Endometrial Stromal Sarcoma
High grade Endometrial Stromal Sarcoma
LG-ESS (JAZF1-SUZ12)  HG-ESS (YWHAE-FAM22)
Spindle cell area (more fascicular fibrous)
Spindle cell area (fibromyxoid)
Gene expression profiles of uterine sarcoma

3’ end sequencing gene expression profile analysis on FFPE tumor tissues (PLoS One. 2010: 19;5:e8768)

YWHAE-rearranged ESS displays a global gene expression profile that is distinct from JAZF1-rearranged ESS and high grade uterine leiomyosarcoma (Ut LMS).
• YWHAE-FAM22 ESS is a more rapidly progressive disease compared to JAZF1-rearranged ESS

• YWHAE-FAM22 ESS displays higher grade (but non-pleomorphic) histologic features, compared to JAZF1-rearranged ESS

• YWHAE-FAM22 ESS can show a mixture of high grade epithelioid/round cell component (ER/PR/CD10-) and low grade spindle cell component (ER/PR/CD10+)
Proposed classification of uterine sarcoma

**Pleomorphic**
- UES (≈LMS)
  - Complex karyotype
  - High mitotic activity
  - Tumor necrosis
  - Poor prognosis

**Non-pleomorphic**
- HG ESS
  - YWHAE-FAM22A/B (other aberrations)
- LG ESS
  - JAZF1-SUZ12
  - JAZF1-PHF1
  - EPC1-PHF1 (Other aberrations)

- ER/PR/CD10-
  - ↑ Nuclear size/Irregularity in nuclear contour
  - ↑ Mitotic activity
  - Tumor necrosis
  - Intermediate prognosis

- ER/PR/CD10+
  - Good prognosis
Cyclin D1 as a diagnostic immunomarker for endometrial stromal sarcoma with YWHAE-FAM22 rearrangement

Am J Surg Pathol, 2012; 36: 1562-70
Cyclin D1 positive (> 75%) in histologically high grade component
Uterine mesenchymal tumor

Monomorphic tumor *

LG spindle cell (fibrous/fibromyxoid)

Biphasic

HG round cell

Pleomorphic tumor

- UES-P
- LMS
- LM (bizarre nuclei)
- others**

Cyclin D1 CD10 IHC

Diffuse cyclin D1 & negative CD10 in round cell area

Positive

- YWHAE-FAM22 ESS

Negative

- UES-U
- JAZF1-ESS
- non-rearranged classic LGESS or fibrous variant
- others†

Non-diffuse cyclin D1 and/or diffuse CD10 in round cell area

Molecular study

- UES-U
- ESS
- JAZF1
- non-rearranged classic LGESS or fibrous variant
- others†
Undifferentiated Uterine Sarcoma (UUS)
Heterogeneous group of sarcomas lacking diagnostic criteria for:
- ESS*
- LMS
- Adenosarcoma with sarcomatous overgrowth
- Carcinosarcoma/poorly differentiated carcinoma

Some consider UES as 2 groups (Kurihara et al):
- UES-uniform
- UES-pleomorphic
Undifferentiated Endometrial Sarcoma (UES)

Uniform type

Pleomorphic type
UUS is a diagnosis of exclusion!

- More sections often more helpful than large immunoperoxidase panel
- Sampling of intracavitary component/uninvolved endometrium may show features diagnostic of adenosarcoma, carcinosarcoma
- EMA, Cam5.2, reticulin useful for identifying as carcinoma
Perivascular Epithelioid Cell Tumor (PEComa)
The PEComa Family

- Angiomyolipoma
- Clear cell sugar tumor of lung
- Lymphangioleiomyomatosis (LAM)
- Clear cell myelomelanocytic tumor of the falciform ligament/ligamentum teres
- Abdominopelvic sarcoma of perivascular epithelioid cells
- Primary extrapulmonary sugar tumor
Association with Tuberous Sclerosis Complex

- Renal AML, hepatic AML and pulmonary LAM commonly associated with TSC
- Other types of PEComa (including uterine PEComa) are rarely associated with TSC
Perivascular Epithelioid Cell Neoplasm (PEComa) of the Gynecologic Tract: Clinicopathologic and Immunohistochemical Characterization of 16 Cases

Schoolmeester JK, Howitt BE, Hirsch MS, Dal Cin P, Quade BJ, Nucci MR
Nested, epithelioid
Spindled
Radial Arrangement
Foamy Cytoplasm
Large nucleoli
Wreath-like Giant Cells
Intranuclear pseudo-inclusions
PEComa Immunohistochemistry

- PEComa characterized by co-expression of melanocytic (HMB45, Melan A, microphthalmia transcription factor) and muscle markers (smooth muscle actin, calponin, desmin)
- Can express S100 but usually focal
- May be positive for TFE3 and harbor TFE3 gene fusions (AJSP 2010; 34:1395-1406)
<table>
<thead>
<tr>
<th>Antibody</th>
<th>Positives</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMB 45</td>
<td>16/16</td>
<td>16</td>
<td>(100%)</td>
</tr>
<tr>
<td>Melan A</td>
<td>14/16</td>
<td>16</td>
<td>(88%)</td>
</tr>
<tr>
<td>MiTF</td>
<td>11/12</td>
<td>12</td>
<td>(92%)</td>
</tr>
<tr>
<td>Desmin</td>
<td>15/15</td>
<td>15</td>
<td>(100%)</td>
</tr>
<tr>
<td>SMA</td>
<td>14/15</td>
<td>15</td>
<td>(93%)</td>
</tr>
<tr>
<td>h-caldesmon</td>
<td>11/12</td>
<td>12</td>
<td>(92%)</td>
</tr>
<tr>
<td>TFE3</td>
<td>5/13</td>
<td>13</td>
<td>(38%)</td>
</tr>
</tbody>
</table>
Questions to address

How do you separate PEComa from LMS?

Why is it difficult to make this distinction?

Why is distinction of PEComa from LMS important?
How do you separate PEComa from Leiomyosarcoma?
PEComa

• Combination of epithelioid and spindled areas (varying proportions)
• Distinctive cytoplasmic appearance
  – Granular and pale
• Other characteristic morphologic findings
  – Lipidized cells, “spider-like” cells, melanoma-like wreath-like giant cells and macronucleoli, hyalinized stroma (“sclerosing PEComa-like”), arborizing vasculature
• Co-expression of melanocytic and muscle markers
Why is it difficult to make this distinction?
Confounding Findings

- Conventional uterine LMS can express HMB45
- Epithelioid uterine LMS can express HMB45
- Pure spindled PEComa of the uterus can occur
A Question of Definition

• Co-expression of Melan A and smooth muscle markers
  – Uterine LMS are negative for Melan A (Howitt B et al. USCAP abstract 2012)
  – Vast majority of gynecologic PEComa express Melan A (88%)
Diagnosis of PEComa

- Appropriate morphologic appearance
- Expression of at least one muscle marker (desmin, SMA)
- Expression of HMB 45 and Melan A
- In absence of Melan A positivity, diffuse expression of cathepsin K and/or MiTF
Why is distinction of PEComa from LMS important?
Insights into the Molecular Pathogenesis of PEComa

- Renal AML and LAM occur at increased frequency in patients with tuberous sclerosis due to germ line mutations in \textit{TSC1} and \textit{TSC2}
  - \textit{TSC 1} located on 9q; encodes hamartin
  - \textit{TSC 2} located on 16p; encodes tuberin
- \textit{TSC2} mutations or LOH at 16q frequently found in sporadic PEComa
- \textit{TSC1}/\textit{TSC2} mutations leads to activation of mTOR signaling pathway
- mTOR pathway inhibitors offer targeted therapy
  - Studies have shown consistent, although incomplete response
Clinical Activity of mTOR inhibition

• Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. *J Clin Oncol.* 2010 Feb 10;28(5):835-40

• Extrarenal perivascular epithelioid cell tumors (PEComas) respond to mTOR inhibition: clinical and molecular correlates. *Int J Cancer.* 2013 Apr 1;132(7):1711-7.
How do you recognize malignant PEComas?
Histologic Features Associated with Aggressive Clinical Behavior

- Size > 5 cm
- Infiltrative growth pattern
- High nuclear grade
- Necrosis
- Mitotic activity > 1/50 HPF
Proposed Classification

- **Benign (no worrisome features)**
- $< 5$cm, no infiltration, lacks high nuclear grade, no necrosis, no LVI, mitoses $\leq 1/50$ high power fields

- **Uncertain Malignant Potential**
  - nuclear pleomorphism/multinucleated giant cells only
  - size $> 5$ cm only

- **Malignant (2 or more worrisome features)**
- $> 5$cm, high nuclear grade, mitotic rate $> 1/50$ HPF, necrosis, LVI
<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
<th>Cases with Known Metastasis Meeting Criteria</th>
<th>Cases without Known Metastasis Meeting Criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>Tumors showing: &lt;5cm, non-infiltrative, non-high grade nuclear features, no necrosis or vascular invasion and a mitotic rate ≤1/50 hpf</td>
<td>0 of 9 (0%)</td>
<td>0 of 7 (0%)</td>
</tr>
<tr>
<td>Uncertain Malignant Potential</td>
<td>Tumors with only one of the following: nuclear pleomorphism OR multinucleated giant cells OR gross size &gt;5cm</td>
<td>0 of 9 (0%)</td>
<td>0 of 7 (0%)</td>
</tr>
<tr>
<td>Malignant</td>
<td>Tumors with two or more features: gross size &gt;5cm, infiltrative growth, high grade nuclear features, necrosis, vascular invasion or a mitotic index ≥1/50 HPF</td>
<td>9 of 9 (100%)</td>
<td>4 of 7 (57%)</td>
</tr>
<tr>
<td>Classification</td>
<td>Definition</td>
<td>Cases with Known Metastasis Meeting Criteria</td>
<td>Cases without Known Metastasis Meeting Criteria</td>
</tr>
<tr>
<td>----------------</td>
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<td>---------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Benign or Uncertain Malignant Potential</td>
<td>Tumors with fewer than 4 features: (gross size &gt;5cm, high grade nuclear features, necrosis, vascular invasion or a mitotic rate ≥1/50 hpf)</td>
<td>0 of 9 (0%)</td>
<td>7 of 7 (100%)</td>
</tr>
<tr>
<td>Malignant</td>
<td>Tumors ≥4 features</td>
<td>9 of 9 (100%)</td>
<td>0 of 7 (0%)</td>
</tr>
</tbody>
</table>
Take Home Points

• Endometrial stromal sarcoma can be defined into low and high grade categories and this separation is clinically relevant
  – By morphology, immunophenotype, genetics

• Undifferentiated uterine sarcoma is a diagnosis of exclusion (if uniform, consider high grade ESS)

• Recognition of PEComas of the female genital tract is clinically relevant