Endometrial stromal sarcomas: Updates in classification and common diagnostic dilemmas

Karuna Garg, MD
University of California San Francisco

Case

- 54 year old female
- Abdominal pain
- Cholecystectomy
- Surgeon noted ascites and ovarian masses
**Case**

- Gastrointestinal stromal tumor?
CD10

MIB-1

Cyclin-D1

Endometrial biopsy
Case

- Additional stains: Negative for ER/PR, smooth muscle markers, epithelial markers, FOXL-2, WT1

Case

- Patient underwent hysterectomy
Case

- High grade endometrial stromal sarcoma
Outline

• Changes in classification of endometrial stromal neoplasms
  • Low-grade endometrial stromal sarcoma
  • High-grade endometrial stromal sarcoma
  • Undifferentiated uterine sarcoma

Evolution in classification of endometrial stromal tumors

Endometrial stromal tumors
  - Endometrial stromal nodule
    - Low grade ESS
    - High grade ESS

2003 WHO classification

Endometrial stromal tumors
  - Endometrial stromal nodule
  - Low grade ESS
  - Undifferentiated endometrial sarcoma
Evolution in classification of endometrial stromal tumors

2003 WHO classification

Endometrial stromal tumors

Endometrial stromal nodule

Low grade ESS

High grade ESS

Undifferentiated endometrial sarcoma

2014 WHO classification

Endometrial stromal nodule

Low grade ESS

High grade ESS

Undifferentiated uterine sarcoma

Evolution in classification of endometrial stromal tumors: Rationale

Problems with high-grade ESS:
- Definition of high grade ESS not followed (no resemblance with endometrial stroma)
- Range of tumors including leiomyosarcoma, MMMT, undifferentiated sarcoma
- Mitotic count alone not significant

Evolution in classification of endometrial stromal tumors: Rationale

- 117 cases
- Included cases “composed exclusively of uniform cells with scant cytoplasm that resembled the cells of proliferative-phase endometrial stroma” (although cells could have grade 1-3 atypia)
- Stage most important prognostic factor
- On univariate analysis: Mitotic index and cytologic atypia not predictive of clinical outcome in stage 1 patients

Norris and Taylor, Cancer 1966

Evolution in classification of endometrial stromal tumors: Rationale

FIG. 2. Endometrial sarcoma with cellular atypism. The cytologic features illustrated here represent the most severe degree of atypia (Grade 3) we accept within the endometrial stromal sarcoma category. The nuclei are slightly enlarged, and the nuclear membranes are somewhat irregular; but the cells are mostly uniform, and the chromatin is still delicate. Sarcomas composed of cells with greater pleomorphism and nuclear anaplasia are placed in the undifferentiated sarcoma group.


Evolution in classification of endometrial stromal tumors

Endometrial stromal tumors

- Endometrial stromal nodule
- Low grade ESS

2003 WHO classification

- Endometrial stromal nodule
- Low grade ESS
- Undifferentiated endometrial sarcoma

Evolution in classification of endometrial stromal tumors: Rationale

2003 WHO classification:
1. Endometrial stromal nodule
2. Low-grade endometrial stromal sarcoma
3. Undifferentiated endometrial sarcoma

"Increasing cytologic atypia associated with increase in relapse rate"

Evolution in classification of endometrial stromal tumors: Rationale

Problems with 2003 WHO classification:
• Undifferentiated endometrial sarcoma heterogeneous category
• Tumors with intermediate features or high grade ESS like features (grade 2-3 atypia)
• Tumors with components of high grade and low grade ESS

Table: Aberrant p53, ER, JAZF1 fusion, and Dead of disease for LG-ESS, UES-U, and UES-P

<table>
<thead>
<tr>
<th></th>
<th>LG-ESS</th>
<th>UES-U</th>
<th>UES-P</th>
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<tbody>
<tr>
<td>Aberrant p53</td>
<td>0</td>
<td>0</td>
<td>50%</td>
</tr>
<tr>
<td>ER</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
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<tr>
<td>JAZF1 fusion</td>
<td>6/12 (50%)</td>
<td>1/3 (33%)</td>
<td>0/3 (0%)</td>
</tr>
<tr>
<td>Dead of disease</td>
<td>0/13 (0%)</td>
<td>4/7 (57%)</td>
<td>3/5 (60%)</td>
</tr>
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</table>


Evolution in classification of endometrial stromal tumors: Rationale

1. Low grade ESS
2. Undifferentiated endometrial sarcoma with uniform nuclei (UES-U)
3. Undifferentiated endometrial sarcoma with pleomorphic nuclei (UES-P)

The Clinicopathologic Features of YWHAE-FAM22 Endometrial Stromal Sarcomas: A Histologically High-grade and Clinically Aggressive Tumor

Cheng-Han Lee, MD, PhD,*† Adrian Murillo-Enriquez, MD,* Wenbin Ou, PhD,* Meijun Zuo, PhD,* Rola H. Ali, MD,* Sarah Chang, MD,* Frédéric Amant, MD,*§ C. Blake Gilks, MD,* Matt van de Rijn, MD, PhD,† Esther Oliva, MD,* Maria Debies-Reychler, MD,* Paolo Dal Cin, PhD,* Jonathan A. Fletcher, MD,* and Marica R. Nucci, MD*
Endometrial stromal tumors

2014 WHO classification:
1. Endometrial stromal nodule
2. Low grade endometrial stromal sarcoma
3. High grade endometrial stromal sarcoma
4. Undifferentiated uterine sarcoma

Outline

- Changes in classification of endometrial stromal neoplasms

- Low-grade endometrial stromal sarcoma
  - High-grade endometrial stromal sarcoma
  - Undifferentiated uterine sarcoma
Low-grade endometrial stromal sarcoma

Clinical features:
- < 20% of uterine sarcomas
- Mean age 52 years
- 10-25% are premenopausal
- Abnormal bleeding, abdominal pain
- Associated with long term estrogen (tamoxifen) and radiation?

Low-grade ESS

Gross features:
- Variable size
- Polypoid or intramural mass
- Well circumscribed/ill-defined/overtly permeative
- Intravascular tumor plugs
- Fleshy, yellow-tan cut surface
- Hemorrhage and/or necrosis
**Low grade ESS**

*Microscopic features:*
- Resembles proliferative phase endometrial stroma
- Small uniform cells with minimal to no cytologic atypia with delicate vascular network
- Low mitotic activity (usually less than 5 per 10 hpf)
- Permeative (finger-like) myometrial invasion
- LVI may be present
- Foamy histiocytes, hemorrhage, necrosis
Low grade ESS: cholesterol clefts

Low grade ESS: collagen

Low grade ESS: histiocytes

Low grade ESS: Permeative invasion
Low-grade ESS

Variant morphology:
- Smooth muscle
- Sex-cord
- Fibroblastic/fibromyxoid
- Glandular
- Rhabdoid
- Epithelioid

Can arise in extra-uterine sites in endometriosis (only after excluding uterine origin)
Low grade ESS: Ancillary techniques

- Immunohistochemistry
- Molecular genetics
Low grade ESS: Immunohistochemistry

- CD10, ER, PR
- Can display some staining for smooth muscle markers (SMA, desmin) and keratin
- Nuclear staining for beta-catenin (?)

Low grade ESS: Molecular genetics

- **JAZF1-SUZ12** (most common ~50% of tumors)
- **JAZF1-PHF1**
- **EPC1–PHF1** (tumors with sex cord features)
- **MEAF6–PHF1**
- **MBTD1–Cxorf67**
- **ZC3H7B–BCOR**

Low-grade ESS: Clinical course

- Stage most important prognostic factor
  - 5 year survival for stage I-II >90%
  - 5 year survival for stage III-IV 40-50%
- Recurrence in up to half of patients
- Median time to recurrence: 3-5 years (may exceed 20 years)
- Most frequent sites of recurrence: pelvis and abdomen
- Lung metastases in ~10% stage I tumors

Koontz JI. Proc Natl Acad Sci U S A 2001
Low-grade ESS

- Treatment:
  - Surgical resection
  - Radiation therapy
  - Hormonal therapy

Problematic issues with low-grade ESS

- Endometrial stromal nodule versus endometrial stromal sarcoma
- Biopsy/curettage specimens
- ESS versus cellular leiomyoma and intravenous leiomyomatosis

Endometrial stromal nodule versus low-grade ESS

- Well circumscribed
- Can be very large (>20 cm)
- Myometrium or endometrium based
- Morphology is identical to low grade ESS
- Benign clinical course

Tavassoli FA, Norris HJ. Histopathology 1981
Endometrial stromal nodule versus low-grade ESS

**Distinction:**
1. Myometrial invasion
2. Lymphovascular invasion

**Endometrial stromal nodule versus low-grade ESS**

**Myometrial invasion:**
- Up to 3 foci of myometrial invasion each measuring less than 3 mm permitted in endometrial stromal nodule (Tavassoli and Norris 1981)
- Deeper (but limited) myometrial invasion permitted and designated “endometrial stromal nodule with limited myometrial invasion” but not sufficient clinical follow-up (Dionigi A. Am J Surg Pathol 2002)

**Sample tumor-myometrial junction well!**
Minimal myometrial invaginations permitted in endometrial stromal nodule.

The presence of definitive LVI clinches a diagnosis of low-grade ESS.
Biopsy/curettage/myomectomy specimens

- Distinction between low-grade ESS and ESN not possible
- Diagnosis: “Endometrial stromal neoplasm, distinction between ESS and ESN requires extensive assessment of tumor-myometrial interface”
- Young patients: correlate with radiologic and hysteroscopic findings

Low-grade ESS with smooth muscle metaplasia versus cellular leiomyoma and intravenous leiomyomatosis (IVL)
Low-grade ESS with smooth muscle metaplasia versus cellular leiomyoma

- Important distinction clinically
- Can be problematic
- Morphologic and immunophenotypic overlap

<table>
<thead>
<tr>
<th>Gross features</th>
<th>Endometrial stromal with smooth muscle metaplasia</th>
<th>Cellular leiomyoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopic features:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Spiral like arterioles</td>
<td>Large thick-walled blood vessels</td>
</tr>
<tr>
<td>Peripheral clefts</td>
<td>Absent</td>
<td>Often present</td>
</tr>
<tr>
<td>Areas of typical endometrial stromal morphology</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Starburst nodules</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>
Low-grade ESS with smooth muscle differentiation: Starburst nodules

Low-grade ESS with smooth muscle differentiation: areas of typical low-grade ESS confirm the diagnosis
### Low-grade ESS with smooth muscle metaplasia versus cellular leiomyoma

<table>
<thead>
<tr>
<th>Immunohistochemistry</th>
<th>Endometrial stromal with smooth muscle metaplasia</th>
<th>Cellular leiomyoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD10</td>
<td>+</td>
<td>-/+</td>
</tr>
<tr>
<td>Desmin</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>SMA</td>
<td>-/+</td>
<td>+</td>
</tr>
<tr>
<td>H-caldesmon</td>
<td>+/- (positive only in areas with smooth muscle metaplasia)</td>
<td>+</td>
</tr>
<tr>
<td>Beta-catenin (nuclear)</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Molecular abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JAZF1 fusion</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Only present in areas of smooth muscle metaplasia.

**CD10 not specific: Often positive in cellular leiomyoma and leiomyosarcoma**

**Smooth muscle markers: Can be positive in ESS in areas of smooth muscle metaplasia (h-caldesmon most specific marker)**

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**Intravenous leiomyomatosis**

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**Intravenous leiomyomatosis**

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**An Immunohistochemical Analysis of Endometrial Stromal and Smooth Muscle Tumors of the Uterus: A Study of 54 Cases Emphasizing the Importance of Using a Panel Because of Overlap in Immunoreactivity for Individual Antibodies.**

Oliva, Esther; Young, Robert; Amin, Mahul; Clement, Philip

Outline

• Changes in classification of endometrial stromal neoplasms

• Low-grade endometrial stromal sarcoma
  • High-grade endometrial stromal sarcoma
  • Undifferentiated uterine sarcoma

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High grade endometrial stromal sarcoma

**WHO definition:**

“A malignant tumor of endometrial stromal derivation with high-grade, round-cell morphology sometimes associated with a low-grade spindle cell component that is mostly fibromyxoid” (ESS with YWHAE rearrangement)

“Rarely a high grade sarcoma is seen with areas that have the appearance of a conventional low-grade ESS and can also be diagnosed as high-grade ESS”

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**YWHAE-NUTM2 rearranged ESS**

• **YWHAE-FAM22**
• t(10;17)(q22;p13)
• 28-67 years (mean 50 yrs)
• Abnormal vaginal bleeding
• Pelvic mass
• Extra-uterine disease at presentation


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**YWHAE-NUTM2 rearranged ESS**

**Gross features:**

• Exophytic polypoid or intramural mass
• Tan-yellow cut surface
• Hemorrhage and necrosis
• Often deep myometrial invasion
• Extra-uterine disease
The Clinicopathologic Features of YWHAE-FAM22 Rearranged Endometrial Stromal Sarcoma: A Histologically High-grade and Clinically Aggressive Tumor

Lee, Cheng-Han; MD, PhD; Marino-Enriquez, Adrian; Ou, Wenbin; Zhu, Meijun; Ali, Rola; Chiang, Sarah; Amant, Frederic; ... a large mass (9 cm) in the posterior uterine wall (A) bivalved uterus, (B) cross-sections of the posterior uterine wall.

YWHAE-NUTM2 rearranged ESS

Like low-grade ESS:
- Tongue-like myometrial invasion
- Rich capillary network
- Vascular invasion
- No pleomorphism

Unlike low-grade ESS: Higher grade nuclei, mitoses and necrosis

**YWHAE-NUTM2 rearranged ESS**

**Round cell component:**
- High cellularity
- Nested growth
- Epithelioid cells
- Large irregular nuclei
- Necrosis present
- High mitotic activity

**Spindle cell component:**
- Low cellularity
- Diffuse growth
- Spindle cells
- Small bland nuclei
- Necrosis absent
- Low mitotic activity

May be composed of one or both components
**YWHAE-NUTM2 rearranged ESS**

**Round cell component:**
- CD10 negative
- ER/PR negative/focal
- Cyclin-D1: Positive
- C-kit: Positive
- MIB-1: 20-30%

**Spindle cell component:**
- CD10 positive
- ER/PR positive
- Cyclin-D1: weak/patchy
- C-kit: weak/patchy
- MIB-1: Low

**Cyclin-D1 in spindle cell component**
- Strong nuclear staining in >70% of tumor cells

**Cyclin-D1 in round cell component**

**YWHAE-FAM22 rearranged ESS: Cyclin-D1**

- Sensitive
- Not specific for the presence of YWHAE rearrangement

**YWHAE ESS = Cyclin-D1 +/- CD10-**
CD117: Cytoplasmic and membranous staining in round cell component

YWHAE-FAM22 rearranged ESS: c-kit

- Moderate to strong cytoplasmic and membranous staining for c-kit in round-cell component
- Fibromyxoid/spindle component negative or patchy cytoplasmic staining
- No c-kit mutations detected
- DOG-1 negative

Lee CH, et al. Mod Pathol 2014

YWHAE-FAM22 rearranged ESS

Molecular analysis:
- FISH
- RT-PCR

- Specific rearrangement
- Not seen in multiple adult tumors including smooth muscle tumors, adenosarcoma, carcinosarcoma and undifferentiated uterine sarcoma
- Also seen in clear cell sarcoma of the kidney
- YWHAE and JAZF1 rearrangements mutually exclusive

YWHAE-NUTM2 rearranged ESS

Clinical outcome
- Patients frequently present at high stages
- Clinically aggressive
  - 2/10 dead of disease (2 years)
  - 7/10 alive with disease (1-10 years)
  - 1/10 No evidence of disease (3.75 years)

**YWHAE-NUTM2 rearranged ESS**

**Therapeutic implications:**
- Limited data suggests that adjuvant chemotherapy and radiation may provide survival benefit
- No response to hormonal therapy

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**High-grade ESS**

Back to our case.....

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**Case**

- Tumor sent to Mayo Clinic for FISH
  - No rearrangement of the JAZF1, PHF1 or YWHAE genes identified
  - Diagnosis?
  - High grade ESS (permeative myometrial invasion, resemblance to endometrial stroma and nuclear uniformity)

What other tumor types belong to high-grade ESS?

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1. YWHAE rearranged ESS
2. De-differentiated ESS
3. Other uniform high grade sarcomas that lack YWHAE rearrangements
High grade ESS

De-differentiated ESS:
- Low grade ESS and high grade sarcoma
- Heterologous differentiation
- Cyclin-D1 negative
- At presentation or in recurrence
De-differentiated ESS
- Classification?
- WHO 2014: Included in both high grade ESS and undifferentiated uterine sarcoma
- Clinical outcome? More aggressive?

High grade ESS
- Other uniform high grade sarcomas that lack YWHAE rearrangements?
- Further studies
- Better delineation

High grade ESS: UCSF experience
- 6 high-grade ESS
  1. HG-ESS, YWHAE-NUTM2 (1)
  2. HG-ESS, de-differentiated (1)
  3. HG-ESS, not otherwise specified (4 – variety of somatic mutations and copy number gains and losses)
- 1 undifferentiated uterine sarcoma: p53 mutation
- 4 low-grade ESS: 2 JAZF1, 1 YWHAE (fibroblastic variant)

Problematic issues with high-grade ESS

Distinction from:
- Low-grade endometrial stromal sarcoma
- Gastrointestinal stromal tumor (GIST)
- Undifferentiated carcinoma
- Undifferentiated uterine sarcoma

Low-grade versus high-grade ESS

• Prognostic and therapeutic implications
• Can be problematic

<table>
<thead>
<tr>
<th></th>
<th>Low grade ESS</th>
<th>High grade ESS</th>
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<tbody>
<tr>
<td><strong>Morphology:</strong></td>
<td></td>
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<tr>
<td>Nuclei</td>
<td>Small, smooth contours</td>
<td>Large, irregular contours</td>
</tr>
<tr>
<td>Mitotic activity</td>
<td>Usually &lt;5 mitoses per 10 hpf</td>
<td>High</td>
</tr>
<tr>
<td>Tumor necrosis</td>
<td>Absent</td>
<td>Frequently present</td>
</tr>
<tr>
<td><strong>Immunophenotype:</strong></td>
<td></td>
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<tr>
<td>CD10, ER, PR</td>
<td>Positive</td>
<td>Negative/focal</td>
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<tr>
<td>Mib-1</td>
<td>Low</td>
<td>High</td>
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<tr>
<td>CD117</td>
<td>Focal/patchy</td>
<td>Can be positive</td>
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<tr>
<td>Cyclin-D1</td>
<td>Focal/patchy</td>
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<td><strong>Molecular genetics:</strong></td>
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<td>JAZF1/SUZ12/PHF1/EPC1</td>
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Low-grade versus high-grade ESS?

Cytology is key in distinction.
High-grade ESS versus gastrointestinal stromal tumor (GIST)
- Problematic differential in extra-uterine sites such as ovary
- Morphologic overlap
- Immunophenotypic overlap
High-grade ESS versus GIST

<table>
<thead>
<tr>
<th></th>
<th>CD117</th>
<th>Cyclin-D1</th>
<th>DOG-1</th>
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<tbody>
<tr>
<td>High grade ESS</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>GIST</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
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</tbody>
</table>

Panel should include c-kit, cyclin-D1 and DOG-1

High-grade ESS versus undifferentiated carcinoma

- Morphologic overlap
- Presence of hyperplasia or low grade endometrioid adenocarcinoma
- Presence of lymph node metastasis?
- Immunohistochemistry of limited use
  - Focal but strong staining for epithelial markers
  - Cyclin-D1 not helpful
  - Loss of MMR proteins favor undifferentiated carcinoma
High grade ESS versus undifferentiated uterine sarcoma

- Problematic to separate from uniform undifferentiated uterine sarcoma
- Permeative versus destructive myometrial invasion
- Resemblance with endometrial stroma?

Outline

- Changes in classification of endometrial stromal neoplasms
- Low-grade endometrial stromal sarcoma
- High-grade endometrial stromal sarcoma
- Undifferentiated uterine sarcoma
Undifferentiated uterine sarcoma

- No resemblance with endometrial stroma
- Lacks specific differentiation
- Rare
- Postmenopausal patients
- Often presents at high stages

Undifferentiated uterine sarcoma

- **Gross features:**
  Polypoid mass, fleshy with hemorrhage and necrosis
- **Microscopic features:**
  - Marked cytologic atypia and nuclear pleomorphism
  - Brisk mitotic activity with atypical mitoses
  - Destructive myometrial invasion

Undifferentiated uterine sarcoma

- Immunohistochemistry: ER/PR negative or weak, CD10 +/-, Cyclin-D1 +/-, aberrant p53
- Molecular abnormalities: Complex chromosomal changes including gains and losses, p53 mutation

Undifferentiated uterine sarcoma

- High stage
- Poor prognosis
Undifferentiated uterine sarcoma
Problematic issues with undifferentiated uterine sarcoma

- Undifferentiated uterine sarcoma versus high grade leiomyosarcoma
- Undifferentiated uterine sarcoma versus carcinosarcoma

Undifferentiated uterine sarcoma versus high grade leiomyosarcoma

Undifferentiated uterine sarcoma versus leiomyosarcoma

- Smooth muscle differentiation (morphology and/or immunophenotype)
  - SMA
  - Desmin
  - Caldesmon
Undifferentiated uterine sarcoma versus carcinosarcoma

- Malignant glandular component
- Sample well
Summary

• High grade ESS re-introduced in 2014 WHO classification of endometrial stromal tumors

2014 WHO classification:
1. Endometrial stromal nodule
2. Low grade endometrial stromal sarcoma
3. High grade endometrial stromal sarcoma
4. Undifferentiated uterine sarcoma

Thank you!

References