ESS: Pathologic Insights

Sílvia Bagué
The Royal Marsden Hospital
London (United Kingdom)
I have no conflicts of interest
Endometrial stromal sarcoma

• Three main categories (WHO 2014):
  Low-grade (LG-ESS)
  High-grade (HG-ESS)
  Undiff uterine sarcoma (UUS)
Three main categories (WHO 2014):
- Low-grade (LG-ESS)
- High-grade (HG-ESS)
- Undiff uterine sarcoma (UUS)
Endometrial stromal sarcoma

- <1% all uterine malignancies
- 7-25% malignant mesenchymal uterine tumors (2nd most common type)
- Pick incidence 4th-5th decades
- Abnormal uterine bleeding; pelvic pain
- Intracavitary polypoid / intramyometrial
- Some arise in extrauterine sites (origin in endometriosis postulated)
- Can present as intraabdominal soft tissue tumor
Low-grade ESS (LG-ESS): microscopic pathology

- Diffuse infiltrative growth ("tongue-like pattern"): irregular islands infiltrating myometrium
- No desmoplastic response
Low-grade ESS (LG-ESS): microscopic pathology

- Diffuse infiltrative growth ("tongue-like pattern"): irregular islands infiltrating myometrium
- Lymphovascular invasion
Low-grade ESS (LG-ESS): microscopic pathology

- Cells that resemble those of proliferative endometrium
- Very cellular
- Arteriolar-like vessels
- No significant atypia
- Mitotic rate < 5/10 HPF (but may be high and does not alter prognosis)
- Lymphovascular invasion or not
Low-grade ESS (LG-ESS): morphologic variants

- Smooth muscle differentiation (>30%)
- Myxoid and fibroblastic differentiation
- Sex cord-like elements
- Müllerian-type glands
- Skeletal muscle differentiation
- Epithelioid, rhabdoid appearance
- Clear cell cytoplasm
- Papillae/pseudopapillae
- Adipose metaplasia
- Bizarre nuclei
- Osteoclast-type cells
Low-grade ESS (LG-ESS): morphologic variants

- Smooth muscle differentiation (>30%)
- Myxoid and fibroblastic differentiation
- Sex cord-like elements
- Müllerian-type glands
- Skeletal muscle differentiation
- Epithelioid, rhabdoid appearance
- Clear cell cytoplasm
- Papillae/pseudopapillae
- Adipose metaplasia
- Bizarre nuclei
- Osteoclast-type cells
Immunohistochemistry

CD10 +

ER +

Desmin -

PgR +
Molecular features

LG-EES (50%): t(7;17)(p21;q15) → JAZF1-SUZ12 gene fusion
Others: EPC1-PHF1 > PHF1-JAZF1, MEAF6-PHF1

Prognosis

• Surgical pathologic stage
• 5 year survival 70-84% (stages I, II)
• 10-20% risk (late) recurrence: pelvis, abdomen > lung
• Testing for genetic rearrangement-fusion: no prognostic or therapeutic differences
High-grade ESS (HG-ESS)

- 28-67 years (mean 50)
- Abnormal vaginal bleeding; enlarged uterus
- Frequent extrauterine disease

Courtesy of Dr I Costa. Hospital Parc Taulí. Sabadell
High-grade ESS (HG-ESS): microscopic pathology

Courtesy of Dr E Oliva. MGH, Boston
High-grade ESS (HG-ESS): microscopic pathology
Immunohistochemistry

- Low grade component: CD10 + ER + PR + CD117 -
- High grade component: CD10 - ER - PR - CD117 + Cyclin D1 + BCOR + > 95% tumor cells

Molecular features

HG-ESS: t(10;17)(q22;p13) → YWHAE-NUTM2 A/B gene fusion
(Associated with distinct morphologic characteristics)

Chiang S t al. Mod Pathol 2107

Prognosis

- Intermediate between LG-ESS-UUS
- 80% advanced stage disease
- Hormonal therapy: little benefit
- ChT
HG-ESS with ZC3H7B-BCOR fusion: new category!!
t(X;22)(p11;q13)

Collagen plaques

Courtesy of Dr E Oliva. MGH, Boston

Lewis N et al. Mod Pathol 2018
Mimic myxoid leiomyosarcoma morphologically

CD10 +
Cyclin D1 +
ER, PR variable
BCOR + 50%
<50% myogenic diff

Courtesy of Dr E Oliva. MGH, Boston
Undifferentiated uterine sarcoma (UUS)

- Rare
- Post-menopausal (60 yrs)
- 2/3 stage III/IV
- Intraluminal polypoid, >10 cm

- Monomorphic, pleomorphic
- IHC variable
- Complex chromosomal changes
Uterine HG sarcoma (UUS) with NTRK fusion genes

LMNA-NTRK1 gene fusion

Opportunities for systemic therapy besides hormonal treatment

Endometrial stromal tumors: immunohistochemical and molecular analysis of potential targets of tyrosine kinase inhibitors.

52 LGESS, 13 UES
No mutations KIT, PDGFRA, EGFR
No benefit of TKR inhibitors

Gene expression profiling of low-grade endometrial stromal sarcoma indicates fusion protein-mediated activation of the Wnt signaling pathway
Joanna Przybyl et al. Gynecologic oncology 2018
# Morphologic differential diagnosis of ESS

<table>
<thead>
<tr>
<th>LGESS</th>
<th>HGESS (YWHAE rearranged)</th>
<th>ESS (BCOR rearranged)</th>
<th>UUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESN</td>
<td>LGESS</td>
<td>Myxoid LMS</td>
<td>LGESS</td>
</tr>
<tr>
<td>ESN with limited infiltration</td>
<td>ESS (BCOR)</td>
<td>IMFT</td>
<td>HGESS (YWHAE)</td>
</tr>
<tr>
<td>Adenomyosis with sparse glands</td>
<td>UUS</td>
<td>HGESS with fibromyxoid changes</td>
<td>ESS (BCOR)</td>
</tr>
<tr>
<td>Intravascular menstrual endometrium</td>
<td>LMS</td>
<td>LMS</td>
<td>LMS</td>
</tr>
<tr>
<td>IVL</td>
<td>PNET/Ewing’s</td>
<td>UUS</td>
<td>Adenosarcoma</td>
</tr>
<tr>
<td>LMS</td>
<td>GIST</td>
<td></td>
<td>Carcinosarcoma</td>
</tr>
<tr>
<td>HGESS</td>
<td>PEComa</td>
<td></td>
<td>Lymphoma</td>
</tr>
<tr>
<td>UTROSCT</td>
<td>Synovial sarcoma</td>
<td></td>
<td>Melanoma</td>
</tr>
<tr>
<td>PEComa</td>
<td></td>
<td></td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>GIST</td>
<td></td>
<td></td>
<td>Undifferentiated carcinoma</td>
</tr>
<tr>
<td>HPC/SFT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ESS subtypes

<table>
<thead>
<tr>
<th>ESS subtype</th>
<th>Molecular</th>
<th>Histology</th>
<th>IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LG-ESS</td>
<td>JAZF1-SUZ12 (50%) t(7;17)(p15;q21)</td>
<td>Bland ovoid cells Arterioles May have fibroblastic, myxoid</td>
<td>CD10+ ER+ PR+ Desmin, caldesmon +/- CyclinD1-</td>
</tr>
<tr>
<td><strong>High-grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HG-ESS</td>
<td>YWHAE-NUTM2A/B t(10;17)(q22;p13)</td>
<td>Round cell Mitotic activity Low-grade comp (fibrous, fibromyxoid or conventional low-grade)</td>
<td>CD10- ER- PR- CyclinD1+ BCOR+ CD117+</td>
</tr>
<tr>
<td><strong>High-grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HG-ESS</td>
<td>ZC3H7B-BCOR t(X;22)(p11;q13)</td>
<td>Fascicular spindle cell, myxoid Mitotic activity D.D. myxoid leiomyosarcoma !! NO low-grade component</td>
<td>CD10+ ER, PR (30%) CyclinD1+ BCOR+ (50%) Myogenic markers –ve</td>
</tr>
<tr>
<td><strong>High-grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UUS</td>
<td></td>
<td>Uniform, pleomorphic</td>
<td>Diagnosis of exclusion</td>
</tr>
</tbody>
</table>

### Other uterine sarcomas

<table>
<thead>
<tr>
<th>Uterine sarcoma</th>
<th>Spindle cell</th>
<th>IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyosarcoma</td>
<td></td>
<td>Desmin+, SMA, caldesmon+ ER+ PR+ (40%)</td>
</tr>
<tr>
<td>Fibrosarcoma-like uterine sarcoma</td>
<td>NTRK fusion genes</td>
<td>Spindle cell</td>
</tr>
</tbody>
</table>
Summary

- Novel uterine sarcoma subtypes with characteristic morphology and underlying genotypes
- LG-ESS harbour JAFZ1 genetic alterations; HG-ESS includes tumors with YWHAE and BCOR genetic abnormalities
- New fibrosarcoma-like uterine sarcoma with NTRK fusions with therapeutic target options (TRK inhibitors)
- Molecular profiling necessary in accurate tumor classification and designing future targeted molecular-based therapies.
Thank you for your attention

silvia.bague@rmh.nhs.uk