Diagnostic and molecular aspects of endometrial stromal tumors

Prof. dr. sc. Snježana Tomić
KBC Split, Hrvatska
• Second most common pure mesenchymal tumors of the uterus
• <10% all such tumors
• Most originate in uterus, some of them arise outside the uterus, presumably in endometriosis
ENDOMETRIAL STROMAL TUMORS
WHO classification 2003.

- Endometrial stromal nodule
- Low-grade endometrial stromal sarcoma
- Undifferentiated endometrial/uterine sarcoma
Endometrial stromal nodule and low-grade endometrial stromal sarcoma

- **Shared clinical features:**
  - Frequently diagnosed between 40 and 55 years
  - 1/3 of patients are postmenopausal
  - Abnormal uterine bleeding or pelvic/abdominal pain common presentation
  - May be asymptomatic
Endometrial stromal nodule and low-grade endometrial stromal sarcoma

- **Shared histological appearance**
  - Tumors composed of cells resembling those of the proliferative-phase endometrial stroma.
  - Numerous thin-walled small arteriolar type vessels are characteristically present.
Differential histologic features

- Miometrial and/or vascular invasion
Reporting endometrial stromal tumors in curettage specimens

- Adequate sampling of the tumor-myometrial interface is necessary in order to:
  - Evaluate the degree of infiltration of the tumor into the myometrium
  - Correctly classify the tumor
  - Properly treat the patient
- In 99% of cases, margins cannot be completely assessed in endometrial curettage
- Working diagnosis should be endometrial stromal tumor!
Endometrial stromal nodule

- Unusual benign endometrial stromal tumor characterized by a well delineated expansile margin on microscopic examination
- Presence of focal irregularities in the form of small satellite nodules or finger-like projections into the adjacent myometrium that do not extend more than 3 mm from the main nodule and there is no vascular invasion
Clinical behaviour and treatment of ESN

• Benign
• Hysterectomy because the periphery of the tumor must be carefully evaluated to be sure that it is completely circumscribed and noninvasive
• In occasional cases, in young women small nodules can be treated by local excision
• Patients with limited myoinvasion beyond 3 mm (3 mm – 1 cm) and no vascular invasion may have a favorable outcome but there is insufficient follow up to be certain

• Tumors of this type may be designated as
  – EST with limited infiltration or
  – LG ESS with limited infiltration
LG Endometrial stromal sarcoma

- 10-15% of uterine malignancies with a mesenchymal component
- Staging following carcinoma FIGO staging
- Occasionally association with prolonged estrogenic stimulation, tamoxifen treatment, or prior pelvic irradiation
Growth patterns of LG-ESS

- Intramyometrial nodular masses
- Intracavitary polypoid mass
- Diffuse myometrial infiltration with expansion of the uterine wall
- Any combination of these patterns
• Smooth muscle differentiation is common in EST
• Characteristically epithelioid smooth muscle cells are embedded in aggregates of hyalinized collagen – “start-burst like appearance”
Epithelial like differentiation

- Occurs in about 25% ESS
- Highly variable in appearance
- Most commonly in the form of benign endometrioid-type glands
• Sex cord differentiation may be present

• If sex cord differentiation is prominent, diagnosis of UTROSCT should be considered
Immunohistochemistry

- ESN and LG ESS are typically positive for vimentin.
- Muscle specific and smooth muscle actin staining is variable, often weak and focal.
- Staining for desmin and caldesmon is absent in most stromal tumors.
- Staining for keratin is reported in EST (diffuse or confined to epithelial like structures).
• Nearly all EST stain for CD10
• Smooth muscle tumors, MMMT and rhabdomyosarcomas may be CD10 positive
• This antibody should not be used in isolation!
• Areas of smooth muscle differentiation are usually positive for all smooth muscle markers and CD10

• WT-1, ER, PR are positive in majority of cases, some of them are positive for AR and β-catenin.
Differential diagnosis

- Endometrial stromal nodule
- UES
- Highly cellular leiomyoma with irregular interdigitating interface
- Intravenous leiomyomatosis
- PEComas
- Adenomyosis with sparse glands
- “Intravascular” adenomyosis
- Intravascular menstrual endometrium
Low-grade endometrial stromal sarcoma
Prognosis and treatment

• Hysterectomy and bilateral oophorectomy standard treatment for stage I and debulking of extrauterine tumor in more advanced case

• Progestin therapy, aromatase inhibitors or radiation as other options of treatment. Chemotherapy tends to be ineffective

• Stage is most powerfull prognostic factor!!!!!
Molecular biology

- Most recently, two zinc finger genes — JAZF1 and JJAZ1 were discovered to be fused head to tail in most cases of endometrial stromal tumors.
• The great majority of endometrial stromal nodules and 50% of endometrial stromal sarcomas contain the *JAZF1-JJAZ1* gene fusion, most often as a consequence of the *(7;17)(p15;q21)* chromosomal translocation
• Smaller subset of LG ESS show a 6p21 rearrangement which lead to the fusion of PHF1 with partner genes such as JAZF1 or EPC1
• The product of *JJAZ1* and PHF1 gene is an essential member of the protein complex that in most or perhaps all cells catalyzes specific methylations of histone, leading to chromatin compaction and transcriptional silencing of DNA.
• Consistent molecular feature distinguishing ESSs from ESNs is that the unrearranged *JJAZ1* allele is silenced in ESSs but is active in ESNs.
• Expression of the JAZF1-JJAZ1 gene fusion confers resistance to apoptosis and increased proliferative capacity although the latter occur only when the normal JJAZF1 alleles are suppressed.
• These data are consistent with ESNs arising from normal endometrial stroma through acquisition of the \textit{JAZF1-JJAZ1} gene fusion, and ESSs arising from ESNs after epigenetic silencing of the unrearranged \textit{JJAZF1} allele.
• Assuming that this model is correct it will be an example of a sarcoma developing from a benign precursor
• The translocation can be detected by
  – Traditional cytogenetics
  – Molecular pathologic tests
    • RT-PCR or
    • FISH

• At present, testing for the translocation is a research procedure, not a clinical diagnostic test
Undifferentiated endometrial sarcoma (UES)

- Extremely rare tumors – about 6% of uterine sarcomas
- Grossly: fleshy, gray cut surface with common areas of haemorrhage and necrosis
• Some are composed of monotonous cells that bear at least some resemblance to endometrial stromal cells – in the past HG ESS

• Current WHO classification all high grade ES grouped together in the UES category
LG ESS – monomorphic UES
• **Tumor cells are larger with greater nuclear atypia!!!**

• Mitotic figure is no longer considered to be only criterion for distinguishing between LG ESS and UES, but as a general rule MF tend to be numerous in UES

• Uniform proliferation of small blood vessel is not present in UES
- In LG ESS myometrial invasion is in form of tongue of tumor cells appear to push between smooth muscle bundles.
- In UES myometrial invasion tend to be along broad front with destruction and replacement of involved areas of myometrium.
Occasional tumors have a mixture of ESS and UES usually of the monomorphous type, indicates that, at least occasionally an LG ESS can evolve into a higher-grade sarcoma.
LG ESS

Shared some histological, immunohistochemical, and molecular features

MONOMORPHIC UTERINE ENDOMETRIAL SARCOMA

PLEOMORPHIC UTERINE ENDOMETRIAL SARCOMA

Booth have very poor prognosis
Pleomorphic UES

- Marked cellular pleomorphism and brisk mitotic activity
- Should be diagnosed only after extensive sampling
Diagnosis is made by exclusion!!!

- Leiomyosarcoma
- Rhabdomyosarcoma
- Adenosarcoma, especially with stromal overgrowth
- Carcinosarcoma (MMMT)
- Undifferentiated endometrial carcinoma
• Treatman includes hysterectomy and radiation therapy and/or chemotherapy depending on the stage of the tumor
• Very aggressive behavior (most patients die within 2 years of diagnosis)
• An effective chemotherapy regimen is not available and most UES do not express progesterone receptors or respond to hormonal therapy