An Update on Uterine Mesenchymal Tumours

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Uterine Mesenchymal Tumours

- **Smooth Muscle**
  - Benign
  - Unusual SMT mimics of LMS
  - STUMP
  - Leiomyosarcoma

- **Endometrial Stromal Tumours (WHO 2014)**
  - Stromal nodule
  - Low grade (ESS)
  - High grade (ESS)
  - Undifferentiated Uterine Sarcoma (UUS)
Uterine Mesenchymal Tumours

- Uterine Tumour resembling ovarian sex cord tumours
- Rhabdomyosarcoma
- Perivascular epithelioid cell tumour (PEComa)
- Rare
  - Benign: lipoma, haemangioma and lymphangioma
  - Malignant: angiosarcoma, liposarcoma, osteosarcoma, chondrosarcoma
- Myxoid smooth muscle tumours
  Benign/ malignant
- Epithelioid smooth muscle tumours
  Benign/malignant
ESS: journey through terminology
ESS

• Norris and Taylor 1966

• **Endometrial Stromal Sarcoma** (morphological classification)
  – Cells resemble endometrial stroma in proliferative phase

• 35 cases in study:
  – range of Mitotic activity and nuclear atypia
Norris and Taylor 1966

- Mitotic activity
  - >10MF/10 HPF (50% 5 year survival)
  - <10MF/10 HPF (100% 5 year survival but 30% recurred)
- Nuclear atypia
  - greater in high grade vs low grade group but overlap noted.
- This lead to stratification of ESS on MI
  - low grade ESS
  - high grade ESS
Evans HL 1982

• Cancer 1982
• ESS should be separated from poorly differentiated endometrial sarcoma (resemblance to endometrial stroma and arborising vasculature)
• Poorly differentiated ES:
  – Larger cells
  – Nuclear Hyperchromasia
  – Pleomorphism
  – Stromal vasculature not prominent
  – Frequent necrosis
  – Increased mitotic activity but **MA was not itself an important prognosticator**
Change KL et al  109 ESS (largest study) 1990

- Primary uterine endometrial stromal neoplasms. A clinicopathologic study of 117 cases
  Chang KL, Crabtree GS, Lim-Tan SK, Kempson RL, Hendrickson MR

- Primary uterine tumour > 0.5 cm in size resemble Prolif Endo
- Serpentine infiltration through myometrium
- Intravascular growth
- Mitotic rate does not predict recurrence in Stage I patients
Silverberg and Kurman (1992)

- Recognised 3 categories:
  - Low grade ESS
  - High Grade ESS
  - Undifferentiated Sarcoma

- Made case: importance that tumour must morphologically resemble stromal cells of proliferative endometrium
ESS

- ESN (endometrial stromal nodules)
- ESS ("low grade" endometrial stromal sarcoma)
- UES (Undifferentiated endometrial sarcoma)

Prognosis

5 year survival

ESS 85%
UES <50%
Classification

- Greater emphasis placed on morphology of tumour cells

Must resemble stroma of proliferative phase of endometrium
ESS (WHO 2003)

- Dichotomous system: based on cytology
  - ESS (low grade): tumour cells resemble stroma of proliferative phase of endometrium
  - UES (high grade endometrial sarcoma): no resemblance to proliferative phase endometrial stroma
  - Lacks specific differentiation
  - No longer differentiated on mitotic activity but:
    - On degree of nuclear atypia
    - Tumour necrosis
WHO 2003- Demise of HG-ESS!

• Rationale for demise of HG- ESS:

1. High mitotic activity: Discourage mislabelling of classic low grade ESS as high grade based on mitotic activity

2. Misclassification: Recognition that tumours that had been labelled as HG ESS bore no morphological resemblance to endometrial stroma and were undifferentiated pleomorphic uterine sarcoma
The Grey zone

• Chang et al did recognise a subgroup of ESS that showed nuclear atypia and increased mitotic activity that could not be labelled as low grade ESS
• Low grade ESS with some high grade features
• Low grade transformation into high grade ESS
• 2003 Terry Rollason: made a case to retain HGSS recognising that rare cases encountered where low grade ESS juxtaposed to HGESS (Haines and Taylor editors Fox and Wells)
High grade sarcoma

- Kurihara et al 2008
  - UES-U (with nuclear uniformity)
  - UES-P (with nuclear pleomorphism) - reflects high grade sarcoma

- Sample size was small 31 cases
  - 18 LGESS
  - 7 UES-U (uniform)
  - 6 UES-P (pleomorphism)

- No apparent clinical differences with regards to clinical outcome between these two groups (57% vs 60%)
WHO 2014- Updated grading for EST

- Endometrial stromal nodule
- Endometrial stromal sarcoma (low grade)
- Endometrial stromal sarcoma (high grade) specific t(10:17)
- Undifferentiated Uterine Sarcoma
ESN (Stromal nodule)

- Rare neoplasm
- 23-86 years (mean 53 years)
- Definition: WHO
- Benign endometrial stromal tumour that has a well-circumscribed margin and is composed of cells that resemble proliferative phase endometrial stroma. Finger-like projections or immediately adjacent nests of tumour cells (measuring, 3mm in greatest extent from the main mass) and, <3 in number are acceptable. Lymphovascular invasion excludes the diagnosis.
Endometrial stromal nodule

- Grossly fleshy yellow/tan
- Histology
  - Cellular
  - Hyalinised
  - Cysts (34%)
  - Infarct type necrosis (68%)
- Up to 3mm focal irregularity allowed (Tavasoli and Norris 2002)
  - < 3 in number
  - Lobulated or finger-like projections into adjacent myometrium
  - Endometrial Stromal tumour with limited infiltration
Endometrial stromal nodule
ES neoplasms “endo polyp”

Cellular polypoid lesion no glands as part of lesion

Note base not identified. Diagnosis cannot be made.
ESN vs ESS

- Cannot be differentiated on curettage material unless entire lesion represented in curettage material

- Infiltrative margins/vascular invasion (required)

- Hysterectomy

- EXAMINE PERIPHERY CAREFULLY.
HP endo “polyp”

Need hysterectomy to make a definitive diagnosis
Stromal nodule vs. HC leiomyoma

Cellular leiomyoma
  Fascicular growth

Stromal nodule
Cellular leiomyoma vs. ESN

Small vessels and cellularity compare with endometrial stromal neoplasm
Endometrial Stromal Sarcoma

- **Main site of origin**
  - Uterine corpus

- **Extra-Uterine Sites**
  - Ovary
  - Peritoneum
Endometrial stromal sarcoma- low grade

Clinical features

- Age usually < 50 years
- Dysfunctional uterine bleeding
- Pelvic or abdominal pain
- Variable sized neoplasm (polypoid / bulky)
- Indolent and protracted course (characterised by recurrences)
Endometrial stromal sarcoma
Endometrial stromal sarcoma

Cystic change
LG Endometrial Stromal Sarcoma-cells

- Proliferation of small, round to oval monomorphic cells
- Scant cytoplasm
- Nuclei have smooth contours (round to oval in shape)
ESS

Finger like myometrial permeation
ESS- lymphovascular permeation

Lymphovascular permeation - conspicuous feature
ESS “low grade”

Stroma resembles proliferative phase stroma
Endometrial stromal sarcoma

Cystic change
ESS

Extensive hyalinisation

Glandular differentiation
ESS with glandular differentiation

Marked stromal cellularity with familiar small calibre arterioles
ESS with glandular differentiation


Endometrial stromal sarcoma

“star-burst” pattern of hyalinisation suggests SM differentiation
Myxoid differentiation
ESS with SM differentiation

Dual cell population
ESS epithelioid differentiation

Distinct epithelioid areas
ESS sex cord like pattern
Endometrial stromal sarcoma

- Variants
  - Fibrous/myxoid foci
  - Smooth muscle differentiation
  - Sex-cord like differentiation
  - With endometrial glands
  - Epithelioid morphology
  - Pseudopapillae formation
  - Granular eosinophilic cytoplasm
  - Clear cytoplasm
  - Rhabdoid features/ skeletal muscle differentiation
Immunohistochemistry of LGESS

- CD10 – strong diffuse positive (usually)
- ER/ PR/ WT1 : typically positive
- SMA - often positive
- Desmin- occasionally positive
- H-caldesmon –negative (+ ve smooth muscle differentiation)
- C-Kit (CD117) – may be positive but no c KIT mutations
- Aromatase
- Androgen receptor –may be positive (sex cord like areas)
- AE1/AE3 – epithelial differentiation
- Inhibin/ calretinin/melan-A and CD99- may be positive
**ESS (low grade) Molecular genetics**

- **t(7;17) - 80%**  
  - JAZF1-SUZ12

- **t(6;7) - 6%**  
  - PHF1-JAZF1

- **t(6;10) - 4%**  
  - EPC1-PHF1

- **Am J Surg Pathol. 2011 Sep;35(9):1364-72**

- **Frequency of known gene rearrangements in endometrial stromal tumours**

- **Chiang S et al.**
JAZF1-SUZ12 and JAZF1-PHF1

- Genetic fusions- fusion oncoprotein (transcriptional dysregulation)

- Oncogenic influences mediated through altered transcriptional control in endometrial stromal progenitor cells

- Different genotypes
  - Exhibit similar clinical behaviour
  - Low grade histological features
  - Some genetic re-arrangements may be associated with specific variants (PHF1 rearrangement associated with sex cord differentiation)
Re-birth of HG ESS (WHO 2014)

- **YWHAE-FAM22 (NUTM2)**
  - Arise from uterus
  - Grossly visible mass which is myoinvasive (1-12 cm size)
  - May have extra-uterine component
  - Tongue-like myoinvasion
  - Vascular invasion
  - Arborizing stromal capillary network
  - Dual cell component (high grade round cell component and low grade spindle cell component)
  - Reminiscent of round blue cell component
The Clinicopathologic Features of YWHAE-FAM22 Endometrial Stromal Sarcomas: A Histologically High-grade and Clinically Aggressive Tumor

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YWHAE-NUTM2 high grade ESS

- UES (WHO 2003) with uniform nuclear features 50% harbour t(10:17)(q22;p13) translocation

- NUTM2A/B formerly known as FAM22A/B

- Change of nomenclature- sequence homology to NUT protein (encoded by NUTM1) important in NUT midline carcinoma

- YWHAE-NUTM2 genetic re-arrangements and JAZF1/SUZ12 and EPC1/PHF1 genetic re-arrangements mutually exclusive
Gross appearance uterus
Histology: Variable cellularity
Dual cell population

Rich vascular network comprising thin wall capillaries
Multiple mitoses (>10/10HPF)

Irregular nuclear contours but non-pleomorphic
Myometrial infiltration

Fibromyxoid where tumour permeates myometrium
Cells with round nuclei

Mitoses easily seen, nuclear enlargement 4-6 x size of lymphocyte
Small round blue cell tumour

Focal necrosis
Dual cell population

Rich vascular network comprising thin wall capillaries
Vascular permeation
Cyclin D1 as a Diagnostic Immunomarker for Endometrial Stromal Sarcoma With YWHAE-FAM22 Rearrangement

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Sarah Chiang, MD, ¶ Samuel Leung, MSc,* † Nataliya Nelnyk, MSc, † David G. Huntsman, MD, †
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Matt van de Rijn, MD, PhD, || Esther Oliva, MD, ¶ Jonathan A. Fletcher, MD, ‡ and Marisa R. Nucci, MD, ¶

Cyclin D 1 diffuse positive

Courtesy Dr Esther Oliva
HG-ESS (YWHAE-NUTM2)

- Immunohistochemistry
- High grade component
  - CD10 –ve
  - ER –ve
  - PR –ve
  - Cyclin D1 (>70%) strong, diffuse, nuclear +ve
  - C KIT (cytoplasmic strong)
  - DOG 1(-ve) in high grade and low grade areas
  - Beta-catenin (cytoplasmic) no nuclear positivity
  - Negative for:
  - EMA, SMA, desmin, caldesmon, HMB-45, Melan A and cytokeratin
FISH t(10;17)(q22;p13)

YWHAE-NUTM2 ESS  courtesy Drs Lee and Oliva
Undifferentiated Uterine sarcoma (WHO 2014)

Definition:

• A tumour arising in the endometrium or myometrium, lacking any resemblance to proliferative – phase endometrial stroma, with high-grade cytological features and with no specific type of differentiation

• Rare tumour, patients post menopausal mean age 60 years

• Prognosis: Poor. Patients present with high stage disease (>60%). Even patients with stage I disease DOD within 2 years

• Adjuvant therapy no therapeutic benefit
Undifferentiated Uterine sarcoma (2014)

- Why replace UES with UUS?
- Not all UES arise from the endometrium WHO 2014 acknowledges this
- More accurate terminology UUS
- No specific lines of mesenchymal differentiation
- Diagnosis of exclusion
Histologic features of Undifferentiated Uterine Sarcoma (UUS)

- Heterogeneous group of sarcomas lacking diagnostic criteria for:
  - ESS (high grade)
  - Leiomyosarcoma
  - Rhabdomyosarcoma
  - Adenosarcoma with sarcomatous overgrowth
  - Carcinosarcoma (esp when sarcoma has overgrown carcinoma)
  - Undifferentiated or dedifferentiated endometrial carcinoma
  - Complex Karyotype (many structural and numerical aberrations)
  - High mitotic activity and necrosis

Subset of UUS harbour missense TP53 mutations
DDx leiomyosarcoma

Marked diffuse cytologic atypia
DDx Leiomyosarcoma

Increased cellularity, coagulative necrosis with ghost outlines of cells
DDx Carcinosarcoma

With rhabdomyoblasts-heterologous differentiation
DDx: Adenosarcoma with sarcomatous overgrowth
Adenosarcoma with sarcomatous overgrowth
Sarcomatous overgrowth in adenosarcoma
DDx Undifferentiated carcinoma
DDx Undifferentiated carcinoma

Loss of MMR proteins may be seen
Immunohistochemistry of UUS

- CD10 may be positive NOT- ESS
- Hormone receptors may be positive.
- Focal SMA + (need panel of smooth muscle markers to dx LMS)
- Consider malignant PEComa
- Focal keratin or EMA consider undifferentiated or de-differentiated endometrial carcinoma
2014 WHO Classification-LGESS

- Low-grade ESS (JAZF1 LGESS and classic ESS without genetic re-arrangement)-
- Same histology and immunophenotype
  - (Cyclin D1<10%) or negative
  - CD10 Strong diffuse
  - ER strong diffuse
  - PR strong diffuse
- Presentation: usually with stage I disease (resectable)
- Prognosis: excellent (small risk of late recurrence -10-20%)
- Rx: anti-oestrogenic therapy useful in disease control (aromatase inhibitors)
YWHAE-NUTM2 ESS

- Presentation: advanced disease (stage 2-4)
- Treatment: surgery but rapid recurrence recognised (few months to years)
- Cyclin D1 strong diffuse positive >70% cells
- CD10, ER and PR classically negative in high grade component). Negative for epithelial markers.
- Anti-oestrogenic therapy (no value)
- Some long term survivors stage 2 or higher have had survival benefit with adjuvant Rx
  - Adjuvant chemotherapy
  - Radiation therapy
UUS

- May present at high stage
- Dismal prognosis for patients with stage 2 or greater
- Immunohistochemistry: Variably positive with immunohistochemical markers used for mesenchymal tumour diagnosis (no consistency)
- Subset with uniform nuclei +ve for Cyclin D1 focal ER, PR or CD10 staining may be seen (exclude YWHAE-NUTM2 high grade ESS)
- Mnx: Non-responsive to conventional chemotherapy or radiation Rx
FIGURE 7. Proposed classification for pure uterine sarcomas.
Staging LMS and ESS

FIGO staging for uterine sarcomas (2009).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
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<tbody>
<tr>
<td>(1) Leiomysarcomas and endometrial stromal sarcomas*</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Tumor limited to uterus</td>
</tr>
<tr>
<td>IA</td>
<td>Less than or equal to 5 cm</td>
</tr>
<tr>
<td>IB</td>
<td>More than 5 cm</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends beyond the uterus, within the pelvis</td>
</tr>
<tr>
<td>IIA</td>
<td>Adnexal involvement</td>
</tr>
<tr>
<td>IIB</td>
<td>Involvement of other pelvic tissues</td>
</tr>
<tr>
<td>III</td>
<td>Tumor invades abdominal tissues (not just protruding into the abdomen)</td>
</tr>
<tr>
<td>IIIA</td>
<td>One site</td>
</tr>
<tr>
<td>IIIB</td>
<td>More than one site</td>
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<tr>
<td>IIIC</td>
<td>Metastasis to pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor invades bladder and/or rectum</td>
</tr>
<tr>
<td>IVA</td>
<td>Distant metastasis</td>
</tr>
</tbody>
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(2) Adenosarcomas

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<th>Definition</th>
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<tbody>
<tr>
<td>I</td>
<td>Tumor limited to uterus</td>
</tr>
<tr>
<td>IA</td>
<td>Tumor limited to endometrium/endocervix with no myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>Less than or equal to half myometrial invasion</td>
</tr>
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(3) Carcinosarcomas

Carcinosarcomas should be staged as carcinomas of the endometrium.
DDx- rare but consider.....

- Uterus in pelvis
- Pelvis also site of other soft tissue tumours
- Is tumour Uterine in origin?
  - Mixed tumours (carcinosarcoma or adenosarcoma) (1block/cm)
  - Generous sampling (endometrium)- older people
- Is it arising from outwith the uterus
  - Dedifferentiated liposarcoma
  - PEComa (rarely from within uterus)
  - GIST (gastro-intestinal stromal tumour)
  - Peripheral nerve sheath tumour
  - Low-grade fibromyxoid sarcoma
High grade sarcoma (not mixed tumour)

- Once carcinosarcoma and adenosarcoma with sarcomatous overgrowth excluded:
  - Pleomorphic Uterine sarcoma
    - UUS, leiomyosarcoma, rare heterologous sarcomas (pleomorphic rhabdomyosarcoma)
  - Monomorphic Uterine sarcoma
    - ESS, leiomyosarcoma or IVL, dedifferentiated or undifferentiated endometrial carcinoma
    - PEComa : (HMB45, Melan A, S100, desmin, SMA, h-caldesmon)-mTOR inhibitors (recent studies suggested response)
    - Ewing’s sarcoma : Cyclin D1 +ve, CD 99, FLI-1
DDX

• Tumour
  – morphologically low grade ESS
  – Growth pattern low grade ESS
  – smooth muscle differentiation

• Options?
  – Low grade ESS (JAZF1 LGESS or ESS without demonstrable genetic arrangement) – FISH or RT-PCR for genetic fusions
  – Uterine leiomyoma with intravascular leiomyomatosis
  – Note unlikely to be HGESS no documentation of associated smooth muscle differentiation with YWHAE-NUTM2 ESS
De-differentiated ESS

• Biphasic tumour
  – Monomorphc low grade component (ovoid cells)
  – High grade component (round cells)

• De-differentiated ESS (lacks cyclin D1 positivity)
  – Unlike YWHAE- NUTM2 ESS
Diagnosis of Uterine sarcoma

- Need hysterectomy specimen
- Patience
- Very generous sampling
- Small biopsies may not be representative!
Cervical “polyp”

Small round blue cell tumour

Spindle cell component
fibromyxoid stroma

Spindle cell component
fibromyxoid stroma