Learning objectives:

1. Master new and current terminology of uterine mesenchymal neoplasms.

2. Understand the salient morphologic characteristics, classification and prognostic significance of endometrial stromal tumors, undifferentiated uterine sarcomas, smooth muscle tumors and their mimickers.

3. Develop a differential diagnosis and practical workup in uterine mesenchymal tumors with an understanding of immunohistochemical stain interpretation and role of molecular genetic studies to establish a correct diagnosis.

Background:

1. Mesenchymal neoplasms pose important diagnostic challenges with regards to their classification and characterization.

2. The most commonly encountered uterine mesenchymal tumors include smooth muscle tumors and endometrial stromal tumors.

3. Recent discoveries in the fields of immunohistochemistry and molecular pathology have shed new light into the biology of these tumors.

4. The most recent World Health Organization classification of uterine mesenchymal tumors introduced new terminology based on these discoveries.

5. Recognizing the characteristic morphologic, immunohistochemical and molecular features of each tumor is necessary for an accurate diagnosis.
Endometrial stromal neoplasms and related tumors

- Second most common uterine mesenchymal neoplasm
- Includes endometrial stromal nodule, low-grade endometrial stromal sarcoma, high-grade endometrial stromal sarcoma and undifferentiated uterine sarcoma (which could be of endometrial and non-endometrial stromal origin)
- Pre and post-menopausal women
- Present with non-specific symptoms, including abnormal bleeding, pain, dysmenorrhea and/or enlarged uterus – might present as metastatic disease in cases of sarcoma

1. Endometrial stromal nodule (ESN)

   a. Morphology

      i. Benign, well-circumscribed tumor
      ii. Average size is 7 cm (range 1-22 cm)
      iii. Cells resembling proliferative-phase endometrial stroma
      iv. Might have ischemic necrosis and hemorrhage
      v. Mitotic activity is usually low, but might be focally increased (in cases up to 15 mitotic figures/10 high-power fields) – no atypical mitotic figures
      vi. Might have myxoid/fibrous/smooth muscle/sex-cord/rhabdoid/glandular differentiation

         1. Combined stromal-smooth muscle tumor terminology less commonly used

      vii. Easily identifiable small arterioles with perivascular stromal cell whorling

         1. Large thick-walled vessels might be focally present (particularly in areas of smooth muscle differentiation or at the periphery of the lesion), but are much less evident and less extensive than in smooth muscle tumors

      viii. Collagen bands, histiocytes and cholesterol clefts might be present
b. Immunohistochemistry
   
i. Typically strong and diffusely positive for vimentin, CD10, ER, PR and WT-1
   
ii. Often positive for smooth muscle actin and muscle specific actin
   
iii. Often positive for pan-cytokeratin (AE1/AE3)
   
iv. Might display some desmin positivity
   
v. Generally negative for h-caldesmon and HDAC8
   
vi. If smooth muscle differentiation
      1. Stronger desmin and focal h-caldesmon positivity
      2. CD10 usually remains positive in areas of smooth muscle differentiation
   
vii. If sex-cord differentiation
      1. Positive inhibin, calretinin, melan-A

c. Molecular profile
   
i. Commonly harbor t(7;17)(p21;q15) – \textit{JAZF1-SUZ12}
   
ii. Other rearrangements including \textit{EPC1, PHF1 and MEAF6} (often seen in low-grade endometrial stromal sarcomas have not been identified in ESN)

d. Differential diagnosis
   
i. Low-grade endometrial stromal sarcoma (LGESS)
      1. Entire margin of tumor must be sampled to evaluate for myometrial/lymphovascular invasion
      2. On endometrial biopsy specimens, ESN and LGESS cannot be differentiated – diagnose as endometrial stromal neoplasm with comment
   
ii. Cellular leiomyomas/highly cellular leiomyomas
      1. Larger cells
2. **Fascicular growth pattern**

3. **Large thick walled blood vessels**

4. **Lack of small endometrial stromal-like arterioles**

5. **Strongly positive for all muscle markers**

6. **Commonly have CD10 expression**

2. **Low-grade endometrial stromal sarcoma (LGESS)**

   a. **Morphology**
      
      i. **Variable size, usually 5-10 cm**

      ii. **Microscopic appearance similar to endometrial stromal nodules (see above)**

      iii. **Might show rare bizarre or multinucleated tumor cells or a fibroblastic/myofibroblastic appearance with fusiform/elongated cells**

   iv. **Distinguished from endometrial stromal nodules by:**

      1. **Presence of myometrial invasion at tumor periphery – “tongue-like growth”**

      2. **Lymphovascular space invasion**

   b. **Immunohistochemistry**

      i. **Typically strong and diffusely positive for vimentin, CD10, ER, PR and WT-1**

      ii. **Often positive for smooth muscle actin and muscle specific actin**

      iii. **Often positive for pan-cytokeratin (AE1/AE3)**

      iv. **Might display some desmin positivity**

      v. **Generally negative for h-caldesmon and HDAC8**

      vi. **If smooth muscle differentiation**

         1. **Stronger desmin and focal h-caldesmon positivity**
2. CD10 usually remains positive in areas of smooth muscle differentiation

vii. If sex-cord differentiation

1. Positive inhibin, calretinin, melan-A

c. Molecular profile

i. Most LGESS harbor t(7;17)(p21;q15) – *JAZF1-SUZ12*

ii. Less commonly

1. t(6;7)(p21;p15) – *PHF1-JAZF1*

2. t(6;10;10)(p21;q22;p11) – *EPC1-PHF1*

3. t(10;17)(q22;p13) – *YWHAE-FM22*

4. t(1;6)(p15;q21) – *MEAF6-PHF1*

d. Differential diagnosis

i. Endometrial stromal nodule

1. Entire margin of tumor must be sampled to evaluate for myometrial/lymphovascular invasion

2. On endometrial biopsy specimens, ESN and LGESS cannot be differentiated – diagnose as endometrial stromal neoplasm with comment

ii. High-grade endometrial stromal sarcoma

1. Under the new WHO classification, this differential relies less on mitotic activity and more on other morphologic/immunohistochemical/molecular criteria – see below for full description

iii. Highly cellular leiomyomas

1. Might display peripheral irregularities mimicking myometrial invasion, but does not display the characteristic infiltrative growth pattern of LGESS

2. Does not show lymphovascular space invasion
3. Fascicular growth pattern
4. Large thick walled blood vessels
5. Lack of small endometrial stromal-like arterioles
6. Strongly positive for all muscle markers
7. Commonly have CD10 expression

iv. Intravenous leiomyomatosis (IVL)
   1. Can simulate vascular invasion of ESS when epithelioid
   2. IVL is predominantly intravascular, while LGESS shows a predominantly myometrial based tumor with associated lymphovascular space invasion
   3. Strongly positive for all muscle markers
   4. Usually negative CD10 expression

v. Gland poor adenomyosis/intravascular adenomyosis
   1. Usually do not form a mass

e. Prognosis
   i. Overall indolent tumors if low stage; worse outcome when higher stage tumors
      1. Stage I – 98% and 89% 5 and 10 year survival
      2. Stage III and IV – 5-year survival drops to 38-50%

OF NOTE

- The meaning of mitotic activity and tumor cell necrosis is unclear in the setting of ESN and LGESS, and is believed by many to be of no prognostic significance
- Mitotic activity was used to subclassify endometrial stromal sarcomas into low-grade and high-grade (10 mitotic figures/10 high-power fields used as cut-off) – since new data suggests mitotic activity to be of no significant prognostic value, high-grade endometrial stromal sarcomas are now diagnosed by criteria other than mitotic activity (see below)
3. **High-grade endometrial stromal sarcoma (HGESS)**

- Tumor of endometrial stromal derivation with high-grade, usually round-cell morphology
- Often has an associated low-grade spindle cell component with often fibromyxoid features
- Commonly peri/post-menopausal women
- Presents with vaginal bleeding, pelvic mass or enlarged uterus
- It is likely that significant number of tumors previously diagnosed as “undifferentiated uterine sarcomas with nuclear uniformity” actually represent fall into this category

a. **Morphology**
   i. Average size is 7.5 cm
   ii. Often two distinct morphologies in the same tumor
      1. **High-grade round cell tumor component**
         a. Confluent and destructive growth pattern
         b. Increased mitotic activity
         c. Tumor cell necrosis
         d. Might have neuroectodermal differentiation in the form of Flexner-Wintersteiner-like rosettes or Homer-Wright-like pseudorosettes
      2. **Low-grade spindle cell areas with fibroblastic/fibromyxoid features**
         a. Low-grade component present in 50% of cases
         b. Shows a pattern of myometrial invasion similar to that seen in LGESS

b. **Immunohistochemistry**
   i. Staining pattern is different in the two components
      1. **High-grade round cell component**
a. CD10 negative  
b. ER/PR negative  
c. Cyclin D1 positive (strong and diffuse)  
d. C-Kit positive/Dog-1 negative  

2. Low-grade spindle cell component  
   a. CD10 positive  
   b. ER/PR positive  
   c. Cyclin D1 variable (generally less than 50%)  

c. Molecular profile  
   i. Characteristic t(10;17)(q22;p13) – YWHAE-FAM22  
   ii. No mutations in C-Kit gene exons 11 or 17  

d. Differential diagnosis  
   i. If both components are present, diagnosis is generally relatively straightforward  
   ii. If low-grade spindle cell component is lacking, differential includes  
      1. Epithelioid leiomyosarcoma  
         a. Cyclin D1 negative/ muscle markers positive  
      2. Epithelioid gastrointestinal stromal tumor  
         a. Apart from C-Kit positivity, should also express CD34 and often Dog-1  
         b. Should have extrauterine masses with secondary uterine involvement  
      3. Müllerian adenosarcoma with sarcomatous overgrowth  
         a. Sample extensively to identify benign glandular component  
         b. Cyclin D1 negative
4. Rhabdomyosarcoma
   a. Cyclin D1 negative/muscle marker positive

5. Undifferentiated uterine sarcoma with uniform nuclei
   a. Cyclin D1 negative
   b. Absence of characteristic t(10;17)(q22;p13)

e. Prognosis
   i. Earlier and more frequent recurrences than LGESS (usually within 1 year of initial diagnosis)
   ii. Considered intermediate prognosis between LGESS and undifferentiated endometrial sarcomas
   iii. Relatively new entity – no significant follow-up information available

4. Undifferentiated uterine sarcoma
   - Defined by the WHO as “A tumor 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”
   - Generally a diagnosis of exclusion
   - Usually post-menopausal women
   - Present with vaginal bleeding or commonly with advanced stage disease/extraterine spread

   a. Morphology
      i. Often intraluminal polypoid masses measuring more than 10 cm
      ii. Extensive necrosis and hemorrhage
      iii. Two morphologic patterns
1. Uniform type
   a. Oval to spindled nuclei
   b. Nucleomegaly and hyperchromasia
   c. Relatively monotonous morphology
   d. Absence of bizarre/pleomorphic nuclei
   e. Mixture of destructive and infiltrative growth patterns
   f. Might have an associated LGESS component
   g. Must rule out a translocation-associated HGESS
   h. Probably represent non- t(10;17)(q22;p13)-associated dedifferentiation of a LGESS

2. Pleomorphic type
   a. Marked nuclear pleomorphism
   b. Marked mitotic activity with atypical mitotic figures
   c. Destructive myometrial invasion

b. Immunohistochemistry
   i. If uniform cell type
      1. Variable CD10, ER and PR expression (often focal/weak)
      2. Can be cyclin D1 diffusely positive, but those cases are often CD10 positive, excluding translocation-associated HGESS
         a. If cyclin D1 positivity and CD10 negative – must classify as translocation-associated HGESS
   ii. If pleomorphic cell type
      1. Usually negative CD10, ER and PR
      2. Negative cyclin D1
      3. Might have p53 positivity (strong/diffuse)
   iii. In both types
1. Absent or weak/focal smooth muscle markers – excludes leiomyosarcoma

2. Focal/weak EMA and cytokeratin might be present

c. Molecular profile
   i. Complex chromosomal changes
      1. Gains of 2q, 4q, 6q, 7p, 9q, 20q
      2. Losses of 3q, 10p, 14q

d. Prognosis
   i. High-stage disease at diagnosis
   ii. Even if stage I at diagnosis – high mortality rate within 2 years
   iii. No response to therapy
Diagnostically Challenging Smooth Muscle Tumors

The 2014 WHO Classification of Tumors of the Female Genital Tract updated its diagnostic schema for smooth muscle tumors (SMT) of the uterus. Of the many revisions and additions, four categories persist as among the more diagnostically challenging SMTs — these include leiomyoma with bizarre nuclei, mitotically active leiomyoma, smooth muscle tumor of uncertain malignant potential (STUMP) and leiomyosarcoma.

1. **Leiomyoma with Bizarre Nuclei**
   
a. **Synonyms**
   
i. Atypical leiomyoma
   
ii. Symplastic leiomyoma
   
   b. **Gross Features**
   
i. Vast variation in size
   
ii. Well circumscribed lesion
   
iii. Bulging when cut with white, firm, whorled cross section
   
iv. Edema, necrosis, cyst formation and other degenerative changes often grossly visible
   
   c. **Histologic Features**
   
i. Defined as:
   
   1. Focal/patchy/diffuse moderate-severe cytologic atypia
   
   2. Mitotic figures <5 per 10 hpfs
   
   3. Tumor cell necrosis absent
   
   ii. Often a mix of typical spindled cells of leiomyoma and atypical cells
   
   iii. Zones with atypical nuclei range from focal to patchy to diffuse
   
   iv. Atypical cells have eosinophilic, sometimes rhabdoid, cytoplasm with pleomorphic, uni- or multinucleated nuclei with dense, smudgy chromatin or prominent nucleoli.
   
   v. Atypical zones associated with karyorrhectic debris that may be easily confused with mitotic figures, but actual mitotic index is low
vi. A method to reliably assess degree of cytologic atypia is to compare at intermediate power the size and shape of the surrounding myometrial cells to the tumor cells

vii. Degenerative changes frequently present

viii. Mitotic index averages 1-2 mitotic figures per 10 hpfs

d. Immunohistochemical Features

i. Like most SMTs, leiomyoma with bizarre nuclei is usually an H&E diagnosis

ii. Studies examining p16, p53 and Ki-67 do not recommend ancillary stains
   1. p53 and p16 may be diffusely expressed in leiomyoma with bizarre nuclei
   2. Ki-67 proliferation index is not necessarily an absolute metric of malignant potential and should not guide classification

e. Differential Diagnosis

i. Smooth muscle tumor of uncertain malignant potential
   1. One morphologic combination:
      a. Diffuse moderate-severe cytologic atypia
      b. Mitotic index 5-9 per 10 hpfs
      c. Tumor cell necrosis absent
   2. Second morphologic combination:
      a. Absent-mild cytologic atypia
      b. Mitotic index 5-9 per 10 hpfs
      c. Tumor cell necrosis present

ii. Leiomyosarcoma
   1. One morphologic combination:
      a. Diffuse moderate-severe cytologic atypia
      b. Mitotic index $\geq 10$ per 10 hpfs
      c. Tumor cell necrosis present
2. Second morphologic combination:
   a. Diffuse moderate-severe cytologic atypia
   b. Any mitotic index
   c. Tumor cell necrosis present

3. Third morphologic combination:
   a. Absent-mild cytologic atypia
   b. Mitotic index ≥10 per 10 hpfs
   c. Tumor cell necrosis present

f. Prognosis
   i. Excellent, similar to conventional leiomyoma
   ii. Potential for local recurrence if incompletely excised

2. Mitotically Active Leiomyoma
   a. Clinical Features
      i. Associated with progesterone exposure, usually found in reproductive age group
   b. Gross Features
      i. Typical gross features of conventional leiomyoma
      ii. Tend to have a submucosal distribution
   c. Histologic Features
      i. Defined as:
         1. Absent-mild cytologic atypia
         2. Mitotic figures ≥10, but no greater than 15 per 10 hpfs
         3. Tumor cell necrosis absent
      ii. Otherwise standard morphologic features of spindled leiomyoma
   d. Differential Diagnosis
i. Smooth muscle tumor of uncertain malignant potential
   1. In an SMT with absent-mild cytologic atypia and no tumor cell necrosis, a mitotic index >15 figures per 10 hpfs warrants classification as STUMP

ii. Leiomyosarcoma
   1. If necrosis/degenerative changes present, consider additional sections to convincingly exclude tumor cell necrosis

   e. Prognosis
      i. Excellent, similar to conventional leiomyoma
      ii. Potential for local recurrence if incompletely excised

3. Smooth Muscle Tumor of Uncertain Malignant Potential
   a. Gross Features
      i. May have gross features of leiomyoma or leiomyosarcoma
   b. Histologic Features
      i. Defined as:
         1. One morphologic combination:
            a. Diffuse moderate-severe cytologic atypia
            b. Mitotic index 5-9 per 10 hpfs
            c. Tumor cell necrosis absent
         2. Second morphologic combination:
            a. Absent-mild cytologic atypia
            b. Mitotic index 5-9 per 10 hpfs
            c. Tumor cell necrosis present
      ii. Differentiating tumor cell necrosis:
         1. Infarct-type necrosis
            a. Gradual transition or interface between viable tumor and necrosis
b. Transition zone resembles granulation tissue by its loose stroma, inflammatory infiltrate and hemorrhage

c. Necrotic cells are characteristically “mummified” with residual outlines of cytoplasmic and nuclear membranes

2. Tumor cell necrosis

a. Sharp or abrupt transition between viable tumor and necrosis

b. No granulation tissue-like response

c. “Floating vessels” more common in tumor cell necrosis, but may also be found in infarct-type necrosis

c. Differential Diagnosis

i. Leiomyosarcoma

1. Consider additional sections to convincingly exclude sufficient features to diagnose leiomyosarcoma

d. Prognosis

i. Good, recurrences reported in 10-25% of patients

ii. Patients with tumor cell necrosis as a component are more likely to recur

4. Leiomyosarcoma

a. Gross Features

i. Often solitary mass

ii. Soft, variegated, bulging cut cross section

iii. Necrosis, hemorrhage and cyst formation usually grossly visible

iv. Significant variability in size, but tends to be large, averaging ~10 cm

b. Histologic Features

i. Defined as:

1. One morphologic combination:

a. Diffuse moderate-severe cytologic atypia
b. Mitotic index ≥10 per 10 hpfs

c. Tumor cell necrosis present

2. Second morphologic combination:
   a. Diffuse moderate-severe cytologic atypia
   b. Any mitotic index
   c. Tumor cell necrosis present

3. Third morphologic combination:
   a. Absent-mild cytologic atypia
   b. Mitotic index ≥10 per 10 hpfs
   c. Tumor cell necrosis present

ii. Interface between myometrium and tumor usually shows frank, destructive infiltration

iii. Osteoclast-like giant cells, rhabdoid cells and heterologous elements may be seen in conventional leiomyosarcoma

iv. Since leiomyosarcoma is considered intrinsically high grade in the uterus, grading is controversial

c. Immunohistochemical Features
   i. Studies examining p16, p53 and Ki-67 do not recommend ancillary stains
      1. p53 and p16 tend to be diffusely expressed in leiomyosarcoma, but are not always positive
      2. Ki-67 proliferation index is not necessarily an absolute metric of malignant potential and should not guide classification

d. Prognosis
   i. Poor, 5 year survival ranges 25-75%
   ii. Recurrence common even in stage I tumors
   iii. Stage is most accurate predictor of patient outcome
PEComa

- Rare mesenchymal tumor potentially arising from perivascular epithelioid cells
- Demonstrate myelocytic and smooth muscle differentiation
- Same family of tumors as:
  - Angiomyolipoma
  - Lymphangioleiomyomatosis
  - Clear cell “sugar” tumor of the lung
- Often associated to tuberous sclerosis
- Have been described in multiple locations, including soft tissue, retroperitoneum, liver, pancreas, bladder, and uterus
  - In the uterus, often misdiagnosed as smooth muscle
- Often have mutations of *TSC1* or *TSC2*
  - Causes deregulation of the mTOR pathway
  - Responds to mTOR inhibitors

1. **Morphology**
   a. Epithelioid cells, spindle cells, or mixture
   b. Abundant eosinophilic granular or clear cytoplasm
   c. Multinucleated giant cells
   d. Stromal hyalinization
   e. Arborizing vasculature

2. **Proposed criteria for malignancy**
   i. Less than 4 criteria \(\rightarrow\) benign or uncertain malignant potential
   ii. 4 criteria or more \(\rightarrow\) malignant
   b. Size > 5 cm
   c. Necrosis
d. High grade cytologic features

e. Vascular invasion

f. Mitotic rate ≥ 1 mitosis/50 HPFs

3. **Immunohistochemistry**

   a. Melanocytic markers
      
      HMB45 positive
      
      MiTF positive
      
      Melan-A positive
      
      S100 (positive in 20% of cases)

   b. Smooth muscle markers
      
      Desmin positive
      
      SMA positive
      
      H-Caldesmon positive

   c. Other markers
      
      Negative keratins
      
      Negative PAX-8
      
      Cathepsin-K positive

4. Subset of PEComas demonstrate **TFE3** rearrangement

   a. Often demonstrate clear cytoplasm

   b. Show nuclear expression of TFE3

      *TFE3* rearrangement by FISH

   c. Generally weak/focal Melan-A expression with weak muscle markers

   d. Absent **TSC1** or **TSC2** mutations

      No response to mTOR inhibitors
**Speaker Disclosure**

In the past 12 months, the authors have not had a significant financial interest or other relationship with the manufacturer(s) of the product(s) or provider(s) of the service(s) that are discussed.
References

1. Robert J. Kurman, Maria Luisa Carcangiu, C. Simon Herrington, Robert H. Young (Eds.): WHO Classification of Tumours of Female Reproductive Organs. IARC: Lyon 2014.


