Gynaecological Pathology:
Diagnostic mistakes in gynecological pathology

Case 3

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53 year old woman referred for a growing uterine leiomyoma

Pelvic ultrasound: 8 cm nodule (previous check up 2.5 cm)
other smaller nodules
no adnexal masses or ascites

Laparoscopic hysterectomy
Nodular lesions, ranging from 1 cm to 8 cm, with a white, whorled homogeneous cut surface. No necrosis or haemorrhagic area.
Cellular lesion with pushing border
Two main diagnostic categories

Smooth muscle tumor vs Endometrial stromal tumor

Are we confident with smooth muscle tumor or are we missing something?
Small capillaries network with arcing vessels, thick wall vessels occasionally at the periphery
Microscopy

- Lightly eosinophilic cytoplasm
- Clear, round nucleus with nucleoli
- Occasionally nuclear pseudoinclusions
- Nests or short fascicles

Cells arranged around blood vessels
<table>
<thead>
<tr>
<th>Stain</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>Smooth muscle actin</td>
<td>Positive</td>
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<tr>
<td>H-Caldesmon</td>
<td>Scattered cells</td>
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<tr>
<td>Desmin</td>
<td>Scattered cells</td>
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<tr>
<td>CD10</td>
<td>Patchy positive</td>
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<tr>
<td>Estrogen Receptor</td>
<td>Positive</td>
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<tr>
<td>HMB45</td>
<td>Positive</td>
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<tr>
<td>Cathepsin K</td>
<td>Positive</td>
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</tbody>
</table>
Diagnosis

Uterine mesenchimal neoplasia
SMA/HMB45/Cathepsin K positive

PEComa of uncertain malignant potential
PEComa

Mesenchimal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells

1994 Bonetti et al. «peculiar muscle cell, with a strong immunoreactivity for HMB45»

1996 Zamboni et al. Formaly introduced the term PEComa describing a clear cell sugar tumor of the pancreas
Relation with smooth muscle tumor is controversial as they share morphological and immunohistochemical aspects. The distinction between the two entities still remains a diagnostic challenge.
Highly cellular

Sclerosing PEComa
Epithelioid or spindle appearance with clear to eosinophilic granular cytoplasm, centrally located round to oval nuclei with nucleoli
Atypical nuclei with mutinucleation, macronucleoli and nuclear pseudoinclusion
Immunohistochemical panel

Coeexpression of both melanocytic and smooth muscle markers with HMB45 as the most sensitive stain. Two melanocytic markers or HMB45 and Cathepsin K.

Schoolmeester et al. AJSP 2014; 38: 176-188
Bennett et al. AJSP 2018; 42: 1370-1383
## Criteria for malignancy

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Benign</th>
<th>Uncertain malignant potential</th>
<th>Malignant (≥2 features)</th>
<th>Benign/ Uncertain malignant potential</th>
<th>Malignant (≥4 features)</th>
<th>Uncertain malignant potential</th>
<th>Malignant (≥3 features)</th>
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<tbody>
<tr>
<td>Size ≥ 5 cm</td>
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<td>Necrosis</td>
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<td>Vascular invasion</td>
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<td>Nuclear pleomorphism or multinucleated giant cells</td>
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<td>Mitosis ≥ 1x50HPF</td>
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</tbody>
</table>

References:
- Folpe et al. AJSP 2005; 29:1558-1575
- Schoolmeester et al. AJSP 2014; 38: 176-188
- Bennett et al. AJSP 2018; 42: 1370-1383
Molecular pathways

- **TSC1/2 loss-of-function mutation**
  - Mostly sporadic
  - < 10% in TSC syndrome
  - Spindle and/or epithelioid
  - HMB45: focal/patchy
  - Melan A: focal/patchy
  - SMA: positive

- **TFE3-translocation**
  - Epithelioid clear cells
  - alveolar/nested pattern
  - HMB45: strong/diffuse
  - Melan A: strong/diffuse
  - SMA: negative/focal

- **RAD51B gene-fusion**
  - Few cases reported

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mTOR inhibitors therapy

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*Schoolmeester et al. AJSP 2015; 39: 394-404*

*Agaram et al. AJSP 2015; 39: 813-825*

*Bennet et al. AJSP 2018; 42:1370-1383*
Differential diagnosis

*Broad spectrum of differential depending on morphological aspects*

Top differential

- Epithelioid/spindle smooth muscle tumor
- Epithelioid endometrial stromal tumor
- Melanoma
- Carcinoma
- Gastrointestinal stromal tumor
Conclusions

Differential diagnosis with smooth muscle neoplasms is challenging

Consider the diagnosis of PEComa when branching vascular network and neoplastic cells around vessels

HMB45 and Cathepsin K good markers in the proper morphological setting
Thank you