Commercial or financial interest

We have nothing to disclose
Case 2

- 56 y old women with vaginal bleeding,
- US endometrial thickness 4 mm.

What is your diagnosis

- Papillary proliferation of endometrium
- EIN
- EJC
- Need immunos
Would you order immunos?

Papillary proliferation of endometrium

- Simple and complex papillary branching of endometrium without significant atypia
- Frequently involves polyp
- Epithelium involved with metaplasia
  - Mucinous
  - Ciliated
  - Tubal
  - Eosinophilic
  - Squamous

Papillary proliferation

Simple papillary proliferations
- Postmenopausal women
- Associated with polyp
- Non branching papillae lined by bland epithelium

Complex papillary proliferations
- Complex papillae with second and third-degree branching lined by bland epithelium

Immunohistochemistry

- Not always necessary (not always very helpful)
- MIB-1 low
- p53 wild type
- PTEN, ARID1A and PAX2 usually intact
- P16 positive and not helpful
- ER expressed, PR decreased expression
MULTIFOCAL, EXTENSIVE OR MUCINOUS CHANGE

- higher association with concurrent or subsequent atypical hyperplasia or low-grade endometrioid carcinoma.

Focal distribution with complex branching

Focal distribution, no complex branching but with mucinous metaplasia
**DDx**

- Endometrial intrapithelial neoplasm (EIN)
- Endometrial intrapithelial carcinoma (EIC)
- Artefacts
- Reactive papillary changes with menstrual breakdown
- Reactive papillary and atypical changes due to progesterone treatment
- Benign endocervical tissue and microglandular hyperplasia

**Case 1. Polyp with focal papillary surface change**

**Your diagnosis**

- Papillary proliferation with necrosis metastasis, follow up and clinical correlation
- EIN
- EIC

This is endocervix
Papillary proliferation with mucinous metaplasia, follow up and clinical correlation

- What goes against EIC
  - No significant atypia
  - No prominent nucleoli
  - No mitoses or apoptotic bodies
  - Mucinous metaplasia
  - P53 wild type

Your diagnosis

- Benign simple papillary proliferation
- EIN
- EC
- Pseudopapillary artifact, secretory endometrium
- None of the above

Secretory endometrium with artefactual telescoping and pseudo-papillary artifact

Do not forget to look at the background endometrium!
Case 3. Multiple foci

Atypical papillary proliferation consistent with (progesterone) treated EIN

- What goes against EIN
  - Crowded glands but bland morphology
  - No mitoses
  - No pseudostratification

- What goes against EIC
  - No significant atypia
  - No prominent nucleoli
  - No mitoses or apoptotic bodies
  - p53 wild type

- What would help is history and prior biopsy!
Case 4. Multifocal papillary process

- EIN/ Atypical hyperplasia

- What goes against benign papillary proliferation
- Moderate atypia
- Mitoses
- Pseudostratification, endometrioid look of cells

Do not forget to look at the background.
Case 5. Papillary proliferation on the surface of polyp

What goes against papillary proliferation:

- Marked atypia
- Red cherry nucleoli
- Apoptosis
- Mitoses
- p53

What is your diagnosis:

<table>
<thead>
<tr>
<th>Papillary proliferation, complex, follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIC</td>
</tr>
<tr>
<td>EIN</td>
</tr>
<tr>
<td>I need to see p53</td>
</tr>
</tbody>
</table>

Case 6. Multiple foci like this
Your diagnosis

- papillary synovial metaplasia associated with menstruation
- EC
- Squamous metaplasia
- I had enough of this papillary bosshes
- Papillary proliferation, complex follow up

Ddx: Microglandular hyperplasia

Last case, two for one!
Case 4

- 47 y old female with vaginal bleeding,
- US endometrial thickness of 12.4 mm
- Endometrial biopsy in outside institution, not available for evaluation with the diagnosis of “cancinoma”
- Hysterectomy:
  - Endometrial cavity measures 4.0 x 2.1 cm with the thickness of endometrium measuring 0.2 cm. There is a 2.5 x 1.0 cm polypoid lesion arising from the anterior endometrium in the fundal region.
Undifferentiated and dedifferentiated endometrial carcinoma (UDEC)

- Dedifferentiated endometrial carcinoma
- Biphasic tumor composed of undifferentiated component in combination with endometrioid carcinoma either FIGO 1 or 2
- Undifferentiated endometrial ca
  - Malignant epithelial neoplasm without morphological evidence of epithelial differentiation

What is your diagnosis?

- Carcinosarcoma
- Endometrioid carcinoma FIGO grade 3
- Plasmacytoma and endometrioid carcinoma FIGO grade 1
- Dedifferentiated endometrial carcinoma
Epidemiology and clinical features of (UDEC)

- Rare
- Younger women with median age of 55
- Higher association with Lynch syndrome
  - Abnormal DNA mismatch repair (up to 50%)
- Presents with postmenopausal bleeding
- Most are large polypoid intrauterine masses, often involving LUS
- Highly aggressive with recurrence and death in 55-95%

Dedifferentiated endometrial carcinoma: Key morphological features

Common features
- Monomorphic population of cells
- No obvious differentiation
- Small to medium size
- Discohesive pattern
- Associated with myxoid stroma

Less common morphological features of undifferentiated portion
- Alveolar, nested or trabecular growth pattern
- Larger cells with abundant pink cytoplasm
- Marked pleomorphism
- Multinucleation
- Abrupt keratinization
- Presence of heterologous elements
Undifferentiated endometrial adenocarcinoma

**Immunohistochemistry**

- **High rate of positivity**
- **Rare focal positivity**
- **Negative**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMA</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>CK18</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>Vimentin</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>Neuroendocrine markers</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>C-Kit</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>ER/PR</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>Cytokeratin AE3/AE1</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>Vimentin</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>PAX8</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>P16</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>S100</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>LCA</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>Desmin</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>SMA</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>p53</td>
<td>NONE!!!!</td>
</tr>
<tr>
<td>Abnormal MMR expression</td>
<td>NONE!!!!</td>
</tr>
</tbody>
</table>

**List of markers used in our case**

- EMA
- CK18
- Vimentin
- Neuroendocrine markers
- C-Kit
- ER/PR
- Cytokeratin AE3/AE1
- Vimentin
- E-cadherin
- P16
- S100
- LCA
- Desmin
- SMA
- p53

**DDx for dedifferentiated carcinoma**

- Carcinosarcoma
- Endometrioid carcinoma grade 2 or 3
- Serous carcinoma of uterus

**DDx: Carcinosarcoma**

- Low power biphase look
- Epithelial and non epithelial component intermixed
- Epithelial component usually high grade
- Solid component rarely monomorphous and discohesive
- **Vimentin and cytokeratin positive**
- PAX 8 negative in mesenchymal component
- Abnormal MMR expression is rare
DDx: endometrioid carcinoma grade 2/3

Morphology
• Glandular and solid components usually intermixed
• but can be distinct
• Solid and glandular component with similar degree of atypia

Immunohistochemistry
• Cytokeratin
• PAX 8
• ER and PR
• Vimentin can be focally positive
• E-cadherine

First line immune stain duo

Cytokeratin
Vimentin
DDx: serous carcinoma solid type

**Morphology**
- Higher pleomorphism and atypia
- Cohesive
- Slit like spaces
- Focal papillary arrangement

**Immunohistochemistry**
- AE1/AE3
- p53 mutation
- E-cadherin

DDx: for undifferentiated endometrial carcinoma

- Lymphoma
- Melanoma
- Plasmacytoma
- High-grade neuroendocrine carcinoma
- Undifferentiated (SMARCA4 deficient) uterine sarcoma
DDx: SMARCA4-deficient uterine sarcoma

- Recently described entity with overlapping morphology with UDEC
- Sheets of medium to large epithelioid cells
- Rhabdoid morphology common
- Corded and phyllodiform architecture
- Members of the switch/sucrose non-fermenting complex which is involved in chromatin remodeling
  - SMARCB1 (INI1)
    - Found in tumors with rhabdoid feature
  - SMARCA4 (BRG1)
    - Small cell carcinoma of the ovary, hypercalcemic type

DDx: SMARCA4-deficient uterine sarcoma

- Prominent nuclear pleomorphism
- Phyllodiform architecture present
- p53 and MSI less common
- SMARCA4 and SMARCB1 more common
Take home message

• Think of undifferentiated endometrial adenocarcinoma when features of epithelial differentiation are absent
• It is a diagnosis of exclusion
• Exclude non-epithelial tumors
  • melanoma, lymphoma, plasma cell, sarcoma
• First line immunos: Cytokeratin and Vimentin
• When differential dx include FIGO 3
  • Loss of PAX8 and loss of E-cadherin is helpful

Thank you!