Endometrial Metaplasia
– Benign vs High Risk

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Introduction

• Definition: Epithelial differentiation that differs from conventional endometrioid epithelium
• Associated with range of lesions
• Best to consider “altered differentiation”

Endometrial Metaplasia

Squamous
Tubal
Mucinuous
Eosinophilic
Papillary proliferations

Topography and Mechanism

• Different mechanisms can incite different types of differentiation
• Determine underlying mechanism
• Use appropriate diagnostic terminology that reflects clinical significance

Major Pathogenetic Mechanisms

• Degenerative/reparative
• Hormonal
• Neoplastic
Geometry of Benign, Premalignant, and Malignant lesions

<table>
<thead>
<tr>
<th>Benign</th>
<th>Premalignant</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repair</td>
<td>Anovulatory</td>
<td>EIN</td>
</tr>
<tr>
<td>Surface Repair</td>
<td>Estrogen</td>
<td>Mutation→Clonal</td>
</tr>
</tbody>
</table>

"Regularly irregular"

Differentiation to a Squamous Epithelium

Degenerative/Repair Category – No Risk

- Squamoid change associated with stromal breakdown/surface repair
  - Chronic endometritis
  - IUD
  - Infarcted Polyp
  - Trauma/prior procedure
- Typically focal change

Surface Squamous Change

"Papillary Syncytial Metaplasia" = Degenerative
Neoplastic Category – High Risk

- EIN with squamous morules
- Atypical polypoid adenomyoma (morules)
- Adenocarcinoma with squamous differentiation (morules or stratified squamous)

Squamous Morular Metaplasia

- Diagnosis and management depends on:
  - Degree/extent of glandular proliferation
  - Presence or absence of cytologic demarcation
Endometrial Intraepithelial Neoplasia with Squamous Morular Metaplasia

- Glandular crowding
  (VPS<55%)
- Cytologic demarcation
- Squamous morular metaplasia
Atypical Polypoid Adenomyoma

- Polypoid, biphasic lesion
- Fourth and fifth decades (mean 39 years)
- Lower uterine segment
- Morular metaplasia in >90% of cases

- Persistent, recurrent disease
- Local excision, hormonal therapy and close clinical follow-up vs. hysterectomy
Atypical Polypoid Adenomyoma

- Distinguish from EIN by:
  - Polypoid fragments
  - Distinctive stroma
- Distinguish from myoinvasive adenocarcinoma by:
  - Less architecturally complex
  - Lack of separate fragments of typical adenocarcinoma

Uncertain Diagnostic Category – but with risk of subsequent neoplasia

- Isolated squamous morules
  - Primary abnormality
  - Following treatment of EIN with morules
- Endometrial glandular proliferations, difficult to classify, but associated with morules

Isolated Squamous Morules

Squamous Morular Metaplasia

Risk of subsequent endometrial neoplasia

<table>
<thead>
<tr>
<th>Pattern</th>
<th>N</th>
<th>Morphology</th>
<th>NL</th>
<th>EIN</th>
<th>CA</th>
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</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>29</td>
<td>Isolated/No gland crowding</td>
<td>89.7</td>
<td>6.7</td>
<td>3.4</td>
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<tr>
<td>Grade 2</td>
<td>28</td>
<td>Gland crowding</td>
<td>57.1</td>
<td>28.6</td>
<td>14.3</td>
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<tr>
<td>Grade 3</td>
<td>19</td>
<td>Gland crowding/ Cytologic change</td>
<td>42.1</td>
<td>42.1</td>
<td>15.7</td>
</tr>
</tbody>
</table>

Followup (%) mean 25 mo. Lomo et al, 2004
Isolated Squamous Morular Metaplasia

Descriptive diagnosis and follow-up sampling
- e.g. Proliferative/secretory endometrium with focal squamous morular metaplasia.
- Follow-up sampling in 9-12 months is recommended (if a curetting); earlier if biopsy

Endometrial Alteration with Squamous Morular Metaplasia

Descriptive diagnosis and follow-up sampling
- e.g. Endometrial glandular crowding and complexity associated with squamous morular metaplasia
- Note: Diagnostic features of EIN are not present, nevertheless, close clinical followup with repeat sampling in 6 months is recommended due to the area of glandular crowding.

Differentiation to a Mucinous Epithelium

- Intracytoplasmic mucin droplets
- Well formed mucinous epithelium
  - Most commonly endocervical
  - Rarely, intestinal (gastric, colonic)

Mucinous Differentiation in Endometrial Epithelium

- Syncytial repair and stromal breakdown
- Hormonal therapy
- Endometrial polyp

“Papillary Syncitial Metaplasia” = Degenerative

Degenerative/Repair Category – No Risk

- Syncytial repair and stromal breakdown
- Hormonal therapy
- Endometrial polyp
Hormone Replacement Therapy

Mucinous Differentiation

- Low risk of subsequent neoplasia
  - Simple, typically endocervical type epithelium
  - Involving endometrial surface or glands as a single layer
  - Most commonly seen in samples from perimenopausal women

Mucinous differentiation in Endometrium

Polyp

Endometrial Polyp

Neoplastic Category – High Risk

- EIN with mucinous differentiation
- Well differentiated mucinous adenocarcinoma (villoglandular, microglandular like)
EIN with Mucinous Differentiation

- Meets EIN VPS and size criteria
- Usually localizing lesion
- May blend into more endometrioid lesion

Mucinous Differentiation

- Consider carcinoma if:
  - Complex, microglandular growth pattern
  - Villous architecture
  - Extensive papillary formation (with stromal cores)
Uncertain Diagnostic Category – but with risk of subsequent neoplasia

Diagnosing Carcinoma in the biopsy/curetting:

- Depends on amount and condition (fragmentation) of sample
- Pitfalls to keep in mind:
  - Mitoses rare, cytology bland
  - Exclusion of mimics critical
Mucinous Metaplasia with Complex Architecture

Diagnosis: Complex mucinous epithelial proliferation, see NOTE.

NOTE: Findings are worrisome for a neoplastic process; however the (scant amount/fragmentation/preservation) precludes a more definitive diagnosis. Followup sampling is recommended.

Exclusion of Mimics

- Exclude cervical MGH
  - Endometrial vs. endocervical stroma
  - Presence of reserve cell hyperplasia
  - Presence of sub/supranuclear vacuoles
- Epithelial complexity associated with repair
  - Associated stromal breakdown

Subnuclear Vacuoles

Reserve Cell Hyperplasia
Hormonal Category – Low Risk

- Disordered Proliferative Endometrium with cysts and tubal change (anovulatory type)
- Benign Endometrial Hyperplasia

All due to Unopposed estrogen effect
Neoplastic Category – High Risk

• EIN with tubal differentiation

EIN with tubal differentiation

• Glands have pink cytoplasm, interspersed round cells, +/- cilia
• Tubal glands geographic
• Usual EIN criteria met (VPS, size, mimic exclusion)
Diagnosis: EIN with tubal differentiation

Endometrial Metaplasia – Diagnostic Pitfalls

• Squamous morular metaplasia
  – Adenocarcinoma with squamous differentiation
  – EIN with morular metaplasia
  – Squamous carcinoma
  – Atypical polypoid adenomyoma
• Mucinous metaplasia
  – MGH
  – Well differentiated mucinous carcinoma
• Tubal eosinophilic metaplasia
  – Coexistent EIN or adenocarcinoma

Endometrial Metaplasia – Diagnostic Pitfalls

• If there is a cribriform architecture, consider:
  – Pseudo-cribriform reparative processes
  – Papillary syncytrial metaplasia
  – MGH of cervix
  – Adenocarcinoma (particularly mucinous)
Endometrial Metaplasia

- Regard as alterations in differentiation
- Be aware of their association with both benign and malignant processes, i.e. conceptualize as a spectrum of changes
- Recommend follow-up when necessary