Endometrial Metaplasia, Hyperplasia & Other Cancer Mimics: a Consultant’s Experience

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Endometrial Metaplasia

• Endometrial glandular epithelium that is replaced by other types of cells which are either not seen or very rarely seen in normal endometrial glands

Metaplasia

- Ciliated cell metaplasia (change)
  - with eosinophilic features
- Eosinophilic metaplasia
- Mucinous metaplasia
- Papillary syncytial metaplasia
  - with eosinophilic features
- Simple & complex papillary proliferations
  - with eosinophilic features
- Squamous/morular metaplasia
Ciliated Cell Metaplasia

- Ciliated cells normal in surface endometrium, but not in glands
- May have nucleo-megaly & mild atypia
- Mitotic figures usually absent
- Often mixed with columnar eosinophilic cells: eosinophilic or pink cell change
MICRO: Normal Ciliated cells
MICRO: Normal Ciliated cells

Diagram showing three stages of cell division.
MICRO: Ciliated metaplasia
Ciliated Cell Carcinoma: Does It Exist?

- Rare – pathologic curiosity
- Low grade
- Almost uniformly favorable prognosis
- Better to err on conservative side: atypical hyperplasia with extensive ciliated cell change (metaplasia), cannot exclude very well differentiated adenocarcinoma

Eosinophilic Metaplasia

- Very common
- Eosinophilic, granular cytoplasm – usually columnar cells
- Often mixed with ciliated metaplasia
- May be associated with mucinous metaplasia
- Often mistaken for carcinoma
MICRO: Ciliated metaplasia
MICRO: Eosinophilic metaplasia
MICRO: Ciliated metaplasia
Mucinous Metaplasia

- Common
- Requires presence of intracytoplasmic mucin
- Often focal & mixed in postmenopausal women
- Must distinguish from mucinous carcinoma
- Localization issues: cervix
Minimal Deviation Adenocarcinoma
Mucinous Metaplasia vs Carcinoma

- Mucinous carcinoma may be cytologically very low grade – significant overlap with atypical mucinous metaplasia (= atypical hyperplasia)
- Distinction based on architectural complexity & less commonly, cytology
- In limited samplings, fragmented samplings or borderline cases, always consider possible underlying more significant endometrial lesion or cervical lesion – more about this later
- Beware of isolated mucinous surface metaplasia!
Mucinous Metaplasia vs Carcinoma: Strategy

• If you can localize it to the endometrium: *Complex endometrial hyperplasia with extensive mucinous metaplasia, cannot exclude well differentiated adenocarcinoma (see comment)*

• If you are not sure if it is arising in cervix vs endometrium: *Complex mucinous proliferation (see comment)*
Papillary Syncytial Change (Metaplasia)

- Papillary syncytial change associated with stromal breakdown, atrophy, karyorrhectic debris
- Papillary syncytial metaplasia occurs over surface of endometrium, may be extensive, often mixed epithelial types
- May overlie atrophy, hyperplasia or carcinoma
Papillary Syncytial Change
Papillary Syncytial Metaplasia
Papillary Syncytial Metaplasia
Papillary Syncytial Metaplasia

BE WARY OF THE p53 STAIN!!!
Papillary Syncytial Metaplasia

- Decreased expression of ER
- Increased expression of p53 (although still wild-type staining) and p16, the latter marker typically being diffusely positive
- Low MIB1 proliferation index
- *In problematic cases, IHC may result in a misdiagnosis*

*Int J Gynecol Pathol 2012;31:206-10*
Papillary Syncytial Metaplasia

• Analogous to “icing on a cake”
• Can overlie atrophy, hyperplasia or carcinoma
• May occur in up to 15-20% of carcinoma
Simple Papillary Proliferations

- Atrophic, weakly proliferative, or proliferative cells without atypia lining coarse connective tissue papillary cores
- Spectrum of metaplastic changes
- Frequently focal, in endometrial polyps in atrophic endometria
- “Benign papillary hyperplasia/proliferation”

Simple Papillary Proliferation
Complex Papillary Proliferations

- May be associated with concurrent or subsequent endometrial hyperplasia and carcinoma
- Analogous to atypical hyperplasia (even in the absence of significant cytological atypia)
- “Complex papillary hyperplasia/proliferation"

Papillary Problems: Strategy

- Mixed epithelium argues benignancy
- Some degree of cytologic atypia is permitted in metaplastic papillary lesions (even expected) – but marked nucleomegaly & pleomorphism is not
- Serous carcinoma is a cytologic diagnosis
- p53 & p16 should be used with caution
Squamous-Morular Metaplasia

- May be seen in endometria of all types
- Morules vs keratinized epithelium
- Necrosis in morules is not evidence of malignancy
- Estrogenic states
Squamous Caveats

• Sheets of epithelium don’t necessarily mean malignant – common cause for misdiagnosis of “grade 2 adenocarcinoma”

• Squamous elements are non-informative with respect to ‘benign / malignant’ (atypical hyperplasia vs. grade I adenocarcinoma)

• Recommend re-sampling, imaging when underlying glandular architecture cannot be evaluated
Clear Cell (Secretory) Change

- Secretory endometrioid proliferations
- Non-specific clearing due neither to mucin nor glycogen
- Glycogen-rich squamous proliferations
- May be secondary to hormonal therapy
Clear Cell Change: Differential Diagnosis

- Clear cell carcinoma – very uncommon in the endometrium
- Low grade mucinous endometrial or endocervical carcinoma
- Exclude metastases – rare, but they do occur
The Pathology Report

• Metaplasia can be complex – doesn’t necessarily imply hyperplasia
• Hyperplasia should have increased gland to stroma ratio (3:1)
• Be sure the sample is representative – not always easy to do
• Exclude special variant cancer…to be continued
Endometrial Hyperplasia

- Increased gland proliferation
- Greater than 3:1 gland to stroma ratio
- Can be focal...clinical significance uncertain
- Can be defined by exclusionary criteria – i.e. not cancer
Basic Architectural Patterns

- Small crowded (budding) glands
- Macroglans
- Exophytic papillae: villus (or villoglandular) and non-villus (papillary)
Architecture

Small (budding) glands

Macroglands

Exophytic papillae

High = Carcinoma

Borderline

Low = Complex Hyperplasia

Hyperplasia
Borderline, Cannot Exclude
Endometrial Carcinoma
Borderline, Cannot Exclude
Endometrial Carcinoma
Borderline, Cannot Exclude
Endometrial Carcinoma
Atypical Endometrial Hyperplasia

- Loss of nuclear polarity
- Nuclear rounding
- Nuclear clearing with vesicular chromatin pattern
- Prominent nucleoli
- Eosinophilic cytoplasm

*Cancer* 1985;56:403-412
The Pathology Report

- Complex vs simple hyperplasia no longer a requirement (WHO 2014)
- Atypical vs non-atypical – atypia should be fairly diffuse
- If focal atypia, exclude focal low-grade carcinoma arising in hyperplasia
Indications For Conservative (Medical) Management

- Young women who wish to preserve their fertility
- Women with severe comorbidities – may be only option
- Borderline lesions, e.g. atypical polypoid adenomyoma, other weird polyps, “focal hyperplasia”, etc
Conservative (Medical) Management: The Problem

- Few controlled, prospective long-term studies
- Non-uniform patient selection
- Non-uniform pathology selection (nonatypical hyperplasia vs atypical hyperplasia vs carcinoma)
- Non-uniform pathology documentation
Conservative (Medical) Management: The Problem

- Non-uniform treatment (drug, dose, duration)
- Patient compliance with oral progestins
- Non-uniform documentation of response
- Risk of relapse for responders not well delineated
- Efficacy of office biopsy versus curettage not studied in this setting
Conservative (Medical) Management

- Oral Progestin Therapy
- Levonorgestrel-releasing Intrauterine System (LNG-IUS)
Oral Progestin Therapy

- Side effects
- Requires compliance
- Type of progestin product variable
- Optimal dose not well defined
- Duration of treatment not well defined
Levonorgestrel-releasing Intrauterine System (LNG-IUS)

- Locally acting
- Increased effect on endometrium
- Improved compliance
- Less side effects
- Still relatively new treatment
Response Rate

- Depends on pathology (but data conflicting):
  - Nonatypical hyperplasia > atypical hyperplasia > endometrioid carcinoma
- Depends on menopausal status:
  - Mean time to regression 7.5 months in premenopausal women (range, 4-16 mos)
  - Mean time to regression 6.8 months in postmenopausal women (range, 4-10 mos).
  - Postmenopausal women may have better overall response than premenopausal, but data conflicting

TREATMENT EFFECTS

- Architectural-stromal changes
- Metaplastic changes
- Cytological changes

Architectural-Stromal Changes

- Predecidual change
- Decreased gland confluence and complexity
- Papillary or cystic architecture

Cytological Changes

- Decreased nuclear size
- Decreased cytologic atypia
- Nuclear membrane rounding
- Chromatin finer and more homogenized or smudged
- Nucleoli indistinct or absent
- Mitotic figures decreased or absent
Evaluation of Treated Hyperplasia/Carcinoma

- Compare prior, pre-treatment biopsy & all interval biopsies whenever possible
- Evaluate entire specimen – ensure it is representative
- Consider level sections (persistence of hyperplasia/carcinoma may be focal)
Evaluation of Treated Hyperplasia/Carcinoma

• No response
• Partial response
• Complete response (regression)
No Response*

- No progestin effect – i.e., no stromal predication or metaplasia over and above pre-treatment
- Gland complexity similar to pre-treatment biopsy
- Cytological atypia similar to pre-treatment biopsy (if present)

*Requires at least 6 mos treatment
Complete Response

- Atrophy of glands
- Proliferative or secretory pattern
- Edematous fibrotic stroma
- Stromal pseudodecidualization
- No evidence of hyperplasia/carcinoma – depends on initial diagnosis
- No cytological atypia
Partial Response

- Decreased gland complexity with increased metaplasia
- Persistent atypia may be present, but decreased compared to prior
- Often focal residual gland complexity – must exclude focal process pre-treatment
## Classification of Progestin-treated Lesions of the Endometrium

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestin-treated nonatypical hyperplasia</td>
<td>No cytologic atypia. Crowded, back-to-back glands and/or a confluent glandular pattern</td>
</tr>
<tr>
<td>Progestin-treated atypical hyperplasia</td>
<td>Cytologic atypia. Crowded, back-to-back glands that lack a confluent glandular pattern</td>
</tr>
<tr>
<td>Progestin-treated well-differentiated carcinoma</td>
<td>Cytologic atypia. Confluent glandular pattern (cribriform and/or papillary pattern).</td>
</tr>
</tbody>
</table>

*Modified from Am J Surg Pathol 2007;31:988-998*
Poor Prognostic Signs*

- Persistence of cytological atypia
- Complex papillary architecture
- Cribriform architecture - if more than minor element

Provided sufficient progestin treatment (dose, at least 6 mos duration, etc)

Cribriform Architecture
Cribriform (higher magnification)
The Pathology Report

- Note whether sampling is adequate
- Note whether progestin effect is present
- Compare priors !!!
- Report all findings – requires microscopic description
- Comment required in almost all cases
Endometrial Atrophy

- Common cause of post-menopausal bleeding (approximately 25% of cases)
- Paucity of tissue in an atrophic endometrial biopsy or curettage specimen, is not insufficient or inadequate
- In the appropriate clinical setting, the scant tissue is likely to be the only tissue present and is therefore representative of the endometrium (e.g., “good scrape, but scant tissue”).
Atrophy

- Atrophic and weakly proliferative appearing endometrium is abnormal during the reproductive years, unless there is a history of hormonal medication or premature ovarian failure.
- If the pathologist is unable to assign an etiology for a scant and/or atrophic specimen in this setting it is completely appropriate to make a diagnosis of insufficient for evaluation.
Atrophy

- May see enlarged, atypical cells
- Often smudged nuclei
- Absent or rare mitotic figures
- Suggest further evaluation
Benign polyp with torsion & surface atypia mimicking SEIC
Benign Polyp vs Serous Endometrial Intraepithelial Carcinoma (EIC)

SEIC

- Normal endometrial (often atrophic) glandular structure is preserved
- Marked nuclear atypia, enlargement, and hyperchromasia
- Strong nuclear p53 (be wary!)
- High grade serous carcinoma elsewhere

Benign Polyp

- Degenerative changes in surface endometrium may masquerade as SEIC in uterine sampling
- Paucity of mitotic figures
- Absence of strong nuclear p53
- If uncertainty remains, re-sampling may resolve problem
Thank you

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