Endometrial metaplasia

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Metaplasia

- Transformation of cells to a type not normally found in an organ.
- Most of the alterations commonly classified as endometrial metaplasia do not qualify as such and are best regarded as « cytoplasmic changes »
Endometrial metaplasia (cytoplasmic changes)

- Alteration in mullerian differentiation (aberrant mullerian differentiation)
  - Endocervical mucinous epithelium
  - Exocervical squamous epithelium
  - Endometrial stratified epithelium
  - Tubal ciliated epithelium

- Degenerative/regenerative process related to endometrial breakdown
Endometrial metaplasia

• **Epithelium**
  - *intra-glandulaire process*
  - alteration in mullerian differentiation
  - *surface epithelium*
    - regenerative changes

• **Stroma**
Progenitor/Endometrial stem cells

- Mutations
- Hormones
- Irritative/repair

Qualitative differentiations
Metaplasias and changes

Nicolae and Nogales 2011
Epithelial metaplasia or changes

- Incidence ?: 15 à 25% of endometrial curettage
- Secondary phenomena observed in a variety of conditions (unopposed estrogen stimuli or trauma):
  - IUD
  - Chronic endometritis
  - Breakdown
  - Dysfunctional uterine bleeding (hormonal dysfunction, anovulatory cycles)
  - Polyp
  - Hyperplasia or carcinoma
Epithelial metaplasia or changes

- **Asymptomatic**: “the pathologist disease” (not usually the cause of uterine bleeding)
- Identify the initial endometrial lesion (non-neoplastic or neoplastic)
Endometrial epithelial metaplasia (changes)

1. Tubal (or ciliated) metaplasia
2. Squamous cell metaplasia
3. Mucinous metaplasia
4. Eosinophilic metaplasia
5. Secretory or clear cell metaplasia
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1- ciliated or tubal metaplasia

- Not a true metaplasia: ciliated cells (up to 20%) are normally present along the surface epithelium, most numerous in proliferative endometrium
1- ciliated cell or tubal changes

- In the glandular epithelium: Response to a chronic estrogenic stimulation
- Anovulatory cycles (disordered proliferative endometrium)
- Hyperplasia, polyp
- Carcinoma (endometrioid, variante ciliated cells)
Glands lined by secretory and ciliated cells: eosinophilic cytoplasm, cilia at luminal borders, round and enlarged nuclei.
When seen in hyperplastic glands, rounding and enlargement of nuclei should not be considered as evidence of atypia.
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Squamous cell metaplasia
34%

- Mature
- Immature (morules)
2- Squamous metaplasia: mature

- **Surface epithelium**: regenerative changes
  - chronic endometritis, IUD, cervical stenosis and pyometra in elderly women
  - mature: ichthyosis uteri
2- Squamous metaplasia: immature

- Intra-glandular: morule
Unopposed estrogenic stimuli
• Hyperplasia
• Polyp

• 25% endometrioid carcinoma
Different immunoprofile

*Houghton et al, 2008*

<table>
<thead>
<tr>
<th></th>
<th>P16</th>
<th>B-catenin</th>
<th>RE</th>
<th>CD10</th>
<th>CDX2</th>
<th>P63</th>
<th>HMW keratin</th>
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<tbody>
<tr>
<td>Morule</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Mature squam</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
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*Morule : squamous metaplasia?*
Complex hyperplasia with squamous metaplasia (ER)
CD10
Lin et al, 2009
66 cases of intraglandular squamous metaplasia in biopsy/curettage

<table>
<thead>
<tr>
<th>Morphology</th>
<th>N</th>
<th>Normal</th>
<th>Persistence</th>
<th>Cancer</th>
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<tbody>
<tr>
<td>No glandular lesion</td>
<td>31</td>
<td>77.4</td>
<td>16.1</td>
<td>6.5</td>
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<tr>
<td>Focal complexity of glands</td>
<td>9</td>
<td>88.9</td>
<td>11.1</td>
<td>0</td>
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<tr>
<td>Complex and/or atypical glands (EIN)</td>
<td>26</td>
<td>42.3</td>
<td>38.5</td>
<td>19.2</td>
</tr>
</tbody>
</table>

Mean FU 31 months (%)
Morular metaplasia in endometrial biopsy

• There should be a high index of suspicion of an associated endometrial hyperplasia or neoplasia: recommend curettage

• Over interpretation of morules leading to erroneous dgc of malignancy

• Focus on the associated glandular elements: architectural complexity and cytological atypia: multiple levels
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Mucinous metaplasia 24%

Endocervical type

Intestinal type
Endometrial mucinous lesions (Nucci et al, 1999)

- Reviewed 102 curettages and 36 hysterectomy and classified mucinous lesions according to architectural complexity
- Type A: 19 cases
- Type B: 17 cases
- Type C: 16 cases
Type A (37% cases): average FU 1 year

- Normal glandular architecture or slightly more complex, micropapillary with small tufts projected from otherwise benign appearing glands
- Benign FU in 85% cases
Type B: microglandular pattern (32%) FU 5 M
- Rigid, punched out spaces
- 15/17 cases: ADK grade 1 (12) or ACH (3)
Cervical microglandular hyperplasia

Young lady under hormonal influence (pregnancy or contraception): no atypia or mitosis
Type B

- Cervical microglandular hyperplasia is rare in postmenopausal women (6% with HRT)
- Ask for curettage or new biopsy in 6 months (associated with low grade ADK)
- Need close follow up if not immediate removal
Type C: Complex papillary (31%): average FU 26 days

- High degree of architectural complexity with extensive glandular budding, cribriforming, branching of villous structures
- All had ADK (1/3 grade 2)
Mucinous lesions

Mazur et Kurman

• Without architectural complexity or nuclear enlargement: true metaplasia

• If architectural complexity and/or nuclear enlargement:

  « complex (and/or atypical) mucinous proliferation cannot exclude carcinoma »
Papillary metaplasia 12%

- Polyp (70%), HRT, Tamoxifen
- Associated with metaplasia 70% (90% are mucinous metaplasia)
Papillary metaplasia (lesion)

- Simple
- Complex

Lehman and Hart, 2001 (n = 9)
Philip et al, 2013 (n = 49)
Papillary metaplasia (proliferation)

- **Simple (60% of cases)**
  - localized and limited to 1 or 2 foci or <50% of polyp surface
  - short, non branching stalks or occasional secondary branches or detached papillae
Simple papillary proliferation

• 88% benign outcome
• Usually confined to the polyp and completely removed with it

Lehman and Hart, 2001 (n = 9)
Philip et al, 2013 (n = 49)
Papillary metaplasia (proliferation)

• Complex (40%)
  - complex papillae with frequent secondary and complex branches or diffuse and crowded intracystic papillae
  - > 50% polyp
  - >3 foci within the specimen
complex papillary proliferation
complex papillary proliferation

- 81% had concurrent or subsequent premalignant (atypical or non atypical CH) or carcinoma (35% of cases: associated with or in separate focus)

- Best designated as « complex papillary hyperplasia »

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  Philip et al, 2013 (n = 49)
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Eosinophilic metaplasia

= immature stage of mucinous metaplasia

• Abundant, dense, pink cytoplasm with granulations

• Nuclei centrally located, rounded, small nucleoli
Eosinophilic or oncocytic metaplasia

- Normal endometrium or associated with various non-neoplastic or neoplastic conditions

- The assessment of the architecture of the glands and cytological features should distinguish metaplasia from ACH and oncocytic carcinoma
Eosinophilic (papillary) syncytial metaplasia

- Regenerative changes
- Focal process,
- Surface epithelium
- Associated with glandular and stromal breakdown and bleeding (non-physiological breakdown)
• Syncytial aggregates of cells with abundant eosinophilic cytoplasm and indistinct cell borders
• Pseudopapillae formed by tufting and cell stratification
• Occasional reactive nuclear atypia and rare mitoses
• Nuclear debris and neutrophils
Associated with breakdown: stromal collapse with stromal blue balls, fibrin, neutrophils, nuclear debris
Endometrial surface papillary syncytial change (SPSC)

- Relevant to differential diagnosis with incipient, surface serous papillary carcinoma (intraepithelial carcinoma : EIC)
  - Associated with breakdown changes
  - Focal and surface epithelium
  - Immunophenotype:
    - Weak p53
    - Low or absent Ki67 index
    - Strong p16<sub>INK4A</sub> positivity
Differential diagnosis: intraepithelial carcinoma (EIC)

- Extensive and intraglandular
- Atypia and mitoses ++++
- P53 ++++, Ki67++++
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Clear cell metaplasia (hobnail) 10%

- Pseudo Arias Stella
- Progesteron or tamoxifen therapy
- Radiation therapy
Clear cell metaplasia

- Within endometrial glands and not in the surface
- Cells with clear cytoplasm
- Focal, no atypia or mitosis, no papillary formation
HNF1 beta

- Hepatocyte nuclear factor 1-beta: transcription factor recognized as sensitive and specific marker for ovarian CCC
- In endometrium: it is sensitive but not specific of CCC
  - 73% CCC
  - 60% UPSC
  - 35% endometrioid car.
  - 100% Arias Stella and CC metaplasia (at least some nuclear +)

Fadare and Liang, 2012
Endometrial stromal metaplasia

- Osseous or cartilaginous metaplasia
  - chronic endometritis or previous pregnancy (80%)
  - differential diagnosis:
    heterologous elements in mixed müllerian tumors
    fœtal debris in abortion
Cartilage
• **Smooth muscle metaplasia**: « tumorlet »
  - Small nodule within the stroma not connected to the myometrium (different from submucosal leiomyoma)
Adipose metaplasia
The term metaplasia: is not a diagnostic. It simply declares a lesion to be non-endometrioid in appearance without specifying it as benign, premalignant or malignant.

The pathologist should attempt to determine the underlying lesion, looking the degree of glandular complexity and nuclear atypia:
- reactive/degenerative,
- polyp or simple hyperplasia,
- atypical hyperplasia/EIN or carcinoma (47% of EIN show metaplasia).

Carlson et Mutter 2008