EIN – the final “word” in pre-malignant endometrioid neoplasia

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Outline

• Background: Endometrioid (Type I) endometrial adenocarcinoma
• WHO 1994
• Definition of Endometrial Intraepithelial Neoplasia (EIN)
• How does one diagnose EIN?
• Why do we need EIN?
• Management of EIN
• WHO 2014
• Examples
• Diagnostic dilemmas
Endometrioid type endometrial adenocarcinoma

- 70-80% of newly diagnosed endometrial cancer
- Associated with unopposed estrogen exposure
- Preceded by premalignant disease
- Malignancy develops through complex interactions between multiple genetic events and hormonal selection factors
“Endometrial hyperplasia”

• Term implemented, with various qualifiers (originally stratified by degree of architectural complexity and cytologic atypia), to encompass both:
  • non-premalignant morphologic responses to a hyper-estrogenic milieu
  AND
  • premalignant lesions
The WHO classification (1994) 4-tiered system

<table>
<thead>
<tr>
<th>Hyperplasias (typical)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple hyperplasia without atypia</td>
</tr>
<tr>
<td>Complex hyperplasia without atypia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Atypical hyperplasias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple atypical hyperplasia</td>
</tr>
<tr>
<td>Complex atypical hyperplasia</td>
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</tbody>
</table>
Problems with WHO 1994

- Difficult to teach – entire system based on qualifiers (atypia, complexity) which have never been standardized, thus:
  - Sub-optimal interobserver reproducibility in multiple studies
  - Particularly poor reproducibility for the diagnosis of atypical hyperplasia
Problems with WHO 1994

• Missed some clinically important lesions:
  • additional criteria (such as lesion size, threshold of gland crowding) relevant to increased cancer risk were discovered
  • The presence/absence of “atypia” is not always a reliable indicator of the presence/absence of clinical significance
Legitimate endometrial “hyperplasias”

- Diffuse, polyclonal proliferations of endometrial epithelium in response to abnormal estrogenic stimulus over time
- Morphologic features depend on the extent and duration of estrogen exposure
- Do NOT represent premalignant lesions

Proliferative endometrium → Disordered proliferative endometrium → Benign endometrial hyperplasia
Legitimate endometrial “hyperplasias”

- Proliferative endometrium
- Disordered proliferative endometrium
- Benign endometrial hyperplasia

Estrogen over time
Premalignant endometrial lesion

• Endometrial cancer does NOT represent the end result of a gradual, continuous spectrum of morphologic changes

• A localized, clonal population of genetically-altered glands emerges as a discrete premalignant lesion (i.e., not a hyperplasia)
Endometrial Intraepithelial Neoplasia (EIN)

• Monoclonal proliferation of architecturally and cytologically *altered* (not necessarily classically *atypical*) premalignant endometrial glands

• Distinct from diffuse hormonal effects (benign endometrial hyperplasia)
Endometrial Intraepithelial Neoplasia (EIN)

• Associated with a 45-fold increased risk of endometrioid endometrial adenocarcinoma
• ~ 1/3 to 1/2 of women with EIN on biopsy will be diagnosed with cancer within a year
• Biopsies which lack EIN have a negative cancer predictive value of 99%
Adapted from Mutter GL, www.endometrium.org

- PTEN, PAX2 inactivation, microsatellite instability
- Mutations in K-ras, β-catenin, emergence of mutant clone
- Malignant transformation

Histologically benign → EIN → Adeno-carcinoma

Estrogen
<table>
<thead>
<tr>
<th>Criterion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architecture</td>
<td>Area of glands &gt; area of stroma (often a discrete focus)</td>
</tr>
<tr>
<td>Cytology</td>
<td>Differs between area of gland crowding and background endometrium</td>
</tr>
<tr>
<td>Size</td>
<td>Focus of crowded, cytologically altered glands at least 1 mm</td>
</tr>
<tr>
<td>Benign endometrial mimics</td>
<td>Benign endometrial hyperplasia, secretory endometrium, polyps, fragmented specimens (artifactual crowding)</td>
</tr>
<tr>
<td>Cancer excluded</td>
<td>Mazelike glands, solid areas, significant cribriforming = carcinoma</td>
</tr>
</tbody>
</table>
EIN

Background endometrium
Volume percentage stroma

EIN ~ 40%

Non-EIN ~ 75%
Volume percentage stroma

EIN ~ 40%

Non-EIN ~ 75%

Bottom line: More glands than stroma
Altered vs. “atypical” cytology

- No single cytologic appearance across all EIN lesions
- Always a comparison to background cytology
- Classic “atypia” – round non-polarized nuclei, prominent nucleoli – often present, but not required
- The cytologic change can include nuclear and/or cytoplasmic components
Various patterns of metaplasia in EIN

Tubal

Mucinous

Squamous

Secretory

Eosinophilic

Micropapillary

Jarboe et al 2010
1mm size criterion is not arbitrary

- Confers clinical outcome predictive value
- Prevents over diagnosis of EIN
- Must be achieved in a single focus (not an aggregate measurement)
Why do we need EIN?

• Better interobserver reproducibility than 4-tiered WHO
• Better positive cancer predictive value than 4-tiered WHO:
  • 45-fold increased cancer risk conferred by EIN
  • 14-fold increased cancer risk conferred by presence of “atypia” in WHO 1994 system
Why do we need EIN?

Endometrial Intraepithelial Neoplasia

- Atypical Hyperplasia: 78%
- Complex Non-Atypical Hyperplasia: 44%
- Simple Non-Atypical Hyperplasia: 4%

Hecht et al, 2005
Management of EIN

• Hysterectomy
• Hormonal (progestin) therapy (young women, poor surgical candidates)
  • Up to 90% of endometrial pre-cancers may be ablated by progestin
  • Can’t predict which women will respond
  • Follow-up surveillance is essential
The WHO classification (2014) 2-tiered system

<p>| Hyperplasia without atypia                      |
| Atypical hyperplasia/Endometrioid             |
| Intraepithelial Neoplasia (AH/EIN)            |</p>
<table>
<thead>
<tr>
<th>WHO 2014 Nomenclature</th>
<th>Topography</th>
<th>Functional Category</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial hyperplasia without Atypia</td>
<td>Diffuse</td>
<td>Estrogen Effect (benign)</td>
<td>Hormonal therapy</td>
</tr>
<tr>
<td>EIN/Atypical Endometrial Hyperplasia</td>
<td>Focal progressing to diffuse</td>
<td>Precancer</td>
<td>Hormonal or surgical</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Focal progressing to diffuse</td>
<td>Cancer</td>
<td>Surgical</td>
</tr>
</tbody>
</table>
WHO 2014: Hyperplasia without Atypia (Benign endometrial hyperplasia)

- Spectrum of changes
- Variable gland crowding, cystically dilated glands, gland branching
- Focal areas of breakdown common
- Lined by proliferating columnar epithelium, lacking cytologic atypia
WHO 2014: Atypical Hyperplasia/Endometrioid Intraepithelial Neoplasia (EIN)

- Clonal process emerging from localized lesion in background of non-atypical hyperplasia
- Aggregates of tubular or branching glands, exceeding volume of stroma
- Distinguished from non-atypical hyperplasia by nuclear atypia (variable in degree):
  - May include “classic” features of atypia
  - May include metaplastic changes
  - Diagnosing “atypia” is based on comparison to cytology of background glands (WHO 2014, Figure 5.02)
WHO 2014

- Essentially adopted EIN (begrudgingly, perhaps?)
- Old architecture definitions (simple and complex) are stripped
- EIN definitions are the only ones that remain
- “atypical hyperplasia” = EIN makes the transition easier
  - Definition of atypia changed relative to internal standard
  - Carryforward of “hyperplasia” semantic only
WHO 2014 = EIN system

Non-atypical Hyperplasia
- Diffuse field effect
- Regularly Irregular
- Random Metaplasias

EIN
- Expansile Clonal
- Individual glands
- Glands > Stroma
- Altered cytology

Carcinoma
- Cribiform
- Solid
- Mazelike
- Myoinvasive

Mutter 2013
The American College of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncology (SGO) states:

“Pathologic diagnosis of premalignant lesions should use criteria and terminology that clearly distinguish between clinicopathologic entities that are managed differently. At present, the endometrial intraepithelial neoplasia schema is tailored most closely to this objective.”
EIN Examples
EIN with squamous morules
EIN with squamous morules

• Can create diagnostic pitfall – peripheral “garland” of glands surrounding morule can resemble cribriforming which can be over-interpreted as carcinoma

• “Extract” the morular component when assessing the architectural nature of the glands
**Dx:** EIN by subjective diagnosis and computer morphometric analysis

**WHO 1994:** Complex *non-atypical* hyperplasia

**Follow-up:** Endometrial adenocarcinoma 2 years later

Hecht et al, 2005
EIN in an endometrial polyp
EIN in endometrial polyps

• EIN vs. not EIN in an endometrial polyp can be tricky
  • Polyps exhibit irregularly-shaped and irregularly-distributed glands and variable cytology
• Standard diagnostic criteria for EIN apply, but the reference “background” is the polyp, not the adjacent functionalis
Endometrial adenocarcinoma, endometrioid type, FIGO grade 2, arising in a background of EIN
Dx: EIN by subjective diagnosis and computer morphometric analysis

WHO 1994: Simple non-atypical hyperplasia

Follow-up: Endometrial adenocarcinoma 8 months Later

Hecht et al, 2005
EIN with tubal differentiation
EIN with micropapillary differentiation

• Gland crowding, architectural complexity, cytology is often bland
• Can mimic secretory endometrium
• Can mimic adenocarcinoma when luminal tufting is especially exuberant
Common diagnostic dilemmas – ambiguous “gland crowding”

- Focal (cytologically altered) gland crowding, subdiagnostic of EIN:
  - Size criterion of 1 mm not met
  - Excessively fragmented specimen: focus < 1 mm, on edge of fragment
  - Glands not sufficiently crowded
  - Deeper levels may help
Subdiagnostic "Gland Crowding"

Non-EIN (too small)
Subdiagnostic EIN: “Gland Crowding”
n=143 (0.3% of 71,579 specimens)

- Altered cytology
- Size < 1mm
- Glands < stroma

Outcomes (n=143)
- 77% Benign
- 19% EIN
- 4% Cancer

Dx: “Crowded focus of cytologically altered glands (see comment).”
Comment: Resampling is recommended within 6-12 months”

Nucci et al., 2010
Common diagnostic dilemmas –
High dose progestin therapy

- Stromal expansion decreases gland density
- Makes neoplastic cytology bland
- Nuclear rounding in normal cells
Progestin effect on architecture

PRE-Rx

POST-Rx

Jarboe et al., 2010
Progestin effect on cytology

NL

PRE-Rx

POST-Rx

EIN
Potential diagnostic dilemma – Serous endometrial intraepithelial carcinoma (EIC)

- Completely unrelated to EIN
- Putative precursor of serous adenocarcinoma
- Isolated EIC does not behave like a precancer; can spread causing disseminated abdominal disease
- Must exclude EIC when considering dx of EIN

Jarboe et al., 2010
EIN take home points

- No need to struggle over “atypia” in the classical sense
- Many lesions which were hard to classify with WHO 1994 translate easily to EIN
- Some clinically important lesions missed with WHO 1994 are picked up using EIN
- WHO 2014 adopted EIN – some semantic carryover, but legacy criteria are gone
- At last, down to a 2-class hormonal/precancer system
- Published record of criteria/outcomes all under “EIN” moniker
EIN take home points

- Make everyone happy in your report:
  - “Endometrial intraepithelial neoplasia (atypical hyperplasia)”
  - “Benign endometrial hyperplasia (hyperplasia without atypia)”
EIN take home points

- The EIN vs WHO war is over (or really should be)
References

- WHO Classification: Tumors of Female Reproductive Organs 2014

www.endometrium.org
Objective vs. subjective EIN diagnosis

D-Score <1 corresponds to EIN (computerized morphometric analysis)

Hecht et al, 2005