Atypical Glandular Cells

• Mean rate in U.S.: 0.4%
• Women under 40
  – HSIL and AIS most common
• Post-menopausal women
  – Higher rate of significant abnormality
  – Cervical or endometrial lesion in up to 50%
    • 15-20% Endometrial CA
    • 5% Invasive Cervical CA

Zhao 2009

Atypical Endocervical Cells

Bethesda Definition:
• Endocervical-type cells display nuclear atypia that exceeds obvious reactive or reparative changes but that lack unequivocal features of endocervical adenocarcinoma in situ (AIS) or invasive adenocarcinoma

Reactive Endocervical Cells

• Round to oval nuclei
• Even chromatin
• Smooth nuclear membranes
• Slight thickening of nuclear membranes
• Slight increase N:C ratios
• Slight layering of cells

2001 Bethesda: Glandular Cell Abnormalities

• Atypical
  – Endocervical cells (NOS)
  – Endometrial cells (NOS)
  – Glandular cells (NOS)
• Atypical
  – Endocervical cells, favor neoplastic
  – Glandular cells, favor neoplastic
• Endocervical Adenocarcinoma In Situ (AIS)
• Adenocarcinoma:
  – Endocervical
  – Endometrial
  – Extrauterine
  – NOS
Endocervical Adenocarcinoma In Situ

- Palisading nuclei with feathering, rosettes
- Enlarged, elongate nuclei; stratified
- Hyperchromatic with coarse chromatin
- Irregular nuclear membranes
- Increased N:C ratios
- Mitotic activity

Endocervical Adenocarcinoma In Situ

Liquid-based preparations:
- Feathering less prominent, rosettes uncommon
- More three-dimensional clusters
- Chromatin more open and vesicular

Atypical Endocervical Cells, favor neoplastic

- Cell morphology, either quantitatively or qualitatively, falls just short of an interpretation of endocervical adenocarcinoma, in situ or invasive

Atypical Endocervical Cells (NOS)

- Sheets and strips with some crowding and nuclear overlap
- Nuclear enlargement (3-5x normal)
- Oval or cigar-shaped nuclei (not round)
- Some nuclear membrane irregularities
- Mild hyperchromasia
- +/- Nucleoli
- Rare mitotic figures

Causes of AGC

- Tubal metaplasia
- Direct sampling of lower uterine segment
- Exfoliated or atypical endometrial cells
- Intrauterine device effect
- Atrophy
- HSIL

Tubal Metaplasia

**OVERLAPPING**
- Palisading strips
- Elongate nuclei

**DISTINGUISHING**
- Lack of nuclear stratification
- Smooth nuclear contours
- Cilia
- Not hyperchromatic
- Single cells common

Ducatman 1993; Novotny 1992
Direct Endometrial Sampling

**OVERLAPPING**
- Columnar cells in sheets and strips
- Feathering, rosette formation
- Mild to severe nuclear pleomorphism and hyperchromasia
- Mitotic figures

**DISTINGUISHING**
- Smaller endometrial-like cells, focally associated with endometrial stroma

Exfoliated Endometrial Cells

- Tight 3-D clusters
- Small, round nuclei
- Scant cytoplasm
- Liquid-based:
  - More prominent nucleoli, cytoplasmic vacuoles and apoptosis
  - Single cells more common

Atypical Endometrial Cells

- Clusters of cells with slightly enlarged nuclei
- Mild hyperchromasia
- Small nucleoli
- Scant cytoplasm, occasionally vacuolated; may see intracytoplasmic neutrophils
- Indistinct cell borders

Intrauterine Device

- Endometrial cells can shed at any time
  - Degeneration common
- Reactive endocervical and squamous metaplastic cells
  - Papillary clusters with large cytoplasmic vacuoles or single signet ring like cells
- Ingested neutrophils, psammoma bodies can mimic endometrial carcinoma

HSIL with Endocervical Gland Extension

**OVERLAPPING**
- Hyperchromatic crowded groups
- High N:C ratios
- Hyperchromatic nuclei and irregular nuclear contours

**DISTINGUISHING**
- Circumferentially arranged nuclei along periphery
- Single cells
- Background of LSIL or foci of squamous differentiation

*HSIL & AIS can co-exist*

HPV Testing

- Negative HPV test prior to histologic diagnosis:
  - 37% AIS
  - 80% endocervical adenocarcinoma
  - 13% HSIL
- False negative rate of Pap test
  - 11.7% for AIS vs. 4.6% for HSIL (p<0.001)

Farnsworth, 2011; Renshaw, 2004
HPV Testing

- Endocervical adenocarcinoma
  - 82% HPV types 16 and 18
  - 94% HPV types 16, 18, 45

Sanjose, 2010

Adenocarcinoma in Situ (AIS) histology

- Enlarged oval-to-elongate nuclei with irregular nuclear contours
- Nuclear stratification with crowding
- Apical “floating” mitotic figures
- Apoptotic bodies, basally located
- Hyperchromasia, +/- nucleoli

Superficial (Early) AIS

- Small patch of AIS that blends into endocervical mucosa – easy to miss
- Less prominent mitotic activity, apoptosis, nuclear atypia
- Occurs in younger women, mean age low 20’s
- p16 stain helpful in confirming diagnosis

Borderline Lesions: Scoring System


<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratification</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Nuclear atypia</td>
<td>None</td>
<td>Small</td>
<td>Up to 3x</td>
<td>&gt;3x</td>
</tr>
<tr>
<td>Mitosis + Apoptosis</td>
<td>None</td>
<td>&lt;0.5</td>
<td>0.6-3.0</td>
<td>&gt;3.0</td>
</tr>
</tbody>
</table>

Nuclear enlargement, anisocytosis, hyperchromasia, dyspolarity, nucleoli (at least 2)
Average number per gland in 2 most active glands

Scoring System


<table>
<thead>
<tr>
<th></th>
<th>SCORE</th>
<th>CONCORDANCE</th>
<th>KAPPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BENIGN</td>
<td>0-3</td>
<td>57%</td>
<td>0.6</td>
</tr>
<tr>
<td>GLAND DYSPLASIA (EGD)</td>
<td>4-5</td>
<td>43%</td>
<td>0.6</td>
</tr>
<tr>
<td>AIS vs. NON-AIS</td>
<td>0-5</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>AIS</td>
<td>6-9</td>
<td>95%</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Biomarkers

- P16:
  - Diffuse strong nuclear (or nuclear and cytoplasmic) staining
  - Every cell staining
- Ki67:
  - High
  - Can be used as complimentary marker
AIS: Clinical Management

• Hysterectomy for women who have completed their family or are of post child-bearing age.
• Cone followed by long-term surveillance for reproductive age women
• Positive margins in a cone biopsy is managed by re-excision or follow-up colposcopy, cervical cytology and HPV testing at 6 months.

Early Invasive Endocervical Adenocarcinoma

Corresponds to FIGO Stage IA1:
• Not grossly visible
• <3.0 mm depth of invasion
• ≤7.0 mm maximal horizontal extent

Early Invasive Endocervical Adenocarcinoma

• Must be completely excised to define as early invasive
• Lymphatic-vascular invasion should be noted in report but does not alter stage
• Associated with low rate of LN metastases

AIS vs. Early Invasion

• Can be virtually impossible to distinguish AIS from early invasive adenocarcinoma, especially in curettage specimens
• Important to recognize when the distinction will affect management

Silva System

Invasive Endocervical Adenocarcinoma: Proposal For New Pattern-based Classification System With Significant Clinical Implications: A Multi-institutional Study

*Int J Gynecol Pathol 2013; 32:592-601*
Pattern B: Early Stromal Invasion

- Glands permeate stroma with abnormal architectural pattern
  - Marked gland irregularity
  - Haphazard arrangement of glands
- +/- Altered, edematous stroma and inflammation

Pattern C: Diffuse Destructive Invasion

- Glands permeate stroma with abnormal architectural pattern
  - Marked gland irregularity
  - Haphazard arrangement of glands
- +/- Altered, edematous stroma and inflammation

Silva System: Outcome

<table>
<thead>
<tr>
<th>METHOD</th>
<th>N</th>
<th>DOI</th>
<th>+LN PTS</th>
<th>RECURRENCE</th>
<th>DOD</th>
<th>STAGE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>73</td>
<td>3.8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>73 (100%)</td>
</tr>
<tr>
<td>B</td>
<td>90</td>
<td>4.0</td>
<td>4 (4%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>86 (96%)</td>
</tr>
<tr>
<td>C</td>
<td>189</td>
<td>9.2</td>
<td>45 (24%)</td>
<td>38 (22%)</td>
<td>16</td>
<td>152 (80%)</td>
</tr>
<tr>
<td>STD</td>
<td>352</td>
<td>6.7</td>
<td>49 (14%)</td>
<td>39 (11%)</td>
<td>16</td>
<td>311 (88%)</td>
</tr>
</tbody>
</table>

Silva System

- Better predictor of risk of LN metastasis
- Pattern A:
  - 100% survival, no recurrence
  - No lymph node resection needed
- Pattern B:
  - LVI present in all patients with LN mets
- Pattern C:
  - 22% recurrence
  - Aggressive treatment required

Reporting

- Measurement (use calibrated optics):
  - Depth of invasion
  - Tumor thickness
  - Linear (horizontal) extent of invasion
- Lymphatic-vascular invasion
- Extent of AIS
- Margin status (if excision)
Depth from Gland of Origin

Biopsy or Curettage Specimen

• Issue diagnosis of “adenocarcinoma” with comment indicating complexity of lesion is beyond AIS but definitive features of invasion are not identified.

• Management same for both: cone biopsy

Cone Biopsy

Focus suspicious for invasion:
• Levels of problematic area
• Embed all tissue
• If still unclear, indicate uncertainty in report; include depth & horizontal extent
• Repeat cone and/or imaging studies may be helpful

Management

Stage 1A1:
• Conservative treatment with cone biopsy, if margins are negative, or with simple hysterectomy
• No lymphatic or parametrial involvement identified in patients treated with radical hysterectomy and pelvic lymphadenectomy

McHale, 2001