Hyperchromatic Crowded Groups: What is Your Diagnosis?
Session 3000

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Disclosures

• In the past 12 months, I have not had a significant financial interest or other relationship with the manufacturer(s) of the product(s) or provider(s) of the services that will be discussed in my presentation.
Hyperchromatic Crowded Groups

Term introduced by Dr. DeMay in the mid 90’s

Refers to cellular “microbiopsies” with dark staining nuclei in Pap smears

Almost always benign but in a small percentage of cases may represent a serious process

In some cases the differential diagnosis can be very difficult
Entities associated with HCG’s

**BENIGN**
- Endocervical cells
  - Brush artifact
  - Tubal metaplasia
  - Reactive/Repair
- Endometrial cells
  - Menses
  - IUD effect
- Atrophy
- Follicular cervicitis

**NEOPLASTIC**
- HSIL/Squamous Ca
- EC AIS
- EC adenocarcinoma
- Endometrial neoplasia
- Small cell carcinoma
- Extrauterine Ca
  - Ovary
  - Colon
  - Breast
Benign vs. Neoplastic HCGs

• Important differential diagnostic decision
  – High potential for error when dealing with Hyperchromatic Crowded Groups

• Problem cases often included in the “Atypical glandular cells” categories of the Bethesda system
Evaluating Slides with HCG’s

• The groups

• The background

• The individual cells

• The history
HCG Case Examples
Case 1

51 year-old woman
Liquid based Pap test
What is your interpretation?

1. Tubal metaplasia
2. Endocervical AIS
3. Metastatic adenocarcinoma
4. Reactive endocervical cells
5. Endometrial cells
Diagnosis available at session
Features of Endocervical AIS

- Isolated stratified strips
- Increased N/C

Hyperchromasia
Mitoses
Apoptotic bodies
Features of Endocervical AIS

Feathering
Elongate tapered nuclei

Pseudostratification
Rosettes
Reactive endocervical cells
Tubal Metaplasia
Cytologic Features

• Some features in common with AIS
  – Chromatin (Granularity/distribution)
  – Increased N/C ratio
  – Crowding and Hyperchromasia

• Differential Dx features
  – Large stripped nuclei
  – Cilia/terminal bars
Tubal Metaplasia
Tubal Met

Tubal Metaplasia
Tubal Metaplasia
Endometrial Cells can mimic AIS
Proliferative Endometrium
Metastatic adenocarcinoma
Immunocytochemistry in cytology of Cervical glandular lesions

- p16ink4a
- Ki-67
- ProEX C
Immunocytochemistry in cytology of glandular lesions

CINtec PLUS (p16/Ki-67) demonstrated potential to aide in the diagnosis of cervical glandular lesions in a recent study. (48 Cases)

- 92.5% of adequate neoplastic samples stained +
- 7.5% inconclusive 15 (93.8%) of 16 negative samples stained –
- Sensitivity 88%, Specificity 94%

Immunocytochemistry in cytology of glandular lesions

ProEx C has also demonstrated a potential to help triage atypical glandular cells in liquid based samples. (28 cases)

- 13 with subsequent positive biopsy, 10 were ProEx C +
- 15 with negative biopsy, 13 were ProEx C -, 2 were +
- Sensitivity 77%, Specificity 87%

Case 2

55 year-old postmenopausal woman
Vaginal spotting
Last Pap test three years ago was negative
Case 2: The best interpretation is:

1. Normal Em cells
2. Reactive cell changes (IUD Effect)
3. Atypical Em cells, favor neoplastic
4. Atypical EC cells, favor neoplastic
5. Extrauterine (metastatic) carcinoma
Diagnosis available at session
Atypical EM’s; Differential Diagnosis

- Benign changes
  - IUD effect, normal EM
- Endometrial hyperplasia
- Endometrial adenocarcinoma
- Endocervical adenocarcinoma
- Metastatic adenocarcinoma
- HSIL
IUD EFFECT
## Endometrial Neoplasia

<table>
<thead>
<tr>
<th>Feature</th>
<th>Simple</th>
<th>Complex</th>
<th>Atypical</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Cells</td>
<td>107</td>
<td>142</td>
<td>245</td>
<td>538</td>
</tr>
<tr>
<td>Cell area (Sq micrometers)</td>
<td>89</td>
<td>98</td>
<td>116</td>
<td>149</td>
</tr>
<tr>
<td>Nuclear area</td>
<td>42</td>
<td>49</td>
<td>53</td>
<td>68</td>
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<tr>
<td>Relative nuclear area</td>
<td>47</td>
<td>50</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Irregular chromatin</td>
<td>4</td>
<td>10</td>
<td>21</td>
<td>97</td>
</tr>
<tr>
<td>Nucleoli % cells</td>
<td>2</td>
<td>6</td>
<td>17</td>
<td>88</td>
</tr>
</tbody>
</table>

From: Wilbur, DC. Cytology of endocervix and endometrium. in Bonfiglio, TA and Erozan, YS, Gynecologic Cytopathology, Lippincott-Raven, 1997
# Endocervical vs. Endometrial Adenocarcinoma

<table>
<thead>
<tr>
<th>Feature</th>
<th><strong>Endocervical</strong></th>
<th><strong>Endometrial</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellularity</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Diathesis</td>
<td>Tumor</td>
<td>Watery</td>
</tr>
<tr>
<td>Cell &amp; Nuclear size</td>
<td>Larger</td>
<td>Smaller</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Ampho/Eosinophilic</td>
<td>Cyanophilic</td>
</tr>
<tr>
<td>Cytoplasm amount</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Multiple nucleoli</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Cell configuration</td>
<td>Columnar</td>
<td>Round to Oval</td>
</tr>
<tr>
<td>Group arrangement</td>
<td>2 dimensional</td>
<td>3 dimensional</td>
</tr>
</tbody>
</table>
Ovarian Carcinoma
Metastatic Carcinoma

Metastatic Breast Carcinoma

Metastatic Colonic Carcinoma
Endometrium vs. HSIL

Endometrial

HSIL (Small cell type)
## Endometrial lesions vs.. HSIL

<table>
<thead>
<tr>
<th>Endometrial</th>
<th>HSIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 dimensional clusters</td>
<td>Syncytial like groups</td>
</tr>
<tr>
<td>Smudgy degenerative chromatin</td>
<td>Granular often coarse chromatin</td>
</tr>
<tr>
<td>Presence of endometrial stromal cells</td>
<td>Presence of single dysplastic cells</td>
</tr>
</tbody>
</table>
Case 3

31 year old woman
Routine Pap test
SurePath
Case 3: What is your diagnosis?

1. NILM (Endometrial cells)
2. HSIL (with gland involvement)
3. Atypical EC cells
4. Adenocarcinoma in situ
5. Invasive squamous carcinoma
Diagnosis available at session
Evidence of squamous origin
Evidence of Squamous origin

- Lack of typical AIS features
  - Elongate nuclei
  - Isolated Strips
  - Feathering
  - Rosettes
Summary

• HSIL In Glands Mimics Atypical EC Cells

• HSIL is the most common neoplastic Dx on biopsy after Atypical EC Pap.

• Careful evaluation of features can often but not always lead to correct interpretation.
AIS and HSIL may coexist
Case 4

65 year old

Liquid based Pap

History of Abnormal Pap in past
What is your interpretation?

1. HSIL
2. Negative (Atrophy)
3. Atypical Endocervical Cells
4. Squamous Cell Carcinoma
5. Endometrial Carcinoma
Diagnosis available at session
<table>
<thead>
<tr>
<th></th>
<th>HSIL</th>
<th>Atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher N/C</td>
<td>Single dysplastic cells</td>
<td>Lower N/C</td>
</tr>
<tr>
<td></td>
<td>Coarse chromatin</td>
<td>Parabasal like cells</td>
</tr>
<tr>
<td></td>
<td>Mitoses (rare)</td>
<td>Smudgy or fine</td>
</tr>
<tr>
<td></td>
<td>Usually more hyperchromatic</td>
<td>No mitoses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usually less hyperchromatic</td>
</tr>
</tbody>
</table>
HSIL vs. Atrophy
HSIL vs. Atrophy

Single cells
Squamous cell carcinoma
Uncommon Entities with HCG’s

• Small cell carcinoma
  • Lymphoma
  • EM stromal cells
• Chronic lymphocytic cervicitis
Small cell carcinoma
Cytologic Features

- Similar to SCC at other sites
- Groups and single cells
- Scant cytoplasm
- “Powdery” chromatin
- Inconspicuous nucleoli
- Nuclear molding
- Streaming nuclear material (Conventional Paps)
- Tumor diathesis
Differential Diagnosis

- Basaloid squamous cell carcinoma
- HSIL
- Lymphoma
- Endometrial stromal cells
- Chronic lymphocytic cervicitis
Potentially useful markers

- HPV testing (Commonly HPV 18 positive)
- Neuroendocrine Markers
  - Chromogranin, Synaptophysin, CD 56
- TTF-1 (Small percentage 10-20% in most studies.)
- p63 negative (or weakly positive)