Gyn Cytology slide seminar – the Agatha Christie mysteries

Tuesday 4th October 2016 2:30 – 4:00, Hall 3A

Rana S. Hoda, MD, FIAC
Professor of Pathology &
Chief, Papanicolaou Cytology Lab &
Director of Cytopathology Fellowship Training Program
New York Presbyterian Hospital-Weill Cornell, NY
Case 1

62-year-old,
Prior Paps: negative
History: Breast cancer, 2004
Medications: Estrogen 5 years until 2002
ThinPrep
Cellular, background mucin, architecture variability
Thick mucin, groups, strips, single neoplastic cells
Loose sheets, mucinous cytoplasm
Nuclei, palisaded, lobate, irregular, nucleoli
Cytological Diagnosis

Atypical Glandular Cells of Endocervical Origin
AGC, EC

Cervical & endometrial biopsies & HPV test followed
HPV: Negative

ECC: Dissolved on processing
EMBx: Endometrial polyp
Repeat Pap in 6 months: AGC, EC
Histological Diagnosis:

Minimal Deviation Adenocarcinoma (MDA)
Depth of invasion >7mm
The Pap Test: 
Biggest success in the hx of cancer screening

80% decline in incidence of cervical ca

American Cancer Society, 2016
Invasive Endocervical Adenocarcinoma (ECA)

The great success of the Pap test is attributed only to squamous ca, as the prevention of ECA has not been demonstrated

Liquid-Based Preparations

20 mm methanol

13 mm ethanol

“Greatest Advance in Pap Test…” Meisels

Thinprep | Surepath
Glandular Cells - Bethesda 2014

- Atypical
  - Endocervical cells, nos
  - Endometrial cells, nos
  - Glandular cells, nos
- Atypical
  - Endocervical cells, favor neoplastic
  - Glandular cells, favor neoplastic
- AIS, Adenocarcinoma
AGC
Prevalence, < 1%

Follow-up studies
- Benign 40% - 70%
- Squamous neoplasia 40% - 80%
- Endocervical neoplasia 0% - 10%

The most common diagnosis preceding histologic Adenocarcinoma/AIS

MDA

- Rare, 1-3 %, very well-diff ADCA
- Types: mucinous, clear, endometrioid
- Mean age: 42 years
- Symptom: bleeding, discharge
- Etiology: ? Pill & Peutz-Jegher STK11
- HPV: no association
- Prognosis: poor with PJS association
Detection Rate of MDA by Pap & Bx is Low

- 32% by Pap & 28% by bx
- 50% after multiple bx

MRI & screening of cervical discharge for gastric mucins will improve detection

MDA- Histology

- Low-grade cytology
- Architecturally variable atypical glands
- Lining of single mucinous cell layer
- Glands extend beyond nl endocervix, >7mm
Cytology

- Bland cells, background mucin
- Nuclei: uniform to mildly irregular, fine chromatin, prominent nucleoli
- Cytoplasm is abundant & mucinous

Ishii Cancer 1999;87:245, Mikami Mod Pathol 2004;17:962
MDA – conventional Pap smear
"Golden yellow" mucin in Paps

MDA

Pyloric gland metaplasia

- PAS & HIK1083 +

Hata, Diagn Cytopathol 2002;27:80
Differential Diagnosis

- Reactive endocervical cells
- Atrophy
- Usual type of endocervical adenocarcinoma (ECA)
- Others
MDA - Potential Pitfall

Benign endocervix

MDA
Usual ECA in a 22-year-old, TP
- 2-D clusters
- columnar
- < cytoplasm
- bloody diathesis
- ER, PR (-)

- 3-D clusters
- rounded
- > cytoplasm
- watery diathesis
- ER, PR (+)
A subset of ECA, including MDA & GTA are not HPV-related.

In addition, adenocarcinomas can be endometrial or extrauterine in origin.

1° HPV Screening will not detect these tumors.
Diagnostic dilemma, both on Pap & bx
- Golden-yellow mucin may not be seen on LBP
- HPV test & p16 are negative
Case 2

31-year-old
Routine Pap
SurePath
Large Crowded Group, Loss of Polarity
Oval Nuclei, Wispy Cytoplasm, AGC-like
“Feathering”

Nuclear overlap, Honeycomb-like
Cell flattening at edge

Fraying of peripheral cells
Elongated nuclei at edge of cell group, resembling glandular cells

Irregular nuclear membranes

?Pseudostratification
Cytological Diagnosis

Atypical Endocervical Cells,
Favor Neoplastic
Cannot Exclude HSIL Involving
Endocervical Glands
Frequency of AGC diagnosis

- <1% in conventional and LBP
- significant cx lesion detected in 17–80%
  - 30% are squamous lesions, with 60% HSIL
HSIL in ECG

- 63% HSIL involve ECG
- Accurate recognition reduces AGC diagnoses

Detail is enhanced in LBP

Wilbur DC, Mod Pathol. 2016;29 Suppl 1:S1-11
Kumar, Cytopathol 2009;20:351
HSIL Involving Endocervical Glands

New collecting instruments for endocervical sampling, such as cytobrush increase yield
Challenges of HSIL in ECG Diagnoses

- HG squamous vs glandular neoplasia
- 25–75% HSIL co-exist with AIS
- Poor cyto-histological correlation
  - HSIL in ECG correctly diagnosed in 10%
  - Overdiagnosed in 18%
  - Diagnosed as glandular lesion in 28–54%

Kir G. J Cytol. 2012;29(2):121
Importance of Accurate Diagnosis

- Alerts gynecologist to perform thorough assessment of EC during colposcopy
- Perform deeper cone rather than LEEP
- 5-yr survival for ECA is 44–56%, whereas that for squamous ca is 62–68%
p63 is a useful immunomarker for differentiating primary glandular lesion from HSIL in Paps

When HSIL involves ECG it take on a glandular appearance

Garcia, Cancer Cytopathol 2007;111:54
Architecture of HSIL in ECG
Pattern A

Flattening of cells at periphery of clusters

Kumar Cytopathology 2009, 20, 351
Architecture of HSIL in ECG
Pattern B

Palisading & Pseudostratification of Peripheral Cells
Architecture of HSIL in ECG

Pattern C

Streaming & elongation of cells in a group

Nuclear axis is parallel to each other
Evidence of Squamous Origin

- Central loss of cell polarity
- Syncytial arrangements
- Flattened/layered borders
- Hard squamoid cytoplasm
- Nuclear grooves
- Nucleoli +/-
- Individual dysplastic squamous cells
HSIL with Gland Involvement

“Hard Cytoplasm”
<table>
<thead>
<tr>
<th>Features</th>
<th>HSIL in EC glands</th>
<th>AIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central cell polarity</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Overlapping</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>micro</td>
<td>prominent</td>
</tr>
<tr>
<td>‘Feathering’</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>p63</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>-/+</td>
<td>+</td>
</tr>
<tr>
<td>Mitoses</td>
<td>-/+</td>
<td>+</td>
</tr>
<tr>
<td>High N:C</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>p16 overexpressed</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Hoda RS. Diagn Cytopathol. 2013;41:257
Squamous versus Endocervical Lesions

- Associated HSIL or carcinoma in situ
- Hard, glassy cytoplasm
- Absence of typical features of AIS
- Nuclear axis
HSIL in EC Glands

Small nuclei forming smooth clusters
■ HSIL in ECG can be accurately diagnosed by careful evaluation of the well-established features