Cytopathology Companion Meeting
Case #4

Michael Thrall, M.D.
Director of Digital Pathology
Houston Methodist Hospital, Houston, Texas
Associate Professor of Pathology and Laboratory Medicine
Weill Medical College of Cornell University
Cytopathology Companion Meeting

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No conflicts to disclose
Case History

- A 50 year-old woman presented with vaginal discharge
- A conventional Pap smear was performed
Predominantly glandular cells
Large clusters in irregular sheets
Abundant background mucin
Pitfall Alert!

www.retrogameoftheday.com
Most clusters contain well-ordered cells in honeycomb sheets. The nuclei are mostly uniform.
This case versus normal endocervical cells
Nuclear contours oval/round and smooth
Dispersed chromatin
Prominent chromocenter

Nuclei are slightly larger than those of intermediate squamous cells
“Wide” columnar versus “narrow” normal
“Wide” columnar versus “trumpet” tubal metaplasia
Abundant apical mucin present

Crisp cytoplasmic edges
Focally increased nuclear size and pleomorphism

“Tipsy” honeycomb
Focally increased nuclear size and pleomorphism

“Tipsy” honeycomb
In some areas “rosette”-like architecture is seen

This case

Adenocarcinoma In Situ
The areas with increased nuclear atypia are still relatively bland.

This case

Invasive EC Adenocarcinoma
Large sheets contrast with nodular shed endometrial carcinoma

This case

Invasive EM Adenocarcinoma
Atypical Glandular Cells

- The abundance of glandular cells is itself concerning in this case
- Areas of cytologic and architectural atypia
- No definite AIS morphology
- No obviously malignant cells or diathesis
- Interpretation: Atypical Glandular Cells of Undetermined Significance (AGUS)
Follow-up

- Colposcopy revealed an abnormal enlarged “barrel cervix”
- Hysterectomy was performed
- The cervix showed diffuse involvement by infiltrating glands
Diagnosis

- Invasive endocervical adenocarcinoma with adenoma malignum features
- The case went into the study set
- Upon review for a conference, features not noticed initially were appreciated in light of recent insights
Adenoma Malignum

- Also known as minimal deviation adenocarcinoma
- This unusual variant has been recognized for a long time – a classic “pitfall”
- Small glands with mild atypia and difficult-to-discern desmoplasia
- The relatively subtle features make diagnosis of malignancy difficult, especially on biopsy
The Emergence of a Spectrum

- Over the past 15 years evidence has accumulated that puts adenoma malignum into a broader spectrum of lesions.
- It is now widely accepted that this represents a well differentiated form of endocervical adenocarcinoma with a gastric/pyloric phenotype.
Gastric/Pyloric Metaplasia

- Defined by immunoreactivity to HIK1083
- HIK1083 is a neutral mucin produced by pyloric glands
- MUC6 can also be used to detect this metaplasia
- Alcian blue stains normal acid mucin vs. PAS for the neutral metaplastic mucin
- An abstract from this meeting (Dr. Maeda of Tokyo University) indicates Claudin 18 may be a better marker
What if I don’t have HIK1083?

- By H&E, pyloric metaplasia shows subtly eosinophilic cytoplasm in contrast to the bluish appearance of typical endocervical glands – tough stuff.
- On cytology, characteristic “golden-yellow” mucin can be seen.
Significance of Pyloric Metaplasia

- None - that’s why you don’t have the stain
- We have all been looking at this for years and not seeing it
- The importance lies in understanding the underlying mechanisms of this family of neoplasia
Lobular Endocervical Glandular Hyperplasia (LEGH)

- This rare lesion was described in 1999 by Nucci and colleagues.
- Mikami and colleagues in Japan demonstrated the pyloric/gastric nature of the glands.
- Previously it was often misinterpreted as adenoma malignum.
LEGH Features

- Multicystic mass near internal os
- Often associated with watery discharge
- Small glands surrounding larger glands in an arborizing/flower-like lobular pattern
- “Cosmos” pattern on MRI, gross, and low power under the scope
LEGH Features Continued

- Associated with Peutz-Jeghers syndrome
- Many have STK11 abnormalities
- Possibly arise from tunnel clusters
- Probably more common in Japan
LEGH Histology

- Glands typically have small bland basal nuclei and abundant apical cytoplasm
- Positive for HIK 1083, negative for ER/PR, negative for p16
- Can have foci of intestinal metaplasia
- Atypical areas can be seen
- Associated with invasive carcinoma
- Chromosome gains of 3q and losses of 1p are associated with atypia/malignancy
LEGH Management

- LEEP or even cold-knife cone is often insufficient to excise LEGH due to its location
- Hysterectomy is often needed to rule out malignancy
Gastric-Type Adenocarcinoma

- Many cervical adenocarcinomas (up to 25%) may actually be gastric-type.
- The morphologic distinction from the usual-type is difficult, but gastric-type adenocarcinoma has more abundant clear-to-eosinophilic cytoplasm and distinct cell borders.
- Adenoma malignum and mucinous adenocarcinoma are more recognizable subsets.
A Second Case – 70 y/o With Postmenopausal Bleeding, Pelvic Mass

Mucinous, Hypercellular

Well-defined cell borders
Abundant vacuolated cytoplasm
Nuclear pleomorphism
Gastric Versus Usual-Type

- HIK 1083 may be very focal, limiting utility
- Carbonic anhydrase IX over-expression is common, but this is also present in endocervical-type adenocarcinoma
- P16 staining is negative or weak
- **NOT** HPV-driven, negative for HPV tests
Gastric-Type Adenocarcinoma
Clinical Features

- Despite often being “well-differentiated”, studies indicate a worse outcome with higher stage at diagnosis
- Bland cytologic features, high location in the cervix, and lack of HPV may contribute by making this type more difficult to detect by screening
The HPV “Turkey Moment”
1652 cases with cytology, cobas HPV testing, and biopsy (out of 130,000 total cases)

<table>
<thead>
<tr>
<th>Cytology</th>
<th>CIN2+</th>
<th>CIN1 or less</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial cell Abnormality</td>
<td>230</td>
<td>965</td>
<td>1195</td>
</tr>
<tr>
<td>NILM</td>
<td>23</td>
<td>434</td>
<td>457</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>253</td>
<td>1399</td>
<td>1652</td>
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</tbody>
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Sensitivity: 90.9%

<table>
<thead>
<tr>
<th>Cobas HPV</th>
<th>CIN2+</th>
<th>CIN1 or less</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>hrHPV Positive</td>
<td>231</td>
<td>960</td>
<td>1191</td>
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<tr>
<td>hrHPV Negative</td>
<td>22</td>
<td>439</td>
<td>461</td>
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<tr>
<td><strong>Total</strong></td>
<td>253</td>
<td>1399</td>
<td>1652</td>
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</tbody>
</table>

Sensitivity: 91.3%
Data Presented by Marshall Austin to the FDA at a Public Comment Session

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th># Cervical Cancers</th>
<th>Collection Vial</th>
<th># + HC2</th>
<th>NegHC2 (%)</th>
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</thead>
<tbody>
<tr>
<td>JClinVirol 2006 35:264-269</td>
<td>China</td>
<td>475</td>
<td>STM</td>
<td>427</td>
<td>48 (10.1%)</td>
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<tr>
<td>IntJGynCa 2009 19:924-928</td>
<td>Korea</td>
<td>198</td>
<td>STM</td>
<td>185</td>
<td>13 (6.6%)</td>
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<tr>
<td>IntJGynCa 2006 16: 586-590</td>
<td>Brazil</td>
<td>168</td>
<td>STM</td>
<td>148</td>
<td>20 (11.9%)</td>
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<tr>
<td>ActaDermatoven APA 2009 18: 940-103</td>
<td>Slovenia</td>
<td>95</td>
<td>STM</td>
<td>83</td>
<td>12 (12.6%)</td>
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<tr>
<td>Total</td>
<td></td>
<td>936</td>
<td></td>
<td>843</td>
<td>93 (9.9%)</td>
</tr>
</tbody>
</table>

CIN2+ Sensitivity HC2 = Cobas (JClinMicro 2012;50:2359-65)
Another Lesion Not Detected by HPV Screening

- Primary HPV screening (on cobas platform) has recently been approved by the FDA.
- Adenocarcinoma of the endometrium as well as non-HPV-driven endocervical adenocarcinoma would also be missed.
- Co-testing offers the best means of maximizing the sensitivity of screening.
- Ironically, Europe may have a Thanksgiving “turkey moment” while the US is spared.
Summary

- Gastric/pyloric metaplasia is difficult to recognize but can lead to non-HPV-driven cervical neoplasia
- LEGH and adenoma malignum are rare neoplasms that often have very bland cytology that is easily overlooked
- A high index of suspicion helps to detect subtle atypia and watery diathesis
References