Glandular lesions

Epidemiology
Cytology, Histology
Management Algorithms
Case Studies
Objectives

1. Understand the epidemiology of glandular lesions.
2. Discuss the cytology, histology, and colposcopy findings of AIS and cervical adenocarcinoma.
3. Review the ASCCP guidelines and algorithms on glandular cytology and AIS.
Pap Nomenclature for Glandular Abnormalities:
Bethesda 2001

- Atypical Glandular Cells (AGC)
  - Atypical endocervical cells
  - Atypical endometrial cells
  - Atypical glandular cells not otherwise specified (NOS)

- Atypical Glandular Cells, favor neoplastic
  - Atypical endocervical cells
  - Atypical glandular cells

- Endocervical Adenocarcinoma In Situ (AIS)

- AGC replaces prior terminology, “AGUS”
AGC Cytology: What does it imply?

- Makes up < 0.5% of all cervical cytology.
- Histologic diagnosis after AGC on Cytology
  - Adenocarcinoma In Situ (AIS)
  - Squamous intraepithelial lesion (any)
    - Most common pathology with AGC
    - Often coexist with glandular lesions
  - Adenocarcinoma
    - Cervix, endometrium, tube, ovary, metastatic
  - Reactive, reparative, polyps
  - Microglandular hyperplasia from OCP’s
  - Adenosis
Atypical Endocervical Cells: Cytologic features

- Sheets or strips with minimal nuclear overlapping
- Enlarged nuclei (3-5 x normal endocx)
- Slight hyperchromasia
- Mild variation in size and shape
- Nucleoli may be present
Atypical Endocervical Cells: Differential Dx

- Cervicitis / reactive endocervical cells
- Directly sampled LUS / endometrium
- Microglandular hyperplasia
- Arias-Stella change
- Tubal metaplasia
- SIL (especially HSIL)
- Endocervical AIS
- Endocervical adenocarcinoma
Atypical endocervical cells, NOS

- Reactive endocervical cells
- Endocervical repair
- Immature squamous metaplasia
- Radiation atypia

Cytology images from Bethesda Web Atlas - Thanks to Teresa Darragh, MD
Directly sampled endometrium
Microglandular Hyperplasia
Arias-Stella Reaction
Atypical endocervical cells: Tubal metaplasia
Atypical endocervical cells: Tubal metaplasia

Can be very Difficult!!!
Atypical endocervical cells vs HSIL
Endocervical AIS

60 % will also have CIN 2/3
What is the Correlation of Glandular Pap Test Abnormalities to AIS and Carcinoma?

<table>
<thead>
<tr>
<th>Cytology diagnosis</th>
<th>Likelihood of invasive CA, AIS, or CIN 2,3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGC NOS</td>
<td>9 - 41%</td>
</tr>
<tr>
<td>AGC, favor neoplasia</td>
<td>27-96%</td>
</tr>
<tr>
<td>AIS</td>
<td></td>
</tr>
<tr>
<td>Biopsy-confirmed AIS</td>
<td>48-69%</td>
</tr>
<tr>
<td>Invasive adenocarcinoma</td>
<td>38 %</td>
</tr>
</tbody>
</table>

Atypical Glandular Cells on Pap have higher association with cancer and pre-cancer than ASC-US

Wright et al  JAMA 2002;287:2120-2129.
Significance of Atypical Glandular Cells
Schnatz et.al Obstet Gynecol 2006;107:701-8

Meta analysis of 3,890 AGC Paps +/- ASC-US

Follow-up diagnosis
• HSIL 11.1%
• AIS 2.9%
• Endometrial hyperplasia 1.4%
• Malignancy 5.2%

• AGUS favor neoplasia
  • AIS 13%
  • Malignancy 21%

Cancers found: Endometrium, endocervix, squamous cervix, ovary, fallopian tube, colon, breast
Most likely disease with AGC Pap is squamous. Cancer may be squamous or adeno. Endometrial cancer not related to HPV status and more common in older women.
Atypical endometrial cells: Cytologic criteria

- Small cells groups (5-10 cells)
- Nuclei slightly enlarged
- Slight hyperchromasia
- Small nucleoli
- Cell borders ill-defined
- Scant cytoplasm, +/- vacuoles
Atypical endometrial cells
Atypical endometrial cells: Differential Dx

- IUD effect
- Endometrial polyps
- Chronic endometritis
- Endometrial hyperplasia
- Endometrial adenocarcinoma
Atypical glandular cells: IUD effect
Atypical glandular cells: Endometrial Polyp
Atypical glandular cells: Endometrial Hyperplasia
Atypical endometrial cells

Endometrial hyperplasia

Endometrial carcinoma
Cervical Adenocarcinoma In Situ

- Preinvasive lesion of the endocervical glandular cells
- Increasing incidence
- Average age: 35.8 yr
  - Range: 29-46 years
  - 10-18 years younger than adenocarcinoma
- 10% multifocal skip lesions
- Difficult to detect
  - May be missed on Pap
  - Does not obey usual colposcopy ‘rules’
Histology of AIS

- Glands lined with atypical endocervical cells,
  - Crowding, cribiform pattern
  - Confined to gland
- Multifocal disease common
- Almost half of cases of AIS have associated squamous disease.
AIS: Histology

- Gross architectural pattern “normal”
  - Cellular abnormality confined to gland
- Diagnosis depends on cellular changes
  - Loss of polarity
  - Increased nuclear size
  - Pseudostratification
  - Mitoses
Increasing Incidence of Adenocarcinoma in Situ

- 1.25 cases per 100,000 women (compared with 44 cases of CIN 3 per 100,000).
- Increased by 6 fold since 1970.
  - Absolute increase?
  - Increased rate of detection?

Cervical Adenocarcinoma and Squamous Carcinoma Trends in the U.S.

Smith HO et al. Gynecol Oncol 2000;78:97-105
AIS and Adenocarcinoma are HPV mediated.

- HPV association: type 18 > type 16

<table>
<thead>
<tr>
<th></th>
<th>SCC</th>
<th>AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 16</td>
<td>50-60%</td>
<td>30%</td>
</tr>
<tr>
<td>HPV 18</td>
<td>10-20%</td>
<td>40-60%</td>
</tr>
</tbody>
</table>

- HPV infection can alter squamous cells, glandular cells, or both
- Concurrent squamous HSIL: 46-72%

Screening with HPV diagnoses more glandular lesions than Cytology alone.

331,818 women enrolled in Kaiser N. Cal

Significantly more AIS and Adenocarcinoma diagnosed over 5 yrs if initial screen:

- HPV + vs Pap + (p<0.0001)
- HPV + / Pap – vs HPV -- / Pap + (p<0.0001)

<table>
<thead>
<tr>
<th></th>
<th>AIS</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>70</td>
<td>27</td>
</tr>
<tr>
<td>Pap Negative</td>
<td>42 (60%)</td>
<td>23 (85%)</td>
</tr>
<tr>
<td>Pap Positive</td>
<td>28 (40%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>HPV Positive</td>
<td>56 (80%)</td>
<td>21 (78%)</td>
</tr>
<tr>
<td>Pap -- / HPV +</td>
<td>31 (44%)</td>
<td>17 (63%)</td>
</tr>
<tr>
<td>Pap + / HPV --</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
</tbody>
</table>

AIS is p16 positive.
Colposcopic prediction of Glandular Neoplasia

- \textit{Prediction difficult to impossible}
- Diagnosis often serendipitous when looking for squamous disease
- Features of AIS overlap with squamous lesions and immature squamous metaplasia
- Final diagnosis made by your suspicion and histology
- Features of AIS and Adenocarcinoma may overlap.
  - Adenocarcinoma may have friability, necrosis, and surface ulceration or nodularity
Colposcopy of Glandular Neoplasia

- Most lesions lie within T-zone or close to SCJ
  - When glandular and squamous disease coexist, squamous component is more likely to be visible
- Lesions may be within the endocervical canal
  - “Skip” lesions may exist
Colposcopic Clues for Adenocarcinoma in situ

Surface Patterns
- Often looks like normal ectopy
- Coalescing papillae
  - Variable size, irregular shape
  - Often confused for immature metaplasia
- If AGC on Pap, biopsy anything that looks abnormal.
Colposcopy of AIS

- Milky white lesion surrounded by glandular epithelium
- May appear as variagated white patches on red background
- May or may not be adjacent to SCJ

- Atypical vessels
  - Root-like vessels, hairpin vessels
  - Easily mistaken for cervicitis

- Large gland openings
  - May not have rim of acetowhite
  - “Cuffed” gland openings
29 y.o. with AGC on Pap
Ectropion or glandular lesion?
Variegated red and white lesion
Atypical coalescence of Papillae
Note also root-like and hairpin vessels!
Histology: AIS

Richard Lieberman, MD
AIS - Milky white lesion, superficial ulceration
Milky White Lesion Extends Into Canal

Photo: Alan Waxman, MD
Root-like vessels

Photo: Lisa Flowers, MD
AIS Prominent atypical surface vessels
Copious mucus

Photo: Alan Waxman, MD
AIS: Copious mucus, large ectopic gland openings

Ectopic plug of mucus

Gland opening, mucus plug removed

Same without blue filter

Photo: Alan Waxman, MD
43 y.o.
Pap: atypical endocervical cells favor neoplasia

Wide ectropion with root like vessels

Photo: Alan G. Waxman, MD
Histology:
Adenocarcinoma in situ

Photo: UNM Pathology
Cervical Adenocarcinoma: Colposcopic Features
Similar to AIS, but More Pronounced

- **Color**
  - Milky to densely white after acetic acid
  - Patches of red and white in ectropion
  - Yellow to orange color
- **Papillae of various sizes; may be large, fused**
- **Columnar epithelium may surround lesion**
- **Atypical Vessels: hairpin vessels, inconsistent caliber, root-like**
- **Gland openings: large, irreg., may lack white outlines**
- **Copious mucus production**
- **Hemorrhage and necrosis on surface**
Cervical Adenocarcinoma: Exophytic

Richard Lieberman, MD
Adenocarcinoma
Endophytic (Barrel Shaped)

Don’t forget to do a bimanual exam!
Characteristic features of adenocarcinoma

- Densely acetowhite
- Overlies columnar epithelium
- Patchy red and white lesions
- Atypical vessels

Apgar, Brotzman, Spitzer
Adenocarcinoma: abnormal papillary coalescece

Before acetic acid

After acetic acid

A text and atlas of integrated colposcopy: for colposcopists, histopathologists and cytologists by Anderson, M. C. Reproduced with permission of CHAPMAN AND HALL (UK) in the format electronic usage via Copyright Clearance Center.
Adenocarcinoma: Milky white abnormal papillae
Atypical, Root-like and Hairpin vessels

Photo: Richard Lieberman, MD
Milky white abnormal papillae surrounded by columnar epithelium

Photo: Richard Lieberman, MD
Atypical, Root-like and Hairpin Vessels

Photo: Richard Lieberman, MD
Atypical, Root-like and Hairpin Vessels

Photo: Richard Lieberman, MD
Cervical Adenocarcinoma

Milky white, exophytic, Ulceration and necrosis, atypical vessels
Before Acetic Acid

Endocervical Adencarcinoma - Villoglandular Type

Photos: Alan G. Waxman, MD
Endocervical Adenocarcinoma Villoglandular Type

Photo: UNM Pathology
Vessel pattern: Adenocarcinoma

Note hairpin and root-like vessels
Squamous vs adenocarcinoma?

It’s cancer!
Biopsy needed to confirm histologic type
Management Algorithms

Updated Consensus Guidelines
Initial Workup of Women with Atypical Glandular Cells (AGC)

All subcategories (except atypical endometrial cells)

Colposcopy (with endocervical sampling)
and Endometrial sampling (if ≥ 35 yrs or at risk for endometrial neoplasia *)

Atypical Endometrial Cells

Endometrial and Endocervical Sampling

No Endometrial Pathology

Colposcopy

* Includes unexplained vaginal bleeding or conditions suggesting chronic anovulation.
Atypical Glandular Cells

- Neither HPV testing nor repeat cervical cytology sensitive enough to be used alone as triage test.

- Initial evaluation includes multiple modalities:
  - Colposcopy
  - Endocervical assessment and sampling
  - Endometrial evaluation if indicated.
Subsequent Management of Women with Atypical Glandular Cells (AGC)

**Initial Cytology is AGC - NOS**

- **No CIN, AIS or Cancer**
  - Manage per ASCCP Guideline

- **CIN but no Glandular Neoplasia**

**Initial Cytology is AGC (favor neoplasia) or AIS**

- **No Invasive Disease**
  - Diagnostic Excisional Procedure +

+ Should provide an intact specimen with interpretable margins. Concomitant endocervical sampling is preferred

© Copyright, 2013, American Society for Colposcopy and Cervical Pathology. All rights reserved.
Subsequent Management of Women with Atypical Glandular Cells (AGC)

**Initial Cytology is AGC - NOS**

- **No CIN2+, AIS or Cancer**
  - **Cotest**
    - At 12 and 24 months
  - **Any abnormality**
    - **Colposcopy**
  - **Both negative**
    - **Cotest 3 years later**

- **CIN2+ but no Glandular Neoplasia**
  - **Manage per ASCCP Guideline**

**Initial Cytology is AGC (favor neoplasia) or AIS**

- **No Invasive Disease**
  - **Diagnostic Excisional Procedure +**
    - *Should provide an intact specimen with interpretable margins. Concomitant endocervical sampling is preferred*
Subsequent Management of Women with Atypical Glandular Cells (AGC)

**Initial Cytology is AGC - NOS**

- **No CIN2+, AIS or Cancer**
  - **Cotest**
    - At 12 and 24 months
  - Any abnormality
    - **Colposcopy**
    - **Cotest 3 years later**

- **CIN2+ but no Glandular Neoplasia**
  - **Manage per ASCCP Guideline**

**Initial Cytology is AGC (favor neoplasia) or AIS**

- **No Invasive Disease**
  - **Diagnostic Excisional Procedure**
    - *Should provide an intact specimen with interpretable margins. Concomitant endocervical sampling is preferred*

© Copyright, 2013, American Society for Colposcopy and Cervical Pathology. All rights reserved.
Treatment of glandular lesions

- An intact specimen with interpretable margins is key to direct therapy in glandular abnormalities.

- Therefore clinicians should choose the modality most likely to yield the best pathologic specimen.

- Endocervical curettage is recommended at the time of excisional biopsy in suspected glandular abnormalities.
Mucus conducts electricity very efficiently
Conization versus large loop electrosurgical excision for adenocarcinoma in situ
Positive margins more likely with LEEP

<table>
<thead>
<tr>
<th>Author</th>
<th>Cone Biopsy</th>
<th>Positive Margins</th>
<th>Large Loop Electrosurgical Excision</th>
<th>Positive Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolf et al. (21)</td>
<td>43</td>
<td>18 (42%)</td>
<td>7</td>
<td>5 (71%)</td>
</tr>
<tr>
<td>Widrich et al. (8)</td>
<td>18</td>
<td>6 (33%)</td>
<td>14</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Denehy et al. (20)</td>
<td>24</td>
<td>8 (33%)</td>
<td>13</td>
<td>9 (69%)</td>
</tr>
<tr>
<td>Azodi et al. (32)</td>
<td>25</td>
<td>6 (24%)</td>
<td>8</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Totals</td>
<td>110</td>
<td>38 (38%)</td>
<td>42</td>
<td>27 (62%)</td>
</tr>
</tbody>
</table>
Management of Women Diagnosed with Adenocarcinoma in-situ (AIS) during a Diagnostic Excisional Procedure

- **Hysterectomy** - Preferred
- **Conservative Management**
  Acceptable if future fertility desired

- Margins Involved or ECC Positive
  - **Re-excision**
    Recommended
  - **Re-evaluation***
    @ 6 months - acceptable

- Margins Negative
  - Long-term Follow-up

* Using a combination of cotesting and colposcopy with endocervical sampling

© Copyright, 2013, American Society for Colposcopy and Cervical Pathology. All rights reserved.
AIS, Implications of Conization Margin Status

- Meta-Analysis, 33 studies / 1278 patients
  - Mean follow-up 39.2 months

607 pts. had second excision
  93 repeat conization / 499 hysterectomy

Residual AIS based on margins of first conization
  Negative margins: 20.3%
  Positive margins: 52.8%
  RR: 4 (CI 2.62-6.33)  p<.001

671 followed conservatively after excision

Recurrent AIS based on margins of first conization
  Negative margins: 2.6%
  Positive margins: 19.4%
  Rr:2.5 (CI1.05-6.22)  p<.001
AIS, Implications of Conization Margin Status

29 patients in 13 studies developed invasive adenocarcinoma
  • 5.2% with positive margins/ 0.7% with negative margins

Of 607 patients who underwent second excision
  21 (3.5%) had adenocarcinoma on hysterectomy
  Positive margins on initial conization: 17 patients
  Negative margins on initial conization: 4

Of 671 patients followed conservatively
  8 (1.2%) subsequently developed adenocarcinoma
  Positive margins on initial conization: 6 patients
  Negative margins on initial conization: 2
Histologic AIS
Conservative management

- When future fertility is desired
- Re-evaluation at 6 months using a combination of cervical cytology, HPV DNA testing, and colposcopy with endocervical sampling is acceptable in this circumstance.
- Long-term follow up is recommended for women who do not undergo hysterectomy.

AIS is hard to diagnose on colposcopy. If the Pap test shows AGC, biopsy anything that looks abnormal.

Thank you!