Colposcopy of Adenocarcinoma in situ and Adenocarcinoma of the Cervix

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Objectives

1. Review the Bethesda System terminology for atypical glandular cells on cytology
2. Discuss the challenge in diagnosing adenocarcinoma in situ (AIS) on colposcopy
3. List the clues in making the diagnosis of AIS and Adenocarcinoma of the cervix with colposcopy
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
Cervical Adenocarcinoma In Situ

- Often not diagnosed on pap test
- Difficult to detect
  - 10% of lesions multifocal.
  - Often not adjacent to SCJ
- Does not obey usual colposcopy ‘rules’
Diagnosis of AIS / Adenocarcinoma

- Often a serendipitous finding when looking for squamous disease
- Often coexists with squamous intraepithelial lesions
- Look for AIS / adenocarcinoma with Atypical Glandular Cells on cytology
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"

Solomon D et al. JAMA 2002; 287: 2114-9
Significance of cytology classification AGC and AIS

- Glandular cytologic abnormalities confer a risk substantially greater than cytology of ASC-US or LSIL
  - Risk of CIN (any grade) 9-54%
  - Risk of AIS 0-8%
  - Risk of invasive carcinoma 3-17%
- Most cancers in women >35 with AGC are endometrial
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
AIS and Adenocarcinoma are HPV mediated.

- HPV association: type 18 > type 16

<table>
<thead>
<tr>
<th></th>
<th>SCC</th>
<th>AC</th>
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<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%

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.

Castle et al Obstet Gynecol. 2010
Screening with HPV diagnoses more glandular lesions than Cytology alone.

331,818 women enrolled in Kaiser N. Cal

Significantly more AIS and Adenocarcina 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.
Initial Management of AGC

- AGC, All categories
  - Colposcopy with directed biopsies
  - Endocervical sampling (ECC)
  - Endometrial biopsy if >35 or at risk for endometrial cancer
- AGC, Atypical endometrial cells
  - Endometrial biopsy can be done alone initially or together with colposcopy.
  - If no evidence of pathology on endometrial biopsy then proceed with colposcopy
- AGC favor neoplasia or AIS
  - Colposcopy and ECS
  - If initial pathology doesn’t show cancer, excision is required
    - 2013 ASCCP 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.*
Colposcopic prediction of Glandular Neoplasia

- *Prediction difficult to impossible*
- 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, glomeruloid hairpin, Tendril like, waste-thread like, willow branch-like
  - Easily mistaken for cervicitis

- Large gland openings
  - May not have rim of acetowhite
  - “Cuffed” gland openings
Atypical Vessels in Adenocarcinoma of Cervix

<table>
<thead>
<tr>
<th>glomeruloid hairpin-like (AV-1)</th>
<th>tendril-like (AV-4)</th>
<th>waste-thread-like (AV-5)</th>
<th>willow-branch-like (AV-6)</th>
<th>root-like (AV-7)</th>
</tr>
</thead>
</table>

Diagram of Vascular Patterns

Adenocarcinoma in Situ

Foto: Alex Ferenczy MD
Diapositiva cortesía Ramon M. Cestero, MD
Lesiones acetoblancas sin contacto directo con la union escamocolumnar

Foto: Alex Ferenczy MD
Diapositiva cortesía Ramon M. Cestero, MD
Vellosidades (papilas) irregulares, fusionadas, alargadas

Foto: Alex Ferenczy MD
Diapositiva cortesía Ramon M. Cestero, MD
Lesiones parcheadas rojas/blancas

Foto: Alex Ferenczy MD
Diapositiva cortesía Ramon M. Cestero, MD
29 y.o. with Atypical Glandular Cells on Cytology
Ectropion or glandular lesion?
Patchy red and white lesion

Richard Lieberman, MD
Atypical coalescence of Papillae

Richard Lieberman, MD
Note also root-like and hairpin vessels!
Histology: AIS

Richard Lieberman, MD
AIS - Milky white lesion, superficial ulceration

Photo: Lisa Flowers, MD
Milky White Lesion Extends Into Canal

Photo: Alan Waxman, MD
AIS Root-like vessels
Copious mucus

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

Ectopic plug of mucus

Gland opening, mucus removed

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

Photo: Alan G. Waxman, MD
Wide ectropion
Copious mucus

Large gland openings
without rim of acetowhite

Photo: Alan G. Waxman, MD
Wide ectropion
Copious mucus

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!

Richard Lieberman, MD
Characteristic features of adenocarcinoma

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

Apgar, Brotzman, Spitzer
Adenocarcinoma: abnormal papillary coalescecence

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
Mujer, 41, P3 con dolor y sangrado post-coito

Photo: Alan G. Waxman, MD
Crecimiento papilar anormal

Vasos atípicos que parecen hilos

Photo: Alan G. Waxman, MD
adenocarcinoma
tipo viloglandular

Photo: Alan G. Waxman, MD
Vessel pattern: Adenocarcinoma

Note hairpin and root-like vessels

Apgar, Brotzman, Spitzer
Squamous vs adenocarcinoma?

It's cancer!
Biopsy needed to confirm histologic type

Candice Tedeschi, OGNP
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 *trialege 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 CIN2+, AIS or Cancer
  - Cotest At 12 and 24 months
    - Both negative
      - Cotest 3 years later
    - Any abnormality
      - Colposcopy

**Initial Cytology is AGC (favor neoplasia) or AIS**
- CIN2+ but no Glandular Neoplasia
  - Manage per ASCCP Guideline
- No Invasive Disease
  - Diagnostic Excisional Procedure *

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

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Subsequent Management of Women with Atypical Glandular Cells (AGC)

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No CIN2+ but no Glandular Neoplasia

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Diagnostic Excisional Procedure

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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.
Thermal Effect on Endocervical Glands

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 co-testing and colposcopy with endocervical sampling

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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 (CI 1.05-6.22) 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!