Case 4 — Part I

- 44 y.o. G3 P3 referred with abnormal PAP
- atypical glandular cells of undetermined significance (AGUS). See comment.
- Comment: “a metastatic adenocarcinoma cannot be excluded”

Case 4 — AGUS PAP

Your thoughts...
- risk factors
- cervical
- endometrial
- metastatic!?
Case 4 – AGUS PAP

- PMH
  - no prior abnl PAP
  - regular exams
  - no known h/o HPV
  - + Hypertension
  - + menorrhagia

- PSH
  - C/S x3

- FH
  - father – +breast CA
  - brother – +melanoma

Next?

First Office Visit...

- Exam
  - slightly obese
  - normal breast exam
  - no lymphadenopathy

- Pelvic
  - TNS uterus
  - no cervical enlargement
  - no adnexal mass
  - guaiac negative stool

- Colposcopy
  - no lesions of the cervix, vagina, or vulva

- ECC
  - Endometrial Biopsy

Pathology — Part I

- ECC
  - fragments of benign endocervical glands and squamous epithelium

- Endometrial biopsy
  - Non-hyperplastic secretory endometrium

Case 4 – Additional Workup

- Labs
- Radiographic Studies
- Review the cytology
Case 4 — Additional Workup

- Review of original cytology
  - AGUS... agreed
  - “not worried about metastatic adenocarcinoma”
  - source of “atypia”? indeterminate
- CA 125 < 35
- CXR - negative
- XMG - negative
- CT abdomen/pelvis
  - slightly enlarged uterus
  - no significant abnormalities

What is the next step?

1. repeat cytology in...
   - 3 months...
   - 6 months...
2. cone biopsy not a LEEP
3. D&C

Second Office Visit... 3 months

- Exam unchanged
- Pelvic PAP repeated
- Colposcopy
  - no lesions of the cervix, vagina, or vulva
- ECC repeated
Case 4 – Diagnosis
- ECC
- highly suspicious for Müllerian (mucinous) type endocervical adenocarcinoma

Next?
- A diagnostic procedure is scheduled
- Cold knife conization
  - Not a LEEP
  - With ECC and endometrial curettage
Diagnosis — Part II
- cone biopsy
  - Moderately-well differentiated mucinous adenocarcinoma with superficial invasion. Endocervical margins positive.
- endometrial curettage
- fragments of mucinous adenocarcinoma
- endocervical curettage
- fragments of mucinous adenocarcinoma. Hypermucinous endocervical glands

Radical Hysterectomy
- no gross photo available
- gross description
  - 1.3 x 1 cm hemorrhagic area at upper endocervix
  - cervix 5.5 cm in length

Gross Depiction of Tumor
- false negative
  - Embx sample
  - ECC sampling

Gross Depiction of Tumor
- 5.5 cm
Follow-up: Stage IB Mucinous Adenocarcinoma of the Cervix

- Adjunctive pelvic irradiation
- NED at 3 years
AGUS: Issues to Consider

- What are usual findings with AGUS?
  - False negative initial evaluation
  - What do you do?
- What is appropriate management?
  - Bethesda 2001 recommendations

Outcomes of AGUS*

<table>
<thead>
<tr>
<th>Qualifier</th>
<th>Neo</th>
<th>SIL</th>
<th>AIS</th>
<th>ECCa</th>
<th>EmCa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive</td>
<td>75</td>
<td>22</td>
<td>1.4</td>
<td>0</td>
<td>1.6</td>
</tr>
<tr>
<td>(n=442)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOS</td>
<td>65</td>
<td>26</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>(n=960)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td>20</td>
<td>18</td>
<td>48</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>(n=421)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* % of patients

All AGUS – 10% with carcinoma (AIS, ECCa, & EmCa)

Clinical Management of AGUS

- Colposcopy
- Endocervical sampling
- Possible endometrial biopsy or curettage

Refs:
- Oncology 1999; 13:550-574

Bethesda System 2001

- AGC (atypical glandular cells)
  - Atypical glandular cells, NOS
  - Atypical glandular cells, favor neoplasia
  - Atypical endocervical cells, NOS
  - Atypical endocervical cells, favor neoplasia
  - Atypical endocervical cells, probably AIS
  - Atypical endometrial cells
  - Adenocarcinoma in situ (AIS)
  - AGC (any of the above) with squamous abnormality

AGC, “favor reactive” replaced by NOS

NCI Bethesda System 2001
AGC Recommendation
- All women with AGC
  - colposcopy
  - endocervical sampling
  - repeat cytology not acceptable

NCI Bethesda System 2001

AGC Qualifiers That Increase Risk
- favor neoplasia
- probable AIS
- AIS

- Recommendation*
  - diagnostic cervical excisional procedure
    - cold knife conization

* unless invasive cancer on exam, biopsy or ECC

NCI Bethesda System 2001

Why not LEEP?
Thermal cautery effect renders the endocervical glandular epithelium at the margin... uninterpretable!
AGC - Increased Risk of Endometrial Neoplasia

- atypical endometrial cells
- age ≥ 35
- unexplained vaginal bleeding with AGC at any age

Recommendation
- endometrial sampling (pipelle or D&C)

NCI Bethesda System 2001

AGC - Negative Initial Evaluation

- AGC, glandular or endocervical, NOS
  - repeat PAP every 4-6 months
  - continue for 3-4 negative cytologies

- AGC, favor neoplasia, AIS or carcinoma
  - diagnostic cervical excision (CKC)
  - if negative, consult with cytopathologist

NCI Bethesda System 2001

Negative Colposcopy, ECC, EMC, and CKC

Recommendation
- pelvic ultrasound
- abdominal pelvic CT scan
  - look for non-gynecologic source
- review of cytology
  - original pathologist and second opinion

Case Presentation & AGUS Dilemma: Summary

- uncommon diagnosis
- limited literature
- “qualifiers”
  - assist in projecting outcome
  - “favor neoplasia” et. al. with high probability for disease
- Bethesda 2001 with consensus recommendations

Please avoid LEEP!