The Hyperchromatic Crowded Groups-Cytologic Diagnosis of Glandular Lesions

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APMG
Introduction

- 15-25% of cervical carcinomas are adenocarcinomas
- AIS-Pap smears 55 - 70% sensitivity
- AGUS 0.13 - 0.46% of paps
- True glandular precursors or adenocarcinoma present in only .01 to .015%
Glandular lesions

- Non neoplastic
  - Tubal Metaplasia
  - Exfoliated lower segment endometrium
  - Menstrual endometrial Cells
  - Reactive endocervical cells
  - Microglandular hyperplasia
  - Other
Glandular lesions in Pap Smears

- Neoplastic
  - AIS
  - Invasive adenocarcinoma
  - HSIL with endocervical glandular extension
  - Endometrial carcinoma
  - Squamous Carcinoma
Adenocarcinoma in situ (AIS)

- 37-41 yrs for AIS
  44-54 yrs for Adenocarcinoma
- HPV16 and 18
- Skip areas common
- AIS associated with SIL in 30 - 60% of cases
AIS

GROUPS - Crowded, hyperchromatic

- Glandular differentiation
  - Pale, foamy or vacuolated cytoplasm
  - Stratification and crowding
  - Rosettes and glands
  - Syncytia with "feathering"

- No diathesis
AIS

NUCLEI

- High N/C Ratio
- Oval to elongated or irregular, molding
- Marked hyperchromasia
- Coarse chromatin
- Apoptotic bodies (70%)
- Mitotic figures in 40 - 60% of cases
Invasive Adenocarcinoma of Cervix

- Less nuclear crowding, abnormal glandular arrangements and abundance
- More cytoplasm, larger nuclei, more irregular, vesicular chromatin or coarse and prominent nucleoli
- Diathesis
False Negative

- Small “endometroid” AIS
  - Mistaken for menstrual or LUS
  - Clean background
  - Tight groups with extreme crowding
  - Coarse nuclei
  - Feathering, rosettes, columnar shapes
  - Absence of endometrial tubules, sheets or stroma
False Negative

- AIS or Adenocarcinoma mimicking reactive endocervical cells
  - Uniform population (not a spectrum)
  - Crowding, nuclear enlargement, increased N/C ratio
  - Coarse chromatin
  - Small to prominent nucleoli in every cell
Case 1

37 year old
pap smear - AGUS, r/o IUD
IUD Changes

- DDX adenocarcinoma - lack of malignant features
- DDX CIS - actinomyces
  - few atypical cells
  - Bland dark chromatin
  - No nucleoli
  - No multinucleation
Case 2

68 year old
Pap smear - AGUS r/ o adeno
Reactive Glandular Cells

- Spectrum of atypia
- Fine or smudged chromatin
- Smooth nuclear membranes
- Prominent to absent nucleoli
- Low N/C ratio
- Minimal overlap “lay flat”
- Often associated with SIL
Case 3

Indec, C, 32 year old

Pap smear - AGUS
Tubal Metaplasia

- DDX: Adenocarcinoma
  - Nuclei less crowded
  - Finer chromatin pattern
  - Cilia
  - Clear cytoplasmic vacuoles
Case 4

58 year old

Pap smear - Atypical repair
Atypical repair

- Sheet- like arrangement “school of fish”
- Finely granular chromatin
- Prominent nucleoli
- Cyanophilic vacuolated cytoplasm
- Bi- and multinucleation
- Mitosis
- Small study (Rimm) - 25% of SIL (LSIL)
Case 5

29 year old
Pap smear - AGUS, favor neoplastic
Adenocarcinoma in situ/High Grade Squamous Intraepithelial Lesion

- Neoplastic endocervical cells
  - Tall columnar cells with hyperchromatic nuclei, coarse chromatin, feathery edges, rosettes
  - Uniform population (not a spectrum)
  - Crowding, nuclear enlargement, increased N/C ratio
  - Coarse chromatin
  - Small to prominent nucleoli in every cell
  - No diathesis

- Squamous cells with increased N/C ratio, arranged in clusters but no rosettes or feathery edges
Case 6

62 year old

Pap smear - Adenocarcinoma
Endometrial Papillary Serous Adenocarcinoma

- Numerous papillary groups
- Occasional psammoma bodies
- High grade nuclei with prominent nucleoli
Case 7

56 year old

Papsmear- Psammoma bodies
Endometrial Adenocarcinoma

- Cellularity - less
- Cells - small, round, plump, degenerated
- Groups - balls, molded groups
- Cytoplasm - Vacuolated, basophilic, often with PMNs
- Nuclei - small, < 2.5x intermediate cell, less hyperchromatic with single nucleolus
- Psammoma bodies-Ovarian>endometrial
Pap Smear Psammoma Bodies

- Overall rare find in 1/30,000 Pap smears
- Benign
  - IUD
  - Ovarian inclusion cysts
  - Endometritis, tuberculosis
  - Endosalpingiosis
  - Birth control pills
- Malignant
  - Ovarian, endometrial, cervical, endocervical
    - neuroendocrine carcinoma, fallopian tube, metastasis
Case 8

34 year old
Pap smear - ASCUS
High Grade Squamous Intraepithelial Lesion

- **DDX:** Immature squamous metaplasia
- Some types of HSIL exfoliate as small cells - d/d histiocytes or squamous metaplasia
- **Uncertainty**
  - Wilbur *et al* - atypical immature metaplasia in 11/17 negative paps with subsequent HSIL
  - Sherman - 20 neg paps with retro review 23% HSIL, 30% ASCUS, 14% unsatisfactory
  - Paavonen *et al* - 21% progression to HSIL on biopsy after “metaplastic cell atypia”
CASE 9

91 year old
Pap smear ASCUS r/o HSIL
High Grade Squamous Intraepithelial Lesion

- Atrophy vs. HSIL/SCC
  - Clues to a serious nature:
    - Increased nuclear size
    - Extreme hyperchromasia, crowding
    - Nuclear membrane irregularity
    - Loss of spectrum which links clearly benign atrophic cells to those with more atypia
    - Recommend repeat pap with estrogen or colposcopy and biopsy
Case 10

30 year old

Pap smear - HSIL
Trophoblastic Tissue

- Rare, may be seen in late pregnancy or following delivery
- Numerous cells suggest trophoblastic disease
- Not reliable as indicator of impending abortion
Trophoblastic Tissue

- **Decidual Cells DDX**
  - Dysplasia
  - Repair
  - Carcinoma
  - Sarcoma

- **Multinucleated Giant Cells In Pregnancy**
  - Syncytiotrophoblast
  - Multinucleated giant cell histiocytes
  - Herpes
  - Tumor
  - Dysplasia/Condyloma
Case 11

33 year old

Pap smear - HSIL
Menstrual Changes

- Menstrual endometrial cells
  - Resembles AIS
  - Poorly preserved cells
  - Hyperchromasia of degeneration
  - Stromal balls and histiocytes
  - Absence of feathering and rosettes
False positive

- Lower uterine segment
  - resembles AIS
  - uniform small cells in sheets or tubules
  - lack of feathering or rosettes
  - fine, even chromatin
  - spindled stromal cells attached
  - may have mitotic figures
Case 12

42 year old pap smear was called HSIL
Endometrial Adenocarcinoma

- Overall features dependent upon grade
- Increased N/C ratio
- Hyperchromasias
- Irregular chromatin distribution
- Prominent nucleoli
- Diathesis
Abnormal Shedding of Endometrial Cells

- Endometritis
- Endometriosis
- Submucosal leiomyoma
- Early pregnancy
- Abortion
- IUD
- Instrumentation
- Hormonal therapy (BCP, ERPT)
- DUB
- Endometrial polyp
- Endometrial hyperplasia, neoplasia
Endometrial Adenocarcinoma DDX

- Endometritis
  - Crowded groups with nuclear enlargement and prominent nucleoli, balls
  - Increased neutrophils
  - Uniform nuclei, smooth nuclear membranes and regular chromatin

- Endocervical Adenocarcinoma
  - More cellularity
  - Rosettes
  - Granular cytoplasm
  - Multinucleation common
  - CEA+
Case 13

55 year old

Pap smear was called AGUS, Endometrial
Fallopian Tube Adenocarcinoma

- Postmenopausal
- Nulliparous, usual
- Diagnosis of exclusion:
  - Negative cone biopsy
  - Negative D and C
  - No known primary tumor
## Summary

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<th>Feature</th>
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<th>AIS</th>
<th>Invasive</th>
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<tr>
<td>Crowding</td>
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<tr>
<td>Feathering</td>
<td>0</td>
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<tr>
<td>Rosettes</td>
<td>+/-</td>
<td>++++</td>
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<td>Cilia</td>
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References