Cervical Cytology

Cell types

**Superficial Cells:**
- Small, pyknotic nucleus
- Abundant cytoplasm (Often pink, can be blue)
- Polygonal shape
- Indicate abundant Estrogen

**Intermediate Cells:**
- Abundant blue cytoplasm, polygonal shape
- Larger, round to oval nuclei
- Finer, normochromatic nuclei
  - Nuclei are important reference size

**Basal/Parabasal Cell:**
- Minimal cytoplasm
- Round to oval nuclei
- Fine, but slightly dark chromatin
- Usually few in number, unless atrophic

**Endocervical Cells:**
- Uniform, Columnar cells
- Polar, with round nucleus at one end
- Majority of cytoplasm occupied by mucin
- Arranged in flat sheets → think “Honeycomb”
- Arranged in linear strips → “Palisaded”

**Endometrial Cells:**
- Small, High N:C ratio cells (almost all nucleus!)
- Nucleus about the same size as an intermediate cell nucleus
- Round nuclei with smooth chromatin, possible micronucleoli
- Can be in large groups with outside epithelium and in inside stroma
- Normal finding in first half of menstrual cycle if premenopausal
  - (Report if >50 yrs old)

**Pap Smear Adequacy Criteria**

- Minimum number of well-visualized squamous cells for adequacy
  - Liquid-based preparation: 5,000 cells (ThinPrep and SurePath)
  - Conventional Preparation: 8,000 to 12,000 cells
- If obscuring elements cover >75% of epithelial cells → Unsatisfactory
- Quality indicator: Presence of ≥10 endocervical cells or squamous metaplastic cells (reported, but not required to be satisfactory for evaluation)
- Any specimen with abnormal cells is considered adequate and should be reported!
**Low-Grade Squamous Intraepithelial Lesion (LSIL)**

*Mature Keratinocytes* (with lots of cytoplasm) AND:
- **Enlarged nuclei** (>3x normal intermediate cells)
- Nuclear **membrane irregularities**
- Hyperchromasia (“Rasinoid”)
- NO nucleoli

Optional:
- Perinuclear **Halos = Koilocytes**
  - Large, irregular clearing
  - Thick borders, like it was drawn with a calligraphy pen
- **Multinucleation**

Caused by High and Low-risk HPV
May regress spontaneously!

*Some findings, but “not enough”?*
Consider “Atypical Squamous Cells of Undetermined Significance” (**ASCUS**)
Can be either **Quantitative** (i.e., only rare atypical cells) or **Qualitative** (e.g., only 2x nuclear enlargement)

**High-Grade Squamous Intraepithelial Lesion (HSIL)**

*Immature keratinocytes* (minimal cytoplasm, **High N/C ratios**) with:
- Markedly irregular nuclear contours
  - *(Hint: think in 3-dimensions)*
  - Look like boulders with all the irregularities
- Irregular chromatin and/or **Hyperchromasia**

*Some findings, but “not enough”?*
Consider “Atypical Squamous Cells—Cannot exclude HSIL” (**ASC-H**)
Can be either **Quantitative** (i.e., only rare atypical cells) or **Qualitative** (e.g., only moderate atypia)
**Squamous Cell Carcinoma**

Non-keratinizing SCC may look like HSIL (similar findings)

Clues to invasion: “Tumor diathesis” (Necrotic debris)
- Prominent nucleoli

**Keratinizing SCC:** Pleomorphic cells with hyperchromatic, irregular nuclei, prominent orangeophilic (keratinizing) cytoplasm, and bizarre shapes (like “Tadpoles” or snakes)

**Glandular Abnormalities**

**Reactive Endocervical Cells**
- Nuclear enlargement (4-5x),
- Hyperchromasia, BUT round nuclei with smooth contours and N:C ratios maintained. Prominent nucleoli.
- Not too crowded. Mitoses, but no apoptosis.
- Can see tubal metaplasia → look for cilia!

*For AIS, think “Feathery,” like a bird’s wing.*

**Endocervical Adenocarcinoma In Situ (AIS):**
- Nuclei enlargement and crowding (cigar-like, think GI adenoma)
- High N:C ratios with coarse, dark chromatin.
- Cellular crowding with rosettes and “feathery edges”
- Mitoses and apoptosis. No nucleoli.
- Most strongly associated with HPV18 subtype

**Adenocarcinoma**
- Variable, depending on site of origin/type.
- Generally, more pleomorphic/irregular.
- Endometrial cell nuclei larger than intermediate cell.

- Features suggesting invasion: 1) Macronucleoli, 2) Tumor diathesis, 3) increased single cells, and 4) irregular chromatin

- Factors favoring endometrial adenocarcinoma (vs endocervix): Neutrophils, less cytoplasm, smaller nuclei

Practically speaking, often diagnose as simply: “Atypical Glandular Cells” using Bethesda System unless very pleomorphic
Squamous metaplasia

Thick, “Dense” cytoplasm (consistent, dark teal)
Sharply defined cell borders.
Round, usually central nuclei
Normal nuclear size

Count as sampling of transition zone

Reparative/Inflammatory Changes

Classic “Repair”
Enlarged nuclei with Prominent Nucleoli.
Round nuclear contours with fine, pale chromatin.
Normal N:C ratios, but variably sized
Cohesive flat sheets of cells with “streaming” like pulled taffy
Background inflammation

General inflammatory change
Mild nuclear enlargement (<2x size)
Fine, pale chromatin
Often nucleoli
Can see small perinuclear clearing, but smaller, and more even than koilocytic halos

Atrophy

Seen in LOW estrogen states:
Postmenopausal
Postpartum
Premenarche
Turner syndrome

Predominance of **basal and parabasal cells** (High N:C ratios)
Prone to injury → often inflammation

Immature cells that can mimic HSIL, BUT:
Finely granular chromatin
Smooth nuclear contours

Can see “Blue blobs” (see →) and granular debris (mimicking tumor diathesis, but no karyorrhectic nuclear debris)
Radiation Changes

**Cytomegaly:** Big cells with Big nuclei (proportion N:C maintained)

Large, bizarre cells

**Cytoplasmic vacuolation and polychromasia**

**Multinucleation**

Follicular Cervicitis

Abundant **lymphocytes** (small rim of cytoplasm around round nucleus, unlike HSIL, which is irregular)

Numerous **tingible body macrophages**

Variably sized lymphocytes with plasma cells.

IUD-Effect

Two characteristic findings:

1) **Cells with abundant vacuolated cytoplasm** (mimicking Adenocarcinoma)

2) **Cells with small, dark nuclei** and scant cytoplasm (mimicking HSIL)

Always know history!

Herpes

**3 M’s**

Molding of nuclei
Multinucleation
Margination of chromatin

“**Ground glass**” chromatin with eosinophilic nuclear inclusions

Can treat with acyclovir
**Trichomonas Vaginalis**

*Pear-shaped protozoan STD*
- Pale, eccentric elongate nucleus
- Red cytoplasmic granules

Often associated with *Leptothrix* (non-pathogenic filamentous bacterium).

Often acute inflammation and inflammatory halos
- Treat with antibiotics

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**Candida**

*Fungal* species that can cause infectious throughout the GYN tract (and other areas).
- Thick, “cottage cheese” discharge
- Eosinophilic yeast forms and pseudohyphae and hyphae (“Spaghetti and meatballs”)
- Often tangled or skewering squamous cells

Can have variable associated inflammation or inflammatory halos
- Usually only treat if symptomatic

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**Actinomyces**

Gram-positive *anaerobic bacteria*
- Commonly associated with *IUD* (or other foreign body)
- Long, filamentous organisms
- Tangled clumps of bacteria that look like “cotton balls” or “dust bunnies”

No need to remove IUD or treat if asymptomatic
This is a very generalized and abbreviated (but hopefully still helpful) summarization!
For a full review of current management guidelines, please refer to the ASCCP website:
http://www.asccp.org/guidelines

**Pap result → Next step**

**Unsatisfactory** → Repeat Pap in 2-4 months

**NILM, but HPV positive (> 30 yrs)** → Repeat co-testing at 1 yr, OR, HPV subtyping, if high-risk → colpo

**ASCUS** → HPV testing ("if you Ask Us, you should get an HPV test"), if positive → colpo; Neg → routine

**LSIL** → Colposcopy, unless HPV negative, then can do repeat co-testing at 1 yr

21-24 yo with ASCUS or LSIL → follow-up in 12 months (likely to clear spontaneously)

**ASC-H** → Colposcopy

**HSIL** → Colposcopy or LEEP

**Atypical glandular cells** → Colposcopy with endocervical sampling and endometrial sampling

**Screening Recommendations (according to the USPSTF):**

Women 21-65 Cytology alone every 3 years

**OR** Women 30-65 Co-testing (cytology + HPV testing) every 5 yrs

(Don’t do HPV testing if less than 30 as high rate of positivity, but also clearance)

(Don’t do any testing before age 21, after 65 if they have had good prior screening, or after a hysterectomy for benign reasons)

**Human Papilloma Virus (HPV)**

Sexually Transmitted Disease.

Circular double stranded DNA virus

Infects transformation zone → establishes itself and replicates in basal cells

Detected in the vast majority of cervical cancers.

Viral genes responsible for transforming host cells by integrating into the host DNA and disrupting tumor suppressor genes.

E6 → inactivates p53 (blocks apoptosis)

E7 → inactivates Rb (gets rid of cell cycle arrest → uncontrolled growth)

However, many infections are naturally cleared, so only a minority persist and lead to cancer.

**HPV subtypes**

High-risk (associated with cervical cancer and HSIL, but can also cause LSIL)

16, 18, 31, 33

Type 16 is most commonly detected in cervical cancers

Type 18 is associated with Endocervical Adenocarcinoma

Low-risk (Not associated with HSIL. Instead associated with LSIL/condylomas)

6, 11, 42, 43