The Pap Smear

Current Criteria and Changing Concepts

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Each year approximately 50 million women undergo Pap testing in the US. Of these approximately 3.5 million (7%) are diagnosed with a cytological abnormality requiring additional follow-up or re-evaluation.

### Features of Precancerous and Cancerous Cells
- Abnormality in size and shape of cells
- Variation in cell size and shape
- Increase in nuclear size
- Prominence of nucleoli and irregularity in shape thereof
- Abnormal polarity
- Mitosis, increased number and abnormal forms
- Non-cohesiveness
- Abnormal polarity

### Causes of False-Positive Pap Smears
- Atrophic vaginitis, findings
- Inflammation: sepsis, endometritis, vaginitis
- Foreign objects: diaphragm, IUD

### Causes of False-Negative Pap Smears
- Atrophic endocervical or endometrial squamous cells
- Premalignant epithelial cells
- Abnormalities: foreign objects, inflammation

### Features to Evaluate in Pap Smear
- Adequacy
- Presence of abnormal cells
- Number and distribution of abnormal cells
- Relationship between cells
- Cell size, shape
- Nuclei size and shape
- Nuclear polarity
- Nuclear changes and nucleoli
- Synaptosomal figures
- Background and diathesis

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### Table: Comparative size of Pap smear cells (um)

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Area (um²)</th>
<th>Nucleus (um)</th>
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<tbody>
<tr>
<td>Superficial</td>
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<td>20</td>
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<tr>
<td>Intermediate</td>
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<tr>
<td>Basal</td>
<td>300-50</td>
<td>30-50</td>
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<tr>
<td>Endocervical</td>
<td>300-50</td>
<td>30-50</td>
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<tr>
<td>Endometrial</td>
<td>150-30</td>
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<tr>
<td>Reserve cells</td>
<td>200-30</td>
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### Differential diagnosis of atrophy
- Benign polyps
- Inflammation, variable
- Dysplasia, squamous
- Metaplasia, tubal
- Karyorrhexis, necrotic
- Postmenopausal changes
- Foreign bodies

### Differential diagnosis of atypia
- Benign polyps
- Inflammation, variable
- Dysplasia, squamous
- Metaplasia, tubal
- Karyorrhexis, necrotic
- Postmenopausal changes
- Foreign bodies

### Differential diagnosis of dysplasia
- Benign polyps
- Inflammation, variable
- Dysplasia, squamous
- Metaplasia, tubal
- Karyorrhexis, necrotic
- Postmenopausal changes
- Foreign bodies

### Differential diagnosis of carcinoma
- Benign polyps
- Inflammation, variable
- Dysplasia, squamous
- Metaplasia, tubal
- Karyorrhexis, necrotic
- Postmenopausal changes
- Foreign bodies

### Differentiation of squamous cells
- Basal
- Parabasal
- Intermediate
- Superficial

### Differentiation of endocervical cells
- Parabasal
- Intermediate
- Superficial

### Differentiation of endometrial cells
- Basal
- Parabasal
- Intermediate
- Superficial

### Table: Section 2.1 - Cytological Features

<table>
<thead>
<tr>
<th>Section</th>
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<tr>
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<td>Squamous intraepithelial lesion</td>
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<td>Atypical glandular cells</td>
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<tr>
<td>5</td>
<td>Atypical squamous cells</td>
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<td>6</td>
<td>Abnormal cell nuclei</td>
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<td>“Of corn flakes and raisins”</td>
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### Table: Section 3.1 - Features of Preputitis

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<td>Moderate inflammation</td>
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### Table: Section 3.2 - Features of Atrophy

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### Table: Section 3.3 - Features of Dysplasia

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### Table: Section 3.4 - Features of Carcinoma

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### Table: Section 3.5 - Features of Metastasis

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### Table: Section 3.6 - Features of Invasion

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### Table: Section 3.7 - Features of Staging

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</table>
Defintion- ASC-US:
Cytological changes suggestive of HSIL, but lack criteria for a definitive interpretation. This association with underlying CIN2 and CIN3 for ASC-US is lower than for ASC-H, but sufficiently higher than for ASC-US to warrant consideration of different management recommendations.

ASC-US:
- Increased nuclear atypia
- Basophilic nuclear membrane irregular
- N:C ratio increased
- Mitotic activity increased
- Nuclear membrane irregular

Note: ASC-US cannot be excluded high-grade SIL:
- Inflammation-associated changes
- Radiation
- Chemotherapy

Mimics of ASC-US:
- Atrophy, squamous metaplasia
- Multinucleation
- LSIL
- Opaque in HPV
- Air-drying artifact

Carcinoma is a potential diagnostic nightmare:
- Hyperchromasia
- Proliferation
- Mitotic activity increased
- Mitotic activity increased +

Estimated cervical HPV infections and HPV-related disease

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Microscopic features of types of squamous cell carcinoma

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</table>
Benign endometrial cells
- small clusters - hyperchromatic crowded groups
- degenerated small cells
- rare atypical
- oval nuclei
- round single nucleoli, small and inconspicuous
- hyperchromatic nucleus
- multinucleated

Cytological features of tubal metaplasia
- usual in some fragments, Cilix (+)
- goblet-like cells, in groups
- cells variable in size and shape
- nuclei oval or round and central
- nuclear variability present
- cytoplasm variable and pale
- oval nucleus
- round nucleoli, small and inconspicuous

Cytological features of AIS
- usual in some fragments, Cilix (+)
- arranged in clusters, honeycomb, with palisading in gland-like structures
- varying in size
- minimally enlarged, round-oval, nuclei that overlap
- granules present
- hyperchromatic nuclei
- slightly atypical
- clear background

Differential diagnosis of AIS
- considered aberrant columnals:
  - dark, post-inflammatory phase
  - small nuclei, and not in hormone therapy
- considered atypical columnals:
  - nuclei are larger (than nuclei of intermediate cells)
  - nuclei are conspicuous

Endocervical vs. endometrial carcinoma on Pap smears*
- arranged in rosettes, feathery edge, with palisades in gland-like structures
- endometrial polyp
- scant cytoplasm,
- minimal, round-oval, nuclei that overlap
- granular cytoplasm,
- slight anisonucleosis
- endocervical sampling by brush

Glucocorticoids, post-partum hemorrhage, possible origin
- Fimbriae
- Uterine villi
- Embryonic
- Endometrial
- Peritoneal fluid
- Supernumerary lymphoid tissue
- Glutaraldehyde fixation, radiation or chemotherapy

AIS on thin-layer preparation
- dark cellular groups and sheets with scalloping, single cells common
- "nuclear" density of focus
- variability of nuclei size and shape
- triphasic chromatin, irregular nuclear membrane
- nuclei, single or groups
- glandular, cribriform
- microcystic

Endocervical vs. endometrial carcinoma on Pap smears*
- basal cells
- cervical
- endometrial cells and stroma and histiocytes, days 7-10
- basal cells
- endometrial cells
- endocervical cells
- endometrial cells
- endocervical cells
- endometrial cells
- endocervical cells
- endometrial cells
- endocervical cells
- endometrial cells

Cytogenetic features of endometrial adenocarcinomas
- adenocarcinoma
- metastatic
- endometrial
- squamous
- endocervical
- endometrial

Nuclear features of endometrial adenocarcinomas
- well-defined nuclear membranes
- vesicular nuclei
- granular chromatin
- endometrial
- endocervical
- endometrial
- endocervical
- endometrial
- endocervical

Differential diagnoses of endometrial adenocarcinomas
- endocervical repair
- endometrial cells under degenerative effect
- endometrial cells with tubal metaplasia
- endometrial cells with papillary-cystadenoma
- endometrial cells
- Arias-Stella reaction

Endometrial cells may be seen in:
- Dysfunctional bleeding, hormonal therapy, IVFU, endometriosis, endometriosis, pregnancy, post-partum state, recov endometrium

Endometrial cells on Pap smears:
- considered aberrant columnals:
- dark, post-inflammatory phase
- small nuclei, and not in hormone therapy
- considered atypical columnals:
- nuclei are larger (than nuclei of intermediate cells)
- nuclei are conspicuous

Apical endometrial cells seen in:
- endometrial polyp
- endometrium
- Arias-Stella
- endometrial

Denominator versus glandular carcinoma on Pap smears
- Glandular cells from endocervical carcinoma shed more cells than endometrial carcinoma.
- cells from endocervical carcinoma are larger
- nuclei of endocervical carcinoma are larger
- cells from endocervical carcinoma are more chromatin than cells that are endometrial
- cells from endocervical carcinoma are more commonly have marked nucleoli and are usually larger
- endometrial cells are usually arranged in 2D sheets
- endometrial cells have more mitotic figures
- endometrial cells have more mitotic figures
- apoptosis is more common in endometrial carcinoma

Enzymes
- alpha glucosidase
- beta glucosidase
- N-acetylglucosaminidase
- cathepsin B
- N-acetyl-B-D-glucosaminidase
- neutral proteases
- cathepsin D
- carboxypeptidase A
- neutral proteases
- carboxypeptidase B
- neutral proteases
- cathepsin E
- neutral proteases
- cathepsin H
- neutral proteases
- cathepsin L
- neutral proteases
- cathepsin N
- neutral proteases

Suprapubic versus endometrial carcinoma on Pap smears
- MBP
- keratin
- lymphoepithelioma
- lymphoepithelioma
- lymphoepithelioma
- lymphoepithelioma
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7. DeMay, Practical Principles of Cytopathology, Chicago, ASCP, 1999

ACKNOWLEDGMENTS

Information in this material has been derived from the following textbooks:

- Birder, Comparative Pathology, Philadelphia, 1997
- Key, Journal of Clinical Pathology, Oxford, 1988
- Bibbo, Comprehensive Cytopathology, Philadelphia, Saunders, 1997
- DeMay, Practical Principles of Cytopathology, Chicago, ASCP, 1999
- McKe, Modern Cytopathology, New York, Oxford, 2002
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- DeMay, Practical Principles of Cytopathology, Chicago, ASCP, 1999
- McKe, Modern Cytopathology, New York, Oxford, 2002
10 LEGENDS

Legends to CD-ROM Images

1. Normal squamous cells in Papanicolaou smear. Superficial cells are flattened, brick red abundant cilia and granular cytoplasm are abundant in the cell (Papanicolaou stain; magnification, X400).

2. Normal endocervical cells appear as flat or flattened, basophilic sheets of cells with finely granulated cytoplasm, round nuclei, and small nucleoli. Nuclear chromatin is evenly dispersed in the cell (Papanicolaou stain; magnification, X400).

3. Squamous metaplasia: small punched out cells with variable shape, distinct cell borders, and rounded irregular nuclei (Papanicolaou stain; magnification, X400).

4. Normal endocervical cells: epithelial cells of endocervical epithelium are usually seen in a 3-dimensional sheet. Nuclear size is comparable to superficial cells, and cytoplasm is faintly basophilic (Papanicolaou stain; magnification, X100).

5. Lactobacilli reduce glycogen. Cytochemical changes in intermediate cells are typically due to increases in lactobacilli. Note the "loss" of nuclei, cytoplasmic detail, and faint acid fast bacilli (Papanicolaou stain; magnification, X400).

6. Candida spp: Epithelial cells with pseudopods and spine formation (conventional smear; Papanicolaou stain; magnification, X400).

7. Lichenoid reaction: pleomorphic squamous cells with necrotic debris and intracytoplasmic granules (Papanicolaou stain; magnification, X400).

8. Atypical squamous cells of undetermined significance (ASC-US): Atypical squamous cells without significant atypia (Papanicolaou stain; magnification, X400).

9. Squamous cell with reparative changes arranged in the cobblestone 2-dimensional sheet. Nuclear/cytoplasmic ratio is low. Nuclei show "streaming" with prominent nucleoli. Note intracellular neutrophils. Cytoplasm is usually cyanophilic (thin-layer, Papanicolaou stain; 400X).

10. Reactive endocervical cells are arranged in a honeycomb pattern without cellular cohesion. Cells are large with hyperchromatic nuclei and prominent nucleoli (Papanicolaou stain; magnification, X400).

11. Follicular cervicitis: Follicular cervicitis cells are a patient with immunoosseous disease in place. These cells appear single with high n:c ratio. Cytoplasm is finely vacuolated (conventional smear; Papanicolaou stain; magnification, X100).

12. Basaloid squamous cell carcinoma: Basaloid squamous cell carcinoma cells are arranged in a 3-dimensional sheet. Basaloid squamous cells are usually seen in small groups and are usually confined to the cervix (Papanicolaou stain; magnification, X400).

13. Epidermoid cysts: Tumors lined by squamous epithelium with characteristic neuroendocrine differentiation (Papanicolaou stain; magnification, X400).

14. Amputee: Sheets of prismatic cells with benign nuclei and bland chromatin density. Background shows slight nuclear pseudopods and prominent nucleoli (Papanicolaou stain; magnification, X400).

15. Keratinizing squamous cell carcinoma: Keratinizing squamous cell carcinoma cells are well differentiated (Papanicolaou stain; magnification, X400).

16. Nuclear atypia: Nuclear atypia is seen as aggregates of chromatin, brownish basophilic grains from the denser center, usually seen with FED and SER (conventional smear; Papanicolaou stain; magnification, X400).

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30. Keratinizing squamous cell carcinoma: Keratinizing squamous cell carcinoma cells are well differentiated (Papanicolaou stain; magnification, X400).

31. High-grade squamous intraepithelial lesion (HSIL): Squamous cell carcinoma with high grade squamous intraepithelial lesion (HPV infection) (conventional smear; Papanicolaou stain; magnification, X400).

32. Nuclear atypia: Nuclear atypia is seen as aggregates of chromatin, brownish basophilic grains from the denser center, usually seen with FED and SER (conventional smear; Papanicolaou stain; magnification, X400).

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45. Amputee: Sheets of prismatic cells with benign nuclei and bland chromatin density. Background shows slight nuclear pseudopods and prominent nucleoli (Papanicolaou stain; magnification, X400).
Keratinizing dysplasia: High-grade keratinizing dysplasia showing both nuclear and cytoplasmic pleomorphism. Note orange cytoplasm and large, hyperchromatic nuclei (thin-layer; Papanicolaou stain; 400X).

Keratinizing squamous cell carcinoma: Dispersed cells of spindle to elongated and caudate forms with heavily keratinized cytoplasm. Nuclei are pleomorphic and hyperchromatic. Nucleoli are less conspicuous than the non-keratinizing type. These tumors generally lack tumor diathesis (conventional smear; Papanicolaou stain; 400X).

Non-keratinizing squamous cell carcinoma: Malignant polygonal cells are arranged in either loose clusters or crowded groups of small. Nuclei are large, nearly round, and have coarse chromatin, and numerous nucleoli. Cytoplasm is dense with distinct cell borders. N:C ratio is moderate. Tumor diathesis is generally present (thin-layer; Papanicolaou stain; 400X).

Atypical glandular cells with pseudostratification. These cells may be of endocervical or endometrial in origin. Nuclei show minimal atypia. Differential diagnosis includes tubal metaplasia or glandular neoplasia (thin-layer, Papanicolaou stain; 400X).

Atypical endocervical cells: The cells show focal palisade arrangement (“feathering”), and enlarged hyperchromatic nuclei with small nucleoli (thin-layer; Papanicolaou stain; 400X).

Atypical endometrial cells: In a 3-dimensional cluster. Nuclei show hyperchromatic nuclei with prominent nucleoli. (thin-layer; Papanicolaou stain; 400X).

Atypical endocervical cells-favor neoplastic: A dense cluster of endocervical cells with peripheral palisading and prominent nuclear protrusion. Nuclei are large, elongated, and oval with coarse chromatin. Nucleoli are lacking. Background is clean. Inset shows a group of pseudostratified cells (thin-layer; Papanicolaou stain; 400X).

Endocervical adenocarcinoma in situ seen as a cluster of hyperchromatic crowded group of cells with high n:c ratio and prominent nuclear protrusion. Nuclei are large, elongated, and oval with coarse chromatin. Background is clean. Inset shows a group of pseudostratified cells (thin-layer; Papanicolaou stain; 400X).

Endocervical adenocarcinoma: Well-differentiated endocervical adenocarcinoma showing large group of cells in a predominantly 2-dimensional group. Cells show high n:c ratio, enlarged hyperchromatic nuclei and macroscopic nuclei. Inset shows a rosette (conventional smear; Papanicolaou stain; 400X).

Endometrial adenocarcinoma seen as a papillary tuft of indolent cells from case of papillary serous variant. The malignant cells show nuclear enlargement and pleomorphism. (thin-layer; Papanicolaou stain; 400X).

Atypical glandular cells- favor neoplastic: Strip of cells with large hyperchromatic nuclei. Nucleoli are not conspicuous (thin-layer; Papanicolaou stain; 400X).

Endometrial adenocarcinoma is seen as round cells with cytoplasmic and vacuolated cytoplasm with intracytoplasmic metaplasia. Background shows the characteristic blue-stained, clearly granular “carcino” diathesis (thin-layer left) and conventional smear (right). (Papanicolaou stain; 400X).

Atypical histiocytes in endometrial adenocarcinoma: Large densely stained clusters of cells with intracytoplasmic metaplasia containing intracytoplasmic vacuoli. (conventional smear; Papanicolaou stain; 400X).

Small cell anaplastic carcinoma of cervix shows tight syncytial aggregate of small irregular tumor cells. Nuclei are hyperchromatic and small. Background shows nuclear molding (thin-layer preparation; Papanicolaou stain; 400X).

Metastatic lobular carcinoma of breast shows a cluster of small cells with large irregular nuclei and small cytoplasm. A clean background of the smear is often observed in metastatic tumors. Clinical history is important (thin-layer preparation; Papanicolaou stain; 400X).

Acknowledgements.

Contrary to popular belief, the purpose of the Papanicolaou smear is to screen for cervical cancer, not to diagnose disease. Wang and Ducatman, in The Pap Smear.

Supplement

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US&CAP short course

Pap smear: current criteria & changing concepts

Hoda & Hoda

1. Normal squamous cells

2. Normal endocervical cells

3. Squamous metaplastic cells

4. Normal endometrial cells

5. Lactobacilli inducing cytolysis
coccobacilli ~ bacterial vaginosis

leptothrix and trichomonas vaginalis

trichomonas vaginalis

herpes simplex virus

actinomyces spp
12 squamous cells with repair
13 reactive endocervical cells
14 radiation changes
15 IUD cell
16 vaginal endometriosis
17 menstrual endometrium 'exodus'
18. atrophy

19. atrophic vaginitis

20. follicular cervicitis

21. hyperkeratosis

22. parakeratosis

23. tubal metaplasia
endocervical polyp

syncytiotrophoblast

atypical squamous cells of undetermined significance, ASCUS

low grade squamous intraepithelial lesion, LSIL

LSIL

LSIL
atypical squamous cells cannot exclude HSIL, ASC-H

high grade squamous intraepithelial lesion, HSIL

HSIL

HSIL involving endocervical glands

atypical parakeratosis

keratinizing dysplasia
keratinizing squamous ca

non-keratinizing squamous ca

atypical glandular cells

atypical endocervical cells

atypical endometrial cells

atypical endocervical cells, favor neoplastic
atypical glandular cells, favor neoplastic

endocervical adenocarcinoma in situ - AIS

endocervical adenocarcinoma

endometrial adenocarcinoma

endometrial adenocarcinoma

atypical histiocytes in endometrial adenocarcinoma

Watery diathesis