

GYN- Glandular Cytology
Fadi Abdul-Karim MD MEd

1

Bethesda 2014: Adequacy

- Conventional Smears: 8000-12000 well preserved well visualized squamous or squamous metaplastic cells.
- 5000 squamous cells minimum for LBC.
- 2000 squamous cells is the minimum for vaginal or s/p XRT/Rx smears

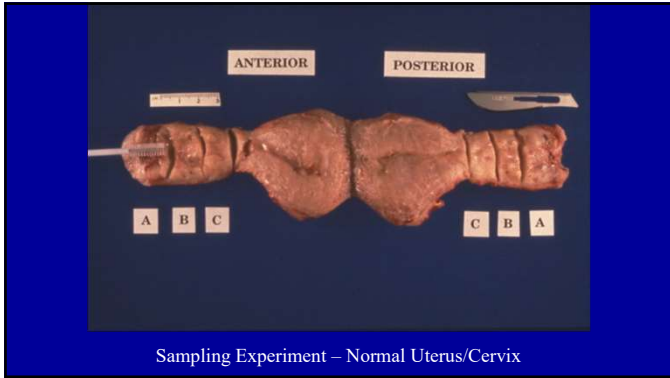
2

**TBS 2014:
Overview of Glandular Abnormalities**

- The Pap test was not designed to screen for glandular lesions of the cervix, and these abnormalities are more difficult to sample and interpret compared to their squamous counterparts.
- Because of improvement in sampling devices and the increase in endocervical adenocarcinoma relative to squamous cell carcinoma over the past 2 decades, cytologists currently encounter more challenging presentations of glandular lesions and their mimics in cervical cytology specimens.

Nayar R and Wilbur D. JASC 2015;4:170-180.

3



4

Glandular Cells: Introduction

- Pap tests with atypical glandular cells are rare (<0.5% of interpretations in most series)
- Women with atypical glandular cells have clinically significant disease (HSIL, AIS, or cancer) in up to 38% of cases
- 3-17% of patients with AGC have invasive carcinoma
- While cervical squamous lesions have decreased in incidence, cervical adenocarcinomas are increasing

5

**TBS 2014:
Epithelial Cell Abnormalities- Glandular cell**

- Atypical
 - Endocervical cells (NOS or specify in comments)
 - Endocervical cells, favor neoplastic
 - Endometrial cells (NOS or specify in comments)
 - Glandular cells (NOS or specify in comments)
 - Glandular cells, favor neoplastic
- Endocervical adenocarcinoma *in situ*
- Adenocarcinoma
 - Endocervical
 - Endometrial
 - Extra-uterine
 - Not otherwise specified (NOS)

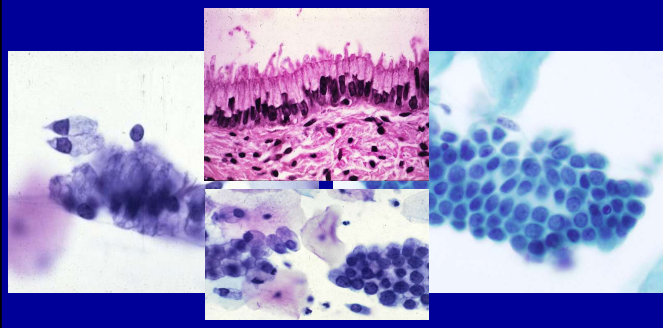
6

**TBS: BIRST-2:
Least Reproducible**

- Glandular lesions
- Reparative problems
- HSIL
- ASC-US/ASC-H

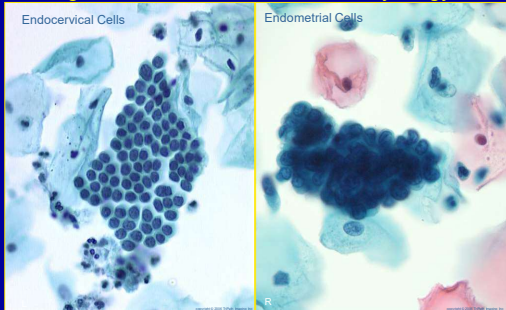
7

Normal Endocervical Cells



8

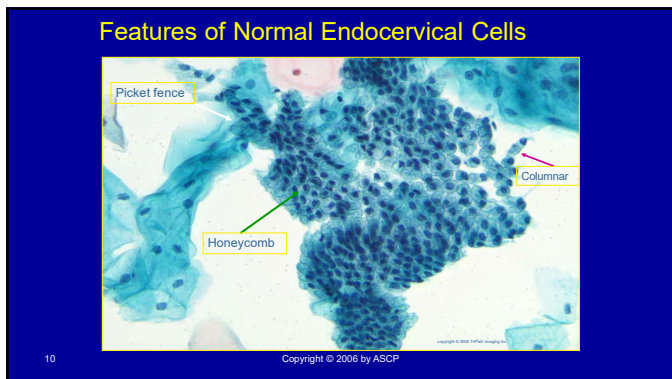
Setting Baselines In LBC Glandular Cytology



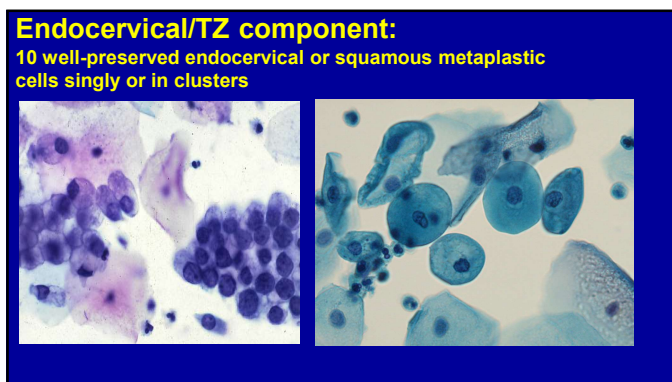
9

Copyright © 2006 by ASCP

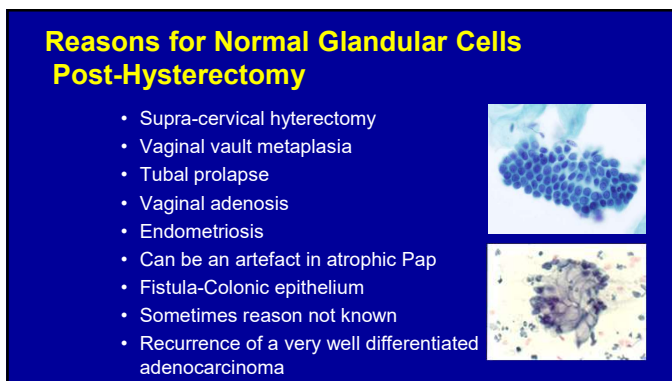
9



10



11



12

Glandular Cells Post Hysterectomy
 History of FIGO 1, IB, Endometrial Cancer. S/P XRT

13

Glandular cells in Vaginal cytology Pap in After Hysterectomy for Endometrial Adenocarcinoma

- <1% of asymptomatic vaginal recurrences are detected by routine vaginal cytology alone.
- Most of the cells called Atypical Glandular, in the absence of a visible lesion on exam were not glandular on histopathology- Atrophic or Post-XRT cells mimicking glandular cells.

Shank E, Abou-Khalil FW. Diagn Cytopathol. 2012 Feb;40(2):138-40

14

TBS 2014: Epithelial Cell Abnormalities- Glandular cell

- **Atypical**
 - Endocervical cells (NOS or specify in comments)
 - Endocervical cells, favor neoplastic
 - Endometrial cells (NOS or specify in comments)
 - Glandular cells (NOS or specify in comments)
 - Glandular cells, favor neoplastic
- **Endocervical adenocarcinoma *in situ***
- **Adenocarcinoma**
 - Endocervical
 - Endometrial
 - Extra-uterine
 - Not otherwise specified (NOS)

15

Epithelial Cell Abnormalities- Glandular cell

Range 0.11 – 2.1% (mean = 0.48, median = 0.27)

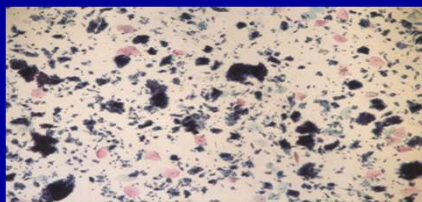
CAP Data - mean = 0.35%, median = 0.3%

Rule of thumb < 1%

16

Hyperchromatic Crowded Groups

Any cellular grouping with features that impede the ability of the cytologist to see the individual cells in the middle



17

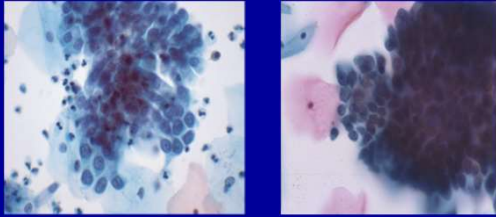
Hyperchromatic Crowded Groups

- Sampling Device
- Voracity of the Sampler
- Anatomic Considerations
- Physiologic Processes
- Neoplastic Processes

3-D groups of darkly staining cells easily detectable at a low magnification
Frequent finding – over ¾ of the specimens
Usually benign but can be derived from clinically significant lesions such as carcinoma (5% of cases)

18

Normal Endocervical Cells: Brush Artifact



TBS (SP): Vigorous sampling with an endocervical "broom" device. The endocervical cells show uniform, evenly distributed, finely granular chromatin, and well- defined cytoplasmic boundaries consistent with a benign etiology

19

Hyperchromatic Crowded Groups

- **Benign**
 - Endocervical cells
 - Endometrial cells
 - LUS
 - Atrophy
 - Tubal metaplasia
 - Micro-glandular hyperplasia
 - Clusters of inflammatory cells
- **Neoplastic/Preneoplastic**
 - HSIL
 - AIS
 - Squamous cell carcinoma.
 - Adenocarcinomas

20

Endocervical Adenocarcinoma in Situ: AIS

21

AIS: Quadrants and Multifocality

- Usually begins as a single focus
- Often extensive horizontal or lateral spread
- Multiple quadrants involved in more than 50% of cases
- True skip lesions are rare
- Nearly 100% HPV +. Type 18>16
- Precursor lesion of endocervical Adenocarcinoma

22

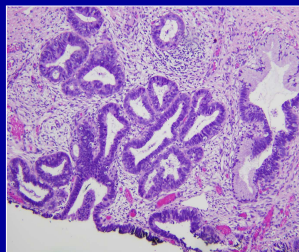
AIS: General Features

- 50% have associated SIL or invasive Squamous cell carcinoma
- Colposcopy usually normal or SIL related changes
- Cytologic diagnosis based on architecture and nuclear features

23

AIS: Histopathologic Features

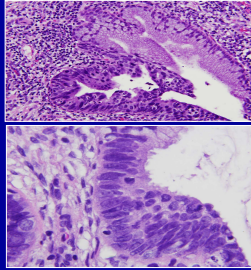
- Preservation of normal glandular architecture
- Coupled with an alteration involving part or all of the epithelium lining glands or forming the surface



24

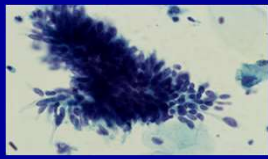
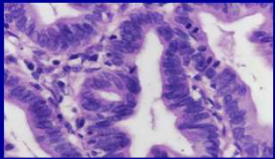
AIS: Histopathologic Features

- Nuclear enlargement, coarse chromatin, small single or multiple nucleoli
- Increased mitotic activity
- Variable stratification of nuclei
- Cytoplasmic mucin may be either reduced in quantity or abundant
- An intraglandular papillary architecture may be present

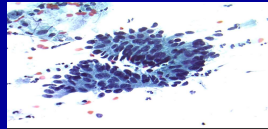


25

AIS: Cytologic Features

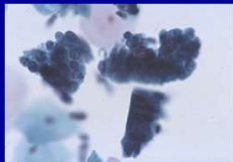
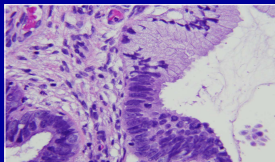


Hyperchromatic crowded groups.
Single cells rare.
Feathering, rosettes, strips
Pseudostratification
Amphophilic granular cytoplasm
Clean /inflammatory background

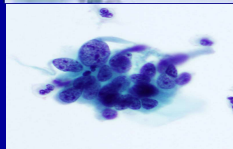


26

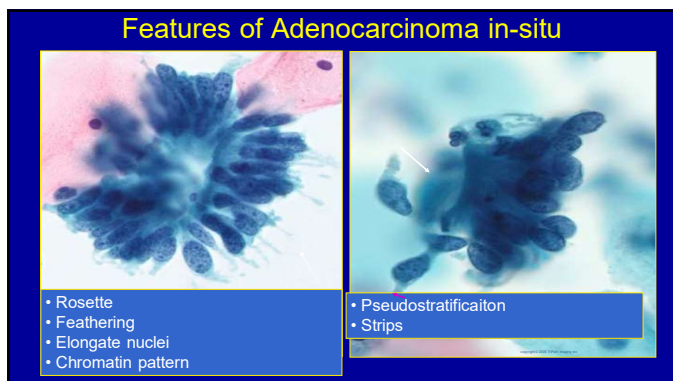
AIS: Cytologic Features



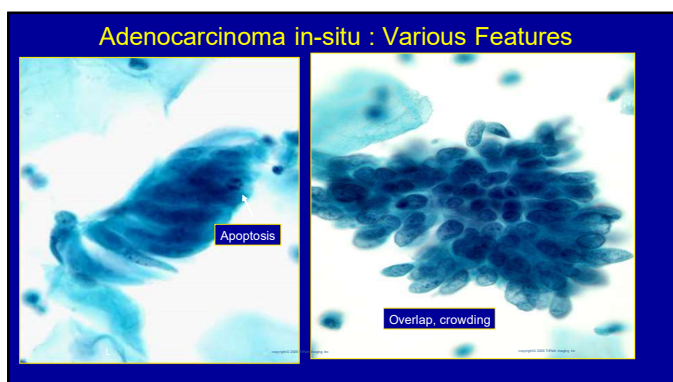
Columnar monomorphous cells
Uniform nuclei. Increased N/C ratio
Nuclei large-elongated/ovoid (75 um²)
Dark even chromatin coarse granularity
Mitosis, apoptotic bodies
Micronucleoli



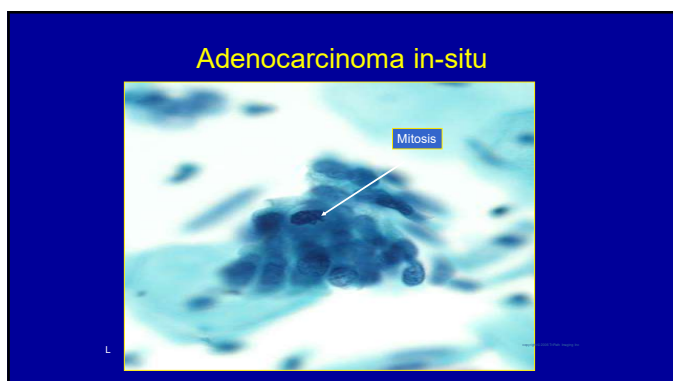
27



28



29



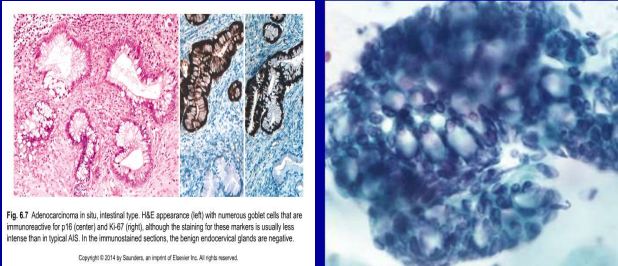
30

AIS: Histopathologic Subtypes

- Endocervical
- Intestinal
- Endometrioid
- Mixed adenosquamous
- Tubal (tentative)

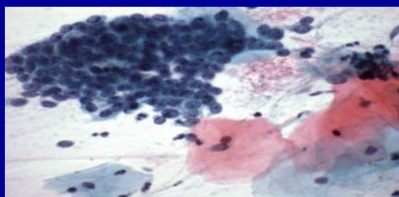
31

AIS: Intestinal Type



32

AIS: Endometrioid Type

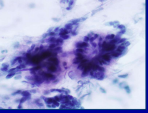
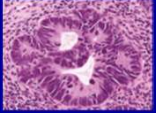
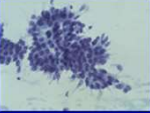


Similar features to the usual type of AIS but shows much smaller average nuclear area. Because of this size difference, endometrioid AIS can be mistaken for directly sampled benign endometrium. Attention to overall architecture and lack of stromal cells can be helpful in differentiation

33

AIS on Pap Sensitivity

- AIS 55-70%
- Endocervical adenocarcinoma 72%
- HSIL 73%
- Squamous cell carcinoma 75%

34

AIS: False Negative Interpretation

- 11,337 responses in Pap Education Program (CAP).
- 10,509 (92%) HSIL positive, 5667 (50.0%) AIS, 4842 (42.7%) HSIL positive, 44 (0.4%) LSIL.
- **FN 6.9%: 482/784: NILM, 189 (24.1%) repair, 60 (7.7%) Atrophy.**
- Higher false negative rate for pathologists than cytotechnology
- No significant difference between TP, SP, CP

Zhao C et al Arch Pathol Lab Med 2017; 14: 666 - 670

35

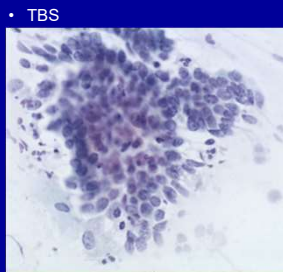
ATYPICAL ENDOCERVICAL CELLS, Favor Neoplastic: Definition

- Cells showing endocervical differentiation that **QUALITATIVELY OR QUANTITATIVELY** fall short of an interpretation of invasive endocervical adenocarcinoma or adenocarcinoma in situ

36

Atypical Endocervical Cells (AEC), Favor Neoplastic

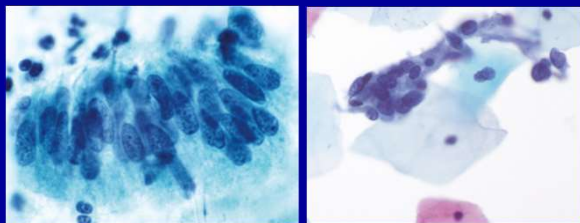
- Sheets or strips of cells with crowding and nuclear overlap.
- Ill defined cell borders.
- Rare groups with rosettes or feathering
- Nuclear enlargement with increased nuclear/cytoplasmic ratios
- Nuclear hyperchromasia
- Occasional mitoses
- Clean or slightly bloody background



37

TBS: Atypical endocervical cells, favor neoplastic

(CP) Pseudostratified strip of endocervical cells with enlarged, elongated nuclei and evenly distributed chromatin granularity
(TP) AEC characterized by round or oval nuclei with nuclear enlargement, crowding, disordered arrangement, and occasional nucleoli. A rosette-like cellular arrangement is present. Follow-up showed endocervical AIS



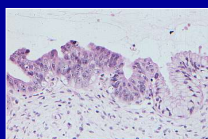
38

“Endocervical Glandular dysplasia”

The diagnostic criteria remain largely subjective.

- A numerical scoring system was proposed but not applied.
- The biologic and clinical significance of GD remains to be determined.

* Imprudent to make an unqualified diagnosis of GD.



39

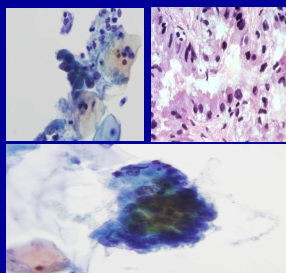
**ATYPICAL GLANDULAR CELLS (AGC):
Definition**

- Cells showing either endometrial or endocervical differentiation displaying nuclear atypia that exceeds obvious reactive or reparative changes but lacks unequivocal features of invasive adenocarcinoma or adenocarcinoma in situ

40

Atypical Endocervical Cells (AEC)

- Sheets and strips of crowded endocervical cells with crowding and overlap/Occasional rosettes-feathering
- Distinct cell borders
- Enlarged nuclei (3-5x > normal) with increased nuclear/cytoplasmic ratios
- Nuclear hyperchromasia and nucleoli
- Occasional mitosis



41

Atypical Glandular/Endocervical Cells

Follow Up Studies – “Rule of Thumb”

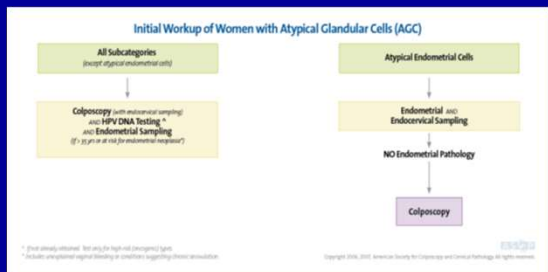
Benign	20- 40%
Squamous Neoplasia	40-80%
Endocervical Neoplasia	0-10%

Clinical importance variable but > ASC-US

Poor reproducibility

42

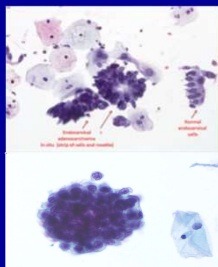
AGC - Management



43

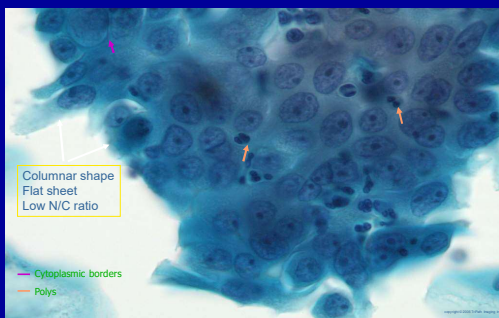
Atypical Endocervical Cells Differential Diagnoses and Mimickers of AIS

- Abundant normal endocervical cells
- Reactive changes/Repair
- Radiation therapy
- Tubal metaplasia
- Endocervical polyps
- Microglandular hyperplasia
- Intrauterine device effect (IUD)
- Squamous neoplastic mimickers
- Directly sampled endometrium/Endometriosis



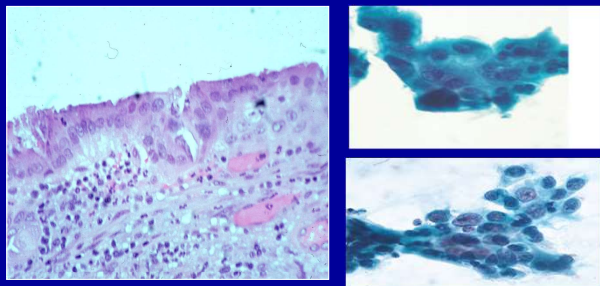
44

Cytologic Criteria: NILM - Reactive Endocervical Cells



45

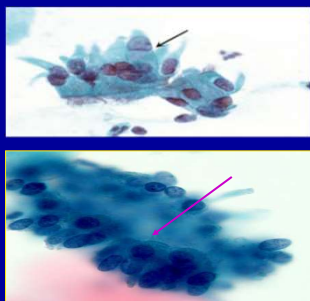
TBS Endocervical Cells Radiation Effect



46

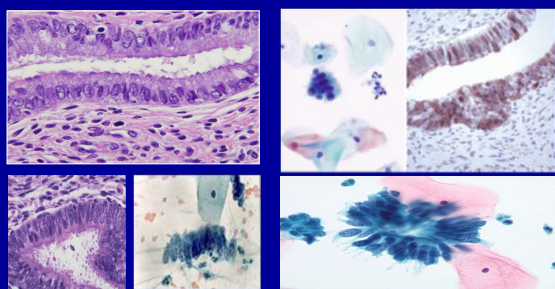
Tubal Metaplasia

- Incomplete features of AIS
- Chromatin (texture/distribution)
- Nuclei "washed-out"
- Nuclear pleomorphism
- N/C increased
- Mitoses/rare apoptosis
- Large stripped nuclei
- Cilia/terminal bars



47

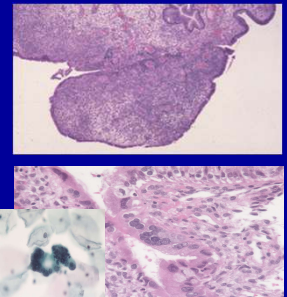
Tubal Metaplasia



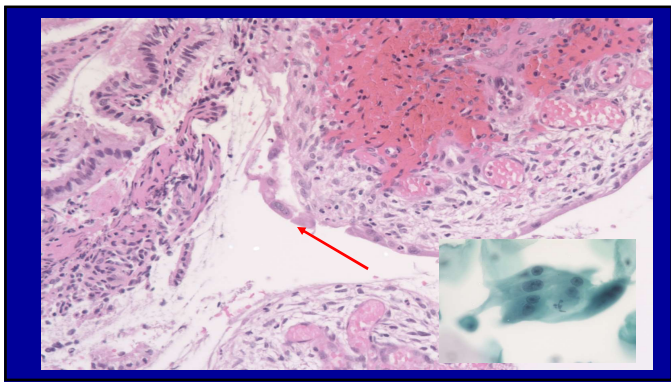
48

Endocervical Polyps

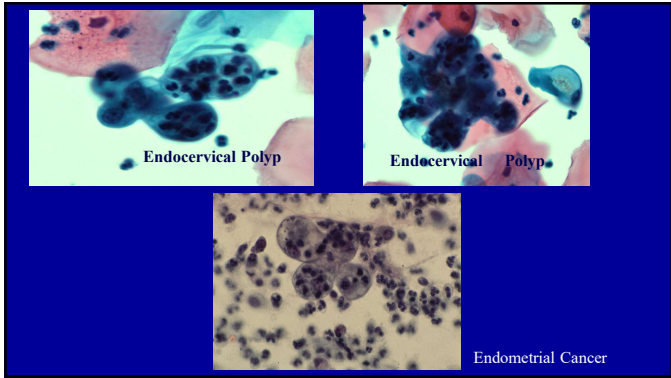
- Common
- Bleeding
- Surface ulceration
- EC proliferation - abundant cellularity - HCG's
- Reactive changes - enlargement, nucleoli, mitoses
- Inflammation - reparative changes
- Can mimic either EC or EM neoplasia



49



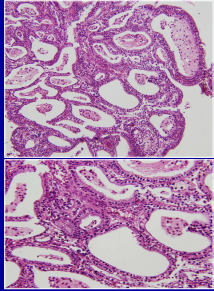
50



51

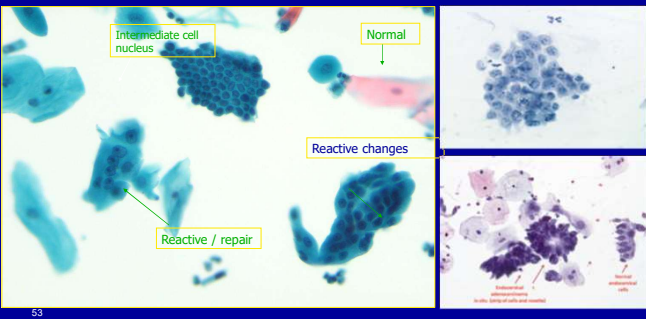
Microglandular Hyperplasia

- Most look like normal endocervicals
- Repair like configuration
- Full spectrum of cell sizes within group
- Nuclei normal or increased in size. Nucleoli may be present and prominent. No mitosis.
- Normal or slight hyperchromasia. Rarely pyknosis.
- Cytoplasm abundant, fine, vacuolated
- Pseudoparakeratosis



52

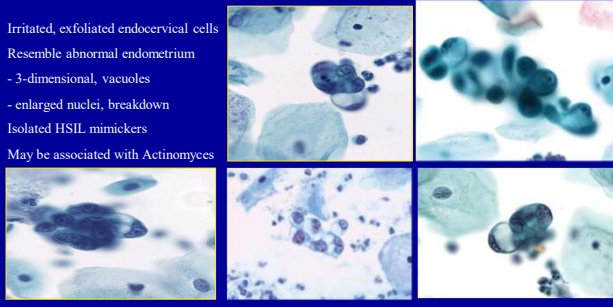
Endocervical Cells (EC): Spectrum of NILM



53

Intrauterine Device Effect

- Irritated, exfoliated endocervical cells
- Resemble abnormal endometrium
- - 3-dimensional, vacuoles
- - enlarged nuclei, breakdown
- Isolated HSIL mimickers
- May be associated with Actinomyces



54

TBS: Arias Stella

Groups of stimulated endometrial glandular epithelium that could be mistaken for a glandular epithelial abnormality.



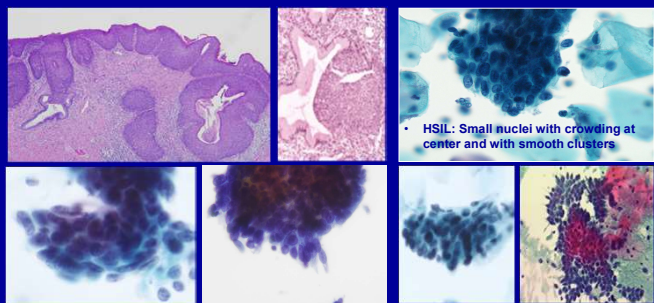
55

Squamous Neoplastic Mimickers

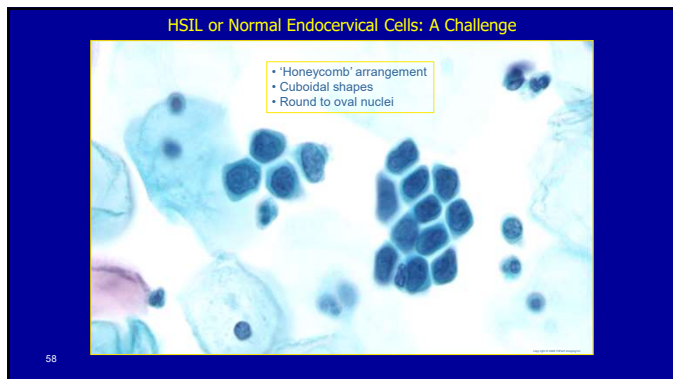
- Most common cause of “EC” atypia
- Most common with broom/brush
- Involvement of EC gland necks
- “Learning curve”

56

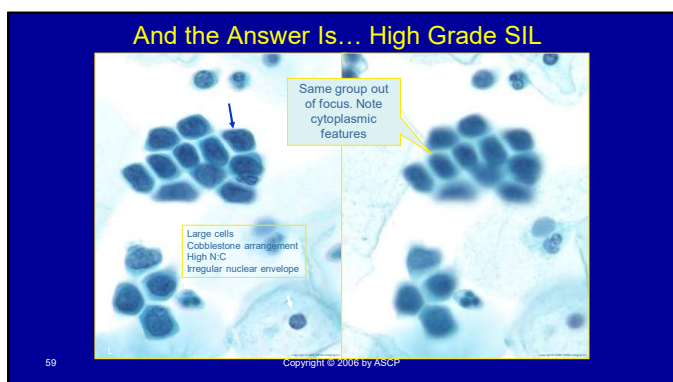
HSIL Involving Endocervical Glands



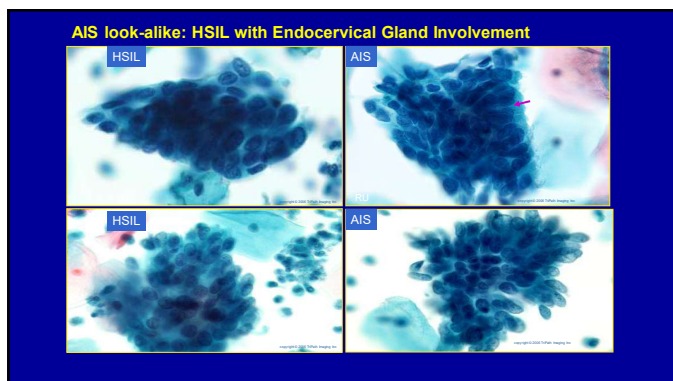
57



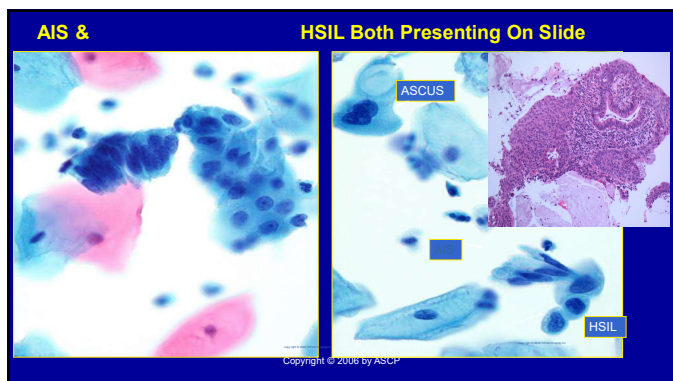
58



59



60

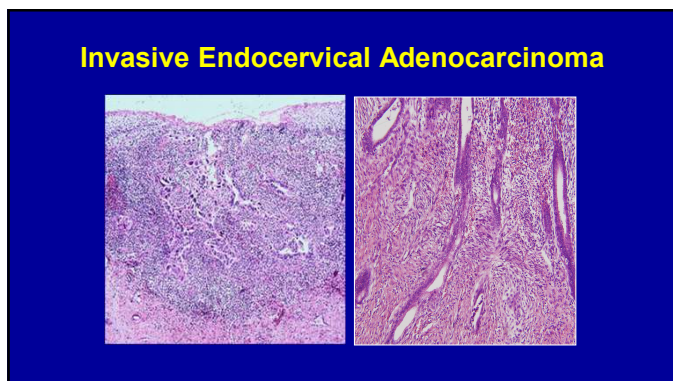


61

Invasive Endocervical Adenocarcinoma

- 16 – 25% of cervical cancers
- 29% increase in incidence in recent years
 - 1970: Adenocarcinoma 12% and sq ca 88%
 - 2000: Adenocarcinoma 29% and sq ca 69%
- Earlier detection: ? New sampling devices
- Gross: variable
- Prognosis: ? Worse than squamous carcinoma

62

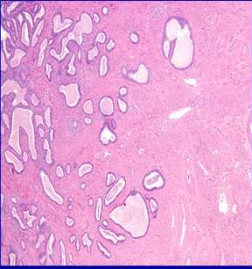


63

Risk Stratification System Invasive Endocervical Adenocarcinomas Based on Pattern of Invasion

Pattern A

- Well-demarcated glands with rounded contours, frequently forming groups
- No destructive stromal invasion
- No single cells or cell detachment
- No lymphovascular invasion
- Complex intraglandular growth acceptable, i.e. cribriform, papillae
- Lack of solid growth, i.e. architecture well-moderately

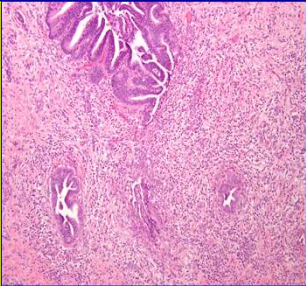


64

Risk Stratification System Invasive Endocervical Adenocarcinomas Based on Pattern of Invasion

Pattern B

- Localized (limited, early) destructive stromal invasion arising from pattern A glands (well-demarcated glands)
- Individual or small groups of tumor cells, separated from the rounded gland, often in a focally desmoplastic or inflamed stroma
- Foci may be single, multiple, or linear at tumor base
- Lymphovascular invasion +/-
- Lack of solid growth, i.e. architecturally well-moderately differentiated

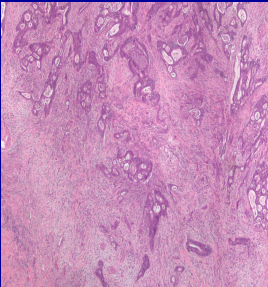


65

Risk Stratification System Invasive Endocervical Adenocarcinomas Based on Pattern of Invasion

Pattern C

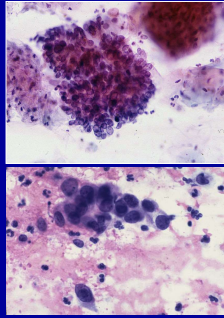
- Diffuse destructive stromal invasion characterized by
 - Diffusely infiltrative glands, with associated extensive desmoplastic response
 - Glands often angulated or with a canalicular pattern, with interspersed open glands
- Confluent growth filling a 4x field (5 mm)
- Solid, poorly differentiated component
- Lymphovascular invasion +/-



66

Endocervical Adenocarcinoma Features of AIS and....

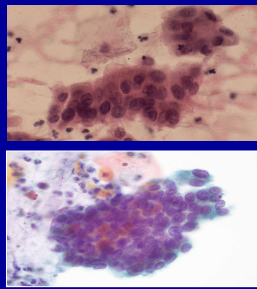
- Hypercellular, sheets, clusters, syncytial aggregates
- Single cells (lack cohesion)
- Finely granular, vacuolated cytoplasm
- Large pleomorphic nuclei/Increased N/C ratio
- Nuclear membrane irregularity , Uneven chromatin.
- Macro-nucleoli
- Tumor diathesis (bloody, necrotic, proteinaceous)



67

Invasive Endocervical Adenocarcinoma: Cytologic Features

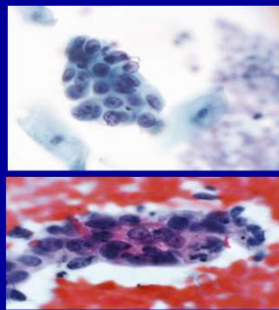
- Abundant Cellularity
- Flat or three Dimensional Sheets
- Many Features of AIS
- Discohesion More Common- Single cells
- Frequent macro nucleoli
- Decreased, finely vacuolated cytoplasm



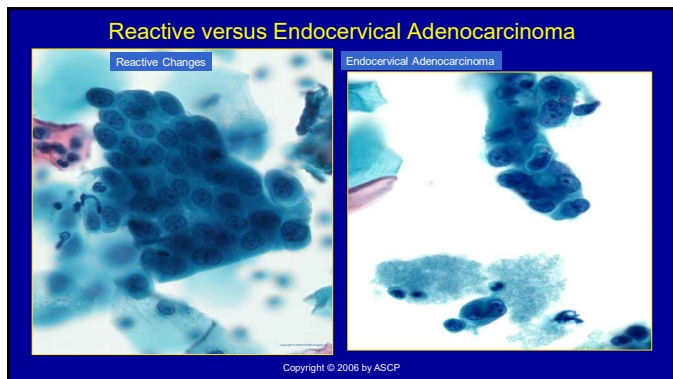
68

Invasive Endocervical Adenocarcinoma: TBS Cytologic Features

- Increasing N:C
- Enlarged pleomorphic nuclei, nuclear irregularity unevenly distributed chrom. Chromatin clearing.
- Necrotic tumor diathesis LBC: may have "clinging diathesis"



69



70

- 1- Tumor Histology (WHO classification 2014) or IECC
- Endocervical Carcinoma, usual type
 - Mucinous carcinoma, NOS
 - Gastric type
 - Intestinal type
 - Signet-ring cell type
 - Villoglandular carcinoma
 - Endometrioid carcinoma
 - Clear cell carcinoma
 - Serous carcinoma
 - Mesonephric carcinoma
 - Adenocarcinoma admixed with neuroendocrine carcinoma

71

Endocervical Glandular Lesions Exhibiting Gastric Differentiation

- Unrelated to HPV
- Contain neutral mucin (stain predominantly red with combined Alcian-blue/PAS)
- Immunohistochemically positive with HIK1083 or other antibodies that react against pyloric-type gastric mucins

72

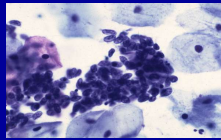
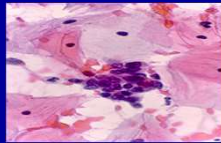
72

Endometrium

76

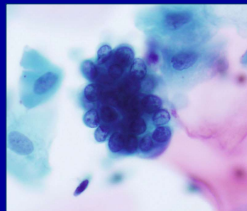
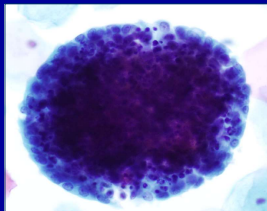
TBS 2001: Endometrial Cells

- Report in all women 40 or older (0.5% to 1.8% of Paps)
- Tight 3-D clusters, loose clusters, or single cells
- Bean-shaped nuclei
- Nucleoli and chromatin pattern more apparent
- Cytoplasmic vacuoles

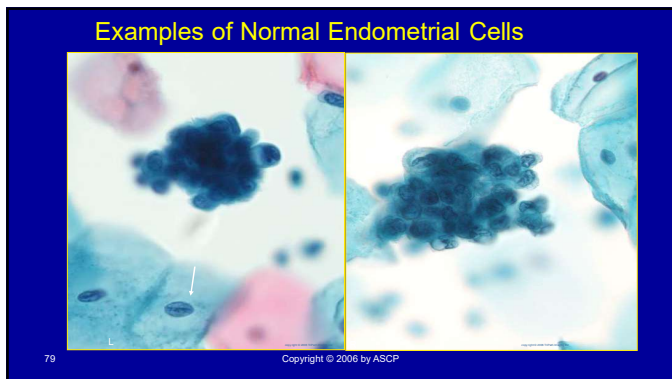


77

Benign Endometrial Cells



78



79

TBS 2014: What has changed

- Report benign-appearing endometrial cells for women ≥ 45 years
- TBS-2001
 - Because menopausal status is often unclear, inaccurate, or unknown to the laboratory, suggested reporting in women aged 40 years to maximize the likelihood of including all postmenopausal women and that clinical correlation should be left to the ordering physician's discretion
- TBS-2014
 - To increase the predictive value of this category, cytologically "benign-appearing" endometrial cells should be reported in women aged 45 years, and the suggested educational note should specify that endometrial evaluation be done only in postmenopausal women.

80

TBS 2014: Sample Report

- Endometrial cells are present in a women 45 years and older
- Negative for squamous intraepithelial lesion

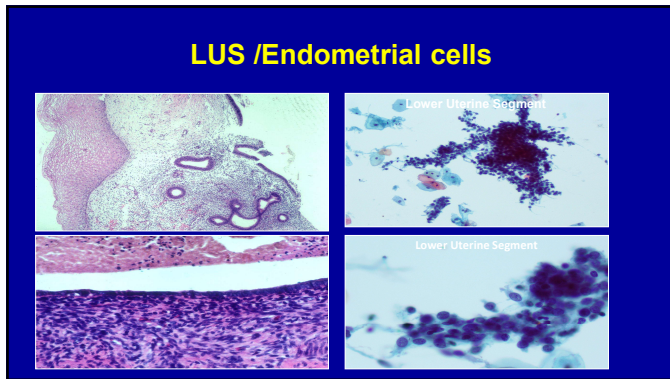
Or

- Endometrial cells correlate with menstrual history

Note: Endometrial cells in women 45 years or older may be associated with benign endometrium, hormonal alterations, and less commonly endometrial uterine abnormalities. Endometrial evaluation is recommended for post menopausal women.

Note: Menopausal status is often unclear, inaccurate, or unknown to the Lab. Mean age in USA 51 years but the coefficient variation is large.

81



82



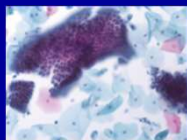
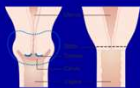
83

Negative for Intraepithelial Lesion or Malignancy - Lower Uterine Segment

- Biphasic appearance (glandular and stromal)
- Liquid-based preps – smaller branching cell fragments
- Stromal cells have matrix and penetrating capillaries
- Disordered bland, oval to elongated nuclei
- Glandular cells are slightly oval and crowded with small nuclei and bland chromatin.
- Occasional mitotic figures and peripheral nuclear palisading

84

Cytologic Findings After Fertility-sparing Radical Trachelectomy



Frequently contain glandular cells from the lower uterine segment epithelium or endometrial stromal cells, which can lead to a misdiagnosis of atypical glandular cells of undetermined significance. Tubal metaplasia is also a potential pitfall in these specimens. Pathologists and gynecologic oncologists should be aware of the potential pitfalls in the surveillance of smears after trachelectomy.

Parabon R 2008_008 25.114(1)14

85

Epithelial Cell Abnormality Atypical Endometrial Cells

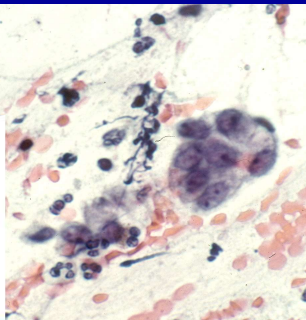
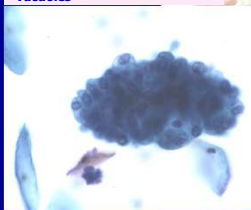
- Glandular cells are in small groups (5-10 cells per cluster) with vacuolated cytoplasm
- Nuclei are slightly larger than normal endometrial cells (>intermediate squamous cell nucleus)
- Ill-defined cell borders
- Small nucleoli
- It can be difficult to distinguish atypia of atypical hyperplasia from a well-differentiated endometrial adenocarcinoma

86

Atypical Endometrial Hyperplasia

(conventional & LBP)

- 3-D clusters
- Slight nuclear enlargement
- Mild hyperchromasia
- Presence of nucleoli
- Vacuoles



87

Atypical Endometrial Cells: Differential

- Endometrial polyps
- Chronic endometritis
- Intrauterine device changes
- Endometrial hyperplasia
- Adenocarcinoma

88

Atypical Endometrial Cells

Small groups (5-10 cells)
 Ill-defined cell borders
 Enlarged nuclei (>1CN)
 •Slight nuclear hyperchromasia
 •Small nucleoli
 •Cytoplasm occasionally vacuolated

89

Atypical Endometrial Cells: Management

```

    graph TD
      A[Initial Workup of Women with Atypical Glandular Cells (AGC)] --> B[All Subcategories (except atypical endometrial cells)]
      A --> C[Atypical Endometrial Cells]
      B --> D[Colposcopy with endocervical sampling and HPV DNA testing, and Endometrial Sampling (if patient at high risk for endometrial cancer)]
      C --> E[Endometrial and Endocervical Sampling]
      E --> F[NO Endometrial Pathology]
      F --> G[Colposcopy]
  
```

90

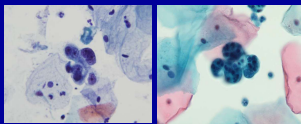
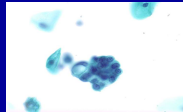
Endometrial Adenocarcinoma

- Most common invasive carcinoma of female genital tract
- Detection dependent on spontaneous exfoliation of cells or extension into LUS or endocervix
- Conventional and liquid-based preparations detect ~ 38 - 65%

91

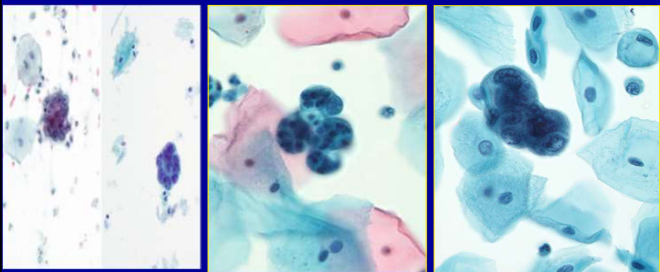
Endometrial Adenocarcinoma

- Single or small loose or tight clusters - HCD
- Pleomorphism in size and shape
- Nuclear size increase with FIGO grade.
- Anisonucleosis with unevenly distributed chromatin.
- Prominent nucleoli
- Small amount of vacuolated cytoplasm/intra-cytoplasmic neutrophils
- May have watery diathesis



92

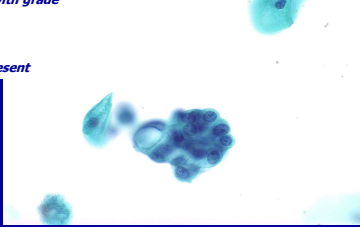
Examples of Endometrial Adenocarcinoma



93

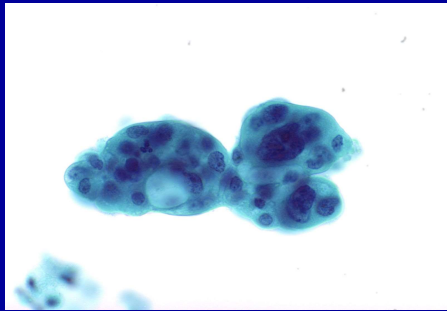
Well-differentiated Endometrial Adenocarcinoma (LBC)

- Cell may be single or in small loose clusters
- Slight increase in nuclear size >ing with grade
- Variation in nuclear size and polarity
- Nucleoli present
- Scant cytoplasm, vacuoles maybe present



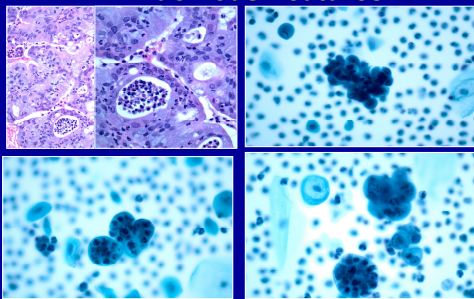
94

Endometrial adenocarcinoma (LBC)

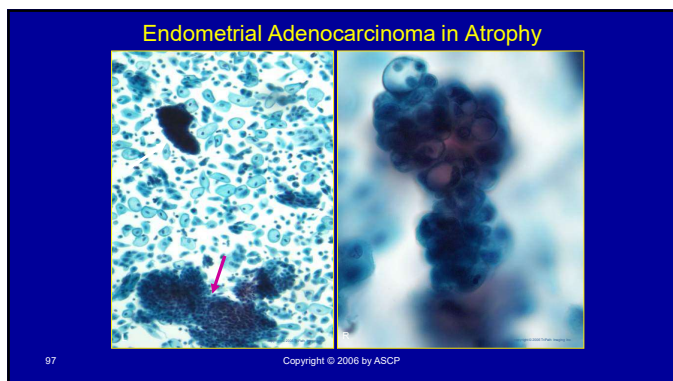


95

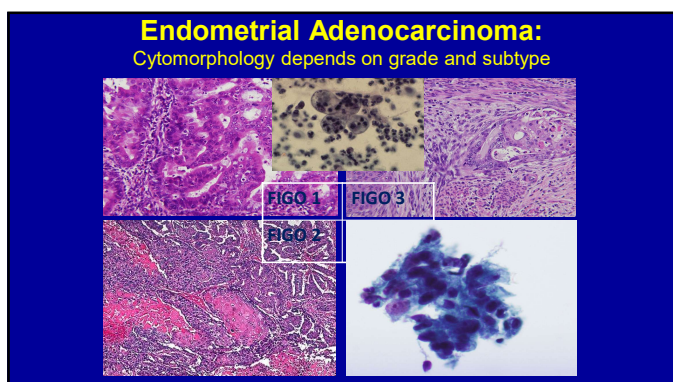
Endometrial Adenocarcinoma with Mucinous Features



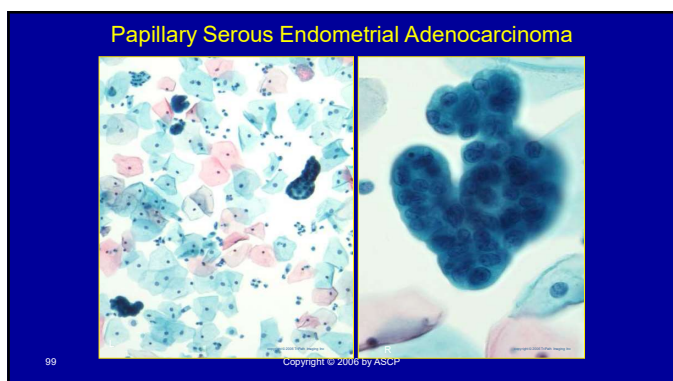
96



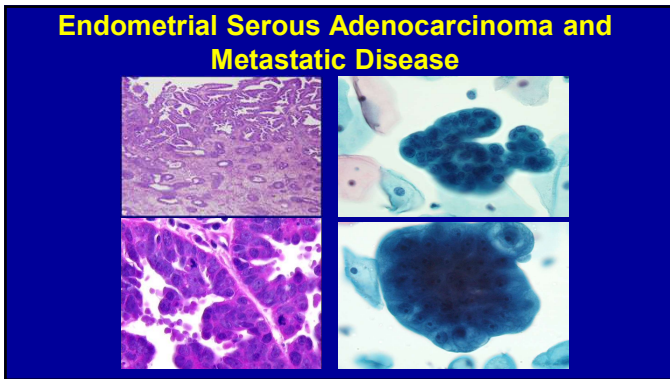
97



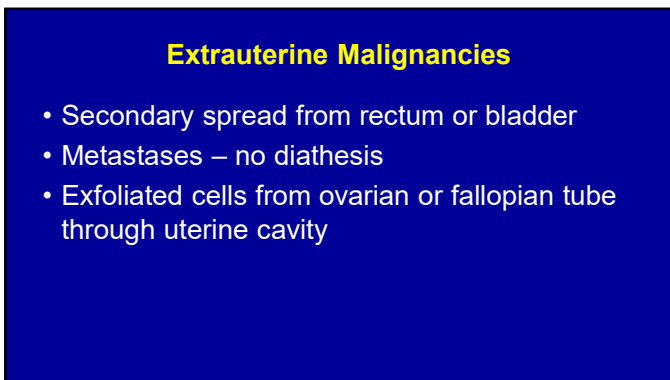
98



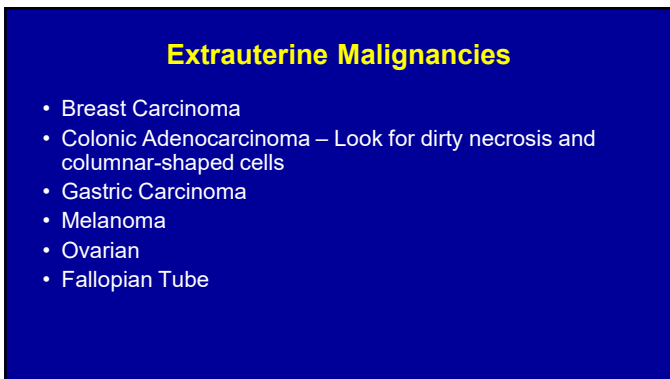
99



100

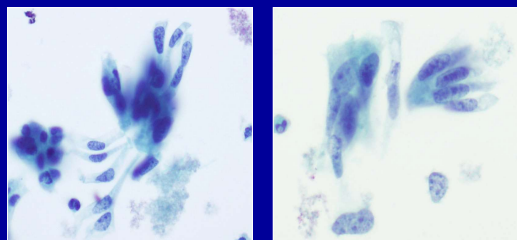


101



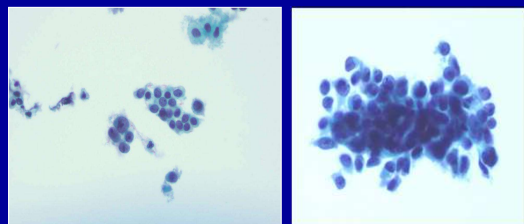
102

Metastatic Colorectal Adenocarcinoma



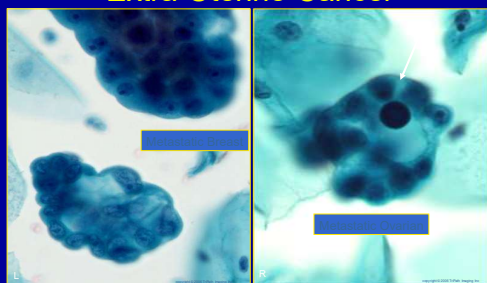
103

Metastatic Breast Carcinoma

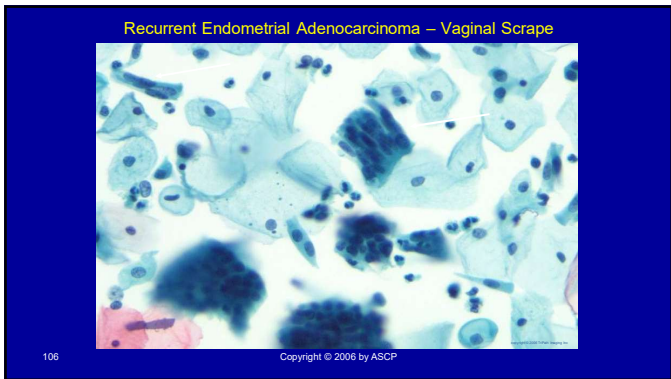


104

Extra-Uterine Cancer



105



106