

Gynecologic Cytology

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INTERNATIONAL ACADEMY OF CYTOLOGY
CHAIR CYTOTECHNOLOGIST EXAM

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BUFFALO, NY, USA



THE
INTERNATIONAL
ACADEMY
OF
CYTOLOGY

Educational Objectives

- Identify and describe diagnostic pitfalls in the evaluation of gynecologic (liquid based) specimens relating to glandular lesions and challenging hyperchromatic crowded groups.
- Illustrate the cytomorphologic differences in liquid-based preparations of benign and neoplastic squamous and glandular lesions in gynecologic cytology.
- Define cytomorphologic criteria for gynecologic lesions presenting as hyperchromatic crowded groups.

Cervical Cancer

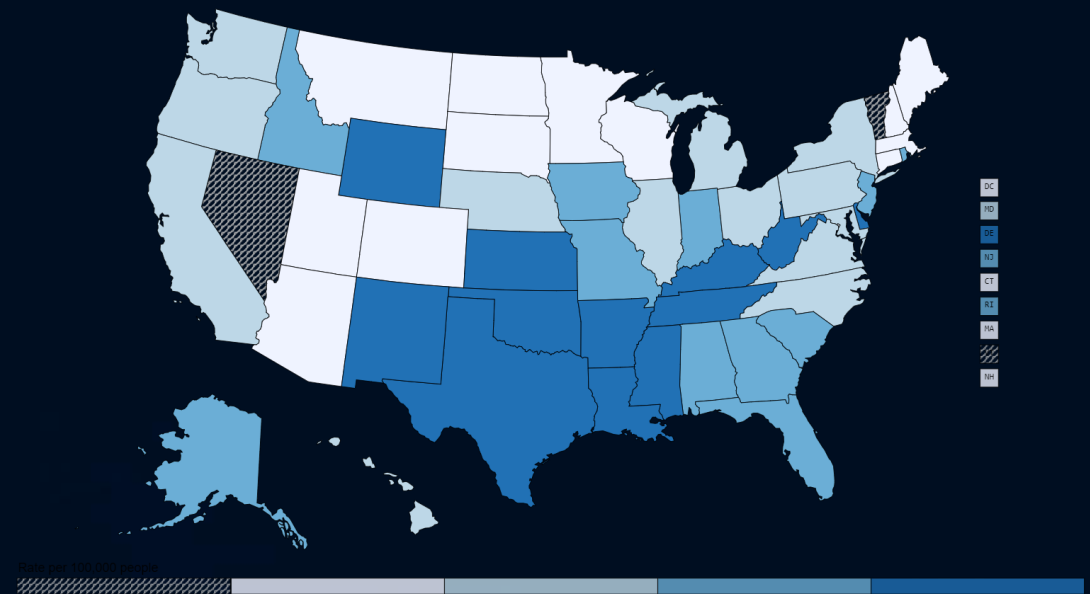
The Pap test decreased cervical cancer incidence and mortality by at least 80%



American Cancer Society Statistics

2023 Cervical Cancer Statistics

- 13,960 new cases diagnosed
- 4,310 deaths



More than

600 000

women were diagnosed with
cervical cancer



and more than

340 000

deaths were caused by
cervical cancer in 2020

Cervical cancer

was the **7th** most common
cancer in the **world**



and the **4th**
most common
cancer among
women in 2020.



Cervical cancer
was the **9th** most
common **cause of**
cancer death
in the world

and the **4th**
most common

cause of cancer death
among women in 2020

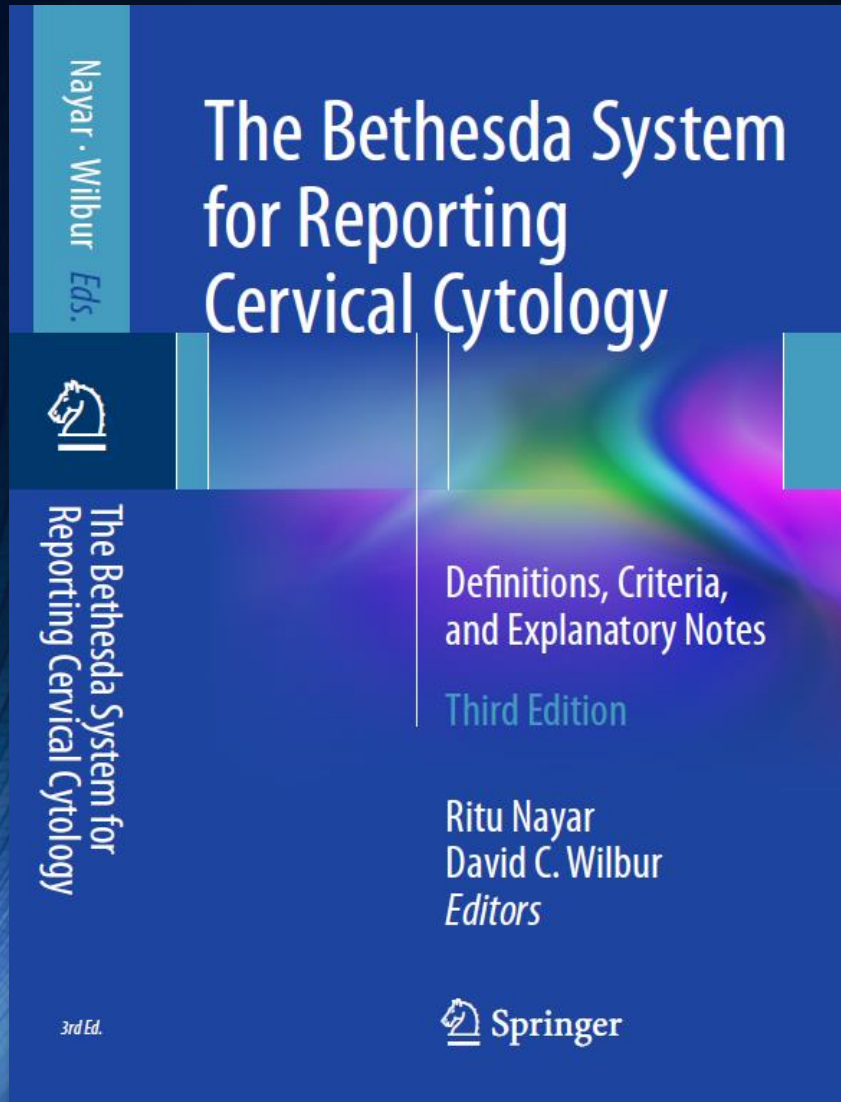


In 2020, cervical cancer was one of the most common gynaecological cancers, and the ninth leading cause of cancer-related mortality in women worldwide



References | 1. World Health Organization International Agency for Research on Cancer. Cancer Fact Sheets – Cervix uteri. Available at: <https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf>. Accessed January 2021. 2. World Health Organization. Cervical cancer. Available at: https://www.who.int/health-topics/cervical-cancer#tab=tab_1. Accessed January 2021.

Bethesda 2014 Atlas



www.cytopathology.org

<http://www.springer.com/us/book/9783319110738>

Bethesda System

for Reporting
Cervical Cytology
2014: Online Atlas



Introduction

SEARCH

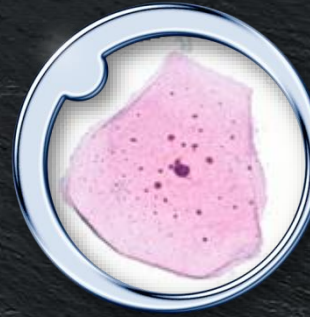
SELF-TEST

BIRST-2

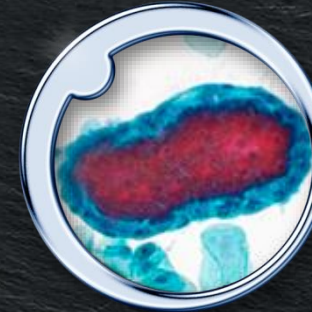
Donate Image



Adequacy



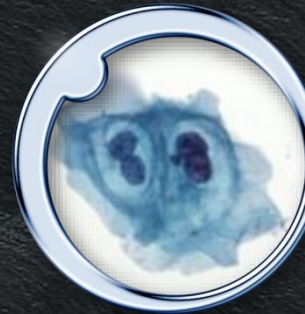
Non-neoplastic



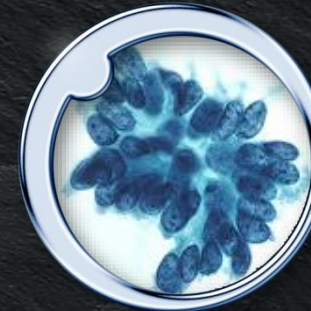
Endometrial > 45



ASC-US/ASC-H



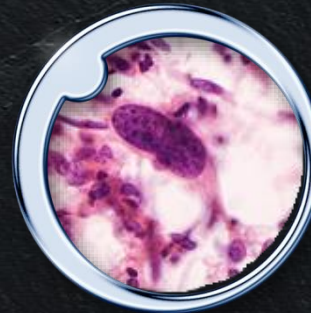
Epithelial Abnormalities
Squamous



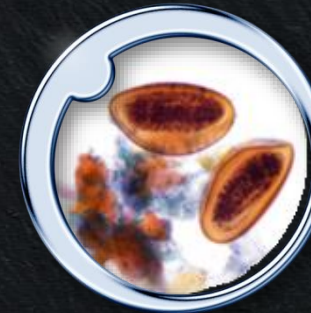
Epithelial Abnormalities
Glandular



Adjunctive Testing



Other Malignant
Neoplasms



Anal Cytology

Squamous Reference Nuclei

35

- Normal intermediate cell (X)

50

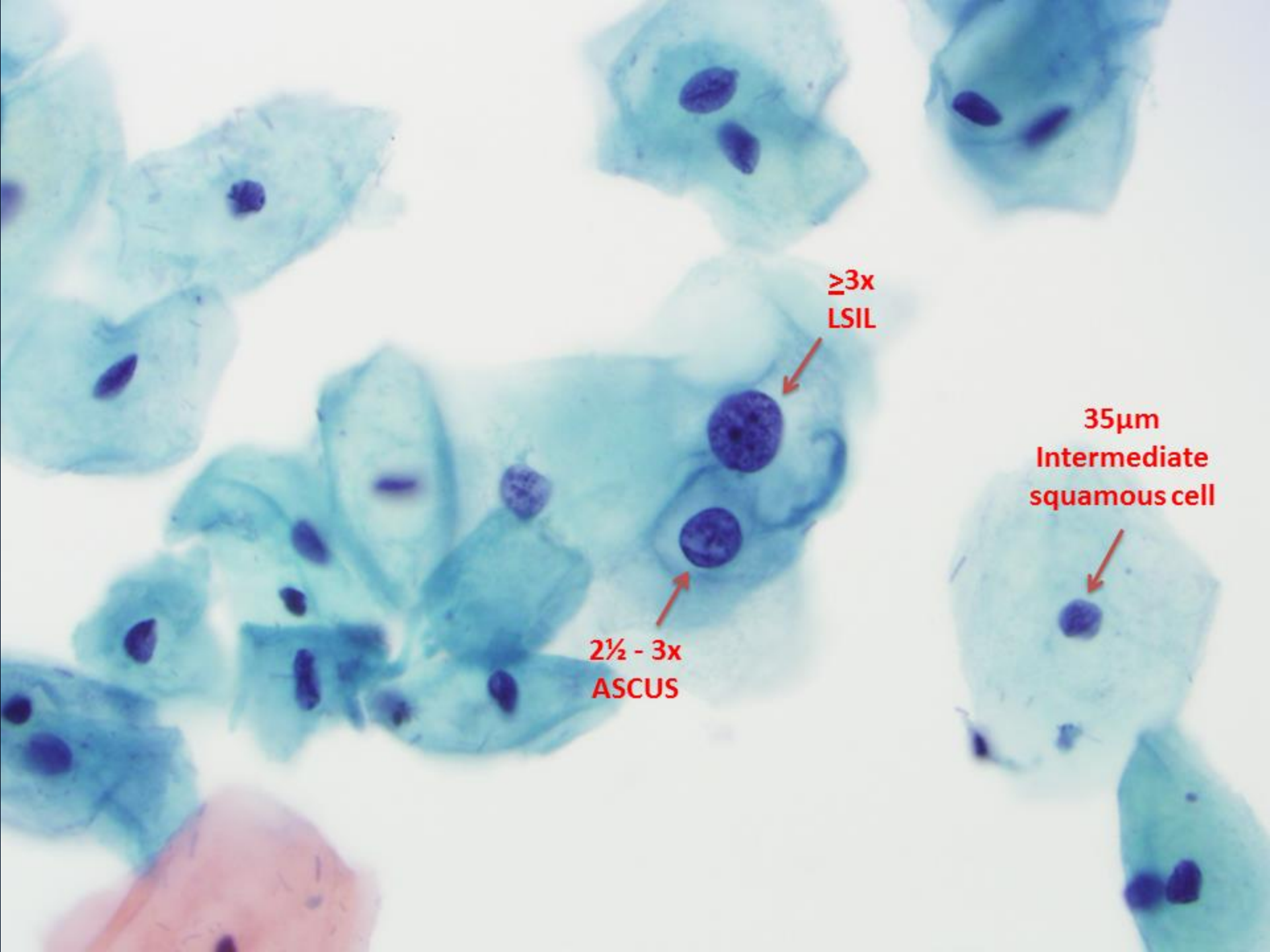
- Normal squamous metaplastic cell

90-
100

- ASC-US (2.5-3X)

>105

- LSIL ($\geq 3X$)

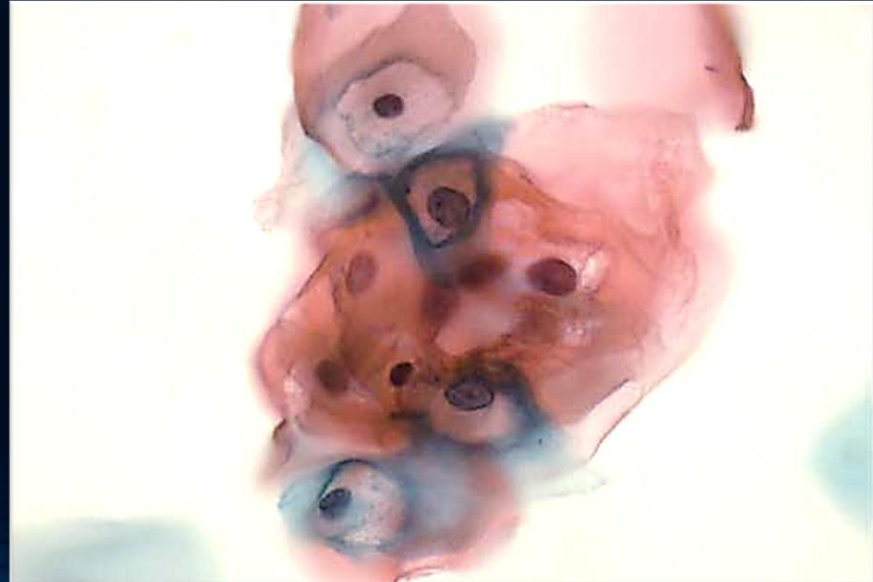
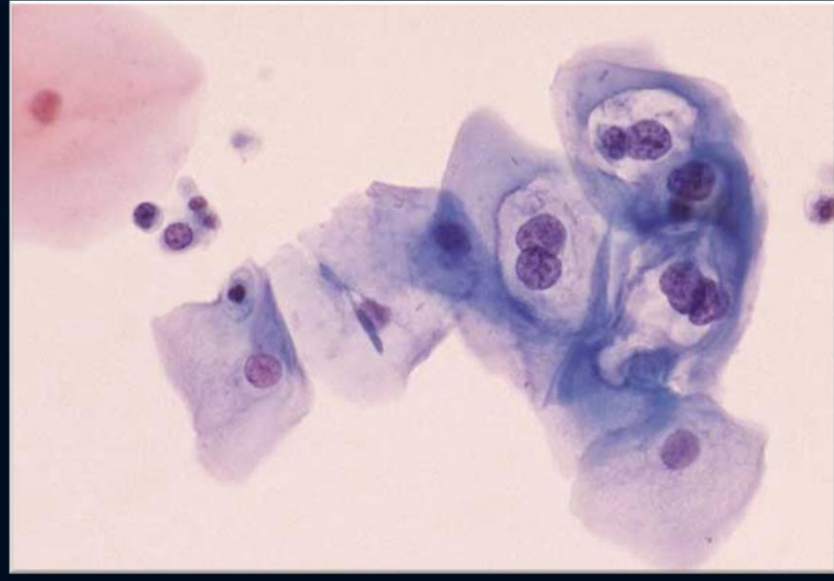
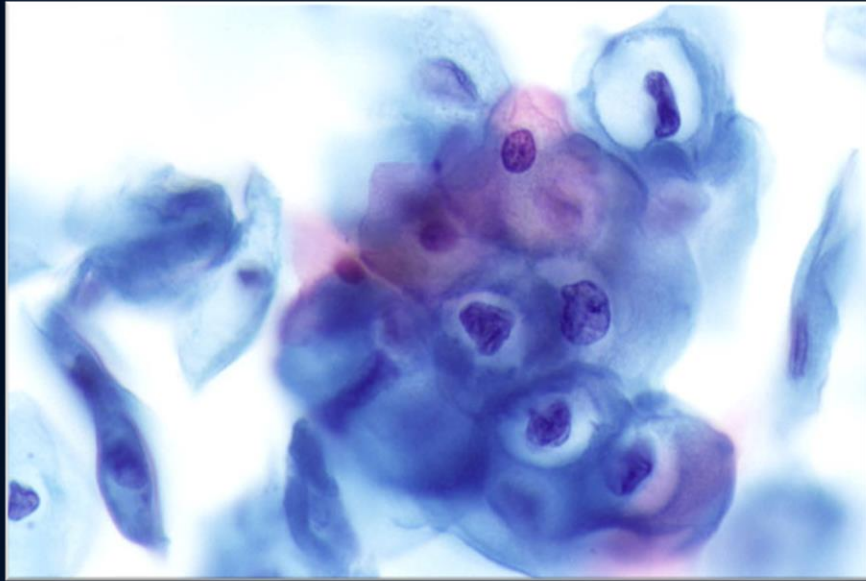


**≥3x
LSIL**

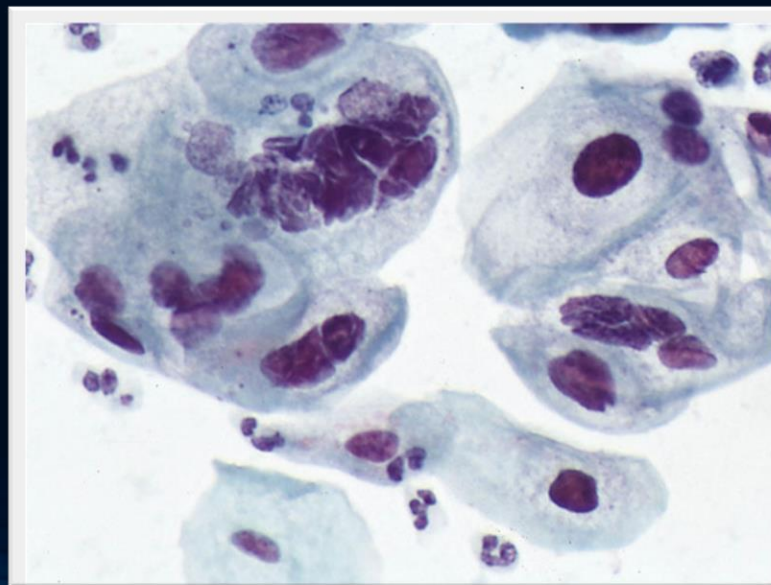
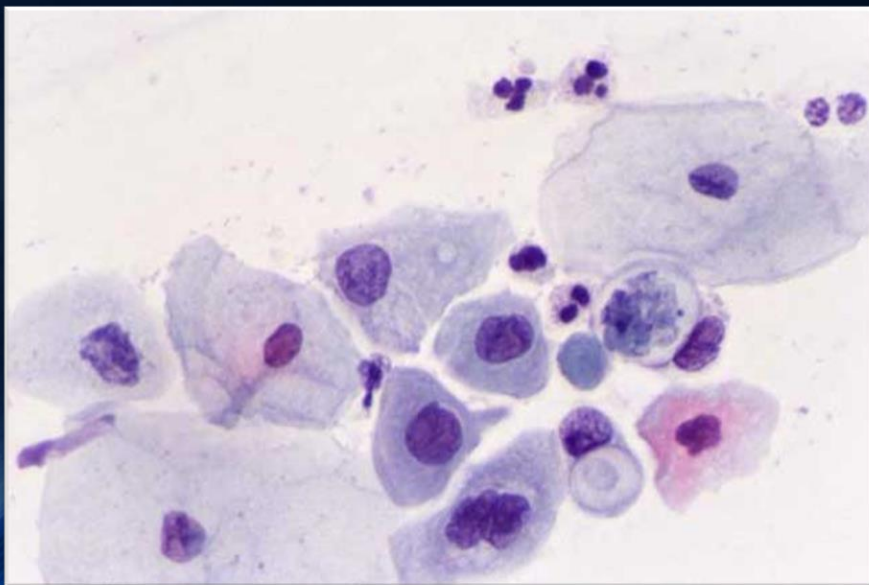
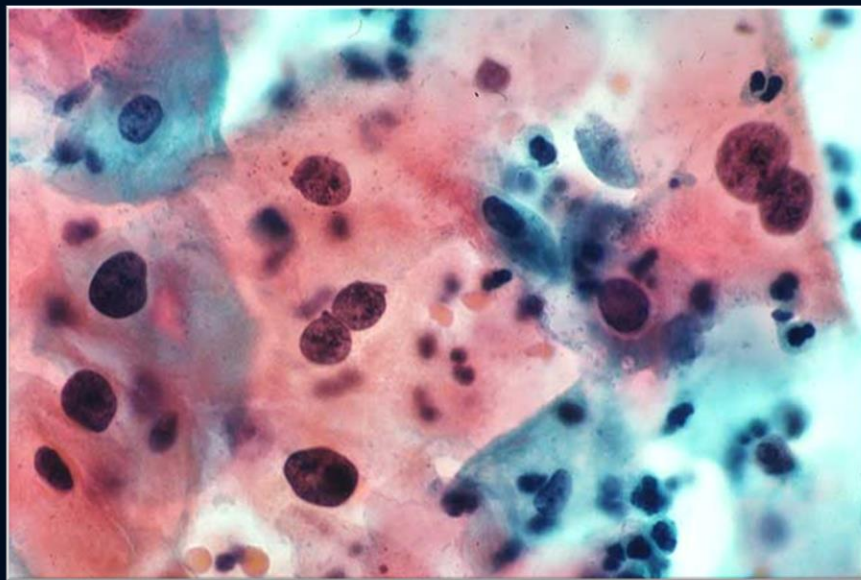
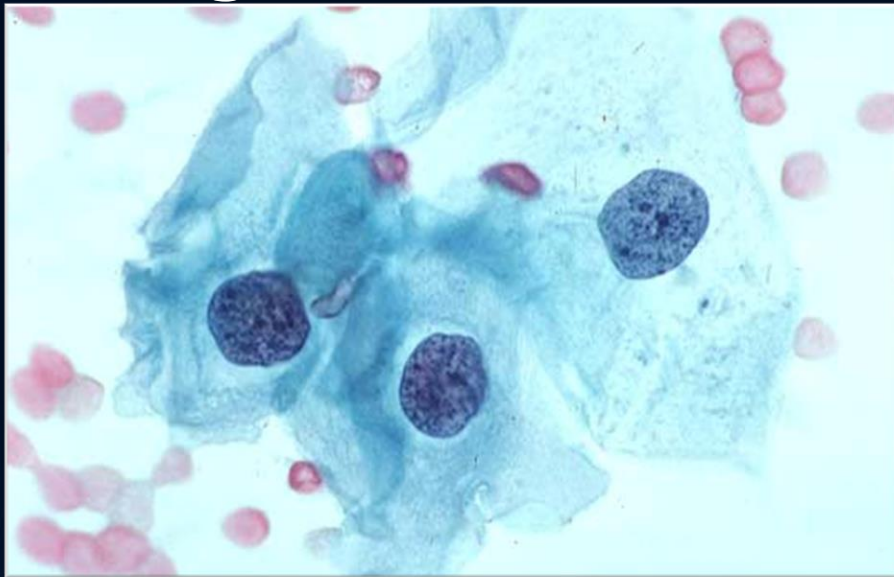
**35µm
Intermediate
squamous cell**

**2½ - 3x
ASCUS**

LSIL

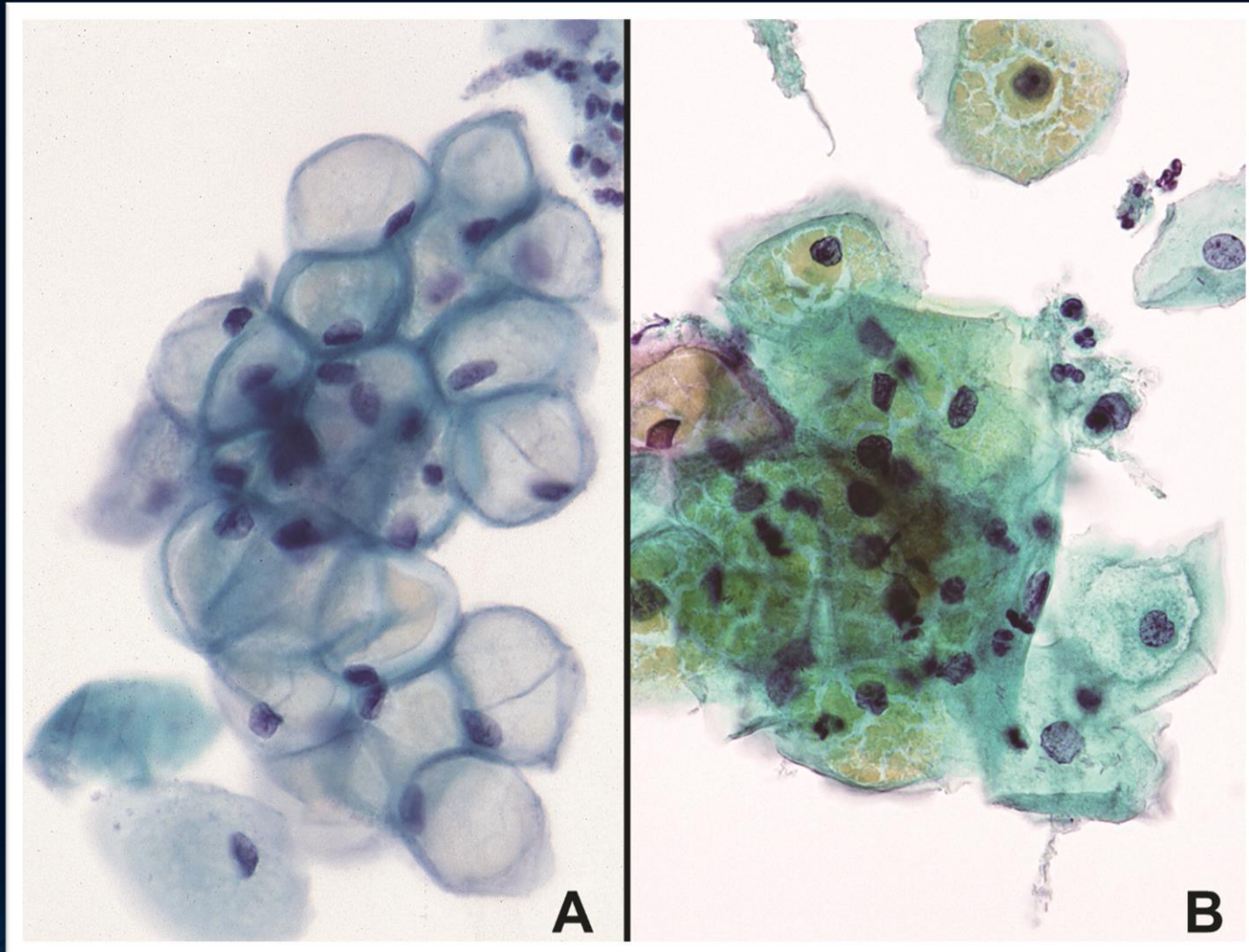


LSIL

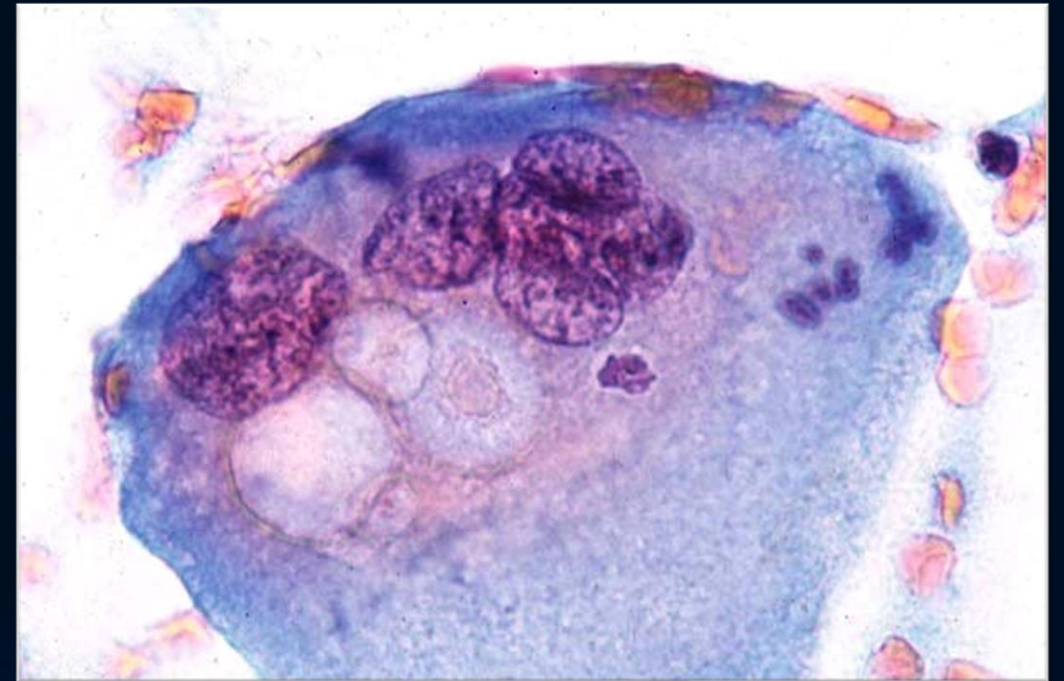
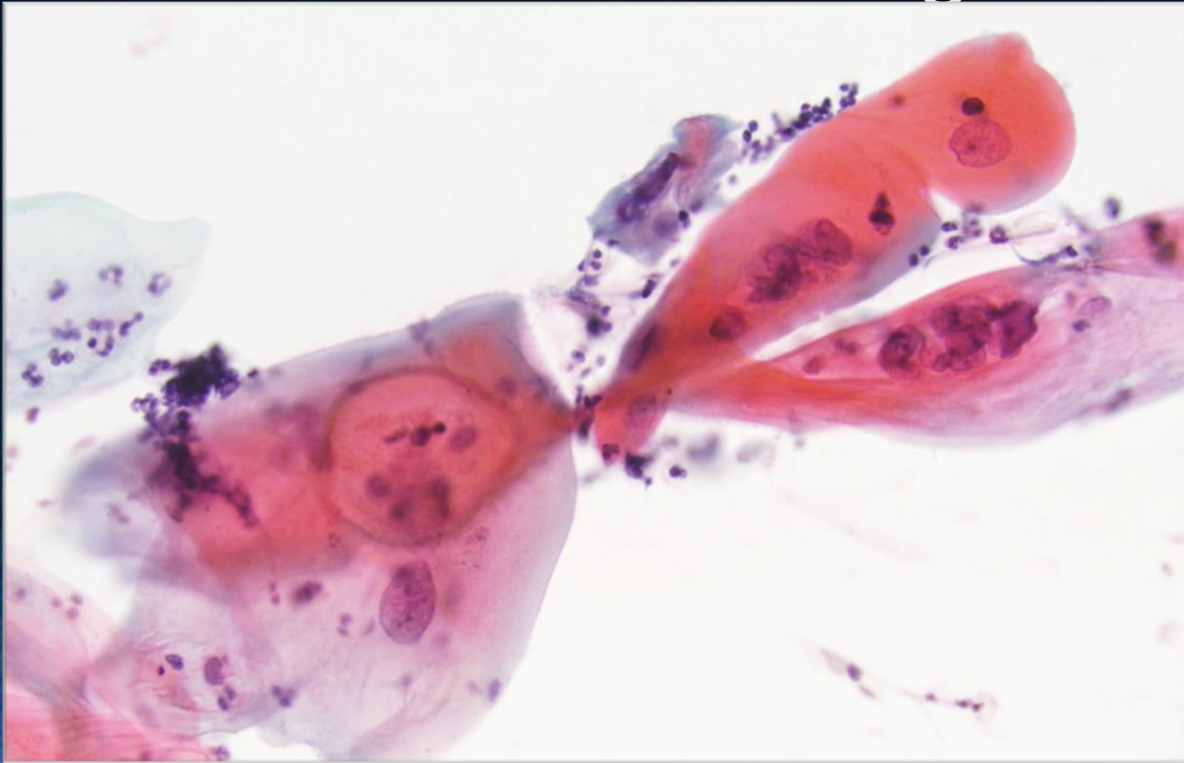


Mimics of LSIL

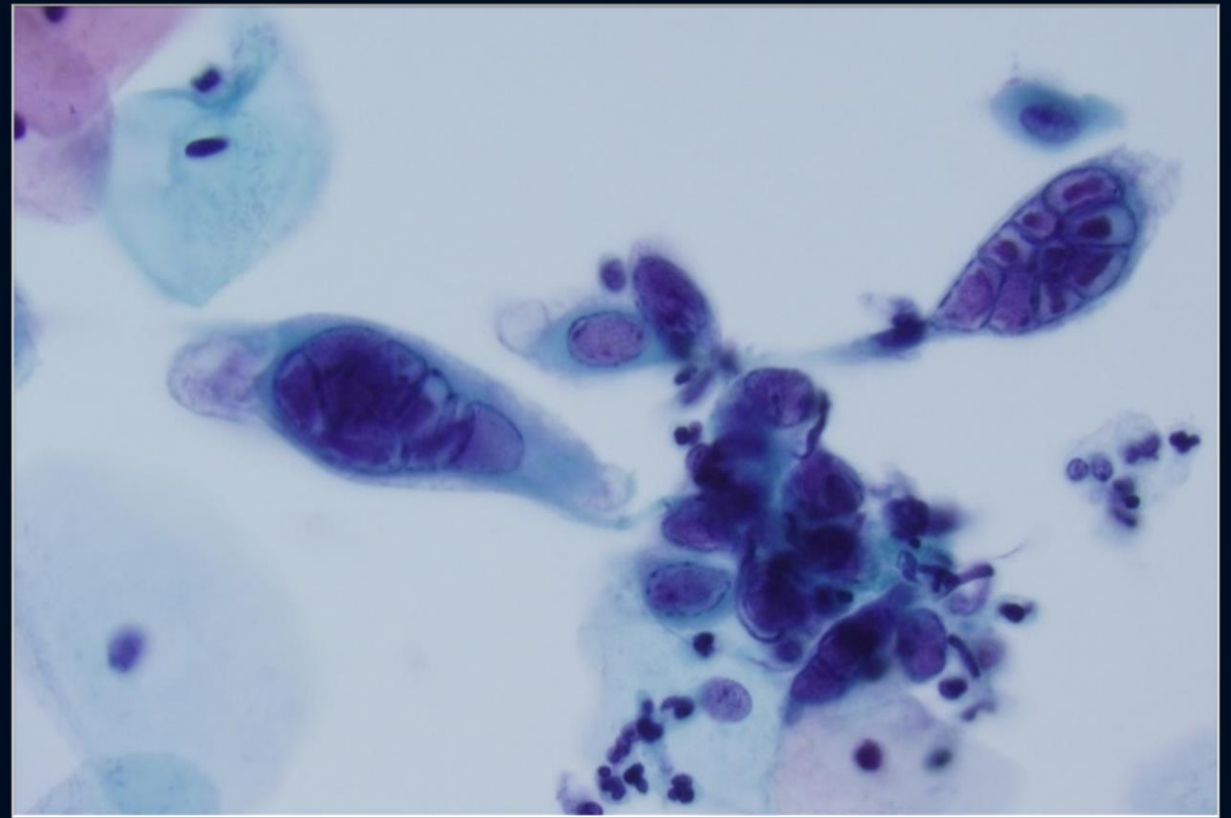
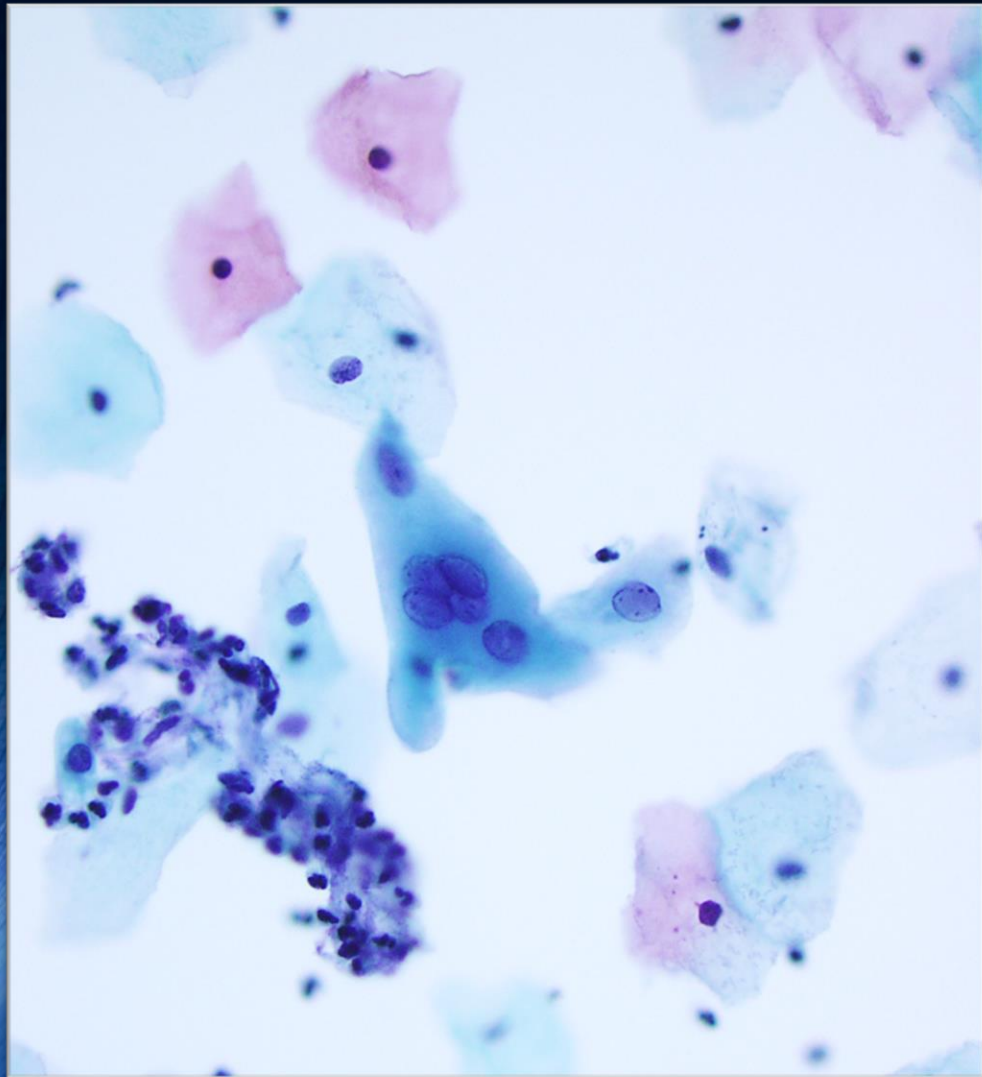
Pseudokoilocytes – Glycogen



Radiation Changes

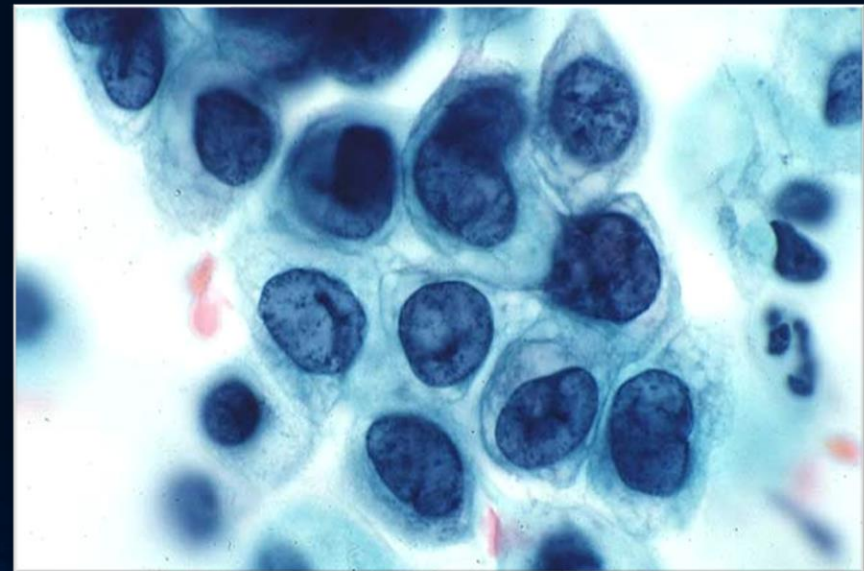
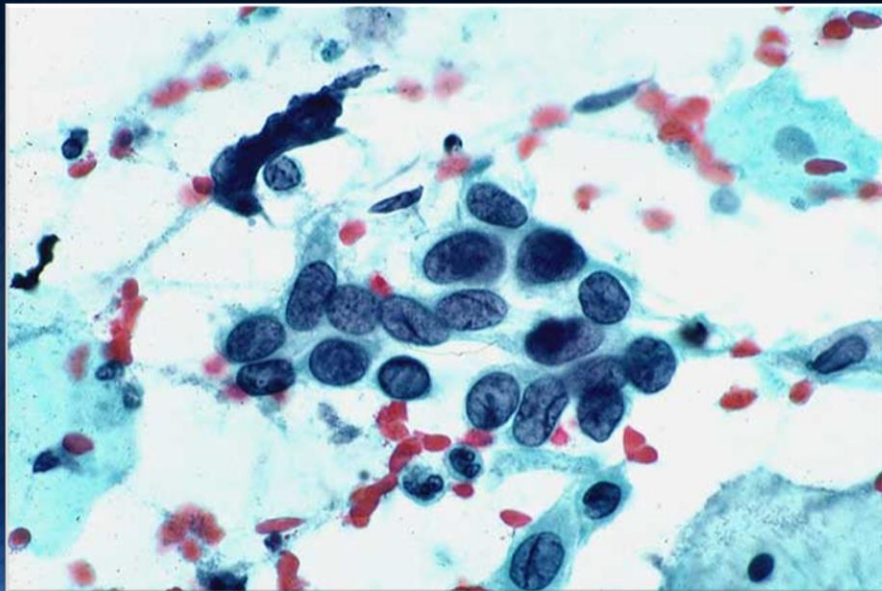
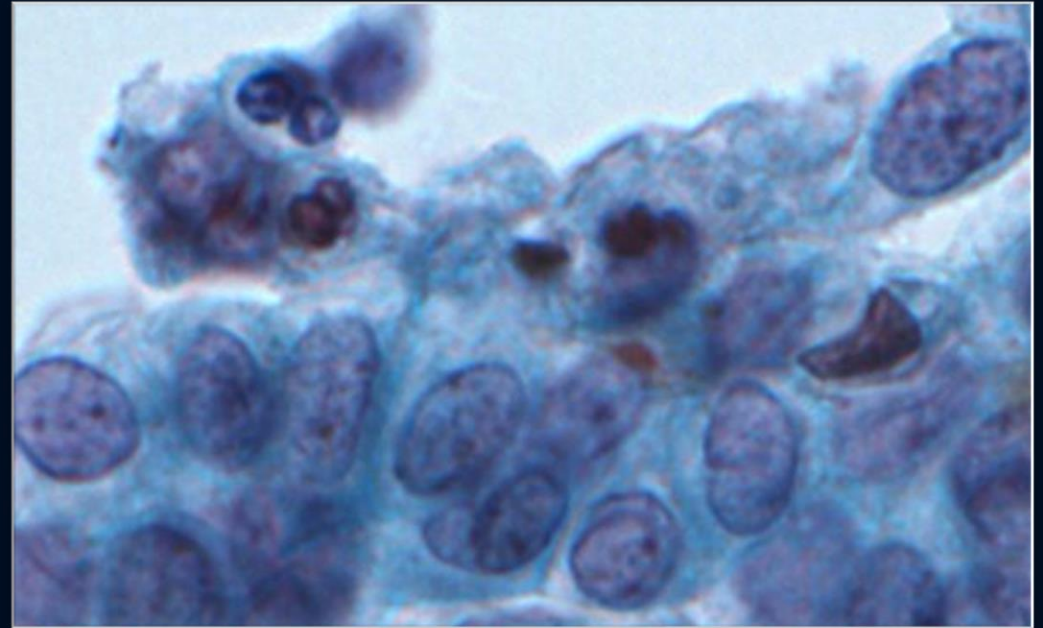


Herpes Simplex Virus



HSIL

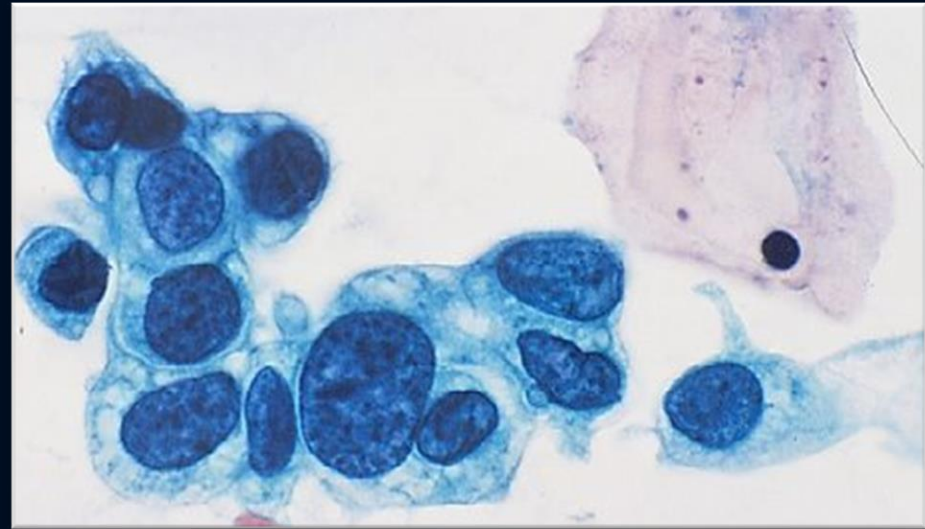
- Nuclear size, shape and chromasia varies
- Nuclear membranes frequently irregular



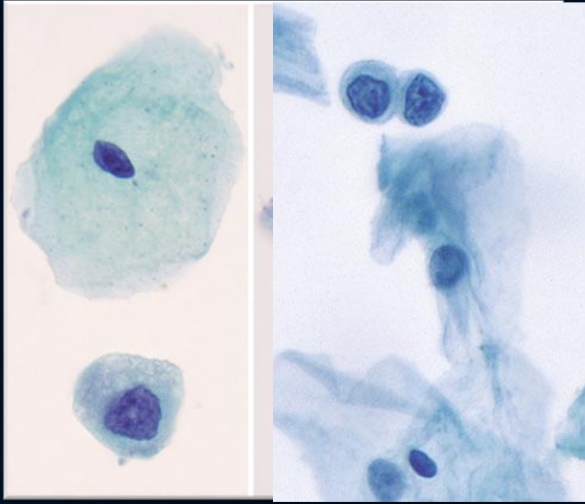
HSIL

Cytoplasm is variable

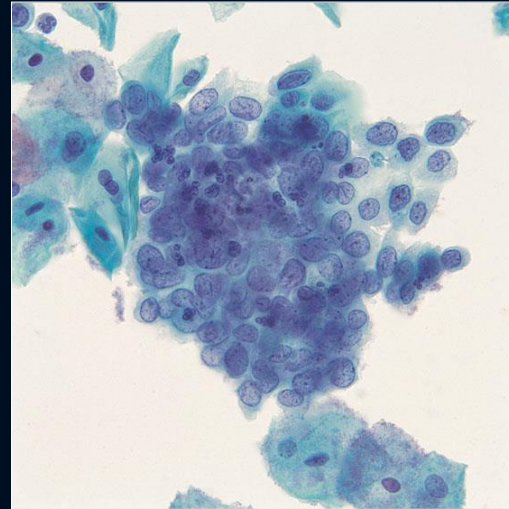
- Immature/ lacy and delicate
 - Distinguish from histiocytes
- or
- Densely metaplastic
 - Distinguish from immature squamous metaplasia



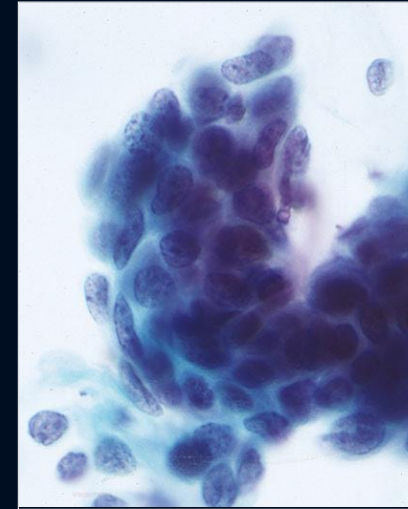
Squamous Epithelial Lesions: HSIL Patterns



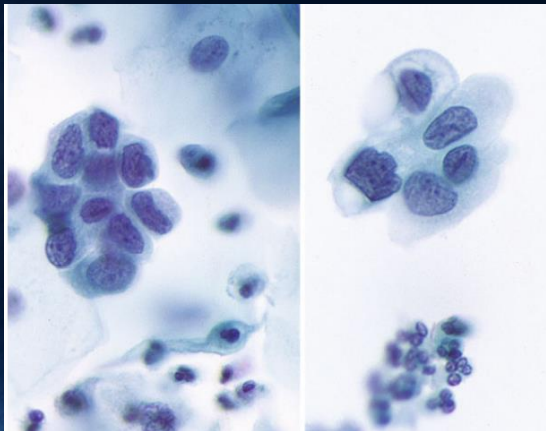
HSIL- single cell



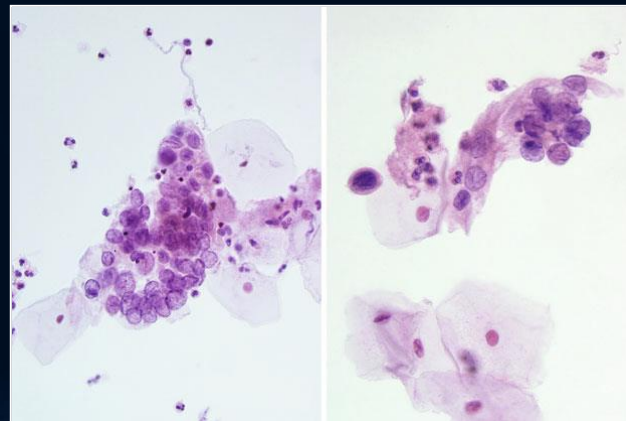
HSIL- syncytial (HCG)



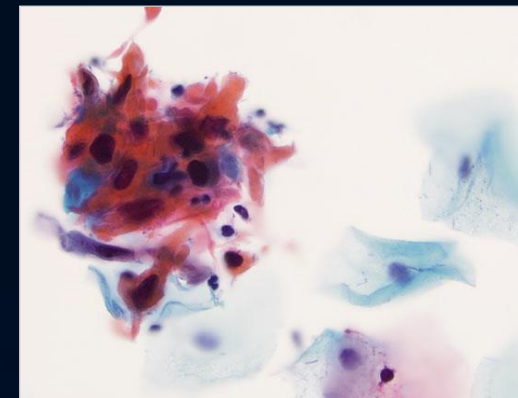
HSIL- with endocervical gland involvement



HSIL- Small cell groups



**HSIL- hypochromatic,
HSIL- stripped nuclei**

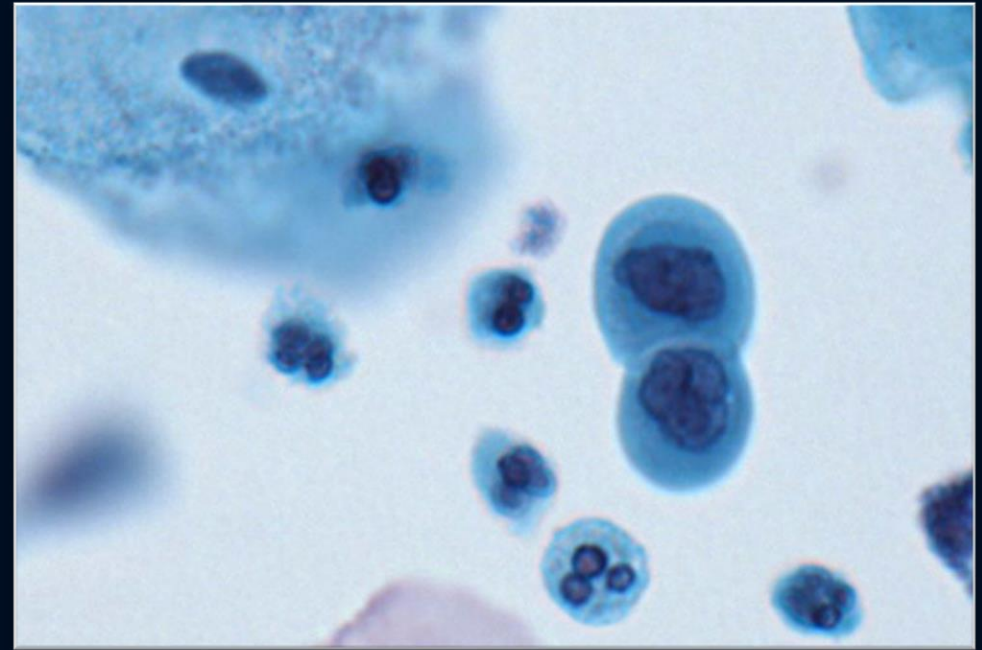


HSIL- keratinizing

HSIL

Single cell pattern

- Isolated cells or small groups
- High N:C ratio
- Irregular nuclear membrane
- Granular chromatin, variable chromasia
- **No nucleoli**



Benign Mimickers of HSIL

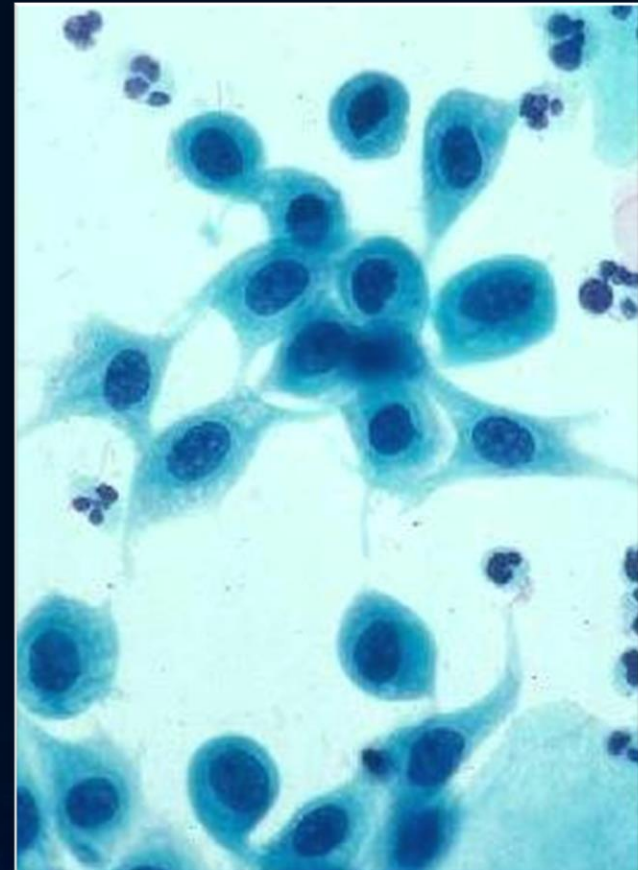
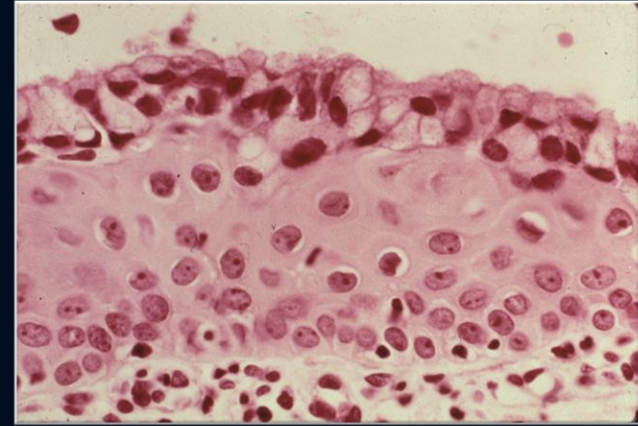
single cell pattern

1. Squamous immature and mature metaplasia
2. Normal endocervical/ endometrial cells
3. Inflammatory cells
4. IUD Change

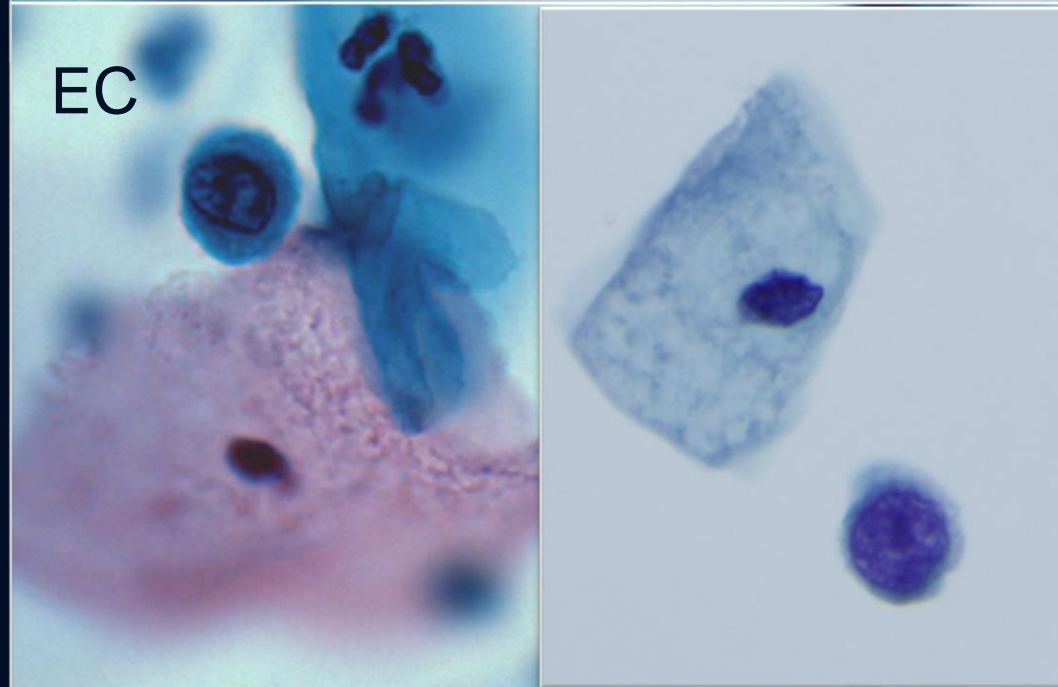
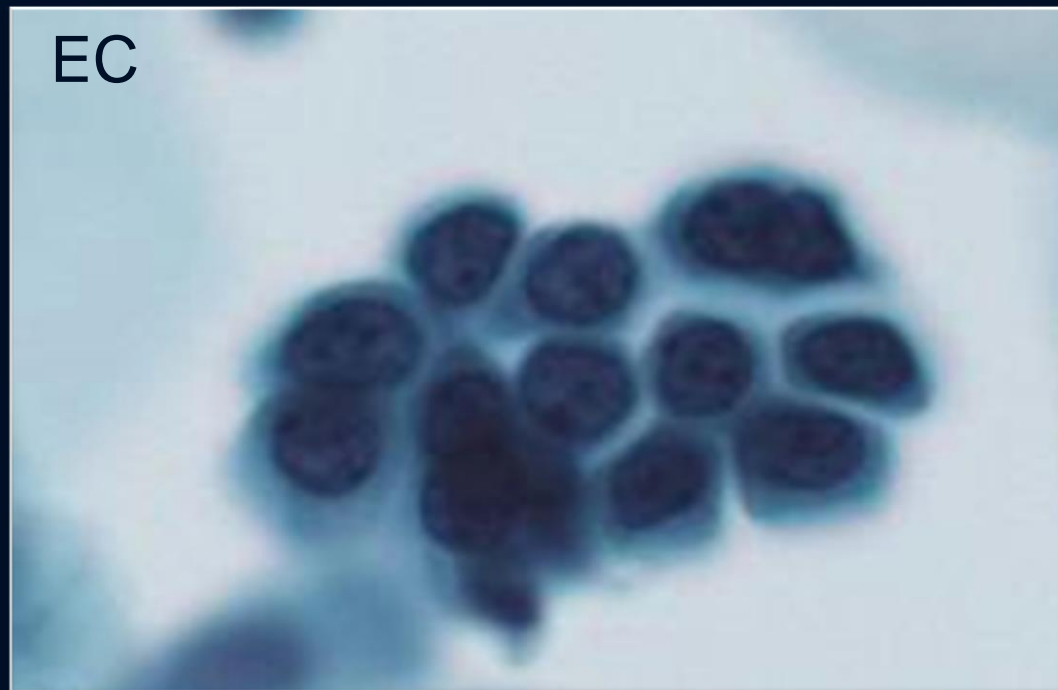
.....can lead to overcall as ASC-H, if not HSIL

Squamous metaplasia

- Squamous metaplastic cells can cause concern for HSIL
- N:C ratio of $<50\%$, smooth nuclear contours, and even distribution of chromatin favor benign squamous metaplasia
- Degeneration can cause nuclei to be hyperchromatic/ wrinkled

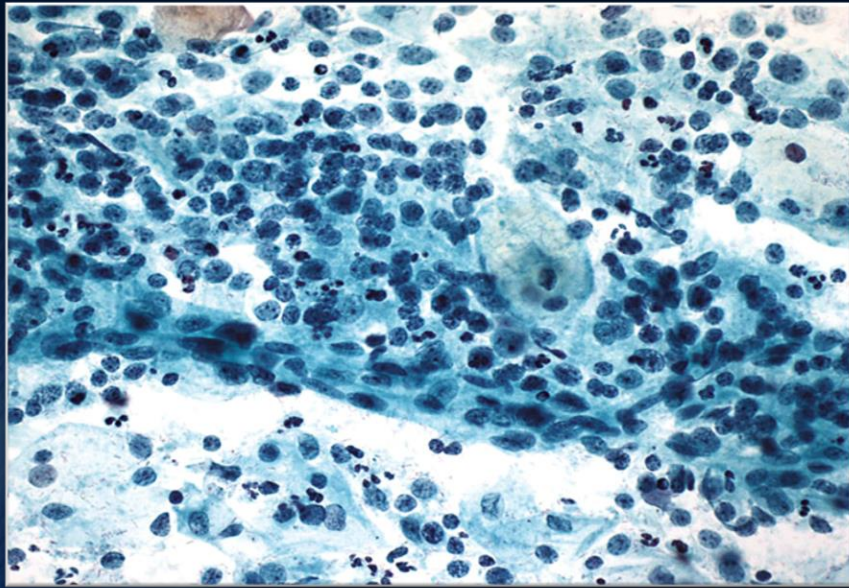


EM/ EC Cells

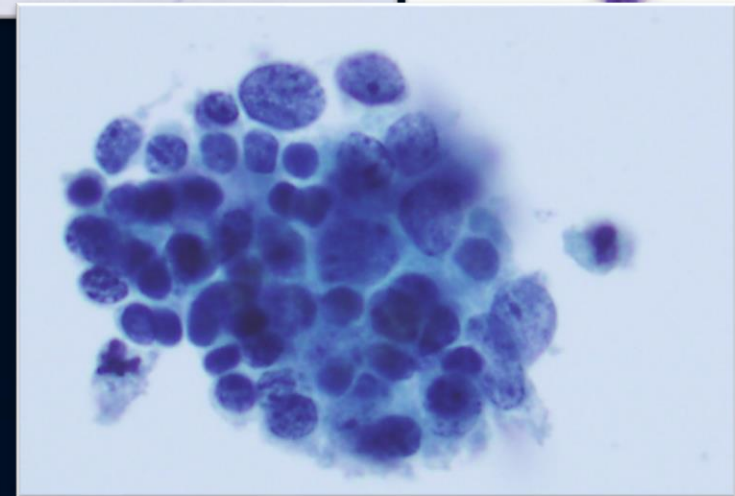
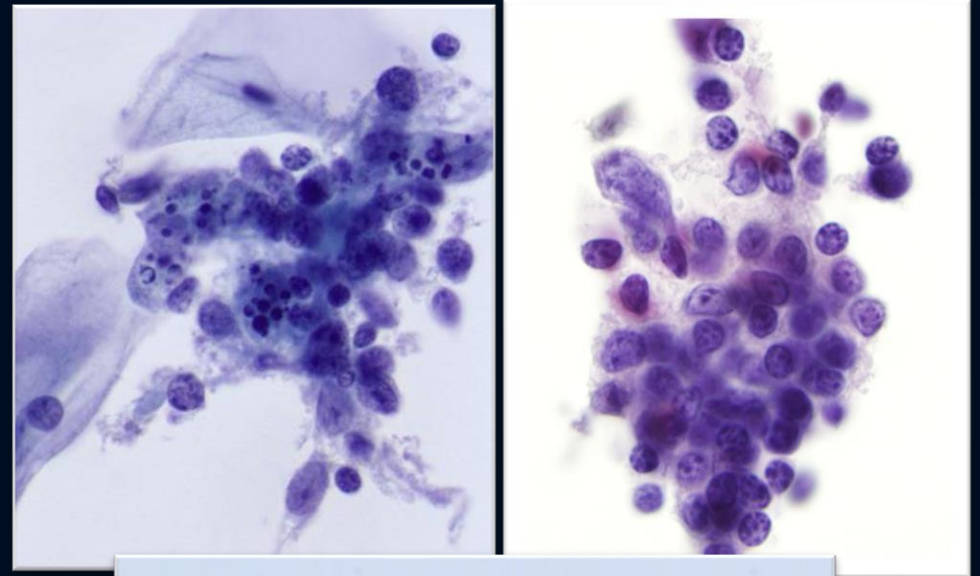


Lymphocytic (Follicular) Cervicitis

- Polymorphous population of lymphocytes, with or without tingible body macrophages

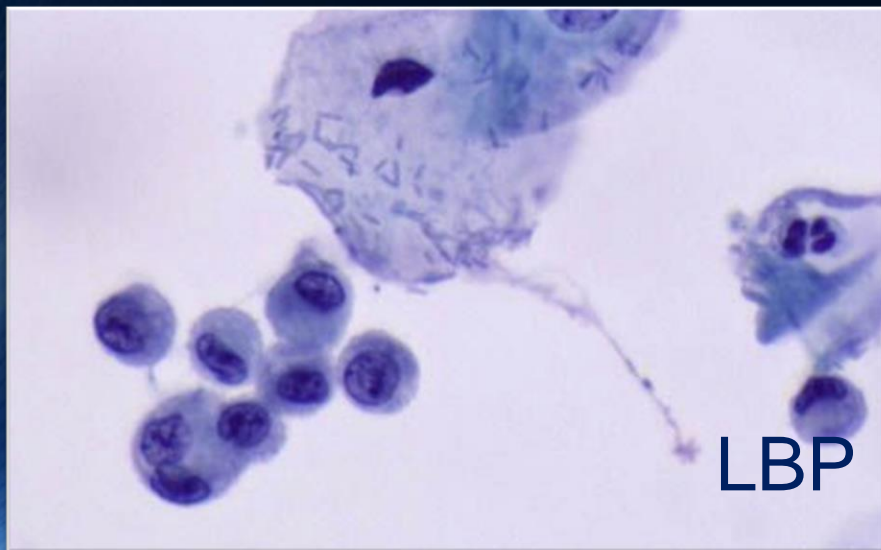
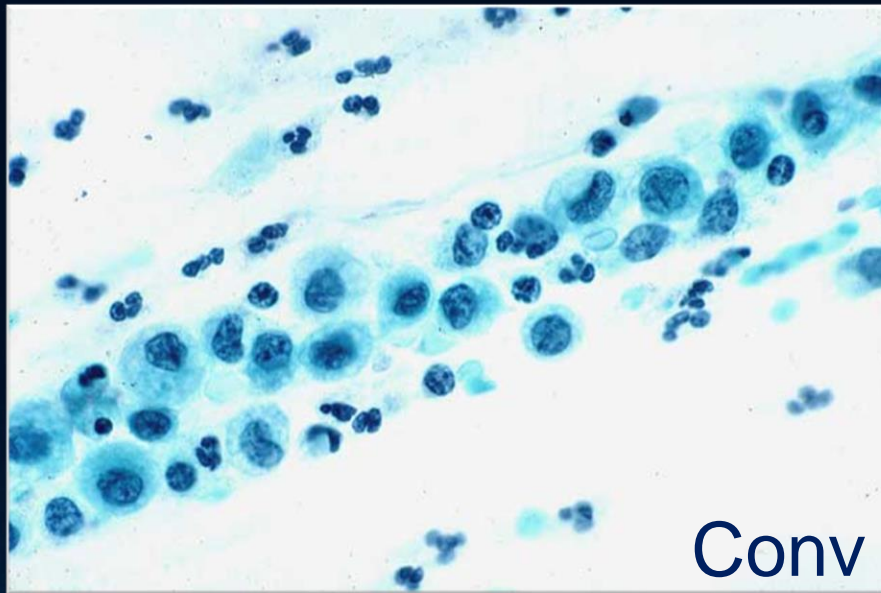


Conventional preps- in clusters or streaming in background

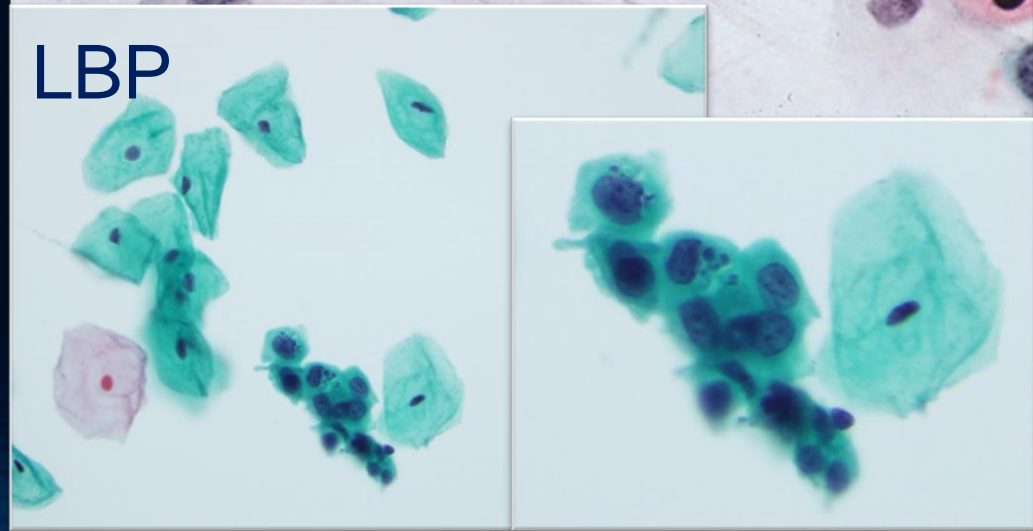
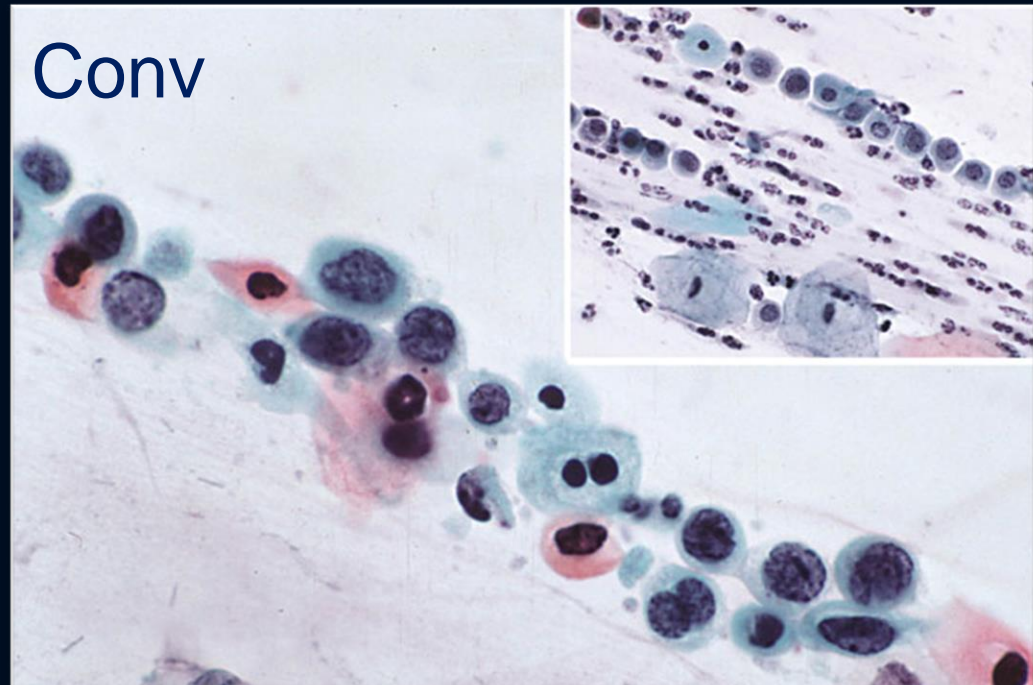


LBP- lymphocytes in clusters or scattered in the background

Histiocytes

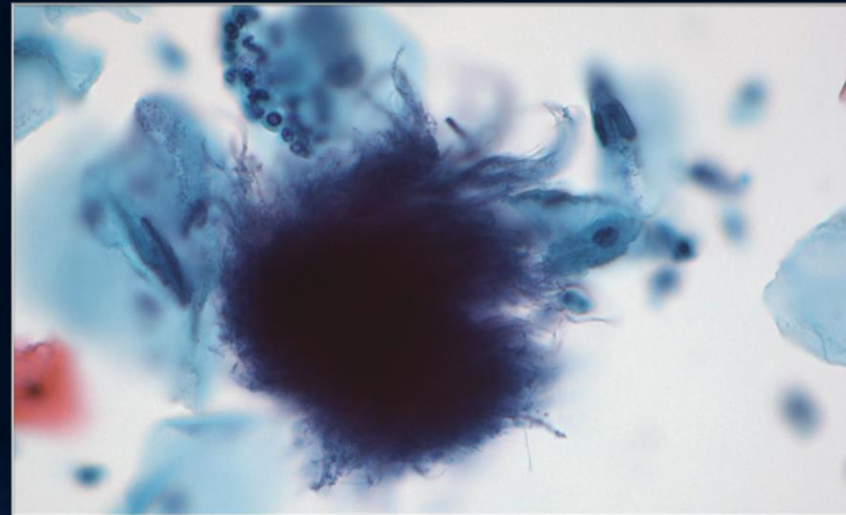
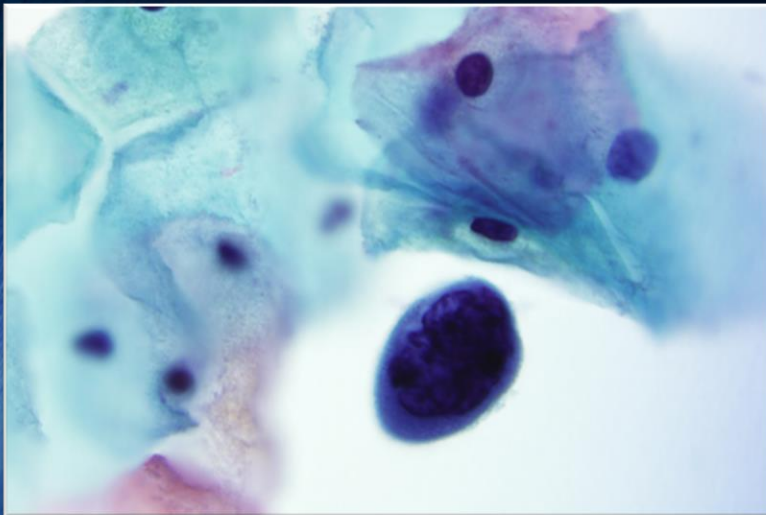
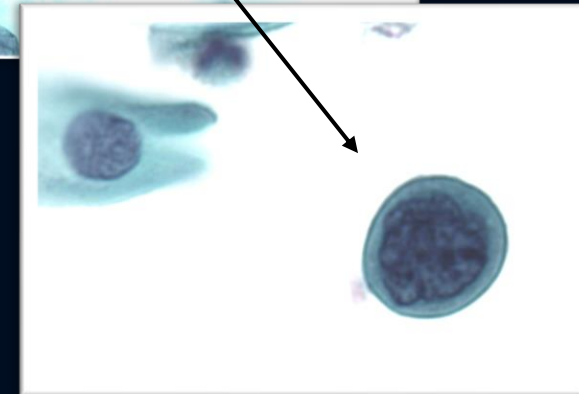
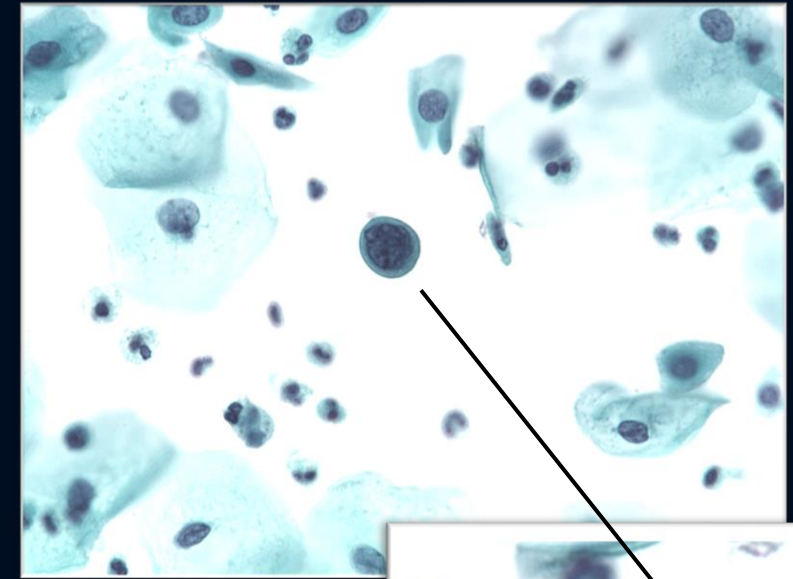


HSIL



Intrauterine Device Effect

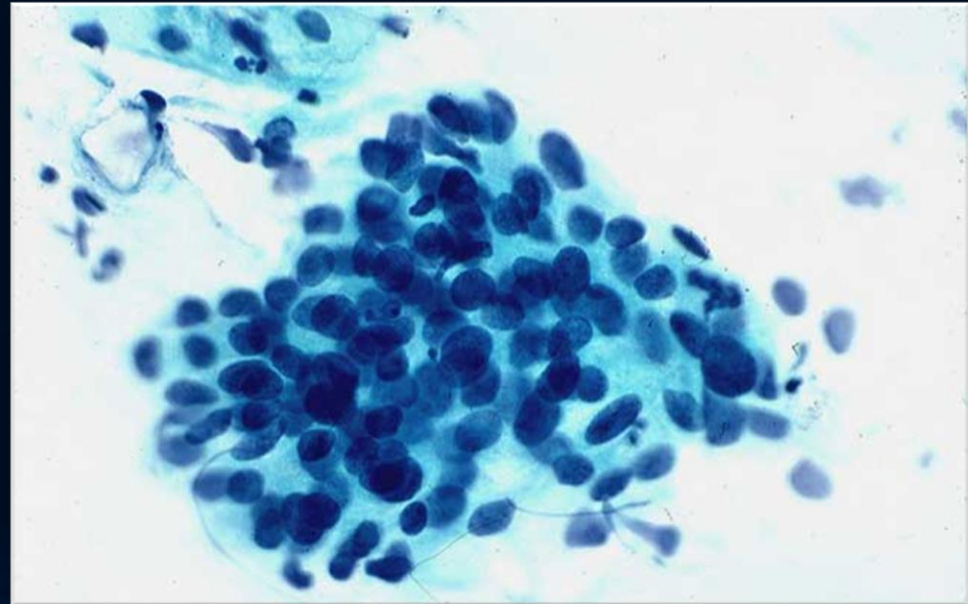
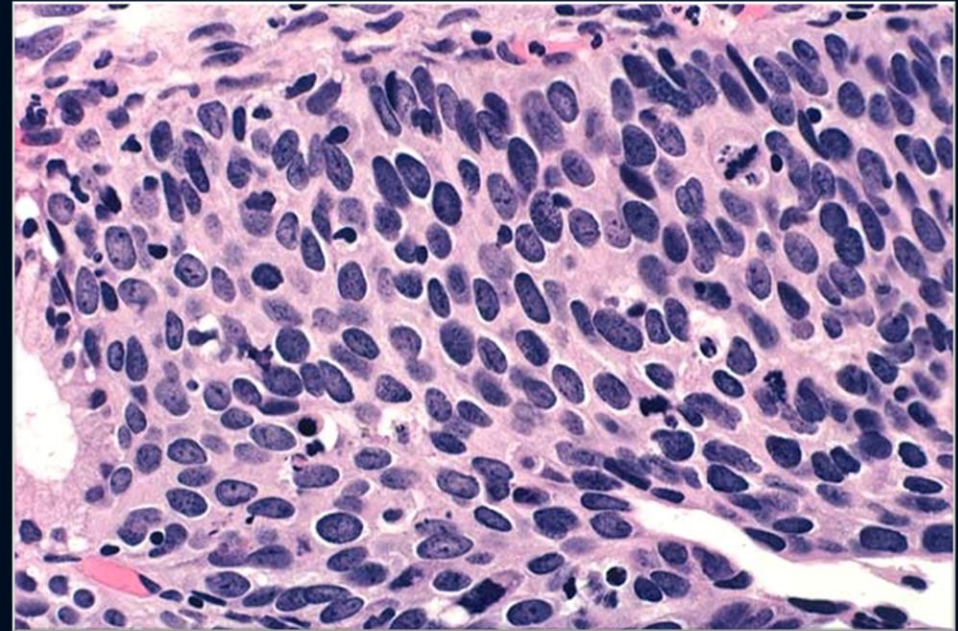
- Irritated, exfoliated endocervical cells
- Isolated cells more often HSIL mimickers
- Smudgy chromatin, degenerated
- May be associated with Actinomyces



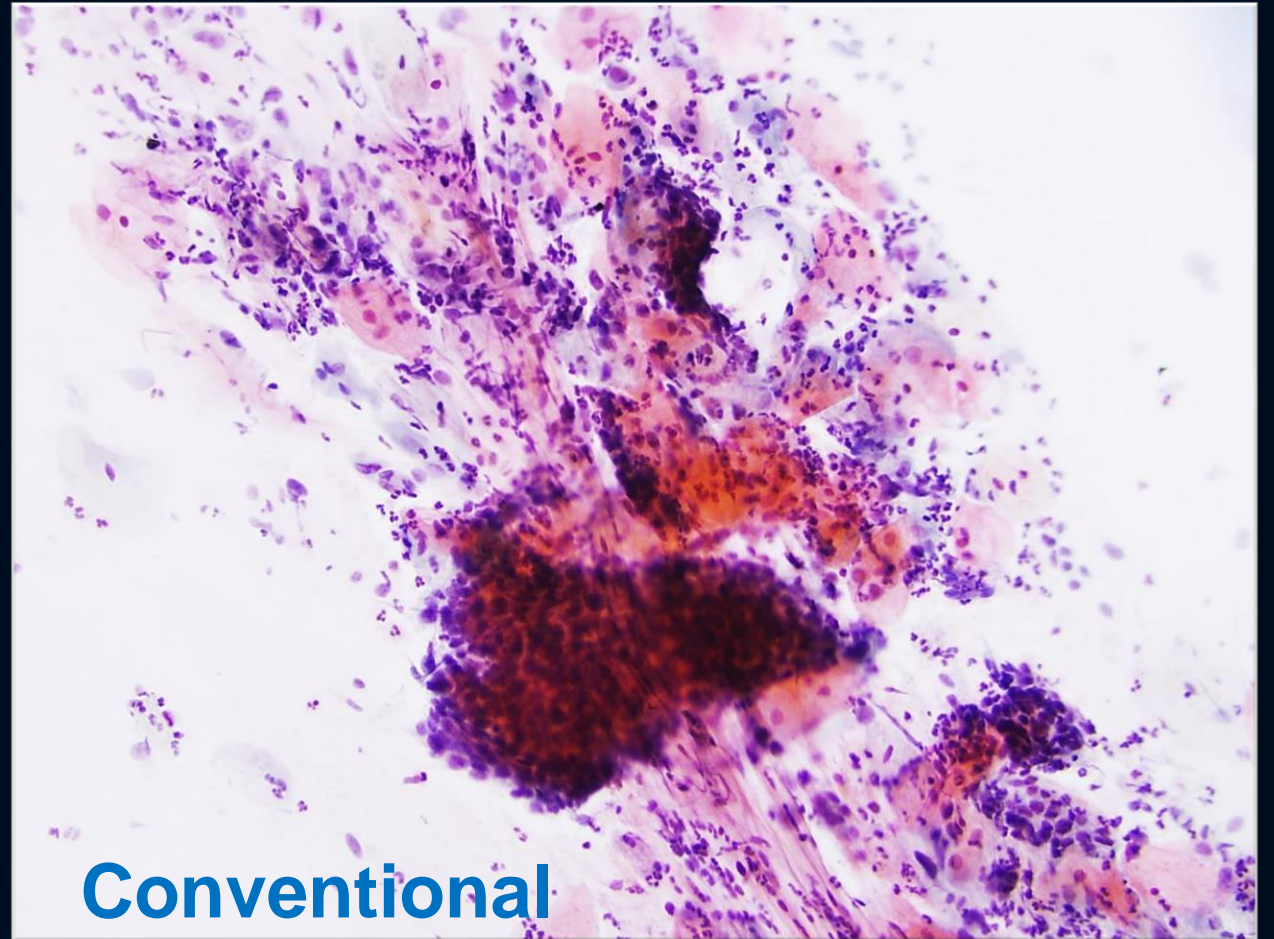
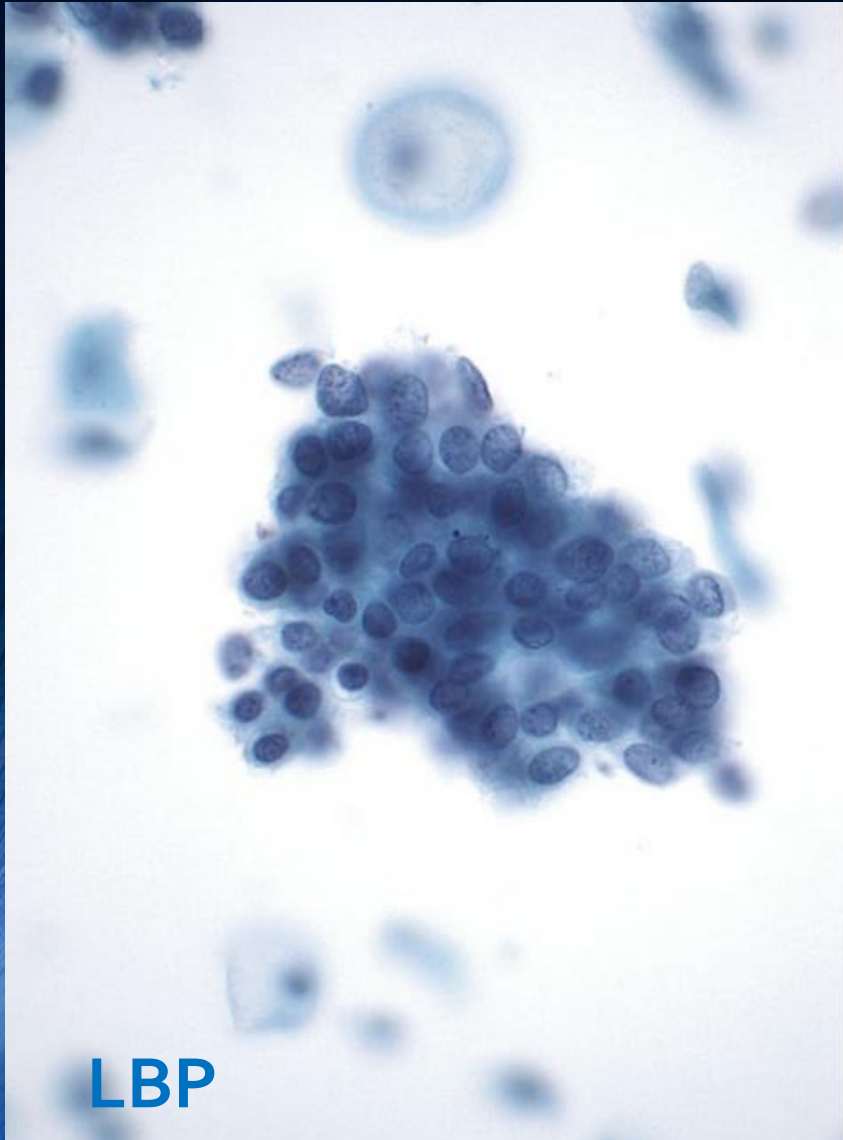
HSIL

Syncytial Pattern

- Hyperchromatic crowded groups
 - Loss of polarity
 - Lack of cytoplasmic boundaries
- Nuclear features similar to single cell pattern HSIL
- Nucleoli usually inconspicuous



HSIL *Syncytial groups/ hyperchromatic crowded groups (HCG)*



Differential Diagnosis of **Syncytial Pattern of HSIL** Hyperchromatic Cell Groups “HCG”

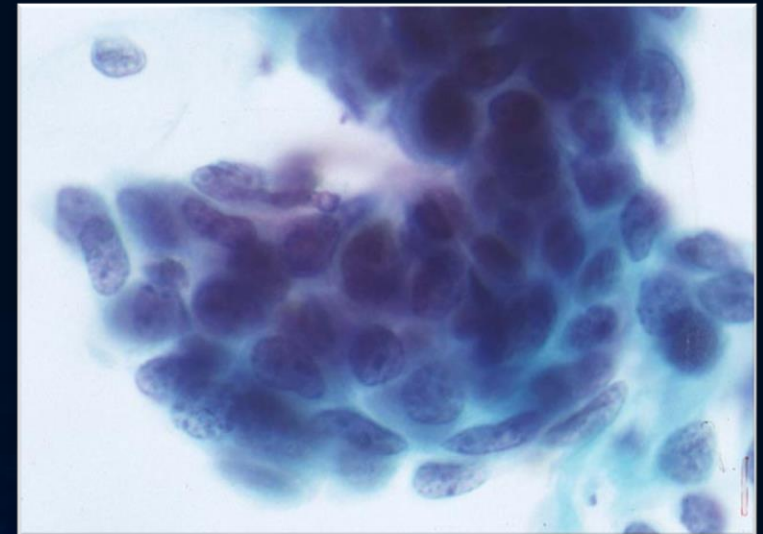
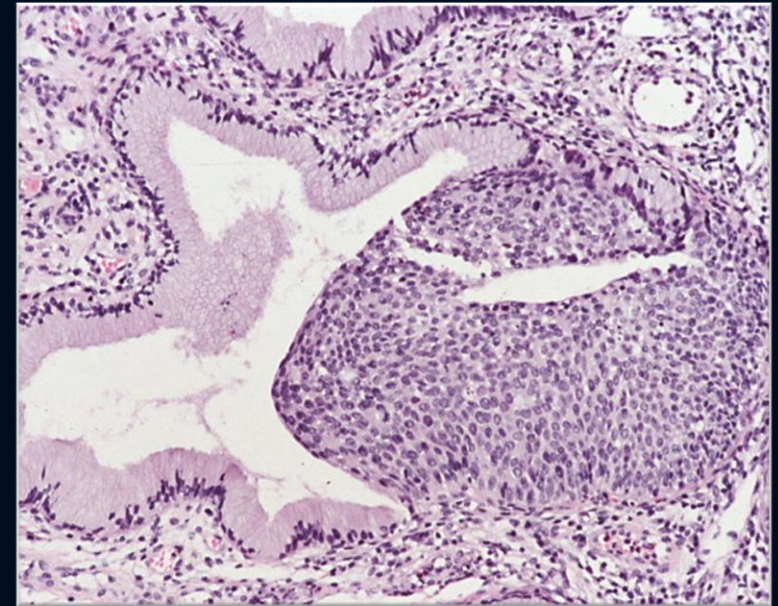
- HSIL
- HSIL extending into endocervical glands
- Endocervical neoplasia (AIS)

- Benign endocervical cells
- Lower uterine segment/ endometrial cells
- Atrophy

HSIL involving endocervical glands

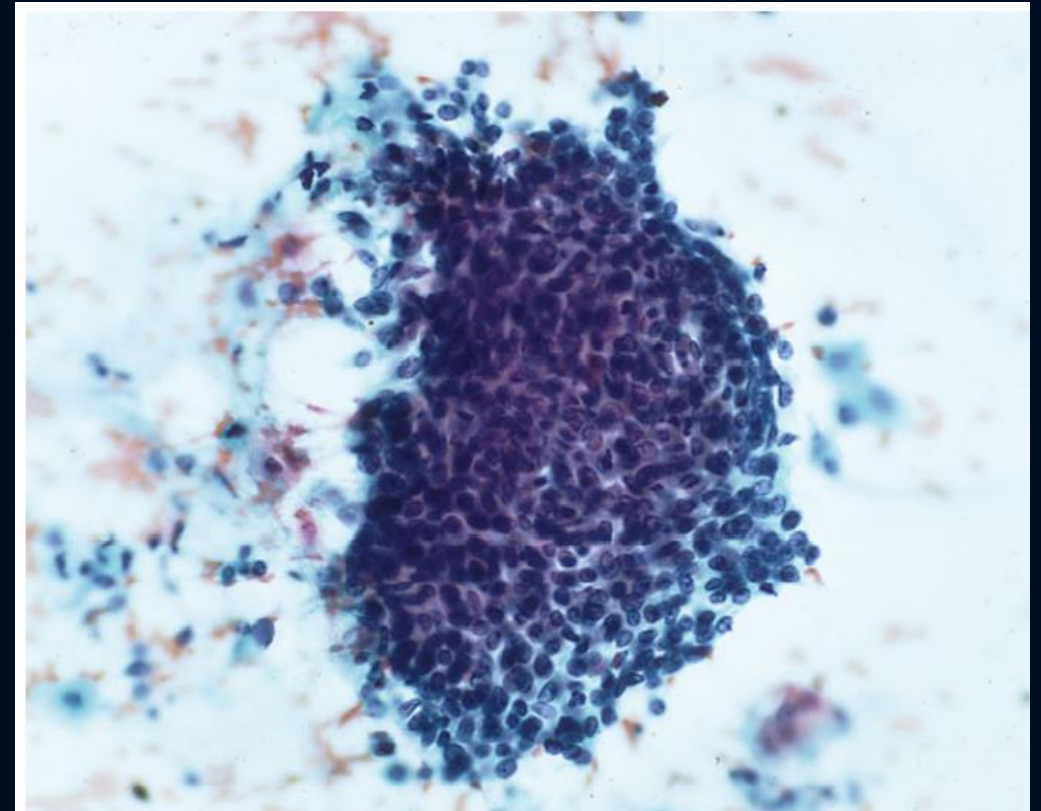
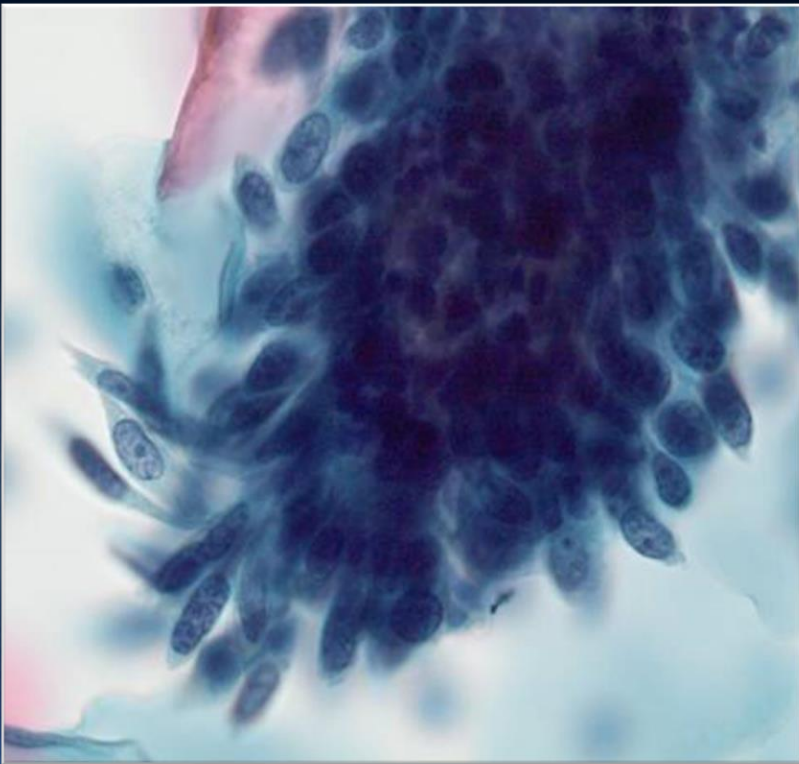
Useful to suggest HSIL

1. Flattening of cells at the periphery of the cluster giving a smooth round border
2. Loss of cell polarity within center of cluster
3. Presence of isolated squamous cells in background
4. Lack of specific AIS features

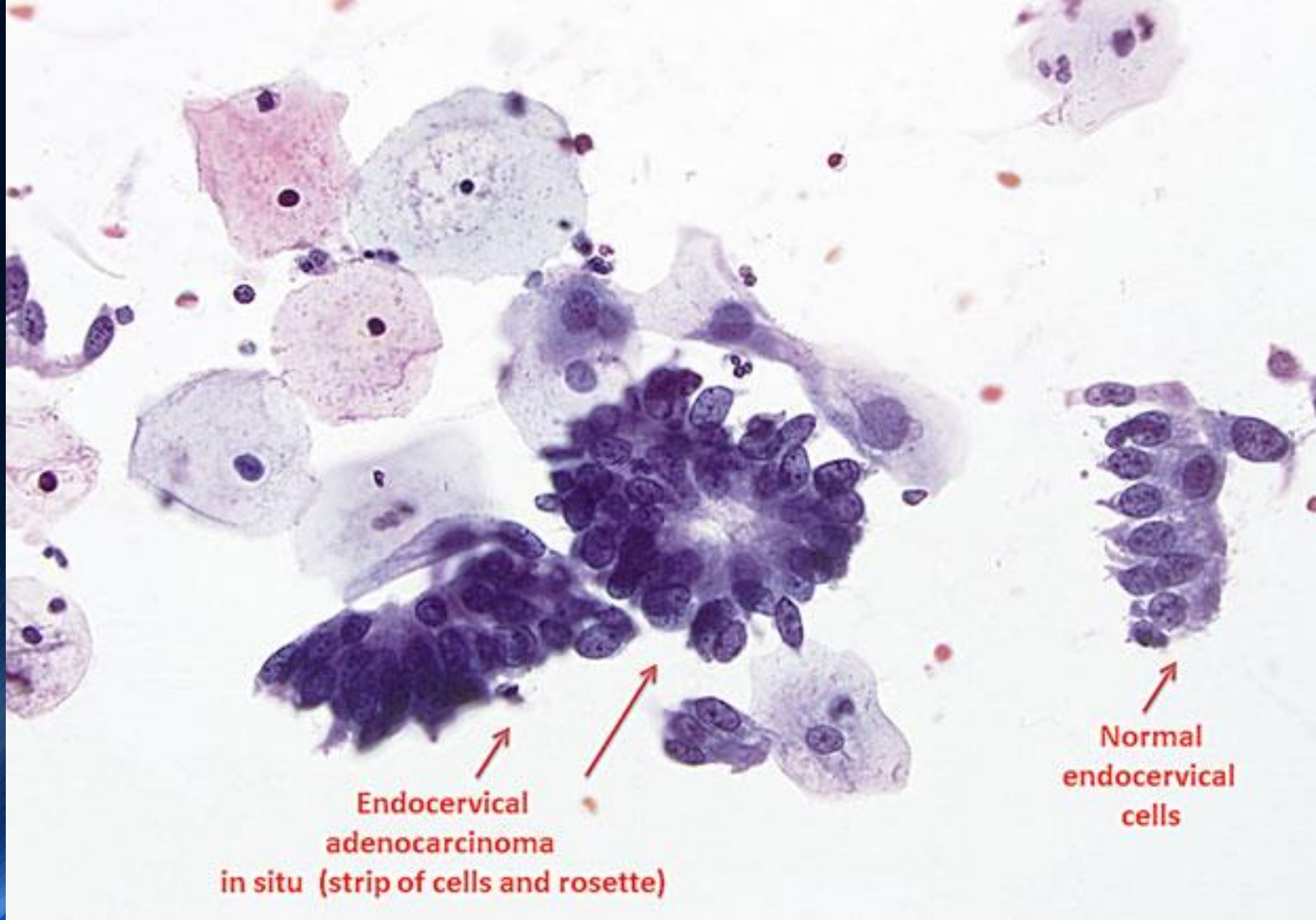


HSIL involving endocervical glands

“Syncytioid” groups with peripheral palisading
of EC cells, nuclear pseudo-stratification



Flattening at the edge of the cell cluster
and whorling in the center are suggestive
of HSIL over a glandular abnormality



Endocervical adenocarcinoma in situ (strip of cells and rosette)

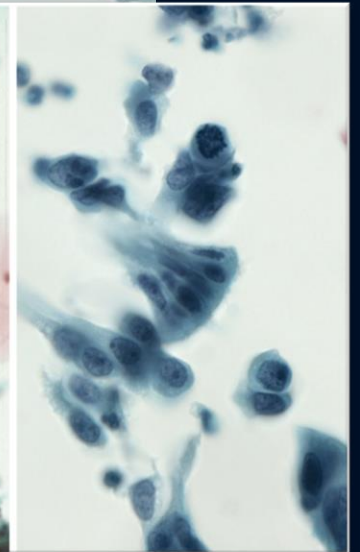
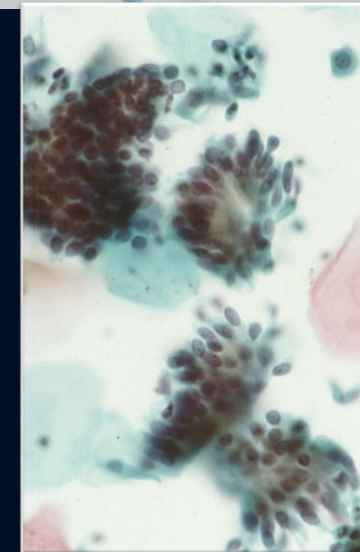
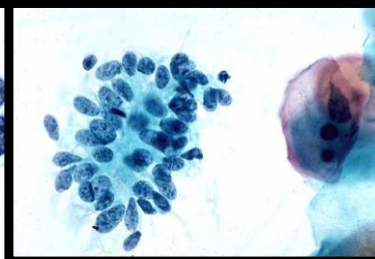
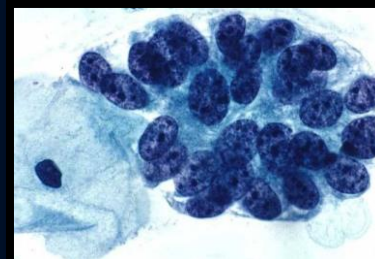
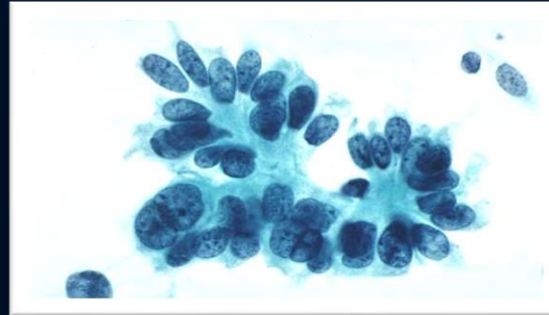
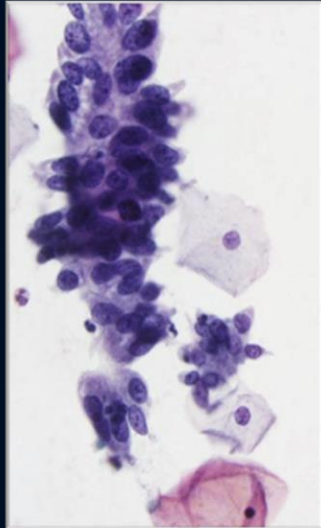
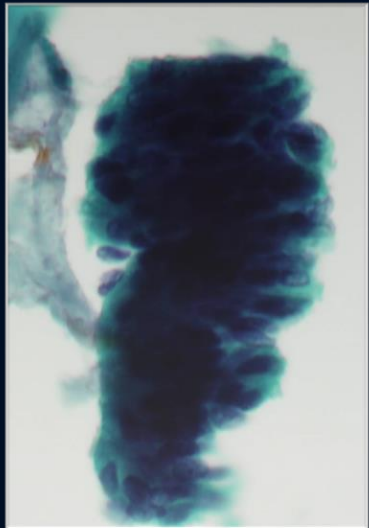
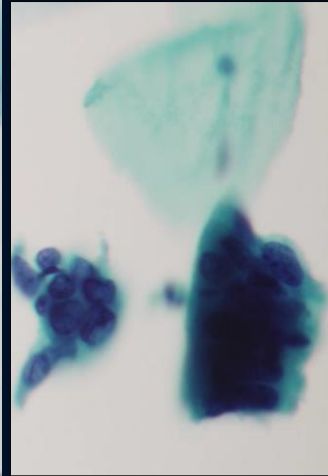
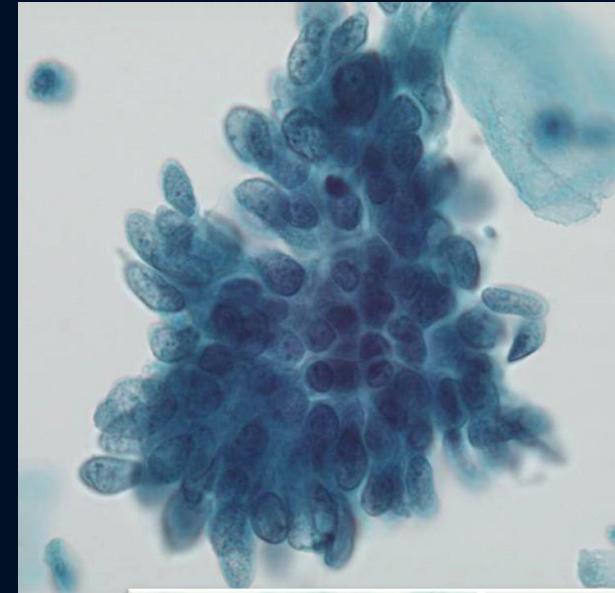
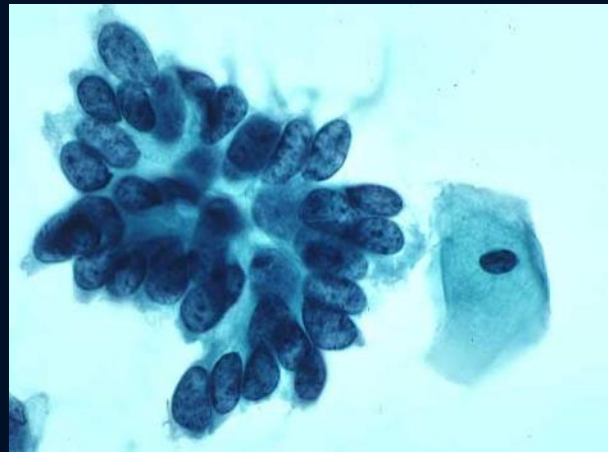
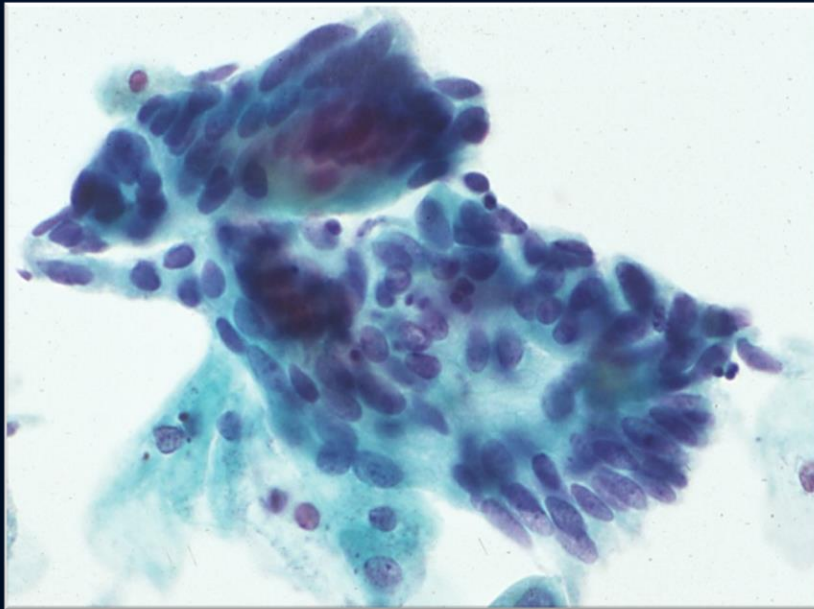
Normal endocervical cells

ThinPrep

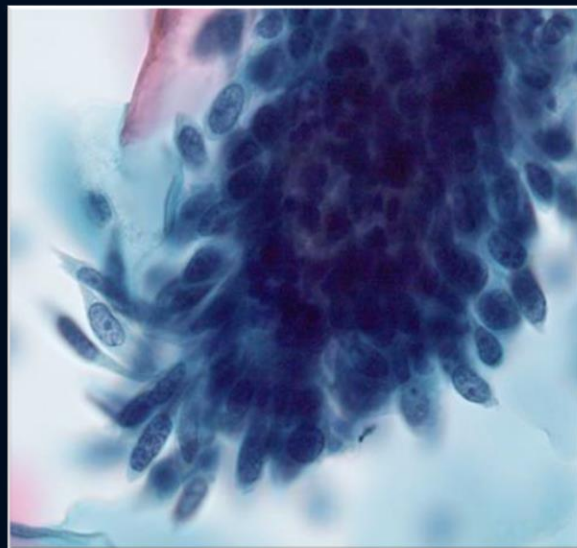
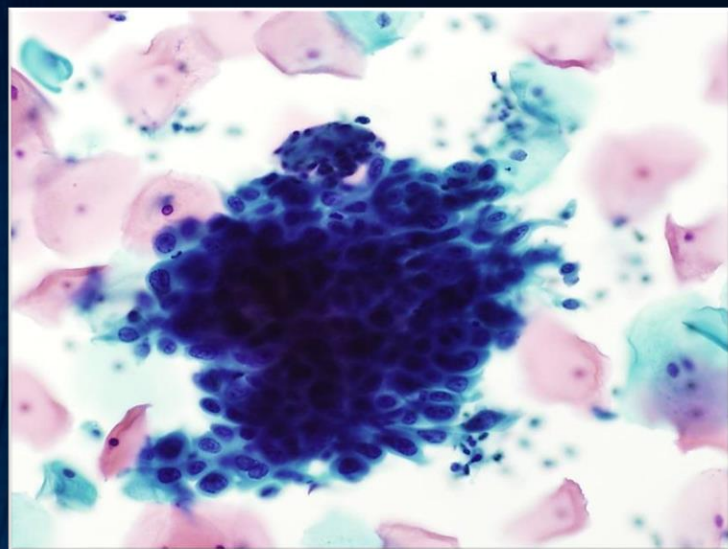
Endocervical AIS: rosettes, large nuclei with coarse granular chromatin, pseudostratification and feathering

Surepath

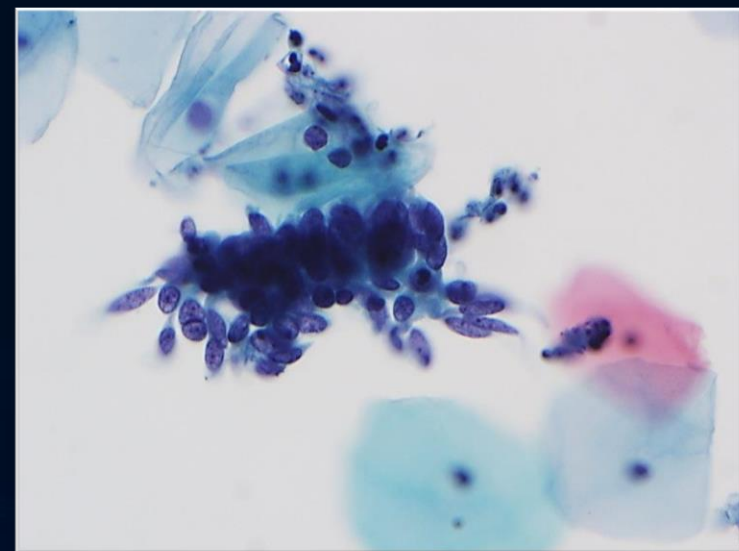
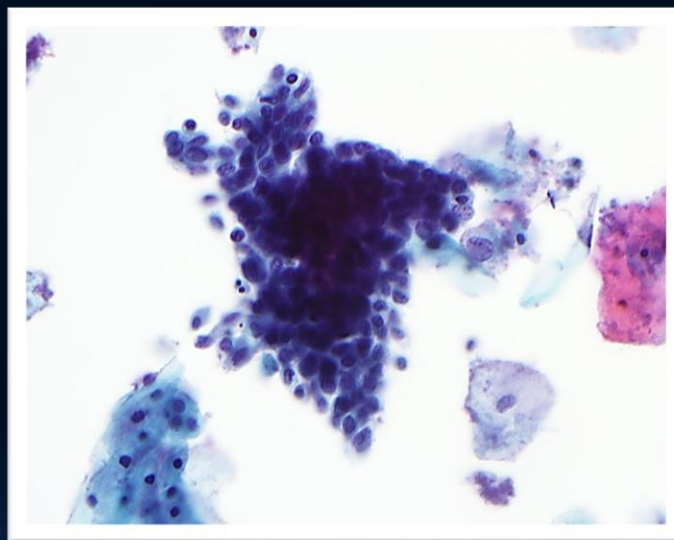
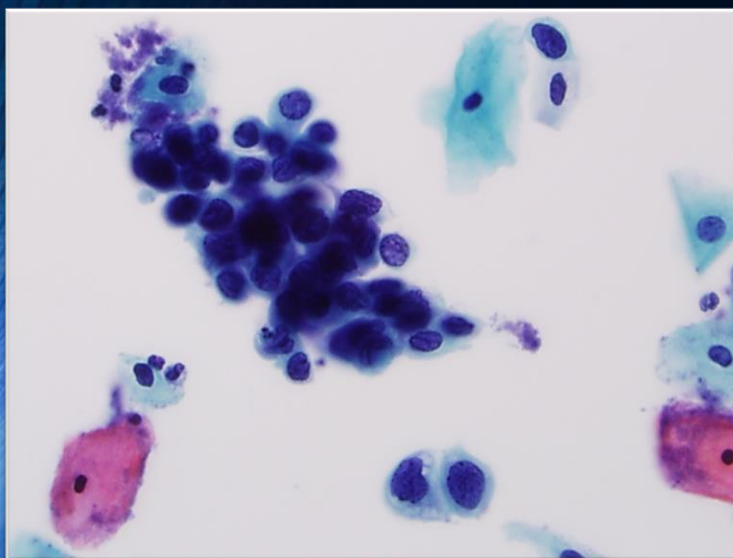
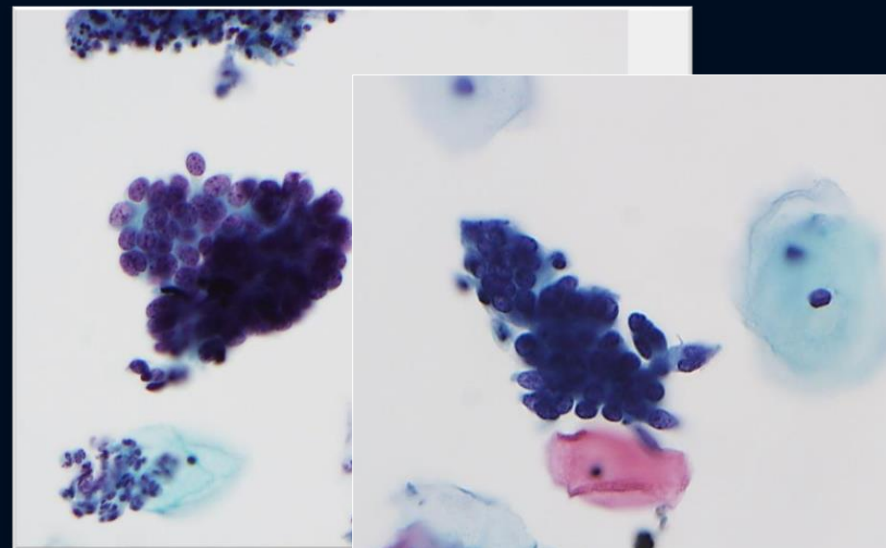
Conventional



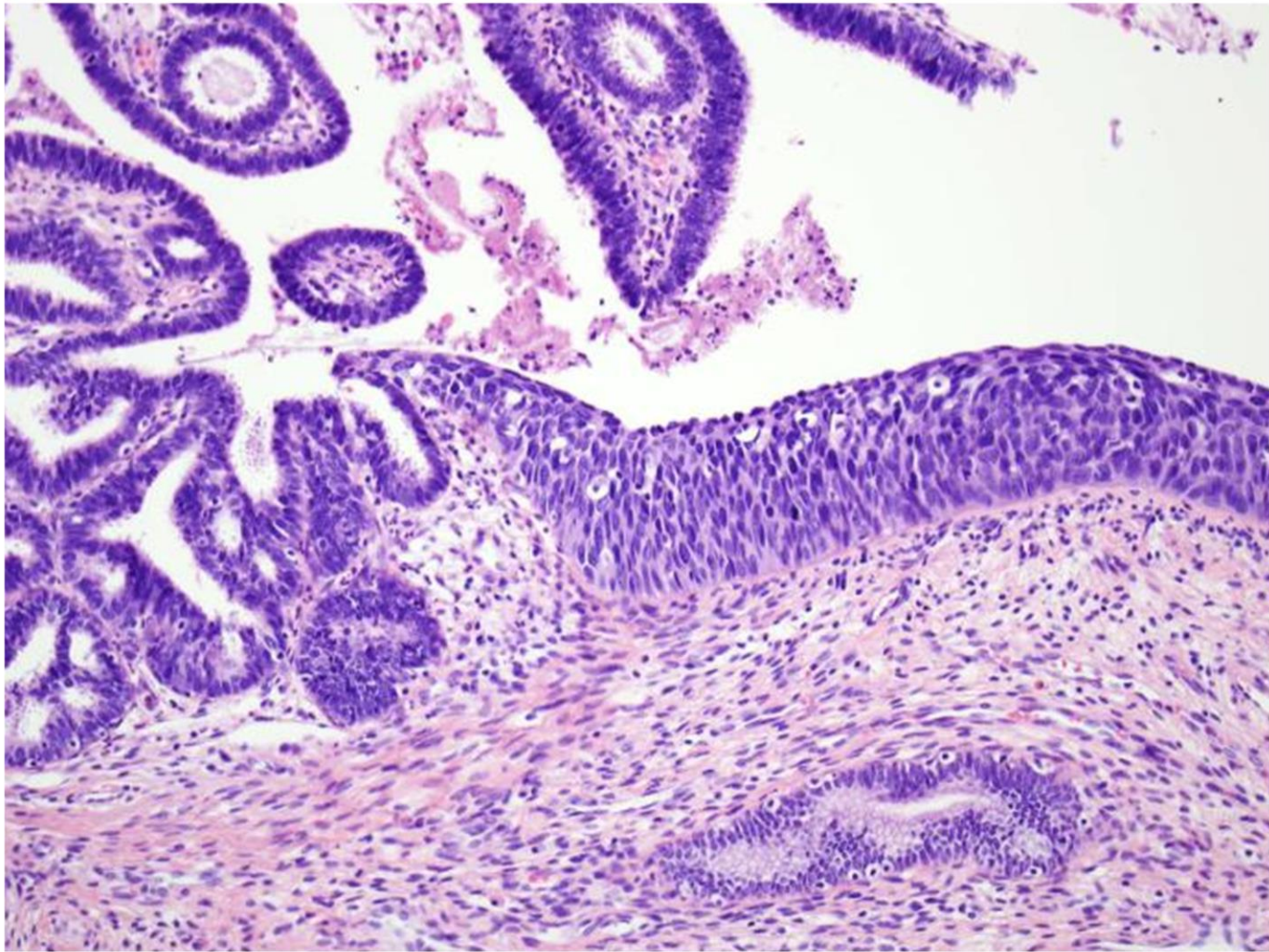
HSIL Gland Involvement



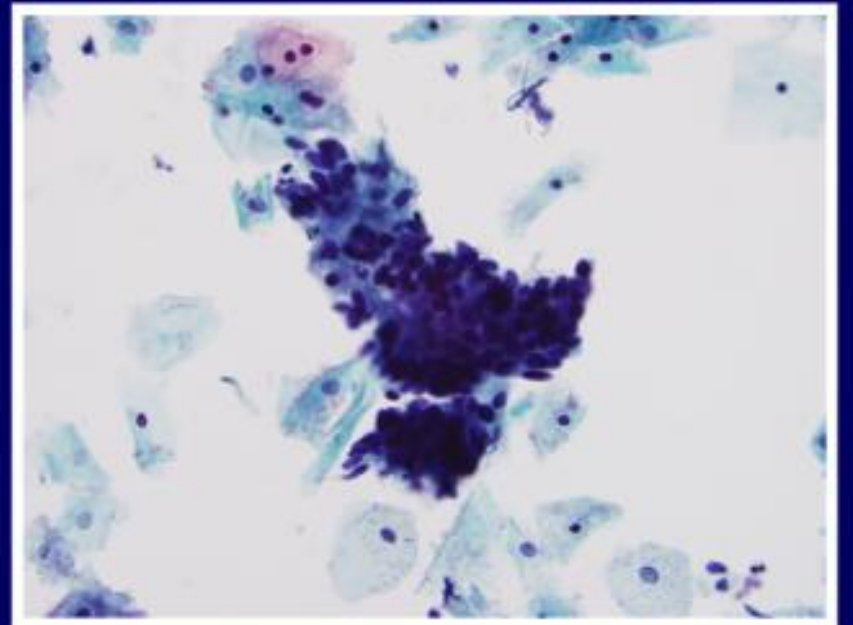
AIS



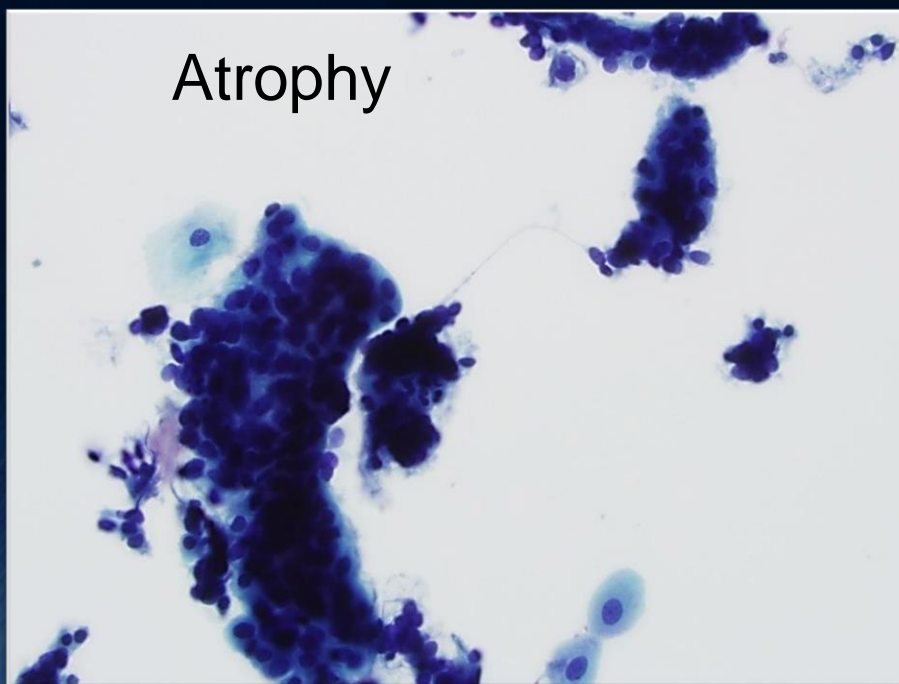
AIS and HSIL may coexist



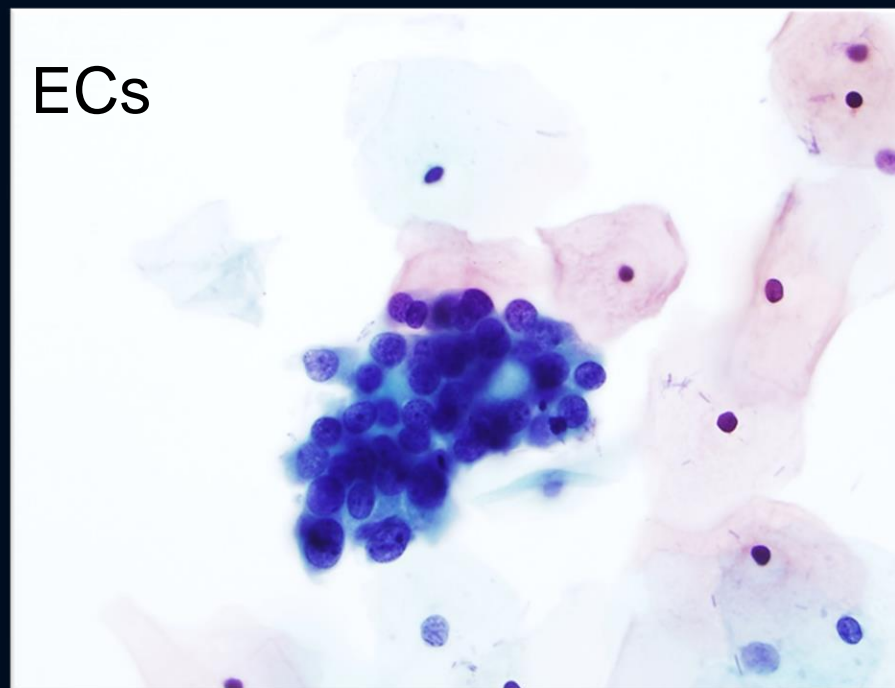
AIS/HSIL



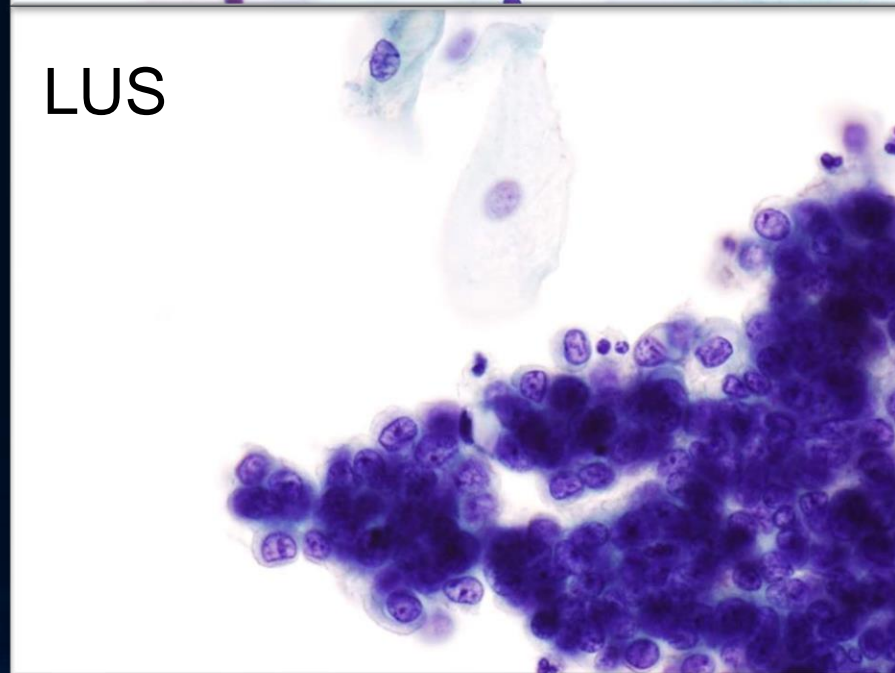
Benign mimics of syncytial HSIL pattern



ECs

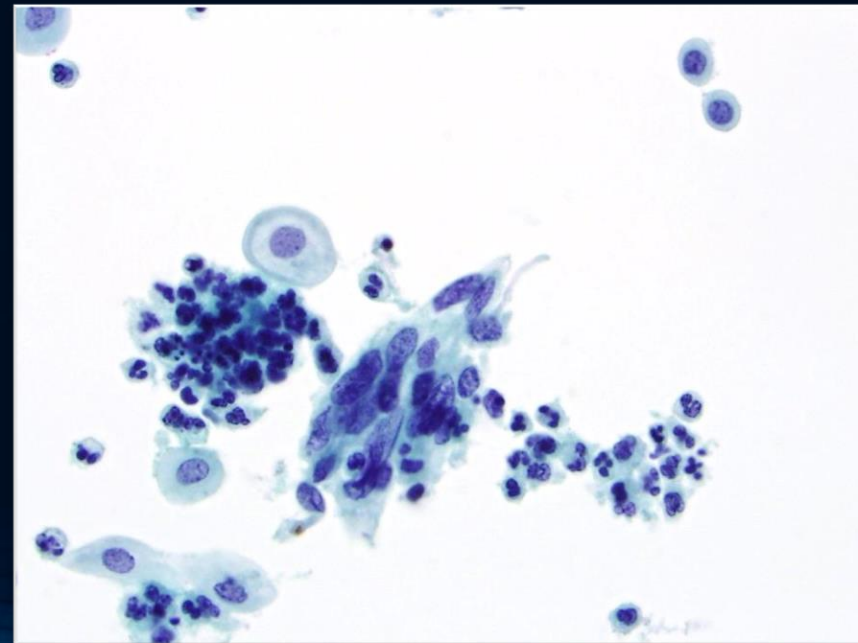
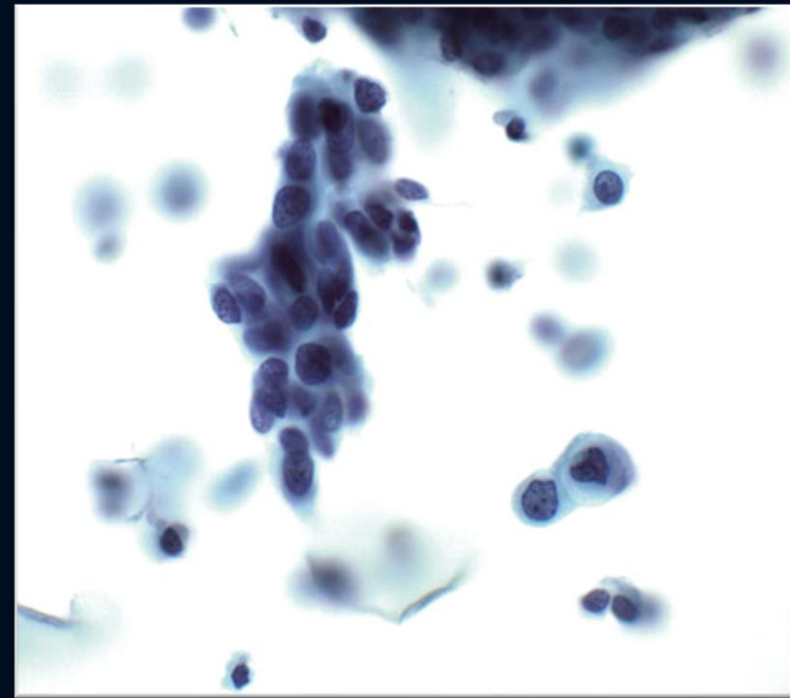


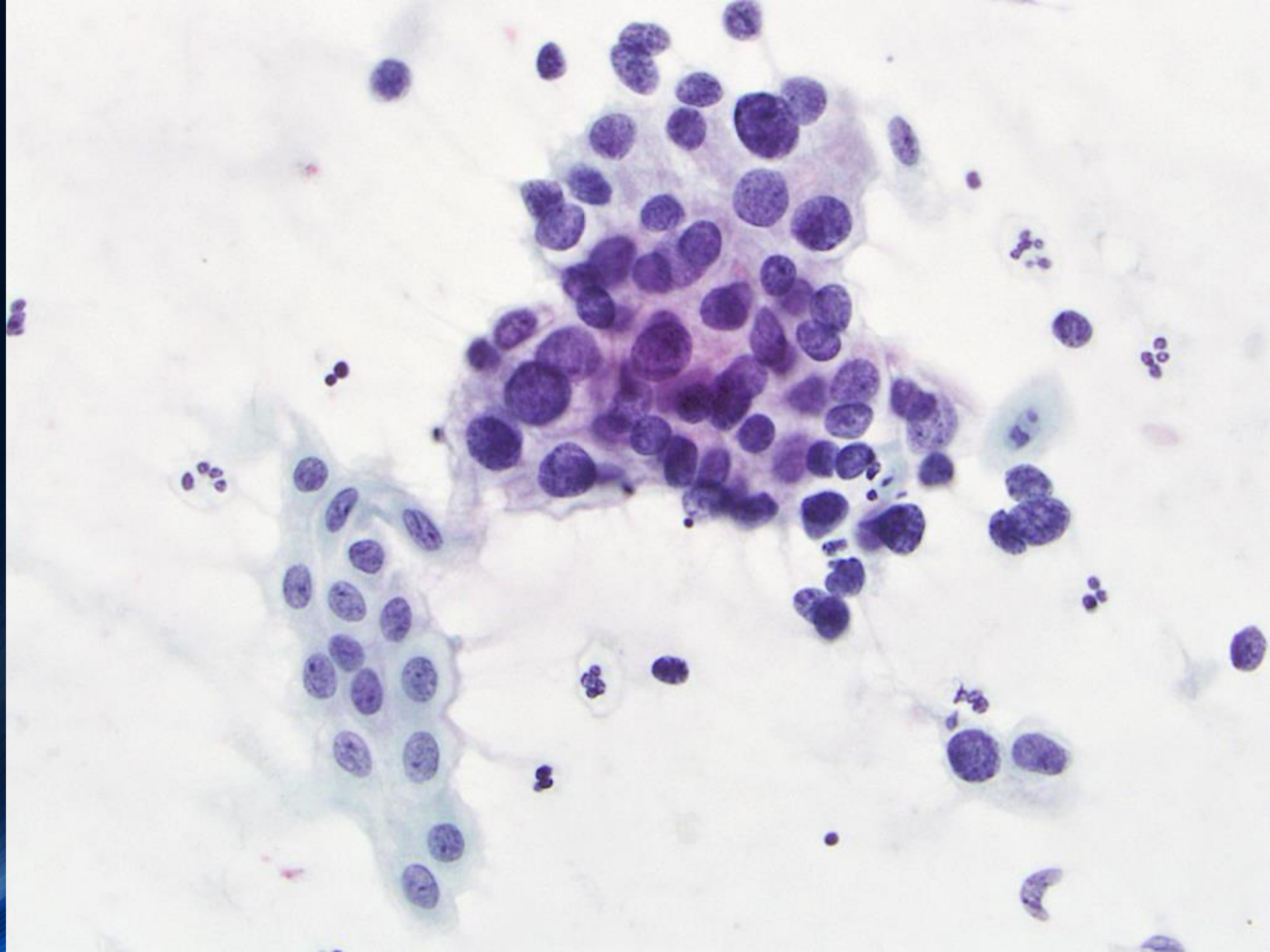
LUS



HSIL in Atrophy

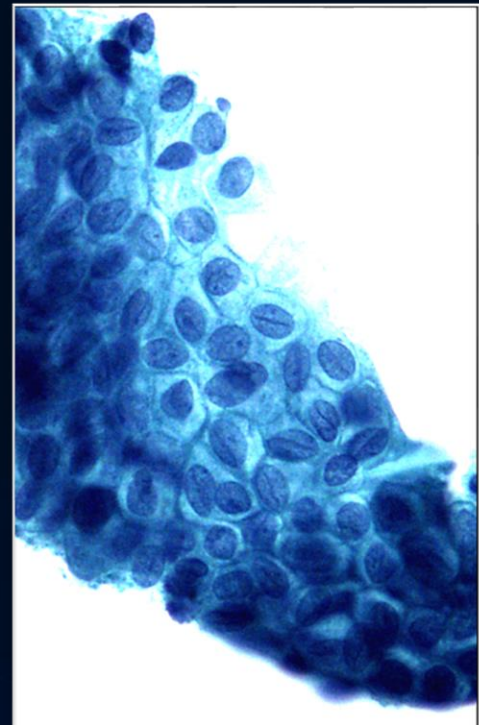
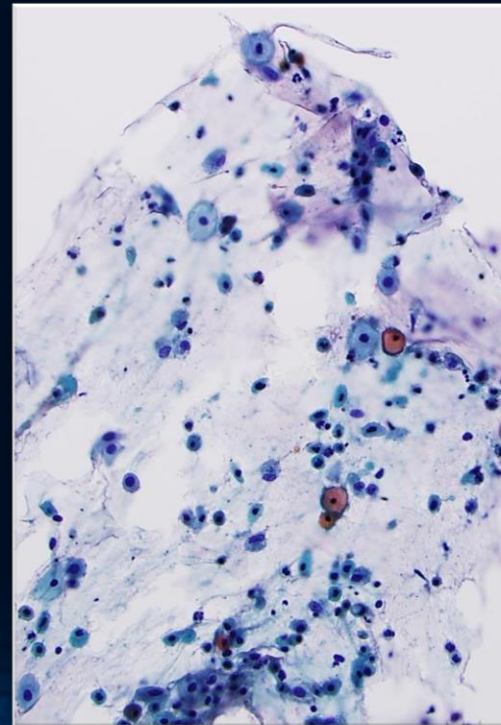
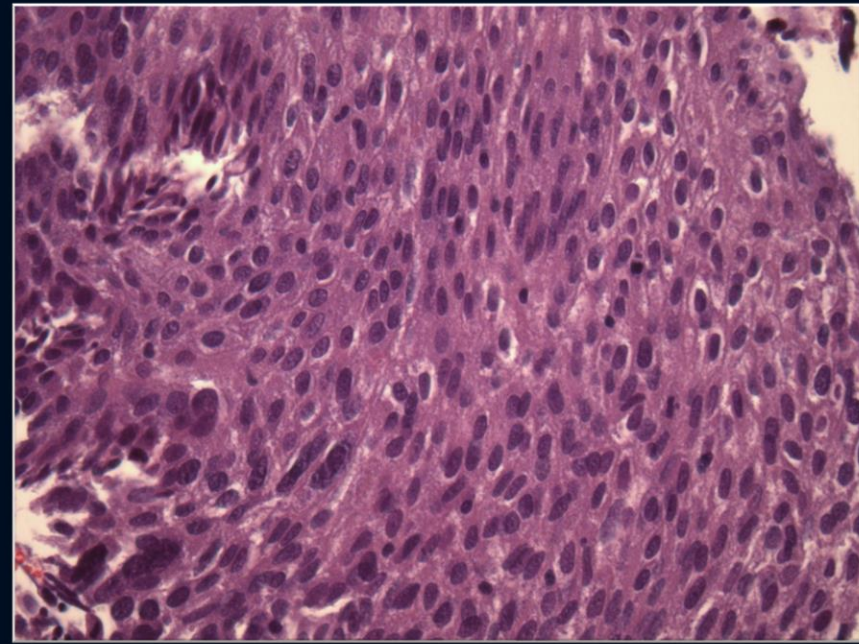
- Hyperchromatic crowded groups
- Small cells
- Palisading
- Background of atrophy includes:
 - Dense parabasal groups
 - Bland chromatin
 - Smooth nuclear contours





Atrophy Pitfalls

- Blue Blobs
- Pseudoparakeratosis
- Transitional cell metaplasia
- PM atypia
- Autolysis in background



Reference Nuclei

35

- Normal intermediate cell

35

- Benign endometrial cell

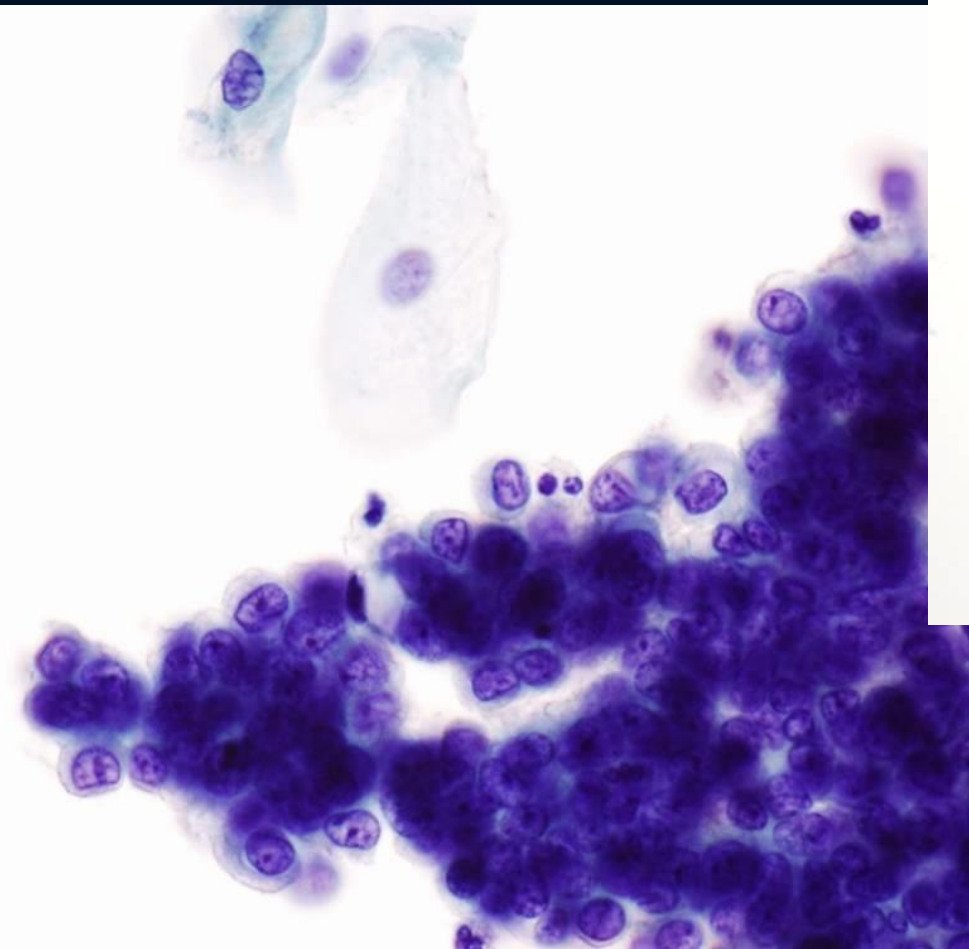
50-70

- Normal /Reactive endocervical cell

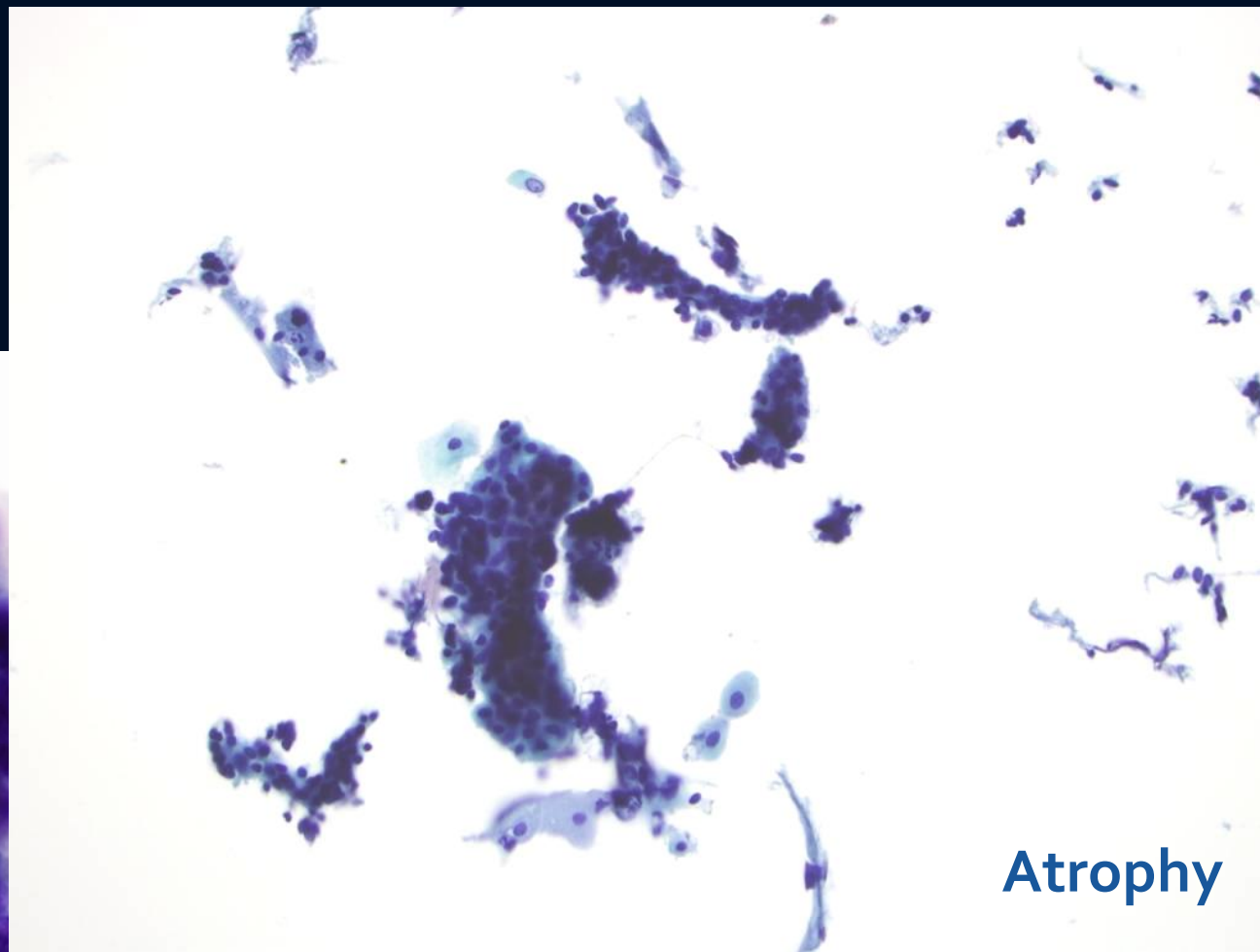
75-100

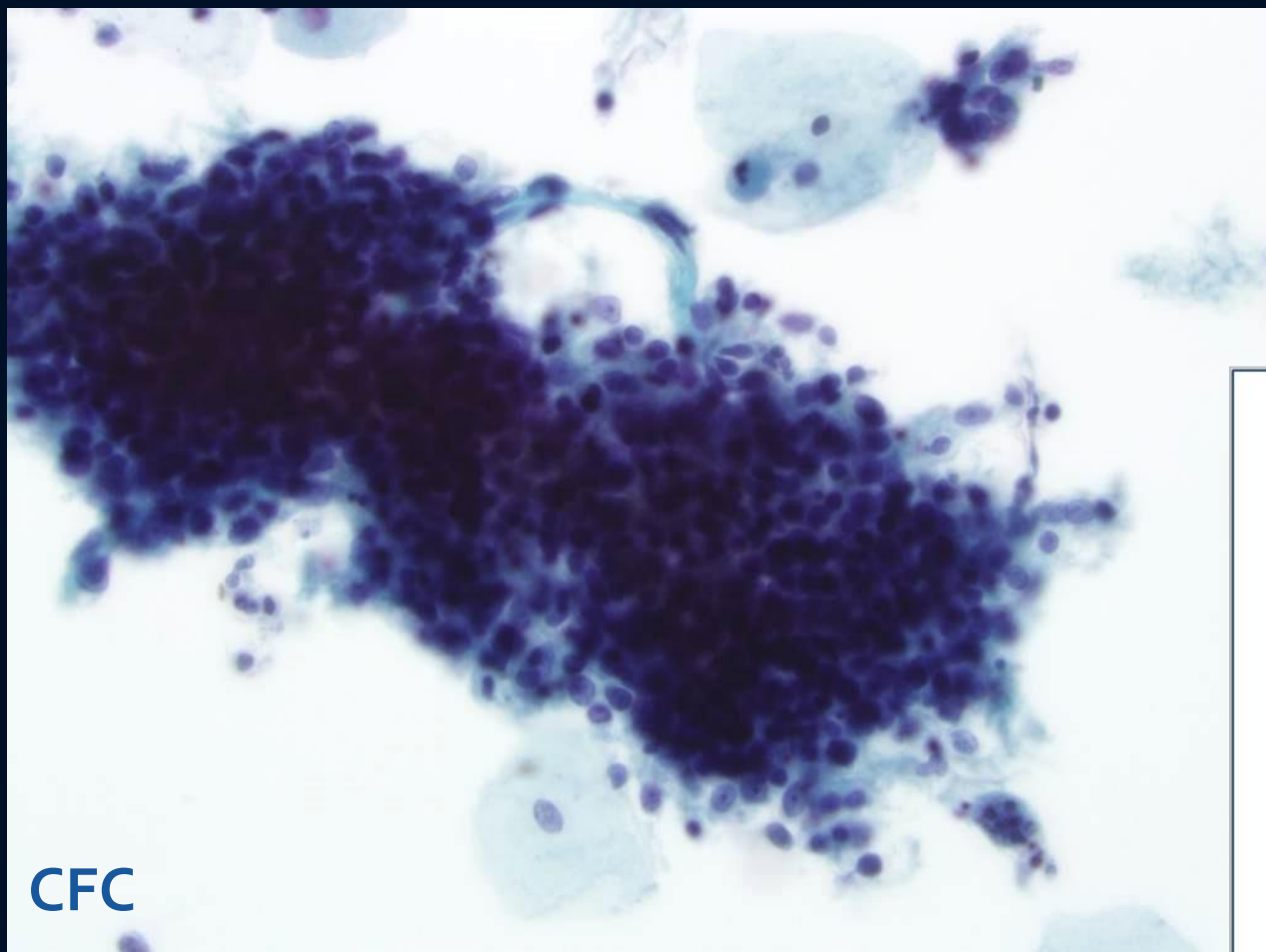
- Endocervical AIS

LUS

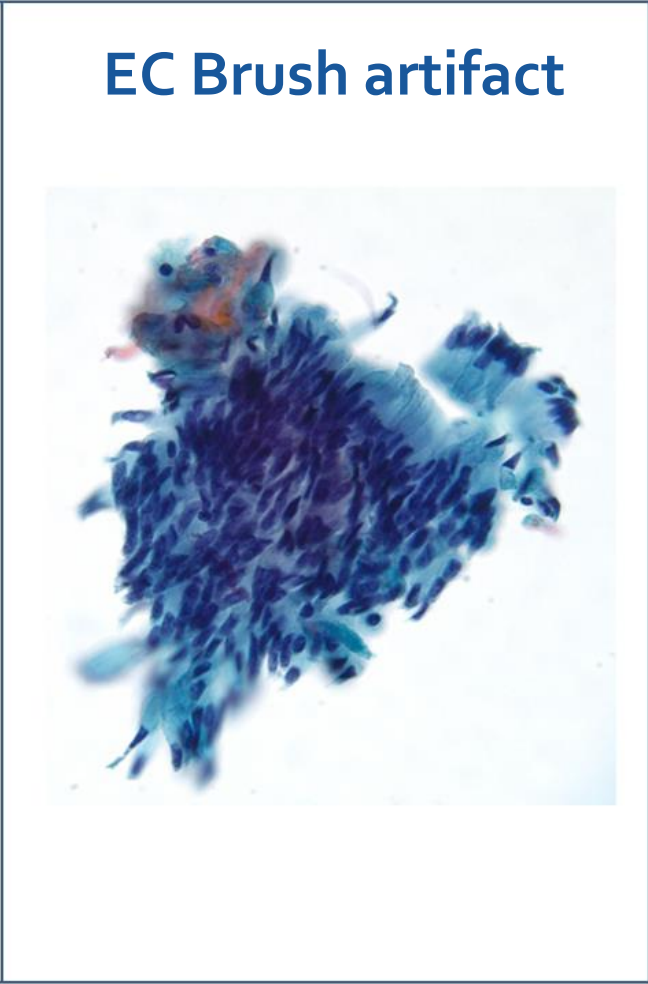
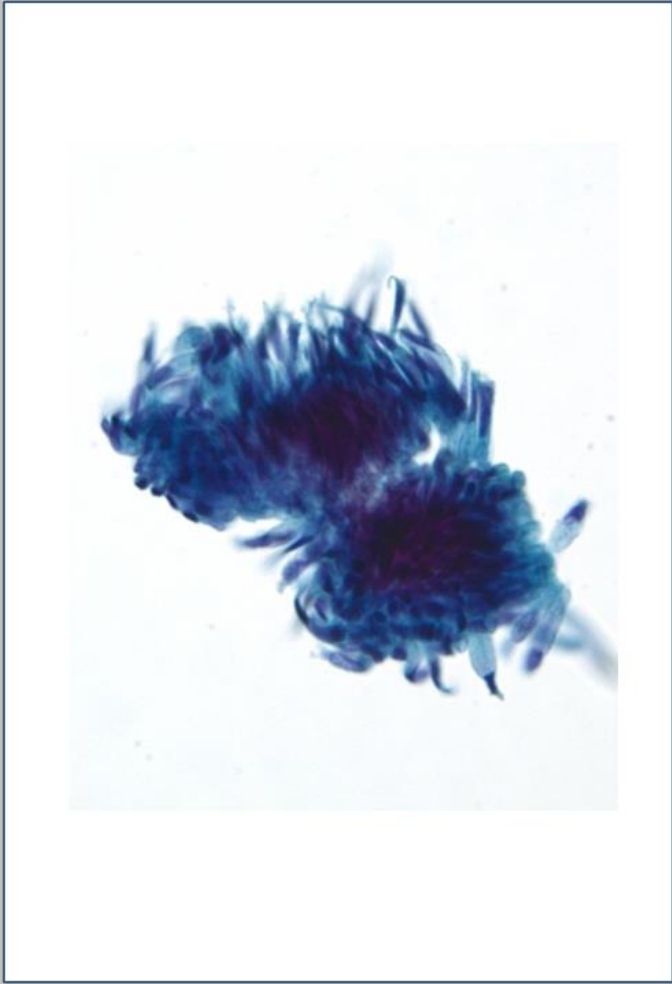


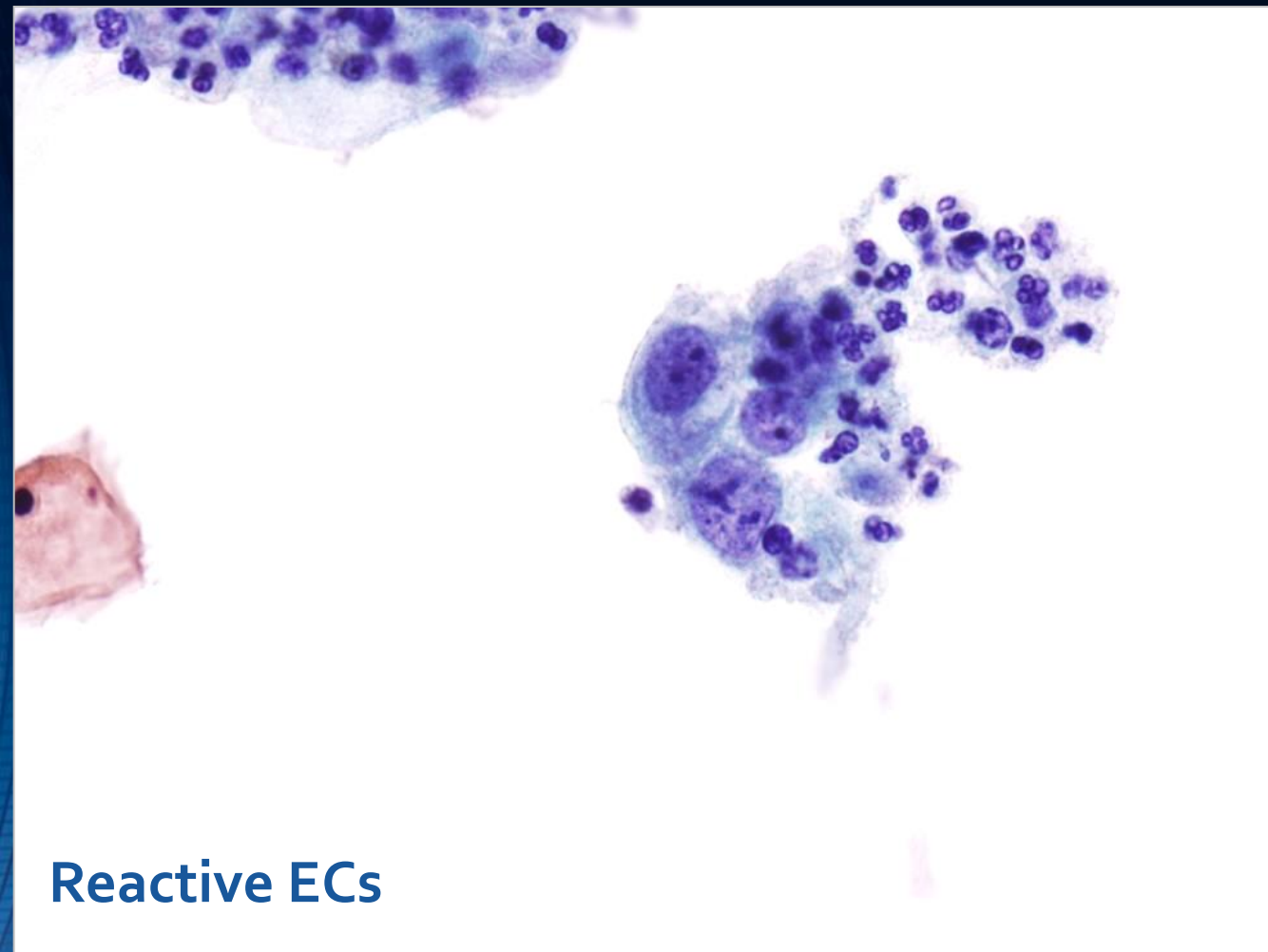
Atrophy



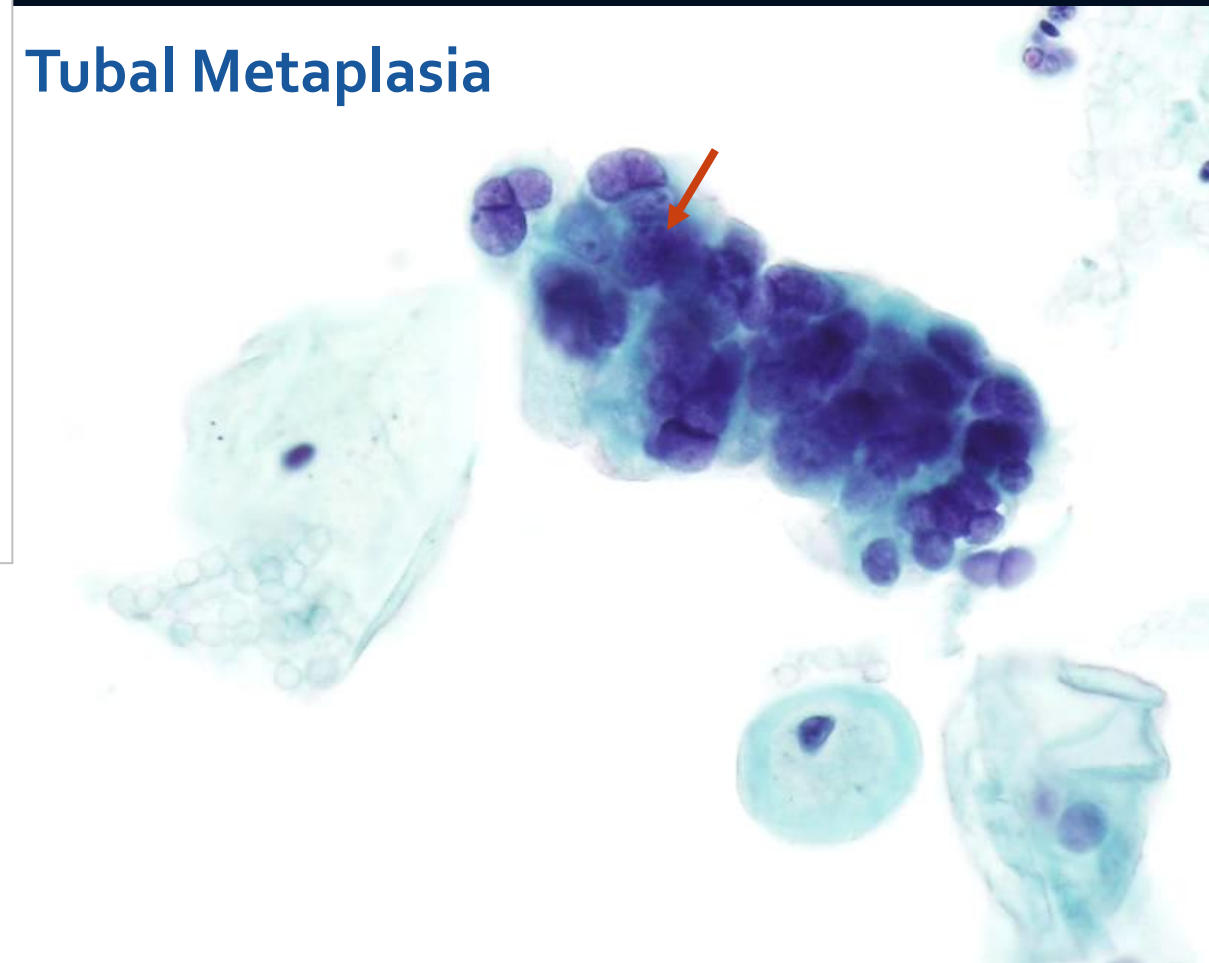


CFC



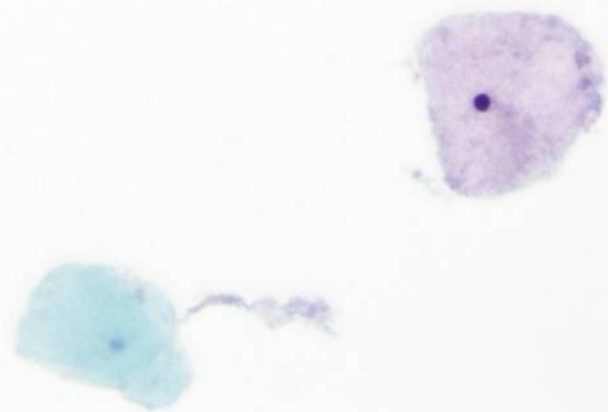
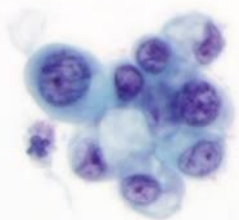


Reactive ECs

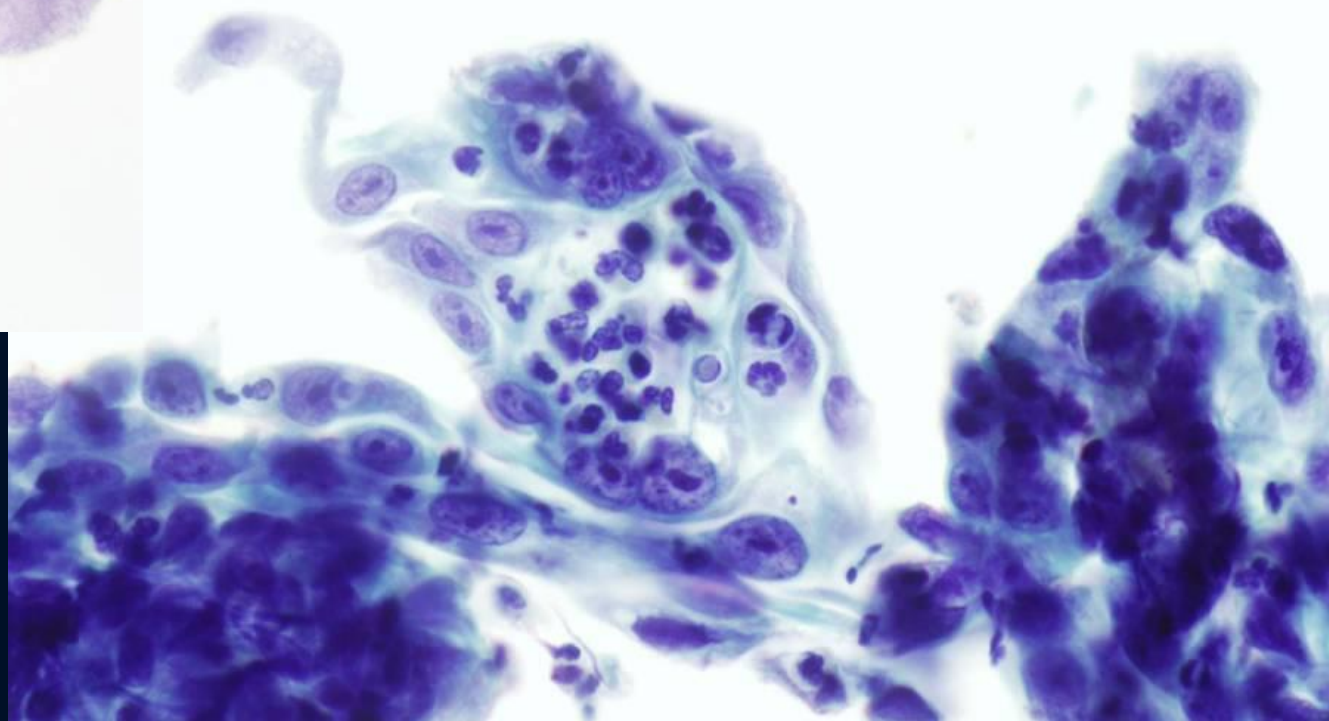


Tubal Metaplasia

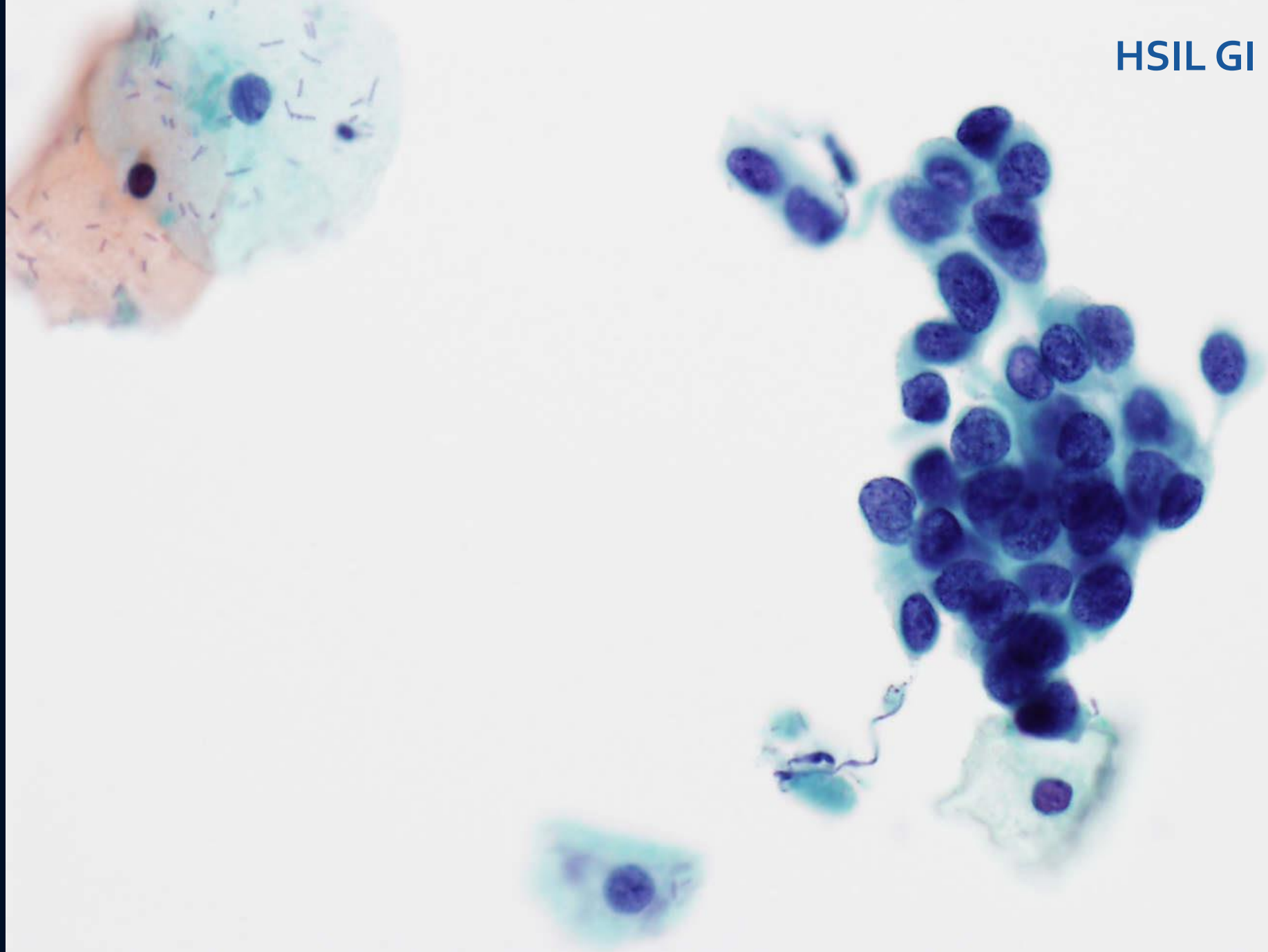
IUD Change



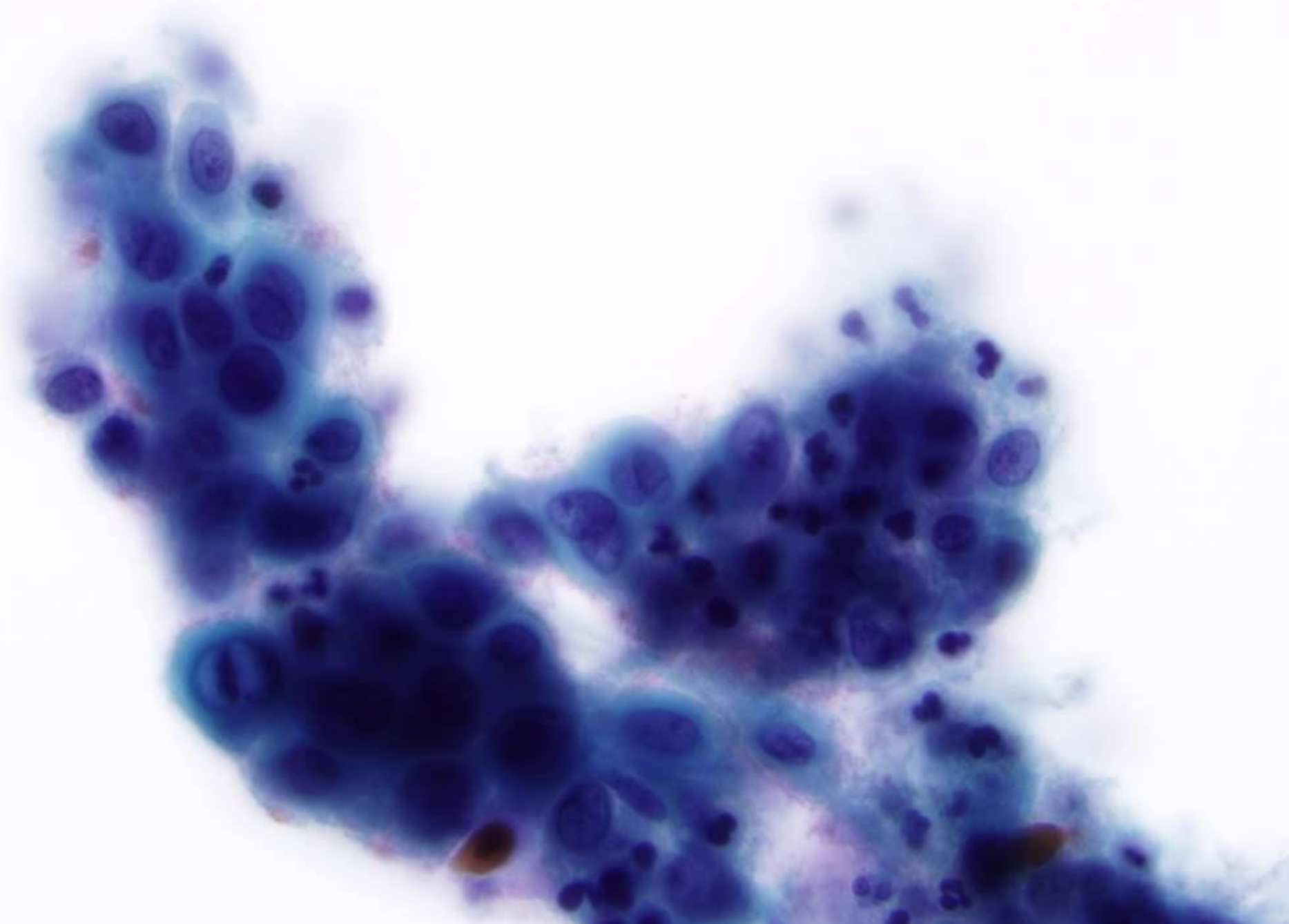
Repair



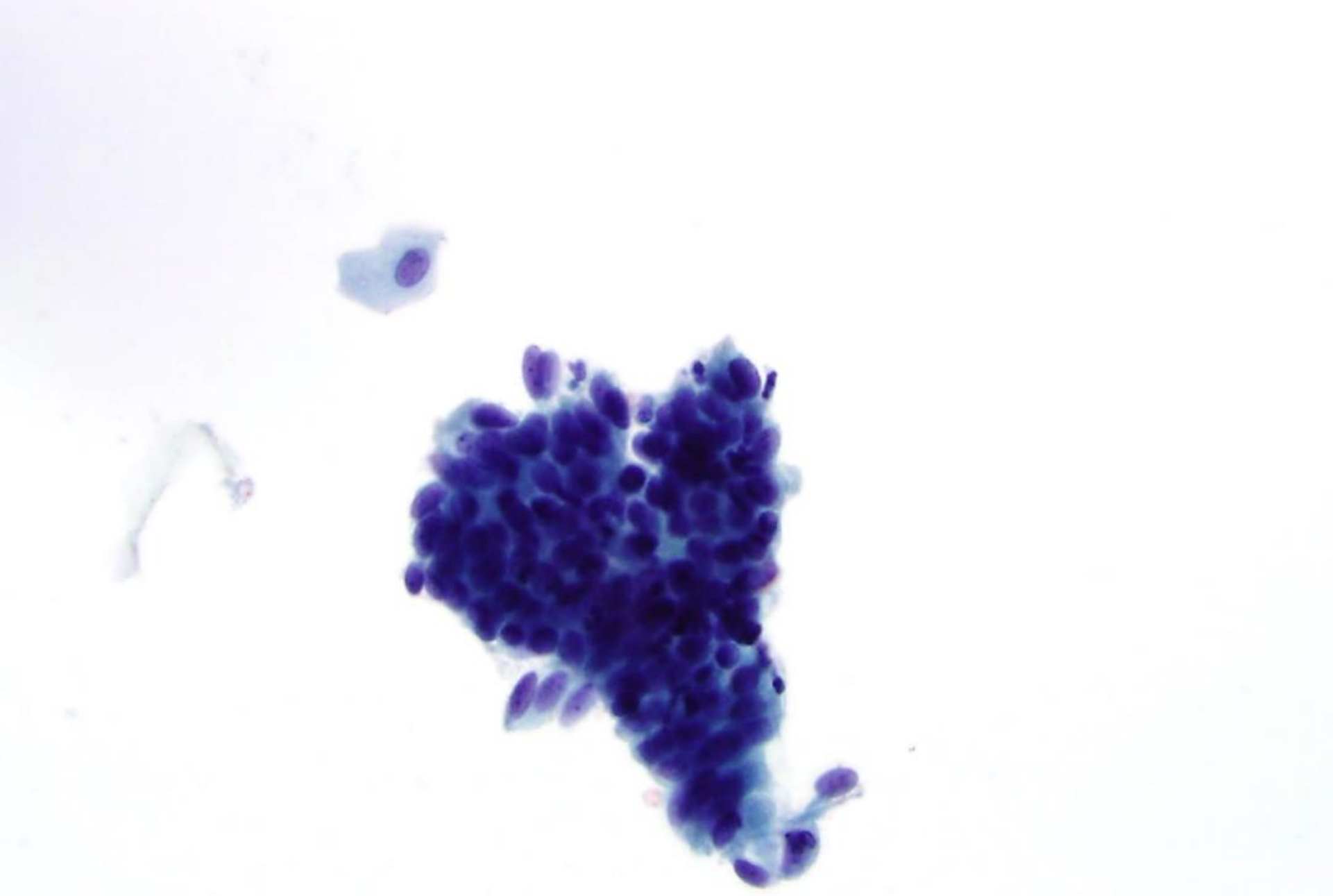
HSIL GI



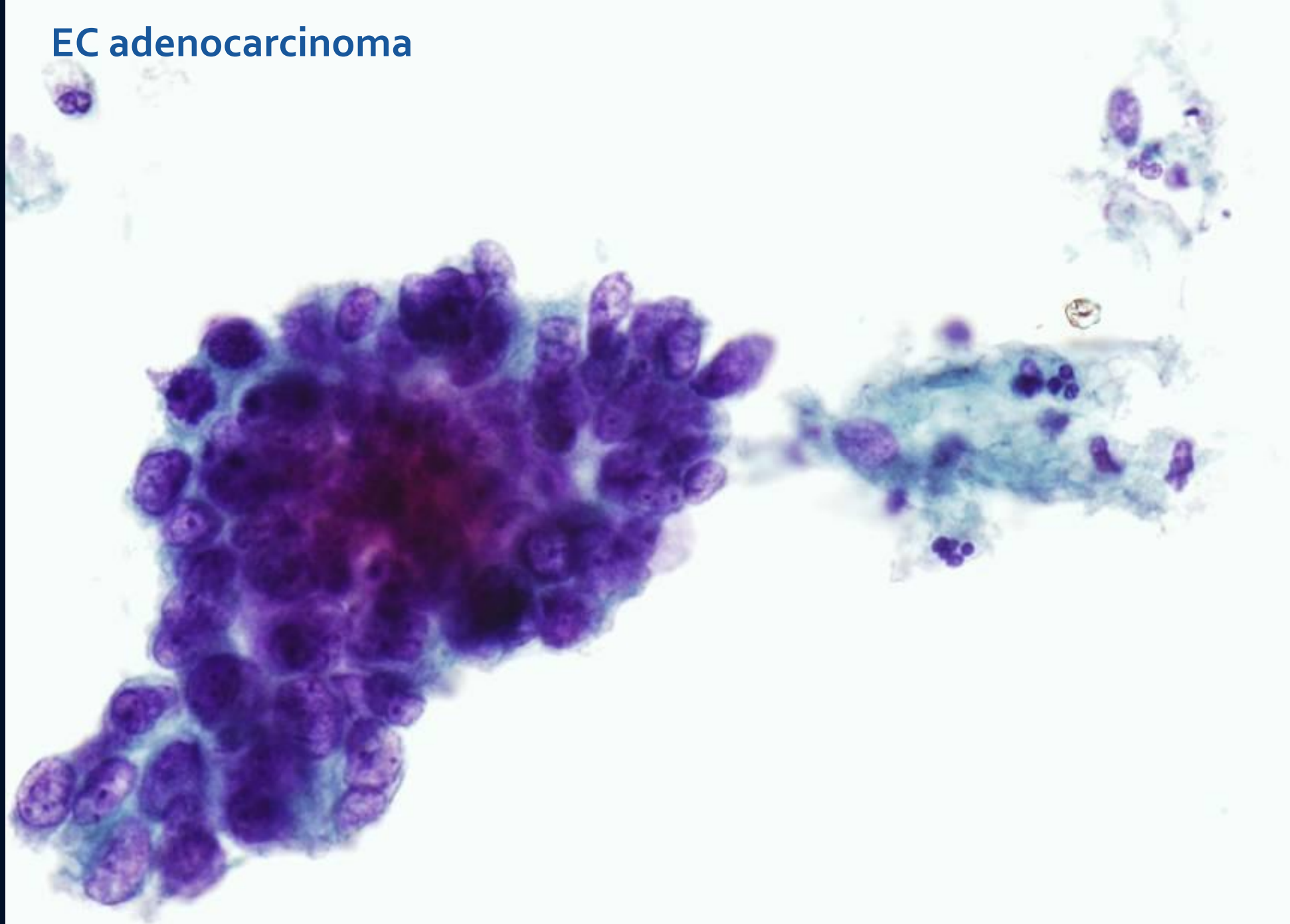
Squamous cell CA



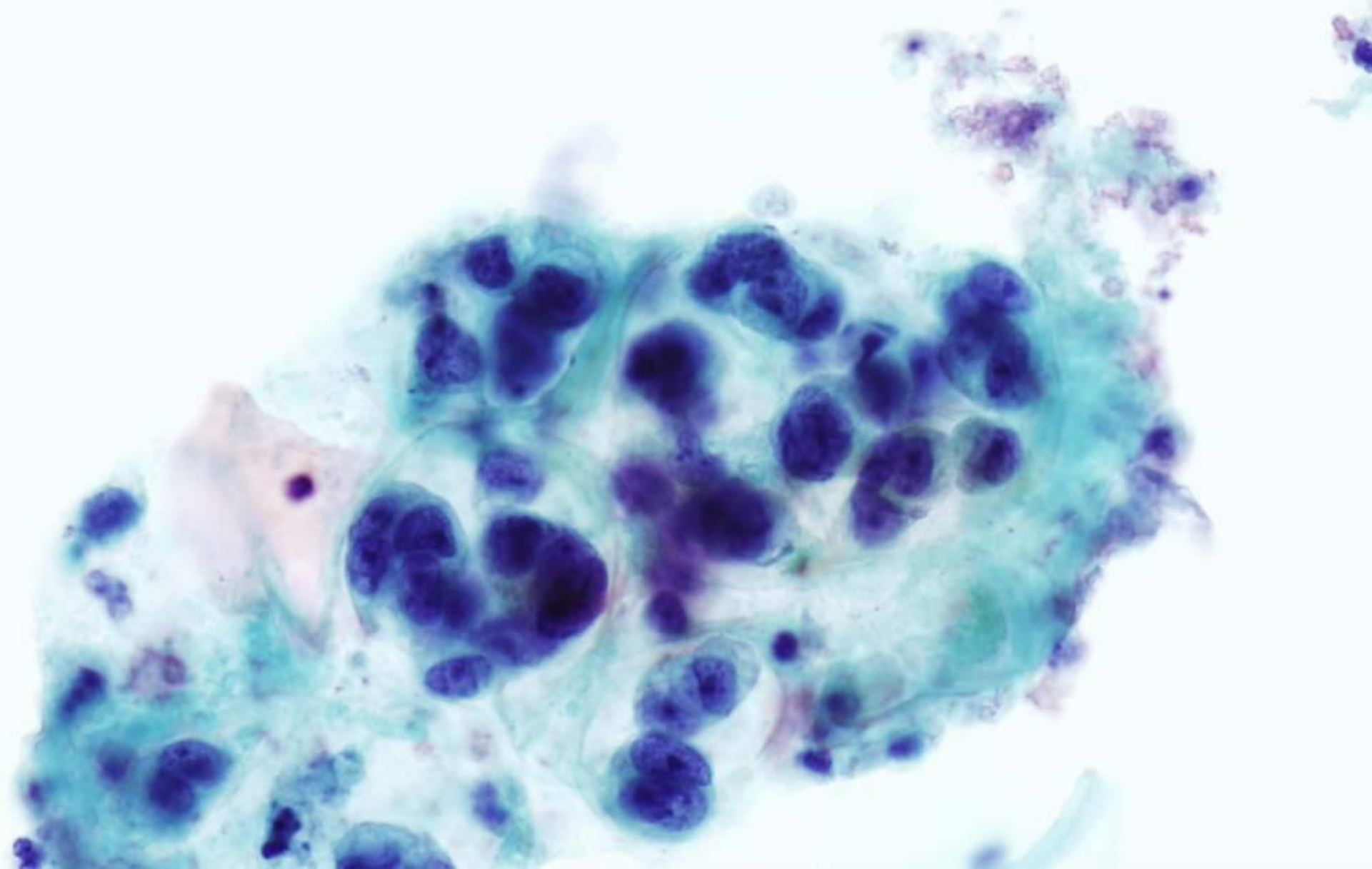
ECAIS



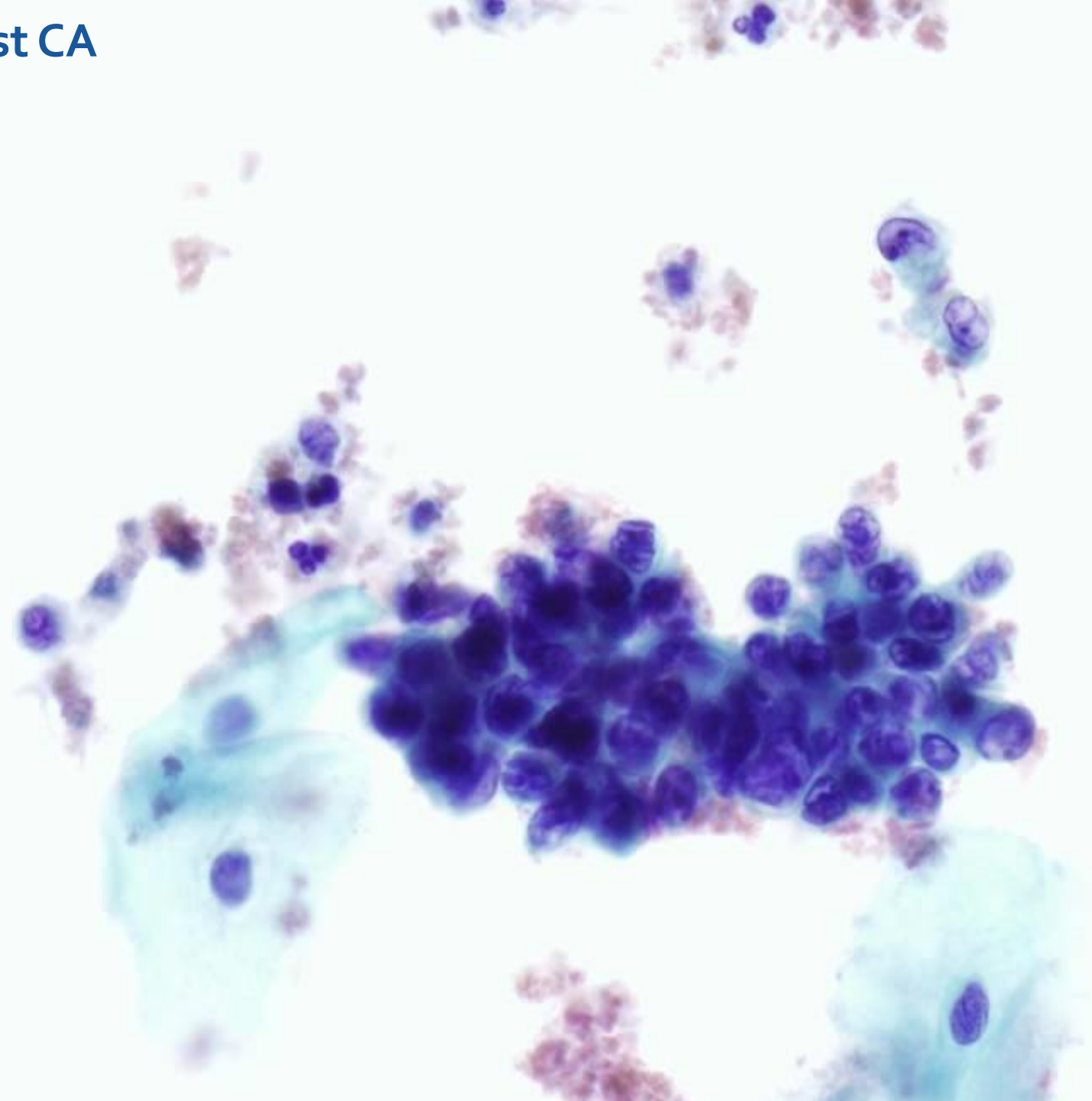
EC adenocarcinoma



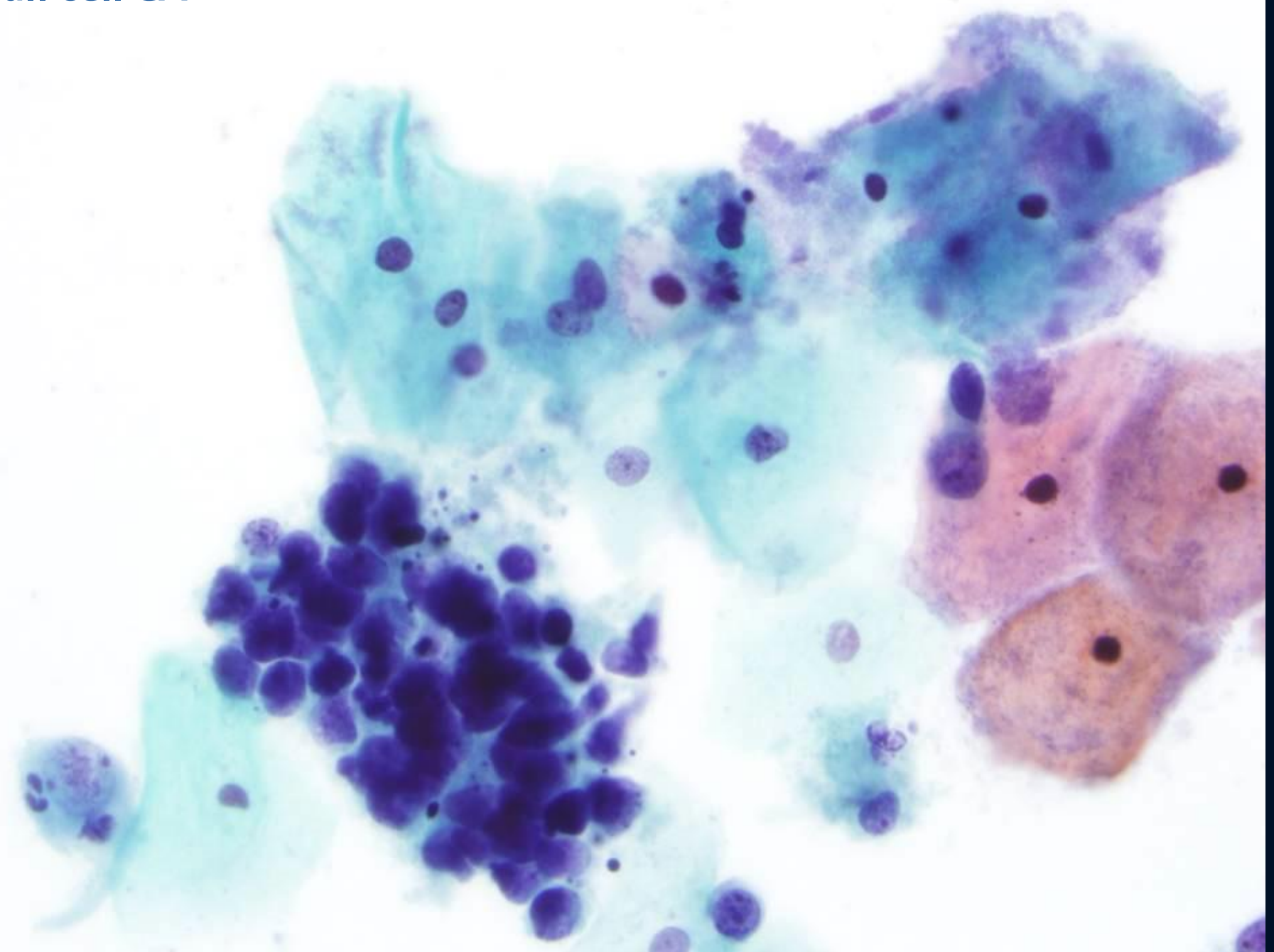
Colon CA



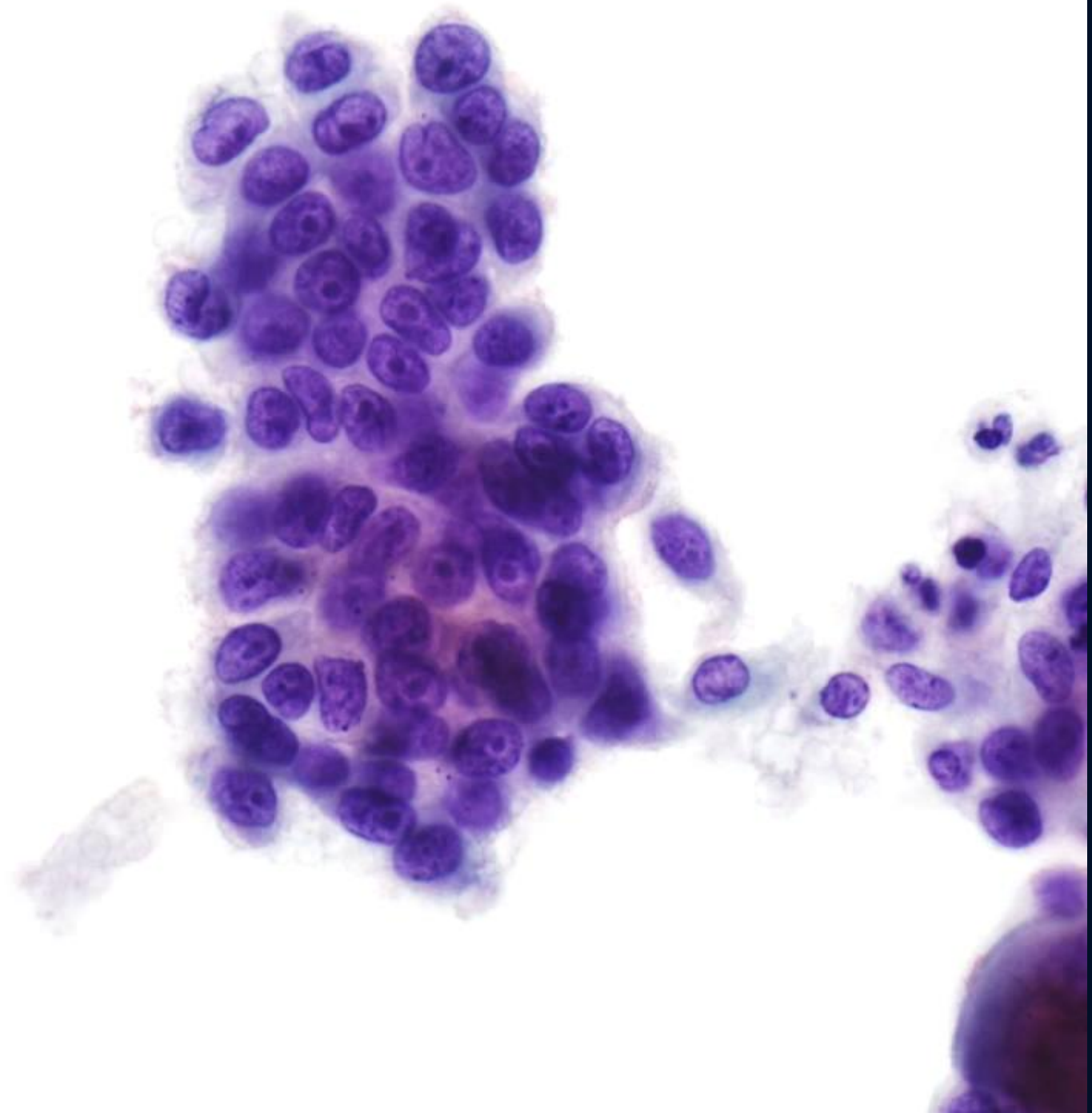
Breast CA



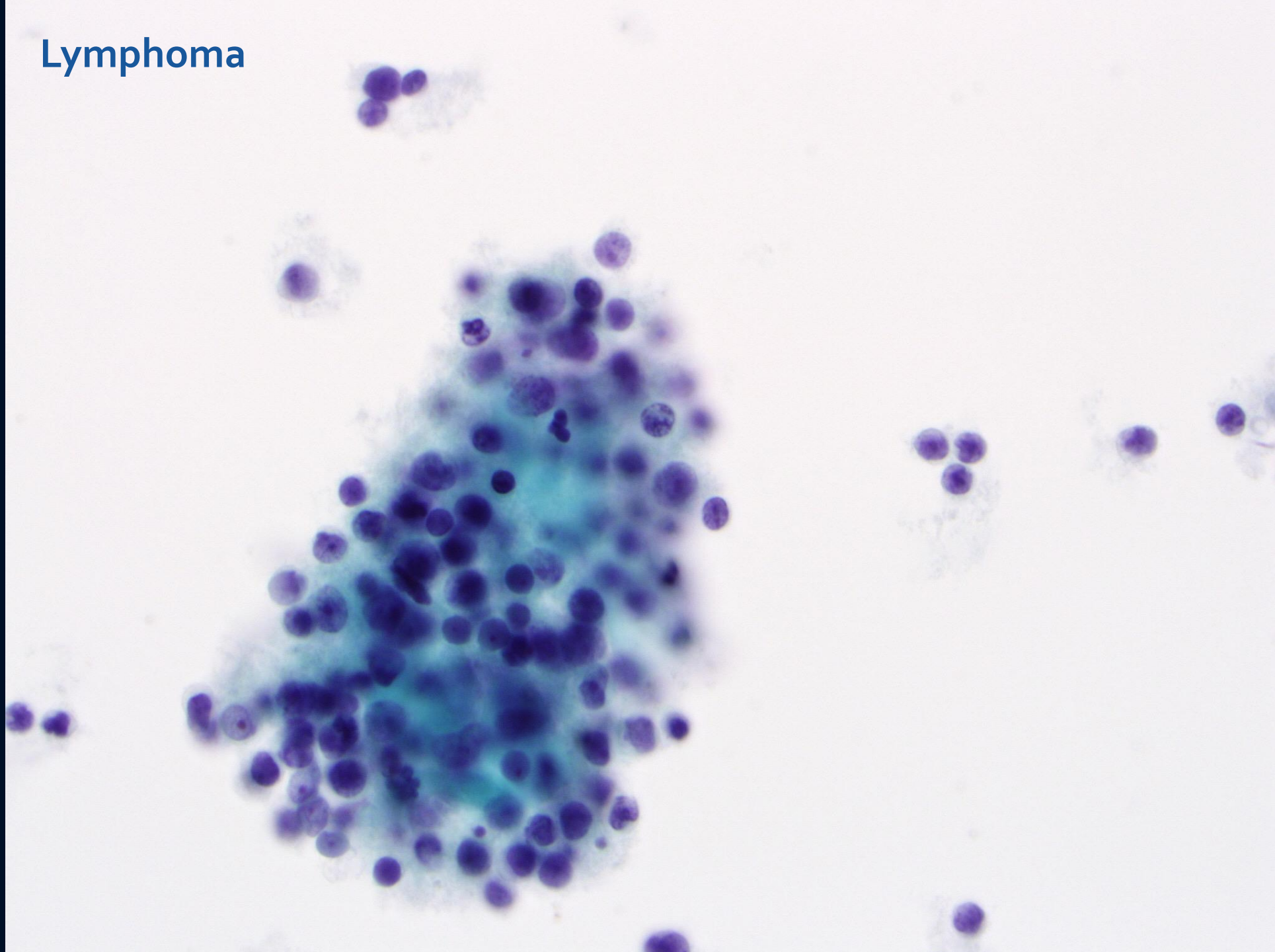
Small cell CA



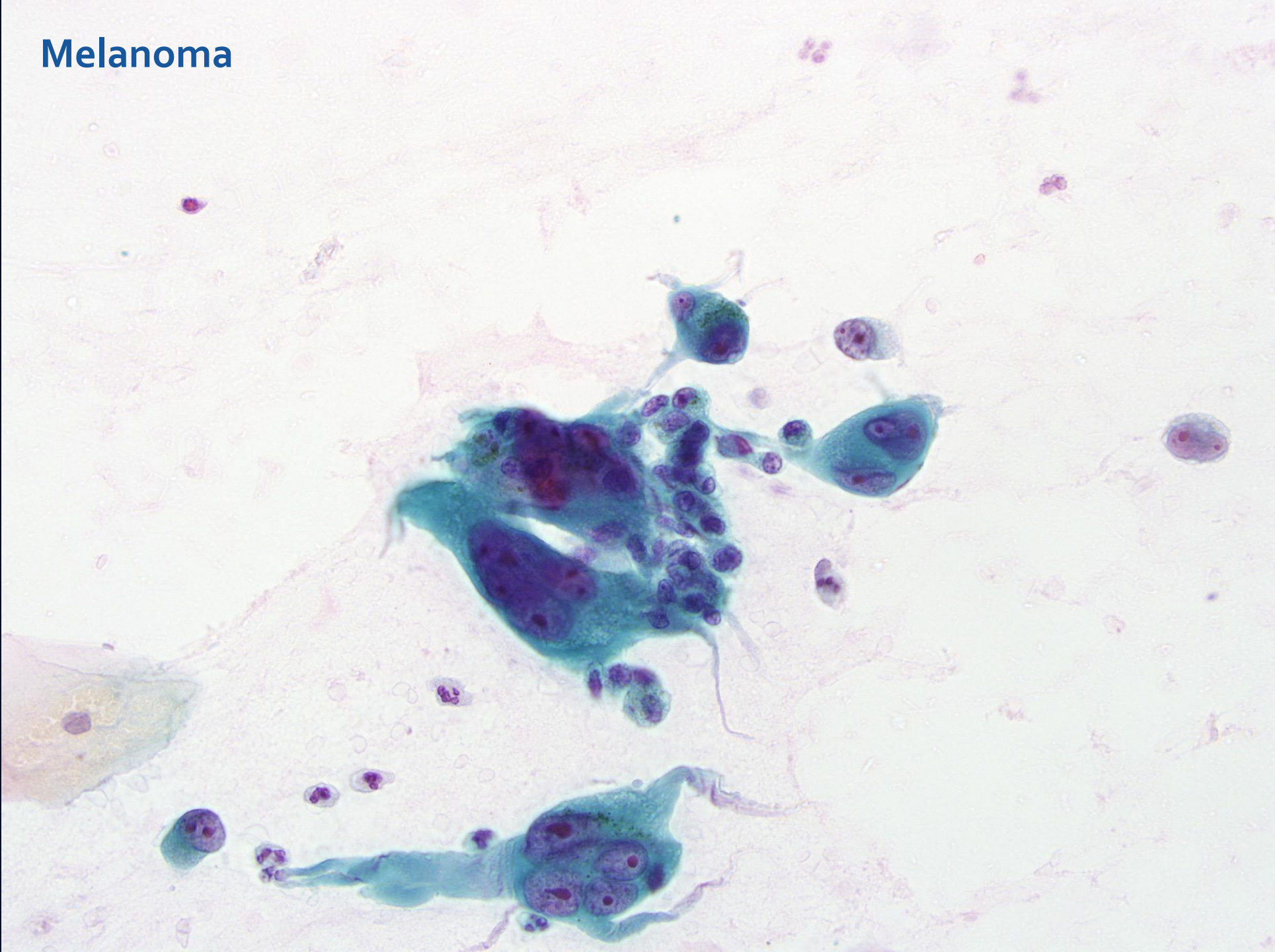
Ovarian CA



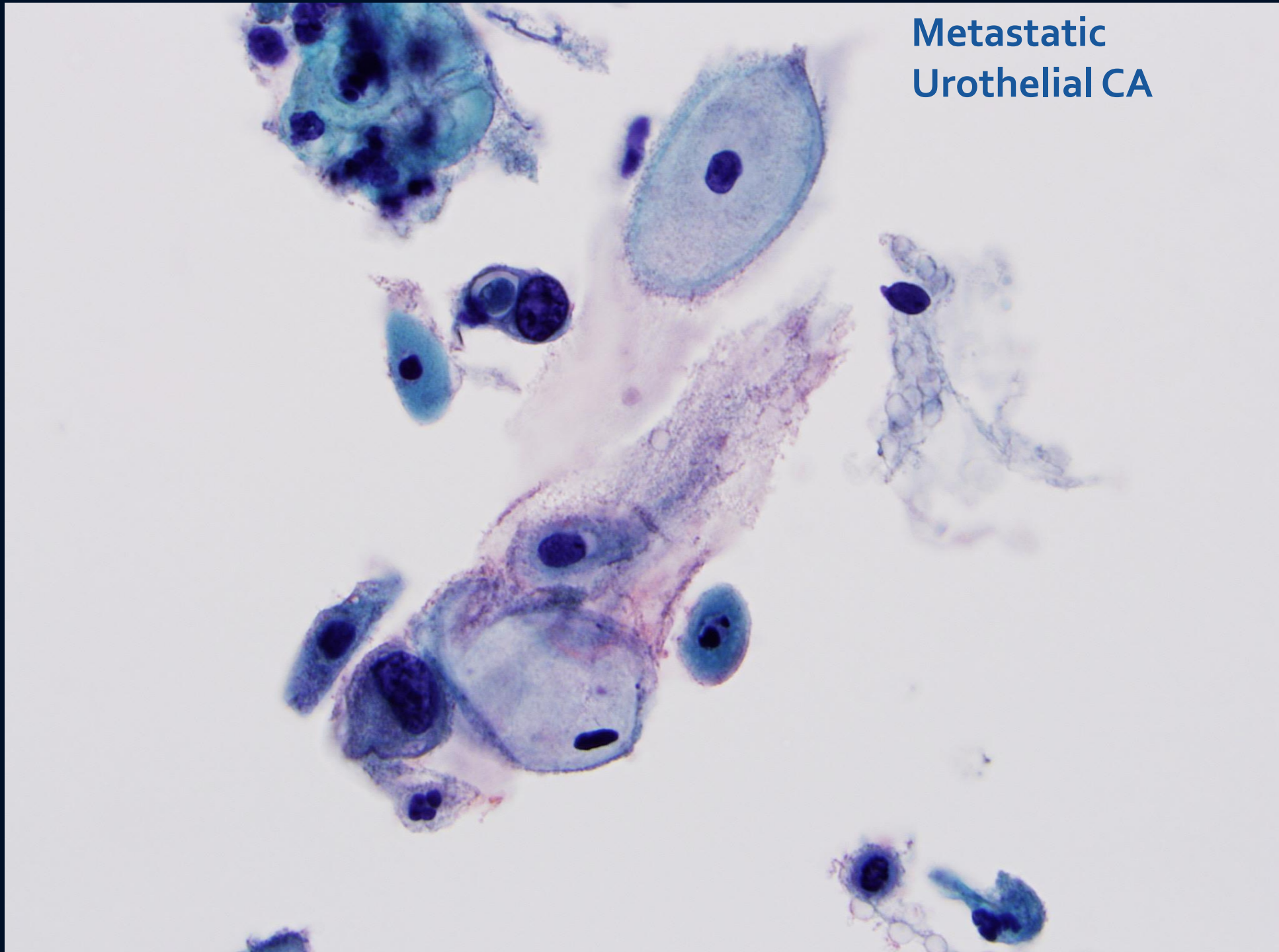
Lymphoma



Melanoma



Metastatic
Urothelial CA



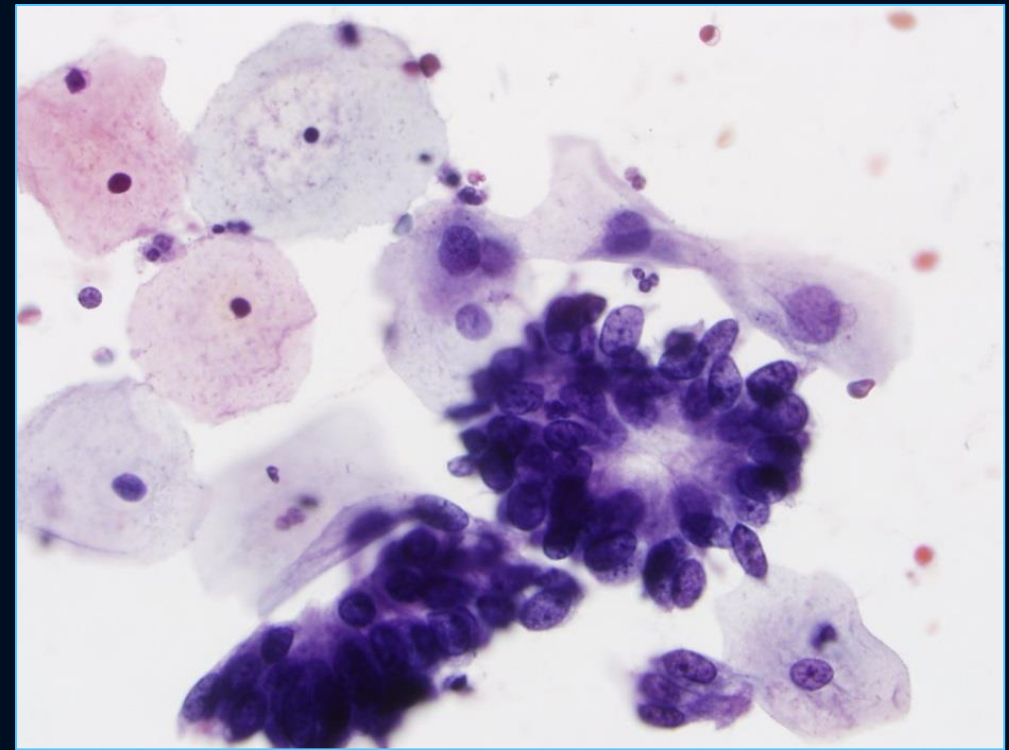
Benign vs Neoplastic HCGs

- **Important differential diagnostic decision**
High potential for error when dealing with cells that present as glandular or rare lesions
- **Problem cases often included in the “Atypical glandular cells” categories of the Bethesda system**
- **Rare lesions may be missed due to limited exposure, often we do not think of them without clinical history provided**

Evaluating Slides with HCG's

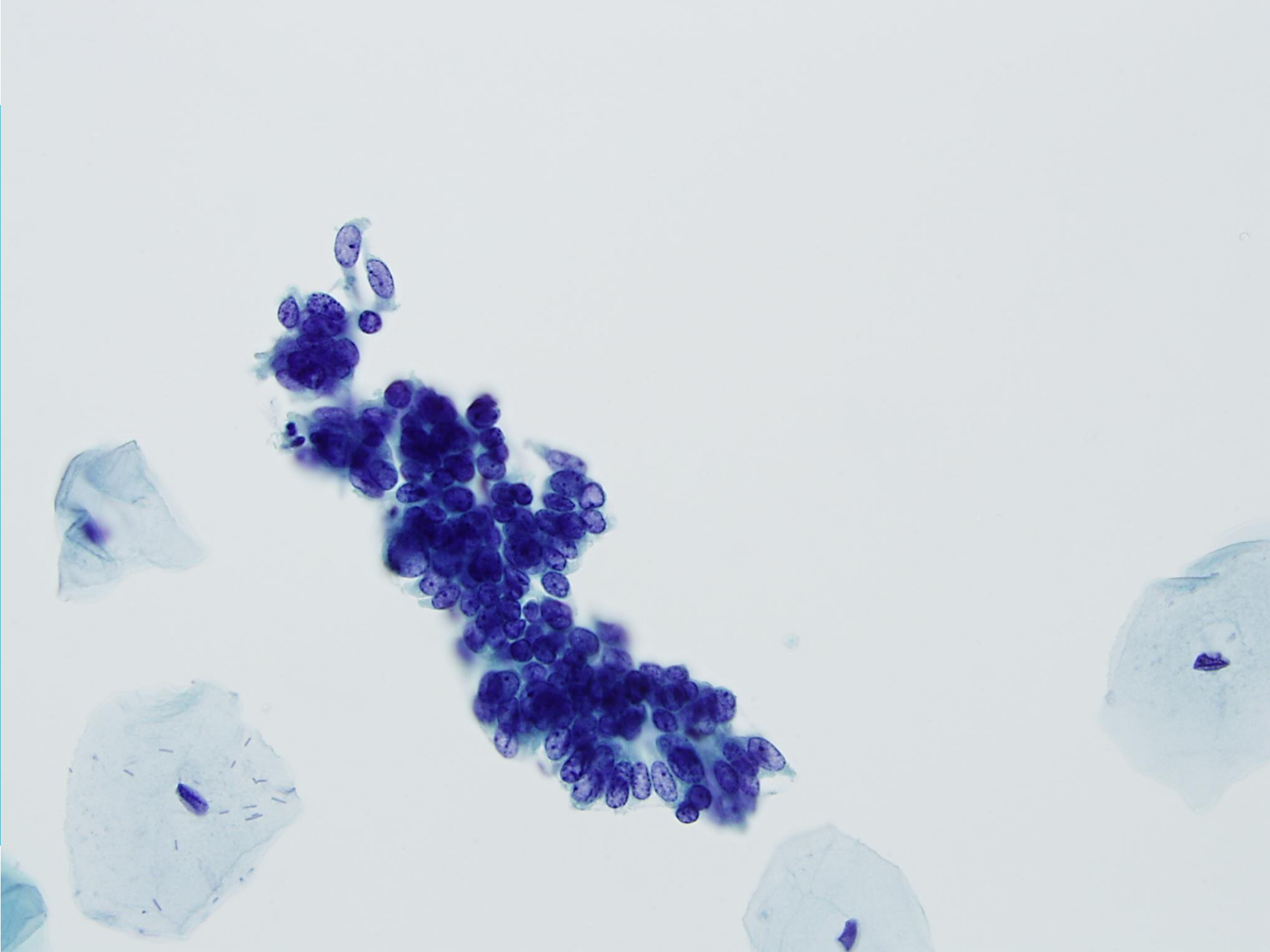
- The groups
- The background
- The individual cells
- The history

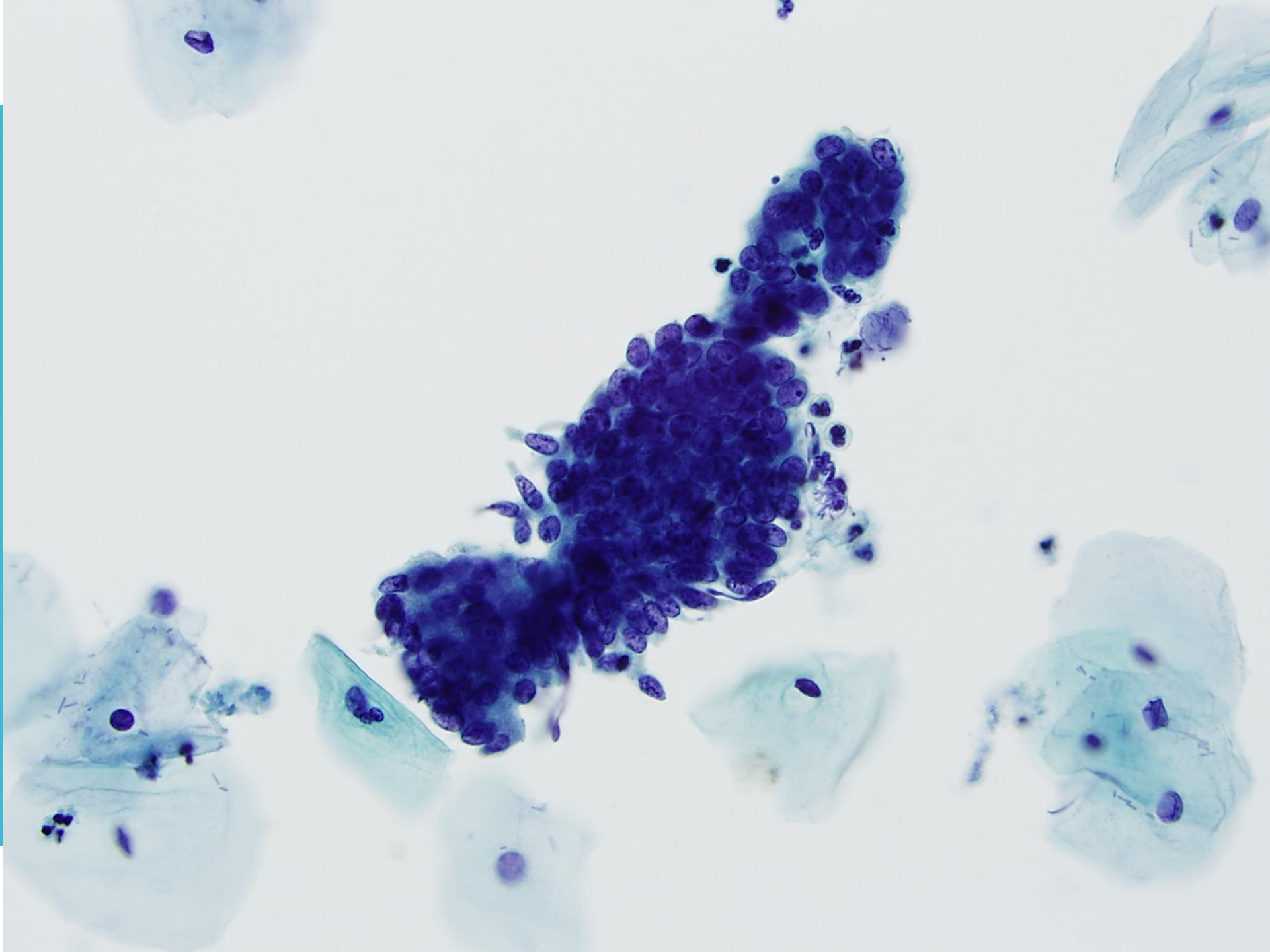
Squamous and Glandular Case Examples



CASE 1:

- 42 year-old woman
- No abnormal history
- Thin Prep Pap test

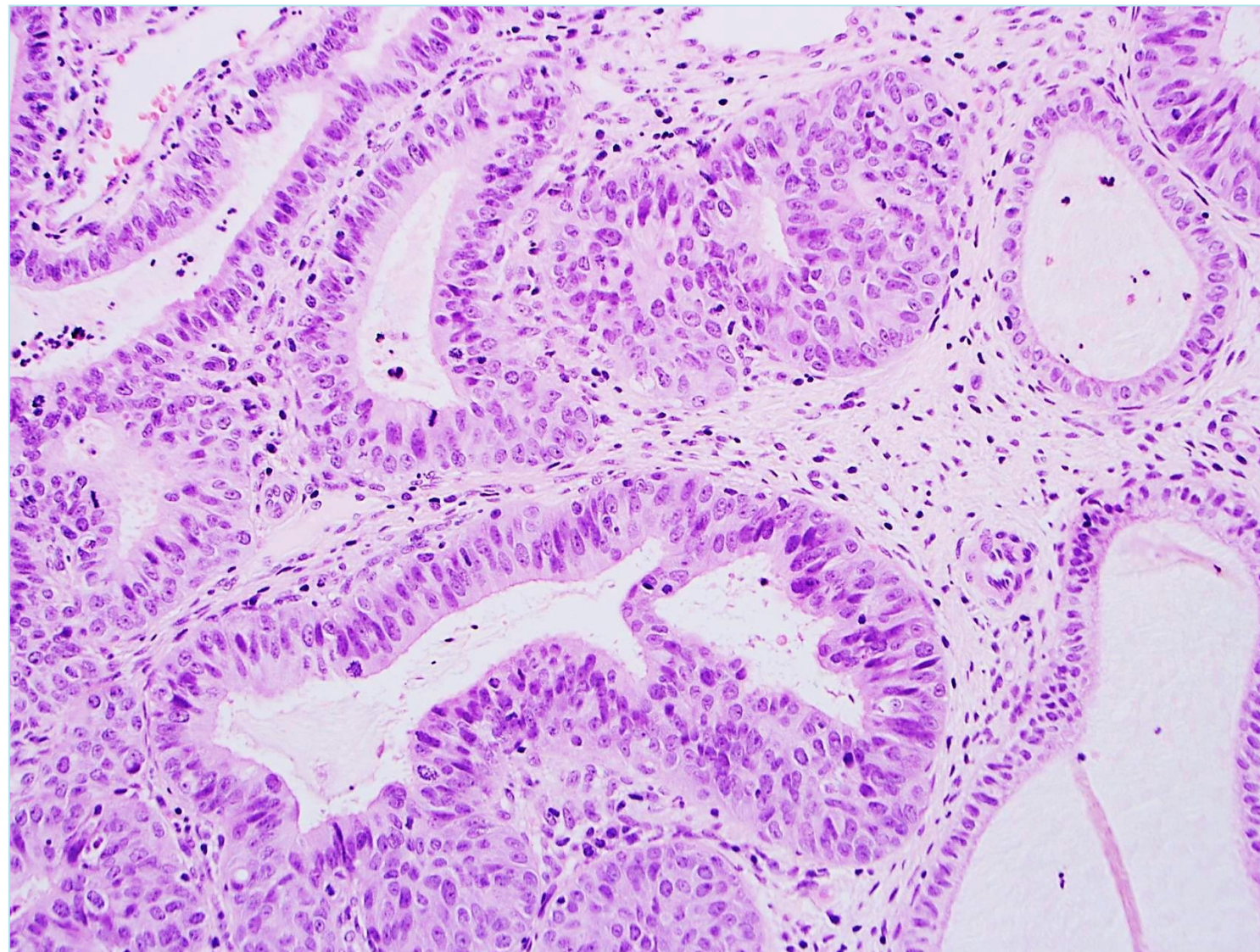




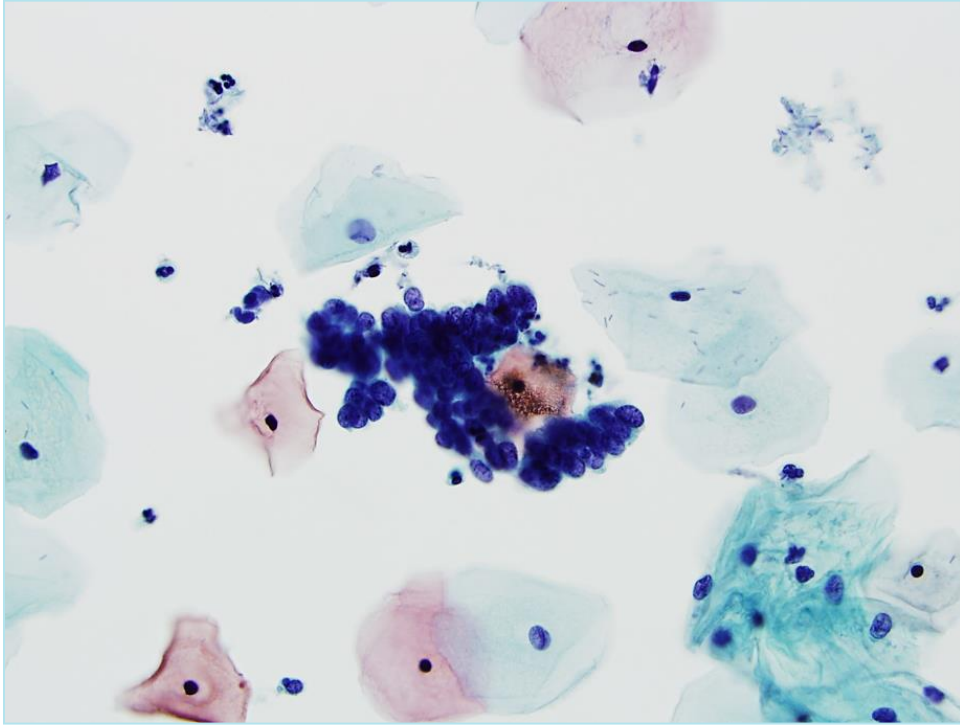
What is your interpretation ?

1. Tubal metaplasia
2. Endocervical AIS
3. Metastatic adenocarcinoma
4. Reactive endocervical cells
5. Endometrial cells

Endocervical adenocarcinoma in situ

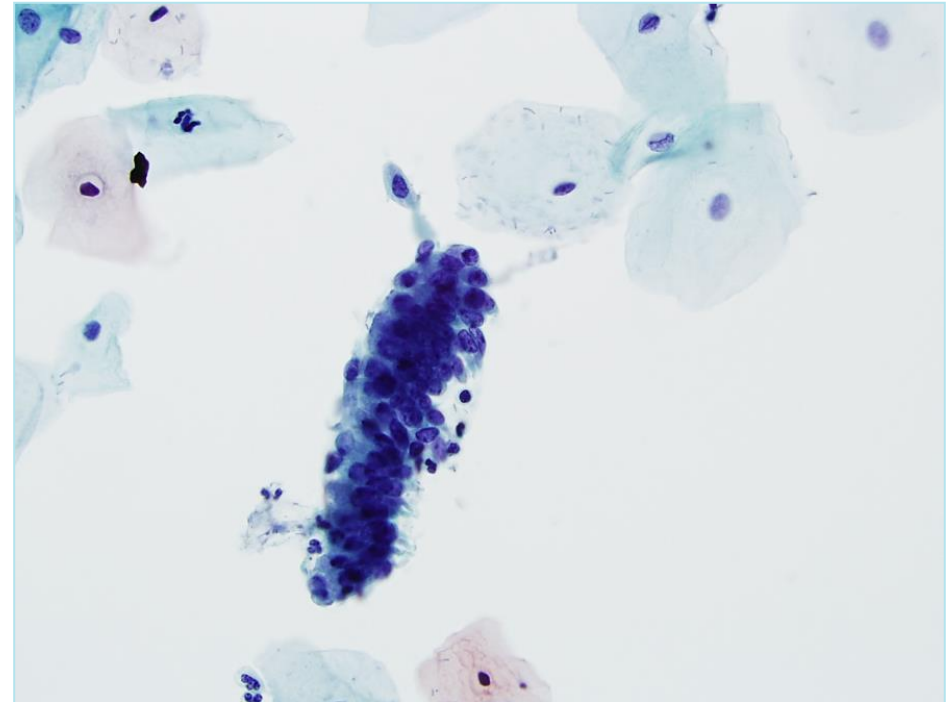


Features of Endocervical AIS

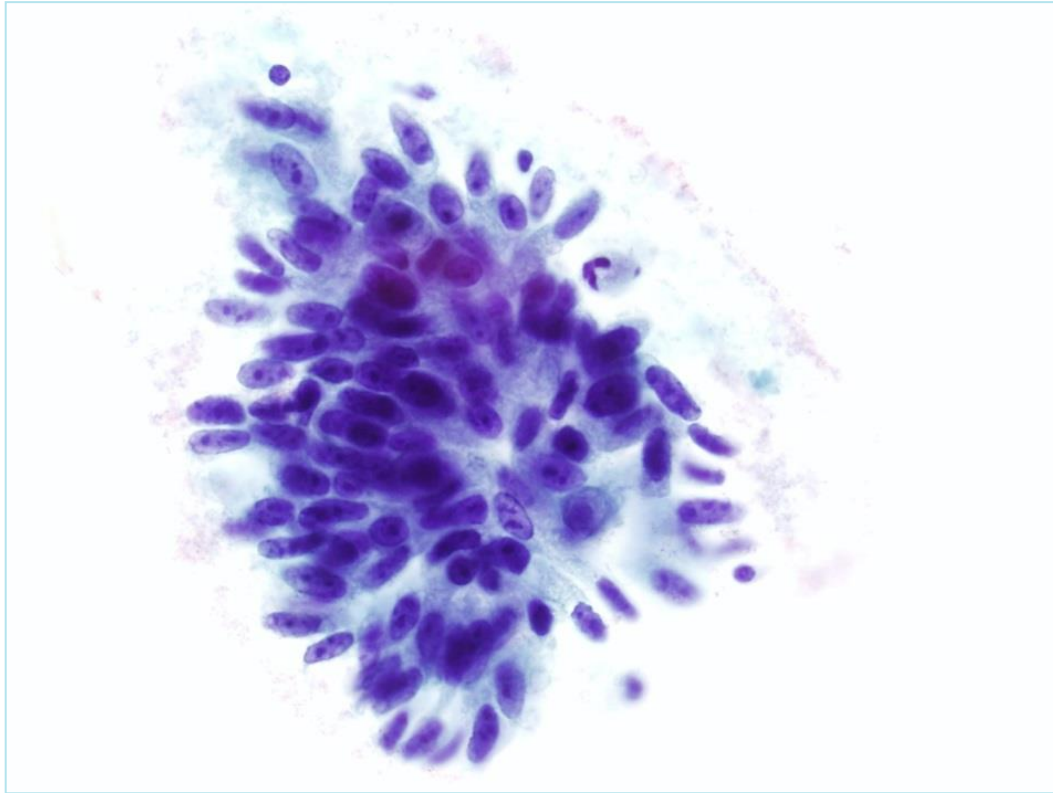


- Hyperchromasia
- Mitoses
- Apoptotic bodies

- Isolated stratified strips
- Increased N/C

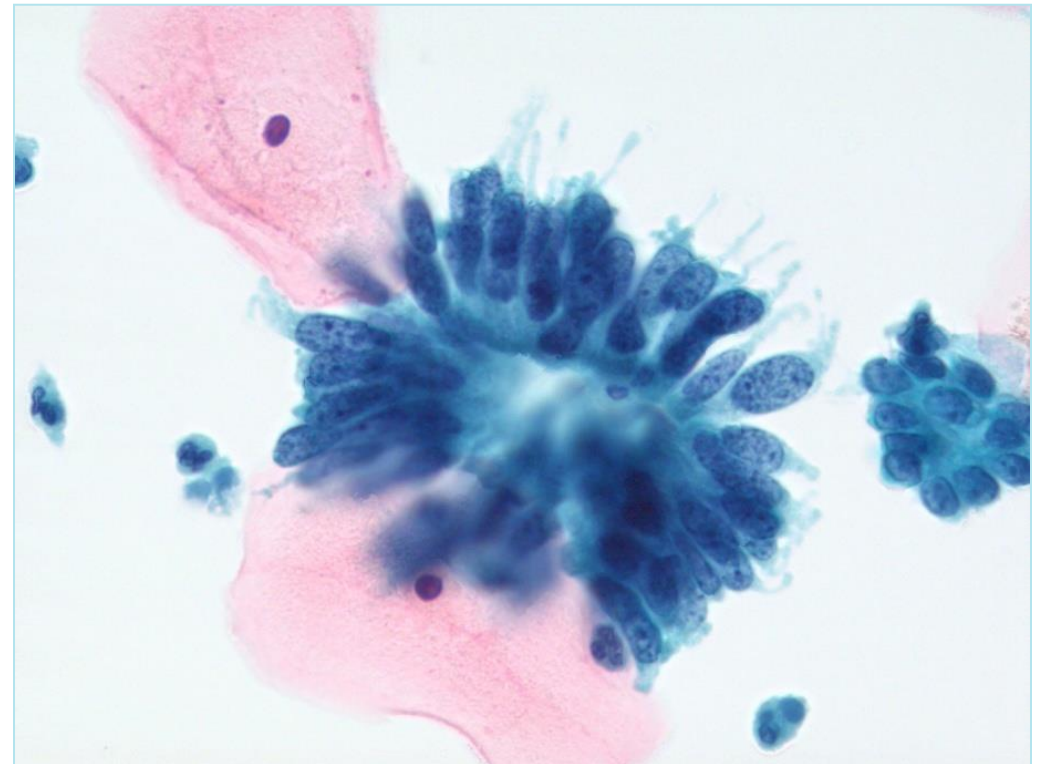


Features of Endocervical AIS

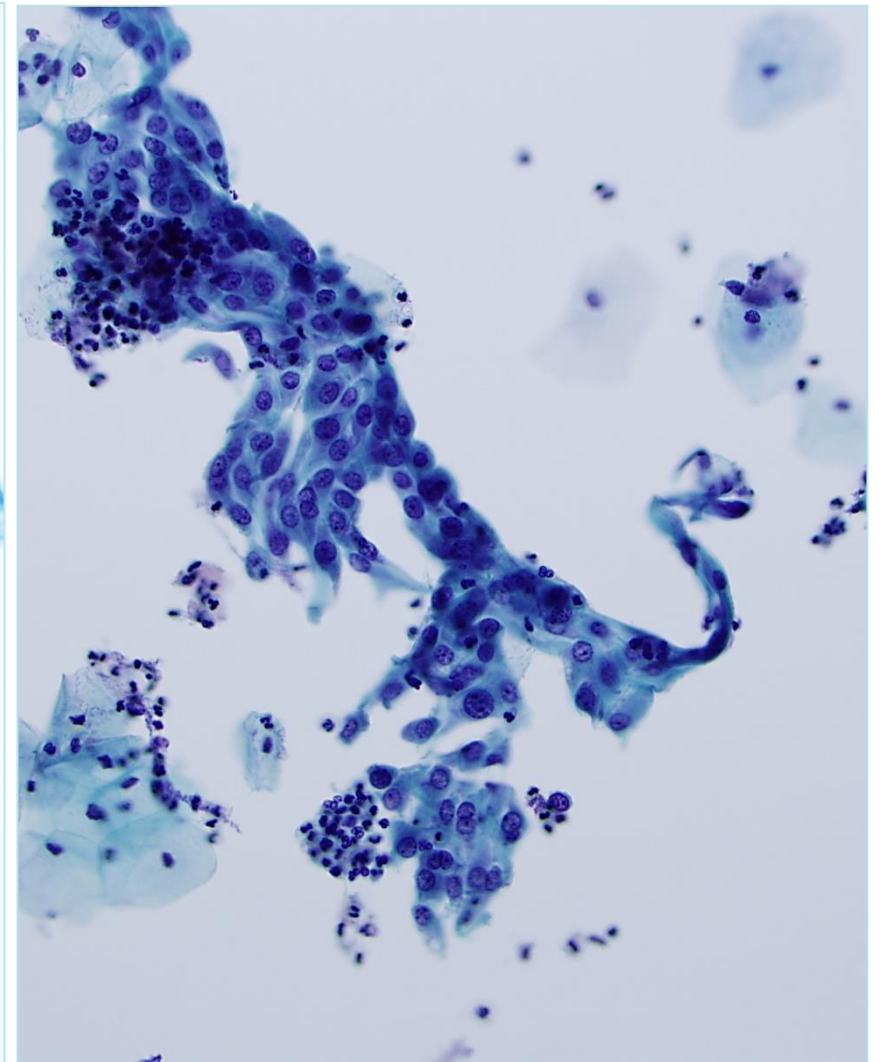
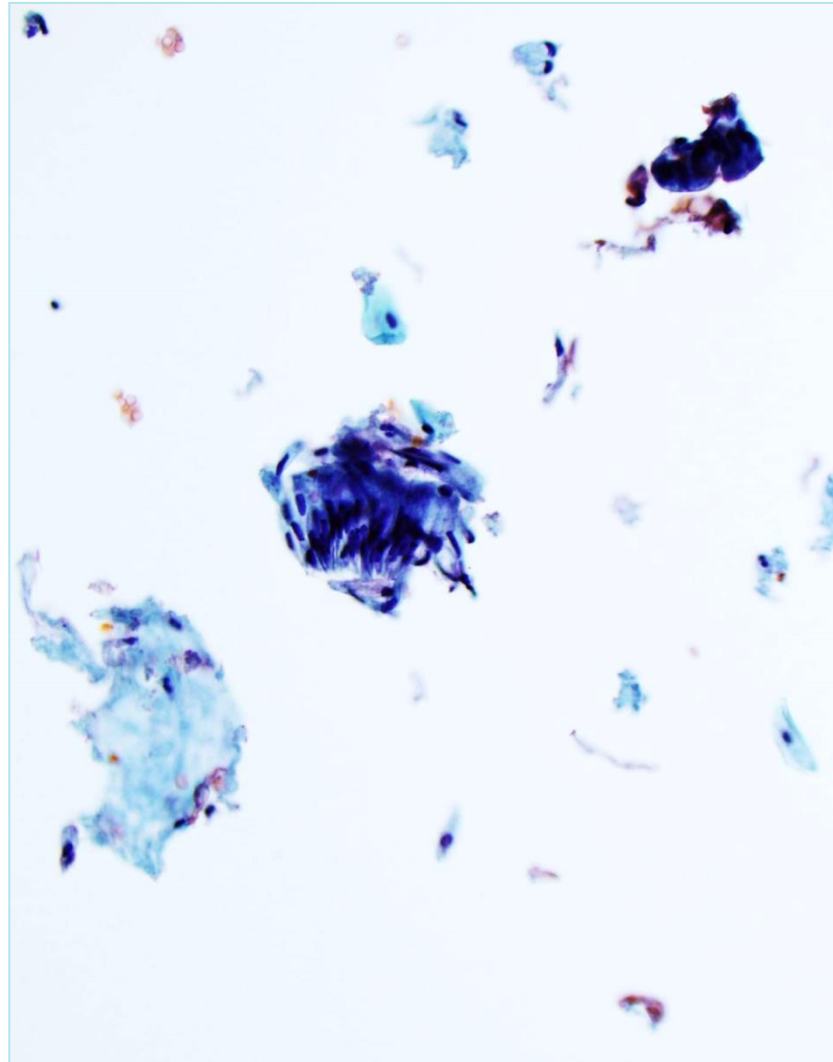


- Pseudostratification
- Rosettes

- Feathering
- Elongate tapered nuclei



Reactive endocervical cells



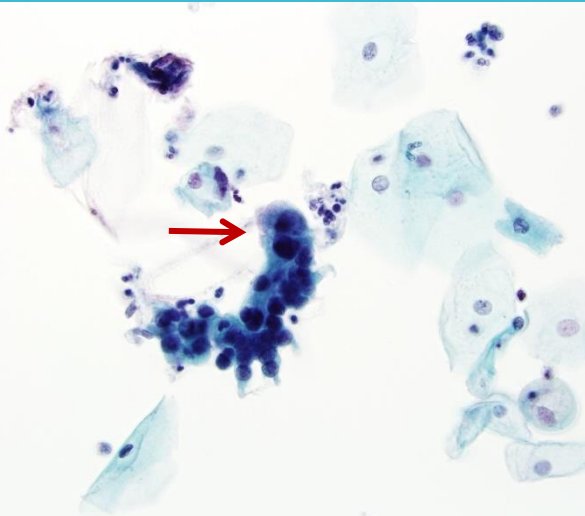
Tubal Metaplasia; Cytologic Features

Some features in common with AIS

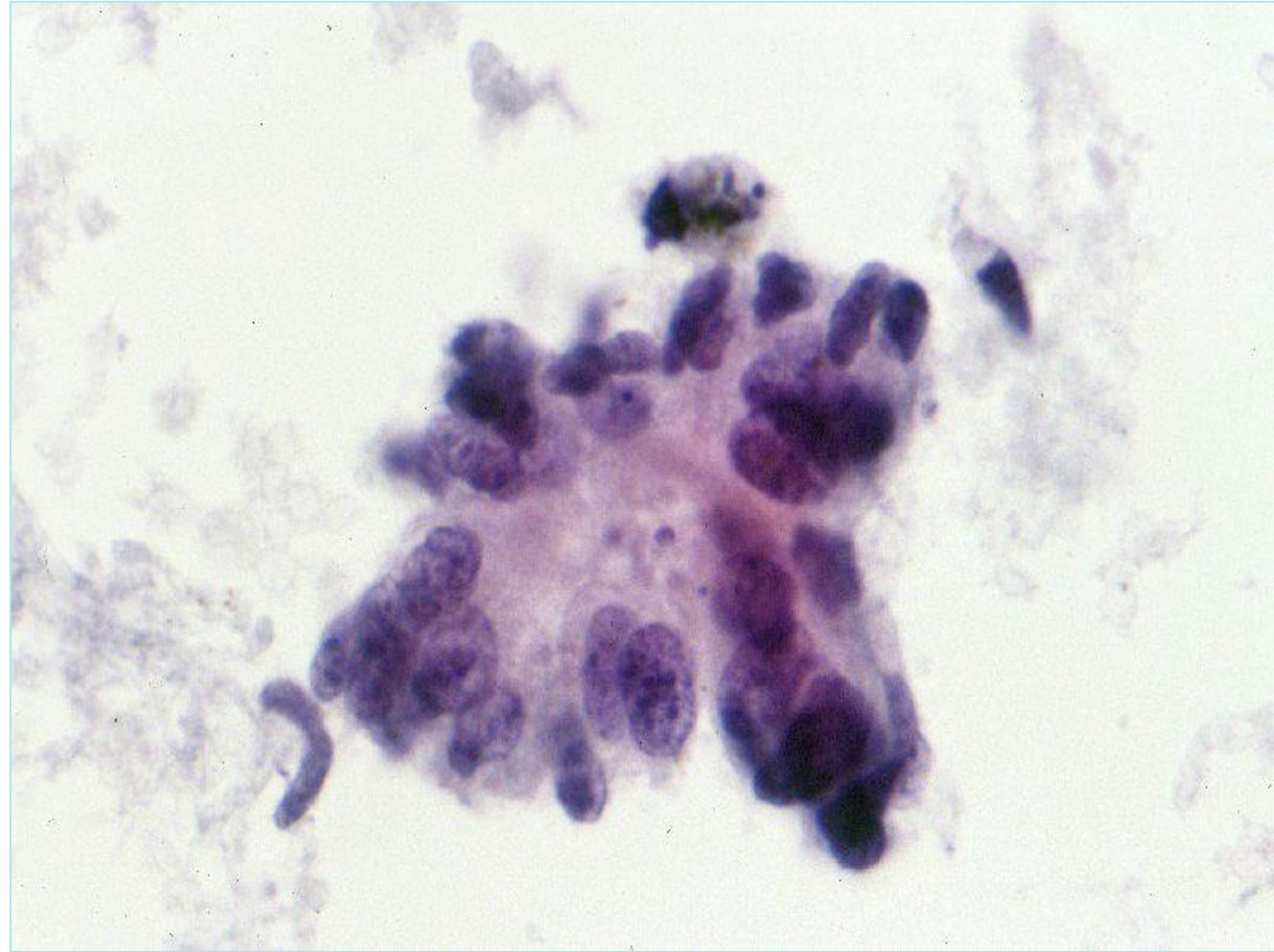
- Chromatin (granularity/distribution)
- Increased N/C ratio
- Crowding and hyperchromasia

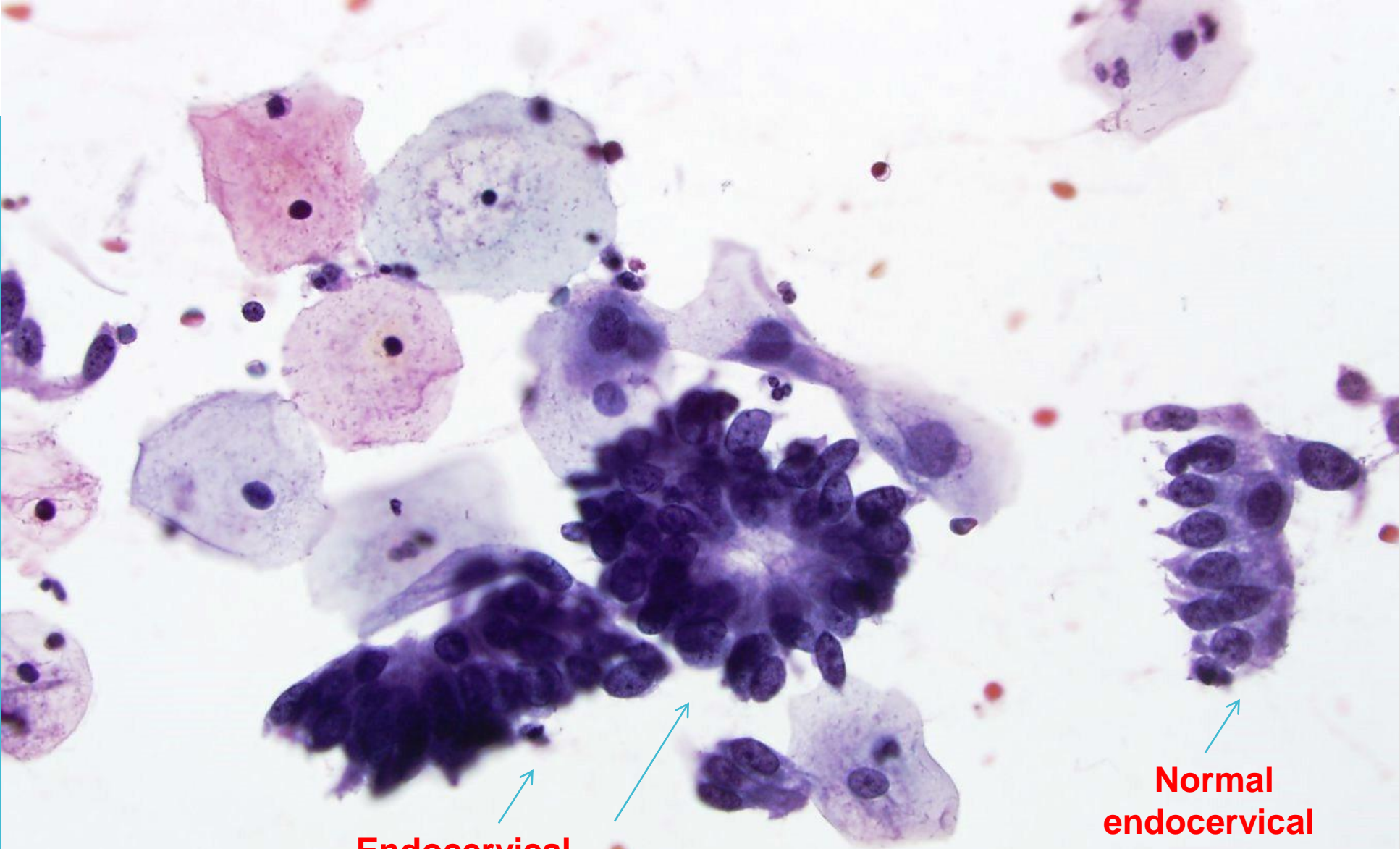
Differential Dx features

- Large stripped nuclei
- Cilia/terminal bars



Metastatic adenocarcinoma



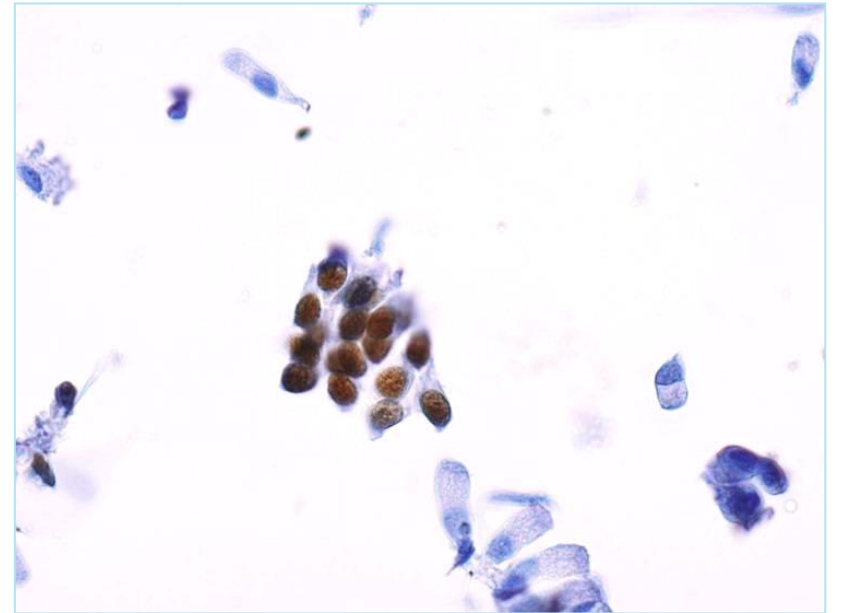
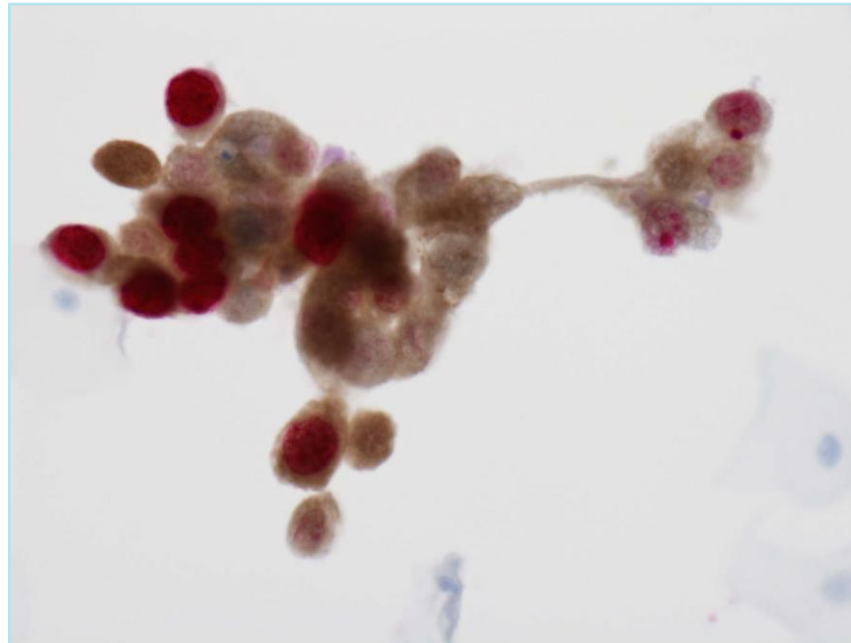


Endocervical adenocarcinoma in situ (strip of cells and rosette)

Normal endocervical cells

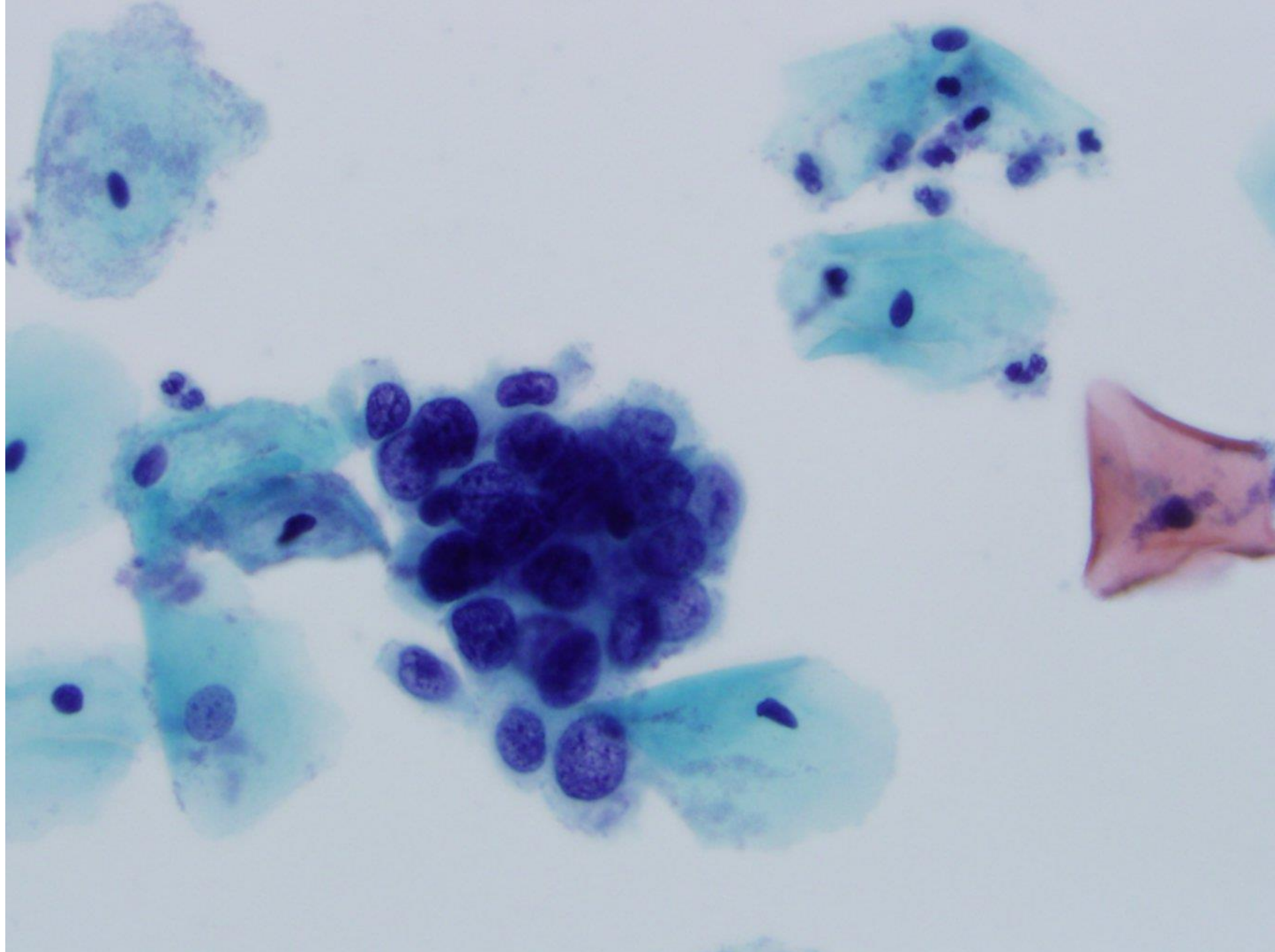
Immunocytochemistry

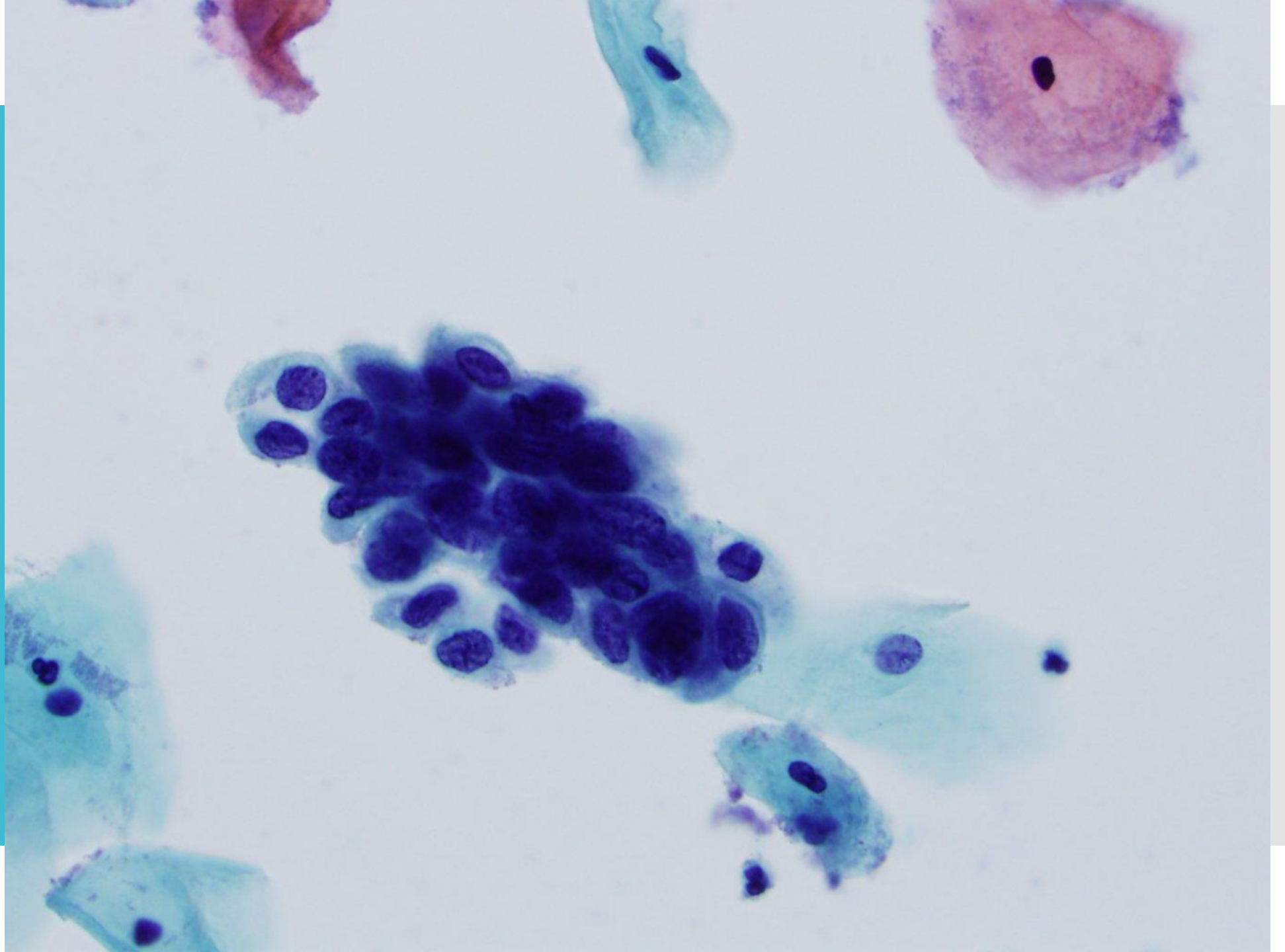
- p16inK4a
- Ki-67
- ProEX C

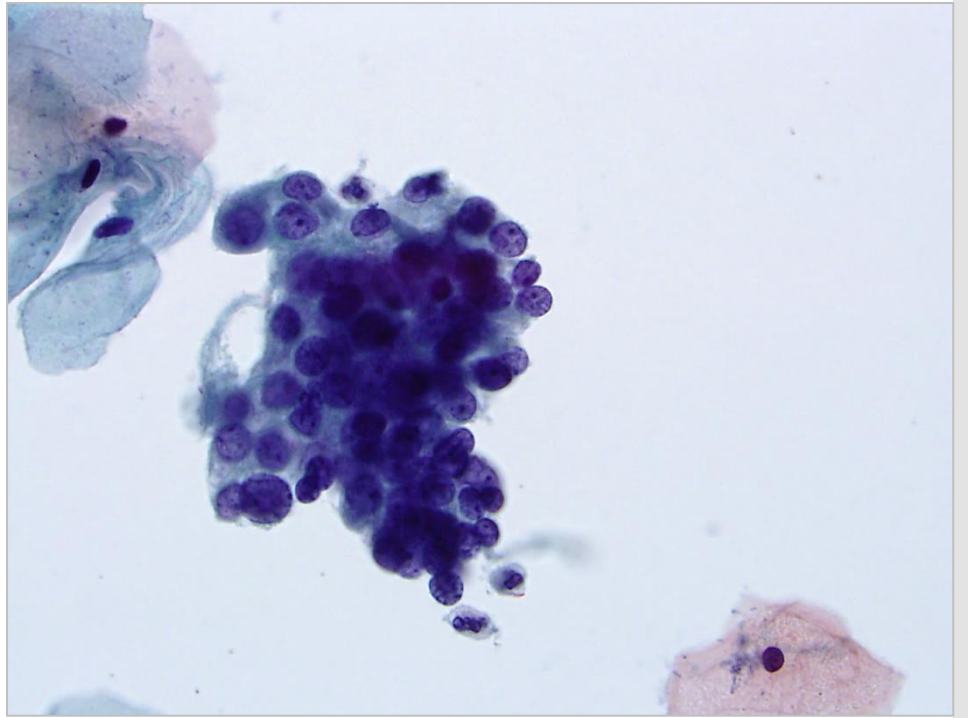
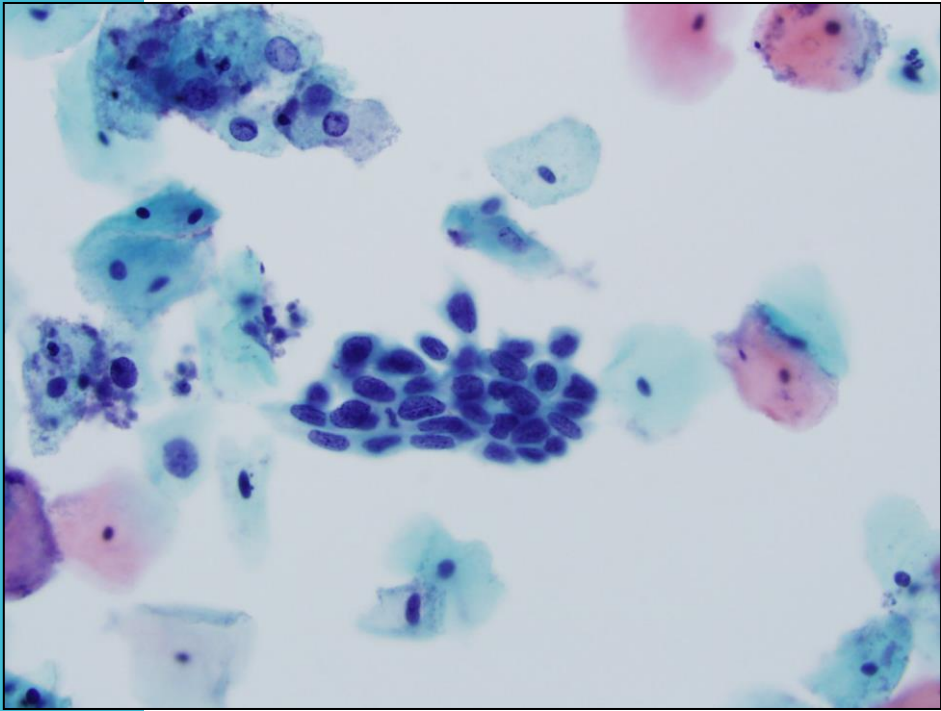


CASE 2:

- 32-year-old woman
- Last Pap test 3 years ago was ASCUS HPV +16
- Thin Prep Pap test 16





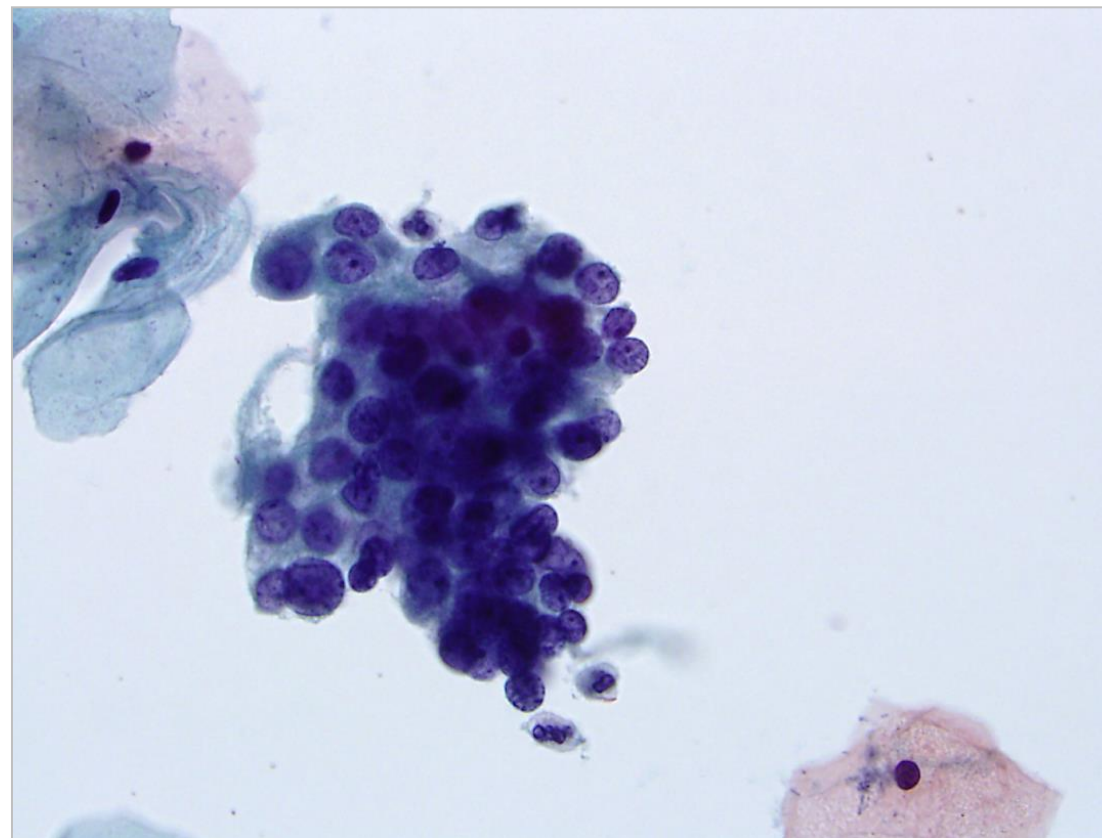


What is your interpretation ?

1. NILM (Endometrial cells)
2. HSIL (with glandular involvement)
3. Atrophy
4. EC adenocarcinoma in situ
5. Invasive squamous cell carcinoma

Cytopathologic Interpretation

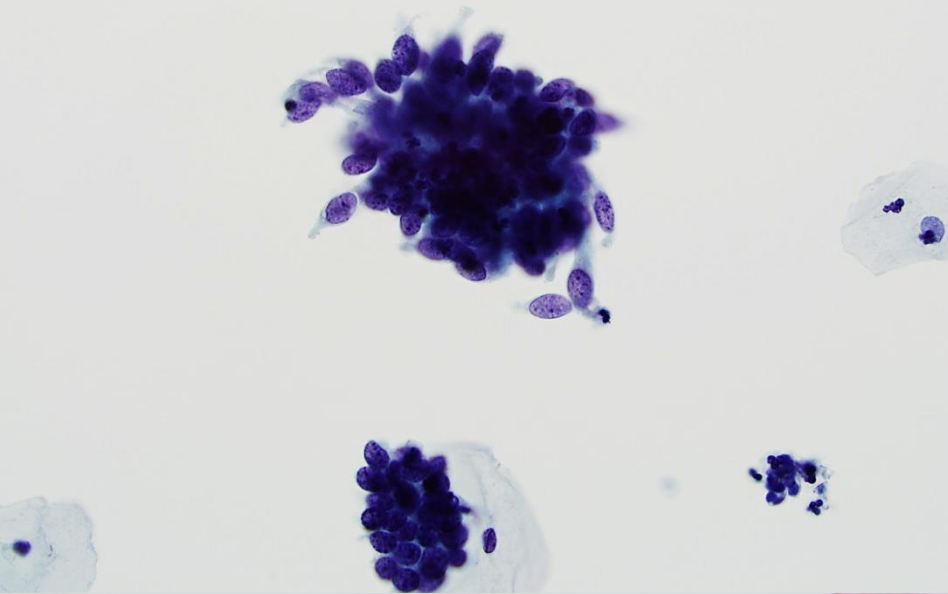
HSIL; gland involvement cannot be excluded



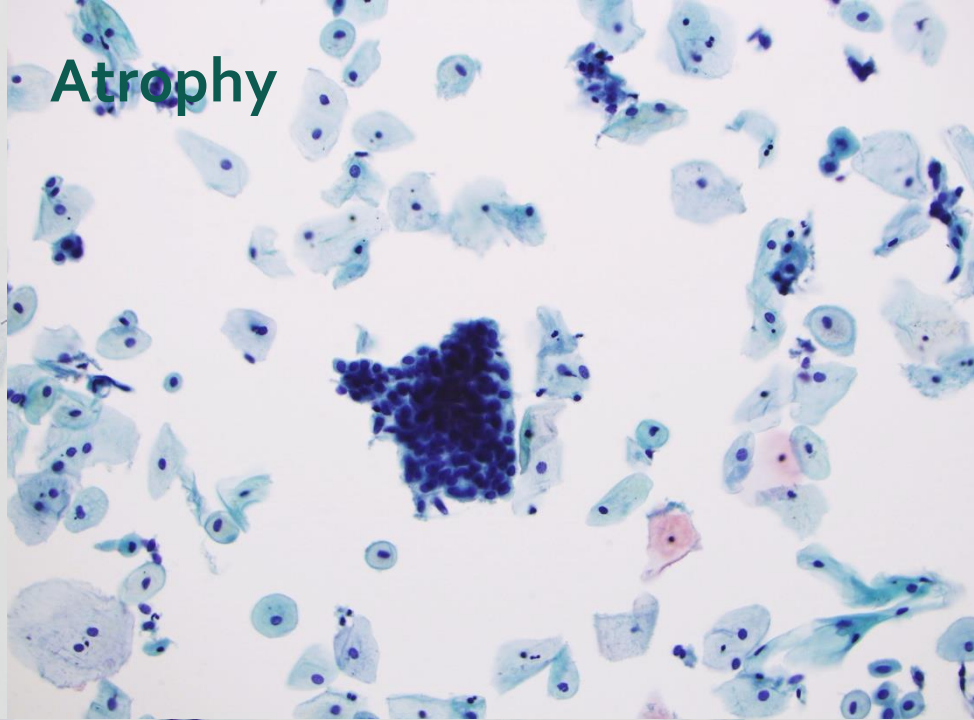
HSIL – Glandular involvement, Differential Diagnoses

- **Normal EM cells**
- **Reactive endocervical cells**
- **Atrophy**
- Endocervical adenocarcinoma in situ
- Invasive squamous cell carcinoma

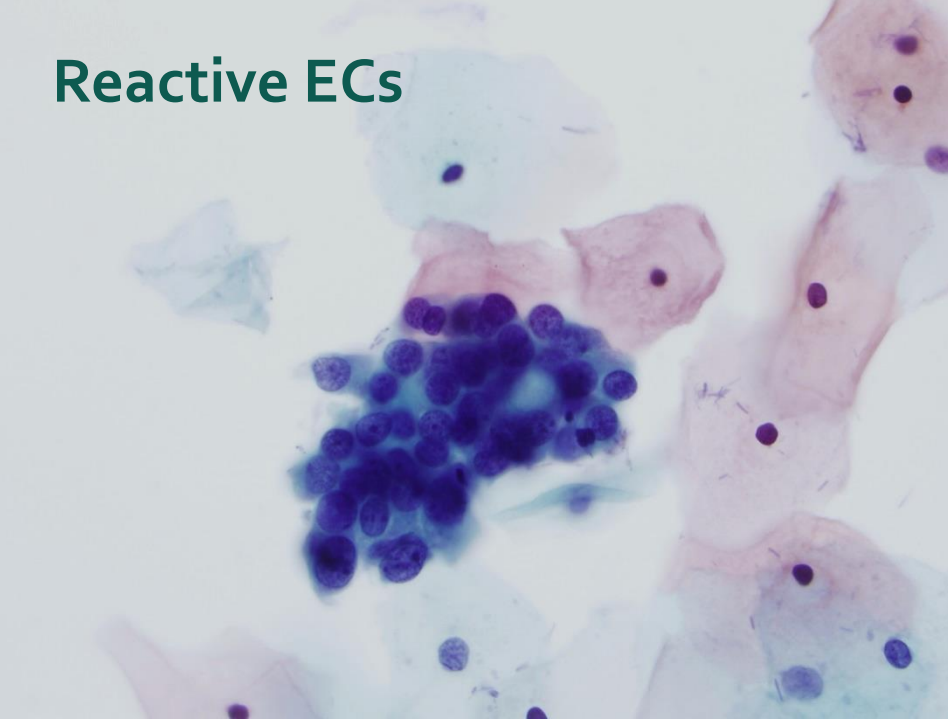
EC AIS



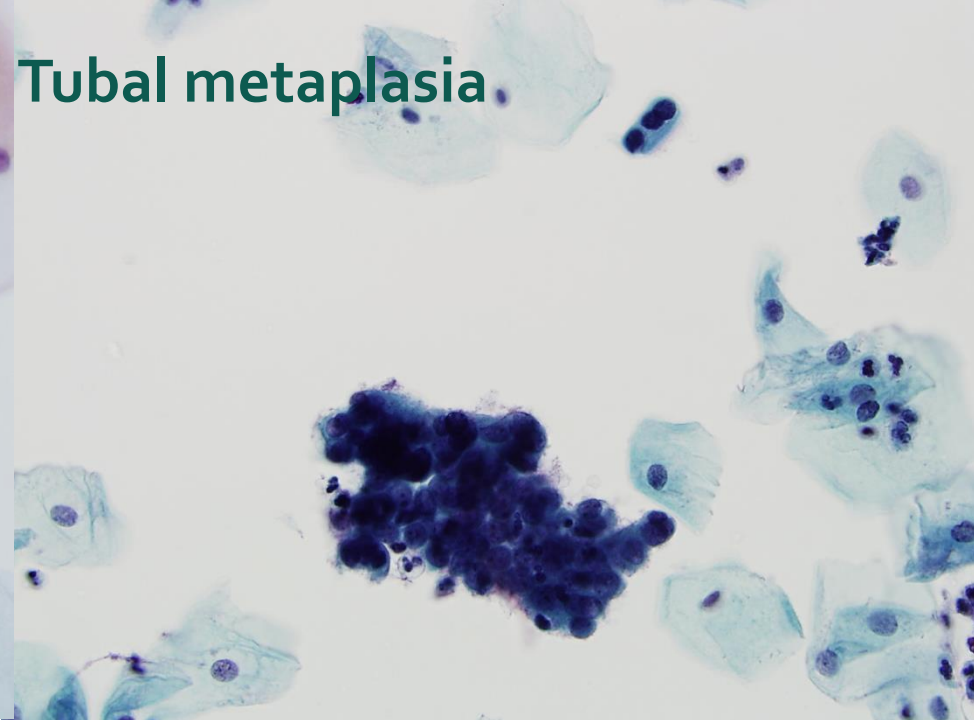
Atrophy

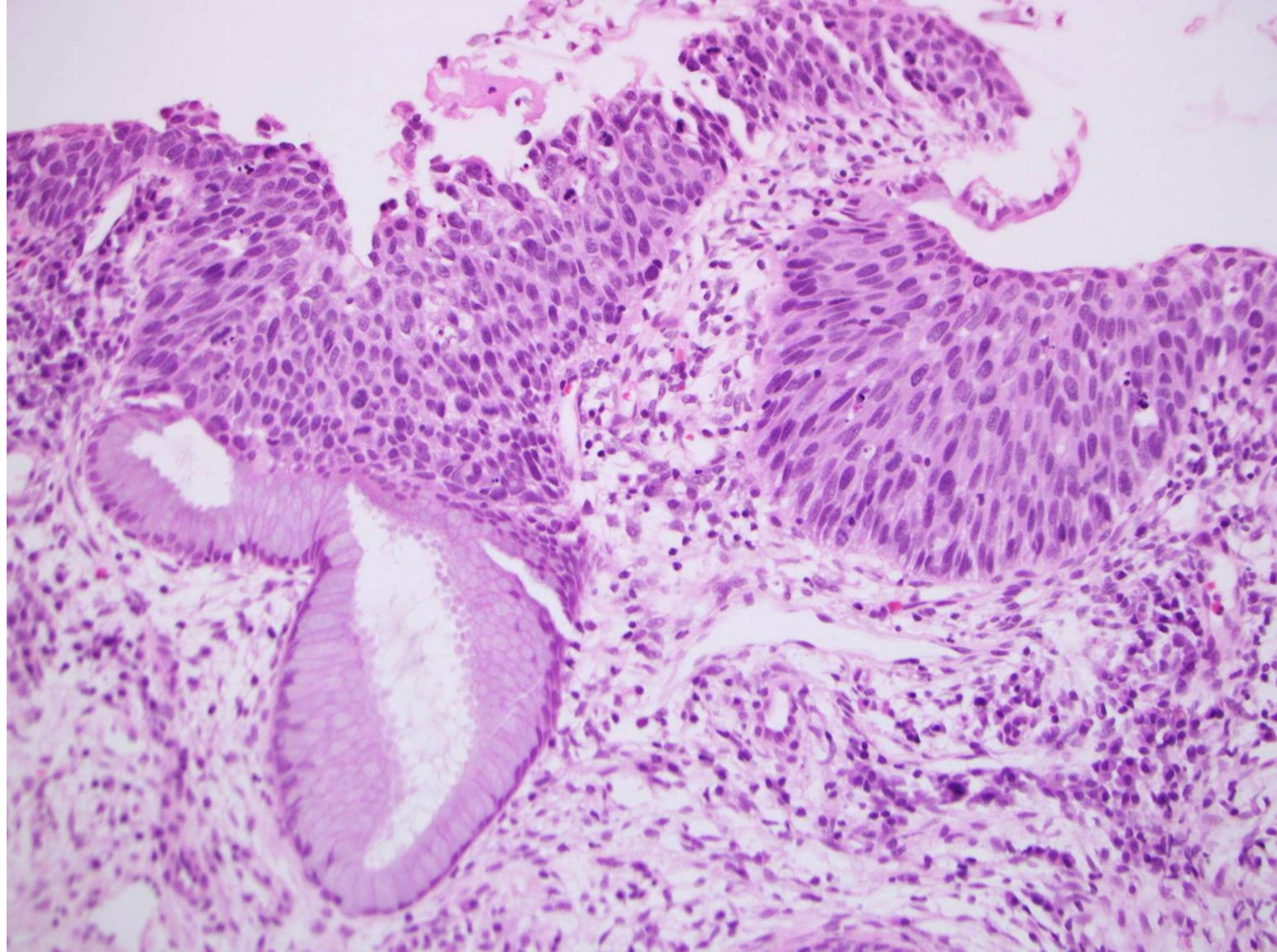


Reactive ECs

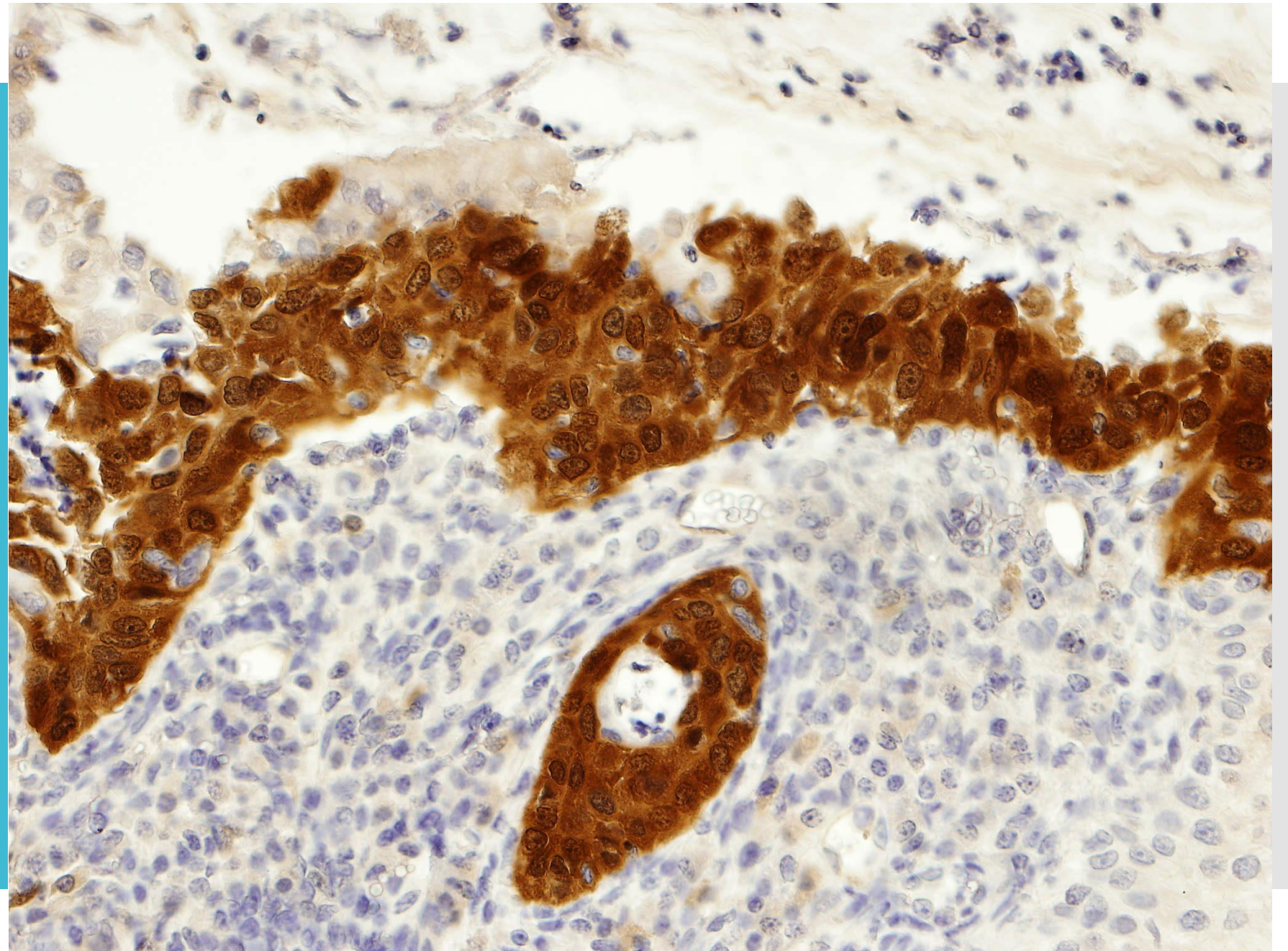


Tubal metaplasia



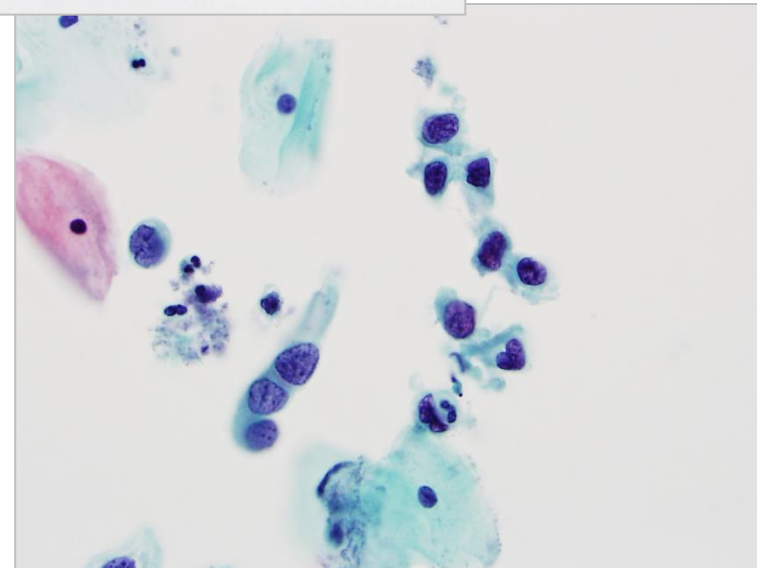
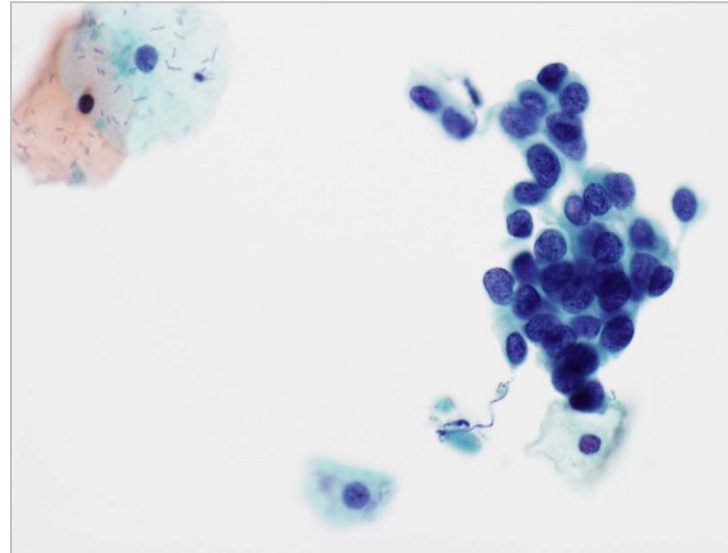


IHC p16



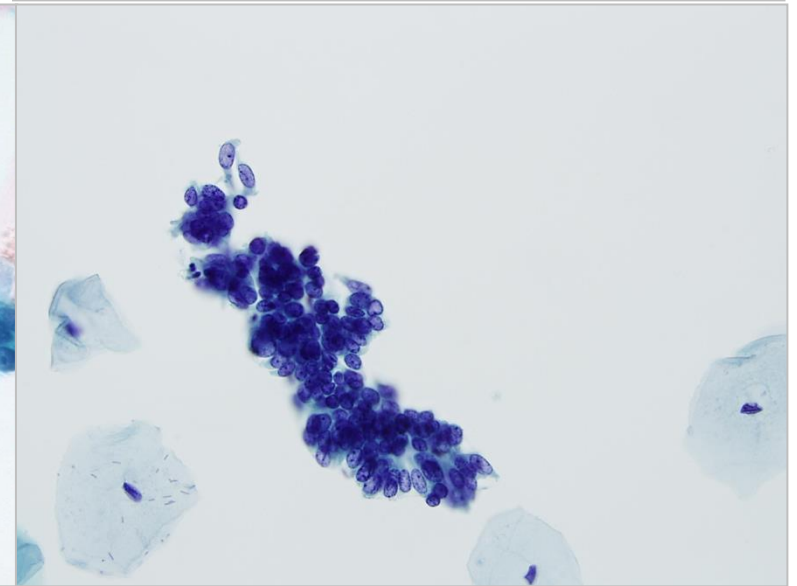
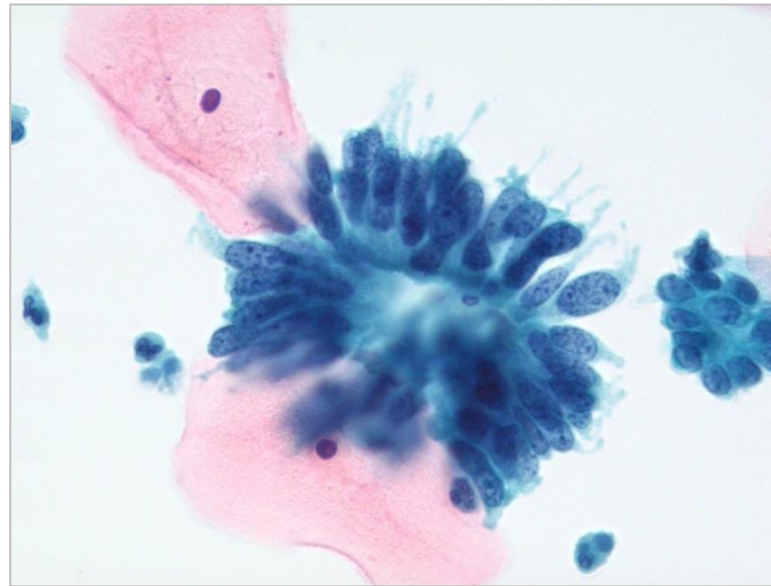
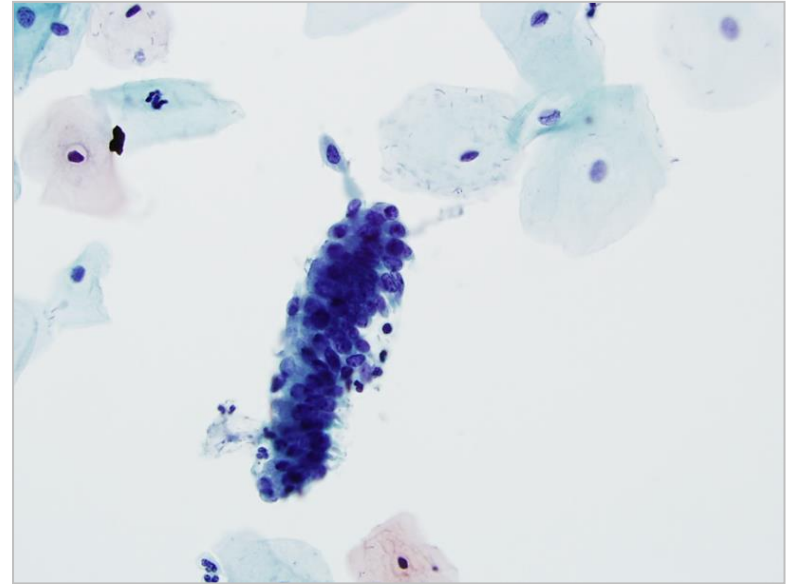
Evidence of squamous origin

- Central loss of cell polarity
- Syncytial arrangements
- Individual dysplastic squamous cells
- Hard squamoid cytoplasm



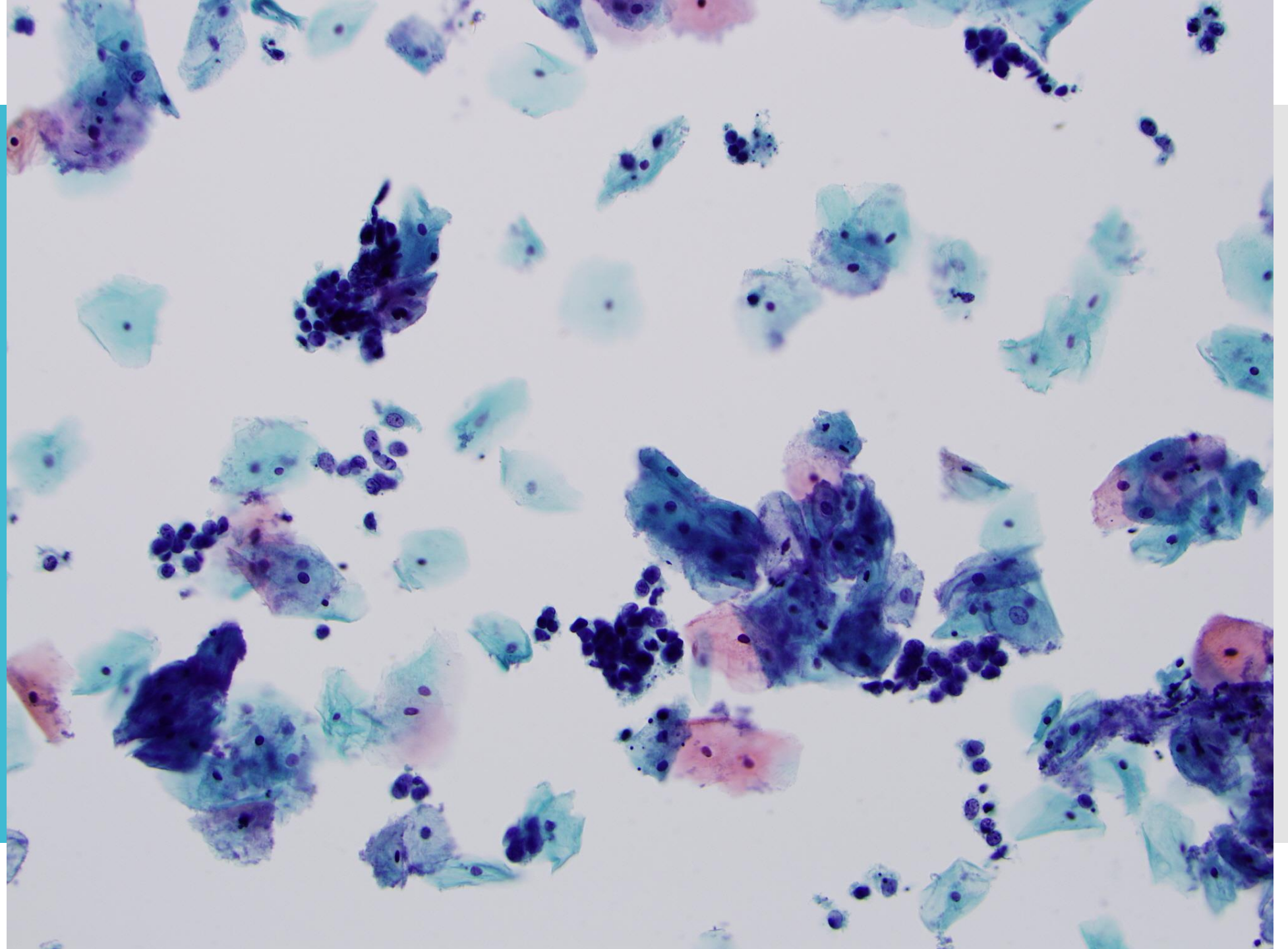
Evidence of squamous origin

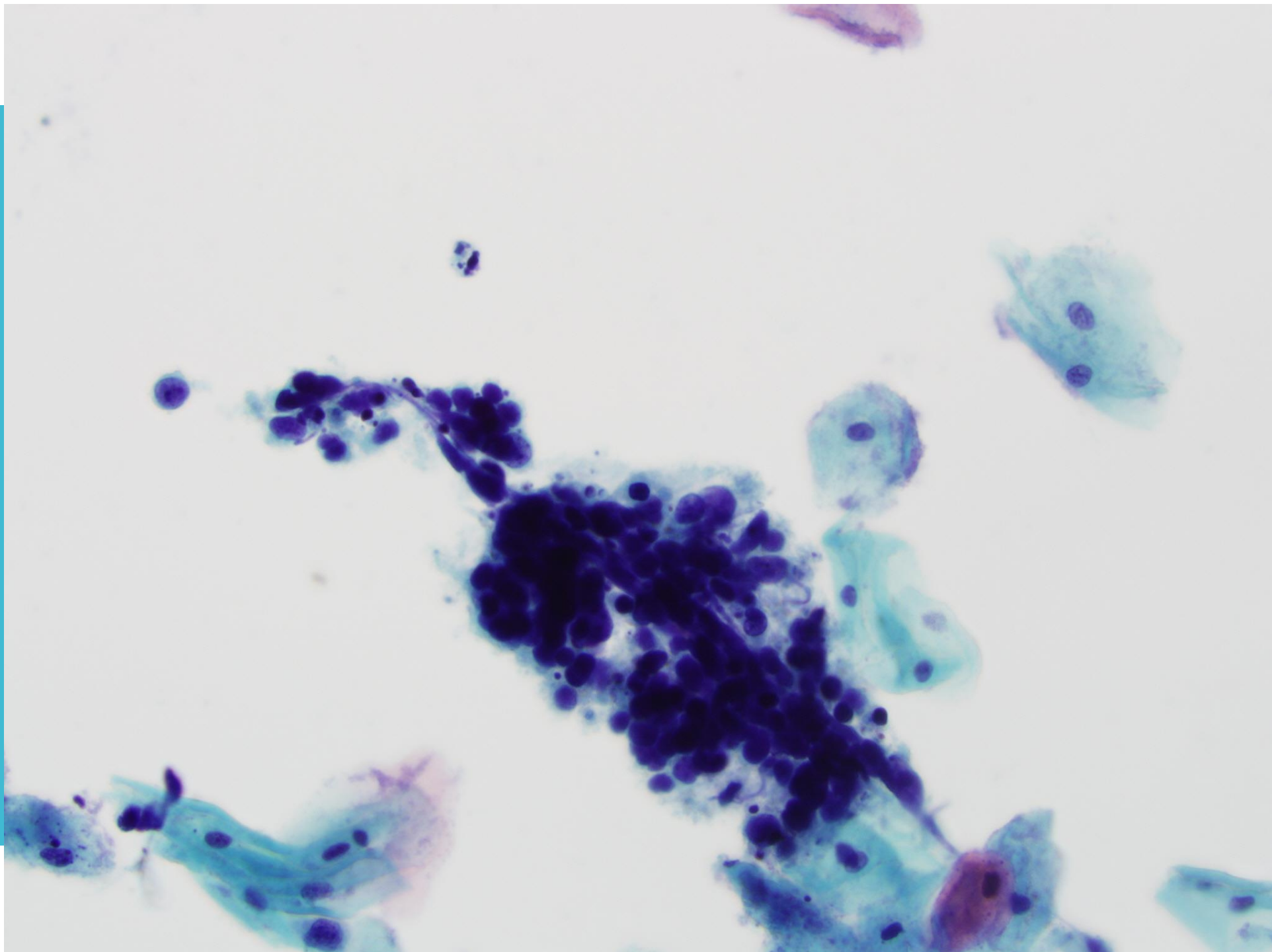
- Lack of typical AIS features
 - Elongate nuclei
 - Isolated Strips
 - Feathering, rosettes

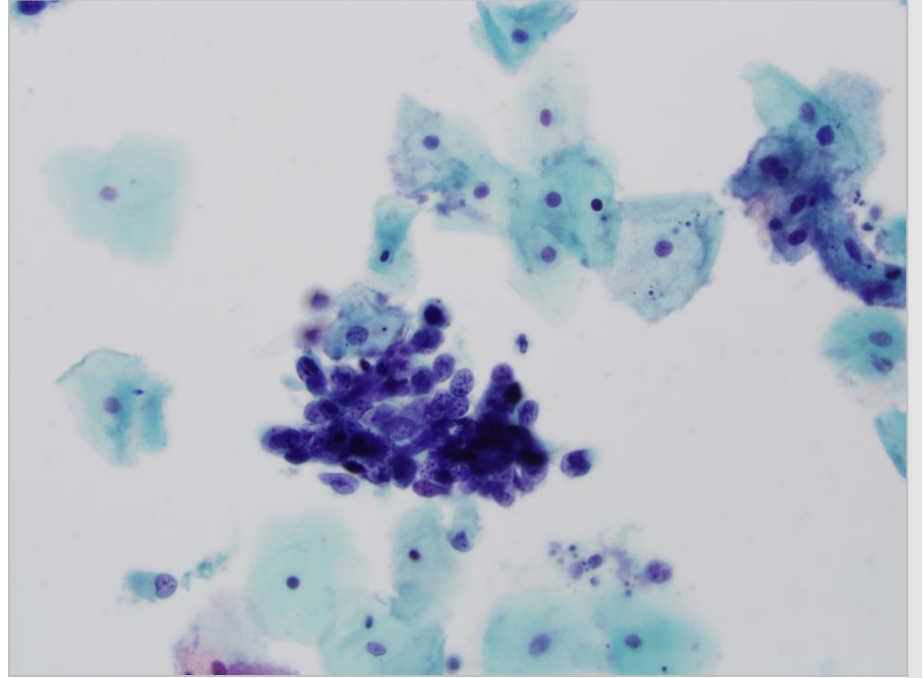
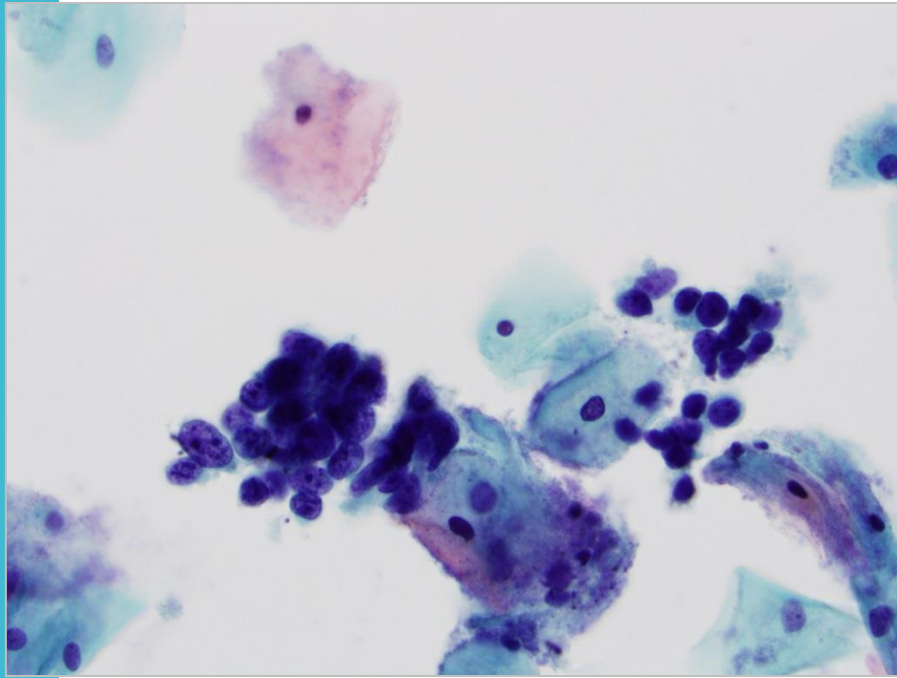


CASE 3:

- 30-year-old woman
- Last Pap test 5 years ago was NILM
- Depo Provera
- Thin Prep Pap test







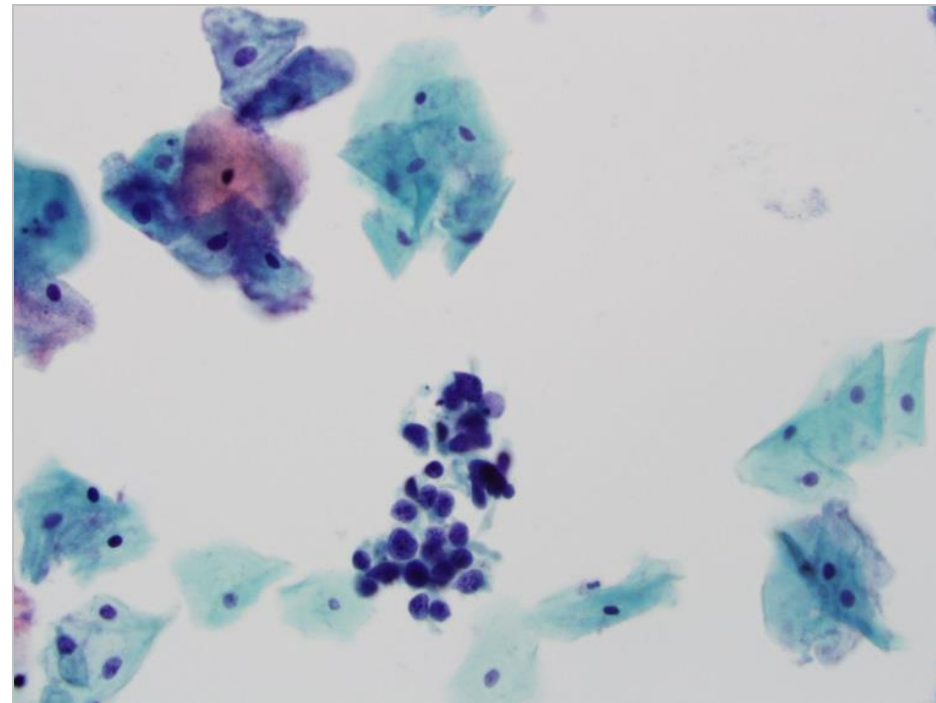
What is your interpretation ?

1. Benign EM stromal cells
2. Lymphoma
3. Chronic follicular cervicitis
4. Small cell carcinoma
5. HSIL

Cytopathologic Interpretation

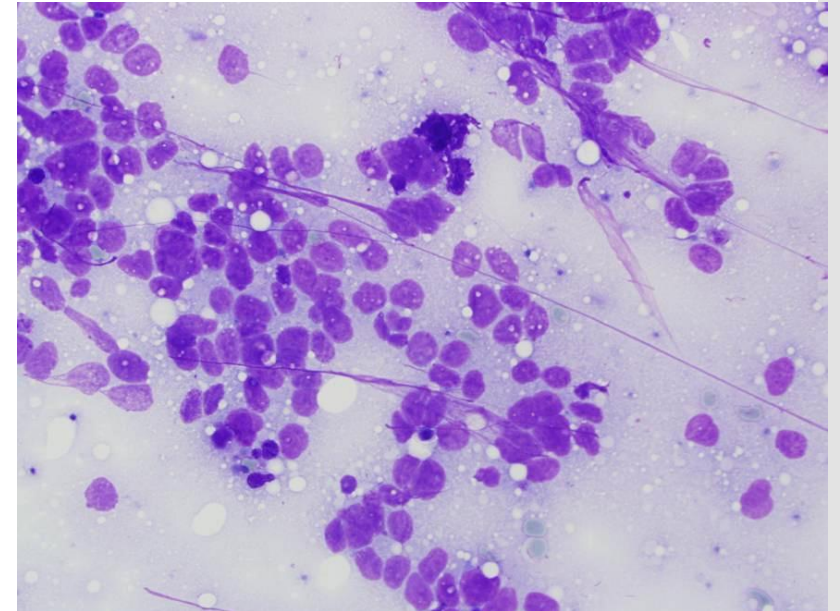
High grade neuroendocrine carcinoma, consistent with small cell carcinoma.

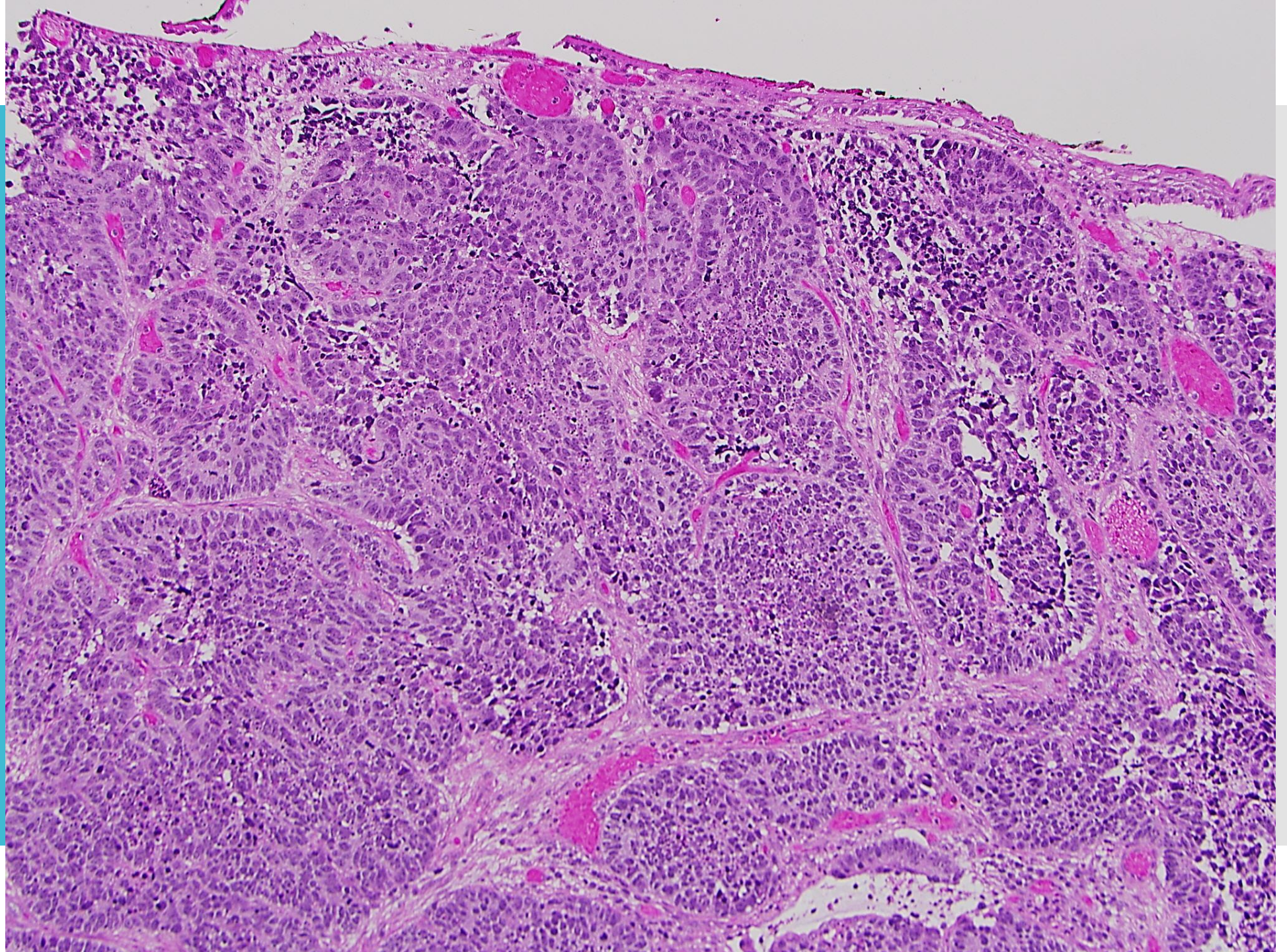
According to the immunohistochemical studies with adequate controls, the tumor cells are positive for CD56 synaptophysin and negative for CK5. The results support the diagnosis of small cell carcinoma.



Small Cell Carcinoma; Cytologic Features

- Similar to SCC at other sites
- Groups and single cells
- Scant cytoplasm
- “Powdery” chromatin
- Inconspicuous nucleoli
- Nuclear molding
- Streaming nuclear material
- Tumor diathesis

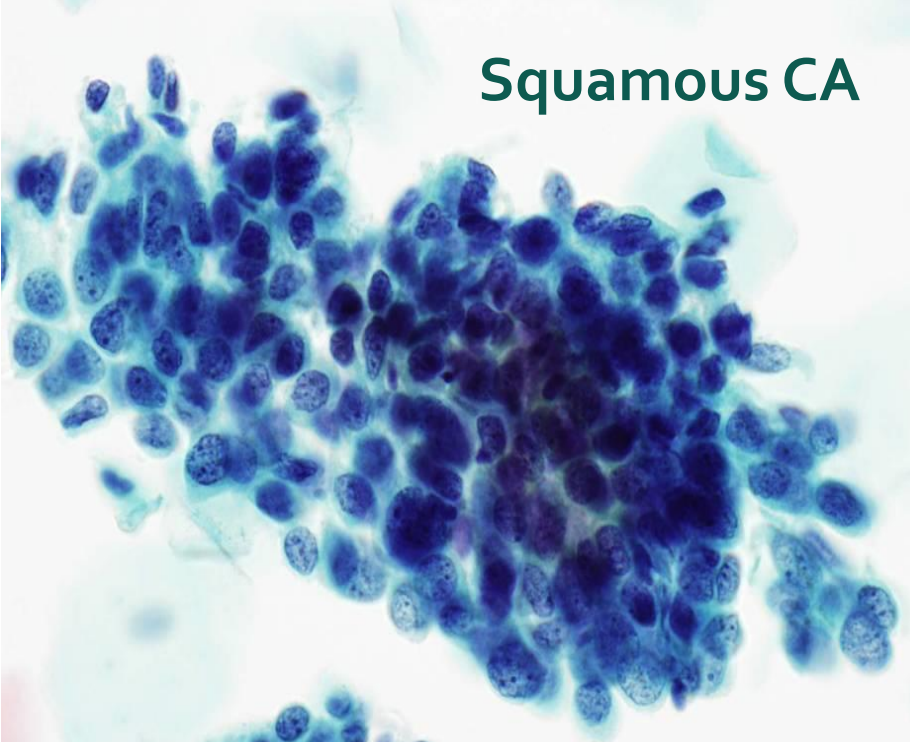




Differential Diagnosis

- Basaloid squamous cell carcinoma
- HSIL
- Lymphoma
- Endometrial stromal cells
- Chronic lymphocytic cervicitis

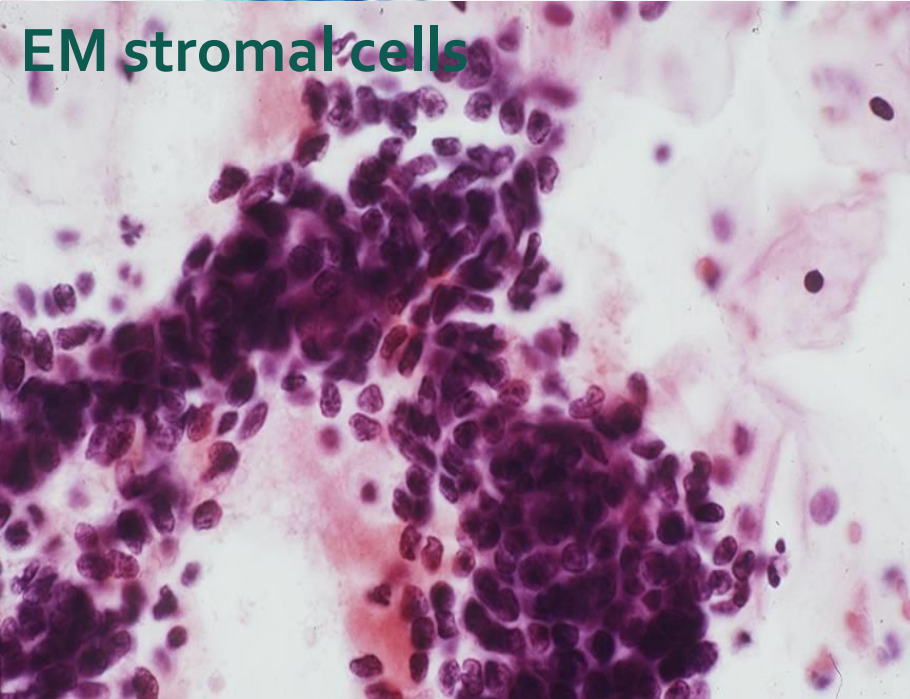
Squamous CA



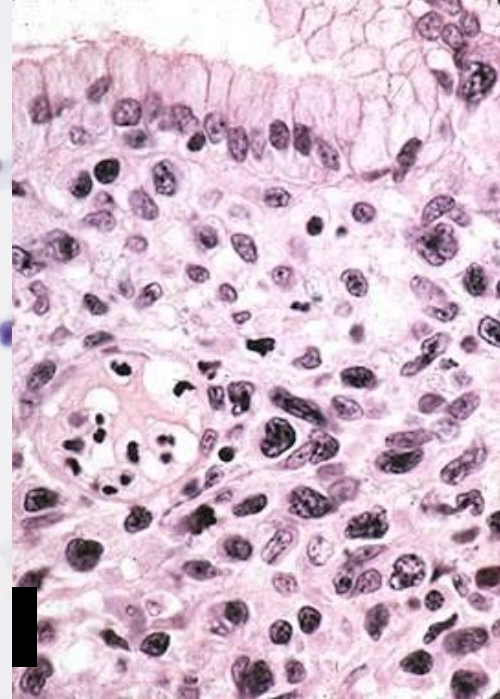
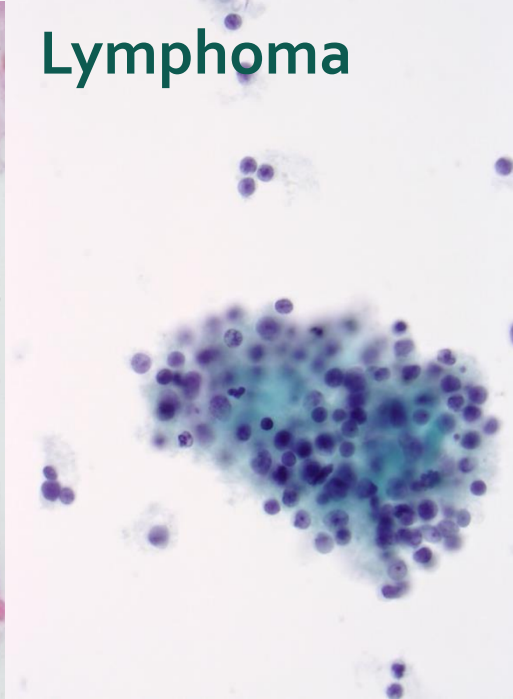
HSIL GI



EM stromal cells



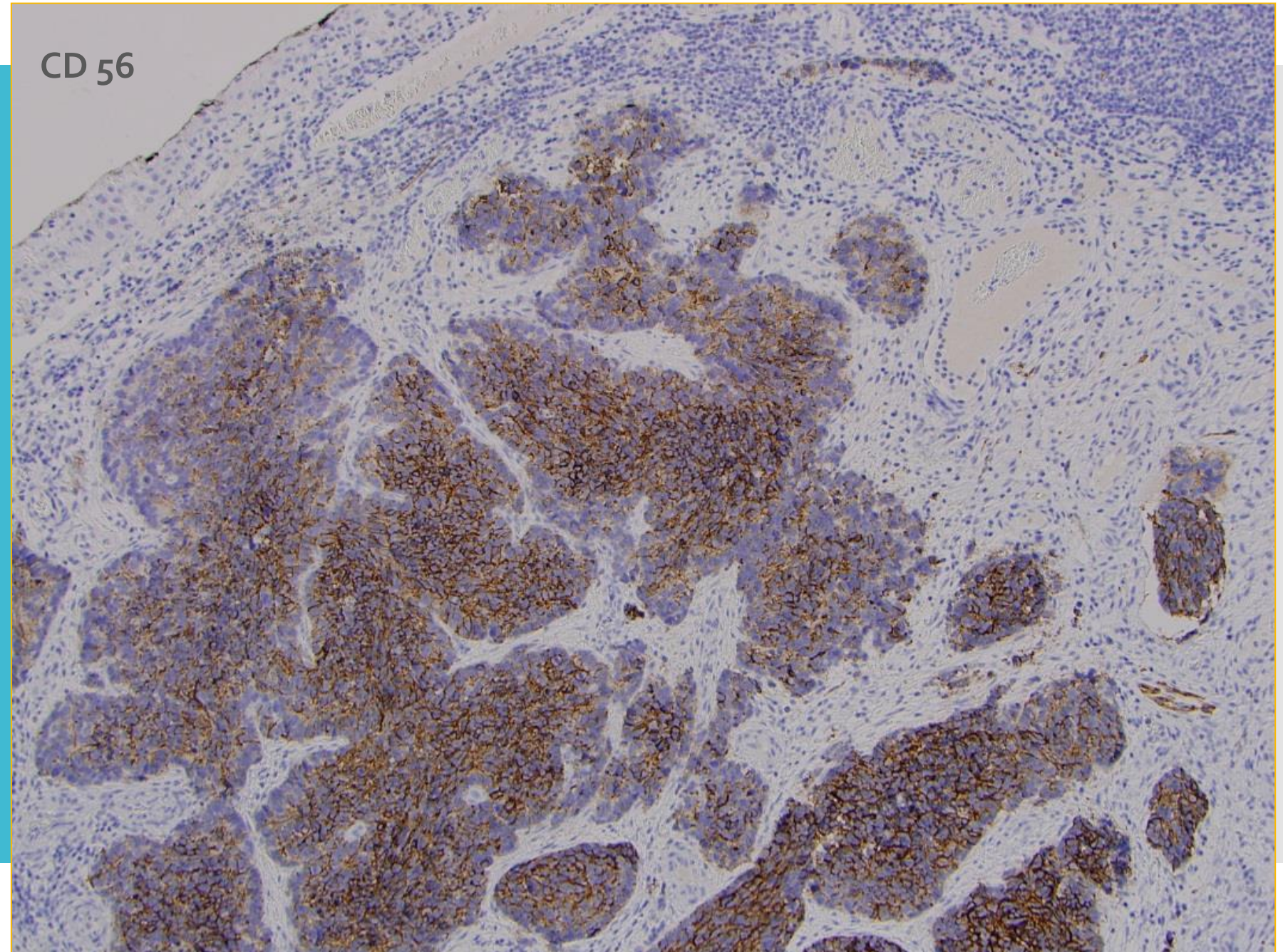
Lymphoma



Potentially useful markers

- HPV testing (commonly HPV 18 +)
- Neuroendocrine Markers
 - Chromogranin, Synaptophysin, CD 56
- TTF-1 (small percentage 10-20 % in most studies)
- p63 negative (or weakly positive)

IHC



Summary

- Rare lesions do exist
- SCC is uncommon 1-5% cervical CA
- Peak age: 30s-40s
- Necrotic background
- Strong association with HPV type 18

Digital Cytology



Digital Slide #1

A Thin Prep Pap test on a 68 year-old post menopausal patient with abnormal bleeding. What is the cytologic interpretation?

Answer options:

- A. Adenocarcinoma, endometrial
- B. Adenocarcinoma, endocervical
- C. High grade squamous intraepithelial lesion (HSIL)
- D. Invasive squamous cell carcinoma

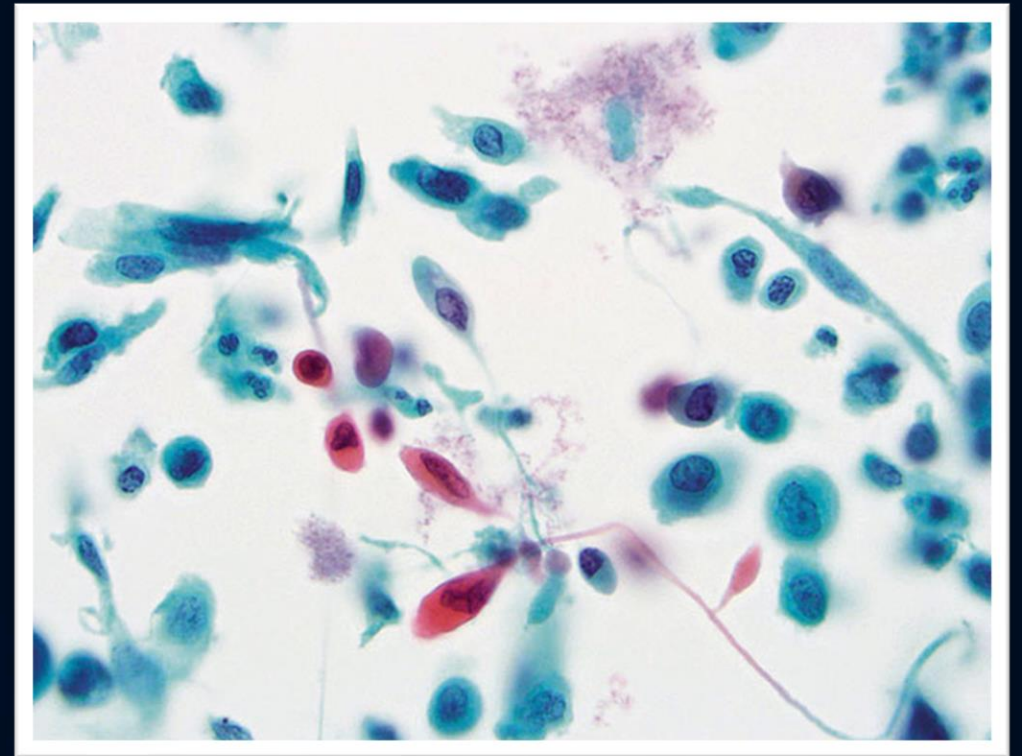


Digital Slide #1

A Thin Prep Pap test on a 68 year-old post menopausal patient with abnormal bleeding. What is the cytologic interpretation?

Answer options:

- A. Adenocarcinoma, endometrial
- B. Adenocarcinoma, endocervical
- C. High grade squamous intraepithelial lesion (HSIL)
- D. Invasive squamous cell carcinoma



Digital Slide #2

A Thin Prep Pap test was performed on a 64 year-old woman who was exhibiting post-menopausal bleeding. What is the cytologic interpretation?

Answer options:

- A. Adenocarcinoma, endometrial
- B. High grade squamous intraepithelial lesion (HSIL)
- C. Invasive squamous cell carcinoma
- D. Metastatic malignancy, melanoma

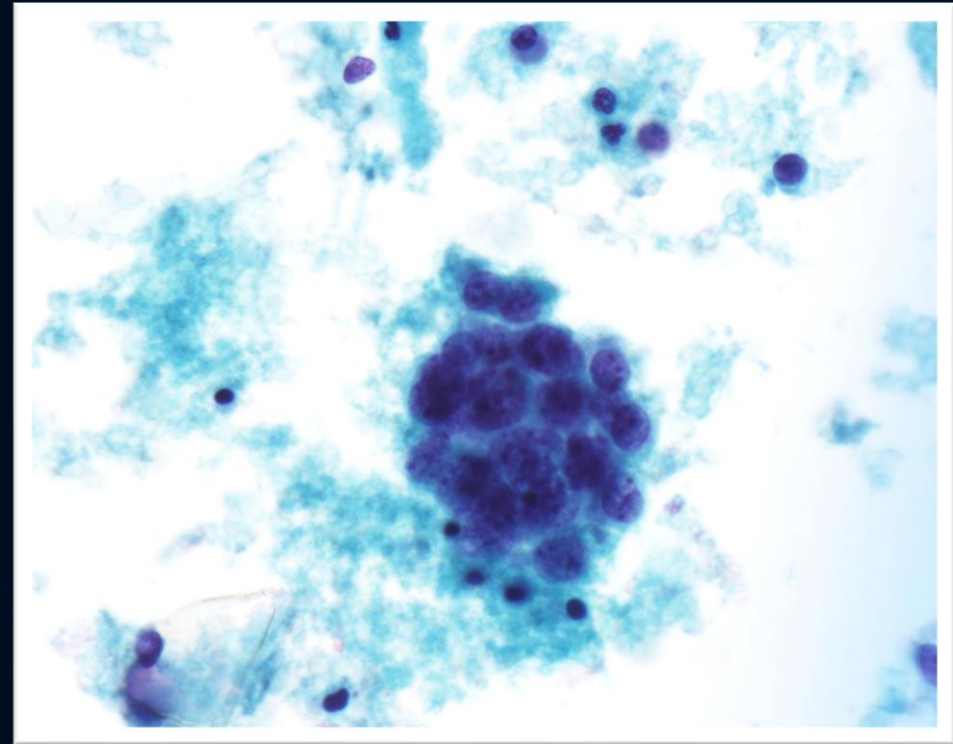


Digital Slide #2

A Thin Prep Pap test was performed on a 64 year-old woman who was exhibiting post-menopausal bleeding. What is the cytologic interpretation?

Answer options:

- A. Adenocarcinoma, endometrial
- B. High grade squamous intraepithelial lesion (HSIL)
- C. Invasive squamous cell carcinoma
- D. Metastatic malignancy, melanoma



Thank You!

