The Hyperchromatic Crowded Groups-Cytologic Diagnosis of Glandular Lesions

Paul K. Shitabata, M.D.

APMG

Introduction

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

Glandular lesions

- Non neoplastic
  - Tubal Metaplasia
  - Exfoliated lower segment endometruim
  - Menstrual endometrial Cells
  - Reactive endocervical cells
  - Microglandular hyperplasia
  - Other

Glandular lesions in Pap Smears

- Neoplastic
  - AIS
  - Invasive adenocarcinoma
  - HSIL with endocervical glandular extension
  - Endometrial carcinoma
  - Squamous Carcinoma

Adenocarcinoma in situ (AIS)

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

AIS

GROUPS - Crowded, hyperchromatic

- Glandular differentiation
  - Pale, foamy or vacuolated cytoplasm
  - Stratification and crowding
  - Rosettes and glands
  - Syncytia with “ feathering”
- No diathesis

AIS

NUCLEI

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

Invasive Adenocarcinoma of Cervix

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

False Negative

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

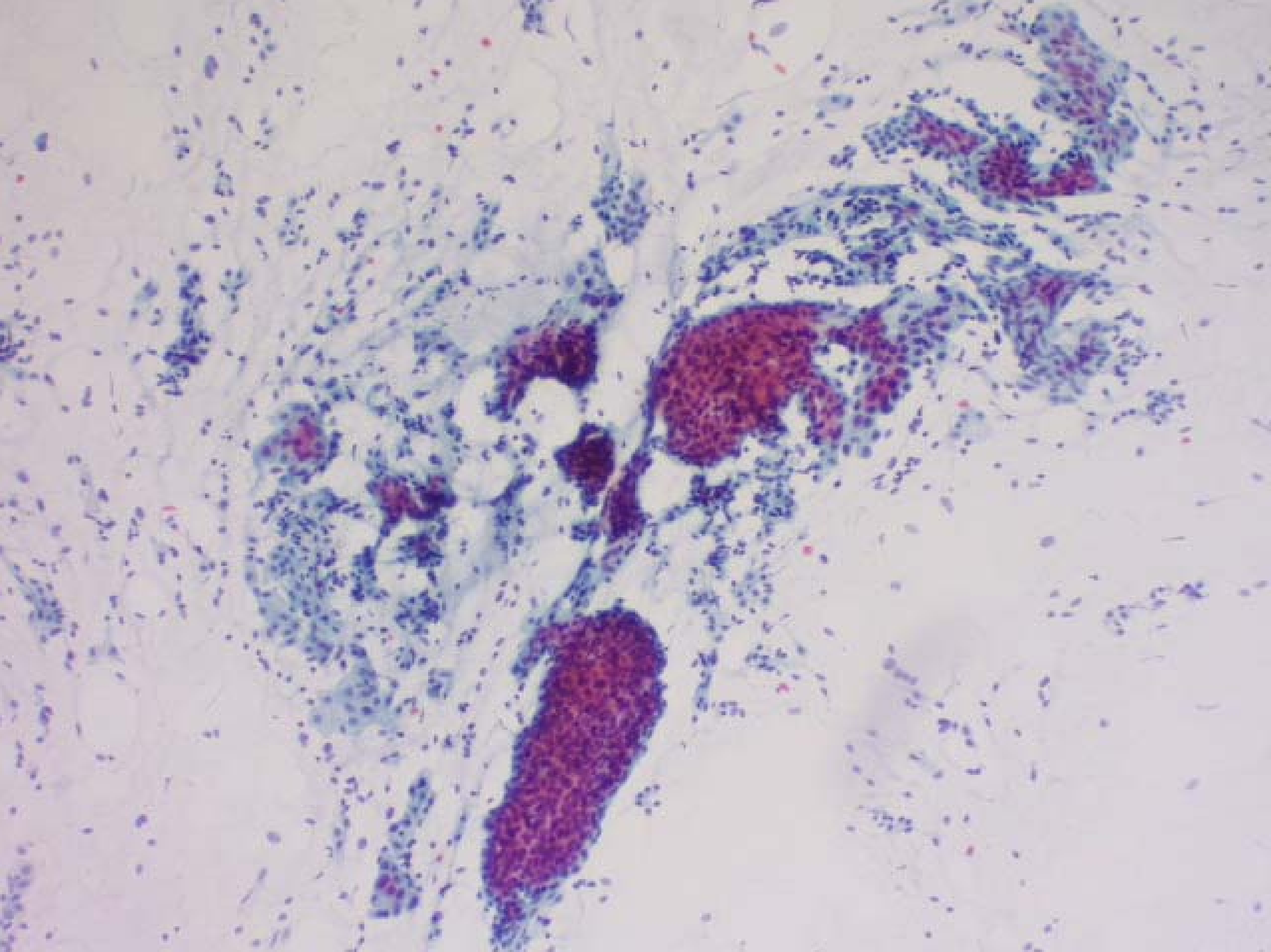
False Negative

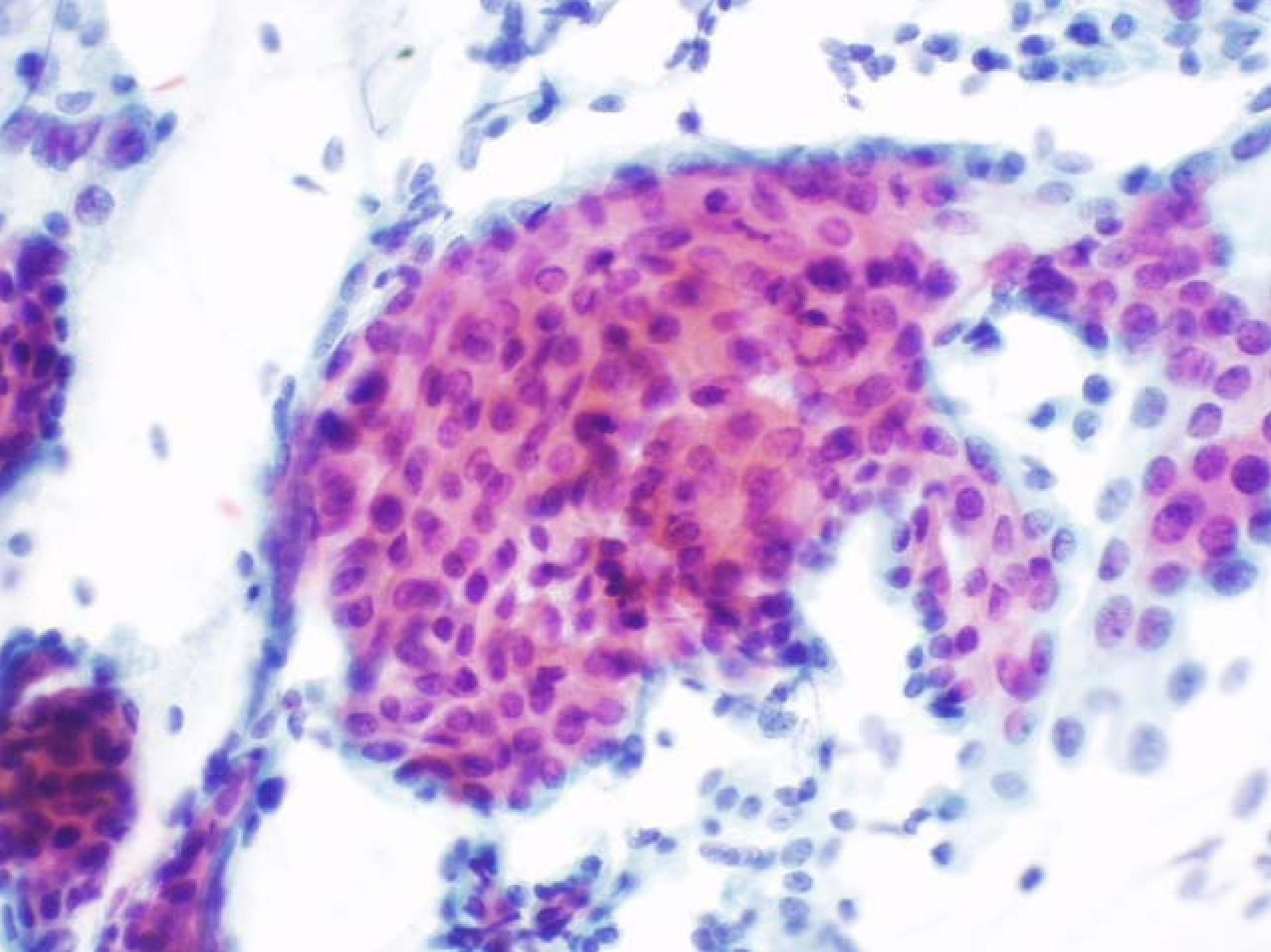
- AIS or Adenocarcinoma mimicking reactive endocervical cells
  - Uniform population (not a spectrum)
  - Crowding, nuclear enlargement, increased N/C ratio
  - Coarse chromatin
  - Small to prominent nucleoli in every cell

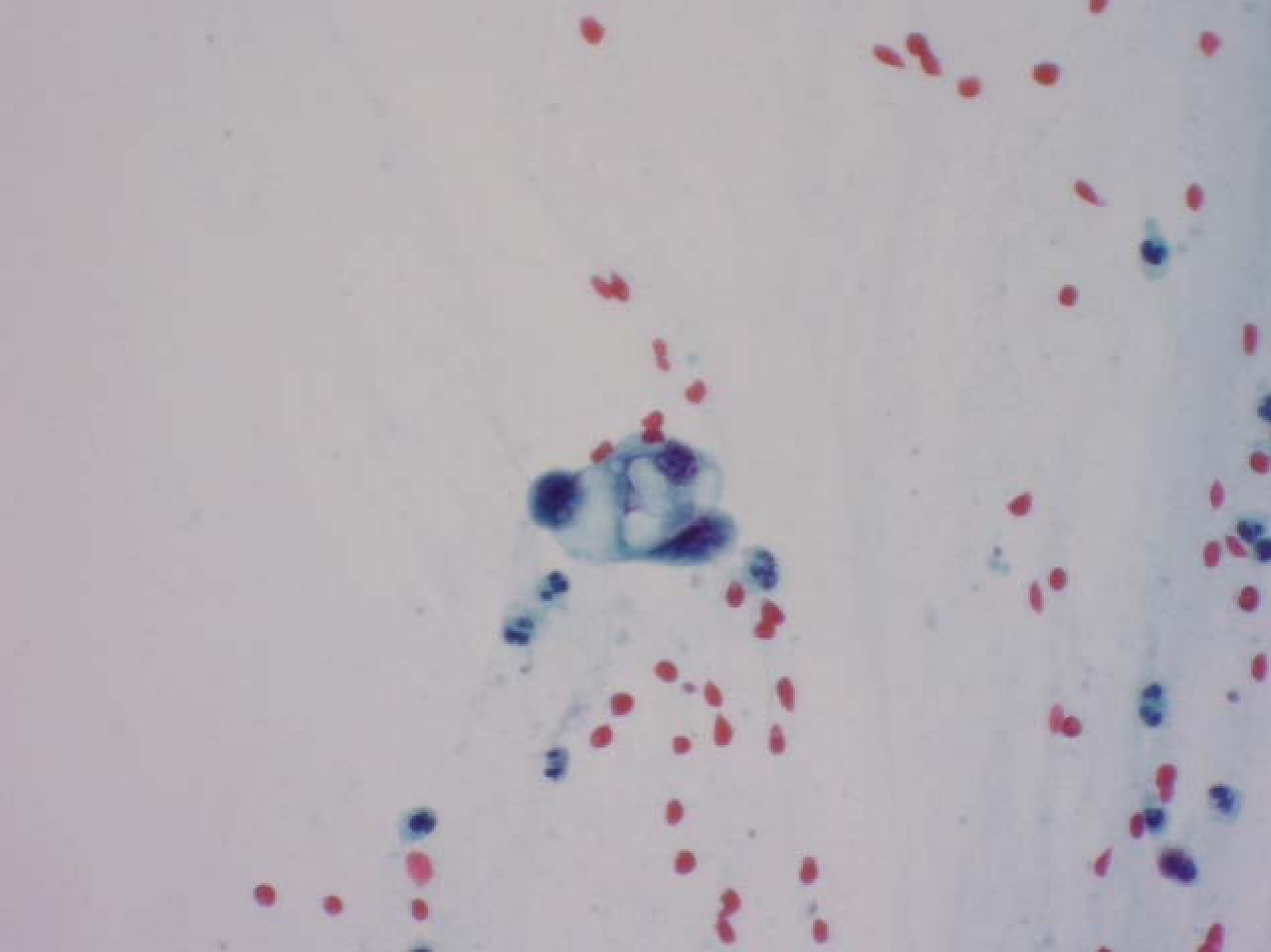
Case 1

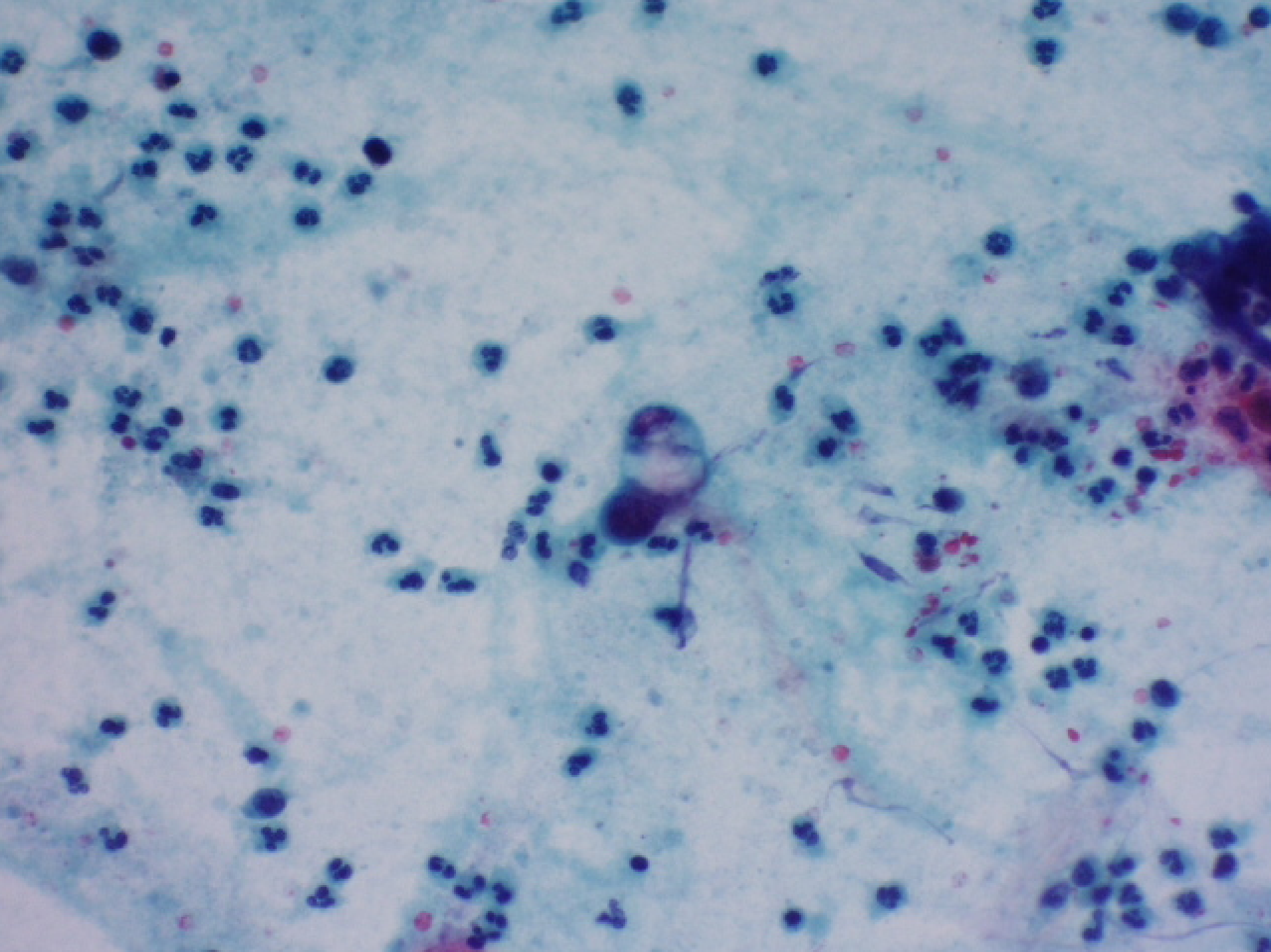
37 year old

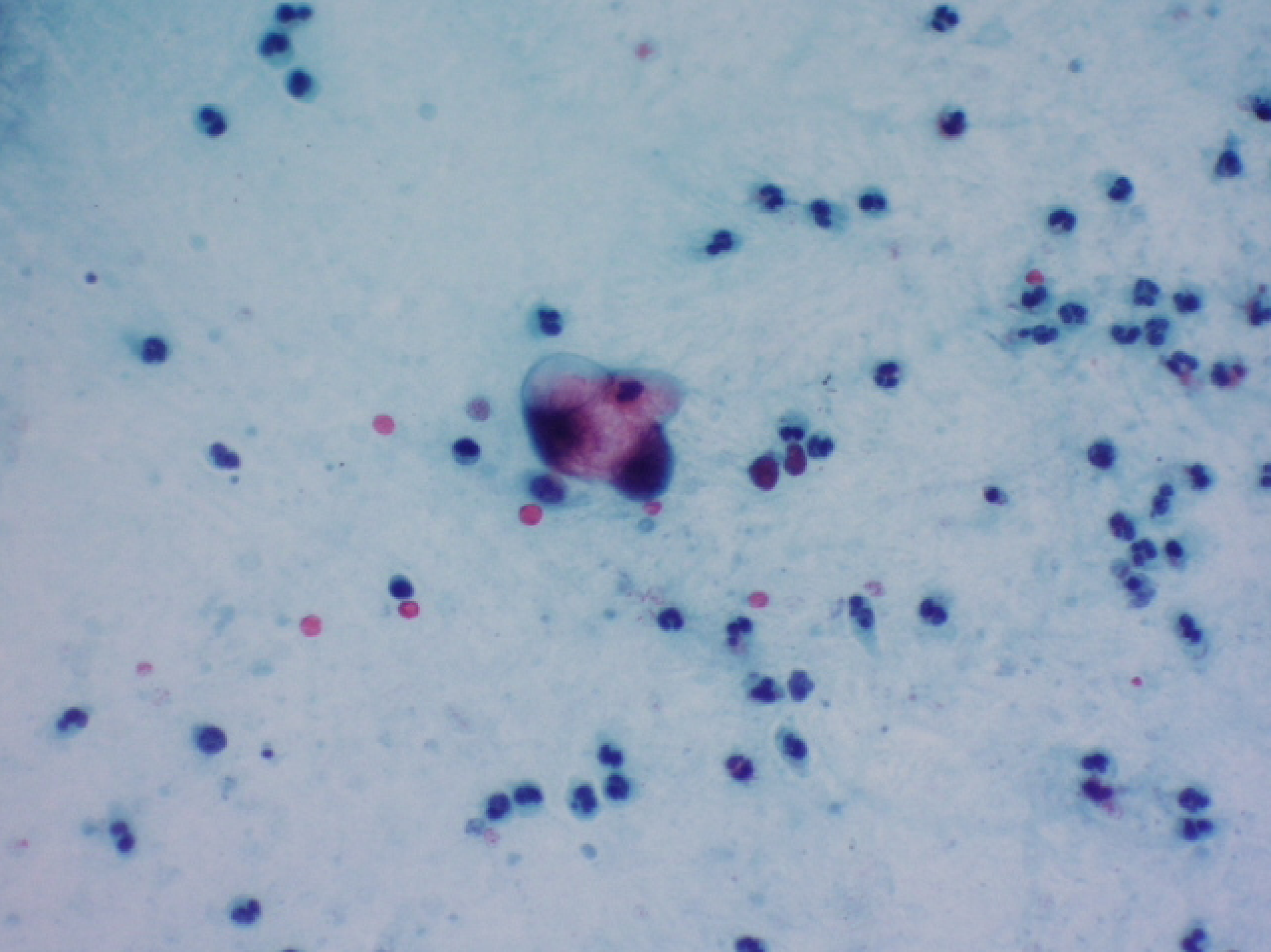
pap smear - AGUS, r/o IUD











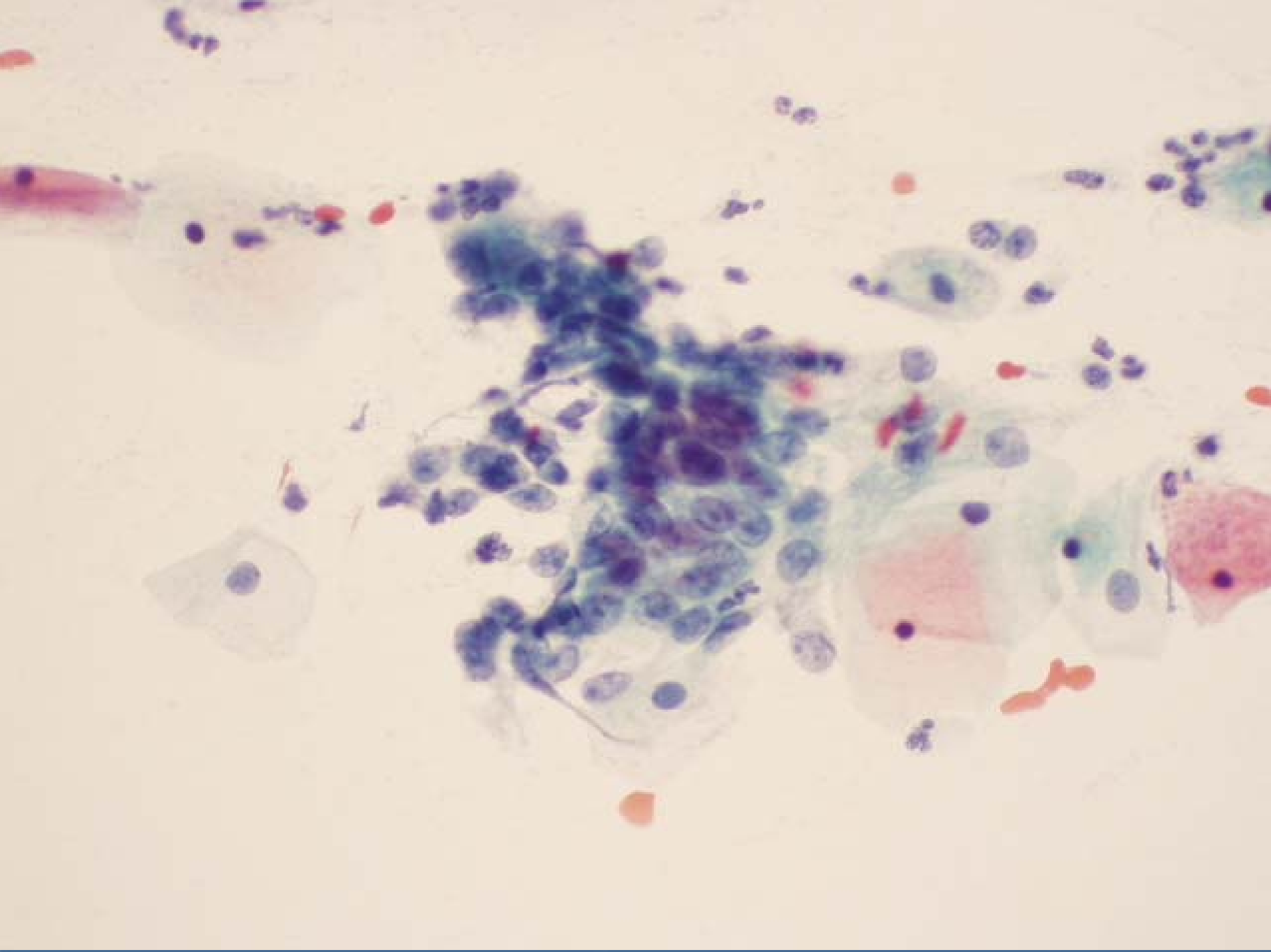
IUD Changes

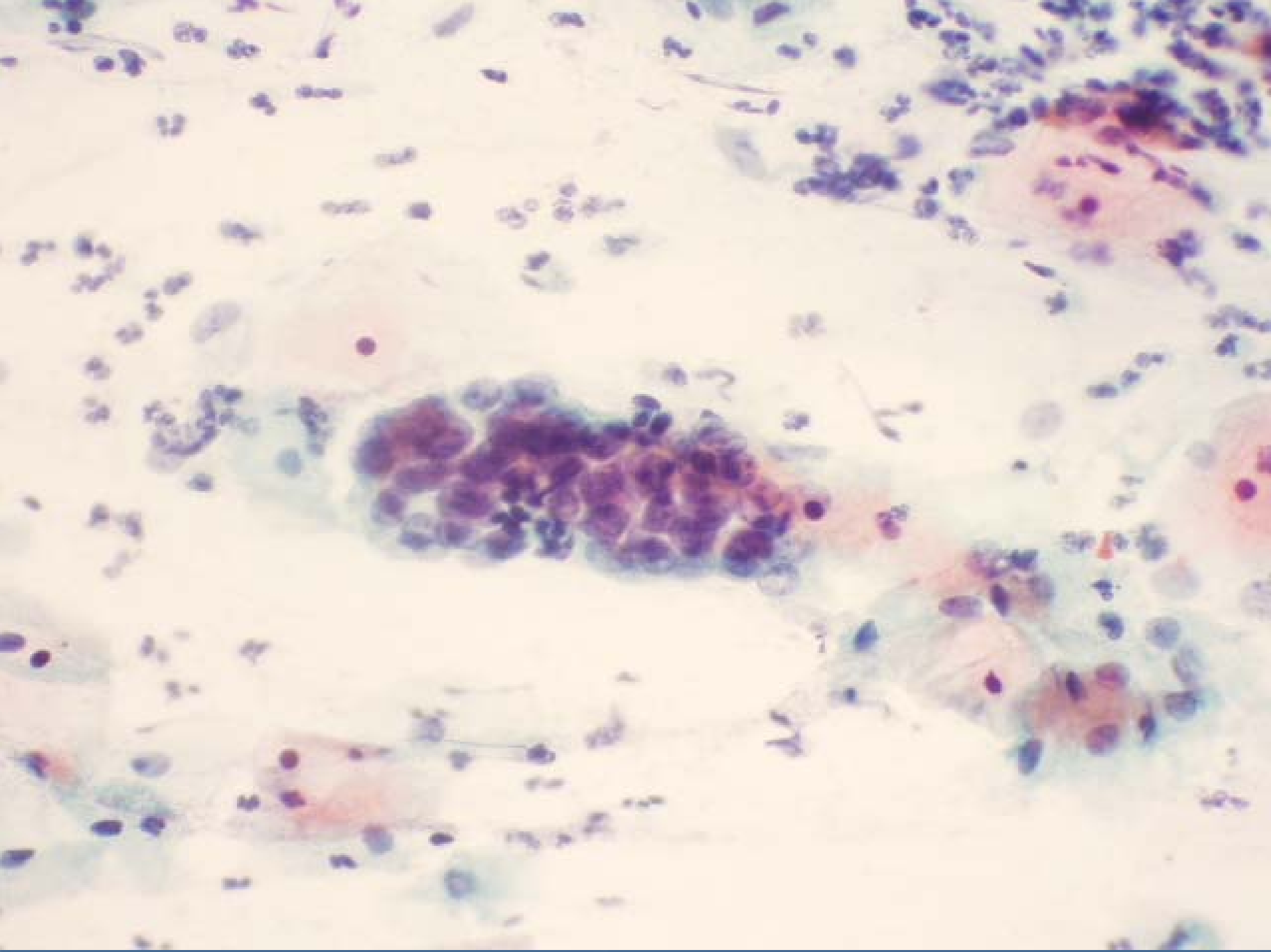
- DDX adenocarcinoma - lack of malignant features
- DDX CIS - actinomyces
  - few atypical cells
  - Bland dark chromatin
  - No nucleoli
  - No multinucleation

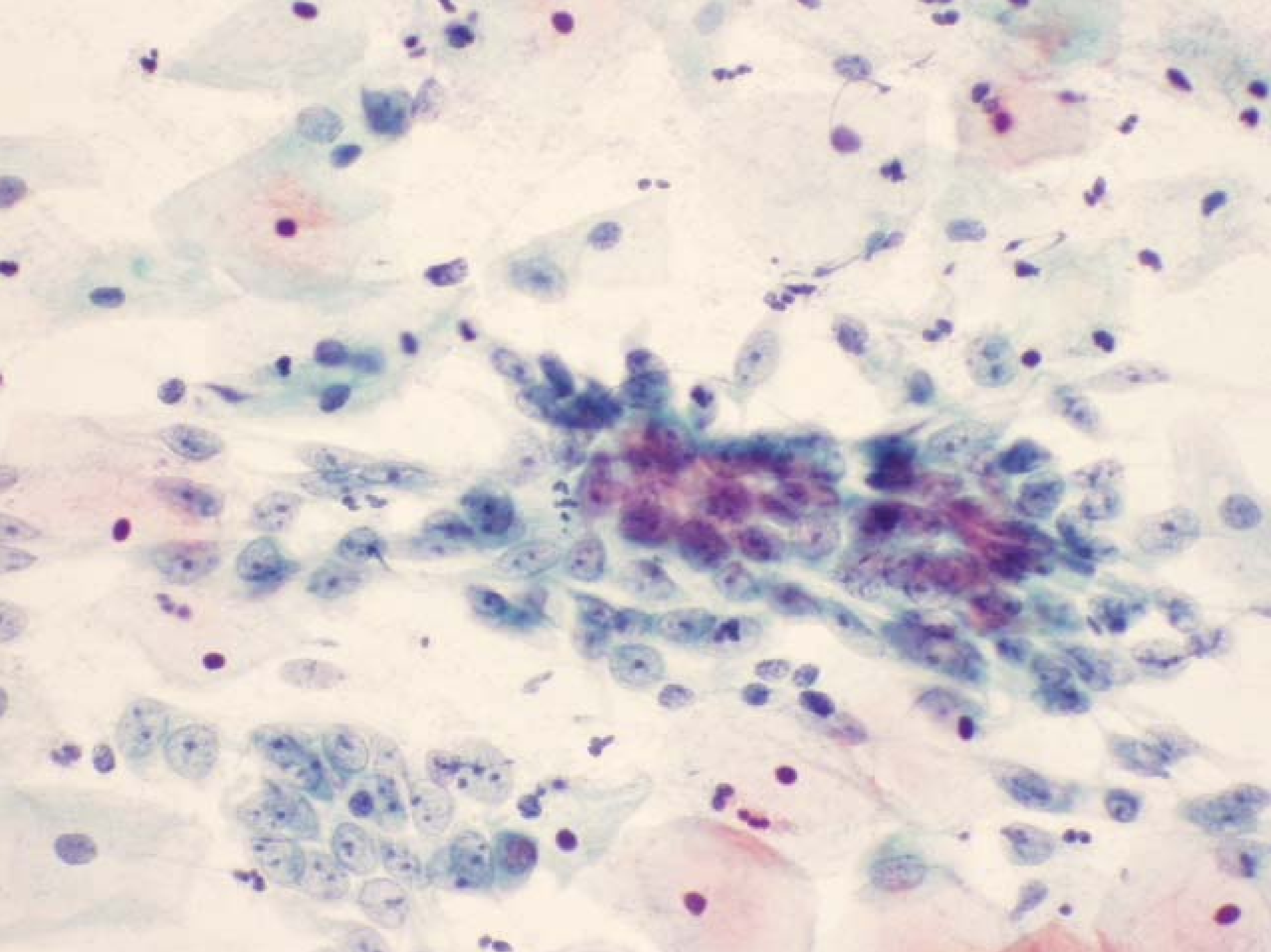
Case 2

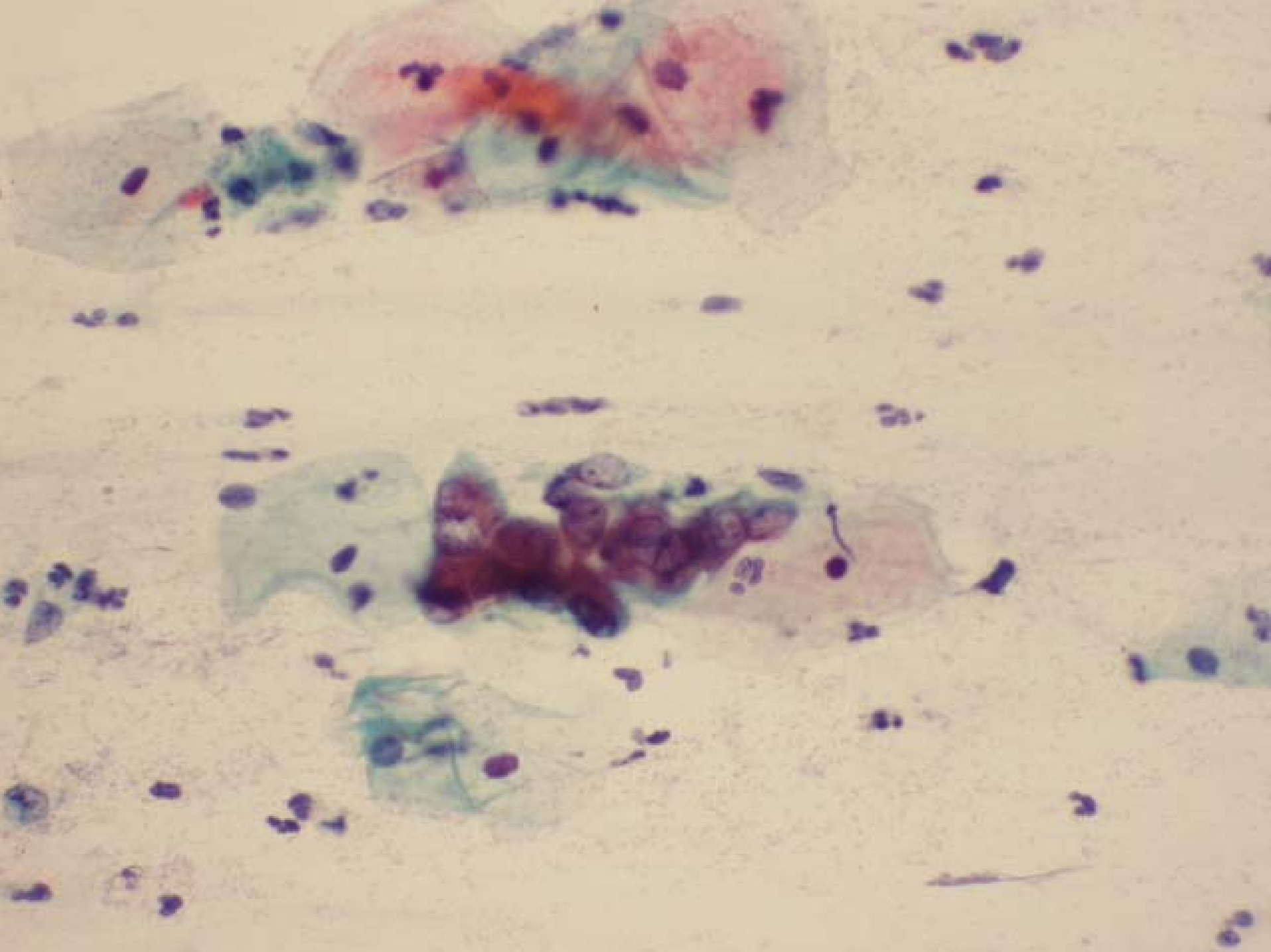
68 year old

Pap smear - AGUS r/o adeno









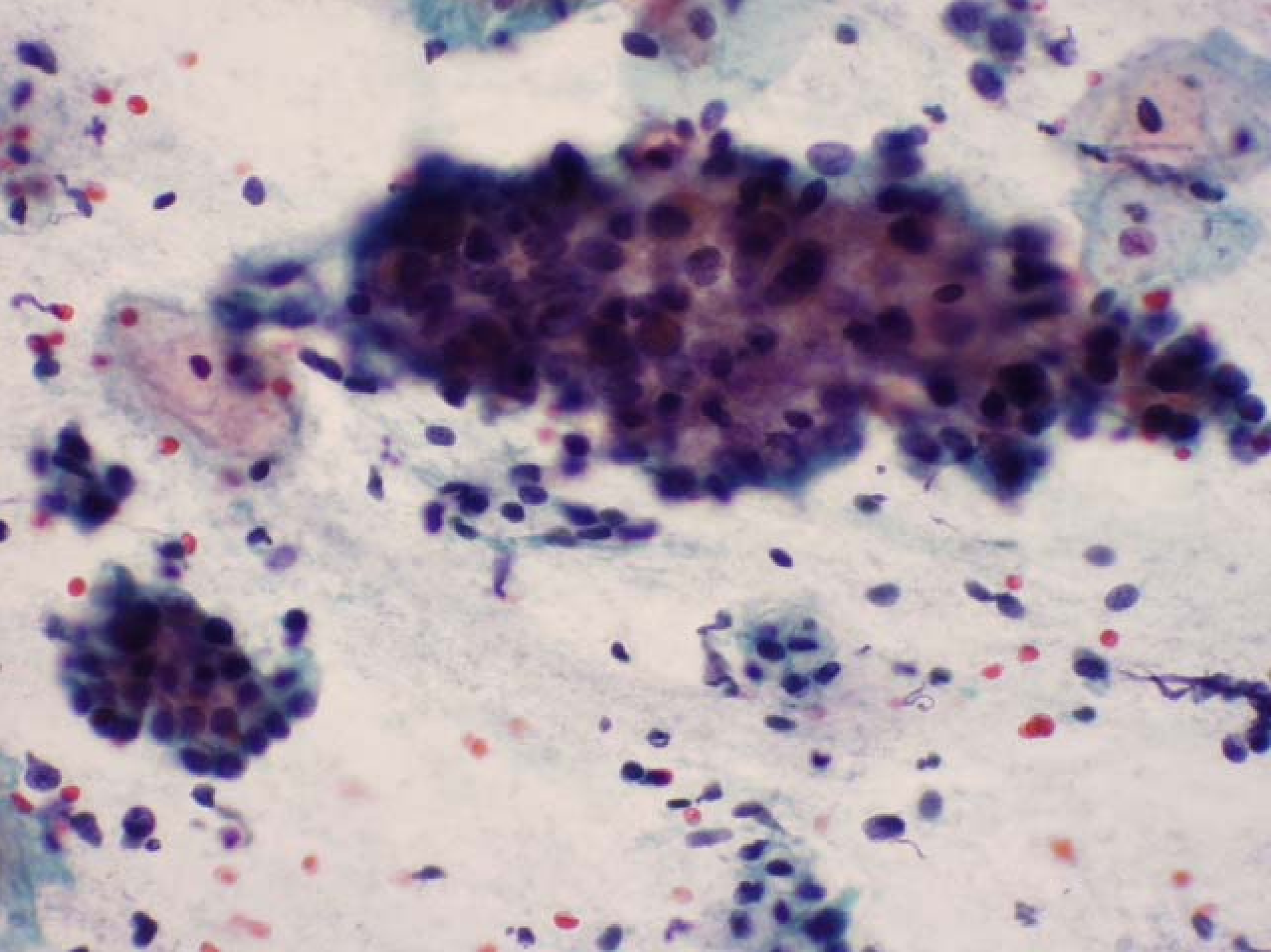
Reactive Glandular Cells

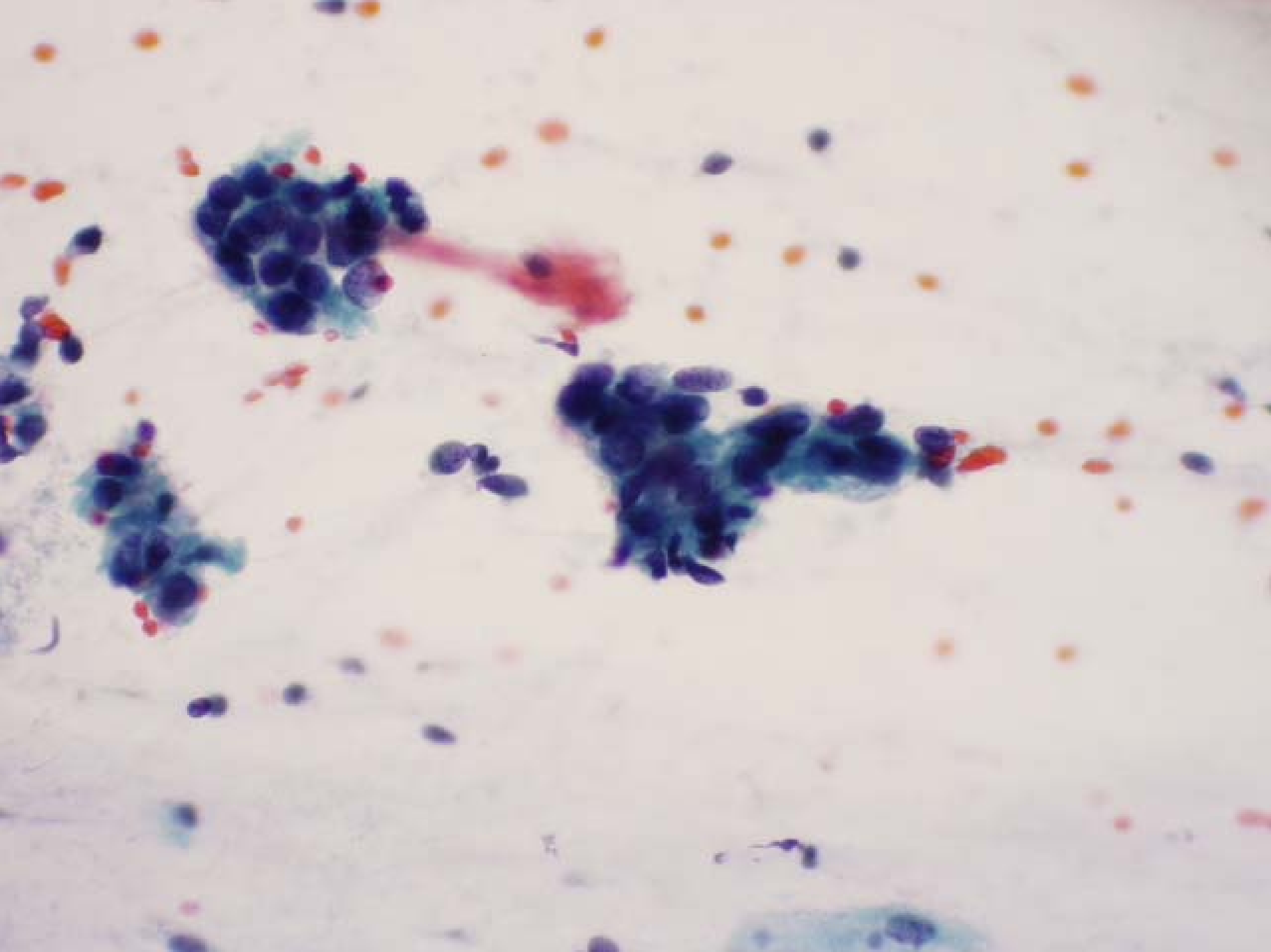
- Spectrum of atypia
- Fine or smudged chromatin
- Smooth nuclear membranes
- Prominent to absent nucleoli
- Low N/C ratio
- Minimal overlap “ lay flat”
- Often associated with SIL

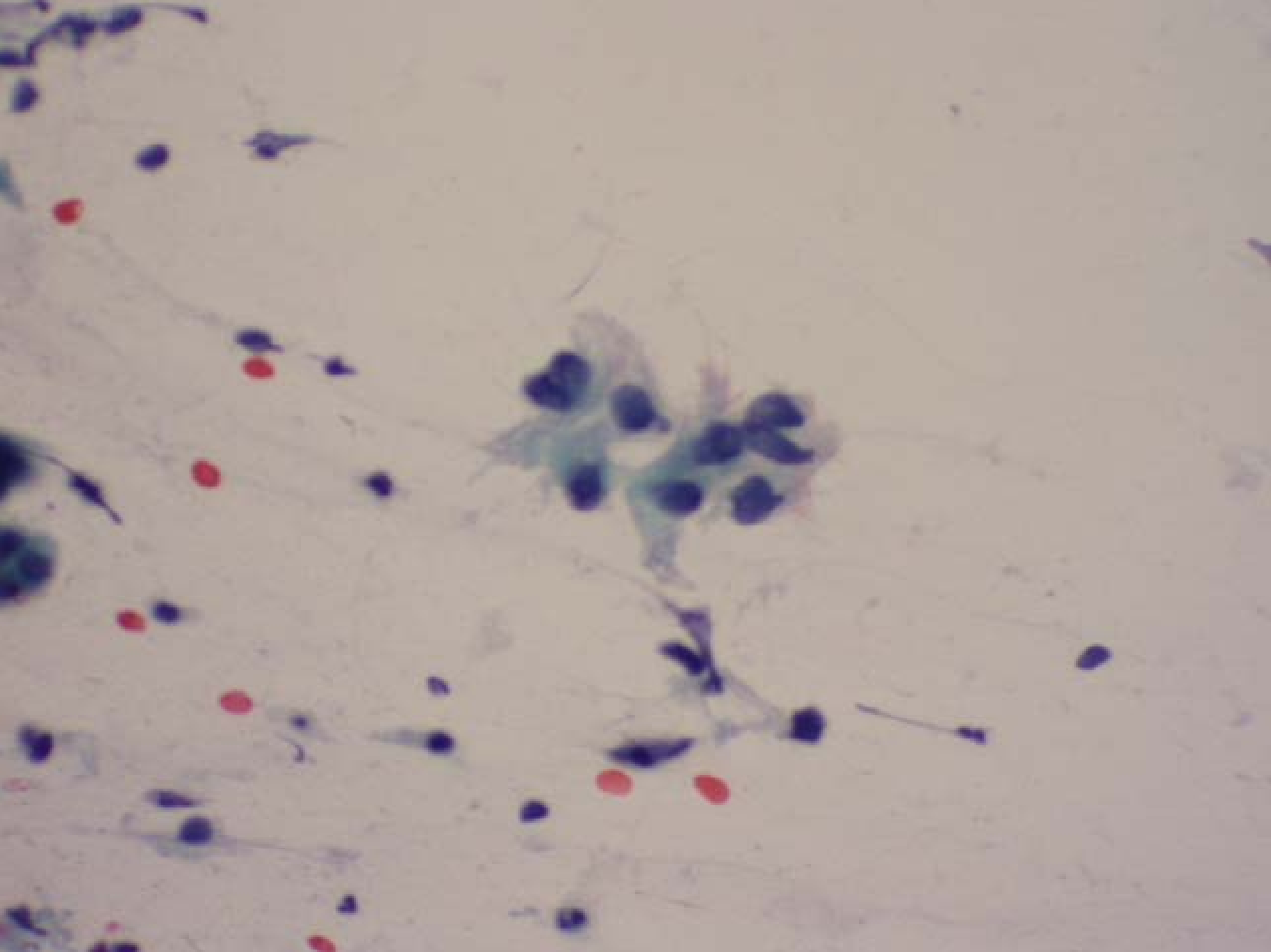
Case 3

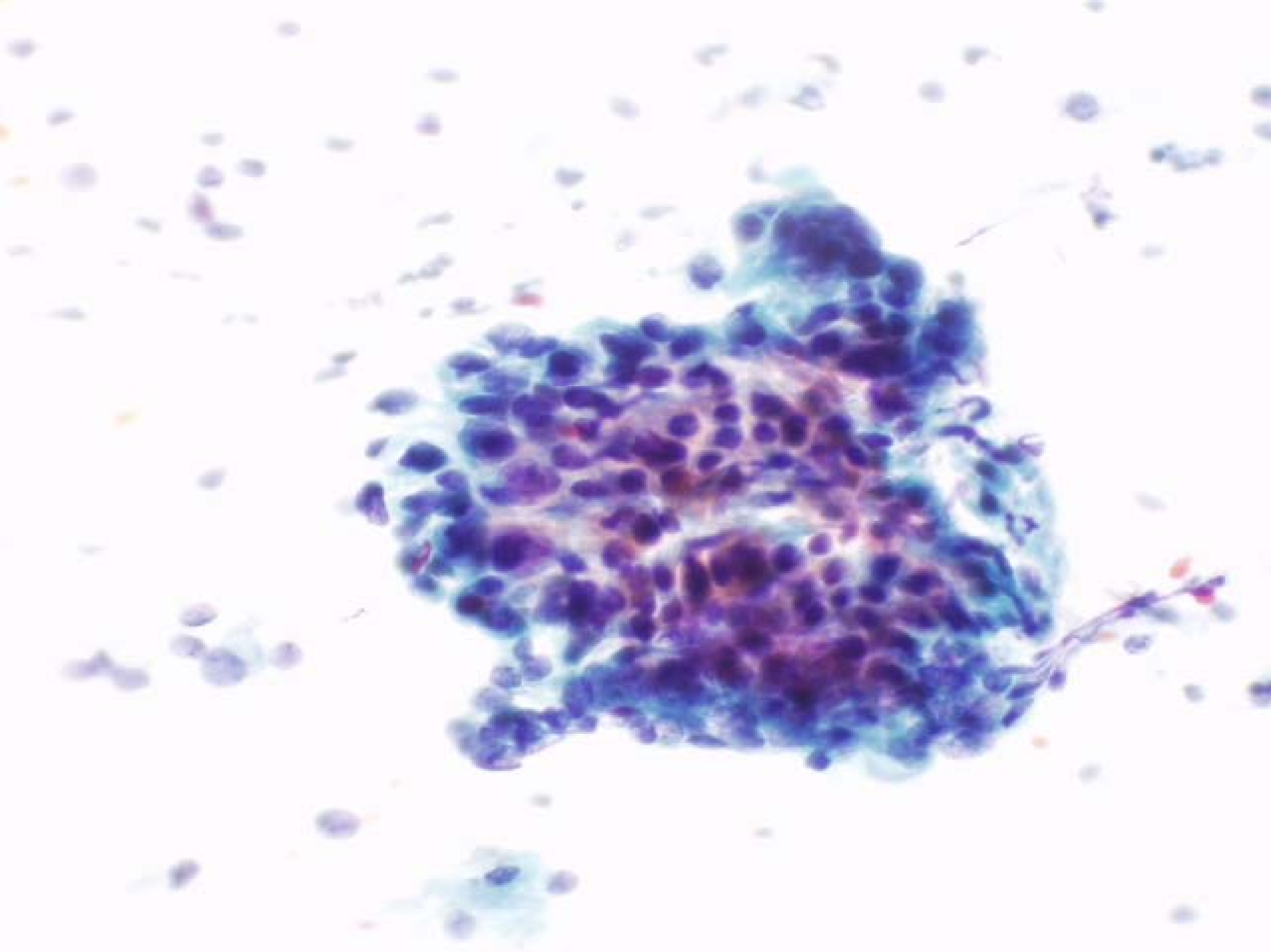
Indec, C, 32 year old

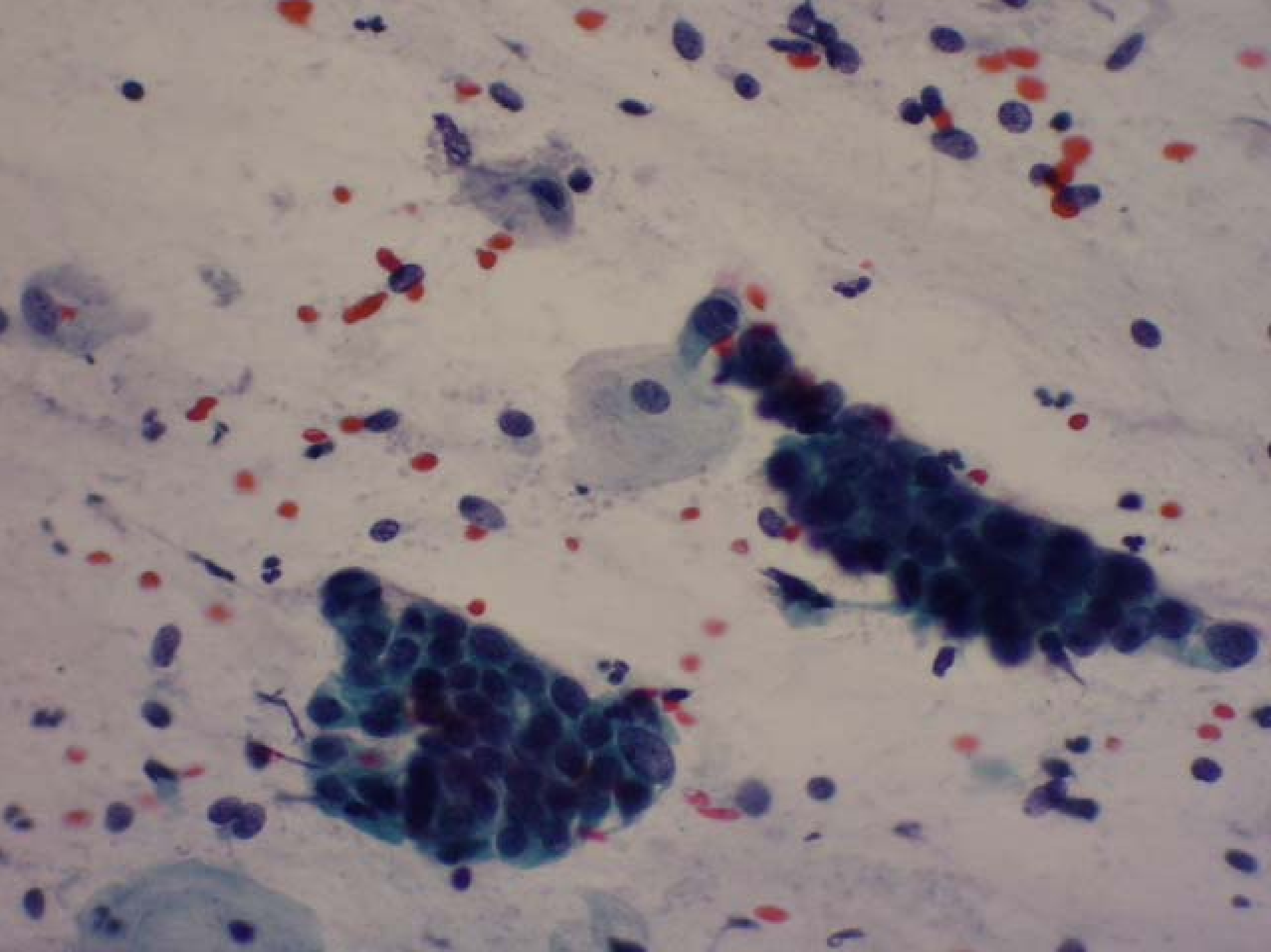
Pap smear - AGUS











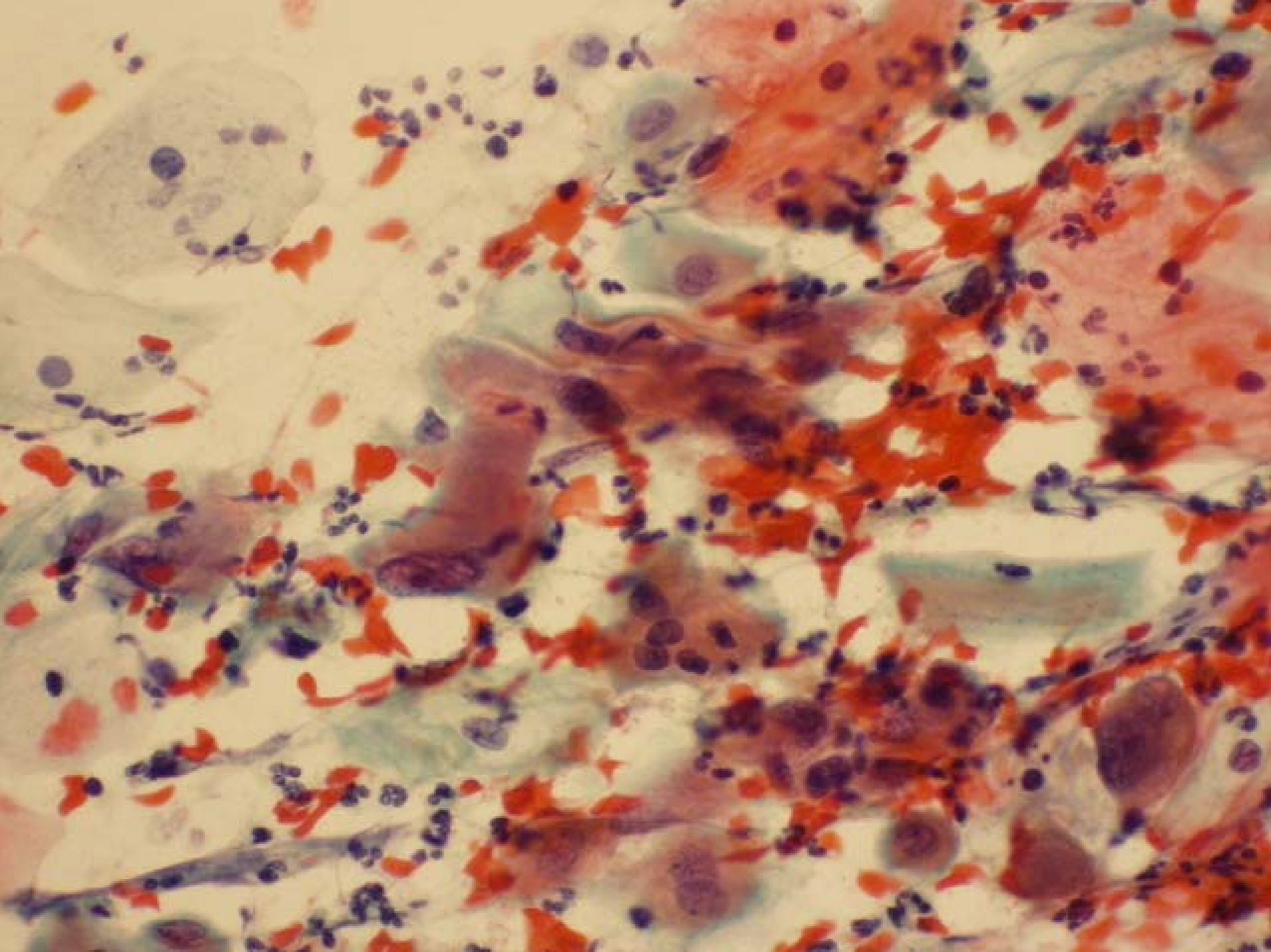
Tubal Metaplasia

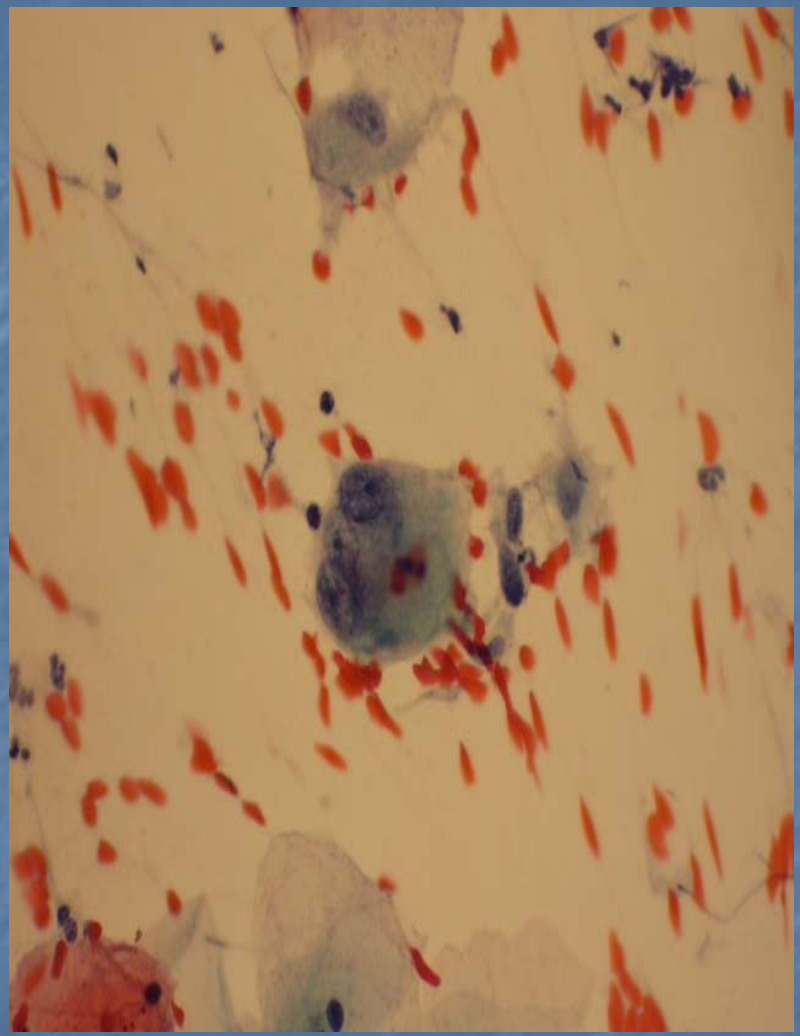
- DDX: Adenocarcinoma
  - Nuclei less crowded
  - Finer chromatin pattern
  - Cilia
  - Clear cytoplasmic vacuoles

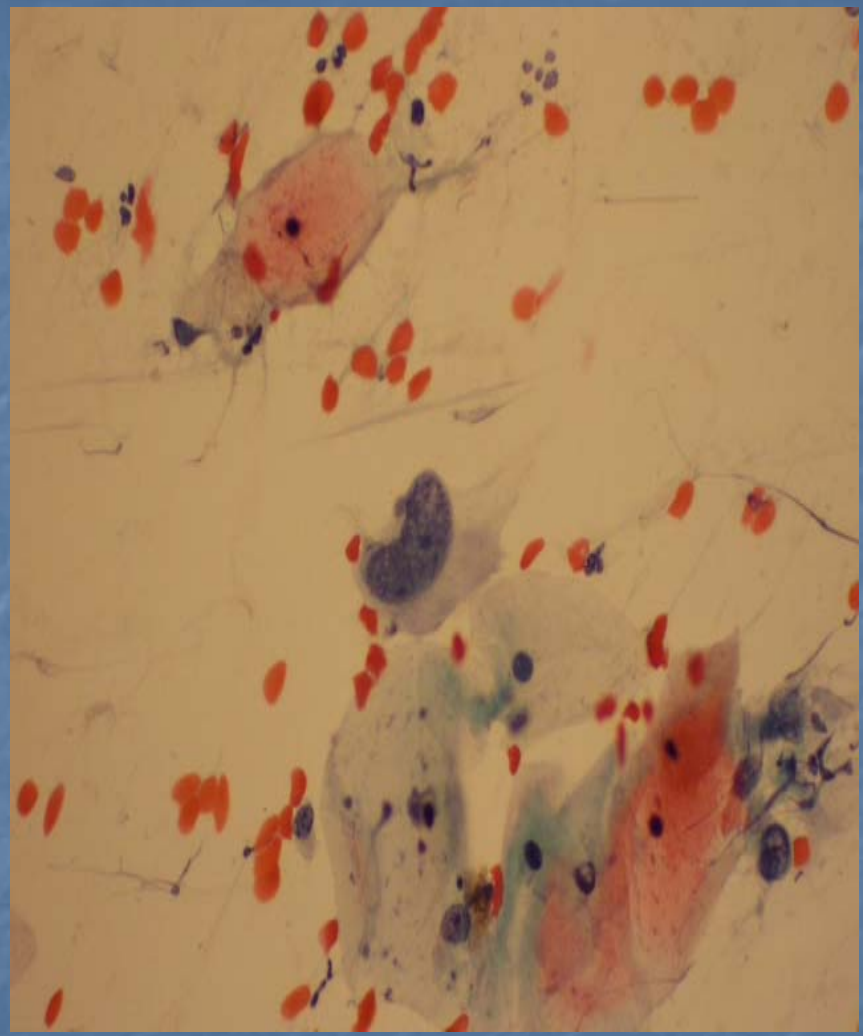
Case 4

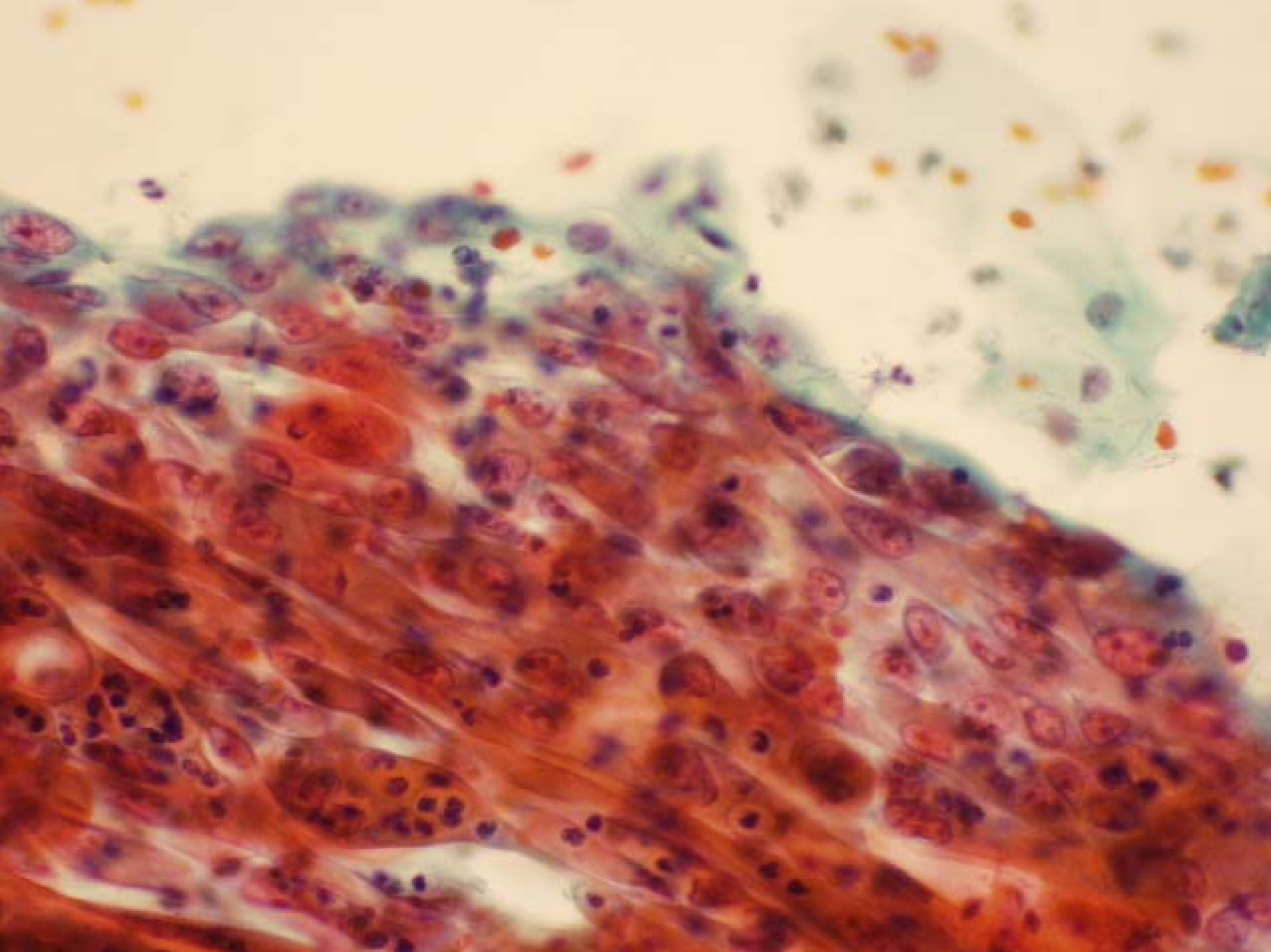
58 year old

Pap smear - Atypical repair









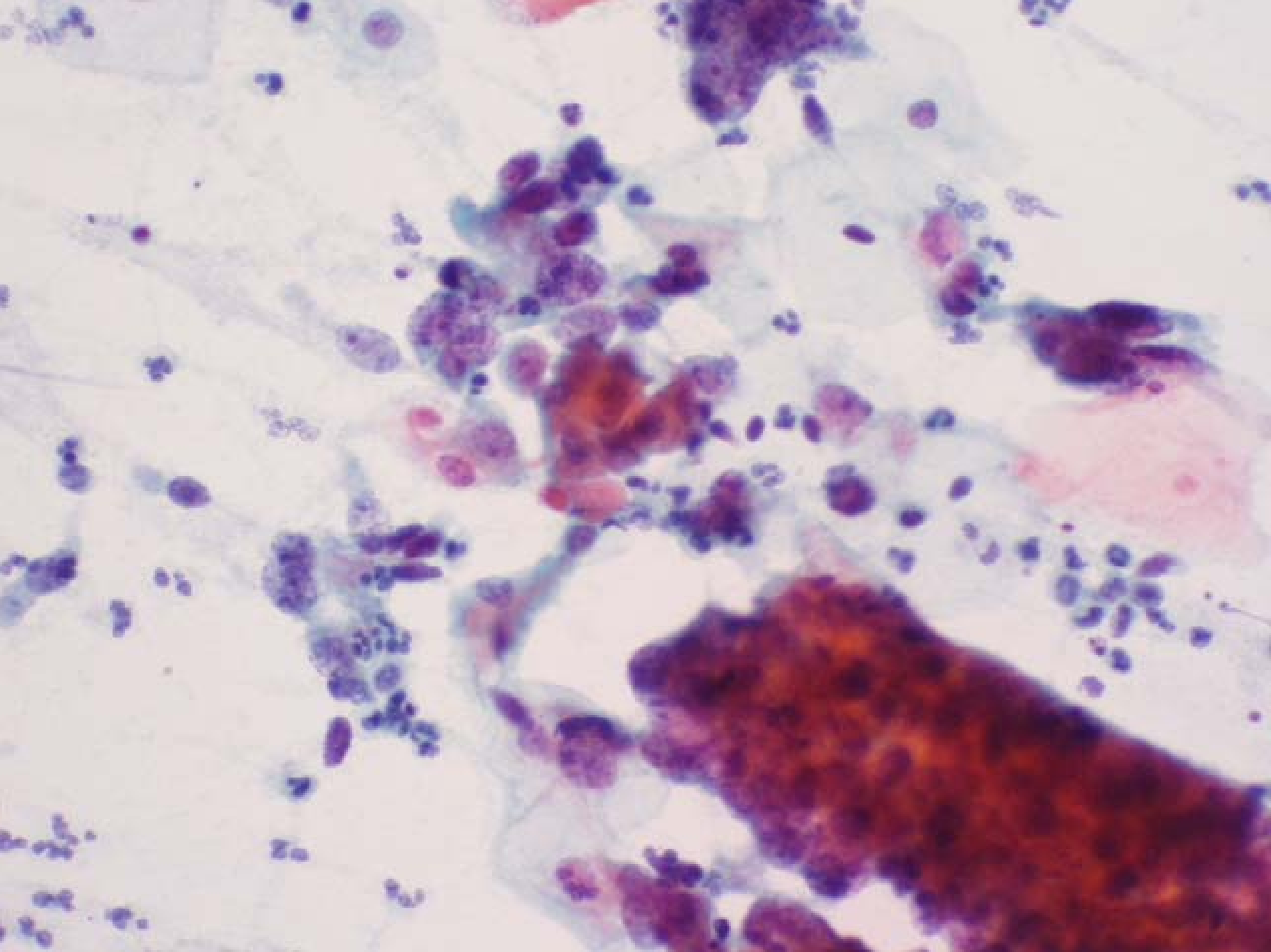
Atypical repair

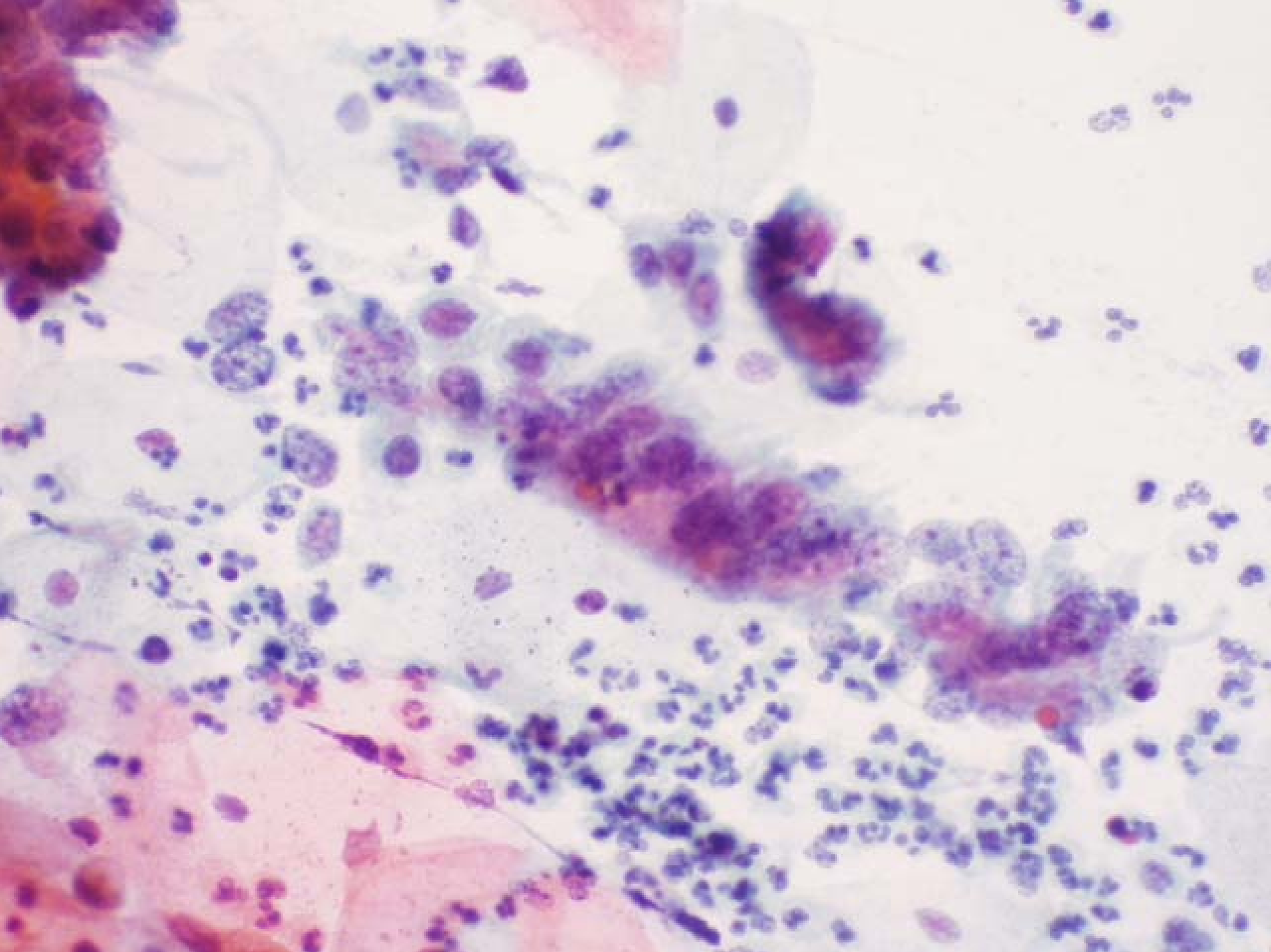
- Sheet- like arrangement “school of fish”
- Finely granular chromatin
- Prominent nucleoli
- Cyanophilic vacuolated cytoplasm
- Bi- and multinucleation
- Mitosis
- Small study (Rimm) - 25% of SIL (LSIL)

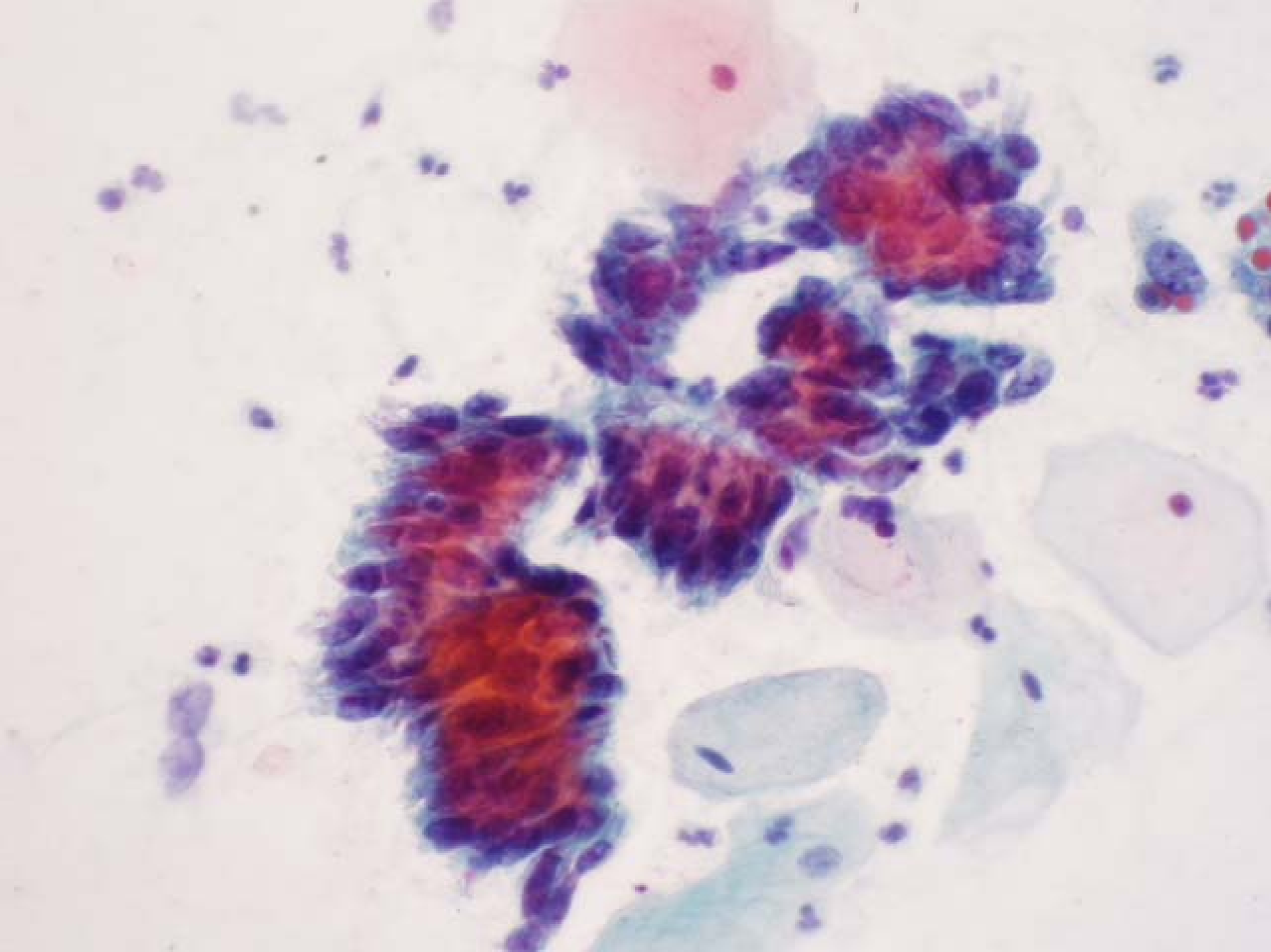
Case 5

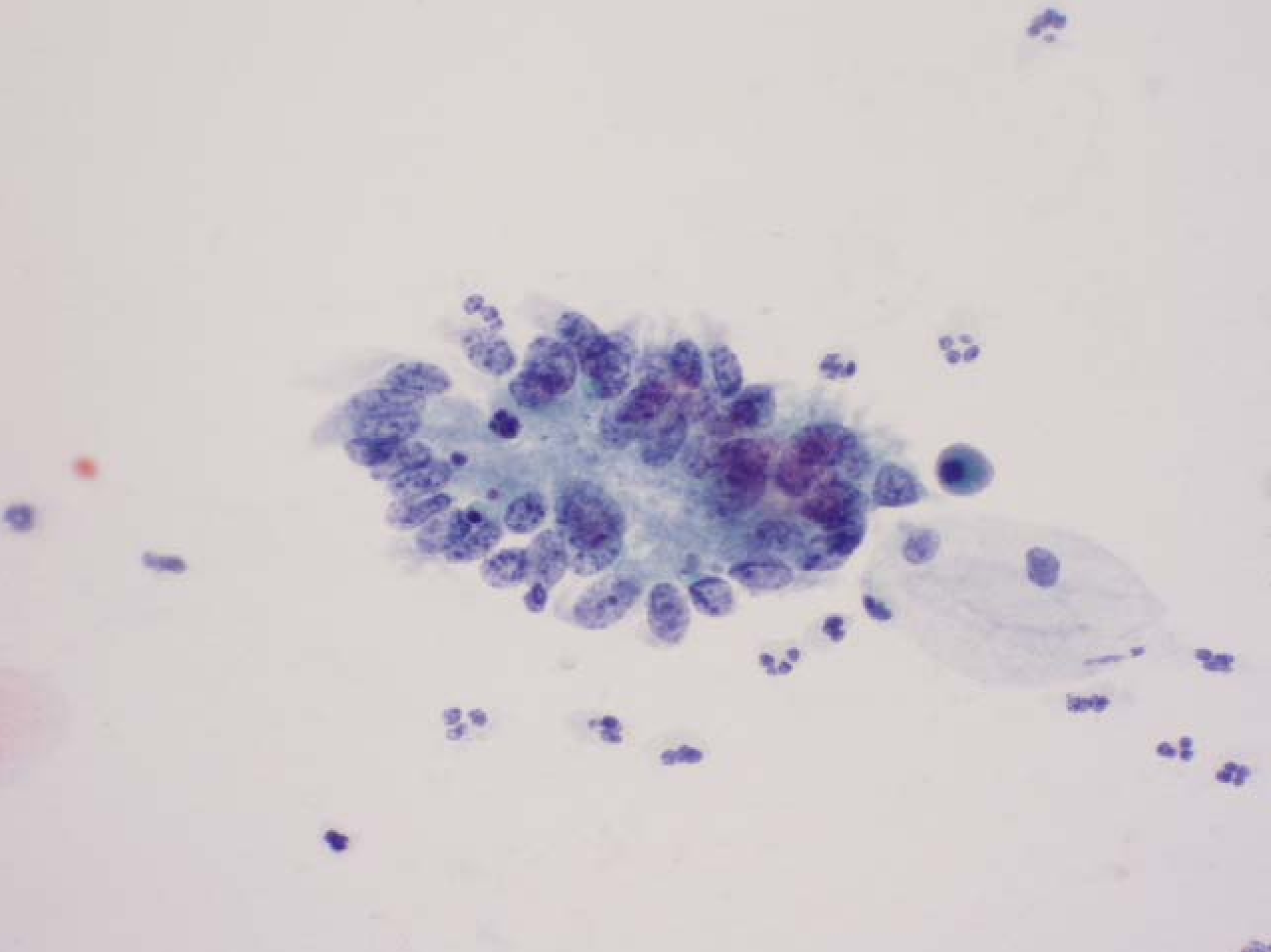
29 year old

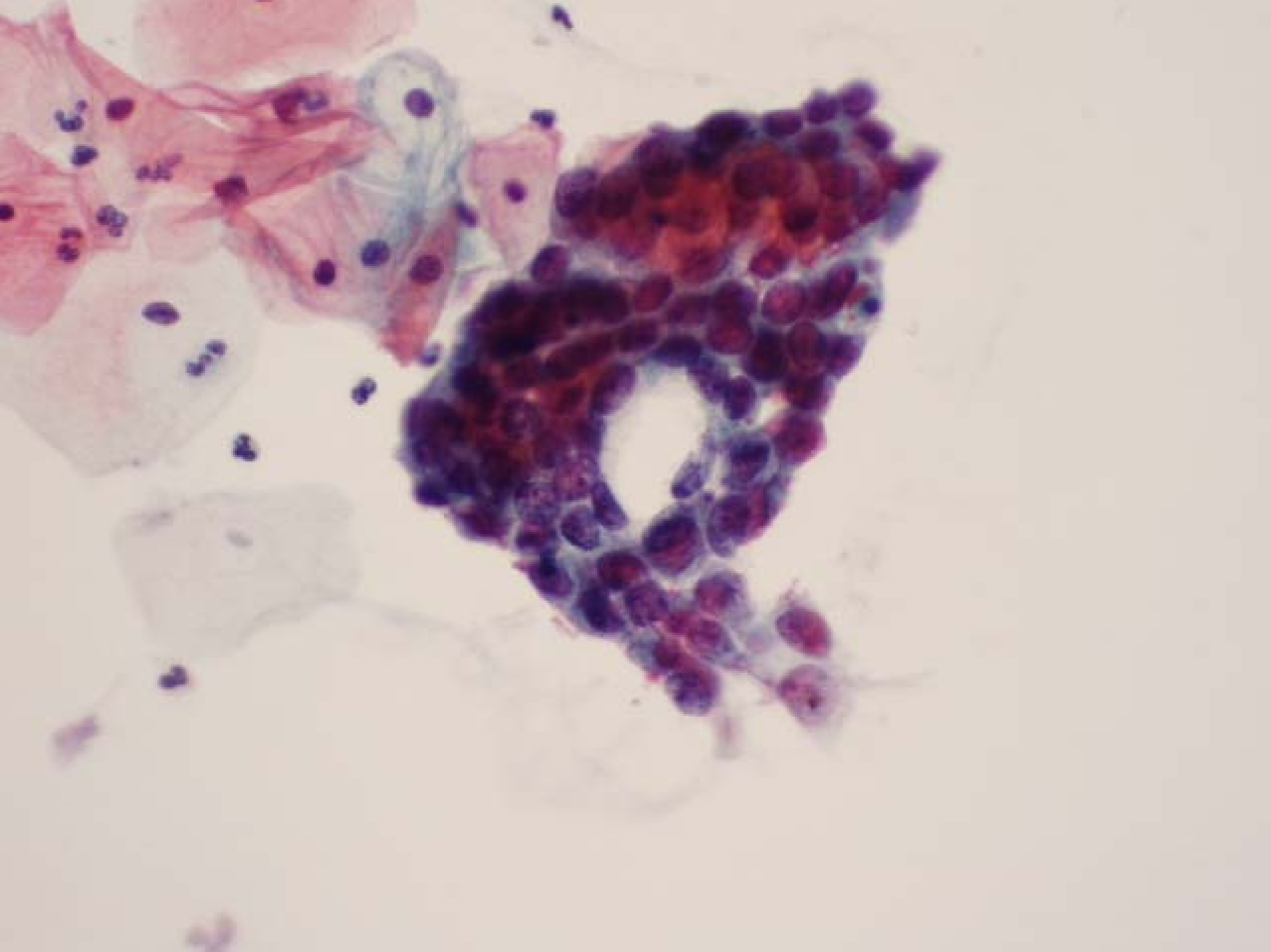
Pap smear - AGUS, favor neoplastic

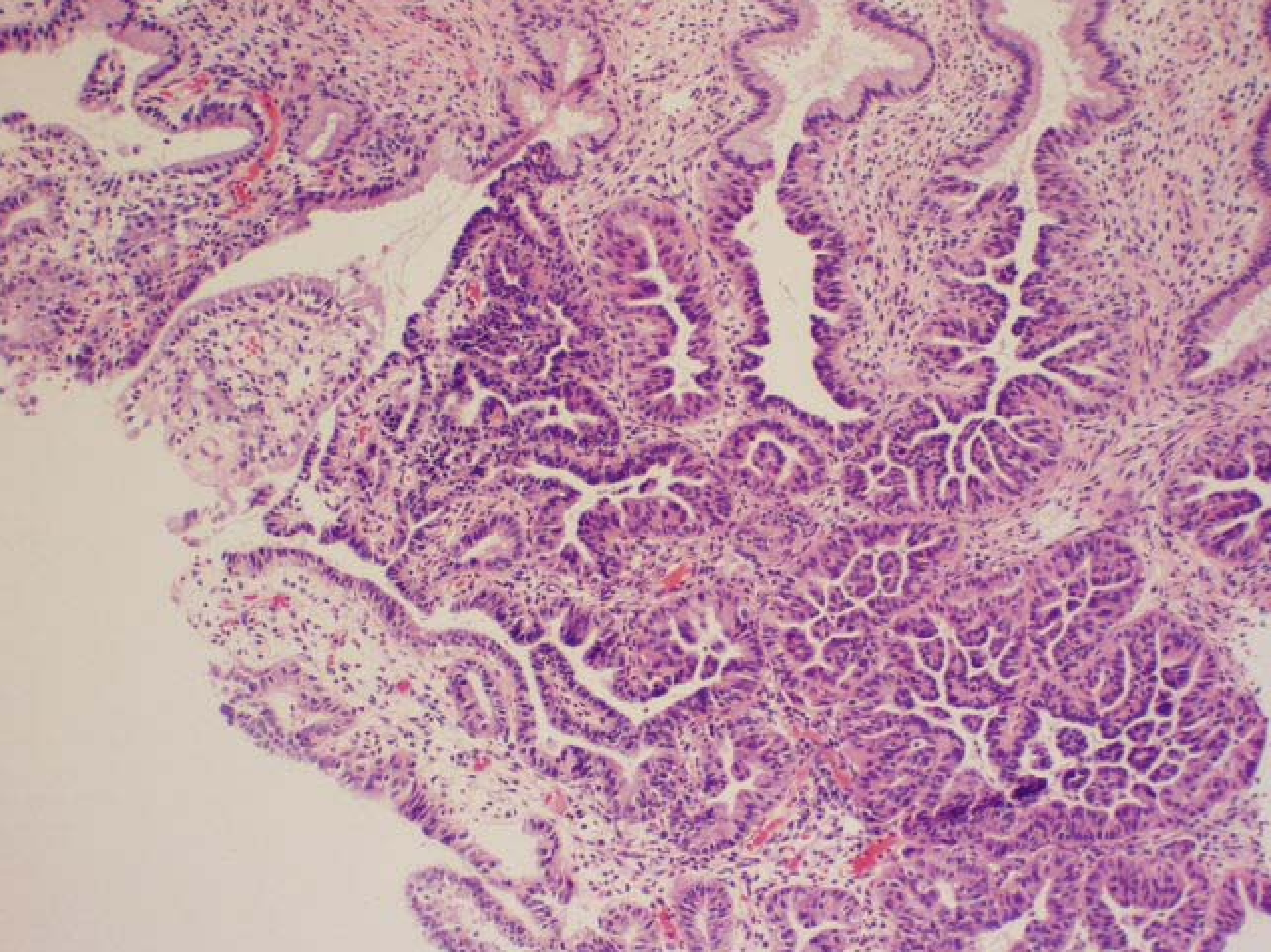


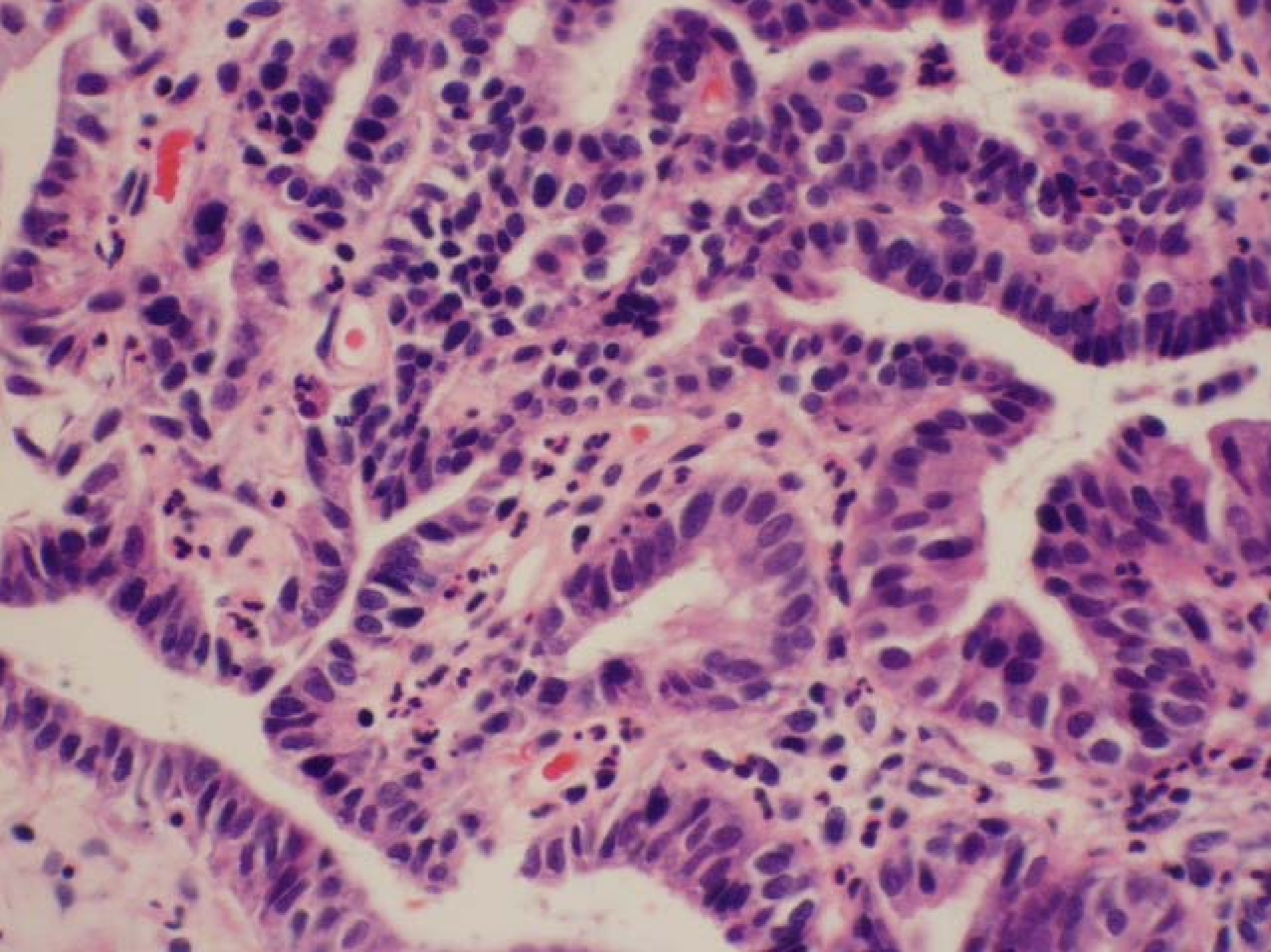


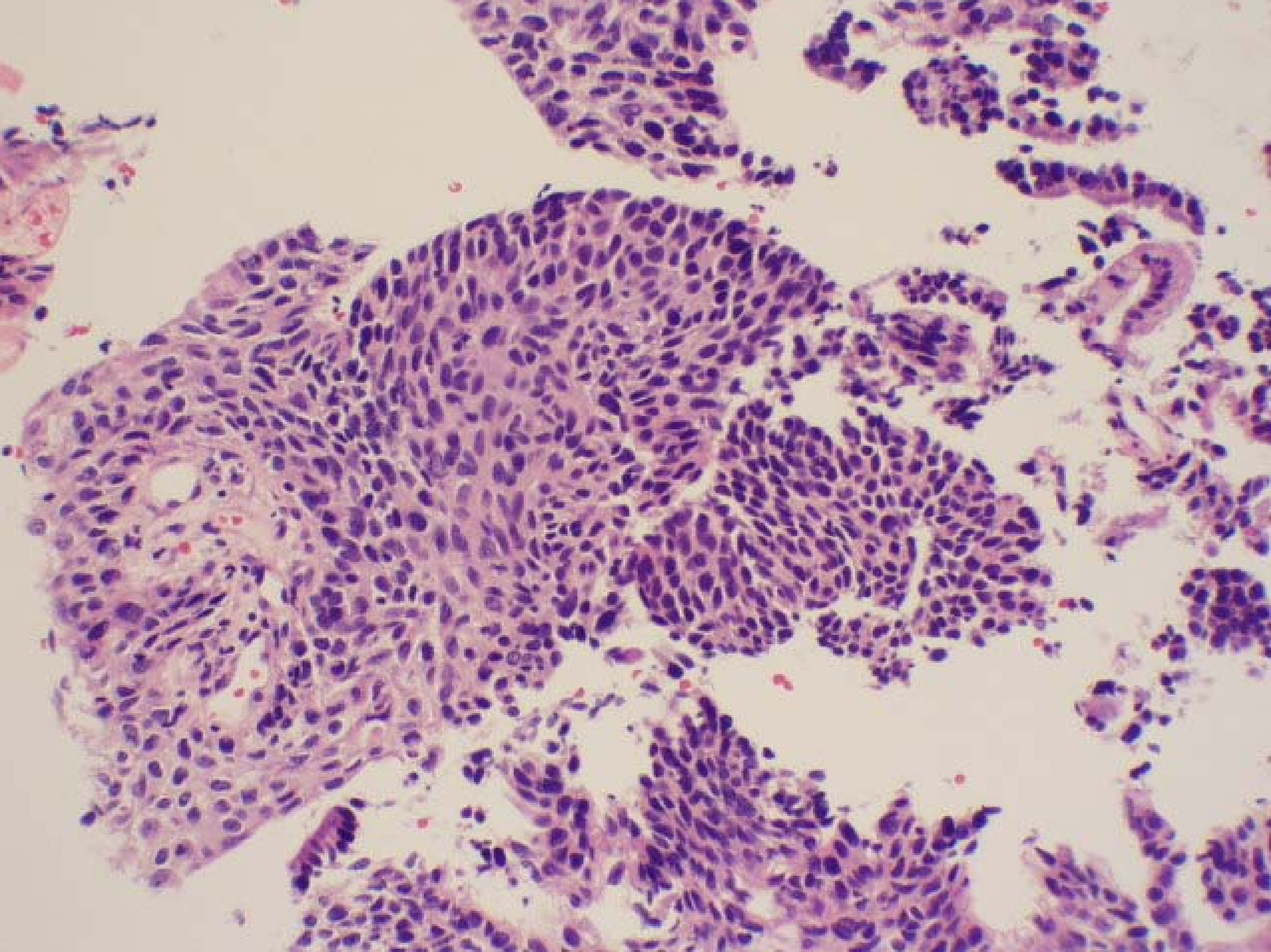












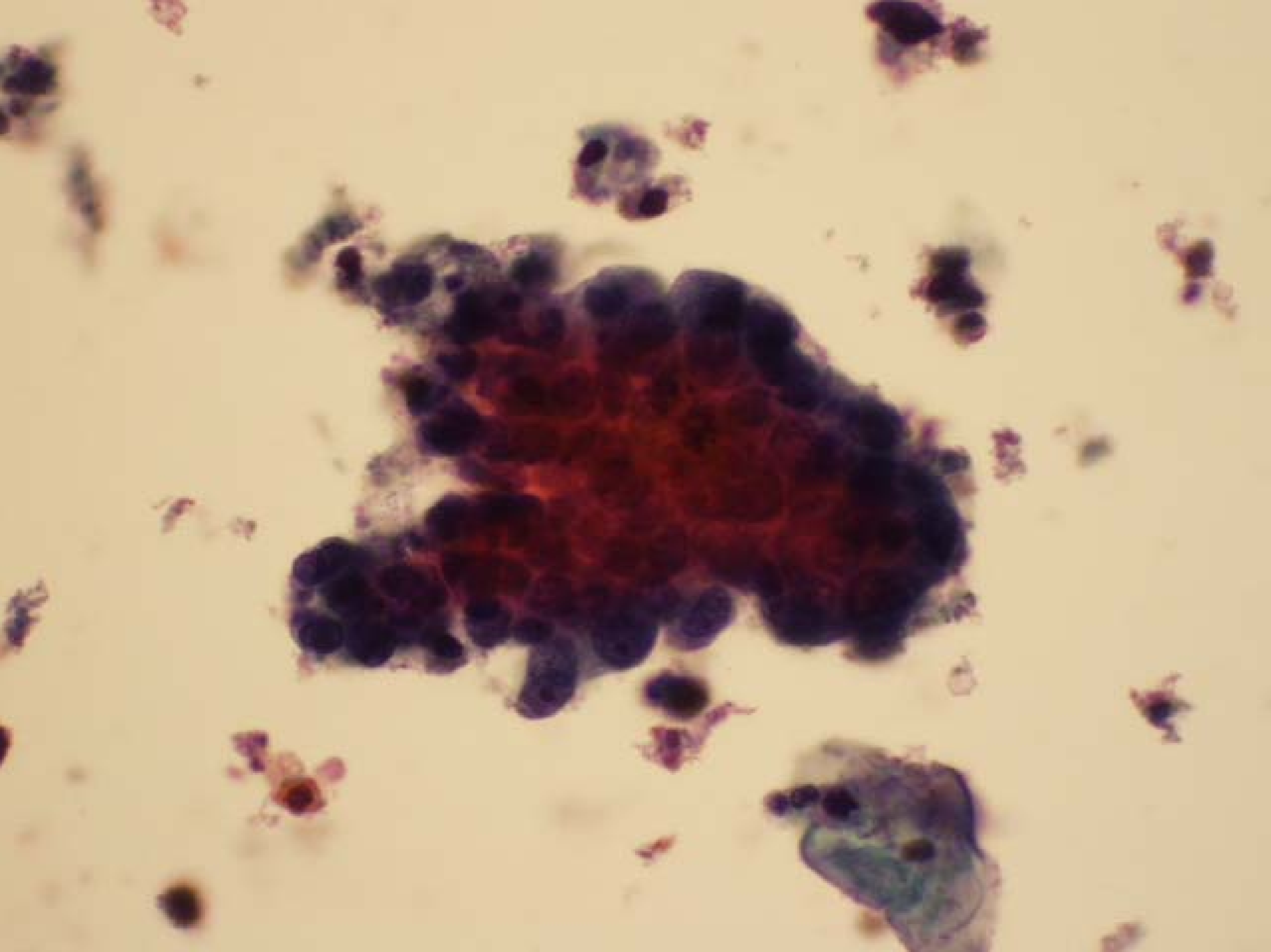
Adenocarcinoma in situ/ High Grade Squamous Intraepithelial Lesion

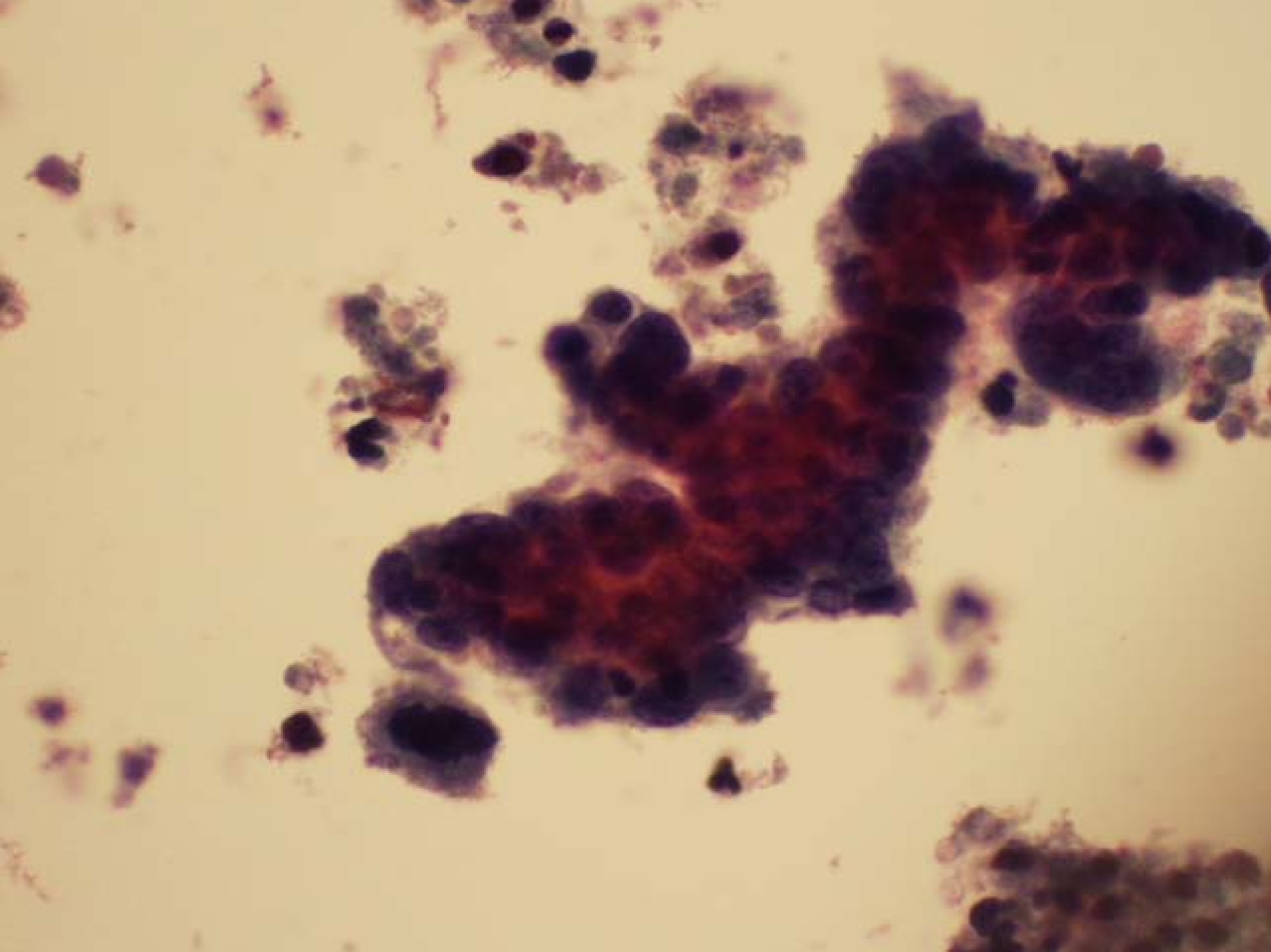
- Neoplastic endocervical cells
  - Tall columnar cells with hyperchromatic nuclei, coarse chromatin, feathery edges, rosettes
  - Uniform population (not a spectrum)
  - Crowding, nuclear enlargement, increased N/C ratio
  - Coarse chromatin
  - Small to prominent nucleoli in every cell
  - No diathesis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

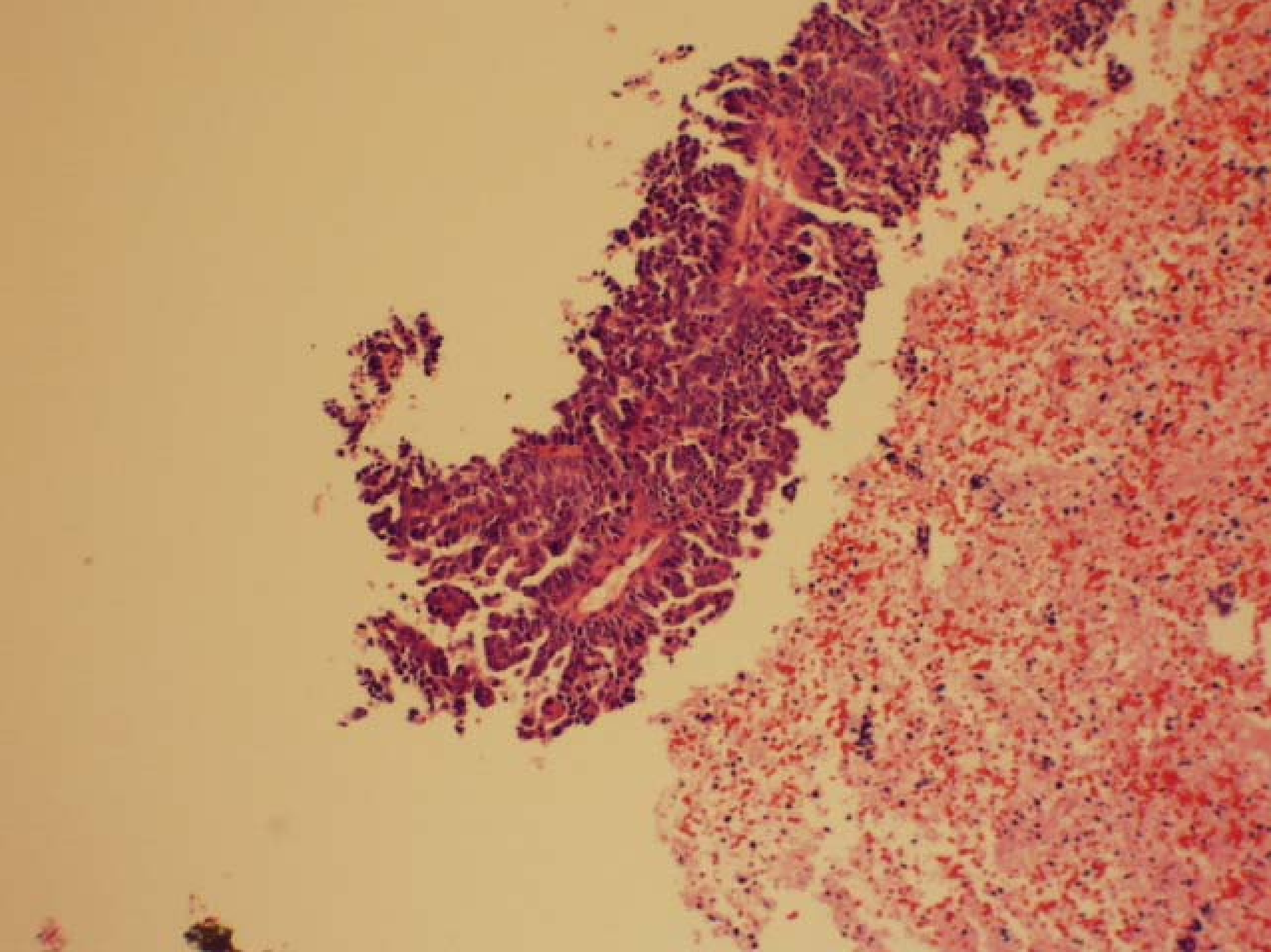
Case 6

62 year old

Pap smear - Adenocarcinoma







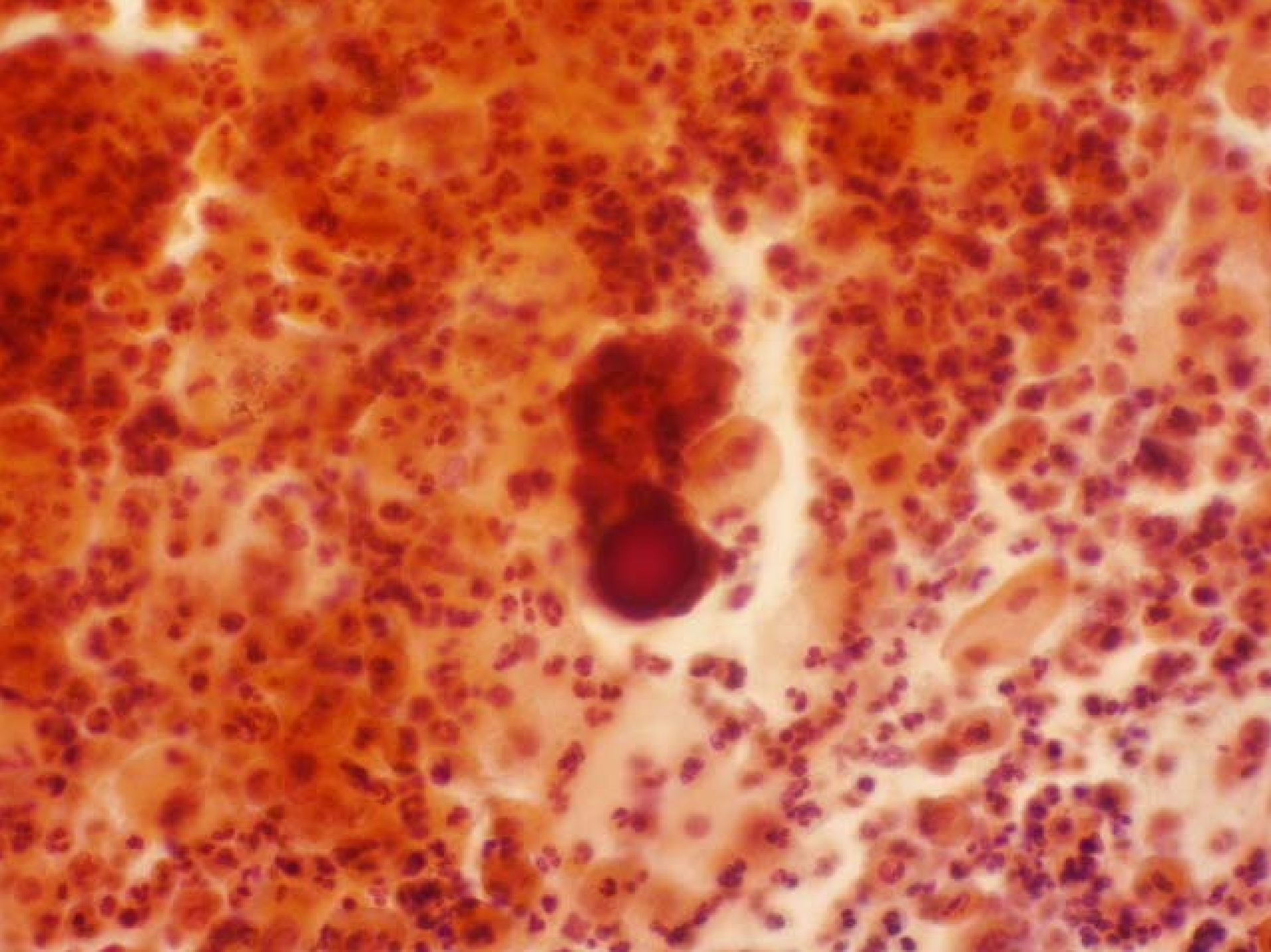
Endometrial Papillary Serous Adenocarcinoma

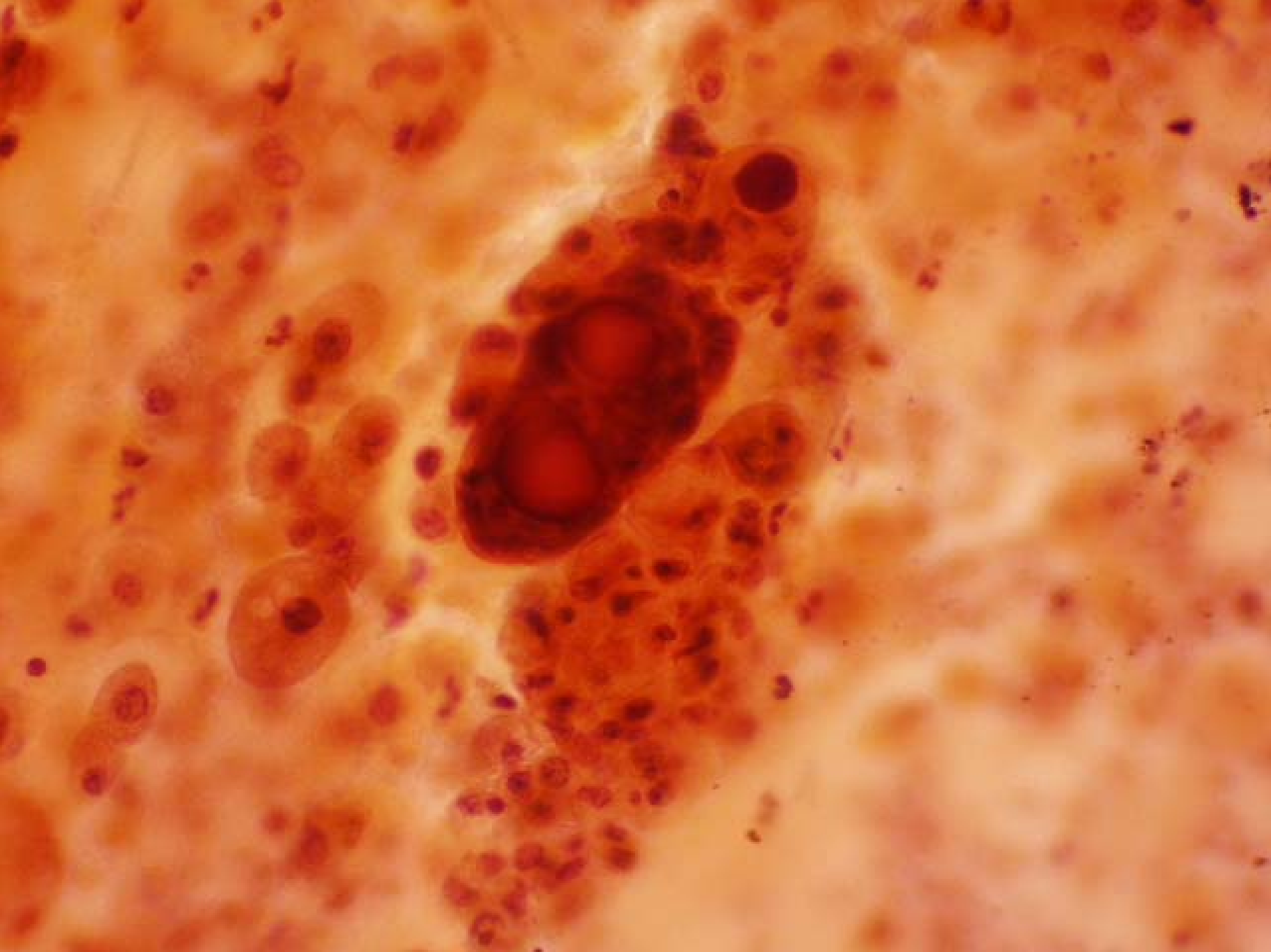
- Numerous papillary groups
- Occasional psammoma bodies
- High grade nuclei with prominent nucleoli

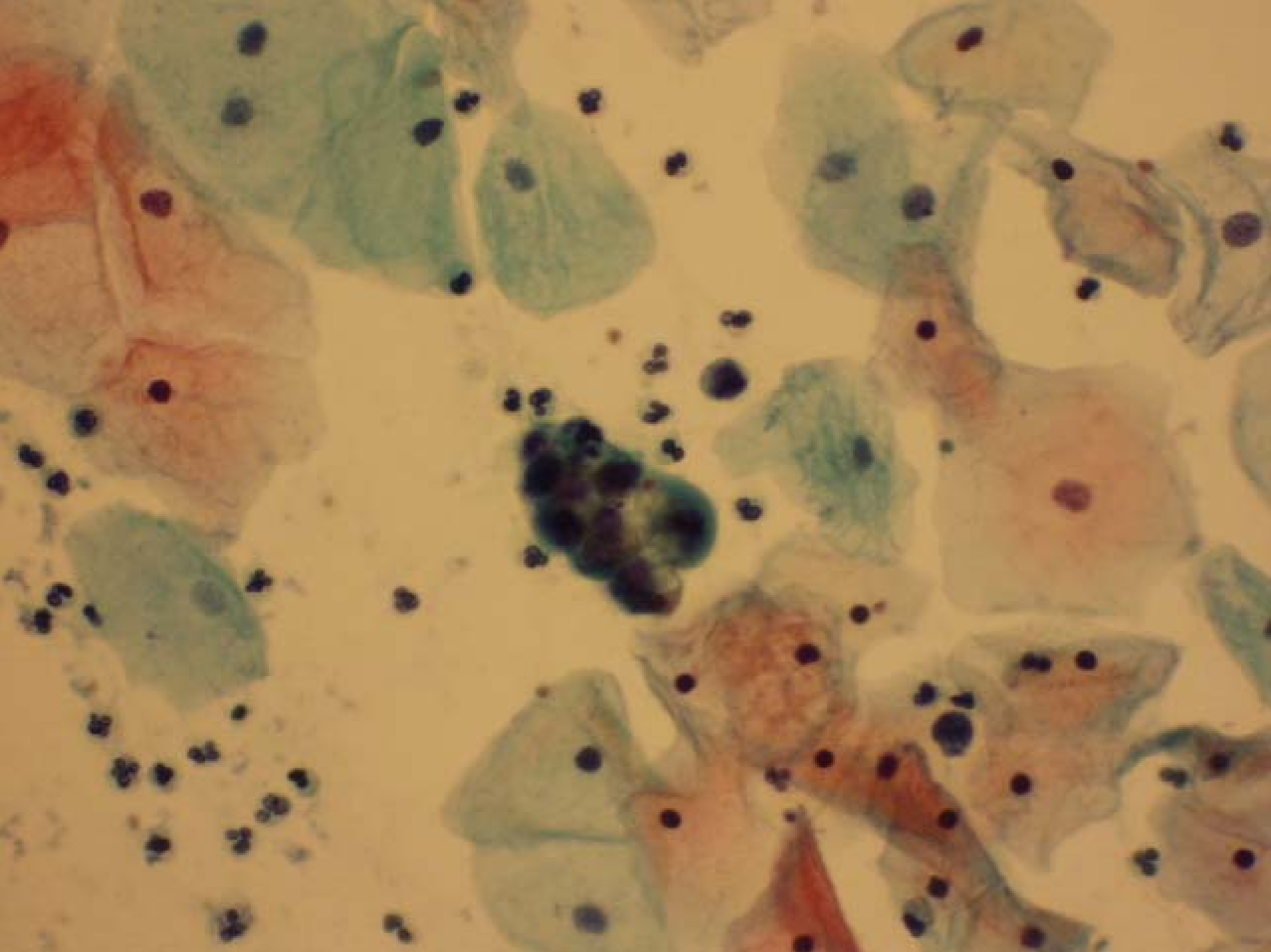
Case 7

56 year old

Papsmear- Psammoma bodies







Endometrial Adenocarcinoma

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

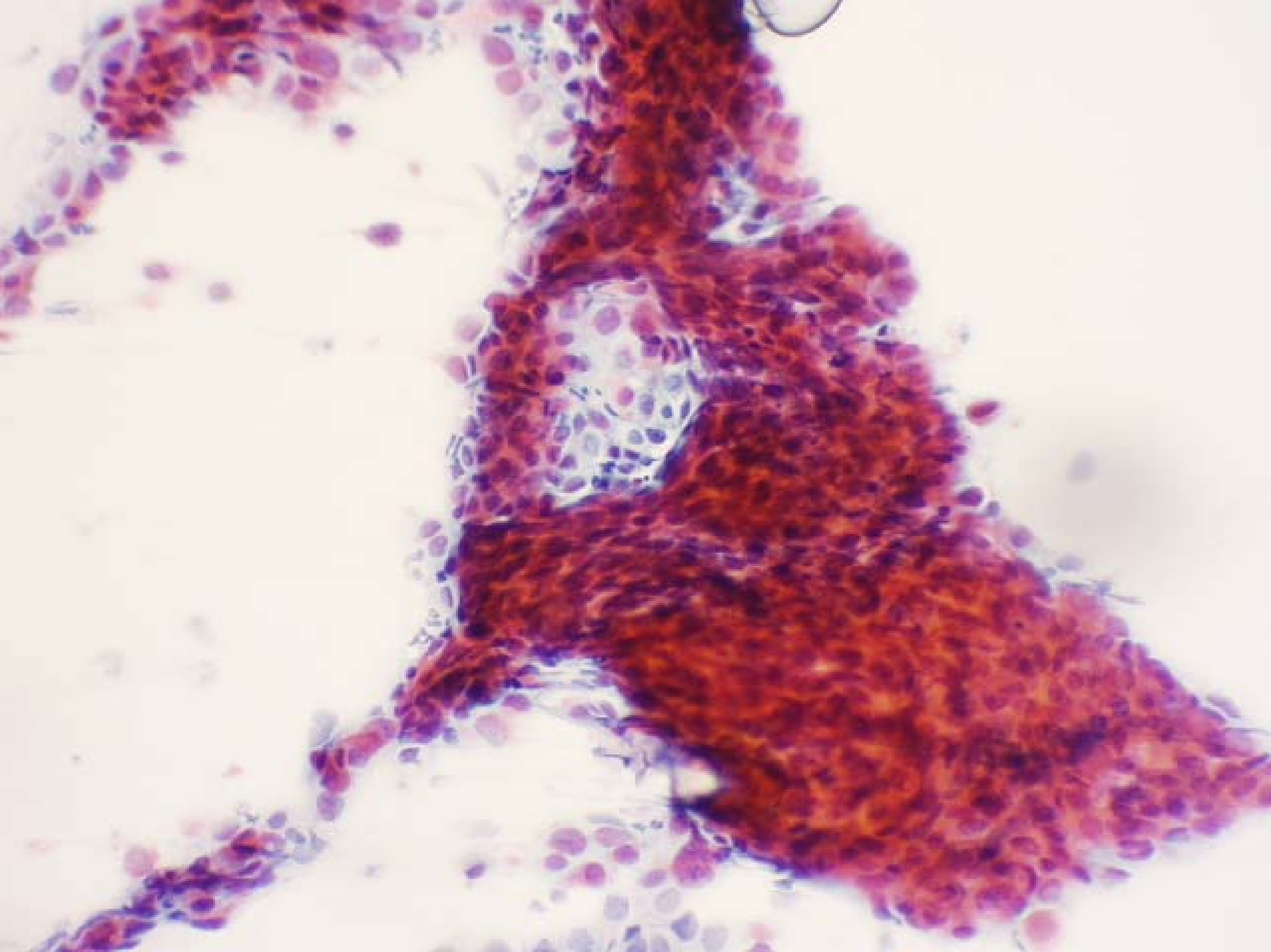
Pap Smear Psammoma Bodies

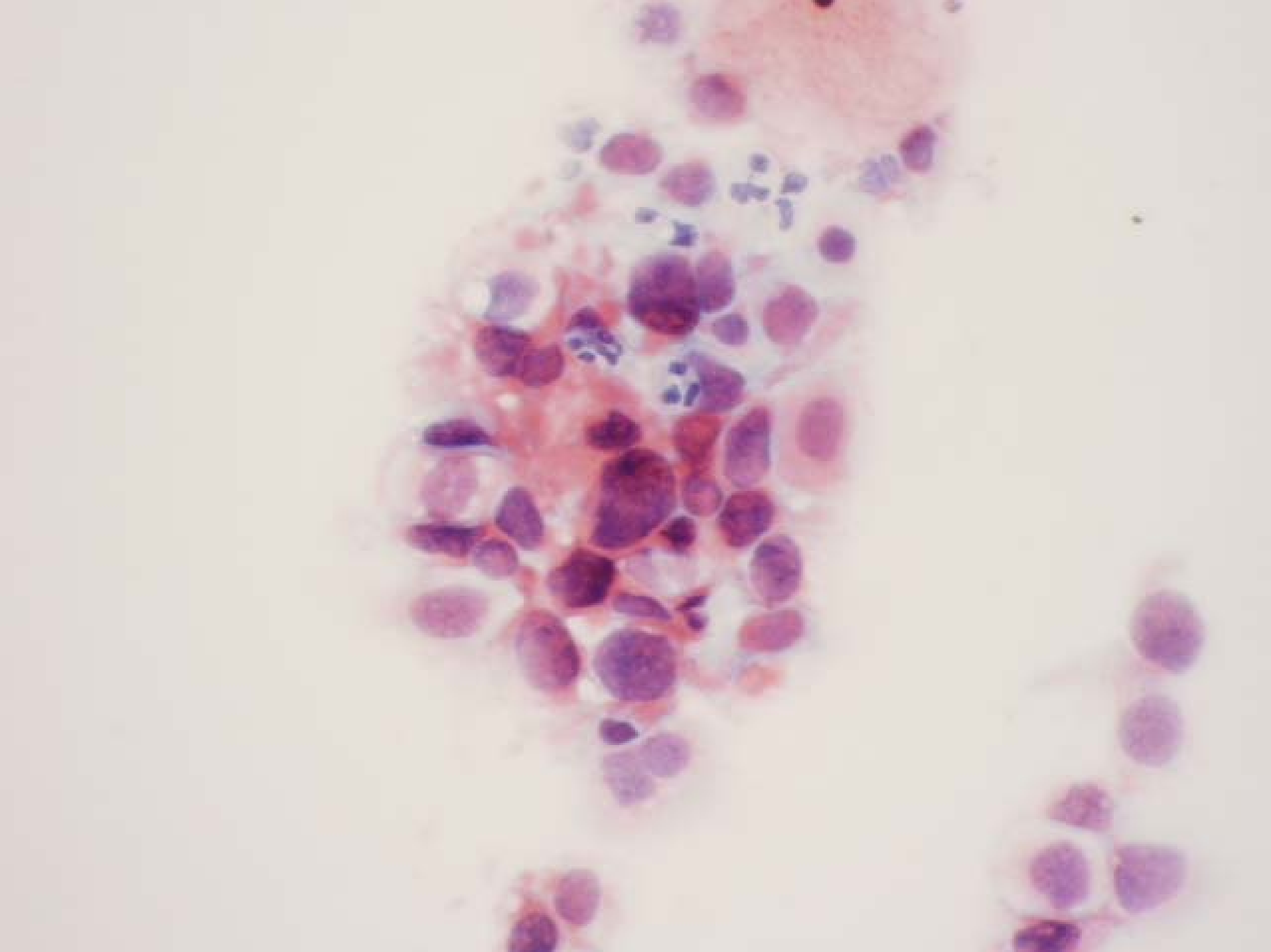
- Overall rare find in 1/30,000 Pap smears
- Benign
  - IUD
  - Ovarian inclusion cysts
  - Endometritis, tuberculosis
  - Endosalpingiosis
  - Birth control pills
- Malignant
  - Ovarian, endometrial, cervical , endocervical neuroendocrine carcinoma, fallopian tube, metastasis

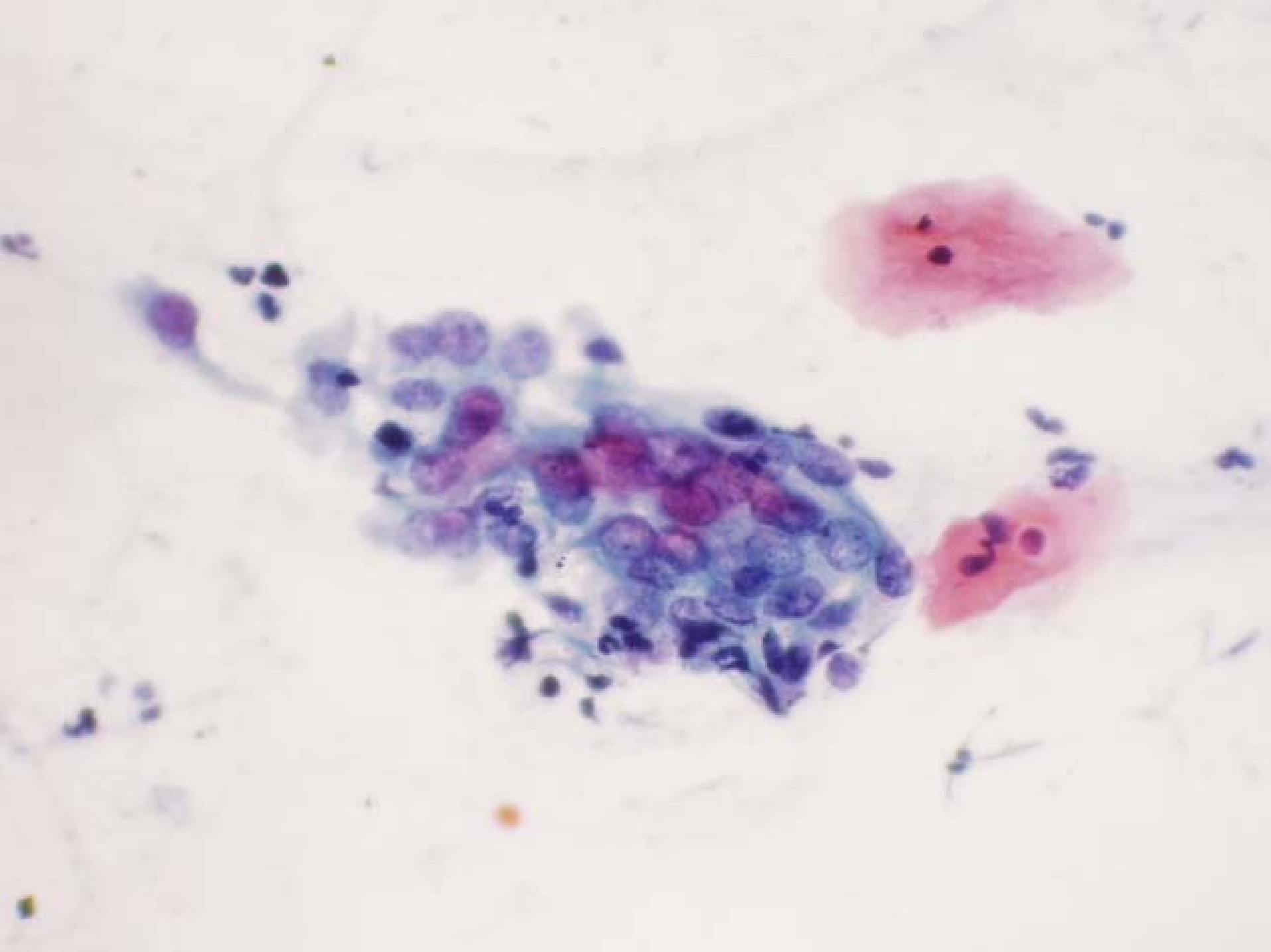
Case 8

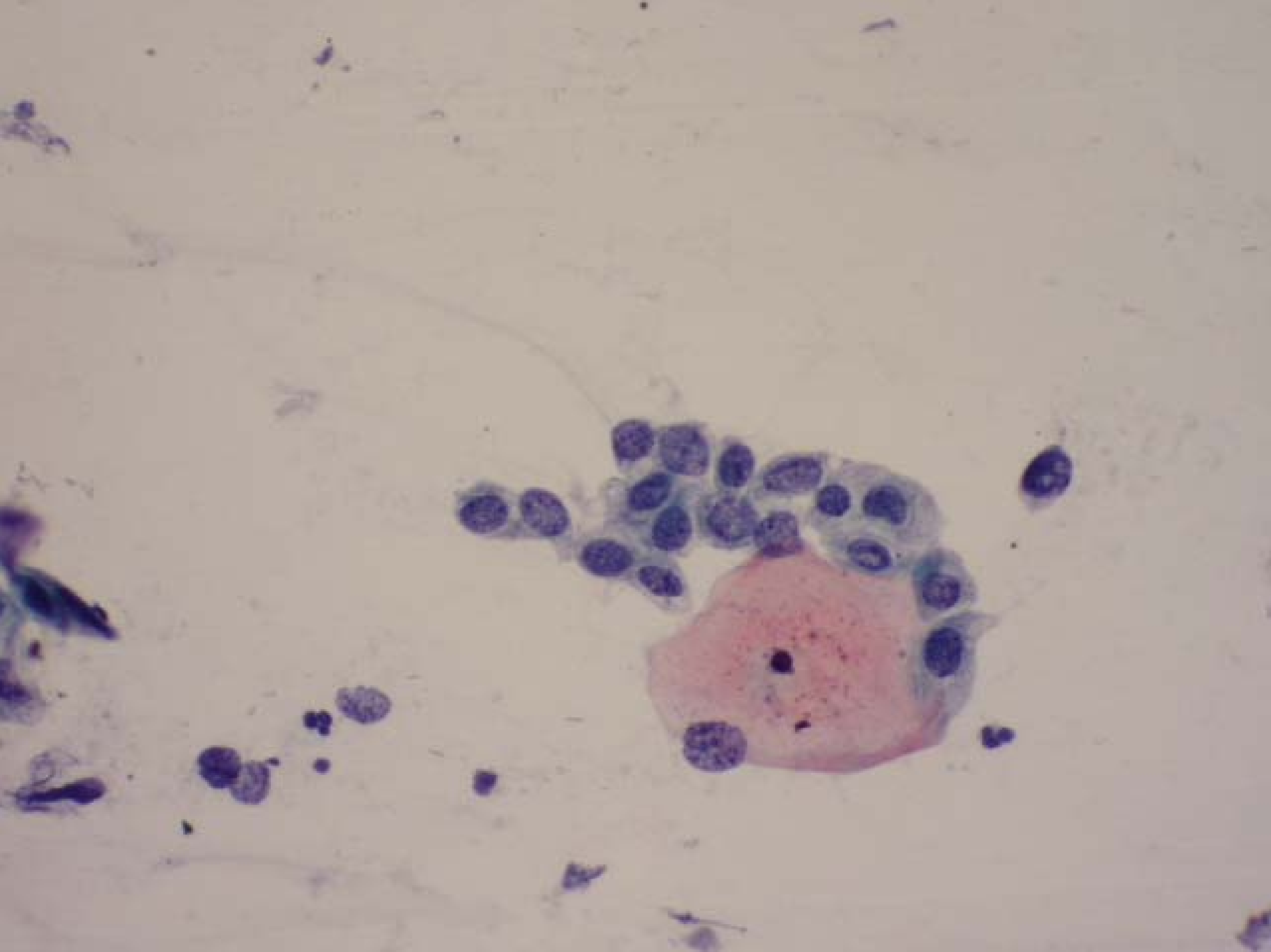
34 year old

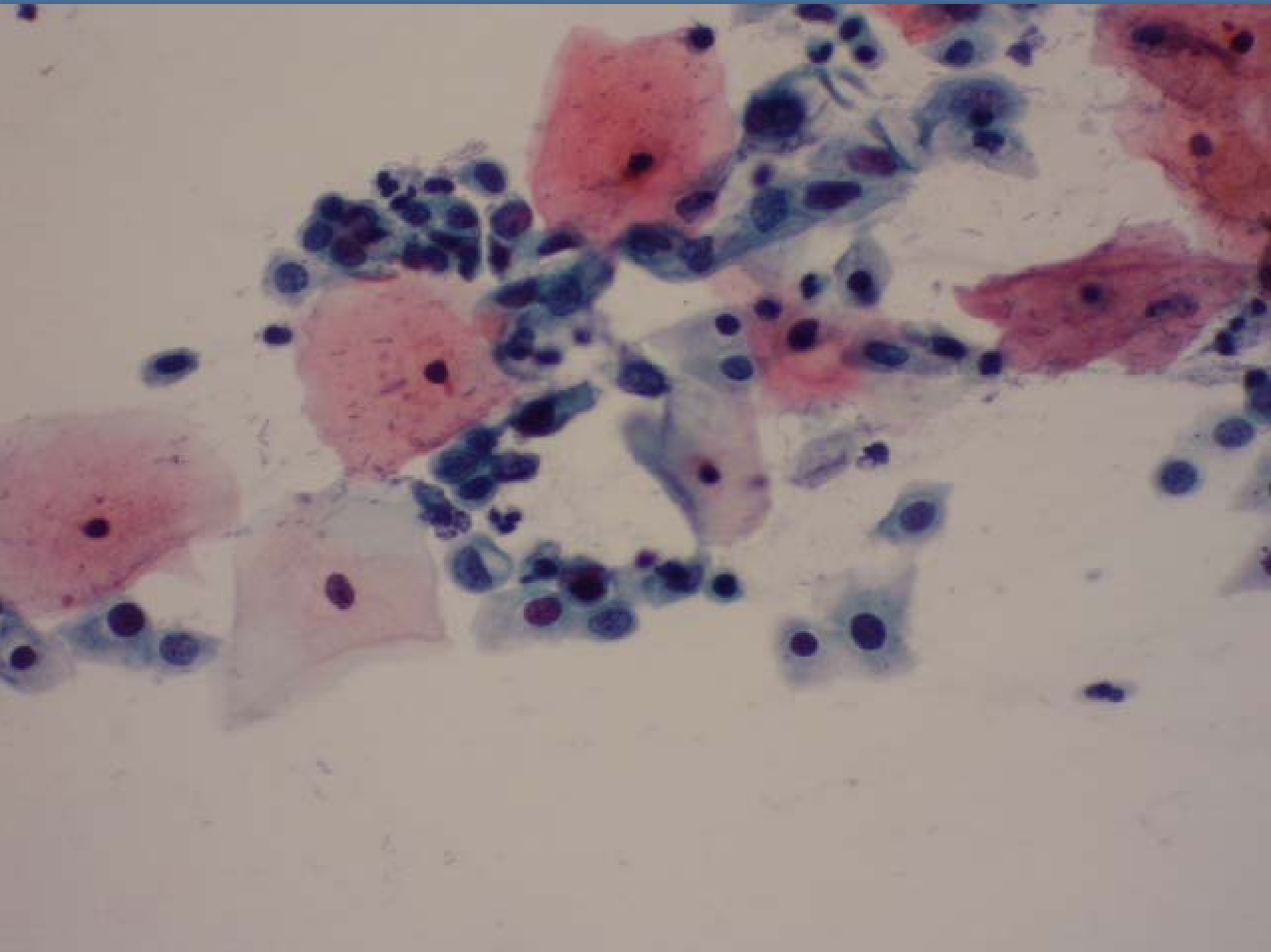
Pap smear - ASCUS

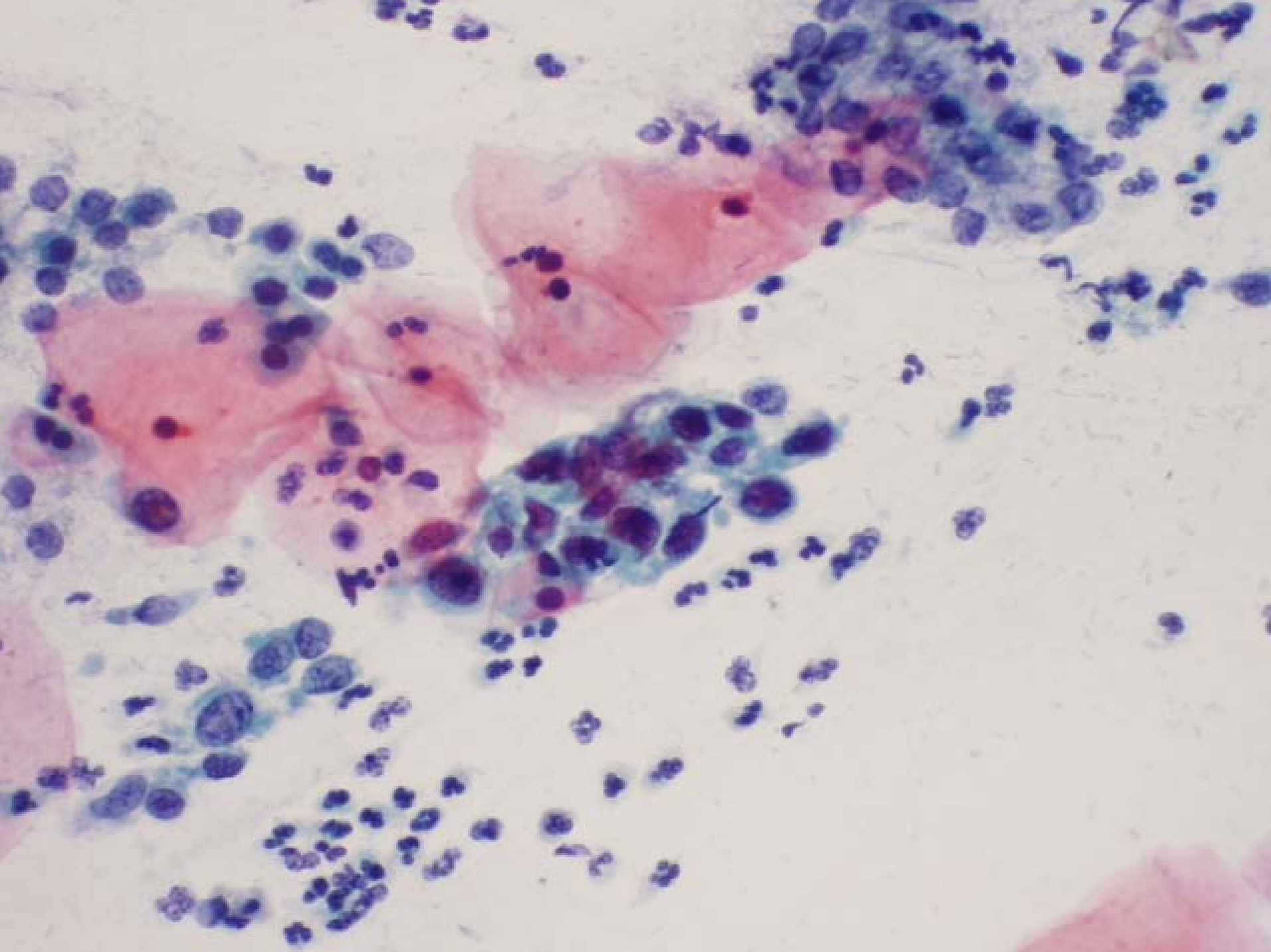


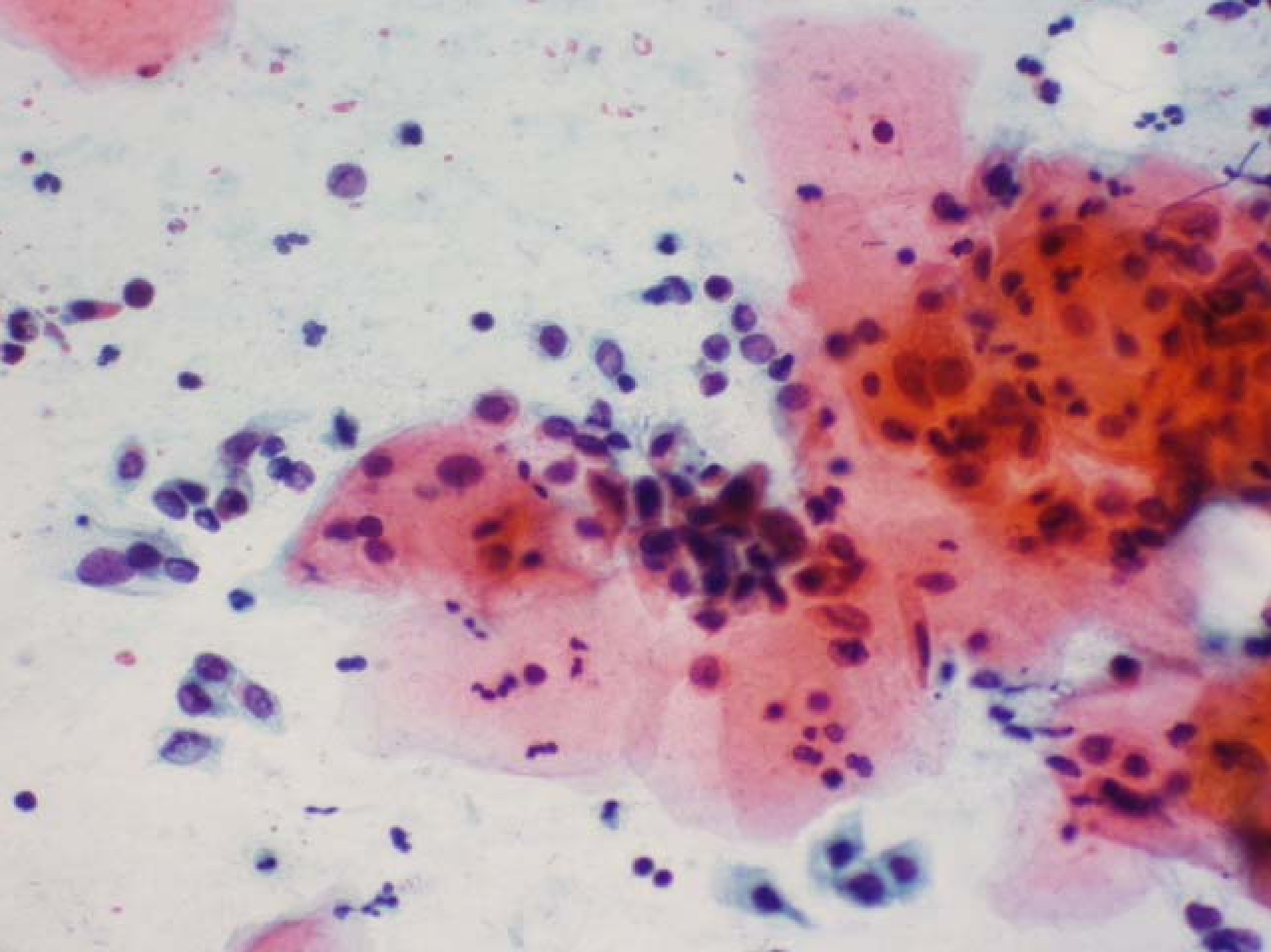


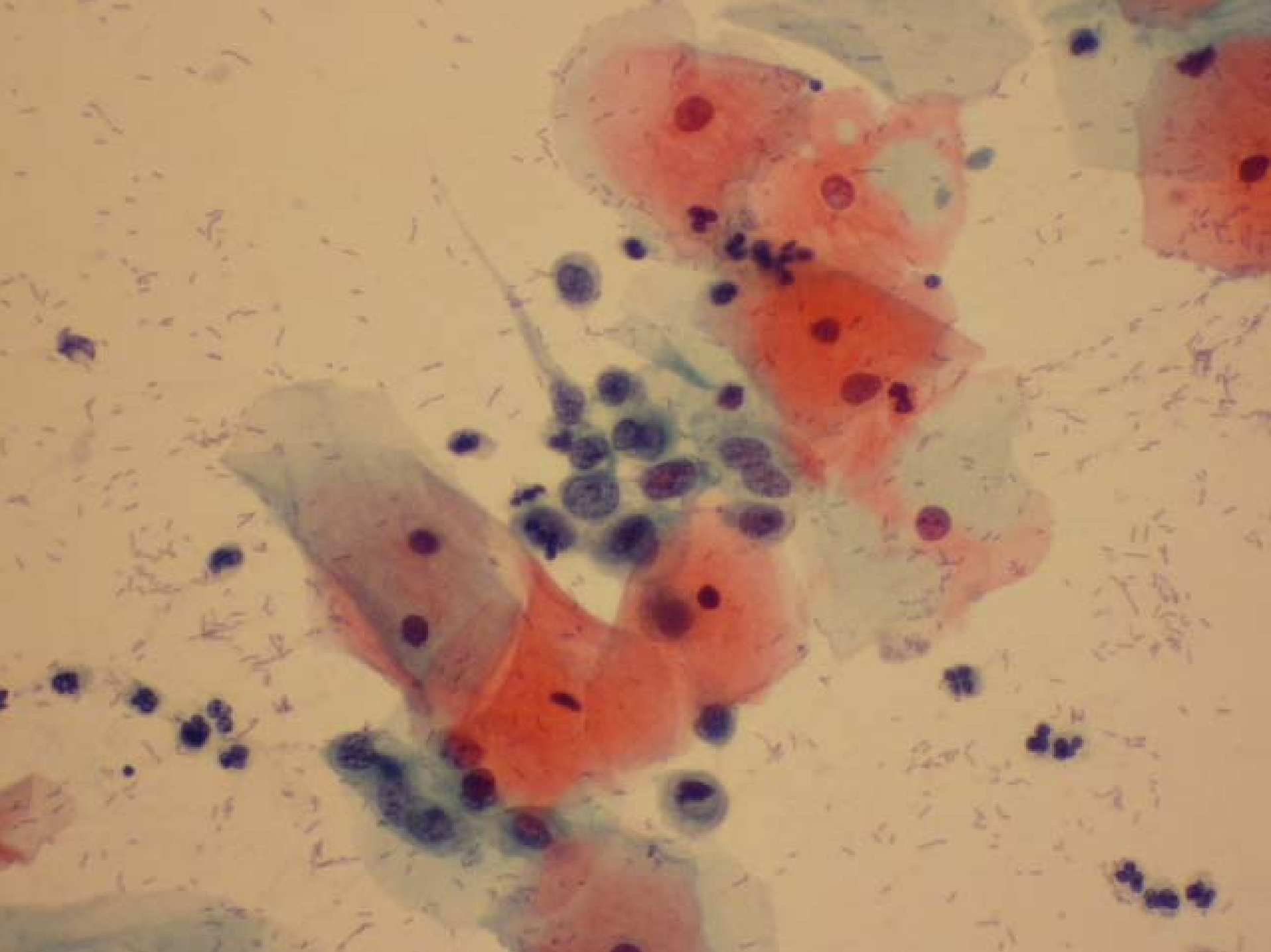


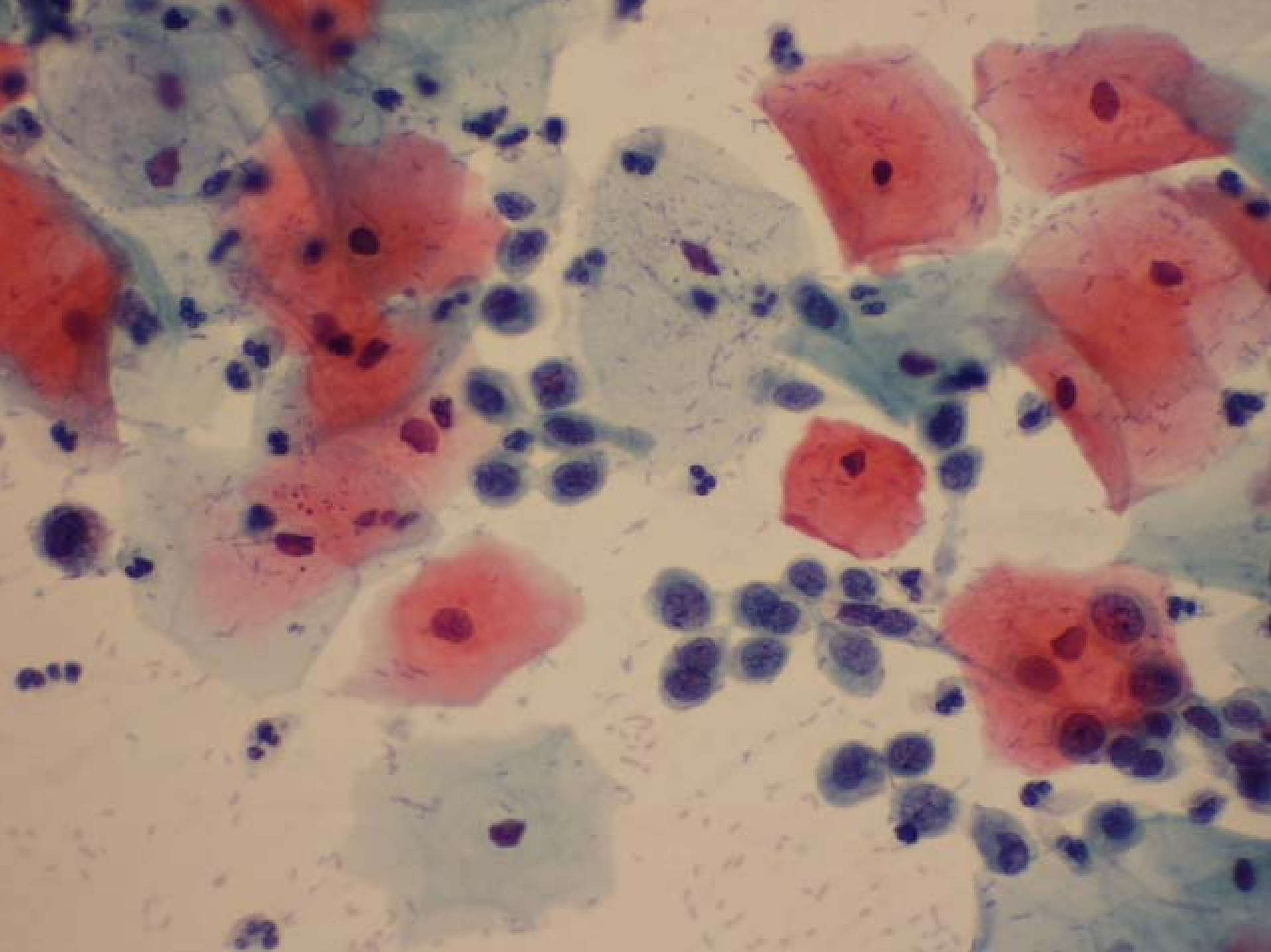












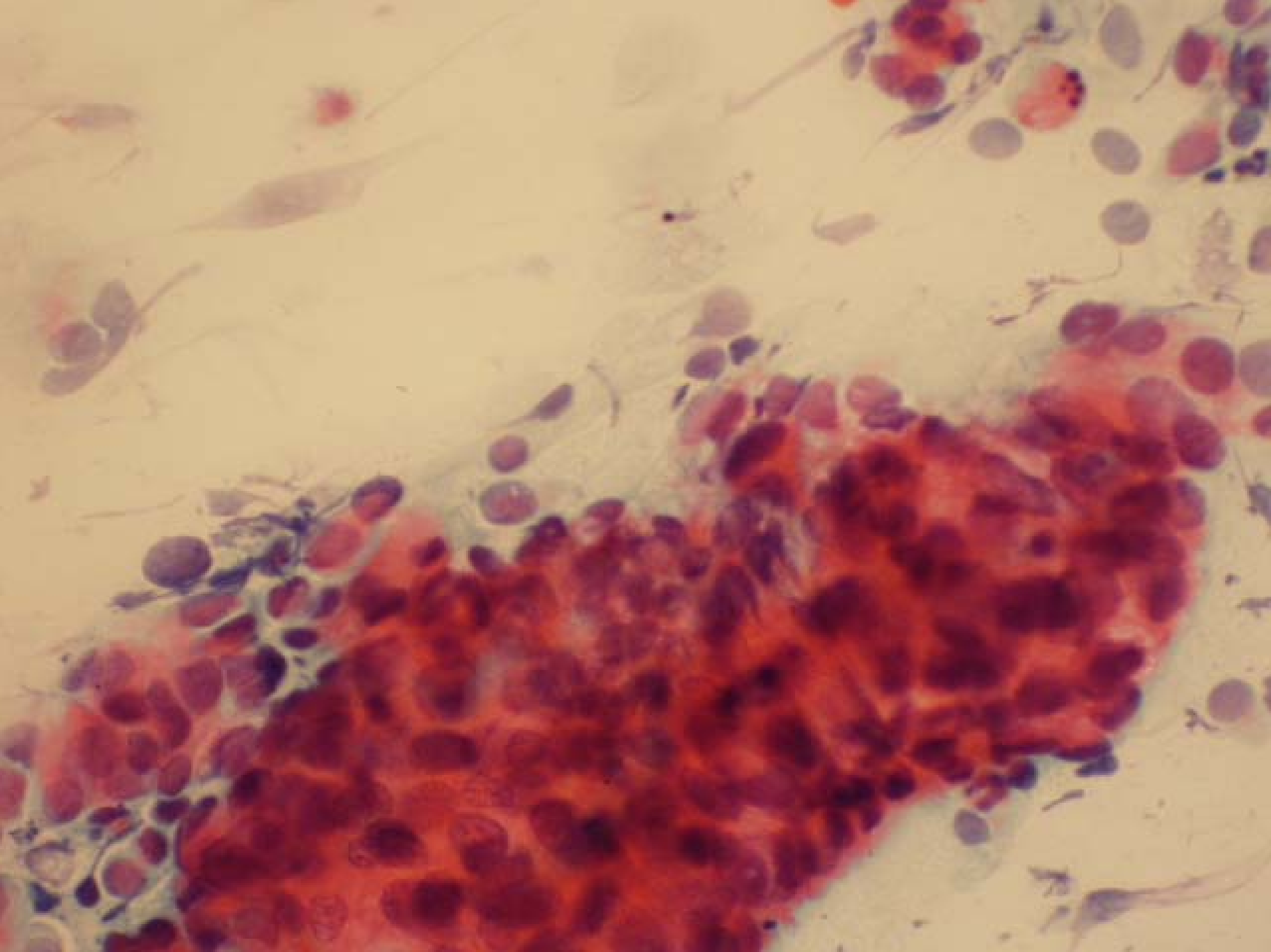
High Grade Squamous Intraepithelial Lesion

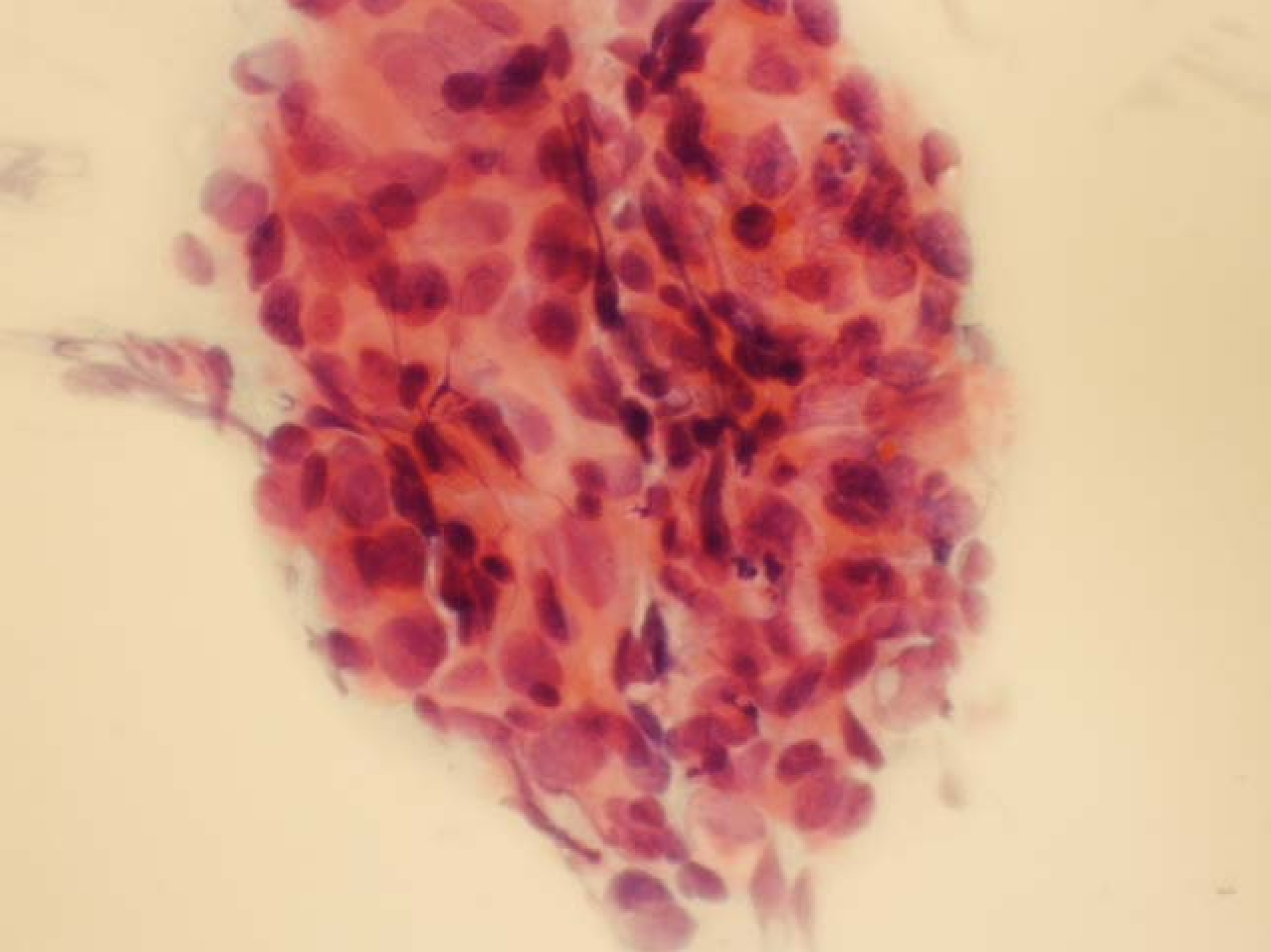
- DDX: Immature squamous metaplasia
- Some types of HSIL exfoliate as small cells - d/d histiocytes or squamous metaplasia
- Uncertainty
  - Wilbur *et al* - atypical immature metaplasia in 11/17 negative paps with subsequent HSIL
  - Sherman - 20 neg paps with retro review 23% HSIL, 30% ASCUS, 14% unsatisfactory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

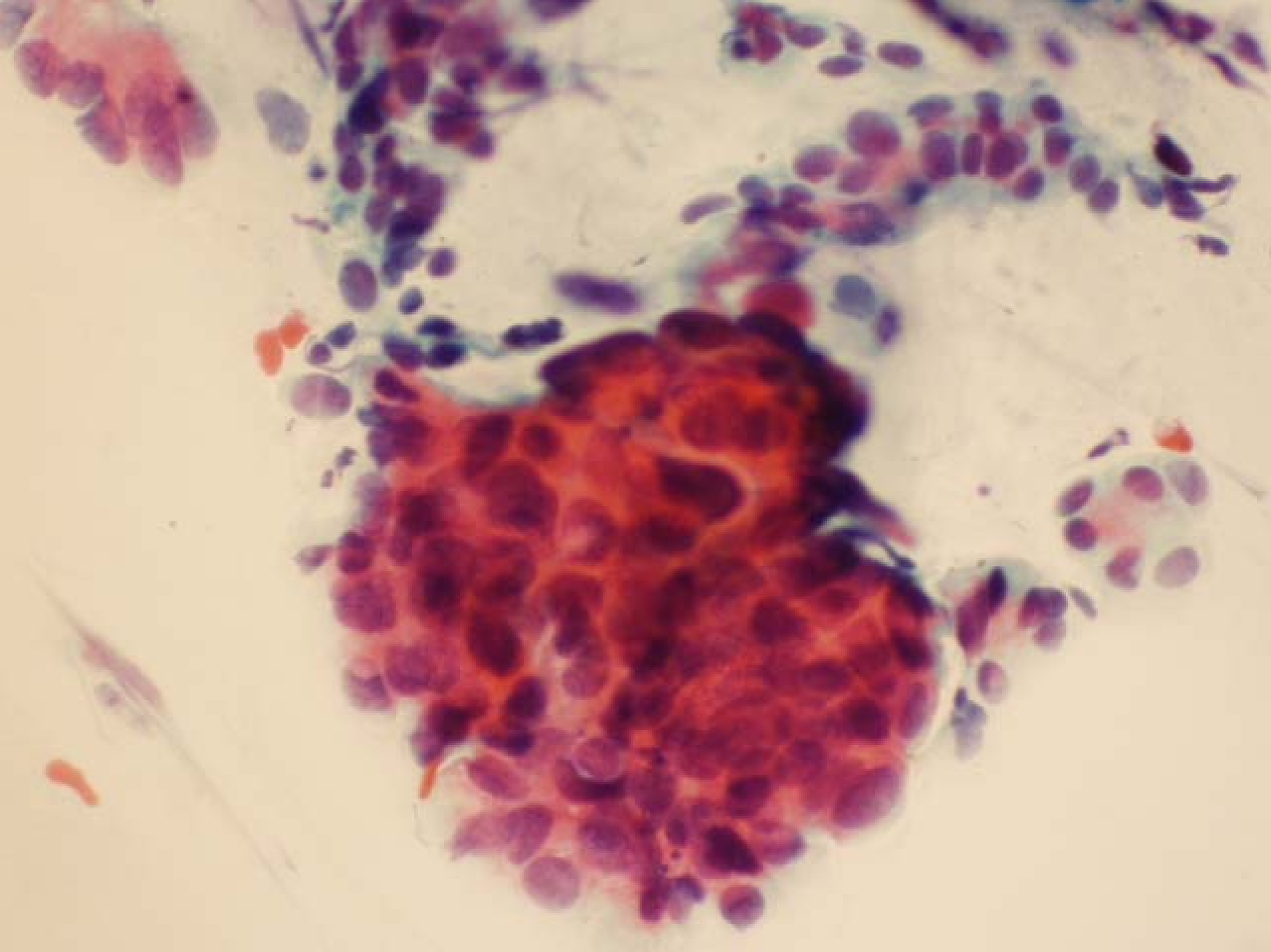
CASE 9

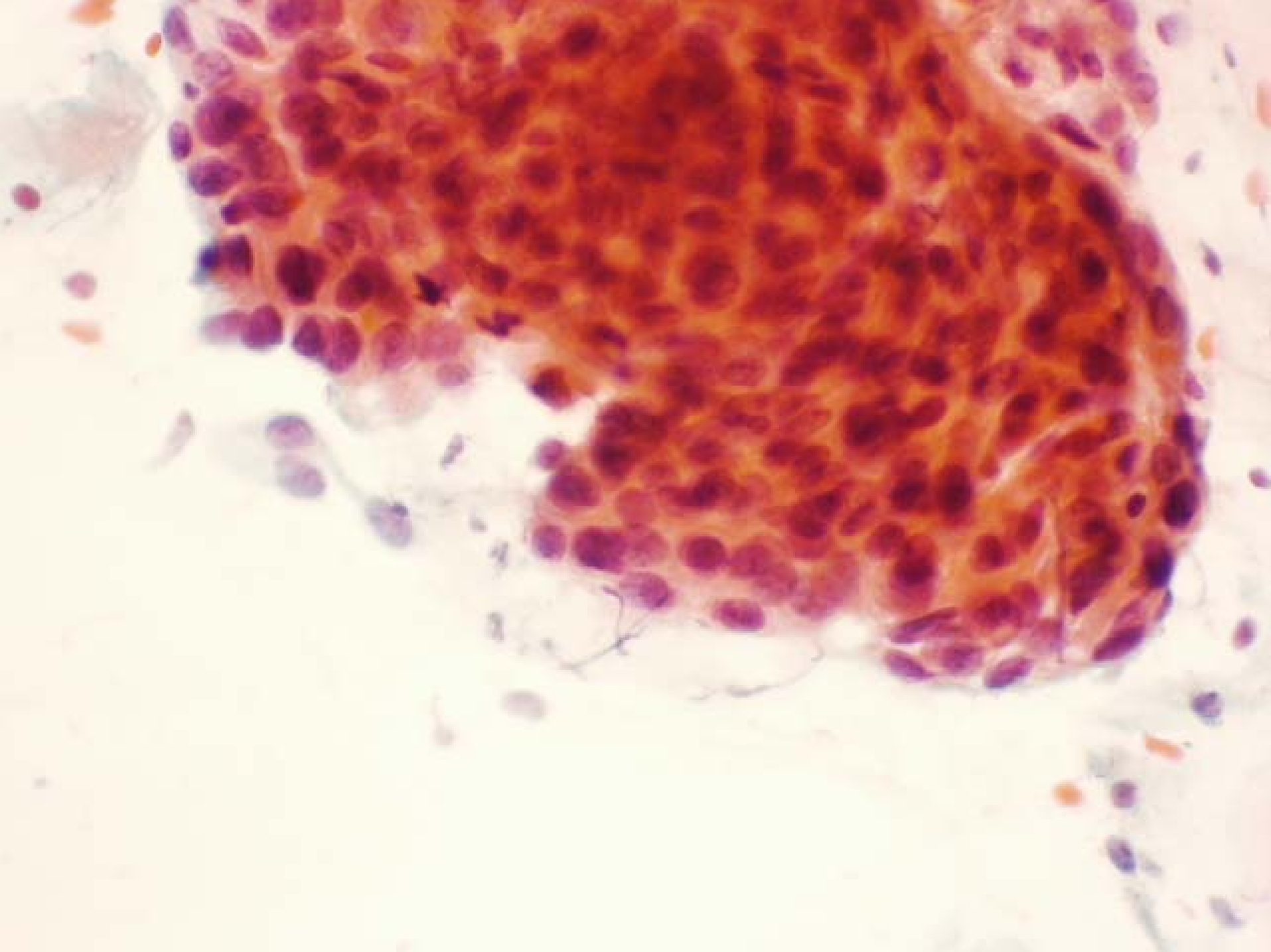
91 year old

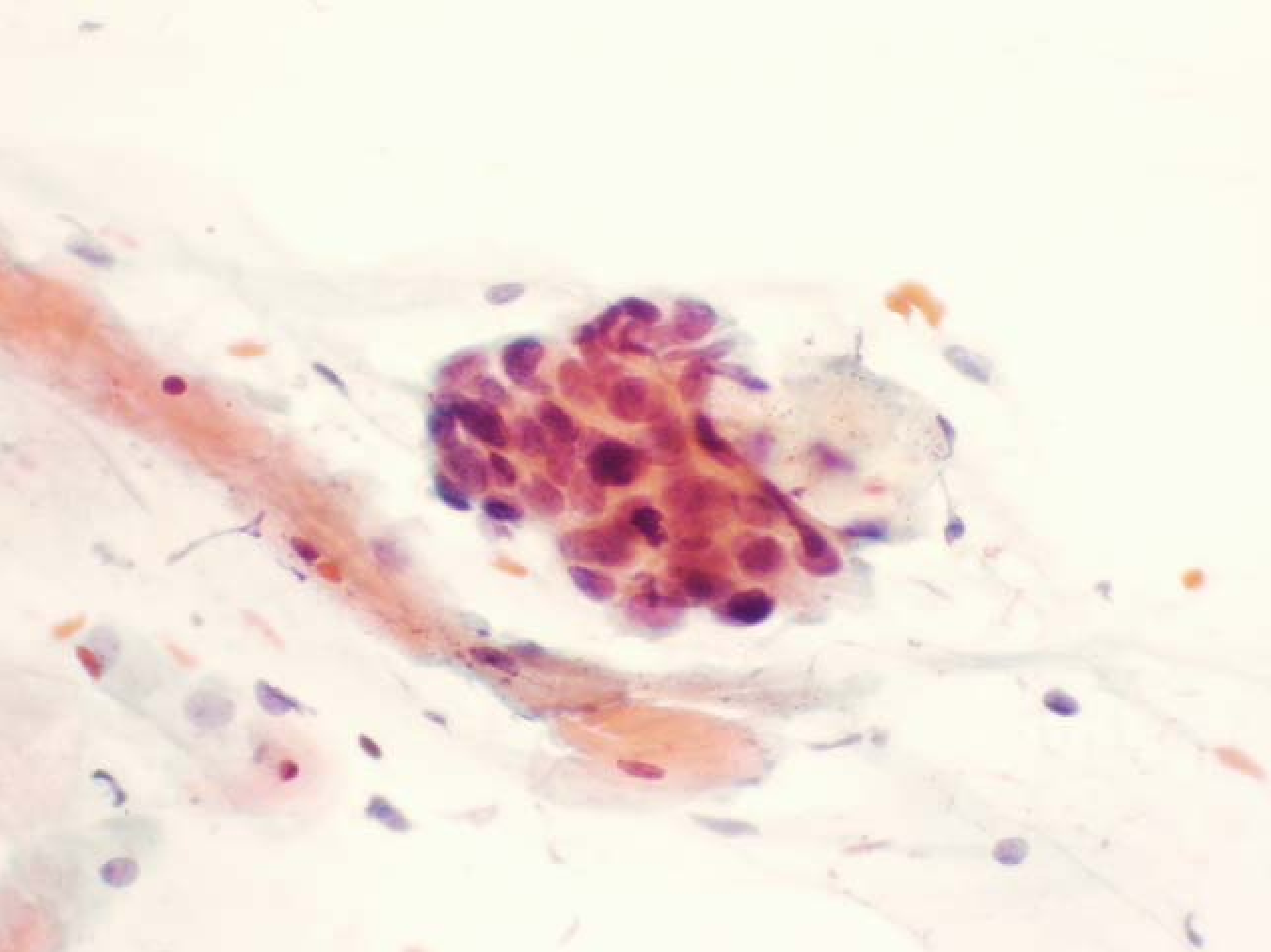
Pap smear ASCUS r/o HSIL

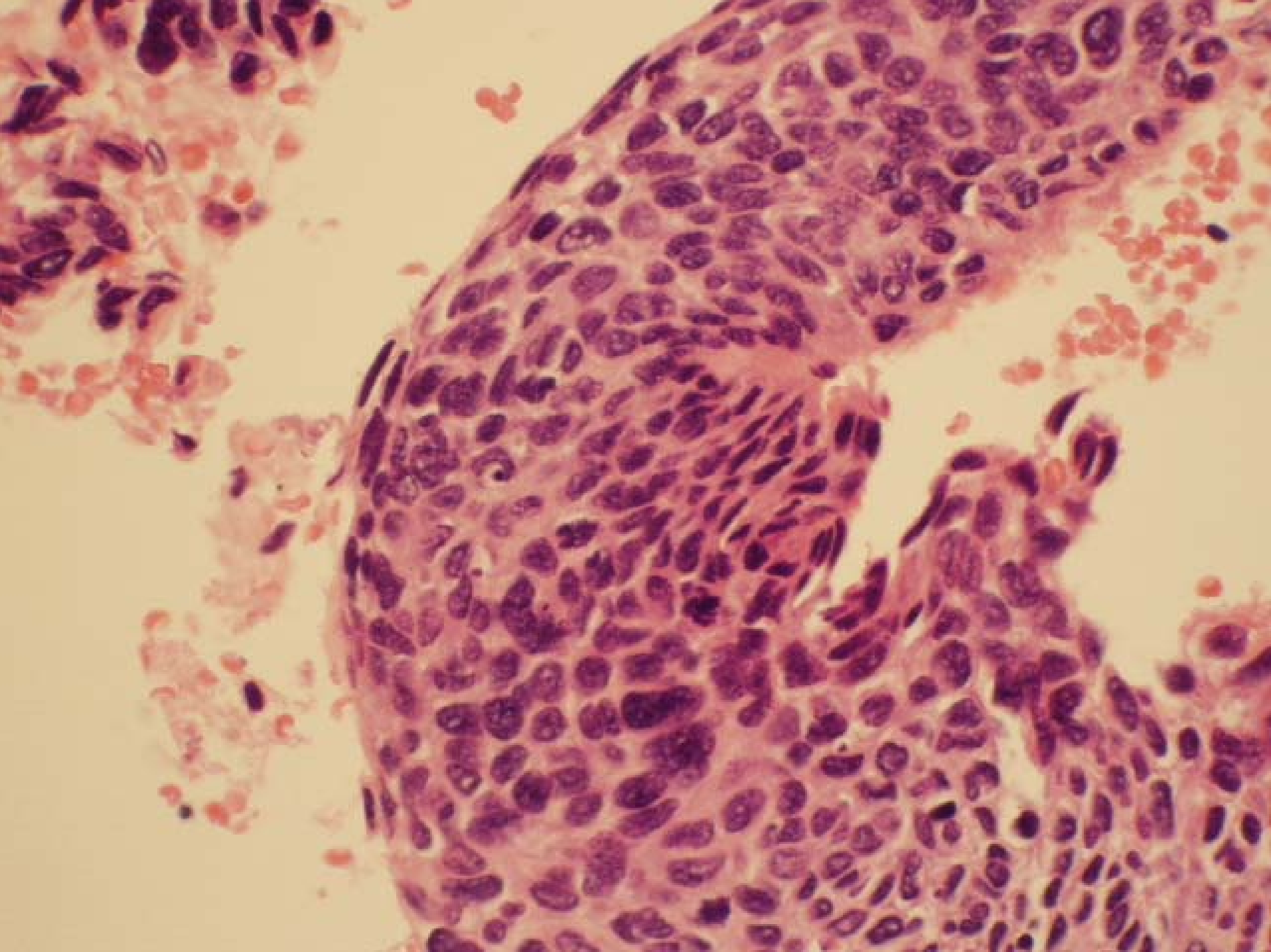


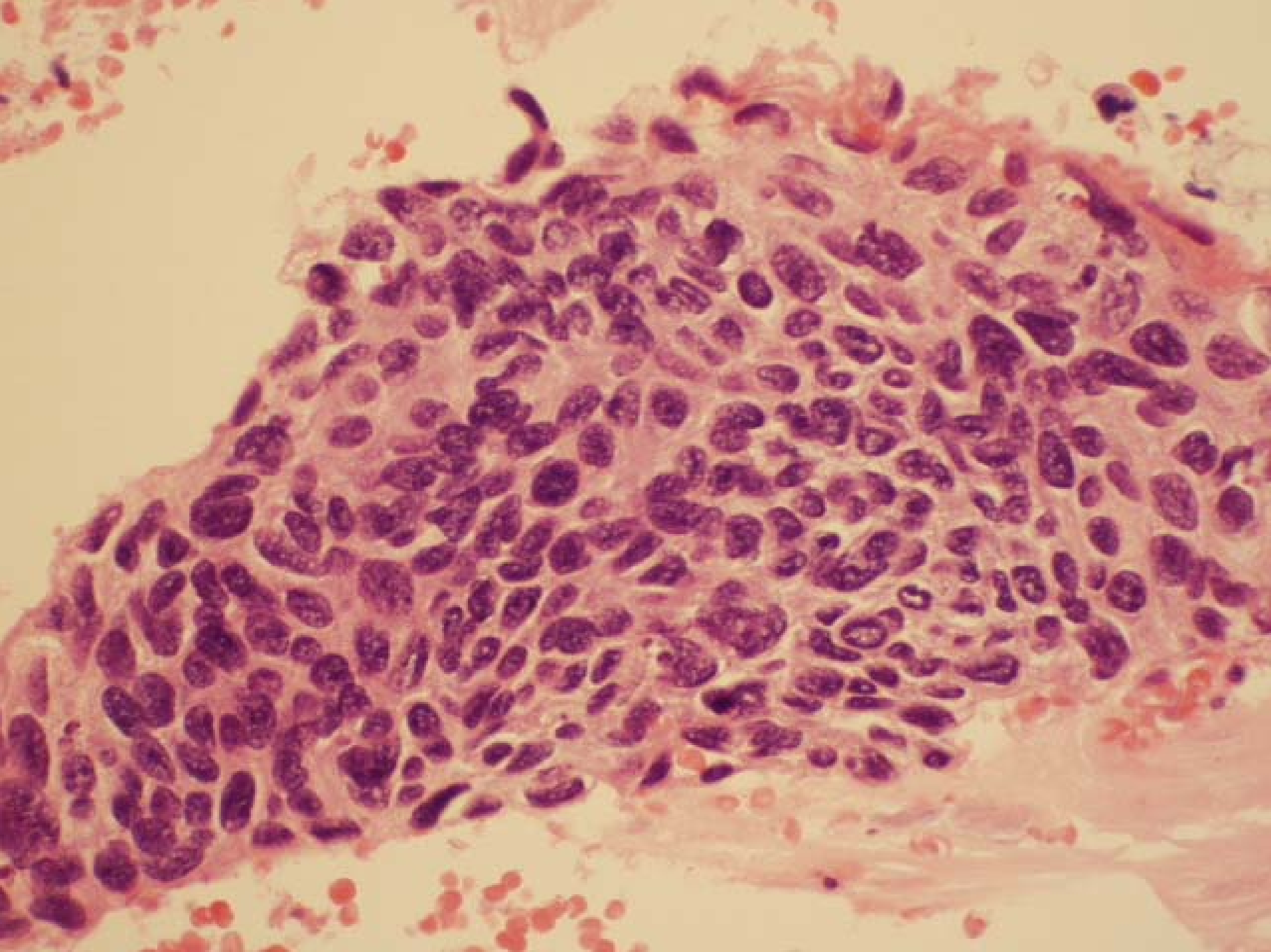












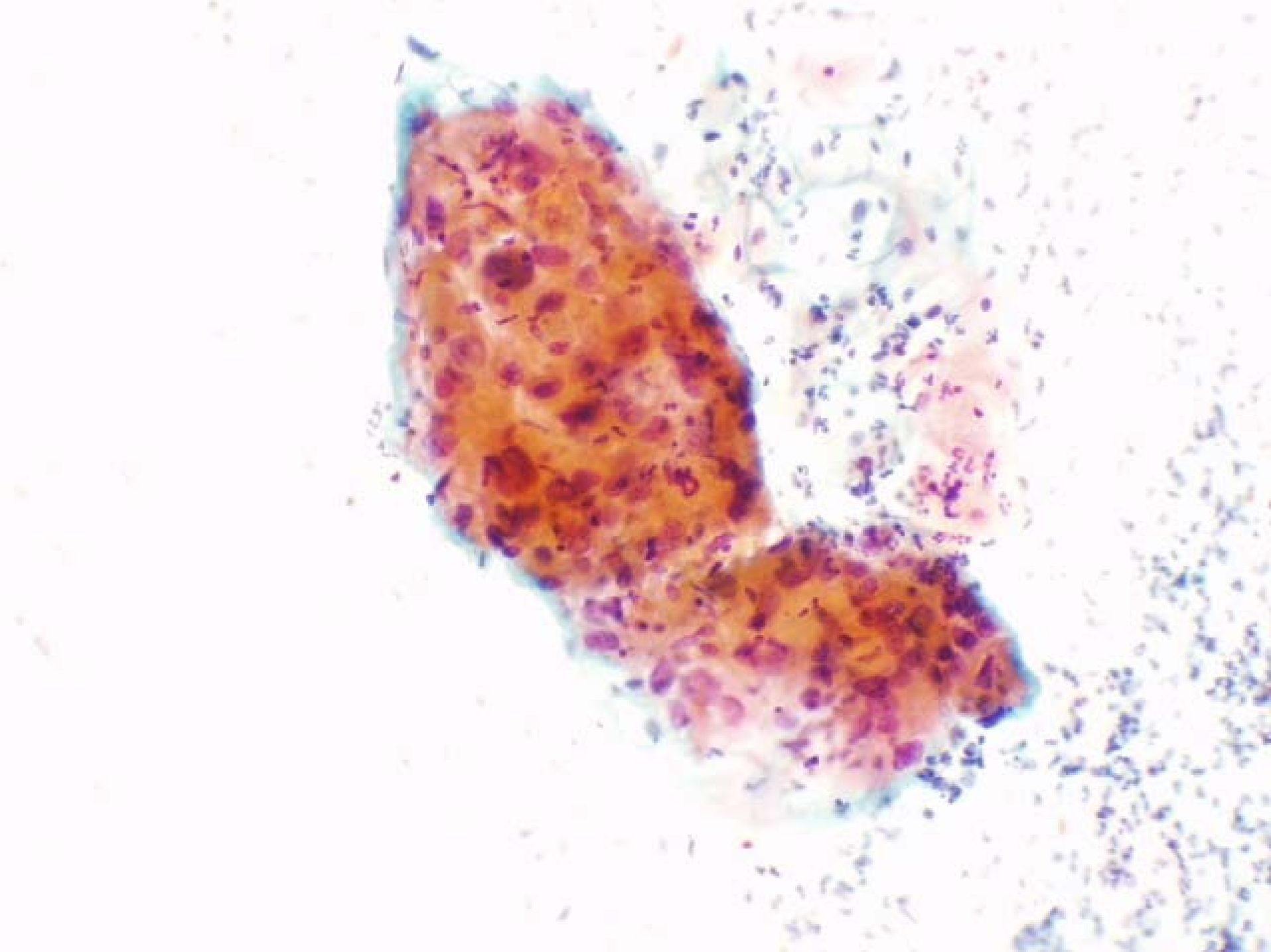
High Grade Squamous Intraepithelial Lesion

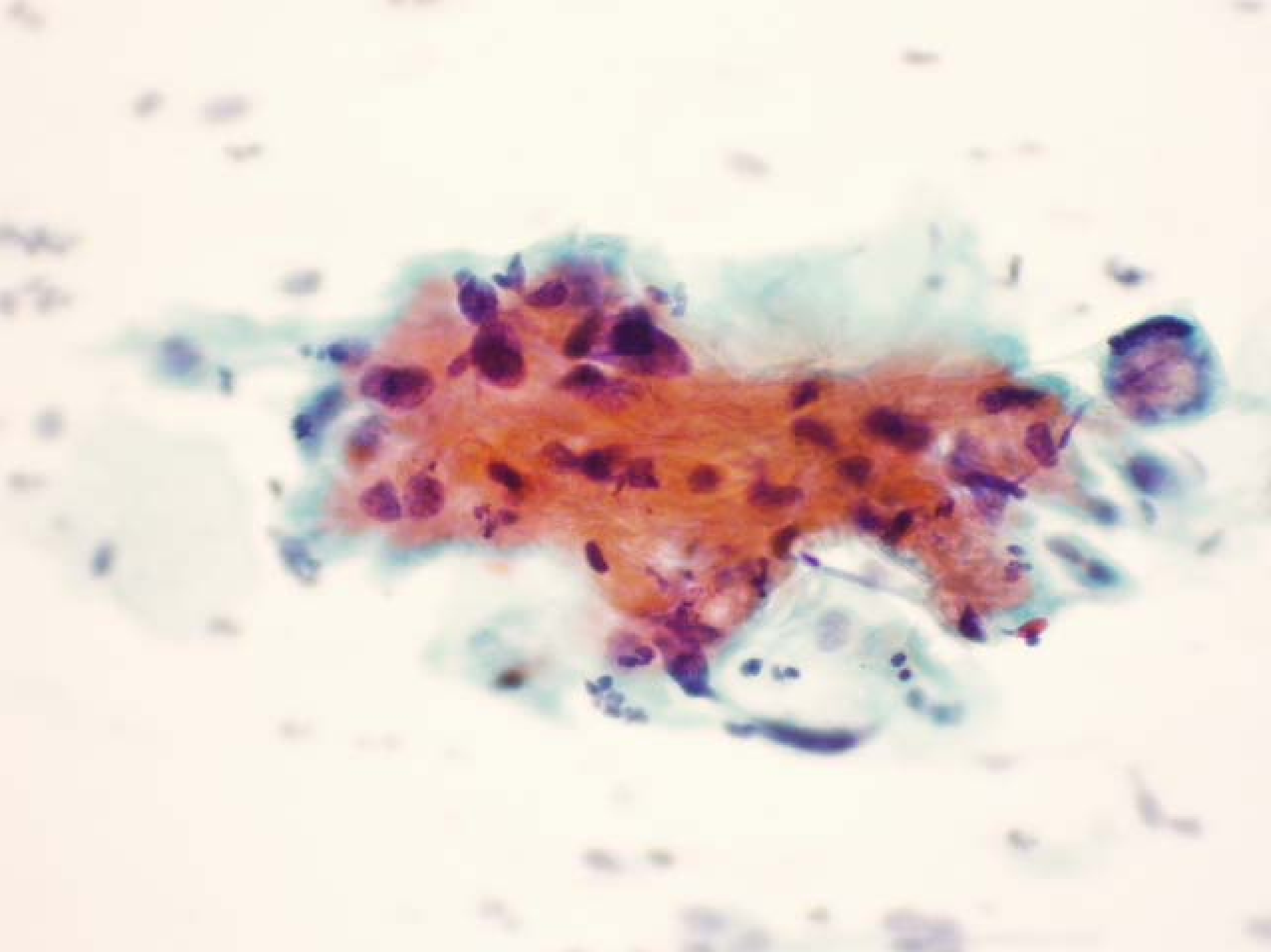
- Atrophy vs. HSIL/SCC
  Clues to a serious nature:
  - Increased nuclear size
  - Extreme hyperchromasia, crowding
  - Nuclear membrane irregularity
  - Loss of spectrum which links clearly benign atrophic cells to those with more atypia
  - Recommend repeat pap with estrogen or colposcopy and biopsy

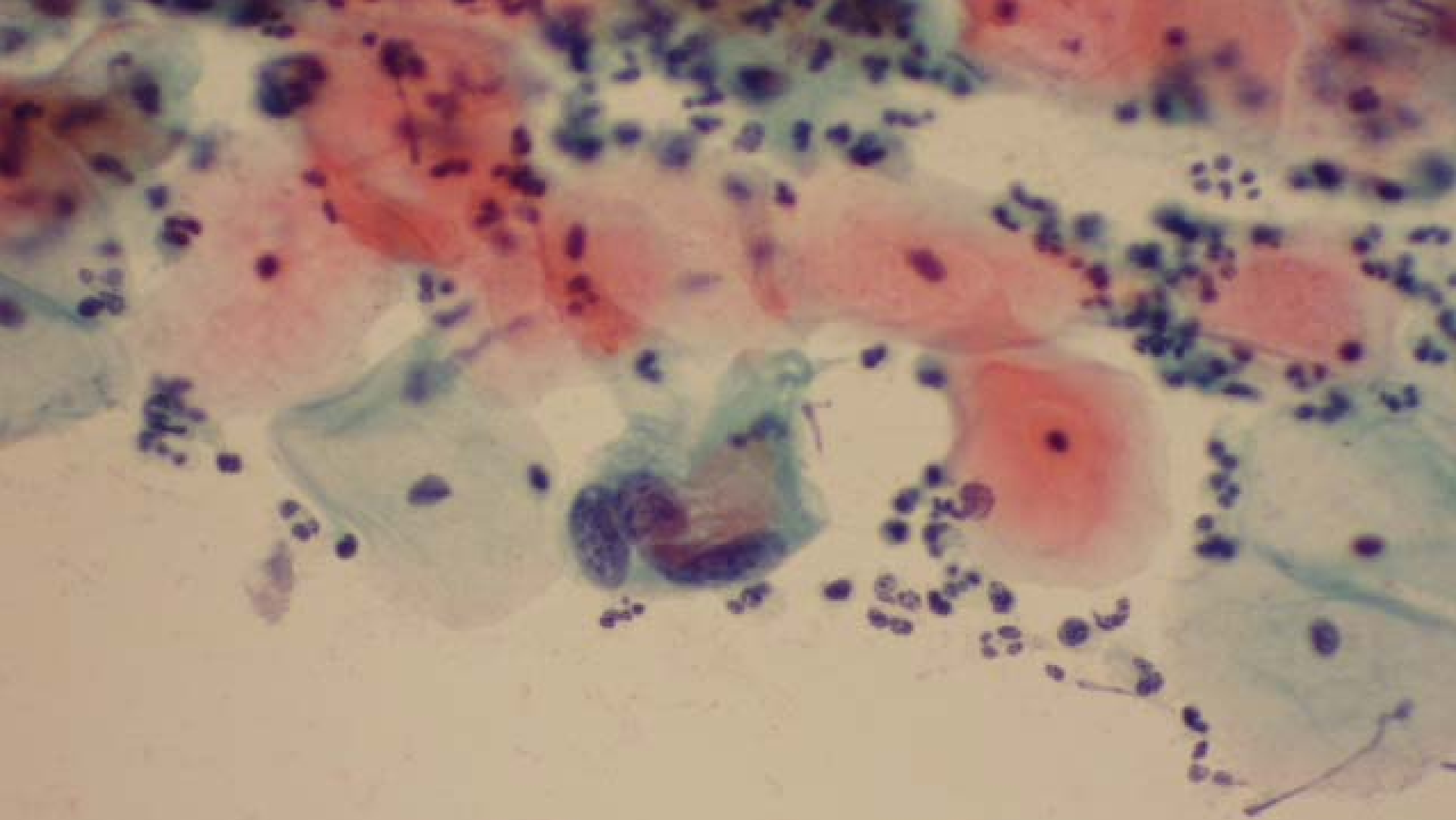
Case 10

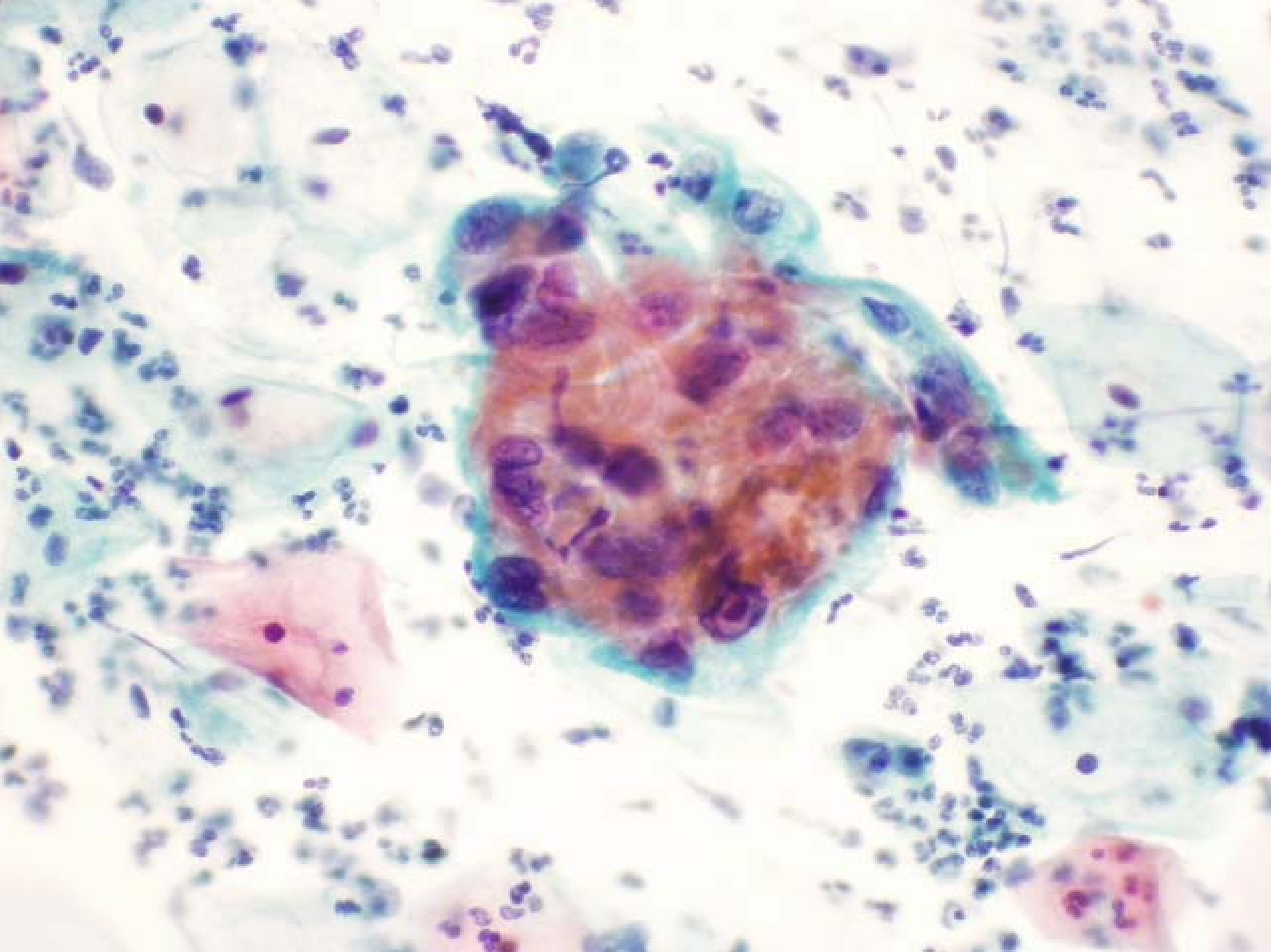
30 year old

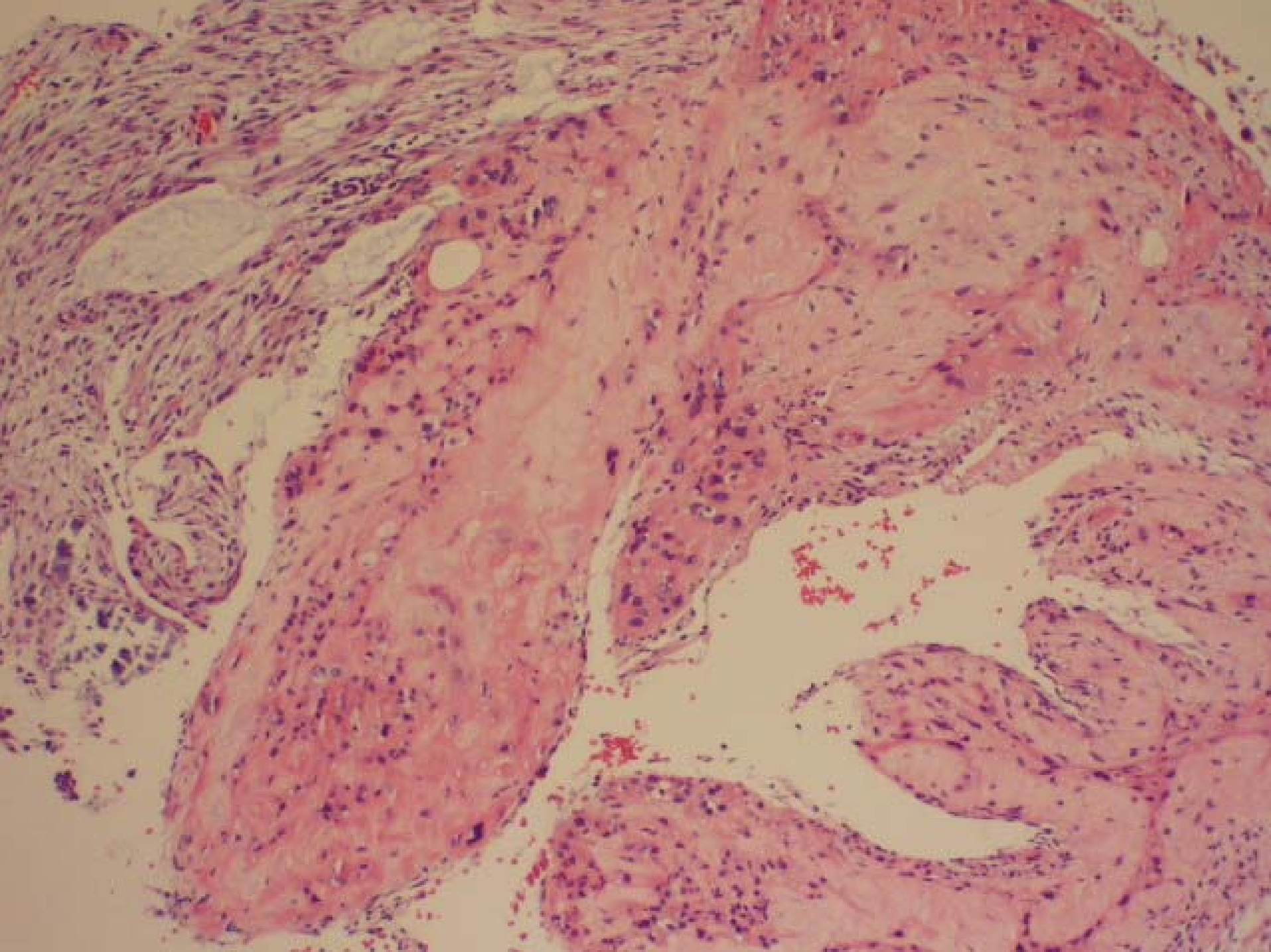
Pap smear - HSIL

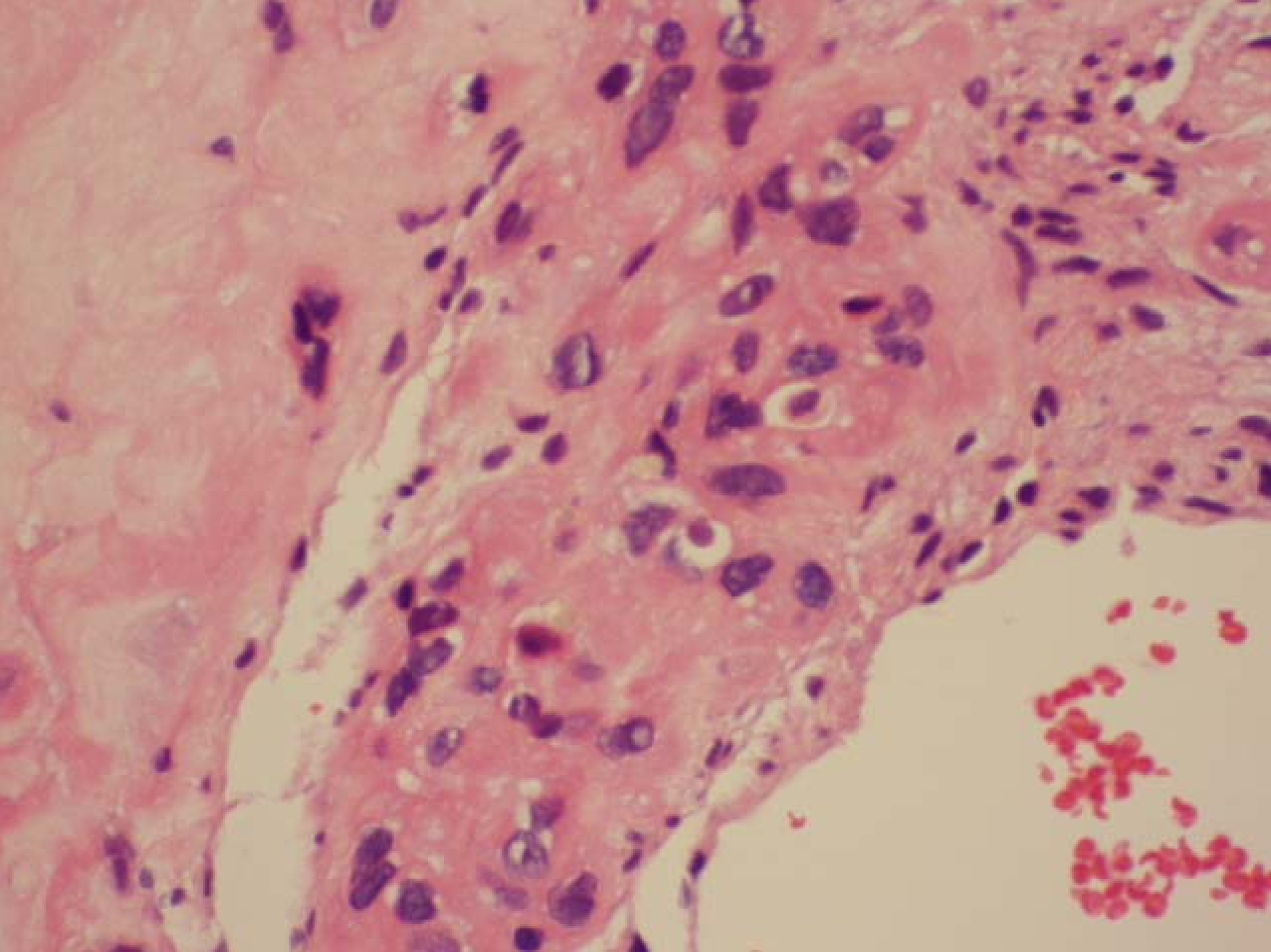












Trophoblastic Tissue

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

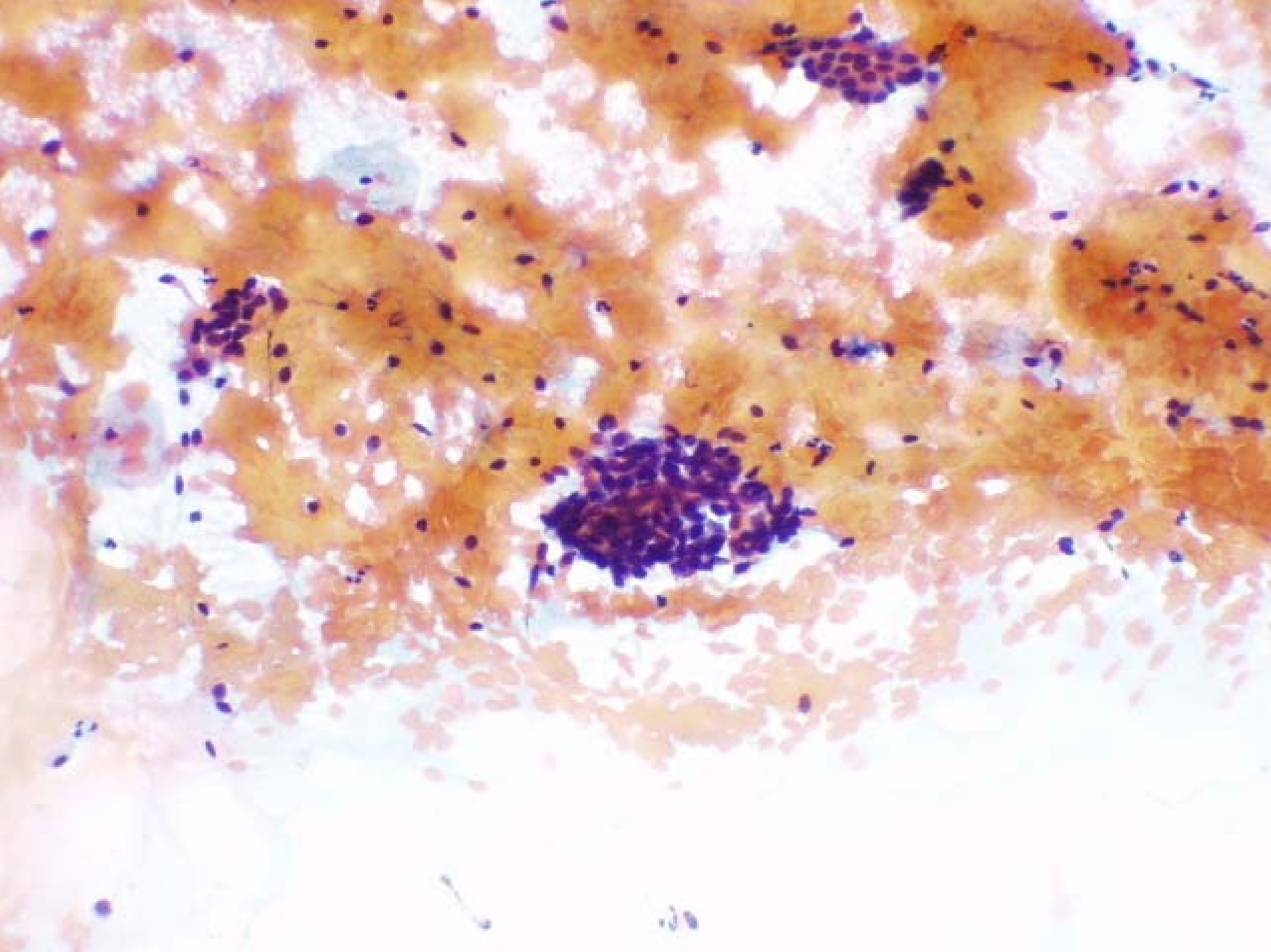
Trophoblastic Tissue

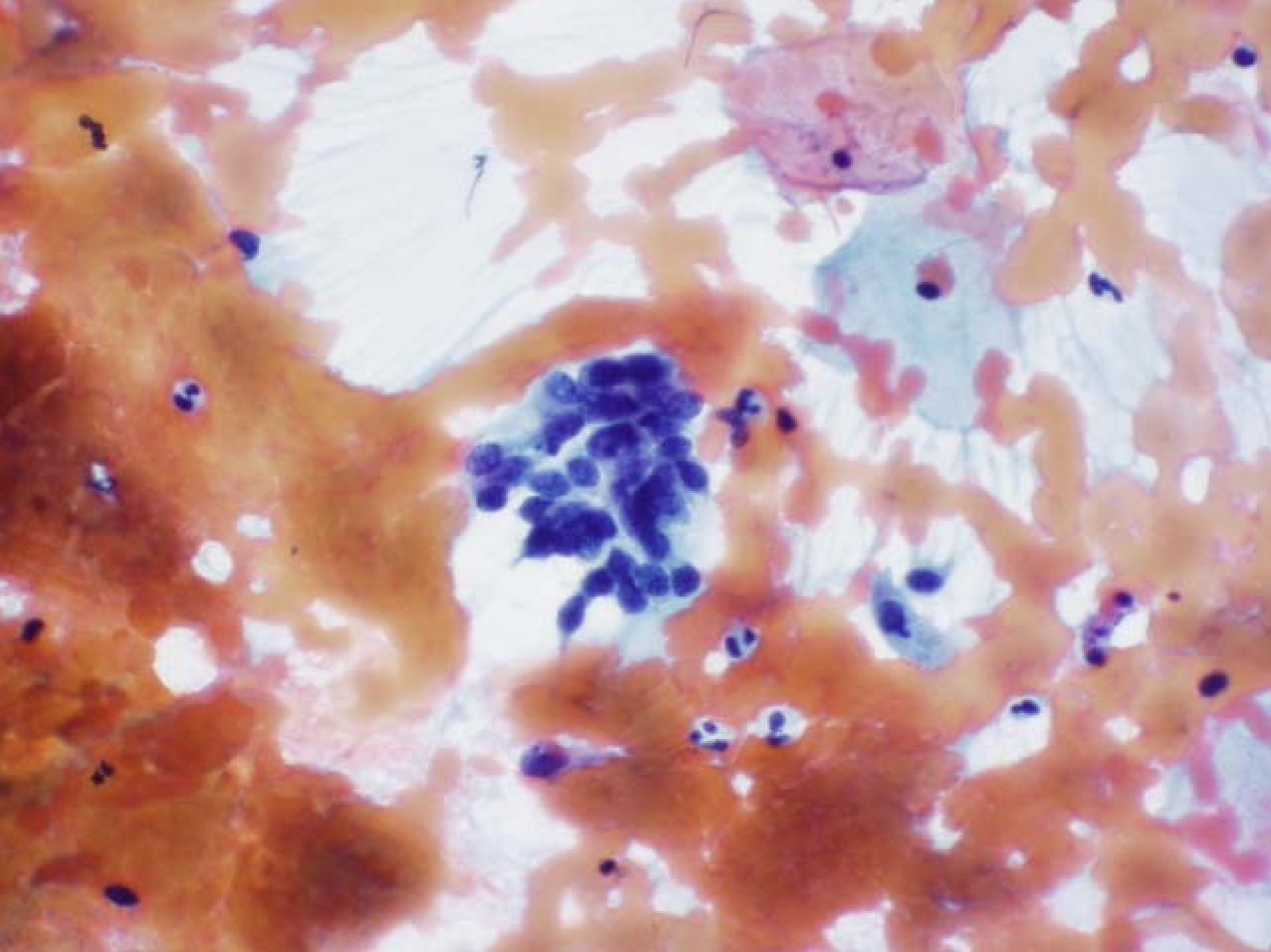
- Decidual Cells DDX
  - Dysplasia
  - Repair
  - Carcinoma
  - Sarcoma
- Multinucleated Giant Cells In Pregnancy
  - Syncytiotrophoblast
  - Multinucleated giant cell histiocytes
  - Herpes
  - Tumor
  - Dysplasia/Condyloma

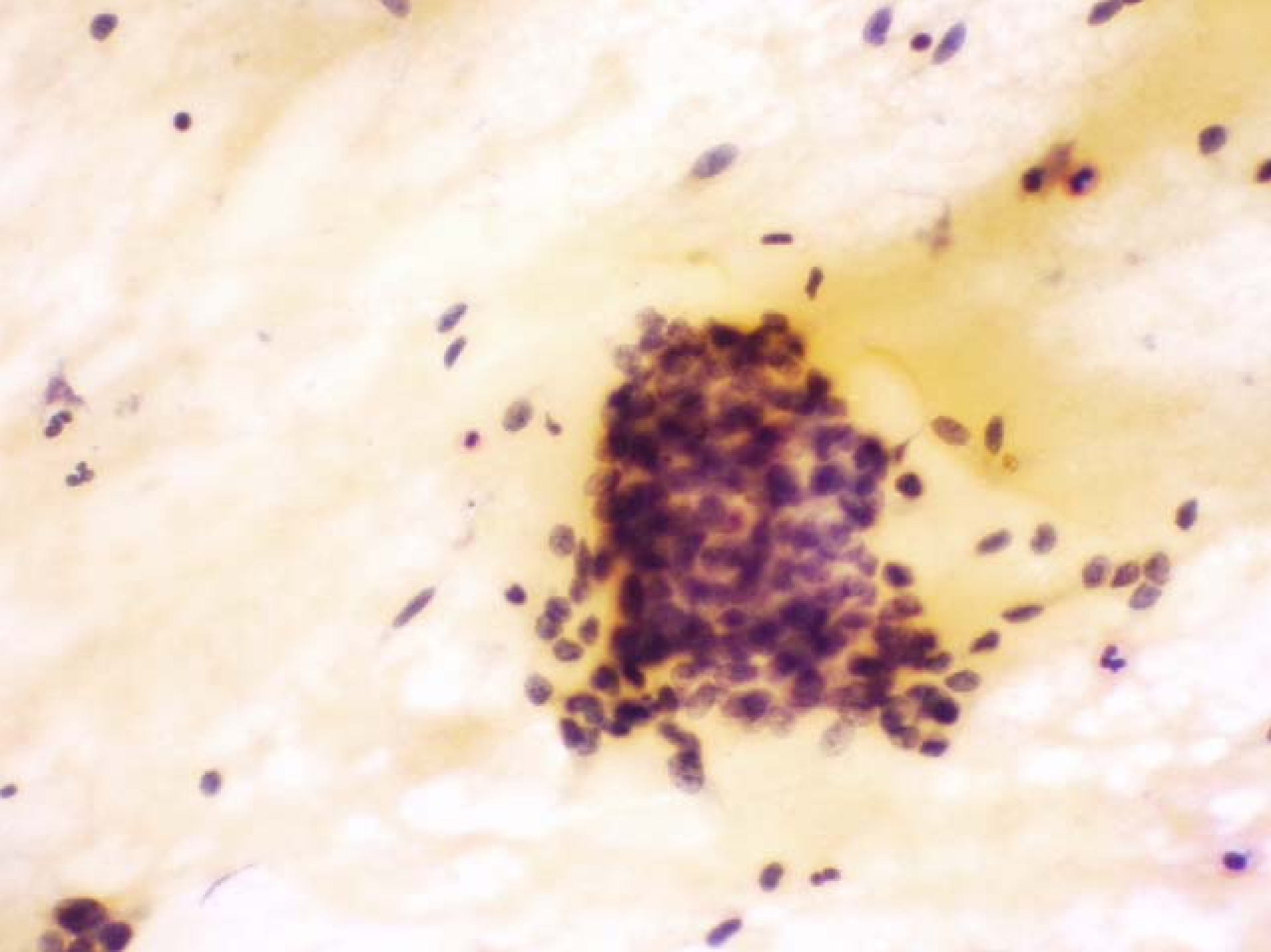
Case 11

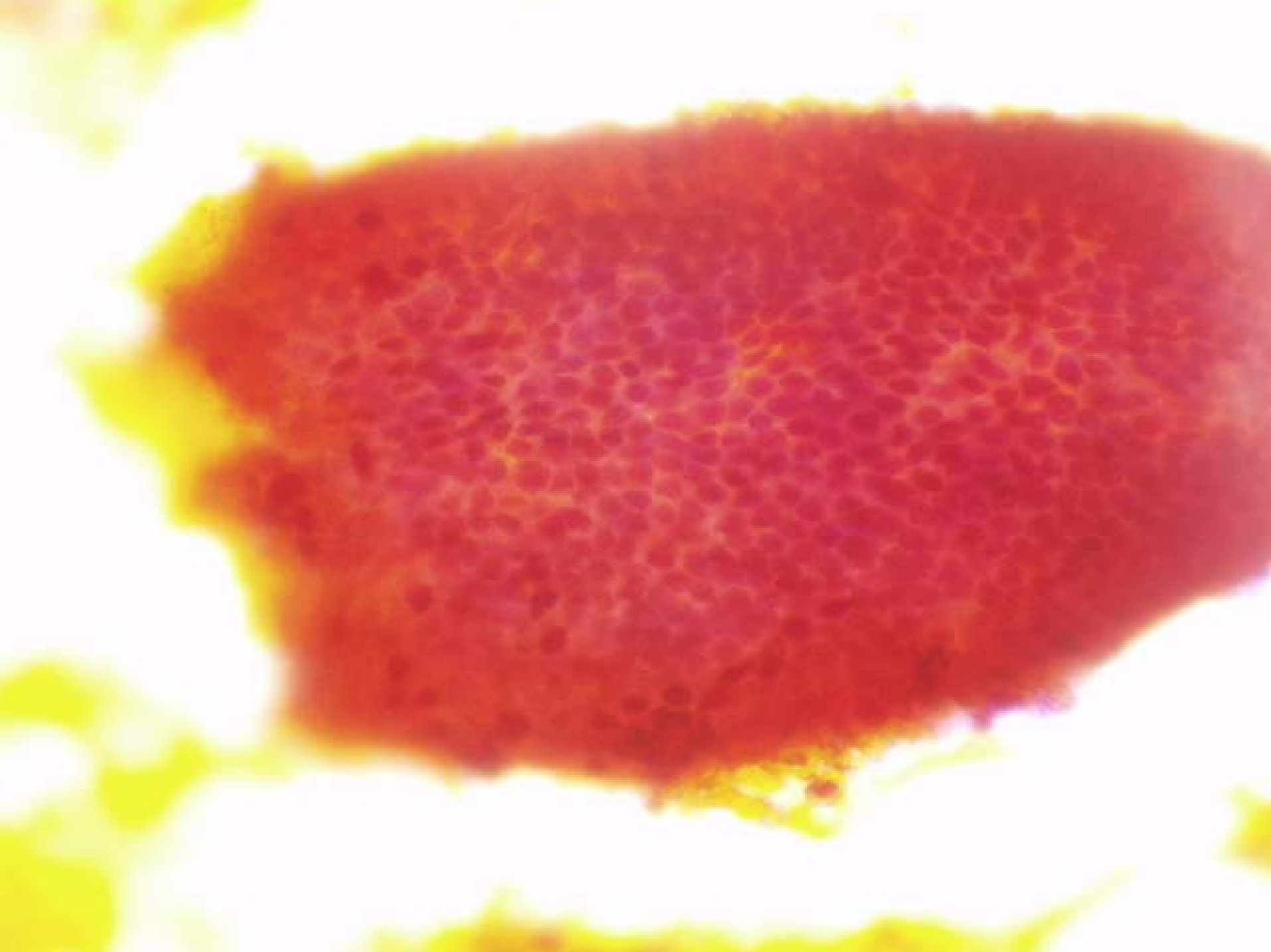
33 year old

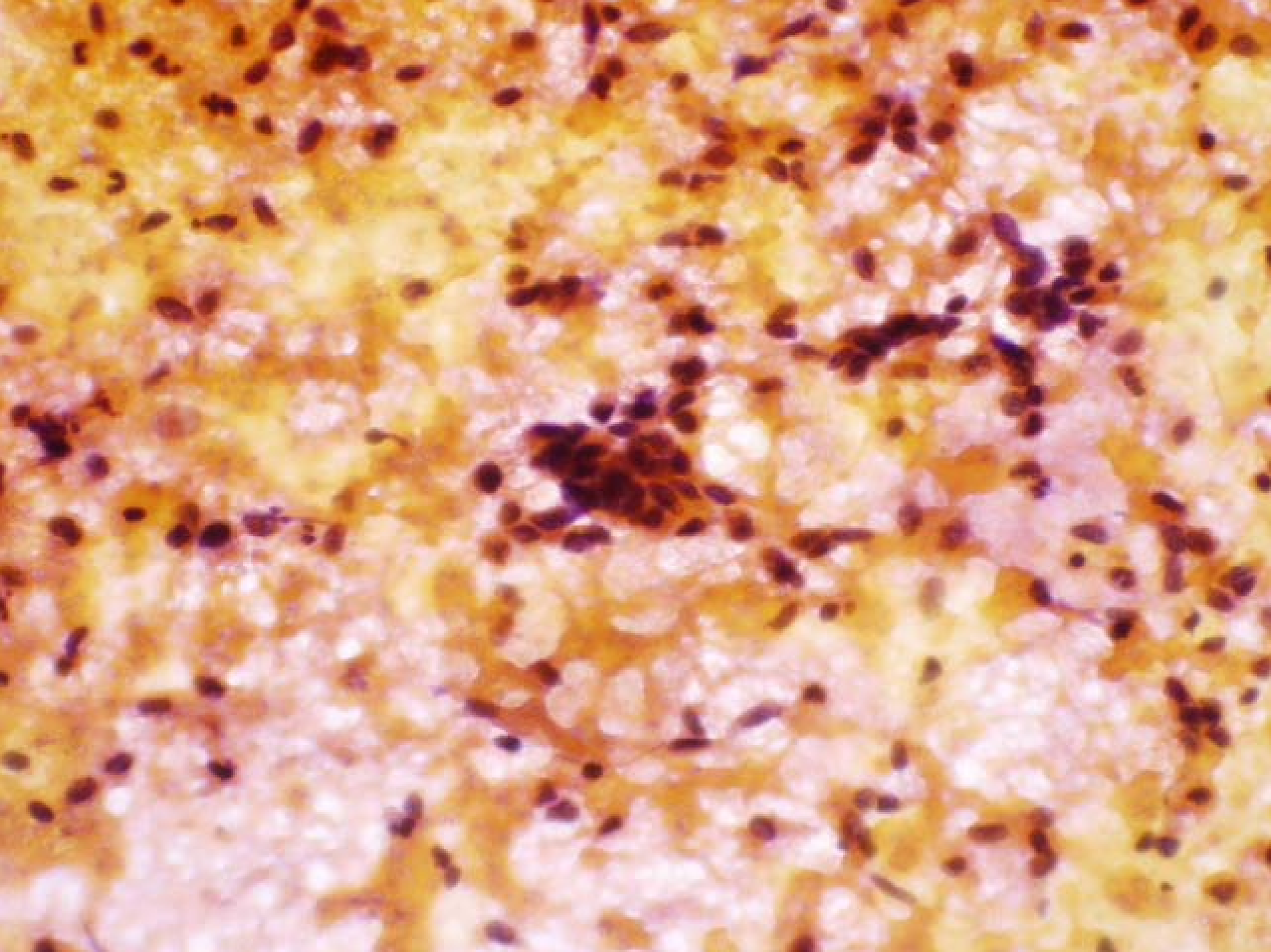
Pap smear - HSIL











Menstrual Changes

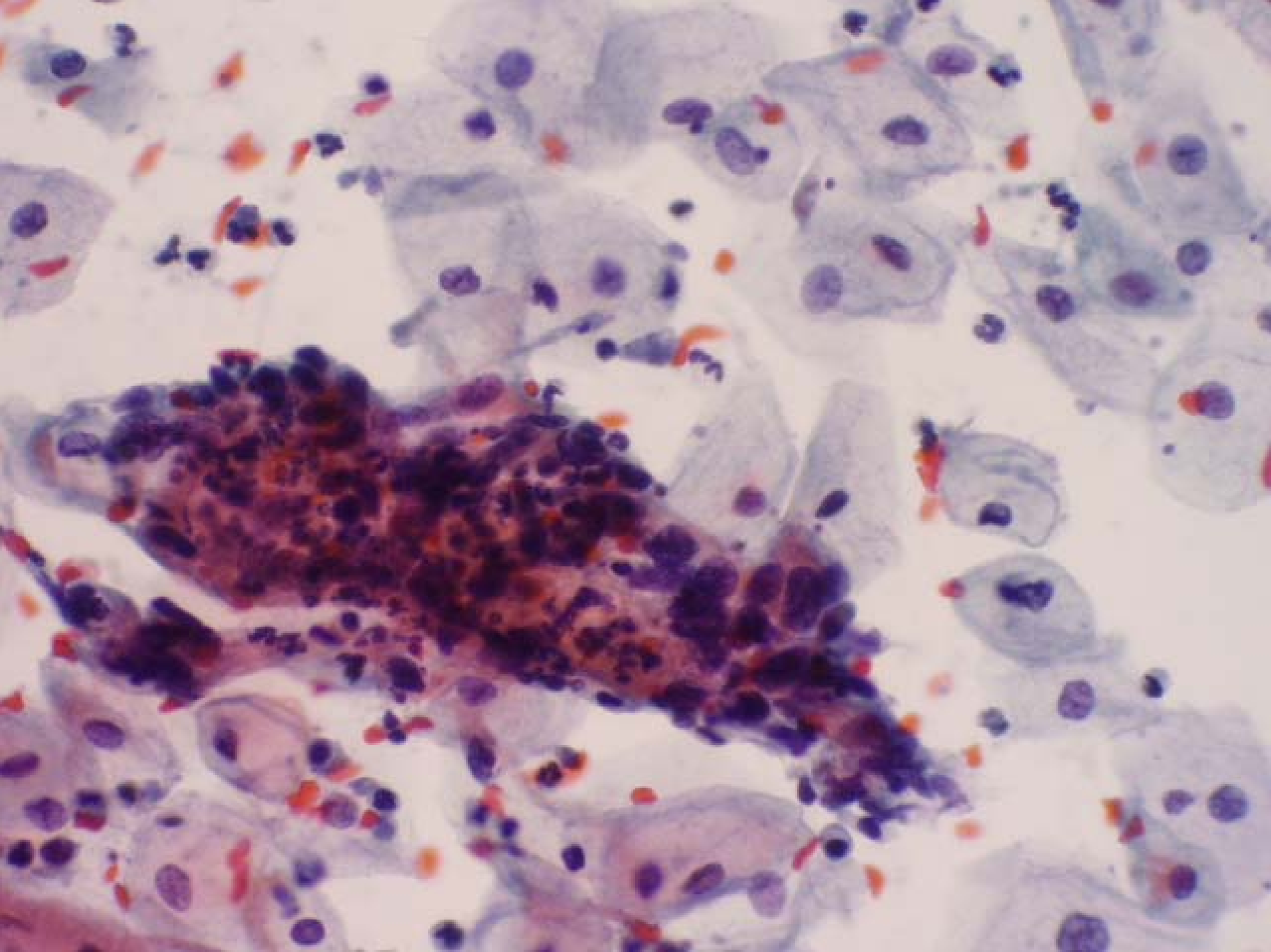
- Menstrual endometrial cells
  - Resembles AIS
  - Poorly preserved cells
  - Hyperchromasia of degeneration
  - Stromal balls and histiocytes
  - Absence of feathering and rosettes

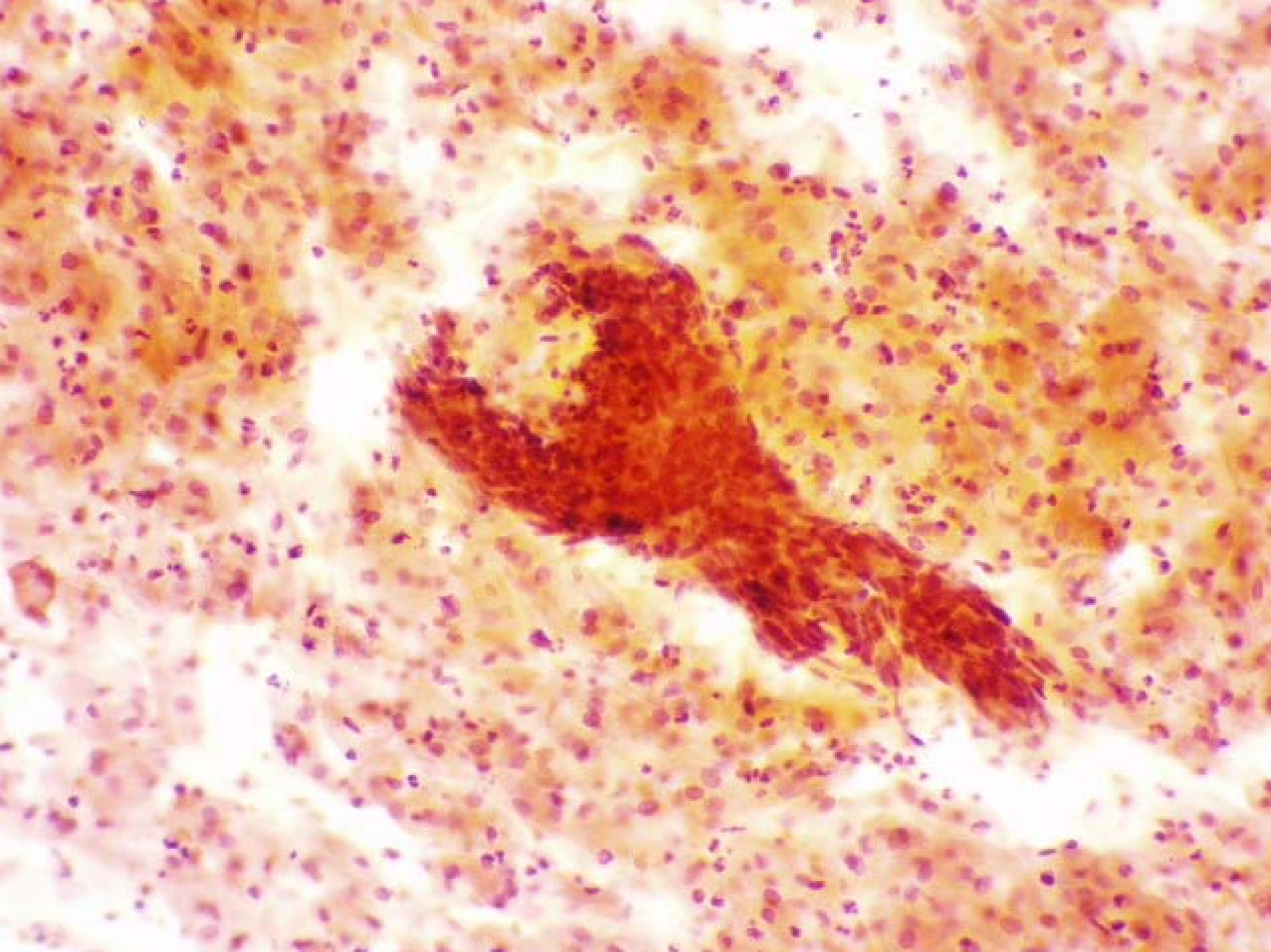
False positive

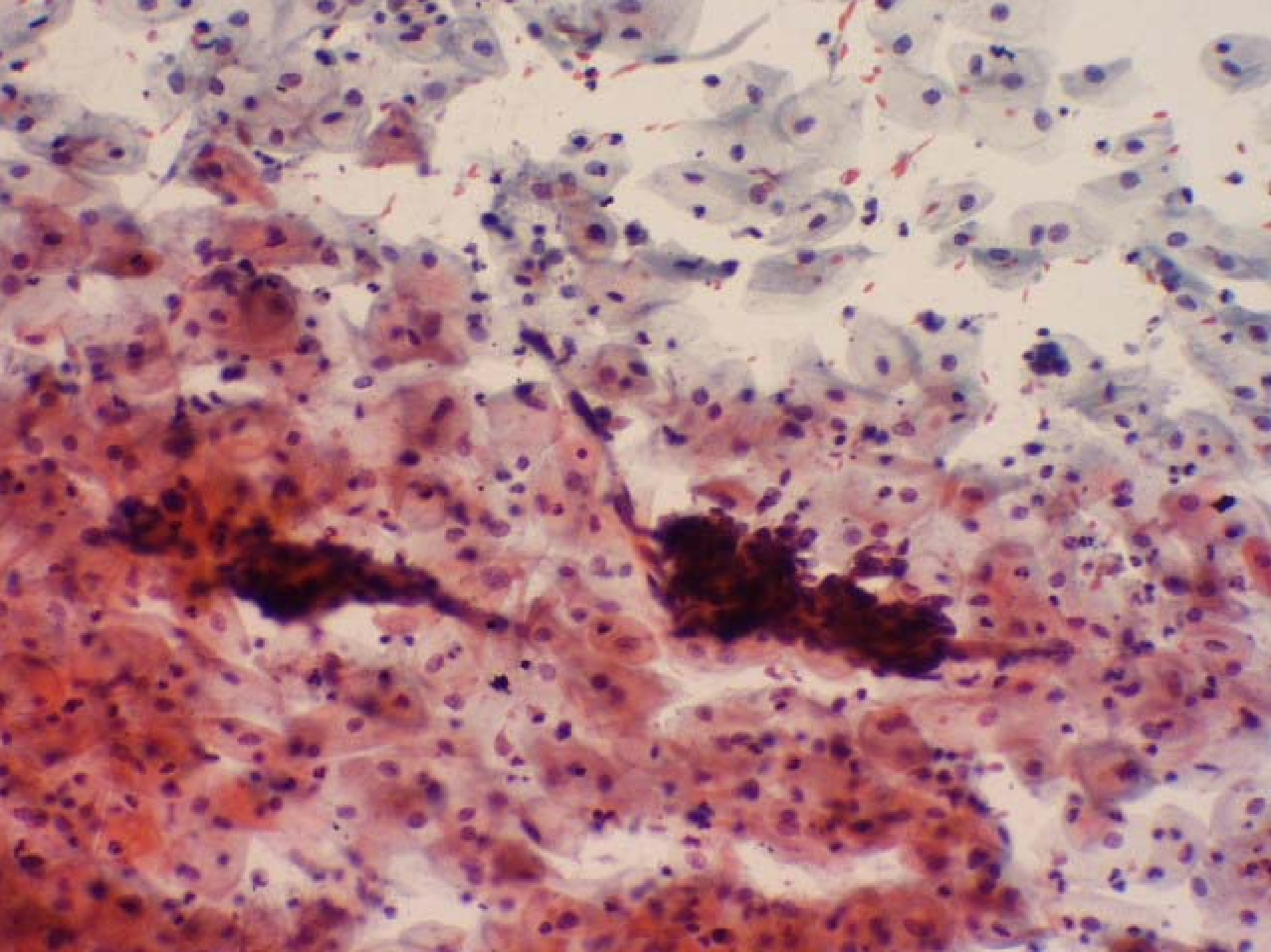
- Lower uterine segment
  - resembles AIS
  - uniform small cells in sheets or tubules
  - lack of featheringor rosettes
  - fine, even chromatin
  - spindled stromal cells attached
  - may have mitotic figures

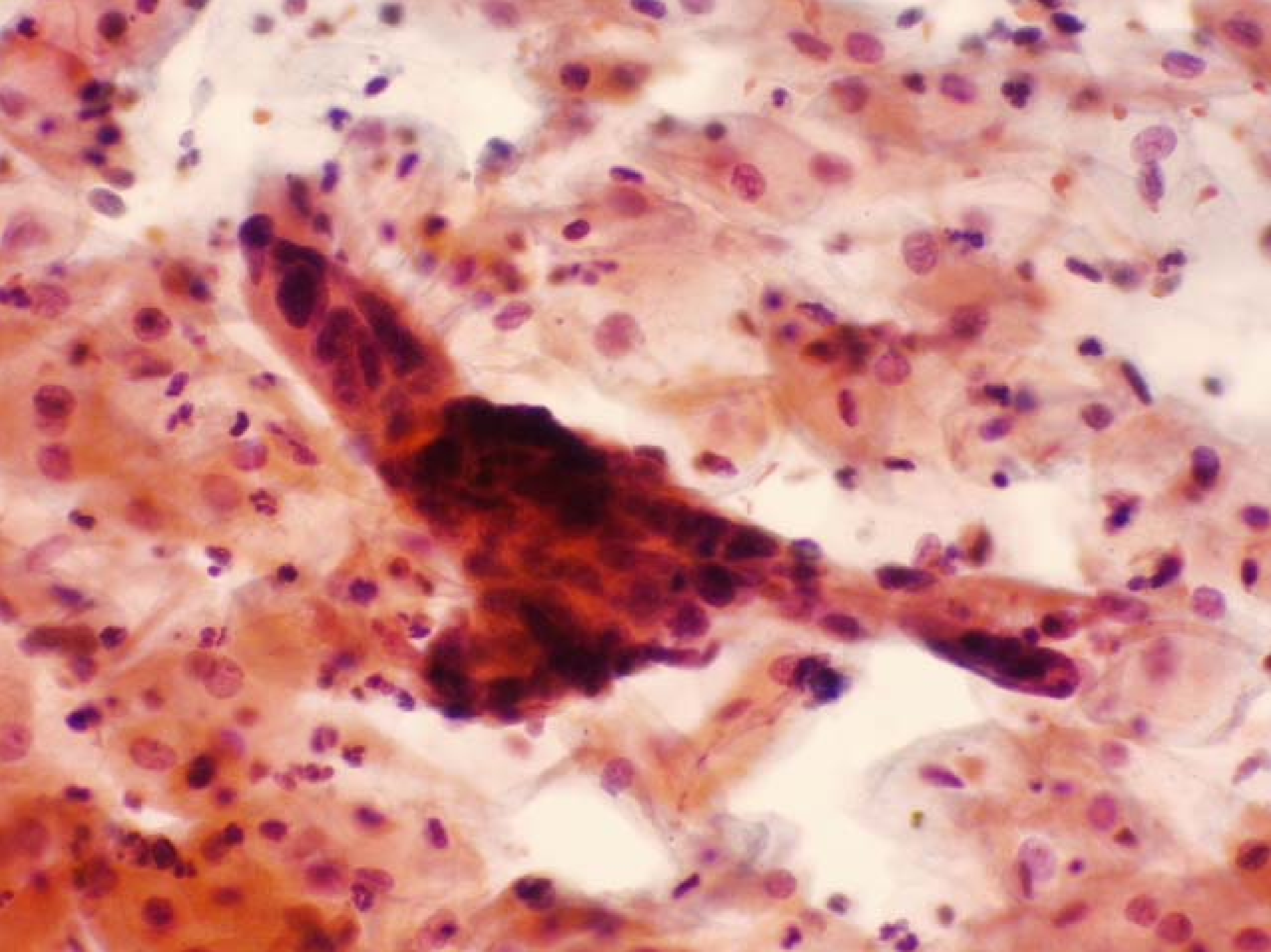
Case 12

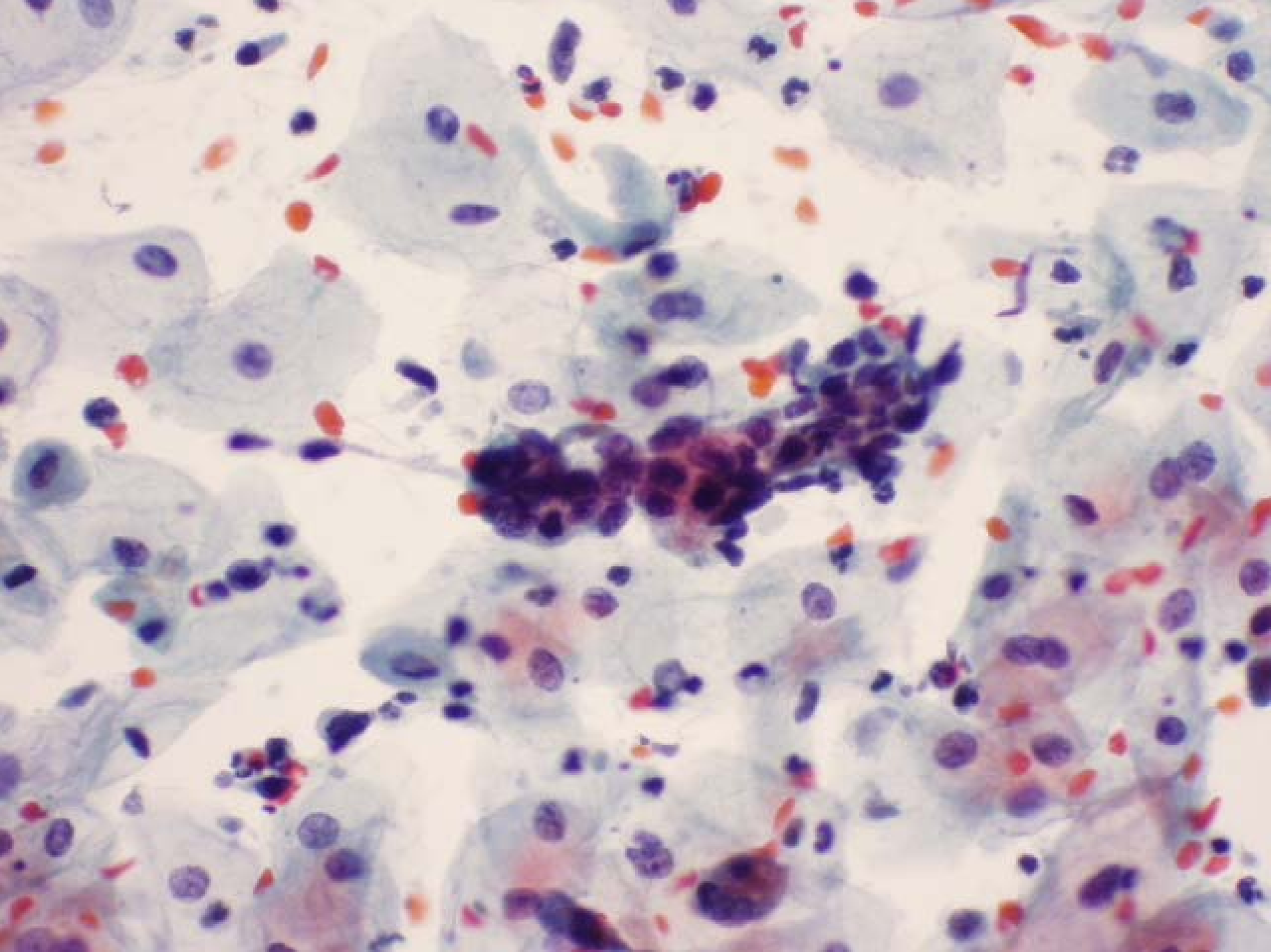
42 year old
pap smear was called HSIL

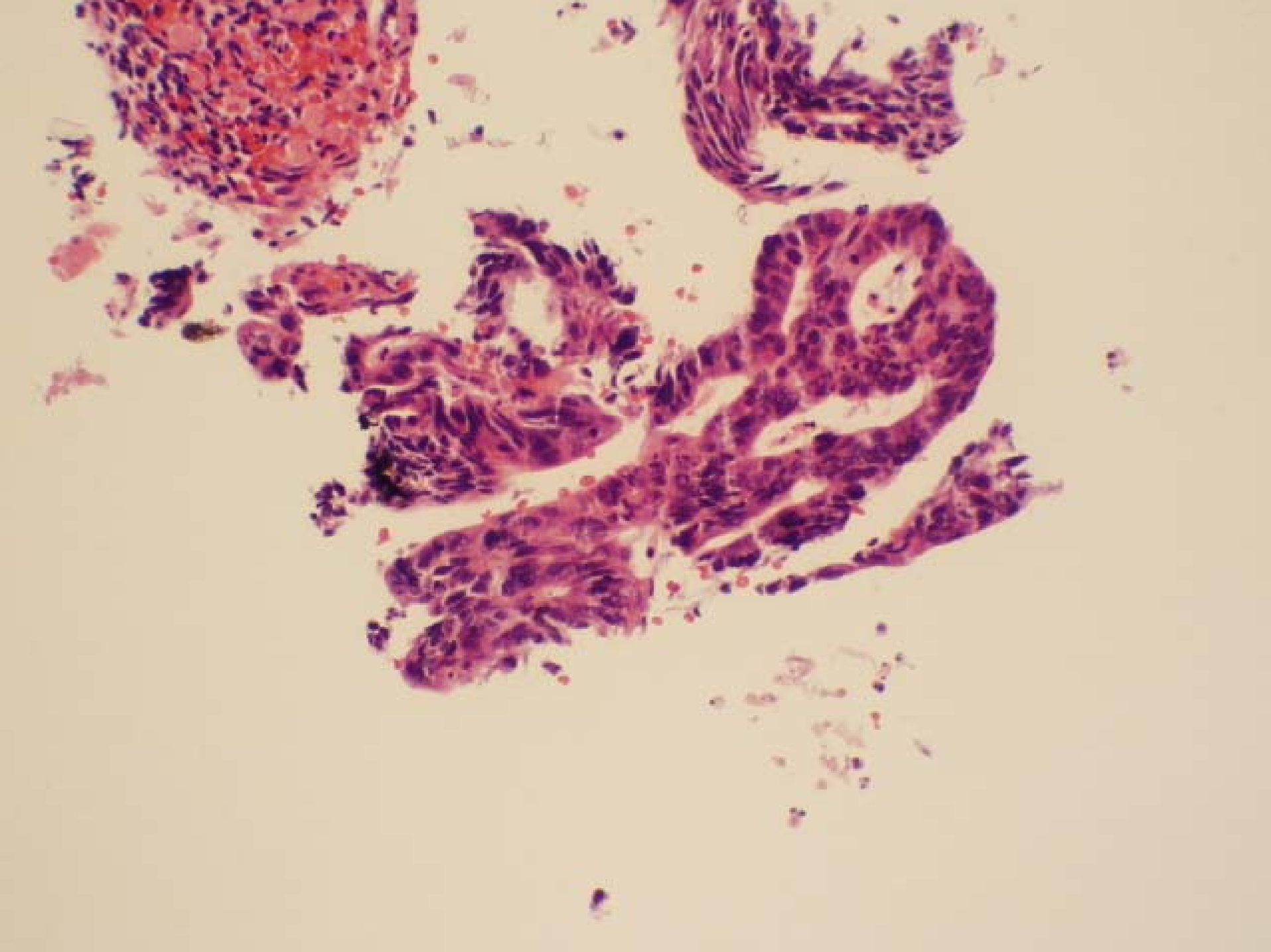












Endometrial Adenocarcinoma

- Overall features dependent upon grade
- Increased N/C ratio
- Hyperchromasia
- Irregular chromatin distribution
- Prominent nucleoli
- Diathesis

Abnormal Shedding of Endometrial Cells

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

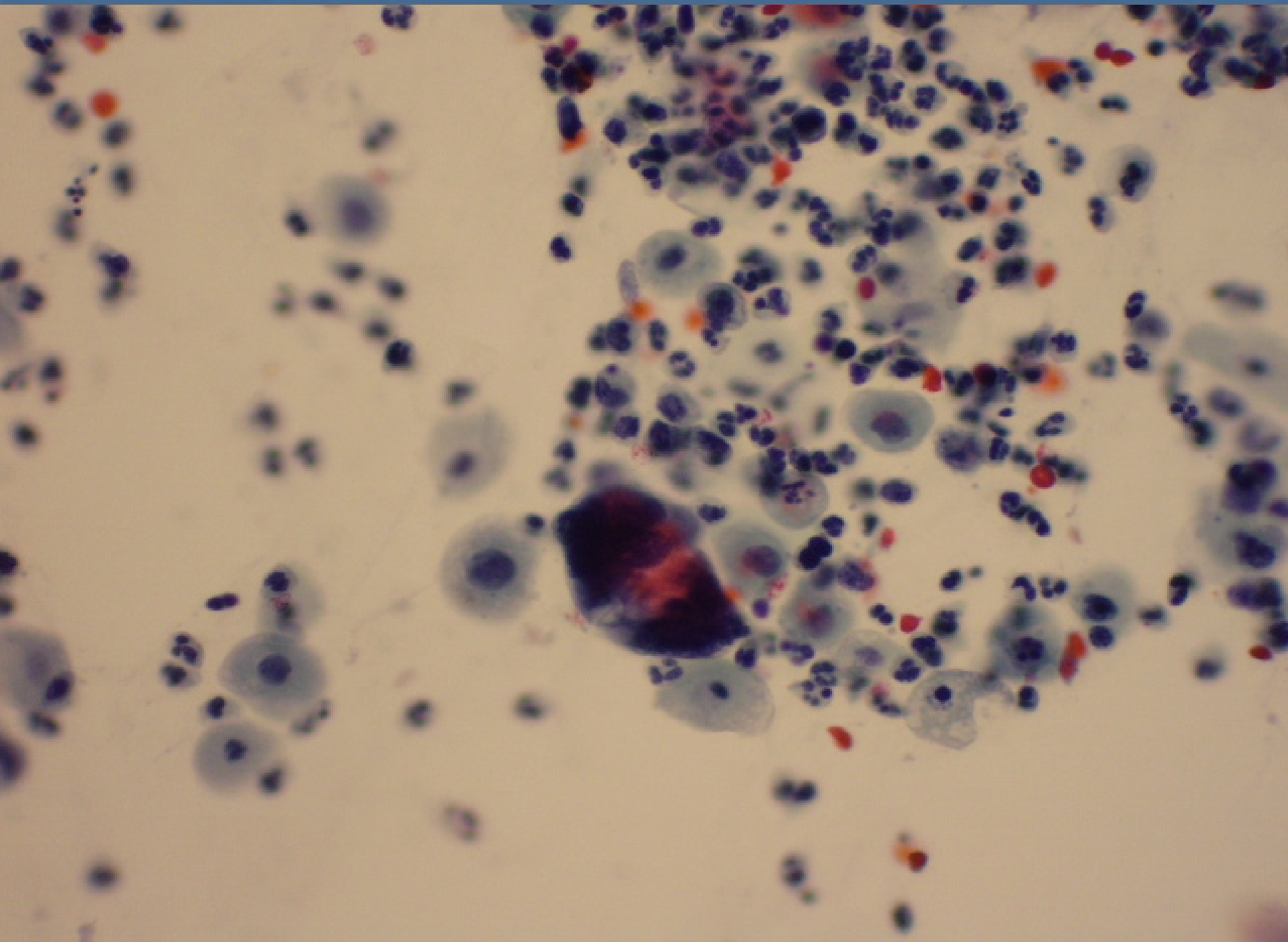
Endometrial Adenocarcinoma DDX

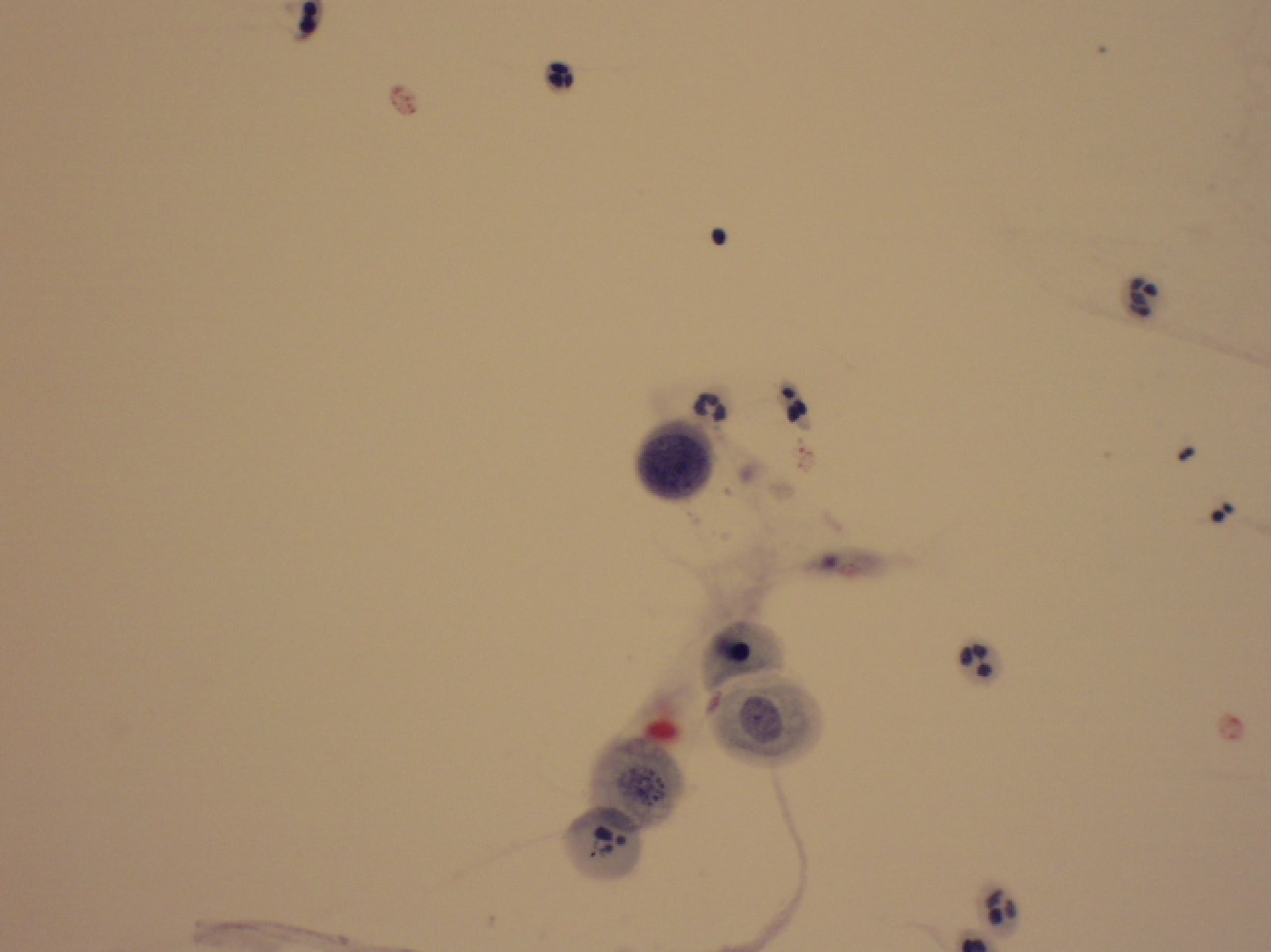
- Endometritis
  - Crowded groups with nuclear enlargement and prominent nucleoli, balls
  - Increased neutrophils
  - Uniform nuclei, smooth nuclear membranes and regular chromatin
- Endocervical Adenocarcinoma
  - More cellularity
  - Rosettes
  - Granular cytoplasm
  - Multinucleation common
  - CEA+

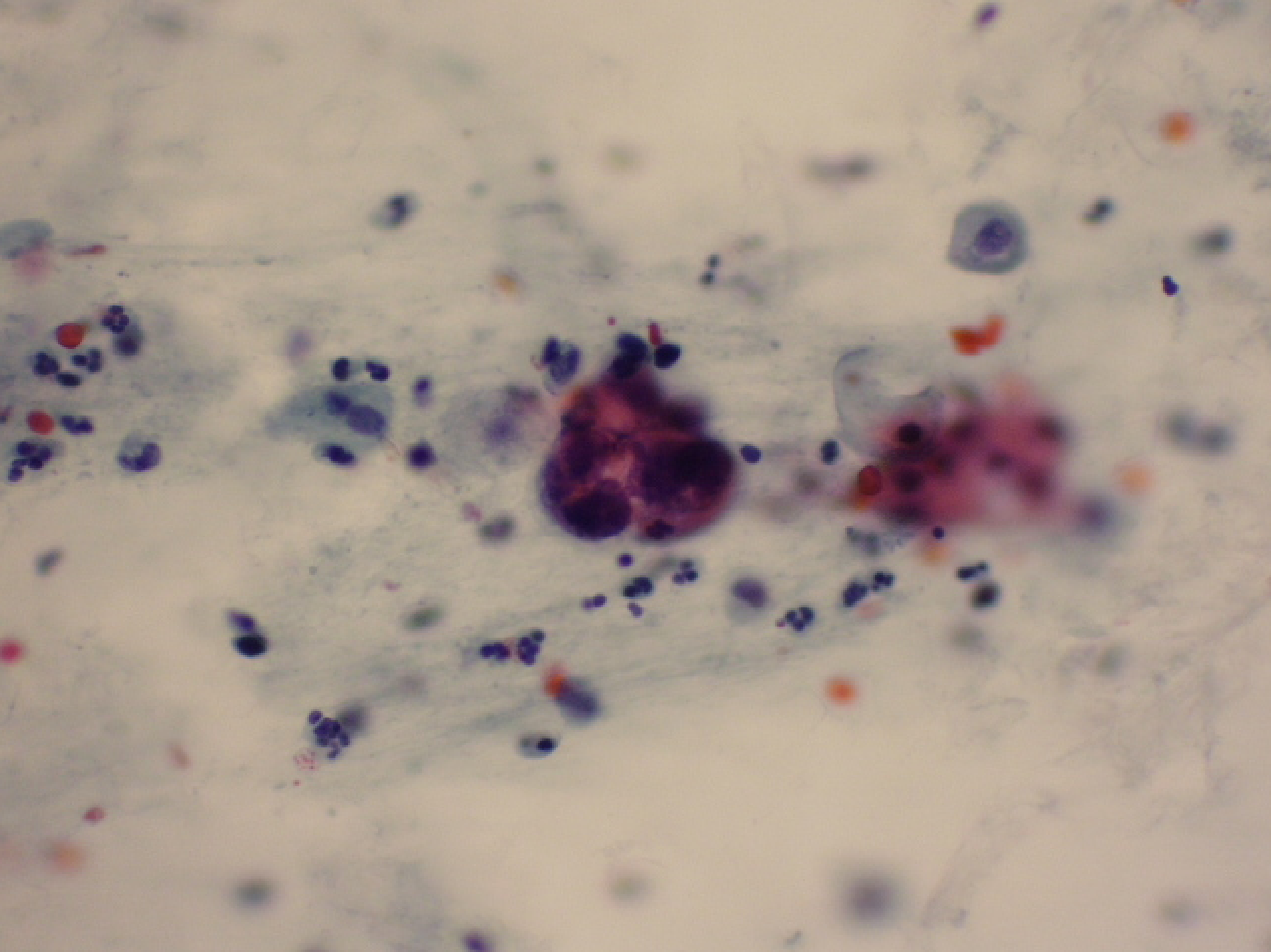
Case 13

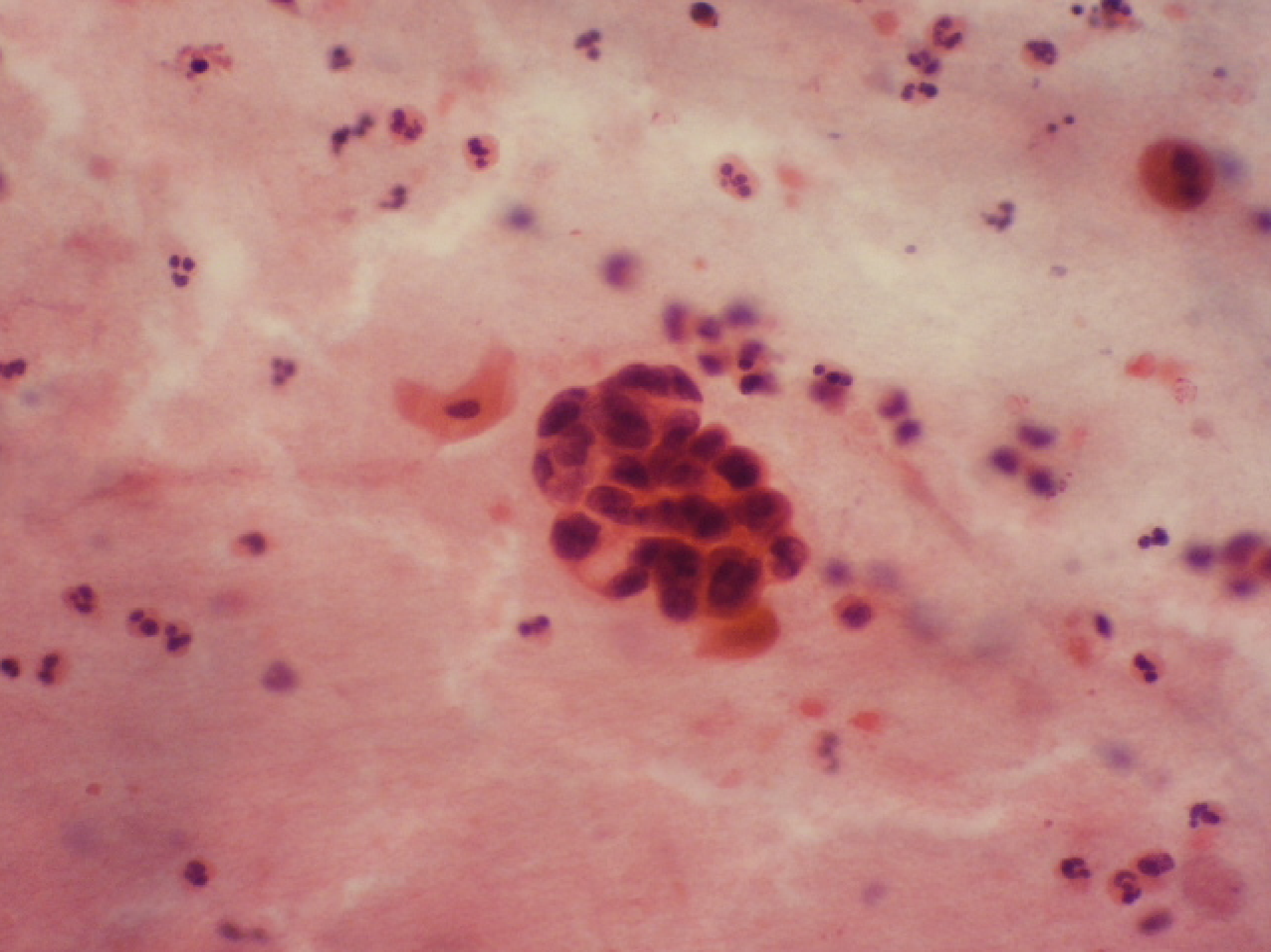
55 year old

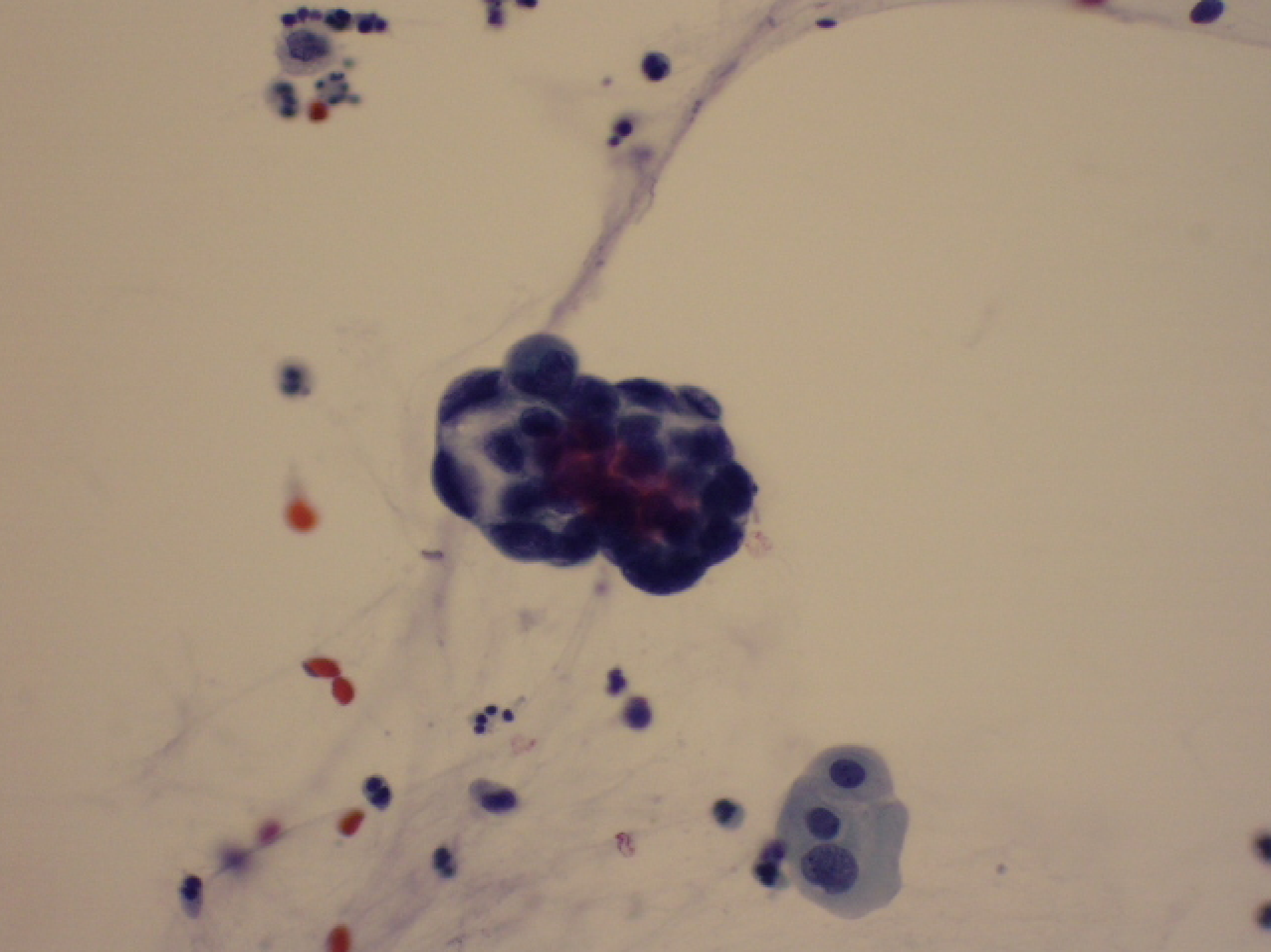
Pap smear was called AGUS, Endometrial

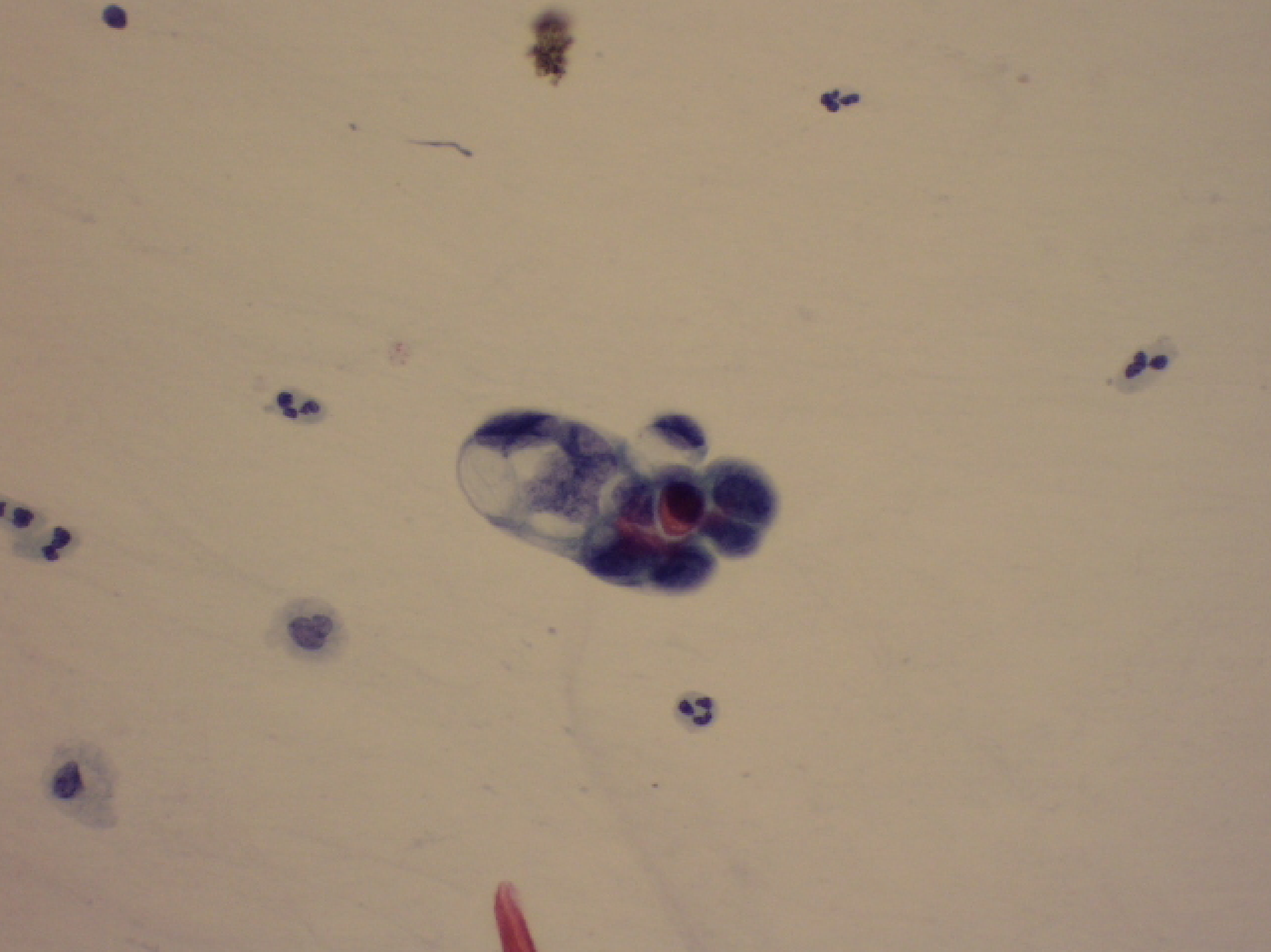


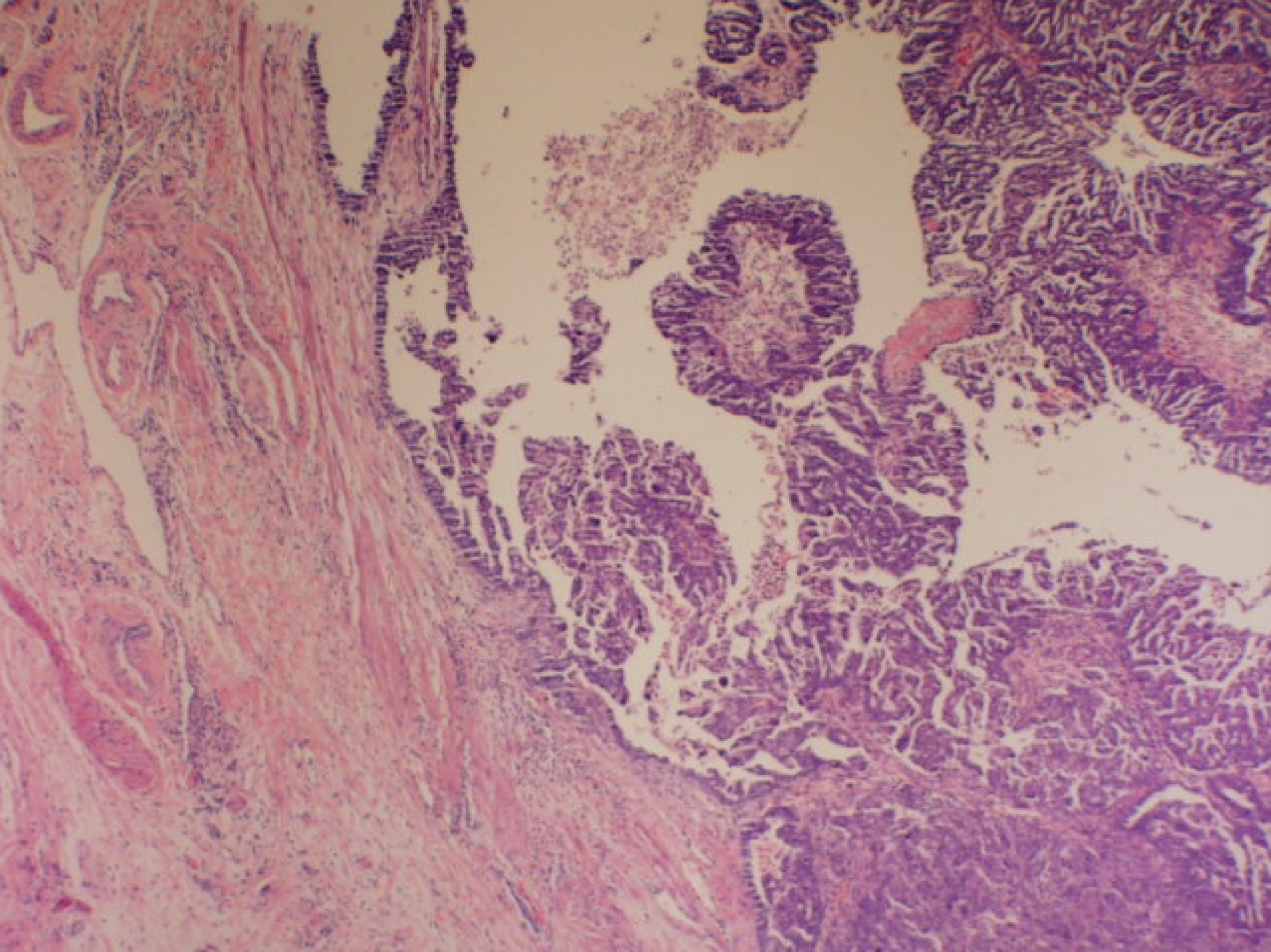


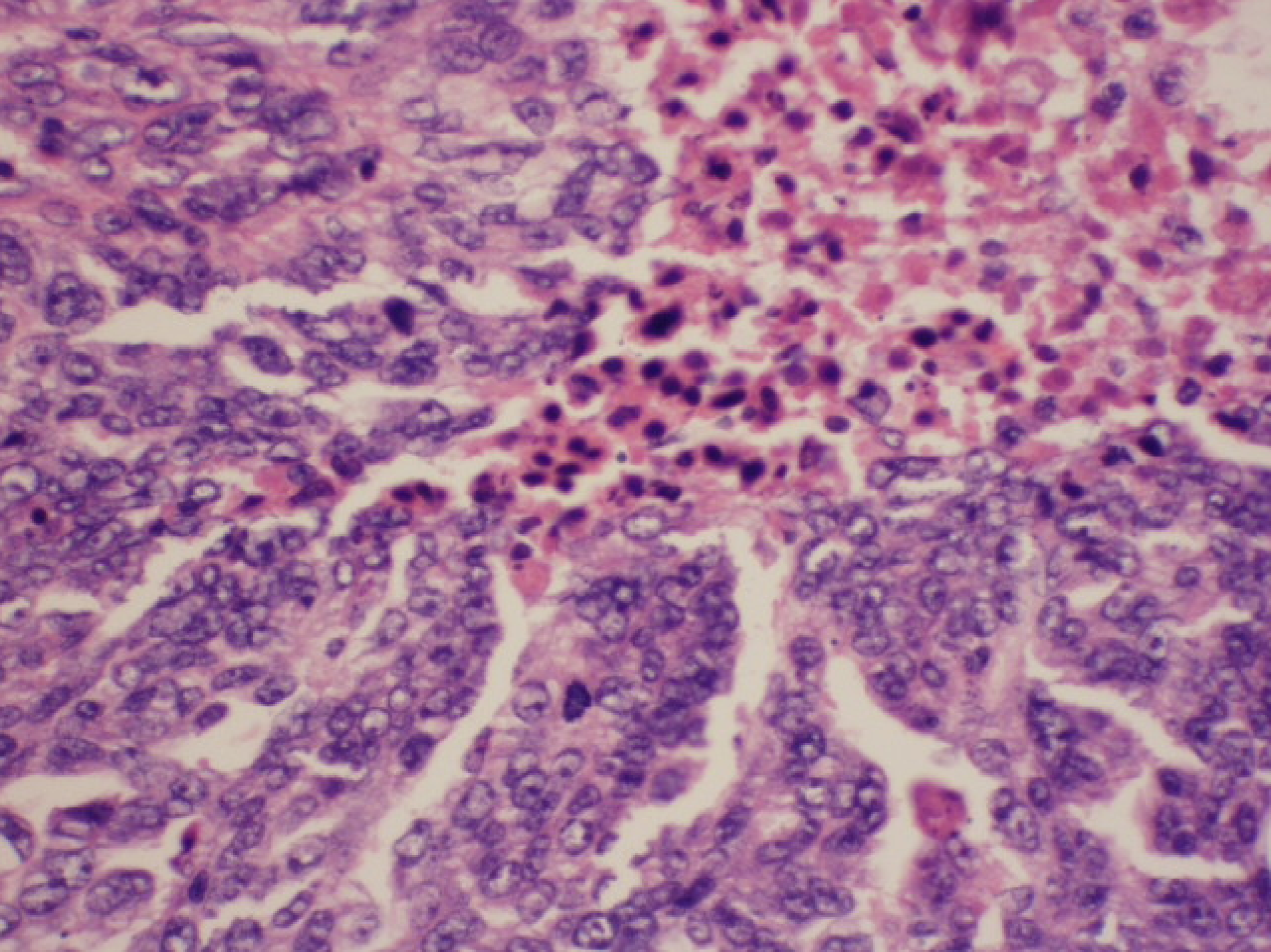












Fallopian Tube Adenocarcinoma

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

Summary

Feature	Reactive	AIS	Invasive
Crowding	+/-	+++	++
Feathering	0	+++	++
Rosettes	+/-	+++	++
Cilia	+/-	0	0
Mitoses	+/-	++	++
Nuclear irregularity	0	+	+++

Summary

Feature	Reactive	AIS	Invasive
Irregular chromatin	0	+/-	+++
High N/C	+/-	+++	++
Nucleoli	Variable	0 or micronucleoli	Macronucleoli
Normal endocervical cells	+++	++	+
Background	Clean/Inflammatory	Inflamm./Clean	Diathesis

References

- DeMay RM. The Art and Science of Cytopathjology-Exfoliative Cytology. ASCP Press 1996