



ALL THE PITTFOLS OF CYTOLOGY: TO BE OR NOT TO BE!

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Few facts that should keep in mind

- Cervical cancer is highly preventable and highly curable if caught early.
- Regional differences in the cervical cancer burden are related to **inequalities in access to vaccination, screening and treatment services**,
- Cervical cancer is the fourth most common cancer in women globally with around 660 000 new cases and around 350 000 deaths in 2022. The highest rates of cervical cancer incidence and mortality are in low- and middle-income countries.
- Findings highlight several concepts including the disharmony between knowledge and practice, prevalent perceived public stigma, cumbersome attitudes on the part of men regarding HPV and cervical cancer, and distrust of the healthcare system.



This global strategy to eliminate cervical cancer proposes:

- a vision of a world where cervical cancer is eliminated as a public health problem;
- a threshold of 4 per 100 000 women-years for elimination as a public health problem;
- the following 90-70-90 targets that must be met by 2030 for countries to be on the path towards cervical cancer elimination:



90%

of girls fully vaccinated
with HPV vaccine by
age 15 years.



70%

of women are screened
with a high-performance
test by 35 years of age and
again by 45 years of age.



90%

of women identified with cervical
disease receive treatment
(90% of women with precancer
treated, and 90% of women
with invasive cancer
managed).



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

North America
14,971

Europe
58,169

Asia
351,720

WHY??

a
16

Latin America and
Caribbean
59,439

Oceania
2,512

Figures displayed represent global incidences.

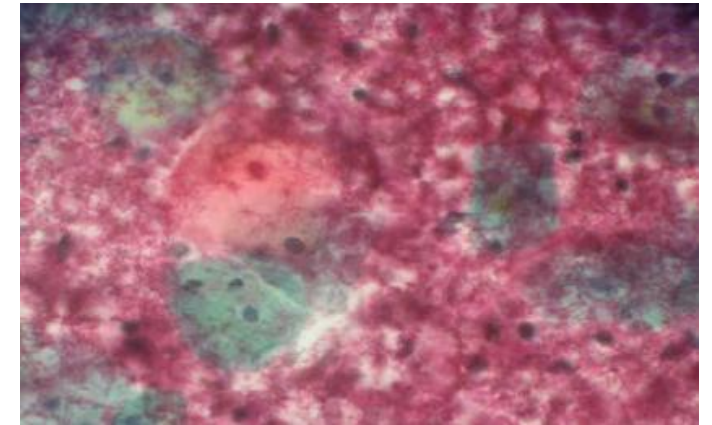
Document ID: Z4-40718 | Date of preparation: December 2021

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 December 2021. 2. World Health Organization. Globocan 2020 Fact Sheet. Available at <https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf>. Accessed December 2021.



Pap test - all traps of cytology

- Who can take a Pap smear?
- What is the effect of staining the smear?
- Who can interpret/read the Pap smear result?"



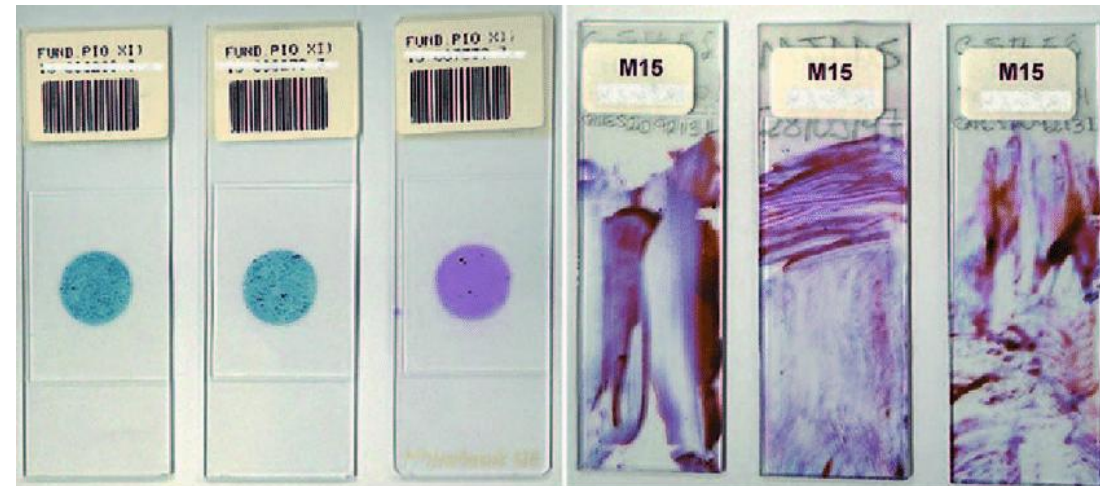
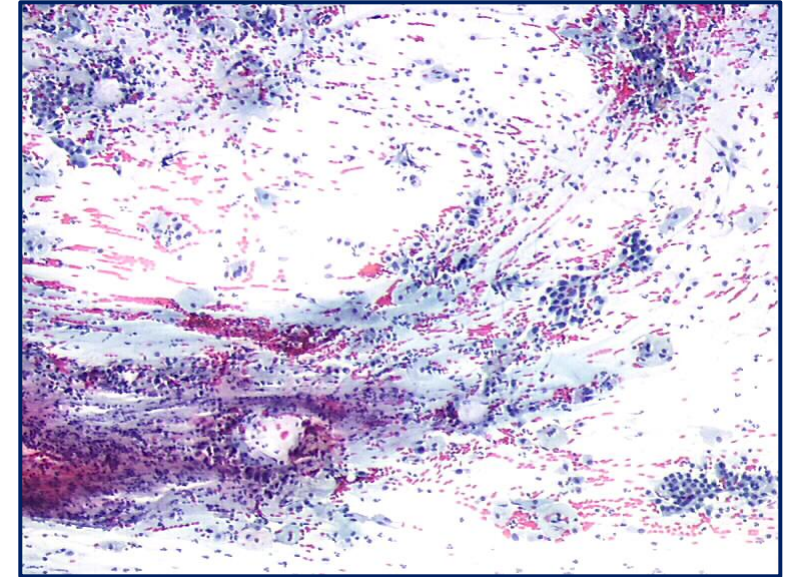
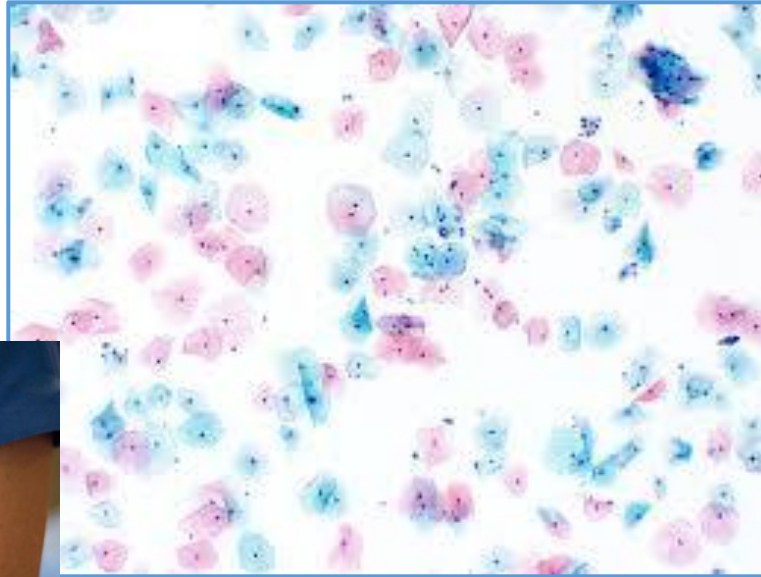


Specimen adequacy

- The reasons for failure of the Pap test to contain abnormal cells in the presence of a histologically proven preneoplastic or neoplastic lesion can be attributed to:
 - The biological properties of the tumour
 - Failure of sampling
 - Failure of screening



Failure of sampling:

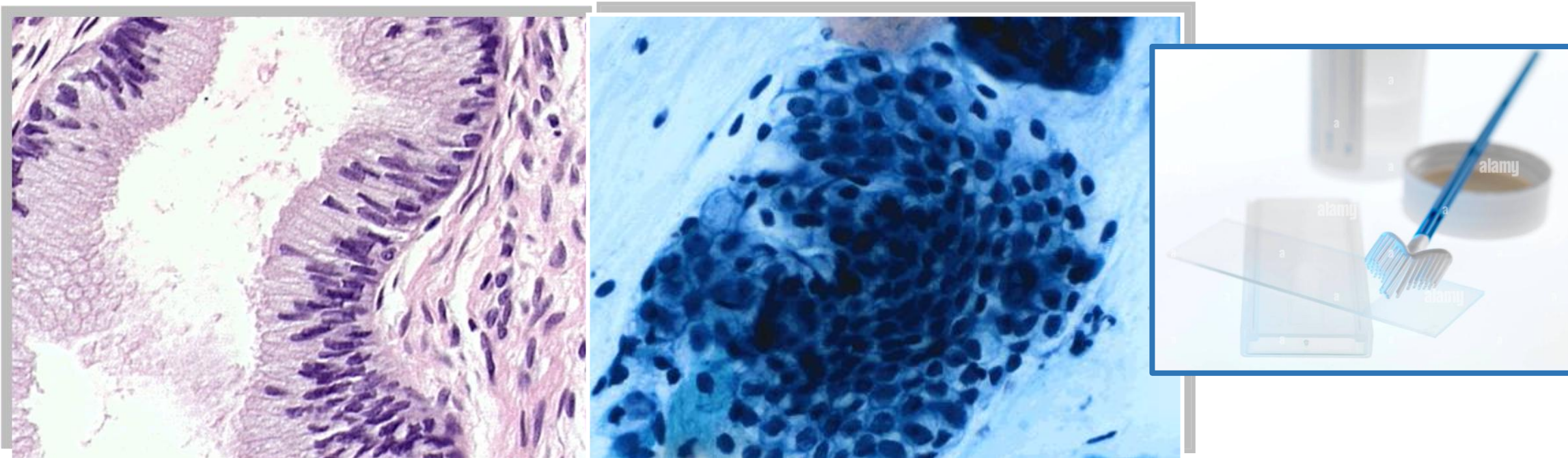


LIQUID-BASED CYTOLOGY

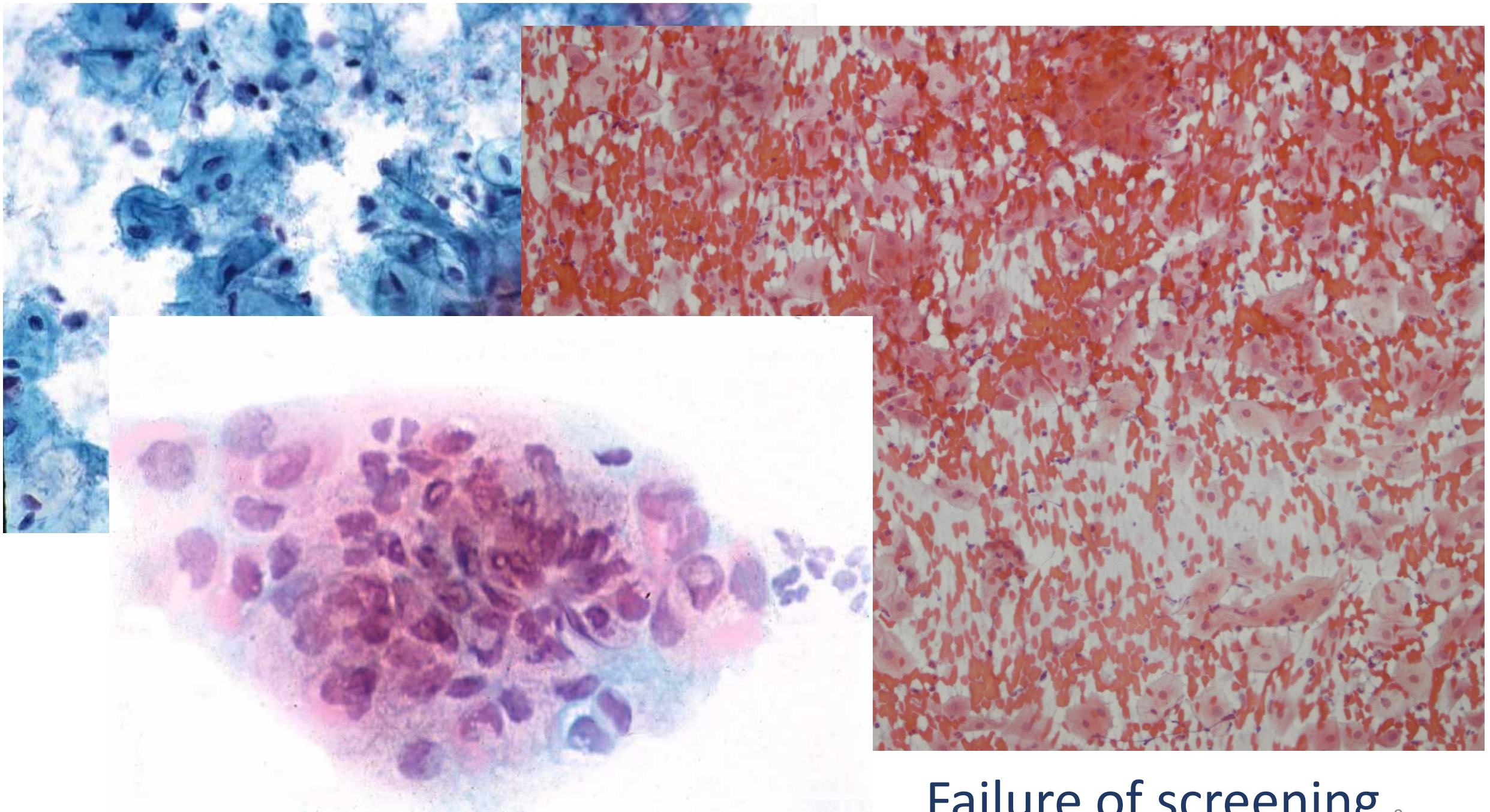
CONVENTIONAL PAP SMEAR



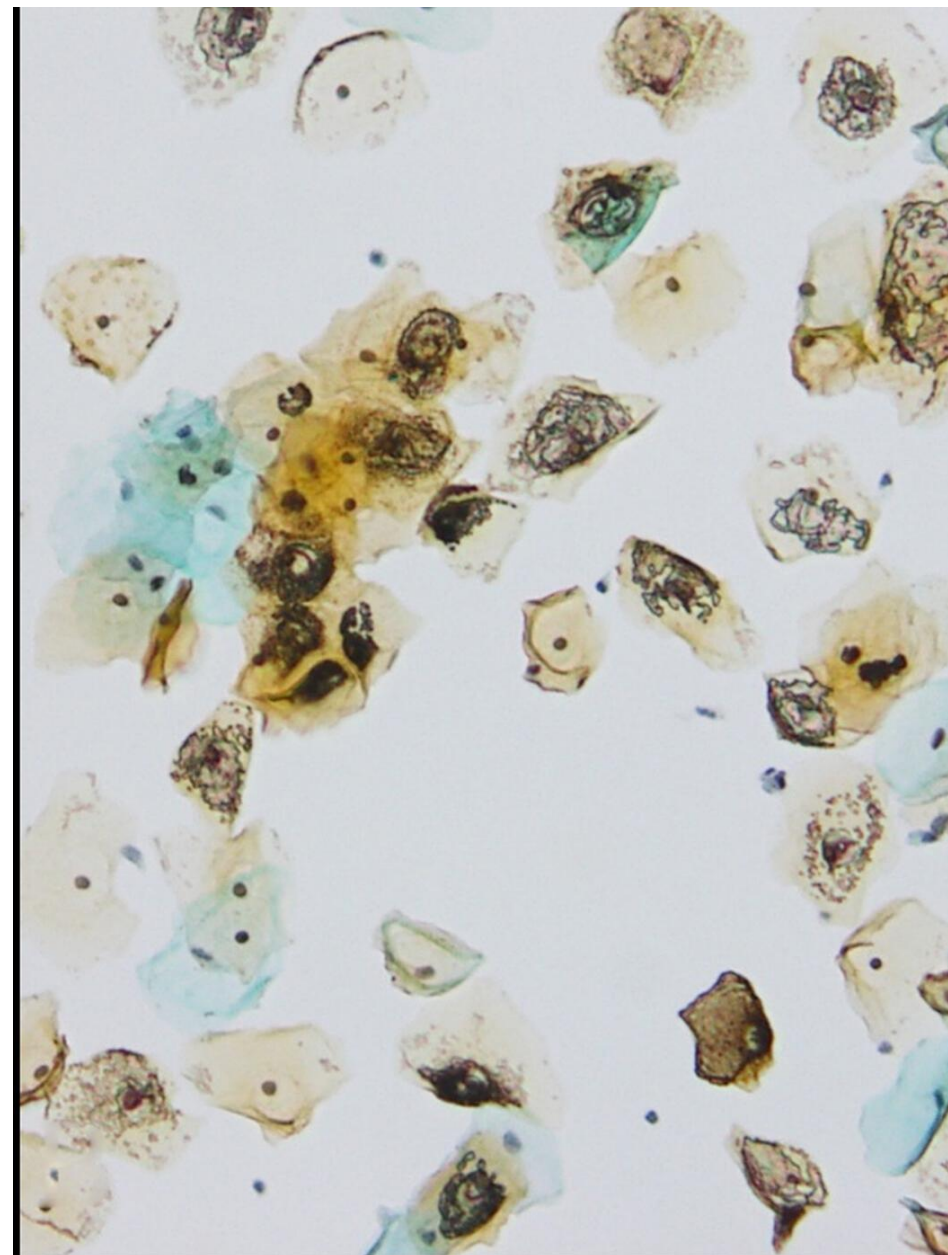
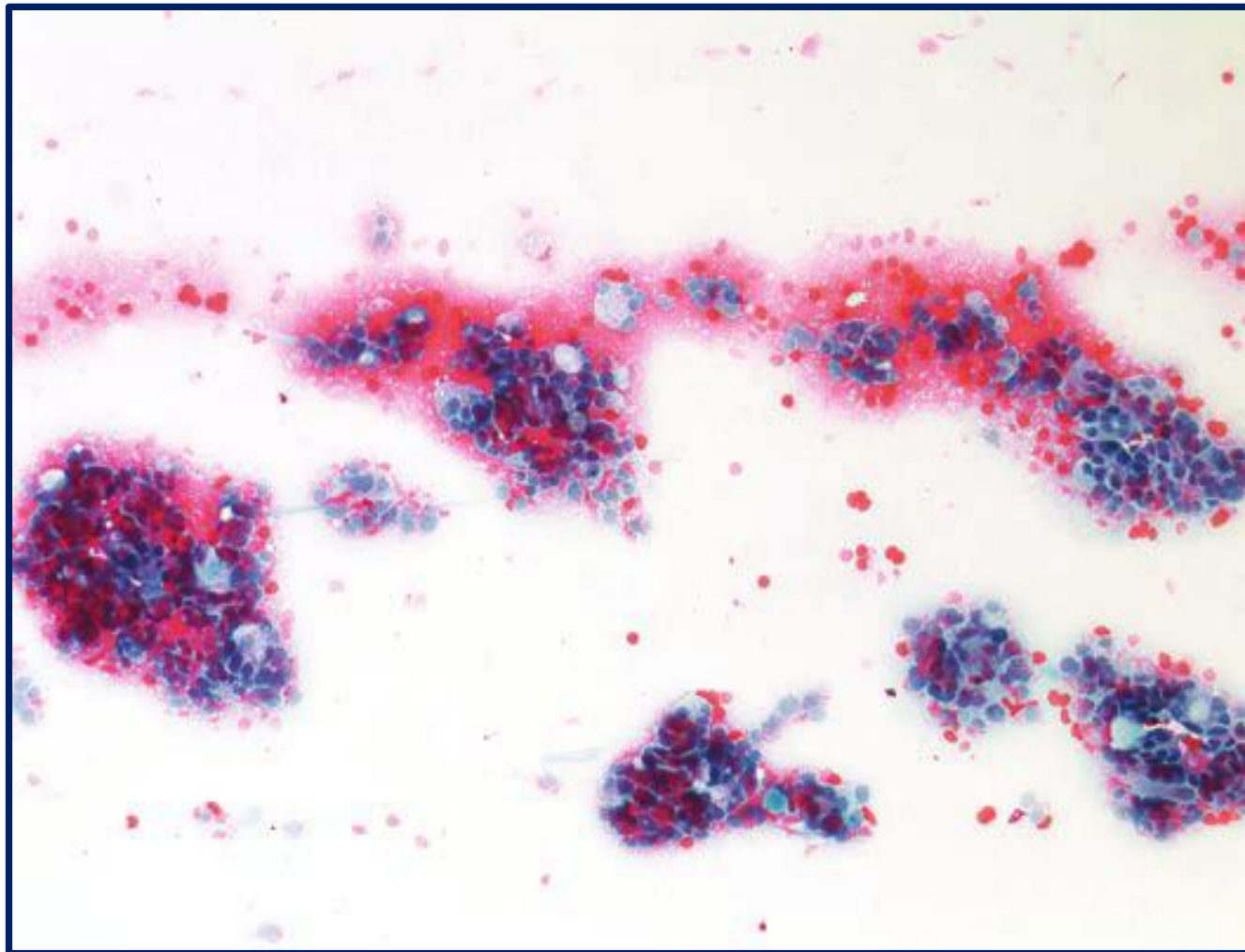
Possible reasons for reduced effectiveness

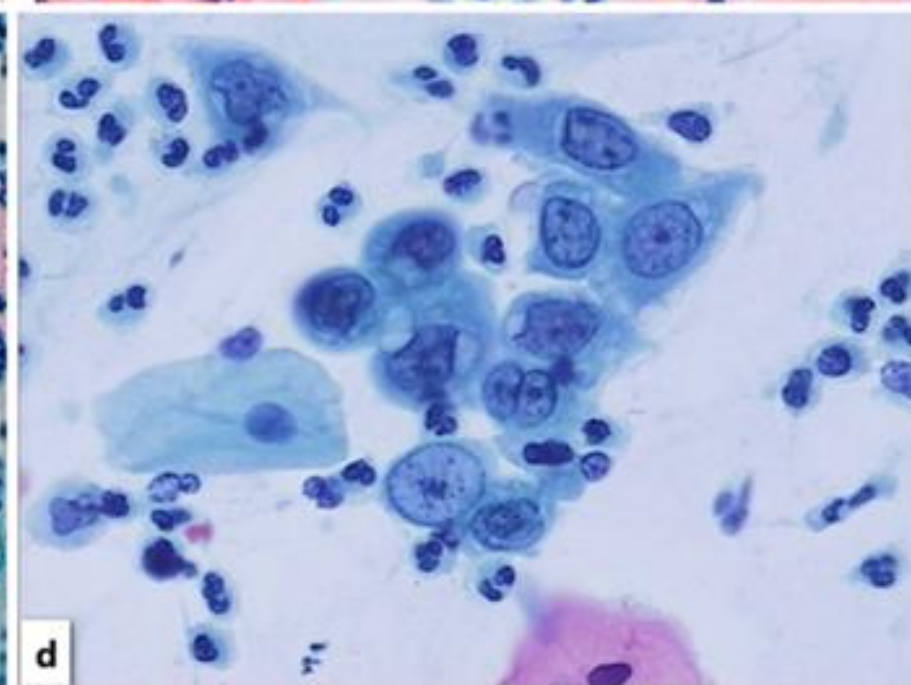
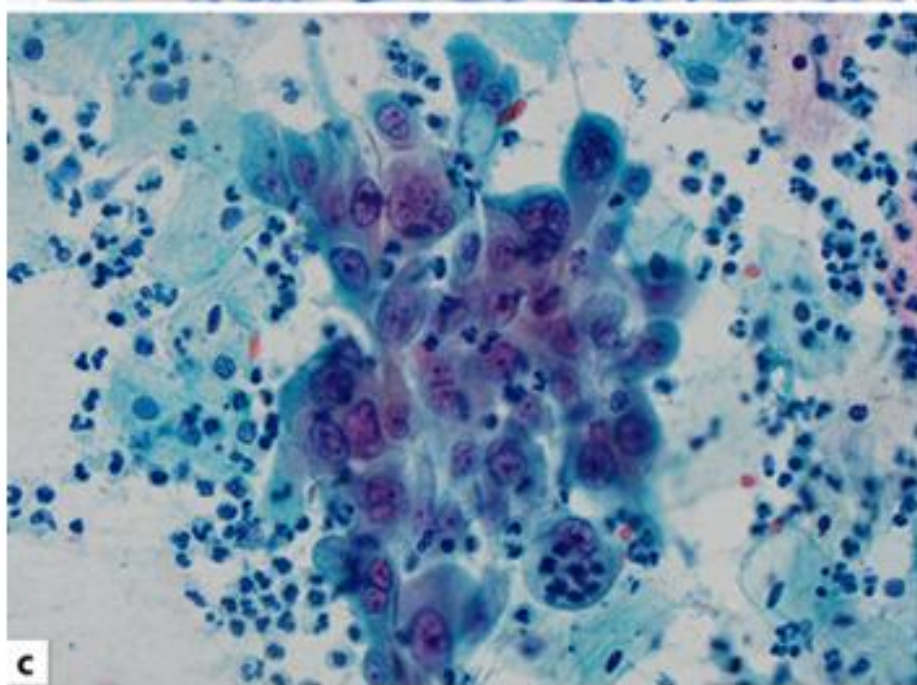
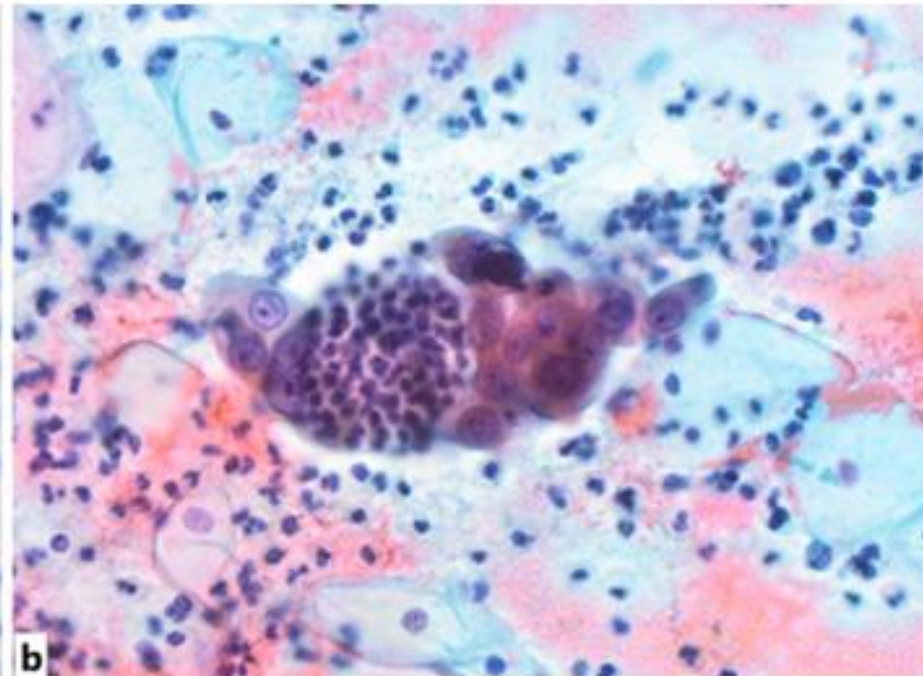
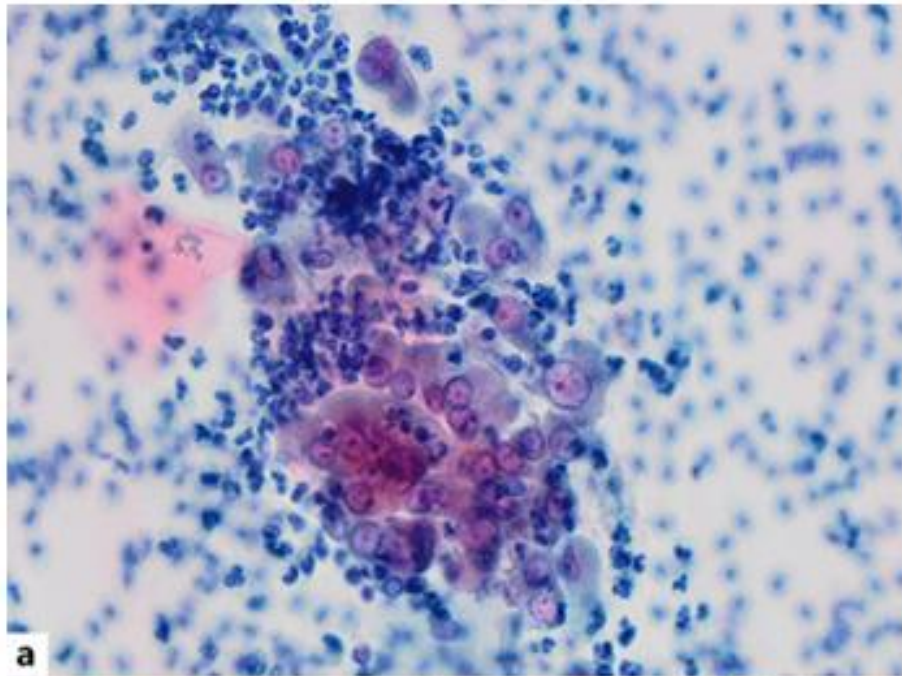


- 1) insufficient sensitivity for detecting precursor lesions, either because of sampling error, false-negative results, or underreporting,
- 2) rapid progression from in situ to invasive carcinoma.



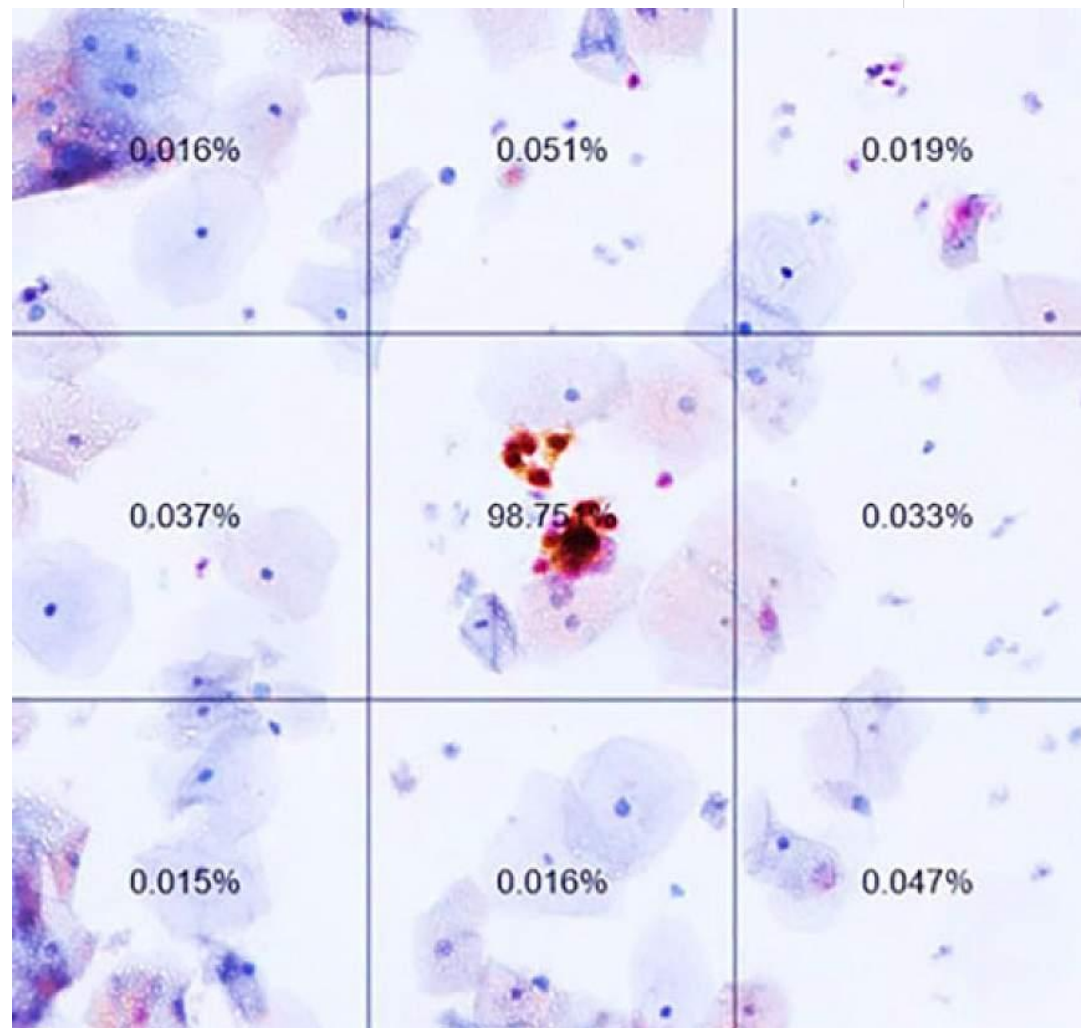
Failure of screening ₉







Case





Patient, age 36

- ✓ Pregnancy: 1pvn; Ab: 0
- ✓ In February 2022, Pap test was BCC. Regularly checked in private Gyn clinic
- ✓ Pap test was performed and interpreted by Gynecologist
- ✓ Between February and July she experienced some unspecific pain in lower abdomen

- ✓ In August 2022 – she performed again Pap test in same private Gyn Clinic;
- ✓ Pap test without abnormality
- ✓ In September she was addmitted in Daily Care Unit of Depth of Gyn/Obs in UCC Tuzla
- ✓ TVUS was performed – no acute gyn disease; cervix – normal, no visible changes on vaginal portion



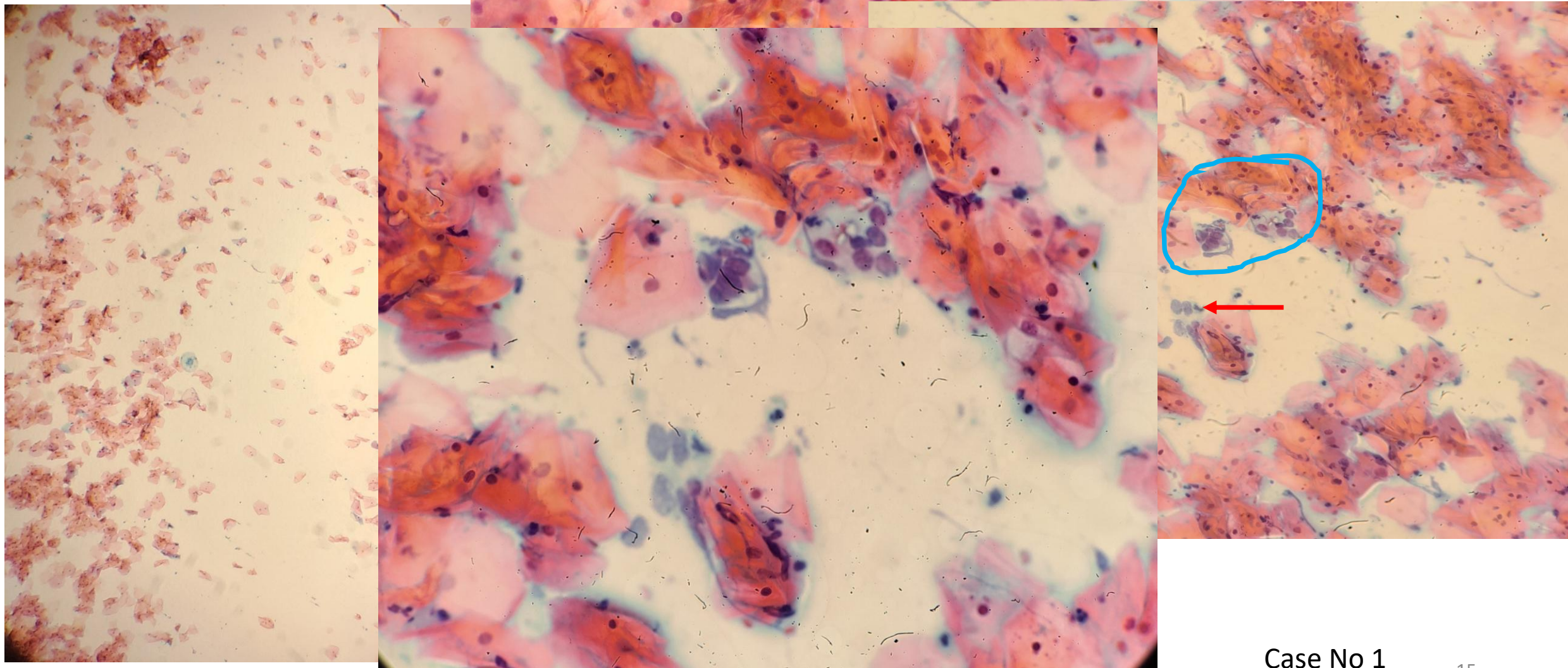
Patient, age 36

- ✓ Biopsy was performed;
- ✓ PHDg: LSIL
- ✓ In January 2023 – she performed again Pap test in same private clinic; Pap test result was BCC
- ✓ In August she referred to another private clinic; Pap test was performed:

- Pap test was done by experienced gynecologist in cervical pathology
- Smear was stained by well trained cytotechnologist, experienced in cervical cytology
- Pap test was interpreted by pathologist
- **Result of Pap test: ASC-H in TZ, possible also in glands; AGUS possible neoplastic in few groups; can't be excluded**



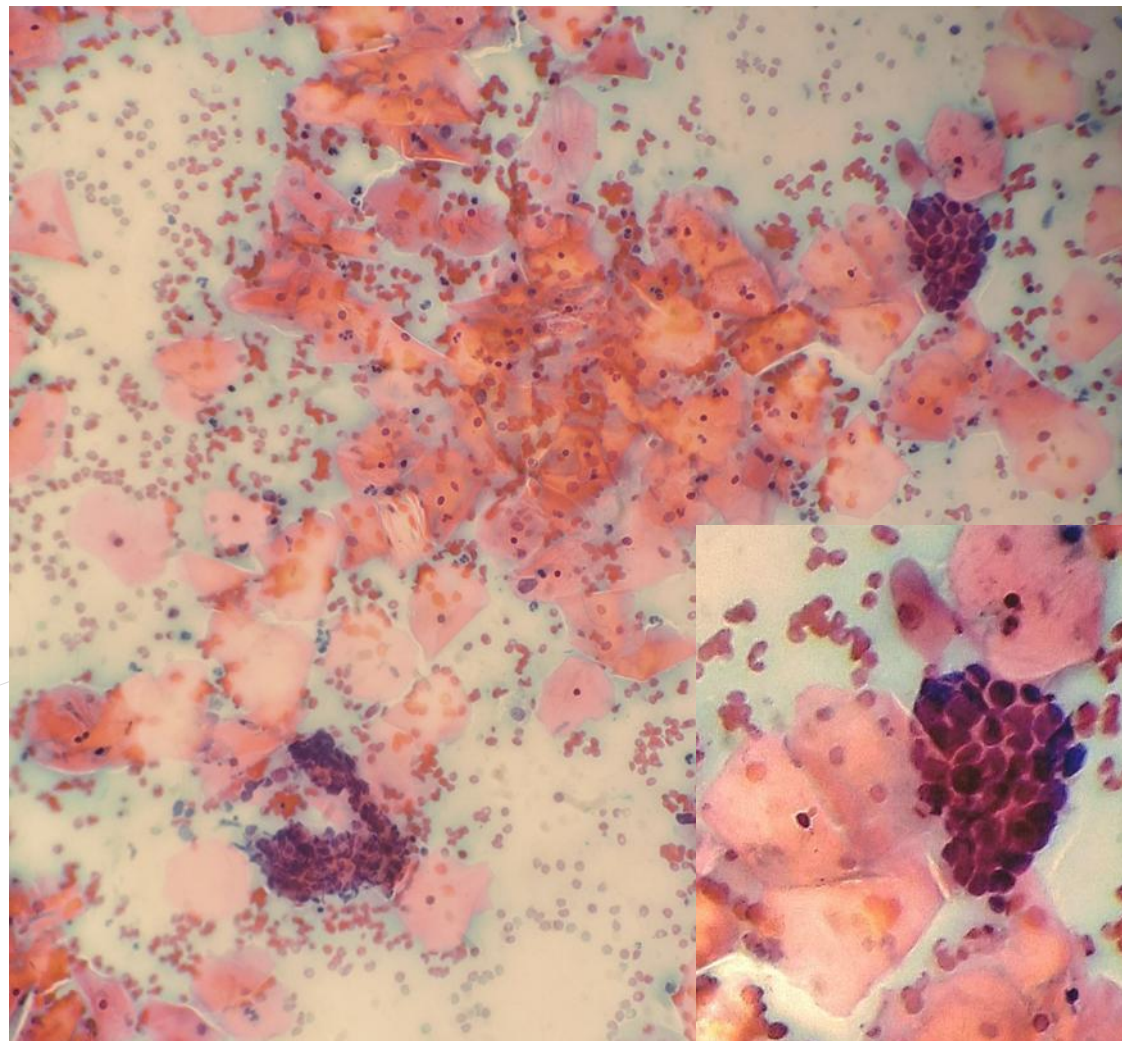
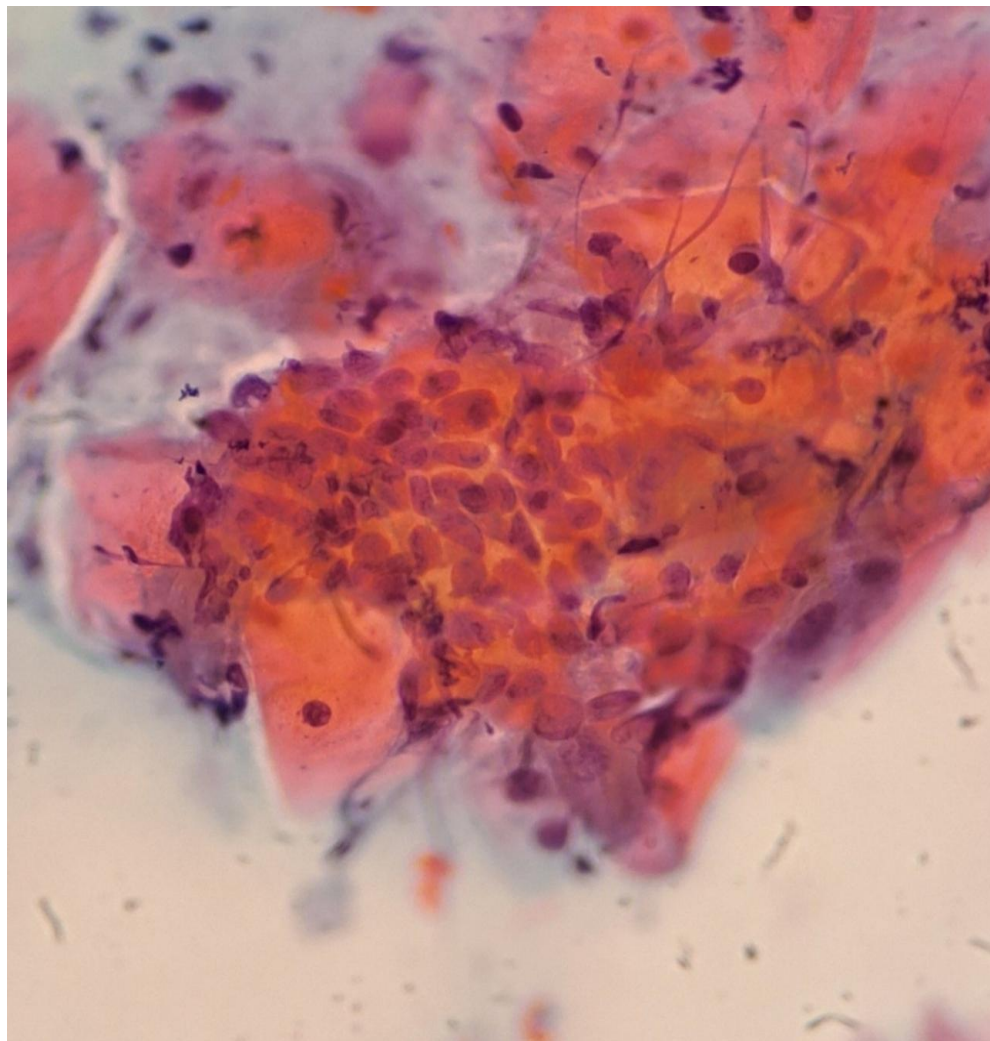
Patients; age 36



Case No 1



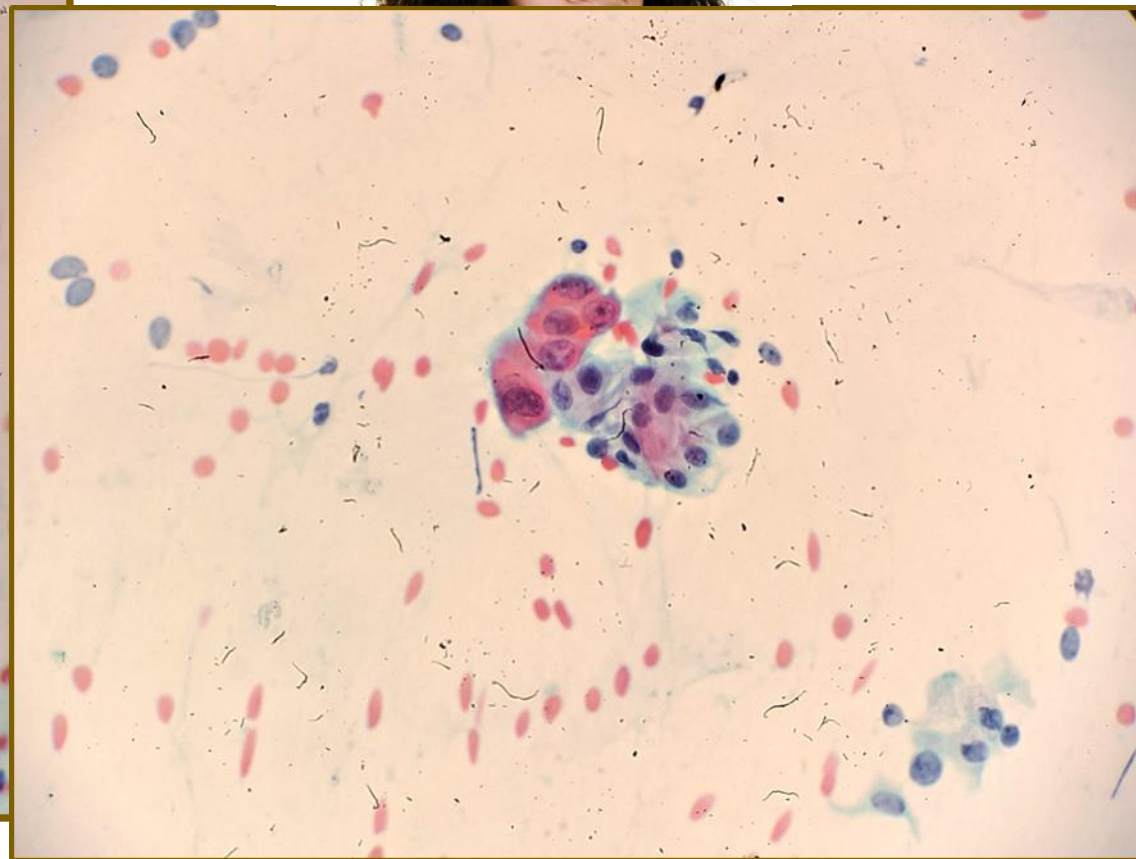
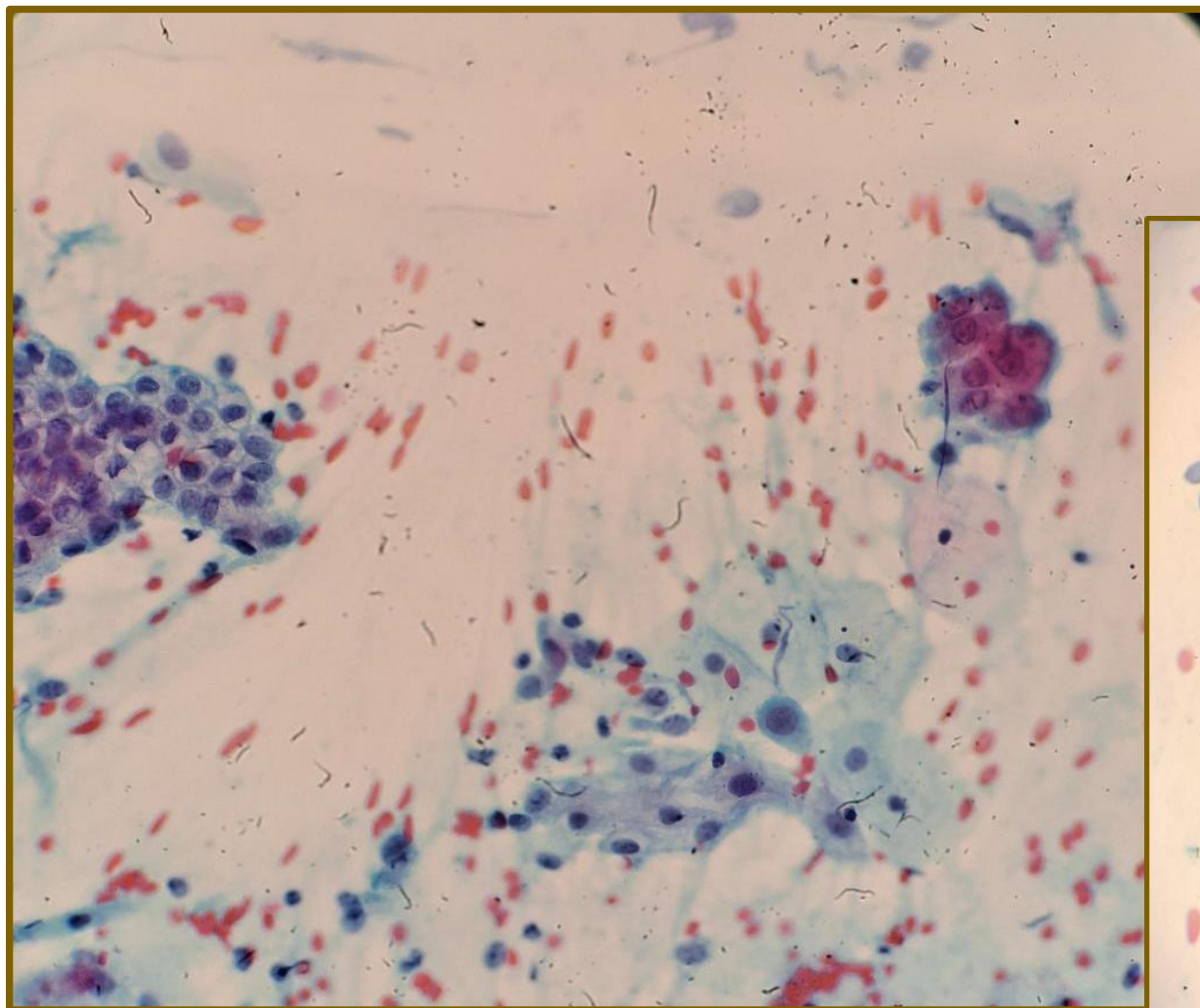
Patients age 36





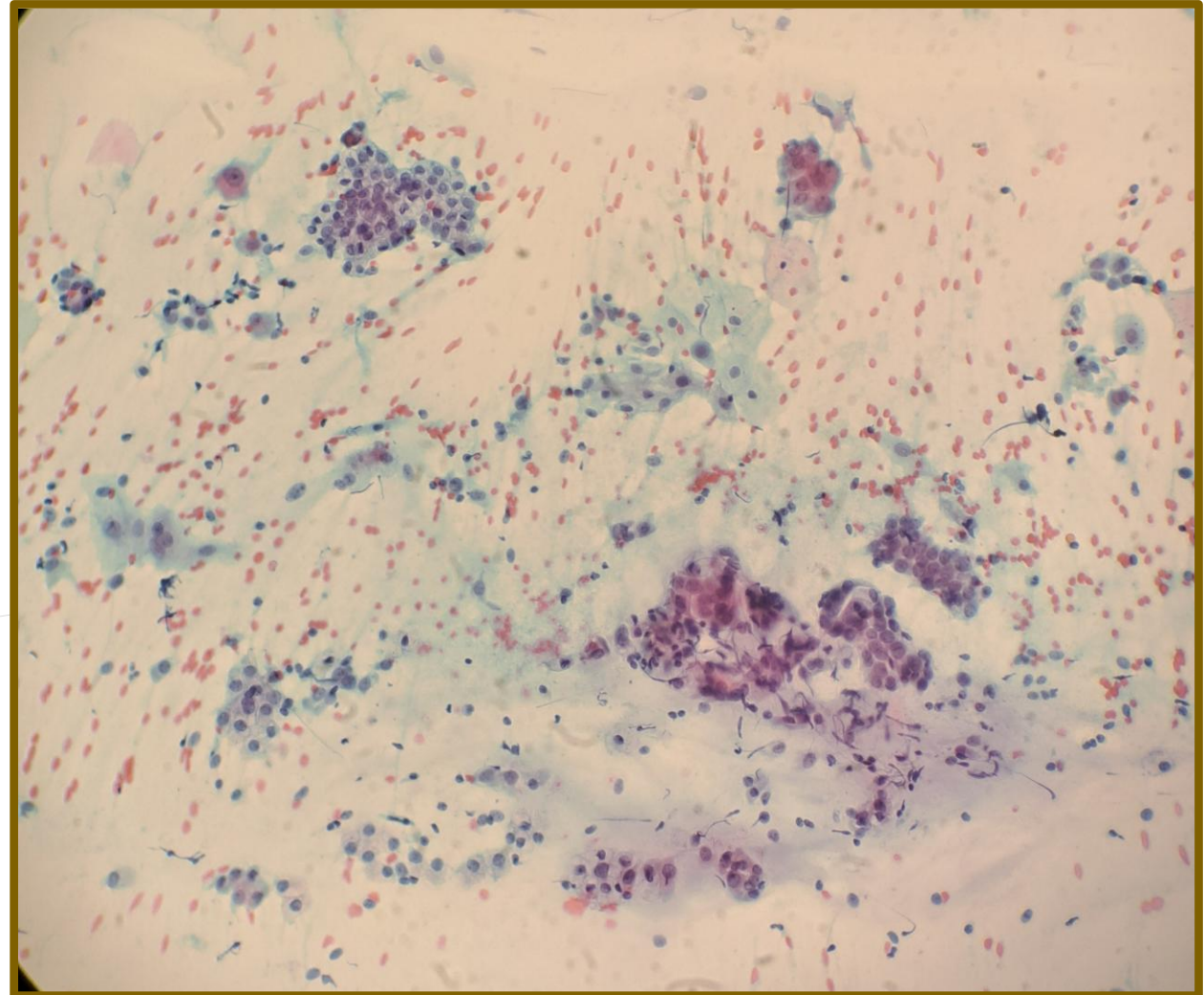
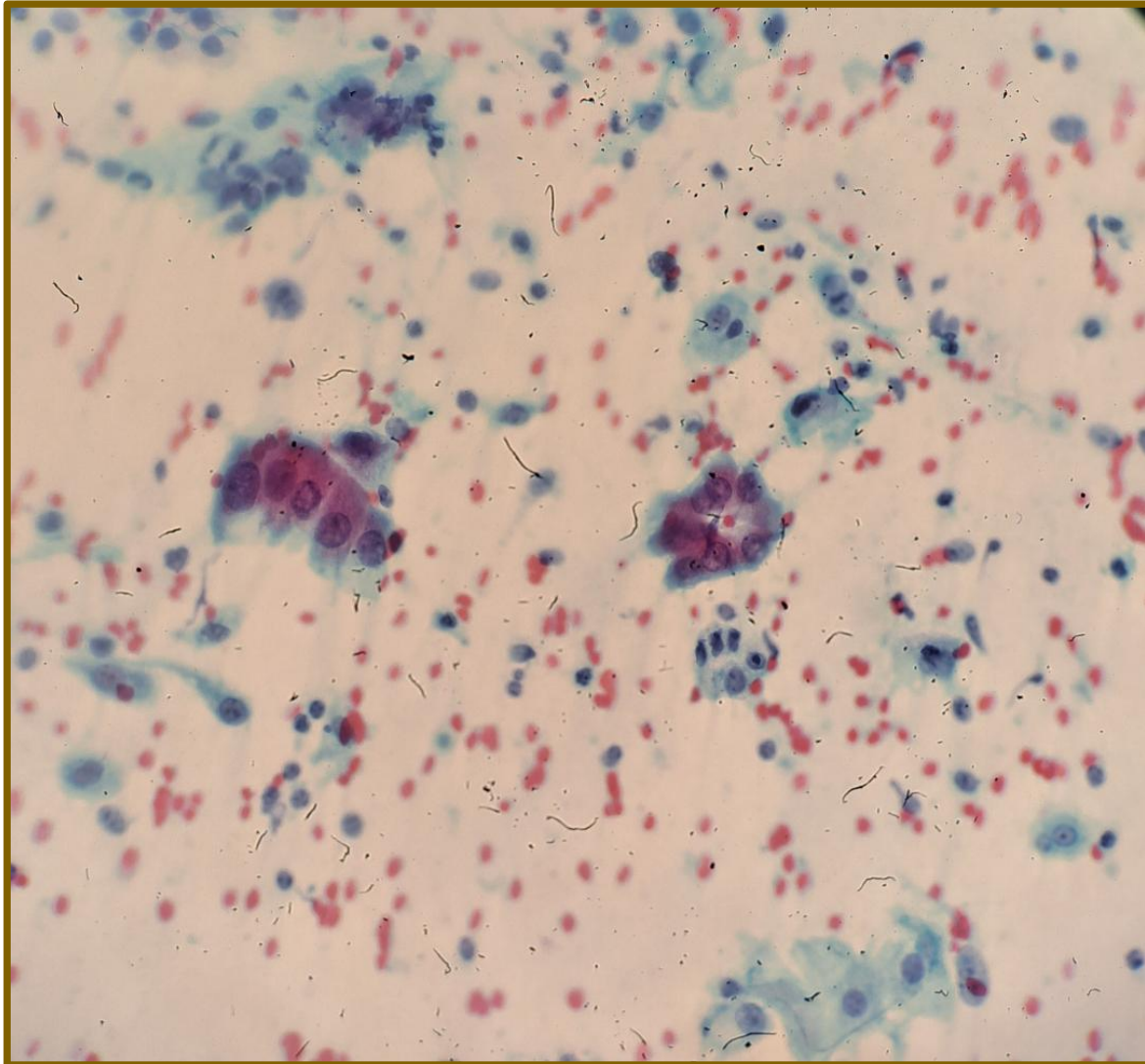
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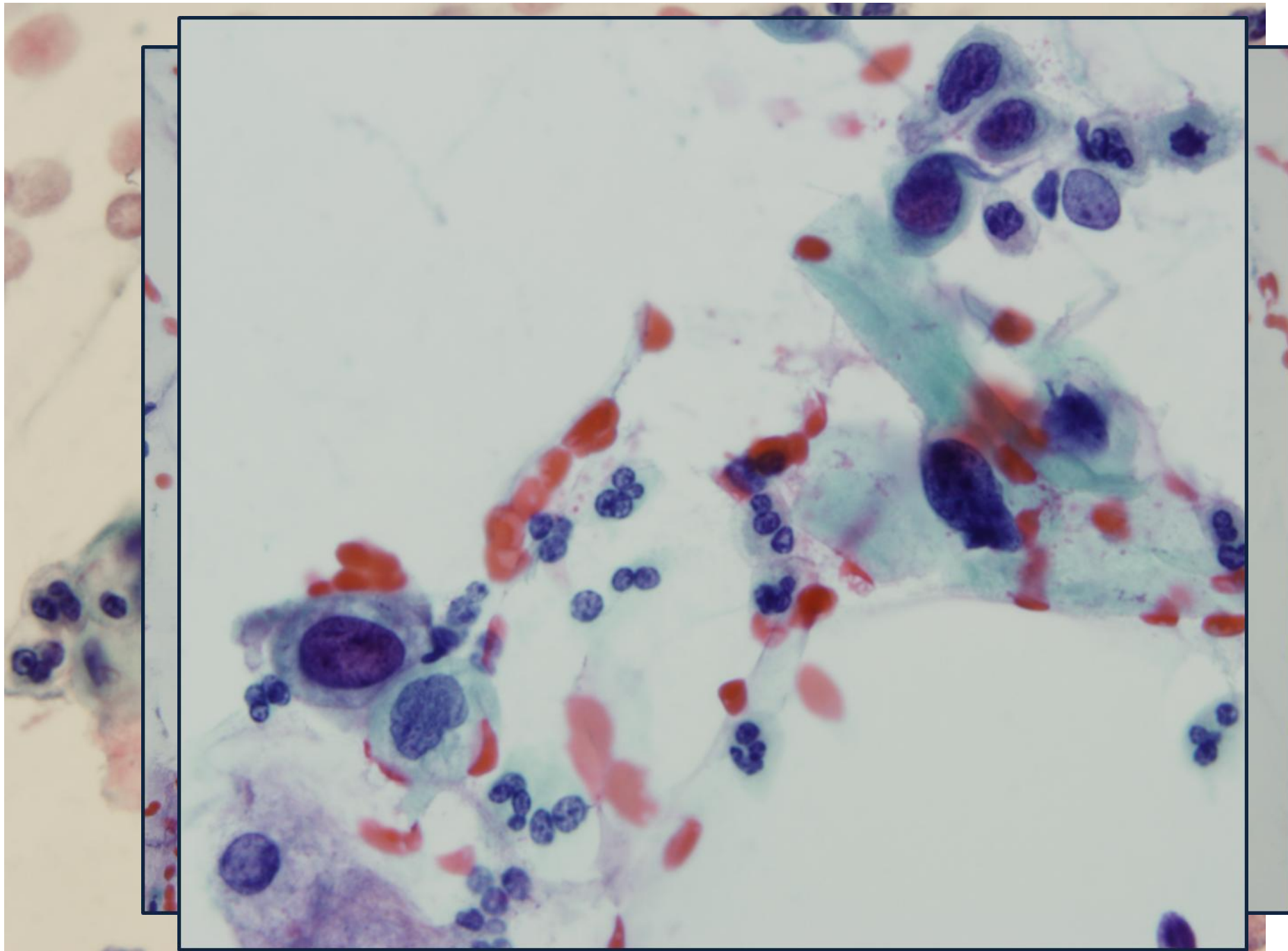
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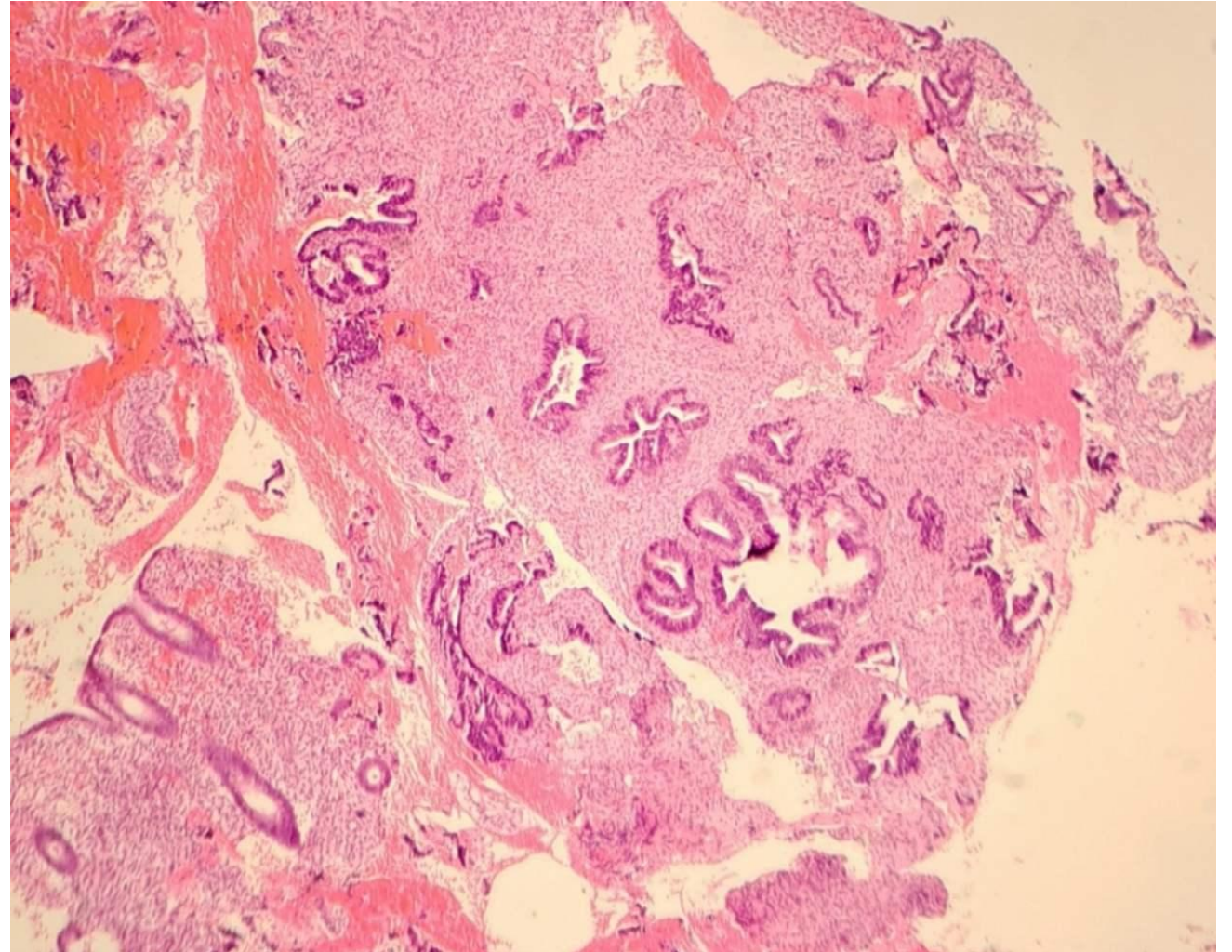
Case





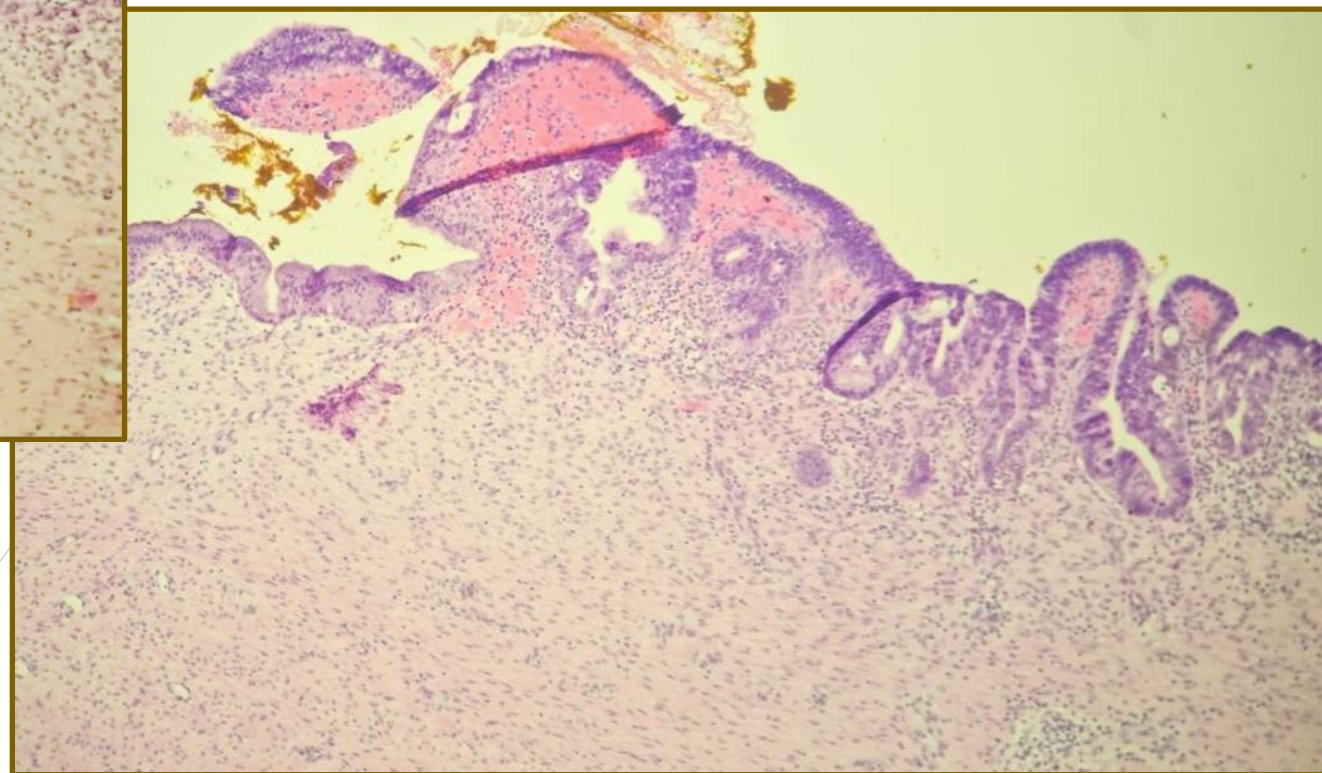
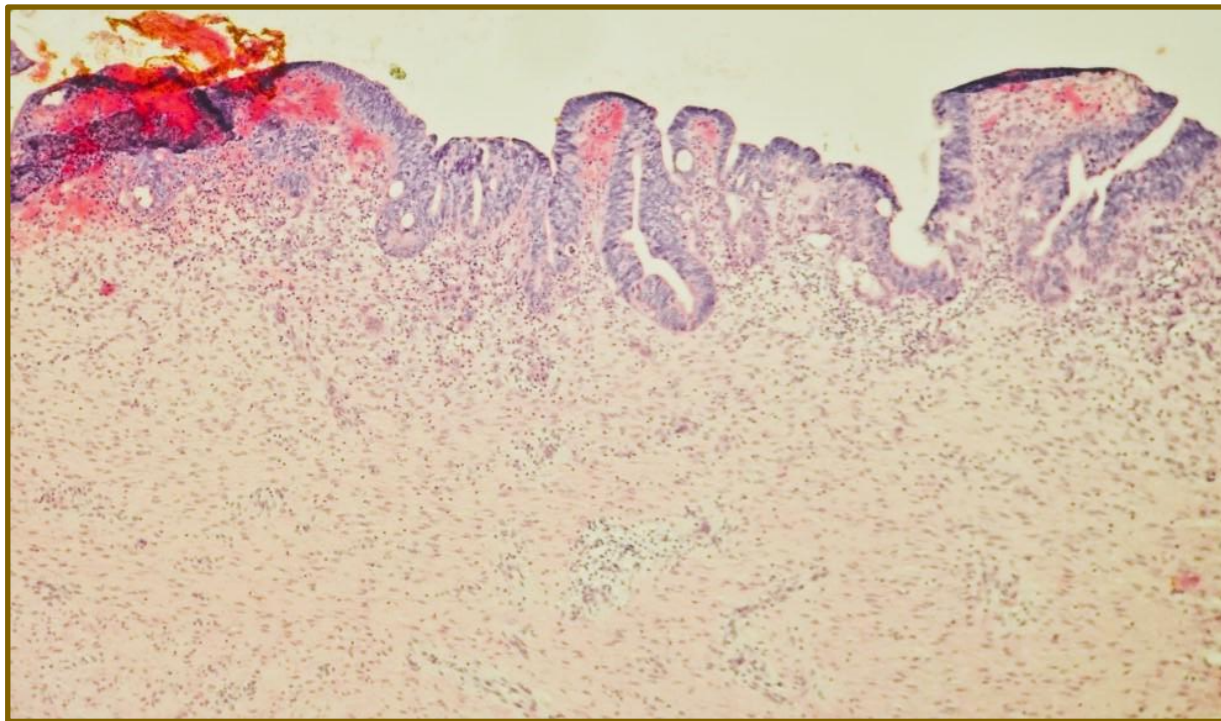
Patients age 36

- Biopsy performed at October 2023 in private clinic in Tuzla
- PHDg: Invasive adenocarcinoma G2 was established on endocervical curetage
- December 2023: LETZ was performed: Cervical adenocarcinoma with Adeno Ca in situ on resection margin



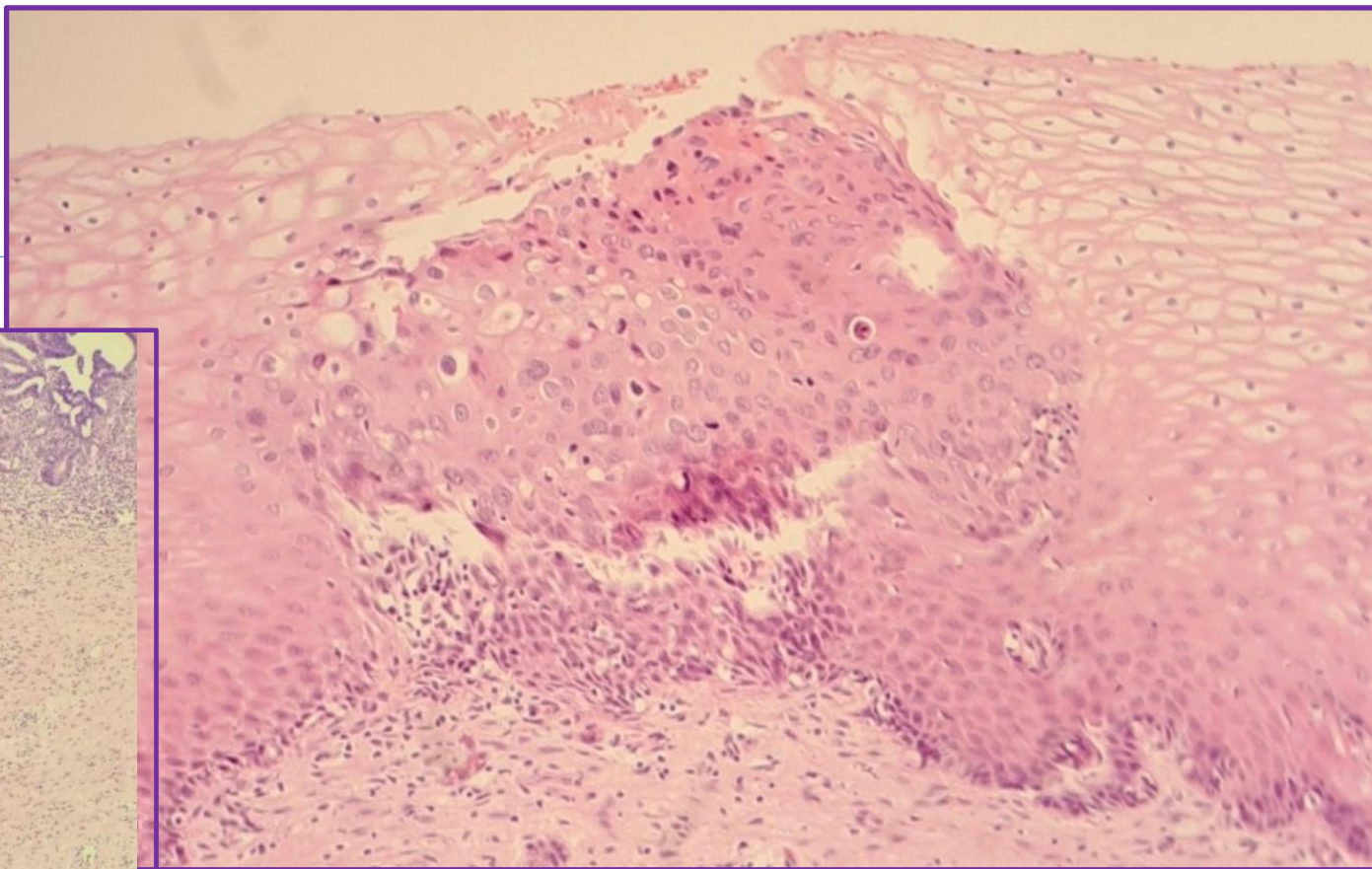
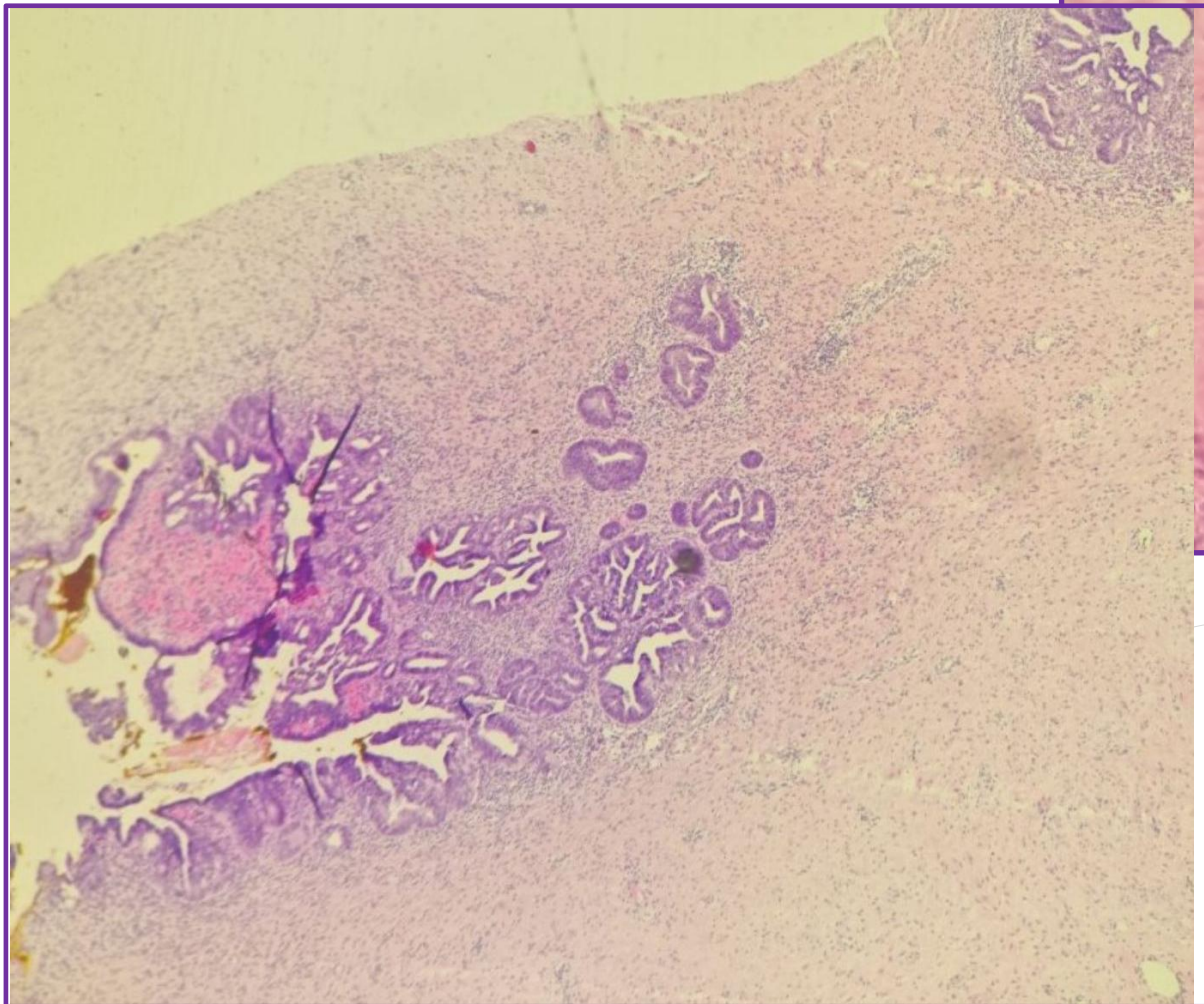


AGUS –possible neoplastic/AdenoCaCx





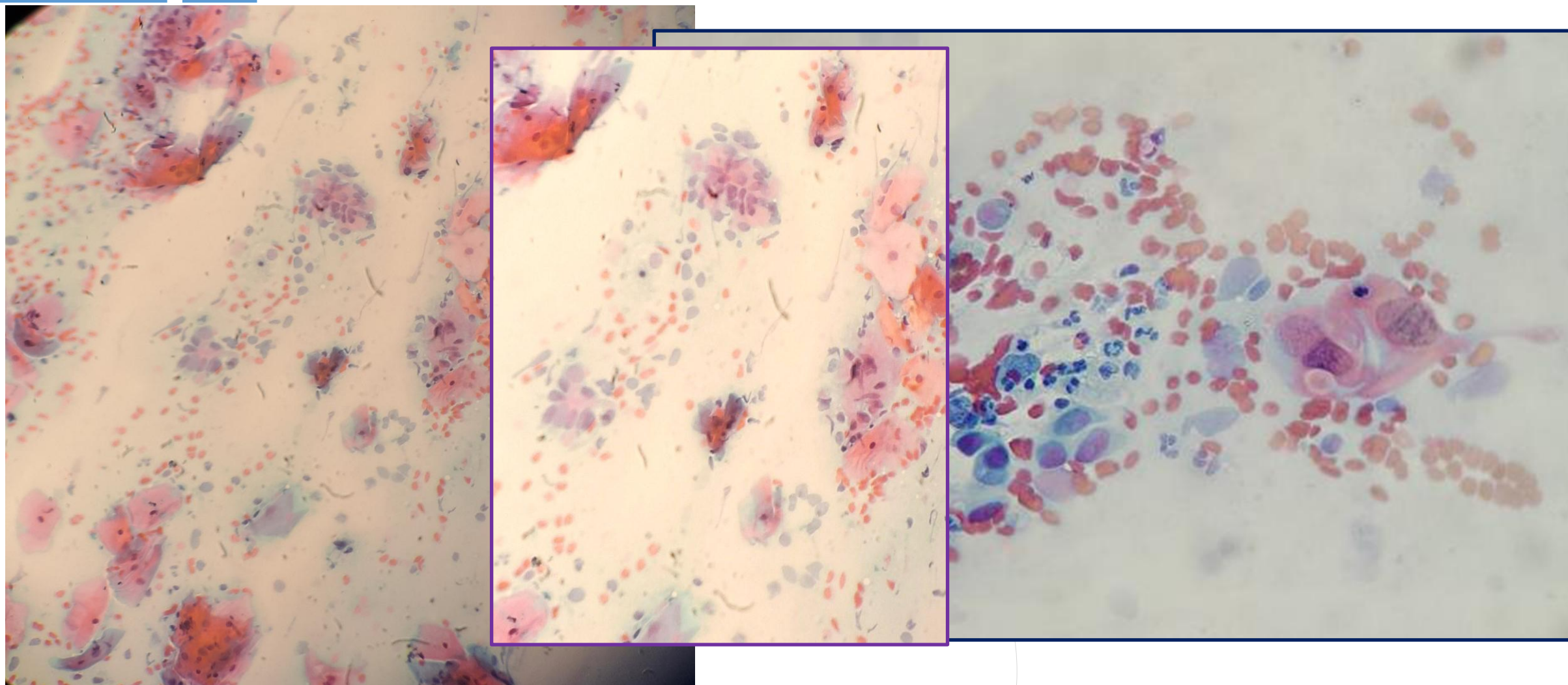
ASC-H/HSIL



Adeno CaCx on resection margins

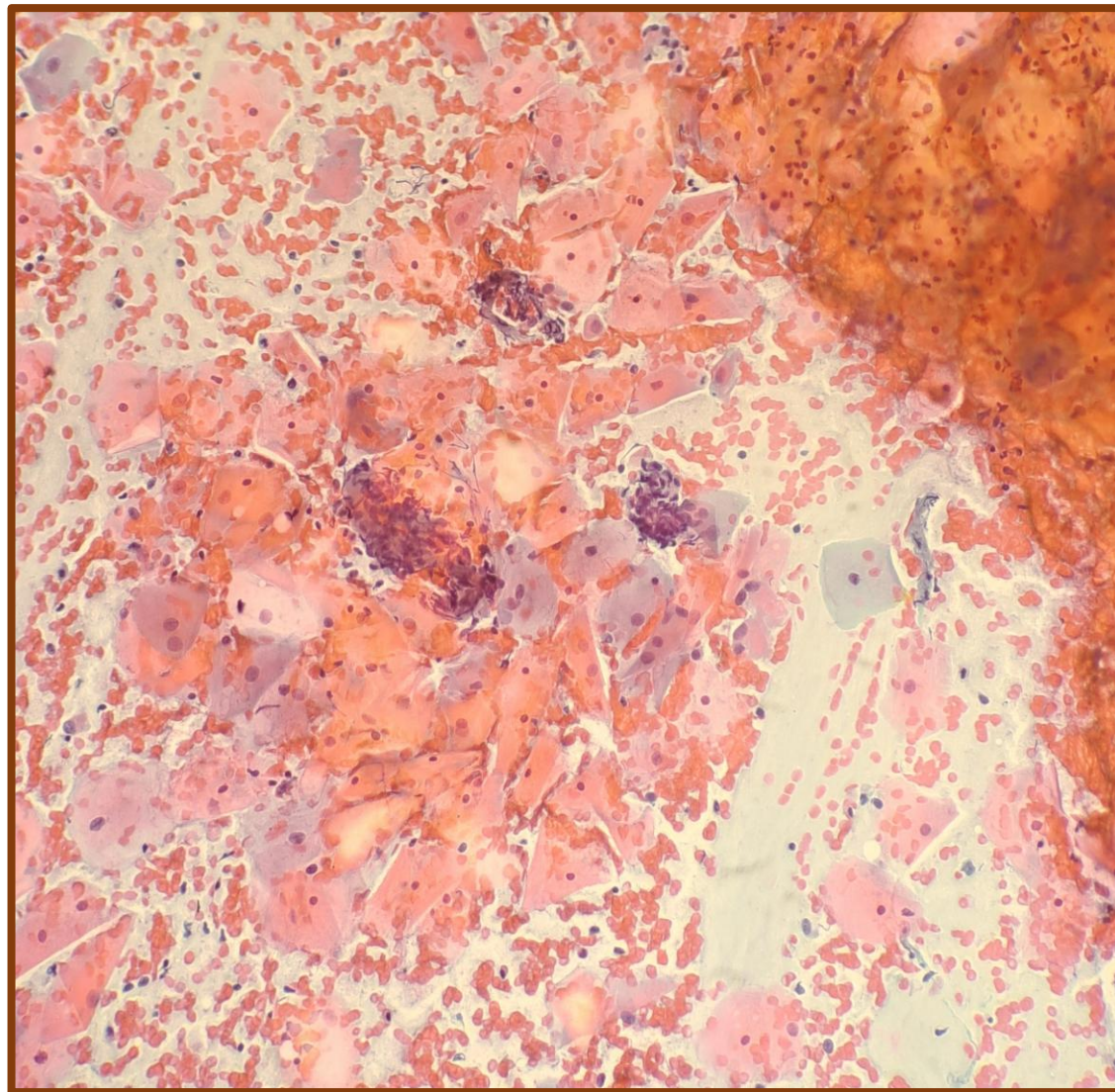
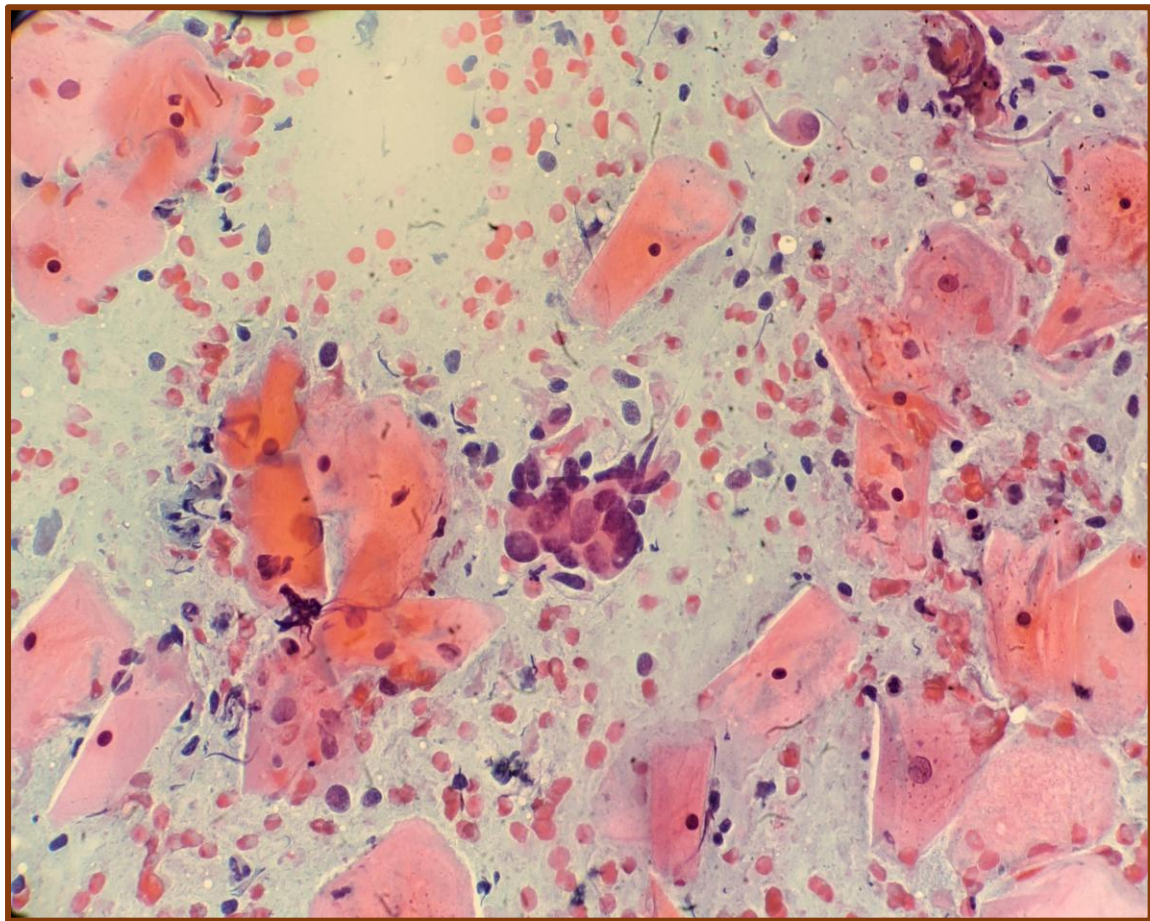


Patients age 36; Revision of Pap test from January 2023





Patients age 36





Definition / general

- Cytopathology is an anatomic pathology specialty that is highly regulated; the quality assurance (QA) program in cytopathology is mandated by CLIA '88 and implemented and constantly updated by the College of American Pathologists (CAP) ([CMS: Clinical Laboratory Improvement Amendments \(CLIA\) \[Accessed 7 September 2023\]](#))
- [Preadanalytical QA measures include review of stain quality, cytologic preparation technical quality and cross contamination checks, among others](#) (CYP.04300 and CYP.04150, respectively)
- Analytical QA measures include [prospective 10% QA rescreening](#) (CYP.07478)



Definition / general

- **Postanalytical QA measures include retrospective review of all negative gynecologic Paps** from the index patient when a new high grade dysplasia is detected (CYP.07517), surgical pathology correlation of nongynecologic cases (CYP.07675) and all gynecologic cases diagnosed as high grade dysplasia (CYP.07543) Reference: [CAP: Accreditation Checklists \[Accessed 7 September 2023\]](#)



ESSENTIAL FEATURES

- ✓ Cytopathology, especially gynecologic cytology, is considered a prototype screening test; therefore;
- ✓ Rigorous regulations revolve around this specialty to reduce (if not eliminate) significant false negative test results, which can have a momentous impact on patient safety and the laboratory's credibility.

- ✓ Other approaches such as rapid random rescreening and targeted rescreening (negative Pap test with positive human papillomavirus [HPV] cotesting and including certain high risk cases into the 10% prospective rescreening pool) can be used as additional measures to enhance the QA program ([Roum Arch Microbiol Immunol 2013;72:93](#))



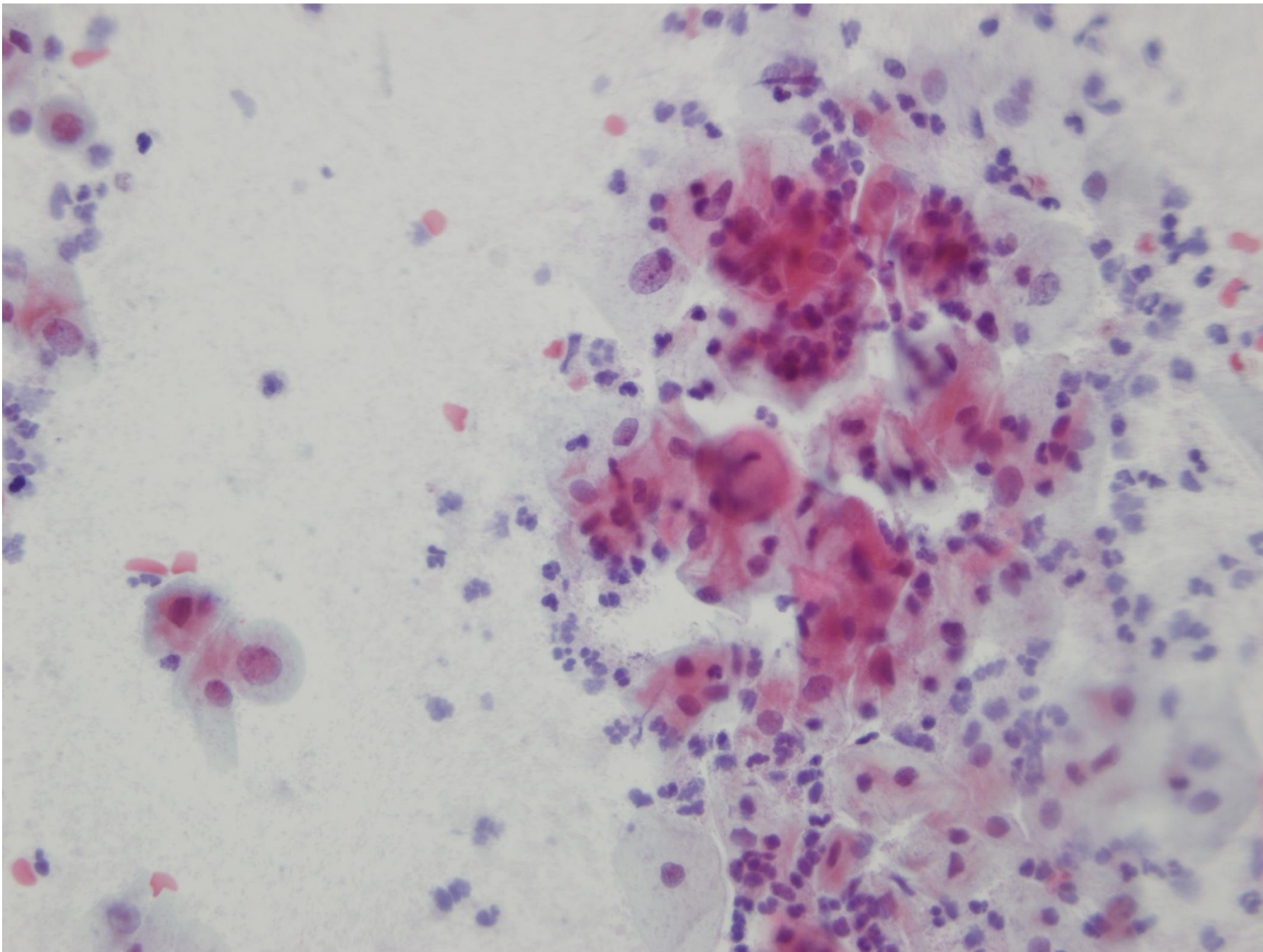
- The previous guidelines recommended repeat smears for patients who are diagnosed with nonspecific minor changes in endocervical cells, whereas the new draft guidelines propose to refer these patients for colposcopy.

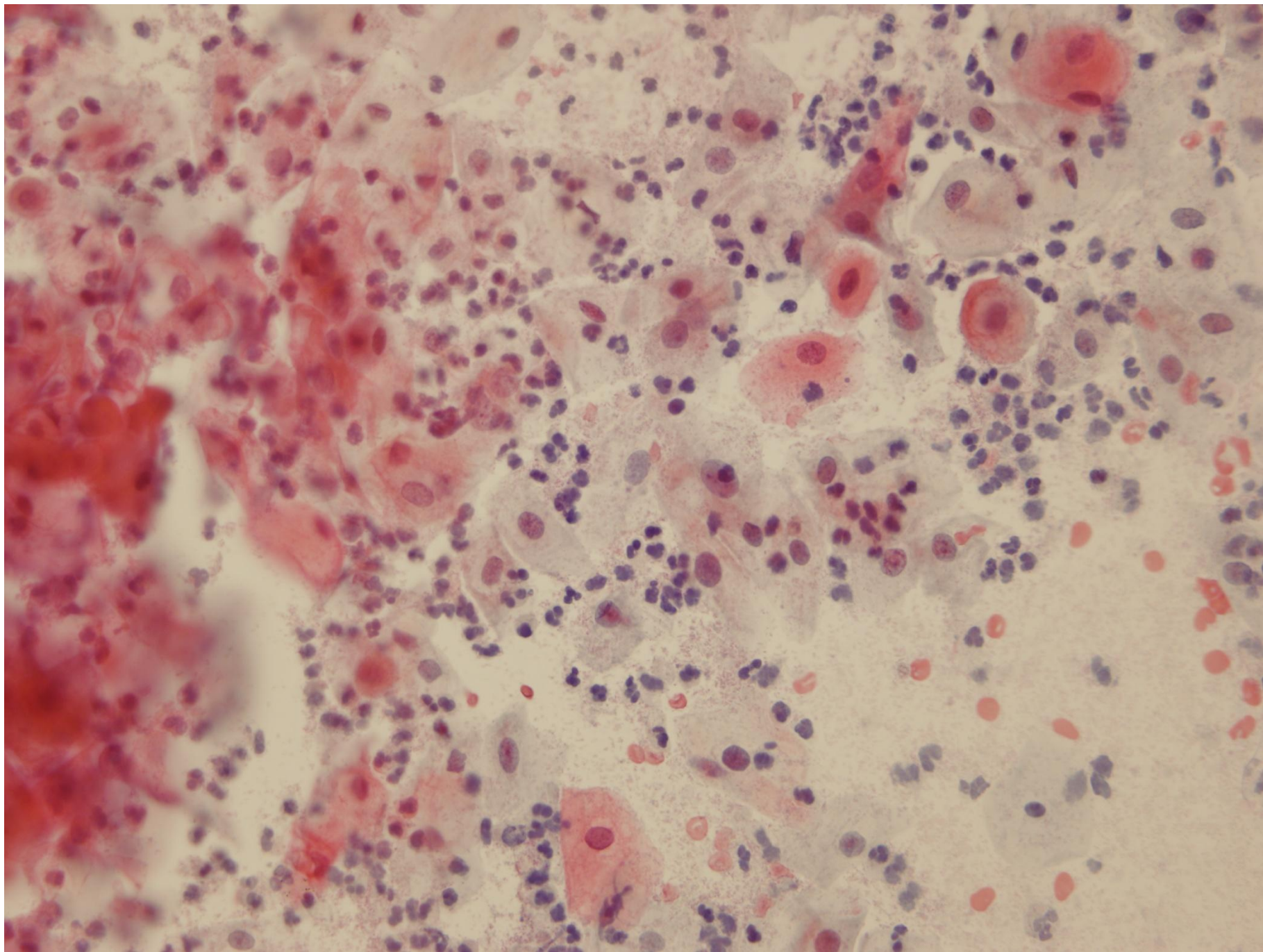
CANCER (CANCER CYTOPATHOLOGY) October 25, 2004, Ruba at all).

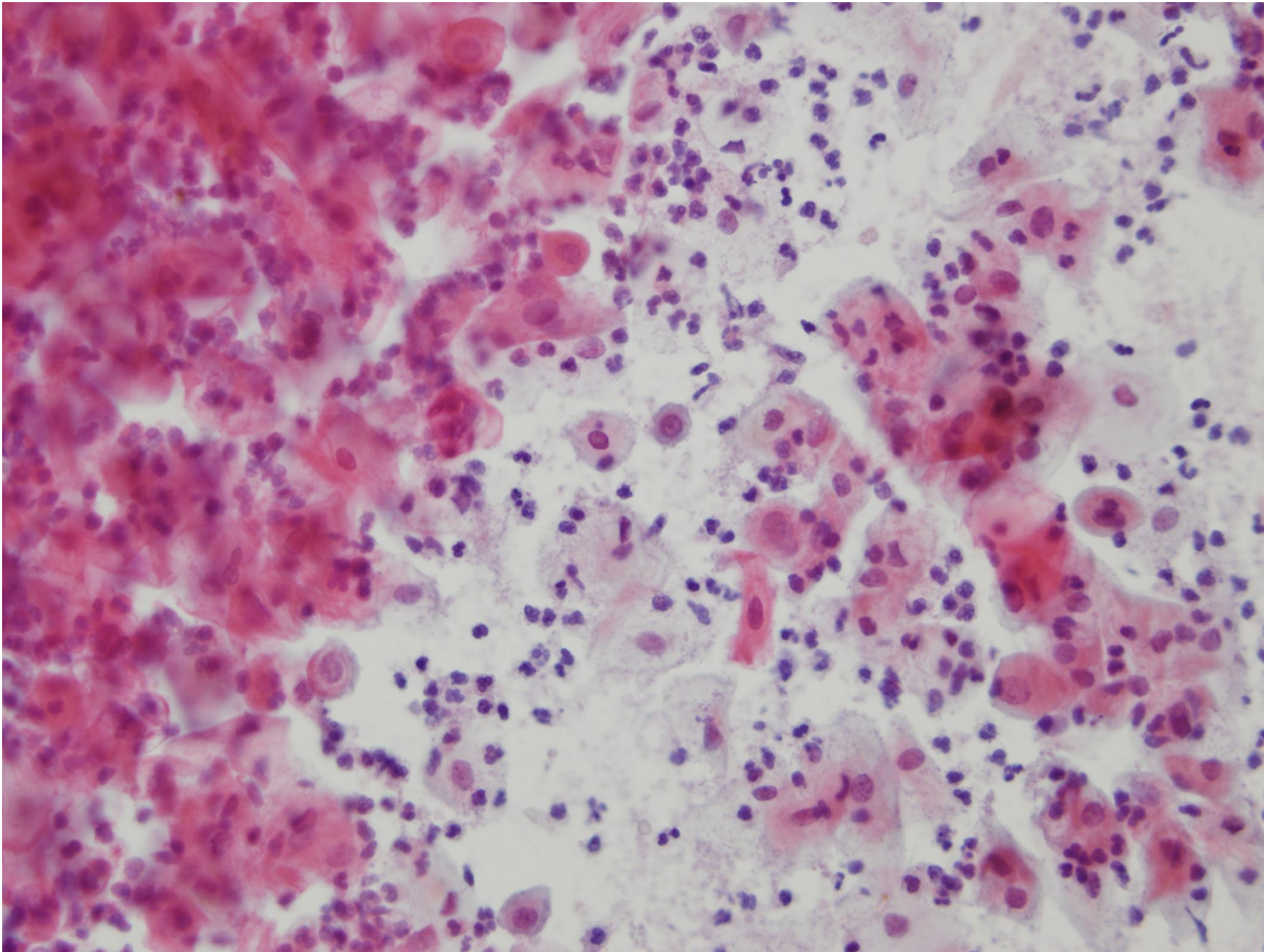


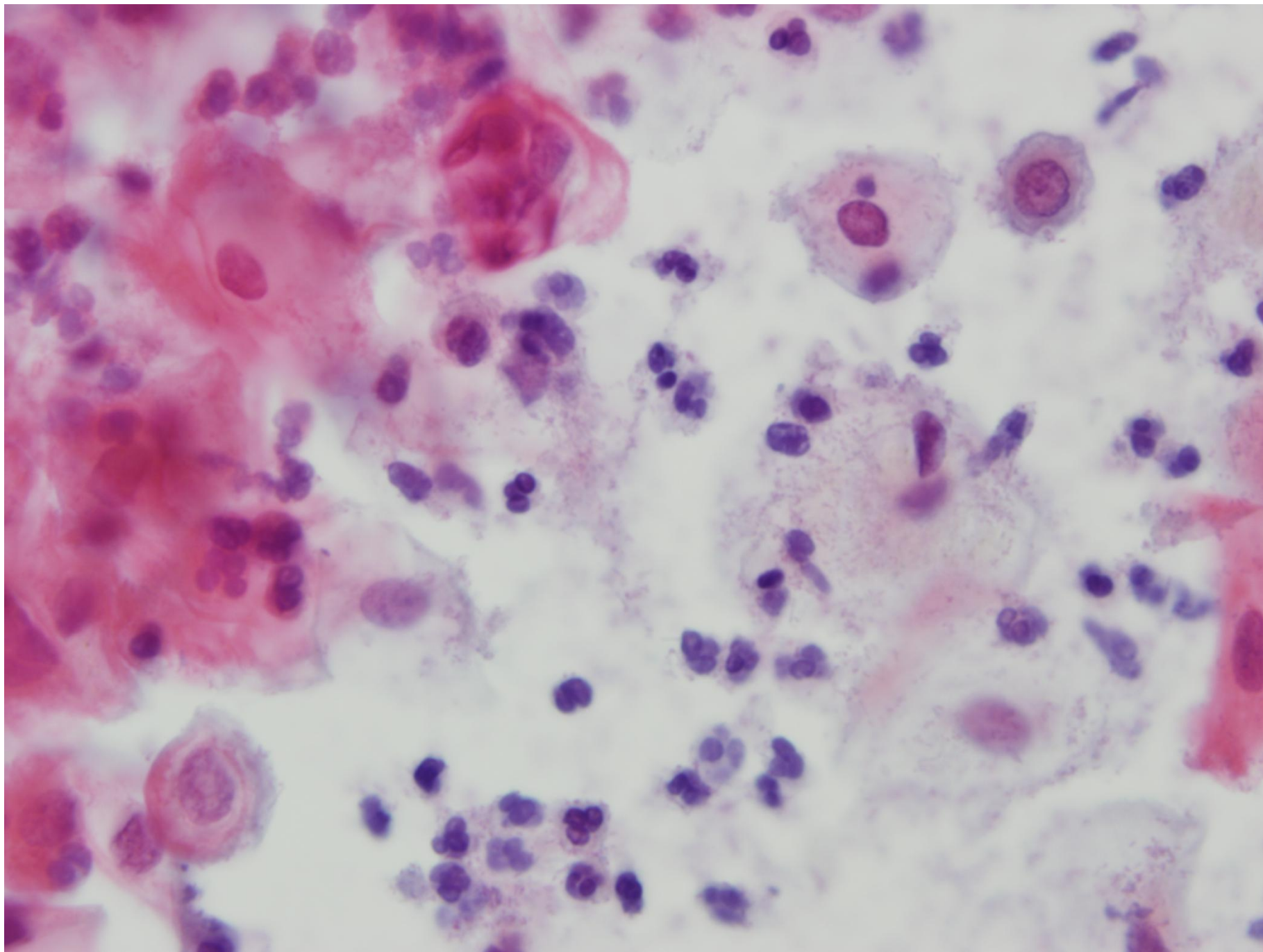
Case #1

- 57 old women, in menopause (6 years)
- Substitutional hormonal therapy
- Not regularly checked PAP-smear





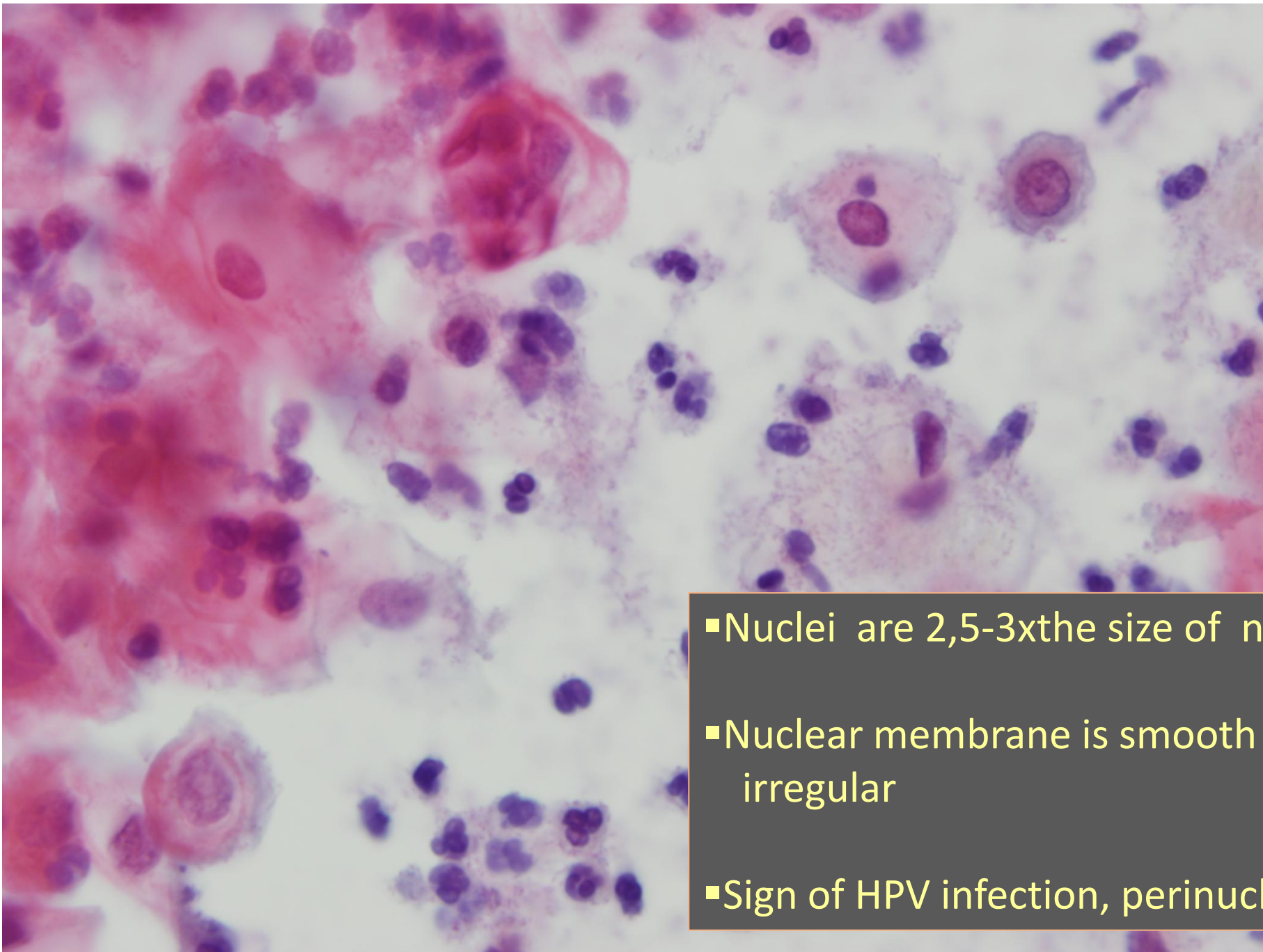




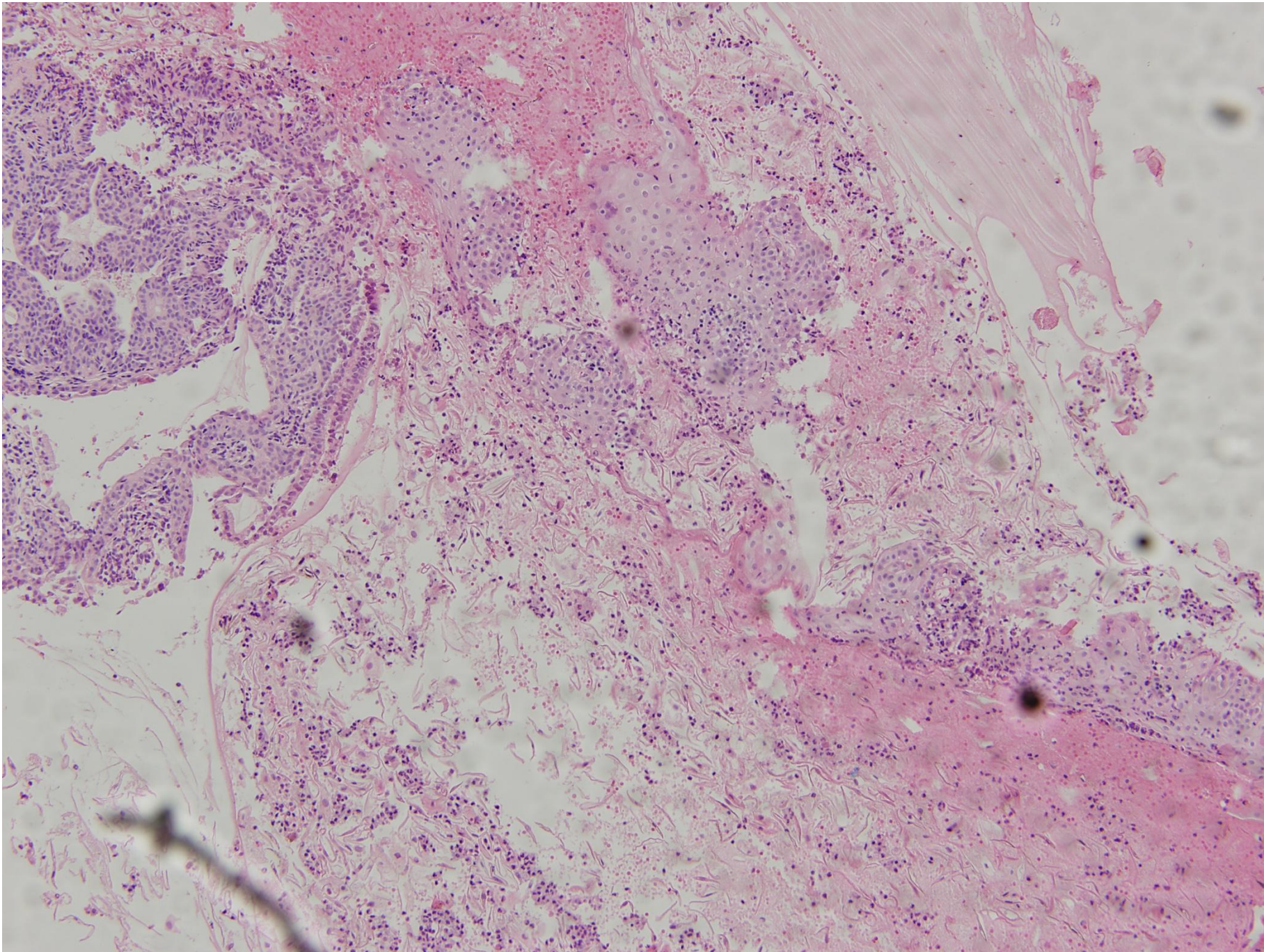


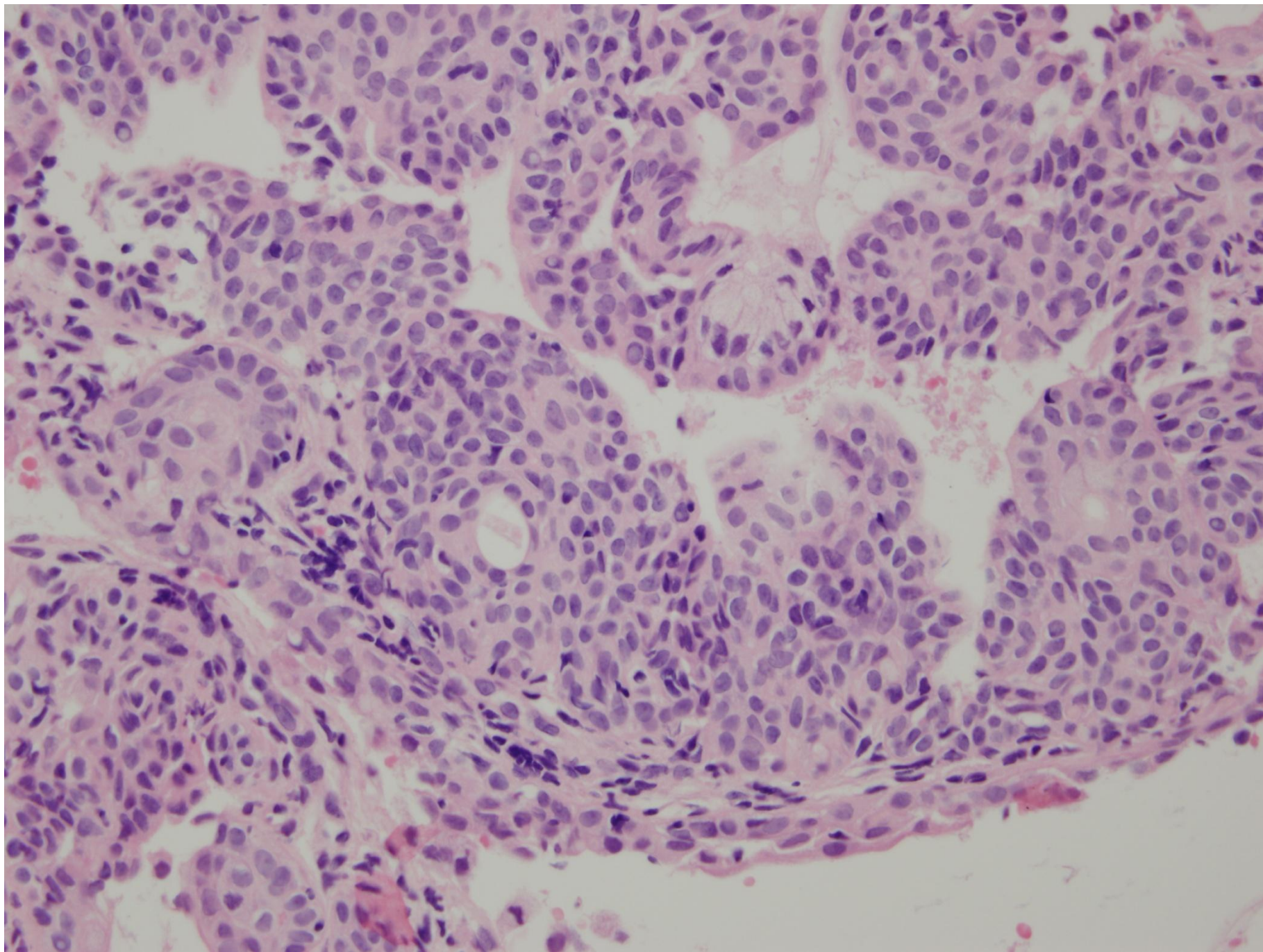
What is PAP smear result?

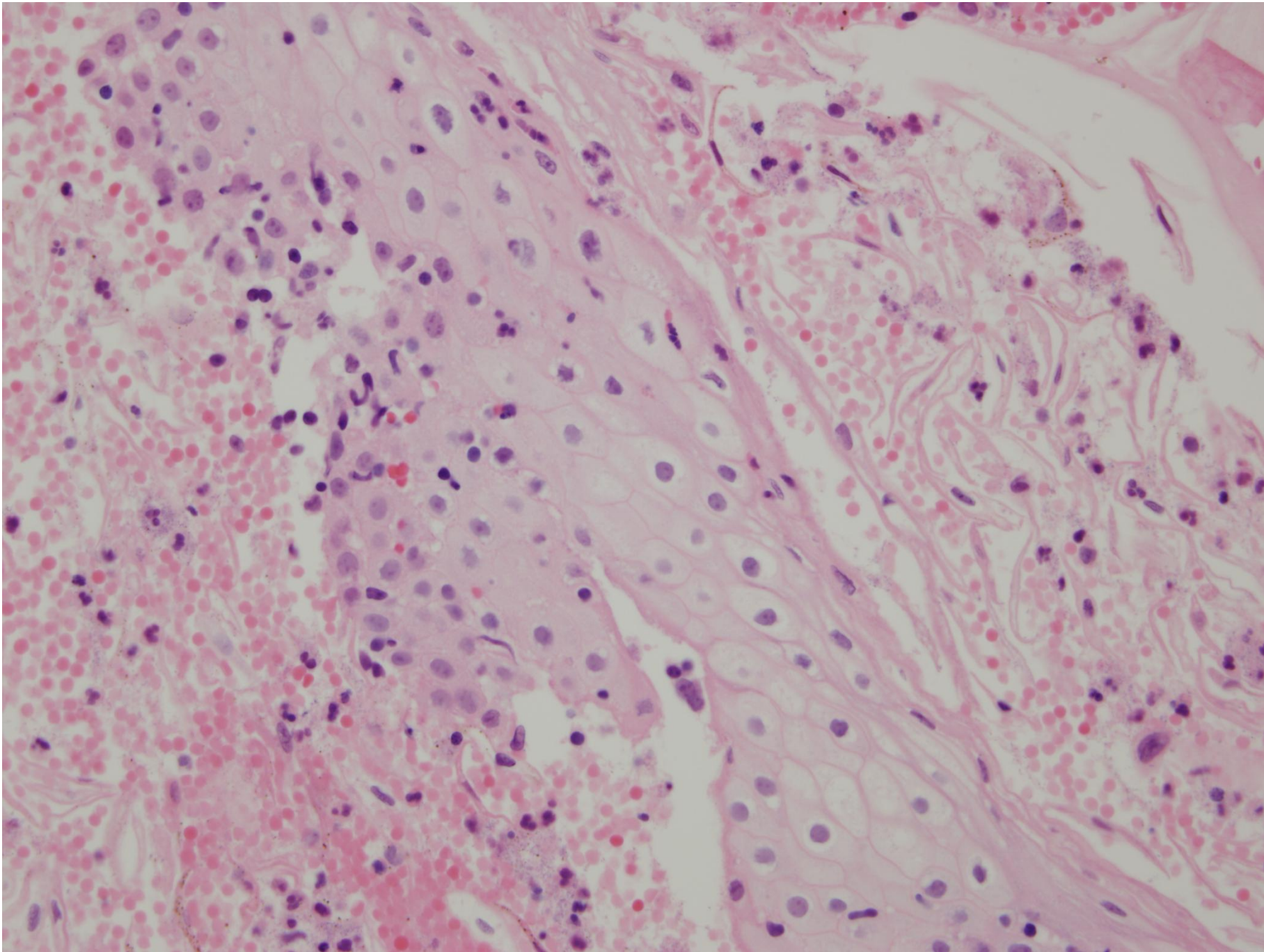
- ASCUS –probably neoplastic, LGSIL

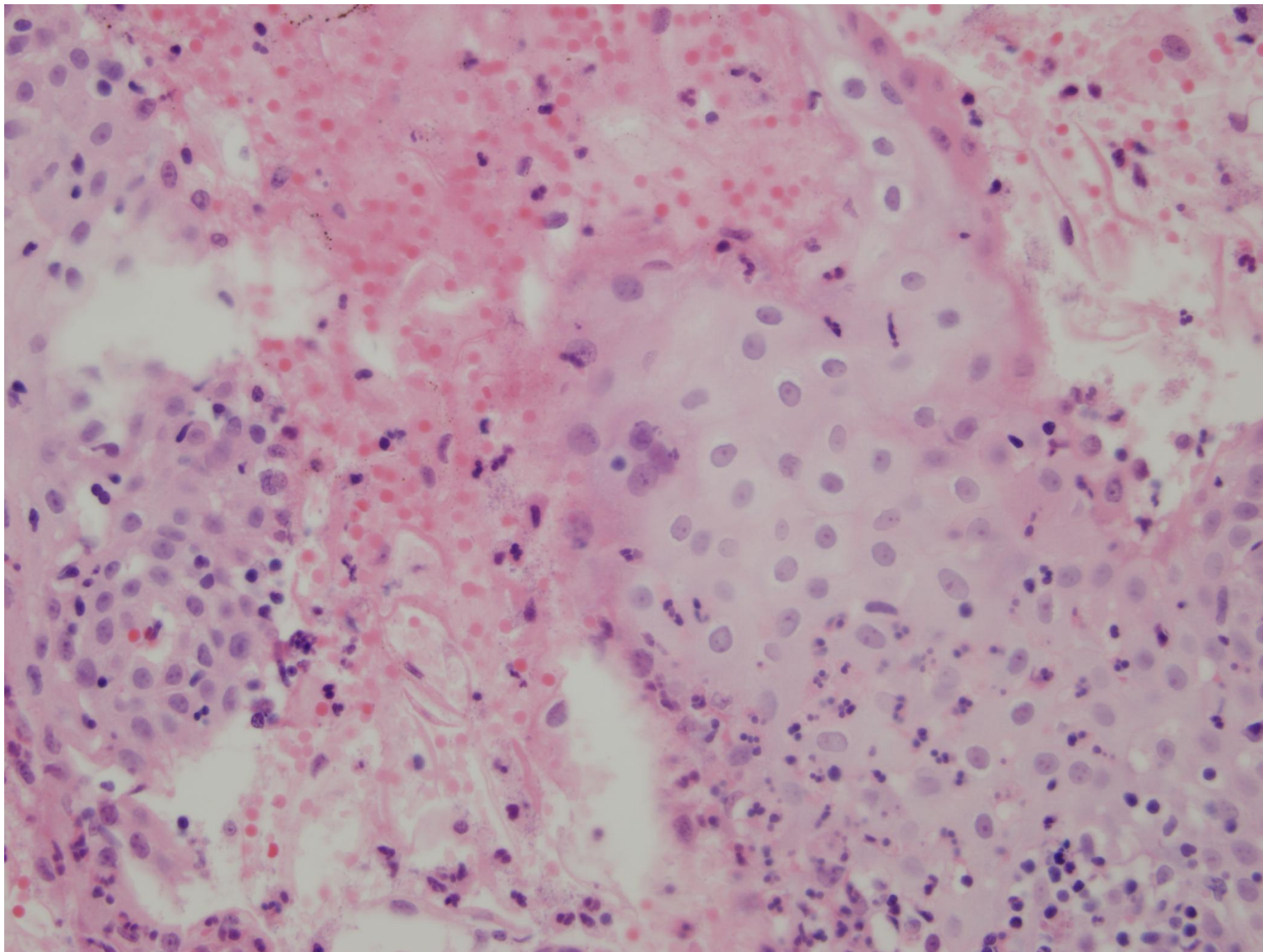


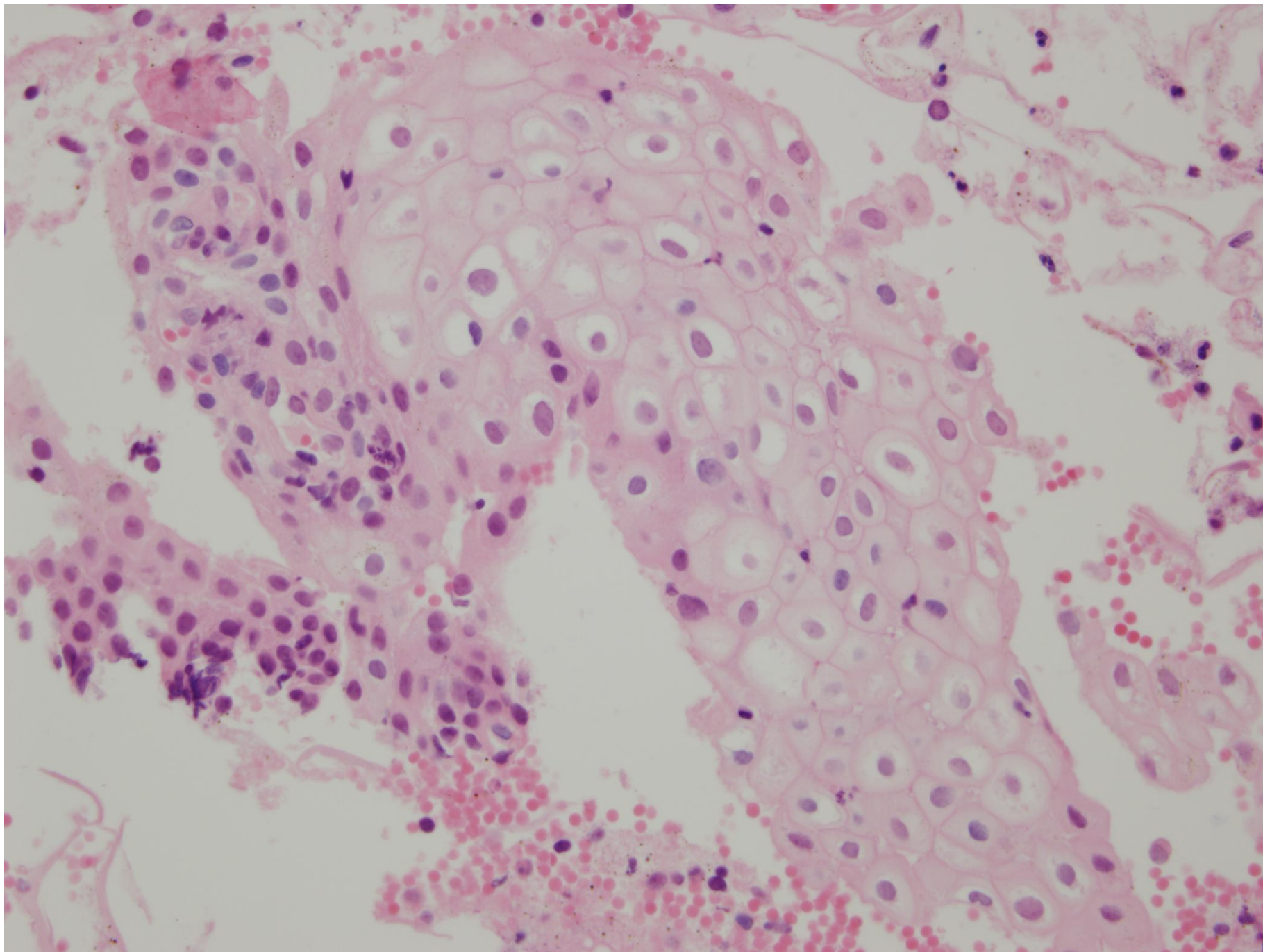
- Nuclei are 2,5-3x the size of normal IMC
- Nuclear membrane is smooth to slightly irregular
- Sign of HPV infection, perinuclear halo







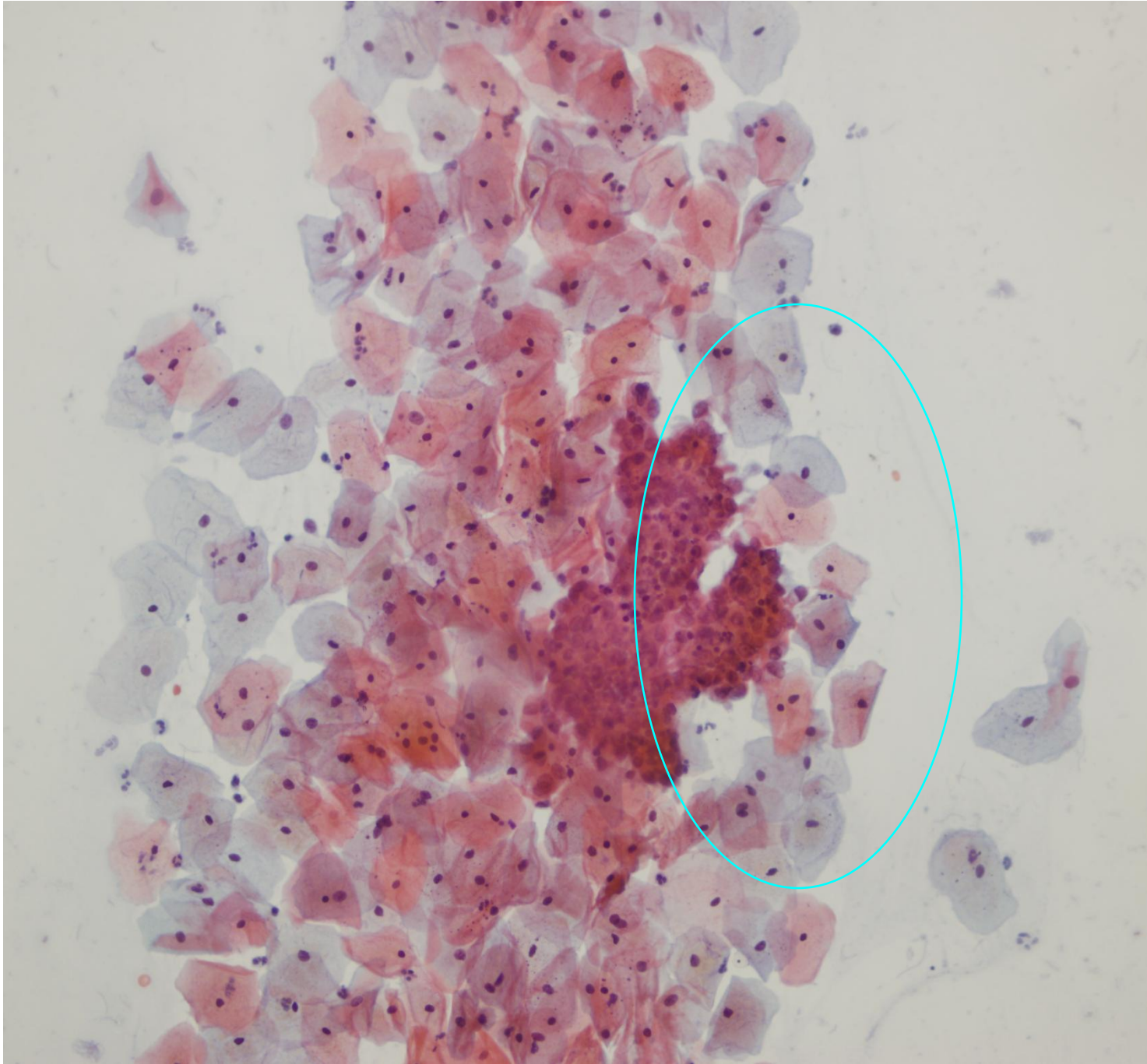


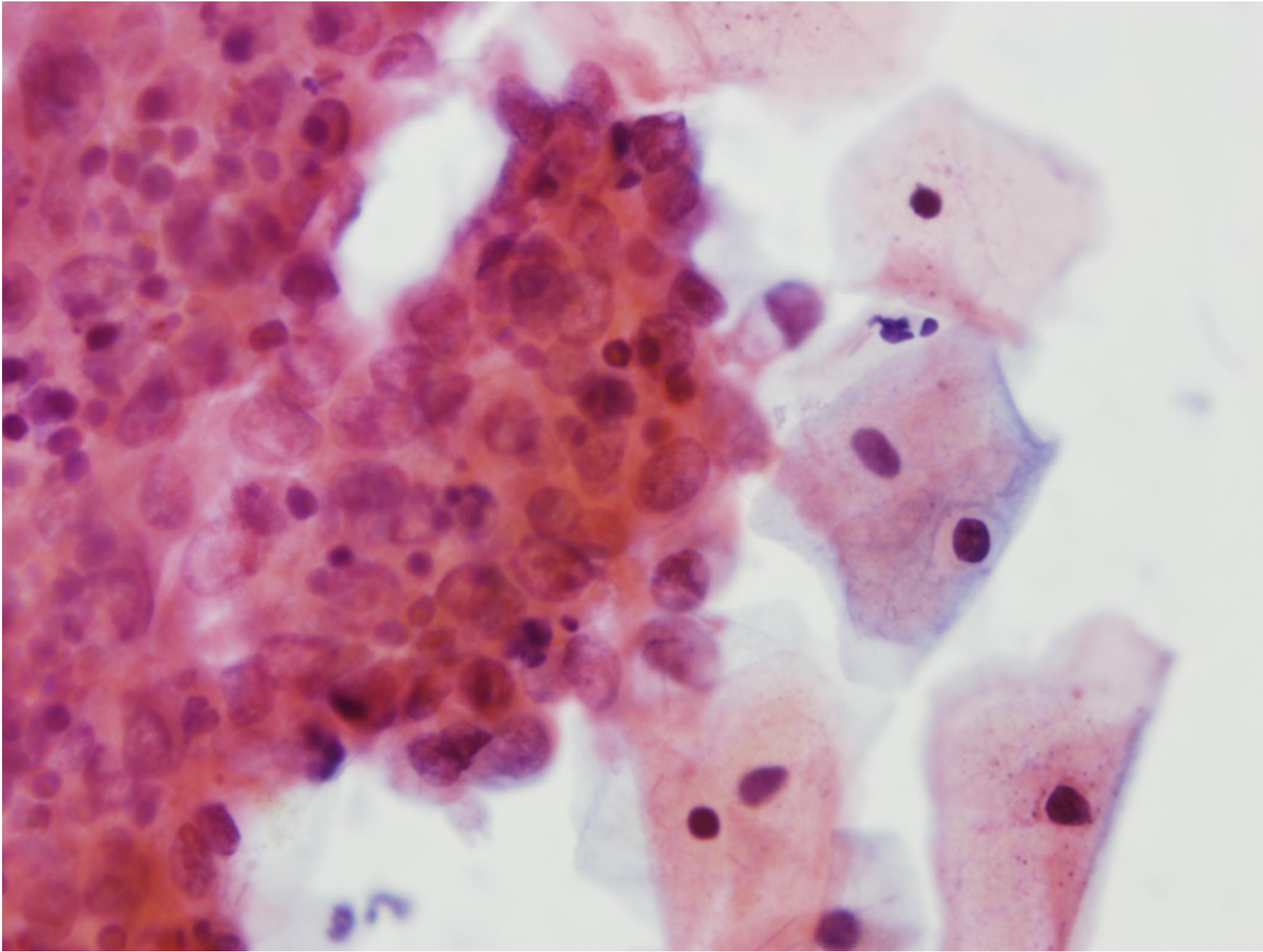


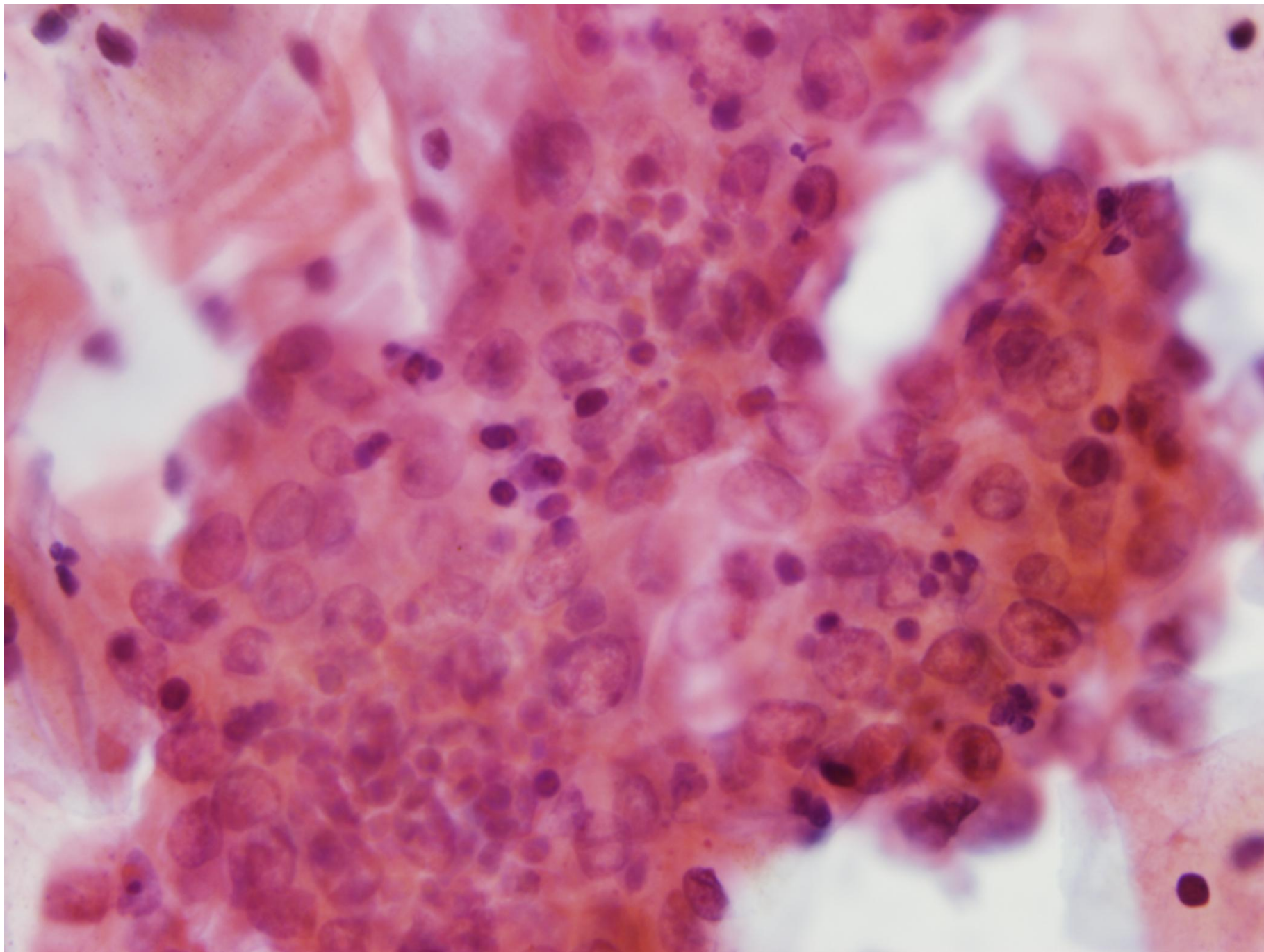


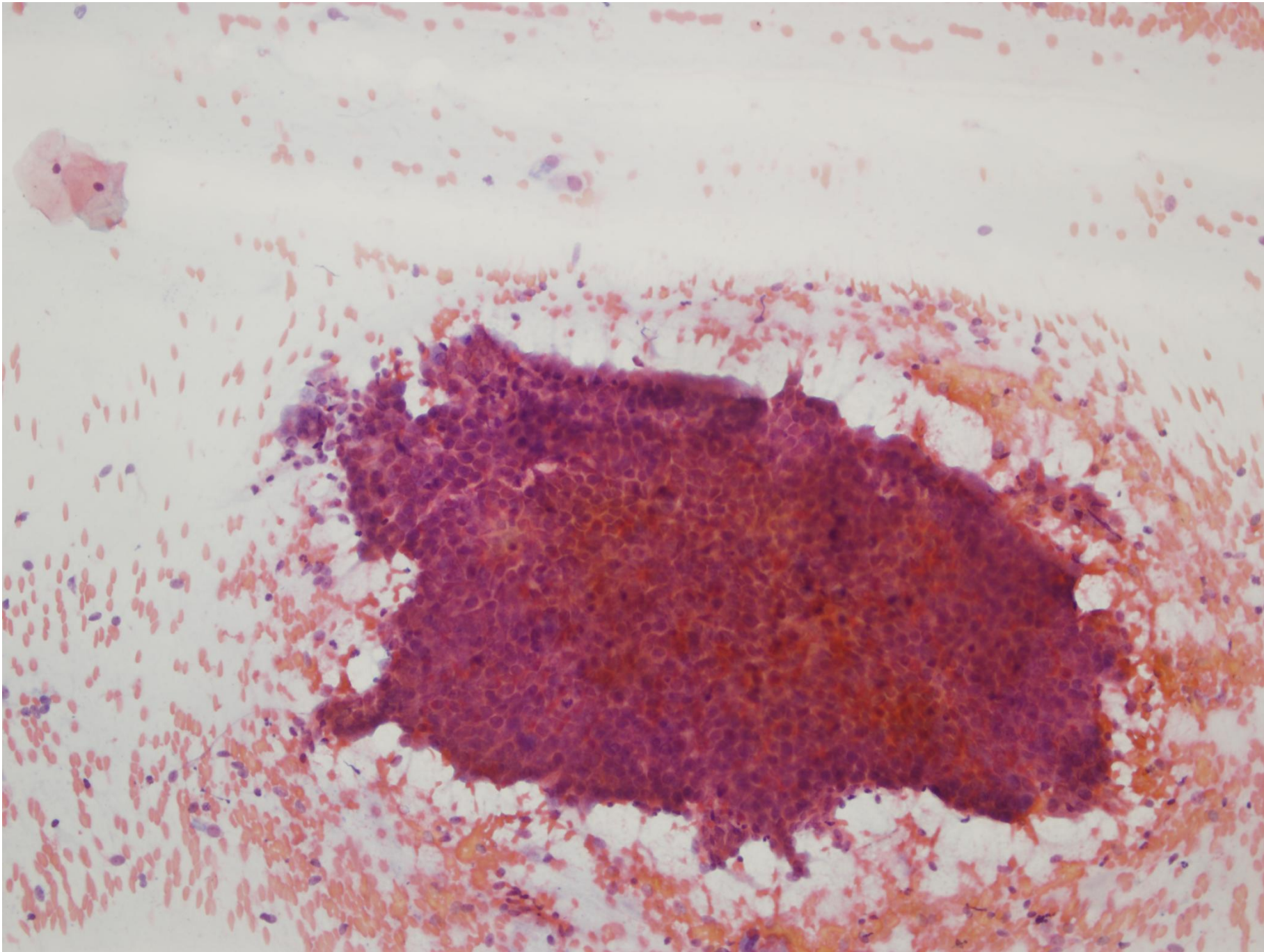
Case # 2

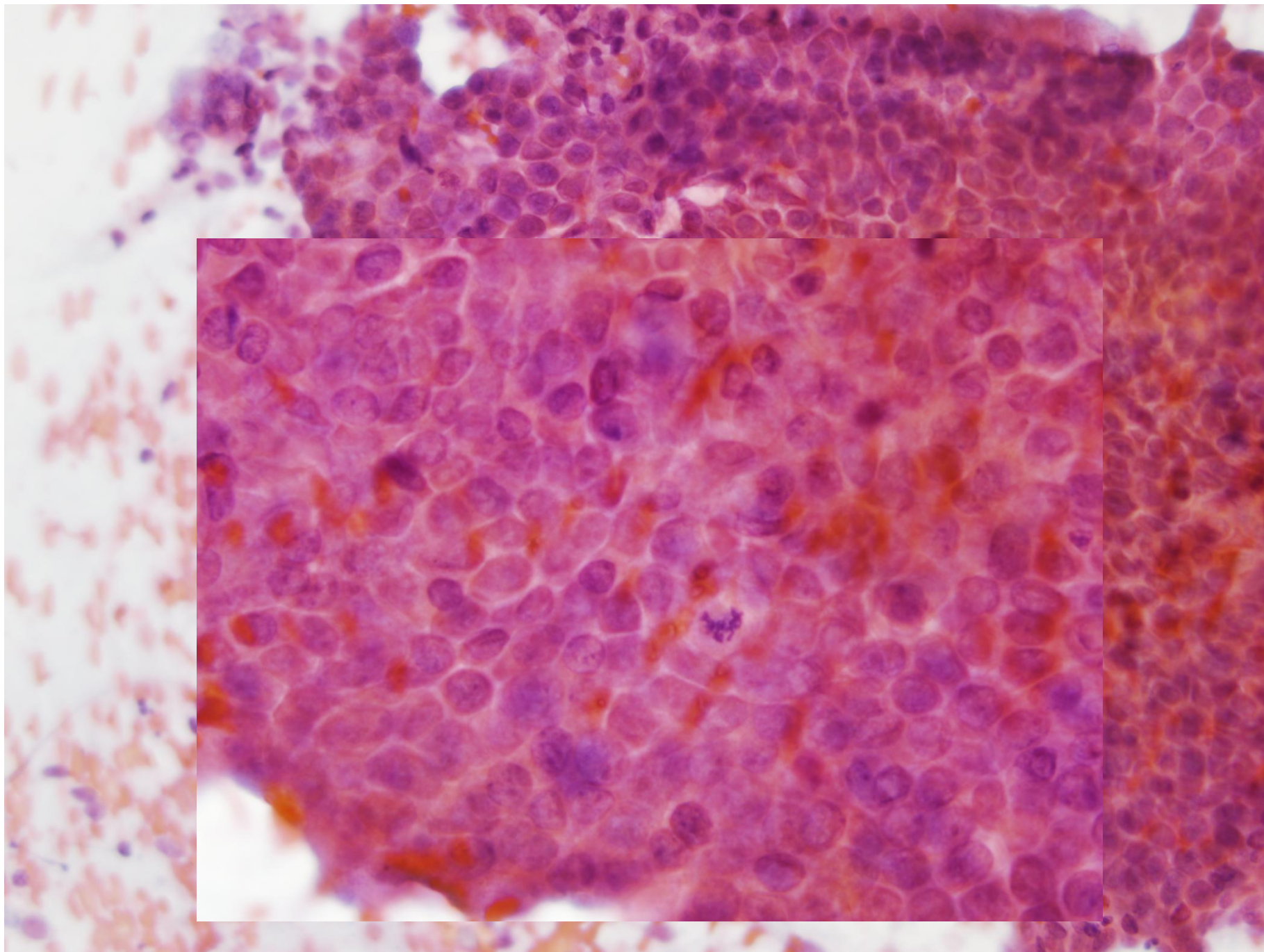
- ✓ Young women, 1978,
- ✓ Conisation 2 years ago; CIS
- ✓ Cin 2 close to the resection margins
- ✓ PAP smear regularly checked













PAP test result:

•HGSIL –CIN 3



Problematic HSIL patterns

- Syncytium-like aggregates / hyperchromatic crowded groups
- Tight clusters should be examined with care for cytomorphologic features of HSIL
 - Mitoses may be seen within these clusters
 - Flattening at the edge of the groups, whorling in the center and lack of glandular architectural features favor HSIL over glandular abnormality
- HSIL with endocervical gland involvement
 - Nucleoli may be seen in HSIL within glands
 - May have peripheral palisading of cells and nuclear pseudostratification (features usually seen in glandular lesions)
 - Central cells with spindling or whorling and flattening of the nuclei at the edge of the clusters favor HSIL over glandular origin
- HSIL resembling endometrial cells and repair
 - Small cells with degenerated nuclei showing pyknosis and scant cytoplasm, resembling shedding endometrial cells
 - Cells with more abundant cytoplasm and may have elongated taffy pull cytoplasmic appendages, enlarged nuclei and prominent nucleoli, resembling repair

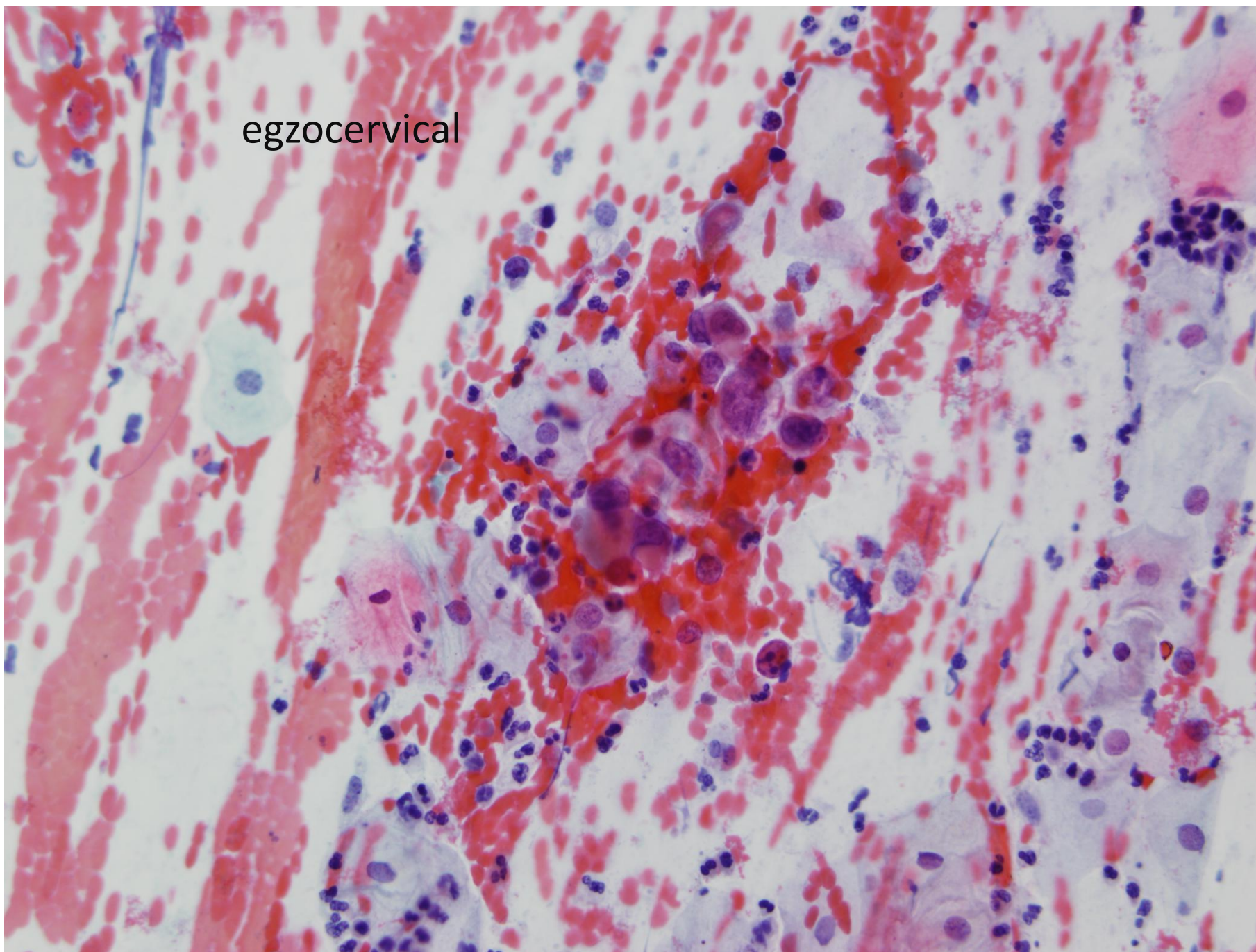


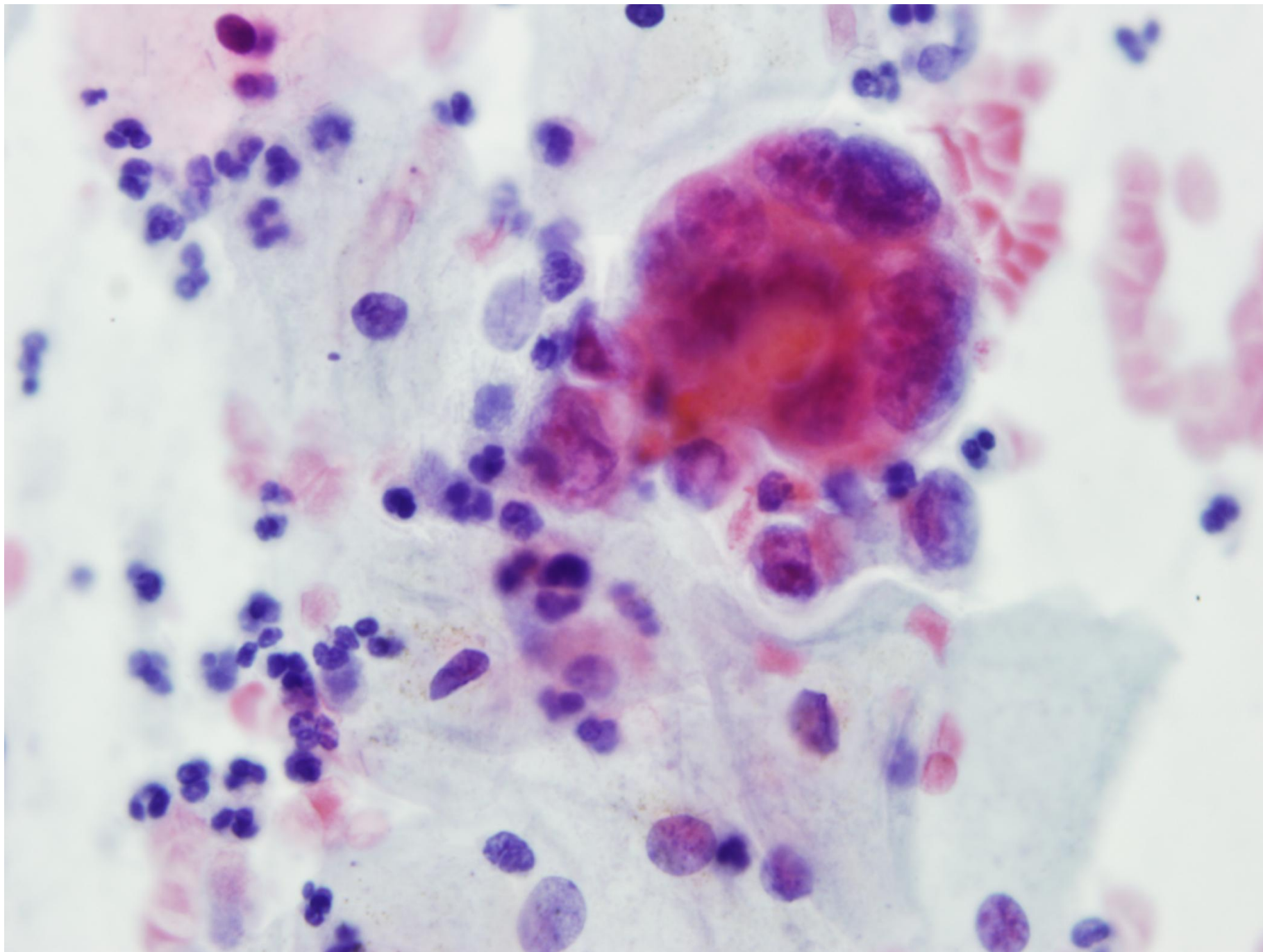
Case #3

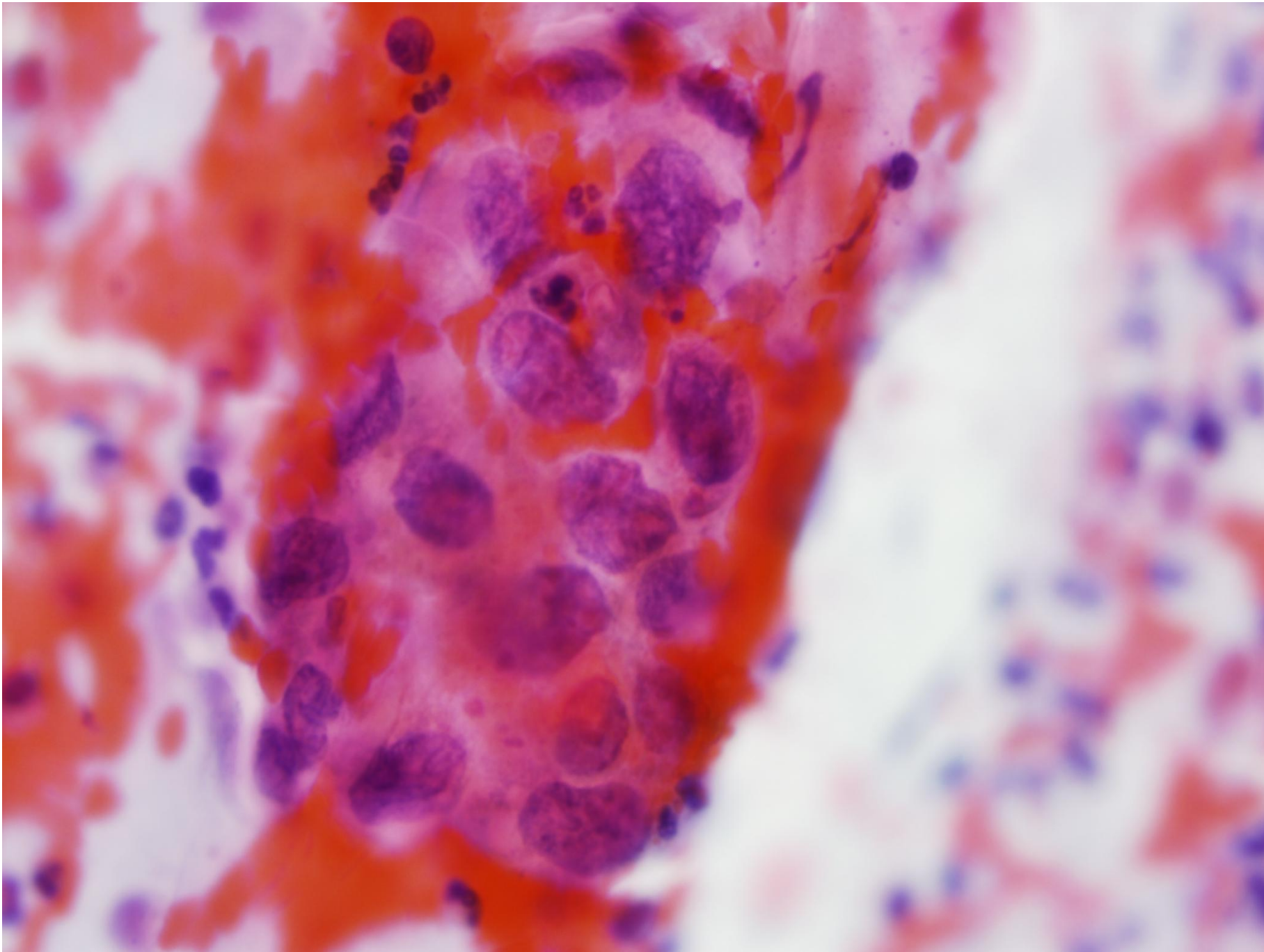
- ✓ 64 years old women
- ✓ Menopause in the age of 38
- ✓ On colposcopy: ectopia, ON, inflammation
- ✓ PAP smear – thick smear, lot of Erythrocyte

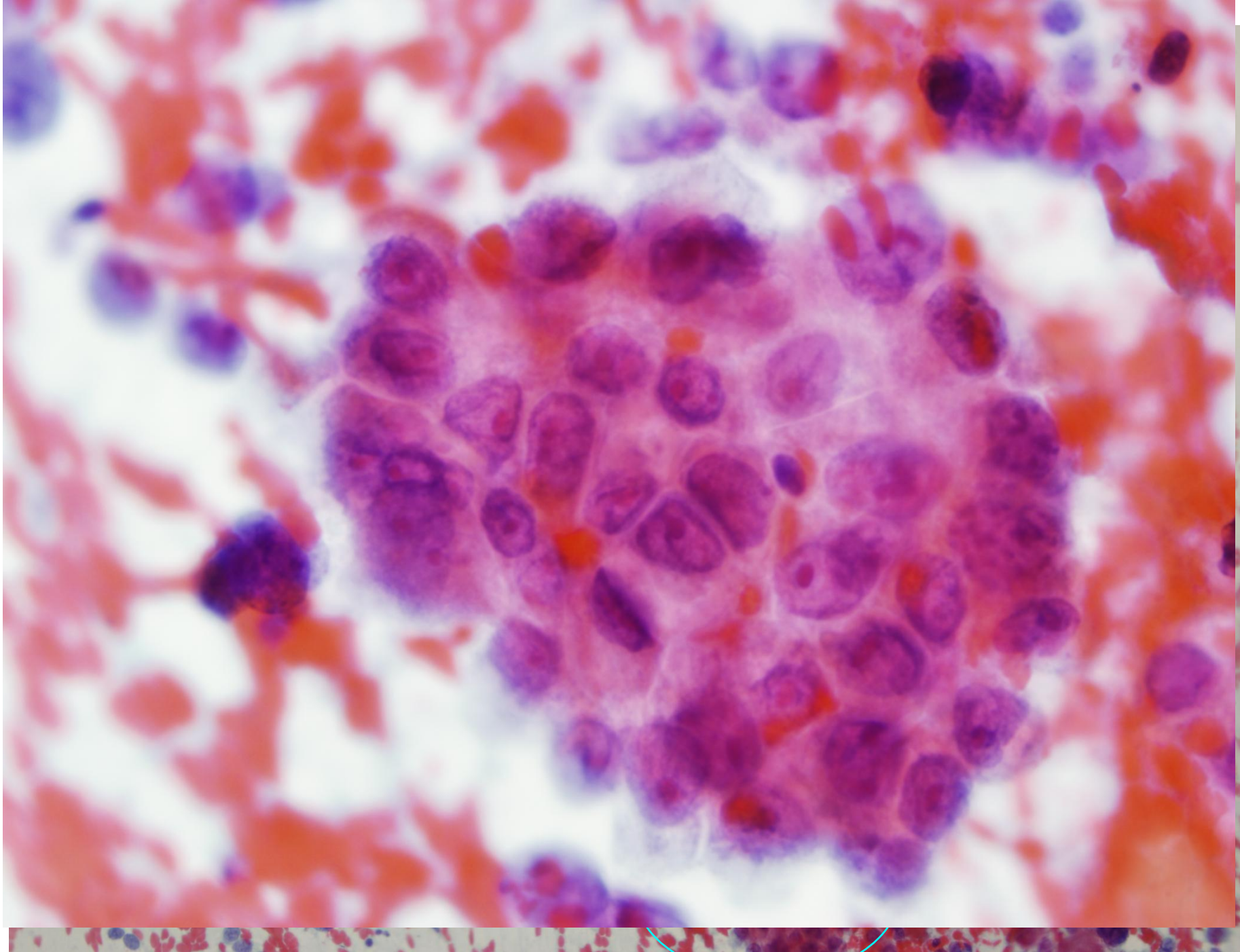


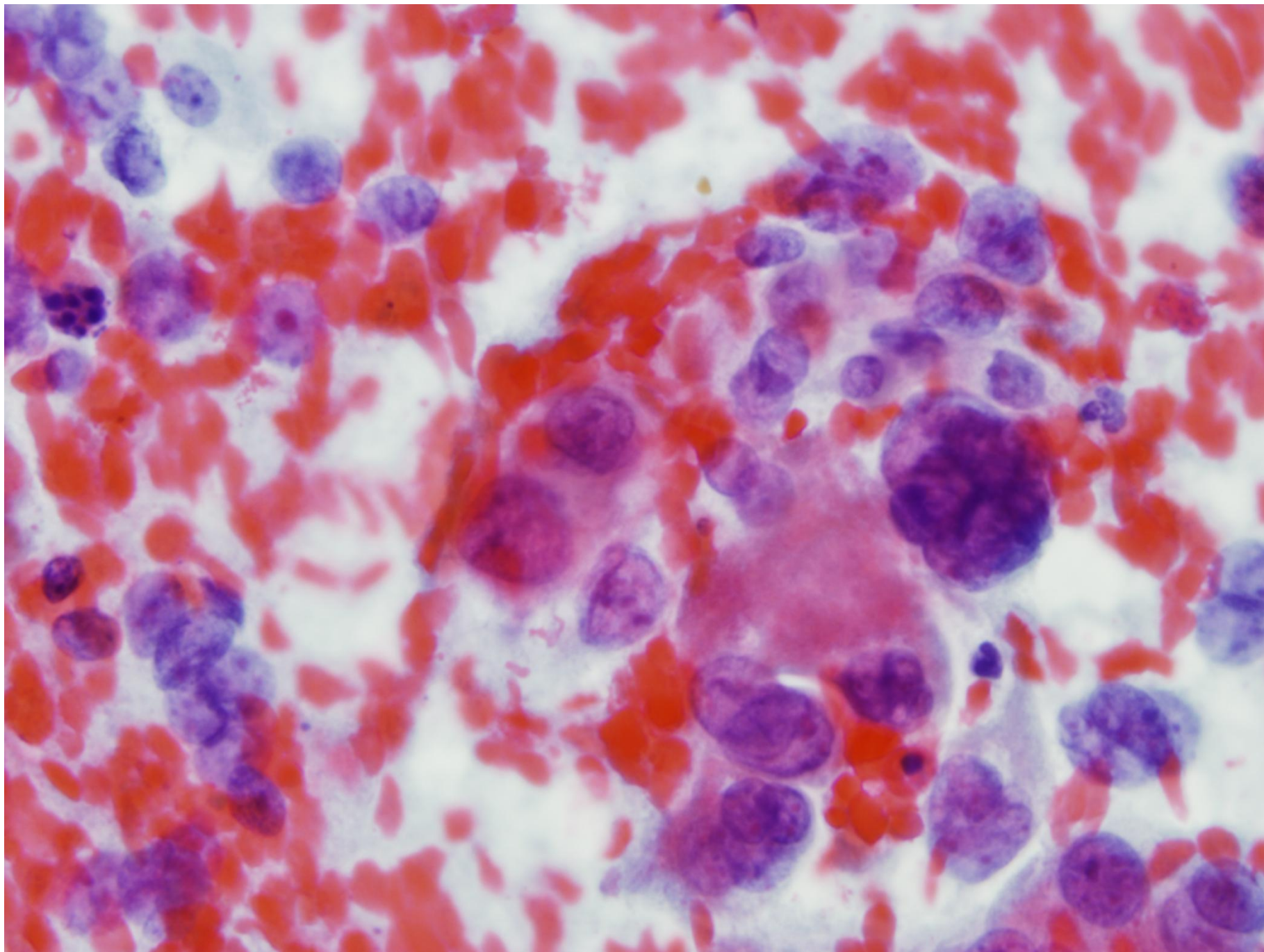
egzocervical













PAP test result:

- AGUS/neoplastic

PhDg: Adenocarcinoma



To be or not to be!



The awareness of pitfalls in cervical cytology, and the knowledge of mimics and differential diagnosis is crucial for cytotechnologists and cytopathologists to minimize errors.

However, on the institutional level, cytology laboratory quality assurance (QA) protocols must be implemented, following national or international recommendations.



Panonian lakes Tuzla

Wojtyla C, Ciebiera M, Kowalczyk D, Panek G. **Cervical Cancer Mortality in East-Central European Countries.** Int J Environ Res Public Health. **2020 Jun 28**;17(13):4639. doi: 10.3390/ijerph17134639. PMID: 32605159; PMCID: PMC7369878.

The study by Arbyn et al. also investigated mortality trends in Bosnia and Herzegovina (1985–1990), as well as Serbia, Montenegro (1995–2000), and Albania. Women's mortality increased in the group under 44 years in Bosnia and Herzegovina, Serbia and Montenegro, but decreased in all other age groups.

Bruni L, Serrano B, Roura E, Alemany L, Cowan M, Herrero R, Poljak M, Murillo R, Broutet N, Riley LM, de Sanjose S. **Cervical cancer screening programmes and age-specific coverage estimates for 202 countries and territories worldwide: a review and synthetic analysis.** Lancet Glob Health. **2022 Aug**;10(8)

VIA as primary screening test†	41 (29%)	1 (2%)	13 (28%)	18 (72%)	9 (75%)
Recommended ages and interval for VIA screening§					
Age 29 years and younger	17/41 (41%)	0	5/13 (38%)	8/18 (44%)	4/9 (44%)
Every 1–2 years	1/17 (6%)	0	1/5 (20%)	0	0
Every 3 years	11/17 (65%)	0	4/5 (80%)	5/8 (63%)	2/4 (50%)
Every 4 years or more	2/17 (12%)	0	0	2/8 (25%)	0
Age 30–49 years	38/41 (93%)	0	13/13 (100%)	16/18 (89%)	9/9 (100%)
Every 1–2 years	3/38 (8%)	0	2/13 (15%)	1/16 (6%)	0
Every 3 years	17/38 (45%)	0	8/13 (62%)	7/16 (44%)	2/9 (22%)
Every 4 years or more	14/38 (37%)	0	3/13 (23%)	7/16 (44%)	4/9 (44%)
Age 50 years and older	18/41 (44%)	0	5/13 (38%)	9/18 (50%)	4/9 (44%)
Every 1–2 years	0	0	0	0	0
Every 3 years	9/18 (50%)	0	3/5 (60%)	5/9 (56%)	1/4 (25%)
Every 4 years or more	6/18 (33%)	0	2/5 (40%)	3/9 (33%)	1/4 (25%)
Underserved populations	4/41 (10%)	1/1 (100%)	2/13 (15%)	1/18 (6%)	0
Screen and treat strategy with VIA	31/41 (76%)	0	7/13 (54%)	16/18 (89%)	8/9 (89%)

HPV=Human papillomaviruses. VIA=visual inspection with acetic acid. *Partial implementation in United Arab Emirates (Abu-Dhabi). †Variability among country regions in Belgium, Canada, and Spain. Organised programmes in small regions in Greece not included. ‡Including introduction of modifications in the recommended primary tests, modifications to ages to start and end screening, and modifications to screening interval. §No information was available about the year of introduction of current recommendations in 19 countries (Bosnia and Herzegovina, Cyprus, Monaco, Guinea, Antigua and Barbuda, The Bahamas, Bermuda, Dominican Republic, Grenada, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Trinidad and Tobago, Venezuela, Cook Islands, Vanuatu, Bahrain, North Korea, and Timor-Leste), about the recommended screening interval for cytological screening in seven countries (Albania, Cyprus, Dominica, Cook Islands, Vanuatu, Iran, and Syria), and about the recommended screening interval for VIA screening in six countries (Guinea, Madagascar, Mozambique, Bolivia, Panama, and Timor-Leste). ¶Combined with other main screening tests or alone. ||Including countries that are transitioning to HPV as the main test. Not including countries that reported plans in 2019 for introduction of HPV-based screening by 2024 (Canada, New Zealand, Belgium, Belarus, Japan, and Trinidad and Tobago).

Table 1: Main characteristics of cervical cancer screening in 139 countries with documented official recommendations