

Chapter

1

The Pap Smear

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Introduction

The Pap Smear

History

- Cervical cytology was first reported by Dr. Georgios Papanicolaou in 1928
- Implementation of The Bethesda system (TBS) for reporting cervical cytology in 1988
- Published cervical cytology TBS atlas (2014, 2004, and 1994)

Sample preparations

- Conventional Pap smears
- Liquid-based cytology (LBC)
 - ThinPrep (use methanol-based fixative, 20 mm diameter circle)
 - SurePath (use ethanol-based fixative, 13 mm diameter circle)

Adequacy

Only the well-visualized and well-preserved nucleated squamous or squamous metaplastic cells are counted

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- General population:
 - Conventional Pap smears: > 8,000–12,000 cells
 - LBC: > 5,000 cells
- With history of radiation, chemotherapy, trachelectomy, or hysterectomy: >2,000 cells
- Transformation zone sampling:
 - Presence of >10 well-preserved endocervical or squamous metaplastic cells
 - Report for quality assurance purpose
 - Not required for adequacy

Reporting

- Follow the recommendations set forth by the most current edition of *The Bethesda System for Reporting Cervical Cytology* (2014)

Cervical Cancer Screening

Screening options

Cervical cancer screening is the most successful cancer screening to date. There are three screening options

- Cervical cytology test alone
- Primary high-risk human papillomavirus (HPV) screening test alone
- Cytology and triage HPV test (cotesting)

Clinicians determine which screening test to use by following the screening and management guidelines.

Screening guidelines

The latest guidelines for cervical cancer screening by the American Cancer Society (ACS) were published in 2020, which emphasized the use of primary HPV screening test. The latest guidelines (which apply to individuals who have a cervix, regardless of their sexual history or HPV vaccination status; not applicable to individuals who have been diagnosed with a high-grade precancerous cervical lesion or cervical cancer, individuals with in utero exposure to diethylstilbestrol, or those who have a compromised immune system) include

- Recommend against screening for cervical cancer in women younger than 25 years
- Recommend screening for cervical cancer every 5 years with primary HPV screening test in women aged 25 to 65 years
- If FDA approved primary HPV screening test is not available, screening for cervical cancer every 3 years with cervical cytology alone, or every 5 years with cytology and triage HPV test (cotesting) are acceptable for women aged 25 to 65 years
- Recommend against screening for cervical cancer in women older than 65 years who have had adequate negative prior screening (2 consecutive negative HPV tests, or 2 consecutive negative cotests, or 3 consecutive negative cytology tests within the past 10 years, with the most recent test occurring within the recommended interval for the test used)

- Recommend against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion (i.e. cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer

HPV Test

HPV biology

- HPV infection is the primary cause of nearly all cervical cancer
- Over 200 types of HPV have been identified, but only about 40 types of HPV infect the genital tract
- 14 types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high risk/carcinogenic
 - HPV 16 is associated with both cervical squamous cell carcinoma and adenocarcinoma
 - HPV 18 is mainly associated with cervical adenocarcinoma
- Most HPV infections clear within two years
- Persistent infection by high risk HPV types can lead to cervical cancers
 - Viral oncoprotein E6: target tumor suppressor protein p53
 - Viral oncoprotein E7: target tumor suppressor protein pRb, and ultimately activate cell cycle S-phase genes such as p16^{INK4A}

HPV test devices

- HPV test devices are class III devices regulated by the Food and Drug Administration (FDA), and are designed to detect high risk type HPVs
- Seven HPV test devices have been approved by FDA by 2018 for atypical squamous cells of undetermined significance (ASC-US) triage and cotesting. They are:
 - Digene HC2
 - Cervista HPV HR
 - Cervista HPV 16/18 genotyping
 - Aptima HPV
 - Aptima HPV 16, 18/45 genotyping
 - Cobas HPV (including genotyping of HPV 16, 18)
 - Onclarity HPV (including genotyping of HPV 16, 18, 45)
- Two devices among these seven are approved for primary HPV screening test (Cobas and Onclarity)

Benign Findings

Endometrial Cells

Clinical Features

- May be found in the first 12 days of the menstrual cycle in premenopausal women and is considered a benign finding

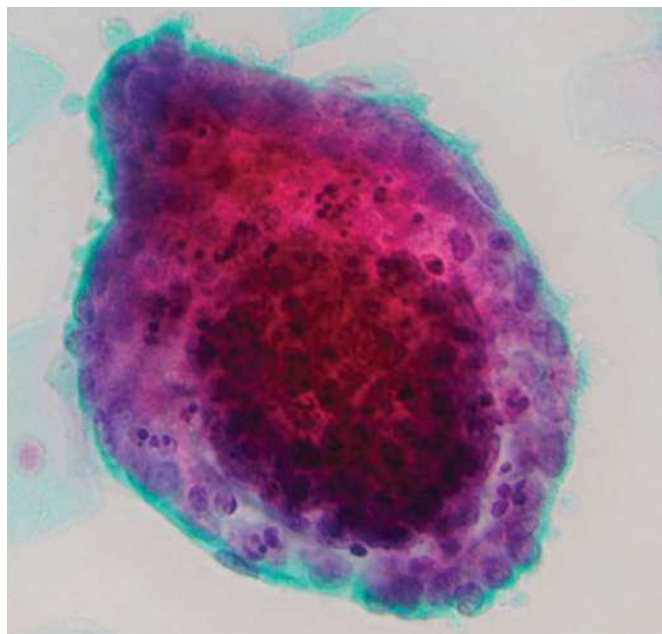


Figure 1–1. “Exodus” (Papanicolaou stain).

- Exodus pattern can be seen on days 6 to 10 of the menstrual cycle
- If the woman is ≥ 45 years of age, the presence of exfoliated endometrial cells should be reported and endometrial evaluation is recommended in postmenopausal women
- The Pap smear is generally not a sensitive test for screening lesions of the endometrium

Cytologic Features

- May be seen as a ball of cells consisting of a central core of endometrial stromal cells surrounded by a single layer of cuboidal or columnar endometrial epithelium. This structure is called “exodus” in cytology
- May be seen as singly dispersed and small clusters of cells in three-dimensional aggregates with round to oval nuclei, fine granular chromatin with or without nucleoli
- Cytoplasm is scant, can be vacuolated or lacy
- Nuclei are small and about the same size as an intermediate cell nucleus

Special Stains and Immunohistochemistry

- Noncontributory

Modern Techniques for Diagnosis

- Noncontributory

Differential Diagnosis

- Well-differentiated endometrial adenocarcinoma
 - Usually occurs in post-menopausal women or in patients with unopposed estrogen therapy
 - Enlarged nuclei with cytologic atypia

- High-grade squamous intraepithelial lesion (HSIL)
 - Coarse chromatin and dense cytoplasm in varying degrees of keratinization
- Histiocytes
 - Usually have moderate amount of cytoplasm and folded nucleus

Pearls

- When singly dispersed, can mimic HSIL

Arias–Stella Change of Pregnancy

Clinical Features

- Clinical history of pregnancy is present
- Very early post-partum changes can also present with Arias–Stella changes in the epithelial and stromal cells, which can be interpreted as atypical glandular cells, not otherwise specified.

Cytologic Features

- Nuclear atypia of degenerative type, including marked nuclear enlargement, smudgy chromatin, pleomorphic nuclei, and prominent nucleoli
- The nuclear to cytoplasmic (N/C) ratio is variable and could be increased
- No or rare mitotic figures

Special Stains and Immunohistochemistry

- CD10 may be helpful in the differentiation between Arias–Stella changes versus a clear cell carcinoma of gynecological tract (negative in the latter); however, Napsin A can be positive in both

Modern Techniques for Diagnosis

- Noncontributory

Differential Diagnosis

- Clear cell adenocarcinoma of Müllerian origin: maybe cytologically difficult to differentiate and may present in young women, therefore, a tissue biopsy and serum β -hCG levels would be necessary to exclude one from the other
- Radiation effect: a history of radiation or pregnancy are the main differentiating factors

Pearls

- Clinical history of recent pregnancy is of paramount importance

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- May be the first presenting finding in a young woman with a tubal or extrauterine pregnancy, such that a serologic β -hCG level may be necessary
- May also be the first presenting finding in women with molar pregnancies
- Can also be seen in patients taking phytoestrogens

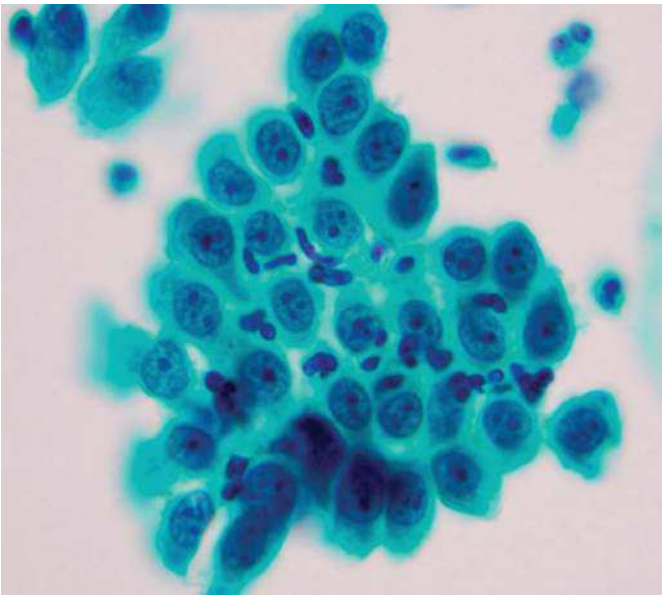


Figure 1-2A. Reactive changes with neutrophils (Papanicolaou stain).

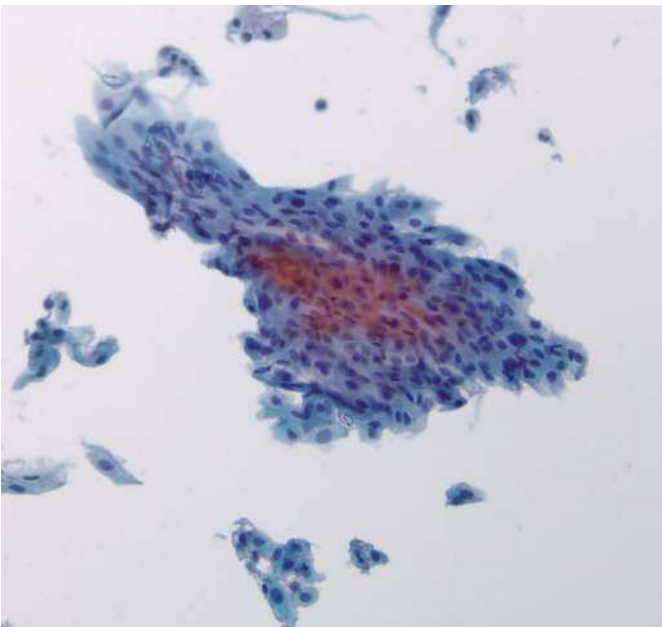


Figure 1-2B. Reactive changes due to atrophy (Papanicolaou stain).

Reactive changes associated with inflammation

Clinical Features

- Could be due to numerous infectious processes such as *Trichomonas*, bacterial vaginosis, *Chlamydia*, gonorrhea, HPV, *Candida*, and herpes
- Usually treated clinically and followed up with repeat Pap smear
- Most cases are symptomatic

Cytologic Features

- A prominent or subtle neutrophilic exudate
- Maybe associated with common infectious processes: *Candida*, *Trichomonas*, *Gardnerella vaginosis*, etc.
- Cells are commonly found in cohesive sheets and tile-like or honeycomb configuration
- Nuclei are enlarged ($1-1.5 \times$ the size of an intermediate cell nucleus), can be binucleated, nuclear outlines are round, smooth and uniform, vesicular and hypochromatic to mildly hyperchromatic

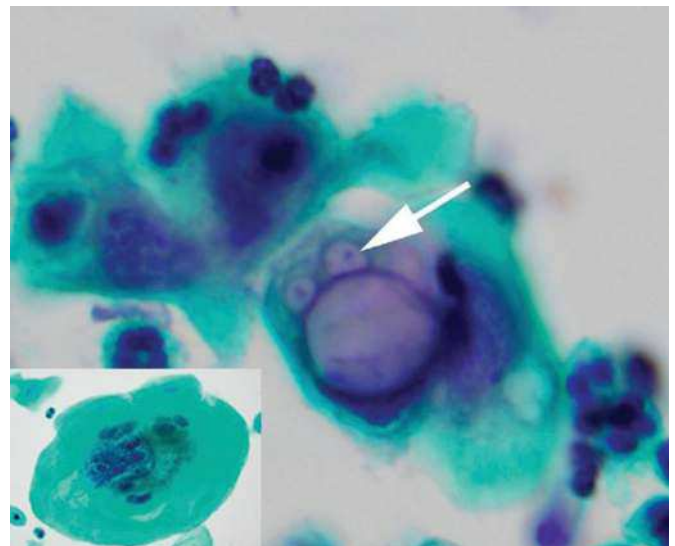


Figure 1-2C. Reactive changes due to radiation (Papanicolaou stain).

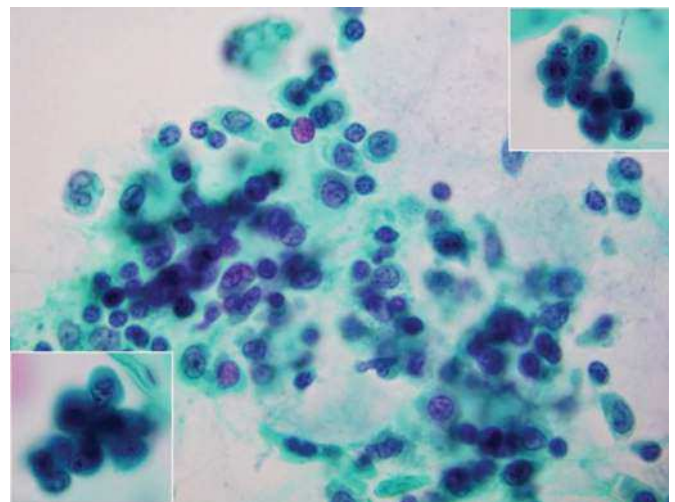


Figure 1-2D. Reactive changes due to IUD. (insets are reactive endometrial cells) (Papanicolaou stain).

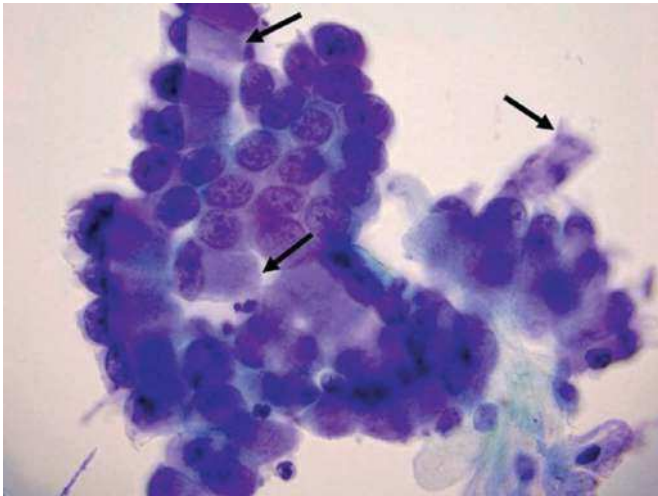


Figure 1-2E. Tubal metaplasia. (Papanicolaou stain).

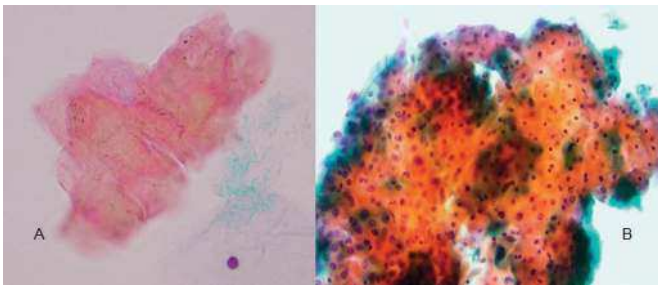


Figure 1-2F. Hyperkeratosis (A) and Parakeratosis (B). (Papanicolaou stain).

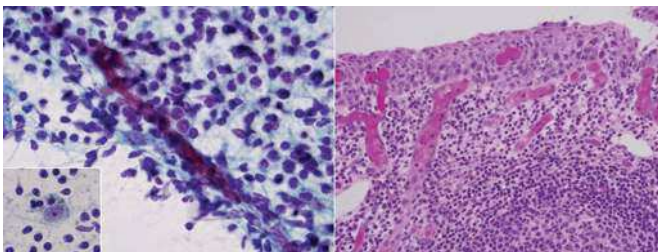


Figure 1-2G. Lymphocytic cervicitis. (Papanicolaou stain).

- Multiple or single nucleoli in most of the cells
- May see small perinuclear halo
- Cytoplasm could be polychromatic and vacuolated

Special Stains and Immunohistochemistry

- The cytologic features of most infectious agents are well-defined and usually do not need special stains

Modern Techniques for Diagnosis

- Nucleic acid tests (NAT) for both *Chlamydia trachomatis* and *Neisseria gonorrhoeae*

Differential Diagnosis

- Atrophy with and without inflammation
 - Age >50, anovulatory syndromes, or history of bilateral oophorectomy for treatment of breast cancers

- Presence of squamous metaplastic cells or parabasal cells is more common
 - Presence of naked nuclei called “small blue cells” due to autolysis
 - Presence of rounded basophilic amorphous material called “blue blobs” (mummified parabasal cells)
 - Presence of granular or degenerated background
 - +/- pseudoparakeratotic cells (degenerated cells with pyknotic nuclei) and histiocytes
 - Lack of maturing squamous epithelium
- Reactive cellular changes associated with radiation
 - History of cervical or endometrial malignancy, status post radiation
 - Markedly enlarged cells with preserved N/C ratio
 - Presence of bizarre cell shapes with multinucleation and polychromasia
 - Presence of cytoplasmic and nuclear vacuolization
 - Reactive cellular changes associated with intrauterine device (IUD)
 - History of IUD placement or recent removal
 - Presence of endometrial cells
 - Presence of small vacuolated cells or histiocytes
 - Presence of nuclear degeneration and prominent nucleoli
 - Tubal metaplasia
 - Very common in reactive endocervices and is composed of endocervical cells with well-defined terminal bars and ciliated borders
 - Hyperkeratoses and parakeratoses
 - Commonly associated with prolapse, but could also harbor a squamous intraepithelial lesion
 - Lymphocytic (follicular) cervicitis
 - Commonly associated with *Chlamydia trachomatis* infection, rather than any other venereal infection
 - Presence of tingible body macrophages and/or follicular dendritic cells in addition to polymorphous lymphoid cells is suggestive of germinal center formation
 - Reactive endocervical cells
 - Commonly have sheets of endocervical cells with multiple nucleoli or prominent chromocenters
 - Preserved architecture (honeycombing or picket fence pattern)

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Pearls

- The search for an infectious agent and an adequate correlation with clinical history is imperative in the diagnosis.

Microorganisms in Pap Smear

Candida albicans

Clinical Features

- Patients typically present with itchy, inflamed skin, and mucous membranes often with a thick white cottage-cheese-like discharge
- Predisposing factors include: HIV infection, diabetes, chemotherapy suppression, and broad spectrum antibiotics

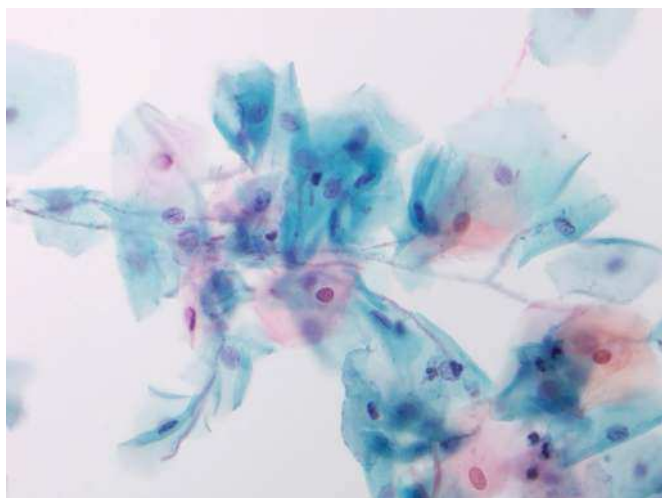


Figure 1-3A. *Candida*. (Papanicolaou stain).

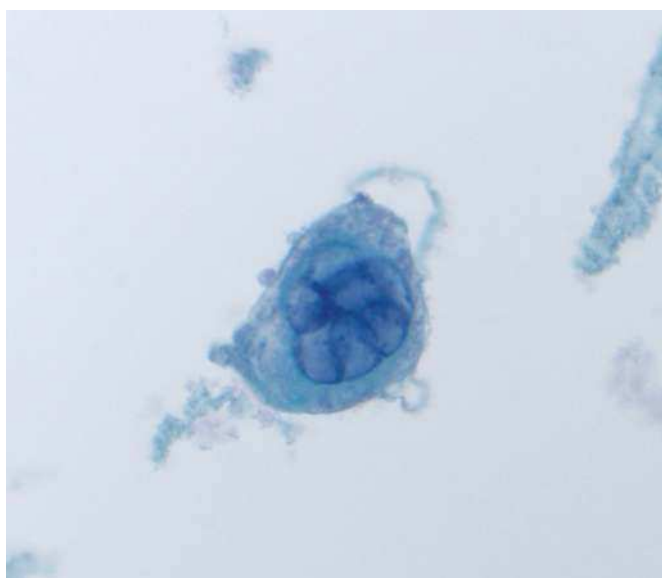


Figure 1-3B. *Herpes*. (Papanicolaou stain).

Cytological Features

- Yeast (3–7 μm) and pseudo hyphal forms of the fungi
- Pseudo hyphae hold squamous cells together and form “shish kebab” patterns

Special Stains and Immunohistochemistry

- Noncontributory

Modern Techniques for Diagnosis

- Noncontributory

Differential Diagnosis

- *Candida glabrata*: morphologically consists only of the yeast form (1–4 μm). Although not commonly seen in Pap smears, speciation to support its presence may represent a more diffuse or disseminated infection involving the cervix in this otherwise opportunistic infection.
- *Geotrichum candidum*: Morphologically consists only of the septate hyphae form with infrequent and irregular branching. This organism is not commonly seen in Pap smears unless as part of a generalized infection.

Pearls

- Although fungi are fairly common occurrence in Pap smear cytology, both *C. glabrata* and *G. candidum* may also herald a disseminated infection.

Herpes Simplex Virus (HSV)

Clinical Features

- Painful anogenital ulcers that start out as blisters and take several weeks to heal are a common presenting symptom. Reinfection and reactivation of either HSV-1 or HSV-2 may be less painful due to antibody production from latent infections
- Pap smear diagnosis during pregnancy is important to prevent direct vertical passage to the neonate, which can present with a potentially fatal infection

Cytologic Features

- Shows enlarged multinucleated cells with prominent nuclear molding and chromatin condensation with peripheral margination producing glassy nuclei

Special Stains and Immunohistochemistry

- HSV-1 and HSV-2 immunohistochemical stains can be used in equivocal cases where the classical cytopathic effect seen in Papanicolaou stain may not be easily identified

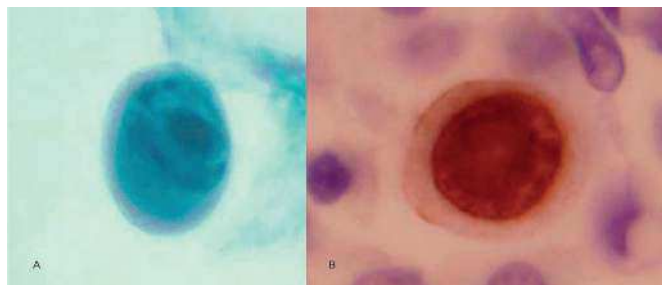


Figure 1-3C. CMV. (A. Papanicolaou and B. IP stain).

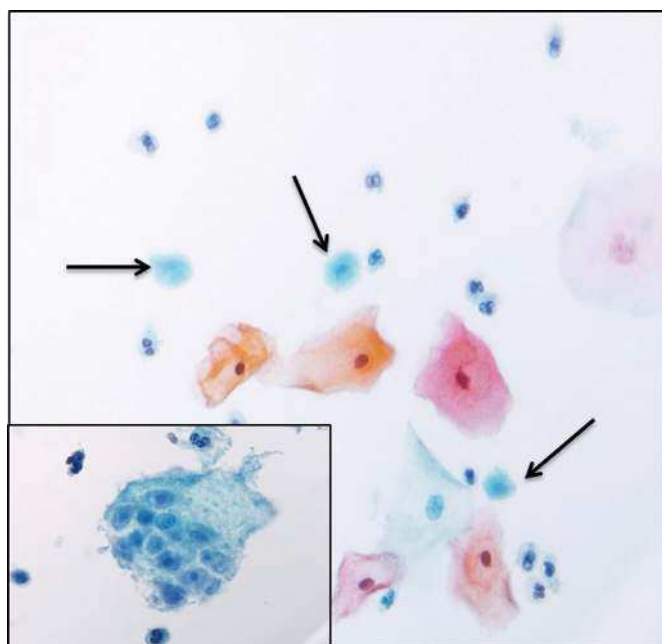


Figure 1-3D. Trichomonads. (Inset, many organisms covered one squamous cells) (Papanicolaou stain).

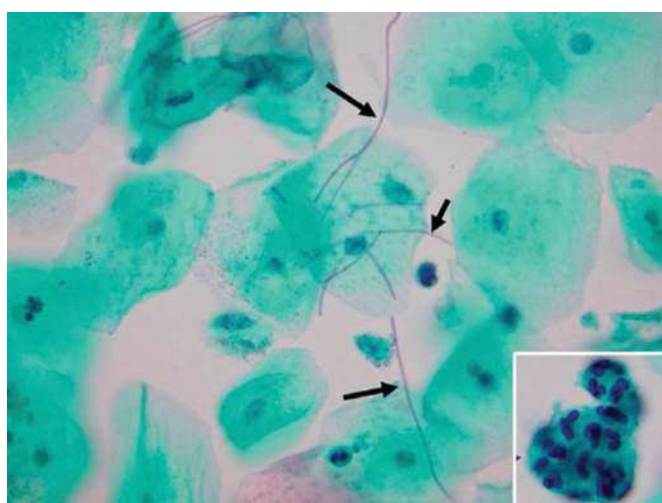


Figure 1-3E. Leptothrix (arrows) are commonly associated with trichomonads and "golf ball" cells. (inset) (Papanicolaou stain).

Modern Techniques for Diagnosis

- PCR based test or viral culture
- Serologic test for herpes antibodies

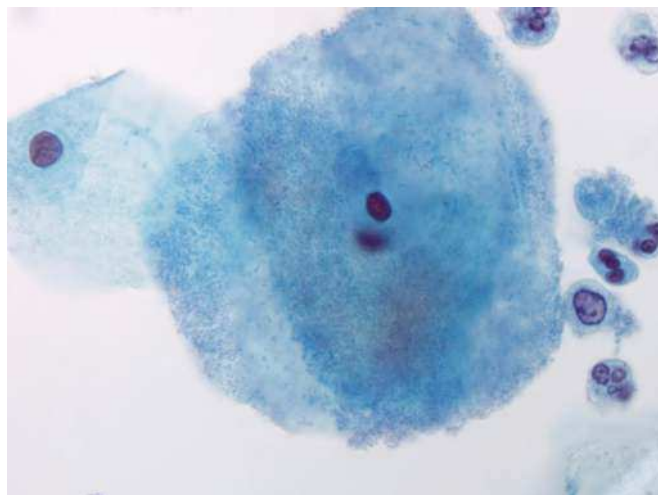


Figure 1-3F. Gardnerella vaginalis (clue cells). (Papanicolaou stain).

Differential Diagnosis

- Multinucleated endocervical cells: lack of the intranuclear inclusions

Pearls

- Diagnosis in Pap smear cytology is important especially in pregnancy so that an elective cesarean section can be explored as an option to the mother

Cytomegalovirus (CMV)

Clinical Features

- Are usually seen in association with immune deficiencies such as an HIV infection, chemoradiation, and patients on steroidal therapy
- Rarely seen in Pap smears and is more commonly seen in urine specimens, endothelial, or stromal cells in tissues
- Co-infection with HPV is not common

Cytologic Features

- Usually present in endocervical glandular cells and rarely in squamous cells
- This shows the prototypically enlarged cell with an enlarged nucleus and centrally placed intranuclear viral inclusion with an "owl's-eye" or "bull's-eye" cytomorphology

Special Stains and Immunohistochemistry

- Immunohistochemical stains for CMV may be used in equivocal cases

Modern Techniques for Diagnosis

- PCR-based test is available

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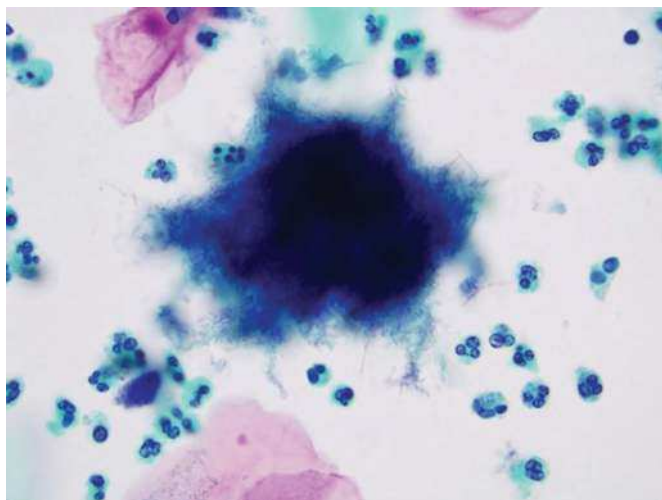


Figure 1-3G. *Actinomyces*. (Papanicolaou stain).

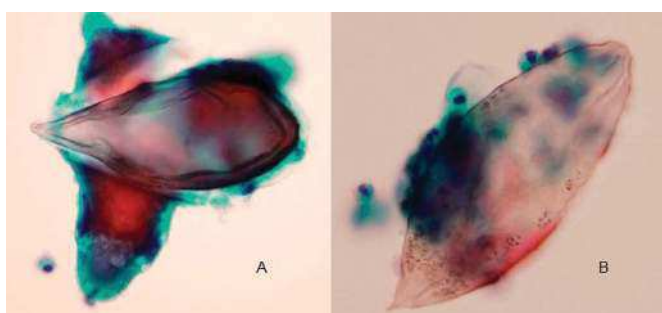


Figure 1-3H. *Schistosoma haematobium* egg (a and b) and miracidium (a). (400× original magnification) (Papanicolaou stain).

Differential Diagnosis

- Differentiation from HSV can be difficult when only mononucleated cells are present

Pearls

- May present as a Pap smear finding even in immunocompetent and asymptomatic hosts. Because of its potential significance in women of childbearing age, identification of this viral cytopathic effect is crucial.

Trichomonas vaginalis

Clinical Features

- Typically causes a frothy greenish discharge with putrid odor
- Itching, painful urination, and abdominal pain are common presenting symptoms.
- When symptomatic, the vagina and cervix have punctate small hemorrhages, clinically dubbed the “strawberry cervix”
- Many can be asymptomatic

Cytologic Features

- These protozoan organisms are typically found either singly dispersed or in aggregates, as in this case, in the cytoplasm of one of the squamous epithelial cells
- Typically “pear-shaped” and have eosinophilic granules in their cytoplasm
- An axostyle where the flagellae is attached is typically seen
- Marked acute inflammation consisting mainly of neutrophils on a Pap smear. At times, “golf-ball” or “pus-ball” cells (neutrophils adherent to squamous cells) are seen in association with this organism

Special Stains and Immunohistochemistry

- A wet prep mount at the clinic is enough to document the presence of this fast-moving flagellate organism. The organisms can also be seen using the Papanicolaou stained slide prepared from either conventional or liquid based media

Modern Techniques for Diagnosis

- Noncontributory

Differential Diagnosis

- Amoebiasis
 - Amoebiasis may be seen in Pap smears in women with concurrent diarrhea at the time of the Pap smear
 - About the same size as trichomonas, parabasal cell nuclei, or neutrophils
 - Do not have a visible axostyle, but the organelles in amoebas may be mistaken for the granules in *Trichomonas*

Pearls

- This infection, including amoebiasis is very easily treatable with metronidazole, therefore its identification in Pap smear is imperative

Leptothrix

Clinical Features

- Does not have a clinical presenting symptom by itself, but is commonly associated with *Trichomonas*
- The presence of *Leptothrix* in a Pap smear heralds the presence of *Trichomonas* (75–80%), but the reverse is not true

Cytologic Features

- Long, filamentous, gram-positive anaerobic bacteria (40–75 μm long), about half the diameter of *Candida* pseudohyphae, but with clear segmentations

- Can be seen in association with bacterial vaginosis and *Trichomonas*

Special Stains and Immunohistochemistry

- Noncontributory

Modern Techniques for Diagnosis

- Noncontributory

Differential Diagnosis

- May be confused with certain forms of *Lactobacillus* species, which is usually shorter (5–15 µm)

Pearls

- Presence of this long filamentous bacterium should prompt a search for *Trichomonas*, which causes a treatable symptomatic infections

Gardnerella vaginalis

Clinical Features

- Facultatively anaerobic gram-negative or gram-variable bacillus commonly seen in sexually active women of childbearing age and causing bacterial vaginosis.
- Most patients are asymptomatic; some present with a frothy vaginal discharge with “fishy” odor due to production of amines
- Usually no associated acute inflammation unless also associated with other infections

Cytologic Features

- A prototypical “clue-cell”: coccoid to somewhat short bacilloid organisms completely covering the squamous epithelium
- The presence of clue cells is one of the four criteria (Amsel criteria) used for diagnosis of bacterial vaginosis

Special Stains and Immunohistochemistry

- Whiff test (amine odor test): add 10% potassium hydroxide to vaginal discharge sample: strong amine order means positive

Modern Techniques for Diagnosis

- Molecular tests such as DNA probe and quantitative PCR

Differential Diagnosis

- Microorganisms that have been described to comprise this spectrum include: *Peptostreptococcus*, *Mycoplasma hominis*, *Mobiluncus*, and *Ureaplasma urealyticum*.

Pearls

- Can be related to frequent douching and subsequent gradual loss of hydrogen-peroxide producing lactobacilli as natural vaginal flora

Actinomyces

Clinical Features

- Anaerobic gram-positive bacteria usually associated with women on IUD or other foreign body such as tampons
- Usually does not cause any clinical symptoms and maybe present without any acute inflammation
- It is the same organism found in the crevices of tonsils, which has been dubbed “sulfur granules” because they are somewhat whitish-yellow in color

Cytologic Features

- Filamentous bacteria form a fuzz-ball that is very dense in the center and thinned out in the periphery
- The filaments formed by this bacterium are thinner than either *Candida* or *Leptothrix*

Special Stains and Immunohistochemistry

- Noncontributory

Modern Techniques for Diagnosis

- Noncontributory

Differential Diagnosis

- A number of organisms, including *Candida*, *Nocardia*, dermatophytes, bacterial aggregates, and foreign substances, such as sulfa drug crystals, may resemble *Actinomyces*

Pearls

- *Actinomyces* is a normal commensal organism in tonsils and female genital tract
- IUD users have higher risk than general population to develop serious infection of the pelvis, ovary, and uterus, thus, routine identification of the organism is still important in Pap smears
- Removal of the IUD and treatment with trimethoprim and sulfamethoxazole (Bactrim[®]) effectively gets rid of the infection
- Removal of the IUD or antibiotic treatment is not indicated in asymptomatic patient

Schistosoma haematobium

Clinical Features

- Schistosome eggs and miracidia are usually found in urine in patients living in areas where the organism is indigenous, such as Egypt or Madagascar

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- It can present visible lesions in the cervix characterized by erosion and induration
- A vaginal or cervical biopsy and Pap smear can also show the eggs of the schistosomes
- Presumably the adult organism finds its way from the bladder to the vagina and cervix and lay its eggs in these soft tissues
- It is the most common cause of squamous cell carcinoma of the bladder in some parts of the world

Cytologic Features

- Eggs of *Schistosoma haematobium* measure somewhere around 120–180 µm by 40–70 µm (seen at a low 100 × light microscopic magnification)
- Eggs have a terminal spine as opposed to *Schistosoma mansoni* where the spine is found laterally
- Miracidia is the hatched form of the organism and is diffusely ciliated

Special Stains and Immunohistochemistry

- Noncontributory

Modern Techniques for Diagnosis

- Noncontributory

Differential Diagnosis

- Other schistosomes: *S. mansoni*, *S. japonicum*, and *S. intercalatum*

Pearls

- Must be kept in mind in Pap smears of new immigrants coming from those parts of the world where the organism is indigenous

Neisseria gonorrhoeae

Clinical Features

- Venereal infection
- Abundant, purulent vaginal exudate
- Urethra and perivaginal glands commonly infected

Cytologic Features

- Bean-shaped gram-negative diplococci
- Often are seen on the surface of squamous cells
- Better seen on air-dried areas of the smears (edges of the glass slide)
- Large numbers of microorganisms can be appreciated within swollen polymorphonuclear leukocytes

Special Stains and Immunohistochemistry

- Gram stain: gram-negative diplococci

Differential Diagnosis

- Other cocci microorganisms
- Chlamydial microorganisms
- Phagocytosed debris

Modern Techniques for Diagnosis

- Nucleic acid amplification test (NAAT)
- Aptima Combo 2 Assay and the Xpert CT/NG are approved by FDA to be used on urine, vaginal, endocervical, and extragenital samples

Pearls

- Along with *Chlamydia trachomatis*, it is the most common and easily treatable cause of infertility in women, therefore, immediate testing based on clinical suspicion at the doctor's office should be done
- *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are two infectious agents that do not have a clear cytopathic effect and for which the Pap smear is NOT the diagnostic modality of choice.

Chlamydia trachomatis

Clinical Features

- *Chlamydia trachomatis* is the most commonly reported sexually transmitted disease in the United States, and the most common cause of pelvic inflammatory disease (PID) in young women of childbearing age.
- Considered a gram-negative bacterium and an obligate intracellular organism

Cytologic Features

- Difficult to identify morphologically on Pap smears, as it does not induce any typical cytopathic change in the cells
- Lymphocytic or chronic inflammatory change within the cervix causing a “follicular cervicitis” consisting of well-formed germinal centers with plasma cells and lymphocytes.

Special Stains and Immunohistochemistry

- Noncontributory

Modern Techniques for Diagnosis

- NAAT is the golden standard
- Cotested with *Neisseria gonorrhoeae*

Differential Diagnosis

- Noncontributory