Pathology of sexually transmitted infections

Sexually transmitted infections (STIs) (sexually transmitted diseases: STDs）are a worldwide health problem and should be recognized by all public health agencies. STIs involve the transmission of organisms between sexual partners through different routes of sexual contact. STIs are curable (gonorrhea, chlamydia, syphilis and trichomonas) or treatable (herpes simplex viruses, human papillomavirus and human immunodeficiency virus). The symptoms can be categorized into 2 patterns: discharge/dysuria or ulcerative lesions. Patient behavior and underlying comorbidities determine the likelihood of contracting STIs. Pathological features of STIs are represented here.

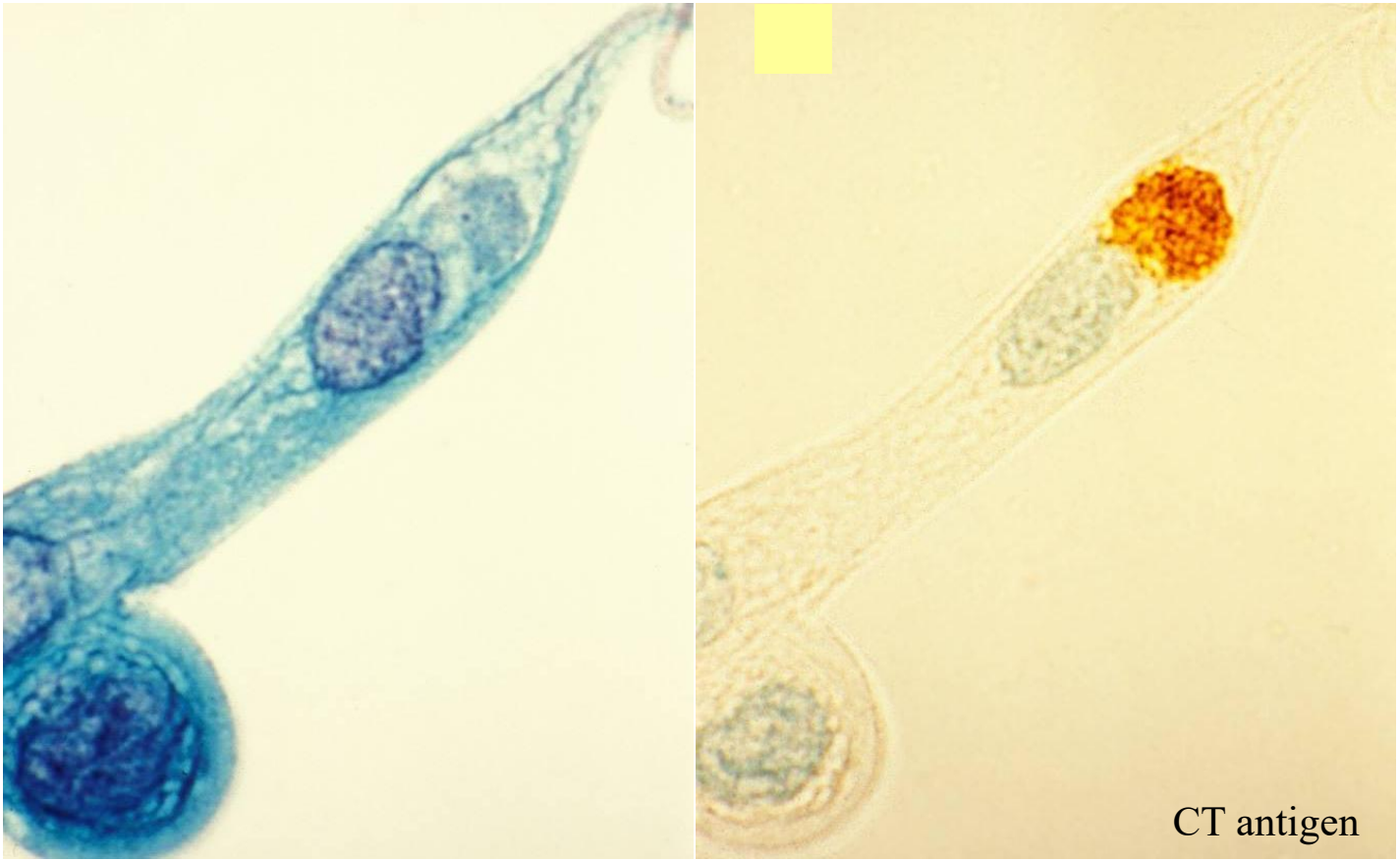
Ref.: Garcia MR, et al. Sexually transmitted infections. In: StatPearls [Internet]. Treasure Island (FL); 2024. https://www.ncbi.nlm.nih.gov/books/NBK560808/

Chlamydial infection

Chlamydiosis is a common sexually transmitted infection caused by a Gram-negative bacterium called *Chlamydia trachomatis*. It is easily treated and cured with antibiotics. Men are often symptomatic with urethritis, while women tend to be asymptomatic. Infection happens through oral sex via asymptomatic chlamydial infection on the throat of the woman. When untreated, women may develop infertility and ectopic pregnancy. *C. trachomatis* may cause infections in a variety of organs.

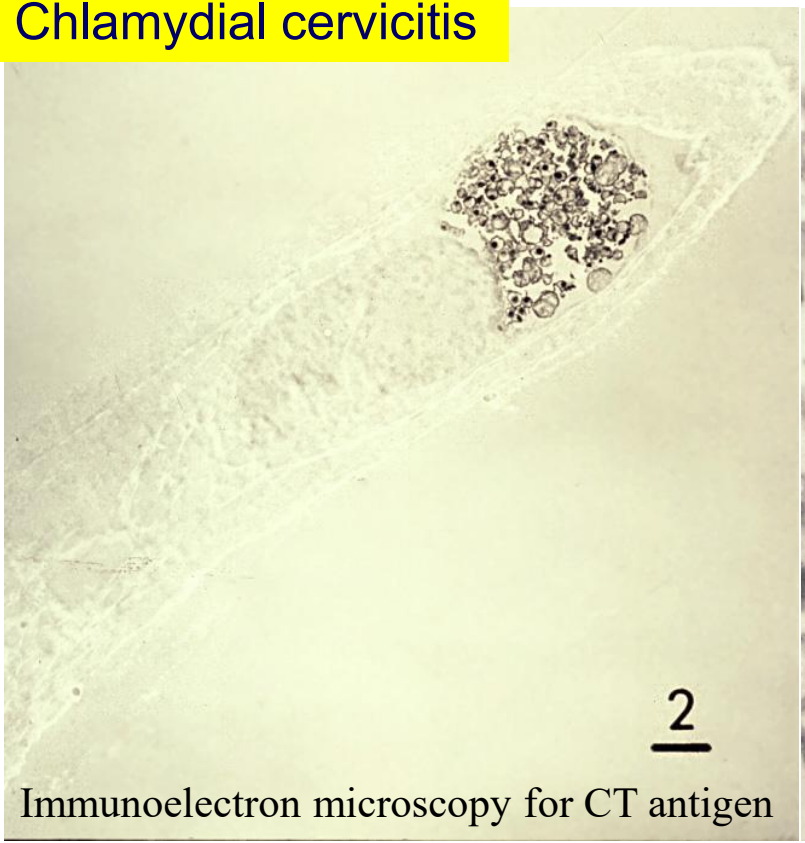
Ref.: Mohseni M, et al. Chlamydia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537286/

Chlamydial cervicitis

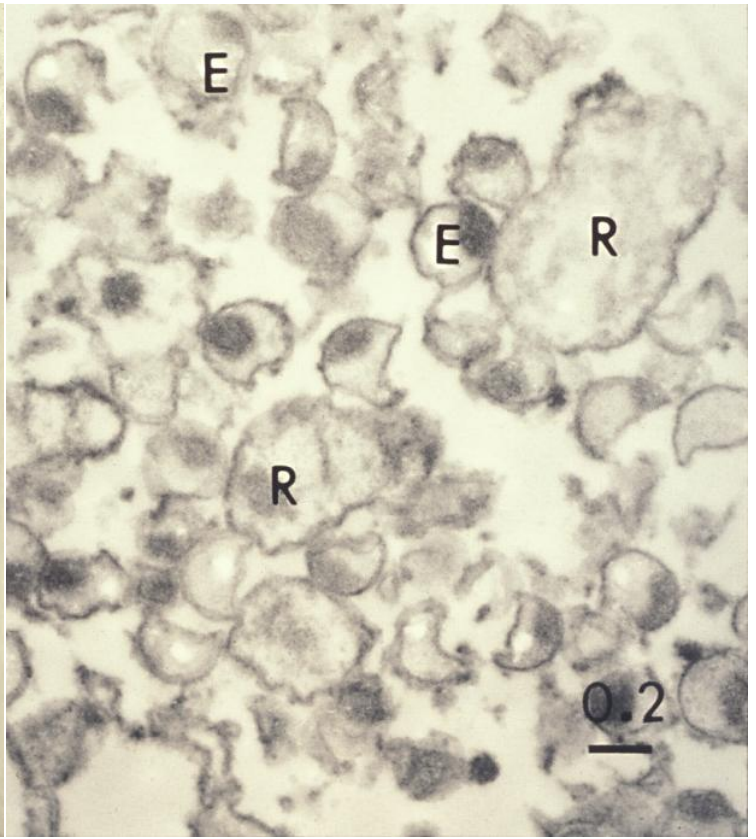


Restaining method: *Chlamydia trachomatis* antigen is visualized in the nevular inclusion body in the cytoplasm of a metaplastic cell seen in the cervical smear.

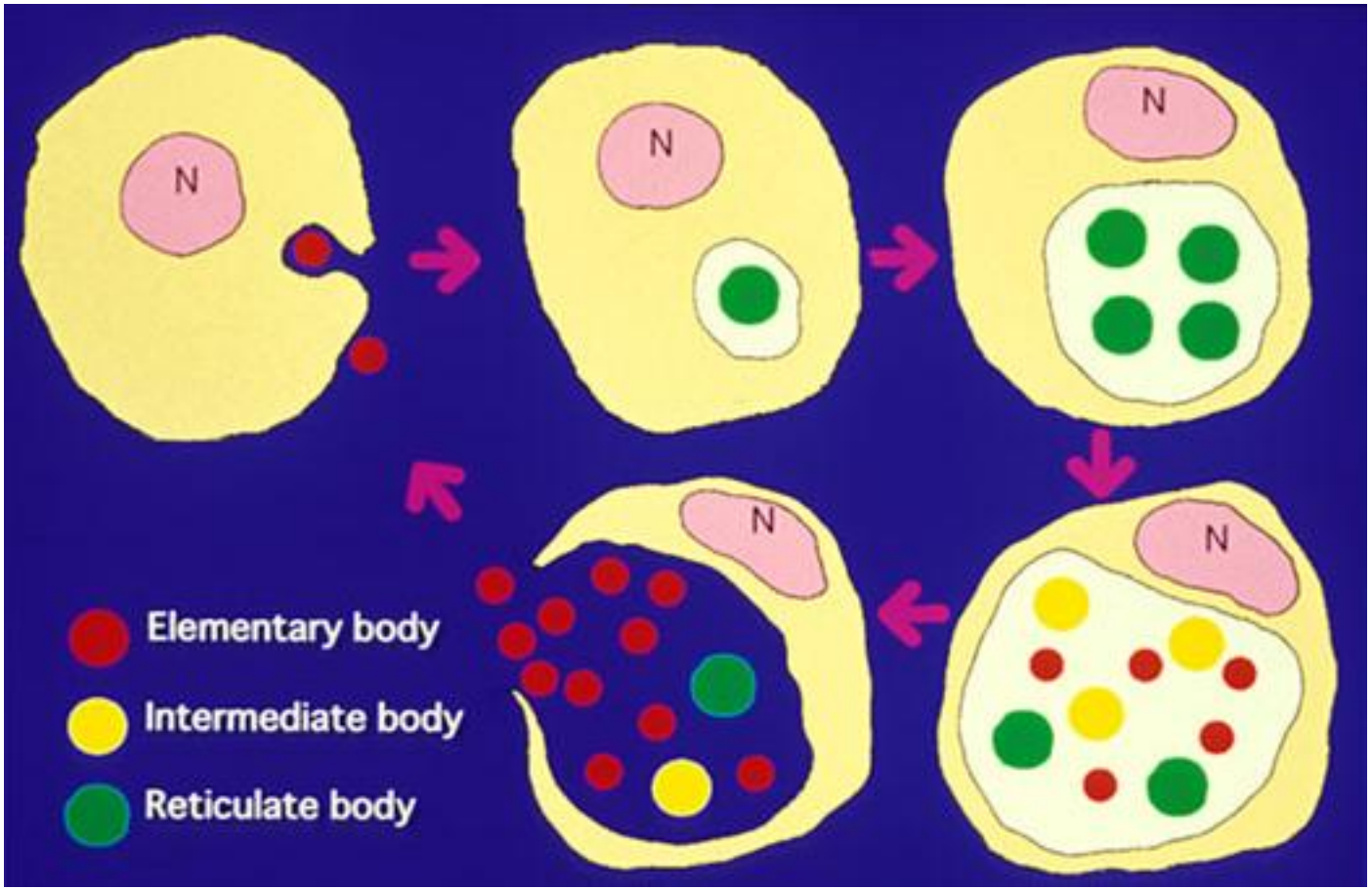
Chlamydial cervicitis



Immunoelectron microscopy for CT antigen



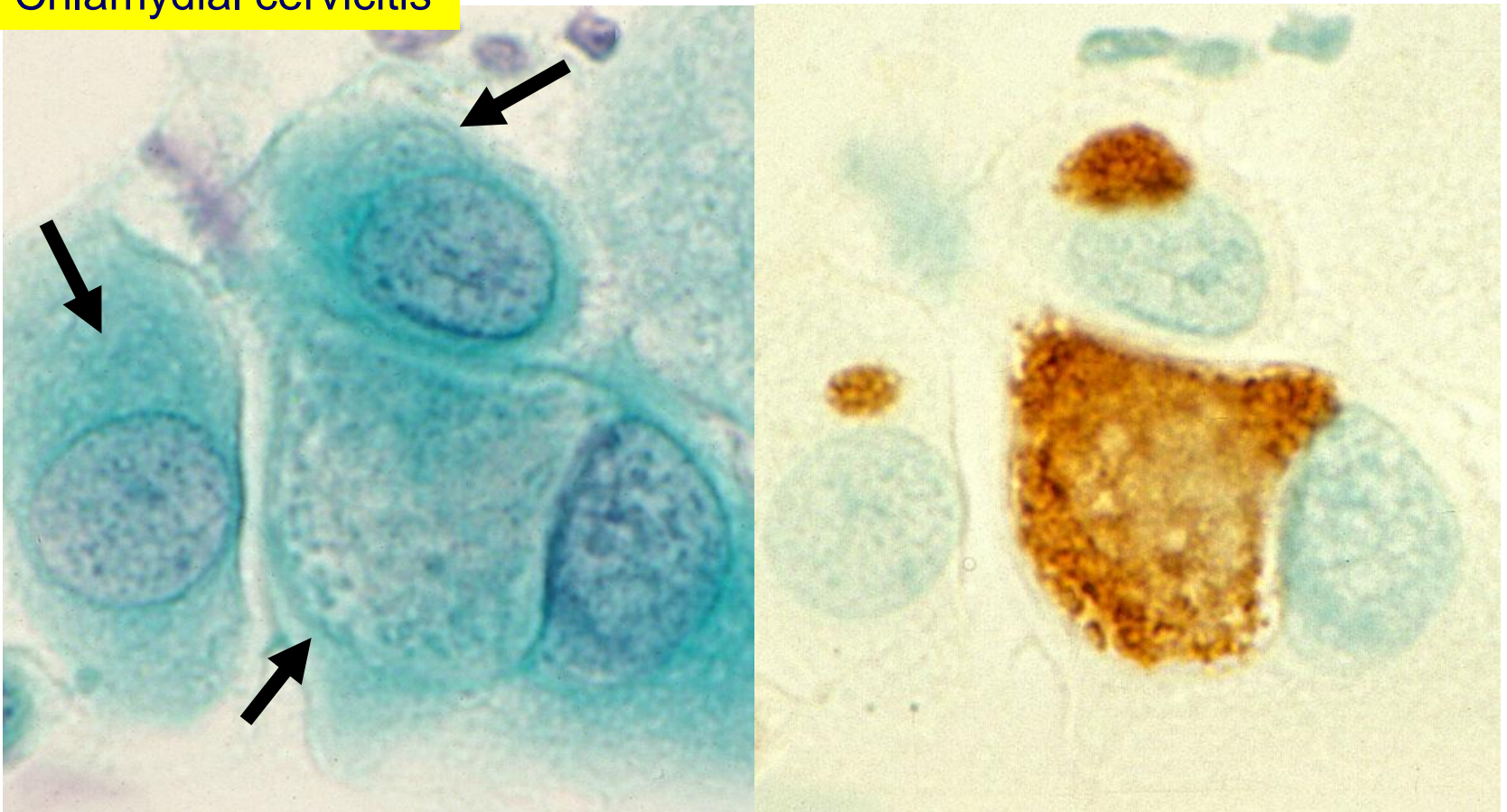
Immunoelectron microscopy, pre-embedding method, using an ethanol-fixed cervical smear of chlamydial cervicitis (see also the previous slide). The cell membrane of *Chlamydia trachomatis* is clearly labeled even after routine alcohol fixation. E: elementary bodies (infectious form), R: reticulate bodies (proliferative form). **Ref.**: Hori S, et al. Immunoelectron microscopic detection of chlamydial antigens in papanicolaou-stained routine vaginal smears. Acta Cytol 1995; 39(4): 835-837. PMID: 7631568



Schema of the growth cycle of Chlamydia

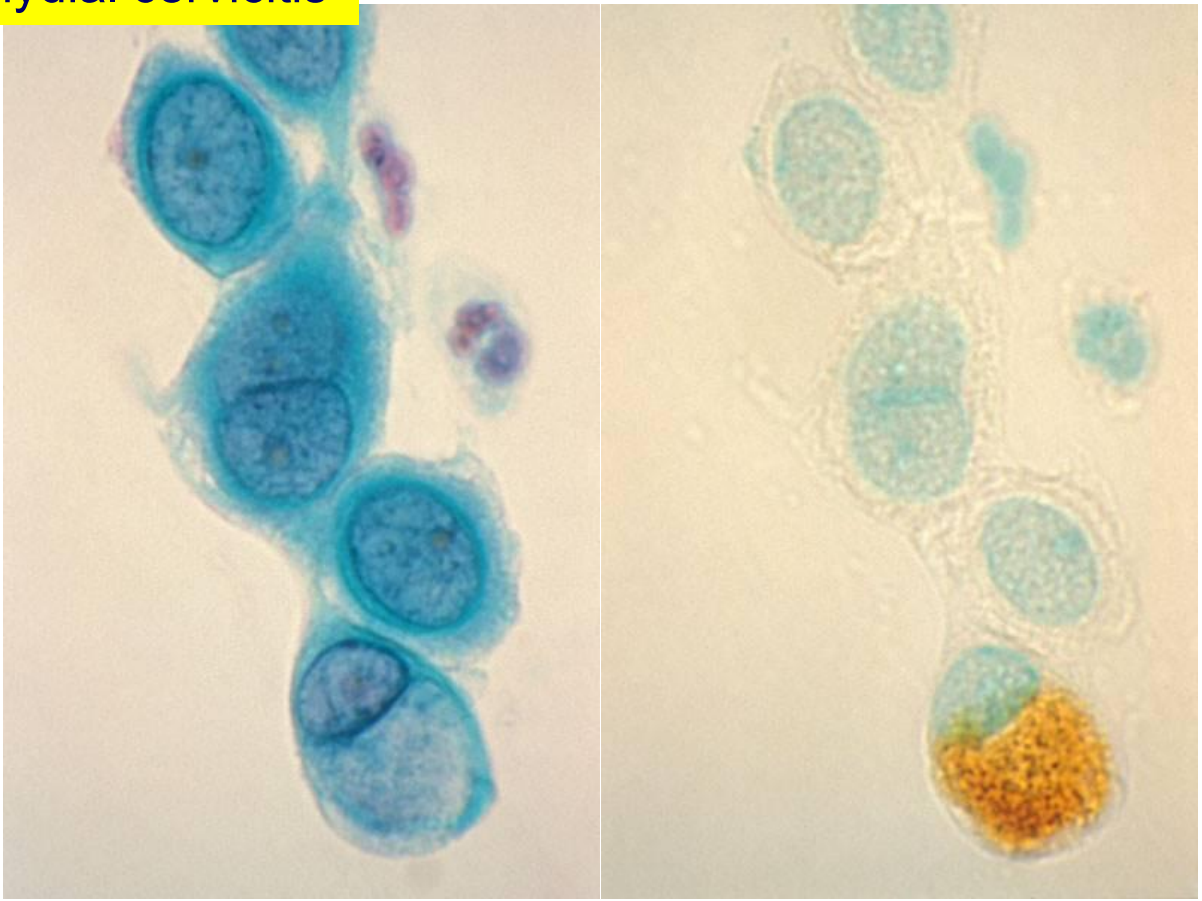
Infectious elementary bodies vs. proliferative reticulate bodies

Chlamydial cervicitis

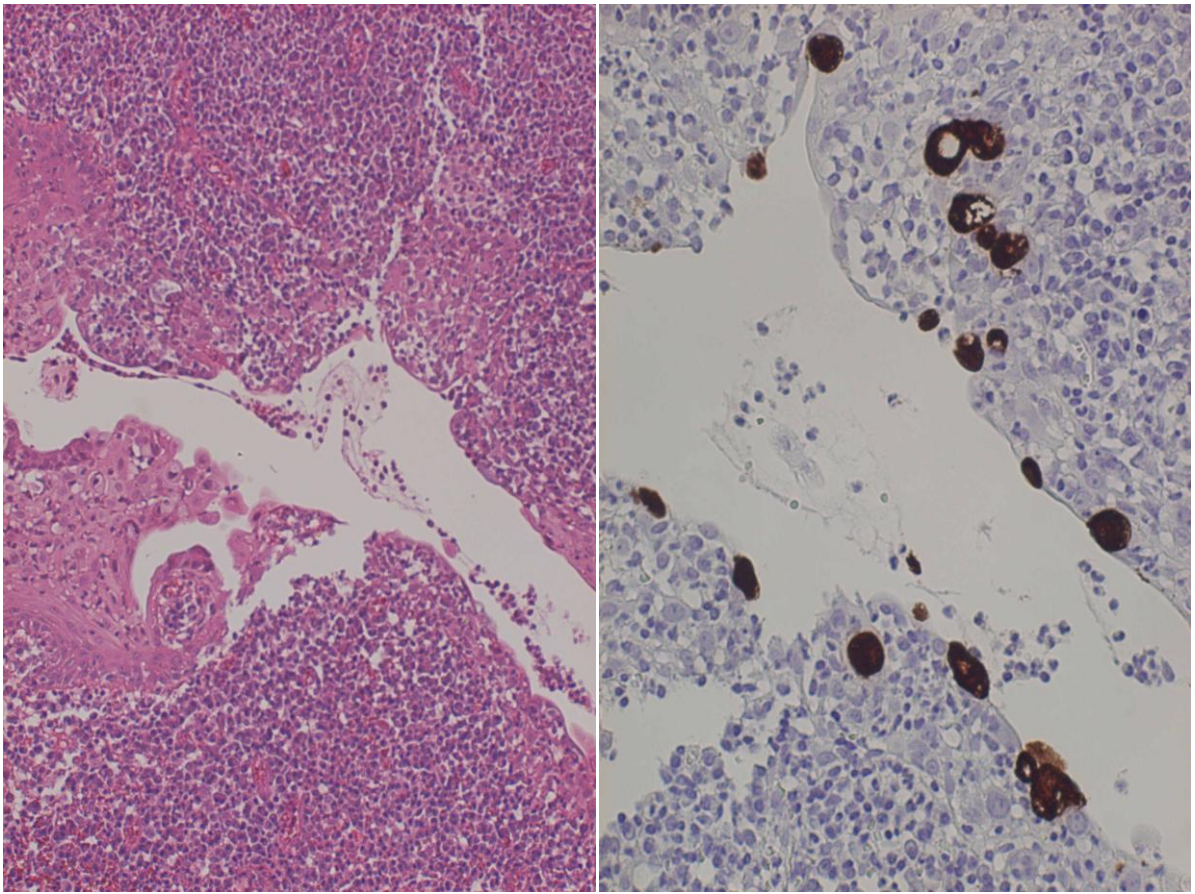


Restaining method. Demonstration of *Chlamydia trachomatis* antigen in the nebular inclusion bodies in the cervical smear preparation. A 20 y-o female patient complained of increased fluor. Pap smear reveals nebular inclusion bodies (arrows, left). The restaining method demonstrates chlamydial antigen in the inclusions (right).

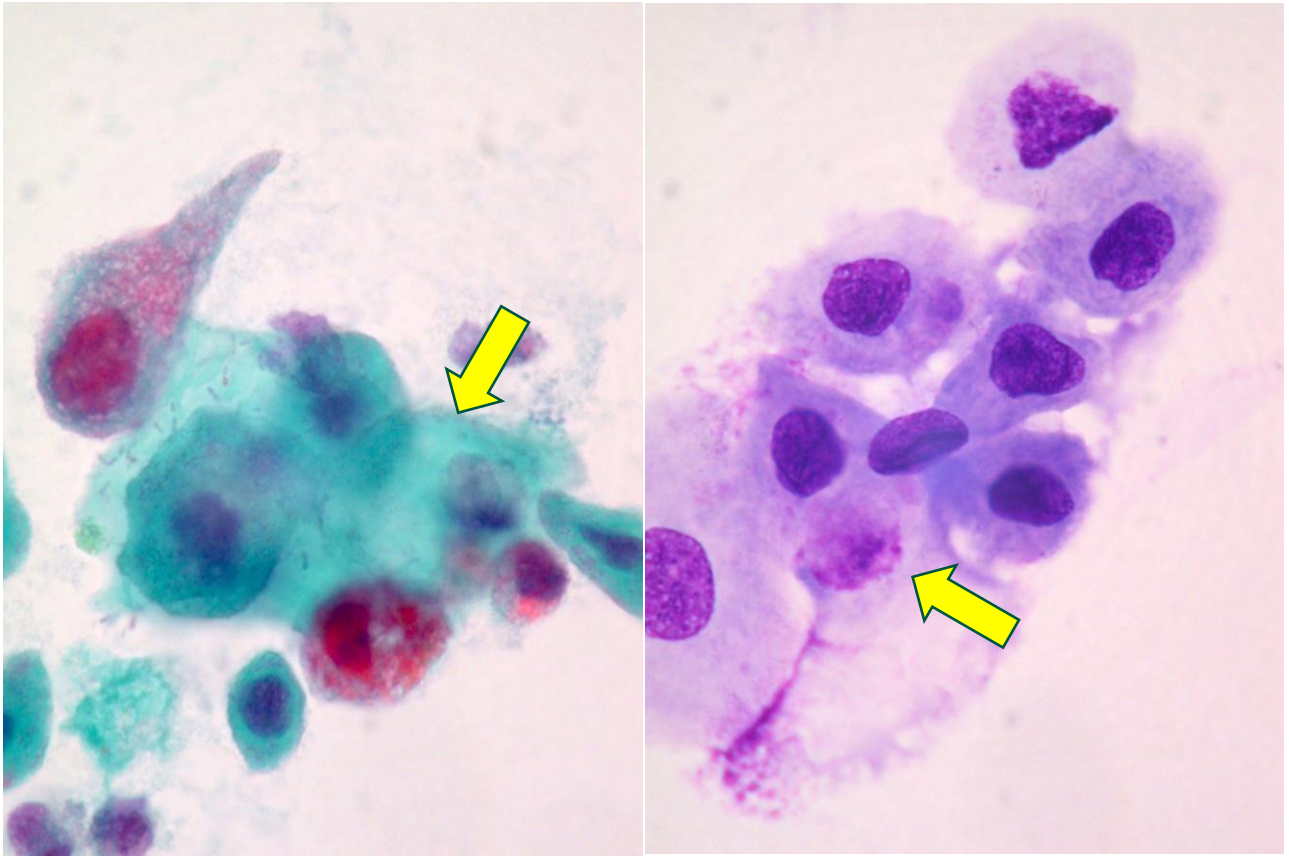
Chlamydial cervicitis



Restaining method. Another specimen demonstrating *Chlamydia trachomatis* antigen in the nebular inclusion bodies in the cervical smear preparation. Pap smear reveals a nebular inclusion body (left), and the restaining method displays chlamydial antigen in the inclusion (right).

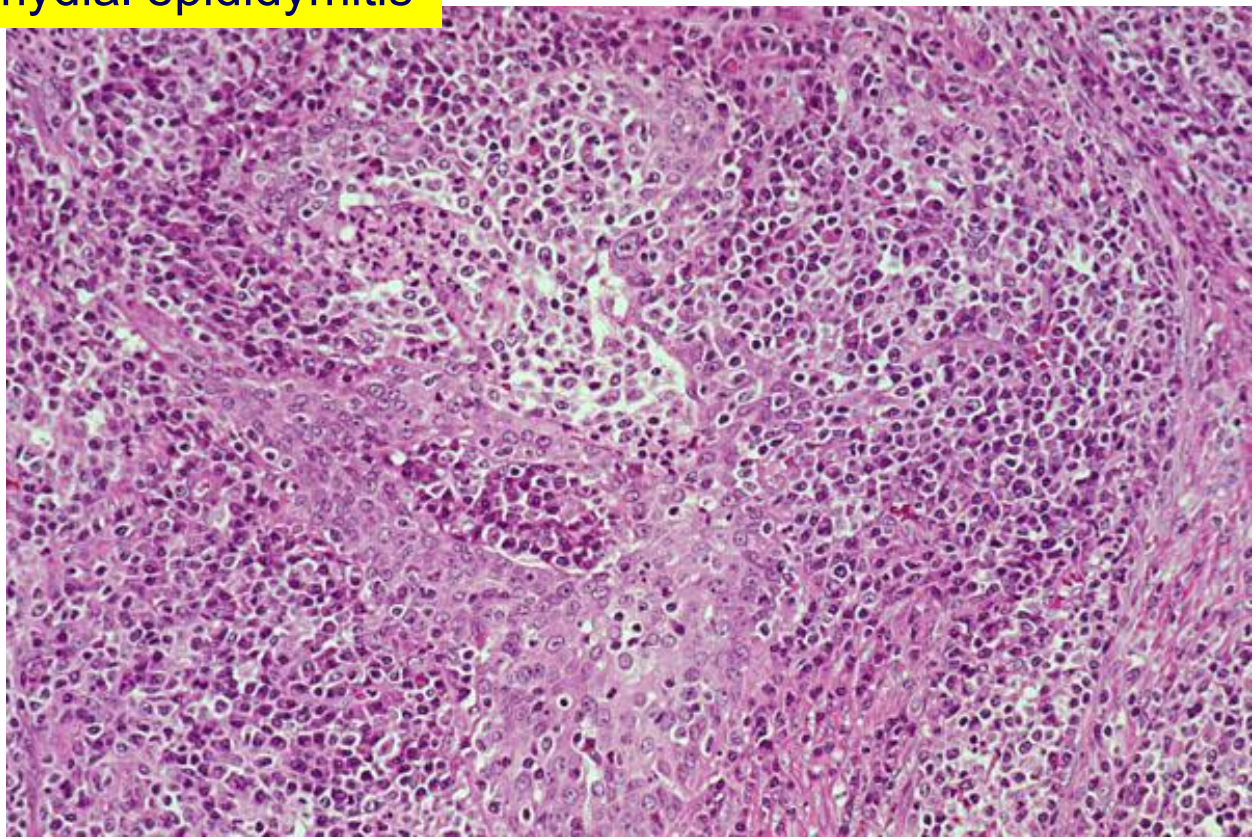


Chlamydial cervicitis. The columnar mucosa of the uterine cervix is heavily inflamed with lymphoplasmacytic infiltration. Lymphoid follicles may be hyperplastic, Immunostaining for *C. trachomatis* antigen is clearly demonstrated in the intracytoplasmic inclusion bodies.



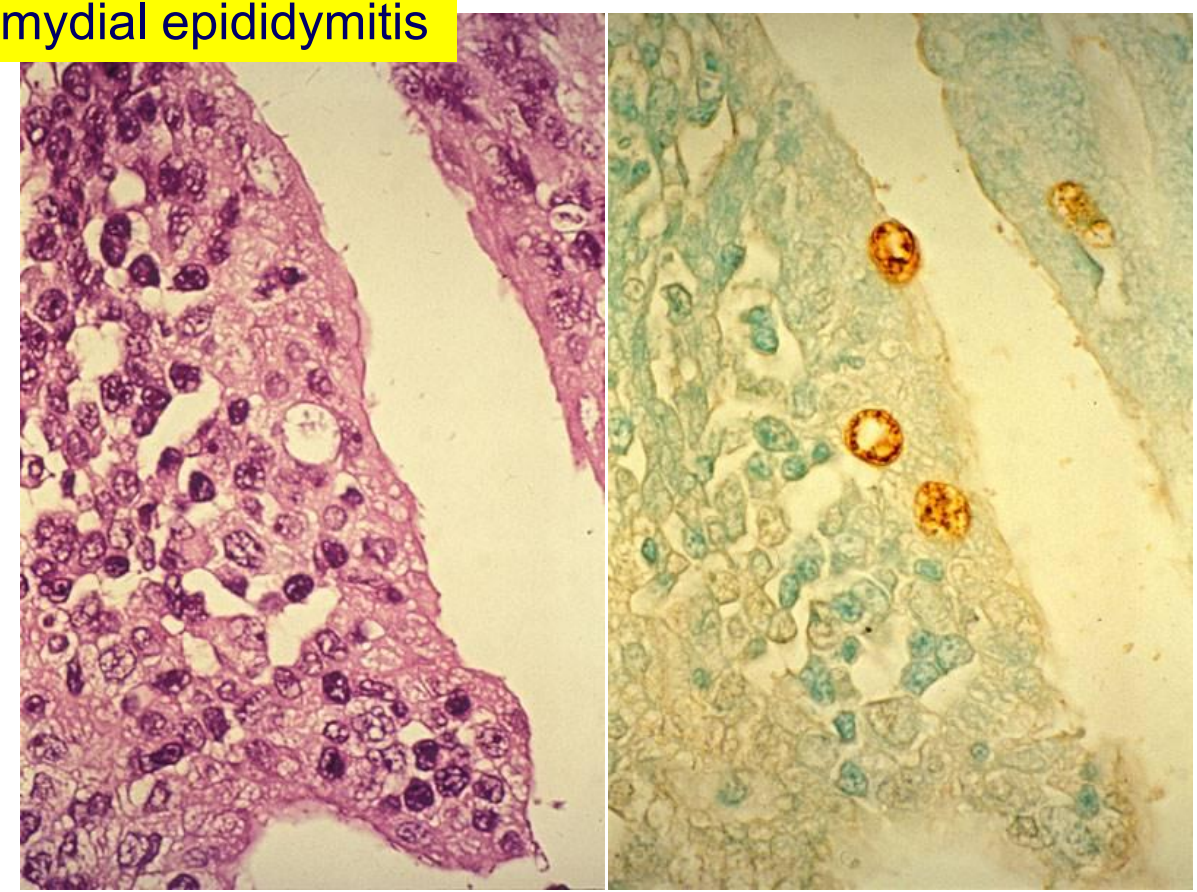
Chlamydial urethritis. Urine cytology in a 21 y-o male patient shows cytoplasmic inclusions (arrows). Chlamydial urethritis shares most cases of non-gonorrheal urethritis. Left: Pap, right: Giemsa

Chlamydial epididymitis



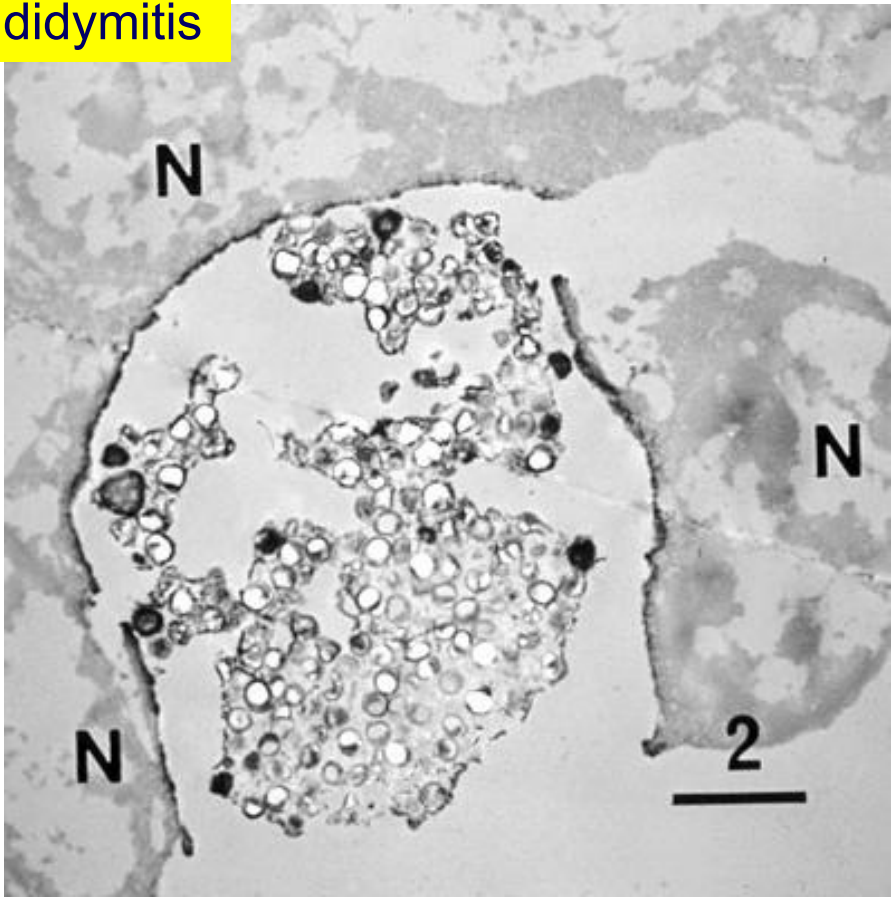
Chlamydial epididymitis, often presenting with an epididymal tumor. The surgical specimen reveals chronic active epididymitis with neutrophilic infiltration in the ductal lumen and lymphoplasmacytic infiltration in the stroma (H&E).

Chlamydial epididymitis



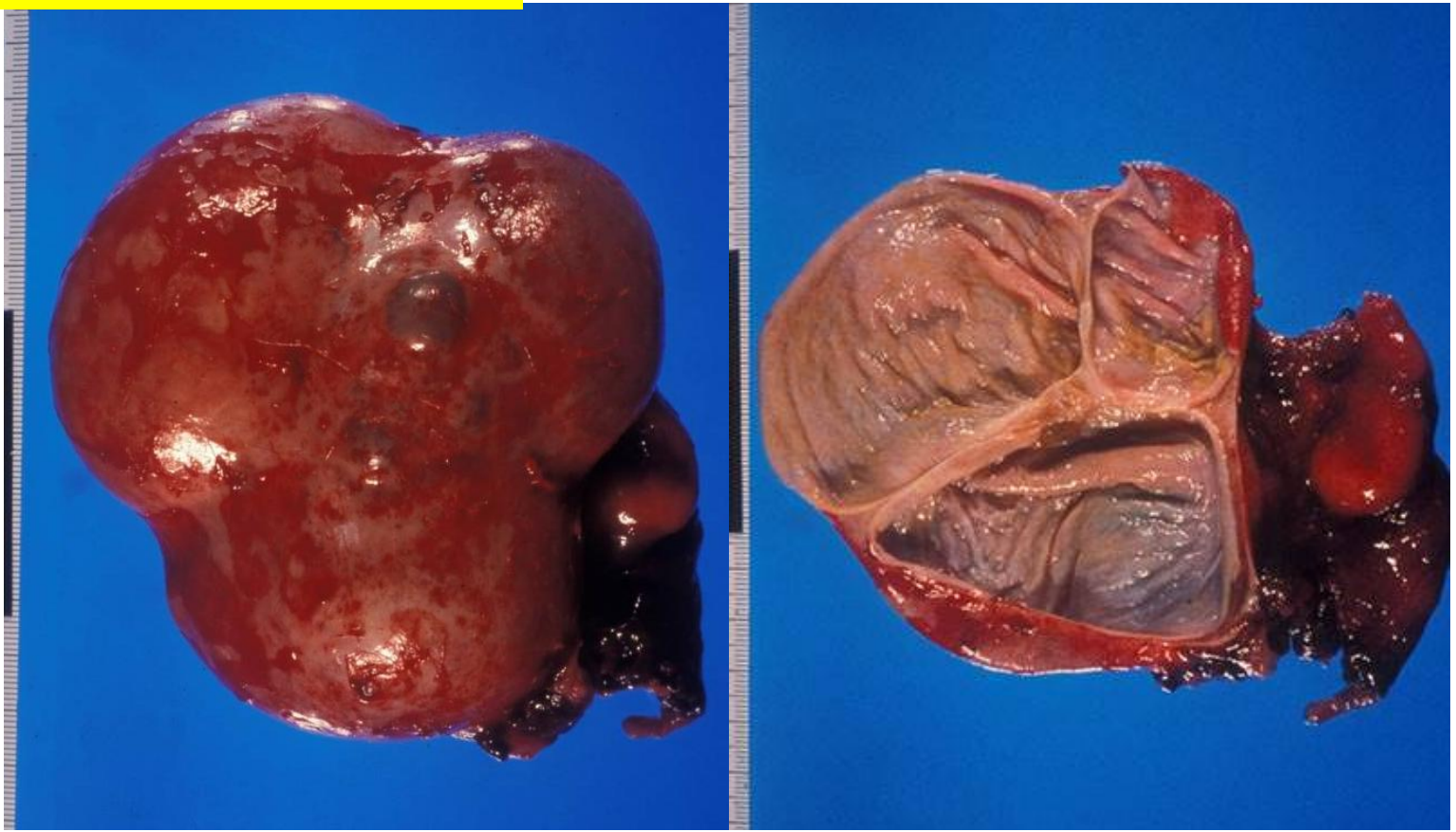
Chlamydial epididymitis. The infected epithelial cells reveal intracytoplasmic inclusion bodies, and immunostaining for *C. trachomatis* antigen is clearly demonstrated in the inclusions. **Ref.**: Hori S, Tsutsumi Y. Histological differentiation between chlamydial and bacterial epididymitis: nondestructive and proliferative versus destructive and abscess forming. Immunohistochemical and clinicopathological findings. Hum Pathol 1995; 26(4): 402-407. doi: 10.1016/0046-8177(95)90141-8

Chlamydial epididymitis



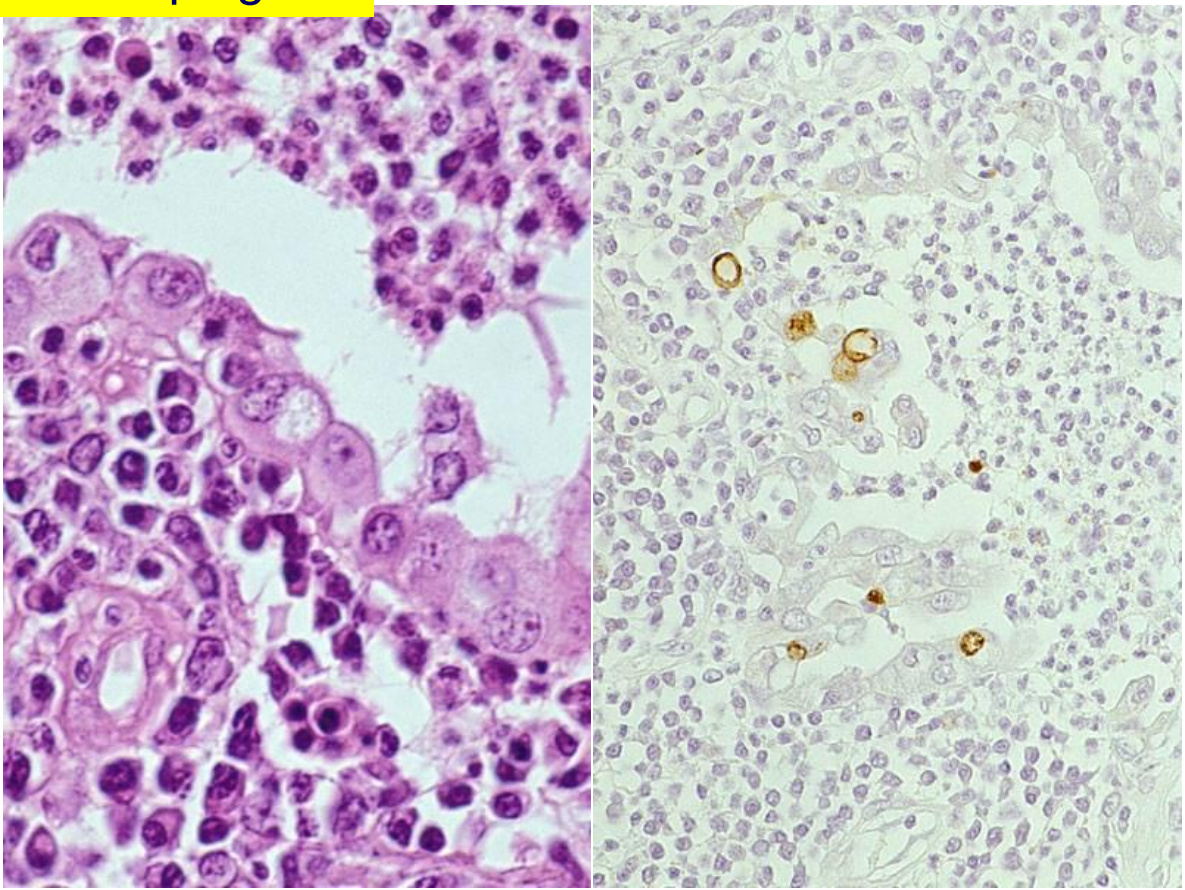
Targeted pre-embedding immunoelectron microscopy using a formalin-fixed, paraffin-embedded section shows positively labeled chlamydial particles in the intracytoplasmic inclusion. N=nucleus

Chlamydial salpingitis



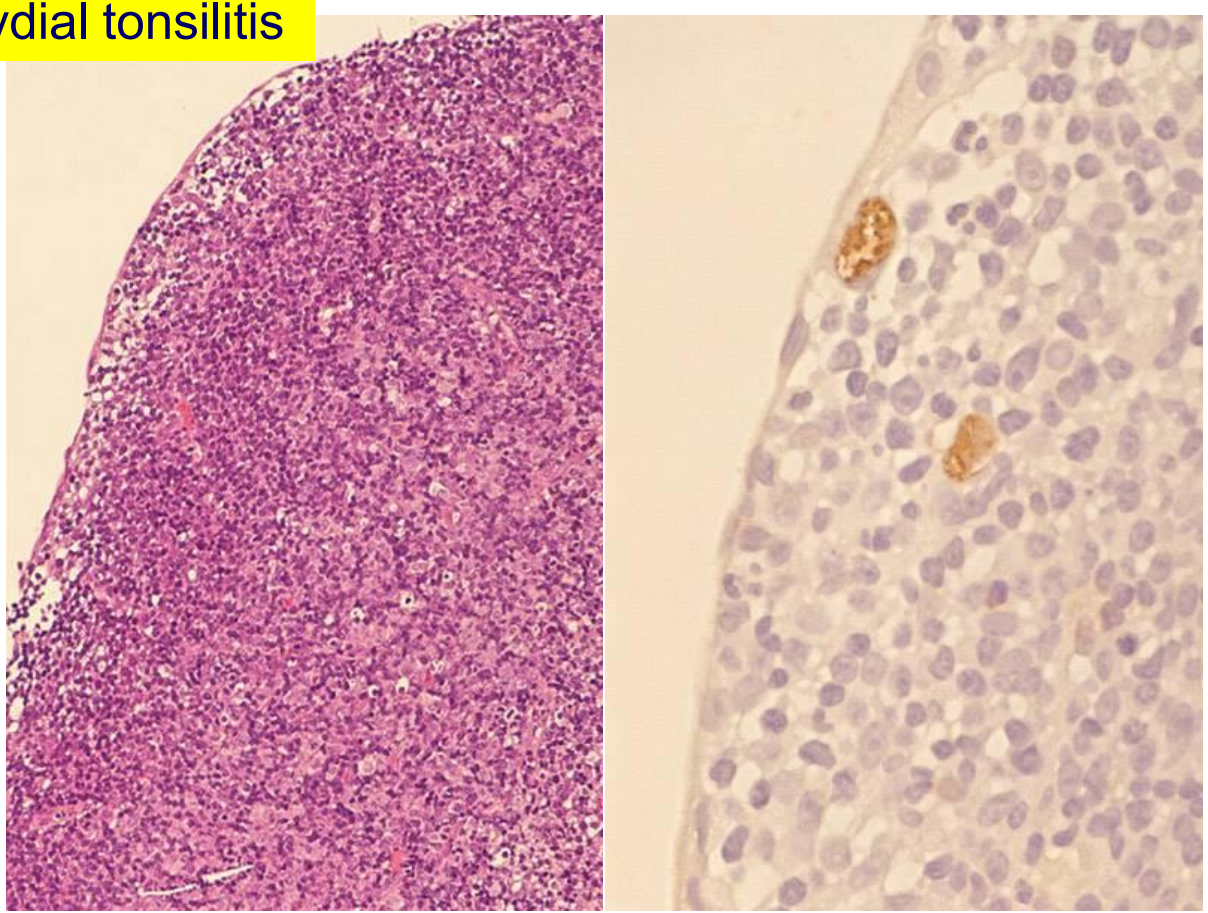
A 30 y-o female patient presented with abdominal pain. The enlarged left oviduct was resected. Sausage-like swelling is evident.

Chlamydial salpingitis



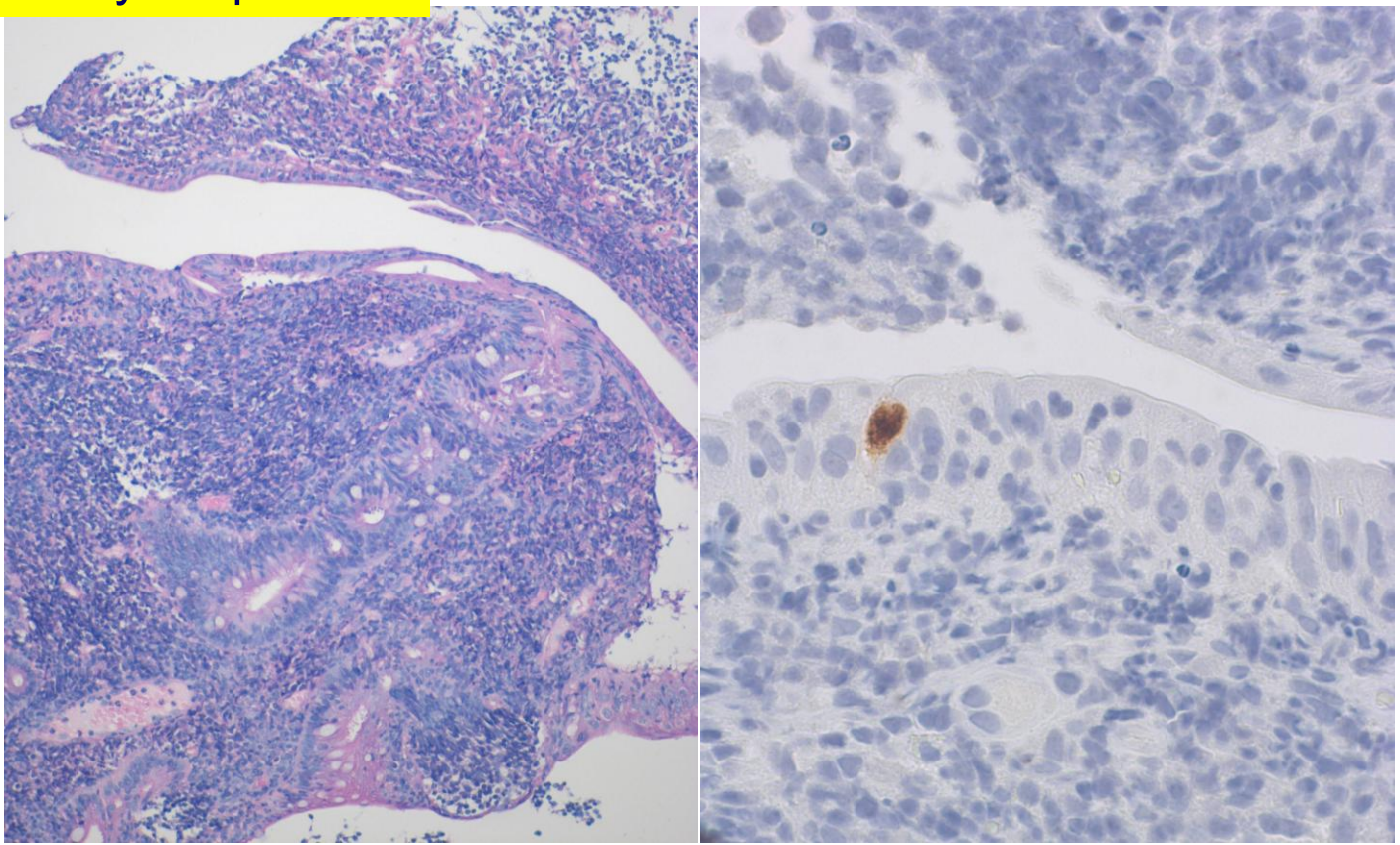
Chlamydial salpingitis. The infected epithelial cells reveal intracytoplasmic inclusion bodies, and immunostaining for *C. trachomatis* antigen is clearly demonstrated in the inclusions.

Chlamydial tonsilitis



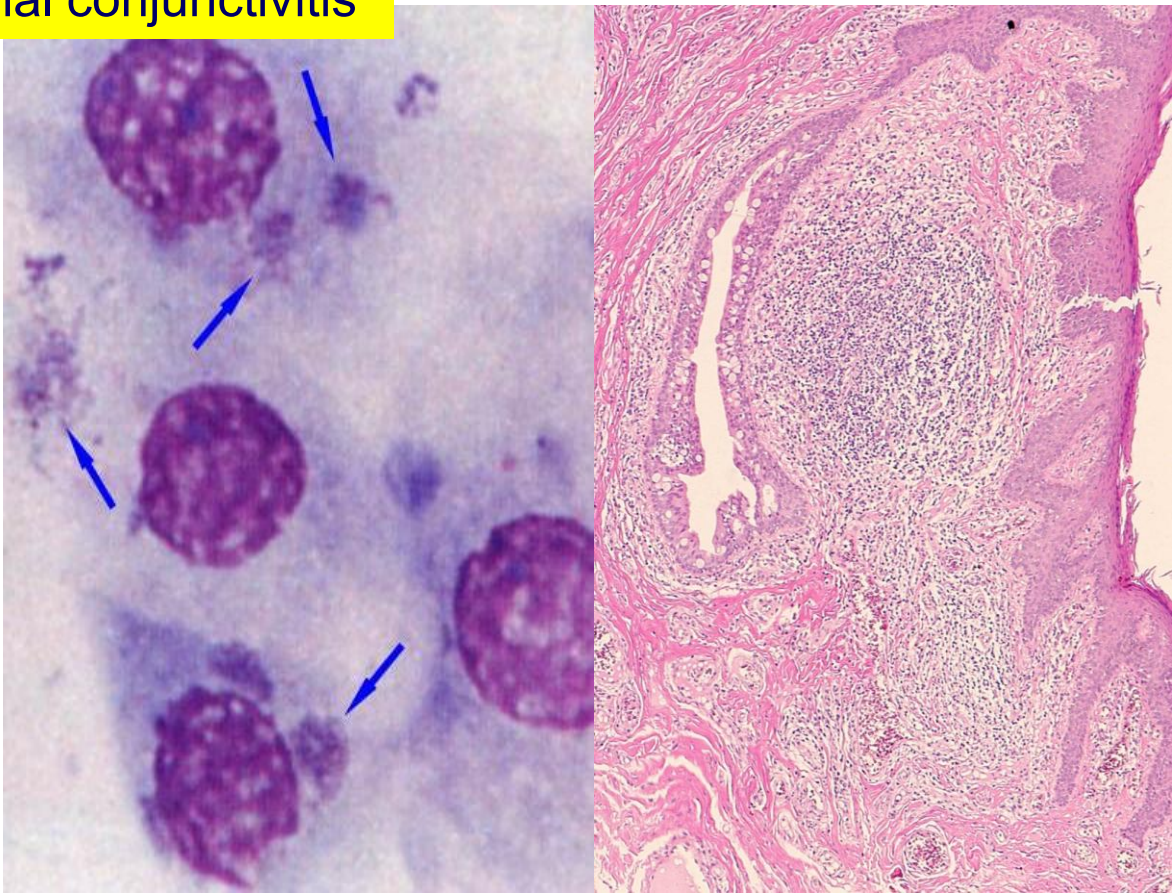
Chlamydial tonsilitis. The infected surface epithelial cells are heavily infiltrated by inflammatory cells. Immunohistochemically, a small number of *C. trachomatis* antigen-positive intracytoplasmic inclusion bodies are noted. The infection is mediated by oral sex.

Chlamydial proctitis

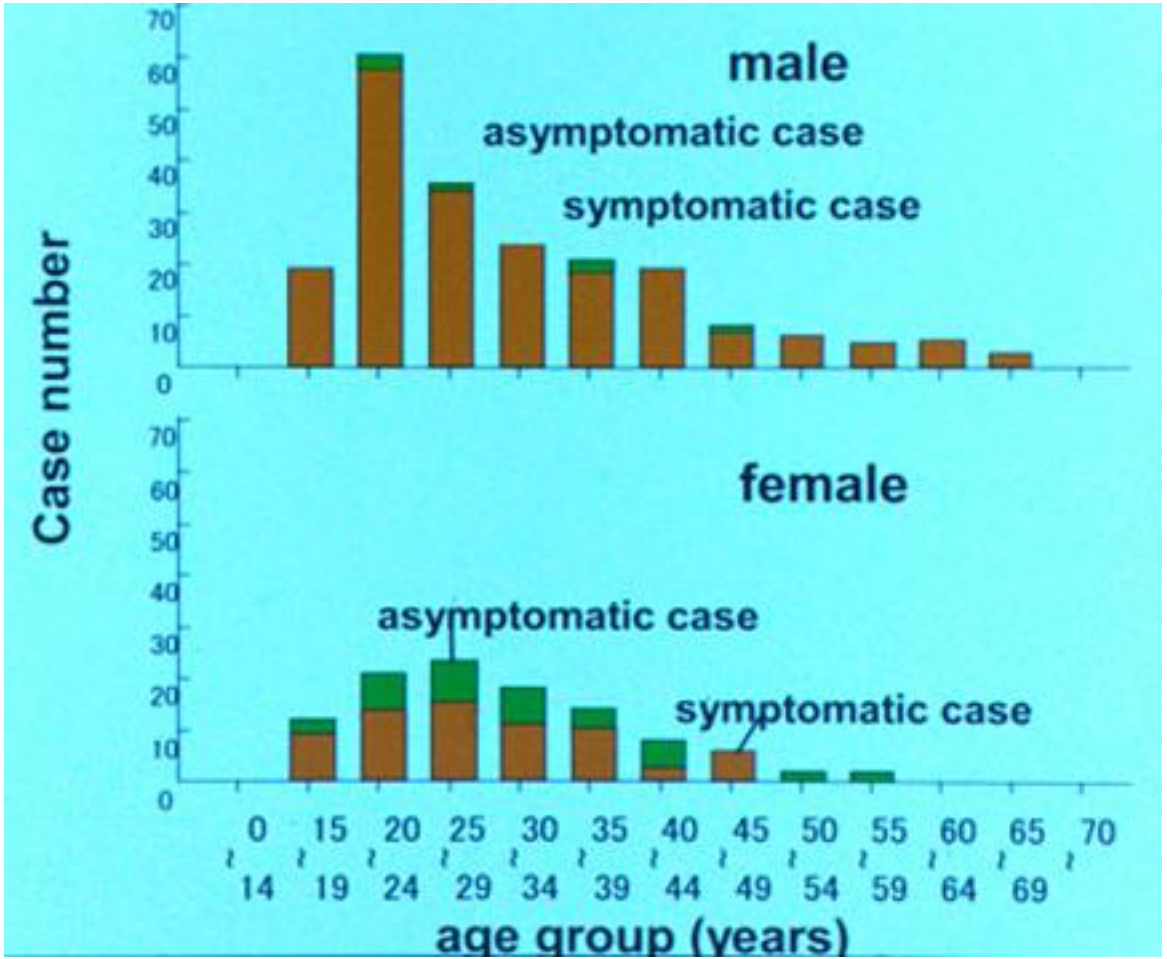


Chlamydial proctitis. The rectal mucosa in this female patient aged 20's is heavily infiltrated by inflammatory cells with lymphoid follicle formation. A few *C. trachomatis* antigen-immunoreactive intracytoplasmic inclusion bodies are noted. The infection is mediated by anal sex.

Chlamydial conjunctivitis



Chlamydial conjunctivitis. Conjunctival smear reveals chlamydial cytoplasmic inclusions (left: Giemsa). Biopsy reveal lymphoid follicle formation beneath the metaplastic conjunctival mucosa (right: H&E). Don't touch the eyes with the contaminated fingers during sexual acts.



Incidence of chlamydial infection by age groups in Japan. The infection often happens in younger ages, and female cases tend to be asymptomatic.

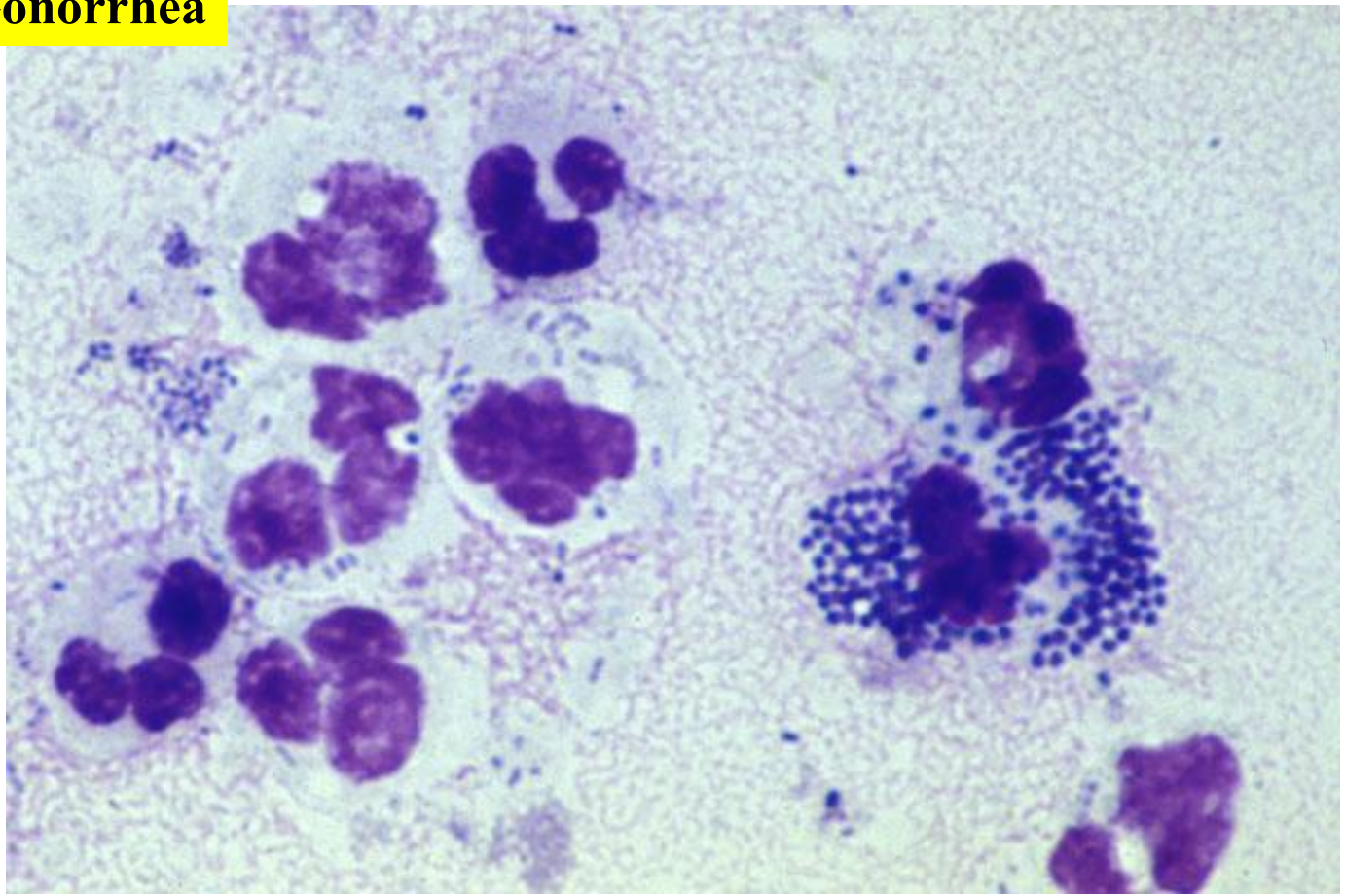
Gonorrhea

Gonorrhea is caused by sexually transmitted infection of *Neisseria gonorrhoeae* (gonococcus). Symptoms include pain during urination and abnormal discharge from the vagina or penis. Gonorrheal urethritis is shown.

Gonorrhea, chancroid, lymphogranuloma venereum and granuloma inguinale

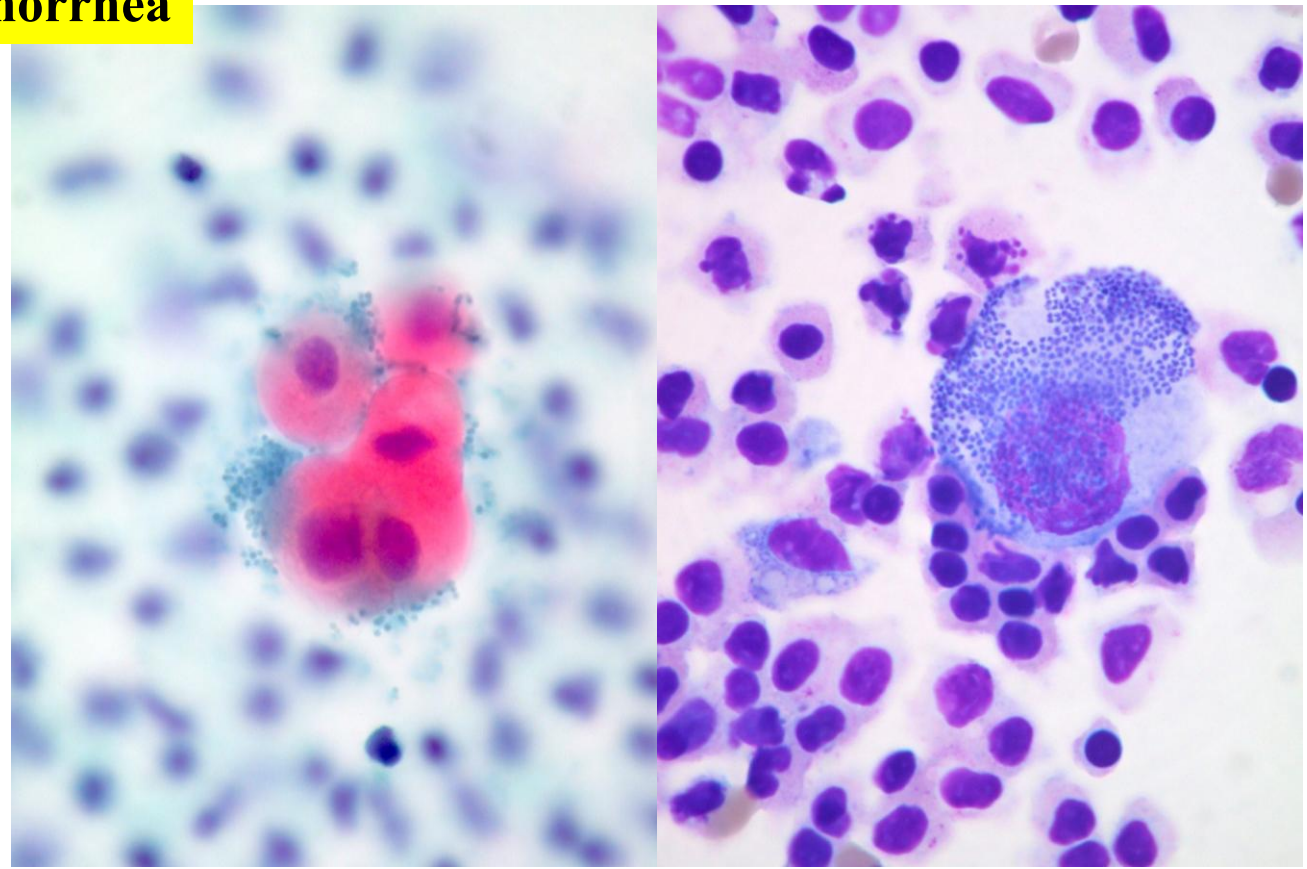
Gonorrhea is a representative sexually transmitted infection by Neisseria gonorrhoeae. Chancroid, lymphogranuloma venereum and granuloma inguinale are rare STIs in the developed countries. Examples of these infections are shown here.

Gonorrhea



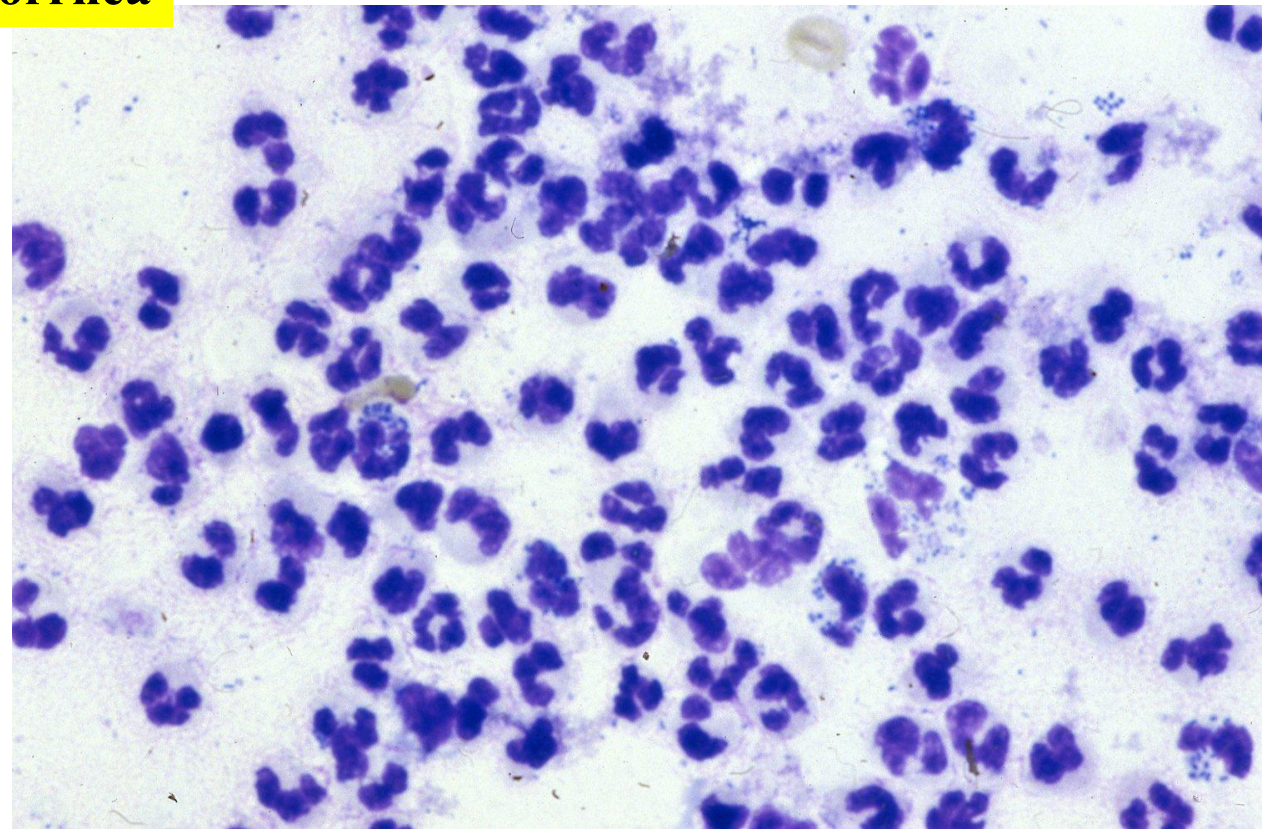
Gonorrhea is caused by sexually transmitted infection of *Neisseria gonorrhoeae* (gonococcus). Smear of the urethral discharge demonstrates diplococci phagocytized by neutrophils (quick Giemsa).

Gonorrhea



Gonorrhea in urine cytology. Left: Pap, right: Giemsa. *Neisseria gonorrhoeae* reveals an affinity specific to urethral squamous epithelial cells. Diplococci are clustered on the epithelial cells of urethral origin. The background urothelial cells of urinary bladder origin are devoid of colonization.

Gonorrhea

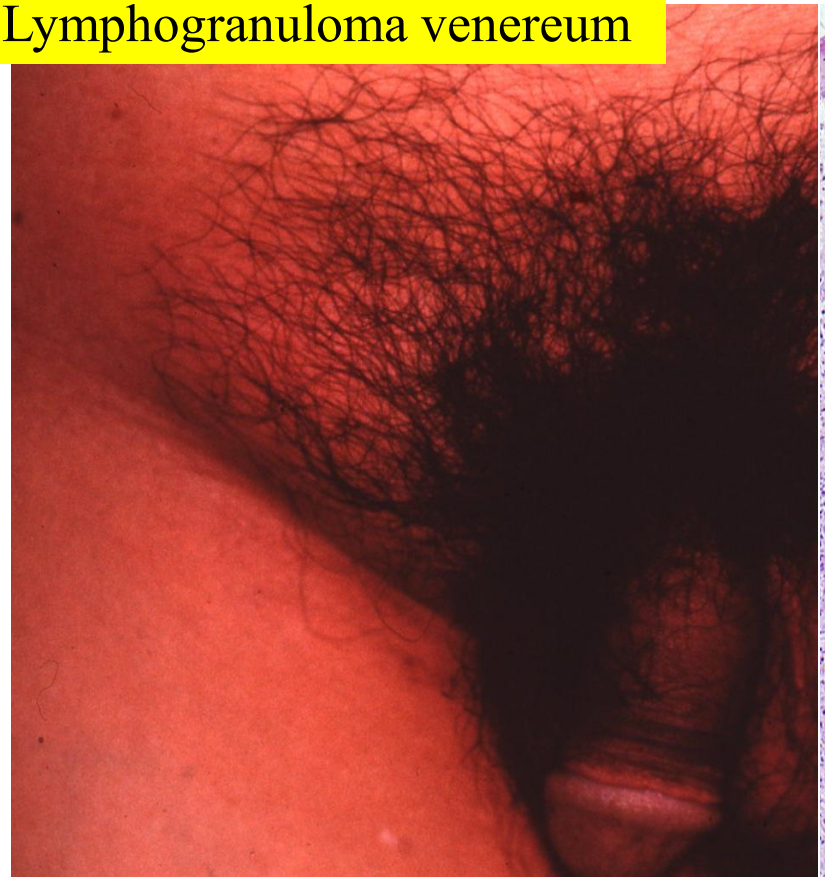


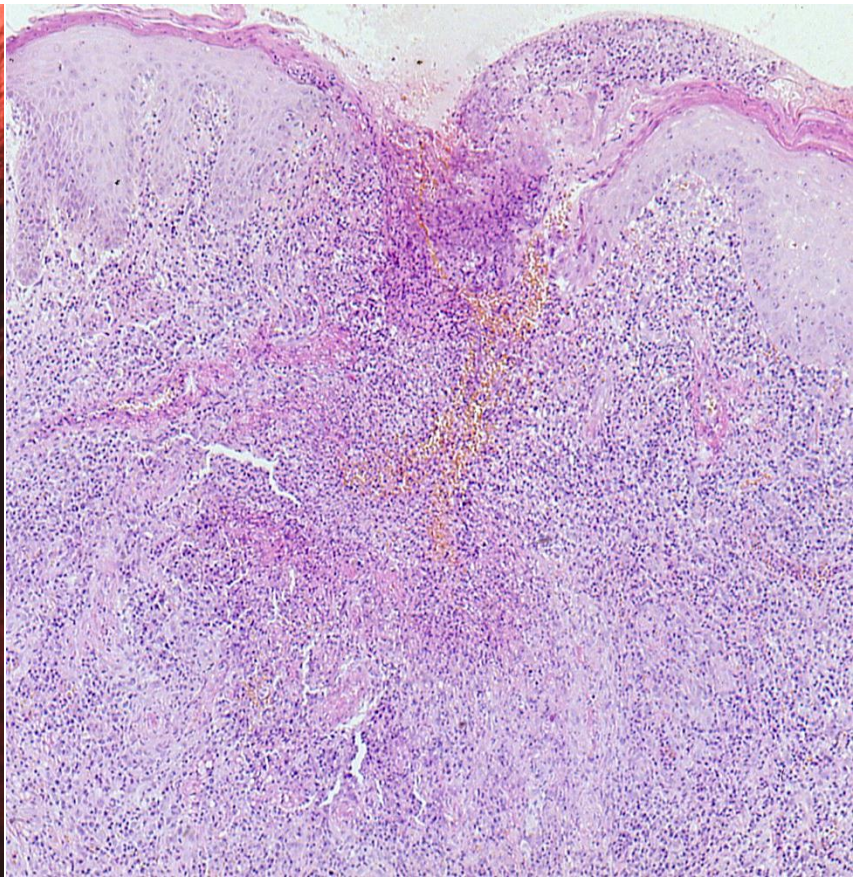
Gonococcal purulent arthritis may be seen in large joints through systemic dissemination of *Neisseria gonorrhoeae*. Aspiration from the swollen knee joint of a male patient aged 40's disclosed gonococci phagocytized by neutrophils (Giemsa). In the outpatient clinic, his unfaithful affair was known by his wife.

Chancroid

Chancroid is a sexually transmitted infection of *Haemophilus ducreyi*, characterized by painful ulcers on the penis/genitalia, and particularly endemic in developing countries. Groin lymph nodes may be enlarged. *H. ducreyi* is a Gram-negative coccobacillus, growing in a long chain (inset: Gram).

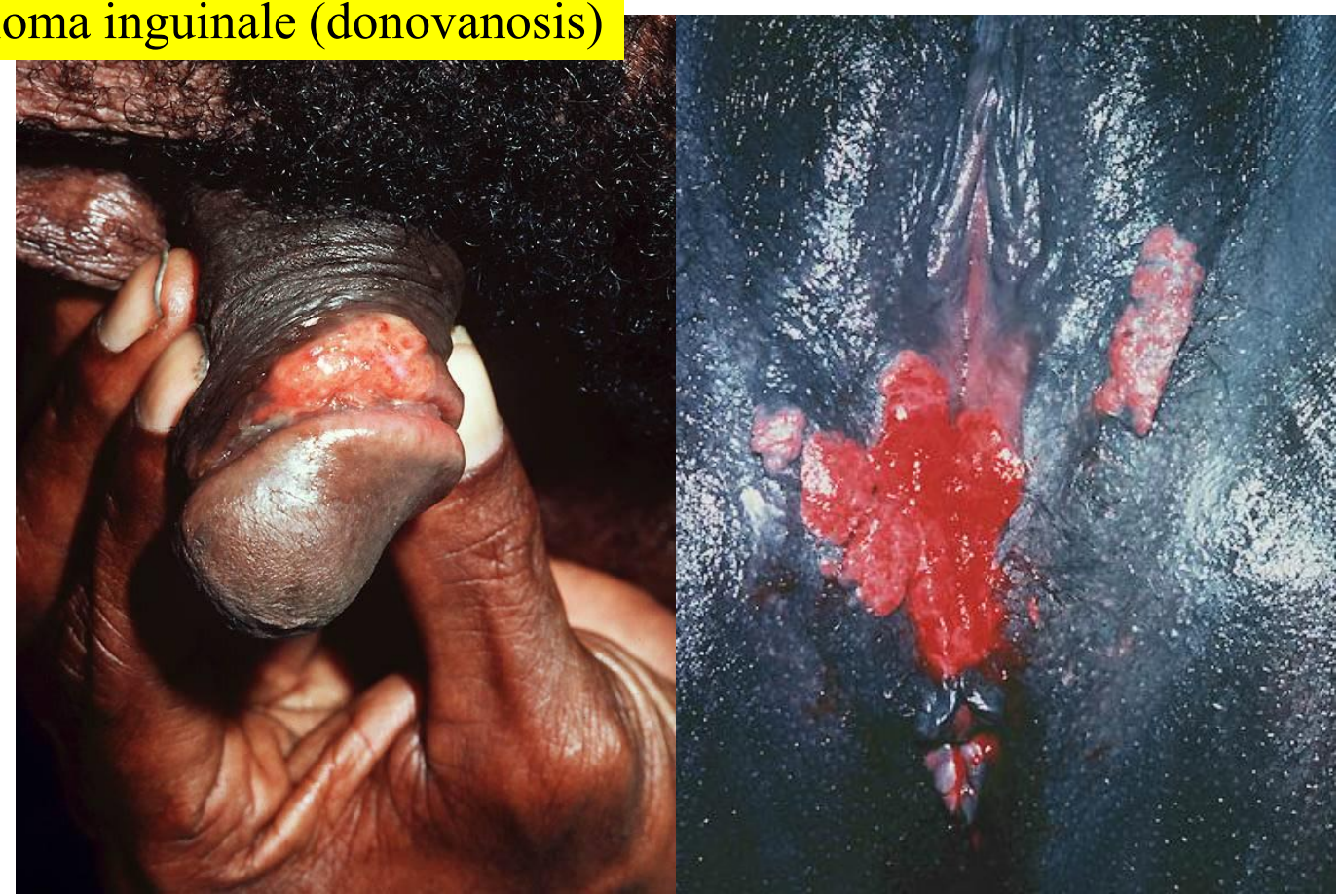
Lymphogranuloma venereum





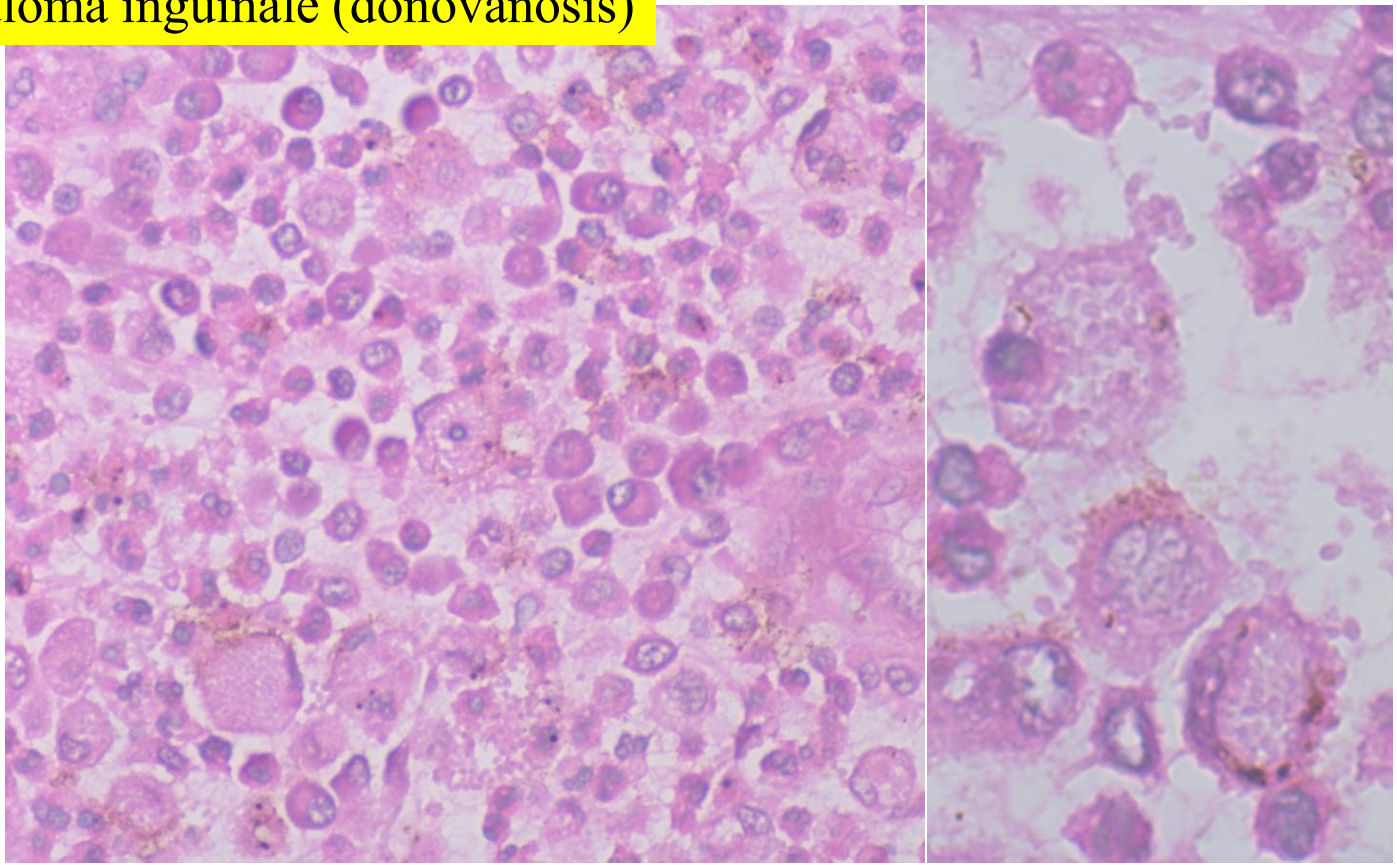
Lymphogranuloma venereum (the 4th venereal disease) is sexually transmitted infection caused by *Chlamydia trachomatis*, serovars L1, L2, L2a, L2b, or L3. Clinically, a self-limited painless genital ulcer is followed by tender inguinal lymphadenopathy (left). The groin skin may be ulcerated with suppurative granulomatous reactions (right, H&E).

Granuloma inguinale (donovanosis)



Granuloma inguinale (donovanosis) is a sexually infected disease caused by *Klebsiella granulomatis* (*Calymmatobacterium granulomatis*), endemic in less-developed counteries. Painless ulcerative nodules in male (left) and female (right) genitalia seen in Papua New Guinea are shown here. Groin lymphadenopathy may be associated.

Granuloma inguinale (donovanosis)



Granuloma inguinale (donovanosis). Biopsy of the genital lesi on demonstrates chronic inflammation with infiltration of lymphocytes, plasma cells and macrophages. Donovan bodies consisting of oval organisms (*Klebsiella granulomatis*) are seen in the cytoplasm of macrophages. Donovan bodies are a microscopic hallmark of granuloma inguinale (H&E).

Syphilis

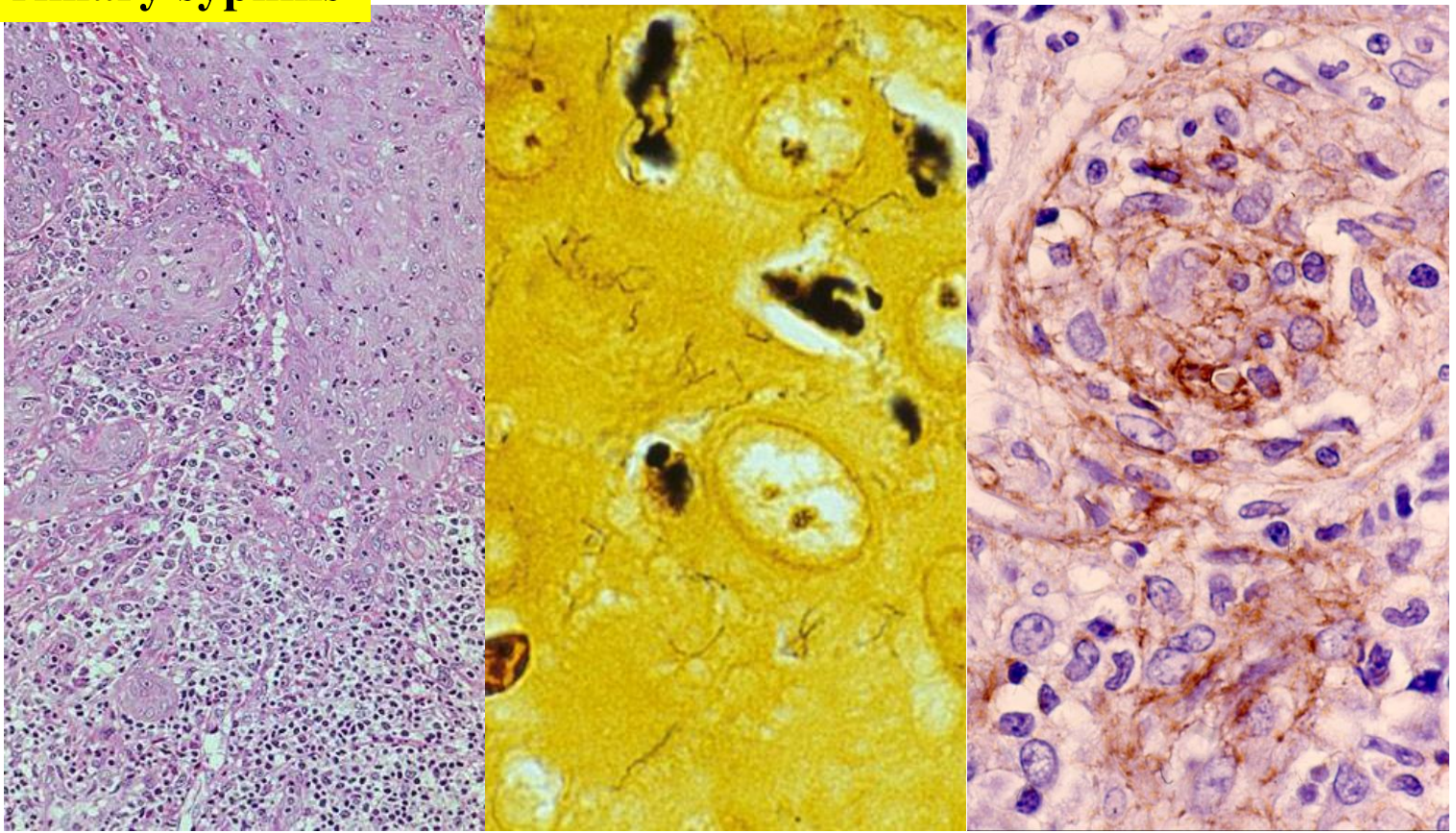
Syphilis is a sexually transmitted infection (STI) caused by *T. pallidum*, an obligate human pathogen. *T. pallidum* is renowned for its invasiveness and immune-evasiveness. Clinical manifestations result from a local inflammatory response elicited by spirochaetes replicating within a variety of tissues. Infected individuals follow a disease course divided into primary, secondary, tertiary and quaternary stages over a period of ≥10 years. The quaternary syphilis included neurosyphilis and cardiovascular syphilis.

Ref.: Peeling R, et al. Syphilis. Nat Rev Dis Primers 2017; 3: 17073. doi: 10.1038/nrdp.2017.73

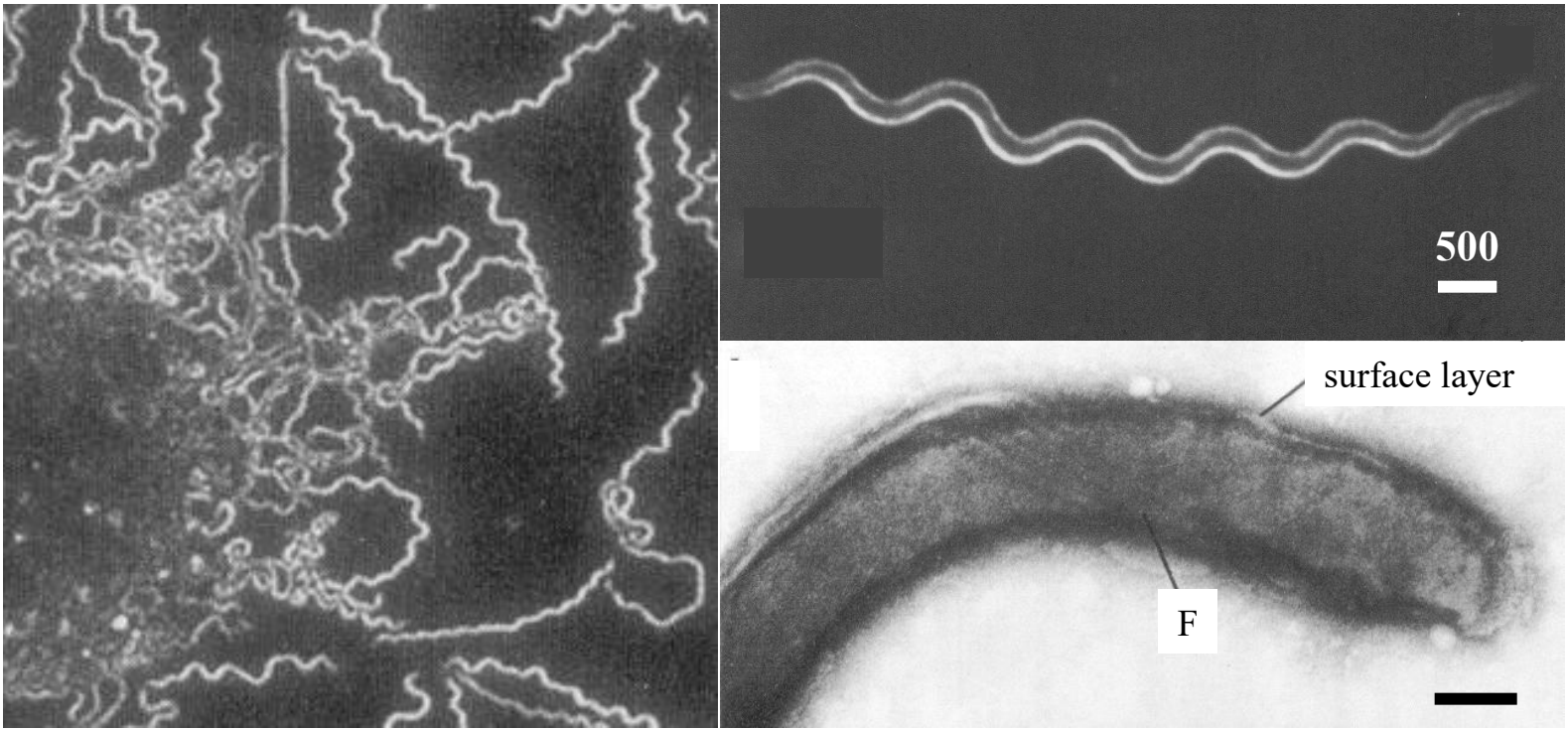
Primary syphilis

Primary syphilis is featured by chancre, a firm, painless, non-itchy and self-limiting skin ulcer on the penis or vulva, measuring 1-2 cm in diameter. The incubation period is 2-6 weeks after contact.

Primary syphilis



Primary syphilis is microscopically featured by reactive acanthosis and dense infiltration of lymphoplasmacytic cells (left: H&E). Warthin-Starry's silver demonstrates black-stained spiral pathogens among the squamous mucosa (center). Immunostaining using antiserum to *Treponema pallidum* discloses spirochaetal infection in both the mucosa and interstitium (right).

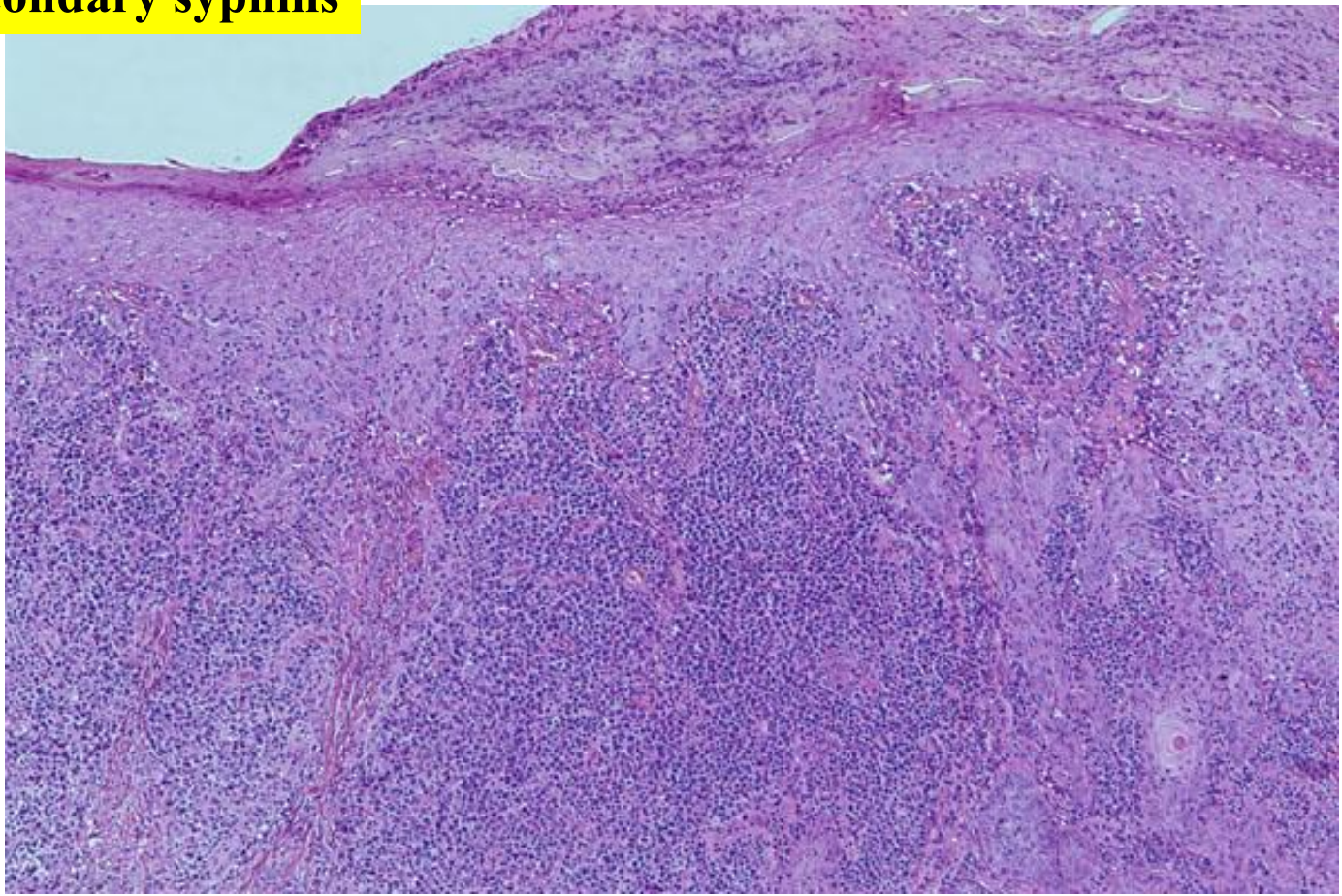


Ultrastructure of *Treponema pallidum*. *T. pallidum* is an anaerobic spiral pathogen, 6-20 μm in length and 0.1-0.02 μm in width, with 6-14 regular spirals. Flagella (F) is important for its movement. It can not be cultured. It glows pale blue light, and therefor the term pallidum (pale in English) was given to the name.

Secondary syphilis

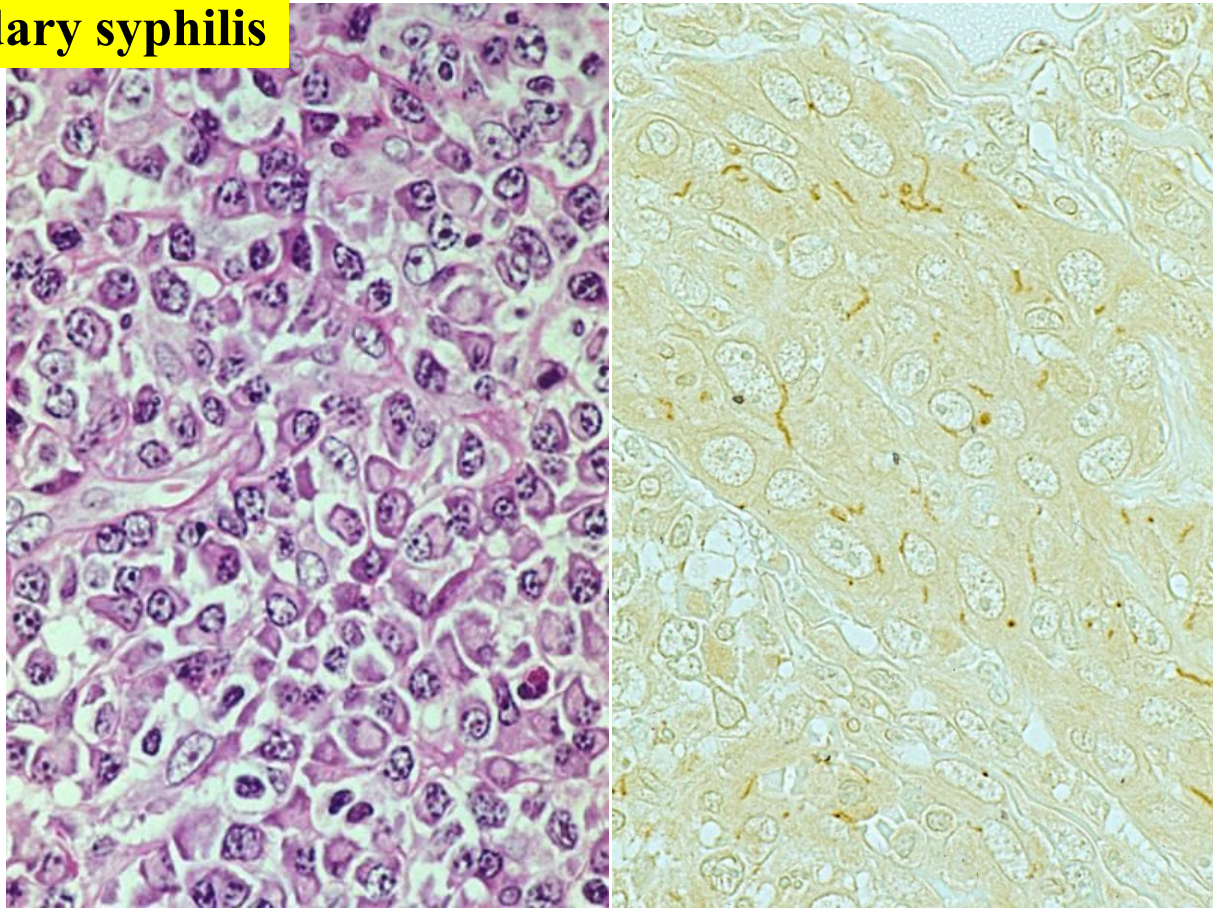
A male patient aged 50's with a history of malignant lymphoma after chemotherapy manifested fever and skin rash on the neck (left) and scalp (right). The clinician suspected skin recurrence of the lymphoma, and the skin papule was biopsied.

Secondary syphilis



Skin biopsy microscopically reveals dense mononuclear infiltration. The epidermis is acanthotic, and covered with crust (H&E).

Secondary syphilis

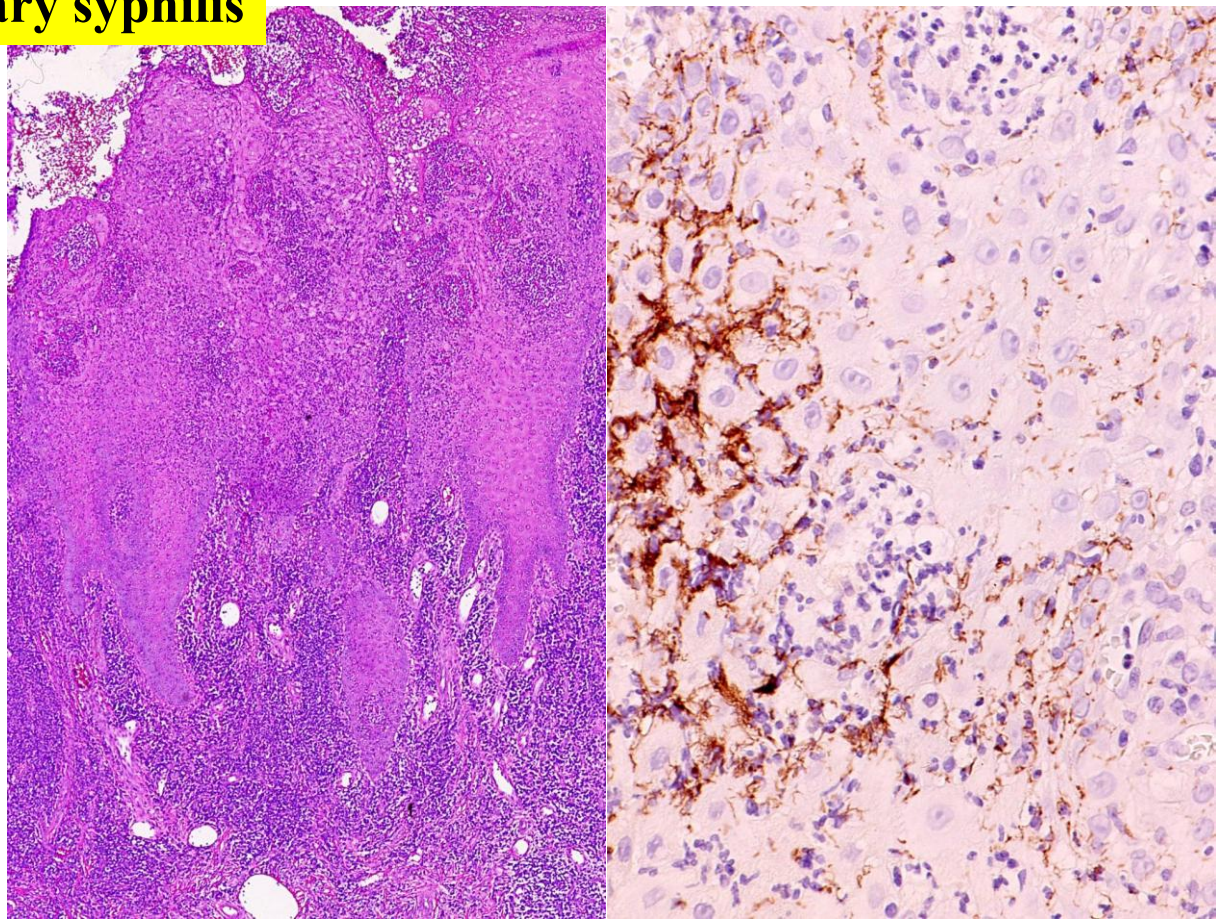


The dermis reveals infiltration of mature plasma cells, excluding the possibility of malignant lymphoma. The possibility of syphilis was pathologically suspected, and immunostaining with antiserum to *Treponema pallidum* clarifies the spiral pathogens, confirming the diagnosis of secondary syphilis. Left: H&E, right: *T. pallidum* antigen.

Secondary syphilis

Secondary syphilides are typically seen as non-itchy rash (papules) on the palm and sole.

Secondary syphilis



Secondary syphilide. Biopsy sampled from the skin rash on the palm shows inflammatory acanthosis (left: H&E). Immunostaining with *Treponema pallidum* antiserum discloses clustered spiral pathogens particularly among the acanthotic epidermis (right).

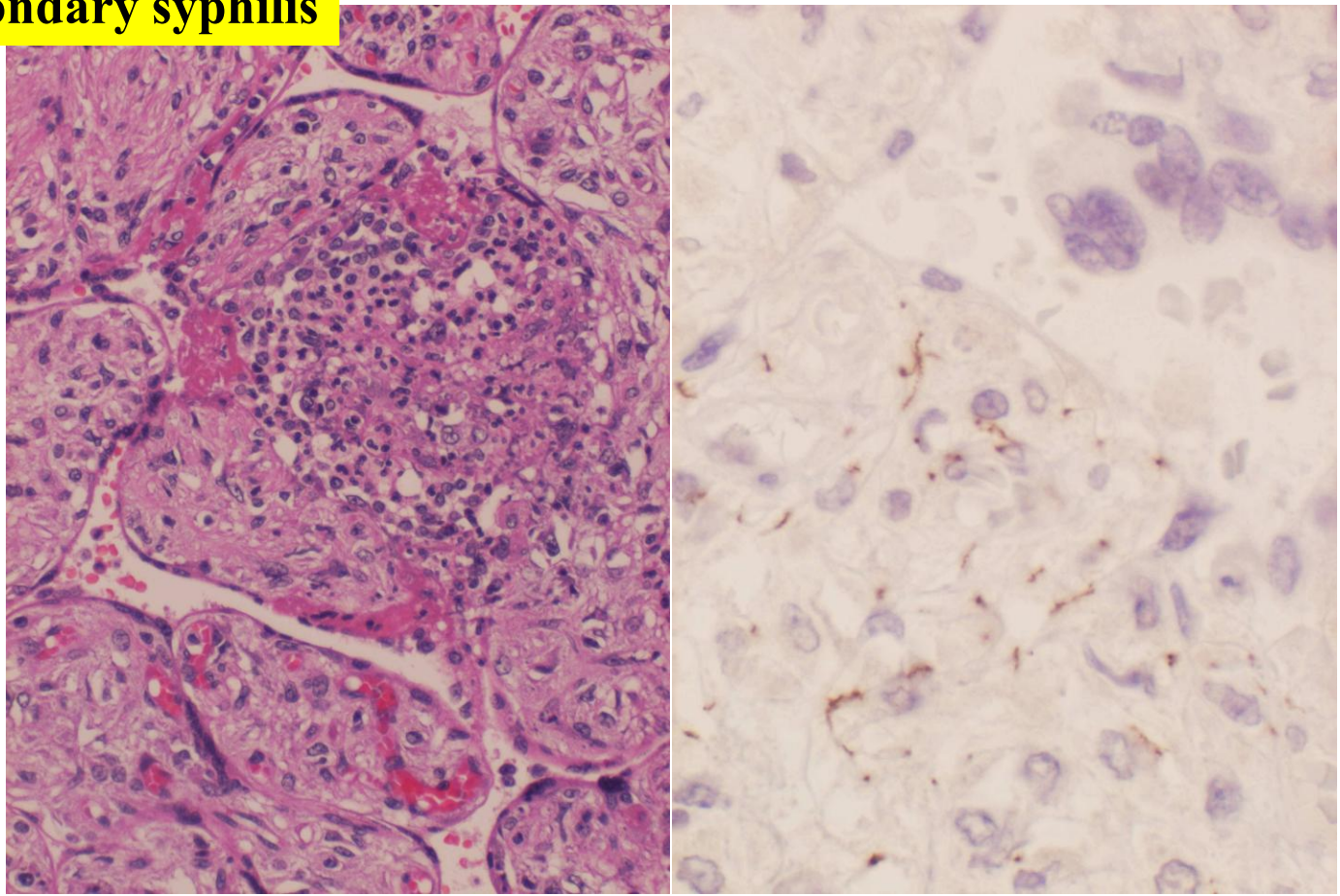
Secondary syphilis

Another case of **secondary syphilides** seen as non-itchy rash (papules) on the palm and sole. These lesions disappear spontaneously without treatment.

Secondary syphilis

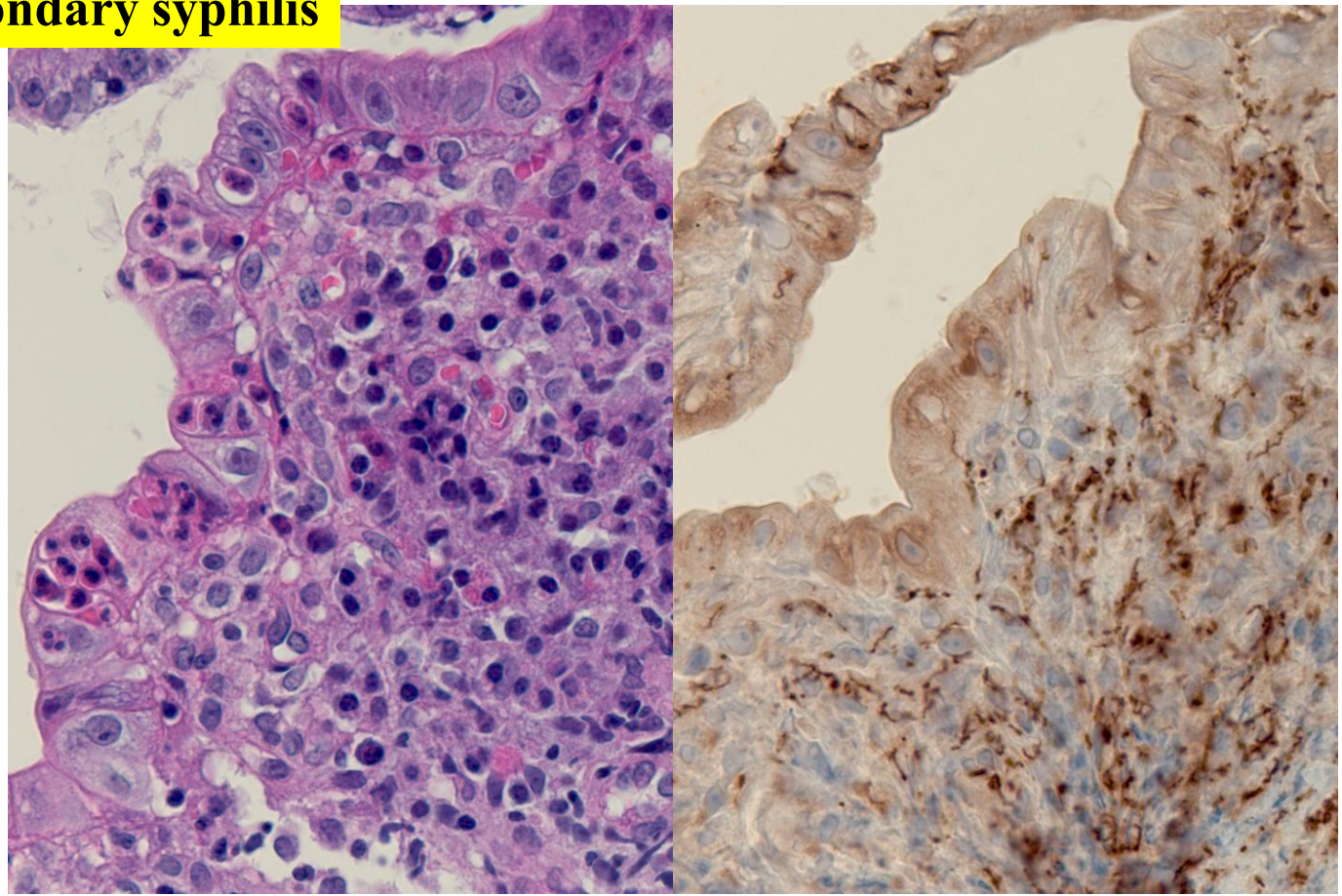
Examples of the **secondary syphilides**. Skin rash on the arms (left) and condyloma lata on the perivulvar/perianal skin (right). The condyloma lata is known to be highly contagious.

Secondary syphilis



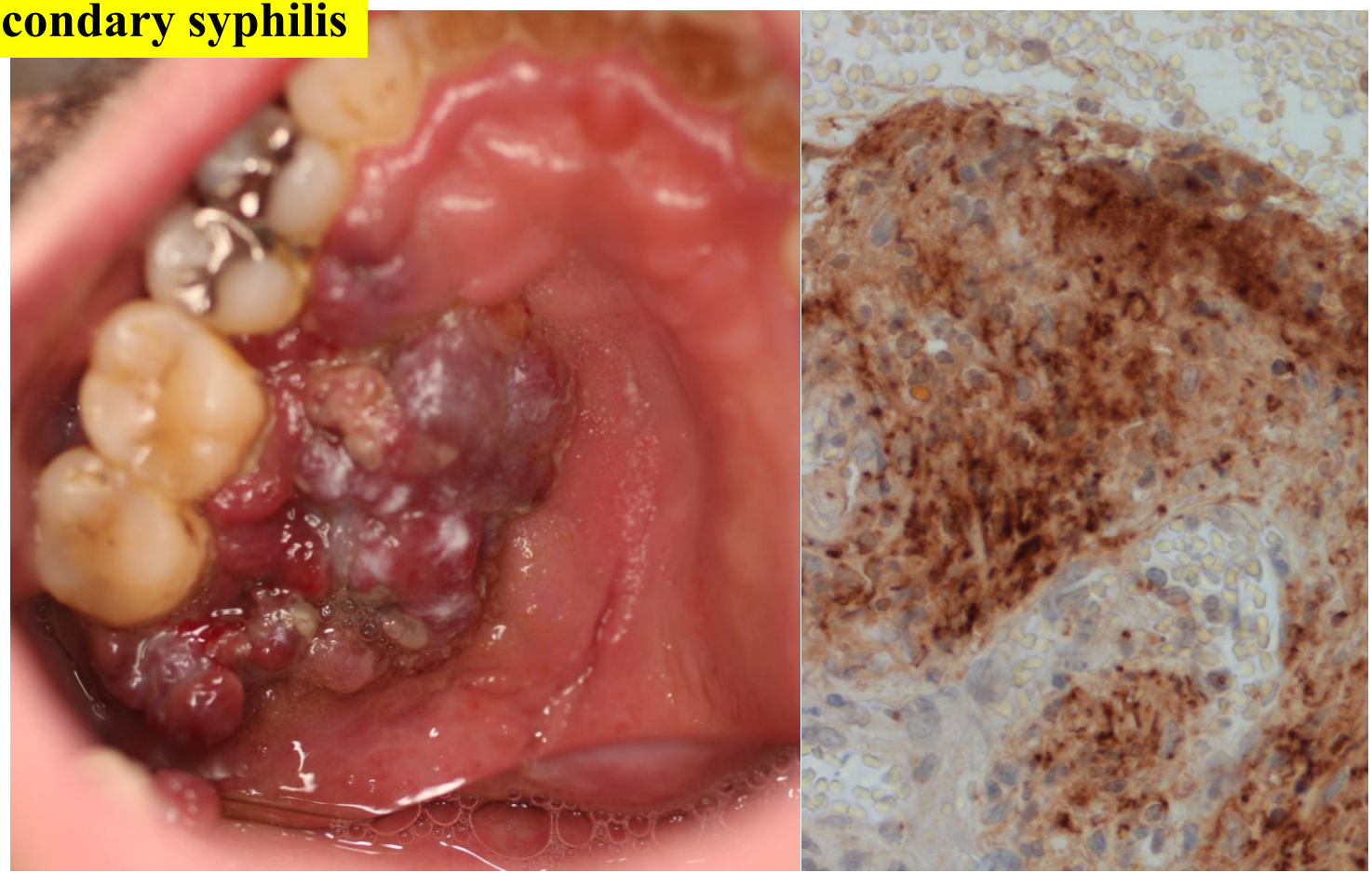
Placental syphilis. The placenta shows focal accumulation of neutrophils (left: H&E). Immunoperoxidase staining for *Treponema pallidum* antigens discloses infection of spral pathogens (right).

Secondary syphilis



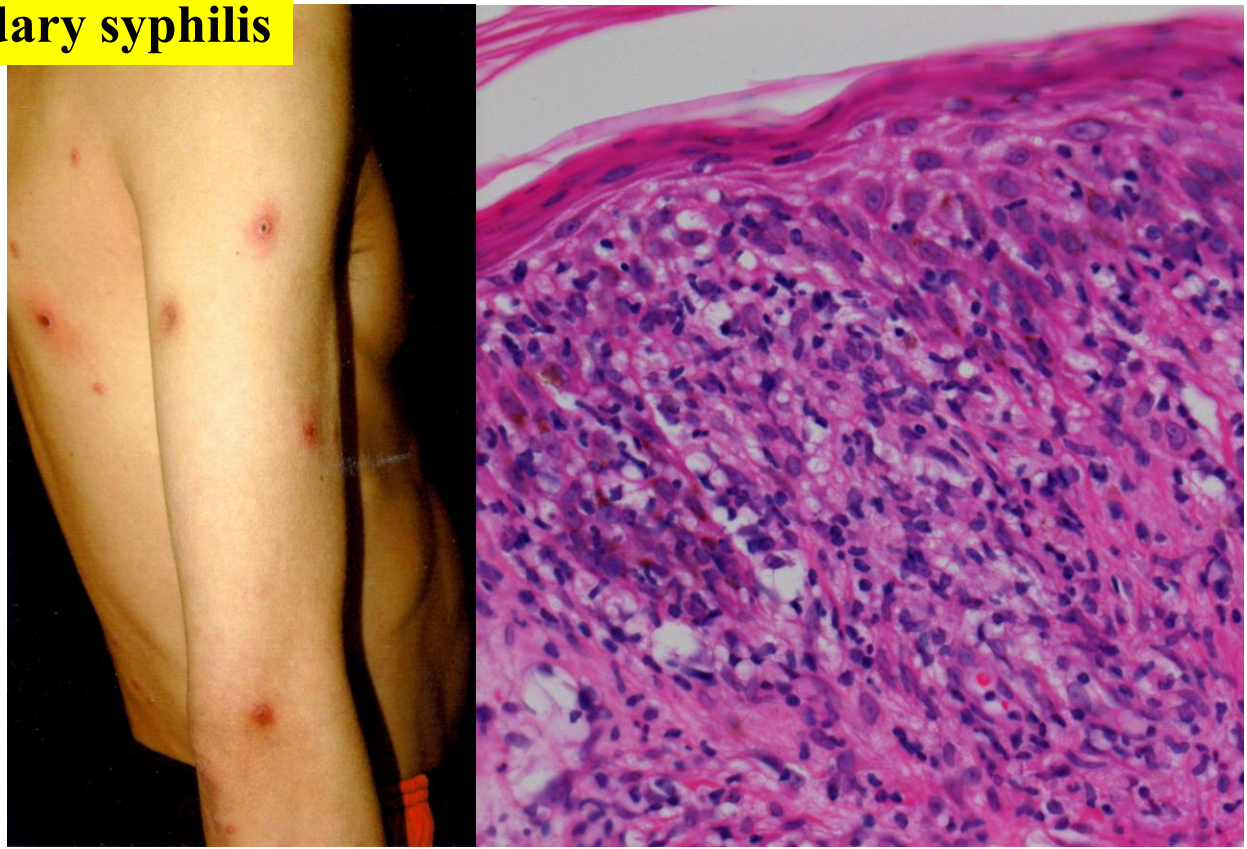
Syphilitic gastritis. The stomach is a favorite site of syphlitic involvement of the internal organs in the second stage. The gastric mucosa is heavily infected with Treponema pallidum.

Secondary syphilis



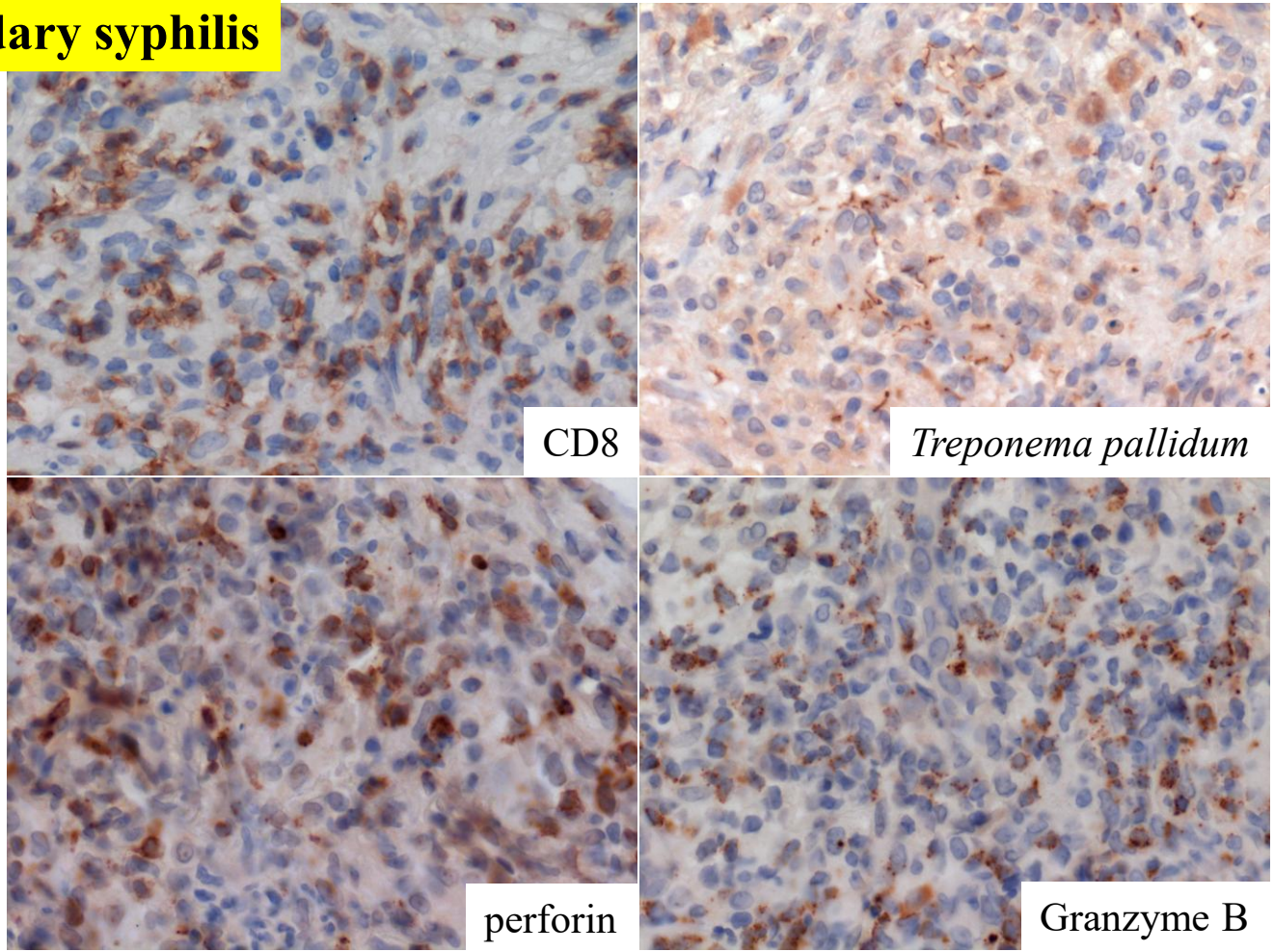
Syphiltic stomatitis as the secondary syphilide. Biopsy taken from the oral tumor (left) reveals massive infection of Treponema pallidum, immunostained for the treponemal antigen (right).

Secondary syphilis



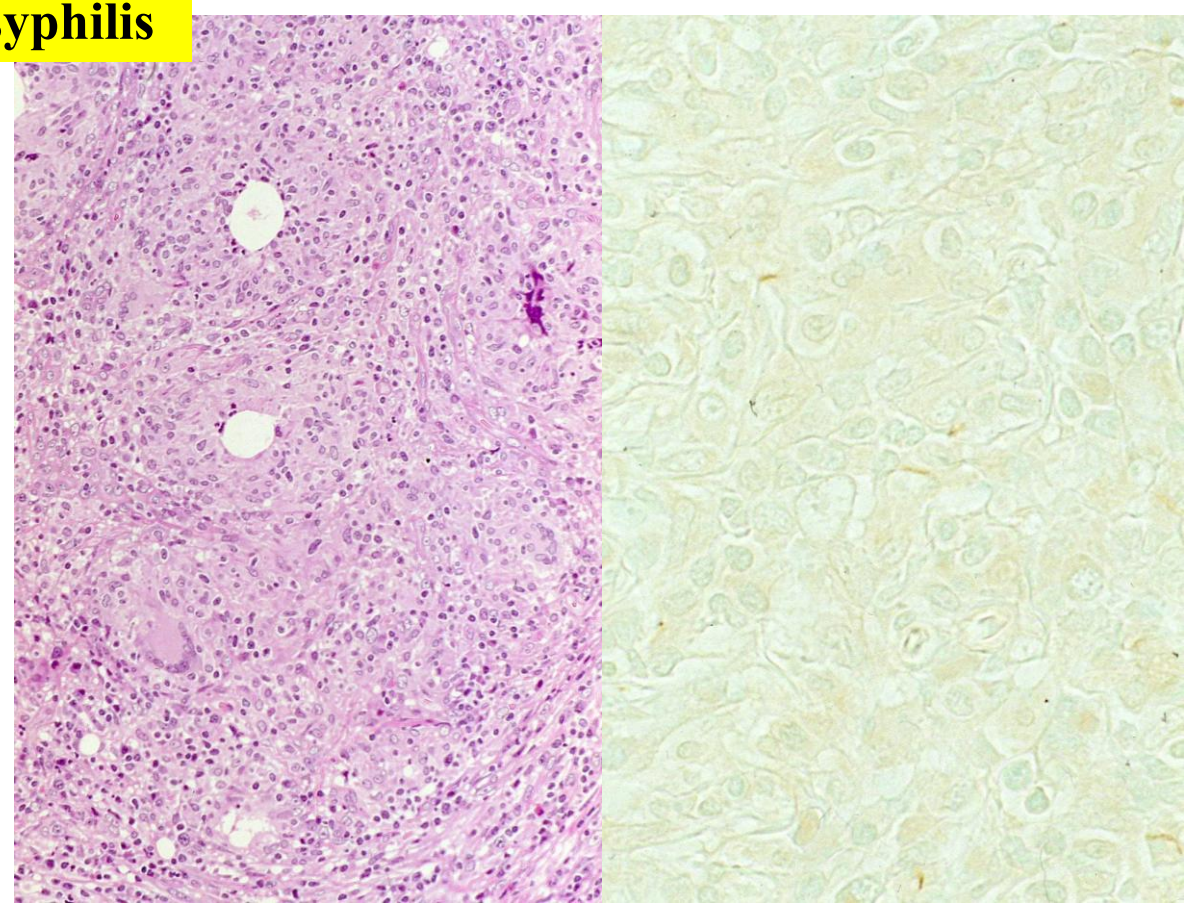
Malignant syphilis (lues maligna) is a severe form of secondary syphilis complicated with HIV infection with very low CD4 lymphocyte count. Erythematous ulcerated papules are multifocally seen on his trunk, extremities, palm and face (left). Biopsy mimics cutaneous CD8+ T-cell lymphoma (right: H&E). Anti-retroviral therapy was dramatically effective. **Ref.**: Yamashita M, et al. Human immunodeficiency virus-positive secondary syphilis mimicking cutaneous T-cell lymphoma. Diagn Pathol 2015; 10: 185. doi: 10.1186/s13000-015-0419-5

Secondary syphilis



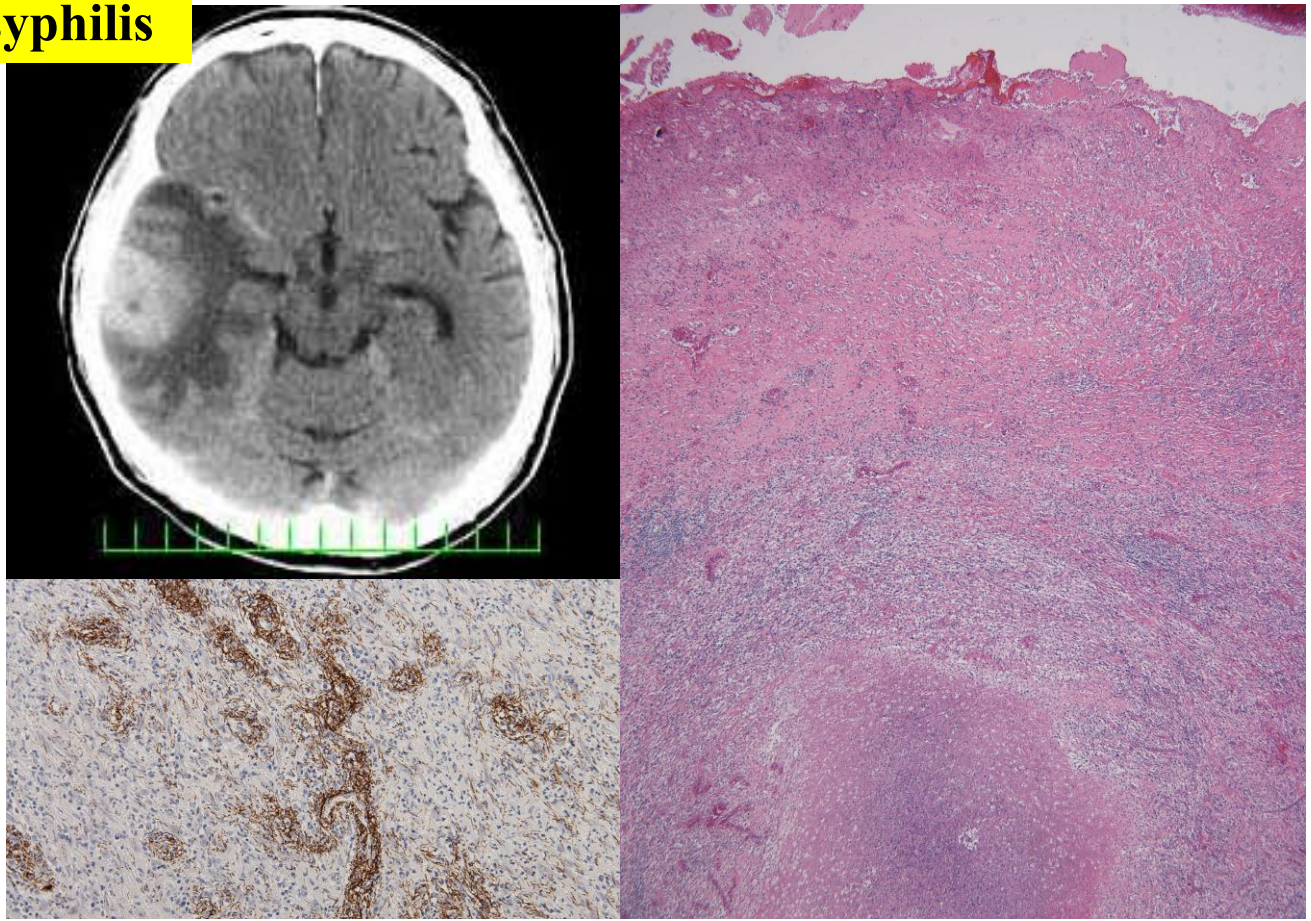
The skin lesion in **HIV-positive malignant secondary syphilis** shows dense infiltration of CD8-positive lymphocytes expressing perforin and granzyme B. A number of Treponema pallidum is immunohistochemically proven within the lesion (right top).

Tertially syphilis



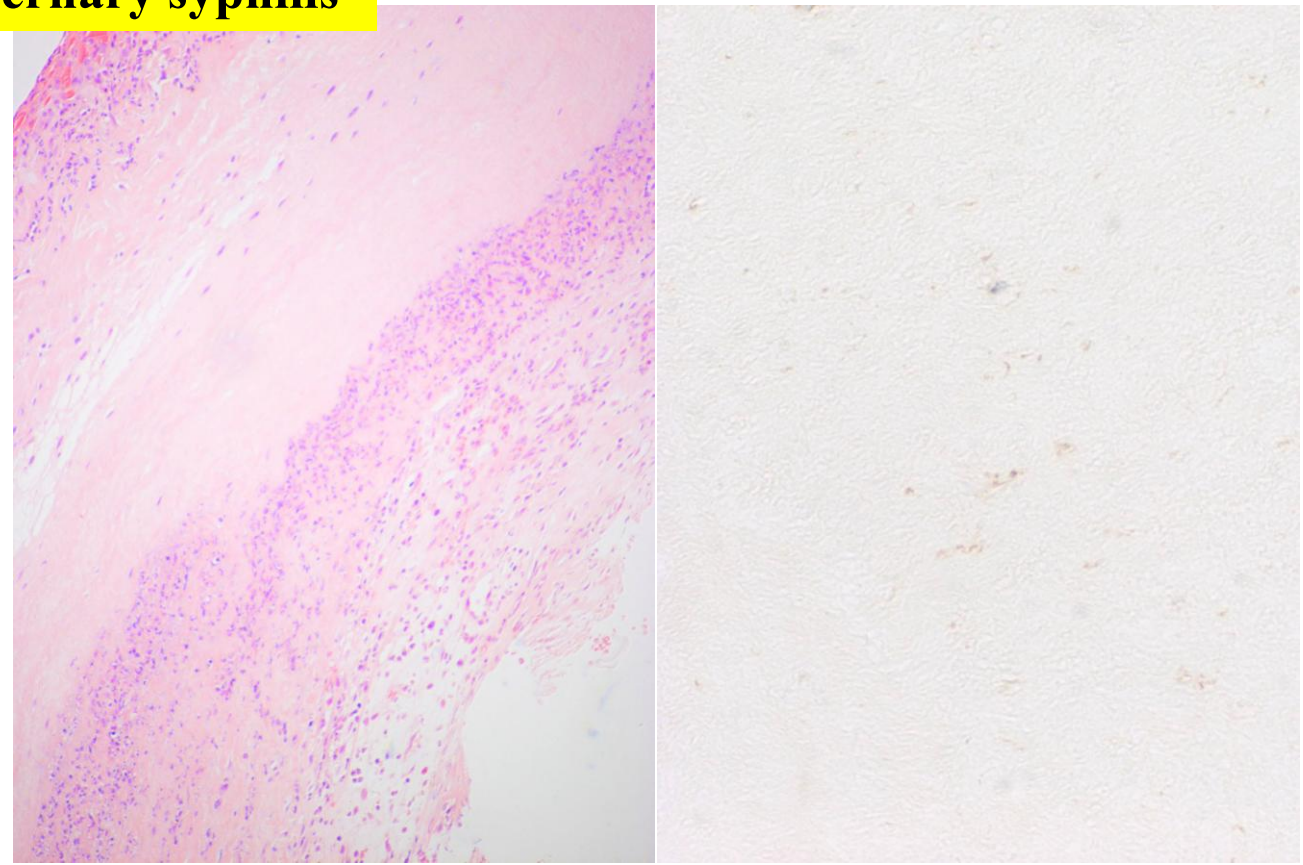
Syphilitic lymphadenitis in the third stage syphilis. Epithelioid granuloma with multinucleated giant cells (gumma) is observed (left). Only a few spiral pathogens are observed by the immunostaining for *Treponema pallidum* antigens (right). Three years have been passed without treatment since the initial infection.

Tertially syphilis



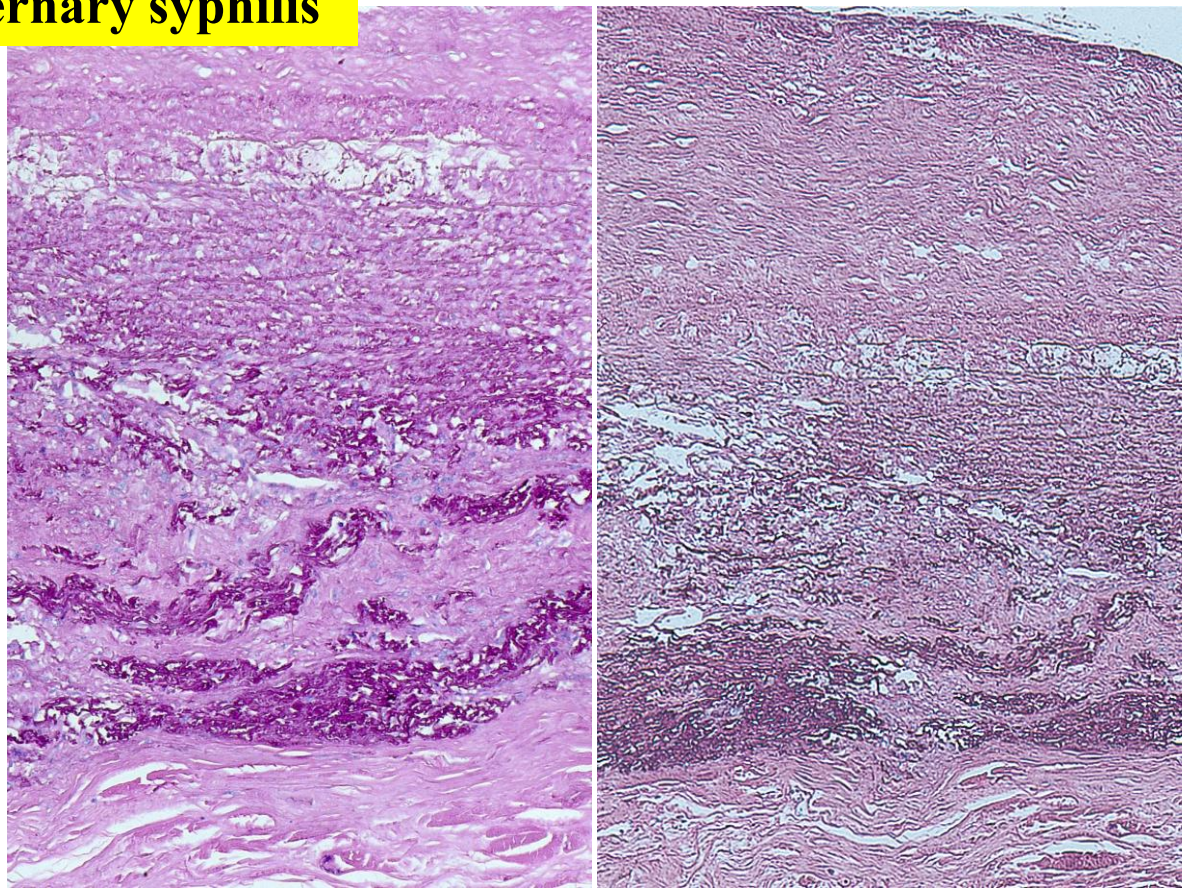
Cerebral gumma as the third stage syphilis. HT scan demonstrates a large tumorous lesion (left top). Brain biopsy reveals gumma wtth central necrosis (right). Immunostaining for *Treponema pallidum* antigens discloses perivascular infection, confirming the diagnosis of gumma (left bottom).

Quaternary syphilis



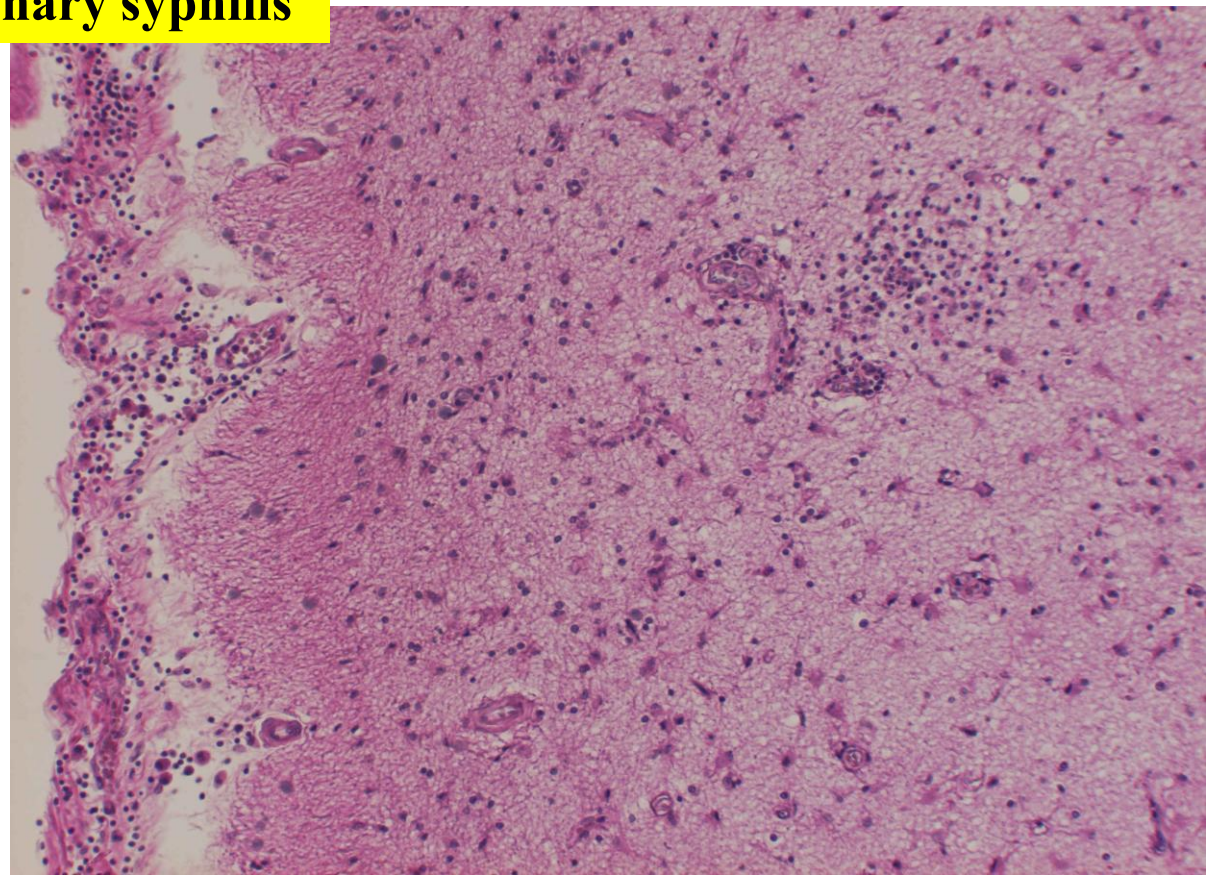
Syphilitic aortic valvulitis accompanying aortic regurgitation in a 66 y-o female patient. Aortic valvulectomy specimen reveals chronic inflammatory infiltration and scattered pathogens, *Treponema pallidum*. Aortic aortitis with aneurysmal dilatation of the ascending aorta is associated. Left: H&E, right: immunostaining for *T. pallidum* antigens

Quaternary syphilis



Syphilitic mesoaortitis as the fourth stage syphilis. Destruction of the elastic lamina is evident in the outer layer of the media of the aortic wall. Involvement of vasa vasorum is the main mechanism of elastolysis. About 10 years are needed for manifesting the aortic involvement of syphilis. Left: H&E, right: EVG

Quaternary syphilis

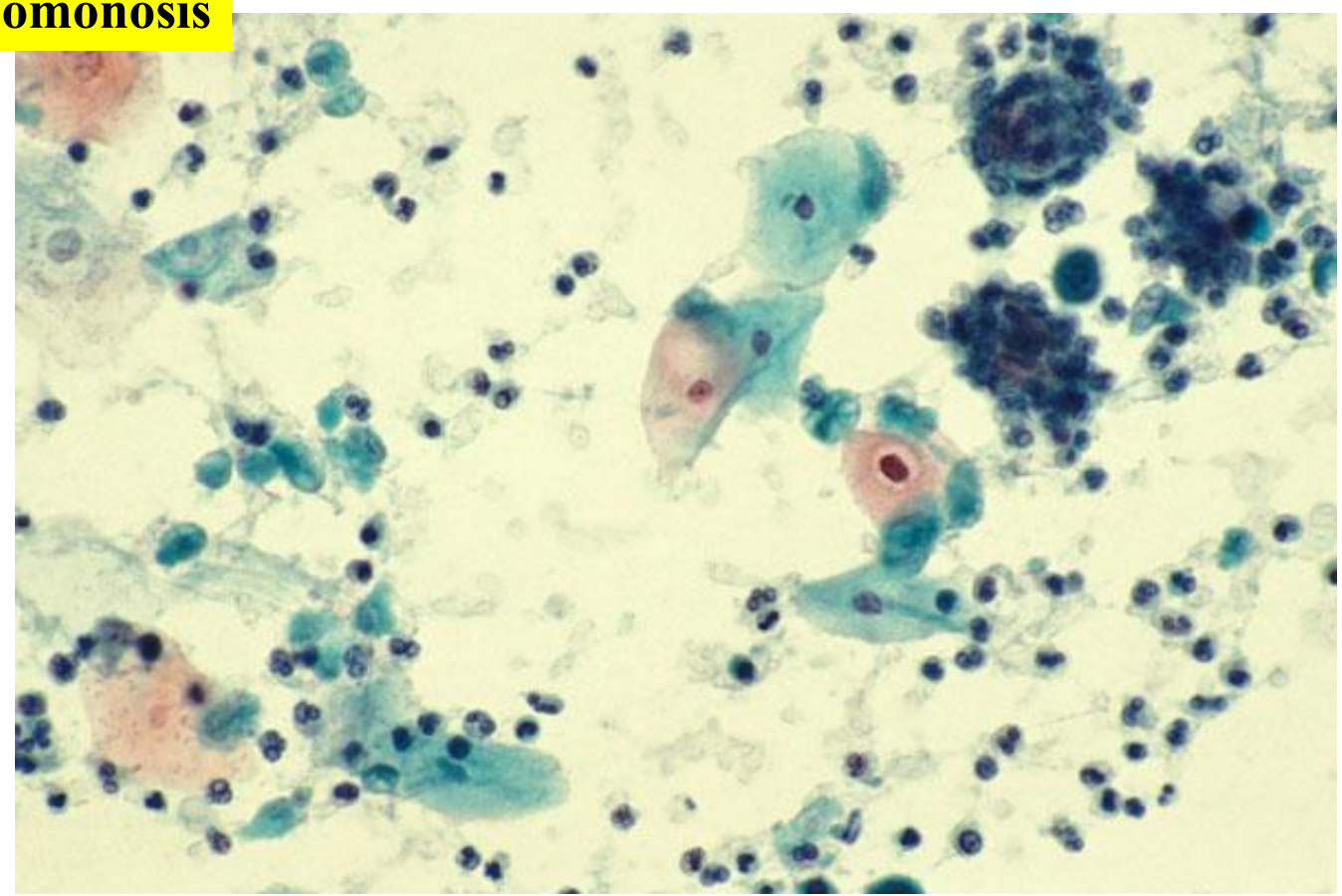


Cerebral tabes (**progressive paralysis**) as the fourth stage syphilis. The patient manifests progressive dementia, personality change and paralysis, 10 years after infection. The cerebral cortex at autopsy reveals diffuse gliosis and lymphocytic infiltration around small vessels and meninges (H&E).

Trichomonosis and herpes simplex infection

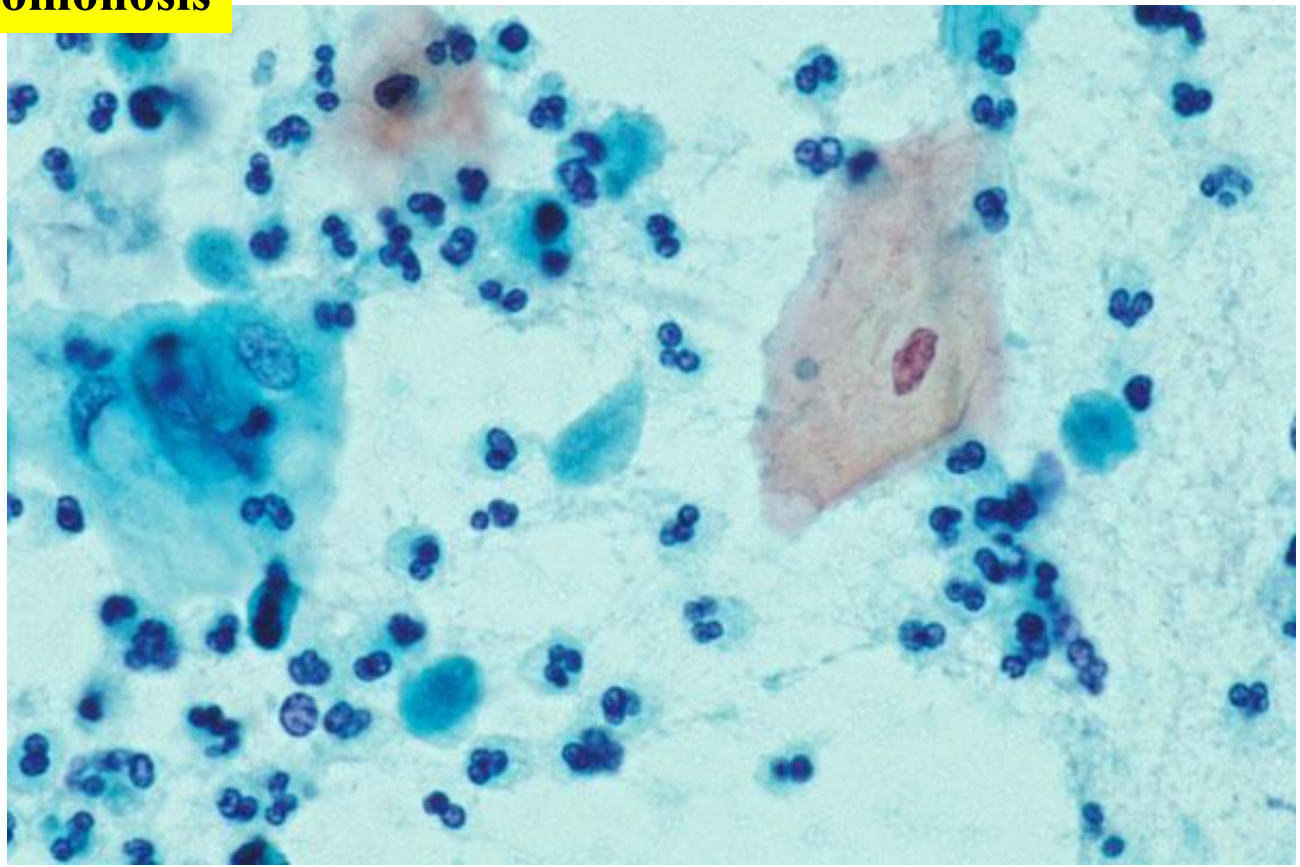
Trichomonosis is a sexually transmitted infection of a flagellated protozoan microbe, *Trichomonas vaginalis*. Herpes simplex virus (HSV), type II, causes painful bullous lesion on the genitalia. Oral sex mediates infection of HSV, type I. The symptoms are severer in HSV, type I infection than in the classical type II infection.

Trichomonosis



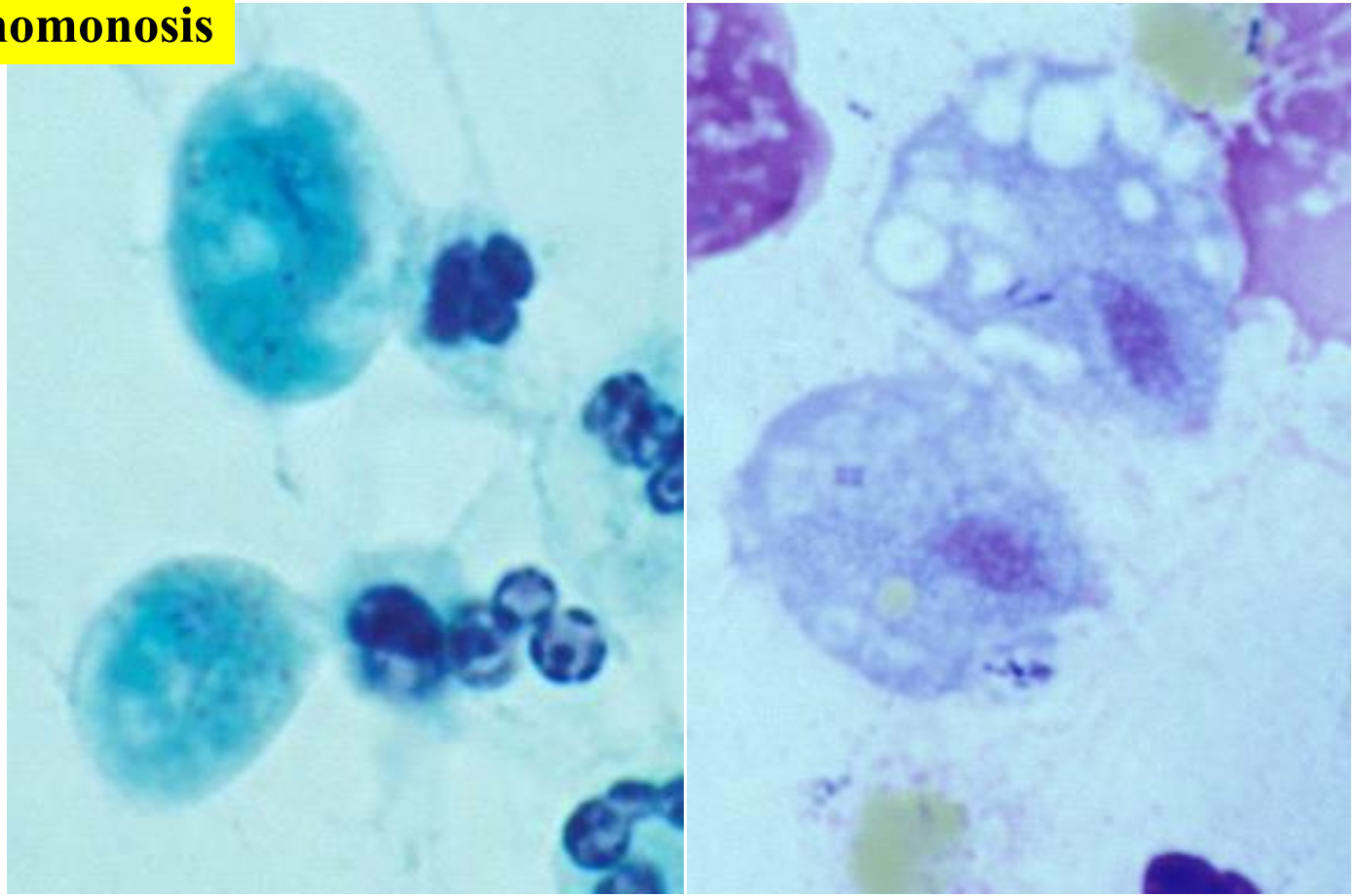
Trichomonosis. The Pap-stained cervical smear preparation reveals *Trichomonas vaginalis* infection particularly around orange-stained superficial-type keratinocytes. Neutrophilic clusters forming so-called “cannon balls” are characteristic (Pap).

Trichomonosis



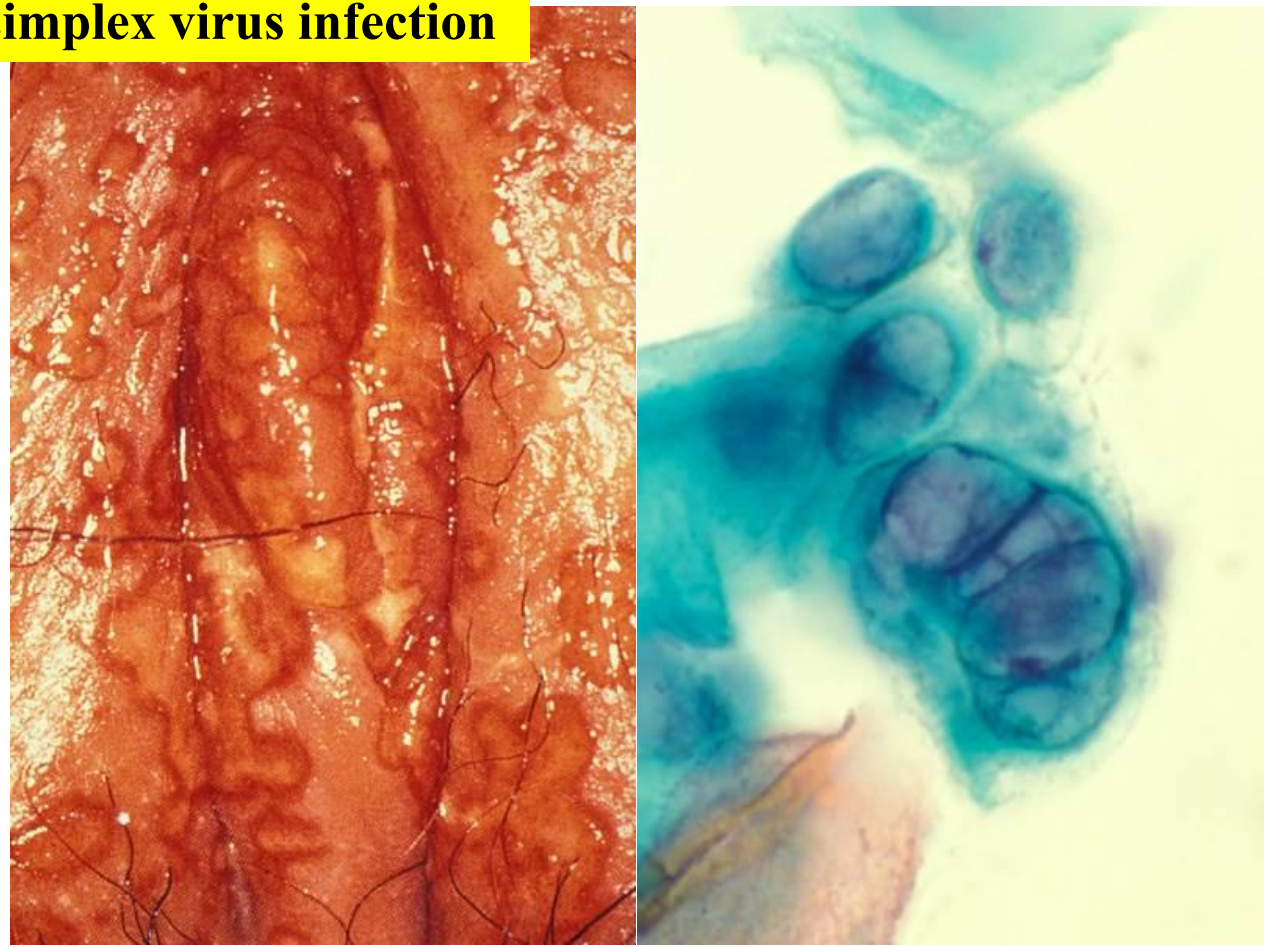
Trichomonosis. The Pap-stained cervical smear preparation reveals *Trichomonas vaginalis* infection with neutrophilic reactions. Normal flora, Doederlein bacilli, are lost, and small bacilli are co-infected (Pap).

Trichomonosis



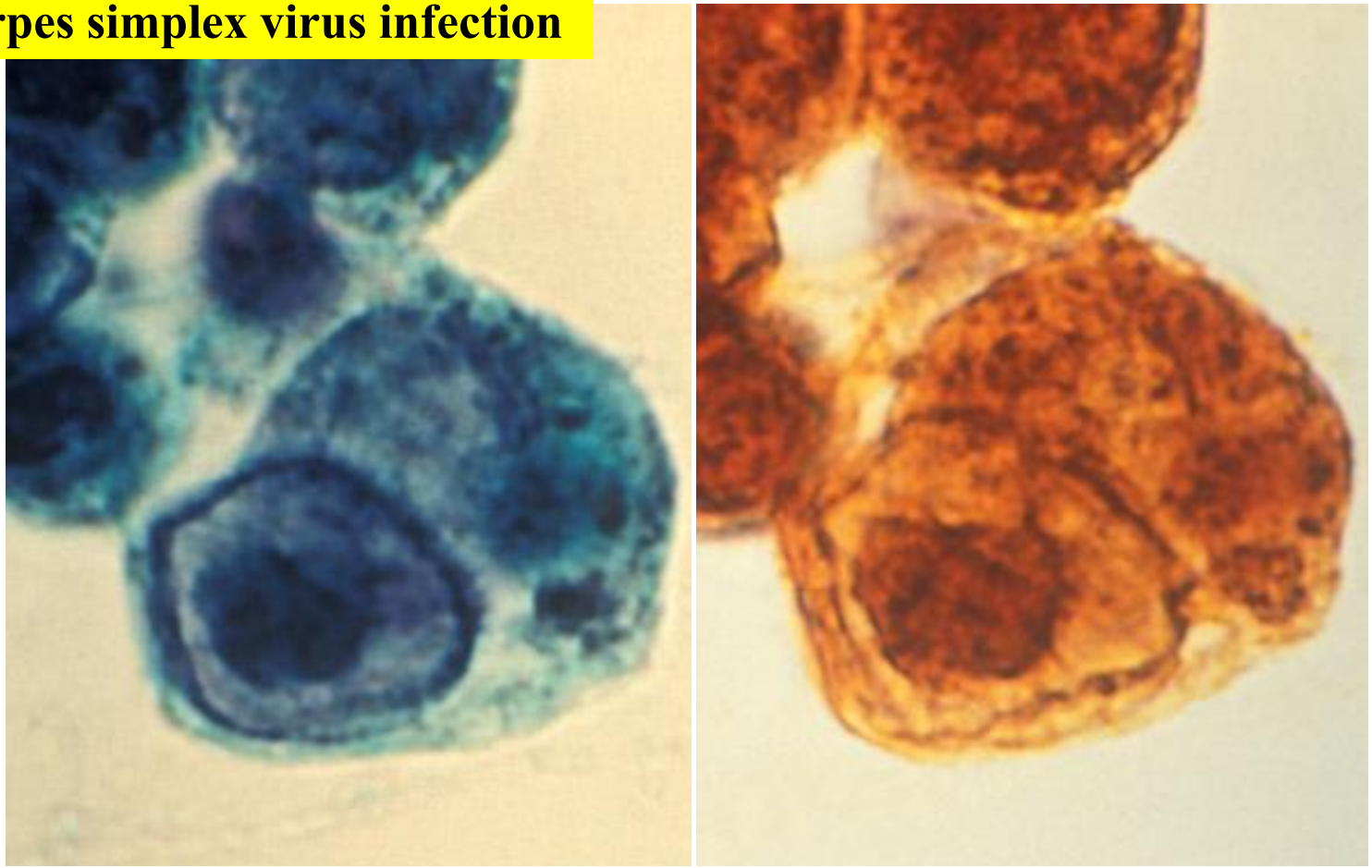
Trichomonosis. Oil immersion observation reveals a single nucleus and granular and vacuolated cytoplasm. It is known that *Trichomonas vaginalis*, anaerobc microbe, lacks mitochondria. The size is a little bit larger than the neutrophil. Left: Pap, right: Giemsa

Herpes simplex virus infection



Herpes simplex virus infection. Painful ulcer is noted on the vulva (left). Smear cytology reveals intranuclear viral inclusions of smudge type. The infected keratinocytes are often multinucleated (right: Pap).

Herpes simplex virus infection



Herpes simplex virus infection. Smear cytology reveals intranuclear viral inclusions of Cowdry A type (left: Pap). Using the restaining method, the infected keratinocytes are immunoreactive for HSV antigen in both the nucleus and cytoplasm (right: immunostain).

Herpes simplex virus infection

Acromastitis (**mamillitis**) caused by herpes simplex virus (HSV). Painful erosion is seen on the bilateral nipples (left). Scraping cytology reveals intranuclear viral inclusions of smudge type in the squamous epithelial cells (right: Pap). The infection is caused by oral contact from the sex partner with labial herpes.

Human papillomavirus (HPV) infection

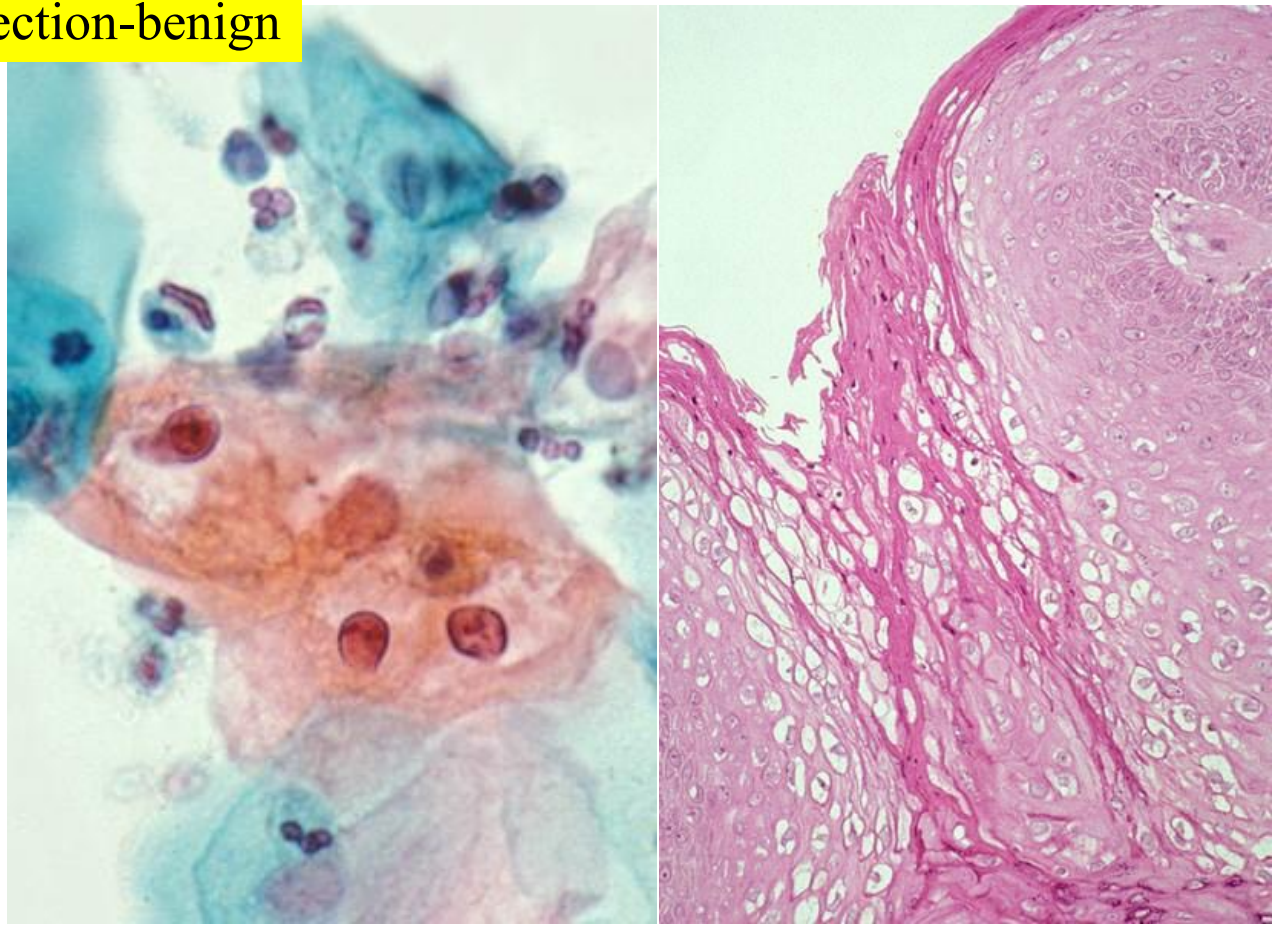
Human papillomavirus (HPV), consisting of a group of epitheliotropic double-stranded small-sized DNA virus, often causes sexually transmitted infection. There are more than 200 types of HPV, divided into 5 groups (α, ß, γ, μ, and ν). The groups ß, γ and μ cause skin warts. Mucosal lesions are caused by α-type HPV, and 15 of the α-types (high-risk-HPV) can lead to carcinoma of squamous cell, adeno or neuroendocrine type. In carcinogenic HPV infection, the viral genome, including E6 and E7, is integrated into the host cell DNA. This results in the inactivation of p53 and Rb tumor suppressors, leading to dysregulation of cell division and apoptosis. Dysplastic and cancerous cells with carcinogenic HPV infection induces the overexpression of p16-INK4a in the nuclei and cytoplasm of the diseased cells.

Ref.: Soheili M, et al. Human papilloma virus: a review study of epidemiology, carcinogenesis, diagnostic methods, and treatment of all HPV-related cancers. Med J Islam Repub Iran 2021; 35: 65. doi: 10.47176/mjiri.35.65

HPV infection-benign

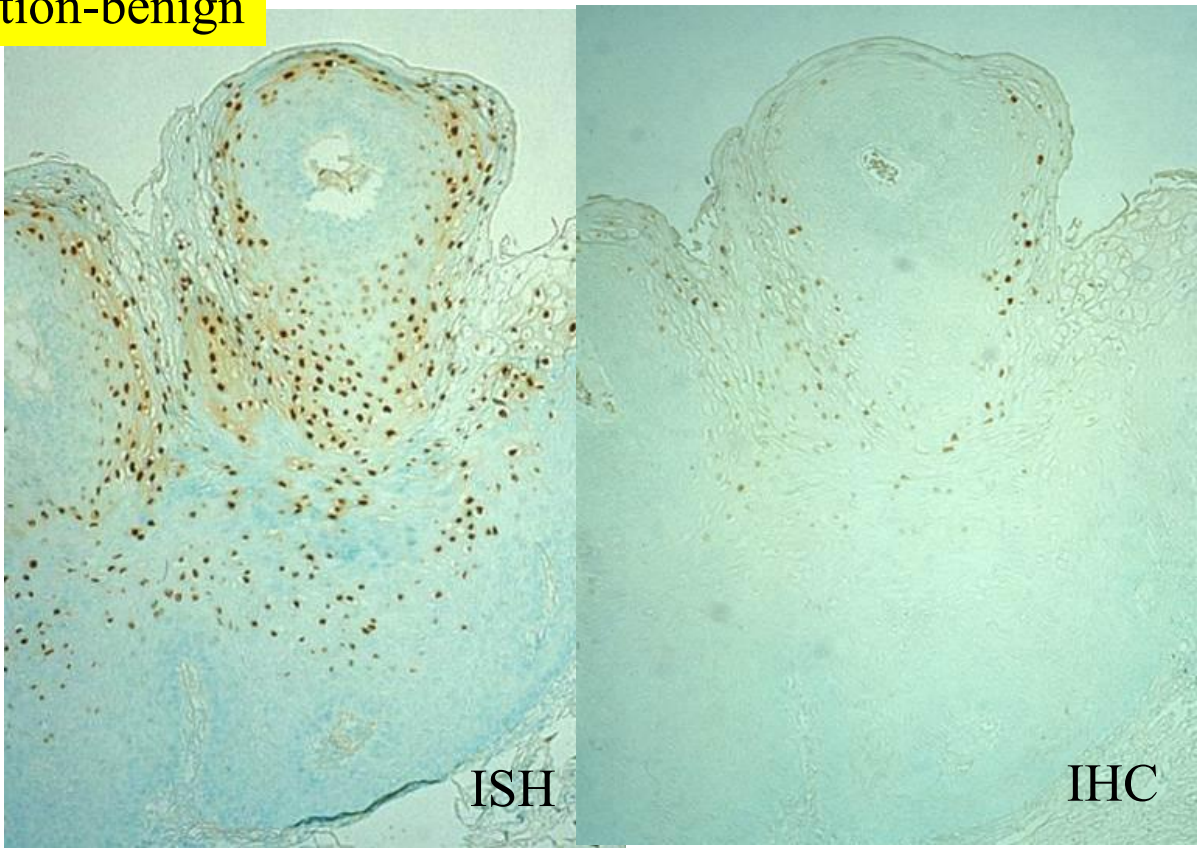
Condyloma acuminatum. Papillary warts are clustered along the glans coronal sulcus. Condyloma acuminatum is a venereal wart caused by infection of human papillomavirus (HPV), type 6/11.

HPV infection-benign



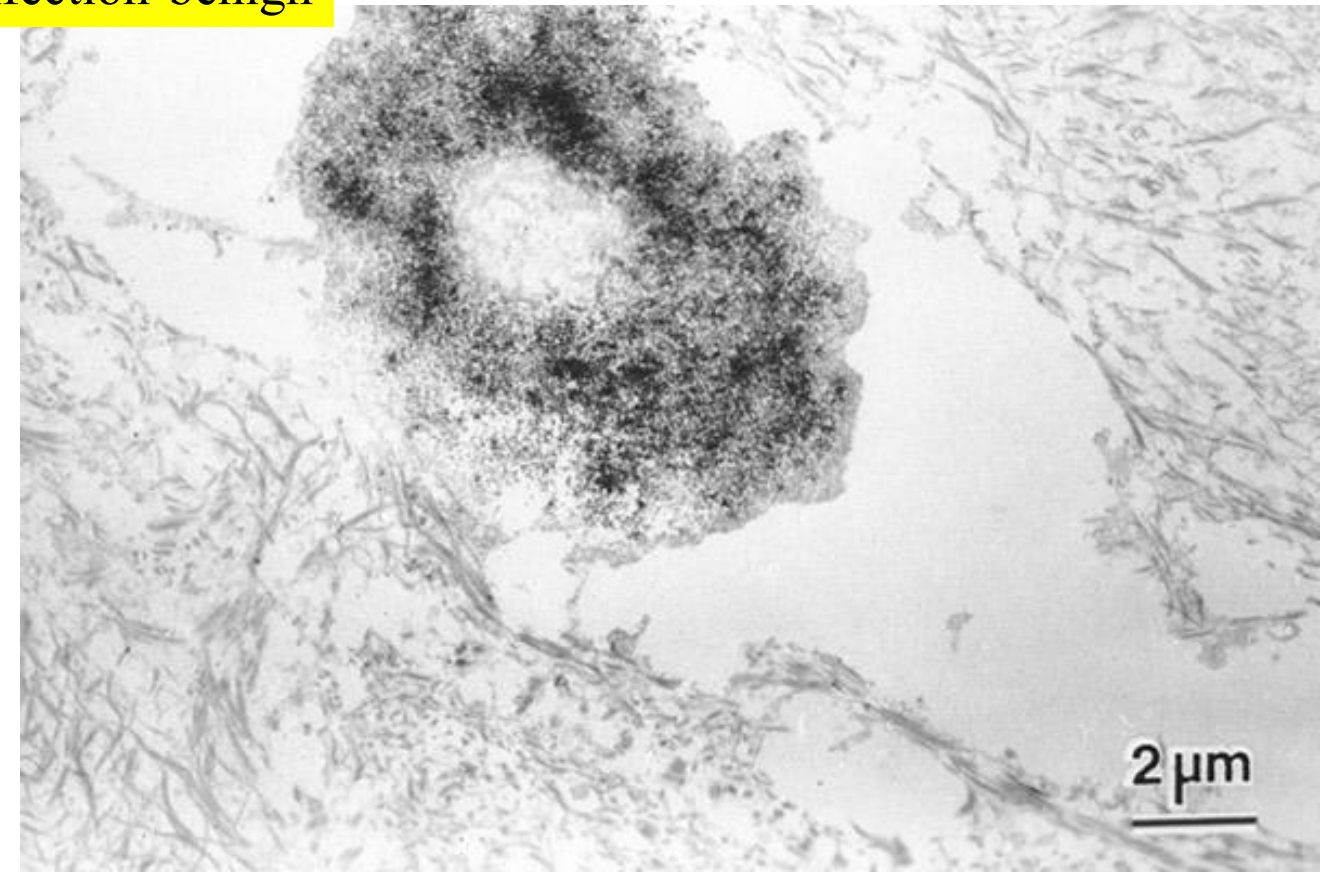
Human papillomavirus (HPV) infection with koilocytc atypia. **Condyloma acuminatum** is caused by sexually transmitted infection of HPV type 6/11. Koilocytosis is a hallmark of HPV infection (left: Pap in the cervical smear, right: H&E in the biopsy specimen).

HPV infection-benign



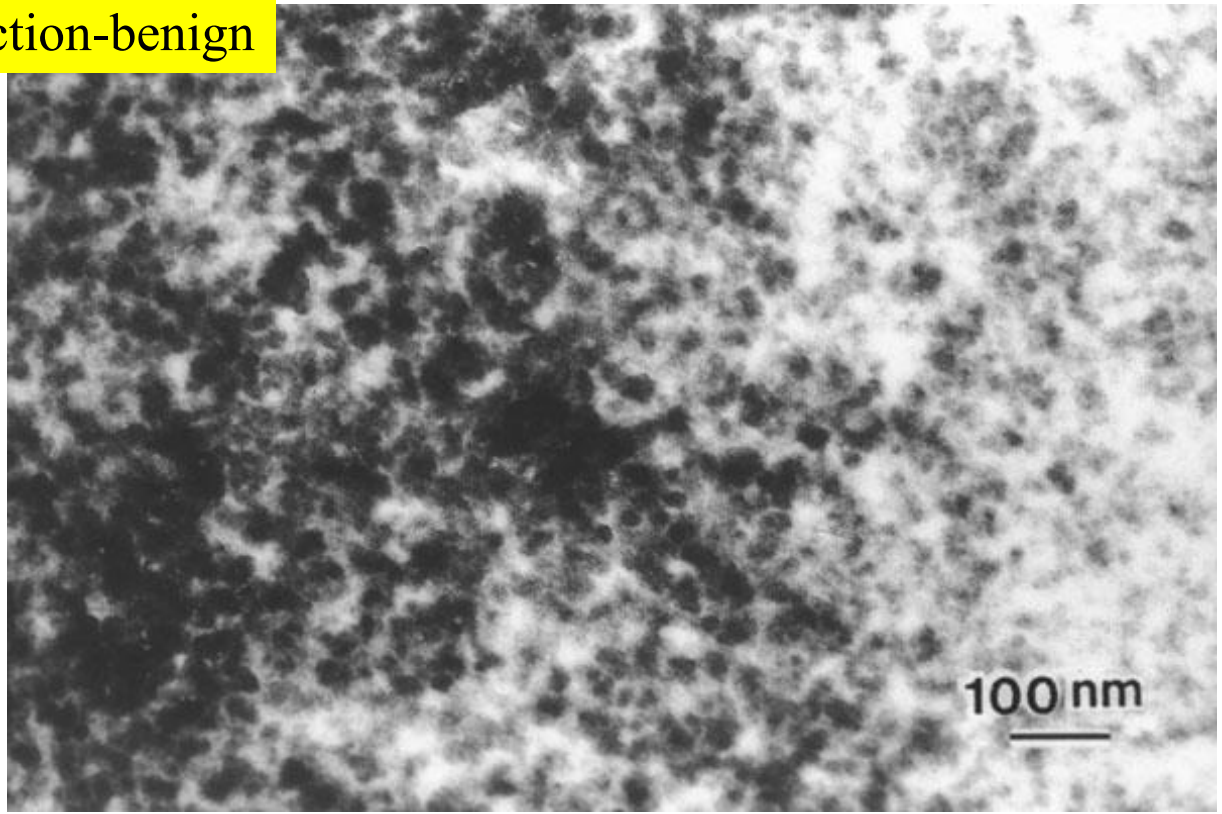
Condyloma acuminatum, caused by HPV 6/11 infection. The virus is demonstrated by both *in situ* hybridization (ISH: left) and immunohistochemistry (IHC: right). More cells are labeled for the HPV 6/11 genome than for the HPV capsid antigens, indicating that the infected cells predominantly contain viral particle-free viral DNA molecules.

HPV infection-benign



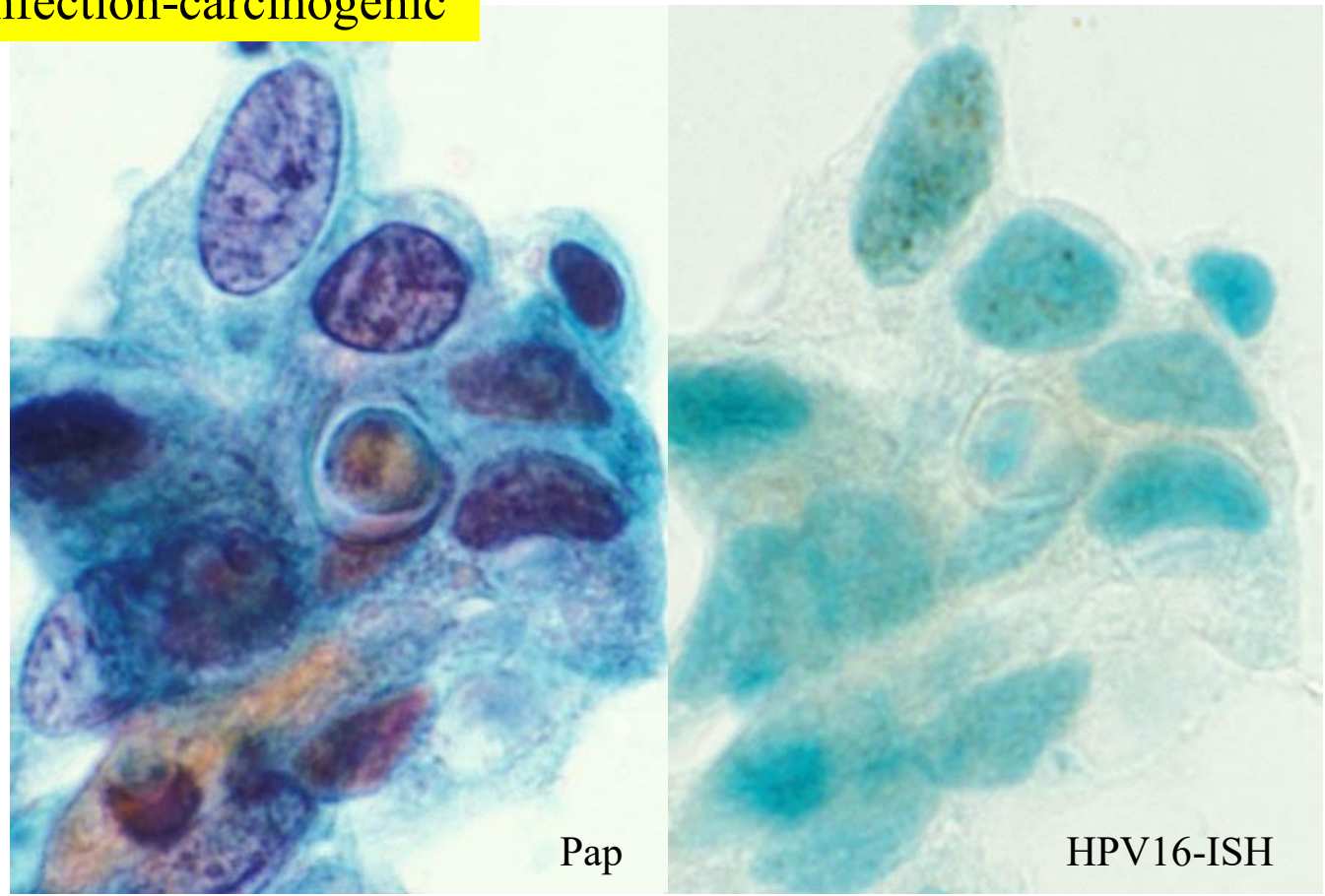
Condyloma acuminatum. Ultrastructural localization of HPV 6/11 genome using a formalin-fixed, paraffin-embedded section. Positive genomic signals are distributed in the nuclear matrix with a fine particular pattern.

HPV infection-benign



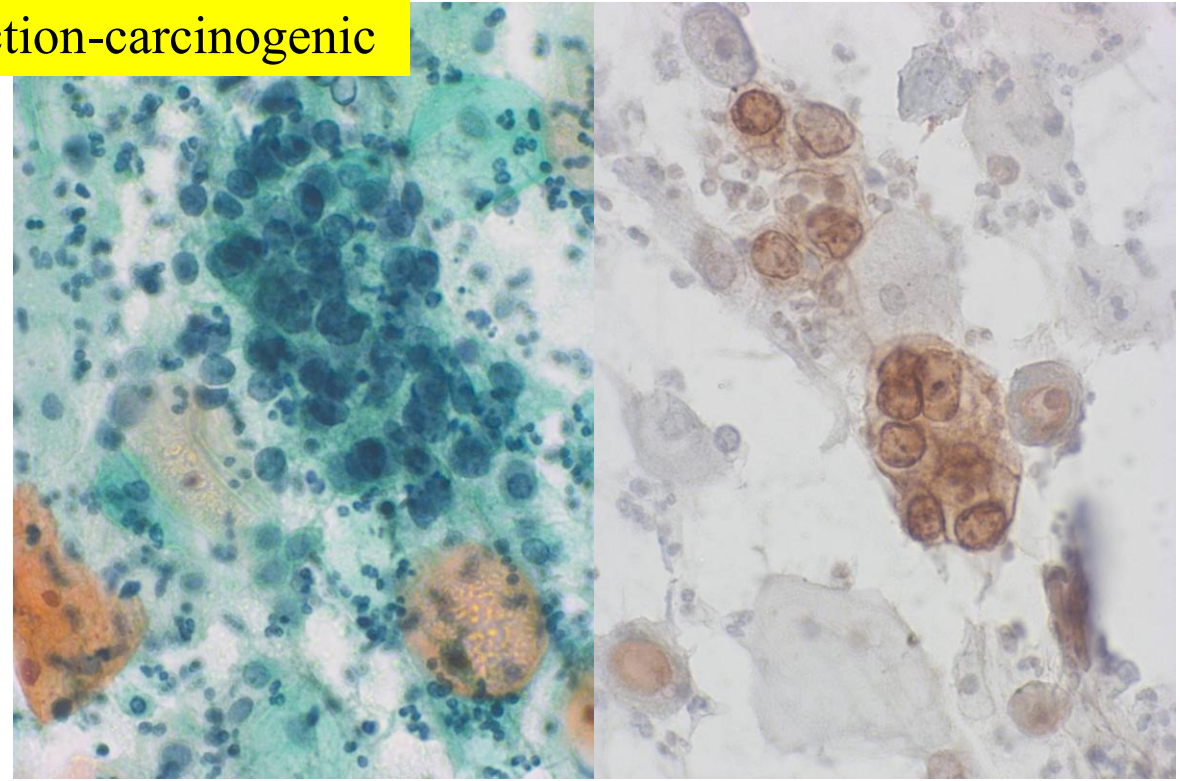
Condyloma acuminatum. Ultrastructural localization of HPV 6/11 genome using a formalin-fixed, paraffin-embedded section. Positive genomic signals in the nuclear matrix are seen as 20 nm-sized fine particles, representing "episomes", clustered free viral DNA. Ref.: Tsutsumi Y, et al. Ultrastructural visualization of human papillomavirus DNA in verrucous and precancerous squamous lesions. Acta Pathol Jpn 1991; 41(10): 757-762. doi: 10.1111/j.1440-1827.1991.tb03348.x

HPV infection-carcinogenic



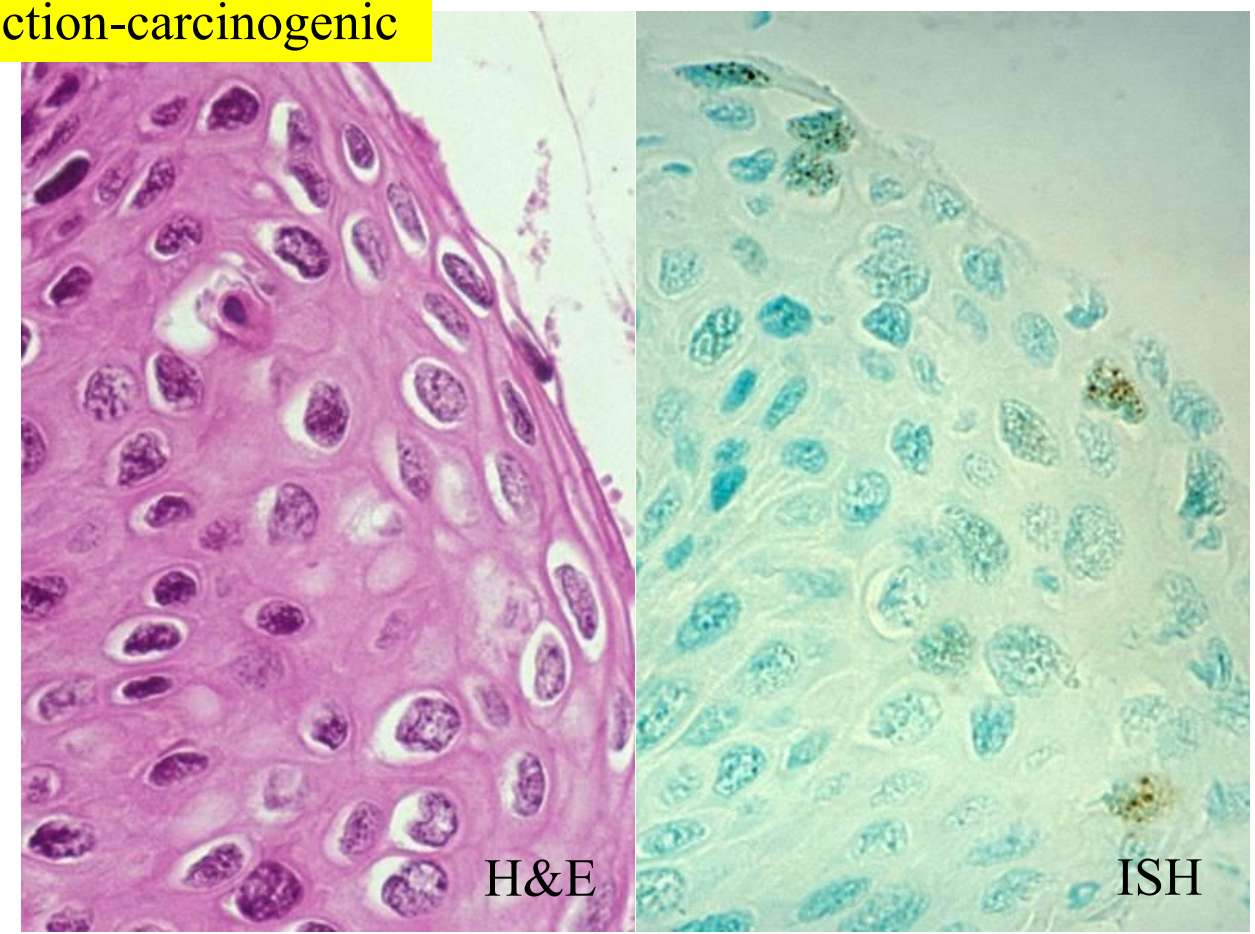
Re-staining method after cell transfer to silane-coated glass slide. Dot-like intranuclear signals of HPV16 genome are observed in the same cells of severe dysplasia of the cervix. The cell transfer technique is indispensable for performing ISH, because a heating step for making double-stranded DNA into single-stranded is included in ISH.

HPV infection-carcinogenic



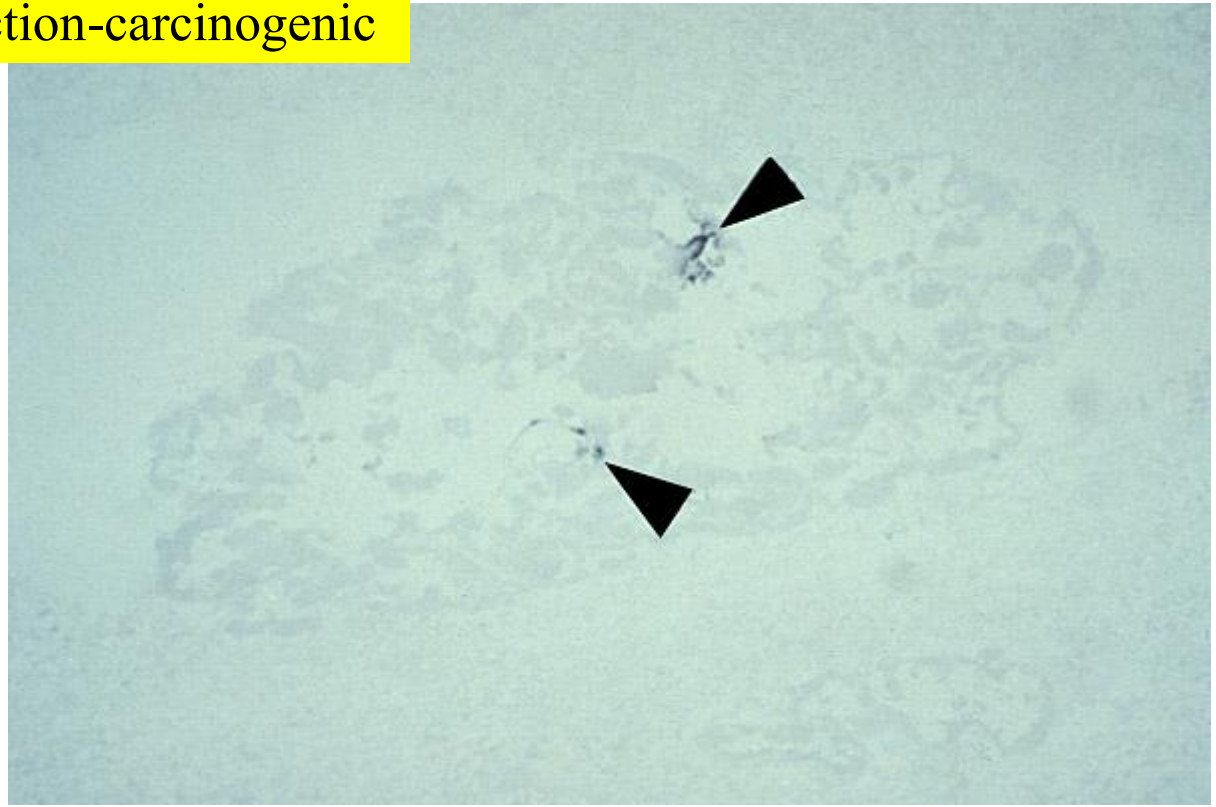
Moderate dysplasia of uterine cervix after menopause (left: Pap, right: immunostaining for p16-INK4a). Dysplastic change and reactive atypia secondary to senile colpitis should be distinguished. The expression of p16-INK4a confirmed the precancerous state of the cervix in this postmenopausal female. After the cell transfer to the silane-coated glass slide, p16-INK4a was immunostained by employing heat-induced antigen retrieval. **Ref**. Tsutsumi Y, et al. p16 immunostaining can avoid overdiagnosis in postmenopausal cervical cytology. Int Res J Med Medical Sci 2021; 9(1): 1-8. doi: 10.30918/IRJMMS.91.20.056

HPV infection-carcinogenic



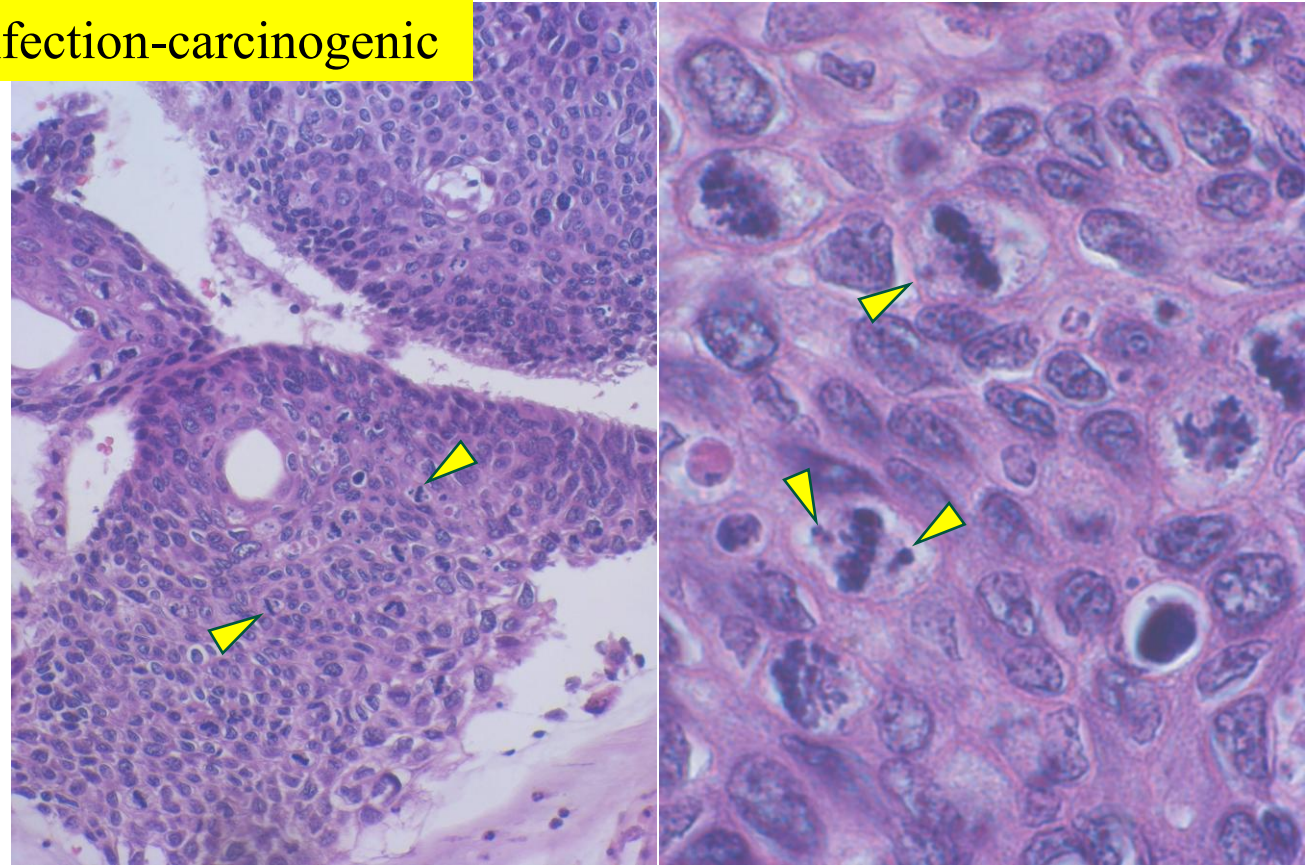
Severe dysplasia (high-grade squamous intramucosal lesion: HSIL) is caused by high-risk HPV, typically HPV16. Dot-like intranuclear signals of HPV16 genome are visualized by ISH technique. Left: H&E, right: ISH

HPV infection-carcinogenic



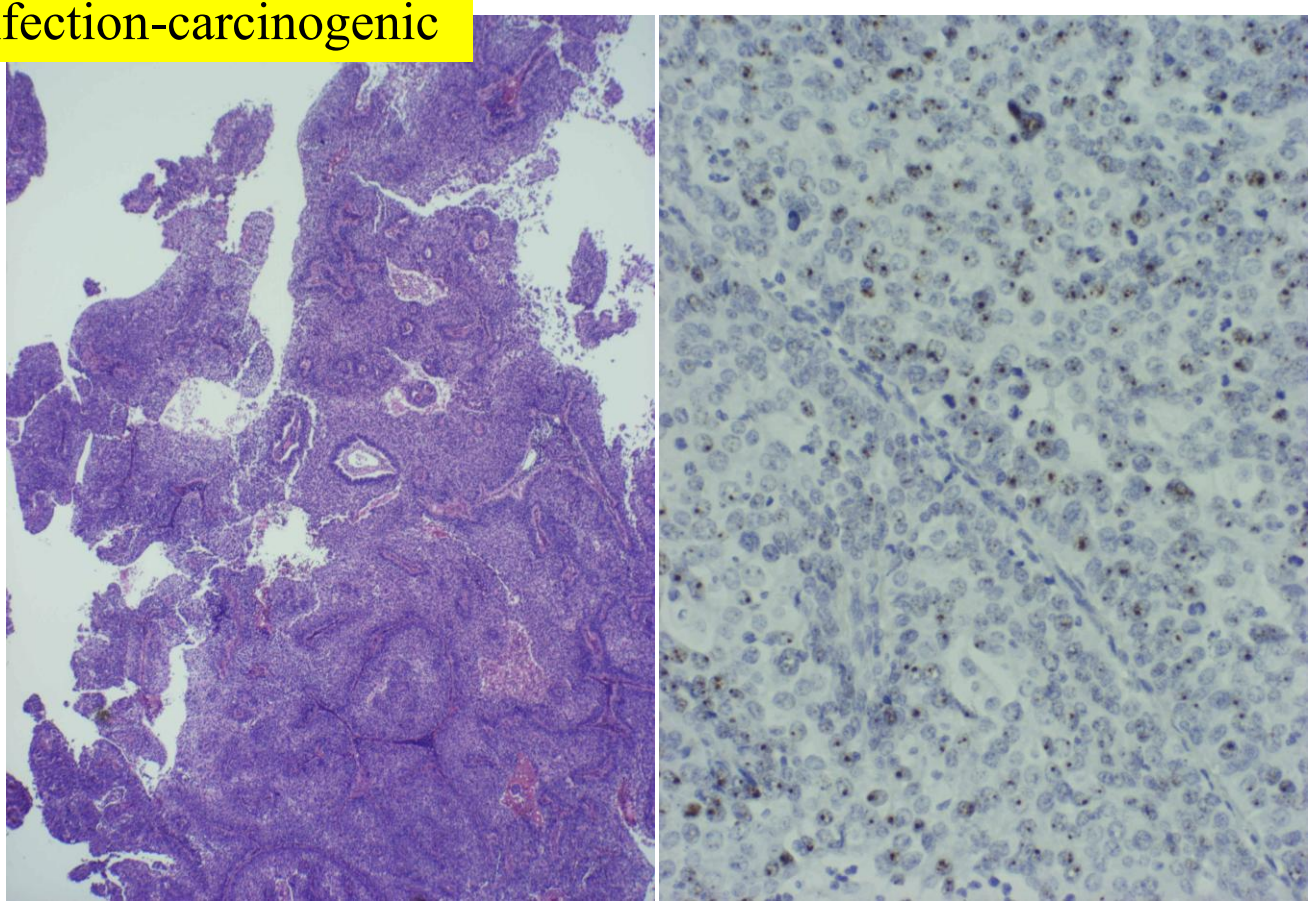
Severe dysplasia. Ultrastructural localization of HPV16 genome using a formalin-fixed, paraffin-embedded section. Positive genomic signals are seen as focal clusters on chromatins (arrowheads), representing high-risk viral DNA integrated into the host DNA. Ref.: Tsutsumi Y, et al. Ultrastructural visualization of human papillomavirus DNA in verrucous and precancerous squamous lesions. Acta Pathol Jpn 1991; 41(10): 757-762. doi: 10.1111/j.1440-1827.1991.tb03348.x

HPV infection-carcinogenic



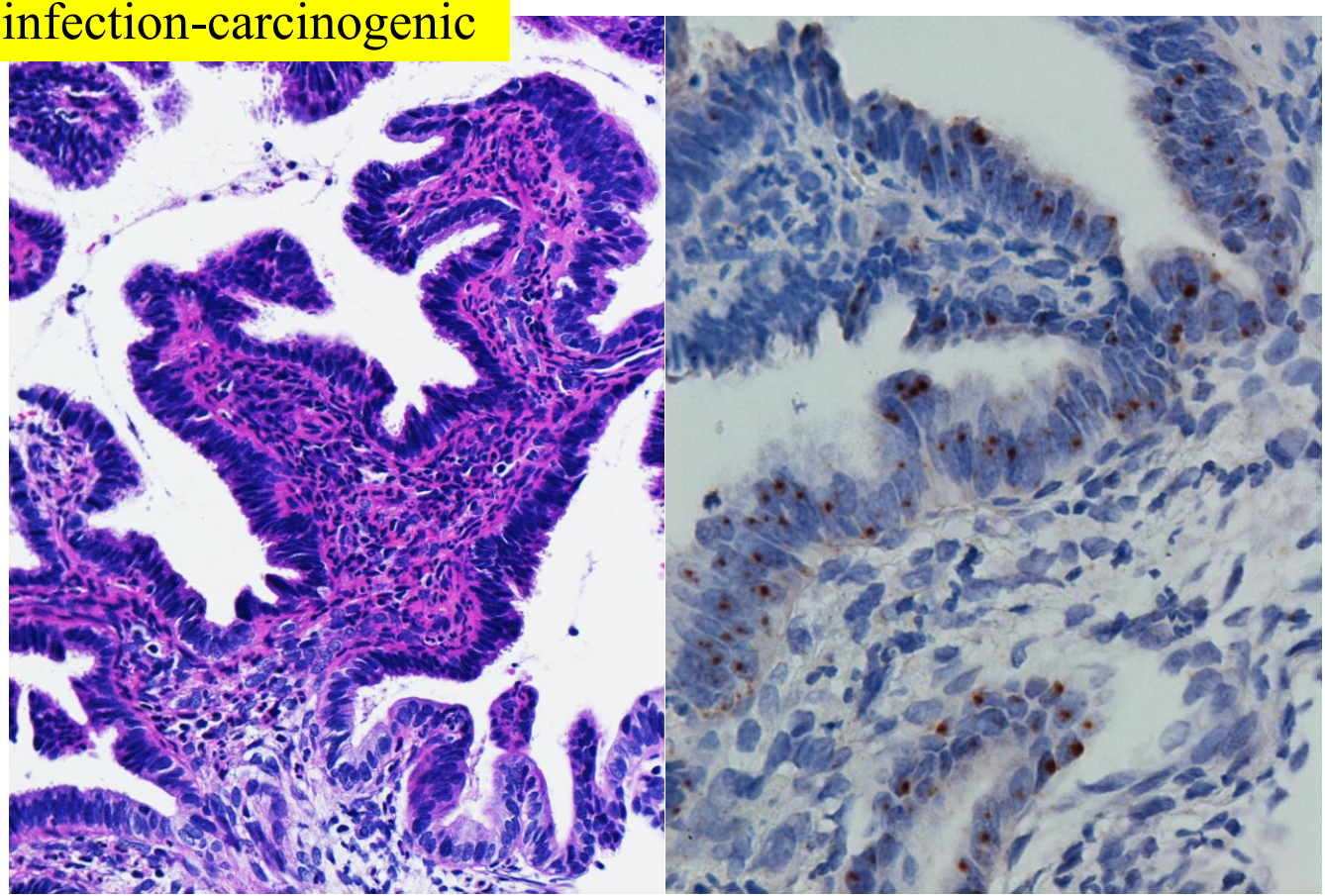
Ectopic chromosome around centrosome (ECAC) is visible on H&E-stained sections as 0.7 μm-sized, round, dark structure often symmetrical at bilateral centrosomes in metaphase cell nuclei. The appearance of ECAC is closely related to high-risk HPV infection. The highest incidence is seen in HPV16-associated CIN II-III. Biopsied **severe dysplasia** (CIN-III) with ECAC (arrowheads) of a 26 y-o lady is shown. **Ref.**: Furuta R, et al. Ectopic chromosome around centrosome in metaphase cells as a marker of high-risk human papillomavirus-associated cervical intraepithelial neoplasias. Int J Cancer 2003; 106(2): 167-171. doi: 10.1002/ijc.11216

HPV infection-carcinogenic



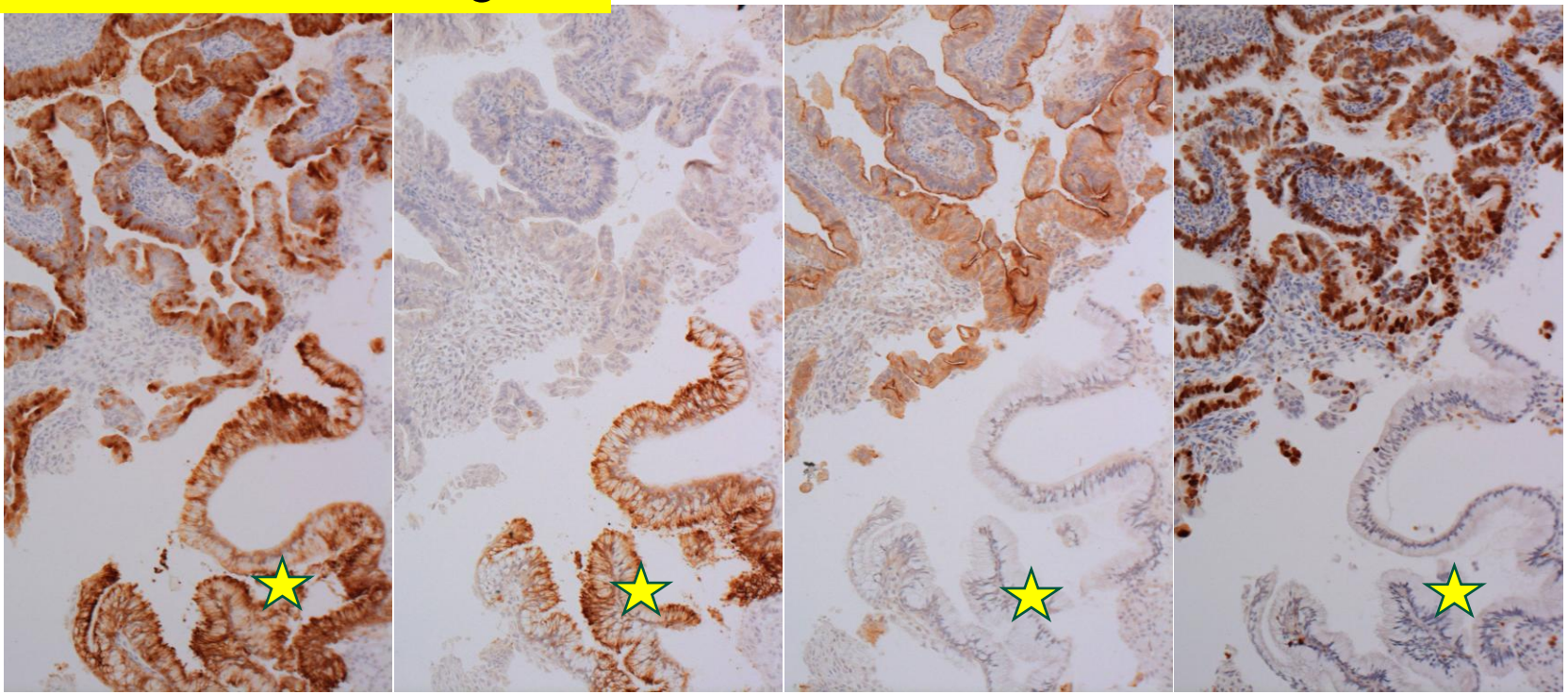
Papillary invasive **squamous cell carcinoma** of the uterine cervix, expressing HPV16 genome seen in a 44 y-o female patient. Papillary protruding growth is evident. Dot-like signals of high-risk HPV genome are seen in most cancer cells.

HPV infection-carcinogenic



Cervical adenocarcinoma infected with HPV18 seen in a 37 y-o female patient. Mucin-producing well-differentiated papillary adenocarcinoma is labeled for high-risk HPV genome with ISH employing wide-spectrum HPV probes. Cervical adenocarcinoma is often positive for HPV type 18.

HPV infection-carcinogenic



HPV18-positive mucin-producing **cervical adenocarcinoma** seen in a 37 y-o female patient. The papillary adenocarcinoma is immunoreactive for MUC5AC and villin, but negative for MUC6. Ki-67 labeling index is very high. In contrast, non-neoplastic cervical mucous cells (asterisks) are positive for both MUC5AC and MUC6, but negative for villin and Ki-67. Cervical adenocarcinoma often expresses gastric phenotype, as shown here with gastric foveolar cell differentiation.

Bowenoid papulosis and condylomatous carcinoma

Bowenoid papulosis, induced by high-risk HPV, is a disease manifested by clinically benign-appearing multicentric papules of the anogenital region. Microscopic changes simulate Bowen's disease of the skin.
Ref.: Nayak SU, et al. Bowenoid papulosis. Indian J Sex Transm Dis AIDS 2015; 36(2): 223-225. doi: 10.4103/0253-7184.167196

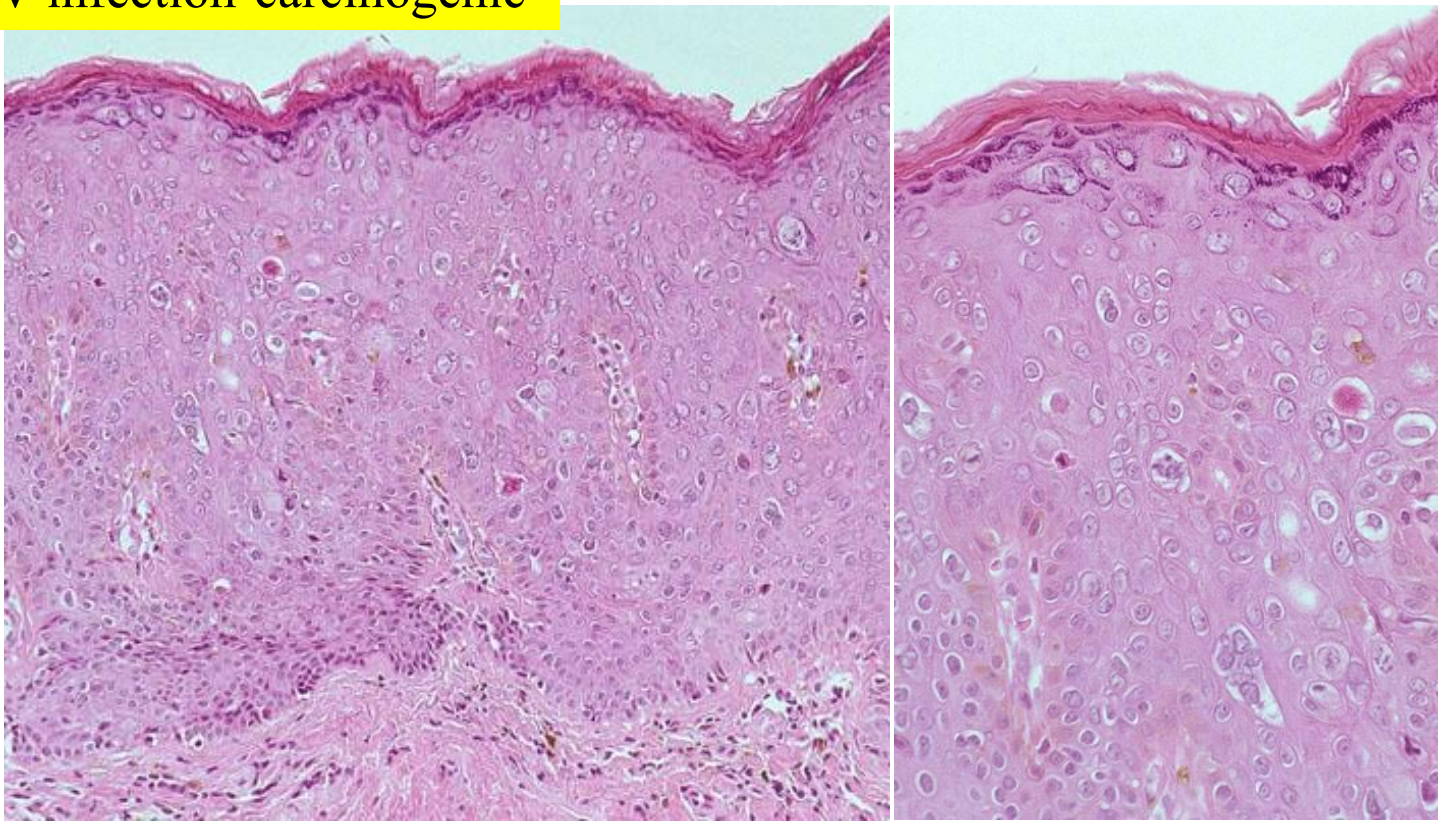
Condylomatous carcinoma (**warty carcinoma**) is a rare subtype of squamous cell carcinoma of the vulva and penis. It resembles condyloma acuminatum but with marked nuclear atypia.
Ref.: Chaux A, et al. Warty–basaloid carcinoma: clinicopathological features of a distinctive penile neoplasm. Report of 45 cases. Mod Pathol 2010; 23: 896-904. doi: 10.1038/modpathol.2010.69

Both lesions, caused by infection of high-risk HPV, are characterized by the production of HPV particles (immunostaining for HPV capsid antigens is positive), an exceptional phenomenon in malignancy.

HPV infection-carcinogenic

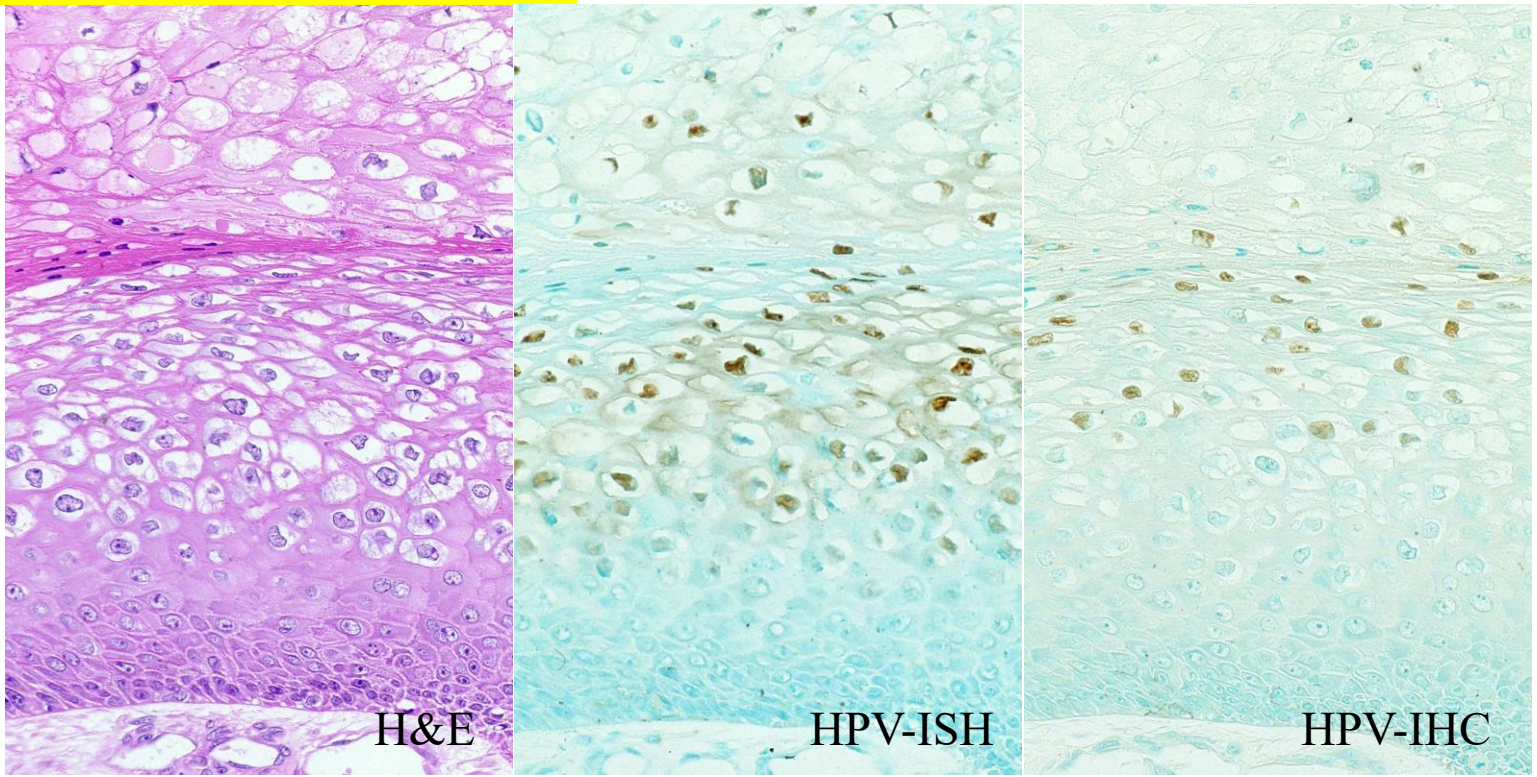
Bowenoid papulosis is a sexually transmitted infection, presenting as pigmented papules on the penis or vulva. Microscopically they closely resemble Bowen' disease of the skin (squamous cell carcinoma *in situ*). It is caused by infection of high-risk HPV. It is now classified as a vulvar or penile high-grade squamous intraepithelial lesion (HSIL). Gross appearance of the vulvar lesion of a 48 y-o female is shown here.

HPV infection-carcinogenic



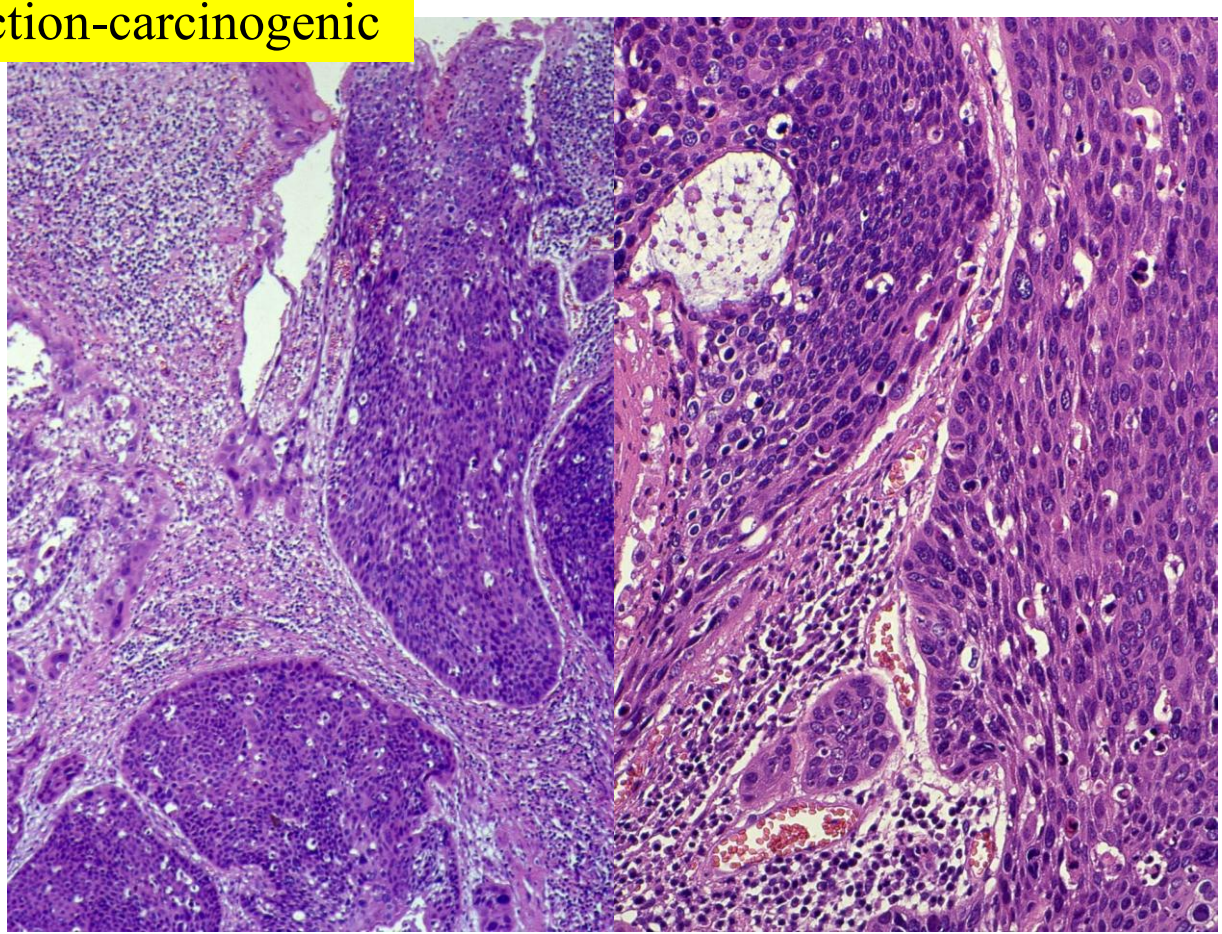
Bowenoid papulosis seen in the vulva of a 48 y-o female patient. Microscopically, it closely resembles Bowen' disease of the skin (squamous cell carcinoma *in situ*) (H&E). Bowenoid papulosis is caused by infection of high-risk HPV. It is now classified as a vulvar or penile high-grade squamous intraepithelial lesion (HSIL).

HPV infection-carcinogenic



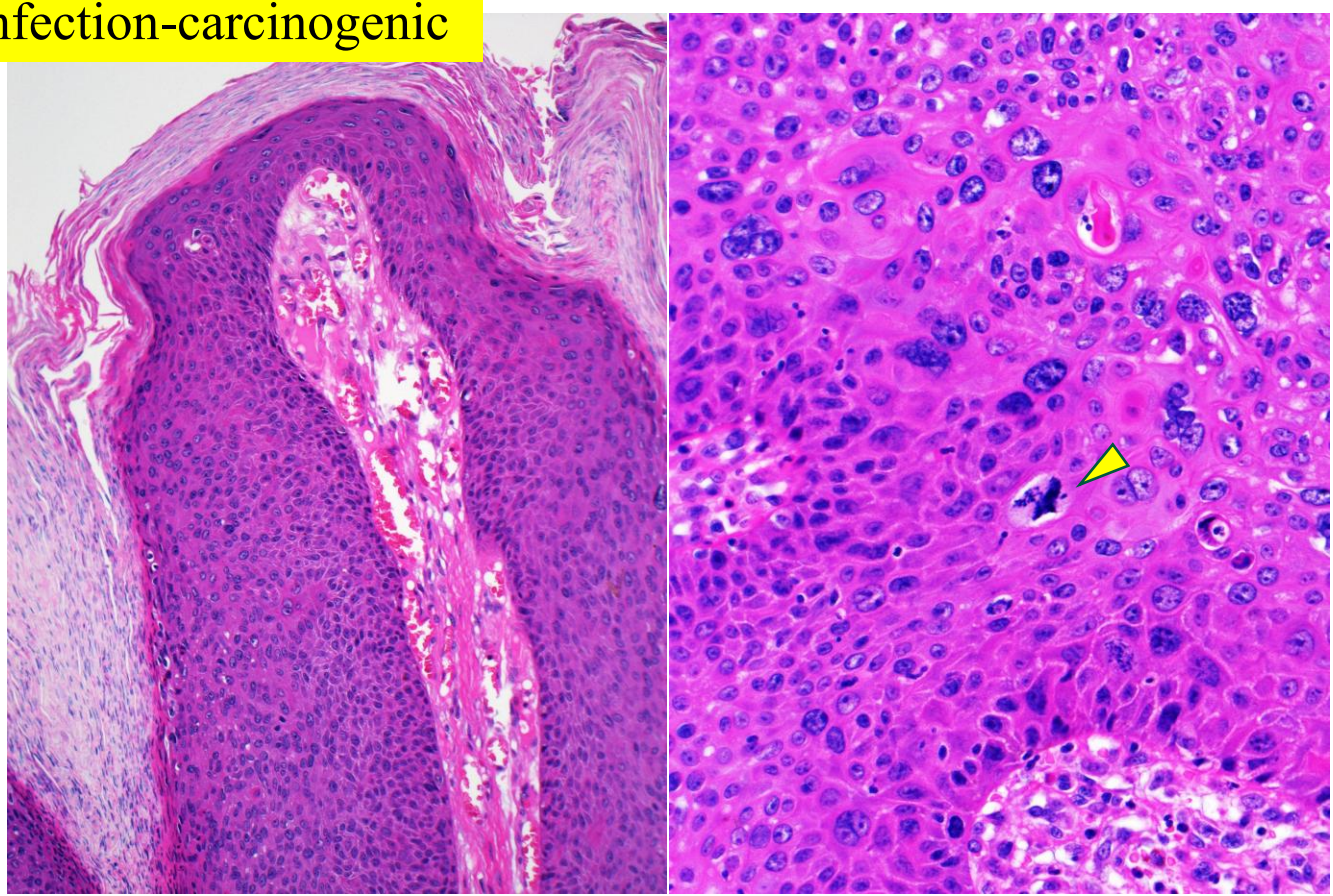
Bowenoid papulosis is a sexually transmitted infection, presenting as pigmented papules on the penis or vulva. In this area, the lesion microscopically reveals prominent koilocytosis (left: H&E). ISH using wide-spectrum HPV genomes demonstrates infection of high-risk HPV genome (center), and immunostaining for HPV capsid antigens shows less number of signals (right). The demonstration of HPV infection is not observed in the dermal Bowen's disease.

HPV infection-carcinogenic



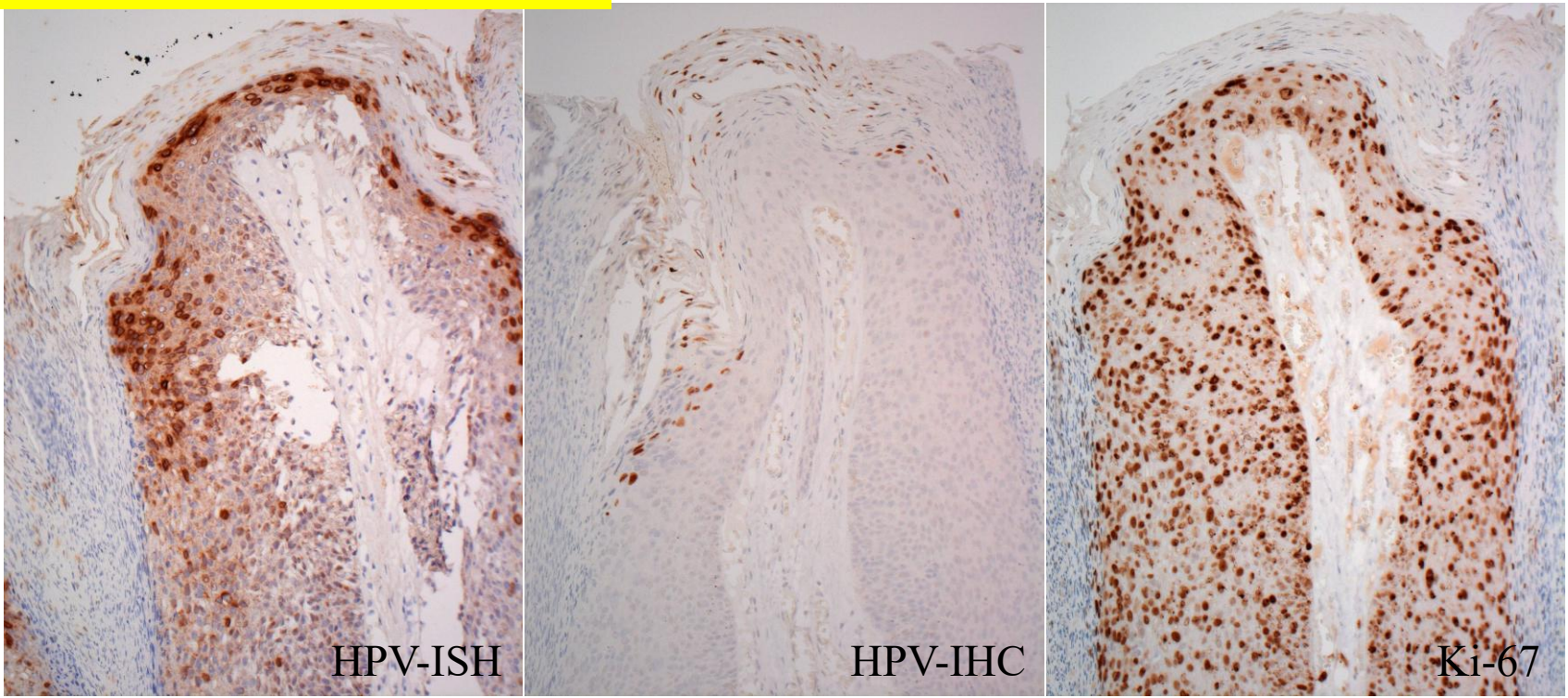
Bowenoid papulosis progressing into invasive squamous cell carcinoma. Five years later when the patient's age being at 53 years, the vulvar lesion of bowenoid papulosis progressed to invasive squamous cell carcinoma. Metastasis to the groin lymph node is associated.

HPV infection-carcinogenic



Condylomatous carcinoma (**warty carcinoma**) seen the vulva of a 48 y-o female patient. A large-sized verrucous/warty tumor is seen in the vulva. The prognosis is excellent. Microscopically, the papillomatous cells show high-grade nuclear atypia with pleomorphism and active mitosis. Ectopic chromosome around centrosome is seen (arrowhead).

HPV infection-carcinogenic



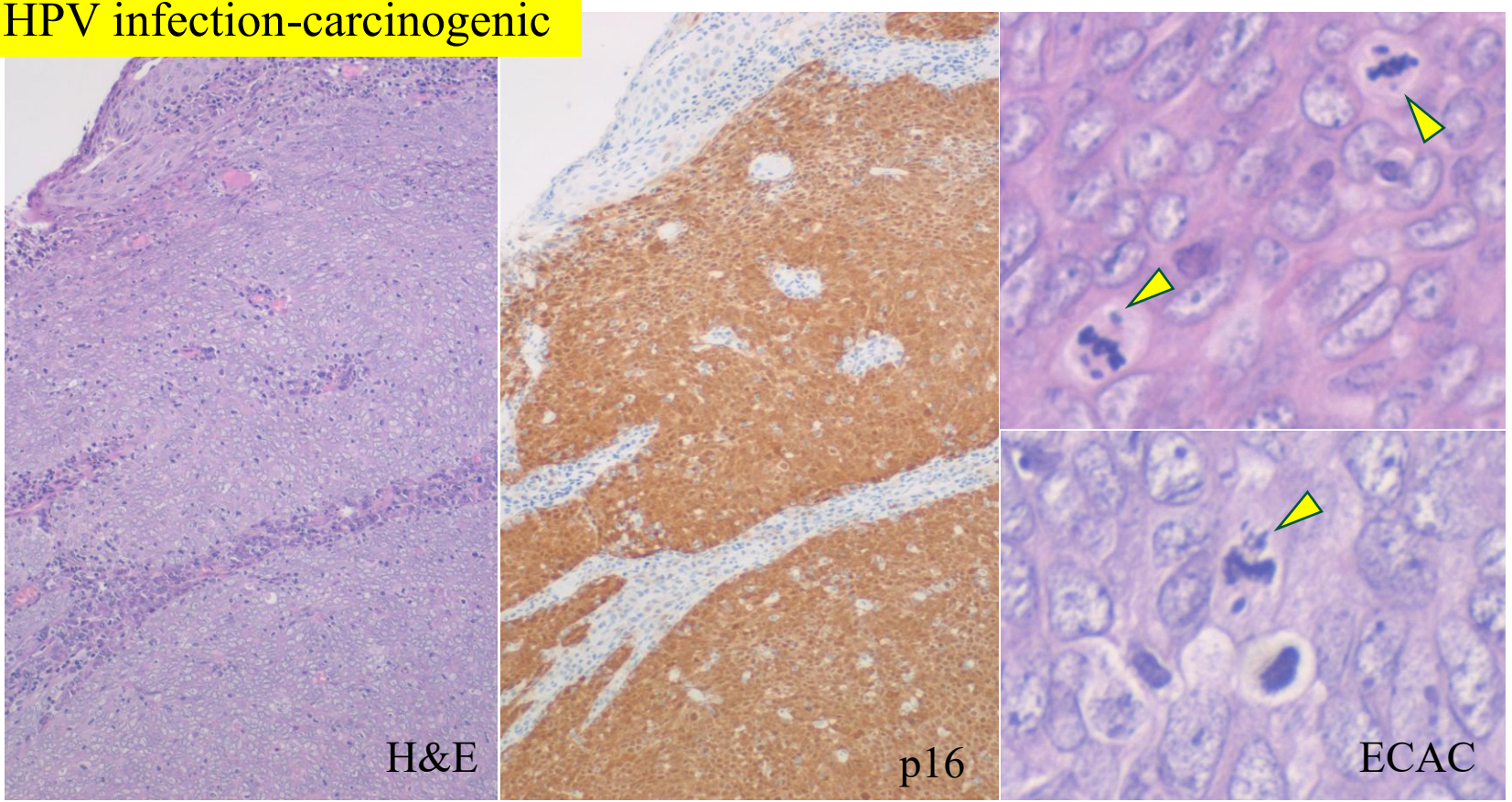
Condylomatous carcinoma (**warty carcinoma**) seen the vulva of a 48 y-o female patient. The atypical and pleomorphic warty cancer cells show positive signals of HPV genome by ISH using wide-spectrum HPV probes (left). A much less number of cells are immunoreactive for HPV capsid antigens in the superficial part, indicating the production of viral particles (center). Ki-67 labeling index is very high (right).

p16-positive mesopharyngeal squamous cell carcinoma

Oropharyngeal non-keratinizing squamous cell carcinoma (SqCC) is known to be associated with human papillomavirus (HPV). HPV-positive SqCC more commonly occurs in younger patients of higher socioeconomic status, and the patients have higher numbers of sex partners and higher oral sex exposure. It is less strongly associated with alcohol and tobacco use, and less frequently harbor p53 mutations, compared with HPV-negative SqCC. The prognosis is better. Overexpression of p16 is consistently demonstrated, but uncommon in HPV-negative SqCC.

Ref.: Lewis JS Jr, Thorstad WL, Chernock RD, Haughey BH, Yip JH, et al. p16 positive oropharyngeal squamous cell carcinoma: an entity with a favorable prognosis regardless of tumor HPV status. Am J Surg Pathol 2010; 34(8): 1088-1096. doi: 10.1097/PAS.0b013e3181e84652

HPV infection-carcinogenic

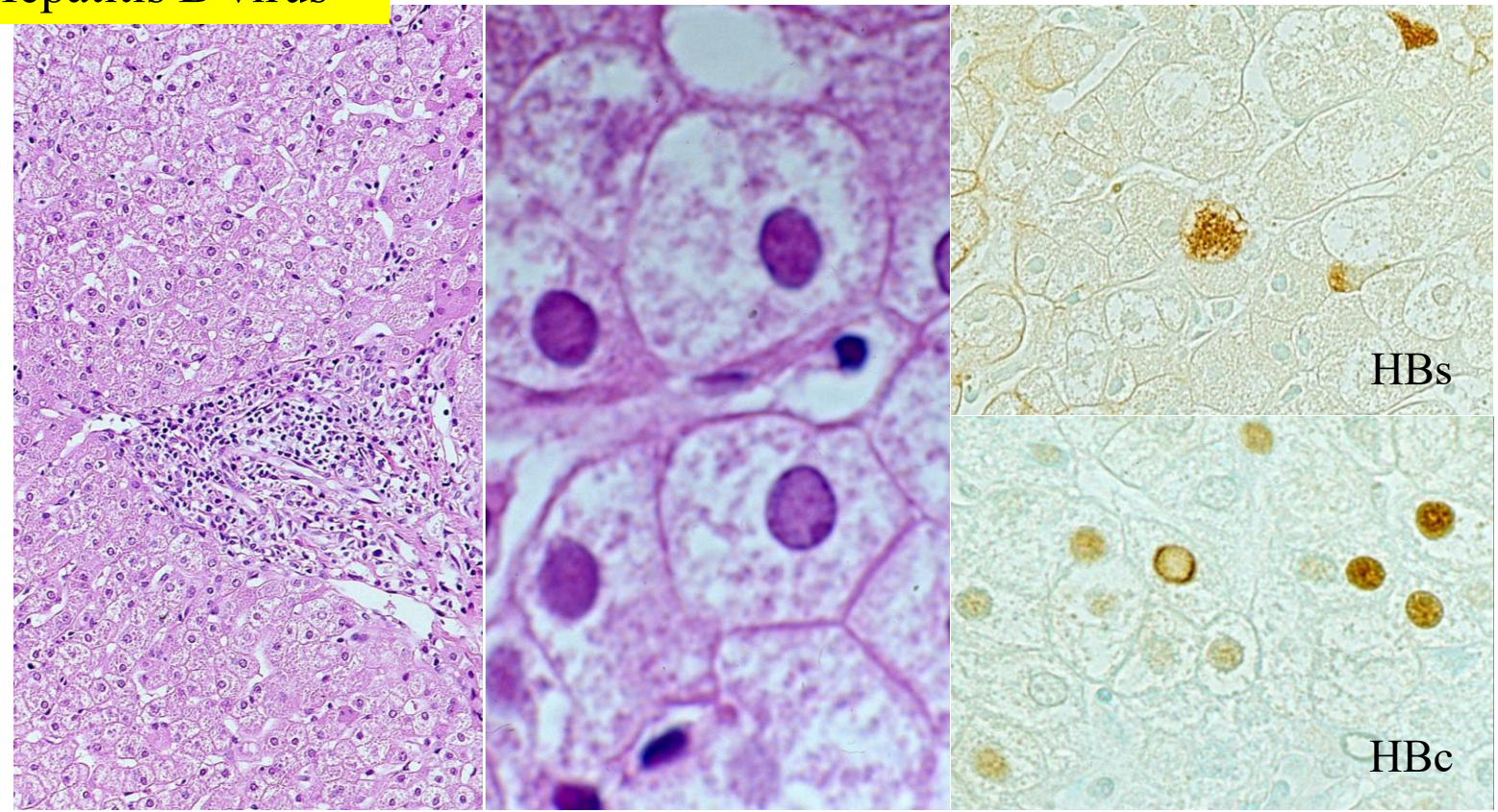


Mesopharyngeal (tonsillar) non-keratinizing squamous cell carcinoma with p16-INK4a overexpression and ectopic chromosome around centrosome (ECAC), seen in a 73 y-o male patient (right: H&E). Overexpression of p16 is closely related to HPV infection of the cancer cells (center). ECAC indicating high-risk HPV infection is observed in the metaphasic cells (arrowheads, right). Reportedly, HPV infection occurred during a younger age period by history of oral sex.

Hepatitis B virus infection, human immunodeficiency virus (HIV) infection, molluscum contagiosum, scabies, pubic louse infestation and *Entamoeba gingivalis* colonization in the uterine cavity

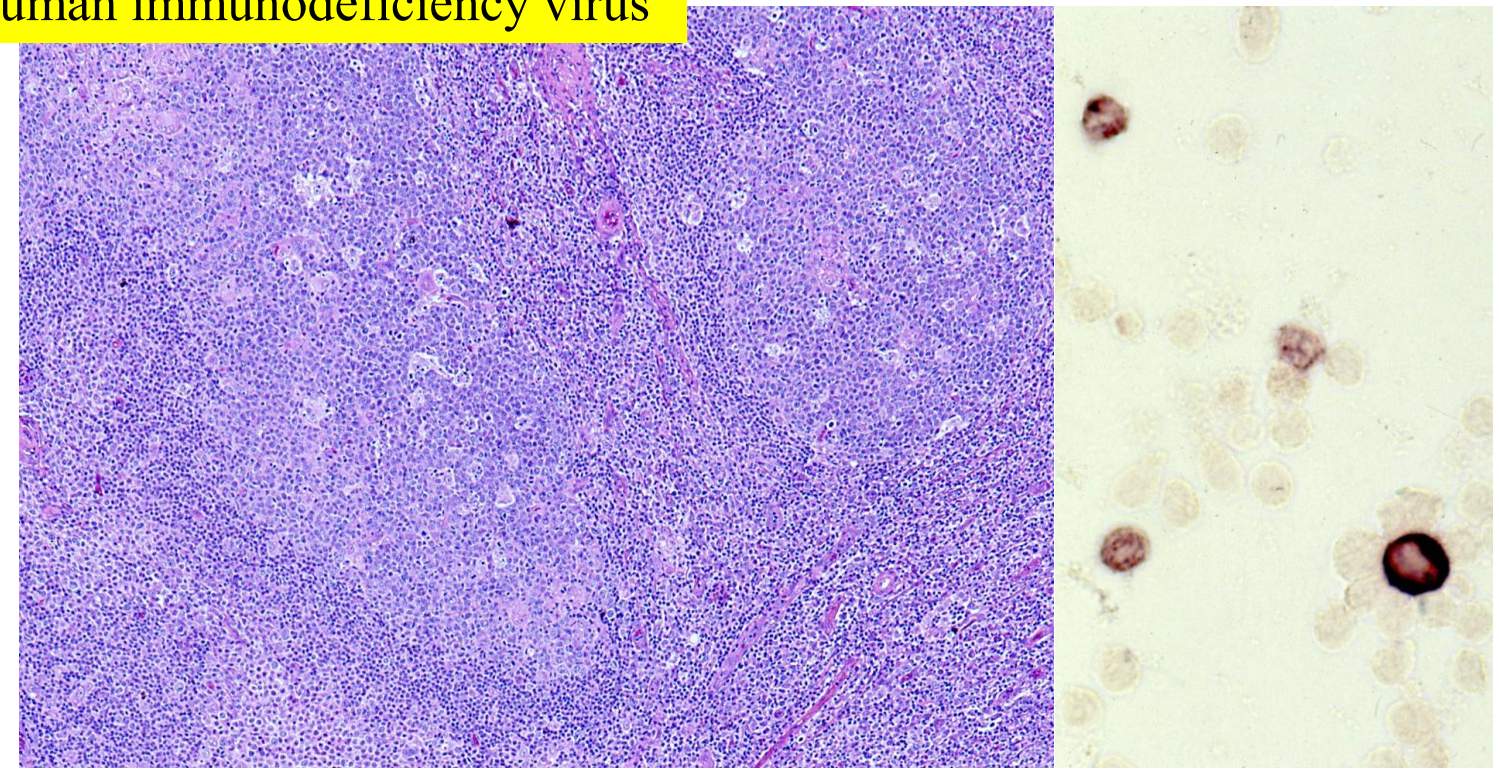
Other forms of sexually transmitted infection listed above are shown below.

Hepatitis B virus



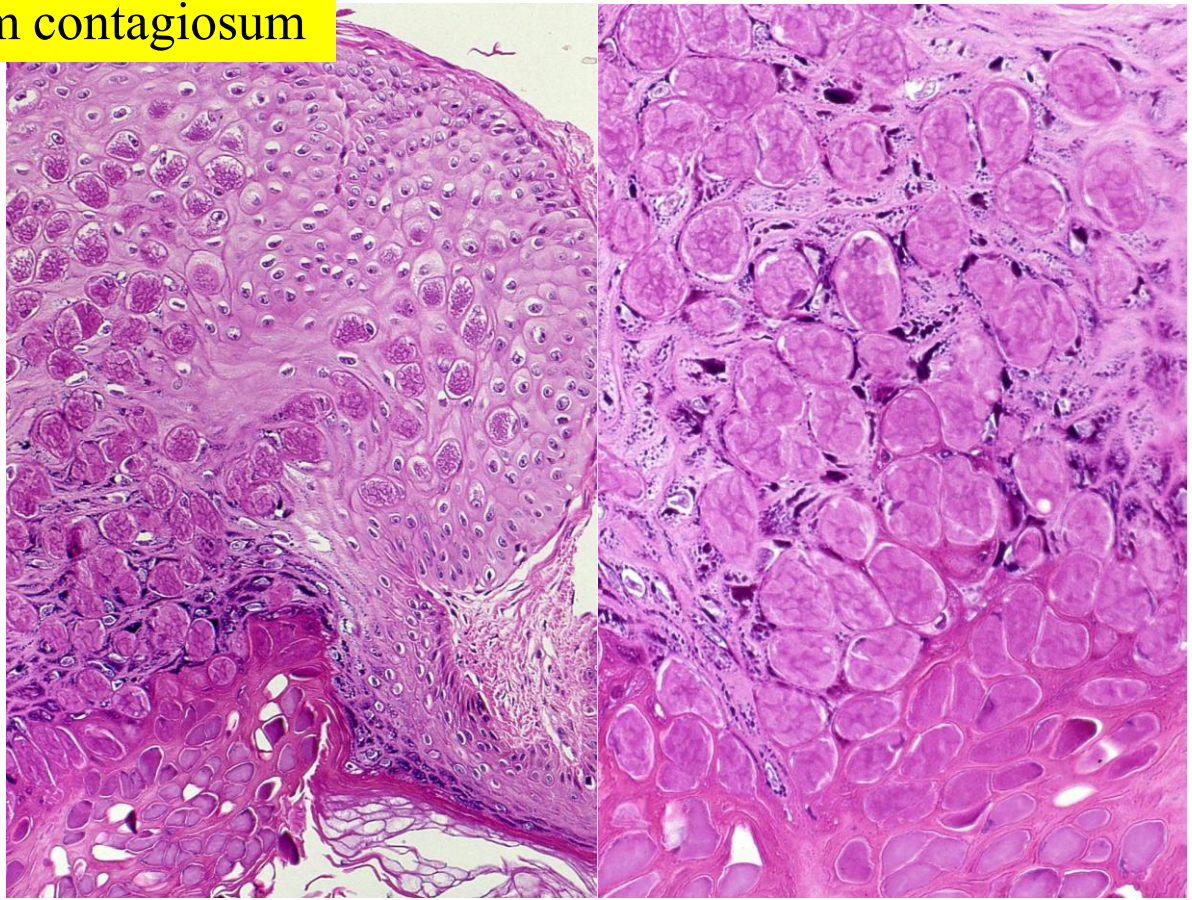
A healthy carrier of **hepatitis B virus**. The liver biopsy shows mild portal inflammation. The presence of sanded nuclei indicates a replicative carrier of HBV. HBs antigen is positive in the cytoplasm and on the cell membrane, while HBc antigen is seen in the sanded nuclei. Sexual activity may provoke acute hepatitis B in the sex partner, known as “honeymoon hepatitis”.

Human immunodeficiency virus



Human immunodeficiency virus infection (acquired immunodeficiency syndrome: **AIDS**) provokes lymphadenopathy with follicular hyperplasia. Folliculolysis is a feature of HIV lymphadenopathy (left: H&E). HIV infects CD4-positive lymphocytes (right; ISH localization of HIV genome in the cytoplasm of cultured lymphocytes). The infection is accelerated by homosexuality. It takes several years from primary infection to the development of symptoms of advanced HIV diseases and immunosuppression.

Molluscum contagiosum



Molluscum contagiosum (water warts) seen in the scrotum of a 43 y-o male patient. Large globular eosinophilic inclusions are seen in the cytoplasm of keratinocytes of the hair follicle. Fundamentally, molluscum contagiosum is a disease of children. The infection of molluscum virus in adults is often sexually transmitted, particularly in the genital skin.

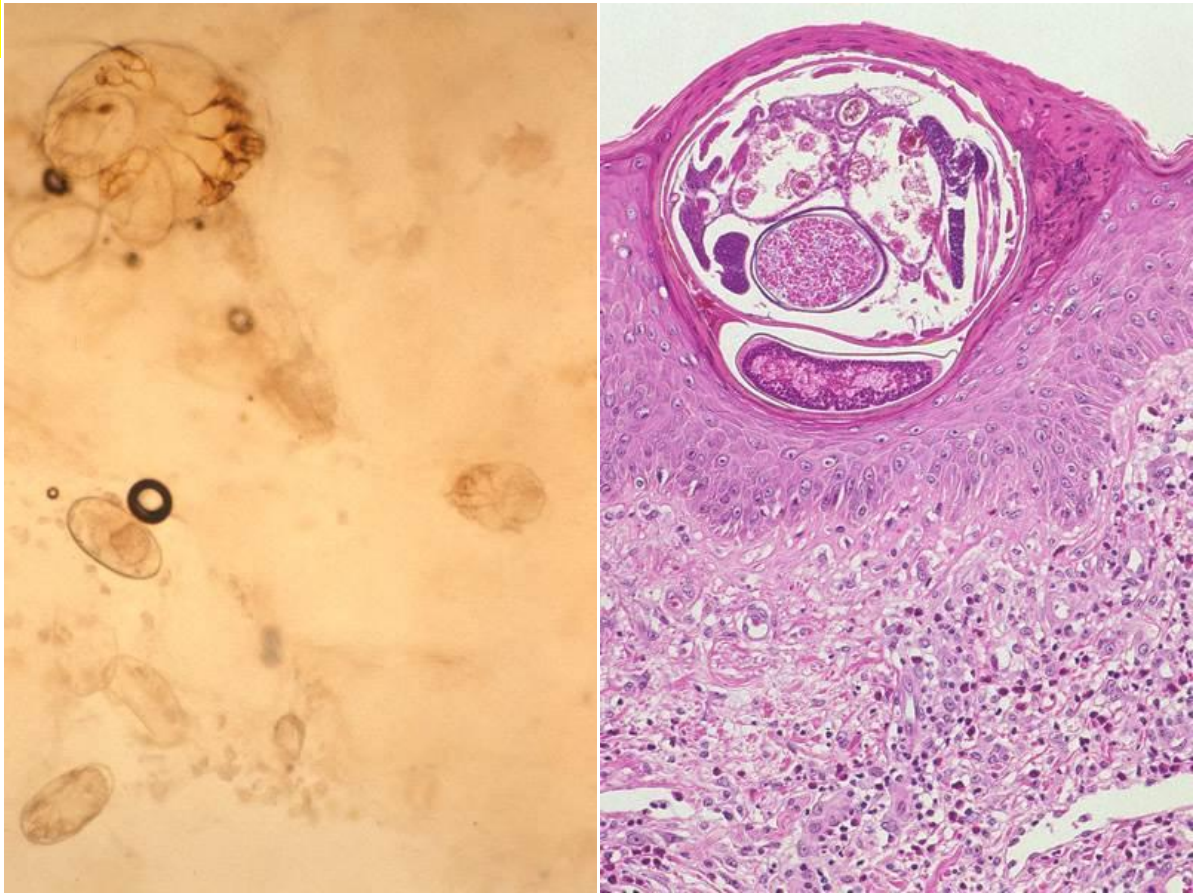
Scabies

Scabies is caused by infestation of a mite, *Sarcoptes scabiei var. hominis*. Scabies causes itchy skin rash. Intense itching occurs in the area where the mite burrows, being stronger at night. Scabies is contagious and can easily spread by close person-to-person contact in a family, child care group, school class, nursing home or prison. A mite burrow at the base of the toe is shown.

Scabies

Scabies causes sexually transmitted infection since it can be acquired through the sexual contact or close body contact with someone with the infection. Multiple itchy papules by scabies are seen on the scrotum and penis.

Scabies

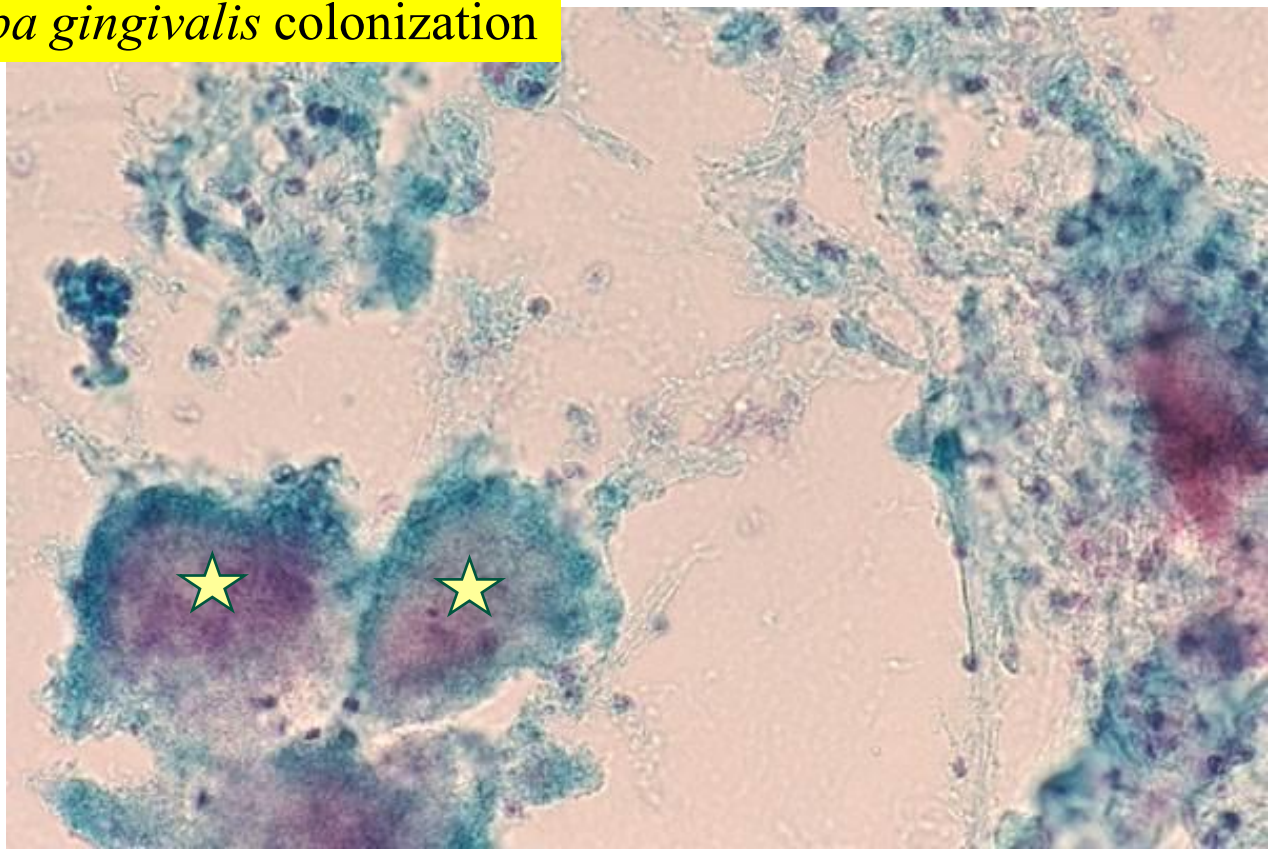


Scabies. Scratch smear from the mite burrow. A larva with three pairs of legs and ova are included (left: unstained preparation). Biopsy from the mite burrow shows a cut surface of an adult *Sarcoptes scabiei var. hominis*. The burrow is formed within the cornified layer. The dermis reveals infiltration of lymphocytes and eosinophils (right: H&E).

Pubic louse

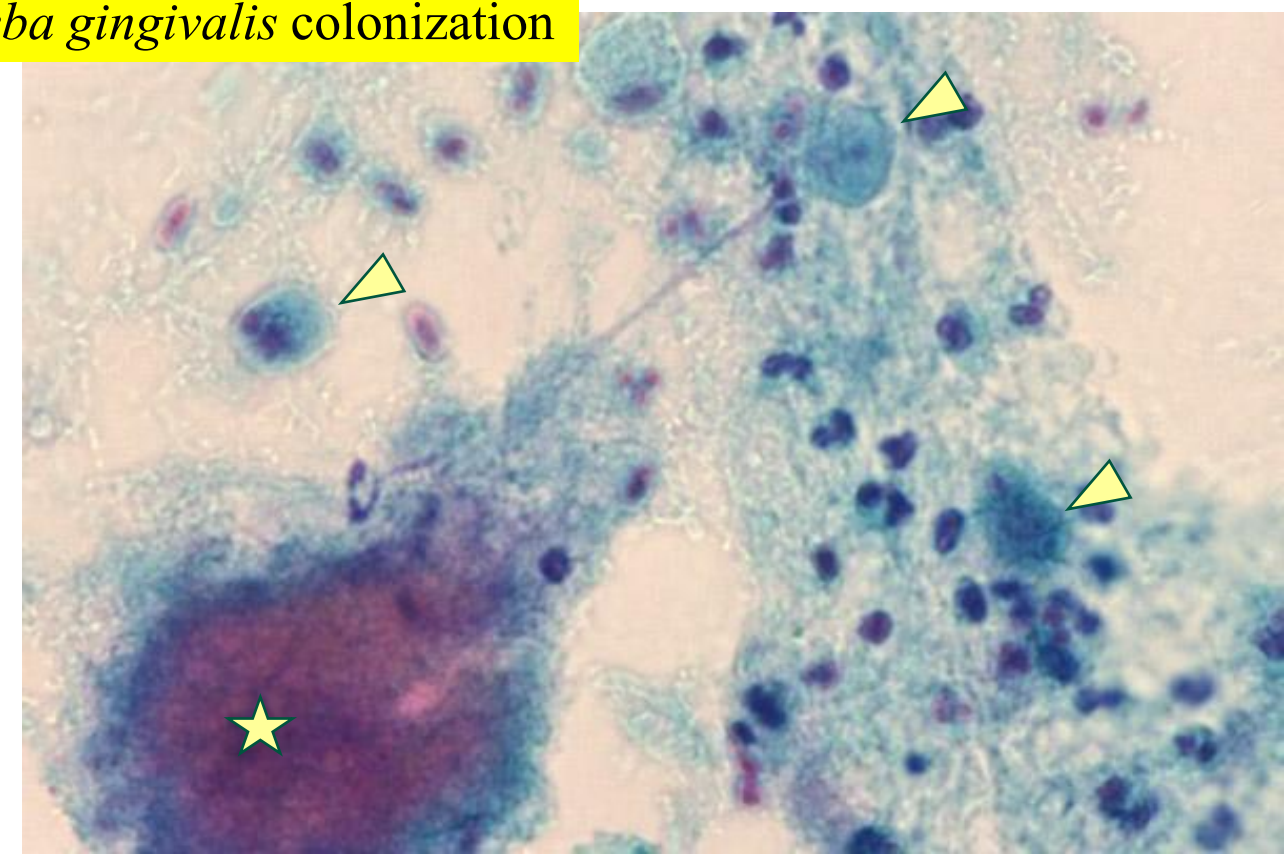
Infestation of **pubic louse** (**crab louse**), ***Phthirius pubis***, on the eyelash. The pubic louse is 1-2 mm in size and crab-like in shape. It has a small head, a pair of antenna and three pairs of legs. The second and third legs are thicker than the front legs, and have curved claws. Sexually transmitted infestation usually occurs in the pubic hair. Eyelashes are another site of infestation. Microscopic appearance is shown in the right panel (H&E).

Entamoeba gingivalis colonization



Actinomycosis with *Entamoeba gingivalis* colonization. A contraceptive intrauterine device (IUD) left in the endometrium accelerated mixed colonization of *Actnomyces israelii* and *Entamoeba gingivalis* in a female patient aged 50's, complaining of increased fluor. Inflammatory exudates on the removed IUD was evaluated cytologically (Pap). Actinomycotic grans are seen in the neutrophilic background (asterisks).

Entamoeba gingivalis colonization



Actinomycosis with *Entamoeba gingivalis* colonization. In the inflammatory exudates on the removed IUD, mixed colonization of *Actnomyces israelii* (asterisk) and *Entamoeba gingivalis* (arrowheads) is observed (Pap). Both *A. israelii* and *E. gingivalis* are obligatory anaerobic microbes. Non-pathogenic *E. gingivalis* can survive in the uterine cavity with the co-colonization of *A. israelii*, giving an anaerobic environment for the amebic trophozoites.

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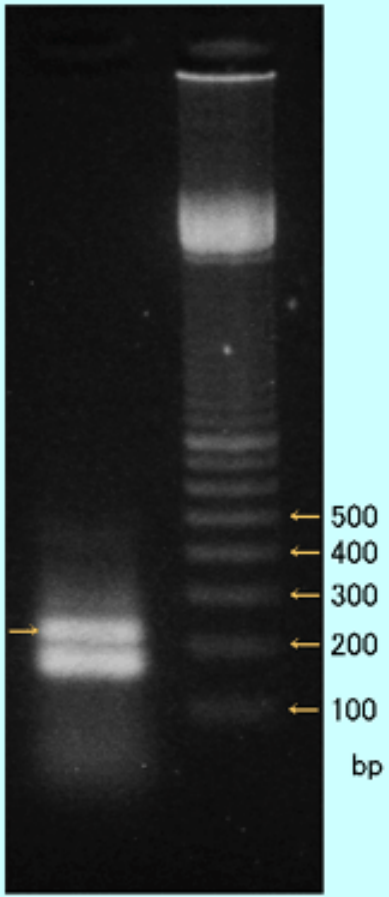
PCR for *Entamoeba* species

primers
- sense: 5'- tcagataccgtcgtagtcct - 3'
- antisense: 5'- cctggtgtgcccttccgt - 3'

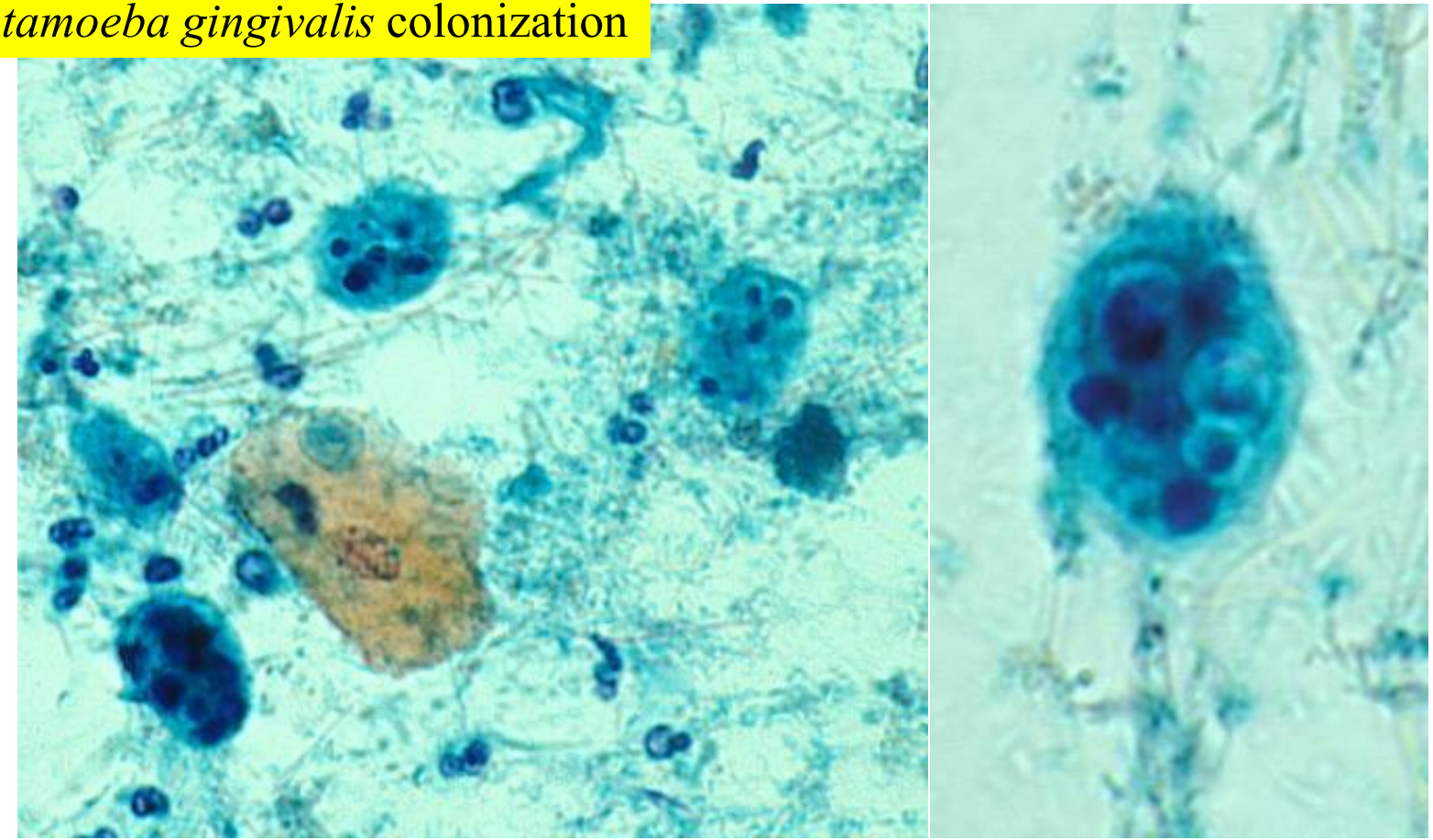
PCR conditions: 94°C 15 sec、55°C 30 sec、72°C 30 sec : 35 cycles

Sequencing of the 221 bp PCR fragment showed a high homology with *Entamoeba gingivalis*.



The cytology specimen was cell transferred to the solidified Malinol membrane, and the membrane was cut into pieces. From one of the pieces, DNA was extracted for PCR analysis of the *E. gingivalis* genome. The infecton was mediated by oral sex.

Entamoeba gingivalis colonization



Entamoeba gingivalis. Smear preparation of the dental plaque sampled from a male patient with oral mucosal squamous cell carcinoma and perodontitis. Trophozoites of *Entamoeba gingivalis* frequently phagocytize neutrophils are seen in the densely bacillary background (Pap). *E. gingivalis* is a non-pathogenc flora of the oral cavity.