**PATHOLOGY OF THE FEMALE GENITAL SYSTEM**

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**LEC.1**

**VULVA**

**VULVITIS**

All skin disorders can be seen but there are specific vulvar infection related to sexually transmitted diseases (STD):

***The most important infectious agents are:-***

*1. Human papillomavirus* (HPV), it is oncogenic virus can cause: condylomata acuminata and vulvar intraepithelial neoplasia(VIN).

*2. Herpes simplex genitalis* (HSV 2), causing a vesicular eruption, Painful ulceration in the skin. Intraepithelial blisters & viral inclusion swelling of epithelial cells, giant cell formation.

*3.* *Gonococci:* producing suppurative infection of the vulvovaginal glands.

Bartholin’s abscess cyst: inflammatory occlusion of the main duct of Bartholin’s vulvo-vaginal gland, most common cause is staphylococcus and gonorrhea.

*4.* *Syphilis*,

Primary syphilis - : Chancer - at the site of inoculation indurated lesion with central painless ulceration & LN – heals even without treatment

Secondary syphilis: Condyloma lata (inflammed hyperplasia of epithelium with underlying chronic inflammation rich in plasma cells & end arteritis obliterans), Silver stain demonstrates the spirochetes.

*5. Candida* albicans causing chronic irritation & inflammation, white thick discharge, may be associated with vaginitis(vulvavaginitis)

**TUMORS**

**Benign tumors**

Condyloma Accuminata

**Premalignant condition**

Vulvar Intraepithelial Neoplasia (VIN= Vulvar Dysplasia)

 **Malignant tumors**

**Invasive vulvar Squamous cell carcinoma**

**1. Condylomas and Low-Grade Vulvar Intraepithelial Neoplasia (VIN)**

**Condylomata accuminata**: are viral (HPV) warts and appear as elevated warty or flat & wrinkled localized lesions. They are often multiple, red-pink lesions that measure up to several centimeters in diameter.

***Microscopically,*** there is acanthosis and hyper/parakeratosis, and ***koilocytosis:*** ***(large cell with raisin nucleus surrounded by perinuclear cytoplasmic vaculation)***. ***The koilocytes are characteristic of HPV infection***. Condyloma *acuminata* are not precancerous but may coexist with foci of low-grade intraepithelial neoplasia in the vulva (VIN 1) and cervix. Indeed, ***VIN I and condylomas are both related to*** ***HPV 6 & 11*** ***infections.***

**2. High-Grade VIN**

A premalignant intramucosal squamous neoplasm that frequently precedes invasive carcinoma occurs 4th – 5th decades.

 Mucosal lesions with cellular anaplasia and marked nuclear atypia,

caused by HPV type 16.

Synonyms: VIN III= carcinoma in situ (CIS)

Tends to progress to invasive carcinoma ( in old & immunosuppressed patients).

**Malignant tumor of vulva**

3% of all genital CA

90% is squamous cc CA

mostly over 60 yr

Carcinoma of the vulva is used to be seen mostly in elderly women. However, there has been an increase in the frequency of high grade VIN principally among younger women.

**Two biologic forms of vulvar carcinoma seem to exist:-**

A. ***HPV-positive carcinoma*** (especially ***type 16***) is seen in younger patients, particularly cigarette smokers. Many cases show coexisting carcinoma in situ, or condylomata acuminata.

B. ***HPV-negative carcinoma*** is seen in older women; frequently it is not associated with VIN.

***VIN and early vulvar carcinomas appear as areas of leukoplakia*** due to epithelial thickening. These areas eventually transform into ***exophytic or ulcerative cancers***.

***Microscopic features:*** HPV-positive neoplasms tend to be poorly differentiated squamous cell carcinoma**,** whereas the HPV-negative lesions tend to be well-differentiated keratinizing. Ultimately, direct invasion with involvement of regional nodes and more distant spread occurs.Women with a tumor ***less than 2 cm*** in diameter have a much better prognosis than those with larger lesions.

**VAGINA**

**Vaginitis and vulvovaginitis:** Since both vulva and vagina are anatomically close to each other, often inflammation of one affects the other**.**is a relatively common problem that produces a vaginal discharge (leukorrhea).

Usually caused by normal commensals that become pathogenic in conditions such as diabetes, systemic antibiotic therapy, after abortion or pregnancy, or in AIDS.

Causative m.o.:

**1-Bacterial Vaginitis** is the most common cause of vaginitis, accounting for 50% of vaginitis cases. Risk factors include pregnancy, intrauterine device (IUD) use like

streptococci,staphalococci, E.coli, Gonorrheal vaginitis may occur and be transmitted to the newborn of the infected mother

**2-Fungal infection**: Candida species (Candida albicans,) are natural inhabitants of the vagina in as many as 50% of women, and vaginal candidiasis is the second most common cause of vaginitis.

Risk factors include oral contraceptive use, IUD use, young age at first intercourse, increased frequency of intercourse, DM, HIV or other immunocompromised states, chronic antibiotic use, and pregnancy.produce curdy white discharge

 **3**-**Protozoa** : the third most common cause of vaginitis caused by Trichomonas vaginalis(flagellated protozoans): produce watery copious gray green discharge in which the organism can identified, it is sexually transmitted.

Trichomona primarily infect vaginal epithelium, and they less commonly infect the endocervix, urethra, and Bartholin and Skene glands.

Trichomona are transmitted sexually and can be identified in as many as 80% of male partners of infected women.

**4-Viral** : HSV type 2

**Vaginal neoplasm:**

**Benign tumors:** uncommon

**Premalignant condition:** vaginal dysplasia

**Vaginal intraepithelial neoplasm( VaIN)**

**Malignant Tumors**

**1. Squamous cell carcinoma** is very rare & usually occurs in elderly women, with risk factors similar to those for cervical carcinoma. Vaginal intraepithelial neoplasia is a precursor lesion associated with HPV infection.

**2. Clear cell adenocarcinoma**

**3. Sarcoma botryoides** (**embryonal rhabdomyosarcoma**),

**THE CERVIX UTERI**

**Cervicitis : inflammation of the cervix**

is a very common condition that is associated with a mucopurulent discharge.

May be acute or chronic; specific or non-specific

Non-specific: Strept., Staph., enterococci, E. coli

Specific (STD): gonococci, Chlamydia, Mycoplasma, Trichomonas, Candida….

Acute cervicitis: - rare (postpartal and nonspecific)

 - Neutrophilic infiltration beneath the lining mucosa

**Chronic cervicitis:**

 - More common, Bacterial growth & alteration in pH

 - May be specific, non-specific or of unknown cause

- clinical presentation: leucorrhoea(whitish discharge)

 **Predisposing factors** – sexual intercourse, trauma of child birth, instrumentation and excess or deficiency of estrogen.

**The most important m.o ar:**

1- Chlamydia trachomatis (40%) associated with numerous plasma cell in the inflammatory infiltrate)

2- Candida, Gonococci, Trichomonas vaginalis

3- Herpes simplex II (may transmitted to infants during passage through birth canal---serious or fatal systemic infection

4- Human papiloma virus (HPV).

Morphology:

hyperemea, edema and granular surface around margin of external os.

Nabothian(retention cysts) may be grossly visible as pearly grey vesicles.

Histopathology - chronic inflammatory cell infiltrate, squamous metaplasia, and Nabothian cysts (due to occlusion of cervical gland ducts

Clinical significance:

1- Cervicitis is not precancerous but secondary epithelial dysplastic changes is favorable soil for carcinogenic influence e.g HPV .

2- Severe cervicitis may lead to sterility through blocking of cervical os &produce unfavorable environment for sperms.

**Cervical Tumors**

**Benign tumors**

 Endocervical polyp:

benign tumors composed of connective tissue edematous stroma showing cystically dilated endocervical glands filled with mucin secretion contain scattered mono nuclear cells , and lined by endocervical epithelium. may be inflammatory in origin, range up to few cm in diameter, soft, covered by smooth glistening surface. these lesion may bleed but have no malignant potential .

 **premalignant condition**

Cervical intraepithelial neoplasia (CIN)

 **Malignant tumors**

Invasive cervical carcinoma

Adeno-squamous

 Endocervical type Adenocarcinama

**Cervical Intraepithelial Neoplasia (CIN)**

The Pap smear, introduced 50 years ago by Papanicolaou, remains the most successful cancer screening test ever developed. *In populations that are screened regularly, cervical cancer mortality is reduced by up to 99%*. Nearly all invasive cervical squamous cell carcinomas arise from precursor epithelial changes referred to as cervical intraepithelial neoplasia (CIN). Detection of CIN by the Pap smear at an early stage permits curative treatment. *Cytological examination can detect CIN long before any abnormality can be seen grossly*. CIN begins as low-grade lesion that may progress to higher grade CIN, or it is a high-grade lesions from the outset; this depends on the location of the HPV infection in the transformation zone, the type of HPV infection (high versus low risk), and other host factors.

*On the basis of histology, precancerous changes are graded as:-*

*CIN I: Mild dysplasia in the lower 1/3of the epithelium*

*CIN II: Moderate dysplasia lower 2/3 of the epithelium*

*CIN III: Severe dysplasia/carcinoma in situ*

The current ***Bethesda system*** divides the precancerous lesions into only two groups:

*1. Low-grade SIL* (SIL for squamous intraepithelial lesions), equivalent to CIN I

*2. High-grade SIL*. Equivalent to CIN II & III

Progression from low- to high-grade SIL may or may not occur. The higher the grade of CIN the greater the likelihood of progression to invasive carcinoma, this reaches to 70% with CIN III.

***Epidemiology and Pathogenesis***

* The peak age of CIN incidence is about 30 years, whereas that of invasive carcinoma is about 45 years i.e. precancerous changes usually take many years to evolve into overt carcinomas.
* *Important risk factors for the development of CIN and invasive carcinoma are:*

 *1.**Early age at first intercourse.*

 *2. Multiple sexual partners.*

 *3. Persistent infection by "high-risk" papilloma viruses.*

 *4. Low socio-economic status.*

* All of the above favor a sexually transmitted causative agent (HPV). Indeed, *HPV can be detected by molecular techniques in nearly all precancerous and cancerous lesions*. Specifically, *high-risk HPV types including 16 & 18,* account for the majority of cervical carcinomas. By contrast, condylomas, which are benign lesions, are caused by *low-risk HPV* types (i.e., 6 & 11). In these benign lesions the viral DNA does not integrate into the host genome.
* By contrast, *HPV types 16 & 18 usually integrate into the host genome with subsequent inactivation of the tumor suppressor genes p53 and RB.* The result is a transformed cell, capable of autonomous growth and susceptible to the acquisition of further mutations (cancer progression). *The recently introduced HPV vaccine is very effective in preventing HPV infections and hence cervical cancers.*
* Although many women harbor these viruses, only a few develop cancer, suggesting other pathogenetic influences play a role e.g. cigarette smoking and immunodeficiency states such as AIDS.

***Microscopic features***

***CIN & Carcinoma in situ***

* CIN begins with *CIN I***.** This lesion is characterized by koilocytotic changes mostly in the superficial layers of the epithelium. *Koilocytosis*is composed of nuclear hyperchromasia and angulation with perinuclear vacuolization produced by cytopathic effect of HPV. The dysplastic epithelium is limited to the lower third of the mucosa.
* In *CIN II* the dysplasia is more severe, involving the lower two-thirds of the mucosa. The superficial layer in some cases shows the koilocytotic changes.
* *CIN III*shows dysplastic changes that affect virtually all layers of the epithelium. Surface cells and their koilocytotic changes are usually absent.
* The next stage is *invasive canrcinoma*.

The above progression sequences do not occur in all the cases.

*Cervical cytology and cervical colposcopy remain the basis of cervical cancer prevention.*

***Invasive Carcinoma of the Cervix***

*The most common cervical carcinomas*  *(75%).*

peak incidence at about 45 years( 10 to 15 years after detection of their precursors (CIN).

* Invasive carcinomas of the cervix develop in the region of the **transformation zone** (the squamo-columnar junction) and range from invisible microscopic foci of early stromal invasion to grossly visible exophytic ulcerating masses or deeply infiltrative cancer that encircle the os

macroscopically:

3 forms:

1. The most frequent, fungating tumor (cauliflower like mass may encircle external os .
2. Ulcerative: sloughing of central surface of tumor
3. Infiltrative: the least frequent ,grow into underlying stroma &with time grow into endo cervical canal &lower uterine segment &through fundus into broad ligament .

Histolog.: squamous cell ca of varying differentiation

**Clinical course:**

**CA in situ** usually asymptomatic except for leucorrhea which related to concurrent cervicitis or vaginitis &cx still normal to naked eye but colposcopy disclose the abnormal area.

**Invasive CA often associated with:**

Irregular vaginal bleeding

Leucorrhea

painful coitus &dysuria

 **Mortality** related to its local effect (obstruction of ureters or penetration of bladder or rectum) than to distant metastasis.