***Female Genital tract Pathology***

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***LEC.2***

**BODY OF UTERUS**

Inflammation: endometritis

Adenomyosis & Endometriosis

Polyps/Hyperplasia

Adenocarcinoma

Leiomyoma & leiomyosarcoma

**Endometritis:** inflammation of endometrium**.**

**predisposing factors are**

1-After delivery

2-Miscarriage(abortion)

3-Retained products of conception , and remission by removal of gestational fragments by curettage

4- foreign body such as an intrauterine device.

Retained tissues or foreign bodies act as a nidus for infection, frequently by flora ascending from the vaginal or anal region.Endometritis is either acute or chronic depending on whether there is a predominant neutrophilic or lymphoplasmacytic response;. *Generally the diagnosis of chronic endometritis requires the presence of plasma cell* .

*Acute endometritis is frequently due to* *Staph., Strept.* *Neisseria gonorrhoeae or Chlamydia trachomatis.*

**Microscopically,** neutrophilic infiltrate in the superficial endometrium and glands coexists with a stromal lymphoplasmacytic infiltrate.

**Chronic endometritis:** occur in:

1- Chronic gonorrheal pelvic disease

2- TB either from miliary spread or drainage of TB salpingitis .

3- Postpartum or post abortal endometritis due to retained gestational tissues.

4- Intrauterine contraceptive device

Histologically: irregular proliferation of endometrial glands with chronic inflammatory cells: plasma cc ,macrophages &lymphocytes

All forms of endometritis may present with menstrual abnormalities, infertility and ectopic pregnancy due to extension of the damaging inflammation to the fallopian tubes.Occasionally *tuberculosis* may present as granulomatous endometritis, frequently with tuberculous salpingitis and peritonitis.

**Adenomyosis**

“invagination of the stratum basalis of endometrium down into the myometrium.” Growth of basal layer of endometrium (endometrial stroma & gland) into myometrium

Mic:Nests of endometrial stroma, glands, or both, are found well down in the myometrium between the muscle bundles which will become hypertrophied. Accordingly, the uterine wall often becomes thickened and the uterus is enlarged and globular. Because these glands derive from the stratum basalis, they do not undergo cyclical bleeding.

Clinically:marked adenomyosis may produce menorrhagia(excessive menstural bleeding), dysmenorrhea, and pelvic pain before the onset of menstruation.

**Endometriosis**

This is characterized by “*the presence of* *endometrial glands and stroma in a location outside the uterus*.” It is frequently multifocal and may involve any tissue in the pelvis (ovaries, pouch of Douglas, uterine ligaments, fallopian tubes, and rectovaginal septum and rarely in vulva, vagina, laparotomy scar, umbilicus, and appendix.), less frequently in more remote sites like: LN ,heart , lung ,GIT.

*It occurs in as many as 10% of women in their reproductive years and in nearly half of women with infertility.*

**Pathogenesis**: Three possibilities have been suggested to explain the origin of these lesions:-

*1. The regurgitation theory,* currently the most accepted, proposes menstrual backflow through the fallopian tubes with subsequent implantation.

*2. The metaplastic theory* proposes endometrial differentiation of coelomic epithelium.

*3. The vascular or lymphatic dissemination theory* has been raised to explain extrapelvic endometriosis.

***Gross features***

* Endometriosis almost always contains functioning endometrium, which undergoes cyclic bleeding. Because blood collects in these ectopic foci, they usually appear grossly as red-blue to yellow-brown nodules.
* They vary in size from microscopic up to 2 cm in diameter and lie on or just under the affected serosal surface. Often individual lesions coalesce to form larger masses.
* When the ovaries are involved, the lesions may form large, blood-filled cysts that are transformed into so-called *chocolate cysts* .
* Seepage and organization of the blood leads to widespread fibrosis, adherence of pelvic structures, sealing of the tubal fimbriated ends, and distortion of the oviducts and ovaries.

***Microscopic features***

* The histologic diagnosis depends on finding two of the following three features within the lesions:-

1. Endometrial glands.

2. Endometrial stroma, or

3. Hemosiderin pigment.

Extensive scarring of the oviducts and ovaries often causes sterility.

**Clinical features:**

It depends on distribution of lesion:

Scarring of oviduct &ovaries---discomfort in the lower abdomen &infertility

Rectal wall involvement ---pain on defecation

Bladder involvement--- dysuria.

In almost all cases , there is dysmenorrhea &pelvic pain because of intra pelvic bleeding & peri uterine adhesion .

**Endometrial hyperplasia**

This is an exaggerated endometrial proliferation induced by sufficiently prolonged excess of estrogen relative to progesterone

Appears histologically as an increase in the number of glands relative to the stroma, appreciated as crowded glands, often with abnormal shapes.

■ caused by unopposed estrogen stimulation and is an important cause of abnormal vaginal bleeding.

■ It is divided into non-atypical and atypical hyperplasia

based on nuclear atypia.

Atypical hyperplasia is associated with an increased risk of endometrial carcinoma.

■ The PTEN tumor suppressor gene is mutated in approximately 20% of endometrial hyperplasias**.**

**causes of increase estrogen level**:

• Obesity (because adipose tissue processes steroid precursors into estrogens)

• Menopause(Failure of ovulation )

• Polycystic ovarian syndrome

• Functioning granulosa cell tumors of the ovary(Estrogen producing ovarian tumor)

• Prolonged administration of estrogenic substances (estrogen replacement therapy)

Atypical EH carry 20-25% risk of progression to CA of endometrium

**Non-atypical hyperplasia**

the cardinal feature is an increase in the gland-to-stroma ratio.

The glands show variation in size and shape and may be dilated).

Although there may be back-to-back glands focally, some intervening stroma is usually retained

These lesions reflect an endometrial response to persistent estrogen stimulation and rarely progress to adenocarcinoma (approximately 1% to 3%).

Non-atypical hyperplasia may evolve into cystic atrophy when estrogen is withdrawn.

**Atypical hyperplasia (endometrial intraepithelial neoplasia EIN)**

is composed of complex patterns of proliferating glands

displaying nuclear atypia. The glands are commonly back-toback

and often have complex outlines due to branching structures.

Individual cells are rounded and lose the normal

perpendicular orientation to the basement membrane. the nuclei have open (vesicular) chromatin and conspicuous

nucleoli.

NON atypical hyperplasia carries a negligible risk, while a woman with **atypical hyperplasia** has a 20% risk of developing endometrial carcinoma. Thus when atypical hyperplasia is discovered, it must be carefully evaluated for the presence of cancer and must be monitored by repeated endometrial biopsy.

23% to 48% of women with a diagnosis of atypical hyperplasia are found to have carcinoma when a hysterectomy is performed.

atypical hyperplasia is managed by hysterectomy or, in young women who desire fertility, a trial of progestin therapy and close follow-up.

Gross features

• In non atypical hyperplasia the endometrium is diffusely thickened

• In complex & atypical hyperplasia there is usually focal thickening of the endometrium.

Microscopic features

• Simple non atypical hyperplasia increase number of the proliferative glands and some are cystically dilated.

• Atypical Complex hyperplasia: there is glandular crowding with little stroma separating the proliferative glands.

• Atypical hyperplasia: characterized by atypical nuclei of the proliferative glands as evidenced by nuclear stratification, nuclear rounding and the presence of nucleoli.

**Tumors of endometrium &myometrium**:

The most common neoplasms of the body of the uterus are:-

1. Endometrial polyps.

2. Smooth muscle tumors(benign: leiomyoma, malignant:leiomyosarcoma)

3. Endometrial carcinomas.

All tend to produce bleeding from the uterus as the earliest manifestation

**Endometrial polyps**: sessile ,hemispheric ,0.5-3 cm in diameter ,larger polyps may project from endometrial mucosa into uterine cavity , May be associated with hyperestrogenism

Usually benign, but may show foci of hyperplasia or cancer.

histology.: Sessile tumors composed of endometrial glands and stroma. covered by columnar cells. Some have cystically dilated glands , thick walled blood vessels.

The clinical significance of these polyps lies in the production of abnormal uterine bleeding and, more important, the risk (however rare), of giving rise to a cancer.

**Leiomyomas** are benign tumors that arise from the smooth muscle cells in the myometrium. Because of their firmness they are also called fibroids. They are the most common benign tumor in females and are found in 30% to 50% of women during reproductive life. Estrogens and possibly oral contraceptives stimulate their growth; conversely, they shrink postmenopausally.

Gross features:

• They are sharply circumscribed, firm gray-white masses with a characteristic whorled cut surface.

• They may occur singly, but are often multiple tumors scattered within the uterus, ranging in size from small seedlings to massive neoplasms that dwarf the size of the uterus.

• Some are embedded within the myometrium (intramural), whereas others may lie directly beneath the endometrium (submucosal) or directly beneath the serosa (subserosal).

• Larger neoplasms may show foci of ischemic necrosis with areas of hemorrhage and cystic softening (red degeneration).

• After menopause they may become densely collagenous and even calcified.

Microscopic features

• There are whorling bundles of smooth muscle cells.

• Foci of fibrosis, calcification, ischemic necrosis, cystic degeneration, and hemorrhage may be present.

Leiomyomas of the uterus may be entirely asymptomatic and be discovered only on routine pelvic examination or imaging studies. The most frequent manifestation, when present, is menorrhagia. Large masses in the pelvic region may become palpable or may produce a dragging sensation.

Benign leiomyomas are not transform into sarcomas.

**Leiomyosarcomas** typically arise de novo from the mesenchymal cells of the myometrium” not from preexisting leiomyoma”. They are almost always solitary tumors, in contrast to the frequently multiple leiomyomas.

Gross features

• The tumor is typically bulky.

• It infiltrates the uterine wall.

• Sometimes it projects into the endometrial cavity.

• They are frequently soft, hemorrhagic, and necrotic.

Microscopic features

• They show a wide range of differentiation, from those that closely resemble leiomyoma to wildly anaplastic tumors.

• The diagnostic features of leiomyosarcoma include tumor necrosis, cytologic atypia, and mitotic activity. Since increased mitotic activity alone is sometimes seen in benign smooth muscle tumors in young women, an assessment of all three features is necessary to make a diagnosis of malignancy.

Recurrence after removal is common with these cancers, and many metastasize, typically to the lungs.

**Endometrial Carcinoma**

After the dramatic drop in the incidence of cervical carcinoma, EMC is currently the most frequent cancer occurring in the female genital tract.

**Epidemiology and Pathogenesis**

Endometrial carcinoma appears most frequently around the age of 60 years. There are two clinico-pathological settings in which endometrial carcinomas arise:-

1. In perimenopausal women with estrogen excess; these are of endometrioid type.

2. In older women with endometrial atrophy; these are of serous type.

risk factors for endometrioid carcinoma include:-

a. Obesity: associated with increased synthesis of estrogens in fat depots.

b. Diabetes.

c. Hypertension.

d. Infertility: women tend to be nulliparous, often with anovulatory cycles.

e. prolong estrogen replacement therapy

f. ovarian estrogen secreting tumors

At least some of these risk factors point to increased estrogen stimulation. Many of these risk factors are the same as those for endometrial hyperplasia, and endometrial carcinoma frequently arises on a background of endometrial hyperplasia.

Mutations in **DNA mismatch repair genes** and **PTEN** have been demonstrated.

**Serous carcinoma** of the endometrium typically arises in a background of atrophy. Nearly all cases of serous type have mutations in the **p53** tumor suppressor gene.

Gross features

• EMC may be exophytic (fungating, polypoid) or infiltrative. Microscopic features

• The endometrioid carcinoma consists of malignant endometrial-like tubular glands of varying grades. Squamous metaplasia is frequent. Sometimes, the tumor is adeno-squamous carcinoma.

• Tumors originate in the mucosa and may infiltrate the myometrium and enter vascular spaces, with metastases to regional lymph nodes.

• Serous carcinoma forms small tufts and papillary arrangements rather than the glands seen in endometrioid carcinoma, and has much greater cytologic atypia. They are particularly aggressive

Patients with Endometrial Carcinoma presents with leukorrhea and irregular bleeding. With progression, the uterus may become palpable, and in time it becomes fixed to surrounding structures by extension of the cancer beyond the uterus.

Endometrial carcinoma are usually late-metastasizing neoplasms, but dissemination eventually occurs, with involvement of regional nodes and more distant sites. The prognosis depends heavily on the stage of the disease.

**Staging:**

Stage I: Carcinoma has involved the corpus.

Stage II. Carcinoma has involved the corpus and the cervix.

Stage III. Carcinoma has extended outside the uterus but not outside the true pelvis.

Stage IV. Carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or the rectum.

**grading**

G1. Well-differentiated adenocarcinoma

G2. Differentiated adenocarcinoma with partly solid (less than 50%) areas

G3. Predominantly solid or entirely undifferentiated carcinoma. Serous and clear cell carcinomas are automatically classified as grade 3.