Tumors of the uterine corpus

The endometrium comprises the zona functionalis zf (superficial two thirds) and the zona basalis zb (deep one third)

The zf responds to hormonal stimulation, is supplied by spiral arteries and is shed during menses.

The zb remains and supplies the regenerating cells.

The menstrual cycle

- Proliferative phase: day 0 to 14; mitotic activity and pseudostratification of glands
- Secretory phase: follows ovulation, day 15 to 27; coiled glands, stromal edema, spiral arteries present
- Menstrual phase: begins day 28, spiral arteries collapse, necrotic endometrium is shed

Abnormal uterine bleeding

- Excessive or reduced menstrual flow
- Bleeding that occurs outside of the normal cycle
  - Intrauterine causes (leiomyoma)
  - Extrauterine (coagulation abnormality)

Causes of abnormal uterine bleeding by age

- Reproductive age:
  - psychosomatic (stress)
  - nutritional and endocrine diseases
  - gonadal (functional tumors)
  - endometrial hyperplasia
  - pregnancy
  - organic (malignant npl, leiomyomas)
- Menopause:
  - organic (malignant neoplasms)
  - endometrial hyperplasia
Dysfunctional uterine bleeding
- Not attributable to a distinct intra- or extrauterine causes, may occur secondary to endocrine disturbances
- The most common cause: anovulatory bleeding

Anovulatory cycle
- Lack of ovulation induces prolonged estrogen stimulation, without a postovulatory rise in progesterone
- This results in a continually proliferating endometrium

Tumors of the uterine corpus

Histologic classification

1. Epithelial tumors and related lesions
   - Endometrial hyperplasia
     - Simple
     - Complex
   - Adenomatous hyperplasia
   - Endometrial polyp
   - Endometrial carcinoma
     - Intestinal
     - Cervical
   - Sarcoma
   - Mixed tumors

2. Nonepithelial tumors and related lesions
   - Endometrial stromal tumors (stromal sarcoma)
   - Smooth muscle tumors
     - Leiomyoma (leiomyoma, leiomyosarcoma)
     - Leiomyosarcoma (leiomyoma, leiomyosarcoma)
   - Fat tumors
   - Other mesodermal tumors

3. Intervening tumors
   - Mixed epithelial-nonepithelial tumors
   - Benign tumors
   - Adenomyosis
   - Adenomyosis (endometrial stromal sarcoma)

4. Miscellaneous tumors
   - Secondary tumors
   - Metastases
   - Lymphomas
   - Others

5. Secondary tumors

Endometrial hyperplasia
- A spectrum of changes induced by estrogenic stimulation

Estrogen excess:
- Anovulatory cycles
- Administration of estrogenic steroids
- Estrogen-producing ovarian lesions (polycystic ovary syndrome)
- Estrogen-producing tumors
- Obesity
Types of hyperplasia

- **simple:**
  - minimal glandular crowding, cystically dilated glands, no cytologic atypia

- **complex:**
  - glandular crowding and complexity, no atypia (the relative risk of development of malignancy-less than 5%)

- **atypical:**
  - glandular crowding (back-to-back glands), cytologic atypia (risk of malignancy-about 30%)

Hyperplasia

**SYMPTOMS:**
- excessive and irregular uterine bleeding
- about 20% risk of progressing to adenocarcinoma

**TREATMENT:**
- high-dose progestins
- hysterectomy

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New type of hyperplasia: EIN: endometrial intraepithelial neoplasia

- Increased number of glands that occupy a greater proportion of the endometrium than the stromal component
- EIN lesions demonstrate loss of function of the PTEN tumor suppressor gene

Simple hyperplasia (without atypia)

Complex endometrial hyperplasia

Complex hyperplasia with atypia
Endometrial adenocarcinoma

- The most frequent cancer of the female genital tract
- Occurs in peri- or postmenopausal women
- Clinical symptom: abnormal uterine bleeding

Endometrial adenocarcinoma – “estrogen-dependent malignancy”

Risk factors
- Increased estrogen stimulation: endometrial hyperplasia
- Prolonged estrogen replacement therapy
  - About 20% of cancers develop without preexisting hyperplasia, and they have poorer prognosis
- Obesity, aromatization of adipose tissue to estrone in adipocytes
- Nulliparity
- Early menarche and late menopause (increased and prolonged estrogen)
- Diabetes
- Hypertension
- Family history of breast and ovarian cancer

Endometrial adenocarcinoma of the uterus

Histologic forms of endometrial carcinoma

1. Endometrioid (accounts for 60% of all endometrial carcinomas)
   - Resemble normal endometrium but
   - Glands contain atypical cells with pleomorphic nuclei and abnormal mitotic figures
   - Graded according to the International Federation of Gynecology and Obstetric system: worsening grade corresponding to areas of solid growth
   - G1 well differentiated >95% of glands
   - G2 moderately differentiated >50% of glands
   - G3 poorly differentiated
   - But significant nuclear atypia changes grade from 1 to grade 2 and so on

Endometrial adenocarcinoma

- Protective factor: cigarette smoking (affects hepatic conversion of estrone to active metabolic forms)?
- “The risk for endometrial cancer was significantly lower for current aspirin users who were obese or postmenopausal?”

Cancer Res. 2008 Apr;68, AN Viswanathan, Harvard Medical School, Boston

Endometrial adenocarcinoma

- Risk factors for young premenopausal women.
  - PT. Soliman, The University of Texas
  - A retrospective cohort study; 12% (188/1531) of all patients with endometrial adenocarcinoma who were younger than 50 years (the mean age at diagnosis was 41)
    - The majority of patients diagnosed with endometrial cancer at a young age were obese and nulliparous
    - In addition: a high incidence of synchronous primary ovarian cancers in this group.

Endometrial adenocarcinoma

- Adenocarcinoma of the uterus
**Endometrioid adenocarcinoma**

- Atypical glands "back to back", scanty stroma

**Well differentiated endometrioid adenocarcinoma**

**Staging**
- Stage 1 confined to the corpus
- Stage 2 involvement of the cervix
- Stage 3 beyond the uterus but within the pelvis
- Stage 4 distant metastases

**Endometrioid carcinoma**

- Five year survival:
  - Tumor limited to the endometrium: 90%
  - Tumor invades less than 1/2 of the myometrium: 70%
  - Spread beyond the uterus: 10-15%

**Endometrioid carcinoma**

**Treatment**
- Simple hysterectomy
- Or additional postoperative radiation
- Retinoid, metabolites of vitamin A, and synthetic peroxisome proliferator-activated receptor (PPAR) gamma ligands may be the important candidates not only for prevention but also for specific endocrine treatment of endometrial carcinoma. Endocr J.2007 Dec 54(5), K. Ito, Japan

**Endometrial adenocarcinoma**

- Not graded:
  2. serous adenocarcinoma
    - epithelium similar to that found in the fallopian tube
    - particularly aggressive
  3. clear cell adenocarcinoma
    - cells are of müllerian origin, large, with cytoplasmic glycogen
    - tumor tends to occur in older women, with no history of estrogen replacement
    - behaves as poorly differentiated cancer (Müllerian ducts – uterus and tubes)
Endometrioid carcinoma
– clear cell variant

Endometrial stromal nodule

Leiomyoma
A benign neoplasm composed of smooth muscle cells with variable amounts of fibrous stroma.

- The most common neoplasm of the uterus
- Is estimated to occur in 20-40% of women beyond the age of 30

Leiomyoma

Clinical features
- small – asymptomatic
- larger or multiple
  - pain (due to the infarction that may occur in larger leiomyomas)
  - bleeding (due to the ulceration of overlying endometrium)
  - may affect fertility (with block of uterine function– rare infertility)
  - in pregnant women:
    - abruptio placentae,
    - premature labor
- Secondary inflammatory changes

Etiology
- Genetic influences? (more common in blacks)
- Estrogens (oral contraceptives)
- Growth is related to female sex hormones
  - the rarity before menarche and their usual regression after menopause
  - occasional rapid growth associated with pregnancy
  - the presence of estrogen and progesterone receptors in leiomyoma cells

Leiomyoma
- Usually multiple
- Sharply circumscribed but not encapsulated!
Intramural and subserous uterine leiomyomas

Leiomyoma

Histology
- Irregular bundles of smooth muscles
- Postmenopausal regressive changes: fibrosis and calcification
- Necrosis, cysts, hemorrhage
- Intramural, submucosal, subserosal

Variants of uterine leiomyoma

Cellular
- A benign smooth muscle tumor that is significantly more cellular than the surrounding myometrium (5%)”
- They do not differ clinically or grossly from other leiomyomas

Differential diagnosis
- Cellular leiomyoma vs low-grade stromal sarcoma:
  - mitotic activity, nuclear atypia, atypical mitoses

Variants of uterine leiomyoma

Epithelioid leiomyoma
- Tumor composed of round cells which resemble epithelial cells
- No significant differences from typical tumors
Epithelioid leiomyoma

Variants of uterine leiomyoma

Bizarre leiomyoma (atypical):
- Characterized by mononuclear or large, pleomorphic, giant cells
- Distinction from leiomyosarcoma – absence of:
  - mitotic figures,
  - necrosis
  - vascular invasion

Atypical leiomyoma

Leiomyomas – clinical symptoms

- Many patients are asymptomatic; or
- Bleeding: ulceration of the overlying endometrium
- Mass-effect: interference with bowel or bladder function (rare)
- Pain: due to infarction that may occur in large leiomyoma

Leiomyoma

Surgical treatment
- Enucleation
- Simple hysterectomy

Leiomyosarcoma

- Malignant sarcoma deriving directly from the mesenchymal cells of myometrium
- NOT from preexisting leiomyomas!
- Solitary mass infiltrating the uterine wall
- Spindle cells, increased mitotic activity
- Recurrence after removal: common
- Distant metastases
- 40% 5-year survival rate
Leiomyosarcoma uteri

Adenomatoid tumor
Tumor of the uterine serosa and myometrium, originating from serosal mesothelium
- Benign mesothelioma?
- Gross findings: in the myometrium, near the serosal surface.
- Histologically, tumor usually infiltrates the myometrium at least focally
  - Anastomosing tubules lined by cells that are flattened to cuboidal
- Differential diagnosis
  - Lymphangioma – shows negative immunostain for cytokeratin
  - Adenocarcinoma – high mitotic activity and desmoplastic stromal reaction

Adenomatoid tumour

Endometrial stromal tumors
- Account for less than 2% of all uterine cancers
- Are composed of stromal or
- a combination of stromal and epithelial components

Endometrial stromal sarcoma
- Highly vascular, spindle cells arranged around blood vessels; nuclear atypia

Stromal sarcoma
Uterine adenosarcoma

- benign epithelium (proliferative endometrial glands) and
- malignant mitotically active stroma surrounding glands

Carcinosarcoma (malignant mixed Mullerian tumor)

- atypical glands and malignant stroma, other mesenchymal elements: bone, muscle
- heterologous elements: the presence of differentiated sarcomatous elements which are not derived from the normal uterus; their presence does not affect survival
- occurs in older patients
- very poor prognosis

Endometrial carcinosarcoma

- The endometrial origin has recently been well established but when compared with high grade endometrioid or clear cell carcinomas
- Carcinosarcoma has a worse outcome, because of a higher incidence of pulmonary metastases

Thank You for Your attention
Underground lake in Wieliczka salt mine nearby Krakow (southern region of Poland)