Diseases of the uterus

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Endometrial hyperplasia

- An excess of estrogen relative to progestin, if sufficiently prolonged or marked, can induce exaggerated endometrial proliferation (hyperplasia...important precursor of type 1 endometrial carcinoma)

- Of the causes of estrogen excess:
  - Failure of ovulation (such as is seen in perimenopause)
  - Prolonged administration of estrogenic steroids without counter-balancing progestin
  - Estrogen-producing ovarian lesions (such as polycystic ovary disease and granulosa-theca cell tumors of the ovary)
  - A common cause of estrogen excess is obesity, as adipose tissue converts steroid precursors into estrogens
Endometrial hyperplasia, morphology

• High gland/stroma ratio (crowding)

• Simple VS Complex

• Typical VS Atypical
Endometrial hyperplasia, cont’d

• Complex hyperplasia without cellular atypia carries a low risk (less than 5%) for progression to endometrial carcinoma

...while complex hyperplasia with cellular atypia is associated with a much higher risk (20% to 50%)

• When hyperplasia with atypia is discovered, it must be carefully evaluated for the presence of cancer and must be monitored by serial endometrial biopsies

• In time, the hyperplasia may proliferate autonomously, no longer requiring estrogen, and eventually may give rise to carcinoma
Endometrial hyperplasia, pathogenesis

• In a significant number of cases, the hyperplasia is associated with inactivating mutations in the PTEN tumor suppressor gene.

• Acquisition of PTEN mutations is believed to be one of several key steps in the transformation of hyperplasias to endometrial carcinomas, which also often harbor PTEN mutations.
Endometrial carcinoma

• The most frequent cancer occurring in the female genital tract in the West

• Age range: mostly between 55 & 65 years...uncommon before age 40

• 2 main types:
  1-Endometrioid (type 1)
  2-Type 2
**Endometrial carcinoma, types**

So: patients with endometrioid carcinoma are more likely to develop breast cancer (shared risk factor).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type I</th>
<th>Type II</th>
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<tr>
<td>Age</td>
<td>55-65 yr</td>
<td>65-75 yr</td>
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<tr>
<td>Clinical setting</td>
<td>Unopposed estrogen &amp; infertility</td>
<td>Atrophy, Thin physique</td>
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<tr>
<td>Morphology</td>
<td><strong>Endometrioid</strong></td>
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<td>Precursor</td>
<td>Hyperplasia</td>
<td>Serous endometrial intraepithelial carcinoma</td>
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<td>Mutated genes/genetic abnormalities</td>
<td><strong>PTEN</strong>&lt;br&gt;ARID1A (regulator of chromatin)&lt;br&gt;PIK3CA (PI3K)&lt;br&gt;KRAS&lt;br&gt;FGF2 (growth factor)&lt;br&gt;MSI*&lt;br&gt;CTNNB1 (Wnt signaling)&lt;br&gt;TP53</td>
<td><strong>TP53</strong>&lt;br&gt;Aneuploidy&lt;br&gt;PIK3CA (PI3K)&lt;br&gt;FBXW7 (regulator of MYC, cyclin E)&lt;br&gt;CHD4 (regulator of chromatin)&lt;br&gt;PPP2R1A (PP2A)</td>
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<tr>
<td>Behavior</td>
<td>Indolent, Spreads via lymphatics</td>
<td>Aggressive, Intraperitoneal and lymphatic spread</td>
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*MSI, Microsatellite Instability; CTNNB1, beta-catenin gene

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Endometrioid carcinoma:

- Mutations in mismatch repair genes and the tumor suppressor gene PTEN are early events in the stepwise development of this type.

- Women with germline mutations in PTEN (Cowden syndrome) are at high risk for this cancer.

- TP53 mutations occur but are relatively uncommon and are believed to be late events in the genesis of this tumor type.
Endometrial carcinoma, pathogenesis

- Serous carcinoma:

  - Nearly all cases have mutations in the *TP53* tumor suppressor gene

  - Mutations in DNA mismatch repair genes and *PTEN* are rare
Endometrioid carcinoma:

- Other than their typical appearance, there may be mucinous, tubal (ciliated), or squamous (occasionally adenosquamous) differentiation.

- Tumors originate in the mucosa and may infiltrate the myometrium and enter vascular spaces.

- They may also metastasize to regional lymph nodes.

- Endometrioid carcinomas are graded I to III, based on the degree of differentiation.
Endometrial carcinoma, morphology

• Serous carcinoma:

- Form small tufts and papillae, rather than the glands seen in endometrioid carcinoma

- Exhibit much greater cytologic atypia

- They behave aggressively and they are by definition high-grade

- Immunohistochemistry often reveals high levels of p53 in serous carcinoma, a finding that correlates with the presence of TP53 mutations (mutant p53 accumulates and hence is more easily detected by staining)
Endometrial carcinoma, morphology
Endometrial carcinoma, clinically:

• Usually manifest with leukorrhea and irregular bleeding, often in postmenopausal women

• With progression, the uterus enlarges and may become affixed to surrounding structures as the cancer infiltrates surrounding tissues

• Usually are slow to metastasize, but if left untreated, eventually disseminate to regional nodes and more distant sites

• For serous carcinoma, even a small tumor in the uterus may seed the peritoneal cavity through the fallopian tube...so during operation of uterine cancer, the gynecologist takes a sample from the peritoneal fluid (peritoneal wash) to be examined in the pathology lab (cytology/pathology)

...and if cancer cells are present in peritoneal fluid, the stage is higher
Endometrial polyps

• Exophytic masses of variable size that project into the endometrial cavity

• Formed of glands and stroma...stromal cells are clonal

• May be single or multiple and are usually sessile, measuring from 0.5 to 3 cm in diameter, but are occasionally large and pedunculated

• Polyps may be asymptomatic or may cause abnormal bleeding (intramenstrual, menometrorrhagia, or postmenopausal) if they ulcerate or undergo necrosis

• Can be caused by tamoxifen

• Rarely, carcinoma can arise in them
Leiomyoma

= Benign tumors that arise from the smooth muscle cells in the myometrium

• They are the most common benign...30-50% of women of reproductive age

• Considerably more frequent in blacks than in whites

• Associated with chromosomal abnormalities, e.g., rearrangements of chromosomes 6 and 12 that also are found in a variety of other benign neoplasms, such as endometrial polyps and lipomas

• Estrogens and possibly oral contraceptives stimulate the growth of leiomyomas; conversely, these tumors shrink postmenopausally
Leiomyoma, morphology

- Sharply circumscribed, firm gray-white masses
- Characteristic whorled cut surface
- They may occur singly, but more often multiple tumors are scattered within the uterus, ranging from small nodules to large tumors
- Intramural, submucosal or subserosal
- Microscopically:
  ...bundles of smooth muscle cells mimicking the myometrium

What are parasitic leiomyomas??

[Check https://ilovepathology.com/leiomyoma-uterus for references]
Leiomyoma, clinical features

• Often asymptomatic

• The most frequent presenting sign is menorrhagia, with or without metrorrhagia

• Large leiomyomas may be palpated by the affected woman or may produce a dragging sensation

• Almost never transform into sarcomas, and the presence of multiple lesions does not increase the risk of malignancy

• Can be complicated by infarction (acute pain)

  *Can cause pressure symptoms (urinary symptoms or constipation)*

  *Myomas in pregnant women increase the frequency of spontaneous abortion, fetal malpresentation, uterine inertia (failure to contract with sufficient force), and postpartum hemorrhage*
Leiomyosarcoma

- Arise de novo from the mesenchymal cells of the myometrium, not from preexisting leiomyomas.

- Almost always solitary and most often occur in postmenopausal women, in contradistinction to leiomyomas, which frequently are multiple and usually arise premenopausally.

- Grossly: may be soft, hemorrhagic & necrotic.

- To differentiate between leiomyoma, leiomyosarcoma & STUMP (smooth muscle tumor of undetermined malignant potential), we need to assess (microscopically):
  - number of mitoses
  - degree of atypia
  - presence of tumor coagulative necrosis.
Adenomyosis

= growth of the basal layer of the endometrium down into the myometrium

• Nests of endometrial stroma, glands, or both, are found deep in the myometrium interposed between the muscle bundles

• Reactive hypertrophy of the myometrium, resulting in an enlarged, globular uterus, often with a thickened uterine wall will occur

• Because the glands in adenomyosis derive from the stratum basalis of the endometrium, they do not undergo cyclic bleeding
  ...However, marked adenomyosis may produce menorrhagia, dysmenorrhea, and pelvic pain before the onset of menstruation
Endometriosis

- Defined by the presence of endometrial glands and stroma in a location outside the endomyometrium

- In 10% of women in their reproductive years and in nearly half of women with infertility

- Frequently multifocal

- Pelvic structures (ovaries, pouch of Douglas, uterine ligaments, tubes, and rectovaginal septum) are the most common

- Less frequently, distant areas of the peritoneal cavity or periumbilical tissues are involved

- Uncommonly, distant sites such as lymph nodes, lungs, and even heart, skeletal muscle, or bone are affected
Endometriosis, proposed origins

- Metaplastic differentiation of coelomic epithelium
- Lymphatic dissemination
- Regurgitation through fallopian tube
- Extrapelvic dissemination through pelvic veins

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Endometriosis, cont’d

• The endometriotic tissue here is not just misplaced but is also abnormal:

...it secretes prostaglandin E2, and produces increased estrogen due to high aromatase activity of stromal cells...these are important for its survival in the location involved

...so: there are beneficial effects of COX-2 inhibitors and aromatase inhibitors in the treatment of endometriosis
Endometriosis, morphology

• In contrast with adenomyosis, endometriosis almost always contains functioning endometrium...cyclic bleeding

• Because blood collects in these aberrant foci, they usually appear grossly as red-brown nodules or implants

• When the ovaries are involved, the lesions may form large, blood-filled cysts that turn brown (chocolate cysts) as the blood ages

• With seepage and organization of the blood, widespread fibrosis occurs, leading to adhesions among pelvic structures, sealing of the tubal fimbriated ends, and distortion of the oviducts and ovaries

• At least 2 of the following must be seen microscopically for diagnosis:
  - Endometrial glands
  - Endometrial stroma
  - Hemosiderin pigment
Endometriosis, clinical features

- Extensive scarring of the oviducts and ovaries often produces discomfort in the lower abdominal quadrants and eventual sterility

- Rectal wall involvement may produce pain on defecation

- Involvement of the uterine or bladder serosa can cause dyspareunia (painful intercourse) and dysuria, respectively

- Almost all cases feature severe dysmenorrhea and pelvic pain resulting from intrapelvic bleeding and periuterine adhesions
Thank You