Premalignant and Malignant Diseases of the Uterus

**Contents:**

1. Endometrial Hyperplasia
2. Endometrial Carcinoma in situ
3. Invasive Endometrial Carcinoma
4. Other Malignant uterine Tumors
I- Endometrial Hyperplasia

- Excessive proliferation of the endometrial glands & to a lesser extent endometrial stroma
- This results in varying degrees of architectural complexity and cytologic atypia.
- Due to excessive estrogen stimulation
- The clinical significance of this diagnosis is progression to endometrial adenocarcinoma.
- Only 25% of Pt with End Ca have Hx of hyperplasia

Classification of Endometrial Hyperplasia

WHO classification

I. Simple hyperplasia - Increased number of glands but regular glandular architecture
II. Complex hyperplasia - Crowded irregular glands
III. Simple hyperplasia with atypia - Simple hyperplasia with presence of cytologic atypia (prominent nucleoli and nuclear pleomorphism)
IV. Complex hyperplasia with atypia - Complex hyperplasia with cytologic atypia
Endometrial Hyperplasia........Cont.

1-Hyperplasia without atypia (not premalignant)
  1-A-Simple
  - Microscopically ➔ crowding of the glands in the stroma
  - Glands are cystically dilated & “Swiss cheese” appearance
  - Commonly asymptomatic
  - <1% progress to Ca over 15 Y
  - 90% regress

Endometrial Hyperplasia........Cont.

1-B-Complex hyperplasia without atypia
  - A complex crowded appearance of the glands with very little stroma
  - Epithelial stratification & mitotic activity
  - 3% progress to Ca over 13 Y
  - 80% regress
  - 85% reversal with progestin
Endometrial Hyperplasia………Cont.

2-Hyperplasia with atypia (premalignant)
- Histologically ➔ endometrial glands are lined by enlarged cells with ↑ nuclear : cytoplasmic ratios
- The nuclei are irregular with coarse chromatin & prominent nucleoli
- 50-94% regress with progestin therapy
- A higher rate of relapse after treatment compared to that of lesions without atypia

2-A-Simple
- Progression to carcinoma occur in 8%

2-B- Complex
- Progression to carcinoma occur in 29%

Endometrial Hyperplasia………Cont.

- **Pathophysiology**
  - Endometrial hyperplasia results from continuous estrogen stimulation that is unopposed by progesterone
  - This can be due to endogenous estrogen (Obesity, PCOD, late menopause, tumors).
  - or exogenous estrogenic sources (unopposed HRT, tamoxifen)
Endometrial Hyperplasia……..Cont.

- **Mortality/ Morbidity**
  - Endometrial hyperplasia is often associated with menorrhagia, metrorrhagia or postmenopausal bleeding.
  - Abnormal Pap smear result in atypical glandular or endometrial cells
  - Diagnosis is usually made by endometrial biopsy using Pipelle (OPD) or D&C in the operating room.

Role of TVS and Hysteroscopy

- Endovaginal US has a sensitivity of 96% for ruling out endometrial carcinoma if endometrial echo complex is less than 5 mm.
- Persistent bleeding, despite a thin stripe still warrants tissue biopsy because of the risk of type 2 cancer that is not associated with endometrial hyperplasia
- If hyperplasia is diagnosed by office biopsy, one should consider D&C +hysteroscopy to rule out atypia or cancer prior to medical management
Endometrial Hyperplasia……..Cont.

- Progestins can effectively treat hyperplasia, control bleeding and prevent cancer.
- Hyperplasia without atypia responds well (98%) in 3-9 months, but response is 90% with atypia.
- Definitive treatment with hysterectomy, due to the high rate of endometrial cancer with atypia.
- D&C and Pipelle biopsy only sample 50% of endometrium, focal carcinoma may be missed.
- Continued surveillance after regression of the lesion every 6-12 months if risk factors persist.

Regimens of Progestin therapy

- Medroxyprogesterone acetate, 10-20 mg continuous, or cyclic 14 days per month
- Micronized vaginal progesterone, 100-200 mg continuous or cyclic 14 days per month
- Levonorgestrel-containing IUD (Mirena), continuous for 1-5 years
- Megestrol acetate, 40-200 mg per day, usually reserved for atypical hyperplasia
II- CARCINOMA IN SITU (Stage 0)

- Histologically differentiated from carcinoma by
  1- Presence of intervening stroma between abnormal (atypical) glands
  2- There is no evidence of invasion of glandular basement membrane
  3- Severe cases is difficult to differentiate from Carcinoma so should managed as Carcinoma
III- Endometrial Cancer

Epidemiology

- The most common GYN malignancy in the U.S. (23:100,000), 4th most common in women
- 2-3% of women develop in lifetime
- Mean age is 60 years
- Majority are diagnosed early due to bleeding
- >90% 5-year survival for stage I disease
- Overall 5-year survival for all stages is 60-

Risk factors for Endometrial Cancer

- Increased estrogen
  - Hormone therapy
  - Obesity
  - Anovulation/PCOS
  - Estrogen secreting tumors
  - Older age
  - Infertility
  - Early menarche
  - Late menopause
- Genetics
  - HNPCC
  - Caucasian
Endometrial Cancer……..cont.

Symptoms & Signs:
- Postmenopausal bleeding (90%)
- Postmenopausal offensive discharge (pyometra)
- Perimenopausal with irregular heavy menses, increasingly heavy menses
- Abnormal Endometrial cells on Pap smears
- Late stage ….symptoms of Local pelvic spread

Preoperative Work-up
- Endometrial biopsy
- Transvaginal Ultrasound
- For suspected advanced stage:
  - Cystoscopy
  - Sigmoidoscopy
  - CT of abdomen/pelvis, chest
- Labs
  - CBC
  - Chem
  - Liver function tests
  - EKG, CXR
Histopathology

Estrogen dependent
- Adenocarcinoma, the most common, is usually preceded by adenomatous hyperplasia with atypia (80%)

NON Estrogen dependent
- Adenosquamous carcinoma (15%) Tamoxifen use
- Papillary serous adenocarcinoma (3-4%)
- Clear cell
- Undifferentiated
Grading of Endometrial Cancer

- FIGO G1: <5% solid/non glandular areas
- FIGO G2: 6-50% of solid/non-glandular areas
- FIGO G3: >50% of solid/non glandular areas

Spread of the tumor

1. Direct/local spread accounts for most local extension beyond the uterus.
2. Lymphatic spread accounts for spread to pelvic, para-aortic, and, rarely, inguinal lymph nodes.
3. Hematologic spread to the lungs, liver, bone, and brain
4. Peritoneal/transtubal spread results in intraperitoneal implants, with papillary serous carcinoma, similar to ovarian cancer.
Staging of Endometrial Cancer

I: Confined to uterine corpus
   0: atypical adenomatous hyperplasia
   IA: Limited to the endometrium
   IB: invades < ½ of myometrium
   IC: invades > ½ of myometrium
II: invades cervix, not beyond uterus
   II-A: endocervical glandular involvement only
   II-B: cervical stromal invasion
III: local and/or regional spread
   III-A: invades serosa/adnexa
   III-B: vaginal or parametrial involvement
   III-C: metastasis to pelvic or para-aortic LN
VI: Spread outside the pelvis
   IVA: invades bladder/bowel mucosa
   IVB: distant metastasis

Treatment of Endometrial Carcinoma

- Based on tumour grade and depth of myometrial invasion
- **Primary Surgical**: TAH/BSO and pelvic washings ± pelvic and periaortic node dissection general trend (controversial)
- **Stage I**: TAH/BSO and washings
- **Stages II and III**: TAH/BSO and washings and LN dissection
- **Stage VI**: NO surgical option
  - **Adjuvant radiotherapy**: based on depth of myometrial invasion, tumour grade, and/or lymph node involvement
  - **Hormonal therapy**: progestins for distant or recurrent disease
  - **Adjuvant chemotherapy**: Cisplatin, if disease progresses
VI- UTERINE SARCOMA

- Rare - 2-6% of all uterine malignancies
- Arise from stromal components (endometrial stroma, mesenchymal or myometrial tissues)
- Greater tendency to disseminate hematogenously
- 5-year survival - 35%

LEIOMYOSARCOMA

- May be associated with leiomyoma with rapid growth+bleeding
- Average age of is 55 years
- Histologic distinction (from leiomyoma)
  - **Dx:** mitotic count (~10 mitosis/10 HPF)
  - tumour necrosis
  - cellular atypia
- Most are diagnosed postoperatively after uterus removed for fibroids
Clinical Features & TREATMENT

- Rapidly enlarging fibroid in a post-menopausal woman
- **Treatment**
- TAH/BSO
- NO adjuvant therapy given if disease confined to uterus and low malignant potential (mitotic index is low)
- Radiation if high mitotic index
- Chemotherapy (-25% response rate) if tumour spread beyond uterus

ENDOMETRIAL STROMAL SARCOMA

- Presents mainly in perimenopausal women (45-50 years) as abnormal uterine bleeding
- Diagnosed by histology of endometrial biopsy or D&C
- **Treatment**
- TAH/BSO, ALWAYS remove ovaries
- Hormonal therapy (progestins) in low grade sarcoma ONLY
MIXED MULLERIAN SARCOMA

- 40% of all uterine sarcomas, poorest overall survival (like high grade leiomyosarcomas)

Clinical Presentation

- post-menopausal bleeding 90% of cases • lesions are soft to palpation
- 1/3 have polypoid tumour protruding through CX.
- Treatment is the same as leiomyosarcoma, radiation often used