Female Genital Tract: Ovary
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Depart. Pathology

Ovary
- Ovarian ca accounts for 3% of all ca’s.
- Fifth MCC of death due to ca in women.
- Most are detected b/c of ascitis when the tumor has already spread beyond the ovary (peritoneal spread).
- Pseudomyxoma peritonei: extensive mucinous ascitis, cystic epithelial implants peritoneal surfaces/adhesions.
  - Can cause death due to GI obstruction
  - Once thought to originate from ovary, NOW we think of appendiceal primary.

Pseudomyxoma peritonei
- Massive overgrowth gelatinous metastatic tumor originating ovary/appendix.

3 main histologic compartments:
1. Surface mullerian epithelium
2. Germ cells
3. Sex cord-stromal cells

Embryology of female lower genital tract

Hypothalamus

Anterior Pituitary

Ovaries

LH
FSH
Estrodiol
Progesterone

Gonadotropins

Luteinizing Hormone

Follicle-stimulating Hormone

Negative feedback

Positive feedback

Stimulatory

Inhibitory

Stimulatory/Inhibitory

Pituitary

Hypothalamus
Nonneoplastic cysts

• Cystic follicle cyst:
  – Originate unruptured graafian follicles or in follicles that have ruptured and immediately sealed.
  – Multiple; considered normal

Follicle cyst

Nonneoplastic cysts

• Granulosa luteal cysts (corpora lutea)
  – Normally present
  – Grossly lined by rim bright yellow tissue containing luteinized granulosa cells.
  – Sometimes hemorrhagic/fibrosis; differential from endometriotic cysts.

Corpus luteal cyst

Polycystic ovary
Sloan-Leventhal syndrome
Anovulatory hyperandrogenism

• Ovaries are 2X nml size
• Gray-white outer cortex w/subcortical cysts
• Microscopically, hyperplasia of theca interna (follicular hyperthecosis).

• Affects 3-6% reproductive-age women
• Numerous cystic follicles
• Persistent anovulation, obesity (40%), hirsutism (50%), and rarely virilism
Classification ovarian tumors

- Surface epithelium (derived from coelomic epithelium)
- Germ cells (which migrate from yolk sac to ovary)
- Stroma (including sex cords)
- Metastatic

Surface epithelial tumors: 3 histologic subtypes

- Serous
  - Benign
  - Borderline
  - malignant
- Mucinous
  - Benign
  - Borderline
  - malignant
- Endometroid

Two different types based on pathogenesis:
1. Those that arise in association with borderline tumors
2. Those that arise as "de novo" carcinomas.
Ovarian serous cystadenoma

- Serous MC, lined by tall, columnar, ciliated and nonciliated epithelial cells.
- Account for 40% of all ovarian ca.
- Risk factors: nulliparity, family history, and heritable mutations (BRCA1, BRCA2); reduced tubal ligation and oral contraceptives.
- Estimated risk in BRCA1,2 is 20-60% by the ripe old age of 70.
- Some people have classified in low-grade/high grade:
  - low gd: KRAS, BRAF
  - high gd: p53
- Recent studies: BRCA1,2 arise from fimbriated ends of fallopian tubes.

Serous tumor of low malignant potential

- Cyst cavity lined by delicate papillary tumor growths.
- Bilateral tumors common (30%).
- Borderline tumors show increased architectural complexity and epithelial cell stratification.

Serous cystadenocarcinoma

- Invasion underlying stroma.
- Bilateral tumors 66%.
- Borderline/malignant involve (originate from) surface ovary.

Serous adenocarcinoma with psammoma bodies

- Multiloculated tumors with mucin, tall columnar epithelium w/apical mucin and absence of cilia.

Mucinous cystadenoma

- Less common than serous tumors, 30% of all ovarian tumors in middle adult life.
- Only 15% of these are malignant.
- Risk factors: smoking (not for serous).
- Consistent KRAS proto-oncogene mutation (found in 85% of malignant tumors).
- Rarity of surface involvement.
- Less frequently bilateral.
- They can be HUGE!!
- Multiloculated tumors with mucin, tall columnar epithelium w/apical mucin and absence of cilia.

Ovarian mucinous cystadenoma

- Multiloculated appearance, delicate septa, mucin within cysts.
Mullerian mucinous cystadenoma

- Benign/borderline tumor arising from endometriosis.
- Looks like endometrial or cervical epithelium.

Ovarian mucinous cystadenocarcinoma

- Areas of solid growth grossly
- Similar morphology to cervical or intestinal epithelium.
- Abundant glandlike or papillary growth with nuclear atypia and stratification, necrosis.(Looks like colon ca)

Endometrioid tumors (cystadenoma/borderline)

- 40% are bilateral.
- Low grade tumors glandular patterns
- 5-year survival for stage 1 is 75%

- Benign endometrioid tumors are called endometrioid adenofibromas.
- Account for 20% of all ovarian ca's.
- Characterized by tubular glands looking like endometrium.
- Can arise from endometriosis, 15-30% (usually borderline)
- Interestingly 15-30% can be accompanied by endometrial ca
- Mutations PTEN tumor suppressor gene and in p53, KRAS, B-catenin oncogenes, as well as microsatellite instability.

Brenner tumor

- Classified as adenofibromas in which the epithelial component consists
- of nests of transitional-type epithelial cells.
- Stroma composed of plump fibroblasts.
- Usually unilateral.
- Range from 1-30 cm in size, can be b9, borderline or malignant.

Germ cell tumors constitute 15-20% of all ovarian tumors, most are benign cystic teratomas.

Teratomas divided in 3 categories:
1. Immature (malignant)
2. Mature (benign)
3. Monodermal or highly specialized

Benign (mature) cystic teratoma

- Most are cystic, also called dermoid cysts.
- Young women.
- Can be incidental or cause paraneoplastic syndrome
- Bilateral 10-15% of cases
- Characteristically unilocular, contains hair, sebaceous material, sometimes teeth, thyroid, cartilage, and neural tissue.
- About 1% can undergo malignant transformation (MC SCC).
**Malignant (immature) teratoma**

- Specialized teratoma includes struma ovarii and carcinosid.
- Can cause hyperthyroidism, and 5-hydroxytryptamine

**Struma ovarii**

- Precocious girls, young women
- Tumors are bulky, solid, varia necrosis and hemorrhage.
- These should have a histologic grade, based on
- Immature neuroepithelium.
- Grow rapidly, stage 3 gets chemo
- Most recurrences occur within 2 yrs (so if you disease free for this time it carries a excellent cure rate)

**Germ cell tumors**

**Yolk sac (endodermal sinus) tumor**

- Rare: children or young women
- Grow rapidly/accelerative
- Derived from malignant germ cells along extra-embryonic yolk sac lineage.
- Schiller-Duval body: glomerulus-like structure composed of central blood vessel enveloped by germ cells within a space lined by germ cells. 
- α-fetoprotein & alpha-antitripsin
- Before chemo, used to be fatal with 2 years. likes

**Germ cell tumors**

**Choriocarcinoma**

- Most coexist with other germ cell tumors
- Ovarian primaries aggressive; met through bloodstream to lungs, liver, bone.
- Syncytiotrophoblasts
- Cytotrophoblasts
- High levels β-hCG (establish dx or detecting recurrences)
- Unresponsive to chemo and often fatal

**Ovarian sex cord-stromal tumors**

**Granulosa cell tumor**

- 5% of all ovarian tumors
- 2/3 postmenopausal women but any age
- Estrogen (precocious sexual development)
- Call–Exner bodies: gland-like structure filled with acidophilic material recall immature follicles
- Composed entirely granulosa or granulosa/theca cells.

**Fibroma-thecoma**

- Composed of fibroblasts (fibromas) or plump spindle cells w/ lipid droplets (thecoma)
- Meigs syndrome: Ovarian tumor, hydrothorax and ascites
- Unilateral 90%, solid, spherical, or slightly lobulated, encapsulated gray white mass
- Genesis unknown
- Association w/ basal cell nevus syndrome
- If malignant (high mitosis) we call it fibrosarcoma
Ovarian sex cord-stromal tumors

- Sertoli-Leydig cell tumor

- Androgenic: atrophy breasts, amenorrhea, loss of hair, hirsutism.
- Occur in women all ages, more so 2-3rd decade
- Unilateral
- Cut surface gray to golden brown
- Tubules composed of Sertoli cells or Leydig cells interspersed with stroma.
- Poorly differentiated tumors can have sarcomatous pattern
- Recurrence <5%

Krukenberg tumor

- Classic example of metastatic GI signet ring ca to bilateral ovaries, usually stomach

Clinical course, detection and prevention

- Lower abdominal pain, enlargement, GI complaints, urinary frequency, dysuria, pelvic pressure.
- Massive ascitis, w/ cachexia (malignant tumors seed the peritoneum)
- Usually go undiagnosed until they are large, and no longer confined to the ovary.
- Early diagnosis, prevention are top priorities
  - CA125 80% serum; useful for monitor disease
  - Can give false elevations with peritoneal irritation
  - Osteopontin newer, can be used in detection.
- Mets can involve liver, lungs, and GI tract.
- Pts with BRCA mutations standard to perform prophylactic salpingooophorectomy.