King Saud University
College of Medicine
Second year – Reproductive Block

Ovarian Cysts and Tumors

Lecture 2

430 Pathology Team

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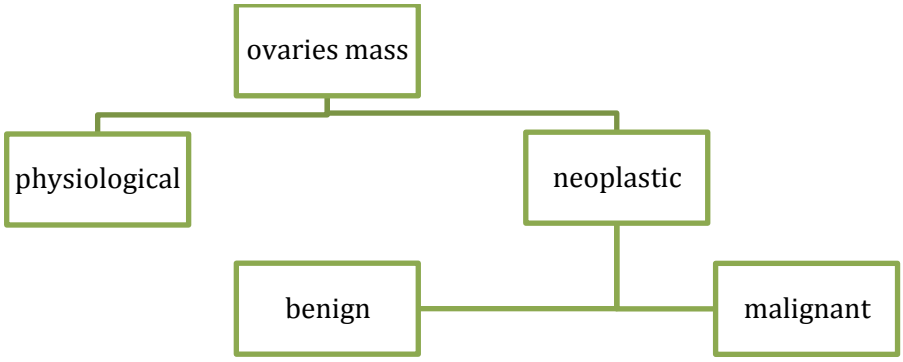
Red: Doctors' and important notes.
Green: Team notes.

Ovaries:



- The most important medical problems in ovaries are the neoplasms.
- Death from ovarian cancers is more than that of cervix and uterus together
- Silent growth of ovarian tumors is the rule which make them so dangerous (because the patient will not complain of anything till late stages)

Cysts and Tumors:

- Non neoplastic cysts are common but they are not serious problems
- Primary inflammation of ovaries is rare (the ovaries are one of the organs that highly resist inflammation to protect the ovum from being destructed by the inflammatory cells)
- Salpingitis of fallopian tubes frequently causes periovarian reaction (Salpingo-Oophoritis) (when we have inflammation in the fallopian tube it causes reactive changes in the ovaries)
- Frequently, the ovaries affected by endometriosis (endometriosis is an endometrial tissue seen outside the uterus corpus and the ovary is most common site of this condition).

Non-Neoplastic and Functional Cysts of ovary:

- Non Neoplastic Cysts are more common than the neoplastic ones
- Follicular and Luteal cysts are most probably physiologic cysts = functional

1. **Follicular cysts**:

- Are thin walled fluid filled structures lined internally by granulosa cells and externally by theca interna cells.
- They arise from the ovarian follicles and are due to distension of unruptured graafian follicle.
- They occur at any age.
- Most of the time the size is less than 2-3 cm and rarely exceeds 5cm in diameter. If they rupture they can cause abdominal pain.

2. Corpus luteum cyst:

- A corpus luteum cyst results from delayed resolution of a corpus luteum's central cavity and from hemorrhage into this persistent mature corpus luteum.
- Rupture of the cyst can cause mild hemorrhage into the abdominal cavity.
- This condition is self-limited.

Chocolate cyst also known as Endometriotic cyst: it is a blood containing cyst resulting from endometriosis with hemorrhage.

Ovarian Tumors:

- Fifth most common cancer in the USA.
- Fifth leading cause of cancer death in women
- 80% are benign when it occurs in young age group (20-45)
- 20% are Malignant when it occurs in older age group (>40)
- 6% of all cancers in women.
- Because ovaries are internal organs unfortunately ovarian cancers go undetected in the early stage when it is still curable causing 50% deaths.
- Most of the patients already have metastasis at the time of diagnosis (because the symptoms appear in late stage of the disease).
- Because the three major cell types (surface epithelium, stroma (sex cord), germ cells) make up the normal ovary, there are more than 25 types of ovarian tumors each with many variants.

Risk factors:

- Null parity
- Gonadal Dysgenesis
- Family History
- Ovarian cancer genes
- BRCA1 (17q12) & BRCA2(13q12) (Cancer suppressor, it is absent in breast & ovary tumors)

Classification:

There are THREE main types of primary ovarian tumors:

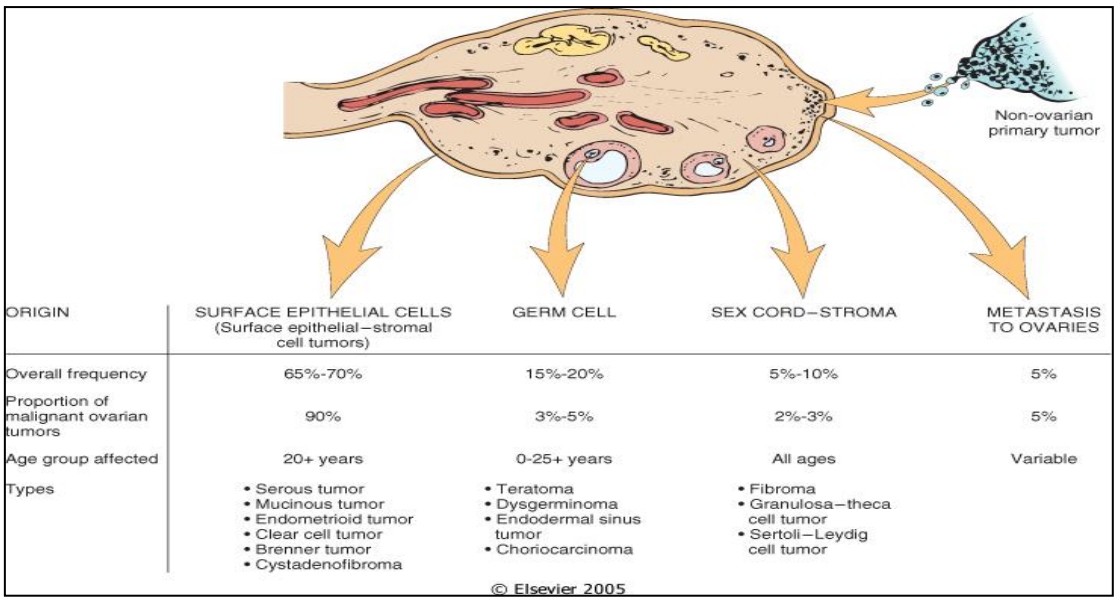
1. Epithelial Surface Tumor: are derived from the cells on the surface of the ovary. This is the most common form of ovarian cancer and occurs primarily in adults. 80%

2. Germ Cell Tumor: ovarian tumors are derived from the egg producing cells within the body of the ovary. This occurs primarily in children and teens and is rare by comparison to epithelial ovarian tumors. 10-15%

3. Sex Cord Tumor: ovarian tumors are also rare in comparison to epithelial tumors and this class of tumors often produces steroid hormones. 10%

In addition cancers derived from other organs can also spread to the ovaries Secondary /Metastatic Tumors.

N.B: the tumors arising from the ovaries are the hardest to classify as well as the lymphomas because of the cells constitute those two organs.



ORIGIN	SURFACE EPITHELIAL CELLS (Surface epithelial–stromal cell tumors)	GERM CELL	SEX CORD–STROMA	METASTASIS TO OVARIES
Overall frequency	65%-70%	15%-20%	5%-10%	5%
Proportion of malignant ovarian tumors	90%	3%-5%	2%-3%	5%
Age group affected	20+ years	0-25+ years	All ages	Variable
Types	• Serous tumor • Mucinous tumor • Endometrioid tumor • Clear cell tumor • Brenner tumor • Cystadenofibroma	• Teratoma • Dysgerminoma • Endodermal sinus tumor • Choriocarcinoma	• Fibroma • Granulosa–theca cell tumor • Sertoli–Leydig cell tumor	

✧ Ovarian Surface Epithelium Tumors:

Incidence:

- Neoplasms of surface epithelium account for the great majority of all primary ovarian tumors either benign or malignant.
- 65 – 70 % of overall tumors
- 90 % of malignant tumors of ovary
- Occurs at the age of 20+

Traditionally divided into:

1. Benign
2. Malignant
3. Borderline/ intermediate, or the borderline tumors are referred as tumors of low malignant potential (LMP) (this class is hardly seen outside the ovary and it is in-between the benign stage and the malignant)

- Benign Tumors: Very rarely life-threatening. Benign tumors can usually be removed and only infrequently grow back.
- Malignant Tumors: will spread beyond the ovary, invading and damaging other organs of the body.
- Borderline/ LMP Tumors: are borderline forms of cancer that may eventually spread and invade other tissues. This is a gray zone. Most of these tumors are benign but a few spread and progress. These appear to be low grade cancers with limited invasive potential. They have better prognosis than malignant. Between the clearly benign and the solid malignant tumors. LMP tumors may seed the peritoneum, the implants of tumors are non invasive. Sometimes may behave as invasive peritoneal implants

Classification:

According to the different cell types in surface epithelium:

1. Serous Tumors (tubal = ciliated columnar) : Benign ,Borderline and malignant
2. Mucinous Tumors (endocx & intestinal = tall columnar with apex filled with mucinoid secretion): Benign ,Borderline , and malignant
3. Endometrioid Tumors : Benign, Borderline, and malignant
4. Clear cell Tumors: Benign, Borderline, and malignant
5. Transitional/ Brenner cell Tumors: Benign, Borderline, malignant and transitional cell carcinoma.
6. Undifferentiated Carcinoma is malignant only

According to Morphology:

a. Cystic – eg: Cystadenomas
b. Solid/cystic –eg: Cystadenofibromas
c. Solid – eg: adenofibromas (high tendency to progress to malignancy)

1. Serous Tumors:

- They are most frequent ovarian tumors.
- Serous ovarian neoplasms are the most common group of epithelial tumors.
- Ovarian surface involvement may be present.

- Age group is 30 -40
- Frequently bilateral (30-66%). The more malignant the lesion, the more likely it is to be bilateral.
- Most of the time the content is solid and usually cystic filled with a clear serous fluid but sometimes may be mucoid.
- The tumors are subdivided into: benign (60%), borderline (15%) and malignant (25%).
- **Benign**: serous cystadenomas:
- **Gross:** are frequently large, entirely cystic and thin-walled, and commonly unilocular (single cavity)
- **Microscopic:** fine papillae, single layer covering (no stratification), no nuclear atypia, no stromal invasion. They are lined by smooth epithelial surface and contain thin, clear yellow fluid.
- **Borderline**:
- **Gross**: cystic with solid foci.
- **Microscopic**: multiple papillary complexity (grape-like clusters), protruding into the lumen stratification, nuclear atypia, no stromal invasion. Thin wall and smooth surface.
- **Malignant:** (serous cystadenocarcinoma) is the commonest malignant ovarian tumor, forming about a third of all cancers of the ovary.
- **Gross:**, solid, hemorrhage, necrosis or adhesions.
- **Microscopic:** papillary complexity, stratification, nuclear atypia, stromal invasion
- The tumors are partly cystic and partly solid with exuberant excrescences, often with necrosis and hemorrhage.

In short, the difference between benign and malignant is the stromal invasion. While the difference between the benign and borderline is that in the benign there is neither atypia nor stratification.

- These tumors usually present with ascietes due to abdominal metastases.
- **Prognosis:** is bad when extension to peritoneum occur.

2. Mucinous Tumors:

- Mucinous tumors form about 25% of all ovarian neoplasms.
- 80% of them benign, 10% LMP, 10% (rarely) malignant
- Rarely bilateral with about 5% in benign, 10% borderline and 20% of malignant carcinomas.
- Mucinous tumors can be very large 20- 40 cm.
- They are typically cystic and multilocular and filled with thick sticky, viscous, less often, thin and watery fluid.
- Epithelium is consists of mucin-producing cells (tall columnar with apical mucin)

3. Endometrioid Tumors:

- The designation endometrioid means "endometrium-like". cells look like endometrium even though they are coming from the ovary.
- Endometrioid tumors form 5% of all ovarian tumors.
- Most are unilateral (40% are bilateral)
- Unlike the serous and mucinous tumors most of the neoplasms are malignant.
- About 20% of all ovarian carcinoma .
- Many are associated with endometrial cancer of the uterus (30%)
- Patient may have concurrent endometriosis

✧ Sex Cord-Stromal tumors:

- Granulosa Cell tumor
- Thecoma –Fibroma
- Sertoli-Leydig cell tumor
- Gynandroblastoma
- Unclassified

N.B: Incidence of these tumors is low but they are very important because these tumors are functional (they secrete hormones) e.g: granulose cell tumor secrets estrogen while Sertoli-Leydig cell tumor secrets androgen that lead to certain clinical pictures depending on the secretion.

1. Granulosa Cell Tumor:

- 1-2% of ovarian tumors
- Unilateral, solid and cystic
- Tiny to large in size
- The most common **estrogenic ovarian neoplasm.**
- Produce estrogen → endometrial hyperplasia and carcinoma
- 2 forms: adult and juvenile. Adult form typically occurs at any age after puberty but is more common in postmenopausal women associated with endometrial hyperplasia and carcinoma. The juvenile form occurs in the first three decades, can present with isosexual precocity (early sexual development)
- can present with abnormal vaginal bleeding
- Have malignant behavior in 5-25% of cases and recurrences can be late

  Microscopically:

  It is composed of sheets of granulosa cells containing spaces lined by the cells to give a follicle-like appearance (Call-Exner bodies).

2. Thecoma-Fibroma:

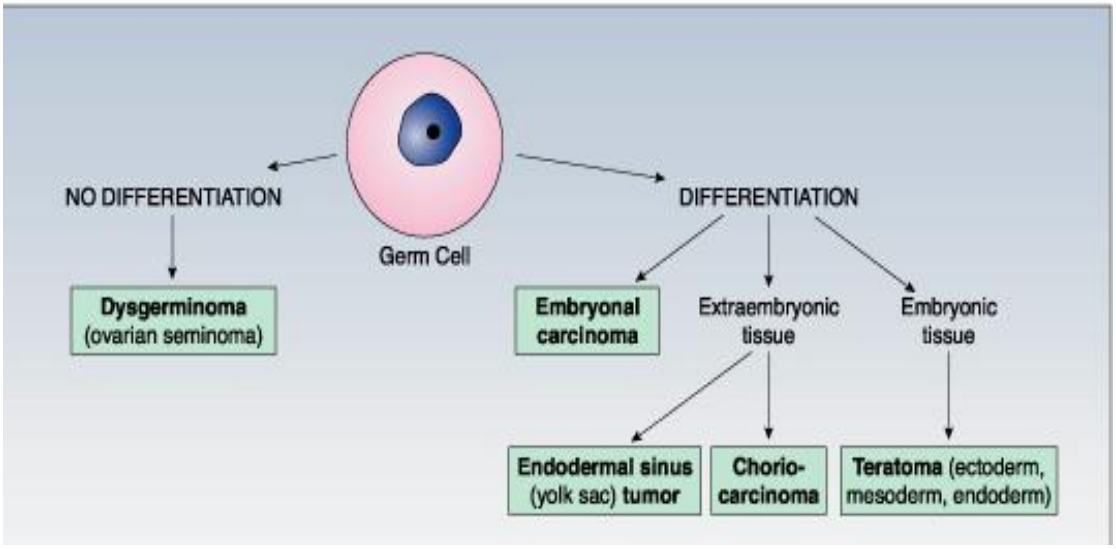
- Fibrothecomas are a mixture of fibromas and thecomas.
- Occur at any age but usually occur in middle-aged perimenopausal women.
- Unilateral
- Most of the time it is benign rarely malignant
- Pure theca cell tumors also occur. They are functional tumors producing estrogen.
- **Grossly:** thecomas vary in size from small to large, Well demarcated solid tumors, whorled cut surface, and vary in color from yellow to orange or gray depending on the amount of lipid content.
- **Microscopically:** sheets of round to oval cells with pale cytoplasm containing lipid and are frequently extensively calcified
- **Fibroma:** This solid tumor consists of bundles of spindle-shaped fibroblasts.
- **Thecoma:** This tumor demonstrates round lipid-containing cells in addition to fibroblasts and it is occasionally estrogen-secreting.
- Fibromas are the commonest ovarian stromal tumors.
- Pure forms are nonfunctioning but others containing theca cells and called fibrothecomas may be estrogenic.

3. Sertoli – Leydig:

- Accounts for less than 0.5% of ovarian tumors
- All ages but most often in young women
- Unilateral Gray to yellow solid and cystic, or even papillary
- Produce androgens and present with virilization in 1/3 of cases (oligomenorrhea, amenorrhea, loss of female secondary sex characteristics with hirsutism, clitoromegaly, deepening of voice)
- Uncommonly malignant
- behavior correlates with degree of differentiation and stage
- **Microscopically:** tubules lined by Sertoli cells and sheet of Leydig cells

✧ Germ Cell Tumors (almost same as those of the testis)

1. **If NO differentiation of germ cells occur** :
   -Dysgerminoma (seminoma in testis)
2. **If the differentiation of germ cells occur**
   -Yolk Sac Tumor
   -Embryonal Carcinoma
   -Choriocarcinoma
   -Teratoma : Mature, Immature
   -Polyembryoma



1. Dysgerminoma:

- 3-5% of ovarian malignant tumors (no benign forms)
- most common malignant ovarian germ cell tumor
- occurs in 2nd and 3rd decades of life. It is the most frequently encountered ovarian malignancy in pregnancy
- typically a unilateral, solid, firm to fleshy
- Counterpart to Seminoma(testis) and germinoma (brain)
- **Marker:** PLAP (placental alkaline phosphates) positive
- **Microscopically:** composed of malignant germ cells, similar to primordial germ cells, admixed with nonneoplastic chronic inflammatory cells and occasionally granulomatous inflammation with some lymphocytes in between.
- **Prognosis:** excellent and the malignant is highly sensitive to radiation and/or chemo therapy

2. *Embryonal carcinoma:*

- uncommon ovarian germ cell neoplasm
- usually occurs in combination with yolk sac tumor
- 2nd and 3rd decade occurs in children and young adults
- Typically unilateral, solid tumor with hemorrhage and necrosis
- **Marker:** CD 30 positive.
  CD30: also known as **TNFRSF8**, is a cell membrane protein of the tumor necrosis factor receptor family and tumor marker.
- Aggressive, highly malignant neoplasm that is radio resistant but responds to combination chemotherapy

3. *Teratoma:*

- 15-20 % of ovarian tumors. Majority of cases are in the first 2 decades of life.
- The younger the patient ,the greater the likelihood of malignancy
- The tumors are subdivided into benign mature (majority), malignant immature (rare) and monodermal.
- Unlike those in the testis, the vast majority of ovarian germ cell tumors are benign mature cystic teratomas.

(A) Mature (dermoid) cystic teratoma:

- most common ovarian teratoma and most common benign ovarian germ cell tumor
- benign neoplasm that typically occurs during reproductive years
- cystic tumor with firm capsule, filled with sebaceous material and hair (occasionally teeth can be found),), thickened area from which hair and teeth arise is called "Rokitansky's protuberance"
- composed of mature elements derived from all three germ layers (ectodermal elements such as skin, hair, sebaceous glands, and mature neural tissue predominate; cartilage, bone, respiratory and intestinal epithelium are common). Calcification can also be seen radiologically.
- Complications include torsion, rupture, infection etc.

(B) Monodermal teratoma:

- Composed predominantly of one tissue element
- Most common type is "struma ovarii", which is mature thyroid tissue

(C) Immature teratoma (malignant neoplasm) :

- occurs in children and young adults
- usually a unilateral, solid tumor
- similar to mature teratoma but contains immature or embryonal tissues
- immature elements are almost always immature neuroepithelium
- graded on the basis of the quantity of immature tissue

4. *Endodermal Sinus (Yolk Sac) Tumor:*

- Second most common malignant ovarian germ cell tumor
- Always malignant
- Occurs in childhood, adolescence, and adult life (most <30 years)
- Can be pure or a component of a mixed germ cell tumor
- Almost always a unilateral solid or solid cystic
- Highly malignant and clinically aggressive neoplasm that is radio resistant but responds to combination chemotherapy

- **Marker:** associated with elevated serum α-fetoprotein (AFP) levels
- Classic pattern shows perivascular formations (Schiller-Duval bodies) and eosinophilic globules that contain AFP
- Stained for α-fetoprotein by immunoperoxidase techniques
- Children or young women presenting with abdominal pain and a rapidly developing pelvic mass.
- **Prognosis:** fatal within 2 years of diagnosis

5. Choriocarcinoma:

- Rare
- Occurs as a pure ovarian neoplasm or as a component of a mixed germ cell tumor
- Occurs in children and young adults
- **Marker:** associated with elevated serum β-HCG (human chorionic gonadotropin) levels
- Typically a unilateral, solid, hemorrhagic tumor
- **Histologically** composed of malignant cytotrophoblast and syncytiotrophoblast
- Metastasizes widely through the bloodstream to the lungs, liver, bone, and other viscera .
- High levels of chorionic gonadotropins that are sometimes helpful in establishing the diagnosis or detecting recurrences.
- Highly malignant neoplasm that responds to combination chemotherapy

✧ Metastatic Carcinoma:

- Metastatic neoplasms involving the ovaries constitute an important group of neoplasms because the therapy for primary ovarian neoplasms is often different from that used for metastatic tumors derived from other organs.
- Accounts for approximately 5% of ovarian tumors
- Older ages, Mostly Bilateral
- Primaries are Breast (in females), lung (in males), G.I.T. and hematopoietic system (in both).
- Features suggesting the metastatic nature of an ovarian neoplasm include bilaterality, presence of multiple nodules of tumor, involvement of the surface and superficial cortex of the ovary, smaller tumor size.

***Krukenberg tumor**:*

One of the most classic forms of metastatic carcinoma involving the ovaries This tumor is composed of signet ring cells embedded within a hypercellular ovarian stroma that mimics sarcoma, and the most common sites of origin include stomach, colon and appendix.

Summary

- Non neoplastic cysts are more common than the neoplastic ones
- **Follicular cysts:** are due to distension of unruptured graafian follicle
- **Corpus luteum cysts:** results from delayed resolution of a corpus luteum's central cavity.
- **Chocolate/ Endometriotic cyst:** is a blood containing cyst resulting from endometriosis with hemorrhage.
- **Ovarian Tumors:** there are THREE main types of primary ovarian tumors: 1. epithelial surface tumor (most common, primarily in adults 80%) 2. germ cell tumor (primarily in children and teens and is rare 10-15%) 3. sex cord tumor (rare, produces steroid hormones 10%) 4. metastatic tumors such as Krukenberg tumor.
- **Surface epithelial tumor** is divided into: Serous tumors, mucinous tumors (endocx & intestinal), endometrioid, clear cell tumors, transitional/ Brenner cell tumors and undifferentiated carcinoma.
- **Serous epithelium:** most frequent ovarian tumors with bad prognosis. Microscopically: it is tubal (ciliated columnar). These tumors usually present with ascietes due to abdominal metastases.
- **Mucinous tumors:** most of them are benign (80%). Epithelium is consists of mucin-producing cells (tall columnar with apical mucin)
- **Endometrioid Tumors:** most are malignant and unilateral. Many are associated with endometrial cancer of the uterus (30%)
- **Sex Cord-Stromal tumors:** rare functional tumors that are classified into: granulosa cell tumor, thecoma –Fibroma, sertoli-Leydig cell tumor, gynandroblastoma and unclassified.
- **Granulosa Cell Tumor:** most common estrogenic ovarian neoplasm that causes endometrial hyperplasia and carcinoma. It has 2 forms: adult and juvenile. Can present with abnormal vaginal bleeding. Microscopically: presence of Call-Exner bodies.
- **Thecoma-Fibroma:** most of the time it is benign. Well demarcated solid gray to yellow.
- **Sertoli – Leydig tumor:** it is a tumor producing androgens and present with virilization.
- **Germ Cell Tumors** classified into: dysgerminoma, yolk Sac Tumor, embryonal Carcinoma, choriocarcinoma, teratoma, polyembryoma
- **Dysgerminoma:** most common malignant ovarian germ cell tumor. It is the most frequently encountered ovarian malignancy in pregnancy. Counterpart to seminoma (testis) and germinoma (brain). Marker is PLAP positive. Microscopically: composed of malignant germ cells admixed with nonneoplastic chronic inflammatory cells and occasionally granulomatous inflammation with some lymphocytes in between.
- **Embryonal carcinoma:** occurs in combination with yolk sac tumor. Solid tumor with hemorrhage and necrosis. Marker: CD 30 positive.
- **Teratoma:** the tumors are subdivided into mature (majority), malignant immature (rare) and monodermal.
- **Mature (dermoid) cystic teratoma**: most common benign ovarian germ cell tumor, characterized microscopically by the presence of "Rokitansky's protuberance"
- **Monodermal teratoma**: most common type is "struma ovarii", which is mature thyroid tissue
- **Immature teratoma**: occurs in children and young adults. graded on the basis of the quantity of immature tissue
- **Endodermal Sinus (Yolk Sac) Tumor:** 2nd most common malignant ovarian germ cell tumor.. **Marker:** associated with elevated (AFP) levels. Microscopically: Schiller-Duval bodies
- **Choriocarcinoma:** rare. Marker: elevated serum β-HCG levels. Histologically composed of malignant cytotrophoblast and syncytiotrophoblast.
- **Metastatic Carcinoma:** Primaries are in breast (in females), lung (in males), G.I.T. and hematopoietic system (in both).e.g: Krukenberg tumor: composed of signet ring cells.

Questions

1. **A 26-year-old woman experiences the sudden onset of left-sided lower abdominal pain with radiation to the back, pelvis, and thigh. Following a negative test for pregnancy, abdominal radiography shows an enlarged left ovary with multiple calcifications. Laparoscopy reveals adnexal torsion and an ovarian tumor. Ovariectomy is performed. The tumor is most likely a**
   (A) granulosa cell tumor.
   (B) Brenner tumor.
   (C) Serous cystadenoma.
   (D) Struma ovarii.
   (E) Dermoid cyst.

   Answer: (E) the radiographic calcification are highly suggestive of a mature teratoma (dermoid cyst)

2. **A 5-year-old girl begins developing secondary sexual characteristics, including pubic hair growth and breast development. Her concerned parents bring her to the pediatrician for evaluation. An abdominal ultrasound examination reveals an ovarian mass. The mass is resected, and pathologic examination reveals it to be a granulosa cell tumor. Which of the following histologic findings is a characteristic of this type of ovarian tumor?**
   (A) Signet-ring cells
   (B) Call-Exner bodies
   (C) Schiller-Duval bodies
   (D) Hyperfunctioning thyroid tissue
   (E) Transitional cell epithelium

   Answer: (B) Call-Exner bodies, small follicles filled with eosinophilic secretion, are an important diagnostic feature.

3. **A 48-year-old woman has noted a small amount of irregular vaginal bleeding for the past 2 months. She has a pelvic examination that reveals no cervical lesions, and a Pap smear that shows no abnormal cells. Next, an endometrial biopsy is performed, and there is microscopic evidence for endometrial hyperplasia. An abdominal ultrasound reveals a solid right ovarian mass. Which of the following neoplasms is this woman is most likely to have?**
   (A) Mature cystic teratoma
   (B) Choriocarcinoma
   (C) Sertoli-Leydig cell tumor
   (D) Fibrothecoma
   (E) Krukenberg tumor

   Answer: (D). Fibrothecomas and granulosa cell tumors can be estrogen producing. The excessive estrogen drives endometrial hyperplasia, which can progress to atypical adenomatous hyperplasia, which can progress to carcinoma.

4. **A 50-year-old woman has noted increasing abdominal enlargement for the past year. On physical examination, there is a fluid wave, but no tenderness. Bowel sounds are present. She has no vaginal bleeding. An abdominal ultrasound reveals bilateral 10 and 7 cm adnexal masses. At surgery there are bilateral mass lesions of the ovaries. A total abdominal hysterectomy is performed. Pathologic examination of the ovarian masses reveals that they**

are unilocular, filled with watery fluid, and covered with papillary excrescences on all surfaces. Which of the following neoplasms is this woman most likely to have?

(A) Granulosa-theca cell tumors

(B) Mature cystic teratomas

(C) Fibrosarcoma with metastases

(D) Serous cystadenocarcinomas

(E) Clear cell carcinomas

Answer: (D). this is a classic appearance for ovarian serous cystadenocarcinoma. However, the gross appearance alone is not diagnostic, and a borderline serous tumor must be distinguished microscopically.