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OVARIAN CYSTS & TUMORS



Lecture Two

Objectives:

- The pathology of the major types of ovarian cysts (follicular and luteal).
- The classification and pathology of common ovarian tumors including surface epithelial, germ cell, stromal and metastatic neoplasms.

References: Lecture Slides & Robbins.









Ovarian Cysts:

- Non-neoplastic cysts are common but they are not serious problems.
- Inflammation of ovaries is rare. It is usually associated with salpingitis of fallopian tubes (salpingo-oophoritis)
- Frequently, the ovaries are affected by endometriosis.
- The most important medical problems in ovaries are the neoplasms
- Death from ovarian cancers is more common than that of cervix and uterus together because ovarian tumors grow silently and are usually diagnosed late, which make them so dangerous.



Non-Neoplastic Cysts of ovary:

More common than the neoplastic ones. They usually cause no problems. **Rarely**, a non-neoplastic cyst can rupture and cause acute pain and intraabdominal hemorrhage.

Chocolate cyst /Endometriotic cyst	The ovary is the most frequent site of endometriosis. And chocolate cyst is a blood-filled cyst of the ovary. It is due to endometriosis in the ovary with hemorrhage .	I don't th you abou
Corpus luteum cvst	Results from hemorrhage into a persistent mature corpus luteum.	
These lutein	Are thin welled syste lined by luteinized	
i neca iutein	Are thin walled cysts lined by luteinized	
cyst/	theca cells. They are associated with high	
hyperreactio	levels of circulating gonadotropins (e.g.	
luteinalis	pregnancy, hydatidiform mole, etc).	
Follicular cyst	Arise from the ovarian follicles & are due to distension of un-ruptured Graafian follicle Primordial follicle or graafian follicle that	
	Decomes cystic	

I don't think anyone will ask you about the **last** three



Follicle & luteal cysts:

- Are so commonplace that they may be considered variants of normal physiology.
- Originate from unruptured graafian follicles or from follicles that <u>have ruptured</u> and then become immediately sealed.
- Such cysts often are multiple and develop subjacent to the serosal covering of the ovary.
- Typically, they are small and filled with clear serous fluid → lined by granulosa lining cells or luteal cells, but as fluid accumulates, pressure may cause atrophy of these cells.
- They might become sufficiently large to produce palpable masses and pelvic pain.
- Might rupture, producing intraperitoneal bleeding and peritoneal symptoms (acute abdomen).



Amazingly varied; why? Because of the presence of 3 cell types in the normal ovary; each of which gives rise to different tumors.

Ovarian Tumors:

- One of the leading cause of cancer death in women.
- Ovarian cancers grow **silently** and go undetected in the early stage when it is still curable. Most of the patients already have **metastasis** at the time of **diagnosis**.
- The WHO Histological Classification for ovarian tumors divides ovarian neoplasms into primary and metastatic (secondary).
- Around 5% to 10% of ovarian cancers are familial, and most of these are associated with mutations in BRCA1 and BRCA2 tumor suppressor genes.

Classification:

There are three main nrimary tynes of ovarian tumors hased on the origin of the tumor cell	arian tumors based on the origin of the tumor cell.	Surface epithelial ovarian tumors (65%)	Derived from the cells on the surface of the ovary . This is the most common form of primary ovarian cancer and occurs in adults. Serous tumors: - Benign (cystadenoma) - Borderline tumors (serous borderline tumor) - Malignant (serous adenocarcinoma) Mucinous tumors: - Benign (cystadenoma) -Borderline tumors (mucinous borderline tumor) - Malignant (mucinous adenocarcinoma) Endometrioid tumors: - Benign (cystadenoma) -Borderline tumors (endometrioid borderline tumor) - Malignant (endometrioid adenocarcinoma) Clear cell tumors: transparent - Benign - Borderline tumors - Malignant (clear cell adenocarcinoma) Transitional cell tumors: - Brenner tumor - Brenner tumor of borderline malignancy - Malignant Brenner tumor - Transitional cell carcinoma (non-Brenner type) & Others.
	There are three main primary types of ova	SCS (10%) Germ cell tumors	 Derived from the egg producing cells of the ovary, i.e. from the ovarian follicles. This occurs mainly in children, teens and young women. They are less common as compared to epithelial ovarian tumors. Teratoma: Immature (malignant) Monodermal (e.g., struma ovarii, carcinoid) Mature (benign): Solid or Cystic (dermoid cyst) Dysgerminoma Yolk sac tumor (endodermal sinus tumor) Choriocarcinoma Embryonal carcinoma Mixed germ cell tumors NOTE: all ovarian GCTs are considered as malignant except mature teratoma Sex cord stromal tumors are derived from the ovarian stroma. Uncommon and this class of tumors often produces steroid hormones. Almost always Benign: Fibromas, Fibrothecomas & Thecomas With Malignant Potential: Granulosa cell tumors & Sertoli-Leydig cell tumors Others
4	5%,	met	astatic tumors: Cancers from other organs can also spread to the ovaries

Surface Epithelial Ovarian Tumors:

- Account for majority of all primary ovarian tumors; & Are 65 70 % of overall tumors.
- They also account for 90 % of malignant tumors in the ovary; Age 20+.

Pathology:

- Majority of ovarian neoplasms are derived from the coelomic epithelium that covers the surface of the ovary.
- With repeated ovulation and scarring, surface epithelium becomes entrapped in the cortex of the ovary, forming small epithelial cysts that can become metaplastic or undergo neoplastic transformation.

1	Benign	 Usually are cystic (cystadenoma) and may have an accompanying stromal component (cystadenofibroma). They do not spread and invade other tissues.
/ided int	Malignant	 Are carcinomas and have potential to metastasize beyond the ovary. They can also be cystic (cystadenocarcinoma) or solid (carcinoma)
Subdiv	Borderline; intermediate; tumors of low malignant potential	 This is a gray zone. They are 'semi-malignant'. These appear to be low grade cancers with limited invasive potential. They have better prognosis than malignant. These tumors may seed or implant into the peritoneum.

Serous Tumors:

Morphology

- The **most common type** of ovarian tumors & the most common group of epithelial tumors.
- The tumor cells are of serous nature. Benign lesions are usually encountered in patients between 30 and 40 years of age, and malignant serous tumors are more commonly seen between 45 and 65 years of age.
- Borderline and malignant serous tumors are the most common ovarian malignancies, accounting for about 60% of all ovarian cancers.
 - Usually cystic filled with clear serous fluid
 - Most are large, spherical to ovoid.
 - Serous tumors are **often bilateral**.
 - **Psammoma bodies** are commonly seen.
 - Malignant serous tumors spread to regional lymph nodes, including periaortic lymph nodes; distant lymphatic and hematogenous metastases are infrequent.

¹ The subtypes of the surface epithelial tumors were mentioned above.



Serous Tumors are Subdivided Into:

Туре	Info	Morphology
s.	• Commonly large,	 Morphology: the serosal covering is smooth and
101 %(cystic and thin-	glistening.
un;	walled, and unilocular.	 Histologic examination:
us t us (s)	• They are lined by	• Reveals a single layer of tall columnar
rou ero ma	serous cells and	epithelial cells (often ciliated) that line the
se se	contain thin, clear	cyst or cysts.
ign ide	yellow fluid.	• Psammoma bodies ² in the tips of papillae.
eni	• About 25% of the	• When frank ³ carcinoma develops, anaplasia
C) B	benign tumors are	of the lining cells appears, as does invasion of
1	bilateral	the stroma.
	Cystic with a thin wall	Exhibit less cytologic atypia and little or no stromal
ine s :	and a smooth surface,	invasion. They may seed the peritoneum, but those
erl ou: %]	but often have multiple	implants usually are " noninvasive ."
rd ser un 15	papillary excrescences ⁴	its limited to certain places; eg., it can go to the bladder
Bo 2 t ((grape-like clusters),	or peritoneum but not to the lungs); it's also called
5.	protruding into the	intermediate tumor or low malignant potential (LMP)
	lumen in places.	

* Previous two are associated with KRAS, BRAF, or ERBB2 mutations.

Туре		Info		Morphology
	•	The commonest malignant ovarian tumor,	•	The surface has nodular
		forming about a $1/3$ of all cancers of the		irregularities representing areas
<u>SN</u>		ovary.		in which the tumor has
<u>ro</u> i 6):	•	Partly cystic and partly solid with		penetrated into the serosa.
<u>(59</u>		prominent excrescences, often with	•	On cut section, it may have a
rs (2		necrosis and hemorrhage & usually		single cavity, but larger ones
no Id		present with ascites due to abdominal		frequently are divided by
tun		metastases.		multiple septa into
us cin	•	Treatment: surgery, chemo and		multiloculated masses.
ar		radiotherapy. Prognosis : poor & depends	•	Cystic spaces usually are filled
: Se		on the stage at diagnosis.		with a clear serous fluid.
ant der	•	Some develop from tubal intraepithelial		Histologically:
gne ta		carcinoma.		Papillary formations (which
ali _i cys	•	High-grade serous tumors develop rapidly.		protrude into cystic cavities)
W	•	Most have mutations in <i>TP53</i> ; we can also		are complex and multilayered
З.		see mutations affecting the Notch signaling		 Nests or undifferentiated
		pathway and FOXM1 ⁵ in a minority of		sheets of malignant cells
		tumors.		invade the axial fibrous tissue.

⁵ A transcription factor previously implicated in the pathogenesis of ovarian carcinoma



² Concentrically laminated calcified concretions.
³ Obvious or clinically evident, such as the unequivocal presence of a condition or a disease.

⁴ Solid mass or solid projections

Mucinous Tumors: second most common

- Form about 25% of all ovarian neoplasms. The tumor cells are mucin-producing cells (which are either endocervical type or intestinal type cells).
- Less likely to be malignant than serous tumors.
- 80% are benign, 10% are borderline & **10% malignant**.

Morphology:

- Can be very large, bilaterality is <u>uncommon</u>, typically cystic (multicystic), multilocular⁶ and filled with thick sticky, viscous mucoid fluid.
- Malignant tumors: we see complex structures, including solid areas of growth, cellular stratification, cytologic atypia, serosal penetration and stromal invasion

Endometrioid Tumors: Third most common

- They have **a tubular gland** that **resembles the endometrium** so the name endometrioid (endometrium-like).
- Form 10 to 20% of all ovarian tumors; **Most** are malignant (carcinomas).
- Some are accompanied by an endometrial carcinoma in the uterus and / or endometriosis in the ovaries
- May be solid or cystic & are bilateral in about 30% of cases.
- Mutations in the PTEN tumor suppressor gene can be seen.

Transitional Cell/ Brenner Tumor: Most are benign. in the urinary tract

- Uncommon, solid, unilateral ovarian tumor consisting of transitional cell type epithelium
- Smoothly encapsulated and gray-white on cut section

Sex Cord-Stromal tumors:

Thecoma-Fibroma:

If tumor arises from (theca cells= thecoma – fibrous tissue = fibroma – granulosa cells =granulosa cell tumor) when the tumor arise from both = theco-fibroma)

- Any age; they can be either pure thecomas, pure fibromas or fibrothecomas (mixture of both).
- About 40% cases are associated with ascites and hydrothorax called as Meig's Syndrome.

Morphology:

- Unilateral, almost always **benign**. Very rarely malignant.
- Pure theca cell tumors produce estrogen
- Fibromas **do not produce estrogen** except when mixed with thecomas.
- They are solid tumors, vary in color from white to yellow. Fibromas are whiter, harder with whorled cut surface.

⁶ Having or divided into many small chambers or vesicles



Granulosa Cell Tumor:

2 forms: adult and juvenile:

- ✓ Adult form is more common in **postmenopausal women**.
- ✓ The juvenile form is seen the **first 3 decades**, can present **with isosexual precocity**.

Morphology:

- Unilateral, solid and cystic; Produce estrogen.
- Can present with abnormal vaginal bleeding; & can be associated with endometrial hyperplasia and carcinoma. About 5 to 25% show malignant behavior

Sertoli – Leydig cell tumor:

- Rare tumors of low malignant potential; All ages; Unilateral yellowish solid tumor.
- Produces androgens and present with virilization in 1/3 of cases (oligomenorrhea, amenorrhea, loss of female secondary sex characteristics with hirsutism, clitoromegaly, deepening of voice)

Germ Cell Tumors:

Teratoma: a collection of different kind of tissues that are not normally present in that organ

- Are 15-20 % of ovarian tumors. Majority in the first 2 decades
- The tumors are subdivided into mature, immature and monodermal.
- The younger the patient, the greater the likelihood of malignant behavior.
- Benign mature type is more than the malignant immature one.
- Subdivided into three types.

1. Mature cystic teratoma	 The most common ovarian germ cell tumor and the most common to ovarian teratoma. Found incidentally on abdominal radiographs or scare Benign neoplasm that typically occurs during reproductive years composed of mature elements of the ectoderm, endoderm and messe Complications include torsion (acute surgical emergency), ruptu infection or limbic encephalitis (in women with teratomas containing mature neural tissue), etc. 	
	Cystic tumor, unilateral (mostly right-sided), filled with sebaceous ma (sebaceous secretion) and hair and occasionally teeth. Skin, hair, sebaceous glands, and mature neural tissue predominate; cartila bone, respiratory and intestinal epithelium are common.	
2. Monodermal	 (Also called Specialized Teratomas) A teratoma composed predominantly of one tissue element. Most common type is "struma ovarii*", which is mature thyroid tissue (may cause hyperthyroidism). The thyroid tissue can sometimes become malignant. (papillary thyroid carcinoma) Sometimes a carcinoid tumor can arise from it. * Ovaries that are completely replaced by thyroid tissue it's called struma ovarii. 	

ture	Info	 Malignant rare neoplasms, occurs in children and young adults (mean age is 18). Usually a unilateral, solid, bulky and pedunculated by areas of necrosis tumor Similar to mature teratoma but in addition they contain immature or embryonal tissues especially immature neuroepithelium They are graded based on the amount of immature tissue.
1. Imma	Morphology	On microscopic examination, the distinguishing feature is presence of immature elements or minimally differentiated cartilage, bone, muscle, nerve, or other tissues. Particularly ominous are foci of neuroepithelial differentiation Immature tissues that are seen in the time of embryogenesis (undifferentiated cells) *When I see immature teratoma I have to tell the oncologist because its consider malignant and can spread *the younger the patient the higher the chances of getting immature teratoma.

Info

Germ Cell

Morphology

Tun	iors	
Dysgermin oma	 Uncommon, All malignant Between 10 to 30yrs of age PLAP positive & Highly sensitive to radiation therapy 	 Unilateral and solid mass Microscopically; looks exactly like its counterpart in testis (Seminoma) and brain (germinoma)
Endodermal Sinus Tumor	 Also known as yolk sac tumor Under 30 years of age Can be pure or a component of a mixed germ cell tumor (teratoma, DYSGERMINOMA and ENDODERMAL SINUS TUMOR) Radioresistant but responds to combination chemotherapy 	 Associated with elevated serum αlpha-fetoprotein and αlpha-1-antitrypsin. Positive immunostain for α- fetoprotein Characteristic histologic feature: Schiller-Duval bodies
Embryonal Carcinoma	 Rare, aggressive, highly malignant, 2nd and 3rd decade (children and young adults) & radioresistant but responds to chemotherapy. Similar to its that in testis, usually occurs in combination with other GCTs (mixed GCT). 	 Unilateral, solid tumor with hemorrhage and necrosis CD 30 immunostain positive.
Choriocarcinoma	 it's a tumor of the placenta appears in the ovaries Rare aggressive, highly malignant, metastasizes widely through the bloodstream to the lungs, liver, bone etc Radioresistant AND chemoresistant Similar to its that in testis, usually occurs in combination with other GCTs (mixed GCT) Can present in the ovaries as ovarian tumor 	 Elevated serum hCG levels; HCG immunostain positive unilateral, solid, hemorrhagic tumor, composed of malignant cytotrophoblast and syncytiotrophoblast.



Metastatic carcinoma in ovary:

- Accounts for approximately 5% of ovarian tumors
- Older ages, Mostly Bilateral and sometimes very large
- Primary tumor can be from Gastro-intestinal tract (most common), Breast and lung.
- One of the most classic forms of metastatic carcinoma involving the ovaries is the <u>Krukenberg tumor (producing bilateral ovarian masses)</u>. This tumor is a metastatic carcinoma composed of signet ring cells in a fibrous background. The most common sites of origin is the GIT (stomach, colon and appendix).

Very important picture:

Neoplasm	Peak Incidence	Usual Location	Morphologic Features	Behavior	
Germ Cell Origin					
Dysgerminoma	Second to third decade of life Occur with gonadal dysgenesis	Unilateral in 80–90%	Counterpart of testicular seminoma Solid large to small gray masses Sheets or cords of large clear cells separated by scant fibrous strands Stroma may contain lymphocytes and occasional granulomas	All malignant but only one third aggressive and spread; all radiosensitive; 80% cure rate	
Choriocarcinoma	First 3 decades of life	Unilateral	Identical to placental tumor Often small, hemorrhagic focus with two types of epithelium: cytotrophoblast and syncytiotrophoblast	Metastasizes early and widely. Primary focus may degenerate, leaving only metastases In contrast with gestational tumors, ovarian primaries are resistant to chemotherapy	
Sex Cord Tumors					
Granulosa-theca cell	Most postmenopausal, but may occur at any age	Unilateral	May be tiny or large, gray to yellow (with cystic spaces) Composed of mixture of cuboidal granulosa cells in cords, sheets, or strands and spindled or plump lipid-laden theca cells Granulosa elements may recapitulate ovarian follicle as Call-Exner bodies	May elaborate large amounts of estrogen (from thecal elements) and so may promote endometrial or breast carcinoma Granulosa element may be malignant (5% to 25%)	
Thecoma-fibroma	Any age	Unilateral	Solid gray fibrous cells to yellow (lipid-laden) plump thecal cells	Most hormonally inactive A few elaborate estrogens About 40%, for obscure reasons, produce ascites and hydrothorax (Meigs syndrome) Rarely malignant	
Sertoli-Leydig cell	All ages	Unilateral	Usually small, gray to yellow- brown, and solid Recapitulates development of testis with tubules or cords and plump pink Sertoli cells	Many masculinizing or defeminizing Rarely malignant	
Metastases to Ovary					
	Older ages	Mostly bilateral	Usually solid gray-white masses as large as 20 cm in diameter Anaplastic tumor cells, cords, glands, dispersed through fibrous background Cells may be "signet ring" mucin-secreting	Primaries are gastrointestinal tract (Krukenberg tumors), breast, and lung	

Table 18-3 Salient Features of Ovarian Germ Cell and Sex Cord Neoplasms



Now Check Your Understanding!

MCQs:

1- Thecoma-Fibroma with ascites and hydrothorax (fluid accumulates in the pleural cavity) is called?

- A. Margret's syndrome
- B. Megan's syndrome
- C. Meig's syndrome

2- Fibrothecoma is?

- A. Sex cord stromal tumor
- B. Almost always benign
- C. Combination of fibroma and thecoma
- D. All the above

3- Which of the following is a clue regarding dysgerminoma?

- A. PLAP positive
- B. Elevated serum α -fetoprotein
- C. Highly sensitive to radiation therapy
- D. Radioresistant but responds well to chemotherapy
- E. A & C
- F. A & B
- G. B & C
- 4- A specimen of a 20-year-old female was examined and revealed Schiller-Duval bodies, further tests revealed elevated alpha-fetoprotein; the doctor explained to the patient that she has a radioresistant tumor, and further discussed the treatment plan, which of the following could be the tumor she was diagnosed with?
 - A. Choriocarcinoma
 - B. Yolk sac tumor
 - C. Teratoma
 - D. Embryonal carcinoma

5- CD30 immunostain positive is a clue regarding which of the following?

- A. Choriocarcinoma
- B. Yolk sac tumor
- C. Teratoma
- D. Embryonal carcinoma

6- Elevated serum levels of HCG are a clue to which of the following tumors?

- A. Choriocarcinoma
- B. Yolk sac tumor
- C. Teratoma
- D. Embryonal carcinoma

7- Most common tumor in the ovaries?

- A. Germ Cell tumors
- B. Sex cord stromal tumors
- C. Surface epithelial tumors
- D. Malignant tumors

MCQ	s:			
1: C	2: D	3: E	4: B	5: D
6: A	7: C			



8- The most common type ovarian tumors are:

- A. Serous tumors
- B. Mucinous tumors
- C. Endometrioid tumors
- D. Clear cell tumors
- 9- Which cyst Results from hemorrhage into a persistent mature corpus luteum:
 - A. Follicular cyst
 - B. Corpus luteum cyst
 - C. Theca lutein cyst
 - D. Endometriotic cyst
- **10-** Neoplastic Cyst are more common than the non-neoplastic ones.
 - A. True
 - B. False

Helpful questions from 434:

- 11- A 25-year-old woman presents with a 6-month history of increasing facial hair, deepened voice, and amenorrhea. Physical examination confirms virilization. A CT scan reveals a left ovarian mass. The tumor is surgically removed. It measures 10 cm in diameter and has a yellowish-tan appearance on cross section. The tumor is malignant and consists of two distinct cell populations. Some cells form solid nests, whereas others are arranged in trabecular and gland-like structures. Which of the following is the appropriate diagnosis?
 - A. Brenner tumor
 - B. Dysgerminoma
 - C. Granulosa cell tumor
 - D. Mature cystic teratoma
 - E. Sertoli-Leydig cell tumor
- 12- A 55-year-old woman presents with fatigue and malaise that have been worsening over the last 2 months. She has also noticed loss of appetite and early satiety. Evaluation finds an ulcerative mass located along the lesser curvature of the stomach along with bilateral ovarian masses. Which of the following is this patient most likely to have?
 - A. Barrett mucosa
 - B. Gastric leiomyosarcoma
 - C. Krukenberg tumor
 - D. Meig's syndrome
 - E. Ovarian dysgerminoma
- 13- A 54-year-old female has had weight loss accompanied by abdominal enlargement for the past 6 months. She is concerned because there is a family history of ovarian carcinoma. An abdominal ultrasound reveals a 10-cm cystic mass involving the left adnexal region, with scattered 1-cm peritoneal nodules.peritoneal fluid cytology reveals the presence of malignant cells, consistent with a cystadenocarcinoma Which of the following mutated genes is most likely a factor in the development of this neoplasm?
 - A. Ras

В.	C-erb-B2(HER2)			
С.	BRCA1	MCQs:		
D.	myc	8: A	9: B	10: B
E.	rb1	11: E	12: C	13: C





Thanks for checking our work! Good Luck.

<u>Done by:</u> نوف التويجري & عمر آل سليمان نوف العبدالكريم نورة الخيال دانة عملة

{ قال صلى الله عليه وسلم: من سلك طريقًا يلتمس فيه علمًا سهّل الله له به طريقًا إلى الجنّة }

