Contact us: Pathology435@gmail.com

Testicular Pathology

{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلَّ الجهل طوال حياتهِ }

Lecture Three

Objectives:

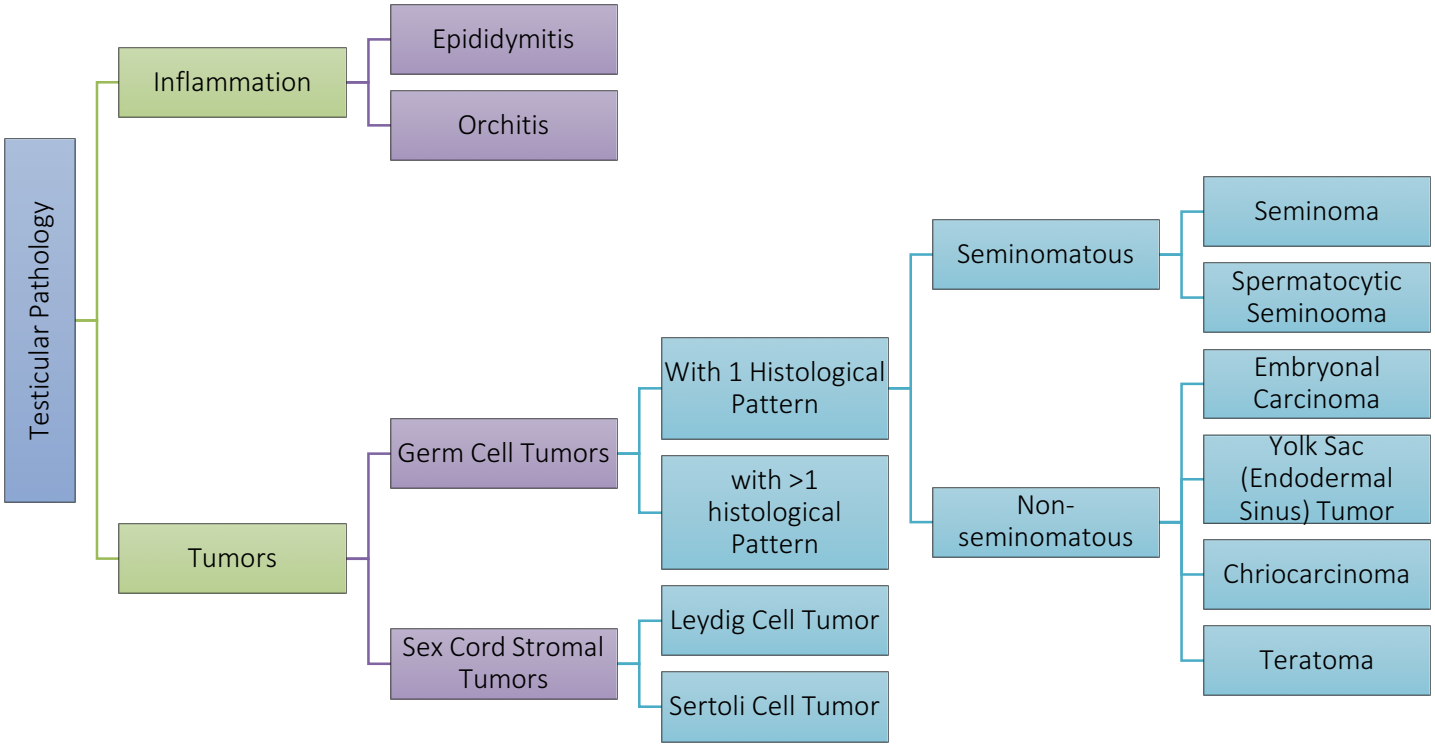
At the end of this lecture, the student should be able to:

A. Have a working knowledge of the normal histology of the testis and epididymis.
B. Know the predisposing factors and pathology of epididymitis.
   Epididymitis and orchitis
   - *Non specific Epididymitis and orchitis* - *Gonorrhea*
   - *Granulomatous/Autoimmune Orchitis* - *Tuberculosis*
C. Be familiar with the basic classification and pathology of testicular tumors.
   Testicular tumors
   - *seminoma* - *yolk sac tumor* - *choriocarcinoma.*
   - *embryonal carcinoma* - *Teratoma*

References: Lecture Slides & Robbins.

Revised by
خولة العماري & هشام الغفيلي

Red: Important. Grey: Extra Notes **Doctors Notes**


Testicular Pathology
Inflammation
Epididymitis
Orchitis
Tumors
Germ Cell Tumors
With 1 Histological Pattern
Seminomatous
Seminoma
Spermatocytic Seminooma
Non-seminomatous
Embryonal Carcinoma
Yolk Sac (Endodermal Sinus) Tumor
Chriocarcinoma
Teratoma
with >1 histological Pattern
Sex Cord Stromal Tumors
Leydig Cell Tumor
Sertoli Cell Tumor

Testicular Diseases:

Epididymitis and orchitis:

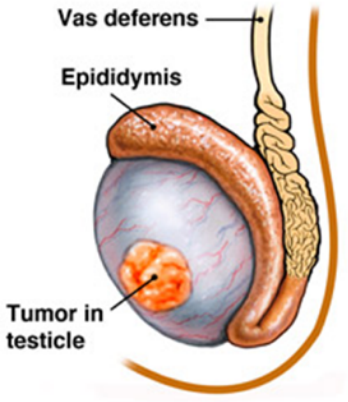
- **Epididymitis**: inflammation of epididymis. **Orchitis**: inflammation of testis
- Inflammatory conditions are generally more common in the epididymis than in the testis.
- However, some infections, notably syphilis, may begin in the testis with secondary involvement of the epididymis.

Inflammation: epididymitis and orchitis:

1. Non specific epididymitis and Orchitis:		○ Commonly related to primary infections in the urinary tract (cystitis, urethritis and genitoprostatitis) ○ Infections reach the epididymis/testis through the vas deference or the lymphatics of the spermatic cord.
	Causative organisms:	(varies with age) ○ **Children**: it is uncommon. Usually associated with a congenital genitourinary abnormality and infection with Gram –ve rods. ○ **Men < 35 years:** we mostly see Chlamydia trachomatis and Neisseria(STD[1]). ○ **Men > 35 Y**: E. Coli and Pseudomonas. ○ Severe mumps orchitis may lead to extensive necrosis, loss of seminiferous epithelium, tubular atrophy, fibrosis, and sterility
	Microscopic findings	○ Testis typically is swollen and tender; we see congestion, edema and histologic examination reveals infiltration by neutrophils, macrophages and lymphocytes. ○ Initially involves the interstitium but later involves seminiferous tubules ○ May progress to frank abscess. ○ Heals by fibrous scarring. ○ Leydig cells are **not** usually destroyed.**(HORMONES ARE NOT AFFECTED)**
2.Granulomatous (autoimmune) epididymitis & orchitis:		▪ Middle–aged men present with **unilateral** testicular mass. ▪ Mimics testicular tumor. Autoimmune basis is suspected. ▪ May be in response to disintegrated sperm, post-infectious, due to trauma or sarcoidosis. ▪ Several conditions including infection and autoimmune injury **(Tuberculosis is most common)** may elicit it.
	Microscopy	Granulomatous inflammation with plasma cells lymphocytes (involves the seminiferous tubules)
3. Gonorrhea		Gonococcal infection can spread from urethra to prostate, seminal vesicles and then to epididymis and testis leading to suppurative orchitis and even abscess.
4. TB		▪ Tuberculosis begins in the epididymis and spreads to the testis. ▪ There is associated tuberculous prostatitis and seminal vesiculitis
	Microscopy	Caseating Granulomas and caseous necrosis **(if you get a Q granuloma with NECROSIS , choose TB)**

[1] Sexually transmitted diseases

Testicular tumors:



- Testicular tumors are the most important cause of firm, painless enlargement of testis.
- Peak incidence between the ages of 20 and 34 years.
- They are the most common tumors of men.

Classification:

A heterogeneous group of tumors divided into germ cell tumors and sex cord stromal tumors:

1. Germ cell tumors	A. **Tumors with One Histologic Pattern (pure form; single type component)**	- ***Seminomatous germ cell tumors:*** ▪ Seminoma "classic" ▪ Spermatocytic seminoma - ***Non-Seminomatous germ cell tumors (NSGCT):*** ▪ Embryonal carcinoma. ▪ Choriocarcinoma. ▪ Yolk sac (endodermal Sinus) tumor. ▪ Teratoma: they can be mature, immature or with malignant transformation.
	B. **Tumors with more than one Histologic Pattern: mixed germ cell tumor (mixed form): 60%;** Mixtures of seminomatous and non-seminomatous components.	
	In adults, 95% of testicular tumors are germ cell tumors, and all are malignant.	
2. Sex Cord Stromal Tumors.	▪ Leydig cell tumor ▪ Sertoli cell tumor	
	Both are uncommon and are usually benign.	

1. Germ cell tumors: (MALIGNANT BUT CURABLE)

- Between 15 to 30 years of age, these are the most common tumor of men.
- Most are highly aggressive cancers, capable of extensive dissemination.
- Most of them can be cured with current therapy.
- Most GCTs originate from precursor lesions called **intratubular germ cell neoplasia** (it is like carcinoma-in-situ).
  - This lesion is present in conditions associated with a high risk of developing GCTs (e.g., cryptorchidism, dysgenetic gonads).
  - These in situ lesions can be found in grossly "normal" testicular tissue adjacent to GCTs in mostly all cases.
- **Clinical Features:**
  - Patients present most frequently with a painless testicular mass that (unlike enlargements caused by hydroceles) is **non-translucent.**

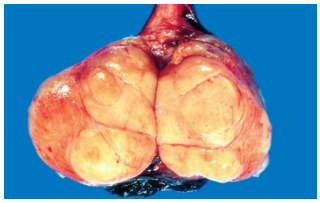
Predisposing factors of GCTs:

- **Cryptorchidism** is associated with a 3 to 5-fold increase in the risk of cancer in the undescended testis and in the contralateral descended testis. About 10% cases of testicular cancer have cryptorchidism.
- Intersex syndromes, including androgen insensitivity syndrome & **testicular dysgenesis**.
- **Genetic factors:** isochromosome of the short arm of **chromosome 12**, i(12p), is found in most GCTs.
- Strong family predisposition; brothers, fathers and sons of testicular cancer patients are at risk.
- There is a high risk of developing cancer in one testis if the contralateral testis has cancer.
- Testicular tumors are more common in whites than in blacks.

Seminomatous germ cell tumors: (identical to dysgerminoma in the ovary)

1. Seminoma

- Most common type of testicular tumors & the most common type of testicular GCT (50%)
- Almost never occurs in infants.
- Peak incidence in the 30s
- Classic seminoma is **highly sensitive to radiation therapy** and tends to remain localized for long periods, and the overall 5-year survival is 90 to 95%.



- Often remain confined to the testis for long intervals and may reach considerable size before diagnosis.
- Sometimes, syncytiotrophoblasts are present which are the source of the **minimally elevated serum hCG** encountered in some males with pure seminoma.

Metastasis

- Most commonly are encountered in the iliac and paraaortic lymph nodes, particularly in the upper lumbar region.
- Hematogenous metastases occur late in the course of the disease.

Morphology

Gross

- Bulky masses, sometimes very large, no necrosis or hemorrhage
- Homogenous , gray-white, lobulated cut surface
- Large tumors **may** contain foci of coagulation necrosis, usually without hemorrhage.

Microscopic

- Sheets of uniform cells divided into lobules by delicate fibrous septa containing lymphocytes.
- Cells are large and round with large nucleus and prominent nucleoli
- Cytoplasm of tumor cell has glycogen
- A lymphocytic infiltrate usually is present
- Positive for PLAP, OCT4 stain and c-kit (CD117).

2. Spermatocystic seminoma (don't need follow up after surgery)

- Uncommon: 1-2 % of testicular GCTs
- Slow growing tumor, **No** metastasis.
- Over age 65.
- Excellent Prognosis.
- No lymphocytic infiltrates, granulomas, or syncytiotrophoblasts.
- Usually comprises polygonal cells of variable size that are arranged in nodules or sheets.

Non-Seminomatous germ cell tumors (NSGCT):

1. Embryonal Carcinoma

Info

- It accounts for about 15 to 35% of testicular GCTs, 20-30y age group.
- More aggressive than seminomas.
- Metastasizes early via both lymphatic and hematogenous routes.
- Can be seen combined with other GCTs (in mixed GCTs)
- Pure embryonal carcinomas account for only 2% to 3% of all testicular GCTs.
- Radiation is **not** as effective as with seminoma, but newer chemotherapeutic agents have greatly improved prognosis.

Morphology

- Smaller than seminoma, poorly demarcated.
- Variegated with foci of necrosis and hemorrhage.
- Large & primitive- looking cells, with basophilic cytoplasm, indistinct cell borders, and large nuclei with prominent nucleoli.
- The neoplastic cells may contain primitive glandular structures.
- Tumor cells are positive for cytokeratin (CK) and CD30 stain.

2. Yolk Sac Tumor

Info

- Also called Endodermal sinus tumor
- Pure YST of the adult testis is rare.
- It is the most common tumor in infants and children up to 3 years of age and it has a very good prognosis in them.
- In adults it occurs as a part or component of mixed GCT (commonly mixed with embryonal carcinoma)
- Patients have elevated serum alpha fetoprotein (AFP). AFP may be used as a marker of disease progression in the patient's serum and also aid in diagnosis.
- The biologic behavior of YST is similar to that of embryonal carcinoma
- **Testicular yolk sac tumors occur in two forms**:
  - As a pure form in young children or
  - As in combination with other NSGCTs, mainly embryonal carcinoma, in adults.

Morphology

Gross: Non-encapsulated, homogenous, yellow white, mucinous

Microscopic-ally

- Discloses low cuboidal to columnar epithelial cells forming microcysts, lacelike (reticular) patterns, sheets, glands, and papillae
- Tumor shows **characteristic** structures resembling endodermal sinuses called as **Schiller-Duval bodies.**
- Resembling primitive glomeruli (glomerular-like structures) flower like
- Hyaline–pink globules.
- Tumor cell are positive for alphafetoprotein (AFP) and alpha-1-antitrypsin stain (Within the eosinophilic hyaline globules).
- AFP can also be detected in the serum.

3. Choriocarcinoma	**Info**	▪ Highly malignant tumor. ▪ Patients have elevated serum human chorionic gonadotropin (HCG). ▪ Pure choriocarcinoma of the testis is extremely rare, and the tumor is much more common as a component of mixed GCT.
	Morphology	▪ Composed of sheets of small cuboidal cells irregularly inter- mingled with or capped by large, eosinophilic syncytial cells containing multiple dark, pleomorphic nuclei; these represent **cytotrophoblastic** and **syncytiotrophoblastic** differentiation, respectively. ▪ Small sized lesions, nonpalpable lesions, even with extensive systemic metastasis. ▪ Prominent hemorrhage and necrosis. ▪ Made up of malignant trophoblastic (placental) tissue (cyto-trophoblastic and syncytio-troblastic cells) (placenta-like tissue, but villi are absent). ▪ Tumor cells positive for human chorionic gonadotropin (HCG) stain.
4. Teratoma	**Info**	▪ It is a tumor composed of different types of cells or organ components. ▪ Any age, infancy to adult life. ▪ **Pure form:** is common in infants and children second to yolk sac tumor (in this age group). But is rare in **adults** & occurs as part of mixed GTC. ▪ Any of the following cell types of various organs can be present: neural/brain, cartilage, bone, squamous epithelium, hair, glandular cells, smooth muscle, thyroid tissue, bronchial epithelium of lung, pancreatic tissue etc. ▪ If any of the cellular/organ tissue undergoes non-germ cell type of malignant transformation, it's called as **teratoma with malignant transformation** (rare) e.g. squamous cell carcinoma or adenocarcinoma.
	Mature teratoma	If the cellular/organ tissue is mature looking
	Immature teratoma	If some of the cellular/organ tissue component is immature (sharing histologic features with fetal or embryonal tissues) When we give you in the exam (embryonal , mesenchymal or neuroepthilial) it means its immature
	Morph-ology	▪ Usually large 5 -10 cm. ▪ Heterogeneous appearance with solid and cystic areas. ▪ Can show bone, cartilage and teeth grossly. ▪ Composed of bizarrely distributed collection of different type of cells or organ structures (heterogeneous).
	Behavior	▪ In infants and children, mature teratomas are benign and immature teratoma is considered malignant. ▪ In post-pubertal male, all teratomas are regarded as malignant, and capable of metastasis, regardless of whether the elements are mature or not.

B. Mixed GCT: (we love them in the exam, we will give you for example alpha fetoprotein positive and HCG positive , it means its MIXED)

- Mixed Germ Cell Tumors are quite common.
- About half of testicular tumors are composed of a mixture of GCTs.
- The common combinations/mixtures are:
  - *Teratoma + embryonal carcinoma +/- yolk sac tumor*
  - *Seminoma + embyronal carcinoma*

Clinical features:

- Present as a painless enlarging mass in the testis.
- **Generally** any solid testicular mass should be considered neoplastic.
- GCTs secrete hormones and enzymes that can be detected in blood (HCG, AFP, and lactate dehydrogenase).
- Biopsy of a testicular tumor is associated with a risk of tumor spillage therefore it is **not recommended.**
- GCTs can spread by direct extension to the epididymis, spermatic cord, or scrotal sac.
- Lymphatic spread is **common** (Retroperitoneal and para-aortic nodes are first to be involved)
- Hematogenous spread to Lung, liver, Brain, and bones.
- Seminomatous tumors are **radiosensitive**.
- Non-seminomatous tumors are **chemosensitive** and respond very well to chemotherapy.
- The standard management of solid testicular tumors is **radical orchiectomy.**

Prognosis:

- More than 95% of patients with seminoma can be cured
- 90% of patients with non-seminomatous tumors can achieve complete remission with aggressive chemotherapy, and most can be cured.
- The rare pure choriocarcinoma is the most aggressive non-seminomatous tumor. Pure choriocarcinoma has a poor prognosis.

Extra Summaries, Pictures and helpful explanations

Table 17–1 Summary of Testicular Tumors

Tumor	Peak Patient Age (yr)	Morphology	Tumor Marker(s)
Seminoma	40–50	Sheets of uniform polygonal cells with cleared cytoplasm; lymphocytes in the stroma	10% of patients have elevated hCG
Embryonal carcinoma	20–30	Poorly differentiated, pleomorphic cells in cords, sheets, or papillary formation; most contain some yolk sac and choriocarcinoma cells	Negative (pure embryonal carcinoma)
Yolk sac tumor	3	Poorly differentiated endothelium-like, cuboidal, or columnar cells	90% of patients have elevated AFP
Choriocarcinoma	20–30	Cytotrophoblast and syncytiotrophoblast without villus formation	100% of patients have elevated hCG
Teratoma	All ages	Tissues from all three germ cell layers with varying degrees of differentiation	Negative (pure teratoma)
Mixed tumor	15–30	Variable, depending on mixture; commonly teratoma and embryonal carcinoma	90% of patients have elevated hCG and AFP

AFP, alpha fetoprotein; hCG, human chorionic gonadotropin.

Seminoma:

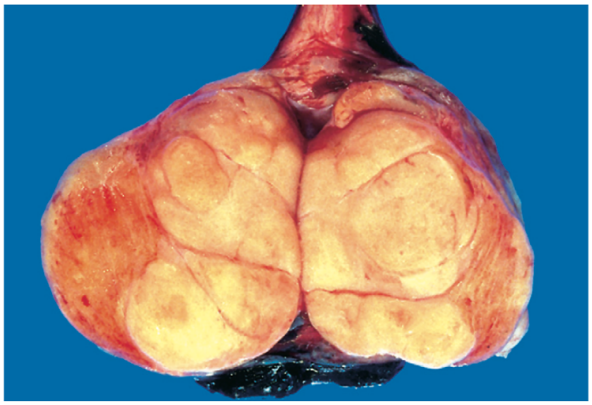


Figure 17–3 Seminoma of the testis appearing as a well-circumscribed, pale, fleshy, homogeneous mass.

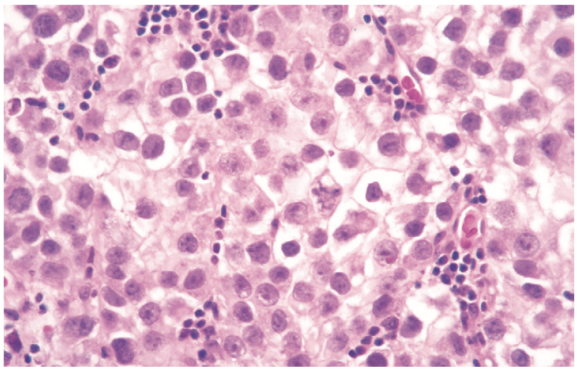
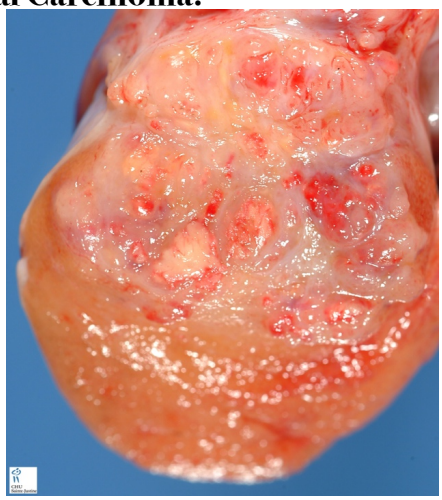


Figure 17–4 Seminoma of the testis. Microscopic examination reveals large cells with distinct cell borders, pale nuclei, prominent nucleoli, and a sparse lymphocytic infiltrate.

Embryonal Carcinoma:



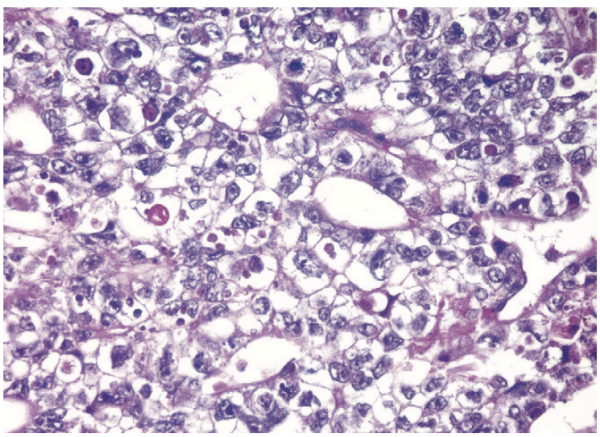


Figure 17–6 Embryonal carcinoma. Note the sheets of undifferentiated cells and primitive gland-like structures. The nuclei are large and hyperchromatic.

Yolk Sac Tumor:

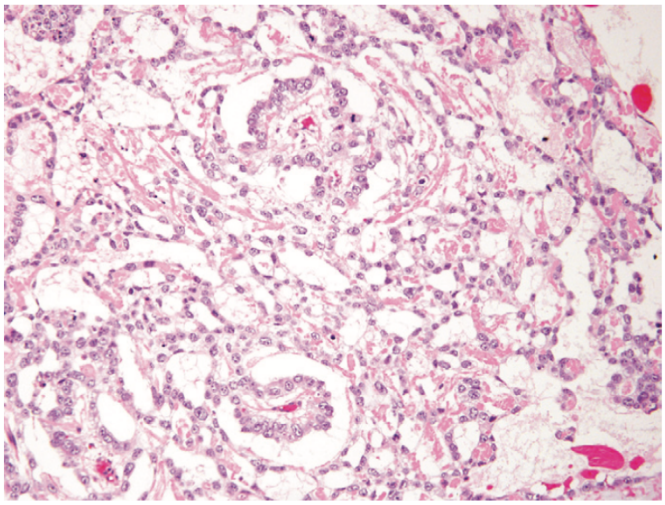


Figure 17–7 Yolk sac tumor demonstrating areas of loosely textured, microcystic tissue and papillary structures resembling a developing glomerulus (Schiller-Duval bodies).

Choriocarcinoma:

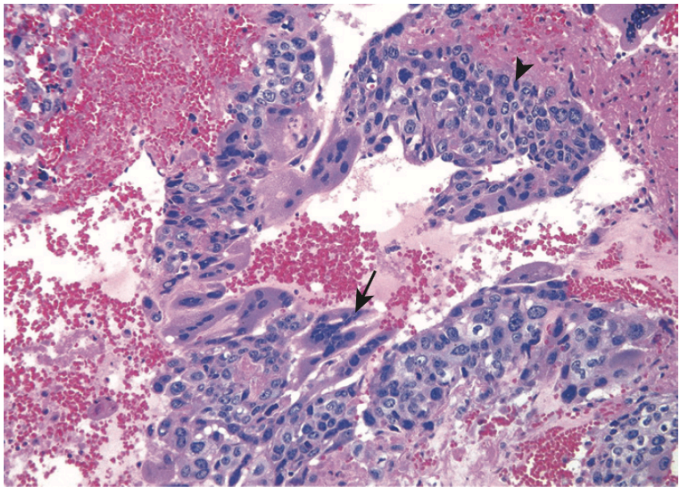
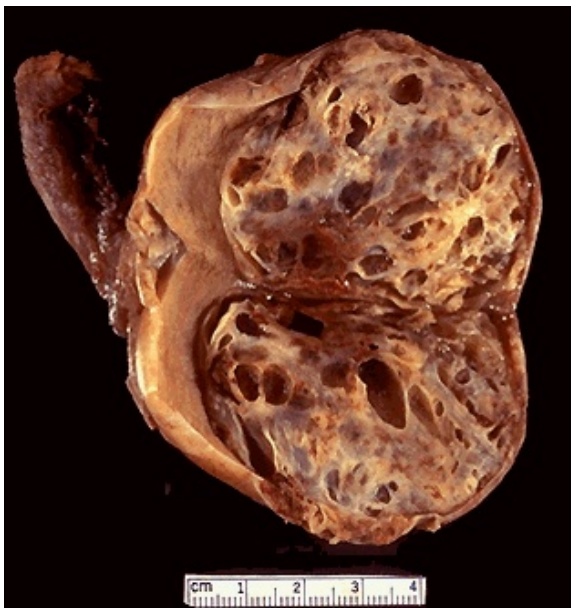
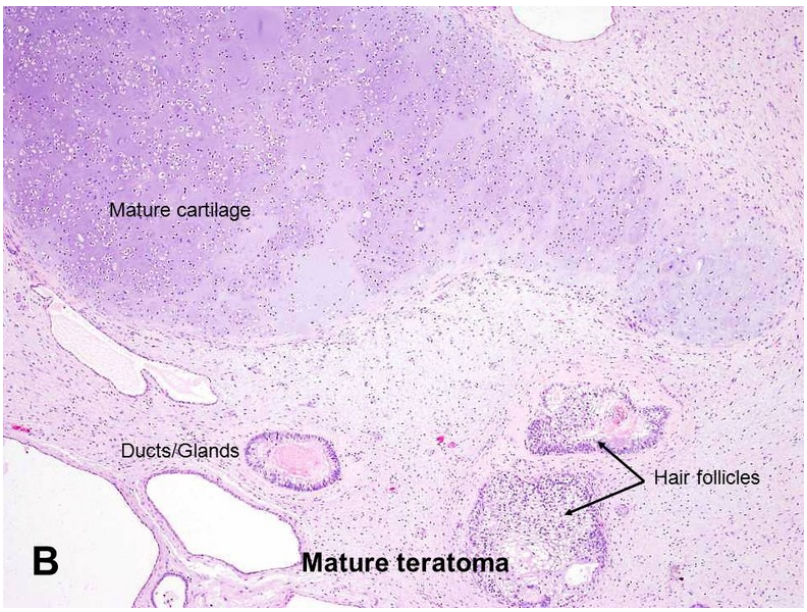


Figure 17–8 Choriocarcinoma. Both cytotrophoblastic cells with central nuclei (*arrowhead, upper right*) and syncytiotrophoblastic cells with multiple dark nuclei embedded in eosinophilic cytoplasm (*arrow, middle*) are present. Hemorrhage and necrosis are prominent.

Teratoma:





Now Check Your Understanding!

MCQs:

1- A 23-year-old male presented to the doctor with an enlarged testicular mass, biopsy shows granuloma with necrosis, the most likely diagnosis:

A. TB
B. Autoimmune granulomatous inflammation
C. STD

2- A 33-year-old male presented with painless testicular mass, it was resected, grossly it shows homogenous mass with lobulated cut surface, with no hemorrhage nor necrosis. what will the pathologist see under the microscope?

A. Malignant cell with atypia
B. Neuroepithelial cells mixed with glandular tissue
C. Sheathes of uniform cells separated by fibrous septa

3- a 28-year-old male presented with enlarged testicular mass, it was resected. grossly it shows cartilage tissue, teeth, and some hair. under the microscope there were chondrocytes, squamous epithelium, neuroepithelial cells and well differentiated glands, what's the most likely diagnosis?

A. Immature teratoma
B. Mature teratoma
C. Mixed tumor

4- A 33 year old male presented with enlarged testicular mass , histological studies show embryonal tissue , syntrophoplasts and cytotrophoblast , whats the most likely diagnosis?

A. Yolk sac tumor
B. Embryonal cell tumor
C. Teratoma
D. Mixed tumor

5- Most common testicular cancers are:

A. Germ cells tumors
B. Congenital
C. Melanomas

6- An isochromosome of the short arm of which chromosome is pathognomonic of GCT?

A. 11
B. 12
C. 13
D. 14

MCQs:
1: A 2: C 3: A 4: D 5: A
6: B

7- Which of the following statements about testicular cancer is false?

A. A testicular mass in a male of age greater than or equal to 50 years of age should be regarded as lymphoma unless proved otherwise.
B. GCTs are 4 or 5 times more common in whites than in African American males.
C. The incidence of the testicular GCTs has been decreasing lately.
D. Cryptorchidism is associated with a several fold higher risk of GCT.
E. Inguinal cryptorchid testis are at a higher risk than abdominal cryptorchid testis.

8- Which ONE of the following statements is INCORRECT regarding testicular cancer?

A. Tumor markers, LDH, Alpha-fetoprotein, BHCG may be elevated
B. A trans-scrotal biopsy is carried out to confirm the diagnosis
C. Seminoma and Teratoma are the two most common types of testicular cancer
D. Metastasizes to the para-aortic lymph nodes
E. An inguinal orchiectomy is the surgical treatment of choice

9- Which of the following statements is true regarding testicular tumors?

A. Are embryonal cell carcinomas in 95% of cases
B. Bilateral in up to 10% cases
C. Teratomas are more common than seminomas
D. Usually present after 50 years of age

10- Regarding testicular tumors, the following are false except ?

A. They are the commonest malignancy in older men
B. Seminomas are radiosensitive
C. Only 25% of Stage I teratomas are cured by surgery alone
D. Chemotherapy rarely produces a cure in those with metastatic disease

11- Most common testicular tumor in prepubertal adults is:

A. Yolk sac tumor
B. Embryonal cell Ca
C. Seminoma
D. Teratoma

MCQs:
7: E 10: B 11: A
8: B, A transcrotal biopsy in testicular cancer is contraindicated. This will lead to seeding of the tumor cells onto scrotal tissue and in turn makes a fairly localized problem more widespread.
9: B, 15% of familial and 5% of sporadic cases of testicular tumor are bilateral.

Thanks for checking our work! Good Luck.

Done by:

نوف التويجري & عمر آل سليمان

فتون الصالح

مريم سعيدان

الجوهرة المزروع

رزان السبتي

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