

PATHO MODIFIED NO.

الكُتّاب: صهيب زعيتر المدققين: إسماعيل العارضة الدكتور/ة: مها شوماف



MALE GENITAL TRACT

DR. Maha Shomaf

Professor of Pathology

Color code

Slides

Doctor

Additional info

Important

<u>Prostate</u>

The normal prostate is composed of two components: glandular and stromal components.

- The normal prostate contains glands with two cell layers:
- 1. Flat basal cell layer
- 2. An overlying columnar secretory cell layer
- The surrounding prostatic stroma contains a mixture of smooth muscle and fibrous tissue.

Prostate zones central zone (CZ), a peripheral zone (PZ), a transitional zone (TZ), and a periurethral zone.



 It is important to know the zones of the prostate, which are normally located surrounding the proximal urethra. Based on this, the prostate is divided into zones: the central zone, which immediately surrounds the urethra; the peripheral zone, which is on the superficial area of the prostate; and the transitional zone.

 Why are these zones important? Because each zone is well-known to produce certain conditions. For example, tumors arise from the peripheral zone, while hyperplasia arises from the central zone, and so on. This is going to be reflected in the patient's clinical presentation.

- Most carcinomas arise from the peripheral glands of the organ
- Nodular hyperplasia arises from more centrally situated glands (inner transitional zone)
- Most carcinomas (70%–80%) arise in the peripheral zones
- Carcinomas (because they arise from peripheral zone) are often detected by rectal examination
- Hyperplasias are more likely to cause urinary obstruction.
- When we say that hyperplasia arises from the central zone, that doesn't mean benign hyperplasia will not affect the peripheral zone. In fact, in advanced stages, the whole prostate can be affected.
- In per rectal (PR) examination, we can palpate the prostate to check for any unusual mass or nodule. Remember that carcinomas often arise on a background of prostate hyperplasia, and prostatic hyperplasia is more diffused in nature.
- If we palpate a prominent or large nodule, we must perform a biopsy to determine the exact nature of the lesion.

• The doctor read the whole slide here.

Benign Prostatic Hyperplasia

- Benign prostatic hyperplasia (BPH) is an extremely common cause of prostatic enlargement
- It results from proliferation of stromal and glandular elements

Sometimes, the glandular component predominates in hyperplasia, and sometimes it is mainly due to stromal hyperplasia.

- It is present in a significant number of men by 40 years of age,
- Its frequency rises progressively thereafter reaching 90% by the eighth decade of life.
- The enlargement of the prostate in men with BPH is an important cause of urinary obstruction.

- Very important point about this condition is that it is associated with the development of significant clinical manifestations. Patients usually require frequent follow-up and management of any acute conditions that may develop as a result of the hyperplasia. Actually, these complications are not caused by the hyperplasia itself, but rather by the **obstruction** resulting from **enlargement of the prostate**.
- As we mentioned, the enlargement mainly arises from the central zone, which causes pressure on the urethra. This leads to **narrowing** of the urethral passage, and sometimes even **complete obstruction**, resulting in various **urinary symptoms**.

- Excessive androgen-dependent growth of stromal and glandular elements has a central role in the pathogenesis of BPH.
- BPH does not occur in males who are castrated before the onset of puberty or in males with genetic diseases that block androgen activity

• This indicates that androgen stimulation is a mechanism in the development of the disease.

- BPH virtually always occurs in the inner transition zone of the prostate.
- The affected prostate is enlarged
- Many well-circumscribed nodules that bulge from the cut surface (Fig.18.11).
- These nodules form in irregular sizes because some of the glands—especially when the predominant component is glandular—can dilate and distend, and may contain secretions. This is actually associated with an increased risk of developing inflammation. The patient frequently suffers from recurrent attacks of inflammation.
 - The nodules may appear solid or contain cystic spaces the latter corresponding to dilated glands.
 - The urethra is usually compressed, often to a narrow slit, by the hyperplastic nodules. Ieading to obstructive manifestations, especially urinary

retention.

Benign nodular hyperplasia of prostate



- This figure compares a normal prostate on the left (homogeneous and smaller in size) with a section of nodular hyperplasia on the right.
- You can see the surface is nodular and separated by fibrous tissue.
- Some areas show fibrosis, and you can also see hole-like structures these represent the glandular component, with some of the glands being dilated.

Clinical Features

- Because there is narrowing of the urethra due to fibrotic prostatic tissue, **urination becomes more difficult.**
- Difficulty in starting the stream of urine (hesitancy).
- <u>Intermittent interruption</u> of the urinary stream while voiding.
- <u>Urinary urgency, frequency, and nocturia, indicative of</u> <u>bladder irritation.</u>
- The presence of residual urine in the bladder due to chronic obstruction increases the risk for urinary tract infections.
 - This can lead to incomplete emptying of the bladder, resulting in **residual urine**. **Residual urine** increases the risk of infection and can cause irritation.

- Complete urinary obstruction with resultant painful distention of the bladder
- Hydronephrosis
- Sometimes, there may be a complete obstruction of the urethra with retention of a large amount of urine, which is an acute emergency. The patient should be treated urgently due to bladder distension.
- This condition can also be chronic, especially if the obstruction is significant and severe. It can lead to the retention of a large volume of urine, dilation of the bladder, and increased bladder pressure.
- This pressure may be transmitted to the ureters and subsequently to the kidneys, causing hydronephrosis.
- As a result, the normal renal parenchyma may be affected, potentially leading to kidney malfunction.

• It originates from the glands and the lining epithelium.

- Adenocarcinoma of the prostate is the most common form of cancer in men, accounting for 27% of cancer cases in the United States in 2014
- > 50 yr of age

Predisposing factors

• 1. Androgens

- Androgen and stimulation of cells and tissues in prostate.
- This might be a mechanism of initiation.

• 2. Heredity

- There is an increased risk among first-degree relatives of patients with prostate cancer.
- Prostate cancer is uncommon in Asians.
- The incidence is highest among African-Americans and in Scandinavian countries.
- Aggressive, clinically significant disease is more common in African-Americans than in Caucasians.

• 3. Environment

- The incidence in Japanese immigrants to the United States rises
- The diet in Asia becomes more westernized

• It involves genes that regulate or control androgen secretion.

- 4. Acquired genetic aberrations
- The most common gene rearrangements in prostate cancer create fusion genes consisting of the androgenregulated promoter of the *TMPRSS2* gene and the coding sequence of *ETS* family transcription factors.
- It occurs in 40-60% of prostate cancers in Caucasian populations, and they occur relatively early in tumorigenesis.
- Tumor suppressor PTEN mutation.

Most prostate cancers are moderately differentiated adenocarcinomas that produce well-defined glands. The glands

- typically are smaller than benign glands and are lined by a single
- uniform layer of cuboidal or low columnar epithelium, lacking
- the basal cell layer seen in benign glands. In further contrast with
- benign glands, malignant glands are crowded together and characteristically
- lack branching and papillary infolding.

Prostate adenocarcinoma



- If you want to describe this prostate, it is enlarged, but the nodules are not gross.
- There are variable-sized cysts, indicating prostatic hyperplasia. However, when comparing the right side to the left, you will notice a solid area. This is a tumor—prostatic carcinoma.
- The malignant glandular tissue is usually small, not dilated, and has lost its normal infolding.
- The left side, which contains the tumor, appears solid compared to the right side.

A very important aspect of diagnosis is the grading of the tumor.

- Prostate cancer is graded by the **Gleason system**, created
- in 1967 and updated in 2014.
- According to this system, prostate cancers are stratified into five grades on the basis of glandular patterns of differentiation.
- Grade 1 represents the most well differentiated tumors, and grade 5 tumors show no glandular differentiation.

Grade 1 is the most differentiated, while Grade 5 is the least differentiated.

- We start with the most predominant component of the tumor.
- The tumor might be entirely well-differentiated or entirely poorly differentiated.
- We begin by scoring the most predominant area, grading the glandular differentiation from 1 to 5.
- Then we move to the second most common area and grade it similarly.
- The two grades are added together to give a total score out of 10.

This total grade helps categorize the tumor as:

Low grade: 6 or less Intermediate grade: 7 High grade: 8, 9, or 10

• Why do we do this? Because the grading reflects the prognosis of the patient.

<u>Clinical features</u>

PSA = Prostate-Specific Antigen.

- 1.Elevated PSA serum levels.
- 2.Palpable nodules on per rectal examination.
- 3. Incidental.
- 4. Bone metastases, particularly to the axial skeleton (osteoblastic (bone-producing) lesions that can be detected on radionuclide bone scans).

- When PSA levels are high—significantly high—it may indicate an increased risk of prostate carcinoma. However, elevated PSA can also occur due to other reasons, such as inflammation.
- At the time of diagnosis, if carcinoma is suspected, a **core biopsy** should be performed. This biopsy is taken from different sites within the prostate and then examined for the presence of carcinoma. Sometimes, the tumor can be very small and may even be found incidentally.
- That's why every prostatic biopsy must be examined carefully, as there is always a possibility of detecting prostatic carcinoma.
- If we look at radiological images of metastatic sites—especially in the axial skeleton—we
 will see that these areas appear white in color. This is because prostate cancer typically
 causes sclerotic (bone-forming) lesions. In contrast, other types of tumors often cause
 destructive (lytic) lesions, which appear black or dark on imaging.

Testicular Neoplasms

- Testicular neoplasms occur in roughly 6/100,000 males.
- Peak in incidence 15-34-year-old age group.
- Neoplasms of the testis are heterogeneous and include:
- 1. Germ cell tumors (95%).
- 2. Sex cord-stromal tumors (5%).
- These tumors are not common because most of them are **malignant**.
- They can affect individuals of all ages.
- They are found lining the **seminiferous tubules**, which are surrounded by a minimal amount of **stromal tissue** which is a fibrous tissue containing **Leydig cells**.
- Tumors arising from germ cells are called germ cells tumors.
- Tumor arising from stromal cells are called sex cord-stromal cells.

- In postpubertal males, 95% of testicular tumors arise from germ cells, and almost all are malignant.
- Sex cord-stromal tumors derived from Sertoli or Leydig cells are uncommon and usually benign.

- Sertoli cells (non-dividing cells) are found within the seminiferous tubules, located between the germ cells. Their function is to support and regulate the division and development of germ cells.
- Leydig cells are located in the interstitial tissue between the seminiferous tubules. Their primary function is to produce testosterone.

<u>Risk factors:</u>

- 1. Whites more than blacks individuals.
- 2. Cryptorchidism is associated with a 3-5 fold increase in the risk for cancer in the undescended testis, as well as an increased risk for cancer in the contralateral descended testis.
- A history of cryptorchidism is present in approximately 10% of cases of testicular cancer.
- **Cryptorchidism** refers to undescended testicles. This condition is important because when the testes remain intra-abdominal, the temperature is approximately 1°C higher than in the scrotum. This temperature difference, along with the abnormal position, can lead to **injury or damage to the testicular tissue**.
- As a result, patients with **unrecognized or delayed repositioning** of the testes are at an increased risk of developing **testicular tumors**, including various types of malignancies.

3. Intersex syndromes, including androgen insensitivity syndrome and gonadal dysgenesis also are associated with an increased frequency of testicular cancer.

 Conditions characterized by hormonal imbalances or inherited maldevelopment of the male genital tract—such as ambiguous genitalia—are also associated with an increased risk of malignancy, particularly in cases like gonadal dysgenesis.

• The doctor read the whole slide

4. Inherited factors

There is an increased risk of 8-10 folds inbrothers of males with germ cell tumors have an 8-10-fold increased risk.

5. The development of cancer in one testis is associated with a markedly increased risk for neoplasia in the contralateral testis.

6. Genetics

- Extra copies of the short arm of chromosome 12, usually due to the presence of an isochromosome 12 [i(12p)] are found in virtually all germ cell tumors.

- Mutations in *KIT gene* are found in up to 25% of tumors.

 If we face difficulty in making a diagnosis or in accurately identifying the type of tumor, we may request chromosomal studies to help confirm our findings.

Classification

I. Seminomas

- Germ cell tumors are classified into two major groups: seminomas and non-seminomas.
- This classification is important because seminomas differ from other germ cell tumors in terms of behavior, incidence, and the age group they affect.

II. Non-seminomatous germ cell tumors(NSGCT)

- embryonal carcinoma
- yolk sac tumor
- choriocarcinoma
- teratoma

Pure or Mixed

 In contrast to ovarian germ cell tumors, testicular germ cell tumors are more commonly mixed rather than pure. Pure forms are rare, unlike in the ovary.

<u>Seminoma</u>

The most common type of testicular tumor

- 50% of all testicular tumors.
- **Classic seminoma:** (Although other types exist, we will focus on the classic form).
 - ➢ Rare in pre-pubertal children.
 - Progressive painless enlargement of the testis.
 - Histologically identical to ovarian dysgerminomas and to germinomas occurring in the CNS and other extragonadal sites.

• The site of origin for seminomas is typically the gonads. However, extragonadal sites can also occur, such as the mediastinum.

1. Seminoma



Seminoma: circumscribed, pale, fleshy, homogeneous mass; usually <u>without hemorrhage or</u> <u>Necrosis.</u> Unless it is recurrent or at a high stage.



Microscopic examination reveals large cells with distinct cell borders, pale nuclei, abundant cytoplasm, prominent nucleoli, and lymphocytic infiltrate.

2. Embryonal carcinoma

Non-Seminomatous Germ Cell Tumors (NSGCT)



ill-defined masses containing foci of **hemorrhage** and **necrosis**.

Sheets of undifferentiated cells & primitive gland -like structures. The nuclei are large and hyperchromatiC with prominent nucleoli, and increased mitotic activity.

- 20-30 years old (Young adults).
- More aggressive than seminoma.

more polymorphic nuclei immature glands

3. Yolk sac tumors

- The most common primary testicular neoplasm in children <3 year.
- Good prognosis in young children.
- In adults, pure form of yolk sac tumors is rare and have a worse prognosis.

- Yolk sac tumors
- Histologically:
- The tumor is composed of low cuboidal to columnar epithelial cells forming Microcysts, Lacelike (reticular) patterns.
- A distinctive feature is the presence of structures resembling primitive glomeruli, called <u>Schiller-Duvall bodies</u>.
- Alpha- feto-protein (AFP) usually detected in serum.

• AFP is secreted by yolk sac tumor.

- We have a space and infolding of epithelium and fibrovascular cords similar to that in glomeruli.
- We need to know the presence of each type of the tumor due to the prognosis.

3. Yolk sac tumor (arrows: Schiller-Duvall bodies)



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4. Choriocarcinoma

- It is important to detect or confirm the presence of choriocarcinoma, as it is a very aggressive tumor. Patients may already have metastasis at the time of diagnosis.
- Highly malignant form of testicular tumor.
- "pure" form is rare, constituting less than 1% of all germ cell tumors.
- Usually mixed with other germ cell tumors.
- Characterized: Elevated serum level of HCG.

Human Chorionic Gonadotropin

• It is not necessary for the choriocarcinoma component to be prominent in the tissue. In fact, it can sometimes be very difficult to identify the tumor cells, as the tumor is often associated with extensive hemorrhage.

Macroscopically:

- The primary tumors may be small even in patients with extensive metastatic disease.
- necrosis and hemorrhage are extremely common.

Microscopic examination: (2 cell types)

- **Syncytiotrophoblasts**: large multinucleated cells with abundant eosinophilic vacuolated cytoplasm producing **HCG**.
- **Cytotrophoblasts**: polygonal cells with distinct borders and clear cytoplasm grow in cords or masses and have a single, fairly uniform nucleus.

Choriocarcinoma

Arrow: Syncytiotrophoblast source of hormone Arrow head: Cytotrophoblast



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- If we are lucky, we may observe **sheets of tumor cells**, but typically, the **amount of tumor cells is very low**. They are often embedded within areas of **extensive hemorrhage**.
- When we see a lack of blood vessels and significant hemorrhage within a tumor, the possibility of choriocarcinoma becomes high. That's why we begin carefully searching for tumor cells.
- If they are not clearly visible, we perform **special stains**, such as **HCG** or other immunohistochemical markers, to help confirm the diagnosis.

5. Teratoma

- The neoplastic germ cells differentiate along somatic cell lines showing various cellular or organoid components.
- Resonant of the normal derivatives of more than one germ layer.
- May affect all ages.
 - Another type of germ cell tumor is the **teratoma**, which is characterized by the presence of differentiated cells that give rise to **various tissue types**.
 - In testicular tumors, teratomas are usually malignant, whereas in ovarian tumors, they are typically benign.

• <u>In children</u>

- Pure forms of teratoma are common being second in frequency to yolk sac tumors.
- In adults
- Pure teratomas are rare (3% of germ cell tumors).
- frequency of teratoma mixed with other germ cell tumors is high.

• An important point about teratomas is that **any of the tissue components can be malignant**. It is not necessary for all components to be malignant—**some may be benign, while others can be malignant**.

2 types:

- Mature teratoma: All components are composed of mature, adult-type tissues.
- Immature teratoma: Contains areas of immature or undifferentiated tissue.

In the testis, teratomas are usually immature.

• Grossly:

Firm masses and cysts with hair, cartilage, bone, and even teeth!

• Histologically:

1. Mature teratomas:

a heterogeneous collection of differentiated cells, such as neural tissue, muscle bundles, islands of cartilage, clusters of squamous epithelium, etc.

2. Immature teratomas:

- Contain fetal primitive tissues

Teratoma



- These tumors often form cystic structures that are filled with various materials.
- The inner surface of the cyst is lined by squamous epithelium, similar to skin, which is why hair components are commonly found inside. This hair is usually embedded within keratinous material.
- In addition, if we examine sections from the cyst wall, we may see a variety of tissue components, such as:

Cartilage, Squamous epithelium, Secretory epithelium, Mucosa, Bone, Muscle tissue.

Teratoma



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- In prepubertal males, mature teratomas usually follow a benign course.
- In postpubertal males, all teratomas are regarded as potentially malignant, being capable of metastasis regardless of whether they are composed of mature or immature elements.

Clinical Features of testicular germ cell neoplasms:

- Present most frequently with a **painless testicular mass** that is non-translucent.
- Some tumors, especially NSGCT, may have <u>metastasized widely</u> by the time of diagnosis.
- Biopsy of a testicular neoplasm is <u>contraindicated</u>, because it's associated with a risk of tumor spillage.
- The standard management of a solid testicular mass is **radical orchiectomy**, based on the presumption of malignancy.

Seminomas and nonseminomatous tumors differ in their behavior and clinical course:

I. <u>Seminomas:</u>

- Often remain <u>confined to the testis</u> for long periods.
- <u>If metastasize</u>, most commonly in <u>iliac and paraaortic lymph</u> <u>nodes</u>.
- <u>Hematogenous metastases</u> occur <u>late</u> in the course of the disease.

II. Nonseminomatous germ cell neoplasms:

- Tend to <u>metastasize earlier</u>, by <u>lymphatic &</u> <u>hematogenous</u> (liver and lung mainly) routes.
- Metastatic lesions may be <u>identical</u> to the primary testicular tumor or <u>different</u> containing elements of other germ cell tumors.
- Lymph node involvement in metastasis from gonadal tumors typically affects the intra-abdominal paraaortic lymph nodes, as these are the primary draining lymph nodes of the testes.
- If a patient first presents with metastasis, it may be **difficult to immediately recognize** that the primary tumor is testicular. This is because **any component of a mixed germ cell tumor** can metastasize.
- In other words, it is not necessary for the metastasis to contain **all components** of the original mixed tumor—**the metastatic site may show only one component**, such as a **choriocarcinoma pattern**.

Serum Assay of tumor markers secreted by germ cell tumors:

- Helpful in diagnosis and follow up (to detect recurrence and response to therapy)
 - ✓ HCG : elevated in patients with choriocarcinoma.
 - ✓ AFP : elevated in patients with yolk sac tumor.
 - ✓ lactate dehydrogenase (LDH):correlate with the tumor burden (tumor size and load); regardless of histologic type.

ثَبْتِ الْعَزِيمَةِ مَاضٍ حَيْثُ يَنْخَرِطُ

Additional sources1. Book pages2. Youtube videos3. Webpages...etc

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لا يُدْرِكُ الْغَايَةَ الْقُصْوَى سِوَى رَجُلٍ

فَاقْذِفْ بِنَفْسِكَ فِي أَقْصَى مَطَالِبِهَا

| VERSIONS | SLIDE # | BEFORE CORRECTION | AFTER CORRECTION |
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