

Lecture 2

Prostate Pathology



432 Pathology Team

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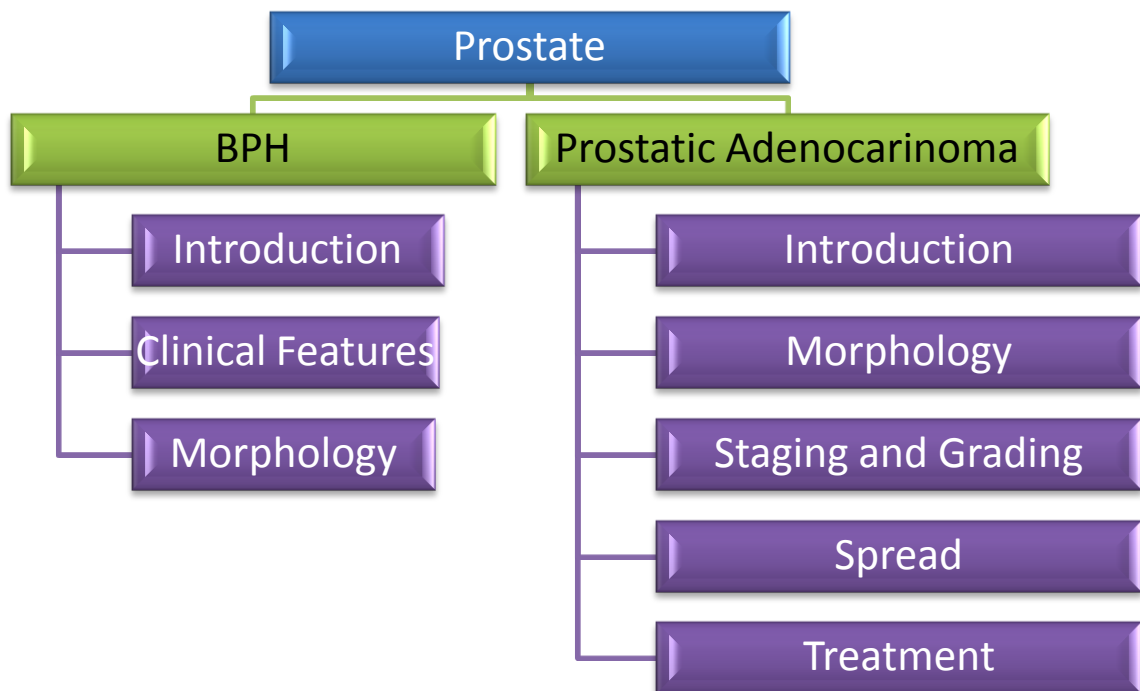
Reviewed By: Abdulmajeed Al Jasser

Reproductive Block



Prostate Pathology

Mind Map:



Objectives:

- At the end of the lecture, the student are expected to be able to:
- Define Benign Prostatic Hyperplasia, mention its causes, clinical features and morphological changes.
- List the causes of Prostatic Adenocarcinoma, its morphology, spread, grading and staging, clinical course and treatment options.

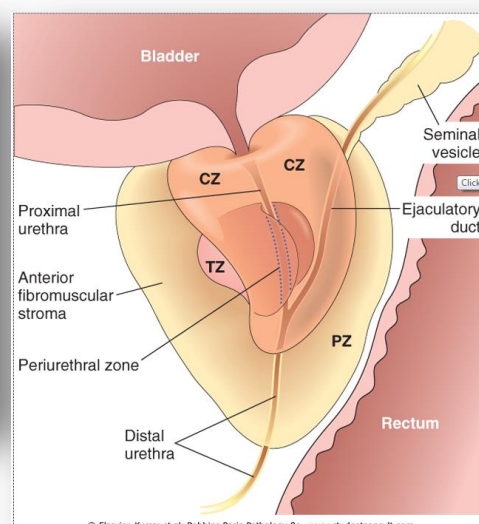
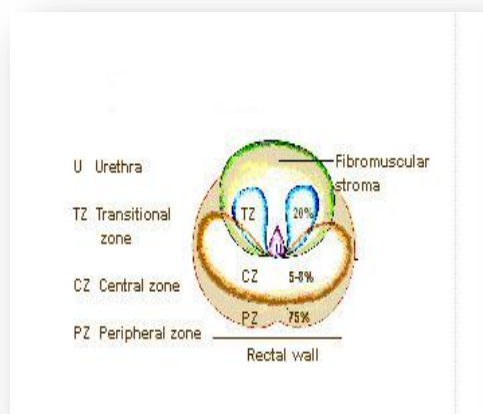
Normal Anatomy of The Prostate

Prostate gland:

- Prostate weighs **20 grams** in normal adult (size of a chestnut).
- Retroperitoneal organ, encircling the **neck of bladder and urethra** (that's why urinary obstruction manifestations occur in case of pathology in the transitional zone).
- **Devoid of a distinct capsule.**
- Divided into **four** biologically and anatomically distinct **zones or regions**: the **peripheral, central, and transitional zones**, and the region of the **anterior fibromuscular stroma**.
- **Histologically** the prostate is composed of glands lined by **two layers** of cells: a **basal layer** of **low cuboidal epithelium covered by a layer of columnar secretory cells.**

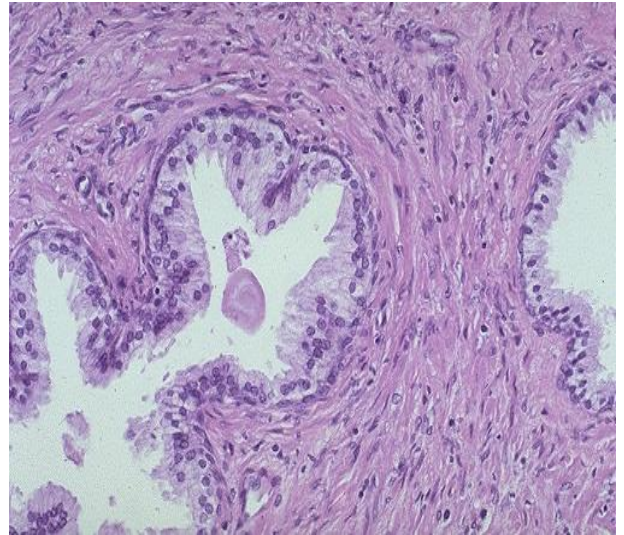
Zones of the Prostate:

- **Peripheral:** is in the outer most part of the prostate and the lower peripheral zone is fairly close to the rectal wall. The peripheral zone is the **most common site for prostatic adenocarcinoma.** {So, when you suspect a neoplasm of the prostate you get your sample through trans-rectal core biopsy of the peripheral zone from different positions (upper, lateral, middle, etc. Treat as 3D)}
- **Central:** is in the center of the prostate and cancer does not originate there often.
- **Transitional:** is above the central zone and is a **common site for benign prostatic hypertrophy**, a non-malignant condition of the prostate, but cancer may originate there as well but not as often as in the peripheral zone.



The normal histology:

The **normal** histologic appearance of prostate glands and surrounding fibromuscular stroma shows a small pink concretion (typical of the **corpora amylacea** seen in benign prostatic glands) appears in the gland just to the left of center. Note the **well-differentiated glands with tall columnar epithelial lining cells**. These cells **do not** have prominent nucleoli



Note:

- Carcinoma arises from the lining epithelium.
- Corpora amylacea, when seen in a crystalline rod shape and is reddish in color you suspect carcinoma of the prostate.

Prostate Pathology

1- Benign Prostatic Hyperplasia (BPH) (Nodular Prostatic Hyperplasia)

- **Extremely common lesion in men over age 50** (20% in men over age 40, up to 70% by age 60, and 90% by age 70). (gradual increase in size with progressing age)
- **Hyperplasia of glands and stroma**
- Fairly **large, well defined nodules**
- Related to the action of **androgen**
- DHT, **Dihydrotestosterone** is the ultimate mediator for prostatic growth (1- proliferation of both stroma, and gland. The glands increase in number is mainly due the absence of apoptosis. 2- DHT comes from testosterone which is secreted by the interstitial cells of leyding under the influence of the anterior pituitary gland)
- **Prepubertal castration prevents BPH** (or if the male is with genetic diseases that blocks the androgenic activity)

Clinical Features:

- Occur in **only about 10%** of men with the disease.
- **Lower urinary tract obstruction.**
- Difficulty in starting the stream of urine (**hesitancy**) and **intermittent interruption of the urinary stream while voiding.**
- Some men may develop **complete urinary obstruction**, with **resultant painful distention of the bladder and, if neglected, hydronephrosis**
- **Symptoms** of obstruction are frequently accompanied by **urinary urgency, frequency, and nocturia**, all indicative of bladder irritation.
- The combination of **residual urine in the bladder and chronic obstruction increases the risk of urinary tract infections.**

NOTE: **Hydronephrosis:** means dilatation and distention of the renal pelvis and calyces

Morphology:

- The prostate weighs between **60 and 100 grams** (normal 20 gm).
- Almost exclusively in the **transitional zone** of the prostate gland
- **Nodules** vary in **color** and **consistency** (it could be muscular or fibrous, or cystic).
- The **hallmark** of BPH **is nodularity** due to glandular proliferation or dilation and to fibrous or muscular proliferation.
- Aggregation of **small to large to cystically dilated glands.**
- Needle biopsy doesn't sample the transitional zone where BPH occur.

Morphology: on gross



A normal prostate gland is about 3 to 4 cm in diameter. This prostate is enlarged due to prostatic hyperplasia, which appears nodular. Thus, this condition is termed either BPH (benign prostatic hyperplasia) or nodular prostatic hyperplasia.

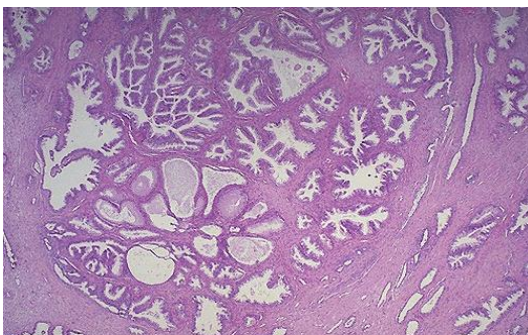


Nodules appear mainly in the **lateral lobes**. Such an **enlarged prostate can obstruct urinary outflow from the bladder and lead to an obstructive uropathy (the diameter here is >5 cm)**

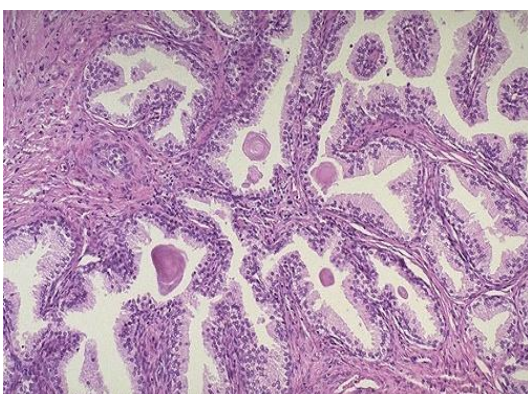


- The enlarged prostate gland seen here **not only** has enlarged **lateral lobes, but also a greatly enlarged median lobe that obstructs the prostatic urethra.**
- This led to obstruction with **bladder hypertrophy (due to difficulty in voiding)**, as evidenced by the **prominent trabeculation of the bladder wall seen here from the mucosal surface. (The mucosa is red and congested from the inflammation)**
- Obstruction with **stasis** also led to the **formation of the yellow-brown calculus (stone).**

Morphology: on microscopy



- BPH can involve both glands and stroma, though the former is usually more prominent. Here, a large **hyperplastic nodule** of glands is seen.
- (The glands can be highly folded with papillary formation, or cystically dilated)



- The glands are **well-differentiated** and still have **some** intervening stroma. The small laminated pink concretions within the glandular lumens are known as **corpora amylacea**.
- (The epithelial lining is normal with the presence of both outer basal and inner tall columnar with no atypia, however due to the crowding of cells, papillary formation occurred)

2- Prostatic adenocarcinoma

- Adenocarcinoma of the prostate is the **most common form of cancer in men**
- Second leading cause of cancer death (after lung cancer colon and prostate cancer come in 2nd place)
- Disease of **men over age 50** (with a peak incidence between 65 and 75)
- More prevalent among **blacks** in the USA

Etiology: several risk factors:

- **Age** (more common in men over 50 years old)
- **Race** (more common in black Americans than in whites, Asians or Hispanics)
- **Family history** (Hereditary, increased risk of the disease in first degree relatives of patients with prostate cancer)
- **Hormone level** (it doesn't develop in males castrated before puberty, indicating that androgens contribute to its development like in prostatic hyperplasia. Also they noticed that many prostatic carcinoma can be inhibited by orchiectomy or administration of estrogen as diethylstilbestrol)
- **Environmental influences** (it's more common in Scandinavian countries and uncommon in Japan and other Asian countries. Males emigrants who moved from Japan to America, for example, maintain a lower risk of prostate cancer but the risk of the disease is intermediate in subsequent generations because of the environmental influences)
- **Androgen** are believed to play a role in the pathogenesis **as explained previously**

NOTE: From Robbins

- Latent cancers of the prostate are more common than those that are clinically apparent (symptomatic) by 50% in males over 80 years old.
- The function of hormones in the pathogenesis of prostatic carcinoma is not fully understood.
- Orchiectomy: surgical procedure to remove one or both testicles in men.

Morphology:

- 70% arises in the **peripheral** zone of the gland
- **Palpable** in rectal exam
- cross-section of the prostate the neoplastic tissue is **gritty and firm**
- Irregular **yellowish nodules**.
- Prostate glands containing adenocarcinoma are not necessarily enlarged.
- Adenocarcinoma may also **coexist with hyperplasia**. However, prostatic hyperplasia is **not a premalignant lesion** (prostatic hyperplasia will never turn into malignancy but it can be associated with adenocarcinoma).



NOTE: From Robbins

- Because of the peripheral location, prostate cancer is less likely to cause urethral obstruction in its initial stages unlike nodular hyperplasia.
- Early lesions appear as ill-defined masses beneath the capsule of the prostate.
- On cut surface, foci of carcinoma appear firm, grey-white to yellow lesions that infiltrate the adjacent gland with ill-defined margins.

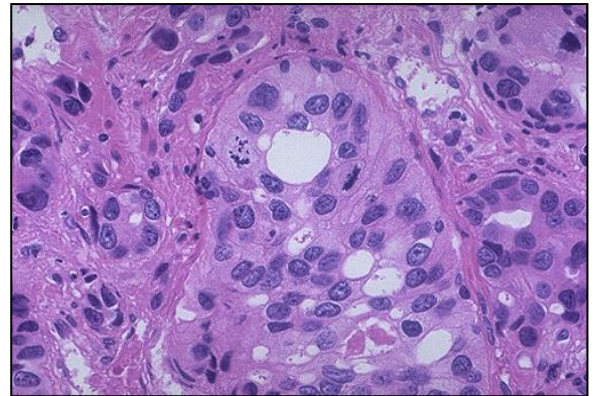
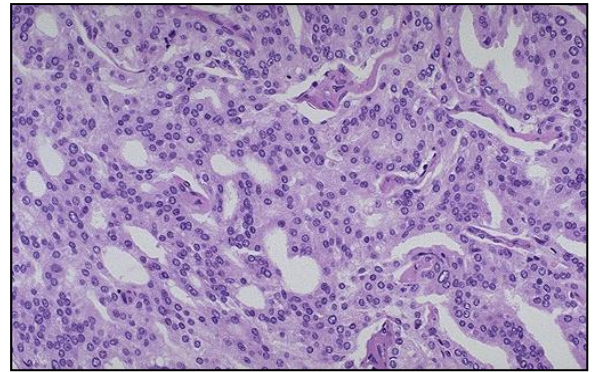
Histopathological features:

- The glands are typically **smaller** than benign glands and are lined by a **single uniform layer** of **cuboidal** or **low columnar epithelium**.
- In contrast to benign glands, prostate cancer glands are more **crowded**, and characteristically **lack branching and papillary infolding**.
- The **outer basal cell layer** typical of benign glands **is absent**. **By immunohistochemical staining**.
- **Nuclei are large** and often contain one or more large **nucleoli**.
- **Peri-neural invasion** is common and typical.

Under the microscope:

- At high magnification, the neoplastic glands of prostatic adenocarcinoma are still recognizable as glands, but there is no **intervening stroma** (little or no stroma at all) and the nuclei are **hyperchromatic**.
- Poorly differentiated prostatic adenocarcinoma demonstrates cells with nucleoli and mitotic figures.

(At high degree of anaplasia: irregular ragged glandular structure, papillary or cribriform epithelial structures and in extreme cases, sheets of poorly differentiated cells are present)



Spread of prostatic Adenocarcinoma:

- By **direct local invasion** and through **blood** stream and **lymph**.
- **Local extension** most commonly involves the **seminal vesicles and the base** of the urinary bladder.
- **Hematogenous** extension occurs chiefly to the bones.
- The bony metastasis are typically **osteoblastic** (In metastases of lung cancer or colon foci in bone tissue always appear translucent but in prostatic carcinoma bone metastases are more commonly osteoblastic –bone producing- lesions which make the foci more dense. It can be osteolytic -bone destructive- lesions but it's infrequent).

REMEMBER:

-The presence of osteoblastic metastases in an older male is strongly suggestive of advanced prostatic carcinoma

In prostatic adenocarcinoma: neoplastic glands are lined by single layer of cuboidal cells or low columnar epithelium, and the glands lie "back to back" with absence of stroma and branching/papillary infolding. Also small crowded neoplastic cells have pleomorphic features (abnormal mitosis, hyperchromatic nuclei,..) and it's invasive.

In Benign prostatic hyperplasia: hyperplastic glands are lined by inner tall columnar epithelial cells and a peripheral layer of outer flattened basal cells, and the crowding of proliferative epithelium **results in papillary projections and branching in some glands**. The lumens of the glands contain protienaceous secretory material "Corpora amylacea". The glands are surrounded by proliferating stroma **which mainly causes the nodularity**.

NOTE: From Robbins

- Microscopically: Most prostatic carcinomas are adenocarcinomas that exhibit variable differentiation. The better differentiated lesions are composed of small glands that infiltrate adjacent stroma in an irregular haphazard fashion.
- **Important:** in contrast to normal and BHP, the glands in carcinomas lie "**Back to back**" and appear to dissect sharply through the native stroma. Also, basal cell layer and papillary infolding are all absent.
- Metastases to regional pelvic lymph nodes may occur early.
- Locally **advanced** cancers often infiltrate the seminal vesicles and periurethral zones and may invade the adjacent soft tissues and the wall of the urinary bladder.
- Denovilliers fascia is a CT layer separates the lower genitourinart structures from the rectum, and prevents the growth of the tumor posteriorly. Therefore, invasion of the rectum in prostatic Adenocarcinoma is less common than the invasion of other contiguous structures.
- Glands adjacent to areas of invasive carcinoma of the prostate often contain foci of epithelium atypia or PIN (prostatic intraepithelial neoplasia). And because of PIN frequent coexistence with infiltrating carcinoma, it has been suggested as a probable precursor to carcinoma of the prostate. And according to the degree of atypia it's divided into high grade and low grade PIN. High grade PIN shares molecular changes with invasive carcinoma, making PIN in this case an intermediate but normal and frankly malignant tissue.

Grading and Staging of Prostatic Adenocarcinoma

- **Gleason grading system** is the best known for grading
- **Five grades** on the basis of **glandular pattern** and **degree of differentiation** as seen under low magnification
- Grading is of particular importance in prostate cancer, because it is the best marker, along with the stage, for predicting prognosis
- **Staging** in prostate cancer depends on the **TNM** system (also by clinical examination, surgical exploration, radiographic imaging techniques, and histologic grading and levels of tumor markers. Anatomic extent of the disease and histologic grade influence the therapy and correlate well with its prognosis)

NOTE:

Gleason grading system is used to help evaluate the prognosis of men with prostate cancer.

-A Gleason score is given to prostate cancer based upon its microscopic appearance. Cancers with a higher Gleason score are more aggressive and have a worse prognosis.

-Gleason Grade can be low, intermediate or high grades based upon the Gleason Score which is interpreted from the Gleasons pattern.

-**Gleason score is based on the sum of two numbers: the first number is the score of the most common tumor pattern, the second number is the score of the second most common pattern. If there are three patterns the first number is the most common and the second is the one with the highest grade. For example, if the most common tumor pattern was grade 3, but some cells were found to be grade 4, the Gleason Score would be $3+4 = 7$ (the doctor used similar example to this to explain the summation process)**

-The Gleason Score ranges from 2 to 10, with 10 having the worst prognosis.

-The low grade tumors are those with a score of 5 or below Intermediate grade with a score of 6, and high grade of 7 or more till 10

TNM: which evaluates the size of the tumor, the extent of involved lymph nodes, and any metastasis (distant spread) and also takes into account cancer grade (Gleason grading system).

Clinical course of Prostatic Adenocarcinoma:

- **Microscopic cancers** are **asymptomatic**, discovered **incidentally** (usually during histologic examination of prostate tissue removed for nodular hyperplasia).
- Patients with clinically **localized disease** do not have urinary symptoms.
- Most arise peripherally, away from urethra, therefore, **urinary symptoms occur late**.
- Careful **digital exam** may detect some early cancers.
- **PSA** (Prostate Specific Antigen) has been used in the diagnosis and management of prostate cancer.
- PSA is **organ specific** but **not cancer specific**.
- PSA could be increased in BPH (also after digital examination and prostatitis).

NOTE:


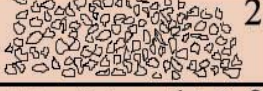



PSA is a 33-kD proteolytic enzyme produced by both normal and neoplastic prostatic epithelium.

- Normally, PSA is secreted in high concentration into prostatic acini and hence into seminal fluid, where it increases sperms motility by maintaining seminal secretions in a liquid state.

- Normal upper limit of PSA is 4.0ng/L. cancer cells produce more PSA but any condition that disrupts the normal architecture of the prostate can cause an increase in PSA (BPH, Prostatitis). Although serum PSA tend to be higher in men with carcinomas than in those with nodular hyperplasia. But in a minority of cases of prostatic cancer, especially those confined to the prostate, serum PSA is not elevated. Because of these problems with sensitivity and specificity, PSA is of limited value when used as isolated screening test for prostate cancer. But its diagnostic value enhanced when used in conjunction with other procedures such as, digital rectal examination, transrectal sonography and needle biopsy. On the other hand, PSA serum level has great value in monitoring patients after treatment of prostate cancer (increase of PSA here indicates recurrence and/or metastases).

Treatment of Prostatic Adenocarcinoma:

- **Combination of Surgery, radiotherapy and hormonal therapy** (surgical or pharmacologic castration, estrogens, androgen receptors blocking agents have all been used to stop the growth of disseminated lesions. hormonal therapy has a central role in the treatment of advanced carcinoma).
- **90% of treated patients expected to live for 15 years.**
- **Currently the most acceptable treatment for clinically localized cancer is radical surgery.**
- **Locally advanced cancers can be treated by radiotherapy.**
- **Hormonal therapy (Anti-androgen therapy)** (because most prostate cancer are androgen sensitive and are inhibited to some degree by androgen ablation) could induce remission after a period of time.

Gleason Scale		Well differentiated	Prostate Cancer	TNM staging
	1	Small, uniform glands	T (tumor)	TX: tumor cannot be assessed T0: no evidence of primary tumor T1: tumor not clinically apparent T1a: tumor found in resected specimen (<5%) T1b: tumor found in resected specimen (>5%) T1c: tumor found at biopsy for elevated PSA T2: tumor confined to prostate T2a: tumor involves one lobe of prostate T2b: tumor involves both lobes of prostate T3: tumor palpable, extends beyond capsule T3a: tumor extends beyond capsule (unilateral, bilateral) T3b: tumor invades seminal vesicles T4: tumor is fixed or invades adjacent anatomy (other than seminal vesicles)
	2	More space between glands		
	3	Infiltration of cells from glands at margins		
	4	Irregular masses of cells with few glands		
	5	Lack of glands, sheets of cells		
			M (metastasis)	
		Poorly differentiated		

Summary from Robbins

Nodular hyperplasia the prostate

-Nodular hyperplasia of the prostate is characterized by Benign proliferation of stromal and glandular elements. DHT, an androgen derived from testosterone is the major hormonal stimulus for proliferation.

-Nodular hyperplasia most commonly affects the inner periurethral zone of the prostate, and the nodules compress the prostatic urethra. Microscopically, been the nodules have variable proportions of stroma and glands. Hyperplastic glands are lined by two cell layers: an inner columnar layer and an outer layer composed of flattened basal cells.

-Clinical symptoms are seen in 10% of affected patients and include hesitancy, urgency, nocturia and poor urinary stream. Chronic obstruction predisposes to recurrent urinary tract infections. Acute urinary obstruction may occur.

-Carcinoma of the prostate is a common cancer of older men between 65 and 75 years of age. It is more common in American blacks than in Caucasians.

-Carcinoma of the prostate arise most commonly in the outer, peripheral glands, and maybe palpable by rectal exam. Microscopically, they are adenocarcinomas with variable differentiations and anaplasia. Neoplastic glands are lined by a single layer of cells. Grading of prostate cancer by the Gleason system correlates with an anatomic stage and prognosis.

-Most localized cancers are clinically silent and are detected by routine monitoring of PSA concentrations in older men. Advanced cancers present with metastases, frequently to the bone. -Serum PSA concentrations under 4 ng/mL are considered normal and values over 10 ng/mL are suggestive of prostate cancer.

-PSA levels may also be elevated above 4ng/ml in non-neoplastic conditions such as nodular hyperplasia, prostatitis, hence biopsy is required for diagnosis. Evaluation of PSA concentrations after treatment has great value in monitoring progressive and recurrent disease.

The disease	Causes	Location	Clinical features	Morphological changes
Benign Prostatic Hyperplasia	<ul style="list-style-type: none"> -Age: common in men > 50 yrs. of age -Hormonal: action of androgen (DHT is the mediator for its growth) 	In the transitional zone of the prostate	<ul style="list-style-type: none"> - LUT obstruction. - Hesitancy and interruption while voiding. - If complete UT obstruction, pain and hydronephrosis if neglected. - Symptoms of obstruction: urinary urgency, frequency, nocturia. - UTI because of residual urine in bladder and chronic obstruction. - Yellow brown calculus (stones) can be developed due to obstruction and stasis. 	<ul style="list-style-type: none"> - Prostate weighs 60-100 g. - Large, well defines nodules, vary in color and consistency (the hall mark of BPH) - Proliferation of glandular cells and fibromuscular stroma. - Central Corpora amylacea. - Well differentiated glands with tall columnar epithelial lining cells, do not have prominent nucleoli. Basal cell layer and papillary projections and branching in some glands are there.
Prostatic Adenocarcinoma	<ul style="list-style-type: none"> -Age: in men > 50 yrs. of age -Race: > black -Family history -Hormonal: Androgens -Environmental influences 	In the peripheral zone of the prostate	<ul style="list-style-type: none"> -Palpable in rectal examination. -Asymptomatic. -No urinary symptoms. -It can coexist with hyperplasia which might cause symptoms of BPH. -Can metastases to other tissues. 	<ul style="list-style-type: none"> -Firm and gritty cross-section of neoplastic prostate. Irregular yellowish nodules, the glands are not necessarily enlarged in PAC. - Small crowded glandular cells, lined by single layer of cuboidal or low columnar cells. - Basal cell layer, papillary projections and branching are all absent. - Nuclei are large with one or more large nucleoli.

Questions

1) A 78-year-old man was admitted to the hospital due to acute urinary tract obstruction. For the past few years, he has had recurrent bouts of cystitis. Two days before being admitted to the hospital, he could not urinate at all. What is the probable cause of bladder outlet obstruction in this patient?

- (A) Nephrogenicmetaplasia
- (B) Nodular prostatic hyperplasia
- (C) Prostaticadenocarcinoma
- (D) Urothelial cell carcinoma of the bladder

2) A 55-year-old man presents with urinary symptoms of urgency and frequency. Rectal examination reveals an enlarged prostate. Laboratory studies show an elevated serum PSA level of 4.9 ng/mL. The patient subsequently undergoes a prostate needle biopsy series, which demonstrates two cancer-positive needle cores: Gleason grades 2+2(4) and 3+2(5). Which of the following is the appropriate diagnosis?

- (A) Adenocarcinoma
- (B) Nodular prostatic hyperplasia
- (C) Prostate intraepithelial neoplasia
- (D) Squamous cell carcinoma

3) A 70-year-old man presents with pain in his back. Relevant clinical findings include a rock-hard, enlarged prostate palpated on rectal examination. Radiologic studies show multi- centric, osteoblastic lesions of the lumbar vertebral bodies. The patient is treated with leuprolide acetate (lupron), an inhibitor of gonadotropin release by the pituitary. Which of the following statements best summarizes the rationale for this treatment?

- (A) Leydig cells release tumor chemotactic factors.
- (B) Prostate carcinomas frequently metastasize to the gonads.
- (C) Tumor cells exhibit androgen-dependent growth.
- (D) The tumor is well known to invade the testes.

Answers:

- 1- B
- 2- A
- 3- C

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If there is any mistake or feedback please contact us on: 432PathologyTeam@gmail.com

