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Prostate

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

Lecture Four

Objectives:

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

A. Understand the basic anatomical relations and zones of the prostatic gland.

B. Know the epidemiology, pathogenesis and histopathologic features of benign prostatic hyperplasia and carcinoma of the prostate.

References: Lecture slides, Robbins & Robbins Review

Revised by

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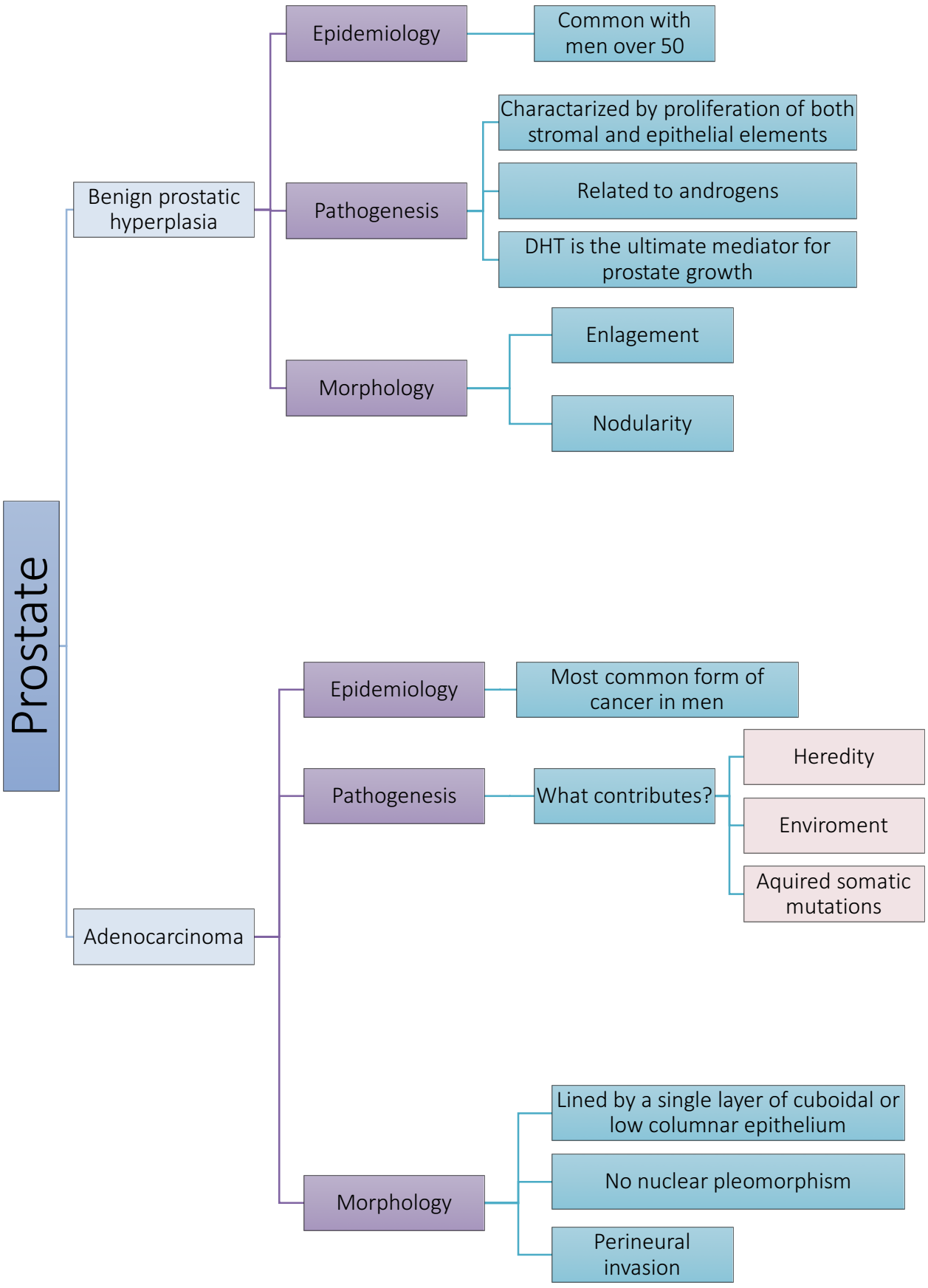
Red: Important. Grey: Extra Notes Doctors Notes


Prostate
Benign prostatic hyperplasia
Epidemiology
Common with men over 50
Pathogenesis
Charactarized by proliferation of both stromal and epithelial elements
Related to androgens
DHT is the ultimate mediator for prostate growth
Morphology
Enlagement
Nodularity
Adenocarcinoma
Epidemiology
Most common form of cancer in men
Pathogenesis
What contributes?
Heredity
Enviroment
Aquired somatic mutations
Morphology
Lined by a single layer of cuboidal or low columnar epithelium
No nuclear pleomorphism
Perineural invasion

Benign Prostatic Hyperplasia (BPH):

"AKA benign nodular hyperplasia[1]"

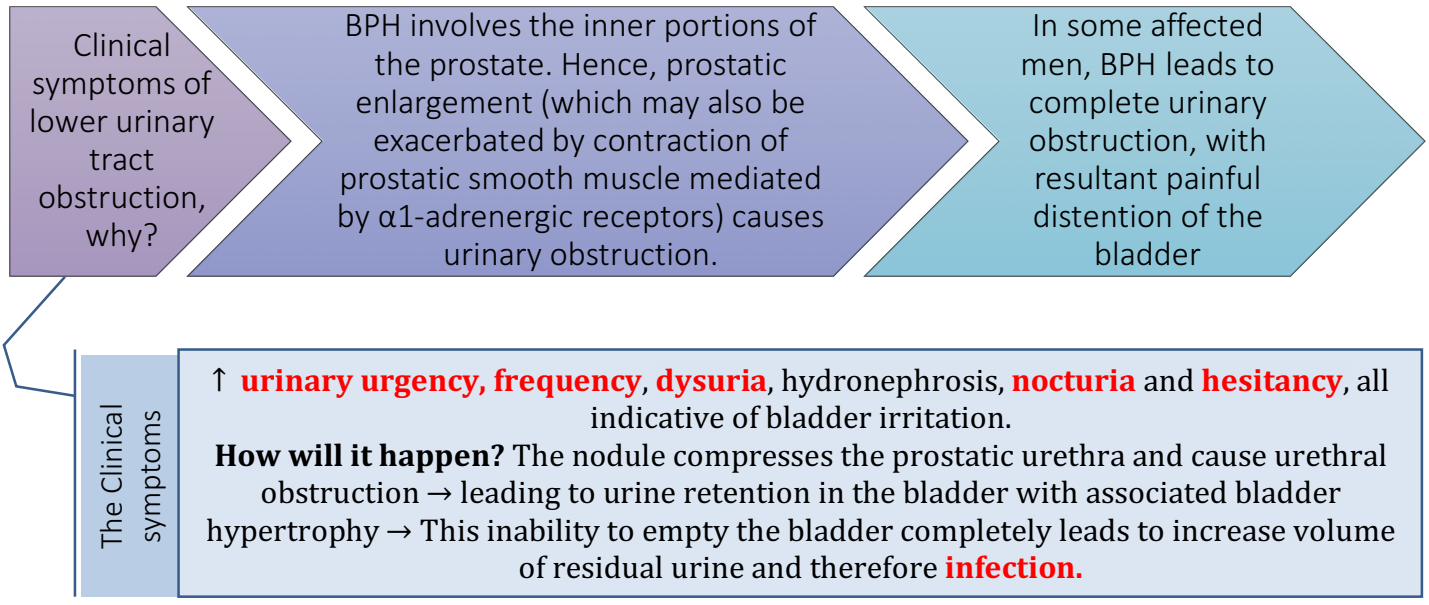
- Characterized by proliferation of both stromal and epithelial elements, with resultant enlargement of the gland and, in some cases, urinary obstruction.
- Extremely common lesion in men over age 50.
- Its frequency rises progressively with age, 20% in men > 40yrs, up to 70% by age 60, and 90% by age 80.

Pathogenesis: The essential cause is unknown

- It is related to the action of androgen; hence, it does **not** occur in males castrated[2] before the onset of puberty or in men with genetic diseases that block androgen activity.
- **Dihydrotestesterone (DHT)** it is the main cause of hyperplasia is the ultimate mediator for prostatic growth. It increases the proliferation of stromal cells and inhibits epithelial cell death. Therefore DHT is implicated in the pathogenesis of both (BPH) and prostate cancer.
  - How? DHT binds to nuclear androgen receptors, which regulate the expression of genes that support the growth and survival of prostatic epithelium and stromal cells. Although testosterone can also bind to androgen receptors and stimulate growth, **DHT is 10 times more potent.**
- Testosterone is converted to (DHT) **by 5-alpha reductase enzymes**.

Clinical Features:

Occur in only about 10% of men. Some patients present with symptoms of lower urinary tract obstruction (discussed below) & Some only present with acute urinary retention.



[1] It is important to know that the prostate have two lining epithelium myoepithelial cells on the outside and columnar cells inside once the myoepithelial lining disappear the gland is considered malignant.
[2] Remove the testicles

Morphology

Gross

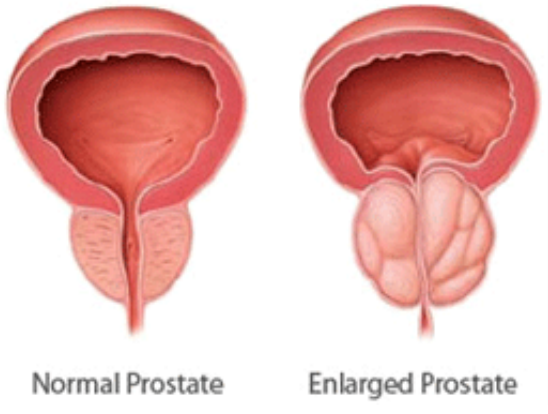
- The prostate is enlarged, weighs between 60 and 100 grams.
- The hallmark is **nodularity** due to **glandular** and **fibro-muscular** proliferation.
- Nodular hyperplasia begins in the **inner** aspect of the prostate gland, the transition zone. (It's **not** a premalignant lesion).
- Cut-section shows nodules which vary in size, color and consistency depending on which element is **proliferating** more (glandular or fibro-muscular).
- It compresses the wall of the urethra resulting in a **slit-like orifice.** Once the nodules become large they compress the prostatic urethra causing either partial, or complete **obstruction** of the urethra.
- In some cases, hyperplastic glandular and stromal elements lying just under the epithelium of the proximal prostatic urethra may project into the bladder lumen as a pedunculated mass, producing a **ball-valve type of urethral obstruction**.

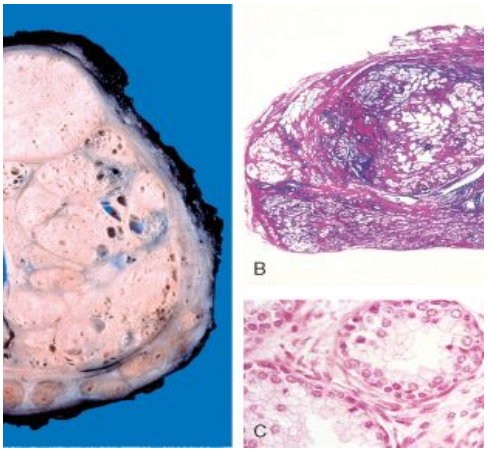
Microscopically

- Hyperplasia of glands and stroma results in large nodular enlargement in the periurethral region of the prostate. In the inner, transitional zone of the prostate.
- The main feature of BPH is nodularity; these nodules are made up of hyperplastic glands and hyperplastic stroma. The nodules can either be:
  - **Purely stromal nodules** composed mainly of **fibromuscular element.**
  - **Fibroepithelial** with **both** glandular and fibromuscular component. There is aggregation of small to large to cystically dilated glands, lined by two layers of epithelium surrounded by fibromuscular stroma.
- The glandular lumina often contain inspissated, proteinaceous secretory material known as **corpora amylacea**.
- Diagnosis of BPH **cannot** be made on needle biopsy. Why? Needle biopsy doesn't sample the transitional zone where BPH begins and occurs, it's made up on radiology only.

Treatment

- Drugs that act as inhibitors of 5-alpha reductase, have an important role in the prevention and treatment of BPH and prostate cancer.
- Initial treatment is pharmacologic, using targeted therapeutic agents that inhibit DHT formation (Finestride) or that relax smooth muscle by blocking alpha adrenergic blockers (Flomax).
- Mild cases of BPH may be treated with α-blockers and 5-α-reductase inhibitors
- Moderate to severe require transurethral resection of the prostate (TURP)





Prostatic Adenocarcinoma (PA):

- The **most common form** of cancer in men, disease of men over age 50.
- More prevalent among African Americans.
- These tumors show a wide range of clinical behaviors
- **Risk factors:** Age, race, family history, hormone level (androgens), environmental influences, and acquired somatic mutations.
- **Androgens** are believed to play a major role in the pathogenesis.
- Just like BPH, cancer of the prostate does not develop in males castrated before puberty, indicating that androgens somehow play a role in prostate cancer development.
- Notably, tumors resistant to anti-androgen therapy often acquire mutations that permit androgen receptors to activate the expression of their target genes even in the absence of the hormones.

Pathogenesis: (A bunch of factors contribute; they are as follows)

- **Heredity**: there is an ↑ risk among first-degree relatives of patients with prostate cancer.
- **Environment**: specific dietary component's relationship to PA risk is unclear.
- **Acquired somatic mutations**:
  - Gene rearrangements that create fusion genes consisting of the androgen-regulated promoter of the TMPRSS2 gene and the coding sequence of ETS family transcription factors **(TMPRSS2-ETS fusion genes).**
  - The **most common** are mutations that inactivate the tumor suppressor gene **PTEN**, which acts as a brake on **PI3K** activity.

Morphology	Info	▪ 70% arises in the peripheral zone of the posterior part of the gland ▪ Tumor is firm, gray-white, gritty and is palpable on rectal exam. ▪ Spread by direct local invasion and through blood stream and lymph ▪ Local extension most commonly involves the periprostatic tissue, seminal vesicles and the base of the urinary bladder (leading to ureteral obstruction)
	Microscopically	▪ Most lesions are adenocarcinomas that produce well-defined gland patterns. ▪ More advanced lesions appear as firm, gray-white lesions with ill-defined margins that infiltrate the adjacent gland ▪ The malignant glands are lined by a single layer of cuboidal or low columnar epithelium with large nuclei and one or more large nucleoli. Nuclear pleomorphism is **not** marked. The outer basal cell layer typical of benign glands is absent. No branching or papillary infolding. Mitotic figures are uncommon. ▪ Commonly there is perineural invasion. ▪ With increasing grade, irregular or ragged glandular structures, cribriform glands, sheets of cells, or infiltrating individual cells are present. ▪ In approximately 80% of cases, prostatic tissue removed for carcinoma also harbors presumptive precursor lesions, referred to as high-grade prostatic intraepithelial neoplasia (HGPIN).

Metastasis

- Metastases first spread via lymphatics: initially to the obturator nodes and eventually to the para-aortic nodes.
- Hematogenous extension occurs chiefly to the bones. Bone metastasis particularly to the axial skeleton, is frequent late in the disease and is typically osteoblastic (bone-producing) commonly to the vertebra

Gleason Grading and Scoring

- It's a histological grading and scoring system for prostatic adenocarcinoma done on the microscopic level.
- There are five grades (1 to 5) depending on the degree and pattern of differentiation as seen microscopically (in which they range from, grade 1= well-differentiated to grade 5= very poorly differentiated).
- The two **most common** types of grades seen in the biopsy for each cancer case are added to produce a combined Gleason score. For example, if I have two biopsy samples one with grade 2 the other with the grade 4 the summation of these two grades gives us the score which in this case = 6. The higher the score the worse the prognosis.
- Very useful in predicting prognosis of the patient. The prognosis after radical prostatectomy is based on the pathologic stage, margin status, and Gleason grade
- Staging in prostate cancer depends on the TNM system. It is the most important indicator of prognosis.

Clinical Features

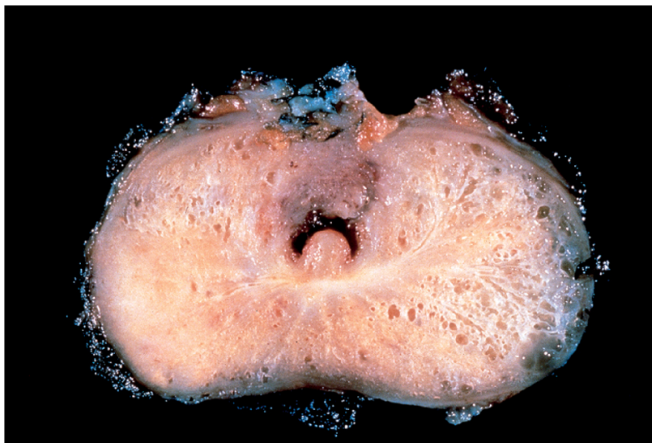
- Microscopic (very small size) cancers are asymptomatic and are discovered incidentally (when checking why PSA is high by needle biopsy).
- Most arise in the **peripheral zone**, away from urethra and therefore the urinary symptoms occur late (less likely to cause urethral obstruction in the initial stages).
- Occasionally patients present with back pain caused by vertebral metastases.
- Careful digital rectal examination may detect some early cancers (because of where they arise "peripherally" they might be palpated).
- PSA[3] (Prostate Specific Antigen) levels are important in the diagnosis and management of prostate cancer. However, 20% - 40% of prostate confined cancers have low PSA. **It doesn't gives us diagnosis but it gives us an idea about wither it is BPH or prostatic cancer.** If the patient shows symptoms of hyperplasia & PSA levels were high so it is BPH but if the patient showed no symptoms of hyperplasia & PSA level were high so it is prostatic adenocarcinoma. PSA is organ specific but not cancer specific because it could be increased in BPH and prostatitis.
- A transrectal **needle biopsy** is required to confirm the diagnosis[4].

Treatment

- Surgery, radiotherapy and hormonal therapy, 90% of treated patients expected to live for 15 years. The prognosis depends on the Gleason score and stage of tumor.
- Currently the most acceptable treatment for clinically localized cancer is radical surgery.
- Locally advanced cancers can be treated by radiotherapy and hormonal therapy. Hormonal therapy (Anti-androgen therapy) can induce remission.
- Advanced, metastatic carcinoma is treated by androgen removal treatment, either by orchiectomy or by hormonal anti-androgen therapy.

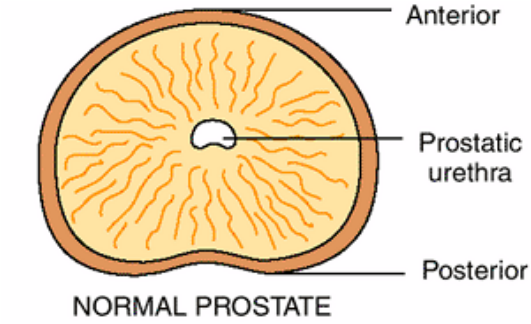
[3] **What is it?** PSA is a product of prostatic epithelium and is normally secreted in the semen. It is a serine protease whose function is to cleave and liquefy the seminal coagulum formed after ejaculation. In most laboratories, a serum PSA level of 4 ng/mL is the cutoff between normal and abnormal.

[4] We use it if we were suspecting malignancy.

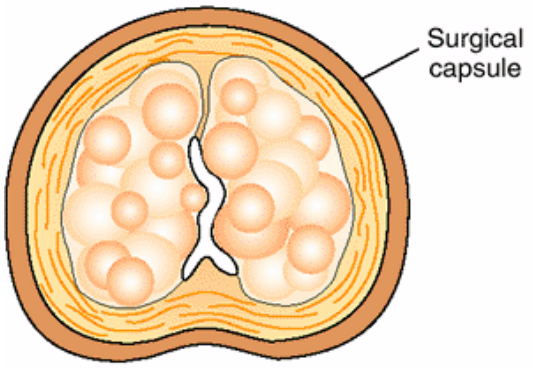


Prostatic intraepithelial neoplasia (PIN): you just have to remember the name only.

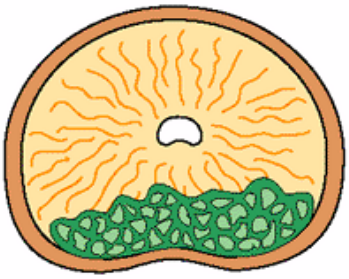
- PIN is the precursor lesion for invasive carcinoma. It can be low grade PIN or high grade PIN. (high grade PIN is like carcinoma in situ)
- PIN like carcinoma occurs in the peripheral zone.
- It is carcinoma in situ.



NORMAL PROSTATE



NODULAR PROSTATIC HYPERPLASIA


CARCINOMA OF PROSTATE

Now Check Your Understanding!

MCQs:

1. **On histologic examination the difference between benign glands and carcinoma is that:**
   A. Carcinoma is smaller than benign glands, and lined by single uniform layer of cuboidal epithelium.
   B. Carcinoma is smaller than benign glands, and lined by single uniform layer of columnar epithelium.
   C. Carcinoma is larger than benign glands, and lined by single uniform layer of cuboidal epithelium.
2. **Most prostate cancers arise in the:**
   A. In the center of the gland.
   B. In the inner gland.
   C. Peripheral (outer) glands.
3. **Prostate specific antigen is specific for:**
   A. Prostate cancer.
   B. Prostate disease.
   C. Prostate prostatic infarcts.
4. **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
   E. Urothelial cell carcinoma
5. **2- 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. Sertoli cells release tumor chemotactic factors.
   D. The tumor is well known to invade the testes.
   E. Tumor cells exhibit androgen-dependent growth.
6. **A 67-year- old man is found on rectal examination to have a single, hard, irregular nodule within his prostate. A biopsy of this lesion reveals the presence of small glands lined by a single layer of cells with enlarged, prominent nucleoli. From what portion of the prostate did this lesion most likely originate?**
   A. Transition zone
   B. Peripheral zone
   C. Periurethral glands
   D. Central zone

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

Thanks for checking our work! Good Luck.

Done by:

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سهى العنزي

سمر العتيبي

لميس آل تميم

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