Male genital tract and bladder pathology

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PSA

Glycoprotein; kallikrein related serine protease produced by secretory epithelium, PSA > 4 seen in 80% with histologically documented cancer but also in 25-30% with nodular hyperplasia, prostatitis, infarcts, prostatic massage, cystoscopy; elevated in 2 of 18 post-race marathon runners, Annual testing recommended for men 50+, men 40+ at increased risk

Nodular hyperplasia
Periurethral nodules may compress urethra and cause obstructive symptoms
Present in 20% of men at age 40, 50% at age 50, 70% at age 60
No correlation between histology and symptoms (50% with histologic disease have clinical enlargement of prostate, 50% of these have symptoms)

Physiology: requires intact testes; testosterone and dihydrotestosterone bind nuclear androgen receptors in stromal and epithelial cells, causing growth factor activation
Estradiol, increased in aging men, may also increase androgen receptors

Symptoms: urinary tract infection, obstruction, acute urinary retention, bladder hypertrophy, trabeculation, diverticula
NOT associated with prostatic adenocarcinoma!

Treatment: transurethral resection of prostate (TURP, #2 most common surgery after cataracts in men); suprapubic prostatectomy; androgen antagonists, smooth muscle relaxers (5 alpha reductase inhibitors decrease DHT and in many cases, prostatic volume and symptoms)
Nodules appear mainly in the lateral lobes. Enlarged lateral lobes and a greatly enlarged median lobe that obstructs the prostatic urethra. Hypertrophy, prominent trabeculation of the bladder.

**Gross:** large, discrete, periurethral nodules; mean size of surgical prostatectomy specimens is 100g; (normal: 20g)
Micro: Hyperplasia of glandular and stromal tissue with papillary buds, infoldings and cysts; associated with squamous metaplasia and infarction; begins around urethra where ejaculatory ducts enter (transitional or periurethral zone); stromal changes are increased smooth muscle.
Basal cell layer is continuous!
Prostatic intraepithelial neoplasia (PIN)

Low grade PIN
Recommended to **NOT** put on surgical pathology report since variability in diagnosis exists even between experts

High grade PIN
Present in 14% of patients in a community hospital study
Indicates 33% risk of carcinoma in subsequent biopsies
Low risk for cancer (13%) if two subsequent biopsies are negative
Number of cores with high grade PIN predicts risk of subsequent cancer (1 core-30%, 3 cores-40%, 4+ cores-75%),
Intermediate-to-large size preexisting glands displaying nuclear and nucleolar enlargement and fragmented basal cell layer

benign glands: continuous basal cell layer;
high-grade PIN glands: fragmented basal cell layer;
malignant glands: complete lack of basal cell layer
Prostatic carcinoma

**Epidemiology:** (#2 after lung cancer)
20% of American men are diagnosed with prostate cancer during their lifetimes; 3% die
99% with clinical disease are age 50+
Latent cancers: 20% in men in 50’s, 70% in men in 70’s;
Not associated with sexually transmitted disease, smoking, occupational exposure, diet, nodular hyperplasia

**Clinical:** detect with rectal exam, transurethral ultrasound, **elevated PSA**

**Core biopsies** "Six pack", 6 samples from selected portions of prostate via a 18-gauge biopsy, has false negative rate of 12% due to sampling error
Transrectal biopsies more accurate than transperineal biopsies
Adenocarcinoma of peripheral ducts and acini

Tumor distribution:
70% arise from peripheral zone (posterior, lateral, anterior), usually spares periurethral zone except in late stages

Tumor extension:
local invasion via seminal vesicle and bladder base

Metastases:
usually skeletal system, lung/pleura, liver, adrenals and lymph nodes

Bony metastases:
multiple, usually osteoblastic not osteolytic, usually lumbar spine, sacrum or pelvis due to tumor spread via Batson's vertebral venous plexus

Treatment:
radical prostatectomy, external beam radiation therapy, watchful waiting (for low grade tumors, localized tumor or limited life expectancy), chemotherapy or hormonal therapy (LHRH analogs, antiandrogens, orchiectomy) for metastatic disease

Most tumors are androgen sensitive, use PSA to monitor tumor response

Prognostic factors:
independently important variables are stage, Gleason score, surgical margins, preoperative PSA

Gleason grades
Grade is 1 to 5, based on glandular differentiation at low power; Score is 2 to 10, based on Gleason grade for first and second most predominant patterns

Grade 1 - single, separate, closely packed, uniform round glands
Grade 2 - like grade 1 but more variability in gland shape
Grade 3 - single, separate, much more variable glands with poorly defined edge
Grade 4 - chopped up fused glands
Grade 5 - carcinomas with minimal glandular differentiation
**Varicocele**
Abnormal dilation and tortuosity of veins in pampiniform plexus of spermatic cord, probably due to insufficiency of venous valves
Often associated with infertility; after treatment, 40-55% are fertile
90% on left; 10% bilateral
**Treatment:** ligation or occlusion of left spermatic vein
**Micro:** variable thickening of venous wall with fibrosis, decreased spermatogenesis in tubules with germ cell degeneration and increased Leydig cells

Varicocele treatment has traditionally involved open surgery. In recent years, however, a safe and effective nonsurgical alternative called varicocele embolization is becoming the treatment of choice for many patients.
Hydrocele
Accumulation of clear serous fluid between visceral and parietal layers of tunica vaginalis; associated with trauma and epididymitis
Diagnose by transillumination
Micro: loose connective tissue with mesothelial lining; if long-standing, may have chronic inflammatory infiltrate, fibrosis, squamous metaplasia.

Large hydrocele of the testis. A hydrocele must be distinguished from a true testicular mass, and transillumination may help, because the hydrocele will transilluminate but a testicular mass will be opaque.
Cryptorchidism
Permanent retention of testis outside scrotum
Due to complete or incomplete failure of intra-abdominal testes to descend into scrotal sac, occasionally associated with other GU malformations such as hypospadias. Occurs in 10% of newborn boys, 1% of 1 year old boys; associated with trisomy 13. Cryptorchid testis usually (80%) found in inguinal canal; usually is no apparent hormonal disorder, bilateral in 25% of cases. Associated with 5-50x increased risk of testicular cancer, usually seminoma. Orchiopexy (placement in scrotal sac) should be done before age 2-3 to reduce risk of malignancy.

**Micro:** marked hyalinization and thickening of tubular basement membrane, prominent Leydig cells, variable intratubular germ cell neoplasia.
Infertility

Causes: pretesticular, testicular, post-testicular

Pretesticular: extragonadal endocrine disorders (hypothalamic, pituitary, adrenal);
Testicular: little treatment currently available

Posttesticular: duct obstruction (congenital, inflammatory, postsurgical);
surgical treatment often successful since spermatogenesis is normal

Evaluation: history and physical examination, semen analysis, detection of anti-sperm antibodies, sperm function tests. Testicular biopsy is helpful for azoospermia (no sperm present) without endocrine abnormalities.

Biopsy results for azoospermia: Germ cell aplasia/Sertoli cell only syndrome (29%): tubular basement membrane thickening, no germ cells, usually normal number of Leydig cells; Spermatocytic arrest (26%): usually early (no spermatids, no spermatozoa); Generalized fibrosis (18%); Normal (27%)

(spermatogonia, primary spermatocytes, secondary spermatocytes, spermatids, spermatozoa)
Klinefelter’s syndrome
47XXY, reduced body and pubic hair, gynecomastia in 40-80%,
Increased risk of breast cancer
**Gross:** small, firm testes
**Micro:** reduced number of intratubular germ cells, some tubules are Sertoli cell only; also tubular sclerosis, Leydig cell nodules (appear hyperplastic due to tubular atrophy), focal spermatogenesis

![Image: hyalinized seminiferous tubules and pseudo-adenomatous clusters of leydig cells]
Granulomatous orchitis
Rare; sudden onset of tender testicular mass, variable fever, usually men 40-59 years
Benign, although also associated with seminoma
Recommend cultures to rule out infectious process (TB, syphilis, sarcoidosis, leprosy)
**Gross:** solid, unilateral, nodular enlargement of testis; resembles lymphoma
**Micro:** lymphocytes and plasma cells infiltrate interstitium and surround seminiferous tubules; histiocytes that resemble but are not actual granulomas
Testicular neoplasms
Less than 1% of all malignancies in males; highly curable even if advanced
95% are germ cell tumors (aggressive but curative), 5% are sex cord-stromal tumors
(usually benign but associated with hormonal syndromes);
Lymphatic spread common to periaortic, iliac, mediastinal and supraclavicular nodes,
not to inguinal nodes
Hematogenous spread to liver, lungs, brain, bones
Serum tumor markers are used for staging (S category), assessing tumor burden (LDH),
response to therapy (AFP, hCG); obtain immediately after orchiectomy and if elevated,
recheck to determine if elevation persists (indicates residual disease)

Classification
WHO classification
Intratubular germ cell neoplasia
Seminoma (classic, tubular)
Spermatocytic seminoma
Nonseminomatous germ cell tumors
   Embryonal carcinoma
   Yolk sac tumor / endodermal sinus tumor
   Teratoma: mature, immature, malignant
   Choriocarcinoma
   Mixed
   Polyembryoma
   Diffuse embryoma

Practical classification
Seminoma or nonseminomatous germ cell tumor (NSGCT)
Biologically, seminoma and NSGCT are closely linked
but treatment is different
Patient with mixed seminoma and NSGCT
Seminoma
30-50% of testicular germ cell tumors
Mean age 40 years vs. 25 years for nonseminomatous germ cell tumors (NSGCT);
In ovary, called dysgerminoma
Also present in mediastinum, pineal gland,
40% have increased serum PLAP (placental-like alkaline phosphatase)
70% of patients have stage 1 disease
May metastasize to lymph nodes or bone; late hematogenous spread may occur
**Treatment:** radiation therapy (very radiosensitive), cisplatin based chemotherapy
**Prognosis:** 95% cure rate for stages 1 or 2
**Gross:** bulky, homogenous gray-white with lobulated and bulging cut surface,
usually well demarcated

Diffuse sheets of tumor cells with clear cytoplasm separated by fibrous trabeculae containing lymphocytes
Embryonal carcinoma
Usually age 20-30's
Pure tumors represent 2% of germ cell tumors, but 85% of NSGCT have embryonal carcinoma component
65% have metastases at diagnosis, often with associated symptoms (back pain, dyspnea, neurologic symptoms)
Treatment is controversial as 97% of stage I are disease free after orchiectomy; some recommend watchful waiting; others retroperitoneal lymph node dissection and chemotherapy if nodal metastases are present
For advanced disease, give cisplatin-based chemotherapy and remove residual masses
**Gross:** Usually doesn't replace entire testes; variegated or pale-gray, poorly demarcated with hemorrhage and necrosis; usually invades tunica albuginea
**Micro:** solid, pseudoglandular, alveolar, tubular or papillary patterns; primitive epithelial type cells with minimal features of differentiation
Leydig (interstitial) cell tumors
1-3% of testicular tumors, 3% are bilateral
Any age, mostly 20-60 years old
Secrete androgens, estrogens or corticosteriods
10% in adults have malignant behavior with metastases to lymph nodes, lung, usually are large (> 5 cm) with necrosis, vascular invasion, nuclear atypia, numerous mitoses
**Symptoms:** gynecomastia with virilism, testicular mass,
**Treatment:** orchiectomy, lymph node dissection if malignant
**Gross:** solid, well circumscribed nodules 5 cm or less, golden-brown homogenous cut surface

sheets, nests, cords of large, round cells with defined cell borders, eosinophilic cytoplasm and round central nuclei

Reinke crystalloids
Epididymitis
Primary cause of epididymal obstruction
Usually related to cystitis, prostatitis, urethritis that spreads through vas deferens or lymphatics
May cause testicular ischemia and necrosis, later scarring and infertility with preservation of Leydig cells and preserved sexual activity
**Acute disease:** epididymis enlarged, covered with fibrin, may contain pus and rupture
Brucellosis, Gonorrhea, Tuberculosis
Adenomatoid tumor
Most common tumor of epididymis, usually age 20-39 years, often painful
Similar tumor in spermatic cord, ejaculatory duct, fallopian tube and uterus
Mesothelial origin
May be peculiar form of nodular mesothelial hyperplasia instead of a neoplasm
Benign, even if it extends into testis
**Treatment:** resection is curative
**Gross:** circumscribed firm gray-white mass up to 5 cm, may be cystic
**Micro:** unencapsulated, cuboidal to flat cells form cords that are either epithelial like or form channels with dilated lumina simulating vessels; cells have cytoplasmic vacuoles
Squamous cell carcinoma
Rare in US (<1% of carcinomas in men vs. 10-20% in Asia [excluding Japan], Africa, South America)
Rare if circumcision at birth, more common if late circumcision (after age 10)
**Risk factors:** paraphimosis, phimosis and long foreskin, HPV 16 or 18 (although most cases are not related to HPV), smoking, psoriasis patients treated with UV B radiation
HPV present in 42% of penile carcinomas, but frequency varies by histologic type: squamous cell 35%, verrucous 33%, basaloid 80%, warty 100%
Most tumors arise from glans or inner foreskin near coronal sulcus as slow growing, irregular mass; patients occasionally present with inguinal nodal metastases with occult penile cancer due to severe phimosis or very small primary tumor
Usually age 40-70 years, median age 58 years
**Metastases:** inguinal and pelvic lymph nodes, liver, lung, heart or bone; 15% have metastases at diagnosis
5 year survival related to nodal involvement: 66% (not involved) vs. 27% (involved)
**Acute cystitis**

Common in young women of reproductive age and older men and women
May be caused by obstruction, cystocele or diverticula
May lead to pyelonephritis

**Causes:** *E. coli*, *Proteus*, *Klebsiella* or *Enterobacter* bacteria;
*Candida* or *Cryptococcus* in immunocompromised, *Schistosoma haematobium* in Egypt,
also adenovirus, chlamydia, mycoplasma
Noninfectious causes are chemotherapy, radiation therapy, trauma

**Gross:** hyperemic mucosa with variable exudate
Chronic cystitis

Gross: heaping of mucosa; red, friable, ulcerated mucosa

Micro: chronic inflammatory cell infiltrate; fibrous thickening of muscularis propria

Cytology: nuclei are enlarged with prominent nucleoli; variable cytoplasmic vacuoles

Reactive urothelial cells. Note the basaloid transitional cells near the top of the field and the binucleated superficial transitional cell (umbrella cell) near the bottom of the field. Enlarged nuclei with prominent nucleoli are the reactive features.
Granulomatous cystitis

Due to tuberculosis, post BCG (bacillus Calmette-Guerin) treatment for papillary urothelial carcinoma or post biopsy / resection
Heals by fibrous scarring

**Tuberculosis:** rare in most countries; often secondary infection from kidney; caseating granulomas with Langhans giant cells, mostly in lamina propria with mucosal ulceration

**BCG:** used to treat high grade papillary carcinoma or carcinoma in situ of bladder; induces chronic inflammation, superficial ulceration and noncaseating granulomas with active and chronic inflammation; changes may extend into prostate

**Post-biopsy / resection:** present in 14% with 2 surgical procedures; either necrotizing and palisading, resembling rheumatoid nodules, or foreign body type
Cystitis cystica and cystitis glandularis

Common incidental findings
Associated with longstanding chronic cystitis, bladder exstrophy, ureteral reimplantation, neurogenic bladder or other causes of mucosal irritation; may regress if cause of bladder irritation is removed

**Cystitis cystica:** Brunn’s nests that grow into lamina propria and are transformed into urothelium lining slitlike or cystic spaces;

**Cystitis glandularis of common type:** glands in lamina propria lined by columnar or cuboidal epithelium; more common than intestinal type

**Cystitis glandularis of intestinal type:** also called intestinal metaplasia; goblet cells present in cystitis cystica that resemble colonic epithelium;

**Gross:** irregular papillary lesions resembling papillary urothelial carcinoma; in trigone, also ureter and renal pelvis
Post-operative spindle cell nodule
Occurs several weeks to months after transurethral resection of bladder tumor in area of surgery. Similar to inflammatory / pseudosarcomatous myofibroblastic tumor, but with a history of surgery
Benign

Intersecting bundles of myo-fibroblastic cells in myxoid matrix. Increased mitotic activity, inflammatory cells, and hemorrhage are often present.
Inflammatory myofibroblastic tumor
Rare in bladder, more common at other sites (lung, soft tissue, bone)
IMT is terminology for neoplastic lesions;”
Similar to postoperative spindle cell nodule, but **without** a history of surgery
Usually middle aged women
Pain, fever, weight loss, anemia, thrombocytosis,
Benign, but frequently misinterpreted as leiomyosarcoma or rhabdomyosarcoma
May recur locally, don’t metastasize
**Treatment:** conservative surgical excision

- **Features favoring inflammatory pseudotumor over sarcoma include**
  1) lack of significant nuclear atypia
  2) lack of necrosis
  3) Alk1 positivity
WHO/ISUP: World Health Organization / International Society of Urologic Pathologists consensus classification

Major changes from prior systems are that papillary urothelial carcinomas must exhibit atypia and carcinoma in situ need not be full thickness

WHO/ISUP grade correlates with tumor stage and recurrence

Has been validated by differences in recurrences and CK20, p53 and Ki-67 staining

**Classification:**

**Papillary urothelial neoplasms:**
papilloma, inverted papilloma,
papillary neoplasm of low malignant potential,
noninvasive papillary carcinoma-low grade,
noninvasive papillary carcinoma-high grade

**Urothelial carcinoma in situ**

**Invasive urothelial neoplasms:**
lamina propria invasion, muscularis propria invasion

**Infiltrative urothelial carcinoma (NOS)**
Infiltrative urothelial carcinoma with squamous differentiation
Infiltrative urothelial carcinoma with glandular differentiation

**Squamous cell carcinoma**

**Adenocarcinoma**
Papilloma
Controversial entity; restrictive diagnostic criteria (less than 1% of bladder tumors)
Benign
Micro: usually simple arrangement of well-formed papillary fronds
papillae usually small with scant stroma and slender fibrovascular cores
lined by normal appearing urothelium with prominent umbrella cells
normal polarity, no hyperplasia, no dysplasia, no fusion of adjacent fronds,
no necrosis, no mitotic figures
Recommended to avoid labeling these patients as having cancer
**Treatment:** simple excision

CK20: -  P53: -
Papillary urothelial neoplasm of low malignant potential
May arise in young patients
1/3 recur, 5% as higher grade; 10 year survival 95% or more
Rarely associated with invasion or metastases
**Micro:** orderly arrangement of cells within papillae with minimal architectural abnormalities and minimal nuclear atypia, regardless of cell thickness
mitotic figures if present are usually confined to basal layer
**Treatment:** resection, follow-up

CK20: + in a few cells  P53: -
Urothelial carcinoma
Also called transitional cell carcinoma (older term)
90% of bladder tumors are urothelial carcinoma
#5 most common type of cancer in US with 63,000 cases and 13,000 deaths/year
Can arise anywhere in bladder; often multifocal; some multiple tumors are independent and some have common origin

**Epidemiology:**
cigarette smoking (50-80% of cancers); Arylamines (2-naphthylamine);
*Schistosoma haematobium* (ova are deposited in bladder wall and cause chronic inflammatory response, squamous metaplasia, dysplasia; 70% are squamous cell carcinomas); phenacetin use (usually long term use in younger women), rarely cyclophosphamide with long term use

**Cytogenetics:** monosomy 9, 9p- (p16 INK4 / MTS1), 13q- (retinoblastoma gene), 14q-, 17p- (p53)
Low grade tumors may begin with 9p/-9q-; some acquire p53 and become invasive; high grade tumors may begin with p53 alterations
Polysomies 1 and 17 are more frequent in pT1 than pTa tumors

**Clinical course:** initial symptoms are painless hematuria, infection, 60% are single tumors (40% are multiple), 70% of tumors are localized to bladder
Tumors tend to recur (50% of low grade tumors recur vs. 80% of high grade), often at higher grade and different site.
Low grade papillary urothelial carcinoma

<5% risk of progression
50-65% recur, low risk of recurrence as high grade lesions, which may lead to invasion and death

Usually diploid, multicentric and noninvasive

Theories of multicentricity are (1) field effect: carcinogenic agents cause malignant transformation of multiple urothelial cells or (2) intramucosal spreading of tumor

**Micro:** papillary with central fibrovascular cores; orderly with recognizable variation of cytologic and architectural features, rare to numerous mitotic figures

**Treatment:** transurethral resection of bladder tumor (TURBT)

CK20: + more cells  P53: -
High grade papillary urothelial carcinoma

Usually aneuploid

15-40% rate of progression

May invade adjacent structures or regional lymph nodes; late dissemination to liver, lung,

**Micro:** predominantly disorderly appearance at low power with prominent architectural and cytologic abnormalities; disorganized epithelium, mitotic figures at all levels, associated with carcinoma in situ, dysplasia in adjacent urothelium

**Treatment:** radical cystectomy, variable chemotherapy or radiation therapy

CK20: + many cells  P53: +
Invasive urothelial carcinoma
Often diagnosed as de novo lesions, possibly originating from flat urothelial alterations
**Lamina propria (pT1):** invasion of lamina propria (pT1 vs. pTa) is subjective and usually not as important as invasion of muscularis propria.
**Muscularis propria (pT2):** assessment of muscularis propria invasion is very important, implies tumor infiltrating thick smooth muscle bundles
**Prognostic factors:** Stage most important, 5 year survival is 75% if T1, 50% for T2 and 20% for T3; Nodal involvement; Grading (high grade vs. low grade); Loss of E-cadherin expression and low p27/Kip1 is associated with poorer overall survival
**Micro:** wide range of morphologic differentiation, squamous differentiation common while glandular metaplasia is less common, can be papillary low and high grade (usualy pT1) whereas most pT2-4 carcinomas are non papillary and high grade.

**Macroscopy:**
can be papillary, polypoid, nodular, solid, ulcerative

**Treatment:** radical cystectomy, variable chemotherapy or radiation therapy
Carcinoma in situ
Also known as high grade intraurothelial neoplasia (HG IUN)
Usually a flat lesion, not papillary
Precursor of invasive cancer in many cases
20-80% of CIS patients develop invasive disease if left untreated
Associated with multifocal high grade invasive carcinoma
**Treatment:** bcg therapy, local resection or total cystectomy
**Micro:** flat lesion composed of cells with large, irregular, hyperchromatic nuclei, prominent nuclear pleomorphism, high N/C ratios, mitotic figures in mid to upper epithelium