GENITOURINARY PATHOLOGY
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Summation of essential points and references

Testis tumors (1A):

Testicular mass = malignant until proven otherwise
Difference between children and adults, pre and post-puberty
Young males, peak 25-30 years

95% = germ cell origin
ITGN = intratubular germ cell neoplasia, premalignant
Seminoma versus non-seminomatous tumors

Seminoma: 40-50% of GCTs (Germ cell tumors), peak = 35-45 yrs, LN mets, radiosensitive
IHC: PLAP, e-kit; tumor cells (larger) with clear cytoplasm, smaller lymphocytes and connective tissue bands; 15% contain syncytiotrophoblastic cells with mild elevation of HCG
Pitfalls: regression with residual scar, granulomatous reaction

Embryonal carcinoma: common in mixed, peak 30 years, primitive malignant cells, frequent necrosis, IHC: keratin, PLAP, CK 30

Yolk sac tumor (aka endodermal sinus tumor): infants/young children (16-17 months) versus young adults (25-30 yrs)
Infants/children: most common testicular tumor, usually pure
Adults: mostly mixed
Morphology – highly diverse – usually “lace-like pattern
IHC: keratin, patchy AFP

Chorionicarcoma = biphasic tumor: syncytiotrophoblast (large, multinucleated) + cytotrophoblast (single nucleus, distinct cell border)
Hemorrhage, necrosis, vascular invasion common, may present with pulmonary mets, also brain, liver
Usually in mixed germ cell tumors
Very high HCG, worse prognosis than other germ cell tumors

Teratoma: tissue derived from ecto-, endo-, and mesoderm
Pre- versus post pubertal
Post-pubertal: common in mixed germ cell tumors, metastatic even if pure, No benign teratomas post pubertal!!!
Pre-pubertal: 40% of testicular neoplasms, pure tumors, benign
Dermoid cyst = type of mature teratoma, rare in testis, common in ovary, skin and appendages
Epidermoid cyst – NO skin appendages

Sex cord-stromal tumors: Leydig cell and Sertoli cell

Leydig cell tumor: most common sex cord stromal tumor
Children 3-9 yo, adults: 2nd-6th decade
3% of testicular tumors
10% clinically malignant
Gynecomastia or precocious puberty
Gross: well circumscribed, golden-brown
Micro: pigment, IHC: inhibin, S-a00

Sertoli cell tumor: 1% of testicular neoplasms, gynecomastia
Features of Sertoli cells, cells arranged in tubules surrounded by basement membrane
IHC: inhibin, vimentin, keratins

Other testicular masses:
Lymphomas: interstitial pattern of involvement with sparing seminiferous tubules
IHC – lymphoma markers, most B cells, children – Burkitt’s, also plasmacytoma
Testicular involvement usually secondary
Older patients – 60s, bilateral 25%

Paratesticular tumors
Importance of tumor location: intratesticular versus paratesticular (during Frozen section!!!)
Mesothelial: adenomatoid tumor (benign), malignant mesothelioma
Sarcomas: children – embryonal rhabdomyosarcoma, adults – liposarcoma, leiomyosarcoma, MFH

Metastatic tumors to the testis:
Presenting manifestation in 10% of cases
Prostate carcinoma – 30%
Pulmonary carcinoma – 20%
Malignant melanoma
Colon, kidney, gastric and pancreatic carcinoma.

Prostate patholgy (1B)

Normal structure:

- Secretory (Acinar) cells
- Basal cells
- Urothelium – urethra, excretory ducts
- Endocrine/paracrine cells
- Stromal elements
"Capsule"
Zones: central, peripheral, transitional

Prostatic carcinoma:
- PSA - age related upper limit
- Early detection
- Rare <40yo
- AA higher
- Heredity
- Mets: regional LN, bones of pelvis, axial skeleton, mets to bone marrow with osteoblastic response

Carcinoma of Prostate (CAP)
- Acinar >95%

Architectural features:
- Glands more crowded
- Haphazard
- Small glands between larger benign glands

No basal cell layer (IHC), peripheral zone, multifocal

CAP architecture: glands, cribriform pattern, solid sheets, single cells
1. no desmoplastic reaction
2. no myxoid stromal response
3. no inflammatory response

CAP – nuclear features: enlargement, nucleoli (not always discernible!)
- cytoplasmic and luminal features:
  - blue tinged mucin,
  - Sharp luminal border
  - NO lipofuscin!
  - Crystalloids
  - Amphophilic cytoplasm

CAP – specific features:
- Metastasis
- Perineural invasion
- Mucinous fibroplasia aka collagenous micronodules
- Glomeruloid features

Usually diagnosis of CAP is based on several features

Gleason scoring (grading) system: based on architectural pattern, no cytologic features considered, sum of 2 patterns
From 1 – 5, grade 1 = AAH (atypical adenomatous hyperplasia), on biopsy lowest score which can be diagnosed = 6(3+3)
- Glandular architecture
- 1<sup>o</sup> pattern = most prevalent
- 2<sup>o</sup> pattern = second most prevalent

- Biopsy – report highest score: two highest scores/patterns
• Prostatectomy – report the most prevalent score: two most prevalent patterns/scores

CAP – variants: ddx: primary versus secondary, mimickers!
• Atrophic adenoca: nuclei larger, IHC-no basal cell layer
  - ddx atrophy: lobular atrophy in prostate: ectatic central duct surrounded by small glandular units; glands with angulated or branching architecture; in cancer glands are round!
• Adenosis (atypical adenomatous hyperplasia): small/crowded glands, lobular architecture preserved, benign cytology, basal cells present (IHC)
• Sclerosing adenosis: thick basement membrane
• Foamy gland adenoca vs benign: very low n/c ratio, round, cytoplasm empty vacuoles (no lipids), intermediate grade, IHC-no basal cell layer
• Mucinous (colloid variant): mucin in lumina and extraglandular, at least 25% of the tumor to show extracellular lakes of mucin, otherwise in a biopsy sign out as CAP “with mucinous features”. Aggressive, cribriform pattern, least common, PAS (+), alcin blue (+), PSA(+), PAP(+), CEA (-); DDX: bladder, rectum, mets, Cowper’s gland adenoca
• Signet ring carcinoma: at least 25% of tumor with signet ring cells to warrant this diagnosis; PSA, PAP (+), CEA (-), NO mucin in vacuoles!
• Pseudohyperplastic
• Oncocytic
• Lymphoepithelioma-like
• Sarcomatoid (carcinosarcoma)

ASAP = atypical small acinar proliferation: suspicious for carcinoma buts scanty evidence

Prostatic duct ca (endometrioid): prostatic urethra, <1%, resembles endometrioid adenoca, pseudostratified columnar cells, PSA (+), PAP (+), aggressive

Prostatic small cell carcinoma: rare in clinical specimens (0.5-2%), age: 65-72y, median serum PSA 4 ng/ml, 42% with history of usual prostatic adenocarcinoma; origin - from neuroendocrine cells of the prostate? Dedifferentiation? Stem cells? IHC: TTF-1 - 52.3% diffusely positive, prostatic markers frequently negative, neuroendocrine markers - 94% express at least 1 NE marker (chromogranin, synaptophysin, NSE, CD56); highly aggressive and overall prognosis is poor, 75% with metastasis at presentation.
Histology: classic oat cell morphology: uniform small cells, hyperchromatic nuclei, salt and pepper chromatin, inconspicuous nucleoli, sparse cytoplasm.
Pure small cell morphology or mixed with usual adenocarcinoma (need to provide %)
Androgen deprivation effects: adenocarcinoma post ADT: pyknotic nuclei, xanthomatous cytoplasm
Radiation changes – “ugly nuclei” but basal cell layer preserved!!!

HIGH GRADE PIN = malignant cells, ca “in-situ”, basal layer preserved!!! Different patterns: flat, tufting, micropapillary (no vascular cores), cribriform.

Cowper’s gland – double cell layer, inner = mucin secreting, low magnification architecture!
Squamous metaplasia (infarction, hormonal therapy), also mucinous metaplasia

Urothelial metaplasia, basal cell hyperplasia – “nuclear crowding”

Seminal vesicles: “monster nuclei”, pigment! IHC: PSA/PAP (-), CEA(+), CA 125 (+) Ck7 (+), Ck20 (-)

IHC:
CK7(+)CK20(-): seminal vesicles PSA (-), ovary, endometrium, breast, lung, m. mesothelioma
Ck7(-)CK20(-): prostate adenocarcinoma (PSA+), SCC, neuroendocrine
CK7(+)CK20(+): urothelial (PSA-)
CK7(-)CK20(+): colon

Common pelvic carcinomas:
Prostate: CK7(-)/CK20(-), CA125(-), PSA/PAP(+)
Urothelial: CK7(+)/CK20(+), CA125(-), PSA(-), 34βE12(+)
Seminal vesicle ca: CK7(+)/CK20(-), CA125(+), PSA/PAP(-)
Colorectal: CK20(+)/CK7(-), CA125(-), CDX2(+) Tripple stain: Racemase (AMACR) – cytoplasmic, carcinoma, 34βE12 – cytoplasmic, basal cells, P63 – nuclear, basal cells
PSA/PAP: epithelial cells of prostate origin
PSA (+) = prostate but caveat: higher grade may be (-), post ADT (-) (androgen deprivation therapy)
PSA (-): seminal vesicle, ejaculatory ducts epithelium, nephrogenic adenoma, mesonephric duct remnants, Cowper’s glands

Prostate carcinoma:
• Staging:
• Clinical vs pathologic
• No pathologic T1!
• Seminal vesicles – muscular coat involvement
• Margins: equivocal, focal, or extensive
• Grading: acinic – yes! Variants? Other? Post ADT? Post radiotherapy?
**Urinary bladder pathology (1C)**

Normal bladder histology – 3 layers: epithelium and subepithelial connective tissue (lamina propria with discontinuous muscularis mucosae), muscularis (detrusor muscle, aka deep muscle), perivesical fat

Reactive, proliferative changes:
- von Brunn’s nests = urothelial nests in lamina propria
- cystitis cystica = cystic change in von Brunn’s nests
- cystitis glandularis = glandular metaplasia of cyst lining

Urothelial papilloma: rare, small, single, benign papillary lesion with normal urothelium and preserved umbrella cells
Inverted urothelial papilloma: endophytic growth pattern with normal urothelium covering the lesion, hence appearance of a smooth mass, minimal atypia and no or only rare mitoses.

PUNLMP = Papillary Urothelial Neoplasia of Low Malignant Potential: resembles papilloma but has >6 cell layers, orderly maturation

**Urothelial carcinoma:** papillary versus flat lesions

Papillary urothelial carcinoma: low grade (non-invasive) versus high grade (invasive)
High grade: cytology, mitoses, necrosis

Flat lesion = urothelial carcinoma in-situ (cis): HIGH GRADE CYTOLOGY
Nuclear anaplasia, mitoses, loss of polarity and intercellular cohesion (“denuding cystitis”, “clinging cis”), nuclear crowding.

Staging: - T2 clinically important based on deep muscle invasion (2a-inner half, 2b-outer half)

**Variants of urothelial carcinoma:** importance for differential diagnosis primary versus secondary tumors and mimickers
- squamous and glandular differentiation
- nested variant
- microcystic variant
- inverted variant
- giant cell
- lymphoepithelioma-like variant (IHC-keratin stain!)
- lymphoma-like, plasmacytoid variant (IHC-lymphoma markers and keratins)
- sarcomatoid variant, may have heterologous elements

Neuroendocrine carcinoma – pure or mixed with conventional urothelial carcinoma
Metaplasia:
Squamous metaplasia: -response to chronic inflammatory stimulus
Keratinizing metaplasia = risk factor for carcinoma
Non-keratinizing squamous epithelium in trigone in women = NORMAL

Villous adenoma – identical to colonic adenoma, risk factor for adenocarcinoma, more common in urachus than bladder

Nephrogenic adenoma: secondary to trauma or inflammation, <1cm, papillary, sessile or polypoid, no atypia or mitoses, DDX: adenoca, clear cell renal cell carcinoma

Paraganglioma – IHC synaptophysin

Bladder melanoma – IHC melanoma markers

Soft tissue: urinary bladder rhabdomyosarcoma, “bunch of grapes”, children

Malakoplakia – chronic infection, may co-exist with cancer!
Endometriosis – mimicker of adenocarcinoma

Kidney tumors:

Main categories of primary renal tumors: tubular origin versus urothelial origin

Main categories of renal masses: primary carcinomas (tubular origin, urothelial origin), oncocytomas, metastatic, soft tissue tumors (angiomyolipoma),

Rare renal tumors: cystic nephroma-MEST spectrum (mixed epithelial and stromal tumor of the kidney), other

Pediatric tumors: “adult-type” carcinomas are rare, instead translocation carcinomas are most common pediatric renal carcinomas, most common = nephroblastic tumor (Wilms tumor)

Evolution of renal cell carcinoma classification:
- initially only 2 categories were recognized: clear cell and granular cell carcinomas. Currently several carcinomas, some of which are derived from proximal nephron, others from the distal nephron. Only one benign epithelial tumor is of importance – oncocytoma (5% of renal tumors in adults)
- renal mass in adult patient = carcinoma until proven otherwise (in children Wilms tumors = most common malignancy)
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- Proximal nephron derivation:
renal cell carcinoma, clear cell type is the most common renal cancer in adults (approximately 75%), not all tumors have clear cytoplasm, hereditary tumors associated with germline mutation of the VHL gene and VHL syndrome

- translocation carcinomas: young-pediatric patient, morphologic overlap with clear cell RCC, immunohistochemistry for TFE3 or cytogenetics for diagnosis

- papillary RCC: two types; type I approximately 10-15% of adult renal cancers while type II is rarer and more aggressive. There are hereditary counterparts for both cancers

- Distal nephron derivation

- oncocytoma: benign, approximately 5% of adult primary renal tumors, need to differentiate from its malignant counterpart – chromophobe RCC

- chromophobe RCC – two types: one with relatively clear cytoplasm and “vegetable” morphology and eosinophilic type with cytoplasmic eosinophilia, mimicking oncocytoma; perinuclear “halo” helpful

- Birt Hogg Dube syndrome: multiple oncocytomas, chromophobe RCC and hybrid tumors with mixed oncocytoma-chromophobe morphology; skin lesions and pulmonary cysts

- Collecting duct carcinoma, rare, very aggressive

- renal medullary carcinoma – sickle cell trait

- mucinous tubular and spindle cell carcinoma – relatively indolent, distinguish from sarcoma!


- Angiomyolipoma – most common soft tissue renal tumor; three components: vessels, smooth muscle and fat but in varying proportions, females, tuberous sclerosis, IHC: smooth muscle and melanocytic markers; epithelioid variant = malignant

- Cystic nephroma – MEST spectrum (mixed epithelial and stromal tumor of the kidney) varying proportion of the stroma, benign, female sex

- Pediatric tumors; most common = Wilms tumor (nephroblastoma), = malignant embryonal neoplasm, replicates the histology of developing kidney, most common=triphasic, chemosensitive!
References:


Picken MM. Editorial comment from Dr Picken to molecular pathology of renal oncocytoma: a review. Int J Urol 2010;17:613


