Challenging and not so uncommon bladder lesions

PSEUDONEOPLASTIC LESIONS OF BLADDER
aka:
Lumps and Bumps in the bladder

Mahul B. Amin
Professor and Chairman,
Garwin Endowed Professor for Cancer Research
Department of Pathology & Lab Medicine
Professor, Department of Urology
University of Tennessee Health Science Center,
Memphis, TN
mamin5@uthsc.edu

The slides and syllabus are provided here exclusively for educational purposes and cannot be reproduced or used without the permission from Dr Mahul B. Amin

mamin5@uthsc.edu

Pseudoneoplastic mimics of bladder cancer

Mimics of CIS
- Reactive atypia
- Radiation atypia
- Polyoma virus infection

Mimics of Invasive Cancer
- Inflammatory lesions (malakoplakia, amyloidosis)
- Pseudocarcinomatous hyperplasia
- Von Brunn's nests
- Cystitis cystica & glandularis +/- intestinal metaplasia
- Nephrogenic adenoma
- Mullerianosis
- Paragangliosis & Paraganglioma
- Ectopic prostate tissue
- Pseudosarcomatous myofibroblastic proliferations

Mimics of Papillary Neoplasia
- Papillary-polyoid cystitis
- Nephrogenic adenoma
- Avulsion and pseudopapillary artifacts
**PAPILLARY/POLYPOID CYSTITIS**

- Clinically mimic papillary urothelial ca (40%)
- Background: In-dwelling catheter, fistula
- Papillary ► polyloid ► bulbous cystitis ► fibroepithelial polyp
- Lining: Normal, reactive or hyperplastic urothelium
- Cores: Edema, granulomatous tissue, fibrosis
- Exquisite branching and then fibrovascular cores – help distinguish from papillary urothelial ca
U Ca. with small tubules

Nephrogenic Adenoma

Update for the practicing pathologist: The International Consultation On Urologic Disease-European association of urology consultation on bladder cancer

Mihail B Arie1,2, Steven C. Smith1,2,3, Victor F. Ret骂1, Jonathan J. Eppinga1, David P. Griffin1, Dennis E. Haney1, Oscar Liu1, Jesse R. McKenney1, Rekha M. Mehan2,3, Gadriel P. Muir1, Hikmat A. Alzabat4, Fermin Alegre6, Sted J. A., Isabel Alvaredo-Cabrer12, Lukas Baumgart12, Linzi Cheung1, John C. Chen12,2

Gan A. Krepinsky1, Richard J. Kote1,4, Scott D. Kuech1,5, John A. Hitt1,2, Elizabeth M. Gleave1,2, Christine Habr-Gama1,4, Amil Hartmann4, Cord Lang12,3, Antonio Lopez-Beltran2,4, Cristina Mapekudou7, Iniesta Monzo9, George J. Nettles1,6, Larry Oliver1,4, Priya Rao1,4, He Y. Re9,10, John R. Sigl12,4, Saitoh K. Takashi1,2, Traversy Tourniel8,4, Sakeen A. Umar12,4, Theo Van der Kant2,6, Robert H. Young1 and Mark R. Soloway1,10
Grading of Non-Invasive Urothelial Neoplasms of the Bladder

<table>
<thead>
<tr>
<th>Flat Lesions</th>
<th>Papillary Tumors</th>
<th>Inverted Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Urothelial Papilloma</td>
<td>Inverted Papilloma</td>
</tr>
<tr>
<td>Urothelial Hyperplasia</td>
<td>PUNLMP</td>
<td>Inverted PUNLMP</td>
</tr>
<tr>
<td>Urothelial Dysplasia</td>
<td>Papillary UCa, Low Grade</td>
<td>Inverted Papillary UCa, Low grade</td>
</tr>
<tr>
<td>Urothelial CIS</td>
<td>Papillary UCa, High Grade</td>
<td>Inverted Papillary UCa, High Grade</td>
</tr>
</tbody>
</table>

• PUNLMP, papillary urothelial neoplasm of low malignant potential.

CLASSIFICATION OF BLADDER LESIONS WITH INVERTED GROWTH PATTERN

• Inverted papilloma
• Inverted urothelial neoplasm of LMP
• Inverted urothelial carcinoma, low grade, non-invasive
• Inverted urothelial carcinoma, high grade, non-invasive
• Inverted urothelial carcinoma, high grade, invasive

Courtesy R. Montironi, Italy
NEPHROGENIC ADENOMA

Pitfalls:
- Papillary surface lesions:
  D. Dx. - urothelial papilloma
- Hobnail cells, clear cells, solid architecture:
  D. Dx. - clear cell carcinoma
- Random distribution including between muscularis mucosae muscle:
  D. Dx. - adenocarcinoma or UCa with tubules
- AMACR/racemase positivity:
  D. Dx. - adenocarcinoma of prostate
NEPHROGENIC ADENOMA
NEPHROGENIC ADENOMA

Clues to benign diagnosis:
- Characteristic admixture of patterns
- Associated inflammation
- Stromal edema
- Lack of significant cytologic atypia
- Rare to absent mitoses
- Thickened basement membrane
- Inspissated colloid-like material
- PAX8 and S100A1 (+)
FLORID REACTIVE PROLIFERATIONS

- Dome-shaped, polypoid mucosal-based lesions
- Cystoscopic or radiographic mass lesions – may be suggestive of malignancy
- Pitfall: Florid proliferations with accompanying atypia
  - Mistaken for carcinoma

POST-RADIATION PSEUDOCARCINOMATOUS PROLIFERATION

- Ulceration of mucosa ±
- Pseudoinvasive nests
- Lining cells – vacuolated nuclei and cytoplasm; reactive atypia
- Wrapping around blood vessels
- Fibrin in blood vessels
- Minimal to absent mitoses
- Inflammation, edema, vascular congestion, hemorrhage, hemosiderin
- Post-RT-induced vascular changes or stromal changes +/-
POST-RADIATION PSEUDOCARCINOMATOUS PROLIFERATION
FLORID REACTIVE Proliferations

- Normal Mucosa
- Florid Proliferation of von Brunn’s Nests
  - Cystic Change
  - Cystitis Cystica
  - Cystitis Cystica Glandularis
  - Goblet Cells
  - Paneth’s Cells
  - Cystitis Cystica Glandularis with Intestinal Metaplasia
UROTHELIAL CARCINOMA WITH MICROCYSTIC PATTERN

Microcystic variant

Cystitis cystica glandularis
FLORID CYSTTTIS GLANDULARIS
WITH MUCIN EXTRAVASTION
FLORID CYSTITIS GLANDULARIS
WITH MUCIN EXTRAVASATION

- Significant clinical, radiographic and histologic mimic of cancer
- Clues to benign disease:
  - Orderly arrangement of epithelium
  - Lack of cytologic atypia
  - Lack of in situ lesion
  - Lack of desmoplasia
  - Lack of cells floating in mucin
Pseudosarcomatous stromal reaction

The slides and syllabus are provided here exclusively for educational purposes and cannot be reproduced or used without the permission from Dr Mahul B. Amin

mamin5@uthsc.edu
PSEUDOSARCOMATOUS MYOFIBROBLASTIC PROLIFERATIONS (PMP)

- 11% multifocal
- Myxoid changes more likely to be superficial
- Fasicular/cellular areas more likely to be deep
- Nodular/fasciitis-like look
- Arborizing granulation – tissue-type vasculature
- Inflammation (acute and chronic) in stroma
- Spindle, stellate, ganglion-like cells
- Cytokeratin (93%) or muscle markers (SMA 64%, desmin 44%) not useful with differential diagnosis

Gross

- Exophytic-polypoid mass
- Soft and gelatinous
- Less commonly – white, submucosal or intramural mass
- Size 1-9 cm
PSEUDOSARCOMATOUS MYOFIBROBLASTIC PROLIFERATIONS (PMP)/IMT

• In spite of muscle invasion, necrosis, cellularity, outcome uniformly favorable
• Large lesions may recur (incomplete excision or persistent reaction to resection); metastasis not documented
• Progression to sarcoma (rare)
• Alk-1 IHC (42%) and t(2:5) in situ controversial

Spindle cell lesions

Benign (PMP) vs. Malignant - H&E diagnosis

• PMP / PSFMT
  * keratin(+/-), SMA(+), desmin(+/-), p63(-), Alk-1(+)

• Sarc. Ca
  * keratin (+/-), SMA(-), desmin(-), p63(+/-), Alk-1 (-), HMCK & CK5/6 (+)

• LMS
  * keratin (-/+), SMA(+), desmin(+), Alk1(-/+), p63(-)
PARAGANGLIOMA OF THE BLADDER

Clinical features:
- **Sex:** F:M : 3:2
- **Age:** Wide range including children and old (mean 41 years)
- **Symptoms:**
  - Micturition attacks (headache, palpitations, blurred vision, etc.) – 75%
  - Hematuria – 60%
- **Radiography:** Arteriography, I-MIBG scintigraphy, etc.
- **Cystoscopy:** Intact or ulcerated mucosa, dome-shaped mass

PARAGANGLIOMA OF THE BLADDER

**Gross:** Lobulated, circumscribed, intramural mass, often with intact mucosa

**Microscopic:**
- Nested, Zellballen pattern, sinusoidal growth
- Delicate fibrovascular stroma
- Eosinophilic granular, basophilic to occasional clear cells
- Nuclear monotony with random nuclear atypia
- Muscularis propria invasion (up to 50%)

PARAGANGLIOMA
**PARAGANGLIOMA OF THE BLADDER – DIFFERENTIAL DIAGNOSIS**

**Immunohistochemistry**

- Synaptophysin, chromogranin: **paraganglioma**
- Keratin, synaptophysin, chromogranin: **carcinoid tumor**
- CK7, CK20, HMWCK, p63, thrombomodulin: **urothelial ca**
- PSA, PSAP (+), p63, HMWCK (-): **metastatic prostate ca**
- RCC, CD10, keratin: **metastatic RCC**
- S-100, HMB-45, Melan-A, MitF: **metastatic melanoma**
- Hepar-1: **Hepatoid adenocarcinoma of the bladder**

**Paraganglioma-like Urothelial Carcinoma**
INVASIVE UROTHELIAL CARCINOMA

• Importance: Prognosis and therapy (radical cystectomy)
• Features against urothelial ca:
  • Age (urothelial ca usually >55 yrs)
  • Male preponderance
  • Multifocal
  • Partly mucosal based, with papillary or CIS lesions
  • Keratin positivity

PARAGANGLIOMA OF THE BLADDER

• Very frequently mistaken for urothelial carcinoma
• Significant pitfall
  • Therapy – partial cystectomy, wedge resection, enucleation, TURBT VS.
  • Radical cystectomy for muscle-invasive urothelial carcinoma
Enucleation

PARAGANGLIOMA OF THE BLADDER

• Significant pitfall – other management implications
  • Associated with multiple endocrine neoplasia – as appropriate, refer to multidisciplinary team including genetic screening
  • Treatment with radionucleotides – malignant cases
  • Sunitinib – tyrosine kinase inhibitor with antitumor and antiangiogenic activity – potential role in malignant cases

PARAGANGLIOMA OF THE BLADDER

• Generic history of bladder tumor provided
• Absent symptoms related to catecholamine production (up to 25-40%)
• Diffuse, sheet-like growth
• Pseudopapillary arrangement, irregular nests, pseudorosettes
• Marked cautery artifact
• Muscle-invasive tumor

Causes for misdiagnosis with urothelial cancer – particularly TURBT specimens
• Generic history of bladder tumor provided
• Absent symptoms related to catecholamine production (up to 25-40%)
• Diffuse, sheet-like growth
• Pseudopapillary arrangement, irregular nests, pseudorosettes
• Marked cautery artifact
• Muscle-invasive tumor
PARAGANGLIOMA OF THE BLADDER

• Rare, but specific proclivity in bladder
• Younger patients (mean 41 yrs), slight female preponderance
• Catecholamine production absent in 25-40% of cases
• Mural not mucosal based

PARAGANGLIOMA OF THE BLADDER

Clues to prevent misdiagnosis:
• Age of patient (mean 41 vs >60 yrs for bladder ca)
• Sex: F>M (reverse for bladder ca)
• Astute urologist: “cystoscopy not typical for bladder ca”
• Zellballen architecture (may be present focally)
• Nuclear uniformity interrupted by “random endocrine atypia”
• Keeping paraganglioma always at the back of the mind when dealing with bladder tumors

PARAGANGLIOMA OF THE BLADDER

Biologic potential
• Metastasis only criterion of malignancy (10-15%)
  • Atypia
  • Mitotic activity
• Size
• Vascular invasion
• Necrosis
• Muscle invasion
• Not predictive of outcome