Mimics of Bladder Cancer

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**Squamous epithelium in bladder**
- Non-keratinising vaginal type mucosa common in trigone region in women
  - Normal variant

**Squamous epithelium in bladder**
- Squamous metaplasia: diagnostic criteria
  - **Men:**
    - Any squamous mucosa in bladder
  - **Women:**
    - Non-keratinising squamous away from trigone
    - Keratinising squamous anywhere in bladder
- **Keratinising squamous metaplasia**
  - Risk factor for squamous cell carcinoma

**Verrucous squamous hyperplasia**
- Spiking (church spire-like) keratosis
- Lacks broad invasive tongues of verrucous carcinoma
- Associated with malignancy
  - Squamous or urothelial

**Condyloma Acuminatum**
- Rare in bladder
  - More common in urethra
- Most have extensive genital lesions
  - Isolated bladder lesions in immunocompromised
- Associated with squamous/urothelial cancer
  - Requires close follow-up

**Squamous Papilloma**
- Rare in bladder
- Papillae lined by mature squamous epithelium
- No koilocytosis
- HPV negative
- Benign: not a risk factor for bladder cancer
**Fibroepithelial Polyp**
- Relatively rare in bladder
- Marked male predominance
- Most near verumontanum or bladder neck
- Broad club-like urothelium lined projections
  - May be lined by squamous/glandular epithelium
- May have atypical stromal cells
- Non-neoplastic
- No association with cancer

**Urothelial lesions**
- Von Brunns nests
- Cystitis cystica
- Urothelial papilloma
- Inverted papilloma
- Fibroepithelial polyp
- Flat urothelial atypia
  - Reactive
  - Post-treatment (BCG, Mitomycin C, Thiotepa)
  - Ketamine cystitis

**Von Brunns nests**
- Distinction from nested TCC
  - Larger nests
  - Regular size
  - Regular shape
  - Lobular or linear arrangement of nests
    - Flat noninfiltrative base
  - No significant nuclear atypia
  - Exception: CIS extending in to Brunn’s nests

**Florid reactive proliferations**

**Urothelial Papilloma (WHO)**
- Rare
- General single, small lesions in young individuals
- Non-branching or minimally branching
- Lined by normal urothelium (architecture and cytology)
- Normal CK20 pattern
- Low risk of recurrence

**Inverted Urothelial Papilloma**
- Rare: <1% of urothelial neoplasms
- 10-94 years (peak 50 – 70 years)
- Solitary, pedunculated or polypoid
- Up to 8cm
- Benign
- No need for routine cystoscopic follow-up
**Inverted Urothelial Papilloma**
- No exophytic component
- Mixed inverted + exophytic papilloma
  - Requires follow-up
- Generally no/minimal cytological atypia
  - Degenerative atypia acceptable
  - Focal nondegenerate atypia may be acceptable but requires follow-up
  - Diffuse atypia = inverted pattern TCC

**Flat urothelial lesions**
- Flat urothelial hyperplasia
  - Markedly thickened with no cytological atypia
  - De-novo: not pre-malignant
- Reactive atypia
  - Nucleomegaly
  - Round uniform nuclei with single prominent nucleolus and evenly distributed chromatin
  - Associated intraurothelial inflammation
  - Mitosis may be frequent but not atypical

**Therapy associated atypia**
- **BCG**
  - Denudation
  - Regenerative atypia (nucleomegaly and prominent nucleoli)
  - Granulomas (no need to do ZN)
- **Mitomycin C and Thiotepa**
  - Atypia of umbrella cells
  - No mitotic activity

**Therapy associated atypia**
- **Cyclophosphamide cystitis**
  - Marked oedema, haemorrhage and ulceration
  - Marked cytological atypia with frequent mitosis
- **Radiation atypia**

**Radiation atypia**
- Time and dose dependent
- May persist for a long time
  - May persist longer in von Brunn's nests
- Oedema, thickened mucosal folds, desquamation, superficial ulceration
- Atypia may be indistinguishable from CIS
  - No/rare mitosis
  - Multinucleate cells with smudged nuclei and abundant cytoplasm with degenerative changes

**IHC: flat urothelial atypia**

<table>
<thead>
<tr>
<th></th>
<th>CK20</th>
<th>CD44</th>
<th>Ki67</th>
<th>p53</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>Superficial cells</td>
<td>Basal layer</td>
<td>low</td>
<td>(-)</td>
</tr>
<tr>
<td><strong>Reactive</strong></td>
<td>Superficial cells</td>
<td>Basal layer</td>
<td>variable</td>
<td>(-)</td>
</tr>
<tr>
<td><strong>Dysplasia/CIS</strong></td>
<td>Full thickness</td>
<td>(-)</td>
<td>High</td>
<td>May be (+)</td>
</tr>
</tbody>
</table>

*Dysplasia/CIS distinction based on morphology*
**Pseudocarcinomatous hyperplasia**
- Generally (but not always) related to radioRx
  - May present several years after radioRx
  - Response to long-standing ischaemia
- Cancer mimic
  - Pseudoinfiltrative pattern
  - Cytological atypia and mitotic activity
  - Eosinophilic cytoplasm mimicking squamous carcinoma
- Distinction from cancer
  - Stromal changes of radioRx

**Ketamine atypia**
- Anaesthetic agent and recreational drug
- CIS mimic
  - Cytological atypia
  - Increased Ki67 and p53
- Distinction from CIS
  - Young patient
  - History
  - CK20 negative

**Glandular lesions**

**Surface Lesions**
- Cystitis glandularis
- Villous adenoma
- Urothelial carcinoma in situ with glandular or micropapillary features
- Adenocarcinoma in situ

**Lamina Propria Based**
- Cystitis glandularis
- Nephrogenic adenoma
- Prostatic polyp
- Inverted papilloma with glandular features

**In muscularis propria**
- Urachal remnants
- Endometriosis
- Urothelial carcinoma with glandular differentiation
- Primary adenocarcinoma
**Cystitis glandularis (CG)**

- Very common
  - Up to 70%, most often in trigone
- Generally microscopic
  - May form nodular/polyoid lesion
- Small risk of adenocarcinoma
  - Only with diffuse intestinal metaplasia
  - No risk with typical CG or focal intestinal metaplasia
- May mimic adenocarcinoma
  - Typical CG: microcystic TCC
  - CG with mucin extravasation: adenocarcinoma

**CG with mucinous metaplasia**

- Only with intestinal metaplasia
- May be large: up to 8cm
- Mimics adenocarcinoma
  - Dissecting mucin
  - Muscularis propria invasion
  - Cellular atypia
  - Mitosis

**Nephrogenic adenoma (NA)**

- Bladder (80%) > urethra > ureter > renal pelvis
- Generally incidental microscopic finding
- 10% are >4cm
- Predisposing factor usually present
  - Trauma, surgery, calculi
  - Immunosuppression esp. post renal transplant

**Nephrogenic Adenoma: Histologic Patterns**

- Variety of patterns
  - Polypoid
  - Papillary
  - Tubular
  - Hob-nail
- No nuclear atypia or mitosis
- Thick peri-tubular basement membrane
- Acute and chronic inflammation

**Origin of Nephrogenic Adenoma**

- ?adenoma ?metaplasia
- ?Urothelial origin
  - Immuno: CK7+, CK20+, uroplakin+
- ?Nephrogenic
  - Immuno: CD10+, RCC marker+, AMACR+
  - FISH: Y chromosomes in nephrogenic adenoma of women who received renal transplant from male donors
  - NEJM 347:653, 2002
- ?Heterogenous: some urothelial, others renal origin
Nephrogenic Adenoma: Differential diagnosis

- Papillary/polyloid cystitis
- Clear cell carcinoma (see next slide)
- Papillary TCC: multilayered
- Microcystic TCC and signet ring carcinoma
  - More cytological atypia
  - Other patterns of NA absent
- Prostate adenocarcinoma

Mullerianosis of bladder

- Order of frequency:
  - Endometriosis > endocervicosis > endosalpingiosis

Endocervicosis

- Often history of caesarean section
- May have menstrual exacerbation
- Generally deep
  - Muscularis propria or extravesical
- Mucin extravasation
- Distinction from adenocarcinoma
  - No/minimal atypia, no mitosis
  - No tissue reaction

Non-epithelial lesions

- Pseudosarcomatous myofibroblastic proliferation
- Paraganglia
- Atypical stromal cells
- Malakoplakia
- Amyloidosis

Myofibroblastic lesions of bladder

- Pseudosarcomatous myofibroblastic proliferation (PMP)
- Pseudosarcomatous myofibroblastic tumour
- Pseudosarcomatous fibromyxoid tumour
- Inflammatory myofibroblastic tumour (IMT)
- Inflammatory pseudotumour
- Post-operative spindle cell nodule (PSN)
- Nodular fasciitis

**Controversial:** same, different or related lesions?

<table>
<thead>
<tr>
<th>Feature</th>
<th>Nephrogenic adenoma</th>
<th>Clear Cell Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>All</td>
<td>&gt;40 years</td>
</tr>
<tr>
<td>Sex</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Incidental</td>
<td>Rare</td>
<td>Large mass</td>
</tr>
<tr>
<td>Common</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Rare</td>
<td>Common</td>
<td>Common</td>
</tr>
</tbody>
</table>

Modified from: Urologic Surgical Pathology: Bostwick and Eble
### PMP/PSN/IMT

- **Relationship controversial**
  - ? Same
  - ? Different
  - IMT: neoplastic
  - PMP and PSN: reactive

- **Virtually identical histology**
- **Differential diagnosis**
  - Sarcoma
  - Sarcomatoid TCC

### Pseudosarcomatous Myofibroblastic Proliferation (PMP)

- Generally large pedunculated masses
  - Unliks small post-op spindle cell nodules
- Often gelatinous/myxoid on macroscopy
- Often extends in to muscularis propria

### PMP: Cancer Mimic

- **May** show following features
  - Detrusor invasion
  - Hypercellularity
  - Small foci of necrosis
  - Frequent mitosis
  - No atypical mitosis
  - “Strap-like cells” mimicking rhabdomyosarcoma
  - May express cytokeratins
  - But usually HMWCK, p63 and EMA negative

### PMP: Distinction from sarcoma and sarcomatoid TCC

- Prominent delicate vascular network
- **Zonation**
  - More myxoid towards surface and more cellular toward base
- No substantial necrosis
- Less cytological atypia
- No atypical mitosis
- Chronic inflammation deep within lesion

### Paraganglia in bladder

- Uncommon
- In bladder neck muscle and extravesical fat
- Misdiagnosis risks upstaging TCC
  - Distinction from TCC
    - Prominent vascular pattern
    - Intimate association with nerves
    - No nuclear atypia
    - Immunohistochemistry
      - Chromogranin A(+), synaptophysin(+), S-100(+)
      - However, like TCC are GATA3(+)