51 Non-neoplastic Diseases of the Genitourinary Tract: A Practical Approach and Diagnostic Pitfalls

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51 Non-neoplastic Diseases of the Genitourinary Tract: A Practical Approach and Diagnostic Pitfalls

Non-neoplastic diseases of the genitourinary tract are common, and it is critical that practicing surgical pathologists are aware of these entities. The assessment of the nonneoplastic kidney is required in all synoptic reports for cancers of the kidney, renal pelvis, and ureter. This pathologic parameter is the most important feature when diagnosing benign renal neoplasms. Various nonneoplastic processes such as papillary, urothelial, glandular, squamous, spindle cell, or inflammatory lesions may mimic or compound evaluation of bladder or prostate malignancy, including assessment of key pathologic variables in transurethral and whole resection specimens. The course will review common nonneoplastic entities, their pathologic features, immunohistochemical profiles, and diagnostic pitfalls. Recognition of all of these nonneoplastic diseases can lead to improved patient outcomes.

- Diagnose common non-neoplastic renal diseases in tumor nephrectomy and nephroureterectomy specimens.
- Evaluate specific renal pathologic parameters that predict clinical outcomes.
- Diagnose non-neoplastic diseases that can mimic malignancy mainly in transurethral resections as well as cystectomy, prostatectomy, or cystoprostatectomy specimens.

FACULTY:
Anthony Chang MD
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Practicing Pathologists
Surgical Pathology
Surgical Pathology (GI, GU, Etc.)
2.0 CME/CMLE Credits

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Non-Neoplastic Diseases of the Genitourinary Tract: A Practical Approach and Diagnostic Pitfalls

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Course Objectives

- Enumerate benign bladder/urethral lesions and to recognize and distinguish malignant differential diagnoses thru pattern-based approach.
- Select appropriate immunostains and present pitfalls in diagnostic scenarios involving benign bladder/urethral lesions.
- Review histologic features of common non-neoplastic kidney diseases associated with renal neoplasms
- Incorporate basic diagnostic renal pathology skills and laboratory techniques to comply with 2010 CAP kidney/renal pelvis/ureter cancer protocols and checklists

Disclosure

None
Benign mimickers of bladder and urethral malignancies: pattern-based approach

1. Papillary
2. Endophytic
3. Glandular/tubular
4. Reactive
5. Spindled

Papillary lesions

A. Papillary urothelial neoplasm of low malignant potential.
B. Urothelial papilloma.
C. Papillary urethelial hyperplasia.
D. Papillary-polyoid cystitis.
**Papillary-polypoid cystitis**

- Nonneoplastic inflammatory lesion.
- Exophytic edematous polypoid or papillary projections.
- Affect any age group with no gender predilection.
- Many related to indwelling catheter.
- May follow regional radiation therapy.

**Papillary-polypoid cystitis**

- Usually small lesions (< 5 mm).
- Exophytic projections of urothelial mucosa with stromal edema (polypoid cystitis) and fibrosis (papillary cystitis).
- Papillae without complex branching.
- Broader at base and taper at tip.
- May have lamina propria inflammation.
- Urothelium may be hyperplastic or reactive.
Papillary-polypoid cystitis

Important Differential Diagnoses:
- Urothelial papilloma.
- Papillary urothelial neoplasm of low malignant potential (PUNLMP).
- Papillary urothelial carcinoma, low grade.
- Papillary urothelial carcinoma, high grade.

Papillary-polypoid cystitis vs. Papillary urothelial neoplasia

- Simple papillae.
- Broader base and tapered tip.
- Edematous lamina propria.
- Lacks cytologic atypia.

- Branch into smaller papillae, complex anastomosis and greater branching in higher grade.
- Thin and delicate in low grade.
- Fusion with increasing grade.
- Range of nuclear atypia and cell disorganization.

Papillary urothelial neoplasms

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papilloma</td>
<td>9-31%</td>
<td>0%</td>
</tr>
<tr>
<td>PUNLMP</td>
<td>17-62%</td>
<td>0-7%</td>
</tr>
<tr>
<td>Low grade</td>
<td>34-78%</td>
<td>3-18%</td>
</tr>
<tr>
<td>High grade</td>
<td>34-74%</td>
<td>8-35%</td>
</tr>
</tbody>
</table>
Urothelial papilloma

Low grade papillary urothelial carcinoma
High grade papillary urothelial carcinoma

Papillary urothelial neoplasms: Simplified approach

- **Urothelial papilloma:**
  - Papillary fibrovascular core + Normal urothelium.

- **PUNLMP:**
  - Papillary fibrovascular core + Hyperplastic urothelium.

- **Low grade papillary urothelial carcinoma:**
  - Papillary fibrovascular core + Urothelial (low grade) dysplasia.

- **High grade papillary urothelial carcinoma:**
  - Papillary fibrovascular core + Urothelial carcinoma in situ.

Other mimic – Papillary urothelial hyperplasia

- Undulating hyperplastic urothelium arranged into thin mucosal folds of varying heights.
- Lacks well developed fibrovascular core (pseudopapillary).
- Lacks cytologic atypia.
- In patients with prior papillary urothelial carcinoma, increase risk subsequent papillary urothelial neoplasia.
Other mimic – Papillary urothelial hyperplasia

A. High grade papillary urothelial carcinoma, with denudation.
B. Urothelial papilloma.
C. “Papillary” clear cell adenocarcinoma.
D. Nephrogenic adenoma.

Nephrogenic adenoma

- Hypothesis for origin:
  - Renal tubular seeding.
    - Implantation and growth of displaced renal tubular cells to injured mucosa.
  - Nephrogenic metaplasia.
    - Alteration of urothelium in response to injury.
- Age 21-77 years.
- Mostly incidental findings.
- Benign, but may recur if inciting etiology persists.
“Papillary” nephrogenic adenoma

- Papillary-polypoid pattern.
- Minimal branching and edematous stroma.
- Papillae monolayered with bland, cuboidal, flattened, or “hobnailed” cells.
- Almost always seen with underlying tubular proliferations.
  - Thickened peritubular basement membrane.
  - Small round to oval tubules, may be small simulating signet ring cells.
  - Intraluminal basophilic or eosinophilic secretions.
“Papillary” nephrogenic adenoma

Important Differential Diagnoses in Bladder:
* Papillary urothelial neoplasm.
** “Papillary” clear cell adenocarcinoma.
**Papillary nephrogenic adenoma** vs. **Papillary urothelial neoplasia**

- **Monolayered.**
- **Minimal branching.**
- **Lacks significant cytologic atypia.**
- **Concurrent tubular proliferations.**

- **Multilayered.**
- **Branch into smaller papillae, complex anastomosis and greater branching in higher grade.**
- **Range of nuclear atypia.**

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**“Papillary” nephrogenic adenoma**

**High grade papillary carcinoma**

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**“Denuded” papillary urothelial carcinoma**
Immunohistochemistry

<table>
<thead>
<tr>
<th>Immunostain</th>
<th>Nephrogenic adenoma</th>
<th>Papillary urothelial neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAN-CK</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Pax-2</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Pax-8</td>
<td>+</td>
<td>-</td>
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<tr>
<td>p63</td>
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</table>

Nephrogenic adenoma

- Papillary, tubulocystic or solid patterns.
- Clear to eosinophilic cells, “hobnailed” arrangement.
- Similar to nephrogenic adenoma, also expresses pax-2, pax-8 and AMACR.
- Densely hyalinized papillary cores.
- Moderate to severe cytologic atypia and frequent mitosis.
- Usually have obvious invasion.

Clear cell adenocarcinoma
Endophytic lesions

A. Inverted papilloma.
B. Inverted papillary urothelial carcinoma.
C. Florid von Brunner's nests.
D. Nested urothelial carcinoma.

Inverted papilloma

- Rare, ~1% of urothelial neoplasms.
- Wide age range (1st to 8th decade).
- Male predominance.
- Gross or microscopic hematuria.
- Mostly in bladder trigone and neck.
- Negligible recurrence rate (<1%).
Inverted papilloma

- Urothelium invaginates into lamina propria.
- Thin cords or trabeculae.
- Peripheral nuclear palisading of basal cells and central nuclear streaming.
- Bland cytology, may have scattered degenerative atypia.
- Endophytic growth with smooth contour and no stromal reaction.
Inverted papilloma

**Important Differential Diagnoses:**
- Papillary urothelial neoplasm with inverted growth (PUNLMP, low or high grade).
- Papillary urothelial neoplasia with inverted growth
  - Prominent or exclusive non-infiltrative growth to lamina propria.
  - Has broader cords or columns with transition into solid areas.
  - Downward projections can be pronounced and may extend adjacent to muscularis propria.
  - Grading essentially parallels WHO 2004 for exophytic tumors.
  - Regular broad pushing bulbous growth:
    - Diagnosis of invasion (in high grade) requires infiltrative nests or single cells in desmoplastic stroma.

Inverted papilloma Vs. Papillary urothelial neoplasia with inverted growth

- Thin cords or anastomosing network.
- Peripheral palisading and central streaming.
- Lack widespread atypia and absent mitosis.
- Expansion of trabeculae, best appreciated on low magnification.
- Range of cytologic atypia and cell disorganization.
- Surface may have true papillae.
Inverted high grade papillary urothelial carcinoma, with invasion

A. von Brunn's nest.
B. Inverted papilloma.
C. Papillary urothelial carcinoma with inverted growth.
D. Nested urothelial carcinoma.

Florid von Brunn's nest.

A. Florid von Brunn's nest.
B. Inverted papilloma.
C. Papillary urothelial carcinoma with inverted growth.
D. Nested urothelial carcinoma.
von Brunn's nests

- Invaginated nests of benign urothelial cells in lamina propria.
- Variant of normal urothelium, may occur due to inflammation.
- Common incidental microscopic finding.
- Frequency increases with age.
- Most common in bladder trigone.
- Completely benign.
- Not a neoplastic precursor lesion.

von Brunn's nests

- Solid nests in superficial lamina propria, typically with smooth, round contours.
- Orderly arrangement of cells.
- Sharp boundary at epithelial-stromal interface.
- Similar normal cytology to surface urothelium.
- May be florid, and associated with cystitis cystica and cystitis glandularis.

Florid von Brunn's nests
Florid von Brunn's nests/Cystitis cystica

Important Differential Diagnoses:
• Nested, tubular or microcystic urothelial carcinoma.
• Papillary urothelial neoplasm with inverted growth (PUNLMP, low or high grade).
• Carcinoid tumor.
• Paraganglioma.
Nested urothelial carcinoma

- Invasive urothelial carcinoma with small infiltrative nests of relatively bland appearance (“deceptively bland”).
- Muscularis propria involvement common.
- Shows architectural complexity and confluence of urothelial nests.
- Increasing degree of cytologic atypia in deeper invasive portions.
- May be admixed with urothelial carcinoma with small tubular formations.
- Presents with higher stage.
Nested urothelial carcinoma

- Superficial.
- Smooth round contour.
- May show glandular change and intestinal metaplasia.
- Distinction can be impossible in limited tissue samples!

Florid von Brunn’s nests vs. Nested urothelial carcinoma

- Superficial.
- Smooth round contour.
- With small nests, architectural complexity, irregular outline, confluence.
- Increasing atypia going deeper.

Glandular/tubular lesions
A. Florid cystitis glandularis.
B. Bladder adenocarcinoma.
C. Urothelial carcinoma with glandular differentiation.
D. Clear cell adenocarcinoma.

**Cystitis cystica/cystitis glandularis**

- **Cystitis cystica**
  - In contrast to von Brunn’s nests, have cystically dilated lumen.
- **Cystitis glandularis**
  - Similar to cystitis cystica except that the central cysts are lined by glandular cells.
- **Cystitis glandularis with intestinal metaplasia**
  - Similar to cystitis glandularis with presence of intestinal type-goblet cells.
- Superficial in location, uncommonly may reach upper muscularis propria.
- Minimal cytological atypia and rare mitosis.

- May be a variation of normal urothelium or a localized inflammatory response.
- Incidental finding.
- No convincing evidence that cystitis cystica or cystitis glandularis are neoplastic precursors.
**Florid cystitis glandularis**

**Important Differential Diagnoses:**
- Bladder adenocarcinoma.
- Urothelial carcinoma with glandular differentiation.
- Nested, tubular or microcystic urothelial carcinoma.
- Urothelial carcinoma with gland-like spaces.

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**Primary bladder adenocarcinoma**

- Well differentiated tumors may overlap with cystitis glandularis (dissecting mucin, muscularis propria extension, nuclear atypia, mitosis).
- In contrast to cystitis glandularis,
  - Architectural complexity.
  - Greater degree of nuclear atypia.
  - Mitosis is frequent.
  - Destructive invasion to muscularis propria.
  - Florid extravasated mucin.
  - Usually high stage or infiltrated deeply.

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Primary bladder adenocarcinoma

Urothelial carcinoma
with glandular differentiation
A. Prostate adenocarcinoma.
B. Nephrogenic adenoma.
C. Urothelial carcinoma with glandular differentiation.
D. Clear cell adenocarcinoma.

“Tubular” nephrogenic adenoma

- Most common in bladder.
- Prostatic urethra involved in ~15% and may extend to prostate parenchyma.
  - Seen incidentally in TUR specimens.
- Differential diagnosis for atypical glands in prostate.

“Tubular” nephrogenic adenoma

- Most common as small round to oval tubules in laminar fashion.
  - Tubules have thickened or prominent peritubular basement membrane.
  - May contain intraluminal basophilic or eosinophilic secretions (thyroid follicle-like).
  - May be small simulating signet ring cells.
- Papillary-polypoid pattern, usually with minimal branching.
- Monolayer of bland cuboidal, flattened, or “hobnailed” cells.
**“Tubular” nephrogenic adenoma**

**Important Differential Diagnoses in Prostate Transurethral Resection**
- Prostatic adenocarcinoma, acinar and microacinar pattern (Gleason pattern 3).
- Clear cell adenocarcinoma.

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**Gleason 3 prostatic adenocarcinoma**
- Usually small monotonous pattern (tubular, cystic, papillary components are absent).
- "Hobnailed" cells, eosinophilic secretions, stromal edema; rare to absent.

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**“Tubular” nephrogenic adenoma** vs. **Gleason 3 prostatic adenocarcinoma**
- Thickened basement membrane.
- Eosinophilic secretions.
- Cystic or papillary component.
- Flattened or hobnailed cells.
- Usually monotonous.
- Lacks thickened basement membrane, eosinophilic secretions, hobnailed cells, cystic or papillary component.
**Immunohistochemistry**

<table>
<thead>
<tr>
<th>Immunostain</th>
<th>Nephrogenic adenoma</th>
<th>Prostatic adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMACR</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PSA/PSAP</td>
<td>-/weak +</td>
<td>+</td>
</tr>
<tr>
<td>Pax-2</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Pax-8</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>S1001A</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

**Nephrogenic adenoma**

**S1001A**

**Reactive lesions**
A. Radiation atypia.
B. Urothelial carcinoma in situ.
C. Polyoma virus inclusion.

**Reactive urothelial atypia**

- Benign reactive or regenerative epithelial changes.
- Secondary to infection, prior therapy, or intravesical catheter.
- Most often associated with inflammatory infiltrates.
- No treatment needed, may regress on alleviating underlying cause.

- Nucleomegaly with prominent nucleoli.
- Nuclear chromatin fine and evenly dispersed.
- Cells often elongated.
- Acute or chronic inflammation.
- May have increased mitotic activity, but lack atypical forms.
- Radiation atypia may show cytoplasmic vacoulation, large nuclei with dark smudgy chromatin.
Reactive urothelial atypia

Important Differential Diagnosis:
- Urothelial carcinoma in situ.
- Polyoma virus inclusions.

Radiation urothelial atypia
Urothelial carcinoma in situ

- Unequivocal high grade cytology.
- Cellular crowding and loss of polarity on low magnification.
- Marked nucleomegaly frequent.
- Coarse dark nuclear chromatin.
- Mitosis may have atypical form.
- Cellular discohesion may be prominent.
- Thickness may vary.

Immunohistochemistry

<table>
<thead>
<tr>
<th>Immunostain</th>
<th>Normal urothelium</th>
<th>Reactive atypia</th>
<th>CIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK20</td>
<td>Superficial umbrella cells</td>
<td>Superficial umbrella cells</td>
<td>Full thickness</td>
</tr>
<tr>
<td>CD44</td>
<td>Basal/para basal cells</td>
<td>Intermediate to full thickness</td>
<td>Residual basal cells or absent</td>
</tr>
<tr>
<td>p53</td>
<td>Absent</td>
<td>Absent</td>
<td>Diffuse and strong</td>
</tr>
</tbody>
</table>
Pseudocarcinomatous hyperplasia

- Usually associated with radiation &/or chemotherapy.
- Florid benign urothelial proliferation with pseudoinfiltrative growth; mimic invasive urothelial carcinoma.
- Urothelial nests with irregular or rounded border.
- Wraps around vessels or fibrin.
- Squamoid or true squamous features.
- Associated stromal changes or radiation induced changes.
Pseudocarcinomatous hyperplasia

Spindle cell lesions

A. Sarcomatoid urothelial carcinoma.
B. Myofibroblastic proliferation.
C. Leiomyosarcoma.
D. Spindle cell sarcoma, NOS.
Myofibroblastic proliferations

• Benign myofibroblastic proliferation of bladder.
• Different terminologies used:
  – Inflammatory myofibroblastic tumor,
  pseudosarcomatous myofibroblastic proliferation,
  etc.
• 2nd – 4th decades.
• May have history of trauma or prior instrumentation (post-op spindle cell nodule).
• Florid myofibroblastic proliferation may be seen associated with invasive urothelial carcinoma.
• 10% recurrence, no metastasis.

Myofibroblastic proliferations

• Loose fascicles composed of tapered cells with elongated cytoplasmic process.
• Enlarged nuclei with nucleoli and fine chromatin.
• Mitosis may be abundant; no atypical mitosis.
• Variably cellularity, myxoid with granulation type vascularity.
• Hypocellular superficially and more cellular deeper.
• May extend to muscularis propria.

Myofibroblastic proliferations
**Myofibroblastic proliferations**

**Important Differential Diagnoses:**
- Sarcomatoid urothelial carcinoma
- Leiomyosarcoma
- Other spindle cell sarcomas
Immunohistochemistry

<table>
<thead>
<tr>
<th>Immunostain</th>
<th>Myofibroblastic proliferation</th>
<th>Sarcomatoid urothelial carcinoma</th>
<th>Leiomyosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA</td>
<td>74-100% (diffuse)</td>
<td>39-74%</td>
<td>76-85% (diffuse)</td>
</tr>
<tr>
<td>PAN-CK</td>
<td>70% (peripheral accentuation)</td>
<td>70-84%</td>
<td>11-58%</td>
</tr>
<tr>
<td>p63</td>
<td>0%</td>
<td>50-58% (intense in epithelial cells)</td>
<td>23% (focal/weak)</td>
</tr>
<tr>
<td>ALK</td>
<td>20-57%</td>
<td>0%</td>
<td>0-3%</td>
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</table>

Myofibroblastic proliferations

Pan-CK

SMA
Myofibroblastic proliferations

ALK

Sarcomatoid urothelial carcinoma

p63

Moving up to the Kidney
What is your comfort level in evaluating the non-neoplastic kidney of tumor nephrectomies?

- Not comfortable (“I recognize glomeruli, tubules and vessels, but that’s about it”)
- Somewhat comfortable (“I know diabetic nephropathy when I see it”)
- Very comfortable (“I don’t need a stinking renal pathologist!”)
- “Who cares about the uninvolved kidney?” Or “I didn’t even know that this is required by the CAP kidney cancer protocol/checklist”

Chronic Kidney Disease (CKD)

- Previously known as chronic renal failure
- Involves 25% of renal cell carcinoma (RCC) patients prior to nephrectomy
- Diabetes and hypertension are risk factors for both RCC and CKD
- ↑ risk of CKD after radical vs partial nephrectomy
- ↑ risk of cardiovascular and non-cardiovascular death

2004 US Renal System Data

- Expected life span on dialysis:
  - 20 - 24 years: 14.6 years
  - 60 - 64 years: 4.3 years
  - 70 - 74 years: 3.1 years
  - 80 - 84 years: 2.2 years
- RCC 5 year survival rates
  - Stage 1 = >90%
  - Stage 2 = 75-90%
  - Stage 3 = 59-70%
  - Stage 4 = <10% (median: 16-20 mos)
**Incidence in TN specimens**

- Arterionephrosclerosis >20%
- Diabetic nephropathy 10-20%
- Focal segmental GS 9%
- Thrombotic microangiopathy 5%
- AA amyloidosis 3%
- Atheroembolic disease 2%
- IgA nephropathy 2%
- Membranous nephropathy <1%

**Algorithm**

- Identification of glomerular abnormalities
  - First, light microscopy!
    - Glomeruli
    - Tubules
    - Interstitium
    - Vessels

**Glomeruli**

- Normal
- Mesangial sclerosis
- Mesangial hypercellularity
- Crescent
- Fibrinoid necrosis
- Endocapillary proliferation
- Diabetic glomerulosclerosis
Algorithm

• If glomerular abnormalities present,
  – Consider Congo red
  – Immunofluorescence microscopy (IgG, IgA, IgM, kappa/lamba light chains, albumin) on paraffin tissue sections
    • Decreased sensitivity compared with frozen tissue
  – Immunohistochemistry
  – Electron microscopy from paraffin block
    • Preservation/processing artifact

Tubules / Interstitium

Normal
Interstitial fibrosis / tubular atrophy
Interstitial inflammation
Acute tubule injury

Vessels

Intimal fibrosis
Hyalinosis
Thrombus
Atheroembolus
Vasculitis
Describe this glomerulus

- Normal
- Segmental glomerulosclerosis
- Diffuse mesangial sclerosis
- Thrombotic microangiopathy

Diabetic Nephropathy

- Diabetes is a risk factor for RCC
- 10-20% of RCC patients have diabetes
- DN in up to 20% of TN specimens
- Diabetic nodular glomerulosclerosis predicts progression of CKD
- Treatment: Strict blood glucose control

Diffuse Mesangial Sclerosis
Nodular Mesangial Sclerosis

Nodular Glomerulosclerosis

- Differential diagnosis
  - Diabetic nephropathy
  - Amyloidosis
  - Monoclonal Immunoglobulin Deposition Disease
    - Light chain deposition disease
    - Light and heavy chain deposition disease
  - Fibrillary GN
  - Immunotactoid glomerulopathy
  - Idiopathic nodular glomerulosclerosis
    - Associated with hypertension and smoking

Arteriolar Hyalinosis
Amyloidosis

- ~3% of RCC with AA amyloidosis
- Rare cases of AL amyloid and other amyloid forming proteins
- Treatment: removal of neoplasm
- Proteinuria may indicate recurrent or metastatic disease

Arterionephrosclerosis

- AKA Hypertensive nephropathy / nephrosclerosis
- Hypertension in 25-60% of RCC pts
- Tumor nephrectomy (TN) specimens
  - 40% with arteriosclerosis and no TI scarring
  - 20% with arteriosclerosis and TI scarring
- >20% global glomerulosclerosis predicts progression of CKD
**Significance of Global Glomerulosclerosis**

- **Bijol V, et al:**
  - Presence of >20% global glomerulosclerosis or nodular diabetic glomerulosclerosis predicted an increase of 0.5 mg/dL in serum creatinine 6 months after surgery

- **Gautam G, et al:**
  - Extent of global glomerulosclerosis correlates with the rate of renal function decline in radical nephrectomy specimens

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**Glomerulosclerosis**

- Normal glomerulus

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**Underestimating global glomerulosclerosis**

- Images showing underestimation of glomerulosclerosis

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Interstitial fibrosis / tubular atrophy

Arteriosclerosis

What is this lesion?

- Thrombotic microangiopathy
- Segmental fibrinoid necrosis
- Segmental glomerulosclerosis
- Mesangial sclerosis
Focal Segmental Glomerulosclerosis

- Up to 9% of TN specimens
  - Often associated with hypertension, arteriosclerosis, and parenchyma scarring
  - May be secondary to reduction of functional nephrons
- Proteinuria, nephrotic-range (>3 g/day)
- IF: negative
- EM: podocyte foot process effacement

Urate Nephropathy
What is this lesion?

- Thrombotic microangiopathy
- Fibrinoid necrosis and crescent
- Segmental glomerulosclerosis
- Collapsing glomerulopathy

Crescentic GN

Pitfall - JGA hyperplasia
Pitfall - Collapsing Glomerulopathy

Crescentic GN

Etiologies

1. Pauci-immune (ANCA-associated) GN
2. Anti-glomerular basement membrane (anti-GBM) GN
3. Immune complex-mediated GN
   - IgA nephropathy
   - Lupus nephritis
   - Membranoproliferative GN
   - Post-infectious GN
   - Etc.

Pauci-immune crescentic GN

- Uncommon in the setting of kidney cancer
- 80% with positive ANCA titer
- Clinicopathologic entities
  - Churg-Strauss syndrome
  - Granulomatosis with polyangiitis (Wegener)
  - Microscopic polyangiitis
Pauci-immune crescentic GN

Miscellaneous

- IgA nephropathy
- Membranous nephropathy
- Thrombotic microangiopathy
- Atheroembolic disease
- Fibrillary glomerulonephritis
- Balkan endemic nephropathy
- Analgesic nephropathy
- Lymphoma

Protocol for the Examination of Specimens from Patients with Invasive Carcinoma of Renal Tubular Origin

Wilms tumors and tumors of urothelial origin are not included.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: October 2009
Protocol effective date: January 2010

Protocol for the Examination of Specimens from Patients with Carcinoma of the Uterus and Renal Pelvis

Protocol applies to invasive and in-situ carcinomas and/or associated epithelial lesions of the uterus and renal pelvis.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: October 2009
Protocol effective date: January 2010
**Actual Parameter**

Pathologic Findings in Non-Neoplastic Kidney (select all that apply)

- Insufficient tissue (partial nephrectomy specimen with <5 mm of adjacent non-neoplastic kidney)
- Significant pathologic alterations
  - Glomerular disease (type)
  - Tubulointerstitial disease (type)
  - Vascular disease (type)
- Other (specify)

**Proposed Parameter**

Non-Neoplastic Kidney (evaluate using PAS and/or Jones methenamine silver stain; check all that apply)

- Insufficient tissue (partial nephrectomy specimen with <5 mm of adjacent non-neoplastic kidney)
- Significant pathologic alterations
  - Glomerulitis (infinitesimal)
  - Tubulointerstitial fibrosis/tubular atrophy

Glomeruli (fill all that apply)

- % of glomeruli with global sclerosis (0-100%)
- Other glomerular disease (specify)
- % of globally sclerosed glomeruli
- Other

Tubulointerstitial compartment (check all that apply)

- No significant abnormalities
- Interstitial fibrosis/tubular atrophy, mild (5-25%)
- IF/TA, moderate (26-50%)
- IF/TA, severe (>50%)
- Other tubulointerstitial diseases (specify)

Vessels (check all that apply)

- No significant abnormalities
- Arteriosclerosis (mild; <25% occlusion)
- Arteriosclerosis (moderate; 26-50% occlusion)
- Arteriosclerosis (severe; >50% occlusion)
- Other vascular injuries (specify)

**Summary**

- Non-neoplastic renal diseases
  - Common
    - Diabetic nephropathy
    - Hypertensive nephropathy/arteriomegalsclerosis
  - Use safeguards
    - Include parameter in synoptic reports
    - PAS/Jones silver stains
    - Adopt systematic approach
Pearls of Pathology

• Carefully examine the non-neoplastic kidney in tumor nephrectomy and nephroureterectomy specimens!
• Don’t forget the non-neoplastic kidney in benign tumors!
• Order PAS and/or Jones methenamine silver stains automatically when grossing specimen (cut 2 micron thick sections)
• Adopt a systematic evaluation of the non-neoplastic kidney parenchyma – glomeruli, vessels, tubules, interstitium

Thank you for your attention!

Please complete the course evaluation before you leave.
I. Non neoplastic and benign mimickers in bladder transurethral resections and biopsy specimens.

Several non-neoplastic and benign lesions in the bladder and urethra may cause diagnostic uncertainties when encountered in resection and biopsy specimens. These lesions may exhibit some morphologic or immunophenotypic overlap with the more aggressive tumors arising from these sites and may cause problems in the diagnosis (Table 1). Familiarity with these benign lesions is essential, including the clinical setting which they arise and the key histological and immunohistochemical features to avoid any potential misdiagnosis.

1. Papillary lesions

   a. Papillary-polypoid cystitis

   These are non-neoplastic inflammatory lesions in the bladder that are most often associated with prolonged indwelling catheters. These lesions may also arise following regional radiation therapy. Cystoscopically, they appear as small edematous bulbous projections, and often the urologists are able to identify its inflammatory nature. This is an example of the many scenarios highlighting the importance of reviewing cystoscopic findings, and pathologists should exercise caution in making a diagnosis of papillary urothelial neoplasm if the urologist’s impression is that of an inflammatory lesion.

   At its “early phase”, these lesions exhibit small exophytic urothelial mucosal projections with prominent stromal edema (polypoid cystitis). The papillae are typically simple without branching and are broader at its base and taper to the tip. The surface is lined by normal-appearing urothelium and may show hyperplastic or reactive changes but
should not exhibit definitive dysplasia. With time, the lamina propria edema may recede and is gradually replaced by fibrosis (papillary cystitis).

The most important differential diagnoses for these lesions are the different types of papillary urothelial neoplasms. The closest mimics are urothelial papilloma and papillary urothelial neoplasm with low malignant potential (PUNLMP). In contrast to papillary-polyloid cystitis, papillary urothelial neoplasm typically has thin delicate papillae, that may exhibit branching and complexities including fusion, with increasing grade. Papillary urothelial neoplasms most importantly exhibit range of cytological atypia and cell disorganization that is most pronounced with higher grade lesions.

b. **Papillary urothelial hyperplasia**

This lesion is characterized as undulating hyperplasic urothelium arranged into thin mucosal folds of varying heights. In contrast to papillary urothelial neoplasm, these lesions although may have occasional small vessels in the stalk, lack a well-developed fibrovascular core (psedopapillae) and typically do not exhibit cytologic atypia.

c. **Urothelial papilloma**

These are uncommon lesions comprising < 1% of papillary urothelial neoplasms in the bladder, typically seen in younger adults and may also occur in children. These lesions often present with gross or incidental microscopic hematuria, similar with the other papillary urothelial neoplasms. Cystoscopically, these lesions are small and almost always occur as isolated growths. The papillary projections are thin delicate exhibiting minimal branching. By definition, the papillae should be lined by urothelium of normal thickness and cytology, and should lack the range of cellular dysplasia and disorganization seen in the higher grade papillary urothelial neoplasms. The umbrella cells are often present and may show cytoplasmic clearing or vacoulations.

d. **“Papillary” nephrogenic adenoma**

These benign lesions present with papillary and tubular growths and are most commonly encountered in the bladder. These two types of growths have different key malignant differential diagnoses usually encountered in separate settings (e.g. papillary growth in bladder lumen mimicking bladder carcinoma, tubular growth in prostatic urethral mimicking prostate carcinoma) and are considered herein as two separate discussions.

There are two hypotheses for the origin of these lesions: a) considered to be implantation and growth of displaced renal tubular cells into an injured mucosa and b) as metaplasia of urothelium in response to injury. These lesions are seen in broad age range often as incidental microscopic findings. Nephrogenic adenoma is not considered as precursor for malignancies.

The papillary component of nephrogenic adenoma is characterized by simple papillary or polyloid growths with minimal branching and may show an edematous stroma. The papillae are typically lined by a monolayer of bland flattened, cuboidal or “hobnailed” cells. Almost always these papillae are seen with subjacent tubular proliferations. These tubules are further described below under the glandular/tubular lesions.
The most important differential diagnoses for the nephrogenic adenoma are clear cell adenocarcinoma, and for its papillary component are the different papillary urothelial neoplasms. Clear cell adenocarcinoma exhibits similarities with nephrogenic adenoma in terms of its papillary and tubulocystic growths, presence of “hobnailed” cells and expression of pax-2, pax-8 and AMACR. However in contrast, clear cell adenocarcinoma typically displays moderate to severe cytologic atypia with frequent mitosis, solid growths, and usually the invasive component is present at diagnosis.

In contrast to the papillary component of nephrogenic adenoma, papillary urothelial neoplasms have multilayered epithelium, show papillary branching and complexities with increasing grade, and exhibit a range of nuclear atypia. Care should be exercised with papillary urothelial growths that do not display epithelial multilayering, such as with denuded epithelium. Epithelial denudation is more often seen in high grade papillary urothelial carcinomas, and careful search should be performed for residual attached high grade cells. Distinction between papillary component of nephrogenic adenoma and papillary urothelial neoplasms can usually be made at the level of morphology. However, in difficult situations use of pax-2, pax-8 or p63 immunostains are helpful in their distinction (Table 2).

e. **Prostatic type polyps (Ectopic prostate)**

These are rare benign papillary lesions seen along the prostatic urethra characterized by presence of benign prostatic-type glandular cells in the stalk stroma. Typically, these are positive for PSA and PAP immunostains. In small tissue samples, these lesions may show overlapping features, morphologically and immunohistochemically, with ductal adenocarcinoma of the prostate. However in contrast, ductal adenocarcinomas are lined by tall columnar cells, often with pseudostratified growth, and with prominent nucleoli. Ductal adenocarcinoma also displays more complex architectures including presence of large cribriform structures, expansile growth and complex branching.

f. **Fibroepithelial polyps**

These are rare benign papillary lesions usually encountered in young adults and children. These lesions show polypoid or elongated projections lined by normal-appearing urothelium and with florid proliferations at the stalk resembling von Brunn’s nests, cystitis cystica or cystitis glandularis. The polypoid growth may resemble the “botryoid growth” of embryonal rhabdomyosarcoma; however this can be differentiated with ease by its cellular stroma containing rhabdomyoblasts and immunoreactivity for desmin, myogenin or MyoD1.

2. Endophytic lesions

a. **Inverted papilloma**

These are rare lesions in the bladder comprising approximately 1% of urothelial neoplasms. These lesions are more often seen in male patients and with a wide age range (1st to 8th decade). They commonly present with gross or microscopic hematuria, similar with the other urothelial neoplasms. The bladder neck and trigone are the most common sites for its occurrence. Risk for recurrence is negligible (<1%).
Inverted papilloma is characterized by invaginations of thin delicate cords or trabeculae exhibiting peripheral palisading of basal cells and with central nuclear streaming. The cells are cytologically bland but may exhibit random degenerative-type of atypia. There should be no stromal response to the downward trabecular growths.

The most important differential diagnoses for inverted papilloma are the different papillary urothelial neoplasms exhibiting a prominent or exclusive inverted pattern of growth. The downward projections of papillary urothelial neoplasms with inverted growth may extend into adjacent to the muscularis propria. In contrast to inverted papilloma, papillary urothelial neoplasm with inverted growth shows expansion of trabeculae that is best appreciated on lower magnification. Further, the surface may show an exophytic papillary component, although purely endophytic growth is not uncommon. Papillary urothelial neoplasms with inverted growth also show a range of cytological atypia and cell disorganization similar to their exophytic counterparts. Grading essentially parallels the WHO 2004 for exophytic papillary urothelial tumors. Particularly in high grade tumors, careful search for stromal invasion should be made and requires presence of destructive infiltrative nests or single cells in desmoplastic stroma for the diagnosis.

b. von Brunn’s nests

These are invaginated nests of benign urothelium into the lamina propria and considered to be a variant of normal urothelium, but may also occur as response to inflammation. These lesions are common incidental microscopic findings and its frequency increases with age. The bladder trigone is the most common site for its occurrence. These lesions are completely benign and do not carry a risk for malignant transformation.

von Brunn’s nests are typically solid nests of urothelium in the superficial lamina propria that exhibits smooth, rounded contours. The proliferation can be florid and the nests may extend adjacent to the muscularis propria. The nests are populated by urothelium with similar normal cytology to surface urothelium and with orderly arrangement. The epithelial-stromal interface is sharp and the nests can be surrounded by chronic inflammatory cells. von Brunn’s nests can be associated with cystitis cystica and cystitis glandularis.

The most important differential diagnosis for florid von Brunn’s nest is the nested variant of urothelial carcinoma. These are invasive urothelial carcinoma with small infiltrative nests of relatively bland (“deceptively bland”) appearance. Muscularis propria involvement is common for this tumor which usually presents with higher stage. The nests may occasionally exhibit tubular formations. In contrast to florid von Brunn’s nests, nested urothelial carcinomas are deeply infiltrative and show increasing atypia with deeper infiltration. However, these features may not be appreciated in superficial biopsies or transurethral resections making the distinction very difficult, if not impossible. At the superficial aspect, in contrast to the round smooth contour of von Brunn’s nest, nested urothelial carcinoma contains smaller irregular nests, exhibits architectural complexity including fusion and does not exhibit glandular (columnar) or intestinal change.

3. Glandular/tubular lesions

a. Cystitis cystica/cystitis glandularis
**Cystitis cystitica** in contrast to von Brunn’s nests, have cystically dilated lumen. **Cystitis glandularis** are similar to cystitis cystica except that the central cysts are lined by glandular cells. **Cystitis glandularis with intestinal metaplasia** are similar to cystitis cystica except that the central cysts are lined by glandular cells. These lesions are superficial in location, although uncommonly when florid may reach the upper muscularis propria. The cells may exhibit minimal cytological atypia and mitosis is rare. There is no current convincing evidence to support that cystitis cystica or cystitis glandularis are neoplastic precursors.

The most important differential diagnoses for florid cystitis glandularis are bladder adenocarcinoma and urothelial carcinoma with glandular differentiation. Well differentiated bladder adenocarcinoma may exhibit some overlap with cystitis glandularis such as presence of dissecting mucin and muscularis propria extension. However, in contrast to florid cystitis glandularis, bladder adenocarcinoma exhibits architectural complexities, greater degree of cellular atypia, frequent mitosis, destructive invasion to muscularis propria and florid extravasated mucin. Further, bladder adenocarcinomas are usually high stage and deeply infiltrative, although these may not be appreciated in superficial biopsies or transurethral resection specimens. Similarly the glandular component of urothelial carcinoma with divergent differentiation also exhibits architectural complexities and greater cytologic atypicality and frequent mitosis than florid cystitis glandularis.

b. **“Tubular” nephrogenic adenoma**

As mentioned above, nephrogenic adenoma consists of papillary and tubular proliferations. This section pertains to the florid tubular growth nephrogenic adenoma at the prostatic urethra that can mimic prostatic adenocarcinoma in biopsy or transurethral resection specimens.

While nephrogenic adenoma is most commonly encountered in the bladder, approximately 15% of these lesions arise in the prostatic urethra and when florid may extend deep into the subjacent prostatic parenchyma. These tubules are typically small round to oval and are arrange in laminar fashion. Some tubules characteristically have thickened or prominent peritubular basement membrane. Some may also contain intraluminal basophilic or eosinophilic secretions, the latter imparting resemblance to tubules of thyroid follicles. The tubules are lined by bland flattened, cuboidal, or “hobnailed” cells, similar to its exophytic papillary component. Occasionally, the tubules may be very small, simulating signet ring cells.

The tubular proliferations of nephrogenic adenoma can mimic acinar or microacinar (Gleason pattern 3) prostatic adenocarcinoma in transurethral resections or biopsy specimens. Compounding the morphologic overlap is the AMACR overexpression and sometimes weak staining with PSA or PSAP in nephrogenic adenoma. In contrast to nephrogenic adenoma Gleason pattern 3 prostatic adenocarcinoma are usually monotonous and lacks the thickened basement membrane, dense eosinophilic secretions, hobnailed cells and cystic dilatations. Papillary component, if present, is helpful in diagnosis of nephrogenic adenoma. In difficult scenarios, use of immunohistochemical stains including pax-2, pax-8 and S1001A are helpful in the distinction (Table 3).

4. Reactive
a. **Reactive urothelial atypia**

Benign reactive or regenerative epithelial changes may occur in the urothelium secondary to infection, prior therapy, trauma, catheterization, etc. These morphological changes, taken out of context, can be mistaken as dysplastic changes of the urothelium. These changes require no treatment and may regress on alleviating the underlying causes.

Reactive urothelial often shows nucleomegaly with prominent nuclei. The chromatin is fine and evenly distributed. The urothelial cells are elongated in keeping with the polarity of normal urothelium. Mitosis can be present, but there should be no atypical forms. Associated acute or chronic inflammatory cells are often present, which should alarm the pathologists for the possible reactive nature of the atypia. Atypia due to radiation therapy may show cytoplasmic vacuolation and large nuclei with dark smudgy chromatin.

Distinction from urothelial carcinoma in situ (CIS) can be challenging. In contrast to reactive atypia, urothelial carcinoma in situ exhibits unequivocal high grade cytology. Cellular crowding and loss of polarity are appreciated even on lower magnifications. Marked nucleomegaly is frequent and with dark coarse chromatin. Mitosis may exhibit atypical forms. However, distinction is not always straightforward. In my practice, I use an immunohistochemical panel of CK20, CD44 and p53 (Table 4) as an adjunct to complement my morphologic interpretation. In contrast to reactive atypia, CIS usually shows full thickness CK20 staining, CD44 is negative or stains only residual basal cells, and p53 shows diffuse and strong nuclear staining.

In the background of intense inflammation, distinction between reactive and dysplastic change may not be possible particularly if the degree of atypia and appears to be out of proportion to the extent of inflammation. In this situation, a diagnosis of “urothelial atypia of uncertain significance” is rendered.

b. **Pseudocarcinomatous hyperplasia**

This reactive change is usually associated with prior regional radiation and/or chemotherapy. This lesion is characterized by benign urothelial proliferation exhibiting infiltrative growth that may mimic invasive urothelial carcinoma. These infiltrative nests may exhibit squamoid or squamous features and characteristically exhibit wrapping around blood vessels or fibrin. In contrast, invasive urothelial carcinoma has greater degree of cytologic atypicality and does not show cell wrapping of blood vessels or fibrin. Involvement of the muscularis propria is the most distinguishing feature, as this does not occur in pseudocarcinomatous hyperplasia. Importance of clinical knowledge for prior radiation therapy cannot be overemphasized.

5. Spindle cells

a. **Myofibroblastic proliferations**

Different terminologies have been used for benign myofibroblastic proliferations in the bladder. Terms such as inflammatory myofibroblastic tumor and pseudosarcomatous myofibroblastic proliferation are being applied. These lesions usually present in patients between the second and fourth decades of life. Some of
these patients may have prior history of trauma or bladder instrumentation (postoperative spindle cell nodule). Florid myofibroblastic proliferation can also be seen in association with invasive urothelial carcinoma. Benign myofibroblastic proliferations, in pure form, may recur (10%) but do not exhibit any metastatic potential.

Histologically, myofibroblastic proliferations are characterized by loose fascicles composed of tapered cells with elongated cytoplasmic process. The nuclei may be enlarged containing nucleoli and the chromatin is fine and dispersed. Mitosis may be abundant, but atypical forms should be absent. The cellularity may vary and can be cellular or myxoid with granulation tissue type vascularity. The lesion tends to be more cellular in the deeper aspect. Myofibroblastic proliferations may extend and involve the muscularis propria. A subset of these tumors expresses ALK1 (20-57%), and can be useful in the diagnosis.

The main differential diagnosis for myofibroblastic proliferations includes sarcomatoid urothelial carcinoma and leiomyosarcoma. In contrast to myofibroblastic proliferations, sarcomatoid carcinoma shows greater degree of nuclear pleomorphism and hyperchromasia, and atypical mitosis can be seen. Admixed CIS or exophytic papillary carcinoma or invasive epithelial nests may be present in sarcomatoid carcinoma. Malignant heterologous elements (carcinosarcoma) may also be present in sarcomatoid carcinoma. Leiomyosarcoma usually exhibits tight fascicles of spindled cells, but the more myxoid areas may resemble myofibroblastic proliferations. Similar to sarcomatoid carcinoma, leiomyosarcoma cells exhibit greater degree of nuclear pleomorphism and hyperchromasia, and atypical mitosis can be seen.

Myofibroblastic proliferations, sarcomatoid carcinoma and leiomyosarcoma may exhibit some immunophenotypic overlap particularly with SMA and pankeratin (Table 5). ALK1 positivity may be helpful to identify myofibroblastic proliferation, but this is not consistently present. Pankeratin may exhibit peripheral accentuation in myofibroblastic proliferations characteristics of myofibroblastic cells. p63 may show positivity in sarcomatoid carcinoma, although most intense staining can be seen in the more epithelioid appearing areas.
References


Table 1. Benign and malignant lesions mimicry in the genitourinary tract.

<table>
<thead>
<tr>
<th>Growth patterns</th>
<th>Benign lesions</th>
<th>Key malignant differential diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Papillary</td>
<td>• Papillary urothelial hyperplasia</td>
<td>• Papillary urothelial neoplasm (PUNLMP, low or high grade)</td>
</tr>
<tr>
<td></td>
<td>• Urothelial papilloma</td>
<td>• “Papillary” clear cell adenocarcinoma (rare)</td>
</tr>
<tr>
<td></td>
<td>• Papillary-polypoid cystitis</td>
<td>• “Papillary” nephrogenic adenoma</td>
</tr>
<tr>
<td></td>
<td>• “Papillary” clear cell adenocarcinoma (rare)</td>
<td>• Papillary urothelial neoplasm, including with denudation</td>
</tr>
<tr>
<td></td>
<td>• “Papillary” nephrogenic adenoma</td>
<td>• “Papillary” clear cell adenocarcinoma (rare)</td>
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<tr>
<td></td>
<td>• Prostatic-type polyp (rare)</td>
<td>• Prostatic ductal adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>• Fibroepithelial polyp (rare)</td>
<td>• “Botryoid growth” embryonal rhabdomyosarcoma</td>
</tr>
<tr>
<td>2. Endophytic</td>
<td>• Inverted papilloma</td>
<td>• Urothelial neoplasms with inverted growth (PUNLMP, low or high grade)</td>
</tr>
<tr>
<td></td>
<td>• Florid von Brunn’s nests</td>
<td>• Nested, tubular or microcystic variants of urothelial carcinoma</td>
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<tr>
<td></td>
<td></td>
<td>• Carcinoid tumor (rare)</td>
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<tr>
<td></td>
<td></td>
<td>• Paraganglioma (rare)</td>
</tr>
<tr>
<td>3. Glandular/tubular</td>
<td>• Florid cystitis cystica/glandularis</td>
<td>• Urothelial carcinoma with glandular differentiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Urothelial carcinoma with gland-like spaces</td>
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<tr>
<td></td>
<td></td>
<td>• Nested, tubular or microcystic variants of urothelial carcinoma</td>
</tr>
<tr>
<td></td>
<td>• Tubular nephrogenic adenoma</td>
<td>• Bladder adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>• Müllerian lesions (female)</td>
<td>• Secondary bladder adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>• Mesonephric remnant hyperplasia (rare)</td>
<td>• Clear cell adenocarcinoma</td>
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<td></td>
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<td>• Prostatic adenocarcinoma</td>
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<td></td>
<td></td>
<td>• Urothelial carcinoma with glandular differentiation</td>
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<td>• Nested, tubular or microcystic variants of urothelial carcinoma</td>
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<td></td>
<td></td>
<td>• Clear cell adenocarcinoma</td>
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<tr>
<td></td>
<td></td>
<td>• Secondary gynecologic clear cell adenocarcinoma (female)</td>
</tr>
<tr>
<td>4. Reactive</td>
<td>• Reactive urothelial atypia</td>
<td>• Urothelial carcinoma in situ</td>
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<td>• Polyoma virus inclusions</td>
<td>• Invasive urothelial carcinoma</td>
</tr>
<tr>
<td></td>
<td>• Pseudocarcinomatous hyperplasia</td>
<td>• Nested urothelial carcinoma</td>
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<tr>
<td>5. Spindle cell</td>
<td>• Myofibroblastic proliferation</td>
<td>• Sarcomatoid urothelial carcinoma</td>
</tr>
</tbody>
</table>
- Leiomyosarcoma
- Other spindle cell sarcoma
- Urothelial carcinoma with myxoid stroma

Table 2. Immunohistochemical staining of nephrogenic adenoma and papillary urothelial neoplasm.

<table>
<thead>
<tr>
<th>Immunostains</th>
<th>Nephrogenic adenoma</th>
<th>Papillary urothelial neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-CK</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pax-2</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Pax-8</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>p63</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Table 3. Immunohistochemical staining of nephrogenic adenoma and prostatic adenocarcinoma.

<table>
<thead>
<tr>
<th>Immunostains</th>
<th>Nephrogenic adenoma</th>
<th>Prostatic adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMACR</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PSA/PSAP</td>
<td>-/ weak+</td>
<td>+</td>
</tr>
<tr>
<td>Pax-2</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Pax-8</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>S1001A</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 4. Immunohistochemical useful in the distinction of reactive atypia versus urothelial carcinoma in situ (CIS).

<table>
<thead>
<tr>
<th>Immunostains</th>
<th>Normal urothelium</th>
<th>Reactive atypia</th>
<th>CIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK20</td>
<td>Superficial umbrella cells</td>
<td>Superficial umbrella cells</td>
<td>Full thickness</td>
</tr>
<tr>
<td>CD44</td>
<td>Basal/parabasal cells</td>
<td>Intermediate to full thickness</td>
<td>Residual basal cells or absent</td>
</tr>
<tr>
<td>p53</td>
<td>Absent or focal</td>
<td>Absent or focal</td>
<td>Diffuse and strong</td>
</tr>
</tbody>
</table>

Table 5. Immunohistochemical staining of myofibroblastic proliferations, sarcomatoid carcinoma and leiomyosarcoma.

<table>
<thead>
<tr>
<th>Immunostains</th>
<th>Myofibroblastic proliferations</th>
<th>Sarcomatoid urothelial carcinoma</th>
<th>Leiomyosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA</td>
<td>74-100% (diffuse)</td>
<td>39-74%</td>
<td>78-85% (diffuse)</td>
</tr>
<tr>
<td>Pan-CK</td>
<td>70% (peripheral accentuation)</td>
<td>70-84%</td>
<td>11-58%</td>
</tr>
<tr>
<td>P63</td>
<td>0%</td>
<td>50-58% (intense in epithelioid cells)</td>
<td>23% (focal/weak)</td>
</tr>
<tr>
<td>ALK</td>
<td>20-57%</td>
<td>0%</td>
<td>0-3%</td>
</tr>
</tbody>
</table>
II. Non-neoplastic renal diseases in tumor nephrectomy and nephroureterectomy specimens

This topic has been well reviewed previously (see reference #3 below), but I have reorganized the information to focus more on practical issues with recent updates for this course. Benign mimics of renal cell carcinoma are not typically problematic. However, chronic kidney disease (CKD, also formerly known as chronic renal failure) is observed in 25% of renal cancer patients before nephrectomy. Therefore, non-neoplastic renal diseases are frequently present in kidney and ureter cancer resection specimens,¹,³ which are often overlooked or ignored.² Given the good long-term outcome for most renal cancer patients, preservation of renal function is an important consideration, as urologists shift towards nephron-sparing surgery which further improves patient outcomes. Due to the importance of evaluating the non-neoplastic kidney in tumor nephrectomy and nephroureterectomy specimens, the College of American Pathologists has added this required parameter to the latest versions of the kidney and ureter cancer protocols and checklists which took effect at the start of 2010. Of note, the evaluation of the non-neoplastic kidney would be the most important element in benign neoplasms and the synoptic reports may not be triggered for these cases. In this session, we will review the common entities that are encountered and demonstrate a practical approach to diagnose non-neoplastic renal diseases.

A systematic evaluation of the non-neoplastic kidney will identify most of the common and clinically significant lesions. Careful light microscopic evaluation of the four anatomic compartments (glomeruli, tubules, interstitium, vessels) is sufficient for the vast majority of cases. Additional immunofluorescence (IF) or electron microscopy (EM) is only necessary in fewer than 5% of cases. These studies can be performed on the formalin-fixed, paraffin-embedded tissue, so storage of tissue in special media prior to formalin fixation is not necessary routinely. On occasion, a prior clinical history of proteinuria or other suspicion of a glomerular disease may be present and in that circumstance, appropriate tissues should be procured for IF and EM. If the glomeruli appear abnormal, some of the common entities will be reviewed below. If the glomeruli demonstrate no significant pathologic abnormalities or significant glomerulosclerosis, then this may be considered within normal limits. The percentage of global glomerulosclerosis should be estimated for every case. I will typically count 100 glomeruli to calculate this percentage. The extent of interstitial fibrosis and tubular atrophy (IF/TA) is an important parameter to assess, because this is generally the best prognostic indicator of clinical outcome for medical renal diseases. Many classification schemes use semi-quantitative grading for IF/TA (5-25% (mild), 26-50% (moderate) and >50% (severe)). The arteries often demonstrate intimal fibrosis and occasionally atheroemboli or thrombi.

Diabetes and hypertension are diseases with large impact worldwide. Therefore, diabetic and hypertensive nephropathy are the most common entities that are encountered in tumor nephrectomy or
nephroureterectomy specimens. The common pathologic features of these entities will be discussed. Diabetes affects 1 in 4 American adults with kidney cancer. Studies have shown that 10-20% of tumor nephrectomy specimens demonstrate features of diabetic nephropathy (DN). DN consists of histopathologic changes affecting all 4 anatomic compartments of the kidney, which can include any combination of the following:

- Glomerular hypertrophy
- Thickening of tubular and glomerular basement membranes
- Diffuse and/or nodular mesangial sclerosis (or matrix deposition)
- Mesangiolysis (dissolution and fraying of the matrix) with aneurysmal dilatation of the glomerular capillaries. Sometimes, mesangial nodules and aneurysmal dilation of the capillaries can still be appreciated within globally sclerotic glomeruli using the PAS or JMS stains.
- Hyalinosis or insudative lesions (“fibrin caps” and “capsular drops”) that represent localized collections of plasma proteins. Fibrin caps represent accumulations of hyaline within glomerular capillaries that may obliterate the lumen. Capsular drops are accumulations of similar hyaline material between the glomerular parietal epithelial cells and Bowman capsule. The hyaline is PAS positive with a homogeneous staining quality that has a staining intensity similar to that of the GBM.
- Hyalinosis can also be present within the arterioles in a subendothelial location, which may be segmental or circumferential. Vascular disease may be advanced and widespread in DN. Intimal fibrosis is often observed in the larger arteries. Characteristic subendothelial hyalinosis often involves both the afferent and efferent glomerular arterioles, but the appropriate tissue section through the vascular pole to visualize both arterioles is uncommon.
- Immunofluorescence microscopy typically demonstrates generally weak linear staining of the glomerular and tubular basement membranes.

There is no single histopathologic feature that is pathognomonic for DN, but the constellation of the aforementioned features is highly suggestive of this important and common diagnostic entity. Although nodular glomerulosclerosis (or nodular mesangial sclerosis) is a characteristic feature for DN, this finding is not specific and should provoke consideration of other entities, including renal amyloidosis, monoclonal immunoglobulin deposition disease, fibrillar glomerulonephritis, and immunotactoid glomerulopathy. A Congo red stain is used to help establish the diagnosis of renal amyloidosis, and the other entities can be diagnosed with the aid of IF and/or EM. Also, cases of idiopathic nodular glomerulosclerosis in association with hypertension and smoking have been reported
in patients without diabetes. Therefore, the pathologic diagnosis of DN should never be made without first establishing or confirming the clinical diagnosis of diabetes.

Arterionephrosclerosis (also called hypertensive nephropathy/nephrosclerosis) is the most common finding in adult tumor nephrectomy specimens. The term benign as a qualifier should be avoided, because this injury process can be quite harmful and frequently leads to ESRD. I prefer the descriptive term of arterionephrosclerosis because the clinical history of hypertension may not always be available at the time of pathologic evaluation. Hypertension affects roughly 25% of the US adult population and is the second most common cause of ESRD in the United States. Depending on the study, 25% to 60% of RCC patients are hypertensive. Bijol et al reported that 37% of nephrectomy specimens demonstrated mild to severe arterial and arteriolar sclerosis with minimal parenchymal changes, and an additional 22% of specimens demonstrated more severe vascular changes with parenchymal scarring. The diagnosis of arterionephrosclerosis is based on a constellation of the following nonspecific histopathologic features:

- Global glomerulosclerosis
- Interstitial fibrosis and tubular atrophy
- Arteriosclerosis

The gross appearance of the kidney shows granularity of the capsular surface, which corresponds to the light microscopic glomerular and tubulointerstitial scarring. Additional light microscopic features include proliferative and fibrotic intimal thickening with narrowing of the arteries that may be accompanied by replication of the internal elastic lamina. Subendothelial hyalinosis affecting primarily the afferent but not efferent glomerular arterioles is often observed. Early glomerular changes can be initiated by ischemic glomerular injury with thickening and wrinkling of the basement membranes, usually in a global distribution along with fraying of Bowman’s capsule. Collagen can accumulate in the urinary space and compress the shrunken glomerular tufts until eventually the entire glomerulus is sclerotic. Globally sclerotic glomeruli (global glomerulosclerosis) may be arranged in wedge-shaped zones of chronic ischemic injury of the outer cortex if the blood flow of larger renal arteries is compromised. Global glomerulosclerosis is associated frequently with tubular atrophy and interstitial fibrosis of the surrounding parenchyma because the blood exiting the efferent glomerular arteriole supplies the adjacent peritubular capillaries. Progressively more glomeruli are involved until the process results in ESRD with few residual intact nephrons. In advanced arterionephrosclerosis, there may be glomerular enlargement and superimposed focal segmental glomerulosclerosis, which has been postulated to be secondary to overloading the decreasing numbers of functional nephrons. There are no pathognomonic features for arterionephrosclerosis. In the absence of an immune complex–mediated injury, the combination of global glomerulosclerosis, IF/TA, and arteriosclerosis is
consistent with the diagnosis of arterionephrosclerosis. Given that global glomerulosclerosis involving more than 20% of glomeruli is predictive of worsening of renal function 6 months after nephrectomy, an estimated percentage of global glomerulosclerosis is an important feature to report.

Focal segmental glomerulosclerosis (FSGS) is the most common primary cause of adult nephrotic syndrome. Focal segmental glomerulosclerosis has been identified in up to 9% of tumor nephrectomies and is associated with hypertension, arteriosclerosis and parenchymal scarring. FSGS is characterized by segmental consolidation with capillary occlusion or collapse of the glomerular tuft. Consolidated segments have foam cells, mononuclear inflammation, and accumulation of extracellular matrix. The affected segments also have prominence or proliferation of visceral epithelium, often with cytoplasmic proteinaceous droplets. Immunofluorescence microscopy may reveal nonspecific trapping of larger molecules like IgM, C3, and sometimes C1q in the sclerosed or hyalinized glomerular regions. Electron microscopy reveals variable effacement and occasional microvillous transformation of podocyte foot processes with or without podocyte detachment from the GBM.

Crescentic glomerulonephritis (GN) is fortunately rare in tumor nephrectomy specimens, but this is a very important lesion to recognize as it represents a severe form of glomerular injury and requires prompt therapy. There are three main immunopathogenic etiologies of crescentic GN as follows: 1) pauci-immune (ANCA-associated); 2) anti-GBM disease; and 3) immune complex-mediated. The glomerular tufts unininvolved by crescents are often normal in appearance for those cases that are due to a pauci-immune or anti-GBM disease process. The presence of anti-neutrophil cytoplasmic antibodies (ANCA) can help establish the diagnosis of a pauci-immune crescentic GN, but ANCA is present in only approximately 80% of cases. There is at most one case report of anti-GBM disease in the setting of kidney cancer, so this entity is exceedingly rare. Crescentic GN due to an immune complex deposition process will demonstrate glomerular abnormalities in the form of leukocyte infiltration, mesangial hypercellularity, duplication of the GBMs or a combination of these features.

Any renal disease, including IgA nephropathy or membranous nephropathy, can be observed by chance in the non-neoplastic kidney of tumor nephrectomy specimens and the pathologic features of these entities are well reviewed in reference 3.
Protocols

Direct immunofluorescence performed on paraffin-embedded tissue:
1. Cut paraffin section at 2 microns.
2. Slides are dried for 20 minutes at 60-80°C.
3. Sections are deparaffinized in 3 changes of xylene for 2 minutes each, rehydrate with graded ethanol then distilled water.
4. Digest with 0.25% Trypsin-EDTA for 1 hour and 30 minutes at 37°C.
5. After digestion, sections are washed 5 times with distilled water and placed in PBS for 5 minutes.
6. Sections are then stained with FITC-conjugated antibodies: IgG, IgA, IgM, fibrinogen, kappa and lambda light chains, and albumin with 1:10 dilution for 1 hour in a moist chamber.
   Note: The complement components C3c and C1q do not generally survive digestion as well as other antigens and may react variably or give false negative reactions.
7. Wash in PBS for 1 minute.
8. Coverslip with Immunomount and examine under fluorescence microscope.

Processing tissue from paraffin for electron microscopy
1. Review stained hematoxylin and eosin slide from paraffin block with pathologist to identify area of interest.
2. Remove with razor blade that portion of block with tissue to be studied. Try to cut into 1.0mm³, if possible.
3. Place in xylene and place vial uncapped in old oven for 5 minutes x3 changes.
4. Wash well in absolute alcohol and follow the processing schedule below:
   Absolute alcohol  5 minutes
   95% ethanol      5 minutes
   70% ethanol      5 minutes
5. Wash well in 0.1M Milonig’s buffer for at least 10 minutes.
6. Post-fix for at least ½ hour with 1.0% osmium tetroxide (OsO₄).
7. Continue with the standard tissue processing schedule.
Relevant references: