PARTICULARLY PROBLEMATIC INTERPRETATIONS IN UROLOGIC PATHOLOGY

Moderators:
Holger Moch, University Hospital of Zürich, Zürich, Switzerland
Liang Cheng, Indiana University School of Medicine, Indianapolis, IN

7:00-7:05 pm
President's Remarks
Brett Delahunt, Wellington School of Medicine and Health Sciences; Wellington, New Zealand

7:05-7:30 pm
The non-neoplastic kidney in tumor resections: host versus tumor-related alterations
Stephen M. Bonsib, Louisiana State Univesity Heath Sciences Center, Shreveport , LA

7:30-7:55 pm
Cancer mimickers of benign prostatic lesions
Cristina Magi-Galluzzi, Cleveland Clinic, Cleveland, OH

7:55-8:20 pm
Diagnostic pitfalls in the pathologic staging of selected urologic malignancies
Mahul B. Amin, Cedars-Sinai Medical Center, Los Angeles, CA

8:20-8:45 pm
Cystic renal tumors: New entities and novel concepts
Holger Moch, University Hospital of Zürich, Zürich, Switzerland

8:45-9:10 pm
Selected problematic issues in bladder specimen interpretation
Robert H. Young, Massachusetts General Hospital, Boston, MA
The non-neoplastic kidney in renal tumors: host versus tumor-related alterations

Stephen M. Bonsib, MD
Louisiana State University Health Science Center, Shreveport, LA

- Perspective on chronic kidney disease
- Impact on the renal function of unilateral nephrectomy:
  - Healthy adult kidney donors
  - Children with Wilms tumor
  - Adults with renal cortical neoplasms
- Renal cortical landscape in which renal tumors develop (host-related alterations)
- Renal cortical manifestations of renal neoplasms (tumor-related alterations)

Key words: Renal cell carcinoma, Wilms tumor, nephrectomy, chronic kidney disease

Chronic kidney disease (CKD):
Definition: the presence of any of these findings
- eGFR <60mL/min per 1.73m²,
- albuminuria
- abnormal imaging study
CKD affects 1 in 9 adults and 60% of older adults have hypertension or diabetes, the two most common causes of CKD

Risk factors for renal cell carcinoma (RCC) also affect the non neoplastic kidney
- Smoking
- Industrial compounds
- End stage kidney disease (ESRD) and acquired renal cystic disease (ARCD)
- Genetic causes

Chronic kidney disease
Expectation: a substantial fraction of nephrectomies in adults should show CKD
Fact: clinical studies indicate that 25% of patients with RCC have CKD
Hope: the diagnosis of medical renal diseases in nephrectomies may affect the medical, non oncologic, management of these patients

What is the impact of nephrectomy on the contralateral kidney in the following patient groups?
- Healthy adult kidney donors
- Children with WT
- Adults with renal cortical neoplasms

Living kidney donation
1954 the 1st transplants were performed by Joseph Murray in Boston. Since the beginning concerns existed about the consequences of living with a single kidney. Over 50 years worth of clinical experience have been accrued; 25,500 LR TPs were performed in 2005

**Effects on remaining kidney in living-related donors**
Renal size increases 20% (see graph below)
GFR reduced 20-25%
Creatinine increases but remains in normal range in majority
BP increases but is lower in donors than age matched controls
Urinary protein increases but remains in the normal range
**Longevity:** Donors live longer than age matched controls
**Reason:** Kidney donors are healthier than controls

![](image)

**1st Author #Pts ESRD Yrs to RF**
- **Rosenblatt** 1,195 0.33% 15.5yr
- **Fehrman** 1,112 0.5% 20yr
- **Rizvi** 736 0.13% 12yr

**What is the impact of nephrectomy in children with WT?**

<table>
<thead>
<tr>
<th>Wilms tumor</th>
<th>#Pts</th>
<th># ESRD</th>
<th>% ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>5,526</td>
<td>28</td>
<td>0.6%</td>
</tr>
<tr>
<td>Bilateral</td>
<td>409</td>
<td>44</td>
<td>10.7%</td>
</tr>
<tr>
<td>Unilat + GU abnl*</td>
<td>179</td>
<td>27</td>
<td>15%</td>
</tr>
<tr>
<td>Bilat + GU abnl*</td>
<td>41</td>
<td>16</td>
<td>39%</td>
</tr>
</tbody>
</table>

*Denys-Drash syndrome, WAGR syndrome, GU anomalies

**What is the impact of nephrectomy adults?**
Risk of renal failure with partial vs radical nephrectomy [Urology 59:816, 2002]
Risk of CKD in partial versus radical nephrectomy
[Huang, et al http/oncology.thelancet.com]

Partial nephrectomy – magnitude of GFR reduction is proportional to the % volume loss

Partial nephrectomy in US is under utilized: 30-65% of procedures at tertiary care centers
Only 7.5 % of procedures nationwide
Summary: renal consequences of nephrectomy
• Organ donation conveys little renal risk because of the age and good health of donors
• Less 2% of Wilms tumor develop ESRD
• Nephrectomy in adults for RCC carries substantial risk for CKD and ESRD, especially with radical nephrectomy (approx. 20%)

What can the non neoplastic kidney in tumor nephrectomies show to forecast future ESRD or influence clinical management?
There have been two studies of medical renal diseases in tumor nephrectomy specimens

Bijol, et. al - 40/110 cases - 36% of cases had significant diseases
• ASVD most common
• DN 2nd most common
• Only 4 “Nephropathology dxs” - CTM, IgAN, Coll gn, thin BMN

Henrikson, et. al. – 24/246 cases - 10% significant glomerular disease
  Diabetic nephropathy most common [ASVD not analyzed]
  Only 5 “nephropathology dxs” - TM, FSGS

Bonsib - retrospective review of 55 renal neoplasms
Summary of peri-tumoral cortex tumor related changes
1. Most RCCs have a peritumoral pseudocapsule of several mms thick likely resulting from a combination of compressive atrophy, ischemic injury and obstruction. Direct parenchymal invasion without a pseudocapsule is uncommon; rarely a tumor appears to grow in harmony without a pseudocapsule.
2. Lymphangiogenesis occurs within the inflamed cortex and these neolymphatics may contain tumor. The normal lymphatics parallel arteries and veins; involvement by tumor is recognized this relationship.
3. Retrograde cortical spread of RCC occurs with extensive sinus vein involvement, to be discussed at the Evening Specialty Conference tomorrow.

Host-related findings in renal cortical neoplasms
Children
  Nephrogenic rests
  Diffuse mesangial sclerosis

Adults
  Papillary adenomas
  Hypertension/vascular disease/atheroembolism
  Diabetic glomerulopathy
  Renal cystic diseases

Host-related changes in Wilms tumors
WT is cured in 90% of pts; the remaining kidney is at risk due to:
• Irradiation and chemotherapy - develops post nephrectomy
• *Contralateral neoplastic disease
• Syndromic diseases associated with WT:
  • *Denys-Drash syndrome
  • WAGR syndrome
GU anomalies
*Exam adjacent cortex for: Diffuse mesangial sclerosis
Nephrogenic rests

Denys-Drash syndrome
Autosomal recessive disease resulting from WT1 mutations (11p13) >90% cases. WT1 is a zinc-finger transcription factor that regulates renal & gonad development
Clinical triad:
- Male pseudohermaphrodite
- Wilms tumor
- Glomerulopathy due to diffuse mesangial sclerosis
Incomplete forms occur. All WT cases need evaluation of non neoplastic cortex

Diffuse mesangial sclerosis
Rapidly progressive disease: renal failure develops within 2-3 years of diagnosis
Clinical forms of diffuse mesangial sclerosis
- Non syndromic/sporadic forms are most common
- Syndromic forms
  - Denys-Drash syndrome: WT1 mutations
  - Galloway-Mowat syn: t(3:16)(p14:p13.3) mutation
  - Oculorenal syndromes
  - Schimke immuno-osseous dysplasia: SMARCAL1 mutation

Nephrogenic rests - persistent foci of embryonal cells capable of developing into nephroblastoma their presence indicates a risk for contralateral WT. There are two types.

Perilobar NGR
Peripheral in renal lobe and sharply demarcated
Blastemal and tubules with scant or sclerotic stroma
Usually multifocal

Intralobar NGR
Random in lobe, irregular and intermingled with nephron elements
Blastema and tubules with predominance of stroma
Often unifocal

17% of patients with nephrogenic rests have syndromic disease

<table>
<thead>
<tr>
<th>All Pts/%</th>
<th>DDS</th>
<th>WAGR</th>
<th>GU anom</th>
<th>BWS</th>
<th>Hemi-hyper</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3,460/58%</td>
<td>37%</td>
<td>18%</td>
<td>44%</td>
<td>20%</td>
</tr>
<tr>
<td>PLNR</td>
<td>1,184/20%</td>
<td>0%</td>
<td>4%</td>
<td>9%</td>
<td>35%</td>
</tr>
</tbody>
</table>
ILNR 1,062/18%  59%  73%  43%  18%  17%
Both  248/4%  4%  4%  5%  27%  10%
Total  5,954  27  45  126  71  156
       100%  0.45%  0.8%  2.1%  1.2%  2.6%

Host-related changes in adults
“Non neoplastic” cortex in papillary RCC may show tubular cytologic atypia (“incipient neoplasms”) and papillary adenomas

Glomerulosclerosis - when is it important? This depends upon extent and type
“Normal” age-related glomerulosclerosis by decade
40 yr – 10% glomerulosclerosis
50 yr – 15% glomerulosclerosis
60 yr – 20% glomerulosclerosis
70 yr – 25% glomerulosclerosis
80 yr – 30% glomerulosclerosis
[Formula: Age/2 – 10 = % “normal” glomerulosclerosis]

Patterns of glomerulosclerosis
- Ischemic obsolescence secondary to hypertension and vascular disease and leading to global sclerosis shows a uniform pattern of collapse and a subcapsular predominance.
- Diabetic mesangial sclerosis in early cases is subtle, but obvious in advanced cases
- Focal segmental glomerulosclerosis and fibrous crescent are important to recognize

Cystic diseases associated with malignancy
Genetic
  • ADPKD - 1:500-1,000
  • Tuberous sclerosis - 1:10,000
  • Von Hippel-Lindau disease - 1:35-50,000

Acquired renal cystic disease

Dominant polycystic kidney disease and RCC
Walters & Braasch 1st description: 1 RCC /85 cases [Surg Gynec & Obst 58: 649, 1934]
The largest series: 3 cases Keith, et al, 1994
            3 cases Hemal et al, 2000
            10pts/Ubara et al, 2008 ASN
Denominator not known!

Questionnaire sent to 507 hospitals - 5,721 patients with renal cell carcinomas
233 pts - renal cystic diseases (3.9%)
  Simple cysts   72 pts
  **Acquired renal cystic disease**  **62 pts**
Cystic renal cell carcinoma   56 pts
Multilocular renal cysts   20 pts
"Polycystic kidney disease"   3 pts (10x)
Miscellaneous/unspecifi ed cysts   10 pts

Intracystic proliferations/polyps are present in 24% pts; precursors to RCC? [Gregoire et al AJKD 9:27-38, 1987]

Tuberous sclerosis complex
Autosomal dominant disease with dysgenic lesions: kidney, brain, skin, heart, lungs retina. TSC results from a mutation of TSC1 or TSC2, tumor suppressor genes that encode for hamartin and tuberin. Renal involvement occurs in 50-80% pts:

- Angiomyolipomas
- Cysts and cystic renal disease
- Malignant renal neoplasms

Renal manifestations of tuberous sclerosis complex
[Rakowski, et. al. Kidney Int. 70:1777, 2006]

<table>
<thead>
<tr>
<th>TSC1</th>
<th>TSC2</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td># Cases</td>
<td>36</td>
<td>75</td>
</tr>
<tr>
<td>Male</td>
<td>39%</td>
<td>57%</td>
</tr>
<tr>
<td>AML</td>
<td>22%</td>
<td>60%</td>
</tr>
<tr>
<td>Cysts &gt;4</td>
<td>17%</td>
<td>56%</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.8%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

Renal malignancy in TSC includes: RCC
Epithelioid AML (1/3 are malignant).

The contiguous gene syndrome
TSC2 gene is adjacent to PKD1 gene on chr 16. Dual mutations affect 5% TSC2 pts and cause the CGS. Renal failure develops early from PKD (<30yrs) and patients are at increased risk of malignancy. In CGS the cysts may be distinctive and lined by large hyperplastic eosinophilic cells

Renal cancers reported in TCS. Not all have the contiguous gene syndrome

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Year</th>
<th>Age (ave.=22 yrs)</th>
<th>B/M</th>
<th>PKD</th>
<th>Metastases/died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoyarna</td>
<td>2007</td>
<td>21 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breysem</td>
<td>2006</td>
<td>6 mo</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Ewalt</td>
<td>1998</td>
<td>7 y</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
von Hippel-Lindau disease
Autosomal dominant disease with: renal lesions, retinal angiomas, CNS hemangioblastomas, pheochromocytomas resulting from mutation (>300) VHL tumor suppressor gene (chr 3p25-26)
Multiple/bilateral clear cell lined cysts in 70-80%
Multifocal/bilateral clear cell RCCs in 40-60%

Acquired renal cystic disease and renal cell carcinoma
Dunhill, et. al. 1st noted an association between ARCD & RCC [J Clin Pathol 30:868, 1977]. 6/14 pts with “extensive bilateral” ARCD developed RCC noted at autopsy

Incidence of ARCD is proportional to duration of dialysis[ Matson, Med 69:217, 1990]

Incidence of RCC is proportional to the duration of dialysis
ARCD
20% - 1-3 years dialysis
33% - 3-5 years dialysis
90% - 5-10 years dialysis
20% patients with ARCD have RCC [Ishikawa, Nephron 97:c11, 2004]

Risk of RCC in ARCD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study</th>
<th>#Pts</th>
<th>ARCD</th>
<th>RCC</th>
<th>CCCa</th>
<th>Pap Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller</td>
<td>1989</td>
<td>Autopsy</td>
<td>155</td>
<td>58%</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gulaniker</td>
<td>1998</td>
<td>US/CT</td>
<td>206</td>
<td>31%</td>
<td>3.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farivar-Mohseni</td>
<td>2005</td>
<td>US/CT</td>
<td>852</td>
<td></td>
<td>1.6%</td>
<td>43%</td>
<td>57%</td>
</tr>
<tr>
<td>Kojima</td>
<td>2006</td>
<td>US/CT</td>
<td>2024</td>
<td></td>
<td>1.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denton</td>
<td>2002</td>
<td>U-neph</td>
<td>266</td>
<td>33%</td>
<td>4.2%</td>
<td>55%</td>
<td>45%</td>
</tr>
<tr>
<td>Schwarz</td>
<td>2007</td>
<td>US/neph</td>
<td>561</td>
<td>23%</td>
<td>4.8%</td>
<td>58%</td>
<td>42%</td>
</tr>
<tr>
<td>Takahashi</td>
<td>1993</td>
<td>3-4mm</td>
<td>50</td>
<td></td>
<td>8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ESK with ARCD
Cysts range from simple to “hyperplastic”; adenomas and RCC are common. All RCC types occur and two new type: ARCD-assoc RCC and Papillary clear cell ca

2,624 patients - ave. 11.2 years dialysis
RCC developed in 44 patients (1.7%): 35/44 had ARCD
9/44 no cysts (not all pts have ARCD!)

Genetic renal cystic diseases and cancer

<table>
<thead>
<tr>
<th>Cystic disease</th>
<th>Incid of RCC</th>
<th>Type of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>vHL</td>
<td>40-60%</td>
<td>Clear cell ca</td>
</tr>
<tr>
<td>TSC +/- CGS</td>
<td>2-3%</td>
<td>Clear cell ca</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epithelioid AML</td>
</tr>
</tbody>
</table>


ESK +/-ARCD  1-2.5%  All usual types  
2 new types  
ADPKD  10x increase  Multiple types  

**Summary: the non-neoplastic cortex**  
**Tumor related changes**  
- Compressive atrophy of nephron elements +/- fibrous pseudocapsule  
- Peritumoral inflammation and lymphangiogenesis  
- Retrograde cortical spread of RCC  

**Major Host related changes**  
- **Children**  
  - Nephrogenic rests  
  - Diffuse mesangial sclerosis  
- **Adults**  
  - Hypertension/vascular disease  
  - Diabetic glomerulopathy  
  - Renal cystic diseases and ESK  

**Significance of chronic kidney disease**  
- Patients with chronic kidney disease are at substantial risk of developing ESRD  
- The life expectancy of older patients with ESRD is 2.2-4.3 years, substantially less that the life expectancy of a patient with stage 1, 2 or 3 RCC.  

**Significance of ASVD and DN**  
<table>
<thead>
<tr>
<th></th>
<th>Ave age</th>
<th>Crt &gt;6mo</th>
<th>Δ crt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>47</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>ASVD - all</td>
<td>63</td>
<td>2.0</td>
<td>0.6</td>
</tr>
<tr>
<td>ASVD - mod/sev</td>
<td>65</td>
<td>2.3</td>
<td>0.7</td>
</tr>
<tr>
<td>DN - all</td>
<td>67</td>
<td>2.5</td>
<td>0.9</td>
</tr>
<tr>
<td>DN- mod/sev</td>
<td>69</td>
<td>4.6</td>
<td>1.9</td>
</tr>
</tbody>
</table>

A small increase in serum creatinine reflects a large decrease in renal function  

**Comments**  
1. Identification of organ damage attributable to diabetes and ASVD may initiate medical intervention or motivate the patient and clinician to monitor treatment of these diseases.
2. There is no data or study that has explored if under diagnosis of medical disease causes harm.
3. Since both diabetes and hypertension are often under treated, a diagnosis with a comment may improve medical care and reduce morbidity.

ADASP and CAP checklists for non-neoplastic kidney findings

ADASP 11/2003 Additional findings & comments:
- Cortical adenoma
- Pyelonephritis
- Cortical infarct
- Arterio/arteriolonephrosclerosis
- Other

CAP 1/2005 Additional pathologic findings:
- Inflammation
- Glomerular disease
- Interstitial disease
- Other

Recommendations
- Pathologists must perform a systematic review of major compartments, glomeruli, tubulo-interstitium and vasculature in a section furthest removed from the tumor.
- Any suspicion of a glomerular abnormality should prompt a PAS and/or silver stain and initiate consultation with a nephropathologist.
- The RPS and ISUP should craft wording to be used for comments when moderate-severe diabetic glomerulopathy and ASVD are present to provoke a clinical response.
Cancer mimickers of benign prostatic lesions
Cristina Magi-Galluzzi,
Director, Genitourinary Pathology
Assistant Professor, Lerner College of Medicine
Cleveland Clinic, Cleveland, OH

- Classification of prostatic adenocarcinoma mimicking benign conditions
- Features helpful in establishing a malignant diagnosis
- Use of immunohistochemical markers as an aid in the differentiation
- Gleason grading and potential prognostic and therapeutic implications

Keywords: Prostate cancer; Variants; Pseudohyperplastic; Atrophic; Treatment effect; Ancillary studies.

As there are many benign conditions, which can mimic cancer, some carcinomas may resemble benign prostate process due to their bland cytology or architectural pattern. A careful correlation of several morphological features along with adjunctive immunohistochemistry stains is necessary to arrive at the correct diagnosis.

<table>
<thead>
<tr>
<th>Prostatic carcinoma variant</th>
<th>Benign condition mimicked</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Well-differentiated PCA</td>
<td>- Adenosis (AAH)</td>
</tr>
<tr>
<td>- Atrophic PCA</td>
<td>- Atrophy</td>
</tr>
<tr>
<td>- Foamy gland PCA</td>
<td>- Xanthoma, Cowper’s glands</td>
</tr>
<tr>
<td>- PCA with inflammation</td>
<td>- Inflammatory atypia</td>
</tr>
<tr>
<td>- Signet ring PCA</td>
<td>- Artifactual changes</td>
</tr>
<tr>
<td>- Hormonal therapy effect</td>
<td>- Histiocytic infiltrate, atrophy</td>
</tr>
<tr>
<td>- Pseudohyperplastic PCA</td>
<td>- Epithelial hyperplasia, HGPIN</td>
</tr>
<tr>
<td>- Hypernephroid/clear cell PCA</td>
<td>- Granulomatous prostatitis</td>
</tr>
</tbody>
</table>
- Ductal adenocarcinoma, papillary pattern

- High-grade prostatic intraepithelial neoplasia (PIN)

Atrophic prostate cancer

Acinar atrophy and postatrophic hyperplasia (PAH) in the prostate are commonly confused with adenocarcinoma. The converse situation may also present a diagnostic dilemma. Prostatic adenocarcinoma (PCA) with atrophic features is an unusual finding that is easily confused with benign acinar atrophy.

PCA with atrophic features, described in 1997, is defined as a proliferation of malignant acini that architecturally resemble atrophy or PAH on scanning magnification owing to the malignant glands' scant cytoplasm, but retain the diagnostic cytologic features of cancer. The acini are round, often dilated and distorted, and lined by flattened attenuated epithelium with scant cytoplasm and a high nucleus-to-cytoplasmic ratio. Each case of atrophic cancer has cytologic features of malignancy in at least some of the acini, including enlarged nuclei and prominent nucleoli and/or an infiltrative pattern.

Although benign atrophy may appear infiltrative as a collection of glands, it lacks the truly infiltrative appearance of some atrophic cancers, where atrophic glands insinuate themselves as isolated units between benign glands.

Egan et al. have reviewed 202 totally embedded whole-mount radical prostatectomy specimens with adenocarcinoma, 100 consecutive routine needle biopsy specimens, and five additional selected needle biopsy specimens, to investigate the frequency of prostatic adenocarcinoma with atrophic features and the histologic criteria that allow its distinction from benign processes. None of the patients had received androgen deprivation therapy before specimen acquisition.

Atrophic features were identified in cancer in six radical prostatectomy specimens (3%) and two routine needle biopsy specimens (2%). Carcinoma involved the peripheral zone in all RP cases, and the transition zone was additionally involved in 3. Carcinoma with atrophic features comprised a mean of 27% of each tumor in the prostatectomy specimens (range 10-60%) and 24% in the needle biopsies (range 10-90%). In the prostatectomy cases, the Gleason score of the cancers was 7 (in five cases) and 5 (in one case); in the biopsy
specimens the Gleason score was 6 (in five cases) and 7 (in two cases). In addition, atrophic cancer in the prostatectomy cases had hard luminal eosinophilic proteinaceous secretions (all cases), blue mucin (five cases), crystalloids (two cases), apocrine blebs (three cases), collagenous micronodules (one case), and high-grade prostatic intraepithelial neoplasia (HGPIN) within two high-power fields (three cases); the histological features were similar in the needle biopsy specimens. Stromal fibrosis was detected in all cases. One case had mild patchy chronic inflammation associated with the atrophic features.

The diagnosis of carcinoma with atrophic features can be challenging and one has to rely on a combination several architectural and cytological features. Reactive cytologic atypia due to inflammation is a frequent problem, and caution should be exercised in the diagnosis of carcinoma with atrophic features in this setting.

**Key histological features helpful to differentiate it from benign atrophy:**
1) Malignant acini invariably infiltrate between preexisting benign acinar structures (particularly on RP).
2) The abnormal architecture is sometimes subtle at low magnification due to the inconspicuous nature of the attenuated epithelium and occasionally spaced acini.
3) Usual concomitant presence of conventional adenocarcinoma of the prostate is typically present and very helpful to facilitate its recognition.
4) Greater cytological atypia than seen in typical benign atrophic glands. The cytoplasm is relatively scant but still more than typical atrophic glands giving them less basophilic appearance then conventional atrophic glands.
5) Basal cell markers are negative. However, the absence of basal cell layer is not sufficient for the diagnosis of carcinoma without other supporting features.
6) AMACR may demonstrate low sensitivity for this cancer (only 69.6% of cases are positive).

<p>| Benign acinar atrophy | Adenocarcinoma with atrophic features |</p>
<table>
<thead>
<tr>
<th><strong>Architecture</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Low-power features</td>
<td>- Preservation of lobular architecture</td>
<td>- Loss of lobular architecture</td>
</tr>
<tr>
<td>- Basal cell layer</td>
<td>- Dilated and/or small and distorted acini</td>
<td>- Dilated and/or small and distorted acini</td>
</tr>
<tr>
<td></td>
<td>- Usually intact</td>
<td>- Absent</td>
</tr>
<tr>
<td><strong>Cytology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Nuclei</td>
<td>- Normal or mild enlargement</td>
<td>- Moderate to severe enlargement</td>
</tr>
<tr>
<td>- Nucleoli</td>
<td>- Usually inconspicuous</td>
<td>- Prominent</td>
</tr>
<tr>
<td><strong>Luminal content</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hard eosinophilic proteinaceous secretions</td>
<td>- Rare</td>
<td>- Very common</td>
</tr>
<tr>
<td>- Basophilic mucin</td>
<td>- Rare</td>
<td>- Common</td>
</tr>
<tr>
<td>- Crystalloids</td>
<td>- Rare</td>
<td>- Occasional</td>
</tr>
</tbody>
</table>

The luminal content of the acini also provides a clue to the malignant nature of the lesion.

Adenocarcinoma with atrophic features usually comprises only a minority pattern of a prostatic carcinoma. The adjacent typical acinar carcinoma, usually Gleason pattern 3, is more easily recognized as malignant and is invariably helpful in arriving at the correct diagnosis.

Prostatic adenocarcinoma with atrophic features is uncommon but is likely to represent a significant diagnostic problem, particularly in small needle biopsy specimens. Familiarity with this pattern will assist the pathologists in recognizing it and avoid underdiagnosis of malignancy.

**Pseudohyperplastic prostate cancer**

PCA resembling architecturally benign hyperplastic prostatic glands and/or HGPIN is a recently recognized entity. Humphrey et al. were the first to study this entity formally in a large series, during which they coined the term
“pseudohyperplastic prostatic adenocarcinoma”. They detected foci of adenocarcinoma with pseudohyperplastic features in 2% and 11% of prostate needle biopsy and radical prostatectomy specimens, respectively. The deceptively benign architectural features of the pseudohyperplastic glands make this pattern of prostate cancer difficult to diagnose, particularly on needle biopsy specimens. This form of PCA is composed of numerous markedly dilated glands that are almost back-to-back with straight even luminal borders, and abundant cytoplasm. Complex undulating architecture and papillary infolding, features more typical of benign glands, are common finding in pseudohyperplastic prostate cancer. At higher magnification, the nuclei are enlarged with numerous prominent nucleoli. Levi & Epstein studied 20 cases (16 needle biopsies, 2 TURP and 2 enucleations) in which ≥60% of the cancer had benign architectural features, including papillary infolding (all cases), large atypical glands (95%), branching (45%), and corpora amylacea (20%). Within the pseudohyperplastic foci, histological features helpful in establishing a malignant diagnosis were: nuclear enlargement, occasional to frequent nucleoli, pink amorphous luminal secretions, and crystalloids. In 25% of the cases, the pseudohyperplastic glands showed an infiltrative pattern of growth, in which neoplastic glands spread diffusely between benign glands.

Key histological features helpful to separate pseudohyperplastic PCA from hyperplasia or HGPIN:

1) Architectural pattern of numerous closely packed glands with complex and undulating architecture and frequent papillary infolding. This diagnosis should be made with extreme caution when the focus of concern is small as the diagnosis of HGPIN cannot be excluded with certainty. Immunohistochemical markers may not be very helpful in this circumstance.

2) Nuclear features are usually typical of conventional adenocarcinoma with enlarged nuclei and prominent nucleoli.

3) The cytoplasm is amphophilic with frequent amorphous secretions and blue mucin.
4) The conventional basal cell markers provide an objective support to the diagnosis. AMACR has lower sensitivity for this type of cancer than conventional adenocarcinoma.

Majority of pseudohyperplastic carcinomas represent Gleason 3 pattern.

Foamy gland and pseudohyperplastic carcinomas are two uncommon variants of prostate cancer and often pose diagnostic challenges on needle biopsies. AMACR is potentially a useful diagnostic marker for pseudohyperplastic prostate cancer when the pathologist favors the diagnosis of this form of cancer on routine stained sections and stains for basal cells are negative, yet still a definitive diagnosis of cancer is difficult because of the cancers' deceptively benign appearance. Positive staining for AMACR can provide the additional confidence to establish a definitive malignant diagnosis. The major caveat in the interpretation of positive staining is that HGPIN cannot be in the differential diagnosis. A total of 70-77% of pseudohyperplastic prostate cancer has been reported positive for AMACR antibodies. Staining was often heterogeneous with different staining intensities within the same lesion.

It is critical not to underdiagnose pseudohyperplastic prostate cancer as a benign process because it shares with atrophic adenocarcinoma and foamy gland cancer the potential to behave aggressively despite its benign appearance.

**Hormonal therapy effect on prostate cancer**

Following androgen deprivation therapy, benign and hyperplastic prostatic acini are atrophic and collapsed, typically with prominent basal cell hyperplasia. The altered epithelium displays involution, lobular and acinar atrophy, cytoplasmic clearing and vacuolization, nuclear and nucleolar shrinkage, and chromatin condensation. Decreased glandular elements are accompanied by increased, sometimes hypercellular stromal tissue with scattered lymphocytic infiltrates. The majority of treated PCA architecturally show compresses fused glands, sheets of tumor cells, small cell clusters, and single-file cells. The cytoplasm is clear or vacuolated. Nuclei are small, round, hyperchromatic and centrally
located. The nucleoli may be large, but are usually inconspicuous. Large clear tumor cells with a dense inflammatory lymphohistiocytic response have been reported in cases with scant residual tumor. In some cases the cells of neoplastic glands may be almost completely degenerated, leaving irregular acid mucinous pools with rare cancerous cells.

Following therapy with LHRH agonists and flutamide, the neoplastic acini may also become atrophic. At higher power, these neoplastic glands are identical to benign atrophic glands. Only their crowded infiltrative appearance is diagnostic of adenocarcinoma. With progressive alterations, the atrophic neoplastic glands develop pyknotic nuclei with abundant xanthomatous cytoplasm. These cells then desquamate into the lumen of the malignant glands where they resemble histiocytes. At low power, these areas may be difficult to identify, and often the only clue to areas of hormonally treated carcinoma is a fibrotic background with scattered chronic inflammation. Some patterns present difficulties in differentiating tumor from treatment-altered benign glands and lymphocytes. Cancer cells can become so inconspicuous to pose a risk of underdiagnosis: individual sparsely distributed cancer cells should be sought at higher magnification.

Immunohistochemistry for PSA or cytokeratin can aid in the diagnosis of carcinoma in these cases, by identifying the individual cells as of prostatic origin.

REFERENCES


INTERNATIONAL SOCIETY OF
UROLOGIC PATHOLOGY

PATHOLOGIC STAGING OF SELECT
UROLOGIC MALIGNANCIES

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TOPICS FOR DISCUSSION
• Discuss changes in pathologic staging categories in urologic malignancies in the 7th edition (2011) AJCC Staging System, to be released later this year
• Select problematic areas:
  • Prostate – bladder neck involvement
  • Urinary bladder – determination of type of muscle invasion
  • Urothelial carcinoma of prostate – evaluation of prostatic stromal invasion

PROSTATE

SUMMARY OF CHANGES
• Extraprostatic invasion with microscopic bladder neck invasion (T4) is included with T3a
• Gleason Score now recognized as the preferred grading system
• Prognostic factors have been incorporated in the Anatomic Stage/Prognostic Groups
  • Gleason Score
  • Preoperative prostate specific antigen (PSA)
### KIDNEY

**SUMMARY OF CHANGES**

- T2 lesions have been divided into T2a (greater than 7 cm but less than or equal to 10 cm) and T2b (greater than 10 cm)
- Ipsilateral adrenal involvement is reclassified as T4 if contiguous invasion and M1 if not contiguous
- Renal vein involvement is reclassified as T3a
- Nodal involvement is simplified to N0 vs. N1

### Tables and Diagrams

**Table:**

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**Diagram:**

- **Sixth Edition:** T2: Tumor more than 7 cm in greatest dimension, limited to kidney
- **Seventh Edition:** T2: T2a (greater than 7 cm but less than or equal to 10 cm) T2b (greater than 10 cm)
<table>
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NCDB- 47,909 cases

URINARY BLADDER

SUMMARY of CHANGES

- Subepithelial invasion of prostatic urethra is not pT4 disease.
  - pT4 defined as prostatic stromal invasion (seminal vesicles, uterus, vagina, pelvic wall, and abdominal wall also qualify)
- Grading: a low and high grade designation will replace previous 4 grade system to match current WHO/International Society of Urologic Pathology (ISUP) recommended grading system
- Nodal involvement is simplified to N1 (single positive) and N2 (multiple positive) - instead of N1, N2, and N3 which had size criteria within
Subepithelial invasion of prostatic urethra is not pT4 disease.

RENAL PELVIS AND URETER

SUMMARY OF CHANGES

Grading: a low and high grade designation will replace previous 4 grade system to match current WHO/International Society of Urologic Pathology (ISUP) recommended grading system.

URETHRA

SUMMARY OF CHANGES

Urothelial (Transitional Cell) Carcinoma Of The Prostate

- pT1: Tumor invades urethral subepithelial connective tissue (for tumors involving prostatic urethra only)
PENIS

SUMMARY OF CHANGES

• T1 has been subdivided into T1a and T1b based on the presence or absence of lymphovascular invasion or poorly differentiated cancers

• T3 category is limited to urethral invasion and prostatic invasion is now considered T4
TESTIS

SUMMARY OF CHANGES
The definition of TNM and the Stage Grouping for this chapter has not changed from the Sixth Edition

Staging of Bladder Cancer:
Evaluation of Muscularis Propria Invasion

Pathologic Staging of Bladder Cancer

- pT1a: non-invasive neoplasm
- pT1b: carcinoma in situ (flat)
- pT1c: invasive into lamina propria
- pT2: invasive into muscularis propria
- pT3: invasive into perivesical fat
- pT4: invasive into adjacent organs

No change in Seventh edition of AJCC
LAMINA PROPRIA-MUSCULARIS MUCOSAE

- Thin wispy muscle bundles
- 94-100% bladders
- Associated with large caliber blood vessels
- Awareness important so as not to overstage T1 as T2

M. mucosae muscle pattern - typical

Wispy or thin muscle bundles, 71/150 (47%)
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**Typical pattern:**
- Arranged in groups
- Distinct compact bundles
- Smooth outline of bundles
- Several layers both horizontally and vertically

**Muscularis propria**

**2 types of muscle - awareness important for pT staging**

LP inv. (M. mucosae)- pT1

M. propria inv. - pT2

**Muscularis mucosae vs. Muscularis propria**
- Inflammatory & desmoplastic response of invasion
- Prior biopsy
  - Lack of parallel orientation
- Hypertrophy of m. mucosae
- Difficult cases - conservative stance
- Express inability to be certain
Muscularis mucosa or muscularis propria?
**Muscle Markers**

- Smooth muscle actin (SMA)
- Desmin
- H-caldesmon
- Smooth muscle myosin heavy chain
- Smoothelin
  - Contractile protein
  - Fully differentiated muscle cells
  - Hyperplastic muscularis mucosa negative to weak
  - Diffuse positivity in muscularis propria
  - 100% specificity with diffuse staining


![Image of muscular tissue with indicated areas of hypertrophic muscularis mucosa]
SMA

Smoothelin: Negative – Suggestive of M. Mucosa

SMOOTHELIN at USCAP 2009

- GP Paner, Poster Monday 9.30
  - Confirms value of smoothelin in TURBT specimens.
  - IR retained in the background of thermal tissue injury & involvement by carcinoma

- Dvorakova et al, Poster Tuesday 9.30 am
  - Smoothelin proved to be a reliable marker

- S Khayyata et al, Poster Monday 1pm
  - Intensity and extent of smoothelin staining accurately distinguishes MP from MM in the intact bladder
  - Documentation of patterns of smoothelin expression is warranted – variable positivity in GU tract smooth muscle may help define functional status (ureter, bladder neck) &/or impact carcinoma staging (bladder, urachus)
Staging Issues in “Urothelial Carcinoma of the Prostate”

- The prostate is involved in approximately 30% of patients with invasive bladder carcinoma
- Occasionally, urothelial carcinoma involving the prostate may be first documented on prostate biopsy
- Staging issues are problematic and not well covered in traditional text books

UROTHelial CARCINOMA INVOLVING THE PROSTATE GLAND

- The prostate is involved in approximately 30% of patients with invasive bladder carcinoma
- Occasionally, urothelial carcinoma involving the prostate may be first documented on prostate biopsy
- Staging issues are problematic and not well covered in traditional text books

INVILOVEMENT OF PROSTATE GLAND

- Direct invasion of prostate gland: pT4a of bladder cancer – poor prognosis
- Urothelial CIS of urethra: if margin status (+), urethrectomy
- Involvement of prostatic glands without stromal invasion (pTCS): not adverse
- Involvement of seminal vesicle without stromal invasion: no ↑ risk of progression
- Involvement of prostate or seminal vesicle stroma (pT2): poor prognosis, ↑ metastasis

*Staging for urothelial carcinoma of prostate
T4 Bladder Carcinoma

- Direct extension of a urothelial carcinoma into prostatic stroma equates to pT4 disease- “urinary bladder cancer staging” system
- Extension of prostatic urethral urothelial carcinoma into prostatic stroma is not pT4 disease- pT2 by “urothelial carcinoma of the prostate staging” system
Bladder neck invasion- pT3a disease in AJCC, 7th Edition
Bladder neck

Histo-anatomy

- Most distal portion of bladder
- It merges with prostate gland in males
- It is formed by trigonal, detrusor, and urethral musculature; internal sphincter present in this region
- Devoid of glandular tissue- occasionally may have prostatic ducts/acini
Bladder neck

- Invasion of bladder neck interpreted as extension beyond prostate - pT4 PCa (AJCC, 6th Edition)
- SEER Site specific coding guidelines - ICD 67.5 for bladder neck (Bladder: 67, Prostate: 61)
- Multiple recent studies have documented that microscopic bladder neck involvement has outcome different from PCa involving rectum or striated sphincter
- Microscopic bladder neck invasion defined as pT3 disease in AJCC, 7th Edition

Microscopic Bladder Neck Invasion (pT3 disease)

- Microscopic involvement of muscular wall of bladder neck by PCa
- Absence of prostatic glands in corresponding slide or prostate glands in stroma distinct from bladder neck muscle

Handling of radical prostatectomy

- Prostate base (bladder neck) margin-inked and handled as a cone
- Microscopic sections - bladder neck tissue may or may not be present - depends on
  - Bladder neck sparing surgery
  - Age of the patient
  - Other surgical factors influencing dissection
Microscopic Bladder Neck Invasion (pT3 disease)

- Outcome of patients with bladder neck involvement is different from pT4 disease and similar to extraprostatic extension at other sites

- Prostate base (bladder neck) margin- positive if tumor inked in coned prostate base and not if tumor in bladder neck muscle

- Prostate base (bladder neck) margin- important adverse parameter- worse than other positive surgical margins
Cystic Renal Tumors: New Entities and Novel Concepts
Holger Moch, Department Pathology, University Hospital Zurich, Switzerland

Department Pathology, University Hospital Zurich, Switzerland
- Differential diagnosis of renal tumors with cysts
- Novel entities of cystic renal tumors
- VHL gene alterations and cyst formation
- A model for cystic and non-cystic tumorigenesis of clear cell carcinoma

Keywords: Multilocular cystic renal carcinoma; Tubulocystic renal cancer; Renal cancer in end-stage renal disease; cilia formation

Overall, cystic change occurs in up to 15% of RCCs. Cystic renal tumors are not classified as separate pathologic entities. Renal tumor entities with characteristic cysts include:

- Cystic Nephroma / Mixed Epithelial and Stromal Tumor
- Tubulocystic carcinoma
- Synovial sarcoma ("Cystic embryonal sarcoma")
- Acquired Cystic Disease-associated Renal Cell Carcinoma
- Clear cell renal cell carcinoma with prominent cysts
- Multilocular cystic renal cell carcinoma

MIXED EPITHELIAL AND STROMAL TUMOR/CYSTIC NEPHROMA
In 1993, Pawade et al. described three cases of a novel cystic renal tumor which they termed “cystic hamartoma of the renal pelvis.” Additional cases have been reported as “mesoblastic nephroma of adults” and as “mixed epithelial and stromal tumor of the kidney.” The last terminology is preferred since these tumors clearly have no relationship to mesoblastic nephroma of infants and since they appear to be mixtures of neoplastic epithelial components and spindle cells. There is a strong predominance of women, often of perimenopausal age. Most of these tumors appear to arise centrally in the kidney and to grow as expansile masses. The tumors lack a thick fibrous wall but compressed renal tissue usually forms a pseudocapsule in the larger tumors. The tumors are grossly composed of multiple cysts and solid areas. The solid areas may be extensive. The septa of the cysts are thicker than is typical of cystic nephroma, cystic partially differentiated nephroblastoma, and multilocular cystic clear cell renal cell carcinoma. These are complex tumors composed of large cysts, microcysts, and tubules. The largest cysts are lined by columnar and cuboidal epithelium which sometimes forms small papillary tufts. The microcysts and tubules are lined by flattened, cuboidal, or columnar cells. The stroma consists of a variably cellular population of spindle cells with plump nuclei and abundant cytoplasm. Areas of myxoid stroma and fascicles of smooth muscle cells may be prominent. Blood vessels with thick walls may be present. Fat cells may be present. Mitotic figures and atypical nuclei have not been reported. The
The relationship between cystic nephroma and mixed epithelial and stromal tumor of the kidney has been controversially discussed. Recently, the term Renal Epithelial and Stromal Tumor (REST) has been proposed as a unifying term of Cystic Nephroma and Mixed Epithelial and Stromal Tumor.

References

Tubulocystic Renal Cell Carcinoma
Tubulocystic Carcinoma of the Kidney is a recently described tumor entity which was not included in the 2004 WHO classification. The tumors were originally thought to represent low grade collecting duct carcinomas. Recently, a large series of 31 cases have been published. (Amin et al.). In the published series, men have predominated. Follow up data are limited but only two patient has been reported to have had metastasis. The tumors have ranged from 2 mm to 85 mm in diameter. Tubulocystic carcinoma has a distinctive gross appearance: well-circumscribed with an off-white cut spongy surface which shows innumerable cysts filled with clear fluid. The cyst lining is smooth and the cysts are fairly uniform in size, compared to the highly variable sizes of the cysts of clear cell renal cell carcinoma. Tubulocystic carcinoma is seen microscopically to be composed of cysts of variable size ranging down to ones of the diameter of a cross section of a renal tubule. The cysts are lined by a single layer of carcinoma cells with eosinophilic cytoplasm. The contours of these cells varies from cuboidal to hobnail or flattened. The nuclei are spherical and nucleoli are usually prominent in many of the nuclei. Necrosis and mitotic figures are rare. The septa between the cysts are thin and composed of fibrous tissue. Immunohistochemically, Azoulay et al. found 11 of 11 tumors to react with antibody to CD10. Yang et al. found 7 of 8 to react focally or weakly with antibody to cytokeratin 7.

References
Primary renal synovial sarcomas

Synovial sarcoma of the kidney is an entity which is characterized by a specific morphology and specific cytogenetic characteristics. They consist of spindle cells and frequently have large cysts. Many cases show local recurrence after nephrectomy. Most cases are diagnosed between the ages of 20 and 50 years. Microscopically, tumors are characterized by monomorphic plump spindle cells. The cysts are lined by mitotically inactive epithelial cells without striking cellular atypia. The tumors have been previously described as embryonal sarcoma of the kidney. There is a slight male predilection (1:6:1). No bilateral tumors were identified yet. The spindle cells are immunoreactive for EMA, CD56 and sometimes for CD99. They are non-reactive for desmin, actin, S100 and cytokeratins. The cyst epithelium is cytokeratin-positive. Synovial sarcoma is cytogenetically characterized by the translocation t(X;18)(p11.2/q11.2), generating a fusion between the SYT-gene on chromosome 18 and one member of the SSX family gene (SSX1;SSX2; SSX4) on chromosome X. Molecularly confirmed primary synovial sarcomas of the kidney have demonstrated the characteristic SYT-SSX gene fusion. In contrast to soft tissue synovial sarcoma where the SYT-SSX gene fusion is more common than the alternative SYT-SSX2 form, the majority of renal synovial sarcomas have so far demonstrated the SYT-SSX2 gene fusion. There is a tendency for a predominance of monophasic spindle morphology of these tumors in the kidney and there are more rarely biphasic tumors. Although prognostic data are limited, there are case reports describing tumors which have responded to chemotherapy. However, recurrence is common.

References


Acquired Cystic Disease-associated Renal Cell Carcinoma
This recently described RCC is associated with end-stage kidneys with acquired cystic disease. Long-term renal dialysis has long been known to predispose to the development of acquired cystic disease and renal cell neoplasms. Many of these appear to be typical clear cell, papillary, and chromophobe renal cell carcinomas. However, morphologically distinctive carcinoma has been discovered in patients with acquired cystic disease. Some appear to be unique to end-stage renal disease and acquired cystic disease. The kidneys are atrophic and have numerous cysts, typical of acquired cystic disease. The carcinomas are usually well-circumscribed and the larger ones often have a thick fibrous pseudocapsule which often contains foci of calcification. More than half the tumors appear to arise in a cyst. The architecture is complex with acinar, compact sheets, microscopic and macroscopic cysts in various combinations. Papillary structure ranging from very focal to more than 50% of the tumor, are present in roughly half the tumors. Oxalate crystals are frequent. In the study by Tickoo et al 1 patient died of widespread metastases and 2 other patients had lymph node metastases at the time of nephrectomy.

References

Clear cell renal cell carcinoma with prominent cysts / Multilocular cystic renal cell carcinoma

In less than 5% of clear cell RCCs, multiple cysts are predominant. Such tumors are well circumscribed, with non-communicating cysts separated by irregular, thick fibrous septa, reminiscent of a multilocular cyst. These so called cystic or multilocular cystic RCCs are considered a subtype of clear cell RCC. The lining epithelium of the cysts is often attenuated or even absent, but the structures do not represent cystic degeneration of a clear cell RCC of the usual type. Multilocular cystic RCCs are distinguished from multilocular cysts by the present
of nodular aggregates of clear cells, in at least some portion of the cyst wall. The identification of small aggregates of low-grade clear cells in the wall of the cysts is important for the correct diagnosis. If a stringent definition of multilocular cystic RCCs is applied, malignant behavior of these tumors has not been reported. Multilocular cystic RCCs must be distinguished from RCCs with cystic changes. The latter have expansile clear cell masses in their cyst walls.

References

The Function of the VHL protein in renal cancer: a new progression model for VHL-associated RCC via cyst-dependent and cyst-independent pathways

Between 24-45% of VHL patients develop clear cell renal cell carcinoma (ccRCC). Inactivating germline mutations of the VHL gene represents the genetic hallmark of this syndrome and have been demonstrated in almost all VHL patients. Sporadic clear cell RCC is characterized by inactivation of the VHL gene by deletion, mutation or promoter hypermethylation in about 70% of the tumors.

The functions of the VHL protein (pVHL) have been extensively studied in the last 15 years. The VHL protein (pVHL) is implicated in cell-cycle control and gene regulation, and requires transcription-dependent nuclear-cytoplasmic trafficking for its function. There are two biologically active VHL protein isoforms: pVHL(30) and pVHL(19). The distribution of VHL protein isoforms varies in the nuclear and cytoplasmic compartments of renal tumors and alteration of subcellular pVHL trafficking is of potential relevance for the biological behavior of clear-cell RCC.

The pVHL functions as a recognition subunit in a E3 ubiquitin protein ligase complex, targeting the hypoxia-inducible transcription factor a (HIF-a) for ubiquitin mediated degradation in the presence of oxygen. Loss of VHL function causes accumulation of HIF-1 subunits in the cytoplasm and their translocation to the nucleus. Loss of VHL function results in strongly enhanced transcription of HIF-a inducible genes, especially in up-regulation of CXCR4. Therefore, the von Hippel-Lindau (VHL) tumor suppressor gene product is one of the major regulators of CXCR4 expression and increased CXCR4 expression levels are most likely a consequence of impaired VHL function in ccRCC.

Other pVHL functions include fibronectin matrix assembly, p53 stabilization and transactivation. In addition, pVHL has the ability to bind and stabilize microtubules by protecting them from depolymerization, which is a prerequisite for cilium formation. Recent evidence highlights a key role for pVHL in the maintenance of the structure of the primary cilium, a microtubule-based cellular sensory organ that inhibits uncontrolled epithelial cell proliferation and cyst formation in the kidney. In fact, two previous in vitro studies showed that by re-expressing pVHL in VHL null ccRCC cell lines pVHL regulates the formation of primary cilia. These observations strongly suggest that loss of VHL function in renal epithelial cells leads to degeneration of primary cilia, which represents a critical step towards cyst formation and ccRCC development in VHL patients.
Interestingly, renal cysts are present in about 60% of individuals suffering from the von Hippel-Lindau (VHL) disease. One might hypothesize that cyst formation is one of the first visible renal alterations in VHL-caused tumor formation. The formation of kidney cysts is a clinical feature of the VHL cancer syndrome and, in at least some cases, is considered a precursor lesion of clear cell RCC. VHL inactivation might be the driving force for the development of kidney cysts that arise in patients with inherited VHL mutations. These new findings draw attention to a primary cilium maintenance network as a new territory for pVHL tumor suppressive activity and have implications for understanding the development of kidney pathology in the setting of VHL disease. On the basis of these findings, a new progression model for VHL-associated CC RCC via cyst-dependent and cyst-independent pathways has been proposed.

References:
THE DIFFICULT DIAGNOSIS IN THE URINARY BLADDER: A SELECTIVE CONSIDERATION, MULLERIAN AND MULLERIAN-LIKE CONDITIONS

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- Benign and malignant müllerian lesions
- Mullerian-like appearances in transitional-urothelial neoplasia
- Urachal lesions with müllerian-like features
- Secondary müllerian neoplasia.

Keywords: Urinary bladder, cancer mimickers, müllerian lesions, secondary müllerian neoplasia.

Not long after I accepted the invitation to speak on problematic bladder lesions, shortly after the US-CAP meeting last year, I realized that the comprehensive coverage of many aspects of non-neoplastic and neoplastic bladder disease at the Long Course last year made it difficult to come up with anything "fresh". That is even more so given that the supplement to Modern Pathology containing the short course proceedings will either have just appeared, or will be about to appear, by the time the spoken version of these words will be presented at the Boston meeting. I endeavored as one of course does for these occasions, to come up with something a little different and original and it struck me that given that I have interests in both gynecologic and urologic pathology a merging of these two with some comments on müllerian and müllerian-like lesions of the urinary bladder might be suitable. I think it is also timely inasmuch as there has been some focused interest in these lesions in recent years and the diversity of issues that may be encountered is quite remarkable. I will approach the topic by considering the following five categories: (1). Benign müllerian lesions; (2). Malignant müllerian lesions; (3). Mullerian-like appearances in transitional-urothelial neoplasia (4). Urachal lesions with müllerian-like features and (5). Secondary müllerian neoplasia.

Benign Müllerian Lesions

The bladder is involved in approximately one percent of women with endometriosis and is the commonest site of urinary tract involvement by this disease (1). Up to fifty percent of the patients have a history of a pelvic operation and in approximately 12 percent of them evidence of extra-vesical endometriosis is lacking. Vesical endometriosis is commonest in the fourth decade with the average age 35 years. The microscopic features of endometriosis are so distinctive that confusion with a neoplasm should not be an issue. This is in marked contrast to the other mullerian glandular lesions which are now considered. Potentially any of the common to rare
features of endometriosis seen elsewhere may be encountered in the bladder but are rarely reported.

Glandular lesions characterized by a prominent component of endocervical-type epithelium may involve the wall of the urinary bladder in women of reproductive age and have been designated “endocerviosis” (2). A mass that ranges up to 2.5 cm. is typically located in the posterior wall or posterior dome. Microscopic examination typically reveals extensive involvement of the involved bladder wall by irregularly disposed benign appearing or milding atypical endocervical-type glands some of which are cystically dilated. Occasionally one may find ciliated cells or a minor component of endometrioid glands and glands lined by non-specific cuboidal or flattened cells with eosinophilic cytoplasm. In some cases the glands are associated with fibrosis or edema in the adjacent stroma. Rarely there is some evidence of endometriotic stroma indicating a relationship of this lesion to endometriosis. This, and other features, such as an occasional association with a history of a cesarean section indicate that this is a unique mullerian lesion of the bladder and it is best considered the mucinous analogue of endometriosis. It is important because lack of awareness of it may lead to confusion with an adenocarcinoma, particularly one of urachal origin. Adenocarcinomas of the bladder, particularly of urachal origin, may have glands lined by tall mucin-rich epithelial cells and as these cancers and endocerviosis both occur at the dome one might think their distinction might be challenging. However, urachal adenocarcinomas broadly speaking fall in two groups, overtly infiltrating lesions with obvious malignant characteristics ruling out endocerviosis, or lower grade mucinous cystic lesions with differing gross characteristics. In some cases of benign mullerian lesions foci of endosalpingiosis are also present and when endometriosis and endocerviosis are present as well the designation “mullerianosis” has been suggested (3). Occasionally endosalpingiosis is seen in pure, or close to pure, form.

**Malignant Mullerian Lesions**

When we last explored the topic of clear cell carcinoma of the urinary bladder (4) we were able to collect together from our own material four cases of clear cell carcinoma morphologically typical of the usual müllerian form of this neoplasm (5) and almost certainly of müllerian origin because of an association in two cases with endometriosis and in two others with müllerian epithelium devoid of typical endometrial stroma but in two cases associated with elastosis, a subtle clue to a diagnosis of endometrial stroma in many cases. The literature on this topic is limited but it does appear that neoplastic transformation from endometriosis of the bladder usually is of clear cell type, something not surprising inasmuch as this carcinoma has the tightest association with endometriosis. There are no unique features to müllerian type clear cell carcinoma arising in the bladder to my knowledge. Potentially any form of müllerian neoplasia that may complicate endometriosis, as seen more commonly elsewhere, is a potential finding in the bladder and one could conjecture that it is perhaps surprising that there is not even more documentation of this in the literature. One wonders if some cases have not been correctly interpreted particularly when there is bulky disease with overgrowth of residual endometrial glands and stroma. At least one case of endometrioid carcinoma (6) and one case of müllerian adenosarcoma (7) are documented.

The differential diagnosis of the clear cell carcinomas is with glandular morphology of very similar type occurring on the background of transitional cell
neoplasia as considered below. Obviously the association with benign müllerian elements is crucial. A similar comment pertains to distinction of endometrioid carcinoma from a tubuloglandular pattern with endometrioid-like characteristics as a variant pattern of transitional cell carcinoma with gland differentiation. Perhaps enigmatically it is the rarest of all these neoplasms complicating endometriosis of the bladder, the müllerian adenosarcoma, which is so distinctive that the diagnosis could be made with confidence even in the absence of associated endometriosis.

MULLERIAN-LIKE APPEARANCES IN TRANSITIONAL (UROTHELIAL) CELL CARCINOMA

The commonest variants of the regular carcinoma of the bladder which I still prefer to refer to as transitional (although many who read this doubtless call them urothelial) are those showing squamous or glandular differentiation. It is obviously those exhibiting gland differentiation that are the focus of our interest here. Gland differentiation may be seen in papillary non-invasive lesions, intramucosal neoplastic proliferations that are not papillary, and of course frank non-papillary carcinoma either projecting into the lumen or invasive of the bladder wall. Different problems arise with each and the extent to which they mimic müllerian lesions varies. The papillary carcinomas, when they show gland differentiation which is uncommon, typically show rather punched out pretty glands without any particular müllerian-like morphology. The intramucosal abnormalities that may be associated with invasive carcinoma elsewhere or a classic in-situ lesion cause their own problems, such as in some instances distinction from true glandular neoplasia, but they rarely mimic a müllerian lesion. Frank carcinomas may potentially mimic any of three common forms of müllerian carcinoma: serous, endometrioid and clear cell. These are considered in turn.

The best known of these is the micropapillary (serous-like) variant of transitional cell (urothelial) carcinoma first described by Amin and colleagues in 1994 (8). I refer the reader to Dr. Amin's outstanding summary of this entity in his recently (or about to be) published short course essay (9). I cannot improve on it but will make a few brief summary remarks. As he notes, a variety of patterns may be observed. Slender delicate filiform papillae, uncommonly having a fibrovascular core, dominate surface foci. When cut in cross section the papillae may appear glomeruloid. In invasive foci the tumor cells are typically arranged as small nests very reminiscent of the so-called "tight knots" of familiar serous carcinoma of the genital tract. However, unlike serous carcinoma psammoma bodies are rare but described (10). In many of the invasive cases just as may be seen with serous carcinoma, nests of cells are associated with retraction artifact and appear to be sitting in spaces which may be misconstrued as vascular invasion. Despite this particular aspect being artifactual mimicry of vessel space invasion, true vessel space invasion is common. An argument has been made that micropapillary variant of transitional cell (urothelial) carcinoma is an adenocarcinoma; however, transitional cell (urothelial) derivation is supported by frequent concurrence and/or transition with more typical areas of transitional cell (urothelial) carcinoma. Further, immunohistochemistry including CK7, CK20, uroplakin 3 and high molecular weight cytokeratin (HMCK) are further supportive of transitional cell origin.

The second form of müllerian carcinoma that may be mimicked is endometrioid carcinoma. Some transitional cell carcinomas have a tubuloglandular pattern
indistinguishable from endometrioid carcinoma. Obviously as in countless areas of diagnostic pathology everything must be put in context with the site of occurrence of the process and the associated findings. In other words, any co-existent carcinoma of usual type or even history thereof drives the diagnosis very much towards primary of bladder carcinoma of transitional-urothelial type with gland differentiation. That goes for invasive and intramucosal cases of glandular neoplasia in the urinary bladder in my opinion. Of course if associated endometriosis was present one would very quickly move to a diagnosis of a very rare true endometrioid carcinoma primary in the bladder. Parenthetically, in the differential diagnosis, one must also include an extension of a prostatic carcinoma with ductal morphology into the urinary bladder. The homology of this pattern with müllerian lesions is best exemplified by the initial use of the term “endometrioid carcinoma” of the prostate for these tumors. The immunoprofile of endometrioid carcinoma extending from the gynecologic tract into the bladder is Estrogen receptor+, CK7+, CK20-, vimentin +, p63+/-, HMCK+/- and uroplakin 3-; the immunoprofile of transitional cell (urothelial) carcinoma is CK7+, CK20+, vimentin-, p63+/-, HMCK+/-, Estrogen receptor- and uroplakin 3+; and immunoprofile of prostatic adenocarcinoma including ductal pattern is PSA and PSAP+, CK7-, CK20-, vimentin -, p63-, HMCK- and uroplakin 3-.

The final form of müllerian carcinoma (other than I suppose transitional cell carcinoma itself!) that may be mimicked is clear cell carcinoma. Although there is still limited information overall on this topic, appreciable knowledge has accrued over the past quarter century. In 1985 Dr. Robert E. Scully and I reported three clear cell adenocarcinomas of the bladder and urethra and reviewed the literature as of that time. One of our cases was in the bladder and two in the urethra. Since that time urethral clear cell adenocarcinoma has become well-established as a distinct variant of adenocarcinoma of that structure and is not the domain of our interest here. In retrospect our one bladder case was likely of müllerian origin because many years later a tiny focus of atrophic endometriosis that had originally been overlooked was noted. In the discussion of the paper being referred to we considered the various possible origins of clear cell adenocarcinoma of the bladder, müllerian, mesonephric, and urothelial-transitional. That has of course been one theme of the subsequent limited literature (4, 12, 13). The focus of the paper of Gilcrease et al. (12) was on the purported relation of nephrogenic adenoma and clear cell adenocarcinoma, a relation I have never favored. It can, however, be a significant problem in differential diagnosis as has been discussed in that paper and elsewhere. Gilcrease et al. found that two of their four bladder tumors had small foci of transitional cell carcinoma and favored a variant of transitional cell carcinoma with gland differentiation as the explanation, quite logically, for those two cases. Subsequently Drew et al. (13) reported another series of cases exploring primarily histogenesis of this neoplasm.

When we reported a larger series of clear cell carcinomas in 2002 we were able to collect together 13 cases, 4 of which are noted above in the section on true müllerian clear cell carcinoma. The remaining 9 tumors were considered by us to be of definite or probable transitional cell nature because of an association of some with unequivocal transitional cell neoplasia, or, by exclusion, a lack of evidence directing to a müllerian origin. We did not see striking differences in the morphology of the clear cell tumors that were definitely of müllerian type, compared to the others. At this time immunohistochemical differences are not clear cut. There is, however, only limited information on this topic (4, 12, 13). An additional cause of confusion with clear cell
carcinoma is based on cell morphology rather than patterns. Occasional transitional cell carcinomas have cells with striking clear cytoplasm (14) and that may reflexively make the pathologist think of a true clear cell carcinoma. The point should be made that the designation "clear cell carcinoma" both here and elsewhere is applied to a tumor with distinctive patterns rather than one that by definition has clear cells. The latter are certainly usually present but some clear cell carcinomas, enigmatically, do not even have clear cells and various other tumors, certainly transitional cell carcinoma, can have clear cells. In the latter tumors the overall patterns are generally typical of conventional transitional cell neoplasia.

**Uracial Lesions with Müllerian-like Features**

I include this category because the majority of urachal neoplasms have a mucinous nature and accordingly may resemble mucinous tumors as seen in the genital tract which, albeit many might actually be of teratomatous origin, are, pragmatically, for the most part considered in the müllerian family of neoplasms. Dr. Amin and colleagues are currently finishing up a study of 45 glandular neoplasms of the urachus which is focusing on their wide morphologic spectrum and similarity in many cases to mucinous cystic tumors of the ovary. 24 of the cases in his series resembled primary mucinous cystic neoplasms as seen more commonly in the ovary ranging from mucinous cystadenoma, to cystic tumors of borderline malignancy with or without intraepithelial carcinoma, and to cystadenocarcinomas. The remaining 21 cases in his total series of 45 were invasive non-cystic tumors ranging from pure mucinous to typical enteric to mixed in morphology. The immunoprofile of urachal carcinomas with enteric differentiation is similar to metastatic colonic carcinomas to the urinary bladder (CK7-, CK20+, CDX2+); nuclear beta catenin staining in metastatic colon cancers may be the only helpful differential stain, although it positive in only a small subset of cases. Dr. Amin and colleagues point out that the importance of subclassifying these tumors because of the great variation in behavior from benign to almost certainly benign, to in some cases of course having an ominous prognosis.

**Secondary Müllerian Neoplasia**

Obviously the consideration would be incomplete without noting that primary müllerian tumors of the female genital system may secondarily involve the urinary bladder. Although spread to the bladder in general has not received the attention that spread to certain other organs, the ovary perhaps being the most noteworthy, has received, a variety of problems in differential diagnosis may be encountered and representative examples, some of which have tricked this writer, will be presented at the meeting. One of these has been reported (15). Good reviews of the general topic of secondary involvement of the urinary bladder are few, but some thankfully exist (16-19). In one large series (17) spread of gynecologic cancers were third (after colo-rectal and prostate primaries) most common but only in the category of ovarian primaries did antemortem cases exceed postmortem cases in number. In this as in so many other areas of diagnostic pathology the pathologist will do themselves a disservice if they do not pay appropriate attention to the clinical findings and even in the absence of any helpful clinical findings unusual morphologic features that could conceivably be related to a tumor spreading to the bladder from elsewhere, hopefully will be noted. In certain
situations immunohistochemistry, of course, may be helpful as in the situation of secondary involvement from endocervical adenocarcinoma which may be supported by immunohistochemical staining for p16, and even HPV analysis, if indicated, as has been recently shown to be helpful in the more common issue of endocervical carcinoma spreading to the ovary.

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