Pathology of Renal Neoplasia

Epithelial Tumors of the Kidney
Diagnostic Problems and
Recently Described Entities

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CURRENT CLASSIFICATION

EPITHELIAL KIDNEY TUMORS
CLASSIFICATION (2004)

BENIGN
Papillary adenoma
Metanephric adenoma
Metanephric adenofibroma
Oncocytoma

Adenoma
EPITHELIAL KIDNEY TUMORS
CLASSIFICATION (2004)

MALIGNANT
Clear cell
Multilocular cystic
Papillary
Type 1
Type 2
Chromophobe
Classic
Eosinophilic

EPITHELIAL KIDNEY TUMORS
CLASSIFICATION (2004)

MALIGNANT
Collecting duct
Medullary
Mucinous tubular and spindle cell
Xp11 translocation carcinomas
Other specified
Unclassified

DISTRIBUTION OF
EPITHELIAL RENAL TUMORS

FREQUENCY
EPITHELIAL KIDNEY TUMORS
CLASSIFICATION (20…)

Tumors not included in 2004
• Tubulocystic carcinoma
• Acquired cystic kidney disease associated RCC
• Clear cell papillary RCC
• Specific hereditary types of RCC
  – Birt-Hogg-Dube Syndrome
  – Hereditary leiomyomatosis and RCC syndrome
• (Oncocytic papillary RCC)
• (Renal cell neoplasm of oncocytosis)
• (RCC with angioleiomyoma-like stroma)
• (Renal cell neoplasm of oncocytosis)
• (Thyroid-like follicular carcinoma)
• Others

RENAL CORTICAL ADENOMA

• Cortical epithelial lesions common and increase with age
• Autopsy series: overall incidence 21%; with 10% at ages 20-40 yrs, increasing to 40% at ages 70-90 yrs.
• over 80% of lesions < 1.0 cm are papillary
• Kovacs: cytogenetics can distinguish benign from malignant papillary lesions (+7, +17 only = benign)

Definition: size 5 mm or less with tubulopapillary architecture
**RENAL CORTICAL ADENOMA**

Middle age, F:M; 2:1
Incidental
Polycythemia

**PATHOLOGIC FEATURES**
Well circumscribed, solid, grey-tan, variable size
Closely packed tubules
Small cells with scant cytoplasm

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**RENAL CORTICAL ADENOMA**

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**METANEPHRIC ADENOMA**

**CLINICAL FEATURES**
Middle age, F:M; 2:1
Incidental
Polycythemia

**PATHOLOGIC FEATURES**
Well circumscribed, solid, grey-tan, variable size
Closely packed tubules
Small cells with scant cytoplasm
**METANEPHRIC ADENOMA**

**DIFFERENTIAL DIAGNOSIS**

<table>
<thead>
<tr>
<th>Feature</th>
<th>MA</th>
<th>Pap Ca</th>
<th>Wilms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Middle age</td>
<td>Middle to older age</td>
<td>Children</td>
</tr>
<tr>
<td>Sex (F:M)</td>
<td>2:1</td>
<td>1:3-4</td>
<td>1:1</td>
</tr>
<tr>
<td>Clinical</td>
<td>Incidental</td>
<td>Hematuria, flank pain</td>
<td>Mass congenom</td>
</tr>
<tr>
<td>Gross</td>
<td>Single, circumscribed</td>
<td>Multiple (1/2)</td>
<td>Bulging</td>
</tr>
<tr>
<td>Histology</td>
<td>Packed small tubules</td>
<td>Papillae, foam cells</td>
<td>Grey-white</td>
</tr>
<tr>
<td>Immuno</td>
<td>Ck7 Weak +, Vim +, EMA -</td>
<td>Ck7 ++++, Vim +/-, EMA +++</td>
<td>Ck ++, Vim -</td>
</tr>
</tbody>
</table>

**Differential Diagnosis of Tumors with Pink Cells**

- ONOCYTOMA
- CHROMOPHOBEC RCC
- TRANSLOCATION CARCINOMAS
- EPITHELIOID ANGIOMYOLIPOMA
- UNCLASSIFIED RCC

**ONOCYTOMA**

**CLINICAL**

- 5% of kidney tumors in adults
- wide age range; 2-3:1 F:M ratio
- majority asymptomatic

- Cytogenetic changes:
  - -1 (1p), -Y, t(9p23:11q13)
RENAL ONCOCYTOMA: ATYPICAL FEATURES

- Cystic change
- Papillary architecture
- Nuclear pleomorphism
- Perinephric fat invasion
- Clear cell change
- Mitotic activity
- Oncoblastic cells
- Renal vein invasion

CYSTIC CHANGE

PAPILLARY ARCHITECTURE
MITOTIC FIGURES

ONCOCYTOMA - ONCOBLASTS

RENAL VEIN INVASION
<table>
<thead>
<tr>
<th>MARKER</th>
<th>Oncocytoma</th>
<th>Chromophobe</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>++ isolated cells</td>
<td>++ diffuse</td>
</tr>
<tr>
<td>Vimentin</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>CD10</td>
<td>Negative</td>
<td>10% +</td>
</tr>
<tr>
<td>RCC</td>
<td>Negative</td>
<td>50% +</td>
</tr>
<tr>
<td>EpCAM</td>
<td>++ isolated cells</td>
<td>Diffuse ++</td>
</tr>
<tr>
<td>KspCad</td>
<td>Small % +</td>
<td>Diffuse ++</td>
</tr>
</tbody>
</table>
CHROMOPHOBECARCINOMA

CLINICAL FEATURES
- 5% of adult kidney tumors
- middle age; no sex predilection
- excellent prognosis (>90% at 10 years)

• Cytogenetic features:
  • -1, -2, -6, -10, -13, -17, -21
CHROMOPHOB RCC (EOSINOPHILIC TYPE)

CHROMOPHOB CARCINOMA

CHROMOPHOB CARCINOMA
HALE’S COLLOIDAL IRON

CHROMOPHOBES CARCINOMA IMMUNOHISTOCHEMISTRY

PAPILLARY CARCINOMA

• CLINICAL FEATURES
  – 15% of adult kidney tumors
  – hereditary form well described
  – better prognosis than clear cell, 80% vs 50% overall survival

• PATHOLOGIC FEATURES
  – encapsulated with thick capsule
  – friable, red-brown cut surface
  – multifocality most common with this type
PAPILLARY CARCINOMA

MICROSCOPIC PATHOLOGY
- Fibrous capsule
- Papillary and tubular architecture
- Basophil or eosinophil cell types
- Foamy macrophages
- Hemosiderin pigment
PAPILLARY CARCINOMA

SIGNIFICANCE OF SUBTYPES

**TYPE 1**
- Older age group
- Smaller size
- Lower grade (2% grade 3-4)
- pT3/4: 16%

**TYPE 2**
- Younger age
- Larger size
- Higher grade (37% grade 3-4)
- pT3/4: 67%

*Delahunt and Eble, Modern Pathol 10:537, 1997*

PAPILLARY CARCINOMA

SIGNIFICANCE OF SUBTYPE

**“HYBRID” TUMORS**

- **RENAL ONCOCYTOSIS**
  - Bilateral, multiple tumors
  - Oncocytoma, chromophobe RCC and hybrid tumors

- **BIRT HOGG DUBE SYNDROME**
  - Skin tumors (trichofolliculomas, achrocdrons), multiple renal tumors and pneumothoraces
  - Oncocytoma, chromophobe and clear cell RCC, and hybrid tumors
  - Autosomal dominant, 17p11.2 (folliculin)

- **DE NOVO**
  - 4/425 cases in recent series

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**BIRT HOGG DUBE SYNDROME**

TUMOR #1

TUMOR #2

TUMOR #3

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**BIRT HOGG DUBE SYNDROME**

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RENAL ONCOCYTOSIS

SO-CALLED HYBRID TUMOR or RENAL TUMOR OF ONCOCYTOSIS
MUCINOUS TUBULAR AND SPINDLE CELL CARCINOMA

- Females predominate (3-4:1)
- Wide age range (17-82 yrs; median 56 yrs)
- Majority organ confined: 19 pT1, 13 pT2, 2 pT3; 2 with + LN
- Limited follow up available:
  - 32 A+W with NED (1 mos to 7 yrs);
  - 1 patient with 3 tumors on the same kidney over 22 years;
  - 2 deceased of unknown cause
- High grade/sarcomatoid variants
MUCINOUS TUBULAR AND SPINDLE CELL CARCINOMA

Immunohistochemistry

- CK7
- Vimentin
- EM
- P504s
MUCINOUS TUBULAR AND SPINDLE CELL CARCINOMA: Immunohistochemistry

- CK 7
- 34BE12
- P504S

MUCINOUS TUBULAR AND SPINDLE CELL CARCINOMA

- PAS
- AB
- Mucicarmine

Renal mass biopsy, 30 yr old woman

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### IMMUNOHISTOCHEMISTRY

<table>
<thead>
<tr>
<th>MARKER</th>
<th>REPORTED CASES + (%)</th>
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<tbody>
<tr>
<td>Epithelial membrane antigen</td>
<td>81%</td>
</tr>
<tr>
<td>Cytokeratin AE1/AE3</td>
<td>83%</td>
</tr>
<tr>
<td>Cytokeratin 7</td>
<td>91%</td>
</tr>
<tr>
<td>Cytokeratin 19</td>
<td>78%</td>
</tr>
<tr>
<td>Cytokeratin 34βE12</td>
<td>32%</td>
</tr>
<tr>
<td>RCC marker</td>
<td>49%</td>
</tr>
<tr>
<td>CD10</td>
<td>9%</td>
</tr>
<tr>
<td>Tamm Horstall protein</td>
<td>0</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>93%</td>
</tr>
<tr>
<td>AMACR (p504s)</td>
<td>100%</td>
</tr>
<tr>
<td>Aquaporin 1</td>
<td>18%</td>
</tr>
<tr>
<td>Aquaporin 3</td>
<td>18%</td>
</tr>
<tr>
<td>Vimentin</td>
<td>55%</td>
</tr>
</tbody>
</table>

*Felicot et al. Virch Arch 447:978, 2005  Proximal - Distal*

### CYTOGENETICS

- CGH: -1, -4, -6, -8, -9, -13, -14, -15, -22 (all in 5/5 cases studied); others included –X (3 cases) and -18 (1 case)
  
  *Rakozy et al, Mod Pathol 15:1162, 2002*

- CGH: -1, -4q, -6, -8p, -9p, -13, -14, -15 in 8/8 cases; also -11q and gains in 11q, 12q, 16q, 17 and 20q
  
  *Srigley et al, Mod Pathol 15:182A, 2002*

### TUBULOCYSTIC CARCINOMA

- First described by Farrow in 1994
- Included in old “low grade collecting duct carcinoma” category
- Wide age range (34 – 74 yrs; mean 54)
- Male predominance (7:1)
- Majority localized at diagnosis (pT1-2)
- 3 of 46 cases with metastases (lymph node, liver, bone)
- Cytogenetic profile by CGH similar to but not identical to papillary RCC
- Overlapping trisomies with papillary RCC by FISH
TUBULOCYSTIC CARCINOMA
CYSTIC NEPHROMA

X:1 (TRANSLOCATION)
ASSOCIATED CARCINOMAS

- Predominantly teenagers and young adults but any age can be affected
- Often present with high stage and protracted clinical course (limited clinical follow up data available)
- T(X;1)(p11.2;q21) most common
- Fusion of PRCC/TFE3 genes
### X-ASSOCIATED CARCINOMAS

<table>
<thead>
<tr>
<th>TRANSLOCATION</th>
<th>AGE</th>
<th>FUSION</th>
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<tbody>
<tr>
<td>(p11.2;q21)</td>
<td>2-70</td>
<td>PRCC-TFE3</td>
</tr>
<tr>
<td>(p11.2;q25)</td>
<td>2-68</td>
<td>ASPL-TFE3</td>
</tr>
<tr>
<td>(p11.2;q25)</td>
<td>5-40</td>
<td>ASPL-TFE3</td>
</tr>
<tr>
<td>(p11.2;p34)</td>
<td>3-68</td>
<td>PSF-TFE3</td>
</tr>
<tr>
<td>(p11.2;q12)</td>
<td>39</td>
<td>NonO-TFE3</td>
</tr>
<tr>
<td>(11.2q23)</td>
<td>14</td>
<td>CLTC-TFE3</td>
</tr>
</tbody>
</table>
X:1 TRANSLOCATION ASSOCIATED CARCINOMA

CK AE1/AE3  EMA  TFE-3

MELANOTIC Xp11 TRANSLOCATION CANCER

Pan CK  TFE3

6:11 TRANSLOCATION CARCINOMA
6:11 TRANSLOCATION CARCINOMA

Type IV collagen

CK 7
CK AE1/AE3
EMA
Melan A

6:11 TRANSLOCATION CARCINOMA

ACQUIRED CYSTIC KIDNEY DISEASE

- Patients with renal failure +/- dialysis
- Incidence increases with time on dialysis
  - 3 years 10 – 20%
  - 5 years 40 – 60%
  - 10 years 90%
- About 25% of patients develop tumors
- 4% to 7% with tumors develop metastases
- Papillary neoplasia most common
ACQUIRED CYSTIC KIDNEY DISEASE

- Examined 66 kidneys from 52 patients
- Identified a variety of tumor types:
  - ACD associated carcinoma 33%
  - Clear cell papillary carcinoma 21%
  - Papillary carcinoma 16%
  - Chromophobe carcinoma 16%
  - Clear cell carcinoma 14%
- Considered the first two potentially unique tumor types


AcqCKD ASSOCIATED CARCINOMA

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AcqCKD ASSOCIATED CARCINOMA

Calcium oxalate crystals
AcqCKD ASSOCIATED CARCINOMA

• First described by Tickoo et al. as a distinct entity in ACKD
• Seven additional tumors in five patients (3M;2F) by Gobbo et al.
• Four not associated with ACKD
• By FISH no cases with trisomy 7 or loss of Y chromosome
• By FISH trisomy 17 in 2 tumors
• By FISH no 3pTEL deletion in any case

CLEAR CELL PAPILLARY RCC

UNCLASSIFIED RENAL CELL CARCINOMA

EPITHELIOID ANGIOMYOLIPOMA
“This study indicates that unclassified renal cell carcinoma is an uncommon variant of renal cell carcinoma that typically presents with significantly larger, more aggressive tumors and is associated with poor clinical outcomes.”


• Needle biopsy “always indicated”
  – Prior to ablation therapy
  – Prior to systemic therapy if no prior histologic diagnosis
  – In surveillance strategies
• Role of biopsy is to:
  – Distinguish benign from malignant
  – Histologic type of tumor
  – Grade of tumor

EAU Guidelines on Renal Cell Carcinoma: The 2010 Update

Eur Urol 58:398-406, 2010