“Clear cell-papillary renal cell carcinoma: diagnostic criteria and what have we learned in the 6 years since its first description”

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CASE 1

Clinical History
- 65 year-old male
- Hypothyroidism and hypercholesterolemia
- Non specific abdominal pain
- CT scan showed gallstones and 2.3 cm renal mass
- Partial nephrectomy – right upper pole mass
CASE 1

Diagnosis: Renal Cell Carcinoma with following features:

* Clear cell – papillary renal cell carcinoma, histologic subtype
* Size: 2.3 cm
* Fuhrman Nuclear Grade: 2
* No evidence of perinephric extension
* Pathologic stage: pT1a
CLEAR CELL-PAPILLARY RCC

Gross
- Usually small tumors, 0.8-5 cm, rarely multifocal
- Well circumscribed
- Variably, often with prominent cystic change
- Organ-confined

GROSS: CC-Pap RCC

Microscopic
- Fibrous capsule (+/-)
- Papillary architecture
- Tubules & acini
- Clear cytoplasm
- Nuclei aligned & away from basement membrane
Clear-cell papillary RCC
DISCUSSION

• Where do clear cell - papillary renal cell carcinomas fall in the scheme of the contemporary understanding of the spectrum of adult renal neoplasia?

• What does this diagnosis mean?

CLASSIFICATION OF RENAL TUMORS (1975-2012)

• “Tumors of kidney, renal pelvis and ureter”
  - 2nd series AFIP fascicle (1975)

• “Renal carcinoma has many faces”
  - clear cell carcinoma
  - granular cell carcinoma
### Classification of Renal Tumors

<table>
<thead>
<tr>
<th>Year</th>
<th>Author(s)</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>Klein and Valensi</td>
<td>Oncocytoma</td>
</tr>
<tr>
<td>1985</td>
<td>Theones et al</td>
<td>Chromophobe RCC</td>
</tr>
<tr>
<td>1986</td>
<td>Fleming &amp; Lewi</td>
<td>Collecting duct Ca</td>
</tr>
<tr>
<td>1995</td>
<td>Davis CJ et al</td>
<td>Renal medullary Ca</td>
</tr>
<tr>
<td>1995</td>
<td>Jones et al</td>
<td>Metanephric adenoma</td>
</tr>
<tr>
<td>1997</td>
<td>Störkel, Eble, Adlkha, Amin et al</td>
<td>Consensus Classification of renal tumors</td>
</tr>
</tbody>
</table>

### Renal Cell Carcinoma

**WHO and TNM Classification of Renal Tumors 2004**
- Clear cell RCC
- Multilocular cystic RCC
- Papillary RCC
- Chromophobe RCC
- Carcinoma of the collecting ducts of Bellini
- Renal medullary carcinoma
- Renal carcinoma associated with Xp11.2 translocations/TFE3 gene fusions
- RCC associated with neuroblastoma
- Mucinous tubular and spindle cell carcinoma
- RCC unclassified

### Epithelial Tumors Described Beyond 2004

- Tumors associated with ESRD (2006)
  - Acquired cystic disease of kidney-associated RCC
  - Clear cell-papillary RCC
- Hereditary Leiomyomatosis and RCC (2007)
- Clear cell-papillary RCC (non-ESRD) (2008)
- Thyroid-like carcinoma (2009)
ESRD Kidney Neoplasms

- Acquired cystic disease-associated RCC (36%)
- Clear-cell papillary RCC of the end stage kidney (23%)
- Sporadic type renal tumors (41%)
  - Clear cell RCC (18%)
  - Papillary RCC (15%)
  - Chromophobe RCC (8%)

Multifocal, bilateral tumors
Behave less aggressively than sporadic types
Tickoo, Amin et al
First series of 5 patients with sporadically occurring clear cell papillary RCC.

GROSS: RAT

Renal angiomylipomatous tumor: morphologic, immunohistochemical, and molecular genetic study of a distinct entity


Virchows Arch 2009; 454:89-99
Questions relationship of RAT to clear cell papillary RCC

We have several cases of clear cell papillary renal cell carcinoma in our files and we must state that this type of carcinoma is so much different from RAT that we did not (and do not) consider it worth listing in the differential diagnosis of RAT. Just for mentioning a few major differences between RAT and clear cell papillary renal cell carcinoma: RAT is not a papillary tumor at all and is not composed of clear cells either. When present...
Larger series of clear cell papillary RCC published recently

Am J Surg Pathol 2010; 34:1608-1621

Histopathology 2011; 58:1064-1071

Manuscript in preparation

- CCPap-RCC (sporadic and ESRD-associated): identical morphology & immunophenotype
- Molecular studies (FISH, virtual karyotyping & VHL mutation): genetically stable tumors
- CCPap-RCC and RAT: identical morphology, immunophenotype & molecular studies
- Outcome: no patients with evidence of disease progression (in over 100 patients - our experience plus published cases to date)

SPECTRUM OF CLEAR CELL PAPILLARY RCC

In VHL Patients
- Our anecdotal experience - 1 case (2012)
- Aydin et al – 1 case
- Nigwekar et al – 3 cases (2012)
## Differential Diagnosis

### Clear cell-papillary RCC
- **Clear cell RCC**
- **Papillary RCC**
- **Translocation associated RCC**
- **Unclassified RCC**
- **Metastatic carcinoma**

## Renal Clear and Papillary Tumors

<table>
<thead>
<tr>
<th>Clear cell &amp; Papillary RCC</th>
<th>Papillary RCC only</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCC (+)</td>
<td>CK7 (+)</td>
</tr>
<tr>
<td>Pax2, Pax8 (+)</td>
<td>Racemase (+)</td>
</tr>
<tr>
<td>Vimentin (+)</td>
<td></td>
</tr>
<tr>
<td>CA-9 (+)</td>
<td></td>
</tr>
<tr>
<td><strong>Clear cell only:</strong></td>
<td></td>
</tr>
<tr>
<td>CK7 &amp; racemase (-)</td>
<td></td>
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</tbody>
</table>

## Approach to dx of renal epithelial tumors

- **Virtually any tumor:**
  - clear
  - granular cells
  - papillary
  - Spindle cell features or sarcomatoid growth
  - cystic architecture

**Careful attention to:**
- Gross appearance
- Microscopy: architecture
  - Nuclear
  - Cytoplasmic features
  - Adjunctive features
- Ancillary diagnostic studies
  - IHC
  - FISH
  - EM

*Hence: “clear cell”, “granular cell”, “papillary”, “sarcomatoid”, “cystic” RCC is not a diagnosis based on a single feature*
Clear cell RCC with papillary features

PAPILLARY RCC

PAPILLARY RCC
PAPILLARY RCC

Papillary RCC with clear cell change
Papillary RCC with clear cell change

Xp11.2 TRANSLOCATION/TFE3 GENE FUSION CARCINOMA

Gross:
- Tan yellow
- Often necrotic
- Occasionally hemorrhagic
  May resemble clear RCC

May occur in a post-treatment setting
ADULT RENAL EPITHELIAL TUMORS
Clinico-pathologic entities:
• Distinctive chromosomal and molecular abnormalities
• Clinically e.g. Metanephric adenoma- polycythemia, Medullary carcinoma- sickle cell disease etc.
• Syndromic associations e.g. Clear cell - V H Lindau, Chromophobe - Birt Hogg Dube etc.
• Prognostically: RO & Clear cell papillary > CHRCC> PRCC> Clear cell RCC
• Therapeutically: Differs between subtypes
• Patterns of Metastasis : distinct for subtypes of RCC

Accurate subtying of renal epithelial tumors is a clinically important exercise !!

Subtyping of adult renal epithelial neoplasms
Clear Cell
Papillary RCC
Chromophobe RCC
Renal Oncocytoma
Collecting duct RCC
Others

n = 10,060 renal tumors, 8 series, 1999-2005

<table>
<thead>
<tr>
<th>Subtype</th>
<th>5 yr</th>
<th>10 yr</th>
<th>5 yr</th>
<th>10 yr</th>
<th>5 yr</th>
<th>10 yr</th>
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</thead>
<tbody>
<tr>
<td>Clear cell RCC</td>
<td>43.76%</td>
<td>44.70%</td>
<td>61.87%</td>
<td>66.86%</td>
<td>78-100%</td>
<td>80-100%</td>
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</tbody>
</table>
Therapy for Metastatic Disease

**Clear Cell RCC**
Immunomodulatory therapies: Interleukins, Cytokines
Anti-angiogenesis targeted therapies against HIF1 and mTOR pathways
Targeted therapy against VEGF tyrosine kinases (Sunitinib) and MET pathway
Limited response to vascular growth factor kinase receptors and mTOR pathways

**Papillary RCC**

**Chromophobe RCC**

Therapy for Metastatic Disease

**Collecting Duct Carcinoma**
Carcinoma of unknown primary or urothelial carcinoma chemotherapy

**Translocation-associated RCC**
MET and HIF1 pathway inhibitors

**HLRCC**
Fumarate dehydrogenase gene inactivating mutations- drugs against Krebs cycle molecules (experimental)

**PEComa**
mTOR inhibitor (sirolimus) EGFR inhibitor (gefitinib)

**Therapy aimed at one subtype may not be effective for another Gene expression profiling and molecular analysis may yield newer therapeutic targets**

Therapy for Metastatic Disease

**Sporadic RCC**
• Clear cell RCC
• Chromophobe RCC
• Papillary RCC
• Collecting Duct Ca

**Familial**
• VHL
• Birt-Hogg-Dube
• HPRCC
• HLRCC
• Renal medullary

**Post treatment RCC**
• Post chemotherapy RCC
• Post neuroblastoma RCC

**ESRD**
• ACD-assoc RCC
• Clear-papillary RCC

**RCC Development Pathways**