Emerging Subtypes in Renal Cancer

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Some General Comments

• Fuhrman nuclear grading – clear cell and papillary primarily

• Staging
  – Applied to most renal cancers
  – Outcomes often directly correlate with stage and may be biased by early or late tumor detection

• Clinical symptoms
  – Generally the same for most adult patients – hematuria, flank pain, mass
  – Not specific
  – More and more identifying tumors incidentally due to imaging
Outline

• Conventional epithelial neoplasms

• Recently described variants and distinction from conventional neoplasms

• Medullary and collecting duct carcinoma

• Morphology suggestive of hereditary syndromes

• Other neoplasms important to recognize in the kidney
“Conventional” Forms of Renal Cancer

• Generally includes clear cell, papillary and chromophobe carcinoma

• Many recently described entities have historically been grouped into these categories or considered “unclassified”

• Use of selective immunohistochemical stains and molecular analysis have helped delineate subtypes
Clear Cell Renal Cell Carcinoma

• Most common form of renal cancer (60-70%)

• Gross appearance
  – golden-yellow color, hemorrhage

• Microscopic
  – Nests of tumor cells surrounded by delicate vascular network
  – Clear to eosinophilic cells
  – Cyst formation is common in this entity
  – May be associated with sarcomatoid or rhabdoid features
  – Fuhrman nuclear grading applied

• Immunostains
  – CA9, PAX2 and PAX8, Cam5.2 positive
  – CK7, racemase negative
Molecular Features

• Chromosome 3p alterations or mutation/hypermethylation of 3p25-26 (VHL gene)
  – HIF1α does not undergo degradation under hypoxic conditions with loss of VHL
  – Results in increased VEGF, CA9, growth factors

• Targeted therapy includes inhibitors of vascular growth and/or mTOR signaling
Differential Diagnosis

• Clear cell papillary RCC
  – CK7 and CA9 diffusely positive
  – AMACR negative

• Translocation carcinoma
  – TFE3 or TFEB positive

• Intrarenal adrenal gland
  – Inhibin and calretinin positive
  – Negative cytokeratins and CA9
Multilocular Cystic Renal Cell Carcinoma

- Similar alterations in \( VHL \) gene support this to be a variant of clear cell renal cell carcinoma

- Excellent prognosis

- Gross appearance
  - Multilocular cyst, thin septae
  - Clear to bloody fluid
  - No solid areas

- Microscopic
  - Cysts lined by single to multiple layers of clear cells
  - Often Fuhrman nuclear grade 1
  - Small clusters of clear cells in the wall of the cysts

- Immunostains
  - Limited studies, but cytokeratin and CD10 positive; likely stains similar pattern to clear cell RCC
Differential Diagnosis

• Benign simple cyst (renal cortical cyst)
  – Flat lining, no clear cells

• Cystic nephroma
  – Flat lining, no clear cells

• Clear cell papillary renal cell carcinoma
  – Generally has solid areas/expansile tumor growth
Papillary Renal Cell Carcinoma

- Approximately 15% of renal cancers (2nd most common type)

- Gross appearance
  - Well circumscribed with fibrous pseudocapsule
  - Tan to brown in appearance with hemorrhage, necrosis
  - Often multifocal, associated with adenomas (<5 mm) and tubulopapillary hyperplasia

- Microscopic
  - Frequently has thin papillae with central fibrovascular core
  - Also tubular and solid patterns
  - Foamy macrophages, psammoma bodies
  - Subdivided into type 1 (small cells, lower nuclear grade) and type 2 (eosinophilic larger cells with higher nuclear grade)
  - Fuhrman nuclear grading applies

- Immunostains
  - Positive for CK7 (diffuse, especially type 1), AMACR (diffuse), CD10, PAX 2
  - Negative for CA9
Molecular Features

- Trisomy of chromosomes 7 and 17

- Loss of chromosome Y

- Hereditary papillary renal cell carcinoma syndrome has activating *MET* mutations (7q31) - also some in sporadic; hereditary leiomyomatosis and RCC syndrome has fumarate hydratase mutations (1q42.3-43)

- Targeting of MET pathway; VEGF/vascular growth targeting
Type 1 papillary
Type 2 papillary
Differential Diagnosis

• Clear cell RCC with cell dropout, resulting in pseudopapillary formation
  – CA9 positive, CK7 negative

• Translocation carcinomas (vs type 2 papillary)
  – TFE3 or TFEB positive

• Clear cell papillary RCC
  – Nuclear stratification distinct from conventional papillary

• Mucinous tubular spindle cell carcinoma (vs type 1 papillary)
  – Has myxoid stroma
Chromophobe RCC

- 3rd most common form of RCC (5%)
- Multiple chromosome abnormalities

- Relatively good prognosis – 5 year survival >90%

- Gross appearance
  - Well circumscribed with tan/beige cut surface

- Microscopic
  - Polygonal cells with pale to pink cytoplasm
  - Prominent cell membrane
  - Binucleation, wrinkled nuclei

- Immunostains
  - CK7 diffusely positive
  - EMA positive
  - Also diffuse colloidal iron stains
Sarcomatoid differentiation
Differential Diagnosis

• Oncocytoma
  – Round nuclear contours; limited colloidal iron staining

• Clear cell RCC
  – CK7 negative and CA9 positive

• Epithelioid angiomyolipoma
  – HMB45 positive, CK7 negative
Oncocytoma

• Benign neoplasm, even when involving fat or vessels
• Rare chromosomal losses (chromosome 1 and Y)

• Gross appearance
  – Non-encapsulated, well circumscribed
  – Brown-tan, often with central scar

• Microscopic
  – Nests, microcysts, tubules
  – Loose stroma at central scar
  – Eosinophilic cytoplasm
  – Round nuclei
  – Occasional oncoblastic cells

• Immunostains/other stains
  – CD117 diffusely positive
  – CK7 negative or focally positive
  – Focal/luminal Hale’s colloidal iron
Differential Diagnosis

- Papillary oncocytic tumor
  - Areas that are distincttently papillary or oncocytic cells that form primitive papillary formations

- Oncocytic neoplasmin
  - More atypia, but not reaching the level of chromophobe RCC
  - Solid areas, rather than nests
Recently Described Epithelial Neoplasms

- Clear cell papillary RCC
- MITF/TFE translocation carcinomas
- Mucinous tubular and spindle cell carcinoma
- Tubulocystic carcinoma
- Thyroid like follicular carcinoma
- Acquired cystic disease associated RCC
Clear Cell Papillary RCC

- May be found in end stage renal disease or otherwise
- Often pT1, may have good prognosis
- No molecular alterations shared with clear cell RCC

- Gross appearance
  - Encapsulated
  - Often cystic

- Microscopic
  - Thin papillary fronds lined by clear cells
  - Nuclei are low grade and arranged linearly

- Immunostains
  - Diffuse CK7 and CA9
  - AMACR and CD10 negative
Differential Diagnosis

• Papillary RCC
  – CA9 negative, AMACR positive, CD10 positive

• Clear cell RCC
  – CD10 positive, CK7 negative

• Translocation carcinoma
  – TFE3 or TFEB positive
MITF/TFE translocation carcinomas

• A number of translocations in the MiTF/TFE family of DNA binding proteins define this entity, including TFE3 (Xp11.2) and TFEB [6p21]

• Numerous genes are linked to translocations with these two loci

• May occur in children and is often associated with a precedent chemotherapy history

• ASPL-TFE3 carcinomas are often especially aggressive

• TFEB carcinomas may behave much more indolently
Diagnostic Features

• Gross appearance
  – Circumscribed, but not encapsulated
  – Tan-yellow appearance

• Microscopic
  – May be overlap in appearance, thus testing for TFE3 and TFEB
  – ASPL-TFE3: Pseudopapillary/papillary, abundant cytoplasm, sharp cell borders, open nuclei, prominent nucleoli, psammoma bodies
  – PRCC-TFE3: Nested/papillary pattern, central lumen formation, scant cytoplasm
  – Alpha-TFEB: Nested/sheets, abundant clear cytoplasm, prominent nuclei

• Immunostains
  – TFE3 or TFEB immunostains
Differential Diagnosis

• Papillary RCC
  – Cytokeratins positive, AMACR positive

• Clear cell papillary RCC
  – CK7 and CA9 positive

• Clear cell RCC
  – Cytokeratins positive
Mucinous tubular and spindle cell carcinoma (MTSCC)

- Often indolent behavior
- Multiple chromosomal abnormalities but no trisomy of 7 and 17

- Gross appearance
  - Circumscribed, +/- capsule
  - Gray to yellow

- Microscopic
  - Flattened spindled tubules with slit-like spaces
  - Blue extracellular mucin
  - Low grade nuclei

- Immunostains
  - Similar to papillary RCC (CK7 and AMACR positive; CD10 negative)
    BUT no trisomy of 7 or 17
Differential Diagnosis

• Papillary RCC (solid variant)
  – Difficult differential
  – Lacks mucin and often has some rudimentary papillary structures
  – Trisomy 7/17 may be useful if available

• Collecting duct carcinoma
  – High grade nuclei and stromal reaction
Tubulocystic carcinoma

• Virtually always in men
• Most are pT1 disease, but a small proportion can metastasize

• Gross appearance
  – Circumscribed, not encapsulated
  – Multilocular cysts, clear fluid
  – May appear to be primarily based in the medulla in some cases

• Microscopic
  – Tubules and cysts lined by hobnail cells
  – Eosinophilic cells
  – Prominent nucleoli

• Immunostains
  – CK7 variable positive, AMACR positive, CD10 and PAX2 positive
Differential Diagnosis

• Multilocular cystic RCC
  – Single to multiple layers of clear cells
  – CA9 positive, AMACR negative

• MEST/cystic nephroma
  – Flattened cyst lining
  – Ovarian stroma in MEST

• Collecting duct carcinoma
  – Desmoplasia and marked atypia
Thyroid like follicular carcinoma

- Overall, may have better prognosis, but 1 case reported to metastasize

- Gross appearance
  - Circumscribed, encapsulated
  - Tan brown appearance

- Microscopic
  - Follicular architecture
  - Pink secretions mimicking colloid
  - Relatively bland nuclei, round nuclei, no nucleoli

- Immunostains
  - Negative for PAX2, WT1, vimentin, AMACR, thyroglobulin, TTF-1
Differential Diagnosis

• Metastatic thyroid cancer
  – Clinical history?
  – Thyroglobulin and TTF-1 immunostains
Acquired cystic disease associated RCC (ACD RCC)

- Occurs in the setting of end stage kidneys, especially in patients with a history of dialysis
- Other tumors can also occur in this setting – not specific
- Often pT1 disease and indolent course

Gross appearance
- Multiple tumors may be present
- May arise in wall of cysts present in background kidney
- Variable calcification

Microscopic
- Cystic/solid/sheets/papillary in appearance that may appear cribriform
- Eosinophilic cells with prominent nucleoli
- Oxalate crystals present within lumens

Immunostains
- Positive for cytokeratins, CD10, AMACR
- Negative for CK7
Differential Diagnosis

- **Papillary RCC**
  - CK7 and AMACR positive
  - Lacks oxalate crystals

- **Translocation carcinoma**
  - TFE3/TFEB immunostains
  - Often different demographic
## Comparison of IHC

<table>
<thead>
<tr>
<th></th>
<th>EMA/Cam5.2/AE1/3</th>
<th>CK7</th>
<th>CA9</th>
<th>AMACR</th>
<th>CD10</th>
<th>PAX2/PAX8</th>
<th>Vimentin</th>
<th>CD117</th>
<th>TFE3/TFEB</th>
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Medullary carcinoma

- Virtually always in patients with sickle cell trait
- Often younger patients
- Aggressive tumor

- Gross appearance
  - Localized to medullary area of kidney
  - Infiltrative borders
  - Gray white

- Microscopic
  - Variety of patterns, including cribriform/reticular/sheets/nests
  - Desmoplastic stroma
  - Often neutrophilic infiltrate
  - High grade cytology
  - Sickled RBCs may be seen

- Immunostains
  - Cytokeratins positive
Molecular Features

- ABR-BCL translocations and amplification of ABR and BCL in a subset of cases
- INI1 protein loss
- Tissue hypoxia may influence pathogenesis
- One study suggests gene expression similar to urothelial carcinoma
Differential Diagnosis

• Collecting duct carcinoma
  – Usually no history of sickle cell/hemoglobinopathy
  – Lacks neutrophils
  – Challenging differential
Collecting Duct Carcinoma

- May affect children/young adults, but not as commonly as medullary carcinoma
- Very aggressive

- Gross appearance
  - Centered in renal medulla
  - Gray-white appearance
  - Infiltrative
  - Satellite nodules common

- Microscopic
  - Solid/papillary/cribriform
  - High grade cytology
  - Desmoplastic stroma and inflammatory infiltrate may be present

- Immunostains
  - EMA variable; negative for PAX8, AMACR, CD10 and p63
Differential Diagnosis

• Papillary RCC
  – CK7 and AMACR positive

• Renal medullary carcinoma
  – Sickle cell present; trait known

• Hereditary leiomyomatosis renal cell cancer
  – Syndrome present; genetic testing required
Hereditary Syndromes

- Renal tumors may be first indicator of hereditary syndrome, so important to keep in mind

- Multiple different tumors in the same kidney may raise the concern for hereditary syndrome

- Comment that there are “unusual findings in renal tumor that may indicate presence of hereditary syndrome; referral for further evaluation” is important to add
# Types of Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Renal Tumors</th>
<th>Other Findings</th>
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<tbody>
<tr>
<td><strong>Birt-Hogg-Dube</strong></td>
<td>BHD (17p12)</td>
<td>Hybrid oncocytic tumors, other renal cancers</td>
<td>Fibrofolliculomas, pneumothorax, lipomas, medullary thyroid cancer</td>
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<td><strong>Von Hippel-Lindau</strong></td>
<td>VHL (3p25)</td>
<td>Clear cell RCC</td>
<td>Hemangioblastomas of CNS and retina, pancreatic endocrine tumors, pheochromocytoma</td>
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<tr>
<td><strong>Hereditary leiomyomatosis and RCC</strong></td>
<td>Fumarate hydratase (1q42.3-q43)</td>
<td>RCC with high grade features and organophilic, large nucleoli</td>
<td>Leiomyomas involving the uterus and skin</td>
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<tr>
<td><strong>Hereditary papillary RCC</strong></td>
<td>c-MET (7q31)</td>
<td>Papillary RCC type 1, often multiple</td>
<td>None</td>
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<tr>
<td><strong>Tuberous sclerosis</strong></td>
<td>TSC1 (9q34) and TSC2 (16p13.3)</td>
<td>RCC, angiomyolipoma</td>
<td>Clear cell sugar tumors of lung/pancreas, subependymomas, PEComas, lymphangioleiomyomatosis</td>
</tr>
</tbody>
</table>
Hybrid Oncocytic Tumor (BHD)

• May have combination of oncocytoma and chromophobe areas

• Occasionally, cytoplasmic clearing reminiscent of clear cell RCC may be present in the tumors

• A subset of tumors that fall into “oncocytic neoplasm” likely represent this group of tumors; if multiple or bilateral more likely to be associated with syndrome and can suggest possibility in comment
Angiomyolipoma (TS)

- Related to PEComa family of tumors
- Combination of abnormal vessels, fat and spindled smooth muscle cells that spin off vessels
- Occurs in >50% of TS patients
- Most are benign, but epithelioid morphology indicates worse outcome
- HMB45, Melan-A, MiTF, tyrosinase positive
Epithelioid AML
Thank you!!