Objectives

• Review specific differential diagnostic considerations in renal neoplasia
  – Clear cell RCC vs other

• Review RCC subtypes that are not as well recognized

Importance

• Renal carcinoma subtypes are prognostic, but for current standard of care practice…
  – Clear Cell RCC vs NOT Clear Cell RCC
    • Sufficient for most treatment decisions after nephrectomy
    • Must know what is NOT clear cell RCC
      – Major prognostic difference

• However…. recognition of a hereditary syndrome may have very significant screening implications for the individual patient and their family
Clear Cell “Tumors”

Clear Cell RCC:
When did this become so complex?

and why?

Clear Cell RCC: Classic Pattern
What Links These Patterns of Clear Cell RCC?

• VHL alterations
  – Somatic mutation VHL gene
  – Hypermethylation of VHL promoter
  – Chromosomal loss (3p-)
• High risk for metastasis
  – Late metastasis

Tumors with “Clear Cell” Features

• Clear cell (conventional) carcinoma
• Multilocular cystic renal neoplasm LMP
• Clear cell-papillary carcinoma
• Papillary RCC with cytoplasmic clearing
• RCC with angioleiomyomatous stroma
• Atypical renal cysts

Multilocular Cystic Renal Neoplasm of LMP
**Strict Criteria Multilocular Cystic LMP**

- Numerous cysts lined by clear cells with small clusters of clear cells in tumor septa
- NO solid, grossly recognizable clear cell component
  - or microscopic “nodules”

**Multilocular Cystic LMP: Gross**
Genetics are distinct from both Clear Cell RCC and Papillary RCC.

RCC, Clear Cell-Papillary Type (Macrocystic)

RCC, Clear Cell-Papillary Type
Immunophenotypic Comparison

<table>
<thead>
<tr>
<th>IHC</th>
<th>CC-P</th>
<th>Clear cell</th>
<th>Papillary</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CD10</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Racemase</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CA9</td>
<td>+</td>
<td>(cup-like)</td>
<td>circumferential -</td>
</tr>
</tbody>
</table>

Not always clear cut!!!
Genetic Approach

“discordant immunohistochemical pattern typically correlates with loss of material from chromosome 3p in tumors with incomplete morphology of clear cell papillary renal cell carcinoma”

Outcome Approach

• Type 1: Mixed features of CC-P and CC
  • Variable immunophenotype - significant overlap
  • Risk for malignant clinical course
• Type 2: CC-P RCC with adjacent high grade component
  • Risk for malignant clinical course

1. RCCs in VHL may have features of clear cell-papillary RCC
2. Still have VHL mutation
RCC #1: Suggestive of Clear Cell-Papillary?

Strict Criteria for Clear Cell-Papillary

- Because CC-P has a very favorable outcome, features must be perfect
  - And... no features of von Hippel Lindau
- If unusual, we default to...
  - Clear Cell RCC or Unclassified RCC
Papillary RCC
(with cytoplasmic clearing)
Papillary RCC

• If the features are predominantly characteristic of papillary RCC, then some cytoplasmic clearing should NOT change the diagnosis

• True “mixed” RCC subtypes do NOT exist
RCC with Angioleiomyomatous Stroma
(provisional WHO entity)

Renal Cell Carcinoma Associated With Prominent Angioleiomyomatous-like Proliferation
Report of 5 Cases and Review of the Literature

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

RCC with Smooth Muscle Stroma
- Clear cell-papillary RCC
- Renal angioleiomyomatous tumor
- RCC with angioleiomyoma-like stroma
- Leiomyomatous RCC
- TCEB-1 mutant RCC
- RCC associated with TSC
RCC with Smooth Muscle Stroma

Desmin

CK7

TCEB1-mutated renal cell carcinoma: a distinct genomic and morphological subtype

Current thoughts on RCC with angioleiomyomatous stroma

- Clear cell-papillary
  - TSC associated RCC
  - TCEB1 mutant RCC
  - Others?

Current thoughts...

- To date, TCEB1 have benign clinical course
- Similar cases of TSC associated RCC
  - 2 reported with regional lymph node mets
  - No further progression

Renal Cysts with Early Epithelial Proliferation
Simple Renal Epithelial Cysts

Atypical Renal Epithelial Cysts vs. Clear Cell Papillary?
No clinical risk when excised

Diagnostic Categories

- High clinical risk
  - Clear cell RCC
- Low clinical risk
  - RCC with smooth muscle stroma
- Very low clinical risk... no risk?
  - Multilocular cystic renal neoplasm of LMP
  - Clear cell-papillary RCC
- No clinical risk (when excised)
  - Atypical Cysts

Less Familiar Renal Neoplasms

- Epithelioid AML
  - Close mimic of RCC
- Uncommon RCC types
  - MiTF Family Translocation RCC
  - Tubulocystic
  - SDHB deficient RCC
  - FH deficient RCC (HLRCC associated RCC)
  - ACKD associated RCC
  - ESC RCC
Epithelioid Angiomyolipoma

Epithelioid Angiomyolipoma
- Actin +, HMB-45 +, CK -
- PAX8 -, CD117 -

Atypical Epithelioid Angiomyolipoma
Xp11.2 Renal Translocation Carcinomas

- Characterized by translocation creating TFE3 or TFEB gene fusion
  - Heterogeneous morphology and immunophenotype
- Of RCC in children, TFE3 is very common
  - Some associated with past chemotherapy
  - Can be indolent, even with nodal mets
  - Deaths reported
- Occurs in adults
  - Aggressive compared to other types?
  - More rapid course?
RENAL CELL CARCINOMA IN CHILDREN: A REVIEW OF THE LITERATURE AND REPORT OF TWO CASES
C. D. SCHEUGS AND TEMPLE AINSWORTH
J Urol 1961;86(6):728-733

LE CARCINOME TUBULO-PAPILLAIRE DU REIN DE L'ENFANT
A propos de 9 observations (*)
M. C. DEBRET, E. GIROD-MARCIOT, D. MONTAGNE et C. MÉDIZON

Renal cell carcinoma in children: A clinicopathologic study of 15 cases and review of the literature
Louis P. Delahay, Lieutenant (HC) USN, Jon E. Sorenson, Major, USMCR (MC), and E. P. Parks, Jr., MD
J Pediatrics 1970; 76(3):358-68

Xp11/TFE3 RCC
Conventional Cytogenetics

Aberrant Nuclear Immunoreactivity for TFE3 in Neoplasms With TFE3 Gene Fusions
A Sensitive and Specific Immunohistochemical Assay

FISH: TFE3 Break-apart
When should we FISH retrospectively?

- Unusual morphology?
  - Abundant clear or granular cytoplasm
- Nested architecture
  - Granular cytoplasm
  - Psammoma bodies!!!!!
- Biphasic (dimorphic) pattern
- Patient age < 40 yrs with allowable morphology

When should we FISH retrospectively?

- Cytokeratin negative RCC?
  - CK mix
  - CK 7
  - Cathepsin-K positive?

TFE3 positive IHC is NOT sufficient
- Technically challenging antibody

SDHB Deficient RCC
Germline SDH Mutation

- Families with hereditary paraganglioma syndrome occasionally have members with RCC
  - Type 4: Germline SDHB mutations (PGL4)
Differential Diagnosis

- More commonly in younger patients
  - Oncocytoma/oncocytic renal neoplasia
  - Fumarate hydratase deficient RCC

Germline SDH Mutation

- Oncocytic renal neoplasm with eosinophilic cytoplasmic inclusions
  - Verification of SDHB loss by IHC
  - Low index of suspicion in young patients
- Associated neoplasms
  - Family history of familial paraganglioma syndrome
  - SDH mutant gastric GISTs

Tubulocystic RCC
Tubulocystic Carcinoma of the Kidney
Clinicopathologic and Molecular Characterization

Xiaoying Li, Yang, MD, PhD,*,† Ming Zhou, MD, PhD,† Jose Lopez, MD, PhD,‡ Raper W. Shah, MD,‡***
Yu Yang, MD, PhD,† Sheng-Fang Chuang, DDS,† Fan Lu, MD, PhD,†‡
Norio Takahara, MD, PhD,§ Eric J. Kott, MD,†§ and Bin Yuan, MD, PhD,†§

Abstract The nature of tubulocystic carcinoma, a rare renal tumor composed of tubular and cystic structures, is poorly understood. It has been suggested that it may represent a low-grade collecting duct carcinoma of the kidney despite the lack of sufficient morphologic and pathologic evidence. The aim of this study was to describe the clinicopathologic and molecular features of 11 cases of tubulocystic carcinoma of the kidney. Furthermore, we analyzed the molecular signatures of this cancer by sequencing it with other renal tumors to our previously established renal tumor profile database. Histologically, all 11 tumors were composed of tubular and cystic structures reminiscent of collecting ducts. The tubular lining was either flat and cuboidal, or the tumor was characterized by a multifocal, papillary growth pattern. In addition, 7 of the 11 cases showed intratumoral micropapillary nodules. Five of the 11 cases had molecular signatures as well as its histologic behavior to develop metastasis either by local or by metastasis with pulmonary metastases. In contrast, tubulocystic carcinomas of the kidney should be recognized as a distinct subtype of RCC and be distinguished from other papillary and clear cell RCC. We recommend the current World Health Organization classification for renal tumors be updated to recognize tubulocystic RCC as a distinct entity. The clinical course of tubulocystic RCC is still controversial due to the lack of strong supportive evidence by molecular and histopathologic analysis.
Tubulocystic Carcinoma

Tubulocystic Carcinoma

Fumarate Hydratase Deficient RCC (HLRCC)
**HLRCC**

- Autosomal dominant syndrome
  - Leiomyomas of skin and uterus
  - Renal cell carcinoma
- Germline activating mutation in gene for *fumarate hydratase*

**HLRCC Syndrome**

- Spectrum of neoplasia
  - Leiomyomas of skin and uterus
    - Most patients develop cutaneous leiomyomas
    - Early hysterectomy for myomas
  - Renal carcinomas
    - Often solitary and unilateral
    - Low penetrance (20-35%)

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**The Morphologic Spectrum of Kidney Tumors in Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) Syndrome**

María J. Merino, MD* Carlos Toro-Cabada, MD* Peter Pavlov, MD†
and William Marion Lichtner, MD‡

*Abstract:* Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is an autosomal dominant familial syndrome characterized by the development of cutaneous and uterine leiomyomas as well as renal tumors. The mutation of this condition has been identified in the *fumarate hydratase* (FH) gene, which encodes the enzyme fumarate hydratase. We removed 46 renal tumors excised from 36 patients belonging to HLRCC families with proven FH germline activating mutations. Patients ranged in age from 1 to 75 years of age. Tumors were collected at all but 2 cases. The size of the tumors varied between 2.2 and 20 cm and there was a predominance of solid tumors (63%), 50% were myxoid/mixed (7 cases), 38% were pleomorphic (7 cases), and 2% were papillary. Fumarase dehydrogenase (FDH) and Matrix metalloproteinase 2 (MMP2) were measured in formalin-fixed, paraffin-embedded tissue sections using immunohistochemical staining. Most tumors stained positive for both proteins except for a clear cell RCC, which showed no staining for FDH. Renal tumors associated with tuberous sclerosis are most frequently angiomylipomas, although clear cell RCC has also been reported. Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome is usually inherited in an autosomal dominant fashion with variability in the development of cutaneous leiomyomas. The majority of patients with HLRCC syndrome have leiomyomas of the skin and uterus. Patients with HLRCC syndrome have an increased risk of developing renal cell carcinoma. The majority of renal cell carcinomas associated with HLRCC syndrome are clear cell RCC. The most common histologic type of renal cell carcinoma is clear cell RCC, which is characterized by the presence of clear cells with eosinophilic cytoplasm and oval nuclei. Clear cell RCC is the most common type of renal cell carcinoma and accounts for over 70% of all renal cell carcinomas. Clear cell RCC is characterized by hypercellularity, nuclear pleomorphism, and frequent mitotic activity. Clear cell RCC is associated with a poor prognosis, with a 5-year survival rate of less than 50%. Clear cell RCC is distinguished from papillary RCC by its lack of papillary architecture and its higher degree of nuclear pleomorphism. Clear cell RCC is also distinguished from chromophobe RCC by its lack of chromatin clumping and its higher degree of nuclear pleomorphism. Clear cell RCC is also distinguished from papillary RCC by its lack of papillary architecture and its higher degree of nuclear pleomorphism.

Renal Cell Carcinoma in HLRCC

Renal Cell Carcinoma in HLRCC: Perinucleolar Halo
Renal Cell Carcinoma in HLRCC

Tubulocystic Carcinoma of the Kidney With Poorly Differentiated Foci
A Frequent Morphologic Pattern of Fumarate Hydratase-deficient Renal Cell Carcinoma

Original Article

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Luong Cheng, MD, PhD,25 Jonathan J. Ercolani, MD, PhD,26 Victor E. Revier, MD,27 Satish K. Takan, MD,28 Scott A. Green, MD, PhD,28,29,30 Amin, MD,30

Am J Surg Pathol 2016 (ePub ahead of print)

Renal Cell Carcinoma in HLRCC:
Tubulocystic Pattern
Renal Cell Carcinoma in HLRCC: Tubulocystic Pattern

HLRCC: Recognition

- Unusual RCC with features of type II Papillary RCC and perinucleolar halos
  - Multiple cutaneous or uterine leiomyomas
    - Uterine leiomyomas <30 years of age
- Differential Diagnosis (solitary, unilateral)
  - Papillary RCC, Type II
  - Collecting Duct Carcinoma
  - Translocation RCC

When should we test retrospectively?

- High grade RCC
  - Eosinophilic
  - Papillary/cribriform/solid
  - Perinucleolar halos
- Fumarate hydratase IHC screen?
  - Not all syndromic; Not 100% sensitive
  - Long comment regarding subtype

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Re-evaluation of 23 “Unclassified” Eosinophilic Renal Cell Carcinomas in Young Patients

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Histopathology 2017 (Epub ahead of print)
1) 35% of patients on dialysis get ACKD
2) 5.8% of these patients develop RCC

1) Increasing percent of patients get ACKD with increased number of years on dialysis
2) Reports that 3-7% develop RCC
ACKD-RCC: Mixed Sieve and Papillary

LN Metastasis with Cystic Architecture
Background Cysts: Variation

Background Cysts: Tumorlet

**Clinical Behavior**

- Frequently present at lower stage because patients are on surveillance
  - May explain relatively indolent course
- Metastases and tumor related deaths do occur
Eosinophilic, Solid, Cystic (ESC) RCC

ESC RCC (Emerging Subtype)

- Almost exclusively in women
- Younger age at onset (<50 yrs common)
- In the past, likely called “unclassified RCC”
- Sporadic form more common…
  - Subset associated with tuberous sclerosis
  - Relationship to oncocytoid RCC after NB??
ESC RCC

- IHC: Often CK20+/CK7- phenotype
  - Not all strong and diffuse!

- Prognosis: To date...
  - 2 of approximately 70 known cases with metastasis

- Warrants separation from "unclassified"

Summary

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- Clear cell (conventional) carcinoma
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- Atypical renal cysts
“Easy to Miss” Renal Neoplasms

- Epithelioid AML
- SDHB Deficient RCC
- FH Deficient RCC (HLRCC associated RCC)
- Tubulocystic RCC
- ACKD associated RCC
- ESC RCC