50 Shades of Pink: New Pink Cell Renal Tumors

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Disclosures

None
37 y/o female, right renal mass 4.5 cm
Your Diagnosis?

1. High grade clear cell RCC with granular cytoplasm
2. Oncocytoma
3. Chromophobe RCC
4. Eosinophilic solid cystic RCC
Three-step Pattern-based Approach to Diagnosis of Renal Tumors

1. Look for predominant pattern at low power

   Pink Cell Tumor

2. Generate differential diagnosis based on the predominant pattern

3. Rule in or out each tumor on the list by looking for a constellation of histological features relatively specific for the tumor
Pink Cell Renal Tumors

Common RCC types
- Clear cell RCC with granular cytoplasm
- Papillary RCC, type 2
- Chromophobe RCC, eosinophilic variant
- Oncocytoma

New RCC entities
- Translocation RCC
- Acquired cystic disease associated RCC
- Succinic dehydrogenase (SDH)-deficient RCC
- Fumarate hydratase (FH)-deficient RCC, including HLRCC/RCC
- TSC1/mTORC mutated RCC, including eosinophilic solid cystic RCC
- Hybrid oncocytic tumor (HOT) in Birt-Hogg-Dube syndrome (BHD)

Non-epithelial tumors
- Ectopic adrenal cortical tissue
- Epithelioid angiomyolipoma
Three-step Pattern-based Approach to Diagnosis of Renal Tumors

1. Look for predominant pattern at low power

2. Generate differential diagnosis based on the predominant pattern

3. Rule in or out each tumor on the list by looking for a constellation of histological features relatively specific for each tumor
Diagnosis of “Pink Cell Tumors”
Morphological Clues

**Tumor/normal interface**
- Infiltrative vs circumscribed
- Entrapped renal tubules

**Architectural features**
- Acinar
- Papillary
- Tubular
- Cystic
- Biphasic rosette
- Ca oxalate crystals
- Hyalinized cores

**Cytoplasmic features**
- Cell borders
- Two tone cytoplasm
- Cytoplasmic granules
- Cytoplasmic vacuoles

**Nuclear features**
- Raisinoid nuclei
- Prominent nucleoli
- Perinucleolar halo
- Cytoplasmic/nuclear synchronization
Diagnosis of “Pink Cell Tumor”

**Rule #4**

Look for cytoplasmic features
Two tone cytoplasm (partially clear/eosinophilic cytoplasm)

Translocation RCC
Coarse basophilic cytoplasmic granules (basophilic stippling):

Eosinophilic solid cystic RCC
Cytoplasmic vacuoles:

Succinate dehydrogenase (SDH) deficient RCC
Succinate Dehydrogenase (SDH) Deficient RCC

- Rare
- Germline mutations in SDH subunit A, B, C and D
- Paraganglioma/pheochromocytoma/pediatric gastric GIST
- Majority indolent but may dedifferentiate and metastasize

SDHB

- “Oncocytoma”-like
- Cytoplasmic vacuoles
- Negative SDHB IHC
Marked cytoplasmic vacuolation:

RCC with mutations in *TSC* and *mTORC1* genes
RCC with Eosinophilic and Vacuolated Cytoplasm Harbors Mutations in TSC/mTORC1 genes

- 7 unclassified oncocytic tumors
- 3/5 somatic inactivating mutations of TSC2
- 2/5: activating mutations of mTORC1

Chen YB et al, AJSP, 2019
Diagnosis of “Pink Cell Tumor”

Rule #5

Look for nuclear features
Prominent nucleoli with perinucleolar clearing (resembling CMV inclusions or melanoma nuclei)

RCC in hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC)
Renal Cell Carcinoma in Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome (HLRCC)

- Autosomal dominant
- Germ-line mutation in fumarate hydratase gene (FH, 1q42.3-q43)
- Young patients with multiple skin leiomyomas or early uterine fibroids
- RCC resembles “type 2” PRCC or collecting duct RCC
- Very poor prognosis; up to 50% with metastasis at diagnosis
HLRCC often has multiple patterns in the same tumor

- Papillary
- Tubular
- Tubulocystic
- Cribriform
- Solid

Polymorphous patterns: 1st clue for HLRCC
Nuclear Features
(Pan X et al, J Clin Pathol, 2019)

Low grade morphology
To Confirm the Diagnosis…

1. Sequence $FH$ gene, or
2. Surrogate IHC markers
   - FH (loss or reduced expression)
   - S-(2-succinyl) cysteine protein (2SC) (strong increased expression)
FH-deficient RCC

FH retained RCC

FH-/2SC+: FH deficiency, strongly correlates with *FH* mutation and HLRCC syndrome

Trpkov AJSP 2016
HLRCC

Genetically confirmed germline mutation in *FH* gene

**FH deficient RCC**

1) Morphology compatible with HLRCC

2) IHC: FH -, and/or 2SC +

3) Clinical and family history of skin and uterine leiomyomas: uncertain

4) Genetic status of *FH* at the time of case sign-out: unknown
37 y/o female, right renal mass 4.5 cm
Coarse basophilic granules (basophilic stippling)
Eosinophilic solid cystic RCC (ESC RCC)?
Eosinophilic solid cystic RCC (ESC RCC)
### TIER 2 - VARIANTS OF POSSIBLE CLINICAL SIGNIFICANCE

<table>
<thead>
<tr>
<th>VARIANT</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSC2</td>
<td>Diagnosis: There are two distinct copy number states within the TSC2 gene. Some sections are at a one copy loss, and others are at a two copy loss. This likely represents biallelic inactivation of the gene. RNA expression analysis also shows that this has lower expression than any case we’ve previously tested across tumor types.</td>
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</tbody>
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| Pos: chr16:2075770-2229129 | Copy Number: 0 | Aberration Type: loss |

**Chart:**
- X-axis: Copy Ratio (log2)
- Y-axis: Various copy ratio values
- Chr 16
- TSC2
- 5'
- 3'
Eosinophilic solid cystic (ESC) RCC with somatic $TSC2$ mutation
TSC-mTOR Pathway

Amino acids → Rags → mTORC1

Subunits of mTORC1:
- mTOR
- Raptor
- mLST8
- PRAS40
- DEPTOR

Protein Synthesis → 4E-BP1
Autophagy → S6K1

Cell growth/proliferation → Akt

Subunits of mTORC2:
- mTOR
- Rictor
- mLST8
- mSIN1
- PROTOR
- DEPTOR

PTEN → PI3K

Akt → PDK1

Pathway regulation:
- TSC1, TSC2
- RAS/PI3K/AKT signaling
- mTORC1/mTORC2 activity

Protein synthesis and autophagy control cell growth and proliferation.
### RCC in Tuberous Sclerosis Complex (germline mutations in *TSC1/2*)

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<tbody>
<tr>
<td><strong>RCC w/ SM stroma</strong></td>
<td>24 (52%)</td>
<td>17 (30%)</td>
</tr>
<tr>
<td><strong>Oncocytic tumors resembling onco/ChRCC</strong></td>
<td>15 (33%)</td>
<td>34 (59%)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Unclassified 7 (15%)</td>
<td>Eosinophilic solid cystic RCC 6 (10%)</td>
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Morphologically very similar to eosinophilic solid cystic RCCs in tuberous sclerosis complex (TSC)

Sporadic; patients without TSC
Sporadic ESC RCC Morphological Features

1. Solid and cystic components
2. Voluminous eosinophilic cytoplasm
3. Basophilic granules in the cytoplasm (basophilic stippling)
4. CK20 at least focally +; Cathepsin K +; CK7-
## Genetic Characteristics of Sporadic ESC RCC

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<tr>
<td>2</td>
<td>7</td>
<td>19 (including 3 ESC-like, 1 oncocytoid RCC s/p neuroblastoma)</td>
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</table>

<table>
<thead>
<tr>
<th>TSC2 (2)</th>
<th>TSC2 (5)</th>
<th>TSC2 (11)</th>
<th>TSC2 (18/26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSC1 (2)</td>
<td>TSC1 (6)</td>
<td>TSC1 (8/26)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Somatic (2)</th>
<th>Somatic (7)</th>
<th>Somatic ?</th>
<th>Somatic (9/9)</th>
</tr>
</thead>
</table>

| Biallelic? | Biallelic (6) | Biallelic? | Biallelic (6/6) |
RCC with Eosinophilic and Vacuolated Cytoplasm Harbors Mutations in TSC/mTORC1 genes (Chen YB et al, AJSP, 2019)

- 7 unclassified oncocytic tumors
- 3/5 somatic inactivating mutations of TSC2
- 2/5: activating mutations of mTORC1
RCC with Somatic \textit{TSC/mTORC1} Mutations: A Distinct Entity

Similar morphology

✓ Pink cell tumor with abundant eosinophilic cytoplasm
✓ Basophilic stippling +/-, and/or vacuolation
✓ CK20 f+, cathepsin K+
Working up “pink cell tumors”…

Common RCC types
- Clear cell RCC with granular cytoplasm
- Papillary RCC, type 2
- Chromophobe RCC, eosinophilic variant
- Oncocytoma

Looking for well-differentiated areas to classify

<table>
<thead>
<tr>
<th>Immunohistochemistry</th>
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<tr>
<td>CK7</td>
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<tr>
<td><strong>Diagnosis</strong></td>
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<tr>
<td>CCRCC with granular cytoplasm</td>
</tr>
<tr>
<td>PRCC, type 2</td>
</tr>
<tr>
<td>ChRCC, eosinophilic type</td>
</tr>
<tr>
<td>Oncocytoma</td>
</tr>
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Working up “pink cell tumors”…

New RCC entities
- Translocation RCC
- Acquired cystic disease associated RCC
- Succinic dehydrogenase (SDH)-deficient RCC
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"Odd" Oncocytic Tumors

Characteristic Morphology

Translocation RCC
SDH-deficient RCC
FH-deficient RCC
TSC/mTORC 1 RCC

Confirm with IHC/FISH/sequencing

YES

IHC panel
SDHB
FH
CK20/Cathepsin K
TFE3/TFEB

NO

RCC, unclassified type