Pattern Based Diagnosis and Classification of Renal Tumors

Ming Zhou, MD, PhD
Dr. Charles T. Ashworth Professor of Pathology
Director, Anatomic Pathology
The University of Texas Southwestern Medical Center
Dallas, TX
Ming.Zhou@utsouthwestern.edu
MZhou3@tuftsmedicalcenter.org (after 6/1/2019)
Quiz
Classification of Renal Cell Neoplasms

- Based primarily on morphology

- Genetic classification plays increasingly important role

  - Translocation RCC, SDH deficient RCC, FH-deficient RCC, TSC/mTORC-mutated RCC, etc
Morphology-based Classification Inherently Imprecise

- Same morphological pattern may be seen in different tumors
- Same tumor may have two or more different patterns
- Poorly differentiated tumors may not have a distinct pattern or architecture
Pattern-based Diagnosis of Renal Tumors

1. Do not rush to a diagnosis at first sight; rather, look for predominant pattern at low magnification

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

4. Use ancillary diagnostic tools
   1. Immunohistochemistry
   2. Genetic studies
Major Morphological Patterns in Renal Tumors

1. Clear cell/pale cytoplasm
2. Tubulopapillary
   - Lined with basophilic cells (type 1)
   - Lined with eosinophilic cells (type 2)
   - Lined with clear cells
3. Pink cell
4. High grade infiltrative
5. Extensive cystic
6. Spindle cell/sarcomatoid
Pattern-based Diagnosis of Renal Tumors

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3. Rule in or out each tumor on the list by looking for a constellation of histological features relatively specific for the tumor
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Tumors with clear (light-staining) cytoplasm

- Clear cell RCC
- Clear cell papillary RCC
- Multilocular cystic renal tumor of LMP
- RCC with smooth muscle stroma
- Papillary RCC with clear cells
- Chromophobe RCC, classical form
- Translocation RCC
- Pelvic urothelial carcinoma
- Epithelioid AML
- Intrarenal adrenal tissue
Pattern-based Diagnosis of Renal Tumors

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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 diagnostic of a particular tumor

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   1. Immunohistochemistry
   2. Genetic studies
Pattern-based Diagnosis of Renal Tumors

1. Do not rush to a particular diagnosis at first sight; rather, look for predominant pattern at low magnification

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3. Rule in or out each tumor on the list by looking for a constellation of histological features diagnostic of a particular tumor

4. Use ancillary diagnostic tools
   - Immunohistochemistry
   - Molecular genetic studies
Case 1. 40 y/o male, right renal mass 9.5 cm
“Type 2” Papillary Pattern

- Papillary RCC, type 2
- Translocation RCC
- Fumarate hydratase (FH)-deficient RCC, including hereditary leiomyomatosis/RCC syndrome (HLRCC)
- Tuberous sclerosis complex (TSC) RCC
- TSC/mTORC-mutated RCC, sporadic form
- ALK translocation RCC
- Acquired cystic disease RCC
Type 2 Papillary RCC

1. Rarely made with the discovery of other subtypes with specific genetic mutations

2. Prototypic morphology
   ✓ Fibrous capsule with “intracystic growth”; hemorrhage, hemosiderin, foamy histiocytes
   ✓ CK7-/+; AMACR+

3. Must consider and rule out other subtypes
Fibrous capsule

“ Intracystic growth”

Cholesterol clefts

PRCC
Type 2 Papillary RCC
Xp11/TFE3 Translocation Carcinoma

- Young age
- Papillae/nests with partially clear/eosinophilic cytoplasm
- Hyalinized cores, Ca^{2+}
Acquired Cystic Disease RCC

- Background end stage kidney
- Intensely eosinophilic cytoplasm
- Ca oxalate crystals

Papillary pattern

Tubulocystic pattern

Ca oxalate crystals
EML4-ALK translocation RCC
(Dr. Kengo Takeuchi, Tokyo, Japan)
## Immunohistochemistry

<table>
<thead>
<tr>
<th>Positive stains:</th>
<th>Negative stains:</th>
</tr>
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<tbody>
<tr>
<td>PAX8</td>
<td>CA9</td>
</tr>
<tr>
<td>EMA (patchy)</td>
<td>CK7</td>
</tr>
<tr>
<td>CD10 (patchy)</td>
<td>CK20</td>
</tr>
<tr>
<td>AMACR</td>
<td>CK5/6</td>
</tr>
<tr>
<td>INI1</td>
<td>OCT4</td>
</tr>
<tr>
<td>SDHB</td>
<td>Cathepsin K</td>
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Fumarate Hydratase (FH)
Diagnosis:

Fumarate hydratase (FH)-deficient RCC, consider *FH* gene sequencing to rule out hereditary leiomyomatosis/RCC syndrome
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 resemble “type 2” PRCC or “collecting duct”-like RCC
- Very poor prognosis; up to 50% with metastasis at diagnosis
The Morphologic Spectrum of Kidney Tumors in Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) Syndrome

Maria J. Merino, MD,* Carlos Torres-Cabala, MD,* Peter Pinto, MD,† and William Marston Linehan, MD‡

Architectural patterns (n=40):

- Papillary (25, 63%)
- Tubulo-papillary (8, 20%)
- Tubular (2, 5%)
- Solid (1, 2%)
- Mixed (4, 10%)

Nuclear feature:

- Prominent nucleoli with halo
Tubulocystic (41%) and tubular (26%)
Papillary (74%) + other patterns!

Multiple patterns in a tumor:
Think about HLRCC!
To Confirm the Diagnosis...

1. Sequence *FH* gene
2. Surrogate IHC markers
   - IHC for FH
   - IHC for 2SC-protein (currently not commercially available)
2SC Protein Is a Surrogate Marker for Loss of Fumarate Hydratase

Fumarate

\[
\text{HO-CO} \quad \text{OH}
\]

Fumarate Hydratase

\[
\text{HO-CO} \quad \text{OH}
\]

Fumarate

\[
\text{HO-CO} \quad \text{OH}
\]

Fumarate Hydratase

\[
\text{HO-CO} \quad \text{OH}
\]

Malate

+ SH

Protein

S-(2-succinyl) cysteine protein (2SC)

Bardella et al J Pathol 2011
FH-/2SC+: FH deficiency, strongly correlates with FH mutation and HLRCC syndrome

Trpkov AJSP 2016
FH deficient RCC

1) Compatible morphology

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

3) Uncertain clinical and family history of skin and uterine leiomyomas and RCC

4) Unknown genetic status at the time of case sign-out

HLRCC

Genetically confirmed germline mutation in FH gene
Reappraisal of Morphologic Differences Between Renal Medullary Carcinoma, Collecting Duct Carcinoma, and Fumarate Hydratase–deficient Renal Cell Carcinoma

Chisato Ohe, MD,* Steven C. Smith, MD, PhD,† Deepika Sirohi, MD,* Mukul Divatia, MD,‡ Mariza de Peralta-Venturina, MD,* Gladell P. Paner, MD,§ Abbas Agaimy, MD,¶ Mutual B. Amin, MD,¶ Pedram Argani, MD,¶ Ying-Bei Chen, MD, PhD,** Liang Cheng, MD,†† Maurizio Colecchia, MD,‡‡ Eva Compérat, MD, PhD,§§ Isabela Werneck da Cunha, MD, PhD,|| Jonathan I. Epstein, MD,# Anthony J. Gill, MD, FRCPath,** Onďrej Hes, MD, PhD,## Michelle S. Hirsch, MD, PhD,*** Wolfram Jochum, MD,††† Lakshmi P. Kunju, MD,‡‡‡ Fiona Maclean, FRCPA,§§§ Cristina Magi-Galluzzi, MD, PhD,|||| Jesse K. McKenney, MD,||| Rohit Mehra, MD,‡‡‡ Gabriella Nesi, MD, PhD,¶¶¶ Adeboye O. Osunkoya, MD,#### Maria M. Picken, MD, PhD,***** Priya Rao, MD,†††† Victor E. Reuter, MD,** Paulo Guilherme de Oliveira Salles, MD, PhD,‡‡‡‡ Luciana Schultz, MD,§§§§ Satish K. Tickoo, MD,** Scott A. Tomlins, MD, PhD,‡‡‡ Kiril Trpkov, MD, FRCPath,||||| and Mahul B. Amin, MD*¶¶¶

25% (13/51) cases previously diagnosed as CDC reclassified as FH-deficient RCC upon review and IHC for FH and 2SC
Fumarate Hydratase-deficient RCC: Diagnostic Algorithm

Any high grade RCC, consider FH-deficient RCC

Look for “inclusion-like nucleoli with halos”

RCC, unclassified type, with features of FH-deficient RCC, suggest *FH* mutation detection

FH- or +/- 2SC+

FH-deficient RCC

IHC for FH/2SC

Clinical stigmata of HLRCC

Germline mutation in *FH*

HLRCC

No further testing
“Type 2” Papillary Pattern
(Summary)

- Papillary RCC, type 2
  - Strict criteria and rule out other tumors
- Translocation RCC
- Fumarate hydratase (FH)-deficient RCC, including hereditary leiomyomatosis/RCC syndrome (HLRCC)
- Tuberous sclerosis complex (TSC)-mutated RCC
- TSC/mTOR-mutated RCC, sporadic form
- ALK translocation RCC
- Acquired cystic disease RCC
37 y/o female, right renal mass 4.5 cm
Oncocytic/Pink Cell 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
- TSC1/2-mTORC1 mutated RCC, including eosinophilic solid cystic RCC
- Hybrid oncocytic tumor (HOT) in Birt-Hogg-Dube syndrome (BHD)

**Non-renal tumors**
- Ectopic adrenal cortical tissue
- Epithelioid angiomyolipoma
Diagnosis of “Pink Cell Tumors”

Morphology Tip #1

Do extensive tissue sampling to look for “low grade”, better differentiated, areas to make a diagnosis
Clear Cell RCC with “Granular Cytoplasm”
Diagnosis of “Pink Cell Tumor”
Morphology Tip #2A

Look at tumor/normal interface and capsule
Sharp circumscription, no capsule, entrapped renal tubules: Benign or low grade tumor (oncocytoma/ChRCC)
Diagnosis of “Pink Cell Tumor”
Morphology Tip #2B

Diagnostic clues are often found at the periphery of the tumor!
Center- oncocytic tumor

Periphery- ChRCC
Diagnosis of “Pink Cell Tumor”
Morphology Tip #3

Look at the cell borders/cell membrane
Distinct, thick cell borders (plant-like): ChRCC
Separation between cells:

Oncocytoma
Diagnosis of “Pink Cell Tumor”

Morphology Tip #4

Look for cytoplasmic features
Basophilic stippling (coarse basophilic cytoplasmic granules: Eosinophilic solid cystic RCC
Cytoplasmic vacuoles:
Succinate dehydrogenase (SDH) deficient RCC
Marked cytoplasmic vacuolation:

RCC with somatic mutations in *TSC* and *mTORC1* genes
Pericellular fibrosis:
Translocation RCC
Diagnosis of “Pink Cell Tumor”

Morphology Tip #5

Look for nuclear features
Nuclear/cytoplasmic synchronization:

Clear cell RCC
No nuclear/cytoplasmic synchronizatio:

Not Clear cell RCC
(oncocytoma)
Raisinoid nuclei with perinucleolar halos:

ChRCC
Multinucleated giant cells:

Epithelial AML
Diagnosis of “Pink Cell Tumor”

Morphology Tip #6

Other features
Biphasic rosette

TFEB
translocation
RCC
Calcium oxalate crystals: 
Acquired cystic disease associated RCC
Current case

Basophilic stippling

Eosinophilic solid cystic RCC?
Case #2

CK20

Melan A
Diagnosis

Eosinophilic Solid Cystic RCC
Morphologically very similar to RCCs in tuberous sclerosis (TSC)

Sporadic; patients without TSC
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-
5. No h/o TSC
Solid/Cystic Patterns
Solid/Nested
Cystic Septae
Basophilic stippling
Cytoplasmic eosinophilic globules/vacuolation
Mutually exclusive bi-allelic loss of TSC1 or TSC2 genes in 85% of ESC RCCs

ESC RCC can be considered a sporadic form of TSC RCC
TSC-mTOR Pathway

Amino acids

- Rags
- Rheb

mTORC1
- mTOR
- Raptor
- mLST8
- PRAS40
- DEPTOR

mTORC2
- Rictor
- mLST8
- mSIN1
- PROTOR
- DEPTOR

Subunits

PDK1

TSC1

TSC2

Akt

PTEN

PI3K

4E-BP1

S6K1

Akt

SGK

PKCα

?
Oncocytic tumors other than ESC RCC may also contain genetic alterations involving TSC1/2 and mTORC1 genes.

“High-grade oncocytic renal tumor”: morphologic, immunohistochemical, and molecular genetic study of 14 cases

Huiying He · Kiril Trpkov · Petr Martinek · Ozlem Tanas Isikci · Cristina Maggi-Galuzzi · Reza Alaghehbandan · Anthony J Gill · Maria Tretiakova · Jose Ignacio Lopez · Sean R. Williamson · Delia Perez Montiel · Maris Sperga · Eva Comperat · Fadi Brimo · Ali Yilmaz · Kristyna Pivovarcikova · Kveta Michalova · David Slouka · Kristyna Prochazkova · Milan Hora · Michael Bonert · Michal Michal · Ondrej Hes

ORIGINAL ARTICLE

Somatic Mutations of TSC2 or MTOR Characterize a Morphologically Distinct Subset of Sporadic Renal Cell Carcinoma With Eosinophilic and Vacuolated Cytoplasm

Ying-Bei Chen, MD, PhD, Leili Mirsadraei, MD, Gowtham Jayakumaran, MS, Hikmat A. Al-Ahmadie, MD, Samson W. Fine, MD, Anuradha Gopalan, MD, S. Joseph Sirintrapun, MD, Satish K. Tickoo, MD, and Victor E. Reuter, MD
RCC with Eosinophilic and Vacuolated Cytoplasm

(Chen YB et al, AJSP, 2019)

- 7 unclassified oncocyctic tumors
- 3/5 somatic inactivating mutations of TSC2
- 2/5: activating mutations of mTOR
38 y.o female, 5 cm mass in left kidney

- Solid with focal cysts and type 2 papillae (? Solid PRCC)
- Basophilic cytoplasmic stippling
- CK20+/Melan A f+/Cathepsin K -
- TSC1 c.1328del; p.Gly443AspfsTer14

CK20
Are They Distinct RCC Subtype?

- Similar morphology
  - Abundant eosinophilic cytoplasm
  - Basophilic stippling +/-
  - CK20+, cathepsin K+/-, Melan A+

- Alteration involving mTORC1 pathway

Sporadic TSC/mTORC1-mutated RCC
Why should we recognize this class of tumor?

- Precise molecular classification
- Therapeutic implications
  - Metastatic tumors reported
  - May be treated with mTOR inhibitors
Renal Oncocytic Tumors

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- Papillary RCC, type 2
- Chromophobe RCC, eosinophilic variant
- Oncocytoma

New RCC entities
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Non-renal tumors
- Ectopic adrenal cortical tissue
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Odd Oncocytic Tumors

Characteristic Morphology

- Translocation RCC
- SDH-deficient RCC
- FH-deficient RCC
- TSC/mTORC1 RCC

- IHC panel
  - SDHB
  - FH
  - CK20/Cathepsin K
  - TFE3/TFEB

YES

NO

unclassified OT

Confirm with IHC/FISH/sequencing

RCC, unclassified type
Questions?

Ming.zhou@utsouthwestern.edu