Hereditary Renal Tumors

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Hereditary renal tumors: General

• 5-8% of all renal tumors are hereditary
• Clinical history
• Younger age of onset
• Bilaterality and multifocality
• Pathologic features?

Hereditary renal tumors: Syndromes

• Von Hippel-Lindau (VHL)
• Hereditary papillary renal cell carcinoma syndrome (HPRC)
• Birt Hogg-Dube syndrome (BHD)
• Tuberous sclerosis
• Succinate dehydrogenase B syndrome (SDHB)
• Hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC)

Hereditary renal tumors: Syndromes

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von Hippel-Lindau (VHL)

- Autosomal dominant
- Germline mutations of VHL gene at 3p25-26
  - Hemangioblastoma of CNS or retina
  - Pheochromocytoma
  - Pancreatic tumors
  - Renal tumors
  - Epididymal and broad ligament cystadenomas

VHL associated renal lesions

- Mean age of presentation with kidney tumors 37 years (16-67 years)
- Bilateral and multiple

1. Renal cysts
2. Microscopic nodules of clear cells
3. Clear cell renal cell carcinoma

VHL associated renal lesions

Renal cysts:
- Multiple, small, unilocular or multilocular
- Lined by clear cells (single layer or stratified)

Gross: Multiple cystic and solid lesions

Solomon D, Hum Pathol 1988
VHL associated renal lesions

Clear cell RCC:
- Mean age 44 years
- 70% of patients develop RCC by age 60
VHL associated renal lesions

- Microscopic nodules (tumorlets) of clear cells in background kidney

von Hippel-Lindau: Diagnosis

- Mutation analysis

von Hippel-Lindau

**Key morphologic features:**
- Multiple and bilateral clear cell RCCs
- Cysts lined by clear cells
- Microscopic nodules of clear cells
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Hereditary papillary renal cell carcinoma (HPRC)

- Autosomal dominant
- Activating mutations in MET oncogene
- Late presentation (50-70 years)
- No extrarenal manifestations

- Bilateral multiple (hundreds to thousands) papillary renal cell carcinomas (type 1) and papillary adenomas
- Resemble sporadic type 1 papillary RCC
Hereditary papillary renal cell carcinoma (HPRC): Diagnosis

- Mutation analysis

Hereditary papillary renal cell carcinoma (HPRC)

Key morphologic features:
- Bilateral and multiple type 1 papillary RCCs
- Background kidney with numerous papillary adenomas (but can be sporadic)

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Birt-Hogg-Dube Syndrome

- Autosomal dominant
- Mutations in BHD gene that encodes folliculin on 17p11.2
  1. Skin papules (fibrofolliculomas)
  2. Lung cysts (spontaneous pneumothorax)
  3. Renal tumors

Renal tumors in BHD

- Multiple, often bilateral
- Mean age at diagnosis ~50 years
  1. Chromophobe RCC
  2. Oncocytoma
  3. Hybrid oncocytic/chromophobe tumors (HOCT)
  4. Clear cell renal cell carcinoma

Renal tumors in BHD

- Hybrid oncocytic/chromophobe tumors of BHD
  - Mixture of areas resembling oncocytoma and chromophobe renal cell carcinoma
  - Scattered chromophobe cells in a background of classic oncocytoma
  - Large eosinophilic cells with intracytoplasmic clearing

Renal tumors in BHD

- Renal oncocytosis:
  - Numerous oncocytic masses of variable sizes
  - Often one dominant mass (hybrid features)
  - Can have a diffuse infiltrative pattern
  - Oncocytic change in non-neoplastic tubules
  - Cysts lined by oncocytic cells

Birt-Hogg-Dube Syndrome: Diagnosis

- Mutation analysis

Birt-Hogg-Dube Syndrome

Key morphologic features:
- Hybrid oncocytic tumors
- Multiple/bilateral chromophobe RCC or hybrid tumors
- Background kidney with oncocytosis (not specific)
Hereditary renal tumors: Syndromes

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Tuberous Sclerosis

- Autosomal dominant
- Mutations in \( TSC1 \) or \( TSC2 \) gene
- No family history (new mutations and variable penetrance)
- Mental retardation and seizures
- Tumor like lesions of multiple organs including brain (subependymal giant cell tumor), skin (angiofibromas) and heart (rhabdomyomas)
- Perivascular epithelioid cell tumors (PEComas)

Tuberous Sclerosis associated renal lesions

- Renal involvement in 50% of patients
- Younger age
- Kidney lesions:
  1. Multiple renal cysts
  2. Angiomyolipoma
  3. Renal cell carcinoma

Renal cysts in tuberous sclerosis

- 30-40% of patients
- Small cysts lined by granular eosinophilic cells with large nuclei (can be papillary/tufted)
Renal cysts in tuberous sclerosis

Angiomyolipoma in tuberous sclerosis

- Common (80%)
- Multifocal and bilateral
- AML in other organs (including lymph nodes)
  - More likely to have an epithelioid component?
  - Angiomyolipoma with epithelial cysts (AMLEC)?
  - Microscopic AML foci in background kidney

Combination of epithelioid AML, presence of associated epithelial cysts and microscopic AML foci is highly suggestive of tuberous sclerosis

Epithelioid angiomyolipoma

Microscopic AML foci

Angiomyolipoma with epithelial cysts (AMLEC)

Three components:
1. Cystic spaces lined by cuboidal to columnar epithelium
2. Condensed stroma immediately adjacent to the cyst lining
3. Muscle predominant AML
Angiomyolipoma with epithelial cysts (AMLEC)

Tuberous Sclerosis associated renal cell carcinoma
- Clear cell carcinoma most common
- Chromophobe RCC
- RCC with prominent smooth muscle stroma
- Unclassified cystic and solid tumors with large cells and eosinophilic granular cytoplasm
Tuberous Sclerosis: Diagnosis

- Mutation analysis

Tuberous Sclerosis

Key morphologic features:
- Bilateral and/or multiple angiomyolipomas (epithelioid and AMLEC)
- Multiple cysts lined by large eosinophilic cells
- Microscopic AML foci
- Renal cell carcinoma and concurrent angiomyolipoma

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Succinate dehydrogenase B syndrome (SDHB)

- Rare
- Mutations in SDH-B
- Patients at increased risk for pheochromocytoma, paraganglioma, GIST, pituitary adenoma and renal tumors
- Early onset
- Bilateral
**SDH deficient RCC**

- Well circumscribed
- Variably sized cysts with pale eosinophilic fluid
- Stroma with myxoid change or hyalinization
- **Intracytoplasmic eosinophilic inclusions**
- Flocculent cytoplasm with vacuolization and wispy eosinophilic material
- Entrapped tubules and glomeruli
- Can be higher grade, sarcomatoid transformation


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**SDH deficient RCC: Clinical**

- Low grade tumors (Fuhrman grade 2) have good prognosis
- Higher grade tumors (Fuhrman grade 3-4 or presence of sarcomatoid transformation) more aggressive
- Can show late recurrence/metastasis

Gill et al. American Journal of Surgical Pathology 2011
**Succinate dehydrogenase B syndrome (SDHB): Diagnosis**

- Immunohistochemistry
- Mutation analysis

**SDH deficient RCC**

**Immunohistochemistry:**
- Cytokeratins and EMA can be negative or only focally positive
- PAX8 positive (can be focal)
- **Loss of staining for SDH-B**
- C-kit negative

**Succinate dehydrogenase B syndrome (SDHB)**

**Key morphologic features:**
- Intracytoplasmic pale eosinophilic inclusions
- Flocculent vacuolated cytoplasm with wispy eosinophilic material

Gill et al. American Journal of Surgical Pathology 2014
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Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome (HLRCC)

- Autosomal dominant
- Germline mutations in fumarate hydratase (FH) gene
- Cutaneous and uterine leiomyomas (high penetrance)
- Renal cell carcinoma (low penetrance)

HLRCC associated RCC

- Often unilateral and single
- 3rd-4th decade (can present late)
- Often no apparent personal or family history
- Clinically aggressive

- Included as a distinct tumor subtype in the recent ISUP classification of renal tumors

Architecture (not specific): Often mixed pattern

- Papillary
- Tubulo-papillary
- Solid
- Cysts
- Collecting-duct like
- Sieve like/cribriform

HLRCC associated RCC

Characteristic cytology:
- Large nucleus with prominent eosinophilic nucleolus surrounded by perinucleolar halo
- May not be uniformly present throughout tumor

HLRCC associated RCC

- Poor prognosis
- Presentation at high stages
- 7 of 9 patients with distant metastases
- 5 of 9 patients died within 15 months

- Early detection of syndrome??

HLRCC associated uterine smooth muscle tumors

- Present in virtually all women with HLRCC
- Often present in 2nd decade
- Large and symptomatic
- Early surgical intervention
- Can be cellular and/or atypical

- Detection of HLRCC could provide opportunity for renal tumor surveillance
- Morphologic features?

Sanz-Ortega et al, USCAP 2008

HLRCC associated uterine smooth muscle tumors

- Large eosinophilic macronucleoli surrounded by perinucleolar halos

Sanz-Ortega et al, USCAP 2008

Morphologic features of uterine leiomyomas associated with hereditary leiomyomatosis and renal cell carcinoma syndrome: A case report.

Garg, Karuna; Tickoo, Satish; Soslow, Robert; Reuter, Victor

American Journal of Surgical Pathology. 35(8):1235-1237, August 2011. DOI: 10.1097/PAS.0b013e318223ca01

HLRCC associated uterine smooth muscle tumors

- Large eosinophilic nucleoli surrounded by perinucleolar halos
- Eosinophilic cytoplasmic globules
- Hemangiopericytomatosus blood vessels

Reyes C, et al. Mod Pathol 2014
HLRCC associated uterine leiomyoma

HLRCC associated uterine leiomyoma

HLRCC associated uterine leiomyoma

HLRCC associated uterine leiomyoma
HLRCC associated uterine smooth muscle tumors

- 194 uterine smooth muscle tumors from patients ≤40 years
- *Fumarate hydratase* gene aberration detected in 5 cases (2.6%)
- 4 of 5 cases showed morphologic features suspicious for HLRCC
- Immunohistochemistry for 2SC and FH helpful


HLRCC associated cutaneous leiomyomas

- Multiple uterine and cutaneous leiomyomatosis (MCUL) or Reed syndrome
- Multiple, grouped lesions on trunk or limbs, painful
- Morphologic features not well described

HLRCC associated cutaneous leiomyomas

- 22 patients with multiple cutaneous leiomyomas and 25 patients with single cutaneous leiomyomas
- Lack cytologic features seen in renal tumors and uterine leiomyomas
- Majority of multiple leiomyomas showed *FH* gene aberrations
- Good correlation between IHC for 2SC and FH and mutation status

Buelow B, et al. USCAP 2015 abstract
HLRCC: Diagnosis

- FH mutation analysis
- Immunohistochemistry
  1. 2SC (2 succino-cysteine)
  2. FH (fumarate hydratase)

2SC immunohistochemistry:
- Genetic ablation of FH leads to high levels of protein succination
- 2SC serves as a metabolic biomarker for FH deficiency
- 2SC positive in FH deficient renal cysts and known renal tumors with FH mutations
- Negative in normal tissue (n=200) and non-HLRCC tumors (n=1342)


2SC staining in HLRCC associated renal cell carcinoma

9/9 HLRCC associated tumors were 2SC positive
Numerous other tumor types negative (cytoplasmic only staining in rare cases)

5 of 5 cases with \( \text{FH} \) gene mutations were 2SC positive. All 2SC negative cases also negative for \( \text{FH} \) mutations.


**HLRCC: Diagnosis**

**FH immunohistochemistry**
- Complete loss of staining indicative of \( \text{FH} \) gene aberration
- Specific
- Not sensitive (missense mutations lead to retained staining)
- Retained staining does not exclude HLRCC

**Hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC)**

**Key morphologic features:**
- **Kidney tumors:** Prominent eosinophilic nucleoli surrounded by perinucleolar halo
- **Uterine smooth muscle tumors:** Eosinophilic cytoplasmic inclusions, prominent eosinophilic nucleoli surrounded by perinucleolar halo
- **Cutaneous leiomyomas:** Multiple, distinct morphologic features absent
- Consider IHC for 2SC and FH in suspicious cases
Summary

• Some renal tumors are hereditary
• Patient age, clinical history and radiology can be helpful (but often not)
• The presence of some morphologic features can raise the possibility of an underlying syndrome and should be reported (classify tumor as usual and raise the possibility of a syndrome in the comment section)

References


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