Renal cell carcinoma with clear cells: why has it become so complicated?

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RCC with clear cells

• One issue is that we are increasingly classifying RCCs by their molecular phenotype
• Defining them by the underlying driving force of these tumors
• Sometimes, but not always, an immunomorphology correlates with the molecular phenotype
• Impractical to perform tests on all RCCs to look for vHL mutations/ 3p deletions or TCEB1 mutations
Clear cell RCC

• Most common RCC—accounts for 65-70% of all RCCs (with the exception of clear cell papillary RCC, all the remaining RCCs in this talk are relatively rare!)

• For all practical purposes, clear cell RCC defined by presence of biallelic vHL (3p25-26) alterations through mutation/deletion and/or 3p loss
**Normoxia**

- VHL
  - β-domain
  - α-domain
  - PHD
  - 2-OG
  - HIF-α
  - HIF-α degradation

**Hypoxia**

- VHL
  - β-domain
  - α-domain
  - E2
  - Elongin B
  - Elongin C
  - Rbx1
  - HIF-α
  - HIF-α accumulation
  - VEGF
  - GLUT1
  - PDGF

**b**

- Mutant VHL protein
  - β-domain
  - Mutant α-domain
  - VHL complex disrupted

- VEGF
- GLUT1
- PDGF
Clear cell RCC

- CK7- or only focally positive
- CAIX positive (diffuse membranous)
- CD10 positive (diffuse)
- AMACR generally negative, but can be patchy positive
Does it matter?

• RCC generally does not respond to conventional chemotherapy
• In metastatic clear cell RCC, VEGF receptor TKI (sunitinib) (or, in those with poor prognostic factors, mTOR inhibitors)+/- supportive measures (cytoreductive therapy, metastatectomy, bone strengthening agents) first line therapy
• Most clinical trials only studied clear cell RCCs—to get approval for adjuvant therapy (i.e., TKIs), need to have documented clear cell RCC
• Mostly care about clear cell versus non-clear cell RCC (particularly important in metastatic RCCs)
Xp11.2 translocation associated RCC

- Harbor gene fusions involving TFE3 (Xp11)
- Xp11 translocation associated RCC account for 40% of pediatric RCCs, 1.6-4% of adult RCCs (probably absolute number > in adults)
- Age range in adults 22-78
- Young age is still a helpful clue!
Xp11 translocation associated RCC

- Cytokeratin cocktail negative or only very focally positive
- CK7-
- CAIX negative/focal
- CKCKTL, CAIX good screening markers
- FISH assay for TFE3 rearrangement is gold standard
- Can sign out cases as unclassified, with a comment that FISH can be performed if clinically necessary in the future
Does it matter?

• Prognosis in adults similar to clear cell RCC; in children, may have a slightly better prognosis
• Different molecular pathogenesis, so treatments for CC-RCC may or may not apply
• Eligibility for clinical trials
Clear cell papillary RCC

• Only recently described (2006), now included in most recent editions of WHO
• Previously misclassified as clear cell RCC
• First described in patients with ESRD, now known to occur more commonly sporadically
• Fourth most common RCC
• Has a characteristic morphologic appearance and immunohistochemical profile, but no described distinct molecular phenotype (lacks vHL alterations/3p deletions)
Clear cell papillary RCC

• Nearly all clear cell papillary RCC are WHO/ISUP grade 2
• If it has sarcomatoid/rhabdoid, obviously high grade/high stage features/metastases, would not call a clear cell papillary RCC!!
Clear cell papillary RCC

- CK7 diffusely positive (nearly 100% of cells)
- AMACR negative
- CAIX cuplike distribution
- 34betaE12 positive
- CD10 only focally positive
Does it matter?

• Clear cell papillary RCC have never been described to metastasize or recur
• Some consideration to reclassifying as a “tumor of low malignant potential”
• Clear prognostic significance
Tumors with hybrid/borderline features

• Known that clear cell RCC can have areas which resemble clear cell papillary RCC

• If there are any classic areas of clear cell RCC, best to classify as clear cell RCC

• If the immunohistochemistry is not perfect for clear cell papillary RCC (CD10 or AMACR positivity), best to classify as clear cell RCC

• Extensive grade 3 or 4 areas, sarcomatoid areas, high stage—likely clear cell RCC

• In studies of RCC with borderline features, some have a aggressive clinical course—should classify such tumors as clear cell RCC
RCC with clear cells and prominent smooth muscle/mesenchymal stroma

- Have low grade clear cells
- Have a prominent smooth muscle stroma which dissects the tumor into lobules
- CK7 positive
- Lack vHL alterations/3p loss
- Rare, but with the exception of some rare TS cases, are likely have a more indolent course compared to conventional clear cell RCC
RCC with clear cells and prominent smooth muscle/mesenchymal stroma

• TCEb1 mutated RCC
• Tuberous sclerosis associated RCC
• RCC with angioleiomyomatous stroma (smooth muscle stroma, leiomyomatous stroma)
RCC with clear cells and prominent smooth muscle/mesenchymal stroma

- All have a similar morphology
  - Prominent smooth muscle stroma which imparts a lobulated appearance to the tumor at low power
  - Smooth muscle can extend beyond the tumor borders to entrap the adjacent extratumoral fat
  - Smooth muscle stroma desmin + and is likely reactive
  - Typically tubular architecture, can be papillary/pseudopapillary
  - Generally lacks a well developed racemose vascular pattern
  - Vessels can envelop individual scattered glands, imparting a myoepithelial or basal layer look to the glands
  - Lacks well developed apical linear arrangement of nuclei
RCC with clear cells and prominent smooth muscle/mesenchymal stroma

• All have a similar immunohistochemistry:
  • CK7 +, typically diffuse (can be patchy in some cases of TCEB1 mutated RCC)
  • CAIX positive (variably cup like or box like)
  • CD10+
TCEb1 mutated RCC

• Not discovered through morphology, but through large scale whole genome and whole exome sequencing of clear cell RCC

• Lack vHL mutations/3p loss, but instead exhibit mutations at TCEb1 (8q21.11) and LOH on chromosome 8q, affecting the binding site of vHL (elongin C)

• Very rare
Tuberous sclerosis

• 1 in 6000 to 1 in 10000 worldwide
• Autosomal dominant
• Mutation in either TSC1 (Chromosome 9q34), encoding the protein hamartin, or in TSC2 (chromosome 16p13), encoding the protein tuberin
• Act together as tumor suppressors and are components of the mTOR (mammalian target of rapamycin) signaling pathway
Tuberous sclerosis

• Usually affecting CNS resulting in combination of symptoms, i.e. seizures, developmental delay, behavioral problems

• Tumors or tumor like lesions including
  • Cortical tubers, subependymomas, giant cell astrocytomas of brain
  • Retinal hamartomas
  • Cardiac rhabdomyomas
  • Clear cell “sugar” tumors or lung, pancreas, uterus
  • Lymphangioleiomyomatosis of lung
  • AMLs and PEComas
  • RCC
Tuberous sclerosis

• Risk of RCC is relatively low (2-3%), but higher than the general population
• Age of presentation with RCC varied (7-76, mean 42), slightly younger than sporadic RCC
• RCC very uncommonly first presentation of TS
Tuberous sclerosis associated RCC

- Three distinct morphologies:
  - RCC with clear cells and prominent smooth muscle stroma
  - Chromophobe RCC-like (or chromophobe RCC)
  - Granular eosinophilic and macrocystic (eosinophilic solid and cystic?)

- Commonly multifocal (50%, synchronous and metachronous)
- AMLs
RCC with angioleiomyoma-like (smooth muscle or leiomyomatous stroma)

- Similar morphology, but doesn’t have either TCEb1 mutations and isn’t associated with TS
- Controversial entity
  - Are you obligated to get molecular tests to rule out a vHL alteration or TCEb1 mutation to make this diagnosis?
  - Is this just a variant of clear cell papillary RCC?
• What to do in a real, life case where it has this morphology but it’s impractical to do molecular testing?
DX: Low grade renal cell carcinoma with clear cells and prominent fibromuscular stroma. See comment

Comment: This tumor has features of renal cell carcinoma with (angio)leiomyomatous stroma. This tumor subtype is currently included in the WHO list of emerging/provisional renal cell carcinomas, but was historically categorized as clear cell renal cell carcinoma or clear cell papillary renal cell carcinoma. Renal cell carcinomas with (angio)leiomyomatous stroma can occur sporadically or in association with tuberous sclerosis. Recently, hotspot mutations in TCEB1 (a gene that contributes to the VHL complex to ubiquitinate hypoxia-inducible factor) have been reported in tumors with similar features (Hakimi et al. Mod Pathol 2015;28:845-53). Although limited follow-up is available, renal cell carcinoma with (angio)leiomyomatous stroma may be associated with a more indolent outcome compared with conventional clear cell renal cell carcinoma.
Conclusions

• Classic trabecular look with a well developed racemose vascular pattern pretty specific for clear cell RCC
• Clear cell RCCs and Xp11 translocation RCC have morphologic overlap, but immunohistochemistry can help distinguish between them
• Clear cell RCC and clear cell papillary RCC are distinct entities and can be distinguished by morphology and immunohistochemistry
• Should be perfect morphologically and immunohistochemically for clear cell papillary RCC to make that diagnosis (borderline or high grade/high stage cases should be favored to be clear cell RCC)
• RCC with smooth muscle stroma are enriched for TCEb1 mutated RCC, TS, but some don’t harbor TCEb1 or have TS; it is controversial whether those without TCEb1 mutations or TS are a distinct entity or a variant of clear cell papillary RCC
Questions?

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