Renal Tumors with Granular Cytoplasm: Clues to Accurate Diagnosis

Current Issues in Surgical Pathology
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Lesions that can have Granular Cytoplasm

- Renal Oncocytoma
- Chromophobe RCC
- “Hybrid” tumors of Birt-Hogg-Dube’ Syndrome
- Clear Cell RCC
- Angiomyolipoma (epithelioid type)
  - Translocation RCC family (Alveolar Soft Part Sarcoma)
- Carcinoid / Neuroendocrine Tumors / Paraganglioma

- Papillary RCC (Hereditary Leiomyomatosis Syndrome)
- Acquired Cystic Disease RCC
- RCCs status post Neuroblastoma
- Juxtaglomerular cell tumor
- Urothelial cell carcinoma, Collecting Duct carcinoma
- Malakoplakia / Xanthogranulomatous Pyelonephritis
- Adrenal rests and Adrenal tumors
- Stromal Tumors, Melanoma

Granular Renal Cell carcinoma: A Diagnostic Entity?

Granular Variants of other Recognized Diagnostic Entities
(Clinical behavior, Cytogenetics, Morphology, etc.)

Renal Tumor Incidence (General)

- clear cell 68%
- papillary 15%
- chromophobe 5%
- Oncocytoma 6%
- Others 1%
- Unclassified 4%
- collecting duct 1%
- Others
Renal Tumor Incidence (T < 1cm)


Motivation:
- Smaller tumors more likely benign
  - Incidence up with increased “screening” imaging
  - Ablation therapies where diagnostic tissue is severely limited
- Some tumor types have characteristic cytogenetic profiles
  - Can help with diagnosis (Molecular characterizations)
  - Relationship to certain familial (genetic) syndromes
  - Targeted therapy development (Anti-angiogenics)

Renal Oncocytoma:
- Benign
- Gross (characteristic): Cortex, Mahogany brown, central scar (bigger tumors?), circumscribed, no necrosis
- Microscopic architecture: Nests, sheets of nests, syncytial growth in myxoid / hyaline stroma (maybe fine vascular meshwork at periphery), rarely encapsulated (~10%)
- Cytology: Oncocytic cells with small round central nuclei, small nucleolus
- Karyotype: inconsistent -Y, -1
- IHC +: CD117, Vim, E-Cadherin, PAX-2,8, S-100A
- IHC -: CK7, RCC, CA IX, AMACR
Renal Oncocytoma:

• Features causing “imagined” concern:
  - Infiltration / entrapment of adjacent kidney (no capsule!)
  - Infiltrating adipose tissue (~ 15%).
  - Vessel invasion (~ 2–3%)
  - Hypercellularity (focal oncocytsis)
  - Enlarged irregular nuclei (degenerative atypia)
  - Wrinkled nuclei and binucleates (chromohobe)
  - Cyst formation
  - Hale’s colloidal iron positive (common in stroma, not uniform)
  - Perinuclear halos (rare)

• Features that are of definite concern
  (WORRY a lot; to the point of maybe changing your Dx!)
  - Areas of Sacromatoid / high grade / or recognizable RCC types
  - Prominent necrosis (scant necrosis can be OK)
  - Atypical mitoses ( ? Frequent mitoses ?)
  - Macronucleoli ( ? How big is too big? )
Chromophobe RCC:

- Malignant (Low grade)
- Gross: Cortex, tan to mahogany, central scar (~10%), circumscribed, encapsulated
- Microscopic architecture: Broad sheets to nests in fine vascular meshwork (vascular), encapsulated
- Cytology: Variably granular cytoplasm (clear cells at periphery, more eosinophilic towards center), THICK cell membranes, wrinkled central nuclei with binucleates and perinuclear clearing, Hale’s colloidal Fe diffusely +
- Karyotype: Inconsistent losses 1,2,6,10,12-15,17,Y
- EM: Microvesicles (gives perinuclear clearing)
- IHC + : CD117, CK7, PAX-8, EMA, E-Cadherin
- IHC - : Vimentin, RCC, Pax-2, CA IX, AMACR

Chromophobe RCC:

- Features causing confusion:
  - Heavily eosinophilic cytoplasm (~30% of cases)
  - Smaller cells with rounded nuclei and perinuclear clearing not consistent
  - Round nuclei with nucleoli
  - Unimpressive cell borders (not completely gone)
  - No capsule (~30%)
  - Multi-lobular, multifocal (~10%, ? Worse?)
  - Hyaline / myxoid stroma (focal, ~10% (central scar))
  - Nuclei wrinkled, ? How to grade ? (Sarcomatoid areas vs. none)

- Features that are of definite concern
  - Sarcomatoid areas (Grade 4 chromophobe vs. other)
  - No perinuclear clearing or clear cells throughout

CD 117
“Hybrid” Oncocytic tumors:

- Oncocytoma, but some “Chromophobe” features
  Dx: Oncocytic Neoplasm of uncertain malignant potential
- Chromophobe, but some “Oncocytoma” features
  Dx: Chromophobe RCC
"Hybrid" Oncocytic tumors:

- Oncocytoma, but some "Chromophobe" features
  Dx: Oncocytic Neoplasm of uncertain malignant potential
- Chromophobe, but some "Oncocytoma" features
  Dx: Chromophobe RCC

- ? Is there a diagnostic entity lurking?
  - Poorly defined, small numbers, outcome lacking
**“Hybrid” Oncocytic tumors:**

- **Oncocytoma**, but some “Chromophobe” features  
  *Dx:* Oncocytic Neoplasm of uncertain malignant potential

- **Chromophobe**, but some “Oncocytoma” features  
  *Dx:* Chromophobe RCC

- **? Is there a diagnostic entity lurking?**  
  - Poorly defined, small numbers, outcome lacking

- **Oncocytoma cells mixed with Chromophobe cells**  
  - True Hybrid Tumor  
  - Birt-Hogg-Dube’ Syndrome Tumor (NO METS YET)

- **Needle Cores:** Oncocytic Neoplasm (comment on possibilities)

**Clear cell RCC (Conventional, hypernephroma):**

- **Malignant** (very unpredictable)

- **Gross:** Variable, irregular lobules, yellow, orange, white, BLOODY, soft, necrosis, cystic, Vascular invasion

- **Architecture:** Variable, nests, sheets, tubular, alveolar, multilobulated, variably encapsulated, pushing borders, with fine vascular meshwork.

- **Cytology:** Clear cytoplasm to variably granular, cell membranes, central nucleus, variable nuclear features

- **Cytogenetics:** -3p (VHL)

- ** Syndromes:** VHL (retinal angiomas, cerebellar hemangioblastoma, pheochromocytoma), others

- **IHC +:** Vim, EMA, CD10, RCC, PAX-2,8, CA IX, S-100alpha

- **IHC -:** CD117, CK7, E-Cadherin

**BHD Syndrome:**

- **Autosomal Dominant:** LOF Mutations in Folliculin Gene (tumor suppressor gene at 17p11.2)

- **Skin fibrofolliculomas, Spontaneous Pneumothorax**

- **Kidney tumors in ~ 30% of affecteds**

- **50% Hybrid tumors, 35% Chromophobe, 10% clear cell RCC, 5% oncocytoma**

Clear cell RCC:

- Features causing confusion (sampling):
  - Eosinophilic cytoplasm throughout
    - Prognostic (yes, but not independent of grade)
    - DDx is grade dependent
  - Alveolar pattern throughout (translocation tumor ASPS-like)
  - Thick cell membranes (chromophobe)
  - Infiltrative growth (think urothelial, collecting duct, mets.)
  - Extremely uniform cells (neuroendocrine tumors)
  - Rhabdoid type cells (epithelioid AML)

- Features of great concern (think something else):
  - Papillary architecture (translocation tumors, papillary RCC, clear cell and papillary RCC)
  - No fine vascular meshwork (xanthogranuloma, malakoplakia)
  - Eosinophilic tumor with prominent perivascular cellularity (AML).
  - Spindled / sarcomatoid throughout (RCC unclassified).

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clear RCC</th>
<th>Chromo RCC</th>
<th>Oncocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor contour</td>
<td>variable</td>
<td>Usu spherical</td>
<td>Usu spherical</td>
</tr>
<tr>
<td>Tumor color</td>
<td>variable</td>
<td>Tan to mahogany</td>
<td>Mahogany brown</td>
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<td>Gross scarring</td>
<td>variable</td>
<td>Central scar ~ 10%</td>
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<tr>
<td>Hemorrhage</td>
<td>Common</td>
<td>Possible</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cystic change</td>
<td>Not uncommon</td>
<td>uncommon</td>
<td>Uncommon (rare)</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Usually clear</td>
<td>Can be granular</td>
<td>Usually granular</td>
</tr>
<tr>
<td>Cell membranes</td>
<td>Variable</td>
<td>Thick, “Plant-like”</td>
<td>Usually inconspicuous</td>
</tr>
<tr>
<td>Nuclei</td>
<td>Variable</td>
<td>Wrinkled, binucleates</td>
<td>Uniform, round, mononucleate</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>Variable (grading)</td>
<td>Uncommon (grading)</td>
<td>Prominent, single, small, central</td>
</tr>
<tr>
<td>Perinuc. clearing</td>
<td>Absent</td>
<td>Prominent</td>
<td>Rare (focal)</td>
</tr>
<tr>
<td>Stroma</td>
<td>Vasc., fibrous</td>
<td>vascular</td>
<td>Myxoid, few vessels</td>
</tr>
<tr>
<td>Hale’s colloidal Fe</td>
<td>Negative</td>
<td>Positive diffuse</td>
<td>Peripheral, stromal</td>
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<tr>
<td>Invasion</td>
<td>Yes</td>
<td>Yes</td>
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</tr>
<tr>
<td>Fibrous capsule</td>
<td>Variable</td>
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IHC Ab

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<tr>
<td>CKIT (CD117)</td>
<td>Negative</td>
<td>Positive</td>
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</tr>
<tr>
<td>Mitochondrial</td>
<td>Variable</td>
<td>Variable</td>
<td>Positive</td>
</tr>
<tr>
<td>S-100A1</td>
<td>Variable</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>CK7</td>
<td>Negative</td>
<td>Positive</td>
<td>negative</td>
</tr>
<tr>
<td>Cadherins (E, KS)</td>
<td>Variable</td>
<td>Positive</td>
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</tr>
<tr>
<td>RCC</td>
<td>Positive</td>
<td>Negative</td>
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<tr>
<td>PAX2, PAX8</td>
<td>Positive</td>
<td>Variable</td>
<td>Positive</td>
</tr>
<tr>
<td>CA IX</td>
<td>Positive</td>
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- Associated (possible) cytogenetic

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<tr>
<th>3p- (VHL LOF)</th>
<th>Losses (1,2,6,10,13, 17,Y)</th>
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- Syndromes

| VHL, many others | BHD (hybrid tumor) | BHD (hybrid) |

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Immunohistochemistry:

- Extremely Heterogeneous staining patterns
  - Ischemic areas stain differently
  - Cyst fluids and blood can affect reactions
  - Heterogeneous or biphasic tumors?
  - Significance?

- Studies performed on clear-cut examples
- Antibody may not be 100% specific
  - Mitochondrial Ag likely positive in any granular tumor.
Summarize:

- Classic features - > Easy to tell apart
- Rare “hybrid” tumors do exist
  - Uncertain malignant potential or unclassified
- Always think Clear Cell RCC first
  - Poorer outcome and survival
  - Sampling, sampling, sampling
- Extra care on needle cores
  - Clear cell & chromophobe can have oncocyes
- Syndromes associated with these tumors
  - Molecular characterization

AML (epithelioid):

- Malignant (? Subset ?)
- Eosinophilic epithelioid and spindled cells
- Perivascular hypercellularity (benign?)
- Mimicker of Clear cell RCC and Melanoma
- Tuberous sclerosis association (TSC1), ~ 30%
  - Recently reported Translocation tumor association (non-renal tumors only & without TSC; ~ 25%)
- Risky features: TSC association, multifocal, necrosis, T > 7cm, stage > pT2, “carcinoma-like growth”
- IHC + : HMB-45, melan-A, SM Actins
- IHC - : Keratins, EMA, S-100 (weak focal at best)
Carcinoid / Neuroendocrine:
- RARE (21 cases is largest series)
- Seem locally aggressive & low grade malignant

- Typical neuroendocrine growth patterns:
  Nested/organoid with fine vascular meshwork (sometimes fibrohyaline stroma), uniform nuclei (either round or columnar), granular chromatin (salt and pepper)

- IHC +: Synaptophysin, Chromogranin, Cam 5.2, Vimentin
- IHC -: RCC, PAX2, PAX8, CA IX, CK7 (rare pos.), CK20


Translocation tumors (pediatric PRCC):
- ~ ½ of child RCCs (? 1-4% of adult tumors?)
- Gross: similar to clear cell RCC
- Microscopic: Mixed clear and Papillary areas
  - t(X)(p11.2), TFE3 gene locus (TFE3 IHC +)
    - t(X,1)(p11.2,q21) PRCC
    - t(X,17) ASPL (alveolar soft part sarcoma)
    - Other rare ones t(6;11)
  - IHC +: RCC, CD10, Pax 2,8, TFE3 (TFEB), HMB45, melan-A, cathepsin-K
  - IHC -: CKs, EMA, Vim (all weak)

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