Renal Tumors with Eosinophilic Cytoplasm: A Contemporary Approach to a Challenging Differential Diagnosis

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The modern classification of renal cell carcinoma (RCC) was firmly established in 1996 when two separate consensus groups met to propose an updated system. The eradication of the granular RCC subtype, which was endorsed by both groups, was a critical step in the evolution of our knowledge into eosinophilic renal neoplasms and has allowed the identification of additional distinct subtypes. With an expanding list of eosinophilic renal tumors and the ongoing refinement of targeted therapies potentially based on RCC subtype, distinction of these entities has become more challenging at a time of increasing clinical relevance. Below, the spectrum of eosinophilic renal neoplasms is discussed with emphasis on diagnostic criteria, potential adjunctive studies, and differential diagnostic considerations.

General Classification Comments

Morphology

For most subtypes, H&E morphology still allows a definitive diagnosis in the majority of cases. Morphology is also a powerful screening tool to decide which specific adjunctive studies should be sought for a given case (e.g. evaluation of Xp11/TFE3 translocation or hereditary leiomyomatosis RCC).

Immunohistochemistry

The number of immunohistochemical stains of reported utility in the differential diagnosis of eosinophilic renal tumors is seemingly endless. The more widely used stains are discussed below. These stains have been studied mostly in classic examples of each subtype, and may be useful in carefully chosen diagnostic scenarios (such as angiomyolipoma versus RCC). The prognostic prediction or prediction of therapeutic response based solely on immunoprofile in an otherwise unclassifiable eosinophilic RCC has not been fully addressed (with the exception of TFE3).

Other adjunctive testing modalities

FISH probes have been utilized to demonstrate the characteristic genetic abnormalities of several of the RCC subtypes. This technique may become more commonly used in clinical practice as more subtype specific therapy protocols emerge. PCR testing for translocation status may also be applied in suspicious cases. Gene expression array studies have also been applied to renal tumors, and they do show distinctive expression patterns for different subtypes. This is not generally applied in a clinical setting, but has led to the discovery of many novel markers.
Therapy by Subtype

Since different RCC subtypes have unique genetic changes, they have different responses to therapy. In the past, many adjunctive therapies were based on clear cell versus non-clear cell histology. There are now many active trials examining subtype specific therapies, and it is likely that additional treatment algorithms based on RCC subtype will soon be commonplace.

Chromophobe RCC

Chromophobe RCC is the prototypical RCC characterized by abundant pink cytoplasm. It has two distinct morphologic patterns that may be pure or intermixed: the classic (“plant cell”) type, which has a more clear appearance, and the eosinophilic type. Although the combination of nested growth and abundant granular eosinophilic cytoplasm may closely mimic oncocytoma, irregular wrinkled nuclear contours reminiscent of koilocytes, prominent binucleation, and perinuclear halos are distinctive features of chromophobe RCC. In the eosinophilic type, these nuclear features and the perinuclear clearing may be present more focally. In fact, morphologic heterogeneity is not uncommon and some foci in chromophobe RCC have features practically indistinguishable from oncocytoma. Other rare morphologic patterns include: foci with bizarre nuclear atypia, a pseudoglandular “adenoid” pattern, and small papillae or tufting. Electron microscopy of chromophobe RCC shows cytoplasmic microvesicles, often in a perinuclear location, that are not seen in other renal neoplasms. By immunohistochemistry, these tumors commonly express CK7 (more patchy in eosinophilic), CD117, Ksp-cadherin, claudin7, and EpCAM. CD10 is typically negative. Hale’s colloidal iron stains characteristically show diffuse, granular, or reticular cytoplasmic staining, but the difficulty in performing this stain with consistency makes its utility questionable. When multiple chromophobe RCC, oncocytomas, or hybrid chromophobe-oncocytoma tumors are present, the possibility of the Birt-Hogg-Dube, an autosomal-dominant genodermatosis, syndrome should be considered.

Cytogenetic findings: Multiple chromosomal losses- 1, 2, 6, 10, 13, 17, 21, and Y

Differential diagnosis

**Oncocytoma:** No perinuclear halos, No irregular nuclear membranes with nuclear hyperchromasia; CK 7 and claudin 7 immunoreactivity focal or negative

**Clear cell RCC with eosinophilia:** Generally does not have irregular nuclear membranes with nuclear hyperchromasia reminiscent of koilocytes; Delicate branching fibrovascular septae surround small nests and alveoli; often has typical clear cell histology at least focally; Negative for CK7; Positive for CD10
Oncocytoma

Renal oncocytoma is most commonly comprised of small rounded nests of eosinophilic cells set in an edematous or hyalinized background, but varying sized cysts/tubules may also be seen. The nuclei are round with small nucleoli, but scattered foci with “bizarre” degenerative atypia are not uncommon (up to 30%). In densely hyalinized areas, small nests may contain clear cytoplasm. Perinuclear clearing and irregular nuclear contours are not seen. Additionally, some foci may have neoplastic cells with very little cytoplasm imparting a more cellular round blue cell appearance, a feature referred to as “oncoblastic”. In some cases, oncocytoma may have features that suggest aggressive behavior such as vascular invasion and extrarenal extension. These features do not change the expected benign behavior and should not be used to distinguish oncocytoma from chromophobe RCC. CD117 and Ksp-cadherin immunohistochemistry typically shows diffuse immunoreactivity, while CK7 and claudin 7 are negative or only focally positive.

Cytogenetic findings: No consistent abnormality; Loss of chromosome Y and 1; chromosome 11q13 alterations [some with translocation t(5;11) or t(9;11)]

Differential diagnosis:
- **Chromophobe RCC**: Perinuclear halos and irregular nuclear membranes with nuclear hyperchromasia; typically CK7 and claudin 7 positive
- **RCC, unclassified, with cytoplasmic eosinophilia**: Greater degree of nuclear atypia and mitotic activity than allowed in oncocytoma

Epithelioid Angiomyolipoma/PEComa (AML)

Epithelioid AML may have nested or alveolar pattern and a mixture of epithelioid and spindled cells. The neoplastic cells have variable clear to eosinophilic cytoplasm, which may appear granular. Variable degrees of cytologic atypia and mitotic activity are also seen. The identification of scattered cells with prominent intracytoplasmic lipid or the association of the neoplastic cells with blood vessel walls should prompt consideration of AML. Local lymph node involvement may be seen in some cases. The neoplastic cells of AML often co-express smooth muscle actin and melanocytic markers, but are non-reactive for keratin and S-100 protein.

Cytogenetic findings: Alterations of tuberous sclerosis complex genes (TSC1 and TSC2); reports of TFE3 over-expression in subset of AML/PEComa needs further study

Differential diagnosis:
- **Clear cell RCC**: Immunoreactive for keratins/EMA, but not melanocytic markers and actin; typical vascular patter of clear cell carcinoma
- **RCC, unclassified**: Immunoreactive for keratins/EMA, but not melanocytic markers and actin
- **RCC, Xp11/TFE3 translocation type**: May be negative for keratins; Mixed papillary component common; Psammoma bodies common; Does not show intimate association between neoplastic cells and blood vessels; Reports of TFE3 positive AML (PEComa) warrants further study
- **Metastatic melanoma**: Diffuse S-100 protein immunoreactivity
Clear Cell RCC with Eosinophilic Cytoplasm (Including Rhabdoid)

Clear cell carcinoma commonly has foci with eosinophilic cytoplasm (at least focally in up to 70% in our patient population), and some tumors may be predominantly eosinophilic. In cases with rhabdoid histology, abundant eosinophilic cytoplasm “pushes” the nuclei peripherally creating an appearance mimicking rhabdomyoblasts. The key morphologic feature of an eosinophilic clear cell carcinoma is the delicate fibrovascular septae that separate tumor nests, sometimes with associated lymphocytic inflammation. Eosinophilic clear cell carcinomas are typically higher grade and some examples show a sheet like growth with an unclassifiable histology. In the later setting, identification of a more conventional clear cell carcinoma component is required for diagnosis. Immunophenotypically, clear cell carcinoma expresses CK mix, EMA, CD10, and vimentin. CK7, AMACR, CD117, and Ksp-cadherin are typically negative.

Cytogenetic findings: Mutation in VHL gene or 3p loss (somatic mutation, loss, hypermethylation)

Differential diagnosis:
- **RCC, unclassified**: No areas with the diagnostic vascular pattern of clear cell; no typical cytogenetic abnormality
- **Chromophobe RCC**: Perinuclear halos and irregular nuclear membranes with nuclear hyperchromasia; Express CD117 and Ksp-cadherin
- **RCC, Xp11/TFE3 translocation type**: May be very close morphologic mimic, but often has mixed papillary pattern and admixed psammoma bodies; Adjunctive studies should be sought if diagnosis questioned
- **Epithelioid angiomylipoma**: Express actin and melanocytic markers; May have intracytoplasmic lipid focally or the characteristic association with blood vessels.

Acquired cystic disease RCC

This recently described RCC subtype occurs exclusively in patients with acquired cystic kidney disease, usually secondary to dialysis. They usually present at low stage with a well-circumscribed growth within a cyst or encapsulation, most likely because the patients are on screening protocols for their underlying renal disease. Morphologically, acquired cystic disease RCC may have a mixture of solid, cystic, and papillary patterns, but a sieve-like, cribriform appearance is typical. The neoplastic cells usually have abundant eosinophilic cytoplasm and nucleoli. Intratumoral oxalate crystals are a distinctive feature seen in most examples. Immunohistochemically, these tumors show diffuse reactivity for AMACR with negative or focal staining with CK7.

Cytogenetic findings: Reported chromosomal gains- 1, 2, 3, 6, 7, 16, 10, and Y in few cases studied

Differential diagnosis:
- **Other RCC Subtypes**: Typically not associated with end-stage kidney disease (except clear cell and papillary) and do not generally contain numerous oxalate crystals. Closest mimic is likely collecting duct carcinoma, but that tumor is based in the medulla and is typically diffusely infiltrative.
Xp11/TFE3 RCC

This RCC subtype, which is characterized by a translocation involving Xp11, was first reported in children, adolescents, and young adults and is becoming more widely recognized. With knowledge of the various morphologic patterns and better confirmatory tests to help in the distinction from clear cell and papillary RCC, it is also becoming more recognized in older adults. Morphologically, the TFE3 translocation tumor has a wide spectrum with mixed nested, alveolar, and papillary patterns. The neoplastic cells often have abundant clear to eosinophilic cytoplasm, and numerous psammoma bodies may be admixed. Rarely, spindled cells or multinucleated cells may be seen. Immunophenotypically, the neoplastic cells express only focal cytokeratin, in contrast to other RCC subtypes. Melanocytic markers may be focally positive in some cases. They also show diffuse nuclear immunoreactivity for TFE3. Additional confirmatory tests include break-apart FISH probe for Xp11/TFE3 translocation or other molecular studies. Conventional cytogenetics should be considered at the time of gross evaluation in patients under 40 years of age.

Cytogenetic findings: Translocation involving Xp11 (TFE3)
Differential diagnosis:

Other RCC subtypes: Do not have the translocation and/or TFE3 immunohistochemical over-expression

(t;6;11) RCC

This RCC subtype has significant morphologic overlap with the Xp11/TFE3 RCC, but has a characteristic biphasic pattern with a population of smaller cells present within the center of nests, typically encircling round aggregates of basement membrane. Some Xp11/TFE3 RCCs may have a similar biphasic pattern, but usually without the basement membrane material. These (t;6;11) RCCs are more commonly immunoreactive with melanocytic markers, and also show nuclear over-expression of TFEB.

Cytogenetic findings: Translocation (6;11)
Differential diagnosis:

Other RCC subtypes: Do not have the translocation and/or TFEB immunohistochemical over-expression

Papillary RCC

Papillary RCCs have well-formed papillae with central fibrovascular cores and are often encapsulated. A compact papillary-trabecular, solid, or glomeruloid pattern may also be seen. Psammoma bodies and foamy histiocytes are often present. Prominent eosinophilic cytoplasm has been described in both type I (small cells with scant cytoplasm) and type II (nuclear stratification, higher grade, more cytoplasm) papillary RCC. These tumors often show diffuse immunohistochemical expression for CK7 and AMACR.

Cytogenetic findings: Trisomy 7 and 17; loss of Y; activating mutation of c-MET gene (in familial forms and approximately 10% of sporadic cases)
Differential diagnosis:

Hereditary Leiomyomatosis RCC: Prominent macronucleoli with perinucleolar halos should prompt consideration and further molecular testing (see below)

RCC, Xp11/TFE3 translocation type: Lack the diffuse cytokeratin expression typical of papillary RCC; TFE3 over-expression; Xp11 translocation

Hereditary Leiomyomatosis RCC

This rare subtype of RCC typically has a prominent papillary pattern, but admixed cystic/tubular, solid, or cribriform patterns may also be seen. The individual cells have abundant eosinophilic cytoplasm, but the presence of prominent macronucleoli with perinucleolar halos is the most helpful diagnostic feature. Associated leiomyomas in the uterus, dermis, or other sites are usually present.

Cytogenetic findings: Germline mutation of the Krebs cycle enzyme, fumarate hydratase (FH)

Differential diagnosis:

Papillary RCC: Does not have the FH mutation

Collecting duct carcinoma

These high grade adenocarcinomas are based in the medulla and typically show diffuse destructive permeation of the renal parenchyma, often with stromal desmoplasia, nuclear pleomorphism, and brisk mitotic activity. They have a variety of architectural patterns including tubular, solid, papillary, and cribriform. A brisk inflammatory infiltrate rich in neutrophils may be present. In addition, adjacent renal collecting ducts may show dysplastic changes. Medullary carcinoma, which occurs in younger patients with sickle cell trait, is similar and may be a variant of collecting duct carcinoma.

Cytogenetic findings: Few cases tested- Monosomy 1, 6, 14, 15, 22; LOH at 1q, 6p, 8p, 13q, 21q; chromosome 3 losses (clear cell RCC) and 7/17 trisomy (papillary RCC) should be absent

Differential diagnosis:

Metastatic adenocarcinoma: Must be excluded clinically/radiographically

Invasive urothelial carcinoma (with glandular differentiation): Associated urothelial carcinoma in situ or papillary urothelial carcinoma within the renal pelvis is most specific; may have squamous differentiation

RCC, unclassified: May be difficult distinction in some cases

Papillary RCC: Usually encapsulated/well-circumscribed; Often has associated foamy histiocytes within papillary cores; Typically show diffuse cytoplasmic expression with AMACR (usually negative in collecting duct carcinoma)

RCC post NB (and other related tumors)

These post-neuroblastoma associated tumors have occurred in patients both with and without prior chemotherapy. They are characterized by solid and papillary architecture with abundant eosinophilic cytoplasm, very similar to MITF/TFE3 translocation
carcinomas. Similar tumors have been reported after therapy for neoplasms other than neuroblastoma.

Cytogenetic findings: Aneuploid; may have 14q31 and 20q13 abnormalities
Differential diagnosis:
RCC, Xp11/TFE3 translocation type: Confirmation of translocation; rare Xp11 RCCs are reported in patients with history of neuroblastoma

RCC Unclassified (with oncocytic features)

These heterologous RCCs, by definition, do not have morphologic features that allow classification into another subtype. Cytogenetic findings: No recurring abnormality (variety of poorly differentiated subtypes)

REFERENCES


