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## Diagnostic Approach to Eosinophilic Renal Neoplasms

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### Abstract

**Context**—Eosinophilic renal neoplasms include a spectrum of solid and papillary tumors ranging from indolent benign oncocytoma to highly aggressive malignancies. Recognition of the correct nature of the tumor, especially in biopsy specimens, is paramount for patient management.

**Objective**—To review the diagnostic approach to eosinophilic renal neoplasms with light microscopy and ancillary techniques.

**Data Sources**—Review of the published literature and personal experience.

**Conclusions**—The following tumors are in the differential diagnosis of oncocytic renal cell neoplasm: oncocytoma, chromophobe renal cell carcinoma (RCC), hybrid tumor, tubulocystic carcinoma, papillary RCC, clear cell RCC with predominant eosinophilic cell morphology, follicular thyroid-like RCC, hereditary leiomyomatosis–associated RCC, acquired cystic disease–associated RCC, rhabdoid RCC, microphthalmia transcription factor translocation RCC, epithelioid angiomyolipoma, and unclassified RCC. In low-grade nonpapillary eosinophilic neoplasms, distinction between oncocytoma and low-grade RCC mostly rests on histomorphology; however, cytokeratin 7 immunostain may be helpful. In high-grade nonpapillary lesions, there is more of a role for ancillary techniques, including immunohistochemistry for cytokeratin 7, CA9, CD10, racemase, HMB45, and Melan-A. In papillary eosinophilic neoplasms, it is important to distinguish sporadic type 2 papillary RCC from microphthalmia transcription factor translocation and hereditary leiomyomatosis–associated RCC. Histologic and cytologic features along with immunohistochemistry and fluorescence in situ hybridization tests for *TFE3* (Xp11.2) and *TFEB* [t(6;11)] are reliable confirmatory tests. Eosinophilic epithelial neoplasms with architecture, cytology, and/or immunoprofile not qualifying for either of the established types of RCC should be classified as unclassified eosinophilic RCC and arbitrarily assigned a grade (low or high).

Eosinophilic/oncocytic renal cell neoplasms constitute a major proportion of renal tumors. In low-grade non-papillary neoplasms, the major question is if the tumor meets criteria of oncocytoma, one of the few benign epithelial renal neoplasms. In high-grade tumors, one is expected to come up with an accurate diagnosis for prediction of clinical behavior and

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potential application of correct nonsurgical therapies. Herein we have organized a review describing first oncocytoma and tumors that may be considered in the differential diagnosis, and then high-grade nonpapillary and papillary tumors where a correct diagnosis may need more robust ancillary testing. Although there is extensive literature regarding each tumor type described in this review, we focus on the important morphologic aspects and controversial features prone to be missed or misinterpreted, and describe the ancillary tests recommended for clinical use. The Table summarizes the renal tumors that may display eosinophilic cytoplasm.

## NONPAPILLARY NEOPLASMS

### Oncocytoma

Oncocytoma is a benign epithelial renal neoplasm representing less than 10% of renal tumors.<sup>1</sup> Oncocytomas are usually seen in the sixth to seventh decade of life, with men affected 2 to 3 times more often than women.<sup>2</sup> These tumors are incapable of metastases and, when large, may only pose a risk of intratumoral and retroperitoneal bleeding.<sup>1</sup> The differential diagnosis of oncocytoma versus carcinoma is one of the most common reasons that low-grade nonpapillary oncocytic renal neoplasms are submitted for consultation.

To render the diagnosis of oncocytoma, the tumor needs to meet all diagnostic criteria and should not have features that are considered incompatible with this diagnosis. The classic macroscopic features of oncocytoma are a mahogany brown, well-demarcated lesion with central stellate scar. Presence of the stellate scar is one of the radiologic features of oncocytoma as well.<sup>3</sup> However, a central scar is seen in only roughly 30% of the cases<sup>4</sup> and consequently its absence does not impact the diagnosis. Moreover, the presence of the central scar is not specific, as it may be seen in other low-grade renal tumors.

One of the most important criteria for the diagnosis of oncocytoma is that at low-power magnification tumors are composed of small solid nests of cells within a myxoid or hyalinized stroma (Figure 1, A). Tubular or macrocystic structures with hemorrhage are seen in more than 70% of the cases (Figure 1, B).<sup>1</sup> Extrarenal extension with fat involvement may be seen in 11% to 20% of cases and should not be considered a sign of malignancy.<sup>1,2,4</sup> Even vascular invasion, including larger veins, may be seen in a minor subset of oncocytomas.<sup>1</sup> Because of the likelihood of misinterpretation, cases showing especially the latter feature should be considered for expert consultation.<sup>5</sup> By definition, renal oncocytomas lack significant areas of clear cells, papillary formation, and necrosis. An exception is that occasional simple papillary projections may be seen in dilated tubules. Clear cell changes are seen in up to 15% of cases and usually localized to areas of central scar.<sup>4</sup> Necrosis should not be seen unless related to prior embolization or biopsy. Because oncocytomas can involve perinephric adipose tissue, when signing out resection specimens, it should be explained that this is not a feature of malignancy or increased likelihood of recurrence. Rather, the diagnosis should include the size (even though it is of no prognostic significance) and margin status.

Cytologic features are among the major defining criteria of renal oncocytoma. Cells of oncocytomas usually have voluminous, densely eosinophilic cytoplasm. Background nuclei

are uniform and round, and may have prominent nucleoli, typically lacking binucleated forms (Figure 1, C). The only exception is that some oncocytomas have prominent degenerative-appearing nuclear atypia, which is usually clustered in small foci but less commonly can be more diffuse (Figure 1, D).<sup>6</sup> In contrast to the notched raisinoid nuclei with detailed chromatin in chromophobe carcinoma, the degenerative atypia consists of large, often multinucleated cells with smudgy hyperchromatic nuclei and poorly preserved chromatin detail. Despite the atypia, mitoses are usually absent or very rare. Some cases may have clusters of small cells with scant cytoplasm and hyperchromatic nuclei, termed oncoblasts.<sup>1</sup> These may be a source of diagnostic difficulty, especially in biopsy specimens. However, their admixture with more classical areas of oncocytoma, uniform small nuclei with smooth nuclear border, absence of mitoses and necrosis, and immunoprofile compatible with oncocytoma should assist with the correct identification. The presence of oncoblasts and cells with degenerative nuclear atypia has no clinical significance.

Many ancillary tests have been suggested for confirmation of oncocytoma.<sup>7</sup> However, immunohistochemistry has limited applications in the differential diagnosis of oncocytoma and chromophobe renal cell carcinoma (chRCC). The only stain that may be useful is cytokeratin 7 (CK7), which typically shows isolated scattered cell staining in oncocytoma and diffuse strong staining in chRCC (Figure 1, E). Clear cells localized in the central scar of oncocytoma may be immunoreactive with CK7. However, the pitfall of this immunostain is that, according to some publications, up to 18% of chRCCs are negative for CK7.<sup>8,9</sup> Hales colloidal iron stain in our experience has low reproducibility and is significantly operator dependent, and distinction of patterns of staining is prone to diagnostic errors.<sup>10</sup>

It is controversial whether a definitive diagnosis of oncocytoma can be rendered on needle biopsy. Although some experts make a definitive diagnosis on biopsy, for needle core biopsy specimens that have morphologic and immunophenotypic findings of oncocytoma (Figure 1, F), we interpret them as *oncocytic renal cell neoplasm*. We add the following comment: “If this biopsy is representative of the entire lesion, it would be consistent with an oncocytoma. However, renal cell carcinoma (RCC) and hybrid tumor may uncommonly show focal areas with oncocytic features.” Although in excision specimens with the classic morphology of oncocytoma the use of CK7 may be avoided, in core biopsy specimens CK7 immunostain is more widely accepted to avoid misclassification of low-grade RCC as oncocytoma.<sup>11,12</sup> Frozen sections to assess status of resection margins in partial nephrectomies may show normal proximal tubules with their characteristic abundant eosinophilic cytoplasm, which could be misinterpreted as a low-grade oncocytic neoplasm. The presence of intermixed glomeruli is a reliable sign of benign histology, as none of the low-grade oncocytic renal tumors has an infiltrative growth pattern.

### Chromophobe RCC

Chromophobe RCC is in general a low-grade renal malignancy with the capability to demonstrate aggressive clinical behavior, yet having a more favorable prognosis than clear cell RCC (ccRCC) and papillary RCC (pRCC).<sup>13</sup> Chromophobe RCC affects almost equally men and women and typically develops in the sixth decade of life.<sup>14,15</sup> According to different studies, its incidence varies from 3% to 10% of all RCC.<sup>14,16</sup> Although many of

these tumors qualify as Fuhrman nuclear grade 3, the Fuhrman nuclear grading system does not accurately reflect their prognosis. In general, patients with stage pT1 and pT2 chRCC are almost always cured by surgery, and presentation with pT3 or pT4 disease is rare. Consequently, some urologic pathologists do not recommended assigning Fuhrman nuclear grade to chRCC.<sup>17,18</sup> Other grading systems have been suggested for chRCC, but none of them has found general acceptance amongst practitioners.<sup>19,20</sup>

Microscopically, chRCC usually has a solid growth pattern with thin fibrovascular septa (Figure 2, A). However, foci with less cellularity and a tubulocystic growth pattern may overlap with oncocytoma.<sup>21</sup> Myxoid or hyalinized background is usually not a feature of chRCC. Similar to oncocytoma, recognition of cytologic features typical of chRCC is diagnostic. Chromophobe RCC has abundant cytoplasm with prominent cell borders (“vegetable cells”) and may not have classically described perinuclear halos. However, diagnostic of chRCC is the presence of nuclei with preserved chromatin and irregular, wrinkled nuclear membrane (“raisinoid” nuclei) (Figure 2, B).<sup>6</sup> This atypia is different from the degenerative atypia seen in oncocytoma. Atypical cells in chRCC may be encountered in different proportions but are rather evenly disturbed and do not tend to cluster.

CK7 is the best immunostain to distinguish chRCC from oncocytoma. Although CK7 is usually diffuse in chRCC, it is negative or only focal in oncocytoma. However, it should be recognized that there will be cases demonstrating classic cytologic features of chRCC yet are negative for CK7.<sup>8,9</sup> In such cases, correct diagnosis of chRCC should be made by histomorphology alone. Some authors advocate using c-Kit (CD117) for diagnosis of oncocytoma.<sup>22</sup> Although it is not expressed in most other RCCs,<sup>23</sup> this stain is not specific and is also expressed in almost all chRCCs.<sup>24</sup>

### Hybrid Tumor

This terminology refers to a specific tumor type that combines morphologic and immunohistochemical features of both oncocytoma and chRCC.<sup>25</sup> Other tumors combining more than one pattern of neoplasm should be reported as unclassified. Its true incidence is not well established, which in part may be because of its rarity and subjectivity in its diagnosis. The existence of hybrid tumors is one of the examples precluding a definitive diagnosis of oncocytoma in needle core biopsy samples. Although these tumors may be sporadic, many are seen in patients with Birt-Hogg-Dubé syndrome.<sup>26,27</sup> This syndrome can manifest with multifocal oncocytomas (oncocytosis) and chRCC and should be suggested by a pathologist when more than one lesion is present unilaterally or bilaterally. Fibrofolliculoma is a typical skin finding in patients with Birt-Hogg-Dubé syndrome.<sup>25</sup> The clinical behavior of tumors in these settings is less aggressive than that of sporadic carcinomas, and active surveillance or kidney-sparing resection of the tumors should be considered by the surgeons.<sup>26,28,29</sup>

### Tubulocystic Carcinoma

This is a rare variant of RCC with less than 100 cases reported.<sup>5,30,31</sup> Its incidence is less than 1% of all renal carcinomas.<sup>32</sup> Patients are usually in their sixth decade of life at presentation and demonstrate a striking male predominance (7:1).<sup>30</sup> In older reports,

tubulocystic RCC was proposed to be a low-grade carcinoma of collecting ducts of Bellini.<sup>33</sup> However, subsequently it has been demonstrated that tubulocystic carcinoma and collecting duct carcinoma are distinct entities molecularly.<sup>34</sup> Although the clinical behavior of tubulocystic carcinoma is usually favorable,<sup>30,32</sup> we have seen 3 cases in which poorly differentiated foci were seen in otherwise classical tubulocystic carcinomas, imparting an adverse clinical behavior.<sup>35</sup>

Microscopically, tubulocystic carcinoma is composed of tightly packed tubules and cysts separated by thin fibrovascular septa (Figure 2, C). Papillary RCC architecture is seen in a minority of cases. The epithelial lining is represented by cuboidal or columnar cells with abundant eosinophilic cytoplasm containing large nuclei with prominent nucleoli.<sup>30,32</sup> The latter is one of the major diagnostic pitfalls, as prominent nucleoli are one of the diagnostic features of tubulocystic carcinoma and should not be interpreted as evidence of a high-grade malignancy. Thus, Fuhrman nuclear grade is not assigned to tubulocystic carcinomas, recognizing their more favorable clinical behavior. The tubular pattern can mimic the tubular pattern seen in oncocytoma. The distinction is that typically in oncocytoma, in addition to the tubular pattern, there are other more classic areas with the fibromyxoid stroma. Also, although oncocytomas often have prominent nucleoli, the nuclei are perfectly round, whereas they are irregular in tubulocystic RCC.

Immunohistochemically and cytogenetically, there are overlapping findings with pRCC, both expressing racemase, CK7, CD10, and RCC antigen, and having gain of chromosomes 7 and 17 and loss of Y chromosome.<sup>31,32</sup> However, in view of its distinct morphology and clinical behavior, tubulocystic carcinoma is best treated as a separate clinicopathologic entity.<sup>30,36</sup> Distinguishing tubulocystic RCC and oncocytoma usually rests on morphology and is not aided by immunohistochemical stains.

### **ccRCC With Predominant Eosinophilic Cell Morphology**

Clear cell RCC is the most common type of RCC, representing approximately 70% of the newly diagnosed cases, with peak incidence in the sixth to seventh decade. It affects men more often than women (2:1–3:1).<sup>37</sup> Clear cell RCC has the worst prognosis among the most common types of RCC.<sup>38</sup> Fuhrman nuclear grade was originally validated on ccRCC.<sup>39</sup> Despite the name “clear cell,” a proportion of high-grade tumors acquire eosinophilic morphology, previously named granular cell RCC. However, designation of this tumor as clear cell (conventional) RCC is the current practice because these tumors with eosinophilic cytoplasm demonstrate the same molecular characteristics as those with classic clear cell morphology.<sup>37,40</sup>

Eosinophilic ccRCC grossly often has extensive hemorrhage and necrosis. Microscopically, it usually has a nested pattern of growth. One of the most pathognomonic morphologic features of ccRCC regardless of grade is a rich sinusoidal vasculature surrounding nests of neoplastic cells (Figure 2, D).<sup>37,38,41</sup> This pattern of vasculature is preserved even in metastatic lesions, and it is a useful diagnostic clue in patients with metastatic disease of unknown primary.<sup>42</sup> A wide spectrum of immunohistochemical stains is available to help discriminate this neoplasm from its mimickers. Clear cell RCC is usually positive for CD10 and CA-9 and negative for CK7 and high-molecular-weight keratin.<sup>11,43</sup> Other useful

positive markers are epithelial membrane antigen (EMA), vimentin, and RCC antigen. In contrast to microphthalmia transcription factor translocation RCC, ccRCC diffusely expresses epithelial markers (AE1/AE3 and EMA). Vimentin is positive in ccRCC, whereas it is negative in chRCC. Although having a limited role in differential diagnosis, PAX2 and PAX8 are reliable antibodies to establish renal origin in metastatic lesions. With the recognition of the morphology and immunoprofile, one may diagnose ccRCC even in the absence of clear cells.

### Acquired Cystic Kidney Disease–Associated RCC

This is a recently recognized tumor that, as the name implies, develops only in the setting of acquired cystic disease.<sup>44</sup> According to Tickoo et al,<sup>45</sup> acquired cystic kidney disease (ACKD)–associated RCC is the most common cancer subtype developing in end-stage kidney. It has a more favorable clinical behavior than carcinomas occurring in a sporadic setting.<sup>37,44</sup> However, it is not clear if the tumor is indeed more indolent or simply detected at earlier stages because of regular screening of patients with end-stage kidney.<sup>12</sup>

Microscopically, the tumors are composed of large cells with abundant, deeply eosinophilic cytoplasm and large nuclei with prominent nucleoli (Figure 3, A). Different architectural patterns constituting different proportions of tumor may be observed. Solid and microcystic/macrocytic patterns are the most common. Intracytoplasmic vacuoles are a very common finding, creating a cribriform or sieve-like appearance of the neoplasm. Intratumoral oxalate crystals are consistently seen and are considered to be related to pathogenesis of ACKD-associated RCC.<sup>44,45</sup> Fuhrman grade is not assigned to ACKD-associated RCC. Thorough examination of nephrectomy specimens with ACKD-associated RCC often reveals its precursor lesion—a cyst lined by atypical eosinophilic cells with hobnail appearance and containing intraluminal crystals (Figure 3, B). Papillary formation may be seen in a precursor lesion. Such cysts may be identified in otherwise nonneoplastic explants and should be reported as precursor lesions of ACKD-associated RCC. Although immunostains are rarely needed to diagnose these lesions, it is usually positive for racemase, CD10, and RCC and negative for CK7.

### RCC With Rhabdoid Features

This tumor is not a distinct type of carcinoma, but rather an extreme of dedifferentiation from any type of RCC. There is no specific immunoprofile of rhabdoid differentiation in RCC; rather, it should be identical to the immunoprofile of underlying RCC. The term *rhabdoid* designates a high-grade tumor cell with abundant eosinophilic cytoplasm and peripherally located nuclei, thus resembling rhabdomyoblasts (Figure 3, C).<sup>46,47</sup> These highly aggressive morphologic patterns are more likely to be seen in high-grade tumors<sup>47</sup> and, according to Gökden et al,<sup>48</sup> none of the 84 Fuhrman nuclear grade 1 tumors in their study had such changes.

In pediatric pathology a distinct neoplasm termed *rhabdoid tumor of the kidney* is recognized as a high-grade malignancy composed entirely of rhabdoid cells without true skeletal muscle differentiation.<sup>49,50</sup> Rhabdoid differentiation seen in adult RCC is not related to pediatric rhabdoid tumor. Most rhabdoid tumors of kidney occur early in life (80%



<2 years old; median age, 7–11 months).<sup>37,49,50</sup> In the proper age range, loss of staining for INI-1 antibody is diagnostic of rhabdoid tumor.<sup>51</sup> Expression of INI-1 is typically not lost in rhabdoid differentiation occurring in other defined types of high-grade RCC.

### Follicular Thyroid-like Carcinoma

This is the least-frequent and least-studied variant of RCC. Eleven cases have been found in an unrestricted PubMed search.<sup>52–56</sup> Two of these had metastasis—1 to hilar lymph node<sup>53</sup> and 1 to lung<sup>54</sup>—proving their designation as a carcinoma. The nature of the tumor has no relationship to thyroid carcinoma, and the nomenclature stems purely from their light microscopic appearance.

Morphologically, these carcinomas have thick fibrous capsule and are composed of microfollicular and macro-follicular structures with light pink or dense red colloid-like secretions (Figure 3, D). The folliculi are lined by low cuboidal cells with lightly eosinophilic cytoplasm. Most of the tumors are reported as low Fuhrman nuclear grade. Immunohistochemical experience is limited, but thyroid transcription factor 1, thyroglobulin, RCC, and racemase appear to be negative. Some cases are reported to be immunoreactive with CK7, CD10, and PAX2. In addition to limited immunohistochemical experience, the light microscopy diagnosis may be problematic, as pRCC, clear cell pRCC, and some low-grade unclassified carcinomas may have areas that morphologically overlap with follicular thyroid-like carcinoma.

### Eosinophilic Unclassified RCC

Unclassified RCC represents 1% to 5% of all RCCs.<sup>57–59</sup> The definitions of unclassified RCC include (1) morphologic features that do not fit into any recognized RCC class, (2) combinations of 2 or more morphologic types by light microscopy, and (3) purely sarcomatoid carcinoma.<sup>12,37</sup> Most unclassified RCC are more high-grade undifferentiated tumors and the Fuhrman grade has not been applied to these neoplasms.<sup>58,59</sup> Consequently, if a tumor is diagnosed as unclassified RCC without any qualifiers, the assumption by clinicians is that it is high grade. However, it has been our experience that a subset of tumors that cannot be classified into well-known subtypes lack high cellularity, have minimal pleomorphism, do not exhibit necrosis, and have a low mitotic rate. We have termed these cases *low-grade unclassified RCC*, although there is no formal recognition of this dichotomization of unclassified RCC. In this review we restrict our description to only the less commonly seen low-grade unclassified RCC with cytoplasmic eosinophilia (oncocytoma-like).<sup>12</sup>

Low-grade eosinophilic unclassified RCC may architecturally mimic oncocytoma, but its nested arrangement is usually denser without the myxoid/hyalinized background (Figure 3, E). Cytologically, although these tumors do not have the nuclear features of chRCC (ie, raisinoid nuclei), binucleation and mitotic activity may be seen in excision specimens. In our experience, diffuse CK7 immunoreactivity is a helpful immunostain to rule out a definitive diagnosis of oncocytoma, keeping in mind that positive immunostaining is not equivalent to chRCC and pRCC. There are no prospective or retrospective studies describing these tumors, as this category of tumors represents an amalgamation of various distinct tumor

types. Partial nephrectomy and ablation therapy may be acceptable treatment options for low-grade eosinophilic unclassified RCC.<sup>37</sup>

### Epithelioid Angiomyolipoma

Epithelioid angiomyolipoma (EAML) may be misdiagnosed as unclassified high-grade carcinoma. Epithelioid angiomyolipoma represents approximately 8% of all angiomyolipomas.<sup>60,61</sup> In contrast to triphasic angiomyolipomas, which are seen in the sixth decade of life, the mean age of the patients affected with EAML is 32 to 38 years according to different studies.<sup>60,61</sup> Epithelioid angiomyolipoma is more commonly seen in tuberous sclerosis patients than its triphasic counterpart.<sup>60</sup> Patients with tuberous sclerosis also have significantly larger angiomyolipomas.<sup>61</sup>

Histologically, there is no established cutoff of the percentage of epithelioid morphology required for a tumor to be designated as EAML, which in part could explain the diverse reports on the incidence of EAML in the literature. As such, it may be reasonable to report the percentage of tumor represented by EAML component. Epithelioid angiomyolipoma usually lacks a significant amount of intratumoral fat and malformed vessels. Architecturally, EAML grows in solid sheets or a large alveolar pattern. Cytologically, there may be 2 types of cells in EAML: (1) clear cells with finely granular cytoplasm and small monomorphic nuclei and (2) eosinophilic cells with abundant cytoplasm, epithelioid morphology, and large nuclei with prominent nucleoli, also known as amoeboid cells (Figure 3, F).<sup>12</sup> The latter may demonstrate significant atypia and mitoses, leading to misdiagnosis of sarcoma or carcinoma.<sup>62</sup> There are controversial data regarding clinical behavior of EAML.<sup>60,61,63–65</sup> In our prior study we established criteria predicting clinical behavior of EAML with 78% sensitivity and 100% specificity.<sup>64</sup> The presence of at least 3 of the following characteristics indicated a risk for malignant behavior: (1) at least 70% atypical epithelioid cells, (2) at least 2 mitoses per 10 high-power fields, (3) atypical mitoses, and (4) necrosis. Another group reported criteria for malignancy that partially overlap with ours, adding that extrarenal extension and renal vein involvement are also important prognostic factors.<sup>63</sup> Although the 2 latter publications are based on consultation material and may be skewed towards more aggressive cases, a recent series by He et al<sup>66</sup> analyzed 437 consecutive angiomyolipomas from 3 institutions and found only 20 cases of EAML, defined as showing more than 80% EAML morphology. Only one of these patients developed distant metastasis, and the authors concluded that overall the rate of aggressive behavior among EAMLs is very low. Epithelioid morphology without atypia has no prognostic significance per se. This entity can be confirmed using an immunohistochemical panel of pancytokeratin, EMA, PAX8, Melan-A, and HMB-45, with the latter 2 being immunoreactive in EAML. Diffuse reactivity with epithelial markers and PAX8 distinguishes sarcomatoid and high-grade unclassified RCC from EAML. The only other renal cell neoplasm positive for melanocytic markers, usually nonreactive with pancytokeratin and EMA, and variably reactive with PAX8 (~50%), is TFEB [t(6;11)] microphthalmia transcription factor translocation carcinoma. However, as described below, positive cathepsin K immunostain and specific molecular methods can reliably distinguish the latter.



## PAPILLARY NEOPLASMS

### Papillary RCC

Papillary RCC is the second most common renal cancer after ccRCC and comprises approximately 15% of renal cancers.<sup>67</sup> The highest incidence of pRCC is in the sixth to seventh decade of life, with reported male predominance.<sup>68,69</sup> Two types of pRCC are distinguished: type 1 is composed of linear arrays of small cells with scant amphophilic cytoplasm and low-grade nuclei, and type 2 has abundant eosinophilic cytoplasm with large crowded stratified nuclei with prominent nucleoli (Figure 4, A). A worse clinical behavior is attributed to type 2 pRCC.<sup>70</sup> In addition to cytologic difference, presence of foamy macrophages and intracellular hemosiderin accumulation is uncommon in type 2 pRCC. Cytokeratin 7 immunoreactivity is seen in roughly 20% of type 2 pRCC cases, compared with around 80% in type 1 pRCC.<sup>68</sup> Racemase is another useful marker expressed in pRCC.<sup>11</sup> The oncocytic variant of pRCC is considered in the spectrum of type 2 carcinoma.<sup>28</sup> Type 2 pRCC is usually higher grade (nucleolar grade 3), and this may account for the worse prognosis when compared with pRCC type 1, which is usually low-grade RCC. The identification of papillary architecture is usually not a challenge in most cases.

### Hereditary Leiomyomatosis and RCC

This rare syndrome is characterized by cutaneous leiomyomas and aggressive renal tumors developing in younger individuals (fourth decade of life) than sporadic tumors.<sup>71</sup> Germline mutation in the fumarate hydratase gene is the underlying genetic alteration of hereditary leiomyomatosis and RCC.<sup>72</sup> At time of presentation, lymph node metastases are not uncommon, and more than 50% of patients have advanced locoregional recurrent disease or succumb to renal cancer.<sup>71</sup> Morphologically, by virtue of high-grade cytology, this type of RCC is reminiscent of type 2 pRCC, and some tumors may look akin to collecting-duct carcinoma. The distinctive morphologic feature of hereditary leiomyomatosis and RCC is prominent eosinophilic nucleoli with perinucleolar clearing (Figure 4, B).<sup>71</sup> In isolation, however, these observations do not constitute sufficient ground for definitive diagnosis of hereditary leiomyomatosis and RCC. In our practice we call such tumors type 2 pRCC, assign them Fuhrman nuclear grade 3, and comment on peculiar morphology, highlighting that this may be seen in hereditary leiomyomatosis and RCC. Clinical information and genetic testing are essential for correct diagnosis.

### Microphthalmia Transcription Factor Translocation Carcinoma

Two well-described entities with established diagnostic tools are included in this group: Xp11.2 and t(6;11) translocation RCC. A tendency toward young age at presentation is common to both neoplasms. There are specific immunostains for nuclear proteins produced by both translocations. However, the procedures are demanding and sensitive to preanalytical processing of the specimen, making it sometimes mandatory to use corresponding fluorescence in situ hybridization.

**Xp11.2 Translocation RCC**—*TFE3* transcription factor gene maps to the short arm (p112) of the X chromosome. A number of translocations involving *TFE3* resulting in fusion with other genes have been reported. Overall, although these carcinomas are relatively

uncommon, comprising approximately 1% of adult RCC, they may represent up to 50% of RCC in children.<sup>28,73–76</sup> Although behavior of these carcinomas in children is more favorable even in cases with lymph node metastases, adult disease is often lethal.<sup>77,78</sup> Older age and advanced stage (distant metastases) are unfavorable prognostic factors.<sup>79</sup>

Histologically, the lesion is characterized by papillary architecture lined by clear and eosinophilic cells with abundant psammoma bodies (Figure 4, C). Xp11.2 RCC usually has clear to pale pink fluffy cytoplasm. Xp11.2 RCC often does not express epithelial markers (cytokeratin and EMA), but PAX2 and PAX8 are expressed in more than 50% of cases and useful for metastatic workup.<sup>80</sup> The immunohistochemical marker for diagnosis of Xp11.2 RCC is the antibody against TFE3 protein.<sup>73</sup> TFE3 immunohistochemistry may yield inaccurate results because of fixation issues. TFE3 break-apart fluorescence in situ hybridization may be performed on formalin-fixed, paraffin-embedded tissue and typically is more definitive.<sup>81</sup> In a study by Martignoni et al,<sup>82</sup> cathepsin K immunoreactivity was demonstrated in 60% of Xp11.2 and 100% of t(6;11) carcinomas, and not seen in other types of RCC.

**t(6;11) translocation RCC**—There is limited experience with this renal cancer. Originally, it was considered to be a pediatric neoplasm, but later reports describe it in young adults.<sup>83,84</sup> Most cases behave indolently, but rare tumors have metastasized and killed the patient. Molecularly, t(6;11) carcinoma is less heterogeneous than Xp11.2, and the underlying abnormality is  $\alpha$ -TFEB gene fusion. Microscopically, t(6;11) carcinomas typically have a biphasic pattern (Figure 4, D). The majority of cells are large epithelioid eosinophilic and clear cells occasionally forming papillae. Clusters of small eosinophilic cells with small hyperchromatic nuclei are scattered throughout the tumor and often have rosettelike arrangement with accumulation of basement membrane–like material. TFEB carcinomas are uniformly positive for cathepsin K and melanocytic markers (HMB-45 and Melan-A), and only some may demonstrate focal staining with keratins.<sup>85</sup> Antibodies against TFEB protein labeling nuclei and break-apart fluorescence in situ hybridization probes are available for clinical use.<sup>84,86</sup>

## Summary

We have described common renal neoplasms with eosinophilic cytoplasm. Although many of those tumors have overlapping findings, recognition of key morphologic features and selection of correct ancillary tests (when needed) usually allow for a correct classification.

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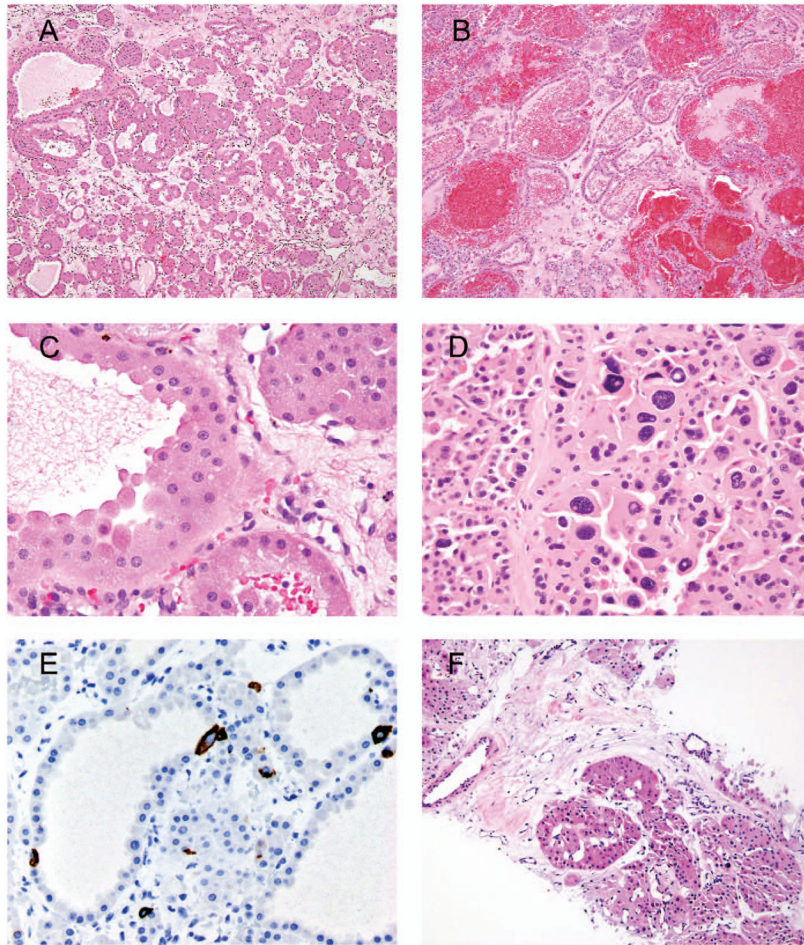
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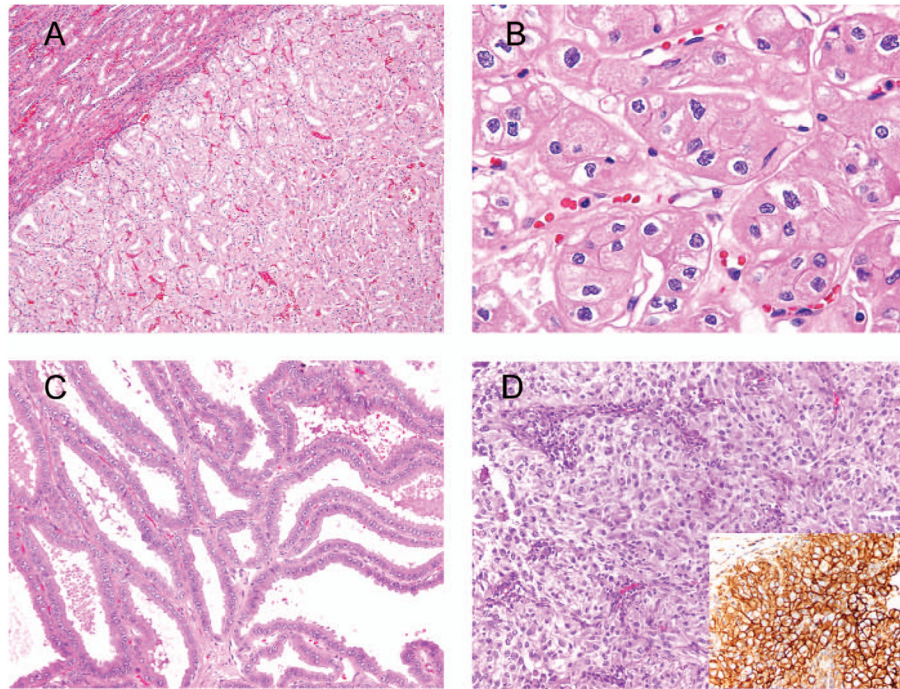


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**Figure 1.**

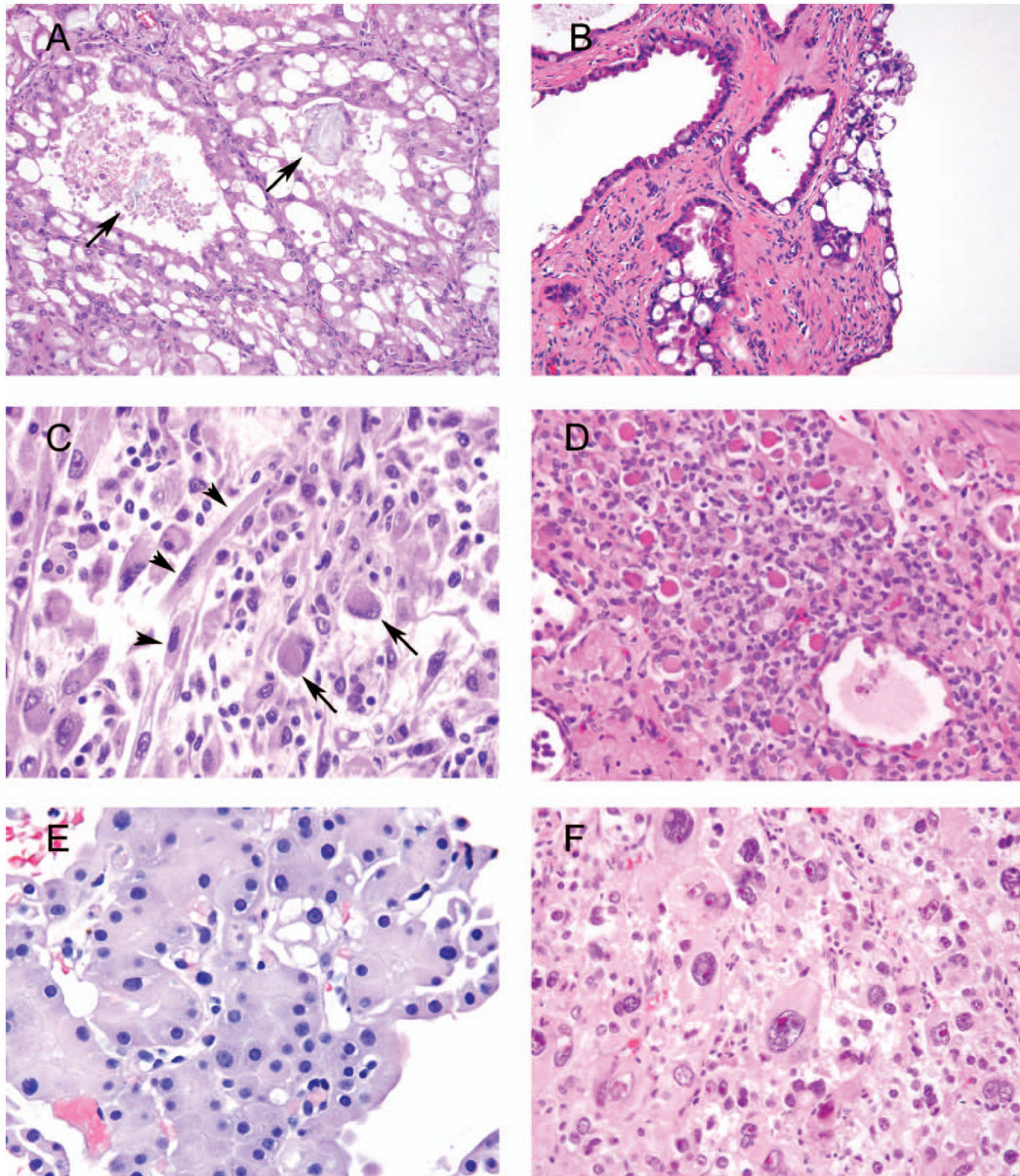
A, Classic appearance of oncocytoma with small solid nests with myxoid or hyalinized background. B, Tubular architecture of oncocytoma with hemorrhage. C, Classic cytology of oncocytoma with abundant eosinophilic cytoplasm; indistinct cell borders; small, uniform nuclei; and prominent nucleoli. D, A cluster of degenerative-type atypia seen in oncocytoma. E, Scattered cyokeratin 7 immunoreactivity in oncocytoma. F, Biopsy of an *oncocytic renal neoplasm* consistent with oncocytoma (hematoxylin-eosin, original magnifications  $\times 100$  [A, B, and F],  $\times 600$  [C], and  $\times 400$  [D]; original magnification  $\times 400$  [E]).



**Figure 2.**

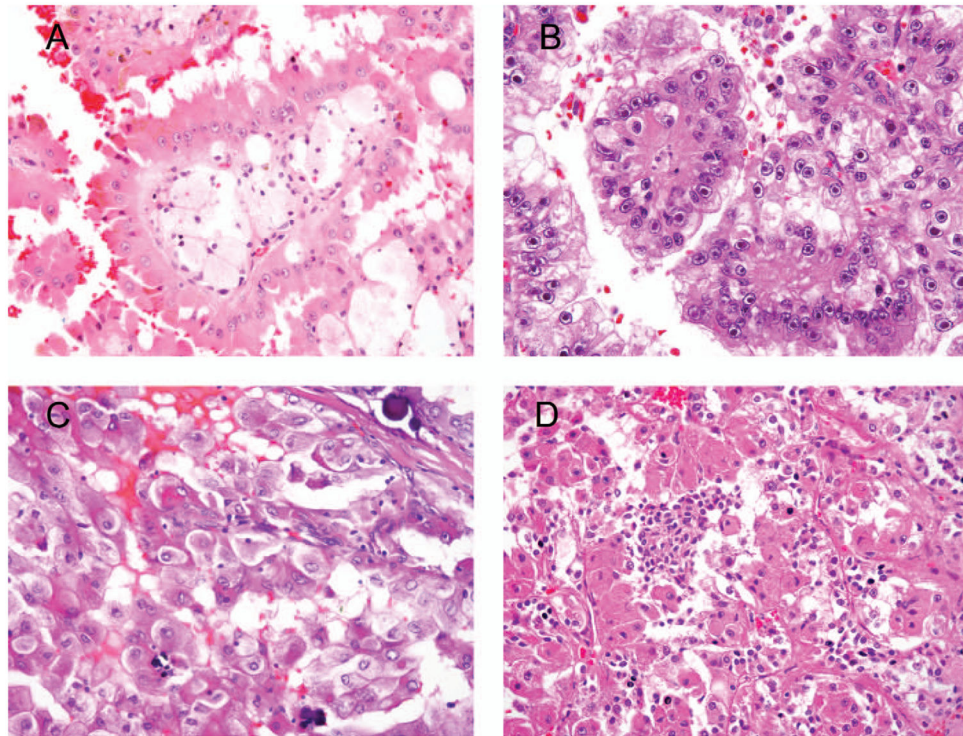
A, Chromophobe renal cell carcinoma (RCC) with dense microtubular architecture. B, Enlarged pleomorphic nuclei with preserved chromatin and irregular, wrinkled nuclear membrane (“raisinoid” nuclei) diagnostic of chromophobe RCC. C, Tubulocystic carcinoma composed of tightly packed tubules and cysts. Prominent nucleoli are noted. D, Eosinophilic clear cell RCC with rich sinusoidal-like vasculature. Inset demonstrates CA-9 immunostain (hematoxylin-eosin, original magnifications  $\times 100$  [A],  $\times 600$  [B], and  $\times 200$  [C and D]; original magnification  $\times 400$  [D inset]).





**Figure 3.**

A, Acquired cystic kidney disease (ACKD)–associated renal cell carcinoma (RCC) with intratumoral oxalate crystals (arrows). B, Atypical cysts in end-stage kidney disease with lining the same as ACKD-associated RCC, yet not forming solid mass. C, High-grade clear cell RCC (not shown) with rhabdoid (long arrows) and sarcomatoid (short arrows) differentiation. D, Microfollicular and macrofollicular architecture of follicular thyroid-like carcinoma with dense red and light pink secretions, correspondingly. E, Although cytologically this low-grade unclassified renal cell neoplasm is suggestive of oncocytoma, its dense growth pattern is not seen in the latter. F, Epithelioid angiomyolipoma composed of large bizarre cells with eosinophilic cytoplasm and smaller cells with pale cytoplasm and uniform small nucleoli (hematoxylin-eosin, original magnifications  $\times 200$  [A, B, and D],  $\times 600$  [C and E], and  $\times 400$  [F]).



**Figure 4.**

A, Type 2 papillary renal cell carcinoma (RCC) with tall cell with eosinophilic cytoplasm, prominent nucleoli, intracytoplasmic pigment, and foamy macrophages (the latter 2 features are not common for type 2 papillary RCC). B, Hereditary leiomyomatosis-associated RCC composed of clear and eosinophilic cells. Large prominent nucleoli and perinucleolar halos are distinctive features. C, Xp11.2 (TFE3) translocation carcinoma with multiple psammoma bodies. D, Biphasic t(6;11) (TFEB) translocation carcinoma composed of large cells forming papillae and small cells clustered in between (hematoxylin-eosin, original magnifications  $\times 400$  [A, C, and D] and  $\times 600$  [B]).

**Table**

<b>Renal Tumors With Eosinophilic Cytoplasm</b>
Oncocytoma
Chromophobe RCC
Hybrid tumor
Tubulocystic carcinoma
Papillary RCC
Clear cell (conventional) RCC
Follicular thyroid-like carcinoma
Hereditary leiomyomatosis–associated RCC
Acquired cystic kidney disease–associated RCC
Rhabdoid RCC
MiTF translocation carcinomas
Epithelioid angiomyolipoma
Unclassified RCC

Abbreviations: MiTF, microphthalmia transcription factor; RCC, renal cell carcinoma.

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