MiT Family Translocation-Associated Renal Cell Carcinoma

A Contemporary Update With Emphasis on Morphologic, Immunophenotypic, and Molecular Mimics

Martin J. Magers, MD; Aaron M. Udager, MD, PhD; Rohit Mehra, MD

Translocation-associated renal cell carcinoma (t-RCC) is a relatively uncommon subtype of renal cell carcinoma characterized by recurrent gene rearrangements involving the TFE3 or TFEB loci. TFE3 and TFEB are members of the microphthalmia transcription factor (MiT) family, which regulates differentiation in melanocytes and osteoclasts, and MiT family gene fusions activate unique molecular programs that can be detected immunohistochemically. Although the overall clinical behavior of t-RCC is variable, emerging molecular data suggest the possibility of targeted approaches to advanced disease. Thus, distinguishing t-RCC from its morphologic, immunophenotypic, and molecular mimics may have important clinical implications. The differential diagnosis for t-RCC includes a variety of common renal neoplasms, particularly those that have less abundant cytoplasm and lower nuclear grade, whereas t-RCC, on the other hand, might demonstrate a distinctive set of nonepithelial renal tumors may also warrant consideration. Directed ancillary testing is an essential aspect to the workup of t-RCC cases and may include a panel of immunohistochemical stains, such as PAX8, pancytokeratins, epithelial membrane antigen, carbonic anhydrase IX, HMB-45, and Melan-A. Dual-color, break-apart fluorescent in situ hybridization for TFE3 or TFEB gene rearrangement may be helpful in diagnostically challenging cases or when molecular confirmation is needed.

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From the Department of Pathology (Drs Magers, Udager, and Mehra), and the Comprehensive Cancer Center (Dr Mehra), University of Michigan Health System, Ann Arbor; and the Michigan Center for Translational Pathology, Ann Arbor (Dr Mehra).

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Reprints: Rohit Mehra, MD, Department of Pathology, University of Michigan Health System, Room 2G32 UH, 1500 E Medical Center Dr, Ann Arbor, MI 48109 (e-mail: mrohit@med.umich.edu).
### Table: Salient Microscopic Features and Ancillary Studies That May Aid in Diagnosis of Translocation-Associated Renal Cell Carcinoma and Its Morphologic, Immunophenotypic, and Molecular Mimics

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<th>Morphologic Features</th>
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<tr>
<td>Xp11 RCC</td>
<td>Diverse morphologic spectrum: high-grade cells with abundant clear or eosinophilic cytoplasm and papillary/nested architecture; psammomatosus calcifications</td>
<td>PAX8: +/-; Pan- CK: -P; CK7: -P; EMA: -P; CAIX: -P; HMB-45: -P; Melan-A: -P; Cathepsin K: +/-</td>
<td>TFE3 FISH</td>
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<td>t(6;11) RCC</td>
<td>Classic biphasic appearance: (1) larger epithelioid cells with clear to eosinophilic cytoplasm and (2) small, eosinophilic cells forming rosettelike structures within basement membrane–like material</td>
<td>PAX8: +/-; Pan- CK: -P; CK7: -P; EMA: -P; CAIX: -P; HMB-45: +/-; Melan-A: +; Cathepsin K: +</td>
<td>TFE3 FISH</td>
</tr>
<tr>
<td>CCRCC</td>
<td>Medium cells with clear cytoplasm in nests with delicate fibrovascular septations, or high-grade cells with eosinophilic cytoplasm and papillae/pseudopapillae</td>
<td>PAX8: +; Pan-CK: +; CK7: +; EMA: +; CAIX: +; HMB-45: +; Melan-A: +; Cathepsin K: +</td>
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<td>PRCC</td>
<td>Medium cells with clear to eosinophilic cytoplasm and variably enlarged nuclei; papillae with delicate fibrovascular cores; +/- foamy macrophages</td>
<td>PAX8: +; Pan-CK: +; CK7: +; EMA: +; CAIX: +; HMB-45: +; Melan-A: +; Cathepsin K: +</td>
<td>7/17 FISH</td>
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<tr>
<td>TCEB1-mutated RCC</td>
<td>Medium cells with clear cytoplasm; tubular and/or papillary architecture; well-circumscribed; thick intervening fibromuscular stromal bands</td>
<td>PAX8: +; Pan-CK: +/+; CK7: +/P; EMA: +; CAIX: +; HMB-45: +; Melan-A: +; Cathepsin K: +</td>
<td>None</td>
</tr>
<tr>
<td>CCPRCC</td>
<td>Medium cells with clear cytoplasm with prominent papillary architecture and low-grade, apically oriented nuclei</td>
<td>PAX8: +; Pan-CK: +; CK7: +; EMA: +; CAIX: +; HMB-45: +; Melan-A: +; Cathepsin K: +</td>
<td>None</td>
</tr>
<tr>
<td>EAML</td>
<td>Triphasic myxolipomatous tumor (smooth muscle, adipose, and vessels) with large epithelioid cells (&gt;80% of cells)</td>
<td>PAX8: +; Pan-CK: +; CK7: +; EMA: +; CAIX: +; HMB-45: +; Melan-A: +; Cathepsin K: +</td>
<td>Smooth muscle actin IHC</td>
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<td>ASPS</td>
<td>Large cells with eosinophilic cytoplasm and large, eccentric nuclei with macronucleoli; solid nests and/or alveolar-like spaces with intervening fibrous septa</td>
<td>PAX8: +; Pan-CK: +; CK7: +; EMA: +; CAIX: +; HMB-45: +; Melan-A: +; Cathepsin K: +</td>
<td>TFE3 FISH</td>
</tr>
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</table>

Abbreviations: ASPS, alveolar soft part sarcoma; CAIX, carbonic anhydrase IX; CCPRCC, clear cell papillary RCC; CCRCC, clear cell RCC; CK7, cytokeratin 7; CL, cuplike membranous staining; D, diffuse membranous staining; EAML, epithelioid angiomyolipoma; EMA, epithelial membrane antigen; FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; P, patchy, predominantly cytoplasmic staining; Pan-CK, pancytokeratins; PRCC, papillary RCC; RCC, renal cell carcinoma; +, positive; −, negative.

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than ASPL-TFE3 t-RCC. However, although certain microscopic features might correlate with the molecular subtype of Xp11 t-RCC, the degree of morphologic overlap between these subtypes prevents definitive classification on a purely histologic basis. Furthermore, although these features should generally raise suspicion for Xp11 t-RCC, the overall morphologic spectrum of Xp11 t-RCC is quite variable and can overlap other RCC subtypes; this underscores the need to consider this entity in the differential diagnosis of renal tumors with clear cell and/or papillary features.

t(6;11) t-RCC is much less common than Xp11 t-RCC and results from a gene fusion between TFE3 on chromosome 6p21 and the Alpha gene on chromosome 11q12, leading to overexpression of the full-length TFE3 protein. Similar to Xp11 t-RCC, t(6;11) t-RCC can occur in both children and adults, and a subset of tumors has been described in patients who had previously received cytotoxic chemotherapy. t(6;11) t-RCC typically demonstrates an indolent clinical course, with only rare metastases and subsequent death. No distinctive gross appearance for t(6;11) t-RCC has been described, and these tumors range from predominantly cystic to solid and mahogany in color (mimicking an oncocytic tumor). Microscopically, t(6;11) t-RCC typically exhibits a biphasic pattern (Figure 1, E and F). The majority of the tumor is composed of large, epithelioid cells with clear to eosinophilic cytoplasm, which may mimic conventional clear cell RCC. Distributed throughout the tumor, however, is a minor population of small, eosinophilic cells with hyperchromatic nuclei that form rosettelike structures within basement membrane–like material. Though classically associated with t(6;11) t-RCC, this morphology may also rarely be seen in Xp11 t-RCC.
Figure 1. Xp11 and t(6;11) translocation–associated renal cell carcinoma (t-RCC). A through D, Hematoxylin-eosin (H&E) images demonstrating the diverse morphologic spectrum of Xp11 t-RCC, including papillary architecture and cells with voluminous clear and/or eosinophilic cytoplasm; inset (D) shows a TFE3 gene rearrangement by dual-color, break-apart fluorescent in situ hybridization (FISH). E and F, H&E images showing the classic biphasic appearance of t(6;11) t-RCC; inset (F) demonstrates a TFEB gene rearrangement by dual-color, break-apart FISH (original magnifications ×200 [A through F] and ×1000 [D and F insets]).
otherwise morphologically suspicious cases and may also suffer from technical difficulties involving the available commercial antibodies. Dual-color, break-apart FISH for TFE3 and/or TFEB is the most sensitive and specific diagnostic tool for t-RCC (insets in Figure 1, D and F) and is currently available for clinical use in a number of tertiary care centers across the world.

DIFFERENTIAL DIAGNOSIS OF t-RCC

A better recognition of the morphologic features and clinical spectrum of t-RCC, coupled with the availability of confirmatory molecular techniques, has led to a greater understanding of this neoplasm, as well as its morphologic, immunophenotypic, and molecular mimics. In the appropriate clinical and morphologic context, t-RCC can be routinely diagnosed with the help of ancillary studies; however, the presence of a papillary architecture in a renal tumor with cells with clear to eosinophilic cytoplasm may bring several considerations into the differential diagnosis. Although the majority of entities that morphologically mimic t-RCC are sporadic renal tumors, a few syndromic renal neoplasms, as well as primary/metastatic tumors within the kidney that harbor TFE3 gene aberrations, may also need to be excluded in specific clinical scenarios. A detailed description of all of these entities is beyond the scope of this manuscript, but salient morphologic features and ancillary studies that might help resolve this differential diagnosis are presented below.

CLEAR CELL RCC

One of the most important considerations in the differential diagnosis of t-RCC is high-grade clear cell RCC (CCRCC) with focal or prominent papillary/pseudopapillary architecture. Clear cell RCC is an aggressive renal malignancy that typically affects older adults, has a predilection to metastasize to unusual sites long after primary treatment, and has a limited response to chemotherapy and radiation. Clear cell RCC has a characteristic bright yellow, solid and/or cystic gross appearance with frequent areas of hemorrhage and necrosis but may be grossly indistinguishable from t-RCC. Microscopically, CCRCC is typically composed of cells with optically clear cytoplasm arranged in solid nests with a delicate, branching fibrovascular pattern; cystic areas with hemorrhagic lakes are common, particularly in areas with small, round, low-grade nuclei and inconspicuous nucleoli. Clear cell RCC also frequently demonstrates high-grade cytomorphology and nuclear features, and in these areas, eosinophilic cytoplasm and papillary/pseudopapillary architecture may predominate (Figure 2, A). It is these cases that might merit consideration of t-RCC.

From a clinical standpoint, the distinction between CCRCC and t-RCC is important because the well-established treatment protocols for CCRCC may or may not apply to t-RCC. Indeed, the unique genetic alterations that define t-RCC appear to drive tumorigenesis through very different molecular mechanisms than CCRCC. Clear cell RCC, for example, is associated with mutations or deletions of the von Hippel–Lindau (VHL) gene on chromosome 3p. Subsequent loss of heterozygosity at the VHL locus (ie, chromosome 3p deletion) results in constitutive activation of the hypoxia-inducible factor (HIF) pathway (so-called pseudohypoxic drive) with downstream target expression, including CAIX. Translocation-associated RCC, on the other hand, may be associated with upregulation of MET, a tyrosine kinase receptor that signals through multiple downstream pathways—including phosphoinositide 3-kinase and RAS—to drive oncogenesis. Interestingly, in a preliminary report from the Juvenile RCC Network, targeted therapy for t-RCC patients with vascular endothelial growth factor receptor or mammalian target of rapamycin (mTOR) pathway inhibitors achieved objective clinical responses in a subset of patients. Thus, in this rapidly developing era of personalized medicine, targeted therapy for t-RCC warrants continued investigation and may need to be tailored to specific underlying molecular mechanisms in order to achieve enhanced clinical outcomes.

Although CCRCC and t-RCC may demonstrate substantial morphologic overlap, differences in immunophenotype and underlying genomic alterations can aid in diagnosis. In contrast to t-RCC, CCRCC strongly and diffusely expresses pancytokeratins and EMA in the majority of cases and is negative for Melan-A, HMB-45, and cathepsin K. In addition, secondary to VHL loss of heterozygosity in CCRCC, these tumors characteristically demonstrate strong and diffuse membranous expression of CAIX (Figure 2, B). Finally, although not used routinely in clinical practice, locus-specific FISH may demonstrate chromosome 3p deletions in CCRCC but not t-RCC; in contrast, CCRCC would be negative for TFE3 and TFEB gene rearrangements by dual-color, break-apart FISH.

PAPILLARY RCC

Papillary RCC (PRCC), the second most common subtype of RCC, may also exhibit overlapping morphologic features with t-RCC. Characteristically, PRCC is a circumscribed tumor, often surrounded by a fibrous pseudocapsule with a solid and cystic, hemorrhagic appearance. Microscopically, PRCC may be further subclassified into 2 broad morphologic groups: type 1 and type 2. Type 1 PRCC typically is composed of small, low cuboidal-type cells with small, round nuclei lining papillary structures with well-defined fibrovascular cores stuffed by foamy macrophages. Type 2 PRCC, on the other hand, is typically composed of medium to large cells with eosinophilic cytoplasm and nuclear enlargement, pleomorphism, and pseudostratification lining papillary structures with thin, delicate fibrovascular cores without foamy macrophages. In some cases, PRCC may also demonstrate cytoplasmic clearing (Figure 2, C and D), and in such situations, these features may create a diagnostic challenge to distinguish it from t-RCC.

The molecular basis for PRCC is not yet fully understood; however, some clear genomic differences from t-RCC have been identified. For example, PRCC is typically characterized by trisomy 7 and/or 17, which is not commonly seen in t-RCC; in contrast, the TFE3 and TFEB gene rearrangements characteristic of t-RCC are not present in PRCC. Similar to CCRCC, ancillary studies may be helpful in the differential diagnosis of PRCC and t-RCC. Papillary RCC usually strongly and diffusely expresses pancytokeratins and EMA, and cytokeratin 7 expression is generally positive but might be variable. In addition, PRCC demonstrates variable expression of alpha-methylacyl-CoA racemase (AMACR) and CD10 but is negative for Melan-A, HMB-45, cathepsin K, TFE3, and TFEB expression. Expression of CAIX in PRCC may be variable but should not demonstrate the strong and diffuse membranous pattern characteristic of CCRCC. Finally, centromeric FISH
Figure 2. Renal tumors with clear cells and papillary architecture, mimicking translocation-associated renal cell carcinoma. A and B, Hematoxylin-eosin (H&E) image of clear cell renal cell carcinoma (CCRCC) with papillary/pseudopapillary architecture (A); carbonic anhydrase IX immunohistochemical staining (B) shows a strong, diffuse membranous pattern, characteristic of CCRCC, and the inset demonstrates the absence of a TFE3 gene rearrangement by dual-color, break-apart fluorescent in situ hybridization. C and D, H&E images of papillary renal cell carcinoma with cytoplasmic clearing. E and F, H&E images of a renal tumor with features of TCEB1-mutated renal cell carcinoma, demonstrating a neoplasm with clear cells, papillary architecture, and abundant fibromyxomatous stroma (original magnifications ×200 [A through D and F], ×40 [E], and ×1000 [B inset]).
for chromosome 7 and/or 17 gain and dual-color, break-apart FISH for TFE3 and TFEB gene rearrangements may be useful adjunct techniques, although it is important to note that chromosome 7 and/or 17 gain is more frequently associated with type 1 PRCC.

OTHER RCC WITH CLEAR CELLS

A distinct group of RCC with clear cells and prominent fibromuscular stroma has been characterized recently. As they may demonstrate a papillary architecture with cells containing voluminous clear cytoplasm, these tumors might be considered in the differential diagnosis of t-RCC. TCEB1-mutated RCC is a recently identified subset of RCC with morphologic features similar to those of CCRCC but mutations in TCEB1 rather than VHL. TCEB1-mutated RCC is characterized by thick fibromuscular stromal bands, cells containing clear or granular cytoplasm, and tubular and/or papillary architecture (Figure 2, E and F). Distinction between TCEB1-mutated RCC and t-RCC can generally be made based on CAIX staining, as TCEB1-mutated RCC characteristically exhibits diffuse CAIX expression. RCC with angioleiomyoma-like stroma is another recently described entity, a subset of which may share a molecular phenotype with TCEB1-mutated RCC; these tumors are composed of medium cells with clear or eosinophilic cytoplasm and occasionally papillary architecture, separated by angioleiomyoma-like stroma. RCC with angioleiomyoma-like stroma typically expresses CAIX and cytokeratin 7, and thus, similar to TCEB1-mutated RCC, these tumors can usually be distinguished from t-RCC by routine immunohistochemistry. Interestingly, the immunophenotype of both TCEB1-mutated RCC and RCC with angioleiomyoma-like stroma overlaps that of clear cell papillary RCC (CCPRCC), an indolent tumor that very rarely may enter the differential diagnosis of t-RCC. Morphologically, CCPRCC is composed of medium cells with clear cytoplasm arranged in a prominent papillary architecture; the nuclei are conspicuously low grade and classically arranged in a linear fashion away from the basement membrane. Similar to TCEB1-mutated RCC and RCC with angioleiomyoma-like stroma, CCPRCC typically demonstrates strong CAIX expression, a feature that should facilitate its distinction from t-RCC. Interestingly, however, CAIX staining in CCPRCC is characteristically absent from the apical cell membrane, which imparts a distinctive cuplike pattern that may be useful diagnostically.

HEREDITARY LEIOMYOMATOSIS AND RCC–ASSOCIATED RCC

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)–associated RCC is an emerging subtype of high-grade RCC that often demonstrates morphologic overlap with type 2 PRCC and rarely may be a consideration in the differential diagnosis of t-RCC. HLRCC is a rare, familial cancer syndrome in which patients develop cutaneous and uterine leiomyomata and aggressive, high-grade renal tumors. HLRCC is characterized by germline mutations in the fumarate hydratase (FH) gene on chromosome 1q42, which encodes a Krebs cycle enzyme that catalyzes the conversion of malate to fumarate. The development of HLRCC-associated RCC is associated with loss of heterozygosity at the FH locus, which, similar to VHL inactivation and loss of heterozygosity in CCRCC, results in pseudohypoxic activation of the HIF pathway. FH loss in HLRCC-associated RCC also results in intracellular accumulation of succinicated proteins (2-SC), which can be exploited for diagnostic purposes in morphologically suspicious cases (see below). Although the morphology of HLRCC-associated RCC is classically described as similar to that of type 2 PRCC, recently, the spectrum has expanded to include a range of tumors with high-grade cytoplastic features and papillary, tubulopapillary, and/or solid architecture (Figure 3, A)47,48; in these tumors, the defining characteristic remains the presence of large nuclei with very large eosinophilic or orangeophilic macronucleoli and perinuclear clearing (inset, Figure 3, A).47,49

The presence of papillary architecture and cells with eosinophilic cytoplasm and high-grade nuclei, in conjunction with the fact that the classic nuclear/nucleolar features of HLRCC may be seen only focally within these tumors, might lead to HLRCC-associated RCC being considered in the differential diagnosis of t-RCC. Although the immunophenotype of HLRCC-associated RCC is not currently well characterized, these tumors reportedly lack cytokeratin 7, cytokeratin 20, and high-molecular-weight cytokeratin expression.47,48 Interestingly, despite the fact that FH loss in HLRCC-associated RCC results in pseudohypoxic drive and HIF pathway activation, the expression of CAIX and other HIF targets (e.g., vascular endothelial growth factor) in these tumors has not been extensively studied. Nevertheless, emerging data indicate that immunohistochemistry for FH and/or 2-SC (either alone or in combination; Figure 3, B) have relatively high sensitivity and specificity for identifying FH-deficient tumors, including HLRCC-associated RCC.46,49

COLLECTING DUCT CARCINOMA (CDC)

Collecting duct carcinoma (CDC) is a rare, aggressive renal tumor with high-grade cytromorphology and nuclear features, which in some cases may enter the differential diagnosis of t-RCC. Collecting duct carcinoma typically arises in the renal medulla and presents over a broad age range; it is often metastatic at the time of diagnosis, and overall survival is very poor. Grossly, CDC is usually pale gray and solid with areas of hemorrhage and/or necrosis. The tumor is often poorly circumscribed and has an infiltrative border with the uninvolved kidney; owing to its predominantly medullary location, CDC often involves the renal sinus adipose tissue. Microscopically, CDC is characterized by large, pleomorphic cells with eosinophilic cytoplasm. A variety of architectural patterns can be seen in CDC, including tubular, solid, and papillary; however, marked desmoplastic stroma is frequently present and may be a clue to diagnosis. Collecting duct carcinoma is also somewhat unusual among RCC subtypes in that it may be associated with dysplasia of the adjacent renal tubular epithelium. Immunohistochemistry may be helpful to distinguish CDC from t-RCC and other high-grade RCC, as CDC typically expresses high-molecular-weight cytokeratin, EMA, and cytokeratin 7 but is negative for CD10, AMACR, and CAIX. The molecular oncogenesis of CDC is not currently well understood, which limits the role for diagnostic molecular testing and/or targeted therapy in these tumors.

TUBEROUS SCLEROSIS–ASSOCIATED RCC

Tuberous sclerosis (TS)-associated RCC is a heterogeneous group of distinctive renal tumors that rarely may have morphologic overlap with t-RCC. Tuberous sclerosis is an
Figure 3. Other epithelioid tumors in the differential diagnosis of translocation-associated renal cell carcinoma. A and B, Hematoxylin-eosin (H&E) image of hereditary leiomyomatosis and renal cell carcinoma (HLRCC)–associated renal cell carcinoma (A) demonstrating a renal tumor with papillary architecture, enlarged and pleomorphic nuclei, and prominent, inclusion-like macronucleoli (inset in A); fumarate hydrate immunohistochemistry demonstrates loss of protein expression in tumor cells but retained staining in admixed endothelial cells (arrowheads in B). C and D, H&E images of tuberous sclerosis–associated renal cell carcinoma showing a renal tumor with a solid architecture and large epithelioid cells with abundant eosinophilic, granular cytoplasm and variable intracytoplasmic vacuolization. E, H&E image of epithelioid angiomyolipoma showing a renal tumor with solid sheets of epithelioid cells with abundant pink cytoplasm. F, H&E image of alveolar soft part sarcoma demonstrating large epithelioid cells with eosinophilic cytoplasm arranged in loose alveolar structures (original magnifications ×200 [A, B, and D through F], ×100 [C], and ×400 [A inset]).
autosomal dominant disorder associated with germline mutations in the tuberous sclerosis 1 (TSC1) or tuberous sclerosis 2 (TSC2) genes, resulting in mTOR pathway dysregulation and characteristic tumors that involve multiple organs, including brain, kidney, retina, skin, heart, and lung. The most common renal tumor in TS is angiomyolipoma (AML), which occurs in up to 75% of patients and is often bilateral and multifocal. Although less common than AML, TS patients also frequently develop RCCs, which occur at a much younger age than sporadic RCC subtypes and are frequently bilateral and multifocal. Two recent large, independent studies have characterized the morphologic spectrum of TS-associated RCC and identified at least 3 distinct histologic patterns: renal angiomyoepithelial tumor–like; chromophobe-like; and granular eosinophilic type. Renal angiomyoepithelial tumor–like TS-associated RCC is composed of large, clear cells with variable but predominantly low-grade nuclear morphology and admixed solid, tubular, and/or papillary architecture; prominent intervening smooth muscle stroma is an important diagnostic feature for this histologic type. Chromophobe-like TS-associated RCC is a predominantly low-grade oncytic tumor with varying mixtures of chromophobe (typical and eosinophilic variant) and oncocyoma-like morphology. Finally, granular eosinophilic type TS-associated RCC is an intermediate-grade oncytic tumor composed of large cells with abundant eosinophilic, granular cytoplasm, variable intracytoplasmic vacuolization, and medium, round nuclei with prominent nucleoli; these cells are arranged in a single layer that lines microcystic and macrocystic structures and often have a hobnail appearance, although areas of papillary, tubular, and solid architecture are variably present (Figure 3, C and D). With this broad morphologic spectrum, TS-associated RCC, especially the renal angiomyoepithelial tumor–like and the granular eosinophilic type, may be considered in the differential diagnosis of t-RCC; fortunately, ancillary studies are helpful in distinguishing between these tumors. Immunohistochemistry for HMB-45 and TFE3 is uniformly negative in all TS-associated RCC. Furthermore, in diagnostically challenging cases, TS-associated RCC are negative for TFE3 gene rearrangement by dual-color, break-apart FISH. Epithelioid AML (EAML), a member of the perivascular epithelioid cell tumor (PEComa) family, is an uncommon renal tumor that can be mistaken for RCC and may have morphologic and immunophenotypic overlap with t-RCC. Epithelioid AML accounts for approximately 5% of AML cases and generally occurs in younger adults. Similar to conventional AML, EAML is a triphasic mesenchymal tumor composed of varying amounts of smooth muscle, adipose tissue, and vessels, and associated TSC1 or TSC2 mutations result in mTOR pathway dysregulation. Unlike conventional AML, however, EAML also contains a significant population of large, epithelioid cells (Figure 3, E); although there is currently no defined threshold for the number of epithelioid cells required to diagnosis EAML, in general, they should account for the predominant population (>80%) of the total tumor cells. The morphologic spectrum of epithelioid cells in EAML is diverse: cytoplasm can be clear or eosinophilic; nuclei can be low or high grade (including marked pleomorphism and/or multinucleation); and cells can be arranged in small nests, alveolar-like clusters, and/or solid sheets and hence may closely mimic t-RCC. Although routine immunohistochemistry is generally sufficient to distinguish EAML from common RCC subtypes, the immunophenotypic overlap with t-RCC can present a diagnostic dilemma. Epithelioid AML usually expresses HMB-45, Melan-A, and cathepsin K and is negative for pancytokeratins and EMA expression. Importantly, in contrast to t-RCC, EAML may express smooth muscle actin (particularly in nonepithelioid elements) and is usually negative for PAX8 expression. Finally, although a small subset of PEComas may harbor TFE3 gene rearrangements (see below), EAML is usually negative for TFE3 gene fusions; therefore, dual-color, break-apart TFE3 FISH may be helpful in diagnostically challenging cases.

**MOLECULAR MIMICS OF t-RCC**

Finally, a discussion of the differential diagnosis of t-RCC, particularly Xp11 t-RCC, is not complete without acknowledging its molecular mimics. Although these tumors may or may not primarily involve the kidney, they may be mistaken for primary or metastatic t-RCC in the absence of sufficient clinical information. Alveolar soft part sarcoma is a malignant soft tissue tumor that typically occurs in young patients and harbors a TFE3 gene rearrangement with ASPL on chromosome 17q25—the same gene fusion present in a large proportion of Xp11 t-RCC. Alveolar soft part sarcoma (ASPS) is composed of large cells with eosinophilic cytoplasm and large, eccentric nuclei with clumped chromatin and macronucleoli, arranged in solid nests and/or alveolar-like spaces with prominent intervening fibrous septa (Figure 3, F). By immunohistochemistry, ASPS strongly and diffusely expresses TFE3 and is typically negative for HMB-45 and pancytokeratin expression; dual-color, break-apart FISH may be useful to confirm the ASPL-TFE3 gene fusion in ASPS. Pervascular epithelioid cell tumors are a group of morphologically heterogeneous myomelanocytic tumors with unpredictable clinical behavior that can present at essentially any site in the body, including solid organs and soft tissue. Concordant with their myomelanocytic morphologic appearance, PEComas variably express smooth muscle actin, HMB-45, and Melan-A, but are typically negative for cytokeratin and vimentin expression. As previously discussed, a small subset of PEComas also harbors TFE3 gene rearrangements, although the predominant gene fusion partner in these tumors is not known; immunohistochemistry for TFE3 and/or dual-color, break-apart FISH for TFE3 may indicate the presence of a TFE3 gene fusion in these rare situations. Finally, very rare examples of melanotic epithelioid neoplasms with TFE3 gene rearrangements have been described, including renal-based tumors in young patients, and these tumors have morphologic and immunophenotypic overlap with melanoma, PEComa, and t-RCC. Morphologically, these rare tumors are composed of large epithelioid cells, with clear to eosinophilic cytoplasm and melanin pigment, arranged in solid nests enveloped by thin vascular septa. Immunohistochemistry typically demonstrates strong and diffuse TFE3 and variable HMB-45 and Melan-A expression, whereas other immunohistochemical stains are usually negative (including smooth muscle actin, pancytokeratin, and PAX8); dual-color, break-apart FISH for TFE3 may be helpful to confirm the presence of a TFE3 gene fusion.
In summary, t-RCC is a rare subtype of RCC with recurrent gene fusions involving members of the MIT family of transcription factors, including TFE3 and TFEB. Although uncommon, t-RCC is an important consideration in the differential diagnosis of high-grade epithelioid neoplasms involving the kidney, particularly in children and young adults. The morphologic spectrum of t-RCC is diverse and has potential overlap with common RCC subtypes (CCRCC and PRCC), which represent the main differential diagnostic considerations. Rarely, entities such as syndromic RCC subtypes (ie, HLRCC-associated RCC and TS-associated RCC), the recently characterized renal tumors with clear cells and prominent fibromuscular stroma (TCEB1-mutated RCC), and a distinctive set of nonepithelial renal tumors (EAML, ASPS, PEComa, and melanotic epithelioid neoplasms) may also merit consideration. The diagnostic workup for t-RCC may benefit from screening immunohistochemistry with PAX8, pan-cytokeratins, EMA, CAIX, plectin, HMB45, and Melan-A (see Table). Dual-color, break-apart FISH for TFE3 gene rearrangement may be helpful in diagnostically challenging cases or if molecular confirmation is needed (for example, for clinical trial enrollment).

CONCLUSIONS

References


