New Entities, New Technologies, New Findings: A Review of the Cytologic Features of Recently Established Subtypes of Renal Cell Carcinoma

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Several new renal tumor types with distinctive pathologic, epidemiologic, and genetic signatures have recently been adopted in the fourth edition of the World Health Organization classification. In succeeding years, the cytologic features of most of these new types have been described, adding to the trend of increasing diagnostic accuracy for most common renal cell carcinoma subtypes and the important diagnostic role of cytologic sampling in the management and personalization of therapy. The current article reviews the cytologic findings from these recently established renal cell carcinoma subtypes. Emphasis is placed on cytologic diagnostic clues, confirmatory ancillary testing, salient differential diagnoses, and challenges that can be encountered in an attempt to render accurate interpretations in small samples.

Cancer Cytopathol 2019;127:79-97. © 2019 American Cancer Society.

KEY WORDS: acquired cystic disease-associated renal cell carcinoma; aspiration cytology; clear cell papillary renal cell carcinoma; fumarate hydratase-deficient renal cell carcinoma; microphthalmia-associated transcription factor (MiT) family translocation renal cell carcinoma; succinate dehydrogenase-deficient renal cell carcinoma; tubulocystic renal cell carcinoma.

INTRODUCTION

Cytologic evaluation has an important role in the diagnosis and management of renal cell carcinoma (RCC).\textsuperscript{1} Sampling of primary renal lesions is indicated in instances of indeterminate radiologic findings, low-risk lesions for which ablation or conservative treatment is considered, or when a radical nephrectomy is contraindicated (high disease stage, extensive metastasis, comorbidities). Metastatic lesions, aside from pathologic staging, may provide the only diagnostic tissue for prognosis and therapy selection in patients who are not candidates for surgery. The latter scenario is likely to prospectively increase the role for (and stakes of) cytologic and/or biopsy sampling in the metastatic setting, given recent findings and trends against cytoreductive nephrectomy.\textsuperscript{2,3} Finally, contemporary National Comprehensive Cancer Network guidelines emphasize the importance of a diagnosis of clear cell RCC versus other RCC entities in management decisions,\textsuperscript{4} given the greater efficacy of angiogenesis-directed tyrosine kinase inhibitor therapies in this subtype. Moreover, clinical trials have demonstrated the efficacy of targeted inhibitors against the MET proto-oncogene receptor tyrosine kinase ($MET$) mutations observed in a subset of papillary RCCs (PRCCs),\textsuperscript{5,6} further emphasizing the increasingly actionable nature of RCC subclassification.
Fine-needle aspiration (FNA) and core-needle biopsy (CNB) have exhibited increasing diagnostic utility for the classification of most common types of RCC. Cytologic diagnoses are highly accurate compared with histopathologic diagnoses, and most discrepancies are attributed to small sample size, tumor heterogeneity, and certain diagnostic groups, particularly oncocytic neoplasms. However, as new RCC entities emerged, their cytologic findings also needed to be defined. This was most often accomplished by a retrospective review of cytology material from a relatively limited number of patients who had diagnoses established on surgical specimens, describing the most distinctive cytologic features and emphasizing those that can either pinpoint the diagnosis or suggest a targeted differential among RCC subtypes. Those studies also demonstrated that adequate CNBs or cell blocks can provide adequate histologic information and material for ancillary studies, which are essential for rendering accurate diagnoses.

In this article, we review the cytologic findings in new entities incorporated into the 2016 fourth edition World Health Organization (WHO) classification (2016). It is noteworthy that several of the tumor types involved highlight recent themes in RCC histopathology, including the recognition of RCC types arising in the increasingly prevalent setting of end-stage kidney disease with or without acquired cystic changes, such as clear cell papillary RCC (CCP RCC), acquired cystic disease (ACD)-associated RCC, and, rarely, tubulocystic carcinoma. The increasingly recognized microphthalmia-associated transcription factor (MiT) family translocation RCCs also were formalized as an entity. One final category concerns the recognition of histologically distinctive RCC types with strong hereditary associations, including succinate dehydrogenase (SDH)-deficient RCC and the fumarate hydratase (FH)-deficient RCCs arising in hereditary leiomyomatosis syndrome-associated RCC (HLRCC RCC). This new group of entities subtypes tumors of dramatically differing prognosis, varying from indolent to among the most aggressive renal tumors, with corresponding diagnostic implications. For hereditary entities, these extend even beyond the affected patient, with the potential through genetic counseling and testing to impact and prevent disease for affected family members. It is evident that the recognition of these tumors on what is sometimes the only available sample becomes pivotal in directing management.

**RCC SUBTYPES RECOGNIZED IN END-STAGE KIDNEY DISEASE**

Two of the recently adopted entities, CCP RCC and ACD-associated RCC, were first characterized in studies of the often multifocal tumors that arise in end-stage kidneys, many of which exhibit acquired cystic changes, especially with long-term dialysis. It has been observed that CCP RCC also occurs frequently in the sporadic setting, whereas ACD-associated RCC remains defined by the clinical scenario of acquired cystic disease and essentially does not occur outside of this setting, as discussed below.

**Clear Cell Papillary RCC**

CCP RCC is a distinct subtype of RCC acknowledged by the International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. It is now recognized that these tumors, which initially were described in the setting of end-stage renal disease, occur sporadically.

CCP RCCs may be solid or cystic and histologically display usually mixed papillary, tubular, acinar, or compact nested growth patterns. The neoplastic cells have clear cytoplasm, low nuclear grade nuclei (WHO/ISUP nucleolar grade 1 or 2-4), and, most characteristic, a linear arrangement of the nuclei, away from the basal aspect and toward the cell luminal surface (Fig. 1A,B). CCP RCC also may have variable fibrous or myomatous stroma, which renders overlapping features with a related entity: renal angiomyoadenomatous tumor. CCP RCC has a unique immunohistochemical signature that includes diffuse, strong staining with CK7; a specific, cup-like, basolateral distribution of CAIX; and negative staining with AMACR, CD10, and RCC, in contrast to the findings in both clear cell RCC and PRCC. Few additional positive markers have been proposed, including high-molecular weight-cytokeratin and cyclin D1. At the molecular level, CCP RCC lacks the chromosome 7 and 17 gains frequently observed in PRCC and the 3p deletions observed in clear cell RCC. However, rare tumors with von Hippel-Lindau (VHL) gene mutations have been described. Although the molecular pathogenesis of CCP RCC is not entirely known, recurrent chromosomal imbalances or dysregulation of microRNA associated with a poor prognosis have not been identified.
CCP RCC is the fourth most common, but a distinctly indolent variant of RCC, which, with few exceptions, exhibits low pathologic stage at presentation. Large studies have reported a lack of progression and no reported metastases, raising the possibility that CCP RCC can be reclassified as a tumor of “low malignant potential” rather than carcinoma. In this context, the cytologic diagnosis of this subtype may be beneficial for clinical decisions, which may range from surveillance to therapeutic protocols, including ablation and partial/total nephrectomy, depending on a close correlation with imaging findings.

The cytologic findings of CCP RCC have been reported in only a few studies, which included retrospective evaluations of existing FNA and CNB of renal masses with a subsequent surgical diagnosis of CCP RCC. The direct smears, aspirations, or touch preparations of CNB range from nondiagnostic to moderate cellularity and most often are composed of small clusters/strips or variably sized arrays of monomorphic cells (Fig. 1C,D). The uniform cells are round to oval and have finely granular chromatin and indistinct nucleoli. Most important, in all cases reported, the nuclei are placed eccentrically at one pole of the cells or in parallel configuration. Scattered benign elements also are present, including few macrophages and clusters of renal tubular cells, which, given their granular cytoplasm and irregularly spaced nuclei, provide a good contrast with the clonal-appearing neoplastic cells. Finally, small fragments of smooth muscle stroma are noted occasionally on touch preparations, and it is believed that such fragments reflect
the myomatous stroma observed in many surgical specimens of these tumors.29

The small tissue fragments in cell blocks and biopsies have presented a spectrum of findings. In some cases, the diagnosis was strongly suggested by the presence of clear cell and papillary features or by a prominent tubular or tubulopapillary growth pattern of cells with clear-to-delicate, eosinophilic cytoplasm and, at least focally, luminal displaced nuclei. In other cases, the findings were more discrete, but soft clues—such as the presence of fibrous, myoid, or hyalinized stroma in a background of monotonous epithelial cell proliferation or a small, atypical, papillary proliferation of clear cells lining a cyst wall—raise the possibility of CCP RCC and elicit further confirmatory workup. The distinct positivity for CK7 and CAIX in a cup-shaped, membranous pattern and negativity for AMACR in most cases facilitate the differential diagnosis with clear cell or PRCC. When focally positive, CD10 had a reverse staining pattern of cell luminal surfaces and lateral cell border.

Both studies described above29,30 demonstrate that, with increased experience, recognizable cytologic features are sufficient to raise a suspicion for CCP RCC and differentiate it from other subtypes with overlapping features. Compared with CCP RCC, findings strongly favoring clear cell RCC are the presence of high-grade nuclei; cells with ample, clear cytoplasm; and large, cytoplasmic vacuoles or sheets with traversing capillaries. In addition, true papillary architecture should not be present, or at least not extensively, in clear cell RCC. CCP RCC and PRCC with low-grade nuclei may have similar growth patterns, but the neoplastic cells should present different cytoplasmic characteristics, ranging from scant basophilic in “type 1” PRCC to ample granular on “type 2” PRCC. Background macrophages are less prevalent and are not associated with fibrovascular cores in CCP RCC. Finally, MiT family translocation RCC (see below) often can be distinguished from CCP RCC by the presence of cells with voluminous, clear-to-eosinophilic cytoplasm and high-grade nuclei. However, in some cases, the findings including cytoplasmic features, and nuclear location may not be entirely specific to one RCC subtype, rendering it difficult to obtain a definitive smear interpretation. In such cases, histologic features in cell block or CNB material, ancillary studies, and correlation with clinical and radiologic findings, in most cases, should support the diagnosis of CCP RCC.

Other cytologic findings raise additional differential diagnoses. When small cyst wall fragments are noted with a lining of clear cell or papillary clusters, the possibility of a multilocular cystic neoplasm of low malignant potential should be considered. The immunoprofile, with positivity for CK7, CAIX, and diffuse membranous staining for CD10, may render the diagnosis, whereas some authors have postulated a close correlation between these tumors.31 Even if the distinction is not possible, both entities are regarded as carrying a favorable prognosis. The presence of smooth muscle stroma as small fragments in smears or CNBs may raise additional differential diagnoses, including a myoid-predominant angiomyolipoma (PEComa), positive for melanocytic markers, or TCEB-mutated RCC. Finally, tumors with CCP RCC histology in patients with von Hippel-Lindau disease may not represent CCP RCC.32

**Acquired Cystic Disease-Associated RCC**

ACD of the kidney (ACDK) develops in end-stage renal disease, most often in the setting of long-term hemodialysis, but also in patients who have uremia and in transplantation recipients who have chronic rejection. ACDK is generally defined as multiple, macroscopic cysts in each kidney in the absence of a hereditary cause; in contrast to hereditary polycystic kidney disease, in which the kidneys are large and are populated by innumerable cysts, ACD kidneys tend to be atrophic-to-normal in size.33 Patients with ACDK are at a significantly increased risk of developing RCC, 100 times that of general population,34 and ACD-associated RCC is the most common subtype of RCC in this setting.13

These tumors most often are diagnosed radiologically as part of the long-term follow-up of patients who have chronic disease or in those who undergo nephrectomy for complications of renal cysts. ACD-associated RCC may be multiple or bilateral and can arise in cysts or as solid masses, with areas of necrosis and hemorrhage.12,13 Histologically, the tumors exhibit various proportions of acinar, alveolar, cystic, solid, and papillary patterns as well as characteristic intracellular and intercellular lumens, imparting a cribriform or sieve-like architecture. The cells have abundant, granular, eosinophilic cytoplasm and large nuclei with prominent nucleoli. Finally, most, but not all tumors have intratumoral calcium oxalate (Fig. 2A).
Cytologic evaluation of ACD-associated RCC is encountered less often in clinical practice. To date, we are aware of only two prior reports illustrating the touch preparation of a surgically resected tumor or computed tomography-guided FNA of metastatic lesions located in the retroperitoneum and the abdominal left upper quadrant. In the former case, imprint cytology revealed a sheet-like growth pattern and cytoplasmic microscopic lumina. The FNA smears in the latter cases were moderately to highly cellular and contained papillary clusters and flat sheets with clear spaces suggestive of a cribriform pattern (Fig. 2B). In all cases, the neoplastic cells were polygonal to columnar; had distinct cell borders; had abundant, granular, eosinophilic cytoplasm; and had only rare cells with clear cytoplasm or occasionally small cytoplasmic vacuoles. The nuclei were round and centrally placed, with finely granular chromatin and prominent central nucleolus, meeting the criteria for WHO/ISUP nucleolar grade 3 or 4. Characteristic of this tumor, oxalate crystals were detected within or around the clusters. Immunohistochemical stains performed on one cell block and a representative tumor section revealed neoplastic cells that were diffusely positive for AMACR and CD10 but negative for CK7 and EMA, results that were diagnostic of ACD-associated RCC.

The most significant differential diagnosis is with PRCC, particularly “type 2.” Cytologically, criteria favoring ACD-associated RCC include the presence of architectural patterns other than papillary, intercytoplasmic and intracytoplasmic lumina, oxalate crystals, and the immunohistochemical profile, which contrasts with CK7-positive PRCC. Furthermore, and nicely illustrated in the article discussed above, ACD-associated RCC does not have trisomy of chromosome 7 or 17 or loss of 3p, as do PRCC and clear cell RCC, respectively, but does display combined gains of chromosomes 3, 7, 16, 17, and Y.

Because of early, most often low-stage detection, ACD-associated RCC has a relatively good prognosis. However, it does have more aggressive behavior compared with other RCC subtypes in the setting of end-stage kidney disease. Few instances of metastatic ACD-associated RCC have been reported, both in typical cases and in tumors with sarcomatoid or rhabdoid features. No distinct, actionable therapies are known at this time.

MiT Family Translocation RCC

MiT family translocation RCC is a category of tumors of renal tubular origin characterized by gene rearrangements of the TFE3 or TFEB loci and a distinctive, aberrant expression of melanocytic markers. The t(6;11) translocation-associated RCC was recently recognized by the 2013 International Society of Urological Pathology Vancouver Classification of Renal Neoplasia and is characterized by a specific translocation that results in the fusion of Alpha, also known as MALAT1 and TFEB. There are fewer than 60 reported cases of t(6;11) RCC, mostly in young adults, but these tumors occur at any age, with no sex preference and a relatively indolent course.

Also notable in this category is Xp11 translocation RCC, a distinct entity that was recognized in the 2004 WHO renal tumor classification. This tumor is characterized by fusions between TFE3 and multiple gene partners, most commonly ASPSCR1/ASPL, resulting in
the t(X;17)(p11.2;q25) translocation, or PRCC, resulting in t(X;1)(p11.2;q21). Xp11 translocation RCC represents up to 4% of adult RCCs, with a prognosis comparable to that of clear cell RCC, and approximately 40% of pediatric RCCs, with a more favorable outcome. Grossly, both t(6;11)-associated and Xp11-associated RCC are tan-yellow and solid, with cystic changes and variable hemorrhage or necrosis. Histologically, MiT translocation RCCs exhibit largely overlapping, but also distinct patterns, depending on the oncogenic fusion present. The t(6;11) RCC subtype has a distinctive biphasic morphology, consisting of the nested or solid growth of large epithelioid cells with ample cytoplasm and round, small nuclei interspaced with smaller cells that have hyperchromatic nuclei forming rosette-like structures around basement membrane-like material. However, the second cell population may be not present, very focal, or present as an overlapping feature in Xp11 translocation RCC. Xp11 ASPL-TFE3 translocation RCC is characterized by a papillary or nested pattern, often with psammomatus calcifications, of large epithelioid cells with abundant clear-to-oncocytic cytoplasm and high-grade nuclei. PRCC-TFE3 translocation RCC has a more nested growth pattern of cells, sometimes papillary or solid, with less cytoplasm, often lower nuclear grade features, and fewer psammomatus calcifications.

However, a wider spectrum of morphologic patterns has been described for each entity, thus raising differential diagnoses not only between these two translocation types but also among other RCC subtypes, including PRCC, clear cell RCC, or chromophobe RCC, and non-RCC entities. In this context, their cytologic diagnosis may be challenging and requires familiarity with the entities to recognize the possibility of an unusual RCC subtype and trigger ancillary testing for an accurate diagnosis.

Immunohistochemistry and cytogenetic analyses are useful in distinguishing MiT translocation RCC from its morphologic mimics. They are positive for Pax8, RCC, and CD10, consistent with their renal tubular origin, but have reduced expression of pancytokeratins and other epithelial markers (EMA). Uniquely, they are positive for melanocytic markers and cathepsin K. Although t(6;11) RCC consistently expresses Melan A, it may be negative for HMB-45. The most specific markers are strong nuclear TFEB or TFE3 positivity, respectively, although these antibodies are known to be technically fastidious. However, their adequate detection is impacted by varying time or suboptimal fixation. Molecular studies most often are needed for an accurate diagnosis, with break-apart fluorescence in situ hybridization (FISH) assays for TFEB or TFE3 the most commonly used.

Several reports have been published describing the cytologic findings of MiT translocation RCC, and all are instances of Xp11 translocation RCC. They included evaluations of touch imprints of image-guided CNBs of renal masses; FNAs of a renal mass, lung, and mediastinal metastases; and urine cytology. The patients were ages 1 to 58 years and had an equal distribution according to sex. Consistently through all specimens, the smears had moderate-to-high cellularity. Architecturally, various patterns were noted and included variably sized loose clusters, papillary groups with hyalinized stroma or fibrovascular cores, and isolated single cells. The predominant cell population had well defined or rarely indistinct cell borders and ample cytoplasm, which varied from clear, to microvesicular, to finely granular eosinophilic and scattered, large, vacuolated cells (Fig. 3B). The nuclei were round to oval, occasionally irregular, and had finely granular-to-clumped chromatin. Nucleoli were prominent in most cases and inconspicuous in others (Fig. 3C). Psammoma bodies and hyaline globules also were noted. Similar findings were appreciated in all cell blocks or CNBs (Fig. 3D). Overall, through their variety of patterns and morphologic features, the cytologic interpretation raised the suspicion for RCC, favoring clear cell, papillary, or an unusual type. In one instance, the presence of a putative second population of smaller cells distributed around acellular hyaline globules raised upfront the possibility of t(6;11) RCC.

An analysis of voided or catheterized urine also was very interesting, with cytospin slides revealing variably sized papillary clusters along with large cells that had clear-to-eosinophilic cytoplasm. Despite the presence of papillary clusters, the cytologic interpretations did not favor urothelial carcinoma, which was excluded with an UroVysion test in one instance. Instead, a clear cell RCC was favored.

Ancillary studies performed on CNBs and cell blocks of FNA and urine specimens revealed that the tumors were negative or focally positive for pancytokeratin,
negative for EMA, but consistently positive for CD10, indicating that these stains are very useful screening tests for translocation carcinomas. CAIX evaluation, which was performed in only one tumor, was negative.\textsuperscript{54} In contrast, AMACR was positive in all tumors tested\textsuperscript{37,53,54} and although, by itself, may have raised the possibility of a PRCC, coupled with negativity or very focal positivity for CK7, was unusual. It is noteworthy that, when performed, the melanocytic markers Melan A and HMB45, as well as cathepsin K, were negative.\textsuperscript{37,53,54} Most specific, TFE3 was positive in all cases tested,\textsuperscript{37,50,52-54} and molecular confirmation was obtained in 4 cases.\textsuperscript{46,51,54,55}

Overall, the cytologic features overlap to a certain degree with those of clear cell RCC, PRCC, and oncocytic RCC. However, the presence of various patterns and, in some cases, psammoma bodies, hyaline globules, or potentially a dual cell population, should alert cytopathologists to the possibility of an MiT family translocation RCC and trigger additional testing. Another significant differential diagnosis is represented by epithelioid angiomyolipoma (epithelioid PEComa); and, in this context, the Pax8 positivity\textsuperscript{48} and cytogenetic analysis prove to be the most useful tests in confirming an RCC.

Although specific reports of cytologic findings in t(6;11) RCC are not currently available, the findings and, most important, the diagnostic approaches illustrated in patients with Xp11 translocation RCC, including additional testing in younger patients when unusual patterns or a mixture of cytomorphologic patterns are noted, pave the way to capturing further entities for an accurate diagnosis. Although generally regarded as an RCC subtype with indolent behavior, metastases have been reported,\textsuperscript{14,45,56} leading to death in some patients.\textsuperscript{14}

Figure 3. (A-C) Fine-needle aspiration smears and (D) a resection sample of microphthalmia-associated transcription factor (MiT) family translocation renal cell carcinoma are shown. (A) A large cluster has a papillary configuration containing small globules of hyaline material (DiffQuik stain, original magnification x100). (B) Large cells have abundant, clear cytoplasm, and high-grade nuclei associated with hyaline material (DiffQuik stain, original magnification x400). (C) Cells have well defined borders, abundant clear or microvesicular cytoplasm, and naked nuclei in background (Papanicolaou stain, original magnification x400). (D) Histologic features include well defined cellular borders, high-grade nuclei, a psammoma body (arrow), and acellular hyaline material (H&E stain, original magnification x200).
Tubulocystic RCC

Tubulocystic RCC (TB RCC), which initially was designated to differentiate it from what was considered a low-grade collecting-duct carcinoma, was subsequently characterized in multiple studies. This rare entity, with <100 reported cases, occurs usually in asymptomatic, middle age patients and has a strong male predominance.

Imaging and gross findings describe a complex cortical or corticomedullary cystic lesion that is well circumscribed and usually encapsulated. Histologically, the tumor is composed of variously sized tubules and cysts, embedded in a fibrotic stroma, and lined by a single layer of cuboidal-to-flat epithelial cells with granular eosinophilic cytoplasm (Fig. 4A). The nuclei are large, with irregular contours and prominent nucleoli, resembling WHO/ISUP nucleolar grade 3 or 4. Immunophenotypically, these tumors are diffusely positive for CK7, AMACR, and CD10. The molecular pathogenesis is not entirely understood, and reports vary from loss of multiple chromosomes to gains of chromosomes 7 and 17, similar to PRCC. More recently, in a well characterized cohort of tumors that had a pure tubulocystic pattern, we observed more distinctive findings, including losses of chromosomes 9 and Y, gains at chromosome 17, as well as recurrent mutations in chromatin-modifying genes, such as KMT2C and KDM5C.

To our knowledge, there is only a single report of TB RCC cytology. It describes 2 cases, a primary renal lesion and a bone metastasis, that were sampled with FNA and CNBs. In both cases the aspirate smears were cellular and consisted of large sheets of cells with distinct borders and intercellular windows. The neoplastic cells had abundant, eosinophilic, granular cytoplasm; rare, cytoplasmic small vacuoles; and large nuclei with prominent nucleoli and occasional grooves. Smaller groups of cells with less variable cytoplasm also were noted, sometimes resembling spherules. The CNBs reproduced the characteristic histologic findings. The immunohistochemical profile, with CK7, AMACR, and CD10 positivity, supported the diagnosis and was correlated with that observed in resection specimens.

The cytologic findings raise several differential diagnoses, including RCC subtypes and non-RCC entities. On smears, PRCC is the most difficult differential diagnosis because of common features of lesional cells with abundant, granular cytoplasm and small groups resembling spherules. However, PRCCs reportedly exhibit more heterogeneity; the cells in spherules do not uniformly present with granular cytoplasm, and there is an associated eosinophilic single-cell population. On cell blocks or CNBs, the presence of cellular proliferations or papillary projections favor PRCC, because they are only rarely and focally encountered in TC RCC. Despite the clues described above, this differential remains difficult; and, given the overlapping ancillary immunohistochemical and molecular profiles, it is conceivable that a definitive interpretation may not be possible in several cases.

Differentiating clear cell RCC is more feasible, because tumor cells in TC RCC are more uniformly granular and are organized in large flat sheets with windows (Fig. 4B) rather than cohesive tridimensional structures (and CK7 positive). Similarly, chromophobe RCC and oncocytes, although composed of eosinophilic cells, present a
more dominant single-cell pattern and occasional binucleation. In addition, the CK7 positivity and the absence of thickened cytoplasmic membrane, raisinoid nuclei, and AMACR positivity argue against oncocytoma and chromophobe RCC, respectively.

In conclusion, although it is rare, with appropriate sampling and in the correct clinical and radiological context, a definitive cytologic interpretation of TC RCC or, in some cases, a more specific differential can be rendered. The majority of TC RCCs are identified incidentally at a low stage and have a good prognosis. However, as depicted in the single report discussed above and elsewhere, cases with bone or liver metastases or with unfavorable histology, such as poorly differentiated or sarcomatoid foci, have been reported. In this latter case, we emphasize the importance, as noted in the Vancouver classification, of not diagnosing tubulocystic carcinoma if a case has unclassified, poorly differentiated, or papillary areas. Indeed, we have observed that a substantial number of such cases represent FH-deficient RCC, as described below.

DISTINCTIVE RCC TYPES WITH STRONG HEREDITARY ASSOCIATIONS

One of the remarkable trends in recent years in the WHO classification of RCC has been the recognition of distinctive subtypes of RCC with strong hereditary associations, including syndromal neoplasia. To some extent, these tumor types can be viewed as the reverse concept of some of the most common types of RCC, such as conventional clear cell RCC or conventional PRCC, both of which present very commonly as sporadic tumors in individuals without a germline mutation or predisposition but also present as part of a hereditary cancer syndrome, such as von Hippel-Lindau syndrome and hereditary PRCC syndrome, respectively. In contrast to either of these tumors, which, if they arise in either syndrome, exhibit cytologic and histopathologic features identical to those of the wild-type equivalent, 2 newly adopted types, SDH-deficient RCC and HLRCC RCC, both exhibit distinctive histopathology that is currently thought to be strongly linked to germline mutation of the relevant gene. Coupled with their distinctive histopathology, these tumors exhibit strikingly different prognoses compared with each other and with other RCC types and strikingly different syndromal features, engendering important differential diagnostic and management consequences if encountered in an aspiration or other cytopathologic sample. Their features are described below follows.

**Fumarate Hydratase-Deficient RCC**

In the third edition of the WHO classification, HLRCC RCC was grouped as a subtype of a broader category of “familial RCC” and, based on subsequent scholarship, is recognized in the Vancouver classification and in the current WHO classification as a distinctive entity. These tumors are thought to arise almost exclusively in the setting of HLRCC, also known as Reed syndrome or multiple cutaneous and uterine leiomyomatosis (MCUL), which is characterized by a penetrant phenotype of cutaneous (approximately 70% of males and females) and uterine (approximately 70%-80%) leiomyomatosis and less penetrant (approximately 20%) high-grade RCC. Affected individuals harbor loss-of-function mutations or deletions of the FH gene on chromosome 1. Although it originally was characterized as a high-grade RCC with predominantly papillary features, greater experience has characterized a wide range in tumor histopathology and architecture, including papillary, collecting-duct carcinoma (infiltrative tubular adenocarcinoma), solid, and cribriform patterns. Prevalent in every case are high-grade nucleolar features with prominent, viral inclusion-like macronucleoli and perinucleolar halos of pallor apparent in the nucleoplasm (Fig. 5A,B). Moreover, and perhaps pertinent to the above-mentioned cases of TC RCC demonstrating clinical aggression, a significant subset of these cases have a striking tubulocystic pattern, particularly in conjunction with a poorly differentiated, infiltrative adenocarcinomatous component. Both the tubulocystic pattern and a pattern of intracystic papillary growth, often with hyalinized fibrovascular cores, have been useful in the discrimination of these tumors from simulants, such as collecting-duct carcinoma or renal medullary carcinoma. Most recently, it has been demonstrated that the sheer number or multiplicity of the patterns present is suggestive of these tumors. These tumors are remarkably clinically aggressive, with the vast majority in the larger cohorts demonstrating metastasis, often at presentation, and death from disease in less than 2 years.

We recently studied the features of well characterized FH-deficient RCCs, including large numbers of bona fide HLRCC-RCCs in individuals who had
proven germline $FH$ mutations.\textsuperscript{83} Across a wide variety of sample types, including effusions and aspirations of primary or metastatic, $FH$-deficient RCCs, we noted that cytologic samples, which frequently were moderately cellular, exhibited large, pleomorphic cells, often in tridimensional clusters or abortive papillae. The character of the cytoplasm, which usually was most apparent in Diff-Quik–stained samples, was voluminous and finely vacuolated, and a few cases had larger vacuoles. Many cases, at least focally, exhibited an unusual pattern of two-toned cytoplasm, with the appearance of clearing or lighter staining of peripheral cytoplasm (Fig. 5C). Most distinctive were the nuclear features; the aforementioned viral inclusion-like nucleolus often was present (Fig. 5D), although the appearance of the perinuclear halo generally was less apparent than that in histopathologic sections. One distinctive feature, which was present in a minority of cases, was that of intranuclear cytoplasmic pseudoinclusions, reminiscent of those observed in papillary thyroid carcinoma. CNBs and cell block samples also revealed suggestive features, some echoing the histopathologic features described above.

The cytologic differential diagnosis includes several entities, generally other high-grade RCCs. In the metastatic setting, the most common entity is conventional clear cell RCC, which may exhibit cellular samples with abundant, vacuolated cytoplasm, albeit generally with less prominent nucleolar features.\textsuperscript{8} It is worth mentioning in this setting that CAIX may be positive in $FH$-deficient RCC,\textsuperscript{81,84} and should not be interpreted as supportive of classification as clear cell RCC. We note that Xp11 translocation RCCs also may exhibit voluminous cytoplasm and high-grade nuclear features,\textsuperscript{52} although such tumors often have weaker/patchy

![Figure 5](image-url)
Cytokeratin expression and expression of melanocytic markers like HMB45 and Melan A. Given the relatively frequent papillary pattern in FH-deficient RCC, conventional PRCC deserves mention. In this regard, in our review of cytologic features of FH-deficient RCCs, we have not observed the abundance of foamy macrophages or the relatively uniform appearance of cells reported in conventional PRCC.8,85 Certainly, the low-grade, monomorphic appearance of CCP RCC29 was not simulated by any FH-deficient RCC. The greatest challenge may be between FH-deficient RCC and the high-grade, so-called “type 2” PRCCs sampled in cytology.86 Overall, our bias is to regard many such tumors as unclassified and to recommend the use of FH and S-[2-succino]2SC immunostains, which are often lost/reduced and strongly nucleocytoplasmic positive, respectively, in FH-deficient tumors. This “type 2” group also likely includes an emerging group of unclassified RCCs with TFEB amplification and melanocytic differentiation,87-90 which can simulate the nucleolar features of FH-deficient RCC and for which FH and 2SC immunostains can be quite helpful.

Succinate Dehydrogenase-Deficient RCC

One additional group of RCCs is that of SDH-deficient RCC, which is considered an emerging/provisional entity in the Vancouver classification14 and has been formalized as a distinctive entity in the WHO classification.27 These tumors arise in the setting of germline mutation of one of the subunits of the SDH complex (SDHA, SDHB, SDHC, or SDHD), most frequently SDHB in RCC. Germline mutations of the SDH complex are associated with the familial multiple paraganglioma/pheochromocytoma syndromes (PGL1, PGL2, PGL3, and PGL4), which include both paragangliomas and epithelioid gastrointestinal stromal tumors. Renal tumors were previously considered an additional, infrequent syndromal feature, which, using SDHB immunohistochemistry, were established as a specific manifestation through a “two-hit” tumor-suppressor model.91 SDHB immunohistochemistry has the useful property of being able to triage for mutation/loss of function of any of the SDH complex subunits because of the instability of the monomeric SDHB subunit.92 Although SDH-deficient RCCs are much less aggressive than FH-deficient RCCs, metastatic progression has been reported in approximately 10% to 20% of cases,93,94 which is likely greater than that reported on oncotic tumors, such as chromophobe RCC. Prospective recognition of these tumors, whether by clinical correlation or use of SDHB immunostaining, also is important for evaluating the risk of paragangliomas, which tend to be aggressive when arising in this syndrome.95

The kidney tumors arising in this scenario exhibit a pattern of usually low-grade, oncotic RCC with a cytologically uniform, well circumscribed, solid, nested, and often focally tubular neoplasm of polygonal cells with eosinophilic cytoplasm and low-grade nuclei. (B) A direct smear reveals small clusters of cells with abundant, granular cytoplasm and nuclei with round contours and uniform chromatin distribution, imparting a neuroendocrine appearance (Papanicolaou stain, original magnification x400).
with dense pink inclusions (Fig. 6A). The tumors tend to show weak staining with broad-spectrum cytokeratins and lack the oncocytic RCC marker CD117, which highlights the often numerous admixed mast cells. To our knowledge, the aspiration cytologic findings from only a single SDH-deficient RCC have been reported to date.\(^9^3\) This case, an aspiration of a lung metastasis, demonstrated clusters of monotonous, low-grade–appearing epithelioid cells with granular cytoplasm on Diff-Quik stains. The distinctive neuroendocrine-like chromatin was highlighted on Papanicolaou staining (Fig. 6B). Some of the telltale cytoplasmic vacuoles with inclusions were observed on the cell block, which was SDH-deficient on immunostaining, emphasizing the utility of this marker in triage of these cases.

**DISCUSSION**

The new RCC subtypes included into the 2016 fourth edition WHO classification are rare entities, and their cytologic features have been described on relatively small numbers of cases. However, prior reports and the current review emphasize that, with appropriate awareness, these RCC subtypes can be diagnosed in cytology specimens. Each entity has a spectrum of unique cytomorphologic and ancillary testing profiles that, in the context of appropriate sampling, will render an accurate diagnosis or a significant, limited differential diagnosis to set up appropriate management. The tables summarize the clinical settings (Table 1), cytologic features (Tables 2 and 3), and characteristic immunohistochemical and molecular findings of these variants (Table 4).

Although we argue that it is an emerging responsibility for the diagnostic pathologist to recognize these tumors prospectively, there are significant challenges.

The defining cytologic features of these variants highlight a spectrum of neoplasms that have overlapping findings among each other and, most important, with most common RCC subtypes (Tables 2 and 3). However, each entity has at least a few distinctive features, from unique architectural patterns, to large or small cells with various cytoplasmic characteristics, to nuclei with specific intracellular distribution, chromatin, or nucleoli appearance. When present, unusual findings, such as oxalate crystals, psammoma bodies, hyaline globules, or stromal fragments, should further raise the possibility of a special tumor type. Finally, the multiplicity of coexisting patterns is sometimes most suggestive of these tumors. When enough consideration is taken, in most cases, the subsequent ancillary studies will support a specific diagnosis.

The diagnosis of these entities may be rendered for both primary and metastatic lesions sampled by FNA or CNB (Table 1). Rapid on-site evaluation (ROSE) of either aspirates or touch preparation smears can help ensure that sufficient material is collected for morphologic diagnosis. Because there are no defined adequacy criteria for renal FNA, general ROSE principles of adequate cellularity with minimal necrotic material contamination should be used.\(^1\) In certain instances, the specimen cellularity becomes key to the diagnosis. Although increased representation of a monomorphic population may be the most reliable indicator of a neoplastic process, the presence of atypical but sparse cells should limit the diagnosis to “suspicious,” especially in the context of sampling cystic lesions.

Both diagnostic clues and pitfalls may be provided by background benign renal elements, particularly in the context of low-cellularity sampling of renal cystic lesions. The presence of benign renal tubular cells may facilitate the diagnosis of a small but contrasting, clonal-appearing neoplastic cell population in certain RCC subtypes, particularly TC RCC and CCP RCC. Conversely, degenerative or reactive changes, such as hyperchromasia accompanied by poorly preserved nuclear detail or atypia noted predominantly in naked nuclei, may mimic malignancy. Therefore, when these changes are suspected, caution should be used before rendering a malignant diagnosis, especially in sparse specimens.

In addition to cytologic features, specific diagnoses most often require immunohistochemical, cytogenetic, and/or molecular analyses (Table 4). Thus, a specific task on ROSE is the collection of sufficient material for ancillary testing, which can be adequately performed on CNBs, cell blocks or even smears, and cytospin preparations.\(^9^6\) The diagnostic material procurement protocols may be adjusted by various institutions to best suit their laboratory practices and resources.

Another significant adjunct to an accurate diagnosis is the integration of clinical and radiologic findings. Special consideration should be given to entities that have an increased prevalence in various clinical settings, as detailed above. These range from specific RCC
subtypes being identified in young patients, some with a male predominance; to end-stage kidney disease and acquired cystic changes, especially after long-term dialysis; and, finally, to hereditary associations. In addition, although some tumors lack metastatic potential, others display aggressive behavior and should be considered in the differential diagnosis of metastases, sometimes at their initial presentation. The radiologic features of kidney masses also are significantly important. For cystic lesions, consideration should be given to RCC types such as CCP RCC, TC RCC, as well as related entities (ie, multilocular cystic renal tumor of low malignant potential) or unrelated entities (eg, mixed epithelial and stromal tumor). Other findings, such as large tumor size with a significant solid component or aggressive features, such as extrarenal extension or vascular involvement, should preclude diagnoses in small cytology samples of RCC subtypes that otherwise have predicted, rather indolent behavior.

Finally, we acknowledge that particular challenges pertain to the hereditary entities. The diagnostic terminology used by the WHO complicates the diagnosis by essentially labeling such a tumor as a syndrome, a standard that requires genetic consultation and workup usually unavailable at case sign out. Although the hallmark of FH-deficient RCC has been described as the

### TABLE 1. Patients Who Had New Renal Cell Carcinoma Entities With Reported Cytologic Findings

| RCC Type                                      | No. of Patients | Age, y | Sex       | Clinical Setting                  | Cytology Specimens |
|----------------------------------------------|----------------|--------|-----------|-----------------------------------|--------------------|
| Tubulocystic RCC (Renshaw & Gould 2018)      | 2              | 50 and 63 | Male      | Renal mass; metastasis to bone    | TP, CNB, FNA, CB   |
| Clear cell papillary RCC                     | 13             | 34-74  | Male and female | Renal mass, sporadic; renal mass, ESRD | TP, CNB, FNA, CB   |
| Acquired cystic disease-associated RCC       | 3              | 39-69  | Male      | Renal mass, ACKD; metastases to abdomen | TP, FNA, CB        |
| MIT family translocation RCC                 | 8              | 1-58   | Male and female | Renal mass; metastases to lung, mediastinal LN; urine | TP, CNB, FNA, CB, cytopsins |
| HLRCC-RCC (Shyu 2018)                        | 18             | 22-69  | More males than females | Renal mass; metastases to liver, LN, adrenal, chest wall; effusions-pleural and ascites | TP, CNB, FNA, CB, cytopsins |
| SDH-deficient RCC (Williamson 2015)          | 1              | 40     | Female    | Metastasis to lung                | FNA, CB            |

**Abbreviations:** ACKD, acquired cystic kidney disease; CB, cell block; CNB, core-needle biopsy; ESRD, end-stage renal disease; FNA, fine-needle aspiration smears; HLRCC-RCC, hereditary leiomyomatosis and renal cell carcinoma syndrome-associated renal cell carcinoma; LN, lymph node; MIT, microphthalmia-associated transcription factor; RCC, renal cell carcinoma; TP, touch preparation.

### TABLE 2. Cytologic Features of Low Nucleolar Grade Tumors

| RCC Type                              | Clear Cell Papillary RCC                                                                 | SDH-Deficient RCC                                                                 |
|---------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Cellularity                           | Variable, generally moderate                                                             | Low                                                                             |
| Presentation                          | Sheets, small nests/strips, or papillary clusters; occasional tubular/acinar pattern     | Clusters                                                                        |
| Cells                                 | Monomorphic                                                                              | Monomorphic                                                                     |
| Nucleus                               | Medium-sized with, ill-defined borders                                                  | Small                                                                           |
| Nuclei                                | Cuboidal                                                                                  | Cuboidal                                                                        |
| Cytoplasm                             | Moderately clear, or small vacuoles                                                      | Neuroendocrine-like chromatin, inconspicuous nuclei                              |
| Other                                 | Macrophages in background, not associated with fibrovascular cores; smooth muscle stromal fragments | Eosinophilic, granular                                                          |
| Differential diagnoses                | CCRCC, PRCC-1, MCN LPM, angiomyolipoma                                                  | Oncocytic renal neoplasm                                                       |
| Cytology: diagnostic clues            | Small clusters, eccentrically placed nuclei                                              | Neuroendocrine-like chromatin                                                  |
| Clinical setting                      | Sporadic, ESRD                                                                          | Young adults, personal or family history                                         |
| Imaging findings                     | Small, solitary, renal cortex; solid and cystian                                         | Mostly solitary, confined to the kidney                                         |

**Abbreviations:** CCRCC, clear cell renal cell carcinoma; ESRD, end-stage renal disease; MCN LPM: multilocular cystic neoplasm of low malignant potential; PRCC-1, papillary renal cell carcinoma type 1; RCC, renal cell carcinoma; SDH, succinate dehydrogenase.
markedly enlarged, cytomegalovirus viral inclusion-like nucleolus, often with a perinucleolar halo of pallor, this feature may be present in other high-grade, unrelated RCCs of various types. In contrast, recent studies have used FH immunohistochemistry, with or without 2SC immunohistochemistry, to label tumors phenotypically and provisionally as “FH-deficient,” a diagnostic term we recently proposed that does not appear to make a genetic diagnosis still relevant to (probably rare) tumors arising sporadically by somatic FH mutation.

| RCC Type                     | Tubulocystic RCC | Acquired Cystic Disease-Associated RCC | FH-Deficient RCC | MIT Family Translocation RCC |
|------------------------------|------------------|---------------------------------------|------------------|------------------------------|
| Cellularity                  | Variable         | Moderate to high                      | Moderate         | Moderate to high             |
| Presentation                 | Large flat sheets with intercellular windows; occasional, small, spherule-like clusters | Papillary clusters, sheets with spaces suggesting cribriform pattern | Tridimensional clusters, abortive papillae | Variably sized clusters, papillary fragments, isolated cells |
| Cells                        | Large cells, well defined borders, abundant cytoplasm; smaller cells have scant cytoplasm | Medium to large, well defined borders | Large, well defined borders | Large, well defined borders; rarely second population of smaller cells |
| Nucleus                      | Large, prominent nucleoli, rare grooves | Round, centrally placed; prominent nucleoli | Pleomorphic, inclusion-like, macronucleoli nuclear pseudo-inclusions | Round to oval, sometimes irregular; mostly prominent nucleoli |
| Cytoplasm                    | Abundant, eosinophilic, granular; rare intracytoplasmic vacuoles | Abundant, eosinophilic, granular; rarely clear | Abundant, finely vacuolated, peripheral clearing | Abundant, variable; clear, granular, eosinophilic, microvesicular, or large vacuoles |
| Other                        | Oxalate crystals associated with cell clusters | Inflammatory background: chronic or mixed | Psammoma bodies, acellular hyaline globules, naked nuclei | Psammoma bodies, acellular hyaline globules, naked nuclei |
| Differential diagnoses       | PRCC, ORCC, MITRCC, CCRCC, FHD RCC | PRCC-2 | CCRCC, PRCC-2, MITRCC | CCRCC, PRCC, ORCC, epithelioid angiomyolipoma |
| Cytophysiology: diagnostic clues | Abundant granular cytoplasm, occasional two-cell populations | Cribriform-like lumina in cell sheets, oxalate crystals | Large cells, inclusion-like macronucleoli, two-tone cytoplasm on Diff-Quik, pseudo-inclusions on Pap | Large cells with abundant cytoplasm, psammoma bodies, hyaline material more evident in Diff-Quik |
| Clinical setting             | Sporadic, middle age, males > females | End-stage renal disease, acquired cystic disease | Hereditary leiomyomatosis-RCC syndrome | Mostly pediatric, mean and median patient age 31 y |
| Imaging findings             | Solitary, cystic, subcapsular | Multiple or bilateral; arises in cysts or as solid masses; hemorrhage, necrosis | Frequently presents as metastatic disease | Solid with cystic areas |

**Table 3. Cytologic Features of High Nucleolar Grade Tumors**

| Abbreviations: CCRCC, clear cell renal cell carcinoma; FHD RCC, fumarate hydratase-deficient renal cell carcinoma. MITRCC, microphthalmia-associated transcription factor family translocation renal cell carcinoma; ORCC, oncocytic renal cell carcinoma; Pap, Papanicolaou stain; PRCC papillary renal cell carcinoma; PRCC-2, papillary renal cell carcinoma type 2. |

**Table 4. Diagnostic Ancillary Studies of New Renal Cell Carcinoma Subtypes**

| RCC Type                     | Diagnostic Immunohistochemical Profile | Cytogenetic Analysis |
|------------------------------|---------------------------------------|----------------------|
| Tubulocystic RCC             | CK7 (+), AMACR (+), Pax8 (+), CD10 (+) | Gains chrs 7, 17; loss of multiple chrs |
| Clear cell papillary RCC     | CK7 (+), CAIX (+ cup-like), CD10 (+ luminal), HMWCK (+), cyclinD1 (+); AMACR (+) | Gains chrs 3, 7, 16, 17, Y FISH TFE3/TFEB |
| Acquired cystic disease-associated RCC | AMACR (+), CD10 (+), CK7 (-), EMA (-) | Gains chrs 3, 7, 16, 17, Y FISH TFE3/TFEB |
| MIT family translocation RCC | TFE3 (+), Melan A (+), HMB45 (+), cathepsin K (+); Pax8 (+), CD10 (+), RCC (+); CK A1/A3 (-), EMA (-/rare, focally +); AMACR (-), CAIX (-), c-KIT (+/-) | Unknown |
| FH-deficient RCC             | FH (-) or decreased, 2SC strong nucleocytoplasmic (+), Pax8 (+), CAIX (+) | Unknown |
| SDH-deficient RCC            | SDHB (+), keratin (weak+), c-KIT (-), Pax8 (+) | Unknown |

Abbreviations: (-), negative; (+), positive; 2SC, 2-succinocystine; Chrs, chromosomes; FH, fumarate hydratase; FISH, fluorescence in situ hybridization; RCC, renal cell carcinoma; SDH, succinate dehydrogenase.
Although consensus recommendations regarding the use of FH immunostains for triage of RCC cases are not available, for prospective workup of cytologic samples, we emphasize a careful review of cytologic features (nucleolar prominence, suggestion of perinucleolar halo, intranuclear pseudoinclusions, two-toned cytoplasm) or hints at architectural patterns characteristic of these tumors (tubulocystic pattern, intracystic papillary with hyalinized cores) as morphologic triggers for this stain. Certainly in the setting of any syndromal stigmata or history, young age, or early metastasis from a clinically small tumor would trigger an FH immunostain in our practice as well.

However, although experience is even more limited, we use SDHB immunostains for any cytologic (or surgical) sample of a morphologically suggestive (especially cytoplasmic vacuolation) oncocytic renal tumor. We also currently use SDHB immunostaining for the workup of any oncocytic renal tumor that exhibits unclassified morphology (not characteristic of oncocytoma, chromophobe, or eosinophilic solid and cystic RCC, etc), and particularly if there is any suggestion of a hereditary disposition (often clinical multifocality). We acknowledge that this approach results in additional use of stains and additional cost, although the recognition of hereditary disease is paramount for family members. We also note that approaches like these have been significant in the detection of a priori, unrecognized, FH-deficient and SDH-deficient tumors in otherwise unclassifiable cases in retrospective cohorts. With use of these newer tools, and especially with clinicopathologic correlation, prospective recognition of these tumors and triage for genetic counseling has become a real possibility, whether based on surgical specimens or cytologic samples.

We anticipate future updates to the classification of RCC; in the few years since publication of the fourth edition WHO classification, several new entities have very rapidly come to light and are being studied in increasing detail. One striking example is that of the tumor called eosinophilic solid and cystic RCC. Recognized first as a pattern of carcinoma arising in the setting of tuberous sclerosis complex (TSC), which exhibited granular, eosinophilic, and variable cystic morphology, and then, sporadically, most frequently in middle-aged women, with somatic mutations in the TSC1/TSC2 pathway. Histologically, these tumors demonstrate variably dense solid and cystic architecture but are most characteristic for striking eosinophilic cytoplasm with granular cytoplasmic stippling, often with multinucleate, hobnail-shaped cells protruding into cystic spaces. Whereas these tumors appear to be relatively indolent, metastatic progression has been described; although cytologic samples have not been described, the distinctive and consistent expression of CK20 by these tumors deserves mention for use in their triage. Another example of a rapidly emerging tumor type includes biphasic squamoid alveolar PRCCs which are now recognized as a variant of PRCC with frequent multifocality and distinctive histopathology, including two cell populations, the first with classic PRCC features and the other with a variously prominent subset of larger cells with eosinophilic cytoplasm, emperipolysis, and higher nucleolar grade. A subset of these variants, perhaps somewhat more than conventional PRCC, demonstrate progression; and, although the features of cytologic samples have not been described, characteristic expression of cyclin D1 in the larger cell population may be helpful in prospective recognition. We would also mention an emerging group of tumors in the differential of high-grade infiltrative RCC that have histopathology essentially identical that of renal medullary carcinoma but arise in individuals in whom sickle cell trait or disease has been excluded; for this reason, we have proposed to designate these tumors as unclassified RCCs with medullary phenotype. They exhibit poorly differentiated, infiltrative glandular, solid, and rhabdoid features with inflamed desmoplastic stroma, marked aggression, and a prognosis similar to that of renal medullary carcinoma in the patients who have been described. Fortunately, similar to renal medullary carcinoma, loss of SMARCB1/INI1 expression is characteristic, as is the induction of OCT4 expression, which can help prospectively identify such cases.

**FUNDING SUPPORT**
No specific funding was disclosed.

**CONFLICT OF INTEREST DISCLOSURES**
Steven Christopher Smith reports royalties from Elsevier/Amrisys Publishing outside the submitted work. Valentina Robila and Adele O. Kraft made no disclosures.
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37. Yamaguchi T, Kuroda N, Imamura Y, Hes O, Kawada T, Nakayama K. Immunocytologic features in renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusion in an adult: a case report. Acta Cytol. 2009;53:693-697.

38. Kuroda N, Yamashita M, Kakehi Y, Hes O, Michal M, Lee GH. Acquired cystic disease-associated renal cell carcinoma: an immunohistochemical and fluorescence in situ hybridization study. Mod Mol Morphol. 2011;44:228-232.

39. Pan CC, Chen YJ, Chang LC, Chang YH, Ho DM. Immunohistochemical and molecular genetic profiling of acquired cystic disease-associated renal cell carcinoma. Histopathology. 2009;55:145-153.

40. Enoki Y, Katoh G, Okabe H, Yanagitawa A. Clinicopathological features and CD57 expression in renal cell carcinoma in acquired cystic disease of the kidneys: with special emphasis on a relation to the duration of haemodialysis, the degree of calcium oxalate deposition, histological type, and possible tumorigenesis. Histopathology. 2010;56:384-394.

41. Kuroda N, Tamura M, Hamaguchi N, et al. Acquired cystic disease-associated renal cell carcinoma with sarcomatoid change and rhabdoid features. Ann Diag Pathol. 2011;15:462-466.

42. Argani P, Hawkins A, Griffin CA, et al. A distinctive pediatric renal neoplasm characterized by epithelioid morphology, basal membrane production, focal HMB45 immunoreactivity, and t(6;11)(p21.1;q12) chromosome translocation. Am J Pathol. 2001;158:2089-2096.

43. Magers MJ, Udager AM, Mehra R. MIT family translocation-associated renal cell carcinoma: a contemporary update with emphasis on morphologic, immunophenotypic, and molecular mimics. Arch Pathol Lab Med. 2015;139:1224-1233.

44. Argani P. MIT family translocation renal cell carcinoma. Semin Diagn Pathol. 2015;32:103-113.

45. Rao Q, Liu B, Cheng L, et al. Renal cell carcinomas with t(6;11)(p21;q12): a clinicopathologic study emphasizing unusual morphology, novel alpha-TFEB gene fusion point, immunohistomarkers, and ultrastructural features, as well as detection of the gene fusion by fluorescence in situ hybridization. Am J Surg Pathol. 2012;36:1327-1338.

46. Manucha V, Sessums MT, Lewin J, Akhtar I. Cyto-histological correlation of Xp11.2 translocation/TFE3 gene fusion associated renal cell carcinoma: a report of a case with review of literature. Diagn Cytopathol. 2018;46:267-270.

47. Argani P, Antonescu CR, Courtier J, et al. PRCC-TFE3 renal cell carcinomas: morphologic, immunohistochemical, ultrastructural, and molecular analysis of an entity associated with the t(X;1)(p11.2;q21). Am J Surg Pathol. 2002;26:1553-1566.

48. Smith NE, Illei PB, Allaf M, et al. T(6;11) renal cell carcinoma (RCC): expanded immunohistochemical profile emphasizing novel RCC markers and report of 10 new genetically confirmed cases. Am J Surg Pathol. 2014;38:604-614.

49. Martignoni G, Pea M, Gobbo S, et al. Cathepsin-K immunoreactivity distinguishes MITF-TFE family renal translocation carcinomas from other renal carcinomas. Med Pediatr Oncol. 2009;42:1016-1022.

50. Mansouri D, Dimet S, Couanet D, et al. Renal cell carcinoma with an Xp11.2 translocation in a 16-year-old girl: a case report with cytological features. Diagn Cytopathol. 2006;34:757-760.

51. Barroca H, Correia C, Castedo S. Cytopathologic and cytogenetic diagnosis of pediatric renal cell carcinoma associated with t(X;17). Acta Cytol. 2008;52:384-386.

52. Schinstine M, Filice AC, Torres-Cabala C, Abati A, Linehan WM, Merino M. Fine-needle aspiration of an Xp11.2 translocation/TFE3 fusion renal cell carcinoma metastatic to the lung: report of a case and review of the literature. Diagn Cytopathol. 2006;34:751-756.

53. El Naiidi R, Nicolas M, Gorena A, Policaarpio-Nicolás ML. Fine-needle aspiration findings of Xp11 translocation renal cell carcinoma metastatic to a hilar lymph node. Diagn Cytopathol. 2017;45:456-462.

54. Kuroki M, Murai Y, Endo Y, Masago T, Kuroda N, Horie Y. Cytologic features of renal cell carcinoma associated with Xp11.2 translocations/TFE3 gene fusions: a case report with voided and catheterized urine cytology and a literature review. Acta Cytol. 2014;58:406-412.

55. Moltrasio F, Brenna A, Bovo G, et al. Pathological features of Xp11 translocation renal cell carcinoma using urine liquid-based cytology with Fish. Cytopathology. 2015;26:325-328.

56. Argani P, Lee M, Hutchinson B, et al. Renal carcinomas with the t(6;11)(p21;q12): clinicopathologic features and demonstration of the specific alpha-TFEB gene fusion by immunohistochemistry, RT-PCR, and DNA PCR. Am J Surg Pathol. 2005;29:230-240.

57. Murphy WM, Beckwith JB, Farrow GM, Armed Forces Institute of Pathology (US). Universities Associated for Research and Education in Pathology. Tumors of the Kidney, Bladder, and Related Urinai Structures. Washington, DC: Available from the American Registry of Pathology, Armed Forces Institute of Pathology; 1994.

58. MacLennan GT, Cheng L. Tubulocystic carcinoma of the kidney. J Urol. 2011;185:2348-2349.

59. Amin MB, MacLennan GT, Gupta R, et al. Tubulocystic carcinoma of the kidney: clinicopathologic analysis of 31 cases of a distinctive rare subtype of renal cell carcinoma. Am J Surg Pathol. 2009;33:384-392.

60. Yang XJ, Zhou M, Hes O, et al. Tubulocystic carcinoma of the kidney: clinicopathologic and molecular characterization. Am J Surg Pathol. 2008;32:177-187.

61. Azoulay S, Vieillefond A, Paraf F, et al. Tubulocystic carcinoma of the kidney: a new entity among renal tumors. Virchows Arch. 2007;451:905-909.

62. Zhou M, Yang XJ, Lopez JJ, et al. Renal tubulocystic carcinoma is closely related to papillary renal cell carcinoma: implications for pathologic classification. Am J Surg Pathol. 2009;33:1840-1849.

63. Chen N, Nie L, Gong J, et al. Gains of chromosomes 7 and 17 in tubulocystic carcinoma of the kidney: 2 cases with fluorescence in situ hybridization analysis. J Clin Pathol. 2014;67:1006-1009.

64. Sarungbam J, Mehra R, Tomlins SA, et al. Tubulocystic renal cell carcinoma: a distinct clinicopathologic entity with a characteristic genomic profile. Mod Pathol. published online January 2010.

65. Renshaw AA, Gould EW. Fine-needle aspiration of tubulocystic renal cell carcinoma. Diagn Cytopathol. 2008;36:267-270.

66. Iakovleva G, Iakovlev V, Ordon M, Srigley J, Yousef GM. Tubulocystic carcinoma of the kidney with poorly differentiated foci: a series of 3 cases with fluorescence in situ hybridization analysis. Virchows Arch. 2015;461:905-909.

67. Chen N, Nie L, Gong J, et al. Gains of chromosomes 7 and 17 in tubulocystic carcinoma of the kidney: 2 cases with fluorescence in situ hybridization analysis. J Clin Pathol. 2014;67:1006-1009.

68. Renshaw AA, Gould EW. Fine-needle aspiration of tubulocystic renal cell carcinoma. Diagn Cytopathol. 2008;36:267-270.

69. Al-Hussain TO, Cheng L, Zhang S, Epstein JI. Tubulocystic carcinoma of the kidney with rhabdoid features. Am J Surg Pathol. 2010;34:253-257.

70. Przybycin CG, Magi-Galluzzi C, McKenney JK. Hereditary syndromes with associated renal neoplasia: a practical guide to histologic and molecular recognition in renal tumor resection specimens. Urology. 2011;78:1071-1072.

71. Al-Hussain TO, Cheng L, Zhang S, Epstein JI. Tubulocystic carcinoma of the kidney with poorly differentiated foci: a series of 3 cases with fluorescence in situ hybridization analysis. Hum Pathol. 2013;44:1406-1411.

72. Moehl MC, Smith SC. Kidney tumors associated with hereditary cancer syndromes: an emerging opportunity and responsibility in surgical pathology. AJR Am J Roentgenol. 2017;22:313-328.

73. Przychyn CG, Magi-Galluzzi C, McKenzie JK. Hereditary syndromes with associated renal neoplasia: a practical guide to histologic recognition in renal tumor resection specimens. Adv Anat Pathol. 2013;20:245-263.

74. Adeniran AJ, Shuch B, Humphrey PA. Hereditary renal cell carcinoma syndromes: clinical, pathologic, and genetic features. Am J Surg Pathol. 2015;39:e1-e18.

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72. Ebene JN, Saiger G, Epstein J, Sesterhenn I, eds. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. WHO Classification of Tumours. 3rd ed. Volume 7. Lyon, France: IARC Press; 2004.

73. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs. pt A: Renal, Penile, and Testicular Tumours. Eur Urol. 2016;70:93-105.

74. Smit DL, Mensenkamp AR, Badeloe S, et al. Hereditary leiomyomatosis and renal cell cancer in families referred for fumarate hydratase germline mutation analysis. Clin Genet. 2011;79:49-59.

75. Muller M, Ferlicot S, Guillaud-Bataille M, et al. Reassessing the clinical spectrum associated with hereditary leiomyomatosis and renal cell carcinoma syndrome in French FH mutation carriers. Clin Genet. 2017;92:606-615.

76. Gardie B, Remenieras A, Kattyanrath D, et al. Novel FH mutations in families with hereditary leiomyomatosis and renal cell cancer (HLRCC) and patients with isolated type 2 papillary renal cell carcinoma. J Med Genet. 2011;48:226-234.

77. Toro JR, Nickerson ML, Wei MH, et al. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. Am J Hum Genet. 2003;73:95-106.

78. Alam NA, Barclay E, Rowan AJ, et al. Clinical features of multiple cutaneous and uterine leiomyomatosis: an underdiagnosed tumor syndrome. Arch Dermatol. 2005;141:199-206.

79. Merino MJ, Torres-Cabala C, Pinto P, Linehan WM. The morphologic spectrum of kidney tumors in hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. Am J Surg Pathol. 2007;31:1578-1585.

80. Smith SC, Trpkov K, Chen YB, et al. Tubulocystic carcinoma of the kidney with poorly differentiated foci: a frequent morphologic pattern of fumarate hydratase-deficient renal cell carcinoma. Am J Surg Pathol. 2016;40:1457-1472.

81. Muller M, Guillaud-Bataille M, Salleron J, et al. Pattern multiplicity and fumarate hydratase (FH)/S-(2-succino)-cysteine (2SC) staining but not eosinophilic nucleioli with perinuclear halos differentiate hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinomas from kidney tumors without FH gene alteration. Mod Pathol. 2018;31:974-983.

82. Trpkov K, Hes O, Agaimy A, et al. Fumarate hydratase-deficient renal cell carcinoma is strongly correlated with fumarate hydratase mutation and hereditary leiomyomatosis and renal cell carcinoma syndrome. Am J Surg Pathol. 2016;40:865-875.

83. Shyu I, Mirsadraei L, Wang X, et al. Clues to recognition of fumarate hydratase-deficient renal cell carcinoma: findings from cytologic and limited biopsy samples [published online ahead of print October 19, 2018]. Cancer Cytopathol. doi: 10.1002/ cncy.22071.

84. Udager AM, Alva A, Chen YB, et al. Hereditary leiomyomatosis and renal cell carcinoma (HLRCC): a rapid autopsy report of metastatic renal cell carcinoma. Am J Surg Pathol. 2014;38:567-577.

85. Granter SR, Perez-Atayde AR, Renshaw AA. Cytologic analysis of papillary renal cell carcinoma. Cancer. 1998;84:303-308.

86. Renshaw AA, Cibas ES. Kidney and adrenal gland. In: Cibas ES, Ducatman BS, eds. Cytology, 4th edn. New York; Elsevier; 2014:423-451.

87. Gupta S, Johnson SH, Vasmatzis G, et al. TFEB-VEGFA (6p21.1) co-amplified renal cell carcinoma: a distinct entity with potential implications for clinical management. Mod Pathol. 2017;30:998-1012.

88. Skala SL, Xiao H, Udager AM, et al. Detection of 6 TFEB amplified renal cell carcinomas and 25 renal cell carcinomas with MTFF translocations: systematic morphologic analysis of 85 cases evaluated by clinical TFE3 and TFEB FISH assays. Mod Pathol. 2018;31:179-197.

89. Martin EE, Mehra R, Jackson-Cook C, Smith SC. Renal cell carcinoma With TFEF translocation versus unclassified renal cell carcinoma with TFEB amplification. AJSP Rev Rep. 2017;22:305-312.

90. Williamson SR, Grignon DJ, Cheng L, et al. Renal cell carcinoma with chromosome 6 amplification including the TFEB gene: a novel mechanism of tumor pathogenesis. Am J Surg Pathol. 2017;41:287-298.

91. Gill AJ, Pachter NS, Clarkson A, et al. Renal tumors and hereditary pheochromocytoma-paraganglioma syndrome type 4. N Engl J Med. 2011;364:885-886.

92. Gill AJ, Benn DE, Chou A, et al. Immunohistochemistry for SDHB triages genetic testing of SDHB, SDHC, and SDHD in paraganglioma- pheochromocytoma syndromes. Hum Pathol. 2010;41:805-814.

93. Williamson SR, Ebene JN, Amin MB, et al. Succinate dehydroge- nase-deficient renal cell carcinoma: detailed characterization of 11 tumors defining a unique subtype of renal cell carcinoma. Mod Pathol. 2015;28:80-94.

94. Gill AJ, Hes O, Papathomas T, et al. Succinate dehydrogenase (SDH)-deficient renal cell carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients. Am J Surg Pathol. 2014;38:1588-1602.

95. Andrici J, Gill AJ, Hornick JL. Next generation immunohistochem- istry: emerging substitutes to genetic testing? Semin Diagn Pathol. 2018;35:161-169.

96. Dal Cin P, Qian X, Cibas ES. The marriage of cytology and cytoge- netics. Cancer Cytopathol. 2013;121:279-290.

97. Smith SC, Trpkov K, Mehra R, et al. Is tubulocystic carcinoma with dedifferentiation a form of HLRCC/fumarate hydratase-deficient RCC [abstract]? Mod Pathol. 2015;28(suppl 2):260A.

98. Cancer Genome Atlas Research Network, Linehan WM, Spellman PT, et al. Comprehensive molecular characterization of papillary re- nal-cell carcinoma. N Engl J Med. 2016;374:135-145.

99. Ohe C, Smith SC, Sirohi D, et al. Reappraisal of morphologic dif- ferences between renal medullary carcinoma, collecting duct carci- noma, and fumarate hydratase-deficient renal cell carcinoma. Am J Surg Pathol. 2018;42:279-292.

100. Smith SC, Sirohi D, Ohe C, et al. A distinctive, low-grade oncocytic fumarate hydratase-deficient renal cell carcinoma, morphologically reminiscent of succinate dehydrogenase-deficient renal cell carci- noma. Histopathology. 2017;71:42-52.

101. Li Y, Reuter VE, Matos A, Netto GJ, Epstein JI, Argani P. Re-evaluation of ‘3 Unclassified’ eosinophilic renal cell carcinomas in young patients. Histopathology. 2018;72:588-600.

102. Trpkov K, Hes O, Bonert M, et al. Eosinophilic, solid, and cystic renal cell carcinoma: clinicopathologic study of 16 unique, sporadic neoplasms occurring in women. Am J Surg Pathol. 2016;40:60-71.

103. Trpkov K, Abou-Ouf H, Hes O, et al. Eosinophilic solid and cystic renal cell carcinoma (ESC-RCC): further morphologic and molec- ular characterization of ESC RCC as a distinct entity. Am J Surg Pathol. 2017;41:1299-1308.

104. Guo J, Tretiakova MS, Trosell ML, et al. Tuberous sclerosis-associ- ated renal cell carcinoma: a clinicopathologic study of 57 separate carcinomas in 18 patients. Am J Surg Pathol. 2014;38:1457-1467.

105. Mehra R, Vats P, Cao X, et al. Somatic bi-allelic loss of TSC genes in eosinophilic solid and cystic renal cell carcinoma. Am J Surg Pathol. 2017;41:287-298.

106. Palsgrove DN, Li Y, Pratilas CA, et al. Eosinophilic solid and cystic renal cell carcinoma with TFEB translocation versus unclassified renal cell carcinoma With TFEB amplification: a study of 28 cases. Histopathology. 2018;72:777-785.
109. Singh JA, Ohe C, Smith SC. High grade infiltrative adenocarcinomas of renal cell origin: new insights into classification, morphology, and molecular pathogenesis. *Pathol Int*. 2018;68:265-277.

110. Amin MB, Smith SC, Agaimy A, et al. Collecting duct carcinoma versus renal medullary carcinoma: an appeal for nosologic and biological clarity. *Am J Surg Pathol*. 2014;38:871-874.

111. Sirohi D, Smith SC, Ohe C, et al. Renal cell carcinoma, unclassified with medullary phenotype: poorly differentiated adenocarcinomas overlapping with renal medullary carcinoma. *Hum Pathol*. 2017;67:134-145.

112. Scarpelli M, Mazzucchelli R, Lopez-Beltran A, et al. Renal cell carcinoma with rhabdoid features and loss of INI1 expression in an individual without sickle cell trait. *Pathology*. 2014;46:653-655.