REVIEW

Renal cell carcinoma: Evolving and emerging subtypes

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Author contributions: Crumley SM and Divatia M contributed equally to the writing of the text and revisions of the manuscript; Truong L contributed to the revisions and some of the photographs in the figures; Shen S and Ayala AG contributed to the revisions and editing of the manuscript; Ro JY contributed to the conception and revisions of the manuscript.

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Abstract

Our knowledge of renal cell carcinoma (RCC) is rapidly expanding. For those who diagnose and treat RCC, it is important to understand the new developments. In recent years, many new renal tumors have been described and defined, and our understanding of the biology and clinical correlates of these tumors is changing. Evolving concepts in Xp11 translocation carcinoma, mucinous tubular and spindle cell carcinoma, multilocular cystic clear cell RCC, and carcinoma associated with neuroblastoma are addressed within this review. Tubulocystic carcinoma, thyroid-like follicular carcinoma of kidney, acquired cystic disease-associated RCC, and clear cell papillary RCC are also described. Finally, candidate entities, including RCC with t(6;11) translocation, hybrid oncocytoma/chromophobe RCC, hereditary leiomyomatosis and RCC syndrome, and renal angiomyoadenomatous tumor are reviewed. Knowledge of these new entities is important for diagnosis, treatment and subsequent prognosis. This review provides a targeted summary of new developments in RCC.

Core tip: New concepts in selected renal cell carcinoma (RCC) subtypes are reviewed. We describe evolving concepts in Xp11 translocation carcinoma, mucinous tubular and spindle cell carcinoma, multilocular cystic clear cell RCC, and carcinoma associated with neuroblastoma. Additionally, tubulocystic carcinoma, thyroid-like follicular carcinoma of kidney, acquired cystic disease-associated RCC, and clear cell papillary RCC are described. Finally, candidate entities, including RCC with t(6;11) translocation, hybrid oncocytoma/chromophobe RCC, hereditary leiomyomatosis and RCC syndrome, and renal angiomyoadenomatous tumor are discussed. This review provides a targeted summary of recent updates for those who diagnose and treat renal cancer.

Crumley SM, Divatia M, Truong L, Shen S, Ayala AG, Ro JY. Renal cell carcinoma: Evolving and emerging subtypes. *World J Clin Cases* 2013; 1(9): 262-275 Available from: URL: http://www.wjgnet.com/2307-8960/full/v1/i9/262.htm DOI: http://dx.doi.org/10.12998/wjcc.v1.i9.262

INTRODUCTION

Many new discoveries have been made with regards to renal cell carcinoma (RCC) in recent years. At the recent meeting of the International Society of Urologic Pathology, the newly defined, recently described, and candidate entities within RCC were discussed. An understanding of these new subtypes is essential for the surgical
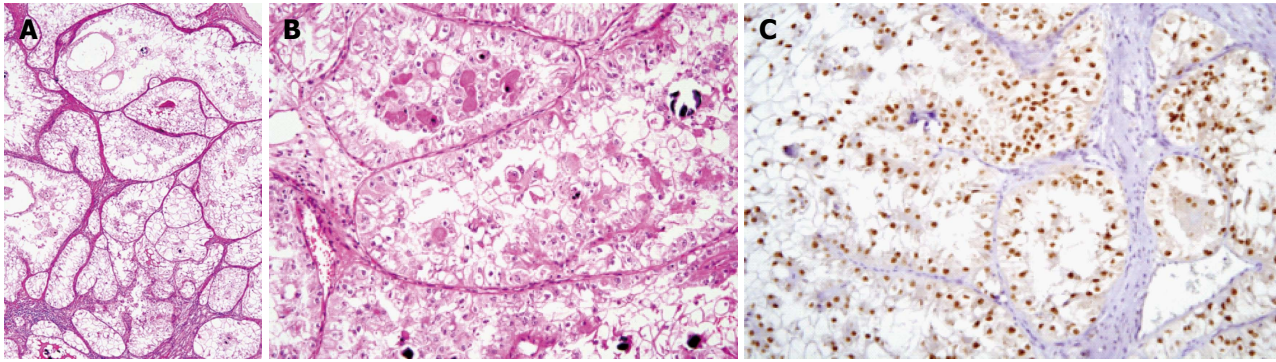
Figure 1 Xp11 translocation carcinoma (hematoxylin and eosin). A: The tumor is composed of cells with clear to eosinophilic, abundant voluminous cytoplasm (× 40); B: Psammoma bodies in stromal hyaline nodules are frequently seen, but are not required for diagnosis (× 100); C: TFE3 nuclear immunohistochemical stain can assist with confirmation of the diagnosis (× 100), but can also be positive in tumors without the molecular translocation.

pathologist and urologist. An awareness of the current knowledge among these physicians will enable effective communication for proper diagnosis, prognosis, and treatment.

The five traditional and well-defined subtypes of RCC (conventional clear cell, papillary, chromophobe, collecting duct, and unclassified) comprise the overwhelming majority of RCC, but will not be discussed in detail here. In this review, we discuss three categories of evolving and emerging entities of renal tumors. The first category includes the newly defined RCC subtypes, the second includes recently described entities and the final category includes candidate entities for RCC subtypes (Table 1). The category of recently described tumors includes neoplasms with accruing evidence that they should be considered independent subtypes. The category of candidate entities includes both renal carcinomas seen in familial cancer syndromes and neoplasms on which there is still speculation to whether they deserve designation as distinct entities. The tumors within all three categories have received much scrutiny in recent years with important updates.

NEWLY DEFINED RCC SUBTYPES

Xp11 translocation carcinoma

Xp11 translocation RCC was first established by the World Health Organization (WHO) as an independent subtype in 2004[1]. This tumor is defined by a translocation involving the *TFE3* gene with various gene partners, the most common of which are *ASPL* and *PRCC*. The name Xp11 translocation RCC comes from the chromosomal location of the *TFE3* gene (specifically Xp11.2). The tumor is defined by both papillary and clear cell morphology. These tumors can also have a nested architecture, and the type (location) of gene translocation may be reflected in the tumor morphology. *ASPL-TFE3* translocation carcinomas have more abundant cytoplasm and frequent psammoma bodies, while *PRCC-TFE3* translocations have less cytoplasm, less frequent psammoma bodies, and closely nested tumor cells[2]. In general, these tumors have voluminous, clear to eosinophilic cytoplasm, and well-defined cell borders[2-4] (Figure 1). Cystic

Table 1 Renal cell carcinoma subtypes

Renal cell carcinoma	
Newly defined subtypes	Xp11 Translocation RCC
	Mucinous tubular and spindle cell carcinoma
	Multilocular cystic clear cell RCC
	Carcinoma associated with Neuroblastoma
Recently described entities	Tubulocystic carcinoma
	Thyroid-like follicular carcinoma of kidney
	Acquired cystic kidney disease-associated RCC
	Clear cell papillary RCC
Candidate entities	RCC with t(6;11) translocation
	Hybrid oncocytoma/chromophobe RCC
	Hereditary leiomyomatosis and RCC syndrome
	Renal angiomyoadenomatous tumor

RCC: Renal cell carcinoma.

change, psammoma bodies, spindle cells, giant cells, and biphasic appearance have been described[5,6]. Grossly, they appear similar to clear cell RCC. Xp11 translocation RCC has traditionally been described as occurring more frequently in young adults and children. Recent reports speculate whether these carcinomas may be associated with chemotherapy[7].

These tumors are typically negative for cytokeratin and positive for CD10, RCC marker, vimentin, PAX2, and PAX8[3-5]. A strongly positive nuclear stain for the C-terminal of the *TFE3* gene product is indicative of Xp11 translocation RCC. However, recently, some have questioned the specificity of the TFE3 staining. A recent series by Klatte *et al*[8] examined 848 patients over a 20-year period and found 75 RCCs with features morphologically consistent with Xp11 translocation RCC or occurring in patients 40 years or younger. Of these 75 tumors, 17 (23%) tumors had strong nuclear TFE3 expression. However, only two of these cases had a translocation detected by FISH, yielding a dismal positive predictive value of 12%. This study suggests that the TFE3 immunohistochemical stain can also stain non-translocated *TFE3* product. The average age of patients with RCC positive for TFE3 immunohistochemical staining in this study was 33.4 years. Interestingly, this study also found that strong TFE3 expression in both non-translocated and translocated tu-
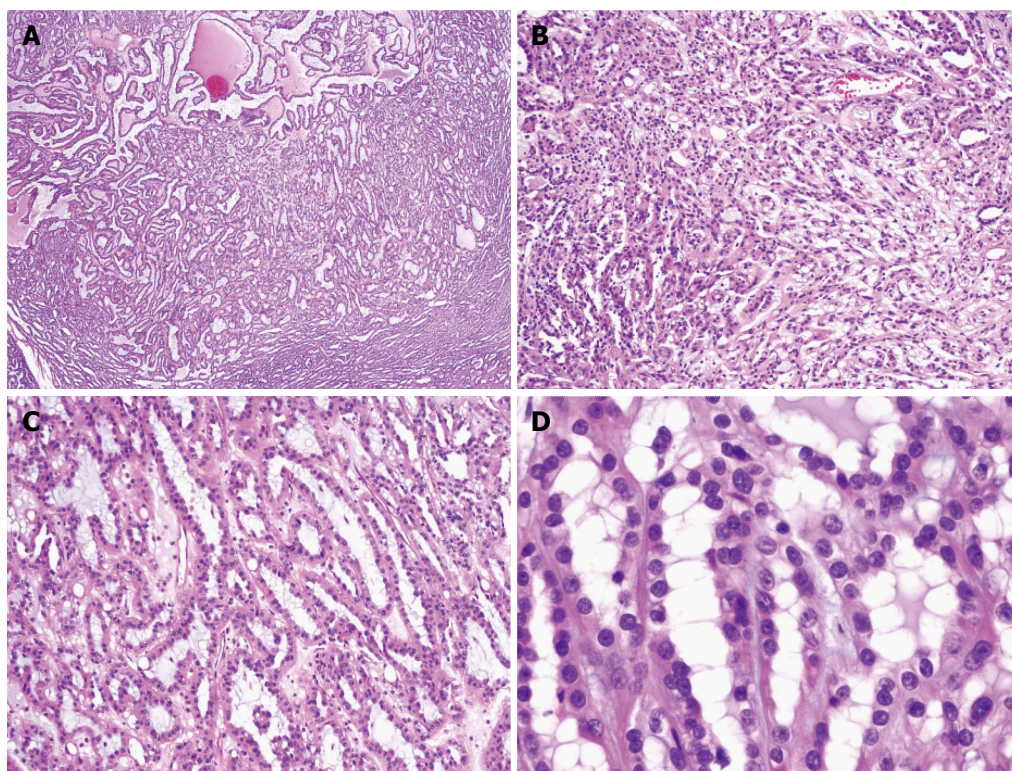
Figure 2 Mucinous and tubular spindle cell carcinoma (hematoxylin and eosin). A: The tumor has a tubular pattern on low power with mucin present between glands (× 20); B: In some areas, a spindle cell pattern is also seen (× 40); C: The tubular pattern with intervening mucin is prominent in some tumors (× 100); D: Round nuclei with prominent nucleoli are evident on higher power (× 400).

mors was associated with larger tumor size, lymph node involvement, and metastasis[8]. Positive TFE3 staining was also associated with worse survival in univariate analysis ($P = 0.032$), albeit this was not significant in multivariate analysis ($P = 0.404$). This evidence suggests that strong TFE3 immunohistochemical staining in adults may be informative for prognosis as well as diagnosis.

Traditionally, Xp11 translocation carcinoma is described primarily in children and young adults. However, recent studies have suggested the presence of these tumors in adults may go unrecognized. A recent study by Zhong *et al*[9] of 121 consecutive RCCs from 2001-2009 in adults at one institution found 6 tumors with Xp11 translocation for a frequency of 5%[9]. While in pediatric RCC, Xp11 translocation RCC has been found in up to one third of all tumors[3], RCC, in general, is much more frequent in adults than in children. Therefore, the majority of Xp11 translocation RCC may occur in the adult population. Additionally, in adults, these tumors may behave more aggressively and have an association with the female gender. Xp11 translocation RCC in adults has been found to present with advanced stage, lymph node metastases, and have a poor survival rate[5]. A recent commentary by Klaassen *et al*[10] in the *Journal of Urology* suggests that adult patients with Xp11 translocation RCC should be classified as high risk for metastasis. They suggest these patients should follow a vigilant surveillance protocol, which includes lifelong follow-up after diagnosis[10].

The differential diagnosis for Xp11 translocation RCC includes clear cell RCC, clear cell papillary RCC,

papillary RCC (especially type 2), and the closely related translocation 6;11 carcinoma (discussed below). The *TFE3* translocation is diagnostic for tumors with overlapping morphology. The diagnosis of Xp11 translocation RCC should be investigated in children and young-to-middle-aged adults with characteristic histology that is negative for cytokeratins[9]. New evidence suggests that if the classic morphology is present, the diagnosis should also be considered in adults. Based on these clinicopathologic features, we recommend a cytokeratin stain using a broad spectrum antibody in all RCCs diagnosed before the age of 30. If the cytokeratin is negative or weakly and focally positive, then proceed with a TFE3 stain and/or translocation study to confirm the diagnosis. A translocation carcinoma should be suspected in adults when papillary or nested pattern carcinoma, containing very voluminous clear to eosinophilic tumor cells (with or without psammoma bodies), are present, usually within hyaline stromal nodules. We recommend doing a similar battery of immunostains for RCCs of young adults and children.

Mucinous tubular and spindle cell carcinoma

Mucinous tubular and spindle cell carcinoma (MTSCC) is a fairly newly described tumor which is included in the 2004 WHO classification[11]. This is a tumor defined by the presence of three histologic components: mucin, tumor cells forming tubules, and spindle cells, herein earning its appropriately descriptive name (Figure 2). This tumor occurs throughout life (age range 17-82 years) and is more
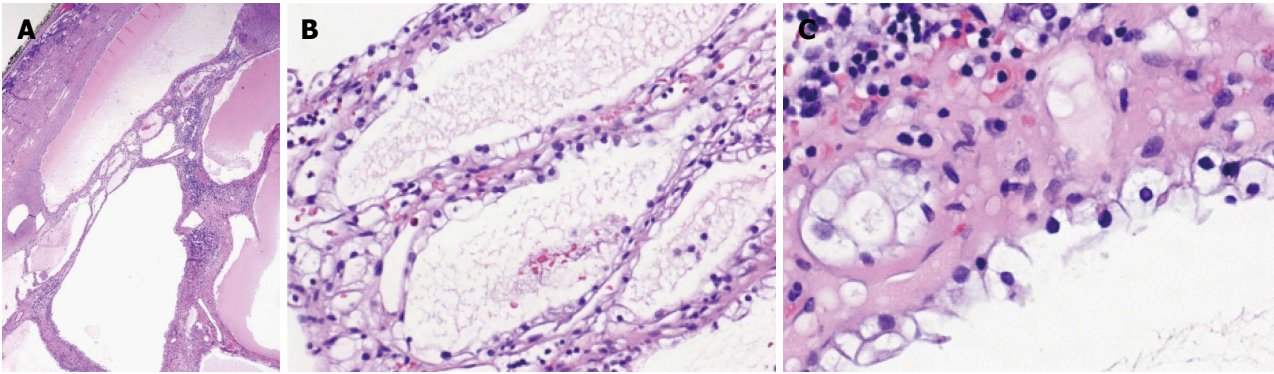
Figure 3 Multilocular cystic clear cell renal cell carcinoma (hematoxylin and eosin). A: The tumor is composed of multiple cysts with intervening thin, fibrous septa and scattered chronic inflammatory cells (× 40); B: On higher power, the cysts are lined by a single layer of cells with clear cytoplasm (× 200); C: Low-grade nuclear features (Fuhrman nuclear grade 1) are seen and clear cells are present within the cyst wall and on the surface lining (× 400).

frequent in females[11]. MTSCC has a similar gross appearance to papillary RCC. Similarly, the immunohistochemical staining pattern of MTSCC is nearly identical to papillary RCC (positive for CK7 and AMCAR, and negative for CD10 and RCC-marker)[12], leading some to speculate that they may be a variant of papillary RCC[13]. However, genetic studies have shown that MTSCC does not show the characteristic molecular aberrations as seen in papillary RCC[14]. The characteristic gains of chromosome 7 and 17 and loss of chromosome Y typically seen in papillary RCC are not seen in MTSCC[14], which instead displays frequent losses and gains of other chromosomes[15].

MTSCC is a rare neoplasm, and can be a difficult diagnosis due to its morphologic heterogeneity. A study by Fine *et al*[16] describes the histologic variations of MTSCC and, in particular, what they described as the "mucin-poor variants". These variants show a predominance of tubular or spindle cell components and only minimal pale mucinous background. In addition, focal papillations or papillary cores and foamy histiocytes can be seen, creating confusion with papillary RCC. They note that helpful features in recognizing these variants are bland cytologic features and adjacent tubular and spindle cell components. It is important to be aware that focal areas of clear cells and oncocytic change can also be present[16].

MTSCC is considered a low-grade entity, with only rarely described cases of lymph node metastasis and recurrence. However, two cases of MTSCC with sarcomatoid change have been described, one with widespread metastasis to distant organs, including lung and bone[17]. A spindled component is characteristic of MTSCC, but the presence of significant pleomorphism with prominent nucleoli and mitotic activity, and necrosis should raise concern for a sarcomatoid change[17]. Microscopic necrosis alone can be seen focally in MTSCC, but it's significance is unknown. The presence of any necrosis should be mentioned in the final diagnosis[16].

Multilocular cystic clear cell RCC

Multilocular cystic clear cell RCC is defined as a distinct entity in the 2004 WHO classification. It is defined by the presence of low-grade clear cells lining cystic spaces and by the lack of a solid or expansive nodular component (Figure 3)[18]. Clear cells are commonly seen within the cyst wall (Figure 3), and can sometimes be difficult to distinguish from histiocytes. However, the neoplastic clear cells will be positive for cytokeratin and carbonic anhydrase IX (CA-IX), distinguishing them from histiocytes[19].

Multilocular cystic RCC shares similar genetic abnormalities with clear cell RCC, *i.e.*, the characteristic 3p deletions[20]. However, there have been no reported cases of progression or metastasis of this tumor, with a 5-year survival of 100%. In fact, the prognosis of this tumor is so favorable that, in the largest review utilizing the strict 2004 WHO criteria (45 cases), they suggested renaming this entity "multilocular cystic renal cell neoplasm of low malignant potential" and conservative management was suggested[21].

The distinction between a low grade (Fuhrman nuclear grade 1-2) clear cell RCC or clear cell papillary RCC can be difficult. A recent paper by Williamson *et al*[19] examined the immunohistochemical characteristics of multilocular cystic RCC. In contrast to conventional clear cell RCC, they found that CK7 was frequently diffusely positive and CD10 was less frequently positive in multilocular cystic RCC. This is similar to clear cell papillary RCC, which is also typically cystic. However, the absence of true papillae and the lack of CA-IX apical staining should distinguish these two entities[19]. Clear cell RCC with extensive cystic or necrotic change is important to include in the differential. Clear cell RCC will typically have large solid areas of neoplastic cells, which are not present in multilocular cystic RCC.

Carcinoma associated with neuroblastoma

Carcinoma associated with neuroblastoma is a distinct entity included in the 2004 WHO classification. It is defined as RCC which occurs in survivors of neuroblastoma[22]. A series of four cases from 1999 described RCC with papillary and solid patterns, abundant cytoplasm, and occasional oncocytic morphology, which occurred in patients with a previous diagnosis of neuroblastoma[23]. The tumors initially described were considered a distinct subset, morphologically and genetically distinct from other RCC subtypes. In recent years, Xp11 translocation
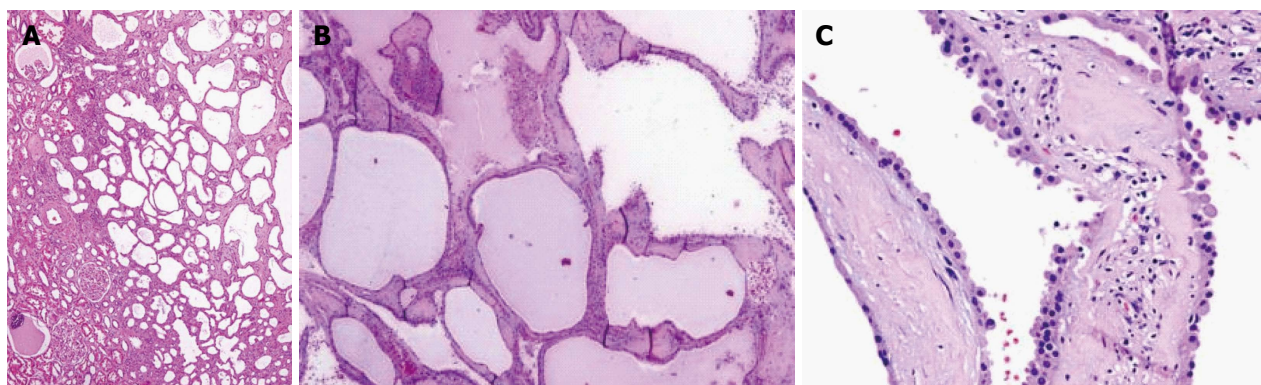
Figure 4 Tubulocystic carcinoma (hematoxylin and eosin). A: Tubulocystic carcinoma, on low power, is composed of many small cystic spaces with intervening fibrous septae (× 20); B: The cysts vary in size and shape (× 40); C: On higher power, bland cuboidal and hobnail-shaped cells are identified lining the cystic spaces (× 200).

RCC and papillary RCCs have also been described in neuroblastoma survivors[7,24,25].

The risk of developing another malignancy after neuroblastoma is well known[26]. RCC is the second most common type of such tumor, following thyroid carcinoma[26]. A survey of survivors of childhood cancer found a 329-fold risk of RCC in children with neuroblastoma[27]. The health risk after neuroblastoma is not limited to malignancy. A survey of 954 neuroblastoma survivors found an 8-fold likelihood of chronic health conditions, compared to their matched siblings, including musculoskeletal complications, endocrine abnormalities, and sensory abnormalities such as deafness and blindness. Many of these long-term effects are associated with treatment, which could also be associated with development of RCC[7]. However, there is evidence that the carcinoma associated with neuroblastoma is not related to therapy, but instead to an underlying genetic defect that predisposes individuals to development of cancer[23,27]. Regardless of the pathogenetic mechanism, knowledge of this entity in neuroblastoma survivors is essential for monitoring and early diagnosis.

RECENTLY DESCRIBED TUMORS

Tubulocystic carcinoma
Tubulocystic RCC is a recently described tumor composed of variably sized cystic tubules lined by a single epithelial layer with intervening fibrotic stroma (Figure 4). The neoplastic cells lining the cystic spaces have eosinophilic cytoplasm, hobnail nuclear morphology, and prominent nucleoli[28]. Tubulocystic RCC is not currently recognized by the WHO. However, accruing evidence suggests tubulocystic RCC merits consideration as a distinct entity.

Tubulocystic RCC was initially believed to derive from the collecting duct; in fact, it was originally considered a well-differentiated variant of collecting duct carcinoma. However, recent gene expression profiling evidence tends to refute this possibility[29]. The immunohistochemical staining pattern, ultrastructural features, and gene expression profiling favor a proximal convoluted tubule or intercalated cell origin[28,29]. In fact, some suggest that tubu-

locystic RCC may be closely related to papillary RCC[30,31]. One study of tubulocystic RCC found that 5 of their 13 cases of TCRCC had coexistent papillary renal cell neoplasms. In addition, a similar immunohistochemical staining pattern and gene expression profile between papillary RCC and TCRCC was identified[30]. This finding was supported by another study, which had 10 of 12 TCRCC cases with associated papillary neoplasms, including admixed TCRCC and papillary RCC in 4 cases[31]. This study also found gains of chromosome 17 in 8 of 12 cases of TCRCC[31]. Synchronous TCRCC with clear cell RCC has also been reported[32].

The largest clinicopathologic study to date on TCRCC was compiled by Amin *et al*[28] in 2009. They found TCRCC is more common in males and is a low-grade entity, with the majority of tumors presenting as stage pT1. Often, the tumor is an incidental finding. Tumors were both subcapsular (61.5%) and cortico-medullary or medullary (38.5%) in location. Only one case had local recurrence (3%) and two cases (6%) developed metastases. All cases had a Fuhrman nuclear grade of 3 despite an indolent behavior in the majority of cases, suggesting little value of Fuhrman grading in these neoplasms[28].

The differential diagnosis includes other cystic renal neoplasms, including multilocular cystic RCC. Focal cytoplasmic clearing has been noted in TCRCC[28]. Multilocular cystic clear cell RCC typically has lower Fuhrman grade nuclei, and scattered clear cells will be seen within the intervening fibrous stroma. Cystic nephroma could also be considered, but typically has larger cystic spaces and inconspicuous nucleoli. Mixed epithelial and stroma tumor also has cystic spaces, but will display an ovarian-type stroma. Oncocytoma with prominent tubules and cysts could also be considered, but typically will have nests of oncocytic cells, which are not present in TCRCC[28].

Thyroid-like follicular carcinoma of kidney
Thyroid-like follicular RCC was first described by Jung *et al*[33] in 2006. They described a case of primary renal carcinoma with morphology similar to a thyroid follicular carcinoma[33]. To date, only about 10 cases of this entity
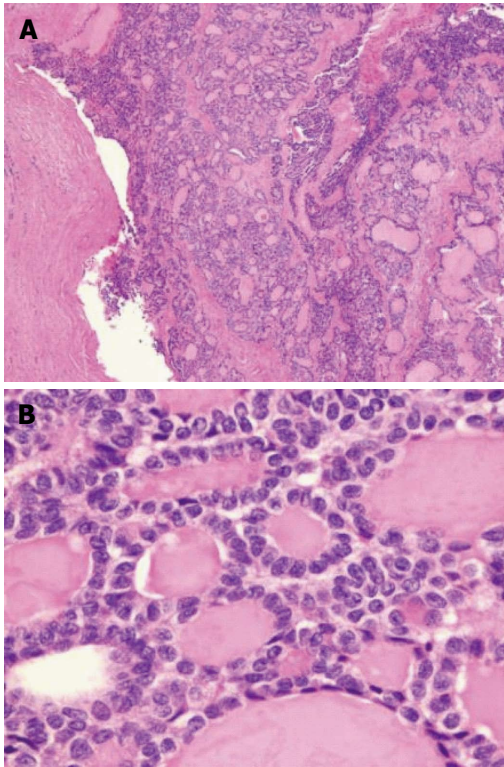
Figure 5 Thyroid-like follicular carcinoma of kidney (hematoxylin and eosin). A: The tumor has thyroid-like follicles filled with colloid-like material on low power (× 40); B: On high power, cells with enlarged, irregular nuclei and follicular architecture, similar to the follicular neoplasms of the thyroid, are seen; Nuclear grooves are also evident (× 400). Courtesy of Dr. Pheroze Tamboli, MD Anderson Cancer Center.

have been described in the literature[33-37].

The largest case series to date was compiled by Amin *et al*[34] in 2009 and includes 6 cases. They describe well-circumscribed tumors which grossly resemble thyroid parenchyma. The microscopic morphology mimics follicular carcinoma of the thyroid and contains colloid-like material (Figure 5). They are predominantly of low grade, but metastases to lymph nodes and to the lungs have been reported[34,35]. Six of the 10 reported cases in the literature occurred in patients in the 2nd and 3rd decades of life. However, the age range is wide, with cases reported from 29-83 years. Equal gender distribution is seen, and most of the cases are incidental findings (7 of 10 cases). No deaths from disease have been reported[37].

Distinction from a metastatic thyroid carcinoma is essential. The characteristic morphology and negative staining for thyroglobulin and thyroid transcription factor 1 confirms the diagnosis. The differential diagnosis also includes metastases from a teratoma (struma ovarii). Thyroidization of the kidney is also common in end-stage renal disease, but the cells lining the tubules are bland. Also, end-stage renal disease, in general, does not form a distinct tumor mass.

Acquired cystic kidney disease-associated RCC
Renal tubular cystic changes may develop in end-stage renal disease (ESRD), and this condition is termed ac-

quired cystic kidney disease (ACKD). Renal tumors often occur in kidneys with ESRD with or, less frequently, without ACKD. The risk of RCC in patients with ACDK is greater than 100 times that of the general population, although the incidence is less than 10%[38-41]. A prior history of dialysis is often associated with the development of ACDK and RCC, with direct correlation to duration of dialysis[42]. The various tumor types encountered in cases with ESRD include the three common subtypes of RCC, *i.e.,* clear cell (conventional) RCC, papillary RCC, and chromophobe RCC, with papillary RCC as the most common. However, there are at least two other subtypes of RCC that are more frequently associated with ESRD: ACKD-associated RCC and clear cell papillary RCC. ACKD-associated RCC is reported only in patients with ESRD and ACKD, thus the name; whereas clear cell papillary RCC can be seen in patients with both cystic and non-cystic ESRD, as well as in those without ESRD[42-44].

The ACD-associated RCC is usually multifocal and bilateral. These tumors may be incidentally discovered on imaging studies or in nephrectomy specimens performed for renal cysts with complications or renal parenchymal bleeding, which not infrequently masks the underlying tumor. Most tumors are well circumscribed, and often appear to arise within cysts. Tumors which are larger in size are grossly solid with a thick, fibrous capsule and may be accompanied by foci of necrosis and hemorrhage.

Microscopically, the tumors demonstrate a growth pattern comprised of various proportions of acinar, alveolar, solid, cystic, and papillary architectural patterns. Tumor cells display characteristic features, including abundant granular, eosinophilic cytoplasm and large nuclei with prominent nucleoli (Figure 6). A cribriform or sieve-like appearance is characteristic and present in most cases. Most, but not all, cases also show intratumoral oxalate crystals, a relatively specific feature quite consistently observed in ACD-associated RCC and not in other tumor types[42,45]. Immunohistochemical stains aid in distinguishing these tumors as ACD-associated RCC stains diffusely positive for a-methylacyl-coenzyme A racemase (AMACR), but is negative or only focally positive for CK7. Stains for CD10, RCC antigen, and glutathione S-transferase A are also reported to be positive[46]. On a molecular level, these tumors do not show trisomy of chromosomes 7/17 or loss of 3p, characteristic of papillary and clear cell RCC, respectively. A recent study by Pan *et al*[46] on 9 cases of ACD-associated RCC showed variable combined gains of chromosomes 3, 7, 16, 17, and Y using fluorescence *in situ* hybridization and comparative genomic hybridization. It is also important to note that the nonneoplastic renal parenchyma often contains cysts lined by large eosinophilic cells that show an immunophenotype similar to that of ACD-associated RCC.

The biologic behavior of RCCs in ESRD in general is reported to be less aggressive than that of the RCCs in non-ESRD settings. These tumors often present at a lower stage and are smaller in size[47]. However, there are
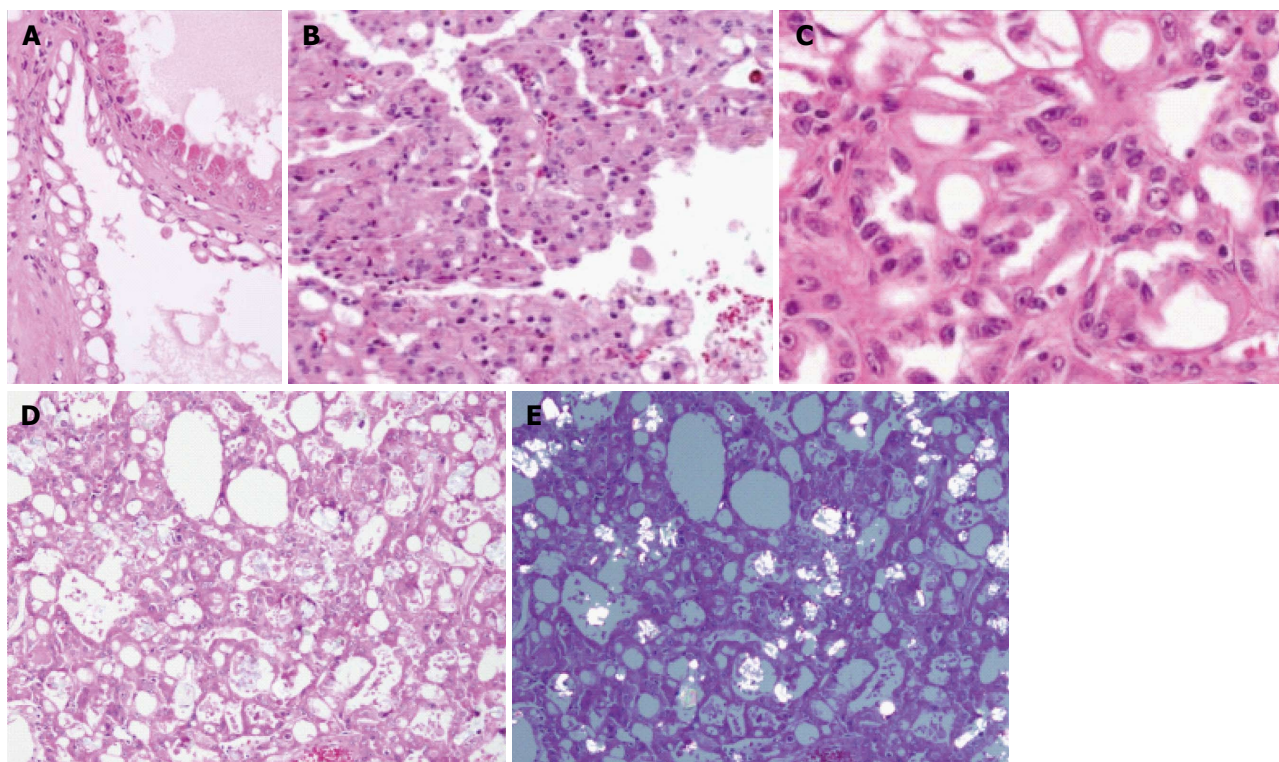
Figure 6 Acquired cystic disease-associated renal cell carcinoma. A, B: The tumor cells in acquired cystic disease-associated renal cell carcinoma typically have abundant eosinophilic cytoplasm and are seen lining the cystic spaces (A, × 400), and sometimes also show a solid growth pattern (B, × 200); The tumor characteristically arranges in a sieve-like cribriform pattern; C: The nuclear features are consistent with a Fuhrman nuclear grade 3, with prominent nucleoli (× 600); D, E: Calcium oxalate crystals are often associated with these tumors, and can be seen on hematoxylin and eosin staining (D, × 600) and with polarization (E, × 100).

a few case reports with metastasis or aggressive behavior. ACD-associated RCC may have a greater potential for aggressive behavior than other tumor types in ESRD. Rare cases with sarcomatoid features and unfavorable clinical outcomes have been reported[43,48].

The exact mechanisms underlying the increased incidence of RCC in ESRD, especially in those with superimposed ACDK are not completely understood. Multiple molecular alterations in diverse types of renal tumors indicate an acquired mechanism for renal tumorigenesis. Possible precursor lesions in ESRD include papillary adenomas and dilated tubules or clustered microcystic lesions lined by the eosinophilic cells[49]. Further research is necessary in order to delineate an etiologic relationship for these tumors.

Clear cell papillary renal cell carcinoma

Clear cell papillary RCC is a recently recognized renal tumor. This tumor was originally described in a background of ESRD and ACKD, although it has subsequently been reported in normal kidneys[42,43,50]. Metastasis from a clear cell papillary RCC has not been reported, highlighting the likelihood that these tumors are less aggressive than other RCC subtypes[42-44,50-53].

Clear cell papillary RCC is usually small and grossly encapsulated. The tumors may be solid, white tan, pale yellow or reddish brown in external appearance; however, the typical bright or golden-yellow heterogeneous cut surface of clear cell RCC is not identified. The cystic component is usually located at the periphery of the tumor, near its junction with renal parenchyma, and may be angulated, flattened, or irregular. Bilaterality and multifocality have been documented, especially in tumors arising in a background of ACKD[42-44,50-53].

On microscopic examination, clear cell papillary RCC is composed of a varying admixture of cystic, glandular, solid, and papillary components. The tumor cells have clear cytoplasm and are usually of low nuclear grade (Figure 7). One of the most distinctive features of clear cell papillary RCC is the linear positioning of the nuclei away from the basement membrane (inverted polarity). It is the presence of this feature within these tumors that aids in identification, irrespective of the architectural growth pattern, which can be markedly variable[43,44]. Papillary architecture is almost always present, but may be focal, and is commonly branched. Stellate tubular structures may also be seen. Some cases may have a prominent tubular pattern, as supported by previous reports describing this entity as tubulopapillary carcinoma. Other growth patterns include cystic, alveolar/nested, and retiform[43,50]. These tumors often have a fibrous capsule of varying thickness and often have variable amounts of eosinophilic hyalinized or sclerotic stroma[42-44,50-53]. Clear cell papillary RCCs sometimes contain foci of calcification or ossification, often within the tumor pseudocapsule[53].

In most cases, the morphologic features of clear cell papillary RCC are unique enough to allow for distinction from clear cell RCC based on HE-stained slides. In some
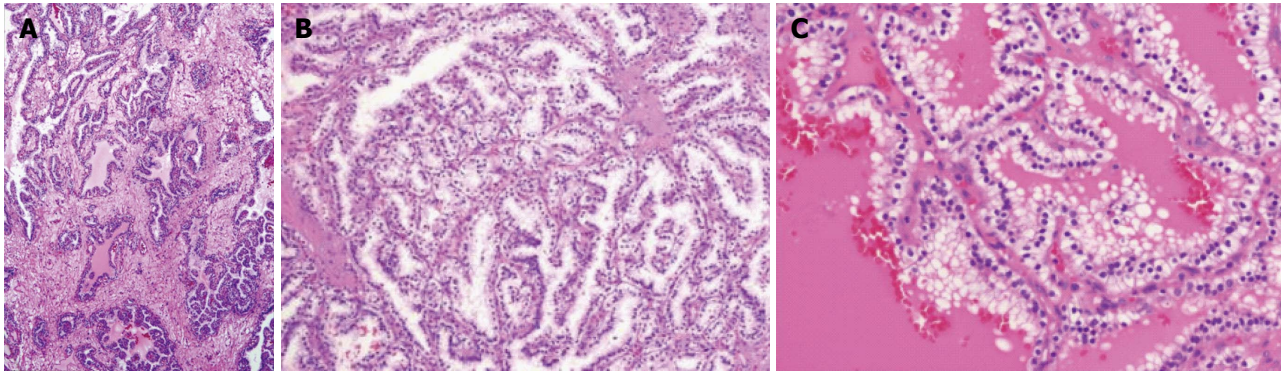
Figure 7 Clear cell papillary renal cell carcinoma (hematoxylin and eosin). A: The tumor has both a tubular and papillary architecture within a dense fibrous stroma (× 40); B: Other areas show a tubulopapillary growth pattern with delicate fibrovascular cores and conspicuous cytoplasmic clearing (× 100); C: The characteristic clear cells with low Fuhrman nuclear grade are seen with inverted linear positioning of the nuclei away from the basement membrane (× 200).
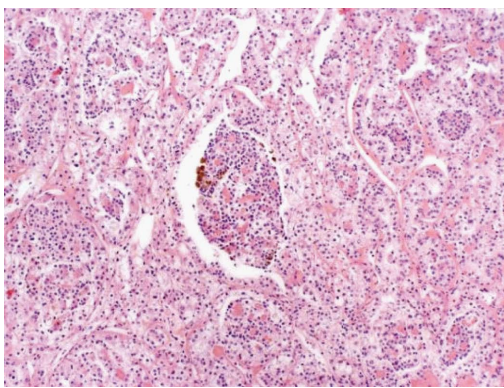

Figure 8 Renal cell carcinoma with t(6;11) translocation (hematoxylin and eosin). The tumor is composed of large epithelioid cells with abundant clear to eosinophilic cytoplasm; the distinctive feature of hyaline material with surrounding cells "rosette forming" is seen (× 100). Courtesy of Dr. Liang Cheng, Indiana University.

cases, immunohistochemical stains can be helpful, as clear cell papillary RCC and clear cell RCC have different immunoprofiles. Both clear cell papillary RCC and clear cell RCC typically express CA-IX, but the former usually exhibits weak expression, which is localized to the basal and lateral aspects of the tumor cells, so-called cup-shaped expression[44]. CD10 and 34βE12 show variable expression in these 2 tumor types, with the former more frequently positively expressed in clear cell papillary RCC. CK7 appears to be the most reliable marker for differentiating these 2 entities, as it is nearly always diffusely, strongly positive in clear cell papillary RCC, while only infrequently positive in clear cell RCC[43,44]. In general, when CK7 labeling is present in a clear cell RCC, it is focal or, at most, patchy and centered around cystic spaces[44]. Expression of AMACR is usually negative in both of these tumor types; thus, it is not of any use in this differential, but it can be extremely useful in cases of clear cell papillary RCC if the differential diagnosis includes papillary RCC[42-44,50-53].

Molecular changes in clear cell papillary RCC are distinctly different from those identified in clear cell and papillary RCCs. Sporadic clear cell papillary RCCs lack

VHL mutations, 3p25 deletions, hypermethylation of the VHL promoter, and other recurrent copy number changes which are characteristically seen in clear cell RCCs. Of the cases reported to date, there has been only 1 *VHL* mutation occurring in a clear cell papillary RCC in a patient with known VHL disease, and 1 case of loss of heterozygosity of the *VHL* locus has been described[43]. Although low copy number gains of chromosomes 7 or 17 have been documented in a small subset of cases, the vast majority of clear cell papillary RCCs do not exhibit these findings[43,44,54,55]. No pathognomonic genetic alteration has been identified. However, a recent gene expression profile meta-analysis of clear cell RCC by Brannon *et al*[56] identified 3 distinct molecular subgroups within clear cell RCC. One of these groups corresponded to a VHL wild-type pattern of gene expression and, from the images provided in the article, morphologically appears to represent clear cell papillary RCC. This study highlights the fact that many clear cell papillary RCCs were incorrectly diagnosed as clear cell RCC in the past, while also emphasizing that clear cell papillary RCC and clear cell RCC are distinct entities.

CANDIDATE ENTITIES

RCC with t(6;11) translocation

An extremely rare subset of renal translocation tumors is associated with t(6;11) (p21;q12)/Alpha-TFEB gene fusion. This distinctive tumor was first described by Argani *et al*[57] in 2001. Since then, a handful of cases of this rare entity have been documented in the literature. TFEB RCCs are predominantly seen in younger patients and are generally indolent, with rare reported cases of metastatic disease[58-66]. The most common histologic pattern is large epithelioid cells with voluminous clear to slightly eosinophilic cytoplasm, and clusters of small cells, usually clustered around hyaline material (rosette-forming) (Figure 8). However, TFEB RCCs may demonstrate unusual morphologic features, such as papillary, tubular, chromophobe RCC, clear cell RCC, and epithelioid angiomyolipoma-like structures[58-66].
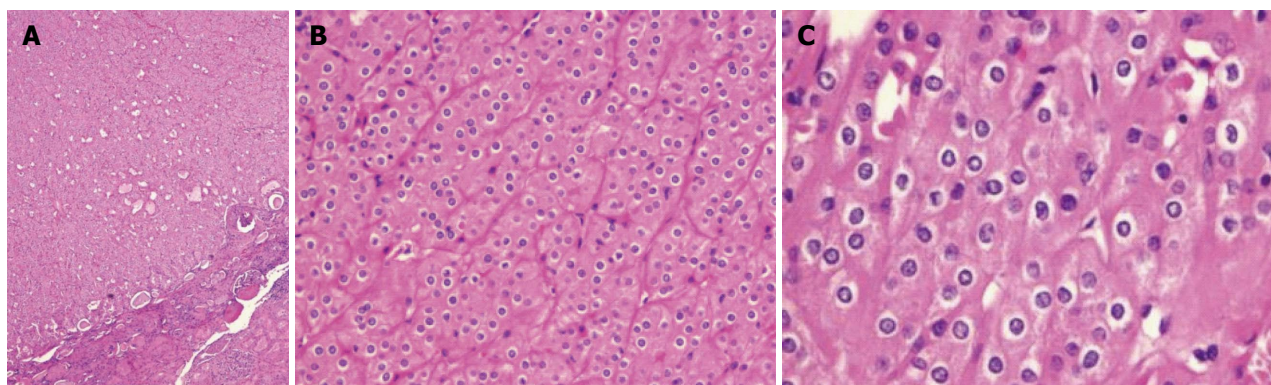
A recently developed antibody to TFEB and cathep-

Figure 9 Hybrid oncocytoma/chromophobe renal cell carcinoma (hematoxylin and eosin). A: Low power assessment of the tumors shows a well-circumscribed tumor with a solid growth pattern (× 40); B: The tumor cells have abundant eosinophilic cytoplasm and round, monotonous nuclei (× 200); C: Perinuclear halos are prominent throughout, with some areas showing mild nuclear irregularity (× 400). The overlapping features of oncocytoma (round nuclei with abundant eosinophilic cytoplasm) and chromophobe (perinuclear halos) are noted.

sin K proteins is highly sensitive and specific for TFEB RCCs[58,67]. It is important to recognize there must be nuclear positivity for TFEB, as the fusion product will be present in the nucleus. Non-translocated TFEB can cause falsely positive cytoplasmic staining[58]. Both *TFEB* and *TFE3* (described above in Xp11 translocation RCC) are part of the microphthalmia transcription factor/transcription factor family translocation RCCs. Overexpression of *TFE3* and *TFEB* in these neoplasms is known to increase the expression of cathepsin K proteins[67]. A study by Martignoni *et al*[67] showed that 7 of 7 TFEB RCC and 6 of 10 Xp11 translocation RCC had strong expression of cathepsin K, which was not seen in any other renal neoplasms[67]. In the study by Rao *et al*[66], all of the tumors showed moderate to strong immunoreactivity for TFEB, Ksp-cadherin, and vimentin, but were negative for TFE3, CD10, and CK7. Cathepsin K, HMB45, and melan A are moderately or strongly expressed in TFEB RCCs[58-67].

TFEB RCCs are often diagnosed based upon their distinctive morphology and immunophenotype. However, molecular methods such as PCR, RT-PCR, and FISH are extremely helpful and sometimes mandated for an accurate diagnosis. An interphase FISH assay is useful in the definitive identification of TFEB RCCs, and plays an essential role in identifying previously undiagnosed cases[66,68].

As these are rare tumors, there is still a degree of uncertainty regarding the final clinical outcome of patients. In the study by Rao *et al*[66], all 6 patients with follow-up available were alive with no recurrent disease. Their follow-up ranged from 6 to 55 mo, with a mean follow-up time of 31 mo. Other studies have shown a similar good prognosis[59,61], and TFEB RCC appears to be a relatively indolent tumor. However, further studies are warranted to determine long-term clinical outcomes.

To detect this tumor, we recommend the same approach of immunostains as for Xp11 translocation carcinoma in young patients under 30. If the initial cytokeratin stain is negative or weakly to focally positive, a TFE3 stain is recommended. If the TFE3 stain is negative, TFEB and HMB45 immunostains are recommended to diagnose a RCC with t(6;11) translocation tumor (both TFEB and HMB45 positive), and exclude the possibility of epithelioid angiomyolipoma (TFEB negative and HMB45 positive).

Hybrid oncocytoma/chromophobe RCC

Hybrid oncocytoma/chromophobe RCC was first recognized in patients with Birt-Hogg-Dubé (BHD) syndrome, a rare autosomal dominant condition characterized by fibrofolliculomas, renal tumors, pulmonary cysts, and spontaneous pneumothorax[69]. Mutation of the *BHD* gene on chromosome 17, a tumor suppressor gene, is attributed to this syndrome[70]. The renal tumors in these patients are characterized by the morphologic features of both oncocytoma and chromophobe RCC within the same tumor, known as hybrid oncocytoma/chromophobe RCC[69]. BHD patients also have an increased incidence of other RCCs, including chromophobe and clear cell RCC. The renal tumors in BHD patients are frequently bilateral and multifocal, and background renal oncocytosis within the kidney may be seen[69]. Renal oncocytosis is characterized by oncocytic change in the renal tubules and multiple oncocytomas.

Hybrid oncocytoma/chromophobe has been described as occurring in patients with renal oncocytosis; however, there has been an increased recognition of this entity in sporadic tumors without a background of renal oncocytosis or BHD syndrome[71-73]. These tumors are composed of cells with abundant granular eosinophilic cytoplasm, round nuclei, perinuclear halos, and CK7 positivity (Figure 9). Some of these sporadic hybrid tumors have distinctly different morphology in separate areas, while others have mixed features throughout[71].

The heightened awareness of hybrid tumors leads to questions of the utility of core needle biopsy in oncocytic neoplasms, which may miss a chromophobe component in a hybrid tumor due to sampling error. The distinction between oncocytoma and chromophobe RCC is clinically important, and the behavior of these hybrid entities is yet unknown. However, small, retrospective studies have
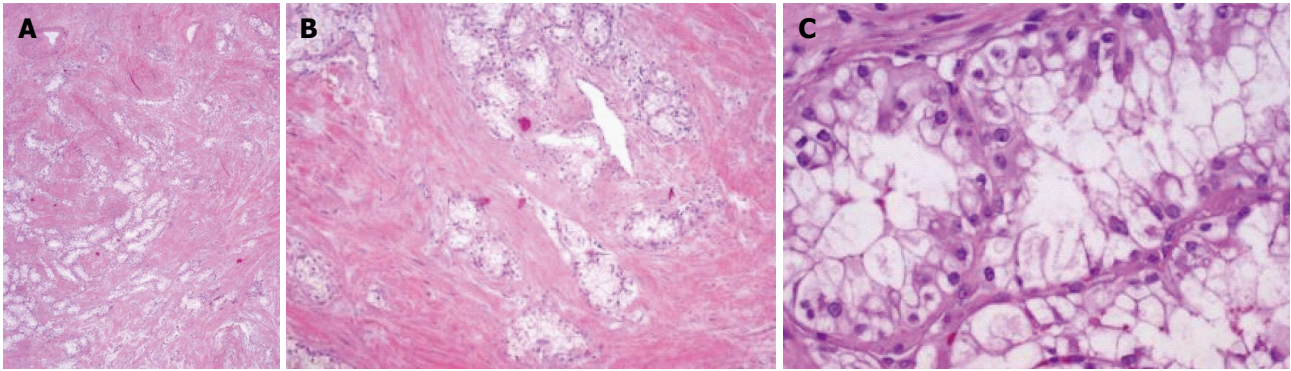
Figure 10 Renal angiomyoadenomatous tumor (hematoxylin and eosin). A, B: The tumor is composed of epithelioid cells in a background of dense, leiomyomatous stroma (A, × 40 and B, × 100); C: The tumor cells have oval nuclei of low Fuhrman nuclear grade with clear to eosinophilic cytoplasm and protrude into the lumen, resembling a so-called "shark's smile" (× 400). Courtesy of Dr. Melissa Stanton, Mayo Clinic, Arizona.

shown that these hybrid oncocytoma/chromophobe tumors have a clinically indolent course[73]. Further studies are needed to determine the behavior and pathogenesis of these neoplasms.

Hereditary leiomyomatosis and RCC syndrome

Hereditary leiomyomatosis and RCC (HLRCC) is an autosomal dominant familial syndrome characterized by the development of cutaneous and uterine leiomyomata, as well as renal tumors[74]. The hallmark mutation in this syndrome is the fumarate hydratase (*FH*, 1q42.3-q43) gene, but the exact prevalence of HLRCC is unknown. Kidney cancers are less penetrant than the leiomyomatous manifestations in HLRCC-affected families[75-77]. The association between cutaneous and uterine leiomyomata has been known for many years as Reed syndrome[78].

The renal tumors in this syndrome are aggressive, as demonstrated by the fact that 9 out of 13 patients in the first reported cohort of North American families died of metastatic disease within 5 years of initial diagnosis[75]. Other studies have shown lymph node metastasis is common, and there is a poor prognosis[79]. In the largest series published by Merino *et al*[79], 40 renal tumors resected from 38 HLRCC patients with proven fumarate hydratase germline mutations were studied. The patient age ranged from 17 to 75 years and tumors ranged in size from 2.3 to 20 cm. A papillary architecture was most common (25 of 40 cases), but tubulopapillary, tubular, solid, and mixed patterns were also seen. Immunohistochemical stains were nonspecific. The defining characteristic of HLRCC, as described by Merino *et al*[79], is the presence of a large nucleus with a prominent inclusion-like eosinophilic nucleolus, surrounded by a perinucleolar clearing. This distinctive morphology is also seen in the leiomyomata of these patients (described below).

Leiomyomatosis is a condition defined by the occurrence of multiple leiomyomas throughout the body, with often poorly defined nodules involving areas of the skin on the arms, chest, legs, and, in extremely rare cases, the uterus. In a study by Sanz-Ortega *et al*[80], uterine leiomyomata were identified in HLRCC patients at a young age (median age of 32 years). They were often multiple

and ranged from 1 to 8.5 cm in size. Histopathologically, HLRCC leiomyomata frequently had increased cellularity, multinucleated cells, and atypia. All cases showed tumor nuclei with large orangeophilic nucleoli surrounded by a perinucleolar halo similar to the changes found in HLRCC[79]. This study also showed that loss of heterozygosity (LOH) at 1q43 was frequent in HLRCC leiomyomas (8/10 cases), similar to the molecular alterations in renal tumors. LOH is considered to be the second hit that inactivates the *FH* gene, and FH mutations and LOH at 1q43 are unusual in sporadic leiomyomas.

Uterine leiomyomas and renal tumors in HLRCC share similar morphologic changes and genotypic features. It is important to recognize these features in leiomyomata so patients undergo early genetic testing for germline *FH* mutations and screening for renal cell cancer.

Renal angiomyoadenomatous tumor

Michal *et al*[81] reported a series of 5 cases which they designated as renal angiomyoadenomatous tumor, wherein the tumors were composed of clear cells, leiomyomatous stroma, and adenomatous structures with apical snouting (described as resembling a "shark's smile") (Figure 10). The epithelial tumor cells were positive for EMA, CK7, CK20, AE1-AE3, CAM5.2, and vimentin. In this series of cases, no *VHL* mutation was identified.

Cases of clear cell papillary RCC with smooth muscle metaplasia of intratumoral stroma, also recently described as "RCC with angioleiomyoma-like proliferation" or "clear cell RCC with smooth muscle stroma", share a significant degree of morphologic overlap with this entity[82,83]. It is currently debated whether these two tumors are related, or perhaps even variants of the same tumor[84-88]. Losses of chromosome 3 and 3p have been demonstrated in at least a subset of these tumors[83]. Some studies report that these lesions have demonstrated abnormalities of chromosomes 3 and the *VHL* gene, in addition to abnormalities of chromosomes 1, 11, and 16[83,85,86,88].

CONCLUSION

Our understanding of RCC continues to evolve. The

review of recent updates in selected tumors herein will hopefully serve as a useful prognostic and treatment guide for both the urologist and surgical pathologist, particularly in the era of personalized medicine.

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