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Review

Update on selected renal cell tumors with clear cell features. With emphasis on multilocular cystic clear cell renal cell carcinoma

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Summary. Clear cell renal cell carcinoma (CCRCC) is the most common malignant tumor of renal epithelial origin and, with the exception of some rare tumors, the most deadly. The exception is represented by the multilocular cystic CCRCC, whose prognosis is excellent with survival rates of 100% when diagnosis is made according to the WHO definition. For this reason a proposal has been made to rename this tumor as multilocular cystic renal cell neoplasm of low malignant potential. Another exemption could be the clear cell (tubulo) papillary renal cell carcinoma/clear cell papillary renal cell carcinoma (CCPRCC), a tumor with tubulopapillary architecture and clear cytoplasm. Published data indicates that these are neoplasms with indolent clinical behavior. No cases with metastasis have been reported. Neoplasms meeting criteria for CCPRCC will subsequently be reclassified as of "low malignant potential" rather than carcinoma. The stroma of CCPRCC not infrequently demonstrates smooth muscle metaplasia. It should be remembered, however, that smooth muscle stromal metaplasia and proliferation are not entirely specific to this entity. Hence, it is suggested that smooth muscle metaplasia in the kidney may be a nonspecific common reaction to a variety of stimuli. Xp11 translocation renal cell carcinomas are a group of neoplasms distinguished by chromosomal translocations with breakpoints involving the *TFE3* transcription factor gene, which maps to the Xp11.2 locus. The most distinctive histologic pattern of the Xp11 translocation renal cell carcinoma is that of a neoplasm with both clear cells and papillary architecture, and abundant psammoma bodies. TFE3 immunohistochemical staining is reported to be sensitive and specific for a diagnosis of translocation-associated carcinoma as long as the labeling is strong, diffuse, and nuclear. This immunostaining is particularly useful if the differential diagnosis includes CCRCC and CCPRCC. In conclusion, recognition of CCRCC and differentiation from other renal cell neoplasms with clear cytoplasm is important not only for prognostication but also for treatment-related reasons.

Key words: Clear cell renal cell carcinoma, Multilocular cystic CCRCC, Clear cell (tubulo) papillary renal cell carcinoma/clear cell papillary renal cell carcinoma, Xp11 translocation renal cell carcinoma

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Introduction

The classification of renal tumors synthesizes morphologic, immunohistochemical, and molecular findings to define more than 40 tumor types. Of these, clear cell renal cell carcinoma (CCRCC) is the most common malignant tumor in adults and—with the exception of some rare tumors—the most deadly. The diagnosis of CCRCC on morphologic grounds alone is generally straightforward, but challenging cases are not infrequent. A misdiagnosis of CCRCC has clinical consequences, particularly in the current era of targeted therapies. The aim of this review is to highlight morphologic mimics of CCRCC and provide strategies

to help differentiate CCRCC from other renal tumors and lesions. This review will focus on multilocular cystic CCRCC and on the main mimics of CCRCC, such as clear cell (tubulo) papillary renal cell carcinoma /clear cell papillary renal cell carcinoma (CCPRCC) and Xp11 translocation renal cell carcinomas (RCCs). Chromophobe RCC, oncocytoma, unclassified RCC, and epithelioid angiomyolipoma can occasionally mimic CCRCC. Details on these entities are given in recent reviews (MacLennan and Cheng, 2014; Srigley et al., 2013).

Clear cell renal cell carcinoma

CCRCC represents the most common RCC type, comprising more than 60% of all renal tumors. It is almost two-fold more common in males than females, with a peak incidence in the sixth and seventh decades.

CCRCC presents grossly as a solitary golden yellow mass (Fig. 1A), which reflects the high lipid content of its cells. Cysts with areas of necrosis and hemorrhage may be prominent in higher grade tumors, which have less lipid and are thus less distinctly yellow (Reuter and Tickoo, 2009; Ficarra et al., 2010).

The predominant histologic architecture is solid or acinar, with clear cells separated by hypervascular thin fibrous septa (Fig. 1B,C). The neoplastic cells of low nuclear grade CCRCC (Fuhrman grade 1–2) typically have water-clear, virtually agranular cytoplasm. However, high nuclear grade CCRCC typically has more granular eosinophilic cytoplasm (Fig. 1D). A helpful feature is the presence of eosinophilic cytoplasm in high grade tumors rather than clear cytoplasm. Rarely, true cases of low grade CCRCC with well-developed papillae do exist. In some low grade tumors, small papillations lined by clear cells protrude into cystic spaces. High

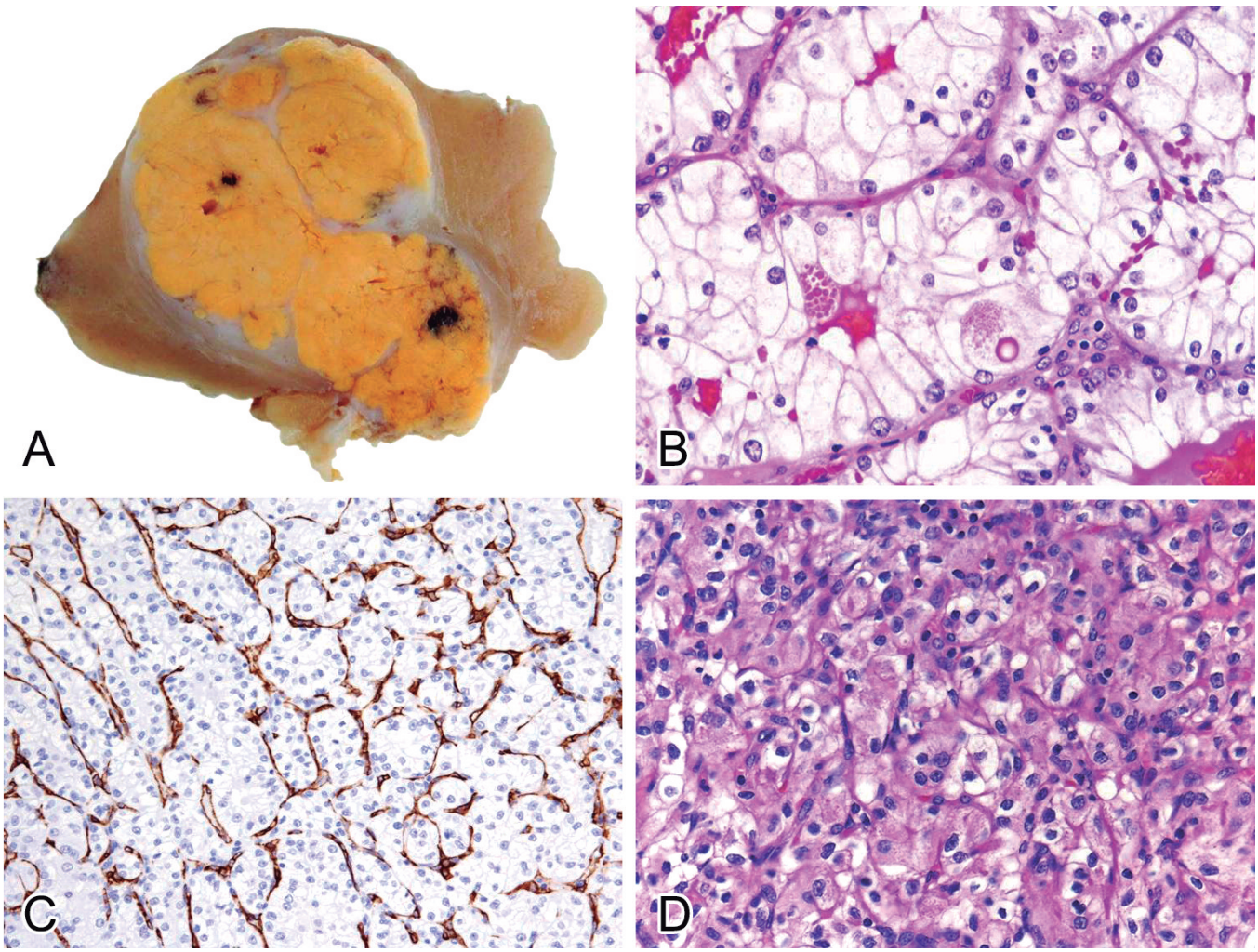

Fig. 1. Clear cell renal cell carcinoma presents grossly as a solitary golden yellow mass **(A)**. The predominant histologic architecture is solid or acinar, with clear cells **(B)** separated by hypervascular thin fibrous septa (**C**; immunohistochemistry for CD34). High nuclear grade clear cell renal cell carcinoma typically has more granular eosinophilic cytoplasm (**D**).

grade CCRCCs with necrosis demonstrate pseudopapillae resulting from fragmentation of the acinar architecture (Ficarra et al., 2010; Goyal et al., 2013).

The immunohistochemical (IHC) profile of CCRCC typically includes strong reactivity to CAM5.2, vimentin, CD10, EMA, RCC marker, as well as PAX8 and PAX2 (Algaba et al., 2011). Diffuse membranous staining for CAIX is present, reflecting inactivation of the von Hippel-Landau (*VHL*) gene and constitutive activation of the hypoxia-inducible-factor (HIF) pathway. CCRCCs are negative for cytokeratin 7 (CK7) and α-methylacyl-CoA racemase (AMACR), cathepsin K, and TFE3 (Table 1).

CCRCCs have consistent genetic abnormalities (van den Berg and Buys, 1997; Nickerson et al., 2008; Cheng et al., 2010; Rohan et al., 2011). A deletion on chromosome 3p, where the *VHL* gene resides, is present in the overwhelming majority of sporadic and familial tumors (Brunelli et al., 2011). *VHL* gene mutations have been reported in at least one half of these tumors. Recently, molecular analysis of 205 well-characterized CCRCCs revealed *VHL* gene mutations in 82% of cases. An additional 8% showed hypermethylation in the *VHL* promoter CpG islands. The *VHL* gene product, pVHL, regulates transcription of genes through HIF. Normal pVHL targets HIF1α for degradation in normoxemic states. When the *VHL* gene is mutated or the VHL protein is absent, conditions of hypoxia are simulated and HIF1α accumulates. HIF1α activates multiple downstream genes including vascular endothelial growth factor (*VEGF*), a glucose transporter (*GLUT1*), and carbonic anhydrase IX (*CA9* or *CAIX*). The latter causes the characteristic diffuse IHC labeling for CAIX in CCRCC.

Papillary renal cell carcinoma may also have a clear cell component. Ancillary studies may be critical in those challenging cases (Gobbo et al., 2008a).

Multilocular cystic clear cell renal cell carcinoma

Multilocular cystic CCRCC is a renal cortical neoplasm with a distinct multilocular gross appearance, and is regarded as a variant of CCRCC (Halat et al., 2010; Moch, 2010; Kuroda et al., 2012; Williamson et al., 2012; Montironi et al., 2013). This entity accounts for approximately 4% of all CCRCCs, and affects middle age adults with a male to female ratio of 1.2–2.1:1. Up to 90% of cases are discovered incidentally on radiologic evaluation for other causes (You et al., 2011). This cystic tumor usually presents as a unilateral solitary lesion (Lopez-Beltran et al., 2006).

Macroscopically, multilocular cystic CCRCC consists exclusively of variably sized cysts separated by thin septa and filled with clear, serous, or gelatinous fluid or, much less frequently, with hemorrhagic debris. Solid, grossly discernible tumor mural nodules are incompatible with the diagnosis. This means that 100% of this neoplasm is cystic. This is in agreement with the macroscopic and microscopic definition accepted by the WHO.

Microscopically, the cysts are lined by a single layer of tumor cells with abundant clear cytoplasm and small nuclei without nucleoli (Fuhrman nuclear grade 1) (Fig. 2A). Rare cysts have different types of lining, including multilayering, cells with granular cytoplasm, and small intracystic papillations. The septa consist of fibrous tissue with calcification or ossification. An important diagnostic feature, which is seen in almost all cases, is the presence within the fibrous septa of clusters of tumor cells similar to those lining the cysts (Fig. 2B). Vascular invasion, sarcomatous transformation, and metastatic spread have not been reported in any of the series in which the WHO definition was adopted.

According to the definition given by the WHO, multilocular cystic CCRCC is a "tumor composed entirely of numerous cysts, the septa of which contain groups of clear cells indistinguishable from grade 1 clear cell carcinoma." The delegates attending the 2012 RCC Consensus Conference in Vancouver were asked the following question: "Is it acceptable for multilocular cystic CCRCC to have Fuhrman grade 2 nuclei?" the following options being available: 1. Yes; 2. No; 3. Uncertain even with personal experience/knowledge; 4. Not enough personal experience/knowledge. Seventy-eight percent of the participants were in favor of "yes" (i.e., Fuhrman grade 2 nuclei are acceptable in multilocular cystic CCRCC); whereas 20% were against

Table 1. Immunohistochemical features of the kidney tumors predominantly composed of clear cells.

Tumor type	CAIX	CD10	CK7	AMACR	CD117	Cathepsin K	HMB45
Clear cell RCC	Positive, diffuse membranous	Positive	Negative	Negative	Negative	Negative	Negative
Papillary RCC	Positive	Positive	Positive	Positive	Negative	Negative	Negative
Clear cell papillary RCC	Positive, cup-like	Negative	Positive	Negative	Negative	Negative	Negative
Chromophobe RCC	Negative	Variable, focal	Positive	Negative	Positive, membranous	Negative	Negative
Epithelioid angiomyolipoma	Negative	Variable, focal	Negative	Negative	Negative	Positive	Positive
Xp11 RCC	Variable, focal	Variable, focal	Negative	Variable	Negative	Positive (50%)	Variable, focal

AMACR, alpha-methylacyl-CoA racemase (P504); RCC, renal cell carcinoma; CAIX. Carbonic anhydrase IX.

it and the remaining 3% were either uncertain or not enough experience.

Studies have been conducted in multilocular cystic RCC and CCRCC (Halat et al., 2010; von Teichman et al., 2011). *VHL* mutations have been identified in 25% of tumors, the neoplastic cells in the majority of the cases being strongly reactive to PAX2 and CAIX, similar to typical low-grade CCRCC. Chromosome 3p deletion has been identified in 89% of the CCRCC cases and 74% of the multilocular cystic RCC cases, with no significant difference in the status of chromosome 3p deletion between CCRCC and multilocular cystic RCC. These findings are consistent with the concept of multilocular cystic RCC as a variant of CCRCC.

In line with the minimal tumor burden present in these tumors, their prognosis is excellent. Multiple publications based on more than 200 patients with followup time of more than 5 years showed that there was no recurrence or metastases in patients whose tumor

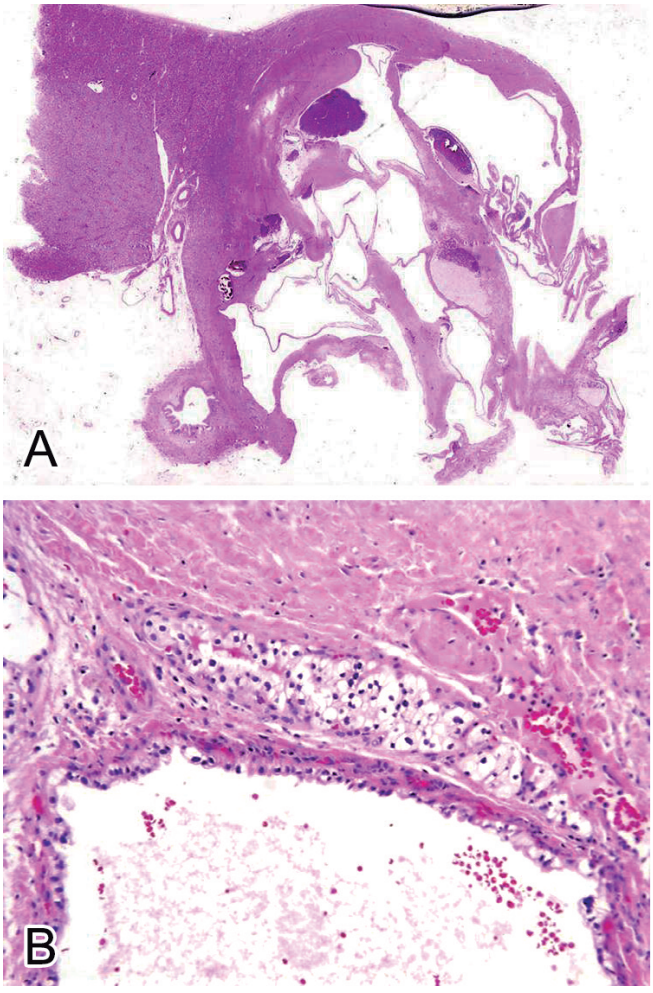

Fig. 2. Multilocular cystic clear cell renal cell carcinoma **(A)**. Presence within the fibrous septa of clusters of tumor cells similar to those lining the cysts **(B)**.

was defined according to the definition adopted by the WHO (see above). Based on the excellent outcomes, some have suggested redesignation of these lesions as 'multilocular cystic renal cell neoplasms of low malignant potential' (Suzigan et al., 2006).

A possible change in the terminology for a multicystic renal neoplasm with minute areas of bland clear cells in the septa (i.e., multilocular cystic RCC), was discussed at the RCC Consensus Conference in Vancouver. The delegates were asked to vote for one of the following items: 1. Multilocular cystic RCC, 2. Multilocular cystic renal cell neoplasm of low malignant potential; 3. RCC with extensive cystic change; 4. Multicystic renal epithelial neoplasm with focal clear cell change; 5. None of the above or Uncertain. Sixty-four percent of the delegates were in favor of a change in the current terminology, favoring the following designation: multilocular cystic renal cell neoplasm of low malignant potential. Thirty-four percent of the delegates were in favor for the current name; i.e., multilocular cystic RCC. The remaining 2% were split between RCC with extensive cystic change (1%) and none of the above or uncertain (1%).

Even though it was not part of the consensus conference, the possibility to broaden the definition of multilocular cystic RCC by also accepting under this entity tumors that are not 100% cystic, as done in very few studies, was discussed. The majority of those who took part in the discussion favored the strict WHO definition, mentioning that by accepting tumors even with a small proportion of tumor not cystic, the boundary with CCRCC would become unclear, thus affecting the excellent prognosis observed for multilocular cystic RCC and for which 64% of the delegates asked to change the name.

The differential diagnoses mainly include RCC with cystic necrosis, tubulocystic carcinoma of the kidney, cystic nephroma, CCPRCC with predominant cystic configuration, and benign multilocular renal cortical cysts (Halat et al., 2010; Algaba et al., 2011).

Cystic RCC due to extensive tumor necrosis usually belongs to the clear cell group. It is composed of multiple cysts filled with hemorrhagic and necrotic debris and separated by irregularly thick shaggy walls composed of variable mixtures of fibrous tissue and tumor cells. Gross solid tumor areas are frequent and serve to differentiate cystic RCC from multilocular cystic RCC. Even extensively necrotic cystic RCCs (99% necrotic) have been shown to be capable of aggressive clinical behavior (Williamson et al., 2013b).

Tubulocystic carcinoma has a distinctive gross appearance: well circumscribed with an off-white cut spongy surface that shows innumerable cysts filled with clear fluid (MacLennan and Cheng, 2011). The cyst lining is smooth and the cysts are fairly uniform in size, compared with the highly variable sizes of the cysts of multilocular cystic RCC. The cysts are lined by a single layer of carcinoma cells with eosinophilic cytoplasm. The contours of these cells vary from cuboidal to

hobnail or flattened. The nuclei are spherical and nucleoli are usually prominent in many of the nuclei. Necrosis and mitotic figures are rare. The septa between the cysts are thin and composed of fibrous tissue. CD10 and AMARC are positive in more than 90% of tumors. CK7 is variably expressed, although that pattern may be weak and focal. Staining for kidney-specific cadherin and PAX2 may also be seen. The 34ßE12 is nearly always negative.

Cystic nephroma (Stamatiou and Sofras, 2009), typically located close to renal hilum and pelvis, appears as an encapsulated multilocular mass. The cysts measure a few millimeters to 4 cm and are only rarely larger. They are filled with serous fluid or, less frequently, with gelatinous or bloody fluid, have a smooth lining, and are separated by thin septa. The cysts are lined by a single layer of nondescript, flattened, or cuboidal cells. Quite characteristic for cystic nephroma is the presence of cysts lined by "hobnail" cells with abundant eosinophilic cytoplasm and large apical nuclei. Rare areas lined by a single layer of clear cells can be seen and should not raise the possibility of cystic RCC. The septa are thin and mold to the cyst contour without forming any expansive nodules. They are composed of connective tissue, which may be myxoid, collagenous, fibrous with low to moderate cellularity, or, rarely, reminiscent of the ovarian stroma. While cystic nephroma may have at least some clear cells lining the septa, the lining clear cells tend to be focally rather than diffusely distributed, and there are no clusters of clear cells in the walls. The ovarian-like stroma in cystic nephroma, if present, distinguishes it from multilocular cystic RCC. Cystic nephroma shows reactivity of epithelial component with antibodies to cytokeratins. In particular, cystic nephroma frequently reacts with CK7. Focal positivity for high molecular weight cytokeratin (34ßE12) has also been noted. The stromal component in both lesions expresses vimentin, smooth muscle actin, caldesmon, and desmin. ER and PR are detected in the nuclei of the stromal cells. Another differential diagnosis is clear cell (tubulo) papillary RCC/CCPRCC whose distinctive features are discussed in the next paragraph (see below).

Simple cortical cysts constitute the most common renal cysts, with a reported incidence of more than 27% on radiological evaluation in individuals older than 50 years (Chen and Tickoo, 2012). The cysts are usually unilocular, oval to round with a smooth outline and lined by a single layer of flattened to cuboidal epithelium, often filled with transudate-like clear or straw-colored fluid. Infrequently, such cysts may be multilocular and demonstrate radiologic complexity, which may raise the possibility of a cystic neoplasm and lead to surgical resection. The lining epithelium in these unilocular or multilocular cysts occasionally shows more complex architectural patterns. The lining in some cysts displays papillary proliferation comprising cuboidal, hobnail cells with either eosinophilic or basophilic cytoplasm; in some others the lining may be composed of clear cells in single or multiple layers, but distinct from multilocular cystic RCC, without any mural clear cell clusters or nodules. Ancillary studies performed by us on a very limited number of cases have shown that the cysts with clear cells often demonstrated positivity for CK7 and CAIX, and negative staining for CD10 and racemase; and the cysts with papillary proliferation, while exhibiting positive staining for CK7 and occasionally racemase, were negative for trisomy 7/17 by FISH.

Clear cell (tubulo) papillary renal cell carcinoma/ clear cell papillary renal cell carcinoma

CCPRCCs are composed of clear cells of low nuclear grade, variable papillary, tubular/acinar and cystic architecture, and a characteristic linear arrangement of nuclei away from basal aspect of cells (Gobbo et al., 2008a; Williamson et al., 2013a; MacLennan and Cheng., 2014). These neoplasms have a distinctive immunohistochemical profile of CK7/CAIX/high molecular weight cytokeratin positivity and CD10 and AMACR negativity. The original term CCPRCC and a proposed synonym, clear cell tubulopapillary RCC, have been used interchangeably (Gobbo et al., 2008b; Aydin et al., 2010). Tumors of similar morphology and immunophenotype but with prominent smooth muscle stroma have been reported under the name renal angiomyoadenomatous tumor (Michal et al., 2009a,b). CCRCC with diffuse CK7 positivity is now considered to be the same tumor as CCPRCC (Mai et al., 2008).

CCPRCC was initially reported in patients with end stage renal disease (Tickoo et al., 2006); however, the majority of cases reported subsequently have been sporadic (Gobbo et al., 2008b; Aydin et al., 2010; Adam et al., 2011; Rohan et al., 2011; Bhatnagar and Alexiev, 2012). Based on a few reports, CCPRCC comprises about 1% of all renal cell neoplasms (Aydin et al., 2010; Tickoo and Reuter, 2011). The age at presentation is similar to that for RCCs in general years (mean, 60 years; range, 18–88 years) and there is no gender predilection (Aydin et al., 2010; Adam et al., 2011; Rohan et al., 2011).

Macroscopically, CCPRCC are well circumscribed and usually well-encapsulated (Fig. 3A). The cut surface is tan-white to yellow with grossly apparent fibrotic areas, and ranges from completely solid to predominantly cystic. These tumors are usually unicentric, unilateral and small, the largest one in the literature being 6 cm in diameter. Multifocality and bilaterality, however, may be present in some cases (Sule et al., 2005; Tickoo et al., 2006; Enoki et al., 2010); the latter setting raises the differential diagnosis of VHL associated renal neoplasia.

Microscopically, CCPRCC have variable tubular/acinar, papillary, and cystic architecture (Sule et al., 2005; Tickoo et al., 2006; Gobbo et al., 2008b; Aydin et al., 2010; Tickoo and Reuter, 2011). In some cases, papillae are tightly packed, giving rise to a solid appearance. Sometimes these papillary structures project

into cystic spaces. In other cases, the tubules show branching and infoldings, imparting an incipient papillary architecture. Still other tumors have markedly crowded, very small, 'collapsed' acini, containing scant cytoplasm, giving the tumor a solid nested appearance. Fibrous stroma separating tumor nodules within a single tumor mass is frequently evident. Some tumors with grossly apparent fibrotic cut surface show extensive myoid metaplasia of the capsule with extensions of smooth muscle into the tumor mass and encasing nests of tumor cells. Tumors with 'collapsed' acini, variable tubular/acinar architecture, myoid metaplasia, and diffuse CK7 positivity have been considered to be separate tumor entities (renal angiomyoadenomatous tumor/RCC with diffuse CK7 immunoreactivity) by some authors (Mai et al., 2008; Michal et al., 2009a). However, these morphologic patterns can be seen in otherwise typical CCPRCC, and most experts believe that they are part of the morphologic spectrum of CCPRCC (Aydin et al., 2010; Tickoo and Reuter, 2011; Behdad et al., 2011).

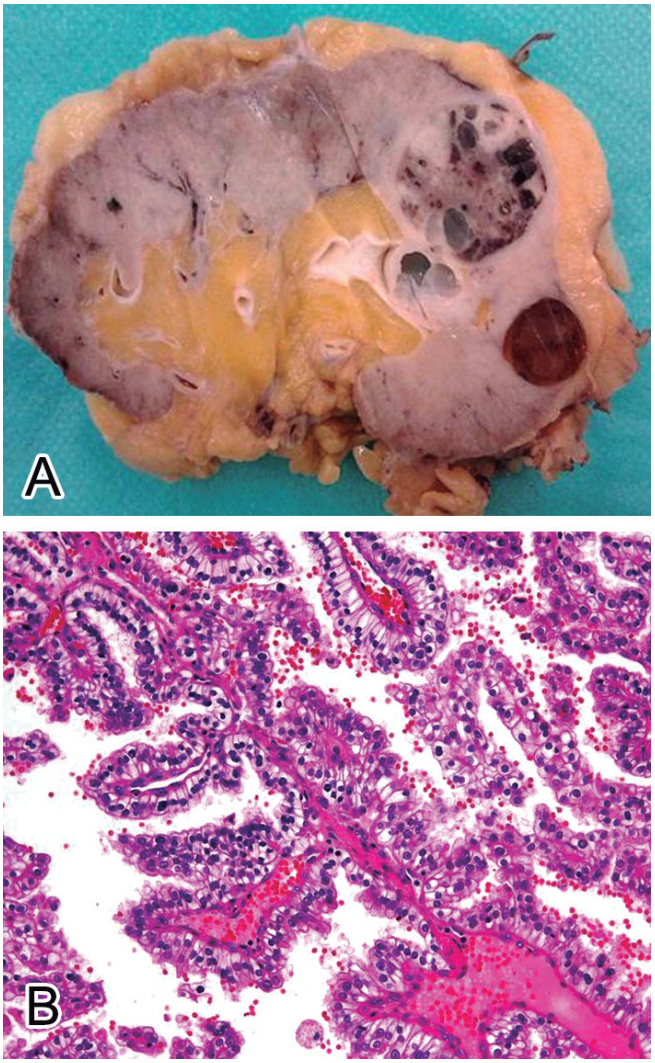

Fig. 3. Clear cell (tubulo) papillary renal cell carcinoma/clear cell papillary renal cell carcinoma presents grossly as well circumscribed and usually well encapsulated **(A)**. Tubular/acinar, papillary, and cystic architecture with the neoplastic cells have clear cytoplasm with low nuclear grade and linear arrangement of the nuclei away from the basal aspect, towards the middle or the apex of the cells **(B)**.

By definition, the neoplastic cells have clear cytoplasm with low nuclear grade (nucleolar grade 1 or 2). The existence of cases of CCPRCC of higher nuclear grade is not well established at this time though it is certainly possible. One characteristic feature of this tumor is the linear arrangement of the nuclei away from the basal aspect, towards the middle or the apex of the cells (Fig. 3B) (Tickoo et al., 2006; Aydin et al., 2010; Kuroda et al., 2010; Adam et al., 2011; Tickoo and Reuter, 2011; Rohan et al., 2011). Foamy macrophages, tumor necrosis, and vascular invasion are not seen. Most tumors are small and confined to the renal parenchyma, although rare cases extending into the renal sinus have been described (Adam et al., 2011; Rohan et al., 2011).

The immunohistochemical features of the tumor are quite characteristic (Tickoo et al., 2006; Gobbo et al., 2008b; Aydin et al., 2010; Adam et al., 2011; Tickoo and Reuter, 2011; Williamson et al., 2013a-c; MacLennan and Cheng, 2014). The tumors show diffuse and intense staining with CK7, almost always in 100% of the tumor cells. Tumor cells also express CAIX diffusely in a membranous distribution; the absence of staining along the luminal borders of the tumor cells is quite characteristic (cup-shaped distribution) (Tickoo and Reuter, 2011). Stains for AMACR, CD10, and RCC are negative in most cases, while it is common to see patchy to diffuse immunoreactivity for high molecular weight cytokeratin (34ßE12) in the majority of these neoplasms. Given that the proposed definition of CCPRCC includes typical morphology and IHC findings, cases with typical morphology, but without the typical IHC profile, cannot be definitively placed in this category, although it does seem likely that they do belong.

The main differential diagnosis of CCPRCC is with CCRCC. Some CCRCCs may have foci resembling CCPRCC with subnuclear clearing causing linear arrangement of the nuclei (Tickoo and Reuter, 2011; Kuroda et al., 2011a). Some cases may even show CK7 positivity, but such positivity is only focal. Unlike CCPRCC, they are also CD10 positive and 34ßE12 negative. The CAIX staining pattern is also different, with the luminal aspects of the cells also staining positive (box-shaped distribution) in CCRCC. At the molecular genetic level, CCPRCC lacks deletions of 3p25, *VHL* gene mutations, VHL promoter hypermethylation, or trisomies of chromosomes 7 and 17 (Gobbo et al., 2008b; Aydin et al., 2010; Kuroda et al., 2011b; Tickoo and Reuter, 2011). However, while the mechanism is not clear, VHL transcripts are underexpressed and SNP-array and microarray CGH analyses have confirmed such findings in two different series (Adam et al., 2011; Rohan et al., 2011). Low copy

number gains of chromosome 7 and 17 have been reported in a few cases (Gobbo et al., 2008b; Aydin et al., 2010). Rare cases considered as CCPRCC with other chromosomal aberrations have also been reported (Wolfe et al., 2011). Clear cell papillary renal cell carcinoma-like tumor should be distinguished from patients with VHL disease (Williamson et al., 2013c).

The number of cases in the literature with extended clinical follow up information is small; however, published data indicates that these are neoplasms with indolent clinical behavior. No cases with metastasis have been reported (Tickoo et al., 2006; Gobbo et al., 2008b; Srigley and Delahunt, 2009; Aydin et al., 2010; Adam et al., 2011; Rohan et al., 2011; Tickoo and Reuter, 2011; Bhatnagar and Alexiev, 2012). If further experience confirms their apparent indolent course, it is possible that neoplasms meeting criteria for CCPRCC will subsequently be reclassified as 'low malignant potential' rather than carcinoma (Mazzucchelli et al., 2012).

Renal cell carcinoma associated with prominent angioleiomyoma-like proliferation

The stroma of CCPRCC not infrequently demonstrates smooth muscle metaplasia (Figs. 4, 5). The extreme end of this spectrum includes likely tumors reported as renal angiomyoadenomatous tumor (RAT) to reflect the prominence of smooth muscle (Michal et al., 2000, 2009a,b; Iczkowski et al., 2013). RATs appear to have the same clinicopathologic and immunohistochemical characteristics as CCPRCC. Despite vigorous arguments to the contrary (Michal et al., 2009b), a recent abstract comparing these two entities suggests that they can now be considered as a spectrum in the same category of tumors (Behdad et al., 2011). It should be remembered, however, that smooth muscle stromal metaplasia and proliferation is not entirely specific to this entity. For example, smooth muscle stromal metaplasia has been reported in association with CCRCC (Kuhn et al., 2006; Shannon et al., 2009). Although these reported tumors showed prominent angioleiomyoma-like stroma, some have demonstrated chromosome 3 aberrations typical of CCRCC (Shannon et al., 2009). It should be noted, however, that recent data has questioned the relationship of these smooth muscle rich neoplasms to CCRCC (Brunelli et al., 2009). In addition, Xp11 translocation RCC may show smooth muscle stroma (Kuroda et al., 2009). Hence, it is suggested that smooth muscle metaplasia in the kidney may be a nonspecific common reaction to a variety of stimuli.

Xp11 translocation renal cell carcinomas

Xp11 translocation RCCs are a group of neoplasms

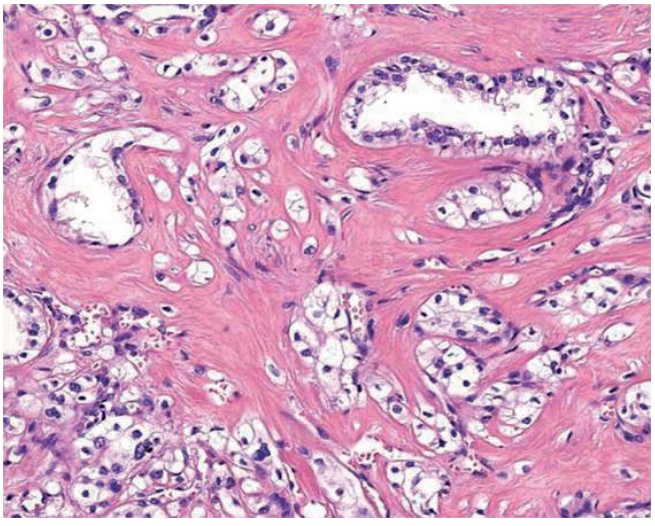

Fig. 4. Renal cell carcinoma associated with prominent angioleiomyoma-like proliferation.

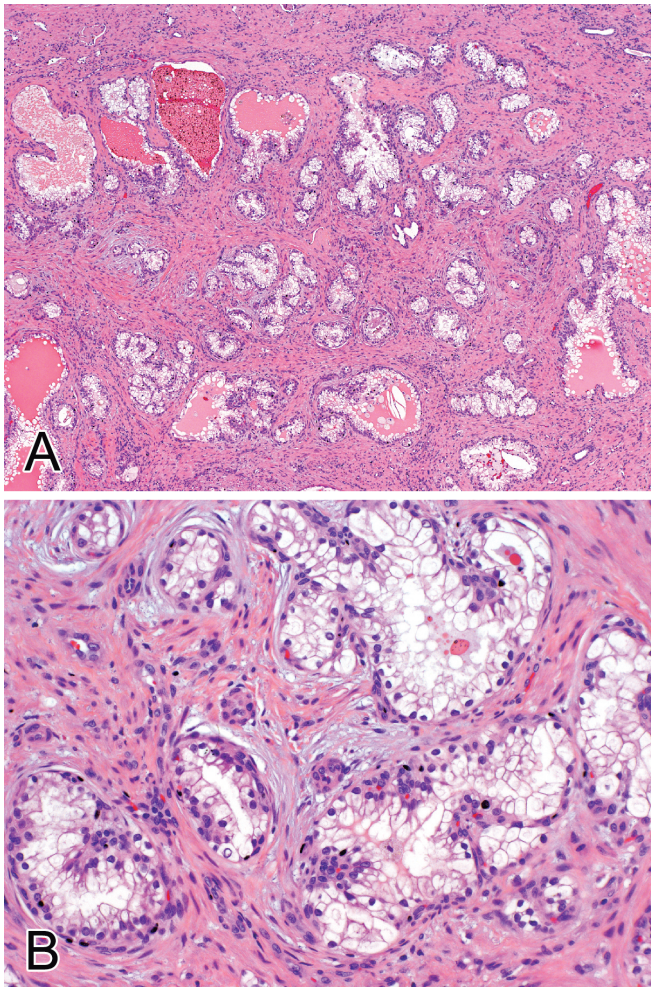

Fig. 5. Another case of renal cell carcinoma associated with prominent angioleiomyoma-like proliferation. **A.** Lower power view. **B.** High power view.

distinguished by chromosomal translocations with breakpoints involving the *TFE3* transcription factor gene, which maps to the Xp11.2 locus. The result is a *TFE3* transcription factor gene fusion with one of multiple reported genes including *ASPL*, *PRCC*, *NonO* (*p54nrb*), *PSF*, and *CLTC* (Clark et al., 1997; Argani et al., 2001, 2002, 2003a; Ladanyi et al., 2001; Rao et al., 2013b). Variant translocations with no known fusion partner include a t(X;3)(p11.2;q23) translocation and a t(X;10)(11.2;q23).

Although RCCs account for less than 5% of renal tumors in children, Xp11 translocation RCCs most likely constitute approximately 50% of these cases. It has been estimated that 1–4% of adult RCCs are Xp11 translocation RCCs (Argani et al., 2007; Komai et al., 2009; Zhong et al., 2010). While Xp11 translocation RCC is relatively rare in the adult population, RCC is overall much more common in adults than in children. Thus, adult Xp11 translocation RCC may vastly outnumber pediatric Xp11 translocation RCC due to the much higher incidence of RCC in the adult population. Up to 15% of patients with Xp11 translocation RCC had a history of prior chemotherapy exposure (Argani et al., 2006).

The most distinctive histologic pattern of the Xp11 translocation RCC is that of a neoplasm with both clear cells (Fig. 6A) and papillary architecture, and abundant psammoma bodies. Xp11 translocation RCCs can also present with unusual morphology mimicking other types of RCCs, including multilocular cystic RCC-like features, pleomorphic giant cells, tubular growth reminiscent of collecting duct carcinoma, and well-developed fascicles of spindled neoplastic cells with bland nuclei and focal myxoid stroma (Argani et al., 2007).

Xp11 translocation RCCs underexpress epithelial markers such as cytokeratins and EMA. In contrast, Xp11 translocation RCCs consistently express CD10 and RCC marker, and most express PAX2 and PAX8 (Argani et al., 2010). Some Xp11 translocation RCCs with typical morphology express melanocytic markers such as melan-A and HMB45.

The most sensitive and specific immunohistochemical marker for the Xp11 translocation RCC is strong nuclear *TFE3* immunoreactivity, using an antibody to the C-terminal portion of *TFE3* (Fig. 6B) (Argani et al., 2003b). One drawback is that the assay is technically challenging, and suboptimal fixation or detection methods can result in detection of native *TFE3* protein causing high background staining. Another is that genetic mechanisms other than *TFE3* gene fusions, such as *TFE3* amplification, can upregulate *TFE3* expression (Macher-Goeppinger et al., 2012). A *TFE3* breakapart fluorescence in situ hybridization (FISH) assay performed on paraffin embedded tissue has been reported for molecular confirmation of alveolar soft part

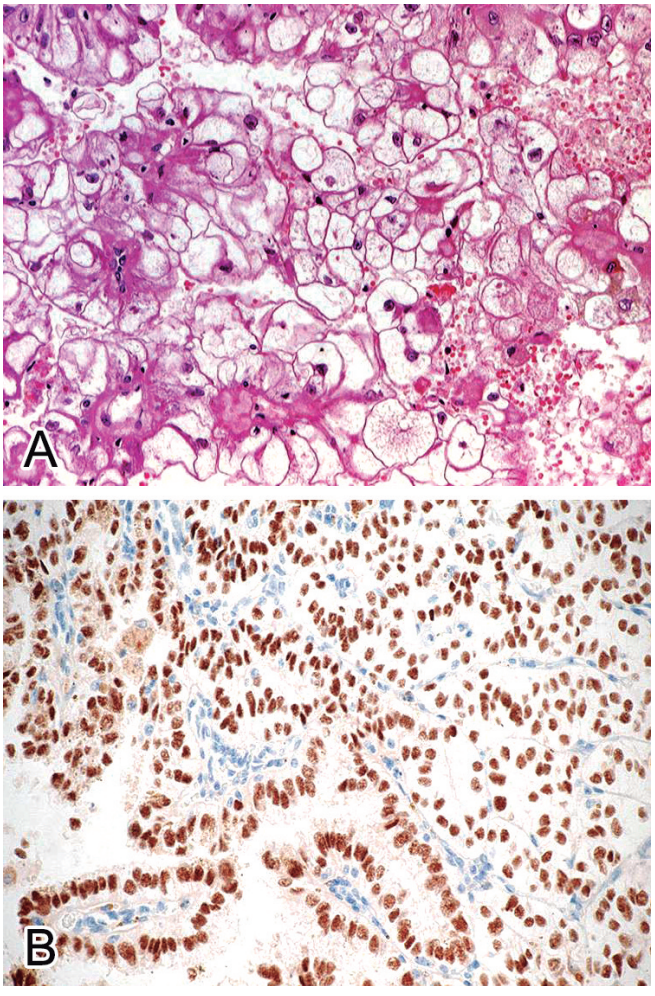

Fig. 6. Xp11 translocation renal cell carcinoma with clear cells **(A)** and strong nuclear TFE3 immunoreactivity (**B**).

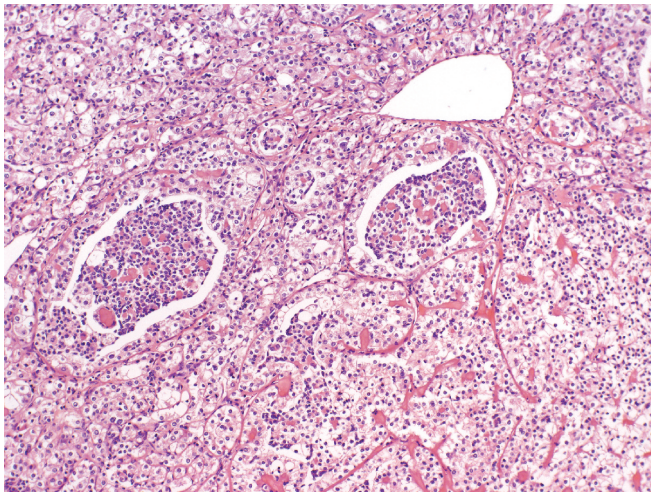

Fig. 7. Renal cell carcinoma with t(6;11) translocation. Note "pseudorosette" formation - small grouped cells surrounding collagenous stroma formed by hyaline materials.

sarcoma and Xp11 translocation RCC. Hybridization with probes centromeric and telomeric to *TFE3* normally show a fusion signal but *TFE3* rearrangement results in a split signal (Green et al., 2013; Mosquera et al., 2011). This assay is very useful for detecting *TFE3* gene fusions in Xp11 translocation RCC and suffers less from the technical issues involved with the *TFE3* immunohistochemical assay.

Expression of cathepsin K has been shown to be mediated by overexpression of MiTF in osteoclasts. Since TFE3 belongs to the MiTF family, Martignoni et al. hypothesized that overexpression of TFE3 protein in Xp11 translocation carcinoma might also mediate cathepsin K expression. As suspected, cathepsin K labels approximately 60% of Xp11 translocation RCC, almost all t(6;11) RCCs (Fig. 7), but no other common RCC subtypes (Martignoni et al., 2009, 2011; Rao et al., 2012, 2013a).

Since these neoplasms have only been recently recognized as a distinct entity by the WHO, outcome data on Xp11 translocation RCC are still premature at this time. Children with regional nodal metastases but without hematogenous spread have a favorable short-term prognosis, even though these cases qualify as high stage presentation. In a literature review, over 90% of these patients remained disease free at last followup having a median of 4.4 years and a mean of 6.3 years (Geller et al., 2008). Adults may have a worse prognosis and do poorly when presenting with systemic metastases. Unfortunately, Xp11 translocation RCCs in adults often present with advanced disease and distant metastases. Mean survival after diagnosis is in the range of 1–2 years (Meyer et al., 2007; Argani et al., 2007). Regardless of the age of the patient, Xp11 translocation RCCs have the potential to metastasize late, as many as 20 or 30 years after diagnosis. Satisfactory long-term follow up data are necessary before any favorable short-term outcome can be confirmed. Specific therapies for Xp11 translocation RCC are not clear at this time. Because of upregulation of C-Met, these tumors are eligible for clinical trials using Met inhibitors. Overexpression of phosphorylated S6 suggests the potential utility of mTOR pathway inhibitors in therapy (Argani et al., 2010).

Conclusions

CCRCC is the most common malignant tumor of renal epithelial origin and, with the exception of some rare tumors, the most deadly. Recognition of CCRCC and differentiation from other renal cell neoplasms with clear cytoplasm is important not only for prognostication but also for treatment-related reasons.

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