Multilocular Cystic Renal Cell Neoplasms of Low Malignant Potential

Multilocular cystic renal cell carcinoma (RCC) is a renal cortical neoplasm with a distinct multilocular gross appearance and is regarded as a variant of clear cell RCC. This entity accounts for approximately 4% of all clear cell RCCs and affects mid-age adults with a male to female ratio of 1.2–2.1:1. Up to 90% cases are discovered incidentally on radiologic evaluation for other causes. This cystic tumor usually presents as a unilateral solitary lesion.

Macroscopically, multilocular cystic RCC (Figure 1A) 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 discernable 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). 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 (Figure 1B). Vascular invasion, sarcomatous transformation, and metstatic spread have not been reported in all the series in which the WHO definition was adopted.

According to the definition given by the WHO, the multilocular cystic RCC 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 RCC Consensus Conference organized by the International Society of Urological Pathology in Vancouver, BC, on March 17, 2012, were asked the following question: “Is it acceptable for multilocular cystic RCC to have Fuhrman grade 2 nuclei?” The following options were available: (1) Yes, (2) No, (3) Uncertain even with personal experience/knowledge and (4) Not enough personal experience/knowledge. Of the participants 78% answered “Yes,” i.e., Fuhrman grade 2 nuclei are acceptable in multilocular cystic RCC, whereas 20% answered “No,” with the remaining 2% either uncertain or not enough experience.

Studies have been conducted on multilocular cystic RCC and clear cell RCC. Von-Hippel Lindau mutations have been identified in 25% of tumors, the neoplastic cells in a majority of the cases being strongly reactive to PAX2 and CAIX, similar to typical low-grade clear cell RCC. Chromosome 3p deletion has been identified in 89% of the clear cell RCC cases and 74% of the multilocular cystic RCC cases, with no significant difference in the status of chromosome 3p deletion between clear cell RCC
and multilocular cystic RCC. These findings are consistent with the concept of multilocular cystic RCC as a variant of clear cell RCCs.

In line with the minimal tumor burden present in these tumors, their prognosis is excellent. Multiple publications based on >200 patients with follow-up time of >5 years showed that there was no recurrence or metastases in patients whose tumor was defined according to the definition adopted by the WHO (see above). Based on the excellent outcomes, some of our group suggested redesignation of these lesions as multilocular cystic renal cell neoplasms of low malignant potential.7

A possible change in the terminology for a multilocystic 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 renal cell carcinoma, (2) Multilocular cystic renal cell neoplasm of low malignant potential, (3) Renal cell carcinoma with extensive cystic change, (4) Multicystic renal epithelial neoplasm with focal clear cell change, or (5) None of the above or Uncertain. A total of 64% 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; 34% were in favor of the current name, i.e., multilocular cystic renal cell carcinoma; the remaining 2% were split between renal cell carcinoma 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 of broadening the definition of multilocular cystic RCC by accepting under this entity also tumors that are not 100% cystic, as done

Figure 1  (A) Macroscopically, multilocular cystic RCC consists exclusively of variably sized cysts separated by thin septa. (B) 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). An important diagnostic feature is the presence within the fibrous septa of clusters of tumor cells similar to those lining the cysts.
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 clear cell RCC would become unclear, thus affecting the excellent prognosis observed for multilocular cystic RCC, and for this reason 64% of the delegates were in favor of changing the name.

The differential diagnoses mainly include RCC with cystic necrosis, tubulocystic carcinoma of the kidney, cystic nephroma, clear cell papillary RCC with predominant cystic configuration, and benign multilocular renal cortical cysts.\textsuperscript{4,8}

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.

Tubulocystic carcinoma has a distinctive gross appearance: well circumscribed with an off-white cut spongy surface that shows innumerable cysts filled with clear fluid. 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 > 90% of tumors. CK7 expression is variable, although that pattern may be weak and focal. Staining for kidney-specific cadherin and Pax-2 may also be seen. 34βE12 is nearly always negative.

Cystic nephroma (CN),\textsuperscript{9} typically located close to the 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 CN 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 ovarianlike stroma in cystic nephroma, if present, distinguishes it from multilocular cystic RCC. CN shows reactivity of epithelial component with antibodies to cytokeratins. In particular, CN frequently reacts with cytokeratin 7. Focal positivity for high molecular weight cytokeratin (34βE12) also has 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.

Clear cell papillary RCC is well-circumscribed and often variably cystic with fibrous capsule. Most tumors exhibit variable papillary and tubular/acinar architecture. The tumoral cells have predominantly clear cytoplasm with low-grade (equivalent to Fuhrman grade 1–2) nuclei. One of the most characteristic features of the tumor is the linear arrangement of the tumor nuclei away from the basal aspects of the cells, either in the middle of the cell or closer to the apex. The immunoprofile is characteristic: tumor cells express carbonic anhydrase IX (CA IX) in a diffuse membranous distribution but with absence of staining along the luminal borders of the tumor cells (cup-shaped distribution). CK7 staining is diffusely positive, whereas racemase (AMACR) is negative. CD10 is also negative in most cases.

Simple cortical cysts constitute the most common renal cysts, with a reported incidence of > 27% on radiological evaluation in individuals older than 50 years.\textsuperscript{10} 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 com-
prising 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 in distinction 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 demonstrate positivity for CK7 and CA IX and negative staining for CD10 and racemase, and the cysts with papillary proliferation, while exhibiting positive staining for CK7 and occasionally racemase, are negative for trisomy 7/17 by FISH.

In conclusion, multilocular cystic RCC is a tumor composed entirely of numerous cysts, the septa of which contain groups of clear cells indistinguishable from grade 1 clear cell carcinoma. Based on the excellent outcomes, some authors have suggested redesignation of this lesion as multilocular cystic renal cell neoplasm of low malignant potential.

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References

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