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Clear cell renal cell tumors: Not all that is "clear" is cancer

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Abstract

Continued improvement of our understanding of the clinical, histologic, and genetic features of renal cell tumors has progressively evolved renal tumor classification, revealing an expanding array of distinct tumor types with different implications for prognosis, patient counseling, and treatment. Although clear cell renal cell carcinoma is unequivocally the most common adult renal tumor, there is growing evidence that some "clear cell" renal neoplasms, such as exemplified by multilocular cystic clear cell renal neoplasm of low malignant potential (formerly multilocular cystic renal cell carcinoma), do not have the same potential for insidious progression and metastasis, warranting reclassification as low malignant potential tumors or benign neoplasms. Still other novel tumor types such as clear cell papillary renal cell carcinoma have been more recently recognized, which similarly have shown a conspicuous absence of aggressive behavior to date, suggesting that these too may be recategorized as noncancerous or may be premalignant neoplasms. This importance for prognosis is increasingly significant in the modern era, in which renal masses are increasingly found incidentally by imaging techniques at a small tumor size, raising consideration for less aggressive management options guided by renal mass biopsy diagnosis, including imaging surveillance, tumor ablation, or partial nephrectomy.

Keywords: Kidney; Renal cell carcinoma; Multilocular cystic clear cell renal neoplasm of low malignant potential; Clear cell papillary renal cell carcinoma; Overdiagnosis; Terminology

Integration of clinical, histologic, and genetic features continues to reshape the classification of renal tumors, establishing novel variants with distinct prognoses, different genetic underpinnings, and unique histology associated with inherited syndromes [1]. In general, it is well known that renal cell carcinoma has the capacity for late recurrence and metastasis to unusual sites [2], conferring a need for long-term surveillance and a high level of clinical suspicion after resection. However, accumulating insight into the behavior of particular renal tumor variants suggests that not all are necessarily capable of this insidious progression, such as exemplified by multilocular cystic renal cell carcinoma [1-3], a distinct tumor type now endorsed as a tumor of low malignant potential rather than a carcinoma (multilocular cystic clear cell renal neoplasm of low malignant potential) in the International Society of Urological Pathology (Vancouver Classification of Renal Neoplasia and the 2016 World Health Organization Classification of Tumors of the Urinary System and Male Genital Organs [1].

Multilocular cystic renal cell neoplasm of low malignant potential is defined as an entirely cystic tumor, composed of cells with clear cytoplasm lining the cysts and small aggregates of similar cells within the cyst walls (Fig. 1). By definition, a solid, mass-forming component is absent [1,4]. Although there is molecular evidence for shared genetic pathways with usual clear cell renal cell carcinoma, such as chromosome 3p loss [4] and mutation of the *VHL* gene [5], no report of aggressive behavior has been described to date, supporting the reclassification of these

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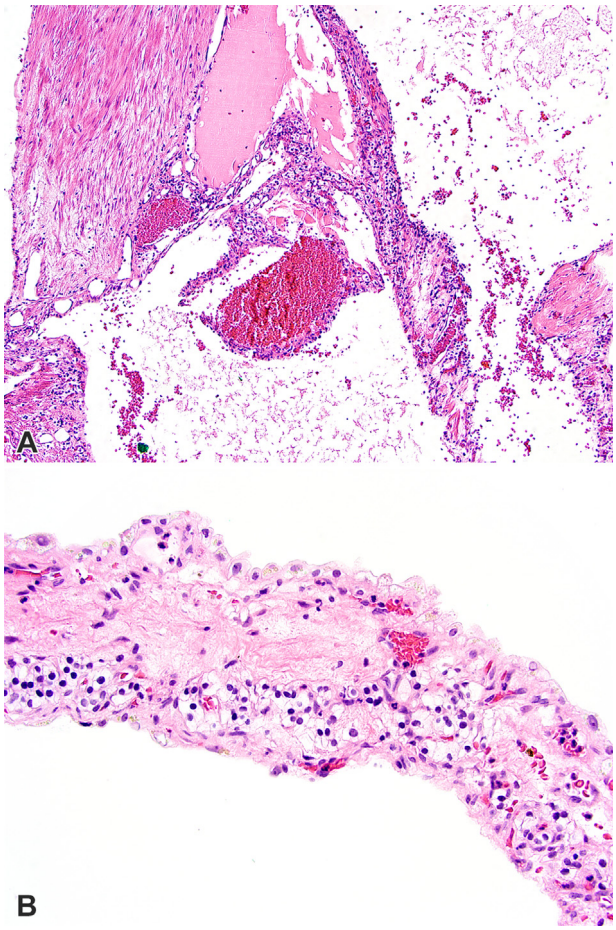

Fig. 1. Multilocular cystic clear cell renal neoplasm of low malignant potential (formerly known as multilocular cystic renal cell carcinoma) is composed of multiple cystic spaces, lined by cells with clear cytoplasm (A), similar to the cells of low-grade clear cell renal cell carcinoma. Within the cyst walls, clusters and aggregates of histologically similar cells are present (B); however, these do not form a gross mass or expand the septa.

indolent lesions as neoplasms of low malignant potential rather than carcinomas [1]. Interestingly, although these multilocular cystic clear cell renal neoplasms of low malignant potential are strictly defined as entirely cystic, there is also evidence that renal cell carcinomas with a substantial cystic component similarly behave in a predominantly indolent fashion, even when a variable degree of solid tumor cellularity is present [6–8], suggesting that distinct molecular mechanisms may be involved or absent in tumors with a predilection for cystic growth or degeneration [5,9].

Although multilocular cystic renal cell neoplasm of low malignant potential is one of the most widely accepted examples of a tumor previously classified as a renal cell carcinoma and now regarded as a low malignant potential tumor, other histologic tumor types show promise for similar reclassification as benign or low malignant potential neoplasms in the future, such as clear cell papillary renal cell carcinoma [1]. Clear cell papillary renal cell carcinoma was first recognized as a unique histology in end-stage kidneys [10]; however, accumulating evidence indicates that these are more common in non–end-stage kidneys, and likely they represent the fourth most common renal cell carcinoma subtype, after clear cell, papillary, and chromophobe renal cell carcinomas [11–15]. Although these tumors bear substantial histologic resemblance to clear cell renal cell carcinoma (Fig. 2) and usually would have been diagnosed as such in the past [12], the main driver genetic events of clear cell renal cell carcinoma are lacking, particularly chromosome 3p deletion and *VHL* gene mutation [13,14,16–24], and the immunohistochemical staining characteristics are distinctive [12,16]. To date, there remains no well-established aggressive behavior in the usual form for this novel tumor entity [25]. Very rare tumors in recent reports have been found to have focal tumor necrosis or perinephric fat extension, yet even these have not been shown to exhibit progression or metastasis [26]. A single tumor from a large series contained clear cell papillary-like and sarcomatoid areas and behaved aggressively [27], although the authors proposed that in the absence of such obvious malignant histology, these tumors be regarded as low malignant potential neoplasms [27]. It also remains debatable whether such examples with aggressive histology truly represents a progression or transformation of this indolent tumor type, or histologic mimicry by another high-grade form of renal cell carcinoma [28,29].

A recent report [30] combining insights from the Cancer Genome Atlas clear cell renal cell carcinoma dataset [31] and another large-scale molecular analysis of renal cell carcinoma [32] found that a small minority of renal tumors resembling clear cell renal cell carcinoma lack its expected characteristic genetic alterations and instead harbor mutation and loss of heterozygosity for the *TCEB1* gene [30]. Although, histologically closely resembling usual clear cell renal cell carcinoma, these tumors were found to have a few subtle differences in histologic features and immunohistochemical staining findings, suggesting that they may also be pathogenetically and potentially behaviorally distinct, as none in this small cohort behaved aggressively over intermediate term follow-up [30].

These insights into renal tumor classification are likely to have increasingly important effects on patient management in the future. Historically, renal cell carcinomas have been detected at a higher tumor size and stage, often because of patient symptoms or detection of a large palpable mass. However, in the era of modern imaging techniques, treatment of the small, incidentally detected renal mass is a growing area of study and debate, with management options including surveillance and tumor ablation emerging as major considerations, sometimes driven by renal tumor biopsy diagnosis and grading [33]. Whereas previously renal tumor biopsy was considered unfavorable because of concerns of nondiagnostic samples, patient complications, or tumor seeding of the biopsy tract, this practice is now increasingly widely used, often showing a high diagnostic