THE ENIGMA OF MULTILOCULAR CYSTIC RENAL TUMORS: LOW MALIGNANT POTENTIAL POSING AS CYSTIC CLEAR CELL CARCINOMA – INSIGHTS FROM A UROLOGIST

Abstract

Multilocular cystic renal neoplasm of low malignant potential (MCRNLMP) is a rare subtype of clear cell renal cell carcinoma (CCRCC), constituting approximately 2-4% of CCRCC cases. Formerly classified as multilocular cystic renal cell carcinoma (MCRCC), it was redefined by the World Health Organization (WHO 2016) and the International Society of Urological Pathology (ISUP 2013) due to its distinct pathological features and lack of metastatic potential. MCRNLMP is characterized by cysts encapsulated by fibrous tissue lined by clear cells with low nuclear grade, without expansile nodules or invasive growth. These features and specific immunohistochemical markers distinguish it from other cystic renal tumors and underscore its favourable prognosis.

We present the case of a 46-year-old male who exhibited dull loin pain and was subsequently diagnosed with a Bosniak category IV renal cystic mass on imaging. A laparoscopic partial nephrectomy was performed, and histopathology confirmed MCRNLMP. The patient's postoperative course was uneventful, and a three-year follow-up showed no evidence of recurrence or metastasis.

In reviewing the literature, we found that MCRNLMP is associated with a benign clinical course, with neither recurrence nor metastasis reported in patients with adequate follow-up. It remains difficult to differentiate this entity radiologically from other cystic renal masses, necessitating histopathological evaluation for definitive diagnosis. Urologists should recognize MCRNLMP to avoid over-treatment and reduce anxiety for patients. With complete resection,

prolonged disease-free survival can be expected, supporting the adoption of longer intervals for follow-up and reduced imaging. This case and literature review highlight the importance of precise histological criteria to identify and manage MCRNLMP effectively.

Keywords

Multilocular cystic renal neoplasm of low malignant potential, clear cell RCC, renal tumour histopathology, cystic renal tumours, partial nephrectomy, WHO/ISUP renal tumour classification.

Introduction: Two to four percent of clear cell renal cell carcinoma (CCRCC) is multilocular cystic renal cell carcinoma (MCRCC), a highly uncommon subtype of CCRCC. MCRCC is a cystic kidney tumor with characteristics of cellular and cytogenetic changes (3p mutation, VHL) similar to those of CCRCC [1,2]. The World Health Organization (WHO 2016) and the International Society of Urological Pathology (ISUP 2013) have updated the classification of kidney tumors [3-5]. Due to its unique pathological characteristics and the absence of metastasis or recurrence, multilocular cystic renal neoplasm of low malignant potential (MCRNLMP) replaced MCRCC as the new terminology [6].

According to WHO (2016), MCRNLMP is "a neoplasm composed entirely of numerous cysts surrounded by a fibrous capsule and septa that contains clear cells without expansile growth or mural nodules." The organization has established relatively strict diagnostic criteria. Morphologically and radiologically, these tumors are identical to low-grade cystic CCRCC.

Low malignant potential replaced the term "carcinoma" in ISUP (2013) [7, 8]. After compiling information from all relevant sources in the literature, Tretiakova et al. [9] concluded that MCRNLMP patients who had at least a five-year follow-up had neither a recurrence nor a

metastatic event. This chapter aims to raise awareness among urologists about this potentially treatable illness and to stress the significance of recognizing these entities using precise histological criteria outlined by WHO (2016). This set of lesions is classified as lower risk regardless of TNM staging. Upon long-term follow-up, no cases of metastasis or recurrence have been reported following total resection through radical or partial nephrectomy, contrary to CCRCC [10].

Why Multilocular Cystic Renal Neoplasm is controversial?

Multilocular Cystic Renal Neoplasm of Low Malignant Potential (MCRNLMP) is controversial due to several factors related to its classification, diagnosis, and treatment implications. Here are some of the main reasons why this renal neoplasm generates debate:

1. ***Classification Challenges***

MCRNLMP was historically grouped with cystic renal cell carcinoma (RCC) subtypes, such as cystic clear cell RCC. It wasn't until 2004 that the World Health Organization (WHO) classified MCRNLMP as a distinct entity with low malignant potential. This classification shift has led to ongoing discussions about where it should sit within renal neoplasm taxonomies, especially as some pathologists still question its place as a distinct category.

2. ***Histological and Radiological Similarities to Clear Cell RCC***

MCRNLMP and cystic clear cell RCC share overlapping features on imaging and histology, which can make them difficult to distinguish preoperatively. Both can present as multilocular cystic masses within the kidney, leading to diagnostic confusion. Radiologists and pathologists must rely on subtle differences, making accurate diagnosis challenging and sometimes subjective.

3. ***Uncertain Malignant Potential***

Although MCRNLMP is defined as having low malignant potential, some cases have been reported to exhibit invasive behavior or even metastasis, though these are rare. This creates

uncertainty about the true nature of its malignancy risk, which impacts clinical decision-making. Some urologists and oncologists may still treat it cautiously, similar to more aggressive RCCs, until more is known about its long-term outcomes.

4. ***Management and Treatment Debate***

The low malignant potential associated with MCRNLMP suggests that conservative management, such as active surveillance or nephron-sparing surgery, may be appropriate. However, the resemblance to clear cell RCC often leads clinicians to recommend partial or radical nephrectomy. This discrepancy creates a dilemma where the desire to avoid overtreatment conflicts with the need for caution in potentially malignant tumors.

5. ***Prognostic Implications***

MCRNLMP generally has an excellent prognosis with low recurrence risk, which theoretically should allow for more conservative management. However, the potential for rare, aggressive cases contributes to uncertainty about prognosis, making it difficult to establish universally accepted treatment protocols.

6. ***Lack of Consensus in Literature***

The limited number of cases and relative rarity of MCRNLMP contribute to the lack of large-scale studies that could provide more definitive data on its behavior and optimal management. This leads to variability in clinical practice, with some institutions treating it conservatively while others take more aggressive approaches.

In summary, the controversy around MCRNLMP stems from its ambiguous classification, diagnostic overlap with more aggressive RCCs, unclear malignant potential, and lack of consistent treatment guidelines. Ongoing research into its molecular and genetic profile may eventually clarify its place among renal tumors and aid in standardizing its management.

This chapter aims to highlight the controversies and reach a consensus on making a prompt diagnosis, thereby facilitating early and appropriate treatment.

Case report

A 46-year-old gentleman who was a nonsmoker presented with a one-month history of dull left loin pain. There was no history of bothersome lower urinary tract symptoms. He didn't have a history of any co-morbidities. His liver and kidney function tests and blood biochemical analyses were all within normal limits.

Abdominal ultrasonography indicated a cystic renal tumor in the left lower pole. A well-defined, single, partially exophytic mass with solid components inside was visible on a contrast-enhanced computed tomography (CECT KUB) scan (Bosniak Category—IV). Measuring 3.8X3.6cm, it was a heterogeneously enhancing left lower pole renal tumor (Figure 1). The patient underwent a laparoscopic partial nephrectomy. The perioperative phase was uneventful.

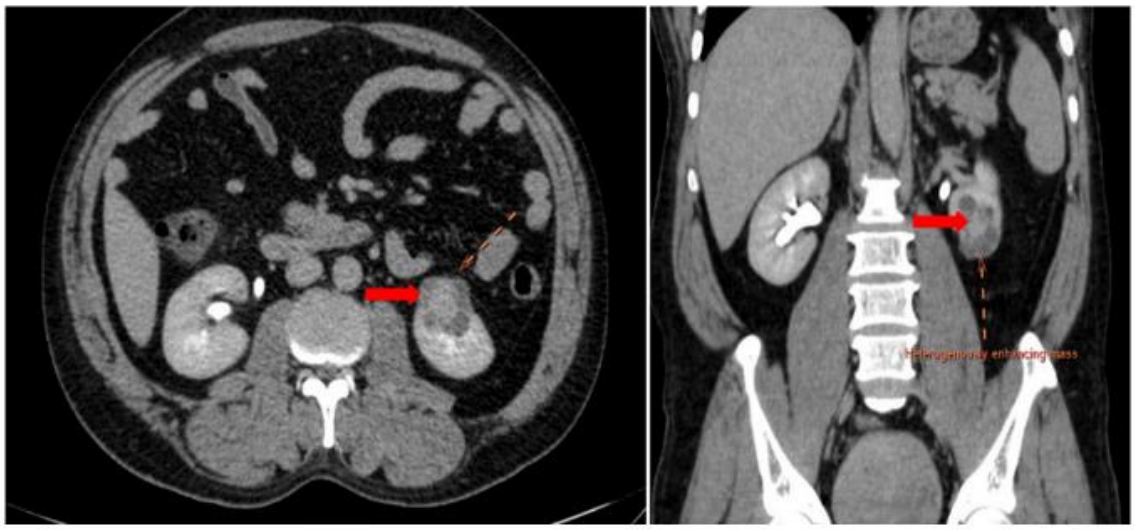

Figure 1. Contrast-enhanced CT-KUB showing a well-defined, solitary, partially exophytic, multicystic lesion with a solid component, heterogeneously enhancing left lower pole renal mass.

The gross specimen revealed a single, 4.2 × 3 cm, well-encapsulated single lesion with a clear, serous, or gelatinous substance inside, including non-communicating cysts of various sizes. Solid nodules or necrosis were absent. A multi-cystic lesion with thin septal walls of fibro-collagenous connective tissue and single or occasionally numerous layers of transparent cuboidal cells with copious cytoplasm were observed under a microscope (Figure 2A, 2B). These cells (ISUP grade 1 - low grade) exhibited tiny hyperchromatic nuclei with uniform borders and little or non-existent nucleoli.

There were few mitotic figures. There was no vascular invasion, necrosis, expansile mural nodules, hyalinization, or sarcomatoid variations seen. Strong membrane positivity for vimentin and epithelial membrane antigen (EMA) was observed in immunohistochemistry (Figure 3A, 3B). The tumor had an ISUP nuclei grade of 1 and TNM staging of T1bN0M0. The patient has a disease-free survival of over three years and receives routine follow-up with imaging studies and clinical examination.

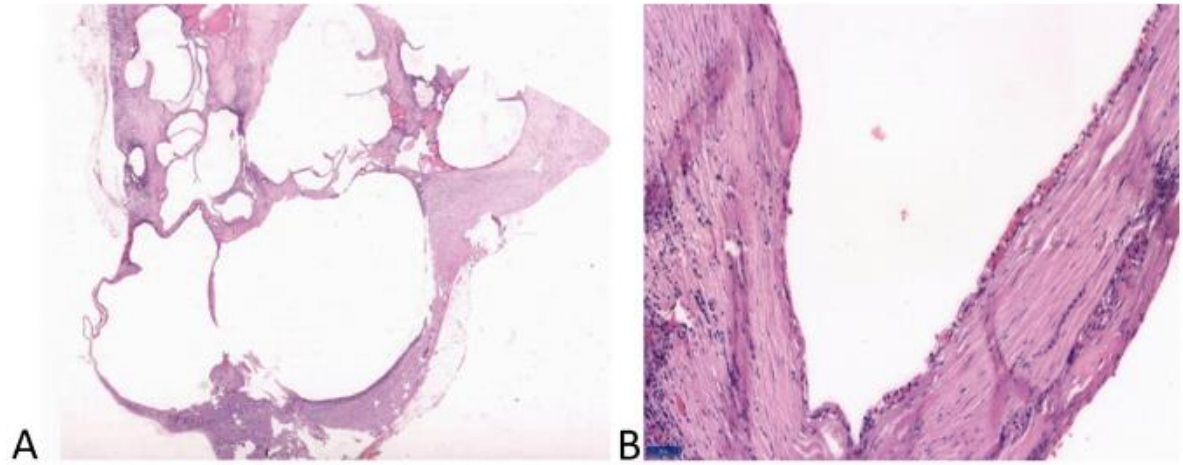

Figure 2: Haematoxylin & Eosin staining of the cystic lesion. (A) Multiple cystically dilated spaces separated by thin fibrous septae (20X); (B) Cystic spaces are lined by a single layer of low cuboidal epithelial cells with clear cytoplasm (100X).

Discussion

In our day-to-day urological practice, renal cysts are one of the most common findings in the ultrasonography of the abdomen. These are mostly benign and asymptomatic. When there is internal bleeding or a secondary infection, they start to show symptoms. The incidence of renal cysts increases with age, affecting more than 50% of patients over 50 [11]. According to Hartman [12], cystic renal cell carcinomas can make up as much as 15% of all renal cell carcinoma cases. However, MCRNLMP barely makes up 2–4% of the total CCRCC [13]. These tumors grow due to significant renal tubular cystic regression or expansion, which obstructs fluid flow and eventually forms into cysts.

Suzigan et al. [14] initially suggested the term MCRNLMP in 2006 when they reviewed the 2004 WHO classification of renal tumors. In his studies, 45 individuals with multilocular cystic RCC were shown to have a 100% five-year disease-specific survival rate and a favorable prognosis for the condition. They noted that 82% of their cases were in the T1 stage, and 100% (G1-62%

and G2-38%) had low nuclear grades. Following surgery, none of the individuals in their series showed any recurrence.

In 2013, ISUP replaced the word MCRCC with MCRNLMP. The WHO Classification of 2016 subsequently acknowledged this adjustment in nomenclature.

According to the definition, MCRNLMP is a multilocular cystic tumor bordered by low ISUP grade (1-2) clear cells identical to CCRCC immunohistochemically and molecularly [15]. It would have had some clinical significance if imaging studies had provided criteria for differentiating between partly cystic RCC, MCRNLMP, and atypical renal cysts [16]. Imaging results for all three disorders are comparable, which precludes a urologist or a radiologist from diagnosing this disease. Histopathological analysis, however, could differentiate the three categories with clarity. Well-encapsulated multilocular non-communicating cysts without tumour necrosis, clear serous or gelatinous fluid, and occasionally hemorrhagic debris were among the gross features [17]. Solid nodules were also absent. Cysts with septae lined by transparent cuboidal cells with low-grade nuclei, either in a single layer or in aggregation, are among the microscopic characteristics. One trait common to these circumstances is the absence of substantial nodules or expansile growth [18]. Immunohistochemistry was positive for vimentin, EMA, and CD10.

Cystic nephroma, tubulocystic RCC, and cystic clear cell papillary RCC are other differential diagnoses [19]. A characteristic feature that sets females with cystic nephroma apart is the presence of ovarian-type stroma. The papillary architecture is a distinguishing characteristic of cystic clear cell papillary RCC, which also has clear cells with low-grade nuclei.

Clear cells are replaced by eosinophilic cytoplasm and high-grade nuclei in tubulocystic RCC lining cells. As stated earlier, the existence of expandable nodules is what distinguishes cystic

CCRCC from other conditions. In one of the most extensively documented case series with 76 patients, Li et al. [20] found that these tumours were primarily low nuclear grade regardless of tumour size and TNM staging and recommended a longer follow-up period to reduce needless testing. MCRNLMP was described by Nassir et al. [21] as a predominantly cystic lesion with neoplastic clear cells, most likely a subtype of CCRCC with a benign clinical course.

According to Gong et al.'s [22] analysis of 31 patients, multilocular cystic RCC had a great outcome, and neither tumour development nor metastasis was seen. In one of the longest follow-ups of six patients of MCRNLMP, Murad et al. [23] found no evidence of metastasis or recurrence, concluding that these tumours represent a low-grade form of RCC with an excellent prognosis.

Tretiakova et al.'s comparative study [9] between MCRNLMP and cystic CCRCC found that MCRNLMP exhibited consistently favourable behaviour and supported the ISUP's recommendation for its non-carcinoma classification. They also concluded that CCRCC that was primarily cystic, had a better prognosis than solid or non-cystic CCRCC and that the reporting pathologist should note the degree of the cystic component in the histopathology report.

According to these studies, MCRNLMP is a low-grade, well-defined tumour. Most cases were successfully treated with partial nephrectomy, with no metastasis or recurrence. In our case, a three-year follow-up after a partial nephrectomy, which involved annual imaging studies

and clinical assessments, showed no signs of metastasis or recurrence. This indicates that we can implement longer follow-up periods for patients with this type of tumor to minimize unnecessary examinations and investigations.

Summary:

Distinct Entity with Excellent Prognosis: MCRNLMP is a unique renal tumor with low malignant potential and generally excellent long-term outcomes. Recognizing it as a separate entity from more aggressive renal cell carcinomas is essential for optimal patient management.

Diagnostic Challenges Persist: MCRNLMP can mimic cystic RCC on imaging, making it challenging to differentiate preoperatively. Histopathological analysis is crucial for accurate diagnosis, as MCRNLMP lacks the invasive features found in malignant RCCs.

Histopathology Remains the Gold Standard: A definitive diagnosis of MCRNLMP requires histopathology, showing multiple cysts lined by clear cells without solid tumor growth or invasive characteristics. This helps differentiate it from more aggressive cystic renal tumors.

Potential for Over-Treatment: MCRNLMP may not require aggressive treatment like radical nephrectomy due to its low malignancy risk. However, diagnostic uncertainty often leads to overtreatment. Recognizing MCRNLMP can help guide more conservative, kidney-sparing management.

Emerging Molecular and Genetic Insights: Molecular markers may aid in differentiating MCRNLMP from cystic RCC in the future, potentially reducing diagnostic ambiguity and supporting less invasive management strategies.

Need for Standardized Guidelines: Consistent diagnostic and treatment guidelines are necessary to ensure appropriate, uniform care for patients with MCRNLMP. These guidelines can help clinicians confidently choose conservative management when appropriate.

In summary, accurate identification and conservative management of MCRNLMP can prevent overtreatment and support kidney preservation in patients with this low-risk tumor type.

Conclusions

Diagnosing MCRNLMP accurately is essential for preventing overtreatment and optimizing patient outcomes. Improved diagnostic precision through histopathological assessment and emerging molecular markers, alongside clear clinical guidelines, could further enhance the management of this unique renal neoplasm. Accounting for about 2-4% of all CCRCC instances, it is an uncommon subtype with a minimal propensity for malignancy. Most instances were discovered incidentally, and imaging tests cannot distinguish them from other cystic lesions. According to WHO recommendations, histopathology aids in conclusive identification. Regardless of TNM stage, they are considered low risk, and with complete resection, there is no record of recurrence or metastasis. Urologists who are thoroughly aware of this entity might help patients feel less anxious by avoiding time-consuming imaging studies and adopting longer follow-up intervals.

References

1. Teichman A, Compérat E, Behnke S, Storz M, Moch H, Schraml P: VHL mutations and dysregulation of pVHL- and PTEN-controlled pathways in multilocular cystic renal cell carcinoma. Modern Pathology 2010, 24(4): 571-578.

2. Grignon DJ, Bismar TA, Bianco F, et al: VHL gene mutations in multilocular cystic renal cell carcinoma: evidence in support of its classification as a type of clear cell renal cell carcinoma. Mod Pathol 2004, 17 (suppl1): 154A.

3. Srigley JR, Delahunt B, Eble JN, et al. The International Society of Urological Pathology (ISUP) Vancouver classification of renal neoplasia. Am J Surg Patho 2013, l37: 1469-1489.

4. International Agency for Research on Cancer: WHO Classification of Tumours of the Urinary System and Male Genital Organs. 2016, ISBN: 9789283224372.

5. Moch H, Humphrey PA, Ulbright TM, Reuter VE: WHO classification of tumours of the urinary system and male genital organs, 4th edn. Lyon, France. 2016.

6. Montironi R, Mazzucchelli R, Scarpelli M, Lopez-Beltran A, Cheng L: Update on selected renal cell tumors with clear cell features. With emphasis on multilocular cystic clear cell renal cell carcinoma. Histopathology 2013, 28(12): 1555-1566

7. Hes O et al: International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia 2012 [International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia 2012].

8. Kristiansen G, Delahunt B, Srigley JR et al: [Vancouver classification of renal tumors: Recommendations of the 2012 consensus conference of the International Society of Urological Pathology (ISUP)]. Pathologe 2015, 36(3): 310-316.

9. Tretiakova M, Mehta V, Kocherginsky M et al: Predominantly cystic clear cell renal cell carcinoma and multilocular cystic renal neoplasm of low malignant potential form a low-grade spectrum. Virchows Arch 2018, 473: 85-93.

10. Bhatt JR, Jewett MA, Richard PO et al: Multilocular cystic renal cell carcinoma: pathological T staging makes no difference to favorable outcomes and should be reclassified. J Urol 2016, 196: 1350-1355.

11. Chang CC, Kuo JY, Chan WL, Chen KK, Chang LS: Prevalence and clinical characteristics of simple renal cyst. J Chin Med Assoc 2007, 70(11): 486-491.

12. Hartman DS, Davis CJ Jr, Johns T, Goldman SM: Cystic renal cell carcinoma. Urology 1986, 28: 145-153.

13. Halat S, Eble JN, Grignon DJ et al: Multilocular cystic renal cell carcinoma is a subtype of clear cell renal cell carcinoma. Mod Pathol 2010, 23: 931-936.

14. Suzigan S, López-Beltrán A, Montironi R et al: Multilocular cystic renal cell carcinoma: a report of 45 cases of a kidney tumor of low malignant potential. Am J Clin Pathol 2006, 125: 217-222.

15. Montironi R, Lopez-Beltran A, Cheng L, Scarpelli M: Words of wisdom: re: multilocular cystic renal cell carcinoma with focus on clinical and pathobiological aspects. Eur Urol 2013, 63: 400-401.

16. Aubert S, Zini L, Delomez J, Biserte J, Lemaitre L, Leroy X: Cystic renal cell carcinomas in adults. Is preoperative recognition of multilocular cystic renal cell carcinoma possible? J Urol 2005, 174: 2115-2119.

17. Mazzucchelli R, Scarpelli M, Montironi R, Cheng L, Lopez Beltran A: Multilocular cystic renal cell neoplasms of low malignant potential. Anal Quant Cytopathol Histopathol 2012, 34: 235-238.

18. Williamson SR, MacLennan GT, Lopez-Beltran A, et al. Cystic partially regressed clear cell renal cell carcinoma: a potential mimic of multilocular cystic renal cell carcinoma. *Histopathology*. 2013;63(6):767-779. doi:10.1111/his.12239.

19. Ebin JN, Bonsib SM: Extensively cystic renal neoplasms: Cystic nephroma, cystic partially differentiated nephroblastoma, multilocular cystic renal cell carcinoma and cystic hamartoma of renal pelvis. Semin Diagn Pathol 1998, 15: 2-20.

20. Li T, Chen J, Jiang Y et al: Multilocular Cystic Renal Cell Neoplasm of Low Malignant Potential: A Series of 76 Cases. Clin Genitourin Canc 2016, 14(6): pp. e553-e557.

21. Nassir A, Jollimore J, Gupta R, Bell D, Norman R: Multilocular cystic renal cell carcinoma: a series of 12 cases and review of the literature. Urology 2002, 60: 421-427.

22. Gong K, Zhang N, He Z, Zhou L, Lin G, Na Y: Multilocular cystic renal cell carcinoma: an experience of clinical management for 31 cases. J Cancer Res Clin Oncol 2008, 134: 433-437.

23. Murad T, Komaiko W, Oyasu R, Bauer K: Multilocular cystic renal cell carcinoma. Am J Clin Pathol 1991, 95: 633-637.