

Multilocular cystic renal neoplasm-low malignant potential (MCRN-LMP) - review

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Abstract

Multilocular Cystic Renal Neoplasm of Low Malignant Potential (MCRN-LMP), previously known as multilocular cystic renal cell carcinoma as a rare variant of cystic kidney. It is composed of multiple cysts separated by thin septa covered with clear cells with no expansile growth. The term MCRN-LMP should be used exclusively to identify a cystic kidney lesion with a small clusters of neoplastic clear cells in the cyst walls. Clinically these cases may present with flank pain or the majority of these tumors are incidentally found on radioimaging. Grossly, the tumor is well demarcated and consists of multiple various-sized cysts. The fibrous septa are generally thin and there is no discernible expansile nodule. The WHO/ISUP nuclear grade is generally low and usually corresponds to grade 1 or 2. In the World Health Organisation (WHO) 2016 classification of kidney tumors recognizes MCRN-LMP as a rare variant of cystic kidney. MCRN-LMP generally exhibits a low stage of TNM classification. These tumors have a favorable clinical course. The clinical course of these lesions suggests that patients may benefit from nephron-sparing surgery. The aim of this review is to bring attention, that MCRN-LMP is a low aggressive neoplasm with no recurrence and no metastatic potential. The updated diagnostic modalities and conservative line of management may be applicable for this rare entity for the better care of patients.

Key words Cystic renal tumors, renal multilocular cysts, renal neoplasm of low malignant potential, histopathology

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Introduction

The cystic renal neoplasms in adults are a heterogeneous group of tumors with characteristic histogenesis, radioimaging, pathological findings, immunohistochemistry and variable biological profiles. The recent advances in cytogenetics and molecular biology have provided unique processes involved in the pathogenesis of a number of renal cystic diseases in adults [1, 2].

The renal cystic disease is a common cause of end stage renal disease in adults. It comprises a wide spectrum of hereditary, acquired, developmental, and neoplastic conditions [3]. These are classified in adult as:

Renal Cystic Diseases in Adults

a) Hereditary diseases - Autosomal dominant polycystic kidney disease, Medullary cystic kidney disease, Von Hippel-Lindau disease, Tuberous sclerosis complex etc.

b) Nonhereditary disease -Acquired cystic kidney disease, Medullary sponge kidney, Multicystic dysplastic kidney, Localized renal cystic disease.

They are associated with the development of a wide spectrum of benign and malignant renal neoplasms.

The terminology has changed and so called "multilocular cystic renal cell carcinoma" is currently named as multilocular cystic renal neoplasm of low malignant potential in the International Society of Urological Pathology Vancouver Classification of Renal Neoplasia and the 2016 World Health Organization revised Classification of Tumors of the Urinary System and Male Genital Organs [4, 5].

Multilocular cystic renal neoplasm-low malignant potential (MCRN-LMP)

From various new publications studies, the data showed excellent prognosis is related to this entity and in 2016, WHO published a new classification of renal tumors, these tumors are now termed as "MCRN-LMP" with ICD code-8316/1 [5]. Use of "Multilocular Cystic Renal Cell Carcinoma" is considered obsolete.



Figure 1. Gross appearance multilocular cystic neoplasm of low malignant potential: Left radical nephrectomy specimen showing a gray-brown cystic lesion surrounded by a fibrous wall.

The WHO 2016 has defined the criteria proposed for MCRN-LMP in revised classification are as follows:

a) Tumor containing numerous cysts with low grade tumor cells in it (ISUP-International Society of Urological Pathology/WHO grade 1/2).

b) Cysts are lined by single layer of tumor cells with abundant clear cytoplasm of low grading.

c) Septa contain few groups of clear cells without expansile growth [5].

The MCRN-LMP accounts for approximately 1 to 2% of all renal tumors [6]. It is included in the group of tumors of undetermined malignant potential with low nuclear grade. The male to female ratio for MCRN-LMP is 3:1 and the mean age is of 51 years.

Radio Imaging

It is noted that, clinically about 90% cases are discovered incidentally on radiology for other purposes. Contrast-enhanced ultrasound have the same sensitivity and high specificity as contrast-enhanced computed tomography for the detection of multilocular cystic renal neoplasm of low malignant potential. The ultrasonography and CT images obtained in the study by Kim et al showed that MCRN-LMP appeared as a well-defined multilocular hypodense cystic mass filled with serous or hemorrhagic fluid, with no expansile solid nodules in the thin septa may with dystrophic calcification [7].

The imaging patterns of MCRN-LMP are variable. The various studies revealed correlation between the gross pathologic appearance of the tumors with the corresponding imaging appearance.

The radioimaging various renal lesions mimics for MCRN-LMP includes hemorrhagic cysts, localized cystic disease of the kidney, atypical cysts, cystic nephroma, tubulocystic carcinoma, papillary RCC, extensively cystic RCC and other subtypes of RCC.

Most MCRN-LMPs are Bosniak category III, some are category IIF (more fluid, minimal solid component), and others are category IV (large amount of enhancing fibrous tissue). It has been observed that the correlation did not persist for tumors smaller than 3 cm. In such situation histopathological study plays important role in confirmatory diagnosis with added immunohistochemistry and molecular evaluation.

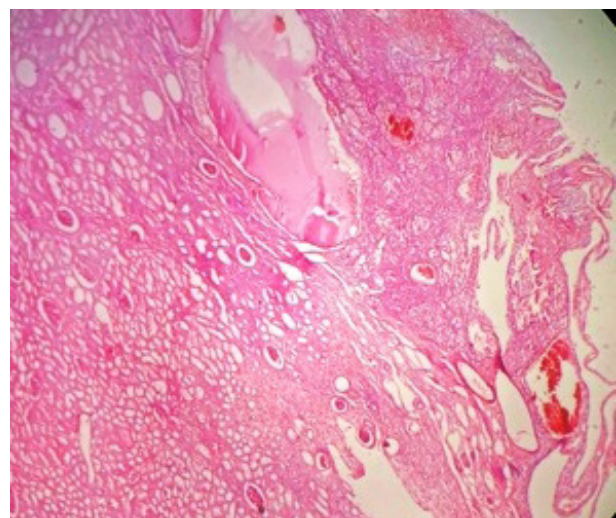


Figure 2. Renal tissue showing numerous cysts, the septa contain low grade tumor cells in it, (H & E Stain, 40x).

Table 1. MCRN-LMP and other cystic lesions of kidney: clinical, histopathological, IHC, and molecular features.

Renal Cell Tumor types	Clinical Features	Histopathological/ Immunohistochemical Features	Molecular Features
MCRN-LMP	Asymptomatic, excellent prognosis Children	Numerous cysts lined by clear cells; positive for CAIX and CK7	VHL mutation, Ch 3p deletion
Cystic nephroma	< 5 years asymptomatic, may have abdominal mass or obstructive symptoms	shows variably sized cysts lined by flat / cuboidal / hobnail cells with thin fibrous septae lined by bland non clear cells. The ovarian-type stromal cells are positive for ER, PR and CD10 epithelial cyst lining positive for HMWCK, CK19 and AMACR	DICER 1 gene mutations is well established in paediatric cystic nephroma
ccRCC with cystic changes	good prognosis	Numerous cysts lined by clear cells >75% cystic are as with expansile growth	miR-122, miR-124-3p, miR-137, miR-141, miR-182-5p, miR-203, and miR-217
Cystic PRCC	TYPE 1- better prognosis	Papillae are lined by a single layer of cells with scanty basophilic cytoplasm and low nuclear grade	+7, +17 and other trisomies, MET mutations
Tubulocystic RCC	Mostly in Males, mean age 60 years, indolent course	Dilated tubules with a single layer of cells lining by cells showing nuclear enlargement. Tumor cells show oncocytic change with hobnailing and nucleolar grade of 3	Gain of Ch 7 and 17, loss of Ch Y
ACD-associated RCC	End-stage renal disease or ACD, indolent	Eosinophilic cytoplasm, sieve-like pattern, intratumoral oxalate crystals; positive for AMACR and CD10, negative for CK7	Gain of Ch 3, 16, and Y

MCRNLMP -Multilocular cystic renal neoplasm of low malignant potential, Ch-Chromosome, miR-microRNA, ACD- acquired cystic disease, RCC- Renal Cell Carcinoma. VHL-von Hippel Lindau, Cystic PRCC-Cystic Papillary RCC.

Pathological features

On the gross pathologic features- MCRN-LMPs are encapsulated, multilocular cystic appearance, variably sized cysts filled with clear, serous, gelatinous material or hemorrhagic debris, absent expansile nodules, and absent tumor necrosis (**Figure 1**). Before making a diagnosis of MCRN-LMP, the tumor should be extensively sampled.

The microscopic features of MCRN-LMP include cysts lined by cuboidal clear cells or flattened epithelium with septa containing aggregates of epithelial cells with clear cytoplasm and of low WHO/ISUP nuclear grade 1 or 2 (**Figure 2, 3**). The septae may be lined by multilayered clear cells. The capillary vessel proliferation under epithelium are important features of MCRN-LMP [8]. The solid expansile mass-forming areas by definition are absent. In few cases, cysts lining may show multilayering and few papillary feature. The septa may contain calcification, ossification, and or capillary proliferation (**Figure 4**). There is no evidence of necrosis, vascular invasion or sarcomatoid change.

We reported a case of MCRN-LMP in a 70 year male with history of intermittent left flank pain and hematuria. On histopathology, the left renal lesion showed a multicystic tumor, and the cysts were separated by thin fibro-collagenous septa lined by aggregates of clear cells with low nuclear grade-1 with no expansile growth [9]. On regular follow up it has been noted that there was no recurrence or metastases in this case.

Differential diagnosis

The various conditions like cystic nephroma, ACD-associated RCC, cystic papillary renal cell carcinoma, tubulocystic carcinoma, regressing clear cell renal cell carcinoma (ccRCC) with cystic degeneration should be kept as histopathological differential diagnoses [10].

Cystic nephroma shows variably sized cysts with thin fibrous septae lined by bland non clear cells. The ovarian-type stromal cells are positive for ER, PR and CD10 (**Table 1**).

Another differential is kept is tubulocystic carcinoma. On histopathology it shows regular, small to medium sized tubules may cystically dilated lined by high nuclear grade tumor cells. The tumor cells show oncocytic change with hobnailing and nuclear grade of 3 with prominent nucleoli. The intervening septa are fibrotic. The monolayered flattened or hobnail epithelial cell lining and presence of cellular stroma with or without tubules in the septae in tubulocystic RCC differentiate them from MCRN-LMP. These cells express CD10, AMACR and sometimes CK7 and HMWCK with less than half expressing CAIX.

The MCRN-LMP should be differentiated from regressing ccRCC with cystic degeneration, which often has cysts filled with hemorrhage, necrosis and hemosiderin deposits; may have extensive hyalinization and often has areas of expansile growth of neoplastic cells.

In cystic papillary RCC- Papillary architecture with fibrovascular cores containing foamy macrophages, psammoma bodies and hemosiderin is important to diagnose this type. In Type 1 PRCC, the papillae are lined by a single layer of cells with scanty

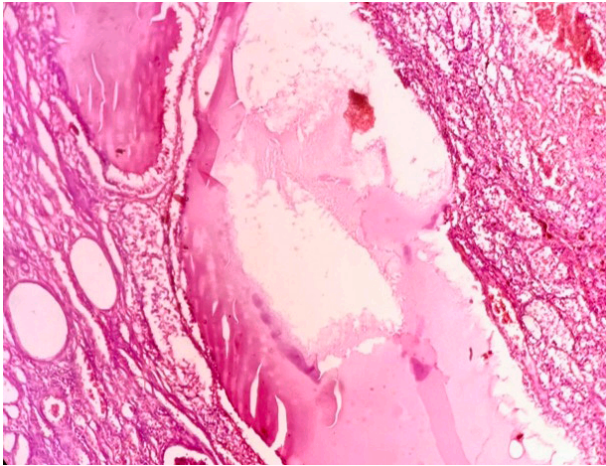


Figure 3. Renal cysts with septa containing tumor cells with abundant clear cytoplasm of low nuclear grade (H & E Stain, 100x).

basophilic cytoplasm and low nuclear grade while in Type 2 PRCC papillae are lined by pseudostratified layers of cells with more abundant eosinophilic cytoplasm and higher nucleolar grade. Tumor shows CK7 expression and diffuse AMACR expression.

Immunohistochemistry

The MCRN-LMP and ccRCC with cystic changes are morphologically indistinguishable. Kim et al studied various tissue markers with differential expression between MCRN-LMP and ccRCC with cystic changes and stated that it can provide a clue to understanding their distinct pathophysiology [11]. They studied the 25 tissue markers, among these only HIF1a, PDGFR α , SMA, VEGFR1, VEGFR2, VEGFR3, CD10, CD31, CD34, CK7-tubule, TGase-2, and Ki-67 showed significantly different expression between these groups. The immunoreactivity for cytokeratin 7 is resemble that of clear cell papillary RCC characterized by prominent cystic architecture. However, clear cell papillary RCC is generally negative or focally positive for CD10.

Yu et al's study showed that MCRN-LMP (reported under MCRCC) is usually positive for CD10, Vimentin, EMA, CA-IX, PAX-2 and stated it will be helpful for differentiating variable other cystic renal tumors [12].

Genetic and molecular research in MCRN-LMP

These neoplasms are genetically related to ccRCC. The deletion of chromosome 3p was identified in one third of tumors using FISH analysis and VHL gene mutation was identified in 25% of MCRN-LMP [13, 14].

Kim et al [15] studied the tumor tissues from 5 MCRNLMP and 16 ccRCC with cystic change cases for gene sequencing to detect mutations among 88 genes selected from a kidney cancer gene panel after quality control. The six genes showed a significantly different frequency of mutation between MCRNLMP and ccRCC with cystic change groups: GIGYF2 (odds ratio [OR], 5.735), FGFR3 (OR, 6.787), SETD2 (OR, 4.588), BCR (OR, 6.266), KMT2C (OR, 8.167), and TSC2 (OR, 4.474).

MCRNLMP -Multilocular cystic renal neoplasm of low malignant potential, Ch-Chromosome, miR-microRNA, ACD-acquired cystic disease, RCC- Renal Cell Carcinoma. VHL-von Hippel Lindau, Cystic PRCC-Cystic Papillary RCC.

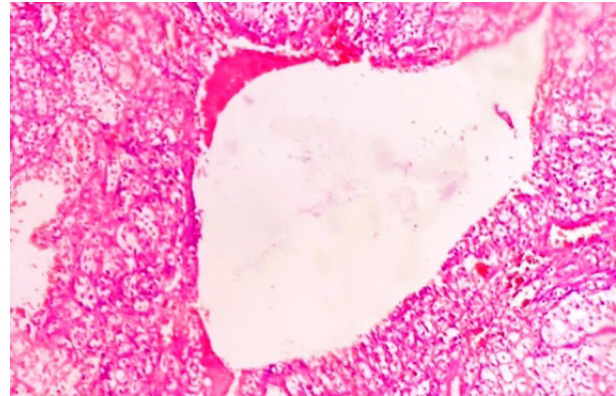


Figure 4. Renal cysts filled with blood, wall showing capillary proliferation, the septa containing tumor of low nuclear grade (H & E Stain, 40x).

Therapy and Prognosis

Based on the fact that this is tumor with low nuclear grade and confined to the kidney, their survival rate is significantly better than conventional RCC. MCRN-LMP has been classified as a neoplasm with an intrinsically cystic growth pattern, and no, or at most uncertain malignant potential. Accurate diagnosis is always important in a cancer context even the low or uncertain malignant potential of this tumors. The treatment options are either simple nephrectomy or nephron sparing surgery. MCRN-LMP usually has an excellent prognosis, nephron sparing surgery is first recommended as a therapeutic strategy. Suzigan et al. in their recent large series of the 45 cases of MCRN-LMP published under MCRCC, they found 82% of their cases in T1 stage and low nuclear grade found in 62% cases of them. Also Suzigan et al in their study showed the 5-year survival rate was 100% [16]. This paper has been published in 2006 under the name of MCRCC, but should be MCRN-LMP.

The benign clinical course has been observed by Nassir et al. who defined MCRN-LMP as a cystic lesion with neoplastic clear cells, an uncommon subtype of conventional ccRCC [17].

In difficult situation of distinguishing ccRCC from MCRN-LMP, the best morphologic feature is demonstration of presence of expansile growth clear cell in ccRCC. In MCRN-LMP, the expansile growth of clear cells should not be present. The International Society of Urological Pathology, has clearly defined MCRN-LMP as a least aggressive neoplasm with no recurrence and no metastatic potential after surgical treatment [18].

In the future it will probably represent an era of research and application of immune check point inhibitor treatment in renal tumors [19]. As suggested by Li et al. [22] in their study, the nuclear grade of MCRN-LMP cases was unrelated to the tumor size and TNM stage. In their largest published series of 76 cases of MCRN-LMP, 66 patients were followed up for median of 52 months. No recurrence was observed. The treatment of patients with MCRN-LMP were 18 underwent radical open nephrectomy, 18 laparoscopic radical nephrectomy, 22 open partial nephrectomy, and 18 laparoscopic partial nephrectomy.

In another study the 6 cases of MCRN-LMP were reported by Murad et al and they were followed for a minimum of 2 years and noted no recurrence or metastasis was observed. They have concluded that the tumor was a low-grade variant of RCC [20]. Nephron sparing surgery is only advisable to those patients with single kidney or those where contralateral kidney tend to be nonfunctioning in near future [21].

The study by Bhatt et al proposed that since postoperative followup protocols are dictated by staging, that for this entity of MCRN-LMP the T staging should be abandoned or reassigned as pT1c to guide clinicians and nonsurgical management when feasible [22]. Also Li T et al. stated that the patients with MCRN-LMP have an excellent prognosis, the follow-up interval after surgery can be longer to minimize unnecessary examinations [23]. The study by Alekseev BY et al. showed that patients with MCRN-LMP have the best oncological prognosis among renal tumors. The necessity of classification of this tumor in accordance with the TNM system is currently dubious. Only organ-preserving surgeries should be used in treatment of the disease [24].

Conclusions

Multilocular cystic renal neoplasm of low malignant potential is a newer entity. The various modalities are required for it are clinical, histomorphological, radiologic evaluation, and immunohistochemical assay. It will be useful to differentiate between various cystic renal conditions allowing an accurate diagnosis.

The aim of this review is to bring attention, that MCRN-LMP is a least aggressive neoplasm with no recurrence and no metastatic potential. The updated diagnostic modalities and conservative line of management may be applicable for this rare entity for the better care of patients.

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Ethical policy

Approval was taken from institutional ethical committee. The study was performed in accordance with the Declaration of Helsinki. Patients gave their informed consent for their participation.

Author contributions

SVJ designed the study, drafted the manuscript, searched literature, revised it critically for important intellectual content, read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

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