Case Report

Uretheral invagination of multilocular cystic nephroma; a case report of a new pathologic variant

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Abstract: Background: The multilocular cystic nephroma (MLCN) is a unilateral cystic neoplasm of the kidney exhibiting benign biological behavior. The etiology and histopathogenesis of the disease is controversial (dysplastic/hamartomous/neoplastic). MLCNs show bimodal age distribution, with peak incidence occurring at 2-4 years of age and between the fourth and sixth decades. The male to female ratio in patients aged below 4 years is 3:1, which reverses to 1:8 between the fourth and sixth decades. Patients and methods: A 59-year-old female patient presented with left flank pain and abdominal pain. Ultrasound (US) revealed 220×109×82 mm multiple septated hyperechoic kidney cysts with a semi-solid appearance. MRI showed a 245×119×98 mm multilocular cystic renal mass in the left kidney with hypointense appearance in T1-weighted images and hyperintense in T2-weighted images, and multicystic appearance in ureter projection, the largest portion measuring 17 mm in diameter. Radical nephrectomy was planned with the pre-diagnosis of multilocular cystic nephroma or multicystic renal cell carcinoma. Results: The patient underwent transperitoneal radical nephroureterectomy. The immunohistopathological examination revealed MLCN with ureteral invagination. Conclusion: The etiology, pathogenesis, and genetic basis of multilocular cystic neoplasms are currently unknown. This tumor is confused with cystic partially differentiated nephroblastoma and cystic Wilms tumor in childhood, and multilocular cystic renal cell carcinoma, clear cell papillary renal cell carcinoma, and tubulocystic carcinoma in adults. The association of this tumor with pleuropulmonary blastoma in children exhibits genetic inheritance. US control is particularly recommended in siblings of these children. Albeit rare, the disease can occur as a bilateral synchronous or metachronous lesion. There are four reports of cases with recurrence in the literature. The laparoscopic partial nephrectomy is the recommended treatment method in patients with sufficient renal reserve that are found to be free of malignancy in the frozen section examination. The symptoms of hematuria and flank pain can be associated with invagination of the cysts into the pelvis and intrarenal rupture of the cysts. The invagination of cysts into the pelvis has been previously described. The authors consider that this was the first case of MLCN in the literature exhibiting invagination into the ureter.

Keywords: Multilocular cystic nephroma, renal cystic mass, multilocular cystic renal tumors, Bosniak classification of renal cysts

Introduction

The multilocular cystic nephroma (MLCN) is an extremely rare unilateral cystic neoplasm of the kidney, exhibiting non-genetic patterns and benign biological behavior [1]. It was first described in 1892 as cystic adenoma of the kidney, and over 200 cases have been reported in the literature thus far [2, 3]. The name multicystic nephroma was first proposed in 1951 and later modified and further subdivided into cystic nephroma and cystic partially differentiated nephroma, depending on the absence or presence of the blastemal element, respectively [4]. The etiology and histopathogenesis of the disease is controversial. Thus, its origin is designated as being dysplastic/hamartomas/neoplastic. MLCN shows bimodal age distribution. Although the disease has been also described in newborns, 73% of the patients are male and aged between 2-4 years. The second peak occurs between the fourth and sixth decades. The male to female ratio below 4 years of age is 3:1, and this ratio of males to female becomes 1:8 between the fourth and sixth decades [5]. The disease is considered to
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There is no symptom specific to the disease. However, the patients may exhibit non-specific symptoms such as flank pain, urinary infection, hypertension, and macroscopic or microscopic hematuria. The disease can be diagnosed radiologically using US, CT, or MRI. Nonetheless, none of the methods show typical findings diagnostic for MLCN. Although the Bosniak classification system is the most commonly used classification method, the level of evidence is low due to diagnostic difficulties in differentiating type II and type III cystic lesions and its low performance in guiding the decision of surgery [9].

The invagination of MLCN into the pelvis renalis has been described in the literature. To our knowledge, this is the first report of MLCN in the literature exhibiting ureteral invagination. In this regard, this case report is important for the presence of local invagination by MLCN.

Case report

Ethical statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Clinical features

A 59-year-old female patient presented with left flank pain and abdominal pain. The physical examination showed a mobile and painful mass in the left lumbar region on palpation. The results of the biochemical tests were as follows: glucose: 159 mg/dL, creatinine: 0.88 mg/dL, urea: 32 mg/dL, AST-ALT-ALP-GGT: all.
within normal ranges, WBC: 9.40 $10^3$/uL, and Hgb: 12.6 g/dL. The patient’s past medical history was remarkable for DM and she was using oral anti-diabetic medications. The patient had undergone a hysterectomy eight years prior due to uterine fibroids. The patient was a non-smoker.

**Radiologic findings**

Ultrasound (US) revealed 220×109×82 mm multiple septated hyperechoic kidney cysts with a semi-solid appearance. IVP showed soft tissue density with lobulated contours in the left renal region, and the left kidney could not be visualized. MRI showed a 245×119×98 mm multilocular cystic renal mass in the left kidney with hypointense appearance in T1-weighted images and hyperintense in T2-weighted images, and a multicystic appearance in ureter projection, the largest portion measuring 17 mm in diameter. Radical nephrectomy was planned with the pre-diagnosis of multicystic RCC or multilocular cystic nephroma (Figures 1-3).

**Immunohistopathological findings**

The researchers received a nephroureterectomy specimen measuring 30×18×17 cm, ureter segment measuring 18 cm, and weighing 1237 grams. The outer surface was unremarkable (Figure 4). The cut surface showed relatively well circumscribed lesion composed of multiple, small, non-communicating cysts (Figure 5). The macroscopic examination revealed multiple cysts attached to the inner wall of the ureter (Figure 6). The microscopic examination revealed cuboidal and hobnail cells in the epithelial areas and ovarian-type stroma areas composed of occasional fusiform cells (Figure 7, H&E, ×50) (Figure 8, H&E, ×200).

**Treatments**

Based on the above findings, a preoperative clinical diagnosis of MLCN was established, and the patient underwent right-sided nephroureterectomy.

**Discussion**

The first case of MLCN in the literature was reported by Edmund et al. as cystic nephroma of the kidney [2]. The etiology and pathogenesis of MLCN is not clear. The pathological diagnostic criteria for MLCN were first described by Boggs and Kimmelstiel and revised by Joshi and Beckwith. According to these criteria: a) the entire lesion is composed of cysts with differing sizes and septae separating the cysts; b) cystic mass lesion is clearly distinguished from the normal renal parenchyma; c) the only solid component of the cysts are formed by the septae; d) the cysts are lined by cuboidal or hobnail cell epithelium, e) the septae are made up of fibrous tissue and may include well-differentiated renal tubules [10]. Recent evidence suggests that in the adult population, tumors that were initially diagnosed as cystic nephroma
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Figure 6. Ureteral invagination of MLCN.

Figure 7. The microscopic examination of hematoxylin and eosin-stained specimens revealed cuboidal and “Hobnail” cells in the epithelial areas (with ovarian-type stroma areas composed of occasional fusiform cells) [H&E, ×50].

Figure 8. The microscopic examination of hematoxylin and eosin-stained specimens revealed cuboidal and hobnail cells in the epithelial areas (with ovarian-type stroma areas composed of occasional fusiform cells) [H&E, ×200].

Tive studies are required since the distinction line between CPDN and CWT is not always clear [13]. According to one notion, MLCN and CWT share a common metanephric origin. These two conditions are thought to represent two separate poles, and CPDN remains between the two poles with pathological features resembling both entities [10] (Figure 9). The etiology and classification of MLCN has not been clearly identified. There are numerous proposed theories indicating the etiology as a developmental defect. It has also been postulated that it could be neoplastic in origin, probably arising from the ureteral bud [14].

The authors consider that this was the first case of MLCN in the literature exhibiting invagination into the ureter. The theory that the disease may have originated from the ureteral bud is among the possible theories for the present case; however, MRI findings and macroscopic appearance suggested that MLCN may have first invaginated into the renal pelvis and then into the ureter. Although MLCN is often regarded to have a non-genetic origin, there are studies in the literature that suggested familial occurrence of this condition [15, 16]. In genetic studies conducted by Doros et al., DICER1 mutations were suggested to play an important role in the development of cystic nephroma. In addition to the findings of these genetic studies, cystic nephroma and pleuropulmonary blastoma have similar DICER1 loss of function and ‘hotspot’ missense mutation rates, which
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Figure 9. Infantile MLCN and other conditions in differential diagnosis (can occur together with MLCN and pleuropulmonary blastoma).

Figure 10. Adult MLCN and other conditions in differential diagnosis (MLCN can co-occur with MRCC).

involve specific amino acids in the RNase IIIb domain [17]. It is considered that it would be beneficial to perform follow-up with US in the siblings of the children diagnosed with this tumor.

MLCN occurring in adults is often confused with multilocular cystic renal cell carcinoma (MCRCC), a variant of RCC described by WHO in 2004. Other rare cancers, such as clear cell papillary renal cell carcinoma and tubulocystic carcinoma, should also be considered in the differential diagnosis [18]. MCRCC accounts for less than 1% of all RCCs. Due to the good prognosis of this tumor and the fact that no recurrence or metastasis has been described to date, this tumor is called “multilocular cystic renal cell neoplasm with low malignant potential” [19]. It is not possible to differentiate based on the clinical and radiological findings. The cystic nephroma is histopathologically characterized by cystic structures lined by hobnail cells with dense eosinophilic cytoplasm and large apical nuclei. These features are particularly important in the differential diagnosis [20]. The studies in the literature suggested that no relationship exists between MLCN and MCRCC [21]. MLCN is not a pre-malignant lesion. However, MLCN can co-occur with MCRCC. There are two cases reported in the literature that were found to have both tumors simultaneously [22, 23]. The presence of variable-sized cysts lined by flattened to cuboidal cells, foci of calcification, inflammatory cells, ovarian-like stroma, corpora albicans-like structures, slings of smooth muscle fibers, and tubules with eosinophilic secretions have all been described in cystic nephroma. MLCN may have a few clear cells focally lining the septa, but multiple cysts lined by clear cells and clusters of clear cells in the cyst walls are never found. MCRCC has cysts lined by clear cells, which are of low Fuhrman grade, with septae containing aggregates of cells with clear cytoplasm. Rich vascularity, occasionally with hemosiderin-containing cells, may be noticed. MCRCC is a subtype of RCC, and therefore can be immunohistochemically stained with CK, EMA, CD10, and vimentin [21]. Mukhopadhyay et al. studied cases with MLCN and found aberrant renal tubular differentiation and focal or diffuse marker positivity. These immunohistochemical features suggest that MLCN can differentiate into MCRCC [24] (Figure 10). The tubulocystic carcinoma of the kidney (TCCK) was not included in RCC classification made by WHO in 2004. Immunohistochemically, the tumor shows positive staining for CD10, BHK, vimentin, and AMACR, and show ultrastructural (abundant long brush border microvilli) characteristics of proximal renal tubules. Similar to MLCN, TCCK is common in adulthood. The prognosis considerably good,
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and no local recurrence or metastasis has been described [25].

The disease can occur at any anatomic site of the kidney parenchyma; however, the lower pole of the kidney is more commonly involved. On the contrary, Wilkinson et al. studied six cases with MLCN and reported more common occurrence in the upper pole of the kidney [3]. Even though MLCN often occurs unilaterally, there are reports on cases with bilateral synchronous or metachronous tumors [5, 26-28]. The patients usually present with nonspecific symptoms. Abdominal pain, hematuria, and urinary tract infection are common in adults. The hematuria is the common symptom across all age groups and generally develops as a result of cysts invaginating into the pelvis [29]. Nonspecific flank pain and hematuria in patients with MLCN can be caused by intermittent incomplete intrarenal rupture of these cysts into the collecting ducts [3]. Although the disease is benign in nature, there are reports on cases with spontaneous rupture in the literature. Fujimoto et al. reported MLCN in the pathological examination of the nephrectomy material that was removed after spontaneous rupture of the cystic renal mass that presented with right renal colic pain [30].

In the US, the cysts usually appear as hypoechoic lesions delineated by hyperechoic septae and this feature can be suggestive of MLCN, but not diagnostic. These cysts are 10 cm, on average. The calcification on the cyst wall is extremely rare [5]. Hirai et al. suggested that needle-guided aspiration assisted with color Doppler US could be used to differentiate malignant and benign multilocular cysts in the kidney [31]. However, it is difficult to establish a diagnosis of MLCN with fine needle aspiration cytology (FNAC) due to low cellularity [32]. On CT, MLCN typically appears as a well-circumscribed, encapsulated, multicycstic mass with variably enhancing septa and no excretion of contrast agent into the loculi. The content of the cyst may have similar or slightly higher attenuation than that of water, and if the cystic spaces are very small, the closely packed septa can mimic a solid mass [27]. The septae and cysts have a brighter appearance on CT scans of MLCN. Calcification is rarely observed on CT as in US. Ossification can be observed in the septae or renal capsule. However, dense calcium rings in multiple cysts have been reported [33]. CT scan can better show herniation of the cysts into the renal pelvis. These cysts are mostly classified as Bosniak II or III. On MRI, the cysts have a hypointense appearance on T1-weighted images and a hyperintense appearance on T2-weighted images. The cysts may appear as avascular, hypo-vascular, or hyper-vascular lesions on MRI angiography. The vascularity detected on MRI is non-specific for the disease [3]. MRI findings of the present case were consistent with those reported in the literature. The MRI showed ureteral invagination and ureteral septae in T1- and T2-weighted images (Figures 1-3). Radiological and pathological features of MLCN are summarized in Figure 11.

Nephrectomy is the treatment of choice in MLCN. However, laparoscopic, partial nephrectomy is the recommended surgical therapy in patients with reserved renal functions due to
the benign behavior of the lesion, if the renal arterial system has been previously delineated and the lesion has clearly identified margins [34]. The partial nephrectomy option should be considered first, due to the low potential for local recurrence and the development of metastasis. Furthermore, this method is specifically preferred by urologists, due to the reports on patients with metachronous MLCN in the literature. However, the possibility of malignancy should be ruled out with preoperative frozen biopsy. Castillo et al. performed partial nephrectomy in a series of 29 patients, and they did not report local recurrence or distant metastasis in cases with MLCN [5]. Due to the benign biological behavior of MLCN, Okada et al. recommended nephron-sparing surgery in children in the presence of sufficient renal reserves [34]. Frozen section could be an option in deciding between radical and nephron-sparing nephrectomy, but partially cystic renal cell carcinoma may be potentially missed on frozen section. Ferre et al. found that the partial nephrectomy option should be attempted in a patient with metachronous MLCN due to the benign biological behavior of the disease and the anatomy of the renal arteries should be delineated in the pre-operative period with early phase MRI angiography [26]. Although MRI angiography has been known as a perfect non-invasive diagnostic tool, the side effect of systemic fibrosis should be kept in mind. MLCN in adults is known to have benign characteristics. However, recurrent cases have also been reported in the literature. Recurrent disease most commonly occurred in patients who have undergone partial nephrectomy. There are four cases with recurrent disease reported in the literature. The disease recurrence can occur in the short-term, but also after a three-year, disease-free follow-up [35]. It remains unknown by which characteristics of the disease the patients develop recurrent disease. This can be caused by unrecognized MCRCC in the residual tissue, differentiation into MCRCC or sarcomatoid differentiation due to unknown reasons. The follow-up of the patients is therefore particularly recommended in the post-operative period.

In conclusion

The etiology, pathogenesis, and genetic basis of multilocular cystic nephroma are yet to be determined. In childhood, at the time of peak incidence, the disease is often confused with cystic partially differentiated nephroblastoma and cystic Wilms tumor. There are studies in the literature showing co-occurrence with genetically inherited pleuropulmonary blastoma. It is considered that it would be beneficial to perform follow-up with US in the siblings of the children diagnosed with this tumor. Due to the possibility of bilateral occurrence, laparoscopic partial nephrectomy is the recommended first line treatment option, provided that frozen section examination was performed and the patient had sufficient renal reserves and clearly identified tumor margins. In adults, this tumor is most commonly confused with multilocular cystic renal cell carcinoma (MCRCC), clear cell papillary renal cell carcinoma, and tubulocystic carcinoma. MLCN is not a pre-malignant lesion. However, there are case reports in the literature suggesting the co-occurrence of MLCN with MCRCC. It is unknown if the second condition develops by differentiation of MLCN or occurs as a primary carcinoma. The partial nephrectomy option should be considered first in adults due to the low potential for local recurrence and the development of metastasis.

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Written informed consent was obtained from patient who participated in this case.

Disclosure of conflict of interest

None.

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