Ureteral inflammatory myofibroblastic tumor
A case report and literature review

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Abstract
Rationale: Inflammatory myofibroblastic tumor (IMT) is a rare soft-tissue neoplasm which has been described in a variety of locations. In the urogenital system, IMT predominantly occurs in the bladder and the kidney. IMT arising from the ureter is exceedingly rare and has been sporadically reported before.

Patient concerns: We reported an extremely exceptional case of IMT arising from the ureteral submucosa in a 54-year-old man. The patient was hospitalized with the main complaint of intermittent and moderate left abdominal pain for 2 months.

Diagnoses and Interventions: Computed tomography scan revealed a nearly circular mass in the left upper ureter. Ureteroscopy showed that the ureteral lumen mucosa was smooth. However, the upper ureter was compressed and narrow. Renal dynamic imaging was performed and the measured glomerular filtration rate was 46.98 mL/min (right renal) and 9.77 mL/min (left renal), respectively. A retroperitoneoscopic radical nephroureterectomy was performed. The histopathologic examination revealed that the soft-tissue neoplasm was mainly composed of myofibroblastic spindle cells proliferation with mixed inflammatory infiltrate, containing lymphocytes, neutrophils, and eosinophils. On immunohistochemical staining, the tumor was positive for smooth muscle actin and Ki-67 (<1%), indicating a confirmed diagnosis of ureteral IMT.

Outcomes: The patient recovered well with no occurrence of complications. At 3-year follow-up, there was no radiologic evidence of tumor recurrence or metastasis and the man was well.

Lessons: Ureteral IMT is extremely rare and often asymptomatic, resulting in delayed diagnosis. Radiologic evidences may be suggestive of the diagnosis of IMT. However, it is necessary to make an accurate diagnosis in terms of histopathologic assessment. Complete lesion excision is the best therapeutic approach with rare recurrences and excellent survival.

Abbreviations: ALK = anaplastic lymphoma kinase, CD = cluster of differentiation, CT = computed tomography, F = female, GFR = glomerular filtration rate, HHV-8 = Human herpesvirus 8, IMT = inflammatory myofibroblastic tumor, IPT = inflammatory pseudotumor, Ltr = left, M = male, MRI = magnetic resonance imaging, NR = not recorded, NU = nephroureterectomy, Rt = right, SMA = smooth muscle actin, SR = segmental resection, UR = ureteral reimplantation.

Keywords: diagnosis, histopathology, immunohistochemical, inflammatory myofibroblastic tumor, ureter

1. Introduction

Inflammatory myofibroblastic tumor (IMT) is a rare soft-tissue neoplasm and characterized histologically by a myofibroblastic spindle cell proliferation with inflammatory cell infiltration. According to World Health Organization (WHO) classification, IMT is an intermediate tumor that primarily occurs in children and young adults. IMT has been described in multiple anatomic sites, but typically located in liver and biliary tract (32%), lung (27%) and gastrointestinal tract (10%). In the urogenital system, IMT most frequently occurs in the bladder and the kidney. IMT arising from the ureter is extremely rare with an unknown etiology. To the best of our knowledge, there are only 7 cases in the English literatures over recent decades. Herein, we report an additional case of ureteral IMT in a middle aged man and perform a literature review to highlight the most common clinical manifestations, the most useful diagnostic methods, and management of IMT.

2. Case presentation

A 54-year-old man presented to the First Hospital of Jilin University (Changchun, China) with the main complaint of intermittent and moderate left abdominal pain for 2 months. Physical examination revealed percussion tenderness over the left kidney region. Gastroenteric history was not significant. Furthermore, medical and surgical histories were unremarkable as well. In addition to the elevated serum creatinine and blood urea nitrogen (1.67 and 20.90 mg/dL, respectively), laboratory findings were nonspecific. Abdominal computed tomography (CT) demonstrated a nearly circular hypodense mass (2.1 × 2.0 cm) arising from the left upper ureter (Fig. 1A). On contrast-enhanced CT scan, the lesion showed heterogeneous enhancement with relatively well-defined margination and no invasion of adjacent lymph nodes (Fig. 1B). Ureteroscopy reviewed that the

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The study protocol was approved by the medical center’s ethical committee. Informed written consent was obtained from the patient for publication of this case report and accompanying images.

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ureteral lumen mucosa was smooth, while the upper ureter was compressed and narrow. Subsequently, renal dynamic imaging was performed to measure glomerular filtration rate (GFR). The results were 46.98 mL/min of right kidney and 9.77 mL/min of left kidney, respectively.

Due to the left nonfunctional kidney, the patient underwent a retroperitoneoscopic radical nephroureterectomy under general anesthesia. The tumor was located at approximately 3.0 cm beneath the ureteropelvic junction, wrapping the ureter. Because of firmly adhesion with the surrounding tissue, intraoperative blood loss was about 600 mL. The subsequent histopathology revealed a mesenchymal neoplasm mainly composed of myofibroblastic spindle cells proliferation and a mixed inflammatory infiltrate of lymphocytes, neutrophils, and eosinophils (Fig. 2A–C). On immunohistochemical staining, the tumor was positive for smooth muscle actin (SMA) and Ki-67 (<1%+), indicating a confirmed diagnosis of ureteral IMT (Fig. 2D).

The postoperative course was uncomplicated. The patient did not receive any treatment postoperatively and recovered well with no occurrence of complications. At 3-year follow-up, there was no radiologic evidence of tumor recurrence or metastasis and the man was well.
Table 1

| Case report | Age | Sex | Chief complaint | Size, cm | Location in ureter | Treatments | Original diagnosis | Follow-up | Outcome at time of report |
|-------------|-----|-----|-----------------|---------|--------------------|------------|-------------------|-----------|--------------------------|
| [6]         | 64 y | M   | Left renal pain, fever | 2.5 × 1.5 | Lt lower | NU | IPT | 4.1 y | Alive |
| [7]         | 54 y | M   | Left back pain | 4.0 × 3.0 | Lt lower | SR | IPT | 7 mo | Alive |
| [8]         | 6 mo | M   | Gross hematuria | 4.0 × 3.0 | Lt lower | SR + UR | IPT | 1 y | Alive |
| [9]         | 12 y | M   | Hematuria | NR | NR | NU | IMT | NR | Alive |
| [10]        | 13 y | M   | Left flank pain | 1.5 × 1.0 | Lt lower | SR | IPT | 1 y | Alive |
| [11]        | 70 y | M   | Gross hematuria | 3 | Lt upper | NU | IMT | 6 mo | Recurrences (1 and 4 mo) |
| [12]        | 66 y | M   | None | 3 | Lt upper | NU | IMT | NR | NR |
| Present case | 54 y | M   | Left abdominal pain | 2.1 × 2.0 | Lt upper | NU | IMT | 2 y | Alive |

F = female; IMT = inflammatory myofibroblastic tumor; IPT = inflammatory pseudotumor; Lt = left; M = male; NR = not recorded; NU = nephroureterectomy; Rt = right; SR = segmental resection; UR = ureteral reimplantation.

3. Discussion

The IMT is an extremely rare tumor and predominantly affects children and young adults.[13] The age at presentation varies from 3 to 89 years.[14] IMT has been described in multiple anatomic sites, but typically located in liver and biliary tract (32%), lung (27%), and gastrointestinal tract (10%).[15] In the urogenital system, IMT most frequently occurs in the bladder[16] and the kidney.[17] Nevertheless, IMT arising from the ureter is exceedingly rare. To the best of our knowledge, only 7 cases of IMT arising in the ureter have been published in English since 1997.[18–21] The etiology of IMT remains unclear and the immunologic and infectious hypotheses still need to be validated.[15]

The clinical summary of ureteral IMT is listed in Table 1, including the 7 cases reported in the English literatures and an additional case from the present study. All patients were male. The age of onset ranged from 8 months to 70 years. The mean age of the 8 patients was 41.7 years, and 3 patients were younger than 14 years. Of the 8 patients, there were 4 patients presenting with pain and 3 with hematuria. The size of tumors ranged from 1.5 to 4.0 cm in greatest dimension. The left ureter was more commonly affected. There was no significant difference in the incidence of IMT arising from the upper and lower ureters. In 1 patient, the IMT was accompanied with separate nidus of sarcomatoid carcinoma and high-grade urothelial carcinoma. Unfortunately, the patient died of sarcomatoid carcinoma 6 months after operation. According to the review of the limited literatures, it is premature to establish an epidemiologic profile of ureteral IMT. However, on the basis of the analysis above, we may draw a conclusion that ureteral IMT predominantly affects males with left ureteral predominance and better prognosis.

There are various hypotheses about the pathogenesis of IMT, such as allergic mechanism, immune mechanism, and infection mechanism.[16] However, many proponents believe that the development of IMT is predominantly related to polyfactorial mechanisms including inflammatory response and chromosomal aberrations.[17] Molecular genetics studies have found that anaplastic lymphoma kinase (ALK) gene rearrangement is the initiating factor of IMT formation. A clonal rearrangement of the ALK gene was detected in about 34% to 56% of both pulmonary and extrapulmonary IMT.[18–21] The identification of ALK gene alterations in bladder IMT indicated that they were neoplastic, although the lesions were frequently similar to nodular fasciitis.[22,23] Urinary IMT might be associated with recurrent urinary tract infections and cystoscopy. In addition, it was reported that some drugs such as cyclophosphamide or foreign body in bladder could induce bladder IMT.[24] Moreover, Chen et al reported a case of renal IMT combined with renal calculus, suggesting that IMT might be associated with recurrent and chronic inflammation.[25,26] In this work, the routine urinalysis of the patient was normal and there was no history of urinary tract infection or urolithiasis. The expression of ALK gene was not detected by immunohistochemical staining.

The clinical manifestations of IMT, which are nonspecific, depend on multiple factors, including tumor size, location, growth rate and individual tolerance. The main symptoms of IMT arising from ureter are pain and hematuria, followed by fever, abdominal mass, nausea, and so on. In the current case, the patient presented to hospital with the main complaint of left abdominal pain for 2 months. The lesion was located at the upper ureter and encapsulated the ureter, resulting in upper ureteral obstruction and hydronephrosis. The laboratory tests showed high level of serum creatinine and blood urea nitrogen, which were consistent with left nonfunctional kidney (GFR = 9.77 mL/min). Of the 7 cases reported previously, 3 patients suffered from pain, 3 patients suffered from hematuria, and 1 patient suffered from fever. In addition, 1 case was asymptomatic and left hydronephrosis was noted during a medical checkup. After further examination, the tumor was detected. From what has been discussed above, it can thus be concluded that pain is the most common symptom (Table 1).

Ureteral IMT is extremely rare and often asymptomatic, resulting in delayed diagnosis. Although imaging and endoscopic examination play an important role in the diagnosis of IMT, histologic assessment is the gold standard.[26,27] CT scan can confirm the relationship between the lesions and ureter, while ureteroscopy is usually performed when there is a suspect of endoluminal lesions. Ureteroscopy is a useful diagnostic and therapeutic tool because it possesses the functions of removing tumor obstruction and providing biopsy samples. If conditions permit, small samples of the lesion can be collected under ureteroscopy for a biopsy.[23] Differential diagnosis includes ureteral carcinoma, idiopathic ureteral inflammation, retroperitoneal tumor, and tumor invasion from ureteral peripheral tissue.

Data collected from the literatures showed that 4/8 patients underwent CT or ureteroscopy, suggesting solid masses arising from the ureter. These lesions were characterized as a single, well-defined, nearly circular mass, and frequently located at the left ureter (Table 2). Only by imaging examination, the mass can be easily misdiagnosed as retroperitoneal tumor or tumor invasion from ureteral peripheral tissue. Therefore, scintigraphy and...
intravenous pyelogram are inevitably performed for further treatment.\(^{6,10}\)

Radiologic presentation and contrast-enhancement of ureteral IMT were variable and nonspecific. The final diagnosis of IMT mainly depended on histopathology assessment. The histopathology assessment showed that IMT was usually characterized by spindle cell proliferation with inflammatory cell infiltration, including lymphocytes, neutrophils, and eosinophils (Table 2).

Immuno-histochemical findings confirmed the definitive diagnosis when mesenchymal cells were positive for vimentin, desmin, SMA, and S100 protein and negative for cluster of differentiation 34 (CD34).\(^ {34,35}\) Up to 50% IMT cases were positive for ALK in tumor cells.\(^ {36}\) Moreover, positive ALK status was more common in aggressive tumors and associated with a high recurrence rate.\(^ {30,31}\) Positive expression of SMA, desmin, vimentin, and Ki-67 was reported in both previous and present ureteral cases (Table 2).

At present, due to sporadic reports of ureteral IMT, clinicians have had limited experience in treatment. Based on the review of the literatures, it was supported that the complete surgical resection of the lesion as an effective treatment for IMT. The negative margin was an important prognostic indicator for local recurrence. A retrospective study was performed by Ong et al. in 28 patients with IMT treated by surgical resection. The researchers found that negative surgical margin was associated with 87% reduction in mortality, and was considered as the most important prognostic indicator for local recurrence.\(^ {32}\)

Surgery was not the only treatment. It was reported that radiotherapy was performed for unresectable lesions, nonresponsive IMT, and was used as an adjunctive therapy for IMT with ALK-1 and Ki-67 expression.\(^ {33}\) In addition, anti-inflammatory drugs combined with corticosteroids were also reported to treat IMT successfully.\(^ {34,35}\) However, most ureteral IMT can lead to upper urinary tract obstruction and hydronephrosis, which may result in renal failure. Therefore, surgical resection is an essential therapeutic tool to relieve obstruction and conserve the function of kidney. The most appropriate surgical procedure depends on the localization and size of the tumor, the relationship with the surrounding structures and the surgeons’ experience. Among all reported cases, 5 patients underwent ureteronephrectomy and 2 patients underwent segmental resection. In addition, because the stalk of tumor originated from the lumen of the distal ureter, partial cystectomy, and distal ureterectomy with ureteral reimplantation were performed in 1 patient (Table 1).

The IMT is usually considered as a neoplasm with low malignant potential and low local recurrence rate. The recurrence rate is related to large size, abdominopelvic location, and occurring in the elderly.\(^ {14}\) Literatures reported that the recurrence rate ranged from 2% to 25%.\(^ {16}\) A case of IMT with extrapulmonary recurrence 9 years after the primary resection was reported by Morotti et al.\(^ {37}\) On the contrary, Mergan et al. evaluated retrospectively 16 children who underwent surgery for IMT. Then, the researchers found that no IMT recurrence occurred later than 2 years after surgery and follow-up was unnecessary and useless after 3 years.\(^ {39}\)

In addition, aggressive IMT invaded bladder or ureter was not encountered. This confirmed the reports that there was no local recurrence or malignant metastasis in the urologic IMT.\(^ {5,38}\) The patient in the present work had been followed up for 2 years without any sign of recurrence. Among all patients reviewed above, only 1 patient had tumor recurrence and even relapsed twice (1 and 4 months, respectively).

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