

Multi-centers clinicopathological prognosis study of inflammatory myofibroblastic tumors of urogenital system in China

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Abstract

Purpose: We aimed at investigate a series of inflammatory myofibroblastic tumors (IMTs) of urogenital system in multi-centers in China. **Materials and methods:** Within the pathologic databases at West China Hospital of Sichuan University and the Third People's Hospital of Chengdu, we identified 33 individuals with IMTs from May 2009 to January 2019. **Results:** A total of 33 patients with IMTs of urogenital system were identified. The median age of all the individuals was 39.5 years (range 0-74 years). The most common presentations were hematuria (13patients), pain (12 patients), and mass (12 patients). In addition, other clinical symptoms included dysuria, urinary frequency, and fever. Fourteen individuals were diagnosed with anemia, including 10 mild anemia patients and 4 moderate anemia cases. Moreover, neutrophil was the dominant inflammatory cell type. The main positive markers of immunohistochemistry staining included SMA (22/25), MSA (8/9), CD34 (15/17), and CD68 (3/3). Surgery resection was the sole treatment for all the patients. Follow-up was available in 23 patients during a median follow-up period of 78.3 months (range 19.2-118.8 months), and either recurrence or metastasis was detected in any patients except one patients died from retroperitoneum IMTs. **Conclusion:** This study confirmed that urogenital system IMTs, with potential of recurrence or metastasis, are extremely rare. In summary, although favorable prognosis was observed in IMTs of urogenital system, closely follow-up is essential and needed.

Background

Inflammatory myofibroblastic tumors (IMTs), a rare entity of spindle cell tumors, composed of myofibroblastic mesenchymal spindle cells with an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils^[1]. According to World Health Organization (WHO) classification, IMTs are intermediate tumors with potential for recurrence. The first report of IMTs was demonstrated by Brunn on two cases of "myoma of the lung" in 1939, and IMTs of urinary system was firstly described by Roth in 1980^[2]. The lung is the most common site (95%) of IMTs, and other potential sites (5%) including abdomen, retroperitoneum, pelvic cavity, head, neck, trunk, and limbs^[3]. What's more, urinary bladder is the most common site of IMTs. Nevertheless, IMTs comprise less than 1% of all bladder neoplasms^[4].

Nevertheless, IMTs of urinary system couldn't be recognized precisely because of clinical symptoms, laboratory test results and imaging lacking specificity for the diagnosis of IMTs. So far, surgical resection is the dominant and preferred therapy for IMTs. In addition, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), chemotherapy, and radiotherapy have been used as adjuvant therapy if necessary^[5]. Up to now, there are only several studies^[3, 6-8] of urinary system IMTs relied on enormous population. Unfortunately, these studies described mainly the clinicopathological characteristics so that all of them maybe not illustrate the incidence, survival, mortality and prognosis of urinary system IMTs.

In this study, we are aiming to retrospectively investigate the clinic characteristics, pathological features, treatment, survival and prognosis of urinary system IMTs in China.

Methods

We searched pathologic databases at the West China Hospital of Sichuan University and the Third People's Hospital of Chengdu from May 2009 to January 2019. Our search terms included inflammatory myofibroblastic tumor, inflammatory pseudosarcoma, and spindle cell lesion. Finally, 33 patients were included in our study.

Patients characteristics including age, sex, signs and symptoms (including pain, dysuria, urinary frequency, anemia level, tumor size in maximal dimension, tumor location, treatment given, and presence of any tumor recurrence or distant metastases were recognized. Hematuria was defined as red blood cell of urine more than 3/HP.

Available immunohistochemistry (IHC) performed on the diagnostic specimens was reported and staining for ALK, SMA, MSA, Vimentin, Desmin, EMA, CK, BCL-2, Myogenin, CD34, CD21, CD117, Caldesmon, CD10, CD30, CD68, CD99, S100, PCK, and Ki67. Recurrence free survival (RFS) was measured from the time of diagnosis to disease recurrence. Disease free survival (DFS) was defined as the time of diagnosis to disease recurrence or death from any cause. Overall survival (OS) was measured from the time of diagnosis to the time of death from any cause or of last follow-up.

Results

Baseline characteristics

Thirty-three patients diagnosed with urogenital system IMTs were identified, which met the eligibility criteria for our study from May 2009 to January 2019. The baseline characteristics are shown in Table 1. A total of 13 patients (39.4%) were kidney IMTs vs. 10 bladder IMTs (30.3%) vs. 10 other sites IMTs (30.3%) which included one urinary tract IMT, one adrenal gland IMT, three testis IMTs, one groin IMT, two pelvis IMTs, and two retroperitoneum IMTs. For all the patients, median age was 39.5 years (range 0-74 years). Median age of kidney IMTs vs. bladder IMTs vs. other sites IMTs was 39 years (range 6-74 years) vs. 51.5 years (range 25-72 years) vs. 30.5 years (0-70 years). Female involvement was slightly more common than male (51.5% vs. 48.5%). Median tumor size of all the patients was 4 cm (range 1-15 cm), and the median tumor size of kidney IMTs was 4 cm (range 1-15 cm) vs. 4.25 cm (range 2-7.5 cm) of bladder IMTs vs. 4.4 cm (range 3-11 cm).

The most common presentations were hematuria (13 patients, 39.4%), pain (12 patients, 36.4%), and mass (12 individuals, 36.4%) for all the patients. Moreover, the most common clinical symptoms of kidney IMTs were pain (7 patients, 53.8%) and mass (6 patients, 46.2%) vs. hematuria (7 patients, 70%) for bladder IMTs. Thirteen patients with hematuria included three kidney IMTs patients, seven bladder IMTs patients, and three other sites IMTs patients. Twelve individuals with pain were composed of seven kidney IMTs patients, two bladder IMTs patients, three other sites IMTs patients. In addition, twelve patients with mass consisted of six kidney IMTs patients, three bladder IMTs patients, and three other

sites IMTs. Other clinical symptoms included dysuria (one patients), urinary frequency (two patients), and fever (two patients). What's more, of all patients, anemia was detected in fourteen patients (42.1%), including two kidney IMTs patients, seven bladder IMTs, and five other sites IMTs individuals. Ten patients with mild anemia consisted of two kidney IMTs patients, four bladder IMTs patients, and four other sites IMTs. Nevertheless, four patients with moderate anemia included three bladder IMTs patients and one other sites IMTs patient. In general, anemia was recognized in seven patients (70%) with bladder IMTs.

Significant inflammatory cell types were reported in a total of 16 (48.5%) patients. Among 16 patients, significant numbers of neutrophils, eosinophils, plasma cells, and lymphocytes were reported in 5 (31.3%), 8 (50.0%), 15 (93.8%), and 8(50.0%) individuals.

Patients' treatment

The therapy administrated is summarized in Table 2. In our study, all the patients were treated with surgery. Among patients with kidney IMTs, 5 (38.5%) patients underwent partial nephrectomy and 8 (61.5%) patients received radical nephrectomy. Beyond that, among bladder IMTs individuals, most patients (7 patients, 70.0%) was administrated with transurethral resection of bladder tumor (TURBT), followed by partial cystectomy (5 patients, 50.0%), and radical cystectomy (1 patients, 10.0%). Among those patients who had TURBT performed, specifically, 3 (42.9%) patients had further partial cystectomy. Therefore, among patients with bladder IMTs, 3 (30.0%) patients were treated with TURBT plus partial cystectomy. In addition, among other sites IMTs patients, 3 (30.0%) patients underwent orchiectomy, and other patients (70.0%) were treated with pure tumor resection. What's more, all the patients didn't undergo additional therapy apart from surgery.

Patients' outcome

Follow-up was available in 23 patients. After a median follow-up of 78.3 months (range 19.2-118.8 months), the survival data of all the individuals was collected. Interestingly, among thirty-three patients diagnosed with IMTs, only one (3.0%) patient died from retroperitoneum IMTs at three months after retroperitoneum tumor resection. In addition, among other thirty-two (97.0%) IMTs patients, none of them developed any local recurrence or distant metastasis upon computed tomography scan and laboratory tests results.

Immunohistochemistry features

Upon review of the immunohistochemistry results, it was noted that different sets of staining were performed for each patients of our study. The immunohistochemistry results were summarized in Table 3. Anaplastic lymphoma kinase (ALK) was positive in 10 out of 23 (43.5%) patients. Smooth muscle actin (SMA) was positive in 22 out of 25 (88.0%) patients. Muscle-specific actin (MSA) was positive in 8 out of

9 (88.9%) patients. Vimentin was positive in 1 out of 1 (100%) patients, and CD68 was positive in 3 out of 3 (100%) individuals. Desmin was positive in 13 out of 23 (56.5%) patients. One out of 3 individuals (33.3%) was positive for cytokeratin (CK). CD34 was positive in 15 out of 17 (88.2%) patients. Both CD117 and CD99 were positive in 1 out of 4 (25.0%) patients. Caldesmon was positive in 2 out of 4 (50.0%) cases, and CD10 was positive in 1 out of 2 (50.0%) individuals. One out of 18 (5.6%) patients was positive for S100. PCK was positive in 3 out of 11 (27.3%) cases. What's more, none of the 33 individuals were positive for epithelial membrane antigen (EMA) (0/13), Bcl-2 (0/3), Myogenin (0/5), CD21 (0/3), CD30 (0/1). The expression of Ki67 was detected in 15 out of 33 (45.5%) patients. Median of Ki67 expression in IMTs was 2% (range 1%-25%). Last but not least, among 3 patients performed fluorescence in situ hybridization (FISH) analysis, a total of 2 (67.7%) patients showed a positive *ALK* translocation.

Discussion

IMTs, a rare subtype with unique clinical and pathologic characteristics, in which the dominant components is spindle cells, and other components including alterable extracellular collagen, lymphocytes, and plasma cells [9]. IMTs, originally reported in the lung, has been recognized at multiple extrapulmonary sites, particularly the soft tissue and solid organs of children and young adults [1, 3, 8]. The the most common site of IMTs of genitourinary system is the urinary bladder. The alternative terminologies of IMTs, including plasma cell granuloma, inflammatory pseudotumor, pseudosarcomatous fibromyxoid tumor, and inflammatory myofibroblastic tumor, demonstrated that further studies are needed to explore the pathogenesis of IMTs. Nevertheless, a crowd of studies, including our study, agree with the myofibroblastic nature of IMTs with expression of SMA, desmin, vimentin, CD34, and CD68. At the same time, we found that the significant inflammatory cell types of IMTs included neutrophil, eosinophil, plasma cell, and lymphocyte, which supported the prior reports [10]. According to the current WHO Classification of Tumors of Soft tissue and Bone [11], moreover, IMTs are categorized as intermediate grade tumors in view of the potential for local recurrence and distant metastasis.

The first case report of IMTs of the kidney was published in 1976, closely followed by a series of case reports and rare studies [9, 12-16]. The median age of kidney IMTs 39 years (range 6-74 years) in our study doesn't consist with the mean age 57.1 years in a large study [9], but consists with the mean age 43.3 years of literatures review in the 13 case reports. In addition, it agrees with other reports that the age of onset, concentrated in 25-72 years (median 51.5 years), and the most common symptom is hematuria with more than half of them being anemia upon presentation of bladder IMTs in our study [6, 8, 17]. Sarcomatoid urothelial carcinoma et al are the most significant subtypes in the differential diagnosis of IMTs. What's more, both IMTs and sarcomatoid urothelial carcinoma exhibit similar biological characteristics resulting in the differential diagnosis becoming the most difficult [6]. According to the study of Liang et al [18], however, the good news is that contrast-enhanced CT may be valuable in the diagnostic imaging of the urinary system IMTs.

The ALK gene translocation was detected by FISH in 2/3 (67.7%) individuals, which is consistent with 30%-67% ALK gene rearrangements of IMTs on FISH testing in other studies [6, 17, 19, 20]. As is well-known, more than half of anaplastic large cell lymphoma (ALCL) patients presented ALK gene translocation accompanied with tyrosine kinase activation. Moreover, ALK gene rearrangement was confirmed in testis IMTs too [21]. Therefore, IMTs were considered as neoplastic rather than reactive in nature on the basis of ALK gene rearrangement. In 2014, Chun et al [10] published a systematic review in which they demonstrated that had a marked female predilection (male: female=1: 1.67) was recognized in ALK-positive IMTs.

Nowadays, surgical resection is the dominant therapy of urogenital system IMTs. In 2003, a 12 kidney IMTs cases study was published in which all the patients underwent kidney resection, was administered with no adjuvant treatment, and no recurrent tumors was recognized in the patients available for follow-up [9]. Our study happened to coincide with this series [9] on kidney IMTs patients' prognosis.

In terms of the urinary bladder IMTs, according to previous reports, partial or radical cystectomy can insure no residual IMTs [10]. In consideration of benign behavior of the urinary bladder IMTs, nevertheless, TURBT maintained as a selection in reserve for patients who are unwilling to received partial or radical surgery. Studies including our series demonstrated that local management can make patients acquire favorable recurrence free survival and overall survival [3, 6, 17]. Until now, although extremely rare recurrence was reported in fewer individuals, no distant metastasis was illustrated in literatures already. In our study, one patient with retroperitoneum IMTs appeared poor prognosis after retroperitoneum tumor resection. In addition, a systematic review published in 2014 also demonstrated local tumor recurrence in five bladder IMTs cases [10]. Therefore, although further chemotherapy or radiotherapy is not needed, close follow-up, regular cystoscopy and imaging tests are necessary for the early diagnosis of tumor recurrence and metastasis.

Conclusion

This study confirmed that urogenital system IMTs, with potential of recurrence or metastasis, are extremely rare. In summary, although favorable prognosis was observed in IMTs of urogenital system, closely follow-up is essential and needed.

Abbreviations

IMTs=Inflammatory myofibroblastic tumors;

IHC=immunohistochemistry;

RFS=Recurrence free survival;

DFS=Disease free survival;

OS=Overall survival;

TURBT=transurethral resection of bladder tumor;

FISH=fluorescence in situ hybridization;

ALK=anaplastic lymphoma kinase;

SMA=smooth muscle actin;

MSA=muscle-specific actin;

EMA=epithelial membrane antigen;

CK=cytokeratin;

Declarations

Ethics approval and consent to participate

The research was based on a retrospective study. Ethics approval was not needed because the study is a secondary analysis of an existing public internal database of our hospital.

Consent for publication

Not applicable

Availability of data and materials

All data on which the conclusions of the manuscript rely are available from reasonable request.

Competing interests

All the authors declared no competing interests.

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Authors' contributions

BC and HX designed the study, collected and drafted the manuscript. DC, JG, ZC participated in the design of the study, performed the procedures. SQ and TL performed the economic and statistical analysis. NM and YH participated in the study design and coordination. LL and QW conceived of the

study, participated in its design and coordination, supervised the draft. All authors read and approved the final manuscript.

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None

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Tables

Table1. Clinical characteristics of patients diagnosed with IMTs.

| Characteristics | Total(n=33)% | Kidney(n=13)% | Bladder(n=10)% | Other sites* (n=10)% |
|------------------------------------|--------------|---------------|----------------|-------------------------|
| Age(years) | | | | |
| Median | 39.5 | 39 | 51.5 | 30.5 |
| Range | 0-74 | 6-74 | 25-72 | 0-70 |
| Sex | | | | |
| Female | 17(51.5) | 5(38.5) | 7(70.0) | 5(50.0) |
| Male | 16(48.5) | 8(61.5) | 3(30.0) | 5(50.0) |
| Tumor size(cm) | | | | |
| Median | 4 | 4 | 4.25 | 4.4 |
| Range | 1-15 | 1-15 | 2-7.5 | 3-11 |
| Clinical presentation | | | | |
| Hematuria | 13(39.4) | 3(23.1) | 7(70.0) | 3(30.0) |
| Dysuria | 1(3.0) | 0 | 0 | 1(10.0) |
| Urinary frequency | 2(6.1) | 0 | 2(20.0) | 0 |
| Pain | 12(36.4) | 7(53.8) | 2(20.0) | 3(30.0) |
| Fever | 2(6.1) | 2(15.4) | 0 | 0 |
| Mass | 12(36.4) | 6(46.2) | 3(30.0) | 3(30.0) |
| Anemia | | | | |
| Mild | 10(30.0) | 2(15.4) | 4(40.0) | 4(40.0) |
| Moderate | 4(12.1) | 0 | 3(30.0) | 1(10.0) |
| Inflammatory cell types# □n=16□ | | | | |
| Neutrophils | 5/16(31.3%) | | | |
| Eosinophils | 8/16(50.0%) | | | |
| Plasma cells | 15/16(93.8%) | | | |
| Lymphocytes | 8/16(50.0%) | | | |

* Other sites include urinary tract, adrenal gland, testis, pelvis, retroperitoneum, and groin.

Inflammatory cell types, among 33 cases, only 16 patients' exact inflammatory cell types was reported.

Table2. Patients' treatment

| Tumor entity | Treatment administrated | No. (%) | |
|------------------------|----------------------------|-----------------|---------|
| Kidney IMTs(n=13) | Partial nephrectomy | 5(38.5) | |
| | Radical nephrectomy | 8(61.5) | |
| Bladder IMTs(n=10) | TURBT | 4(40.0) | |
| | TURBT + partial cystectomy | 3(30.0) | |
| | Partial cystectomy | 2(20.0) | |
| | Radical cystectomy | 1(10.0) | |
| Other sites IMTs(n=10) | Urinary tract(n=1) | Tumor resection | 1(10.0) |
| | Adrenal gland(n=1) | Tumor resection | 1(10.0) |
| | Testis(n=3) | Orchiectomy | 3(30.0) |
| | Pelvis(n=2) | Tumor resection | 2(20.0) |
| | Retroperitoneum(n=2) | Tumor resection | 2(20.0) |
| | Groin(n=1) | Tumor resection | 1(10.0) |

IMTs, inflammatory myofibroblastic tumors; TURBT, transurethral resection of bladder tumor

Table3. Results of immunohistochemistry staining of all patients with IMTs

| Markers(No. of tests) | Positive (No. and %) | Negative (No. and %) |
|-----------------------|----------------------|----------------------|
| ALK(n=23) | 10(43.5) | 13(56.5) |
| SMA(n=25) | 22(88.0) | 3(12.0) |
| MSA(n=9) | 8(88.9) | 1(11.1) |
| Vimentin(n=1) | 1(100) | 0 |
| Desmin(n=23) | 13(56.5) | 10(43.5) |
| EMA(n=13) | 0 | 13(100) |
| CK(n=3) | 1(33.3) | 2(66.7) |
| BCL-2(n=3) | 0 | 3(100) |
| Myogenin(n=5) | 0 | 5(100) |
| CD34(n=17) | 15(88.2) | 2(11.8) |
| CD21(n=3) | 0 | 3(100) |
| CD117(n=4) | 1(25.0) | 3(75.0) |
| Caldesmon(n=4) | 2(50.0) | 2(50.0) |
| CD10(n=2) | 1(50.0) | 1(50.0) |
| CD30(n=1) | 0 | 1(100) |
| CD68(n=3) | 3(100) | 0 |
| CD99(n=4) | 1(25.0) | 3(75.0) |
| S100(n=18) | 1(5.6) | 17(94.4) |
| PCK(n=11) | 3(27.3) | 8(72.7) |

IMTs, inflammatory myofibroblastic tumors; ALK, anaplastic lymphoma kinase; SMA, smooth muscle actin; MSA, muscle-specific actin; EMA, epithelial membrane antigen; CK, cytokeratin.