Review Article

Inflammatory myofibroblastic tumor of the genitourinary tract: a narrative review

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Background and Objective: Inflammatory myofibroblastic tumor (IMT) is a rare entity that is described in several organ systems. This comprehensive review aims to identify IMTs occurring at various genitourinary (GU) organ sites and describe patterns of clinical management in adult and pediatric patients.

Methods: A comprehensive search of PubMed and Web of Science was conducted according to the Preferred Reporting Items for Systematic Review and meta-analyses statement. Two reviewers performed independent initial screening of abstracts. Eligible articles underwent full review and data extraction. The clinical features, diagnostic tests, treatment, and outcomes at each GU organ site were analyzed individually and summarized into a comprehensive review.

Key Content and Findings: Of the 270 articles identified, 112 met inclusion criteria. Articles primarily consisted of case reports or small series describing a total of 167 cases, of which 30 (18%) occurred in children. Most patients (96%) were symptomatic at presentation. The most frequently involved sites included bladder (106 cases) and kidney (n=33) followed by epididymis (n=6), urachus (n=6), ureter (n=5), prostate (n=4), testis (n=4), and spermatic cord (n=3). Complete surgical excision of the mass including partial or total removal of involved organs provided excellent outcomes. Incomplete excision was associated with early local recurrence and progression. Late recurrence or metastatic transformation was rarely noted (<2%).

Conclusions: IMTs exhibit locally invasive, symptomatic and progressive phenotypes that affect all urologic organs in adults and children. Clinical features and imaging results are similar to those noted with urologic cancers. These tumors require complete surgical excision since incomplete resection increases the risk of symptomatic recurrence.

Keywords: Anaplastic lymphoma kinase (ALK); genitourinary neoplasm (GU neoplasm); cystectomy; crizotinib; inflammatory pseudotumor

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Introduction

Inflammatory myofibroblastic tumor (IMT) of the genitourinary (GU) tract, previously known as inflammatory pseudotumor or pseudosarcoma, is a rare clinical entity that has been described in most GU organs (1). The World Health Organization (WHO) defined IMT in 2002 as a mesenchymal tumor composed of differentiated myofibroblastic spindle cells with prominent, usually plasmocytic and/or lymphocytic infiltration. As many as 50% of IMT demonstrate activating translocations of the anaplastic lymphoma kinase (*ALK*) tyrosine kinase gene (2,3).

While generally regarded as tumor with low metastatic potential, IMT often exhibits a locally invasive behavior.

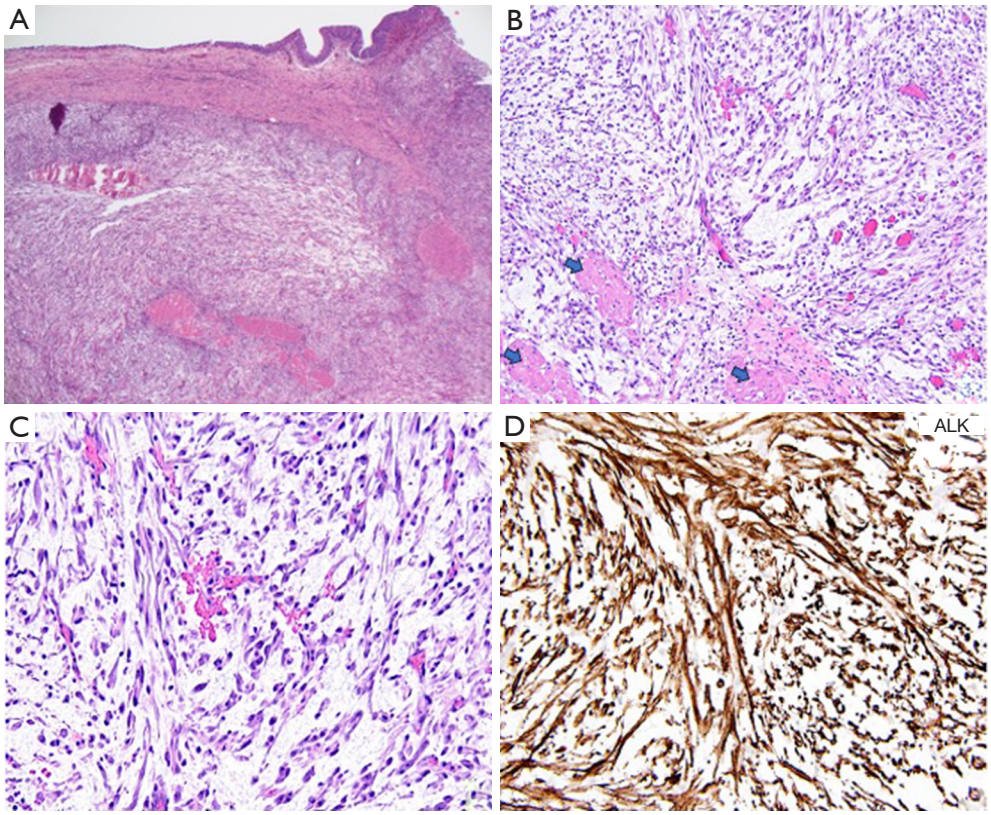

Figure 1 Inflammatory myofibroblastic tumor of the urinary bladder, seen as "nodular fasciitis-like" submucosa spindle cell proliferation. (A) HE staining, 20×. (B) HE staining showing haphazard spindle cell proliferation which can infiltrate muscularis propria (40×, arrows indicate muscularis propria). (C) HE staining high-power magnification showing eosinophilic spindle cells with varying degrees of cytologic atypia and mixed inflammatory infiltrate and occasional extravasated blood (100×). (D) Immunohistochemical staining for anaplastic lymphoma kinase (ALK) expression is seen (100×). Photomicrograph credits: Dr. Ankur R. Sangoi from Stanford University and Dr. Sean R. Williamson from Cleveland Clinic Foundation.HE, hematoxylin and eosin.

IMT exhibits signs and symptoms that are typically associated with GU malignancies such as a mass, hematuria, and urinary symptoms. Presenting symptoms of IMT can be highly variable and primarily depend on the size, and the anatomic location of the tumor. A systemic inflammatory syndrome has been reported in 15% to 30% of cases. It consists of nonspecific systemic manifestations (fever, weight loss) and laboratory findings (microcytic anemia, elevated inflammatory markers) (4). It can be difficult to distinguish an IMT from a GU malignancy based on imaging studies or intra-operative findings (5,6).

The diagnosis of IMT requires expertise in urologic pathology due to its relative rarity and the presence of several neoplastic and non-neoplastic entities mimicking IMT. Hallmark histologic features include haphazard spindle cell proliferation intermixed with inflammatory infiltrate in a background of loose, edematous stroma (7). Spindle cells have usually eosinophilic cytoplasm with occasional atypia, and mitotic figures may be present (7). Inflammatory infiltrate is usually lymphoplasmacytic, although polymorphonuclear leukocytes are not uncommon. Infiltration to the adjacent benign structures, such as vasculature and muscularis propria, can be present. Different histologic growth patterns, including nodular fasciitis-like (the most common), fibrous histiocytoma-like, and scar-desmoid-like can be seen (*Figure 1A-1C*). Immunohistochemical profile of IMT is variable; most consistent markers are smooth muscle actin and vimentin, although they can be focally expressed (8). Expression of pancytokeratin is well-known and does not exclude IMT (8). Disease-defining biomarker is ALK; nearly 50% of the IMT demonstrate positive expression by ALK

Table 1 Search strategy summary

Items	Specification
Date of search	01-02-2021 through 05-10-2023
Databases and other sources searched	PubMed, Web of Science
Search terms used	("Inflammatory Pseudotumor" OR "Pseudosarcoma" OR "Inflammatory Pseudo-Tumor" OR "Inflammatory Myofibroblastic Tumor") AND ("Urology" OR "Urologic" OR "Genitourinary" Or "Bladder" OR "Kidney" OR "Prostate" OR "Testis" OR "Epididymis") AND ("Adult" or "Pediatric")
Timeframe	All available
Exclusion criteria	Duplicates, non-English, non-full text, review articles, non-genitourinary articles, non-clinical articles
Selection process	N.M. and D.S. performed selection with supervision from senior author B.M.M.

immunohistochemical assay (*Figure 1D*). This expression is more consistently noted in younger patients, with 67% to 75% of reported cases demonstrating ALK reactivity (8-10). ALK gene synthesizes a neural tissue specific transmembrane tyrosine kinase receptor, and its activation through rearrangement, mutations, or amplification. ALK activation affects cell growth, transformation and anti-apoptotic signaling and has been detected in several tumor types (11). Differential diagnoses include post-operative spindle cell nodule, leiomyosarcoma, embryonal rhabdomyosarcoma, and sarcomatoid urothelial carcinoma (8). Currently, discussions about IMT's terminology continue; some authors suggest the term "pseudosarcomatous myofibroblastic proliferation" in these tumors in the absence of *ALK* gene rearrangement (12).

Due to infrequent occurrence of GU IMT, the literature largely consists of case reports and small series. This, coupled with the historic absence of a singularly agreed upon definition, the prevalence and incidence of IMT have been difficult to ascertain (13). In this comprehensive narrative review, we detail the clinical manifestations, diagnostic work up, therapeutic interventions, pathologic features, and post-treatment outcomes of IMT at various GU organ sites. We present this article in accordance with the Narrative Review reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-471/rc).

Methods

Information sources and search strategy

Our review was registered in PROSPERO (CRD42023405186). A search of PubMed and Web of Science was conducted according to the Preferred Reporting Items for Systematic Review and meta-analyses (PRISMA) statement to gather data systematically. The following search terms were used: ("Inflammatory Pseudotumor" OR "Pseudosarcoma" OR "Inflammatory Pseudo-Tumor" OR "Inflammatory Myofibroblastic Tumor") AND ("Urology" OR "Urologic" OR "Genitourinary" Or "Bladder" OR "Kidney" OR "Prostate" OR "Testis" OR "Epididymis") AND ("Adult" or "Pediatric"). In addition, the references in the retrieved articles were reviewed for any additional case reports (*Table 1*).

Screening and eligibility

The retrieved articles were screened for inclusion eligibility—first by title, then by abstract, and finally by full text review. Only full text reports on IMT involving a GU organ were included. The following criteria were used to exclude some records during the screening process: duplicates, language other than English, full text not available, review articles, articles without GU organs involvement, articles without clinical details (e.g., pathology review only) or pathology other than IMT.

Data synthesis

Each record was screened by two investigators (N.M., D.S.) for eligibility, followed by data extraction by one of the two investigators. Any questions or disputes were resolved by the senior investigator (B.M.M.). The following information was extracted from the included articles: age, sex, race, organ site, clinical signs and symptoms, diagnostic workup, treatment, follow up, and recurrence. Each organ site was

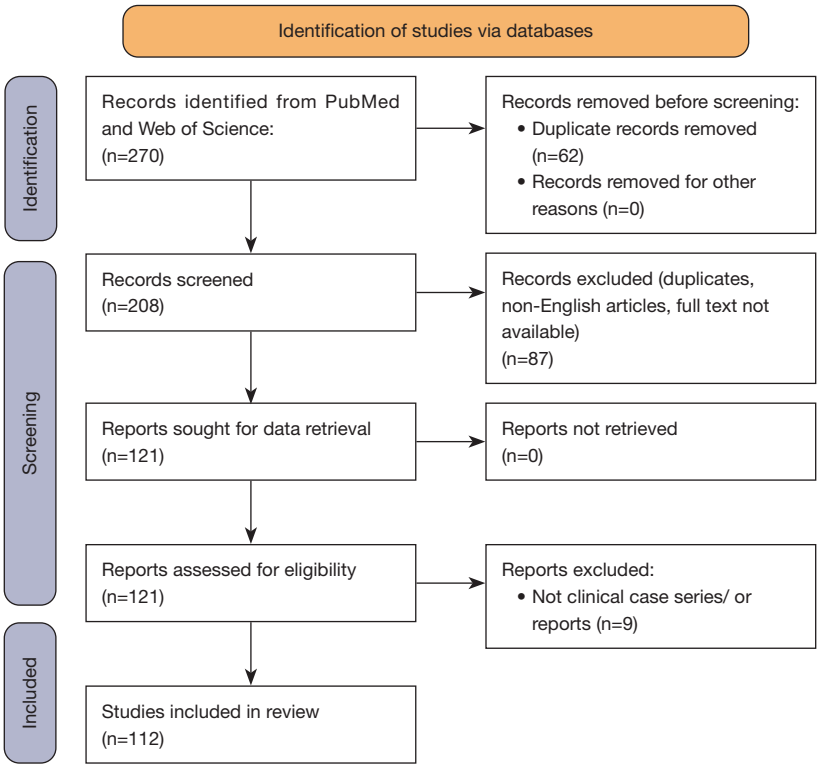

Figure 2 Study inclusion flow diagram.

analyzed separately. The references to all articles included in this review are listed at the end of the manuscript (more recent cases or rare cases) and the remaining references are provided in Appendix 1. Data were synthesized into a comprehensive narrative review.

Results

After screening and full text review, 112 of 121 articles met the inclusion criteria (*Figure 2*). Nine articles that initially met the inclusion criteria were excluded due to a lack of clinical information. These 112 articles described 167 cases of IMT, with only nine (5%) articles reporting >1 case. The frequency of IMT at various organ sites in adults and children is presented in *Figure 3*.

Bladder was the most frequently involved organ, accounting for 106 cases (63.5%), of which 35 were reported in a single-center case series spanning 22 years (14). There were 33 cases (19.8%) of IMT of kidney, followed by epididymis (6 cases, 3.6%), urachus (6 cases, 3.6%), ureter (5 cases, 3.0%), prostate (4 cases, 2.4%), testis (4 cases, 2.4%), and spermatic cord (3 cases, 1.8%).

Vast majority of IMT presented with symptoms, with only 7 cases (4.2%) of IMT presenting as an incidental finding. The clinical presentation and management of IMT at each GU organ site are analyzed separately and divided into adult and pediatric groups.

Urinary bladder

Adult

Of the 86 reported cases, 44 (51%) occurred in men and 42 (49%) in women. Median age at diagnosis was 39 [interquartile range (IQR), 30–55] years. The most frequent presenting symptom was gross hematuria which was reported in 51 patients (59%). Other presenting symptoms included lower urinary tract symptoms (LUTS), abdominal or pelvic pain, and urinary retention (*Table 2*). All patients underwent one or more diagnostic imaging studies, with computed tomography (CT) scan and ultrasound being utilized in over 75% of cases. In a few reports, the imaging studies were reported as cross sectional imaging, without mentioning the specific type of study.

Treatment of bladder IMT primarily consisted of transurethral resection (TUR) in 46 cases (53%), partial cystectomy in 29 cases (34%), and radical cystectomy in

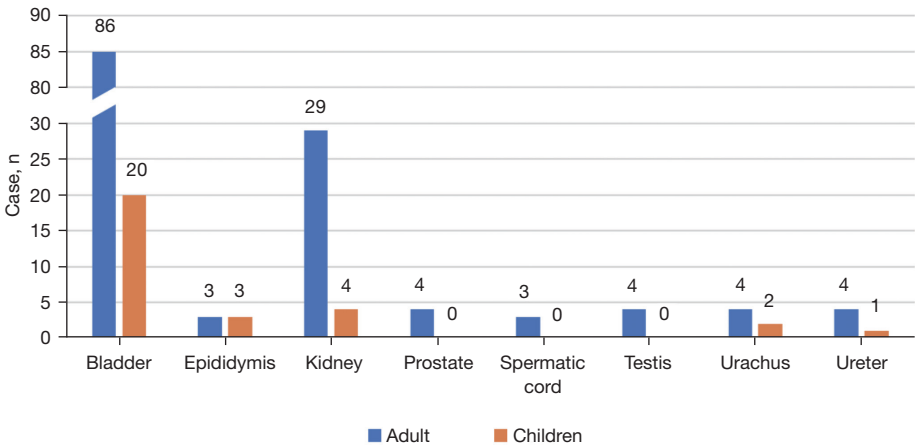

Figure 3 Case distribution by organ site.

15 cases (17%). Follow-up care was reported for 75 cases (87%), with mean follow up of 17.5 months (range, 2–60 months). Sixty-four patients (74%) underwent follow up cystoscopy and imaging studies, utilizing a surveillance strategy that was similar to what is used for non-muscle invasive bladder cancer (15,16).

Recurrence of bladder IMT was reported in 12 patients (14%). All cases of recurrent disease were noted within the first six months after treatment. Eleven of the 12 patients who experienced recurrent IMT were initially treated with a TUR procedure alone. One patient initially treated with partial cystectomy experienced recurrence in the bladder which required radical cystectomy (17). Another patient with an initial TUR developed a recurrent mass requiring radical cystectomy, but progressed to metastatic disease and died six months later (18). A patient who had undergone three TUR procedures for recurrent IMT progressed to metastatic disease (19). Amongst the patients undergoing initial radical cystectomy, there were no reports of loco-regional recurrence or metastatic disease.

Systemic therapy was utilized in only 3 (3.5%) cases of IMT of bladder. One patient with a large mass was diagnosed with IMT after biopsy specimen demonstrated ALK rearrangement. Initial treatment with neoadjuvant crizotinib did not demonstrate any tumor response. However, a partial response was noted within five weeks of starting lorlatinib, allowing the patient to undergo partial cystectomy (20). Hensley *et al.* reported significant objective response with crizotinib in a 39-year-old male with diffuse metastatic disease (14). A patient who declined surgical treatment was treated with corticosteroids and azathioprine, however, no follow-up information was provided (21).

Pediatric

Twenty cases of bladder IMT have been described in children, with 12 (60%) occurring in male and 8 (40%) in female patients (*Table 3*). Median age was 11 years (IQR, 6.5–15.5 years). The most common presenting symptoms were hematuria (40%), followed by LUTS, and pain. Most frequently utilized imaging study was CT scan, which was performed in nearly 65% of cases, followed by ultrasound and magnetic resonance imaging (MRI).

Various combinations of medical therapy were utilized in 6 (30%) patients including non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, steroids, and chemotherapy (22-24). All patients receiving medical therapy also underwent surgical resection of the tumor. A TUR was performed in 9 (45%) cases, 4 of which required additional surgical procedures. Partial cystectomy was performed in 14 patients, and no cases of total cystectomy were reported in the pediatric group. One child was treated using holmium laser *en bloc* excision (25).

Information on follow up care was available for 19 of 20 cases. The follow up intervals and surveillance modalities varied greatly amongst the reports. There were no cases of recurrence or metastatic disease identified in the pediatric group with bladder IMT.

Epididymis

Adult

Three cases of IMT arising from the epididymis were reported with the median age of 48 years (IQR, 30–73 years). The presenting symptom in each case was a palpable mass, including one that had been treated for presumed

Table 2 Adult inflammatory myofibroblastic tumor presentation and management

Organ	Bladder (n=86)	Epididymis (n=3)	Kidney (n=29)	Prostate (n=4)	Spermatic cord (n=3)	Testis (n=4)	Urachus (n=4)	Ureter (n=4)
Age (years), median [IQR]	39 [30–55]	48 [30–73]	52.5 [47–61]	66 [22–77]	56 [40–82]	43 [35–49]	43.5 [36–63.5]	51.5 [46–64.5]
Sex, N [%]								
Male	44 [51]	3 [100]	16 [55]	4 [100]	3 [100]	4 [100]	2 [50]	4 [100]
Female	42 [49]	–	13 [45]	–	–	–	2 [50]	–
Presentation, N [%]								
Hematuria	51 [59]	–	5 [17]	–	–	–	2 [50]	1 [25]
Mass	–	3 [100]	10 [34]	–	3 [100]	4 [100]	–	–
Pain	13 [15]	–	7 [24]	1 [25]	–	–	2 [50]	2 [50]
LUTS	14 [16]	–	3 [10]	1 [25]	–	–	–	–
Urinary retention	2 [2]		–	1 [25]	–	–	–	–
Incidental	–	–	5 [17]	1 [25]	–	–	–	1 [25]
Imaging, N [%]								
CT	45 [52]	–	16 [55]	3 [75]	2 [67]	1 [25]	3 [75][b]	4 [100]
US	23 [27]	3 [100]	6 [21]	2 [50]	2 [67]	4 [100]	–	–
MRI	11 [13]	–	4 [14]	1 [25]	1 [33]	1 [25]	–	2 [50]
VCUG	2 [2]	–	–	–	–	–	–	–
PET	–		–	–	1 [33]	–	–	–
Cross sectional imaging[a]	22 [26]							
Treatment, N [%]								
Partial excision	29 [34]	–	4 [14]	–	–	1 [25]	4 [100]	–
Complete resection	15 [17]	3 [100]	24 [83]	2 [50][d]	3 [100]	3 [75]	–	4 [100]
Endoscopic	46 [53]	–	–	2 [50]	–	–	–	–
Other	2 [2]	–	1 [3][c]	–	–	–	–	–
Recurrence, N [%]	12 [14]	None	None	None	None	None	None	None

[a], the type of imaging studies was not specified in the report by Hensley *et al.* (14). [b], one case did not use imaging, but the patient underwent ureteroscopy with biopsy. [c], case was discovered incidentally and noted to resolve without treatment. [d], one patient underwent radical prostatectomy while the other underwent radical cystectomy for local invasion. IQR, interquartile range; LUTS, lower urinary tract symptoms; CT, computed tomography; US, ultrasound; MRI, magnetic resonance imaging; VCUG, voiding cystourethrogram; PET, positron emission tomography.

epididymitis for three months. Scrotal ultrasound was the only imaging study used in all cases. Surgical resection was performed in each case which consisted of removal of the mass in two cases and epididymectomy one case.

There was no follow up information provided for any of these patients.

Pediatric

There were three reported cases of IMT of the epididymis in children, with the median age of 17 years (IQR, 14–17 years) (23,26,27). The presenting symptom in all cases was a palpable mass. Scrotal ultrasound was performed in all three cases, and an MRI and CT scan were utilized in one case.

Table 3 Pediatric inflammatory myofibroblastic tumor presentation and management

Organ	Bladder (n=20)	Epididymis (n=3)	Kidney (n=4)	Prostate (n=0)	Spermatic Cord (n=0)	Testis (n=0)	Urachus (n=2)	Ureter (n=1)
Age (years), median [IQR]	11 [6.5–15.5]	17 [14–17]	12.5 [7–15]	–	–	–	6.5 [3–10]	15
Sex, N [%]								
Male	12 [60]	3 [100]	1 [25]	–	–	–	2 [100]	1 [100]
Female	8 [40]	–	3 [75]	–	–	–	–	–
Presentation, N [%]								
Hematuria	8 [40]	–	1 [25]	–	–	–	1 [50]	–
Mass	–	3 [100]	–	–	–	–	–	–
Pain	4 [20]	–	2 [50]	–	–	–	1 [50]	1 [100]
LUTS	7 [35]	–	–	–	–	–	–	–
Urinary retention	2 [10]	–	–	–	–	–	–	–
Incidental	–	–	–	–	–	–	–	–
Other	1 [5][a]	–	1 [25][b]	–	–	–	–	–
Imaging studies, N [%]								
CT	13 [65]	1 [33]	4 [100]	–	–	–	2 [100]	1 [100]
US	12 [60]	3 [100]	2 [50]	–	–	–	1 [50]	–
MRI	5 [25]	1 [33]	1 [25]	–	–	–	1 [50]	–
Treatment, N [%]								
Partial excision	7 [35]	–	1 [25]	–	–	–	2 [100]	–
Complete resection	7 [35]	3 [100]	2 [50]	–	–	–	–	1 [100]
Endoscopic	12 [60]	–	–	–	–	–	–	–
Other	6 [30][c]	–	1 [25][d]	–	–	–	–	–
Recurrence	1 patient, residual mass	None	None	–	–	–	None	None

[a], enuresis. [b], fevers. [c], included a combination of medical therapy and other surgical approaches—see results section. [d], treated with antibiotics, mass reduced in 8 weeks. IQR, interquartile range; LUTS, lower urinary tract symptoms; CT, computed tomography; US, ultrasound; MRI, magnetic resonance imaging.

Complete surgical resection was performed in all cases, which included orchiectomy in two cases and removal of the mass in one case.

Two case reports provided follow up information which included an office visit at six weeks and two years, without any evidence of recurrence.

Kidney

Adult

IMT arising from the kidney were reported in 29 adult patients at the median age of 52.5 years (IQR, 47–61 years). Sixteen cases (55%) were reported in male patients while 13 cases (45%) were reported in female patients. Presenting signs and symptoms included renal mass (34%), pain (24%), hematuria (17%), LUTS (10%), and incidental findings on imaging study (17%). A CT scan was the most frequently utilized imaging study (55%), followed by ultrasound and MRI.

Surgical excision was performed in all except one case. Twenty-four patients (83%) underwent radical nephrectomy, and four patients (14%) underwent partial

nephrectomy. One case that was discovered incidentally on a kidney biopsy resolved spontaneously without treatment (28). Follow up information was reported for 23 (79%) patients.

Follow up ranged from six months to 36 months (mean 15.8 months), and included serial imaging with CT scan and/or ultrasound. There were no reports of recurrent or metastatic renal IMT.

Pediatric

Four cases of IMT of the kidney were reported in children. The median age at diagnosis was 12.5 years (IQR, 7–15 years). Three of the four cases were reported in female patients. Presentation included flank pain in two cases, as well as fevers and hematuria in one case each. Diagnostic imaging included a CT scan in all cases.

Radical nephrectomy was performed in two cases, and partial nephrectomy in one case. One patient with 7 cm mass and persistent fevers was found to have IMT when the mass was biopsied due to its abnormal appearance and size in a young patient. The mass regressed completely after 8 weeks of treatment with antibiotics (29).

Follow up information was reported for all cases, ranging from 9 to 20 months, without any evidence of recurrence.

Prostate

All four cases of IMT of the prostate were reported in adult patients, with median age of 66 years (IQR, 22–77 years) (30-33). One case was discovered incidentally in imaging studies for percutaneous drainage of a liver abscess. The remaining three cases presented with urinary symptoms such as dysuria, obstructive LUTS, and acute urinary retention. Diagnostic imaging included CT scan, MRI, and ultrasound. Transrectal biopsy in one patient revealed spindle cell morphology consistent with IMT.

Initial surgical management included TUR of prostate (TURP) in three cases (75%), and radical prostatectomy in one case where needle biopsy had demonstrated adenocarcinoma but not in the final specimen. Initial TURP alone resulted in incomplete removal, and required repeat TURP in two cases. Imaging studies in one patient, who had undergone three TURP procedures, revealed tumor progression and invasion of the bladder necessitating radical cystectomy (30).

Follow up was reported for three cases, ranging from four months to two years. At follow up, there was no evidence of recurrent disease in any patient.

Spermatic cord

Three cases of IMT of the spermatic cord occurred in adult patients at the median age of 56 years (IQR, 40–82 years) at diagnosis (34,35). Two patients presented with painless swelling in the scrotum and groin, and one patient with a left lower quadrant mass in the setting of a known undescended left testis. Diagnostic imaging studies included CT, ultrasound, MRI, and positron emission tomography.

Complete resection was performed in all cases using an approach that was similar to a radical orchiectomy procedure. Follow up ranged from 30 to 46 months, and the follow up protocol mimicked the follow up of testicular cancer. There was no evidence of recurrence or metastasis in any patient.

Testis

Four cases of IMT of the testis were reported in adult patients at the median age of 43 years (IQR, 35–49 years) (36-39). All cases presented as a palpable scrotal mass. Two of 4 patients were HIV-positive. Diagnostic Imaging included ultrasound in all cases, CT scan and MRI in one case, each.

Radical orchiectomy was performed in three cases. In one patient with suspicion of non-malignant tumor based on MRI findings (low signal intensity, minimal gadolinium enhancement) and intra-operative frozen section. The histology was consistent with an IMT, and a partial orchiectomy with complete resection of the tumor was performed. Medical treatment with antibiotics and NSAIDs was attempted in one patient. Repeat ultrasound demonstrated interval increase in mass size which was then treated with total orchiectomy.

Follow up was reported for two of the four cases, at three months and one year, without any evidence of recurrent disease.

Urachus

Adult

Four cases of IMT arising from the urachus were reported in adults (40-43). The median age at diagnosis was 43.5 years (IQR, 36–63.5 years). Two patients were male and two patients were female. Patients presented with pain in two cases (50%) and hematuria in two cases (50%). CT scan was used for diagnosis in three cases, and a diagnostic transurethral biopsy bladder dome in one case. Complete

surgical excision of the mass, including partial cystectomy, was performed in all patients.

Follow up for all four patients ranged from five months to three years using CT scans. There were no reports of recurrent urachal IMT.

Pediatric

Two cases of IMT arising from the urachus were reported in children. The age at diagnosis was three years and 10 years (44,45). The presentation included suprapubic pain and gross hematuria in one patient each. Ultrasound and MRI were used in one case and CT scan the other case. Both patients were treated with complete removal of the mass along with partial cystectomy. No follow up information was available for these patients.

Ureter

Adult

There were four reported cases of IMT arising from the ureter in adults (46-49). All four patients were male. The median age at diagnosis was 51.5 years (IQR, 46–64.5 years). Two patients presented with abdominal pain and one patient with hematuria. The diagnostic work up included CT scan and cystoscopy. The remaining patient was diagnosed as an incidental finding on a staging CT scan for prostate cancer.

Surgical approach included nephroureterectomy in one case, radical nephrectomy with proximal ureterectomy in one case, and distal ureterectomy in two cases. Medical treatment was not utilized in any of these cases.

Follow up was provided for three patients, ranging from 10 months to 3 years. There was no evidence of recurrence or metastasis in follow up imaging studies.

Pediatric

The only pediatric IMT involving the ureter involved a 15-year-old male who presented with left flank pain and a CT scan demonstrating a ureteral mass (23). The management included left ureteral stent placement and biopsy which confirmed the diagnosis of IMT.

The patient was treated with prednisone and celecoxib. However, repeat imaging demonstrated an increase in the size of the mass. This led to an exploratory laparotomy, ureterolysis and complete excision of the mass. At the six month follow up, an MRI did not show any evidence of recurrence.

Discussion

This comprehensive review of literature highlights the patterns of clinical presentation, diagnosis, treatment, and outcomes of IMT of all GU sites. Although IMT of the urinary bladder has been described with the greatest detail, including small case series, information on IMT of other GU organs has been limited to case reports. Clinical presentation of IMT of GU organs often mimics the presentation of various GU malignancies, such as hematuria, LUTS and a mass. However, pain appears to be a more frequently associated with IMT compared to malignant tumors which are often painless. Interestingly, incidental detection of IMT was rare as 96% of reported cases presented with one or more GU symptoms.

The etiology of the IMT remains unclear. One of the existing hypotheses includes infections by bacterial (*Klebsiella pneumonia*, *Mycobacterium avium intracellulare*, *Escherichia coli*) in studies from urinary bladder, or viral (EBV, HHV-8) agents, from the studies on the pulmonary or hepatosplenic IMT. Another hypothesis regarding autoimmune conditions is based on anecdotal reports of IMT with polyclonal gammaglobulinemia or thrombocytopenic purpura.

There are no distinct features of IMT in diagnostic imaging studies (CT, MRI, ultrasound). Diagnosis of IMT requires tissue evaluation, and as such, the final diagnosis is made only after removal of the tumor through endoscopic resection or open complete resection, or excisional biopsy, depending upon the organ site. Medical treatment was used variably, and infrequently, across organ sites. Medications were utilized more often in children with suspected or confirmed IMT of bladder or testis, including NSAIDs, steroids, and occasionally anti-neoplastic agents. However, the majority of cases also required surgical resection of the tumor. The use of medical therapy in these few cases typically demonstrated either minimal to no response or worsening of the tumor, requiring delayed surgical resection.

While neoadjuvant or concurrent use of available systemic therapies is often ineffective, recent approval by the Food and Drug Administration (FDA) of crizotinib for adult and pediatric patients is promising. It was approved for use in unresectable, recurrent, or refractory ALK-positive IMT. In one study, 14 pediatric patients were treated with crizotinib for a median duration of 20.5 months. Dose interruptions due to an adverse reaction occurred in 71%.

Twelve of these 14 patients demonstrated an objective response. In the other study, seven adult patients were treated with crizotinib, with five demonstrating an objective response. These new data suggest that patients with locally advanced IMT of GU tract may be offered crizotinib or similar ALK-targeted therapies in an effort to downstage the tumor to facilitate complete, but possibly less extensive, surgical excision.

Follow up after treatment of IMT at various GU organ sites varied significantly in frequency, duration, and methodology. Although detailed follow up information was not available for some patients, it appears that IMT recurrence is rare, especially after complete surgical resection. Recurrent or residual disease was primarily noted in cases where the initial procedure included TUR of bladder or prostate, requiring additional procedures such as partial or radical cystectomy, or radical prostatectomy. There were no cases of recurrence in patients whose initial treatment included partial nephrectomy or partial cystectomy, except one case. In one study, 11 of 12 patients undergoing a planned repeat TUR of bladder six weeks after diagnosis were noted to have residual disease (14). Thus, a planned repeat TUR of bladder (and likely prostate) at short interval should be considered essential in order to prevent local progression which could necessitate more extensive surgery. Since all of the reported recurrences occurred in the first six months, this can provide guidance as to the minimum required follow up period for GU IMT.

Our comprehensive review of IMT of GU tract has some limitations. The follow up data is quite variable and does not provide any distinct patterns of follow-up care to the clinicians. However, a follow-up strategy similar to that used for GU malignancies appears to be safe. Further, the included studies primarily consist of case reports, and few small case series, we are unable to assess the quality of the report in a systematic fashion. Although, we made every attempt to avoid duplication of cases, it is possible that a case reported individually may have been included in subsequent case series which could affect the total number and follow up data.

Conclusions

IMT can arise from any GU organ site, and are often symptomatic, with pain being a frequent presenting feature. Due to the overlap in symptoms and imaging findings, the clinical management is similar to that of GU malignancies. Systemic therapies targeting ALK are now available, but their role appears to be limited. Complete surgical resection is the cornerstone of the management of all GU IMT.

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Footnote

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Appendix 1

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