Review Article

Inflammatory myofibroblastic tumor of the urinary bladder: A systematic review of the literature and report of a case

Lory Hage, Michael A O'Donnell[1], Mohamad Abou Chakra[1]*, Amel Kime[2], Mathilde Sibony[2], Michaël Peyromaure, Igor Duquesne

Departments of Urology [2]Pathology, Cochin Hospital, Assistance Publique-Hopitaux de Paris, Universite Paris Cite, Paris, France, [1]Department of Urology, The University of Iowa Hospitals and Clinics, Iowa City, IA, USA

*E-mail: mohamedabouchakra@hotmail.com

ABSTRACT

Introduction: Inflammatory myofibroblastic tumors (IMTs) are intermediate-grade lesions that frequently recur and rarely metastasize. There are currently no guidelines on the management of bladder IMTs. This systematic review aims to describe the clinical presentation and compare the management options for bladder IMTs.

Methods: A PubMed/Medline search was conducted, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, using the following Mesh terms: ("inflammatory myofibroblastic") AND ("tumor") OR ("tumor") AND ("bladder") AND ("case report"). A total of 75 case reports were included in the analysis.

Results: The mean age of the patients was 36 years. 65% of the cases initially presented with hematuria. 68% of the tumors stained positive for anaplastic lymphoma kinase, and 20% invaded the muscularis. Patients underwent either transurethral resection of the bladder tumor (TURBT) only (34%), TURBT followed by complementary partial cystectomy (16%), or TURBT followed by radical cystectomy (4%). 36% and 9% of the cases underwent partial and radical cystectomy after the initial diagnosis, respectively. Cystectomies were performed using an open (74%), laparoscopic (14%), robotic-assisted (10%), or unknown (2%) approach. At a mean follow-up of 14 months, the recurrence and metastasis rates were about 9% and 4%, respectively. In addition, we present the case of a 49-year-old woman with a bladder IMT who underwent TURBT followed by laparoscopic partial cystectomy. The patient remains tumor free postoperatively (follow-up period of 12 months).

Conclusion: A complete surgical excision of the bladder IMT is crucial for the optimal management of these cases. Proper differentiation of this tumor from sarcoma or leiomyosarcoma leads to the best outcomes.

INTRODUCTION

Inflammatory myofibroblastic tumors (IMTs) are lesions of intermediate biologic potential that frequently recur and rarely metastasize.[1,2] They are composed of myofibroblastic mesenchymal spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils. IMTs most frequently occur in the abdominal cavity and lungs, but they have recently been described in other locations also, such as the head and neck.[3,4] This disease has been reported in less than 1% of the bladder tumors and is difficult to distinguish because of it's non-specific clinical and histological presentation. The past literature describes that the bladder-sparing treatment modalities, such as the transurethral resection of bladder tumors (TURBTs) or partial cystectomy are the most common management option.[5] However, currently there are no guidelines or

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.iju_50_24

Received: 30.01.2024, **Revised:** 07.03.2024,

Accepted: 08.03.2024, **Published:** 01.04.2024

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

recent reviews on the diagnosis and management of IMTs of the bladder. The aim of this systematic review was to determine the most appropriate management strategy in line with the methods used for the diagnosis and treatment of bladder IMTs in the literature. This will provide the urologists with guidance for the management of these cases. Additionally, we have put these data into perspective by presenting a case of bladder IMT in a 49-year-old woman, diagnosed on TURBT and treated effectively with a partial cystectomy.

METHODS

Search strategy

A systematic review of IMTs of the bladder was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[6] A PubMed/Medline web-based search was conducted using the following MeSH terms key words: ("inflammatory myofibroblastic"[All Fields]) AND (("tumor"[All Fields]) OR ("tumor"[All Fields])) AND ("bladder"[All Fields]) AND ("case report"[All Fields]). The search led to a total of 75 articles. Reference lists of the retrieved articles were not considered.

Selection process

Any original research article published in English providing data on IMTs of the urinary bladder was eligible. Only case reports were included in the study, regardless of whether a review of the literature was performed or not. Exclusion criteria were (i) studies describing other types of tumors and/or (ii) location of the IMT other than the bladder. A total of 75 articles were selected by the authors and included in the analysis. Only case reports from 2003 to 2024 were selected to avoid the risk of including other similar tumors, such as the pseudosarcomatous myofibroblastic proliferation, in the analysis of the outcomes of bladder IMTs. In fact, pseudotumors were only recently distinguished from IMTs, and pathological findings before 2003 were insufficient to rule out the differential diagnosis. Additionally, previously published cohorts had a small sample size and could not contribute to a systematic review. Thus, mixing results of cohort studies and case series with case reports may have increased the heterogeneity of the data. The search strategy is described in the flowchart [Figure 1].

Qualitative analysis

Patients' characteristics, including age, sex, medical history, clinical presentation, initial laboratory results, tumor characteristics (localization, size, pathology, and immunohistochemistry), management of the tumor (assessment of extension, systemic treatment, surgical intervention, and lymph node dissection [LND]), and follow-up (complications, recurrence, mortality, and modality of follow-up), were reviewed.

The pathologic results of all the reported cases were reviewed and classified into four categories: cell type and/or inflammatory cell infiltrate, muscle invasion, mitotic activity, and the presence of edema and/or necrosis. Immunohistochemical staining of each individual case was also recorded.

Continuous data were reported as the mean (± standard error of the mean) and binary and ordinal data were reported as counts and percentages.

RESULTS

Case presentation

A 49-year-old female patient presented with a 2-week history of lower abdominal pain without hematuria or lower urinary tract symptoms (LUTS). Significant medical history included Hashimoto's disease, on levothyroxine replacement medication, obesity (body mass index = 31.2 kg/m^2), and a past history of tobacco smoking.

Upon physical examination, the patient presented with tenderness in the hypogastric region of the abdomen, without any palpable mass. Laboratory tests and urine analysis were unremarkable.

A computed tomography (CT) urogram revealed a 23 by 18 mm irregularly enhancing mass-like density on the right side of the anterior wall of the bladder [Figure 2]. The kidneys and the upper urinary tract were unremarkable. A complete TURBT was performed. Pathological assessment of the specimen showed tumoral tissue located in the submucosal layer of the bladder, infiltrating the muscle, and composed of spindle cells with low mitotic activity. The stroma showed poor cellularity, with a few inflammatory cells. Some necrotic areas were seen. On immunohistochemistry, the tumor expressed smooth muscle actin (SMA), cytokeratin (CK) AE1/AE3, and anaplastic lymphoma kinase (ALK) proteins. These observations strongly suggested the presence of an IMT.

Following a multidisciplinary team meeting, a laparoscopic partial cystectomy was performed. A 6 cm × 2 cm × 2 cm sized portion of the anterior wall of the bladder was resected. The final pathological assessment confirmed the 1.5 cm × 1 cm IMT infiltrating the muscle layer but not breaching the surrounding fatty tissue. The margins of the surgical excision were clear.

The patient had a smooth recovery and was uneventfully discharged on the 3rd day of hospitalization. The patient's condition improved significantly, and she remains tumor-free throughout the follow-up period of 12 months.

Summary of cases reported in the literature

Clinical presentation of inflammatory myofibroblastic tumors

In total, 75 case reports describing bladder IMTs with a mean age of 36 ± 3 years at the diagnosis were included in

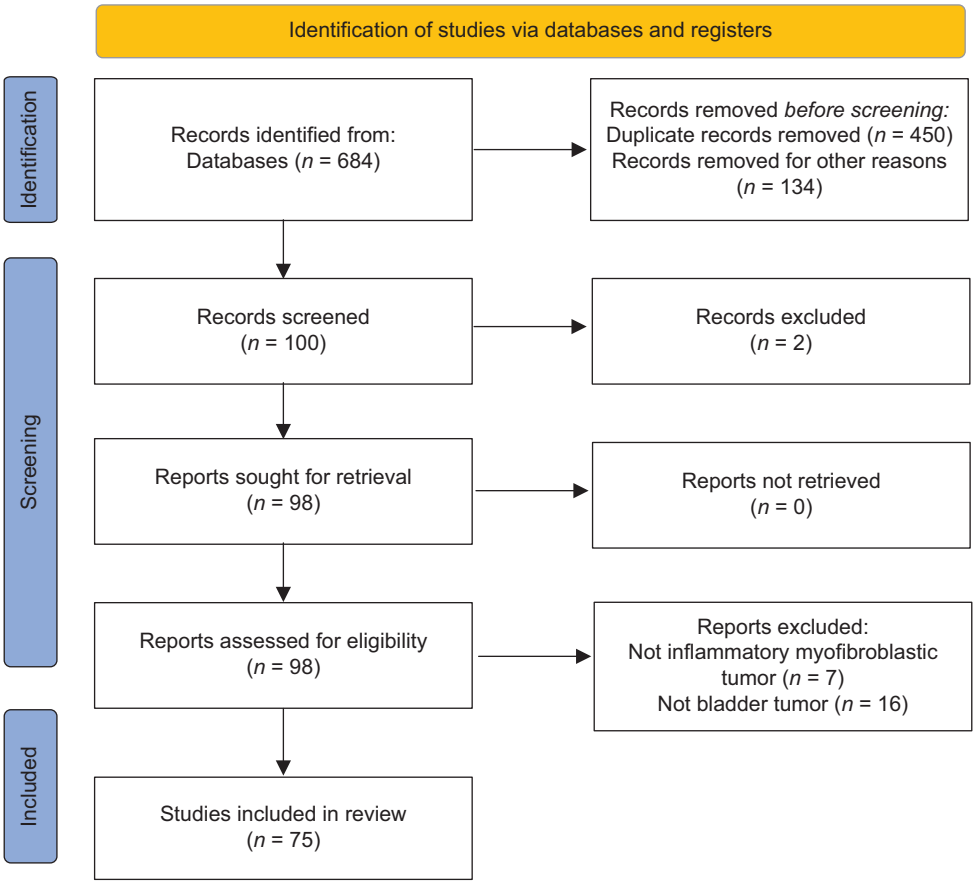

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram

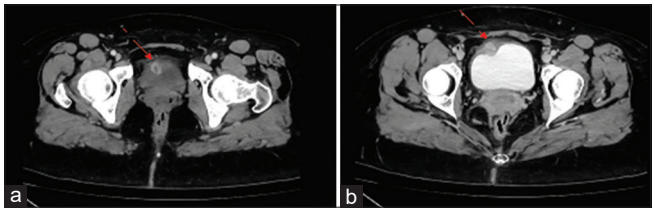

Figure 2: Computed tomography (CT) urogram of the reported case. CT urogram showed a 23 by 18 mm irregularly enhancing lesion (arrow) on the right side of the anterior wall of the bladder during arterial (a) and portal venous (b)

the analysis [Supplementary Table 1]. The sex ratio (male to female) was approximately 0.78 (44% of males vs. 56% of females). No past medical history seemed to stand out. 65% of the patients presented with gross hematuria, while 40% reported LUTS, which led to the diagnosis.

Tumors were located on the lateral wall of the bladder in 33% of the cases, dome in 28%, anterior wall in 18%, posterior wall in 14%, and in other locations in 7% of the cases, such as the trigone.

Diagnosis of inflammatory myofibroblastic tumors

Although rare in the bladder, IMTs have been widely described in other organs, particularly the lung, liver, and gastrointestinal tract, and their diagnosis appears to be one of the exclusions. Because of the nonspecific radiological appearance of the tumors and their frequent misdiagnosis into malignant neoplasms, pathology is critical for proper diagnosis.[1,7] Histological features, including dominant spindle cell proliferation, a pronounced chronic inflammatory component, low mitotic activity, and a lack of tumor necrosis, can help rule out the other differential diagnoses.[8]

In addition, IHC staining can be used to confirm the phenotype of a spindle cell tumor. IMTs are typically positive for vimentin, SMA, and desmin and variably express ALK. ALK positivity also seems to be an important predictive factor. In fact, IMTs expressing ALK may be associated with a good response to the treatment, whereas ALK-negative tumors were generally more locally advanced and metastasized more frequently.[3,4]

Being a key element for the diagnosis of IMTs, IHC analysis was described in all the cases. Tumors stained positive for ALK (68%), SMA (57%), and, to a lesser extent, CK and vimentin (21% and 31% of cases, respectively). ALK-negative tumors were generally larger and more locally advanced, with a mean size of 7 cm along the longer axis, compared to 4 cm for the ALK-positive tumors.

Tumor characteristics

The pathological aspects of IMTs were previously described by Coffin *et al*.[9] who classified them into three patterns:

the myxoid or vascular pattern, the compact spindle cell pattern, and the hypocellular fibrous pattern. These patterns may coexist within a single tumor.

In our review, we found that the tumor was mainly composed of spindle cells. Infiltration of the inflammatory cells, such as lymphocytes, plasma cells, and eosinophils, was seen in 72% of the histological assessments. 20% of the tumors invaded the muscle layer of the bladder. None of the tumors described in the cases had a high mitotic activity. Necrosis was found in 10% of the tumors.

The tumor size was variable and ranged from 2 to 12 cm. This is important because a complete resection of the tumor depends on its size.

Management and surgical treatment

The extension of the tumor was mostly evaluated using an abdomino-pelvic CT scan (81%), with or without contrast. Biopsies were performed in 25% of the patients before the surgical management. Magnetic resonance imaging (MRI) and ultrasound were performed in 27% and 12% of the patients, respectively, whereas a PET scan was rarely obtained (2.7%).

Thirty-four percent of the patients underwent only TURBT as the surgical management, while 16% underwent TURBT with complementary partial cystectomy and 4% underwent TURBT with complementary radical cystectomy. Additionally, 36% and 9% of the patients underwent partial and radical cystectomy, respectively, without the initial tumor resection. In 1% of the cases, the type of cystectomy was not specified. A complementary cystectomy was performed when the endoscopic resection of the tumor was deemed insufficient, or the tumor invaded the muscularis.

When cystectomy was performed, surgeons used an open approach in 74% of the cases. The laparoscopic approach was used in 14% of the cases and the robot-assisted approach was used in 10% of the cases. Altogether, a decision to perform radical cystectomy rather than a partial cystectomy was mainly made due to the misdiagnosis of the tumor initially and tumor recurrence. Takagi *et al*.[10] and Machioka *et al*.[11] described an initial pathological misdiagnosis of carcinosarcoma and sarcomatoid carcinoma of the bladder, respectively. Another indication for radical cystectomy was multiple tumor recurrence, as found in the reports by Ayati *et al*.[12] and Zhang *et al*.[13].

When partial and/or radical cystectomies were performed, a LND was performed in 4 (8%) of them. In some cases, the indication of the LND was the presence of lymphadenopathy on the imaging.[11-14] As for the case reported by Machioka *et al*.[11], the initial misdiagnosis of a malignant neoplasm led to the decision of a radical cystectomy with LND, as per the surgical management guidelines.

No postoperative complications were identified in our review except for one case of urinary extravasation following laparoscopic partial cystectomy which was successfully treated with an indwelling catheter.[15]

Details of final pathology reports were rarely described, but there were no cases of lymph node invasion among the reported cases.

Four cases were administered systemic anti-ALK therapy: alectinib, entrectinib, lorlatinib, and crizotinib. In the case described by Bonvini *et al*.,[16] the treatment was prescribed in view of lung and bone metastasis found at the initial presentation, while in other cases,[17-19] the treatment was offered to reduce the tumor size before the surgery. Additionally, due to the initial misdiagnosis of the tumor as eosinophilic cystitis, Fuller *et al*.[20] first treated their patient with steroids and cetirizine before reassessment and surgical management. Tsuma *et al*. reported down-sizing a large tumor with the administration of a cyclooxygenase-2 inhibitor, allowing the bladder to be preserved in a 13-year-old patient.[21]

Patient follow-up

For most of the patients, the postoperative follow-up was done by cystoscopy (41%), and/or other imaging techniques (27%), such as CT scans, MRI, and ultrasound, or an unspecified technique (32%). The mean follow-up duration, on an average, was 14 months. A total recurrence and metastasis rate of 9% and 4%, respectively, was recorded. Metastasis occurred in the lung, bone, peritoneum, and lymph nodes. In the cases where metastasis occurred, one patient received entrectinib (an ALK inhibitor) for 33 months and remained disease-free thereafter. In two additional cases, patients did not receive an ALK inhibitor as the tumor was ALK negative, and they died shortly after the diagnosis due to the rapid progression of the disease.[22,23]

DISCUSSION

Bladder IMT remains an exceedingly rare diagnosis. We compared the results of published case reports to collate the existing evidence derived from retrospective cohorts and case series.[24-32] Despite that, the literature remains scarce regarding the optimal diagnosis, management, and follow-up protocol for IMTs of the bladder. The largest systematic review on the topic included 182 patients, but included both the IMTs and pseudosarcomatous myofibroblastic proliferation of the bladder.[33] Nowadays, these two tumors are considered different entities.[34] IMTs are considered malignant, while inflammatory pseudotumors are more reactive and have no malignant potential.[35] Thus, the results of the previous systematic review are not discussed.

In cohort studies and case series,[24-32] the age of the patients diagnosed with bladder IMTs ranged between 3 and 89 years (mean age of 44 years), and the most common

clinical presentation was gross hematuria, in more than 60% of the cases. While the pathological type was variable, the most common type of bladder IMT was the spindle cell pattern [Table 1]. These results are in conjunction with the results revealed in our review. This means that the IMTs occur at a relatively younger age than the urothelial carcinoma. Additionally, in patients with IMTs of the bladder, gross hematuria was less frequently the initial presentation as compared to in those with urothelial carcinoma, where gross hematuria occurs in up to 80% of the cases.[36]

Recently, IHC staining for ALK, SMA, desmin, and vimentin has been described and is used to confirm the diagnosis of bladder IMTs. Furthermore, previous studies have demonstrated the role of IHC analyses not only in the diagnosis but also in the prognosis of IMTs. For instance, ALK positivity seems to correlate with a higher recurrence rate, whereas ALK-negative tumors tend to be more locally advanced and frequently metastasize.[4] In this review, 68% of the tumors stained positive for ALK and altogether showed a good prognosis and postoperative course, with an improvement in the clinical symptoms and a low recurrence rate at follow-up. Among the cases included in our review, 2 of the 7 cases where the tumors recurred were positive for ALK, and 1 of the 3 cases where the tumor metastasized was positive for ALK [Table 2]. The data is inadequate to make any formal conclusions about the prognostic role of IHC staining in the tumor and the oncological outcomes of bladder IMTs.

It is crucial to differentiate bladder IMTs from leiomyosarcoma and sarcomatoid carcinoma, as the latter have similar histologic features to the IMTs. The expression of ALK-1 favors the diagnosis of IMT. In addition, IMTs have mild cytologic abnormalities without aberrant mitoses or nuclear hyperchromasia.[37] This differentiation has a major clinical impact, as bladder preservation therapy is indicated only for IMTs and not for leiomyosarcoma or sarcomatoid carcinoma, where a more aggressive approach should be considered.

The role of abdominal and pelvic CT scans in the diagnosis of bladder IMTs is crucial in guiding the management, considering that the tumor size may reach more than 10 cm in diameter, as reported in our review and the previous studies.[24-32] This may help to assess the feasibility of complete resection of the tumor. Usually, these tumors

Table 1: Comparison between data obtained from our review and other retrospective cohorts and case series

Author, (year)	Evidence type	*n*	Age range (years)	Sex ratio (male/ female)	Clinical presentation (%)	Diagnostic test (%)	Tumor size (largest diameter) (cm)	Pathology findings	IHC (%)
Current review (2024)	Case reports	75	14–77	1	Hematuria (65.71%) LUTS (42.86%)	Cystoscopy (91.43%) CT scan (94.29%)	2–12	Spindle cell proliferation Invasion of muscularis (20%)	ALK (68%) SMA (57%) CK (21%) vimentin + (31%)
Montgomery *et al*. (2006)[24]	Retrospective cohort	46	3–89	1.8	Hematuria (60%)	N/A	1.2–12	Spindle cell proliferation Invasion of muscularis (41%)	ALK (57%) Actin (92%) CK (100%)
Chen *et al*. (2022)[25]	Retrospective cohort	14	12–74	0.5	Hematuria (64.3%) LUTS (50%)	N/A	2–7	Spindle cell pattern (57.1%) Invasion of muscularis (71.4%)	ALK (75%) SMA (100%) CK (64%)
Teoh *et al*. (2015)[26]	Case series	9	11–78	0.8	Hematuria (88.9%)	N/A	0.5–5.5	Spindle cell pattern (77.8%) Invasion of muscularis (55.6%)	ALK (75%) SMA (60%)
Liang *et al*. (2023)[27]	Case series	9	7–75	0.8	Hematuria (100%)	CT scan (100%)	2.1–5.1	N/A	ALK (67%) SMA (78%)
Li *et al*. (2020)[28]	Case series	8	7.4	1.6	Hematuria (50%)	N/A	1–8	N/A	ALK (87.5%) Desmin (100%) SMA (87.5%)
Freeman *et al*. (2004)[29]	Case series	9	13–51	1.25	N/A	N/A	2–7.5	N/A	ALK (89%) SMA (89%) Desmin (78%)
Xu *et al*. (2018)[5]	Case series	3	25–75	2	Hematuria (100%)	CT scan (100%)	4.8–5.6	Spindle cell proliferation	ALK (100%) SMA (33%)
Cresser *et al*. (2021)[30]	Case series	2	20, 50	-	Low abdominal pain	CT scan (100%)	3.4	Spindle cell proliferation	ALK (100%) SMA (100%)
Santos Lopes *et al*. (2016)[31]	Case series	2	38, 56	-	Hematuria (100%)	CT scan (100%)	2.3 and 6	Spindle cell proliferation	ALK-1 (100%)
Raja *et al*. (2018)[32]	Case series	2	13, 19	1	Hematuria (100%)	CT scan (100%)	4.4 and 8.2	Spindle cell proliferation	Actin and desmin (50%)

n=Number of patients included in the study, IHC=Immunohistochemistry, ALK=Anaplastic lymphoma kinase, SMA=Smooth muscle actin, CK=Cytokeratin, N/A=Not available, CT=Computed tomography, LUTS=Lower urinary tract symptoms

Table 2: Immunohistochemistry markers of tumors in cases where recurrence or metastasis occurred during follow-up

Recurrence	Metastasis	IHC
0	1	ALK, SMA, desmin, CK
1	0	Vimentin, SMA, ALK
1	0	SMA, desmin
1	0	SMA
0	1	SMA
1	0	ALK1, CK7, CK-AE1/AE3, S100
1	0	SMA, pan-CK, vimentin
1	1	CK
1	0	N/A

Two different clones of anti-CK monoclonal antibodies. 1=Yes, 0=No, IHC=Immunohistochemistry, ALK=Anaplastic lymphoma kinase, SMA=Smooth muscle actin, CK=Cytokeratin, N/A=Not available

have a cauliflower like appearance with a wide base on the CT scan, and most of the time they are endophytic. Early-stage tumors appear as thickening of the bladder wall, and establishing the diagnosis can be challenging. It has been shown that a symmetrical enhancement of the lesion in the arterial phase of an enhanced CT scan is typical of bladder IMT.[27]

Currently, guidelines on the best management for IMTs in the bladder, are unavailable. It appears unlikely that a study with a higher level of evidence will be feasible, given the rarity of this disease. The last systematic review on bladder IMTs was published in 2006 and reported limited results on the management of the disease.[24] However, the use of a bladder preserving approach can be considered oncologically safe, as patients who undergo TURBT or partial cystectomy do not have any increased risk of recurrence or metastasis [Table 3]. TURBT is performed in more than 50% of the cases initially, and subsequent cystectomy (mainly partial) is required in 10% to 20% of the cases, mainly due to incomplete endoscopic resection. The decision to perform a partial cystectomy or TURBT after an initial diagnosis should be based on the tumor size as estimated on the preoperative imaging and/or cystoscopy [Table 3]. If the tumor invade the muscularis, TURBT should be followed by cystectomy. When to perform a radical cystectomy is not well defined, as in most of the cases, it was performed following a misdiagnosis of the initial tumor as sarcoma.

Partial cystectomy may be performed using a laparoscopic or robot-assisted approach. These methods yield similar results to the open technique in terms of the oncological outcomes, safety, and the quality of life. Early hospital discharge and a lower requirement for blood transfusions are the two advantages of minimally invasive surgery.[38] The main selection criteria for partial cystectomy is the presence of a solitary tumor, the ability to remove the tumor with a 1.5–2 cm margin without requiring reimplantation of the ureters, and a normal bladder capacity. The location of the tumor and the surgeon's experience are also important in deciding which approach should be used.[39] In our review, laparoscopic and robotic approaches were used in 14% and 10% of the cases, respectively. Other case series in the literature documented the use of laparoscopic and robotic approaches in their cases without an increase in the complication rates.[5,31,32] This suggests that minimally invasive surgery can be used safely to treat bladder IMTs.

The U. S. Food and Drug Administration formally approved crizotinib, a first-generation ALK-tyrosine kinase inhibitor (TKI), as an ALK TKI in 2020 to treat unresectable ALK + IMT. It is indicated in unresectable, recurrent, or refractory tumors.[40] In our review, ALK-TKI has been used to down-size the tumor before the surgery in three cases and for metastatic disease in one case. Although the use of an ALK-TKI inhibitor is rational in bladder IMTs positive for ALK, the long-term efficacy and toxicity of such a therapy remain unknown in this setting and should be reserved for refractory cases.

The long-term prognosis of bladder IMTs is good. The recurrence rate ranges between 9% and 21%, and the metastasis rate is about 4% [Table 3]. Although the mean follow-up period in our review was limited to 14 months, we should keep in mind that IMTs have metastatic potential and a longer follow-up is warranted.

The strength of our review is that it included a high number of patients with bladder IMT. IMTs and inflammatory pseudotumors are regarded as separate entities, which supports the rationale to restrict our search specifically to IMTs. Thus, this study has a more homogeneous population with a definitive diagnosis of IMT. When it comes to uncommon diseases, case reports are crucial for their identification, thorough description, and therapy development. Additionally, we compared the data in our review with the existing data from large cohorts or case series, which helped us understand the oncological outcomes of this rare entity. We did not merge the data from case reports, cohort studies, or case series as the quality of the data is different in each. Combining results from case reports with cohort studies and case series may lead to bias in the outcomes. This may be due to the fact that cases in cohort studies are not examined thoroughly, and most of the time some missing data is allowed. Finally, we demonstrated that bladder IMTs could be managed conservatively, which can avoid invasive surgical management and subsequent higher rates of complication.

A few limitations of our review deserve a mention. Although, evidence from case reports has been used to help understand the diagnosis and management, in rare cases[41] some challenges, such as data heterogeneity, are still unavoidable. In some cases, long-term follow-up was not provided, and this may influence the assessment of the disease prognosis.

Table 3: Comparison between data obtained from our review of case reports and other retrospective cohorts and case series

Authors, (year) (reference number)	Type of evidence	*n*	Treatment modality (%)	Cystectomy approach	Mean follow-up time (months)	Recurrence rate (%)	Metastasis rate (%)
Current review (2024)	Case reports	75	TURBT alone (34%) TURBT then complementary PC (16%) TURBT then complementary RC (4%) PC (36%) RC (9%)	Open (74%) Lap (14%) Robotic (10%) NS (2%)	14	9	4
Montgomery *et al*. (2006)[24]	Retrospective cohort	46	TURBT (82%) Cystectomy 18%: 87.5% PC and 12.5% RC	NS	33	21	0
Chen *et al*. (2022)[25]	Retrospective cohort	14	Partial cystectomy (71.4%) TURBT (21.4%) RC (7.1%)	NS	43.9	7	Chen *et al*. (2022)[28]
Teoh *et al*. (2015)[26]	Case series	9	TURBT (60.8%) (complementary PC 17.8% and RC 1.4%) PC (29.2%) RC (9.2%) Cystoscopy, biopsy, and fulguration (0.8%)	NS	43.4	0	0
Liang *et al*. (2023)[27]	Case series	9	TURBT (33%) TURBT then PC (11%) PC (22%) RC (11%) Fulguration (22%)	NS	5	0	0
Li *et al*. (2020)[28]	Case series	8	TURBT (100%)	-	43.5	0	0
Freeman *et al*. (2004)[29]	Case series	9	PC (55.5%) RC (33.3%) TURBT (11.2%)	NS (100%)	19.5	0	0
Xu *et al*. (2018)[5]	Case series	3	TURBT (33%) PC (67%)	Lap (50%) Robotic (50%)	24	0	0
Cresser *et al*. (2021)[30]	Case series	2	TURBT (50%) PC (100%)	NS (100%)	6	0	0
Santos Lopes *et al*. (2016)[31]	Case series	2	TURBT (50%) PC (100%)	Lap (100%)	36	0	0
Raja *et al*. (2018)[32]	Case series	2	TURBT then PC (50%) PC (50%)	Robotic (50%) NS (50%)	13	0	0

n=Number of patients, TURBT=Trans urethral resection of bladder tumor, PC=Partial cystectomy, RC=Radical cystectomy, Lap=Laparoscopic, NS=Not specified

CONCLUSION

Bladder IMTs are rare intermediate-grade tumors that are mostly composed of spindle cells. Because of their nonspecific radiological appearance and indistinguishable clinical presentation, they are often misdiagnosed as malignant bladder tumors. Similarly, their histological presentation is not specific, which makes their differential diagnosis difficult. All in all, this study highlighted the limitations in the diagnosis of IMTs and the need for clinical guidance. Added knowledge on the management of bladder IMTs can be used to determine appropriate guidelines for their diagnosis and treatment. Considering the benefits of minimally invasive surgery and the management of bladder IMTs presented in this review, it is strongly recommended that bladder IMTs be initially treated by TURBT followed by laparoscopic partial cystectomy whenever feasible.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

REFERENCES

1. Cantera JE, Alfaro MP, Rafart DC, Zalazar R, Muruzabal MM, Barquín PG, *et al.* Inflammatory myofibroblastic tumours: A pictorial review. Insights Imaging 2015;6:85-96.
2. World Health Organization. Classification of tumours. In: Pathology and Genetics of Tumours of Soft Tissue and Bone. Lyon, France: IARC Press; 2002.
3. Siemion K, Reszec-Gielazyn J, Kisluk J, Roszkowiak L, Zak J, Korzynska A. What do we know about inflammatory myofibroblastic tumors? A systematic review. Adv Med Sci 2022;67:129-38.
4. Coffin CM, Hornick JL, Fletcher CD. Inflammatory myofibroblastic tumor: Comparison of clinicopathologic, histologic, and immunohistochemical features including ALK expression in atypical and aggressive cases. Am J Surg Pathol 2007;31:509-20.
5. Xu H, He B, Tu X, Bao Y, Yang L, Zhuo H, *et al.* Minimally invasive surgery for inflammatory myofibroblastic tumor of the urinary bladder: Three case reports. Medicine (Baltimore) 2018;97:e13474.
6. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
7. Kovach SJ, Fischer AC, Katzman PJ, Salloum RM, Ettinghausen SE, Madeb R, *et al.* Inflammatory myofibroblastic tumors. J Surg Oncol 2006;94:385-91.

8. Palaskar S, Koshti S, Maralingannavar M, Bartake A. Inflammatory myofibroblastic tumor. Contemp Clin Dent 2011;2:274-7.
9. Coffin CM, Watterson J, Priest JR, Dehner LP. Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor). A clinicopathologic and immunohistochemical study of 84 cases. Am J Surg Pathol 1995;19:859-72.
10. Takagi K, Takai M, Kameyama K, Horie K, Kikuchi M, Kato T, *et al.* ALK gene translocation in inflammatory myofibroblastic tumor of the urinary bladder: A case report. Urol Case Rep 2015;3:138-40.
11. Machioka K, Kitagawa Y, Izumi K, Kitamura S, Ikeda H, Namiki M. Inflammatory myofibroblastic tumor of the urinary bladder with benign pelvic lymph node enlargement: A case report. Case Rep Oncol 2014;7:571-5.
12. Ayati M, Nowroozi MR, Momeni SA, Moghadam SO, Saffar H, Valizadeh F. Radical cystectomy for management of inflammatory myofibroblastic tumor of the urinary bladder: A rare case report. Urol Case Rep 2019;27:100997.
13. Zhang HH, Qi F, Zu XB, Xu L, Liu LF, Qi L. Recurrence of inflammatory myofibroblastic tumor in bladder secondary to prostate treated with laparoscopic radical cystectomy. Med Sci Monit 2012;18:S63-6.
14. Nauman M, Hasan AS, Sultan G, Kumar P, Hussain M, Hashmi A. Inflammatory myofibroblastic tumour of genitourinary system. J Pak Med Assoc 2021;71:2467-9.
15. Wang K, Zhou H, Lu Y, Lu Q, Zhang C, Zhou X, *et al.* ALK-negative urachal inflammatory myofibroblastic tumor in an elderly female: A case report. Medicine (Baltimore) 2018;97:e13619.
16. Bonvini P, Rossi E, Zin A, Manicone M, Vidotto R, Facchinetti A, *et al.* Case report: Circulating tumor cells as a response biomarker in ALK-positive metastatic inflammatory myofibroblastic tumor. Front Pediatr 2021;9:652583.
17. Nagumo Y, Maejima A, Toyoshima Y, Komiyama M, Yonemori K, Yoshida A, *et al.* Neoadjuvant crizotinib in ALK-rearranged inflammatory myofibroblastic tumor of the urinary bladder: A case report. Int J Surg Case Rep 2018;48:1-4.
18. Reinhart S, Trachsel Y, Fritz C, Wagner U, Bode-Lesniewska B, John H, *et al*. Inflammatory myofibroblastic tumor of the bladder with FN1-ALK gene fusion: Different response to ALK inhibition. Urology 2020;146:32-5.
19. Fujiki T, Sakai Y, Ikawa Y, Takenaka M, Noguchi K, Kuroda R, *et al.* Pediatric inflammatory myofibroblastic tumor of the bladder with ALK-FN1 fusion successfully treated by alectinib. Pediatr Blood Cancer 2023;70:e30172.
20. Fuller TW, Dangle P, Reese JN, Ristau BT, Lyon TD, Jaffe R, *et al*. Inflammatory myofibroblastic tumor of the bladder masquerading as eosinophilic cystitis: Case report and review of the literature. Urology 2015;85:921-3.
21. Tsuma Y, Miyachi M, Ouchi K, Tsuchiya K, Iehara T, Naitoh Y, *et al.* Neoadjuvant treatment with cyclooxygenase-2 inhibitor and prednisolone allows conservative surgery for inflammatory myofibroblastic tumor of the bladder. J Pediatr Hematol Oncol 2016;38:e283-5.
22. Kim HW, Choi YH, Kang SM, Ku JY, Ahn JH, Kim JM, *et al.* Malignant inflammatory myofibroblastic tumor of the bladder with rapid progression. Korean J Urol 2012;53:657-61.
23. Libby EK, Ellis LT, Weinstein S, Hammer RD, Murray KS. Metastatic inflammatory myofibroblastic tumor of the bladder. Urol Case Rep 2019;23:10-2.
24. Montgomery EA, Shuster DD, Burkart AL, Esteban JM, Sgrignoli A, Elwood L, *et al.* Inflammatory myofibroblastic tumors of the urinary tract: A clinicopathologic study of 46 cases, including a malignant example inflammatory fibrosarcoma and a subset associated with high-grade urothelial carcinoma. Am J Surg Pathol 2006;30:1502-12.
25. Chen C, Huang M, He H, Wu S, Liu M, He J, *et al.* Inflammatory myofibroblastic tumor of the urinary bladder: An 11-year retrospective study from a single center. Front Med (Lausanne) 2022;9:831952.
26. Teoh JY, Chan NH, Mak SM, Lo AW, Leung CY, Hui Y, *et al.* Inflammatory myofibroblastic tumours of the urinary bladder: Multi-centre 18-year experience. Urol Int 2015;94:31-6.
27. Liang P, Zhu BB, Ren XC, Gao JB. Inflammatory myofibroblastic tumor of the bladder: Computed tomographic features. Mol Clin Oncol 2023;18:40.
28. Li YP, Han WW, Yang Y, He LJ, Zhang WP. Inflammatory myofibroblastic tumor of the urinary bladder and ureter in children: Experience of a tertiary referral center. Urology 2020;145:229-35.
29. Freeman A, Geddes N, Munson P, Joseph J, Ramani P, Sandison A, *et al.* Anaplastic lymphoma kinase (ALK 1) staining and molecular analysis in inflammatory myofibroblastic tumours of the bladder: A preliminary clinicopathological study of nine cases and review of the literature. Mod Pathol 2004;17:765-71.
30. Cresser S, Nzenza T, Tripathy S, Hall R. Case series: Inflammatory myofibroblastic bladder tumor in regional Australia. Int J Surg Case Rep 2021;82:105898.
31. Santos Lopes S, Furtado A, Oliveira R, Cebola A, Graça B, Ferreira Coelho M, *et al.* Inflammatory myofibroblastic tumor of the bladder: 2 rare cases managed with laparoscopic partial cystectomy. Case Rep Urol 2016;2016:4976150. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5126425/.
32. Raja NS, Lee T, Kaffenberger S, Kraft K, Udager A, Ivancic V. Localized inflammatory myofibroblastic tumor involving the genitourinary system: Adolescent case series and review. Urology 2018;122:162-4.
33. Teoh JY, Chan NH, Cheung HY, Hou SS, Ng CF. Inflammatory myofibroblastic tumors of the urinary bladder: A systematic review. Urology 2014;84:503-8.
34. Acosta AM, Demicco EG, Dal Cin P, Hirsch MS, Fletcher CD, Jo VY. Pseudosarcomatous myofibroblastic proliferations of the urinary bladder are neoplasms characterized by recurrent FN1-ALK fusions. Mod Pathol 2021;34:469-77.
35. Höhne S, Milzsch M, Adams J, Kunze C, Finke R. Inflammatory pseudotumor (IPT) and inflammatory myofibroblastic tumor (IMT): A representative literature review occasioned by a rare IMT of the transverse colon in a 9-year-old child. Tumori 2015;101:249-56.
36. Edwards TJ, Dickinson AJ, Natale S, Gosling J, McGrath JS. A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic. BJU Int 2006;97:301-5.
37. Alderman M, Kunju LP. Inflammatory myofibroblastic tumor of the bladder. Arch Pathol Lab Med 2014;138:1272-7.
38. Khetrapal P, Wong JK, Tan WP, Rupasinghe T, Tan WS, Williams SB, *et al.* Robot-assisted radical cystectomy versus open radical cystectomy: A systematic review and meta-analysis of perioperative, oncological, and quality of life outcomes using randomized controlled trials. Eur Urol 2023;84:393-405.
39. Peak TC, Hemal A. Partial cystectomy for muscle-invasive bladder cancer: A review of the literature. Transl Androl Urol 2020;9:2938-45.
40. Wang QA, Chen HW, Wu RC, Wu CE. Update of diagnosis and targeted therapy for ALK(+) inflammation myofibroblastic tumor. Curr Treat Options Oncol 2023;24:1683-702.
41. Nakamura T, Igarashi H, Ito T, Jensen RT. Important of case-reports/series, in rare diseases: Using neuroendocrine tumors as an example. World J Clin Cases 2014;2:608-13.

How to cite this article: Hage L, O'Donnell MA, Abou Chakra M, Kime A, Sibony M, Peyromaure M, *et al.* Inflammatory myofibroblastic tumor of the urinary bladder: A systematic review of the literature and report of a case. Indian J Urol 2024;40:88-95.

Supplementary Table 1: Cases of urinary bladder inflammatory myofibroblastic tumors with presentation, characteristics, and management

Case report			Patient characteristics					Tumor characteristics				
First author	Journal	Year	Age	Sex	Medical history	Clinical presentation	Blood test results	Localization	Size (cm)	Cystoscopy	Pathology	IHC
Ding M	Asian J Surg	2024	66	Male	0	Lower abdominal pain	-	Right lateral wall	7×6	-	Spindle cells, inflammatory infiltrate	Desmin, SMA, ALK
Dergamoun H	Pan Afr Med J	2023	36	Male	0	Hematuria, dysuria, pollakiuria	WBC - 9.6× 10^9/L, Hb - 10.3 g/dL, creatinine - 0.8 mg/dL, CRP - 13 mg/L	Trigone, left lateral wall of dome	-	Large mass and necrotic floating lesions	Spindle cells, inflammatory infiltrate, muscle invasion, low mitotic activity	Desmin, SMA, ALK
Guan L	Urol Case Rep	2023	12	Female	0	Hematuria and light-headedness	Hb - 8.2 g/dL	Right lateral wall	5.4×4.5	Large mass	Spindle cells, inflammatory infiltrate	ALK1, vimentin
Son SM	Oncol Lett	2023	45	Female	-	Hematuria	-	Anterior and superior wall	2.2×2	Solid erythematous mass	Spindle cells, inflammatory infiltrate, low mitotic activity, focal necrosis	Vimentin, CK-AE1/AE3, ALK, desmin
Prijovic N	Medicina (Kaunas)	2023	62	Male	0	Dysuria, hematuria	WBC - 5.5×10^9/L, Hb - 13.6 g/dL	Front wall and dome	2×5	Wide base and smooth surface	Spindle cells, inflammatory infiltrate	SMA
Neuenschwander L	Urol Case Rep	2023	50	Female	-	Hematuria, abdominal pain		Posterior wall	10.4×6.8	Highly vascular, large, nodular mass	Spindle cells, inflammatory infiltrate	ALK
Derimachkovski G	Urol Case Rep.	2023	59	Male	-	Hematuria	-	Trigone	3.4×3	-	Spindle cells, inflammatory infiltrate	ALK1, vimentin, SMA
Fujiki T	Pediatr Blood Cancer	2023	6	Female	-	Hematuria	-	Dome	4	-	Spindle cells, inflammatory infiltrate	ALK
Sun Z	Front Oncol	2022	57	Female	-	Severe lower abdominal pain, shock	-	Dome	12.6×6.5×4	-	Spindle cells, inflammatory infiltrate, muscle invasion	CK broad, vimentin, ALK, SMA, desmin
Buksh O	Cureus	2022	23	Female	Cesarean	Hematuria	Hb - 9.7 g/dL	Left lateral wall, base, right ureterovesical junction	6.1×6×6	-	Spindle cells, inflammatory infiltrate, edematous background	vimentin, pan-CK, CAM5.2, desmin, SMA
Marais B	Ther Adv Urol	2022	27	Male	Smoking	Suprapubic discomfort, hematuria	Hb - 10 g/dL	Dome, superior and anterior wall	4.9×4.5	Large sessile nodular mass	Spindle cells, inflammatory infiltrate, edematous background, mitosis	SMA, ALK

Contd...

Supplementary Table 1: Contd...

Case report			Patient characteristics					Tumor characteristics				
First author	Journal	Year	Age	Sex	Medical history	Clinical presentation	Blood test results	Localization	Size (cm)	Cystoscopy	Pathology	IHC
Balagobi B	Int J Surg Case Rep	2022	47	Male	0	Urgency, frequency, lower abdominal pain	-	Dome, left lateral wall	6×5.7×5.5	Solitary extramucosal exophytic polypoidal tumor	Spindle cells, focal necrosis, low mitotic activity, muscle invasion	Vimentin, ALK
Khondakar NR	Urology	2022	16	Male	0	Syncope, hematuria, dysuria	Hb - 6.9 g/dL, creatinine - 0.8 mg/dL, WBC - 12×10^9/L	Posterior dome, left lateral wall	3×5	Sessile nonpapillary mass with an overlying bleeding mucosa	Spindle cells	ALK, CK-AE1/AE3, desmin
Furukawa Y	Case Rep Oncol	2022	6	Male	0	Abdominal pain	-	Superior wall	1.8×1.7×1.6	Broad base tumor	Spindle cells	ALK, SMA, desmin
Ma W	BJR Case Rep	2022	26	Female	0	Hematuria		Left posterior wall	5.8×2.5×1.3	-	Spindle cells, inflammatory infiltrate	ALK, SMA, desmin, vimentin
Batie SF	Urol Case Rep	2022	6	Female	0	Hematuria and dysuria	-	Right lateral wall	4	Infiltrative mass with cystic components	Spindle cells, inflammatory infiltrate	-
Nauman M	J Pak Med Assoc	2021	30	Female	-	Lower abdominal pain	-	Dome	5×3.3	Sessile growth	Spindle cells, inflammatory infiltrate, muscle invasion	Vimentin
Bonvini P	Front Pediatr	2021	19	Male	-	Hematuria, progressive anemia	-	-	-	-	Spindle cells, inflammatory infiltrate	ALK, SMA, desmin, CK
Abou Zahr R	Case Rep Urol	2021	37	Female	0	Hematuria	-	Right lateral wall	2×2	-	Spindle cells, minimal mitotic activity, vascularized and edematous stroma, necrosis, inflammatory infiltrate, muscle invasion	CK-AE1/AE3, SMA
Fachini Cipriani RF	Urol Case Rep	2021	55	Female	Lymphoma and hypothyroidism	Hematuria	-	Fundus and right lateral walls	8	-	Spindle cells	AE1/AE3, ALK
Matsui Y	Urol Case Rep	2021	55	Male	-	Hematuria and shock		-	-		Spindle cells, inflammatory infiltrate	AE1/AE3, ALK, vimentin, SMA

Contd...

Supplementary Table 1: Contd...

Case report			Patient characteristics					Tumor characteristics				
First author	Journal	Year	Age	Sex	Medical history	Clinical presentation	Blood test results	Localization	Size (cm)	Cystoscopy	Pathology	IHC
Chandora A	Urology	2021	12	Male	VACTERL syndrome	Hematuria	-	Native and augmented bladder junction	7		Spindle cells, inflammatory infiltrate	ALK1, SMA
Wang CS	Clin Case Rep	2021	74	Male	-	Hematuria	-	Anterior wall	3		Spindle cells with a fascicular pattern	ALK1, desmin
Higazy A	Urol Case Rep	2020	40	Female	-	Micturition, dyspareunia, protruding painless mass through the urethra	-	Left lateral wall, left ureteric orifice	4	Encroaching the left ureteric orifice and prolapse through the urethra	Spindle cells, vascular stroma, inflammatory infiltrate	ALK
Laylo JCV	Urol Case Rep	2020	28	Female	0	Hematuria	-	Right superior bladder wall	4.3×4.7×4.6	Large smooth wall mass	Spindle cells, inflammatory infiltrate	SMA, ALK, desmin
Reinhart S	Urology	2020	43	Female	0			Anterior wall	7	Solid tumor	Spindle cells	ALK1, desmin
Ayati M	Urol Case Rep	2019	42	Female	0	Hematuria, clot retention, and over-distended bladder	Hb - 7 g/dL, creatinine - 3 mg/dL	Dome, left lateral wall, interior wall	-	Blood clots	Spindle cells, vascular edematous background, inflammatory infiltrate, mitotic activity, necrosis	Vimentin, SMA, ALK
Fadaak K	Case Rep Oncol	2019	14	Female	0	Urgency and frequency, painless hematuria	-	Right posterolateral wall	2×1.5	Bladder mass with intact mucosa	Spindle cells, inflammatory infiltrate, muscle invasion, rare mitosis	SMA, ALK1
Gass J	J Endourol Case Rep	2019	51	Male	BPH, erectile dysfunction	Dysuria, hematuria	Creatinine 0.84 mg/dL	Right posterolateral wall	3.5×3.5×4	Large sessile smooth-walled bladder lesion	Spindle cells, muscle invasion	ALK
Song D	Medicine (Baltimore)	2019	28	Female	2 cesareans	Hematuria with clots	Hb 6.2 g/dL	Trigone	2×3×4	-	Spindle cells, inflammatory cells, muscle invasion	SMA, ALK
Inamdar	Bladder (San Franc)	2019	93	Female	-	Hematuria	-	Posterior and right lateral wall	5	Large mass with a stalk	Spindle cells, inflammatory cells	SMA
Tsuboi I	IJU Case Rep	2019	76	Male	-	Hematuria	-	Tumor within diverticulum	11×9×8	Tumor within diverticulum	Spindle cells, inflammatory cells	SMA, desmin

Contd...

Supplementary Table 1: Contd...

Case report			Patient characteristics					Tumor characteristics				
First author	Journal	Year	Age	Sex	Medical history	Clinical presentation	Blood test results	Localization	Size (cm)	Cystoscopy	Pathology	IHC
Wang K	Medicine (Baltimore)	2018	77	Female	Diabetes, hypertension, renal cysts	Suprapubic mass	-	Dome	9.5×10×5	Irregular topography of bladder wall and smooth bladder mucosa	Spindle cells, inflammatory infiltrate, muscle invasion, interstitial edema, small abscess formation and necrosis	CD34, SMA, vimentin
Nagumo Y	Int J Surg Case Rep	2018	17	Male	-	Painful urination and frequency	-	Posterior wall and dome	5	Nodular tumor with locally thickened and edematous mucosa	Spindle cells, inflammatory infiltrate, hyalinizing area	ALK
Libby EK	Urol Case Rep	2018	61	Male	0	Hematuria	-	Floor extending to left lateral ureteral orifice	-	Large tumor	Spindle cells infiltrating muscularis	SMA
Kumar S	Urol Ann	2018	19	Female	0	Hematuria	-	Anterior wall and dome	6×5	-	Spindle cells, inflammatory infiltrate	-
Kato M	Urol Case Rep	2017	17	Female	-	Hematuria, lower abdominal pain	-	Dome and right anterolateral wall	10×5×4.5	-	Spindle cells, inflammatory infiltrate, mucosa ulceration, muscle invasion	ALK/p80, SMA, CK-AE1/AE3, CK-CAM5.2
Rotenberry C	Urol Case Rep	2017	29	Male	0	Hematuria		Dome and left lateral wall	4	Nodular mass	Spindle cells	ALK1
Koukoura O	BMJ Case Rep	2017	46	Female	0	Suprapubic pain and dyspareunia	-	Posterior wall	3×4	Broad-based, lobulated tumor	Spindle cells	ALK
Nkwam N	J Surg Case Rep	2016	62	Female	-	Hematuria	Hb 5.8 g/dL	Anterior wall	4	-	Spindle cells, inflammatory infiltrate, muscle invasion	ALK1, CK7, CK-AE1/AE3, S100
Kondo T	Case Rep Oncol	2016	36	Male	Hyperlipidemia, diabetes, asthma, bipolar disorder	Hematuria	-	-	4×2.5	Broad-based tumor of 4 cm	Spindle cells, inflammatory infiltrate, no mitoses	ALK, SMA, CK-AE1/AE3, p53
Etani T	Case Rep Oncol	2016	52	Male	Rheumatoid arthritis	Hematuria	-	Dome, anterior wall	3	Solitary nonpapillary tumor with surrounding edema	Spindle cells, inflammatory infiltrate, muscle invasion	Vimentin, SMA, ALK

Contd...

Supplementary Table 1: Contd...

Case report			Patient characteristics					Tumor characteristics				
First author	Journal	Year	Age	Sex	Medical history	Clinical presentation	Blood test results	Localization	Size (cm)	Cystoscopy	Pathology	IHC
Yaghi MD	Urol Ann	2016	71	Female	-	Urgency, frequency, lower abdominal pain, dysuria, cystitis	Hb 8.6 g/dL	Posterior wall	3	Solid tumor, smooth surface	Spindle cells, necrosis	-
Tan Tanny SP	Urol Case Rep	2016	40	Male	Hypertension, type 2 diabetes, hyper cholesterolemia, ex-smoker, obesity	Hematuria, dysuria, lower abdominal pain	Creatinine 50 μmol/L	Right lateral wall	5	Large solid bladder mass, smooth surface	Spindle cells, edematous and fibrous stroma, necrosis, and hemorrhage	CK-AE1/AE3, vimentin, actin, ALK, desmin
Tsuma Y	J Pediatr Hematol Oncol	2016	13	Male	-	Dysuria and lower abdominal mass	-	Left ureteral orifice	4.7	-	Spindle cells	ALK; COX-2
Alam R	Case Rep Urol	2016	39	Female	-	Hematuria	-	Right anterior wall	3.2×2×2.7	-	Spindle cells invading the muscularis	ALK
Takagi K	Urol Case Rep	2015	26	Female	-	Hematuria, severe anemia	-	Dome	3.3	Solitary nonpapillary tumor with surrounding edema	Spindle cells, muscle invasion, inflammatory infiltrate	CK-AE1/AE3, vimentin, ALK1, SMA
Ren X	Oncol Lett	2015	31	Female	Pregnant at the time of diagnosis	Hematuria	Hb 3.7 g/dL	Lateral right and anterior wall	8×7	Not performed	Spindle cells	CD34, CD68, SMA
Fuller TW	Urology	2015	9	Male	0	Hematuria, intermittent penile pain	-	Anterior wall and trigone	2	Anterior bladder mass near the bladder neck	Spindle cells, inflammatory infiltrate, superficial calcification	ALK1, CK-AE1/AE3, S100
Singh A	Int J Appl Basic Med Res	2015	30	Male	-	Hematuria		Posterior wall	6×4×4	-	Spindle cells, inflammatory infiltrate	ALK1, AE1/AE3, SMA
Wang X	J Pediatr Hematol Oncol	2015	14	Male	-	Urgency and dysuria	-		4×5×5	-	Spindle cells, inflammatory infiltrate	ALK1, SMA, vimentin
Machioka K	Case Rep Oncol	2014	69	Female	hysterectomy	Lower abdominal discomfort, residual urine sensation	-	Trigone and left posterior wall	-	Edematous inflammatory changes of the mucosa of the trigone and posterior bladder wall	Spindle cells, inflammatory infiltrate	Vimentin, CK-AE1/AE3, ALK
Kataoka TR	World J Surg Oncol	2014	31	Female	-	Painful urination	-	Right lateral wall	4.5	Submucosal tumor lying beneath the normal mucosa	Spindle cells, inflammatory infiltrate	ALK

Contd...

Supplementary Table 1: Contd...

Case report			Patient characteristics					Tumor characteristics				
First author	Journal	Year	Age	Sex	Medical history	Clinical presentation	Blood test results	Localization	Size (cm)	Cystoscopy	Pathology	IHC
Wu S	Exp Ther Med	2014	73	Male	Hypertension, mild diabetes, BPH	Dysuria, frequency, urgency, urodynia	-	Right and front wall	3×2	Not performed	Spindle cells, inflammatory infiltrate, muscle invasion	-
Yi XL	World J Surg Oncol	2013	17	Male	0	Frequency and urgency, weight loss, fixed mass in the suprapubic area	CRP - 8.9 mg/dL, WBC - 9.18×10^9/L, Hb - 11.9 g/dL	Posterior wall	5×6×7	Not performed	Spindle cells, inflammatory infiltrate	SMA, CD68
Marte A	Case Rep Urol	2013	8	Female	Wolf–Hirschhorn syndrome	Hematuria and abdominal pain	-	Dome and left lateral wall	5×4.5	-	Spindle cells	ALK, SMA, vimentin
Regmi SK	Urol Int	2014	38	Female	0	Hematuria, urine retention, mass protruding from the urethra	-	Trigone, base, and urethra	-	Highly vascular mass	Spindle cells, inflammatory infiltrate	-
Alderman M	Arch Pathol Lab Med	2014	38	Female	0	Dysuria and pelvic pain	-	-	-	-	Spindle cells, inflammatory infiltrate	ALK-1, SMA
Dobrosz Z	Diagn Pathol	2014	19	Female	0	Pelvic pain		Anterior wall of the bladder	3×4	-	Spindle cells, inflammatory infiltrate	AE1/AE3, SMA
Powell C	Urol Case Rep	2014	21	Female	0	Dysuria and urgency	-	Left lateral wall	2.5×2	-	Spindle cells	SMA, desmin
Wei L	Can Urol Assoc J	2013	23	Female	0	Hematuria	-	Dome	3	Broad-based tumor, bleeding, and necrosis on surface	Spindle cells, muscle invasion	ALK, SMA
Pradhan MR	Korean J Urol	2013	17	Female	0	Dysuria, frequency, urgency		Anterior wall and dome	8×5×5	Broad base, lobulated mass	Spindle cells, inflammatory infiltrate	ALK-1, SMA, vimentin
Chandra-mouleeswari K	J Clin Diagn Res	2012	17	Female	0	Lower abdominal pain, hematuria	-	Right posterolateral wall	7×4×3.2	-	Spindle cells, edematous stroma, inflammatory infiltrate	Mucin, vimentin, ALK1, CK 8/18/19, SMA, desmin
Zhang HH	Med Sci Monit	2012	62	Male	0	Dysuria	-	Prostatic urethra (prostate)	7×5	Intumescence of the prostate, and obstructing the lumen of the urethra	Spindle cells, inflammatory infiltrate	SMA, pan-CK, vimentin
Kim HW	Korean J Urol	2012	71	Male	0	Hematuria	Hb level of 9.1 g/dL	Left lateral wall	3	-	Spindle cells, inflammatory infiltrate	CK

Contd...

Supplementary Table 1: Contd...

Case report			Patient characteristics					Tumor characteristics				
First author	Journal	Year	Age	Sex	Medical history	Clinical presentation	Blood test results	Localization	Size (cm)	Cystoscopy	Pathology	IHC
Lecuona AT	Urology	2012	3	Male	0	Hematuria	-	-	8.2×5.5×5.6	-	Spindle cells, inflammatory infiltrate	ALK-1, desmin
Süer E	Urology	2012	10	Female	0	Dysuria and enuresis	-	Dome	4×4	-	Spindle cells, inflammatory infiltrate	ALK-1, desmin, SMA
Rao RN	Urol Ann	2012	27	Female	0	Hematuria		Anterior wall	8×8×5	-	Spindle cells, inflammatory infiltrate	Vimentin desmin, SMA
Kwon SY	Female Pelvic Med Reconstr Surg	2012	62	Female	Neuro fibromatosis	Hematuria	-	-	5.8×5.2×5.8	-	Spindle cells	SMA, desmin, AE1/AE3
Yagnik V	Urol Ann	2010	30	Male	0	Hematuria		Base and posterior wall		Large sessile smooth-walled	Spindle cells, inflammatory infiltrate	Desmin, SMA and ALK-1
Chatzidarellis E	Case Rep Med	2010	58	Male	Von Recklinghausen's	Hematuria	-	Dome	3	-	Spindle cells	SMA, vimentin
Pristauz G	Histopathology	2009	48	Female	Malignant mixed Mullerian tumor	Palpable mass	-	-	3.5	-	Spindle cells	Vimentin
Hoene KA	Int J Urol	2008	27	Female	Systemic lupus erythematosus	Weight loss and fatigue	-	Left lateral wall	6.5×4.5×3.8	-	Spindle cells, inflammatory infiltrate	ALK-1, SMA, AE1/AE3
Berger A	Urology	2007	4	Male	-	Hematuria	-	-	3.5×4.3×4	-	Spindle cells, inflammatory infiltrate	Desmin
Debiec-Rychter M	Genes Chromosomes Cancer	2003	46	Male			-	Posterior wall	4	-	Spindle cells, inflammatory infiltrate	ALK

Case report			Management				Postoperative course				
First author	Journal	Year	Assessment of extension	Systemic treatment	Surgical intervention	LND	Complications	Follow-up	Recurrence	Follow-up time (months)	Metastasis
Ding M	Asian J Surg	2024	AP CT scan	0	Robot-assisted partial cystectomy	0	0	-	-	-	-
Dergamoun H	Pan Afr Med J	2023	AP CT scan	0	TURBT	-	0	Cystoscopy	0	9	0
Guan L	Urol Case Rep	2023	AP CT scan	0	TURBT	-	0	-	-	-	-
Son SM	Oncol Lett	2023	AP CT scan	0	TURBT	-	0	-	0	18	0
Prijovic N	Medicina (Kaunas)	2023	AP CT scan	0	TURBT + open partial cystectomy	0	0	US + cystoscopy	0	3	0
Neuenschwander L	Urol Case Rep	2023	-	0	TURBT + robot-assisted partial cystectomy + TAH-BSO	1	0	Cystoscopy + MRI	0	12	0
Derimachkovski G	Urol Case Rep.	2023	AP CT scan	0	TURBT	0	0	-	-	-	-

Contd...

Supplementary Table 1: Contd...

Case report			Patient characteristics				Tumor characteristics				
First author	Journal	Year	Age Sex	Medical history	Clinical presentation	Blood test results	Localization	Size (cm)	Cystoscopy	Pathology	IHC
Fujiki T	Pediatr Blood Cancer	2023	MRI	Neoadjuvant anti-ALK therapy (alectinib)	TURBT	0	0	Cystoscopy	0	12	0
Sun Z	Front Oncol	2022	AP CT scan	0	Open partial cystectomy	0	0	CT scan + cystoscopy	0	6	0
Buksh O	Cureus	2022	AP CT scan + MRI	0	TURBT + open partial cystectomy	0	0	Cystogram + MRI	0	15	0
Marais B	Ther Adv Urol	2022	AP CT scan	0	TURBT	-	0	Cystoscopy	0	6	0
Balagobi B	Int J Surg Case Rep	2022	AP CT scan	0	Biopsy + open partial cystectomy	0	0	CT urogram + cystoscopy	0	6	0
Khondakar NR	Urology	2022	AP CT scan	0	TURBT	-	0	Cystoscopy + biopsy of resection site	0	3	0
Furukawa Y	Case Rep Oncol	2022	AP CT scan + MRI	0	TURBT	-	0	-	-	-	-
Ma W	BJR Case Rep	2022	MRI	0	TURBT	-	-	-	-	-	-
Batie SF	Urol Case Rep	2022	AP CT scan	0	Robot-assisted laparoscopic partial cystectomy	-	0	-	-	-	-
Nauman M	J Pak Med Assoc	2021	AP CT scan	0	Biopsy + open partial cystectomy	1	0	-	-	-	0
Bonvini P	Front Pediatr	2021	AP CT scan + MRI	Neoadjuvant anti-ALK therapy (entrectinib)	TURB-T	-	0	Cystoscopy	0	33	Lung, bone
Abou Zahr R	Case Rep Urol	2021	AP CT scan + MRI	0	Biopsy + laparoscopic partial cystectomy	0	0	Cystoscopy + CT scan	0	60	0
Fachini Cipriani RF	Urol Case Rep	2021	MRI	0	Laparoscopic partial cystectomy		-	-	-	-	-
Matsui Y	Urol Case Rep	2021	AP CT scan	0	TURBT	0	0	Cystoscopy	0	3	0
Chandora A	Urology	2021	-	0	Open partial cystectomy	0	0	Cystoscopy	0	4	0
Wang CS	Clin Case Rep	2021	AP CT scan	0	TURBT	0	0	Cystoscopy + CT scan	0	42	0
Higazy A	Urol Case Rep	2020	Ultrasound + AP CT scan	0	TURBT + ureteric stent	-	0	Cystoscopy + ultrasound	0	12	0
Laylo JCV	Urol Case Rep	2020	AP CT scan	0	TURBT + open partial cystectomy		0	-	0	18	0
Reinhart S	Urology	2020	AP CT scan	Neoadjuvant ALK inhibitor (lorlatinib)	Robot-assisted laparoscopic partial cystectomy	0	0	Cystoscopy + CT scan	0	12	0

Contd...

Supplementary Table 1: Contd...

Case report			Patient characteristics				Tumor characteristics				
First author	Journal	Year	Age Sex	Medical history	Clinical presentation	Blood test results	Localization	Size (cm)	Cystoscopy	Pathology	IHC
Ayati M	Urol Case Rep	2019	AP CT scan	0	Open partial cystectomy + radical cystectomy	1	0	-	1	6	0
Fadaak K	Case Rep Oncol	2019	Ultrasound + AP CT urogram	0	TURBT	-	0	-	-	-	-
Gass J	J Endourol Case Rep	2019	CT urogram	0	TURBT	-	0	Cystoscopy	0	3	0
Song D	Medicine (Baltimore)	2019	AP CT scan	0	TURBT	-	0	CT scan + Cystoscopy	0	3	0
Inamdar	Bladder (San Franc)	2019	AP CT scan	0	TURBT	-	-	Cystoscopy	1	9	0
Tsuboi I	IJU Case Rep	2019	MRI	Adjuvant chemotherapy and radiation	Open partial cystectomy		-	CT scan	1	9	0
Wang K	Medicine (Baltimore)	2018	AP CT scan	0	Biopsy + laparoscopic partial cystectomy	0	Urinary extravasation	CT scan	0	22	0
Nagumo Y	Int J Surg Case Rep	2018	AP CT scan + MRI	Neoadjuvant anti-ALK therapy (crizotinib)	TURBT + open partial cystectomy	0	0	-	0	12	0
Libby EK	Urol Case Rep	2018	AP CT scan	-	TURBT + open radical cystectomy	-	Ileus	-	0	<1	Peritoneum and colon
Kumar S	Urol Ann	2018	AP CT scan	-	Laparoscopic partial cystectomy		-	-	0	-	0
Kato M	Urol Case Rep	2017	MRI	0	TURBT + open partial cystectomy	0	0	Imaging + cystoscopy	0	12	0
Rotenberry C	Urol Case Rep	2017	AP CT scan + MRI	0	Robot-assisted partial cystectomy	0	0	-	-	-	-
Koukoura O	BMJ Case Rep	2017	MRI	0	Laparoscopic partial cystectomy	0	0	Cystoscopy	0	4	0
Nkwam N	J Surg Case Rep	2016	Ultrasound + AP CT scan	0	2 TURBT + open partial cystectomy	0	0	Cystoscopy + MRI	1	6	0
Kondo T	Case Rep Oncol	2016	MRI	0	TURBT	-	0	-	0	10	0
Etani T	Case Rep Oncol	2016	AP CT scan + MRI	0	TURBT + open partial cystectomy	0	0	-	0	36	0
Yaghi MD	Urol Ann	2016	CT urogram	0	TURBT	-	0	Cystoscopy	1	3	0
Tan Tanny SP	Urol Case Rep	2016	CT urogram + AP CT scan + CT chest	0	TURBT	-	0	CT urogram	0	6	0
Tsuma Y	J Pediatr Hematol Oncol	2016	PET scan	COX-2 inhibitor	Open partial cystectomy		0	-	0	28	0
Alam R	Case Rep Urol	2016	AP CT scan	0	TURBT		0	Cystoscopy	0	3	0
Takagi K	Urol Case Rep	2015	AP CT scan + MRI	0	TURBT + open radical cystectomy	0	0	-	0	10	0

Contd...

Supplementary Table 1: Contd...

Case report			Patient characteristics				Tumor characteristics				
First author	Journal	Year	Age Sex	Medical history	Clinical presentation	Blood test results	Localization	Size (cm)	Cystoscopy	Pathology	IHC
Ren X	Oncol Lett	2015	Ultrasound + AP CT scan	0	Open partial cystectomy	0	0	Cystoscopy	0	12	0
Fuller TW	Urology	2015	AP CT scan + ultrasound	Steroids and cetirizine	Biopsy + open partial cystectomy	0	0	Ultrasound	0	-	0
Singh A	Int J Appl Basic Med Res	2015	AP CT scan	0	Biopsy + open partial cystectomy	0	0	-	0	-	-
Wang X	J Pediatr Hematol Oncol	2015	AP CT scan	-	Open radical cystectomy	0	0	-	0	15	0
Machioka K	Case Rep Oncol	2014	Ultrasound + AP CT scan + MRI	0	Biopsy (transvaginal) + open radical cystectomy	1	0	-	0	48	0
Kataoka TR	World J Surg Oncol	2014	AP CT scan + MRI	0	TURBT	-	0	-	0	36	0
Wu S	Exp Ther Med	2014	AP CT scan + PET scan	0	Open partial cystectomy	0	-	-	0	-	0
Yi XL	World J Surg Oncol	2013	AP CT scan	0	Open partial cystectomy	0	0	Ultrasound + cystoscopy	0	6	0
Marte A	Case Rep Urol	2013	AP CT scan	0	Open partial cystectomy	0	0	-	0	13	0
Regmi SK	Urol Int	2014	Ultrasound + CT urogram	0	TURBT	-	0	-	0	6	0
Alderman M	Arch Pathol Lab Med	2014	AP CT scan	0	TURBT	-	0	-	-	-	-
Dobrosz Z	Diagn Pathol	2014	-	0	Open partial cystectomy	-	0	-	-	-	-
Powell C	Urol Case Rep	2014	AP CT scan	0	Open partial cystectomy	-	0	-	-	-	-
Wei L	Can Urol Assoc J	2013	Ultrasound + CT urogram	0	TURBT + open partial cystectomy	0	0	-	-	-	0
Pradhan MR	Korean J Urol	2013	AP CT scan	0	Laparoscopic partial cystectomy	0	0	Cystoscopy	0	22	0
Chandra-mouleeswari K	J Clin Diagn Res	2012	Ultrasound + AP CT scan	0	Biopsy + open partial cystectomy	0	0	-	0	12	0
Zhang HH	Med Sci Monit	2012	AP CT scan	0	3 TURP + Laparoscopic radical cystectomy	1	0	-	1	24	0
Kim HW	Korean J Urol	2012	AP CT scan	0	TURBT	0	0	Cystoscopy + CT scan	1	12	Pelvic lymph nodes, bone, lung, peritoneum, GI tract
Lecuona AT	Urology	2012	MRI	0	TURBT + open partial cystectomy	0	0	MRI scan + cystoscopy	0	7	0

Contd...

Supplementary Table 1: Contd...

Case report			Patient characteristics				Tumor characteristics				
First author	Journal	Year	Age	Sex	Medical history	Clinical presentation	Blood test results	Localization	Size (cm)	Cystoscopy	Pathology	IHC
Süer E	Urology	2012	MRI		0	TURBT + open partial cystectomy	0	0	Cystoscopy	0	12	0
Rao RN	Urol Ann	2012	AP CT scan		0	Open partial cystectomy		0	-	0	15	0
Kwon SY	Female Pelvic Med Reconstr Surg	2012	AP CT scan + MRI		0	TURBT + open partial cystectomy		0	CT scan + MRI	0	24	0
Yagnik V	Urol Ann	2010	AP CT scan		0	TURBT	0	0	-	-	-	-
Chatzidarellis E	Case Rep Med	2010	AP CT scan		0	TURBT + open radical cystectomy	0	0	-	-	-	-
Pristauz G	Histopathology	2009	AP CT scan		0	Open radical cystectomy	0	0	-	0	10	0
Hoene KA	Int J Urol	2008	AP CT scan		0	Open radical cystectomy	0	0	-	0	6	0
Berger A	Urology	2007	AP CT scan		0	Open partial cystectomy	0	0	Cystoscopy	0	18	0
Debiec-Rychter M	Genes Chromosomes Cancer	2003	-		0	Cystectomy (no data provided on the type of cystectomy)	0	0	-	-	-	-

Two different clones of anti-CK monoclonal antibodies (AE1 and AE3). IHC=Immunohistochemistry, ALK=Anaplastic lymphoma kinase, SMA=Smooth muscle actin, CK=Cytokeratin, WBC=White blood cells count, Hb=Hemoglobin, CRP=C-reactive protein, BPH=Benign prostatic hyperplasia, LND=Lymph node dissection, TURBT=Transurethral resection of the bladder tumor, AP CT=Abdominal pelvic computed tomography, MRI=Magnetic resonance imaging, US=Ultrasound, PET scan=Positron emission tomography scan, GI=Gastrointestinal, COX-2=Clooxygenase-2, TAH-BSO=Total abdominal hysterectomy, and bilateral salpingo-oophorectomy