# Inflammatory Myofibroblastic Tumors of the Urinary Bladder: A Systematic Review

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We systemically reviewed the literature on inflammatory myofibroblastic tumors (IMTs) of the urinary bladder and compared between anaplastic lymphoma kinase (ALK)-positive and ALK-negative IMTs. An extensive search of the literature was performed in Medline and Web of Science using the following terms: "inflammatory myofibrolastic tumor," "inflammatory pseudotumor," and "bladder." A manual search was also performed using the web-based search engine Google Scholar. Reference lists of the retrieved articles were reviewed for other relevant studies. Patients' and disease characteristics of each individual case were reviewed. Further analyses were performed to compare between ALK-positive and ALK-negative IMTs. Forty-one studies were identified, and 182 patients were included for review and subsequent analyses. Of the IMTs, 65% were ALK-positive. Local tumor recurrence rate was 4%, and no cases of distant metastases have been reported. Compared with ALK-negative IMTs, ALK-positive IMTs had a female predilection with a sex ratio (male:female) of 1:1.67 ($P = .048$). ALK-positive IMTs also appeared to occur in younger patients ($P = .072$). No significant differences were noted in terms of their clinical presentations and histologic features. On immunohistochemical staining, ALK-positive IMTs had more positive results for desmin ($P = .042$) and p53 ($P = .05$), and more negative results for clusterin ($P = .003$). In summary, ALK-positive IMTs of the urinary bladder had a female predilection, appeared to occur more frequently in younger patients, and had different immunohistochemical staining patterns when compared with ALK-negative IMTs. Regardless of its ALK status, IMT of the urinary bladder has a good prognosis after surgical resection. UROLOGY 84: 503–508, 2014. © 2014 Elsevier Inc.

The first report possibly representing inflammatory myofibroblastic tumor (IMT) was described by Brunn[1] on 2 cases of "myoma of the lung" in 1939. Such lesion in the genitourinary tract was then described by Roth[2] in 1980. The term "inflammatory pseudotumor" was often used to describe a wide range of reactive or neoplastic lesions. Many different terminologies have been proposed to further classify the different members within this broad category of inflammatory pseudotumors.[3-10] However, it is often difficult to differentiate between them because of their overlapping histologic features. Until the recent 15 years, the results of anaplastic lymphoma kinase (ALK) expression shown in IMTs[11-15] have gained it a distinct entity with characteristic immunohistochemical and molecular features. However, the disease nature of IMT and whether the ALK status translates into any clinical significance remained largely unknown. We systemically review the literature on this rare pathologic entity and look into the differences between ALK-positive and ALK-negative IMTs.

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## METHODS

A systematic search was conducted from January 1900 to June 2013 in Medline and Web of Science using a combination of the following terms: "inflammatory myofibrolastic tumor" or "inflammatory pseudotumor" and "bladder," A manual search using the web-based search engine Google Scholar was also performed. Reference lists of the retrieved articles were reviewed for other relevant studies. The retrieved articles were then screened for inclusion eligibility.

The following inclusion criteria were included:

- Human studies in any form of study design.
- Any original full research article published in English.
- Full-length text available for further review.
- Studies on any pathologies that were related to IMTs.
- Urinary bladder as the primary site of involvement. If the primary site of tumor was not certain on screening, these articles would be included for full-text review.

All articles included were then subjected to full-text review with the following exclusion criteria:

- Studies without additional cases of IMT.
- Primary site of tumor other than the urinary bladder.
- Inadequate pathologic or immunohistochemical information to ascertain the diagnosis of IMT.
- Inflammatory lesion which developed within 3 months of urinary tract instrumentation, that is, postoperative spindle cell nodule.

Patients' characteristics including age, presenting symptoms, initial investigation results, tumor characteristics, treatment information, follow-up duration, and the presence of any tumor

recurrence or distant metastases were reviewed. Pathologic results of all the reported cases were reviewed and classified into the 3 patterns as described by Coffin et al[16]: the myxoid or vascular pattern, the compact spindle cell pattern, and the hypocellular fibrous pattern. Other histologic features including the presence of necrosis, atypia, pleomorphism, abnormal mitosis, mitotic figure per 10 high-power fields, and the presence of significant numbers of neutrophils, eosinophils, plasma cells, and lymphocytes were reviewed. Immunohistochemical staining results of each individual case were also recorded.

Continuous variables were either presented as mean values with standard deviations or median values. Categorical variables were presented as frequencies and percentages calculated from the results retrieved from the selected articles. For the comparison between ALK-positive and ALK-negative IMTs, independent samples *t* test was used for continuous variables, and the Fisher exact test was used for categorical variables. *P* value of $<.05$ is considered to be statistically significant. All statistical analyses were performed with SPSS version 20.0 (SPSS Inc, Chicago, IL).

## RESULTS

### Systematic Review of the Literature

A total of 344 studies were identified during the systematic literature search (including 332 studies through database search and 12 studies through manual search from other sources). After removing duplicates, 327 records remained. Of them, 240 were excluded after screening, resulting in 87 full-text articles for further assessment of eligibility. After reviewing the full text of each article, 46 of them were further excluded. After all, 41 studies were included for review and statistical analyses (Fig. 1). In the 41 studies being included, 13 were case series (31.7%) and 28 were case reports (68.3%).

### Clinical Features

A total of 182 patients were included with a mean age of 38.9 ± 16.6 years. Of the total, 51.7% were female patients. The commonest presentation was hematuria (71.9%), followed by dysuria (19.8%), urinary frequency (18.8%), lower abdominal pain (13.5%), and loin pain (2.1%; Table 1). Of the total, 3.1% patients had hemodynamic instability on presentation. None of them developed hydronephrosis. Of the total, 6.3% patients were noted to have anemia, and 1.1% developed impaired renal function. Presence of abnormal urine cytology was never reported.

### Tumor Characteristics

The mean tumor size in maximal dimension was 4.48 ± 2.12 cm. The commonest tumor location in the urinary bladder was the posterior wall (33.3%), followed by the dome (22.2%), right lateral wall (19.4%), left lateral wall (13.9%), anterior wall (11.1%), and the trigone (0%; Table 1).

### Treatment

Most patients (60.8%) were treated with transurethral resection of bladder tumor (TURBT), followed by partial cystectomy (29.2%), radical cystectomy (9.2%), and cystoscopic biopsy (0.8%). Among those patients who had TURBT performed, 24.7% of them had further treatment including partial cystectomy (17.8%), second TURBT (5.5%), and radical cystectomy (1.4%; Fig. 2).

### Outcome

The mean follow-up was 30.0 months ± 28.2 months. Five of 120 patients (4%) were noted to have local tumor recurrence on follow-up. One of them was found to have local recurrence at 6 months, which was treated with TURBT and remained recurrence free afterward.[17] One patient was found to have local recurrence at 1 month; TURBT was performed but unfortunately the tumor recurred again at 4 months and the patient finally underwent partial cystectomy as the definitive treatment and remained recurrence free afterward.[17] The form of treatment was not well documented for the other 3 patients. For that particular patient who underwent cystoscopic biopsy as the definitive treatment, no tumor recurrence was reported.[17] There was no reported case of distant metastases from IMTs of the urinary bladder.

### Histologic Features

Of the total number of patients, 83.8% were noted to have a myxoid or vascular pattern, 55.9% had a compact spindle cell pattern, and 5.9% had a fibrous hypocellular pattern. Up to 41.2% of these patients had mixed histologic patterns. Significant numbers of neutrophils, eosinophils, plasma cells, and lymphocytes were reported in 34.5%, 58.6%, 82.8%, and 69% of the cases. Presence of necrosis, atypia, and pleomorphism was noted in 40.3%, 39.1%, and 63.2% of the cases. The median mitotic figure was 2 per 10 high-power fields. Invasion to the muscularis propria was noted in 60% of the cases. The histologic features were summarized in Table 1.

### Immunohistochemical Features

The immunohistochemical staining results were positive for ALK, smooth muscle actin, cytokeratin AE1/AE3 (CK AE1/AE3), p53, and vimentin in 65%, 71.9%, 75.3%, 77.8%, and 98.3% of the cases. The vast majority of the cases were negative for CD 21, CD 34, CD 35, and myogenin (97.7%-100%). There was a wide range of immunohistochemical staining results among the cases and the results were summarized in Table 1.

### Comparison Between ALK-positive and ALK-negative IMTs of the Urinary Bladder

The male to female ratio was 1.5:1 in ALK-negative IMTs and 1:1.67 in ALK-positive IMTs ($P = .048$). ALK-positive IMTs appeared to occur in relatively younger patients with a mean age of 38.8 ± 14.0 years but it was statistically insignificant ($P = .072$). The commonest presentation was hematuria in both ALK-positive and ALK-negative IMTs. No significant differences were noted in terms of their clinical presentations. The mean tumor sizes in maximal dimension were similar