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ORIGINAL ARTICLE

Inflammatory myofibroblastic tumor in pediatric patients: a Bosnian cohort

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ABSTRACT

Aim Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal neoplasm of intermediate biological potential, characterized by spindle cell proliferation and significant inflammatory component. This study aimed to determine the clinicopathologic characteristics, clinical outcomes of IMT patients in the low-volume pediatric surgery service in Bosnia and Herzegovina.

Methods The study included data from three pediatric patients with IMT (two females, one male) diagnosed and operated from 2010 to 2024 at the Clinic of Pediatric Surgery, Clinical Centre, University of Sarajevo. Demographic, clinical, histopathological, immunohistochemical, and outcome parameters were analysed.

Results All tumors were located in the abdominal or abdominopelvic region; a median age of 4 years. Clinical manifestations included non-specific gastrointestinal symptoms (N=2) and systemic signs such as fever (N=2), weight loss and weakness (N=1). Complete surgical resection was conducted in all patients, and all experienced complete remission without recurrence. Histopathological analysis revealed consistent presence of spindle cells within a prominent inflammatory milieu, rich in plasma cells and lymphocytes. Immunohistochemically, all tumours were positive for vimentin, anaplastic lymphoma kinase (ALK), and smooth muscle actine (SMA), while ALK-FISH (fluorescence in situ hybridization) analysis (performed in one case) was negative.

Conclusion The constant of heterogeneous morphology, and significance of IMTs immunophenotype, particularly with the inflammatory component more pronounced, was found. ALK gene alterations were commonly associated with IMT, as well as with other types of pediatric neoplasms, however, favourable outcomes in our patients raise a question regarding further need to clarify the prognostic significance of molecular findings and their potential therapeutic implications.

Keywords: anaplastic lymphoma kinase, child, myofibroblasts, soft tissue neoplasms

INTRODUCTION

Inflammatory myofibroblastic tumor (IMT) is defined as a rare soft tissue neoplasm primarily composed of myofibroblasts and fibroblasts, infiltrated by inflammatory cells such as lymphocytes and eosinophils (1). Due to its described origin, the localization of this neoplasm varies significantly. It can occur in any region rich in soft tissue, but it is most commonly found in the lungs and abdominal cavity (2,3). Studies have shown that IMT is most frequently located in the liver and biliary tract (31.8% of cases), followed by the head and neck (20.6%), lungs (18.2%), abdomen (15.5%), and the urogenital tract (7.4%) (4).

Although initially considered a benign neoplasm, IMT is now classified as a subtype of sarcoma due to cases in which the tumor exhibited highly aggressive behaviour and poor prognosis (1,3). It is characterized by intermediate biological potential, as the likelihood of recurrence and metastatic potential is low (5). Specific data on the incidence in children remain unclear (6).

The aim of this study was to investigate the clinicopathologic, immunohistochemistry and molecular cytogenetics characteristics, and outcome of IMT patients in the low-volume pediatric surgery service in Bosnia and Herzegovina (B&H).

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PATIENTS AND METHODS

Patients and study design

This clinical, retrospective study was conducted at the Clinic of Pediatric Surgery of the Clinical Centre, University of Sarajevo, covering the period from 1 January 2010 to 31 December 2024. Three patients (two girls and one boy), who were diagnosed with inflammatory miofibroblastic tumor, were included.

The Ethics Committee of the Clinical Centre, University of Sarajevo, approved this study (No: 51-45-1-9463/25).

Methods

The data were collected by reviewing the available medical documentation through the electronic database of the Clinical Centre and the archives of the Clinic of Pediatric Surgery of the Clinical Centre.

The following features were reviewed: gender, age at the time of diagnosis, history, clinical presentation, tumor localization and characteristics, diagnostic workup, histopathological findings, molecular cytogenetics treatment and surgical intervention performed, disease outcome, complications, and recurrence.

Clinical diagnosis. The diagnostic workup for all patients included a detailed clinical history, physical examination, and comprehensive laboratory analyses: complete blood count, C-reactive protein, coagulation profile, and tumor markers including Alpha-fetoprotein (AFP), Cancer antigen 125 (Ca-125), and Carbohydrate antigen 19-9 (Ca 19-9). Imaging diagnostic techniques were used as well, including abdominal and pelvic ultrasonography (US) as the initial imaging modality, followed by computed tomography (CT) and/or magnetic resonance imaging (MRI) to characterize tumor's site, relation to adjacent structures and other characteristics.

Macroscopic descriptions. Surgical specimens (tumor masses with involved bowel segments, appendix, mesocolic lymph nodes, depending on the case) were fixed in 10% neutral buffered formalin. Upon examination, the size, weight, external appearance, cut surface characteristics (colour, consistency, presence of necrosis, cystic changes, or haemorrhage) and surgical margins.

Histopathological methods. Tumor tissue samples were fixed in 10% neutral buffered formalin, embedded in paraffin, and sectioned at 4-5μm. These sections were stained with Hematoxylin and Eosin (H&E) for light microscopic evaluation.

Immunohistochemistry and molecular cytogenetics. Immunohistochemical (IHC) analysis was performed on prepared histopathological samples, using standard technique. The antibody panel that was applied included: anti smooth muscle antibody (ASMA), smooth muscle actine (SMA), anaplastic lymphoma kinase (ALK), leucocyte common antigen (LCA); actine, muscle specific monoclonal antibody (HHF35), cytokeratin (CK), CD34, CD117, S100, vimentin and/or desmin.

Statistical analysis

The data were processed, and the results presented in numerical and tabular form. Descriptive statistical methods were used.

RESULTS

In total of three patients IMTs were identified. The median age was 4 years. Female to male ratio was 2:1. All of the patients (N=3) had tumor localized in the abdomen; in two patients the tumor was extensive, it was simultaneously presented in the abdomen and pelvis (Figure1). No recurrences were evident. The presence of elevated body temperature (N=2), occasional abdominal pain (N =1), nausea with vomiting (N =1), poor appetite and weight loss (N =1), diarrhoea (N =1), fatigue (N =1), and visible swelling in the abdomen (N =1) were noted. All of the patients showed complete remission (Table 1).

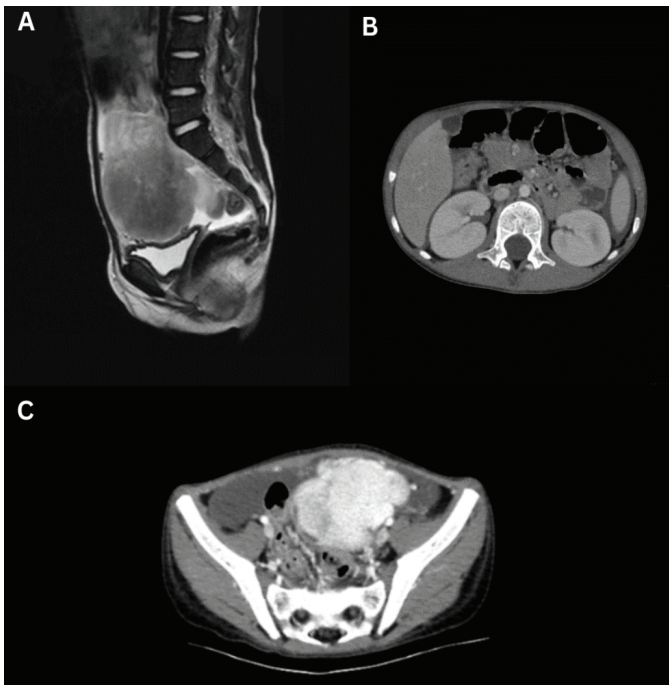

Figure 1. A) Magnetic resonance imaging (MRI) of inflmmatory myofibroblastic tumor (IMT) in patient ID2: a well-defined soft tissue mass (103x78.5x75 mm) with a pseudorenal shape and internal cystic components (12 mm). The tumor was compressing the bladder, uterus, ovaries, and iliac vessels without direct invasion of the sacrum or spinal canal. B) CT imaging of IMT in Patient ID2: a heterogeneous tumor mass (102x75x78 mm) in the midline of the pelvis, cranial to the bladder, compressing surrounding structures including iliac vessels and intestinal loops; C) CT imaging of IMT in patient ID3: an expansive tumorous lesion, parasagittal and on the left in location, that mildly protrudes into the anterior abdominal wall. It appears lobular and it is clearly demarcated from the surrounding soft tissue and vascular structures. The lesion shows intense enhancement, and laterally on the right, shows zones of lower opacification.

Macroscopic examination of the tumor and lymph nodes showed unencapsulated (N=2), multinodular (N=2) tumor, with the necrotic surface, covered with purulent debris (N=1), and with internal cystic components (N=1). Resected lymph nodes showed no metastases, but displayed reactive changes (N=2). The tumor sizes varied from 4 to 10 cm, with the average size of 7 cm (Figure 2). There was no evidence of infiltration of the surrounding tissues.

A description of histologic pattern of sampled tissues was found in the clinical histories of all patients (N=3). Spindle-shaped cells were found in all three patients, within fascicular arrangement (N=2), with prominent vascular network (N=3). Each pattern had strong inflammatory cell infiltration, with plasma cells (N=3), lymphocytes (N=2), eosinophils (N=2), neutrophils (N=1), hystiocytes (N=1) and mast cells (N =1). In one patient, a cellular mesenchymal tumor was defined. In other patient, smaller nodules exhibiting blood vessels resembling granulation tissue were observed, while remaining parts of the sample showed dilated vessels, macroscopically

mimicking cystic spaces. There were no signs of significant nuclear pleomorphism or atypical mitotic figures (Table 2).

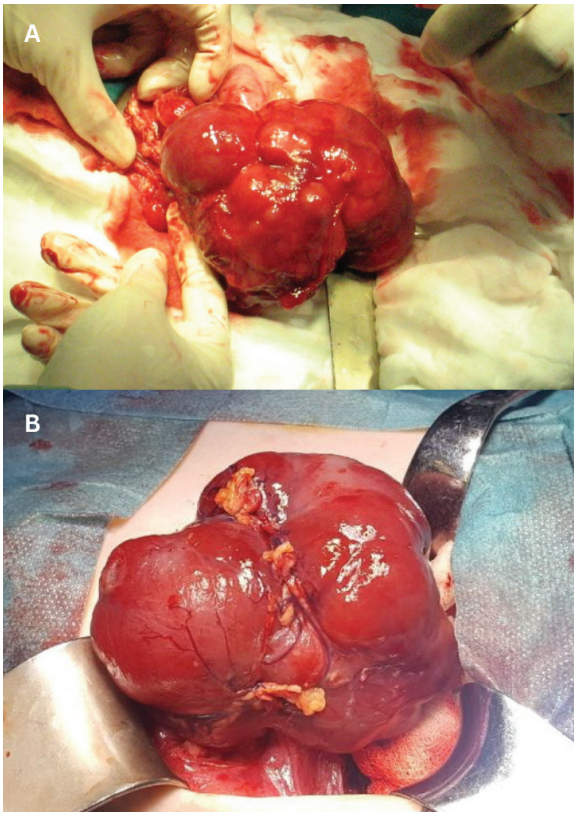

Figure 2. A) Intraoperative view of inflammatory myofibroblastic tumor (IMT) in patient ID3; B) intraoperative view of IMT in patient ID2 (E.M K.D. Images courtesy of the Clinic of Paediatric Surgery, Clinical Centre, University of Sarajevo (KCUS) (2020: A; 2013: B)

Immunohistochemical analysis demonstrated positivity for the intermediate filament protein type III, vimentin, as well as for ALK, and SMA, in all three patients. Protein S100 was variably negative, except in one patient, where it was focally positive. Desmin was positive, negative and variably negative. Additionally, analysed immunohistochemistry markers were mostly negative, with one exception showing positive results for CK and one showing variably negative results for HHF35 (Table 2).
ALK-FISH analysis was conducted in one patient and it was negative. Remaining two patients had no medical documentation available, regarding molecular cytogenetic studies.

DISCUSSION

Although IMT is a rare entity, several studies have described its clinical features and management; however, its low incidence usually makes it difficult for pediatric surgeons to accumulate experience in this disease (1-2). This is especially true for low-volume pediatric surgery centres in developing countries with low birth rates, such as B&H. The clinical information on IMT from B&H is very limited, and the present analysis is the first study with a long follow-up.
Histologic architecture and cellular features are highly variable, and while IMT is mostly locally aggressive with low metastatic potential, rare cases may demonstrate highly invasive behaviour and metastases. Tumor can appear in a wide range of localizations; any site rich in soft tissue. (1-5). Collectively, these factors accentuate the need for continued research to better understand IMT.
The heterogenic localization is one of the characteristics of this tumor, with mostly abdominopelvic site of primary tumor, but with a significant number in lungs and retroperitoneum, as well as other sited of soft tissues (3,4,7). Our patients showed 100% homogeneity regarding the site of development of IMT, orig-

Table 1. Clinical presentation, tumor site, and outcome of three patients with inflammatory myofibroblastic tumor

Patient ID	Age (years)	Sex	Location	Clinical presentation	Follow up (months)	Outcome
1	9	F	Abdomen	Occasional abdominal pain started 14 days ago, nausea, occasional vomiting, occasional diarrhoea with calm periods lasting 1-2 days, poor appetite, weight loss of 4 kg	110	CR
2	4	F	Abdomen, pelvis	Fatigue, elevated body temperature, visible swelling from the umbilicus to the pubis	6	CR
3	3	M	Abdomen, pelvis	Elevated body temperature	14	CR

F, female; M, male; CR, complete remission

Table 2. Morphologic, immunophenotypic, and molecular findings of three patients with inflammatory myofibroblastic tumor

ID	Tumor size (cm)	Immunohistochemical marker expression											ALK - FISH
		Vimentin	ASMA	SMA	S100	ALK	Desmin	LCA	CD34	CD117	HHF 35	CK	
1*	4	3+	N/A	2+	+	+	-	-	-	N/A	N/A	-	N/A
2†	10	+	N/A	+	-	+	-/+	-	-	-	-/+	-	N/A
3‡	7	3+	3+	2+	-	2+	+	N/A	-	-	N/A	+	Negative

N/A, not available/performed; Vimentin; fibroblast intermediate filament; ASMA, anti-smooth muscle antibody; SMA, smooth muscle actine; S100, calcium binding protein; ALK, anaplastic lymphoma kinase; Desmin, muscle-specific member of the intermediate filament, LCA, leucocyte common antigen; CD34, transmembrane glycoprotein, cell surface marker; CD117, cell-surface receptor; HHF-35, actine monoclonal antibody; CK, cytokeratin; ALK FISH – ALK gene fluorescence in situ hybridization test
Histologic pattern: *Spindle-shaped cells arranged in interwoven fascicles, intermixed with inflammatory infiltrates predominantly composed of lymphocytes and plasma cells; †Spindle-shaped myofibroblasts and fibroblasts with vesicular nuclei, arranged in fascicular and whorled patterns, with the stroma infiltrated by a prominent inflammatory component composed of plasma cells, lymphocytes, histiocytes, neutrophils, eosinophils, and occasional mast cells; marked vascular proliferation; ‡ Spindle cells, stroma rich in blood vessels and inflammatory infiltrates, consisting of plasma cells and eosinophils.

inating in the abdominal cavity. In our patients, clinical presentation included abdominal or gastrointestinal complaints, with unspecific symptoms such as elevated body temperature. A combination of symptoms such as fever, weight loss and overall weakness was found in one patient. Usual prevalence of 15-30% was noticed in other studies (8). More dominant gastrointestinal symptoms were found in our oldest patient (9-year old girl), in comparison with the younger ones (3 and 4 years of age).

Mean size of 6 cm found in other studies is similar to ours of 7 cm (7). The morphological abnormalities, such as necrosis, haemorrhage or calcification, are not often spotted within these tumors (8). We confirmed that finding, with traces of necrosis found in only one case. Even though it was found that abdominopelvic IMTs showed greater prevalence of recurrence in the comparison to other primary location sites, our patients went into complete remission after surgical treatment (7).

Three histological patterns with various combinations, were defined within the IMTs: a myxoid/vascular pattern, a compact spindle cell pattern, and a hypocellular fibrous pattern (8). There were no dominant morphologic subtypes of the tumor defined in our study. Plasma cells and lymphocytes are the most often inflammatory cells in IMTs (7). That is consistent with our findings. Myxoid hypocellular pattern, without dominant inflammatory component, can be found in infants, due to their immature inflammatory cell development (9). However, all our patients were older than one year. While no histopathological pattern was dominant, the tumor samples in these older children consistently demonstrated a significant inflammatory component. Observation might suggest that a more mature system can have influence on the tumor microenvironment (10).

Considering their myofibroblastic component, IMTs are positive for SMA in 85% of cases, and desmin in 65% (8). All of our patients showed positivity for these markers, underlining its connection with myofibroblasts.

ALK, anaplastic lymphoma kinase gene rearrangements were consistently found in IMT patients (7,8). ALK is a gene commonly associated with malignancies, such as anaplastic large cell lymphoma, rhabdomyosarcoma, leiomyosarcoma, Ewing sarcoma, and other “small blue cell” tumors (11-13). In IMTs, around 50% of tumors are associated with different kinds of ALK gene anomalies, including ALK rearrangements and discoveries of ALK fusion partners (14,15). Additionally, ALK expression is more common in younger patients (13).

In our three-patient series, no ALK gene abnormalities were detected (in the single case tested by FISH). Today, there is a rising of new hypotheses regarding whether ALK gene mutation can be connected to overall behaviour of tumor and prognosis of the disease, as in other kinds of pediatric tumors, such as neuroblastoma (16). Some studies raise questions of the correlation between potential *atypical* forms of IMTs and ALK rearrangements (15). However, it is yet very indefinite in what extent ALK can be connected to IMTs as well as how ALK rearrangements would be formed (14,17).

Our study is limited by its retrospective design and a small number of recruited patients. The study was conducted in a single institution, limiting its generalizability.

IMT is a very rare entity among children. We confirm the rarity and relatively good clinical outcomes of the patients with IMT in the low-volume pediatric surgery service from the developing country. Importance of surgery in its treatment is undeniable. Future efforts must be made on clarifying the molecular driver and immune interaction within IMT to potentially guide development of risk stratification strategies and less invasive therapies.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

CrediT Author Contributions

Conceptualization: Asmir Jonuzi, Ilhana Tinjak and Zlatan Zvizdic. Methodology: Asmir Jonuzi, Ilhana Tinjak, Benjamin Kulovac, Nusret Popović, Emir Milisic, Predrag Ilić, Zlatan Zvizdic. Formal analysis and investigation: Asmir Jonuzi, Ilhana Tinjak, Melika Bukvić, Zlatan Zvizdic. Writing - original draft preparation: Asmir Jonuzi, Ilhana Tinjak, Benjamin Kulovac, Nusret Popović, Emir Milisic Predrag Ilić and Zlatan Zvizdic. Writing - review and editing: Asmir Jonuzi, Ilhana Tinjak and Zlatan Zvizdic. Supervision: Benjamin Kulovac and Zlatan Zvizdic.

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