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CLINICAL CASE

Inflammatory myofibroblastic tumor: variable presentation of the same pathology

Tumor miofibroblástico inflamatorio: presentación variable de una misma patología

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Abstract

The inflammatory myofibroblastic tumor is an infrequent benign neoplasm with unpredictable clinical behavior. Objectives: to describe three clinical cases at the San Borja Arriarán Clinical Hospital between March 2014 and January 2018 and to carry out an updated review of the literature. **Case 1:** 14-year-old male adolescent, hospitalized due to abdominal pain, diagnosed with jejunojejunal intussusception secondary to an intestinal wall tumor. The histology was compatible with an inflammatory myofibroblastic tumor. **Case 2:** 12-year-old female adolescent, hospitalized due to pneumonia and low-back pain under study associated with weight loss. A retroperitoneal mass was diagnosed involving the right psoas muscle, paravertebral muscles, vertebrae, right kidney, and ipsilateral diaphragm. A puncture biopsy was performed and the result was compatible with an inflammatory myofibroblastic tumor. **Case 3:** 11-year-old female pre-adolescent, hospitalized to study recurrent urinary tract infection. A bladder tumor was identified, and the biopsy showed compatibility with inflammatory myofibroblastic tumor. **Conclusion:** Due to the variable behavior of the inflammatory myofibroblastic tumor, its management will depend on the location, expression of the anaplastic lymphoma kinase (ALK), tumor behavior, and the resection possibility.

Keywords:
Inflammatory myofibroblastic tumor; tumor markers; surgical treatment

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Introduction

An inflammatory myofibroblastic tumor (IMT) is a benign tumor of intermediate biological behavior[2,3]. It is also known as inflammatory pseudotumor[1], plasma cell granuloma, histiocytoma, xanthoma, fibroxanthoma, or inflammatory fibrosarcoma[1,3,5,8].

It was first described in 1937 in a case with pulmonary disease[8,12] and has been reported in different anatomical areas since then.

It occurs more frequently in infancy and in young adults[2,3] and despite still having an uncertain etiology, it is associated with different factors such as trauma, infections, genetics, and autoimmune pathologies[1,3]. The definitive diagnosis is histological[3,4,5] and the treatment of choice is the surgical resection[1,3,5].

Due to the infrequent nature of this pathology and the presence of three patients diagnosed with this tumor at the *Hospital Clínico San Borja Arriarán* (HCSBA), our main objective was to describe three IMT cases, diagnosed between March 2014 and January 2018. In addition, we will review and update the literature about this pathology.

Clinical Cases

Case 1

A 14-year-old male adolescent with no history of disease.

He consulted the Children's Emergency Service due to a 7-days history of crampy abdominal pain and recurrent vomiting in the last 24 hours. The patient was evaluated on an outpatient basis and treated his symptoms without response, therefore, he consulted the HCSBA.

At admission, he was in poor general condition, dehydrated, and in a lot of pain. Resuscitation was initiated with saline solution, analgesics, and antiemetics. His tests showed: leukocytes: 15,240 x mm^3; CRP: 1 mg/dl; liver profile in normal range; amylase: 197 mg/dl; and creatinine: 1.52 mg/dl.

In abdominal x-ray (Figure 1A) was observed scarce distal gas related to a stack of coins sign close to the mesogastrium and left flank (small intestine).

The study was completed with abdominal ultrasound where a suggestive image of jejunal intussusception secondary to polyp with proximal intestinal obstruction was observed.

The patient underwent an exploratory laparotomy where jejunal intussusception was observed (Figure 1B), associated with a 5 x 3.5 cm mass in the intestinal wall, projected towards the lumen. Subsequently, *en bloc* resection was performed (Figure 1C and D).

The histology revealed ovoid to spindle-shaped tumor cells, elongated nuclei with moderate pleomorphism and some histiocytoid cells of ganglion-like appearance with some mitosis, without intermixed atypical figures, with prominent lymphoplasmacytic inflammatory infiltration, and some eosinophils. Intestinal wall presented tumor-free margins. Regarding immunohistochemistry tests, vimentin and alpha-SMA were positive; Ki-67 3% positive; CD68-positive in lymphoplasmacytic component, and anaplastic lymphoma kinase (ALK) weak to moderate positive in tumor cells. (Figure 2)

Lesion findings were consistent with IMT.

The patient continues in monitoring with oncology after eight months of surgery, without recurrence episodes.

Case 2

12-year-old female adolescent, with hemoptysis history associated with weight loss and a 4-months low back pain history. She was hospitalized with a diagnosis of pneumonia, received antibiotic therapy and had a positive evolution. Due to the long-standing low back pain associated with weight loss, thoracic, abdominal and pelvic tomography was performed which revealed retroperitoneal tumor involving right psoas, paravertebral muscles, bone infiltration into the spine, right diaphragm, and ipsilateral kidney.

After CT-guided needle biopsy, the sample histology showed little to moderate cellularity, with spindle-shaped cells of wavy and ovoid nuclei, and moderate infiltrate made up of lymphocytes, plasma cells, and histiocytes.

Regarding immunohistochemistry tests, vimentin, alpha-SMA, desmin, and myogenin were positive, and ALK was negative. The findings were consistent with IMT. (Figure 3)

Given the location and infiltrative component, the tumor was classified as unresectable, therefore, anti-inflammatory therapy was initiated with Celecoxib 200 mg every 12 hours and Prednisone 20 mg every 12 hours. Although a partial reduction in tumor size was achieved, the patient continued with pain in the dorsal area, thus it was decided to add to the therapy Infliximab 300 mg IV every 24 hours in 0-2-6 weeks schedule. The patient presented an anaphylactic reaction upon the second dose administration, therefore the use of methylprednisolone was required in the next cycle. Due to the adverse effects recurrence, Infliximab was replaced by another monoclonal antibody drug, Adalimumab, in doses of 40 mg SC every 15 days, associated with Celecoxib 200 mg every 12 hours and Prednisone 20 mg every 12 hours, achieving absence of symptoms and a significant reduction in the tumor lesion size.

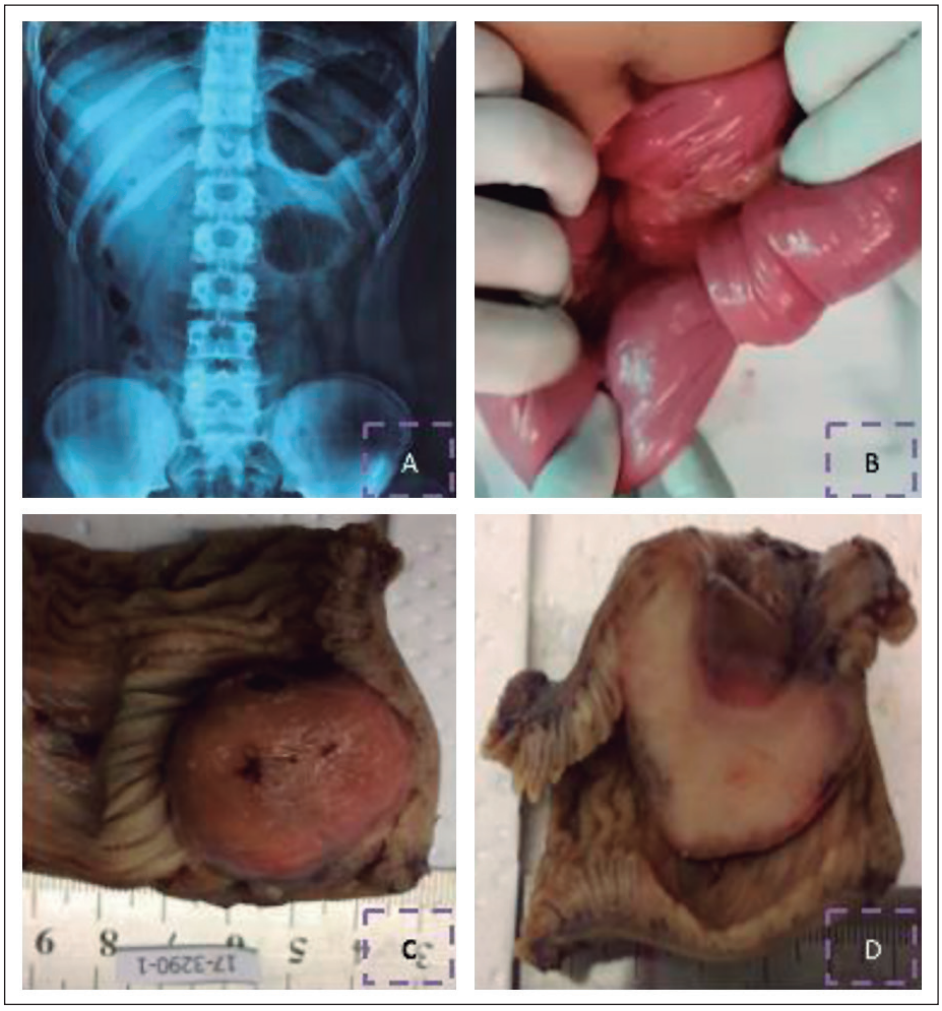

Figure 1. A) At the level of mesogastrium and left flank small bowel loops can be seen with image in a stack of coins and little gas towards distal. **B)** jejunojejunal invagination secondary to intestinal wall tumor. **C)** Tumor seen on the endoluminal side. **D)** Sagittal section of the tumor that compromises the entire wall of the jejunum. Homogeneous appearance and gummy consistency on palpation.

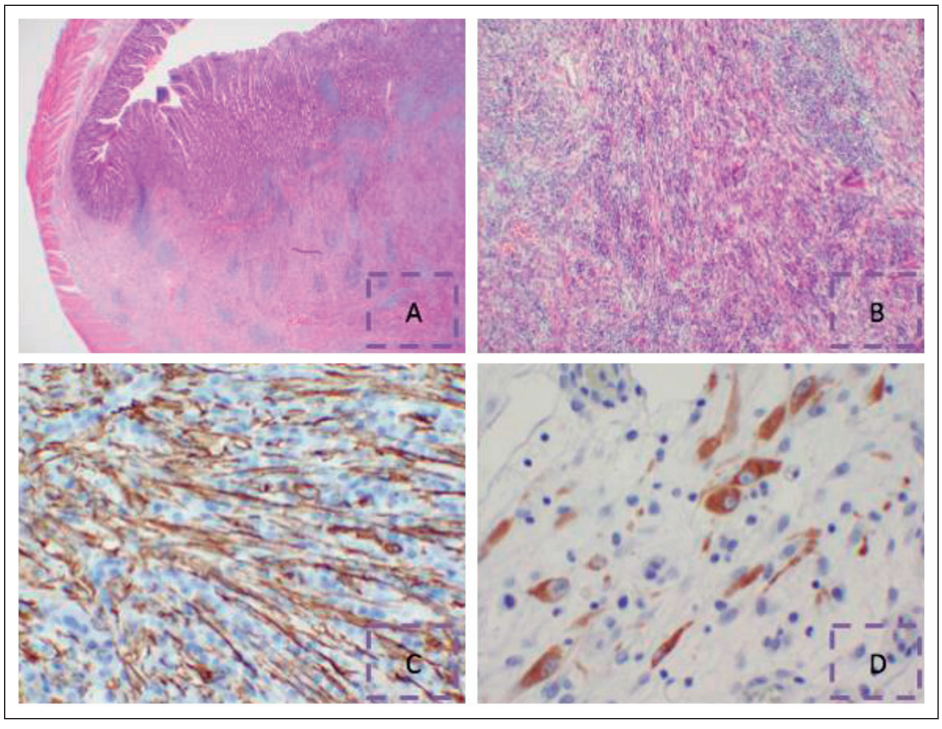

Figure 2. A and **B** HE staining. **C:** cytoplasmic positive ML actin in fused cells. **D:** ALK staining is weak to moderate positive in tumor cells.

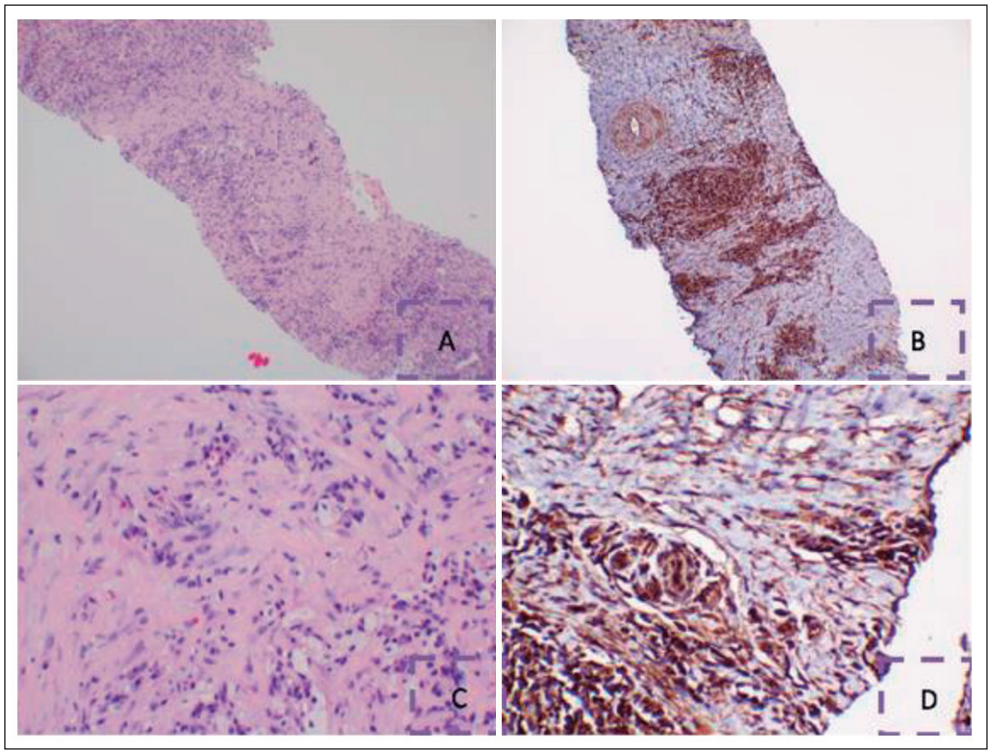

Figure 3. A and **C:** HE staining. **B** and **D** actin ME positive in fused cells.

Case 3

11-year-old female pre-adolescent hospitalized due to repeated urinary tract infection (UTI) study. The abdominal physical examination showed a hypogastric mass.

Imaging studies were performed, where both ultrasound and abdominal CT (Figure 4A and B) showed a 7.8 x 5.5 x 5.7 cm solid vascularized cystic mass, in the posterolateral bladder wall. The lesion infiltrated the bladder wall and affected the mesentery in almost its entire pelvic extension (Figure 4C and D). Considering the radical cystectomy risk during the surgical procedure, it was decided to perform an incisional biopsy, whose histology was compatible with bladder IMT. Regarding immunohistochemistry tests, vimentin, desmin, alpha-SMA, cytokeratin, and ALM were positive, and ALK was negative.

Treatment with COX-2 anti-inflammatory drugs associated with prednisone (there is no medication dose record) was indicated for approximately one year, achieving tumor remission. After the treatment period, an ultrasound was carried out identifying a residual lesion limited to a small segment of the bladder wall. Through cystoscopy, which showed a papillary lesion on the back side of the bladder (Figure 5A and B), the lesion was delimited, and a partial cystectomy was performed with tumor-free margins. The biopsy (Figure 5C and D) showed a lesion compatible with IMT associated with *Actinomyces israelii* infection, which was probably the reason for the inflammatory reaction that causes the tumor. The patient was evaluated by the infectious diseases department, starting antibiotic therapy with Sodium Penicillin IV for seven days and then Amoxicillin 1 g every 12 hours for six months with favorable response.

She currently remains in oncology monitoring, with no recurrence evidence.

Discussion

IMT, also known as inflammatory pseudotumour[1], is an infrequent benign neoplasm[2,3,12], however, it is classified in the group of myofibroblastic tumors with intermediate behaviour[4,6] due to its malignant potential, characterized by invasion of adjacent structures, recurrence, and future metastasis, where the latter is exceptional[13,8].

It often occurs in children and young adults[2,3,5,6], with a slight preference towards the male gender (M/F = 1.3/1)[3].

Its etiology is uncertain but may be associated with trauma, surgeries, autoimmune pathologies, inflammation, and viral or bacterial infections such as the Epstein-Barr virus, herpes simplex virus, mycobacteria, and mycoplasma, among others. Genetic studies prove chromosomes translocation and genes fusion[3,5,6,7,8,10].

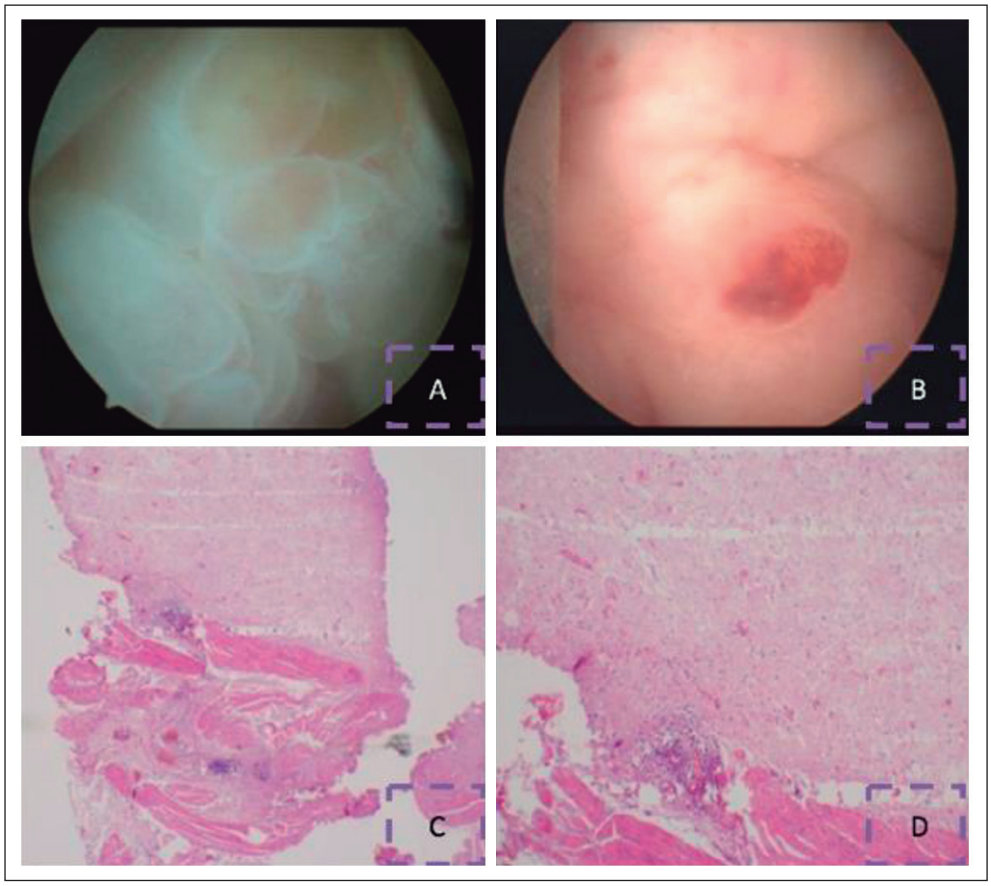

Figure 4. A and **B** show TMI located in the posterior bladder wall. **C** and **D** evidence of TMI displacing pelvic structures to the left.

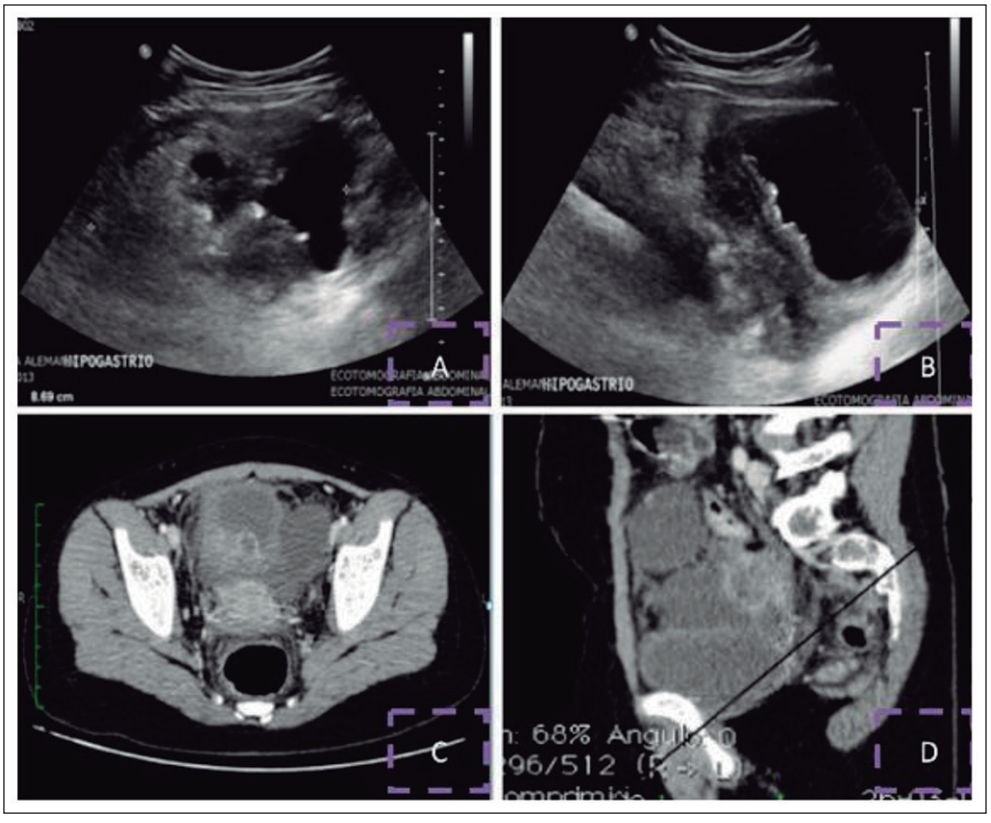

Figure 5. A and **B** cystoscopic image of TMI. **C** and **D** muscular wall with smooth muscle infiltrated by myxobacterial myxoid tissue with foci of lymphoplasmacytic infiltrate and eosinophils.

This tumor is found in different anatomical areas[1,2,3], most frequently in the lung[7,10]. However, recent studies described in Table 1, show higher incidence in extra-pulmonary spots such as the abdominopelvic cavity, where the liver is the main affected[5]. Atypical areas are also described[8,9], such as the intestine, pancreas, genitourinary system, and bones.

The clinical presentation usually depends on the tumor location and may be asymptomatic[2,11]. Approximately 5 to 10% have systemic and physical manifestations such as fever, weight loss, anorexia, microcytic and hypochromic anemia, hypergammaglobulinemia, and thrombocytosis (probably due to tumor production of IL-1 and IL-6)[4,5].

The lesion is generally single, although in 5% of cases it may be multiple[5], and it is difficult to distinguish from other neoplasms through imaging studies[1,2,5,6].

The definitive diagnosis is made with histology and immunohistochemistry studies[7,9].

Three histological patterns have been described. The myxoid vascular pattern, the compact one of spindle-shaped cells with intermixed inflammatory cells, and the fibrous hypocellular one (dense collagen matrix predominance)[3,4,5,13]. Wang et al.[3] showed that the spindle-shaped cell pattern was the most frequently represented in 96% of cases.

Microscopic study is not enough to differentiate it from other tumors such as stromal, leiomyosarcoma, and inflammatory malignant fibrous histiocytoma, so immunohistochemistry study is necessary to confirm the diagnosis. Mesenchymal cells are usually immunoreactive for vimentin, desmin, alpha-SMA, and S100[8] protein and negative for c-kit[12].

Up to 71% of these tumors are positive for ALK-1[8,12], which gives IMT greater susceptibility to drug treatment than those who do not express it[4], but with a higher recurrence rate[8]. Genetic studies have determined that 50% of IMT will have an alteration in the ALK gene structure (chromosome 2p23), generating different fusion patterns[7,9,14].

Tateishi Y et al.[9] present a case of intraosseous IMT, where an ATIC-ALK fusion is identified through the FISH (fluorescence in situ hybridization) method.

Differential diagnosis is made with benign lesions such as giant cell granuloma, solitary fibrous tumor, myoepithelioma, myxofibroma[7,9], and with malignant tumors such as low-grade myofibroblastic sarcoma, teratomas, rhabdomyosarcomas, and lymphomas[3,7].

The IMT management will depend on its location, the ALK expression, its behavior, and the surgical resection feasibility.

In relation to behavior, cases of local infiltration, recurrence, and metastasis are described, however, there are also publications reporting spontaneous resolution[6,12].

Table 1. Anatomical location of inflammatory myofibroblastic tumor

Authors	Total sample	Location	% of patients
Dalto, et al.	32	Abdomen and pelvis	28%
		Head and neck	22%
		Chest	22%
		Genitourinary	9%
		Intestine	6%
		Liver	6%
		Musculoskeletal	6%
Karnk, et al.	7	Chest	15%
		Abdominal	85%
Wang, et al.	23	Abdomen and pelvis	74%
		Lung	8.6%
		Head and neck	4.3%
		Trunk	4.3%
		Extremities	8.6%

Zhao et al.[6] presented two cases of adult patients diagnosed with an intra-abdominal inflammatory myofibroblastic tumor, cataloged as unresectable, and that regressed without any treatment. In addition, they presented a systematic review with a total of 36 patients with intra-abdominal tumors which presented spontaneous regression without surgical intervention[6]. The reason for spontaneous regression is not clear, but three factors are proposed that could influence:

1. Lesion location: Liver lesions have a better prognosis compared to those located elsewhere in the abdomen, pelvis, or retroperitoneum.
2. Age of presentation: regression was more frequent in middle age and older patients.
3. Other factors such as aneuploidy, atypia, and ganglion-like cells were associated with increased recurrence and malignant transformation[6].

In relation to the therapeutic approach based on the inflammatory origin hypothesis, cases of non-steroidal anti-inflammatory drugs and corticosteroids use have been reported[12]. It is suggested that anti-inflammatories would have an inhibitory effect on angiogenesis and cell proliferation through the induction of fibroblast apoptosis and therefore may inhibit tumor vascularization, endothelial proliferation, and tumor growth[12]. Tsuma et al. presented the case of a 13-year-old adolescent with IMT diagnosis, treated with COX-2 inhibitors and prednisolone, achieving a reduction in the lesion size for later resection. Immunohistochemical analysis revealed COX-2 tumor expression which justified the selective COX-2 inhibitors efficacy in reducing tumor size[14].

The literature describes two cases of patients who did not respond to anti-inflammatory therapy and it was decided to use Infliximab, obtaining a favorable response and achieving lesions stability and a decrease in symptomatology in one of the cases[12], and almost complete mass regression, associated with the symptomatology absence in the other one[13].

The role of radiotherapy and chemotherapy is not yet clear[4,12] since it has not shown a definitive benefit[5], therefore, the treatment of choice is surgical resection which is healing[1,3,5,8,12].

Recurrence ranges from 25 to 40% and is more frequent in extra-pulmonary lesions and during the first year after resection[3,5,7]. If the removal is complete and the lesion shows tumor-free margins, the recurrence rate is less than 10%[3]. Metastases are infrequent and around 2%[8,11].

The characteristics that can predict a worse prognosis, recurrence and metastasis probability are female gender, age over 25 years, abdominopelvic location, large size, multinodular mass, incomplete resection, and ALK negative[12].

Dalton B. et al. evaluated 32 patients with IMT diagnosis, determining a higher association with mortality the disease persistence and recurrence (67 vs 0%)[1].

Regarding follow-up, ultrasound monitoring is suggested after resection, at 3, 6 and 12 months[1, 3].

Conclusion

IMT is classified as an intermediate behavioral myofibroblastic tumor. Its clinical manifestations are diverse and will be determined by the affected anatomical area. Management will depend on its location, ALK expression, behavior, and surgical resection feasibility.

In this work, three cases were presented with different clinical manifestations, management, and results, which supports the diversity of this entity. Until the review, the use of monoclonal antibodies is described in only three patients worldwide, and our case is the second described in Chile. Although its results seem to be encouraging, more studies are needed to establish it as a therapy scheme in the management of ALK-negative IMT that is not susceptible to surgical resection.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

References

1. Dalton B, Thomas P, Sharp N, et al. Inflammatory myofibroblastic tumors in children. J Pediatr Surg. 2016;51:541-4.
2. Karnak I, Senocak M, Ciftci A, et al. Inflammatory Myofibroblastic Tumor in Children: Diagnosis and Treatment. J Pediatr Surg. 2001;36(6):908-12.
3. Wang Z, Zhao X, Li K, et al. Analysis of clinical features and outcomes for inflammatory myofibroblastic tumors in China: 11 years of experience at a single center. Pediatr Surg Int 2016;32:239-43.
4. Pfeifer JD, Dehner LP. Soft tissue and Bone. En: Humphrey ed. The Washington manual Of Surgical Pathology, segunda edición, Washington DC. Wolters Kluwer Health/Lippincott Williams y Wilkins. 2012. pp 754-5.
5. Osnaya H, Zaragoza T, Escoto J, et al. Tumor miofibroblástico inflamatorio (pseudotumor inflamatorio) ocasionando abdomen agudo. Rev Chil Cir. 2014;66(3):264-8.
6. Zhao JJ, Ling JQ, Fang Y, et al. Intra-abdominal inflammatory myofibroblastic tumor: Spontaneous regression. World J Gastroenterol. 2014;20(37):13625-31.
7. Liu HK, Lin YC, Yeh ML, Chen YS, Su YT, Tsai CC. Inflammatory myofibroblastic tumors of the pancreas in children A case report and literature review. Medicine 2017;96:2(e5870).
8. Oeconomopoulou A, de Verney Y, Kanavaki K, Stefanaki K, Pavlakis K, Salakos C. Inflammatory myofibroblastic tumor of the small intestine mimicking acute appendicitis: a case report and review of the literature. J Med Case Rep. 2016;10:100.
9. Tateishi Y, Okudela K, Kawai S, et al. Intraosseous inflammatory myofibroblastic tumor of the mandible with a novel ATIC-ALK fusion mutation: a case report. Diagn Pathol. 2016;11:132.
10. Izumi G, Narugami M, Saita Y, et al. Successful sleeve lobectomy of pediatric inflammatory myofibroblastic tumor. Pediatr Int. 2016;58:1087-9.
11. Delgado Duatis G, Bejar Sánchez R, Alonso Jiménez L. Invaginación atípica por tumor miofibroblástico inflamatorio. Anales de pediatría. 2015;83(3):221-2.
12. Grunoholz D, Appiani F, Abarca C, Manriquez M, Pinilla J, Wainstein E. Tumor miofibroblástico peritoneal. Respuesta favorable asociada a infliximab. Caso clínico. Rev Med Chile 2015;143:943-7.
13. Germandis G, Xanthakis I, Tsitouridis I, et al. Regression of Inflammatory Miofibroblastic Tumor of the Gastrointestinal Tract Under Infliximab Treatment. Digestive diseases and Sciences. 2005;50(2):262-5. DOI: 10.1007/s 10620-005-1593-1.
14. Tsuma Y, Miyachi M, Ouchi K, et al. Neoadyuvante Treatment With Cyclooxygenase-2 inhibitor and Prednisolona Allows Conservative Sugery for Inflamatory Myofibroblastic Tumor of the Bladder. Journal Pediatrics Hematology Oncology 2016;38:e283-5.