Received: 4 August 2021 | Revised: 1 October 2021 | Accepted: 18 October 2021

DOI: 10.1002/pbc.29460

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

ONCOLOGY: RESEARCH ARTICLE

Clinical, pathologic, and molecular features of inflammatory myofibroblastic tumors in children and adolescents

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Abstract

Background: Inflammatory myofibroblastic tumors (IMT) are rare, intermediate malignant tumors harboring frequent somatic molecular rearrangements. The management of IMT has not been standardized.

Methods: A retrospective multicenter study was conducted on all pediatric patients treated for IMT between 2000 and 2019.

Results: This series included 39 cases of IMT, with a median age at diagnosis of 7 years (range 20 days to 16 years). Tumor location included pelvis-abdomen (n = 16), thorax (n = 14), head and neck (n = 7), and limbs (n = 2). One patient had metastatic disease. Immunochemistry showed 21/39 (54%) anaplastic lymphoma kinase (ALK)-positive tumors. Somatic tyrosine kinase rearrangement was present in 31/36 (86%) of the tumors analyzed: 21 ALK, five ROS1, and five NTRK. Immediate surgery was performed in 24 patients (62%), with adjuvant therapy for three patients. Delayed surgery after neoadjuvant therapy was possible in 10 cases. Exclusive systemic therapy was delivered to four patients; one patient with orbital IMT was managed by watchful waiting. After a median follow-up of 33 months (range 5–124), eight (20%) recurrences/progressions occurred after surgery (seven after primary surgery and one after delayed surgery), after a median interval of 7 months (range 2–21), all in thoracic locations. The 3-year overall and disease-free survivals were 96.8% (95% CI: 79.2%–94.0%) and 77.4% (95% CI: 59.6%–88.1%), respectively. Relapses/progressions were more common in patients with a thoracic primary ($p < .001$) or after incomplete surgery with no adjuvant therapy ($p = .027$).

Conclusion: Surgery is effective in most cases of pediatric IMT. Systematic analysis of tyrosine kinase rearrangement is recommended. When the tumor is deemed only partially resectable to preserve organs and function, neoadjuvant therapy may be proposed to allow adequate conservative surgery.

Abbreviations: ALK, anaplastic lymphoma kinase; CR, complete remission; CT, conventional chemotherapy; DFS, disease-free survival; FISH, fluorescence in situ hybridization; FU, follow-up; IHC, immunohistochemistry; IMT, inflammatory myofibroblastic tumor; NSAID, nonsteroidal anti-inflammatory drug; OS, overall survival; PR, partial remission; TKI, tyrosine kinase inhibitors.

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Previously published meetings:
1. Pire A, Orbach D, Galmiche L, Berrebi D, Irtan S, Boudjemaa S, Brisse H, Berteloot L, Moalla S, Mussini C, Philippe-Chomette P, Tilea B, Guerin F, Minard-Colin V, Sarnacki S. The place of surgery in the treatment of inflammatory myofibroblastic tumors. Belgian Surgical Week (BSW) 2020 Light Virtual, Free paper session; Brussels, Belgium; November 26, 2020.
2. Pire Aurore. Les tumeurs myofibroblastiques inflammatoires. 39ème Séminaire d'enseignement de la Société Française de chirurgie pédiatrique (SFCP), Place du chirurgien pédiatre dans les tumeurs de l'enfant en 2020; virtual meeting; December 2–3, 2020.
3. Pire A, Galmiche L, Orbach D, Berrebi D, Irtan S, Boudjemaa S, Brisse HJ, Berteloot L, Moalla S, Mussini C, Philippe-Chomette P, Tilea B, Guerin F, Minard-Colin V, Sarnacki S. Clinical and biopathology analysis of Inflammatory myofibroblastic tumors in children and adolescents: A report from 5 pediatric tertiary oncology centers. International Society of Pediatric Oncology (SIOP), poster session; Lyon; October 23–26, 2019.

KEYWORDS
inflammatory myofibroblastic tumors, nonmutilating surgery, target therapy

1 | INTRODUCTION

Inflammatory myofibroblastic tumors (IMTs) are rare tumors of intermediate malignancy with a risk of local recurrence, but a low metastatic potential (<5%).[1–4] While IMT may occur in any site, the main locations are abdominal and thoracic, but the head and neck, central nervous system, or the limbs may also be involved.[4,5] IMTs mainly affect children and young adults.[6] Histologically, these lesions are characterized by the presence of a myofibroblastic mesenchymal spindle cell proliferation associated with inflammatory infiltration, predominantly.[1,5] In more than 50%–75% of cases, somatic molecular analysis reveals the presence of a translocation involving the "anaplastic lymphoma kinase (ALK)" gene.[4,7,8] Other chromosomal fusion transcripts have been reported in this disease, including ROS 1 and, more recently, NTRK.[9–12] While the cornerstone of treatment of IMT remains surgical excision for localized tumors, the place of neoadjuvant or adjuvant therapy and the impact of the quality of resection remain unclear.[6,13–15] Systemic therapies for large unresectable tumors consist of steroids and nonsteroidal anti-inflammatory drugs (NSAIDs), conventional chemotherapy (CT), and, more recently, tyrosine kinase inhibitors (TKI).[13,16]

The purpose of this multicenter retrospective study was to define the place of surgery and systemic therapy in the management of pediatric IMT in the era of systematic molecular profiling and targeted therapies.

2 | MATERIALS AND METHODS

We retrospectively retrieved information from the medical charts of all pediatric patients (age ≤16 years) treated between 2000 and 2019 for IMT involving any anatomical compartment in five large hospitals in Paris and the Île-de-France area. All pediatric cancer cases were discussed by the multidisciplinary tumor board of the Pediatric Cancer Network. A central pathology review of all cases was performed to validate the diagnosis together with more detailed molecular biology.[17–19] Nine patients were excluded, with a diagnosis of

nodular fasciitis for four, IgG4-related disease for three, low-grade myofibroblastic sarcoma for one, and myxoma for one. ALK immunohistochemistry (IHC) staining was systematically performed. Screening for specific somatic gene fusions (ALK, ROS1, or NTRK) was performed by fluorescence in situ hybridization (FISH). Depending on tumor tissue availability, next-generation RNA sequencing was performed on paraffin-embedded and/or fresh frozen tissue (Supporting Material). Treatment strategy was defined in the regional multidisciplinary tumor board certified by the French National Cancer Institute and in accordance with the recommendations of EpSSG NRSTS-05 protocol (European Union Drug Regulating Authorities Clinical Trial No. 2005-001139-31).[13] When complete macroscopic resection of a localized tumor could be achieved without mutilation, immediate surgery was recommended.[13,15,20] Surgery was defined as follows: tumor resection when resection was conservative, "en bloc" resection when resection included part of the affected organ without functional impairment, mutilating resection was defined as major resection or amputation with functional impairment, and partial resection was defined as voluntarily incomplete resection to avoid mutilating surgery.[9,15,20] The quality of surgical resection was defined as follows: R0 was defined as microscopically complete resection (radical resection), R1 was defined as microscopically incomplete marginal resection (and applied to resections for which the tumor was fragmented, such as endoscopic resection), and R2 was defined as macroscopically incomplete (intralesional) resection.[19,21] The postoperative outcome was evaluated according to the Clavien–Dindo classification.[22]

Steroids or NSAIDs were proposed as first-line treatment when the tumor location was deemed unresectable at diagnosis with a risk of mutilating surgery (such as orbit or lung), or when the patient required emergency treatment for severe symptoms.[13,15] Conventional CT drugs were also delivered to some patients with unresectable tumors, distant metastases, or recurrent disease.[15,23] When molecular somatic anomalies were present, TKI were considered mainly after failure of anti-inflammatory therapy.[8,13,16,24]

Statistical analysis compared the frequency of an event between two or more groups. Statistical significance was calculated by Fisher's exact tests. This choice was justified by the fact that the small number of events, sometimes with zero frequency for some groups, only allowed empirical formulas of uncertain significance for chi-square or log-rank tests. To estimate the trend of a frequency according to groups of ranked values, the Kolmogorov–Smirnov test was used, for which it is easy to calculate the exact significance for small numbers without resorting to asymptotic formulas. The confidence intervals of the percentages were calculated according to the binomial distribution, together with the 95% confidence interval and a limit of significance of $p = .05$. Overall survival (OS) was calculated from the date of histologic diagnosis to death from any cause or to the last follow-up (FU), and disease-free survival (DFS) was calculated from the date of diagnosis to tumor progression or relapse. Survival curves with their log-rank tests were generated and calculated by the Kaplan–Meier method.

3 | RESULTS

3.1 | Population

A total of 39 patients were included (Table 1). The male/female sex ratio was 1:1.4, with 69% of patients aged <10 years at diagnosis (median age: 7 years, range: 20 days to 16 years). Tumor locations were mainly pelvis-abdomen ($n = 16$, 41%) and thorax ($n = 14$, 36%). One patient (patient 25) with a thoracic primary presented with brain metastases. One patient (patient 16) developed a pelvic IMT during treatment of a pinealoblastoma.

3.2 | Diagnosis and histological characteristics

Biopsy was performed in 27 cases and allowed the diagnosis of IMT in 21 cases (78%). In the remaining 18 cases (including six cases after inconclusive biopsy), the diagnosis was established on the surgical specimen after excision of the primary tumor (17 cases) or brain metastases (one case).

IHC revealed 21/39 (54%) ALK-positive tumors. ALK gene rearrangements were confirmed in 17 tumors tested by either FISH and/or RNA sequencing (RNAseq) with the following partners: EML4-ALK ($n = 3$), CLTC-ALK ($n = 3$), TIMP3-ALK ($n = 1$), TMP4-ALK ($n = 1$), MYH9-ALK ($n = 1$), RANBP2-ALK ($n = 1$), and PRKAR1A-ALK ($n = 1$). The partner remained unknown in six cases tested by FISH only. ROS1 rearrangements were detected in five cases (four of five with positive ROS1 IHC staining) with a known partner in two cases (TGF-ROS1; FN1-ROS1). NTRK fusion transcripts were detected in five cases, four with ETV6-NTRK3 fusion and one with an unknown partner (FISH analysis only). Five tumors (three orbital tumors, one limb tumor, and one liver tumor) did not display any RNAseq gene rearrangements. For the last three cases, the remaining tumor materiel was not sufficient to perform any additional molecular biology studies. Overall, somatic tyrosine kinase rearrangement was present in 31 (86%) of the 36 tumors analyzed. The type and incidence of tyrosine kinase rearrangements according to clinical characteristics are detailed in Table 2.

3.3 | Therapeutic strategies

3.3.1 | Patients treated by primary surgery ($n = 24$)

Primary surgery was performed in 24 cases (62%) and consisted of tumor resection in nine cases, "en bloc" resection in eight cases, partial resection in six cases, and mutilating resection in one case (Table 3).

R0 complete resection was obtained in 10/24 cases (41.7%), all of whom remained in first complete remission (CR_1) after a median of 39.5 months (range 5–112).

R1 resection (microscopic residue) was achieved in eight of 24 cases (33.3%). Four of these patients did not receive any adjuvant therapy

TABLE 1 Patient and tumor characteristics ($n = 39$)

n	Age (years)	Gender (M/F)	Primary	Maximum tumor size (cm)	Treatment(s)	Surgical resection margin	ALK IHC Pos/neg	Molecular alteration (technic)	Tumor events	Status at last FU(months)
1	1	M	Mesentery	9	Surgery	R0	Pos	TMP4-ALK (RNAseq)	0	CR1 (52 m)
2	2	M	Mesentery	14	Surgery	R0	Pos	ALK (FISH)	0	CR1 (44 m)
3	4	M	Mesentery	17	Surgery	R0	Neg	ND	0	CR1 (38 m)
4	0	M	Mesentery	10	Steroids/TKI/surgery	R2	Neg	ETV6-NTRK3 (RNAseq)	0	CR1 (12 m)
5	0	F	Mesentery	5.5	Surgery/CT/TKI	R2	Neg	TGF-ROS1 (RNAseq)	0	PR1 (17 m)
6	1	F	Mesocolon	6	Surgery	R1	Pos	CLTC-ALK (RNAseq)	0	CR1 (10 m)
7	6	F	Peritoneum	15.7	Steroids/surgery	R1	Pos	EML4-ALK (FISH)	0	CR1 (6 m)
8	15	F	Gastroesophageal	4.7	Surgery	R1	Neg	TGF-ROS1 (RNAseq)	0	CR1 (21 m)
9	2	F	Adrenal gland	5	Surgery	R1	Pos	ALK (IHC)	0	CR1 (88 m)
10	2	F	Liver	15	Surgery	R0	Neg	Neg (RNAseq)	0	CR1 (32 m)
11	14	M	Pelvis (bladder)	2.5	Surgery	R0	Pos	ALK (FISH)	0	CR1 (41 m)
12	7	F	Pelvis (bladder)	2.5	Surgery	R0	Pos	ALK (IHC)	0	CR1 (112 m)
13	3	F	Pelvis (vagina)	4	NSAIDs/surgery	R2	Pos	ALK (FISH)	0	CR1 (28 m)
14	13	M	Pelvis	11.2	Steroids/TKI/surgery	R2	Pos	RANBP2-ALK (FISH)	0	CR1 (34 m)
15	11	M	Pelvis	8	TKI/surgery	Unknown, MC	Pos	CLTC-ALK (RNAseq)	0	CR1 (5 m)
16	8	F	Pelvis (para-vesical)	5	CT/surgery	R0	Pos	ALK (IHC)	0	CR1 (58 m)
17	3	M	Lung	7.5	Surgery	R1	Neg	Ros1 (FISH)	Relapse	CR2 (85 m)
18	6	M	Lung	6	Surgery	R2	Neg	Ros1 (IHC)	Progression	PR2 (124 m)
19	11	M	Lung	6.2	Steroids/surgery	R0	Pos	MYH9-ALK (RNAseq)	Relapse	Died (60 m)
20	10	M	Lung	11	Surgery	R1	Neg	ETV6-NTRK3 (RNAseq)	Relapse	Died (17 m)
21	10	M	Lung	4.3	Surgery	R0	Neg	ND	0	CR1 (47 m)

(Continues)

TABLE 1 (Continued)

n	Age (years)	Gender (M/F)	Primary	Maximum tumor size (cm)	Treatment(s)	Surgical resection margin	ALK IHC Pos/neg	Molecular alteration (technic)	Tumor events	Status at last FU(months)
22	16	F	Lung	8	Steroids/surgery	R0	Pos	ALK(IHC)	0	CR1 (61 m)
23	7	M	Lung	3.5	Surgery	R0	Neg	ETV6-NTRK3 (RNAseq)	0	CR1 (15 m)
24	2	F	Lung	5.7	Steroids/TKI/surgery	Unknown, MC	Neg	ETV6-NTRK3 (RNAseq))	0	CR1 (22 m)
25	15	F	Lung (+brain metastases)	11	CT/surgery/TKI	R0	Pos	EML4-ALK (FISH)	0	CR1 (37 m)
26	8	M	Mediastinum	10	Surgery	R2	Pos	ALK (FISH)	Progression	PR2 (65 m)
27	4	F	Mediastinum (trachea)	1.5	Surgery	R1	Pos	ALK (FISH)	Relapse	PR2 (35 m)
28	9	F	Mediastinum (trachea)	Unknown	Surgery	R1	Pos	PRKAR1A-ALK (RNAseq)	0	CR1 (12 m)
29	9	F	Mediastinum (trachea)	4.2	Surgery/TKI	R2	Neg	FN1-ROS1 (RNAseq)	Relapse	On therapy with residue (38 m)
30	3	F	Mediastinum (trachea)	2.2	Surgery	R2	Pos	EML4-ALK (FISH)	Progression	PR2 on therapy (22 m)
31	0	F	Tongue	1.3	Surgery	R1	Pos	TIMP3-ALK (FISH)	0	CR1 (27 m)
32	8	M	Orbit	4.6	Surgery/steroids	R2	Neg	Neg (RNAseq)	0	CR1 (19 m)
33	14	F	Orbit	0.3	Surgery	R0	Pos	ALK (FISH)	0	CR1 (21 m)
34	13	F	Orbit	3.7	Steroids	/	Neg	Neg (RNAseq)	0	CR1 (51 m)
35	10	F	Orbit	4.8	Steroids	/	Neg	Neg (RNAseq)	0	CR1 (82 m)
36	9	F	Orbit	2.4	Steroids/TKI	/	Neg	LMNA-NTRK1(FISH)	0	CR1 (26 m)
37	7	M	Orbit	2	None	/	Neg	ND	0	PR1 (94 m)
38	6	F	Shoulder	10	Steroids/TKI	/	Pos	CLTC-ALK (RNAseq)	0	PR1 on therapy (12 m)
39	5	F	Shoulder	1.3	Surgery	R0	Neg	Neg (RNAseq)	0	CR1 (5 m)

Abbreviations: CR1, primary complete remission; CR2, secondary complete remission; CT, chemotherapy; F, female; FISH, fluorescence in situ hybridization; FU, follow-up; IHC, immunohistochemistry; m, months; M, male; MC, macroscopic complete resection; ND, not done; Neg, negative; NSAIDs, nonsteroidal anti-inflammatory drugs; Pos, positive; PR1, primary partial remission; PR2, secondary partial remission; R0, microscopic complete resection; R1, microscopic incomplete resection; R2, macroscopic incomplete resection; RNAseq, RNA sequencing; TKI, tyrosine kinase inhibitor.

TABLE 2 Somatic tyrosine kinase rearrangement: type and incidence according to clinical characteristics ($n = 36$)

	Somatic rearrangement	Molecular alteration	95% CI	*p*-Value
Location Abdomen Thorax Orbits Limb Tongue	14/15 (93%) 13/13 (100%) 2/5 (40%) 1/2 (–) 1/1 (–)	1ALK/1NTRK/2ROS 7ALK/3NTRK/3ROS 1ALK/1NTRK 1ALK 1ALK	68.1%–99.8% 75.3%–100.0% 0.0%–82.9% 1.3%–98.7%	.0072
Age at diagnosis <10 years ≥10 years	22/25 (88%) 9/11 (82%)	14ALK/4NTRK/4ROS 7ALK/1NTRK/1ROS	75.3%–100.0% 59.0%–100.0%	.79
Tumor size ≤5 cm >5 cm	16/20 (80%) 15/16 (94%)	11ALK/2NTRK/3ROS 10ALK/3NTRK/2ROS	62.5%–97.5% 81.9%–100.0%	.96

Note: The three immunohistochemistry ALK-negative inflammatory myofibroblastic tumors (IMTs), for which no further molecular analysis was possible (insufficient materiel), were excluded.

TABLE 3 Surgery characteristics and complication of inflammatory myofibroblastic tumor ($n = 34$)

	Type of surgery and number of patients		Quality of resection	Dindo–Clavien score
Thorax	8 Tumor resection			
	4	Endotracheal resection by endoscopy	3 R1/1 R2	I
	1	Tumor resection by thoracotomy	1 R2	I
	2	Tumor resection by thoracoscopy (with 1 diaphragmatic patch)	1 R0/1 unknown[a]	I
	1	Tumor resection by tracheobronchotomy by sternotomy	1 R2	I
	6 "En bloc" resection			
	5	Lobectomy by thoracotomy	5 R0	I
	1	Wedge lung resection with diaphragmatic and pericardic patch resection	1 R2	I
Abdomen	5 Tumor resection			
	2	Partial tumor resection	2 R2	I
	1	Tumor resection by laparotomy	1 R0	I
	1	Tumor resection by laparoscopy-robot assisted	1 R1	I
	1	Endovaginal tumor resection	1 R2	I
	10 "En bloc" resection			
	3	Partial bowel resection by laparotomy	2 R0/1 R1	I
	3	Partial bladder resection by laparotomy	3 R0	2 I/1 II
	1	Partial bowel resection by laparoscopy-robot assisted	1 Unknown[a]	I
	1	Adrenal gland resection	1 R1	I
	1	Left hepatectomy with diaphragmatic patch resection	1 R0	I
	1	Wedge pancreatic resection	1 R2	I
	1 Mutilating resection			
	1	Oesogastrectomy by laparoscopy-robot assisted	1 R1	IIIb
Head and neck	3 Tumor resection		1 R1/1 R0/1 R2	I
Extremity	1 Tumor resection		1 R0	I

Abbreviations: R0, microscopically complete resection; R1, microscopically incomplete; R2, macroscopically incomplete resection.
[a]Unknown due to tumor fragmentation in the bag before extraction.

and remained in CR_1. One patient, with a thoracic tumor ruptured during initial surgery, developed pleural relapse 2 months after resection, which was treated by NTRK inhibitor therapy. He developed delayed resistance and died 15 months after recurrence despite additional CT. In two patients with tracheal primaries and one patient with bronchial primary, a piecemeal endoscopic resection, considered to be R1, was performed. Two of them subsequently developed recurrence, 2 and 10 months after resection: one was treated by steroids (three 4-month courses) and is in secondary partial remission (PR_2) and off therapy for 11 months; the other case was treated by "en bloc" resection with R1 margins, resulting in CR_2 for 67 months.

A voluntary conservative partial resection (R2 margin) was performed in the remaining six cases. Three of these cases received adjuvant therapy, two of whom are in CR_1 after steroid therapy ($n = 1$) and methotrexate–vinblastine followed by crizotinib ($n = 1$). One patient with a *ROS1*-positive IMT received crizotinib as maintenance therapy and remained in CR for 24 months but developed tumor relapse 7 months after stopping therapy; he is alive with stable residual disease 5 months after resuing crizotinib. Three patients did not receive any adjuvant therapy and all experienced tumor progression: two with local progression (7 and 8 months after resection) and one with combined local and metastatic progression, 21 months after surgery. Local progressions were treated by steroids for 12 months in one patient in PR_2 with FU of 45 months and by steroid therapy and incomplete tumor resection with adjuvant TKI therapy. This last patient is alive with stable residue (PR_2) and is still on crizotinib with FU of 12 months. The patient with a combined recurrence received steroids and CT (methotrexate–vinblastine), incomplete tumor resection and adjuvant crizotinib and is off therapy with a stable residue after FU of 33 months (PR_2).

3.3.2 | Patients treated by neoadjuvant therapy ($n = 10$)

Delayed surgery after systemic therapy was performed for 10 patients whose tumors were deemed unresectable without mutilation (nine cases) and one patient with thoracic IMT with brain metastases. Eight patients with localized IMT received various drug regimens, which resulted in stable disease in three cases, after steroids ($n = 2$) and NSAIDs ($n = 1$); and partial response in five cases, after treatment with steroids and crizotinib ($n = 1$), steroids and larotrectinib ($n = 2$), crizotinib or steroids (one case each). One patient with abdominal IMT was receiving chemotherapy for treatment of a pinealoblastoma. The patient with metastatic thoracic *EML4-ALK*-positive IMT was first operated for intracranial hypertension. Surgery of the thoracic primary was delayed after one course of chemotherapy (vinblastine and methotrexate) due to respiratory deterioration ("en bloc" R0 resection). Adjuvant chemotherapy was delivered with no response on residual brain metastases; 16 months of crizotinib achieved complete remission (CR_1, 18 months after stopping therapy). Overall, delayed surgery achieved gross tumor resection (R0/R1) in seven (70%) out of 10 patients: four R0, one R1, and two unknowns due to tumor fragmentation in the bag before extraction. Conservative incomplete resection (R2) was performed in the last three cases. Finally, of these 10 patients, one patient with tumor rupture during initial biopsy of a thoracic lesion (*MYH9-ALK*-positive IMT) developed pleural relapse 4 months after surgical resection. He received subsequent therapies including CT and three different *ALK* inhibitors due to acquired *ALK*-resistant mutations and died 52 months after recurrence.

3.3.3 | Patients treated with exclusive systemic therapy ($n = 4$)

Exclusive systemic therapy was delivered to four patients (orbital primary: three cases, shoulder: one case). Steroid therapy resulted in CR1 in two orbital fusion ALK-negative IMTs, transient PR in one orbital NTRK-positive IMT, and PR in one ALK-positive shoulder primary. For these last two patients, second-line therapy with TKI achieved CR for the orbital IMT and a very good partial tumor response for the shoulder IMT.

3.3.4 | Patient managed by watchful waiting ($n = 1$)

One patient with an orbital *ALK*-negative IMT was managed by watchful waiting and was alive with a stable residue after FU of 94 months.

3.4 | Surgery and complications

Among the 34 patients treated by surgery, only one case required mutilating surgery and this same patient experienced a grade IIIb complication (repeated surgery for bowel obstruction) (Table 3).

3.5 | Outcome

Tumor recurrences/progressions were observed in eight of the 34 operated patients (23.6%) after a median interval of 7 months (range 2–21 months). Seven patients developed local recurrence and one patient developed combined local and metastatic recurrence. These tumors presented various somatic tyrosine kinase rearrangements: four *ALK* positive (one *EML4-ALK*; one *MYH9-ALK*; two ALK-unknown), three *ROS1* positive, and one *ETV6-NTRK3* positive.

After a median FU of 33 months (range 5–124), 37 patients were alive, 29 patients were in CR ($CR_1 = 27$, $CR_2 = 2$), five patients presented stable residue (PR) off therapy for a median of 33 months (range 2–94) ($PR_1 = 2$, $PR_2 = 3$), and three patients were still on TKI therapy. Two patients died from their disease 17 and 60 months after diagnosis: one after primary R1 and one after delayed R0 surgery, respectively. The 3-year OS and DFS were 96.8% (95% CI: 79.23%–94%) and 77.4% (95% CI: 59.6%–88.1%), respectively (Figure 1).

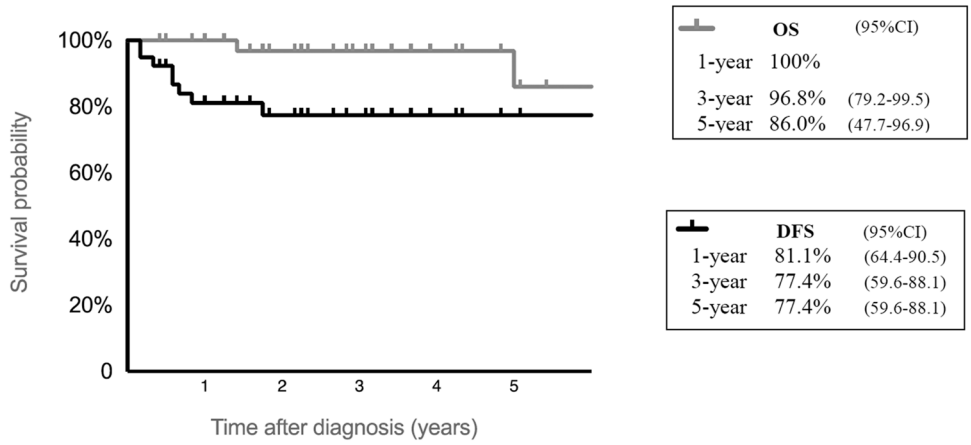

FIGURE 1 Overall (OS) and disease-free survivals (DFS) of patients with inflammatory myofibroblastic tumors ($n = 39$)

TABLE 4 Outcome of patients with inflammatory myofibroblastic tumor according to clinical characteristics

		Tumor events		
	Total $N = 39$	$N = 8$	LFR (95% CI)	*p*-Value
Gender Male Female	16 23	5[a] 3	31.3% (8.5–54) 13% (0–26.7)	.23
Age at diagnosis <10 years ≥10 years	27 12	6[a] 2	22.2% (6.5–37.9) 16.7% (0–37.7)	.82
Primary Abdomen-pelvis Thorax Head and neck Limb	16 14 7 2	0 8[a] 0 0	0% (0–20.6) 57.1% (28.9–82.3) 0% (0–41) % (0–100)	<.001
Tumor size ≤5 cm >5 cm	22 17	5 3[a]	22.7% (5.2–40.2) 17.6% (0–35.8)	.71
Somatic tyrosine kinase gene rearrangement Any type None *ALK* *ROS1* *NTRK*	31 8 21 5 5	8 0 4 3[a] 1	25.8% (11.9%–44.6%) 0% (11.9%–44.6%)	.17
Quality of surgical resection (at any time) R0 R1 R2 Unknown	14 9 9 2	1 3 4[a] 0	7.1% (0.2–33.9) 33.3% (7.5–70.1) 44.4% (13.7–78.8)	.13

Abbreviations: CI, confidence interval; LFR, local failure rate; R0, microscopic complete resection; R1, microscopic incomplete resection; R2, macroscopic incomplete resection.

[a]One patient had local and metastatic recurrence.

3.6 | Analysis of prognostic factors

The primary site influenced outcome, as thoracic tumors displayed a higher risk of recurrence than other locations ($p < .001$). Gender, age at diagnosis, tumor size, type of somatic molecular rearrangement, and metastatic status were not statistically associated with the risk of recurrence (Table 4). The risk of local recurrence tended to increase with decreasing quality of resection (R0 7.1% [95% CI: 0.2–33.9] vs. R1 33.3% [95% CI: 7.5–70.1] vs. R2 44.4% [95% CI: 13.7–278 78.8]; Kolmogorov–Smirnov test: $p = .033$). When primary surgery was performed, macroscopically incomplete resection (R2) ($n = 3$) was associated with a higher risk of recurrence compared to R0 ($n = 10$) and R1

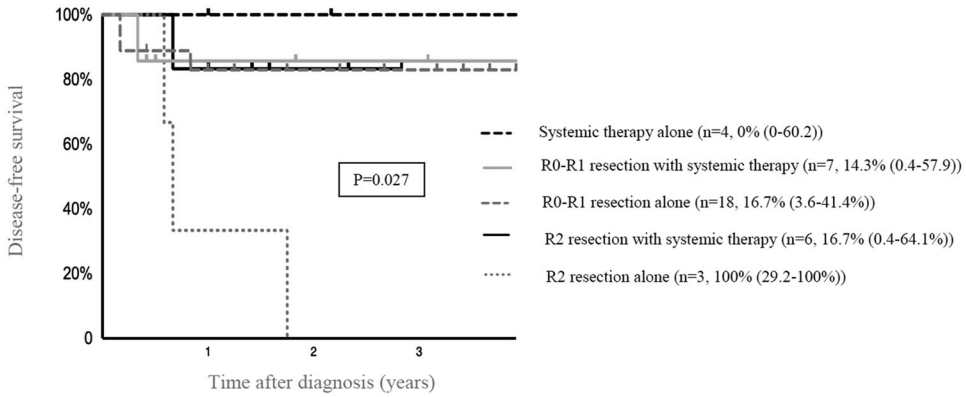

FIGURE 2 Local failure rate (95% confidence interval in parentheses) according to treatment strategy and quality of resection for patients with inflammatory myofibroblastic tumors ($n = 38$, the patient who was managed by observation only was excluded)

($n = 8$): R2: 100% (95% CI: 29.2–100) versus R1: 37.5% (95% CI: 8.5–75.5) versus R0: 0% (95% CI: 0–30.8); $p = .0016$ (Figure 2).

4 | DISCUSSION

This study reports the clinical and molecular characteristics and outcome of a large, unselected population of pediatric IMT with systematic pathology and molecular biology review. Abdominopelvic and thoracic tumors appeared to be the most common sites of this disease in young patients (median age: 7 years).[6,25] We confirmed that detection of somatic gene rearrangements is a major element for confirmation of the diagnosis of IMT, as more than one-half (54%) of all patients in our series presented ALK fusion, in line with other reports in adult and pediatric populations.[6] Although ALK rearrangements were the most common molecular anomalies identified, various other gene partners have been highlighted over recent years in ALK-negative IMTs, including NTRK and ROS1 found in 16% of cases each in the present population of IMT.[9,10] Our experience showed that more systematic molecular testing reveals somatic tyrosine kinase rearrangements in 86% of cases.

The management of IMT remains nonstandardized and is always complex, especially in children, for whom long-term organ and function preservation is crucial. Overall, surgical resection was performed in 87% of patients and remained the basis of IMT treatment. Primary surgery was recommended when nonmutilating macroscopic complete resection was possible, which was deemed feasible in 24/39 patients (61%). In patients with unresectable tumor at diagnosis, the use of neoadjuvant therapy allowed subsequent conservative gross tumor resection (R0/R1) in 70% of cases. In addition, systemic adjuvant therapy prevented recurrence in half of the cases where resection was macroscopically incomplete and most of the recurrences occurred in patients treated by surgery alone. Systemic adjuvant therapy thus appears to increase the quality of resection, while avoiding mutilating surgery and also appears to prevent recurrence as neoadjuvant therapy when surgery is incomplete. Interestingly, patients with thoracic tumors (lung or mediastinal, $n = 14$) had primary surgery in most of the cases ($n = 10$), which resulted in R2 in 40% of cases and a high recurrence rate (70% relapse/progression). In contrast, the four who received neoadjuvant therapy had all an R0/R1 resection, with only one recurrence in a patient with an ALK rearrangement. The high risk of incomplete resection and recurrence in thorax primary may be related to the voluntary wish of nonmutilation surgery shared by all the centers in this study. This location has by definition many surgical risk factors (closeness with main bronchus, lung pedicles, and/or major mediastinal vessels) and it could thus be suggested to indicate more systematically neoadjuvant systemic therapy in thoracic tumors.

This analysis suggested to consider the thoracic location as a risk factor for recurrence and to propose more systematically neoadjuvant therapy before surgery. In head and neck IMTs, for which nonmutilating surgery may be difficult or even impossible, exclusive systemic therapy appeared to be effective to achieve CR_1 (in four out of seven orbital IMTs in this series). Systemic therapy should therefore be proposed in IMT when resection entails a high risk of mutilation, such as in head and neck tumors multifocal disease or when incomplete resection is expected after primary surgery.

Detection of molecular rearrangements, including *ALK*, *ROS1*, *NTRK* fusions, opens the way for new potentially very active targeted therapies. Several TKIs targeting ALK, ROS, and NTRK have demonstrated their efficacy in various diseases provided they harbor this molecular rearrangement.[8,14,16] Tumor response, development of resistance or potential side effects influence the duration of treatment.[26–29] In our series, targeted therapy was indicated in one-third of patients (13/39 cases) in the neoadjuvant or adjuvant setting. Four patients received TKI (three of four after steroids) before a nonmutilating surgery, two patients after steroids and treated by only systemic treatment, two patients in second line of treatment after an incomplete resection, and five patients for the relapse therapy. The use of these new therapies remains indicated in case of recurrence, metastasis and/or resistance to other treatments. Their use as first-line therapy to improve quality of resection while avoiding mutilating resection is not currently evaluated. These drugs should be used as a short-term treatment to achieve optimal tumor shrinkage, as a bridge treatment, preventing thus the onset of side effects or resistance and allowing a delayed conservative and complete tumor resection; and in the setting of recurrence,

metastasis and/or resistance to other treatments. There is currently no data showing any correlation between tumor molecular anomalies and rate of response of targeted therapies.

Recurrence/progressive tumor occurred in eight cases, that is, 23% of patients who underwent surgery, with a maximum interval of 21 months after initial surgery. Notably, all patients with relapse presented a tumor with somatic gene rearrangement, although this factor did not appear to influence outcome on univariate analysis ($p = .17$). In the literature, tumor recurrences were observed more frequently in extrapulmonary IMT (25% vs. 2% in lung),[6,30] a feature not observed in the present series, in which recurrences were mostly observed in thoracic locations ($p < .001$). Notably, brain metastases were observed in two cases of pulmonary IMT, one at diagnosis and one at relapse (5%), with the detection of *ALK* and *ROS1* fusions, respectively. Targeted therapy was very effective in these two cases, as both patients are alive in CR and PR, respectively.

We are aware that estimating the frequency of recurrence by percentages is not the perfect static approach, as we have neglected censoring for some patients for whom the observation period is short. This choice is imposed by the nature of the data and is justified in the statistical methods section. We accept it considering that the recurrences are early (Q1: 5.7 months; Q2: 8.0 months; Q3: 10.5 months) and the observation setbacks relatively long (Q1: 16.5 months; Q2: 28.4 months; Q3: 49.0 months). Comparison of the crude percentage of recurrences for the entire population with the Kaplan–Meier estimate results in a difference of 2.6%, which suggests that one additional recurrence would have been diagnosed if all FUs had been longer.

In conclusion, systematic analysis of all tyrosine kinase rearrangements, ideally with RNA sequencing, is highly recommended in pediatric IMT, as it contributes not only to diagnosis, but also guides the decision-making process. For localized tumors, when at least complete macroscopic resection can be achieved without mutilation, immediate surgery should be proposed. When the tumor is deemed only partially resectable to preserve organs and function, neoadjuvant therapy should be proposed to allow adequate conservative surgery. Conventional therapies, such as anti-inflammatory drugs or low-dose chemotherapy, can be considered, especially in cases with no somatic molecular abnormalities. When a TK rearrangement is detected, targeted therapies should be considered as first-line or second-line treatment, as a bridge to conservative surgery. Finally, our experience argues in favor of more systematic adjuvant therapy after R2 resection to avoid recurrence and to potentially allow repeated R0/R1 resection. Our conclusions are certainly limited by the small size of this series and appeals for a large prospective multicentric study in the pediatric population, with systematic molecular screening.

ACKNOWLEDGMENTS

Francis Zech of the Institute of Experimental and Clinical Research (Université Catholique de Louvain, Brussels, Belgium) performed statistical analysis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Aurore Pire: conceptualization, data curation, methodology, writing the original draft and writing the review, and editing. Sabine Sarnacki, Daniel Orbach, and Véronique Minard-Colin: conceptualization, data curation, methodology, writing the review, and editing. Louise Galmiche, Dominique Berrebi, Sabah Boudjemaa, and Charlotte Mussini: data interpretation, central histology review, and approval of final version. Sabine Irtan and Gaelle Pierron: data curation and interpretation, and approval of final version. Hervé J. Brisse, Laureline Berteloot, Salma Moalla, Pascale Philippe-Chomette, Bogdana Tilea, and Florent Guerin: data interpretation and approval of final version.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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REFERENCES

1. Coffin CM, Watterson J, Priest JR, et al. Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor). A clinicopathologic and immunohistochemical study of 84 cases. *Am J Surg Pathol*. 1995;19(8):859-872.
2. Kovach SJ, Fischer AC, Katzman PJ, et al. Inflammatory myofibroblastic tumors. *J Surg Oncol*. 2006;94(5):385-391.
3. Marie-Cardine A, Berrebi D, Orbach D. Guidelines for management of localized inflammatory myofibroblastic tumours in children. *Bull Cancer*. 2011;98(2):209-216.
4. Telugu RB, Prabhu AJ, Kalappurayil NB, et al. Clinicopathological study of 18 cases of inflammatory myofibroblastic tumors with reference to ALK-1 expression: 5-year experience in a tertiary care center. *J Pathol Transl Med*. 2017;51(3):255-263.
5. Gleason BC, Hornick JL. Inflammatory myofibroblastic tumours: where are we now? *J Clin Pathol*. 2008;61(4):428-437.
6. Coffin CM, Hornick JL. Inflammatory myofibroblastic tumor: comparison of clinicopathologic, histologic, and immunohistochemical features including ALK expression in atypical and aggressive cases. *Am J Surg Pathol*. 2007;31(4):509-520.
7. Li J, Yin WH, Takeuchi K, et al. Inflammatory myofibroblastic tumor with RANBP2 and ALK gene rearrangement: a report of two cases and literature review. *Diagn Pathol*. 2013;8:147.
8. Butrynski JE, D'Adamo DR, Hornick JL, et al. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. *N Engl J Med*. 2010;363(18):1727-1733.
9. Lovly CM, Gupta A, Lipson D, et al. Inflammatory myofibroblastic tumors harbor multiple potentially actionable kinase fusions. *Cancer Discov*. 2014;4(8):889-895.
10. Preobrazhenskaya E, Iyevleva A, Suleymanova A, et al. Gene rearrangements in consecutive series of pediatric inflammatory myofibroblastic tumors. *Pediatr Blood Cancer*. 2020;67:e28220.

11. Hornick JL, Sholl LM, Dal Cin P, et al. Expression of ROS1 predicts ROS1 gene rearrangement in inflammatory myofibroblastic tumors. *Mod Pathol*. 2015;28(5):732-739.
12. Alassiri AH, Ali RH, Shen Y, et al. ETV6-NTRK3 is expressed in a subset of ALK-negative inflammatory myofibroblastic tumors. *Am J Surg Pathol*. 2016;40(8):1051-1061.
13. Casanova M, Brennan B, Alaggio R, et al. Inflammatory myofibroblastic tumor: the experience of the European pediatric Soft Tissue Sarcoma Study Group (EpSSG). *Eur J Cancer*. 2020;127:123-129.
14. Trahair T, Gifford A, Fordham A, et al. Crizotinib and surgery for long-term disease control in children and adolescents with ALK-positive inflammatory myofibroblastic tumors. *JCO Precis Oncol*. 2019;3:1-11. https://doi.org/10.1200/PO.18.00297
15. Kube S, Vokuhl C, Dantonello T, et al. Inflammatory myofibroblastic tumors—a retrospective analysis of the Cooperative Weichteilsarkom Studiengruppe. *Pediatr Blood Cancer*. 2018;65(6):e27012.
16. Felkai L, Bánusz R, Kovalszky I, et al. The presence of ALK alterations and clinical relevance of crizotinib treatment in pediatric solid tumors. *Pathol Oncol Res*. 2019;25(1):217-224.
17. Qiu X, Montgomery E, Sun B. Inflammatory myofibroblastic tumor and low-grade myofibroblastic sarcoma: a comparative study of clinicopathologic features and further observations on the immunohistochemical profile of myofibroblasts. *Hum Pathol*. 2008;39(6):846-856.
18. Kallen ME, Hornick JL. The 2020 WHO classification: what's new in soft tissue tumor pathology? *Am J Surg Pathol*. 2021;45(1):e1-e23. https://doi.org/10.1097/pas.0000000000001552
19. Sbaraglia M, Bellan E, Dei Tos AP. The 2020 WHO classification of soft tissue tumours: news and perspectives. *Pathologica*. 2021;113(2):70-84.
20. Zhang N, Zeng Q, Chen C, et al. Clinical characteristics and prognosis of pulmonary inflammatory myofibroblastic tumor: an over 10-year retrospective analysis. *Pediatr Investig*. 2020;4(3):192-197
21. Wittekind C, Compton CC, Greene FL, et al. TNM residual tumor classification revisited. *Cancer*. 2002;94(9):2511-2516.
22. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213.
23. Favini F, Resti AG, Collini P, et al. Inflammatory myofibroblastic tumor of the conjunctiva: response to chemotherapy with low-dose methotrexate and vinorelbine. *Pediatr Blood Cancer*. 2010;54:483-485.
24. Gaudichon J, Jeanne-Pasquier C, Deparis M, et al. Complete and repeated response of a metastatic ALK-rearranged inflammatory myofibroblastic tumor to crizotinib in a teenage girl. *J Pediatr Hematol Oncol*. 2016;38(4):308-311.
25. Dishop MK, Kuruvilla S. Primary and metastatic lung tumors in the pediatric population: a review and 25-year experience at a large children's hospital. *Arch Pathol Lab Med*. 2008;132(7):1079-1103.
26. Rafee S, Elamin YY, Joyce E, et al. Neoadjuvant crizotinib in advanced inflammatory myofibroblastic tumour with ALK gene rearrangement. *Tumori*. 2015;101(2):e35-e39.
27. Mossé YP, Voss SD, Lim MS, et al. Targeting ALK with crizotinib in pediatric anaplastic large cell lymphoma and inflammatory myofibroblastic tumor: a Children's Oncology Group study. *J Clin Oncol*. 2017;35(28):3215-3221.
28. Sparber-Sauer M, Orbach D, Navid F, et al. Rationale for the use of tyrosine kinase inhibitors in the treatment of paediatric desmoid-type fibromatosis. *Br J Cancer*. 2021;124(10):1637-1646.
29. Orbach D, Sparber-Sauer M, Laetsch TW, et al. Spotlight on the treatment of infantile fibrosarcoma in the era of neurotrophic tropomyosin receptor kinase inhibitors: international consensus and remaining controversies. *Eur J Cancer*. 2020;137:183-192.
30. Mehta B, Mascarenhas L, Zhou S, Wang L, Venkatramani R. Inflammatory myofibroblastic tumors in childhood. *Pediatr Hematol Oncol*. 2013;30(7):640-645.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Pire A, Orbach D, Galmiche L, et al. Clinical, pathologic, and molecular features of inflammatory myofibroblastic tumors in children and adolescents. *Pediatr Blood Cancer*. 2022;69:e29460. https://doi.org/10.1002/pbc.29460