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Inflammatory myofibroblastic tumors in children☆

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ABSTRACT

Background: Inflammatory myofibroblastic tumor (IMFT) is an uncommon neoplasm in children.
Methods: Retrospective review from 1993 to 2014 of patients ≤18 years of age with a histopathologic diagnosis of IMFT treated at two tertiary centers.
Results: Thirty-two patients were diagnosed with IMFT. Mean (±SD) age was 9.3 ± 5.7 years at diagnosis. Tumor location was variable: abdomen/pelvis (28%), head/neck region (22%), intrathoracic (22%), genitourinary (9%), bowel (6%) liver (6%), and musculoskeletal (6%). Median follow-up was 2.6 ± 4.6 years, with 3 recurrences and 2 deaths, which occurred only after recurrence. Positive microscopic margin after resection was associated with recurrence, compared to those that had a negative margin (40% vs. 0%, $p = 0.04$). Recurrence was associated with increased mortality (67% vs 0%, $p = 0.01$). Time from first symptoms to resection was shorter in those with recurrence (25.8 ± 22 vs. 179 ± 275 days, $p = 0.01$) and in nonsurvivors (44.0 ± 8.0 vs. 194.3 ± 53.4 days, $p = 0.02$). Adjuvant chemotherapy, not including steroid monotherapy, either given before or after resection, was administered more often to nonsurvivors (100% vs 4%, $p = 0.009$), and use of corticosteroids was also higher in the nonsurvivors (100% vs. 15%, $p = 0.04$).
Conclusions: IMFT is a rare pediatric neoplasm with variable locations. Complete excision is critical for cure. Proposed guidelines for diagnosis, treatment and surveillance of theses tumors in children are reported.

Inflammatory myofibroblastic tumor (IMFT), also known as inflammatory pseudotumor, is a rare and poorly understood neoplasm. IMFTs are composed of inflammatory cells and mesenchymal spindle cells and can occur in variable anatomic locations; although they are most commonly found in the lung or liver [1–7]. Originally described by Umiker and Iverson in 1954, IMFT was felt to be a benign inflammatory process, but some have malignant behavior or can undergo malignant transformation [8–11]. These tumors are difficult to distinguish from other neoplasms based on radiographic imaging alone and histologic analysis is required to establish the diagnosis [12]. Complete surgical resection serves as the only known cure for this disease process [13]. Because of the rare nature of IMFT, guidelines have yet to be established for ideal management of these tumors based on specific location and extent of disease. Therefore, we reviewed the experience of two tertiary referral centers to more clearly define the natural history of the disease and patient outcomes. Proposed guidelines for diagnosis, treatment and surveillance are also reported.

1. Methods

With institutional review board approval from both centers, a retrospective review was performed on patients ≤18 years of age with a diagnosis of IMFT from 1993 to 2014. Patient medical records were reviewed and the following data were obtained: patient demographics, presenting clinical symptoms and signs, diagnostic evaluation, treatment(s) pursued, pathologic results, immunohistochemical (IHC) analysis, tumor cytogenetics, tumor recurrence, and rates of survival. Data for continuous variables are expressed as mean ± standard deviation unless otherwise stated. Statistical comparisons were made using unpaired Student's *t* test for continuous data and chi-square (with Yates correction) or Fisher's exact test for nominal data depending on the sample size.

2. Results

Over the study period, 32 patients had histopathologically confirmed IMFT using the World Health Organization definition. Patient characteristics are outlined in Table 1. The mean age at diagnosis was 9.3 ± 5.7 years and the mean age at resection was 9.5 ± 5.7 years; 56% of patients were female. Mean follow-up was 2.6 years (range 1 month to 18 years) including 7 patients who were lost to follow-up.

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Table 1
Patient characteristics.

Pt	Age	Presentation	Primary	Treatment	Years of follow-up	Recurrence	Survival
1	13	Unknown	Lung	CE	0.1	No	Yes
2	4	Abdominal pain	Liver	CE	10.5	No	Yes
3	15	Abdominal mass	Pelvis	excision	6.5	No	Yes
4	0.7	Recurrent Epistaxis	Nasopharynx	Neoadjuvant, CE	3.9	No	Yes
5	17	Abdominal mass	Pelvis	excision	0.2	No	Yes
6	1	Lymphadenopathy	Neck	CE	0.2	No	Yes
7	4	Cough, dyspnea	Mediastinum	excision	3.7	No	Yes
8	13	Abdominal pain	Abdomen	CE	0.1	No	Yes
9	13	Dysphonia	Face	excision, steroids	2.1	No	Yes
10	3	Stridor	Trachea	excision, steroids	1.2	No	Yes
11	6	Feeding intolerance	Colon	CE	2.9	No	Yes
12	0.9	Unknown	Abdomen	CE	18.6	No	Yes
13	17	Unknown	Nasopharynx	excision	2.4	No	Yes
14	2	Abdominal mass	Abdomen	CE	14.2	No	Yes
15	18	Testicular mass	Testicle	CE	10.5	No	Yes
16	1	Fever, lethargy	Abdomen	CE	7.5	No	Yes
17	12	Dyspnea	Lung	CE	0.1	No	Yes
18	13	Gluteal mass	Musculoskeletal	CE	4.2	No	Yes
19	8	Chest pain	Lung	CE	10.0	No	Yes
20	10	Constipation	Bladder	Neoadjuvant, CE	5.1	No	Yes
21	17	Chest pain	Lung	CE	0.5	No	Yes
22	14	Hemoptysis	Lung	CE	4.0	No	Yes
23	16	Dysuria	Bladder	CE	4.4	No	Yes
24	6	Fever, lethargy	Stomach	CE	4.0	No	Yes
25	1	Palpable mass	Musculoskeletal	CE	2.4	No	Yes
26	13	Wheezing	Trachea	PE	1.6	No	Yes
27	7	Jaundice	Liver	PE	0.2	No	Yes
28	11	Abdominal mass	Abdomen	PE	1.9	No	Yes
29	8	Cough, pneumonia	Lung	PE, adjuvant	1.3	No	Yes
30	9	Lymphadenopathy	Neck	PE, steroids	11.0	Yes	Yes
31	13	Constipation	Pelvis	PE, adjuvant, steroids	0.4	Yes	No
32	6	Fever, lethargy	Abdomen	excision, adjuvant, steroids	1.6	Yes	No

CE = complete excision, PE = partial excision (microscopic of gross + margin), excision = unknown margin status.

Tumor location varied among patients. The most common site of occurrence was in the abdomen/pelvis ($n = 9$). Seven patients had IMFT in both the head/neck and thoracic regions. Three patients were found to have an IMFT arising from the genitourinary tract. Two patients each were found to have IMFTs in the GI tract, liver and musculoskeletal system. Four patients reported prior infection involving the organ system (3 lung, 1 bladder). One patient with a history of a myeloproliferative disorder was found to have an IMFT in her left neck. IMFT was also identified in the testicle of a patient with aplastic anemia. Only three patients presented with constitutional symptoms (fever, lethargy), all of whom had abdominal IMFT.

Twenty-eight patients had information about their diagnostic imaging. Computed tomography (CT) was used most frequently. In 10 patients (35%) more than one modality was utilized. The use of different imaging modalities is as follows: CT (79%), ultrasound (25%), magnetic resonance imaging (18%), and plain films (11%). Not all patients had inflammatory markers drawn at the time of diagnosis. However, only one patient (4%) had an elevated white blood cell count ($N = 25$), while a larger percentage had elevated erythrocyte sedimentation rate (70%, $N = 10$) or C-reactive protein (70%, $N = 10$).

A preoperative biopsy was performed in 15 patients and the initial pathology was inaccurate in 4 patients, who were initially diagnosed with nodular fasciitis, rhabdomyosarcoma, and lymphohistiocytic infiltrate with squamous metaplasia. Needle biopsy was utilized in 7 patients and was inaccurate in 3. Incisional or excisional biopsy was used in eight patients and was accurate in 7 patients. The remainder of patients were diagnosed at the time of definitive resection. Two patients received neoadjuvant therapy based on the biopsy results. The first patient, by preliminary pathology results, was diagnosed with rhabdomyosarcoma. The patient was started on vincristine and cyclophosphamide with resultant decrease in size of the mass. Final pathology of the biopsy revealed IMFT of the nasopharynx with extension to the orbit. The tumor was then completely excised endoscopically. The second patient was initially misdiagnosed with rhabdomyosarcoma; and after complete resection by a partial cystectomy with ureteral reimplantation, IMFT was diagnosed. Both are still disease free.

Immunohistochemistry (IHC) was not standardized for all patients over the time period of the study and, accordingly, the markers studied by IHC were highly variable. Vimentin, actin, Alk-1, and CD68 had a high rate of positive staining whereas S-100 and myogenin had a high rate of negative staining. The results for the most commonly utilized markers are outlined in Table 2. Cytogenetics was available in 11 patients, with 5 abnormalities. However, the tumors did not share common changes in the cytogenetic profile. Two patients with cytogenetically abnormal tumors suffered recurrence of the tumor.

All children underwent surgical excision of the tumor. Mean tumor size was 6.4 ± 1.0 cm. Six patients had partial excision: 5 with microscopically positive margins, and gross disease remained for one patient because of unresectability. Seven patients had excision but margin status was not available. Nineteen patients had pathology confirmed margin negative status or complete excision. There were no recurrences when the margin status was microscopically negative. Alternatively, a positive microscopic margin after resection was associated with a higher recurrence rate (40 vs 0%, $p = 0.04$). All 4 known recurrences occurred within one year of original resection. Overall survival was 94%.

Table 2
Immunohistochemistry results.

	Positive stain (%)	Negative stain (%)
Vimentin	10 (100)	0 (0)
Actin	15 (88)	2 (12)
Alk-1	10 (56)	8 (44)
CD68	7 (100)	0 (0)
S-100	1 (8)	12 (92)
Myogenin	0 (0)	11 (100)