TREATMENT AND OUTCOMES IN PEDIATRIC INFLAMMATORY MYOFIBROBLASTIC TUMORS – A SYSTEMATIC REVIEW OF PUBLISHED STUDIES

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Abstract

Inflammatory myofibroblastic tumor (IMT) is a soft tissue neoplasm which can be locally invasive, recur, or in rare cases metastasize. Often originating from the abdomen or thorax, IMT most commonly affects children and young adults. Due to its rarity comprehensive reports detailing clinical management and outcome(s) are sparse and often based on limited index case numbers. This study systematically analyzes outcome metrics of pediatric IMT and identifies risk factors for mortality. Medline/Embase databases were searched in accordance with PRISMA guidelines. Final analysis included 57 studies with 673 IMT patients (355 males, 53%). Individual patient data was available for 405 cases with a median follow-up period of 36 months. Tumor sites included abdomen/pelvis (n=233, 58%), thorax (n=125, 31%), head/neck (n=34, 8%), and extremities (n=13, 3%). Surgical tumor resection was the mainstay of treatment, while only 20 patients (5%) were treated non-operatively. Recurrence(s) were reported in 80 patients (20%) with 34 (12%) requiring reoperation. Positive tumor margins were a significant risk factor for tumor recurrence ($p<0.0001$). Chemo/radiotherapy was reported in 98 patients (25%). Most patients (94%) survived; 81% (n=237) with no evidence of recurrent disease, 14% (n=41) were alive with disease, and 25 (6%) died of disease. Positive margins at primary operation, and metastatic disease were associated with mortality ($p<0.0001$ for both). IMT is a rare tumor with favorable outcome for the majority of patients. Whilst most patients will present with benign tumors, complete surgical resection (R0) is crucial, as positive surgical margins are a significant risk factor for tumor recurrence and mortality.

Keywords: inflammatory myofibroblastic tumor; pediatric; plasma cell granuloma; outcome(s)

Abbreviations: IMT – inflammatory myofibroblastic tumor; ALK - anaplastic lymphoma kinase

Introduction

Inflammatory myofibroblastic tumor (IMT), also known as inflammatory pseudotumor or plasma cell granuloma, is a spindle cell soft tissue tumor which can be locally invasive, recur, or in rare cases metastasize [1]. This tumor, often originating from the thorax or abdomen, most commonly affects children and young adults with a median age of 9 year at diagnosis [2, 3]. Symptoms vary depending on the tumor location and size. It is estimated that one third of the IMT patients have systemic manifestations such as fever, malaise, growth deficiency or anemia [3, 4].

Complete surgical tumor resection is the mainstay of treatment for localized IMT. However, this may not be feasible in advanced stage disease or in those considered to harbor inoperable tumor sites. Conservative treatment options have traditionally included high-dose corticosteroids, non-steroidal anti-inflammatory drugs, and chemotherapeutics such as methotrexate and vincristine, and / or local radiotherapy [3, 4]. Anaplastic lymphoma kinase (ALK), which is positive in almost half of IMTs, presents a promising target for ALK inhibition personalized therapy(s) [5].

Due to the rarity of IMT, comprehensive reports detailing clinical management and outcome(s) are sparse and often based on very limited index case numbers. Against this background, this study aims to systematically analyze the outcomes of pediatric IMT and identify pertinent risk factors for mortality.

Material and Methods

Identification and Selection of Studies

According to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [6], a comprehensive search in PubMed and Embase databases was performed using the following terms as keywords: ‘inflammatory myofibroblastic (tumor)’ and ‘plasma cell granuloma’ in combination with terms ‘child’, ‘p(a)ediatric’, ‘outcome(s)’, ‘adolescent’, ‘surgery’, and ‘teenagers and young adults’. All articles published up to February 29, 2024, were included in the final study review.

Inclusion and Exclusion Criteria

All original articles reporting on outcomes of pediatric IMT (0 – 18 years) were included in the study. Non-English language papers, and case reports (<3 patients) were excluded with title and abstract screening. We excluded papers where pediatric patients could not be analyzed separately from adult ones and those where IMT could not be analyzed separately from other diagnoses. Also, manuscripts with insufficient numbers (<3) of pediatric IMT patients were similarly excluded - (Figure 1).

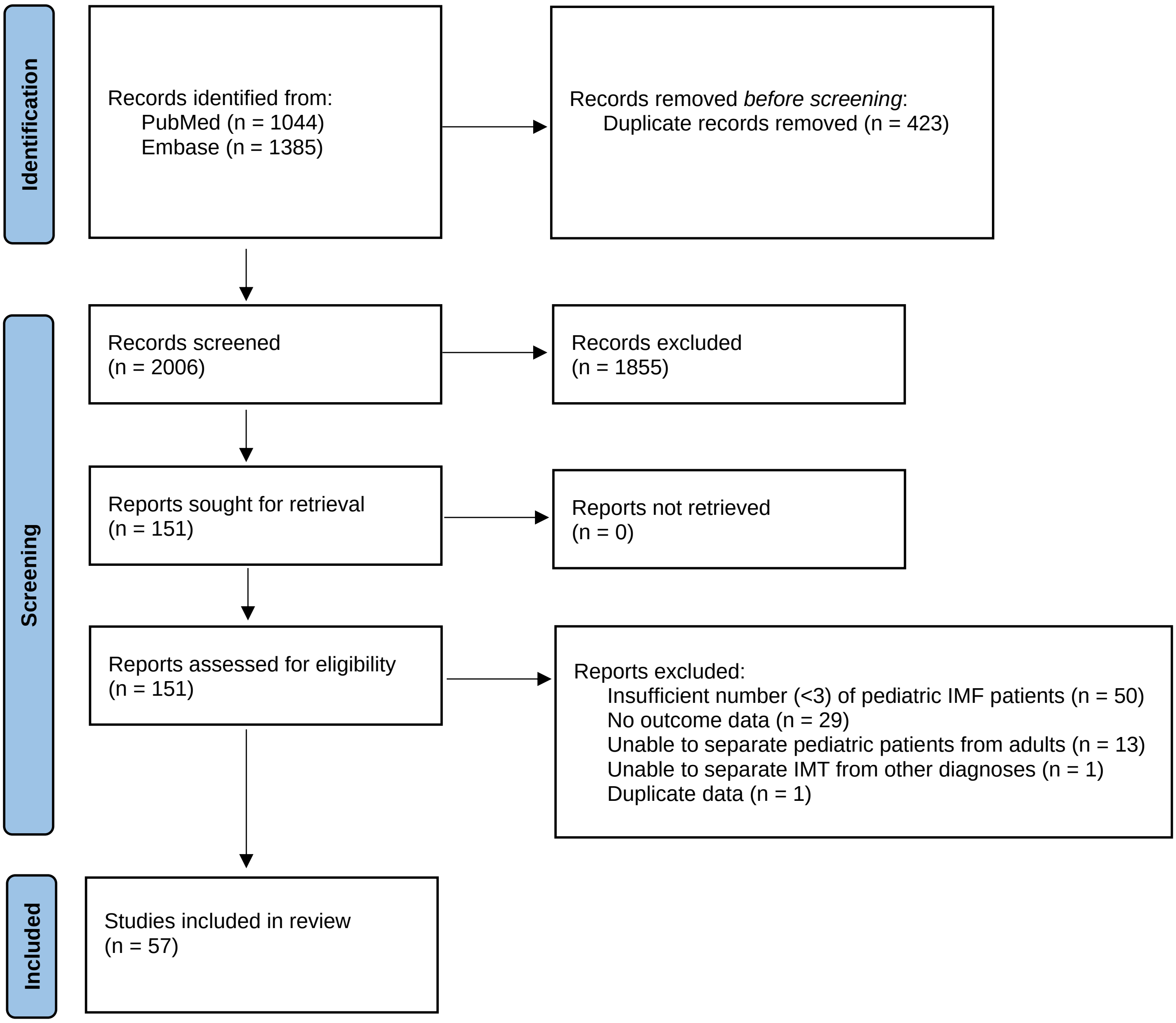

Figure 1. PRISMA study selection flow diagram.

Data Extraction and Analysis

Identified papers were independently reviewed by both study authors and final selection approved by the senior author (PDL). The extracted data included patient sex, tumor size, location, histology and immunohistochemical features, treatment, length of follow-up, outcome(s), and mortality. Surgical resection was defined as complete (no residual tumor with clean margins) or incomplete (residual tumor and/or tumor extension to resection margin) where available.

Statistical Analysis

Chi-Square and Fisher's exact tests were utilized to analyze categorical variables. A significance level of $p \leq 0.05$ (two-tailed) was set. Analyses were performed using JMP Pro, version 17.0.0 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

The initial search through different databases identified 2398 and a total of 1985 studies were then evaluated in screening of titles and abstracts after exclusion of duplicates. Inclusion criteria were met in 150 papers and those were retrieved for full text review. After full text review, the final analysis included 57 studies (Figure 1) with 673 IMT patients (355 males, 53%). The published studies covered the time period(s) 1986 – 2024 [2-4, 7-60] and the number of individual patients ranged from 3 to 60.

Individual patient data was available for 405 patients (42 studies) with a median follow-up period of 36 months. The median age at diagnosis was 84 months (7 years) with equal gender distribution (175 males, 50%). Tumor sites included abdomen/pelvis (n=233, 58%), thorax (n=125, 31%), head/neck (n=34, 8%), and extremities (n=13, 3%). Surgical tumor resection was the mainstay of treatment, while only 20 patients (5%) were treated nonoperatively. Nonoperative management was typically more common in tumors located in the extremities (15%) and head/neck (15%) than in thoracic (3%) or abdominal cavity tumors (4%), p=0.04). Recurrence(s) were reported in 80 patients (20%) with 34 (12%) requiring reoperation. Chemo/radiotherapy was reported in 98 patients (25%). Most patients (94%) survived; 81% (n=237) with no evidence of disease, 14% (n=41) were alive with disease, and 25 (6%) died of disease. Positive tumor margins were a significant risk factor for tumor recurrence, reoperation, and mortality - (Table 1). Similarly, metastatic disease was associated with mortality (%) (p<0.0001).

	Negative tumor margin	Positive tumor margin	P value
Reoperation	16 (9.8%)	15 (22.7%)	0.0013
Tumor recurrence	14 (6.8%)	54 (51.0%)	<0.0001
Mortality	2 (1.0%)	14 (13.2%)	<0.0001

Table 1. Positive tumor margin at primary resection was a significant risk factor for reoperation, tumor recurrence and mortality.

Anaplastic lymphoma kinase (ALK) status was reported in 229 (positive in n=112, 49%) patients with no association on outcome(s) including tumor recurrence and mortality. Other immunohistochemical analyses were sparsely available in the included eligible published studies. Fluorescent in situ hybridization (FISH) was reported in 39 patients, Desmin in 48, cytokeratin (CK) in 27, smooth muscle actin (SMA) in 44, Vimentin in 25, and Myogenin in 13. None of these markers were associated with disease outcome. Similarly, patient sex, age, tumor location and size were likewise not associated with the outcome(s).

Discussion

This systematic review clearly demonstrates that pediatric IMT is a benign tumor in the majority of affected patients. However, incomplete surgical resection in the primary operation predisposes patients to recurrence and ultimately mortality, which was seen in 6% of the index population.

The current study observed a tumor recurrence rate of 20%, which is comparable with previous reports from the European pediatric Soft Tissue Sarcoma Study Group [13] and Italian Cooperative study group [8] studies with 83% and 73% 5-year and 10-year event-free survival, respectively. Previous studies including those having more than ten patients reported variable survival rates ranging from 85% to 100%

[33, 54]. According to our current study we now report - IMT appears to be associated with a 6% mortality rate which was observed in both the complete analysis of some 56 studies (41 mortalities in 673 patients, 6.1% mortality) and from the individual patient data sets (25 deaths in 405 patients, 6.2% mortality). Alaggio et al. concluded that the treatment of choice for IMT is a complete, non-mutilating tumor excision complemented by chemotherapy in patients with microscopic or macroscopic tumor residue [8]. The key importance of complete surgical resection (R0) at index operation was further emphasized by the findings of this systematic review study we now report where positive tumor margins were a significant risk factor for tumor recurrence as well as mortality.

According to the literature, some 50% of IMTs are apparently positive for ALK [3, 5]. These findings are supported by the data from this comprehensive systematic review reporting 49% of IMT tumors positive for ALK. Alaggio et al. reported that positive ALK status is more frequent in those patients with seemingly aggressive tumors but of interest those considered with truly malignant ‘ like behaviour ‘ with metastatic disease sites were ALK negative in their series. We observed no significant differences in ALK status regarding tumor recurrence(s) - (43% ALK positive with recurrence vs. 51% ALK positive without recurrence, p=0.28) nor in metastasizing IMT (71% ALK positive in metastatic IMT vs. 48% ALK positive non-metastatic IMT, p=0.11). Regardless, ALK status was not associated with mortality risk (%) in the current study and these findings were similarly reported in the largest single individual study of 60 IMT index patients by the European Pediatric Soft Tissue Sarcoma Study Group [13].

Tumor location had no impact on the health outcomes of pediatric IMT regardless of the difference(s) in rates of surgical resection vs. nonoperative management. This difference is perhaps we believe partially a reflection of the inclusion of orbital tumors in head/neck tumor groups, where the majority are not readily amenable for full surgical resection [56]. Also noteworthy in this current study there were only 13 patients with IMT in extremity sites with two of the affected patients treated non-operatively.

To the best of our knowledge, this is the first comprehensive systematic review study seeking to address and more fully understand the behavior of this rare fascinating tumor. We fully acknowledge there are certain inherent limitations to the current study including variations in follow-up times, methods of data reporting, and incomplete data on tumor immunohistochemistry.

Conclusion

Pediatric IMT is a very rare neoplasm largely presenting as a benign tumor with favorable outcomes in the majority of index patients. Regardless, complete surgical resection (R0) is crucial, as positive surgical margins are a significant risk factor for tumor recurrence and mortality (%).

Author Contributions

The study was conceived and designed by PDL. AR conducted the literature review, data collection, analysis, and interpretation under supervision by PDL. The manuscript was first drafted by AR. All authors have fully participated in manuscript drafting, editing and revisions and approved the final submitted manuscript.

Declaration of Competing Interest

Dr Raitio reports research grants from Päivikki and Sakari Sohlberg Foundation. Funder had no role in the current study.

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