RESEARCH ARTICLE

Clinical Importance of Lymphocytopenia in Pediatric Head and Neck Lymphatic Malformations

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Abstract

Introduction: Small case series have suggested that lymphocytopenia may be associated with a more aggressive lymphatic malformation (LM) disease course; however, the clinical importance of lymphocytopenia in the setting of LM still remains unclear. The objective of this study was to determine if LM-associated lymphocytopenia was associated with higher rates of antibiotic use and more frequent hospitalizations for infections.

Methods: An IRB-approved, retrospective case series review was performed on all patients with the ICD-10 codes corresponding to LM between 2008 and 2018 at a single institution. Patients with a complete blood cell count and lymphocyte differential were included. Lymphocytopenia was defined as <1500/cm^3. Variables including LM location, lymphocyte count, frequency and duration of antibiotic utilization, and number of infection-related hospitalizations were recorded. Data was analyzed with Mann-Whitney U and Fisher's Exact tests.

Results: From a total of 131 patients with a diagnosis of head and neck lymphatic malformation, there were 45 pediatric patients with documented laboratory values included in the cohort. Lymphocytopenia was present in 24 (53%) patients. There were no differences in the number of patients requiring hospitalization for infection (8 vs 7, p=1.000), mean length of hospital stay (0.38 vs 0.48, p=0.891), or mean duration of antibiotic course (14 vs 15 days, p=0.833) between those with and without lymphocytopenia, respectively. Similarly, the subset of 5 patients on sirolimus treatment had no increased infection-related parameters when compared to the remainder of the cohort.

Discussion: Lymphocytopenia was not associated with higher rates of infection requiring hospitalization or increased duration of antibiotic course in head and neck LM. Furthermore, patients receiving sirolimus did not incur higher rates of infection. Larger prospective studies are needed to follow disease course in patients with and without LM-associated lymphocytopenia.

Introduction

Lymphatic malformations (LM) are congenital vascular anomalies that consist of abnormal lymphatic channels. These malformations are most commonly seen in the head and neck, resulting in significant cosmetic and functional sequelae[1,2]. Infection can be a complication for patients with LM, particularly microcystic or mixed suprahyoid lesions with mucosal involvement[2,3]. Some patients present with recurrent local infections as well as systemic infections that can significantly impact vital functions such as breathing and swallowing, raising the question of whether or not LM patients have systemic immune dysfunction as a consequence of the abnormal lymphoid growth[4].

Studies have shown a correlation between patients with large bilateral or microcystic LM and significant lymphocytopenia involving T, B, and NK cell subsets[5]. The authors postulate that lymphocytopenia may be a consequence of the development of the LM, as there is no histologic evidence to support lymphocyte sequestration within the malformation itself. This finding further brings into question the functional impact of low circulating lymphocytes.

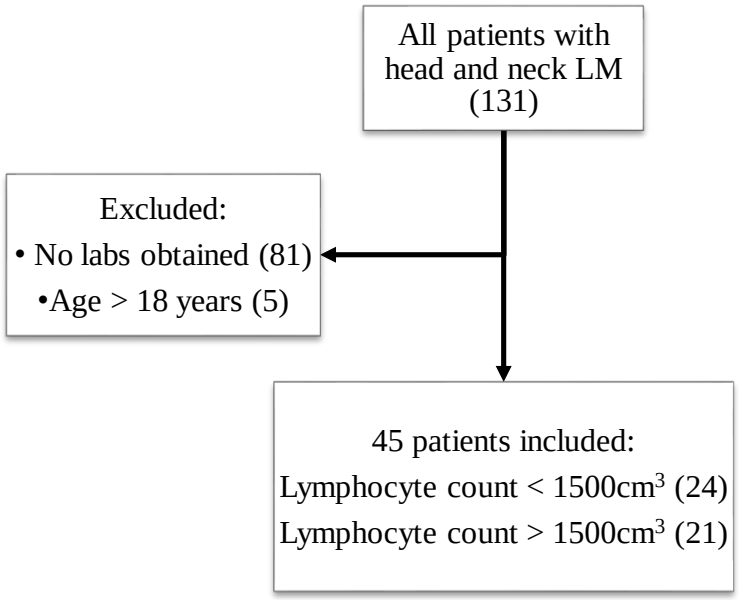
A small case series has suggested an increase in hospitalization, rate of infection, and increase antibiotic use in patients with LM associated lymphocytopenia[6]. These data do not show causality between lymphocytopenia and related infectious clinical outcomes and recurrent infections may simply be a result of significant chronic disease. Given that the clinical importance of lymphocytopenia in the setting of LM remains unclear, our objective was to evaluate a larger cohort to determine if lymphocytopenia in LM patients was associated with higher rates of antibiotic use or infections requiring hospitalization when compared to LM patients with a normal lymphocyte count.

Methods

This study was approved by the Children's Hospital of Pittsburgh Institutional Review Board. A retrospective review of consecutive patients from 2006 to 2018 with a diagnosis of head and/or neck lymphatic malformation who were captured in a pre-existing registry through the Vascular Anomalies clinic was performed. Patients over 18 years of age and patients without documented complete blood cell count and lymphocyte differential were excluded from analysis (Figure 1). Clinical data was collected for each patient including: patient demographics, LM location, absolute

lymphocyte count, De Serres stage, sirolimus use, frequency and duration of antibiotic utilization, and number of infection-related hospitalizations[7]. Lymphocyte count could have been collected at any time during clinical diagnosis or management. In keeping with previously published literature, lympho-cytopenia was defined as a lymphocyte count less than 1500 cm^3 and all patients were categorized into two groups, with and without lymphocytopenia[6,8].

Figure 1: Flow diagram detailing study inclusion criteria for pediatric patients with head and neck lymphatic malformation.



Descriptive statistics were used to report the prevalence of LM, LM location, LM stage, sirolimus use, and frequency and duration of antibiotic use and number of infection-related hospitalizations. Patient groups with and without lymphocytopenia were compared using Mann-Whitney U and Fisher's Exact tests. The relationship between sirolimus use and clinical measures of infection was assessed using Fisher's Exact test.

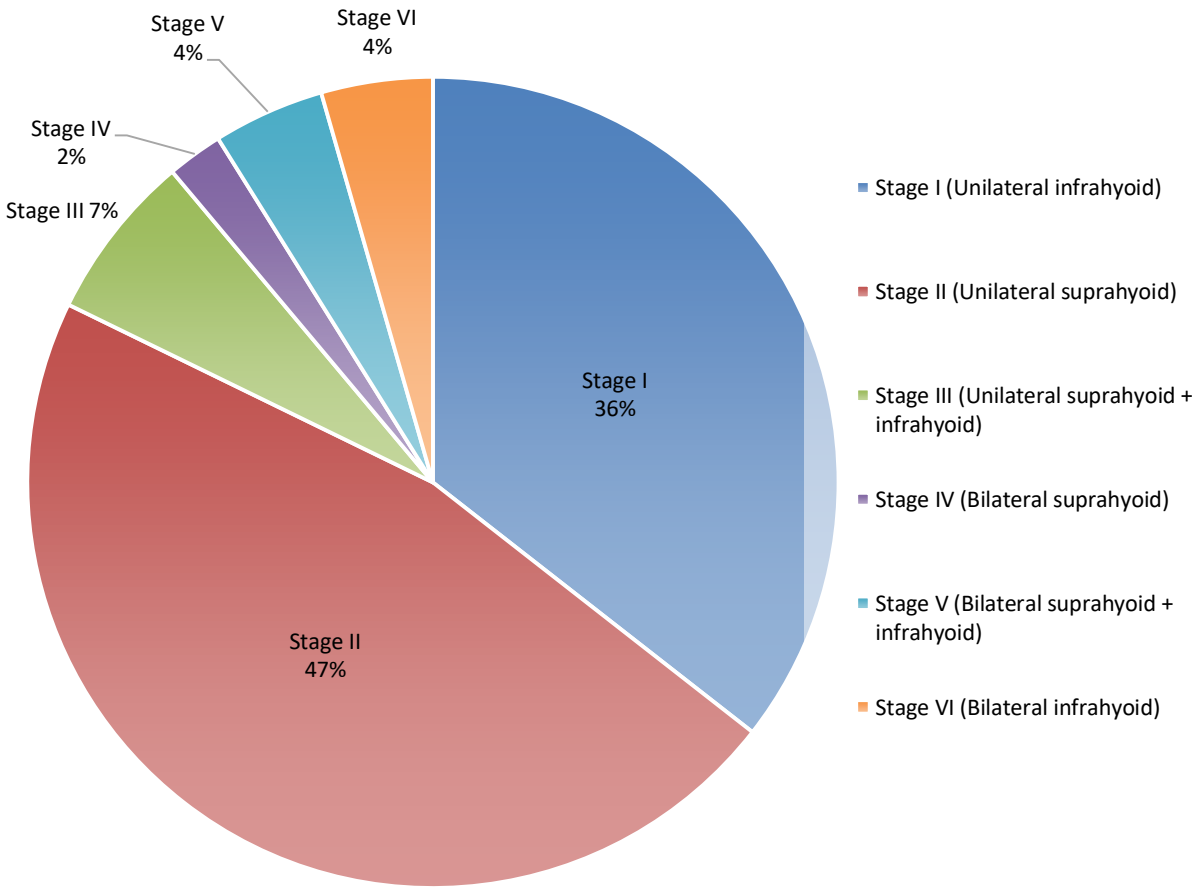
Results

From a total of 131 patients with a diagnosis of head and neck lymphatic malformation, patients were excluded for age > 18 years at time of initial clinic appointment (5 patients)

and lack of documented laboratory values (81 patients). There were 45 patients who met inclusion criteria. Mean age at the time of first evaluation for LM was 5.9 years (range 0-17). Twenty-five patients (56%) were male. Forty-one patients (91%) were Caucasian and 4 (9%) African American. In laboratory value evaluation, twenty-four patients (53%) were lymphocytopenic and 21 (47%) had a normal lymphocyte count.

With respect to the DeSerres LM staging (Figure 2), the majority of patients were classified as either stage I (16 patients; 36%) or stage II (21 patients; 47%). Of stage I patients, 4 had mediastinal extent of disease. There were 3 patients with macroglossia due to tongue involvement. No patients had isolated tongue disease.

Figure 2: De Serres lymphatic malformation staging of study cohort.



Of the 45 patients with head and neck LM, 15 required at least one hospitalization related to site-specific infection. As shown in Table I, when comparing patients with and without lymphocytopenia, there was no difference with respect to the frequency of patients requiring hospitalization for infection (8 (33%) versus 7 (33%), p=1.000) nor the mean number of infection-related hospitalizations when analyzed as a continuous variable (0.38 versus 0.48, p=0.891). Similarly, neither the duration of antibiotic course nor the mean length of hospital stay was significantly different between groups, p>0.05.

There were 4 patients requiring 2 or more hospitalizations for infection, with 1 patient with lymphocytopenia and 3 without lymphocytopenia. No patients required a central line nor were hospitalized for infection in a location other than localized to the site of LM. No patients were placed on empiric antibiotic prophylaxis. Two patients were treated with a 4-week antibiotic course for infection.

Table 1: Infection-related outcome measures in head and neck lymphatic malformation patients with and without lymphocytopenia.

	Lymph < 1500cm^3 (n=24)	**Lymph > 1500cm^3 (n=21)**	***p* value**
Patients with ≥ 1 infection-related hospitalization (%)	8 (33.3)	7 (33.3)	p=1.000
Mean infection-related hospitalizations/patients (SD)	0.38 (0.58)	0.48 (0.81)	p=0.891
Mean length of hospital stay, days (SD)	6.6 (6.9)	3.8 (2.0)	p=0.329
Mean duration of antibiotic course, days (SD)	13.6 (9.1)	14.8 (12.1)	p=0.833

With respect to sirolimus treatment, there were 5 total patients receiving Sirolimus, 4 of whom were lymphocytopenic and 2 required hospitalization for infection. Patients treated with sirolimus did not have increased length of hospital stay nor increased duration of antibiotic course when compared to the subset of patients not receiving sirolimus (4 compared to 5 days, p=0.547 and 9 compared to 15 days, p=0.229, respectively).

Discussion

Head and neck lymphatic malformations remain a source of significant cosmetic, functional, and infectious sequelae for patients. Our series describes 45 pediatric patients with head and neck LM at a single tertiary care institution, with 33% of patients requiring at least one hospitalization for infection. In our series, infection-related parameters including hospitalization frequency, length of hospital stay, and the duration of antibiotic course was not different between patients with and without lymphocytopenia.

In 2007, Perkins et al described a 20-patient cohort with head and neck LM, finding significantly increased hospital admission rates, antibiotic prophylaxis, and mean number of antibiotic courses per year amongst patients with lymphocytopenia compared to patients with a normal lymphocyte count[6]. Interestingly, our results somewhat contrast these data, yielding no difference in infection parameters between patients with and without lymphocytopenia. This discrepancy is likely, at least in part, due to differences in study endpoints, as our data analyze infection-related hospitalization rates rather than all-cause admissions. Moreover, our institution tends towards lesser use of chronic antibiotic prophylaxis in all patients with LM, with only 1 patient without lymphocytopenia and 1 patient with lymphocytopenia receiving a 4-week antibiotic course following an infection.

In addition to the limitation inherent within retrospective review, the majority of patients evaluated within our vascular anomalies multi-disciplinary outpatient clinic do not routinely undergo screening laboratory work. As such, there exists significant selection bias towards patients who develop infectious or other disease-related complications in meeting study inclusion criteria, as the majority of patients with head and neck LM were excluded from our patient cohort due to lack of laboratory values (81 of 131 patients). While our study does represent the largest currently reported series of head and neck LM patients with respect to lymphocytopenia and

infection parameters, our patient cohort still remains relatively small. Our cohort captured only LM patients that were previously entered into a database through the Vascular Anomalies Clinic. Furthermore, the diagnosis of "infection" remains variable. Using more objective data in the future studies such as presence or absence of parameters such as fever, redness, and swelling may more accurately document the presence of infection.

As ablative and excisional treatment options to address LM have the potential for incomplete treatment and/or risk to critical neurovascular structures throughout the head and neck, the potential role for sirolimus therapy has emerged in recent years[9]. While the optimal role for sirolimus in the current treatment algorithm remains somewhat unclear, preliminary studies show promise particularly with respect to treating large, high-stage lesions[10-11]. While only 5 patients within our series received sirolimus, infection-related parameters were interestingly not different from the remainder of the cohort.

In the current treatment paradigm of patients with LM, the use of empiric chronic antibiotics in patients with recurrent infections is institution- and provider-dependent[2]. The etiology of these recurrent infections and the importance of host immune factors including lymphocytopenia remain unclear[12]. As our understanding of the genetic basis of LM and available treatment strategies grow, lymphocytopenia, infection risk, and optimal antibiotic management amongst LM patients will be optimally studied in a prospective, randomized fashion in order to optimize treatment algorithms for the management of head and neck lymphatic malformations.

Conclusions

In our series, 33% of pediatric patients diagnosed with head and neck LM developed at least one LM-related infection requiring hospitalization. Lymphocytopenia was not associated with higher rates of infection requiring hospitalization or increased duration of antibiotic course in head and neck LM. Larger, prospective studies are needed to follow disease course in patients with lymphatic malformations of the head and neck.

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