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Active Observation as an Alternative to Invasive Treatments for Pediatric Head and Neck Lymphatic Malformations

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Objectives: An increasing number of treatment modalities for lymphatic malformations are being described, complicating therapeutic decisions. Understanding lymphatic malformation natural history is essential. We describe management of head and neck lymphatic malformations where decisions primarily addressed lesion-induced functional compromise (ie, breathing, swallowing) to identify factors associated with invasive treatment and active observation. We hypothesize that non-function threatening malformations can be observed.

Study Design: Retrospective case series.

Methods: Retrospective case series of consecutive head and neck lymphatic malformation patients (2000–2017) with over 2 years of follow-up. Patient characteristics were summarized and associations with invasive treatment (surgery or sclerotherapy) tested using Fisher's exact. In observed patients, factors associated with spontaneous regression were assessed with Fisher's exact test.

Results: Of 191 patients, 101 (53%) were male, 97 (51%) Caucasian, and 98 (51.3%) younger than 3 months. Malformations were de Serres I–III 167 (87%), or IV–V 24 (12%), and commonly located in the neck (101, 53%), or oral cavity (36, 19%). Initial treatments included observation (65, 34%) or invasive treatments such as primary surgery (80, 42%), staged surgery (25, 13%), or primary sclerotherapy (9, 5%). Of 65 initially observed malformations, 8 (12%) subsequently had invasive treatment, 36 (58%) had spontaneous regression, and 21 (32%) elected for no invasive therapy. Spontaneous regression was associated with location in the lateral neck (P = .003) and macrocystic malformations (P = .017).

Conclusion: Head and neck lymphatic malformation treatment selection can be individualized after stratifying by stage, presence of functional compromise, and consideration of natural history. Recognizing the spectrum of severity is essential in evaluating efficacy of emerging treatments, as selected malformations may respond to observation.

Key Words: Lymphatic malformation, lymphatic abnormalities, head and neck, treatment, observation, surgery.

Level of Evidence: 4

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INTRODUCTION

Head and neck lymphatic malformations (HNLM) are rare, congenital, low-flow vascular lesions that arise from abnormal lymphatic system development, through activating somatic mosaic mutations in the phosphatidylinositol-4,5-bisphospate 3-kinase, catalytic subunit alpha (*PIK3CA*) gene.[1,2] Optimal HNLM treatment is debated and much of the existing medical literature does not provide high-level evidence to support known treatment modalities.[3,4] Now that the presence of genotypic mosaicism within HNLM cells is known, HNLM treatment algorithms need review.[5]

Lymphatic malformations (LM) have an estimated incidence of 1.2 to 2.8 in 10,000 live births, and are often detected in-utero.[6,7] LM are most common in the head and neck, and their presence can compromise normal function, development, and quality of life.[8] Bilateral, midface, suprahyoid HNLM (De Serres stage II, IV, V) cause facial disfigurement through soft and bony tissue asymmetry. The resulting facial disproportion (ie, mandibular hypertrophy, malocclusion, macroglossia, etc.) causes dysfunction in mastication, dental hygiene, and swallowing, and affects psychological development and social and community interactions. HNLM primarily in the lateral neck (De Serres stage I and III) present as large cystic masses that can also impair swallowing, breathing, and cause disfigurement, but are not always associated with oral and pharyngeal mucosal disease, and sometimes can regress spontaneously. In general, more extensive, bilateral HNLM induce greater dysfunction and are associated with more systemic symptoms (ie, lymphocytopenia).[8–10]

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HNLM can be treated with surgery and/or sclerotherapy. Current evidence suggests that both treatment modalities are likely equally effective for low De Serres stage neck lesions.[3,11] Spontaneous HNLM regression has been reported especially with lateral macrocystic neck lesions.[9,12,13] Refining the type and timing of HNLM therapy is difficult, especially since the exact developmental molecular/cellular mechanisms are not known and treatment goals/endpoints are not well defined in the literature. Now that there are novel medications that suppress *PIK3CA* activation and have HNLM treatment potential, understanding optimal treatment for specific types of HNLM is essential.[5,14–16]

Since invasive treatment of patients under 6 months of age increases procedure frequency and some HNLM regress without treatment, Seattle Children's vascular anomalies program adopted a conservative, shared decision-making model for HNLM not causing functional compromise in 2000; this is a significant change in our management philosophy.[11,12,17,18] At diagnosis, after thorough HNLM evaluation and staging, treatment plans are developed with patient family input with a goal of reducing the number of invasive procedures and episodes of anesthesia. Invasive interventions are pursued when a lesion causes functional compromise, such as difficulty breathing or feeding. If there is no functional compromise, patients and families are counseled regarding HNLM natural history and active observation is offered for 6–9 months. We hypothesized that active observation could be an effective strategy for managing HNLM patients without functional compromise. This report describes our experience in managing HNLM with this treatment paradigm.

MATERIALS AND METHODS

Population and Setting

The study cohort was identified in our prospectively maintained vascular anomalies quality improvement database. Consecutive pediatric patients with HNLM evaluated and treated between 2000 and 2017 at a tertiary pediatric academic medical center were included. All these patients had physical exams, assessment of functional impairment (ie, breathing, feeding, speaking), imaging (CT or MRI), and counseling concerning all HNLM treatment options. Patients with LM outside of the head and neck were excluded. The study was approved by the Seattle Children's Institutional Review Board.

As part of our conservative, shared decision-making approach to management, patients and families were counseled on the natural history and treatment options for HNLM at their clinic visit. Patients who had HNLM without functional compromise and the family was willing to observe their child for 6–9 months were categorized as observed. Patients who received surgery or sclerotherapy due to functional compromise and/or family desire for treatment were categorized as invasive treatment. Surgery encompassed all management interventions performed in the operating room (ie, airway evaluation, supraglottoplasty, HNLM resection, among others). If possible, this invasive treatment was delayed until the patient was older than 6 months of age in an attempt to reduce treatment number/frequency. Medical therapies for HNLM were not common in clinical practice during the study period and were therefore not included as a treatment modality.

Data Collection

Clinical data obtained via chart review included age at diagnosis, ethnicity, age at initial treatment, family history, history of EXIT procedure, presence of tracheotomy, stage, site, and laterality of the HNLM. A complete blood count (CBC) was obtained for extensive lesions when there was concern for anemia, recurrent inflammation/infection, or lymphocytopenia.[10,19] Lymphocytopenia was documented when the absolute lymphocyte count was below the age-appropriate reference range, and the lowest lymphocyte number and percentage were recorded. Treatment history included type/goal of treatment, age at treatment and occurrence of spontaneous regression. Treatment was categorized as observation, primary, staged, and salvage surgery, primary sclerotherapy or combination surgery and sclerotherapy. Spontaneous regression was defined as no clinical evidence of HNLM by the treating physician and family assessment.[12]

Statistical Analysis

Frequency and rate of initial management modality (invasive treatment, active observation) were calculated. Clinical factors, including age, HNLM site, De Serres stage, and laterality, were described for the study cohort, and separately for actively observed patients and those initially receiving invasive treatment via frequency and percentage. Median and interquartile range (IQR) are reported for continuous measures such as time to treatment initiation. Clinical associations were tested using Fisher's exact testing, or Wilcoxon rank sums for continuous measures.

Association of patient demographic and clinical characteristics with invasive treatment (surgery or sclerotherapy) were identified using Fisher's exact tests. The number and proportion of patients initially managed by active observation who experienced spontaneous regression were calculated. In exploratory analyses, rates of spontaneous regression were stratified by relevant clinical factors. Factors associated with higher probability of spontaneous regression were identified using Fisher's exact tests. Analyses were conducted at the $\alpha = 0.05$ level of significance using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Clinical Characteristics of Study Cohort

We identified 191 patients with HNLM managed at our institution from 2000–2017. The majority were diagnosed under 3 months of age (98/191 [51%], Table I), 101/191 (53%) were male, 97/191 (50%) were Caucasian, none had a family history HNLM, and 24/191 (13%) were diagnosed in-utero. EXIT procedures were done in 12/191 (6%) and tracheotomy in 17/191 (9%). Of the patients with a CBC (74/191 [39%], 31/74 [42%] had lymphocytopenia with median lowest lymphocyte number of 1740 (range 1135–3314). Patients with lymphocytopenia had bilateral stage IV and V HNLM. Other pertinent clinical findings in this cohort are summarized in Table I. Presentation prior to 3 months of age was associated with higher De Serres staging (III/IV/V: 38/98, 39%), compared with presentation at 3 years or older (III/IV/V: 4/53, 8%; $P = .0006$). Further, 26/36 (77%) HNLM of the mouth and tongue were identified prenatally or within 3 months of birth. The vast majority of HNLM were stage I or II (76%), in the lateral head and neck (75%) and had an epicenter in the neck (53%). Imaging studies determined

lesions were predominantly macrocystic or a mixture of micro and macrocystic structures.

Treatment Type

Initial treatment for HNLM by stage is summarized in Table II. Note, 65/191 (34%) HNLM had no functional compromise and were actively observed following diagnosis, evaluation, and counseling. Most observed malformations were stage I and II, as low stage lesions were unlikely to have functional compromise, whereas stage III, IV, and V malformations were more likely to have dysfunction and invasive treatments (I/II observed 61/65 [94%] vs. III/IV/V 42/126 [35%] treated invasively, $P < .01$. Table III). The type of initial treatment by age groups is presented in Figure 1. Invasive therapy was most commonly performed in the patients under 3 months of age as they were most likely to have high stage HNLM. Active observation was more common among HNLM presenting in older children, as these were likely low stage malformations (Table III).

Significant differences in choice of initial treatment modality, observation versus invasive are shown (Table III, Fig. 2). HNLM that were observed were more likely: predominantly macrocystic (37/65 [53%]), in the lateral neck (42/65 [65%]), and low stage (I/II 61/65 [94%]). Prenatal diagnosis was not associated with treatment type ($P = .07$). If lymphocytopenia, an EXIT procedure, or tracheotomy were performed, not surprisingly, invasive therapy was used (lymphocytopenia 28/31 [90%], $P = .0015$; EXIT procedure, 11/12 [92%], $P = .06$; tracheotomy 16/17 [94%], $P = .01$). All patients with EXIT procedure had high stage HNLM (III: 4/12 [33%], IV: 3/12 [25%], V: 5/12 [42%]). Most patients with tracheotomy were treated with combined surgery and sclerotherapy (7/16 [44%]) or staged surgery (5/16 [31%]); however, primary surgery (3/16 [19%]) and primary sclerotherapy (1/16 [6%]) were also used. Six patients had both EXIT procedure and tracheotomy. Initial management modality did not differ based on age at initial treatment or first evaluation at SCH.

TABLE I.
Descriptive Clinical Data of Study Cohort (N = 191).

	n (% of 191)
Age at Presentation	
Prenatal to <3 mo	98 (51)
3 mo to <3 yrs	40 (21)
>3 yrs	53 (28)
De Serres Staging	
Stage I	60 (31)
Stage II	85 (45)
Stage III	22 (12)
Stage IV	16 (8)
Stage V	8 (4)
Laterality	
Lateral	144 (75)
Bilateral	27 (14)
Midline	20 (10)
Malformation site (Epicenter)	
Neck	101 (53)
Parotid, parapharyngeal Space	24 (13)
Oral cavity	36 (19)
Orbit, skull base, or Scalp	8 (4)
Midface and lip	22 (12)
Predominate radiographic characteristics	
Macrocystic	70 (37)
Microcystic	35 (18)
Mixed	86 (45)

Treatment Timing

For the group where active observation was the planned initial treatment there was no time to treat period (n = 65). For patients who had invasive treatments, the median time from diagnosis to treatment was 268 days (IQR 41 to 545 days). In the whole study cohort

TABLE II.
Initial HNLM Treatment Modality and Age at Presentation by De Serres Stage (N = 191).

	Stage I	Stage II	Stage III	Stage IV	Stage V	Total Cohort
Treatment modality						
Observation	31 (16)	30 (16)	3 (2)	0	1 (0.1)	65 (34)
Primary surgery	23 (12)	37 (19)	14 (7)	5 (3)	1 (0.1)	80 (42)
Staged surgery	1 (0.1)	12 (6)	3 (2)	6 (3)	3 (2)	25 (13)
Primary Sclerotherapy	4 (2)	4 (2)	1 (0.1)	0	0	9 (5)
Salvage surgery	1 (0.1)	0	0	0	0	1 (1)
Combined Surgery/Sclerotherapy	0	2 (1)	1 (0.1)	5 (3)	3 (2)	11 (6)
Age at presentation						
Prenatal to <3 mo	22 (12)	38 (20)	16 (8)	14 (7)	8 (4)	98 (51)
3 mo to <3 yrs	14 (7)	22 (12)	3 (2)	1 (1)	0 (0)	40 (21)
>3 yrs	24 (13)	25 (13)	3 (2)	1 (1)	0 (0)	53 (28)

HNLM = head and neck lymphatic malformations.

TABLE III.
Clinical Factors Associated with Initial HNLM Treatment Modality.

	Initial Management		*P* value*
	Observation	Invasive	
Age at Presentation	n (% of 65)	n (% of 126)	.004
Prenatal to <3 mo	23 (35)	75 (60)	
3 mo to <3 yrs	16 (25)	24 (19)	
>3 yrs	26 (40)	27 (21)	
De Serres Staging			.0001
Stage I	31 (48)	29 (23)	
Stage II	30 (46)	55 (44)	
Stage III	3 (5)	19 (15)	
Stage IV	0 (0)	16 (13)	
Stage V	1 (2)	7 (7)	
Laterality			.005
Lateral	56 (29)	88 (46)	
Bilateral	2 (3)	25 (20)	
Midline	7 (11)	13 (10)	
Malformation site (Epicenter)			.01
Neck	42 (65)	59 (47)	
Parotid, parapharyngeal space	5 (8)	19 (15)	
oral cavity	5 (8)	31 (25)	
Orbit, skull base, or scalp	4 (6)	4 (3)	
Midface and lip	9 (14)	13 (10)	
Predominate radiographic characteristics			.0035
Macrocystic	33 (51)	37 (29)	
Microcystic	12 (18)	23 (18)	
Mixed	20 (31)	66 (52)	

*Determined using Fischer Exact Test. HNLM = head and neck lymphatic malformations.

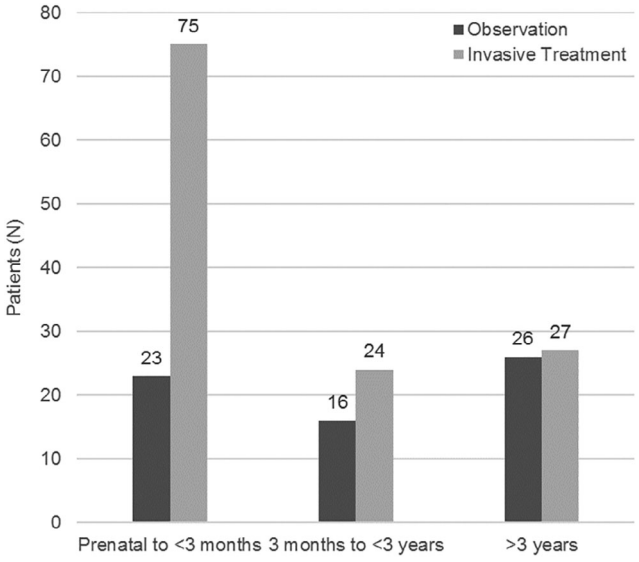

Fig. 1. Distribution of age at diagnosis by observation or invasive therapy. Bar graph depicting the number of patients who were observed or had invasive treatments for patients diagnosed prenatally to 3 months (n = 98), 3 months to 3 years (n = 40) or after 3 years of age (n = 53).

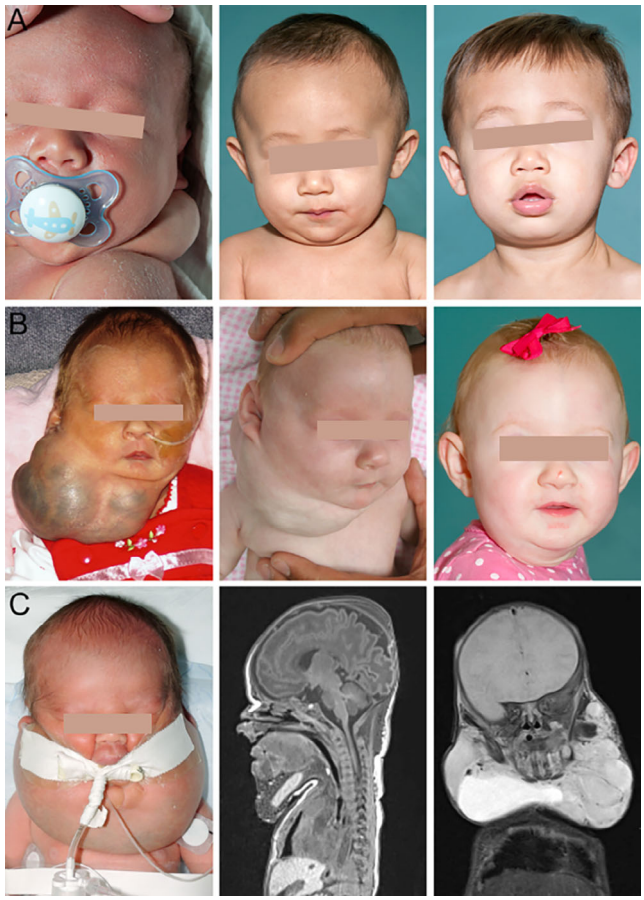

Fig. 2. Observed HNLM without functional compromise compared a HNLM treated invasively. A) Patient with stage 1 posterior neck HNLM that regressed over 6 months, no invasive therapy. B) Patient with stage 3 HNLM without functional compromise that regressed over 7 months and had removal of excess neck skin. C) Patient with stage 4 HNLM adversely impacting breathing and swallowing, treated invasively. HNLM = head and neck lymphatic malformations. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

intervals greater than 365 days from diagnosis to first invasive treatment were observed across all age groups, including 45 HNLM presenting prenatally or prior to 3 months, 14 presenting after 3 months and prior to 3 years of age, and five presenting at 3 years or older.

Treatment Outcomes with Active HNLM Observation

Of 65 patients who were initially observed, 36 (58%) experienced spontaneous regression of HNLM (Fig. 2). Factors significantly associated with regression were macrocystic structure and lateral neck location (Table IV). Eight patients (12%) subsequently had invasive treatments that consisted of resection of neck HNLM (n = 5), laser treatment of a tongue malformation (n = 1), biopsy of a cheek HNLM with adenotonsillectomy (n = 1), and sclerotherapy (n = 1). On two patients with neck HNLM parents elected to treat due to acute exacerbations. The

TABLE IV.
Factors Associated with HNLM Regression.

	Regression		
	No n (% of 65)	Yes n (% of 65)	*P* value*
Laterality			.003
Lateral	23 (35)	33 (51)	
Bilateral	1 (2)	1 (2)	
Midline	5 (8)	2 (3)	
Malformation Site (Epicenter)			.003
Neck	11 (17)	31 (48)	
Parotid, parapharyngeal space	3 (5)	2 (3)	
Oral cavity	5 (8)	0 (0)	
Orbit, skull base, or scalp	3 (5)	1 (2)	
Midface and lip	7 (11)	2 (3)	
Predominate Radiographic Characteristics			.017
Macrocystic	10 (15)	23 (35)	
Microcystic	9 (14)	3 (5)	
Mixed	10 (15)	10 (15)	

*Determined using Fischer Exact Test. HNLM = head and neck lymphatic malformations.

remaining 21 (32%) patients elected not to have invasive therapy or were waiting for lesion regression at the end of the study period. Of observed HNLM lesions, stage and age at presentation were not associated with regression (P = .08 and .49, respectively). Oral cavity malformations did not demonstrate spontaneous regression (0/5).

DISCUSSION

This report describes how a shared decision-making process was used to implement active observation as treatment in HNLM without functional compromise. Observed patients were more commonly older, with lower De Serres stage, and mixed macro and microcystic HNLM. Among the observation group, over half HNLM had spontaneous regression. All other subjects in this study had some type of invasive treatment or treatments to minimize HNLM induced morbidity and dysfunction. Invasive treatments were more common in high De Serres stages, lymphocytopenia, presence of a tracheotomy, diagnosis under 3 months of age, or HNLM in areas critical to basic functions, such as breathing and eating. These findings support our hypothesis that active observation in non-function threatening HNLM is a viable therapeutic option. Noninvasive management of select HNLMs can be individualized based on complete pretreatment evaluation and staging, absence of functional compromise, while considering HNLM natural history and patient family desires.

Planned active observation as an initial HNLM treatment modality is not suggested in most reports on HNLM treatment.[3,20–22] Our findings demonstrate that low stage HNLM, located in the neck not causing functional compromise, can be safely observed. These HNLM can regress without invasive therapy, unlike HNLM above the hyoid bone. This unique natural history is important to consider when counseling families and patients about treatment options. How this natural history relates to *PIK3CA* causing HNLM is unknown.[23] In this study over half of the patients actively observed regressed spontaneously. Other reports have shown HNLM regression in 12.5% to 50.3% of patients, after a period of observation of 4.5 months (range 4–7 months).[12,13] Regressing HNLM have had characteristics similar to this study cohort.[12,13] Informing patient families of HNLM-specific factors can help balance pretreatment counseling with realistic treatment expectations.[3]

Traditional HNLM treatment has been invasive and centered on surgery or sclerotherapy without regard to malformation natural history or objective measures of treatment efficacy. Both modalities have been shown to be effective in reducing HNLM size, especially in low stage predominantly macrocystic malformations, where both seem to be similarly effective.[3,24] However, these treatments have not been directly compared to observation. High stage HNLM, which were mostly diagnosed in young patients in this study, have often necessitated multimodal treatment approaches. This study's data show that high stage HNLM represent around 15% of all HNLM and that all stage IV and V malformations had invasive therapy to preserve life and function. Since most HNLM are low stage careful selection of invasive therapy is warranted, especially when the use of targeted medical therapy to inhibit the PI3K pathway in HNLM is potentially available.[15,23,25,26] Of real interest is the timing of invasive therapy seen in this study. The median age for initiating therapy was 268 days from diagnosis and this length of delay was observed in all age groups. While early treatment for large HNLM would seem to be critical to survival, careful prenatal delivery planning and experienced neonatal intensive care seemed to reduce the need for urgent early invasive therapy in many patients. While the timing of invasive therapy has not always been considered in HNLM treatment, these data support the idea that it could be delayed safely and requires multidisciplinary team collaboration.

Implementation of a shared decision making (SDM) protocol involves improving clinician-parent/patient communication through discussion of evidenced based information (ie, disease natural history, treatment risks, etc.) to aid treatment decisions and allow family preferences and values to be included in these decisions.[17,18] This SDM approach is best utilized when there is clinical treatment equipoise and treatment is elective.[18] Through SDM all treatment alternatives, invasive, medical and observation, can be presented and the patient's family can take time to consider these treatments. This study demonstrates that with careful diagnosis and treatment planning most HNLM, especially low stage, do not cause significant urgent dysfunction, which means there is time for SDM to be used during HNLM management. This data demonstrates that families willingly choose active observation after SDM and in some cases this resulted in no medical or invasive therapy.

This study has the inherent limitations of retrospective studies. Data collected was limited to the information recorded in the medical records. Not all data collected were complete, as demonstrated by the lymphocytopenia data. Future prospective study is needed to determine if active observation of HNLM and delaying invasive therapy affects patients' outcomes and reduces therapies for individual malformations.

CONCLUSION

HNLM management in select malformations not causing functional compromise can be safely accomplished with a period of active observation. In some HNLM, spontaneous regression eliminates the need for invasive treatments. Invasive treatments were used in HNLM with high De Serres stage, lymphocytopenia, tracheotomy, and diagnosis at a younger age or in critical locations (oral cavity and parotid/parapharyngeal space). Understanding the spectrum of HNLM severity and how this affects their natural history is essential in HNLM treatment planning. Observation is reasonable and is an acceptable therapeutic option, while invasive treatments are necessary to preserve function.

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