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TREATMENT STRATEGIES AND EFFECTIVENESS IN LYMPHATIC MALFORMATIONS: A 10-YEAR RETROSPECTIVE STUDY

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ABSTRACT

Recurrence is a major challenge in treatment of lymphatic malformations (LMs) worldwide. The objectives of the current study were to investigate risk factors associated with LM recurrence and to compare effectiveness of surgical and endovascular treatments. A multicenter 10-year retrospective chart review was conducted on all consecutive patients treated for LMs from 2009 to 2019. Data collected included post-treatment size, symptoms, and recurrence. Stepwise multiple regression analysis was used to identify risk factors and to compare treatment modalities. A total of 13 patients with 20 treatment cases were included. No significant difference was observed in size reduction and symptom alleviation between the treatment groups. Resection showed the highest recurrence rate of 36.4% (p=0.04) and lymphaticovenular anastomosis (LVA) presented excellent results in post-treatment size, symptoms, and recurrence despite lack of statistical significance. Microcystic type of LMs was identified as an independent risk factor for recurrence. Both surgery and sclerotherapy are effective in improving size and symptoms of LMs. This data will help physicians and patients choose the optimal treatment and potentially predict progression.

Keywords: Lymphatic malformations; Recurrence; Microcystic; Macrocystic; Lymphatic-venous anastomosis.

INTRODUCTION

Lymphatic malformations (LMs) are relatively rare benign vascular malformations characterized by an abnormal collection of very small lymphatic vesicles that grow in size and number over time (1). Management has substantially evolved over the last 20 years with currently a variety of pharmacological and nonpharmacological treatment modalities available. The overall goals of treatment are to restore and preserve body function, provide symptomatic relief, and restore aesthetic ap-

pearance. Sclerotherapy is traditionally considered the first-line treatment for LMs. It is sometimes used in combination with surgical resection, which is generally reserved for life-threatening, enlarging, or symptomatic LMs (2). Advances in microsurgery have further broadened the surgical options for LMs. We previously reported the successful treatment of a large abdominal LM with severe chylous leak using multiple lymphaticovenular anastomosis (LVA) (3). In addition, recent advancements in identifying germline and somatic mutations of LMs has led to the development of several potential therapeutic drugs such as mTOR Inhibitor Rapamycin (Sirolimus), p110α Inhibitor Alpelisib (BYL719), and MEK Inhibitor Trametinib (4). Sirolimus is the leading targeted small molecule modulator and has progressed to clinical trials (5,6).

Due to side effects, non-pharmacological approaches including sclerotherapy and surgical treatments are still considered as a gold-standard in LMs. However, reported effectiveness of non-pharmacological strategies is varied and recurrence is one of the common concerns following non-pharmacological treatment of LMs with few studies available to date exploring the factors contributing to recurrence of LMs (2,7). In this study, we aimed to investigate the risk factors associated with LM recurrence and compared the effectiveness of non-pharmacological treatment.

METHODS

Population and study design

We retrospectively analyzed clinical data of all consecutive patients with lymphatic malformations who underwent treatment managed by a single surgeon at two centers from April 2009 to December 2019. In general, patients who underwent treatment were enrolled in this study if they fulfilled the following criteria: received treatment including embolic therapy, sclerotherapy, surgical resection, or LVA; and had a follow-up duration of more than 6 months from completion of a particular treatment session with each session and follow-up considered as a separate treatment case. The exclusion criteria included inappropriate follow-up periods and patient factors such as death or poor understanding of the study due to severe neurological or psychiatric disorders.

All study procedures were approved by the local research ethics committees (The University of Tokyo Hospital IRBMED Number 2020315N1; Mie University Hospital IRBMED Number H2020-179) and were conducted in accordance with the Declaration of Helsinki. This study used an opt-out system at the official website of the University of Tokyo Hospital and Mie University Hospital.

Sclerotherapy procedures

Sclerosant injections were performed using palpation or ultrasound (US) guidance. Utilizing an US image to identify a LM with abnormal lymphatic flow, a needle was then confirmed to be inserted within the lesion. A concentration of 5% ethanolamine oleate (Oldamin, Fuji chemical industry Co., Ltd., Tokyo, Japan), 1% Polidocanol form (Polidocasklerol, Kaigen Pharma Co., Ltd., Tokyo, Japan), absolute ethanol (Anhydrous Ethanol Injection"Fuso", Fuso Pharmaceutical Industries, Ltd., Tokyo, Japan), or OK-432 (Picibanil, Chugai Pharmaceutical Co., Tokyo, Japan) was applied to the LM lesions. A mixture of 5% ethanolamine oleate and iodized oil (Lipiodol; Laboratoire Guerbet, France) (ratio 5:1-5:2) was injected with a volume range of 2 to 20 mL (8). The polidocanol foam consisted of 0.5% polidocanol foam with a mean of 3 procedures/patient (range 2–5) required. The maximum dose recommended for each case was 20 mg/day (9). Absolute ethanol was injected and then aspirated after 5 min exposure to the LMs. The injected maximum ethanol dose per case was 70–260 ml (10). OK-432 solution was prepared by dissolving 0.1 mg of OK-432 in 10 mL of normal saline. After aspirating as much intracystic fluid as possible, the volume of aspirated fluid was replaced with an equal volume of OK-432 solution with a maximum of 0.2 mg OK-432 in a single injection (8).

TABLE 1
Demographics of Study Subjects (N = 13)

Item	N	Percent
Number of patients	13	100%
Age, mean (SD)	20.6 (20.3)	
Sex		
Male	5	38.5 %
Female	8	61.5 %
Follow-up period, mean months (SD)	37.5 (27.9)	
Location of vascular anomalies		
Head and neck	5	38.5%
Upper extremities	3	23.1 %
Trunk	4	30.8 %
Lower extremities	3	23.1 %
Diameter of the lesion, mean cm (SD)	7.10 (3.96)	
Lesion site		
Subcutaneous only	8	61.5 %
Intramuscular only	1	7.7 %
Cutaneous and Subcutaneous	3	23.1 %
Cutaneous, Subcutaneous, and Intramuscular	1	7.7 %
Type of lesion		
Macrocystic	7	53.8 %
Microcystic	2	15.3 %
Mixed	3	23.1 %
Pretreatment symptom		
Color change	3	23.1 %
Increase temperature	1	7.7 %
Enlargement	12	92.3 %
Bleeding	2	15.4 %
Ulcer	1	7.7 %
Pain	4	30.8 %

Data Collection and Measurements

Data collected included demographics, age, sex, type of LM, lesion location, diameter, pretreatment symptoms, treatment, and post-treatment complications. Patients with LM who received pharmacological treatments were excluded from our cohort. The lesion size and symptoms were also recorded and evaluated by a physician at a follow-up visit at least 6 months after the treatment in all patients. The post-treatment lesion size was divided into 2 categories evaluated by magnetic resonance imaging (MRI) compared to the pre-treatment status: decreased or not decreased. The post-treatment symptoms were also categorized into 2 types; improved or not improved. In addition, recurrence of the lesion was also evaluated by a physician according to the following criteria including increased lymphatic flow in the lesion and enlarged lesion size after treatment. A stepwise multiple regression analysis for recurrence was performed using variables shown in *Table 1* including age, sex, location of LMs, the diameter of the lesion, location site, symptoms, and treatment methods.

TABLE 2
Summary Clinical Data of Participants with Lymphatic Malformations (N = 13)

Case #	Sex	Age at initial treatment	Location	Type	Treatment choice	Regrowth
1	M	72	Lt. neck	Macrocystic	1) Sclerotherapy	-
2	F	56	Pelvis	Mixed	1) Sclerotherapy	-
3	M	14	Rt. hand	Microcystic	1) Resection + Skin graft	-
4	F	28	Rt. neck	Macrocystic	1) Sclerotherapy 2) Sclerotherapy	-
5	M	18	Rt. axilla	Macrocystic	1) Sclerotherapy + Resection	-
6	M	49	Lt. neck	Macrocystic	1) Sclerotherapy 2) Sclerotherapy	-
7	M	9	Rt. hand	Microcystic	1) Resection 2) Resection + Local Flap	+
8	M	35	Rt. foot	Macrocystic	1) Sclerotherapy + Resection 2) Sclerotherapy Resection + Skin graft	+
9	M	31	Pelvis	Mixed	1) Resection + Local Flap	-
10	F	5	Jaw	Mixed	1) LVA 1) Resection	-
11	M	1	Face	Macrocystic	1) Resection + Sclerotherapy 2) Resection + Sclerotherapy	-
12	F	9	Lt. lower limb	Macrocystic	1) LVA 2) LVA	-
13	M	36	Lt. hip	Microcystic	1) Sclerotherapy + Resection	+

M: Male; F: Female; Rt.; Right; Lt.: Left; LVA: Lymphaticovenular anastomosis.

Statistical Analysis

The study was powered to detect a statistically significant odds ratio greater than or equal to 1.96. The assumptions of this estimation were acceptable with the following: an alpha risk of 0.05 and a beta risk of 0.20 in a two-sided test. Continuous variables were summarized as medians or means and standard deviations. The chi-square test was used for comparison of categorical variables. Adjusted standardized residuals were computed to identify cells in the cross-tabulation in which there were significantly more participants than expected (positive adjusted standardized residual of >1.96) or fewer participants than expected (negative adjusted standardized residual of <1.96). All analyses were performed using SPSS v.29.0 (IBM Corp., Armonk, NY, USA). A p value < .05 was considered statistically significant.

RESULTS

A total of 20 LM patients with 35 treatment cases were identified. Seven patients with 15 treatment cases were excluded due to inadequate follow-up, resulting in 13 patients with 20 treated cases included in the final analysis. This included 5 males and 8 females with ages ranging from 1 to 72 years and a mean age ± SD of 20.6 ± 20.3 years. The mean follow-up period was 37.5 ± 27.9 months. The most common sites were the head and neck (n = 5, 38.5%) followed by the trunk (n = 4, 30.8%), the upper extremities (n = 3, 23.1%), and lower extremities (n = 3, 23.1%). The mean diameter of the lesion was 7.10 ± 3.96 cm with the most common lesion site being subcutaneous (n = 11, 84.6%) followed by

TABLE 3
Treatment Options Utilized for Cases of Lymphatic Malformations (N = 26)

Treatment		N	Percent
Non-surgical		12	46.2 %
Sclerotherapy			
	Ethanolamine oleate	6	23.1 %
	Polidocanol	2	7.7 %
	Absolute ethanol	2	7.7 %
	OK432	2	7.7 %
Surgical		14	53.8 %
	Total resection	3	11.5 %
	Partial resection	8	30.8 %
	LVA	3	11.5 %
Coverage of surgical defect			
	Primary closure	7	26.9 %
	Skin graft	2	7.7 %
	Local or regional flap	2	7.7 %

LVA: Lymphaticovenular anastomosis.

cutaneous (n = 3, 23.1%) and intramuscular (n = 2, 79.4%). Seven patients had microcystic LM (53.8 %), 3 had mixed (23.1 %), and 2 had microcystic (15.3 %). Enlargement (n = 12; 78.9 %), pain (n = 4; 30.8 %), and color change (n = 3; 23.1 %) were the most common patient symptoms (*Table 1*). The summary data for each case are presented in *Table 2*.

A total of 13 patients received treatment including sclerotherapy (n = 12), surgical resection (n = 11), and LVA (n =3) (*Table 3*). No patient received pharmacotherapy or laser treatment in our cohort. Ethanolamine oleate (n = 6), Polidocanol (n = 2), Absolute ethanol (n = 2), and OK-432 (n = 2) were used as sclerosants. Sclerotherapy was combined with surgical resection in 4 patients. As for the closure of the surgical defects in 11 resection cases, 7 cases were closed with primary closure, 2 with skin grafts, and 2 with local or regional flaps. More than 6 months intervals between treatments were achieved in patients with LM undergoing multiple treatments.

Examining post-treatment size, the number of patients who reported a size decrease and complete remission was 6 (50.0 %) in sclerotherapy and 7 in resection (63.6 %). On the other hand, all the patients who underwent local or regional flap and LVA presented a size decrease and complete remission (*Fig. 1*). No statistical difference was observed among treatment options. In assessing lack of post-treatment symptoms, all treated cases reported alleviation or disappearance of symptoms. The standardized difference between the observed count and the expected count was not statistically different from the expected in all treatment procedures (*Fig. 2*). Resection had a recurrence rate of 36.4% (p = .04) whereas sclerotherapy had a rate of 16.6% (*Fig. 3*). Regression analysis revealed that microcystic type of lesion was identified as an independent risk factor associated with recurrence (coefficient (β) 0.68, 95% confidence interval (CI) 0.33 to 1.05, p = .04).

DISCUSSION

The present study focused on factors associated with recurrence of LMs and treatment effectiveness of LM treatment modalities. Regression analysis revealed microcystic type of LM as the only associated risk factor

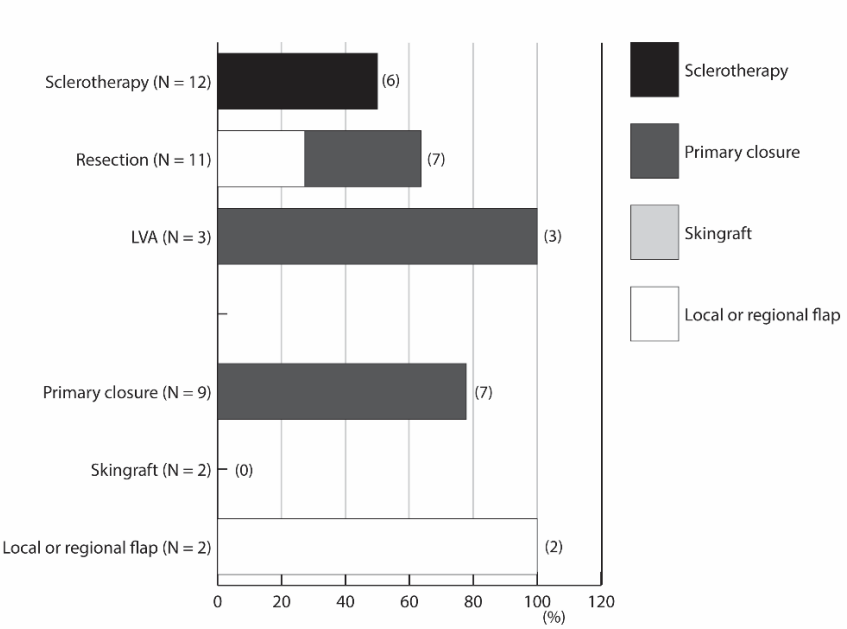

Fig. 1. *Post-treatment size reduction for sclerotherapy, resection, or LVA treatment of lymphatic malformation anomalies and the type of skin closure. Sclerotherapy was performed with resection in 4 treatment cases. LVA: Lymphaticovenular anastomosis.*

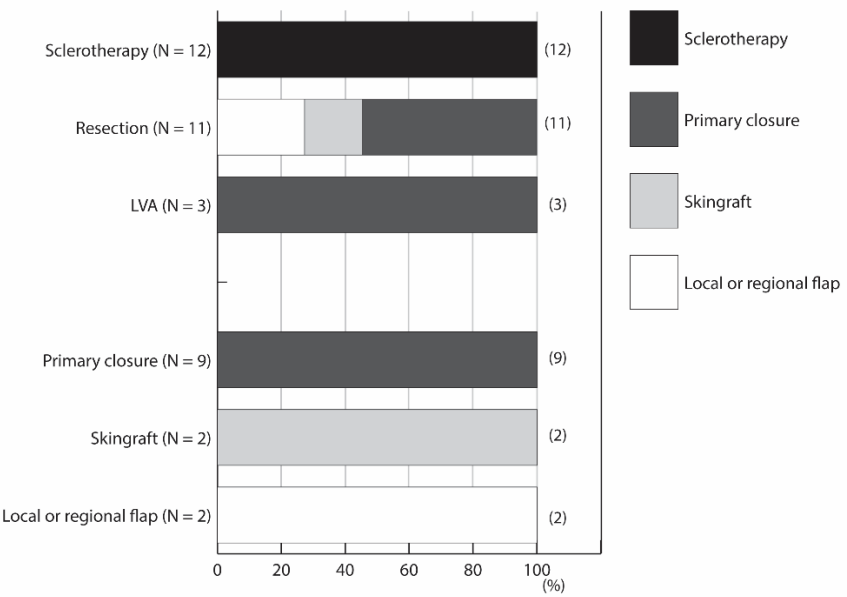

Fig. 2. *Post-treatment symptom reduction for sclerotherapy, resection, or LVA treatment of lymphatic malformation anomalies and the type of skin closure. Sclerotherapy was performed with resection in 4 treatment cases. LVA: Lymphaticovenular anastomosis.*

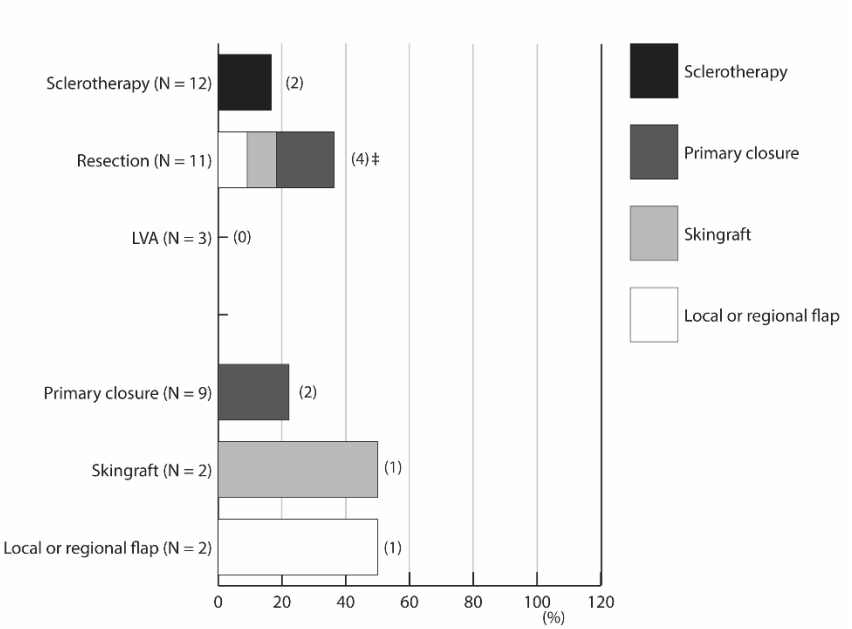

Fig. 3. *Recurrence rate for sclerotherapy, resection, or LVA treatment of lymphatic malformation anomalies and the type of skin closure. Sclerotherapy was performed with resection in 4 treatment cases. ‡ Positive adjusted standardized residual, indicating that the standardized difference between observed count and expected count was higher than expected. LVA: Lymphaticovenular anastomosis.*

for recurrence. All treated patients reported an improvement in post-treatment size and symptoms with no significant difference observed in size reduction and symptom alleviation between the treatment groups.

Regarding factors associated with recurrence, microcystic type of lesion was detected as an independent risk factor. This result was consistent with recent studies. (11,12) Lerat, et al. followed up 23 cases of head and neck LMs, and all the recurrent cases (8 cases; 34.78 %) were microcystic or mixed types (11). In addition, Moreno-Alfonso, et al. also reported that sequelae after LM treatment was associated with microcystic type (p = .002; Odd ratio (OR) 4.26) (12). Microcystic type of lesions typically extend across various anatomic levels without clear borders making a total resection rarely feasible. These collectively suggest that the microcystic type of LM is associated with recurrence.

In this study, surgical resection of LMs had a higher recurrence rate (36.4%) than expected. Surgical removal has been recognized as standard treatment for lesions undergoing enlargement, (2) with previous clinical series, mostly in children, reporting a recurrence rate of 17 to 40% after resection (13-16). Flanagan, et al. conducted a clinical and pathological investigative cohort study of 158 patients with cutaneous LMs and observed recurrence in almost all cases within 14 months of the initial resection, with 54% recurring within the first three months (13). These previous reports are consistent with our results. In our cohort, patients who underwent surgical resection presented the highest recurrence rate of 36.4% among the treatment groups. Although effectiveness of surgical resection on size reduction and symptom alleviation was not statistically different from other treatment modalities, complete remission after surgical resection can sometimes be achieved in specific cases. To improve aesthetic results, procedures such as liposuction, skin grafting, or flap reconstruction are sometimes attempted (17-19).

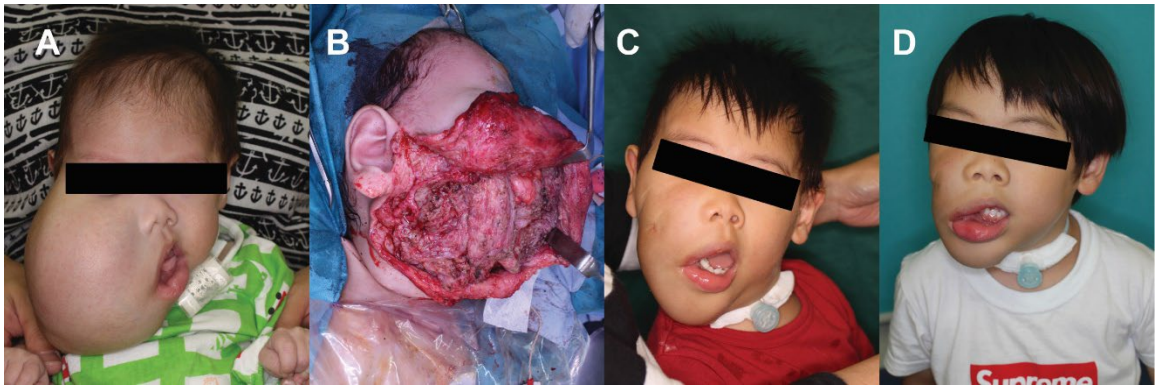

Fig. 4. *A 1-year-old boy with macrocystic lymphatic malformations (LMs) on the right side of his face (A). Intraoperative view of the partial resection that was first performed (B). A year after initial treatment (C), multiple cases of sclerotherapy using OK-432 were conducted. Three years after initial operation, no sign of recurrence was observed (D). Case #11 in Table 2.*

In our cohort, 2 cases used local or regional flaps just after resection resulting in excellent post-treatment size and symptoms. Therefore, if a large skin defect is anticipated after resection, skin grafts or flaps can be considered for closure of the resulting defects.

Interestingly, the 2 patients treated with LVA in this study presented excellent results in post-treatment size and symptoms with no recurrence recorded in either patient. Due to the small number of LVA patients, detailed statistical analysis and comparison with other treatment groups was not possible. Advances in reconstructive supermicrosurgery are increasingly expanding the use of LVA in the treatment of lymphatic disorders (20). Kato, et al. introduced flow-oriented LVA modification on LMs (21). About 50% of patients who underwent afferent lymph vessel of LM to venous anastomosis (LMVA) reported more than 50% size reduction after operations. Case reports describing the successful results of LVA on abdominal LMs and submandibular LMs are available (3,22). LVA can be a potential novel treatment for LMs when other options are less feasible, however, more evidence is required to understand which LM are suitable for LVA and the optimal application of the technique either in anastomosing the LM to venous drainage or anastomosing the proximal afferent lymphatic inflow to venous drainage for bypass.

Besides surgery, intralesional sclerotherapy has been utilized with various sclerosants including bleomycin, doxycycline, ethanol, Ethibloc, OK-432, and sodium tetradecyl sulfate with successful response in 20 to 64 % of patients with LMs (8,15,23-25). As for ethanolamine oleate, Kim, et al. conducted a retrospective cohort study of 16 patients with cervical LMs who underwent ethanolamine oleate injection. A total of 14 patients (88%) presented almost complete or complete responses (8). Alexander, et al. reported that 40.0% of 10 patients with LMs of the head and neck following ethanolamine oleate treatment showed excellent results (26). With regard to polidocanol, Górriz-Gómez, et al. investigated the effect of polidocanol in 15 patients with LMs in the face and oral cavity (9). The relapsed lesion was detected and further symptoms developed in only one case. Moreover, OK-432 was first introduced as an emerging sclerosing therapy agent for LMs by Ogita, et al. (27). OK-432 is a lyophilized biological preparation containing cells of *Streptococcus pyogenes* Su-strain treated with benzylpenicillin (28). Although its therapeutic effects have been reported, its mechanism of action is not still fully understood (29). Excellent results were achieved in 45 to 68.8% of patients with LMs in the head and neck region (16,30). In our cohort, patients treated with sclerotherapy achieved a 60% postoperative size decrease, 100% symptom

alleviation or remission, and a recurrence rate of 20.0%. Occasionally, the combinational use of surgical resection and sclerotherapy leads to better results (*Fig.4*). This outcome did not show any statistical difference from other therapies; however, the effectiveness seems to be similar to previous studies. In addition, most of the previous reports focus on LMs in the head and neck. (7,11,26,29,30). Our cohort includes different parts of the whole body and thus presents additional evidence to the growing body of knowledge on LM treatment.

Strengths and limitations

The strengths of this study are firstly the broad inclusion of patients with LMs on different parts of the body focusing on recurrence of LMs after treatment over a relatively long 10-year period. Secondly, the study group included patients from two different centers. The main limitations of this study are the relatively short follow-up period of 37.5 ± 27.9 months. Recurrence of LMs may occur several years after treatment and therefore much longer follow-up periods may be required. Secondly, treatment selection was not randomized nor matched in this study. In clinical practice, different modalities are used to treat different LMs to achieve different treatment goals. Complete surgical resection for instance may not be feasible in some lesions while sclerotherapy on the other hand may not provide sufficient immediate relief required in rapidly growing lesions of the head and neck regions. This limits direct comparison of the different treatment modalities. Nevertheless, results of this study still provide a useful guide for both clinicians and patients in understanding the effectiveness of the different modalities. Lastly, the sample size was relatively small due to low prevalence of patients who receive surgical and endovascular treatments. This precluded more detailed statistical analysis.

CONCLUSIONS

Recurrence remains a major challenge in the clinical management of LMs and it is noted that microcystic type of LM is an independent risk factor for LM recurrence. Our experience demonstrates that both surgical resection and sclerotherapy are effective in improving post-treatment size and symptoms of LMs. We believe these data will help physicians and patients choose the optimal treatment and predict their progression after treatment.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare no competing financial interests exist.

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