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Flow-oriented Venous Anastomosis to Control Lymph Flow of Lymphatic Malformation

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Background: Less-invasive surgeries, such as lymphaticovenular anastomosis (LVA), are the widely accepted intervention for lymphedema. This study aimed to assess the outcomes of flow-oriented LVA modification on lymphatic malformation (LM).
Methods: We included 19 patients diagnosed with LM mixed type or microcystic type, who came to our clinic from June 2015 to December 2017. Under general anesthesia, all patients were administered an indocyanine green lymphography injection subcutaneously. In the case of a strong inflow, the patient underwent afferent lymph vessel of LM to venous anastomosis (LMVA). Otherwise, the side wall of LMVA was performed to the cysts. Outcomes were classified into the following groups based on the size changes: treatment effect (TE) 4 = >80% reduction rate; TE 3 = 50%–80% reduction rate; TE 2 = 20%–50% reduction rate; and TE 1 = 0%–20% reduction rate.
Results: All cases underwent surgery, with no case having an increased size. The results were as follows: TE 4 = 4 (21%) patients; TE 3 = 6 (32%) patients; TE 2 = 5 (26%) patients; and TE 1 = 4 (21%) patients. No case required study termination due to disease progression. Minor complication occurred in 3 cases. One vesicle increased at the labial mucosa and one wound dehiscence that epithelized within 1 month.
Conclusion: LMVA could be a novel, minimally invasive lymph flow-oriented surgical method for intractable LM. *(Plast Reconstr Surg Glob Open 2019;7:e2199; doi: 10.1097/GOX.0000000000002199; Published online 29 July 2019.)*

INTRODUCTION

The etiology and pathophysiology of lymphatic diseases have been investigated extensively. Recently, some novel surgical treatments based on the lymph flow assessments have been widely accepted for lymphedema treatment. However, lymphatic malformation (LM), one of the most common lymph disorders in pediatric patients, still remains to be a challenging situation, especially the microcystic type. This is because the conventional sclerotherapies and surgical resections for LM seem to have limited efficacy and have high complication rates.[1,2]

Our previous research about spontaneous regression of LM suggested that some LMs have stronger lymph flow in and out, whereas others did not.[3] Therefore, we hypothesized that flow assessment of LMs and flow-oriented surgery might be effective as a novel surgical strategy.

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MATERIAL AND METHODS

Patients

This cohort study included 19 consecutive pediatric patients diagnosed with LM mixed type or microcystic type who were referred to our clinic from June 2015 to December 2017. All diagnoses were performed using magnetic resonance imaging (MRI) and the pathologies with $3 \times 3 \times 3\,mm^3$ biopsies during the surgery. All patients with macrocystic-type LM or with lesions that were completely treatable with a simple resection were excluded from this study.

Under general anesthesia, patients underwent indocyanine green (ICG) fluorescence lymphography. A 0.05-ml Diagnogreen (ICG 2.5 mg/ml; Daiichisankyo, Japan) solution was injected subcutaneously, distal to the LM. The flow was observed and assessed using an original red wave camera until the linear fluorescence reached to the proximal lymph nodes beyond the LM area.

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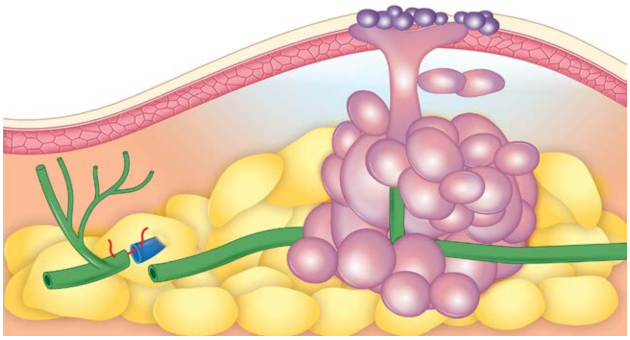

Fig. 1. Schema of afferent lymph vessel of LMVA. For cases with high-flow LM, lymphatic venous anastomosis is performed on the lymphatic inflow to decrease the burden of the fluid.

Patients with clear inflow to the LM underwent lymphatic venous anastomosis distal to the LM, as the flow ran into the venous system through the created bypass (afferent LM to venous anastomosis; A-LMVA) (Fig. 1).[4] Patients who did not show a clear inflow to the LM underwent venous anastomosis directly to the lymphatic cysts creating small holes manually, as the pooled lymph ran out to the venous system through the created bypass (side wall of LMVA; S-LMVA) (Fig. 2).[5] The anastomoses were performed under a surgical microscope. The venule and the afferent lymph vessel (A-LMVA) or the cyst wall (S-LMVA) were carefully dissected. The venule and lymph vessel/cyst hole were anastomosed manually using an 11-0 or a 12-0 nylon with 4–6 sutures depending on their sizes. The anastomosis numbers were determined according to the number of the afferent lymph vessels found for A-LMVA, and the intact venule can be possibly detected around the LM for S-LMVA. The total surgery time must not exceed 3 hours. The postanastomosis patency was checked under a microscope intraoperatively.

At 3 months postoperatively, the outcomes were evaluated (details described below). In cases wherein the cyst size was not reduced or the patients' health status did not improve, S-LMVA was performed under general anesthesia with consent from the patient and the guardian. For those cases with observed size reduction and clinical improvement after the primary surgery, a follow-up 6-month postoperative assessment was performed without any additional treatments. Those with progressive diseases or who did not improve after 2 surgeries were to be excluded from this study as initially designed and would undergo further medical and conventional treatments, such as surgical resections or sclerotherapy.

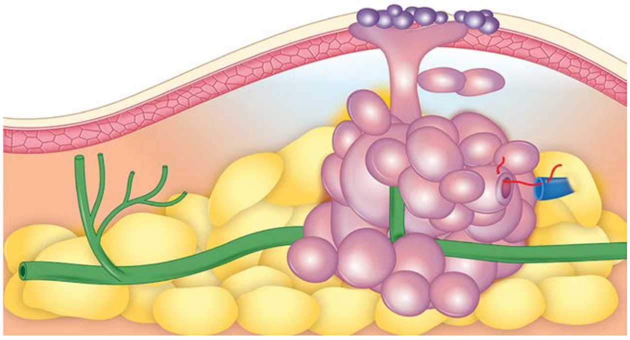

Fig. 2. Schema of side wall of LM to the venous anastomosis. For cases with low-flow LM, venous anastomosis is performed directly to the side wall of the cyst to increase the outflow.

One month before the surgery, all patients were advised to undergo compression therapies until the outcome assessment periods. In some patients, such as those with lesions on the face, external genitals, and on extremities, the compression was impossible to complete because they were unable to tolerate the therapy. Compression therapy was not performed again after the surgery in any of these cases. Moreover, no medications were administered preoperatively and postoperatively during the study period.

All patients and their guardians provided informed consent, and the study design was approved by the institutional ethical board.

MRI Examination, Volume Analysis, and Outcome Assessment

The outcome of solitary LM size was measured using MRI and 3D volumetric data, comparing preoperative and postoperative analyses. The volumetric data with 0.1-mm thickness were acquired using a 1.5T MRI unit (Achieva 1.5T A-series, Philips, Tokyo, Japan). The reconstructed data were 0.5-mm thick based on the T2-weighted image. The postprocessing software that we used was a commercially available volume analyzer (Synapse Vincent 3D, version 5.2, Fujifilm Medical, Tokyo, Japan). The MRI images were compared preoperatively and postoperatively. The LM voxels were segmented manually from the surrounding voxels using Synapse 3D as 3D regions of interest (Fig. 3).

Depending on the cyst reduction size, all results were classified into 4 groups: treatment effect (TE) 4 as more than 80% size reduction, TE 3 as 80%–50% reduction, TE 2 as 20%–50% reduction, and TE 1 as 0%–20% reduction.[6] Statistical analysis was performed using a direct Fisher test (nonparametric analysis).

RESULTS

Patients

All patients completed this study with more than 1-year follow-up. None of the patients dropped out because of disease progression. Among the 19 patients, 14 (74%) were male. The mean age was 5.0 years (range: 11 months to 14 years) at the time of surgery. Sixteen patients had microcystic type and 3 had mixed type. Symptoms related to the presence of cysts were pain, ptosis, and bleeding. The preoperative sizes had a maximum diameter of 24–276 (mean: 97.1) mm and a volume of 8.1–777 ml (Table 1). The compression therapy was completed successfully in only 4 patients (cases 8, 9, 10, and 17).

Outcomes

The final postoperative outcomes were as follows: TE 4 = 4 (21%) patients, TE 3 = 6 (32%) patients, TE 2 = 5 (26%) patients, and TE 1 = 4 (21%) patients. The total anastomoses were 49, including 21 A-LMVA (43%) and 28 S-LMVA (57%). All symptoms had improved within 6

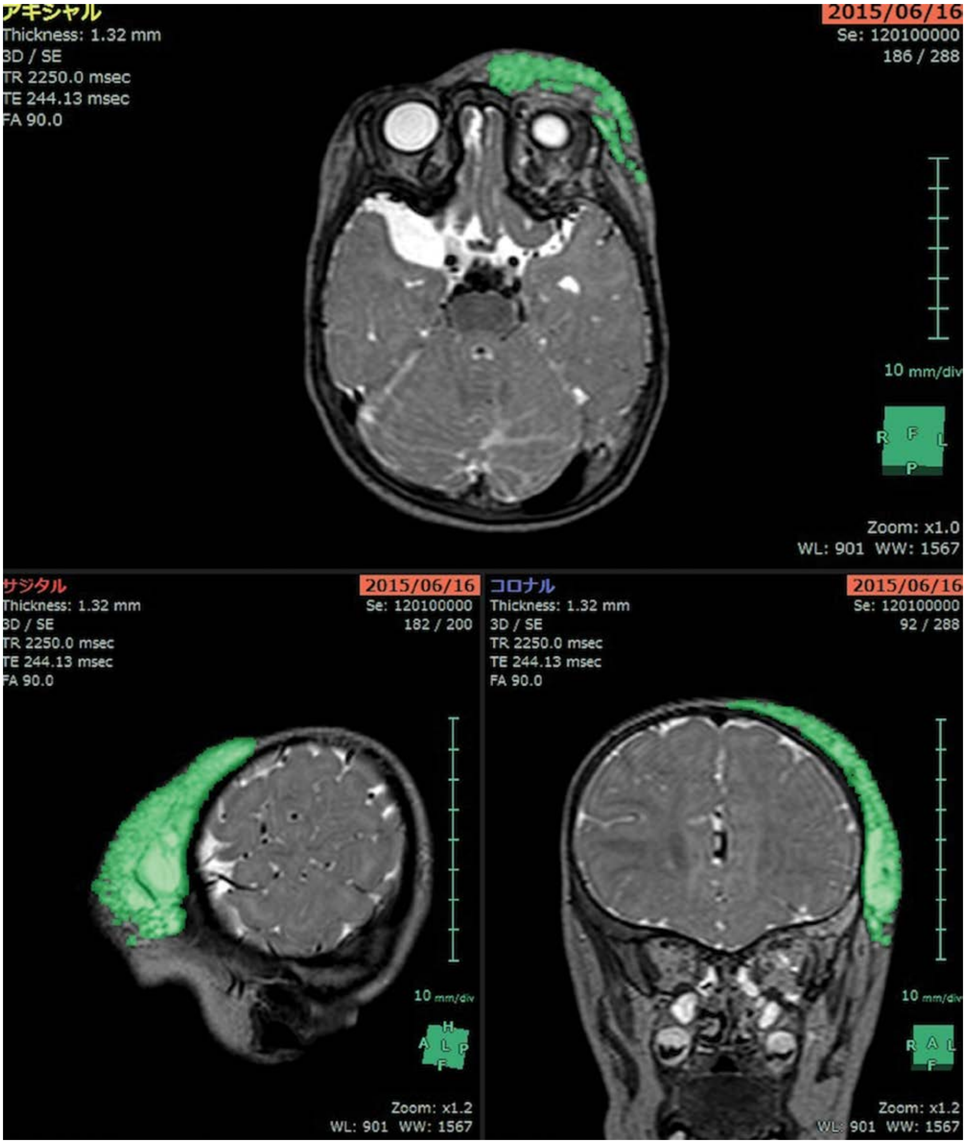

Fig. 3. The volume assessment of LM using an MRI volume analyzer (Synapse Vincent 3D) (case 3, preoperatively). The LM voxels are segmented manually from the surrounding voxels using Synapse 3D as 3D regions of interest.

months after the surgery. Complications occurred in 2 patients. One case of wound dehiscence on the lower extremity healed up within 1 month after surgery with ointment therapy. One patient had increased vesicles at the surgical site of the upper lip mucosa (Table 1).

The lymphatic flow assessment for solitary LM patients revealed high- and low-flow patterns in 7 (37%) and 12 (63%). Each result after the surgery was not significantly different in relation to the primary flow patterns.

Five patients required secondary surgery, followed by TE 1 after the first procedure. After the secondary surgery, TE 4 and TE 3 were achieved in 1 and 2 cases, respectively. The other 2 cases did not show size reduction of more than 20% of the primary size even after the secondary surgery, finally resulting in TE 1. However, none was classified as TE 0, as all cysts increased in size through this study. Of the 5 patients who had 2 surgeries, 3 were initially diagnosed with high-flow pattern, and A-LMVA was performed in the first surgery (Table 1).

To further assess the relationships between LM characteristic and the effectiveness of the present venous anastomosis technique, the outcomes were compared and statistically analyzed. Age, primary volume, type, location, and flow pattern were compared between TE 3 and TE 4 and TE 1 and TE 2. Unfortunately, there was no significant difference between size reduction rate and the outcomes mentioned above (Table 2).

Cases

Case Number 2

An 11-month-old boy had congenital mixed-type LM on his left thigh (Fig. 4A, C). He underwent OK-432 sclerotherapy twice before the LMVA ineffectively. Therefore, flow-oriented super-microsurgery was conducted, and he

Table 1. The Patient List and the Outcome of the Flow-oriented Surgery

No	Years	Months	Sex	Diagnosis	Laterality	Location	Type	Symptom	Previous Surgery	Flow Pattern	No. Anastomoses	No. Surgeries	Preoperative Size (mm^3)	Preoperative Volume (ml)	Postoperative Volume (ml)	Shrink Rate (%)	TE	Complication
1	0	11	F	LM	R	Axial	Mix	None	Screlotherapy OK-432 3 times	High	2	1	139×91×118	702	205	70.8	3	None
2	0	11	M	LM	L	LE	Mix	None	Screlotherapy OK-432 2 times	High	2	1	83×61×48	205	29.9	85.4	4	One WD 1 mo
3	1	5	M	LM	L	Face	M	Ptosis	None	Low	4	2	125×90×12	60.7	51.9	14.5	1	None
4	1	10	M	LM	L	Neck	M	None	None	Low	1	1	47×56×57	76	0.8	98.9	4	None
5	2	8	M	LM	R	Face	M	None	None	Low	1	1	60×57×31	67	0.15	99.8	4	None
6	3	3	M	LM	R	Axial	M	None	None	Low	3	2	91×71×26	71.3	23.7	66.8	3	None
7	3	3	M	LM	LR	Face	M	None	None	Low	3	1	24×16×15	8.1	6.7	17.3	1	Vesicle increase
8	3	5	M	LM	L	Foarm	M	None	None	Low	1	1	115×64×30	118	76.7	35	2	None
9	3	6	F	LM	L	LE	M	None	None	High	3	1	91×53×17	39.8	23.7	40.5	2	None
10	3	11	F	LM	L	LE	M	None	none	High	2	1	100×60×17	49.3	25.5	48.3	2	None
11	4	0	M	LM	R	Face	Mix	None	Screlotherapy OK-432 2times	Low	3	1	55×32×40	70.6	49.7	29.6	2	None
12	6	0	F	LM	L	Face	M	None	Resection once	Low	1	1	67×67×17	19.4	7.6	60.8	3	None
13	7	3	M	LM	L	Face	M	None	Screlotherapy OK-432 3 times, EtOH 4 times	Low	1	1	113×121×95	349	338	3.2	1	None
14	7	3	M	LM	L	LE	M	Bleeding	None	High	2	2	60×36×16	26.4	6.09	76.9	3	None
15	8	0	M	LM	L	Neck	M	None	None	Low	3	1	38×60×18	63.2	18.4	70.9	3	None
16	8	10	F	LM	R	LE	M	None	None	High	10	2	276×82×19	777	705	9.3	1	None
17	9	2	M	LM	R	LE	M	none	None	High	3	2	144×86×28	280	22	92.1	4	None
18	9	8	M	LM	R	Face	M	Bleeding	Resection once	Low	1	1	82×66×24	13.7	9.2	32.8	2	None
19	10	2	M	LM	R	Shoulder	M	None	None	Low	3	1	94×59×11	52	12.2	76.5	3	None

EtOH, Ethanol; F, Female; L, Left; LE, Lower Extremities; M(Sex), Male; M(type), Micro cyst; R, Right; WD, Wound Dehiscence.

Table 2. The Comparison of the Treatment Effect and Outcomes

Results	TE 3,4	TE 1,2	*P*
No	10	9	
Age (mo, mean ± SD)	60 ± 40	60 ± 32	0.99
Primary volume (ml, mean ± SD)	156 ± 198	165 ± 251	0.93
Type; No. microcyst (%)	8 (80)	8 (89)	0.66
Location face	2	5	0.11
Location extremities	3	4	0.51
High flow	5	3	0.67

had 2 anastomoses. He had TE 4 with a reduction rate of 85%. Although wound dehiscence occurred in one scar of the anastomosis, it healed up within 2 weeks after the dehiscence. No recurrence was observed within 2 years after the surgery (Fig. 4B, D).

Case Number 6

A 3-year-old boy had congenital microcystic LM (Fig. 5A). His cyst presented with a low-flow pattern on the ICG lymphography; hence, we performed S-LMVA on the chest. After the primary surgery, the size reduction was limited. Therefore, we conducted an additional S-LMVA on his chest wall. The total cyst size reduced to more than 60%. At 1 year postoperatively from the initial S-LMVA, no recurrence was observed. The bulk almost improved clinically, but the deep LM remained (Fig. 5B).

Case Number 11

A 4-year-old male patient had enlargement of the cheek area with disfigurement by mixed-type LM. We performed OK-432 sclerotherapy twice with no size reduction (Fig. 6A). Therefore, we performed S-LMVA to increase the outflow. The laterality still remained; however, he and

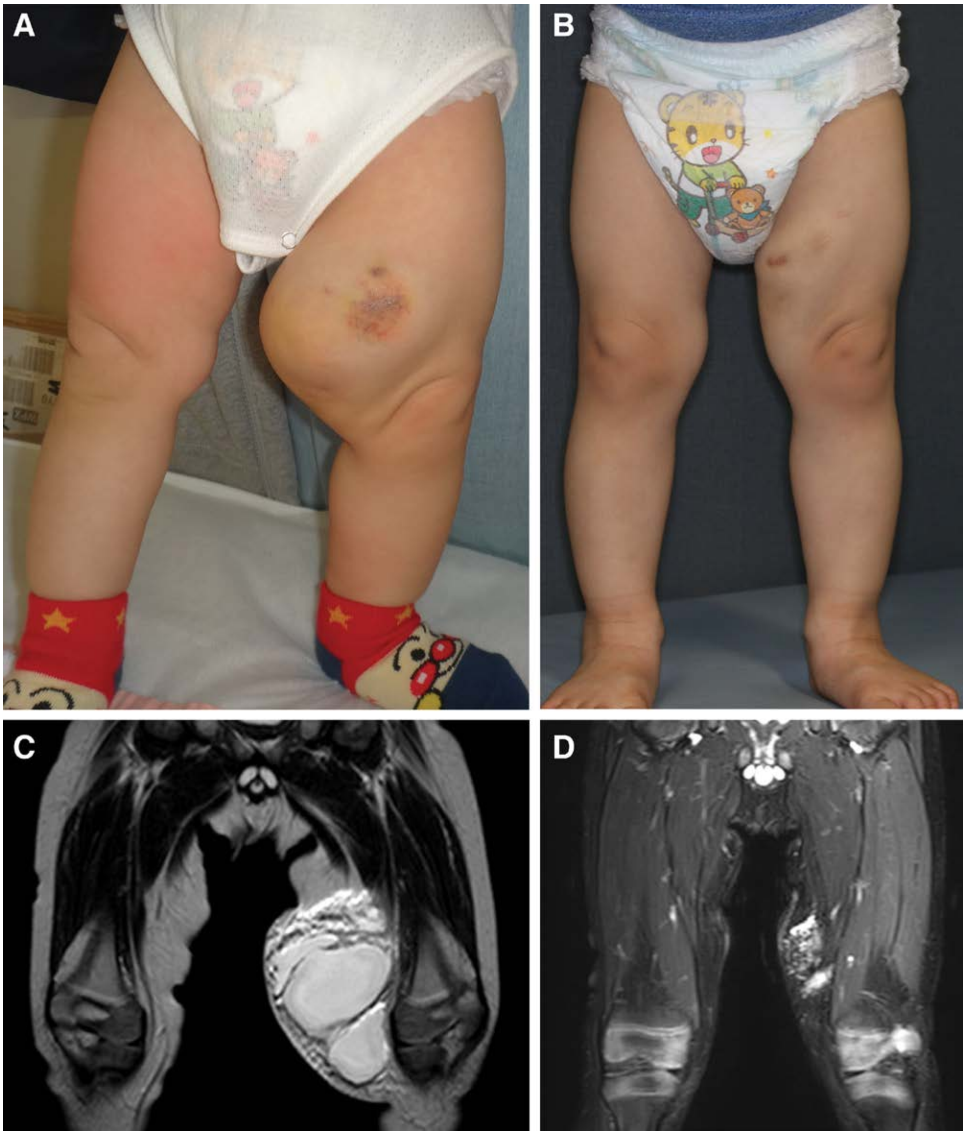

Fig. 4. A, An 11-month-old boy with mixed-type LM on his thigh preoperatively (case 2). B, Eight months after lymphaticovenular anastomosis. The anastomosis site is located at the left medial thigh. Cysts are still present; however, the size is reduced, and the patient could wear normal-sized pants (case 2). C, MRI preoperatively (case 2). D, MRI postoperatively (case 2).

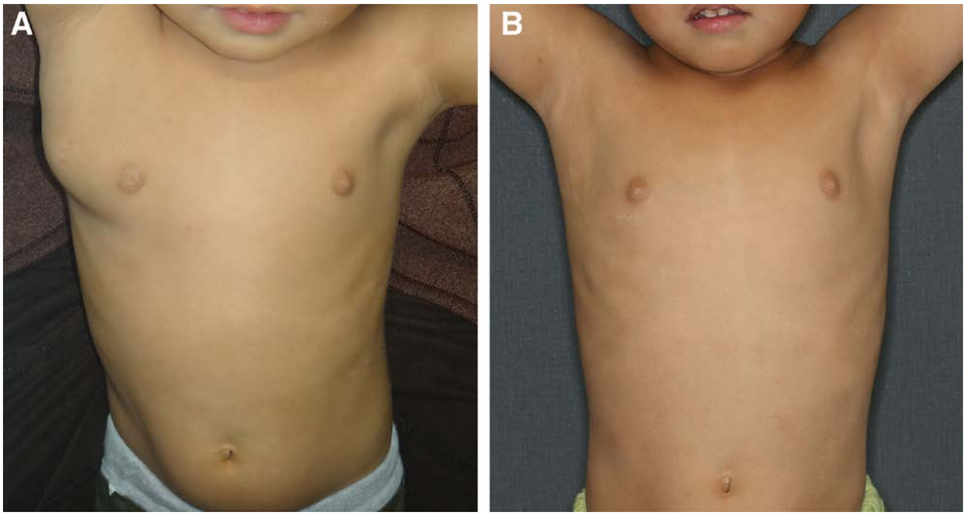

Fig. 5. A, A 3-year-old boy with axial microcystic LM preoperatively (case 6). B, One year after the surgery (case 6).

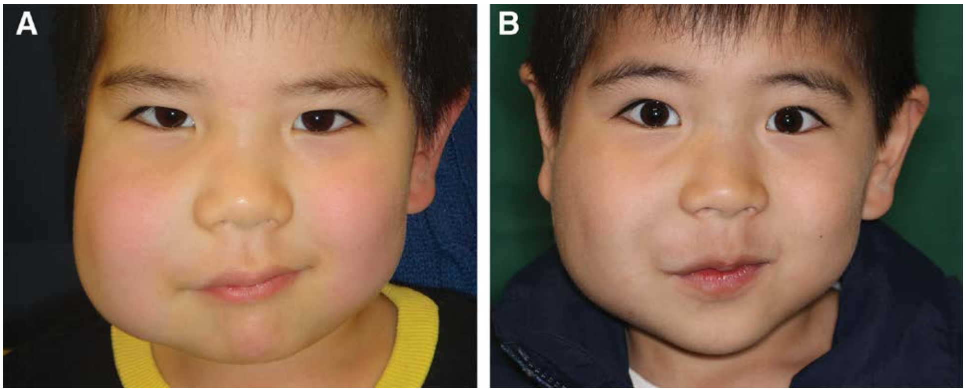

Fig. 6. A, A case of mixed-type LM on the cheek of a 4-year-old boy. Two sessions of sclerotherapy were ineffective (case 11). B, Postoperatively, the disfigurement improved. No recurrence is detected after 1 year from the surgery (case 11).

his family are satisfied with the result. No recurrence was observed after 1 year from the surgery (Fig. 6B).

DISCUSSION

The intractable LMs, such as large microcystic types, are usually treated by either surgical resection or sclerotherapy, in the case of unsuccessful medical treatments.[1] However, sclerotherapy has limited efficacy,[7] and surgical resections have high complication rates.[8,9] Therefore, a novel approach is required to achieve better surgical results. In fact, modified methods were developed based on either sclerotherapy or surgical resections, which reported fair results.[10–12] However, these approaches did not consider lymphatic flow.

To treat lymphedema, lymph flow assessment by scintigraphy and/or ICG lymphography is frequently applied.[13,14] Lymphatic venous anastomosis is recently considered among the most frequently applied surgical procedures for less-invasive flow-oriented treatments.[15,16]

The flow assessment of LM by scintigraphy or lymphangiography had been reported.[17–21] However, the existence of inflow had been controversial.[17,20] Our previous clinical trials revealed that some LMs had strong inflow, and the inflow lymph vessels could be bypassed into the vein, which results in the reduction of the cyst sizes due to the decrease of the inflow to the cysts.[3,4] Another trial suggested that cases with undetectable inflow, direct drainage bypass from the cysts to the veins could result in the reduction of the cyst sizes.[5] As a matter of fact, our retrospective LM lymph flow study suggested that some LMs have stronger lymph flow in and out the cysts, and the others have weak or no connection to the flow around the cysts.[3,22] Therefore, we hypothesized that flow-oriented surgery based on the lymph flow assessment should be possible.

To decrease the inflow, ligation of the lymphatic vessel might be effective in inflow reduction temporarily. It may also lead to a regeneration of the collateral pathway within a week. Lymphangiogenesis is considered to be accelerated under acute inflammation, such as surgical interventions.[23–25] In fact, no reconnection to the inflow of LM was observed later after a successful A-LMVA. Therefore, A-LMVA is an ideal procedure to decrease lymph load on LM without relapse from lymphangiogenesis.

We preferred to use ICG lymphography for the detection of the lymph flow, because the precise location of the lymph vessels could be observed in real time without radiation exposures. In fact, safe assessment could be completed even for infants.[26,27] To achieve successful LVA, the precise detection of lymph flow location was mandatory; therefore, ICG lymphography was suitable for LVA and LMVA.[22,28]

Before the study, we hypothesized that high lymph flow LM contained a strong lymph outflow also; thus, the cyst maintained its size. Therefore, the bypass creation of the inflow would decrease the fluid amount of the cysts due to the remaining strong outflow. However, we experienced 4 unsuccessful A-LMVA cases requiring a secondary surgery. After conducting S-LMVA, they improved and resulted in 1 TE 4, 2 TE 3, and 1 TE 1 case. This indicated that the high-flow LM was considered to contain strong inflow and outflow, which balanced the fluid; however, the flow may have varied, and not all high-flow LM remained to have a strong outflow enough to reduce the cyst size. In such cases, performing S-LMVA was considered effective. Conversely, the effectiveness of S-LMVA without A-LMVA for high-flow LM remained unclear, because all high-flow LM cases had A-LMVA first in this study.

No case had recurrence after the surgery. None caused inflammation postoperatively. This might be advantageous for those with neck LM lesion around the trachea, for they could cause airway obstruction itself and/or following to sclerotherapies.

The limitation of this study included a small number of cases. Furthermore, we were unable to assess the postoperative patency of the anastomosis, because the cysts were too small to inject an agent inside, and the vessels were too small to be assessed percutaneously by ultrasound. Therefore, we could only observe the outcome according to the clinical improvements, such as cyst size reduction or symptom remission. More cases and long-term results should be included in future studies for further assessment. It is important to note that the technical procedure of A-LMVA is similar to conventional LVA, with some modifications. It can be said that LMVA is a variation of LVA. We propose that A-LMVA and S-LMVA are classifications of LMVA within the concept of LVA, and are used exclusively for LM treatment. Thus, LMVA does not imply any effectiveness to treat lymphedema, which needs to be further evaluated.

CONCLUSION

The venous anastomosis procedure based on lymph flow assessment was considered an effective and minimally invasive surgery for intractable LM.

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