Spontaneous Regression of Lymphangiomas in a Single Center Over 34 Years

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Background: A lymphangioma, also called a lymphatic malformation, is a congenital condition that frequently occurs in young children. It is classified into 3 groups depending on the size of the cysts (macrocystic, microcystic, and mixed). Spontaneous regression occurs in some cases; however, the characteristics of patients who show regression have not been studied previously. Furthermore, the types and the timing of the initial treatment are still controversial. Therefore, we statistically analyzed the occurrence of short-term spontaneous regression, patient age at original occurrence, cyst types, cyst sizes, and cyst locations in patients diagnosed with peripheral localized lymphangiomas in a single children center over 34 years.

Methods: We retrospectively collected the data of 153 patients and reviewed the medical charts.

Results: Spontaneous regression occurred only in macrocystic or mixed type; regression was most frequent in patients who, at the time of onset, were more than 2 years old.

Conclusions: We concluded that elderly patients with macrocystic or mixed type lymphangioma may have to wait for treatment for over 3 months from the initial onset. Conversely, microcystic type could not be expected to show regression in a short period, and prompt initiation of the treatments may be required. The difference of the regression or not may depend on the characteristics of the lymph flow. (Plast Reconstr Surg Glob Open 2017;5:e1501; doi: 10.1097/GOX.0000000000001501; Published online 25 September 2017.)

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RESULTS

A total of 153 patients (87 male patients, 57%) were enrolled in this study. Of these 153 patients, 111 had macrocystic lymphangiomas, 14 had mixed lymphangiomas, and 28 had microcystic lymphangiomas. The patient ages ranged from 0 to 16 years (mean, 1.9 years). The mean maximum lesion diameters were 4.2 cm for macrocystic lymphangiomas and 4.8 cm for mixed lymphangiomas.

Spontaneous regression was observed in 77 patients (50%). Of these 77 patients, 72 (94%) had macrocystic lymphangiomas and 5 (6%) had mixed lymphangiomas. Spontaneous regression was not noted in patients with microcystic lymphangiomas (Table 2).

In both patients with macrocystic lymphangiomas and those with mixed lymphangiomas, spontaneous regression mainly occurred in older patients. Among patients with macrocystic lymphangiomas, those who showed regression had a mean age of 2.7 years (range, 0–12 years), whereas those who did not show regression had a mean age of 1.2 years (range, 0–16 years; \( P = 0.01 \)). Among patients with mixed lymphangiomas, those who showed regression had a mean age of 3.2 years (range, 0–6 years), whereas those who did not show regression had a mean age of 0.3 years (range, 0–1 years; \( P = 0.0004 \); Figs. 2, 3). In the ROC curve analysis, the cutoff age for spontaneous regression of macrocystic lymphangiomas was 1.6 years (sensitivity, 0.53; specificity, 0.87; area under the curve, 0.712; Fig. 4).

The original diameters of the lesions that showed spontaneous regression ranged from 1.5 to 10.0 cm (mean, 3.9 cm), and these lesions were not specifically smaller than the nonregressed lesions. Most macrocystic lymphangiomas were on either the neck or axial region; however, mixed and microcystic lymphangiomas were more common on the extremities, trunk, and scalp (Table 3). The lesion size and patient age were not correlated among patients who showed spontaneous regression.

Among the spontaneously regressed patients, 2 patients required resection after 1 year of observation. Of the 77 patients, recurrence was not observed in 60 patients (78%) during our follow-ups. Recurrence was observed in 17 (22%) cases from 6 months to 6 years after the initial regression, and 3 of them had recurrence twice even after spontaneous regression of the second swelling. Among 17 cases, 16 (21%) had macrocystic type and 1 (1%) had mixed type. The recurred mixed-type case had re-regressed during our observation without any treatment. Among 16 recurred macrocystic cases, 7 (44%) underwent treatment, 3 underwent sclerotherapy, 2 underwent suction, 1 underwent resection, and 1 underwent sclerotherapy followed by resection.

### Table 1. Number of Patients Included in this Study and Reasons for Exclusion

| No. Patients Included | Reason for the Exclusion | No. Patients Excluded | Subtotal |
|-----------------------|--------------------------|-----------------------|----------|
| 501                   | Lacking data for assessment | 87                    | 414      |
|                       | Misdiagnosis (different pathological diagnosis) | 78                    | 336      |
|                       | Other than superficial of the body (visceral, etc.) | 37                    | 299      |
|                       | Treated before 3 months follow-up period | 146                   | 153      |

**Fig. 1.** List of misdiagnosis and other diseases excluded from the study criteria.
DISCUSSION

We retrospectively analyzed lymphangioma characteristics and the factors that related to spontaneous regressions. Spontaneous regression was only observed in macrocystic and mixed lymphangiomas and not in microcystic lymphangiomas. This difference can be explained as follows. Pathologically, macrocystic and microcystic lymphangiomas have similar structures; therefore, the balance of lymph in-flow and out-flow may differ between these groups. For microcystic lymphangiomas, early intervention could be a valid approach in the case of possible functional loss or disfigurement because spontaneous regression does not occur.

The etiology of lymphangiomas has long been discussed, and it remains controversial. The following 2 major hypotheses have been proposed: congenital misconnection of lymph cysts and congested lymph flow due to blockage resulting in cyst expansion. The finding that spontaneous regression is more likely to occur in older patients may help in the understanding of a lymphangioma and its etiology. We hypothesized that there are flow pattern differences between patients showing regression and those not showing regression. A lymphangioma could expand when the balance of in-flow and out-flow is lost (Fig. 5).

In patients not showing regression, out-flow appears to be damaged initially, resulting in a congested lymph cyst, followed by a decrease in in-flow. Occasional expansion may occur after an increase in in-flow associated with conditions, such as intracystic bleeding and infection, which can last for a long time. This could be an indication of congenital misconnection of the lymph cysts. In our study, congenital onset was noted in 46% (18/39) of patients who did not show regression and 19% (14/72) of patients who showed regression. Additionally, β-catenin is necessary for lymphatic valve formation, and a mouse model expressed congenital macrocystic lymphangiomas on the neck owing to obstruction or valve malformation at the venous angle of the thoracic duct. Furthermore, previous lymph flow studies of lymphangiomas with lymphangiog-
raphy or scintigraphy mentioned that direct injection of an agent into macrocysts resulted in the agent remaining for a long time, with a weak out-flow, probably leading to weak in-flow.\(^8\)–\(^1\)\(^1\) (Fig. 5A).

Patients who showed regression had intact out-flow; however, the in-flow sometimes suddenly increased and overcame the out-flow drainage capacity, resulting in temporary expansion. The increase in lymph in-flow was mainly associated with intracystic bleeding or infection, which can occur not only congenitally but also in older children.\(^1\)\(^2\)–\(^1\)\(^4\) Therefore, spontaneous regression can occur in both congenital and older patients. This theory is compatible with the strong in-flow to macrocystic lymphangiomas reported previously with lymphangiography and lymphoscintigraphy.\(^1\)\(^5\)–\(^1\)\(^7\) Some patients with macrocystic lymphangiomas who showed regression [22% (16/72)] experienced recurrence after 0.5 to 6 years (mean, 2.9 years), and these lesions again spontaneously regressed over a couple of months. Therefore, lymphangiomas may be associated with other conditions that can increase in-flow, such as the presence of a vulnerable vein that can cause intracystic bleeding and malfunction of the immune system that can cause cyst-localized infections (Fig. 5B).\(^1\)\(^8\) Most previously reported spontaneous regressions were macrocysts, and this is compatible to our findings (Table 4).\(^1\)\(^9\)–\(^2\)\(^9\)

The appropriate time to start treatment for lymphangiomas is unclear. This study suggested that macrocystic and mixed lymphangiomas, which suddenly occur in patients aged 2 year or older, could be observed for a couple of months without treatment to avoid possible complications and unnecessary expenses associated with drainage, sclerotherapy, medication, and/or surgery. Furthermore, microcystic lymphangiomas should be treated earlier because of the limited possibility of spontaneous regression. Classification of the natural drainage potential of cysts was informative for indicating flow-oriented surgery, as reported previously.\(^3\)\(^0\)

The present study had some limitations. The study included a short observation period of the natural course. Spontaneous regression sometimes occurs more than 3 months after the initial onset, which could be a bias in this study. Furthermore, in many of our patients, early interventions were planned within 3 months after the initial onset, resulting in a short observation period for treatment exclusion. Moreover, patients who showed spontaneous regression were...
more likely to cancel treatment and to be followed for a long period without treatment; therefore, they tended to be included. Further detailed investigations involving multicenter, international, and mass data analyses would help in the understanding of the pure natural course of lymphangiomas.

### Table 3. Clinical Characteristics, Cyst Types, and Spontaneous Regression

| Patient Characteristics | Macrocytic Type | Mixed Type | Microcytic Type |
|-------------------------|-----------------|------------|-----------------|
|                         | Positive (n = 72) | Negative (n = 39) | Positive (n = 5) | Negative (n = 9) | Positive (n = 0) | Negative (n = 28) |
| Spontaneous regression  | Mean ± SD or n (%) | Mean ± SD or n (%) | Mean ± SD or n (%) |
| Sex (F:M)               | 34:38           | 14:25       | 3:2             | 1:8             | 0               | 14:14           |
| Age (y)                 | 2.7 ± 3.0       | 1.2 ± 2.8   | 3.2 ± 1.9       | 0.31 ± 0.4      | 0.0004†         | 0.89±1.4        |
| Maximum diameter (cm)   | 3.9 ± 1.6       | 4.6 ± 1.9   | 4.1 ± 1.8       | 5.3 ± 1.9       | 0.32            | —               |
| Location                |                 |             |                 |                 |                 |                 |
| Neck                    | 37 (51)         | 24 (62)     | 0               | 2 (22)          | 0               | 3 (11)          |
| Axial                   | 16 (22)         | 5 (13)      | 0               | 0               | 0               | 0               |
| Other                   | 19 (26)         | 10 (26)     | 5 (100)         | 7 (78)          | 0               | 25 (89)         |

**CONCLUSIONS**

We retrospectively analyzed the spontaneous regression of lymphangiomas in a single center over 34 years. Spontaneous regression was not noted in microcystic lymphangiomas. Patients older than 2 years with macrocystic or mixed lymphangiomas were more likely to show...
spontaneous regression within 3 months after the initial onset, and this might be associated with lymph flow pattern variations.

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