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ORIGINAL ARTICLE
Reconstructive

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.)*

MATERIALS AND METHODS

We retrospectively reviewed the medical charts of 501 patients who were diagnosed with lymphangiomas or lymphatic malformations in our hospital over 34 years (April 1983 to December 2016). Lymphangioma cases that showed peripheral localization and were observed for more than 3 months without medical or surgical intervention were included. The diagnosis was reconfirmed on the basis of radiological findings and the clinical course according to the vascular anomalies classification of the International Society for the Study of Vascular Anomalies.[1]

Patients diagnosed with lymphangiomatosis, Gorham disease, combined vascular anomalies (Klippel–Trenaunay syndrome, Proteus syndrome, and Maffucci syndrome), intraabdominal lesions, and/or intrathoracic lymphangiomas were excluded from this study. Additionally, patients who were misdiagnosed, those who did not undergo radiological assessments (ultrasound, computed tomography, or magnetic resonance imaging), those who were not followed for 6 months after onset, and those who were administered treatments for the lesions (medication, aspiration, sclerotherapy, and/or surgery) within 3 months after the original onset were excluded (Table 1; Fig. 1). Patients who were prescribed acetaminophen and/or antibiotics for pain and/or infection and those with peripheral lesions that connected to the intrapleural region were included.

Spontaneous regression was considered as an over 20% decrease in the lesion size over 3 months when compared with the size at the original onset. We analyzed the patient age at the original onset, original lesion size, and lesion location retrospectively. Congenital lesions were considered as having an onset at 0 years of age, even when diagnosed prenatally.

Statistical analyses involved the 2-sided *t* test for normally distributed data and the F-test for assessment of less than 5 patients. A receiver operating characteristic (ROC) curve was drawn using the SPSS software (IBM Corp., Ar-

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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

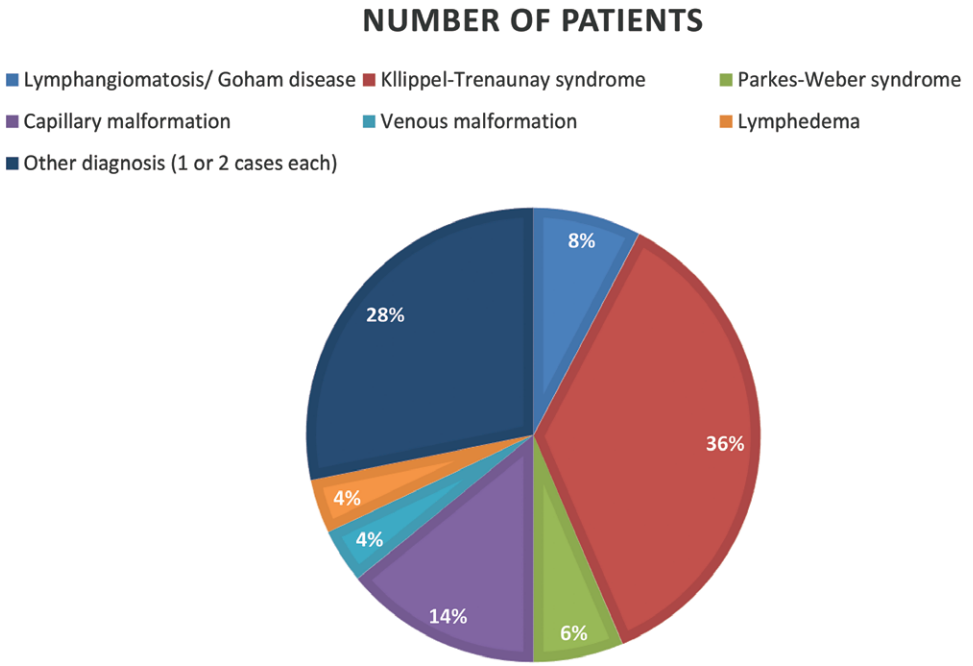

Fig. 1. List of misdiagnosis and other diseases excluded from the study criteria.

monk, N.Y.). This study was approved by the Saitama Children's Medical Center's institutional ethical board.

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 2. Clinical Characteristics of the Patients

Types	Macrocystic	Mixed Type	Microcystic	Total
Subtotal	111	14	28	153
Sex (F:M)	48:63	4:10	14:14	66:87
Age (y), mean ± SD	2.2±3.0	1.4±1.9	0.89±1.4	1.9±2.8
Maximum diameter (cm), mean ± SD	4.2±1.7	4.8±1.9	—	—
Spontaneous regression				
Positive	72	5	0	77
Negative	39	9	28	76

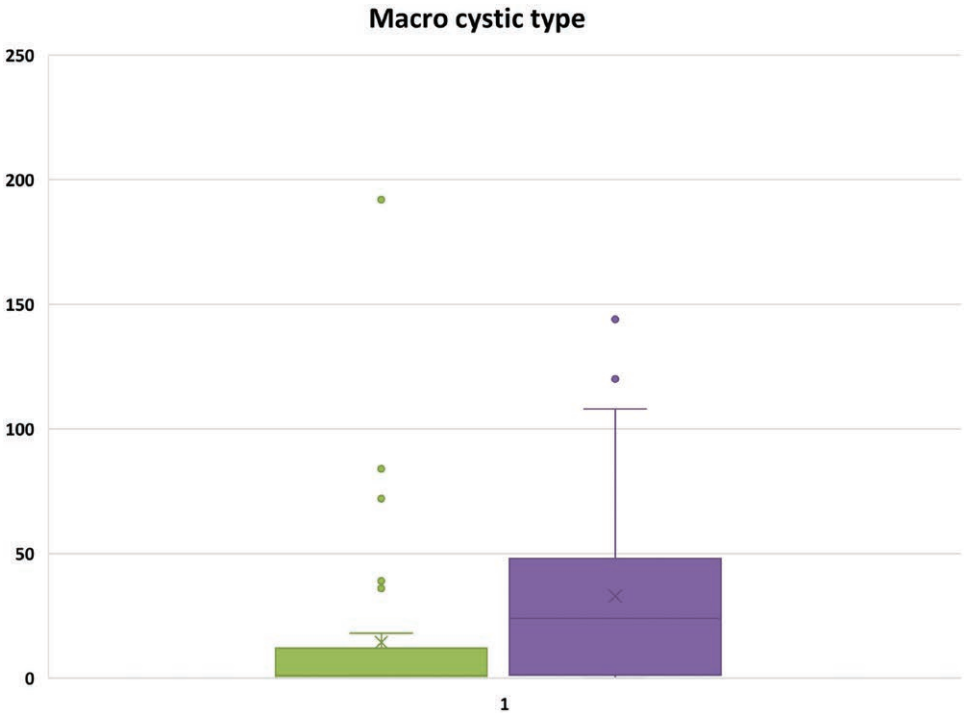

Fig. 2. Macrocystic lymphangiomas. Spontaneous regression is common in older patients (mean, 2.2 years; range, 1.2–2.7 years; $P = 0.005$).

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[2]; 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[3,4] and congested lymph flow due to blockage resulting in cyst expansion.[5,6] 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.[7] Furthermore, previous lymph flow studies of lymphangiomas with lymphangiog-

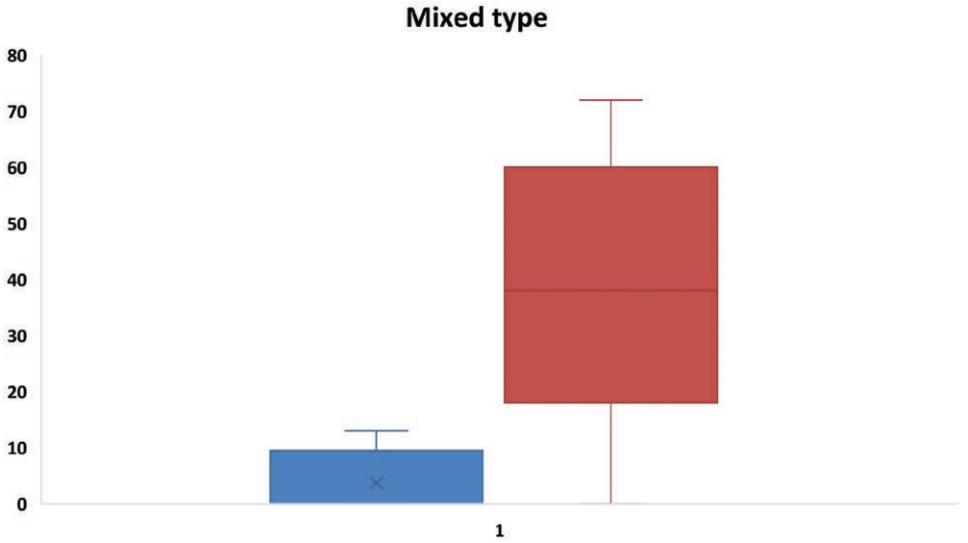

Fig. 3. Mixed lymphangiomas. Spontaneous regression is common in older patients, similar to macrocystic lymphangiomas (mean, 1.4 years; range, 0.3–3.2 years; $P = 0.001$).

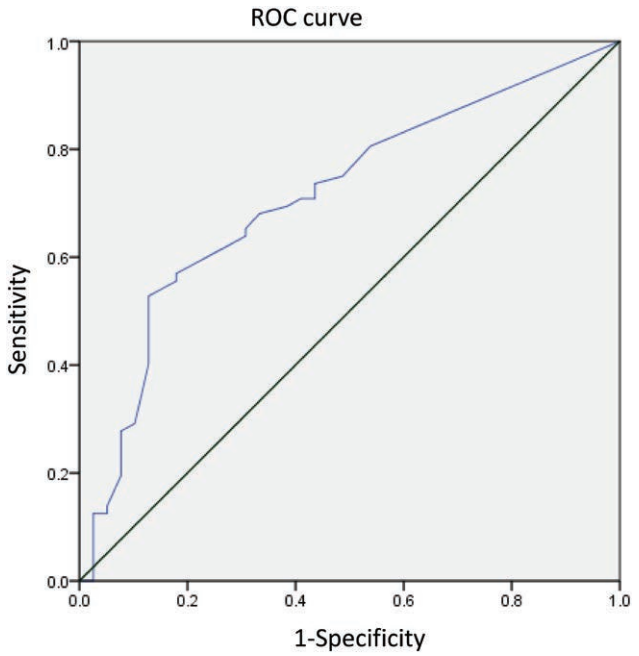

Fig. 4. ROC curve for spontaneous regression. The cutoff age for spontaneous regression of macrocystic lymphangiomas is 1.6 years (sensitivity, 0.53; specificity, 0.87; AUC, 0.712).

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[8–11] (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.[12–14] 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.[15–17] 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).[18] Most previously reported spontaneous regressions were macrocysts, and this is compatible to our findings (Table 4).[19–29]

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.[30]

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

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

Patient Characteristics	Macrocystic Type		*P*	Mixed Type		*P*	Microcystic Type	
Spontaneous regression	Positive (n = 72)	Negative (n = 39)		Positive (n = 5)	Negative (n = 9)		Positive (n = 0)	Negative (n = 28)
	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	0.01*	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	0.06	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)

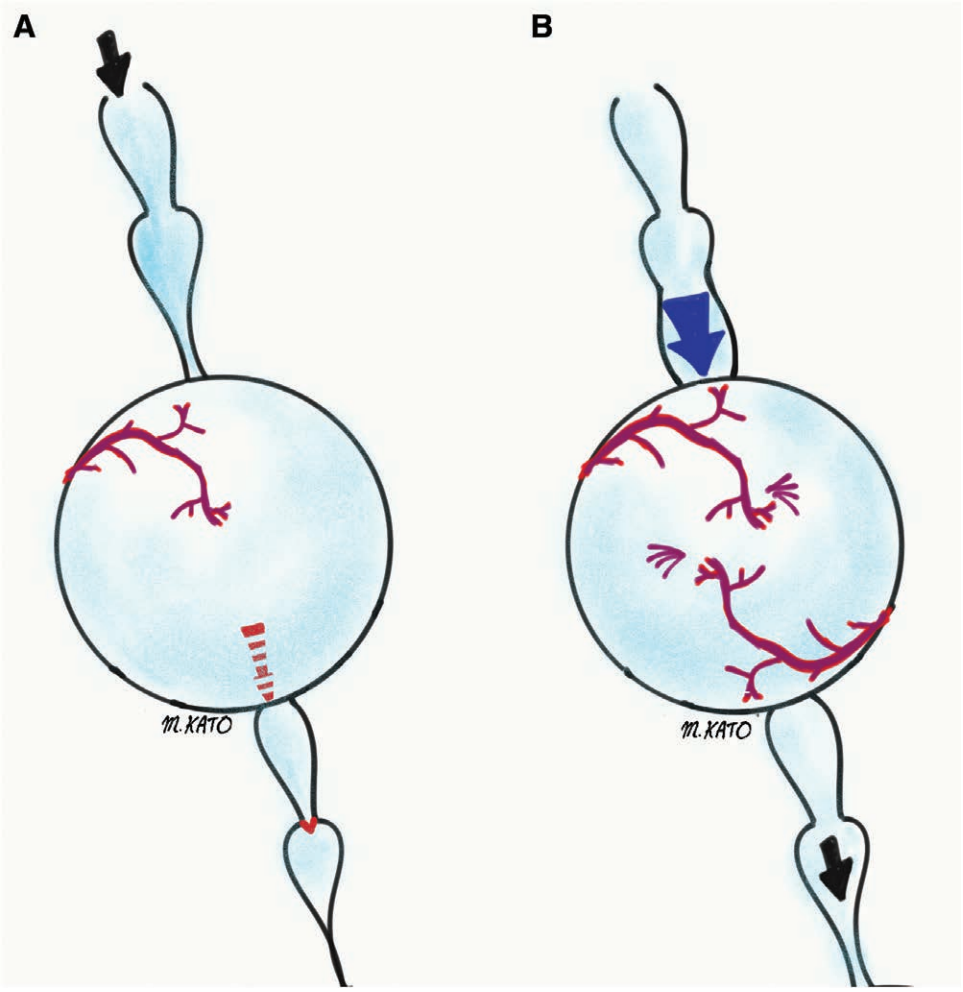

Fig. 5. Concepts of the difference in lymph flow in lymphangiomas. Black arrow shows normal lymph flow. Blue large arrow shows an increased lymph flow. Red interrupted arrow shows a decreased lymph flow. Red small triangle shows valve malformations. A, Nonregression model of lymphangioma. Due to the obstruction or damaged out-flow, in-flow also decreased. B, Regression model of lymphangioma. In-flow increased more than the out-flow capacity. Out-flow may be intact.

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.

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

Table 4. Previously Reported Cases of Spontaneously Regressed Lymphangiomas

No.	Author	Year	Journal	Number	Type	Gene	Onset Age	Size	Location	Time to Shrink	Citation
1	Rodis et al.[19]	1988	*Obstet Gynecol*	1	Macro	21 Trisomy	Prenatal 14th week	N/A	Neck	2 wk	19
2	Warner et al.[20]	1990	*Prenat Diagn*	3	Macro	18 Trisomy	Prenatal 13th week	N/A	Neck	2 wk, 5 wk	20
3	Hill et al.[21]	1991	*Prenat Diagn*	3	Macro	18 Trisomy	Prenatal 13th, 14th week	N/A	Neck	3–4 wk	21
4	Wu et al.[22]	1995	*Int J Gynaecol Obstet*	1	Macro	None	Prenatal 31st week	5.1×2.4 cm	Mediastinum	10 wk	22
5	Kennedy et al.[23]	2001	*Laryngoscope*	11	Macro	N/A	At birth to 42 years old	N/A	Neck	N/A	23
6	Joo et al.[24]	2007	*Yonsei Med J*	1	Macro	None	18 years old	11 cm	Intraabdomen	2 mo	24
7	Kiyota et al.[25]	2008	*Fetal Diag Ther*	3	Macro	Noonan 2, Turner 1	Prenatal 13th week	3.3×3.2 cm	Neck	3–17 wk	25
8	Lee et al.[26]	2011	*World J Gastroenterol*	1	N/A	None	54 years old	Multiple	Colon	12 mo	26
9	Vasconcelos et al.[27]	2011	*An Bras Dermatol*	1	Macro	None	4 mo	5.8×4.8×4.0 cm	Parotid grand	1 mo	27
10	Gilony et al.[28]	2012	*J Pediatr Surg*	11	Macro or mixed	None	N/A	N/A	N/A	6 mo to 7 y, details not shown	28
11	Gelas et al.[29]	2016	*J Pediatr Urol*	3	Macro	None	Mean 6 years old	N/A	Testis	N/A	29

PubMed database; search words "regression," "resolution," and "involution" combined with "lymphangioma," "lymphatic malformation," or "hygroma" on February 28, 2017.
N/A, not available.

spontaneous regression within 3 months after the initial onset, and this might be associated with lymph flow pattern variations.

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