

# Primary Intestinal Lymphangiectasia and its Association With Generalized Lymphatic Anomaly

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## Abstract

**Background:** Lymph is a fluid originating in the interstitial spaces of the body that contains cells, proteins, particles, chylomicrons, and sometimes bacteria.

**Objectives:** The aim of the present study is to demonstrate that primary intestinal lymphangiectasia (PIL) results from a disruption of lymphatic circulation, thus corresponding to a secondary rather than a primary event in the context of generalized lymphatic anomaly.

**Materials and Methods:** In this case series and record review, an analysis of intestinal lymphatic involvement was performed on patients diagnosed with PIL between 1965 and 2013. Of the 21 patients included in the study, 10 had been diagnosed before 5 years of age (1 prenatal), 8 between 5 and 18 years of age, and 3 while older than 18 years of age. The follow-up period varied between 1 and 34 years. Clinical data, blood and fecal parameters, imaging studies, endoscopy results, biopsy analyses, treatment details, and outcome information were collected from medical records. Endoscopy, histological studies, magnetic resonance imaging, and lymphoscintigraphy were performed on all patients. Dynamic intranodal lymphangiography was performed on 8 patients.

**Results:** Central lymphatic channel obstruction was identified in 12 patients (57%). Associated lymphatic malformation (LM) was present in 16, diarrhea in 10, chylothorax in 11, chylous ascites in 10, pericardial effusion in 6, coagulopathy in 3, and osteolysis in 7.

**Conclusions:** We consider intestinal lymphangiectasia not as an entity in itself, but as a consequence of lymphatic flow impairment in the thoracic duct, producing chylous reflux into the intestinal lymphatics.

**Keywords:** Primary Intestinal lymphangiectasia, Lymphangiomatosis, Protein-Losing Enteropathy, Generalized Lymphatic Anomaly

## 1. Background

Lymph is a fluid originating in the interstitial spaces of the body that contains cells, proteins, particles, chylomicrons, and sometimes bacteria. It enters the lymphatic system, a complex network of fine vessels with unidirectional valves, and gains access to the lymph nodes before joining the cisterna chyli (CC). The lymph then reaches the thoracic duct (TD), which drains into the major circulation system. A large proportion of the total amount of lymph, called chyle, originates in the abdominal organs, particularly the intestine and the liver (1).

As Mulliken et al. suggested in 1982 (2), the nomenclature of congenital vascular anomalies is the greatest obstacle to understanding and managing them effec-

tively. Although currently unused, congenital lymphatic anomalies have historically been classified according to their anatomopathological characteristics (3-5); however, these classifications sometimes overlap and are generally quite confusing. To obtain a homogeneous classification and to promote its use, the international society for the study of vascular anomalies (ISSVA) published a classification scheme in 1996, which was expanded and updated in 2014 (6).

Primary intestinal lymphangiectasia (PIL) is a rare entity first described by Waldmann in 1961 (7). Its general prevalence is unknown, since less than 500 cases have been reported worldwide. PIL was traditionally thought to have been caused by a congenital intestinal lymphop-

athy featuring dilated intestinal lacteals, resulting in lymph leakage into the small bowel lumen responsible for protein-losing enteropathy leading to lymphopenia, hypoalbuminemia, and hypogammaglobulinemia. It can appear in isolation or in association with other extraintestinal lymphatic anomalies. The diagnosis requires an endoscopic and histologic confirmation of the lymphatic anomaly. The keystone of treatment is a low-fat diet (8, 9).

Generalized lymphatic anomaly (GLA), which is synonymous with “generalized cystic lymphangiomas,” “cystic angiomas,” or “lymphangiomas,” has systematically been reported in the literature to have initially been described by Redenbacher in 1828 (wrongly referred to as Rodenberg in most reports) (10, 11). However, this account is not true, because in Redenbacher and De Ranula *Sub Lingua* 1828 thesis concerning a lymphatic malformation, he referred to a ranula without implying the existence of any lymphatic pathogenesis (12). Thus, the first description of a GLA was actually provided by Milligan in 1926 (13), and the first description with bone involvement was delivered by Harris and Prandoni in 1950 (14). GLA is a rare multisystem disorder that is characterized by diffuse infiltration of common lymphatic malformations (LMs) in any tissue with lymphatic vessels (3). Its general prevalence is unknown, since less than 200 cases have been reported worldwide, and its diagnosis and treatment still remain challenging.

Among the scientific community, the belief is widespread that each symptom of congenital lymphatic anomalies is a primary entity. However, the nomenclature used frequently overlaps, and is in many cases confusing. This nomenclature is based on the established classifications of congenital lymphatic anomalies, which are based, above all, on histology (3-5). An updated classification scheme was adopted by the ISSVA in 2014 (6) (Box 1).

The ISSVA 2014 classification scheme is not yet widely used by the scientific community. According to this classification, common LMs correspond to the previously misnamed lymphangioma due to an improperly developed lymphatic system. On the other hand, channel-type LMs are entities that are the result of an obstruction, aplasia, or defect in the chyle evacuation process. GLA is a generalized lymphatic disorder with visceral involvement, osteolysis, and/or central conducting lymphatic anomalies. Gorham’s syndrome is characterized by osteolysis with cortical destruction. It is essential to differentiate between these various lymphatic malformations because their morbidity rates and treatment methods differ according to the type.

Several disorders belong to the channel-type LMs group, including chylothorax, chylous ascites, lymphangiectasia with protein-losing enteropathy in the context of a LM (previously called PIL), chylopericardium, and chyluria. According to this classification, intestinal lymphangiectasia must not be considered as a primary

disorder. Moreover, because it can be part of a generalized lymphatic disorder, such as GLA, it must be named lymphangiectasia with protein-losing enteropathy in the context of an LM. The same affirmations are applicable to primary chylothorax and primary chylous ascites. Along these lines, Servelle (15) observed 120 patients with congenital malformations of the intestinal lymphatic vessels by intestinal lymphography and found that the malformations were secondary to hypoplasia of the CC and to anomalies in the mesenteric nodes. Consequently, the intestinal vessels could not drain effectively, dilating and losing their valve function and thus allowing chyle to reflux. When one of these lymphatic vessels of the mesentery or the gastrointestinal wall was dilated excessively, it broke toward the abdominal cavity, producing chylous ascites. When the dilated vessel was in the intestinal mucosa and broke toward the lumen, protein-losing enteropathy was produced. Due to the hypoplasia of the CC, the chyle absorbed by the intestine had to drain through diaphragmatic collaterals that could dilate and break toward the pleural cavity or pericardium, producing chylothorax or chylopericardium.

Following the ISSVA classification, it is necessary to substitute “diffuse lymphangiomas” for the term “generalized lymphatic anomaly.” The suffix “oma” implies increased endothelial turnover. However, as Meijer-Jorna et al. (16) and Dellinger (17) have shown, there is no cellular proliferation in LMs.

## 2. Objectives

Our purpose is to show that primary intestinal lymphangiectasia (PIL) is a secondary event which results from a disruption of lymphatic circulation in the context of generalized lymphatic anomaly. Increasing knowledge of the pathology of this entity could improve its treatment in the future.

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### Box 1. ISSVA 2014 Classification for Lymphatic Malformations (6)

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#### ISSVA 2014 Classification

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#### Common (cystic) Lymphatic Malformations (LM)

#### Generalized Lymphatic Anomaly (GLA)

#### LM in Gorham Stout disease

#### Channel type LM

#### Primary lymphedema

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## 3. Materials and Methods

This is a case series and record review of 21 patients with intestinal lymphatic involvement who were di-

agnosed and/or followed up on in a tertiary hospital between 1965 and 2013. The diagnoses included in this study were PIL, primary chylous ascites, intestinal LM, and protein-losing enteropathy in the context of an associated LM. Most patients received different diagnoses depending on the specialist in charge (e.g., gastroenterologist, radiologist, pathologist, general practitioner, or surgeon). We kept the original nomenclature on each patient's file for the first diagnosis, taking into consideration that all of them clinically presented with evident protein-losing enteropathy and were matched with the typical clinical course of the so-called primary intestinal lymphangiectasia.

Patients with any of these entities secondary to pathology other than a primary LM were excluded from consideration, as well as patients with primary LM but without intestinal lymphatic involvement. Access to medical records was a limiting factor: 5 patients' records had already been destroyed due to the significant length of time since their death.

Informed consent was obtained formerly from each patient included in the study and was available in each patient's records. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by our institution's human research committee.

The following data were systematically collected from the patients' files: demographic information, clinical symptoms, complications (growth, digestive symptoms, frequency of infections, tetany, associated LM, edema, thrombosis, coagulopathy, and osteolysis), diagnostic tools (blood parameters, imaging studies, endoscopy, and biopsies), and treatments. The blood parameters analyzed included total proteins, albumin, lymphocytes, calcium, cholesterol, immunoglobulins, stool fat, and  $\alpha_1$ -antitrypsin. The chylous effusion diagnosis (chylothorax or chylous ascites) was based on the findings of the liquid attained by puncture: milky aspect, triglyceride levels > 110 mg/dL, and presence of chylomicrons.

A histologic diagnosis was made for each patient, complementing regular hematoxylin-eosin stains with immunohistochemistry for D2-40, a monoclonal antibody to an Mr 40,000 O-linked sialoglycoprotein, which is a selective marker of lymphatic endothelium (18). In these cases, paraffin-embedded tissue blocks were selected and sections from the blocks were cut off and placed on glass slides coated with 3-aminopropyltriethoxysilane. They were then incubated with the human D2-40 monoclonal antibody (Signet laboratory, Dedham, MA, USA) at 1:200 dilution for 60 minutes at room temperature, then with biotinylated anti-mouse immunoglobulin for 15 minutes, and then with avidin-biotin complex reagent (LSAB kit, Dako, Carpinteria, CA) for another 15 minutes. After these procedures, they were reacted with a 3, 3'-diaminobenzidine tetrahydrochloride (Mutoukagaku, Tokyo, Japan) solution

and 0.01% (weight/volume) hydrogen peroxide for 2 to 5 minutes at room temperature, and counterstained with hematoxylin.

The intranodal lymphography was performed by first positioning the patient on the radiologic table. Then, under ultrasonography guidance, both the right and left inguinal nodes were punctured with a 21 G catheter. Lipiodol was injected into the inguinal node by a slow-speed bomb (infusion rate 0.21 mL/s) with an approximate total dose of 4 mL. Next, radiographs were conducted in anteroposterior and posteroanterior projections every 15 minutes for the first hour, and at 12 and 24 hours afterward.

In the intradermal lymphoscintigraphy, the first step was the subcutaneous injection of the radiotracer ( $^{99m}\text{Tc}$ -nanocolloid or  $^{99m}\text{Tc}$ -MAA, dose 37 - 185 MBq) in the first interdigital space of the lower limb with a 25 - 30G catheter. The patients were then asked to walk. The images were made with anteroposterior and posteroanterior projections using a gamma camera at 20 minutes, and at 2 and 24 hours afterward.

Some diagnostic procedures were not available when some patients were first diagnosed, and were therefore performed during their follow-up instead.

The data were analyzed with SPSS statistic 17 multilanguage. Medium, median and standard error were used for quantitative variables, and absolute and relative frequencies for qualitative ones.

## 4. Results

### 4.1. Demographic Data and Clinical Evolution

A total of 21 patients with PIL were enrolled for analysis, of whom 11 were male and 10 were female. Demographic data and clinical evolution are presented in Table 1. Ten patients had been diagnosed before 5 years of age (1 prenatally), 8 patients at between 5 and 18 years of age, and 3 patients at older than 18 years of age. The follow-up period varied between 1 and 34 years (median 6). One patient had Noonan syndrome, and two patients were siblings.

Patients presented with associated LM (16), diarrhea (10), chylothorax (11), chylous ascites (10), pericardial effusion (6), coagulopathy (3) and osteolysis (7). Two patients presented with thrombosis (one in the superior mesenteric vein and the other in the right jugular vein). The right jugular vein thrombosis could be explained by prolonged vessel catheterization for parenteral nutrition. In the patient with thrombosis in the superior mesenteric vein, no related cause was identified. As for analytical evolution, all of the patients but 5 presented with a pattern of chyle loss (hypoproteinemia, hypoalbuminemia, lymphopenia, hypogammaglobulinemia and tendency to hypocalcemia); 7 presented with steatorrhea and 11 with fecal loss of protein.

**Table 1.** Demographic Data and Clinical Evolution

Data	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Sex	Male	Female	Female	Male	Male	Female	Male	Female	Male	Male	Man	Female	Female	Male	Male	Female	Female	Female	Male	Male	Female	Male
Age at diagnosis, y	4	11	1.5	18	12	39	9	0.2	0 <sup>a</sup>	2	3	12	25	9	3	33	0 <sup>b</sup>	15	1	1	16	
Follow-up period, y	5	11	34	14	3	3	5	24	1.5	17	22	6	14	2	1 <sup>c</sup>	4	12	1	2	9	3	
Current age, y	9	22	36	32	15	42	14	24	1.5	19	25	18	39	11	4	37	12	15	3	10	19	
Extraintestinal lymphatic malformation	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Current weight, percentile	3	90	50	50	3	40	65	35	3	38	75	3 <sup>d</sup>	65	25	60	10	25	25	<15	80	60	
Current height, percentile	<3	97	50	90	3	75	50	45	<1	41	50	3	59	10	5	25	50	25	<3	75	75	
Diarrhea	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No
Infections	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Hypocalcemic tetany	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No
Chylothorax	No	Yes	No	No	No	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Chylous ascites	No	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No
Chylopericardium	No	No	No	No	No	Yes	No	No	No	No	No	Yes	No	Yes	Yes	No	No	No	Yes	No	Yes	Yes
Edemas	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	No	No	No	No	No
Thrombosis	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No
Coagulopathy	No	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	Yes	No	No	No
Osteolysis	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

<sup>a</sup>Diagnosed at birth.

<sup>b</sup>Diagnosed prenatally.

<sup>c</sup>Death due to respiratory insufficiency secondary to chylothorax.

<sup>d</sup>Gastrostomy.

#### 4.2. Endoscopy and Histological Study

An endoscopy and a histological study were performed on each of the patients, resulting in the diagnosis of intestinal lymphangiectasia in 11 patients. A single endoscopy was sufficient for all of the patients except for 2, for whom this diagnosis was not obtained until the third endoscopy. The previous histological diagnoses were either nonspecific chronic duodenitis or no alterations. An exploratory laparotomy was performed on only one patient (patient 12), in whom a profuse milky liquid was observed in the abdominal cavity. Multiple biopsies were collected with no significant result. The examination was compatible with intestinal lymphangiomas.

A biopsy of extraintestinal lesions was performed on 9 patients. Samples were acquired from the skin, pleura, masses of several locations, and/or bone. Of these patients, 4 were diagnosed histologically with LM using a single biopsy; in 2 patients, it was necessary to repeat the biopsy to reach this diagnosis. Another 2 patients required reevaluation of the histological study once the case was clarified by the clinical course and imaging, thus confirming the diagnosis, and in 1, the biopsy was inconclusive.

#### 4.3. Magnetic Resonance Imaging (MRI)

Thoracoabdominal MRI was performed on all of the patients. The findings revealed thrombosis (2), an increase in mesenteric or mediastinic fat density (10), pleural effusion (8), pericardial effusion (2), ascites (5), gastrointestinal wall thickening (11), interlobular septa thickening (3), an increase in the number of adenopathies (5), associated LMs (16), and bone lesions (7).

#### 4.4. Intradermal Lymphoscintigraphy

Intradermal lymphoscintigraphy of one or several limbs was performed on all of the patients. The findings were as follows:

- No significant alterations: 5 patients (24%).
- Lymphatic obstruction, defined as the presence of collateral circulation, no radiotracer progression, reflux, or lymphatic leak: 8 patients (38%).
- Limb lymphedema, defined as the absence of lymphatic nodes with remarkable lymphatic backwater: 9 patients (43%).

#### 4.5. Intranodal Lymphography

Intranodal lymphography was performed on 8 patients due to the difficulty of controlling chylous effusions. Lymphatic obstruction was identified in 6 of these patients, in 2 of whom the obstruction had already been detected by lymphoscintigraphy. Therefore, a total of 12 patients were identified as having lymphatic obstructions (57%).

#### 4.6. Diagnosis

In the medical records, the first 8 patients were classified with PIL, with or without chylous effusions and/or limb lymphedema and/or genital lymphedema in an independent diagnosis. Patient 9 was diagnosed with primary chylous ascites and associated LM. At first, patients 10, 11, and 12 were diagnosed with PIL, and their diagnosis changed to lymphangiomas when chylous effusions and LM appeared during their evolution. Patients 13 - 16 were diagnosed with lymphangiomas. Initially, patients 17, 19, 20 and 21 had been diagnosed with Gorham's syndrome, which was changed afterwards to lymphangiomas. Patient 18 was first diagnosed with lymphoma, then with Gorham's syndrome, and finally was diagnosed as having lymphangiomas.

#### 4.7. Treatments

All of the patients were administered a low-fat diet supplemented with medium-chain triglycerides (MCT), vitamins, and calcium; other treatments are shown in Table 2.

The medical treatments used were sirolimus (9 patients), octreotide (6), propranolol (4), interferon- $\alpha$  (4), corticoids (3), tranexamic acid (2), azatioprin (1), sildenafil (1), thalidomide (1), vincristine (1), bevacizumab (1), and zoledronic acid (1). The surgical treatments used were total or partial removal of LMs (6), hydrocelectomy (2), chemical pleurodesis (2), pleurectomy (1), limb lymphedema liposuction (1), percutaneous TD embolization (1), TD ligation (1), LM sclerotherapy with OK-432 (1), and orthopedic surgery (1). At the end of the follow-up period, 11 patients were stable, defined as not having required hospitalization in the last 2 years. It must be noted, however, that sirolimus had just been initiated in patients 10, 12, 14, and 18, and TD ligation had just been performed on patient 20. Therefore, the effectiveness of these treatments cannot be evaluated. All of the patients were alive at the end of the follow-up period except for patient 15, who died of chylothorax complications months after his diagnosis.

#### 4.8. Groups According to the Lymphatic Involvement

According to the lymphatic involvement, our patients could be classified into two groups: Group 1 includes patients without evidence of soft tissue LM, and group 2 includes patients with evidence of soft tissue LM. The first 5 patients presented with diarrhea and without LMs or osteolysis, and 2 patients had chylous effusions. Patient 5 had Noonan syndrome. In all of the patients, only a single endoscopy was required for them to be diagnosed with PIL. The thoracoabdominal MRIs showed no LM or osteolysis. The intradermal lymphoscintigraphy was normal in 1 patient and detected obstructions in 4 patients. All of the patients were diagnosed as having PIL with or

**Table 2.** Treatments Other Than Diet and Stabilization

Patient	Treatments		
	Medical	Surgical	Stabilization
1			Yes
2			Yes
3			Yes
4			Yes
5	Tranexamic acid + octreotide <sup>a</sup> ; Propranolol <sup>a</sup> ; Thalidomide <sup>a</sup> ; Sirolimus		No
6	Corticoid; Azatioprin <sup>a</sup>	Chemical pleurodesis	No
7		Hydrocelectomy	Yes
8	Tranexamic acid + octreotide	Both hand liposuction	No
9	Octreotide		No
10	Sirolimus	Genital LM extirpation; Lymphedema extirpation	No
11		Hydrocelectomy; Lymphedema extirpation; Foot LM extirpation	Yes
12	Octreotide <sup>a</sup> , Propranolol <sup>a</sup> ; Sildenafil; INF- $\alpha$ <sup>a</sup> ; Corticoid, Sirolimus		No
13		Several LM extirpation	Yes
14	Octreotide <sup>a</sup> ; Propranolol; Bevacizumab <sup>a</sup> ; Sirolimus		Yes
15	INF- $\alpha$	Several C; Right pleurectomy; Sclerotherapy with OK-432, unsuccessful.	Died due to respiratory insufficiency
16	INF- $\alpha$		No
17	Sirolimus		Yes
18	Sirolimus		Yes
19	Corticoid <sup>a</sup> ; Vincristin <sup>a</sup> ; Sirolimus		No
20	INF- $\alpha$ +; Zoledronic acid; Octreotide <sup>a</sup> ; Propranolol; Sirolimus	Orthopedic surgery; Several LM extirpation; Percutaneous TD embolization; unsuccessful TD ligation	No
21	Sirolimus	Chemical pleurodesis	Yes

<sup>a</sup>Removed due to lack of effectiveness.

without chylous effusions as an independent and primary diagnosis. They were all stable with conservative treatment, except for patient 5, in whom several treatments were attempted: tranexamic acid with octreotide, propranolol, thalidomide, and recently, sirolimus.

The remaining 16 patients presented with LMs. Of these, 5 had diarrhea, 11 had chylous effusions, and 7 had osteolysis. Six patients were diagnosed as having PIL by endoscopy and histological study, with a second and third endoscopy being required for 2 of the patients. One patient required the exploratory laparotomy previously described. The thoracoabdominal MRIs showed associated LMs in all patients and bone lesions in 7. The intradermal lymphoscintigraphy was normal in 3 patients, detected obstructions in 5 patients, and revealed lymphedema in

9 patients. Intranodal lymphography was performed on 8 patients because of difficulty in controlling chylous effusions. In 6 of these patients, lymphatic obstructions were identified; of these patients, the obstruction had already been observed by lymphoscintigraphy in 2.

The first 3 patients were classified as having PIL, with or without chylous effusions and/or limb lymphedema and/or genitals lymphedema as an independent diagnosis. Patient 9 was diagnosed with primary chylous ascites and associated LM. The rest of the patients had finally been diagnosed with lymphangiomatosis. All of the patients received other therapies in addition to conservative treatment. At the end of the follow-up period, 7 patients were stable; all were alive at the end of the follow-up period, except for patient 15, who died of chylothorax complications.

## 5. Discussion

We have analyzed central conducting lymphatic anomalies, evaluating their repercussions on the digestive system, and we have reclassified their lymphatic involvement in the function of primary lymphatic disorder according to the ISSVA 2014 classification scheme. Furthermore, as one of the great contributions of this study, we have demonstrated that intestinal lymphangiectasia is not a primary entity, but is rather part of the clinical spectrum of TD disruption.

### 5.1. Need of a New Classification

Our study is a good example of the confusion that the classic nomenclature creates. Some patients had the same symptoms but different diagnoses. For example, patients 6, 8, 10, and 12 had the same symptoms of protein-losing enteropathy, chylous effusions, and LM; patients 6 and 8 were diagnosed with PIL, chylous effusions, and LM as primary and independent diagnoses, and patients 10 and 12 were diagnosed with diffuse lymphangiomatosis. In the same way, patients 17, 18, 19, 20, and 21 were first classified as having Gorham's syndrome, but the diagnoses were eventually changed to lymphangiomatosis. Therefore, a new nomenclature based on a more comprehensive classification scheme is clearly necessary. According to the ISSVA 2014 classification, we believe that all of our patients had channel-type LM and/or GLA. The first 5 patients only had intestinal involvement, whereas the other 6 patients had osteolysis and involvement of the intestines, soft tissue, and viscera. None of the patients had common LM.

Three of our patients presented with coagulopathy with recurrent bleeding. One is patient 5, who has Noonan syndrome, which has an established association with coagulopathy and recurrent bleeding (19, 20). However, the combination of coagulopathy, recurrent bleeding, and chylous effusions in the other two patients lead us to believe that these patients could instead have kaposiform lymphangiomatosis (21-23). These patients' biopsies would need to be reviewed to confirm this conclusion.

### 5.2. Diagnosis Procedures

Biopsy and histology have traditionally been considered the gold standard in testing for lymphatic anomalies. However, histological classifications can lead to misunderstanding. Increasing numbers of authors believe that their diagnoses should be based not only on histological information, but also on clinical and radiological characteristics (10,11). Authors such as Wunderbaldinger et al. (11) and Nesbit et al. (24) have shown that distinguishing the type of vascular malformation (arterial, venous, lymphatic, or mixed) is possible with image tests (MRI, sonography, TAC, angiography, and scintigraphy). Kreindell and Alomari have described patterns in the images revealed by MRI and/or TAC in 41 patients with cen-

tral conducting lymphatic anomalies (25). Along these lines, Lala et al. has reclassified 51 patients with lymphatic anomaly with bone involvement in GLA or Gorham's syndrome according to the radiologic characteristics (10).

In our study, biopsies of extraintestinal lesions were taken from 9 patients. The first sample was diagnostic in 44%; with a second sample, the diagnostic capacity increased to 67%. In 22%, biopsy was only useful for confirming the diagnosis already determined based on the presented symptoms and radiology, and in 11 the biopsy was inconclusive. We agree that the diagnosis of LM is necessarily based on clinical analysis and radiology histology is not sufficient, and is even unnecessary and iatrogenic in some cases (rib biopsies are contraindicated, because they can lead to chronic pleural effusion) (17, 26).

According to the imaging results, 2 patients presented with cutaneous involvement, and 7 had bone lesions; there was thoracic involvement in 7 and abdominal involvement in all of them. In 14 patients, there was thoracoabdominal involvement and in 7 such involvement was in a single region. These findings are consistent with the results displayed by Kreindell and Alomari (25). Therefore, we agree with these authors that clinical examination and imaging tests are the first diagnostic step in central conducting lymphatic anomalies.

Regarding the specific case of intestinal lymphangiectasia, biopsy has been considered the predominant method of diagnosis. However, due to the patched pattern, sometimes no anomalies are found in these tests, which forces their repetition or the requirement for an enteroscopy or laparotomy. In our sample, although all of the patients had intestinal involvement, only 11 patients were diagnosed with intestinal lymphangiectasia by endoscopy and a biopsy. No alteration was found in those patients with ascites and/or gastrointestinal wall thickening on the MRI, which shows its incapacity to detect all of the cases with intestinal lymphangiectasia, only detecting those cases with mucosal involvement. Therefore, we believe that the diagnosis of intestinal lymphangiectasia can be assumed if the MRI shows diarrhea, fecal protein loss, chylous effusions, LM and/or intestinal involvement (that is, lymphangiectasia with protein-losing enteropathy in the context of GLA). However, endoscopy and a biopsy are necessary if there is only diarrhea and/or fecal protein loss and/or intestinal involvement shown on the MRI, because these findings are not pathognomonic of intestinal lymphatic involvement.

Moreover, it is necessary to reintroduce lymphatic imaging in the study of central conducting lymphatic anomalies, above all intranodal lymphography and dynamic lymphography, because although scintigraphy is easier to perform, it is less specific and precise (27-30). With these tests, it is possible to identify the delay or non-opacification of the proximal ducts, chylous reflux, a focal leak, or anomalies in the terminal portion of the TD, which is crucial information given that their possible treatments are very different.

In our study, lymphatic obstruction was detected in 57% of the patients. Although it had not been identified in all of the cases, we believe that an obstruction or a leak is the cause of all of the clinical symptoms of the central conducting lymphatic anomalies in our sample, protein-losing enteropathy, chylous ascites, and gastrointestinal wall thickening observed on the MRI. We completely agree with the current ISSVA classification scheme and with those authors who advocate that these anomalies are not primary disorders, but are instead secondary to a disruption in chyle evacuation.

One example demonstrating that it is not always possible to show the disruption in chyle evacuation by intranodal lymphography, and much less by intradermal scintigraphy, is the case of patient 20. Although both of those tests were normal, we performed a percutaneous TD embolization (which was ineffective), and afterwards, a surgical ligation with resolution of the recurrent chylothorax that this patient presented. This successful result confirms the TD disruption and the presence of lymphatic collaterals as the cause of her chylothorax.

### 5.3. Treatment

For all complex lymphatic anomalies, conservative treatment is essential; other therapies must be considered according to the clinical impact of the lesion. For intestinal symptoms, a low-fat diet supplemented with MCT must be followed. Treatment of complex lymphatic anomalies varies by the mechanism of lymphatic dysfunction and the location of active complications (26). Unfortunately, for the majority of children with engorged lymphatics, dysmotility, and reflux, interventional and surgical treatments are largely palliative. For symptoms related to reflux of lymphatic fluid, diversion of the fluid by embolization or surgical resection can improve symptoms, although recurrence or redirection of lymphatic fluid is inevitable. When lymphangiography demonstrates TD dysfunction, surgical resection of the terminal TD and microanastomosis to a valved vein is indicated. Focal leaks can potentially be treated by direct puncture of the CC, with subsequent embolization of the TD.

Systemic medical therapy is rapidly evolving. Cases have been described in which treatments such as sildenafil (31), propranolol (32-34), and bevacizumab have been effective (35), but cases of resistance to these drugs have also been reported (36, 37). Sirolimus, an mTOR inhibitor, has been reported to improve pleural effusions and mediastinal mass size (38-40). Preliminary results of a phase 2 clinical trial with sirolimus in the treatment of complex vascular anomalies were shown in the 20th workshop of ISSVA (41), not yet published. Regarding lymphatic anomalies, 25 patients were included and partial clinical response was observed in GLA, Gorham's syndrome and common LM. No activity was observed, however, in central conducting lymphatic anomalies.

In our sample, the conditions of 4 out of 5 patients

without visceral or bone involvement were controlled effectively with conservative treatment. The remaining patients received other treatments. Nine patients were treated with sirolimus, and in 1 patient a TD ligation was performed. It is too early to determine the treatments' efficacy because the treatments of the 5 patients with sirolimus and the patient with a TD ligation are in very early stages. Sirolimus could be described as effective in 2 patients: one used sirolimus only and the other used sirolimus in combination with bevacizumab and propranolol. In both patients, dose decrease is being undertaken.

### 5.4. Limitations

The primary limitation of our study is the rarity of complex lymphatic anomalies, which has resulted in a small sample size (despite our hospital being the primary reference center in the country for these anomalies) and the consequent inability of finding statistically significant differences in more variables. This limitation can also be observed in the literature. Another limitation is that we did not have access to 5 deceased patients' medical records because of the prolonged time since their death. Therefore, we could not investigate the vital prognosis of the described anomalies because we did not know these patients' causes of death. Finally, there are the limitations derived from the study design in terms of descriptive application, since we can only describe associations and not causal relationships.

### 5.5. Major Points for Clinical Practice

Intestinal lymphangiectasia is not a primary entity, but is instead part of the clinical spectrum of TD disruption. By lymphatic imaging, the mechanism of lymphatic disruption and the location of active complication can be detected, and, consequently, effective treatment can be administered. Further studies are needed to increase knowledge about this rare entity and to continue to improve treatment methods.

### 5.6. Conclusions

A new classification of lymphatic anomalies is needed, based on symptoms, radiology, histology, and physiology. The classification presented in 2014 by the ISSVA meets these requirements. Therefore, diagnoses must be reviewed, given that terms such as intestinal lymphangiectasia and lymphangiomatosis have changed. Intestinal lymphangiectasia is not a primary entity, but is instead a consequence of a TD disruption. This same physiopathology produces chylopericardium, chylothorax, and chylous ascites. Therefore, primary intestinal lymphangiectasia should be renamed lymphangiectasia with protein-losing enteropathy in the context of LM, lymphangiomatosis, and GLA. Finally, to choose an effective therapy, the treatment of LM must be directed toward the physiopathology of the lesion.

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