

Individual Approach for Treatment of Primary Intestinal Lymphangiectasia in Children: Single-center Experience and Systemic Review

Yiyoung Kwon

Samsung Medical Center <https://orcid.org/0000-0001-5600-2070>

Mi Jin Kim (✉ mijin1217.kim@samsung.com)

Samsung Medical Center, Sungkyunkwan University School of Medicine <https://orcid.org/0000-0002-4505-4083>

Eun Sil Kim

Samsung Medical Center <https://orcid.org/0000-0003-2012-9867>

Yon Ho Choe

Samsung Medical Center <https://orcid.org/0000-0003-1525-7688>

Research article

Keywords: Primary intestinal lymphangiectasia, children, individual approach, systemic review

Posted Date: September 8th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-61085/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published on January 7th, 2021. See the published version at <https://doi.org/10.1186/s12887-020-02447-5>.

Abstract

Background: Intestinal lymphangiectasia is a rare disease. Thus, prospective studies are impossible, and therapy is still controversial. Several medicines are suggested for treatment but there are no existing indications for drug choice and treatment guidelines. We experienced seven patients with primary intestinal lymphangiectasia who showed clinical improvement with different treatments.

Aim: We aimed to introduce the action mechanism of each drug and treatment overview in a single-center experience and a systemic review of second-line therapy for primary intestinal lymphangiectasia.

Method: Children under 18 years old diagnosed with intestinal lymphangiectasia from June 2000 to June 2020 were included in the study. Capsule endoscopy, MR lymphangiography, or whole-body MRI for investigating the extent of abnormal lymphatic vessels in addition to endoscopy and biopsy were conducted. The individual treatment approaches depended upon the lymphangiectasis locations involved.

Results: Only one patient showed a response to dietary therapy. One patient was successfully cured after two therapeutic lymphatic embolization. Octreotide was tried for two patients who had extensive lymphangiectasis. Lymphangiectasis recurred when octreotide was used for three months in one patient, and there was no effect in the other patient. Sirolimus was tried for four patients. Two of them had abnormal lymphatic lesions only in the intestine, and the others had extensive lymphangiectasis. The former group showed clinical improvement after 3 – 4 months of sirolimus treatment, whereas the latter group showed clinical improvement only after one month of sirolimus treatment.

Conclusion: Intervention is a potential therapeutic option for patients with focal abnormal lymphatic lesions. Octreotide is not an optimal choice for patients with extensive lymphangiectasis. Sirolimus is an effective and safe drug and can be the first drug of choice for patients with extensive lymphangiectasis.

Background

Intestinal lymphangiectasia is a rare disease that causes protein-losing enteropathy[1]. Clinical symptoms are induced by the excessive loss of lymphatic contents including protein, fat, and lymphocytes, resulting in hypoproteinemia and edema. Depending on the location of the injured lymphatic channel, pleural effusion, pericardial effusion, and retroperitoneal effusion can develop as clinical features[1, 2].

All factors causing elevated lymph drainage pressure could lead to dilatation and even rupture of the lymphatic vessels[3]. Intestinal lymphangiectasia is classified into primary or secondary intestinal lymphangiectasia. In secondary intestinal lymphangiectasia, known factors trigger lymphatic channel injuries, such as heart surgery, chemotherapy, infection, or toxic substances[4]. Primary intestinal lymphangiectasia is also called idiopathic lymphangiectasia because of the absence of a known cause and is often congenital.

Since Waldmanin reported the first case of intestinal lymphangiectasia in 1961, many case reports and articles have been published worldwide[3]. Nevertheless, treatment is still controversial, especially in primary intestinal lymphangiectasia because it is a rare disease. Therefore, prospective studies are impossible. The treatment of underlying disease is the main treatment strategy for secondary intestinal lymphangiectasia. In contrast, there is no existing consensus on the treatment for primary intestinal lymphangiectasia. To date, medicines like propranolol, octreotide, antiplasmin (e.g., tranexamic acid), and immunosuppressants (eculizumab and sirolimus) are suggested for treatment but there are no guidelines on indications for drug choice and treatment.

We experienced 18 pediatric patients with intestinal lymphangiectasia over 20 years. Among these patients, seven were diagnosed with primary intestinal lymphangiectasia. These seven patients showed clinical improvement with different treatment options. Our individual treatment approach depended upon the lymphangiectasis location involved. In this article, we aimed to introduce the action mechanism of each drug and an overview of our single-center treatment experience and systemic review of second-line therapy for primary intestinal lymphangiectasia.

Methods

Patient Characteristics and Diagnosis

Children under 18 years old diagnosed with intestinal lymphangiectasia from June 2000 to June 2020 in the Department of Pediatric Gastroenterology and Nutrition were evaluated retrospectively. We included patients who were followed-up for more than two years. Initially, the total number of patients diagnosed with intestinal lymphangiectasia was 18. We excluded nine patients found to have

secondary intestinal lymphangiectasia. Two patients were also excluded because they were lost to follow-up. Thus, seven patients were included in this study.

The diagnosis was based on typical endoscopic small bowel findings and confirmed by histology. Endoscopic findings like a snowflake appearance, diffusely prominent white villi, and small whitish patches were taken as suggestive features of intestinal lymphangiectasia[5]. Two or three biopsy segments were taken from the second or third part of the duodenum. Histological analysis revealed dilated lymphatic channels in the lamina propria.

Some patients underwent capsule endoscopy, MR lymphangiography, or whole-body MRI to investigate the extent of abnormal lymphatic vessels[6, 7]. Serum albumin and globulin levels and lymphocyte counts were checked. Also, the alpha-1 antitrypsin level in the stool was evaluated during the diagnostic process[8].

We roughly divided the patients into two main groups. Group A had only intestinal involvement and Group B had extensive involvement. Then, the intestinal involvement-only group was further divided into two subgroups, the focal and diffuse groups. Based on these divisions, the patients were classified into three groups for treatment. Group 1 was the focal intestinal group in which the abnormal lymphatic lesion(s) was only focally located in some segment of the intestine. Group 2 was another intestinal group in which the abnormal lymphatic lesion(s) was only located in the intestine but the lesion was diffusely located in all small bowel segments and the colon. Group 3 was an extensive-type in which abnormal lymphatic lesions existed as extra-intestinal lesions, such as in the pleural space, mediastinum, or retroperitoneum (Fig. 1).

Treatment and Follow-Up

All patients were initially managed with supportive therapies, such as correcting electrolyte imbalances, replacing albumin, and using diuretics. Some patients required paracentesis or thoracentesis because of effusion and total parenteral nutrition (TPN). After an improvement in their general condition, all patients were routinely supported with dietary therapy composed of high protein and medium-chain triglycerides, but not long-chain triglyceride. Calcium and fat-soluble vitamins were also supplemented[9].

Patients who did not show clinical improvement after 1–2 months of dietary therapy were considered for second-line therapy. Second-line therapy referred to lymphangiectasis treatment after the initial treatment (the first-line treatment was dietary therapy in this study) failed. The options for second-line therapy were surgery or radiologic intervention for focal-type lymphangiectasia, or medications like octreotide and sirolimus for the extensive-type of lymphangiectasia.

There are no standardized recommended doses or duration of octreotide therapy. We injected 1 to 10 mcg/kg/dose subcutaneously two times daily for two weeks as induction therapy. After induction, we injected the same dose subcutaneously at 4-week intervals.

Sirolimus was administered orally on a continuous dosing schedule at a starting dose of 2 mg daily. The drug trough level was checked regularly, twice weekly. The trough levels were maintained between 5 to 15 ng/mL[10]. We monitored adverse effects like cytopenia, tachycardia, hepatotoxicity, hyperglycemia, and electrolyte imbalance.

After discharge, all patients were followed-up regularly in the outpatient department with physical examinations, evaluation of growth, and blood tests.

Results

Information about the disease characteristics of all seven patients is described in Table 1. Dietary therapy was initially applied to all seven patients. Only one patient (Patient No. 1) responded to dietary therapy. The patient showed improvement not only in the serum albumin level but also in clinical symptoms like diarrhea and anasarca. A therapeutic effect was seen after only one week of dietary therapy. The albumin level, which was initially 1.8 g/dL, was elevated to 2.7 g/dL. The other six patients also tried more than three months of dietary therapy, but dietary therapy was insufficient for them. They showed refractory hypoalbuminemia and worsening of generalized edema, including ascites. Additional second-line therapies were considered after several aggravating events that required hospitalization.

When we chose second-line therapy, we primarily considered two main factors, the location and extent of abnormal lymphatic channels. We had information on these factors because of initial evaluations conducted with capsule endoscopy, whole-body MRI, or MR lymphangiography.

Patient No. 2 had abnormal lymphatic lesions only in the small intestine (Group 1), but the lesions were broad. Small bowel resection was planned for his lymphangiectasis. Resection from 70 cm below the Treitz ligament to 130 cm above the IC valve was completed

successfully without complications. The albumin level, which was initially 2.0 g/dL, was elevated to 4.4 g/dL after surgery.

Patient No. 3 had abnormal lymphatic channels only in the duodenal lesion (Group 1). After a multidisciplinary discussion, we decided to attempt lymphatic embolization instead of surgery. If surgery was considered, a pylorus-preserving pancreatoduodenectomy should be performed because of the location of the abnormal lesion. The albumin level, which was initially 1.5 g/dL, was elevated to 4.9 g/dL after two lymphatic embolization (Fig. 2).

Patients No. 4 (Group 3) and No. 5 (Group 3) had extensive abnormal lymphatic lesions in their bodies. The lesions not only involved broad intestinal segments but also lymphatic channels in the mediastinum and retroperitoneum. Even the extremities in Patient No. 5 were involved. The patients had ascites, generalized edema, and pleural effusions. With the use of diuretics as a supportive therapy, the patients were treated with octreotide. Patient No. 4 was maintained with octreotide for one year. Octreotide seemed to be effective for three months, but the patient's symptoms started to aggravate again without any specific event and the drug was discontinued. Patient No. 5 underwent octreotide induction therapy three times, but there was no efficacy at all. After repeated hospitalization, we decided to use another trial of sirolimus treatment. Clinical improvement emerged in both patients after one month of sirolimus use (Fig. 3). In the case of Patient No. 4, sirolimus treatment was maintained for three years. She presented with clinical remission (no lymphangiectasis symptoms) after treatment with sirolimus for about two years. In the case of Patient No.5 who had presented with severely refractory lymphangiectasis, his albumin level was still low at 3.1 g/dL with sirolimus use, but he no longer needed paracentesis or thoracentesis. He was treated with sirolimus only for four months, and we are still following him in the outpatient clinic.

Patients No. 6 (Group 2) and No. 7 (Group 2) were recently diagnosed and still young for intervention or surgery, necessitating a decision for second-line therapy for them. They also had broad abnormal lymphatic lesions in the intestine, duodenum, and all sections of the small intestine. Therefore, we decided to start medication therapy and chose sirolimus, not octreotide, based on our prior experience with octreotide treatment failure in extensive-type lymphangiectasis. We regularly checked the sirolimus trough and albumin levels and clinical symptoms. The albumin levels started to increase after three months of sirolimus use and the symptoms slowly relieved (Fig. 4).

Discussion

Dietary therapy for our patients consisted of high protein and low fat substituted with MCTs. The exclusion of long-chain fatty acids reduces lymphatic flow and pressure, and thus prevents the rupture of malformed lymphatics, while MCTs are directly absorbed into the portal venous circulation and bypass the enteric lymphatics[11]. Several case reports and articles have introduced the long-term effect of dietary therapy[12-19]. One patient in our study responded to dietary therapy (Table 1) and maintained clinical improvement for more than five years.

Having response to dietary therapy is ideal but some patients are non-responsive to dietary therapy. For that reason, more than 10 reports have introduced secondary therapy like surgery, octreotide, or sirolimus, but there is no consensus on how to choose and apply these therapies to patients who are refractory to dietary therapy[2, 20-32]. We tried to suggest a reasonable choice of second-line therapy because we had several experiences with therapeutic challenges and success with multimodal treatment options.

We emphasize that the initial evaluation of the location and the extra-intestinal extent of abnormal lymphatic lesions is important for a therapeutic strategy. We divided our patients into three groups to distinguish and assess the efficacy of the second-line treatments. We also analyzed other published cases using the same protocol and conducted a systemic review of second-line therapy (Table 2).

We evaluated capsule endoscopy and MRI after imaging modality has been developed in addition to esophagogastroduodenoscopy. After confirming the locations of the abnormal lymphatic lesions, we considered surgery after dietary therapy failure for the patients with focal abnormal lesions because surgery is the only treatment option with a chance of a complete cure. Cases reporting surgical treatment for patients with focally affected lesions have been published, and all patients showed clinical remission, consistent with our case (Table 2).

With the development of radiologic intervention, we attempted lymphatic embolization instead of surgery in one patient and the result was very successful. This was the first case of recovery from primary intestinal lymphangiectasia and clinical remission in a child or an adult treated with embolization. This procedure minimizes the risk of complications and decreases the treatment period commonly associated with surgery[33-35]. Embolization is a potential therapeutic option for focal lesions of primary intestinal lymphangiectasia in children. Surgery can be considered after embolization treatment failure.

For the patients whose disease extent is broad, and undergo embolization or surgery, medical therapy should be considered for second-line therapy. We have treatment experience with octreotide and sirolimus. Choosing the appropriate drug for patients is challenging for all clinicians.

Octreotide is a somatostatin analog whose mechanisms include decreased intestinal absorption of fats, inhibition of gastrointestinal vasoactive peptides, and stimulation of the autonomic nervous system[22]. Because of its mechanisms, we hypothesized that it is optimal for patients who have only intestinal involvement of the abnormal lymphatics with severe diarrhea, but we only have experience using the drug with extensive-type lymphangiectasis. Octreotide had little therapeutic effect in these patients. Eight case reports presenting experience treating with octreotide have been published. Consistent with our experience, octreotide showed little effect in patients with extensive abnormal lymphatic lesions. There are also reports that describe the recurrence of lymphangiectasis after the discontinuation of octreotide. Sari et al. (2010)[30], Prasad et al. (2019)[29], and some other reports described clinical improvement after octreotide treatment but there is no information on the long-term efficacy of octreotide (Table 2).

Only two case reports presented treatment experience with tranexamic acid [27, 29]. Tranexamic acid 25 mg/kg/dose three times a day was used orally (maximum 1,000 mg) for five days [29], and patients showed clinical improvement after one month of treatment [27]. The mechanism of antiplasmin therapy is the normalization of tissue fibrinolytic activity[36]. Increased fibrinolytic activity, which causes intestinal protein loss, has been proposed as a mechanism. Mine et al.[37] suggested that there is a subset of patients with lymphangiectasia who may have increased tissue or plasma fibrinolytic activity and may respond to antiplasmin therapy. Elevated D-dimers may reflect increased fibrinolytic activity. Tranexamic acid can be a choice for patients who present with refractory symptoms of lymphangiectasis.

Sirolimus acts on lymphatic endothelial cells and changes mTOR signaling, suppressing lymphatic sprouting and proliferation, and inducing apoptosis[38]. We tried sirolimus in four patients (Patients No. 4, 5, 6, and 7) who failed to respond to dietary therapy initially and two of them also failed to respond to octreotide therapy (Table 1). Among the four patients, two patients (Patients No. 6 and 7) with abnormal lymphatic lesions only in the intestine showed clinical improvement after 3 – 4 months of sirolimus treatment, whereas the other two patients (Patients No. 4 and 5) who had extensive-type lymphangiectasis showed clinical improvement only after one month of sirolimus treatment (Figures 3 and 4). The way sirolimus acts on lymphatic channels resulted in different effect onset times in these two groups. Because sirolimus acts on endothelial cells of the lymphatic channel, not by controlling lymphatic flow like octreotide or dietary therapy, it can affect any lymphatic vessels in the body. We concluded that patients who had the extensive form of abnormal lymphatic channels could be initially considered for sirolimus treatment rather than octreotide for a fast response and cure (Figure 1). One case report of treatment experience with everolimus (an mTOR inhibitor drugs) was published in Japan. Everolimus was prescribed because it was not possible to use sirolimus in the hospital. Their patient characteristics were similar to our patients who had extensive abnormal lymphatic lesions in the body (Table 2). A drug effect was seen after four weeks of use, like in our cases. However, the appropriate drug discontinuation time is debatable because there is no current consensus or guidelines [39, 40].

The primary limitation of our study was its retrospective nature and the small number of patients. It is practically impossible to perform prospective studies because primary intestinal lymphangiectasia is a very rare disease. We also need more follow-up information after the discontinuation of sirolimus.

Conclusion

In conclusion, intervention is a potential therapeutic option for patients with focal abnormal lymphatic lesions. Octreotide can be tried for patients with abnormal lymphangiectasis only in the intestine, with symptoms of diarrhea. However, it is not optimal for patients with extensive lymphangiectasis. Sirolimus is an effective drug for patients with extensive lymphangiectasis and a safe drug even for young pediatric patients.

Our future challenge is formulating recommendations for ideal treatment periods and the timing of sirolimus discontinuation. An individual therapeutic approach after an objective diagnostic evaluation improves the chances of disease remission.

Abbreviations

MR
Magnetic resonance
MRI
Magnetic resonance imaging
No.
Number
MCT
Medium chain triglyceride

mTOR
mammalian target of rapamycin

Declarations

Ethics approval and consent to participate

The medical records of the patients were reviewed retrospectively with the approval of the Clinical Research Ethics Committee, and the requirement for a consent form was waived. (IRB File No. SMC 2020-07-004).

Competing interests

No potential conflicts of interest relevant to this article were reported.

Author contributions

All authors have read and approved the manuscript

Conception or design: M.J.K. and Y.H.C

Acquisition, analysis, or interpretation of data: Y.Y.K. and E.S.K.

Drafting the work or revising: Y.Y.K. and M.J.K

Final approval of the manuscript: Y.Y.K. and M.J.K.,

Consent for publication

Not Applicable

Funding

No funding was obtained for this study

Acknowledgement

Not Applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article

References

1. Vignes S, Bellanger J. Primary intestinal lymphangiectasia (Waldmann's disease). *Orphanet J Rare Dis.* 2008;3(1):5.
2. Altın Z, et al. Primary intestinal lymphangiectasia and a review of the current literature. *The Turkish Journal of Gastroenterology.* 2018;29(6):714.
3. Lee J, Kong M-S. Primary intestinal lymphangiectasia diagnosed by endoscopy following the intake of a high-fat meal. *Eur J Pediatrics.* 2008;167(2):237–9.
4. Wilkinson P, Pinto B, Senior JR. Reversible protein-losing enteropathy with intestinal lymphangiectasia secondary to chronic constrictive pericarditis. *N Engl J Med.* 1965;273(22):1178–81.
5. Asakura H, et al. Endoscopic and histopathological study on primary and secondary intestinal lymphangiectasia. *Digestive diseases sciences.* 1981;26(4):312–20.
6. Lee EW, et al. Lymphangiography to treat postoperative lymphatic leakage: a technical review. *Korean J Radiol.* 2014;15(6):724–32.
7. Rivet C, et al. Use of capsule endoscopy in children with primary intestinal lymphangiectasia. *Gastrointest Endosc.* 2006;64(4):649–50.
8. Bernier J, et al. Diagnosis of protein-losing enteropathy by gastrointestinal clearance of alpha1-antitrypsin. *The Lancet.* 1978;312(8093):763–4.

9. Jeffries GH, Chapman A, Sleisenger MH. Low-fat diet in intestinal lymphangiectasia: its effect on albumin metabolism. *N Engl J Med.* 1964;270(15):761–6.
10. Ingle GR, Sievers TM, Holt CD. Sirolimus: continuing the evolution of transplant immunosuppression. *Ann Pharmacother.* 2000;34(9):1044–55.
11. Suresh N, et al., *Primary intestinal lymphangiectasia.* *Indian pediatrics,* 2009. 46(10).
12. Aroor S, et al. Waldmann's disease (primary intestinal Lymphangiectasia) with atrial Septal defect. *Journal of clinical diagnostic research: JCDR.* 2017;11(4):SD03.
13. Desai A, Guvenc B, Carachi R. Evidence for medium chain triglycerides in the treatment of primary intestinal lymphangiectasia. *European journal of pediatric surgery.* 2009;19(04):241–5.
14. Isa HM, Al-Arayedh GG, Mohamed AM. Intestinal lymphangiectasia in children: A favorable response to dietary modifications. *Saudi Med J.* 2016;37(2):199.
15. Mohammad L, et al. Primary intestinal lymphangiectasia in a 23-month-old girl. *Oxford Medical Case Reports.* 2019;2019(7):omz065.
16. Surampalli V, et al. Primary Intestinal Lymphangiectasia (Waldmann's Disease) Presenting with Chylous Effusions in a 15-Year-Old. *Journal of Clinical Diagnostic Research: Jcdr.* 2017;11(8):OD17.
17. Wang X, Jin H, Wu W. *Primary intestinal lymphangiectasia manifested as unusual edemas and effusions: a case report.* *Medicine,* 2016. 95(10).
18. Tang Q-Y, et al. Clinical outcome of nutrition-oriented intervention for primary intestinal lymphangiectasia. *World Journal of Pediatrics.* 2011;7(1):79–82.
19. Tift W, Lloyd J. Intestinal lymphangiectasia. Long-term results with MCT diet. *Arch Dis Child.* 1975;50(4):269–76.
20. Ozeki M, et al., *Everolimus for primary intestinal lymphangiectasia with protein-losing enteropathy.* *Pediatrics,* 2016. 137(3).
21. Strauss J, Gidrewicz D, McKenzie L. A148 SIROLIMUS FOR PRIMARY INTESTINAL LYMPHANGIECTASIA IN A PEDIATRIC PATIENT. *Journal of the Canadian Association of Gastroenterology.* 2019;2(Supplement_2):294–5.
22. Suehiro K, et al. Late-onset primary intestinal lymphangiectasia successfully managed with octreotide: a case report. *Annals of Vascular Diseases.* 2012;5(1):96–9.
23. Acer-Demir T, Ötgün I, Özçay F. First report of treatment with pancreas-sparing duodenectomy in a child with primary intestinal lymphangiectasia. *Journal of Indian Association of Pediatric Surgeons.* 2020;25(2):106.
24. Chen C-P, et al. Surgical resection of duodenal lymphangiectasia: a case report. *World Journal of Gastroenterology: WJG.* 2003;9(12):2880.
25. Kneist W, et al. Surgical therapy of segmental jejunal, primary intestinal lymphangiectasia. *Z Gastroenterol.* 2013;51(6):576.
26. Kuroiwa G, et al. Primary intestinal lymphangiectasia successfully treated with octreotide. *Journal of gastroenterology.* 2001;36(2):129–32.
27. MacLean JE, Cohen E, Weinstein M. Primary intestinal and thoracic lymphangiectasia: a response to antiplasmin therapy. *Pediatrics.* 2002;109(6):1177–80.
28. Mari J, et al. Pediatric localized intestinal lymphangiectasia treated with resection. *International medical case reports journal.* 2019;12:23.
29. Prasad D, et al. Clinical profile, response to therapy, and outcome of children with primary intestinal lymphangiectasia. *Dig Dis.* 2019;37(6):458–66.
30. Sari S, Baris Z, Dalgic B. Primary intestinal lymphangiectasia in children: is octreotide an effective and safe option in the treatment? *J Pediatr Gastroenterol Nutr.* 2010;51(4):454–7.
31. Troskot R, et al. How to treat an extensive form of primary intestinal lymphangiectasia? *World Journal of Gastroenterology: WJG.* 2015;21(23):7320.
32. Zhu L-h, et al. Partial enterectomy: treatment for primary intestinal lymphangiectasia in four cases. *Chin Med J.* 2010;123(6):760–4.
33. Kawasaki R, et al. Therapeutic effectiveness of diagnostic lymphangiography for refractory postoperative chylothorax and chylous ascites: correlation with radiologic findings and preceding medical treatment. *Am J Roentgenol.* 2013;201(3):659–66.
34. Nadolski GJ, Itkin M. Feasibility of ultrasound-guided intranodal lymphangiogram for thoracic duct embolization. *J Vasc Interv Radiol.* 2012;23(5):613–6.
35. Rajebi MR, et al. Intranodal lymphangiography: feasibility and preliminary experience in children. *J Vasc Interv Radiol.* 2011;22(9):1300–5.

36. Kondo M, et al. Experimental protein-losing gastroenteropathy: role of tissue plasminogen activator. *Gastroenterology*. 1976;71(4):631–4.
37. Mine K, et al. Intestinal lymphangiectasia markedly improved with antiplasmin therapy. *Gastroenterology*. 1989;96(6):1596–9.
38. Baluk P, et al., *Rapamycin reversal of VEGF-C–driven lymphatic anomalies in the respiratory tract*. *JCI insight*, 2017. 2(16).
39. Hu S, et al. Long-term efficacy and safety of sirolimus therapy in patients with lymphangioleiomyomatosis. *Orphanet J Rare Dis*. 2019;14(1):206.
40. Wiegand S, Wichmann G, Dietz A. Treatment of lymphatic malformations with the mTOR inhibitor sirolimus: a systematic review. *Lymphatic Research Biology*. 2018;16(4):330–9.

Tables

Table 1. Clinical characteristics of 7 patients diagnosed with primary intestinal lymphangiectasia.

wks; week-old, yr.; year-old

Patient number	Age at diagnosis	Age at 2 nd -line therapy	Group	Type of lymphangiectasia	Intestinal involve	3 rd space involved	Response to diet therapy	Type of 2nd-line therapy
1	4mo	-	1	Focal intestine	Focal	No	Yes	None
2	7yr	7.5yr	1	Focal intestine	Focal	No	No	Surgery
3	7yr	15yr	1	Focal intestine	Focal	No	No	Embolization
4	15yr	15.7yr	3	Extensive	Diffuse	Yes	No	OctreotideàSirolimus
5	At birth	3yr	3	Extensive	Diffuse	Yes	No	OctreotideàSirolimus
6	3wks	9yr	2	Diffuse intestine	Diffuse	No	No	Sirolimus
7	9yr	9.7yr	2	Diffuse intestine	Diffuse	No	No	Sirolimus

Table 2. Summary of case reports of primary intestinal lymphangiectasia treated with second-line therapy

wks; week-old, yr.; year-old

Author	Age	Group	Type of lymphangiectasia	Intestinal involve	3 rd space involve	Response to diet therapy	Type of 2nd-line therapy	Results of 2nd-line therapy
CP Chen et al. (2003) [24]	49yr	1	Focal intestine	Focal	No	No	Surgical resection	Remission
L Zhu et al. (2010) [32]	22yr	1	Focal intestine	Focal	No	Limited data	Surgical resection	Remission
	44yr	1	Focal intestine	Focal	No	Limited data	Surgical resection	Remission
	71yr	1	Focal intestine	Focal	No	Limited data	Surgical resection	Remission
	55yr	1	Focal intestine	Focal	No	Limited data	Surgical resection	Remission
W Kneist et al. (2013) [25]	58yr	1	Focal intestine	Focal	No	No	Surgical resection	Remission
J Mari et al. (2019) [28]	10yr	1	Focal intestine	Focal	No	Limited data	Surgical resection	Remission
G Kuroiwa et al. (2001) [26]	21yr	1	Focal intestine	Focal	No	No	Octreotide	Recurred after discontinuation
S Sari et al. (2010) [30]	N=6, age limited	Limited data	Limited data	Limited data	Limited data	No	Octreotide	Clinical improvement
Suehiro et al. (2012) [22]	63yr	1	Focal intestine	Focal	No	No	Octreotide	Clinical improvement
Troskot et al. (2015) [31]	42yr	2	Diffuse intestine	Diffuse	No	No	Octreotide	Clinical improvement
Z Altın et al. (2018)[2]	34yr	3	Extensive	limited	Yes	No	Octreotide	Recurred after discontinuation
Acer-Demir et al. (2020) [23]	3yr	3	Extensive	Diffuse	Yes	No	Octreotide à Surgical resection	Died d/t uncontrolled symptoms
MacLean et al. (2002) [27]	14yr	3	Extensive	Diffuse	Yes	No	Octreotideà Tranexamic acid	Clinical improvement
D Prasad et al. (2019) [29]	N=2, age limited	2	Diffuse intestine	Diffuse	No	No	Octreotide	Clinical improvement
	N=4, age limited	3	Extensive	Diffuse	Yes	No	Octreotide + Tranexamic acid	Clinical improvement
Ozeki et al.	12yr	3	Extensive	Diffuse	Yes	No	PropranololàEverolimus	Remission for 12 months

Figures

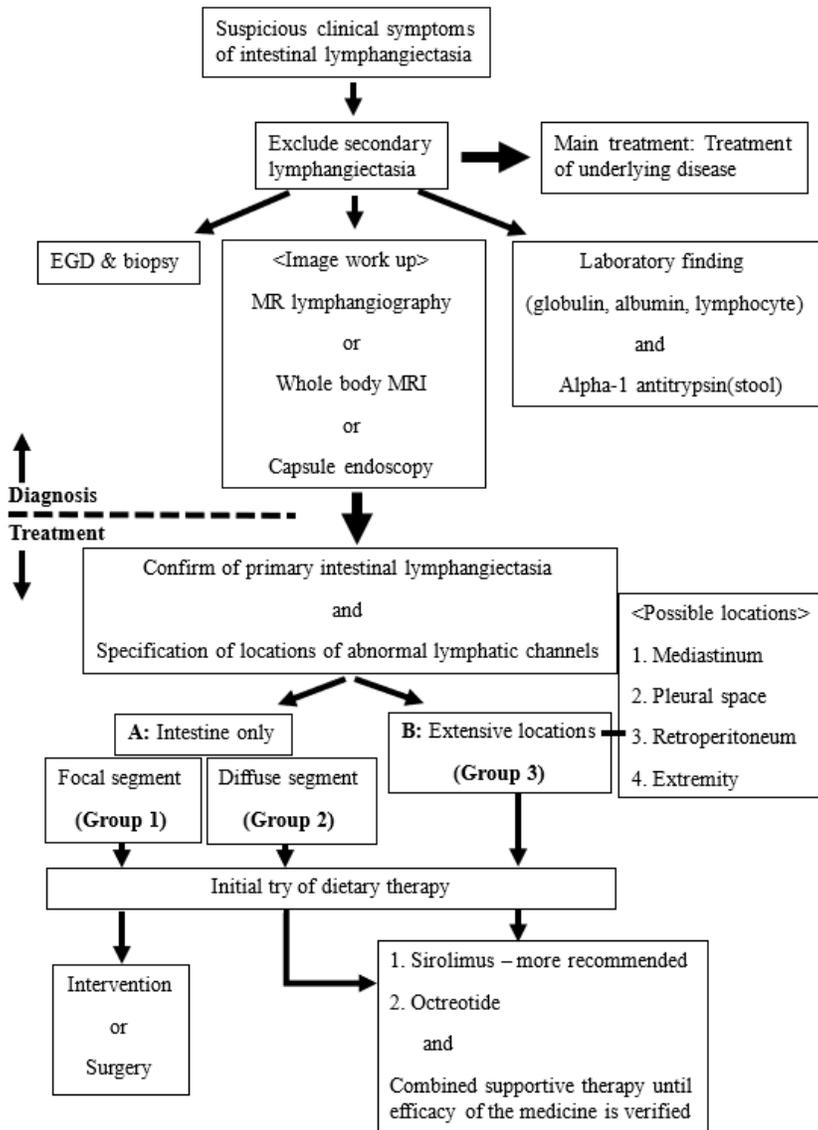


Figure 1

Diagnostic flow and individual therapeutic strategy of primary intestinal lymphangiectasia

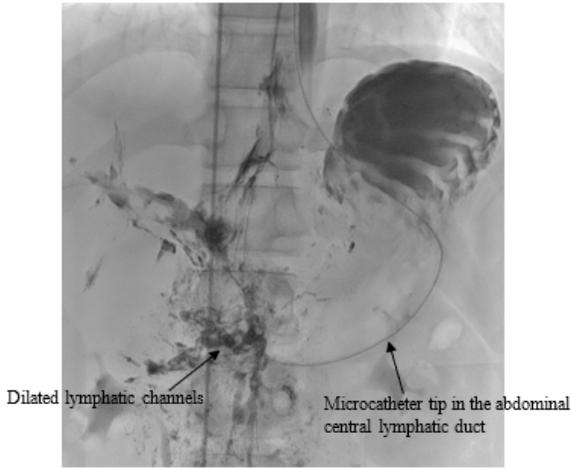


Figure 2

Nodal lymphangiography and therapeutic embolization is performed using diluted glue in patient No. 3.

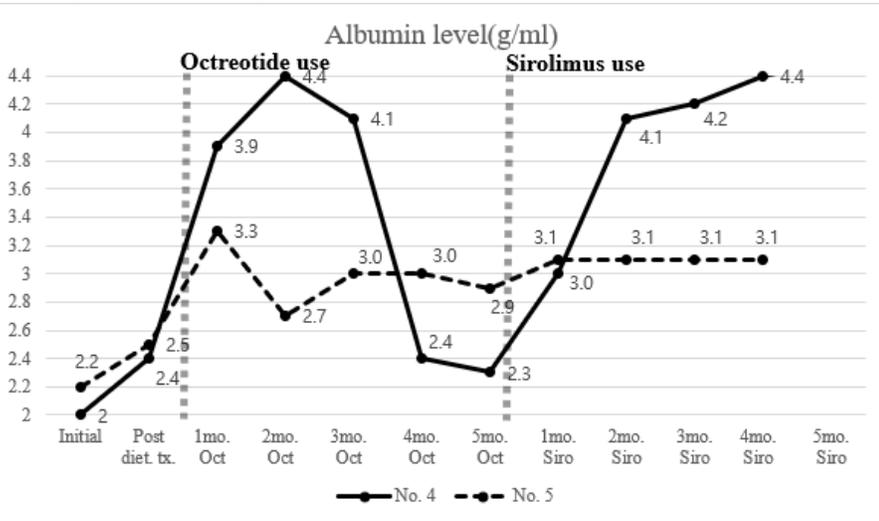


Figure 3

Serum albumin level trends of patients who are treated with Sirolimus after octreotide failure. Diet.; dietary, mo.; month, Oct.; Octreotide, Siro.; Sirolimus, No. 4; patient number 4, No. 5 patient number 5.

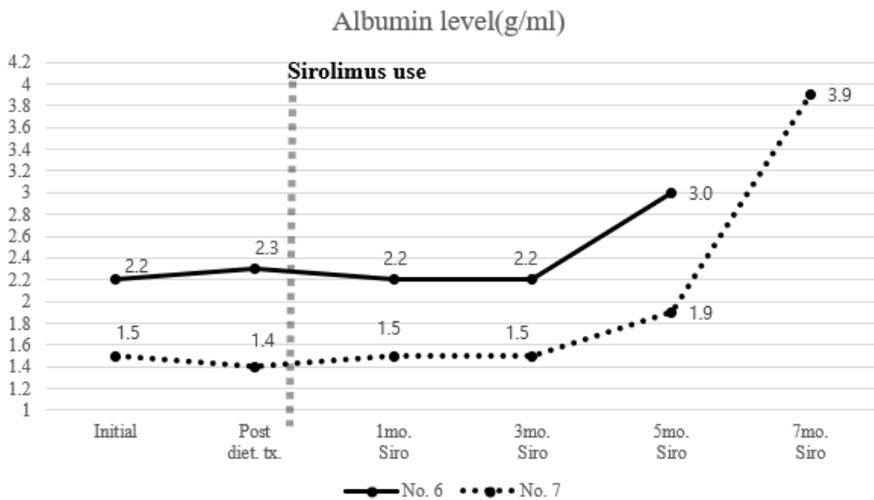


Figure 4

Serum albumin level trends of each patient who are treated with Sirolimus as secondary medication therapy Diet.; dietary, mo.; month, Siro.; Sirolimus, No. 6; patient number 6, No. 7; patient number 7.