ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2020 December 28; 26(48): 7593-7718

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 26 Number 48 December 28, 2020

MINIREVIEWS

7593 Research advances of vasoactive intestinal peptide in the pathogenesis of ulcerative colitis by regulating interleukin-10 expression in regulatory B cells

Sun X, Huang Y, Zhang YL, Qiao D, Dai YC

7603 Gut microbiota mediated molecular events and therapy in liver diseases

Qi X, Yang M, Stenberg J, Dey R, Fogwe L, Alam MS, Kimchi ET, Staveley-O'Carroll KF, Li G

ORIGINAL ARTICLE

Basic Study

7619 Pretreatment with intestinal trefoil factor alleviates stress-induced gastric mucosal damage *via* Akt signaling

Huang Y, Wang MM, Yang ZZ, Ren Y, Zhang W, Sun ZR, Nie SN

Case Control Study

7633 Gegen Qinlian decoction enhances immunity and protects intestinal barrier function in colorectal cancer patients *via* gut microbiota

Li Y, Li ZX, Xie CY, Fan J, Lv J, Xu XJ, Lv J, Kuai WT, Jia YT

Retrospective Cohort Study

7652 Impact of colorectal cancer screening participation in remote northern Canada: A retrospective cohort study

Smith HA, Scarffe AD, Brunet N, Champion C, Kandola K, Tessier A, Boushey R, Kuziemsky C

Retrospective Study

7664 Prostate-specific membrane antigen expression in hepatocellular carcinoma, cholangiocarcinoma, and liver cirrhosis

Chen LX, Zou SJ, Li D, Zhou JY, Cheng ZT, Zhao J, Zhu YL, Kuang D, Zhu XH

Observational Study

7679 Oral microbiome and pancreatic cancer

Wei AL, Li M, Li GQ, Wang X, Hu WM, Li ZL, Yuan J, Liu HY, Zhou LL, Li K, Li A, Fu MR

SYSTEMATIC REVIEWS

7693 High prevalence of hepatic steatosis and vascular thrombosis in COVID-19: A systematic review and meta-analysis of autopsy data

Díaz LA, Idalsoaga F, Cannistra M, Candia R, Cabrera D, Barrera F, Soza A, Graham R, Riquelme A, Arrese M, Leise MD, Arab JP

CASE REPORT

7707 Primary intestinal lymphangiectasia in an adult patient: A case report and review of literature

Huber R, Semmler G, Mayr A, Offner F, Datz C

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Dr. Tsolakis is an interventional endoscopist (Senior Consultant) and group leader for endoscopic ultrasound and duodenal polyps at Karolinska University Hospital, Stockholm, Sweden. Dr. Tsolakis became a Specialist in Internal Medicine (2010) and Gastroenterology (2011) at the Uppsala University Hospital, Sweden, where he was subsequently appointed as Consultant Gastroenterologist focusing on endoscopy and neuroendocrine tumors in the Departments of Gastroenterology and Endocrine Oncology. He completed training in advanced therapeutic endoscopy in Canada, initially at the University of Calgary (2014) and later at St. Michael's Hospital in Toronto (2015). His ongoing career research interests include advanced endoscopy and neuroendocrine tumors, yielding several peer-reviewed publications in the field of endoscopy and neuroendocrine tumor disease. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Report® cites the 2019 impact factor (IF) for *WJG* as 3.665; IF without journal self cites: 3.534; 5-year IF: 4.048; Ranking: 35 among 88 journals in gastroenterology and hepatology; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ji-Hong Liu*; **Production Department Director:** *Yun-Xiaojian Wu*; **Editorial Office Director:** *Ze-Mao Gong*.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
December 28, 2020

COPYRIGHT
© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2020 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2020 December 28; 26(48): 7707-7718

DOI: 10.3748/wjg.v26.i48.7707

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

CASE REPORT

Primary intestinal lymphangiectasia in an adult patient: A case report and review of literature

Rudolf Huber, Georg Semmler, Alexander Mayr, Felix Offner, Christian Datz

ORCID number: Rudolf Huber 0000-0001-8485-406X; Georg Semmler 0000-0002-0411-166X; Alexander Mayr 0000-0001-9216-1431; Felix Offner 0000-0001-7384-9695; Christian Datz 0000-0001-7838-4532.

Author contributions: Huber R, Mayr A, Datz C and Offner F contributed to patient management and histological evaluation; Huber R, Semmler G and Datz C contributed to literature review and drafting of the manuscript. All authors contributed to revision for important intellectual content and approved the final version of the manuscript.

Informed consent statement: The patient consented to her case being published anonymously.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest regarding the submitted work. However, the following authors declare conflicts of interest outside the submitted work: Christian Datz serves as an advisory board member of SPAR Österreich Warenhandels AG.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Rudolf Huber, Georg Semmler, Alexander Mayr, Christian Datz, Department of Internal Medicine, General Hospital Oberndorf, Teaching Hospital of the Paracelsus Medical University Salzburg, Oberndorf 5110, Austria

Felix Offner, Department of Pathology, General Hospital Feldkirch, Feldkirch 6800, Austria

Corresponding author: Christian Datz, MD, Professor, Department of Internal Medicine, General Hospital Oberndorf, Teaching Hospital of the Paracelsus Medical University Salzburg, Paracelsusstraße 37, Oberndorf 5110, Austria. c.datz@kh-oberndorf.at

Abstract

BACKGROUND

Primary intestinal lymphangiectasia (PIL), first described in 1961, is a rare disorder of unknown etiology resulting in protein-losing enteropathy. The disease is characterized by dilatation and leakage of intestinal lymph vessels leading to hypoalbuminemia, hypogammaglobulinemia, and lymphopenia. Since the severity and location of lymph vessels being affected can vary considerably, the range of associated symptoms is wide from mild lower-limb edema to generalized edema, abdominal and/or pleural effusion, and recurrent diarrhea, among others. Although usually developing in early childhood, we present the case of a 34-year-old woman with PIL. Moreover, we performed a literature review systematically assessing clinical presentation, and provide a practical approach to facilitate diagnosis and therapy of PIL in adults.

CASE SUMMARY

Our patient presented with unspecific symptoms of abdominal discomfort, fatigue, nausea, and recurrent edema of the lower limbs. Interestingly, a striking collinearity of clinical symptoms with female hormone status was evident. Additionally, polyglobulia, hypoalbuminemia, hypogammaglobulinemia, and transient lymphocytopenia were evident. Due to suspicion of a bone marrow disease, an extensive diagnostic investigation was carried out excluding secondary causes of polyglobulinemia and hypoalbuminemia. The diagnosis of primary intestinal lymphangiectasia was established after 22 wk by histological analysis of biopsy samples obtained *via* enteroscopy. Consecutively, the patient was put on a high-protein and low-fat diet with medium-chain triglycerides supplementation leading to significant improvement of clinical symptoms until 2 years of follow-up.

CONCLUSION

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Austria

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B, B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: October 2, 2020
Peer-review started: October 2, 2020
First decision: November 23, 2020
Revised: November 29, 2020
Accepted: December 6, 2020
Article in press: December 6, 2020
Published online: December 28, 2020

P-Reviewer: Li J, Mao Y, Wang ZJ, Yang JS
S-Editor: Zhang L
L-Editor: A
P-Editor: Wang LL

PIL can be the reason for cryptogenic hypoalbuminemia, hypogammaglobulinemia, and lymphopenia in adulthood. Due to difficulty in correct diagnosis, treatment initiation is often delayed despite being effective and well-tolerated. This leads to a significant disease burden in affected patients. PIL is increasingly been recognized in adults since the majority of case reports were published within the last 10 years, pointing towards an underestimation of the true prevalence. The association with female hormone status warrants further investigation.

Key Words: Primary intestinal lymphangiectasia; Waldmann´s disease; Protein losing enteropathy; Hypoproteinemia; Case report

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Although Primary intestinal lymphangiectasia usually develops in early childhood, we present the case of a 34-year-old woman. We observed a striking collinearity with female hormone status in our patient, presenting a potential area of future research. Moreover, we performed a literature review of all published case reports so far and systematically assessed clinical presentation to provide a practical approach to facilitate diagnosis and therapy of primary intestinal lymphangiectasia in adults for the first time.

Citation: Huber R, Semmler G, Mayr A, Offner F, Datz C. Primary intestinal lymphangiectasia in an adult patient: A case report and review of literature. *World J Gastroenterol* 2020; 26(48): 7707-7718
URL: https://www.wjgnet.com/1007-9327/full/v26/i48/7707.htm
DOI: https://dx.doi.org/10.3748/wjg.v26.i48.7707

INTRODUCTION

Primary intestinal lymphangiectasia (PIL) has been first described by Waldmann *et al*[1] in 1961 as a rare disorder of intestinal lymphangiectasia that results in protein-losing enteropathy (PLE)[1]. PIL is caused by a diffuse or localized dilatation and/or rupture of intestinal lymphatic vessels in the mucosa, submucosa, or subserosa due to high pressure in lymphatic vessels[2]. Importantly, prevalence and etiology are yet unknown. However, genetic associations are been discussed since the diagnosis is generally established in childhood with very rare cases in adults[3].

Symptoms largely relate to the severity of lymph loss and consecutive loss of proteins resulting in hypoproteinemia, lymphopenia, and decreased serum levels of immunoglobulins. Among others, these symptoms include pitting edemas of the lower limbs, generalized edema, as well as pleural, epicardial, or often chylous abdominal effusion[4]. Here, we present the case of PIL in a 34-year-old female patient, together with a literature review of all case reports on PIL in adulthood (using the terms "Primary intestinal lymphangiectasia" and "Waldman's disease"), focusing on clinical presentation, and providing a diagnostic and therapeutic overview for clinicians to enhance recognition and facilitate diagnosis.

CASE PRESENTATION

Chief complaints

In October 2018, a 34-year-old woman presented with recurring nausea independent of food intake, episodes of abdominal discomfort, fatigue, occasional episodes of diarrhea as well as a feeling of increased susceptibility to opportunistic infections.

History of present illness

After the end of pregnancy earlier this year, she reported on more frequently observed limb edema. The other medical history including comorbidities and drug intake were

unremarkable.

History of past illness

Interestingly, temporary facial edema were occasionally reported already during childhood starting at the age of 12. After puberty, pronounced edema of the lower limbs, recurring nausea and fatigue were continuously reported, but vanished when using oral contraceptives or during pregnancy.

Physical examination

The physical examination at the initial contact did not reveal any abnormalities. Especially, no edema of the upper or lower limb were observed and weight was stable with a body mass index of 18.3 kg/m^2.

Laboratory examinations

During several routine blood tests after pregnancy, polyglobulia [hemoglobin 17.4 g/dL (normal range: 12.3-15.3 g/dL), blood count 5.82 (normal range: 3.60-5.00)], normal leukocyte count (4.48, normal range: 4.40-11.30) with diminished lymphocyte count (14.6%, normal range: 19.3%-51.7%) following differential blood count, and reduced total serum protein (4.9 g/dL, normal range: 6.2-8.2 g/dL) with hypoalbuminemia (2.8 g/dL, normal range: 3.4-5.0 g/dL) were observed. Additionally, quantitative immunoglobulin analysis displayed hypogammaglobulinemia of 7.3% (normal range: 11.1%-18.8%) with a pronounced deficiency of the IgG class (268 mg/dL, normal range: 700-1600 mg/dL), moderate deficiency of IgA class (54 mg/dL (normal range: 70-500 mg/dL), and reduced IgG-1 and IgG-2 subclasses (193 mg/dL, normal range: 405-1011 mg/dL; 93 mg/dL, normal range: 169-786 mg/dL). Additionally, the CD4: CD8 T-cell ratio was reduced [0.9 (normal range: 1.0–3.6) and kappa and lambda light-chains were diminished [75 mg/dL (normal range: 173-383 mg/dL), 46 mg/dL (normal range: 81-192 mg/dL)]. The urinary sediment showed no proteinuria and no signs of renal, hepatic, pancreatic, or cardiac disease. Since the laboratory constellation pointed towards a cellular and humoral immune defect, exhaustive investigations were started. Negative results for JAK2 mutations (JAK2-exon 12 sequencing and JAK2-mutation V617F) and negative BCR/ABL ratio ruled out polycythemia vera. Additionally, bone marrow analysis neither showed myeloid neoplasia nor infiltration by lymphoma, and ß2-microglobulin was within the normal range ruling out a hematogenous disease. Autoantibody screening and virus serology including hepatitis viridae, cytomegalovirus, Epstein-Bar virus, and human immunodeficiency virus were negative, and pancreatic insufficiency was excluded.

Imaging examinations

Incidentally, abdominopelvic computerized tomography (CT) showed a thickened wall of the ileum and jejunum with enlarged mesenteric lymph nodes up to 32 mm localized in the lower abdomen. Therefore, an ileocolonoscopy with exploration of > 8 cm of the ileum was performed showing a normal result. After CT-findings were confirmed on magnetic resonance imaging, a gastroduodenoscopy with standard intubation to the mid-descending duodenum revealed creamy white spots of the duodenal mucosa, suggesting lymphedema (Figure 1A). However, the histological evaluation did not show evidence for dilated lymph vessels or PIL, giardiasis, celiac disease, Whipple disease, or intestinal bowel disease, which was additionally excluded by normal calprotectin levels. Following video capsule endoscopy that showed a snowflake appearance of the mucosa (Figure 1B), double-balloon enteroscopy exploring approximately 70 cm of the jejunum verified mucosal lesions compatible with lymphangiectasia macroscopically (Figure 1C).

FINAL DIAGNOSIS

Finally, PIL was confirmed on histological and immunohistological analyses from jejunal biopsies (Figures 2 and 3).

TREATMENT

After putting the patient on a medium-chain triglyceride (MCT) diet rich in protein,

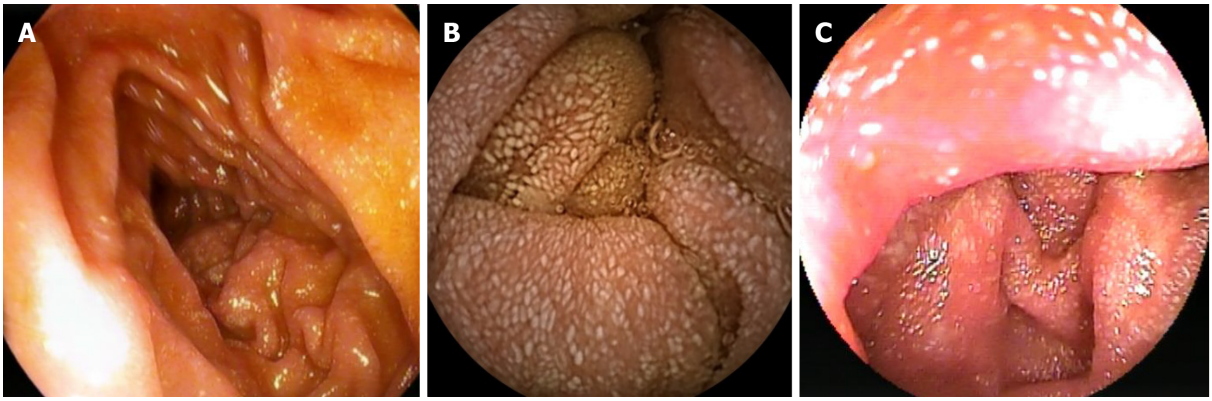

Figure 1 Imaging examinations. A: Endoscopic view of the descending part of the duodenum showing spots of lymphangiectasia suggestive for lymphedema; B: Video capsule endoscopy with a snowflake appearance of the jejunum compatible with dilated mucosal lymphatic vessels; and C: Double-balloon enteroscopy of the jejunum with an almost identical image to video capsule endoscopy.

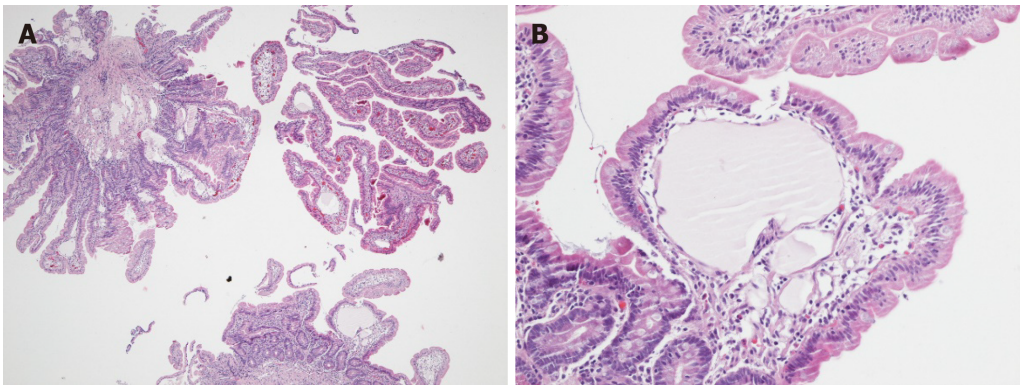

Figure 2 Histological and immunohistological analyses. A: Jejunal biopsies showing a mild and focal blunting of the villi in particular above the prominent ecstatic mucosal lymph vessels (4-fold magnification); B: Ecstatic lymph vessel without inflammatory changes or abnormalities of the epithelial intestinal cell lining (200-fold magnification).

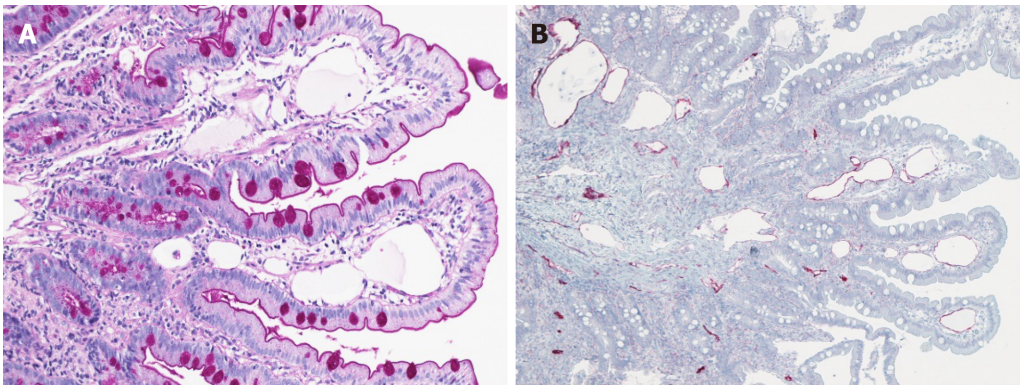

Figure 3 Histological and immunohistological analyses. A: Periodic Acid-Schiff staining did not reveal any collections of periodic acid-schiff positive histiocytes or inclusions, demonstrating the perfectly normal intestinal brush border (200-fold magnification); B: Immunohistochemistry for D2-40, a marker of lymphatic endothelial cells, confirms the endothelium to be of lymphatic origin and highlights the presence of multiple ecstatic lymph vessels in both the mucosa and submucosa (100-fold magnification).

the clinical condition of the patient significantly improved within 4 wk.

OUTCOME AND FOLLOW-UP

Until 2 years after diagnosis, mild lower limb edema were only observed between the

end of breastfeeding period and a second pregnancy, and abdominal discomfort, fatigue and nausea significantly improved. Laboratory improvement was characterized by increase in total serum protein, albumin, and quantitative immunoglobulin levels.

DISCUSSION

Due to the rarity of this disease, the worldwide incidence of PIL in humans is unknown[3]. However, a genetic predisposition is been discussed since if mostly affects children below 3 years of age[5]. This is supported by familial forms of specific syndromes that have been associated with PIL, including the yellow-nail syndrome, von Recklinghausen's disease, Turner, Noonan, Klippel-Trenaunay or Hennekam syndrome[3,6,7]. Nevertheless, cases in adult patients exist. We performed a literature review and could identify 49 cases from 46 case reports of PIL in adults in which the onset of symptoms occurred after the 18th birthday (Table 1, Supplementary Table 1[8-53]). Notably, 27/46 (58.7%) were published since 2010, indicating that this entity is increasingly been recognized and the prevalence might be underestimated. Median age at diagnosis was 43 (range: 20-83) years while median time from onset of symptoms to final diagnosis was 3 (range: 0-40) years, highlighting the difficulty in the correct diagnosis of this entity. Although a literature review of PIL cases existed reporting a mean age of 13.3 years at symptom onset and 8.5 years until diagnosis, it has to be pointed out that 75% of cases in this review included patients with symptom onset before 20 years of age[54]. In terms of gender distribution, 22 male (44.9%) and 27 female (55.1%) cases were reported.

Our case describes a 34-year-old female being diagnosed with PIL around 22 years after the first occurrence of edema, and 22 wk after the first contact at our institution. She presented with nausea, abdominal discomfort, diarrhea, and bilateral limb edemas. From 48 patients reporting on symptoms in the literature, 40 patients (83.3%) reported the presence of any peripheral/generalized edema while only 2 patients did not present with edema and 6 case reports did not report on this symptom. The majority (n = 27, 56.3%) only reported bilateral edema of the lower limb. 9/48 patients (18.8%) presented with abdominal pain, 13 patients (27.1%) presented with (chylous) ascites, 10 patients (20.8%) with pleural, and 4 patients (8.3%) with pericardial effusion. Diarrhea was present in 20/48 patients (41.7%). Other rare unspecific symptoms include changes in weight, nausea, general weakness, pallor, and gastrointestinal bleeding. These findings go in line with a former literature review of 84 PIL cases (including predominantly children), reporting limb edema, diarrhea, ascites, and lymphedema in 78%, 62%, 41%, and 22% respectively[54]. These symptoms and their varying extent can largely be explained as a consequence of lymphatic/protein and subsequently watery loss due to lower oncotic pressure in interstitial fluid.

The fact that pregnancy and oral contraception led to the vanishing of edemas in our patient is indeed surprising as this has not yet been reported. Of note, symptoms completely resolved when taking oral contraceptives and re-appeared during pill-free days in between. One may hypothesize that differences in estradiol might influence the severity of lymphedema: Morfoisse *et al*[55], who explored the role of estrogens on lymphatic endothelial cells, found that estradiol is protective of lymphedema, and blockage of the estrogen receptor is associated with stronger lymphatic leakage. However, this was only shown in an animal model of secondary lymphedema, and no other studies providing further evidence on this mechanism are available.

Among the most frequently observed laboratory findings in literature were anemia in 16 patients (33.3%), lymphocytopenia in 30 (62.5%), hypoproteinemia in 26 (54.2%), and hypoalbuminemia and hypogammaglobulinemia/reduced serum IgG level in 35 (72.9%) while no patients specifically reported the absence of the latter two laboratory findings. However, these numbers might be underestimated since not all case reports reported on these features. 12 patients (25.0%) specifically reported reduced serum levels of calcium and 5 patients (10.4%) reduced levels of magnesium, leading to occasional muscle seizures in several patients. Other findings include hypoglobulinemia with reduced numbers of IgM, IgA, and IgG, and reduced numbers of CD3+ and CD4+ cells. Profound hypoproteinemia, hypoalbuminemia, and hypogammaglobulinemia and reduced CD4:CD8 ratio could also be confirmed in our patient. However, lymphocytopenia was only transient and leucocyte count was within the normal range indicating that these parameters might be very unspecific and significantly influenced by temporary inflammatory processes in the body. This is especially true since an increased susceptibility to opportunistic infections based on

Table 1 Clinical presentation, laboratory findings and endoscopic diagnosis of all case reports describing adult patients[1] with primary intestinal lymphangiectasia

Clinical presentation		*n*
Patient characteristics	Number of adult patients with PIL	49
	Age at diagnosis, yr	43 (20-83)
	Time to final diagnosis, yr	3 (0-40)
	Male, *n* (%)	21 (42.9)
	Female, *n* (%)	28 (57.1)
Symptoms, *n* (%)	Edema	40/48 (83.3)
	Recurrent diarrhea	20/48 (41.7)
	Abdominal effusion	13/48 (27.1)
	Pleural effusion	10/48 (20.8)
	Abdominal pain	9/48 (18.8)
Laboratory findings, *n* (%)	Hypogammaglobulinemia	35/48 (72.9)
	Hypoalbuminemia	35/48 (72.9)
	Lymphocytopenia	30/48 (62.5)
	Hypoproteinemia	26/48 (54.2)
	Hypocalcemia	12/48 (25.0)
	α1-antitrypsin (stool)	10/48 (20.8)[2]
CT-scan, *n* (%)	Normal	8/27 (29.6)
	Thickened wall of small bowel	11/27 (40.7)
Diagnosis possible, *n* (%)	Gastro-duodenoscopy	21/35 (60.0)
	Ileo-colonoscopy	5/21 (23.8)
	Enteroscopy	13/13 (100)

[1]Diagnosis established after the 18th birthday.
[2]All patients (100%) in which α1-antitrypsin levels or α1-antitrypsin clearance was measured in stool samples reported elevated results. CT: Computerized tomography.

lymphocytopenia and hypogammaglobulinemia could be present. This was reported in our patient, 2 case reports of adult patients with additional 2 patients suffering from cryptococcal meningitis at initial presentation, and 3 case reports of children[5]. This humoral and cellular immunodeficiency is assumed to be due to a lymphatic loss of B- and T- lymphocytes. Interestingly, 4 patients in the literature report an extensive presence of warts, probably representing the end-stage of acquired immunodeficiency.

Notably, fecal α1-antitrypsin levels or α1-antitrypsin-clearance seem to be a good indicator for the presence of PLE/PIL in these patients with positive results in all patients who reported on this feature (10/48, 20.8%). Since α1-antitrypsin is resistant to degradation by digestive enzymes, it indicates the presence of blood proteins in the intestinal tract[56].

Because of persistently diminished IgG and IgA, an abdominal/pelvic CT scan was performed to rule out lymphoma or thymoma in our patient. This incidentally revealed a thickened wall in the jejunum and ileum with enlarged lymph nodes. Interestingly – when looking into the literature – 11/27 of patients (40.7%) undergoing a CT scan reported abnormalities in the small bowel wall while 8/27 (29.6%) had a completely normal result. However, other imaging modalities such as lymphangioscintigraphy or technetium-labeled human serum albumin (99TmTc-HSA) scintigraphy might be of higher accuracy pointing towards the diagnosis of PIL, demonstrating abnormal lymphatic, or protein leakage.

When comparing endoscopic findings in these patients, 21/35 (60.0%) gastroduodenoscopies performed in symptomatic PIL patients revealed an endoscopic view suggestive for PIL with "snowflake appearance" of the duodenal mucosa indicating lymphatic dilations while in 2 patients the diagnosis could be made

histologically despite normal macroscopic appearance. On the contrary, ileocolonoscopy was inferior with only 5/21 (23.8%) showing characteristic features in the terminal ileum that led to the diagnosis. However, it has to be mentioned that considering the improvement in technology, this rate might be underestimated due to the large number of studies performed > 10 years ago. Enteroscopy, which was performed in 14 patients including our patient to establish the diagnosis, is highly sensitive and should be regarded as the gold-standard for diagnosis. Video capsule endoscopy could be used to help with diagnosis, being similarly sensitive to detect lymphedema in the small bowel.

In our case, although a gastroduodenoscopy was performed showing an endoscopic snowflake appearance of the duodenal mucosa indicating lymphatic dilations, the histological report was normal. To our opinion, two possible explanations exist for this phenomenon: On the one hand, the dilated lymphatic endothelial cells can be distributed in different locations in the intestine to a different extent, hence the histology specimens might not show dilated lymphatic endothelial cells despite endoscopic and macroscopic appearance. On the other hand, the lack of experience of pathologists with this entity could result in an insufficient evaluation of the histological specimens and delay of diagnosis, as this was the case in our patient.

Lifelong adherence to a diet rich in protein with substitution of MCT remains the cornerstone in the therapy of PIL. Because MCTs are directly absorbed into the portal venous system bypassing the lymphatic system, they can be used to overcome chronic malnutrition. The need for dietary control in people appears to be permanent because clinical and biochemical findings seem to reappear after low-fat dietary withdrawal. 16/26 patients (61.5%) receiving MCT alone reported significant improvement in symptoms while 2 patients reported only moderate improvement. Octreotide can be regarded as the preferred treatment in patients in whom dietary changes fail to achieve significant improvement. Octreotide is a long-acting somatostatin analogue that suppresses gastrointestinal motility and hormone secretion in the pituitary gland, pancreas, and intestine. Although the mechanism of action of octreotide in diminishing protein loss through the gastrointestinal tract is unclear, theorized mechanisms of octreotide's action in PIL include decreased intestinal fat absorption, inhibition of gastrointestinal vasoactive peptides, and stimulation of the autonomic nervous system[57-59]. Octreotide is usually given at doses of 150-200 μg subcutaneously twice daily[14]. From all 29 cases that reported efficacy of therapy, octreotide was added to MCT in 6 patients and started as initial treatment in one patient, with 2 patients having an insufficient response and 2 patients report in recurrence of symptoms after discontinuation of octreotide with otherwise good response. Other medical therapeutic options include propranolol, which is thought to downregulate the RAF mitogen-activated protein kinase signaling pathway with reduced expression of VEGF, and everolimus, which is an mTOR inhibitor. mTOR is a serine/threonine kinase, representing a key enzyme for numerous cellular processes including angiogenesis and cell growth. Ozeki *et al*[60] found significant mTOR expression in tissues affected by PIL and applied everolimus (1.6 mg/m^2/day) as a treatment of PIL improving diarrhea and hypoproteinemia. However, no case report on an adult patient with PIL exists using these two substances. Surgical resection seems to be the last option both for diagnosis and therapy of PIL. In 6/49 patients, diagnosis of PIL was established after surgical resection, however in most cases without performing an enteroscopy before. All 7 patients that reported surgical resection as the form of treatment – sometimes after the failure of conservative therapy – described improvement of the clinical condition after surgery. However, long-term follow-up does not exist in these patients.

Nevertheless, long-term follow-up is needed since lymphoma have been described as long-term complications in patients with PIL. Laharie *et al*[40] reported on 12 cases of lymphoma after PIL, which was adopted for the present case report and completed by literature review of additional cases until 2020[61]. So far, 13 cases have been published with lymphoma occurring after a median of 14 years (range: 0-39) after PIL diagnosis (Supplementary Table 2).

CONCLUSION

In conclusion, PIL can be a rare cause of PLE in adults. Unspecific symptoms and a wide range of clinical manifestations can significantly hamper establishing the definite diagnosis, leading to a "diagnostic roller coaster" for the individual patient. Despite good treatment options, low recognition of this entity leads to significant morbidity in

these patients. Following review of published case reports, we present a practical overview of symptoms, laboratory findings, the accuracy of diagnostic modalities, and a potential treatment approach to facilitate diagnosis, and management of these patients. Finally, we highlight the striking collinearity with female hormone status in our patient, presenting a potential area of future research (Figure 4).

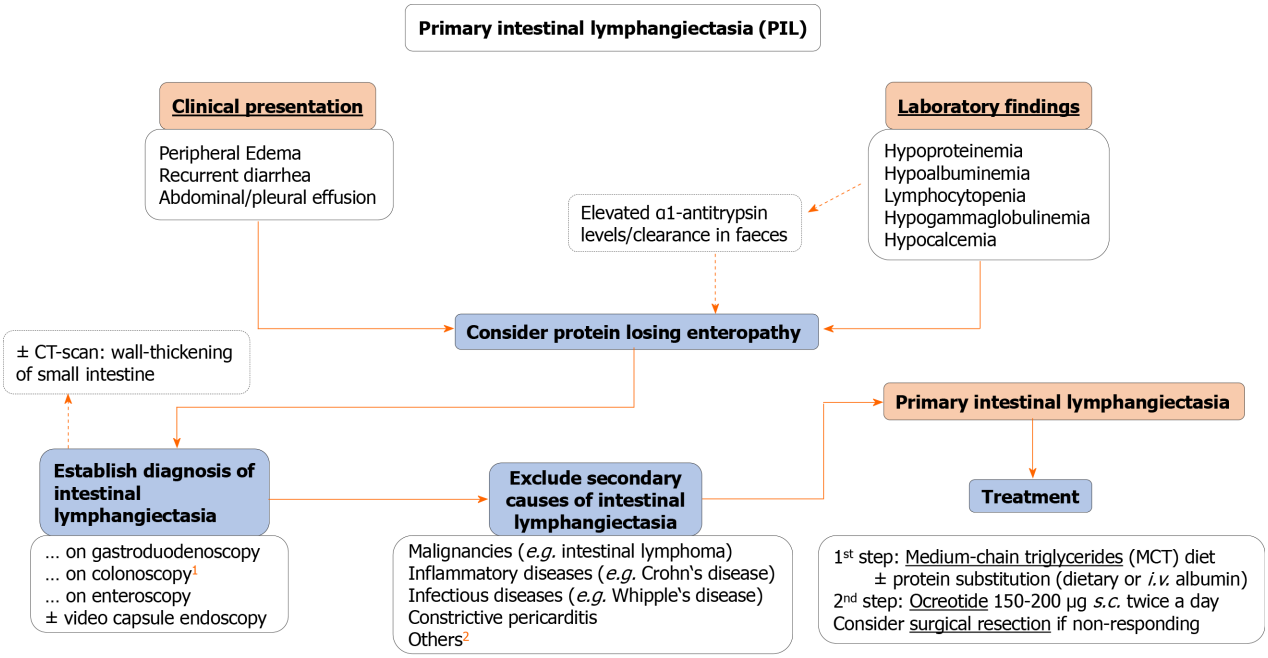

Figure 4 Proposed algorithm for diagnosis and therapy of primary intestinal lymphangiectasia in adults. [1]Including intubation of the terminal ileum. [2]Other secondary causes include: Retroperitoneal fibrosis following radio-/chemotherapy, sarcoidosis, intestinal tuberculosis, systemic sclerosis, human immunodeficiency virus-related enteropathy, Fontan-surgery.

REFERENCES

1 **Waldmann TA**, Steinfeld JL, Dutcher TF, Davidson JD, Gordon RS Jr. The role of the gastrointestinal system in "idiopathic hypoproteinemia". *Gastroenterology* 1961; **41**: 197-207 [PMID: 13782654 DOI: 10.1016/S0016-5085(19)35130-3]

2 **Levitt DG**, Levitt MD. Protein losing enteropathy: comprehensive review of the mechanistic association with clinical and subclinical disease states. *Clin Exp Gastroenterol* 2017; **10**: 147-168 [PMID: 28761367 DOI: 10.2147/CEG.S136803]

3 **Vignes S**, Bellanger J. Primary intestinal lymphangiectasia (Waldmann's disease). *Orphanet J Rare Dis* 2008; **3**: 5 [PMID: 18294365 DOI: 10.1186/1750-1172-3-5]

4 **Freeman HJ**, Nimmo M. Intestinal lymphangiectasia in adults. *World J Gastrointest Oncol* 2011; **3**: 19-23 [PMID: 21364842 DOI: 10.4251/wjgo.v3.i2.19]

5 **Lopez RN**, Day AS. Primary intestinal lymphangiectasia in children: A review. *J Paediatr Child Health* 2020; **56**: 1719-1723 [PMID: 32463559 DOI: 10.1111/jpc.14837]

6 **Samman PD**, White WF. The "Yellow Nail" Syndrome. *Brit J Dermatol* 1964; **76**: 153-157 [DOI: 10.1111/j.1365-2133.1964.tb14499.x]

7 **Hennekam RCM**, Geerdink RA, Hamel BCJ, Hennekam FAM, Kraus P, Rammeloo JA, Tillemans AAW. Autosomal recessive intestinal lymphangiectasia and lymphedema, with facial anomalies and mental retardation. *Am J Med Genet* 1989; **34**: 593-600 [PMID: 2624276 DOI: 10.1002/ajmg.1320340429]

8 **Singh AK**, Zameer A, Sood R, Verma S, Samanta J, Bal A, Sinha SK, Kochhar R. Chronic diarrhea with white colon: Primary Intestinal lymphangiectasia. *QJM* 2020 [PMID: 32330275 DOI: 10.1093/qjmed/hcaa139]

9 **Crutzen B**, Poncelet PA. Protein-Losing Enteropathy in Primary Lymphangiectasia. *J Belg Soc Radiol* 2020; **104**: 34 [PMID: 32676544 DOI: 10.5334/jbsr.2136]

10 **Tseng YJ**, Ding WQ, Luo ZG. Protein-losing enteropathy and primary intestinal lymphangiectasia. *QJM* 2020; **113**: 224-225 [PMID: 31309229 DOI: 10.1093/qjmed/hcz177]

11 **Tominaga K**, Tsuchiya A, Kawata Y, Yokoyama J, Terai S. Novel Magnified Single-Balloon Enteroscopy Enables Observation of Jejunal White Spots Associated with Lymphangiectasia. *Dig Dis* 2019; **37**: 170-174 [PMID: 30466073 DOI: 10.1159/000493578]

12 **Zafar Y**, Gondi KT, Tamimi T, Colson J, Lankachandra K, El-Halawany H. Primary Intestinal Lymphangiectasia Causing Intussusception and Small Bowel Obstruction. *ACG Case Rep J* 2019; **6**: e00233 [PMID: 31832461 DOI: 10.14309/crj.0000000000000233]

13 **Cappell MS**, Edhi A, Amin M. Case report of primary intestinal lymphangiectasia diagnosed in an octogenarian by ileal intubation and by push enteroscopy after missed diagnosis by standard colonoscopy and EGD. *Medicine (Baltimore)* 2018; **97**: e9649 [PMID: 29505002 DOI: 10.1097/MD.0000000000009649]

14 **Altın Z**, Atabay Y, Özer S, Karakoyun M, Ekmekçi S, Yürekli EY, Akar H. Primary intestinal lymphangiectasia and a review of the current literature. *Turk J Gastroenterol* 2018; **29**: 714-716

[PMID: 30381277 DOI: 10.5152/tjg.2018.18596]
15 **Martins CR**, Gagnaire A, Rostain F, Lepage C. Waldmann's disease: a rare cause of protein losing enteropathy in an adult patient. *Rev Esp Enferm Dig* 2017; **109**: 385-388 [PMID: 28376626 DOI: 10.17235/reed.2017.4593/2016]
16 **Lu J**, Zhai H. Exacerbation of primary intestinal lymphangiectasia during late pregnancy and recovery after delivery: A case report and literature review. *Medicine (Baltimore)* 2017; **96**: e7928 [PMID: 28858117 DOI: 10.1097/MD.0000000000007928]
17 **Huber X**, Degen L, Muenst S, Trendelenburg M. Primary intestinal lymphangiectasia in an elderly female patient: A case report on a rare cause of secondary immunodeficiency. *Medicine (Baltimore)* 2017; **96**: e7729 [PMID: 28767614 DOI: 10.1097/MD.0000000000007729]
18 **Balaban VD**, Popp A, Grasu M, Vasilescu F, Jinga M. Severe Refractory Anemia in Primary Intestinal Lymphangiectasia. A Case Report. *J Gastrointestin Liver Dis* 2015; **24**: 369-373 [PMID: 26405709 DOI: 10.15403/jgld.2014.1121.243.bal]
19 **Lee SJ**, Song HJ, Boo SJ, Na SY, Kim HU, Hyun CL. Primary intestinal lymphangiectasia with generalized warts. *World J Gastroenterol* 2015; **21**: 8467-8472 [PMID: 26217101 DOI: 10.3748/wjg.v21.i27.8467]
20 **El-Etreby SA**, Altonbary AY, Sorogy ME, Elkashef W, Mazroa JA, Bahgat MH. Anaemia in Waldmann's disease: A rare presentation of a rare disease. *World J Gastrointest Endosc* 2015; **7**: 567-572 [PMID: 25992197 DOI: 10.4253/wjge.v7.i5.567]
21 **Huber T**, Paschold M, Eckardt AJ, Lang H, Kneist W. Surgical therapy of primary intestinal lymphangiectasia in adults. *J Surg Case Rep* 2015; **2015** [PMID: 26169531 DOI: 10.1093/jscr/rjv081]
22 **Raithel M**, Rau TT, Hagel AF, Albrecht H, de Rossi T, Kirchner T, Hahn EG. Jejunitis and brown bowel syndrome with multifocal carcinogenesis of the small bowel. *World J Gastroenterol* 2015; **21**: 10461-10467 [PMID: 26420973 DOI: 10.3748/wjg.v21.i36.10461]
23 **Troskot R**, Jurčić D, Bilić A, Gomerčić Palčić M, Težak S, Brajković I. How to treat an extensive form of primary intestinal lymphangiectasia? *World J Gastroenterol* 2015; **21**: 7320-7325 [PMID: 26109821 DOI: 10.3748/wjg.v21.i23.7320]
24 **Milazzo L**, Peri AM, Lodi L, Gubertini G, Ridolfo AL, Antinori S. Intestinal lymphangiectasia and reversible high liver stiffness. *Hepatology* 2014; **60**: 759-761 [PMID: 24449480 DOI: 10.1002/hep.27025]
25 **Ersoy O**, Akin E, Demirezer A, Yilmaz E, Solakoglu T, Irkkan C, Yurekli OT, Buyukasik S. Evaluation of primary intestinal lymphangiectasia by capsule endoscopy. *Endoscopy* 2013; **45** Suppl 2 UCTN: E61-E62 [PMID: 23526519 DOI: 10.1055/s-0032-1325976]
26 **Jabeen SA**, Murthy A, Kandadai RM, Meena AK, Borgohain R, Uppin MS. Cryptoccocal menigitis as a primary manifestation in a patient with intestinal lymphangictasia. *Ann Indian Acad Neurol* 2012; **15**: 218-220 [PMID: 22919199 DOI: 10.4103/0972-2327.99725]
27 **Suehiro K**, Morikage N, Murakami M, Yamashita O, Hamano K. Late-onset primary intestinal lymphangiectasia successfully managed with octreotide: a case report. *Ann Vasc Dis* 2012; **5**: 96-99 [PMID: 23555496 DOI: 10.3400/avd.cr.11.00085]
28 **Maamer AB**, Baazaoui J, Zaafouri H, Soualah W, Cherif A. Primary intestinal lymphangiectasia or Waldmann's disease: a rare cause of lower gastrointestinal bleeding. *Arab J Gastroenterol* 2012; **13**: 97-98 [PMID: 22980601 DOI: 10.1016/j.ajg.2012.03.001]
29 **Kneist W**, Drescher DG, Hansen T, Kreitner KF, Lang H. [Surgical therapy of segmental jejunal, primary intestinal lymphangiectasia]. *Z Gastroenterol* 2013; **51**: 576-579 [PMID: 23229460 DOI: 10.1055/s-0031-1273473]
30 **Koçak G**, Koçak E, Akbal E, Duranay M, Köklü S. A rare cause of severe hypoalbuminemia in a patient with primary hypoparathyroidism: intestinal lymphangiectasia. *Acta Clin Belg* 2011; **66**: 246-247 [PMID: 21837942 DOI: 10.2143/ACB.66.3.2062563]
31 **Choi EH**, Reidel W, Coyle W. Forty years of shortness of breath and lower extremity edema. Diagnosis: Primary intestinal lymphangiectasia (Waldmann's disease). *Gastroenterology* 2011; **141**: e6-e7 [PMID: 21641905 DOI: 10.1053/j.gastro.2010.04.059]
32 **Wiedermann CJ**, Kob M, Benvenuti S, Carella R, Lucchin L, Piazzi L, Chilovi F, Mazzoleni G. Digital clubbing in primary intestinal lymphangiectasia: a case report. *Wien Med Wochenschr* 2010; **160**: 431-436 [PMID: 20812055 DOI: 10.1007/s10354-010-0815-0]
33 **Steines JC**, Larson JH, Wilkinson N, Kirby P, Goodheart MJ. Intestinal lymphangiectasia mimicking primary peritoneal carcinoma. *Am J Obstet Gynecol* 2010; **203**: e9-e11 [PMID: 20801422 DOI: 10.1016/j.ajog.2010.07.009]
34 **Zhu LH**, Cai XJ, Mou YP, Zhu YP, Wang SB, Wu JG. Partial enterectomy: treatment for primary intestinal lymphangiectasia in four cases. *Chin Med J (Engl)* 2010; **123**: 760-764 [PMID: 20368101]
35 **Paggi S**, Ferrero S, Braidotti P, de Rai P, Conte D, Basilisco G. Neuromuscular alterations in the dilated ileum of an adult patient with segmental lymphangiectasia. *Eur J Gastroenterol Hepatol* 2008; **20**: 935-938 [PMID: 18794610 DOI: 10.1097/MEG.0b013e3282f5dda4]
36 **Herfarth H**, Hofstädter F, Feuerbach S, Jürgen Schlitt H, Schölmerich J, Rogler G. A case of recurrent gastrointestinal bleeding and protein-losing gastroenteropathy. *Nat Clin Pract Gastroenterol Hepatol* 2007; **4**: 288-293 [PMID: 17476211 DOI: 10.1038/ncpgasthep0812]
37 **Cole SL**, Ledford DK, Lockey RF, Daas A, Kooper J. Primary gastrointestinal lymphangiectasia presenting as cryptococcal meningitis. *Ann Allergy Asthma Immunol* 2007; **98**: 490-492 [PMID: 17521035 DOI: 10.1016/s1081-1206(10)60765-x]
38 **Fang YH**, Zhang BL, Wu JG, Chen CX. A primary intestinal lymphangiectasia patient diagnosed by

capsule endoscopy and confirmed at surgery: a case report. *World J Gastroenterol* 2007; **13**: 2263-2265 [PMID: 17465517 DOI: 10.3748/wjg.v13.i15.2263]

39 **Chamouard P**, Nehme-Schuster H, Simler JM, Finck G, Baumann R, Pasquali JL. Videocapsule endoscopy is useful for the diagnosis of intestinal lymphangiectasia. *Dig Liver Dis* 2006; **38**: 699-703 [PMID: 16527553 DOI: 10.1016/j.dld.2006.01.027]

40 **Laharie D**, Degenne V, Laharie H, Cazorla S, Belleannee G, Couzigou P, Amouretti M. Remission of protein-losing enteropathy after nodal lymphoma treatment in a patient with primary intestinal lymphangiectasia. *Eur J Gastroenterol Hepatol* 2005; **17**: 1417-1419 [PMID: 16292099 DOI: 10.1097/00042737-200512000-00024]

41 **Goktan C**, Pekindil G, Orguc S, Coskun T, Serter S. Bilateral Breast Edema in Intestinal Lymphangiectasia. *Breast J* 2005; **11**: 360 [PMID: 16174162 DOI: 10.1111/j.1075-122X.2005.21578.x]

42 **Cammarota G**, Cianci R, Gasbarrini G. High-resolution magnifying video endoscopy in primary intestinal lymphangiectasia: a new role for endoscopy? *Endoscopy* 2005; **37**: 607 [PMID: 15933946 DOI: 10.1055/s-2005-861338]

43 **Filik L**, Oguz P, Koksal A, Koklu S, Sahin B. A case with intestinal lymphangiectasia successfully treated with slow-release octreotide. *Dig Liver Dis* 2004; **36**: 687-690 [PMID: 15506669 DOI: 10.1016/j.dld.2004.06.002]

44 **Lynn J**, Knight AK, Kamoun M, Levinson AI. A 55-year-old man with hypogammaglobulinemia, lymphopenia, and unrelenting cutaneous warts. *J Allergy Clin Immunol* 2004; **114**: 409-414 [PMID: 15316525 DOI: 10.1016/j.jaci.2004.02.033]

45 **Chen CP**, Chao Y, Li CP, Lo WC, Wu CW, Tsay SH, Lee RC, Chang FY. Surgical resection of duodenal lymphangiectasia: a case report. *World J Gastroenterol* 2003; **9**: 2880-2882 [PMID: 14669360 DOI: 10.3748/wjg.v9.i12.2880]

46 **Strehl J**, Schepke M, Wardelmann E, Caselmann WH, Sauerbruch T. [Chronic diarrhea in a 43-year-old patient]. *Internist (Berl)* 2003; **44**: 626-630 [PMID: 12966790 DOI: 10.1007/s00108-003-0856-1]

47 **Klingenberg RD**, Homann N, Ludwig D. Type I intestinal lymphangiectasia treated successfully with slow-release octreotide. *Dig Dis Sci* 2003; **48**: 1506-1509 [PMID: 12924644 DOI: 10.1023/a:1024707605493]

48 **Kuroiwa G**, Takayama T, Sato Y, Takahashi Y, Fujita T, Nobuoka A, Kukitsu T, Kato J, Sakamaki S, Niitsu Y. Primary intestinal lymphangiectasia successfully treated with octreotide. *J Gastroenterol* 2001; **36**: 129-132 [PMID: 11227670 DOI: 10.1007/s005350170142]

49 **Keberle M**, Mörk H, Jenett M, Hahn D, Scheurlen M. Computed tomography after lymphangiography in the diagnosis of intestinal lymphangiectasia with protein-losing enteropathy in Noonan's syndrome. *Eur Radiol* 2000; **10**: 1591-1593 [PMID: 11044930 DOI: 10.1007/s003300000384]

50 **Alfano V**, Tritto G, Alfonsi L, Cella A, Pasanisi F, Contaldo F. Stable reversal of pathologic signs of primitive intestinal lymphangiectasia with a hypolipidic, MCT-enriched diet. *Nutrition* 2000; **16**: 303-304 [PMID: 10758368 DOI: 10.1016/s0899-9007(00)00223-9]

51 **Bouhnik Y**, Etienney I, Nemeth J, Thevenot T, Lavergne-Slove A, Matuchansky C. Very late onset small intestinal B cell lymphoma associated with primary intestinal lymphangiectasia and diffuse cutaneous warts. *Gut* 2000; **47**: 296-300 [PMID: 10896925 DOI: 10.1136/gut.47.2.296]

52 **Gumà J**, Rubió J, Masip C, Alvaro T, Borràs JL. Aggressive bowel lymphoma in a patient with intestinal lymphangiectasia and widespread viral warts. *Ann Oncol* 1998; **9**: 1355-1356 [PMID: 9932170 DOI: 10.1023/a:1008496900822]

53 **Lenzhofer R**, Lindner M, Moser A, Berger J, Schuschnigg C, Thurner J. Acute jejunal ileus in intestinal lymphangiectasia. *Clin Investig* 1993; **71**: 568-571 [PMID: 8374252 DOI: 10.1007/bf00208483]

54 **Wen J**, Tang Q, Wu J, Wang Y, Cai W. Primary intestinal lymphangiectasia: four case reports and a review of the literature. *Dig Dis Sci* 2010; **55**: 3466-3472 [PMID: 20198428 DOI: 10.1007/s10620-010-1161-1]

55 **Morfoisse F**, Tatin F, Chaput B, Therville N, Vaysse C, Métivier R, Malloizel-Delaunay J, Pujol F, Godet AC, De Toni F, Boudou F, Grenier K, Dubuc D, Lacazette E, Prats AC, Guillermet-Guibert J, Lenfant F, Garmy-Susini B. Lymphatic Vasculature Requires Estrogen Receptor-α Signaling to Protect From Lymphedema. *Arterioscler Thromb Vasc Biol* 2018; **38**: 1346-1357 [PMID: 29650694 DOI: 10.1161/ATVBAHA.118.310997]

56 **Florent C**, L'Hirondel C, Desmazures C, Aymes C, Bernier JJ. Intestinal clearance of alpha 1-antitrypsin. A sensitive method for the detection of protein-losing enteropathy. *Gastroenterology* 1981; **81**: 777-780 [PMID: 6973500 DOI: 10.1016/0016-5085(81)90506-0]

57 **Reubi JC**, Laissue JA, Waser B, Steffen DL, Hipkin RW, Schonbrunn A. Immunohistochemical detection of somatostatin sst2a receptors in the lymphatic, smooth muscular, and peripheral nervous systems of the human gastrointestinal tract: facts and artifacts. *J Clin Endocrinol Metab* 1999; **84**: 2942-2950 [PMID: 10443702 DOI: 10.1210/jcem.84.8.5878]

58 **Ballinger AB**, Farthing MJ. Octreotide in the treatment of intestinal lymphangiectasia. *Eur J Gastroenterol Hepatol* 1998; **10**: 699-702 [PMID: 9744700]

59 **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**: 454-457 [PMID: 20512058 DOI: 10.1097/MPG.0b013e3181d1b162]

60 **Ozeki M**, Hori T, Kanda K, Kawamoto N, Ibuka T, Miyazaki T, Fukao T. Everolimus for Primary

Intestinal Lymphangiectasia With Protein-Losing Enteropathy. *Pediatrics* 2016; **137**: e20152562 [PMID: 26908672 DOI: 10.1542/peds.2015-2562]

61 **Patel KV**, Goel RM, Wong T. Diffuse large B-cell lymphoma recurrence complicating primary intestinal lymphangiectasia. *Clin Gastroenterol Hepatol* 2013; **11**: e86-e87 [PMID: 23591283 DOI: 10.1016/j.cgh.2013.03.028]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2020 Baishideng Publishing Group Inc. All rights reserved.