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CASE REPORT | SMALL BOWEL

Adult-Onset Primary Intestinal Lymphangiectasia With Liver Enzymes Elevation

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ABSTRACT

Primary intestinal lymphangiectasia is a rare disorder that may result in protein-losing enteropathy. We report a 21-year-old man with malabsorption syndrome, an unintentional weight loss of 30 kg over 10 months, lymphocytopenia, and hepatic aminotransferase elevation. His diagnosis was established by a combination of enteroscopy, histopathology, and secondary etiology exclusion. Institution of parenteral nutrition, followed by a low-fat diet, medium-chain triglycerides, and octreotide, resulted in the resolution of his symptoms and laboratory abnormalities and led to weight gain. Aminotransferase abnormalities are an atypical finding in primary intestinal lymphangiectasia and were most likely due to nonalcohol steatohepatitis after rapid weight loss. Primary intestinal lymphangiectasia should be considered in patients with protein-losing enteropathy and lymphocytopenia.

INTRODUCTION

Primary intestinal lymphangiectasia (PIL), which usually develops in early childhood, is an uncommon etiology of protein-losing enteropathy with an unknown prevalence. Since 1961, when it was first described by Waldmann et al, there have been approximately 50 cases reported in adults.[1,2] To the best of our knowledge, the involvement of the liver in the PIL scenario has not been well-defined, with only 3 reports that describe this finding.[3–5] We present a case of PIL accompanied by hepatic aminotransferase elevation, which was successfully managed with dietary modification and octreotide.

CASE REPORT

A 21-year-old man presented with a 10-month history of watery diarrhea and a 30 kg weight loss over this period. He first noted mild facial and ankle swelling and subsequently developed watery, nonbloody diarrhea with 15–20 bowel movements daily. Moreover, he suffered from many severe episodes of tetany and even seizures, which forced him to be admitted to the local hospital 6 times. There was no significant medical history, and he did not drink alcohol or use any drugs. Physical examination was significant for mild periorbital edema, lower extremity pitting edema, and conjunctival pallor. The abdomen was soft and mildly distended; bowel sounds were hyperactive.

Laboratory data were significant for lymphocytopenia, iron deficiency anemia (hemoglobin 7.2 g/dL, serum iron 1.91 μg/mL, serum ferritin 18 ng/mL), hypogammaglobulinemia (immunoglobulin G <2.89 g/L, immunoglobulin A <0.44 g/L), prolonged international normalized ratio (3.26), hypoproteinemia (2.8 g/L), hypoalbuminemia (1.4 g/L), hypocalcemia (ionized calcium 0.83 mmol/L), and hypovitaminosis D (<3.5 mmol/L). Infectious enteritis workup comprised fecal *Clostridioides difficile* toxin, ova, and parasites; examination for *Strongyloides stercoralis*, *Toxocara canis*, and *Entamoeba histolytica* antigens was all negative. Urinalysis showed no protein, and fecal calprotectin was normal. The stool alpha-1 antitrypsin clearance test was not performed because it is not

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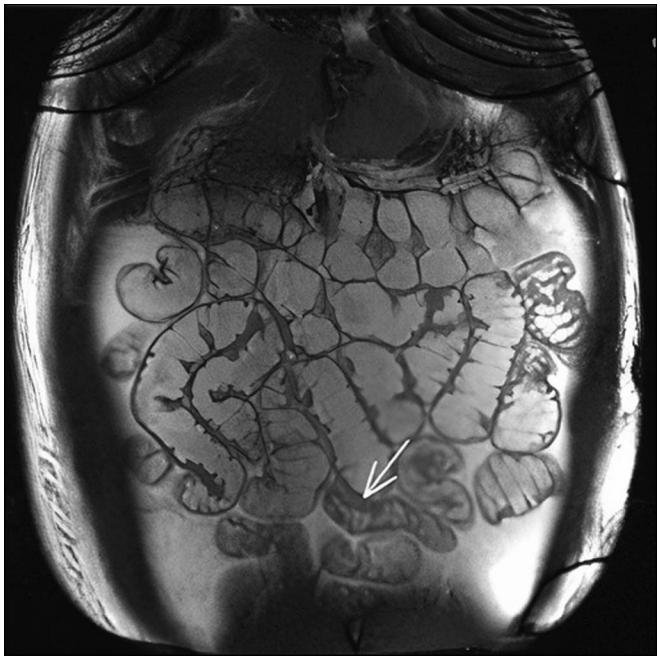

Figure 1. Terminal ileum thickening on magnetic resonance enterography.

accessible in our nation. Alkaline phosphatase and total bilirubin were normal, although both aspartate aminotransferase and alanine aminotransferase were 700 IU/L. The results of tests for hepatitis etiology, such as viral serology (A and B), autoimmune antibodies, and genetic disorders (e.g., Wilson's disease and alpha-1 antitrypsin deficiency), were all negative.

Abdominal ultrasound revealed diffuse fatty liver with patent hepatic vessels, normal common bile duct and moderate ascites. Magnetic resonance enterography showed terminal ileum thickening (Figure 1). Liver biopsy was planned but was refused.

Single-balloon enteroscopy revealed scattered white spots overlying the jejunal mucosa (Figure 2). Histopathological examination of biopsies showed dilated lymphatic channels lying beneath the epithelium (Figure 3). Colonoscopy and biopsies were unremarkable. After excluding secondary causes by combining histopathology and laboratory findings, the final diagnosis of PIL was made.

Initially, loperamide was prescribed for his diarrhea while parenteral nutrition (PN) was used to correct his nutrition status. His hepatic aminotransferase concentrations decreased significantly during PN but returned to high values once PN was stopped. After establishing the final diagnosis, a low-fat diet with medium-chain triglyceride (MCT) supplementation (180–200 g of protein, 50–70 g of lipid, 520–530 g of carbohydrate; 3,000–3,200 kcal in total) was prescribed in combination with PN. Two weeks later, his condition was not improved, and octreotide was administered subcutaneously at a dosage of 100 μg 3 times per day. With these therapies, his symptoms, including diarrhea, borborygmi, and tetany, resolved completely after 1 week. A low-fat diet, MCTs, and octreotide were key elements of his outpatient treatment. One month later, aminotransferase levels returned to normal. After 10 months, he gained more than 15 kg and his liver was found to be normal on ultrasound. Unfortunately, our country was quarantined owing to the coronavirus disease of 2019 outbreak at this time, so octreotide was not available to him. He had no choice but to stop taking octreotide after 10 months. Fortunately, his condition remained stable, so we decided to discontinue octreotide and just focus on modifying his diet.

DISCUSSION

PIL is associated with dilated, distorted, and obstructed lymphatic vessels, leading to the rupture of intestinal lacteals, which in turn causes loss of their contents into the gut lumen. This pathophysiology explains why hypoalbuminemia, hypogammaglobulinemia, and lymphocytopenia are prominent features. Consequently, peripheral or generalized edema is the typical clinical symptom (83.3% of patients) while chronic diarrhea is the second most common presentation (41.7% of patients).[2] Although severe hypocalcemia related to vitamin D deficiency occurs only in 1 of 4 adult patients with PIL, tetany or seizures associated with PIL, as in our case, has been described previously in only 2 reports of children.[6,7]

Enteroscopy is extremely useful to capture the snowflake appearance of the mucosa, a distinctive aspect indicating lymphatic dilation (as observed in 14 of 14 cases and in our case).[2] Definitive diagnosis can be established by histological assessment of small intestinal mucosal biopsies and exclusion of secondary intestinal lymphangiectasia such as Crohn's disease, intestinal tuberculosis, intestinal lymphoma, and constrictive pericarditis. Because PIL is diagnosed predominantly in children younger than 3 years, the possibility of a genetic predisposition has been proposed and is supported by its association with several inherited syndromes, including Turner, Noonan, or Henekam.[2]

As far as we know, there are only 3 reports of PIL that describe an association between liver abnormalities and PIL. Jain et al[5] described 3 family members with PIL and chronic liver disease of unknown origin. Their symptoms of edema and ascites resolved with dietary therapy, but the outcome of liver disease was not described in this report. Milazzo et al reported a middle-aged woman with PIL and high-grade liver stiffness on FibroScan that resolved after dietary modification. Fibrosis was hypothesized to result from lymphatic stasis, which is similar to hepatic venous congestion in right-sided heart failure.[3] The third report described a 17-year-old adolescent girl with slightly increased hepatic aminotransferases and hepatic fibrosis. After treatment, only the aminotransferase levels became normal, but the fibrosis worsened. Malnutrition-induced steatohepatitis was believed to cause liver enzyme abnormalities, whereas the etiology of fibrosis was unknown and assumed to be congenital.[4]

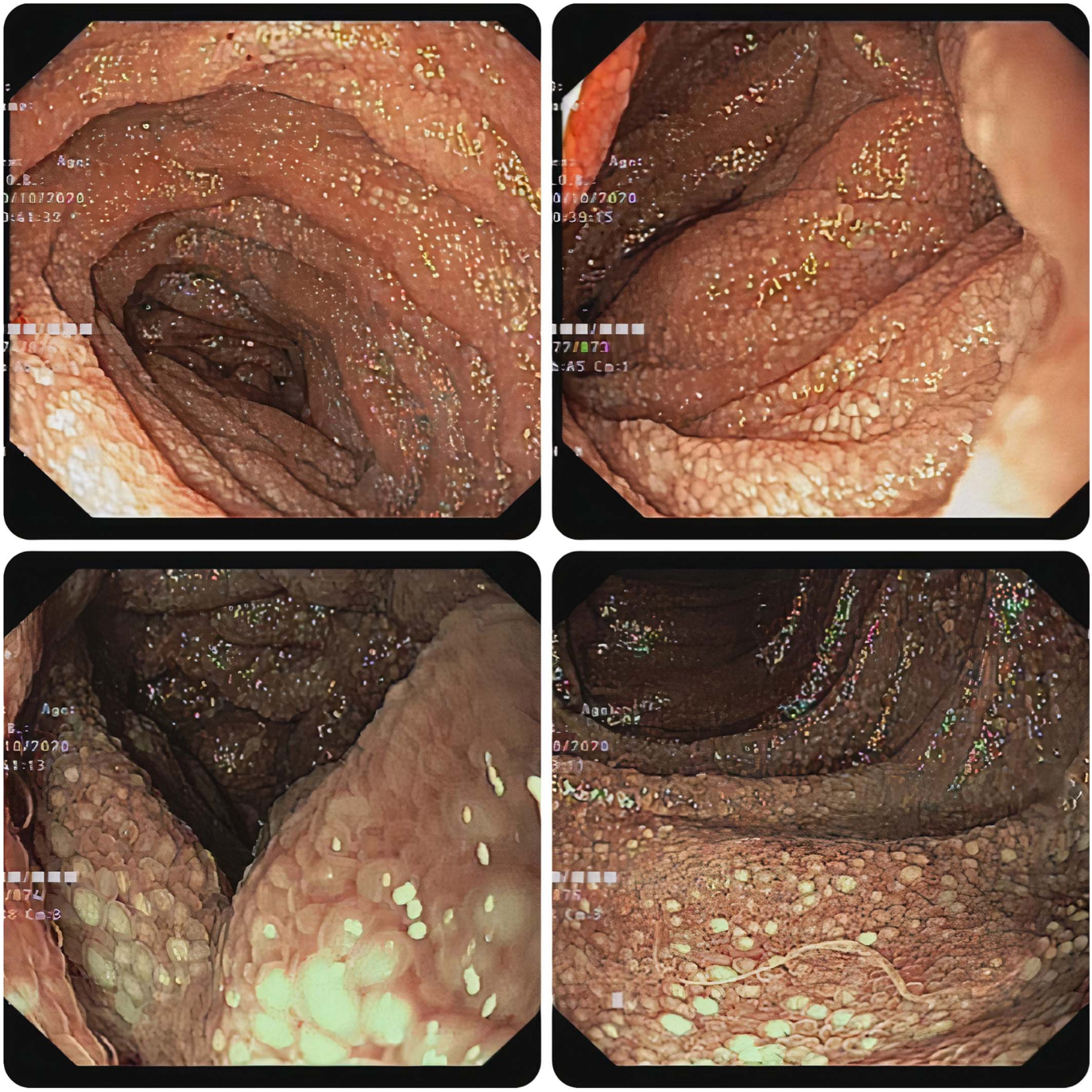

Figure 2. Single-balloon enteroscopy revealed multiple white spots on the jejunal mucosa (snowflake appearance).

Treatment of PIL consists of dietary modification comprising a high-protein (2 g/kg/d) and low-fat (<2.5 g/d) diet. The fat component should consist of more than 90% MCTs.[8] MCTs are absorbed directly into the portal venous system and, thus, decrease intestinal lymphatic flow and prevent further degradation of the lymphatic vessels. The result of dietary modification should be assessed by symptoms, physical examination, and laboratory tests related to protein-losing enteropathy such as albumin, fat-soluble vitamins, and immunoglobulin. The resolution of signs and symptoms as well as the improvement of these laboratory data are characteristic of successful treatment. The reduction of stool alpha-1 antitrypsin clearance may also indicate a good response.[9] The exact interval for repeating these laboratory tests is not clearly described in previous literature and should be determined individually.

Approximately one-third of patients, however, do not show clinical improvement with dietary therapy and require second-line therapies.[2] Bowel resection or lymphatic embolization is only suitable for focal lesions while medications can be used for

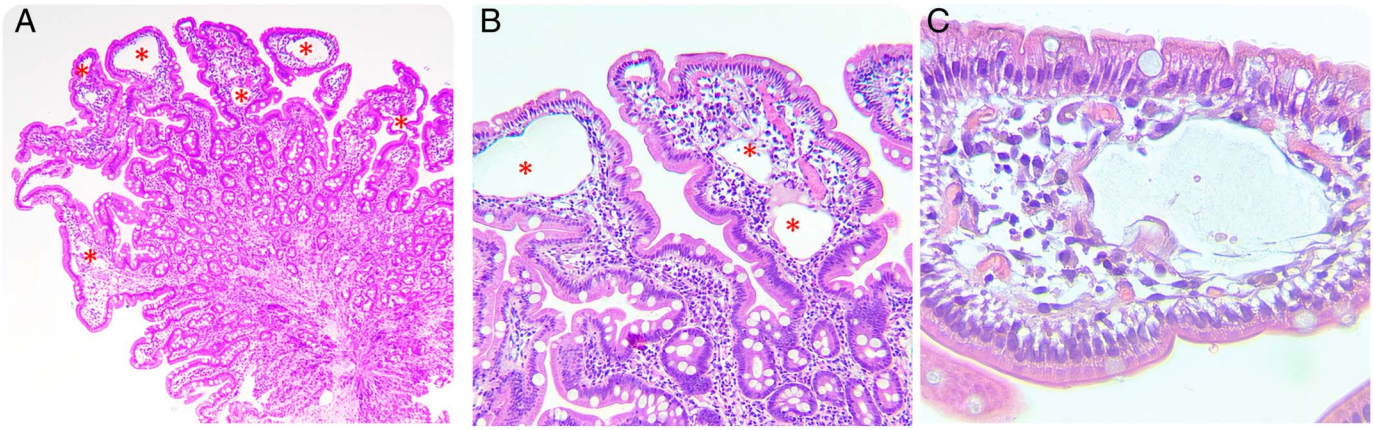

Figure 3. Histopathology of jejunal specimens stained with conventional hematoxylin and eosin stains. Lymphangiectasia tended to confine to the mucosa. (A) Low-power photomicrograph of small polypoid lesions of the jejunum showed dilated lymphatic vessels (hematoxylin and eosinophil stain, ×4). (B) Medium-power photograph revealed several single villi on the mucosal surface containing extremely dilated vascular space (hematoxylin and eosinophil stain, ×10). (C) High-power field demonstrated a large dilated lymphatic vessel with some lymphoid aggregation in the lamina propria (hematoxylin and eosinophil stain, ×20).

both diffuse and local intestinal lymphangiectasia.[8] Octreotide is a somatostatin analog whose theorized mechanisms in the treatment of PIL consist of decreased splanchnic blood flow, intestinal motility, and triglyceride absorption. In a series of 7 cases of adult-onset PIL treated with octreotide, 5 of 7 patients reported good responses. The authors did not specify the length of therapy in these cases that were effectively treated with octreotide. Similarly, no standardized recommended dosage of octreotide exists. Octreotide at the dosage of 150–200 μg subcutaneously displayed good results.[2] In addition, PN or enteral nutrition using either an elemental diet or a low-fat-containing polymetric diet may play a role in such cases. Aoyagi et al showed that an elemental diet and PN were equally efficient and may be more effective than a polymeric diet, most likely because of the elemental diet's very low-fat content. This study was conducted on 7 patients with PIL who did not respond to a low-fat diet.[10] Makowska-Wierzbicka et al recently reported a severe PIL case affecting the entire gastrointestinal tract that was successfully managed with a combination of enteral nutrition and PN.[11] Sirolimus, everolimus, steroids, propranolol, and tranexamic acid have also been used, but data are available from isolated reports only.[8]

Our case was distinguished from other reports because the abnormal liver enzymes were a very prominent finding. They improved to some degree with PN before the specific dietary change for PIL suggesting that malnourishment-associated hepatitis steatosis was the main pathophysiology. In addition to malnutrition, rapid weight loss (lost 30 kg over 10 months like our case) enhances lipolysis and releases endogenous free fatty acids from adipose deposits, which in turn creates reactive oxygen species damaging hepatocytes.[12]

In conclusion, we report a case of PIL associated with abnormal liver tests that responded to treatment with PN, a low-fat diet, MCTs, and octreotide.

DISCLOSURES

Author contributions: AT-L Pham, DT-N Vo, LM Dang, VH Vo, and CD Nguyen were involved in the treatment of this case. CD Nguyen, LM Dang, and VH Vo reviewed the literature and wrote the manuscript. A.Buchman, HH Bui, AT-L Pham, and DT-N Vo revised the manuscript for important intellectual content. CD Nguyen is the article guarantor. All authors approved the final manuscript.

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Informed consent was obtained for this case report.

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