CASE REPORT

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Severe Refractory Anemia in Primary Intestinal Lymphangiectasia. A Case Report

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ABSTRACT

Background: Primary intestinal lymphangiectasia (Waldmann's disease) is a rare disease characterized by dilated lymphatics in the small bowel leading to an exudative enteropathy with lymphopenia, hypoalbuminemia and hypogammaglobulinemia.
Case presentation: We report the case of a 23 year-old male who presented with chronic anemia and in whom primary intestinal lymphangiectasia was diagnosed. A low-fat diet along with nutritional therapy with medium-chain triglyceride supplementation improved the protein-losing enteropathy, but did not solve the anemia. Octreotide was also unsuccessful, and after attempting angiographic embolization therapy, limited small bowel resection together with antiplasmin therapy managed to correct the anemia and control the exudative enteropathy.
Conclusions: Although primary intestinal lymphangiectasia is usually adequately managed by nutritional therapy, complications such as anemia can occur and can prove to be a therapeutic challenge.

Key words: intestinal lymphangiectasia – anemia – refractory – antiplasmin.

Abbreviations: CD: celiac disease; EMA: anti-endomysial antibodies; GI: gastrointestinal; Hb: hemoglobin; MCT: medium-chain triglycerides; PIL: primary intestinal lymphangiectasia; tTG: tissue transglutaminase.

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INTRODUCTION

First described by Waldmann in 1961 [1], primary intestinal lymphangiectasia (PIL) is a rare disease characterized by dilated lacteals in the small bowel, which result in a protein-losing enteropathy. Lymph leakage into the small bowel lumen leads to lymphopenia, hypoalbuminemia and hypogammaglobulinemia, which are the main biological features of this disease [2]. Primary intestinal lymphangiectasia is usually diagnosed in childhood, but adult cases have also been reported. Worldwide, few over 200 cases have been described [3]. The diagnosis is confirmed by the endoscopic appearance of the small bowel lymphangiectasia and the corresponding histology on the biopsies. Management of this disease consists of a low-fat diet (to avoid lacteal stimulation) and supplementation with medium-chain triglycerides (MCT), which bypass the lymphatic circulation and are absorbed directly into the portal venous system. The need for nutritional therapy is permanent, because on withdrawal the exudative enteropathy reappears [2]. In refractory forms of PIL, there are reports of successful treatment with antiplasmin agents (tranexamic acid), somatostatin analogues (octreotide), corticosteroids, segmental bowel resection, peritoneovenous shunt and intestinal transplant [2, 3].

CASE REPORT

The patient, a 23 year old male, nonsmoker, had been treated intermittently with iron supplements for chronic anemia since adolescence. He had complained of soft, dark-colored stools. Besides the anemia, the medical history was unremarkable. Physical examination revealed significant pallor, without any other particularities. Upon primary evaluation, laboratory tests revealed moderate microcytic anemia, lymphopenia, hypoalbuminemia, hypocholesterolemia, sideropenia, hypocalcemia and hypogammaglobulinemia (Table I). Based on this biochemical aspect of malabsorption, we considered

Table I. Laboratory values

	At presentation	30 days after tranexamic acid
Lymphocytes (/mm3)	600	1100
Albumin (g/dl)	3.1	3.6
Cholesterol (mg/dl)	113	139
Serum iron (µg/dl)	18.1	46
Serum calcium (mg/dl)	8	9.1
Stool parasites	Negative	NA
TSH	Normal	NA
ANA	Normal	NA
Anti-tTG IgA antibodies	Negative	NA
EMA	Negative	NA
Anti-HIV Ab	Negative	NA
Anti-Scl-70	Negative	NA

TSH: thyroid -stimulating hormone; ANA: anti-nuclear antibodies; EMA: anti-endomysial antibodies; tTG: tissue transglutaminase; NA: not assessed.

celiac disease (CD) as a first option for the diagnosis. Specific celiac-type serology was negative. Abdominal ultrasound was unremarkable. Upper gastrointestinal (GI) endoscopy revealed an edematous aspect of the duodenal mucosa with multiple whitish spots suggestive of lymphangiectasia, which were biopsied (Fig. 1). On ileocolonoscopy we identified multiple cystic lesions protruding into the bowel lumen at the level of the transverse and ascending colon, which proved to contain serous fluid upon puncturing. We also performed anterograde enteroscopy and found lesions similar to the duodenal ones on the first 40 cm of the jejunum, with diffusely scattered white spots and segmental pseudopolypoid thickening of the mucosa, covered with whitish, swollen villi (Fig. 2). The lesions were disseminated throughout the entire small bowel, except the last ileal loops, as shown by videocapsule examination. Contrast-enhanced CT scan showed edema in the small bowel wall, diffuse infiltration of the mesentery with nodular appearance, and small pleural and peritoneal effusions.

The histopathology report of the enterobiopsy specimens confirmed the diagnosis of PIL (Figs. 3, 4). Immunohistochemistry was negative for lymphoma. In addition, the presence of CD specific epithelial transglutaminase 2 (TG2) targeted IgA antibody deposits were evaluated in a frozen small-bowel mucosal specimen by direct immunofluorescence using IgA staining and double color staining for both IgA and TG2.

After exclusion of secondary causes of lymphatic obstruction, we established the diagnosis of PIL and recommended a low-fat, high-protein diet and MCT supplementation.

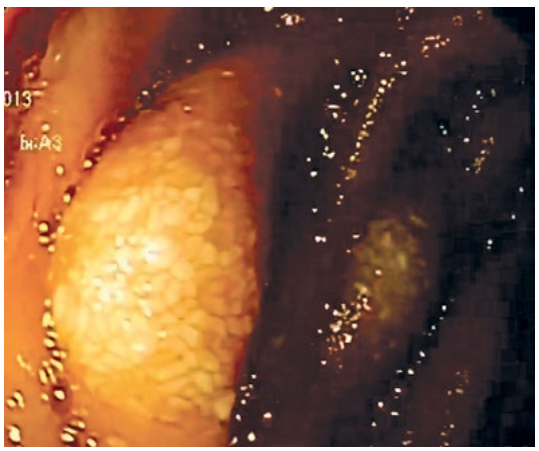

Fig. 1. Multiple whitish villi seen on upper gastrointestinal endoscopy, suggesting lymphangiectasia.

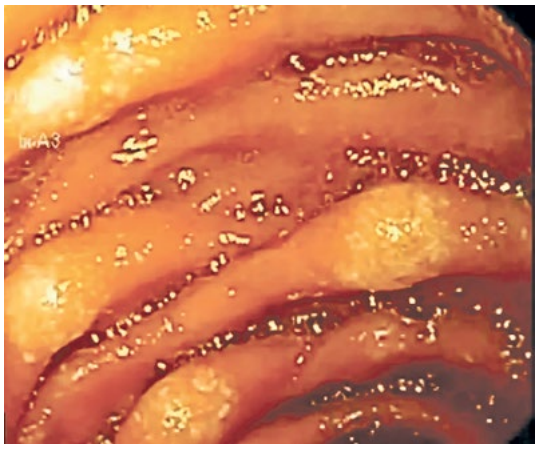

Fig. 2. Segmental pseudopolypoid thickening of the small bowel mucosa, with diffuse white spots, seen on enteroscopy.

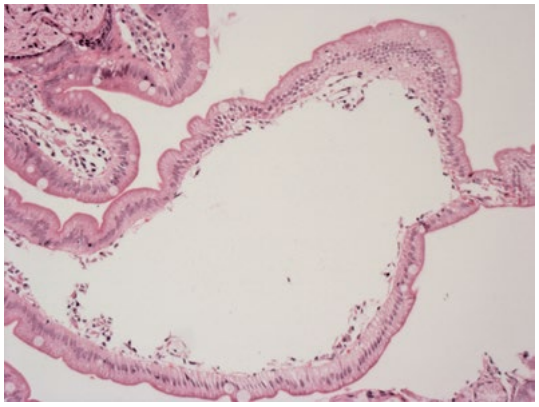

Fig. 3. Small bowel biopsy sample (H&E, x10): marked dilation of the central lacteal of the villi with peripheral displacement of the nuclei in the lymph vessel wall.

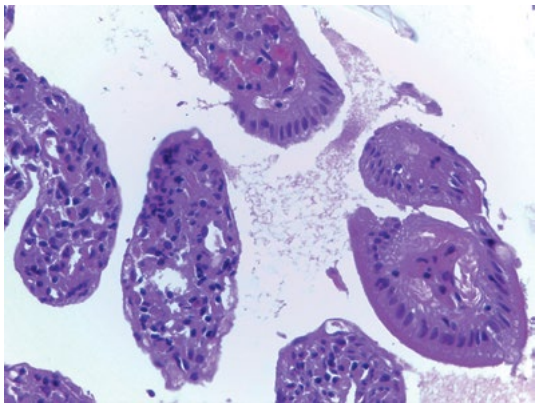

Fig. 4. Small bowel biopsy sample (H&E, x40): hemosiderin-laden macrophages, secondary to mucosal bleeding.

At follow-up, the dilated lacteals in the small bowel were considerably reduced, fecal alpha-1 anti-trypsin normalized (to 203 μg/g feces), but anemia (Hb 7.2 g/dl) and a mild hypoalbuminemia (3.3 g/dl) persisted. As a trial of octreotide was unsuccessful in correcting the anemia and the levels of hemoglobin continued to drop (up to 5 g/dl, without obvious GI bleeding), we performed a scintigraphic study with marked red blood cells (^{99m}Tc) to evaluate for active bleeding. The scintigraphic report revealed possible bleeding in the projection area of the first small bowel loops on the flanks. Consequently, after a diagnostic study evidenced a tortuous pattern of first jejunal artery branches suggestive of angiodysplasia, an angiography embolization with Gelaspon was performed (Figs. 5, 6).

However, because control of the bleeding was not successful and a follow-up CT scan showed enteral pneumatosis suggestive of small bowel necrosis, laparotomy was performed with a 10 cm jejunal resection, lavage of the peritoneal cavity and evacuation of cysts of the jejunal wall; at this point, ectatic vessels were seen in the bowel serosa.

Fig. 5. Selective arteriography, with the catheter positioned in the superior mesenteric artery: a tortuous aspect of the arterial branches of the first jejunal loops is seen, compatible with angiectasia.

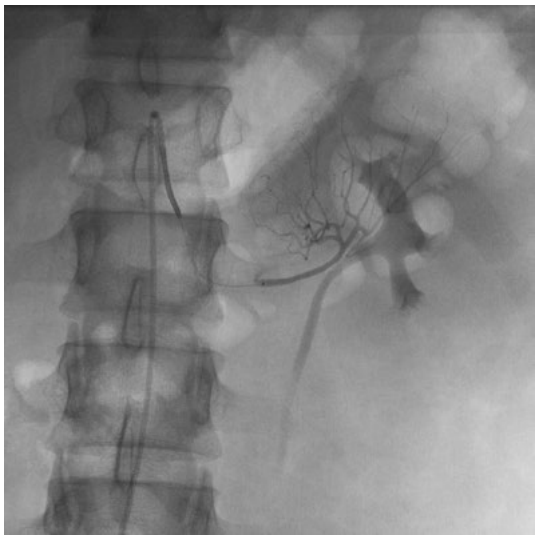

Fig. 6. Ultraselective catheterization of the arterial branch of the first jejunal loop after partial embolization.

Postoperative recovery was uneventful, and we then initiated treatment with tranexamic acid. The patient had a favorable evolution under antiplasmin therapy, with correction and control of the anemia and hypoalbuminemia at 30 days. The anemia relapsed when the patient discontinued tranexamic acid for two weeks (up to a Hb of 5.6 g/dl), and this was resolved quickly after restarting antiplasmin therapy.

DISCUSSION

Primary intestinal lymphangiectasia is a rare disease usually diagnosed in children, but which can also be diagnosed in adulthood [2]. A pubertal worsening or uncovering has been reported in PIL [4], which may be the case for our patient, who was diagnosed in early adulthood but who had been treated for anemia since adolescence. Although PIL can usually be managed appropriately with dietary interventions, in some patients nutritional therapy is not sufficient and additional measures are required. In our patient, PIL associated refractory anemia proved to be a therapeutic challenge.

The classic clinical picture of PIL consists of a child with diarrhea, edema and ascites. Adults on the other hand usually present with few clinical features of malabsorption [5], as in our patient: because hypoalbuminemia was mild, the serous effusions were small and clinically silent, and there was no peripheral edema. Meanwhile, anemia by occult GI bleeding was the chief complaint.

The principal biochemical findings of PIL include lymphopenia, hypoalbuminemia, hypogammaglobulinemia, hypocalcemia and hypocholesterolemia, which were all present in our patient. Lymphocytes and protein-rich fluid are all lost by the rupture of the ballooned villi and leakage of the lymph inside the small bowel lumen. All these laboratory changes are suggestive of malabsorption, and CD is often considered at this diagnostic stage: an association of CD and intestinal lymphangiectasia has been described in the pediatric population [6]. Moreover, there are childhood cases of CD who actually proved to be PIL [7]. In our patient, CD was excluded after negative specific celiac-type serology and absence of transglutaminase-2 targeted IgA epithelial deposits in the frozen small bowel mucosal specimens. Iron deficiency anemia can be seen in PIL, and the mechanism is either impaired absorption or chronic blood loss (from ulcerations or coincident angiodysplasia) [2, 8-10]. Although rare, massive, potentially life-threatening bleeding can occur [8-10]. As shown in our patient, anemia can be the main presenting feature and it can seriously complicate a relatively benign disease.

Despite the typical endoscopic appearance (white villi and spots, submucosal elevations) [9] and definite histopathology, further small bowel work-up was needed in our patient to evaluate for concomitant lesions which could contribute to the anemia. Anterograde enteroscopy and videocapsule endoscopy were negative for such lesions. Abdominal imaging and serological work-up were performed to exclude secondary causes of intestinal lymphangiectasia (Table II).

Table II. Causes of protein losing enteropathy [2]

Intestinal lymphangiectasia
Celiac disease
Intestinal lymphoma
Whipple's disease
Crohn's disease
Intestinal tuberculosis
HIV-related enteropathy
Constrictive pericarditis
Fontan surgery
Sarcoidosis
Retroperitoneal fibrosis
Systemic sclerosis

The cornerstone of PIL medical treatment is nutritional intervention. A low-fat diet prevents the engorgement of intestinal lacteals with chyle, thus preventing their rupture with lymph leakage [2]. The diet recommendation is permanent, as the symptoms and laboratory abnormalities recur upon withdrawal; few cases with complete remission on withdrawing diet intervention have been reported [10]. A review of 84 PIL cases showed that dietary intervention is more effective in children than in adults [11]. This also applies to our patient, which showed only partial improvement after MCT diet, without resolution of the anemia. Octreotide has been described as a therapeutic option in PIL, but data are controversial [7, 12-14]. In our patient, octreotide was unsuccessful in correcting the anemia associated with PIL. Several reports have also described the benefits of antiplasmin therapy in PIL, in terms of serum albumin, GI bleeding and endoscopic lesions [15]. Our patient responded well to tranexamic acid, with resolution of anemia and hypoalbuminemia. The relapse on discontinuation of the drug and remission while recommencing it further supports its therapeutic effect.

Primary intestinal lymphangiectasia is a chronic disabling disease, which requires lifetime diet adherence. One of the complications of PIL is malignancy, in particular lymphoma, which can occur late in the disease course [16]. Therefore, we are closely following our patient. Another complication is GI bleeding, which can be quite difficult to manage, as seen in our patient. The mechanism of GI bleeding in PIL is considered to consist of the opening of the lymphatic-venous and lymphatic-arterial connections as a result of the chyle flow obstruction in the small bowel; this causes a retrograde blood flow in the lymphatics and upon rupture of the engorged villi, blood is lost as well [17, 18]. A decrease in clotting factors and increased fibrinolysis can also contribute to GI bleeding [19, 20], explaining the beneficial effect of antiplasmin therapy in this setting.

CONCLUSION

Primary intestinal lymphangiectasia is a rare disease which should be suspected also in adults in the context of a protein-losing enteropathy. Although lifetime dietary intervention is sufficient to manage most cases, some patients with PIL have persistent disease and severe complications, which may prove difficult to manage, as in our patient.

Conflicts of interest: No conflict to declare.

Authors' contribution: V.D.B., A.P. and J.M. concieved and designed the manuscript. V.D.B. and A.P. drafted the manuscript and searched the literature. A.P. and F.V. evaluated the histologic samples. M.G. performed the radiology interventions and prepared the figures. F.V. and M.J. critically reviewed the manuscript. All authors approved the final version of the manuscript.

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