Primary intestinal lymphangiectasia and a review of the current literature

Zeynep Altın[1], Yusuf Atabay[1], Serhat Özer[2], Miray Karakoyun[3], Sümeyye Ekmekçi[4], Ezgi Yıldız Yürekli[1], Harun Akar[1]

[1]Department of Internal Medicine, Health Sciences University, İzmir Tepecik Health Practice and Research Center, İzmir, Turkey
[2]Department of Gastroenterology, Artvin State Hospital, Artvin, Turkey
[3]Department of Pediatric Gastroenterology, Health Sciences University, İzmir Tepecik Health Practice and Research Center, İzmir, Turkey
[4]Pathology Clinics, Health Sciences University, İzmir Tepecik Health Practice and Research Center, İzmir, Turkey

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Dear Editor,

Primer intestinal lymphangiectasis is a rare disorder manifested by the presence of large lymphatic ducts leading to protein-losing enteropathy. In protein-losing enteropathies, loss of protein from the gastrointestinal tract may reach symptomatic levels (1). Protein-losing enteropathy (PLE) is a terminology used to describe extensive amount of protein loss to the intestinal lumen. Mucosal capillaries and lymphatics may lose protein to the intestines. Lymphatic pressure increases in the case of primary intestinal lymphangiectasis. We herein share a clinically diagnosed intestinal lymphangiectasia case responding well to octreotide.

A 34-year-old Syrian female patient presented with recurrent dyspnea and edema in the distal part of the upper and lower extremities (Figure 1) since the age of 6. She had had multiple recurrent hospital admissions following symptomatic approaches. Family history revealed that her sister was bedridden and mentally handicapped. On physical examination; dry and pale skin, marked pitting peripheral edema, short body stature and prominent front teeth were noted. Biochemical workup revealed anemia of iron deficiency, lymphopenia, hypoalbuminemia, hypomagnesemia, hypokalemia, hyponatremia and compensatory metabolic alkalosis. Antinuclear antibody was positive at 1/160 titer. ANCA, celiac autoantibodies, and other markers of connective tissue disease were negative. Free fluid between mesenteric fat planes and intestines along with pleural & pericardial effusions were documented. Neither urinary protein loss, chronic diarrhea nor coagulopathy were noted. Sampling of the pleural effusion was characteristic of transudate. Pleural fluid adenosine deaminase (ADA) level was low. Pleural fluid cytology was benign. Gastrointestinal system endoscopies were performed to exclude enteral causes causing hypoalbuminemia. There was no finding compatible with the villous adenoma. Biopsies were taken from duodenum and bulbus to exclude Giardiasis, Whipplei, maltoma and intestinal lymphangiectasia. Macroscopically, millimetric white granular features were observed in the duodenum (Figure 2). The lymphatic vessels in the villi of the lamina propria were ectatic, and D2-40 positive & CD34 negative stainings were observed (Figure 3). The parasitology tests for filariasis was negative. The secondary causes of intestinal lymphangiectasia were ruled out. Based on these information, the diagnosis of primary intestinal lymphangiectasia was established. In addition to ocreotide, she was put on a low-fat diet. In response to octreotide, the patient's ascites was reduced, the edema disappeared. The patient's exercise tolerance improved. In the follow-up, the patient's hospitalizations were reduced in number, pericardial & pleural effusions disappeared. Discontinuation of the therapy resulted in recurrence of the edema; restarting the therapy resulted in remission.

Primary intestinal lymphangiectasia (PIL) is a seldom disease manifested by extensive and large intestinal lympatic vessels resulting in lymph fluid loss into the lumen and responsible for serious hypoalbuminemia and therefore manifest generalized edema (2). Waldmann and his colleagues described the concept of intestinal lymphangiectasis for the first time (2). Histopathologically, small bow-

ORCID IDs of the authors: *Z.A. 0000-0003-3682-1479; Y.A. 0000-0003-3051-7628; S.Ö. 0000-0001-7552-2776; M.K. 0000-0002-6533-6256; S.E. 0000-0003-1607-500X; E.Y.Y. 0000-0002-9295-7592; H.A. 0000-0002-0936-8691.*

Corresponding Author: ***Serhat Özer; serhatozer84@gmail.com***
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Figure 1. Edema at distal part of the extremities

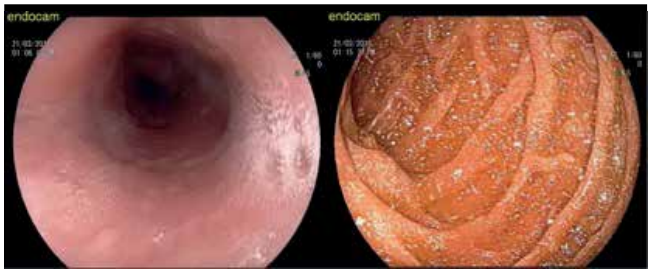

Figure 2. Endoscopic features

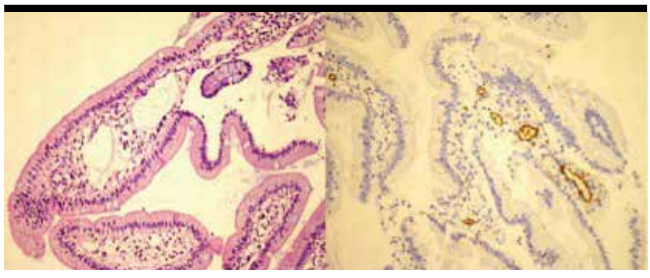

Figure 3. Dilated lymphatics (H&E, x200), Positive staining with D2-40 immunohistochemistry in lymphatics (x200) in the duodenum mucosa

el biopsies showed marked dilatation of the mocosal and submucosal lymphatics (2). Depending on involvement sites, different clinical scenarios may develop.

The disease can affect all or only a small part of the small intestine. The lymphatic vessels dilate and become ruptured, causing loss of protein-rich fluid.

PIL mainly affects young adults (2). Familial forms of PIL have rarely been reported (2,3). The basic clinical feature is pitting edema due to low oncotic pressure. Hypoalbuminemia may manifest as generalized edema. Lymphoedema, however, is a rare disorder and usually not linked to another disease, and may be associated with intestinal lymphangiectasia. The etiology of PIL is unknown. Five syndromes have been reported associated with intestinal lymphangiectasia: von Recklinghausen, Turner or Noonan, Klippel Trenaunay and Hennekam (4). It has been reported that these syndromes can be easily distinguished by the presence of mental retardation (Hennekam, Noonan), seizures (Hennekam), severe extremity and / or facial lymphedema (Hennekam) (2,4). At present, the diagnosis is based on endoscopic and histopathological findings. Suggestive findings are hypoproteinemia, hypoalbuminemia, hypogammaglobulinemia and/or lymphocytopenia.

The detection of PLE is ideally based on the fecal alpha-1 antitrypsin clearance.

Modification in diet, medium chain triglycerides (MCT), octreotide and surgical procedures have been reported as treatment options. Removal of long chain fatty acids (LCT) from the patients' diet reduces lymphatic pressure, therefore prevents the rupture of large lymphatics. MCT are directly absorbed into the portal venous circulation. Essential fatty acids should be added to the MCT regimen. Enteral and total parenteral nutrition may be useful in intestinal lymphangiectasia. Octreotide treatment in patients with PIL was associated with a decrease in enteral protein loss. Ocreotide is preferred in patients in whom dietary changes are inadequate. Although the mechanism of action of octreotide Is not known, octreotide has been reported to have good results at doses of 150-200 mcg subcutaneously twice daily. Ocreotide discontinuation causes symptoms to recur. In acute situations, short-term albumin infusions can be used only as bridging intervention by increasing plasma oncotic pressure.

On the other hand, propronalol was reported in the treatment of intractable diffuse lympangiomatosis and lymphatic malformation (5). Propranolol is thought to cause downregulation of the RAF mitogen-activated protein kinase signaling pathway with reduced expression of VEGF. Ozeki et al. also found significant mTOR expression in tissues affected by primary Intestinal lymphangiectasia. They predicted that mTOR inhibitors might be effective in the treatment of PIL. They used everolimus (1.6 mg/m 2 / day) in the treatment of PIL as an antiangiogenic agent. It has been reported that everolimus treatment relieves diarrhea and requires less replacement therapy for hypoproteinemia.

Our patient was given medium chain triglycerides (MCT) based diet. Hypoalbuminemia and general edema in our patient showed sufficient improvement after octreotide. Patients with intestinal lymphangiectasia typically present with edema in the distal part of the upper and lower extremities. Physical examination and laboratory studies aid in narrowing the differential diagnosis. Initial laboratory tests can shed light on the underlying diagnosis. Diag-

nosis can be aided by endoscopic and histopathologic examination. This patient's constellation of symptoms and sings including edema in the distal part of the upper and lower extremities, hypoproteinemia, hypoalbuminemia, lymphocytopenia and ectasia of the enteric lymphatics supports intestinal lymphangiectasia.

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