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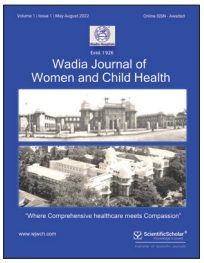

Case Report

Chronic diarrhea in a toddler – A case of intestinal lymphangiectasia

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ABSTRACT

Intestinal lymphangiectasia (IL), a rare form of protein losing enteropathy, is a benign condition characterized by focal or diffuse dilation of the mucosal, submucosal, and subserosal lymphatics causing loss of lymph fluid into the gastrointestinal tract, leading to edema, hypoproteinemia, lymphocytopenia, hypogammaglobulinemia, and immunological abnormalities. This is a case report of an 18-month-old male child who presented to us with complaints of diarrhea for 6 weeks associated with failure to thrive but without fever and edema which was diagnosed as IL on gastroenteroscopy and confirmed by histopathology.

Keywords: Chronic diarrhea, Protein losing enteropathy, Intestinal lymphangiectasia

INTRODUCTION

Primary intestinal lymphangiectasia (PIL) or Waldmann's disease was first described by Waldmann in 1961. This disorder is characterized by diffuse or localized ectasia of the enteric lymphatics often associated with lymphatic abnormalities elsewhere in the body. The etiology of abnormal lymphatic structure is varied. Ectatic lymphatics may be located in the mucosa, submucosa, or subserosa, leading to loss of protein and lymphocytes into the gut or the peritoneal cavity. The mechanism of this loss is believed to be from rupture of lymphatics across the mucosa with subsequent leakage of lymph into the bowel lumen. Children with this disorder usually present in the first 3 years of life,[1] initially with chronic diarrhea causing failure to thrive, and later with features of malabsorption, micronutrient deficiency, hypoproteinemia, and generalized edema.

So far, less than 200 cases of PIL have been reported globally[2] and the most common presentation is in toddlers. Syndromic association, although rare, is seen in PIL, namely, von Recklinghausen, Turner, Noonan, Klippel-Trenaunay, and Hennekam syndrome.[1]

CASE REPORT

L, 18-month-old male, first child born of non-consanguineous union with normal birth history and development was brought with complaints of loose stools for past 6 weeks. Loose stools

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were seven to-eight episodes per day of large volume, watery, sticky, frothy, foul smelling, not blood stained, and not containing mucus but associated with bloating and flatulence. Initially, the child had 2-3 episodes of vomiting per day, non-projectile, non-bilious, containing food particles. Vomiting stopped after taking symptomatic treatment. Loose stools persisted throughout the past 1½ month, although decreased in frequency (4–5 times/day) and semisolid in consistency, there was a documented weight loss of 1.5–2 kg as noticed by the parents.

There was no history of fever, abdominal pain, blood in stools, worms in stools, perianal itching or rash, gastrointestinal surgeries in past, or recurrent skin infections and respiratory illnesses. There were no similar complaints in the family.

The child was exclusively breastfed until 4 months of age and after that cow's milk was introduced, which the child did not tolerate, and hence started on formula feed and complementary feeding was started at 6 months of age. At present, the child was fed homemade mixed diet. Calorie and protein intake were adequate for his age.

On examination, the child was hemodynamically stable, had no signs of dehydration and micro-nutrient deficiency or edema. Child had normal male genitalia and no perianal rash. His weight at 6.080 kg (<−3 SD) and height 70 cm (<−3 SD) and head circumference 42.5 cm (<−3 SD) was suggestive of chronic malnutrition (weight for height <−3 SD). Per abdominal examination revealed a distended abdomen with everted umbilicus, no tenderness or guarding or rigidity, and no organomegaly on palpation was noted. On percussion, no flank fullness or shifting dullness and tympanic note was heard with normal bowel sounds heard on auscultation. Other system examinations were normal.

On investigation, the child was found to have absolute lymphocytopenia, a low total protein with low albumin and globulin levels but normal differential immunoglobulin levels and normal lymphocyte subset assay [Table 1]. In view of chronic diarrhea to rule out infectious causes, a stool Polymerase Chain Reaction (PCR) was sent which showed *Blastocystis hominis,* for which the child was treated with oral metronidazole. Ultrasonography of abdomen and routine stool examination was normal. Despite adequate treatment with metronidazole, the child persistently had loose stools. Stool reducing substance and fat globules were present. Tissue transglutaminase IgA and cow milk protein allergen were negative [Table 1]. As loose stools were persistent, upper and lower gastrointestinal (UGI and LGI) scopy was done which showed multiple scattered white spots in the mucosa of the duodenum, jejunum, and ileum suggestive of IL. No ulcers, erosions, erythema, or bleeders were seen as shown in [Figure 1].

Histopathology report of jejunal biopsy was suggestive of moderately dilated mucosal and submucosal lymphatic vessels with few proliferated lymphoid follicles, plasma cells, and mature lymphocytes which confirmed the diagnosis of IL [Figure 2].

The child was started on a low fat and high protein diet with fat soluble vitamin supplements. Child started gaining weight and frequency and consistency of his stools normalized. There was no secondary cause derived based on clinical presentation and investigations; hence, diagnosis of PIL was made. Further, workup for IL, namely, Magnetic resonance

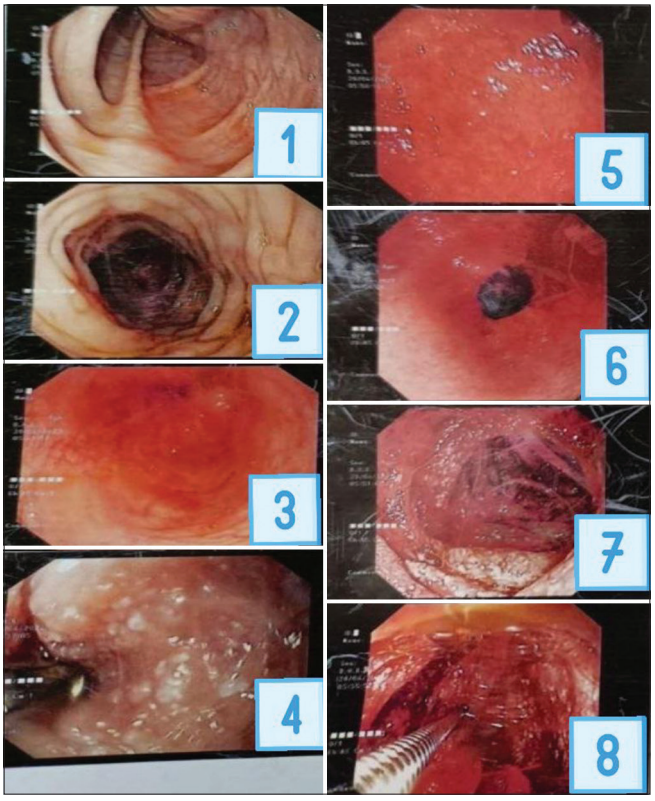

Figure 1: Endoscopic images showing multiple scattered white dilated lymphatics in the mucosa of the duodenum.

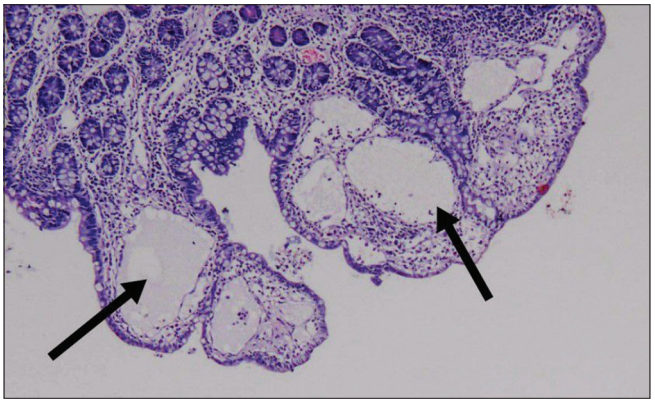

Figure 2: Dilated lacteals (pointed with black arrows) with distortion of villi of the bowel mucosa of the jejunum.

Table 1. Investigation chart

Investigations	Observation	Normal range
Hemoglobin (gm/dL)	12.8	11.2-14.5
Total leukocyte count (c/mm3)	11,040	4500 – 11000
Absolute neutrophil Count (c/µl)	7380	1500-8000
Absolute lymphocyte count (c/µl)	1970	6000-9000
IgA (mg/dl)	96	20-100
TTG IgA (U/ml)	0.3	0-3
CMPA	Non reactive	
Total protein/Albumin/Globulin (g/dL)	4.8/3/1.8	6-8.3/3.5-5.5/2-3.5
S. Immunoglobulin G / S. Immunoglobulin M (mg/dl)	392/25	312-994/19-146
LSSA	Normal	
Sonography Abdomen	Normal	
HIV spot	Negative	
Stool routine	3-4 pus cells, no RBCs/occult blood, reducing substance and fat globules present	

TTGIgA; Tissue transglutaminase immunoglobulin A, CMPA; Cow milk protein allergen, LSSA; Lymphocyte subset assay

(MR) lymphangiogram and echocardiography was not done due to cost constraints.

DISCUSSION

Primary Intestinal Lymphangiectasia (PIL) is an uncommon disorder and an important cause of chronic diarrhea. PIL is generally diagnosed before 3 years of age, with equal affection of boys and girls. The prevalence of the disease is unknown. Patients with PIL often present with edema, lymph-edema, diarrhea, and ascites that may be complicated by fatigue, abdominal pain, nausea, vomiting, weight loss, inability to gain weight, iron deficiency anemia, and obstructive ileus. Other major features are lymphopenia, hypoalbuminemia, and hypogammaglobulinemia due to lymph leakage from the ruptured lymph vessels. Secondary intestinal lymphangiectasia is caused due to lymphatic obstruction with elevated lymphatic pressure or direct injury to lymphatic channels from causes such as retroperitoneal fibrosis, chronic pancreatitis, abdominal or retroperitoneal tumors, mesenteric tuberculosis, Crohn's disease, intestinal malrotation, Whipple's disease, celiac disease, constrictive pericarditis, and congestive heart failure.

In a retrospective multicentric study, conducted in 2010, after reviewing the literature of 84 pediatric cases of PIL, the most common symptoms found were edema, diarrhea, ascites, and lymphedema, present in 78, 62, 41, and 22%, respectively. Our patient presented with diarrhea and failure to thrive. PIL diagnosis in our patient was achieved under the age of 3 years as is seen commonly.[2]

The etiology of primary IL is unknown. Several genes, including vascular endothelial growth factor receptor 3, prospero-related homeobox 1-transcriptional factor, forkhead transcriptional factor 2, and SRY (sex determining region Y)-Box 18, regulate the development of the lymphatic system and have been shown to have altered expression in the duodenal mucosa in patients with PIL.[3] Recently, mutation in CD55, a regulator of complement activation, was described as a cause for PIL.

The diagnosis of PIL is suggested by the typical clinical and laboratory findings in association with an elevated fecal α1-antitrypsin clearance.[4] Ultrasonography findings of symmetric thickening of mucosal folds throughout the small intestine are characteristic but not specific. Small bowel mucosal biopsy in patients with IL can show dilated lacteals with distortion of villi and no inflammatory changes.

UGI and LGI scopy with biopsies and histopathology examination is mainstay of diagnosis of IL.[5] Other methods, such as capsule endoscopy and double-balloon enteroscopy, are also used for diagnosis. Other than endoscopic and histologic findings, imaging may also have a role. For instance, intestinal technetium-dextran lymphoscintigraphy to specify the location of intestinal protein loss was described many years ago.

In PIL, the mainstay of treatment is the use of a low fat and high protein diet rich in medium chain triglycerides (MCTs).[3] MCT is directly absorbed by the intestinal cell and thus bypass the enteric lymphatics and directly enters the portal system. It is believed that the reduction in long chain fatty acids reduces lymphatic flow and pressure within the lymphatic system and decreases the amount of lymph leakage. Severe steatorrhea may result in hypocalcemic tetany. Therefore, some children require additional supplementation with calcium salts, in addition to fat soluble vitamins.[4] Our patient was advised to follow a similar diet with calcium and multivitamin supplements. On follow-up, the child is gaining weight and loose stools have decreased. Other pharmacological options that are included in the

management of PIL are intravenous albumin, octreotide, corticosteroids, heparin, rapamycin, and everolimus. The role of surgical intervention is unclear and the long-term outcomes of a limited resection are not known.[6]

In an Indian study performed in 2019, the clinical profile, response to various therapies, and outcomes were studied. Twenty-eight children with PIL were studied; pedal edema (93%), chronic diarrhea (78.6%), and recurrent anasarca (64%) were the common presentations. Ascites, pleural, and pericardial effusion were seen in 64% (chylous – 17% and non-chylous – 46%), 18%, and 18% cases, respectively. Duodenal biopsy established the diagnosis in 86% cases, while 14% required distal small bowel biopsies. Dietary therapy was given in all and six cases required additional therapy with octreotide, Total Parenteral Nutrition (TPN), tranexamic acid.[7]

Another recent study done in Korea in 2021 discussed the recent treatment options for diet refractory PIL. It stated that, after exclusion of secondary IL, magnetic resonance lymphangiography is a promising tool for determining the extent of the lesion and provides direction for treatment options. The study classified the disease into focal, diffuse and extensive PIL, and accordingly, treatment options of intestinal resection, embolization, and drug therapy with octreotide, sirolimus, propranolol, and tranexamic acid were used.[8]

CONCLUSION

IL must be kept in mind as an important differential diagnosis while treating and evaluating infants with chronic diarrhea. Hypogammaglobulinemia with edema in case of diarrhea should raise suspicion of IL and endoscopy should be performed for diagnosis. Fecal alpha 1 antitrypsin level though a sensitive test, it is not specific for PIL as its levels are raised in other protein losing enteropathies too. Child should be monitored for increasing disease severity and parents must be counseled regarding the danger signs to watch for. Evaluation with MR lymphangiogram can be done to look for the extent of disease and medical and surgical treatment options can be provided to patients with disease refractory to dietary modifications.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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