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Case Series

Lymphopenia: a clue to diagnose primary intestinal lymphangiectasia

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ABSTRACT

Primary intestinal lymphangiectasia (PIL) is a rare protein-losing gastroenteropathy characterized by dilatation of the intestinal lymphatics and loss of lymph fluid into the gastrointestinal tract, leading to the development of hypoproteinaemia, oedema, lymphocytopenia, hypogammaglobinaemia, and immunologic abnormalities. We report a series of 4 children from Bangalore, India presenting with anasarca, diarrhoea, and hypoproteinaemia. All four patients were confirmed to have of PIL on histopathology. We retrospectively reviewed the case records of children diagnosed with primary intestinal lymphangiectasia presenting to department of pediatric gastroenterology within the time frame of July 2015 to September 2018. Four patients were diagnosed with primary intestinal lymphangiectasia. All of them presented with features of protein losing enteropathy (generalized oedema, ascites and low albumin), chronic diarrhoea, lymphopenia, hypercalcemia, and hypogammaglobulinemia. Endoscopically mucosa was normal in two patients and showed Snowflake appearance in other 2 patients. Intestinal biopsies were characteristic of lymphangiectasia in all four patients.

Keywords: Primary intestinal lymphangiectasia, Protein-losing gastroenteropathy, Oedema, Lymphopenia, Hypogammaglobinemia, Snowflake appearance

INTRODUCTION

Primary intestinal lymphangiectasia (PIL), an uncommon but an important cause of protein-losing enteropathy, caused by a congenital defect or obstruction of intestinal lymphatic drainage.[1] The obstruction causes lead on to increased pressure within lymphatic channels of intestinal wall causing dilation and rupture of lymphatic vessels which in turn, causes the leakage of lymphatic fluid.[2]

Intestinal lymphangiectasia (IL) can be either primary (idiopathic) or secondary. Leakage of lymph will result in hypoproteinaemia, lymphocytopenia and decreased serum levels of immunoglobulins.[3] In 1961, Waldmann published the first description of PIL, now known as Waldmann's illness.[1] The etiology and the exact prevalence PIL are unknown. PIL is usually diagnosed before 3 years of age.[4] Hypoproteinaemia, hypoalbuminemia, lymphocytopenia, hypogamma-globulinemia, and reduced levels of transferrin and fibrinogen are the typical laboratory features.[5] Diagnosis is by radiologic and endoscopic findings, confirmed by histologic findings of the dilated lymph ducts in the lamina propria.[6] Here we describe clinical, biochemical, radiologic, and endoscopic features of children with PIL.

CASE SERIES

The inpatient charts of patients diagnosed with IL between the time frame of July 2015 to August 2018 were reviewed. In addition to endoscopic findings, we collected clinical variables such as: age at the time of diagnosis, sex, and presenting clinical symptom. Laboratory tests collected included total lymphocyte count, albumin, cholesterol, serum calcium, and immunoglobulins.

Four patients were diagnosed to have IL, between July 2015 to August 2018. Male female ratio was 2:2. The mean age at the time of diagnosis was 22 months (range 9-39 months). Table 1 displays the clinical manifestations symptoms, while Table 2 displays the laboratory test results.

All the children presented with similar history of watery diarrhoea. On examination all had anasarca. One of the patients had post inflammatory hyperpigmented lesions over lower limbs secondary to recurrent impetigo (Figure 1). Blood investigations showed picture of lymphopenia, low haemoglobin, and albumin levels in all children (Table 1). Upper gastrointestinal (GI) endoscopy showed snow flake appearance of duodenal and jejunal mucosa in two patients and two patients had normal appearing bowel mucosa. Histopathology of small bowel mucosa showed dilated lymphatics in the villous stroma and in the lamina propria confirming the diagnosis of PIL in all the children.

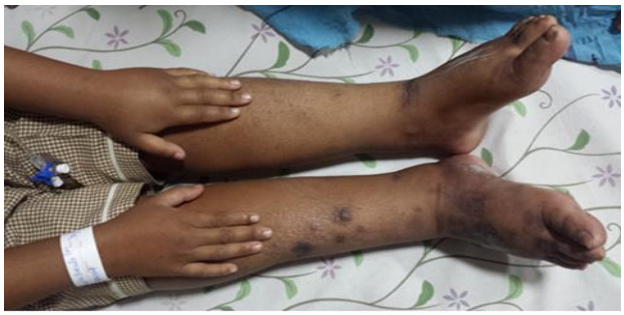

Figure 1: Edema of upper limbs and lower limbs with skin changes secondary to recurrent impetigo in a patient with PIL.

Table 1: Clinical characteristics of the patients with primary intestinal lymphangiectasia.

Patient no.	Age at diagnosis in months/years	Sex	Duration of symptoms	Edema/ascites/pleural effusion	Weight in kgs (centile)	Height/length in cm (centile)
1	12 years	Male	10 years	Yes (Anasarca)	40.8 (50th)	130 (10th)
2	6 months	Female	1 month	Yes (edema)	7 (10th)	63 (25th)
3	6 months	Female	1.5 months	Yes (Anasarca)	6.3 (10th)	58 (3rd)
4	14 months	Male	1 month	Yes (Anasarca)	9 (10th)	78 (50th)

Table 2: Blood investigations of the patients with primary intestinal lymphangiectasia.

Patient no.	Albumin gm/dl (2.5- 4.7)	Hb gm/dl (11.1-14.1)	Lympho-cyte % (40-70%)	IgA mg/dl	IgM mg/dl	IgG mg/dl	Globulin in gm/dl (2–3.5)	CD-3 lympho-cytes (%)	CD-4 lympho-cytes %
1	1.6	11.5	13.8	121.2 (58-358)	60.5 (35-239)	1216.0 (759-1549)	3.5	Not done	Not done
2	0.8	5.4	2.4	32.7 (0-83)	51.2 (231-1411)	240 (0-145)	1.5	24.78 (60.2-91.3)	13.99 (28.04-70.63)
3	1.3	6.0	18.0	--	--	--	1.7	16.97 (60.2-91.3)	11.41 (28.04-70.63)
4	0.8	5.5	10.4	26 (20-100)	18 (19-146)	38.4 (453-916)	1.6	42.37 (60.2-91.3)	4.95 (28.04-70.63)

DISCUSSION

PIL is an uncommon benign digestive disease with fewer than several hundred reported cases in the literature. It is characterised by focal or diffuse dilation of the mucosal, submucosal and subserosal lymphatics resulting in lymphatic fluid leakage into the lumen of intestines. The prevalence and aetiology are unknown. Sex distribution was equal in our case series, as noted in other small case series.[2,5] However male predominance reported in the literature.[6] In order to establish sex preponderance, further large cases series are required. PIL can occur alone or in conjunction with other diseases to form a syndrome. There have been reports of extremely rare familial variations of Waldmann's illness in the past.[1]

The development of the lymphatic system involves several genes, including the vascular endothelial growth factor receptor 3 (VEGFR3), the PROX1 factors, the FOXC2 and the SOX18. Hokari et al reported altered expression of regulatory molecules of lymphatic system in the duodenal mucosa of PIL patients.[7]

The CHAPLE syndrome, which is a hereditary disorder characterised by CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy related to primary intestinal lymphangiectasia, has been identified.[8] PIL may also be a component of the Hennekam syndrome, which is distinguished by the coexistence of facial dysmorphism, intestinal lymphangiectasia, and moderate mental impairment.[9] None of our patients in the series had history for genetic diseases and there were no dysmorphic features, excluding possibility of genetic disorder. PIL usually presents in childhood and early adolescence.[10] However, it can present in second or third decade.[11] It is still unclear how prevalent and common IL is globally. Too few cases exist for a conclusive statement to be made.

Diarrhoea, edema, and ascites are common symptoms of PIL patients, other clinical features include obstructive ileus, iron deficiency anaemia, weight loss, inability to gain weight hypoproteinaemia, and lymphocytopenia.[4,11] Hypogammaglobulinemia may also be present due to lymph leakage from the ruptured lymph vessels.[2]

All except one in our series presented before the age of three years. One patient presented at the age of 13 years even though he was symptomatic since the age of 2 years (Table 1). He was mis-manged as nephrotic syndrome. In a retrospective analysis of 84 cases the common symptoms of IL were edema, diarrhoea, ascites and lymphedema, in 78%, 62%, 41% and 22%, respectively[2]. Hypoalbuminemia, hypocalcaemia, lymphocytopenia, and reduced immunoglobulin levels (IgM, IgA and IgG) are the main laboratory features described previously in the literature.[2,4] In our study all 4 patients presented with anaemia, diarrhoea, and ascites/pedal oedema (Table 1). Investigations in all of our patients revealed anaemia, lymphopenia, and hypoalbuminemia. Hypogammaglobulinemia was present in 3 out of 4 patients with low IgA, IgM and IgG levels (in 2 patients) (Table 2). Lymphocyte subset analysis in 3 patients revealed low CD4 and CD3 cell count. Low CD4 and CD3 counts cell is due to loss of lymphocytes in the lymph rich fluid into the intestine.[12] Diagnosis of PIL is mainly by upper gastrointestinal endoscopy and biopsy. During an endoscopic examination, several whitish mucosal spots or creamy yellow jejunal villi that correspond to noticeably dilated lymphatics often described as having a snow flake appearance are typically seen.[5,13] If the mucosal involvement is patchy, endoscopy might be normal, and in that case, video capsule endoscopy aids in localisation.[14]

In our series endoscopy showed snow flake appearance in 2 patients and was normal in another 2 patients. Small bowel biopsies are required to confirm the diagnosis.[15] Biopsies show prominent and dilated lymphatics in the lamina propria region, often with extension into submucosa.[15] All 4 patients in our series showed characteristic histology (Figure 2).

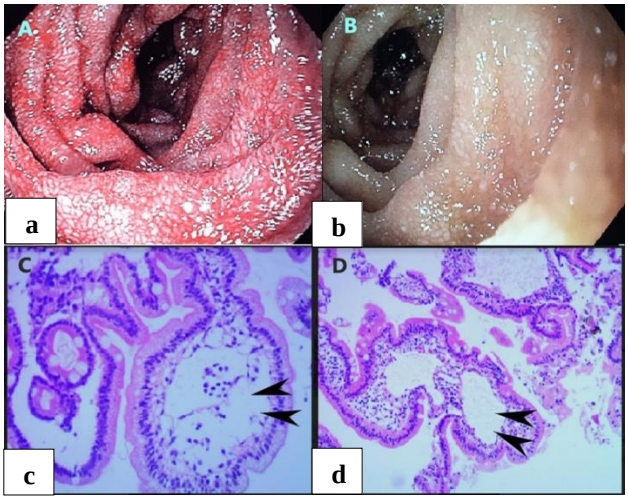

Figure 2: (a) and (b) Endoscopy picture showing snow flake appearance of duodenal mucosa; (c) and (d) histopathology showing dilated lymphatic vessels (arrowheads).

Treatment guidelines in PIL are not well established as the disease is rare. The cornerstone of PIL management is lifelong dietary modification, that includes fat restriction, replacement with medium chain triglycerides (MCT), and vitamin supplementation.[5] Exclusion of fat from the diet prevents the intestinal lymphatics from becoming engorged with chyle, which prevents their rupture and stops the loss of protein and T cells. MCTs directly enter the portal venous circulation, providing nutrient fat while preventing lacteal engorgement.[1,2] Rare cases of IL with segmental disease benefit from surgical resection.[1]

Other therapies with varying degrees of effectiveness have been mentioned in the literature, such as antiplasmin therapy, octreotide, corticosteroids, small bowel resection, albumin infusions, everolimus, and intestinal transplant.[1,4,6,16] All these mentioned treatment modalities can be used after or in combination with a low-fat diet along with MCT supplementation. Their efficacy is variable and insufficiently evaluated.

The management of our patients included intravenous human albumin administration with diuretics, intravenous immunoglobulin and octreotide during the acute phase. A low-fat diet combined with the administration of MCTs and vitamin supplements constituted the long-term treatment. Patient number 1 and 4 improved with dietary therapy. Currently they are doing well on MCT based diet at follow up of 6 years and 3 years from the time of diagnosis. The other 2 patients (2 and 3) did not show much improvement with dietary therapy. They were also treated with octreotide injections without any benefit. Both of these children continued to have diarrhoea, severe failure to thrive and needed multiple hospital admissions. Both patients died (no. 2: two years from diagnosis, no. 3: one month from diagnosis) in the community.

Both intestinal and extraintestinal lymphomas occur with increased frequency in patients with PIL. Few cases of lymphoma have been reported in conjunction with PIL.[6,17] Four cases (5%) of lymphoma were reported in a series of 84 PIL patients.[2] Although the mediastinum and the retroperitoneum can also be affected by lymphoma, the digestive system (stomach, small intestine, and ileum) is the primary site of involvement.[2]

Children with PIL are prone for recurrent and opportunistic infections. Due to moderate to severe hypogammaglobulinemia and lymphopenia, PIL patients have a greatly increased risk of infection. (e.g., *Salmonella*, *Pneumococcal*, *Cryptococcus*, cytomegalovirus).[18,19] In our series patient number 1 had recurrent skin infection (impetigo and cellulitis) of both lower limbs needing frequent antibiotics. The 3rd patient had multidrug resistant Escherichia coli in the stool culture needing systemic antibiotics.

Histopathology was confirmatory of PIL all 4 patients in our series. Lymphopenia served as an important clinical clue. In our series two patients showed a good clinical response to dietary therapy. Whereas two infants who had early onset disease didn't respond well, suggesting poor prognosis in early. Further reports are needed to ascertain the long-term outcome of IL patients.

CONCLUSION

PIL is a chronic disabling disorder that necessitates long-term dietary control with a low-fat diet and supplemental MCT. The predominant clinical symptom is diarrhoea and lower limb edema. Lymphopenia can serve as an important clue to the diagnosis of a child with chronic diarrhoea with hypoproteinaemia. Normal mucosa on endoscopy does not rule out IL and small bowel biopsy and histopathology must be considered in all children with suspected IL. These children need correct and timely diagnosis and multidisciplinary care from the gastroenterologist, nutritionist, and immunologist, given that they can present with serious, concurrent infections that are life-threatening and should be treated as though they are children with secondary immunodeficiencies. The risk of malignancy in these cases should be taken into account.

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