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Case report

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A Family with Primary Intestinal Lymphangiectasia and Its Association with Liver Fibrosis

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Abstract

Primary intestinal lymphangiectasia (PIL) is a rare disorder of unknown etiology usually diagnosed before three years of age. Its characteristic features are chronic diarrhea and bilateral pitting edema of the lower limb. Reports of multiple members of a family affected by PIL are rare, as are reports of a relationship between PIL and liver fibrosis. We diagnosed a family of three adults, who were being managed as chronic liver disease. We found that all three members of a family were suffering from long-term PIL and also had features of liver cirrhosis, which is an extremely rare association.

Keywords

Lymphangiectasia; Liver fibrosis; Chylous ascites

Introduction

Primary intestinal lymphangiectasia (PIL) is a rare disorder of unknown etiology. It is generally diagnosed before three years of age but may be diagnosed in older patients. Its characteristic features are diffuse or localized dilation of the enteric lymphatic vessels in the mucosa, submucosa, and/or subserosa. The lymphatics eventually rupture, leaking protein and lymphocyte-rich lymph into the gastrointestinal tract. This then causes hypoproteinemia and lymphopenia. Chronic diarrhea and bilateral pitting edema of the lower limb are the main clinical manifestations mimicking systemic disease and posing a diagnostic challenge to clinicians to differentiate it from more common systemic diseases. Reports of multiple members of a family affected by PIL are rare, as are reports of a relationship between PIL and liver fibrosis. This association of PIL and liver fibrosis has been the subject of a few recent case reports. We report, herein, a case series of three members of a family with longstanding PIL and features of liver cirrhosis.

Case Report

Case I (Index Case):

A 27-year-old male was referred to our institute for a suspected diagnosis of chronic liver disease (CLD) and ascites unresponsive to diuretics. He had a 9-month history of pedal edema and abdominal distension, shortness of breath for five months, and unintentional weight loss of approximately 8 kg in 9 months altered sensorium, jaundice, hypertension, or connective tissue disorder. On examination, he had engorged neck veins, pallor, pedal edema, and ascites. There was no hepato- splenomegaly. He mentioned that his mother and brother had similar complaints of abdominal distension.

Case II:

A 50-year-old female, mother of the index case, had a history of abdominal distension for 10 years and pedal edema for the same duration. She had undergone repeated therapeutic paracentesis for drainage of milky-whitish fluid to control her abdominal discomfort. There was minimal response to the prescribed diuretics. Her medical history included a hysterectomy and 6 months of antitubercular treatment, both about 10 years back. On examination, she had no engorged veins, was pale with pedal edema, ascites, and mild hepatomegaly.

Case III:

A 24-year-old male, who was the younger brother of the index case, had a history of progressive abdominal distension and pedal edema for the last few years. Clinical examination revealed pallor and moderate ascites with pedal edema. He had also been diagnosed with liver cirrhosis and was started on diuretics; however, the ascites did not show response to diuretics. Sonography and contrast-enhanced computed tomography examination of all three patients revealed features of CLD with splenomegaly and ascites. There was no evidence of a mass or lymphoma (Figure 1). A magnetic resonance venogram in Case no. 3 ruled out any hepatic venous outflow tract obstruction. Ascitic fluid examination of all three patients revealed turbid milky-white fluid. The ascitic fluid triglycerides were significantly higher than the serum triglyceride level in the index case and Case no. 2 but 1.8 times higher in Case no. 3 (Table 1). Further investigations revealed lymphopenia, the platelet count was at the lower limit of normal, and the albumin was low. An etiological workup for CLD in the index case and Case no. 2 was inconclusive; however, extrahepatic portal vein obstruction was noted in Case no. 3. All investigations are summarized in (Table 2). Upper gastrointestinal endoscopy in all patients showed numerous creamy white, discrete, punctate ("snowflake") lesions on the small intestinal mucosa, which are characteristic of lymphangiectasia (Figure 2). A biopsy from the second part of the duodenum showed dilated lacteals, which are also suggestive of lymphangiectasia (Figure 3). Case no. 1 and 3 had moderate pericardial and pleural effusions.

All three patients were started on a low-fat, high-to-medium-chain triglyceride (MCT), high-protein diet and prescribed diuretics, calcium, and vitamin supplementation. The edema and ascites gradually decreased. On follow-up at 12 months, the edema, ascites, and pericardial effusions had significantly reduced.

Discussion: PIL is a rare disease characterized by congenital malformation of the intestinal lacteals, lymph leakage into the

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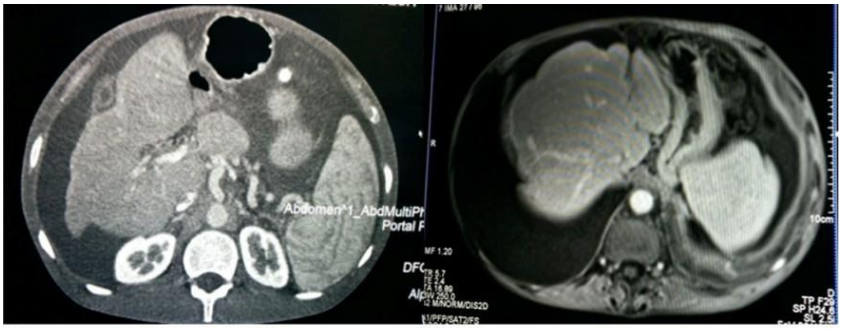

Figure 1: Imaging showing changes of chronic liver disease in the index case with primary intestinal lymphangiectasia. (A) Contrast-enhanced computed tomography of the upper abdomen in the index case and (B) Magnetic resonance venogram in the index case.

Table 1: Ascitic fluid analysis. SAAG, Serum ascitic fluid albumin gradient; WBC, White blood cell; DLC, Differential leukocyte count; RBC, Red blood cell; TG, Triglycerides; HPF, high-power field.

	Index case	Mother	Brother
Ascitic fluid			
Appearance	Turbid	Milky	Turbid
Color	White	White	White
Proteins (g/dL)	1.9 (SAAG-2.0)	4.3 (SAAG-1.22)	1.7 (SAAG-0.9)
Glucose (mg%)	102	121	95
WBC - total	200	100	300
DLC	L-60%, P-40%	L90% P10%	L60% P40%
RBC (million/cm^3)	6-8/HPF	10-12/HPF	4-6/HPF
Ascitic TG vs. serum TG (mg%)	357/55	983/64	91/51
Ascitic fluid cytology	Scattered and clusters of reactive mesothelial cells	Reactive mesothelial cells, RBCs, few lymphocytes	Reactive mesothelial cells with few lymphocytes

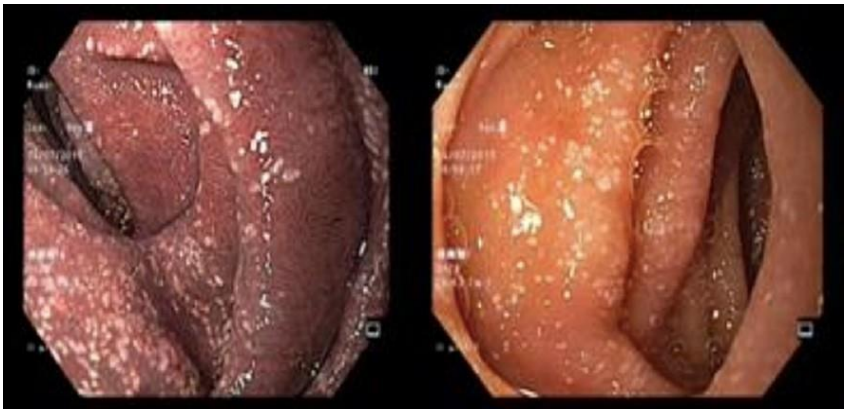

Figure 2: Upper gastro-intestinal endoscopy showing numerous, creamy white, discrete, punctate lesions: typical changes in lymphangiectasia.

intestines, and protein-losing enteropathy, leading to lower limb edema and serosal effusion [1]. Indications that all three family members might have PIL, rather than a more common cause of ascites, edema, and hypoalbuminemia, include chylous ascites on paracentesis and the pericardial effusions in two patients with lymphopenia. The diagnosis was confirmed by the characteristic endoscopic picture obtained on UGI endoscopy and duodenal biopsy, which revealed markedly dilated villous lymphatics and moderate inflammatory infiltrates in all three patients. Familial association of PIL is rare, with only a few case reports in the literature [2]. However, based on ultrasonography suggestive of CLD and ascites, these patients were initially treated for liver cirrhosis with decompensation, before being referred to our institution for refractory ascites. Further investigations conducted at our institute confirmed that all three members of the family were experiencing PIL, but they all had features of CLD, with one of them having features of extrahepatic portal vein obstruction. There are a few recent reports of the association of PIL with hepatic disorders [3,4], which suggest that the liver changes may

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Table 2: Summary of laboratory investigations. ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; SAP, Serum alkaline phosphatase; GGT, Gamma-glutamyl transpeptidase; ASMA, Anti-smooth muscle antibodies; AMA, Anti-mitochondrial antibodies; ANA, Antinuclear antibodies; Anti-tTG, Anti-transglutaminase antibodies; HDL, High-density lipoprotein; LDL, Low-density lipoprotein.

	Index case	Mother	Brother
Platelet count (Lacs/cm^3)	1.3	1	1.66
Serum creatinine (mg%)	1	0.8	0.83
Total bilirubin/direct (mg%)	0.80/0.40	1.20/0.6	0.54/0.27
ALT/AST (IU/L)	50/59	15/35	39/30
SAP/GGT (IU/L)	74/41	47/11	58/17
Total protein	5.3	6.3	5.2
Albumin (g/dL)	2.8	3.8	2.7
A:G ratio	1.1	1.5	1.1
INR	1.11	1.07	1.08
HBsAg	NR	NR	NR
Anti-HCV	NR	NR	NR
ASMA/	Negative/	Negative/	Negative/
AMA	Negative	Negative	Negative
ANA	Negative	Negative	1:100, Cytoplasmic
Serum ferritin (mg/L)	147	79	7.44
IgA Anti-tTG	Negative	Negative	Negative
Serum ceruloplasmin	0.47	0.55	0.4
Lipid profile (mg/dL)			
Cholesterol	90	165	103
HDL	45	53	32
LDL	44	107	64
Triglyceride	55	64	51

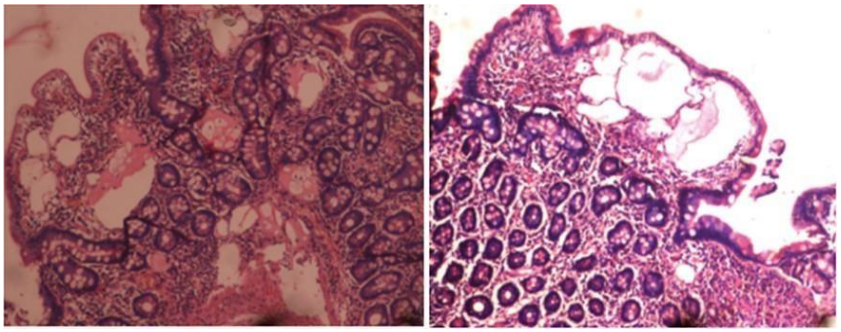

Figure 3: Duodenal biopsy showing dilated lacteals typical of lymphangiectasia.

be due to increased hydrostatic lymphatic pressure in the liver or decreased oncotic pressure secondary to lymph loss. Approximately 50% of the lymph flowing through the thoracic duct is produced in the liver and mostly drains into the portal lymphatic vessels [5]. Another possible explanation for the elevated liver stiffness in PIL is that the elevated hydrostatic lymphatic pressure in the bowel vessels is transmitted to the upstream hepatic circle because they merge with hepatic lymphatics before draining into the thoracic duct. This may lead to lymph stasis with impaired tissue fluid flow, similar to that described in cardiac failure as a result of volume changes [6]. Alternatively, due to the high permeability of sinusoidal endothelial cells, more fluid might flow into the space of Disse because of the low oncotic pressure, which may ultimately lead to fibrosis.

The interconnections between the lymphatic system and blood circulation in portal hypertension may play a role in the pathogenesis of ascites and edema formation in cirrhosis [7,8]. Therefore, the complex interplay between the lymphatic and circulatory systems might create a reverse mechanism for increased liver stiffness resulting from impairment of the splanchnic lymphatic circulation.

The reduced liver stiffness after dietary modification suggests a partially reversible mechanism similar to that reported in patients with acute decompensated heart failure [5]. Milazzo et al. [3] reported a case of PIL with liver fibrosis with high stiffness on elastography. They noted that a six-month low-fat diet and MCT supplementation could improve the liver changes by reducing fibrosis, which they attributed to lymphatic stasis, similar to that occurring in the cardiac congestive liver. However, this remainsspeculative.

Conclusion

This is probably the first report of three family members with PIL, with changes of CLD without significant portal hypertension. This association is extremely rare and has only recently been described in a few case reports. It is difficult to prove whether this lymphangiectasia is secondary to portal hypertension or whether the patients had PIL with coexistent cryptogenic CLD.

This case series suggests that, in patients with PIL, one should also monitor liver morphology with in-depth investigations including ultrasonography and elastography for associated chronic liver disease.

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