Intestinal lymphangiectasia: a forgotten cause of chronic diarrhea

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SUMMARY. Intestinal lymphangiectasia is a rare autosomal dominant disorder or acquired condition that leads to lymph obstruction, poor chyle transport and concomitant problems. We describe the cases of two women with chronic diarrhea in whom the common signs of lymphangiectasia-hypoalbuminemia, lymphopenia and distal edema- were found. One of them also had pleural effusion and chylous ascites. The diagnosis was performed by intestinal biopsy. We herein review the histopathologic, radiographic and endoscopic features of this disorder and case reports in Mexican population.

Key words: Intestinal lymphangiectasia, poor chyle, intestinal biopsy.

INTRODUCTION

In 1961, Waldman\(^1\) reported a group of patients with “idiopathic hypoproteinemina”, presumably secondary to excessive loss of protein into the gastrointestinal tract, and demonstrated marked lymphatic dilation on the intestinal biopsies of these patients. Waldman called this disease “intestinal lymphangiectasia” (IL), a term which is now firmly established within the clinical literature.\(^2\) In most patients the lymphatic defect is congenital and therefore is called “idiopathic” or “primary lymphangiectasia”; in other patients, however, this condition may be acquired, thus naming it “secondary lymphangiectasia”. IL reflects a general disorder on the development of the lymphatic channels. The hallmark lesion seen in all cases is gross dilation of the lymphatics in the lamina propria of the small bowel. These engorged lymphatics frequently distort and enlarge individual villi, though no villous atrophy is seen. Clinically, IL is characterized by the usual early onset of massive edema, frequently asymmetric in distribution. Chylous effusions develop throughout the course of the disease in 45% of the patients.\(^3\) All patients have hypoalbuminemia and hypogamma-globulinemia. Proportionately less marked reductions of serum fibrinogen, transferring and ceruloplasmin are also frequently present. The mechanism of hypoproteinemina is explained by the excessive loss of serum protein into the intestine. Lymphopenia secondary to loss of lymphocytes into the bowel is present in over 90% of the patients. Patients with hypoproteinemia and edema, chylous effusions or malabsorption often represent puzzling diagnostic cases of IL. The purpose of this report is to review the histopathologic, radiographic and endoscopic features of this disorder.

CASE 1

A 30-yr-old Mexican woman, born in Irapuato, Guanajuato, Mexico, initially presented to our clinic with chronic
diarrhea, fever, gastrointestinal hemorrhage, weight loss and history of fatigue for 20 years. Even when the patient had had melonic evacuations for 10 years, multiple upper gastrointestinal series had always shown negative results. The patient referred colic pain with abdominal distension and flatulence with progressive edema of the lower extremities. Physical examination revealed an afebrile woman in no distress whatsoever, but was pale. A 3/6 systolic ejection murmur, a mild left inferior quadrant tenderness without hepatosplenomegaly, and a 2+ pitting edema of both lower extremities extending proximally to the midthighs could be noticed. Laboratory tests indicated the following: Hb: 5.9 g/dL, Ht: 21.8%, MCV: 57 fL, white blood cell count: 6280/mm³ with lymphocytes 310/mm³, total proteins: 4 g/dL, albumin: 1.7 g/dL, total cholesterol: 130 mg/dL and triglycerides: 72 mg/dL. Quantitative faecal fat test, D-xylene absorption test and carotene determinations were negative. Other tests performed were: gammaglobulin 0.8 g/dL (normal, 0.6 to 1.6 g/dL), IgG 3.53 g/L (normal 8.0-15 g/L), IgM 0.37 g/L (normal 0.45-1.5 g/L) and a negative tuberculin test. Blood, urine and sputum bacterial cultures were negative. Chest X-rays were normal. An upper gastrointestinal series with small bowel follow-through (UGI-SBFT) revealed hiatal hernia, coarse mucosal folds and dilatation of the duodenum and jejunum. Because of the finding in the UGI/SBFT, an endoscopy was performed with an Olympus GIF-100 endoscope (Olympus America Inc., Lake Success, N.Y.). The mucosa showed a prominent white-tipped villous pattern. Intestinal biopsy specimens were obtained with punch biopsy forceps through the fiber endoscope. Histologic examination revealed marked dilatation of the lymphatic channels in the lamina propria with distortion of villi consistent with the diagnosis of intestinal lymphangiectasia (Figure 1).

The patient was placed on a low-fat diet and also started a vitamin and mineral supplementation with iron. Her condition improved, and a 6-month follow-up visit showed she was essentially asymptomatic with significantly less peripheral edema, with a serum albumin of 2.9 g/dL and Hb of 10.2 g/dL levels.

**CASE 2**

A 15-yr-old woman, born in Mexico City, was admitted to the hospital with a 6 months history of easy fatigability, accompanied by diarrhea, epigastric pain, general edema, pleural effusion and ascites. Her family history was irrelevant, but had had frequent pulmonary infec-

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*[Figura 1.]*

*[Figura 2.]*
sis of contrast into the mesenteric lymphatics. Exploratory laparotomy was performed with the hope of finding a localized, resectable lesion. Greatly enlarged lymphatics in the bowel wall and mesentery were evident. A transmural yeyunal biopsy was performed. Pathologic examination showed numerous dilated submucosal lymphatics (Figure 2). The patient was then placed on a low-fat diet without success, and recurrent episodes of massive peripheral edema, ascites and pleural effusion ensued. An ectract infiexional treatment was proposed, but her parents refused it, so the patient left the hospital.

**DISCUSSION**

Intestinal lymphangiectasia, a rare disorder, is often not limited to the intestine but is rather associated with a generalized lymphatic disturbance. It is characterized by the loss of serum proteins and lymphocytes into the bowel, resulting in hypoproteinemia, edema and lymphocytopenia. Associated lymphatic disorders include primary lymphoedema due to abnormal peripheral lymphatics, chylothorax and chyrous ascites due to malformations of the thoracic duct, cistern chyli, or mesenteric nodes, and lymphangiomas and lymphangiomatosis. Manifestations appear early in life and are generally diagnosed during childhood. When the onset is before age 10 years, growth retardation is common. Both sexes are equally affected. Clustering of cases in some families suggests a genetic cause, but most cases appear to be sporadic. Secondary forms of lymphangiectasia occur more commonly when originated by retroperitoneal carcinomas, lymphoma, retroperitoneal fibrosis, chronic pancreatitis, sarcoidosis, tuberculosis. Crohn’s disease, Budd-Chiari Syndrome, Whipple disease, Castleman disease, nephrotic syndrome and cardiac insufficiency. IL has been associated with Noonan’s syndrome, *peliosis hepatis*, Charcot-Marie-Tooth syndrome, Turner’s syndrome, and hypobetalipoproteinemia. Little is known about the progression of the abnormality during development although in most young people it seems to remain relatively constant or progress only slowly with a fluctuating course. Episodes of protein losing enteropathy may occur acutely in relationship to oral allergens or infective agents. This can explain the relapsing symptoms in the second case. Exacerbation of intestinal lymphangiectasia has been reported in association with pregnancy and hepatitis. The proteins affected most are those with the lowest half-life. On the first patient, the greatest proportional fall was in IgG, with no reduction of IgM. Both patients had lymphocyte counts below the lower normal limit. Neither had faecal fat excretion exceeding 7 g/day, but great faecal fat excretion can be found in about one-third of the patients suffering from IL.

IL may be manifested by a wide spectrum of clinical and laboratory abnormalities. The major symptoms are diarrhea, nausea, vomiting, and edema. Diarrhea may occur at a certain time in up to 93% of the affected patients. In the cases presented herein, this was the principal alteration that required medical attention.

Steatorrhea has been described in 20% of the patients. Abdominal pain is infrequently found, almost always in less than 10% of the patients. Edema may be present at birth or appear later. Chyious pleural, peritoneal, or pericardial effusions develop at some point during the course of the disease in 33% to 43% of the patients. Cholesterol levels are classically low or normal, as opposed to those in nephrotic hypoproteinemia. This is because of the bulk loss of serum constituents in the lipid-rich lymphatic fluid, which escapes from the dilated lymphatics into the gastrointestinal tract.

Characteristic abnormalities include decreased plasma concentrations of albumin, gammaglobulin, fibrinogen, ceruloplasmin, lipoproteins, transferring and alpha-1-antitrypsin. Red cells, iron and folic acid may also escape into the intestinal tract and can explain the anemia, which was seen in the first women.

Barium contrast radiography shows thickening of folds, disorganized spiculated configuration, punctuate lucencies and dilution of the barium and dilation of the bowel lumen. Lymphangiography may reveal hypoplasia or aplasia of lower extremity lymphatics, distorted or obstructed lymphatic channels and lymph nodes in the mesentery and para-aortic region. Microscopically, dilated lymphatic vessels in the lamina propria and submucosa of the small intestine may be seen. Three cardinal endoscopic findings may be observed: scattered white spots, shite villi, and chyle-like substances covering mucosa. As in our patients, the natural course of the disease appears to be relatively constant, with occasional episodes of protein-losing enteropathy and worsening of the edema during periods of non-adherence to dietary modifications. The therapy for IL should be directed towards the treating of the pathophysiologic consequences, and in the case of secondary lymphangiectasia, the underlying disease should be diagnosed and treated. In our patients no secondary etiology was found, thus the disease was classified as primary lymphangiectasia.
Intestinal lymphangiectasia and diarrhea

Introduction of a low-fat, medium-chain triglyceride-supplemented diet, the mainstay treatment for IL, abated this symptoms.\textsuperscript{15-17}

Short-chain fatty acids are more water-soluble and may be more readily absorbed through portal venous channels than through the lymphatics. The concomitant reduction in dietary long-chain fatty acids presumably reduces chylomicrons in the obstructed lymphatics and thereby decreases the lymphatic pressure and rate of lymph loss. A small number of recent reports advocate the use of octreotide in intestinal lymphangiectasia\textsuperscript{18} or antiplasmin therapy in a patient with increased plasma fibrinolytic activity, yet it is probable that the majority of the patients do not respond to this treatment.\textsuperscript{19} Peripheral edema can be minimized by postural drainage and elastic stockings to reduce the risk of cellulites and lymphangitis.

Patients with IL do not appear to have an increased risk of developing opportunistic infections despite the marked lymphopenia and hypogammaglobulinemia. The risk for lymphomatous transformation is not clear, as only a few cases of IL preceding the diagnosis of lymphoma have been reported.\textsuperscript{20}

Since IL is a rare disorder, we investigated the cases reported in Mexico. A literature search from 1963 to June 2005 was conducted using the National Library of Medicine PubMed database using the terms “intestinal lymphangiectasia AND Mexico”. Also a literature search from 1999 to 2005 was made entering www.medigraphic.com (an internet site for Mexican journals). Finally, a manual search of the following journals (\textit{Rev Gastroenterol Mex, Bol Med Hosp Infant Mex, Ginecol Obstet Med}) published since 1980 was also conducted to ensure that all published reports were included. We found only three cases in our country.\textsuperscript{21-24} The characteristics of these patients are shown in table 1.

The recognition of the existence of this abnormality in a mild form and as one of the etiologies of anemia and chronic diarrhea indicates the need for an increased awareness of the possibility of IL diagnosis in patients with protein-losing enteropathies.

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\begin{center}
\textbf{TABLE 1}
\end{center}

\begin{center}
\textbf{CASE REPORTS OF MEXICAN PATIENTS WITH INTESTINAL LYMPHANGIECTASIA}
\end{center}

<table>
<thead>
<tr>
<th></th>
<th>Sanchez(21)</th>
<th>Loredo(23)</th>
<th>Ibargüengoitia(24)</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Female (pregnant)</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Age (years)</td>
<td>2</td>
<td>1</td>
<td>27</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Born</td>
<td>Mexico City</td>
<td>Mexico City</td>
<td>Veracruz</td>
<td>Irapuato</td>
<td>Mexico City</td>
</tr>
<tr>
<td>Time with diarrhea</td>
<td>8 months</td>
<td>4 months</td>
<td>22 years</td>
<td>20 years</td>
<td>6 months</td>
</tr>
<tr>
<td>Edema</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Anemia</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
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<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>N.R.</td>
</tr>
<tr>
<td>D-Xylosa test</td>
<td>Abnormal</td>
<td>Normal</td>
<td>N.R.</td>
<td>N.R.</td>
<td>N.R.</td>
</tr>
<tr>
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<td>Abnormal</td>
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<td>Performed</td>
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</tr>
<tr>
<td>Endoscopy</td>
<td>Performed</td>
<td>Not performed</td>
<td></td>
<td></td>
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REFERENCES


