Waldmann’s disease: a rare cause of protein losing enteropathy in an adult patient

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ABSTRACT

Primary intestinal lymphangiectasia or Waldmann’s disease is an uncommon cause of protein losing enteropathy with an unknown etiology and is usually diagnosed during childhood. It is characterized by dilation and leakage of intestinal lymph vessels leading to hypoalbuminemia, hypogammaglobulinemia and lymphopenia. Differential diagnosis should include erosive and non-erosive gastrointestinal disorders, conditions involving mesenteric lymphatic obstruction and cardiovascular disorders that increase central venous pressure. Since there are no accurate serological or radiological available tests, enteroscopy with histopathological examination based on intestinal biopsy specimens is currently the gold standard diagnostic modality of intestinal lymphangiectasia. We report a rare case of a primary intestinal lymphangiectasia in a 60-year-old Caucasian female who presented with asymptomatic hypoalbuminemia and hypogammaglobulinemia. After the diagnosis of a protein losing enteropathy, the patient underwent an enteroscopy and biopsies were taken, whose histological examination confirmed dilated intestinal lymphatics with broadened villi of the small bowel. Secondary causes of intestinal lymphangiectasia were excluded and the diagnosis of Waldmann’s disease was recorded. The patient was put on a high-protein and low-fat diet with medium-chain triglyceride supplementation with improvement.

Key words: Protein losing enteropathy. Primary intestinal lymphangiectasia. Single-balloon enteroscopy.

INTRODUCTION

Protein losing gastroenteropathies, characterized by an excessive loss of serum proteins into the gastrointestinal tract, are an important cause of hypoproteinemia, and their diagnosis should be considered in patients when other causes of hypoproteinemia have been excluded, such as malnutrition, heavy proteinuria and impaired protein synthesis due to liver diseases. A high fecal alpha-1-antitrypsin clearance suggests exudative enteropathy.

Intestinal lymphangiectasia is an uncommon cause of protein losing enteropathy (PLE) due to congenital malformation or secondary obstruction of intestinal lymphatic drainage (1). As lymphatic fluid contains a lot of proteins, fat and lymphocytes, leakage of lymph will cause hypoproteinemia, lymphopenia and decreased serum levels of immunoglobulins (2).

Depending on the cause of the disease, it can be classified into primary or secondary. Primary intestinal lymphangiectasia (PIL) or Waldmann’s disease, originally described by Waldmann in 1961 (3), is a rare cause of PLE, whose prevalence and etiology are unknown. The diagnosis is generally established before the third year of life but can be rarely seen in adults (4). The gold-standard diagnostic modality is enteroscopy with the respective histological examination of the intestinal biopsy specimen. The confirmation of the primary nature of disease requires the exclusion of secondary causes (4). Main differential diagnosis includes congestive cardiac failure, constrictive pericarditis, intestinal lymphoma, Crohn’s disease, intestinal tuberculosis, sarcoidosis, Whipple’s disease, human immunodeficiency virus (HIV)-related enteropathy, cytomegalovirus (CMV)-related enteropathy or systemic sclerosis.

A low-fat diet associated with medium-chain triglycerides (MCT) supplementation is the cornerstone of PIL medical management (5).

We report an uncommon case of PIL diagnosed in an adult asymptomatic female during etiological investigation of hypoproteinemia.

CASE REPORT

We present a 60-year-old Caucasian female that was referred to our Department due to asymptomatic hypoalbuminemia and hypogammaglobulinemia. She reported a medical history of hypothyroidism, hypercholesterolemia and gastroesophageal reflux disease under treatment with levothyroxine, simvastatin and omeprazole. There was no
history of diarrhea, limb swelling, abdominal pain, fever, vomiting, anorexia, weight loss, skin rash or urinary symptoms. Physical examination was unremarkable.

Initial laboratory tests showed no anemia (hemoglobin 13.6 g/dL), normal total white blood cells count (4.18 x 10^9/L) with normal lymphocytes (1,720/µL) and platelet count (200,000/µL); protein electrophoresis with hypoproteinemia (4.6 g/dL), hypoalbuminemia (2.9 g/dL) and hypogammaglobulinemia (2.6 g/L); normal calcium levels, liver and kidney function tests. Further investigations showed no proteinuria and fecal alpha-1-antitrypsin clearance was increased. These results were consistent with a PLE.

In order to clarify the etiology of exsudative enteropathy, the patient underwent an upper gastrointestinal endoscopy with gastric and duodenal biopsies which were normal. Computed tomography (CT) scan enterography and magnetic resonance imaging (MRI) enterography revealed diffuse and regular thickening throughout the jejunum; there were no adenopathies (Fig. 1). A single-balloon enteroscopy was performed and scattered white spots with a “snowflake” appearance overlying the jejunum were observed (Fig. 2). These findings were consistent with diffuse intestinal lymphangiectasia. Multiple biopsies were taken and the histopathological examination revealed broadened villi with dilated lymphatic channels in mucosa and submucosa.

To exclude secondary causes of intestinal lymphangiectasia an additional study was performed. Coprocultures, parasitological stool sample examination, serological testing for HIV and CMV and interferon-gamma release assay were negative. Antinuclear antibodies, anti-double stranded DNA and immunoglobulin A (IgA) anti-tissue transglutaminase were negative. Erythrocyte sedimentation rate and serum beta-2 microglobulin were normal. Immunophenotypic analysis of peripheral blood revealed no atypical cells. Transthoracic echocardiogram was normal.

These findings were fully consistent with PIL (Waldmann’s disease). The patient was put on a high-protein and low-fat diet with supplementation of medium chain triglyceride with good response.

DISCUSSION

Intestinal lymphangiectasia, an uncommon but important cause of protein losing enteropathy, is characterized by an impaired small intestinal lymph drainage associated with dilated lymphatic channels. It can be due to primary disorders of intestinal lymphatics or due to secondary causes. Regardless of the cause, the impaired flow and increased pressure in intestinal lymphatics lead to decreased absorption of fat-soluble vitamins (A, D, E and K), reduced recirculation of intestinal lymphocytes into the peripheral circulation and leakage of intestinal lymph into the intestinal lumen (6).

PIL, first described in 1961 by Waldmann et al. (3), is a rare disorder whose prevalence and etiology are unknown. After 1961, as per available literature, less than 200 cases have been reported. It is mainly seen in pediatric patients, usually diagnosed before three years of age, with an equal incidence in both genders (4). Although most cases are sporadic, PIL has been reported in multiple siblings of several families, suggesting a genetic contribution. Furthermore, PIL can occur as an isolated disorder or as a part of a syndrome such as Von Recklinghausen, Turner, Noonan, Klippel-Trenaunay-Weber, Hennekan and yellow-nail syndrome.

In a retrospective analysis of 84 cases in 2010, the most common symptoms were limb edema, diarrhea, ascites and lymphedema, present in 78, 62, 41 and 22%, respectively (7). Other non-specific symptoms are fatigue, abdominal pain, nausea, vomiting, weight loss, failure to thrive, iron deficiency anemia, obstructive ileus, steatorrhea and...
fat-soluble vitamin deficiency (2). Due to leakage from the ruptured lymph vessels, other major features are lymphopenia, hypoalbuminemia and hypogammaglobulinemia. However, in a few cases, patients are asymptomatic and the diagnosis is made during etiological investigation of hypoproteinemia (13).

In this report, we present a rare case of a PIL in an asymptomatic adult patient diagnosed during etiological investigation of hypoproteinemia, hypoalbuminemia and hypogammaglobulinemia. Taking into account the high fecal alpha-1-antitrypsine clearance and after excluding other causes of hypoproteinemia, such as malnutrition, proteinuria and liver disease, a PLE was considered.

Currently, diagnosis of intestinal lymphangiectasia is based on typical findings during enteroscopy with further confirmation by histopathological examination of corresponding biopsy specimens (4). Other tests proposed to demonstrate the abnormal intestinal lymphatic vessels are albumin scintigraphy, contrast lymphangiography and magnetic resonance lymphangiography. However, their sensitivity and specificity have not been studied in a sufficient number of patients to justify routine use.

The definitive diagnosis of Waldmann’s disease requires the exclusion of secondary causes of intestinal lymphangiectasia, which includes erosive and non-erosive intestinal disorders, conditions involving mesenteric lymphatic obstruction and cardiovascular disorders that increase central venous pressure. Therefore, the main differential diagnoses are constrictive pericarditis, intestinal lymphoma, lymphoenteric fistula, Whipple’s disease, Crohn’s disease, sarcoidosis, intestinal tuberculosis, systemic sclerosis, radiation and/or chemotherapy with retroperitoneal fibrosis, HIV and CMV-related enteropathy and Fontan operation to treat cardiac malformations.

Lifelong dietary modification with high protein, fat restriction and substitution with MCT and vitamin supplements remains the cornerstone in the management of PIL. Exclusion of long-chain fatty acids prevents the engorgement and rupture of malformed lymphatics while MCT get directly absorbed into the portal venous circulation. In patients not responding to a low fat diet, enteral nutritional therapy (elemental, semi-elemental and polymeric diets) may be required. In a few severe cases, total parenteral nutrition is warranted (8). Alternative treatment options with variable efficacy are discussed in several publications. They include antiplasmin therapy, octreotide, corticosteroids, small bowel resection, albumin infusions, peritoneovenous (Levine) shunt and intestinal transplant.

The prognosis of PIL is highly variable depending on the age of onset, extent and severity of disease and response to therapy. Regarding the main complications, it is not clear if malignancy, especially lymphoma, is fortuitous or related to the disease. Among 84 PIL patients reviewed in 2010, four (5%) had malignant lymphoma, and the average time from PIL onset to lymphoma diagnosis was 31 years (range 19-45 years) (7). Lymphoma mainly affects the gastrointestinal tract but may also be seen in the retroperitoneum and the mediastinum. Recurrent and opportunistic infections are not rare due to moderate or severe hypogammaglobulinemia and lymphopenia (e.g., Streptococcus G, meningitis, cryptococcus, cytomegalovirus) (9,10).

In our case, enteroscopy reveals scattered white spots with a “snowflake” appearance, which are the typical findings of intestinal lymphangiectasia. Histopathological examination of their biopsies confirmed diagnostic suspicion. Regarding the length, and also taking into account IRM enterography findings, the disease involved the entire jejunum. After the exclusion of secondary causes of intestinal lymphangiectasia, the diagnosis of Waldmann’s disease was recorded and the patient was put on a high protein and low-fat diet with medium-chain triglyceride supplementation with a good response.

In conclusion, PIL is a rare condition that can be asymptomatic or appear with common features such as limb edema, diarrhea, hypoproteinemia and hypogammaglobulinemia. Careful endoscopic examination and meticulous histopathological evaluation is mandatory to achieve a correct pathological diagnosis and, thus, to decide the proper treatment plan. It can be severe, affecting the entire small bowel, persistent and difficult to manage, leading to lifetime disease. The risk of cancer in these cases should be taken into account. On the other hand, the disease can be mild, affecting part of the bowel, transient and easy to manage with dietary interventions.

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