An Uncommon Cause of Generalized Edema: Protein-Losing Gastroenteropathy with Primary Sjögren’s Syndrome

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Abstract

Protein-losing gastroenteropathy (PLGE) is a rare etiology of generalized edema. It is caused by a loss of serum protein into the gastrointestinal tract, resulting in hypoproteinemia, generalized edema, ascites, pleural effusions and occasionally, pericardial effusions. PLGE is associated with various conditions, such as gastrointestinal malignancy, cardiac diseases, inflammatory bowel disease, autoimmune diseases, and various infections. Here, we report a 69-year-old woman with a presentation of generalized edema. PLGE was confirmed via a fecal alpha-1 antitrypsin clearance test. Sjögren’s syndrome was consequently diagnosed according to the symptoms, high level of anti-SSA/SSB antibodies, positive Schirmer’s test, sialoscintigraphy, and salivary gland biopsy. Remission was noted by treatment with intravenous methylprednisolone followed by oral prednisolone. A review of the literature was also performed to evaluate the clinical manifestations, treatment, and outcome. Nephrologists should consider PLGE as one of the different diagnoses of generalized edema if common causes are excluded.

KEY WORDS: edema, protein-losing enteropathies, Sjögren’s syndrome

Introduction

Generalized edema is one of the most common symptoms in the clinical practice of nephrology. It is often caused by heart failure, cirrhosis, chronic kidney diseases, or nephrotic syndrome.

Protein-losing gastroenteropathy (PLGE) is a rare cause of generalized edema. It is characterized by leakage of serum protein into the gastrointestinal tract, resulting in hypoproteinemia, edema, and, in some cases, pleural or pericardial effusions. Many disorders are reported to be associated with PLGE, including gastrointestinal malignancy, cardiac diseases, inflammatory bowel diseases, autoimmune diseases, and various infections (1). In autoimmune diseases, most reports have been associated with systemic lupus erythematosus (2). Here, we report a 69-year-old woman diagnosed with primary Sjögren’s syndrome and PLGE. We also performed a review of the published literature on primary Sjögren’s syndrome-associated PLGE. A PubMed search was conducted to identify all articles, in all languages, on Sjögren’s syndrome-associated PLGE, from 1966 to 2011. Using medical subject headings (MeSH) to modify the keywords, including Sjögren’s syndrome and protein-losing gastroenteropathy, ten articles were
The patient was suspected to have PLGE owing to edema, severe hypoalbuminemia, and negative proteinuria. For the diagnosis of PLGE, gastrointestinal bleeding was excluded first by negative result of stool occult blood. Omeprazole 20 mg daily was prescribed for 3 days and fecal alpha-1 antitrypsin clearance (A1Ac) was checked. The result of A1Ac was 368 mL/day (normal < 13 mL/day). Therefore, PLGE was confirmed.

To identify the cause of PLGE, a series of studies were performed. Screening tests for hepatitis B, C and human immunodeficiency virus (HIV) were negative. Steatorrhea was excluded and serum amylase was normal. Panendoscopy showed only a mild mucosa inflammation of the stomach. No tumor, erosive ulcerative lesions, or giant folds were noted. Small intestine series showed a normal mucosa appearance. Colonoscopy disclosed mild edema at the entire colon without evidence of tumor, polyps, or erosive ulcerations. Serum anti-nuclear antibody (ANA) was positive in speckle type with a high titer of 1:320. The anti-dsDNA level was 2.7 IU/mL (normal < 10 IU/mL) and the rheumatoid factor was 43 IU/mL (normal < 20 IU/mL). Anti-SSA (> 240 IU/mL) and anti-SSB (129 IU/mL) were markedly elevated (normal 7-10 IU/mL). Anti-Sm, anti-RNP and anti-Scl-70 levels were within normal ranges. Serum IgG, IgA and IgM level were 1550 mg/dL, 496 mg/dL and 216 mg/dL respectively. C3 was 87.1 mg/dL (normal 79-152 mg/dL) and C4 was 27.6 mg/dL (normal 16-38 mg/dL). Schirmer’s test was abnormal (OD: 4 mm, OS: 4.5 mm). Sialogingraphy revealed very poor radiotracer uptake of the bilateral parotid and submandibular glands. A minor salivary gland biopsy disclosed chronic sialadenitis. Sjögren’s syndrome was diagnosed according to the criteria proposed by the American-European consensus group (8).

The patient was treated with methylprednisolone 500 mg/day for 3 days, followed by oral prednisolone 10 mg twice per day for 4 months. The fecal A1Ac level decreased to 128.6 mL/day by the second month, and further decreased to 4.0 mL/day by the fourth month. The serum albumin level rose to 1.9 g/dL by the second month and 3.5 g/dL by the fourth month (Fig. 1). The patient’s oral dryness, ocular dryness, weakness, and edema improved, and she was able to walk with mobility aids four months after treatment.

Discussion

PLGE is a rare cause of generalized edema. It is usually diagnosed by low serum albumin and globulin levels in the absence of renal and hepatic disease. The exact mechanism of edema formation in PLGE is unclear, but may possibly be explained using the

Case Report

A 69-year-old Taiwanese woman presented to us in Oct 2010 with a 2-month history of progressive weakness and generalized edema. The patient had a history of subtotal thyroidectomy because of primary hyperthyroidism at the age of 39 years. About two months ago, she began to present with edema over the bilateral lower legs. She visited the local outpatient clinic and took oral furosemide 40 mg twice per day plus spironolactone 25 mg per day. However, the edema progressed to the trunk and hands, and weight gain of about 6 kg was noted. She also had oral and ocular dryness for more than 6 months and became weak and almost completely bed-ridden in the past 2 weeks. She did not show a skin rash, purpura, arthralgia, foamy urine, melena or diarrhea. The main laboratory findings collected at the local hospital one week previously showed serum albumin 2.0 g/dL, serum cholesterol 273 mg/dL, serum blood urea nitrogen 20 mg/dL, and serum creatinine 1.0 mg/dL. A chest film disclosed bilateral pleural effusion. Abdominal sonography showed a small mucosa inflammation of the stomach. No tumor, erosive ulcerative lesions, or giant folds were noted. Small intestine series showed a normal mucosa appearance. Colonoscopy disclosed mild edema at the entire colon without evidence of tumor, polyps, or erosive ulcerations. Serum anti-nuclear antibody (ANA) was positive in speckle type with a high titer of 1:320. The anti-dsDNA level was 2.7 IU/mL (normal < 10 IU/mL) and the rheumatoid factor was 43 IU/mL (normal < 20 IU/mL). Anti-SSA (> 240 IU/mL) and anti-SSB (129 IU/mL) were markedly elevated (normal 7-10 IU/mL). Anti-Sm, anti-RNP and anti-Scl-70 levels were within normal ranges. Serum IgG, IgA and IgM level were 1550 mg/dL, 496 mg/dL and 216 mg/dL respectively. C3 was 87.1 mg/dL (normal 79-152 mg/dL) and C4 was 27.6 mg/dL (normal 16-38 mg/dL). Schirmer’s test was abnormal (OD: 4 mm, OS: 4.5 mm). Sialogingraphy revealed very poor radiotracer uptake of the bilateral parotid and submandibular glands. A minor salivary gland biopsy disclosed chronic sialadenitis. Sjögren’s syndrome was diagnosed according to the criteria proposed by the American-European consensus group (8).

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originaly identified. Limiting the findings to the English language reduced the number of publications to eight. Of these, four were related to our topic (3-6). Examination of the references in these reports resulted in the addition of one more study to our review (7).
In clinical practice, the relationship between findings were not specific to autoimmune disorders even if these meability due to venulitis, and mucosal defect due including lymphangiectasia, increased capillary permeability of protein loss according to the pathologic findings, hypotheses had been proposed to explain the cause with autoimmune disorders remains unclear. Some mechanism responsible for PLGE in association Japan, Taiwan, and Hong Kong (Table 1). The exact Sjögren’s syndrome-associated PLGE is extremely rare. All reports have come from East Asia, including Japan, Taiwan, and Hong Kong (Table 1). The exact mechanism responsible for PLGE in association with autoimmune disorders remains unclear. Some hypotheses had been proposed to explain the cause of protein loss according to the pathologic findings, including lymphangiectasia, increased capillary permeability due to venulitis, and mucosal defect due to inflammatory cell infiltration (4, 5, 7) even if these findings were not specific to autoimmune disorders (1). In clinical practice, the relationship between PLGE and its possible cause was usually determined by clinical judgment rather than pathologic findings. In our review, the association of Sjögren’s syndrome was often diagnosed by clinical manifestations and serologic studies (Table 1). Our patient presented classic symptoms, positive serologic studies, and showed remission in both sicca syndrome and PLGE after steroid treatment. Therefore, we considered PLGE in our patient was associated with Sjögren’s syndrome.

There are two common methods of making a diagnosis of PLGE: 24-hour fecal A1Ac, and nuclear radiology testing. Alpha-1 antitrypsin is a glycoprotein synthesized by the liver with a molecular weight of 54,000 daltons similar to albumin (67,000 daltons). It is a protease inhibitor and is resistant to proteolysis when it leaks into the intestinal lumen. Therefore, measurement of fecal A1Ac can serve as albumin leakage in stool. The normal rate of alpha-1 antitrypsin excretion in the stool is less than 2.6 mg/g stool, reflecting a fecal A1Ac of less than 13 mL/day (10). Note, increases in the level of fecal A1Ac also develop in normal subjects (without PLGE) with diarrhea or gastrointestinal bleeding (11). Thus, the values for diagnosis of PLGE are fecal A1Ac greater than 24 mL/day in patients without diarrhea and greater than 56 mL/day in patients with diarrhea (11). Gastrointestinal bleeding must be excluded before measurement of fecal A1Ac. In addition, because alpha-1 antitrypsin is apparently degraded by the acidic gastric juice below pH 3.5 (10), if a status of protein loss from stomach is suspected or gastric acid hypersecretion is known, it is recommended the test be performed while the individual is receiving acid suppression therapy (12).

Nuclear radiology testing is another method in the diagnosis of PLGE and has the benefit of confirming the site of protein loss. Technetium-99m-labeled human serum albumin (Tc-99m HSA) and other scintigraphy have been shown to be useful not only for diagnosis, but also in monitoring treatment response (13, 14). Note, active gastrointestinal bleeding also results in a false-positive finding in Tc-99m HSA scintigraphy because of the leakage of radiotracer into the bowel lumen with blood (15). On the other hand, a false-negative result may develop in some patients who had delayed the image 24 hours after radiotracer injection or with intermittent protein loss in the gut (16). Another flaw may be human serum albumin used in the manufacture of Tc-99m HSA is extracted from the blood of pooled human donors. Although the blood is screened for hepatitis B, C and HIV, there is currently no screening test to detect contaminants from transmissible agents, such as variant Creutzfeldt-Jakob Disease (17). Safety concerns have limited the use of Tc-99m HSA in several countries, and have resulted in the development of a
Table 1. Reported patients with primary Sjögren syndrome-associated protein-losing gastroenteropathy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Presentations</th>
<th>Serum albumin (g/dL)</th>
<th>99mTc-HSA scintigraphy radioisotope accumulation</th>
<th>Fecal A1Ac (mL/24h)</th>
<th>Treatment</th>
<th>Outcome of PLGE</th>
<th>Outcome of Sjögren syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsutsumi, 1991 (7)</td>
<td>47/F</td>
<td>Ocular and oral dryness for 3 months; pretibial edema and increased body weight</td>
<td>1.2</td>
<td>No data</td>
<td>No data</td>
<td>Oral Pred 60 mg daily × 8 weeks, slowly tapering to 10 mg every two days</td>
<td>Remission</td>
<td>No data</td>
</tr>
<tr>
<td>Mok, 1997 (3)</td>
<td>54/F</td>
<td>Ocular and oral dryness for 6 months; bilateral ankle edema for one month</td>
<td>1.4</td>
<td>No data</td>
<td>115</td>
<td>Oral MTP 60 mg daily × 2 weeks, followed by oral CP 100 mg daily × 8 weeks</td>
<td>Failure</td>
<td>No data</td>
</tr>
<tr>
<td>Hsieh, 2002 (4)</td>
<td>37/F</td>
<td>Ocular and oral dryness for 6 years; face and leg edema for 2 months</td>
<td>1.4</td>
<td>Stomach and intestine</td>
<td>No data</td>
<td>IV MTP 750 mg × 3 days for 2 courses monthly; followed by oral Pred 30 mg daily plus hydroxychloroquine 200 mg twice daily</td>
<td>Remission</td>
<td>No data</td>
</tr>
<tr>
<td>Hsieh, 2002 (4)</td>
<td>50/F</td>
<td>Oral dryness for 2 year; general anasarca for 4 months</td>
<td>1.1</td>
<td>Intestine</td>
<td>No data</td>
<td>IV MTP 750 mg × 3 days for 3 courses monthly; followed by oral Pred 30 mg daily plus hydroxychloroquine 200 mg twice daily</td>
<td>Remission</td>
<td>No data</td>
</tr>
<tr>
<td>Nagashima, 2009 (5)</td>
<td>41/M</td>
<td>Recurrent erythema over cheek, neck, ear and trunk for 3 years; facial and leg edema for 2 months</td>
<td>1.3</td>
<td>Stomach and small intestine</td>
<td>280.5</td>
<td>IV Pred 70 mg × 2 weeks, followed by oral Pred, tapering to 7 mg daily one year later</td>
<td>Failure</td>
<td>No data</td>
</tr>
<tr>
<td>Nasu, 2011 (6)</td>
<td>59/F</td>
<td>Ocular and oral dryness for one month; facial and leg edema for one month</td>
<td>2.8</td>
<td>Stomach</td>
<td>205</td>
<td>Oral Pred 50 mg daily for 3 weeks; IV MTP 1 gm × 3 days plus CP &amp; mizoribine</td>
<td>Failure</td>
<td>No data</td>
</tr>
<tr>
<td>Present case</td>
<td>69/F</td>
<td>Ocular and oral dryness for 6 months; facial and leg edema for 2 months</td>
<td>1.0</td>
<td>No data</td>
<td>368</td>
<td>IV MTP 500 mg × 3 days, followed by oral Pred 20 mg daily × 3 months</td>
<td>Remission</td>
<td>Improvement of ocular and oral dryness</td>
</tr>
</tbody>
</table>

Abbreviations: A1Ac: alpha-1 antitrypsin clearance; CP: cyclophosphamide; HSA: human serum albumin; IV: intravenous; MTP: methylprednisolone; PLGE: protein-losing gastroenteropathy; Pred: prednisolone.
new diagnostic tool to replace Tc-99m HSA (18-20). Treatment of autoimmune PLGE is mainly immunosuppression therapy. In cases associated with primary Sjögren’s syndrome, initial therapy was oral prednisolone or pulse intravenous steroid. In the review (Table 1), three patients receive oral prednisolone with an initial dose of 50 to 60 mg daily and remission was noted in one. Pulse intravenous steroid was initially performed in four including our patient, and remission was noted in three. In the three patients who had a failed initial treatment, remission was noted after rescue therapy by intravenous methylprednisolone. Of them, one was treated in combination with alkylating agents.

In conclusion, PLGE, although uncommon, should be considered as one of the possible causes of generalized edema. In East Asians, it can be associated with Sjögren’s syndrome. Steroid treatment is effective and the outcome is good.

References