PRIMARY SJÖGREN’S SYNDROME WITH PROTEIN-LOSING GASTROENTEROPATHY: REPORT OF TWO CASES

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Protein-losing gastroenteropathy is defined as a disorder with excessive loss of plasma protein into the gastrointestinal tract [1]. The common symptoms are edema and diarrhea. Gastrointestinal malignancy, cardiac diseases, allergic gastroenteritis, eosinophilic gastroenteritis, inflammatory bowel diseases, ischemic bowel disease, amyloidosis, and various bacterial or viral infections have been found to be associated with protein-losing enteropathy [2]. Other reported causes include various systemic autoimmune diseases, such as progressive systemic sclerosis (PSS), systemic lupus erythematosus (SLE), mixed connective disease, and rheumatoid arthritis (RA) [2–5]. Only two cases of Sjögren’s syndrome with protein-losing enteropathy have been reported [6, 7]. Because sicca symptoms might be trivial, primary Sjögren’s syndrome as a cause of protein-losing enteropathy could easily be overlooked.

In the past, the diagnosis of intestinal protein loss relied on the detection of the passage of intravenous injected iodine-131 (I-131) or chromium-51 (Cr-51) labeled albumin in stools [8, 9]. Urine contamination of stool [8] and radiation hazard [9] limited the clinical application of these tracers. Alpha-1-antitrypsin clearance in stool was then employed as a major diagnostic method for protein-losing enteropathy [10]. However, alpha-1-antitrypsin clearance in stool is not an ideal tool because of the inability to locate the site of protein loss and pseudo-negative results of protein loss obtained from low pH sites such as the stomach [11, 12]. In contrast, Tc-99m labeled albumin scintigraphy of the abdomen is a rapid and convenient method for diagnosis, location of the protein-losing site (including stomach), and monitoring of treatment response [11–15]. Here, we report two cases of primary Sjögren’s syndrome with protein-losing enteropathy diagnosed by Tc-99m labeled albumin scintigraphy of the abdomen and successfully treated with corticosteroids. One of these is the first reported case of primary Sjögren’s syndrome with hypertrophic gastropathy and protein-losing gastroenteropathy from both the stomach and intestines.
Case Reports

Case 1
A 37-year-old female hairdresser was admitted because of puffy face and pitting edema in both lower legs for 2 months. There was no preceding abdominal pain, nausea, vomiting, or diarrhea. She had a 6-year history of dry eye and dry mouth symptoms. Physical examination revealed general anasarca, decreased breathing sounds in the right lower lung, and positive shifting dullness on abdominal percussion. Roentgenography of the chest and kidneys, ureter, and bladder showed pleural effusion and ascites. Laboratory data showed low serum albumin (1.4 g/dL) and high cholesterol (479 mg/dL) concentrations. Urine analysis was normal. Concentrations of serum creatinine and liver enzymes and measures of thyroid function were within normal ranges. No parasite ova were found in repeated stool microscopic examinations. Results of Doppler echocardiography and abdominal sonography excluded the presence of cardiac disease or liver cirrhosis. Schirmer's test was abnormal with an OD of 5 mm and an OS of 3 mm. Tc-99m sialoscintigraphy disclosed class II (mild/moderate involvement) abnormality. Serum antinuclear antibody (ANA) was positive with a titer of 1:320. Antibody to extractable nuclear antigen (ENA) was positive for Sjögren’s syndrome A (SSA) antigen by double immunodiffusion. Serum rheumatoid factor was 13.3 IU/mL (normal, < 9 IU/mL). Sjögren’s syndrome was diagnosed according to the criteria proposed by the European Community Study Group [16]. Tc-99m labeled albumin abdominal scintigraphy showed intense tracer retention over the stomach and intestines, compatible with protein-losing gastroenteropathy (Fig. 1A). Upper gastrointestinal (UGI) series revealed thickened stomach rugae. Stomach biopsy showed mucosal dense mononuclear cell infiltration. A biopsy from the duodenum showed dense mononuclear cell infiltration, superficial erosion in the mucosa, and atrophy of villi (Fig. 2).

Methylprednisolone pulse therapy at a dose of 750 mg/day for 3 days was given monthly from February 1999 for 2 months. Oral prednisolone (30 mg/day) and hydroxychloroquine (200 mg bid) were also prescribed. General anasarca subsided in the third month after corticosteroid treatment. Serum albumin increased from 1.9 to 3.9 g/dL. Follow-up Tc-99m labeled albumin scintigraphy showed normal tracer retention in stomach and intestines (Fig. 1B). Follow-up UGI-series revealed normal stomach and duodenal mucosa 4 months later.

Case 2
A 50-year-old housewife was admitted because of general anasarca for 4 months. A 2-year history of dry mouth and mild intermittent diarrhea could be traced. Physical examination on admission showed abnormal Schirmer’s test (OD: 2 mm; OS: 4 mm), general anasarca, and shifting dullness on abdominal percussion. Low serum albumin (1.1 g/dL) and high serum cholesterol (317 mg/dL) concentrations were found. There was no proteinuria. No parasite ova were found in microscopic examination of stool. Concentrations of serum creatinine and liver enzymes and measures of thyroid function were normal. Doppler echocardiography and abdominal sonography excluded the presence of cardiac disease or liver cirrhosis. Tc-99m sialoscintigraphy disclosed class II abnormality. Serum ANA was positive, with a titer of 1:640. ENA antibody test was positive for SSA. Serum rheumatoid factor was 15.5 IU/mL. Sjögren’s syndrome was diagnosed [16]. UGI endoscopy revealed mild chronic gastritis. Biopsy of the duodenal mucosa showed chronic active inflammation with mononuclear cell infiltration and edematous changes in the duodenal villi. Upper and lower gastrointestinal series showed entirely normal results, except for the presence of mild lymphoid hypertrophy in the terminal ileum. Abdominal Tc-99m labeled albumin scintigraphy disclosed tracer retention in the intestines, a finding compatible with protein-losing enteropathy.

Monthly methylprednisolone pulse therapy, at a dose of 750 mg/day for 3 days, was given for 3 months. Oral predniso-
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Fig. 2. Biopsy from the stomach of Case 1 reveals dense mononuclear cell infiltration (arrowhead), superficial erosion, and atrophy of villi (white arrow). (Hematoxylin & eosin, x 200)

Prednisolone (30 mg/day) and hydroxychloroquine (200 mg bid) were also prescribed. Edema improved gradually. After 4 months, serum albumin increased from 1.1 to 3.6 g/dL. Follow-up of Tc-99m labeled albumin scintigraphy performed at that time revealed no tracer retention in the intestines.

Discussion

Protein-losing enteropathy associated with primary Sjögren’s syndrome is rare and only two cases have previously been reported [6, 7]. We report another two cases of primary Sjögren’s syndrome initially presenting with protein-losing enteropathy. One of these is the first reported case of Sjögren’s syndrome with protein-losing gastropathy. Tc-99m labeled albumin abdominal scintigraphy was used to locate the site of protein-losing enteropathy.

Tsutsumi et al reported the case of a 47-year-old woman with primary Sjögren’s syndrome with protein-losing enteropathy diagnosed by increased excretion of I-125 labeled polyvinyl pyrrolidine in stool [6]. The histopathologic findings in the small intestine revealed edema and mononuclear cell infiltration in mucosa and mild dilatation of the lymphatic vessels. She responded well to oral prednisolone 60 mg/day in 8 weeks. Mok and Lau reported the case of a 54-year-old woman with primary Sjögren’s syndrome [7]. Hypoalbuminemia and increased alpha-1-antitrypsin clearance in stool was noted. Biopsy from UGI endoscopy and colonoscopy showed mild inflammatory infiltrations of the mucosa. This patient failed to respond to oral prednisolone 60 mg/day for 2 weeks initially, so oral cyclophosphamide was added, with clinical improvement. Our primary Sjögren’s syndrome patients with protein-losing gastroenteropathy had similar pathologic findings in biopsies and responded well to treatment with corticosteroids.

Tc-99m labeled albumin scintigraphy can locate the site of protein loss [12, 14], including low pH sites such as in the stomach (Fig. 1A). We followed the method of Divgi et al to diagnose protein-losing enteropathy using Tc-99m labeled albumin abdominal scintigraphy [12]. This scan can be completed rapidly within 6 to 24 hours, and the results correlate well with the results of alpha-1-antitrypsin clearance [12, 13]. In our patients, the decrease in tracer uptake in the gastrointestinal tract in follow-up Tc-99m labeled albumin abdominal scintigraphy paralleled the rise in serum albumin concentration and disappearance of peripheral edema. We previously reported the same finding in lupus patients with protein-losing enteropathy [15].

Biopsies from the gastrointestinal tract in our two patients revealed chronic mononuclear inflammatory infiltrations (Fig. 2). The histopathologic findings were similar to those in the two previously reported cases of primary Sjögren’s syndrome with protein-losing enteropathy [6, 7]. Lymphangiectasia [17, 18], venulitis [19], or vasculitis [20] reported in intestinal biopsy from protein-losing enteropathy associated with SLE, PSS, and RA were not found. These differences reflect the fact that pathophysiologic mechanisms might be different in various autoimmune protein-losing enteropathies.

Although the mechanisms of autoimmune protein-losing enteropathy remain unknown, there have been several proposed hypotheses according to pathologic findings. Tilburg et al suggested that increased pressure in the lymphatic system may be related to excessive intestinal protein loss in systemic sclerosis patients with intestinal lymphangiectasia [18]. Leakage of protein due to increased permeability of vessels and villi was suggested by Weiser et al, based on biopsy findings of venulitis and marked thickening of intestinal epithelial basement membrane in patients with SLE [19]. However, only mononuclear cell infiltrations and superficial erosion of villi were found in our biopsy samples. Excessive intestinal protein loss might be due to increased permeability of the mucosa under the effects of inflammatory prostaglandins and cytokines in Sjögren’s syndrome.

In summary, protein-losing gastroenteropathy may be the presenting manifestation of primary Sjögren’s syndrome. It should be emphasized that protein loss from the stomach cannot be detected by measurement...
of alpha-1-antitrypsin clearance in stool. Tc-99m labeled albumin scintigraphy is convenient and effective in establishing diagnosis, locating sites of protein loss, and monitoring treatment effect. Corticosteroids in sufficient doses can be considered as the main treatment of primary Sjögren's syndrome with protein-losing gastroenteropathy.

References