Protein-losing gastroenteropathy in a patient with concomitant systemic lupus erythematosus and Sjögren’s syndrome

Mizuna Eguchi⁠a, Nozomi Iwanaga⁠b,c, Kosuke Sakai⁠a, Tohru Michitsuiji⁠b, Yoshika Tsuchii⁠c, Chieko Kawahara⁠i, Hitomi Kobayashi⁠d, Yoshiro Horai⁠a,b,e, Takahiro Moria, Yasumori Izumia, Masahiro Itoe,f and Atsushi Kawakamig

1. Introduction

Protein-losing gastroenteropathy (PLGE) is a condition characterized by the loss of proteins into the gastrointestinal lumen, which results in hypoproteinemia and various physical manifestations such as edema, ascites, and pleural effusion [1]. PLGE is broadly categorized into primary and secondary PLGE; various connective tissue diseases (CTD) such as systemic lupus erythematosus (SLE) [2], Sjögren’s syndrome (SS) [3], and mixed connective tissue disease (MCTD) [4] are some of the reported underlying causes of secondary PLGE.

We herein describe a woman in her twenties who developed PLGE associated with SLE and SS.

2. Case Report

A woman in her 20s developed pyrexia, general malaise, and arthralgia in the summer, which was relieved by symptomatic therapy. Approximately one month later, she developed generalized edema accompanied with weight gain. She visited a neighborhood clinic where she was diagnosed with mild proteinuria. She was referred to our department because of suspected nephritic syndrome.

Medical interview revealed a history of photosensitivity, intermittent urticaria, and Raynaud’s phenomenon occurring in the winter season. She had also suffered from dry eye symptoms, for which she was prescribed eye drops at an ophthalmology clinic for about 1 year. Physical examination at admission showed alopecia, generalized edema, as well as erythema of the neck, arms, and limbs. No lymphadenomegaly or oral ulcers were detected. Any bowel symptoms such as abdominal pain and diarrhea were not observed. The results of laboratory investigations at admission were as follows: white blood cell count, 5100/μL (66.4% neutrophils, 24.0% lymphocytes, 7.4% monocytes, 0.4% basophils); hemoglobin, 11.7 g/dL; platelet count, 412,000/μL; total bilirubin, 0.2 mg/dL; aspartate aminotransferase, 22 1U/L; alanine aminotransferase, 121 1U/L; serum total protein, 4.8 g/dL; serum albumin, 0.9 g/dL; blood urea nitrogen, 6.6 mg/dL; serum creatinine, 0.41 mg/dL; total cholesterol, 306 mg/dL; C-reactive protein (CRP), <0.14 mg/dL; thyroid stimulating hormone, 1.343 μU/mL; free T4 level,
0.81 ng/dL; C3, 58 mg/dL; C4, 7 mg/dL, prothrombin activity, 110.1%; erythrocyte sedimentation rate, 62 mm/h. Test result for occult blood in urine was negative. Estimated urinary protein excretion was 0.15 g/d [urine protein/urine creatinine (g/gCr)]. Cellular casts were not detected in urine. She tested positive for antinuclear antibody (ANA) (×1280, speckled pattern) and anti-Sm antibody (10.6 U/mL), while tests for anti-ribonucleoprotein antibody (0.7 U/mL), anti-cardiolipin antibody IgG (<8 U/mL), anti-β2-glycoprotein-I antibody (<0.7 U/mL), lupus anticoagulant (dilute Russell’s viper venom time) (1.0), and anti-double-stranded DNA antibody (<10 U/mL) were negative. She tested positive for both anti-SS-A (>1200 U/mL) and anti-SS-B (>1000 U/mL) antibodies. Chest X-ray showed no abnormal findings such as cardiomegaly. Fluorescein staining test demonstrated prominent keratoconjunctivitis. Saxon’s test result was positive (0.75 g/2 min). Computed tomography scan revealed the thickening of walls of proximal small intestine, increased density of mesenteric fat and signs of mesenteric edema (Figure 1(A)). Mucosal edema extending from duodenum to jejunum was also identified on endoscopy (Figure 1(B)).

The diagnosis of SLE was established based on clinical manifestations (photosensitivity and alopecia), the detection of anti-Sm and antinuclear antibodies, and low blood complement levels; she qualified five of the Systemic Lupus International Collaborating Clinics Classification criteria for SLE [5]. She also fulfilled the 1997 American College of Rheumatology (ACR) classification criteria for SLE (qualified four of the 11 ACR criteria for SLE) [6]. The SLE disease activity index score at the time of diagnosis was 4. In addition, she was also diagnosed with SS based on the detection of anti-SS-A/SS-B antibodies and the findings of ocular staining, in accordance with the classification criteria of SS published by the ACR in 2012 [7]. The European League Against Rheumatism SS Disease Activity Index at the time of diagnosis of SS was 6. The generalized edema was considered to be caused by hypoproteinemia. Lupus nephritis was considered unlikely in the absence of any significant abnormalities in kidney function and in the presence of only modest proteinuria at admission (spontaneously resolved after admission); other potential causes such as heart failure, liver, and/or thyroid dysfunction were also unlikely, which necessitated further work-up of the patient for evaluating the possibility of PLGE. Colonoscopy results did not reveal mucosal erosions; however, adenomatous polyps were observed in the descending colon. Tc-(99m) albumin scintigraphy could not be performed; however, stool examination revealed α 1-antitrypsin clearance of 195 mL/d, which indicated the loss of protein into the intestinal lumen. Histopathological examination of jejunal biopsy specimen obtained under double balloon enteroscopy revealed interstitial mononuclear cell infiltration, mild dilatation of lymphatic vessels and mild villous atrophy due to inflammation (Figure 2).

Based on the findings of α 1-antitrypsin clearance and histopathology, PLGE was identified as the cause of hypoproteinemia and other associated symptoms, which was refractory to albumin infusions. Prednisolone (PSL) therapy (50 mg/d) was initiated, following which there was a rapid resolution of general edema. The administered dose of PSL was gradually reduced to 17.5 mg/d with no associated relapse; her serum albumin and C3 levels also increased. Although her dry eye symptoms had persisted, her serum immunoglobulin G (IgG) levels, which might have been related to the disease activity of SS, were declined after the start of PSL (Figure 3).

**Figure 1.** (A) Computed tomography scan: wall thickening of upper intestine, increased density of mesenteric fat and mesenteric edema are observed. (B) Intestinal endoscopy: mucosal edema is observed.
PLGE is a rare manifestation of SLE; in a study conducted by a Chinese group, approximately 3.2% of patients with SLE developed complication of PLGE [8]. Al-Mogairen described clinical characteristics of SLE-related PLGE, such as a predilection for Asian population and a relatively good prognosis [9]. In the present case, the patient responded to steroids, the dose of which could be decreased with no associated relapse. Despite there is no consensus as to how fast we can decrease steroid for PLGE, gradual decrease seems to be better since relapses of PLGE during a decrease of steroid are often observed. In the presented case, therefore, we decreased the dose of PSL by about 10% every week. Whereas this case has responded to PSL alone as of now, not a few cases relapse and require additional immunosuppressive therapy. In a previous study, 34% of patients responded to steroids alone, while the other patients required additional immunosuppressive

**Figure 2.** Histopathological examination of jejunal biopsy specimen showing interstitial mononuclear cell infiltration (A and B: hematoxylin and eosin staining) and mild dilatation of several lymphatic vessels (C: anti-podoplanin antibody staining). No signs of amyloid deposits are observed (D: periodic acid-Schiff staining).

**Figure 3.** Clinical course. Alb: albumin; PSL: prednisolone.
drugs, including cyclophosphamide, azathioprine, cyclosporine, and etanercept [9]. Sansinanea reported the case of a patient with refractory SLE-related PLGE who was resistant to steroids, cyclophosphamide, azathioprine, and cyclosporine; however, the patient responded to rituximab [10]. Although these immunosuppressants are effective for refractory PLGE, possibilities of adverse effects such as opportunistic infection have to be considered. Recently our group reported a case of PLGE with severe immunocompromised status, in which mizoribine was effective [11].

The patient in this case revealed positivity for anti-SS-A/SS-B-antibodies which are diagnostic markers of SS, and was thus diagnosed as a case of SS. While 68,483 cases of SS were identified in a Japanese nationwide study conducted in 2014 [12], only nine cases of SS complicated with PLGE have been reported in literature [11,13–15]. To the best of our knowledge, the case of only one Japanese patient with PLGE who had concomitant SLE and SS has been reported as a case report [14]. Chen et al. analyzed 44 patients with SLE-related PLGE and 88 patients with active SLE (control group), and found significantly higher frequency of anti-SS-A and anti-SS-B antibodies in the PLGE group. Further, the presence of anti-SS-A antibodies was an independent predictor of SLE complicated with PLGE, although the frequency of SS was not significantly different between the two groups. These findings suggest that anti-SS-A/SS-B-antibodies may induce injury to intestinal columnar epithelium cells as well as to the labial and salivary gland cells [2]. Although SS-related PLGE is considered to be responsive to steroid therapy [13], the case of PLGE associated with both SLE and SS reported by Kubo was refractory to immunosuppressants, including steroids, cyclosporine, and rituximab; octreotide was found to be effective in this patient [14]. The patient reported by Kubo had a past history of autoimmune hepatitis [which was relieved by PSL (30 mg/d)], elevated level of anti-double-stranded DNA antibodies, positivity for platelet-associated IgG and progressive thrombocytopenia (3.3 × 10⁴/μL at admission) as well as PLGE, which implied an increased activity of SLE and/or SS. Indeed, Kubo et al. concluded PLGE was not related to SS but SLE because dry symptoms and hypergammaglobulinemia were not observed when PLGE developed. On the contrary, our case revealed persistent sicca symptoms and relatively high serum IgG levels, which might have reflected disease activity of SS, were decreased after the initiation of immunosuppressive therapy. Based on the findings of this case, we speculated that patients with co-existing SLE and SS associated with PLGE and a high systemic disease activity level tend to be refractory and require aggressive immunosuppressive therapies. However, complication rates of PLGE in cases diagnosed SLE as well as SS have not been clarified. Studies with larger sample size of patients are required for clarifying optimal therapies for PLGE with concomitant SLE and SS.

In this report, we described a rare case of PLGE with concomitant SLE and SS. Although CTD has been recognized as an underlying cause of PLGE, the occurrence of PLGE in a patient with two concomitant CTDs has been rarely reported. Further investigations on more similar cases would help characterize the pathophysiology of CTD-related PLGE.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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