Protein-losing Gastroenteropathy Related to Mixed Connective Tissue Disease: A Case Report of a Successful Outcome and Literature Review

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Abstract

We herein report the case of a 44-year-old woman who developed protein-losing gastroenteropathy (PLGE) with hypoalbuminemia as the first manifestation of mixed connective tissue disease (MCTD). Albumin leakage from the stomach and intestinal tract was demonstrated by $^{99m}$Tc-labeled human serum albumin scintigraphy. The patient’s response to prednisolone therapy was insufficient; therefore, additional cyclosporin A (CsA) treatment was administered, and clinical remission was achieved. We concluded that although PLGE is a rare complication of MCTD, it may manifest as an initial clinical episode of MCTD. Furthermore, CsA can be a useful treatment option for refractory PLGE related to MCTD.

Key words: mixed connective tissue disease, protein-losing gastroenteropathy, hypoalbuminemia, $^{99m}$Tc-labeled human serum albumin scintigraphy, cyclosporin A

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Introduction

Protein-losing gastroenteropathy (PLGE) is a disorder characterized by a leakage of serum protein into the gastrointestinal tract, resulting in hypoproteinemia, which in turn leads to general edema, ascites, and pleural and pericardial effusions (1). Various disorders are known to be associated with PLGE; however, it is a rare complication of autoimmune diseases (2). Among these, systemic lupus erythematosus (SLE) has been recognized as a relatively common cause of PLGE, while mixed connective tissue disease (MCTD) is a rare cause (2, 3). We herein report a case of PLGE that presented as an initial clinical episode of MCTD. Successful treatment was achieved in this patient with cyclosporin A (CsA) administration, despite a deficient response to monotherapy with prednisolone (PSL). In addition, we review the previous literature on PLGE associated with MCTD.

Case Report

A 44-year-old Japanese woman with hypoalbuminemia and Raynaud’s phenomenon, finger stiffness, edema in the lower legs, and abdominal distension that had persisted for 1 year was admitted to our hospital. She had received albumin supplementation therapy at another hospital because she had experienced facial and conjunctival edema simultaneously with malaise and a periodic fever two months prior to admission. A physical examination revealed a body temperature of 37.3°C, submandibular and cervical lymphadenopathies, and swollen fingers with slight skin thickness on the distal portions and edematous findings on her face, bulbar conjunctiva, and lower legs.

A laboratory examination revealed decreased serum levels of total protein and albumin (4.1 and 1.3 g/dL, respectively), although indicators of the hepatic and renal function were within the normal range, and there was no significant protein leakage in the urine. An increase in the erythrocyte sedimentation rate (105 mm/h; normal, <10 mm/h) was

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shown, but the C-reactive protein levels were within the normal range (0.05 mg/dL; normal, <0.10 mg/dL). In addition, leukocytopenia (1,450/μL), lymphopenia (380/μL), and positive reactions to autoantibodies, namely anti-nuclear antibody (1:2,560, speckled pattern) and anti-U1-RNP antibody (550 U/mL; normal, <10 U/mL), were reported along with low levels of complement factors such as C₃ (49.0 mg/dL; normal, 86-160 mg/dL) and C₄ (14.9 mg/dL; normal, 17-45 mg/dL), and CH₅₀ (29.0 U/mL; normal, 30-53 U/mL). However, immune complex (C1q) was undetected in the serum. No positivity for other autoantibodies, including anti-neutrophil cytoplasmic antibodies specific for either myeloperoxidase (MPO-ANCA) or proteinase-3 (PR3-ANCA), anti-dsDNA, anti-Sm, anti-SS-A, anti-SS-B, anti-Scl-70, anti-centromere antibodies, and anti-RNA polymerase III antibody, was detected. Since the clinical and laboratory findings satisfied the diagnostic criteria proposed by the Japanese Ministry of Health and Welfare (4), the patient was diagnosed with MCTD. No malignancy, infection, or pulmonary hypertension was detected on a systemic assessment at admission, although computed tomography indicated bilateral interstitial fibrotic changes in the lower lung fields and ascites.

To clarify the cause of hypoalbuminemia, the gastrointestinal tract was examined. ⁹⁹mTc-labeled human serum albumin scintigraphy (⁹⁹mTc-HAS) showed accumulation of the radioisotope in the stomach after 2 and 4 hours and in the intestine after 6 and 24 hours (Fig. 1). On the basis of these findings, PLGE was diagnosed. Alpha-1-antitrypsin clearance (α₁-AT) could not be examined because of persistent constipation. An endoscopic examination revealed edematous findings in the gastric mucosa (Fig. 2) but no significant findings in the intestinal tract. A histopathological examination of the gastric wall tissue indicated infiltration of lymphocytes and plasma cells without lymphangiectasis or immune complex deposition (Fig. 3).

The hypoalbuminemia persisted even after PSL was administered at a dose of 50 mg daily, suggesting that PSL alone was incapable of suppressing the disease activity (Fig. 4). As a supplementary treatment, azathioprine (AZA) was administered; however, it was terminated because of skin eruptions and thrombocytopenia attributed to the use of

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**Figure 1.** ⁹⁹mTc-labeled human serum albumin scintigraphy showing 2-hourly images of albumin leakage prior to treatment (A-D) and after treatment (E-H). Radioactivity accumulation was detected in the stomach (white triangle) at 2 and 4 hours (A, B) and in the intestine (black arrow) at 6 and 24 hours (C, D) after injection of the radioisotope. No abnormal radioactivity was detected at any time point.
the drug. After recovery from this adverse event, the patient was administered CsA at a dose that ensured its blood trough concentration was between 100 and 150 ng/mL, together with methylprednisolone pulse therapy (1 g daily for 3 days). With this treatment, the albumin leakage detected by 99mTc-HAS disappeared (Fig. 1), and the serum albumin level returned to the normal range. The patient has shown sustained remission with a constant dose of CsA and a gradually decreasing dose of PSL.

Discussion

The present case showed leukocytopenia and lymphadenopathy as SLE-like findings along with sclerodactyly and pulmonary fibrotic changes as systemic sclerosis (SSc)-like findings, but general edema and abdominal distension ascribable to albumin leakage were eventually the principal symptoms determining the diagnosis of MCTD in this patient. SLE is a relatively common cause of PLGE associated with autoimmune disease, and the prevalence of PLGE with SLE has been reported to range from 0.94% to 7.5% (2, 5, 6). SSc is also recognized as a cause of PLGE (7, 8). In contrast, only seven reports of PLGE associated with MCTD have been described previously, of which two are in Japanese (3, 9-14) (Table).

Of these seven patients, whose cases have been summarized in Table, four concomitantly demonstrated symptoms associated with PLGE when diagnosed with MCTD, suggesting that PLGE can manifest as the initial episode of MCTD. All patients showed peripheral edema, and six also had ascites and pleural and/or pericardial effusion. Abdominal symptoms such as pain or distension were only found in three of the patients. Thus, it appears that regardless of abdominal symptoms, PLGE should be suspected in MCTD unless other causes of hypoalbuminemia, such as hepatic dysfunction and nephritis, are detected.

To establish the diagnosis of PLGE and monitor the efficacy of treatment, α1-AT and 99mTc-HAS are commonly used. The latter is especially useful for detecting the location of albumin leakage (2, 6, 15). On reviewing PLGE related to SLE, the small intestine seems to be the most common site of albumin leakage, while the stomach is a rare site, with a leakage frequency of up to 9%, as determined using 99mTc-HAS (2, 5). Interestingly, the stomach was involved as the target organ in the present case and in another case (14), although albumin leakage into the intestine has been reported in many previous patients with MCTD who underwent 99mTc-HAS (12-14). In the present patient, an endoscopic examination of the gastrointestinal tract showed no significant visible impairment, such as inflammatory colitis. Furthermore, the significant findings on 99mTc-HAS led to the decision regarding the site to biopsy for the histopa-
Figure 4. The clinical course of the patient after administration of prednisolone (PSL). *Skin eruptions and thrombocytopenia ascribable to the adverse event of azathioprine (AZA). mPSL: methylprednisolone pulse therapy, CsA: cyclosporin A.
The authors state that they have no Conflict of Interest (COI).

Clinical experience regarding PLGE to clarify the details of this disease.

### Table. Review of Cases of PLGE Related to MCTD.

| Reference No. | age/sex | Clinical presentation associated with PLGE                      | Alb (g/dL) | Definitive diagnosis | Endoscopic findings | Histological findings | Treatment | Outcomes                  |
|--------------|---------|-----------------------------------------------------------------|------------|----------------------|---------------------|----------------------|-----------|---------------------------|
| 9            | 37/F    | ankle and sacral edema, abdominal pain, loose bowel motions, pericardial effusion | 1.8        | chronic-chloride test | ulcerative esophagitis | n.s.                 | PSL       | relapse after stopping PSL |
| 3            | 26/F    | leg edema, pericardial effusion, pleural effusion, ascites     | 1.7        | PVP test             | n.s.                | mucosal edema, lymphangiectasis | PSL       | remission                 |
| 10           | 59/F    | palpebral edema, dyspnea, pleural effusion, ascites             | 2.3        | α1-AT                | n.s.                | n.d.                 | mPSL, PSL, IVCY | remission                 |
| 11           | 35/F    | severe edema in all four extremities                           | 1.2        | α1-AT                | chronic gas troduodenitis | lymphocytic infiltration | PSL, IVCY, AZA | remission                 |
| 12           | 52/F    | anasarca, epigastralgia, diaphragm, abdominal distension        | 2.5        | ⁹⁹mTc-HAS            | thickened fold of jejum and duodenum | mucosal edema, lymphangiectasis | PSL       | relapse during tapering PSL |
| 13           | 47/M    | conjunctival edema, dyspnea, pleural effusion, ascites          | 2.6        | ⁹⁹mTc-HAS, α1-AT     | n.s.                | lymphocytic infiltration, immune complex deposit | mPSL, PSL, IVCY | relapse during tapering PSL |
| 14           | 58/F    | leg edema, abdominal distension, pleural effusion, ascites     | 1.5        | ⁹⁹mTc-HAS, α1-AT     | duodenal and ileal mucosal edema | mucosal edema, lymphocytic and plasmocytic infiltration | PSL       | remission                 |
| Present case | 44/F    | conjunctival edema, eye lid edema, leg edema, abdominal distension, ascites | 1.3        | ⁹⁹mTc-HAS            | gastric mucosal edema | lymphocytic and plasmocytic infiltration | mPSL, PSL, CsA, (AZA) | remission                 |

PLGE: protein-losing gastroenteropathy, n.s.: not significant findings, Alb: serum albumin, PVP test: excretion of ¹²⁵I-labelled polyvinyl pyrrolidine, PSL: prednisolone, α1-AT: α1-antitrypsin clearance, n.d.: not demonstrated, mPSL: methylprednisolone pulse therapy, IVCY: intravenous cyclophosphamide, AZA: azathioprine, ⁹⁹mTc-HAS: ⁹⁹mTc-labeled human serum albumin scintigraphy 

†point at which PLGE was detected after the diagnosis of MCTD, ††AZA was terminated because of adverse events.
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