Successful Long-term Treatment with Cyclosporin A in Protein Losing Gastroenteropathy

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Abstract

Protein-losing gastroenteropathy (PLG) can occur as a manifestation of various diseases including autoimmune disorders, and optimal therapy of these underlying diseases may be the only effective remedy for PLG. In the present report, we describe a case of a 54-year-old woman with PLG associated with an autoimmune disease, presumably CREST syndrome. She failed to respond to steroid treatment. Subsequently, cyclosporine was initiated, which resulted in a rapid recovery. The patient was successfully treated with low-dose cyclosporine for five years. There has not been, to our knowledge, any report of PLG successfully treated with cyclosporine. Cyclosporine therapy may be effective not only in inducing but also in maintaining complete remission in patients with autoimmune-associated PLG, especially refractory or intolerable to steroids and/or immunosuppressive therapies. (Internal Medicine 43: 397–399, 2004)

Key words: protein-losing gastroenteropathy, autoimmune disease, CREST syndrome cyclosporine

Introduction

Protein-losing gastroenteropathy (PLG) is a comparatively rare condition resulting from increased mucosal microvascular permeability, inflammation, disordered mucosal cell structure, mucosal desquamation, or increased lymphatic hydrostatic pressure. It has been described in association with a number of diseases including allergic gastroenteropathy, inflammatory bowel disease, intestinal lymphangiectasia, thoracic duct obstruction, sprue, Ménétrier disease and GI tract infections, amyloidosis and malignances. Also, PLG is a well-recognized entity in autoimmune diseases, such as systemic lupus erythematosus and systemic sclerosis (1–3). Prednisolone (PSL) is a classic first-line therapy for autoimmune-associated PLG and achieves complete remission in most patients. In case of failure, more aggressive immunosuppression may increase the overall response, but these therapies increase the risk of severe complications. Here, we present a first patient with PLG successfully and safely treated with long-term use of low-dose cyclosporine (CsA).

Case Report

A 54-year-old Japanese woman who had been diagnosed with hypothyroidism six months earlier, was admitted to our department with edema in May 1994. Her family history was noncontributory. Physical examination revealed marked systemic edema. The serum albumin was 2.1 g/dl. Upper GI endoscopy revealed no abnormality. The presence of protein loss in the gut was confirmed by an elevated α1-antitrypsin clearance (94 ml/day; normal, 0.4–13) and Indium-111-chloride scintigraphy showing abnormal radioactivity in the upper GI tract. Thus, the diagnosis of PLG was made. She was treated with oral PSL and high-dose intravenous corticosteroids, which resulted in no improvement. After a high protein and fat-restricted diet with intravenous administration of albumin was initiated for PLG, her clinical symptom was relieved. After discharge, she continued to have asymptomatic mild hypoalbuminemia despite diet therapy with intravenous administration of mixed amino acid preparations. In March 1996, however, she developed worsening generalized edema and was admitted to our department again. On admission, physical examination revealed marked...
anasarca. Laboratory examination showed leucocytes 5,500/μl; hemoglobin 13.2 g/dl; platelets 342×10^3/μl; albumin 1.3 g/dl; total protein 4.1 g/dl; IgA 505 mg/dl (normal, 150–310); IgM 499 mg/dl (80–180); IgG 942 mg/dl (800–1,800); C3 43 mg/dl (60–120); C4 13 mg/dl (20–50); TSH 9.7 μU/ml (0.45–3.46); FT3 2.2 pg/ml (2.47–4.34); FT4 0.74 ng/dl (0.97–1.79); anti-thyroglobulin 643.1 U/ml (<0.3); anti-thyroid peroxidase antibodies 72.0 U/ml (<0.3); antinuclear antibody 1/1,280 (discrete pattern); anti-single-strand DNA antibody 1/100; antimitochondrial antibody 1/20; antinucleomere antibody 1/1,280; erythrocyte sedimentation rate 123 mm/h. Anti-RNP antibodies, rheumatoid factors and LE cell preparation were negative. The urine was negative for protein. Liver and renal function tests were normal. A chest radiograph showed a normal cardiovascular shadow and mild pleural effusion. Ultrasonography and computed tomographic scanning of the abdomen revealed soft-tissue edema, massive ascites, and normal liver, spleen, and pancreas. A barium radiographic series of the GI tract revealed no abnormalities. Indium-111-chloride scintigraphy confirmed loss of large amount of protein into the stomach and duodenum (Fig. 1). Upper and lower GI endoscopy showed no macroscopic abnormality, but several biopsy specimens taken from the duodenum revealed interstitial edema and mild inflammatory cell infiltration without lymphangiectasia and vasculitis. Immunohistological studies demonstrated deposits of IgG, C3 and C4 in the lamina propria of the duodenum (Fig. 2). The patient did not improve with a high protein and low-fat diet with intravenous administration of albumin. Because an autoimmune mechanism was suspected to be involved in the pathogenesis of PLG, oral PSL (30 mg/day) was then initiated, without improvement. After obtaining an informed consent, oral CsA (200 mg/day) was given, and her clinical symptoms and hypoproteinemia gradually became alleviated. The improvement was confirmed in terms of 111-indium chloride scintigraphy. After discharge, CsA at a dosage of 3 mg/kg/day (150 mg/day) was continued orally for five years, with complete remission and no side-effects. In August 2001, however, CsA was discontinued because of hypertension caused by an adverse effect of CsA. The remission has continued until the present, December 2002.

**Discussion**

PLG is a comparatively rare condition, and can occur not only as an idiopathic disorder, but also as a manifestation of various diseases including autoimmune disorders. In some patients PLG could be the initial manifestation of an autoimmune disorder. However, autoimmune disorders can not necessarily be diagnosed at the time of the onset of PLG (1). Indeed, the present patient did not show any typical symptoms suggestive of autoimmune disorders, although the laboratory findings suggested the presence of an autoimmune disorder. Several mechanisms for autoimmune disease-associated PLG have been postulated. These include vasculitis, intestinal lymphangiectasia (3), and increased...
capillary permeability caused by activated immune deposits (4,5). In the present patient, immunohistological examination showed deposits of IgG, C3 and C4 in the basement membrane underlying epithelial cells and the walls of mucosal capillaries of the duodenum. These findings suggest that immune deposits involve in an autoimmune disease can lead to PLG in the present patient.

Corticosteroids have been effective for the treatment of autoimmune-associated PLG (1,6–8). However, PLG in the present patient was not improved by steroid treatment. In those who fail to respond to such treatment, more aggressive immunosuppression may increase the overall response, but these therapies may increase the risk of severe complications. Recently, CsA has been increasingly applied to the treatment of patients with autoimmune diseases, with varying degrees of success. In our case, long-term CsA therapy at a low dose was effective for PLG. The safety of long-term immunosuppression with CsA in organ transplantations and autoimmune disorders (9) has been reported. CsA is an immunomodulatory drug, which acts selectively on T cells. This immunosuppressant does not affect hematopoiesis and immunity mediated by neutrophils or macrophages, leading to the decreased risk of secondary infection compared with other immunosuppressive agents. Therefore, rapid alleviation of hypoalbuminemia in this patient by CsA suggests that T cell-mediated inflammation is important in the pathogenesis of certain types of PLG.

An elevation of anticentromere antibodies, as observed in the present patient, has been reported in a high percentage of patients with limited cutaneous scleroderma (CREST syndrome) and rarely in other autoimmune diseases. But our patient has not shown any of the typical symptoms or signs suggestive of autoimmune diseases as well as CREST syndrome (calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia), although long-term CsA therapy for PLG might prevent the progression of the disease. During the treatment with CsA, the patient also experienced an improvement of laboratory findings on autoimmune disease. It is reported that typical symptoms of CREST syndrome began about 4 years after anticentromere antibodies were found (10), and that CsA could be effective to inhibit the progression of the syndrome in the initial phases of scleroderma (11). Based on these findings, CREST syndrome in the initial phase was suspected to be involved in this patient. There has been no report on PLG associated with CREST syndrome, based on MEDLINE search. In lupus-associated PLG, relapse was reported to occur in at least 30% of cases in which steroids and/or immunosuppressive drugs were tapered or withdrawn (1). In the present case, during 5 years of the treatment with low-dose CsA, no relapse and side-effects appeared, and the remission has continued 17 months after discontinuation of CsA. Low-dose CsA treatment for more than 3 years is reported to be effective to stabilize disease activity in scleroderma patients (9). Therefore, long-term suppression of disease activity with CsA, especially in non-progressive phase of autoimmune disease, may be important to maintain complete remission of PLG caused by an autoimmune mechanism.

In conclusion, we present a first case report of a patient with autoimmune-associated PLG showing a good and long-term therapeutic effect of low-dose CsA. This experience suggests that a T cell-mediated autoimmune mechanism could be involved in the pathogenesis of certain types of PLG. A trial of CsA, therefore, is worthy of consideration for patients with autoimmune-associated PLG refractory or intolerable to steroids and/or immunosuppressive therapies.

**References**