A case of systemic lupus erythematosus presenting with protein-losing enteropathy

Protein kaybettiren enteropati ile seyreden bir sistemik lupus eritematozus vakası

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We report an unusual case of systemic lupus erythematosus presented with protein-losing enteropathy. A 24-year-old girl was referred to our hospital with generalized edema, thrombocytopenia, hypoalbunemia, hypercholesterolemia, hypocomplementemia, antinuclear antibody (ANA) (speckled pattern) and anti-SSA/Ro positivities, and elevated CA125 antigen appeared in the blood examination. On the radiological studies, she had mild pleural effusion and moderate ascites which were transudate. A diagnosis of protein-losing enteropathy was made on the basis of increased ⁹⁹mTc-labelled human immunoglobulin scintigram showing abnormal radioactivity. Endoscopic gastric, duodenal and jejunal biopsies showed chronic inflammation, but vasculitis and immune complex deposition findings were not present. Renal biopsy revealed no definitive findings of lupus nephritis. By the administration of corticosteroids, hypoalbuminemia began to improve, but steroid doses were decreased due to steroid-induced myopathy. Temporary hemiparesis and facial paralysis developed in the patients' follow up. Her cranial magnetic resonance imaging revealed chronic ischemia, and the patient was considered to have neurological involvement due to systemic lupus erythematosus. Protein-losing enteropathy and other symptoms then improved dramatically after monthly intravenous cyclophosphamide (three times) combined with oral low-dose corticosteroids. The combination of azathioprine and low-dose steroids was used as maintenance medication. Although about 30 protein-losing enteropathy-associated systemic lupus erythematosus cases have been reported, the patients having initial symptoms as protein-losing enteropathy are rare in the literature. Protein-losing enteropathy-associated systemic lupus erythematosus cases probably represent a subgroup of systemic lupus erythematosus, the characteristics of which are hypocomplementemia, protein-losing enteropathy, ANA positivity showing speckled pattern and anti-ds DNA negativitys. In the patients with systemic lupus erythematosus with edema and hypoalbuminemia without renal protein loss, protein-losing enteropathy-associated systemic lupus erythematosus should be kept in mind.

Key words: Protein losing enteropathy, systemic lupus erythematosus

Protein kaybettiren enteropati ile başvuran sızdırıbs sistemik lupus eritematozus vakası sunulmaktadır. 24 yaşında bayan hasta, jeneralize ödem tablosu ve kan tıtkıklarında saptanan trombositopeni, hypoalbümüminemi, hiperkolesterolemi, hipo-complementemini, ANA (noktalı paternde) ve anti-SSA/ Ro pozitifiği ve yüksek CA125 antijeni seviyeleri ile hastaneye kabul edildi. Radyolojik tıtkıklarında hasıf bir plevral effüzyonu ve transüda niteliğinde olan orta düzeyde asısti mevcuttu. Arımış anormal aktivite gösteren ⁹⁹mTe-iflaretli insan immunoglobulin scintigram sağlayarak anormal aktivite gösteren ⁹⁹mTc- iflaretli insan immunoglobulin scintigramda anormal aktiviteyi gösteren ⁹⁹mTc- iflaretli insan immunoglobulin scintigramda anormal aktiviteyi gösteren ⁹⁹mTc- labelled human immunoglobulin scintigram showing abnormal radioactivity. Endoscopic gastric, duodenal and jejunal biopsies showed chronic inflammation, but vasculitis and immune complex deposition findings were not present. Renal biopsy revealed no definitive findings of lupus nephritis. By the administration of corticosteroids, hypoalbuminemia began to improve, but steroid doses were decreased due to steroid-induced myopathy. Temporary hemiparesis and facial paralysis developed in the patients' follow up. Her cranial magnetic resonance imaging revealed chronic ischemia, and the patient was considered to have neurological involvement due to systemic lupus erythematosus. Protein-losing enteropathy and other symptoms then improved dramatically after monthly intravenous cyclophosphamide (three times) combined with oral low-dose corticosteroids. The combination of azathioprine and low-dose steroids was used as maintenance medication. Although about 30 protein-losing enteropathy-associated systemic lupus erythematosus cases have been reported, the patients having initial symptoms as protein-losing enteropathy are rare in the literature. Protein-losing enteropathy-associated systemic lupus erythematosus cases probably represent a subgroup of systemic lupus erythematosus, the characteristics of which are hypocomplementemia, protein-losing enteropathy, ANA positivity showing speckled pattern and anti-ds DNA negativitys. In the patients with systemic lupus erythematosus with edema and hypoalbuminemia without renal protein loss, protein-losing enteropathy-associated systemic lupus erythematosus should be kept in mind.

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Anahat kelimeler: Protein kaybettiren enteropati, sistemik lupus eritematozus

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INTRODUCTION

Protein-losing enteropathy (PLE) represents a variety of abnormalities resulting in the loss of plasma proteins from the gastrointestinal tract. The mechanisms for the gastrointestinal protein loss include lymphatic obstruction, mucosal disease with erosions, or ulcerations. Mucosal disease without erosions or ulcerations may also be associated with protein loss. The most common presenting symptom is peripheral edema secondary to decreased plasma oncotic pressure. A more severe hypoalbuminemia causes pleurisy, pericarditis and ascites. If PLE is related with other systemic diseases such as congestive heart failure, amyloidosis, connective tissue disease, or protein dyscrasias, the clinical presentation may be that of primary disease process (1).

The incidence of common gastrointestinal symptoms due to SLE was reported to be very low. Gastrointestinal manifestations of systemic lupus erythematosus (SLE) include mouth ulcers, dysphagia, anorexia, nausea, vomiting, hemorrhage and abdominal pain. Hypoalbuminemia in SLE is most commonly due to excessive loss through the kidney causing nephrotic syndrome. It can rarely be due to a PLE (1-14). PLE has rarely been reported in patients with SLE, and it might be the initial manifestation of the disease (8, 13, 15-19). Herein, we report a patient with SLE who presented with PLE.

CASE REPORT

A 24-year-old Caucasian girl was referred to us with the complaint of swelling of the legs, abdomen and face, mild but not localized, widespread abdominal pain, and diarrhea two or three times a day without bleeding. Her symptoms started two months ago but she was previously healthy. She had gained 4 kg and had had no menstruation for the last three months. The family history was non-contributory, and a review of systems was negative for rheumatologic symptoms including malar rash, photosensitivity, arthritis, Raynaud’s phenomenon, dry mouth and dry eyes. The physical examination showed anasarca with the evidence of ascites, mild bilateral pleural effusion, and edema in her eyelids and lower extremities. She had live-doo reticularis on the lower and upper extremities. Her gynecologic examination was normal and secondary amenorrhea was thought to be due to hypoalbuminemia. Laboratory investigations revealed a white blood cell of 3.9X10^9/L with normal differential, hemoglobin 12.5 g/dl, hematocrit 37.3%, platelets 79X10^9/L, and normal C-reactive protein, but erythrocyte sedimentation rate was 78 mm/hour. Urine analyses were normal. 24-hour urine protein collections were 150-270 mg/24 hours (normal, 50-100 mg/24 hours), but all the measures were lower than 500 mg/24 hours. On the microbiological examinations of the feces, no pathogen bacteria, parasites or blood was found. Alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, lactate dehydrogenase, creatinine phosphokinase, serum electrolytes, amylase and lipase were normal, but she was found to have an obviously decreased serum albumin at 1.0 g/dl (normal, 3.5-5.2 g/dl) and markedly increased total cholesterol at 454 mg/dl (normal, 120-200 mg/dl), low density lipoprotein (LDL)-cholesterol at 349 mg/dl (normal, 70-130 mg/dl), and triglyceride at 304 mg/dl (normal, 60-165 mg/dl). On protein electrophoresis, the serum albumin markedly decreased at 18.6% (normal, 49.7-64.4%), and alpha-1 globulin and alpha-2 globulin increased at 10.2% and 48%, respectively (normal, 4.8-10.1% and 8.5-15.1%, respectively) with normal immunoglobulins. Complements (C) C3 and C4 were low at 0.045 g/L and 0.05 g/L, respectively (normal, 0.9-2 and 0.1-0.4, respectively). Serological tests for hepatitis B and C virus, human immunodeficiency virus (HIV), cytomegalovirus, mumps and rubella were all negative. Her thyroid function tests were normal. The antinuclear antibody (ANA) was positive at a titer of 1:1000 showing a speckled pattern (++, positive) and anti-extractable nuclear antigen (ENA) antibodies were positive for SSA/anti-Ro. The anti-double-stranded DNA, anti-Sm, rheumatoid factor, antineutrophil cytoplasmic antigen (ANCA) and all anti-phospholipid antibodies were negative. The serum levels of CA125 and CA15.3 antigens were markedly increased at 3906 U/ml (normal, 0-35) and 70.81 U/ml (0-25), respectively. The characteristic feature of the ascites fluid was transudate. Radiological studies revealed bilateral effusions on chest radiographs and moderate ascites on ultrasound. Renal and portal vein Doppler ultrasounds were normal. An abdominal computed tomography appeared normal, except for a mild diffuse wall thickening in the duodenal, jejunal and ileal segments and ascites. All small intestine segments had edematous images and thickened folds.
with multiple wall irregularities on the small-bowel passage graphs. Endoscopic examination showed noticeable mucosal edema and hyperemia on the gastric, duodenal and jejunal mucosa. Biopsy specimens obtained from the antrum and duodenum revealed submucosal edema and villous atrophy with inflammatory infiltrates, but a dilatation in the venules and lymphatics was not observed, and vasculitis was not found. Immunofluorescence studies showed no definitive stainings for IgG, IgM, C3 and C4. Biopsy specimens from the descending portion of the duodenum showed chronic inflammatory cell infiltration. A 99mTc-labelled human immunoglobulin (HIG) scintigram showed extravasation in the small bowel (Figure 1). In the capsule endoscopy, distal small intestinal mucosa and in part the colon mucosa had patchy type hyperemia and small millimetric ulcerations (Figure 2), but these were non-diagnostic.

A renal biopsy was performed for the diagnosis of lupus nephritis, but biopsy specimens showed no obvious proliferation of mesangial matrix and cells, and in an immunofluorescence study, no IgG, IgA, IgM, C3 or C4 deposits were seen. The Doppler ultrasonographic examination of the portal system was normal and echocardiography appeared normal except for minimal pericarditis.

During her follow up, polyarthritis including bilateral elbows, wrists and the second and third metacarpophalangeals and a mild malar rash developed and photosensitivity was observed. A diagnosis of SLE presenting with initially primary PLE was made. The initial treatment consisted of furosemide, albumin infusions, anti-hyperlipidemics, low-dose aspirin and high-protein diet. Prednisolone treatment was started with a dose of 56 mg/day (1 mg/kg/day), but steroid doses were decreased to

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Prednisone 56-40 mg/day</th>
<th>1st dose cyclophosphamide + prednisolone 16 mg/day</th>
<th>2nd dose cyclophosphamide + prednisolone 8 mg/day</th>
<th>3rd dose cyclophosphamide + prednisolone 8 mg/day</th>
<th>Azathioprine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dl)</td>
<td>1.0</td>
<td>1.8</td>
<td>2.3</td>
<td>2.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>454</td>
<td>444</td>
<td>374</td>
<td>283</td>
<td>221</td>
</tr>
<tr>
<td>CA125 (U/L)</td>
<td>3906</td>
<td>2364</td>
<td>1935</td>
<td>855</td>
<td>144.3</td>
</tr>
<tr>
<td>CA15.3 (U/L)</td>
<td>70.87</td>
<td>68.31</td>
<td>64.66</td>
<td>58</td>
<td>28</td>
</tr>
</tbody>
</table>

Table 1. Patients’ treatments and course of serum albumin, total cholesterol, CA125 and CA15.3 levels
16 mg/day because of a steroid-induced myopathy 30 days later. Meanwhile, temporary hemiparesis and facial paralysis developed in the patient’s follow up. Her cranial magnetic resonance imaging revealed chronic ischemia in the bilateral periventricular white substance, left centrum semiovale and right lentiform nucleus. A neurological involvement due to SLE was considered and pulse iv cyclophosphamide (850 mg/month with mesna, three times) and a low-molecular-weight heparin were administered. At the end of the third dose, the levels of cyclophosphamide, albumin, cholesterol and CA125 were within normal range (Table 1). She then continued azathioprine and low-dose aspirin on her own, and she has had no recurrence for six months and her menstrual cycles returned to normal.

DISCUSSION

The positive findings on a 99mTc-labelled HIG scintigram confirmed the suspicion of protein loss into the gastrointestinal tract in the patient. 99mTc-labelled HIG has been used instead of 123I-labelled human albumin scintigram in our laboratory. The cause of PLE is unknown, but several theories have been postulated. One is non-necrotizing vasculitis of mesenteric/intestinal vessels because they give rise to increased intestinal vascular permeability to protein. Although intestinal venulitis has been described in one patient by Weiser et al., no vasculitis was demonstrated in the full thickness jejunal biopsies in any of the other patients (23). We also did not show vasculitis on jejunal and duodenal biopsies of the patient. Another theory is complement conversion with associated vasodilatation and increased vascular permeability. Low levels of serum complement occurred in all reported cases, but immune complex deposition did not appear in any of the biopsy specimens. Serum complements (C3 and C4) were low, but we also did not show immune complex deposition in the duodenal and jejunal biopsies. The last theory, of steroid responsive lymphangiectasia, has been postulated by Chase et al. (17). Lymphangiectasia was seen on an open ileal biopsy in a patient; however, it has not been confirmed by the others. Intestinal lymphangiectasia was not seen in the biopsy specimens of our patient. Improvements in all PLE-associated SLE cases in the literature were observed with immunosuppressive drugs including corticosteroid, azathioprine and cyclophosphamide. It may also be suggested that a complement-associated cytotoxic reaction contributes to tissue destruction by autoantibodies, excessive immune complex formation and possible roles of cytokines, and thus they may cause a capillary hyperpermeability (1).

The patients with PLE-associated SLE usually respond well to corticosteroid treatments. Cases with resistance to corticosteroid are rare. This case also responded well to corticosteroids, however, the steroid doses were decreased to small doses and pulse cyclophosphamide treatment was added to her medication due to a development of steroid-induced myopathy and a central nerve involvement. The combination of azathioprine and low-dose steroid was then used as maintenance medication.

Consequently, PLE-associated SLE cases probably represent a subgroup of SLE, the characteristics of which are hypocomplementemia, PLE, ANA positivity showing speckled pattern and anti-ds DNA negativity. In the patients with SLE having edema and hypoalbuminemia without renal protein loss, PLE-associated SLE should be kept in mind.

REFERENCES