Turk J Gastroenterol 2006; 17 (3): 226-230

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

Protein kaybettiren enteropati ile seyreden bir sistemik lupus eritematozus vakası

Nuran TÜRKÇAPAR[1], Nil ÖZYÜNCÜ[2], Kubilay ÇINAR[3], Arzu ENSARİ[4], Özlem KÜÇÜK[5], Ramazan İDİLMAN[3], Neval DUMAN[6], Ali ÖZDEN[3]

Departments of Clinical [1]Immunology and Rheumatology, [2]Cardiology, [3]Gastroenterology, [4]Pathology, [5]Nuclear Medicine, [6]Nephrology, Ankara University, School of Medicine, Ankara

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, hypoalbuminemia, 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 ^{99m}Tc-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 negativities. 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 sıradışı bir sistemik lupus eritematozus vakası sunulmaktadır. 24 yaşında bayan hasta, jeneralize ödem tablosu ve kan tetkiklerinde saptanan trombositopeni, hipoalbüminemi, hiperkolesterolemi, hipokomplementemi, ANA (noktalı paternde) ve anti- SSA/Ro pozitifliği ve yüksek CA125 antijen seviyeleri ile hastaneye kabul edildi. Radyolojik tetkiklerinde hafif bir plevral effüzyonu ve transüda niteliğinde olan orta düzeyde assiti mevcuttu. Artmış anormal aktivite gösteren ^{99m}Tc- işaretli insan immunoglobulin sintigrafisine dayanarak protein kaybettiren enteropati tanısı konuldu. Gastrik, duedonal ve jejunal bölgelerden alınan endoskopik biyopsi sonuçları kronik inflamasyon ile uyumlu geldi, ancak vaskülit veya immün kompleks depolanma bulgusuna rastlanmadı. Renal biyopsi lupus nefriti lehine tanımlayıcı bir bulgu vermedi. Kortikosteroid kullanımı ile beraber hipoalbüminemide düzelme başladı, ancak steroidin indüklediği miyopati nedeniyle doz azaltıldı. Hastanın takibinde geçici hemiparezi ve fasyal paralizi gelişti. Kraniyel manyetik rezonans görüntülemesi kronik iskemi ile uyumlu idi ve hastada sistemik lupus eritematozusiye bağlı nörolojik tutulum düşünüldü. Daha sonrasında, oral düşük doz kortikosteroide eklenen ayda üç kez intravenöz siklofosfamid ile beraber protein kaybettiren enteropati ve diğer semptomlarda dramatik bir düzelme sağlandı. Azotioprin ve düşük doz steroid kominasyonu idame tedavisi olarak kullanıldı. Şimdiye kadar protein kaybettiren enteropati ile ilişkili sistemik lupus eritematozus vakası olarak otuz vaka bildirilmesine rağmen, başvuru semptomu olarak protein kaybettiren enteropati literatürde oldukça nadirdir. Protein kaybettiren enteropati ile ilişkili sistemik lupus eritematozus vakaları büyük bir ihtimalle hipokomplementemi, protein kaybettiren enteropati, noktalı paternde ANA pozitifliği ve anti-ds DNA negatifliği ile prezente olan sistemik lupus eritematozusun bir alt grubuna dahil olmaktadır. Ödem ve renal protein kaybı olmadan hipoalbüminemi ile başvuran sistemik lupus eritematozus hastalarında protein kaybettiren enteropati ile ilişkili sistemik lupus eritematozus akılda tutulmalıdır.

Anahtar kelimeler: Protein kaybettiren enteropati, sistemik lupus eritematozus

Address for correspondence: Nuran TÜRKÇAPAR
4. Sokak 22/50 Manolya Apt. Söğütözü, Ankara, Turkey
Phone: +90 312 284 88 68 • Fax: +90 312 466 26 76
E-mail: nurant@tr.net

Manuscript received: 10.10.2005 **Accepted:** 24.11.2005

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 noncontributory, 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 livedo 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, anti-neutrophil 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 ^{99}mTc-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.

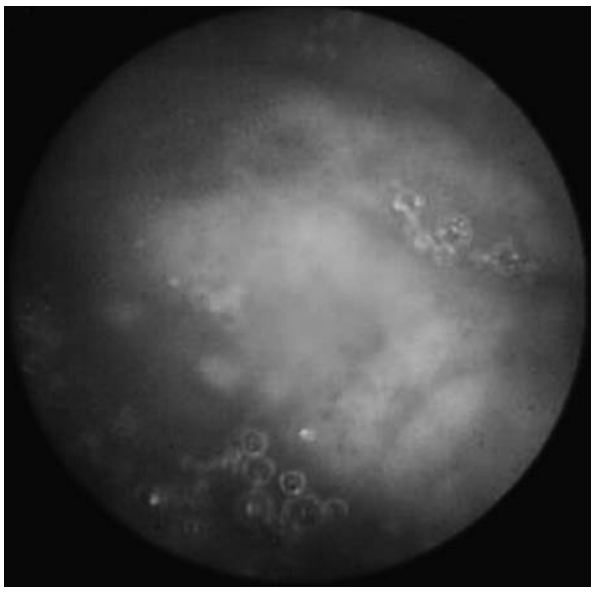

Figure 2. Capsule endoscopy showing distal small intestinal mucosa with patchy type hyperemia and small millimetric ulcerations

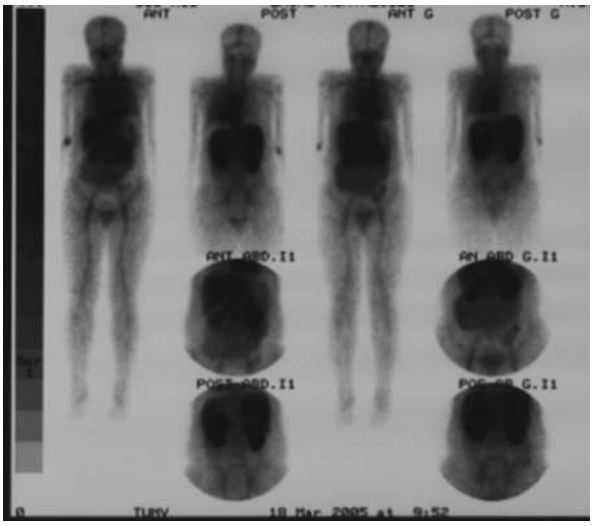

Figure 1. ^{99m}Tc-human serum immunoglobulin (HIG) scintigram shows protein loss from duodenal and jejunal segments. The arrows indicate the sites where leakage occurred

A renal biopsy was performed for the diagnosis of lupus nephritis, but biopsy specimens showed no obvious proliferation of mesengial 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 1. Patients' treatments and course of serum albumin, total cholesterol, CA125 and CA15.3 levels

	Pretreatment	Prednisone 56-40 mg/day	1st dose cyclophosphamide + prednisolone 16 mg/day	2nd dose cyclophosphamide + prednisolone 8 mg/day	3rd dose cyclophosphamide + prednisolone 8 mg/day	Azathioprine + prednisolone 8 mg/day
Albumin (g/dl)	1.0	1.8	2.3	2.7	3.1	3.6
Total cholesterol (mg/dl)	454	444	374	283	221	208
CA125 (U/L)	3906	2364	1935	855	144.3	30.39
CA15.3 (U/L)	70.87	68.31	64.66	58	28	12

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 ^{99m}Tc-labelled HIG scintigram confirmed the suspicion of protein loss into the gastrointestinal tract in the patient. ^{99}mTc-labelled HIG has been used instead of ^{99}mTc-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

1. Sultan SM, Ioannou Y, Isenberg DA. A review of gastrointestinal manifestations of systemic lupus erythematosus. Rheumatol 1999; 38: 917-32.
2. Tsutsumi A, Sugiyama T, Matsumura R, et al. Protein-losing enteropathy associated with collagen diseases. Ann Rheum Dis 1991; 50: 178-81.
3. Sunheimer RL, Finck C, Mortazavi S, et al. Primary lupus-associated protein-losing enteropathy. Ann Clin Lab Sci 1994; 24: 239-42.
4. Wood ML, Foulds IS, French MA. Protein losing enteropathy due to systemic lupus erythematosus. Gut 1984; 25: 1013-5.
5. Hirabayashi Y, Saito S, Makeshita MW, et al. Mononeuritis multiplex, protein-losing gastroenteropathy, and choroidopathy seen together in a case of systemic lupus erythematosus. Mod Rheumatol 2003; 13: 265-9.
6. Park JM, Ahn SY, Shin JI, et al. A systemic lupus erythematosus patient with protein losing enteropathy. Yonsei Med J 2004; 45: 923-6.
7. Northcott KA, Yoshida EM, Steinbrecher UP. Primary protein-losing enteropathy in anti-double-stranded DNA disease. J Clin Gastroenterol 2001; 33: 340-1.
8. Werner de Castro GR, Appenzeller S, Bertolo MB, Costallat L. Protein-losing enteropathy associated with systemic lupus erythematosus. Rheumatol Int 2005; 25: 135-8.
9. Nakajima A, Ohnishi S, Mimura T, et al. Protein-losing enteropathy associated with hypocomplementemia and antinuclear antibodies. J Gastroenterol 2000; 35: 627-30.
10. Chung U, Oka M, Nakagawa Y, et al. A patient with protein-losing enteropathy associated with systemic lupus erythematosus. Intern Med 1992; 31: 521-4.

11. Weinstein PJ, Noyer CM. Rapid onset of massive ascites as the initial presentation of systemic lupus erythematosus. AJG 2000; 95: 302-3.
12. Gattorno M, Buoncompagni A, Barabino A, et al. Severe hypoalbuminaemia in a systemic lupus erythematosus-like patient. Eur J Pediatr 2002; 161: 84-6.
13. Yoshida M, Miyata M, Saka M, et al. Protein-losing enteropathy exacerbated with the appearance of symptoms of systemic lupus erythematosus. Intern Med 2001; 40: 449-53.
14. Edmunds SE, Ganju V, Beveridge BR, et al. Protein-losing enteropathy in systemic lupus erythematosus. Aust NZ Med 1988; 118: 868-71.
15. Edworthy SM, Fritzler MJ, Kelly JK, et al. Protein-losing enteropathy in systemic lupus erythematosus associated with intestinal lymphangiectasia. Am J Gastroenterol 1990; 85: 1398-402.
16. Benner KG, Montanaro A. Protein-losing enteropathy in systemic lupus erythematosus: diagnosis and monitoring immunosuppressive therapy by α-1 antitrypsin clearance in stool. Dig Dis Sci 1989; 34: 132-5.
17. Chase GJ, O'Shea PA, Collins E, Brem AS. Protein-losing enteropathy in systemic lupus erythematosus. Hum Pathol 1982; 13: 1503-15.
18. Aoki T, Noma N, Takajo I, et al. Protein-losing gastropathy associated with autoimmune disease: successful treatment with prednisolone. J Gastroenterol 2002; 37: 204-9.
19. Yazici Y, Erkan D, Levine DM, et al. Protein-losing enteropathy in systemic lupus erythematosus: report of a severe, persistent case and review of pathophysiology. Lupus 2002; 11: 119-23.
20. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997; 40: 1725.
21. Perkins GL, Slater ED, Sanders MD, Prichard JG. Serum tumor markers. Am Fam Physician 2003; 68: 1075-82.
22. Furuya T, Suzuki T, Onoda N. Mixed connective tissue disease associated with protein losing enteropathy: successful treatment with intravenous cyclophosphamide therapy. Intern Med 1992; 31: 1359-62.
23. Weiser MM, Andres GA, Brentjens JR, et al. Systemic lupus erythematosus and intestinal venulitis. Gastroenterology 1981; 81: 570-9.