Protein-losing enteropathy in systemic lupus erythematosus: case report

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ABSTRACT

Protein-losing enteropathy is rarely seen in patients with systemic lupus erythematosus. This clinical condition should be suspected in the presence of persistent hypoalbuminemia despite normal liver function, adequate protein intake, and no significant proteinuria. We report the case of a 48-year-old female with weight loss, cavity effusions (ascites and pleural effusion), and lower extremity edema. The diagnosis of lupus was established based on the presence of lymphopenia, proteinuria, ANA, and positive autoantibodies (anti-Sm, anti-DNA, and anti-Ro). Because hypoalbuminemia persisted even with corticosteroid therapy at the dose of 1 mg/kg, protein-losing enteropathy was diagnosed by use of Tc-99m albumin scintigraphy. After adding azathioprine to the treatment, the symptoms subsided and serum albumin levels improved.

Keywords: systemic lupus erythematosus, protein-losing enteropathies, technetium Tc-99m albumin aggregates.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects several systems, including the gastrointestinal tract.[1,2] The gastrointestinal manifestations most commonly reported are as follows: gastroesophageal reflux; dysphagia; abdominal pain; constipation; diarrhea; intestinal pseudo-obstruction; perforation; and hemorrhage.[1]

Protein-losing enteropathy is a rare gastrointestinal condition that has been related to SLE and should be investigated in the presence of persistent hypoalbuminemia and lack of the following: significant proteinuria; liver disease; malabsorption syndrome; and deficient protein intake.[1–3] That enteropathy can manifest clinically with edema or cavity effusions, depending on serum levels of albumin. In addition, the following symptoms can be present: nausea; vomiting; abdominal pain; diarrhea; and anorexia.[2] We report the case of a female patient with SLE and protein-losing enteropathy. The diagnostic approach and treatment used are also discussed.

CASE REPORT

The patient is a 48-year-old female of mixed heritage, who worked as housemaid. She reported that edema of her lower limbs and deterioration of her general state of health began in December 2009. She sought medical care in July 2010, when bilateral pleural effusion was evidenced, and thoracocentesis and pleural biopsy (discrete chronic and unspecific pleuritis) were performed. In September 2010, she was admitted to a regional hospital complaining of pain and increased abdominal volume, being then referred to our service in October 2010.

On admission, she complained of diffuse abdominal pain, increased abdominal volume, dyspnea on mild exertion, and asthenia. She reported significant weight loss (approximately 25 kg in 10 months). The physical examination showed an emaciated, tachycardic, tachypneic patient, with reduced respiratory sounds in both pulmonary bases, diffuse abdominal pain on palpation, shifting dullness and positive fluid wave test, and edema of lower limbs.

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Table 1
Major results of the laboratory tests with respective reference values

Variable	Result	Reference
Hemogram		
Hemoglobin (g/dL)	9.43	12–17
Hematocrit (%)	27.8	36–50
Mean corpuscular volume (fL)	86.8	80–100
Mean corpuscular hemoglobin (pg)	29.4	28–32
Leukocytes (/µL)	6,360	4,000–11,000
Neutrophils	5,316 (83%)	45%–70%
Lymphocytes	625 (9%)	20%–45%
Platelets (/µL)	80,400	150,000–450,000
Prothrombin time (s)	13.2	12.7–15.4
Partial thromboplastin time (s)	33.7	26.3–39.4
Urea (mg/dL)	42	10–50
Creatinine (mg/dL)	0.7	0.6–1.2
Erythrocyte sedimentation rate (mm/h)	4	≤ 20
C-reactive protein (mg/dL)	4.3	≤ 6
Protein electrophoresis		
Albumin (g/dL)	1.61	4.30–5.10
Gamma globulin (g/dL)	1.89 (polyclonal)	0.60–1.10
Aspartate transaminase (U/L)	24	7–41
Alanine transaminase (U/L)	17	12–38
Urinalysis		
pH	6.0	4.5–8.0
Density	1.020	1.010–1.025
Proteins	+	Absent
Hemoglobin	+	Absent
Red blood cells (cells/field)	10	0–3
Leukocytes (cells/field)	6	0–5
Urinary casts	Absent	Absent
24-hour proteinuria (mg/24h)	264	30–300
Ascitic fluid		0
Cells (cells/µL)	95	
Neutrophils	59%	
Lymphocytes	27%	
Monocytes	8%	
Mesothelial cells	6%	
Serum-ascites albumin gradient (SAAG)	0.8	≥ 1.1 = portal hypertension < 1.1 = probable peritoneal disease
Acid-fast bacillus	Negative	Negative
Culture	Negative	Negative
Adenosine deaminase (ADA, U/L)	12.0	≤ 40
Oncotic cytology	Negative	Negative
ANA	1:1,280 Homogeneous nuclear	No reaction
Anti-Sm	Reaction	No reaction
Anti-dsDNA	1:320	No reaction
Anti-Ro	Reaction	No reaction
Anti-La	No reaction	No reaction
Complement		
C3 (mg/dL)	23.8	90–170
C4 (mg/dL)	8.5	12–36
CH-50 (u/CAE)	41	≥ 60

Diagnostic investigation was initiated, and the major diagnostic hypothesis was neoplasm of unknown origin. The laboratory tests are shown in Table 1. Upper digestive endoscopy and colonoscopy ruled out neoplasm of the upper and low digestive tract. The chest, abdomen, and pelvis tomographies showed large volume ascites, bilateral pleural effusion, and pericardial effusion.

The diagnosis of systemic lupus erythematosus was established based on abnormal antinuclear antibody (ANA) titers, presence of specific autoantibodies (anti-Sm and anti-DNA), serositis, and lymphopenia. Prednisone, at the dose of 1 mg/kg, was initiated. Initially, the lower limb edema and ascites worsened, requiring repeated relief paracentesis. Due to significant and persistent hypoalbuminemia, with no significant proteinuria, normal liver function tests, and adequate protein intake, protein-losing enteropathy was investigated by use of Tc-99m albumin scintigraphy. Protein leakage was confirmed in the right lower abdominal quadrant four hours after beginning the study and in the subsequent images (6, 8, and 24 hours) (Figure 1).

Azathioprine at the dose of 100 mg/day was added for four weeks, and the cavity effusions and lower limb edema subsided, and her serum albumin levels normalized.

DISCUSSION

Protein-losing enteropathy is a condition characterized by excessive protein loss via the gastrointestinal tract, resulting in hypoproteinemia, edema, and, sometimes, cavity effusions.[4] It has been related to erosive gastrointestinal disorders (inflammatory bowel disease, pseudomembranous colitis, sarcoidosis, intestinal lymphoma, erosive gastropathy), non-erosive gastrointestinal disorders (celiac disease, microscopic colitis, rheumatic disorders, tropical sprue, Whipple's disease, hypertrophic gastropathy), and disorders involving increased interstitial pressure (intestinal lymphangiectasia, congestive heart failure, portal hypertension, intestinal lymphatic fistula, retroperitoneal fibrosis, and mesenteric tuberculosis).[4,5]

Protein-losing enteropathy should be considered in the presence of hypoalbuminemia whose most common causes have been ruled out, such as massive proteinuria, malnutrition, and decreased protein synthesis due to liver disease. The clinical manifestations vary, being determined by the underlying disease.[5] Diarrhea and other gastrointestinal symptoms might not be present.[4] From the laboratory viewpoint, in addition to hypoalbuminemia, the following can be found: hypercholesterolemia due to the hepatic response to hypoalbuminemia;

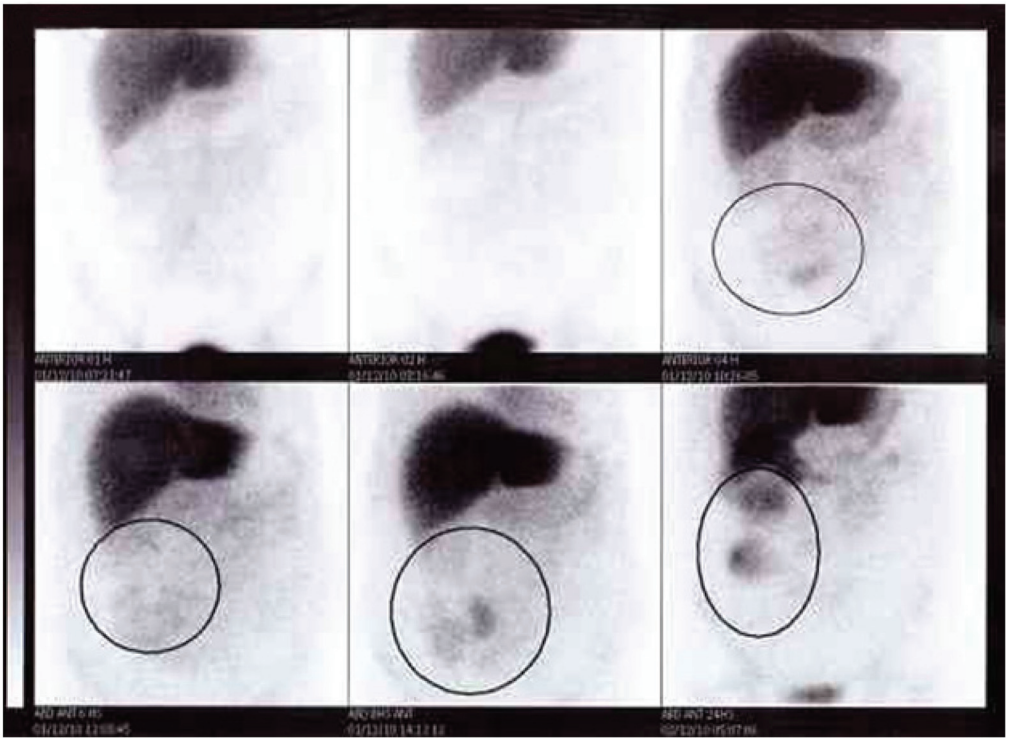

Figure 1
Tc-99m albumin scintigraphy showing leakage of the radiotracer in the right lower abdominal quadrant (4-hour static images), which increased in subsequent images.

hypogammaglobulinemia (IgA, IgG, and IgM); and decreased transferrin, ceruloplasmin, and fibrinogen, because the intestinal loss depends on neither protein load nor protein molecular weight, similarly to that of nephrotic syndrome.[2,4,5]

Some reviews have already described protein-losing enteropathy as a condition secondary to lupus.[1–3] One review carried out in Asia has shown predominance of female patients aged around 30 years, the disorder being, in most cases, the initial manifestation of lupus.[2] The Asian study by Mok et al.[6] has reported a 3.2% prevalence of protein-losing enteropathy in patients with lupus. Similar data have been reported by Zheng et al.[7] and Kim et al.[8]

In our patient, the criteria for diagnosing systemic lupus erythematosus[9] were as follows: serositis (pleural and pericardial effusion); hematological changes (lymphopenia); immunological changes (positive anti-dsDNA and anti-Sm); and abnormal ANA titers. However, there is no characteristic autoantibody to identify protein-losing enteropathy in patients with lupus. Those laboratory findings are related to lupus, and not necessarily to the protein-losing enteropathy.[6]

A mechanism that might justify protein-losing enteropathy in connective tissue diseases is the increased permeability of the intestinal microvasculature.[2] Some cytokines, such as INF-γ, IL-6, and TNF-α, have been implicated in that process, but controlled studies on the relation of those cytokines and disease activity and therapeutic response still lack.[7,10] Other mechanisms reported are immune complex-mediated vasculitis, lymphatic dilation, and mucosal injury, which are difficult to demonstrate microscopically.[2,6]

Two methods are used for diagnosing protein-losing enteropathy: 24-hour fecal clearance of alpha-1-antitripsin; and Tc-99m albumin scintigraphy. The former is non-invasive and can monitor the treatment response of the underlying disease.[4,5,11] Its normal value is 2.6 mg/g of stools, reflecting an intestinal clearance < 13 mL/day. Diarrhea and gastrointestinal bleeding can result in falsely elevated values. Alpha-1-antitripsin is degraded at a gastric pH < 3.5, interfering with the result. The fecal clearance of alpha-1-antitripsin does not define whether the site of protein leakage is gastric or intestinal.[5]

We used the Tc-99m albumin scintigraphy, which enables locating the site(s) of protein leakage.[2] It is less expensive than other radiotracers (^{111}In-chloride or ^{111}In-transferrin), has *in vivo* stability, high sensitivity, and rare side effects (nausea, vomiting, dyspnea, tachycardia, confusion, and abdominal pain). False-positive results occur in the presence of gastrointestinal bleeding. Serial images should be obtained up to 24 hours, increasing protein loss detection rate, possibly because of the intermittent nature of the process.[12]

The association of protein-losing enteropathy with lupus requires identifying the clinical and laboratory characteristics of the disease and ruling out other conditions by use of echocardiography, abdominal tomography, endoscopy, and colon biopsy.[13]

There is no controlled study for the treatment of protein-losing enteropathy in lupus. Reports have suggested that therapy should be initiated with corticosteroid alone. In case of no response, the association of immunosuppressants (cyclophosphamide, azathioprine or cyclosporine) provides rapid and long-lasting results. Relapses have been more frequently reported when corticosteroids were used in isolation, and those relapses have responded well to an increase in corticosteroid doses.[2,6,7,13]

Protein-losing enteropathy should be considered whenever patients with lupus have unexplained hypoalbuminemia. Those patients respond well to treatment with corticosteroids and immunosuppressants, and, in most cases, the prognosis is good.

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