Primary Lupus-associated Protein-losing Enteropathy*

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ABSTRACT

A 79-year-old native American female with a history of diabetes mellitus, but no history of hepatic or renal disease, presented with anasarca and hypoalbuminemia. Laboratory tests for fecal α₁-antitrypsin and an indium III-labeled plasma transferrin nuclear scan revealed a protein-losing enteropathy. A serological test was positive for antinuclear antibody in a titer of 1:1250 with a homogeneous pattern. This finding combined with low normal serum complement levels suggested the diagnosis of systemic lupus erythematosus (SLE). This case is unusual in that protein-losing enteropathy was the only presenting symptoms. The late onset of this disease is also unusual.

Introduction

There are numerous conditions associated with gastrointestinal loss of protein and hypoalbuminemia. Among the most common are congestive heart failure, intestinal lymphangiectasia, lymphoma, sprue, Whipple's disease, abdominal tuberculosis, retroperitoneal tumor, and regional enteritis.¹ Recently, it has been reported that systemic lupus erythematosus (SLE) can be a cause of protein-losing enteropathy (PLE).¹²³ This association is rare with a total of 17 cases having been reported in the English language literature. In 14 of these cases, PLE was the only significant manifestation of disease.¹ In a review of 13 of these cases, in which PLE was the only manifestation of disease, including the presentation of one additional patient with diagnosed SLE and PLE, it was noted that the diagnosis of SLE in these patients was made on the basis of an elevated antinuclear antibody (ANA) titer. The ruling out of the other possible causes of protein-losing enteropathy was based on intestinal biopsies, the absence of steatorrhea, lymphopenia, hypoglobulinemia, and, in many of these patients, an elevated cholesterol level.¹ All of these patients except one were females of young age (median 28 years, oldest 59). A 15th case is reported of this rare association of PLE and SLE in a 79-year-old female patient with elevated...
ANA titers, protein-losing enteropathy, anasarca, endoscopic findings that are un-characteristic of the usual causes of protein-losing enteropathy, absence of lymphopenia, hypoglobulinemia, and steatorrhea, and the presence of hypo-complementemia, all of which suggest SLE-associated protein-losing enteropathy.

Besides reporting another case of this rare association where PLE was the sole manifestation of disease, this case is noteworthy in that the age of the patient is significantly greater than the median age of the patients reported thus far and is greater by 20 years than the oldest patient reported to date. In addition, the ANA pattern was homogenous in this patient, a finding that was reported for only one of the 14 patients studied to date. The anti-nuclear antibody did not react with double stranded DNA.

Case Report

A 79-year-old native American female with a history of diabetes mellitus presented to SUNY Health Science Center early in 1991 with progressively worsening anasarca. She was previously admitted in 1988 and diagnosed as having congestive heart failure. She denied having shortness of breath, substernal chest pain, palpitations, anorexia, or weight loss. The patient reported that her lower extremities had become progressively weaker and more edematous. She had no history of melena or diarrhea.

On admission her medications were Lasix™ 40 mg p.o. qid, and NPH Humulin™ (20 units s.c.) every morning. She had no known allergies to medications. Her past medical history was significant for diabetes mellitus during the past seven years. She was status post-cholecystectomy, hysterectomy, and appendectomy.

Physical examination was remarkable for bibasilar rales, an S4 gallop, ascites with a positive fluid wave, and 4+ pitting edema over the abdominal wall area and in the lower extremities up to the inguinal area. She also had an umbilical hernia. Doppler examination to the lower extremities revealed venous insufficiency secondary to valvular insufficiency.

Chest x-ray revealed bilateral pleural effusion with no evidence of heart failure. The heart was normal in size. An echocardiogram revealed a thickened mitral valve but was otherwise normal.

An abdominal sonogram was performed and revealed only ascites. Angiodynography of the portal venous system revealed no abnormality and no obstruction. Paracentesis revealed a transudate of fluid. Computer tomography (CT) scan of the abdomen showed massive body wall edema with a large amount of ascites.

Complete blood count was significant for anemia (hematocrit, 31.4%; hemoglobin, 9.7 g/dL). White count was normal at 6000/ cu mm. Erythrocyte sedimentation rate was 75 mm/hr; lactate dehydrogenase and alkaline phosphatase were both slightly elevated at 255 and 187 U/L, respectively. Albumin was 19 g/L and total protein, 55 g/L. Cholesterol was normal at 1040 g/L. No steatorrhea was observed in stool samples. Globulin levels were normal at 36 g/L. Urinalysis revealed no protein.

Fecal studies for α1-antitrypsin were found to be positive in a titer of 1:640, suggesting a protein-losing enteropathy.

Immunologic testing revealed antinuclear antibody, positive at a titer of 1:1250 showing a homogeneous pattern. Serum C3 (56 mg/dL) and C4 (17 mg/dL) levels were low normal (reference intervals for C3 and C4: 54 to 112 and 15 to 49 mg/dL, respectively). An anergy panel was negative. Anti-double stranded deoxyribonucleic acid (DNA) antibody was also negative.

Diagnostic procedures for possible causes of protein-losing enteropathy were undertaken. Colonoscopy revealed mild mucosal edema and hemorrhage. Upper gastrointestinal tract endoscopy showed only a mild antritis and no other abnormalities. Biopsy of the small bowel revealed mild villous abnormalities. Biopsy of the antrum showed superficial chronic inflammation. An indium III-labeled plasma transferrin nuclear scan was performed revealing marked protein loss localized to the stomach and small bowel. The patient was discharged on a regime of diuretics for her edema, which significantly subsided. Her serum total protein on discharge was 78 g/L, and her serum albumin was 31 g/L.

Discussion

Besides severe protein-losing enteropathy, as documented by very low serum total protein and albumin, high fecal α1-antitrypsin and a positive indium III scan, with attendant anasarca, the only other major finding for this patient was a positive ANA in high titer (1:1250), with a homogeneous pattern. She was also borderline hypocomplementemic. These results are suggestive of SLE, although her titers of anti-double
stranded DNA were negative. As with many of the patients in the recent survey of the 14 patients with SLE who presented only with PLE, and all of whom were diagnosed as having SLE on the basis of a positive ANA, this patient was hypoalbuminemic but normoglobulinemic. Also this patient, like those in the prior studies, had a normal white blood cell count, and an absence of steatorrhea. None of the patients, including the one in this study, presented with any of the typical symptoms of SLE, such as maculopapular facial rash, renal failure, pleural effusions, pericarditis, or vasculitis.

It is interesting that in many of the patients reported, the ANA titers were lower than those reported here, and often the pattern observed was not homogeneous but speckled or rim. Speckled and rim patterns are seen in collagen vascular diseases other than SLE such as Sjögren’s syndrome. Also, in several of the 14 patients in the prior studies, hypocomplementemia often found in SLE was not observed.

In the 14 patients studied to date with PLE as the sole manifestation of SLE, the ANA patterns of eight of these patients have been described. In seven of these, a homogeneous pattern, characteristic of SLE, was not found. In one of seven patients, no ANA was found initially, and the highest subsequent ANA titer was 1:300.

In our patient, a homogeneous pattern was detected, although antibodies to double stranded DNA were not. No studies on the specificity of the anti-nuclear antibodies of the other 14 patients were described.

Thus, while our patient has findings that would classify her as belonging to the group of patients with PLE as the sole symptom of SLE, there are unique findings worthy of note. In particular, this patient is much older than those in the previous studies, first having presented with PLE at the age of 79 years. Her ANA pattern was reproducibly homogeneous, unlike most of those patients in the prior reports. Further investigation of the ANA specificity shows non-reactivity with double-stranded DNA. This latter result may indicate that this unusual form of SLE may be caused by anti-nuclear antibodies that have different specificities from those found in the more usual varieties of SLE.

In diagnosing PLE caused by SLE, it is important to rule out other possible causes of the enteropathy, such as intestinal lymphangiectasia, lymphoma, Whipple’s disease, tropical sprue, abdominal tuberculosis, retroperitoneal tumor with fibrosis, and regional enteritis. Also, congestive heart failure, especially in association with constrictive pericarditis, can cause enteropathy. While this patient has a history of congestive heart failure, this condition has been well-controlled and there was no associated constrictive pericarditis. Thus, none of these other conditions pertain to the patient reported here.

The pathophysiological mechanism underlying lupus-associated protein-losing enteropathy is unknown. Theories include direct disruption of the intestinal mucosa, lymphangiectasia, and immune-complex vasculitis with widespread capillary leakiness. In the patient presented in this case report, lymphangiectasia was absent. Also, biopsy of the colon, stomach and small bowel revealed only mild edema and some chronic inflammatory changes. This suggests that possible vasculitis played a role in her enteropathy, but the exact mechanism by which this would occur is unknown.

It should be cautioned that positive ANAs can occur in a wide variety of non-lupus related diseases such as progressive systemic sclerosis (PSS), Sjögren’s syndrome, polymyositis, and approximately 10% of normal individuals. The
patient reported in this study presented with a high titer of ANA in a homogeneous pattern, strongly suggestive of SLE. However, because anti-double stranded DNA titers were negative, it is possible that another as-yet undiagnosed condition may pertain to this patient and to those in the prior studies.1 Future study of this unusual association is clearly warranted.

References