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CASE REPORT | PATHOLOGY

Protein-Losing Gastroenteropathy Associated With Sjögren's Syndrome: First Known Case Reported Outside of Asia

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Abstract

Protein-losing gastroenteropathy (PLGE) is a rare extraglandular manifestation of Sjögren's syndrome, reported in fewer than 10 cases. We report a 58-year-old white woman with Sjögren's syndrome, type 1 renal tubular acidosis, and PLGE, who presented with cachexia and 100-pound weight loss. The diagnosis was made based on hypoalbuminemia in the absence of significant proteinuria, low levels of fat soluble vitamins, low transferrin, and an elevated alpha-1 antitrypsin (A1AT) fecal clearance, supported by imaging and endoscopy, with biopsy showing lymphocytic infiltration. She was successfully treated with cyclophosphamide and prednisone. To our knowledge, this is the first such case outside of Asia.

Introduction

Protein-losing gastroenteropathy (PLGE) is a rare condition characterized by the loss of serum protein through the gastrointestinal tract, resulting in hypoproteinemia with subsequent edema, ascites, and pleural and pericardial effusions.[1] PLGE is associated with multiple autoimmune conditions, most commonly systemic lupus erythematosus (SLE).[2] PLGE has also been seen with Sjögren's syndrome, a systemic autoimmune disease characterized by chronic inflammation of the salivary and lacrimal glands.[1-3] Sjögren's syndrome-associated PLGE is extremely rare: there are 10 reported cases in Asia, 9 of which were women.

Case Report

A 58-year-old white woman presented with a history of 43-kg unintentional weight loss over 5 years and 6 months of worsening crampy abdominal pain, diarrhea, nausea, vomiting, and electrolyte abnormalities. She noted non-bloody stools occurring 6-7 times per day with occasional incontinence. She had a history of Sjögren's syndrome diagnosed 5 years earlier by positive anti-Sjögren's-syndrome-related antigen A (anti-SSA), anti-Sjögren's-syndrome-related antigen B (anti-SSB), and lip biopsy. Antibodies to double-stranded DNA (dsDNA) were negative.

On presentation, she appeared cachectic, with exam notable for dry mucous membranes and diffuse mild abdominal tenderness without organomegaly. Laboratory results revealed hemoglobin (Hgb) 8.6 g/dL, bicarbonate 14 mmol/L, potassium 3.3 mmol/L, transferrin saturation 17%, prealbumin 19 mg/dL, erythrocyte sedimentation rate 78 mm, C-reactive protein 0.5 mg/dL, and INR 1.0. Her renal function was otherwise normal. The total protein and albumin nadir during this hospitalization was 4.9 g/dL and 2.6 g/dL, respectively. Serum levels of fat-

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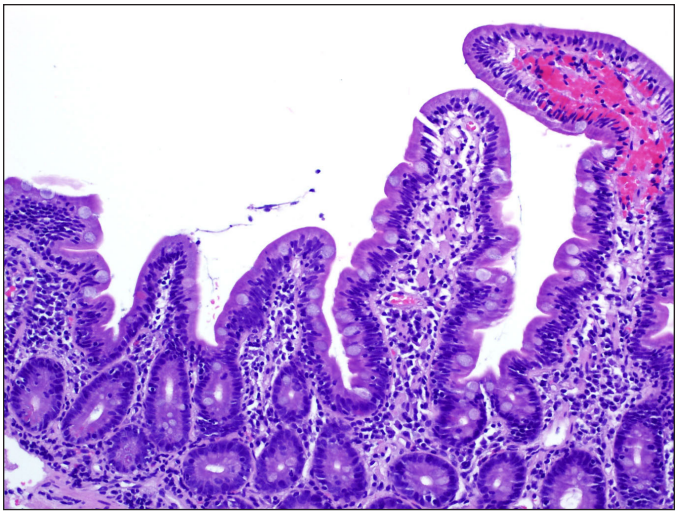

Figure 1. Duodenal biopsies demonstrating architecturally normal small bowel mucosa with increased intraepithelial lymphocytes (>30 lymphocytes/100 enterocytes).

soluble vitamins were low except for vitamin E. Stool studies were negative for occult blood, *Clostridium difficile*, and fecal fat; alpha-1 antitrypsin (A1AT) fecal clearance was 13 mL over 18 h (normal <13 mL/day). Normal labs included thyroid stimulating hormone, Hgb A1c, tissue transglutaminase IgA and IgG antibodies, quantitative immunoglobulins, C3, C4, and urine protein electrophoresis. She had a positive nuclear antibody (1:1280). Urine labs were consistent with a diagnosis of a distal renal tubular acidosis.

CT enterography was significant for mild ascites and body wall edema without evidence of cirrhosis, bowel wall thickening, enhancing masses, or mesenteric lymphadenopathy. Echocardiogram was normal. Esophagoduodenography (EGD) with small bowel enteroscopy showed erythematous gastropathy, and biopsies showed inactive chronic gastritis without *Helicobacter pylori*. Random duodenal biopsies demonstrated architecturally normal small bowel mucosa with increased intraepithelial lymphocytes (>30 lymphocytes/100 enterocytes; Figure 1). Colonoscopy with random biopsies was normal.

The patient's abdominal discomfort, nausea, renal tubular acidosis, and duodenal biopsies supported active Sjögren's syndrome with systemic involvement. We proceeded with treatment of PLGE secondary to Sjögren's syndrome with immunosuppressive treatment of oral prednisone 60 mg daily and intravenous cyclophosphamide 800 mg monthly. Two months after discharge, she had resolution of diarrhea and abdominal pain. She had regained 18 kg, and her albumin and chemistry panel had normalized. Her prednisone was tapered to 10 mg daily and she continued to receive monthly cyclophosphamide.

Discussion

This is the first reported case of PLGE associated with Sjögren's syndrome outside of Asia in a white patient. The prevalence of this condition is unknown in U.S. patients with Sjögren's syndrome. PLGE was suspected in our patient after exclusion of other causes of low protein such as malnutrition, nephrotic syndrome, and liver dysfunction. The new diagnosis of a distal renal tubular acidosis supported active systemic Sjögren's syndrome and raised suspicion for PLGE as another extraglandular manifestation of her Sjögren's syndrome. Given active systemic Sjögren's syndrome, diagnosis of PLGE, presence of common gastrointestinal manifestations of Sjögren's syndrome, and exclusion of other causes of PLGE, she was diagnosed with PLGE secondary to Sjögren's syndrome.[4,5]

PLGE is usually diagnosed with nuclear radiology testing and/or a fecal clearance of A1AT >13 mL/day.[6] No targeted systemic treatment is available for systemic Sjögren's syndrome, and there is no accepted standard treatment for PLGE associated with Sjögren's syndrome. Many patients with extraglandular manifestations have improved with a variety of treatments, including glucocorticoids, hydroxychloroquine, cyclophosphamide, and rituximab.[7] Systematic review of prior PLGE cases showed successful treatment with steroids alone in 4 cases, steroids and hydroxychloroquine in 2 cases, and steroids and cyclophosphamide in 2 cases.[2,8-13] Rituximab alone was successful in 1 case.[14] Our patient was successfully treated with prednisone and cyclophosphamide.

The exact mechanism of PLGE in Sjögren's syndrome remains unclear.[12,15] Duodenal biopsies from our patient showed architecturally normal mucosa with increased intraepithelial lymphocytes. Intestinal biopsies described in prior case reports all showed chronic inflammatory cell infiltration.[8-10,12,13] Immune staining in 3 cases demonstrated immune deposits in the vascular endothelium of the lamina propria.[11,12,14] Follow-up intestinal biopsies were generally not pursued. Better understanding of the histologic changes in PLGE associated with Sjögren's syndrome is a potential area for further study, as this may lead to more targeted therapy.

Disclosures

Author contributions: A. Gupta and NL Cohen performed the literature search and wrote the manuscript. S. McCarthy reviewed the manuscript. JB McHugh reviewed the biopsies and the manuscript. R. Kwon is the article guarantor, and edited the manuscript.

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