Seronegative Adult Autoimmune Enteropathy in a Patient With Rheumatoid Arthritis

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ABSTRACT

Autoimmune enteropathy is a rare disorder of the immune system. We present a 75-year-old woman with rheumatoid arthritis who presented with 4 months of intractable vomiting, diarrhea, and unexplained weight loss. Initial workup was negative for infection and celiac disease, but her symptoms progressed. Repeat esophagogastroduodenoscopy showed duodenal scalloping and friability. Biopsies of the duodenum and terminal ileum showed glandular destruction, epithelial apoptosis, and goblet cell depletion. Colonoscopic examination was normal, and random colon biopsies did not show evidence of microscopic colitis. She was diagnosed with autoimmune enteropathy, and treatment consisted of an extended corticosteroid taper, with the resolution of symptoms.

INTRODUCTION

Autoimmune enteropathy (AIE) is a rare and complex disorder of the immune system characterized by 6 or more weeks of severe diarrhea with malabsorption and histologic changes on small intestinal biopsy. This condition is primarily seen in neonates and children but rarely has been reported in adults.1–3 A high index of suspicion is necessary to make a timely diagnosis. Although AIE is associated with major morbidity, current understanding of this condition and its treatment are limited to what has been reported in case reports and case series.

CASE REPORT

A 75-year-old woman with rheumatoid arthritis (RA) and type 2 diabetes presented to the clinic with 4 months of intractable nausea, vomiting, diarrhea, and an unintentional 30-pound weight loss. She denied fatigue, fever, loss of appetite, abdominal pain, melena, or hematochezia. Her symptoms were not associated with particular foods and did not resolve with a strict gluten-free diet or low-residue diet. She was on methotrexate from 2013 to 2016 for RA, but never took any other immunosuppressive agents.

Investigations at a community hospital included negative stool testing for enteric pathogens and negative celiac testing (antitissue transglutaminase immunoglobulin A (IgA) 1 U/mL and IgA 123 mg/dL). Esophagogastroduodenoscopy (EGD) revealed nonspecific inflammation of the esophagus, stomach, and duodenum. Biopsy testing for Cytomegalovirus, herpes simplex, and Helicobacter pylori was all negative. Duodenal biopsies showed nonspecific acute and chronic inflammation without villous blunting. Colonoscopy appeared normal, and random colon biopsies were not obtained. She was diagnosed with viral gastroenteritis and irritable bowel syndrome with diarrhea, for which she was treated with rifaximin and ondansetron. However, her symptoms progressed, requiring admission to our hospital for further workup.

Physical examination revealed an emaciated woman with stable vital signs and a benign abdominal examination. Laboratory testing demonstrated severe hypoalbuminemia (1.7 g/dL) and hypomagnesemia (1.3 mg/dL). C-reactive protein, liver, and thyroid function tests; antinuclear antibody, HIV, immunoglobulin levels; and QuantiFERON Gold were normal or negative. Abdominal and pelvic computed tomography with contrast was unremarkable. Repeat EGD showed duodenal scalloping and friability with contact (Figure 1).
Colonoscopic examination was normal to the terminal ileum. Biopsies of the duodenum and terminal ileum showed glandular destruction, epithelial apoptosis, and goblet cell depletion without significant intraepithelial lymphocytosis (Figure 2). The periodic acid-Schiff stain did not show evidence of Whipple disease, and random biopsies of the colon were normal without evidence of microscopic colitis. Antienterocyte antibodies were negative.

She was diagnosed with AIE based on her symptomatology, affirmative histopathologic findings, and exclusion of related conditions. Her treatment consisted of temporary total parenteral nutrition and 40 mg IV methylprednisolone daily for 5 days, followed by a prolonged oral prednisone taper at the time of discharge. At her 2-month follow-up, she was transitioned from low-dose prednisone to budesonide, had gained back 10 pounds, and had complete resolution of her nausea, vomiting, and diarrhea. She discontinued corticosteroid treatment at 3 months, and 6 months later, she was still in remission.

**DISCUSSION**

AIE is an emerging diagnosis in the adult population and should be included in the differential diagnosis for patients with intractable diarrhea. A diagnostic criterion includes malabsorptive diarrhea for more than 6 weeks that does not improve with dietary changes and characteristic histological findings. Small bowel histology shows partial or complete blunting of the villi, deep crypt lymphocytosis, increased crypt apoptosis, and minimal intraepithelial lymphocytosis. Diagnosis is supported by positive antienterocyte antibodies in approximately 80% of cases. Differential diagnosis includes celiac disease, common variable immune deficiency (CVID), refractory sprue, small bowel lymphoma, and medication-related enteropathy most notably from olmesartan. These related conditions should be excluded before making a diagnosis of AIE. Celiac disease, unlike AIE, typically responds to a gluten-free diet. Refractory celiac disease does not respond to dietary changes but more often has histological findings of increased intraepithelial lymphocytes (>40 per 100 epithelial cells) compared with patients with AIE. Furthermore, AIE can be distinguished from CVID because the latter would have serum studies showing 2 or more immunoglobulin deficiencies, and most patients (83%) with CVID do not have plasma cells on histology.

Once a diagnosis has been performed, consider any potential polyendocrinopathy syndromes, such as immunodysregulation polyendocrinopathy, enteropathy X-linked syndrome and autoimmune phenomena, polyendocrinopathy, candidiasis, and ectodermal dystrophy, given their known association with AIE. This patient did not have any of the features of these or other polyendocrinopathies such as psoriasis, anemia, nephritis, pneumonitis, candidiasis, hypoparathyroidism, or Addison disease. Furthermore, these endocrinopathies are generally pediatric diseases, and it would be highly unlikely to make a new diagnosis in an adult. However, our patient had a history of RA, and a rare association between AIE and RA has been reported in the literature.

Treatment of AIE usually starts with corticosteroids, and then, patients with refractory symptoms may advance to other immunosuppressive medications on a trial and error basis. Previous case studies have documented the use of cyclosporine, tacrolimus, azathioprine, sirolimus, 6-mercaptopurine, rituximab, infliximab, adalimumab, and vedolizumab. Generally, patients

![Figure 1](image1.png) **Figure 1.** Esophagogastroduodenoscopy showing mild scalloping of mucosa in the second portion of the duodenum.

![Figure 2](image2.png) **Figure 2.** Duodenal mucosa at (A) low magnification showing crypt destruction and depletion with villous blunting and at (B) high magnification showing epithelial apoptosis, intraepithelial neutrophilic infiltrates, and lamina propria with lymphoplasmacytic and eosinophilic infiltrates.
require total parenteral nutrition as well for their caloric needs. Our patient had a complete response after 8 weeks of prednisone and stopped treatment after 12 weeks without return of symptoms. Approximately 60% of patients have symptom resolution after 1–8 weeks of steroids with or without additional immunosuppression, whereas 20% of patients achieve partial response and 20% do not respond. Prognosis varies widely based on the severity of symptoms and extent of histological lesions, and more research is needed to better understand the natural history and treatment for this emerging condition.

This case is unique in that the patient had an initial nondiagnostic EGD and small intestinal histopathology despite having chronic malabsorptive diarrhea and weight loss for at least 2 months duration. The fact that her initial EGD sampling was histopathologically normal but her repeat EGD 9 weeks later had villous blunting on direct visualization and histopathology raises the possibility of sampling error because of patchy villous blunting or a slowly evolving small intestinal inflammatory process, whereby the characteristic histologic features of AIE may be missed if sampled too early in the disease process. This case highlights the importance of maintaining a broad differential diagnosis for patients with chronic diarrhea. It also emphasizes the utility of repeat EGD and biopsy in patients with unexplained diarrhea with an initial nondiagnostic EGD and persistent symptoms because villous blunting may be patchy and chronic inflammatory changes of AIE may evolve over time.

DISCLOSURES

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