ACG CASE REPORTS JOURNAL

CASE REPORT | INFLAMMATORY BOWEL DISEASE

Autoimmune Enteropathy in an Ulcerative Colitis Patient

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ABSTRACT

Autoimmune enteropathy is a rare but severe disorder with significant immune-mediated changes. We present a 54-year-old woman with history of refractory ulcerative colitis status post total colectomy with end ileostomy who presented 1 month after her surgery with high ostomy output of 4 L/d. After a negative workup, ileoscopy with biopsies showed severe chronic active ileitis. Enteroscopy revealed diffuse chronic enteritis concerning for autoimmune enteropathy. She was started on budesonide and intravenous solumedrol, but her ostomy output remained high. She was then started on cyclosporine and later tacrolimus with significant clinical improvement and normalization of ostomy output on tacrolimus.

INTRODUCTION

Autoimmune enteropathy (AIE) is usually diagnosed in children and rarely in adults.[1] Histologically it can resemble focal diseases such as celiac disease, but it can also involve the small and large bowel.[2-4] Furthermore, AIE is frequently associated with other autoimmune conditions.[2,5] Without early recognition and treatment, patients are at risk for major life-threatening complications.[1,2] The treatment of autoimmune enteropathy includes immunosuppressive therapies.

CASE REPORT

Our patient is a 54-year-old woman with a past medical history of endocarditis status post bioprosthetic aortic valve replacement, adrenal insufficiency, and refractory ulcerative colitis (UC) presenting 1 month status post total colectomy with end ileostomy and green, nonbloody, high ostomy output (HOS) of 4 L/d. She had no other history of gastrointestinal or autoimmune disease. She was adopted with unknown family history. Physical exam was significant for epigastric and suprapubic pain. Her initial labs showed acute kidney injury (creatinine 1.1, baseline 0.3–0.8) and anemia (hemoglobin 9.1, baseline 10.5).

The patient was originally diagnosed with UC in 2009 after new-onset diarrhea. Endoscopy at that time showed inflammation characterized by congestion with edema, erosions, erythema, friability, and granularity in a continuous and circumferential pattern from the anus to the cecum with no sites of sparing. Biopsies were consistent with inflammatory bowel disease (IBD), thought to be UC. She was treated with steroids, infliximab, mesalamine, and adalimumab. However, immunosuppressants were stopped due to recurrent bacteremia. She ultimately developed septic shock with persistent hypotension despite pressors, and she required stress-dose steroids, leading to a diagnosis of adrenal insufficiency. Despite a trial of immunosuppressants, she had clinical relapse with persistent diarrhea and continued colitis on colonoscopy, leading to a total colectomy in November 2015. Biopsies of the small intestine and foregut prior to surgical resection showed normal histology.

The patient was admitted for a total of 5 months in the setting of ongoing HOS. Output ranged from 4 L to 10 L daily despite maximum medical therapy, including trials of loperamide, atropine/diphenoxylate, cholestyramine, octreotide, tincture of opium, scopolamine, codeine, and proton pump inhibitor therapies. Initially, HOS was thought to be due to poor ileal accommodation and adaption in the setting of recent colectomy with end

ACG Case Rep J 2018;5:e78. doi:10.14309/crj.2018.78. Published online: November 7, 2018.

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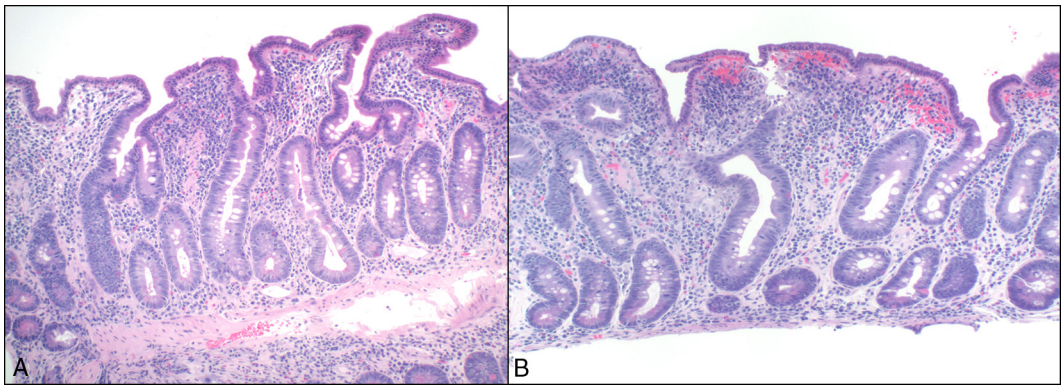

Figure 1. Microscopic images of duodenal biopsies showing (A) partial to (B) total villous blunting with expanded lamina propria lymphoplasmacytic inflammation and crypt hyperplasia.

ileostomy. Other possible diagnoses included enteropathic infection, hypersecretory conditions (e.g., dietary intolerance), carcinoid tumor, obstruction, Crohn's Disease, or UC-associated enteritis.[6,7] Infectious workup was negative for viral, atypical, and hospital-acquired infections. A neuroendocrine workup and magnetic resonance enterography were also both unrevealing. The patient was subsequently tried on a low-lactose, low-fat, low-fiber diet, none of which significantly decreased the ostomy output. She was eventually placed on total parenteral nutrition. This decreased her ileostomy output dramatically to <1 L/d. However, the patient continued to experience nausea, vomiting, and abdominal pain.

A subsequent ileoscopy was limited by the inability to advance the scope past 3–4 cm due to peristomal hernia. Biopsies obtained were consistent with severe chronic active ileitis; however, given the proximity of the biopsy site to the ileostomy site, it was difficult to differentiate anastomotic changes versus other forms of enteritis. An enteroscopy obtained gastric and small-intestine biopsies. Pathologic examination of small-bowel biopsies showed partial to total villous blunting, crypt hyperplasia, and diffusely increased lamina propria chronic inflammation, including many plasma cells (Figure 1). Surface and crypt acute inflammation were present throughout (Figure 2). Intraepithelial lymphocytes were not increased. There were no granulomas to suggest Crohn's disease or viral cytopathic changes. Paneth cells and goblet cells appeared preserved. Focal crystals, consistent with cholestyramine and sevelamer, were also present. The changes in the stomach were similar and showed no intestinal metaplasia, atrophy, or hyperplasia of endocrine cells. The stomach biopsies also showed chronic gastritis with abundant plasma cells, and they were negative for *Helicobacter pylori*. Together, these histologic features raised the possibility of AIE. Repeat enteroscopy and ileoscopy showed similar results with no evidence of enteropathy-associated T-cell lymphoma. Various stains, flow cytometry, and T-cell rearrangement were all negative. HLA DQ8 was positive, but TTG was negative, suggesting that this was unlikely refractory sprue. There was no recent drug use that was felt to predispose the patient to drug-induced enteropathy. Although anti-enterocyte antibody was nonspecific, management for AIE was initiated.

Budesonide was started with some initial improvement in nausea. Intravenous solumedrol was initiated with transition to

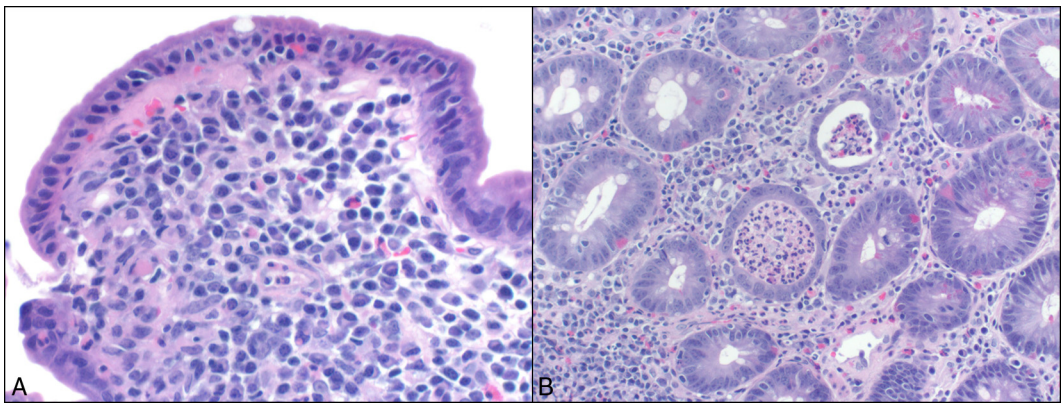

Figure 2. Microscopic images of duodenal biopsies with (A) no intraepithelial lymphocytosis seen in the surface epithelium and (B) patchy areas of acute cryptitis.

prednisone, also resulting in some improvement in nausea, but this ultimately did not resolve the diarrhea with consistent HOS at 4 L/d. Cyclosporine was initially considered for treatment, but a lipid panel demonstrated low cholesterol, thus ruling out cyclosporine due to risk of neurotoxicity. As an alternative, tacrolimus was considered given that anti-tissue necrosis factor agents were ineffective for the patient and she was intolerant to 6-mercaptopurine. Five months after initial presentation, the patient was started on tacrolimus 0.1 mg/kg/d, divided into twice-daily doses, with slow titration. She exhibited significant clinical improvement and normalization of ostomy output.

DISCUSSION

AIE is more common in pediatric patients, but it does affect the adult population.[2] AIE causes significant immune-mediated changes in the intestine, and it can be diagnosed histologically even though antibodies do not necessarily confirm the diagnosis.[4] There is some literature to discuss a rare association between AIE and IBD.[1] Our case is unique in that the patient had initial signs and symptoms of AIE shortly after total colectomy with end ileostomy. She had a history of UC as well as adrenal insufficiency; AIE has a close association with autoimmune disorders, so these could have predisposed her to developing AIE.[2,5] The diagnosis in this case was made histologically; autoimmune markers such as anti-goblet cell antibodies were not positive in our case. Anti-enterocyte and anti-goblet cell antibodies correlate with the diagnosis of AIE but are not required. The main differential diagnosis for AIE in this patient was UC-associated enteritis, a poorly understood enteropathy that occurs in UC patients post-colectomy with significant histologic overlap with AIE.[8,9] Thus, the diagnosis of AIE is challenging given the lack of objective markers because autoimmune markers have a poor specificity and can be positive in other conditions, such as patients with IBD and celiac disease.[1] AIE is thought to develop due to a defect in regulatory T-cells.[1] Histological changes seen in diagnosis include blunting of intestinal villi with mononuclear inflammation and neutrophilic cryptitis.[1] The histological changes typically mimic celiac disease, but the changes often extend beyond the small bowel.[4]

The first-line treatment of AIE often consists of immunosuppression with steroids.[2] Other agents that have been used to manage AIE include cyclosporine, tacrolimus, infliximab, and 6-mercaptopruine.[2,4] In our case, the patient had been intolerant to 6-mercaptopruine and was not a candidate for cyclosporine; therefore the patient was started on tacrolimus with eventual normalization of ostomy output. Our case is unique in that tacrolimus produced significant improvement in the symptoms and demonstrates the efficacy of tacrolimus in refractory cases of AIE.

DISCLOSURES

Author contributions: NJ Rodriguez and N. Gupta wrote the manuscript. J. Gibson provided images. NJ Rodriguez is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received November 24, 2017; Accepted August 6, 2018

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