Successful Treatment of Refractory Autoimmune Enteropathy With Ustekinumab

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ABSTRACT

Autoimmune enteropathy (AIE) is a rare autoimmune disorder that has been described both in pediatric and adult patients and usually causes intractable watery diarrhea. The management of AIE is not standardized because the disease shows variable response to different immunosuppressive regimens including corticosteroids, azathioprine, cyclophosphamide, 6-mercaptopurine, tacrolimus, cyclosporine-A, infliximab, vedolizumab, and abatacept. We present a patient with adult-onset AIE and intractable high-volume diarrhea resulting in numerous hospitalizations and temporary parenteral nutrition, who is now successfully maintained on ustekinumab. Therefore, ustekinumab should be considered for further evaluation as a therapeutic option in cases of refractory AIE.

INTRODUCTION

Autoimmune enteropathy (AIE) belongs to a group of disorders that cause small intestinal villous atrophy and can present with severe refractory diarrhea and intestinal malabsorption.1,2 Histologic changes, such as the loss of goblet cells or Paneth cells, and the presence in serum of antienterocyte/antigoblet cell antibodies are inconsistent, suggesting that defects in different immunologic pathways might converge in the diagnosis of AIE.1 Consistent with this heterogeneity, the success of numerous described medical regimens ranges from complete control with macroscopic and histologic remission in some patients to incomplete remission with chronic total parenteral nutrition (TPN) dependence and ongoing mucosal inflammation in others.1–6 Additional treatment modalities for the management of AIE are therefore needed. Recently, the successful use of antitumor necrosis factor (TNF) therapy in AIE has been reported.3–5 However, the use of this medication class in patients with congestive heart failure (CHF) therapy in AIE should be carefully considered, given the reports of CHF exacerbations after anti-TNF therapy.7

CASE REPORT

A 75-year-old man with a history of CHF, coronary artery disease, and atrial fibrillation presented to our institution with intractable diarrhea and weight loss. He had been healthy until 4 months before, when he developed progressively worsening, watery diarrhea. He had a negative evaluation for infectious diarrhea and celiac disease with his outside providers. The patient subsequently presented on numerous occasions to an emergency department with severe dehydration, hypotension, hypokalemia, and renal insufficiency because of ongoing profuse diarrhea.

The patient was referred to Massachusetts General Hospital (MGH) for further evaluation. At the time of admission, his physical examination revealed normal vital signs. He reported 30 watery bowel movements daily with a total stool output of 8 L over 24 hours, including nocturnal bowel movements. He also reported a 30-pound weight loss over the 3 months before admission. Stool electrolytes were K 53 mmol/L and Na 58 mmol/L, resulting in a stool osmotic gap of 68 mOsm/kg. Basic laboratory findings were as follows: Na 137 mmol/L, K 4.1 mmol/L, Cl 109 mmol/L, bicarbonate 17 mmol/L, Mg 1.5 mg/dL, serum lipase 14 U/L, albumin 2.5 g/dL, total protein 5.5 g/dL, C-reactive protein 6.7 mg/L, and white blood cell count 9.3 K/UL with a normal differential. Some causes of chronic diarrhea were excluded with the following tests, all of which were normal: celiac serology, stool culture with ova/parasite screen, stool Clostridium difficile toxin assay, serum gastrin, serum vasoactive intestinal peptide, serum somatostatin, serum calcitonin, serum thyroid stimulating hormone.
morning serum cortisol, serum chromogranin A, urine metanephrine, urine normetanephrine, and urine 5-Hydroxyindoleacetic acid (all from a 24-hour urine collection).

Cranial, thoracic, abdominal, and pelvic computed tomographies and an octreoscan were unremarkable. A review of his medication list did not reveal any known causes of small intestine villous blunting such as olmesartan, high-dose colchicine, mycophenolate mofetil, methotrexate, or azathioprine. Because of his worsening nutritional status, he was placed on TPN. Complete bowel rest lead to almost complete resolution of his diarrhea within 3 days. A push enteroscopy showed macroscopic villous atrophy in his duodenum and jejenum (Figure 1). Microscopically, duodenal and jejunal biopsies showed villous atrophy with a marked reduction in the number of goblet cells and Paneth cells and increased numbers of intraepithelial lymphocytes and crypt apoptoses (Figure 1). The patient’s serum was negative for antienterocyte/antigoblet cell antibodies in an indirect immunofluorescence assay on sections of normal small bowel which was performed at the Children’s Hospital of Philadelphia. The diagnosis of seronegative AIE was made based on endoscopic appearance and the pathology from his duodenal biopsies. He was subsequently started on high-dose IV prednisone (which was later transitioned to per os (PO)) and PO open-capsule budesonide and azathioprine.

On this regimen, he tolerated a regular diet with 1–2 soft bowel movements daily with marked improvement in his nutritional status and was discharged home. Push enteroscopy 4 weeks after his discharge from MGH mirrored his clinical improvement in that the distal duodenum and proximal jejunum were markedly improved macroscopically but with persistent villous blunting in the duodenal bulb. Microscopically, villous architecture in the duodenum and jejunum were improved with increased goblet cell numbers and decreased intraepithelial lymphocytes but ongoing crypt apoptoses. Immunohistochemistry for T-cell markers (CD2, CD3, CD5, and CD7) did not reveal an aberrant T cell phenotype. A slow taper of his prednisone was initiated. However, he was not able to decrease his prednisone dose below 20 mg daily without experiencing recurrent voluminous diarrhea despite continued PO open-capule budesonide (9 mg/d) and azathioprine (with adequate 6-thioguanine levels). Follow-up enteroscopy 4 months later showed mucosal improvement compared with his initial enteroscopy but ongoing signs of enteritis; microscopically, the biopsies showed patchy villous blunting and continued reduction in the number of goblet cells and Paneth cells (Figures 1). Given his dependence on prednisone and endoscopic and histologic signs of ongoing villous injury, we decided to initiate treatment with a biologic agent.

Although infliximab has been reported to lead to clinical improvement in cases of refractory AIE, this drug was not our preferred choice, given concerns about exacerbating the patient’s underlying CHF. We elected to start ustekinumab with continuation of budesonide and azathioprine, and after 8

![Figure 1](https://acgcasereports.com)

**Figure 1.** Endoscopic and histologic appearance throughout treatment. (A) Endoscopic image from the second part of the duodenum during our initial evaluation showing villous blunting and mucosal edema. (B) High power view of the duodenal biopsy from the same endoscopy shows absent villi, expansion of the lamina propria with a lymphoplasmacytic infiltrate, and absence of goblet cells. Paneth cells are markedly reduced in number. Scattered intraepithelial lymphocytes and crypt apoptotic figures can be seen. 200× magnification. (C) Endoscopic image from the third part of the duodenum during follow-up evaluation, 5 months after discharge from MGH. Compared with our initial endoscopy mild improvement of villous architecture is appreciated with ongoing mucosal edema. (D) Microscopic evaluation from that endoscopy shows partial reconstitution of villous architecture (right) but continued absence of goblet cells and reduced numbers of Paneth cells. Occasional intraepithelial lymphocytes are noted in crypt epithelium (lower left). 100× magnification. (E) Endoscopic image from the second part of the duodenum 5 months after starting ustekinumab. Compared with findings during previous endoscopic examinations, markedly improved villous architecture and mucosal edema are appreciated. (F) Microscopic examination of the duodenum from the same endoscopy shows reconstituted villous architecture with normal numbers of goblet cells. No significant increase in intraepithelial lymphocytes or crypt apoptopes is noted. 100× magnification. MGH, Massachusetts General Hospital.
weeks, we were able to discontinue prednisone with ongoing improvement in his nutritional status (last albumin 4.1 g/dL). A repeat enteroscopy 5 months after initiating ustekinumab was notable for mild macroscopic villous blunting in the proximal duodenum, but a normal appearing jejunum (Figure 1). Microscopic examination of his biopsies showed reconstitution of villous architecture; goblet cells and Paneth cells were present (Figure 1). After being on ustekinumab for 9 months, with stable improvement in his nutritional status and having 1 bowel movement daily, azathioprine was discontinued. The patient remains asymptomatic on ustekinumab and was able to discontinue budesonide 2 months ago without recurrence of diarrhea.

DISCUSSION
Currently, no treatment guidelines exist for AIE and treatment responses to immune suppression and immune modulation vary, likely because of different aberrant pathways involved in different patients. Further treatment modalities for AIE are therefore needed. Ustekinumab is a human antibody directed against the p40 subunits of IL12 and IL23, which interferes with T cell activation and is currently approved for treatment of Crohn’s disease, ulcerative colitis, plaque psoriasis, and psoriatic arthritis.10–13 Given our concern for exacerbating CHF in our patient, we were reluctant to start TNF inhibitors that had been shown to be efficacious in some cases of refractory AIE. In addition, the histological appearance of his biopsies and absence of serum enterocyte antibodies suggested a mainly T cell–mediated process which leads us to believe that ustekinumab’s ability to interfere with T cell activation might be especially beneficial in this case of seronegative AIE. More basic research is necessary to shed light on the exact pathways involved in AIE and if seronegative and seropositive disease should be treated differently. Given our experience, ustekinumab should be considered for further evaluation in this setting.

DISCLOSURES
Author contributions: JF Scheid wrote the manuscript and is the article guarantor. J. Misdraji provided the pathology images. B. Nath and JC Yarze edited the manuscript.

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REFERENCES
1. Akram S, Murray JA, Pardi DS, et al. Adult autoimmune enteropathy: Mayo Clinic Rochester experience. Clin Gastroenterol Hepatol. 2007;5(11):1282–85; quiz 1245.
2. Gentile NM, Murray JA, Pardi DS. Autoimmune enteropathy: A review and update of clinical management. Curr Gastroenterol Rep. 2012;14(5):380–5.
3. Elwing JE, Clouse RE. Adult-onset autoimmune enteropathy in the setting of thymoma successfully treated with infliximab. Dig Dis Sci. 2005;50(5):928–32.
4. Hasan SS, Siddiqui NS, Chaitanya Arudra SK, de Las Casas L, Akpunor B, Nawras A. Difuse autoimmune enteropathy and colopathy in an adult patient successfully treated with adalimumab and a review of the literature. Am J Ther. 2016;23(3):e63–8.
5. Montalto M, D’Onofrio F, Santoro L, Gallo A, Gasbarrini A, Gasbarrini G. Autoimmune enteropathy in children and adults. Scand J Gastroenterol. 2009;44(9):1029–36.
6. Gupta NK, Yilmaz O, Fisher M, Yajnik V. Abatacept: A new treatment option for refractory adult autoimmune enteropathy. J Clin Gastroenterol. 2014;48(1):55–8.
7. Kwon HI, Coté TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med. 2003;138(10):807–11.
8. Kamboj AK, Oxentenko AS. Clinical and histologic mimickers of celiac disease. Clin Transl Gastroenterol. 2017;8(8):e114.
9. Sharma A, Choung RS, Wang XJ, et al. Features of adult autoimmune enteropathy compared with refractory celiac disease. Clin Gastroenterol Hepatol. 2018;16(6):877–83.e871.
10. Reddy M, Davis C, Wong J, Marsters P, Pendley C, Prabhakar U. Modulation of CLA, IL-12R, CD40L, and IL-2Ralpha expression and inhibition of IL-12- and IL-23-induced cytokine secretion by CNTO 1275. Cell Immunol. 2007;247(1):1–11.
11. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371(9625):1665–74.
12. Sandborn WJ, Feagan BG, Fedorak RN, et al. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn’s disease. Gastroenterology. 2008;135(4):1130–41.
13. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2019;381(13):1201–14.