

Acute Flare of Adult-Onset Autoimmune Enteropathy Associated With Cyclophosphamide

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ABSTRACT

This is a case of adult-onset autoimmune enteropathy (AIE) in a 46-year-old man with multiple autoimmune conditions who presented with worsening disease process after receiving cyclophosphamide. We describe the investigations and management of this patient over a 6-year timeline. The diagnosis and management of AIE is challenging given the heterogeneity in clinico-pathologic findings and a small number of adult case reports. We describe the current diagnostic criteria, review the literature on treatment options and outcomes, and discuss the evidence for cyclophosphamide in the treatment of AIE. Adult-onset AIE should be considered in the differential diagnosis of refractory diarrhea and weight loss.

INTRODUCTION

Autoimmune enteropathy (AIE) is a rare immune-mediated disorder characterized by chronic diarrhea, malabsorption, and villous atrophy. It presents mostly in the pediatric population and was first described by Unsworth and Walker-Smith.¹ Their patient was a 1 1/2-year-old boy who presented with chronic diarrhea and failure to thrive. His serology and intestinal biopsies were suggestive of celiac disease (CD), but he was unresponsive to a gluten-free diet (GFD). In addition, they discovered the presence of a gut epithelial antibody. Only a small number of adult cases have been reported, making adult-onset AIE an uncommon entity. In this case report, we highlight the diagnostic challenges of adult-onset AIE and describe a disease flare associated with cyclophosphamide, a treatment that has been used to manage AIE.

CASE REPORT

Our patient is a 46-year old man with a medical history of polyglandular autoimmune disease, pernicious anemia, pure red cell aplasia (PRCA) associated with T-cell large granular lymphocytic leukemia, adrenal insufficiency, and parathyroid disease. He was diagnosed in 2013 with CD after presenting with a 10-year history of intermittent diarrhea, malabsorption, and difficulty gaining weight. Initial investigations included endoscopy, with duodenal biopsies revealing intraepithelial lymphocytosis and focal villous blunting (Figure 1). Celiac serology from 2002 was negative. ANA, anti-intrinsic factor, anti-smooth muscle, anti-parietal cell, and anti-mitochondrial antibodies were negative.

In June 2017, the patient was admitted to the hospital for severe hypokalemia and a 7-month history of profuse diarrhea despite being GFD compliant. There was no known dietary, infectious, or medication triggers. He was taking prednisone 20 mg daily for the management of PRCA and adrenal insufficiency, and he weighed 38 kg. Repeat anti-tissue transglutaminase antibody was negative. He underwent upper endoscopy and colonoscopy during the admission. Duodenal biopsies showed mild subtotal villous atrophy and mild to minimal intraepithelial lymphocytosis.

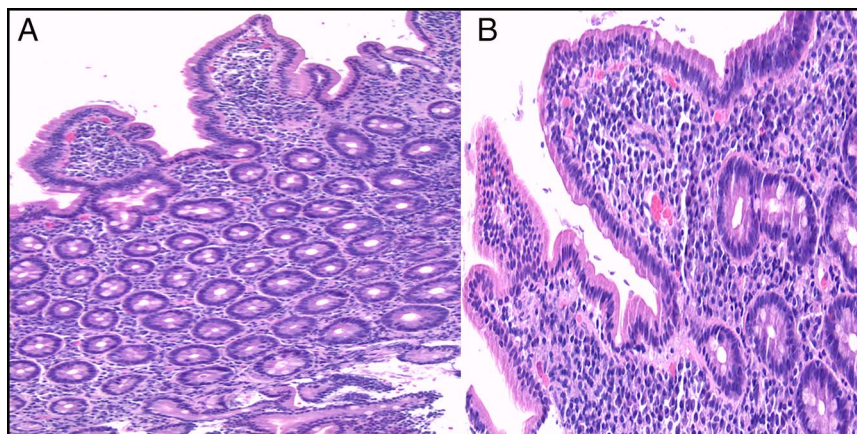


Figure 1. (A) Small intestinal mucosa with subtotal villous atrophy (hematoxylin and eosin stain, 2× magnification) and (B) blunted villi with intraepithelial lymphocytosis (hematoxylin and eosin stain, 20× magnification).

In addition, there was diffuse acute colitis with prominent apoptotic colopathy (Figure 2). CT enterography demonstrated no evidence of small bowel Crohn's or intestinal lymphoma. HLA-DQ2/DQ8 was later reported negative. Given his history of autoimmunity, lack of response to a GFD, negative gluten-sensitivity antibodies, negative HLA DQ2/DQ8, and intestinal histology, he was diagnosed with AIE. Prednisone was increased to 40 mg daily, and the patient's stool volume significantly decreased.

In July 2019, the patient was readmitted with severe hypokalemia and a 2-week history of worsening diarrhea. He had been on prednisone 10 mg daily, which was just increased because of recurrent diarrheal symptoms. Of note, he was started on cyclophosphamide (CY) 50 mg daily in March 2019 for treatment of PRCA, and this was increased to 100 mg daily in mid-June.

Infectious etiologies were ruled out and CY was discontinued as it was the only identifiable trigger. The patient was trialed on an elemental diet and switched to methylprednisolone 40 mg daily for 2 weeks with significant improvement in stool volume. His diarrhea resolved, and he was discharged on prednisone 35 mg

daily with a slow taper. At 1-month follow-up, the patient was having formed stools and his weight was stable.

DISCUSSION

This case highlights the overlap between AIE and CD, resulting in treatment delays and increase in morbidity. Clinicians should consider AIE in their differential diagnosis in patients with a diagnosis of CD when there is a lack of response to a strict GFD. Literature has described cases with AIE and both positive gluten sensitivity antibodies and celiac-associated HLA markers. There is also documented overlap in small-intestinal biopsy findings between the 2 disease entities, where patients diagnosed with AIE have demonstrated the classic CD or a mixed CD-AIE pattern.² Villous atrophy is seen in both CD and AIE, but AIE is characterized by the absence of significant intraepithelial lymphocytosis² and mucosal injury to other locations outside the small bowel including the esophagus, stomach, and colon.²⁻¹⁴ The most commonly involved site appears to be the colon with 1 large case series showing colonic involvement in more than 60% of patients diagnosed with AIE.⁶ It is well-documented that AIE is associated with other autoimmune diseases.^{2,9,15-17}

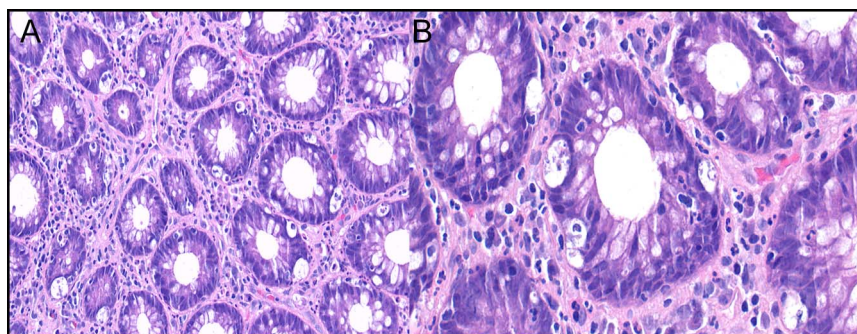


Figure 2. (A) Colonic mucosa showing apoptotic colopathy (hematoxylin and eosin stain, 20× magnification) and (B) the colonic crypt with apoptotic bodies (hematoxylin and eosin stain, 40× magnification).

Unsworth and Walker-Smith have proposed diagnostic criteria¹ for AIE, which requires the fulfillment of 4 criteria: (1) presentation with protracted diarrhea and severe enteropathy, (2) no response to exclusion diet or total parenteral nutrition, (3) evidence of predisposition to autoimmune diseases (presence of circulating autoantibodies) and/or associated disease also believed to be autoimmune, and (4) no severe immunodeficiency. Akram et al later proposed diagnostic criteria² in the adult-onset population, which requires the fulfillment of criteria 1-4: (1) adult-onset chronic diarrhea (>6 weeks' duration), (2) malabsorption, (3) specific small bowel histology (partial complete villous blunting, deep crypt lymphocytosis, increased crypt apoptotic bodies, and minimal intraepithelial lymphocytosis), (4) exclusion of other causes of villous atrophy including CD, refractory sprue, and intestinal lymphoma, and (5) anti-enterocyte and/or anti-goblet cell antibodies.

Our patient would have fulfilled both sets of proposed diagnostic criteria. As suggested by Akram et al, there is an association between AIE and gut epithelial antibodies, but the clinical significance and utility in diagnosis is not clear. They are not specific to AIE and have been found in other diseases such as inflammatory bowel disease and HIV.^{18,19} Gut epithelial antibody testing was never performed in our patient because of limited access. There is no standard treatment for AIE. In the literature, the most commonly used treatment for adult-onset AIE has been systemic steroids with partial to complete therapeutic response. Patients have been treated with any combination of systemic steroids, antimetabolites (azathioprine and 6-mercaptopurine), biologics, budesonide, tacrolimus, intravenous immunoglobulin, mesenchymal stromal cells, and CY.^{3-11,13,14,17,20-30}

CY has documented use in a variety of autoimmune diseases and has been used to treat AIE in the pediatric population. In a case report,³¹ an infant with refractory AIE was treated with high-dose intravenous CY at 50 mg/kg/d for 4 consecutive days. She improved dramatically with resolution of both symptoms and histopathological features without any further need for immunosuppressive therapy. In adults, there is 1 documented case of treatment with CY,⁹ which was dosed at 50 mg/d in combination with prednisolone 60 mg/d. There was no symptomatic response to therapy. In our patient, CY was initiated to treat refractory PRCA. By the time of admission in July 2019, he was on the typical 100 mg/d dose, which was much lower on a weight basis compared with what was effective in the aforementioned pediatric patient.

The pathophysiology of AIE is not well understood but could be the result of intestinal immune dysregulation. CY may paradoxically exacerbate inflammation through its effect on CD4⁺25⁺ T_{REG}, a particular subpopulation of regulatory T cells involved in maintaining self-tolerance and suppressing autoimmune and inflammatory disease.³²⁻³⁵ Another study showed that CY-treated mice had increased lung inflammation and reduced lung expression of FoxP3,³⁶ a

specific marker of CD4⁺25⁺ T_{REG} cells.³⁷ Given the timeline and lack of an infectious trigger, it was suspected that CY contributed to disease relapse in our patient. Unlike the treatment of other autoimmune diseases, the role of biologics in AIE is undetermined. The available evidence is based on case reports which describe the use of infliximab, adalimumab, and rituximab.^{5,6,10,14,21} Patient responses were variable from none to sustained remission at 10-month follow-up. This highlights how insufficient evidence is available on steroid-sparing treatment options, and the challenge of managing patients with the steroid-refractory disease remains.

DISCLOSURES

Author contribution: J. Liu, Z. Hindi, and S. Albashir wrote the manuscript. T. Aziz revised the manuscript. J. Liu is the article guarantor.

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