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Case Report
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# Successful Outcome of Ineffective Infliximab-Treated Autoimmune Enteropathy with Oral Budesonide: A Case Report

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## Abstract

**Introduction:** Autoimmune Enteropathy (AIE) is a rare disease that causes chronic diarrhea due to small intestinal villus atrophy. Because of its low morbidity and the lack of specific symptoms, it is often misdiagnosed or delayed in diagnosis. Currently, its treatment also faces great challenges.

**Case Report:** A 35-year-old woman reported persistent diarrhea with significant weight loss for two months. Capsule endoscopy showed a reduction of the small intestinal folds and shortening or disappearance of villi. Small colonoscopy biopsy revealed severe villus atrophy, disappearance of goblet cells, crypt epithelial hyperplasia, crypt apoptosis, and massive lymphoplasmacytic infiltration within the lamina propria. Diseases that could easily cause small intestinal villus atrophy, such as celiac disease and CVID, were ruled out based on medical history and laboratory examination. Thus, AIE was diagnosed. The patient's diarrhea gradually improved with methylprednisolone 40 mg/d iv. The symptoms worsened again when methylprednisolone was reduced to 12 mg/day, and treatment with infliximab 5 mg/day failed three times. Finally, treatment with oral budesonide (9 mg/day) was initiated. Diarrhea decreased significantly after one week and returned to normal after three weeks, with no recurrence so far.

**Conclusion:** Due to its low morbidity and lack of specific symptoms, it is often misdiagnosed or the diagnosis is delayed. Oral budesonide would still be a preferable option for patients with AIE when traditional hormone dependence and biological agents are ineffective.

**Keywords: Autoimmune enteropathy; Infliximab; Budesonide**

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## Introduction

Autoimmune Enteropathy (AIE) is a rare disease that causes chronic diarrhea due to small intestinal villus atrophy [1]. Akram et al. proposed AIE's diagnostic criteria in adults, including: 1. Persistent diarrhea >6 weeks; 2. Evidence of malabsorption; 3. Specific histological findings in small bowel biopsy, including partial or complete villus atrophy with exclusion of other causes of villus atrophy [2]. The features of AIE biopsies most commonly present in the small intestine with villous blunting, the loss of goblet cells or Paneth cells, expansion of the lamina propria caused by lymphatic plasma cells and neutrophil infiltration, and Cystitis [3]. Nonetheless, misdiagnosis of AIE remains common. This might be due to its low morbidity and lack of specific symptoms.

The treatment of AIE is also extremely challenging. While corticosteroid hormone is commonly used as the first-line treatment [4], it often fails with most AIE patients [5]. A variety of treatments such as infliximab, Ustekinumab and adalimumab are currently being trialed for AIE [1,6]. However, most of these methods are only published in case reports, and the effects are still unclear. Also, the side effects of these methods still need to be considered.

## Case Presentation

A 35-year-old female patient was admitted on January 25th, 2017, for persistent diarrhea with malabsorption that lasted for 2 months.

The patient developed diarrhea with yellow-green watery stools 6 to 10 times/day. Stool amount approximately 1~2 L/day. Without abdominal pain, abdominal distension, vomiting and fever. Antidiarrheal drugs and antibiotic treatment were ineffective. Colonoscopy showed terminal ileal ulcer. Pathology showed severe mucosal chronic inflammation. Chest CT showed calcification in the

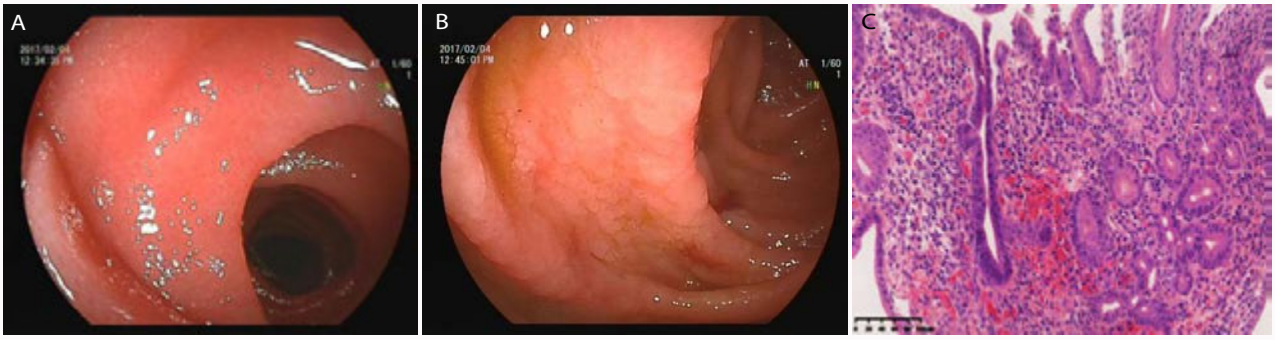


**Figure 1:** Endoscopic and histologic appearance. (A) Endoscopic image from the duodenum showing villous blunting. (B) Endoscopic image from the terminal ileum showing villous blunting, small erosions and ulcers. (C) High power view of the terminal ileum biopsy from the same endoscopy showing severe villus atrophy, disappearance of goblet cells, crypt epithelial hyperplasia and apoptosis at the base of the crypt. Small amount of lymphocyte infiltration was present in the epithelium. There were abundant lymphoplasma cells and minor neutrophil infiltration in the lamina propria. Cystitis and crypt abscess were occasionally seen, HE×200.

left upper lobe, and T-Spot was positive. Fecal occult blood, parasites, *C. difficile* toxin assays, fungi and bacteria were negative. Considering nephronophthisis, the patient was given empirical anti-tuberculosis treatment for three weeks. Diarrhea symptoms aggravated to more than 10 times/day, stool amount approximately 3 to 5 L/day. The patient presented to the hospital again, with hypokalemia, metabolic acidosis, and severe malnutrition. Her BMI was 11.9 kg/m$^2$.

The stool routine indicated full field leukocytes and positive occult blood. Fecal *C. difficile* toxin assays, fungi and parasites, and other bacterial pathogens were tested negative. ESR, CRP, serum iron, autoimmune antibodies, liver and kidney function tests were all normal. Serum albumin was only 20 g/L, K+ 2.36 mmol/L and Na+ 132 mmol/L. Immunoglobulin and gastrin test showed no abnormalities. No significant abnormalities were seen on the abdominal-pelvic enhanced CT. Double-balloon enteroscopy showed shortened or disappeared small intestinal villi, and ulcers in the terminal ileum. The biopsy histology of duodenum, jejunum and ileal mucosa indicated severe villus atrophy, disappearance of goblet cells, crypt epithelial hyperplasia and apoptosis at the base of the crypt. Small amount of lymphocyte infiltration was present in the epithelium. There were abundant lymphoplasma cells and minor neutrophil infiltration in the lamina propria (Figure 1).

The patient presented with chronic diarrhea, malabsorption, together with endoscopic findings, small bowel biopsy pathological results, and various fecal pathogens, a final diagnosis of AIE was made. Therapy with methylprednisolone 1 mg/kg QD was started on February 12$^{th}$, 2017. The patient's bowel movement reduced to 1 to 2 times/day. Her enteral nutrition was gradually restored. When methylprednisolone tablets were reduced to 12 mg/day on April 4$^{th}$, 2017, her symptoms worsened again with watery diarrhea 7 to 8 times/day, approximately 1000 to 2000 ml/day. All stool etiology tests were rechecked and all came back negative, so the patient was considered for traditional hormone dependence. Infliximab was administered at 5 mg/kg three times (05/21/2017, 06/04/2017, 07/02/2017), but ineffective. Treatment was adjusted to oral budesonide (9 mg/day). After 1 week, the patient's bowel movement significantly reduced to 1 to 2 times/day. Diarrhea completely stopped after three weeks and her diet returned to normal. After discharge, the patient received oral budesonide 9 mg QD for 2 months, 6 mg QD for 3 months, and 3 mg QD for 3 months, and then discontinued medication treatment. The patient's weight returned to basal level 3 months after discharge and no side effects occurred during oral budesonide treatment. Patient follow-up was conducted up to date, stating that she has discontinued medication for nearly 4 years with no recurrence, and has yet reexamined endoscopy.

## Discussion

Causes of chronic diarrhea in adults with malabsorption as the main manifestation include IBD, lymphoma, eosinophilic enteritis, drug-related enteropathy, tuberculosis, infection, Whipple's disease, CVID, Celiac Disease (CD), and AIE [7]. The histological features of both CVID and CD were small intestinal villous atrophy. However, CVID pathology had no plasma cell infiltration [8] while AIE showed increased plasma cells in the lamina propria [3]. Sharma et al. reported no significant difference in the degree of AIE and CD villus atrophy. While a Gluten-free diet was effective for CD. Therefore, both CVID and CD were excluded, and a final diagnosis of AIE was made.

Glucocorticoids are commonly used as the first-line therapy. However, only 26% of the patients received positive results from hormone treatment alone [9]. This patient had a transient reduction of symptoms after treatment with 40 mg methylprednisolone, but diarrhea worsened when the hormone was reduced to 12 mg. Infliximab was ineffective too. Oral budesonide enteric-coated capsules and received satisfactory results. Sharma et al. reported a clinical efficacy rate of 85% in open-capsule budesonide at a daily dosage of 9 mg in 30 patients with AIE, who were refractory to conventional hormones, over a mean follow-up period of 28 months [5]. The possible mechanism was that traditional hormones act on the whole body, so the intestinal local concentration and anti-inflammatory effect would be weakened. On the other hand, oral budesonide was released in the small intestine and colon, acting directly on the intestinal mucosa surface. This could make the local concentration of the intestinal tract higher, thus having a strong anti-inflammatory effect on the intestinal tract. Unfortunately, gastroenteroscopy and biopsy were not reviewed in the later stage, hence no evidence of histological remission was found. However, five years of follow-up showed that the patient had reached complete remission. This case further confirmed that oral budesonide has a more positive efficacy on AIE, achieving a long-term remission with no need of maintenance treatment. Therefore, oral budesonide would still be a preferable option for patients with AIE when there were traditional hormone dependence and biological agents were ineffective.

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